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ABSTRACT SUPPLEMENT

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The Liver Meeting: 2024 Abstracts

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0001 | CLINICALLY DISTINCT METABOTYPES OF PEDIATRIC METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE: AN UNSUPERVISED MACHINE LEARNING ANALYSIS OF CHILDREN ENROLLED IN NASH CRN STUDIES ★

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Background: Phenotypic heterogeneity among children with MASLD is poorly understood. This study aimed to identify metabolic phenotypes (metabotypes) among pediatric patients with MASLD based on clinical, histological, and high-resolution metabolomics data. **Methods:** We analyzed the clinical and untargeted metabolomics data of 517 children ages 5-18 years with biopsy-proven MASLD from three NASH Clinical Research Network (NASH CRN) studies. The following predictors informed an unsupervised machine learning algorithm (k-means clustering): age, BMI percentile, waist circumference (WC), systolic blood pressure (SBP), uric acid, alanine aminotransferase (ALT), aspartate aminotransferase (AST), fasting triglycerides, very low-density lipoprotein (VLDL), LDL, and homeostatic model of insulin resistance (HOMA-IR). Integrative network analysis of the metabolomics and clinical data was performed using xMWAS software (v.0.552) to examine metabolic features associated with each metabotype. **Results:** We identified three pediatric MASLD metabotypes: 1) Early-mild (49.7%, younger with lowest levels of lipids, liver enzymes, and insulin resistance), 2) Adipo-lipid-SBP (35.8%, highest BMI percentile, WC, lipids, and SBP), 3) Inflammatory-fibrotic (14.5%, highest levels of liver enzymes, and advanced fibrosis). Network analysis within the Inflammatory-fibrotic metabotype revealed a positive association between ALT and several glycerophospholipids (LysoPC(20:2), PE(32:0), CL(68:5)) as well as bile acid species (3-oxocholadienoic acid). The Adipo-lipid-SBP metabotype network demonstrated a positive association between fasting triglycerides and various glycerophospholipid species (PC(28:7), LysoPC(14:0)), while in the Early-mild metabotype network, age was negatively associated with monoacylglycerol and PC species. **Conclusion:** Our findings reveal significant heterogeneity among children with MASLD, identifying three clinically distinct metabotypes characterized by unique metabolic profiles and varying disease severity. These metabotypes could inform targeted interventions and management strategies, enhancing precision healthcare for children with MASLD. Further research is needed to validate our novel findings.

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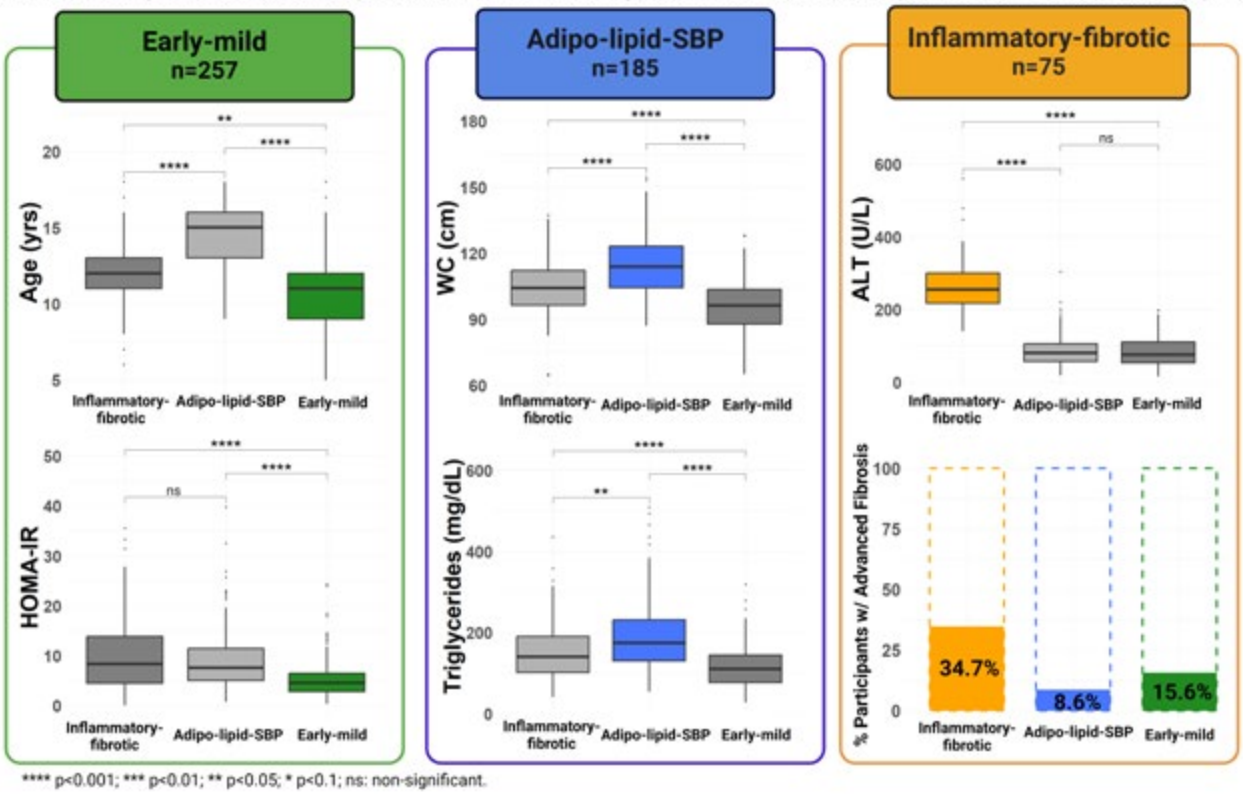
Figure 1. Clinical profiles of the three pediatric MASLD metabotypes identified using unsupervised k-means clustering (n=517).



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0002 | IDENTIFICATION OF NOVEL CLASS I HLA ALLELES AND T-CELL REPERTOIRE FEATURES ASSOCIATED WITH INDETERMINATE PEDIATRIC ACUTE LIVER FAILURE

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Background: Pediatric Activated T-cell Hepatitis is the most common cause of indeterminate pediatric acute liver failure (IND-PALF), characterized by liver and peripheral blood predominance of clonally expanded effector memory CD8 T-cells. IND-PALF can be associated with acquired aplastic anemia (AA), an autoimmune bone marrow aplasia caused by CD8 T-cell-mediated attack on hematopoietic cells. The close association between IND-PALF and AA has been hypothesized to involve cross-reactivity of T-cell-mediated attack against hepatic and hematopoietic antigens. Recently multiple human leukocyte antigen (HLA) Class I risk alleles have been

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implicated in the pathogenesis of AA. We hypothesized that IND-PALF may have similar pathogenesis and investigated HLA associations and T-cell receptor (TCR) sequences in IND-PALF. **Methods:** HLA genotyping for 36 patients with IND-PALF and 11 with known diagnoses (DX-PALF) from the Pediatric Acute Liver Failure Study Group (PALFSG) was performed using next generation sequencing on frozen explant liver tissue DNA. An in-house method was used to enumerate TCR beta chain sequences. HLA frequency data in the study cohort were compared to ethnically-matched controls (National Marrow Donor Program database) with a significant P<0.005 (Chi-square test adjusted for multiple comparisons). T-cell clonality was assessed by measuring percentage of reads that comprise the top 20 clones. **Results:** 5 HLA class I alleles, including a risk allele associated with AA (HLA-A*68:01), were significantly overrepresented among the 33 Caucasian IND-PALF patients compared to ethnicity-matched controls (Table 1). Overrepresented HLA A and B alleles were more common in IND-PALF (14 of 33 (42%) compared to 1 of 11 (11%) in DX-PALF, p=0.067). Acquired HLA loss is a common mechanism of immune evasion by hematopoietic cells in AA. We wondered whether a similar phenomenon may occur in IND-PALF hepatocytes and examined liver explants for somatic HLA loss measured as allele imbalance. 4 IND-PALF patients had apparent HLA-A or HLA-B allele imbalance, 2 with known AA risk alleles (HLA-A*68:01 and HLA-B*40:02) at the affected loci. TCR sequencing found mean 17.2% ± 8.2% of reads composing the top 20 clones, consistent with clonal expansion, but did not reveal a dominantly expressed shared TCR that would identify a common antigenic trigger. **Conclusion:** This is the first study to identify HLA class I alleles associated with IND-PALF and a potential genetic predisposition linking IND-PALF and AA. This discovery, coupled with clonal expansion in liver T-cells, suggests that HLA class I-restricted CD8 T-cells mediate liver injury in IND-PALF. These findings support the hypothesis that the Activated T-cell Hepatitis phenotype of IND-PALF and AA may exist on a disease spectrum with antigens presented by HLA alleles serving as the target of CD8 T-cells in both the bone marrow and the liver.

Table 1. HLA alleles significantly over-represented in Caucasian IND-PALF cohort.

	Allele Frequency				
HLA Allele	IND-PALF N=33	Control N=15,738	P value	OR	95% CI
A*23:01	12.1	1.7	<0.0001	8.054	3.016-22.07
A*68:01	12.1	2.5	0.0008	5.025	1.891-13.52
B*35:03	12.1	1.6	<0.0001	8.685	3.251-23.83
B*52:01	9.1	1.0	<0.0001	10.32	3.271-30.96
C*04:01	30.3	10.5	0.0002	3.693	1.804-7.543

HLA: human leukocyte antigen, IND-PALF: indeterminate pediatric acute liver failure, N: number of individuals, OR: odds ratio, 95% CI: 95% confidence interval

Disclosures: Catherine Chapin: Nothing to Disclose, Tamir Diamond: Nothing to Disclose, Michelle Lau: Nothing to Disclose, Wenzhao Meng: Nothing to Disclose, Eline Luning Prak: Nothing to Disclose, Kathleen Loomes: Mirum: Consultant, Albireo/Ipsen: Consultant, Mirum: Clinical trials, Albireo/Ipsen: Clinical trials, Estella Alonso: Nothing to Disclose, Daria Babushok: Nothing to Disclose, Anat Tambur: Nothing to Disclose, Edward Behrens: Nothing to Disclose

0003 | OPTIMAL MEAN ARTERIAL PRESSURE TARGETS IN THE MANAGEMENT OF CRITICALLY ILL PATIENTS WITH DECOMPENSATED CIRRHOSIS AND SEPTIC SHOCK

Kavish Patidar[1] Lauren Hall[2] Rakhi Maiwall[3] Constantine Karvellas[4] Gerald Ogola[2] Sumeet Asrani[5]

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Background: Short term mortality remains high for critically ill patients with cirrhosis and septic shock in the ICU and targets for end organ perfusion are not well defined to achieve improvement in survival. Though recent AASLD guidance suggests a mean arterial pressure (MAP) target of ≥65, an even higher target may be needed to improve survival and organ recovery. We examined association of MAP targets with survival and acute kidney injury (AKI) recovery after AKI. **Methods:** We assessed all patients with decompensated cirrhosis admitted with septic shock in the ICU (2014-2022, 26 hospitals). Septic shock was defined using Sepsis-3 criteria. AKI and renal recovery were

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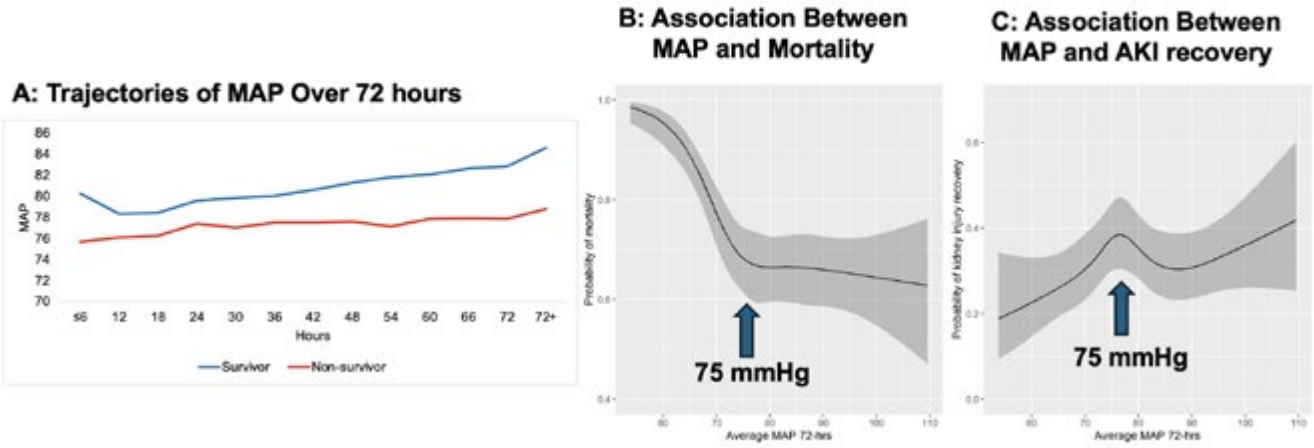
defined based on International Club of Ascites criteria. We looked at association of MAP trends over the first 72 hours and its association with mortality within 28 days and achievement of AKI recovery in patients that presented with AKI. We examined the independent association of MAP improvement after adjustment for early fluids (4hrs), early antibiotics (4hrs), demographics, MELD score and age with consideration of MAP thresholds as a restricted cubic spline. **Results:** There were 1,729 patients in the ICU with septic shock (mean age 64, MELD 23: 43% female, 19% non-White, 23% Hispanic, 37% alcohol-related cirrhosis) with 151,734 MAP observations (mean MAP observations/patient within 72 hours was 136). AKI was present in 72% of patients, of which 42% achieved AKI recovery. Mortality within 28 days was 54%. Patients who survived had on average higher MAP through the clinical course (Figure 1A). Survivors had a greater increase in delta MAP from admission to 72 hours (5.75% vs. 2.85%, p<0.01). On multivariable analysis, improvement in MAP to a target 65-75 mmHg was significantly associated with improved 28-day survival and AKI recovery even after adjusting for other interventions. The relationship between achievement of MAP thresholds over 72 hours both for survival and AKI recovery is shown in Figure 1B/1C. An inflection point of approximately 75 mmHg was found to be optimal for both AKI recovery as well as survival. We found no relationship between absolute % increase in MAP, survival, and AKI recovery. Finally, we examined the additive impact of MAP improvement as compared to other interventions. Odds of mortality was significantly lower with early fluids and antibiotics (OR=0.54), MAP and early antibiotics (OR=0.44) Receipt of all 3 interventions had an additive effect with 67% lower odds of mortality (OR 0.37, 95% CI 0.23-0.60). **Conclusion:** Improvement of MAP in decompensated patients with septic shock remains a cornerstone, with a target of 75 mmHg providing balance of survival and AKI recovery in addition to other early goal directed therapy.

Figure:



Disclosures: Kavish Patidar: Madrigal Pharmaceuticals: Medical Advisory Board, Lauren Hall: Nothing to Disclose, Rakhi Maiwall: Nothing to Disclose, Constantine Karvellas: Consultant relationship with Mallinckrodt; Has not ended; Advisor relationship with Baxter; Has not ended; Advisor relationship with Grifols; Has not ended; Data safety monitoring board for clinical trial relationship with Miromatrix; Has not ended, Gerald Ogola: Nothing to Disclose, Sumeet Asrani: Nothing to Disclose

0004 | RESMETIROM EFFECTS ON NASH WITH LIVER FIBROSIS IN PATIENTS WITH NASH GENETIC RISK ALLELES

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Background: MAESTRO-NASH (NCT03900429) is an ongoing 54-month, randomized, double-blind, placebo-controlled Phase 3 trial evaluating the efficacy of resmetirom in patients with biopsy-confirmed nonalcoholic steatohepatitis (NASH) and fibrosis. 966 patients with biopsy-confirmed NASH were randomized 1:1:1 to resmetirom 80 mg, resmetirom 100 mg, or placebo administered once daily. Histologic endpoints were assessed after 52 weeks. Dual primary endpoints at Week 52 were achieved with both resmetirom 80 mg and 100 mg: NASH resolution with no worsening of fibrosis (NR) or ≥1-stage reduction in fibrosis with no worsening of NAS (FI). In this analysis, we examined the impact of baseline *PNPLA3*, *TM6SF2* and *MBOAT7* genotypes on the

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response to resmetirom on serial liver biopsy and MRI-PDFF (magnetic resonance imaging proton density fat fraction). **Methods:** In the Phase 3 study (MGL-3196-11), *PNPLA3 rs738409*, *TM6SF2 rs58542926* and *MBOAT7 rs6141738* were genotyped in patients consenting to DNA collection and genetic testing for the response to resmetirom on serial liver biopsy and MRI-PDFF. The NASH resolution and fibrosis improvement responses on liver biopsy and the MRI-PDFF (median percent change from baseline at Week 52) response were analyzed within each treatment arm, comparing wild type, heterozygote and homozygote for each genetic risk allele. **Results:** Across three treatment arms, 740 patients had genotyping and serial liver biopsy data. The frequency of *PNPLA3 GG* (wild type), *PNPLA3 CG* (heterozygous), and *GG* (homozygous) genotypes across 3 treatment arms were 30-32%, 45-50% and 20-24% respectively. The frequency of *TM6SF2 CC* (wild type), *TM6SF2* CT (heterozygous), and *TM6SF2* TT (homozygous) genotypes were 79-82%, 15-21% and 0-3% across 3 treatment arms. The frequency of *MBOAT7* CC (wild type), *MBOAT7* CT (heterozygous) and *MBOAT7 TT* (homozygous) genotypes were 28-29%, 47-50%, and 21-24% across 3 treatment arms. There were no differences observed in the level of response on biopsy or MRI-PDFF to resmetirom or placebo treatment in patients with genetic risk alleles for PNPLA3 and TM6SF2 (Table) or TMC4 (not shown). **Conclusion:** NASH risk alleles were prevalent in the MAESTRO-NASH population and did not influence the treatment response to resmetirom

	N (%)	NASH Resolution (% response)	Fibrosis Improvement (% response)	MRI-PDFF Median % change from baseline
PNPLA3				
80 mg	248			
No Mutation	74 (30%)	39%	30%	-47
Heterozygous	124 (50%)	27%	29%	-41
Homozygous	50 (20%)	24%	25%	-41
100 mg	230			
No Mutation	72 (31%)	38%	33%	-51
Heterozygous	103 (45%)	36%	28%	-52
Homozygous	55 (24%)	36%	36%	-50
Placebo	262			
No Mutation	85 (32%)	11%	15%	-12
Heterozygous	117 (45%)	6%	14%	-9
Homozygous	60 (23%)	7%	14%	-15
TM6SF2				
80 mg	248			
No Mutation	203 (82%)	30%	29%	-42
Heterozygous	38 (15%)	29%	24%	-46
Homozygous	7 (3%)	43%	43%	-49
100 mg	230			
No Mutation	185 (79%)	37%	33%	-51
Heterozygous	42 (18%)	31%	27%	-45
Homozygous	3 (1%)	67%	33%	-70
Placebo	262			
No Mutation	207 (79%)	10%	16%	-10
Heterozygous	55 (21%)	5%	10%	-11
Homozygous	0			

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0005 | PREEMPTIVE TIPS: THE NEW STANDARD FOR GASTRIC VARICEAL BLEEDING IN PATIENTS WITH CIRRHOSIS? RESULTS OF A LARGE MULTICENTER RANDOMIZED CONTROLLED TRIAL

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Background: Gastric variceal bleeding, which accounts for 10% of portal hypertension-related bleeding, is associated with a poor prognosis. Variceal glue obturation (GO) is recommended for the management of acute variceal bleeding, and to prevent rebleeding. The value of transjugular intrahepatic portosystemic shunt (TIPS) in this setting is not clear. The aim of this study was to compare preemptive TIPS (p-TIPS) and GO plus non selective betablockers (NSBB) in acute gastric variceal bleeding episode. **Methods:** Patients with gastric variceal bleeding (excluding gastroesophageal varices (GOV) 1), initially treated with GO were randomized after stabilization to receive either p-TIPS with covered stent (<72 hours) or to continue GO plus NSBB. The primary objective was to compare the 1-year survival free of rebleeding (SFR). Secondary objectives were: all-cause mortality at D42 and 365; rebleeding rate at D42 and 365; hospital stay (days) during follow-up. Analysis of the primary endpoint was based on Kaplan-Meier survival estimates, with comparisons using the log-rank test. Relative risks for SFR were calculated using a Cox model. The risk of rebleeding after adjustment for the competing risk of death was assessed using Fine & Gray model. **Results:** One hundred and one cirrhotic patients (90% alcoholic, 80% male, median age 59 [IQR 53-65] years, 84% Child-Pugh B/C, median MELD 14 [IQR 13-17]) were included. GOV2 were the most frequent (58%) followed by IGV1 (48%); associated with esophageal varices in 55% of cases (band ligations associated with GO in 17% of patients). A complication of the initial GO was observed in 20% of procedures (11% bleeding, 8% glue migration). After initial GO, 47 patients received p-TIPS and 54 continued with GO and NSBB. The 1-year was SFR was 33% (CI95%: 22%-49%) vs. 73% (CI95%: 62%-88%) (HR 0.29, CI95% [0.15-0.56], p<0.001) in pTIPS and GO, respectively. The cumulative incidence of rebleeding was lower in the p-TIPS arm at D42 (HR 0.25, CI95%: 0.08-0.75; p=0.014) and D365 (HR 0.20, IC95%: 0.08-0.49; p<0.001). Survival in pTIPS group compared to GO group at D42 (98% vs. 94%) and 1 year (85% vs. 80%) were not significantly different; however, 17 patients (31%) in GO group were treated with TIPS as a rescue and among them only one die. The median number of days in hospital was 15 in p-TIPS group (IQR 10-32) and 22 in the group GO (IQR 14-37 p=0.10). **Conclusion:** Preemptive TIPS triples the one-year survival free of rebleeding and should become the new standard for gastric variceal bleeding in cirrhotic patients.

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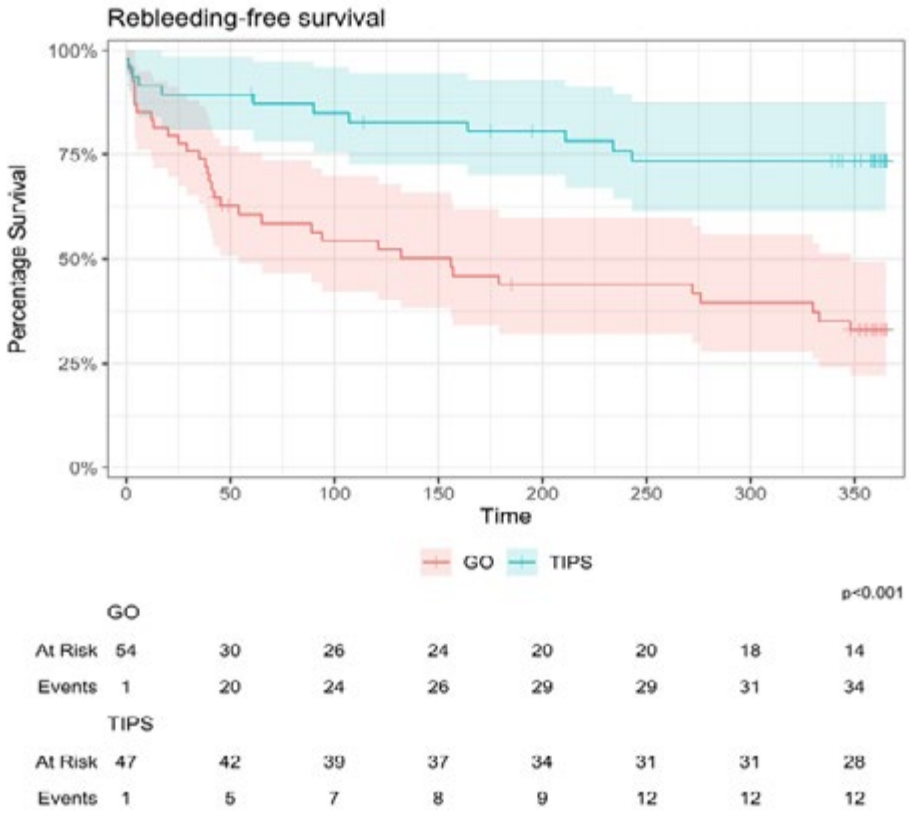

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0006 | HEPATIC ARTERY FLOW-INDUCED PORTAL TRACT REMODELING AND FIBROSIS IN PORTAL HYPERTENSION: THE ROLE OF VCAM-1 AND OSTEOPONTIN-EXPRESSING MACROPHAGES ★

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Background: The liver undergoes significant hemodynamic changes due to surgery, transplantation, or cirrhosis with portal hypertension (PH). The molecular mechanisms by which these changes influence liver structure and function remain largely unknown. In PH, the hepatic artery (HA) flow increases to compensate for decreased portal venous flow, a phenomenon known as HA buffer response (HABR). We hypothesized that the HABR induces pathological portal tract remodeling and investigated the underlying molecular mechanisms. **Methods:** PH was induced in Sprague-Dawley rats via partial portal vein ligation (PPVL) surgery. Structural evaluation (microCT), immune cell profiling, and hemodynamic analyses were conducted. Macrophages/ Kupffer cells (MØ) from sham or PPVL rats underwent transcriptomic analysis. Sincle-cell RNA sequencing (scRNA-seq) data (GSE171904) was used for confirmation. **Results:** MicroCT showed decreased portal vein flow in PPVL rats. HA flow positively correlated with portal pressure (r=0.799, p<0.01). Sirius red staining revealed increased portal tract fibrosis (2-fold increase vs. sham, p<0.001, accompanied by increased a-SMA+ myofibroblasts in PPVL rats. CD68+ MØ peaked at 10 days post-PPVL and receded by 30 days. MØ depletion significantly reduced portal tract fibrosis (p<0.001), indicating MØ involvement in remodeling. VCAM-1 levels were elevated in HA endothelium and portal tract area in PPVL. VCAM-1 neutralizing antibody reduced collagen accumulation (p<0.05), CD68+ MØ by 46.3% (p<0.01), and CD3+ T cells 18% (p<0.05). In vitro, MØ conditioned medium (CM) increased VCAM-1 level in rat portal fibroblasts (PF) 8-fold (p<0.001) and enhanced PF migration, while VCAM-1 knockdown decreased it (p<0.01). However, VCAM-1 did not promote extracellular matrix synthesis in PFs. Cell-cell communication analysis of scRNA-seq data revealed increased interaction between osteopontin (Spp1)+ MØ and PF in cholestatic mice, suggesting the involvement of Spp1+ MØ in portal tract fibrosis. Transcriptomic analysis of isolated liver MØ revealed increased Spp1 expression in PPVL-3d MØ (1.74-fold, p<0.001). RNA fluorescent in situ hybridization (RNA-FISH) and CD68+ MØ co-immunofluorescence confirmed this. Co-culturing PFs with Spp1 knockdown MØ decreased Col1a1 and Acta2 mRNA expression (p<0.05). Recombinant Spp1 upregulated Col1a1 (1.6-fold, p<0.001), Fn1 (1.8-fold, p<0.001), Acta2 (2.5-fold, p<0.001), and several integrins in PFs, indicating a fibrogenic role of Spp1+ MØ during flow-induced liver remodeling. **Conclusion:** Our findings reveal that increased VCAM1 in hepatic arterial endothelial cells and PFs recruits osteopontin (Spp1)+ MØ, driving HA flow-mediated vascular remodeling and portal tract fibrosis. In the case of cirrhosis with PH, this arterial flow-induced fibrosis may trigger progression to a decompensated state.
Disclosures: Ruixue Ma: Nothing to Disclose, Li Gong: Nothing to Disclose, Chao Dong: Nothing to Disclose, Matthew McConnell: Nothing to Disclose, Teruo Utsumi: Nothing to Disclose, Yasuko Iwakiri: Nothing to Disclose

0007 | POINT-OF-CARE ULTRASOUND (POCUS) TO ASSESS IMPACT OF CIRRHOTIC CARDIOMYOPATHY AND RENAL BIOMARKERS IN PATIENTS WITH CIRRHOSIS AND ACUTE KIDNEY INJURY

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Background: Point-of-care ultrasound (POCUS) is used to diagnose cirrhotic cardiomyopathy (CCM), and volume status in cirrhosis accurately. We aimed to longitudinally assess Echocardiographic parameters- LV systolic function [ejection fraction& cardiac index (CI)], and diastolic dysfunction (E/e integral', mitral e' velocity, left atrial volume index, and Tricuspid jet velocity) and inferior vena cava dynamics in relation to acute kidney injury (AKI) in cirrhosis. **Methods:** Serial POC-Echo with tissue Doppler imaging was done at presentation, and at 24 and 48 hours from the 1st assessment in patients with decompensated cirrhosis and AKI admitted to the Liver Intensive Care Unit. Patients with shock, those with active variceal bleeding or known end-stage renal

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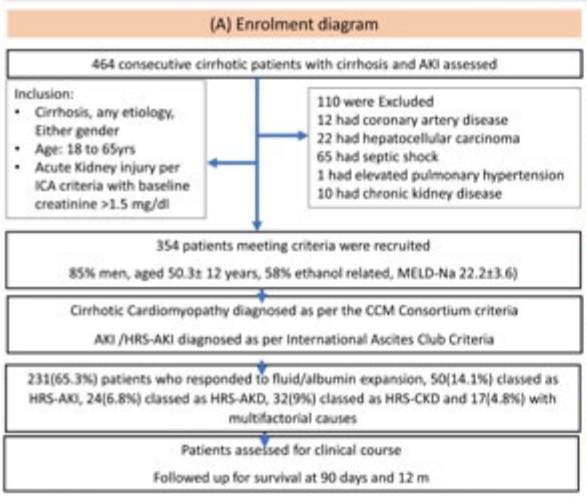
disease, coronary artery disease, valvular heart disease and hepatocellular carcinoma were excluded. Clinical data, serum biomarkers, and survival data were prospectively collected. **Results:** We enrolled 354 patients with AKI [(85% men, aged 50.3± 12 years, 58% ethanol related, MELD-Na 22.2±3.6]. There were 231(65.3%) patients who responded to fluid/albumin expansion, 50(14.1%) classified as HRS-AKI, 24(6.8%) as HRS-AKD, 32(9%) as HRS-CKD and 17(4.8) as multifactorial AKI. Patients with HRS-AKI received terlipressin (n=74), and noradrenaline(n=30) as vasopressors.Forty-seven (13%) underwent RRT. CCM was noted in 112 (31.6%); 70 (66.5%) of fluid responders, 36(57.8%) of HRS AKI and 6 (5.3) of HRS-AKD. Overall mortality was 37(10.5%) at 90 days and 98(27.7%) at 1 year. In a Cox Proportional Hazards model adjusted for age, gender, and creatinine at presentation, presence of CCM in patients with HRS-AKI was associated with mortality at 90 days (aHR 23.1, 95%CI 2.4-224.1, *P*=0.007) and at 1 year (aHR8.4, 95%CI 1.6-44.9, *P*=0.013). Similarly, Cardiac Index at enrolment predicted mortality at 90 days (aHR 0.3, 95%CI-0.15-0.63, *P*=0.019) and at 1 year (aHR 0.3,

Figure 1: POCUS assessment of patients with Acute Kidney Injury **(A)** Enrolment Diagram (B) Presence of CCM in patients with AKI **(C)** AKI progression and mortality **(D)** Cox PH model for mortality prediction adjusted for age gender and baseline creatinine **(E)** Kaplan Meier survival analysis based on presence of CCM.



(B) Presence of CCM

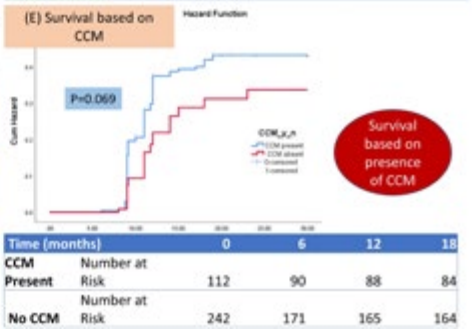
	Total (n=354)	CCM present (N=112)	CCM absent (N=242)
Fluid Responders	231(65.3)	70(62.5)	161(66.5)
HRS-AKI	50(14.1)	36(32.1)	14(5.8)
HRS-AKD	24(6.8)	6(5.4)	18(7.4)
HRS-CKD	32(9)		032(13.2)
Multifactorial	17(4.8)		017(7)

C. 90 day and 1 year mortality based on AKI progression

	90-day mortality		P Value	1 year mortality		P Value
	Dead (n=37)	Alive (n=317)		Dead (n=98)	Alive (n=256)	
Fluid Responders	10(27)	221(69.7)	<0.001	50(51)	181(70.7)	0.001
HRS-AKI	20(54.1)	30(9.5)		22(22.4)	28(10.9)	
HRS-AKD	5(13.5)	19(6)		15(15.3)	9(3.5)	
HRS-CKD	2(5.4)	30(9.5)		8(8.2)	24(9.4)	
Multifactorial	0	17(5.4)		3(3.1)	14(5.5)	

(D)Cox PH analysis for prediction of mortality based on cardiac index. Adjusted for age, baseline creatinine and gender

Cardiac Index at presentation	90-day mortality			1 year mortality		
	aHR	95% CI	P value	aHR	95% CI	P value
All Patients	0.35	0.22-0.53	<0.001	0.69	0.57-0.86	0.001
Fluid Responders	0.38	0.17-0.85	0.019	0.85	0.66-1.1	0.228
HRS-AKI	0.3	0.15-0.63	0.001	0.3	0.15-0.61	0.001
HRS-AKD	0.02	0.01-3	0.123	1.04	0.57-1.87	0.908
HRS-CKD	0.73	0.72-1	0.078	0.37	0.11-1.19	0.096



95% CI 0.15-0.61, *P*=0.001) in HRS-AKI. On receiver operating characteristic analysis, serum Cystatin C >2 mg/l (C-statistic 0.748; sensitivity 83% and specificity 65%, *P*=0.021) and NGAL >180 ng/ml (C-statistic 0.648; sensitivity 73% and specificity 62%, *P*=0.036) performed best for prediction of mortality. CCM markers i.e. septal E/e' (aHR 1.3, 95%CI: 1.1-4.3, *P*=0.033) and e' (aHR 0.8 95%CI 0.2-0.9, *P*=0.045) were predictive of need for renal replacement therapy (RRT), adjusting for age, and gender. Figure 1: POCUS assessment of patients with Acute Kidney Injury (A) Enrolment Diagram (B) Presence of CCM in patients with AKI (C) AKI progression and mortality (D) Cox PH model for mortality prediction adjusted for age gender and baseline creatinine (E) Kaplan Meier survival analysis based on presence of CCM. **Conclusion:** CCM and change in cardiac index adversely impact outcomes in patients with HRS-AKI. POCUS variables (Cardiac index, e' and E/e') can inform prognosis and predict progression of AKI towards needing RRT.

Disclosures: Madhumita Premkumar: Nothing to Disclose, Kamal Kajal: Nothing to Disclose, Manhal Izzy: Nothing to Disclose, Bhupendra Sihag: Nothing to Disclose, Ajay Bahl: Nothing to Disclose, Vishesh Kumar: Nothing to Disclose, Ajay Duseja: Nothing to Disclose, Akash Roy: Nothing to Disclose, Sahaj Rathi: Nothing to Disclose, Harish Bhujade: Nothing to Disclose, Rohit Mehtani: Nothing to Disclose, Nipun Verma: Nothing to Disclose, SUNIL TANEJA: Nothing to Disclose, Jasvinder Nain: Nothing to Disclose

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0008 | NOVEL GENETIC ARCHITECTURE AND METABOLIC INTERACTIONS FOR ALL-CAUSE CIRRHOSIS AND HEPATOCELLULAR CARCINOMA DEFINED IN MULTI-ANCESTRY META-ANALYSES

Marijana Vujkovic[1] David Kaplan[1] Jonas Ghouse[2] Michael Levin[1] Joseph Brancale[3] Adam Lewis[4] Olivia Veatch[5] Carolin Victoria Schneider[6] Bao-Li Chang[1] Anurag Verma[1] Kirk Wangensteen[7] Dipender Gill[8] Chigoziri Konkwo[3] Tae-Hwi Schwantes-An[9] Kyung Lee[10] Abraham Shaked[1] Kim Olthoff[11] Maarouf Hoteit[1] Daniel Dochtermann[12] Trina Norden-Krichmar[13] Craig Teerlink[10] Poornima Devineni[12] Kara Maxwell[1] Saiju Pyarajan[12] Daniel Rader[1] Yasuhito Tanaka[14] Benjamin Voight[1] Silvia Vilarinho[3] Lisa Bastarache[4] Stefan Stender[2] Philip Tsao[15] Timothy Morgan[16] Julie Lynch[10] Kyong-Mi Chang[1]

[1]University of Pennsylvania, [2]Rigshospitalet, Copenhagen University Hospital, [3]Yale University, [4]Vanderbilt University Medical Center, [5]University of Kansas Medical Center, [6]RWTH Aachen University, [7]Mayo Clinic, [8]Imperial College London, [9]Indiana University School of Medicine, [10]Salt Lake City VA Medical Center, [11]Hospital of the University of Pennsylvania, [12]Boston VA Medical Center, [13]University of California Irvine, [14]Kumamoto University, [15]Stanford University, [16]VA Long Beach Healthcare System

Background: Liver cirrhosis and hepatocellular carcinoma (HCC) are long-term complications of chronic liver disease (CLD) including metabolic-dysfunction associated steatohepatitis (MASLD), with a need to better define their genetic underpinnings. **Methods:** We conducted the largest multi-ancestry genome-wide meta-analysis of all-cause cirrhosis and HCC, including 35,481 cirrhosis cases and 1,914,739 controls, as well as 7,126 HCC cases and 1,757,505 controls from large biobanks including as the Million Veteran Program (MVP), Copenhagen Hospital Biobank, UK Biobank, FinnGen, DeCODE, BioBank Japan, BioVU, AllofUS, and Penn Medicine Biobank. Given that many loci are known risk factors for CLD, we hypothesized that the relationship between these variants and cirrhosis might be mediated by underlying etiologies. We applied counterfactual mediation analysis to estimate the direct and indirect effects of genetic variants on cirrhosis through mediators including metabolic dysfunction, alcohol use, viral hepatitis, and other causes of liver disease in 11,738 cirrhosis cases and 444,882 controls using individual-level longitudinal electronic health record (EHR) data from MVP. Finally we examined whether individuals with CLD and a high polygenic risk score (PRS) for cirrhosis (e.g., top 5th percentile) were at increased risk of cirrhosis, HCC, and liver mortality using multi-state Markov survival models using the transitional states of CLD, cirrhosis, HCC, and liver mortality over a 20 year follow-up period in 134,841 Europeans (EUR), 20,068 Hispanics (HIS), and 39,397 African Americans (AA) in MVP. **Results:** We identified 27 risk variants for cirrhosis and 12 variants for HCC, of which 8 were shared between cirrhosis and HCC (*PNPLA3*, *HSD17B13*, *TM6SF2*, *APOE*, *HLA*, *IFNL3*, *CD81*, and *HFE*). Most loci showed evidence of partial mediation, indicating that genetic variants contribute to cirrhosis directly and indirectly by increasing susceptibility to CLD. Complete mediation was observed in two loci only (e.g., *ADH1B* via alcohol use, and *HFE* via hereditary hemochromatosis). A high PRS for cirrhosis was associated with progression from CLD to cirrhosis (EUR hazard ratio (HR)=1.94, P=2E-68; HIS HR=1.55, P=4E-06; AA HR=1.3, P=5E-04) and from cirrhosis to HCC (EUR HR=1.65, P=7E-08; HIS HR=1.46, P=0.05; AA HR = 1.26, P=0.19). In a separate model including interaction terms in EUR only, metabolic dysfunction showed interactions with PRS on cirrhosis (P=0.005), with alcoholic use on cirrhosis (P=5E-28), and with viral hepatitis on cirrhosis (P=9E-11), HCC (P=0.001) and liver mortality (P=2E-07). **Conclusion:** We identify novel genetic risk variants and complex genetic architecture of cirrhosis and HCC in which metabolic dysfunction is both an independent risk factor and a multiplicative accelerator of disease risk when combined with a high genetic burden or other causes of liver disease.

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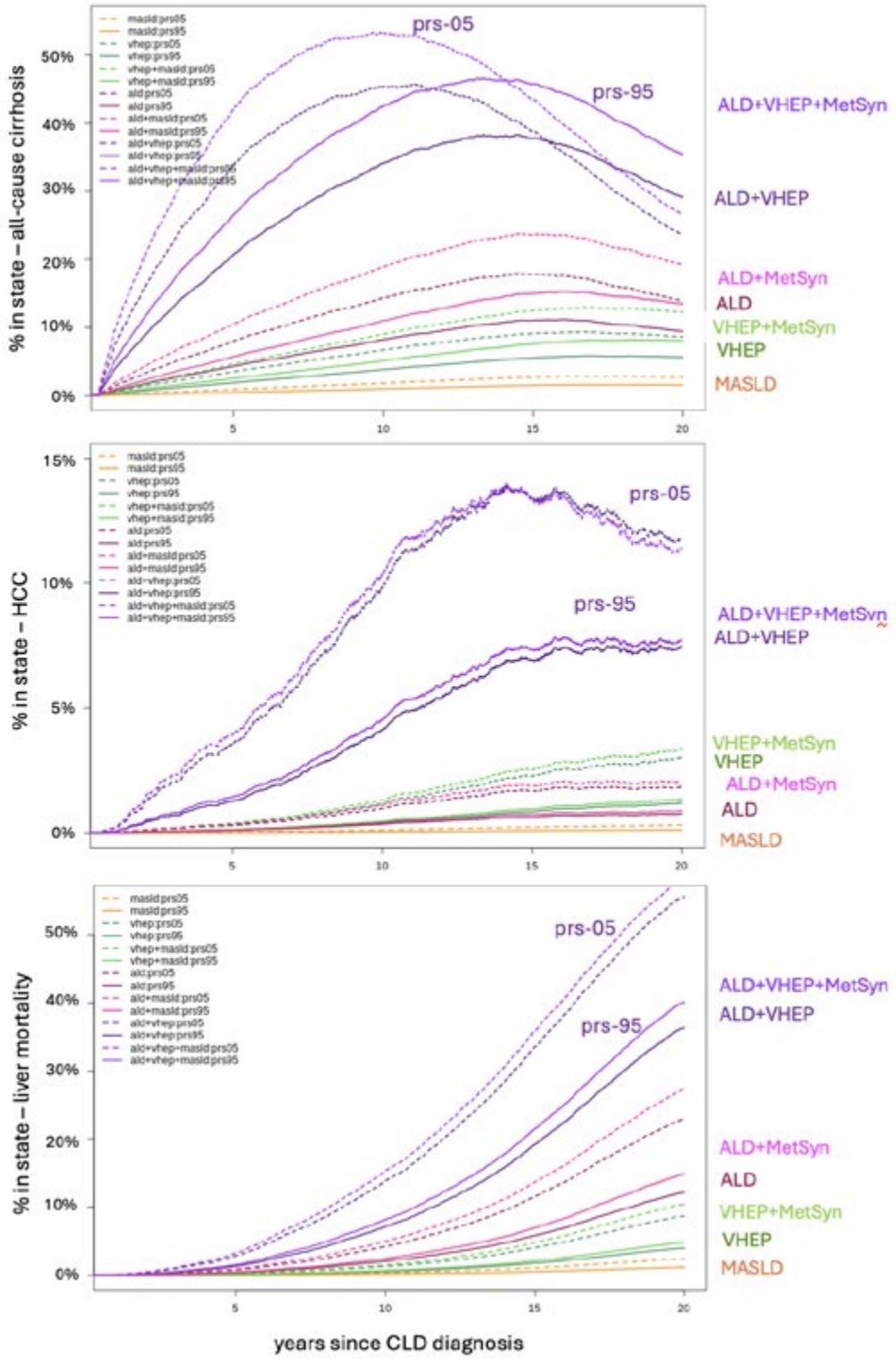

Disclosures: Marijana Vujkovic: Nothing to Disclose, David Kaplan: Independent Contractor relationship with Roche Genentech; Has not ended; Grant/Research Support relationship with AstraZeneca Inc; Has not ended; Advisor relationship with AstraZeneca; Has ended; Advisor relationship with Exelixis; Has ended; Grant/Research Support relationship with Gilead; Has not ended; Advisor relationship with Sirtex; Has ended; Grant/Research Support relationship with Exact Sciences; Has not ended; Grant/Research Support relationship with Glycotest; Has ended, Jonas Ghouse: Nothing to Disclose, Michael Levin: Nothing to Disclose, Joseph Brancale: Nothing to Disclose, Adam Lewis: Nothing to Disclose, Olivia Veatch: Nothing to Disclose, Carolin Victoria Schneider: Nothing

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to Disclose, Bao-Li Chang: Nothing to Disclose, Anurag Verma: Nothing to Disclose, Kirk Wangensteen: Nothing to Disclose, Dipender Gill: Nothing to Disclose, Chigoziri Konkwo: Nothing to Disclose, Tae-Hwi Schwantes-An: Target RWE: Consultant, Kyung Lee: Nothing to Disclose, Abraham Shaked: Nothing to Disclose, Kim Olthoff: Nothing to Disclose, Maarouf Hoteit: HepQuant, LLC: Advisor, Daniel Dochtermann: Nothing to Disclose, Trina Norden-Krichmar: Nothing to Disclose, Craig Teerlink: Nothing to Disclose, Poornima Devineni: Nothing to Disclose, Kara Maxwell: Nothing to Disclose, Saiju Pyarajan: Nothing to Disclose, Daniel Rader: Nothing to Disclose, Yasuhito Tanaka: Nothing to Disclose, Benjamin Voight: Nothing to Disclose, Silvia Vilarinho: Moderna Therapeutics Inc: Grant/Research Support, Albireo: Speaking and teaching, Mirum Pharma: Consultant, Lisa Bastarache: Nothing to Disclose, Stefan Stender: Nothing to Disclose, Philip Tsao: Nothing to Disclose, Timothy Morgan: Nothing to Disclose, Julie Lynch: Nothing to Disclose, Kyong-Mi Chang: Data Monitoring Committee member relationship with Virion Therapeutics; Has not ended; Advisor relationship with GSK; Has ended

0009 | IMPACT OF GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS ON THE RISK OF ADVERSE LIVER OUTCOMES AMONG PATIENTS WITH ALCOHOL-ASSOCIATED LIVER DISEASE AND TYPE 2 DIABETES ◆ ★

Zayed Rashid[1] Selamawit Woldesenbet[1] Mujtaba Khalil[1] Sidharth Iyer[1] Muhammad Muntazir Mehdi Khan[1] Muhammad Musaab Munir[1] Abdullah Altaf[1] Giovanni Catalano[1] Khalid Mumtaz[1] Timothy Pawlik[1]

[1]The Ohio State University

Background: Pathways involved in glycemic control and aversion to drinking alcohol can be a common target for glucagon-like peptide-1 receptor agonists (GLP-1RA). Therefore, we sought to study the impact of GLP-1RA on adverse liver outcomes (ALO) among patients with alcohol-associated liver disease (ALD) and type 2 diabetes mellitus (T2DM). **Methods:** Patients with T2DM who were newly diagnosed with ALD between 2013 and 2020 were identified using the IBM-Marketscan database. Patients were categorized based on GLP-1RA exposure, treated as a time-varying factor. To account for confounders, Overlap Propensity Score Weighting (OPSW) was utilized. Poisson regression models were used to analyze the adjusted risk of ALO, a composite endpoint defined by the first occurrence of any hepatic decompensation (HD), portal hypertension (PH), hepatocellular carcinoma (HCC) or liver transplantation (LT) relative to GLP-1RA. **Results:** Among 14,730 patients, the majority was male (n= 9,752, 66.2%) with a median age of 57 (IQR 52-61) years; 2.2% (n=317) had GLP-1RA exposure. Overall, 32.0% (n=4,717) of patients experienced HD, 15.9% (n=2,345) had features of PH, 3.8% (n=563) developed HCC, and 2.5% (n=374) received a transplant. Patients taking GLP-1RA were less likely to experience HD (22.4% vs. 32.2%) and HCC (0.3% vs. 3.0%) compared with individuals not taking GLP-1RA (both $p<0.001$); there was no association of GLP-1RA with the incidence of PH and LT (both $p>0.05$). After OPSW matching, 46 patients taking GLP-1RA had ALO over 379 person-years, with an absolute incidence rate difference of -9.0% (95% CI -15.0% to -3.0%) and an adjusted incidence rate of 0.57 (95%CI 0.39-0.82; p=0.003) compared with non-GLP-1RA patients. In examining the composite ALO, patients exposed to GLP-1RA had lower HD with 33 events over 400 person-years and a lower adjusted incidence rate of 0.56 (95%CI 0.36-0.86; p=0.008) relative to non-GLP-1RA group (Figure). **Conclusion:** GLP-1RA can potentially mitigate the risk of adverse liver outcomes, particularly decompensation, among patients with alcohol-associated liver disease. Future trials are needed to further investigate the role of GLP-1RA among patients with liver disease.

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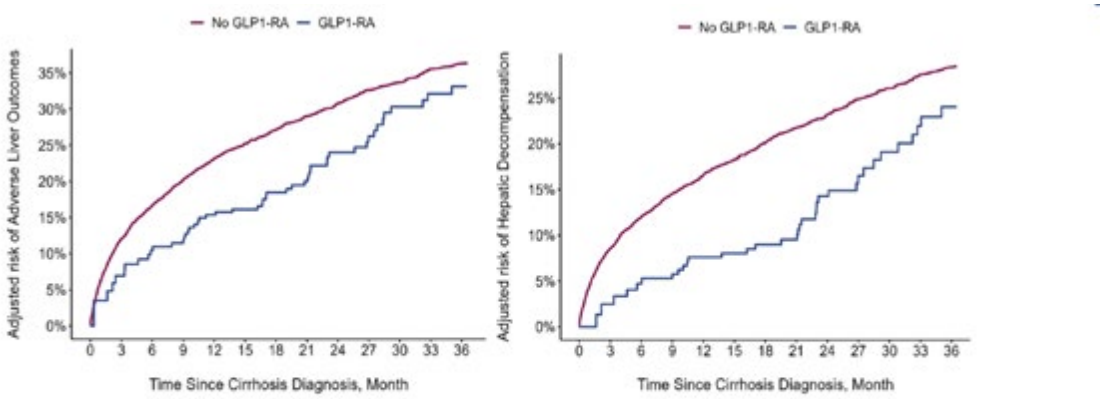

Overlapping weight-adjusted cumulative incidence of (A) Adverse liver outcome and (B) Hepatic decompensation by glucagon-like peptide-1 receptor agonists (GLP-1RA) initiation status in adults with alcoholic liver disease and type 2 diabetes. GLP-1RA initiation status was modeled as a time-dependent variable. The models were adjusted using overlapping weights estimated using age, sex, region of residence, type of health insurance, year of diagnosis, employment status, history of Smoking, obesity, dyslipidemia, hypertension, Charlson Comorbidity Index, claims-based frailty index, Metformin, SGLT-2, DPP-4, Sulfonylureas, Thiazolidinediones, and Statins.

Disclosures: Zayed Rashid: Nothing to Disclose, Selamawit Woldesenbet: Nothing to Disclose, Mujtaba Khalil: Nothing to Disclose, Sidharth Iyer: Nothing to Disclose, Muhammad Muntazir Mehdi Khan: Nothing to Disclose, Muhammad Musaab Munir: Nothing to Disclose, Abdullah Altaf: Nothing to Disclose, Giovanni Catalano: Nothing to Disclose, Khalid Mumtaz: Nothing to Disclose, Timothy Pawlik: Nothing to Disclose

0010 | ALCOHOL-INDUCED TRAINED IMMUNITY CONTRIBUTES TO DYSFUNCTIONAL IMMUNE RESPONSES INVOLVING PD1 AND EXACERBATED INFLAMMATION IN MICE AND HUMAN IMMUNE CELLS

Prashanth Thevkar Nagesh[1] Adriana Ramos[2] Arman Patel[2] the AlcHepNet clinical investigators[2] Gyongyi Szabo[3]

[1]Beth Israel Medical Center, [2]BIDMC Harvard Medical School, [3]Beth Israel Deaconess Medical Center

Background: Patients with alcohol-associated hepatitis (AH) exhibit systemic inflammation and increased susceptibility to infections. “Trained immunity” is characterized by long-term epigenetic and transcriptomic reprogramming of innate immune cells to a primary insult which may exhibit heightened proinflammatory and dysfunctional immune response to a secondary insult. The role of trained immunity in AH is unknown. We hypothesized that in AH, alcohol represents the first insult to train immune cells and predisposes to dysfunctional immune response to secondary insults (infections). **Methods:** Liver tissue and peripheral blood mononuclear cells were tested from AH patients and healthy controls (HC). Female, C57Bl6 mice aged 10-12 weeks received either saline or alcohol binge (5g/kg) for 4 consecutive days (“training”) followed by 1-week resting period. After the resting period, mice received saline or LPS (5mg/kg, i.p.) to mimic bacterial infection and were euthanized 9hrs post LPS. Multiomics (snRNA+scATAC seq) was performed in whole liver tissue. Liver damage was assessed by serum ALT. Serum cytokines were measured by ELISA. Histone acetylation/methylation was assessed in human and mouse livers by Western blotting, and in bone marrow (BM) progenitors or liver immune cells by flow cytometry. T cell activation was performed using CD3/CD28 cross linked magnetic beads. **Results:** Alcohol-trained (AT) mice exhibited increased proinflammatory cytokines and liver damage in response to LPS. AT mice displayed increased frequency and activation of monocytes and neutrophils (myelopoiesis) in the bone marrow, circulation, and liver. We also found increases in features of trained immunity in monocytes/neutrophils from AH patients similar to AT mice, including increase in H3K27 acetylation and H3K9methylation. Multiomics analysis of AT mice liver revealed unique neutrophil and monocyte clusters and gene expression profile that corresponded with increased proinflammatory gene expression and immune cell exhaustion markers, specifically PD1. These changes in gene expression corresponded with increase in chromatin accessibility as assessed by scATAC seq. Finally, using flow cytometry, we found an increase in PD1 expression in circulating monocytes/neutrophils of both AH patients and in AT mice. Functionally, neutrophils from AH patients (exhibiting trained immunity) displayed impaired T cell proliferation and IFNg secretion when co-cultured with autologous T cells. **Conclusion:** Our findings identify a novel role for alcohol in inducing trained immunity. Monocytes/neutrophils from human AH patients and alcohol-trained mice show altered

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transcriptomic and epigenetic profile associated with dysfunctional immune cell phenotype indicating that alcohol-induced trained immunity is associated with a novel neutrophil/monocyte-specific role for PD1.

Disclosures: Prashanth Thevkar Nagesh: Nothing to Disclose, Adriana Ramos: Nothing to Disclose, Arman Patel: Nothing to Disclose, the AlcHepNet clinical investigators: Nothing to Disclose, Gyongyi Szabo: Advisor relationship with Glympse Bio, Inc (acquired by Sunbird Bio); Has not ended; Consultant relationship with Terra Firma; Has not ended; Consultant relationship with Pfizer; Has not ended; Consultant relationship with Pandion Therapeutics; Has ended; Consultant relationship with Merck; Has ended; Consultant relationship with Durect Corporation; Has ended; Advisor relationship with Satellite Biosciences; Has not ended; Consultant relationship with Zomagen Bioscience/Ventyx Biosciences; Has ended; Consultant relationship with CYTA Therapeutics; Has ended; Royalties or patent beneficiary relationship with Springer Nature Group; Has not ended; Royalties or patent beneficiary relationship with UpToDate Inc; Has not ended; Consultant relationship with LabCorp; Has not ended; Advisor relationship with Evive; Has not ended; Advisor relationship with Surrozen; Has not ended; Consultant relationship with Takeda; Has ended

0011 | PRE-EMPTIVE ADMINISTRATION OF CONTINUOUS RENAL REPLACEMENT THERAPY IN PATIENTS WITH ACUTE LIVER FAILURE WITH CEREBRAL EDEMA IMPROVES OUTCOMES- A RANDOMIZED CONTROLLED TRIAL

Rakhi Maiwall[1] Meenu Bajpai[2] HarshVardhan Tevethia[2] Samba Siva Rao Pasupuleti[3] Fagun Sharma[2] Bindiya Arora[2] Sumegh Talwalkar[2] Mohit kumar Prajapati[2] Prashant Agarwal[2] Rajendra Prasad Mathur[2] Chandani Bhagat[2] Sherin Thomas[2] Shiv Kumar Sarin[2]

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Background: Therapeutic plasma exchange (TPE) is effective in removing small to large toxic molecules in patients with acute liver failure (ALF). Continuous renal replacement therapy (CRRT) has shown a reduction in deaths due to cerebral edema. There are no studies evaluating combining an early initiation of CRRT (continuous venovenous hemodialfiltration) (CVVHDF) with TPE in ALF patients with cerebral edema. **Methods:** Altogether, 86 patients with ALF underwent a 1:1 open-label randomization. Cerebral edema was diagnosed on brain imaging. Patients underwent TPE by centrifugal apheresis after initial resuscitation. Group 1 received CRRT within the first 12 hours of TPE. In group 2, CRRT was initiated in patients with worsening hyperammonemia despite two sessions of TPE or in those meeting renal indications. The primary endpoint was 28-day mortality. Secondary end-points included improvement in ammonia, mean arterial pressure (MAP) and arterial lactate. Intention-to-treat(ITT) and per-protocol(PP) analysis was performed. **Results:** ALF patients [group 1(n=44) vs.group 2(n=42)] aged 30.6±11.4 yrs,76% viral, 62% hyperacute,70% with SIRS, 33% meeting KCH criteria, with mean SOFA score of 10.2±3.2 and arterial lactate 4.1±3.5umol/L were included. At 28-days, 47% died, and 8% underwent live donor liver transplant(LDLT). The sessions of TPE, mean 1.69±1.83(range 1-9) were not different between the groups.The time to CRRT (in hours) initiation after TPE was lower for group 1 vs. 2 [(9.0 ± 3.8) vs.(36.4±31.3);p<0.001]. There were a total of 27(31.4%) protocol violations significantly more in group 2 [22(52.4%) vs.5(11.4%)]; p<0.001]. Reasons included post-TPE worsening of ammonia [10 (24%) vs.0(2%)], spontaneous recovery [6(27%) vs. 1 (0%)] and LDLT [6(27%) vs.4 (9%)] in group 2 vs. 1 respectively. On ITT, there was no difference in the 28-day mortality in group 1 vs. 2 [21 (48%) vs. 19 (45%); HR 0.89, 0.48-1.65]. However, on PP analysis a significantly lower 28-day mortality was noted for group 1 [18 (46.2%)vs.15(75%);HR 0.37,0.19-0.74]. A significant improvement in MAP (p=0.003), arterial lactate(p=0.04), ammonia (p=0.009),and SOFA score (p=0.04) on day 3 was seen in group 1. Each hour delay in CRRT from TPE was associated with increased mortality [HR1.03,1.02-1.04;p<0.001]. **Conclusion:** A pre-emptive initiation of CRRT following TPE improves hemodynamics, causes faster reduction of arterial lactate, and ammonia, and reduces mortality in ALF patients with cerebral edema. NCT04991259

Disclosures: Rakhi Maiwall: Nothing to Disclose, Meenu Bajpai: Nothing to Disclose, HarshVardhan Tevethia: Nothing to Disclose, Samba Siva Rao Pasupuleti: Nothing to Disclose, Fagun Sharma: Nothing to Disclose, Bindiya Arora: Nothing to Disclose, Sumegh Talwalkar: Nothing to Disclose, Mohit kumar Prajapati: Nothing to Disclose, Prashant Agarwal: Nothing to Disclose, Rajendra Prasad Mathur: Nothing to Disclose, Chandani Bhagat: Nothing to Disclose, Sherin Thomas: Nothing to Disclose, Shiv Kumar Sarin: Nothing to Disclose

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0012 | APPLYING LARGE LANGUAGE MODELS TO BETTER UNDERSTAND PSYCHOSOCIAL FACTORS CONTRIBUTING TO LIVER TRANSPLANT WAITING LIST DECISIONS ★

Emily Robitschek[1] Savyon Sordean[2] Kathryn Horwath[2] Jennifer Lai[2] Mark Pletcher[2] Irene Chen[1] Jin Ge[2]

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Background: Social determinants of health (SDOH) are contributors to liver transplant (LT) candidates' successful registration on the waiting list. Prior studies of SDOH factors have been challenging due to unstructured data "locked" in LT psychosocial evaluations. There is an unmet need for semi-automated methods to conduct large-scale analyses of these notes. **Methods:** We utilized the gpt-4-turbo-128k large language model (LLM) and other machine learning (ML) techniques to analyze psychosocial evaluation notes from 4150 adult LT candidates at UCSF Medical Center between 2012-2023. We used prompt engineering to construct a data pipeline that extracted 23 SDOH dimensions/factors in psychosocial evaluation notes with an overall accuracy of 0.86 (95%CI0.84-0.88) compared to manual annotations for random subset (n=51): specific accuracies for each SDOH factors ranged from 0.59 (95%CI0.45-0.73) to 0.98 (95%CI0.94-1.00). We then combined SDOH factors with demographic and clinical characteristics and associated them with the outcome of registration on LT waiting list ("listing") using L1-regularized logistic regression. P-values were adjusted for multiple comparisons. **Results:** Of clinical and demographic characteristics, HCC diagnosis was associated with listing (OR1.63, 95%CI1.32-2.01, p=0.0001) while the MELD score (OR0.84/point, 95%CI0.77-0.91, p=0.0009) and unknown/declined race/ethnicity (OR0.40, 95%CI0.29-0.55, p<0.0001) were less associated with listing. With regards to SDOH factors (excluding formal psychosocial listing recommendation and factors associated with liver disease etiology), positive associations with listing included understanding of the LT processes (OR1.59, 95%CI1.15-2.21, p=0.031) and adequate coping skills for medical illness (OR1.69, 95%CI1.26-2.28, p=0.0073). Conversely, negative associations with listing included recent alcohol consumption (within 6m) (OR0.50, 95%CI0.32-0.79, p=0.019), concerns with caregiving plan (OR0.60, 95%CI0.44-0.81, p=0.0079), active mental health issues (OR0.72, 95%CI0.58-0.89, p=0.0023), and ongoing non-alcohol substance use (OR0.73, 95%CI0.60-0.88, p=0.0079). **Conclusion:** This study is one of the first to systematically extract SDOH factors from psychosocial evaluation notes for listing decisions. This methodology demonstrates how advanced LLM and ML methods could be utilized to better elucidate important SDOH factors for successful listing. Our results showed potential social work intervention points to better prepare patients for successful listing.

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0013 | FECAL MICROBIOTA THERAPY IS A SAFE AND EFFECTIVE OPTION IN STEROID INELIGIBLE ALCOHOLIC HEPATITIS (FEMTAH TRIAL): A RCT ◆

Rahul khajuria[1] Shasthry S M[2] Shiv Kumar Sarin[2] Akhil Deshmukh[2] Vishnu Girish[2] Tushar Madke[3] Ravinder Singh[2]

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Background: Modulation of gut microbiota and correction of dysbiosis in steroid eligible Severe Alcohol Associated Hepatitis (SAH) through healthy donor Fecal microbiota transplantation (FMT) therapy has shown to improve gut dysbiosis and survival compared with prednisolone therapy with reduced incidence of new onset complications. We evaluated the safety of FMT and its efficacy in improving survival and disease severity scores in patients with steroid ineligible SAH patients with no option of liver transplantation. **Methods:** Of 242 patients screened, 39 patients of SAH were randomized (2:1) into FMT versus standard of care SOC [26 in the FMT arm; 13 in the standard of care arm (SOC)]. FMT was administered as per previously described ILBS FMT protocol through naso-duodenal route for 7 consecutive days. Patients were followed-up for a period of six months. The SOC included adequate nutrition, albumin and antibiotics/antifungals. The primary outcome was 90-day transplant free survival. **Results:** FMT and SOC groups were comparable at baseline (discriminant function score 85±15.1

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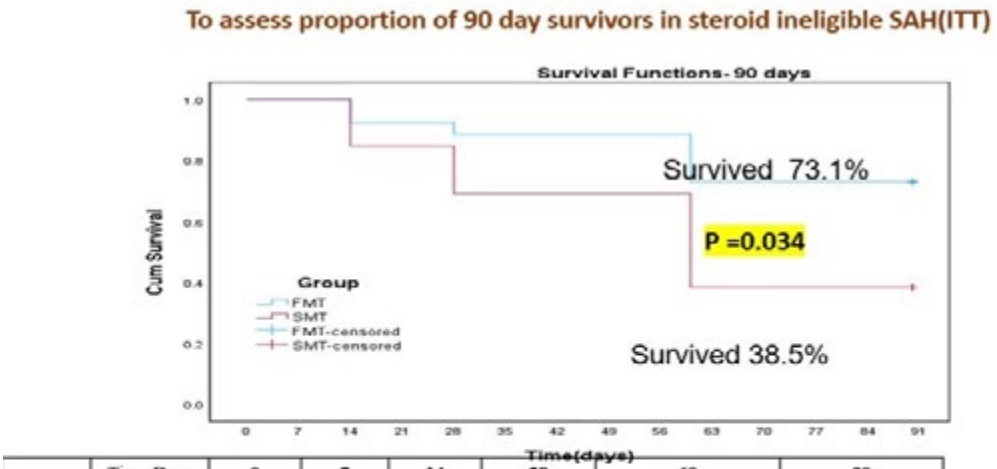
and 83±17.6, MELD score 31±3.56 and 29±4.3 respectively). 90 day survival was significantly better in the FMT than SOC arm (73.1% versus 38.5%, p=0.034). Secondary outcomes-survival at 28 and 180 days were better with FMT arm compared to SOC (92.3% versus 69.2%, p=0.06, 61.5% versus 30.8%, p=0.06 respectively). In FMT arm at day 90, incidence of hepatic encephalopathy was lower (8.3% vs. 46.1% p=0.005) and alcohol relapses fewer (11.5 % vs 46.1%, p=0.01). In FMT arm compared to the SOC, the delta MELD reduction (4±4.9 versus 0.23±6.0 p= P=0.021) and delta m-DF reduction (12.4±20.4 vs 2.15±20.9 p=0.02) were greater at 90 days. Additionally, greater reduction in pro-inflammatory markers, TNFa (39±11.1vs 21±13.3 p=0.001) and IL-6 (44±19 vs 31±18.8, p=0.05) was noted with FMT. No difference in major adverse events was noted in the two groups. **Conclusion:** In patients with steroid ineligible SAH, FMT can be considered as a safe option in improving the transplant free long-term survival.



	Time-Days	0	7	14	28	60	90
FMT	Events	0	0	1	2	4	0
	At risk	26	26	25	23	19	19
SMT	Events	0	1	1	2	4	0
	Risk	13	12	11	9	5	5

Disclosures: Rahul khajuria: Nothing to Disclose, Shasthry S M: Nothing to Disclose, Shiv Kumar Sarin: Nothing to Disclose, Akhil Deshmukh: Nothing to Disclose, Vishnu Girish: Nothing to Disclose, Tushar Madke: Nothing to Disclose, Ravinder Singh: Nothing to Disclose

0014 | IMPACT OF PRE-TRANSPLANT IMMUNE CHECKPOINT INHIBITORS ON DOWNSTAGING OUTCOMES: A PROSPECTIVE INTENTION-TO-TREAT ANALYSIS FROM A MULTI-CENTER US STUDY

Parissa Tabrizian[1] Matthew Holzner[2] Edison Xu[3] Maarouf Hoteit[4] Veeral Ajmera[5] Tara Ghaziani[6] Neehar Parikh[7] Kali Zhou[8] Amy Kim[9] Rebecca Marino[2] Francis Yao[3] Sander Florman[2] Neil Mehta[3]

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Background: The use of immune checkpoint inhibitors (ICI) in patients with advanced hepatocellular carcinoma (HCC) has shown promising outcomes. However, safety and intention-to-treat (ITT) outcomes in the intermediate stage pre-transplantation (LT) remain based on small, heterogeneous single-center reports. **Methods:** Consecutive patients with HCC tumor burden meeting UNOS-DS (n=201), all comers (AC) criteria (n=122), and ICI pre-LT (n=64) at eight LT centers were enrolled prospectively from 2015-2024. Patients with complete response to first locoregional therapy (LRT) were excluded (ICI n=18, UNOS-DS n=103, AC n=36). ICI was used in patients who exhausted LRT options or with more aggressive tumor biology. Kaplan-Meier analysis was used to estimate ITT and multivariable

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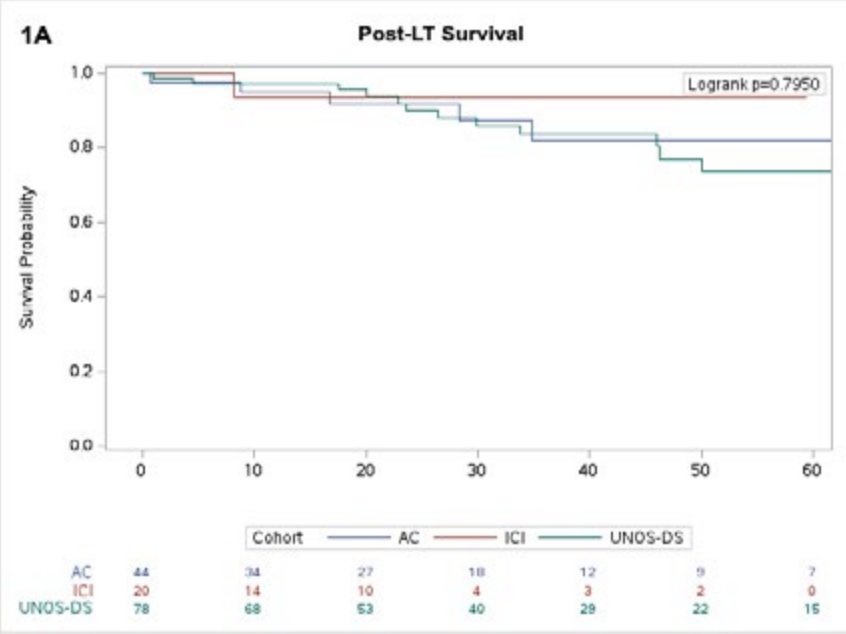
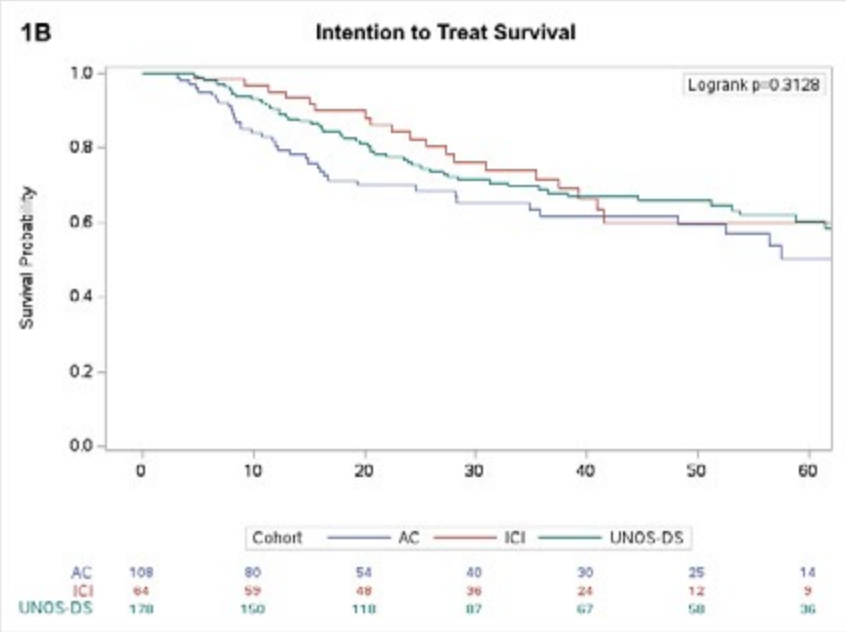
Cox regression was used to identify predictors of outcomes. **Results:** Characteristics were similar in age, gender, underlying liver disease, Child-Pugh (CP) scores, alpha-fetoprotein (AFP) levels, and number of LRTs between the groups (p >0.05). Median total tumor diameter was 6.4 cm (IQR 5.6-7.2) in the UNOS-DS, 9.4 cm (IQR 8.1-12) in the AC, and 5.9 cm (IQR 3.7-9.5) in the ICI group (p <0.001). The cumulative probability of dropout at 3 years was similar among the groups (ICI 48% vs. UNOS-DS 42% vs. AC 43%, p=0.953). ICI patients required a longer median time for successful downstaging (7.2 months vs. 2.8 for UNOS-DS vs 4.6 for AC group, p<0.001). Post-LT survival at 3 years was 94% for the ICI group, 83% for UNOS-DS, and 82% for AC (p=0.795) (Figure 1a). ITT survival at 3 years was 72% in the ICI group, 69% in the UNOS-DS group, and 62% in the AC group, (p=0.313) (Figure 1b). Risk factors for inferior ITT survival included CP B/C class (HR 1.56, p=0.033) and stable disease vs response (HR>1). No grade 4/5 ICI related adverse events occurred on the waitlist, with 10 (50%) receiving their last ICI dose within one month of LT (median washout 34 days IQR 13.5-55.5). Three (15%) ICI patients experienced post-LT rejection with washout periods of 22, 54, and 57 days. **Conclusion:** In this first multicenter study, ICIs show promising outcomes in the downstaging of HCC pre- LT. Post-LT survival at 3 years was 94%. In patients requiring downstaging with high risk of dropout (e.g. initial tumor beyond UNOS-DS, viable tumor despite LRT, elevated AFP) initiation of ICI may be warranted to improve ITT outcomes.





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Disclosures: Parissa Tabrizian: AstraZeneca: Speaking and Teaching, Aztrazeneca: Speaking and Teaching, Boston Scientific: Speaking and Teaching, Matthew Holzner: Nothing to Disclose, Edison Xu: Nothing to Disclose, Maarouf Hoteit: HepQuant, LLC: Advisor, Veeral Ajmera: Nothing to Disclose, Tara Ghaziani: Nothing to Disclose, Neehar Parikh: Grant/Research Support relationship with Exact Sciences; Has not ended; Consultant relationship with AstraZeneca; Has not ended; Consultant relationship with Exelixis; Has not ended; Grant/Research Support relationship with Exelixis; Has ended; Advisor relationship with Fujifilm Medical; Has ended; Grant/Research Support relationship with Genentech; Has ended; Consultant relationship with Exact Sciences; Has not ended, Kali Zhou: Nothing to Disclose, Amy Kim: Nothing to Disclose, Rebecca Marino: Nothing to Disclose, Francis Yao: Nothing to Disclose, Sander Florman: Nothing to Disclose, Neil Mehta: Merck: Consultant, FujiFilm WAKO: Consultant

0015 | TARGETING MACROPHAGE-MEDIATED MECHANISMS OF IMMUNE EVASION AS ADJUVANT THERAPY IN TACE-RESISTANT HEPATOCELLULAR CARCINOMA ★

Lea Lemaitre Reshma Reguram[1] Aishwarya Ghonge[1] Renumathy Dhanasekaran[2]

[1]Stanford University, [2]stanford

Background: A key obstacle to progress in treatment of hepatocellular carcinoma (HCC) is the notorious tenacity of HCC to recur. Transarterial chemoembolization (TACE) is the most common treatment for unresectable HCC, however, it fails to provide a durable cure. The crux of the problem lies in residual cancer cells that persist after TACE. Our goal is to understand how these residual cells escape immune detection and survive after TACE in order to develop effective adjuvant therapies. **Methods:** We used both in vitro and in vivo methods to mimic TACE-resistance by generating doxorubicin resistant- residual HCC models. We performed single-cell RNA sequencing on 3D tumoroids (31,000 cells) of doxorubicin resistant vs control HCC in coculture with macrophages. In addition, HCC patient-derived tumor cells and macrophages were used for validation. We developed an immunocompetent mouse model of syngeneic orthotopic allograft model of HCC, using doxorubicin-resistant or control HCC cell lines to test adjuvant therapies. **Results:** Using scRNAseq of 3D tumoroid model, we show that doxorubicin-resistant cancer cells exhibit a stem-cell-like phenotype with high expression of stemness markers (CK19, CD44), TGFb pathway (TGFBR1) and cytokines driving pro-tumor macrophage polarization (CXCL8, CCL2). On the other hand, the macrophages co-cultured with doxorubicin-resistant HCC showed a pro-tumor phenotype with increased PDL1 expression. We validated this finding using patient-derived samples, showing that doxorubicin resistant HCC tumoroid co-culture increased PDL1 expression on macrophages. Further, mRNA FISH showed that the CD68+ macrophages expressed higher levels of TGFB1 in TACE-resistant HCC than primary HCC (p=0.0011). Based on our in vitro analysis we identified the TGFB pathway and PDL1 as potential synergistic targets for adjuvant therapy of TACE-resistant HCC. In our mouse model of doxorubicin-resistant orthotopic allografts, we showed that treatment with combined Tgfbrl and anti-Pdl1 antibodies resulted in significantly reduced liver tumor burden (p=0.01). Flow cytometry analysis revealed immune remodeling with increased infiltration of CD8T cells and M1-like macrophage (CD86+/MHC-II+), along with depletion of macrophages (PDL1+/CD206+) in the liver of treated doxorubicin-resistant orthotopic allografts. **Conclusion:** We generated in vitro 3D models of TACE-resistance in HCC and identified the mechanistic roles of the PDL1+ macrophage-derived TGFβ1 on stem-like cancer cell persistence. We developed a mouse model of doxorubicin-resistant HCC and demonstrated that combined targeting of Pdl1 and Tgfb1 blocks tumor progression and evokes anti-tumor macrophage and CD8T cell immune response. Thus combined targeting of PDL1 and TGFB1 holds therapeutic potential as adjuvant therapy in TACE to eliminate residual HCC, reduce recurrence and improve patient outcomes in HCC.

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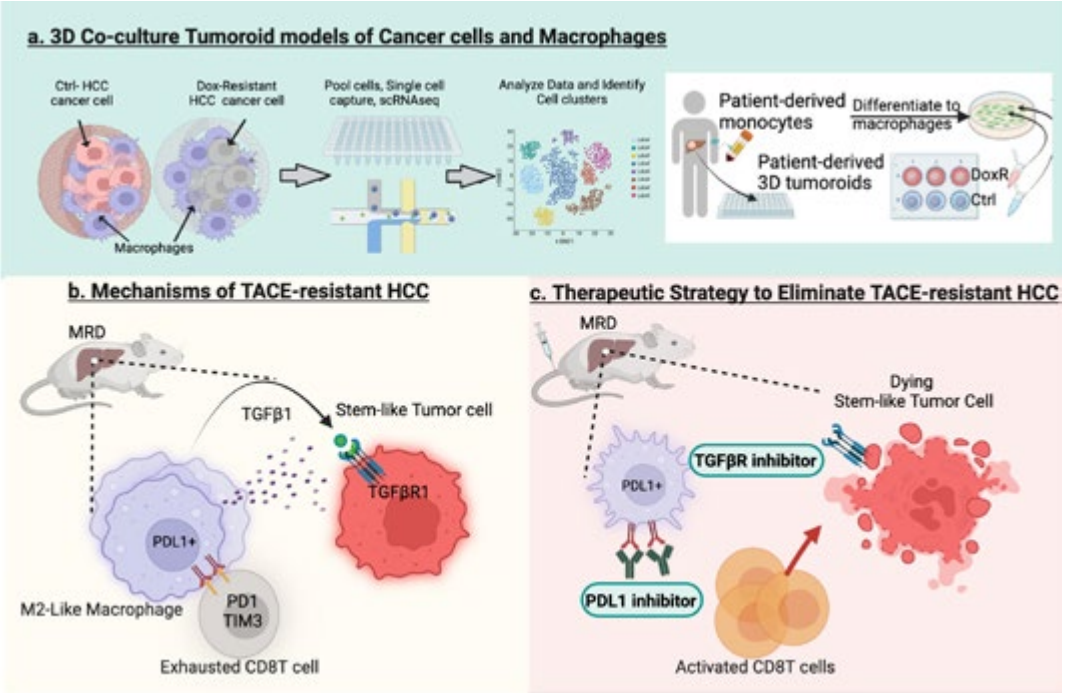

Disclosures: Lea Lemaitre: Nothing to Disclose, Reshma Reguram: Nothing to Disclose, Aishwarya Ghonge: Nothing to Disclose, Renumathy Dhanasekaran: Nothing to Disclose

0016 | THE PLASMA PROTEOMIC PROFILE OF SUBJECTS WITH THE *SERPINA1* PI*ZZ GENOTYPE CORRELATES WITH LIVER DISEASE SIGNATURES: AN ANALYSIS OF POPULATION-LEVEL DATA FROM THE UK BIOBANK PROTEOMICS PROJECT

Erin Smith[1] Ruixue Hou[1] Maria Paraskevopoulou[1] Vinayagam Arunachalam[1] Jen-Chieh Chuang[1] Susana Gonzalez[1] Nirav Desai[1] Dorothée Diogo[1] Sandor Szalma[1] Paresh Thakker[1] Pavel Strnad[2]

[1]Takeda Development Center Americas, Inc., [2]University Hospital RWTH Aachen

Background: Alpha-1 antitrypsin deficiency (AATD) is a genetic disorder caused by mutations in the *SERPINA1* gene, which may manifest as variably progressive liver and/or lung disease. AATD-associated liver disease is usually caused by the *SERPINA1* protease inhibitor (Pi)*ZZ genotype, leading to misfolded Z-AAT protein aggregates, liver proteotoxicity and fibrosis. The underlying molecular mechanisms are not fully understood. Leveraging population-level data from the UK Biobank (UKB) project, we identified a Pi*ZZ genotype-associated proteomic profile and compared it with signatures associated with chronic liver diseases. **Methods:** The UKB includes 500,000 participants with extensive data, such as longitudinal health records and genetic data. The UKB Pharma Proteomics Project includes plasma samples from 54,219 UKB participants and 2,923 proteins profiled by the Olink platform. Existing genotype array data were used to identify subjects with the Z (rs28929474) allele. Using logistic regression, differentially expressed proteins (DEPs) were identified among genotypes and between subjects with versus without a disease diagnosis (ICD-10; 1,942 diagnoses tested). DEPs were integrated with single nucleus RNAseq data to map potential source cells in the liver. **Results:** Overall, 17/141 subjects with the Pi*ZZ genotype had proteomic data and were analyzed. Comparison of the Pi*ZZ and reference (Pi*MM; n=39,265) genotypes identified 97 DEPs, and enrichment for lysosome and elastin fiber formation pathways. These DEPs primarily mapped to hepatocytes, cholangiocytes, immune cells, endothelial cells, and mesenchymal cells. Many mesenchymal cell-enriched DEPs were extracellular matrix components associated with hepatic stellate cell activation and liver damage. The Pi*ZZ signature was most similar to liver disease diagnosis code signatures in the UKB dataset, and showed high similarity to cirrhosis (Figure). **Conclusion:** This study identified a conserved serum proteomics signature between subjects with a Pi*ZZ genotype and patients with chronic liver diseases due to other etiologies. Potential use of these markers in the diagnosis, treatment response, and monitoring of AATD-associated liver disease requires further investigation. Lung function-related proteomics signatures in patients with the Pi*ZZ genotype are being actively examined. Writing assistance provided by A

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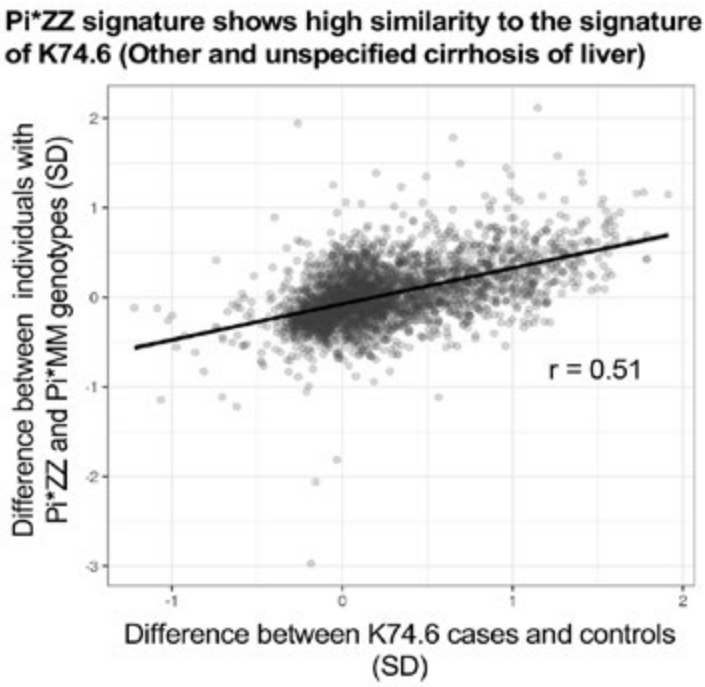
Pecchia-Bekkum, PhD, of Oxford PharmaGenesis. Research conducted using the UK Biobank Resource under application numbers 26041 and 65851.



Scatterplot showing a positive relationship between the change in protein levels associated with the Pi*ZZ genotype versus the change in protein levels associated with K74.6 cases (ICD-10 code; Other and unspecified cirrhosis of liver). Controls were defined as participants without a K74.6 diagnosis. Units are in SD from rank-based inverse normal transformed protein expression data, where a positive value indicates increased expression and a negative value indicates decreased expression. Each point represents a protein on the Olink® Explore 3072 platform. The line was calculated using a linear model.

ICD-10, International Classification of Diseases, Tenth Revision; Pi, protease inhibitor; r, Spearman correlation coefficient; SD, standard deviation.

Disclosures: Erin Smith: Nothing to Disclose, Ruixue Hou: Nothing to Disclose, Maria Paraskevopoulou: Nothing to Disclose, Vinayagam Arunachalam: Nothing to Disclose, Jen-Chieh Chuang: Nothing to Disclose, Susana Gonzalez: Takeda Pharmaceutical: Employee, Nirav Desai: Nothing to Disclose, Dorothée Diogo: Nothing to Disclose, Sandor Szalma: Takeda: Employee, Paresh Thakker: Nothing to Disclose, Pavel Strnad: Arrowhead Pharmaceuticals: Grant/Research Support, CSL Behring: Grant/Research Support, CSL Behring: Speaking and Teaching, BioMarin Pharmaceutical: Consultant, GSK: Consultant, Intellia: Consultant, Takeda Pharmaceuticals: Speaking and Teaching, Novo Nordisk: Consultant, Swedish Orphan Biovitrum: Consultant, Swedish Orphan Biovitrum: Speaking and Teaching, IPSEN: Consultant

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0017 | THE DISTINCT EXPRESSION PATTERNS OF ENO1 IN MALIGNANT CELLS AND CD8+ T CELLS PLAY A CRUCIAL ROLE IN SHAPING THE "EVOLUTION TREE" OF HCC ◆

Jing He[1] *Boqiang Liu*[1] *Liang Shi*[1] *Xiujun Cai*[1]

[1]*Zhejiang University*

Background: Tumour evolution was influenced by cytokines, food metabolism, and cell-cell contact. CD8+ T cells are crucial to the immune system's anticancer response. Similar metabolic "programming" makes CD8+ T cells and cancer cells competitors for glucose. The biological behaviour of malignant and T lymphocytes requires glucose. ENO1 is crucial to glucose metabolism. Existing research have not compared nutritional "looting" with tumour evolution.Our study constructed risk models to predict the "fate" of tumors and identified crucial molecules that could modify the HCC competitive advantage of "looting" nutrients. **Methods:** We constructed risk models that accurately predict the HCC progression using 101 machine learning algorithm combinations. TCGA and ICGC datasets were employed. To perform a thorough analysis of tumor evolution, we employed a dataset (GSE1151530) consisting of 32 HCC samples with single-cell RNA sequencing data. Monocle3 (v1.3.4) was used to study dynamic process of HCC malignant cell evolution. Flow cytometry was used to detect the activity and function of T cells. **Results:** Through an analysis of HCC samples at various stages, we identified crucial genes that influence the tumor progression. Next, we created a risk model for tumour evolution using an integrated machine learning method (Figure. A). And patients were divided into high and low-risk groups (Figure. B). We also validated this risk model at single-cell transcriptional level (Figure. C-D). The activation of canonical HCC pathways including Myc and p53 in high-risk malignant cells validates our model (Figure. E). Malignant cell-CD8+T cell interaction and infiltration were higher in high-risk samples. This suggests that the interaction between cancer cells and T lymphocytes led to the development of HCC. Malignant and T cells (Figure. F -G) show different glycolytic metabolisms as tumours develop. Immunoediting changed malignant cell glycolytic activity in humanised mice, as seen by enhanced glycolytic enzyme expression in tumours (Figure H). ENO1 alterations with tumour development were most noticeable (Figure I). This change may have been caused by competition for glucose between cancer cells and CD8+ T cells. We found that co-cultured T cells absorbed less glucose (Figure J). Glucose concentration also affected ENO1 expression in malignant and T cells (Figures K and L). In general, competition for glucose affected ENO1 expression and tumour evolution. **Conclusion:** This study presents an integrative machine learning algorithm-based risk model for tumor evolution, allowing for detailed examination at the single-cell level. "Competition" of glucose between tumor cells and CD8+T cells, along with alterations in downstream ENO1 expression, play a crucial role in determining the outcome of HCC.

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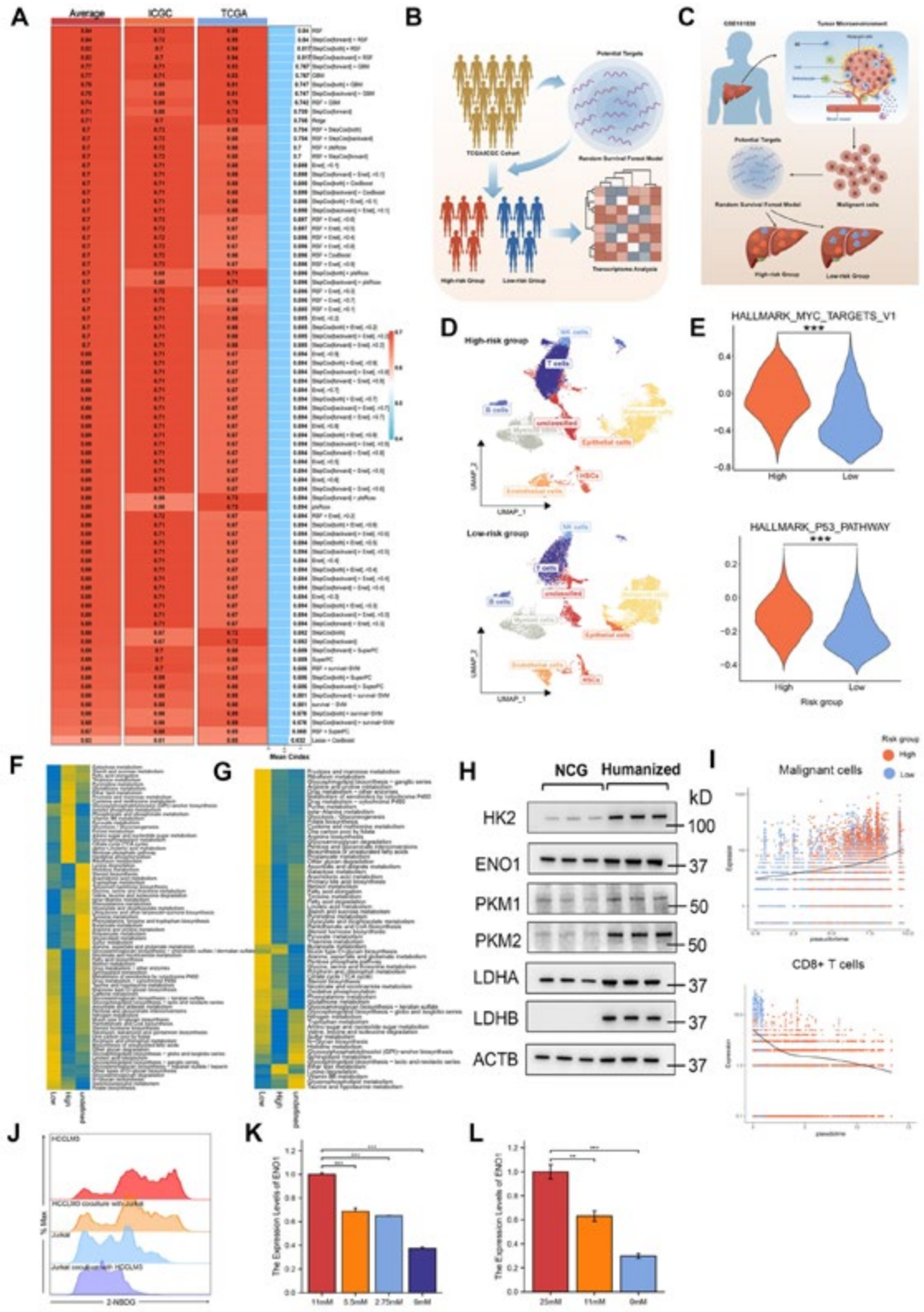

Disclosures: Jing He: Nothing to Disclose, Boqiang Liu: Nothing to Disclose, Liang Shi: Nothing to Disclose, Xiujun Cai: Nothing to Disclose

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0018 | DELETION OF BILIARY ATRESIA CANDIDATE GENE *PKD1L1* IN ISOLATED MURINE CHOLANGIOCYTES CULTURES LEADS TO ENHANCED BASAL AND REACTIVE PRO-INFLAMMATORY GENE EXPRESSION

David Lee[1] *Caroline Klindt-Morgan*[1] *Dominick Hellen*[1] *Ashley Bennett*[1] *Paul Dawson*[1] *Saul Karpen*[2]

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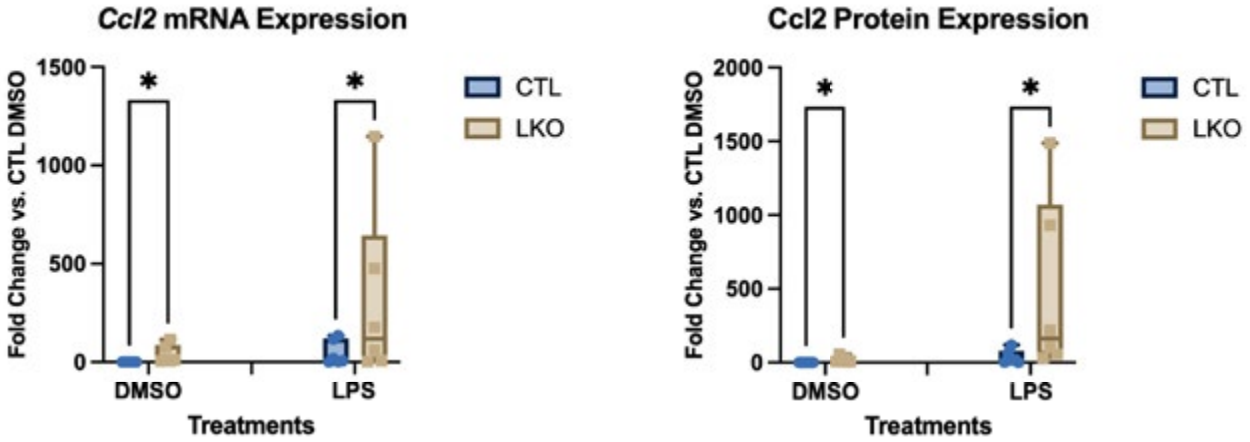
Background: A multicenter effort featuring genomic sequencing of patients with biliary atresia splenic malformation syndrome (BASM) found participants with genetic variants of the ciliary gene *PKD1L1* (polycystic kidney disease 1 like 1), which led to validation of this first BA etiologic gene in a mouse model with liver-specific deletion (LKO) of *Pkd1l1*. Histological analyses of LKO mouse livers revealed delayed biliary maturation and increased peribiliary fibroinflammation with transcriptional upregulation of genes that comprise a reactive ductular phenotype. Whether or not *Pkd1l1* deficient cholangiocytes are inherently pro-inflammatory as a fundamental basis for the BA phenotype is unknown. We hypothesized that isolated *Pkd1l1*-deficient cholangiocytes would exhibit a basal reactive ductular phenotype along with an enhanced response to lipopolysaccharide (LPS), characterized by pro-inflammatory transcriptomic and secretory protein expression. **Methods:** LKO and control (CTL) cholangiocytes were isolated via cell sorting followed by culture on Transwell inserts. Immunofluorescence staining of ZO1 and acetylated tubulin staining proceeded according to standard techniques. Cholangiocytes were exposed to vehicle DMSO, E. coli-derived LPS, or both for 16 h to induce a reactive biliary phenotype. Secreted chemokines were quantified by multiplex immunoassays (Biolegend). RNA was isolated for RNA-Seq analysis (Novogene). **Results:** RNA-Seq analysis revealed > 1700 differentially expressed genes between LKO and CTL cholangiocytes natively, including increased basal expression of the macrophage attractant *Ccl2* (8-fold increase). Pathway analysis revealed differential regulation of Tgfß signaling and ciliary organization pathways. In response to LPS, there was significant NF-κB signal transduction pathway enrichment in LKO cholangiocytes with increases in several chemokines such as *Cxcl2* (8-fold increase) and *Cxcl5* (128-fold increase) as well as the proposed BA diagnostic chemokine *Mmp7* (9-fold increase). Enhanced reactive ductular findings were mirrored in the analysis of secreted proteins multiplex data, which showed increased LPS-induced expression of multiple chemokines (including *Ccl2*) from LKO cholangiocytes. **Conclusion:** These studies reveal that deletion of the BA etiologic gene *Pkd1l1* leads to increased expression of pro-inflammatory mediators in mouse cholangiocytes, both basally and in response to LPS. As such, these intrinsic characteristics may explain the recruitment of peribiliary fibroinflammation in the LKO mouse model. These data support the proposal that the BA phenotype stems from a genetic/developmental cholangiopathy rather than an acquired etiology. Future studies based on the developmental cholangiopathic basis for BA will allow identification of key cholangiocyte-inflammatory cell interactions that drive the profound fibroinflammatory pathogenesis of BA.



Disclosures: David Lee: Nothing to Disclose, Caroline Klindt-Morgan: Nothing to Disclose, Dominick Hellen: Nothing to Disclose, Ashley Bennett: Nothing to Disclose, Paul Dawson: Nothing to Disclose, Saul Karpen: Consultant relationship with Albireo/Ipsen; Has ended; Consultant relationship with Mirum; Has ended; Consultant relationship with HemoShear; Has ended; Consultant relationship with Intercept; Has ended

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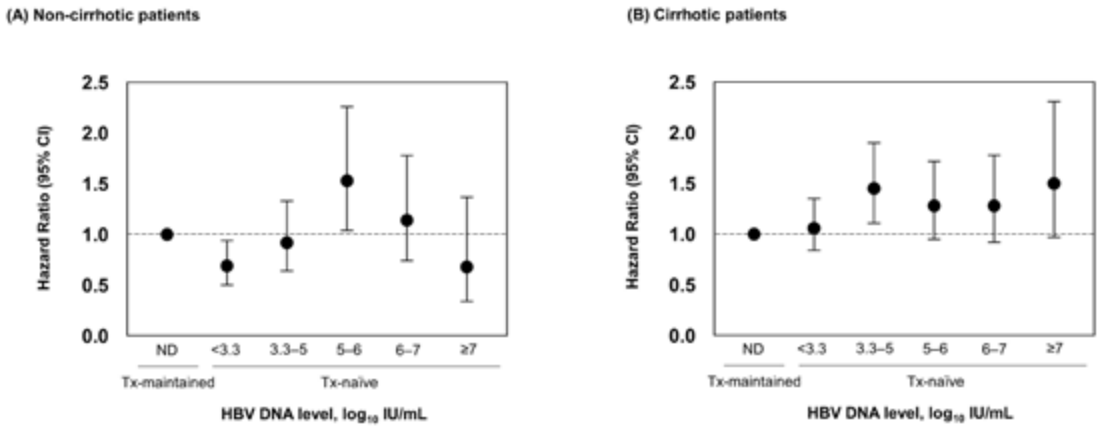
0019 | ASSOCIATION BETWEEN VIRAL REPLICATION ACTIVITY AND RECURRENCE OF HBV-ASSOCIATED HEPATOCELLULAR CARCINOMA AFTER CURATIVE RESECTION

Won-Mook Choi[1] *Subin Heo*[1] *Jiwon Yang*[1] *Jonggi Choi*[1] *Young-Suk Lim*[1]

[1]*Asan Medical Center*

Background: Little is known about the impact of baseline viral replication activity on intrahepatic recurrence in hepatitis B virus (HBV)-associated hepatocellular carcinoma (HCC) after curative resection. **Methods:** A hospital-based cohort of 1,932 patients with very early or early-stage HBV-associated HCC who consecutively underwent curative resection and received either entecavir or tenofovir between 2010 and 2018 were analyzed. Patients were divided into two groups: those who had previously been on antiviral therapy with viral suppression (Tx-maintained group) and those who initiated antiviral therapy due to detectable HBV DNA (Tx-naïve group) at the time of resection. We compared intrahepatic HCC recurrence between these two groups and based on baseline viral replication activity. **Results:** During a median follow-up of 4.9 years, 876 (45.3%) patients developed intrahepatic HCC recurrence. In the multivariable analysis, the risk of intrahepatic recurrence was similar between the Tx-maintained and Tx-naïve groups (hazard ratio [HR], 1.09; 95% confidence interval [CI], 0.94–1.27; *P*=0.23). However, when stratified by cirrhosis, Tx-naïve group showed a higher risk of intrahepatic recurrence than Tx-maintained group in cirrhotic patients (HR, 1.23; 95% CI, 1.01–1.48; *P*=0.04), but not in non-cirrhotic patients (HR, 0.87; 95% CI, 0.68–1.12; *P*=0.27). Intriguingly, in non-cirrhotic Tx-naïve patients, a parabolic association was observed between baseline HBV DNA levels and the risk of intrahepatic recurrence, with patients having HBV DNA levels between 5–6 $\log_{10}$ IU/mL showing significantly higher intrahepatic recurrence risk compared with the Tx-maintained group (HR, 1.53; 95% CI, 1.04–2.26; *P*=0.03). **Conclusion:** Association between HBV replication activity and the risk of intrahepatic HCC recurrence varied depending on cirrhosis, providing important insights for optimizing the timing of antiviral treatment and post-operative surveillance strategies.

Figure. Comparative risk of intrahepatic recurrence between treatment-maintained and treatment-naïve patients with HBV-associated HCC after surgical resection, stratified by baseline HBV DNA levels. (A) non-cirrhotic patients and (B) cirrhotic patients.
Hazard ratio plot adjusted for age, sex, platelet count, HBeAg-positivity, levels of albumin, bilirubin, AST, AFP, and PIVKA-II, statin use, aspirin use, antiviral type, hypertension, diabetes, BCLC stage, tumor size, and presence of microvascular invasion, capsular invasion, and satellite nodules with the Tx-maintained group as a reference.
AFP, alpha-fetoprotein; AST, aspartate aminotransferase; BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; PIVKA-II, prothrombin induced by vitamin K absence-II; Tx, treatment.



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0020 | CHARACTERIZATION AND EVOLUTION OF CAREGIVER BURDEN BEFORE AND AFTER RECIPIENT LIVER TRANSPLANTATION

Stacey Rolak[1] Navine Nasser-Ghodsi[2] Shelby Ebbers[1] Kristin Cole[1] Kymberly Watt[1]

[1]Mayo Clinic, [2]University of Massachusetts Memorial Health Care

Background: The drivers of caregiver burden among caregivers for patients with end stage liver disease (ESLD) undergoing liver transplantation (LT) have not been adequately explored. **Methods:** The aim of this study was to characterize the burden among caregivers of patients with ESLD who undergo LT and evolution over time after transplant. A prospective longitudinal mixed-method survey was administered to the primary caregiver of adult LT recipients at the time of LT, one month post-LT, and four months post-LT. The Burden Scale for Family Caregivers-short form (BSFC-s, higher scores indicate higher burden), a visual analog scale rating level of burden, and a four-item open-ended questionnaire were administered at all three time points. **Results:** Fifty caregivers were enrolled over a one year period at a single tertiary LT center. The majority (n=18, 36%) were ages 60-69, female (n = 36, 72%), and white (48, n = 96%). Most had completed a college degree (n= 19, 36%), were retired (n= 23, 46%), and had zero dependents (n= 30, 63%). Twenty-nine caregivers completed the 1 month survey and 33 completed the 4 month survey. Median level of burden on the visual analog scale decreased between the initial and one month surveys (4, IQR 2,7) vs. the four month surveys (2, IQR 1,4)(p = 0.007). Median BSFC-s score at the initial visit was 10.5 (IQR, 6, 17), one-month was 12 (IQR, 6, 13), and four-month visit was 8 (IQR, 3, 14.5). Of 33 caregivers completing the BSFC-s at both time points, there was a nonsignificant decrease between initial (mean 10.5, SD 6.0) and four month scores (mean 8.67, SD 7.10)(p=0.162). Those feeling exhausted decreased between the one (n=29) and four month visits (n = 14)(p = 0.037). Those reporting that caregiving requires a lot of their own strength decreased between the initial (n = 29) and one month visits vs. the four month (n = 11) visits(p = 0.009). The main stressors experienced by caregivers are highlighted in Table 1. Those concerned about uncertainty of the future (n = 14) decreased between the initial visit compared with the one (n = 6) and four-month (n = 0) visits (p = 0.004). Those noting ‘no’ stressors over the past four months increased significantly between the initial (n=4, 8%) and four-month visits (n=9, 27%)(p=0.003). Caregivers felt that the LT team helped address stressors only 64% of the time (n=23) at the time of LT, compared with feeling more support post-LT (n= 17, 81%). The most helpful resources for caregivers were lodging and financial assistance, educational materials, and communication from the care team. **Conclusion:** Caregiver burden is substantial at the time of LT and improves within four months post-LT. Feelings of exhaustion and loss of personal strength improve after transplant. These results can help inform caregivers what to expect in the pre- and post-transplant periods. Institutions can develop interventions and bolster their resources addressing these major areas of concern to better support caregivers.

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Table 1. Primary stressors identified by caregivers at each time point.

Themes	Examples – Initial Visit (n= 50)	Examples – One Month Visit (n= 29)	Examples – Four Month Visit (n= 33)
Financial	-Out of vacation time -Money n = 14	-Early retirement n = 5	-Paperwork – insurance and billing n = 7
Symptom burden and health decline	-Poor quality of life n = 23	-Uncertainty with setbacks or recovery status -Concern about survival rates n = 13	-Frustrated about complications n = 10
Appointment burden	-Frequent appointments -Difficult attending due to patient frailness n = 5	None	-Travel for appointments n = 1
Uncertainty of the future	-Is he/she going to die? -What will my future look like without him/her? -Always waiting for a call! n = 14	-Nervous about leaving the hospital and returning home for the first time n = 6	None
Daily activities	-Balancing work, care of my spouse -No one to help me at home, unable to relax n = 8	-Helping patient with all daily activities n = 4	-Doing all the yardwork and housework -24/7 caregiver, little or no downtime n = 4
Care plan	-Medication management -Difficult communicating with care team n = 4	-The BIGGEST stressor was the worry about getting meds correct -Understanding lab results -Transitioning care -Not knowing what is normal in healing process n = 7	-Medication schedule -Understanding lab results n = 8

Disclosures: Stacey Rolak: Nothing to Disclose, Navine Nasser-Ghodsi: Boston Scientific: Consultant, Shelby Ebbers: Nothing to Disclose, Kristin Cole: Nothing to Disclose, Kymberly Watt: Madrigal: Stock - publicly traded company, Viking: Stock - publicly traded company

0021 | ASSOCIATION OF HEPATITIS DELTA VIRUS INFECTION AND HEPATOCELLULAR CARCINOMA, HEPATIC DECOMPENSATION, ALL-CAUSE AND LIVER-RELATED DEATH IN A U.S NATIONAL COHORT

Binu John[1] Mahmoud Amoli[2] Robert Wong[3] Donna Evon[4] Shari Rogal[5] David Ross[6] Timothy Morgan[7] Gabriel Villada[8] Seth Spector[9] Hann-Hsiang Chao[10] Bassam Dahman[2]

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Background: Hepatitis Delta Virus (HDV) infection is the most severe form of chronic hepatitis. However, studies on HDV outcomes in a United States-born population, where transmission is mostly horizontal, are lacking. Therefore, the primary aim of this study was to identify the causes and predictors of HCC, hepatic

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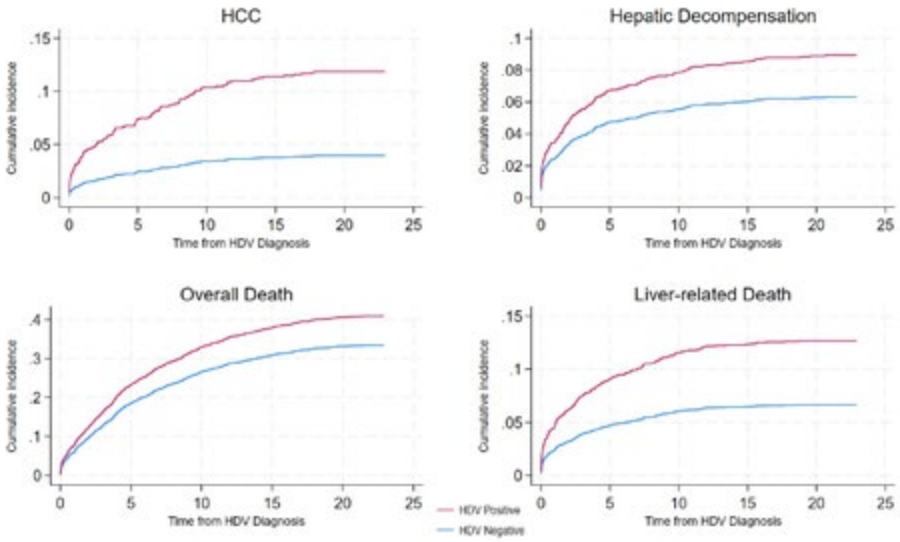
decompensation, all-cause, and liver-related mortality (LRM) in patients with HDV compared to those with HBV mono-infection in a primarily US-born population. **Methods:** This study was a retrospective analysis of U.S Veterans that included participants from the Veteran Health Administration (VHA) between January 2000 and December 2022. Patients were considered to have HDV infection if they were anti-HDV, or HDV PCR positive. We included all patients with evidence of Hepatitis B infection who underwent testing for HDV, defining the date of HDV testing as the baseline for HDV-negative patients, and the date of the first positive HDV test as the baseline for those with HDV. We determined the incidence rates (instances per 1000 person-years), incidence rate ratios (IRR), and 5- and 10-year landmark analyses for outcomes of HCC, hepatic decompensation, all-cause mortality, and LRM. We also employed multivariable Cox proportional hazards models and cumulative incidence graphs for these outcomes. **Results:** A total of 4,521 patients with HBV were tested for HDV; 141 (3.1%) were HDV-positive and 4,380 (96.9%) were HDV-negative. The median age was 56.7 years (IQR 16.3), predominantly male (95.0%), with 31.4% non-Hispanic white, 30.7% non-Hispanic Black, 635 (14.0%) Hispanic, and 461 (10.2%) Asian. The majority of the participants were U.S.-born (99.6%) and the majority had a history of substance use disorders (57.1%). HDV coinfection (vs. HBV monoinfection) was associated with a significantly higher incidence of liver-related outcomes at 10 years, including HCC (14.2 vs. 3.4%, p<0.001), hepatic decompensation (13.5 vs. 5.1%, p<0.001), all-cause mortality (40.4 vs. 23.7%, p<0.001), and LRM (16.3 vs. 6.7%, p<0.001). The most common cause of death was liver-related (34.7% for HDV vs. 24.9% for HBV). The next most common causes of death in the HDV vs. HBV group included non-hepatic malignancies (16.0 vs. 14.9%), cardiac (10.7 vs. 14.7%), and lung disease (5.3 vs. 3.7%). In multivariable models, HDV was associated with an increased risk of HCC (aHR 3.74, 95% CI 2.40-5.82, p<0.001), hepatic decompensation (aHR 2.34, 95% CI 1.49-3.69, p<0.001), all-cause mortality (aHR 1.66, 95% CI 1.30-2.10, p<0.001), and LRM (aHR 1.93, 95% CI 1.27-2.92, p=0.002). **Conclusion:** In a predominantly U.S.-born cohort of Veterans, HDV co-infection was associated with an increased risk of HCC, decompensation, all-cause mortality, and LRM. With the impending arrival of novel antivirals, these findings highlight the need for more widespread HDV testing so that patients with HDV can be identified for treatment.



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0022 | CYP1B1+PRRX1+NR4A2+ HEPATIC STELLATE CELLS IN ALCOHOL-ASSOCIATED HEPATITIS ◆

Hye Yeon Choi[1] Yoann Daniel[1] Sonal Sinha[2] Stephanie Pan[1] Yixin Bai[1] Qihong Yang[1] Hyun Young Kim[3] Sadatsugu Sakane[3] Ryan Weber[4] Zhaoli Sun[5] Stanley Ng[6] Meng Li[1] Tatiana Kisseleva[3]

[1]University of Southern California, [2]Cedars Sinai Medical Center, [3]University of California, San Diego, [4]University of California. Irvine, [5]Johns Hopkins Unviersity, [6]University of California, Irvine

Background: We recently identified a highly fibrogenic, proinflammatory and myofibroblastic (MFB) subpopulation of activated hepatic stellate cells (aHSC) co-expressing the HSC marker *Lrat* and portal fibroblast (PF) marker *Fbln2* in alcohol-associated hepatitis (AH). Genetic lineage tracing revealed *Lrat*$^{+Fbln2+}$ cells originated from *Lrat*$^{+}$ HSC. However, we are yet to determine if they also arise from *Fbln2*+ PF; what drives the *Lrat*$^{+Fbln2+}$ cell fate; and what translational implications they have. **Methods:** *Fbln2-CreERT;Rosa26mTmG* mice were generated for lineage tracing. aHSC from *Col1a1-GFP* mice with F1-2 liver fibrosis by AH, CCl4, or bile duct ligation (BDL), were enriched by FACS and VitA^{+}GFP^{+} aHSC analyzed by scRNA-seq. AH aHSC were subjected to whole genome sequencing (WGS). snRNA-seq data from healthy vs. alcohol-associated liver disease (ALD) patient livers were analyzed. Spatial RNA-seq analysis performed on AH patient liver sections; CRISPR-Cas9 genetic knockdown (KD) performed on FBLN2^{+} LX2 cells. **Results:** *Fbln2-CreERT;Rosa26mTmG* mice faithfully labeled FBLN2^{+} PF with GFP in control livers but failed to generate LRAT^{+}GFP^{+} cells in AH. scRNA-seq identified DEGs uniquely induced in *Lrat*$^{+Fbln2+}$ aHSC in AH vs. CCl4 or BDL fibrosis including *Cyp1b1* and *Nr4a2* and commonly upregulated *Prrx1*. Re-clustering by *Nr4a2* and *Prrx1* identified DEGs in *Lrat*$^{+Nr4a2+Prrx1+}$ aHSCs, which were nearly identical to *Lrat*$^{+Fbln2+}$ cells, suggesting the roles of *Nr4a2* and *Prrx1*. RNA velocity analysis indicated a cell trajectory from *Nr4a2*$^{-Prrx1-}$ toward *Nr4a2*$^{+Prrx1+}$ aHSCs and InferCNV analysis suggested hierarchical clusters of *Nr4a2*$^{+Prrx1+}$ aHSCs with unique and progressive CNV patterns in Chr 1, 4, 8, and 16. Indeed, WGS identified genetic variants of *Nr4a2*$^{+Prrx1+}$ DEGs including *Prrx1*, *Alcam*, *Itga8*, *Nr4a3*, and *Svep1*. *Cyp1b1* was induced only in *Nr4a2*$^{+Prrx1+}$ cells while *Nr4a2* and *Prrx1* were upregulated in *Cyp1b1*$^{+}$ vs. *Cyp1b1*$^{-}$cells, suggesting mutual dependence. This notion was confirmed by selective KD of CYP1B1, PRRX1, or NR4A2 in FBN2+ LX2 cells, each of which repressed others and fibrogenic and MFB genes, the effects which were also reproduced by pharmacologic CYP1B1 inhibition. CYP1B1 was uniquely upregulated in aHSC of ALD patient vs. MASLD or normal livers per snRNA-seq data. *CYP1B1*$^{+}$ vs. *PRRX1*$^{+}$ ALD aHSC showed overlapping unique DEGs (*FGF7, LTBP2, CCDC102B, EFEMP1, FBN1*). Spatial analysis of AH patient liver revealed *ACTA2*$^{+NR4A2+}$spots enriched in regenerative nodules in proximity of *HNF4A*$^{+AFP+}$ spots with upregulated immunoregulatory, inflammatory and MFB genes. **Conclusion:** Our results suggest that LRAT+FBLN2^{+} aHSC are generated from HSC but not from PF in AH through acquired expression and cross-regulation of PRRX1, NR4A2, and CYP1B1 in a manner which appears predicated by genetic and clonal evolution. We propose CYP1B1^{+}PRRX1^{+}NR4A2^{+} aHSC may be a novel therapeutic target for AH.

Disclosures: Hye Yeon Choi: Nothing to Disclose, Yoann Daniel: Nothing to Disclose, Sonal Sinha: Nothing to Disclose, Stephanie Pan: Nothing to Disclose, Yixin Bai: Nothing to Disclose, Qihong Yang: Nothing to Disclose, Hyun Young Kim: Nothing to Disclose, Sadatsugu Sakane: Nothing to Disclose, Ryan Weber: Nothing to Disclose, Zhaoli Sun: Nothing to Disclose, Stanley Ng: Nothing to Disclose, Meng Li: Nothing to Disclose, Tatiana Kisseleva: Nothing to Disclose

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0023 | PROGNOSTIC VALUE OF THE AASLD 2-STEP APPROACH IN THE IDENTIFICATION OF ADVANCED LIVER FIBROSIS IN 16,603 PATIENTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD) IN THE VCTE-PROGNOSIS STUDY

Terry Cheuk-Fung Yip[1] Hye Won Lee[2] Huapeng Lin[3] Emmanuel Tsochatzis[4] Salvatore Petta[5] Elisabetta Bugianesi[6] Masato Yoneda[7] Ming-Hua Zheng[8] Hannes Hagström[9] Jérôme Boursier[10] Jose Luis Calleja[11] Boon Bee George Goh[12] Wah Kheong Chan[13] Rocio Gallego-Durán[14] Arun Sanyal[15] Victor de Ledinghen[16] Philip Newsome[17] Jiangao Fan[18] Laurent Castera[19] Michelle Lai[20] Stephen Harrison[21] Celine Fournier[16] Grace Wong[1] Grazia Pennisi[5] Angelo Armandi[22] Atsushi Nakajima[23] Wen-Yue Liu[8] Ying Shang[9] Marc De Saint Loup[10] Elba Llop[11] Kevin Teh[12] Carmen Lara Romero[14] Amon Asgharpour[15] Sara Mahgoub[17] Mandy Chan[16] Clemence Canivet[10] Manuel Romero-Gómez[14] Seung Up Kim[2]

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Background: The AASLD recommends a 2-step approach using Fibrosis-4 index (FIB-4) followed by a specific fibrosis test such as liver stiffness measurement (LSM) by vibration-controlled transient elastography (VCTE) to identify advanced fibrosis among patients with MASLD. The optimal use of this algorithm and its prognostic value remain unclear. **Methods:** The VCTE-Prognosis Study was a longitudinal study of patients with MASLD who had undergone VCTE examinations at 16 centers from the US, Europe and Asia, among which data were collected prospectively at 14 centers. The primary endpoint was liver-related events, defined as incident hepatic decompensation (ascites, variceal bleeding or hepatic encephalopathy) and/or hepatocellular carcinoma. **Results:** A total of 17,949 patients were screened, and 16,603 patients (mean age 53 years, 42% female, 35% had diabetes, median LSM 6.0 kPa) were included in the final analysis after excluding those aged below 18 or had liver-related events before baseline. Baseline FIB-4, at cutoffs of 1.3 and 2.67, classified 60% of the cohort as low-risk and 10% as high-risk, leaving 30% in the intermediate-risk zone (Figure). Upon further classification of patients with intermediate FIB-4 by LSM at cutoffs of 8 and 12 kPa, 80% of the entire cohort was classified as having low-risk, 5.6% as intermediate-risk, and 15% as high-risk. At a median follow-up of 52 months, 316 patients developed liver-related events. The cumulative incidence of liver-related events at 5 years was 0.4%, 1.5% and 10.7% in the low-, intermediate- and high-risk groups, respectively. Replacing LSM by the Agile 3+ score did not further reduce the intermediate zone (6.0%) or improve event prediction (integrated area under time-dependent receiver operating characteristic curve [AUROC] for liver-related events: 0.85 for LSM and 0.84 for Agile 3+). Performing LSM for all patients with FIB-4 ≥1.3 led to minor reclassification (mainly from high- to intermediate-risk) and mild improvement of integrated AUROC from 0.85 to 0.87. **Conclusion:** The AASLD 2-step approach is effective in predicting liver-related events. If resources are limited, it is reasonable to limit the second fibrosis test to patients with intermediate FIB-4. When FIB-4 is used as the first-line test, substituting LSM by the Agile 3+ score does not improve the prediction further. (This study was supported in part by the General Research Fund of the Hong Kong SAR Government [Project reference 14106923].)

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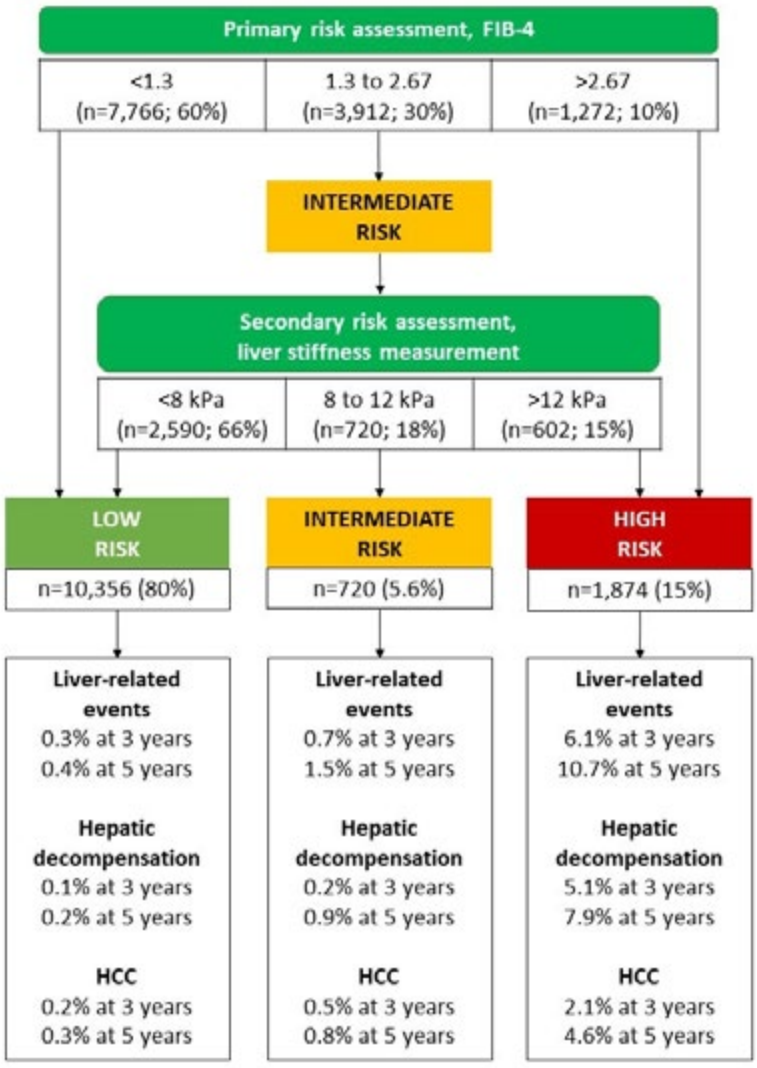

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0024 | INTEGRATIVE MULTIOMICS UNVEILS THE AGGRESSIVE MECHANISMS AND THERAPEUTIC STRATEGIES OF CA19-9 POSITIVE INTRAHEPATIC CHOLANGIOCARCINOMA

Delin Ma[1] *Pengcheng Wei*[1] *Zhao Li*[1]

[1]*Peking University People's Hospital*

Background: Intrahepatic cholangiocarcinoma (ICC) is a highly invasive malignant tumor, with over 50% of patients being CA19-9 positive, and its prognosis is significantly poorer compared to CA19-9 negative patients. However, the intrinsic mechanisms underlying this prognostic difference and the heterogeneity of the tumor microenvironment remain inadequately characterized. Therefore, this study aims to explore the biological differences between CA19-9 positive and negative ICC and to identify potential therapeutic targets. **Methods:** This study collected seven clinical cohorts comprising 1062 ICC patients, two whole-exome sequencing (WES) cohorts, three bulk sequencing cohorts, and 20 single-cell RNA sequencing (scRNA-seq) samples to comprehensively describe the clinical, genomic, transcriptomic, and immunomicroenvironmental features of CA19-9 positive ICC. In addition, key findings were validated using multiplex immunohistochemistry on tissue microarrays from 54 ICC samples. Furthermore, potential therapeutic agents for CA19-9 positive ICC were predicted based on drug sensitivity data of cancer cell lines. **Results:** Compared to the CA19-9 negative group, CA19-9 positive ICC demonstrated enhanced invasive and metastatic capabilities, along with significantly reduced overall survival (OS) and recurrence-free survival (RFS). At the genomic level, the frequency of KRAS mutations was markedly higher in CA19-9 positive ICC, whereas IDH1/2 mutations were more prevalent in the negative group. Transcriptomic analysis revealed that glycolysis pathways were significantly upregulated in CA19-9 positive ICC, with a concurrent downtrend in oxidative phosphorylation pathways. Single-cell transcriptomic analysis further identified specific cell subpopulations with glycolytic characteristics enriched in CA19-9 positive ICC, including SLC2A1+malignant epithelial cells, VEGFA+ tumor-associated fibroblasts, and SPP1+ macrophages, all of which were closely associated with poor ICC prognosis. Pseudotime analysis confirmed that these cell subpopulations were at the terminal end of metabolic transition. These cells were spatially close, forming a highly interactive cell module that not only enhanced tumor metastasis by promoting epithelial-mesenchymal transition (EMT) but also facilitated angiogenesis through high VEGFA expression interacting with endothelial cells, playing a crucial role in shaping a highly invasive tumor microenvironment. Drug sensitivity analysis identified six potential therapeutic agents for the treatment of CA19-9 positive ICC. **Conclusion:** This study systematically elucidated the clinical, genomic, transcriptomic, and immunomicroenvironmental characteristics of CA19-9 positive ICC for the first time and identified a glycolysis-related cell module and its pro-oncogenic mechanisms, which are of significant importance for guiding clinical therapy.

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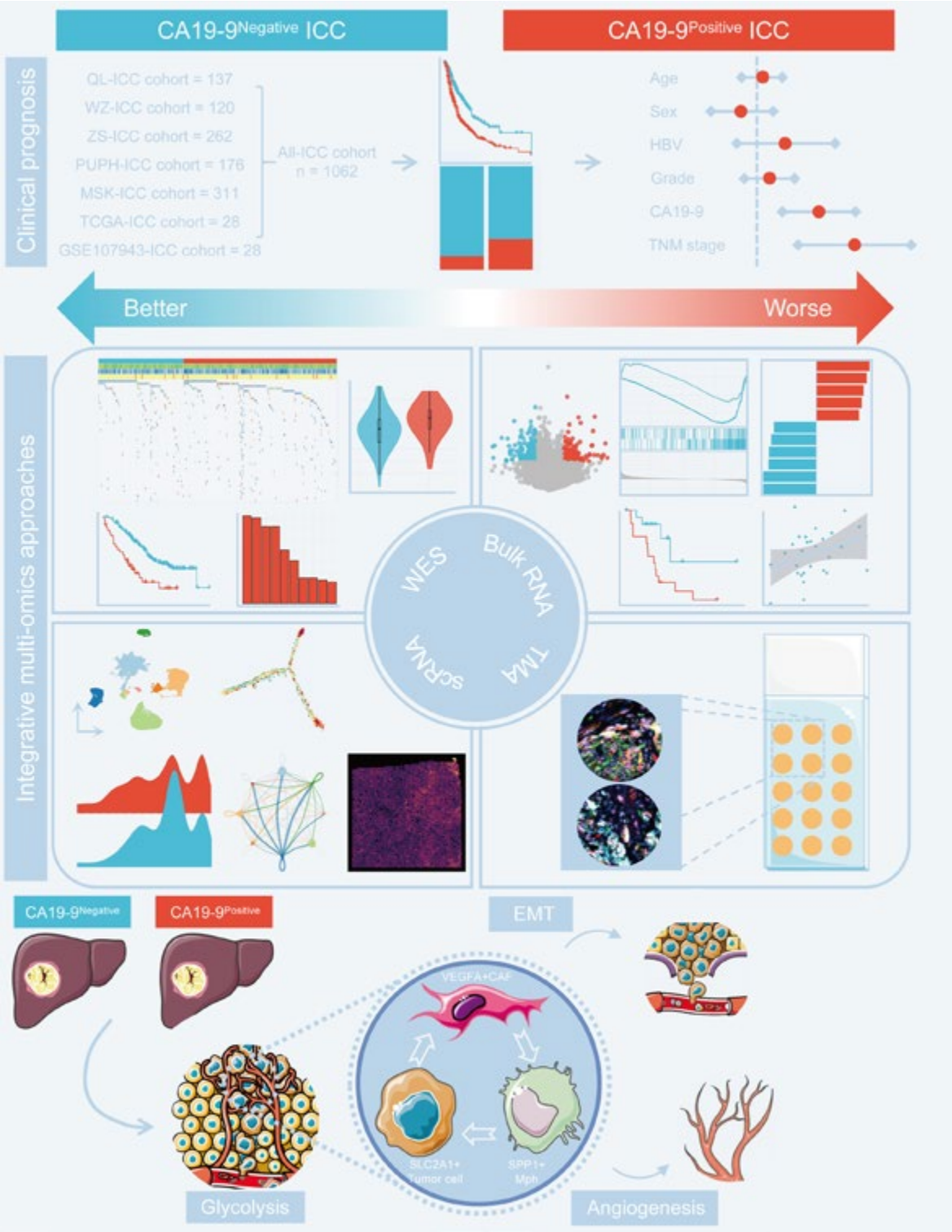

Disclosures: Delin Ma: Nothing to Disclose, Pengcheng Wei: Nothing to Disclose, Zhao Li: Nothing to Disclose, Nothing to Disclose

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0025 | GEOGRAPHIC DISPARITIES IN LIVER TRANSPLANT WAITLIST OUTCOMES FOR CRITICALLY ILL CANDIDATES: THE IMPACT OF POPULATION DENSITY AMID THE ACUITY CIRCLE IN THE UNITED STATES

Tomohiro Tanaka[1] George Wehby[2] Mark Vander Weg[2] Keith Mueller[2] David Axelrod[2]

[1]University of Iowa School of Medicine, [2]University of Iowa

Background: Liver transplant (LT) allocation policies, particularly the Acuity Circles (AC) policy implemented in 2020, aim to address disparities in liver transplant wait times and organ availability in the US. This study investigates the impact of population density on LT waitlist outcomes under the AC policy. **Methods:** A nationwide retrospective cohort study was conducted using data from the United Network for Organ Sharing (UNOS). Adult deceased donor LT recipients listed from June 2013, to May 2023, were included. The target populations were (1) those with chronic end-stage liver disease (ESLD) with a MELD score of 37 or higher (High-MELD cohort) and (2) candidates with acute liver failure (ALF) listed as status 1A. Population density within defined radii around each LT center was calculated (150 miles for the High-MELD and 500 miles for the ALF cohort; expressed as the number of people per square mile). Outcomes, including waitlist mortality/drop-out rate, were analyzed using generalized linear mixed-effect models, which were adjusted for demographic, clinical, social, and geographic confounders, with random intercepts at the center and listing date levels. Fine-Gray competing risk regression was used as a secondary model. **Results:** The study analyzed 5,237 candidates (1,387 in the ALF cohort and 3,850 in the High-MELD cohort) during the pre-AC era and 3,156 candidates (872 in ALF and 2,284 in High-MELD) in the post-AC era. In the High-MELD cohort, the lowest tertile of population density was associated with increased waitlist mortality specifically following the implementation of the Acuity Circles (AC) policy (adjusted odds ratio [aOR]: 1.68, 95% CI: 1.14-2.46, with the middle tertile of population density serving as the reference). A one-unit increase in log-transformed population density was associated with a 15% reduction in waitlist mortality (aOR 0.85, 95% CI: 0.75-0.96). This association was consistent with the results from the Fine-Gray model and was corroborated by multiple sensitivity analyses. However, no statistically significant geographic disparities related to population density were observed in the ALF cohort, either before or after the AC implementation. **Conclusion:** Population density significantly influences LT waitlist outcomes in the United States under the AC policy. Critically ill patients with ESLD and high MELD scores in areas of low population density face increased waitlist mortality risks. This study underscores the need for policy adjustments to improve equity in LT allocations, particularly for patients in centers located in regions with low population density.

Disclosures: Tomohiro Tanaka: Nothing to Disclose, George Wehby: Nothing to Disclose, Mark Vander Weg: Nothing to Disclose, Keith Mueller: Nothing to Disclose, David Axelrod: Nothing to Disclose

0026 | RACIAL/ETHNIC AND SEX DIFFERENCES IN MAJOR ADVERSE CARDIOVASCULAR EVENTS AND MAJOR ADVERSE LIVER OUTCOMES AMONG STEATOTIC LIVER DISEASE SUBTYPES: A NATIONAL COHORT STUDY

Pedro Ochoa-Allemant[1] Rebecca Hubbard[1] David Kaplan[1] Marina Serper[1]

[1]University of Pennsylvania

Background: Steatotic liver disease (SLD) disproportionately affects racial/ethnic minorities and men in the United States. Nonetheless, whether differences exist in the incidence of major adverse cardiovascular events (MACE) and major adverse liver outcomes (MALO) among these populations is not clearly established. **Methods:** We conducted a retrospective cohort study of patients aged 18 years or older with hepatic steatosis identified using natural language processing receiving care from the Veterans Health Administration between fiscal years 2010 and 2021. The main exposures were selected racial/ethnic groups (non-Hispanic [NH] White, NH Black, and Hispanic) and sex (men, women). The primary outcomes were the incidence of MACE (acute myocardial infarction, stroke, heart failure, or cardiovascular mortality) and MALO (cirrhosis, hepatic decompensation, hepatocellular carcinoma, liver transplantation, or liver-related mortality). We estimated cumulative incidence using Kaplan-Meier methods and hazard ratios (HR) using multivariable Cox regression models stratified by SLD subtypes (metabolic dysfunction-associated steatotic liver disease [MASLD], metabolic and alcohol-associated liver disease [MetALD], alcohol-associated liver disease [ALD]). **Results:** Among 514,844 patients with SLD

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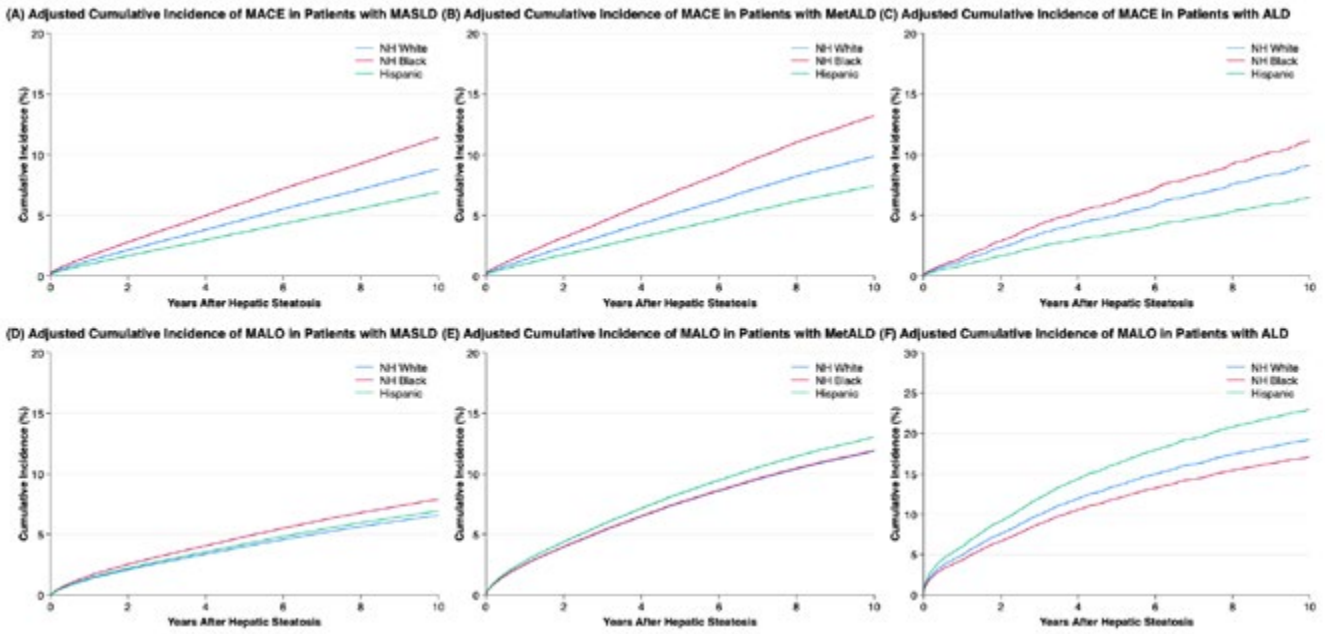
(MASLD 73.3%, MetALD 24.2%, ALD 2.5%), the median age was 60 years (interquartile range [IQR], 51-67 years) and 40,065 (7.8%) were female. Racial/ethnic groups included 370,727 (72.0%) NH White, 85,333 (16.6%) NH Black, and 58,784 (11.4%) Hispanic. The overall median follow-up was 6.3 years (IQR, 3.5-9.3 years). The risk of MACE was higher among NH Black patients with MASLD (10-year cumulative incidence 12.1% vs. 10.5%; adjusted HR [aHR] 1.31, 95% confidence interval [CI], 1.27-1.36), MetALD (10-year cumulative incidence 13.8% vs. 11.0%; aHR 1.36; 95% CI, 1.30-1.43), and ALD (10-year cumulative incidence 12.3% vs. 9.6%; aHR 1.23; 95% CI, 1.04-1.46) than NH White patients. The risk of MALO was higher among Hispanic patients with MetALD (10-year cumulative incidence 15.7% vs. 15.3%; aHR 1.10; 95% CI, 1.04-1.17) and ALD (10-year cumulative incidence 28.2% vs. 22.3%; aHR 1.22; 95% CI, 1.05-1.42) than NH White patients. The risks of MACE and MALO were lower among women than men across SLD subtypes. **Conclusion:** We found substantial racial/ethnic and sex differences in the incidence of MACE and MALO among patients with SLD. Black patients have the highest risk of MACE across SLD subtypes, whereas Hispanic patients have the highest risk of MALO among those with MetALD and ALD. Men have the highest incidence of MACE and MALO across SLD subtypes.



Disclosures: Pedro Ochoa-Allemant: Nothing to Disclose, Rebecca Hubbard: Nothing to Disclose, David Kaplan: Independent Contractor relationship with Roche Genentech; Has not ended; Grant/Research Support relationship with AstraZeneca Inc; Has not ended; Advisor relationship with AstraZeneca; Has ended; Advisor relationship with Exelixis; Has ended; Grant/Research Support relationship with Gilead; Has not ended; Advisor relationship with Sirtex; Has ended; Grant/Research Support relationship with Exact Sciences; Has not ended; Grant/Research Support relationship with Glycotest; Has ended, Marina Serper: Grant/Research Support relationship with Grifols; Has not ended; Grant/Research Support relationship with Eurofins; Has not ended; Grant/Research Support relationship with Transplant Genomics; Has not ended

0027 | THE PORTAL DECOMPENSATION SCORE – A VALIDATED PREDICTIVE MODEL OF PORTAL HYPERTENSION RELATED LIVER DECOMPENSATION EVENTS IN CIRRHOSIS ★

Angus Jeffrey[1] Avik Majumdar[2] Luis Calzadilla Bertot[3] Michael Wallace[1] Gary Jeffrey[1] Ivy Huang[3] John Joseph[4] George Garas[3] Leon Adams[5]

[1]Sir Charles Gairdner Hospital, [2]The Austin Hospital, [3]The University of Western Australia, [4]Pathwest, [5]University of Western Australia

Background: Accurate assessment of portal hypertension is crucial in management and risk assessment. The Baveno VII and recent AASLD 2024 guidelines identified a need for accurate non-invasive risk stratification

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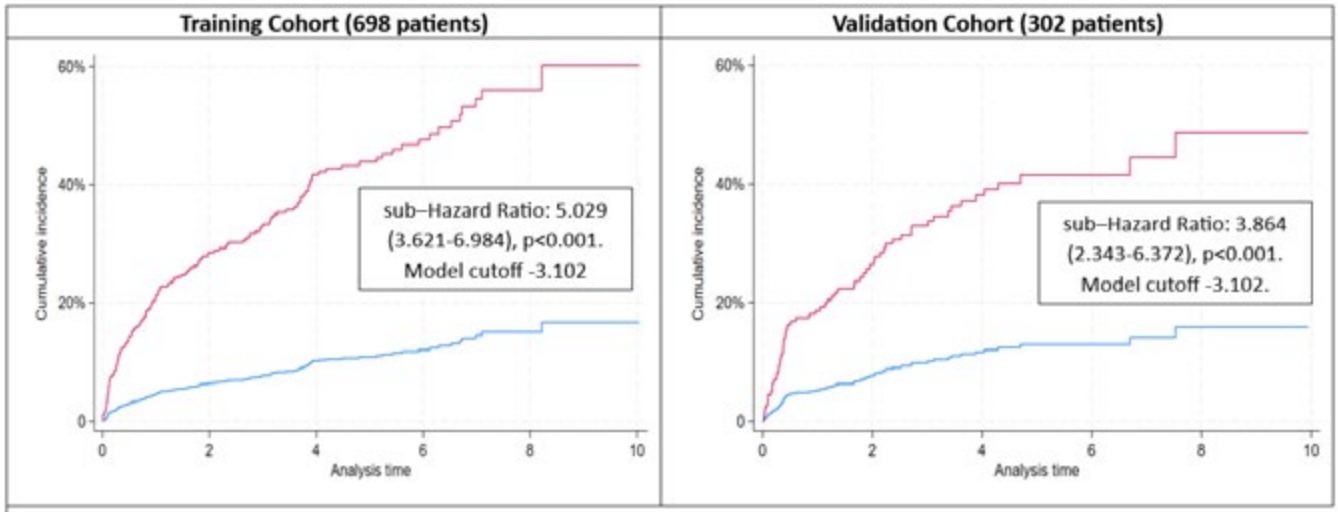
of portal hypertension. The aim of this study was to develop a novel score that accurately predicts portal hypertension related decompensation (variceal haemorrhage, ascites, hepatic encephalopathy). **Methods:** Adults with cirrhosis in Western Australia from 2004 to 2015 were followed until occurrence of a decompensating event. Cirrhosis was defined by baseline Hepascore values using validated cut-points; >=0.95 for alcoholic liver disease, >= 0.96 for non-alcoholic fatty liver disease, >= 0.84 for all other causes. The cohort was split into a training and validation dataset at a 70:30 ratio. Associations between serum markers and decompensation was assessed by competing risk analysis, and model accuracy compared using time dependent area under the curve (tAUC). **Results:** 1384 participants with cirrhosis were included. 698 (72%) and 302 (72%) participants were male in the training and validation cohorts respectively. The median age was 54 years in both groups. There were 172 (17.8%) and 64 (15.3%) episodes of decompensation in the training and validation cohorts (p=0.60) after an average follow-up period of 3.59 (s.d. ± 2.32) and 3.76 (s.d. ± 2.38) years respectively. Average MELD score was 9.4 (± 4.3) and 9.6 (± 4.4) (p=0.43). 85% in the training cohort and 96% in the validation cohort were Child Pugh A, the remainder being Child Pugh B. Competing risk analysis found bilirubin, alanine transaminase (ALT), alkaline phosphatase (ALP), albumin and platelets independent predictors of decompensation and were combined into a final model - the Portal Decompensation Score (PDS). The model produced a calibration slope of 0.99 (training) and 1.00 (validation). A cut-off of -3.102 was selected using the Li and Youden criteria, with a cumulative incidence for decompensation of 6.5% vs 28.5% at 2-years and 10.8% vs. 43.8% at 5-years (sHR 5.0, p<0.001). Accuracy of the model for the entire cohort was very good with tAUC of 0.81 at 2-years and 0.79 at 5-years. By aetiology, the tAUC at 2-years was excellent in Hepatitis C (0.83), Hepatitis B (0.87) and autoimmune hepatitis (0.81), and good for NAFLD (0.71). **Conclusion:** The Portal Decompensation Score (PDS) uses simple, readily available serum markers to accurately identify those patients with liver cirrhosis who are at higher risk of having a portal hypertension related decompensating event. This new model may provide benefit in assessment of patients regarding ongoing surveillance requirements, including those who may benefit from surveillance endoscopy, primary prevention of varices with non-selective beta blockade or even primary prophylaxis for hepatic encephalopathy.



Disclosures: Angus Jeffrey: Nothing to Disclose, Avik Majumdar: Nothing to Disclose, Luis Calzadilla Bertot: Nothing to Disclose, Michael Wallace: Nothing to Disclose, Gary Jeffrey: Nothing to Disclose, Ivy Huang: Nothing to Disclose, John Joseph: Nothing to Disclose, George Garas: Nothing to Disclose, Leon Adams: Novo Nordisk: Advisor, SCL Behring: Advisor, Pfizer: Advisor

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0028 | AEROBIC EXERCISE TRAINING LEADS TO MASH RESOLUTION AS DEFINED BY THE MASH RESOLUTION INDEX WITHOUT BODY WEIGHT LOSS

Theja Channapragrada[1] Breianna Hummer[2] Vernon Chinchilli[3] Daniel Huang[4] Rohit Loomba[5] Kathryn Schmitz[6] Ian Schreibman[7] chris sciamanna[7] Jonathan Stine[8]

[1]Department of Medicine, Penn State He, [2]Penn State Health, [3]Department of Public Health Sciences, [4]National University Hospital, Singapore, [5]University of California, San Diego, [6]UPMC, [7]Penn State, [8]Pennsylvania State University

Background: Exercise training is recommended for all patients with MASLD may improve liver histology. Stopping progression or improving liver histology is a goal all therapeutic interventions, especially lifestyle related, and is closely tied to clinical outcomes. Given the limitations of liver biopsy, there is a greater reliance on non-invasive biomarkers of histologic improvement. Whether exercise training improves liver histology independent of body weight loss remains controversial. We investigated this relationship using the MASH Resolution Index, a validated composite score of multiple serum and imaging-based biomarkers, in a post hoc analysis of an exercise trial where individuals with MASH did not lose significant body weight. **Methods:** The NASHFit Trial was conducted from May 2018 to February 2021 and randomized 28 adults aged 18-69 years with biopsy-proven MASH to receive either 150 min/wk. of moderate-intensity aerobic exercise training or standard of care 20 weeks. Mediterranean-informed dietary counseling was provided to each group. Change in the MASH Resolution Index was measured and compared between the two groups. Data was available to calculate the MASH Resolution Index in 23 subjects (15 exercise, 8 standard of care). **Results:** The study population had a mean age of 52 ± 11 yrs. (range 25-69 yrs.) and a mean BMI of 33.8 ± 5.0 kg/m^2. Thirteen patients were female (57%) and 39% had diabetes. Liver fibrosis (F) stage at study entry was 56% (n=13) F0/F1, 22% (n=5) F2, 17% F3 (n=4), and 4% F4 (n=1). Baseline characteristics were similar between the exercise and the standard of care groups. Specifically, the groups were well matched for age, biologic sex, BMI, metabolic comorbidities, and MASH stage. No clinically significant weight loss (≥5%) occurred in either group. Applying the MASH Resolution Index, those who received exercise training achieved MASH resolution (as defined by MASH Resolution Index ≥ −0.67) nearly three times more often (33% vs. 13%, p<0.01) versus those who received standard of care. Importantly, each individual dynamic parameter contained in the MASH Resolution Index changed more significantly with exercise intervention. Exercise training participants experienced a 24% reduction in ALT (-14 ± 14 IU/L) compared to standard clinical care subjects, who had a 10% reduction in ALT (-6 ± 16 IU/L), p = 0.06. Exercise training reduced absolute MRI-PDFF by -4.3% compared to a +1.2% gain with standard of care (p=0.01). **Conclusion:** Exercise training leads to MASH resolution independent of body weight loss in adults with MASH and at greater rates than standard in-office lifestyle counseling. This study provides novel evidence that the MASH Resolution Index, a non-invasive monitoring tool that is scalable at the population level, can be used to discern therapeutic response to the lifestyle intervention recommended for all individuals worldwide with MASLD/MASH.

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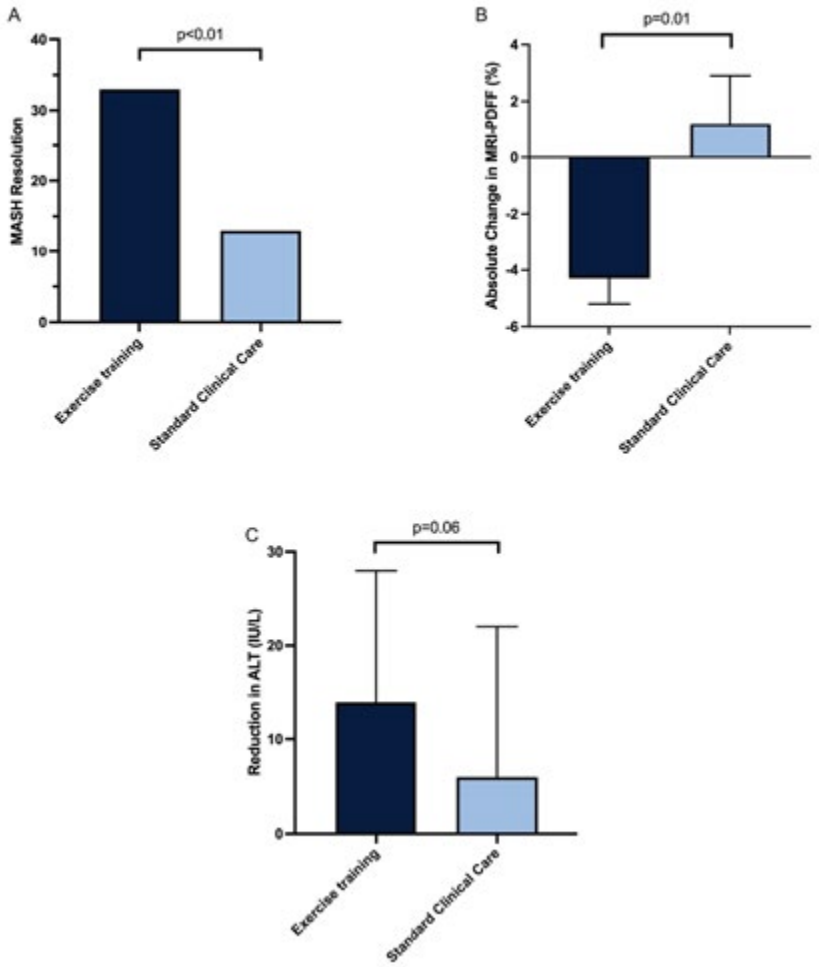
Figure 1. Exercise training leads to greater rates of (A) MASH resolution, (B) MRI-PDFF improvement and (C) ALT reduction in comparison to standard of care.



Disclosures: Theja Channapragrada: Nothing to Disclose, Breianna Hummer: Nothing to Disclose, Vernon Chinchilli: Nothing to Disclose, Daniel Huang: Nothing to Disclose, Rohit Loomba: Eli Lilly and Company: Consultant, 89bio: Consultant, Aardvark Therapeutics: Consultant, Altimmune: Consultant, Alnylam/Regeneron: Consultant, Amgen: Consultant, Arrowhead Pharmaceuticals: Consultant, AstraZeneca: Consultant, Bristol Myers Squibb: Consultant, CohBar: Consultant, Eli Lilly: Consultant, Galmed Pharmaceuticals: Consultant, Gilead: Consultant, Glympse Bio: Consultant, Hightide: Consultant, Inipharma: Consultant, Intercept: Consultant, Inventiva: Consultant, Ionis: Consultant, Janssen, Inc.: Consultant, Madrigal Pharmaceuticals: Consultant, Merck, Metacrine, Inc.: Consultant, NGM Biopharmaceuticals: Consultant, Novartis: Consultant, Novo Nordisk: Consultant, Pfizer: Consultant, Sagimet Biosciences: Consultant, Terns Pharmaceuticals: Consultant, Theratechnologies and Viking Therapeutics: Consultant, 89bio: Stock options, Sagimet Biosciences: Stock options, Arrowhead Pharmaceuticals: Research grant, AstraZeneca: Research grant, Boehringer Ingelheim: Research grant, Bristol Myers Squibb: Research grant, Eli Lilly: Research grant, Galectin Therapeutics: Research grant, Galmed Pharmaceuticals: Research grant, Gilead: Research grant, Hanmi: Research grant, Intercept: Research grant, Inventiva: Research grant, Ionis: Research grant, Janssen, Inc.: Research grant, Madrigal Pharmaceuticals: Research grant, Merck: Research grant, NGM Biopharmaceuticals: Research grant, Novo Nordisk: Research grant, Pfizer: Research grant, Sonic Incytes: Research grant, Terns Pharmaceuticals: Research grant, LipoNexus, Inc.: Co-founder, Kathryn Schmitz: Nothing to Disclose, Ian Schreibman: Nothing to Disclose, chris sciamanna: Nothing to Disclose, Jonathan Stine: Zydus Therapeutics: Grant/Research Support, Novo Nordisk: Consultant, Galectin: Grant/Research Support, Novo Nordisk: Grant/Research Support, Astra Zeneca: Grant/Research Support, Noom: Grant/Research Support, Zydus: Grant/Research Support, Kowa: Grant/Research Support

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0029 | INHIBITION OF NECROPTOSIS REDUCES INFLAMMATION, NEUTROPHIL ACTIVATION, LIVER FIBROSIS AND IMPROVES MULTIORGAN DAMAGE (KIDNEY FUNCTION AND NEUROINFLAMMATION) IN A MURINE MODEL OF ALCOHOL-INDUCED ACLF ★

Marti Ortega-Ribera[1] Prashanth Thevkar Nagesh[2] Veronika Brezani[2] Mrigya Babuta[2] Arman Patel[2] Gyongyi Szabo[2]

[1]BIDMC - Harvard Medical School, [2]Beth Israel Deaconess Medical Center

Background: Necroptosis, mediated by receptor-interacting kinase 3 (RIPK3) activation, has been recently described as the main cell death pathway contributing to liver damage in a model of ACLF induced by alcohol. Here we evaluated the effect of a novel RIPK3 inhibitor, GSK047, in ameliorating ACLF pathophysiology. **Methods:** Liver fibrosis was induced in 10-12 weeks old male C57BL/6J mice by common bile duct ligation (BDL) for 28 days and a single alcohol binge (5g/Kg) was given to induce ACLF. On day 21 after BDL surgery, mice were randomized to receive four doses of 4.5 mg/Kg GSK047 (RIPK3 inhibitor) or vehicle (saline with 2% DMSO) via IP every alternate day (n = 5/6 per group). Tissue collection and analysis was performed 9 hours after alcohol binge. **Results:** Alcohol-induced ACLF in mice was associated with liver failure, kidney damage and neuroinflammation. *In vivo*, RIPK3 inhibition improved survival rate when compared to vehicle-treated ACLF mice (56% vs 36% respectively). RIPK3 inhibition significantly reduced circulating neutrophils ($CD45^+LY6G^+$ cells) and expression of neutrophil activation markers including ICAM1, L-SEL and TLR4. Interestingly, circulating LY6C high and low monocyte populations remained unchanged upon RIPK3 inhibition. Moreover, ACLF mice treated with GSK047 exhibited decreased levels of serum pro-inflammatory cytokines (IL-18, IL-1β and IL-6) and circulating markers of neutrophil extracellular traps (NETs) including neutrophil elastase and calprotectin. In the liver, mice receiving RIPK3 inhibitor showed a significant decrease in RIPK3 levels and improved fibrosis as shown by the reduced gene expression of *Col1a1*, *Acta2* and *Tgfb1*. In addition, expression of pro-inflammatory mediators (*Tnfa* and *Il1b*) and the NET marker neutrophil elastase were significantly reduced in liver lysates from GSK047-treated mice. Serum levels of AST showed a trend towards reduction after RIPK3 inhibition suggesting improved liver damage. Extrahepatically, RIPK3 inhibition improved kidney function indicated by an improvement in kidney histophatological score and a significant reduction in blood urea nitrogen and expression of neutrophil elastase. In the cerebellum, RIPK3 inhibition decreased the expression of inflammatory markers (*Il1b*, *Cdkn1a* and *Cd11b*) in ACLF mice. **Conclusion:** Inhibition of RIPK3 significantly improved ACLF pathophysiology and multi-organ damage in our preclinical model of alcohol-induced ALCF. RIPK3 inhibition attenuated systemic and hepatic inflammation, neutrophil recruitment and activation, hepatic fibrosis and improved kidney function and neuroinflammation compared to vehicle-treated mice, highlighting the potential therapeutic use of RIPK3 inhibition in ameliorating ACLF.

Disclosures: Marti Ortega-Ribera: Nothing to Disclose, Prashanth Thevkar Nagesh: Nothing to Disclose, Veronika Brezani: Nothing to Disclose, Mrigya Babuta: Nothing to Disclose, Arman Patel: Nothing to Disclose, Gyongyi Szabo: Advisor relationship with Glympse Bio, Inc (acquired by Sunbird Bio); Has not ended; Consultant relationship with Terra Firma; Has not ended; Consultant relationship with Pfizer; Has not ended; Consultant relationship with Pandion Therapeutics; Has ended; Consultant relationship with Merck; Has ended; Consultant relationship with Durect Corporation; Has ended; Advisor relationship with Satellite Biosciences; Has not ended; Consultant relationship with Zomagen Bioscience/Ventyx Biosciences; Has ended; Consultant relationship with CYTA Therapeutics; Has ended; Royalties or patent beneficiary relationship with Springer Nature Group; Has not ended; Royalties or patent beneficiary relationship with UpToDate Inc; Has not ended; Consultant relationship with LabCorp; Has not ended; Advisor relationship with Evive; Has not ended; Advisor relationship with Surrozen; Has not ended; Consultant relationship with Takeda; Has ended

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0030 | EVALUATING THE SAFETY AND EFFICACY OF SOF/VEL TREATMENT AND PROPHYLACTIC USE OF TAF IN PATIENTS WITH CHRONIC HBV/HCV COINFECTION: A MULTICENTER STUDY

Yifan Han[1] Ning Lin[1] Dazhi Zhang[2] Zuxiong Huang[3] Minghua Su[4] Jiawei Geng[5] Zhili Wen[6] Xiaobo Lu[7] Weize Zuo[8] Hong You[9] Yuemin Nan[10] Liting Zhang[11] Liaoyun Zhang[12] Qian Kang[13] Hongyu Chen[1] Zhan Zeng[1] yanyan yu[1] Xiaoyuan Xu[1]*

[1]Peking University First Hospital, [2]The Second Affiliated Hospital of Chongq, [3]Mengchao Hepatobiliary Hospital of Fujia, [4]The First Affiliated Hospital of Guangxi, [5]The First People's Hospital of Yunnan, [6]The Second Affiliated Hospital of Nancha, [7]The First Affiliated Hospital of Xinjian, [8]The First Affiliated Hospital of Shihezi, [9]Capital Medical University, [10]Hebei Medical University Third Hospital, [11]The First Hospital of Lanzhou University, [12]The First Affiliated Hospital of Shanxi, [13]Beijing Friendship Hospital

Background: Hepatitis B virus (HBV) infection and hepatitis C virus (HCV) infection are among the leading causes of chronic liver diseases worldwide. Through the same transmission route, HBV/HCV co-infection (HBV/HCV dual infection) widely exists and aggravates severe liver damage. In this study, we assessed the safety and efficacy of sofosbuvir/velpasvir (SOF/VEL) in HBV/HCV co-infection patients, and evaluated prophylactic use of tenofovir alafenamide fumarate (TAF) on HBV reactivation. **Methods:** A multicenter, prospective, single-arm, open-label 12-week trial followed by a 12/48-week observational clinical trial was conducted. 83 adults with chronic HBV/HCV (GT1-6) coinfection were enrolled from May 2021 to November 2023, in thirteen centers in China. 64 non-cirrhotic patients were included in group 1 and 19 compensated cirrhosis patients in group 2. All subjects were enrolled to receive SOF/VEL once daily for 12 weeks. Non-cirrhotic subjects received TAF once daily for 28 weeks and compensated cirrhotic subjects received TAF once daily for 64 weeks simultaneously(Figure 1).Group t-test or nonparametric test were used for comparison between groups. Statistical significance was set at $p < 0.05$. **Results:** The HCV genotype distribution of the patients was shown in Figure 2. At the end of SOF/VEL treatment, the overall sustained virological response (SVR) was 97.6%, of which 100% was achieved in group 2 (Figure 3). HCV RNA and HBV DNA levels were dramatically decreased in all patients (Figure 4). ALT (41.4 vs 17.0, *ppp*=0.006) levels were decreased and ALB (42.4 vs 45.1, *pppp*=0.002), PLT (114.0 vs 127.2, *pp*=0.003), APRI (1.6 vs 0.6, *p*=0.007), and FIB-4 (4.3 vs 1.3, *p*=0.004) were significantly decreased after treatment in group 2 (Figure 6). Only one patient in group 1 with genotype 3 showed HBV reactivation, whose HBV DNA level was elevated to 2.15 log10 IU/ml at the end of SOF/VEL treatment but returned to below the lower limit of quantification at the 12 weeks post-treatment. No drug-related adverse effects were observed in the study. **Conclusion:** SOF/VEL greatly reduces HCV RNA levels and improves liver function in patients with chronic HBV/HCV co-infection, with high safety. Patients with compensated cirrhosis also have significant improvement in indicators of cirrhosis after antiviral therapy. Additionally, prophylactic use of TAF in patients with chronic HBV/HCV coinfection prevents HBV reactivation to some extent.

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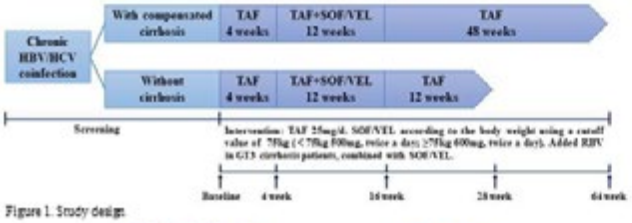

Figure 1. Study design

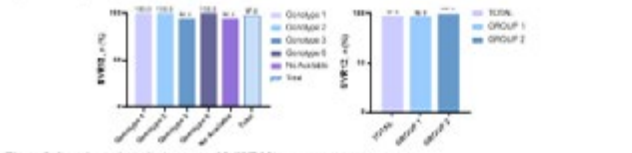

Figure 3. Sustained virological response 12 (SVR12) across genotypes and groups
SVR12, HCV RNA < LLOQ 12 weeks after cessation of therapy.

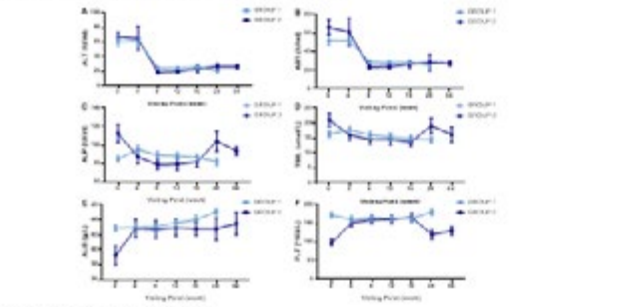

Figure 5. Changes of serological indices.
(A)ALT, (B)AST, (C)ALP, (D)TBIL, (E)ALB, (F)PLT.

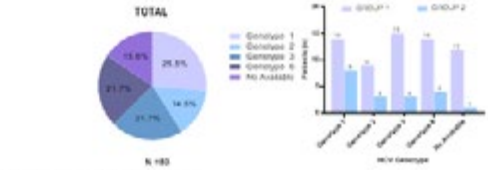

Figure 2. Prevalence of HCV genotype
GROUP 1, HBV/HCV co-infection patients without cirrhosis (n=64); GROUP 2, HBV/HCV co-infection patients with compensated cirrhosis (n=19)

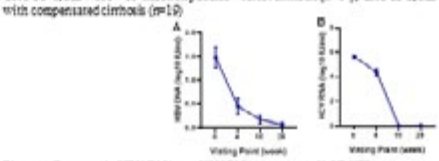

Figure 4. Decrease in HBV DNA and HCV RNA at the end of SOF/VEL treatment.
HBV DNA and HCV RNA were decreased in HBV/HCV co-infection patients(n=83) at the end of SOF/VEL treatment.
(A)HBV DNA; (B)HCV RNA.

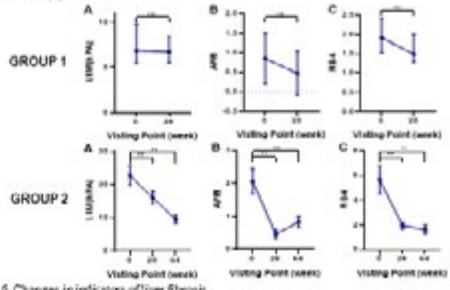

Figure 6. Changes in indicators of liver fibrosis.
(A) LSM, (B) APRI, (C) FIB-4 in HBV/HCV co-infection patients without cirrhosis (GROUP 1), (D) LSM, (E) APRI, (F) FIB-4 in HBV/HCV co-infection patients with compensated cirrhosis (GROUP 2). Results were compared by paired-samples nonparametric test. *P < 0.05, **P < 0.01

Disclosures: Yifan Han: Nothing to Disclose, Ning Lin: Nothing to Disclose, Dazhi Zhang: Nothing to Disclose, Zuxiong Huang: Nothing to Disclose, Minghua Su: Nothing to Disclose, Jiawei Geng: Nothing to Disclose, Zhili Wen: Nothing to Disclose, Xiaobo Lu: Nothing to Disclose, Weize Zuo: Nothing to Disclose, Hong You: Nothing to Disclose, Yuemin Nan: Nothing to Disclose, Liting Zhang: Nothing to Disclose, Liaoyun Zhang: Nothing to Disclose, Qian Kang: Nothing to Disclose, Hongyu Chen: Nothing to Disclose, Zhan Zeng: Nothing to Disclose, yanyan yu: Nothing to Disclose, Xiaoyuan Xu*: Nothing to Disclose

0031 | IMMUNE CHECKPOINT B7-H4 PROMOTES CHOLANGIOCARCINOMA GROWTH VIA TGFβ-INDUCED STROMAL REMODELING, UNVEILING A NOVEL *TARGETABLE* TUMOR-STROMA AXIS

Emily Bramel[1] *Matias Facciuto*[2] *Miguel Torres-Martin*[3] *Eric Park*[2] *Romain Donne*[2] *Ramja Sritharan*[2] *Li Chen*[4] *Sumera Ilyas*[5] *Mathieu Petitjean*[4] *Anna Tocheva*[2] *Swan Thung*[6] *Alexander Tsankov*[2] *Amaia Lujambio*[2] *Daniela Sia*[2]

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Background: Intrahepatic Cholangiocarcinoma (iCCA) is a desmoplastic cancer with largely ineffective therapies. Our recent analysis classified iCCAs into 5 classes, with both *immune hot* and *cold* tumors. Notably, we discovered that the immune checkpoint *B7h4* was upregulated in a large fraction of iCCAs, where it was expressed on the tumor cell membrane and intracellularly. While it is known that membrane B7h4 inhibits T cells, *the functions of intracellular B7h4 remain undefined.* Our goal is to define the mechanisms underpinning the tumor-promoting role of B7h4 in iCCA and translate this knowledge into novel therapies. **Methods:** We analyzed B7h4 expression and performed IHC for CD8, FOXP3, and CD68 in our genomically-annotated human cohort (n=127, GSE33327). Gene set enrichment analysis and immune deconvolution (CIBERSORTx) were performed to unveil pathways and immune composition in B7h4 high vs low tumors. Cancer associated fibroblast (CAF) subtypes and cell-cell interactions were identified using available scRNAseq data (GSE151530). The NICD1/AKT1 mouse model was generated by co-expression of activated *Akt1* and *Notch1* using hydrodynamic tail vein injection. To achieve B7h4 knockout (KO) *in vivo*, *Nicd1* and *Akt1* vectors were modified to express Cas9 and a B7h4 or scramble sgRNA for B7h4. Single fiber analysis of sirius red staining was performed with the FibroNest™ AI-based platform. *In vitro*, we used a cell line derived from NICD1/AKT1 tumor-bearing mice (NAK) and the SB1 cell line to create stable B7h4 KO or overexpression (OE) lines, respectively. Altered pathways downstream of

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B7h4 were identified by RNA-seq and validated by qPCR, western blot, and ELISA. **Results:** B7h4 was highly expressed in ~60% of iCCAs, mainly cold tumors. B7h4^{hi} tumors showed enrichment of TGFβ and NOTCH pathways (FDDR<0.05), low immune infiltration, and abundance of Tregs and M2 macrophages (p<0.05). B7h4^{hi} tumors showed a unique CAF composition, with enrichment of myofibroblastic and inflammatory CAFs and several interactions involved in stroma remodeling. KO of *B7h4* in NICD1/AKT1 mice significantly prolonged survival and profoundly altered the stroma with reduced size and complexity of collagen fibers in WT C57BL/6J and T cell-deficient *Rag2-KO* mice. Mechanistically, in addition to the membrane, B7h4 localizes intracellularly at the ER and its OE increases expression of the docking receptor for latent-TGFβ1, GARP, whose stability and activity are controlled by HSP90, a known B7h4 interactor. As such, B7h4 promotes the release of TGFβ1 and activation of the SMAD2/3 pathway, thereby increasing the deposition of collagen. Combination strategies targeting tumor-stroma interactions are being investigated *in vivo*. **Conclusion:** We identified a B7h4-dependent tumor-stroma crosstalk that contributes to tumor growth in ~60% of iCCAs by altering the structure of the supporting desmoplasia. Our findings unveil new therapeutic opportunities for iCCA.

Disclosures: Emily Bramel: Nothing to Disclose, Matias Facciuto: Nothing to Disclose, Miguel Torres-Martin: Nothing to Disclose, Eric Park: Nothing to Disclose, Romain Donne: Nothing to Disclose, Ramja Sritharan: Nothing to Disclose, Li Chen: Nothing to Disclose, Sumera Ilyas: Nothing to Disclose, Mathieu Petitjean: Nothing to Disclose, Anna Tocheva: Nothing to Disclose, Swan Thung: Nothing to Disclose, Alexander Tsankov: Nothing to Disclose, Amaia Lujambio: Nothing to Disclose, Daniela Sia: Nothing to Disclose

0032 | CARVEDILOL IS ASSOCIATED WITH LOWER MORTALITY THAN OTHER NONSELECTIVE BETA BLOCKERS IN PATIENTS WITH CIRRHOSIS

Michael Mullarkey[1] Gerald Ogola[2] Sumeet Asrani[3] Michael Volk[1]

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Background: Recent practice guidelines from the American Association for the Study of Liver Disease (AASLD) recommend that carvedilol should be the preferred non-selective beta blocker (NSBB) in cirrhosis patients with portal hypertension, primarily due to carvedilol's anti-α-1-adrenergic activity, which causes a significantly greater decrease in the hepatic venous pressure gradient (HVPG) compared to other NSBBs. This recommendation is partly based on evidence showing superiority of carvedilol compared to other NSBBs (such as nadolol and propranolol) in reducing adverse events in patients with gastroesophageal varices. While carvedilol has shown promise in these studies compared to other NSBBs, most of the data available relies on clinically impractical surrogates such as HVPG measurements, or is narrowly focused on variceal bleeding. There is limited head-to-head data comparing carvedilol to other NSBBs in the real-world setting, evaluating broader clinical endpoints such as incidence of new decompensations and overall mortality rate. Our study aims to compare carvedilol to other commonly prescribed NSBBs in this clinical context. **Methods:** We performed a retrospective case-control study from a large health system comparing patients with cirrhosis determined by ICD-10 algorithm and platelet count <150, who were treated with carvedilol versus nadolol or propranolol. Outcomes including hepatic decompensation (ascites, encephalopathy, variceal bleeding) and all-cause mortality were analyzed with adjustment for potential confounding using time-dependent Cox regression. **Results:** Among the 2302 cirrhosis patients meeting inclusion criteria, 1629 (70.8%) were on carvedilol and 673 (29.2%) were on nadolol or propranolol. In risk-adjusted analysis, patients on carvedilol had a lower hazard of hepatic decompensation (p<0.001) and lower hazard of mortality (p=0.031) compared to patients on propranolol/nadolol. The superiority of carvedilol applied equally to each decompensation type – ascites, encephalopathy, and variceal bleeding. **Conclusion:** Patients on carvedilol had a substantially lower adjusted risk of hepatic decompensation and moderately lower adjusted risk of mortality when compared to patients on nadolol or propranolol. This finding persisted across a wide range of sensitivity analyses. When stratified by decompensation, patients on carvedilol were significantly less likely to develop variceal bleeding, ascites and hepatic encephalopathy. These findings support the use of carvedilol in patients with cirrhosis and clinically apparent portal hypertension, to decrease risk of hepatic decompensation and improve survival.

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Table 2. Cox-model (time-dependent)						
	Hepatic decompensation			Mortality		
Characteristic	HR[1]	95% CI[1]	p-value	HR[1]	95% CI[1]	p-value
Treatment						
Propranolol/Nadolol	1.00	—		1.00	—	
Carvedilol	**0.54**	**0.46, 0.64**	**<0.001**	**0.75**	**0.58, 0.97**	**0.031**
Age (years)						
49 or less	1.00	—		1.00	—	
50-59	1.06	0.82, 1.38	0.64	1.35	0.85, 2.14	0.20
60+	0.98	0.78, 1.24	0.86	1.86	1.23, 2.81	0.004
Sex						
Female	1.00	—		1.00	—	
Male	1.15	0.99, 1.32	0.063	1.07	0.88, 1.29	0.50
Race						
White	1.00	—		1.00	—	
Black	1.04	0.84, 1.29	0.72	0.91	0.70, 1.19	0.49
Other	1.11	0.83, 1.50	0.48	0.98	0.64, 1.51	0.94
Platelets per 50 units	0.82	0.73, 0.91	<0.001	0.74	0.64, 0.85	<0.001
Portal hypertension (ICD-10)	7.06	5.99, 8.31	<0.001	0.63	0.50, 0.79	<0.001
MELD score	1.02	1.01, 1.03	<0.001	1.08	1.07, 1.09	<0.001
Systolic BP (first)						
<100	1.00	—		1.00	—	
100-<120	0.82	0.55, 1.23	0.34	0.87	0.55, 1.37	0.54
120-<130	0.61	0.41, 0.91	0.014	0.66	0.42, 1.04	0.073
130-<140	0.79	0.53, 1.17	0.24	0.71	0.45, 1.13	0.15
140+	0.77	0.52, 1.13	0.18	0.74	0.47, 1.14	0.17
Charlson's Comorbidity Index (weighted)						
1 or less	1.00	—		1.00	—	
2	0.80	0.53, 1.23	0.31	1.00	0.51, 1.94	0.99
3	0.96	0.65, 1.41	0.82	1.39	0.79, 2.42	0.25
4	1.29	0.88, 1.90	0.19	1.74	0.99, 3.08	0.056
5+	1.67	1.26, 2.21	<0.001	2.17	1.35, 3.50	0.001
[1]HR = Hazard Ratio, CI = Confidence Interval						

Disclosures: Michael Mullarkey: Nothing to Disclose, Gerald Ogola: Nothing to Disclose, Sumeet Asrani: Nothing to Disclose, Michael Volk: Nothing to Disclose

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0033 | ABDOMINAL AORTIC CALCIFICATION – A NOVEL CARDIAC RISK PREDICTION TOOL IN LIVER TRANSPLANTATION ★

Benjamin Cailes[1] Numan Kutaiba[1] Omar Farouque[1] Avik Majumdar[1] Thalys Rodrigues[1] Anees Enayati[1] Layal Abdelganne[1] Shannon McNamara[1] Nikki Garrard[1] Ali Al-Fiadh[1] Terase Lancefield[1] Matias Yudi[1] Mark Horrigan[1] Julian Yeoh[1] Adam Testro[1] Marie Sinclair[2] Ruth Lim[1] Paul Gow[1] Anoop Koshy[1]

[1]Austin Health, [2]Austin Hospital

Background: Cardiovascular disease is a leading cause of postoperative morbidity and mortality following liver transplantation (LT). Presence of abdominal aortic calcification (AAC) has been linked to cardiovascular events in the general population. We investigated whether AAC on pre-transplant computed tomography (CT) predicts major adverse cardiovascular events (MACE) post-LT. **Methods:** Consecutive LT patients between 2010-2018 from the Victorian Liver Transplant Unit (Australia) were included. Extent of AAC was quantified in a blinded fashion, with high AAC defined as a calcium score of ≥500. MACE was defined as any recorded episodes of acute coronary syndrome (ACS), ventricular arrhythmia, decompensated heart failure, or stroke. The primary outcome was post-LT MACE at 30 days and the secondary outcome was all-cause mortality at maximal follow-up. **Results:** Of 461 patients undergoing LT, 350 had suitable CTs for analysis, of which 90 (25.7%) had also undergone CT coronary angiography. High AAC was identified in 98 patients (28.0%). This finding demonstrated a moderate correlation with high coronary artery calcium score (CACS) ≥400 (r=0.52, p<0.001). Fifty-eight MACE occurred in 42 patients (12.0%) within 30-days. High AAC was associated with increased risk of 30-day MACE (OR=2.68 (95%CI 1.39-5.17), p=0.004) and long-term mortality (HR=2.52 (95%CI 1.29-4.92), p=0.007) at a median follow-up of 4.0 years. In addition, high AAC predicted an increased risk of ACS (OR 3.80 (95%CI 1.18-12.27), p=0.025), heart failure (OR 3.07 (95%CI 1.21-7.80), p=0.020) and atrial fibrillation (OR 2.04 (95%CI 1.02-4.07), p=0.048), with a trend to increased prevalence of ventricular arrhythmia (OR 2.67 (95%CI 0.84-8.50), p=0.10). Following multivariate analysis, high AAC remained a strong independent predictor of MACE (OR=3.49, 95%CI 1.21-10.06, p=0.021). Addition of AAC to the revised cardiac risk index (RCRI) improved model fit for predicting MACE (net reclassification improvement of 52.7% (p<0.001)). **Conclusion:** This study demonstrates for the first time that high AAC on routine abdominal CT scans is associated with a 3-fold increased risk of 30-day MACE post-LT, and improves cardiovascular risk prediction compared to traditional risk scores. Quantification of AAC may offer a simple method of improving cardiovascular risk assessment and implementation of preventative strategies in liver transplant patients, using pre-existing scans without additional cost or patient risk.

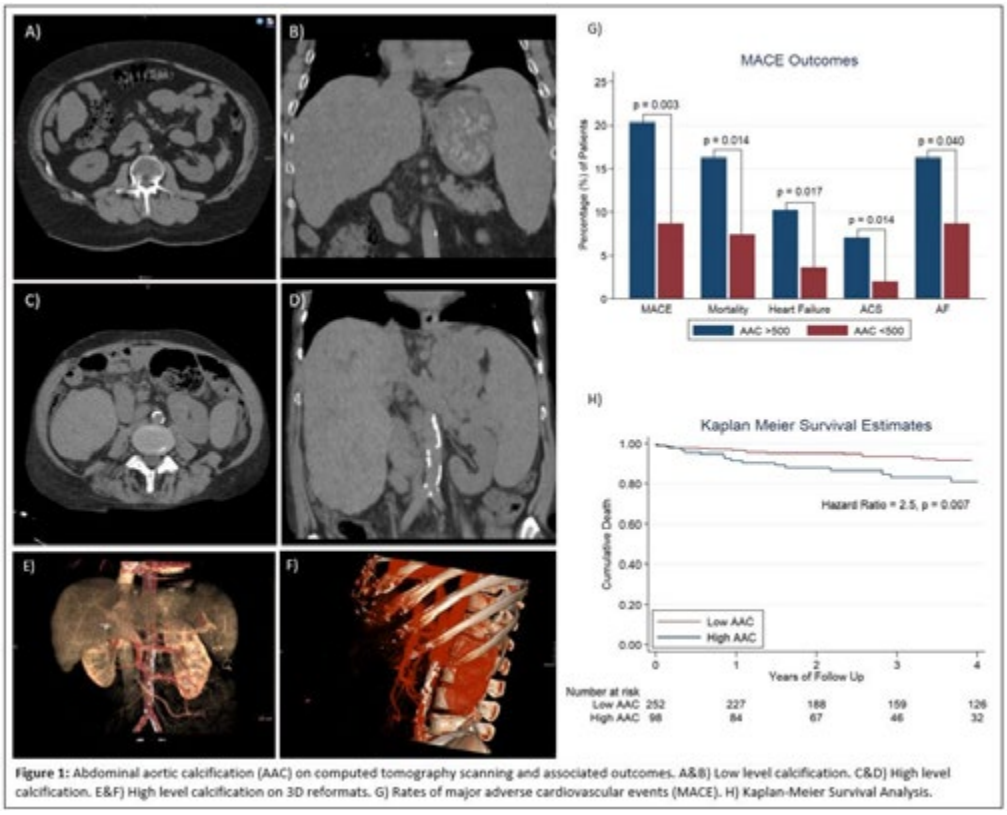

Figure 1: Abdominal aortic calcification (AAC) on computed tomography scanning and associated outcomes. A&B) Low level calcification. C&D) High level calcification. E&F) High level calcification on 3D reformats. G) Rates of major adverse cardiovascular events (MACE). H) Kaplan-Meier Survival Analysis.

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Disclosures: Benjamin Cailes: Nothing to Disclose, Numan Kutaiba: Nothing to Disclose, Omar Farouque: Nothing to Disclose, Avik Majumdar: Nothing to Disclose, Thalys Rodrigues: Nothing to Disclose, Anees Enayati: Nothing to Disclose, Layal Abdelganne: Nothing to Disclose, Shannon McNamara: Nothing to Disclose, Nikki Garrard: Nothing to Disclose, Ali Al-Fiadh: Nothing to Disclose, Terase Lancefield: Nothing to Disclose, Matias Yudi: Nothing to Disclose, Mark Horrigan: Shimadzu Corporation: Grant/Research Support, Julian Yeoh: Nothing to Disclose, Adam Testro: Nothing to Disclose, Marie Sinclair: Nothing to Disclose, Ruth Lim: Boehringer Ingelheim: Research support to my institution for a non-related project, Paul Gow: Nothing to Disclose, Anoop Koshy: Nothing to Disclose

0034 | MACHINE LEARNING RADIOMICS BASED ON CT TO PREDICT RESPONSE TO LENVATINIB PLUS PD-1 INHIBITOR FOR HEPATOCELLULAR CARCINOMA

Zhiyuan Bo[1] Zhengxiao Zhao[2] Xiaozai Xie[3] Yi Wang[3] Gang Chen[3]

[1]the First Affiliated Hospital of Wenzhou Medical University, [2]Zhejiang Chinese Medical Hospital, [3]Wenzhou Medical University

Background: Lenvatinib plus PD-1 inbibitor has been widely used for unresectable hepatocellular carcinoma (uHCC), meanwhile a complex heterogeneity leads to a limited response rate. We aimed to develop novel clinical feature-based and CT radiomic feature-based models through machine learning (ML) algorithms to predict efficacy of lenvatinib plus PD-1 inbibitor for uHCC. **Methods:** uHCC patients who received lenvatinib plus PD-1 inhibitor between 2018 and 2023 were recruited and assigned to training and testing set. Clinical data and pretreatment contrast-enhanced CT images were collected, and treatment response was idenfied by mRECIST guidelines. Arterial and venous phase CT images were segmented and radiomic features were extracted by python software. Six ML algorithms including logistic, random forest, neural network, support vector machine, Naïve Bayes and XGBoost were used to develop clinical feature-based and radiomic feature-based models. The ROC curves, calibration curves and decision curves analysis (DCA) curves were used to evaluate the predictive performance of ML radiomics models. **Results:** A total of 103 uHCC patients who received lenvatinib plus PD-1 inhibitor were included, including 82 in training set and 21 in testing set. Thirty-four patients showed partial response (33%), 44 showed stable disease (42.7%), and 25 showed progressive disease (24.3%). The overall response rate was 33%, and the DCR was 75.7%. Kaplan–Meier analysis showed that responders had a better OS (HR=2.5,95% CI:1.6-3.9,P<0.001) and PFS (HR=3.69,95% CI:2.22-6.12,P<0.001) than non-responders. A total of 224 radiomic features were extracted. The importance of radiomic features was ranked through mRMR algorithm and the top 12 most important features were selected for subsequent analysis. Clinical models based on 34 clinical features and radiomics models based on 12 radiomic features were constructed through six ML algorithms, respectively. The mean AUCs of clinical models were 0.85 in the training set and 0.79 in the testing set, while the mean AUCs of radiomic models were 0.94 in the training set and 0.74 in the testing set. The calibration and DCA curves also indicated satisfactory performance of ML models to predict the response to lenvatinib plus PD-1 inhibitor. **Conclusion:** Valuable clinical feature-based and radiomic feature-based models were constructed through ML algorithms to predict response to lenvatinib plus PD-1 inhibitor for uHCC. This shed new insight into developing new techniques to guide clinical decision making.

Disclosures: Zhiyuan Bo: Nothing to Disclose, Zhengxiao Zhao: Nothing to Disclose, Xiaozai Xie: Nothing to Disclose, Yi Wang: Nothing to Disclose, Gang Chen: Nothing to Disclose

0035 | WILMS TUMOR 1 AND HIF-1α INDUCE HEPATIC STELLATE CELL INVASION THAT DEVELOPS BRIDGING FIBROSIS IN CHRONIC LIVER INJURY

Michitaka Matsuda[1] Tatsuya Kanto[1] Ekihiro Seki[2]

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Background: Chronic liver injury induces the production and deposition of extracellular matrix (ECM) and its further remodeling develops Bridging fibrosis (BF). For the induction of BF, hepatic stellate cell (HSC) invasion plays a critical role, however, the underlying mechanism of HSC invasion and BF formation has not been fully understood. We investigated the mechanism of induction of the invasive HSCs and their downstream effector

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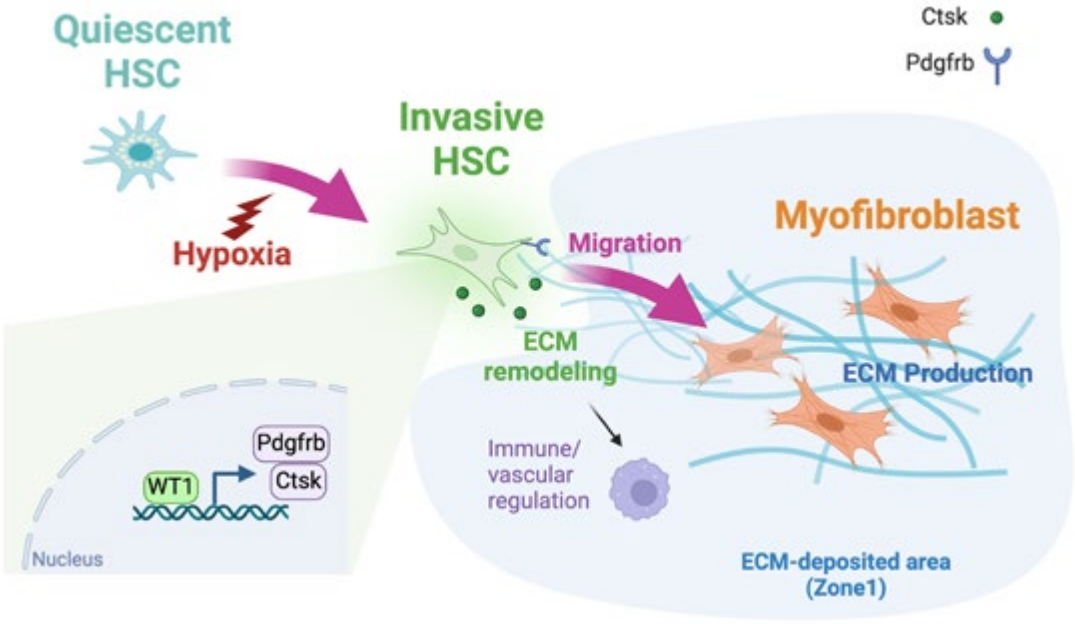
on BF formation by focusing on Wilms Tumor 1 (WT1) and HIF-1α. **Methods:** To examine the invasion and ECM remodeling capacity of HSCs, a 3D collagen-gel invasion assay was used. Transcriptomics of HSCs at the different invasion stages or with hypoxia were analyzed. HSC-specific WT1 and HIF-1α KO mice were generated and subjected to bile duct ligation (BDL) to induce BF in mouse livers. Single-cell RNA-seq (scRNA-seq) and GeoMx spatial transcriptomics were used. With GeoMx, we compared transcriptomics between Zones 1, 2, and 3. The zone-specific transcriptomic was integratively analyzed with scRNA-seq (spatio-temporal single-cell analysis). **Results:** Spatio-temporal single-cell analysis revealed a dynamic change in migration, invasion, and ECM production in fibrotic cell populations. ECM-producing myofibroblastic HSCs were enriched in Zone 1 while migrative and ECM-remodeling HSCs emerged in Zone 2 of the early BF. Notably, the hypoxic gene signature is enriched in Zones 1 and 2 in fibrotic livers in contrast to what we observed in normal livers (Zone 3). Collagen-gel invasion assay indicated that HSCs invasion is required for full activation of HSCs that produce robust ECM. Transcription factor (TF) enrichment analysis revealed WT1 is the most enriched TF in fully invaded HSCs and HSCs under hypoxia. Promoter analysis revealed that WT1 is regulated by HIF-1α. WT1 or HIF-1α knockdown inhibited HSC invasion *in vitro*. HSC-specific WT1 or HIF-1α KO mice failed to develop BF after the BDL. Transcriptomic analysis further indicated Cathepsin K (Ctsk) as a downstream effector of WT1 for HSC invasion and ECM production. Ctsk inhibitor Odanacatib prevented BF formation after the BDL. **Conclusion:** Spatio-temporal single cell analysis of BF liver and functional assay of HSC defined unique invasive phenotype of HSCs that is distinguished from ECM-producing fully activated HSC. The invasive HSCs and BF formation are regulated by TF WT1 and HIF-1α. We also found that Ctsk is a downstream effector of WT1, which can be a promising therapeutic target for liver fibrosis.



Disclosures: Michitaka Matsuda: Nothing to Disclose, Tatsuya Kanto: Nothing to Disclose, Ekihiro Seki: Nippon Zoki: Research Grant Support, Novonordisc: Consultant

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0036 | CIRCULATING ACTIVATED TISSUE RESIDENT MEMORY CD8+ T CELL POPULATION IS A UNIQUE FEATURE OF PEDIATRIC ACTIVATED T-CELL ACUTE LIVER FAILURE AND HEPATITIS ASSOCIATED APLASTIC ANEMIA ★

Tamir Diamond[1] Catherine Chapin[2] Caroline Diorio[1] Timothy Olson[1] Sarah Henrickson[1] Michelle Lau[1] niansheng chu[1] Anna Banc-Husu[3] Jaime Chu[4] M Kyle Jensen[5] Daniel Leung[6] Amrita Narang[7] Katelyn Saarela[8] Beth Carter[9] Scott Elisofon[10] Rima Fawaz[11] Ryan Fischer[12] Steven Lobritto[13] Anna Peters[14] Norberto Rodriguez-Baez[15] Rene Romero[16] Philip Rosenthal[17] David Rudnick[18] James Squires[19] Shikha Sundaram[20] Kyla Tolliver[21] Pamela Valentino[8] Zemin Su[22] Simon Horslen[23] Kathleen Loomes[1] Estella Alonso[2] Edward Behrens[1]

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Background: Pediatric Activated T-cell Acute Liver Failure (TC-PALF) is the most common cause of non-tylenol PALF with poor transplant-free survival. Livers in TC-PALF are infiltrated by effector cytotoxic T lymphocytes with markers suggestive of tissue residence memory (CD8 Trm), and an interferon gamma (IFNg) transcriptional signature. TC-PALF is associated with severe aplastic anemia (AA-Hep) in 8% of cases. The PALF-Immune Response Network (PALF-IRN) and the prospective TReatment for ImmUne Mediated PathopHysiology (TRIUMPH) clinical trial (NCT04862221) aims to address this immune pathology. Open questions in TC-PALF remain the source of IFNg, the transcriptional profile of CD8 Trm, and the degree of overlap of the immune phenotype with AA-Hep. This study addresses these questions using flow cytometry and single cell RNA sequencing (scRNAseq). **Methods:** Peripheral blood mononuclear cells (PBMC) from pediatric (age 1-18yo) patients from 4 groups were compared: 1) TC-PALF patients enrolled in TRIUMPH, 2) AA-Hep patients (ALT and/or AST 3 times upper limit of normal 6 months prior to development of aplastic anemia), 3) patients with aplastic anemia (AA) without hepatitis and 4) healthy age/sex matched controls (Healthy). Flow cytometry analysis included 7 TC-PALF, 5 AA-Hep, 3 AA and 5 healthy patients. scRNAseq analysis included 3 TC-PALF, 2 AA-Hep, 2 AA and 1 Healthy. No patients were exposed to immunomodulation prior to sample collection. **Results:** AA-Hep and TC-PALF patients share a unique CD8 T-cell population bearing markers of Trm (CD45RA-, CCR7lo, CD103+) and activation (HLA-DR) (Fig 1A) not seen in the AA or Healthy groups. Elevated CD8 T-cell perforin expression was only seen in the AA-Hep and TC-PALF groups (Fig. 1B). To transcriptionally characterize the significant population of circulating CD103+CD8 T-cells seen by flow, we examined these cells in the scRNAseq dataset. A clear CD8+ T-cell population in TC-PALF transcribed *ITGAE (*CD103*), ICOS, IFNG*, and *CD69* genes consistent with canonical Trm identity (Fig. 1C denoted in black dots), including expression of the Trm transcription factor *PRDM1.* scRNAseq additionally revealed *IFNG*-expressing CD8 T-cells in all disease states except Healthy, with the largest number in TC-PALF. **Conclusion:** TC-PALF and AA-Hep share a common phenotype of activated CD8 Trm expressing perforin. In TC-PALF, these cells express the bona fide Trm transcription factor *PRDM1* and the matching gene transcription of true Trm. IFNg producing CD8 cells are a shared feature of AA, AA-Hep and TC-PALF suggesting a source for this cytokine, and in particular in Trm in TC-PALF. Circulating perforin positive CD8 Trm cells mirror the populations observed in liver biopsies and could potentially be a less invasive biomarker for disease.

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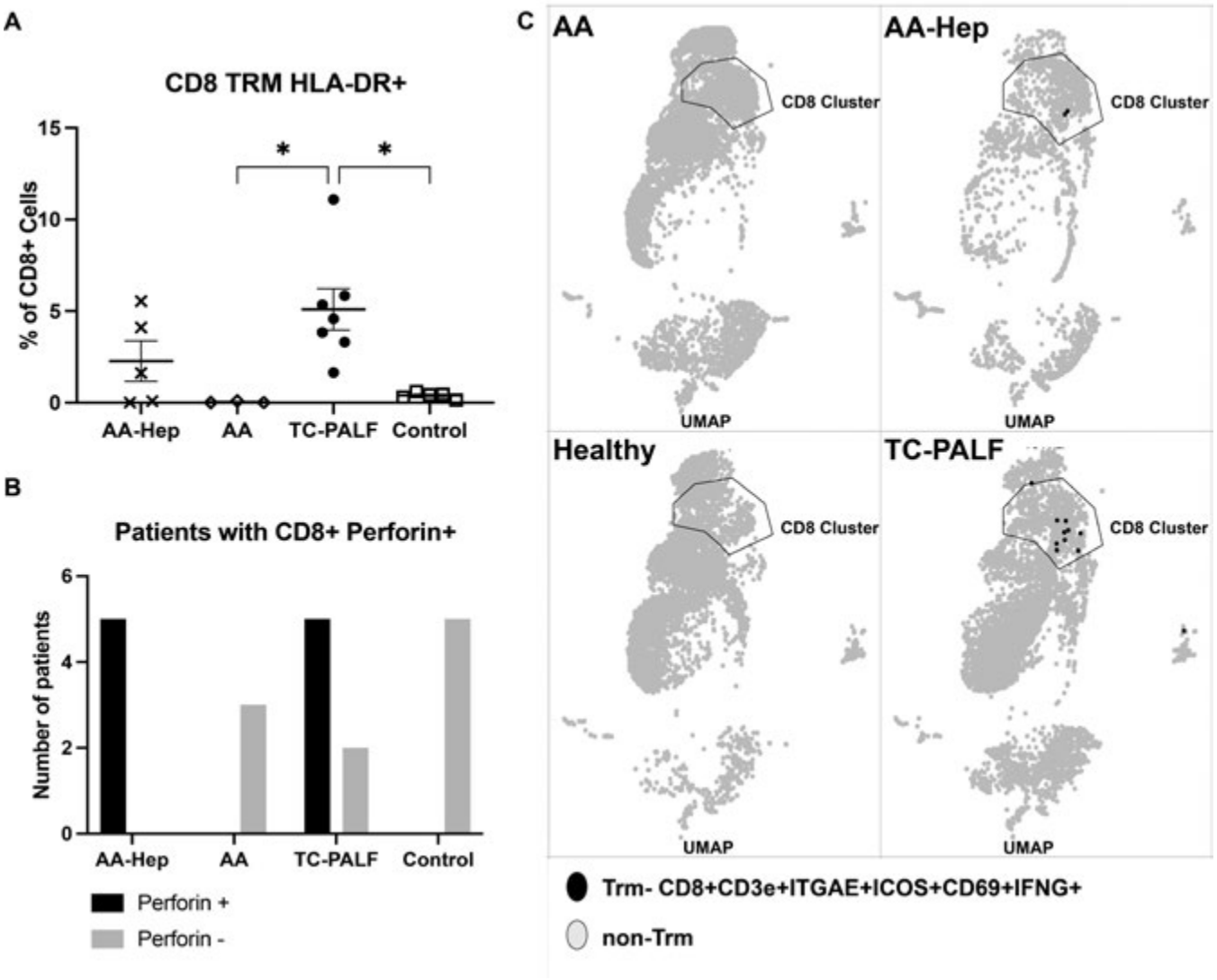

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0037 | PHARMACOKINETICS, SAFETY AND EFFICACY OF THE NOVEL NON-BILE ACID FXR AGONIST FXR314 IN PATIENTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS: RESULTS FROM A PHASE 2 STUDY

Eric Lawitz[1] Kathryn Jean Lucas[2] Kris Kowdley[3] Naim Alkhouri[4] Stephen Harrison[5] Fabrice Piu[6]

[1]Texas Liver Institute, [2]Diabetes & Endocrinology Consultants, PC, [3]Liver Institute Northwest, [4]Arizona Liver Health, [5]University of Oxford, [6]Organovo, Inc

Background: Farnesoid X receptor (FXR) agonism has demonstrated clinical utility for the treatment of non-cirrhotic metabolic dysfunction-associated steatohepatitis (MASH) but clinical development has been hampered by limited efficacy and adverse events (pruritus, dyslipidemia). FXR314 is a novel non-bile acid FXR agonist with a unique chemotype and functionally distinct from other FXR agonists. **Methods:** A double-blind, placebo-controlled study of FXR314 was conducted in patients with a confirmed diagnosis of MASH (via biopsy, MRE or TE Fibroscan). A total of 214 patients were randomized in a 1:1:1 ratio to either 3 mg or 6 mg oral once daily FXR314, or placebo. Treatment was administered for 16 weeks with a 4-week follow-up period (NCT04773964). **Results:** Patients had a mean BMI of 36.6 kg/m^2 with 37% exhibiting type 2 diabetes, mean liver stiffness was 10.20 kPa and CAP 351.0 dB/M by TE Fibroscan. FXR314 plasma levels achieved Cmax at 4 hrs with a half-life of 60-70 hrs across both doses, with steady state reached within 14 days. Dose-dependent reduction in C4 of 59% and 71% and increases in FGF19 plasma levels of 186% and 363% were noted with 3 mg and 6 mg FXR314, respectively. Statistically significant reduction in liver fat content from baseline (MRI-PDFF) was obtained throughout the study. Least square mean percent liver fat reduction at end of treatment was 22.8% (p=0.0010) with 3 mg and 17.5% (p=0.0267) with 6 mg FXR314, compared to 6.1% in the placebo group. Proportion of patients with MRI-PDFF reduction of ≥30% was 29.2% (p=0.0023), 32.2% (p=0.0020), 9.5% in 3mg, 6mg FXR314 and placebo, respectively. Maximum decline from baseline in ALT was 11.0 U/L in 3 mg, 15.5 U/L in 6 mg FXR314 versus 8.1 U/L in placebo. FXR314 was found to be safe and well tolerated. Mild to moderate treatment-emergent adverse events (TEAEs) were similar across the 3 mg (68.1%), 6 mg FXR314 (73.2%) and placebo (67.6%). Drug-related treatment discontinuation was minimal and similar across treatment arms. There was no evidence of FXR class adverse events with FXR314 including pruritus (2.8% in 3 mg, 4.2% in 6 mg FXR314 vs 2.8% in placebo) and LDL-C elevation (1.5% in 3 mg, 4.5% in 6 mg FXR314 vs -3.6% in placebo). **Conclusion:** FXR314, administered orally once daily for 16 weeks, demonstrated dose dependent target engagement, improvement in hepatic fat and biochemical markers and was safe and well tolerated with a unique safety profile compared to other FXR agonists.

Disclosures: Eric Lawitz: Nothing to Disclose, Kathryn Jean Lucas: Nothing to Disclose, Kris Kowdley: Boston Scientific: Grant/Research Support, Corcept: Grant/Research Support, CymaBay: Grant/Research Support, Genfit: Grant/Research Support, Gilead: Grant/Research Support, GSK: Grant/Research Support, Hanmi: Grant/Research Support, Intercept: Grant/Research Support, Ipsen: Grant/Research Support, Janssen: Grant/Research Support, Madrigal: Grant/Research Support, Mirum: Grant/Research Support, Novo Nordisk: Grant/Research Support, NGM: Grant/Research Support, Pfizer: Grant/Research Support, Pliant Therapeutics: Grant/Research Support, Terns: Grant/Research Support, Viking: Grant/Research Support, Zydus: Grant/Research Support, 89bio Inc: Grant/Research Support, UpToDate: Royalties or patent beneficiary, CymaBay: Consultant, Enanta: Consultant, Genfit: Consultant, Gilead: Consultant, HighTide: Consultant, Inipharm: Consultant, Intercept: Consultant, Ipsen: Consultant, Madrigal: Consultant, Mirum: Consultant, NGM: Consultant, Pliant Therapeutics: Consultant, Pfizer: Consultant, Protagonist: Consultant, Zydus: Consultant, 89bio Inc: Consultant, AbbVie: Payment or honoraria, Gilead: Payment or honoraria, Intercept: Payment or honoraria, US Department of Justice: Payment for expert testimony, CTI: Advisor, Medpace: Advisor, Labcorp: Advisor, Worldwide Clinical Trials: Advisor, Inipharm: Stock – privately held company, Velacur: Received equipment, materials, drugs, medical writing, gifts, Naim Alkhouri: Madrigal: Grant/Research Support, Madrigal: Speaking and Teaching, Novo Nordisk: Consulting, Novo Nordisk: Grant/Research Support, Gilead: Grant/Research Support, Corcept: Grant/Research Support, Boehringer Ingelheim: Grant/Research Support, Echosens: Speaking and Teaching, Perspectum: Consultant, Cima: Consultant, Fibronostics: Consultant, 89Bio: Grant/Research Support, Inventiva: Grant/Research Support, Merck: Grant/Research Support, Pfizer: Grant/Research Support, Ipsen: Speaking and Teaching, Intercept: Speaking and Teaching, Madrigal: Consulting, Research Funding, Novo Nordisk: Consulting, Research Funding, Inventiva: Research Funding, Boehringer Ingelheim: Consulting, Research Funding, Corcept: Research Funding, Ipsen: Consulting, Research Funding, Gliead: Consulting, Research Funding, Speaking, Perspectum: Consulting, Research Funding, Cima: Advisor, 89Bio: Consulting, Research Funding, Akero:

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Grant/Research Support, Arbutus: Grant/Research Support, GSK: Grant/Research Support, Regeneron: Grant/Research Support, AstraZeneka: Grant/Research Support, Stephen Harrison: Nothing to Disclose, Fabrice Piu: Organovo Inc.: Employee

0038 | FECAL PROTEOMICS LINKS NEUTROPHIL DEGRANULATION WITH MORTALITY IN PATIENTS WITH ALCOHOL-ASSOCIATED HEPATITIS ◆ ★

Henriette Kreimeyer[1] Carlos Gonzalez[1] Marcos Fondevila[1] Cynthia Hsu[1] Phillipp Hartmann[2] Xinlian Zhang[1] Peter Starkel[3] Francisco Bosques[4] Elizabeth Verna[5] Juan Abraldes[6] Robert Brown[7] Victor Vargas[8] Jose Altamirano[9] Juan Caballeria[10] Debbie Shawcross[11] Alexandre Louvet[12] Michael Lucey[13] Philippe Mathurin[12] Guadalupe Garcia-Tsao[14] Ramon Bataller[15] Susan Mayo[16] David Gonzalez[1] Bernd Schnabl[2]

[1]University of California San Diego, [2]University of California, San Diego, [3]Cliniques Universitaires Saint Luc, [4]Universidad Autonoma de Nuevo Leon, [5]Columbia University Medical Center, [6]University of Alberta, [7]Weill Cornell Medicine, [8]Universitat Autònoma de Barcelona, [9]University of Barcelona, [10]Hospital Clinic Barcelona, [11]Kings College London, [12]Hôpital Huriez, Lille, [13]University of Wisconsin, [14]Yale University, [15]University of Pittsburgh, [16]AlcHepNet

Background: Patients with alcohol-associated hepatitis (AH) have a high mortality. Alcohol exacerbates liver damage by inducing gut dysbiosis, bacterial translocation and inflammation, which is characterized by increased numbers of circulating and hepatic neutrophils. We aimed to characterize the fecal proteome of patients with AH and to elucidate its clinical importance. **Methods:** We performed high-quantitative fidelity Tandem Mass Tag proteomics analysis using LC/MS to characterize the fecal proteome in patients with AH (InTeam cohort; n=80), alcohol use disorder (AUD, n=19), and controls (n=20). Overrepresentation Analysis using Reactome Pathway and Gene ontology were performed. A fecal biomarker and its prognostic effect were validated by ELISA in fecal samples from patients with AH, who were recruited in a second and independent multicenter cohort (AlcHepNet; n=70). **Results:** Fecal proteomic profiles showed distinct patterns between controls, patients with AUD and AH (Bray-Curtis: P=0.001). Overrepresentation Analysis demonstrated that 22.5 – 40% of all upregulated proteins belong to the neutrophil degranulation pathway across all three groups (Fig. 1A). The neutrophil degranulation pathway may also be associated with disease severity, as it was the most upregulated pathway in AH patients that died during follow-up (P=0.002). We then performed a focused analysis including proteins that showed significant differences between all three groups, between patients with AH and AUD patients and a progressive increase or decrease in accordance with disease severity. Twelve proteins, including myeloperoxidase (MPO), fulfilled these criteria. The majority of proteins showing a progressive increase in accordance with ALD severity are expressed in neutrophils, while proteins that are decreased are expressed in muscle. Fecal MPO, a protein which is released from azurophilic granules upon neutrophil activation, predicts 60-day survival in patients with AH (high MPO level HR: 2.84, logrank: P=0.035). These results were confirmed by fecal ELISA in a validation cohort of patients with AH (Fig. 1B, high MPO: HR: 2.86e+08, logrank: P=0.037). There is no correlation of fecal MPO with serum leukocytes or hepatic neutrophil infiltration (R=-0.023, P=0.85; R= 0.082, P=0.62). **Conclusion:** Proteins linked to neutrophil degranulation are more abundant in patients with AH compared to AUD and controls and are associated with disease severity. MPO can predict survival and can serve as a prognostic noninvasive marker. Proteins linked to neutrophil degranulation are more abundant in patients with AH compared to AUD and controls and are associated with disease severity. MPO can predict survival and can serve as a prognostic noninvasive marker.

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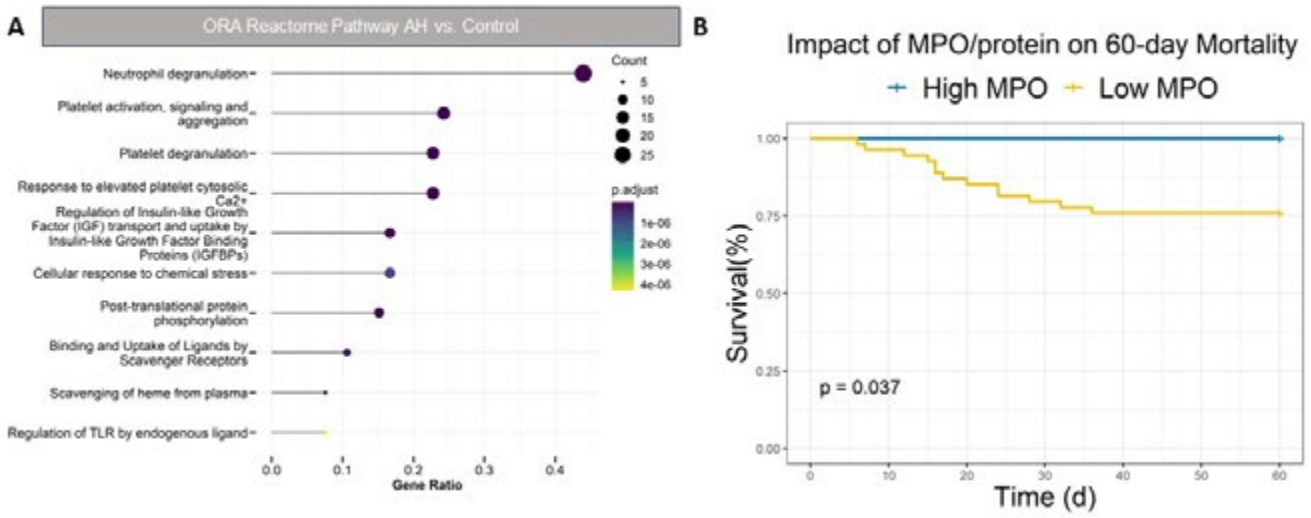

Disclosures: Henriette Kreimeyer: Nothing to Disclose, Carlos Gonzalez: Nothing to Disclose, Marcos Fondevila: Nothing to Disclose, Cynthia Hsu: Nothing to Disclose, Phillipp Hartmann: Nothing to Disclose, Xinlian Zhang: Nothing to Disclose, Peter Starkel: Nothing to Disclose, Francisco Bosques: Nothing to Disclose, Elizabeth Verna: Nothing to Disclose, Juan Abraldes: Gilead: Grant/Research Support, 89bio: Consultant, Boston Pharmaceuticals: Consultant, Novo Nordisk: Consultant, Boehringer Ingelheim: Consultant, Astra Zeneca: Consultant, Agomab: Consultant, Terumo: Speaking and Teaching, Cook: Grant/Research Support, Robert Brown: Consultant relationship with Intercept; Has not ended; Consultant relationship with Gilead; Has not ended; Consultant relationship with Abbvie; Has not ended; Consultant relationship with Madrigal; Has not ended; Consultant relationship with GSK; Has not ended; Consultant relationship with eGenesis; Has not ended; Consultant relationship with mirum; Has not ended, Victor Vargas: Ipsen: Advisor, Orphalan: Speaking and Teaching, Jose Altamirano: Nothing to Disclose, Juan Caballeria: Nothing to Disclose, Debbie Shawcross: Consultant relationship with EnteroBiotix; Has not ended; Advisor relationship with Genfit; Has not ended; Consultant relationship with Apollo Therapeutics; Has not ended; Grant/Research Support relationship with Norgine; Has not ended; Advisor relationship with MRM Health; Has not ended; Consultant relationship with Satellite Bio; Has not ended, Alexandre Louvet: Consultant relationship with Glaxo-Smith-Kline; Has not ended; Consultant relationship with Ipsen; Has not ended; Speaking and Teaching relationship with Astra-Zeneca; Has not ended; Speaking and Teaching relationship with Gilead; Has not ended; Speaking and Teaching relationship with AbbVie; Has not ended, Michael Lucey: Nothing to Disclose, Philippe Mathurin: Nothing to Disclose, Guadalupe Garcia-Tsao: Nothing to Disclose, Ramon Bataller: Nothing to Disclose, Susan Mayo: Nothing to Disclose, David Gonzalez: Nothing to Disclose, Bernd Schnabl: Grant/Research Support relationship with Prodigy Biotech; Has not ended; Grant/Research Support relationship with CymaBay Therapeutics; Has ended; Consultant relationship with Surrozen; Has ended; Grant/Research Support relationship with Intercept Pharmaceuticals; Has not ended; Stock â€“ privately held company relationship with Nterica Bio; Has not ended; Grant/Research Support relationship with Axial Biotherapeutics; Has ended; Consultant relationship with Ambys Medicines; Has ended; Grant/Research Support relationship with ChromoLogic; Has not ended; Consultant relationship with Mabwell Therapeutics; Has not ended

0039 | NADH-REDUCTIVE STRESS LINKS THE ANTIOXIDANT CULLIN3-RING E3 LIGASE-NRF2 AXIS TO REGULATION OF HEPATIC STEATOSIS AND INSULIN SENSITIVITY ◆

Lijie Gu[1] *Yanhong Du*[1] *Jianglei Chen*[1] *Mohammad Nazmul Hasan*[1] *Tiangang Li*[1]

[1]*University of Oklahoma Health Sciences Center*

Background: Obesity and insulin resistance are major pathogenic drivers of metabolic dysfunction-associated steatotic liver disease (MASLD). Cullin RING E3 ligase (CRL) complexes have emerged as regulators of disease modifying pathways and attractive therapeutic targets. Among the 8 Cullin proteins, Cullin 3 (Cul3)-containing CRL (CRL3) has been implicated in the regulation of hepatic insulin sensitivity and oxidative stress, but how

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modulating hepatic CRL3 activity impacts the development of MASLD is unknown. **Methods:** We used AAV-TBG-cre to specifically delete hepatocyte Cul3 in obese mice. We used hyperinsulinemic-euglycemic clamp, comprehensive phenotyping, global metabolomics and transcriptomics to investigate the metabolic impacts of hepatic CRL3 loss-of-function and the underlying mechanisms. **Results:** Acute deletion of hepatocyte Cul3 in obese mice resulted in rapid resolution of liver steatosis. However, without simultaneous reduction of obesity, the remarkable resistance to developing steatosis in hepatocyte Cul3-deficient mice paradoxically caused profound systemic insulin resistance. Liver transcriptomics analysis discovered that hepatocyte Cul3 deficiency caused activation of the NRF2 transcriptional network because CRL3 mediated NRF2 protein turnover. Global metabolomics further revealed that NRF2 activation induced NAD^+-consuming detoxification enzymes aldehyde dehydrogenases to cause hepatic NADH-reductive stress, whereby a redox imbalance of high NADH/NAD^+ ratio reprogramed hepatic metabolism to prevent lipid accumulation in Cul3-deficient livers. Such hepatic metabolic maladaptation to obesity and insulin resistance increased ceramides and fatty acids, which worsened systemic insulin resistance in a vicious cycle. Hepatic lipid accumulation was restored, and insulin resistance was attenuated when NRF2 activation and NADH-reductive stress were abolished in hepatocyte Cul3/Nrf2 double knockout mice. **Conclusion:** This study revealed a critical role of CRL3 in hepatic metabolic regulation and identified NRF2-mediated NADH-reductive stress as a previously unrecognized downstream effector modulating the development of hepatic steatosis. This study underscores the adaptive nature of developing steatosis under obesity, and suggests that therapeutic reduction of hepatic steatosis needs to be accompanied with weight loss and insulin sensitization to prevent potentially detrimental hepatic maladaptive responses.

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0040 | APPLYING THE METABOLIC DYSFUNCTION ASSOCIATED STEATOTIC LIVER DISEASE (MASLD) NOMENCLATURE WITH NATURAL LANGUAGE PROCESSING IN A NATIONAL COHORT

Binu John[1] Dustin Bastaich[2] Catherine Mezzacappa[3] Raphaella Ferreira[4] Austen Hentschel[5] Andres Samos[5] Nadim Mahmud[6] Tamar Taddei[3] David Kaplan[7] Marina Serper[8] Bassam Dahman[2]

[1]Miami VA and University of Miami, [2]Virginia Commonwealth University, [3]Yale University, [4]Larkin Community Hospital, [5]Florida International University, [6]Hospital of the University of Pennsylvania, [7]University of Pennsylvania, [8]University of Pennsylvania Health System

Background: Although metabolic dysfunction-associated steatotic liver disease (MASLD) and MASLD with increased alcohol intake (MetALD) are identified as a separate clinical entities, tools to identify patients from electronic health records are lacking. Applying Natural Language Processing (NLP) to unstructured text to identify steatosis, combined with laboratory and pharmacy data, is a potential method for large-scale identification of patients with MASLD and MetALD using the EHR. The study's primary aim was to define and validate MASLD, MetALD and ALD phenotypes using NLP, laboratory and pharmacy data in a large, national cohort within a single EHR system. **Methods:** In this **r**etrospective study of the Veterans Analysis of Liver Disease (VALID) cohort, assembled from 1/1/2013 to 12/31/2022, a rule-based NLP algorithm searched records for imaging/elastography evidence of hepatic steatosis. Steatosis was defined as participants with a controlled attenuation parameter (CAP) of >288 dB/s or documented steatosis on abdominal imaging performed for any reason. We applied an NLP algorithm to identify steatosis by examining the proximity of steatosis related terms, if the term "fatty" was within 150 characters of "liver" and if the term "steatosis" was present without "no" within 10 characters beforehand. Other terms searched for were "echogenic", "fatty infiltration", "hyperechogenic", "hypoattenuation", "coarse echotexture", "hyperechoic", and "heterogeneous" near "echotexture" (see Figure). This was combined with identification of cardiometabolic risk factors (CMRF) and harmful alcohol use. Algorithm-derived diagnoses of MASLD, MetALD, ALD, and no SLD were validated using a blinded review of over 700 randomly selected charts **Results: Results:** Among 818,892 Veterans with abdominal imaging, the algorithm identified 299,259 participants with MASLD (36.5%), 99,163 with MetALD (12.1%), 38,552 (4.7%) with ALD. The NLP algorithm had a high correlation with steatosis on chart review, with a kappa of 0.86 (95% CI 0.82-0.90), sensitivity of 0.96 and specificity of 0.90. There was a high level of inter-rater reliability between NLP and chart review (Kappa=0.90, 95%CI 0.85-0.95) for the identification of CMRF, with a sensitivity of 0.997 and specificity of 0.86. Classification of MASLD, MetALD, ALD and no SLD by the algorithm also showed high correlation with chart review, with a

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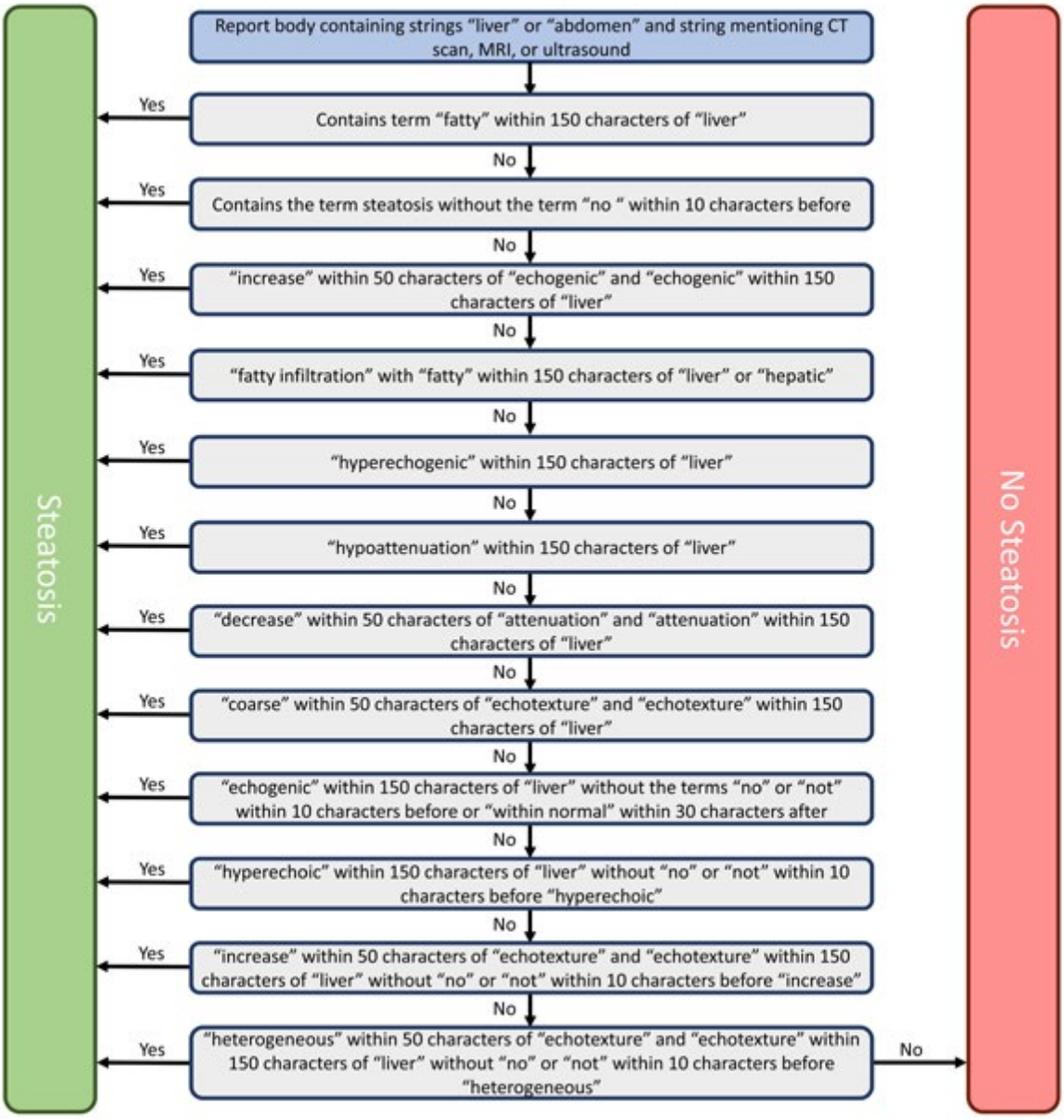
kappa of 0.87 (95% CI 0.82-0.91), and identified 436,974 (53.4%) of participants to have SLD, compared to ICD 9/10 codes in only 23,218 (2.8%) patients. **Conclusion:** We describe an algorithm combining rule-based NLP, identification of cardiometabolic risk factors and alcohol use from laboratory and pharmacy records, that identified steatosis and classified SLD with excellent accuracy, and identifies a significantly higher number of patients with SLD, compared to ICD 9/10 codes.



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0041 | ENHANCING CYTOTOXIC CD8+ T CELL RESPONSE FOR LIVER CANCER TREATMENT USING POLYIC-CONTAINING IONIZABLE LIPID NANOPARTICLES VIA ACTIVATING HEPATOCELLULAR TYPE I IFN PATHWAY ★

Yingluo Liu[1] Gen-Sheng Feng[2]

[1]UCSD, [2]University of California, San Diego

Background: Liver cancer is a major global health challenge with a five-year survival rate of 18%. There remains a significant unmet need for liver cancer patients. PolyIC shows promise in tumor suppresion but is limited by high toxicity. This study aims to use Lipid Nanoparticles (LNPs) for targeted polyIC delivery to the liver, enhancing immune response and anti-tumor effects, and exploring new liver cancer treatment mechanisms. **Methods:** polyIC-LNPs were formulated by combining ALC-0315, DSPC, cholesterol, and DMG-PEG2000. Colorectal cancer liver metastasis model was constructed by intrasplenic injection of MC38 cells. Primary liver cancer model was constructed by hydrodynamic injection of NRas and c-Myc plasmids. **Results:** We first injected polyIC-loaded lipid nanoparticles (polyIC-LNPs) into mice and confirmed liver-specific delivery of polyIC. In a liver tumor metastasis model with MC38 cells, polyIC-LNPs monotherapy eliminated visible liver tumors, while the same dosage of free polyIC showed no significant effects. Remarkably, just 5 μg of polyIC-LNPs maintained potent tumor-inhibitory effects without altering serum ALT levels and extended survival in tumor-bearing mice to over 150 days, compared to 19 days in controls. In a primary HCC model driven by NRas and c-Myc, polyIC-LNPs significantly restricted tumor growth, highlighting their potential. We next isolated non-parenchymal cells for scRNA-seq using the 10x Genomics platform. We found that polyIC-LNPs reshaped the liver microenvironment to a tumor-inhibitory state. Notably, polyIC-LNPs treatment significantly enhanced CD8 T cell infiltration, activation, and proliferation, with CD8 T cell depletion abolishing the tumor-inhibitory effect. Using type I IFN reporter mice, we discovered that type I IFN signaling was primarily enriched in the liver following LNP treatment. Blocking IFNAR abolished the tumor-inhibitory effect of polyIC-LNPs and the activation and proliferation of CD8 T cells. Further investigation revealed that polyIC-LNPs stimulated type I IFN signaling mainly in hepatocytes, which produced several proinflammatory cytokines and chemokines to boost anti-tumor immunity. **Conclusion:** Our findings underscore the potential of polyIC-LNPs as a novel treatment for liver cancer, capable of stimulating hepatocellular IFN signaling and enhancing liver immunity to combat hepatocellular carcinoma HCC.

Disclosures: Yingluo Liu: Nothing to Disclose, Gen-Sheng Feng: Nothing to Disclose

0042 | FECAL CYTOLYSIN IS ASSOCIATED WITH A POORER OUTCOME IN PATIENTS WITH PRIMARY SCLEROSING CHOLANGITIS ★

Burcin Özdirik[1] Hilmar Berger[2] Fernanda Raya Tonetti[3] Noemi Cabre Casares[3] Nicole Treichel[4] Thomas Clavel[5] Frank Tacke[6] Michael Sigal[2] Bernd Schnabl[3]

[1]University of California San Diego, [2]Charité - Universitätsmedizin Berlin, [3]University of California, San Diego, [4]Universitätsklinikum Aaachen, [5]Universitätsmedizin Aachen, [6]Universitätsmedizin Berlin

Background: Primary sclerosing cholangitis (PSC) is an immune-related cholangiopathy for which there are still no definite treatment options other than liver transplantation. The gut-liver axis, with particular focus on specific gut microbes, has emerged as a crucial pathway contributing to PSC pathogenesis [1]. In recent years, *Enterococcus faecalis* and its virulence factor cytolysin, a two-subunit exotoxin known to be a risk factor for mortality in patients with alcohol-associated hepatitis, have gained interest *[2].* Thus, we studied the role of enterococci and especially the abundance of *E. faecalis* and fecal cytolysin in patients with PSC. **Methods:** To assess the relevance of enterococci, we performed 16S ribosomal ribonucleic acid (rRNA) gene amplicon analysis in fecal samples from 58 patients with PSC. Subsequently, we validated and extended our findings by using qPCR on bacterial DNA from fecal samples from 105 patients with PSC, 104 patients with inflammatory bowel disease (IBD) and 68 healthy control subjects. **Results:** High-throughput 16S rRNA amplicon analysis revealed a high relative abundance of enterococci in PSC patients compared to control individuals (healthy, IBD)

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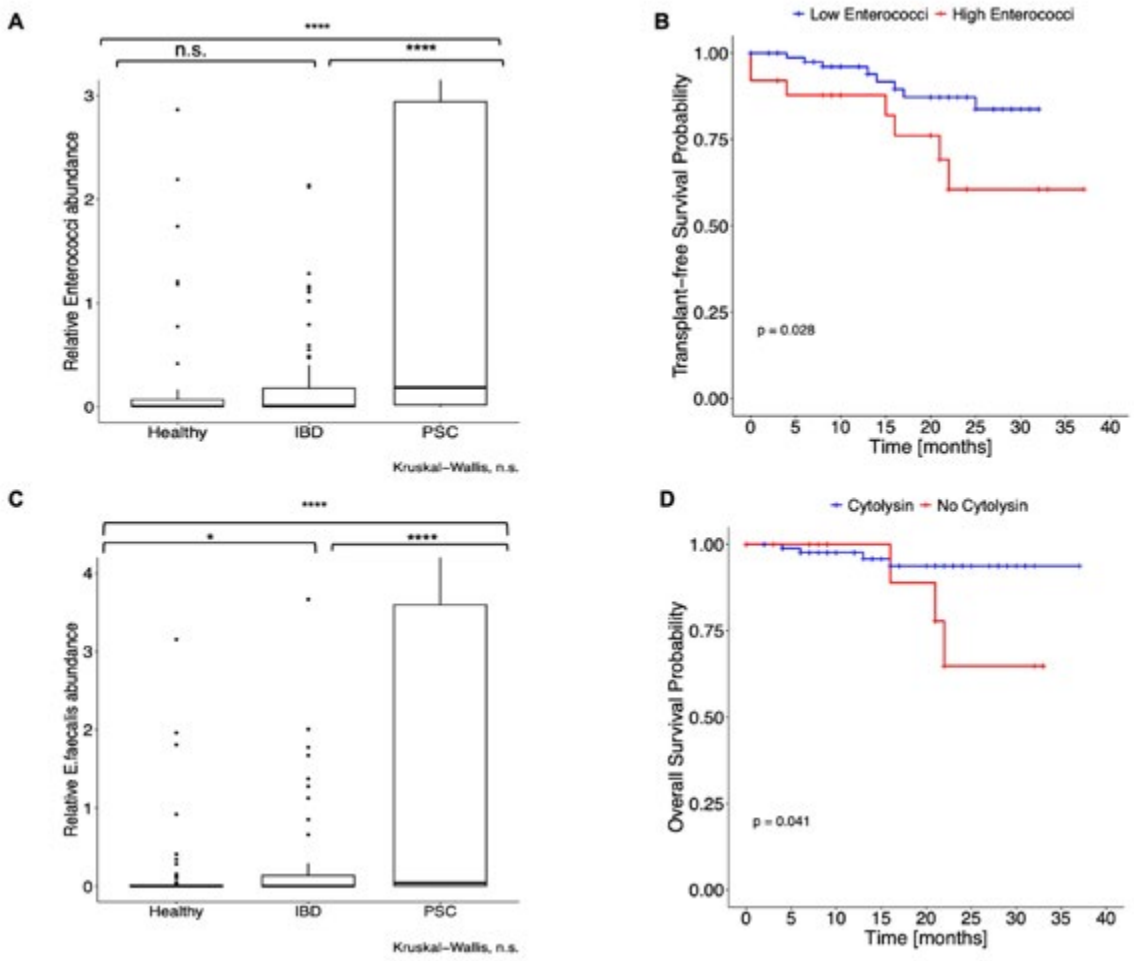
regardless of IBD. We validated these results in a larger PSC cohort (n=105) using qPCR. Using an optimal cut-off calculated by maximally selected rank analysis, PSC patients with high a enterococci abundance had a decreased probability of transplant-free survival (p=0.028) (Fig. 1A,B). We also observed a higher abundance of *E. faecalis* and fecal cytolysin in PSC patients (Fig. 1C), and Kaplan Meier analysis revealed poorer overall survival in patients with higher fecal cytolysin (p=0.04) (Fig. 1D). **Conclusion:** Our data highlights the association of *E. faecalis* and fecal cytolysin with poorer overall survival in patients with PSC. These results validate the need for further mechanistic studies on the role of *E. faecalis* and its virulence factor cytolysin in PSC, highlighting potential new therapeutic targets for a disease without effective treatment options.



Disclosures: Burcin Özdirik: Nothing to Disclose, Hilmar Berger: Nothing to Disclose, Fernanda Raya Tonetti: Nothing to Disclose, Noemi Cabre Casares: Nothing to Disclose, Nicole Treichel: Nothing to Disclose, Thomas Clavel: Nothing to Disclose, Frank Tacke: Gilead: Grant/Research Support, MSD: Grant/Research Support, AstraZeneca: Grant/Research Support, Agomab: Grant/Research Support, NovoNordisk, Boehringer, Gilead, MSD, GSK: Consultant, Pfizer, Sanofi: Advisor, Michael Sigal: Nothing to Disclose, Bernd Schnabl: Grant/Research Support relationship with Prodigy Biotech; Has not ended; Grant/Research Support relationship with CymaBay Therapeutics; Has ended; Consultant relationship with Surrozen; Has ended; Grant/Research Support relationship with Intercept Pharmaceuticals; Has not ended; Stock â€“ privately held company relationship with Nterica Bio; Has not ended; Grant/Research Support relationship with Axial Biotherapeutics;

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Has ended; Consultant relationship with Ambys Medicines; Has ended; Grant/Research Support relationship with ChromoLogic; Has not ended; Consultant relationship with Mabwell Therapeutics; Has not ended

0043 | ONE-YEAR TREATMENT WITH ELAFIBRANOR IN THE PHASE III ELATIVE® TRIAL IMPROVES GLOBE AND UK-PBC PROGNOSTIC SCORES

Kris Kowdley[1] Eric Lawitz[2] Catherine Spearman[3] Vincenza Calvaruso[4] Nuno Antunes[5] Jianfen Shu[5] Claudia Zein[5] Christopher Bowlus[6]

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Background: Elafibranor, a dual peroxisome proliferator-activated receptor-α/δ agonist, is being investigated in primary biliary cholangitis (PBC). In the phase III ELATIVE® trial (NCT04526665), elafibranor efficacy was assessed in patients (pts) with PBC with inadequate response or intolerance to ursodeoxycholic acid (UDCA). GLOBE and UK-PBC are validated prognostic scores that estimate risk of liver transplant or death after one year (yr) of UDCA therapy. The scores have also been used to evaluate the benefit of second-line agents, such as obeticholic acid. **Methods:** In ELATIVE®, pts were randomized 2:1 to once-daily elafibranor 80 mg or placebo (PBO) for 52 weeks. GLOBE and UK-PBC scores are based on levels of alkaline phosphatase (ALP), total bilirubin (TB), aspartate transaminase (AST), alanine transaminase (ALT), albumin, and platelets. GLOBE and UK-PBC scores were analyzed at baseline and Weeks 4, 13, 26, 39, and 52. Contributions of individual parameters to each score were also evaluated. **Results:** Overall, 161 pts received elafibranor (N=108) or PBO (N=53). Mean age was 57 (standard deviation [SD]: 9) yrs; 96% of pts were female. Mean (SD) baseline values were: ALP 321.9 (150.9) U/L; TB 9.6 (5.1) µmol/L; AST 45.7 (27.2) U/L; ALT 49.6 (32.6) U/L; albumin 43.8 (3.0) g/L; platelets 263.6 (76.8) $\times 10^9$/L. At baseline, mean (SD) GLOBE and UK-PBC scores were −0.63 (0.67) and −0.74 (0.90) in the elafibranor group, and −0.73 (0.73) and −0.80 (0.86) in the PBO group, respectively. After one yr of treatment, mean (SD) change from baseline in GLOBE and UK-PBC scores were −0.36 (0.40) and −0.27 (0.53) in the elafibranor group, and 0.13 (0.45) and 0.05 (0.63) in the PBO group, respectively. Changes in both scores were seen after 4 weeks and continued through 52 weeks of treatment, primarily driven by reduction in ALP. Based on GLOBE scores at Week 52, median estimated transplant-free survival rates at 5, 10, and 15 yrs were 97.78%, 94.12%, and 89.71% in the elafibranor group, compared with 97.19%, 92.62%, and 87.15% in the PBO group. Based on UK-PBC scores at Week 52, median estimated transplant-free survival rates at 5, 10, and 15 yrs were 99.46%, 98.19%, and 96.65% in the elafibranor group, compared with 99.20%, 97.35%, and 95.12% in the PBO group (Figure). **Conclusion:** Treatment with elafibranor was associated with improvements in predicted transplant-free survival based on GLOBE and UK-PBC scores as early as Week 4, with further improvement through the 52 weeks of treatment.

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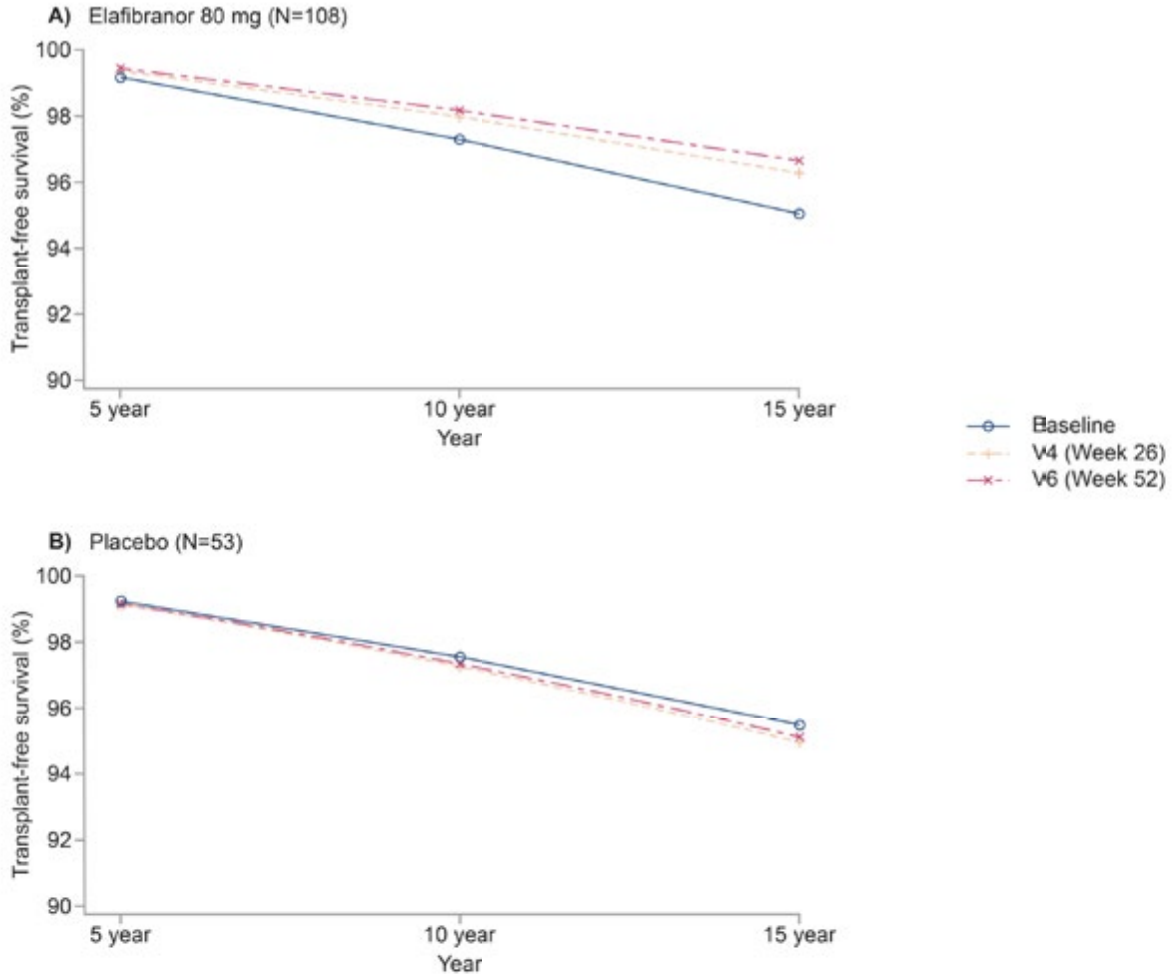
Figure. Median UK-PBC transplant-free survival at baseline and over time to Week 52



UK-PBC prognostic scores are based on levels of ALP, TB, AST, ALT, albumin, and platelets. All patients had similar ALP and TB levels at baseline.

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0044 | NOVEL DGAT2 ANTISENSE INHIBITOR DEMONSTRATES SIGNIFICANT HISTOLOGICAL BENEFIT IN BIOPSY-PROVEN MASH PATIENTS WITH ADVANCED LIVER FIBROSIS STAGE F3: SUBSET ANALYSIS OF A 51-WEEK MULTICENTER RANDOMIZED DOUBLE-BLIND PLACEBO-CONTROLLED PHASE 2 TRIAL

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Background: ION224 is an investigational ligand-conjugated antisense inhibitor of diacylglycerol acyltransferase 2 (DGAT2), an enzyme that catalyzes the final step in hepatic triglyceride synthesis. We previously reported the first clinical evidence that reduction of hepatic fat after DGAT2 inhibition in patients with F2 and F3 fibrosis leads to MASH resolution and the ION224-CS2 study (NCT04932512) met the primary endpoint of ≥2-point reduction in NAS with ≥1-point improvement in hepatocellular ballooning or lobular inflammation without worsening of fibrosis. The current analysis focuses on the effects of ION224 in patients with advanced liver fibrosis (stage F3) from the study. **Methods:** This subset analysis conducted in patients with advanced fibrosis stage F3 included 39 patients treated with 90 or 120mg ION224 (n=26) or placebo (n=13). Biopsy proven MASH patients with MASLD activity score (NAS)≥4 and MRI-PDFF≥10% received monthly subcutaneous injections of ION224 or placebo during a 49-week treatment period followed by a subsequent biopsy evaluation. **Results:** Baseline characteristics were: age 57±10 years (mean±SD), body weight 109.7±27.6 kg, female 51%, type 2 diabetes 59%, MRI-PDFF 21± 7.0%. The primary endpoint of ≥2-point reduction in NAS score was met in 61.5% of ION224-treated patients, compared to 15.4% for placebo (p=0.006). Histological benefit was further supported by a higher proportion of ION224-treated patients demonstrating improvement in both hepatocellular ballooning and lobular inflammation combined (46.2% vs 15.4% in placebo). Also, a higher proportion of ION224-treated patients showed MASH resolution without worsening of fibrosis (30.8% versus 15.4% for placebo) as well as ≥1 stage improvement in fibrosis without worsening steatohepatitis (46.2% vs 30.8% for placebo). A significantly higher proportion of ION224-treated patients showed a post-baseline relative reduction in MRI-PDFF of ≥30% (88.5% vs 38.5% in placebo, p=0.002) or ≥50% (53.8% vs 7.7% in placebo, p=0.005). ION224 was safe and well-tolerated with no treatment-related SAEs, no GI side effects or change in body weight and showed a 0.5% placebo-adjusted improvement in HbA1c at the 120mg dose. **Conclusion:** The current analysis provides evidence of clinical benefit of ION224 in patients with advanced fibrosis independent of changes in body weight. These data support the potential for ION224 treatment to provide benefit to MASH patients with advanced liver fibrosis.

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Yousefi: Nothing to Disclose, Dan Li: Nothing to Disclose, Richard Geary: Ionis Pharmaceuticals, Inc: stock ownership of the same, Sanjay Bhanot: Ionis Pharmaceuticals: Employee

0045 | INJURED HEPATOCYTES-SECRETED EXTRACELLULAR VESICLES PROMOTE CIRRHOSIS-ASSOCIATED SKELETAL MUSCLE INJURY THROUGH MTDNA-CGAS-STING AXIS

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Background: Sarcopenia, an important component of malnutrition, is linked to poor prognosis in cirrhotic patients. Recent studies have indicated that chronic muscle inflammation plays a pivotal role in the progression of sarcopenia, although the mechanism underlying the association between cirrhosis and chronic muscle inflammation remains poorly understood. Therefore, this study aimed to elucidate the specific mechanism by which hepatic-derived extracellular vesicles (EVs) promote proinflammatory responses in muscle macrophages via circulation, leading to the advancement of muscle inflammation during cirrhosis. **Methods:** Liver fibrosis was induced by carbon tetrachloride injection and bile duct ligation. EVs from cirrhotic liver were isolated and characterized. Proteomics was utilized to identify functional mitochondrial components in EVs. Lastly, we conducted a cross-sectional study on patients with cirrhosis to validate these findings. **Results:** Treatment of EVs from cirrhotic liver promoted inflammation in macrophages and muscle inflammation progression via activating the STING pathway. The Sting inhibitor in cirrhotic mice abolished the role of cirrhotic-derived EVs in muscle inflammation. In addition, hepatic-specific deletion of Rab27a and the inhibitor of EV—GW4869, significantly alleviated cirrhosis-induced muscle inflammation progression in cirrhotic mice. The proteomics results showed that mitochondrial proteins and mtDNA were enriched in EVs from cirrhotic liver. Furthermore, mitochondria damage in hepatocytes caused by mitochondrial membrane potential decline led to mitochondrial DNA leakage, which caused macrophage inflammation through the STING pathway. Moreover, EVs from peripheral veins and hepatic veins who underwent transjugular intrahepatic portosystemic shunt in patients with cirrhosis and EV-mtDNA expression were associated with the severity of cirrhosis. **Conclusion:** Hepatocyte-derived EVs promote inflammation in macrophages in muscle and facilitate muscle inflammation progression via the mtDNA/STING axis . Reducing EV secretions in cirrhotic liver or targeting STING may be potential therapeutic approaches to slow the progression of cirrhosis-driven muscle inflammation.

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0047 | DIETARY SALT INTAKE MODULATES TH17-DEPENDENT INFLAMMATION IN CIRRHOTIC PATIENTS AND EXACERBATES LIVER INJURY IN MICE

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Background: It is known that high-salt diet (HSD) promotes T helper (Th)17 differentiation and Th17-mediated autoimmune and inflammatory diseases. While patients with decompensated cirrhosis limit salt intake to prevent ascites, salt intake is not commonly monitored in other types of liver disease such as fibrosis or compensated cirrhosis. Yet, Th17-driven inflammation may promote inflammatory complications or hepatocellular carcinoma in those patients. **Aim:** Assess the impact of HSD on the immunological profile of patients with compensated cirrhosis and its potential to exacerbate liver injury in mice. **Methods:** 40 patients with compensated cirrhosis were recruited. First, blood and urine were collected, and daily salt intake (SI) was assessed at baseline (t=0). Patients got personalized guidelines to reduce SI without affecting other nutrients. After 3 months of salt restriction (t=1), blood was collected, and SI was evaluated as before. At both t=0 and t=1, CD4+ cells were analysed by FACS and stimulated *in vitro* to analyze the production of cytokines. In an acute DEN liver damage model, C57BL6 mice were fed normal diet (ND) or HSD for 3 weeks. Mice were sacrificed 48 hours after one DEN injection and liver damage, inflammation, Th subsets were assessed. **Results:** 29 patients completed the

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protocol. At t=0, a significant positive correlation was found between salt intake and blood Th17 cells (p=0.03), Th17/Th1 ratio (p=0.002), and IL17A production by $CD4^+$ cells stimulated *in vitro*, as well as Th17/Tregs ratio. Using the median value of SI (5.44 g/day) as a threshold, patients were grouped into 'low' and 'high' SI (LS and HS, respectively). No differences in clinicopathological features were observed except for age. Instead, the **HS** group had higher Th17 cell number (p = 0.03) and Th17/Th1 ratio (p = 0.02). An unbiased hierarchical clustering analysis using all numeric clinical variables of the patients linked the salt-Th17 axis with markers of impaired liver function while RNA-seq analysis revealed an enrichment of the salt-induced Th17 gene signature in liver disease. At t=1, 20 patients had reduced their average SI >0.5g/day (compliant), while 9 did not (non-compliant). When comparing individual data between t=0 and t=1, circulating Th17 (p=0.04) and Th17-Th1 cells (p=0.01) were significantly decreased among compliant patients. Contrariwise, non-compliant patients showed no notable changes in these parameters. In mice, HSD aggravated liver damage, evident by serum ALT and histological analysis. Hepatic CD4+ cells displayed increased RORγ mRNA (p=0.006) but reduced Tbet, Gata3, Foxp3 mRNA. Consistently, DEN+HSD mice had more IL17+ cells in the liver (p=0.007) by IHC analysis. **Conclusion:** Overall, the study suggests that a low-salt diet can be an effective non-pharmacological strategy to reduce inflammation in patients with compensated liver disease, potentially slowing disease progression and improving patient outcomes.

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0048 | MEASUREMENT OF EFFECTIVE ALBUMIN CONCENTRATION SIGNIFICANTLY IMPROVED PREDICTION OF ONE YEAR MORTALITY IN PATIENTS WITH ACUTELY DECOMPENSATED CIRRHOSIS WITHOUT ACUTE-ON-CHRONIC LIVER FAILURE

Chenxi Zhang[1] Shuang Meng[2] Yide Lu[1] Yaoxing Chen[1] Minghao Cai[1] Haoshuang Fu[1] Jie Lu[1] Ziqiang Li[1] Zhuping Qian[1] Baoyan An[1] Haiguang Xin[1] Li Xia[3] Zhujun Cao[1] Qing Xie[1]

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Background: Evaluation of effective albumin (eAlb) as opposed to routine serum albumin has recently shown prognostic value on short-term outcome of patients with acute decompensation (AD) of cirrhosis due to a closer association of eAlb with disease severity and albumin dysfunction. However, patients with AD could have a relative long-term survival in the absence of acute-on-chronic liver failure (ACLF) and accurate prediction of survival in them remains challenging. This study aimed to assess the prognostic value of eAlb on long-term outcome in patients with AD without ACLF. **Methods:** Patients admitted for AD without ACLF (n=445) were prospectively enrolled between June 2016 and Oct. 2021. Healthy controls (HC, n=50) and patients with compensated cirrhosis (CC, n=52) were enrolled for comparisons. The baseline redox state of Cys-34 of albumin was assessed by liquid chromatography/mass spectrum, followed by a calculation of eAlb concentration with the relative proportion of native albumin. Association of eAlb with 1-year mortality was assessed with the multivariable competing risk analysis. Prognostic value of eAlb was assessed for the potential of improvement compared to MELD-Na or CLIF-C AD alone. **Results:** eAlb concentration was notably lower in AD than that in CC or HC [6.0 (3.0-9.7) vs. 14.4 (11.1-18.5) or 24.6 (22.9-26.3) g/L, p<0.001] and further decreased in those who died within 1-year follow-up compared to survivors [3.7 (1.8-6.0) vs. 6.7 (3.6-10.3) g/L, p<0.001]. By competing risk analysis, eAlb concentration, not other Cys-34 redox state of albumin, was the independent factor associated with 1-year death in AD (sHR, 0.45 (0.21-0.97), p=0.04). A combination with eAlb concentration could notably improve prognostic accuracy of CLIF-C AD [AUC of eAlb+CLIF-C AD, 0.73 (0.67-0.73) vs. AUC of CLIF-C AD, 0.68 (0.62-0.68), p=0.005] or MELD-Na [AUC of eAlb+MELD-Na, 0.75 (0.70-0.75) vs. AUC of MELD-Na 0.72 (0.66-0.72), p=0.022]. Finally, based on the best cutoff of 1-year mortality by ROC, a threshold of eAlb concentration at 4.0 g/L could effectively stratify patients into different risks of 1-year mortality (p<0.001). **Conclusion:** eAlb concentration could independently predict 1-year death in patients with AD, and be combined with regular prognostic scores to improve the predictive performance, which could be a promising prognostic biomarker for long-term survival in patients with AD without ACLF.

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Figure 1. Flow chart

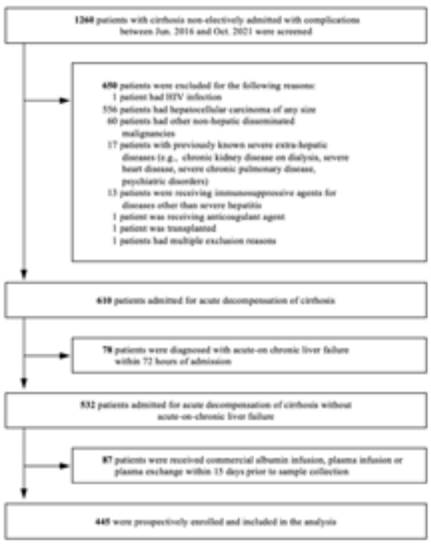


Figure 2. Concentrations of albumin isoforms according to disease groups or 1-year survival outcomes

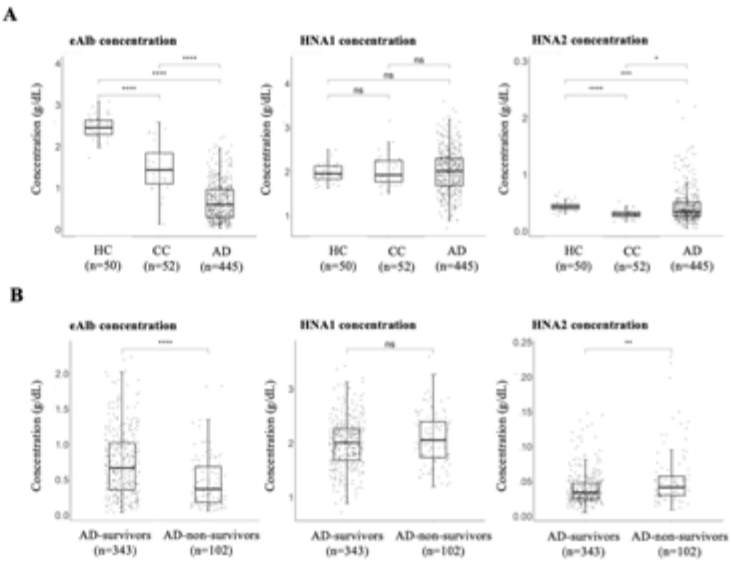
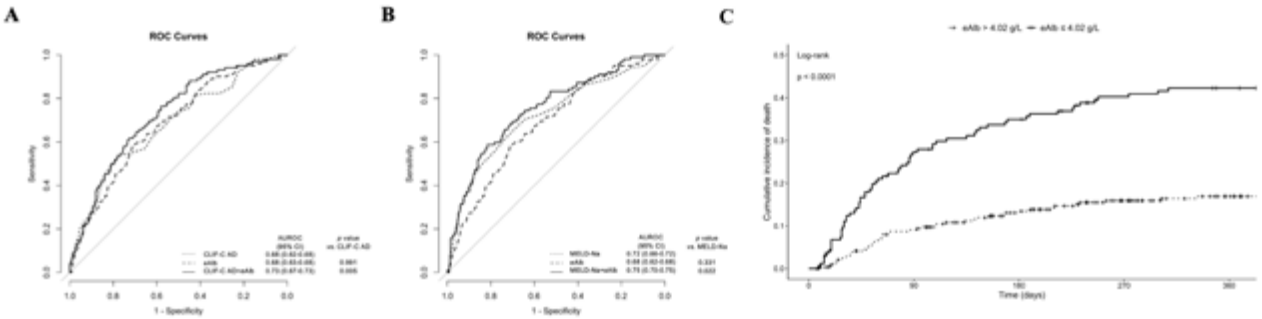


Figure 3. Prognostic performances of albumin isoforms



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0049 | VALIDATION OF THE MASEF SCORE FOR ITS DIAGNOSTIC ENRICHMENT UTILITY FOR AT-RISK MASH IN THE NIMBLE PROJECT

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Background: There is an unmet need for non-invasive tests (NITs) to identify those with metabolic dysfunction associated steatotic liver disease (MASLD) who are at risk of increased liver and all-cause mortality. This has been defined as metabolic dysfunction associated steatohepatitis (MASH) with NAFLD activity score (NAS) ≥ 4 and fibrosis stage ≥ 2 (at-risk MASH). The MASEF® score is a multi-analyte (12 lipids, BMI, AST, ALT) proprietary test for this purpose. **Aims:** To independently evaluate the diagnostic performance of the MASEF score for at-risk MASH and its histological components. **Methods:** A retrospective evaluation of prospectively collected

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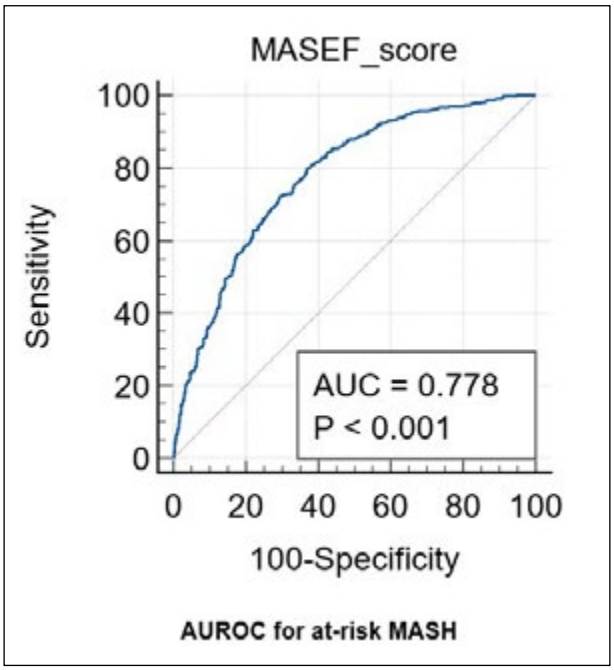
samples from a curated population from the NASH CRN with a relatively even distribution of fibrosis stages was performed. Blood samples were collected within 90 days of a liver biopsy in over 90% and within 180 days in all. Liver histology was scored by the CRN pathology committee using its validated protocol masked to clinical and laboratory data. Lipidomic analyses were performed by One-Way Lipidomics (OWL) and raw MASEF® scores were provided. Data analysis was performed by NIMBLE investigators without involvement of OWL. Our goal was to define the AUROC, sensitivity and specificity for at-risk MASH and its components MASH, NAS ≥ 4, fibrosis stage ≥ 2, ≥ 3 and 4 (cirrhosis). The MASEF® score was compared to ALT for the diagnosis of MASH and FIB-4 for fibrosis cutoffs noted above. **Results:** A total of 1073 individuals were studied (mean age 52.5 yrs, BMI 34.8 kg/m2, T2DM n=490, MASH n=835, NAS ≥4 n=574, fibrosis stage ≥2 n=737, ≥ stage 3 n=475 and cirrhosis n=198). The AUROC, sensitivity, specificity at Youden cut-point for at-risk MASH were 0.78 (p< 0.0001 vs AUROC 0.5), 72%, and 70%, respectively. At 90% sensitivity the specificity was 45%, while at 90% specificity, the sensitivity was 36%. The AUROC/sensitivity/specificity for activity markers were as follows: MASH (0.81/71%/78%, p< 0.0001), NAS ≥ 4 (0.77/81%/60%, p< 0.0001). The AUROC, sensitivity, specificity for fibrosis cutoffs were: stage ≥ 2 (0.77, 70%, 70%p< 0.0001), ≥ stage 3 (0.71, 80%, 53% p< 0.0001), cirrhosis (0.72, 70%. 66%, p< 0.001). MASEF® score outperformed ALT for MASH and NAS ≥ 4 and FIB-4 for fibrosis stage ≥ 2 but not for advanced fibrosis or cirrhosis. **Conclusion:** The MASEF® score enriches the probability of having “at risk” MASH in a population with MASLD. Its performance is weighted toward stage 2 fibrosis rather than cirrhosis.



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0050 | ASSERT-EXT: FINAL DATA FROM AN OPEN-LABEL, PHASE 3 STUDY OF ODEVIXIBAT IN PATIENTS WITH ALAGILLE SYNDROME

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Background: In the 24-week ASSERT study (NCT04674761), the first and only phase 3 randomized study in patients with Alagille syndrome (ALGS), odevixibat significantly lowered pruritus and serum bile acids (sBAs) vs placebo, and most treatment-emergent adverse events (TEAEs) were mild or moderate. The 72-week ASSERT-EXT study (NCT05035030) evaluated the long-term efficacy and safety of odevixibat in patients with ALGS; here, we report final study data from ASSERT-EXT. **Methods:** Patients who completed ASSERT were eligible to enter ASSERT-EXT; all patients in ASSERT-EXT received odevixibat 120 µg/kg/day. The primary efficacy outcome was change in pruritus score from baseline (BL) to weeks 69−72. Other outcomes included change from BL in sBAs, proportion of patients with clinically meaningful decrease in pruritus score (ie, ≥1-point reduction from BL), and TEAE incidence. results were evaluated in patients who received odevixibat in both ASSERT and ASSERT-EXT (ODX/ODX) and those who received placebo in ASSERT and switched to odevixibat in ASSERT-EXT (PBO/ODX); BL was preodevixibat (ie, ASSERT BL for ODX/ODX and ASSERT-EXT BL for PBO/ODX). **Results:** Of 52 patients who completed ASSERT, 50 patients (median [range] age, 5.5 [1.0−15.9] years) continued into ASSERTEXT (ODX/ODX, n=33; PBO/ODX, n=17). Mean (SD) pruritus scores at BL and weeks 69−72 of ASSERT-EXT were 2.8 (0.5) and 0.6 (0.7) for ODX/ODX, respectively, and 2.2 (1.0) and 0.8 (0.8) for

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PBO/ODX; mean (SD) changes from BL to weeks 69−72 of ASSERT-EXT were −2.2 (0.9) points (ODX/ODX; *P*<0.0001 vs BL) and −1.7 (0.8) points (PBO/ODX; *P*<0.0001 vs BL; Figure A). Mean (SD) sBAs at BL and week 72 of ASSERT-EXT were 244 (115) and 119 (100) µmol/L for ODX/ODX, respectively, and 265 (160) and 106 (84) µmol/L PBO/ODX; mean (SD) changes in sBAs from BL to week 72 of ASSERT-EXT were −124 (136) µmol/L (ODX/ODX) and −139 (101) µmol/L (PBO/ODX; Figure B). The proportion of patients who achieved a ≥1point pruritus reduction from BL at weeks 69−72 of ASSERTEXT was 93% (28/30) for ODX/ODX and 77% (10/13) for PBO/ODX. During ASSERT-EXT, drug-related TEAEs were reported in 18% (6/33; ODX/ODX) and 41% (7/17; PBO/ODX) of patients; none were serious. The most common drug-related TEAE, diarrhea, occurred in 6% (2/33; ODX/ODX) and 18% (3/17; PBO/ODX) of patients. A single patient, in PBO/ODX, discontinued the study to undergo liver transplantation. **Conclusion:** Patients with ALGS in ODX/ODX entered ASSERT-EXT with reduced pruritus and sBAs compared with BL; these results were sustained with longer odevixibat treatment. Patients in PBO/ODX had mean reductions in pruritus and sBAs with odevixibat in ASSERT-EXT. The safety profile of odevixibat during longer follow up in ASSERT-EXT was consistent with that from ASSERT. These robust long-term data demonstrate sustained and durable efficacy and tolerability of odevixibat for treatment of cholestatic pruritus in ALGS.

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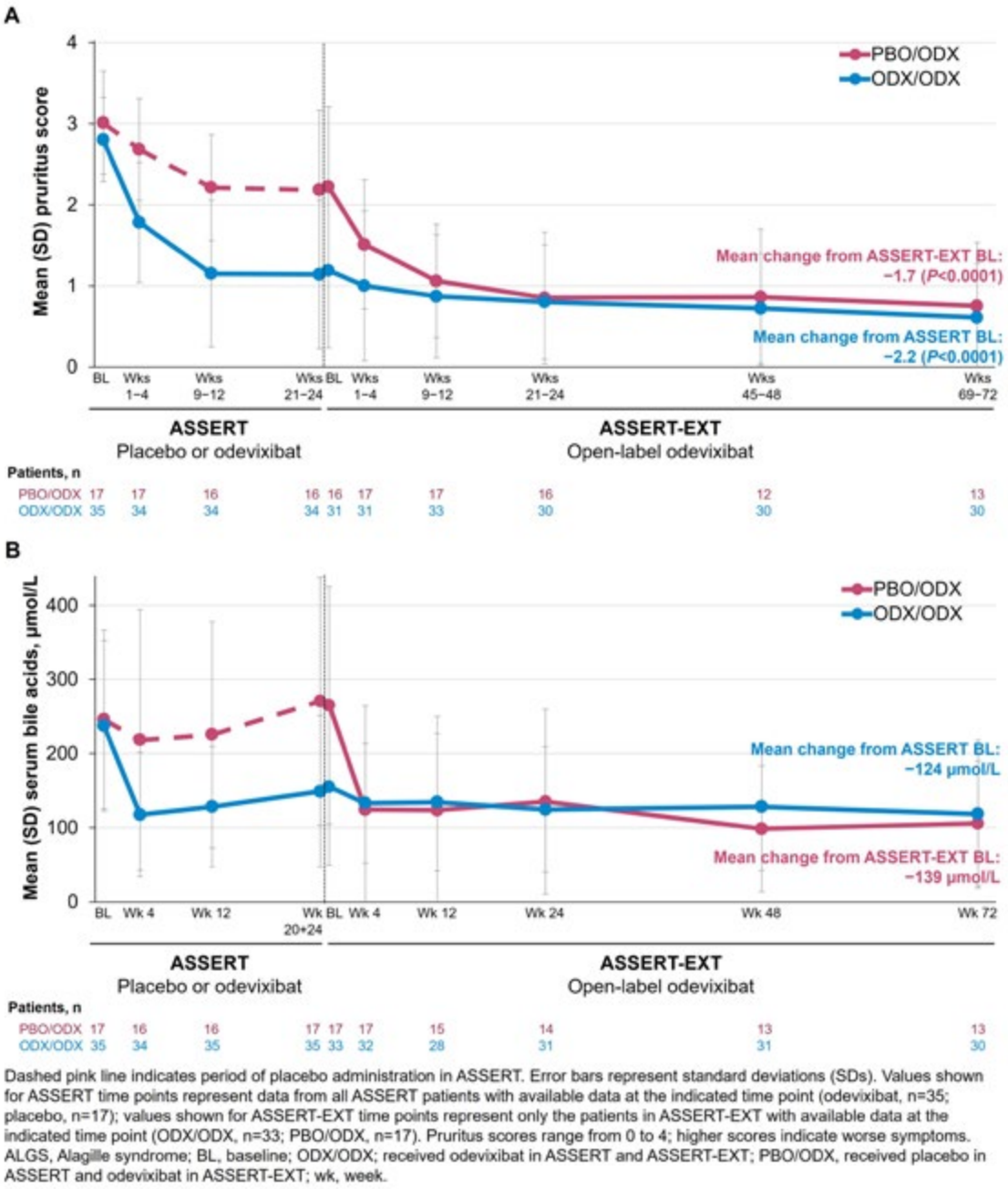
Figure: Mean pruritus scores (A) and serum bile acid levels (B) over time during ASSERT and ASSERT-EXT in patients with ALGS



Dashed pink line indicates period of placebo administration in ASSERT. Error bars represent standard deviations (SDs). Values shown for ASSERT time points represent data from all ASSERT patients with available data at the indicated time point (odevixibat, n=35; placebo, n=17); values shown for ASSERT-EXT time points represent only the patients in ASSERT-EXT with available data at the indicated time point (ODX/ODX, n=33; PBO/ODX, n=17). Pruritus scores range from 0 to 4; higher scores indicate worse symptoms. ALGS, Alagille syndrome; BL, baseline; ODX/ODX; received odevixibat in ASSERT and ASSERT-EXT; PBO/ODX, received placebo in ASSERT and odevixibat in ASSERT-EXT; wk, week.

Disclosures: Nadia Ovchinsky: Ipsen: Consultant, Madeleine Aumar: Nothing to Disclose, Alastair Baker: Nothing to Disclose, Philip Bufler: Nothing to Disclose, Mara Cananzi: Nothing to Disclose, Piotr Czubkowski: IPSEN: Consultant, Ozlem Durmaz: Nothing to Disclose, Ryan Fischer: Mirum Pharmaceuticals: Speaking and Teaching, Albireo/Ipsen Pharma Inc.: Speaking and Teaching, Eurofins Viracor: Grant/Research Support, Giuseppe Indolfi: Nothing to Disclose, Wikrom Karnsakul: Nothing to Disclose, Florence Lacaille: Nothing to Disclose, Way Lee: Nothing to Disclose, Giuseppe Maggiore: Nothing to Disclose, Mathias Ruiz: Nothing to Disclose, Etienne Sokal: Nothing to Disclose, Ekkehard Sturm: Nothing to Disclose, Wendy Van Der Woerd: Mirum pharma: Consultant, Andrew Wehrman: Albireo: Grant/Research Support, Mirum: Advisor, Christof Maucksch: Nothing to Disclose, Jessica Ruvido: Nothing to Disclose, Judy Zhu: Nothing to Disclose, Alejandra Ramirez-Santiago: Nothing to Disclose, Henkjan Verkade: Mirum: Grant/Research Support, Mirum: Consultant, Mirum: Speaking and Teaching, Ipsen / Albireo: Consultant, Ipsen / Albireo: Grant/Research Support, Ipsen / Albireo: Speaking and Teaching, Intercept: Consultant, Orphalan: Consultant

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0051 | PYRUVATE DEHYDROGENASE KINASE 4 PROMOTES MITOCHONDRIAL DYSFUNCTION IN ALCOHOL-ASSOCIATED LIVER DISEASE BY REGULATING ER-MITOCHONDRIA INTERACTION ◆

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Background: Alcohol-associated liver disease (ALD) is a significant public health concern with increasing incidence rates. Its pathogenesis involves multifaceted mechanisms, including mitochondrial (MT) dysfunction, particularly Ca2+ overload-induced MT dysfunction. A key factor in MT Ca2+ overload is the formation of the mitochondria-associated endoplasmic reticulum (ER) membrane (MAM), a specialized ER region that interacts with MT, facilitating Ca2+ transfer from the ER to MT through the MAM Ca2+-Channeling Complex (MCCC). This complex comprises IP3R1 (ER protein), VDAC1 (MT protein), and GRP75 (protein anchoring IP3R1 and VDAC1). However, the precise mechanism driving MT Ca2+ accumulation in ALD remain unclear. We hypothesized that alcohol enhances MCCC, leading to MT Ca2+ accumulation, MT dysfunction, and liver injury. **Methods:** We analyzed liver tissues from patients with ALD and healthy controls to investigate MAM formation. The findings were confirmed using electron microscopy, immunofluorescence, and proximity ligation assay analyses in the livers of chronic-plus-binge alcohol-fed mice, patients with ALD, and an in vitro ALD model. We then utilized RNA-seq, mass spectrometry, and mitochondrial function analysis to explore the role of MAM in the pathogenesis of ALD. Lastly, we validated the mechanisms by perfomging the studies in whole-body and hepatocyte-specific Pdk4 knockout mice. **Results:** We observed a significant increase in MAM formation both in vitro (primary hepatocytes), in vivo (ethanol-fed mice) and ALD patients' livers compared to controls. Transcriptomic analysis revealed a significant upregulation of pyruvate dehydrogenase kinase 4 (PDK4), a MAM-associated gene, in the liver of ethanol-fed mice and ALD patients. Subcellular fractionation showed increased localization of PDK4 along with MCCC proteins in the MAM fraction. We found that ethanol promotes PDK4 phosphorylation at its MT targeting sequence leading to cytosolic translocation. Through immunoprecipitation and mass spectrometry analysis, we found that PDK4 phosphorylates GRP75 at multiple sites. Ethanol treatment increased IP3R1 interaction with WT GRP75 but not with the GRP75 with mutated phosphorylation site, suggesting PDK4 modulating MCCC formation via GRP75 phosphorylation. This phosphorylation event was linked to enhanced MT Ca2+ levels, reactive oxygen species production, and lipid accumulation, contributing to liver injury (See Fig). Ethanol fed *Pdk4*$^{-/-}$ mice had a significant decrease in MAM formation with amelioration of alcohol-induced liver injury. Conversely, forced upregulation of MAM formation using ER-MT linker reversed the protective effect of PDK4 deficiency on alcohol-induced liver injury. **Conclusion:** Our study identifies PDK4 as a causal factor in ALD pathogenesis by mediating MAM formation, MT Ca^{2+} accumulation and dysfunction. PDK4 emerges as a potential therapeutic target for ALD.

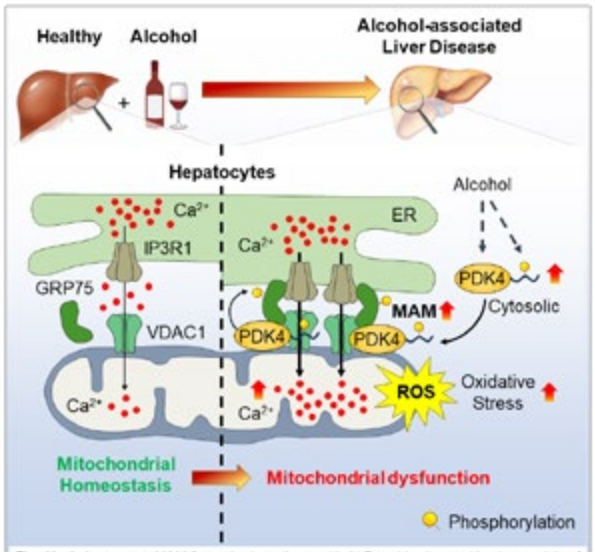

Fig. Alcohol promotes MAM formation in patients with ALD and in vitro and in vivo models of ALD. PDK4 is a causal factor in mediating MAM formation. Phosphorylation of PDK4's mitochondrial leader sequence induced by alcohol mediates its cytosolic localization, where it can phosphorylate GRP75, an MCCC protein at the MAM. Alcohol-induced GRP75 phosphorylation is crucial for MT Ca2+ accumulation, MT dysfunction, and liver injury.

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0052 | CAMRELIZUMAB COMBINED WITH LENVATINIB AND RALOX-HAIC FOR HEPATOCELLULAR CARCINOMA (HCC) IN BCLC STAGE B AND C: A PROSPECTIVE, SINGLE-ARM TRIAL (CAL ERA STUDY)

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Background: The combination of systemic therapies and hepatic arterial infusion chemotherapy (HAIC) showed promising outcomes for advanced hepatocellular carcinoma (HCC). HAIC with raltitrexed plus oxaliplatin (RALOX) was reported to be effective and safe in HCC. This study aimed to investigated the efficacy, safety and predictive biomarkers of combined camrelizumab and lenvatinib plus RALOX-HAIC as a first-line treatment in advanced HCC patients. **Methods:** This single-arm study included treatment-naive patients with HCC in BCLC stage B and C (NCT05003700). Patients were administrated with RALOX-HAIC (oxaliplatin 100mg/m^2, raltitrexed 3 mg/m^2, every 3 weeks), combined with camrelizumab (200mg by IV infusion, every 3 weeks) and lenvatinib (8mg orally once daily) for 4-6 cycles, followed by maintenance therapy with camrelizumab and lenvatinib until disease progression or unacceptable toxicity. The primary endpoint was objective response rate (ORR). The Olink Target 96 Immuno-Oncology panel was used to detect potential biomarkers which were associated with treatment outcomes. **Results:** Between March 2021 and May 2023, 39 patients (35 men and 4 women; median age, 55 years) were enrolled. As of February 4, 2024, the median follow-up was 24.9 months. The confirmed ORR per RECIST v1.1 was 66.7% (95% CI, 49.8−80.9)(Fig.1). The median progression-free survival (PFS) time was 13.8 months (95%CI, 10.5-20.5) per RECIST v1.1. The median overall survival (OS) time was 20.3 months (95%CI, 14.2-20.3). Grade 3-4 treatment-related adverse events (AEs) occurred in 79.5% of patients, and the most common adverse events were decreased neutrophil count (41%), decreased platelet count (30.8%), increased aspartate aminotransferase (23.1%), decreased white blood cell (12.8%) and hypotension (12.8%). All AEs were expected and manageable, and no treatment-related deaths were reported. The levels of three proteins (IL-2, IL-15, and CXCL13) were significantly higher in partial response PR group (n = 14) than in stable disease SD group (n = 7), while the level of one protein (CCL19) was significantly lower in PR group than in SD group (all $P < 0.05$). **Conclusion:** Combination treatment with camrelizumab and lenvatinib plus RALOX-HAIC showed promising antitumor activity and acceptable toxicity in patients with advanced HCC. The plasma proteins could serve as biomarkers to predict the curative effect of this combination treatment.

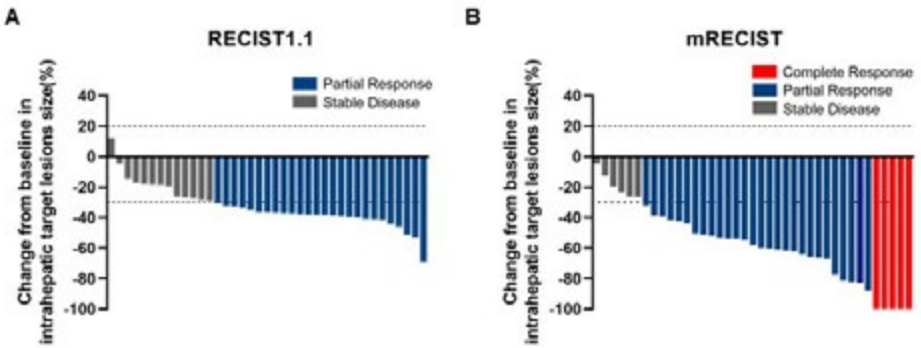

Figure1. (A) Best percentage changes from baseline in size of the intrahepatic target lesions of patients per RECIST 1.1.(B) Best percentage change from baseline in intrahepatic target lesion per mRECIST

Disclosures: Mengya Zang: Nothing to Disclose, Yuanfeng Li: Nothing to Disclose, Guosheng Yuan: Nothing to Disclose, Qi Li: Nothing to Disclose, Xiaoyun Hu: Nothing to Disclose, wenli li: Nothing to Disclose, Chuanjiang Li: Nothing to Disclose, Huajin Pang: Nothing to Disclose

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0053 | FACTORS ASSOCIATED WITH LONG-TERM RISK OF LIVER-RELATED AND NON-LIVER-RELATED DEATH AFTER SUSTAINED VIROLOGIC RESPONSE IN PATIENTS WITH HEPATITIS C VIRUS TREATED WITH DIRECT-ACTING ANTIVIRAL

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Background: Sustained virologic response (SVR) could be achieved in almost all patients with hepatitis C virus (HCV) by direct-acting antiviral (DAA) treatment, and improvement of prognosis is expected in SVR patients. However, long-term risk of liver-related and non-liver-related death after SVR are unclear. This study aimed to clarify the incidence and risk factors of liver-related and non-liver-related death after SVR in the long term among HCV patients treated with DAA. **Methods:** A total of 3,049 HCV patients without a history of hepatocellular carcinoma (HCC) who started DAA treatment between September 2014 and December 2022 and achieved SVR in 26 Japanese hospitals were enrolled in this study. SVR was defined as serum HCV-RNA undetectable at 24 weeks after the end of treatment. Observation period initiated from the time of SVR determination, and the median follow-up period was 58.0 months from SVR. Liver-related death was defined as HCC, intrahepatic cholangiocarcinoma (ICC), liver failure and varix rupture. Factors associated with liver-related and non-liver-related mortality after SVR were examined by Fine-Gray hazard analysis. **Results:** The median age was 69 years, 41% of patients were male, and 15% of patients were liver cirrhosis. During the follow-up period, 23 patients died due to liver-related causes, and 133 patients died due to non-liver-related causes. Among the 23 patients who died due to liver-related causes, 15 died due to HCC, six died due to ICC, one died due to liver failure, and one died due to varix rapture. Among the 133 patients who died due to non-liver-related causes, 30 died due to extrahepatic malignant tumor, 19 died due to infection, 16 died due to cerebrovascular or cardiovascular disease. Liver-related and non-liver-related mortality at 7 years after SVR were 1.2% and 8.1%, respectively. In multivariate analysis, older age ($p=0.003$), liver cirrhosis ($p=0.033$), lower platelet counts at SVR ($p=0.002$), and higher gamma-glutamyl transpeptidase (GGT) level at SVR ($p<0.001$) were significantly associated with liver-related death after SVR, and older age ($p<0.001$), male ($p<0.006$), diabetes mellitus ($p=0.018$), and lower albumin level at SVR ($p<0.001$) were significantly associated with non-liver-related death after SVR. **Conclusion:** Among SVR patients without a history of HCC, approximately 85% of causes of death were non-liver-related death. Older age, liver cirrhosis, lower platelet counts at SVR, and higher GGT levels at SVR were associated with liver-related death, and older age, male, diabetes mellitus, and lower albumin level at SVR were associated with non-liver-related death.

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0054 | A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE 2 TRIAL TO EVALUATE THE EFFICACY AND SAFETY OF CHIGLITAZAR IN NASH PATIENTS

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[1]Beijing Friendship Hospital, [2]The Third People's Hospital of Zhenjiang, [3]The First Hospital of Jilin University, [4]Sun Yat-sen University, [5]Shenyang sixth People's Hospital, [6]Beijing Youan Hospital, [7]Hangzhou Normal University, [8]Shanghai Jiao Tong University, [9]Xi'an Jiao Tong University, [10]Anhui Medical University, [11]Qingdao Municipal Hospital, [12]Fujian Medical University, [13]The First People's Hospital of Foshan, [14]The First Hospital of Lanzhou University, [15]China Medical University, [16]People's Hospital Henan, [17]The Second Hospital of Nanjing, [18]Zhengzhou University, [19]Hebei Medical University Third Hospital, [0]Ningxia Medical University, [21]Southern Medical University, [22]Peking University People's Hospital, [23]Zhejiang University School of Medicine

Background: Non-alcoholic steatohepatitis (NASH) is a severe form of non-alcoholic fatty liver disease linked to insulin resistance (IR) and genetic predisposition. Chiglitazar (Carfloglitazar), a configuration-restricted peroxisome proliferator-activated receptor (PPAR) pan-agonist with moderate transcription activity, regulates glucose, lipids, protein, and energy metabolism, maintaining metabolic balance without safety concerns from excessive subtype activation. Clinical studies have shown that it improves IR, lowers glucose and lipid levels, and reduces liver enzymes, which are part of NASH's metabolic burden. It has also been shown in non-clinical studies to potentially improve tissue fibrosis and reduce complications in organs affected by NASH, showing promise in clinical treatments. The CINAR study, a randomized double-blind placebo-controlled phase 2 trial, evaluated Chiglitazar's efficacy and safety in NASH. **Methods:** Patients with liver fat content (LFC) ≥ 8%, as assessed by magnetic resonance imaging-proton density fat fraction (MRI-PDFF), liver stiffness measurement (LSM) between 6~15kpa by Fibroscan®, and alanine aminotransferase (ALT) > upper limit of normal, were randomized to receive either oral Chiglitazar 48 mg (n=42), Chiglitazar 64 mg (n=41) or placebo (n=21) for 18 weeks. The primary endpoint was the change in relative LFC from baseline at week 18. Secondary endpoints included LFC responders (≥ 5% absolute LFC reduction, ≥ 30% relative LFC reduction), the changes in noninvasive imaging and serum markers of liver injury and fibrosis, and the changes in lipids. **Results:** Chiglitazar significantly reduced LFC compared to placebo. At Week 18, the mean relative change from baseline in LFC was -28.1% for Chiglitazar 48 mg ($p = 0.004$) and -39.5% for Chiglitazar 64 mg ($p < 0.001$), compared to -3.2% for placebo. Chiglitazar dose-dependently reduced ALT levels. While not statistically significant, it showed a trend in improving fibrosis, with a dose-dependent effect. Adverse event (AE) incidence for Chiglitazar 48 mg, 64 mg, and placebo was 61.0%, 75.6%, and 71.4%, respectively. No patients withdrew due to AEs, no drug-related serious AEs were reported, and PPAR receptor-related safety concerns were mild or absent. **Conclusion:** Chiglitazar at both doses effectively reduces LFC, liver inflammation and damage, demonstrating a dose-dependent relationship. It also shows a trend in improving fibrosis, with a dose-dependent effect, and is well-tolerated.

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		Placebo (N=21)	Chiglitazar 48mg (N=42)	Chiglitazar 64mg (N=41)
Primary endpoint				
Baseline LFC (%), mean (SD)		18.5 (6.19)	20.2 (7.79)	19.5 (7.21)
LFC at Week 18, mean (SD)		17.9 (7.75)	14.5 (8.36)	11.4 (5.88)
LS mean for relative change from baseline to Week 18 (95% CI)		-3.20 (-16.81, 10.42)	-28.07 (-37.46, -18.68)*	-39.53 (-49.03,-30.04)**
Secondary endpoints, at Week 18				
LFC responders, n (%)				
≥ 5% absolute LFC reduction		6 (28.6)	18 (42.9)	28 (68.3)*
≥ 30% relative LFC reduction		3 (14.3)	17 (40.5)*	27 (65.9)**
CAP (dB/m)				
Mean (SD), baseline		327.2 (31.56)	318.5 (28.46)	332.3 (31.83)
LS mean change (95% CI)		7.74 (-10.00, 25.48)	-13.73 (-25.98, -1.48)	-20.50 (-32.80,- 8.21)*
CK18-M30 (pg/mL)				
Mean (SD), baseline		1337.8 (1138.31)	1666.9 (1491.44)	1887.4 (1804.80)
LS mean change (95% CI)		59.87 (-477.38, 597.11)	-381.03 (-755.74, -6.31)	-983.34 (-1365.78, -600.89)*
ALT (U/L)				
Mean (SD), baseline		77.9 (31.11)	101.5 (45.84)	94.6 (41.53)
LS mean change (95% CI)		-17.19 (-30.67, -3.72)	-38.04 (-47.50, - 28.59)*	-51.51 (-60.96, -42.06)**
Patients with normal ALT				
Baseline, n		0	0	0
Week 18, n (%)		4 (19.0)	20 (47.6)*	29 (70.7)**
LSM (KPa)				
Mean (SD), baseline		8.1 (1.83)	8.2 (1.98)	7.9 (1.51)
LS mean change (95% CI)		-1.28 (-2.10, -0.47)	-1.08 (-1.64, -0.52)	-1.99 (-2.55, -1.43)
Triacylglycerol (mmol/L)				
Mean (SD) baseline		2.5 (0.83)	2.5 (0.80)	2.7 (0.94)
LS mean change (95% CI)		1.11 (0.37, 1.85)	-0.49 (-1.01, 0.03)*	-0.54 (-1.07, -0.02)**
Safety				
Adverse events, n (%)		15 (71.4)	25 (61.0)	31 (75.6)
Drug related serious adverse events, n		0	0	0
Edema, n (%)		0	1 (2.4)	0
Bone fracture n, (%)		0 (0)	0 (0)	0 (0)
Body weight (Kg)	mean (SD), baseline	89.8 (15.6)	84.7 (15.8)	84.6 (14.6)
	mean (SD), week 18	90.2 (16.7)	85.0 (16.8)	84.3 (15.4)
	mean (SD), change	0.4 (5.1)	0.3 (3.2)	-0.5 (2.8)

LS= least squares; *P < 0.05 vs placebo; **P < 0.001 vs placebo

Abbreviations:

LFC, liver fat content; CAP, controlled attenuation parameters; CK18, cytokeratin protein

ALT, alanine aminotransferase; LSM, liver stiffness measurement

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0055 | MAJOR VARIATIONS IN 90-DAY MORTALITY POST-HOSPITAL DISCHARGE AMONG INPATIENTS WITH CIRRHOSIS: A PROSPECTIVE COHORT STUDY FOR THE CLEARED CONSORTIUM

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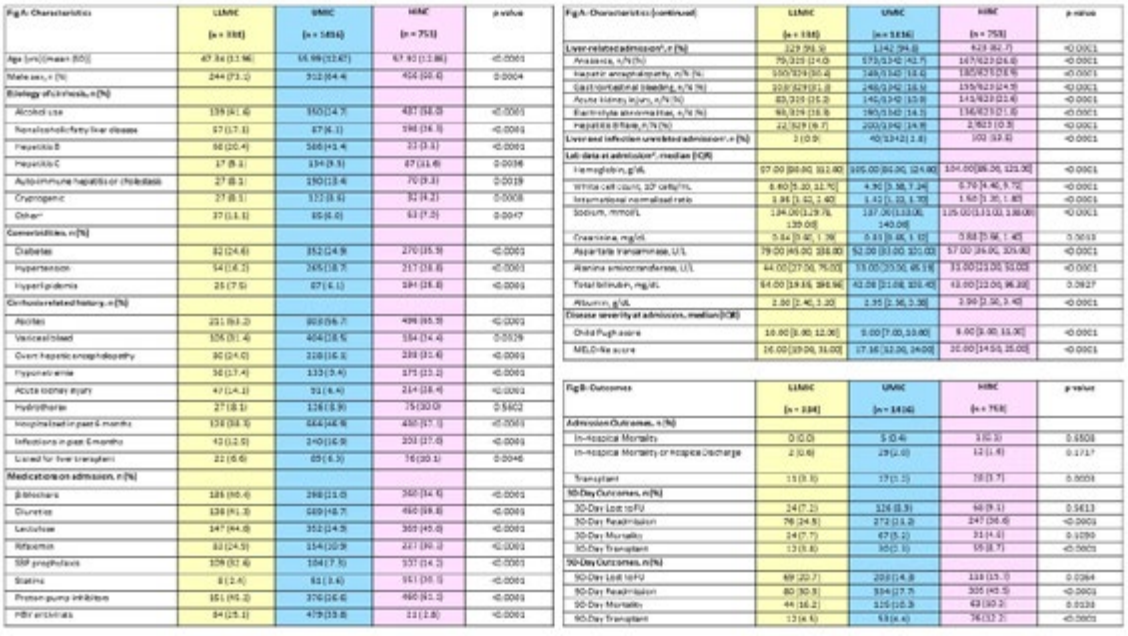
Background: Global variations in care affect 30-day outcomes among patients hospitalized for cirrhosis complications, but it is uncertain whether post-discharge 90-day mortality is impacted. Aim: Define 90-day mortality predictors in a global cohort of hospitalized patients with cirrhosis. **Methods:** CLEARED Consortium is a prospective cohort study that enrolled non-electively hospitalized adults with cirrhosis. Demographics, cirrhosis severity, admission details, and mortality were recorded. Primary outcomes were mortality, liver transplantation (LT), and readmission following index hospitalization or within 90 days post-discharge. Countries were divided into high- (HINC), upper-middle (UMIC), and low/low-middle-income countries (LLMIC) based on the World Bank. Logistic regression to predict outcomes was performed. **Results:** We enrolled 2503 patients from 25 countries who fulfilled eligibility criteria. The mean age was 55.2 years. One thousand six hundred twelve participants (64.4%) were men and 891 (35.6%) were women. Demographics and clinical characteristics are given in Figure A. 232 (9.3%) died, 719 (28.7%) were readmitted, and 141 (5.6%) received LT. The comparison of outcomes of the patients by income level of the country of origin was summarized in Figure B. Prior 6-mth hospitalization (relative risk [RR], 95% confidence interval [CI], 1.18 [1.05-1.34], p=0.007), infection in the past six months (RR, 95%CI, 1.69 [1.03-1.33], p= 0.02), SBP (RR, 95%CI, 0.80 [0.66-0.96], p= 0.017), PPI usage at admission (RR, 95%CI, 1.16 [1.03-1.31], p= 0.017), ALT level (RR, 95%CI, 1.0 [1.0-1.0], p= 0.015), Child score (RR, 95%CI, 1.06 [1.03-1.09], p< 0.0001), and country income (UMIC vs HINC; RR, 95%CI, 0.64 [0.56-0.73], and LLMIC vs HINC; (RR, 95%CI, 0.67 [0.55-0.82], p= <0.0001) were associated with readmission. Patient age (RR, 95%CI 1.03 [1.02-1.04], p= <0.0001), infection in the past six months (RR, 95%CI, 1.52 [1.18-1.95], p= 0.001), prior transplant listing (RR, 95%CI, 0.58 [0.36-0.93], p= 0.023), PPI (RR, 95%CI, 1.42 [1.11-1.82], p= 0.005), admission white blood cell counts (RR, 95%CI, 1.02 [1.0-1.03], p= 0.012), MELD-Na score (RR, 95%CI, 1.09 [1.07-1.1], p< 0.0001), and country income (UMIC vs HINC; 1.43 [1.07-1.90], and LLMIC vs HINC; (RR, 95%CI, 1.88 [1.31-2.70], p= 0.002) were associated with mortality. Previous LT listing (5.26 [3.79-7.28], p< 0.0001), PPI (1.70 [1.36-2.14], p< 0.0001), and country income (UMIC vs HINC; 0.58 [0.46-0.73], and LLMIC vs HINC; (0.52 [0.31-0.87], p< 0.0001) were associated with the likelihood of LT. **Conclusion:** In a global prospective cohort, World Bank income-based country differences were significantly associated with readmission, liver transplant, and 90-day post-discharge mortality in patients with cirrhosis.



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0056 | DECLINE OF PEDIATRIC ACUTE HEPATITIS OF UNKNOWN ETIOLOGY DURING THE CORONAVIRUS DISEASE 2019 PANDEMIC IN JAPAN ◆

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Background: Pediatric acute hepatitis of unknown etiology (AHUE) has been reported globally since April 2022. The purpose of the present study was to investigate the impact of coronavirus disease 2019 (COVID-19) pandemic on the development of AHUE in Japan. **Methods:** A nationwide full-scale survey of AHUE was conducted among 2,510 pediatric hospitals by the Japan Pediatric Society. We retrospectively reviewed AHUE cases, defined by the World Health Organization's working case definition, and compared the incidence, clinical characteristics and causative pathogens before the COVID-19 pandemic period (January 2017-December 2019) and during the pandemic period (January 2020-June 2022). Severe case was defined as patients who were into acute liver failure, required liver transplantation, or died, and the numbers of cases were summarized every 6 months. **Results:** Overall, 707 cases (450 before COVID-19, 257 during COVID-19) were reported. The median age was 3 years (interquartile range 1-9 years), and 310 cases (43.8%) were female. The number of AHUE cases decreased during the COVID-19 pandemic (102.8 cases/year) compared with the one in pre-pandemic period (150.0 cases/year). The most common cause of AHUE was unknown, accounting for 64% and 75% of cases before and during the COVID-19 pandemic, respectively. Among those whose pathogens were identified, Epstein-Barr virus, cytomegalovirus, and influenza were the top 3 common pathogens before and during the COVID-19; however, the rates were lower than those during COVID-19 pandemic (7.0%, 3.5%, 0.4%, respectively) compared to those before the COVID-19 pandemic (9.6%, 6.2%, 4.0%, respectively). SARS-CoV-2 (2.7%) was detected during the COVID-19 pandemic. The detection rates of adenovirus did not differ significantly before (1.6%) and during the COVID-19 pandemic (1.9%). The number of severe cases did not differ through the study period, ranging from 8 to 17 cases/6 months. **Conclusion:** The number of AHUE cases decreased during the COVID-19 pandemic compared with the pre-pandemic period, and no increase in severe cases was observed in Japan.

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0057 | CHARACTERISTICS OF PERSONS TREATED FOR HEPATITIS C IN THE UNITED STATES, 2014–2023

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[1]*Center for Disease Control and Prevention,* [2]*CDC*

Background: Over 2.4 million people are estimated to have hepatitis C in the United States. Highly effective, direct-acting antiviral (DAA) medications to cure hepatitis C have been available since 2014. Despite the safety and effectiveness of these medications, treatment rates have been historically low, particularly among younger persons and Medicaid recipients. We describe recent trends and characteristics of persons treated with DAAs to guide interventions to increase access to treatment. **Methods:** We analyzed data from IQVIA, a national

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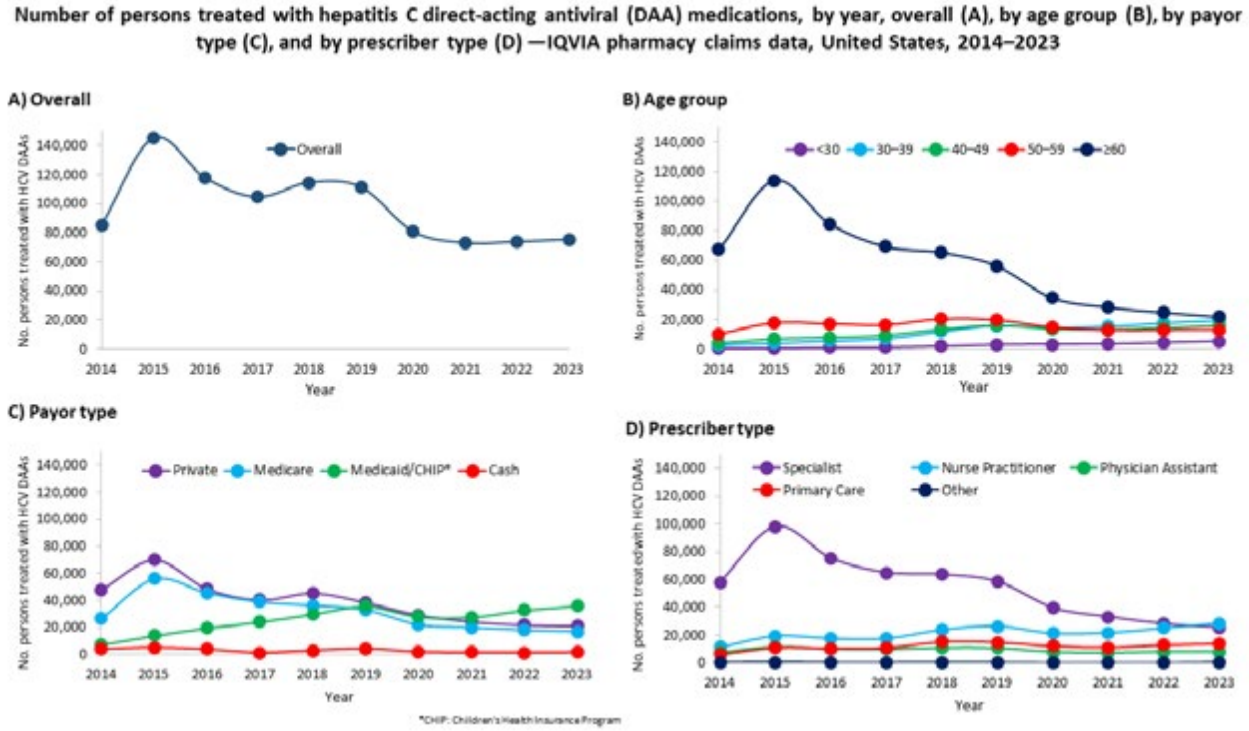
longitudinal database of pharmacy claims, to describe characteristics of persons treated with hepatitis C DAAs in the United States during 2014−2023. Information from the first paid claim was used to determine the number of persons treated for hepatitis C by year, payor type, provider type, and patient demographic characteristics. **Results:** During 2014–2023, 980,462 persons had evidence of treatment with DAAs in the IQVIA database. The annual number of persons treated was highest in 2015 (n=144,834), decreased gradually to a nadir in 2021 (n=73,066), and remained largely unchanged through 2023. Among those treated, 60% were male and 59% were born during 1945−1965; 39% of claims were paid by private insurers. Between 2014 and 2023, there were increases in the annual number of treated persons aged 30-49 years (from 6,600 to 35,544), treatments paid by Medicaid (from 7,070 to 35,926), and persons treated by non-specialists (from 24,915 to 50,103). **Conclusion:** After nearly a decade since DAAs first became available, far too few people with hepatitis C have received curative treatment. Despite these overall low treatment numbers, the increase in the annual number of younger persons treated and number of treatments paid by Medicaid since 2014 is encouraging. Interventions to expand access to treatment, such as removing Medicaid restrictions and prior authorization requirements, innovative approaches to reach younger persons where they already access services, and expansion of the non-specialist provider pool available to treat hepatitis C, will be crucial to eliminate hepatitis C as a public health threat in the United States by 2030.



Disclosures: Eyasu Teshale: Nothing to Disclose, Hasan Symum: Nothing to Disclose, Yuna Zhong: Nothing to Disclose, William Thompson: Nothing to Disclose, Neil Gupta: Nothing to Disclose

0058 | PLASMA MULTI-OMICS INDICATE THAT MITOCHONDRIAL STRESS AND ALTERED AMINO ACID METABOLISM CONTRIBUTE TO SARCOPENIA IN CHILDREN WITH GENETIC CHOLESTATIC LIVER DISEASE

Julia Boster[1] *COLIN ANDERSON*[2] *Julie Reisz*[2] *Ronald Sokol*[1] *Shikha Sundaram*[3]

[1]*University of Colorado School of Medicine,* [2]*University of Colorado School of Med,* [3]*Children's Hospital Colorado*

Background: Background: Reductions in muscle mass (sarcopenia) are common in children with genetic cholestatic liver disease, namely Alagille syndrome (ALGS) and chronic intrahepatic cholestasis (CIC), however the drivers of muscle wasting are not known. Aim: To assess mechanisms of sarcopenia in genetic cholestasis via an unbiased multi-omics approach. **Methods:** Appendicular lean mass was measured by dual energy x-ray

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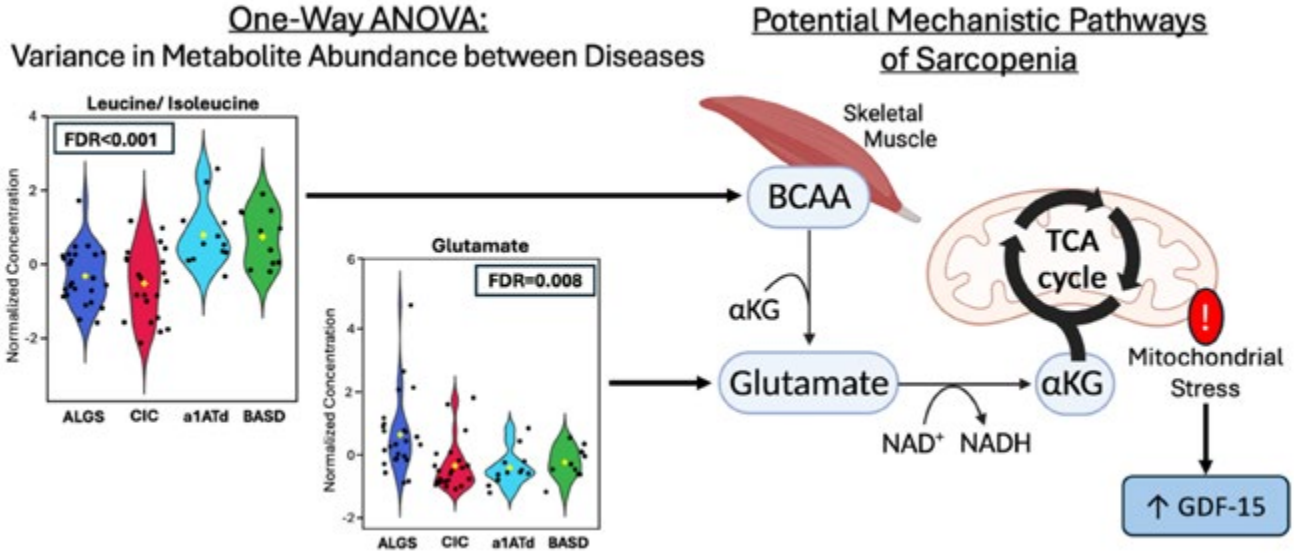
absorptiometry (DXA) obtained in the NIDDK-supported Childhood Liver Disease Research Network (ChiLDReN) study of genetic intrahepatic cholestasis (LOGIC) and used to calculate estimated skeletal muscle mass (eSMM) in children with ALGS, CIC, alpha-1 antitrypsin deficiency (a1ATd), and bile acid synthesis disorders (BASD). EDTA plasma was analyzed via proteomics (SomaLogic®) and mass spectrometry metabolomics. Relative protein abundance was studied in relation to eSMM z-score via Spearman correlation using a false discovery rate (FDR) <0.05 to account for multiple comparisons. Relative metabolite abundance was compared between diseases using ANOVA. **Results:** Muscle mass was severely reduced in ALGS and CIC (with 42% of ALGS and 33% of CIC experiencing eSMM z-score ≤-2). Plasma multi-omic analysis was performed in 79 participants (25 ALGS, 22 CIC, 12 a1ATd, 11 BASD, 9 controls) with available DXA (mean age 9.8 ± 3.9 years; 43% female; 15% Hispanic/Latino, 85% Non-Hispanic/Latino). eSMM z-score inversely correlated with growth/differentiation factor-15 (GDF-15; Rho -0.57, FDR<0.001), a marker of mitochondrial stress response. In diseases with severe muscle wasting (ALGS and CIC), the branched chain amino acids (BCAA) were significantly less abundant, and glutamate significantly more abundant (Fig.1), than in diseases without severe muscle wasting (BASD, a1AT). **Conclusion:** Conclusions: The significant inverse correlation between eSMM z-score and GDF-15 expression suggests a role for mitochondrial stress in the development of sarcopenia in children with genetic cholestasis. The reduced abundance of BCAAs along with the increased abundance of glutamate in diseases with sarcopenia may suggest an increased role for BCAA metabolism to maintain TCA cycle anaplerosis (Fig.1), contributing to muscle wasting observed in children with cholestatic liver disease.



Disclosures: Julia Boster: Nothing to Disclose, COLIN ANDERSON: BioMarin Pharmaceuticals: Employee, Julie Reisz: Nothing to Disclose, Ronald Sokol: Nothing to Disclose, Shikha Sundaram: Nothing to Disclose

0059 | HETEROZYGOUS KNOCKOUT OF BILE SALT EXPORT PUMP INDUCES ALTERATIONS IN THE GUT-LIVER AXIS INCLUDING GUT MICROBIOTA IN MICE FED A HIGH-FAT DIET ★

Kazuya Okushin[1] Kazuhiko Ikeuchi[1] Akira Kado[1] Toshiyuki Kishida[1] Takeya Tsutsumi[1] Kyoji Moriya[1] Hiroshi Yotsuyanagi[1] Kazuhiko Koike[2] Mitsuhiro Fujishiro[1]

[1]The University of Tokyo, [2]Kanto Central Hospital

Background: Bile acid metabolism has been identified as a therapeutic target for MASLD. We previously clarified that the expression of bile salt export pump (BSEP), a main bile acid export transporter from hepatocytes, decreases with the progression of MASLD in human liver tissue, suggesting that BSEP may be involved in the pathogenesis of MASH. To elucidate the mechanism, we further analyzed *Bsep* heterozygous knockout (*Bsep*$^{+/-}$) mice fed a high-fat diet (HFD). *Bsep*$^{+/-}$ mice showed significant alterations in the expression levels of genes related to bile acid and lipid metabolism in both the liver and ileum. In this study, we aimed to elucidate

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the underlying mechanism of BSEP-induced alteration in gut-liver axis, focusing on the microbiome. **Methods:** Male *Bsep*$^{+/-}$ and wild-type (C57BL/6J) mice were fed a HFD (containing 32.0% animal fat) from 8 to 20 weeks of age (n = 4 per group). Histological evaluation was performed by HE staining, and concentrations of total bile acids and lipids in the liver were also assessed. Gene expressions related to bile acid and lipid metabolism in the liver and terminal ileum were analyzed by real-time PCR. In addition, 16S rRNA metagenomic analysis of the gut microbiota was performed before and after HFD consumption. **Results:** *Bsep*$^{+/-}$ mice showed milder weight gain than wild-type mice, as we have previously reported. Total bile acid levels in the liver were relatively higher in *Bsep*$^{+/-}$ mice compared to wild-type mice (152.4 ± 119.4 μg/g vs. 64.8 ± 25.2 μg/g, p = 0.20), whereas there were no differences in hepatic lipid levels. Interestingly, serum total bile acid levels were significantly higher in *Bsep*$^{+/-}$ mice (114.0 ± 82.7 μmol/L vs. 2.0 ± 0.0 μmol/L, p = 0.04). Serum total cholesterol levels were significantly lower in *Bsep*$^{+/-}$ mice (94.8 ± 50.9 mg/dL vs. 184.5 ± 34.5 μmol/L, p = 0.03), whereas TG levels were not significantly different. Regarding the expression of genes in the liver, *Bsep* was significantly downregulated in *Bsep*$^{+/-}$ mice (p = 0.02). Interestingly, regarding gene expression in the terminal ileum, *transmembrane G protein-coupled receptor 5* was significantly decreased (p = 0.001), and *fibroblast growth factor 15* was relatively decreased (p = 0.12) in *Bsep*$^{+/-}$ mice. Analysis of the gut microbiota showed that the Shannon index, which indicates the diversity of the microbiota, was decreased after HFD consumption, especially in *Bsep*$^{+/-}$ mice. In addition, a species within the Coriobacteriia class in the Actinobacteria phylum increased in *Bsep*$^{+/-}$ mice. **Conclusion:** *Bsep*$^{+/-}$ mice on an HFD showed diverse alterations in bile acid and lipid metabolism in the liver and ileum, suggesting alterations in the gut-liver axis through regulation of BSEP. A loss of diversity in the gut microbiota and an increase in certain bacterial species were also observed. Further analysis of this model will be useful for elucidating the pathogenesis of MASLD progression based on bile acid metabolism. **Disclosures:** Kazuya Okushin: Nothing to Disclose, Kazuhiko Ikeuchi: Nothing to Disclose, Akira Kado: Nothing to Disclose, Toshiyuki Kishida: Nothing to Disclose, Takeya Tsutsumi: Nothing to Disclose, Kyoji Moriya: Nothing to Disclose, Hiroshi Yotsuyanagi: Nothing to Disclose, Kazuhiko Koike: Nothing to Disclose, Mitsuhiro Fujishiro: Nothing to Disclose

0060 | KUPFFER CELL REPOPULATION AFTER TOXIC DEPLETION RESULTS FROM PROPAGATION OF EMBRYONIC KCS AND NOT FROM MATURATION OF MONOCYTE-DERIVED REPLACEMENTS

Kyle Yuquimpo[1] Heer Mehta[1] KYO SASAKI[2] Isabel Aranzazu Pulido Ruiz[1] Sheetalnath Rooge[1] Steven Weinman[1]

[1]University of Kansas Medical Center, [2]Kawasaki Medical School

Background: CD163+ embryonic-derived Kupffer cells (eKCs) dominate the normal liver but in multiple different liver diseases, eKCs die and are partially replaced with CD163- monocyte-derived KCs (mKCs). The mechanisms of how CD163+ KCs are restored after long-term liver recovery are not clear and conflicting data suggest that either eKCs eventually replace all the mKCs, or that mKCs ultimately differentiate to become CD163+ and phenotypically identical with eKCs. The **Aim** of this study was to use a one-time KC ablation to study the time course and spatial characteristics of CD163+ KC repopulation and assess the cells of origin. **Methods:** Clec4f-DTR mice fed a chow diet were injected with a single dose of diphtheria toxin (DT). Livers were collected at 12 hours, 3 days, 2 weeks, 4 weeks, and 8 weeks after KC ablation for flow cytometry, immunohistochemistry, and qPCR. Data were presented as mean ± SE. Statistical significance was calculated by 2-tailed unpaired Student's t-test. **Results:** Twelve hours after KC ablation, there were no detectible KCs in the liver but round, monocyte-like, F4/80+ cells were present in small numbers in the sinusoids. At 3 days, F4/80+ KC numbers returned to normal. All of these KCs were CD163-. At 2 weeks, KC morphology and cell number was normal, almost all KCs were CD163- but rare clusters of 4-8 cell clusters of CD163+ KCs were observed. At 4 weeks, CD163+ clusters increased in size and number, and appeared against a background of normally distributed CD163-, F4/80+ KCs. Ki-67 staining showed that while the CD163- KCs were not proliferative, the CD163+ clusters consisted of highly proliferative cells. By 8 weeks, CD163+ KCs had replaced most of the CD163- KCs, were no longer arranged in clusters, and had repopulated the sinusoids throughout the lobule. Whole liver RT-PCR data confirmed these observations. The KC identity genes Clec4f and Vsig4 returned to normal levels by 2 weeks but "mature" KC genes Cd163 and Timd4 only returned to normal by 4-8 weeks. **Conclusion:** KCs rapidly repopulate the liver after KC ablation, but the initial cells are monocyte derived, non-proliferative and have a different gene expression pattern than mature KCs. Restoration of CD163+ KCs occurs from a limited number of proliferative CD163+ KC foci which are slow to appear but by 8 weeks they replace the CD163- KCs throughout the liver. The slow time

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course of mature KC restoration may impact the liver's response to disease states, such as MASH and ASH, in which KC death and replacement is prominent.

Disclosures: Kyle Yuquimpo: Nothing to Disclose, Heer Mehta: Nothing to Disclose, KYO SASAKI: Nothing to Disclose, Isabel Aranzazu Pulido Ruiz: Nothing to Disclose, Sheetalnath Rooge: Nothing to Disclose, Steven Weinman: Nothing to Disclose

0061 | DUAL-TARGET (HBV AND PD-L1 GENE) SIRNA ACHIEVED VERY HIGH AND RAPID HBSAG CLEARANCE AND ANTIVIRAL ACTIVITY IN AAV-HBV MICE

Zhiwei Yang[1] Nan Liu[1] Hongli Zhang[1] Ping Chen[1] Hui Chen[1]

[1]Suzhou Siran Biotechnology Co.,Ltd.

Background: Chronic hepatitis B (CHB) is a global public health burden affecting approximately 257.5 million people worldwide. Low functional cure rate and high percentage of viral rebound after treatments are still two major challenges in CHB drug development. **Results:** of recent clinical trials indicates that the functional cure of CHB requires drugs that help the recovery of depleted HBV specific immune cells, in addition to antiviral agents that directly targeting HBV life cycle. SA1211 is a N-acetylgalactosamine (GalNAc)-conjugated siRNA dimer targeting both HBV and PD-L1 gene expressionin the hepatocytes of patients. Thus, it can directly knockdown HBV mRNA and help to recover acquired immunity in one molecule. Here we report its pre-clinical studies results. **Methods:** SA1211 (also called "Dimer") or the 1:1 mixture composed of HBV siRNA and PD-L1 siRNA (called "Mixture", same sequences as of SA1211) was injected subcutaneously at 6 mg/kg single dose in humanized PD-1/PD-L1 AAV-HBV mice. This study has completed 70 days' observation. Serum HBsAg, HBV DNA and HBsAb were detected at different time points. Additionally, the safety profile was assessed in rat toxicity studies. **Results:** After single dose, 4/5 mice (80%) achieved HBsAg lower limit of quantification (LLOQ) in both the Dimer and Mixture group within D28. No HBsAg rebound was observed till D70. 4/5 mice (80%) and 5/5 mice (100%) achieved HBV DNA LLOQ in the Dimer and Mixture group within D14. 3/5 mice in the Dimer group and 4/5 mice in the Mixture group showed HBsAg seroconversion (HBsAb≥ 40 mIU/mL) at D70. No significant abnormality was observed in rat tox studies. **Conclusion:** SiranBio developed a dual-targeting siRNA dimer SA1211 for the functional cure of CHB. It showed very high and rapid clearance of HBsAg (80%) and HBV DNA (80%). HBsAg seroconversion was observed in >60% of tested mice. No HBsAg rebound was observed till the end of the experiments. In one molecule, SA1211 fights CHB by three mechanisms: inhibiting HBV replication, suppressing serum HBsAg level, and stimulating acquired immunity that can clear residual HBV infection or rebound. These results support its further pre-clinical and clinical development. It shows a unique mode of action and offers great potentials for CHB mono- and combo-treatments.

Disclosures: Zhiwei Yang: Nothing to Disclose, Nan Liu: Nothing to Disclose, Hongli Zhang: Nothing to Disclose, Ping Chen: Nothing to Disclose, Hui Chen: Nothing to Disclose

0062 | THE EFFICACY OF ANTIVIRAL THERAPY FOR HBV-INFECTED CHILDREN: A LARGE-SCALE, MULTICENTER PROSPECTIVE STUDY (SPROUT PROJECT) - AN INTERIM ANALYSIS

Hongfei Zhang[1] Qing He[2] Wenxian Ouyang[3] Shuangjie Li[3] Yilan Zeng[4] Jia Shang[5] Fang Wang[2] Lijuan Ouyang[6] Yujing Tang[6] Xiaoguai Liu[7] Pengfei Xu[7] Chuantiao Zhang[8]

[1]Beijing Huatan Integrative Medicine Hospital, Beijing, China, [2]The Third People's Hospital of Shenzhen, Shenzhen, China, [3]Hunan Children's Hospital, Changsha, China, [4]Public Health Clinical Center of Chengdu, Chengdu, China, [5]Henan Provincial People's Hospital, Zhengzhou, China, [6]Xiamen Traditional Chinese Medicine Hospital, Xiamen, China, [7]Xi'an Children's Hospital, Xi'an, China, [8]Shishi General Hospital, Shishi, China

Background: Nearly two million children in China are HBsAg-positive but data on antiviral treatment for them are limited. We aimed to investigate the efficacy and safety of different antiviral strategies for HBV-infected children, and explore the factors associated with HBsAg loss. **Methods:** This is a prospective, multicenter real-world study in China, three types of HBV-infected children were enrolled, including treatment-naïve, NA-experienced and

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normal ALT level population. All patients were 3-18 years old, HBsAg positive, and received NA monotherapy or in combination with peginterferon α-2b for 96 weeks according to the willing of their own or guardian (NCT05792761). **Results:** A total of 297 children who completed 48 weeks of treatment and had efficacy data were included in this analysis (NA monotherapy group, n=6; combination therapy group, n=291). The average age was 7.9 ± 3.77 years, 57.9% were male, 86.8% were HBeAg positive and 85.4% were HBV DNA positive. The mean baseline HBsAg, HBV DNA and HBeAg were 3.59, 5.85 $\log_{10}$ IU/mL and 2.56 $\log_{10}$ COI, respectively. 63.6% of patients were treatment-naïve chronic hepatitis B. In the total population and treatment-naïve patients, the HBsAg loss rates at week 48 were 24.7% (72/291) and 26.6% (49/184) and HBeAg loss rates were 19.8% (50/252) and 18.3% (31/169) in the combination therapy group, whereas no patients in the NA monotherapy group achieved any of above responses (Figure 1A). Significant HBsAg declines were noted in the combination therapy group as the duration of treatment progressed, reaching 2.10 and 2.29 $\log_{10}$ IU/mL at week 48 in the total and treatment-naïve populations, respectively, and elevated ALT levels were observed during HBsAg decline. Subgroup analysis of the combination therapy group showed that higher HBsAg loss rates existed in younger children. The HBsAg loss rates at week 48 were 30.6% and 19.7% (P = 0.032) for children aged ≥ 3 to < 7 and ≥ 7 to ≤ 18 years, respectively, in the total population, and 33.7% and 19.6% (P = 0.030), respectively, in the treatment-naïve population (Figure 1B). Both therapies were well-tolerated throughout the study. **Conclusion:** HBV-infected children can achieve significant higher HBsAg loss and HBeAg loss rate in peginterferon α-2b combination group, especially for those aged < 7 years. Peginterferon α-based strategies used at an early age in pediatric patients can better pursue functional cure.

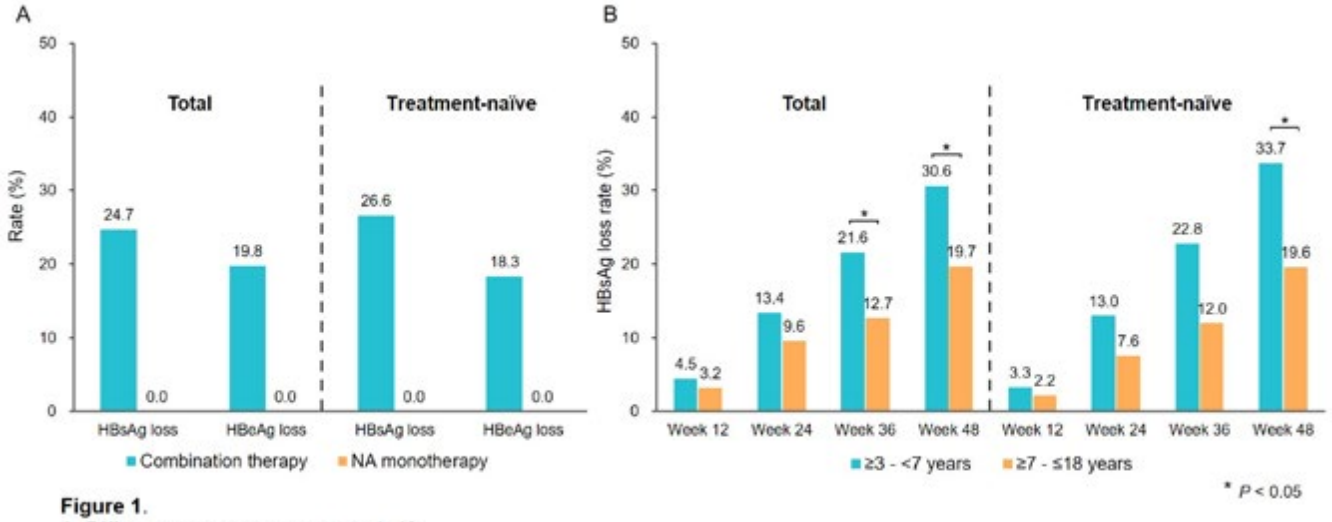

Figure 1.
A. Different response rates at week 48.
B. HBsAg loss rates over time in children aged ≥3 - <7 and ≥7 - ≤18 years in the combination therapy group.

Disclosures: Hongfei Zhang: Nothing to Disclose, Qing He: Nothing to Disclose, Wenxian Ouyang: Nothing to Disclose, Shuangjie Li: Nothing to Disclose, Yilan Zeng: Nothing to Disclose, Jia Shang: Nothing to Disclose, Fang Wang: Nothing to Disclose, Lijuan Ouyang: Nothing to Disclose, Yujing Tang: Nothing to Disclose, Xiaoguai Liu: Nothing to Disclose, Pengfei Xu: Nothing to Disclose, Chuantiao Zhang: Nothing to Disclose

0063 | LIVER STIFFNESS AS A PREDICTIVE FACTOR FOR HEPATOCELLULAR CARCINOMA DEVELOPMENT AFTER SUSTAINED VIROLOGIC RESPONSE BY DIRECT-ACTING ANTIVIRALS FOR CHRONIC HEPATITIS C

Naoto Kawabe[1] *Teiji Kuzuya*[1] *Yoshiki Hirooka*[1]

[1]*Fujita Health University*

Background: Hepatocellular carcinoma (HCC) development after sustained virologic response (SVR) with direct-acting antivirals (DAAs) treatment for HCV (hepatitis C virus) infection have been reported as important issue recently. The aim of the present study was to evaluate the risk of HCC after SVR with DAAs treatment for HCV infection, including changes in liver stiffness. **Methods:** Of 628 patients who treated with DAAs for

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chronic hepatitis C or HCV-related cirrhosis in our department from September 2014 to August 2023, this study included 376 SVR patients with sequential liver stiffness (velocity of shear wave; Vs) measured with shear wave elastography (virtual touch quantification; S-2000, Siemens Healthineers) for at least 1 year after SVR. **Results:** During the follow-up period (median: 57 months), development of HCC was observed in 32 patients (8.8%). HCC occurrence was observed in 11 patients (3.4%) among 326 patients without HCC history, and HCC recurrence was observed in 21 patients (42%) among 50 patients with HCC history. There was no significant decrease in Vs in HCC occurrence group, whereas there was a significant decrease in Vs at 1 year (1.24m/s) and 3 years (1.18m/s)(after the end of treatment (EOT) compared with the start of treatment (baseline; BL) (1.40m/s) and EOT (1.31m/s) (all P<0.01). Platelet count and PT were significantly lower, and age, total bilirubin, hyaluronic acid, AFP, Vs at BL, EOT, 1 year and 2 years after EOT were significantly higher in HCC occurrence group compared with no occurrence group. Multiple logistic regression analysis selected high total bilirubin (beta=7.67092, P=0.0172) at BL, high AFP (beta=0.006060, P=0.0329) at BL, high Vs at 1 year after EOT (beta=7.95061, P=0.0463) as the factors associated with HCC occurrence. In ROC analysis, total bilirubin>0.98 mg/dl and AFP>7.2ng/ml at BL and Vs>1.88m/s at 1 year after EOT are independent risk factors associated with HCC occurrence (AUROC 0.895, 0.807, 0.883). On the other hand, multiple logistic regression analysis selected no factor associated with HCC recurrence after SVR in patients with HCC history. In HCC occurrence group, curative treatments (surgical resection in 9 patients, radiofrequency ablation in 2 patients) were performed in all patients. **Conclusion:** Shear wave elastography reflects not only liver fibrosis but also inflammation to some extent. In this study, liver stiffness at BL reflects liver fibrosis and inflammation with HCV infection. The reason why liver stiffness at 1 year after EOT was associated with HCC occurrence is presumably that liver stiffness at 1 year after EOT reflects only true liver fibrosis, since the inflammation has improved with SVR. These findings suggested that careful monitoring for HCC detection is required even after SVR in patients with high liver stiffness and no decrease after DAAs treatment.

Disclosures: Naoto Kawabe: Nothing to Disclose, Teiji Kuzuya: Chugai Pharmaceutical Co: Speaking and Teaching, Eisai: Speaking and Teaching, Eli Lilly Japan: Speaking and Teaching, AstraZeneca: Speaking and Teaching, Yoshiki Hirooka: Nothing to Disclose

0064 | SAFETY AND EFFICACY OF NAFAMOSTAT MESYLATE ANTICOAGULATION IN CENTRIFUGAL ARTIFICIAL LIVER SUPPORT SYSTEM FOR ALF AND ACLF PATIENTS AT HIGH RISK OF BLEEDING

Zhu Xinfang[1] *Bing-Yao Wang*[1] *Jian-Ming Zheng*[1] *Rong Xia*[1]

[1]*Huashan Hospital, Fudan University*

Background: Patients with acute liver failure (ALF) and acute-on-chronic liver failure (ACLF) are consistently at high risk of bleeding and most exhibit decreased platelet levels, presenting a challenge for the conventional approach to artificial liver support systems (ALSS). Alterations to anticoagulation strategies and procedural may improve outcomes for these critical patients. **Methods:** This study involves patients with ALF and ACLF at high risk of bleeding. Paradigm of ALSS is centrifugal double molecular adsorption system sequential plasma exchange (cDPMAS+PE) administered with nafamostat mesylate (NM) anticoagulation. After cALSS, new bleeding, blood gas analysis, DIC and thromboelastography (TEG) after cALSS 0.5h serve as primary monitors to evaluate safety, while changes in blood ammonia and MELDs after last session are utilized as secondary monitors to assess efficacy. **Results:** A total of 51 patients were included in the study, consisting of 30 patients with ALF and 21 patients with ACLF . Every cALSS session time was about 180.00 (152.50, 193.50) min, and NM dosage was about 32.84 ± 8.88mg. Following cALSS treatment for 0.5 hours, DIC did not deteriorate, as indicated by TEG demonstrating a hypocoagulation state characterized by prolonged reaction time (R) and kinetics time (K) values (2.85 (2.15, 6.73) min, 7.35 (5.80, 11.43) min, respectively, P **Conclusion:** The use of NM anticoagulation in patients with ALF and ACLF who are at high risk of bleeding demonstrates both safety and efficacy. Monitoring platelet and fibrinogen levels before treatment may help determine the appropriate NM dosage.

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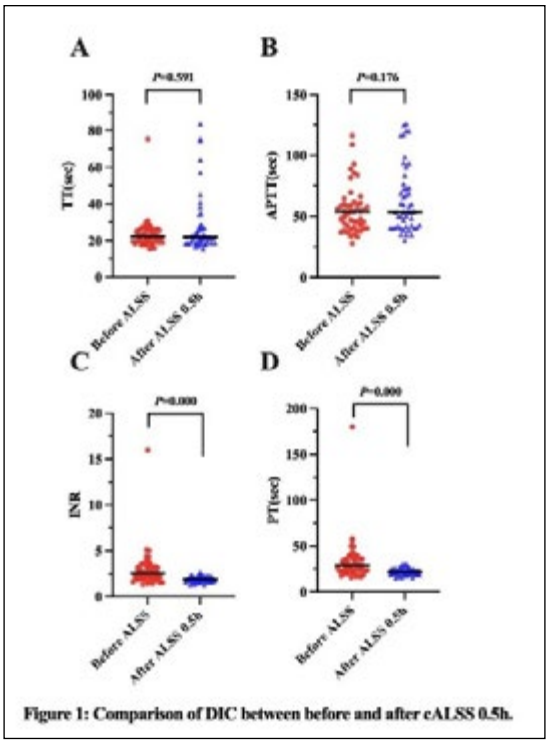

Figure 1: Comparison of DIC between before and after cALSS 0.5h.

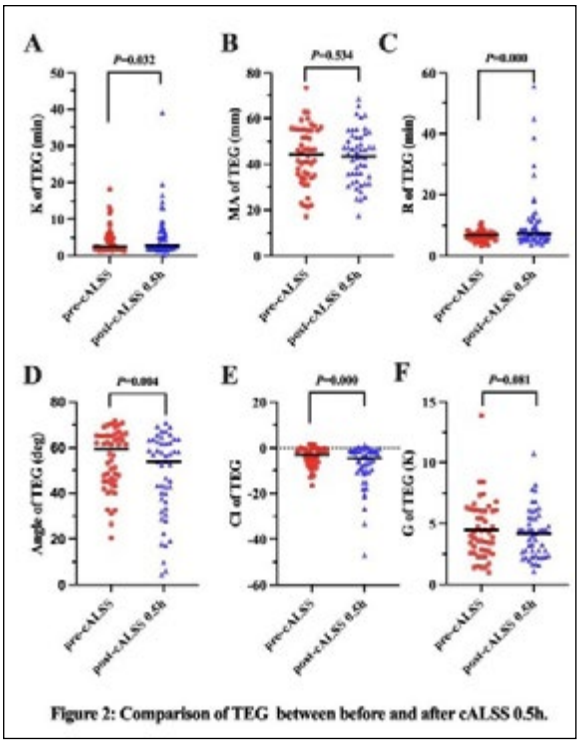

Figure 2: Comparison of TEG between before and after cALSS 0.5h.

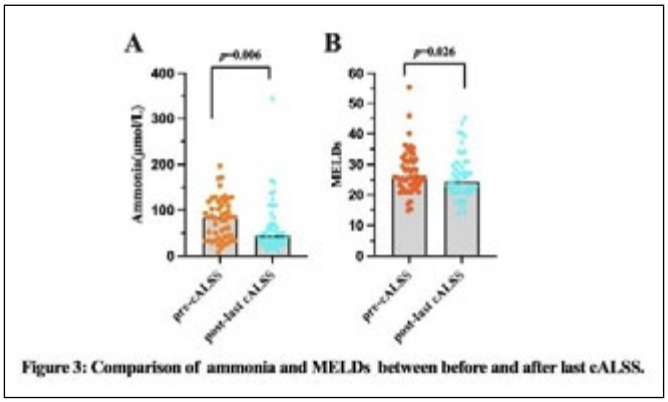

Figure 3: Comparison of ammonia and MELDs between before and after last cALSS.

Disclosures: Zhu Xinfang: Nothing to Disclose, Bing-Yao Wang: Nothing to Disclose, Jian-Ming Zheng: Nothing to Disclose, Rong Xia: Nothing to Disclose

0065 | HEPATIC STELLATE CELLS REGULATE LIVER SIZE, ZONATION, METABOLISM, INJURY AND REGENERATION VIA R-SPONDIN 3

Atsushi Sugimoto[1] Yoshinobu Saito[1] Guanxiong Wang[2] Qiuyan Sun[1] Ki Hong Lee[2] Yana Geng[1] Marcella Steffani[1] Deqi Yin[1] Jingran Qie[1] Adrien Guillot[3] Tian Lan[3] Frank Tacke[3] Jochen Hampe[4] Mario Brosch[4] Presha Rajbhandari[1] Taruna Neelakantan[1] Brent Stockwell[1] Yujin Hoshida[5] Timothy Kendall[6] Jonathan Fallowfield[6] Brandon Lehrich[7] Satdarshan (Paul) Monga[7] Josepmaria Argemi[8] Ramon Bataller[9] Hellmut Augustin[2] Robert Schwabe[1]

[1]Columbia University, [2]Heidelberg University, [3]Charité - Universitätsmedizin Berlin, [4]Technische Universität Dresden, [5]University of Texas Southwestern Medical Center, [6]University of Edinburgh, [7]University of Pittsburgh School of Medicine, [8]University of Navarra, [9]Institut d'Investigacions Biomèdiques August Pi i Sunyer

Background: Hepatic stellate cells (HSCs) have been shown to exert a central pathogenic role in the development of liver fibrosis and progression of chronic liver disease (CLD). In contrast, potentially beneficial and homeostatic functions of HSCs remain largely elusive. **Methods:** HSCs were depleted via LratCre-induced diphtheria toxin receptor expression in mice. HSC ligand-receptor interactions, pathways and candidate mediators

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were analyzed in mouse and human bulk and single cell/nucleus RNA-seq. LratCre-transgenic mice were used for HSC-specific knockout of candidates, including Rspondin-3 (Rspo3$^{\Delta HSC}$). Liver zonation and metabolic changes were studied by multiplex immunohistochemistry, spatial transcriptomics and bulk or spatial metabolomics. Mice were subjected to acetaminophen (APAP) treatment, high-fat or Lieber DeCarli diet or 70% partial hepatectomy (PHx). Outcomes were analyzed in the Steatosite-MASLD and InTEAM-ALD patient cohorts. **Results:** HSC-depleted mice displayed small livers, impaired regeneration following 70% PHx and blunted APAP-induced liver injury. HSC depletion reduced b-catenin activity and target genes in hepatocytes and altered liver zonation, with collapsed Cyp2e1 and Cyp1a2 expression in zones 2-3 and expanded Cyp2f2 in zone 1. Sc/snRNA-seq and CellphoneDB uncovered a strong enrichment of Rspo3, an upstream regulator of b-catenin, in HSCs from mice and patients, mediating interactions with hepatocytes via LGR4. Rspo3$^{\Delta HSC}$ mice phenocopied the alterations in liver size, regeneration, APAP-induced injury, zonation and b-catenin activity of HSC-depleted mice; and displayed increased MASLD- and ALD-induced steatosis and injury, alongside elevated hepatic bile acids and pericentral triglyceride accumulation. These alterations in liver size, regeneration, injury and metabolism mimic changes in Ctnnb1$^{\Delta Hep}$ and Lgr4$^{\Delta Hep}$ mice, suggesting hepatocyte-regulatory roles for HSC-derived Rspo3 via Lgr4 and b-catenin. Accordingly, Rspo3 expression in HSCs correlated strongly (R=0.61-0.81) with b-catenin target gene expression in hepatocytes in human snRNA-seq. Furthermore, Rspo3 in HSCs decreased with disease progression in mice and patients, and low RSPO3 expression was significantly associated with mortality, liver events and HCC development in patients with MASLD and ALD. **Conclusion:** HSCs exert a hitherto unknown role in regulating hepatocyte zonation, metabolism, injury and regeneration via Rspo3 and its downstream target b-catenin. Understanding and targeting the dynamic expression of RSPO3 may restore HSC balance and liver function, and provide novel therapeutic avenues for the treatment of CLD.

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0066 | JAIL LENGTH OF STAY DOES NOT ACCOUNT FOR GENDER DIFFERENCES IN HEPATITIS C TREATMENT INITIATION IN THE NEW YORK CITY JAIL SYSTEM, 2019–2023

Raphael Simonson[1] Batya Koenigsberg[1] Natalia Gonzalez Varela[1] Jacqueline LaPene[1] Richard Figueroa[1] Janet Wiersema[1] Chibuzo Enemchukwu[1]

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Background: Women experiencing incarceration in the New York City (NYC) jail system have shorter median lengths of stay (LOS) than men and initiate jail-based hepatitis C (HCV) treatment at nearly half the rate of men. Short LOS is cited as an important barrier to jail-based HCV care, potentially impeding opportunities for jail-based HCV treatment initiation following diagnosis. However, there is little data examining the effect of LOS on HCV treatment initiation among women experiencing incarceration. This study examines the role of jail LOS on select HCV care cascade outcomes among women and men in the NYC jail system. **Methods:** We performed

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a retrospective cohort analysis of persons in the NYC jail system who completed a medical intake between October 2019 and December 2023. We examined differences in jail LOS, rates of active HCV, demographic characteristics, and key health metrics by documented gender. We used logistic regression to examine gender differences in select HCV cascade steps—specifically, being seen by an HCV clinician and initiating HCV treatment—while accounting for jail LOS. **Results:** 71,130 persons were included in our analysis, of whom 5,085 (7.1%) were women and 66,045 (92.9%) were men. Of 2,520 (3.5%) who underwent confirmatory testing for HCV, women and men had similar rates of active HCV (51.2% vs. 47.8%; p=0.22). Median LOS for women was shorter than for men (18 days vs. 27 days; p<0.001). When adjusting for differences in LOS among women and men, women with active HCV had significantly greater odds of being seen by an HCV clinician (OR 1.714, 95% CI [1.191–2.467]) but significantly lower odds of initiating HCV treatment (OR 0.577, 95% CI [0.355–0.937]). Women had significantly higher rates of homelessness (23.5% vs. 19.5%), HIV (3.7% vs. 2.7%), mental health needs (55.1% vs. 31.8%), and history of select substance use disorders (58.6% vs. 45.8%) when compared to men (p<0.001). **Conclusion:** Shorter LOS among women does not alone account for the large HCV treatment gaps observed between women and men experiencing incarceration in this jail setting. Disproportionally higher rates of comorbid medical, mental health, and substance use disorders, and more re-entry needs among women likely contribute to these treatment disparities. Gender-specific strategies centered on the needs of women with justice involvement are critical to ensuring equitable uptake of jail-based HCV treatment and securing a path toward HCV elimination.

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0067 | IMPROVING HEPATITIS B SCREENING USING EMR HARD-STOP IN RESIDENT PRIMARY CARE CLINIC

Beatriz Torre[1] Joshua Riley[1] Benjamin Young[1] Parker O'Neill[1] Suraj Nyalakonda[1] Daniel Njoku[1] Jonathan Fenkel[1]

[1]Thomas Jefferson University Hospital

Background: In March 2023, the CDC recommended Hepatitis B virus (HBV) universal triple screening for all adults, testing surface antigen (sAg), surface antibody (sAb), and total core antibody (cAb), regardless of perceived risk. Electronic medical record (EMR) systems have proven to be a powerful tool to improve quality metrics like universal screening. We designed a quality improvement (QI) project to explore whether utilizing an EMR-based tool called a Care Gap, a "hard-stop" mechanism of quality improvement, within our academic health system's EPIC-based EMR could increase HBV screening in the primary care resident clinics. **Methods:** The HBV screening Care Gap was instituted on February 13, 2024. Demographic variables and baseline HBV screening rates were collected at two internal medicine resident-focused ambulatory sites during a two-week period, one month prior to (Pre) and one month following (Post) the release of the Care Gap. Variables collected included age, race, gender, and prior HCV screening (another Care Gap viral screening test already in our EMR for several years) and prior HIV screening (with no Care Gap). The pre- and post-intervention groups were compared using descriptive statistics and Chi-squared testing. **Results:** The study cohort included 724 patients (380 Pre and 344 Post intervention). No differences between mean age (48 +/- 16 vs 48 +/- 17 years), race (57 vs 59% AA, 33 vs 30% White), or gender (38% vs 35% male) were observed between the groups. Only 16% of patients in the Pre group had prior HBV triple screening. By comparison, 83% had prior HCV screening and 54% had prior HIV screening. Post-intervention, the observed HBV screening rate increased to 44% (p<0.05). Among the patients who were screened, only 36% were protected against HBV infection. 3% of those screened had chronic HBV, 11% were HBcAb positive and 50% of the patients lacked HBV immunity (See Graph). **Conclusion:** The EMR-based HBV screening Care Gap hard-stop alert resulted in a 175% increase in HBV screening rates in just 1 month after going live, with a 28% absolute increase in HBV screening from 16% to 44%. Half of the adults screened were not protected against HBV and would benefit from vaccination. Importantly, 1 in 9 adults in our academic, resident-focused primary care clinics were HBcAb+ and therefore at risk for HBV reactivation if immunosuppressed. These data support further adoption of the CDC triple screening recommendation and utilization of EMR-based QI tools such as the hard-stop Care Gap to enhance screening.

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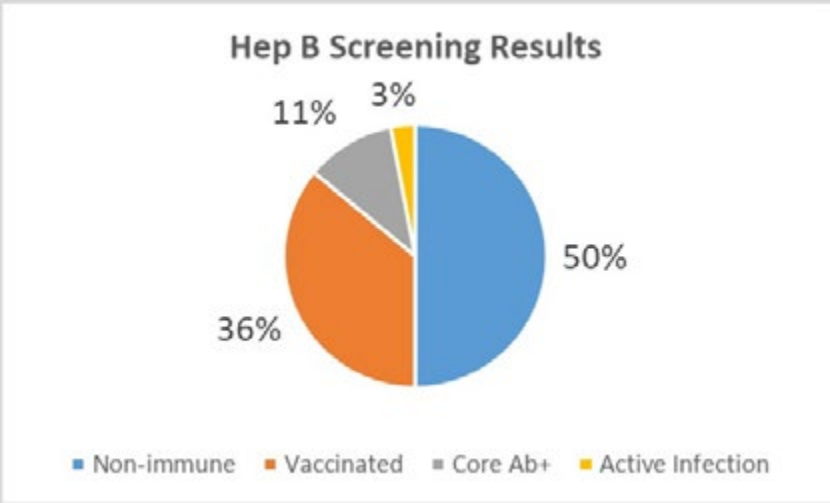

Disclosures: Beatriz Torre: Nothing to Disclose, Joshua Riley: Nothing to Disclose, Benjamin Young: Nothing to Disclose, Parker O'Neill: Nothing to Disclose, Suraj Nyalakonda: Nothing to Disclose, Daniel Njoku: Nothing to Disclose, Jonathan Fenkel: Gilead: Research Support to Institution, Abbvie: Research Support to Institution, Alexion: Research Support to Institution, Ipsen: Research Support to Institution, BMS: Consultant

0068 | CARVEDILOL DOES NOT PREVENT DECOMPENSATION IN PATIENTS WITH COMPENSATED CIRRHOSIS WITHOUT HIGH-RISK VARICES WITH CLINICALLY SIGNIFICANT PORTAL HYPERTENSION DEFINED BY NON-INVASIVE TESTS: A RANDOMISED CONTROLLED TRIAL ★

Syed Ahmed[1]

[1]*All India Institute of medical sciences, New Delhi*

Background: In patients with compensated cirrhosis and clinically significant portal hypertension(CSPH) [hepatic venous pressure gradient(HVPG)≥10mmHg] without high-risk varices, carvedilol reduces all-cause decompensations. Whether this benefit is extendable to pragmatically defined CSPH [based on non-invasive liver-stiffness measurement(LSM)] remains to be seen. **Methods:** In this open-label two-centre randomized-controlled trial with superiority design including patients with aetiologically controlled (alcohol abstinence/ adequately managed metabolic risk-factors; virological control/suppression as applicable) compensated cirrhosis with pragmatic evidence of CSPH without high-risk varices (LSM≥15kPa plus low-risk varices; LSM≥20 kPa plus low-risk/no-varices), participants were randomised to receive either carvedilol (titrated upto 25mg daily as tolerated) or no drug. The primary endpoint was incidence of all-cause decompensation (ascites/ variceal bleed/encephalopathy) at 12-month follow-up. Trial protocol was prospectively registered (CTRI/2022/08/044878) and ethically approved (IECPG-326/28.05.2021, RT-13/23.06.2021). **Results:** We enrolled 269 (carvedilol:135; no-drug:134) participants (age:47.1 ±11.6 years, 28.6% females, etiology: non-alcoholic steatohepatitis (NASH)/alcohol/hepatitis B/hepatitis C: 26%/16%/16%/14%; median MELD:8[IQR:7-10]; median LSM: 26.0[IQR:21.0-38.8]; 72.8% low-risk varices) of whom 236 (87.7%) completed 12-months follow-up. At 12-months, all-cause-decompensations occurred in 12 (8.9%) and 13 (9.7%) participants in carvedilol and no-drug arm respectively (risk-difference:0.8%[95%CI:-7.8–6.1%];p=0.81). Similar incidence of all-cause-decompensation (2.4%,9.4%,21.0% vs 5.5%,10.1%,15.2%) was noted at 6-,12-,24-months respectively, with overall median follow-up of 22 (IQR:12-25) months. Most common decompensation was ascites [17(13.6%) vs 14(11.2%)] followed by variceal-bleed [4(3.2%) vs 2(1.6%)]. High-risk varices developed similarly in both groups(carvedilol:11.9%; no-drug 9.5%; risk-difference:2.5% [95%CI:-6.0–10.9%]). Carvedilol adequately lowered heart-rate [mean 1-yr heart-rate:67.2 ± 5.6bpm vs 77.2±7.9bpm; difference 10.0(95%CI:8.0-12.0)bpm] at median tolerated dose of 12.5mg/daily; 7 (6.1%) required discontinuation due to adverse-effects. **Conclusion:** Carvedilol did not reduce decompensations over 12 months in patients with pragmatically defined CSPH and aetiologically-controlled compensated cirrhosis without high-risk varices.

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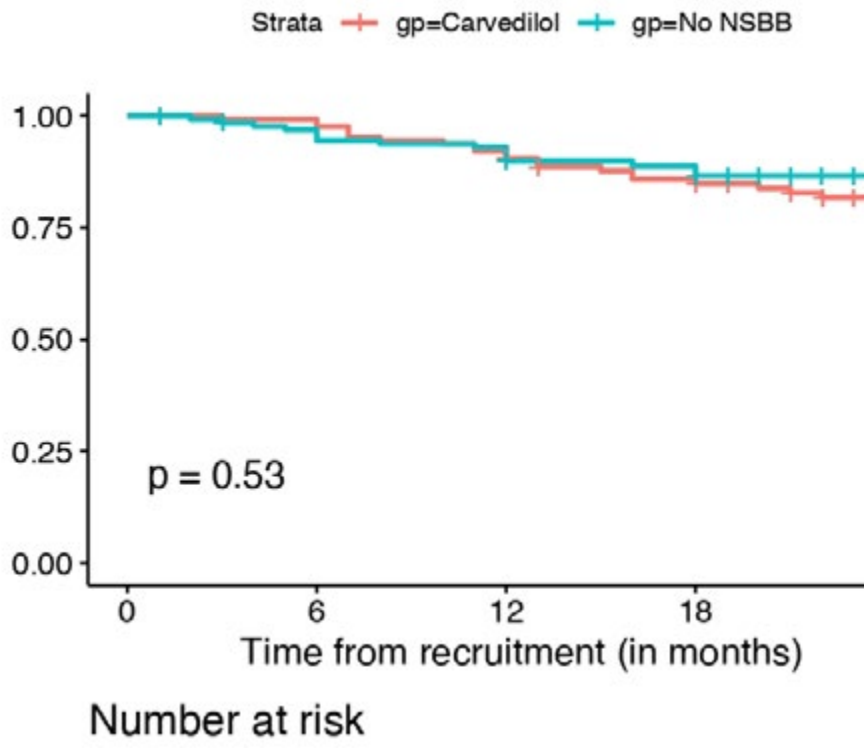

Disclosures: Syed Ahmed: Nothing to Disclose

0069 | GASTROINTESTINAL AND LIVER ADVERSE EFFECTS OF MEDICAL TREATMENTS OF ALCOHOL USE DISORDER: A PHARMACOVIGILANCE ANALYSIS OF THE FDA ADVERSE EVENT REPORTING SYSTEM (FAERS) DATABASE ◆ ★

Soo Young Hwang[1] *Jay Luther*[2] *Wei Zhang*[2]

[1]*University of Maryland Midtown Campus,* [2]*Massachusetts General Hospital*

Background: Despite the high prevalence of alcohol-associated liver disease (ALD), alcohol use disorder (AUD) remains undertreated, partly due to concerns about the safety profile of pharmacological agents. There is a lack of large-scale studies focusing on adverse events, especially gastrointestinal and liver-related side effects, of FDA-approved drugs indicated for AUD. We aim to explore the gastrointestinal and liver adverse effects associated with the 3 FDA-approved therapies for AUD - disulfiram, acamprosate, and naltrexone - in patients with AUD using a large database. **Methods:** Reports from the FDA Adverse Event Reporting System (FAERS) database were collected from the first quarter of 2004 to the last quarter of 2023. The drugs identified were disulfiram, acamprosate, oral naltrexone, and intramuscular naltrexone (Vivitrol). The indication for therapy was alcohol use disorder. A disproportionality analysis was performed to identify gastrointestinal and liver adverse events associated with the three drugs by comparing them with the full drugs indicated for alcohol use disorder in the FAERS database using the reporting odds ratio (ROR) and information component (IC). **Results:** A total of 891 reports on disulfiram, 985 reports on acamprosate, 7,489 reports on oral naltrexone, and 17,617 reports on intramuscular naltrexone were collected for analysis. The most frequently reported gastrointestinal and liver side effects were elevated liver enzymes (568 reports), vomiting (295 reports), nausea (209 reports), and abdominal pain (195 reports). The IC of all gastrointestinal adverse events had a median of 4.34 (95%CI 4.07 to 4.54) in disulfiram, median of 0.92 (95%CI -0.02 to 1.56) in acamprosate, median of -1.42 (95%CI -2.49 to -0.69) in oral naltrexone, and a median of -2.22 (95% CI -2.94 to -1.72) in intramuscular naltrexone. Disulfiram had an ROR of 24.01 (95%CI 11.23-51.85) in acute hepatic failure and 6.31 (95%CI 4.69-8.41) in elevated liver enzymes. Acamprosate had an ROR of 5.66 (95% CI 1.64-15.73) in elevated ammonia levels and 4.86 (95%CI 2.06-10.23) in elevated bilirubin levels. Oral naltrexone had an ROR of 3.08 (95% CI 2.43-3.91) and intramuscular naltrexone had an ROR of 2.37 (95% CI 2.02-2.8) in nausea and vomiting. While the ROR of elevated liver enzymes was

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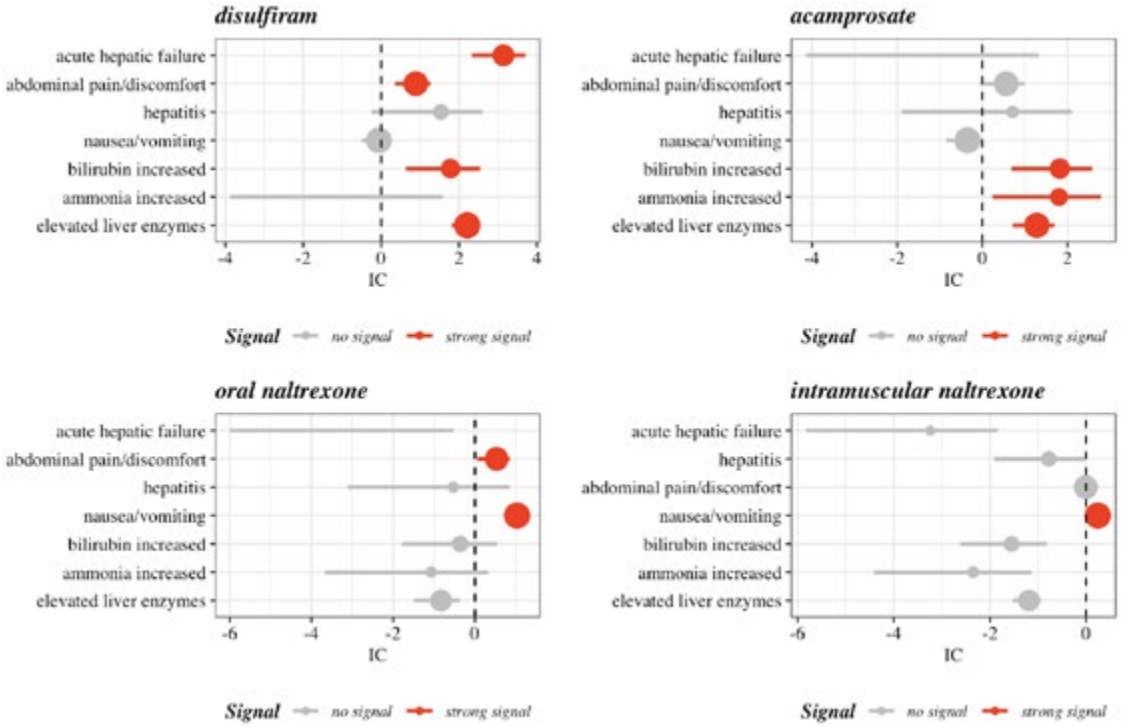
0.48 (95% CI 0.31-0.74) in oral naltrexone and 0.17 (95% CI 0.13-0.22) in intramuscular naltrexone (Figure 1). **Conclusion:** Naltrexone had overall better gastrointestinal and liver safety profile compared to disulfiram and acamprosate, with intramuscular naltrexone showing lower side effects than oral naltrexone. Disulfiram has the highest risk of liver toxicity followed by acamprosate.



Disclosures: Soo Young Hwang: Nothing to Disclose, Jay Luther: Nothing to Disclose, Wei Zhang: Nothing to Disclose

0070 | PREDICTORS OF TREATMENT FAILURE AND RESISTANCE ASSOCIATED SUBSTITUTIONS IN PATIENTS WITH CHRONIC HEPATITIS C INFECTIONS - HCV ELIMINATION EXPERIENCE FROM THE PUNJAB MODEL IN INDIA

Radha Dhiman[1] Madhumita Premkumar[2] Jasvinder Nain[2] Ajay Duseja[2] EkTA Gupta[3] Sahaj Rathi[2] SUNIL TANEJA[2] Surender Singh[1] Akash Roy[1] Anchal Sandhu[2] Prerna Sharma[2] Gagandeep Singh Grover[4]

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Background: The prevalence of HCV is 3.6% in the state of in Punjab, India with an estimated 728,000 viremic chronic hepatitis C (CHC) patients and HCV cure rate the national hepatitis C elimination programme (NVHCP) is 91.6% (Dhiman RK et al, J Hepatol 71(6):1076-1085). We collected the clinical and virological data for the ~8% treatment failure cases to ascertain presence of resistance associated substitutions (RAS) and clinical predictors of treatment failure when using generic direct-acting antivirals (DAAs)- sofosbuvir with an NS5A inhibitor (ledipasvir, daclatasvir or velpatasvir) ± ribavirin in a public health setting. **Methods:** Amplification of relevant portions of the HCV genome was done by polymerase chain reaction with HCV-specific primers targeting the NS5B and NS5A region. We used the Sanger dideoxy nucleotide sequencing method to identify the amino acid substitution (in terms of nucleotide coordinates) at the desired position. **Results:** Between April 2020 and Dec 2022, 50,865 persons with HCV infection were managed under supervision of the hub (Department of Hepatology, Postgraduate Institute of Medical Education & Research, Chandigarh 160012, India). A total of 640 persons [no cirrhosis 439 (68.6%), cirrhosis 121(18.9%)] and decompensated 80 (12.5%) aged 39.2 ± 15.1 years, 66.1% from rural areas, 63 (9.8%) with diabetes, 96 (15%) with hypertension, 57% treatment experienced, 11% with prior defaulter status were included. The HCV viral load (x10^6) had a median value of 1.98 (range: 1.5-2.44). Genotype 3 (GT3) being the most prevalent (73.3%), followed by genotype 1 (GT1) (18.7%), and co-infections (HIV 4.4%; HBV 3.8%). Risk factors for infection included (unsafe injection 57%, Inject Drugs Use 32.8%). Most of these

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patients (n=260; 77.3%) had treatment failure to SOF/DCV. On multivariable analysis, prior treatment experience (aHR 12.8, 95%CI:6.8-42.6, P=0.002), poor adherence (aHR 2.2, 95%CI 1.9-4.3, P=0.004) and deranged INR (aHR 1.3, 95%CI 1.1-1.6, P=0.008) predicted treatment failures. Among them, 243 samples underwent RAS testing, with only 45 patients having detectable mutations and a total of 21 mutations were detected in the NS5A gene, with no clinically significant resistance observed in the NS5B gene (Table 1). **Conclusion:** RAS is not the primary factor for treatment failure in a public health setting in Punjab, India. Factors such as prior treatment experience, poor adherence to treatment, drug compliance and poor liver function predicted treatment failures. (ClinicalTrials.gov number: NCT03488485)

Table 1: Cumulative mutations and RAS detection in the patient cohort

SR. No.	GT	Gene	Type of Mutation	N (%)	RAS (Yes/No)	Interpretations
1	1a	NS5A	30G	2	NO	Unknown significance
2	1a	NS5A	28A	1	YES	Resistance to Daclatasvir-Ledipasvir
3	1a	NS5A	58P	2	YES	Resistance to Daclatasvir-Ledipasvir
4	1a	NS5A	30H	4	NO	Resistance to Daclatasvir-Ledipasvir
5	1a	NS5A	32L	1	YES	Resistance to Daclatasvir-Ledipasvir
6	1a	NS5A	58N	1	YES	Resistance to Daclatasvir
7	1a	NS5A	93K	1	YES	Unknown significance
8	1a	NS5A	93N	4	NO	Unknown significance
9	3a	NS5A	30K	3	YES	Resistance to Ledipasvir
10	3a	NS5A	31M	4	YES	Resistance to Daclatasvir-Ledipasvir and Susceptible to Velpatasvir
11	3a	NS5A	30L	1	NO	Susceptible to Daclatasvir-Ledipasvir- Velpatasvir
12	3a	NS5A	62S	1	NO	Unknown significance
13	3a	NS5A	30P	2	NO	Unknown significance
14	3a	NS5A	62T	3	NO	Unknown significance
15	3b	NS5A	30Q	5	YES	Resistance to Ledipasvir
16	1c	NS5A	28V	1	NO	Unknown significance
17	3a	NS5A	30S	1	NO	Pan Susceptible
18	3a	NS5A	30V	1	NO	Unknown significance
19	3a	NS5A	30Y	1	NO	Unknown significance
20	3a	NS5A	30T	2	YES	Resistance to Daclatasvir
21	3a	NS5A	93H	2	YES	Resistance to Daclatasvir-Velpatasvir

Disclosures: Radha Dhiman: Nothing to Disclose, Madhumita Premkumar: Nothing to Disclose, Jasvinder Nain: Nothing to Disclose, Ajay Duseja: Nothing to Disclose, EkTA Gupta: Nothing to Disclose, Sahaj Rathi: Nothing to Disclose, SUNIL TANEJA: Nothing to Disclose, Surender Singh: Nothing to Disclose, Akash Roy: Nothing to Disclose, Anchal Sandhu: Nothing to Disclose, Prerna Sharma: Nothing to Disclose, Gagandeep Singh Grover: Nothing to Disclose

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0071 | CLINICAL AND GENETIC CHARACTERISTICS OF PATIENTS WITH HISTOLOGIC STEATOSIS DEFINED BY NATURAL LANGUAGE PROCESSING IN THE MVP LIVER BIOPSY COHORT

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[1]Philadelphia VAMC, UPenn, [2]VINCI, [3]VINCI, VA Salt Lake City, [4]University of Pennsylvania, [5]VA Long Beach Healthcare System, [6]VA Boston Healthcare System

Background: Metabolic-Associated Steatotic Liver Disease (MASLD) is a leading cause of chronic liver disease (CLD). While liver biopsy is a gold-standard method to define hepatic steatosis and steatohepatitis, biopsy-confirmed MASLD cohorts have been limited in sample sizes (n<1500) and diversity. Here, we leveraged Natural Language Processing (NLP) in the VA's Million Veteran Program (MVP) to define a Liver Biopsy Cohort with hepatic steatosis for further clinical and genetic analyses. **Methods:** Genotyped MVP participants (n=658,220) were assessed for having a liver biopsy based on CPT codes (47000, 47001, 37200, 75970, 76942) and liver-related key terms in biopsy reports, excluding liver transplant recipients. Biopsy reports were analyzed for steatosis, inflammation, ballooning and fibrosis using rules-based NLP with performance >90% F1 (harmonic mean of Precision and Recall). The NLP readouts were merged with clinical data to define: Steatosis (≥5% steatosis), MASLD (steatosis, no other CLD) and MASH (MASLD + advanced fibrosis or inflammation). Ancestry-specific genome-wide association studies (GWAS) were conducted for the 3 groups relative to 230,982 MVP controls without known liver disease, using the SAIGE software with age, gender and 10 principal components as covariates. Identified signals were evaluated for Linkage Disequilibrium to identify LD independent SNPs using PLINK. Multi-ancestry meta-analysis used a fixed-effects model using METAL with inverse-variance weighting of log odds ratios. $P \leq 5x10^{-8}$ was considered genome-wide significant (GWS). **Results:** As shown in Table 1, the biopsy cohort (n=13,145) was predominantly white males in their 50-60's. Compared to controls, the cohort was more enriched for Blacks (29% vs 17%, p<0.001), Hispanics (11% vs 6%, p<0.001) and metabolic comorbidities. NLP identified 4,009 (30.4%) with steatosis, 1,850 (14%) with MASLD and 1,532 (11.7%) with MASH. MASLD and MASH cohorts had less %cirrhosis and %HCC compared to Steatosis or total biopsy cohort. GWS loci were identified for: Steatosis (PNPLA3, TM6SF2, TRIB1, GCKR, SERPINA1), MASLD (PNPLA3, TM6SF2, LOC157273, TRIB1, GCKR, LOC101927026 fig1) and MASH (PNPLA3, TM6SF2, MYEOV). The MASLD locus (LOC101927026) and MASH locus (MYEOV) were novel. Our MASLD cohort also replicated additional MASLD loci reported in previous studies. **Conclusion:** We developed the largest and most diverse histological steatosis cohort to date using NLP, with GWS associations with known and novel loci.

A. Demographic and Clinical Characteristics	Controls without known liver disease (n=230,982)	Liver Biopsy Cohort			
		Total Biopsy Cohort (n=13,145)	Steatosis+ (n=4,009)	MASLD+ (n=1,850)	MASH (n=1,532)
	%	%	%	%	%
%Male	96%	93%	92%	88%	89%
Age, Median (IQR 25, 75)	68 (62, 74)	60 (54, 67)	58 (51, 64)	58 (48, 66)	59 (48, 66)
Race					
%White	74%	58%	59%	65%	64%
%Black	17%	29%	28%	12%	12%
%Hispanic	6%	11%	15%	19%	20%
%Others	2%	2%	3%	4%	4%
Metabolic and Liver-related Risk Factors					
%T2D	29%	45%	51%	57%	59%
%OBESE	43%	55%	68%	79%	81%
%DL	69%	73%	76%	82%	83%
%HTN	76%	87%	87%	84%	84%
BMI, Median (IQR 25, 75)	29(26, 33)	31(27, 35)	33 (29, 36)	34 (31, 38)	35 (31, 39)
ALT, Median (IQR 25, 75)	20 (17, 24)	45 (28, 75)	56 (36, 88)	53 (33, 82)	54 (34, 82)
Audit-C (Mean +/- SD)	1.45 +/- 1.91	1.50 +/- 2.51	1.59 +/- 2.62	1 +/- 1.57	1.00 +/- 1.57
Alcohol (ICD + Audit-C >5)		4.8%	4.4%	0.0%	0.0%
%HCV		42.6%	36.2%	0.0%	0.0%
%HBV		2.1%	1.6%	0.0%	0.0%
%HH	No known risk	1.8%	2.6%	0.0%	0.0%
%PBC	factor for chronic	1.3%	0.9%	0.0%	0.0%
%PSC	liver disease	2.0%	1.0%	0.0%	0.0%
%AIH		1.7%	1.4%	0.0%	0.0%
%A1AT		0.3%	0.5%	0.0%	0.0%
%WD		0.1%	0.2%	0.0%	0.0%
%Cirrhosis	0.2%	23.0%	24.0%	10.7%	12.1%
%HCC	0.0%	7.6%	4.5%	1.5%	1.6%

Table 1. Clinical characteristics of liver biopsy cohort with hepatic steatosis, MASLD and MASH relative to population controls

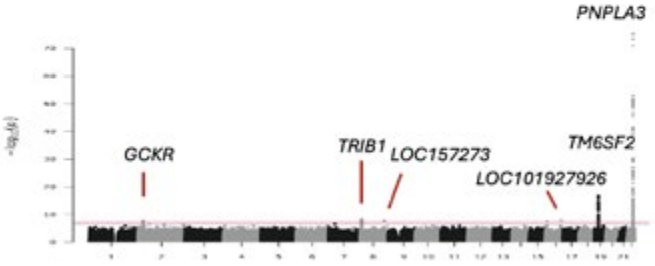

Figure 1. Manhattan plot of trans-ancestry GWAS of MASLD

Disclosures: Samiran Mukherjee: Nothing to Disclose, Patrick Alba: Nothing to Disclose, Anthony Gao: Nothing to Disclose, Craig Teerlink: Nothing to Disclose, David Kaplan: Independent Contractor relationship with Roche Genentech; Has not ended; Grant/Research Support relationship with AstraZeneca Inc; Has not ended; Advisor

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relationship with AstraZeneca; Has ended; Advisor relationship with Exelixis; Has ended; Grant/Research Support relationship with Gilead; Has not ended; Advisor relationship with Sirtex; Has ended; Grant/Research Support relationship with Exact Sciences; Has not ended; Grant/Research Support relationship with Glycotest; Has ended, K Rajender Reddy: Nothing to Disclose, Tia Dinatale: Nothing to Disclose, Timothy Morgan: Nothing to Disclose, Saiju Pyarajan: Nothing to Disclose, Daniel Dochtermann: Nothing to Disclose, Marijana Vujkovic: Nothing to Disclose, Julie Lynch: Nothing to Disclose, Kyong-Mi Chang: Data Monitoring Committee member relationship with Virion Therapeutics; Has not ended; Advisor relationship with GSK; Has ended

0072 | CONVERGENT EVOLUTION OF SOMATIC ESCAPE VARIANTS IN THE LIVER IN ALPHA-1 ANTI-TRYPSIN DEFICIENCY ◆

Natalia Brzozowska[1] Lily Wu[2] Vera Khodzhaeva[2] William Griffiths[2] Adam Duckworth[3] Yvette Hooks[4] Joseph Chambers[2] Peter Campbell[4] Stefan Marciniak[2] Matthew Hoare[2]

[1]Wellcome Sanger Institute, [2]University of Cambridge, [3]Addenbrooke's Hospital, Cambridge, [4]Wellcome Trust Sanger Institute

Background: Somatic variants accumulate in non-malignant tissues with age. Functional variants leading to clonal advantage of hepatocytes accumulate in the liver from patients with acquired chronic liver disease (CLD); clonal expansions in Steatotic Liver Disease (SLD) are frequently driven by mutations in genes involved in lipid metabolism and insulin signalling, thereby protecting hepatocytes from lipid toxicity. Whether these somatic variants are common to CLD from differing aetiologies is not known. We analysed somatic variants in the liver from patients with genetic CLD from alpha-1 anti-trypsin deficiency (A1AD) or haemochromatosis. **Methods:** Here we used laser-capture microdissection to isolate 311 microbiopsies from the liver of 5 patients with ZZ-A1AD and 5 with haemochromatosis undergoing liver transplantation. Whole-genome and exome sequencing was used to analyse the burden and genic locations of somatic variants. *In vitro* modelling of somatic variants was performed in cell lines, before analysis with fluorescence microscopy and immunoblotting. **Results:** We show that somatic variants in SERPINA1, the gene encoding A1AT, are strongly selected for in A1AD, with evidence of convergent evolution: all 5 patients had multiple independent hepatocyte clones with acquired SERPINA1 variants. By contrast, there was no significant evidence for selection in the liver of patients with haemochromatosis. Acquired variants of SERPINA1 are clustered at the 3' end of the gene leading to C-terminal missense or truncation variants of A1AT. In vitro, C-terminal truncation variants reduce disease-associated A1AT polymerisation and ER inclusions compared to germline Z-A1AT, suggesting that they act as somatic escape variants. **Conclusion:** Therefore, somatic escape variants from the deleterious germline Z-A1AT variant are selected for in A1AD, through avoidance of C-terminal domain swap-based polymerisation in A1AD. More broadly, adaptive functional somatic variants are disease-specific in CLD and point to disease-associated mechanisms.

Disclosures: Natalia Brzozowska: Quotient Therapeutics: Consultant, Lily Wu: Nothing to Disclose, Vera Khodzhaeva: Nothing to Disclose, William Griffiths: Nothing to Disclose, Adam Duckworth: Nothing to Disclose, Yvette Hooks: Nothing to Disclose, Joseph Chambers: Nothing to Disclose, Peter Campbell: Nothing to Disclose, Stefan Marciniak: Nothing to Disclose, Matthew Hoare: Pfizer: Grant/Research Support, Boston Scientific: Consultant, AstraZeneca: Consultant, Quotient Therapeutics: Consultant

0073 | INITIATION OF RENAL REPLACEMENT THERAPY IN CRITICALLY ILL PATIENTS WITH CIRRHOSIS/CHRONIC LIVER DISEASE: A SECONDARY ANALYSIS OF STARRT-AKI TRIAL

Constantine Karvellas[1] Fernando Zampieri[1] Oleksa Rewa[1] Ron Wald[2] Sean Bagshaw[1]

[1]University of Alberta, [2]University of Toronto

Background: Acute kidney injury is common in critically ill patients with cirrhosis/chronic liver disease (CLD), many of whom receive renal-replacement therapy (RRT). However, the most effective timing and modality for the initiation of such therapy remains uncertain. **Methods:** We conducted a secondary analysis of the STandard versus Accelerated Renal Replacement Therapy in Acute Kidney Injury (STARRT-AKI) trial. Patients were randomly assigned to receive an accelerated strategy of RRT (therapy initiated within 12 hours after the patient

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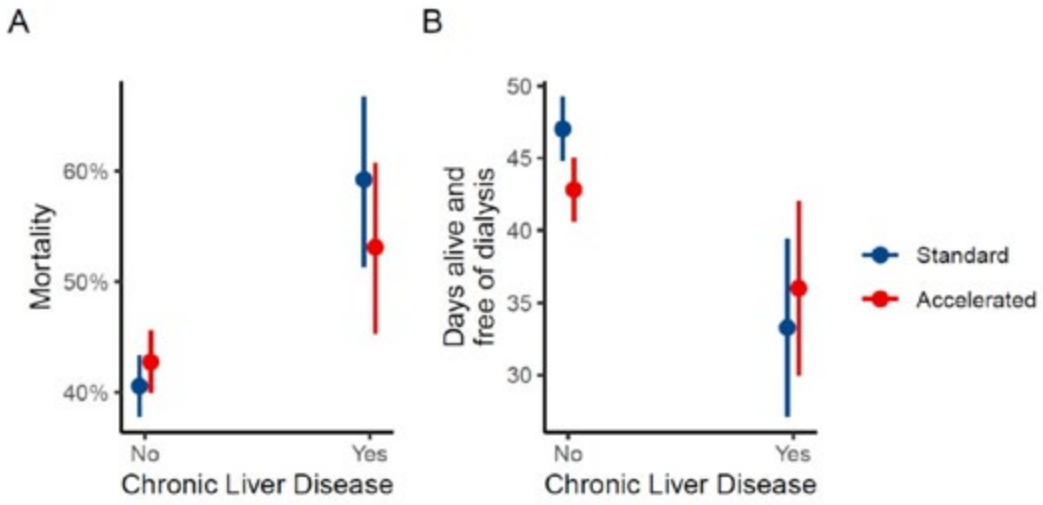
had met eligibility criteria) or a standard strategy (in which RRT was discouraged unless conventional indications developed, or AKI persisted for >72 hours). We compared patients with (n=337) and without (n=2590) CLD and described potential differences in treatment effects according to the presence/absence of CLD in STARRT-AKI. Differences in treatment effects for CLD versus non-CLD patients were assessed using regression models adjusted for illness severity, pre-randomization creatinine, and CLD with interaction for treatment strategy. Results are presented as marginal effects according to group for 90-day mortality and days alive and free of RRT. **Results:** Patients with CLD were younger (60 vs 67 years; p<0.001) and had higher SOFA scores (13 vs. 12; p<0.001) at enrollment. Receipt of mechanical ventilation (75% vs. 77%) and vasopressor support (68% vs. 71%) were similar. The most common initial RRT modality was continuous (CRRT) in both groups (59% vs 54%; p=0.3). 90-day mortality was significantly higher (56% vs. 42%, p<0.001) and number of days alive and free of RRT was significantly fewer (median of 0 versus 64) in CLD patients (p<0.001). The accelerated strategy was not associated with differences in mortality (odds ratio 1.01; 95% 0.98-1.05; p=0.51), with no significant interaction between CLD versus non-CLD patients (p=0.16 for interaction). The accelerated strategy conferred fewer days alive and free of RRT (mean difference of -3.4 days; 95% CI -6.3 to -0.46; p=0.01); however, there was no significant interaction between CLD and treatment strategy (p=0.14). **Conclusion:** Among critically ill patients with severe AKI, those with CLD/cirrhosis had higher mortality and had fewer RRT-free days. In critically ill patients with cirrhosis/CLD, an accelerated RRT initiation strategy was not associated with a lower risk of death at 90 days than a standard strategy. (Funded by the Canadian Institutes of Health Research and others; STARRT-AKI ClinicalTrials.gov number, NCT02568722)



Disclosures: Constantine Karvellas: Consultant relationship with Mallinckrodt; Has not ended; Advisor relationship with Baxter; Has not ended; Advisor relationship with Grifols; Has not ended; Data safety monitoring board for clinical trial relationship with Miromatrix; Has not ended, Fernando Zampieri: Nothing to Disclose, Oleksa Rewa: Nothing to Disclose, Ron Wald: Nothing to Disclose, Sean Bagshaw: Nothing to Disclose

0074 | EFFICACY AND SAFETY OF TOBEVIBART (VIR-3434) ALONE OR IN COMBINATION WITH ELEBSIRAN (VIR-2218) IN PARTICIPANTS WITH CHRONIC HEPATITIS DELTA VIRUS INFECTION: WEEK 24 PRIMARY ENDPOINT ANALYSIS FROM THE PHASE 2 SOLSTICE TRIAL

Tarik Asselah[1] Anca Streinu-Cercel[2] Alina Jucov[3] Edward Gane[4] Heiner Wedemeyer[5] Pietro Lampertico[6] Michael Chattergoon[7] Sophia Chow[7] Pan Wu[7] Cara Pilowa[7] Todd Correll[7] Carey Hwang[7] Kosh Agarwal[8]

[1]Hôpital Beaujon, [2]National Institute for Infectious Diseas, [3]Arensia Exploratory Medicine GmbH, [4]Auckland Clinical Studies, [5]Hannover Medical School, [6]University of Milan, [7]Vir Biotechnology, Inc., [8]King's College Hospital

Background: Hepatitis D virus (HDV) infection causes the most severe form of chronic viral hepatitis with limited treatment options. The SOLSTICE trial is investigating the efficacy and safety of the monoclonal antibody tobevibart (VIR-3434) alone and in combination with the silencing RNA elebsiran (VIR-2218) in chronic HDV

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infection (NCT05461170). **Methods:** Efficacy and safety were assessed in participants receiving either tobevibart 300 mg SC Q2W (tobevibart Q2W) or the combination of tobevibart 300 mg SC + elebsiran 200 mg SC Q4W (Combo *de novo* Q4W) for 24 weeks. Safety and efficacy were also assessed in participants who transitioned to the Combo *rollover* Q4W cohort from early monotherapy cohorts. The combined endpoint (CE) was defined as an undetectable (< LOD, 14 IU/mL) *or* ≥ 2 $\log_{10}$ decrease in HDV RNA plus ALT normalization. The proportion of participants with HDV RNA < LLOQ, HDV Target not detected (TND) and TND plus ALT normalization are also reported. **Results:** Preliminary results to date are presented (Table). HDV < LLOQ was observed in >50% of participants completing Week 24 in tobevibart Q2W and 100% in Combo *de novo* Q4W, with HDV TND achieved by 55% Combo *de novo* Q4W at Week 24. ALT normalization was similar in both cohorts at Week 24 and no ALT flares have been observed to date. This resulted in CE rates of 64% for Combo *de novo* Q4W and 55% for tobevibart Q2W. The combined HDV TND plus ALT normalization response rate of Combo *de novo* Q4W was higher than tobevibart Q2W (46% vs 18%). All participants in the Combo *rollover* Q4W cohort achieved and maintained virologic suppression with 2/5 achieving ALT normalization suggesting a durable on-treatment response. Treatment-emergent adverse events were primarily Grade 1-2, transient in nature, with the most common being Influenza-like syndrome, myalgia, headache, and chills. There were low rates of treatment discontinuation. Week 24 data for all participants, including non-cirrhotic and compensated cirrhotic (approx. 50% of each cohort), receiving tobevibart Q2W and Combo Q4W therapy will be presented. **Conclusion:** In preliminary 24-week data, tobevibart alone or in combination with elebsiran exhibited high rates of virologic suppression against HDV. Greater than 50% of participants in both regimens achieved the primary CE. When applying HDV TND to the combined response, higher response rates were observed in combo therapy with no ALT flares regardless of baseline viral parameters.

	Tobevibart Q2W		Combo *de novo* Q4W		Combo *rollover* Q4W
	Wk 12 N=26[a]	Wk 24 N=11[a]	Wk 12 N=27[a]	Wk 24 N=11[a]	Wk 48 N=5[b]
Change in HDV RNA relative to baseline[c], Mean (SD) $\log_{10}$ IU/mL	-3.05 (1.18)	-4.38 (1.73)	-4.15 (1.16)	-4.94 (1.67)	-3.04 (2.45)
HDV RNA < LLOQ, n (%)	7 (26.9)	6 (54.5)	14 (51.9)	11 (100)	5 (100)
HDV RNA < LOD, n (%)	5 (19.2)	5 (45.5)	10 (37.0)	10 (90.9)	5 (100)
HDV RNA TND, n (%)	2 (7.7)	2 (18.2)	4 (14.8)	6 (54.5)	4 (80)
ALT normalization, n (%)	14 (53.8)	7 (63.6)	12 (44.4)	7 (63.6)	2 (40)
Change in ALT relative to baseline, Mean (± SD)[c], IU/mL	-23.9 (21.6)	-41.5 (28.4)	-32.2 (40.5)	-63.7 (56.9)	-22.0 (22.4)
Combined Endpoint, n (%)	10 (38.5)	6 (54.5)	12 (44.4)	7 (63.6)	2 (40)
HDV RNA TND + ALT normalization, n(%)	0 (0)	2 (18.2)	1 (3.7)	5 (45.5)	2 (40)
TEAE by maximum severity grade, n (%) Grade 1 Grade 2 Grade ≥3		 11 (33.3) 17 (51.5) 1 (3.0)		 9 (28.1) 16 (50) 0 (0)	 0 (0) 4 (66.7) 0 (0)

[a] N is the number of participants who have completed the study visit or discontinued before the study visit

[b] Combo Q4W rollover has 6 total participants enrolled with 5 participants reaching Week 48

[c] For Combo Q4W *rollover* Day 1 = Day 1 of Combination therapy

Disclosures: Tarik Asselah: Nothing to Disclose, Anca Streinu-Cercel: Nothing to Disclose, Alina Jucov: Nothing to Disclose, Edward Gane: Aligos Therapeutics: Advisor, Assembly Biosciences: Advisor, AbbVie: Speaking and Teaching, Intellia Therapeutics: Advisor, Tune Therapeutics: Consultant, Precision Bio: Advisor, Virion

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Therapeutics: Advisor, Gilead Sciences: Advisor, GSK: Advisor, Heiner Wedemeyer: Nothing to Disclose, Pietro Lampertico: ROCHE PHARMA/DIAGNOSTICS, GILEAD SCIENCES, GSK, ABBVIE, JANS: Advisor, Michael Chattergoon: Nothing to Disclose, Sophia Chow: Nothing to Disclose, Pan Wu: Nothing to Disclose, Cara Pilowa: Nothing to Disclose, Todd Correll: Nothing to Disclose, Carey Hwang: Vir Biotechnology, Inc: Employee and stock holder, Kosh Agarwal: Nothing to Disclose

0075 | CANCER-INDUCED REPROGRAMMING OF MACROPHAGE NUCLEOTIDE METABOLISM DISMANTLES ANTI-TUMOR IMMUNITY

Shuang Liang[1] *Chuanli Zhou*[2] *Zhenyu Zhong*[1]

[1]*University of Texas Southwestern Medical Center,* [2]*UT Southwestern Medical Center*

Background: By establishing a pro-inflammatory and pro-tumorigenic environment within the liver, tumor-associated macrophages (TAMs) play a crucial role in propelling the progression of hepatocellular carcinoma (HCC) – the dominant form of primary liver cancer. However, the mechanisms by which tumor-derived elements 'educate' TAMs within the liver to facilitate HCC progression remain largely unknown. **Methods:** Mice with myeloid-specific deletion of SAMHD1 and their littermate controls were subjected to two mouse models of HCC induced by (1) intraperitoneal injection of diethylnitrosamine (DEN) or (2) hydrodynamic tail vein injection (HDI) of different combinations of oncogenic plasmids. By the end of each experiment, serum and liver were collected for histological and biochemistry analysis. Hepatic immune cells, TAMs, and macrophages in the non-tumor regions (non-TAMs) were isolated using $CD45^+$ and $F4/80^+$ magnetic beads, followed by analysis of mitochondrial DNA (mtDNA), cellular dNTP levels, RNAseq, western blot, and flow cytometry. In vitro experiments were performed in human macrophage cell line THP1 cells stimulated with conditioned medium derived from human liver epithelial cells (THLE-3) and HCC cell lines (HepG2 and Huh7). **Results:** In this study, we demonstrate that TAMs exhibit significantly elevated levels of (mtDNA) in contrast to non-TAMs. This is attributable to diminished expression of SAMHD1 – a cytosolic dNTP hydrolase pivotal for maintaining cellular nucleotide homeostasis. We found that HCC cell-secreted factor(s) inhibit(s) SAMHD1 by downregulating its mRNA, leading to the aberrant accumulation of cytosolic dNTPs. These dNTPs are then transported into mitochondria, providing excessive building blocks for mtDNA synthesis. Utilizing two discrete murine HCC models, we found that myeloid-specific deletion of *Samhd1* promotes HCC progression through increased PD-L1 expression and CXCL1/2-mediated recruitment and activation of polymorphonuclear myeloid-derived suppressor cells (PMN-MDSCs). Mechanistically, SAMHD1 deletion precipitates elevation in mtDNA levels and augments mitochondrial ROS production. This cascade activates HIF1α, thereby upregulating PD-L1 and CXCL1/2 expression. The activation of this signaling cascade ultimately results in the suppression of anti-tumor T cell function, thereby enhancing tumor progression. Corroborating our murine data, analysis of human HCC specimens confirmed that augmented mtDNA levels in TAMs are closely associated with immunosuppression and unfavorable patient prognoses. **Conclusion:** Overall, our findings suggest that liver tumor cells can rewire nucleotide metabolism in TAMs, thereby dampening anti-tumor immunity. Strategies aimed at preventing the decline of SAMHD1 mRNA in TAMs to restore macrophage nucleotide homeostasis may be developed for HCC therapy.

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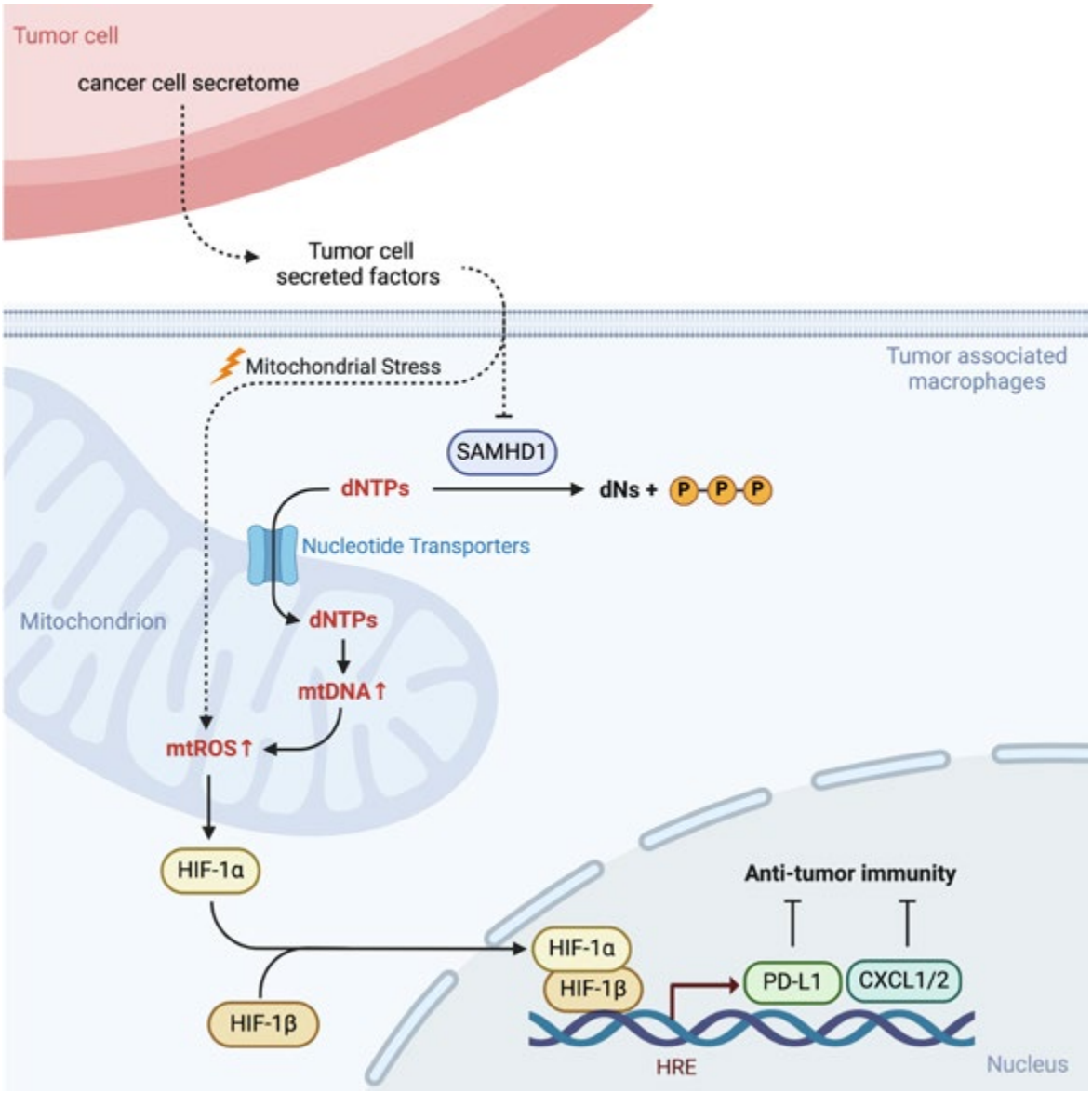

Disclosures: Shuang Liang: Nothing to Disclose, Chuanli Zhou: Nothing to Disclose, Zhenyu Zhong: Nothing to Disclose

0076 | SERUM IGG REFLECTS HISTOLOGICAL ACTIVITY IN CHILDREN WITH AUTOIMMUNE HEPATITIS ★

Or Steg Saban[1] Shannon Vandriel[2] Desiree Vaz[1] Celine Bourdon[1] Amrita Mundh[1] Vicky Ng[2] Simon Ling[1] Robert Bandsma[1] Iram Siddiqui[1] Binita Kamath[1]

[1]The hospital for sick children, [2]Hospital for Sick Children

Background: Autoimmune hepatitis (AIH) is a rare chronic inflammatory liver disease and evaluating disease activity can be a challenge. The gold standard for diagnosis and assessment is a liver biopsy, an invasive procedure. AASLD guidelines recommend a biopsy before attempting treatment cessation, if serum levels of AST, ALT, and IgG normalize for at least 2 years. ESPGHAN position statement also recommends including negative serum autoantibodies in this equation. No literature is available detailing the association between serum biomarkers and histological activity. We hypothesized that IgG would show the strongest association with histologic disease activity. **Methods:** Liver biopsy reports of all children diagnosed with AIH at SickKids between Jan 1, 1997, and Jan 31, 2023, were reviewed. Reports were included if a histological activity grading (Scheuer

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scoring system) was available. Scheuer scoring system differentiates five scales of intrahepatic inflammation, based on portal and lobular activity, and remission is defined as a score of 0. AST, ALT, IgG, total bilirubin (TB), conjugated bilirubin (CB) values, and autoantibodies titer were collected. Spearman's rank correlation tested the relation between histological activity score and serum biomarkers. Stepwise multiple linear regression was also used to define predictors. Finally, logistic regression was used to determine the decision threshold and performance in predicting histological remission. **Results:** 172 reports from 107 children were reviewed of which 123 were eligible. Forty-nine biopsies (40%) were from follow-ups. Histological activity score and IgG levels strongly correlated (r =0.71, p<0.001; n=107). The association was weaker with AST (r=0.62, p<0.001; n=121) and ALT (r=0.59 p<0.001; n=122). The correlation between disease activity and CB, TB and anti-nuclear antibody (ANA) was weak and other autoantibodies showed no relationship. Stepwise multiple linear regression selected IgG as the strongest correlate with histological activity score (standardized β=0.53, p<0.001), followed by ALT (standardized β=0.29, p<0.001). In logistic regression, OR for IgG was 1.48 (95% CI 1.1, 2.0). Above the threshold level of 11.6 IgG, the likelihood of histological activity being >0 was >99% (Figure 1). Area under the ROC curve was high at 0.92 (95% CI 0.86-0.98). **Conclusion:** Serum IgG could be considered the most relevant biomarker reflecting histological disease scores in pediatric AIH, surpassing other standard liver biochemistries. Serial assessment of IgG levels in children with AIH could largely direct decisions regarding treatment discontinuation. Procedural liver biopsies at follow-up could be made obsolete. We aim to validate our findings in independent cohorts.

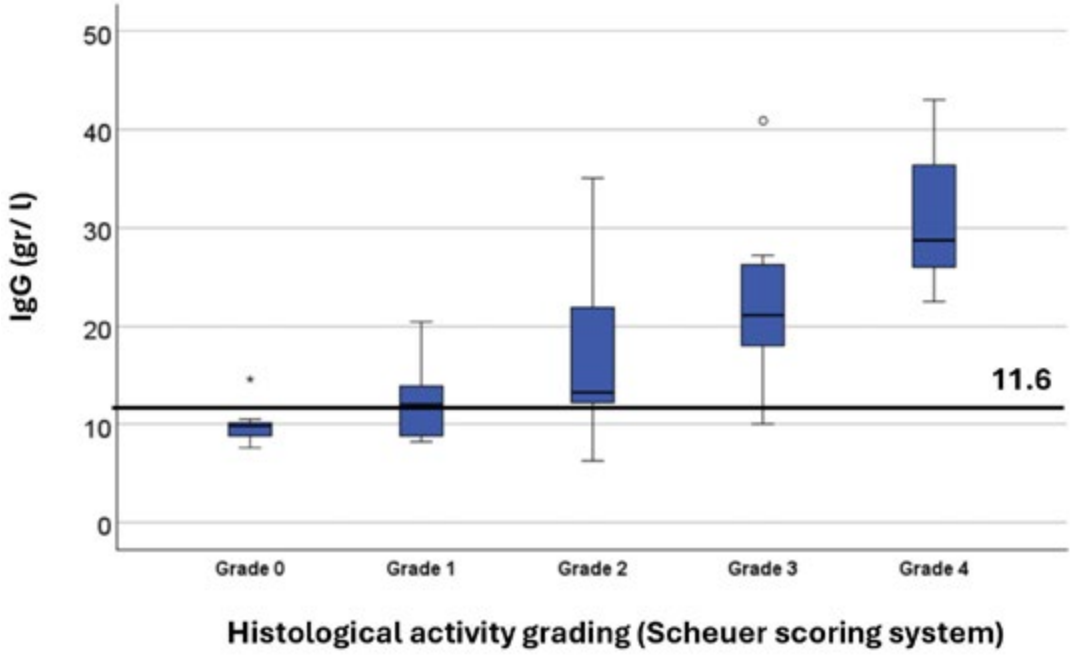

Figure 1. IgG rises with histological activity. Logistic regression showed a threshold of 11.6 gr/ L for histological remission. If IgG is more than 11.6 gr/ L, active disease is very likely (>99%).

Disclosures: Or Steg Saban: Nothing to Disclose, Shannon Vandriel: Nothing to Disclose, Desiree Vaz: Nothing to Disclose, Celine Bourdon: Nothing to Disclose, Amrita Mundh: Nothing to Disclose, Vicky Ng: Nothing to Disclose, Simon Ling: Nothing to Disclose, Robert Bandsma: Nothing to Disclose, Iram Siddiqui: Nothing to Disclose, Binita Kamath: Mirum: Consultant, Mirum: Grant/Research Support, Albireo/Ipsen: Consultant, Albireo/ Ipsen: Grant/Research Support, Audentes: Consultant

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0077 | AUTOPHAGY IMPAIRMENT LEADS TO MULTIPLE FORMS OF CELL DEATH IN THE LIVER

Hyeonggeug Kim[1] Menghao Huang[1] Sheng Liu[1] Chuanpeng Dong[1] Xiuxiu Yang[1] Barry Stein[1] Jun Wan[1] X Charlie Dong[1]

[1]Indiana University

Background: Autophagy is an essential cellular process that facilitates biomaterial recycling and cellular homeostasis. Autophagy related 14 (ATG14) is a key player in the autophagy initiation and autolysosome formation. However, the role of ATG14 in the regulation of hepatic cell survival and function remains incompletely understood. The aim of this study was to characterize the impact of ATG14 deficiency on hepatocytes. **Methods:** Hepatocyte-specific Atg14 knockout (HepKO) mice were generated by injection of AAV-TBG-Cre viral particles into Atg14 floxed mice. For some experiments, wildtype and knockout mice were fed with a Western diet for 4 weeks. RNA-seq was performed to profile differentially expressed genes. Biochemical and imaging approaches were used to illustrate molecular pathways involved. **Results:** Under normal chow conditions, HepKO mouse livers exhibited oxidative stress and DNA damage. Apoptosis and pyroptosis markers were elevated in the HepKO livers compared to wildtype controls. After 4 weeks of Western diet feeding, HepKO mice manifested exacerbated liver injury with high macrophage infiltration and extensive fibrosis in the liver. RNA-seq analysis showed 1,018 up-regulated genes and 2,340 down-regulated genes in the HepKO livers. Inflammation and cell death related pathways were enriched in the up-regulated genes whereas glucose and lipid metabolic pathways were enriched in the down-regulated genes. Biochemical analysis verified highly activated NF-kB and Smad3 pathways in the HepKO livers. Transmission electron microscopy analysis revealed significant mitochondrial damage in the HepKO livers. Mechanistically, our data showed an orchestration of pyroptosis, apoptosis, and necroptosis (collectively also termed as PANoptosis) in the HepKO livers. One of the triggers of pyroptosis was attributed to elevated NLRP3-mediated inflammasome. **Conclusion:** Our data suggest that ATG14 plays a critical role in the maintenance of cellular defense systems and cellular integrity. Hepatic autophagy deficiency can lead to multiple forms of cell death and liver injury.

Disclosures: Hyeonggeug Kim: Nothing to Disclose, Menghao Huang: Nothing to Disclose, Sheng Liu: Nothing to Disclose, Chuanpeng Dong: Nothing to Disclose, Xiuxiu Yang: Nothing to Disclose, Barry Stein: Nothing to Disclose, Jun Wan: Nothing to Disclose, X Charlie Dong: Nothing to Disclose

0078 | THE *PNPLA3* I148M VARIANT INITIATES METABOLIC REPROGRAMMING IN MACROPHAGES ◆

Emmanuel Dixon[1] thierry claudel[1] Jakob-Wendelin Genger[1] Ci Zhu[1] Sarah Stadlmayr[1] Erika Paolini[2] Alexander Nardo[1] Veronika Mlitz[1] Claudia Fuchs[1] Andreas Bergthaler[1] Paola Dongiovanni[2] Wilfried Ellmeier[1] Michael Trauner[1]

[1]Medical University of Vienna, [2]Medical University of Milan

Background: The impact of the patatin-like phospholipase domain-containing protein 3 (PNPLA3) I148M variant on MASLD has been studied extensively in hepatocytes and stellate cells. However, its role in macrophages, as critical players in disease progression, has not been addressed yet. Therefore, we explored the impact of the PNPLA3 I148M variant on the metabolic state, mitochondrial function, and proinflammatory phenotype of macrophages. **Methods:** We established a stable THP-1 cell line overexpressing the PNPLA3 wildtype (WT^{oe}) and I148M variant isoforms. We conducted metabolomics, gene expression analysis, extracellular flux analysis, immunofluorescent imaging by confocal microscopy, and flow cytometry. These *in vitro* studies were complemented by spatial transcriptomics of liver biopsies of metabolic dysfunction-associated steatohepatitis (MASH) patients carrying the PNPLA3 WT and I148M variants. **Results:** In $I148M^{oe}$ M1 macrophages *GLUT1, HK1, LDHA*, and *HIF-alpha* were significantly upregulated compared to the WT^{oe}, consistent with the increase of both the basal (+20%) and maximum (+15%) glycolytic activity. Conversely, reduced *CPT1-alpha* (-63%) in the I148M variant macrophage was in line with reduced mitochondrial respiration (-48%). Furthermore, $I148M^{oe}$ macrophages had an impaired mitochondrial electron transport chain (ETC) system as reflected by significantly reduced cofactors, FAD and NAD metabolites, as well as genes linked to the ETC complexes, *MT-ND1, MT-SHDA, MT-CYTB, MT-CO1, MT-CO2,* and *ATP6* in both MASH patients and macrophages carrying

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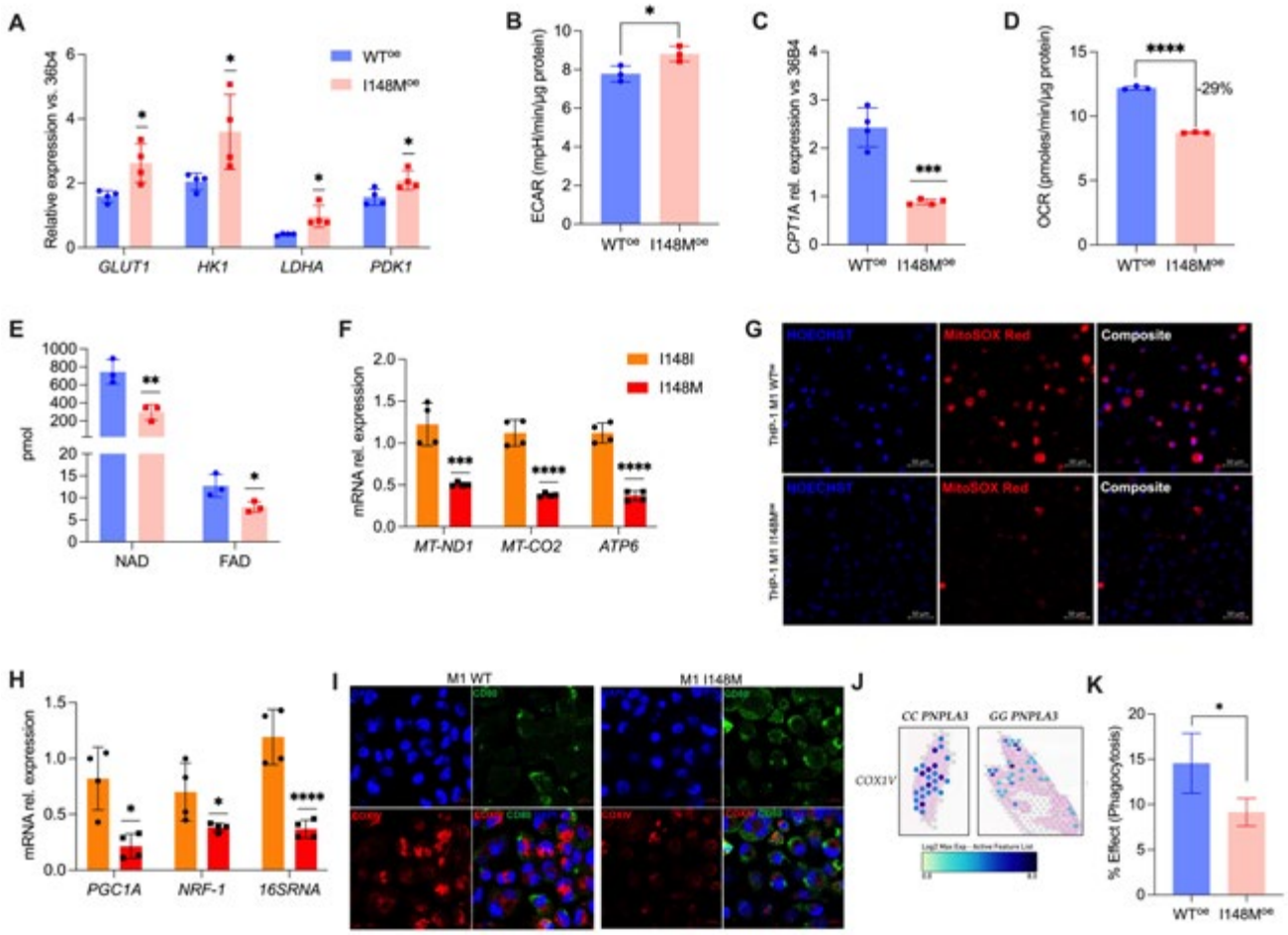
the PNPLA3 I148M variants, accompanied by reduced mitochondrial ROS production (-15%). Liver biopsies from MASH patients and M1 macrophage with the PNPLA3 I148M variant revealed reduced *PGC1-alpha, NRF1/2, mt-ND1,* and *16sRNA* mRNA transcripts compared to wildtype. In line, immunofluorescence showed a pronounced staining for COXIV protein in WT^{oe} macrophage. Spatial transcriptomics data also revealed differentially expressed *COXIV, MT-CO3*, and *MT-ND6* in the livers of MASH patients carrying the PNPLA3 I148M variant. Since phagocytosis involves mitochondrial function, we explored the impact of the PNPLA3 I148M on phagocytosis. Interestingly, phagocytic components like *MAFB* (-57%), *FCgR2B* (-30%), components of the phagolysosome *NOS2*(61%), *NOX2* (55%), and the overall phagocytic effect were reduced in the $I148M^{oe}$ macrophage. **Conclusion:** The PNPLA3 $I148M^{oe}$ reprograms macrophage metabolism because of reduced mitochondria number and/or mitochondrial dysfunction, thus affecting their phagocytotic capacity.



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0079 | S-ADENOSYLMETHIONINE PROTECTS AGAINST FOLFOX-INDUCED LIVER INJURY BY INHIBITING PLASMINOGEN ACTIVATOR INHIBITOR-1 IN MICE

Alexandra Gangi[1] Youngyi Lim[1] Tony Li[1] Andrea Floris[1] Swati Chandla[1] Maria Lauda Tomasi[1] Shelly Lu[1]

[1]Cedars Sinai Medical Center

Background: Folinic acid, 5-Fluorouracil and Oxaliplatin (FOLFOX), a commonly used chemotherapeutic regimen in patients with colorectal liver metastasis (CRLM), can cause liver injury such as sinusoidal obstruction syndrome (SOS) that limits further treatment. The current study investigated whether S-adenosylmethionine (SAMe), a hepatoprotective agent, could prevent FOLFOX-induced liver injury and examined the underlying mechanisms. **Methods:** We used a murine model of FOLFOX-induced SOS in wild type and plasminogen activator inhibitor-1 (PAI-1) knockout (KO) mice. In vitro studies included primary mouse and human hepatocytes, Kupffer cells (KCs), hepatic stellate cells, and liver sinusoidal endothelial cells (LSECs). Assays included co-immunoprecipitation, chromatin immunoprecipitation, western blot, ELISA, TUNEL assay, RT-PCR, Immunohistochemistry and immunofluorescence. **Results:** Several markers known to be increased in SOS, namely *Serpine 1* (encodes for PAI-1) *Tnf*, *Mmp9*, *Cxcl1*, and *Vwf,* were induced by FOLFOX, with a 6-fold increase in *Serpine 1* mRNA levels. SAMe administration completely blocked induction of all five markers and prevented FOXFOX-induced SOS and liver injury. SAMe blocked FOLFOX induced expression and activation of NF-κB, which in turn activated *SERPINE1/Serpine1* promoters. Interestingly, FOLFOX failed to activate hepatic NF-κB or cause liver injury in PAI-1 KO mice. Treatment of mouse hepatocytes with recombinant PAI-1 (rPAI-1) induced NF-κB activation; conditioned media from rPAI-1 or IL-1β-treated hepatocytes, but not exosomes, increased the expression of proinflammatory cytokines and Cd31 in KCs and LSECs, respectively, which were blocked by SAMe. FOLFOX and IL-1β induced interaction between PAI-1 with uPAR in mouse liver and hepatocytes, respectively, which was blocked by SAMe. rPAI-1 requires interaction with uPA for full activation of NF-κB in hepatocytes. Neutralizing antibody against PAI-1 attenuated p65 activation in IL-1β treated hepatocytes and blocked PAI-1 induction completely, suggesting the freely released PAI-1 is required to fully activate p65 and induce PAI-1. **Conclusion:** Our results suggest PAI-1 is required for FOLFOX-mediated NF-κB activation, which then further induce PAI-1 expression and release in a feedforward manner, exerting autocrine and paracrine effects to cause liver injury. SAMe protects against FOLFOX-mediated liver injury in part by inhibiting NF-κB activation and PAI-1 induction.

Disclosures: Alexandra Gangi: Nothing to Disclose, Youngyi Lim: Nothing to Disclose, Tony Li: Nothing to Disclose, Andrea Floris: Nothing to Disclose, Swati Chandla: Nothing to Disclose, Maria Lauda Tomasi: Nothing to Disclose, Shelly Lu: Nothing to Disclose

0080 | ABSENCE OF INTESTINAL MUCIN-2 PROMOTES GOBLET CELL-ASSOCIATED ANTIGEN PASSAGES FORMATION TO PREVENT ETHANOL-INDUCED STEATOHEPATITIS IN MICE ◆ ★

Maria Fernanda Raya Tonetti[1] Noemi Cabre[1] Marcos Fernandez Fondevila[1] Alvaro Eguileor[1] Bernd Schnabl[2] Cristina Llorente[2]

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Background: Goblet cells secrete mucins, cytokines, and antimicrobial peptides and participate in the education of the immune system through goblet cell-associated antigen passages (GAPs). The major mucin expressed in the intestine is Mucin-2 (Muc2). Chronic ethanol disrupts goblet cells function. Notably, Muc2 deficiency and small intestinal GAP formation protects against ethanol-induced liver disease. Our previous work showed that expression of glycoprotein 130 (gp130) receptor on intestinal epithelial cells mediates GAP formation via induction of the muscarinic acetylcholine receptor 4 (mAChR4) receptor on goblet cells promoting protection from ethanol-induced liver disease. The aim of our study was to determine the relative contributions of Muc2 and mAChR4 to GAP formation. **Methods:** Female mice with either selective deletion of mAChR4 on goblet cells (*mAChR4*$^{\Delta GC}$), Muc2 deficiency (*Muc2*$^{-/-}$), Muc2 deficiency and gp130 deficiency in intestinal epithelial cells (*Muc2*$^{-/-}$*gp130*$^{\Delta IEC}$) and wild-type littermates were subjected to the NIAAA model of ethanol feeding. Human SI organoids were used. **Results:** We confirmed that ethanol promotes the formation of a thicker mucus layer, and inhibits small intestinal GAP formation in mice and humans. Compared with wild-type mice, *mAChR4*$^{\Delta GC}$ mice had fewer small intestinal GAPs, leading to an impaired small intestinal immune response, with reduced expression of *CD11b* and *CD11c*.

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They also showed reduced small intestinal antibacterial defense via Reg3g, leading to bacterial overgrowth and increased bacterial translocation to the liver. Thus, GAP inhibition exacerbated ethanol-induced steatohepatitis, evidenced by elevated plasma transaminase levels, increased steatosis, and more hepatic inflammation (*Cxcl1* and *Cxcl2*), despite normal ethanol metabolism. *Muc2*$^{-/-}$*gp130*$^{\Delta IEC}$ lost the protective effect against ethanol-induced steatohepatitis observed in *Muc2*$^{-/-}$ mice. Notably, *Muc2*$^{-/-}$ mice presented increased small intestinal GAP formation compared with wild-type mice. However, GAP formation was inhibited in *Muc2*$^{-/-}$*gp130*$^{\Delta IEC}$ mice leading to a reduced expression of *CD11b* and interleukin-22 (*Il-22*). Lower SI Il-22 expression resulted in diminished Reg3b expression and increased bacterial translocation to the liver. Consequently, *Muc2*$^{-/-}$*gp130*$^{\Delta IEC}$ had higher plasma transaminase levels, and increased hepatic mRNA expression of *Tnf*, *Ccl5*, and *Tgf-β1*. Thus, GAP closure in *Muc2*$^{-/-}$ mice resulted in the loss of protection against ethanol-induced steatohepatitis **Conclusion:** Absence of intestinal Mucin-2 promotes GAP formation to prevent ethanol-induced steatohepatitis in mice. Inhibition of mAChR4-mediated GAP formation exacerbates steatohepatitis and impairs the small intestinal immune response, even in Muc2-deficient mice. Thus, targeting goblet cells function via mAChR4 signaling holds promise for mitigating alcoholic liver disease progression.

Disclosures: Maria Fernanda Raya Tonetti: Nothing to Disclose, Noemi Cabre: Nothing to Disclose, Marcos Fernandez Fondevila: Nothing to Disclose, Alvaro Eguileor: Nothing to Disclose, Bernd Schnabl: Grant/Research Support relationship with Prodigy Biotech; Has not ended; Grant/Research Support relationship with CymaBay Therapeutics; Has ended; Consultant relationship with Surrozen; Has ended; Grant/Research Support relationship with Intercept Pharmaceuticals; Has not ended; Stock â€“ privately held company relationship with Nterica Bio; Has not ended; Grant/Research Support relationship with Axial Biotherapeutics; Has ended; Consultant relationship with Ambys Medicines; Has ended; Grant/Research Support relationship with ChromoLogic; Has not ended; Consultant relationship with Mabwell Therapeutics; Has not ended, Cristina Llorente: Nothing to Disclose

0081 | ARBM-101 RESCUES FULMINANT WILSON DISEASE

Eun-Jung Kim[1] Dasol Kim[1] Banu Akdogan[2] Mikkel Holm Vendelbo[3] Emilie Munk[4] Judith Sailer[5] Adriana Filipa Fontes[2] Jonas Engler[5] Dongsik Park[1] Hongjae Lee[1] Chunwon Jung[1] Byong-Keol Min[1] Eok Park[1] TaeWon Kim[1] Seoyoung Choi[6] So-yeon Kim[1] Alan DiSpirito[7] Thomas Sandahl[4] Weonbin Im[1] So-Young Eun[1] Hans Zischka[2] Valentina Medici[8]

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Background: Wilson disease (WD), a genetic disorder caused by disruptive mutations in the *ATP7B* gene, primarily manifests with copper accumulation in the liver and brain. Currently, life-threatening acute liver failure, cannot be drug-treated, leaving liver transplantation with potential bridging plasmapheresis as ultimate option for rescue from death. Intriguingly, this devastating presentation of WD affects female patients more frequently than males. We have recently reported the exceptional liver copper depleting efficacy of ARBM-101 in still healthy/mildly diseased WD rats, an animal model for hepatic WD. ARBM-101 routed the excess copper via the bile into feces, reestablishing wild-type liver copper levels within days of treatment. Here we present the efficacy of ARBM-101 in rescuing WD rats from fulminant and terminal liver failure. Especially, we present an intensified ARBM-101 treatment regimen that enabled the rescue of female WD rats that present with a very rapid disease progression. Further, we visualize rapid copper excretion *in vivo* by ^{64}Cu-PET scan data, and also present first insights on the trafficking mechanism of ARBM-101. **Methods:** ARBM-101 was tested head-to-head against D-penicillamine (D-PA) in rescuing WD-rats showing fulminant acute liver disease, as determined by body weight loss, AST, ALT, and bilirubin levels. PET-scans were performed using ^{64}Cu-prebound ARBM-101 in WD rats to monitor its rapid biliary/fecal excretion. *In vitro* inhibitor assays in HepG2 cells with or without ATP7B were performed to unravel entry/exit mechanisms of ARBM-101 in the presence or absence of copper. **Results:** Eight days of twice daily treatment with ARBM-101 fully recovered male WD rats from fulminant WD and death. For a full recovery of female WD rats, the regimen had to be intensified to thrice daily for the first two out of eight consecutive treatment days. All animals restored their body weights and liver enzymes to normal ranges upon ARBM-101, but not upon D-PA treatments. This treatment efficacy was due to ARBM-101-enforced systemic copper excretion as unraveled by *in vivo* ^{64}Cu-PET-scans. At hepatocyte level, ARBM-101 was safely taken up by endocytosis and excreted via transporters, including MRP2, but also by exocytosis. **Conclusion:** ARBM-101 induced efficient drug-based rescue and full recovery of life-threatening fulminant hepatitis in female and male rats with WD.

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Disclosures: Eun-Jung Kim: Nothing to Disclose, Dasol Kim: Nothing to Disclose, Banu Akdogan: Nothing to Disclose, Mikkel Holm Vendelbo: Nothing to Disclose, Emilie Munk: Nothing to Disclose, Judith Sailer: Nothing to Disclose, Adriana Filipa Fontes: Nothing to Disclose, Jonas Engler: Nothing to Disclose, Dongsik Park: Nothing to Disclose, Hongjae Lee: Nothing to Disclose, Chunwon Jung: Nothing to Disclose, Byong-Keol Min: Nothing to Disclose, Eok Park: Nothing to Disclose, TaeWon Kim: Nothing to Disclose, Seoyoung Choi: Nothing to Disclose, So-yeon Kim: Nothing to Disclose, Alan DiSpirito: Nothing to Disclose, Thomas Sandahl: Arbormed: Advisor, Orphalan: Speaking and Teaching, Alexion: Grant/Research Support, Univar: Consultant, Ultragenyx: Advisor, Weonbin Im: Nothing to Disclose, So-Young Eun: Nothing to Disclose, Hans Zischka: ArborMed Co., Ltd: Consultant, Valentina Medici: Orphalan: Advisor, Arbormed: Research Grant, Ultragenix: Research Grant, Alexion: Advisor, Vivet: Grant/Research Support

0082 | THE IFN-INDUCIBLE MXB LARGE GTPASE ATTENUATES HBV REPLICATION BY ACTIVATING THE RIG-I INNATE IMMUNITY SIGNALING PATHWAY

Masazumi Onuki[1] Jun Inoue[1] Masashi Ninomiya[1] Mio Tsuruoka[1] Kosuke Sato[1] Satoko Sawahashi[1] Keishi Ouchi[1] Kengo Watanabe[1] Mark McNiven[2] Atsushi Masamune[1]

[1]Tohoku University Graduate School of Med, [2]Mayo Foundation for Medical

Background: Elimination of hepatitis B virus (HBV) from chronically infected patients remains difficult, even though nucleos(t)ide analogs, potent inhibitors of reverse transcription, are widely available. The innate immunity response has been reported to be disrupted by HBV infection and its restoration may be beneficial to control the infection. The role of the IFN-inducible, dynamin family member, myxovirus resistance protein 2 (MxB) in HBV infection remains unclear. Recent studies have reported that MxB localizes to the inner membrane of mitochondria and is involved in morphological maintenance and genomic stability of this organelle. We hypothesized that inducing MxB may support an innate immunological response against HBV via mitochondria alterations. The objective of this study was to elucidate the mechanism by which MxB may suppress HBV replication. **Methods:** MxB knockdown, MxB overexpression, and MxB induction by IFN were performed in either HBV-expressing cells (HepG2.2.15 and HepAD38 cells) and HBV-infected cells (HepG2-NTCP-C4 cells) to compare changes in the release of HBV particles, expression of HBV-related proteins. The involvement of mitochondrial antiviral signaling (MAVS) was detected by its clustering along the mitochondrial surface using immunofluorescence microscopy and semi-denaturing detergent agarose gel electrophoresis (SDD-AGE). The expression levels of MxB mRNA in liver samples from patients with chronic hepatitis B (CHB) were compared with those with acute hepatitis B (AHB) and chronic hepatitis C (CHC). **Results:** Knockdown of MxB in HBV-expressing cells induced morphological changes of mitochondria, such as swelling and fragmentation. These cells exhibited a substantial increase in the release of enveloped HBV particles as determined by immunoprecipitation or sucrose density gradient centrifugation. In addition, the expression of envelope proteins L/M/SHBs in the cells was increased and HBsAg in the culture supernatant was also increased by 4-10 fold. These results suggest that MxB may regulate HBV replication mainly by suppressing envelope protein expression. When cells were stimulated with poly(I:C) and downstream signaling of RIG-I was observed, knockdown of MxB suppressed phosphorylation of both IRF3 and its phosphorylation kinase TBK1, and mRNA of type I and III IFNs. MAVS clustering, which is required for this pathway, was inhibited by MxB knockdown. Finally, MxB mRNA levels in the patient liver tissues showed a reduced expression in AHB and CHB than in CHC, suggesting that HBV infection may not induce MxB sufficiently. **Conclusion:** These findings provide support for a new model of HBV resistance directed by the large GTPase MxB that is initiated by downstream RIG-I signaling that could promote the formation of MAVS clusters on mitochondria. An efficient induction of MxB may be a treatment option for controlling HBV infection.

Disclosures: Masazumi Onuki: Nothing to Disclose, Jun Inoue: Nothing to Disclose, Masashi Ninomiya: Nothing to Disclose, Mio Tsuruoka: Nothing to Disclose, Kosuke Sato: Nothing to Disclose, Satoko Sawahashi: Nothing to Disclose, Keishi Ouchi: Nothing to Disclose, Kengo Watanabe: Nothing to Disclose, Mark McNiven: Nothing to Disclose, Atsushi Masamune: Nothing to Disclose

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0083 | NOVEL MULTIOMICS BIOMARKER SIGNATURE DERIVED FROM BLOOD CIRCULATING HEPATOCYTE-EXTRACELLULAR VESICLES FOR THE EARLY DETECTION OF HCC

Ricardo Figueiras[1] Susana Vagueiro[1] Raissa Kay[1] Elnaz Persia[1] Brian Davidson[2] Carlos Ferreira[3] Vanessa Stadlbauer[4] David James Pinato[5] Pierre Arsène[1] Karin Schmitt[1] Tomas Dias[1]

[1]Mursla Bio, UK, [2]University College London, London, UK, [3]University Hospital of Santa Maria, Portugal, [4]Medical University of Graz, Austria, [5]Imperial College London, UK

Background: The expanding population at risk of developing HCC is placing an increasing economic burden on healthcare systems due to the sub-standard surveillance offered by US and AFP,
which often miss tumors smaller than 1 cm and cannot reliably indicate which patients require further evaluation with MRI or CT. A blood test with improved sensitivity and specificity could alleviate this economic burden and likely enhance patient adherence to surveillance programs. However, identifying HCC-specific blood biomarkers remains challenging due to the complexity of liver disease and the difficulty in distinguishing liver- derived biomarkers from confounding factors in the blood. Here, we present data on the discovery and validation of our blood test using a multiomics biomarker signature, derived directly from hepatocyte extracellular vesicles (H-EVs), for the early detection of HCC. **Methods:** We conducted a case-control study involving retrospective and prospective samples from patients with HCC and cirrhosis, collected from 6 European centers. The samples were divided into two independent cohorts for discovery and validation. H-EVs were isolated and mass-spectrometry as well as small RNA sequencing were used for biomarker discovery. Biomarker validation was performed using NEXOS, a novel EV detection platform, and PCR. **Results:** A total of 464 samples were collected for the study. All HCC patients were treatment-naïve at the time of collection and had confirmed cirrhosis from various etiology backgrounds. About 90% had early or intermediate-stage HCC. Cirrhosis samples were matched for different etiologies. More than 50 multiomic biomarkers were found to be differentially expressed between HCC and cirrhosis. By applying advanced machine learning methods, a refined set of novel biomarkers was identified and these were validated in the second cohort. This approach established an initial multiomics biomarker signature with specificity and sensitivity that significantly surpassed the performance of US and AFP. **Conclusion:** EVs represent a rapidly advancing modality in liquid biopsy diagnostics, capable of tracing back to their parental cells and containing multiomic markers. Our method of selectively isolating H-EVs from patients' blood, enabled the identification of a novel HCC biomarker signature combining proteins & miRNAs. This innovative approach has the potential to revolutionize the early detection of HCC during surveillance, reducing the economic burden on healthcare systems and improving patient outcomes.

Disclosures: Ricardo Figueiras: Nothing to Disclose, Susana Vagueiro: Nothing to Disclose, Raissa Kay: Mursla Bio: Employee, Elnaz Persia: Nothing to Disclose, Brian Davidson: Nothing to Disclose, Carlos Ferreira: Nothing to Disclose, Vanessa Stadlbauer: Merz Pharma: Grant/Research Support, Winclove Probiotics: Grant/Research Support, Institut Allergosan: Grant/Research Support, David James Pinato: Nothing to Disclose, Pierre Arsène: Nothing to Disclose, Karin Schmitt: Mursla Limited: Employee, Mogrify Limited: Employee, Mursla Limited: Stock – privately held company, Mogrify Limited: Stock – privately held company, StemBond: Board Membership, StemBond: Stock – privately held company, National Institute for Health and Care Research, UK: Grant/Research Support, Innovate UK: Grant/Research Support, Tomas Dias: Nothing to Disclose

0084 | CONTRIBUTION OF MYELOID CELL-DERIVED HMGB1 TO THE DEVELOPMENT OF HEPATOCELLULAR CARCINOMA

Sai Santosh Babu Komakula[1] Xiaodong Ge[1] Wei Chen[1] Romain Desert[1] Hui Han[1] Zhuolun Song[1] Sukanta Das[1] Dipti Athavale[1] Nithyananthan Subramaniyam[1] Chao Wang[1] Dan Lantvit[1] Abid Anwar[1] Natalia Nieto[1]

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Background: High mobility group box 1 (HMGB1) is a non-histone chromatin-associated protein involved in the pathogenesis of chronic liver disease. HMGB1 is expressed in myeloid cells, including conventional dendritic cells (cDCs), which play a major role in the tumor microenvironment. However, whether intracellular myeloid cell-derived HMGB1 is involved in hepatocellular carcinoma (HCC) is unknown. We hypothesize that intracellular HMGB1 drives cDC maturation towards LAMP3$^+$ DCs, allowing effective cytotoxic CD8$^+$ T cell responses to reduce HCC. **Methods:** We analyzed publicly available scRNA-seq datasets from human HCC for the expression

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of HMGB1 in all subsets of DCs in HCC tumor and non-tumor tissues and in hepatic draining lymph nodes (dLNs). We generated mice with conditional ablation or overexpression of *Hmgb1* in myeloid cells (*Hmgb1*$^{\Delta Mye}$ and *Hmgb1*$^{KI\ Mye}$). To induce HCC, 14-day-old male mice were injected i.p. with diethylnitrosamine (DEN) and were sacrificed at 5, 6, 8, and 10 months. Histopathological analysis of livers was performed using H&E staining. Immune cell populations were analyzed in tumor and non-tumor tissues using flow cytometry. cDCs were isolated from tumor and non-tumor tissues by FACS, and RNA-seq analysis was performed. **Results:** Analysis of scRNA-seq datasets revealed LAMP3^{+} DCs increased in human HCC tumor tissue and hepatic dLNs. LAMP3^{+} DCs displayed increased activation and migration scores. Moreover, HMGB1 was highly expressed in cDCs (CLEC9A^{+} and CD1C^{+}), which can differentiate into LAMP3^{+} DCs. *Hmgb1*$^{KI\ Mye}$ mice were protected from HCC, whereas control mice developed HCC after 8 months, and *Hmgb1*$^{\Delta Mye}$ mice started developing HCC at 5 months. Macroscopic analysis and H&E staining of the livers from *Hmgb1*$^{\Delta Mye}$ mice showed more tumors and higher tumor volume than control and *Hmgb1*$^{KI\ Mye}$ mice. Immunohistochemistry of HCC tumor sections revealed that *Hmgb1*$^{\Delta Mye}$ mice have fewer LAMP3^{+} DCs in tumor tissues than control and *Hmgb1*$^{KI\ Mye}$ mice. Flow cytometry analysis showed that *Hmgb1*$^{KI\ Mye}$ mice had significantly increased cDCs in tumor tissues and dLNs than control and *Hmgb1*$^{\Delta Mye}$ mice. In addition, there was enhanced CD8^{+} T cell apoptosis in the HCC tumor tissues from *Hmgb1*$^{\Delta Mye}$ mice. RNA-seq data of cDCs unveiled that pathways involved in antigen presentation were downregulated in *Hmgb1*$^{\Delta Mye}$ mice and upregulated in *Hmgb1*$^{KI\ Mye}$ mice compared to control mice. **Conclusion:** Ablation of myeloid-derived HMGB1 accelerates HCC development in mice. Enhancing HMGB1 expression in myeloid cells increased the number and the antigen presentation activity of cDCs. Therefore, increasing HMGB1 expression in cDCs could be a therapeutic approach to protect from HCC.

Disclosures: Sai Santosh Babu Komakula: Nothing to Disclose, Xiaodong Ge: Nothing to Disclose, Wei Chen: Nothing to Disclose, Romain Desert: Nothing to Disclose, Hui Han: Nothing to Disclose, Zhuolun Song: Nothing to Disclose, Sukanta Das: Nothing to Disclose, Dipti Athavale: Nothing to Disclose, Nithyananthan Subramaniyam: Nothing to Disclose, Chao Wang: Nothing to Disclose, Dan Lantvit: Nothing to Disclose, Abid Anwar: Nothing to Disclose, Natalia Nieto: Nothing to Disclose

0085 | PRIMARY GRAFT DYSFUNCTION AND MAJOR ADVERSE CARDIAC EVENTS AFTER HEPATITIS C VIREMIC HEART TRANSPLANTATION TO AVIREMIC RECIPIENTS

Ritika Mazumder[1] *Sarah Khan*[1] *Sakthi Surya Prakash*[1] *Qijun Yang*[1] *Omar Sims*[1] *Randall Starling*[1] *William Carey*[1]

[1]*Cleveland Clinic Foundation*

Background: Although direct-acting antiviral therapy (DAA) has enabled successful use of hepatitis C (HCV) positive allografts with favorable short-term outcomes, there is a notable absence of studies comprehensively examining cardiac events following HCV viremic heart transplantation. This study aimed to investigate the incidence of death attributed to primary graft dysfunction, and long-term major adverse cardiac events (i.e., non-fatal myocardial infarction, percutaneous coronary intervention with stent, coronary artery bypass grafting, or heart re-transplantation) in aviremic recipients of donor HCV positive hearts. **Methods:** This retrospective cohort study included all adult heart transplants performed at our center from January 2018 to September 2022. **Results:** A total of 256 heart transplant recipients were included (23 HCV+ donors, 233 HCV- donors). There was no significant difference in death from primary graft dysfunction between HCV+ and HCV- recipients over a 90-day follow-up period (p=0.52) (Figure 1). Donor HCV status (HR=1.99, CI 0.23-17.1, p= 0.53), age at transplant (HR=1.00, CI 0.95-1.07, p=0.91), sex (HR=0.44, CI 0.05-3.73, p=0.45), and LVAD usage (HR=0.83, CI .015-4.52, p=0.83) were not associated with risk of death due to primary graft dysfunction. The rate of composite major adverse cardiac events was similar in HCV+ and HCV- patient groups (2.6% vs 2.3%, p=1.00). There were no significant differences in the incidence of non-fatal myocardial infarction (1.2% vs 1.2%, p=1.00) and percutaneous coronary intervention with stent (1.2% vs 1.2%, p=1.00) between HCV+ and HCV- patient groups. Coronary artery bypass grafting, and heart re-transplantation did not occur in either group. **Conclusion:** Our study suggests that in the post-DAA era, heart transplantation using HCV+ allograft is not associated with an increased risk of death due to primary graft dysfunction or major adverse cardiac events. Overall, these findings support the safety and efficacy of utilizing HCV positive hearts to expand the donor pool.

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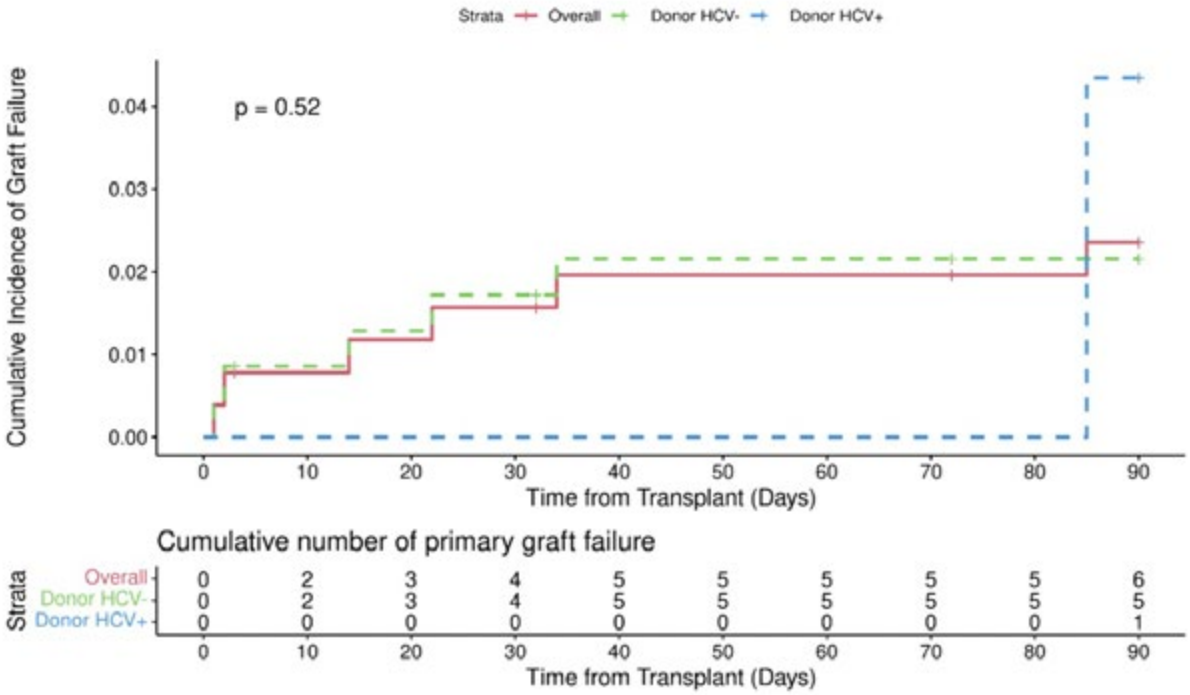
Figure 1. Cumulative incidence Curves of Death due to Primary Graft Dysfunction over 90-day Follow-up



Disclosures: Ritika Mazumder: Nothing to Disclose, Sarah Khan: Nothing to Disclose, Sakthi Surya Prakash: Nothing to Disclose, Qijun Yang: Nothing to Disclose, Omar Sims: Nothing to Disclose, Randall Starling: Nothing to Disclose, William Carey: Nothing to Disclose

0086 | THE ROLE OF REGULATING GUT TRYPTOPHAN METABOLISM ON ANTI-TUMOR IMMUNITY IN LIVER CANCER AND ITS MECHANISM

Liang Wen[1] *Yixiao Yang*[1] *Tingbo Liang*[1]

[1]*Zhejiang University*

Background: Gut flora homeostasis was closely correlated with the initiation and development of liver cancer. Our previous study revealed that gut flora disequilibrium promotes liver cancer initiation by attenuated tryptophan metabolism. However, the role of gut flora tryptophan metabolism in the development of liver cancer remains obscured. **Methods:** 16S rRNA sequencing and liquid chromatography-tandem mass spectrometry (LC-MS/MS) were respectively used to detect gut microbiota composition and tryptophan metabolites in 19 patients with hepatocellular carcinoma (HCC) and 19 healthy individuals. Mouse liver cancer models were built to explore the effect of the high-tryptophan diet on liver cancer development. And immune microenvironment and aryl hydrocarbon receptor (AhR) activation in liver of tumor-bearing mice were also assessed. Then germ-free mice were used to verify whether high-tryptophan-induced anti-tumor effect of liver cancer depends on gut microbiota. Finally, we used fecal microbiota transplantation to verify whether enhancing intestinal tryptophan metabolism is beneficial. **Results:** There are significant differences in the composition of gut microbiota between HCC patients and normal individuals. The abundance of Blautia genus is significantly reduced in the intestines of HCC patients compared with that in normal individuals. And the intestinal tryptophan metabolites of HCC patients are reduced, especially those involving in indole metabolic pathway including indole-3-acetic acid (IAA). In HCC patients, the concentration of fecal IAA is positively correlated with the patient's overall survival. Mouse liver cancer was induced by hydrodynamic co-transfection of cMyc and N-Ras oncogenes or AKT and YAP oncogenes. We found high-tryptophan diet dramatically inhibited the progression of mouse liver cancer, which was not affected in germ-free mice. High-tryptophan diet significantly enhanced the infiltrated CD8 positive cytotoxic T cells in the

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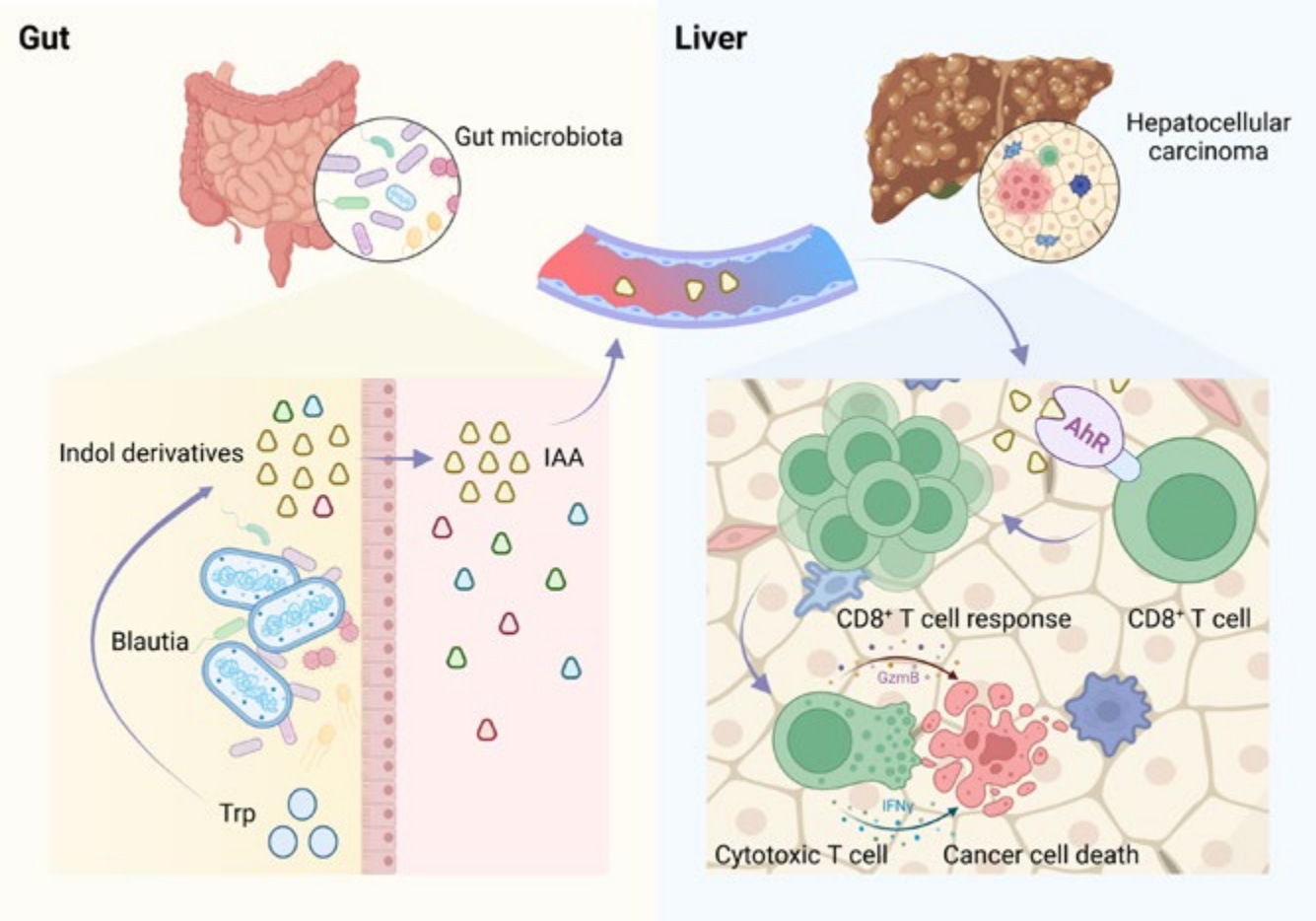
livers of tumor-bearing mice. Furthermore, we found that the high-tryptophan diet increased the production of intestinal tryptophan metabolite IAA and promoted AhR activation on the liver. What's more, AhR agonist Ficz and AhR conditional knockout mice in CD8 positive T cells confirmed that high-tryptophan diet-induced liver cancer inhibition depended on AhR activation on CD8 positive T cells in liver. Finally, we identified that Blautia coccoides, which metabolize tryptophan, could significantly inhibit the development of liver cancer by gavage. **Conclusion:** Impaired gut tryptophan metabolism was associated with the prognosis of patients with liver cancer. High-tryptophan diet enhances the anti-tumor effect on liver cancer through indole metabolite IAA-induced cytotoxic T cells activation via AhR signaling. Regulating gut tryptophan metabolism could be a potential strategy for adjuvant treatment of liver cancer.



Disclosures: Liang Wen: Nothing to Disclose, Yixiao Yang: Nothing to Disclose, Tingbo Liang: Nothing to Disclose

0087 | PREDICTING SURVIVAL AMONG PATIENTS WITH EARLY- TO INTERMEDIATE-STAGE HCC: MIAMI LIVER CANCER ESTIMATOR OF SURVIVAL (MILES) SCORE

David Goldberg[1] David Kaplan[2] Binu John[1] Neelima Gaddipati[1] Sirisha Gaddipati[1] Yalda Zarnegarnia[1] Peter Reese[2] Catherine Blandon[1]

[1]University of Miami, [2]University of Pennsylvania

Background: Staging and prognostication of hepatocellular carcinoma (HCC) differs from other cancers because it must account for tumor burden as well as function of the diseased organ (i.e., liver). Common staging systems, like the Barcelona Clinic Liver Cancer (BCLC), often overlook these dual components or rely on subjective measures such as the Child-Turcotte-Pugh score. While useful guides for immediate clinical care, they are not nuanced enough to predict long-term survival, or to assess the survival benefit of transplantation for HCC. **Methods:** This retrospective cohort study involved patients with cirrhosis and HCC in the Veterans Health

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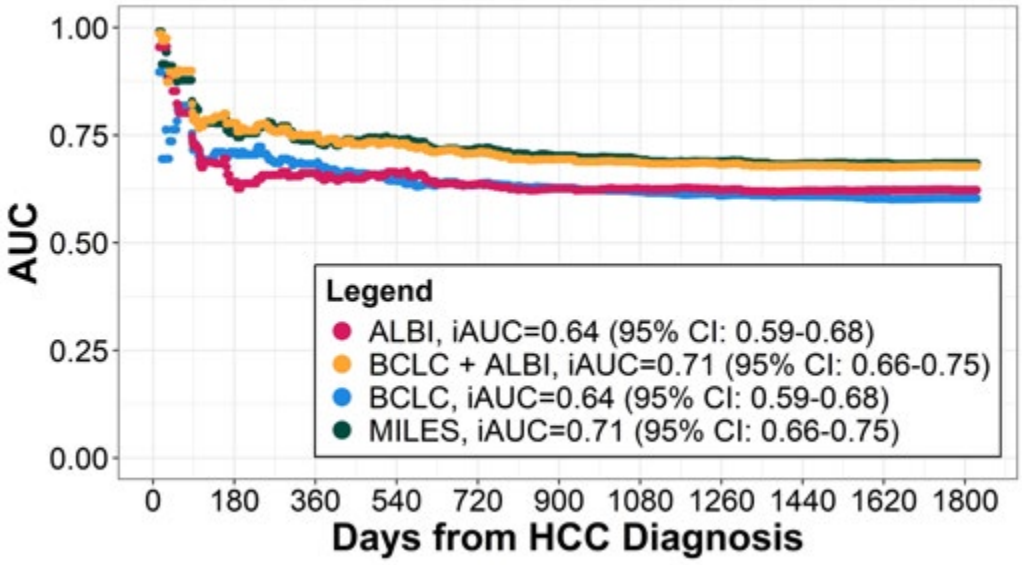
Administration. We included patients with cirrhosis (based on ICD-10 codes) and HCC from 1/24/2014-6/9/2021. All HCC-related data were collected by trained data abstractors, and only patients with LiRADS-5 or biopsy-proven HCC were included. We excluded patients with macrovascular invasion or extra-hepatic disease. We fit accelerated failure time models to predict 1-, 3-, and 5-year overall survival from time of HCC diagnosis using baseline clinical and laboratory data, or BCLC stage and/or ALBI grade. We split data 75:25 for training and testing. **Results:** The cohort included 1,325 patients. The final model included age, renal function (i.e., eGFR), INR, sodium, albumin, bilirubin, history of esophageal varices, history of spontaneous bacterial peritonitis, total tumor size, and AFP. Censoring survival at 5 years, our model achieved an integrated AUC (iAUC) of 0.71 (95% CI: 0.66-0.75), surpassing both the BCLC stage's and ALBI grade's iAUC of 0.64 (95% CI: 0.59-0.68), but not the combined model's iAUC of 0.71 (95% CI: 0.66-0.75) (Figure). When stratified by treatment status (71% received treatment) for HCC, iAUC varied for our model: 0.68 (95% CI: 0.62-0.73) for treated patients and 0.76 (95% CI: 0.67-0.82) for untreated. BCLC had slight iAUC variation, followed by ALBI, but BCLC+ALBI behaved akin to our model. All models exhibited good calibration, confirmed via examination of calibration curves and a low Brier score ranging 0.16-0.17. **Conclusion:** We present an objective model to predict overall survival for patients with newly diagnosed HCC. It exhibits very good discrimination and calibration, underscoring the need to combine dual HCC aspects. If validated, this model could complement BCLC stage and ALBI grade, informing treatment decisions about the survival benefits of therapies like liver transplantation.



Disclosures: David Goldberg: Nothing to Disclose, David Kaplan: Independent Contractor relationship with Roche Genentech; Has not ended; Grant/Research Support relationship with AstraZeneca Inc; Has not ended; Advisor relationship with AstraZeneca; Has ended; Advisor relationship with Exelixis; Has ended; Grant/Research Support relationship with Gilead; Has not ended; Advisor relationship with Sirtex; Has ended; Grant/Research Support relationship with Exact Sciences; Has not ended; Grant/Research Support relationship with Glycotest; Has ended, Binu John: Exact Sciences: Grant/Research Support, Genentech: Grant/Research Support, Glycotest, Inc: Grant/Research Support, Gilead: Grant/Research Support, Exelixis: Consultant, Takeda: Grant/Research Support, GlaxoSmithKline: Consultant, Astra Zeneca: Consultant, Neelima Gaddipati: Nothing to Disclose, Sirisha Gaddipati: Nothing to Disclose, Yalda Zarnegarnia: Nothing to Disclose, Peter Reese: Nothing to Disclose, Catherine Blandon: Bluebird Bio: Stock - publicly traded company, Intellia Therapeutics: Stock - publicly traded company, Editas Medicine: Stock - publicly traded company

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0088 | THREE-DIMENSIONAL MR ELASTOGRAPHY PREDICTS CLINICALLY SIGNIFICANT PORTAL HYPERTENSION IN PATIENTS WITH CIRRHOSIS: A PROSPECTIVE MULTICENTER STUDY

Yu Shi[1] He Zhu[2] Meng Niu[1] Jie Chen[3] Bo Wei[3] Bin Song[3] Zhenghan Yang[4] Hui Xu[4] Dawei Yang[4] Jingjing Liu[5] Yong Zhang[5] Jingliang Cheng[5] Xiaolong Qi[6]

[1]China Medical University, [2]The Sixth People's Hospital of Shenyang, [3]Sichuan University West China Hospital, [4]Beijing Friendship Hospital, [5]First Hospital of Zhengzhou University, [6]Zhongda Hospital, Southeast University

Background: To explore a Three-dimensional MR elastography (3D-MRE) model for noninvasive diagnosis of clinically significant portal hypertension (CSPH, HVPG≥10mmHg) and severe portal hypertension (SPH, HVPG≥12mmHg) in cirrhosis, using hepatic venous pressure gradient (HVPG) as the gold standard. **Methods:** In this prospective and multicenter study, we recruited patients with cirrhosis scheduled for HVPG, and who intended to undergo 3D-MRE (30Hz/60Hz) before the HVPG procedure from August 2022 to April 2024. Patients with liver fibrosis (F0-F1, without clinical evidence of CSPH) were included and marked as non-CSPH to balance the ratio of CSPH 1:1. Multiple viscoelastic parameters, such as Liver/Splenic Shear Stiffness (LSS/SSS), Liver/Splenic Loss Modulus (LLM/SLM), Liver/Splenic Damping Ratio (LDR/SDR) were evaluated independently by two radiologists. Conventional serum-based indexes, including the AAR; GPR; APRI; FIB-4 and so on were included for comparisons. Univariable and multivariable linear regression analyses were conducted to assess the associations between these parameters and HVPG. Diagnostic performance was assessed with the area under the receiver operating characteristic curve (AUC). **Results:** A total of 172 patients were recruited from six institutions, including 86 patients with CSPH and 86 patients without CSPH (61 patients were liver fibrosis F0-F1 without HVPG). Patients were divided randomly into a training set (n=121) and a test set (n=51) with a ratio of 7:3 to assess the proposed model. Multivariable linear regression analysis showed splenic SS at 60Hz (β = 1.57; 95% CI:1.25, 1.88; *P* < .001), splenic DR at 30Hz (β =31.86; 95% CI: 18.34, 45.38; *P*< .001), splenic LM at 30Hz (β =-1.95; 95% CI:-3.46,-0.44; *P* = .012); Total bilirubin (β =-0.04; 95% CI: -0.06, -0.02; *P*= .001); GGT (β =0.009; 95% CI: 0.002, 0.02; *P* = .008) were the independent factors determining HVPG. Approximately 75.4% of the total variability in HVPG was explained by only 3D-MRE parameters and 81.6% was explained by 3D-MRE combining serum-based indexes. Establishing a model with 3D-MRE combining serum-based indexes was excellent performance in training set (AUC, 0.971 [95% CI:0.944, 0.999]) vs test set (AUC, 0.991 [95% CI:0.975, 1]). As for SPH, the model also showed remarkable performance in training set (AUC, 0.971 [95% CI:0.944, 0.998]) vs test set (AUC, 0.986 [95% CI:0.96, 1]). **Conclusion:** Proposed model based on 3D-MRE had good diagnostic consistency for hepatic venous pressure gradient measurement and it is promising in diagnosing the presence CSPH and SPH.

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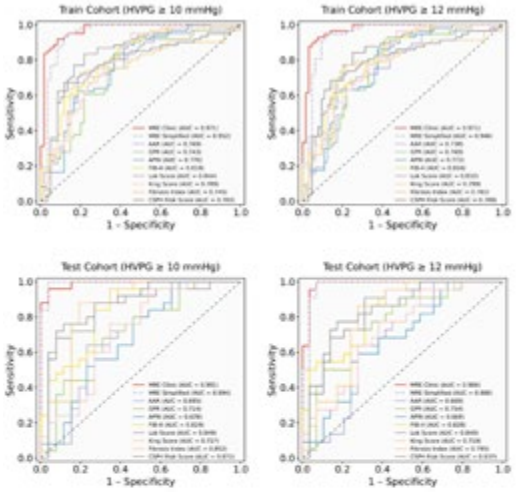

Figure 1 ROC analysis of conventional noninvasive tools for clinically significant portal hypertension and severe portal hypertension. MRE Clinic, 3D-MRE combining serum-based indexes; MRE Simplified; only 3D-MRE parameters; AAR, aspartate aminotransferase to alanine aminotransferase ratio; GPR, g-glutamyl transpeptidase to platelet count ratio; APRI, aspartate aminotransferase to platelet count ratio index; FIB-4, fibrosis index based on 4 factors; Lok Score, -5.56 – 0.0089 * PLT + 1.26 * AST/ALT + 5.27 * INR; King score, Age * AST * INR/PLT; Fibrosis index; 8.28 – 0.01 * PLT – ALB; CSPH Risk Score, -0.193 – 0.359 * ALB + 16.456 * INR – 0.016 * ALT.

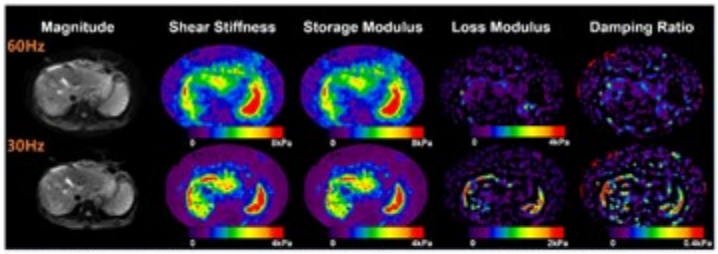

Figure 2 Magnetic Resonance Elastography (MRE) images at 60Hz and 30Hz with HVPG 11 mmHg. The MRE images for a patient with liver shear stiffness of 4.0 kPa at 60Hz, 3.2 kPa at 30Hz and splenic shear stiffness of 10.2 kPa at 60Hz, 4.3kPa at 30Hz. It identified splenic shear stiffness detects increased HVPG earlier than liver stiffness.

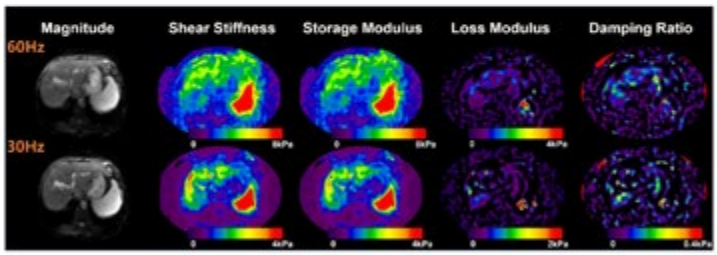

Figure 3 Magnetic Resonance Elastography (MRE) images at 60Hz and 30Hz with HVPG 16 mmHg. The MRE images for a patient with liver shear stiffness of 4.1 kPa at 60Hz, 3.3 kPa at 30Hz and splenic shear stiffness of 13.3 kPa at 60Hz, 8.6kPa at 30Hz. It identified HVPG value is more strongly correlated with the splenic shear stiffness than that of the liver shear stiffness.

Disclosures: Yu Shi: Nothing to Disclose, He Zhu: Nothing to Disclose, Meng Niu: Nothing to Disclose, Jie Chen: Nothing to Disclose, Bo Wei: Nothing to Disclose, Bin Song: Nothing to Disclose, Zhenghan Yang: Nothing to Disclose, Hui Xu: Nothing to Disclose, Dawei Yang: Nothing to Disclose, Jingjing Liu: Nothing to Disclose, Yong Zhang: Nothing to Disclose, Jingliang Cheng: Nothing to Disclose, Xiaolong Qi: Nothing to Disclose

0089 | LONG-TERM LIVER-RELATED OUTCOMES AND LIVER FIBROSIS PROGRESSION OF STATIN USAGE IN STEATOTIC LIVER DISEASE

Xiao-Dong Zhou[1] Seung Up Kim[2] Terry Cheuk-Fung Yip[3] Salvatore Petta[4] Atsushi Nakajima[5] Emmanuel Tsochatzis[6] Jerome Boursier[7] Elisabetta Bugianesi[8] Hannes Hagström[9] Wah-Kheong Chan[10] Manuel Romero-Gómez[11] Jose Luis Calleja[12] Victor de Lédinghen[13] Laurent Castera[14] Arun J. Sanyal[15] George Boon-Bee Goh[16] Philip Newsome[17] Jian-Gao Fan[18] Michelle Lai[19] CELINE FOURNIER POIZAT[12] Hye Won Lee[2] Grace Wong[3] Angelo Armandi[3] Ying Shang[20] Grazia Pennisi[3] Elba Llop[9] Masato Yoneda[3] Marc de Saint-Loup[5] Clemence Canivet[5] Carmen Lara-Romero[20] Rocio Gallego-Durán[20] Amon Asgharpour[21] Kevin Kim-Jun Teh[14] Sara Mahgoub[15] Mandy Sau-Wai Chan[3] Huapeng Lin[18] Wenyue Liu[22] Giovanni Targher[23] Christopher. Byrne[24] Vincent Wai-Sun Wong[3] Ming-Hua Zheng[1]

[1]Wenzhou Medical University, [2]Yonsei University College of Medicine, [3]The Chinese University of Hong Kong, [4]University of Palermo, [5]Yokohama City University, [6]Royal Free Hospital, [7]Angers University Hospital, [8]University of Turin, [9]Karolinska University Hospital, [10]University of Malaya, [11]Virgen Del Rocío University Hospital, [12]Hospital Universitario Puerta de Hierro, [13]Echosens, Paris, France, [14]Université Paris Cité, [15]Virginia Commonwealth University, [16]Singapore General Hospital, [17]King's College London, [18]Shanghai Jiao Tong University, [19]Harvard Medical School, [20]Karolinska Institutet, [21]University Hospital of Bordeaux, [22]the First Affiliated Hospital of Wenzhou, [23]University of Verona, [24]Southampton General Hospital

Background: Statins have multiple benefits in patients with metabolic-associated steatotic liver disease (MASLD). This observational multicenter cohort study aimed to explore the effect of statins on long-term risk of liver-related clinical events (LRE) and liver fibrosis progression in patients with MASLD. **Methods:** This cohort study collected data on MASLD patients undergoing at least two vibration-controlled transient elastography examinations at 16 tertiary referral centers from February 2004 to January 2023. Statin use was defined as 30 or more cumulative defined daily dose. Cox regression analysis was performed to examine the association between

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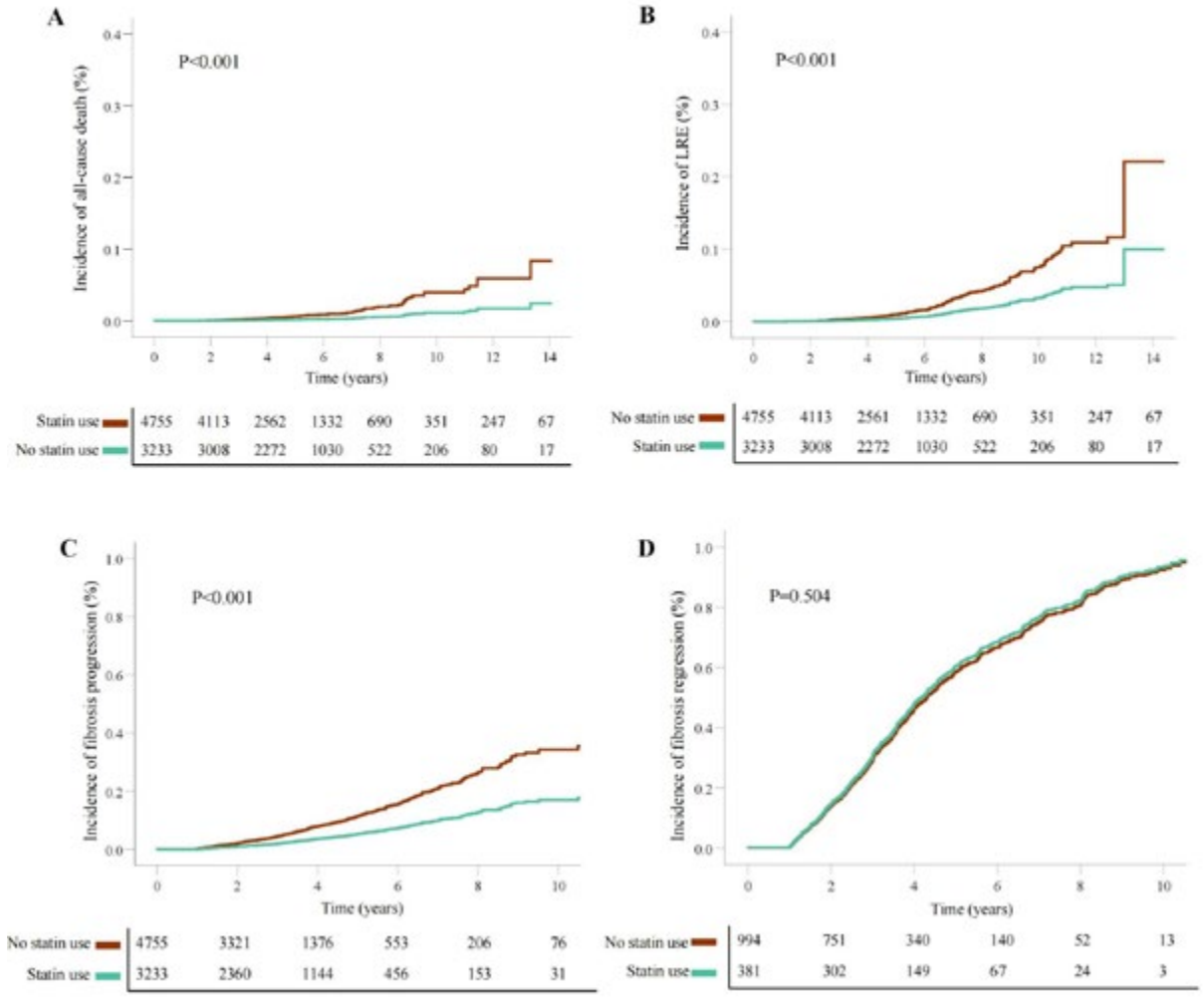
statin usage and long-term risk of all-cause mortality and LREs stratified by compensated advanced chronic liver disease (cACLD: baseline liver stiffness measurement (LSM) of ≥10 kPa). Fibrosis progression was defined as LSM increase of ≥20% for cACLD and from <10 kPa to ≥10 or LSM for non-cACLD. Fibrosis regression was defined as LSM reduction from ≥10 kPa to <10 or LSM decrease of ≥20% for cACLD. **Results:** We followed 7,988 patients with baseline LSM 5.9 kPa (IQR 4.6-8.2). At baseline, 40.5% of patients were using statin, and cACLD was present in 17%. During a median clinical follow-up of 4.6 (IQR: 3.0 - 6.4) years, 87 deaths and 208 LREs occurred. Statin usage was significantly associated with a lower risk of all-cause death (adjusted HR=0.233; 95% 0.127-0.426) and LREs (adjusted HR=0.380; 95% 0.268-0.539) (Figure 1A and 1B). Subgroup analysis also demonstrated the association persisted in non-cACLD and cACLD groups (all P < 0.001). During a median VCTE follow-up of 3.0 (IQR: 1.9 - 4.5) years, statin usage was also associated with lower fibrosis progression rates in cACLD (HR=0.542; 95% 0.389-0.755) and non-cACLD (HR=0.450; 95% 0.342-0.592), but not with fibrosis regression (HR=0.914; 95% 0.778-1.074) (Figure 1C and 1D). Our results remained robust and consistent in all sensitivity analyses. **Conclusion:** This is a large observational multicenter prospective cohort study that includes liver VCTE data both at baseline and follow-up. The results of this study suggest that statin usage may help reduce mortality and LRE rates and slow down liver disease progression in both cACLD and non-cALCD patients.



Disclosures: Xiao-Dong Zhou: Nothing to Disclose, Seung Up Kim: Nothing to Disclose, Terry Cheuk-Fung Yip: Gilead Sciences: Consultant, Gilead Sciences: Advisor, Gilead Sciences: Speaking and Teaching, Salvatore Petta: Nothing to Disclose, Atsushi Nakajima: Nothing to Disclose, Emmanuel Tsochatzis: NovoNordisk: Advisor, Siemens: Advisor, MSD: Advisor, Orphalan: Advisor, Univar: Advisor, Boehringer: Advisor, Echosens: Speaking and Teaching, Orphalan: Speaking and Teaching, Abbvie: Speaking and Teaching, NovoNordisk: Speaking and Teaching, Jerome Boursier: echosens: Consultant, Inventiva: Consultant, Siemens: Consultant, Pfizer: Advisor, Novonordisk: Consultant, Gilead: Royalties or patent beneficiary, Siemens: Independent Contractor, Elisabetta Bugianesi: Nothing to Disclose, Hannes Hagström: Nothing to Disclose, Wah-Kheong Chan: Nothing to Disclose,

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0090 | HIGHLY SENSITIVE HEPATITIS B CORE-RELATED ANTIGEN (HBCRAG) MEASUREMENTS CAN PREDICT HEPATOCELLULAR CARCINOMA (HCC) RISK AND HEPATITIS B SURFACE ANTIGEN (HBSAG) LOSS IN HBEAG-NEGATIVE CHRONIC HEPATITIS B PATIENTS

Tetsuya Hosaka[1] Fumitaka Suzuki[1] Mariko Kobayashi[1] Shunichiro Fujiyama[1] Yusuke Kawamura[1] Hitomi Sezaki[1] Norio Akuta[1] Yoshiyuki Suzuki[1] Satoshi Saitoh[1] Yasuji Arase[1] Hiromitsu Kumada[1]

[1]Toranomon Hospital

Background: Serum hepatitis B core-related antigen (HBcrAg) has been known as surrogate markers of intrahepatic covalently closed circular DNA (cccDNA) and transcriptional activity. The highly sensitive assay (iTACT-HBcrAg) for measuring HBcrAg levels has been recently developed and become available. However, its clinical usefulness is still unclear. In this study, we evaluated some outcomes in HBeAg-negative chronic hepatitis B (CHB) using iTACT-HBcrAg measurements. **Methods:** This study enrolled 1735 HBeAg-negative non-cirrhotic patients without antiviral therapy who had been followed up for at least 1 year and whose baseline HBcrAg levels could be measured by iTACT-HBcrAg. The lower limit of quantification of iTACT-HBcrAg assay is 2.1 Log U/mL. The subjects were classified into the following 4 groups: Group A: < 2.1, Group B: 2.1-2.9, Group C: 3.0-3.9, and Group D: ≥ 4.0. Phase of CHB was determined based on the AASLD guidelines as following: inactive carrier (IC), active (IA), and gray zone (GZ). The outcomes we evaluated were HCC incidences and HBsAg loss (< 0.05 IU/mL) according to iTACT-HBcrAg levels. **Results:** (1) In the entire cohort, 492 patients (28.4%) were categorized into Group A, 445 (25.6%) into Group B, 494 (29.5%) into Group C, and 304 (17.5%) into Group D. Baseline iTACT-HBcrAg levels (median) by CHB phase were 2.2 in IC, 3.1 in GZ, and 4.3 in IA, showing a trend toward higher HBcrAg levels as disease progressed (P-trend < 0.001). (2) Annual incidence rates of HCC were 0.6, 1.6, 1.8, and 8.6 per 1,000 person-years in Group A, B, C, and D, respectively, with an extremely low incidence of HCC in Group A (P < 0.001) (Fig A). Multivariable analysis, adjusted for CHB phases and baseline factors, showed that the hazard ratios for HCC in Group C, B, and A were 0.32, 0.21, and 0.05, respectively. Compared with Group D, Group A seems to be a population with an extremely low risk of HCC. (3) Annual HBsAg loss rates were 23.3, 14.0, 12.6, and 12.3 per 1,000 person-years in Group A, B, C, and D, respectively, with higher incidences of HBsAg loss in Groups A than other three groups (P < 0.001) (Fig B). Multivariable analysis, adjusted for HBsAg levels, CHB phases and baseline factors, hazard ratios of HBsAg loss were 1.43 in Group C, 1.56 in Group B, and 2.67 in Group A, compared with Group D. In the subgroup of HBsAg ≥ 1000 IU/mL, patients in

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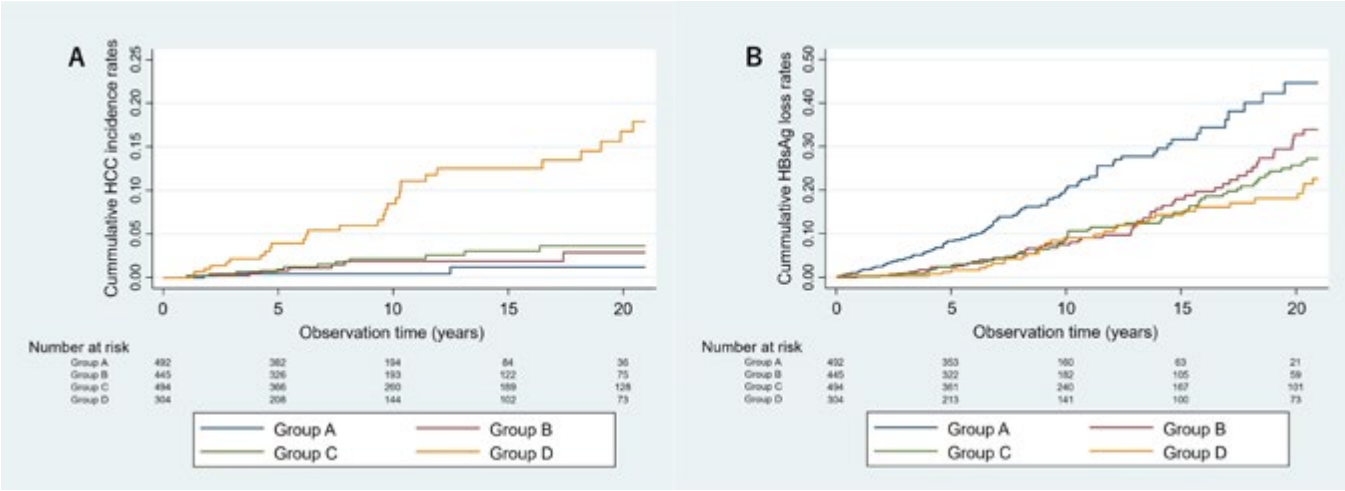
Group A were also more likely to achieve HBsAg loss than other three groups (P = 0.012). **Conclusion:** Patients with undetectable iTACT-HBcrAg in HBeAg-negative CHB had not only the low risk of HCC but were more likely to achieve HBsAg loss. Highly sensitive HBcrAg measurements can be useful for predicting the outcomes in HBeAg-negative CHB.



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0091 | SANKEY PLOTS ARE BETTER THAN EDISH BASED PLOTS FOR INITIAL DILI ASSESSMENT IN TRIALS WITH ABNORMAL BASELINE LIVER TESTS

Jasmine Amirzadegan[1] Bereket Tesfaldet[1] Veronica Pei[1] Eileen Navarro Almario[1] Paul Hayashi[1]

[1]Food and Drug Administration

Background: Background: Accurate categorization & identification of potential DILI cases in clinical trials with abnormal baseline ALT & total bilirubin (TB) are not feasible by eDISH or mDISH (eDISH using multiples of baseline). Neither account for subjects already in Hy's Law, Temple's, or cholestasis quadrants at baseline. Aim: Assess Sankey plots for DILI screening in trials with abnormal baseline ALT & TB. **Methods:** We retrospectively created Sankeys for 2 chronic liver disease trials with abnormal ALT and/or TB at baseline. We created treatment & placebo arm Sankeys to show migration from pre-treatment quadrant [Hy's Law (HL), Temple's (T), Cholestasis (C), and Normal/Near Normal (NNN)] using baseline xULN ALT & TB, to on-treatment quadrant using peak xULN ALT & TB. Quadrant migrations were labeled unfavorable (e.g., NNN to HL), neutral (e.g., no change), or favorable (e.g., HL to NNN). Quadrant names were arranged to have unfavorable migrations (potential DILI) move upward and favorable migrations move downward for easier identification and comparison. Cross tables gave tallies of each unfavorable, neutral, & favorable migration. **Results:** Sankeys provided easy comparisons of upward, unfavorable (potential DILI) & downward, favorable (potential efficacy) migrations between arms by comparing migration thicknesses, which were verified by migration counts in cross tables (Figure). Study 1 mDISH showed more on-drug subjects in "Temple's" quadrant compared to on-placebo (6 vs 1), but the Sankeys & cross tables only showed a minor imbalance in unfavorable migrations into Temple's (7 vs 6) suggesting that mDISH over-estimated DILI risk because it cannot account for subjects already in quadrants of concern. In study 2 there was substantial efficacy with large favorable downward migrations on drug compared to placebo, but also more unfavorable migrations (potential DILI) easily identified as upward migrations. mDISH was unable to provide equivalent data that incorporates quadrants of origin. **Conclusion:** Conclusions: Compared to eDISH based plots, Sankeys provide better visualization, categorization, & comparison of changes in ALT & TB between study arms by incorporating abnormal baseline liver tests in xULN. Sankeys efficiently identify subjects for subsequent composite plotting and adjudication. Sankeys could be used instead of eDISH based plots for initial

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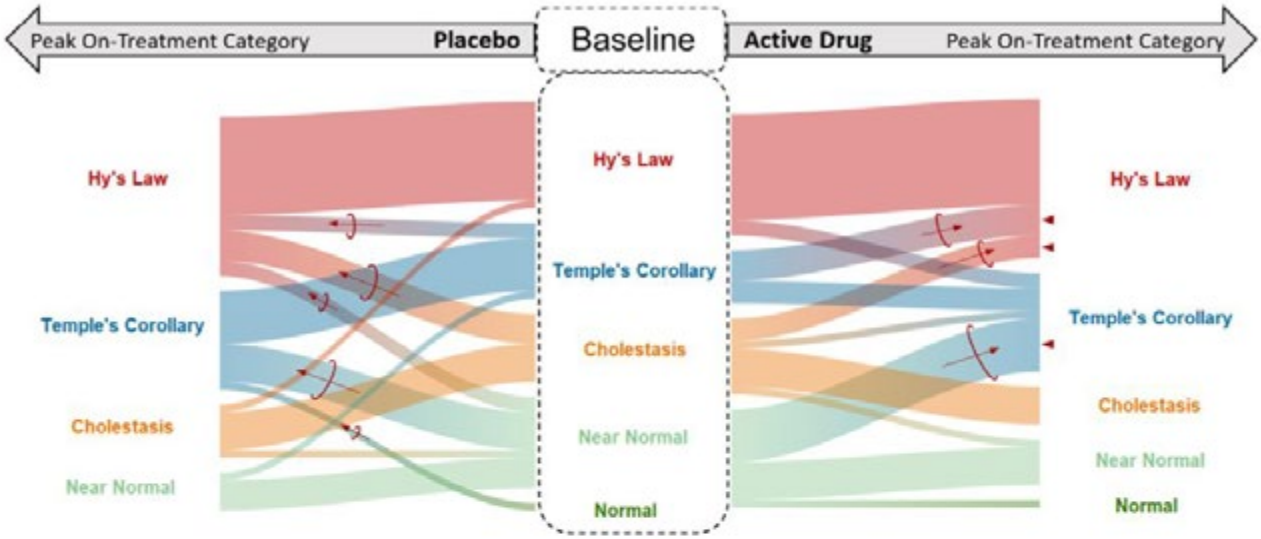
DILI screening in clinical trials with abnormal liver biochemistries at baseline. The data and conclusions presented are the author's and not an official position of the FDA.



	Peak On-Treatment				
Baseline	Normal & NN	Cholestasis	Temple's Corollary	Hy's Law	Total
Normal & NN	3	1	6	2	12
Cholestasis	0	5	0	4	9
Temple's Corollary	2	0	8	2	12
Hy's Law	0	1	0	12	13
Total	5	7	14	20	46

	Peak On-Treatment				
Baseline	Normal & NN	Cholestasis	Temple's Corollary	Hy's Law	Total
Normal & NN	6	0	7	0	13
Cholestasis	1	5	1	2	9
Temple's Corollary	0	0	3	4	7
Hy's Law	0	0	2	15	17
Total	7	5	13	21	46

Figure: Sankey plots & cross table counts for Study 1. Sankey baseline quadrant categorizations are in the middle of the figure. Migrations from baseline for the placebo arm move left, while migrations from baseline for active arm move right. All categorizations are based on ALT and TB levels in xULN. Near normal (NN) = ALT between ULN and 3x ULN. Unfavorable migrations (potential DILI) move upward and are circled. Favorable migrations (potential efficacy) move downward. Cross tables have migration counts with unfavorable (potential DILI) in red, favorable (potential efficacy) in green, and neutral migrations in grey & yellow for each arm.

Disclosures: Jasmine Amirzadegan: Nothing to Disclose, Bereket Tesfaldet: Nothing to Disclose, Veronica Pei: Nothing to Disclose, Eileen Navarro Almario: Nothing to Disclose, Paul Hayashi: Nothing to Disclose

0092 | NR-VALUE GREATER THAN FIVE IS BETTER THAN ALKALINE PHOSPHATASE (AP) LESS THAN TWICE NORMAL CRITERION FOR IDENTIFYING HY'S LAW CASES IN CLINICAL TRIALS

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Background: Background: AP<2x upper limit of normal (ULN) criterion is often used to identify Hy's Law cases in clinical trials, while post-market data suggest nR-value, [(ALT or AST/ULN) ÷ (AP/ULN)] >5, is more sensitive in identifying patients at risk of fatal hepatocellular (HC) DILI; nR-value's superiority is unproven in trials, where DILI may be detected earlier. We assessed nR-value>5 (nRv) vs AP<2x ULN (AP2x) in identifying Hy's Law cases and HC DILI fatalities (death or transplant) in clinical trials. **Methods:** We retrospectively analyzed cases assessed as probable (>50% likelihood) DILI due to study drug from Jul 1, 2020, to Apr 10, 2024, and with ALT or AST >3x ULN & TB >2x ULN in the FDA DILI Team database. We categorized cases as meeting only nRv criterion, only AP2x, both, or neither. We determined sensitivity & positive predictive values (PPV) of nRv and AP2x criteria for fatal HC DILI. **Results:** We assessed 1314 patients for DILI across 73 drug applications. 294 were considered at least probable DILI due to study drug, and 55 of these had ALT or AST >3x ULN & TB>2x ULN. We excluded 1 subject with Gilbert's, 1 with already high baseline enzymes and 1 with HBV reactivation. Of the remaining 52:

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16 (31%) met only nRv criterion, 5 (10%) met only AP2x, 21 (40%) met both, and 10 (19%) met neither. Four fatalities due to DILI occurred. After discounting 1 cholestatic DILI fatality meeting neither criterion, nRv and AP2x had PPVs for HC DILI fatality of 8% and 4%, respectively. Of the 3 fatal HC DILI cases, 2 met only nRv criterion (Table), none met only AP2x criterion, and 1 met both criteria at presentation. Thus, sensitivities for identifying fatal HC DILI were 100% and 33% for nRv and AP2x criteria, respectively. One other patient survived acute liver failure (ALF: INR >1.5, encephalopathy) due to HC DILI and met only nRv criterion (Table). All 3 fatal cases and 1 ALF case had DILI from different drugs. nR-value >5 yielded an HC DILI fatality risk closer to 10% compared to AP<2x ULN (8% versus 4%). nRv criterion identified all 3 HC DILI fatalities and 1 ALF HC DILI, while AP2x criteria identified only 1 of the 4 cases. **Conclusion:** Conclusions: The number of DILI fatalities in clinical trials is low, but correct categorization of these rare cases as meeting Hy's Law is critical to drug approval decisions. nR-value>5 criterion better approximates Hy's Law and may be more sensitive at identifying fatal HC DILI. Conclusions are the authors & not an FDA official position.

Table: Liver tests for two fatalities and one ALF case, meeting only nR-value > 5 criterion.

	Study Drug Day	ALT (U/L)	AST (U/L)	AP (U/L)	TB (mg/dL)	nR-value*	AP (xULN)*
Case 1: Transplanted	43	2673	1933	277	18.5	**23.76**	**2.04**
Case 2: Died	41	1605	1223	332	6.0	**10.09**	**2.64**
Case 3: ALF	41	784	1247	280	9.1	**16.30**	**2.54**

Study Drug Day = day of liver injury presentation (onset); ALF: Acute Liver Failure (INR > 1.5 and hepatic encephalopathy). *local ULNs used.

Disclosures: Paul Hayashi: Nothing to Disclose, Jasmine Amirzadegan: Nothing to Disclose, Edwige Chiogo Vouffo: Nothing to Disclose, Ling Lan: Nothing to Disclose, Eileen Navarro Almario: Nothing to Disclose, Mark Avigan: Nothing to Disclose

0093 | THE PROTECTIVE ROLE OF SULFIREDOXIN-1 (SRXN1) IN ACETAMINOPHEN-INDUCED LIVER INJURY ★

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Background: Acetaminophen (APAP)-induced liver injury is the leading cause of acute liver failure in many Western countries. Hepatotoxicity caused by APAP is characterized by extensive oxidative stress. *S*-sulfinylation, an oxidative post-translational modification, plays an important role in the redox-dependent regulation of protein function. Sulfiredoxin-1 (SRXN1), a member of the oxidoreductase family responsible for de-sulfinylation, has been reported pro-survival factor in cancer cells by alleviating oxidative stress-induced damage. However, the function and underlying mechanism of *S*-sulfinylation and SRXN1 in APAP-induced liver injury have not yet been investigated. **Methods:** Protein *S*-sulfinylation was detected by using a fluorescent derivative electrophilic diazene probe DiaFluo. SRXN1 expression was measured in APAP-induced liver injury in patients and mice. Hepatocyte-specific *Srxn1*-knockout mice were subjected to APAP-induced liver injury. Immunoprecipitation-mass spectrometry (IP-MS) was applied to detect the proteins that can be interacted with SRXN1. **Results:** APAP treatment induced the hepatic *S*-sulfinylation level in vitro and in vivo. SRXN1 was markedly upregulated in the livers of both patients and mice subjected to APAP. Hepatocyte-specific knockout of Srnx1 SRXN1 by using the Alb-Cre (*Srxn1*$^{\Delta HC}$) or AAV8-TBG-Cre (*Srxn1*$^{i\Delta HC}$ system, or pharmacological inhibition of SRXN1 by J14 sensitized mice to APAP-induced hepatotoxicity. In contrast, overexpression of SRXN1 showed a protective effect. Immunoprecipitation-Mass Spectrometry (IP-MS) assay identified USP7 as a potential substrate for SRNX1-mediated de-sulfinylation that may have contributed to the hepatoprotective effect of SRNX1. **Conclusion:** Our results reveal a novel role of protein *S*-sulfinylation and SRXN1 in APAP-induced liver injury. SRXN1 may represent a promising biomarker as well as a therapeutic target for APAP overdose.

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Disclosures: mengyun ke: Nothing to Disclose, Jongwon Kim: Nothing to Disclose, Kate S Carroll: Nothing to Disclose, Wen Xie: Nothing to Disclose

0094 | ANALYSIS OF NON-INVASIVE LIVER BIOMARKERS IN A PHASE II TRIAL OF THE GLUCAGON AND GLP-1 RECEPTOR DUAL AGONIST SURVODUTIDE IN PEOPLE WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS (MASH) AND FIBROSIS

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Background: We evaluated non-invasive liver biomarkers from a phase II trial of survodutide, a novel glucagon receptor/glucagon-like peptide-1 receptor dual agonist for the treatment of metabolic dysfunction-associated steatohepatitis (MASH) and fibrosis. **Methods:** In this multinational, double-blind, phase II trial (NCT04771273), 295 people aged 18–80 years with biopsy-proven MASH (Non-alcoholic fatty liver disease Activity Score ≥4), liver fibrosis (stage F1–F3) and body mass index ≥25 kg/m^2 were randomized to once-weekly subcutaneous injections of placebo (PBO) or survodutide 2.4, 4.8 or 6.0 mg (escalated over up to 24 weeks). In this analysis, we evaluated percentage of participants with >30%, >50% and >70% reduction in liver fat content (LFC; magnetic resonance imaging proton density fat fraction [MRI-PDFF] assessed; restricted to paired MRI data), resolution of steatosis (LFC <5%; MRI-PDFF assessed) with or without >17 U/L reduction in alanine transaminase (ALT; restricted to paired MRI data), absolute change in enhanced liver fibrosis (ELF) score, relative change in propeptide of type III collagen (Pro-C3), >30% reduction in LFC (controlled attenuation parameter [CAP; FibroScan] assessed), and absolute and relative change in liver stiffness (transient elastography [VTCE; FibroScan] assessed) from baseline (BL) to week 48. These biomarkers were analyzed according to the actual dose received at the start of the maintenance period. **Results:** The number of participants with significant >30%, >50% and >70% reduction in LFC (MRI-PDFF) was met in up to 87.0%, 78.2% and 52.7% with survodutide vs. 19.7%, 3.0% and 0.0% for PBO, respectively. LFC <5% with an ALT reduction of >17 U/L was met in up to 45.7% vs. 0.0% and without ALT reduction in up to 54.3% vs. 0.0% with survodutide vs. PBO, respectively. Absolute change in ELF score was up to –0.619 with survodutide vs. –0.003 with PBO; relative change in Pro-C3 was up to –26.32% vs. 5.47%, respectively. >30% reduction in LFC (CAP) was met in up to 20.3% with survodutide vs. 0.0% with PBO. The absolute (relative) change in liver stiffness (VCTE) was up to –5.09 kPa (–32.99%) with survodutide vs. –1.18 kPa (3.44%) with PBO, respectively. **Conclusion:** Participants that received survodutide had significant improvements in LFC (MRI-PDFF and CAP assessed), liver stiffness (VCTE assessed), liver enzymes and other markers of fibrosis (ELF, Pro-C3) which was correlated with improvements in histological endpoints.

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Table. Significant changes in liver biomarkers after 48 weeks of treatment

	7.4 mg survodutide QW	4.8 mg survodutide QW	6.0 mg survodutide QW	Placebo
Number of participants achieving >30% reduction in LFC (MRI-PDFF assessed)	47/58 (81.0%)	46/55 (83.6%)	40/46 (87.0%)	13/66 (19.7%)
Number of participants achieving >50% reduction in LFC	33/58 (56.9%)	43/55 (78.2%)	35/46 (76.1%)	2/66 (3.0%)
Number of participants achieving >70% reduction in LFC	22/58 (37.9%)	29/55 (52.7%)	23/46 (50.0%)	0/66 (0.0%)
Number of participants achieving LFC <5%	19/58 (32.8%)	26/55 (47.3%)	25/46 (54.3%)	0/66 (0.0%)
Number of participants achieving LFC <5% with ALT reduction >17 U/L	12/58 (20.7%)	18/55 (32.7%)	21/46 (45.7%)	0/66 (0.0%)
Absolute change in ELF score	−0.577 (BL: 9.563)	−0.618 (BL: 9.453)	−0.619 (BL: 9.681)	−0.003 (BL: 9.653)
Relative change in Pro-C3	−26.32% (BL: 41.04 µg/L)	−23.82% (BL: 42.46 µg/L)	−23.15% (BL: 44.94 µg/L)	5.47% (BL: 43.66 µg/L)
Number of participants achieving >30% reduction in LFC (CAP [FibroScan] assessed)	10/93 (10.8%)	14/69 (20.3%)	10/52 (19.2%)	0/79 (0.0%)
Absolute change in liver stiffness (VCTE [FibroScan] assessed)	−3.37 kPa (BL: 10.66 kPa)	−5.09 kPa (BL: 11.79 kPa)	−4.59 kPa (BL: 12.96 kPa)	−1.18 kPa (BL: 12.30 kPa)
Relative change in liver stiffness (VCTE [FibroScan] assessed)	−28.90% (BL: 10.66 kPa)	−32.99% (BL: 11.79 kPa)	−27.57% (BL: 12.96 kPa)	3.44% (BL: 12.30 kPa)

ALT, alanine transaminase; CAP, controlled attenuation parameter; ELF, enhanced liver fibrosis; LFC, liver fat content; MRI-PDFF, magnetic resonance imaging proton density fat fraction; Pro-C3, propeptide of type III collagen, VTCE, vibration controlled transient elastography.

Disclosures: Mazen Noureddin: Principal Investigator for a Drug Study relationship with Viking; Has not ended; Consultant relationship with Eli Lilly; Has not ended; Consultant relationship with AstraZeneca; Has not ended; Consultant relationship with Boston Pharmaceuticals; Has not ended; Principal Investigator for a Drug Study relationship with Genfit; Has not ended; Principal Investigator for a Drug Study relationship with Galectin; Has not ended; Principal Investigator for a Drug Study relationship with Gilead; Has not ended; Principal Investigator for a Drug Study relationship with BMS; Has not ended; Principal Investigator for a Drug Study relationship with BI; Has not ended; Principal Investigator for a Drug Study relationship with Akero; Has not ended; Consultant relationship with Cytodyn; Has not ended; Consultant relationship with GSK; Has not ended; Consultant relationship with BI; Has not ended; Consultant relationship with Madrigal; Has not ended; Terns,Takeda, Zydus. relationship with Itimmune, BI, Cytodyn, 89BIO, GSK, Madrigal, Merck, Novo Nor; Has not ended; Principal Investigator for a Drug Study relationship with Allergan; Has not ended; Consultant relationship with Takeda; Has not ended; Consultant relationship with Terns; Has not ended; Terns, Corcept, Takeda, Madrigal, Novartis, Novo Nordisk, relationship with Allergan, Akero, BI, BMS, Gilead, Galectin, Zydus GSK; Has not ended; Consultant relationship with Novo Nordisk; Has not ended; Stock â€“ privately held company relationship with Rivus Pharma, Cytodyn, and ChronWell; Has not ended; Consultant relationship with Merck; Has not ended; Principal Investigator for a Drug Study relationship with Madrigal; Has not ended; Consultant relationship with Altimmune; Has not ended; Principal Investigator for a Drug Study relationship with Terns; Has not ended; Principal Investigator

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0095 | AUTOLOGOUS MACROPHAGE THERAPY DECREASES MAJOR CLINICAL OUTCOMES IN PATIENTS WITH COMPENSATED CIRRHOSIS: EXTENDED DATA FROM A RANDOMIZED CONTROLLED PHASE 2 TRIAL

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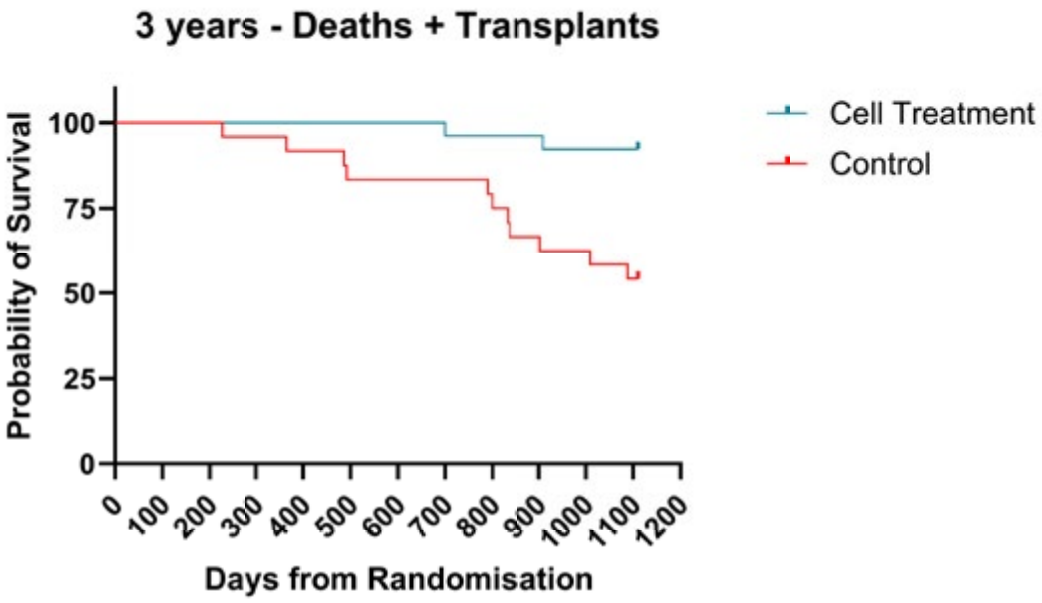
Background: Macrophage therapy has shown promising results in preclinical models and early human studies of cirrhosis. MATCH (ISRCTN10368050) was a multicentre, open-label, Phase 2, randomized controlled trial of autologous monocyte-derived macrophage therapy for cirrhosis. We initiated a 2-year extension to understand the long-term safety and efficacy of this cell therapy. **Methods:** In MATCH, we compared autologous monocyte-derived macrophage therapy with standard medical care in a cohort of adult patients with compensated cirrhosis (≥3 months since any previous decompensation) and MELD score ≥10 and ≤17. Treatment comprised leukapheresis, cell isolation and maturation with reinfusion of macrophages to a maximal concentration of 1 x 10^9 cells. Patients were randomized to triple infusion (n=3), single infusion (n=23) and standard of care (SoC) (n=24). We measured plasma cytokines using MSD V-plex. Significance testing of Kaplan-Meier curves used the log-rank test. Originally patients had 12 months follow-up (Brennan PN et al, Hepatology (2023), 78(S1):S168-169). Here we present an analysis of the 3-year data (currently 90% completed). Analysis of the completed 3-year data will be presented at the meeting. **Results:** After 2 years of extended follow-up (i.e., 3 years post randomization) there were 11 liver-related events (8 deaths, 3 liver transplants), in the control group, compared to 2 events (2 deaths, 0 liver transplants) in the macrophage infusion groups. Excluding these patients, 8% (2/24) of treated and 23% (3/13) of control patients developed new signs of portal hypertension (incident varices or splenomegaly). Kaplan Meier analysis demonstrated significantly improved outcomes in both overall survival (Chi-square=5.26; p=0.022), and transplant-free survival (Chi-square=9.55; p=0.002) with macrophage treatment (see Figure). There were 3 malignancies (0 HCC) in the control and 1 malignancy (HCC) in the treated groups. No upregulation of pro-inflammatory cytokines was observed at any of the timepoints analysed. **Conclusion:** We demonstrate proof-of-concept for the beneficial effect of macrophage cell therapy on clinical outcomes in patients with compensated cirrhosis over a 3-year period. Together, our findings reinforce the longer-term safety profile and tolerability of this class of therapy and encourage further development in patients with end-stage liver disease.



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0096 | PERFORMANCE OF THE CAGE-B AND SAGE-B SCORES FOR PREDICTION OF HEPATOCELLULAR CARCINOMA IN CHRONIC HEPATITIS B PATIENTS WITH ADVANCED FIBROSIS ★

Lesley Patmore[1] Lilian Yan Liang[2] Mai Kilany[3] Arno Furqium d'Almeida[4] Vincent Wong[5] Thomas Vanwolleghem[6] Pieter Honkoop[7] Hans Blokzijl[8] Özgür Muhammet Koc[9] Harry Janssen[10] Matthijs Kramer[9] Joep de Bruijne[11] Apichat Kaewdech[12] Robert De Man[6] Bart Takkenberg[13] Grace Wong[2] Jordan Feld[3] Milan Sonneveld[6]

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Background: Patients with chronic hepatitis B (CHB) treated with nucleo(s)tide analogues (NA) remain at risk for hepatocellular carcinoma (HCC). A recent study showed that risk scores (CAGE-B, SAGE-B) utilizing on-treatment liver stiffness measurement (LSM) might be able to predict subsequent HCC risk. We assessed the performance of these scores in CHB patients with advanced fibrosis. **Methods:** We conducted an international multicenter cohort study of treatment-naïve CHB patients with advanced fibrosis (≥F3 liver biopsy or LSM ≥9.0 kPa) and with on-treatment LSM after at least 3 years of follow-up at different sites in Europe and Asia. The SAGE-B (based on age and on-treatment LSM) and CAGE-B (based on baseline cirrhosis, age and on-treatment LSM) scores were calculated, and classified as low (<6), intermediate (6-10) or high (>10) risk for HCC as previously published. We assessed the 5-year cumulative HCC incidence across CAGE-B/SAGE-B strata and studied the contributing value of the risk score components (age and on-treatment LSM). **Results:** We analyzed 512 patients with a median age at baseline of 50 years (inter quartile range [IQR] 39 – 57), predominantly male (76%), Asian (76%) and 59% had F4. The median time between baseline and on-treatment LSM was 4.5 years with a median on-treatment LSM of 6.9 kPa (IQR 5.1 – 10.3). During a median follow-up of 6.8 years after the on-treatment LSM, 53 patients developed HCC. Median CAGE-B score was 8 (IQR 6 -11), 20% was classified as low, 53% as intermediate and 27% as high risk. The 5-year cumulative HCC incidence in the low risk CAGE-B group was 0% compared to 5.2% in the intermediate and 6.6% in the high risk group (p=0.002). Median SAGE-B score was 6 (IQR 4 – 8), 31% was classified as low risk, 56% as intermediate risk and 13% as high risk. The 5-year cumulative HCC incidence in the low risk SAGE-B group was 2.3% compared to 5.8% in the intermediate and 6.8% in the high risk group. (p=0.031). Interestingly, the association between CAGE-B/SAGE-B scores with HCC appeared to be predominantly driven by age. We observed no HCC in patients aged <40 years, compared to a 5-year cumulative HCC incidence of 5.7% for patients aged >40 years (p=0.024). Among patients aged >40 years (n=441), LSM was not associated with HCC risk (hazard ratio 1.004, p=0.832), and 5-year HCC risk was comparable for patients with LSM <6 kPa (5.6%), 6–9 kPa (6.8%) and >9 kPa (4.7%, p=0.771). **Conclusion:** CHB patients with advanced fibrosis remain at high risk of HCC despite NA therapy. Although low SAGE-B and CAGE-B scores were associated with reduced HCC risk, this was predominantly driven by age, as HCC risk remained high even amongst patients with low on-treatment LSM.

Disclosures: Lesley Patmore: Gilead Sciences: Consultant, Lilian Yan Liang: Nothing to Disclose, Mai Kilany: Nothing to Disclose, Arno Furqium d'Almeida: Nothing to Disclose, Vincent Wong: Nothing to Disclose, Thomas

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0097 | REPRESENTATION OF GENDER, RACIAL, AND ETHNIC MINORITIES IN HEPATOLOGY CLINICAL TRIALS ◆

Kin Li[1] Fouad Bouso[1] Malik Mushannen[1] Joshua Harroch[1] Carla Pellegrino[1] Gres Karim[1] Nicholas Brown[1] Ilan Weisberg[2]

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Background: Historically, clinical trials in the United States have overrepresented White male participants, which may lead to significant gaps in our understanding of disease manifestations and treatment responses among different demographic groups. Inclusivity in clinical trials is crucial for advancing our knowledge of diseases, tailoring treatment strategies, and innovating interventions that are effective and equitable for all. In this cross-sectional study we investigated the diversity and inclusion of racial, ethnic, and gender minorities in hepatology clinical trials. **Methods:** A cross-sectional analysis was performed on completed hepatology clinical trials within the United States between January, 2010 and February, 2024, as listed on clinicaltrials.gov. All interventional phase I-IV clinical trials enrolling a minimum of 10 adult participants (≥18 years old) with results available for evaluation were included. Trials that were ongoing, suspended, terminated, or withdrawn were excluded. The inquiries were reviewed as an aggregate and also subcategorized into cirrhosis, hepatic impairment, MASLD, viral hepatitis, liver cancer or biliary cancer trials. **Results:** A total of 150 hepatology clinical trials enrolling 13,456 adult participants with 5,350 (39.8%) women and 8,106 (60.2%) men were included. Included demographics were compared against an average of the United States Census data from 2010-2021 (Figure I). Female participants were under-represented in all clinical trials except for MASLD (56.9%, 95% CI 55.1-58.8%) and biliary cancer (56.7%, 95% CI 53.8-59.7%). White participants were over-represented in all trials except viral hepatitis (66.4%, 95% CI 65.3-67.4%). African American participants, comprising approximately 12% of the US population, were under-represented in all trials except viral hepatitis (29.2%, 95% CI 28.2-30.2%). Asian participants, comprising approximately 5.5% of the US population, were under-represented in all trials except for liver cancer (7.8%, 95% CI 6.5-9.2%). Hispanic participants, comprising approximately 16% of the US population, were over-represented in cirrhosis (27.3%, 95% CI 23.5-31.0%), hepatic impairment (44.2%, 95% CI 38.8-49.6%), and MASLD (40.4%, 95% CI 38.6-42.2%) trials. American Indian or Alaskan Native participants were under-represented in all trials. **Conclusion:** When compared to US census demographic data, there is substantial heterogeneity in the recruitment of gender, racial, and ethnic minorities within hepatology clinical trials. Researchers should be aware of recruitment shortcomings to ensure better inclusivity and representation in future hepatology clinical trial study designs.

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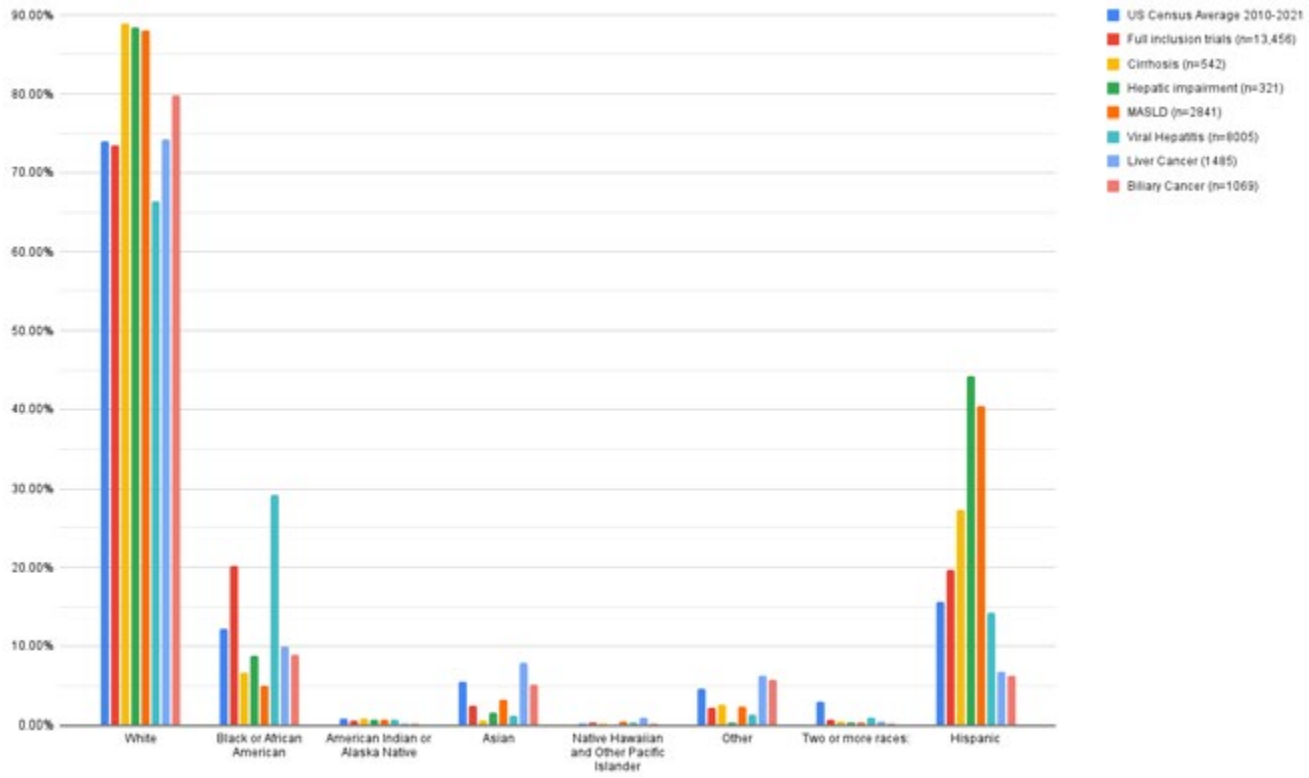

Disclosures: Kin Li: Nothing to Disclose, Fouad Bouso: Nothing to Disclose, Malik Mushannen: Nothing to Disclose, Joshua Harroch: Nothing to Disclose, Carla Pellegrino: Nothing to Disclose, Gres Karim: Nothing to Disclose, Nicholas Brown: Nothing to Disclose, Ilan Weisberg: Nothing to Disclose

0098 | LYSOSOMAL AUTOPHAGY-BASED DEGRADATION OF HEPATOCELLULAR CARCINOMA PD-L1 MODULATES TUMOR MACROPHAGE POLARIZATION TO ACTIVATE ANTI-TUMOR IMMUNITY

Xu Gao[1] Wangxiao He[1] Enrui Xie[1] Zixuan Xing[1] Yue Zhang[1] Jinhai Wang[1] Jin Yan[1] Fanpu JI[2]

[1]Xi'an Jiaotong University, [2]Xi'an Jiaotong University

Background: The response rate of hepatocellular carcinoma (HCC) to ICIs is less than 20%, and with the expansion of the application of ICIs, immune resistance has become another factor restricting the development of ICIs. The development of new therapiesto reverse the ICIs resistance for HCC is an unsolved problem in clinical practice. M2 tumor associated macrophages (TAMs), as a central regulator of the tumor microenvironment, affects tumor development, angiogenesis and immunosuppression. Reprogramming M2 TAMs is an important methodological strategy in tumor drug development and therapy. **Methods:** We developed a biomimetic autophagy degradation peptide (MNP-PDL1) using the lysosomal autophagy system in conjunction with biomimetic membrane technology, which consists of a PD-L1-binding sequence, a PEG3 linker, and a target lysosomal chaperone protein recognition sequence (CIP), which can localize the target protein, PD-L1, to the lysosome for degradation. **Results:** MNP-PDL1, designed to degrade PD-L1 protein via the lysosomal pathway in macrophages and various hepatocellular carcinoma (HCC) cells, exhibits superior anti-tumor efficacy compared to commercially available anti-PD-L1 inhibitors. In HCC in situ mouse model, MNP-PDL1 significantly inhibits tumor growth and PD-L1 degradation within tu mors. In the control group, 68.4% of PD-L1+ TAMs cells were observed, reduced to 48% with anti-PDL1 treatment, and further decreased to 31.8% and 23.5% with NP-PDL1 and MNP-PDL1 treatments, respectively. Moreover, MNP-PDL1 induces M1 polarization of TAMs, with the proportion of CD86+ TAMs cells increasing from 20.6% in the control group to 31.2% and 61.2% in the NP-PDL1 and MNP-PDL1 groups, respectively. Additionally, MNP-PDL1 increases TAMs in the tumor microenvironment (TME)

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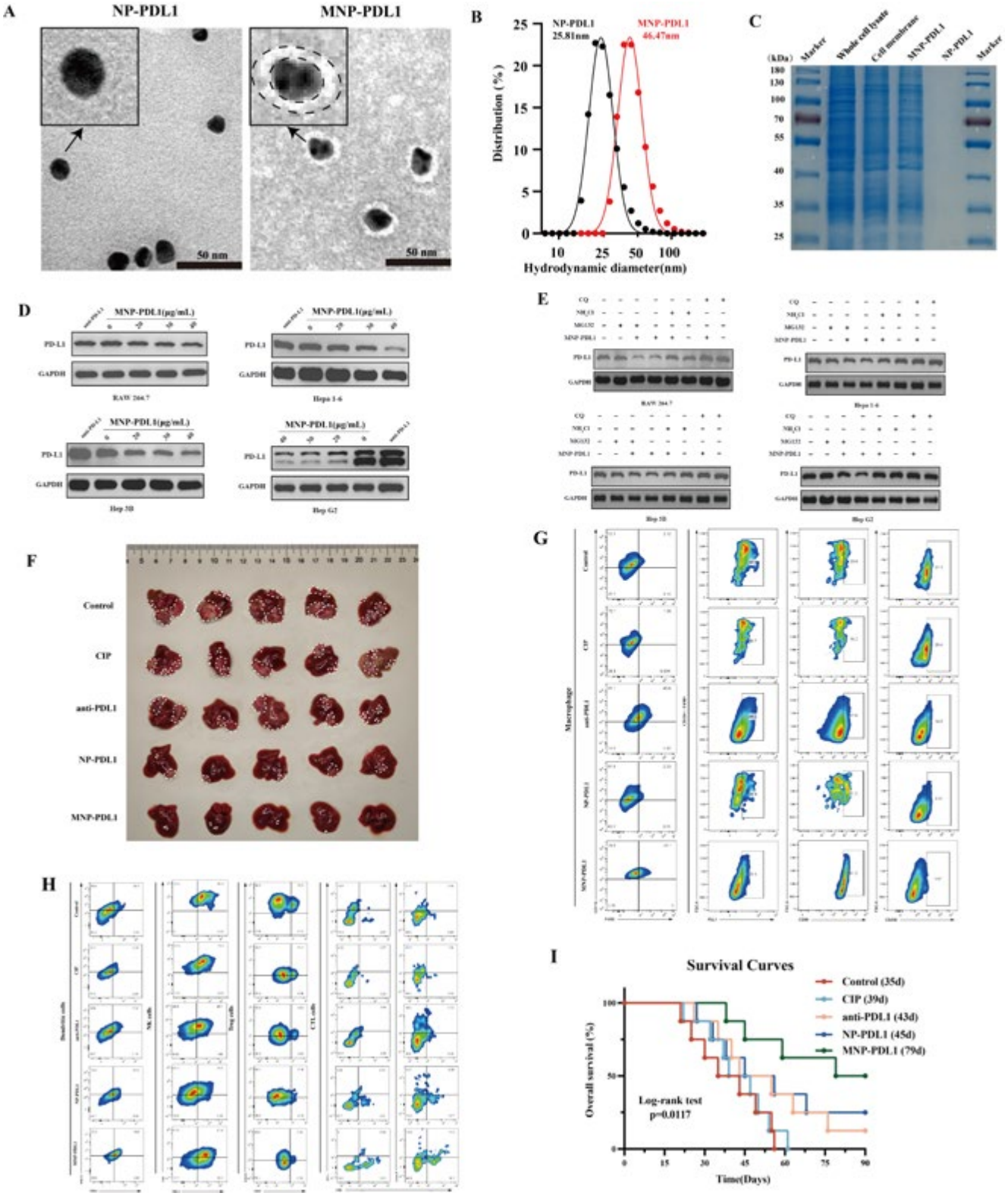
dendritic cells (DC), natural killer (NK) cells, and activated cytotoxic T lymphocytes (CTL) infiltration. Specifically, in the MNP-PDL1-treated group, CD8+ IFNγ+ CTL cells account increased to 6.94% compared to only 1.26% in the control group. Overall, MNP-PDL1 effectively inhibits HCC growth and extends the survival time of treated mice. **Conclusion:** We successfully developed biomimetic lysosomal-targeted PD-L1 degradation peptides that induced M1 polarization of TAMs, increased HCC immune cell infiltration, reversed HCC immune tolerance, and significantly activated anti-cancer responses.



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0099 | THE IMPACT OF WEEKEND ADMISSIONS ON LIVER TRANSPLANT OUTCOMES IN ACUTE LIVER FAILURE IN THE UNITED STATES

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Background: The admissions of patients with acute liver failure (ALF) on weekends has been understudied despite the possibility that it may be associated with delays in transplant evaluation, potentially resulting in higher post-transplant mortality. We aimed to assess the effect of weekend admission on liver transplantation (LT) -related outcomes in adult patients with ALF. **Methods:** In a retrospective cohort of adults who underwent LT for ALF between February 2002 and May 2023 using the United Network for Organ Sharing (UNOS) database, we evaluated post-LT outcomes until June 2023. Patients with previous LT were excluded. A logistic regression model assessed the association of admissions on a weekday (Monday to Friday) and weekend (Weekend or Long Weekend) with waitlisting on Mondays or days after long weekends as a surrogate for potential delays in evaluation and listing for LT. Kaplan-Meier survival analysis with log-rank test and Cox proportional hazard model were used to estimate the effect of waitlisting on Monday or a day after a long weekend on post-LT mortality one year after LT. Potential confounders included in the regression models included age, sex, race, etiology of acute liver failure, primary payer (Medicaid vs. others), and the era when the subjects were listed (before and after Acuity Circle). **Results:** Among 3821 adults who underwent LT for ALF, 2861 patients were in the weekday and 960 in the weekend admission group. A total of 512 patients were listed for LT after a weekend. The demographic and clinical characteristics of patients including age, sex, MELD score, cold ischemia time, race/ethnicity, etiology of ALF, and length of stay, who were listed after a weekend compared to other days, were comparable. The median number of days from admission to waitlisting was 2 (IQR 1-5). Weekend admissions were associated with LT listing after a weekend (adjusted odds ratio 3.56, 95% CI: 2.93-4.32). Overall post-LT survival at one-year follow-up was 20.3% in those who were listed after a weekend and 16.5% otherwise (log-rank test p=0.03, Figure). Listing after a weekend was associated with higher post-LT mortality at one year in unadjusted and adjusted analyses (adjusted hazard ratio 1.25, 95% CI: 1.02-1.55). **Conclusion:** This study demonstrates that among adult patients with ALF who underwent LT, waitlisting after a weekend or a long weekend is associated with higher one-year mortality. This may be because of delays in LT evaluation and waitlisting process on weekends and suggests a need for improvement in weekend listing practices.

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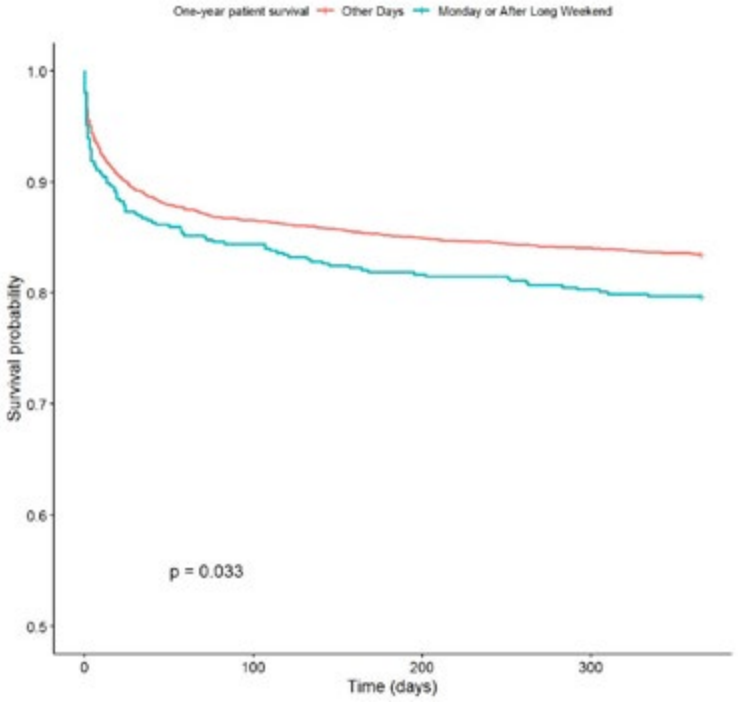

Disclosures: Melis Celdir: Nothing to Disclose, Tomohiro Tanaka: Nothing to Disclose

0100 | THE RISK OF PORTAL VEIN THROMBOSIS IN PATIENTS WITH PORTAL HYPERTENSION TAKING BETA-BLOCKERS: A RETROSPECTIVE COMPARATIVE STUDY FROM A MULTI-INSTITUTIONAL DATABASE

Hazem Abosheaishaa[1] Khaled Elfert[2] Abdullah Olimy[3] Islam Mohamed[4] Mohammed Abusuliman[5] Ahmed Salem[6] Abdellatif Ismail[7] Mohamed El-Kassas[8]

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Background: Portal vein thrombosis (PVT) involves the obstruction or narrowing of the portal vein due to a blood clot and is commonly associated with liver cirrhosis and portal hypertension. Beta-blockers are frequently prescribed to manage portal hypertension, but their role in the development of PVT is not well understood. This study aims to assess the risk of developing PVT in patients with portal hypertension and liver cirrhosis who are taking beta-blockers compared to those who are not. **Methods:** This retrospective cohort study used the TriNetX database, which includes electronic health records from over 110 million patients in 63 US healthcare organizations. The study population consisted of adult patients (≥18 years) with portal hypertension and liver cirrhosis who underwent esophagogastroduodenoscopy with band ligation of esophageal varices, excluding those with liver cell carcinoma. Two cohorts were defined: one receiving beta-blockers (propranolol, carvedilol, or nadolol) and one not receiving beta-blockers. The primary outcome was the incidence of PVT (ICD-10-CM code I81), and the secondary outcome was mortality. Baseline characteristics were balanced using one-to-one propensity score matching (PSM). Outcomes were analyzed using adjusted odds ratios (aOR) with 95% confidence intervals (CI), considering p-values <0.05 as statistically significant. **Results:** Before PSM, the beta-blocker cohort included 15,754 patients, and the control cohort included 8,783 patients. After PSM, each cohort had 6,970 patients with similar baseline characteristics. Before PSM, 8.64% of the beta-blocker cohort developed PVT compared to 4.72% in the control group (aOR 1.911, 95% CI 1.693-2.156). After PSM, 8.85% of the beta-blocker cohort developed PVT compared to 4.74% in the control group (aOR 1.951, 95% CI 1.686-2.257). Mortality was higher in the beta-blocker cohort both before PSM (23.9% vs. 17.37%, aOR 1.494, 95% CI 1.397-1.597) and after PSM (22.8% vs. 18.6%, aOR 1.292, 95% CI 1.190-1.403) **Conclusion:** Beta-blocker use in patients with portal hypertension and liver cirrhosis is associated with a significantly higher risk of developing

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PVT and increased mortality. Further research is needed to explore these associations and assess the safety of beta-blockers in this patient population.

Results before PSM					
Outcome	**Cohort**	**Number of patients PMS**	**Proportion of patients (%)**	**(aOR)**	**95% CI**
PVT	Beta-blockers	1,222	(8.64%)	1.911	(1.693,2.156)
	Control	362	(4.72%)		
Mortality	Beta-blockers	3,868	(23.9%)	1.494	(1.397,1.597).
	Control	1,467	(17.37%)		
Results After PSM					
Outcome	**Cohort**	**No. of patients After PMS**	**Proportion of patients (%)**	**(aOR)**	**95% CI**
PVT	Beta-blockers	546	(8.85%)	1.951	(1.686, 2.257)
	Control	298	(4.74%)		
Mortality	Beta-blockers	1591	(22.8%)	1.292	(1.190, 1.403)
	Control	1298	(18.6%)		

Table 2: Clinical outcomes before and after propensity-matched beta blocker and control cohorts

Disclosures: Hazem Abosheaishaa: Nothing to Disclose, Khaled Elfert: Nothing to Disclose, Abdullah Olimy: Nothing to Disclose, Islam Mohamed: Nothing to Disclose, Mohammed Abusuliman: Nothing to Disclose, Ahmed Salem: Nothing to Disclose, Abdellatif Ismail: Nothing to Disclose, Mohamed El-Kassas: Nothing to Disclose

0101 | HEPATIC GRP78/BIP OVEREXPRESSION PROTECTS AGAINST ENHANCED MASLD BY VINYL CHLORIDE ★

Pooja Muddasani[1] *Charis-Marie Vanderpuye*[1] *Jiang Li*[1] *Sudrishti Chaudhary*[1] *Samuel Taborski*[1] *Lorien Walker*[1] *Ian Sipula*[1] *Michael Jurczak*[1] *Gavin Arteel*[1] *Juliane Beier*[1]

[1]*University of Pittsburgh*

Background: Vinyl chloride (VC), a common environmental pollutant, directly causes liver injury at high exposure levels, but lower concentrations (i.e., < OSHA limits) that do not overtly damage the liver, can also enhance injury due to overnutrition. Previous work from this lab showed that VC induces endoplasmic reticulum (ER) stress and impairs mitochondrial (mt) function. Here, a more detailed analysis of the underlying molecular underpinnings

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was performed by overexpressing hepatic Grp78 (BiP), an ER chaperone and regulator of the unfolded protein response (UPR), which has previously been shown to be decreased by VC. **Methods:** 6-week-old C57Bl/6J mice were exposed to VC (<1 ppm), or room air for 6 hrs/day, 5 days/week in inhalation chambers for 12 weeks. Mice were fed Western (WD) to induce MASLD, or control diet (CD). A subset of mice was administered recombinant adeno-associated virus type 8 vectors (rAAV8; 1×10^{11} PFU/mouse, i.v.) overexpressing murine Grp78 driven by the TBG promoter, or control scrambled rAAV8 vectors. Body composition (total body fat and total lean mass) was measured via echo MRI. Plasma and liver samples were collected to determine liver injury and for histology. **Results:** VC exposure enhanced MASLD caused by WD feeding. This was accompanied by hepatocyte ballooning and increased microvesicular steatosis, indicative of foamy degeneration. VC also caused ER dilation, indicative of proteostasis/ER stress independent of diet. The interaction between VC and WD dramatically decreased protein levels of Grp78 in the liver. While Grp78 overexpression did not cause changes in body weight, it did robustly decrease the magnitude of both hepatic micro- and macrovesicular steatosis, likely via decreasing ER stress and preventing the downstream UPR activation. Moreover, liver-specific Grp78 overexpression significantly attenuated liver injury and inflammation. **Conclusion:** Taken together, these data suggest that VC exposure causes ER stress and that overexpression of Grp78 can protect from this damage. This is in line with our previous research which demonstrated that Grp78 is one of the target genes regulated by VC exposure and is actively involved in the toxic effects by VC. These results further shed light on the observation that the ER appears to be a key target of injury during low-level VC exposure. This research is supported by R01 DK133454-03 and R21 ES036032-01.

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0102 | GUT MICROBIOME PATTERN IMPACTS TREATMENT RESPONSE IN PRIMARY BILIARY CHOLANGITIS ◆

Ruqi Tang[1] Xiong Ma[2] Liu Qiaoyan[2]

[1]Shanghai Jiao Tong Univ. School of Medicine, Renji Hospital, [2]Shanghai Jiao Tong University

Background: Primary biliary cholangitis (PBC) is a progressive autoimmune liver disease. An inadequate response to ursodeoxycholic acid (UDCA) poses a high risk of progression towards end-stage liver disease. Gut dysbiosis has been implicated in PBC. Here, we aimed to investigate microbial signatures that permit risk stratification and provide mechanistic insights into novel therapies for PBC. **Methods:** We prospectively recruited UDCA treatment-naïve patients with PBC and performed metagenomic sequencing and metabolomic profiling using stool and serum samples obtained before (n=132) and after (n=59) treatment. PBC microbiome subtypes were identified using unsupervised machine learning methods and validated in two independent cohorts. **Results:** PBC baseline metagenomes clustered into two community subtypes characterized by varying abundances of Clostridia taxa. Compared with *Clostridia*^{low} microbiomes, *Clostridia*^{high} microbiomes were more similar to healthy controls. Notably, patients in the *Clostridia*^{low} subtype exhibited a twofold-higher UDCA non-response rate compared to those in the *Clostridia*^{high} subtype (41% versus 20%, P=0.015). Integrative analysis of metagenomic and metabolomic data revealed divergent functional modules and metabolic activities between the two metacommunities. Particularly, anaerobic fermentation and the production of bioactive metabolites including tryptophan derivatives and secondary bile acids, crucial for immune regulation and gut barrier maintenance, were markedly diminished in the *Clostridia*^{low} subtype. Moreover, UDCA administration reconfigured the fecal microbial and metabolic profiles only in the *Clostridia*^{high} group. Importantly, the microbiome subtypes and their associations with UDCA response were reproducible in two independent treatment-naive PBC cohorts. **Conclusion:** Characterizing baseline microbiota patterns may enable prediction of treatment outcomes in PBC and facilitate personalized treatment strategies.

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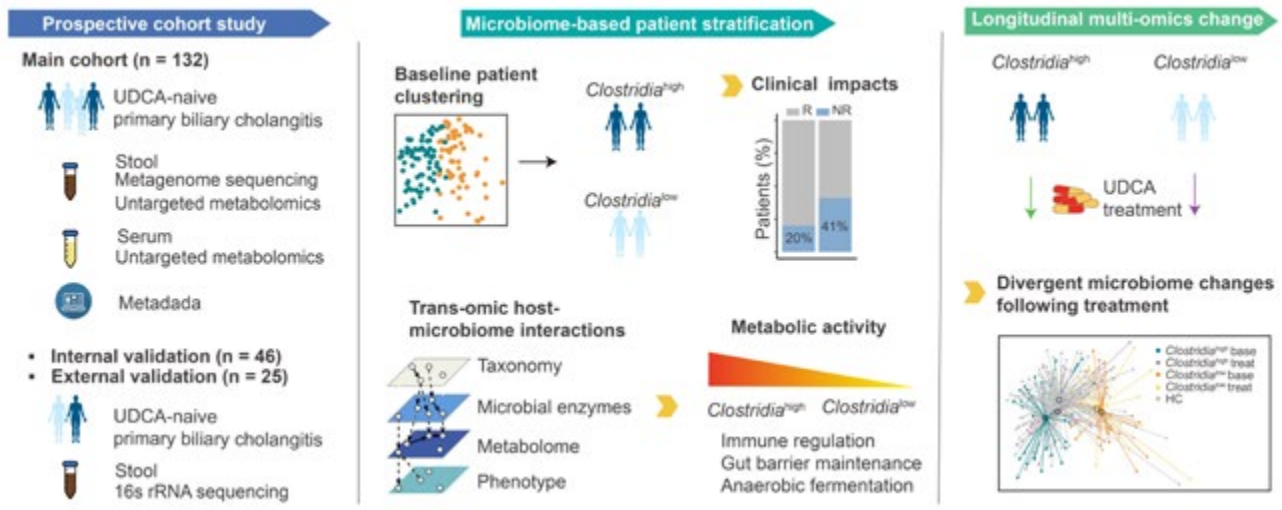

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0103 | DDX3X REGULATES THE FUNCTIONAL TRANSITION OF ENDOPLASMIC RETICULUM STRESS DURING PROGRESSION OF LIVER FAILURE ◆

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Background: The functional transition of endoplasmic reticulum stress (ERS) plays a critical role in the pathogenesis of liver failure (LF), but the underlying molecular mechanisms remain unclear. Here, we explored the role of DDX3X under ERS to regulate cell fate in the progression of LF. **Methods:** Primary hepatocytes were isolated from C57BL/6J mice and induced ERS with tunicamycin (TM). C57BL/6J mice were induced ERS with TM and liver injury with concanavalin A (ConA), respectively. The expression level of DDX3X in liver tissue and serum were analyzed in healthy, chronic hepatitis B (CHB) patients and HBV-associated LF patients. Quantitative real-time PCR (qRT-PCR) and western blotting (WB) methods were used to detect the expression of related genes and proteins; cell viability, cell death rate and cell apoptosis rate was detected by cell counting kit-8 (CCK-8), lactate dehydrogenase (LDH) assays and flow cytometry, respectively; serum alanine transaminase (ALT) and aspartate aminotransferase (AST) levels and hematoxylin-eosin (H&E) staining of liver sections were used to evaluate liver injury in this study. **Results:** We demonstrated that DDX3X increased and translocated into nucleus with prolonged ERS; secondly, DDX3X plays dual roles under different periods of ERS mediated cell fate; in addition, phosphorylation modification of DDX3X is the key mechanism to regulate its subcellular localization. Under short-term ERS, DDX3X was mainly expressed in cytoplasm and interacted with peroxisome proliferators-activated receptor alpha (PPARα), which translationally up-regulated transcription factor EB (TFEB) to promote the adaptive cell response. Under prolonged ERS, phosphorylated DDX3X increased nuclear translocation to promote cell apoptosis by CCAAT enhance-binding protein homologous protein (CHOP) activation. In addition, we demonstrated that DDX3X was increased in ConA-induced liver injury in mice and its nuclear translocation was increased; secondly, DDX3X plays dual roles during ConA-induced liver injury, which exerts a protective effect in early phase (6 h) and a pro-injury effect in the late phase (24 h). Furthermore, we found that DDX3X levels were significantly increased in serum and liver tissues of HBV-related LF patients; secondly, the fluctuation of DDX3X serum level is correlated with the prognosis of HBV-LF patients, which consistent decline was correlated with the good prognosis. **Conclusion:** Our novel findings document the key regulatory function of DDX3X signaling under ERS in the pathophysiology of liver failure, and provide a rationale to target DDX3X as a refined therapeutic strategy to ameliorate liver injury.

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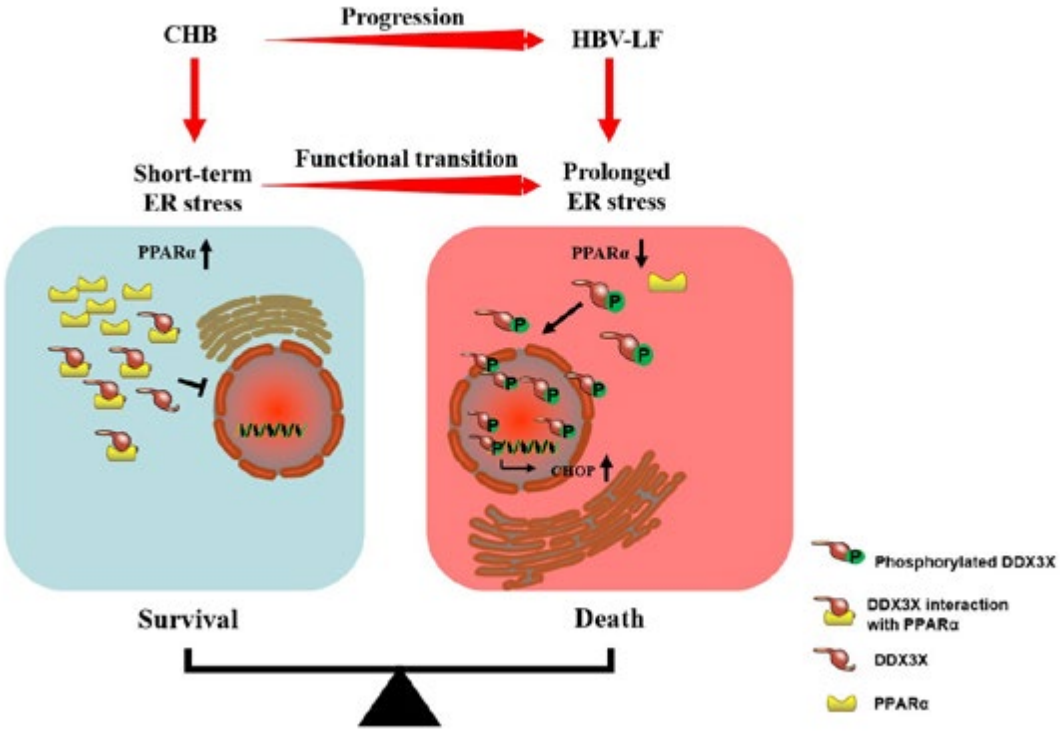

Disclosures: Ling Xu: Nothing to Disclose, Xiangying Zhang: Nothing to Disclose, Feng Ren: Nothing to Disclose

0104 | A PROSPECTIVE / RETROSPECTIVE PROVINCIAL AND NATIONAL LABORATORY SEROSURVEY OF HDV ANTIBODY PREVALENCE IN REFERRED AND NON-REFERRED SAMPLES IN CANADA

Emma Lee[1] Carla Osiowy[2] Jacqueline Day[1] Donald Murphy[3] Vanessa Tran[4] Carmen Charlton[5] Derek Stein[2] Christopher Lowe[6] Nancy Matic[6] Todd Hatchette[7] Carla Coffin[8]

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Background: HBV and HDV coinfected individuals progress to liver cancer and hepatocellular carcinoma faster than HBV monoinfected patients. In Canada, reflex testing (i.e., automatically testing all HBsAg positive samples for anti-HDV) is not performed as current guidelines recommend risk-based HDV screening. Currently only one provincial lab offers anti-HDV testing, i.e., Laboratoire de santé publique du Québec (LSPQ). The other 9 provinces and 3 territories refer anti-HDV testing to the National Microbiology Laboratory (NML) in Winnipeg, MB. Confirmatory HDV RNA testing (including those from Québec) is only done at the NML. We aim to determine the prevalence of anti-HDV and HDV RNA in samples prospectively referred for testing over a 1 year period. The data was compared to seropositivity rates in non-referred samples (banked for research or archived over 6-12 month period from five provincial or hospital labs (samples from YK, BC, AB, MB, ON and NS) **Methods:** Data on prospective anti-HDV testing in samples referred from clinicians to the LSPQ (provincial laboratory in Québec) and the NML (rest of Canada) was collected from 08/2022-08/2023. In addition, non-referred retrospectively or prospectively banked de-identified samples at five other provincial or hospital laboratories were tested locally or shipped to the NML for testing, under an approved research protocol. All laboratories tested for anti-HDV with commercial assay (DiaSorin and/or Wantai), that was set up and validated using reference samples from the NML. All seropositive samples were tested at the NML for confirmatory HDV RNA and genotyped using an in-house PCR / Sanger sequencing. **Results:** From 08/2022 – 08/2023, 3.5% (67/1942) and 5.5% (70/1266) of prospectively referred samples tested positive at the NML and the LSPQ, respectively. Cumulative anti-HDV testing to date of 1,077 non-referred (or banked) samples from three provincial/hospital labs showed seropositivity rate that ranged from 1.0%-1.1%. Data on 1500 non-referred (archived or prospectively banked) samples are in progress from two provincial labs. **Conclusion:** In this nationwide study of HDV testing from 4/6 provincial labs to

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date (2 in progress) and the Canadian National Reference Lab (NML), anti-HDV seropositivity was 4 times higher in referred samples compared to non-referred specimens (4.2 vs. 1.1%). The identification of a few cases in non-referred samples suggests that risk-based screening may miss some individuals at high risk for progressive liver disease.

Disclosures: Emma Lee: Nothing to Disclose, Carla Osiowy: Nothing to Disclose, Jacqueline Day: Nothing to Disclose, Donald Murphy: Nothing to Disclose, Vanessa Tran: Nothing to Disclose, Carmen Charlton: Nothing to Disclose, Derek Stein: Nothing to Disclose, Christopher Lowe: Nothing to Disclose, Nancy Matic: Nothing to Disclose, Todd Hatchette: Nothing to Disclose, Carla Coffin: Grant/Research Support relationship with Gilead Sciences; Has not ended; Grant/Research Support relationship with Janssen Pharmaceuticals; Has ended; Funds paid to the University of Calgary relationship with GSK; Has not ended; Grant/Research Support relationship with Riche Pharmaceuticals; Has not ended; Fund paid to the University of Calgary relationship with Altimmune Pharmacueticals; Has ended; Speaking and Teaching relationship with GSK; Has ended

0105 | MUSCLE MASS, FRAILTY AND CARDIOPULMONARY EXERCISE TESTING: CORRELATIONS AND IMPACT ON LIVER TRANSPLANT OUTCOMES ★

Shivangi Gupta[1] Ben Bull[1] May Kang[1] Luis Calzadilla Bertot[2] Angus Jeffrey[1] Christopher Welman[3] Bhajan Singh[4] Leon Adams[5] George Garas[6] Gerry MacQuillan[1] Michael Wallace[1] Briohny Smith[1] Luc Delriviere[1] Gary Jeffrey[1]

[1]Sir Charles Gairdner Hospital, WA, Aus, [2]University of Western Australia, Perth, [3]Fiona Stanley Hospital, Perth, Australia, [4]Sir Charles Gairdner Hospital, Perth, [5]Sir Charles Gairdner Hospital, Australia, [6]Western Australian Liver Transplant Serv

Background: In liver transplant (LT) candidates, sarcopenia is associated with increased waitlist and post-transplant mortality. This may limit access to LT in these patients. The relationship between sarcopenia (measured objectively by skeletal muscle index (SMI)) and functional status (measured by tests of muscle function (TMF) and cardiopulmonary exercise test (CPET)) is poorly characterized in this cohort of patients. We aimed to evaluate the association of SMI with TMF and CPET, and to assess LT outcomes in patients with sarcopenia and physical frailty. **Methods:** Retrospective data was collected from cirrhotic patients who underwent workup for LT in an Australian center from January 2019 to September 2023. Patients received individualized exercise and nutritional interventions up to the time of transplant or delisting. SMI at the time of workup was calculated from CT images at L3 vertebral level using automated software. Cutoffs for sarcopenia were SMI <50 cm^2/m^2 in men and <39 cm^2/m^2 in women. Data was collected from TMF: hand grip strength (HGS), 30-second Chair Stand Test (30sCST), six-minute walk distance (6MWD), Liver Frailty Index (LFI) score; and from CPET: Anaerobic threshold (AT), peak oxygen uptake (VO_2peak), peak work (Wpeak). Data analysis was performed using SPSS. **Results:** 120 patients were included: 68% males, mean age 53.9±11.4 years, mean MELD 15.8±7. Mean SMI was 47.1±7.3 cm^2/m^2 in males and 37.7±6.3 cm^2/m^2 in females. 60% of all patients were sarcopenic. Using Spearman's correlation analysis, SMI was significantly correlated with BMI (r_s=0.513), HGS (r_s=0.538), LFI score (rs=-0.319), Wpeak (r_s=0.460), all p=0.001; 30sCST (r_s=0.263,p=0.005), AT (r_s=0.278,p=0.021), VO_2peak (r_s=0.245, p=0.042). At the time of data collection, 85 (71%) patients were waitlisted, and 64 (53%) were transplanted. Waitlist mortality was not different between sarcopenic (12.5%) v non-sarcopenic patients (10.8%), p=1.0; or between frail (LFI>4.5, 31%) v non-frail patients (10%), p=0.35. Of the 64 transplanted patients, 57.8% were sarcopenic. Mean follow up post-transplant was 22 months (range 1-53). KM survival at 1 and 3 years was 91% and 87% for sarcopenic patients, compared to 92% and 85% in non-sarcopenic patients, p=0.612. There was no difference between the two groups in the length of post-operative ICU (p=0.274) or inpatient stays (p=0.478). Post-transplant survival for frail patients (LFI>4.5, n=9) was 100% at 1 and 3 years, compared to non-frail patients, which was 90% and 83%, p=0.182. **Conclusion:** SMI was correlated with TMF and CPET. Sarcopenia or frailty did not impact waitlist mortality and post LT survival. Sarcopenic patients can have successful LT outcomes with personalized physiotherapy and nutritional interventions. Further studies are required to validate these findings.

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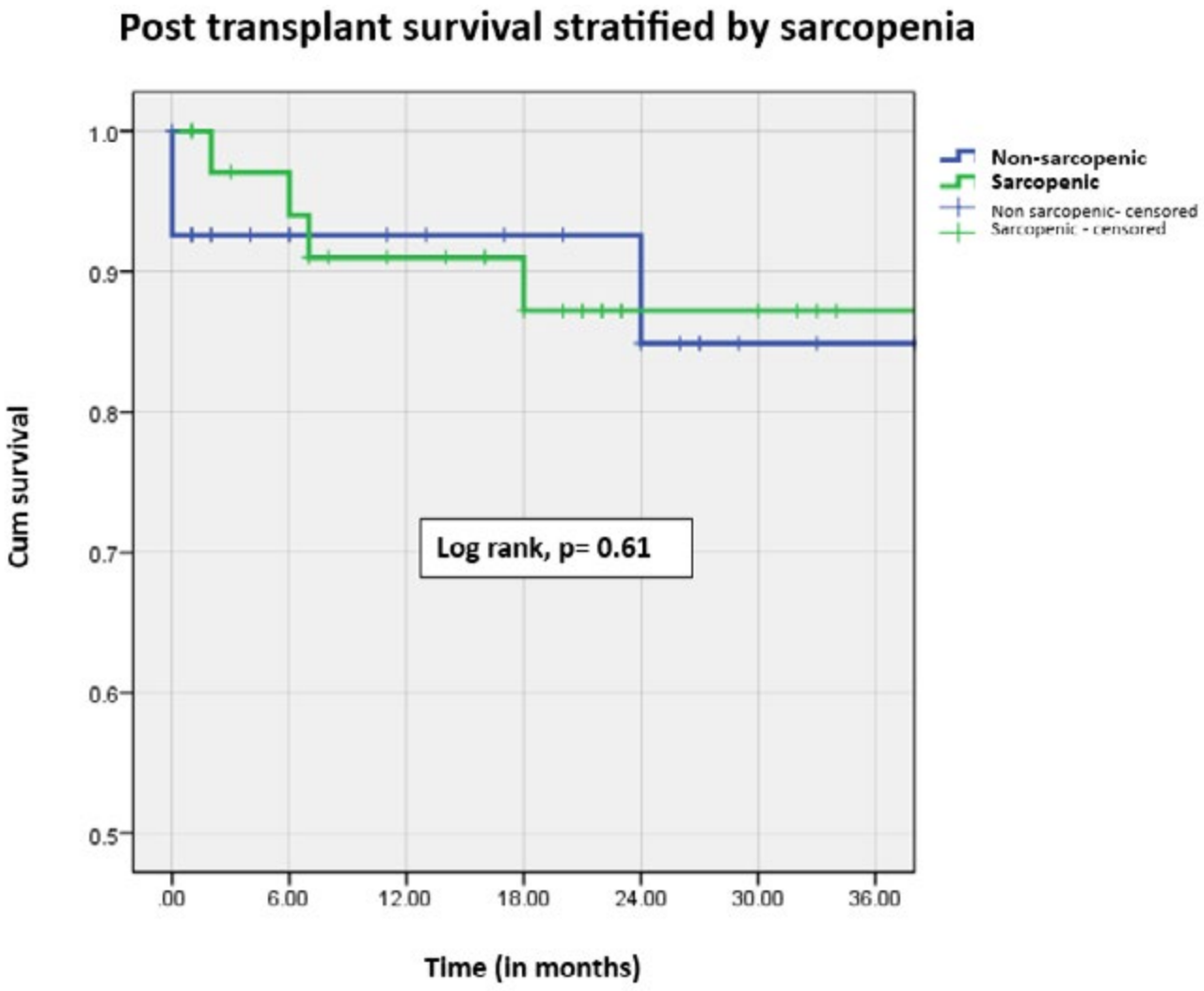

Figure 1: Kaplan-Meier curves depicting cumulative survival post-transplant for sarcopenic and non-sarcopenic patients

Disclosures: Shivangi Gupta: Nothing to Disclose, Ben Bull: Nothing to Disclose, May Kang: Nothing to Disclose, Luis Calzadilla Bertot: Nothing to Disclose, Angus Jeffrey: Nothing to Disclose, Christopher Welman: Nothing to Disclose, Bhajan Singh: Nothing to Disclose, Leon Adams: Novo Nordisk: Advisor, SCL Behring: Advisor, Pfizer: Advisor, George Garas: Nothing to Disclose, Gerry MacQuillan: Nothing to Disclose, Michael Wallace: Nothing to Disclose, Briohny Smith: Nothing to Disclose, Luc Delriviere: Nothing to Disclose, Gary Jeffrey: Nothing to Disclose

0106 | TYPE 2 DIABETES AND GLYCAEMIC CONTROL ARE ASSOCIATED WITH LIVER STIFFNESS PROGRESSION IN PEOPLE WITH MASLD: A MULTICENTER PROSPECTIVE STUDY

Daniel Huang[1] Laura Wilson[2] Cindy Behling[3] Maral Amangurbanova[1] David Kleiner[4] Kris Kowdley[5] Srinivasan Dasarathy[6] Norah Terrault[7] Anna Mae Diehl[8] Naga Chalasani[9] Brent Neuschwander-Tetri[10] Arun Sanyal[11] James Tonascia[2] Rohit Loomba[1]

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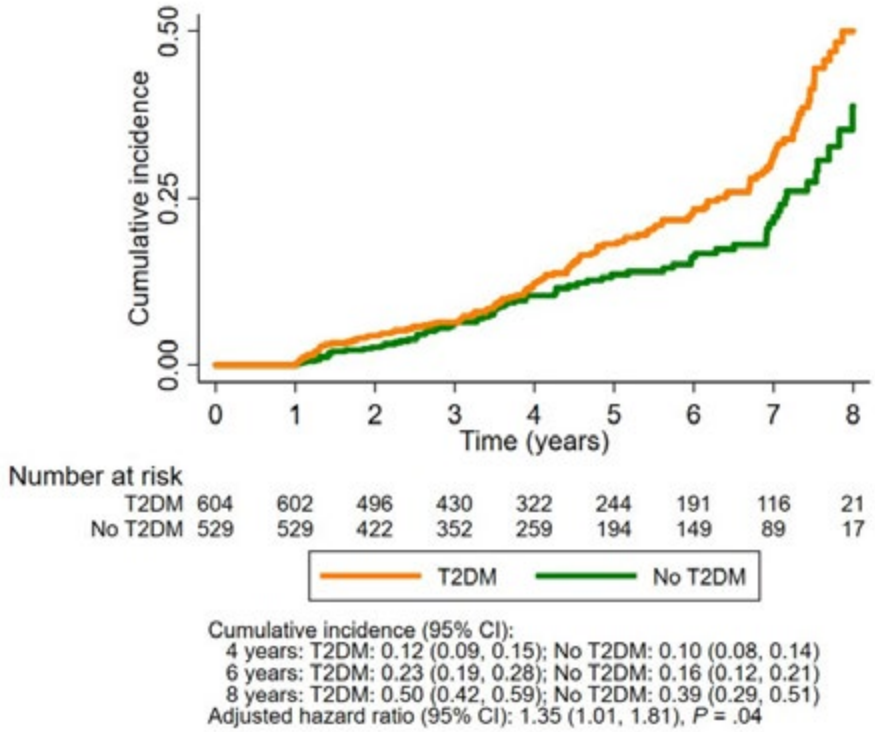
Background: There are limited data on the rate of progression of liver stiffness measurement (LSM) by vibration-controlled transient elastography (VCTE) in biopsy-proven metabolic dysfunction-associated steatotic liver disease (MASLD) patients without or with type 2 diabetes mellitus (T2DM). Therefore, we examined LSM progression in participants with T2DM versus those without T2DM among participants who had paired VCTEs in a large, multicenter, multiethnic cohort study. **Methods:** This prospective study included adult participants with biopsy-proven MASLD who had VCTEs at least one year apart, recruited at eight sites across the United States as part of the NIDDK-sponsored NASH CRN. The Cox proportional hazards model was used to evaluate the hazard ratio (HR) for LSM progression and regression, defined by a ≥20% change in LSM and an upward or downward shift in the Baveno VII LSM categories for compensated advanced chronic liver disease (<10 kPa, 10-14.9 kPa, 15.0-19.9 kPa, 20.0-24.9 kPa, ≥25.0 kPa), compared between T2DM versus non-T2DM at baseline. **Results:** This study included 1,231 adult participants with MASLD (62% female) with more than one VCTE. The mean (±SD) age and body mass index were 51.8 (±12.0) years and 34.0 (±6.5) kg/m^2, respectively. The median (IQR) time between VCTEs was 4.1(2.5-6.5) years. Participants with T2DM (n=680) had a significantly higher cumulative incidence of LSM progression at 4-years (12% versus 10%), 6-years (23% versus 16%), and 8-years (50% versus 39%) compared to participants without T2DM (n=551), *P*=0.04 (Figure 1). Using multivariable Cox proportional hazards model adjusted for age, sex, BMI, and Hispanic ethnicity, the presence of T2DM was associated with an increased incidence of LSM progression (adjusted HR 1.35, 95% CI 1.01 – 1.81, *P*=0.04), but not LSM regression (*P*=0.71). HbA1c was associated with both LSM progression (adjusted HR 1.18, 95% CI 1.06 – 1.32, *P*=0.003) and LSM regression (adjusted HR 0.84, 95% CI 0.72 – 0.97, *P*=0.02). **Conclusion:** Utilizing serial VCTE data from a multicenter study of participants with biopsy-proven MASLD and prospectively collected data, we demonstrate that participants with T2DM have a significantly faster time to LSM progression. These data may have important implications for clinical practice and clinical trial design.



Disclosures: Daniel Huang: Nothing to Disclose, Laura Wilson: Nothing to Disclose, Cindy Behling: Pacific Rim Pathology Lab: Employee, Novo Nordisk: Consultant, Pathology Institute: Consultant, boehringer ingleheim: Consultant, akero: Independent Contractor, Maral Amangurbanova: Nothing to Disclose, David Kleiner: Nothing to Disclose, Kris Kowdley: Boston Scientific: Grant/Research Support, Corcept: Grant/Research Support, CymaBay: Grant/Research Support, Genfit: Grant/Research Support, Gilead: Grant/Research Support, GSK: Grant/Research Support, Hanmi: Grant/Research Support, Intercept: Grant/Research Support, Ipsen: Grant/Research Support, Janssen: Grant/Research Support, Madrigal: Grant/Research Support, Mirum: Grant/Research Support, Novo Nordisk: Grant/Research Support, NGM: Grant/Research Support, Pfizer: Grant/Research Support, Pliant Therapeutics: Grant/Research Support, Terns: Grant/Research Support, Viking: Grant/Research Support,

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0107 | ROBUST AND SUSTAINABLE ELIMINATION OF HBSAG BY EPIGENOME MODULATION ENABLES SEROCONVERSION OF CHRONIC HBV INFECTION IN HBV MOUSE MODEL

Dai-tze Wu[1] Wenbo Peng[1] Junzheng Zhao[1] Leilei Wu[1] Shaoshuai Mao[1] Junjian Liu[1] Yifan Wang[1] Jing Sun[1] Di Sun[1] Ruimin Lv[1] Pinzheng Huang[1] Yingqi Li[1] Qi Zhu[1] Baohong Zhang[1] Yidi Sun[2] Changyang Zhou[3]

[1]Epigenic Therapeutics, Inc., [2]Chinese Academy of Sciences, [3]Chinese Academy of Science

Background: The persistence of HBV surface antigen (HBsAg) expression causes development of immune tolerance to chronic hepatitis B virus (HBV) infection. Reducing the expression of HBsAg can potentially restore the function of HBV-specific immune cells, thereby enhancing the immune response against the virus. We have developed EPIREG®, a CRISPR-derived epigenetic regulation technology comprising an inactivated Cas9 (dCas9) fused with DNA methyltransferase and histone modification effectors, which enables efficient, specific, and durable silencing of targeted HBV genes, especially the HBV surface antigen (HBsAg). Here we evaluated the anti-HBV activity and the potential of restoration of immune response against HBV of EPI-003, discovered by the EPIREG® technology, in eliminating HBV viral antigens by inhibiting the transcription of cccDNA and integrated DNA. **Methods:** EPI-003 was prepared by encaptulating a messenger RNA (mRNA) encoding for a nuclease-independent epigenetic modulation protein and a guide RNA targeting the HBV-specific gene in a lipid nanoparticle. Male transgenic mice that persistently replicate HBV (genotype A, C57B/6N-Tg(1.28HBV)/Vst) and expressed HBsAg at levels relevant to patients were used. The in vivo efficacy of EPI-003 was assessed following by single dose administration. Serum and liver samples were collected and analyzed for HBV-specific immune responses, liver damage, and viral parameters. Mice were immunized subcutaneous twice with 5 ug of HBsAg recombinant vaccine to evaluate the effect of breaking the immune tolerance to chronic HBV. **Results:** Single dose of EPI-003 resulted in reduction of serum HBsAg by up to 2.5 logs following 2 weeks of administration; this reduction was well maintained thereafter in all the animals by more than 40 weeks. Furthermore, among animals treated with safe and efficacious doses, 80% of animals showed further 1 to 2 logs reduction of HBsAg from week 8 to 40, even to the levels close or under the LLOQ (1.5IU/mL). Strikingly, HBsAb was induced in these 4 animals following sustained reduction of HBsAg by single dose administration of EPI-003 without additional immune stimulation. Mechanistically, methylation of HBV cccDNA was introduced and correlated well with the elimination of viral antigens and HBV DNA. Additionally, depletion of HBsAg expression levels by EPI-003 broke the immune tolerance to chronic HBV and enhanced the efficacy of HBV vaccination in transgenic mice. **Conclusion:** EPI-003 has demonstrated superior pharmacological efficacy in eliminating HBV viral antigen and inhibiting HBV DNA

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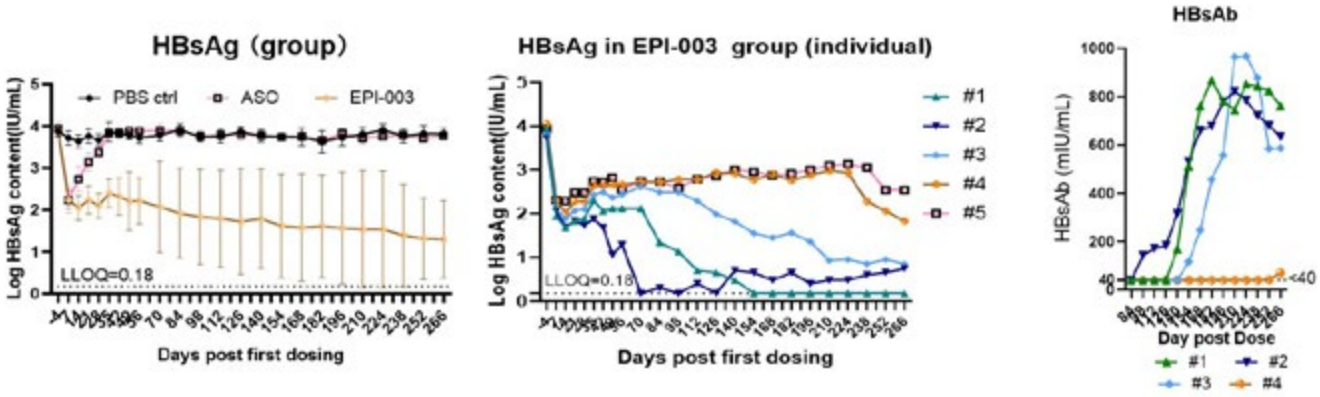
without rebound in preclinical studies compared to other anti-HBV therapies in preclinical development. Moreover, robust and sustainable HBsAg through direct blocking of HBV cccDNA transcription restored the host anti-HBV immnue response, offering therapeutic potential for functional or even complete cure for patients with chronic HBV infection.



Disclosures: Dai-tze Wu: Nothing to Disclose, Wenbo Peng: Nothing to Disclose, Junzheng Zhao: Nothing to Disclose, Leilei Wu: Nothing to Disclose, Shaoshuai Mao: Nothing to Disclose, Junjian Liu: Nothing to Disclose, Yifan Wang: Nothing to Disclose, Jing Sun: Nothing to Disclose, Di Sun: Nothing to Disclose, Ruimin Lv: Nothing to Disclose, Pinzheng Huang: Nothing to Disclose, Yingqi Li: Nothing to Disclose, Qi Zhu: Nothing to Disclose, Baohong Zhang: Nothing to Disclose, Yidi Sun: Nothing to Disclose, Changyang Zhou: Nothing to Disclose

0108 | ASSOCIATION BETWEEN RETREATMENT AND HEPATITIS B SURFACE ANTIGEN SEROCLEARANCE IN PATIENTS WITH CLINICAL RELAPSES FOLLOWING WITHDRAWAL OF NUCLEOS(T)IDE ANALOGUES

Yao-Chun Hsu[1] Chia-Ching Wu[2] Jia-Ling Wu[3] Ying-Nan Tsai[4] Cheng-Hao Tseng[4] Chih-Wen Lin[2] Chih-Lung Hung[5] Mindie Nguyen[6] Jaw-Town Lin[5]

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Background: Withdrawal of nucleos(t)ide analogue (NA) therapy has been proposed for patients with chronic hepatitis B (CHB) to induce seroclearance of hepatitis B surface antigen (HBsAg). However, this approach is frequently followed by clinical relapse (CR) that often indicates treatment resumption. The impact of retreatment on HBsAg seroclearance in patients experiencing CR is unclear. **Methods:** This retrospective, multi-center cohort study systematically reviewed all consecutive patients who received entecavir or tenofovir therapy for CHB and subsequently discontinued the NA in a healthcare group in Taiwan. Eligible patients were documented with negative HBeAg and undetectable HBV DNA before stopping treatment. Patients with a malignancy, organ transplant, or viral coinfection were excluded. CR was defined as an elevation of serum alanine aminotransferase (ALT) to more than twice the upper limit of normal after treatment cessation. The primary outcome was seroclearance of HBsAg following the occurrence of CR. Resumption of NA therapy was analyzed as a time-varying variable and adjusted for potential confounding factors to elucidate its association with HBsAg seroclearance. **Results:** Among the 841 patients who stopped NA treatment and met the eligibility criteria (median duration of treatment, 35.1 months), 320 patients encountered CR with a cumulative incidence of 60.6% (95% CI, 43.5-72.5) at 10 years. In these 320 patients with CR (79.4% male, median age of 51.6 years), 188 patients resumed NA therapy whereas 132 patients remained un-retreated through the posttreatment observation. Following CR, 15 patients cleared HBsAg with a 10-year cumulative incidence of 12.1 % (95% CI, 5.2-18.6). HBsAg seroclearance occurred in 5 patients after they resumed NA therapy and in 10 patients who remained un-retreated. In univariable analysis, retreatment was associated with a lower incidence of HBsAg loss (hazard ration [HR], 0.30; 95% CI, 0.10-0.93; p=0.03). However, after adjustment for covariates including time-varying levels of serum HBsAg, there was no significant association between retreatment and HBsAg seroclearance (adjusted HR, 0.41; 95% CI, 0.13-1.29; p=0.13). Regardless of retreatment or not, the incidence of HBsAg seroclearance was significantly higher with a most recent HBsAg level

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<100 IU/mL (adjusted HR, 7.99; 95% CI, 2.48-25.69; p=0.0005). **Conclusion:** No independent association was found between retreatment and HBsAg seroclearance in CHB patients encountering CR after NA withdrawal. Our findings suggest that CHB patients who stop NA therapy can resume antiviral treatment for CR without the concern of reducing the chance of HBsAg seroclearance.

Disclosures: Yao-Chun Hsu: Gilead Sciences: Grant/Research Support, Gilead Sciences: Advisor, Sysmex: Advisor, Abbvie: Speaking and Teaching, Bristol Myers Squibb: Speaking and Teaching, Gilead Sciences: Speaking and Teaching, Roch: Speaking and Teaching, Chia-Ching Wu: Nothing to Disclose, Jia-Ling Wu: Nothing to Disclose, Ying-Nan Tsai: Nothing to Disclose, Cheng-Hao Tseng: Nothing to Disclose, Chih-Wen Lin: Nothing to Disclose, Chih-Lung Hung: Nothing to Disclose, Mindie Nguyen: Nothing to Disclose, Jaw-Town Lin: Nothing to Disclose

0109 | ALKALINE PHOSPHATASE AND FIBROSIS MARKERS ARE PROGNOSTIC FOR OUTCOME IN RECURRENT PRIMARY SCLEROSING CHOLANGITIS AFTER LIVER TRANSPLANTATION

Lise Katrine Engesæter[1] Peder Rustøen Braadland[1] Andreas Abildgaard[2] Ida Björk[2] Krzysztof Grzyb[3] Henrik Reims[3] Tom Karlsen[1] Kristian Bjøro[1] Kirsten Boberg[1] Morten Karsdal[4] Espen Melum[1] Diana Julie Leeming[4] Johannes Hov[1]

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Background: Recurrent primary sclerosing cholangitis (rPSC) following liver transplantation for PSC is a significant clinical problem associated with graft loss and mortality. There is no therapy that prevent or reduce rPSC and few relevant **Methods:** for measuring disease activity or prognosis. Here we aimed to assess the impact of liver biochemistry and markers of fibrosis in a well-characterized population of rPSC. **Methods:** All people liver transplanted for PSC in a single center in Oslo, Norway, with at least one serum sample after transplant available in our biobank were included (n=161, 77% male, 82% with concomitant inflammatory bowel disease). A total of 575 serum samples were available from up to 6 time points (median 4). Data on recurrence and clinical course was available from an ongoing study, where liver biopsies and MRIs post-transplant from the participants were re-evaluated to establish presence of recurrent PSC. Serum fibrosis biomarker measurements were performed at Nordic Bioscience. Bilirubin, alkaline phosphatase (ALP), the APRI and FIB-4 scores and PRO-C3, PRO-C4, PRO-C5, C3M, C4M were included in the analyses. **Results:** Median age at listing for liver transplantation was 42 years (IQR 36-63). During follow-up, n=104 (65 %) were diagnosed with rPSC after median 3.22 (range 0.24-17.9) years. None of the analyzed markers were prognostic for later development of rPSC, when evaluated at a single time point one year after transplantation. A paired analysis was performed between the last sample (>6 months) before and the first sample after rPSC diagnosis. Only APRI (p=0.01) and FIB-4 (p=0.003) showed a significant increase, suggesting a diagnostic value. Finally, we evaluated whether markers measured at the time of or after an rPSC diagnosis were associated with liver retransplantation-free survival using time-dependent Cox regression (multiple time points per individual possible). In univariable models, six out of nine parameters were associated with retransplantation-free survival (Figure), including ALP_{log2} (HR 2.1, 95% CI 1.4-3.1, p<0.001) and $PRO\text{-}C3_{log2}$ (HR 2.7, 95% CI 1.5-4.7, p<0.001). When adjusting for ALP, only PRO-C3 was independently associated with increased risk of retransplantation or death (HR 2.1, 95% CI 1.2-3.7, p=0.01) (Figure). **Conclusion:** ALP and PRO-C3 were prognostic for outcome in rPSC and represent new clinically relevant biomarkers.

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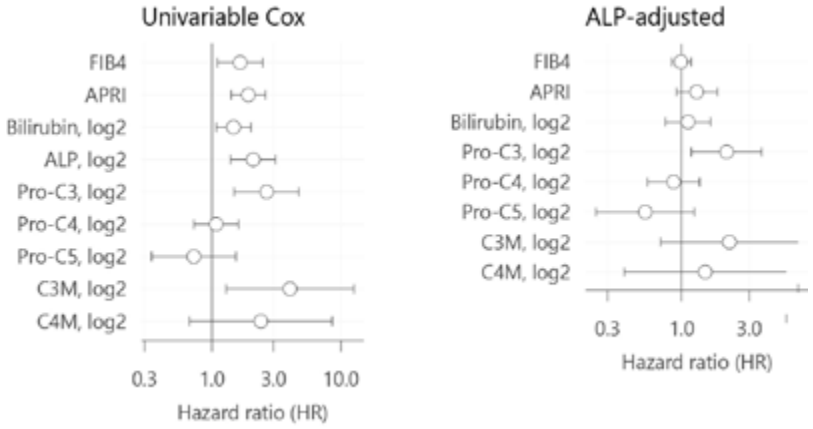

Disclosures: Lise Katrine Engesæter: Nothing to Disclose, Peder Rustøen Braadland: Nothing to Disclose, Andreas Abildgaard: Nothing to Disclose, Ida Björk: GE Healthcare: Speaking and Teaching, Krzysztof Grzyb: Nothing to Disclose, Henrik Reims: Nothing to Disclose, Tom Karlsen: Nothing to Disclose, Kristian Bjøro: Nothing to Disclose, Kirsten Boberg: Nothing to Disclose, Morten Karsdal: Nothing to Disclose, Espen Melum: Nothing to Disclose, Diana Julie Leeming: Nordic Bioscience: Employee, Johannes Hov: Nothing to Disclose

0110 | ACYLCARNITINES ARE PROMISING INDICATORS OF INFECTION AND MORTALITY ASSOCIATED IN IN PATIENTS WITH ACUTE LIVER FAILURE

Anna Cavazza[1] Evangelos Triantafyllou[2] Salma Mujib[3] Phillip Morgan[3] Yun Ma[3] Tasneem Pirani[3] William Lee[4] Constantine Karvellas[5] Mark McPhail[3]

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Background: Acute liver failure (ALF) is a life-threatening syndrome associated with multiorgan failure, immune dysfunction and infection. Acylcarnitine esters (ACN; esters of l-carnitine and fatty acids) activate pro-inflammatory signalling pathways in monocytes and altered serum ACN profiles are associated with progression of metabolic dysfunction associated liver disease and hepatocellular carcinoma. Given the pivotal role of monocytes in ALF, we explored the role of ACNs in ALF. **Methods:** Patients were recruited from the United States ALF Study group, and serum samples transferred to King's College London for metabolic profiling using the p180 Biocrates platform using liquid chromatography-tandem mass spectrometry and flow injection analysis used for absolute quantification of ACNs, phospholipids, sphingomyelins, biogenic amines and hexoses. Principal components analysis (PCA) and orthogonal projection least squares discriminant analysis (PCA; OPLSDA) was used to find metabolic differences associated with mortality and infection in ALF. **Results:** Six healthy controls and 120 ALF patients were analysed. Patient median age was 42 (range 17-80) years and 62.5% (75/120) were female. The cause of ALF was drug induced liver injury (DILI) in 36% (43/120), paracetamol overdose (POD) in 22% (26/120), indeterminate in 21% (25/120), autoimmune hepatitis (AIH) in 8% (10/120). 42% (51/120) died (D), 26% survived with medical treatment (31/120) and 32% were transplanted (38/120). 14% (17/118) had positive bacteraemia. OPLS-DA modelling accurately discriminated between patients who died and survived, with significantly higher ACN concentration in those who died in the following ACNs: C2 (6.67 uM (IQR 3.37-10.85) vs 13 uM (8.45-19.2), p<0.001), C3 (0.29 uM (0.14-0.41) vs 0.53 uM (0.28-0.86), p<0.001), C6 (C4:1-DC) (0.07 uM (0.04-0.11) vs 0.15 uM (0.09-0.24), p<0.001). The AUROC for C6 (C4:1-DC) to predict mortality was 0.75 (p< 0.001). ACNs concentration was higher in those with infection (C2, infection 16uM (10.4-21.0) vs non infection 7.57 uM (3.91-12.8), p 0.004) and bacteraemia (C3, bacteraemia 0.48 uM (0.30-1.11) vs non bacteraemia 0.32 uM (0.17-0.60), p 0.012). C2 correlated with MELD score (r=0.36, p=0.001). **Conclusion:** Serum acylcarnitine concentrations are higher in ALF patients who died with strong correlation demonstrated between ACNs and infection, bacteraemia and MELD score. Exploration of the mechanistic significance of these findings is urgently required.

Disclosures: Anna Cavazza: Nothing to Disclose, Evangelos Triantafyllou: Nothing to Disclose, Salma Mujib: Nothing to Disclose, Phillip Morgan: Nothing to Disclose, Yun Ma: Nothing to Disclose, Tasneem Pirani: Nothing to Disclose, William Lee: Nothing to Disclose, Constantine Karvellas: Consultant relationship with Mallinckrodt;

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Has not ended; Advisor relationship with Baxter; Has not ended; Advisor relationship with Grifols; Has not ended; Data safety monitoring board for clinical trial relationship with Miromatrix; Has not ended, Mark McPhail: Nothing to Disclose

0111 | METABONOMICS AND METAGENOMICS FOR DIAGNOSIS OF CLINICALLY SIGNIFICANT PORTAL HYPERTENSION IN PATIENTS WITH COMPENSATED ADVANCED CHRONIC LIVER DISEASE

Zhou Tiantian[1] Hu han[1] Lai Wei[1] He Jinjing[1] Yu Sicheng[1] Gao Xiang[1] Zhu Jie[1] Yan Huadong[1]

[1]Shulan (Hangzhou) Hospital

Background: According to the Baveno VII consensus, clinically significant portal hypertension (CSPH) is an important stage in the occurrence and development of liver cirrhosis,but precision monitoring of CSPH is still a problem. Our aim is to explore the feasibility of multi-omics technologies to diagnose CSPH. **Methods:** In this study, 135 patients with cACLD were prospectively recruited, 30 healthy controls, and 41 independent validation cohorts. By determining serum metabolomics and metagenomics characteristics, a combined model for predicting CSPH was built. **Results:** In the study population, there were 61(45.2%) patients with CSPH. We performed the basic and combined analysis of metagenomics and metabolomics. 24 bacteria were eventually selected to build a model, with an AUC of 0.84 on the test group. Non-targeted metabolomics screened 60 significantly different metabolites, which was enriched of KEGG pathway analysis were mainly in cholesterol metabolism, bile secretion and primary bile acid biosynthesis. 14 metabolites were used to build a model, with an AUC of 0.88 on the test group. We analyzed the correlation between the selected differential bacteria and differential metabolites and their enriched metabolic pathways. The results showed that the relevant flora surrounding sulfur metabolism, the metabolites of bile acids, and the biosynthetic pathways upstream and downstream of sulfur metabolism are all related to the development of portal hypertension. It was particularly worth noting that Desulfovibrionaceae is significantly related to bile acid metabolism, and its further mechanism still needs to be discussed. Furthermore, a combined model was built and showed great diagnostic performance, with an AUC of 0.97 on the test set and 0.88 in the validation cohort. Compared with the Baveno VII criteria, it demonstrated excellent diagnostic performance and can reduce gray areas. Finally, after 26.3 months of follow-up, the model demonstrated its value in predicting the prognosis of the disease **Conclusion:** The features based on serum metabolites and stool metagenomic analysis have great diagnostic value for predicting CSPH

Disclosures: Zhou Tiantian: Nothing to Disclose, Hu han: Nothing to Disclose, Lai Wei: Nothing to Disclose, He Jinjing: Nothing to Disclose, Yu Sicheng: Nothing to Disclose, Gao Xiang: Nothing to Disclose, Zhu Jie: Nothing to Disclose, Yan Huadong: Nothing to Disclose

0112 | EFFECT OF RESMETIROM OR PLACEBO IN NASH FIBROSIS PATIENTS WITH =5% WEIGHT LOSS AND/OR ON BASELINE GLP-1 THERAPY IN THE MAESTRO-NASH 52 WEEK SERIAL LIVER BIOPSY STUDY

Mazen Noureddin[1] Mary Rinella[2] Rebecca Taub[3] Dominic Labriola[3] Naim Alkhouri[4] Meena Bansal[5]

[1]Houston Methodist Hospital, [2]The University of Chicago, [3]Madrigal Pharmaceuticals, [4]Arizona Liver Health, [5]Icahn School of Medicine at Mount Sinai (ISMMS)

Background: MAESTRO-NASH (NCT03900429) is an ongoing 54-month, randomized, double-blind, placebo controlled Phase 3 trial evaluating the efficacy of resmetirom in patients with biopsy-confirmed nonalcoholic steatohepatitis (NASH) and fibrosis. 966 patients with biopsy-confirmed NASH were randomized 1:1:1 to resmetirom 80 mg, resmetirom 100 mg, or placebo administered once daily. Histologic endpoints were assessed after 52 weeks. Dual primary endpoints at Week 52 were achieved with both resmetirom 80 mg and 100 mg: NASH resolution with no worsening of fibrosis (NR) or ≥1-stage improvement in fibrosis with no worsening of NAS (FI). At baseline 12-16% of patients in the treatment groups were on stable GLP-1 therapy. The effects of resmetirom or placebo with or without weight loss on liver biopsy endpoints and/or GLP-1 baseline therapy were evaluated. **Methods:** Patients in this serial liver biopsy trial were counseled on moderate diet and excersize at each study visit. Patients on baseline GLP-1 therapy and/or

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with < or >=5% weight loss at 52 weeks were evaluated for achievement of NASH resolution (NR) and Fibrosis improvement (FI) liver biopsy endpoints or % change from baseline in MRI-PDFF at Week 52. **Results:** Baseline GLP-1 therapy had been in place for >6 months, 96% in diabetics, the most common dose was 1 mg semaglutide. Patients on GLPs compared to not on GLPs had MRI-PDFF 16% vs 18%; higher % diabetic, higher glucose an HbA1C; more common statin use; lower lipids, liver enzymes, ELF and FIB-4. Seventeen % of randomized patients achieved >=5% weight loss at Week 52, 17-22% in the resmetirom arms and 12% on placebo. GLP-1 treatment was not associated with weight loss: 14% of patients with >=5% weight loss were on GLPs; 15% of patients with <5% weight loss were on GLPs. >=5% weight loss enhanced NR by >20% in resmetirom and placebo groups; the difference between resmetirom and placebo was 25% higher NR in resmetirom at 100 mg (not impacted). FI was increased by ~10% in all treatment arms. GLP-1 treatment had no effect on either NR or FI in resmetirom arms. In the placebo arm, GLP treatment resulted in lower NR and FI responses; both FI and NR were <3% in placebo patients on GLPs who had <5% weight loss, lower than placebo patients not on GLPs with <5% weight loss. MRI-PDFF response was greater in patients with >=5% weight loss in both resmetirom and placebo arms and not changed by GLP treatment. **Conclusion:** A small amount of weight loss (>=5%) enhances the effect of resmetirom on NASH resolution(>50%) and fibrosis improvement ~40% on serial liver biopsy. Stable GLP-1 therapy did not impact liver biopsy endpoints or cause weight loss. In the placebo group, stable GLP-1 therapy did not result in weight loss, and biopsy response rates in GLP-treated placebo patients were similar or slightly lower than placebo patients not on GLP therapy.

	N (%)	NASH Resolution (% response)	Fibrosis Improvement (% response)	MRI-PDFF Median % change from baseline
80 mg				
>=5% weight loss[1]	47	47%	36%	-64.4
<5% weight loss[1]	229	26%	26%	-37.4
On GLP[2]	53	25%	26%	-35.7
Not on GLP[2]	263	26%	24%	-42.8
100 mg				
>=5% weight loss[1]	57	53%	38%	-66.7
<5% weight loss[1]	210	31%	29%	-45.6
On GLP[2]	41	31%	16%	-51.7
Not on GLP[2]	280	30%	27%	-51.2
Placebo				
>=5% weight loss[1]	36	31%	26%	-41.9
<5% weight loss[1]	248	8%	14%	-7.6
On GLP[2]	41	7%	9%	-9.8
Not on GLP[2]	277	10%	15%	-10.4

[1]Week 52 completers; [2]ITT

Disclosures: Mazen Noureddin: Principal Investigator for a Drug Study relationship with Viking; Has not ended; Consultant relationship with Eli Lilly; Has not ended; Consultant relationship with AstraZeneca; Has not ended; Consultant relationship with Boston Pharmaceuticals; Has not ended; Principal Investigator for a Drug Study relationship with Genfit; Has not ended; Principal Investigator for a Drug Study relationship with Galectin; Has not ended; Principal Investigator for a Drug Study relationship with Gilead; Has not ended; Principal Investigator for a Drug Study relationship with BMS; Has not ended; Principal Investigator for a Drug Study relationship with BI; Has not ended; Principal Investigator for a Drug Study relationship with Akero; Has not ended; Consultant relationship with Cytodyn; Has not ended; Consultant relationship with GSK; Has not ended; Consultant relationship with BI; Has not ended; Consultant relationship with Madrigal; Has not ended; Terns,Takeda, Zydus. relationship with Itimmune, BI, Cytodyn, 89BIO, GSK, Madrigal, Merck, Novo Nor; Has not ended; Principal Investigator for a Drug Study relationship with Allergan; Has not ended; Consultant relationship with Takeda; Has not ended; Consultant relationship with Terns; Has not ended; Terns, Corcept, Takeda, Madrigal, Novartis, Novo Nordisk,

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0113 | DIMINISHED ENTERIC HIGH-DENSITY LIPOPROTEIN 3 AND LOW LPS AND SPINGOSINE-1-PHOSPHATE BINDING IN PORTAL BLOOD ASSOCIATED WITH HIGH MORTALITY IN ALCOHOLIC CIRRHOSIS

Sukriti Baweja[1] Shivani Gautam[1] Harshwardhan Tivethia[1] Ashmit Mittal[1] Anjali Singh[1] GURESH KUMAR[1] Amar Mukund[1]

[1]Institute of Liver and Biliary Sciences

Background: High-density lipoprotein (HDL), plays pivotal role in cholesterol homeostasis with anti-inflammatory properties. 75% HDL is synthesized in liver, 25% by intestine. Recently, the physiological functions of enterically derived HDL subtype 3 (HDL_3) have been demonstrated in binding intestinal-leaked lipopolysaccharide (LPS). Also, amount of plasma sphingosine-1-phosphate(S1P) associated HDL, influences the quality and quantity of HDL-dependent functions. We hypothesized that inadequate enteric HDL_3 could be an intrinsic mechanism for gut-liver dysfunction. Investigated enteric HDL distribution and its pathological role in alcohol associated liver cirrhosis (AALC) patients.
Methods: Eighty-nine cirrhosis patients {MELD:16±8} who underwent trans jugular intrahepatic portosystemic shunt (TIPS) [AALC n=67 {age45±10 yr., all ♂}; NASH n=15 {52±9 yr., ♀ 6}, HBV/HCV n=6 {47±7 yr., ♀ 1}] were included and

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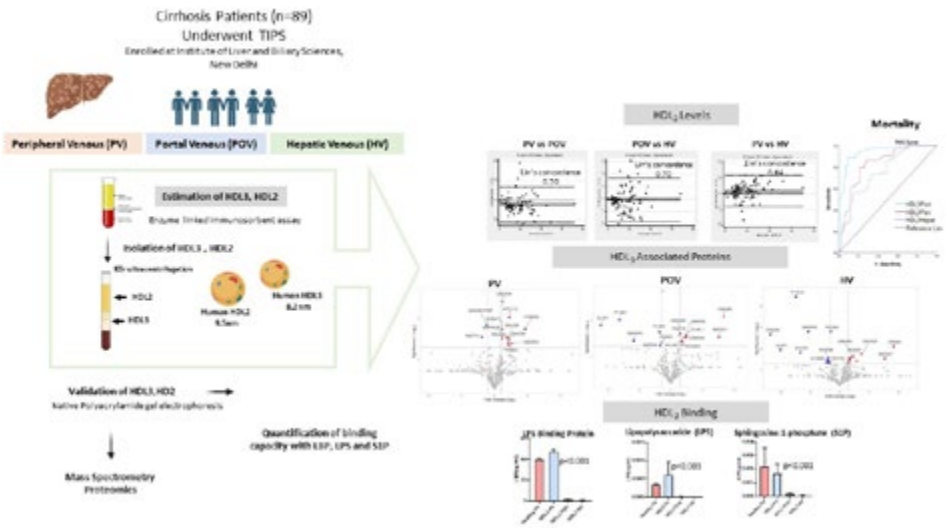
followed up for 3 months post-TIPS. The HDL_3 and HDL_2 (mg/dl) measured in peripheral (PV), portal (POV) and hepatic (HV) venous blood and compared with PV blood of healthy controls. HDL_3 was purified to study the associated proteins, using KBr ultracentrifugation followed by MS-based proteomics. The strength of binding HDL_3 with LPS binding protein (LBP), LPS and S1P was quantified. **Results:** The HDL_3 levels were significantly low in PV blood of AALC than healthy {10.3±4 vs 23.2±8; p=0.001}, but comparable to NASH and viral cirrhosis. No changes were found in HDL_2. The NASH patients had significantly higher HDL_3 and HDL_2 than AALC (p=0.001). No differences found between male and female, in patients with ascites and variceal bleed. Also, the per unit decrease at baseline in POV HDL_3, 85% patients develop hepatic encephalopathy (HE) post TIPS [95% CI {0.42-0.68}; p<0.01]. The overall 3-month mortality post-TIPS was 28%, however, low HDL_3 in POV <6.6 mg/dl showed AUC of 0.94, in PV <8.9 mg/dl; AUC of 0.82, in HV <7.5 mg/dl;AUC of 0.76. The HDL_3 levels among PV {11.3±5}, POV {7.6±3} and HV {8.0±3.8} showed intraclass correlation with agreement of 86% and Lin's concordance of 70%. Upon purification of HDL_3 yielded 345 associated proteins, significantly enriched with immunoglobins, apolipoproteins, caspases irrespective of venous location. The POV HDL_3 showed significantly upregulated [>10 fold {p=0.001}] SerpinA3, ApoB, collagen alpha, tight junctions than HC reflecting intestinal damage. PV HDL_3 with vitamin D binding, Apoc-I, RIP. HV HDL3 with complement C3, IgKappa, E3 ubiquitin, caspases, ApoA1. Unlike, healthy, no association with LBP was found in AALC HDL_3. Low POV and HV HDL_3 binding with LBP, LPS and S1P {p<0.001} was found than PV HDL_3. **Conclusion:** Low enteric HDL_3 in AALC and binding with LPS and S1P depicts HDL_3 fails to clear the intestinal-leaked LPS in portal vein may aid in development of HE and high mortality. The HDL_3 is novel gut derived lipoprotein responsible for modulating hepatic injury.



Disclosures: Sukriti Baweja: Nothing to Disclose, Shivani Gautam: Nothing to Disclose, Harshwardhan Tivethia: Nothing to Disclose, Ashmit Mittal: Nothing to Disclose, Anjali Singh: Nothing to Disclose, GURESH KUMAR: Nothing to Disclose, Amar Mukund: Nothing to Disclose

0114 | THE PROTEOME DIFFERENTIATES METALD FROM MASLD AND IDENTIFIES PATIENTS AT RISK ★

Niharika Jakhar[1] Tobias Seibel[1] Paul-Henry Koop[1] Benjamin Laevens[1] Yazhou Chen[1] Kai Markus Schneider[2] Carolin Victoria Schneider[1]

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Background: Proteins are essential in biological processes and their levels in plasma can be a good indicator of underlying health conditions. Metabolic dysfunction-associated steatotic liver disease (MASLD) and Metabolic and alcohol-associated liver disease (MetALD) are significant liver conditions linked to metabolic dysfunction, with varying risks of mortality. This study uses the proteomics data available in the UK Biobank to investigate the relationships between plasma protein levels. **Methods:** We linked the proteomics data with electronic health records to track disease incidence and mortality focusing on MASLD and MetALD, which were defined using liver MRI and using the criteria of the new nomenclature. To examine the link between protein levels among these liver diseases, we performed differential expression analysis for each protein to identify the significant differences

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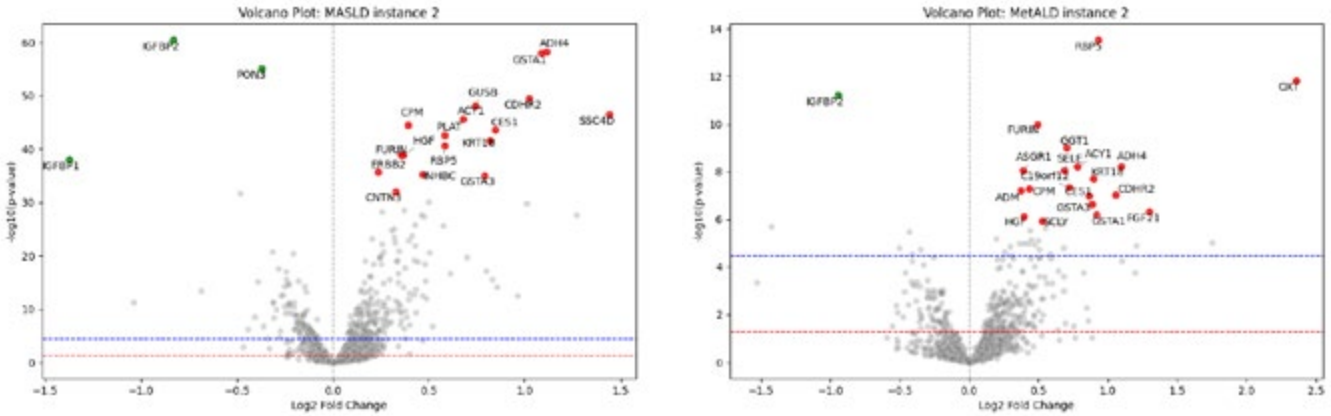
in expression levels between the control and diseased groups. **Results:** Among a total of 40189 patients, the number of patients identified with MASLD was 9692, 861 for MetALD and 29303 for control. Out of these, 205 (2.1%) MASLD patients and 25 (2.9%) MetALD patients died during follow-up of 12 years. Our analysis indicated that Retinol-binding protein 5 and Oxytocin-neurophysin 1 were amongst the most significant for MetALD whereas All-trans-retinol dehydrogenase [NAD(+)] ADH4 and Glutathione S-transferase A1 for MASLD. Notably, IGFBP-1 (Insulin-like growth factor-binding protein 1) was downregulated across both, MASLD and MetALD. Among the MASLD patients, Folate receptor gamma was associated with risk of death among MASLD patients.
Figure 1: displays the distribution of upregulated and downregulated proteins in MASLD and MetALD compared to controls. **Conclusion:** This study highlights the potential of using plasma proteins as therapeutic targets for predicting the risk of MASLD and MetALD, as well as their impact on mortality. The findings suggest that integrating proteomic data with traditional liver function tests could enhance disease prediction, prevention strategies, and mortality risk assessment. Further research is needed to validate these biomarkers in different populations and clinical settings.



Disclosures: Niharika Jakhar: Nothing to Disclose, Tobias Seibel: Nothing to Disclose, Paul-Henry Koop: Nothing to Disclose, Benjamin Laevens: Nothing to Disclose, Yazhou Chen: Nothing to Disclose, Kai Markus Schneider: Nothing to Disclose, Carolin Victoria Schneider: Nothing to Disclose

0115 | INTRAHEPATIC SIGNALING BY NETRIN-1 EXACERBATES ADVANCED FIBROSIS IN NONALCOHOLIC STEATOHEPATITIS ◆

ya jie peng[1] jiahui zhao[2] hongyan lei[2] Tianyi Wang[2] huajuan wang[2] xuelian xiong[2]

[1]Department of Endocrinology, Zhongshan Hospital, [2]Zhongshan Hospital, Fudan University

Background: Advanced hepatic fibrosis, driven by the activation of hepatic stellate cells (HSCs), is the strongest predictor of mortality in nonalcoholic steatohepatitis (NASH). However, intrahepatic signaling mechanism contributing to NASH-associated liver fibrosis remains poorly understood. **Methods:** We examined the expression of Netrin-1 in NASH liver through single-cell RNA sequencing and NASH model. Through gain- and loss- of function studies, Netrin-1 as a key factor of regulating liver fibrosis progression was determined. Immortalized mouse primary HSCs were used to explore the mechanism that Netrin-1 regulated HSCs activation. **Results:** Using single-cell RNA sequencing, we identified that Netrin-1, a HSC-derived cytokine, was elevated in NASH liver. Adenovirus-associated virus-mediated hepatic overexpression of Netrin-1 exacerbated NASH-associated liver fibrosis in mice. Conversely, HSCs-specific deletion of Netrin-1 protected mice from liver fibrosis, indicating that Netrin-1 plays an aggravative and stimulative role in NASH. In vitro experiments with mouse HSCs revealed that UNC5B, the most abundantly expressed receptor of Netrin-1, was specifically expressed in HSCs. Netrin-1 promoted HSC activation in an autocrine manner. In addition, we demonstrated that the binding of Netrin-1 to UNC5B increased the intracellular calcium levels, resulting in the activation of Calcium/calmodulin-dependent protein kinase II (CaMKII) phosphatase. This, in return, promoted Smad2 phosphatase signaling-mediated HSCs activation and extracellular matrix (ECM) deposition. **Conclusion:** Together, Our findings suggest that Netrin-1 is a master regulator of HSCs activation through an autocrine mechanism and contributes to fibrotic progression in NASH. Disrupting this intrahepatic signaling pathway may serve as a potential therapeutic target for NASH-associated fibrosis.

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Disclosures: ya jie peng: Nothing to Disclose, jiahui zhao: Nothing to Disclose, hongyan lei: Nothing to Disclose, Tianyi Wang: Nothing to Disclose, huajuan wang: Nothing to Disclose, xuelian xiong: Nothing to Disclose

0116 | BILIARY SENESCENCE DRIVES HEPATOCYTE VCAM-1 EXPRESSION AND LIVER NEUTROPHIL INFILTRATION ★

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Background: Biliary epithelial cell (BEC) senescence and associated secretory phenotype (SASP) are present in biliary diseases, but their effects on hepatocyte biology and associated liver inflammation are underexplored. This is relevant as cellular senescence and associated inflammation contribute to the pathology of biliary disease. **Methods:** Liver tissue from patients with biliary diseases (primary biliary / sclerosing cholangitis, biliary atresia), and from a murine model of BEC senescence and cholestasis (*CK19*^{CreERT}*Mdm2*$^{flox/flox}$*R26RtdTomato*^{LSL}, DDC diet), was analysed with fluorescence microscopy. Murine BECs were treated with etoposide to induce senescence and co-cultured with naïve primary hepatocytes. The resultant conditioned medium was incubated with bone marrow-derived neutrophils in a migration assay. **Results:** Biliary disease patients showed: 1) increased VCAM-1+ hepatocytes (median %: 5.67 vs 0.59; *P*=0.014); 2) increased p21+ BECs (median %: 17.02 vs 2.52; *P*<0.001), correlating with %CD66b+ neutrophils (*rs*=0.494; *P*=0.014); 3) closer BECs to CD66b+ neutrophils (median nearest distance: 21.4 vs 89.3 µm; *P*<0.001); and 4) %VCAM-1+ section correlation with %MPO+ neutrophils (*rs*=0.438; *P*=0.029). Neutrophils were closer to p21+ BECs than p21- BECs in human livers (median nearest distance: 20.0 vs 29.9 µm; *P*<0.001); and to VCAM-1+ hepatocytes than VCAM-1- hepatocytes in human (mean nearest distance: 18.0 vs 25.2 µm; *P*<0.001) and murine (median nearest distance: 33.8 vs 48.2 µm; *P*<0.001) livers. VCAM-1+ hepatocytes were increased in cholestatic biliary senescent mice vs non-senescent mice (median %: 8.12 vs 5.86; *P*<0.001); and %VCAM-1+ hepatocytes correlated with %Ly-6G+ neutrophils (*rs*=0.762; *P*<0.001). Senescent murine BECs had SASP features of human biliary diseases. Hepatocytes exposed to senescent BECs displayed transcriptional overexpression of *Vcam1* and increased neutrophil activity on functional enrichment analysis. Neutrophil migration was increased following treatment with conditioned medium from murine hepatocytes co-cultured for 72 hours with senescent BECs vs non-senescent BECs (*P*<0.001); there was no difference in monocultures of senescent BECs vs non-senescent BECs (*P*=0.999). **Conclusion:** Neutrophils preferentially migrate towards senescent BECs in biliary diseases. Hepatocytes promote neutrophil migration in biliary senescence, potentially mediated by VCAM-1 expression. Targeting neutrophil recruitment directly, or via VCAM-1, may alter the course of biliary disease progression.

Disclosures: Marisa Ferreira: Nothing to Disclose, Alastair Kilpatrick: Nothing to Disclose, Daniel Rodrigo-Torres: Nothing to Disclose, Sofia Ferreira-Gonzalez: Nothing to Disclose, Victoria Gadd: Nothing to Disclose, Tak Yung Man: Nothing to Disclose, Rhona Aird: Nothing to Disclose, Candice Ashmore-Harris: Nothing to Disclose, Gareth Hardisty: Nothing to Disclose, Wei-Yu Lu: Nothing to Disclose, Juan-Carlos Acosta: Nothing to Disclose, Luke Boulter: Nothing to Disclose, Stuart Forbes: Resolution Therapeutics: Founder

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0117 | PHENOTYPES, NATURAL COURSE, AND OUTCOMES OF ACUTE KIDNEY INJURY (AKI) IN PATIENTS WITH ACUTE-ON-CHRONIC LIVER FAILURE (ACLF): RESULTS FROM THE ICA-GLOBAL AKI STUDY

Elsa Solà[1] Kavish Patidar[2] Adrià Juanola[3] Ann Ma[4] Anna Barone[5] Simone Incicco[5] Anand Kulkarni[6] Jose Luis Perez Hernandez[7] Brian Wentworth[8] Sumeet Asrani[9] Carlo Alessandria[10] Nadia Abdelaaty Abdelkader[11] YU JUN WONG[12] Qing Xie[13] Nikolaos Pyrsopoulos[14] Sung-Eun Kim[15] Yasser Fouad[0] Aldo Torre[17] Eira Cerda Reyes[18] JAVIER DIAZ FERRER[19] Rakhi Maiwall[20] Douglas Simonetto[21] Maria Papp[22] Eric Orman[23] Gioavanni Perricone[24] Cristina Sole[25] Christian Lange[26] Alberto Queiroz Farias[0] Gustavo Pereira[28] Adrian Gadano[29] Paolo Caraceni[30] Delphine Weil Verhoeven[31] Nipun Verma[32] Jeong Han Kim[33] Julio Vorobioff[34] Jacqueline Cordova Gallardo[35] Vasilisa Grechishnikova[36] Juan Pablo Roblero[37] Raoel Maan[38] Claudio Toledo[39] Oliviero Riggio[40] Eduardo Fassio[41] Monica Marino[42] Puria Nabilou[43] Victor Vargas[44] Manuela Merli[45] Luciana Lofego Goncalves[46] Liane Rabinowich[47] Aleksander Krag[48] Lorenz Balcar[49] Pedro Montes[50] Angelo Zambam de Mattos[51] Tony Bruns[52] Abdulsemed Nur[53] Wim Laleman[54] ENRIQUE CARRERA ESTUPIÑAN[55] Maria Cecilia Cabrera[56] Marcos Girala[57] Hrishikesh Samant[58] Sarah Raevens[59] Joao Madaleno[60] W. Ray Kim[1] Juan Pablo Arab[61] Jose Presa[0] Carlos Noronha Ferreira[63] Antonio Galante[64] Claire Francoz[65] Andrew Allegretti[66] Bart Takkenberg[67] Murat Harputluoglu[0] Sebastián Marciano[69] Shiv Kumar Sarin[70] Pere Gines[71] Paolo Angeli[72] Salvatore Piano[73]

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Background: Kidney failure is the most common extrahepatic organ failure in patients with ACLF. The presence of ACLF modifies the phenotype and outcomes of AKI, but detailed information is limited. **Methods:** Multicenter, intercontinental, prospective study including hospitalized patients with decompensated cirrhosis from 67 centers in 5 continents from 7/2022-5/2023. This is a subgroup analysis aimed at assessing the phenotypes and outcomes of AKI in patients with ACLF compared to those with AKI without ACLF. ACLF was defined by EASL-CLIF criteria. The primary endpoint was lack of AKI resolution (return of serum creatinine to within 0.3 mg/dl of baseline). Secondary endpoints were 28-day mortality, AKI severity and AKI phenotypes. **Results:** Among 1,456 patients with cirrhosis and AKI, 863 (59%) had ACLF at admission (54% ACLF-1, 30% ACLF-2 and 16% ACLF-3). At admission, patients with ACLF and AKI had worse liver function (MELD 26 vs 18, p<0.001) and more signs of systemic inflammation (C-reactive protein 4.6 vs 3.2, p=0.001; white blood cell count [WBC] 9.2 vs 7.9, p=0.002). The most common AKI precipitant in patients with ACLF was bacterial infections, compared to volume loss in patients without ACLF. Patients with ACLF had more severe AKI compared to those without ACLF (peak AKI stage

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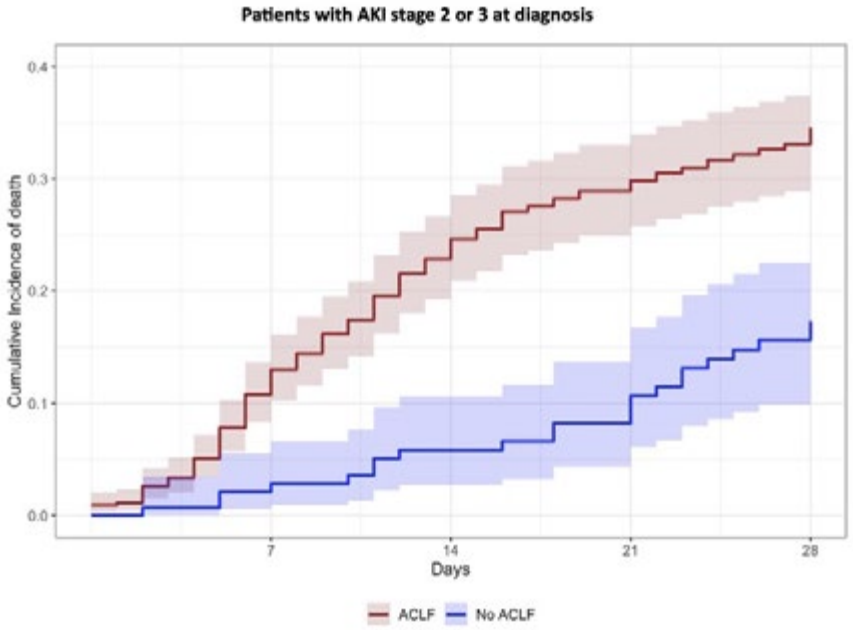
2-3 75% vs 42%, p<0.001). In addition, patients with ACLF had higher frequency of Hepatorenal syndrome-AKI (22 vs 11%) and acute tubular necrosis (ATN; 19 vs 9%, p=0.019). The frequency of ATN increased in parallel with ACLF grade (13, 20, 40% in ACLF-1, 2 and 3, respectively). Lack of AKI resolution occurred in 53% of patients with ACLF compared to 23% of patients without ACLF (p<0.001). In the multivariable analysis, MELD, AKI stage 3, ACLF-3 and ATN phenotype were independent predictors of lack of resolution. Mortality at 28 days was significantly higher in patients with AKI and ACLF compared to those with AKI without ACLF (HR 2.29 [95%CI 1.8-2.9], p<0.001). In the multivariable analysis, age, gender, MELD, WBC and ACLF grades 2-3, but not AKI stage, were independent predictors of mortality. Among patients with severe AKI (stage 2-3), those with ACLF had significantly higher mortality (Figure). **Conclusion:** ACLF has a negative impact on the natural course and outcomes of AKI. While severity of both ACLF and AKI predict lower AKI resolution, increased probability of 28-day mortality is mostly driven by severity of ACLF. Strategies for prevention, early diagnosis and management of AKI and ACLF need to be refined to improve outcomes.



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0118 | SNRNASEQ AND GEOMX® SPATIAL TRANSCRIPTOMICS ELUCIDATE THE CELL-TYPE-SPECIFIC ROLES OF LNCRNA H19 IN CHOLESTATIC LIVER INJURY ★

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[1]Virginia Commonwealth University

Background: Primary sclerosing cholangitis (PSC) causes chronic bile duct blockages and damage, leading to biliary fibrosis, cirrhosis, and liver failure. No pharmacologic treatment is available. Liver transplantation is the only treatment for end-stage disease with up to 30% recurrence rate. Long non-coding RNA H19 was previously shown to exacerbate damage in models of PSC; however, its cell-type-specific roles in PSC are not fully understood and is the focus of this study. **Methods:** Liver tissues from C57/BL6 wild type (WT), Mdr2$^{-/-}$, H19$^{-/-}$ and Mdr2$^{-/-}$/H19$^{-/-}$ (DKO) mice (female, 6-month-old) were processed for snRNAseq. Ambient RNA was removed using SoupX. SnRNAseq clustering, analysis, and differentially expressed genes (DEGs) were identified utilizing the Seurat, and gene set enrichment analysis (GSEA) was performed using clusterProfiler. LASSO regression, followed by random forest machine learning and ROC-AUC analysis (LRR) was used to determine a model for gene expression and disease prediction in macrophage and cholangiocyte subclusters. Pseudotime analysis was performed with Monocle3. Spatial transcriptomics was performed on Mdr2$^{-/-}$ and DKO mice utilizing NanoString GeoMx® Digital Spatial Profiler with the murine whole transcriptome atlas probe set. DEGs and pathway analyses were performed with the DSP software and confirmed with the StandR. **Results:** Macrophages (*Ptprc*$^{+}$*,Adgre1*$^{+}$): LRR produced a 10-gene model (AUC 0.854). *Cd5l* was the most crucial gene for predicting macrophage status, more significant than Clec4f and Cd163, and was highly expressed in KCs. Cholangiocytes (*Epcam*$^{+}$*,Krt19*$^{+}$*,Cftr*$^{+}$*,Sox9*$^{+}$): Cholangiocyte subclustering identified a disease-associated subtype reduced in DKO mice. GeoMx spatial transcriptomics revealed a reduction in Chemical carcinogenesis-reactive oxygen species and HCC pathways in DKO vs Mdr2$^{-/-}$ bile duct regions of interest. GSEA revealed that metabolic pathways in cholangiocytes were reduced in Mdr2KO$^{-/-}$ compared to WT and ameliorated with DKO. LRR identified a 6-gene model (AUC 0.952), with *Clu, Chka*, and *Naaladl2*, showing lower expression under diseased conditions, but *Chka and Naaladl2* are signficantly increased towards WT levels in DKO vs Mdr2$^{-/-}$. *Chka* was also a top gene linked to H19 deletion. *Lama4*, *Kcnip4*, and *Csmd1* are significantly increased in Mdr2$^{-/-}$ vs WT (padj. value < 0.001), and significantly reduced in DKO vs Mdr2KO (padj. value < 0.001) down towards WT levels (DKO vs WT, padj value >0.05 for *Kcnip4, and Csmd1*). **Conclusion:** *Cd5l* is a better marker for healthy state hepatic macrophages, distinguishing KCs from MdMQs. Loss of *Clu*, *Chka*, and *Naaladl2* expression in cholangiocytes is a marker of biliary fibroinflammation and may worsen PSC. H19-mediated upreguation of *Lama4*, *Kcnip4*, and *Csmd1* may exacerbate disease progression.

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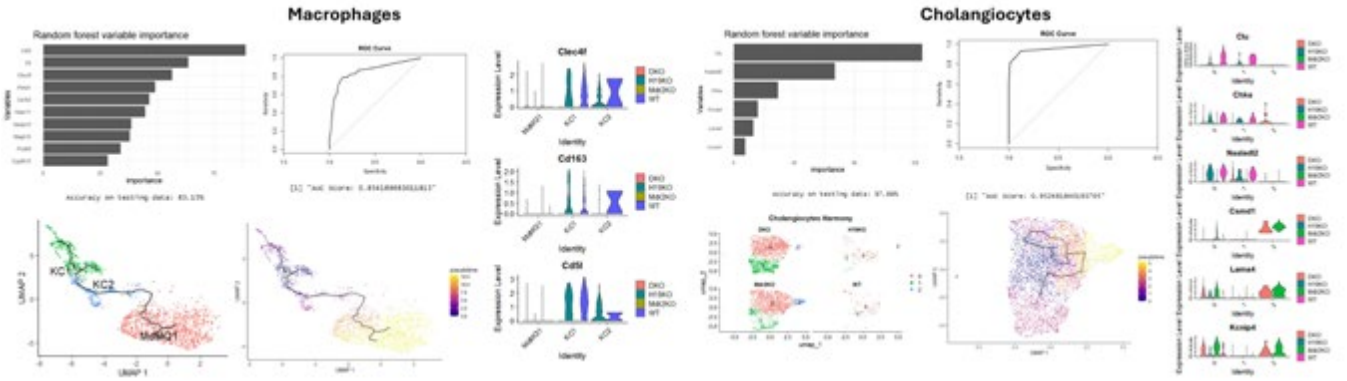

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0119 | EQUITABLE AND INCLUSIVE POLICIES TOWARDS SEXUAL AND GENDER MINORITIZED PATIENTS AT LIVER TRANSPLANT CENTERS

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Background: Approximately 7% of the adult US population reports to be of a minoritized sexual or gender (SGM) identity. SGM patients experience significant health disparities within the healthcare setting including decreased health insurance access, fewer family social supports, and increased rates of mental health disorders. These are often factors that are looked at to determine who is an appropriate recipient of a donor organ. Assessment of liver transplant (LT) centers and their SGM policies has not been assessed. The Healthcare Equality Index (HEI) is a voluntary survey which assesses whether hospitals have SGM policies that are equitable and foster inclusivity for both patients and employees. The HEI is based on 1. Non-Discrimination and Staff Training, 2. Patient Services and Support, 3. Employee Benefits and Policies, 4. Patient and Community Engagement, and 5. Responsible Citizenship. The purpose of this study was to determine how LT center participation, presence, and quality of their SGM policies are affected by LT volume, SGM state population, and participation and score of other inter-state LT centers. **Methods:** HEI scores were obtained for 2022 from the Human Rights Campaign (written communication). These scores were then compared to the OPTN data for LT in 2023 by state and LT center (http://optn.transplant.hrsa.gov). SGM demographic data and percentage of SGM patients residing in the state was obtained from The Williams Institute for each state which and was combined with state-level US census estimates for 2023. A normalized HEI score was calculated for each state based on the sum of the products of the HEI score and LT volume per state normalized by the total number of LTs per state. **Results:** Of the 144 LT centers in 2023, 84 centers (58%) participated in the HEI. Fifty-nine centers (41%) received a perfect HEI score. Of the remaining 85 centers that did not receive a perfect score or participate (59%), 61 are in a state with a center that did receive a perfect score. The SGM population of the state was not related to the state's normalized HEI score (p=0.16) or the fraction of centers participating in the HEI (p=0.12; Fig. 1A). In addition, neither center nor state LT volume had a relationship with HEI participation (p=0.21, p=0.08, respectively; Fig. 1D), and neither had a relationship with center score or state normalized score (p=0.37, p=0.09, respectively; Fig. 1B, C). **Conclusion:** SGM individuals in every state deserve equitable and inclusive LT care, but such policies are severely lacking even at large LT centers in states with increased SGM populations. Greater regulatory oversight and requirements could improve SGM policies at LT centers nationally. Additionally, given the increase in LT volume and inter-center competition [PMID: 26206649], participation in the HEI and advertisement of SGM-friendly policies may provide an avenue for LT centers to stand out and highlight their care.

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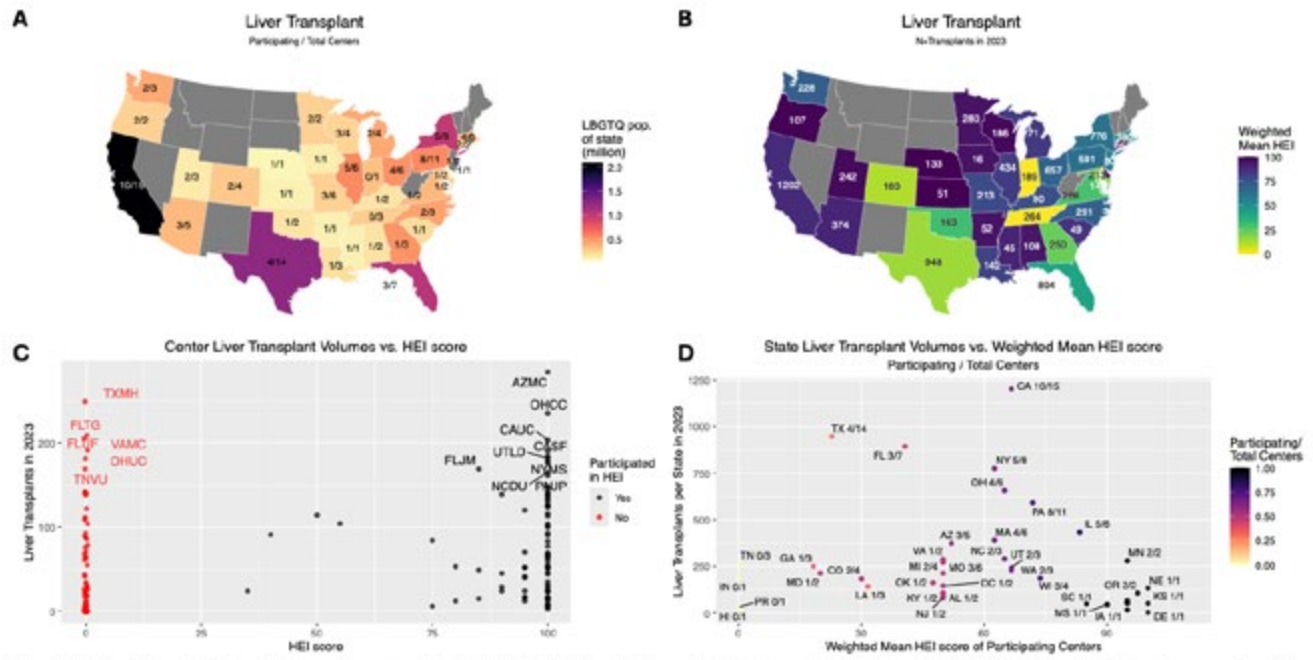

Figure 1. A) Map showing distribution of liver transplant center participation in HEI with shading indicating estimated state population identifying as SGM. B) Map showing distribution of mean normalized HEI scores by shading, with volume of liver transplants in 2023 labeled per state. C) Liver transplant volume was not associated with participation in the HEI. OPTN center names at centers that performed greater than 150 transplants shown. D) State liver transplant volumes did not associate with normalized mean HEI score or participation of liver transplant centers in the HEI.

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0120 | OUTCOMES OF CHILD-PUGH B PATIENTS TREATED WITH SINGLE TREMELIMUMAB REGULAR INTERVAL DURVALUMAB (STRIDE) FOR UNRESECTABLE HEPATOCELLULAR CARCINOMA (UHCC) IN A REAL-WORLD COHORT

Shalini Bansal[1] *Priya Amin*[2] *Stephen Valerio*[2] *David Kaplan*[3]

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Background: Prior research has demonstrated that Veterans Affairs CP-B patients with uHCC had reduced overall survival (OS) (4.7 months) when treated with atezolizumab and bevacizumab (A+B) versus patients with CP-A status. The HIMALAYA I trial demonstrated that STRIDE significantly improved (OS in when compared to sorafenib in a CP-A population. We utilize a real-world cohort to describe the utilization and outcomes of STRIDE in patients with uHCC and CP B cirrhosis. **Methods:** In this retrospective cohort study, we identified all patients within the Veterans Affairs Medical System diagnosed with HCC from 1/1/2015-3/31/2024 who had received at least one dose of the STRIDE regimen using the VA Corporate Data Warehouse (CDW). Demographics, etiology of liver disease, baseline laboratory parameters, and concomitant medications were extracted from the CDW. ECOG performance status, BCLC staging, prior treatments, prior chemotherapy used, number of treatment cycles and adverse events were manually abstracted by a single chart reviewer using REDCAP. Survival outcomes were evaluated using Kaplan-Meier methodologies. **Results:** Of the 117 uHCC patients who received STRIDE, 87 (74.4%) were CP A and 30 (25.6%) were CP B. All CP B patients in this cohort were male with median age 73 years [IQR 66-76], 22 (73.3%) were White with 10/11/8/1 (33/37/27/3%) related to ALD/HCV±ALD/MASH/Other cirrhosis. 16 (53%) had medical controlled ascites and 1 (3%) refractory ascites. Baseline ALBI class was G1/G2A/G2B/G3 19%/19%/30%/33%. CP B patients had a median of 2 tumors [1-5] with largest being 4.9 cm [2.6-11.1]. Three patients (10%) staged BCLC A, 4 (13%) BCLC B and 22 (76%) BCLC C with 15 (50%) with VP3 or VP4 vascular invasion. Six (20%) had malignant LN involvement and 4 (13%) had distant metastates. Median AFP was 466 ng/ml [IQR 8-2067]. The majority 17/30 (59%) had received prior TACE (12/30, 41%), TARE (2, 8%), ablation (2, 8%), or resection (1, 4%) with 10 patients receiving >1 prior LRT. At data capture, a median of 2.5 cycles of STRIDE had been administered and 3 patients continued to be receiving therapy. Grade

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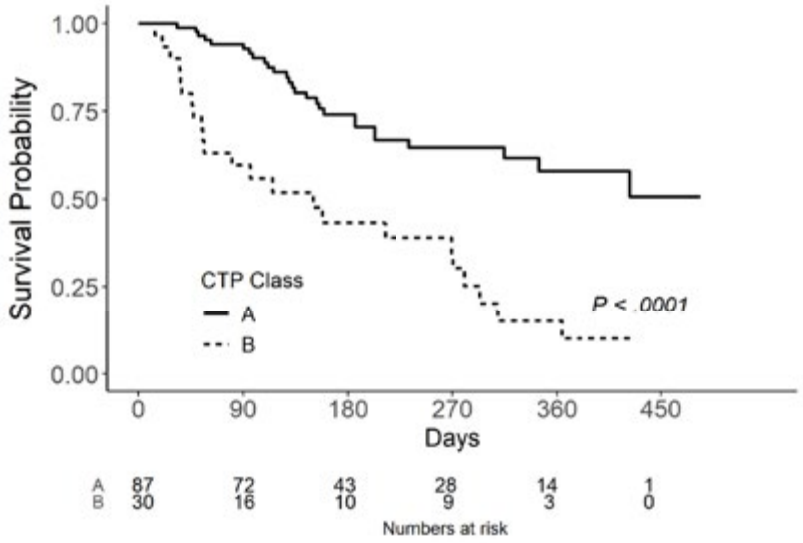
2-4 immune-related adverse events occurred in 9/30 (32%) leading to discontinuation in 2 cases. Reasons for treatment discontinuation were death (12, 44%), progressive disease (8, 30%), IRAE (2, 8%) or other (5, 18%). Median OS was 6.2 months [95%CI 2.9 – 11.8] for the CTP B patients and NE [12.3-NE] for CTP A patients. **Conclusion:** STRIDE was well-tolerated in CP-B patients with uHCC. Survival outcomes were similar to those observed with other IO in CP-B veterans with uHCC and compared favorably to previous published experience for similar CP-B patients receiving sorafenib, nivolumab (Chapin et al. 2023) or A+B.



Disclosures: Shalini Bansal: Nothing to Disclose, Priya Amin: AstraZeneca: Employee, Stephen Valerio: AstraZeneca Pharmaceuticals: Stock, Publicly Traded Company, Speaking, Astrazeneca Pharmaceuticals: Employee, Stock, Publicly Traded Company, Speaking, David Kaplan: Independent Contractor relationship with Roche Genentech; Has not ended; Grant/Research Support relationship with AstraZeneca Inc; Has not ended; Advisor relationship with AstraZeneca; Has ended; Advisor relationship with Exelixis; Has ended; Grant/Research Support relationship with Gilead; Has not ended; Advisor relationship with Sirtex; Has ended; Grant/Research Support relationship with Exact Sciences; Has not ended; Grant/Research Support relationship with Glycotest; Has ended

0121 | OUTCOMES OF THE ALCOHOL-ASSOCIATED HEPATITIS BRIDGE CLINIC AT A SAFETY-NET HOSPITAL: A PROSPECTIVE PILOT STUDY ★

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Background: Alcohol-associated hepatitis (AH) portends high morbidity and mortality. We established a novel clinic for patients recently hospitalized for AH called the Alcohol-associated Hepatitis Bridge Clinic (ABC) at a safety-net hospital. **Methods:** Adults (18-70 years) hospitalized with AH per NIAAA criteria from 12/2022-4/2024 at Los Angeles General Medical Center were referred for follow up within 2 weeks from hospital discharge to ABC. ABC patients received protocolized care for alcohol use disorder and liver disease with gastroenterology fellows during visits (baseline, Day 30, Day 90), including a standardized brief intervention, medications for alcohol use disorder (MAUD), and referrals to social work, addiction medicine, and liver transplantation when appropriate. Alcohol use was evaluated via Timeline Followback and serum phosphatidylethanol (PEth), in addition to blood and urine specimen collection. Feasibility outcomes included study visit attendance, completion of questionnaires, urine/serum collection, referrals to key specialists, and PEth testing at each visit which were compared to a contemporaneous cohort of patients hospitalized with AH (control) seen at hepatology clinic for post-hospitalization visit (due to filled ABC schedule). **Results:** Among 41 patients referred to ABC, there were 20 patients (median age 39; 70% male; 85% Hispanic; 80% renters; 5% homeless) who presented to their ABC appointment, who all enrolled in this prospective study. ABC (vs control n=20) patients were of similar age, %

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male, race, BMI, median length of stay (4 [IQR 2-6] vs 3 [IQR 2-8]), MELD at admission (27 [IQR 23-31] vs 24 [IQR 21-28]) and discharge (28 [IQR 25-30] vs 25 [IQR 20-28]). ABC (vs control) patients had shorter time from hospital admission to post-discharge clinic visit (11 [IQR 6-15] vs 25 [IQR 10-43] p=0.02), higher attended scheduled visits (80 vs 30% p=0.002), and higher rates of transplant referrals (35 vs 15% p=0.27). ABC (vs control) patients had higher rates of consultations for addiction medicine (100 vs 55% p<0.001), social work (90 vs 10% p<0.001), and nutrition (70 vs 0% p<0.001) and more attended visits with addiction medicine (75 vs 15% p<0.001), social work (65 vs 0% p<0.001), and nutrition (40 vs 0% p=0.003). ABC (vs control) patients had higher rates of MAUD prescribed at study intervals (75 vs 60% p=0.31, 75 vs 75% p=1.00, 83 vs 67% p=0.57) and higher rates of PEth testing (50 vs 0% p=0.0003, 88 vs 50% p=0.16, 100 vs 29% p=0.002). 100% of ABC patients filled out questionnaires and the majority provided research blood and urine specimens (Table). **Conclusion:** ABC was feasible to implement at a safety-net hospital. Early results suggest higher rates of clinic attendance, treatment of alcohol use disorder, and referrals to appropriate specialists, potentially due to protocolized care for liver disease, addiction, and nutrition for AH. This may serve as a novel model to improve quality of care for patients with AH.

Overall Outcomes at 3 Month Follow up			
Characteristic	ABC (n=20)	Control (n=20)	P value
Labs available to Calculate MELD 3.0:			
Admission	20 (100%)	20 (100%)	1.00
Discharge	20 (100%)	18 (90%)	0.49
Baseline Clinic Visit	20 (100%)	12 (60%)	0.002
1 month Follow up	16 (100%)	3 (75%)	0.20
3 month Follow up	10 (91%)	3 (60%)	0.26
Completed all study visits	16 (80%)	6 (30%)	0.002
Referred for Liver Transplant	7 (35.0%)	3 (15.0%)	0.27
Reason Why Not Referred to Liver Transplant			
Improving with medical management	6 (46.2%)	5 (29.4%)	
Lack of social support	1 (7.7%)	2 (11.8%)	
Ongoing alcohol use	2 (15.4%)	2 (11.8%)	
Lack of participation in alcohol abstinence programs	0 (0%)	0 (0.0%)	
High risk alcohol use history	2 (15.4%)	4 (20.0%)	
Not documented why transplant not considered	1 (7.7%)	6 (35.3%)	
Addiction Medicine Consulted	20 (100.0%)	11 (55.0%)	<0.001
Saw addiction medicine	15 (75.0%)	3 (15.0%)	<0.001
Social Work Consulted	18 (90.0%)	2 (10.0%)	<0.001
Saw Social Work	13 (65.0%)	0 (0.0%)	<0.001
Nutrition Consult Placed	14 (70.0%)	0 (0%)	<0.001
Saw Nutrition	8 (40.0%)	0 (0%)	0.003
Peth drawn at baseline visit	10 (50.0%)	0 (0%)	<0.001
Peth drawn at 1 month visit	14 (87.5%)	2 (50%)	0.16
Peth drawn at 3 month visit	12 (100%)	2 (28.6%)	0.002
Blood specimens collected at baseline visit	13 (68.4%)		
Blood specimens collected at 1 month visit	9 (56.3%)		
Blood specimens collected at 3 month visit	7 (58.3%)		
Urine specimen collected at baseline visit	16 (84.2%)		
Urine specimen collected at 1 month visit	12 (75.0%)		
Urine specimen collected at 3 month visit	8 (66.7%)		

Disclosures: Divya Ayyala: Nothing to Disclose, Matthew Dukewich: GlaxoSmithKline: Stock - publicly traded company, David Lawrence: Nothing to Disclose, Rachan Narala: Nothing to Disclose, Ariel Lee: Nothing to Disclose, Norah Terrault: Grant/Research Support relationship with Eiger Pharmaceuticals; Has ended; Grant/Research Support relationship with GSK; Has not ended; Royalties or patent beneficiary relationship with Elseiver; Has not ended; Grant/Research Support relationship with Helio Health; Has ended; Grant/Research Support relationship with Durect Corp; Has ended; Executive role relationship with AASLD; Has not ended;

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Board member relationship with HBV Foundation; Has not ended; Grant/Research Support relationship with ImmunoCore; Has ended, Brian Lee: NIAAA: Grant/Research Support, Novo Nordisk: Advisor, GSK: Advisor, DURECT: Advisor, HepaTx: Advisor, CymaBay: Consultant, Ipsen: Consultant, Siemens Healthineers: Grant/Research Support, AltImmune: Advisor

0122 | PASTEURIZED AKKERMANSIA MUCINIPHILA SUPPRESSES HEPATOCELLULAR CARCINOMA GROWTH BY REGULATING THE CD8 MEMORY RESPONSE AND TREG CELLS THROUGH MODULATION OF STING EXPRESSION

Chun-Ying Wu[1] Sin-Ting Wang[2] Shi-Wei Huang[3] Hsin-Ying Hsieh[2] Jeng-Jer Hsieh[4]

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Background: *Akkermansia muciniphila* is a potential gut microorganism that can enhance the effectiveness of chemotherapy or immunotherapy in various cancers, such as hepatocellular carcinoma (HCC), by modulating immune responses. Stimulator of interferon genes (STING) is one of the potential targets regulated by gut microbiota and contributes to tumour control. However, whether *A. muciniphila* can modulate antitumour immunity through the STING pathway remains unclear. Here, we aimed to evaluate the antitumour effect of pasteurized *A. muciniphila* on HCC and investigate the role of STING in the modulation of memory T-cell formation and its impact on immune suppressive cells. **Methods:** The immune-competent C57BL/6 mice-bearing Hep55.1C tumour model was used to evaluate the anti-tumour effect of pasteurized *A. muciniphila*. The modulation of CD8+ and regulatory T (Treg) cells, the formation of central memory T (TCM) cells and the expression level of STING were monitored. Furthermore, the effect of STING on CD8+ and Treg cell populations and on the regulation of TCM cell memory in CD8+ T cells were investigated by using pharmacological inhibitors *in vitro* and *in vivo*. **Results:** The administration of pasteurized *A. muciniphila* mitigated HCC growth and increased the proportion of CD8+ T cells and reduced Treg cell populations in splenocytes, which was correlated with increased infiltration of CD8+ cells and decreased Treg cells in the tumour burden. Treatment with pasteurized *A. muciniphila* not only increased splenic CD8+ T cells with the TCM phenotype but also enhanced their tumour cell killing ability. This effect was mediated by the upregulation of STING in CD8+ T cells with the TCM phenotype as well as reduced Treg cells in both spleen and tumour sections. Moreover, pasteurized *A. muciniphila* directly increased TCM cell memory formation, and pre-treatment with the STING inhibitor C-176 disrupted the increase in the TCM cell population in both isolated mouse and human CD8+ T cells. **Conclusion:** Our results indicate that pasteurized *A. muciniphila* may directly induce STING upregulation to promote CD8 T-cell differentiation toward TCM cells and promote the reduction of Treg cells, which may contribute to the increased cytotoxic killing ability, delayed tumour growth and extended survival rate *in vivo*.

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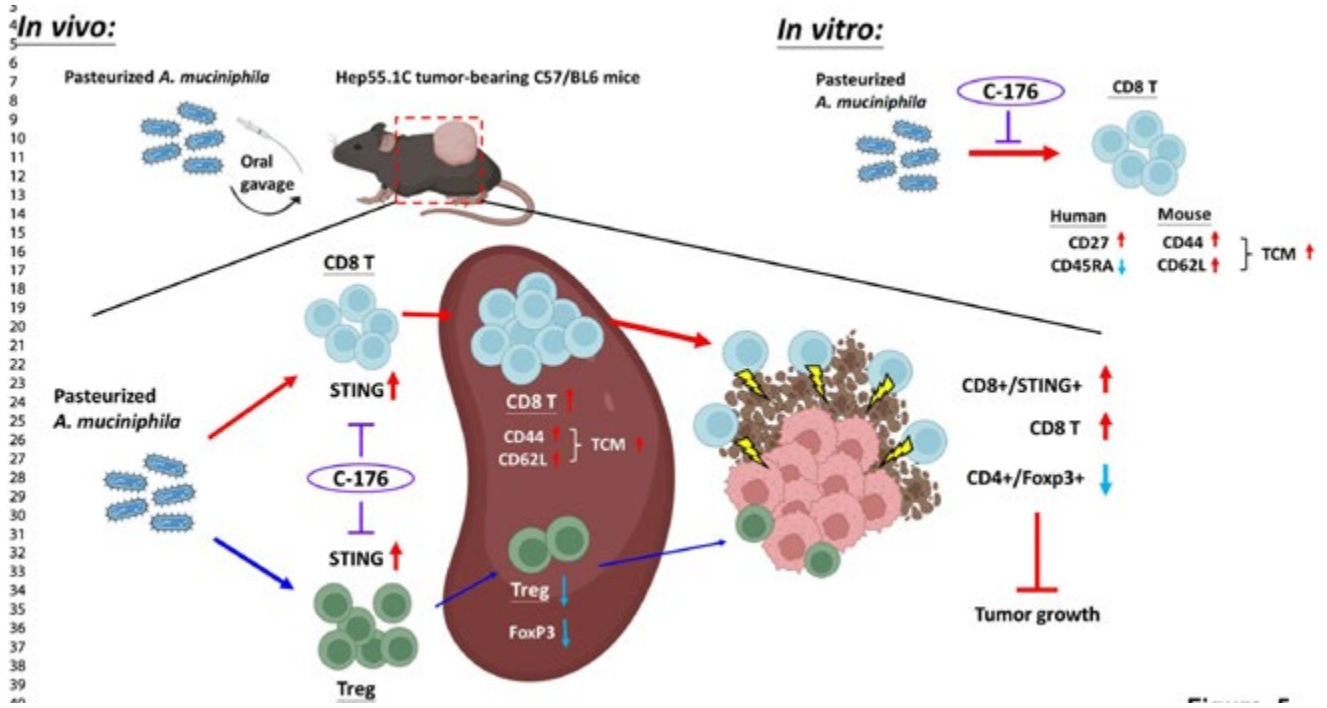

Disclosures: Chun-Ying Wu: Nothing to Disclose, Sin-Ting Wang: Nothing to Disclose, Shi-Wei Huang: Nothing to Disclose, Hsin-Ying Hsieh: Nothing to Disclose, Jeng-Jer Hsieh: Nothing to Disclose

0123 | INTRINSIC NF-&KAPPA;B ACTIVATION CONTROLS CELLULAR DEFECTS, VIRAL SUSCEPTIBILITY, AND MACROPHAGE ACTIVATION IN BILIARY ATRESIA CHOLANGIOCYTES ★

Wenqi Li[1] Ashley Fonseca[1] Reena Mourya[1] Pranavkumar Shivakumar[1] Jorge Bezerra[1]

[1]UT Southwestern Medical Center

Background: Cholangiocyte organoids (COs) from patients with biliary atresia (BA) recapitulate in vivo features of bile duct epithelium defects. However, mechanisms that control these defects are less known. Here, we investigated the molecular events in cholangiocytes that regulate cell defects and immune cell activation. **Methods:** Human COs derived from livers of normal donors (NCOs) and BA patients (BACOs) were analyzed by RNA-Seq, FITC-Dextran permeability, and whole-mount immunofluorescence (WIF) staining of ZO-1. Phosphorylated NF-κB (pNF-κB) was measured in the liver sections of normal controls (NC) and BA patients by immunostaining and in NCOs and BACOs by WIF. Signal intensities were estimated by fluorescence units (FU). Transcription factors were determined using TRRUST database. Human COs were infected with rhesus rotavirus (RRV) and analyzed by H&E and WIF of cleaved caspase 3. BACOs were co-cultured with LPS-treated murine macrophages. **Results:** RNA-Seq profiling of BACOs and NCOs identified 320 differentially expressed genes that clustered to the transcription factor NF-κB ($P=10^{-13}$). In histological sections of BA livers, cholangiocytes showed enhanced nuclear pNF-κB signals (74±16% vs NC: 5±5%, P<0.0001). In parallel, BACOs also showed higher nuclear pNF-κB FUs (1.7-fold, P<0.0001). To investigate if altered NF-κB enhanced susceptibility to viral infection, we infected NCOs and BACOs with RRV. Infection of BACOs induced the expression of inflammation-related genes (N=89) that clustered to NF-κB ($P=10^{-8}$). Immunostaining showed an increase in nuclear pNF-κB signals (1.3-fold, P=0.048) in cholangiocytes, and resulted in a higher percentage of apoptotic cells and disruption of organoids (1.3-1.7-fold; P<0.05). To directly examine if NF-κB promotes epithelial injury, we inhibited NF-κB transactivation with GYY4137 and found that BACOs increased growth to levels of normal NCOs, restored tight junctions, decreased epithelial permeability (4.8-fold decrease in FUs of FITC-Dextran uptake, P<0.0001), and suppressed apoptosis of BACO cells (2.38-fold decrease vs untreated, P=0.03). Exploring if NF-κB enriched BACOs activated immune cells, we co-cultured BACOs with LPS-stimulated macrophages (MΦs) and identified increased TNFα and iNOS expressions in MΦs (3-23-fold increase, P<0.001). **Conclusion:** Our work identified NF-κB activation in cholangiocytes from BA patients that intrinsically promotes cellular defects, enhances

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susceptibility to virus infection and augments macrophage activation. Blocking NF-κB may be a viable therapeutic approach to correct epithelial defects and restore cellular competency in BA.

Disclosures: Wenqi Li: Nothing to Disclose, Ashley Fonseca: Nothing to Disclose, Reena Mourya: Nothing to Disclose, Pranavkumar Shivakumar: Nothing to Disclose, Jorge Bezerra: Nothing to Disclose

0124 | A HEALTH IT INTERVENTION WITH CAREGIVER ENGAGEMENT SIGNIFICANTLY REDUCES AVOIDABLE READMISSIONS IN A MULTI-CENTER RANDOMIZED CLINICAL TRIAL OF >450 PARTICIPANTS: THE HEROIC TRIAL

Jawaid Shaw[1] Chathur Acharya[2] Andrew Fagan[3] Amy Olofson[4] Jennifer Montano[1] Patrick Kamath[4] Jasmohan Bajaj[1]

[1]Virginia Commonwealth University, [2]Ohio State University Medical Center, [3]Richmond VA Medical Center, [4]Mayo Clinic, Rochester

Background: Reducing avoidable readmissions in cirrhosis is challenging. Enhanced engagement using health IT (HIT) interventions & with caregivers (CG) has helped reduce readmissions in an open-label study of Patient Buddy App (PBA) but a multi-center experience is needed. Aim: RCT to reduce preventable 30-day readmissions in HIT vs standard of care (SOC) in cirrhosis. **Methods:** Cirrhosis inpatients admitted non-electively who had an adult CG were enrolled from 3 sites (1 private, 1 VA & 1 safety-net hospital). Pts & CGs were consented separately & formed dyads. Dyads were randomized 1:1 into HIT (PBA) vs SOC & followed for 30 days post-discharge for readmissions. At discharge all dyads were educated about cirrhosis symptoms & provided contact information for study teams. Those randomized to HIT were given one device each for pts & CG loaded with the PBA focused on daily input of medication adherence, bowel movements (BM), daily weight, abdominal girth, temperature, at home. EncephalApp & cognitive testing were performed weekly by CG & reported via the App in the HIT group only. The clinical team monitored PBA-generated alerts/adherence parameters, leading to necessary actions. Decisions regarding avoidable/not readmissions were made by a clinician-led monitoring board blinded to HIT vs SOC grouping based on de-identified discharge summaries. **Results:** 464 subjects (232 dyads) were enrolled across the 3 centers (VCU/120, Mayo Clinic/40, Richmond VA/72). 116 dyads were randomized into SOC vs. HIT each. Most demographics & discharge labs were similar but prior HE was lower in SOC vs HIT (Fig 1A). Most were caregivers were female spouses & had similar characteristics across groups. Main index admission causes were HE, GI bleed, anasarca & infections, which were similar across groups. ***Readmissions:*** Significantly higher pts in the SOC vs HIT(48 vs 35%, p=0.005 Fig 1B) were readmitted. HIT pts got readmitted earlier vs SOC. Leading causes of readmissions were HE (n=22), followed by transplant (n=13), anasarca/AKI (n=14), GI bleed (n=7), infections (n=4) & rest were combinations. Readmitted pts had lower discharge hemoglobin (9.3 ±1.84 vs.10 ±2.24, p=0.01) & higher MELD (20.6±7.41 vs 18.2±7.12, p=0.01). On regression, high MELD (OR 1.05, 1.01-1.09, p=0.03) was associated while being on HIT (OR 0.51, 0.29-0.89, p=0.02) was protective against readmissions. ***Avoidable readmissions:*** These were higher in SOC vs HIT (10 vs 20%, p=0.04). Most avoidable readmissions were because of HE (N=14), then anasarca/AKI (N=8), & others. ***Engagement with App:*** 1660 total alerts were sent; most were related to HE testing and BMs (Fig 1C). **Conclusion:** In a multicenter RCT of 464 cirrhosis inpatients and their caregivers spanning several practice settings, the patient buddy App was associated with lower total and avoidable readmissions. Most readmissions that were prevented were due to HE as determined by alerts generated.

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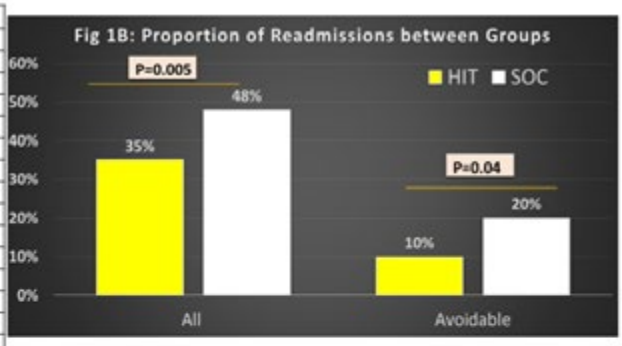
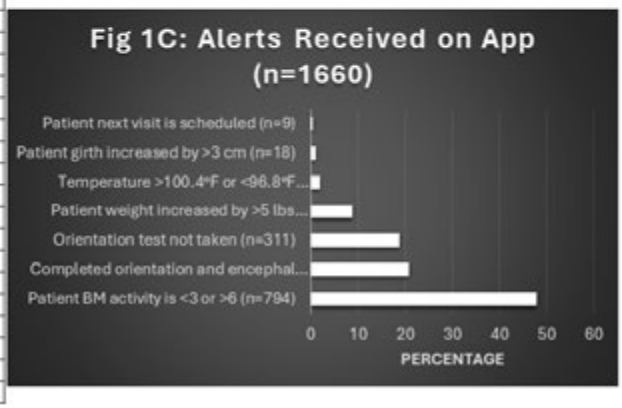
Fig 1A (116 dyads n=232/group)	SOC Group	HIT Group	p value
Age (in years)	59.1±12.38	58.4±8.88	0.62
Patients Male Gender n(%)	76(65.5)	80(68.9)	0.59
Patients Race White/other n	80/36	87/29	0.31
Caregiver age (in years)	56.9±13.89	55.3±12.88	0.36
Caregiver Male Gender n(%)	37(31.9)	32(27.6)	0.47
Caregiver Race White/other n	80/36	83/33	0.66
Caregiver Spouse/Other relation n	78/38	75/41	0.78
Site (VCU/Richmond VA/Mayo)	67/35/14	53/37/26	0.08
Cirrhosis details			
History of HE (%)	**64(55.2)**	**80(68.9)**	**0.03**
History of Ascites (%)	78(67.2)	91(78.5)	0.06
History of variceal bleeding (%)	25(21.5)	30(25.9)	0.54
Etiology (HCV/Alc/ MASH)	9/23/25	18/32/34	0.70
Lactulose alone	28(24.1)	26(22.4)	1.0
Lactulose + Rifaximin	43(37.1)	54(46.5)	0.14
Diuretics	46(39.6)	59 (50.8)	0.09
Beta-blockers	38(32.7)	39(33.6)	1.0
Proton pump inhibitors	88(75.9)	80(68.9)	0.29
Opioids	21(18.1)	16(13.8)	0.37
Index hospitalization details			
Length of stay	6.5±5.40	6±5.59	0.49
Reasons for Index admission n			
Infections	12	12	1.0
Anasarca	16	24	0.09
GI bleeding	17	25	0.10
HE	26	30	0.54
AKI/HRS	10(8.6)	7(6.0)	0.45
Respiratory issues	3(2.7)	3(2.7)	1.0
Other (multiple reasons)	42(36.2)	24(20.7)	0.008
Labs at index discharge			
Na (meq/L)	134.9±4.75	134.9±13.15	1.0
Albumin (mg/dl)	2.9±0.70	2.9±0.59	1.0
MELD Score on index discharge	20.1±7.2	19.0±6.4	0.14





Disclosures: Jawaid Shaw: Nothing to Disclose, Chathur Acharya: Nothing to Disclose, Andrew Fagan: Nothing to Disclose, Amy Olofson: Nothing to Disclose, Jennifer Montano: Nothing to Disclose, Patrick Kamath: Advisor relationship with Sequana; Has ended; Advisor relationship with NovoNordisk; Has ended, Jasmohan Bajaj: Bausch: Grant/Research Support, Sequana: Grant/Research Support, Cosmo: Grant/Research Support, Grifols: Grant/Research Support

0125 | PEGINTERFERON ALPHA-2B COMBINED WITH TDF PROMOTES DURABLE HBSAG LOSS IN PATIENTS WITH CHRONIC HEPATITIS B: A MULTICENTER, RANDOMIZED CONTROLLED, PHASE 3 CLINICAL TRIAL

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Background: Peginterferon alpha (PegIFNα) dominant therapy has been shown in numerous studies and guidelines to improve hepatitis B surface antigen (HBsAg) loss and enable functional cure in chronic hepatitis B (CHB) patients. **Methods:** We conducted a phase 3, randomized controlled, superiority trial (NCT04846491) to confirm the ability of PegIFNα-2b (mipeginterferon alfa-2b, Pegbing®) to eliminate HBsAg. Nucleos(t)ide analogue (NA)-experienced patients were randomly assigned to receive tenofovir disoproxil fumarate (TDF) monotherapy (group 1), TDF combined with PegIFNα-2b 180 μg/week (group 2) or 90 μg/week (group 3). After 48 weeks of treatment, patients in group 1 could continue TDF monotherapy (group 1a) or add PegIFNα-2b 180 μg/week (group 1b). The treatment period was 144 weeks and the follow-up was 24 weeks. PegIFNα-2b were given intermittently in cycles (8 weeks of treatment + 4 weeks of interval, repeating every 12 weeks). Treatment-naïve patients were also enrolled for exploratory study. **Results:** Among NA-experienced patients, a total of 367 were included in the full analysis set (FAS) and 296 in the per protocol set (PPS). In the FAS analysis, 31.4% of patients in group 2 and 0.8% in group 1a achieved HBsAg loss at the end of follow-up (EOF), with a Cochran-Mantel-Haenszel (CMH) adjusted rate difference of 31.4% (95% CI, 23.14%-39.67%; *P*=0.0034). Similar results were obtained by PPS analysis (Figure 1). The superiority of PegIFNα-2b 180 μg/week combined with TDF over TDF monotherapy was confirmed. Groups 1b and 3 achieved HBsAg loss in 24.0% and 25.2% of patients in the FAS and 28.4% and 28.8% in the PPS, respectively, at EOF. The HBsAg loss rates increased as the duration of treatment progressed. By the end of treatment (EOT), HBsAg loss rates in the FAS were 0.8%, 33.9%, 26.9%, and 25.2% for groups 1a, 2, 1b, and 3. Groups 1a, 2, 1b, and 3 had 0, 4, 3, and 1 patient relapsed after HBsAg loss, with maintenance rates of 100.0%, 90.2%, 89.3%, and 96.8%, respectively. Furthermore, the proportion of patients achieving HBsAg loss and HBV DNA undetectable at EOT and EOF, as well as the maintenance rate, were the same as HBsAg loss in different groups. Subgroup analyses showed that lower baseline HBsAg levels were associated with higher HBsAg loss rates. **Conclusion:** This phase 3 trial confirmed that PegIFNα-2b combined with TDF resulted in durable HBsAg loss in over 30% of NA-experienced patients, significantly superior to TDF monotherapy.

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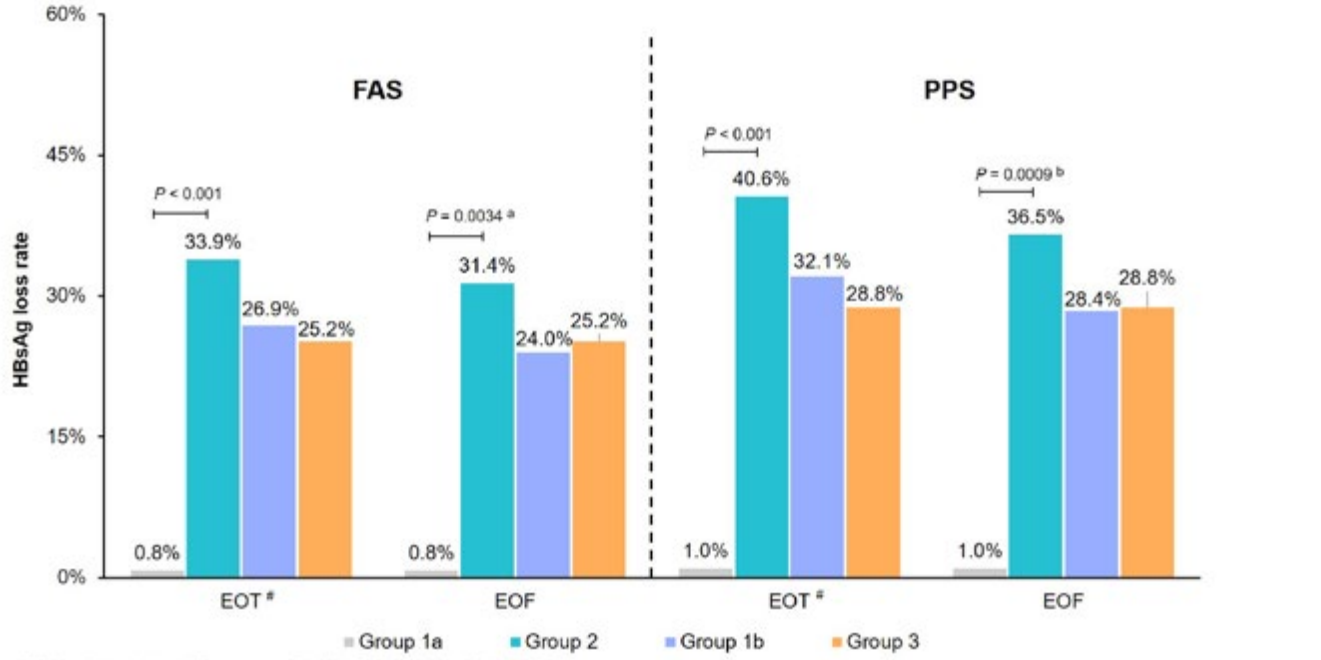

a: CMH adjusted rate difference = 31.4% (95% CI, 23.14% - 39.67%);
b: CMH adjusted rate difference = 35.4% (95% CI, 25.77% - 44.99%).
End of treatment: 1) completed 144 weeks of therapy or 2) achieved HBsAg < 0.05 IU/mL early and completed at least 2 cycles of treatment for consolidation. The missing data were imputed using last observation carry forward (LOCF) method.

Figure 1. HBsAg loss rate at EOT and EOF in NA-experienced patients

Disclosures: Guiqiang Wang: Nothing to Disclose, Fengqin Hou: Nothing to Disclose, Qing Xie: Nothing to Disclose, Chunliang Lei: Nothing to Disclose, Zhiliang Gao: Nothing to Disclose, Jia Shang: Nothing to Disclose, Jianmei Lin: Nothing to Disclose, Guoxin Hu: Nothing to Disclose, Xiaozhong Wang: Nothing to Disclose, Yilan Zeng: Nothing to Disclose, Jiabin Li: Nothing to Disclose, Jun Chen: Nothing to Disclose, Zuxiong Huang: Nothing to Disclose, Liying Zhu: Nothing to Disclose, Yan Huang: Nothing to Disclose, Qianguo Mao: Nothing to Disclose, Guozhong Gong: Nothing to Disclose, Jiming Zhang: Nothing to Disclose, Hongxin Piao: Nothing to Disclose, Ye Gu: Nothing to Disclose, Ping An: Nothing to Disclose, Xiaolu Wu: Nothing to Disclose, Xiulan Xue: Nothing to Disclose, Liaoyun Zhang: Nothing to Disclose, Yueyong Zhu: Nothing to Disclose, Yingren Zhao: Nothing to Disclose, Fusheng Wang: Nothing to Disclose, Jianqi Lian: Nothing to Disclose, Xinyue Chen: Nothing to Disclose, Chao Wu: Nothing to Disclose, Hui Guo: Nothing to Disclose, Huiling Xiang: Nothing to Disclose, Yao Xie: Nothing to Disclose, Dongliang Li: Nothing to Disclose, Qin Ning: Nothing to Disclose, Xiaobo Lu: Nothing to Disclose, Ruoyi He: Nothing to Disclose, Yalin Yin: Nothing to Disclose, Li Sun: Nothing to Disclose

0126 | SAME DAY AND RAPID START HCV MANAGEMENT IN LA BODEGA CLINIC

Anthony Martinez[1] Scott Springer[2] Nariman Hossein-Javaheri[1] Ali Aijaz[1] Tricia Formato[2] Michelle Clark[2]

[1]University at Buffalo, [2]Erie County Medical Center

Background: The WHO aims to eliminate HCV by 2030; however, the United States (US) is unlikely to achieve this until 2037. La Bodega, a co-localized hepatology and addiction medicine program in Buffalo, New York (NY), has treated approximately 5000 individuals and over 1200 active People Who Use Drugs (PWUD), with a 95% sustained virologic response (SVR) rate. Recent changes to NY State Medicaid have enabled same-day HCV treatment to start without prior authorization processes, however, Medicare and commercial plans still require prior authorization. In La Bodega HCV meds are kept on the shelf in an on-site pharmacy, facilitating same-day treatment initiation. **Methods:** Patients were divided into three HCV treatment arms: same-day rapid, Medicare next-day rapid, and telemedicine rapid plans. HCV medications were supplied in 28, 56, or 84-day allotments. In PWUD, active drug use was defined as use within the past six months. Patient preference, medication adherence, loss to follow-up, and SVR were assessed. All data were tested for normality and equal variance and analysis of variance. Significance was determined at p<0.05. **Results:** 210 individuals were identified. 54% were

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younger than 40 (none of whom had cirrhosis), 44% were active PWUD and 61% were on Medication-Assisted Treatment (MAT) for substance use. 85% received same-day treatment and 11% were in the Medicare arm. 4% received medication in a next-day rapid telemedicine format (outcomes pending). Most patients preferred a shorter duration of treatment (50.47%) compared to fewer pills (31.9%). Those with same-day treatment had significantly higher rates of substance use (43.75% vs 16.6%; p<0.001), MAT therapy (60.79% vs 29.66%; p<0.001), lower adherence (68.18% vs 75%; p=0.35) and higher rates of past HCV re-infection (11.36% vs 4.166%; p=0.56). Same-day patients were more likely to be lost to follow-up (31.42% vs 20.83%; p=0.26). The rate of SVR between those with same-day treatment and Medicare was slightly lower but not significantly different at 96.29% vs 100% (p=0.52). PWUD had a greater loss to follow-up (37.67% vs 23.57%; p<0.05), lower adherence (56.47% vs 79.03%; p<0.001), and higher MAT use (77.64% vs 41.93%; p<0.001), however, the SVR rates were not significantly different (96% vs 97.5%; p=0.7). **Conclusion:** We have demonstrated that the rapid start of HCV treatment in a co-localized setting is highly effective in numerous cohorts of patients. Among PWUD, despite variable adherence and potential loss to follow-up, overall SVR rates are high and similar to the general population. Additionally, those with < age 40 are unlikely to have advanced liver disease. This model supports the implementation of a test and treat model of care to achieve HCV elimination.

Disclosures: Anthony Martinez: Gilead: Consultant, Gilead: Speaking and Teaching, Abbvie: Consultant, Abbvie: Speaking and Teaching, Arbutus: Consultant, Braeburn: Speaking and Teaching, Sirtex: Consultant, Roche: Consultant, Syneos/VBI: Consultant, Madrigal: Speaking and Teaching, Altimune: Consultant, Scott Springer: AbbVie: Advisory board, Speaker bureau, GIlead Sciences: Advisory board, Speaker bureau, Nariman Hossein-Javaheri: Nothing to Disclose, Ali Aijaz: Nothing to Disclose, Tricia Formato: Nothing to Disclose, Michelle Clark: Nothing to Disclose

0127 | SERUM ALBUMIN-BINDING CAPACITY CORRELATES WITH SERUM ALBUMIN STRUCTURAL ALTERATIONS AND CLINICAL OUTCOMES IN PATIENTS WITH ACUTELY DECOMPENSATED CIRRHOSIS AND ACUTE-ON-CHRONIC LIVER FAILURE

Chenxi Zhang[1] Yide Lu[1] Baoyan An[1] Shuang Meng[2] Yaoxing Chen[1] Minghao Cai[1] Haoshuang Fu[1] Jie Lu[1] li ziqiang[1] Zhuping Qian[1] Li Xia[3] Haiguang Xin[1] Zhujun Cao[1] Qing Xie[1]

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Background: Post-translational modifications of human serum albumin (HSA), particularly the redox state of Cys-34, are associated with disease severity and clinical outcomes in patients with acutely decompensated cirrhosis (AD) and acute-on-chronic liver failure (ACLF). However, measuring these structural modifications requires liquid chromatography/mass spectrometry, which is challenging for routine clinical use. This study aimed to evaluate the prognostic value of easily measurable functional parameters of HSA as an alternative to complex structural assessments, providing a more feasible method for evaluating albumin function. **Methods:** In this prospective cohort study, patients with cirrhosis non-selectively admitted for AD (n=465) or ACLF (n=63) were enrolled between June 2016 and Oct. 2021. Structural [native HSA, human nonmercaptalbumin 1 (HNA1) and HNA2] and functional characteristics of HSA were both assessed at baseline and compared for the prediction of 1-year mortality. Functional parameters of HSA include albumin hydroxyl radical antioxidant capacity (HORAC), ischemia-modified albumin (IMA), and albumin-binding capacity (ABiC). The prognostic ability of the assessed parameters was evaluated using ROC curves. **Results:** Of 528 patients with AD and ACLF, 128 (24.2%) died, 31 (6.9%) underwent transplant, and 369 (69.9%) survived at 1-year follow-up. Compared to survivors, non-survivors had higher proportions of bacterial infection and renal dysfunction, higher levels of leukocyte count, liver enzymes, total bilirubin, INR and MELD-Na scores but lower levels of serum albumin and sodium. Levels of HORAC and IMA were similar between survivors and non-survivors whereas, ABiC [64.2 (43.0-85.4) % vs. 96.8 (70.1-117.8) %, p<0.001] and native HSA [12.4 (7.8-22.3) % vs. 23.0 (13.0-34.4) %, p<0.001] were significantly lower in non-survivors, and HNA1 [71.2 (62.3-78.5) % vs. 64.0 (51.1-74.5) %, p<0.001], HNA2 [1.7 (1.2-2.7) % vs. 1.2 (0.9-1.8) %, p<0.001] were significantly higher in non-survivors. Structural parameters of HSA, including native HSA and HNA1 were significantly correlated with HORAC and ABiC but not IMA. In the prediction of 1-year mortality, ABiC demonstrated relatively high accuracy that was comparable with that of native HSA (AUC, 0.74 vs. 0.69, p=0.112) or MELD-Na score (AUC, 0.74 vs.0.77, p=0.171). ABiC was also comparable with native HSA

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in improving the 1-year prognostic value of MELD-Na score when being incorporated (AUC of ABiC + MELD-Na vs. AUC of native HSA + MELD-Na, 0.78 vs. 0.79, p=0.179). **Conclusion:** ABiC alone provided high predictive accuracy in predicting 1-year mortality and might be a good alternative marker to the sophiscated assessment of post-translational modifications of serum albumin in patients with AD cirrhosis and ACLF.

Figure 1. Flow chart

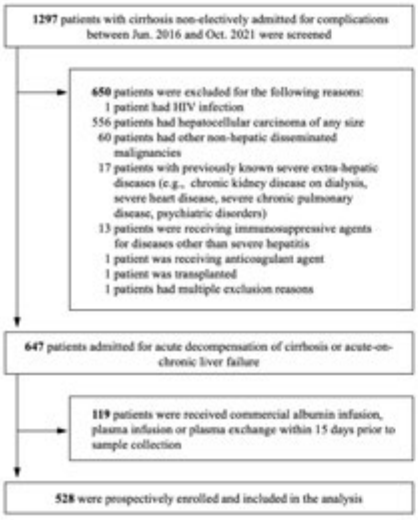


Figure 2. Characteristics of serum albumin structural and functional parameters according to 1-year survival outcomes.

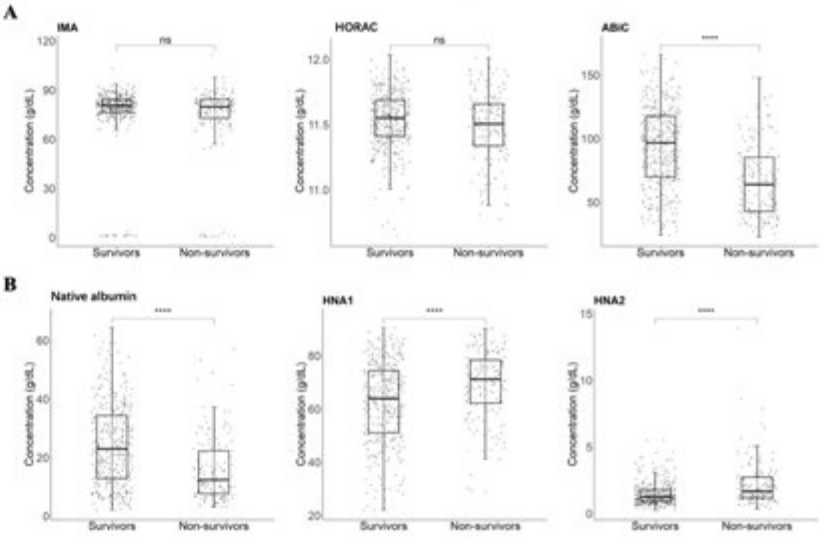


Figure 3. Heatmap of correlations between structural and functional parameters of serum albumin.

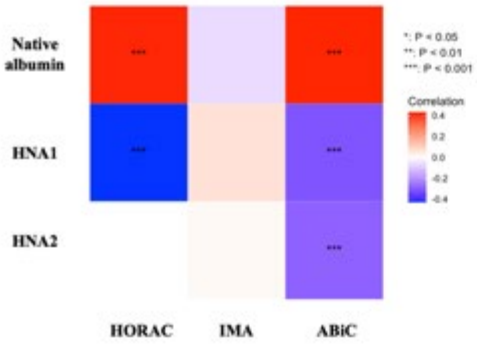
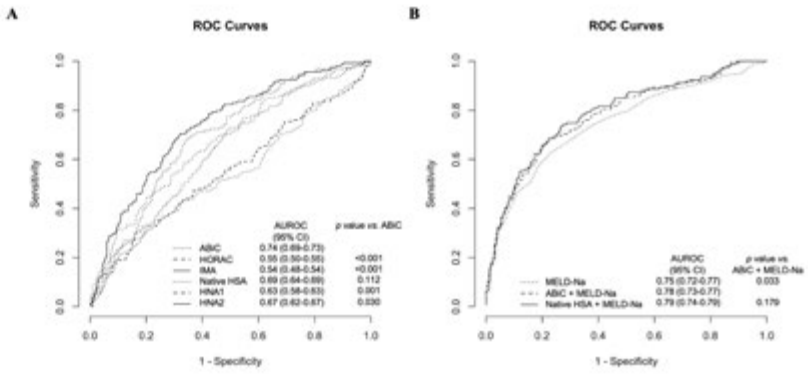


Figure 4. Prognostic performance of serum albumin structural and functional parameters.



Disclosures: Chenxi Zhang: Nothing to Disclose, Yide Lu: Nothing to Disclose, Baoyan An: Nothing to Disclose, Shuang Meng: Nothing to Disclose, Yaoxing Chen: Nothing to Disclose, Minghao Cai: Nothing to Disclose, Haoshuang Fu: Nothing to Disclose, Jie Lu: Nothing to Disclose, li ziqiang: Nothing to Disclose, Zhuping Qian: Nothing to Disclose, Li Xia: Nothing to Disclose, Haiguang Xin: Nothing to Disclose, Zhujun Cao: Nothing to Disclose, Qing Xie: Nothing to Disclose

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0128 | A SERUM BIOMARKER-BASED SCORE TO EVALUATE HCC RISK IN HCV-CURED PATIENTS WITH CIRRHOSIS

Hiroaki Kanzaki[1] Naoto Fujiwara[2] Courtney Katz[1] Sumit Mishra[1] Subhojit Paul[1] Soumith Paritala[1] Michael Gonzalez[1] Lisa Quirk[1] Sneha Deodhar[1] Pratibha Selvakumar[1] Indu Raman[1] Prithvi Raj[1] Atsushi Ono[3] Andrea Branch[4] Chung-Feng Huang[5] Ming-Lun Yeh[5] Ming-Lung Yu[5] Raymond Chung[6] Angelo Sangiovanni[7] Massimo Iavarone[7] Massimo Colombo[8] Hitomi Sezaki[9] Masahiro Kobayashi[9] Hiromitsu Kumada[9] Kiyoshi Hasegawa[10] Ryosuke Tateishi[10] Saira Khaderi[11] Sumeet Asrani[12] Fasiha Kanwal[11] Hashem El-Serag[11] Jorge Marrero[13] Amit Singal[1] Yujin Hoshida[1]

[1]UT Southwestern Medical Center, [2]Mie University, [3]Hiroshima University, [4]Icahn School of Medicine at Mount Sinai (ISMMS), [5]Kaohsiung Medical University, [6]Massachusetts General Hospital, [7]Policlinico di Milano, [8]San Raffaele Hospital, [9]Toranomon Hospital, [10]The University of Tokyo, [11]Baylor College of Medicine, [12]Baylor University Medical Center, [13]University of Pennsylvania

Background: The ongoing efforts of HCV elimination with HCV screening and antiviral therapies have led to a significant increase in HCV-cured patients who are still at risk of HCC and, therefore, need HCC risk stratification. We previously demonstrated the feasibility of etiology-adjusted HCC risk prediction in MASLD by combining an etiology-agnostic Prognostic Liver Secretome signature (PLSec) with a MASLD-specific "plug-in" biomarker panel. In this study, we aimed to develop a similar integrative serum biomarker-based HCC risk score tailored to HCV-cured patients with cirrhosis. **Methods:** We previously defined a hepatic transcriptomic signature associated with HCC risk in 134 HCV-and HCC-cured patients, which was converted into a panel of candidate serum proteins using a computational pipeline (TexSEC) for non-invasive HCC risk assessment. Further optimization of the serum protein panel and validation were conducted in a prospective statewide Texas HCC Consortium (THCCC) cirrhosis cohort on semi-annual HCC screening, which was split into optimization and validation sets (n=121 for each). The optimized panel (PLSec-HCVcure) was integrated with the etiology-agnostic PLSec and clinical variables to generate an etiology-adjusted PLSec-HCVcure (etPLSec-HCVcure), which was subsequently evaluated in the validation set. The HCC risk association was assessed using the sub-distribution hazard ratio (sHR) regarding death and transplantation as competing events. **Results:** Six candidate proteins were computationally identified based on the transcriptomic signature and TexSEC analysis. In the optimization set, a 3-protein PLSec-HCVcure was defined based on association of each protein's abundance with incident HCC. In the validation set, the optimized PLSec-HCVcure identified 38 (31%) patients with high-risk prediction and 83 (69%) patients with low-risk prediction, with annual HCC incidence rates of 4.1% and 1.5%, respectively. A high-risk prediction was associated with incident HCC (sHR, 2.99; 95% CI, 1.05 – 8.51). Time-dependent area under receiver operating characteristics curve at 5 years was 0.72 (95% CI, 0.56-0.87). A high-risk prediction by the etPLSec-HCVcure, i.e., integration of PLSec, PLSec-HCVcure, and clinical variables) was associated with incident HCC (sHR, 6.56; 95% CI, 1.78 – 24.2). **Conclusion:** Our results suggest that etiology-adjusted HCC risk stratification is feasible for HCV-cured patients with cirrhosis and warrants further validation of the integrative score in independent cohorts.

Disclosures: Hiroaki Kanzaki: Gilead Sciences, Inc.: Speaking and Teaching, Naoto Fujiwara: Nothing to Disclose, Courtney Katz: Nothing to Disclose, Sumit Mishra: Nothing to Disclose, Subhojit Paul: Nothing to Disclose, Soumith Paritala: Nothing to Disclose, Michael Gonzalez: Nothing to Disclose, Lisa Quirk: Nothing to Disclose, Sneha Deodhar: Nothing to Disclose, Pratibha Selvakumar: Nothing to Disclose, Indu Raman: Nothing to Disclose, Prithvi Raj: Nothing to Disclose, Atsushi Ono: Nothing to Disclose, Andrea Branch: Gilead Sciences: Research, Pfizer: Research, Chung-Feng Huang: Gilead Sience: Grant/Research Support, Ming-Lun Yeh: Nothing to Disclose, Ming-Lung Yu: Abbvie, Gilead and Roche diagnostics.: Grant/Research Support, Abbott, Abbvie, Gilead, Roche and Roche diagnostics: Consultant, Abbvie, BMS, Gilead, Roche and Roche diagnostics: Speaking and Teaching, Raymond Chung: Nothing to Disclose, Angelo Sangiovanni: Nothing to Disclose, Massimo Iavarone: Nothing to Disclose, Massimo Colombo: Nothing to Disclose, Hitomi Sezaki: Nothing to Disclose, Masahiro Kobayashi: Nothing to Disclose, Hiromitsu Kumada: Nothing to Disclose, Kiyoshi Hasegawa: Nothing to Disclose, Ryosuke Tateishi: Nothing to Disclose, Saira Khaderi: Nothing to Disclose, Sumeet Asrani: Nothing to Disclose, Fasiha Kanwal: Nothing to Disclose, Hashem El-Serag: Nothing to Disclose, Jorge Marrero: Nothing to Disclose, Amit Singal: Consultant relationship with AstraZeneca; Has not ended; Consultant relationship with Sirtex; Has not ended; Consultant relationship with Boston Scientific; Has not ended; Consultant relationship with Bayer; Has not ended; Consultant relationship with Eisai; Has not ended; Consultant relationship with FujiFilm Medical Sciences; Has not ended; Consultant relationship with Elevar; Has not ended; Consultant relationship with Exact Sciences; Has not ended; Consultant relationship with Glycotest; Has not

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ended; Consultant relationship with Exelixis; Has not ended; Consultant relationship with Merck; Has not ended; Consultant relationship with Genentech; Has not ended; Consultant relationship with HistoSonics; Has not ended, Yujin Hoshida: Advisor relationship with Espervita Therapeutics; Has not ended; Advisor relationship with Helio Genomics; Has not ended; Stock - privately held company relationship with Alentis Therapeutics; Has not ended; Stock â€“ privately held company relationship with Espervita Therapeutics; Has not ended; Advisor relationship with Elevar Therapeutics; Has ended; Advisor relationship with Roche Diagnostics; Has ended

0129 | THE LIVER TRANSPLANT COMORBIDITY INDEX (LTCI) : A COMPOSITE INDEX OF AMBULATORY PRE-LT FACTORS TO IDENTIFY PATIENTS AT INCREASED RISK OF POST-LT MORTALITY

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Background: Frailty is strongly associated with mortality after LT. However, national society guidance statements do not recommend that frailty be used as the sole determinant of LT candidacy, as some frail patients still achieve acceptable post-LT outcomes. We aimed to develop a composite index, the Liver Transplant Comorbidity Index, consisting of a combination of comorbidities including frailty, to identify patients who are at highest risk of longer-term (3-year) death after LT. **Methods:** This 8-center prospective Functional Assessment in Liver Transplantation (FrAILT) Study included adults with cirrhosis awaiting LT *in the ambulatory setting* who received primary LT from 2012-22. Excluded were LDLT recipients. The primary predictor was the pre-LT ambulatory frailty assessment [by Liver Frailty Index (LFI)] closest to LT; “frail”= LFI≥4.5. Candidate variables were demographics, labs, ascites, HE, HCC, and non-hepatic comorbidities. Best subset selection with Cox proportional hazards regression identified variable subsets that predicted post-LT death at 3 years. The final model balanced relative model fit (by Aikaike Information Criterion) with clinical pragmatism. **Results:** Of 1,472 LT recipients: 290 (20%) were frail. Demographics were: 31% women, 43% HCC, 21% MASLD, 23% ARLD, median age 60y (IQR 54-65). Median *ambulatory* MELD 3.0 was 17 (IQR 11-22). Rates of hepatic/non-hepatic comorbidities: 12% refractory ascites, 54% HE, 45% HTN, 34% DM, and 6% CAD. Three-year post-LT mortality was higher in frail vs. non-frail pts (13 vs. 8%; p=0.03). Using best subset selection and expert consensus, we developed the LT Comorbidity Index (LTCI) with 5 variables (Figure) [range 0-19]. Using cut points based on time-dependent ROC analysis (≥7) and clinical judgment (≥10), we categorized pts into low- (0-6; 70%), medium- (7-9; 21%), and high-risk (≥10; 9%) for post-LT death at 3y. The LT Comorbidity Index was associated with 3y post-LT death (Figure). Pts in mod- and high-risk groups had 2.03 (95%CI 1.34-3.09) and 2.99 (95% 1.84-4.83) times the risk of mortality, respectively. In multivariable analysis, after adjusting for donor factors (age, DCD), both moderate- (HR 2.23; 95% CI 1.46-3.40; p<0.001) and high-risk (HR 2.78; 95% CI 1.67-4.64; p<0.001) status were associated with post-LT mortality at 3 years. **Conclusion:** The LTCI, comprising 5 pre-LT clinical parameters, effectively identifies patients at increased risk of post-LT mortality at 3 years. By integrating frailty in the context of other adverse risk factors, LTCI can help providers better weigh the relative risks and benefits of LT to support informed and personalized assessments of LT candidates.

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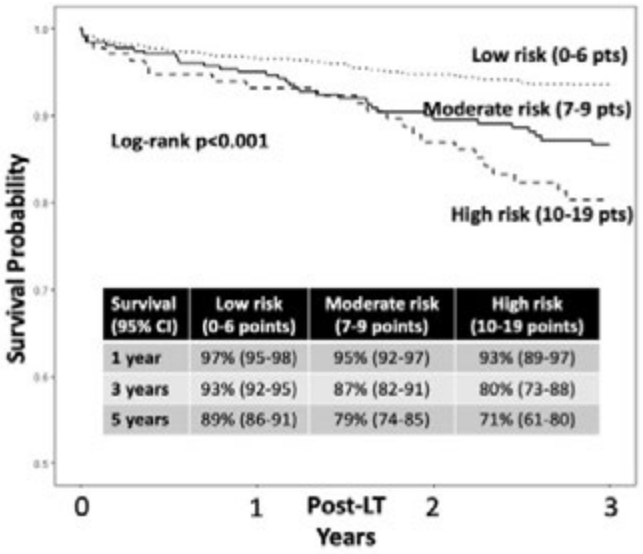
Table. Components and assigned points in the LT Comorbidity Index

Factor	Points
Coronary artery disease	6
Frail (LFI ≥ 4.5)	5
HCC	5
Cr ≥ 1.0 mg/dL *or* on dialysis	3
Diabetes	1

Figure. Kaplan-Meier survival curves of 1,472 LT recipients by categories of the LT Comorbidity Index (LTCI).



Survival (95% CI)	Low risk (0-6 points)	Moderate risk (7-9 points)	High risk (10-19 points)
1 year	97% (95-98)	95% (92-97)	93% (89-97)
3 years	93% (92-95)	87% (82-91)	80% (73-88)
5 years	89% (86-91)	79% (74-85)	71% (61-80)

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0130 | EFFECTIVENESS OF GLECAPREVIR/PIBRENTASVIR FOR 8 WEEKS IN PEOPLE TAKING ANTIPSYCHOTICS, BUPRENORPHINE/NALOXONE, OR ILLICIT DRUGS

tracy gowan[1] Marc Rizzo[2] Arsalan Shah[2] Andrew Seaman[3] Jeanne Gripshover[4] Wendy Chen[4] Jatinder Kaur[5] Yanna Song[5] Barbra Cave[4]

[1]University of Louisville Health, [2]Central City Concern, [3]Central City Concern and Oregon Health & Science University, [4]AbbVie, Inc, [5]AbbVie, Inc.

Background: Hepatitis C virus (HCV) infection disproportionately affects individuals impacted by substance use disorder and psychiatric co-morbidities. People who use drugs (PWUD) may have limited access to HCV treatment so efforts to initiate early treatment are critical. However, providers may be hesitant to initiate direct-acting antiviral therapy due to efficacy concerns in the setting of certain medications and/or specific illicit substances. **Methods:** A retrospective analysis was conducted with the Kentucky Hepatitis Academic Mentorship Program (KHAMP) registry and Central City Concern HCV Elimination Program (CCC-HEP) database. Primary objective: estimate the rate of sustained virologic response (SVR12) for people treated with 8 weeks of glecaprevir/pibrentasvir (G/P) who had reported substance use in the past 12 months. Secondary objectives: 1) describe observed sustained virologic response (SVR12) among subgroups of PWUD taking illicit substances and 2) describe the observed SVR12 in active/recent and non- or former PWUD, taking antipsychotics (e.g., aripiprazole or quetiapine), and/or buprenorphine/naloxone. Active/recent substance use was determined by case report or enrollment or referral in a drug treatment program. **Results:** A total of 627 cases in KHAMP and 1349 in CCC-HEP cases were available for analysis, where 545 in KHAMP and 776 in CCC-HEP were PWUD. KHAMP PWUD were 39.9 (8.6) years old, and 50% male while non- or former PWUD were 40.3 (12.3) years old, and 48.8% male. CCC-HEP PWUD were 49.3 (12.1) years old, and 68.1% male while non- or former PWUD were 49.3 (12.8) years old, and 69% male. In the full analysis set (FAS), PWUD were 45.0 (11.9) years old, and 60.5% male while non-or former PWUD were 18.2 (13.1) years old and 66.5% male. Table 1 displays the results of observed SVR12, virologic failure and loss to follow-up for each sub-group. The overall observed SVR12 rate was 94.5% (396/419) in the FAS for non- or former PWUD and 91.2% (858/941) for PWUD. **Conclusion:** PWUD with active/recent substance use treated with 8 weeks of G/P

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while taking aripiprazole, quetiapine, and/or buprenorphine/ achieve high rates of observed SVR12. G/P is effective in active/recent PWUD and non- or former PWUD taking quetiapine, aripiprazole, and/or buprenorphine/naltrexone.

Table 1.

		Active/Recent PWUD			Non- or Former PWUD		
		CCC-HEP	KHAMP	FAS	CCC-HEP	KHAMP	FAS
Aripiprazole	SVR12	59/63 (93.6%)	5/5 (100%)	64/68(94.1%)	34/36 (94.4%)	1/1 (100%)	35/37 (94.6%)
	Virologic Failure	4	0	4	2	0	2
	LTFU	27	4	31	15	0	15
Quetiapine	SVR12	67/72 (93.0%)	29/30 (96.7%)	96/102 (94.1%)	53/54 (98.1%)	2/2 (100%)	55/56 (98.2%)
	Virologic Failure	5	1	6	1	0	1
	LTFU	25	14	39	19	1	20
Buprenorphine/naloxone	SVR12	118/133 (88.7%)	40/42 (95.2%)	158/175 (90.3%)	84/92 (91.3%)	8/8 (100%)	92/100 (92%)
	Virologic Failure	15	2	17	8	0	8
	LTFU	44	12	56	36	1	37
Opioid Use	SVR12	281/312 (90.1%)	149/156 (95.5%)	430/468(91.9%)			
	Virologic Failure	31	7	38			
	LTFU	141	54	195			
Methamphetamine	SVR12	21/23 (91.3%)	7/8 (87.5%)	28/31(90.3%)			
	Virologic Failure	2	1	3			
	LTFU	5	2	7			
Cocaine Use	SVR12	27/32 (84.4%)	2/2 (100%)	29/34 (85.3%)			
	Virologic Failure	5	0	5			
	LTFU	9	0	9			
Stimulant Use	SVR12	223/254 (87.8%)	6/6 (100%)	229/260 (88.1%)			
	Virologic Failure	31	0	31			
	LTFU	108	1	109			
Alcohol Use	SVR12	133/156 (85.3%)	11/11 (100%)	144/167(86.2%)			
	Virologic Failure	23	0	23			
	LTFU	70	7	77			

Note: FAS= Full analysis set. SVR12= observed rate of sustained virologic response 12 weeks after last dose. The observed cases are those with an SVR12 lab result. Virologic failure are those who had viral breakthrough during treatment or at the time SVR12 labs were collected. LTFU= Lost to follow-up.

Disclosures: tracy gowan: Nothing to Disclose, Marc Rizzo: Nothing to Disclose, Arsalan Shah: AbbVie Inc: Speaking and Teaching, Gilead: Speaking and Teaching, Andrew Seaman: Abbvie Pharmaceuticals: Investigator initiated research, Jeanne Gripshover: Nothing to Disclose, Wendy Chen: AbbVie: Employee, Jatinder Kaur: AbbVie: Employee, Yanna Song: Nothing to Disclose, Barbra Cave: AbbVie: Employee

0131 | CRYOPRESERVED HUMAN ALTERNATIVELY ACTIVATED MACROPHAGES PROMOTE THE RESOLUTION OF ACETAMINOPHEN-INDUCED LIVER INJURY

Maria Elena Candela[1] Melisande Addison[1] Rhona Aird[1] Tak Yung Man[1] Anna Drape[2] Mark Barnett[3] Donna Mitchell[2] Colin McLean[2] Neil McGowan[2] Marc Leighton Turner[2] James Dear[4] Stuart Forbes[1]

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Background: Acute liver failure (ALF) has a high mortality. The most common cause in the Western world is an overdose of acetaminophen (APAP). The standard treatment, N-acetylcysteine, is limited by a narrow therapeutic window and this limitation underscores the urgent need for innovative treatments. Advancements in cellular therapy, particularly using macrophages, have shown promising results in modulating inflammatory responses and facilitating organ repair. This study investigated the therapeutic potential of cryopreserved human alternatively activated macrophages (hAAMs), derived from universal blood group O donors, as a novel treatment strategy for ALF. **Methods:** The study aimed to evaluate the efficacy and safety of cryopreserved hAAMs. Initially, CD14+ monocytes were stimulated into an anti-inflammatory phenotype, cryopreserved, and upon thawing, assessed for viability (Trypan Blue exclusion test), functional integrity (CD163 and CD169 expression), and phagocytic activity. Their therapeutic efficacy was tested in an APAP mouse model where the cells were injected 16 hours after APAP, when the necrosis is already established, by evaluating the reduction in hepatic necrosis, modulation of inflammatory responses (Ly6G expression – marker of monocytes, granulocytes and neutrophils), and enhancement of tissue regeneration (Ki67 expression). Additionally, hAAM safety was assessed by monitoring for adverse effects and conducting organ and blood analyses. **Results:** Cryopreserved hAAMs retained over 87% viability v fresh cells (95%), key phenotypic markers such as CD163 and CD169 (81%) v fresh cells (88%) and robust phagocytic capabilities when compared with naïve macrophages. *In vivo*, the highest dose of cells (1*10^6) significantly reduced hepatic necrosis when compared with the vehicle control group (Figure A), confirmed by a significant reduction in serum HMGB1 concentration (Figure B). The highest dose of cryopreserved hAAM also modulated the inflammatory response in both male and female mice, as evidenced by a significant decrease of the inflammatory markers Ly6G (Figure C), and enhanced hepatocellular proliferation, evidenced by elevated Ki-67 levels, when compared to the vehicle control group (Figure D). Safety assessments revealed no adverse

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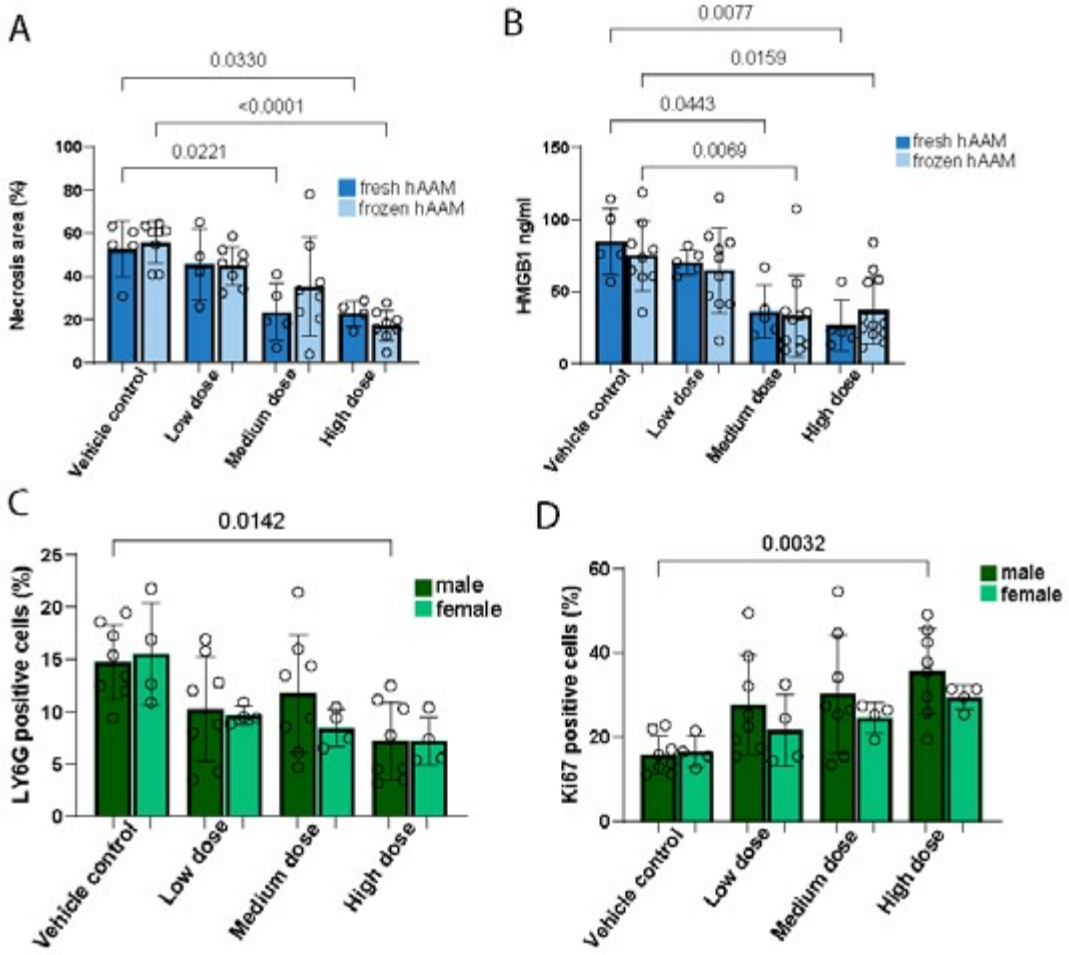
effects, normal safety blood results, and histopathological examination showed no tissue damage in healthy mice (N=6). **Conclusion:** Cryopreserved hAAMs effectively reduced liver necrosis, modulated immune responses, and enhanced regeneration in ALF. A phase 1 clinical trial is now recruiting to determine the safety and tolerability of cryopreserved hAAMs in patients with APAP-induced hepatotoxicity (ISRCTN number: ISRCTN12637839).



(A) Necrosis quantification of liver tissues from APAP mice, injected with vehicle control or 3 different doses of fresh or thawed hAAMs (low dose (0.25x10^6 cells), medium dose (0.5x10^6 cells), and high dose (1x10^6 cells). (B) HMGB1 analysis of serum from APAP mice treated with vehicle control or the 3 doses of fresh and thawed hAAMs. C) Quantification of Ly6G immunostaining of liver tissues from APAP male and female mice, injected with vehicle control or 3 different doses of thawed hAAMs. (D) Quantification of Ki67 immunostaining of liver tissues from APAP mice, injected with vehicle control or 3 different doses of thawed hAAMs. Mean ± SD, n = 4-8; comparison was done with one-way ANOVA test, significant diff. among means ($P < 0.05$).

Disclosures: Maria Elena Candela: Nothing to Disclose, Melisande Addison: Nothing to Disclose, Rhona Aird: Nothing to Disclose, Tak Yung Man: Nothing to Disclose, Anna Drape: Nothing to Disclose, Mark Barnett: Nothing to Disclose, Donna Mitchell: Nothing to Disclose, Colin McLean: Nothing to Disclose, Neil McGowan: Nothing to Disclose, Marc Leighton Turner: Nothing to Disclose, James Dear: Nothing to Disclose, Stuart Forbes: Resolution Therapeutics: Founder

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0132 | DNA METHYLATION OF TUMOR TISSUES AND CIRCULATING TUMOR DNA IN EARLY DETECTION OF HEPATOCELLULAR CARCINOMA ★

Siyu Fu[1] Ruben Boers[1] Joachim Boers[1] Michael Doukas[1] Saskia Wilting[1] Joost Gribnau[1] Dave Sprengers[1] Robert De Man[1] Jose Debes[2] Andre Boonstra[3]

[1]Erasmus MC, [2]University of Minnesota, [3]Erasmus University Medical Center

Background: Hepatocellular carcinoma (HCC) represents more than 90% of primary liver cancers, with an overall 5-year survival rate of 19.6%. In clinical practice, alpha-fetoprotein (AFP) and liver ultrasound are applied in HCC surveillance for early detection and cure implementation. However, these methods lack sensitivity and better non-invasive biomarkers are urgently needed for early-stage detection of HCC. **Methods:** We performed whole genome methylated DNA sequencing (MeD-seq), covering more than 50% CpG sites throughout the genome, to explore candidate DNA methylation markers (DMMs) in genomic DNA from 46 frozen liver tissues (6 cirrhotic HCC, 8 non-cirrhotic HCC, 15 cirrhosis, 10 non-cirrhotic, and 7 hepatic benign lesions) and 42 cell-free DNA (cfDNA) from blood (10 early-stage HCC, 10 late-stage HCC, 12 cirrhosis, and 10 healthy individuals). All samples were from individuals with alcohol-related liver disease. MeD-seq derived DMMs were validated using quantitative methylation-specific PCR (qMSP) in liver tissues (n=161) and blood (n=45). Data processing was carried out using DEseq2 for MeD-seq, and the Mann–Whitney U test for comparing DNA methylation levels in qMSP data. **Results:** MeD-seq analysis on liver tissues demonstrated a high number of hypermethylated genes in both non-cirrhotic and cirrhotic HCC tissues compared to controls. 10 MeD-seq derived DMMs that were validated by qMSP, including *FOXD3* and *SPAG6*, showed good performance in discriminating cirrhotic HCC from cirrhotic liver tissue (n=161). Evaluation of these tissue-derived DMMs in cfDNA showed that in comparison to cirrhotic controls (n=15), altered DMM methylation levels in blood were only observed for late-stage HCC, but not for early-stage HCC by qMSP (n=15 each group). Finally, MeD-seq on ctDNA from plasma of 42 patients showed that patients with liver disease have higher DNA methylation patterns as compared to healthy individuals. However, no differentially methylated DMMs were found in early-stage HCC compared to late-stage HCC and cirrhosis. **Conclusion:** Extensive methylation DNA sequencing and validation in well-defined cohorts of liver tissue from alcohol-related liver diseases demonstrated DNA methylation patterns that discriminated cirrhotic HCC from cirrhosis, and non-cirrhotic HCC from benign hepatic lesions. However, methylation levels in ctDNA from blood differed from controls in late-stage HCC, but not early-stage HCC, suggesting that current sensitivity limits the application of DNA methylation markers as non-invasive biomarkers for early-stage HCC.

Disclosures: Siyu Fu: Nothing to Disclose, Ruben Boers: Nothing to Disclose, Joachim Boers: Nothing to Disclose, Michael Doukas: Nothing to Disclose, Saskia Wilting: Nothing to Disclose, Joost Gribnau: Nothing to Disclose, Dave Sprengers: Nothing to Disclose, Robert De Man: roche diagnostics: Grant/Research Support, Jose Debes: Nothing to Disclose, Andre Boonstra: Gilead: Grant/Research Support, Janssen Pharma: Grant/Research Support, GSK: Grant/Research Support, Fujirebio: Grant/Research Support

0133 | QUANTITATIVE MRCP METRICS HAVE UTILITY IN ASSESSING CHANGES IN BILIARY TREE HEALTH IN PSC PATIENTS: A TEN-YEAR EVALUATION

Kartik Jhaveri[1] Sarah Finnegan[2] Amy Herlihy[2] Elizabeth Shumbayawonda[2] Tom Davis[2] Aliya Gulamhusein[1] Gideon Hirschfield[3]

[1]University of Toronto, [2]Perspectum Ltd., [3]Toronto General Hospital

Background: Progression of large duct disease is a hallmark of the natural history of PSC. Lack of objective biomarkers hampers clinical surveillance of cholangiopathy and development of surrogate endpoints for clinical trials. Clinical guidelines have noted that quantitative MRCP (MRCP+) may have utility in objectively monitoring PSC. Here, we perform a natural history study examining the change in quantitative biliary metrics over time using quantitative MRCP (MRCP+) in adults followed over a 10-year period. **Methods:** Patients with PSC undergoing non-contrast 3D MRCP as part of standard-of-care were enrolled retrospectively from a single centre. All patients had at least two follow-up MRCP scans (in addition to a baseline scan) over the 10-year follow-up period. Linear (LMM) and generalised (GLMM) linear mixed effects models were used to assess the temporal variation in MRCP+ metrics. Random slopes and intercepts were used for each, with years since the baseline scan as the predictor, controlling for repeated measures and participant variation. **Results:** Retrospective MRCP images were

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evaluated from 134 adult patients (54% male) recruited from a single center. Results are indicative of a significant average percentage increase per annum in the number of ducts (4.2%, β=1.04, p<0.001), number of strictures (5.1%, β=1.05, p<0.001), number of dilatations (6.7%, β=1.05, p<0.001), and number of ducts with a stricture or dilatation (5.4%, β=1.05, p<0.001) from baseline. There was also a 5.0% (p<0.001) increase in both the length of strictures and dilatations over the follow-up period from baseline, respectively. **Conclusion:** Quantitative MRCP metrics have utility to assess changes in the biliary tree resulting from disease progression over time.

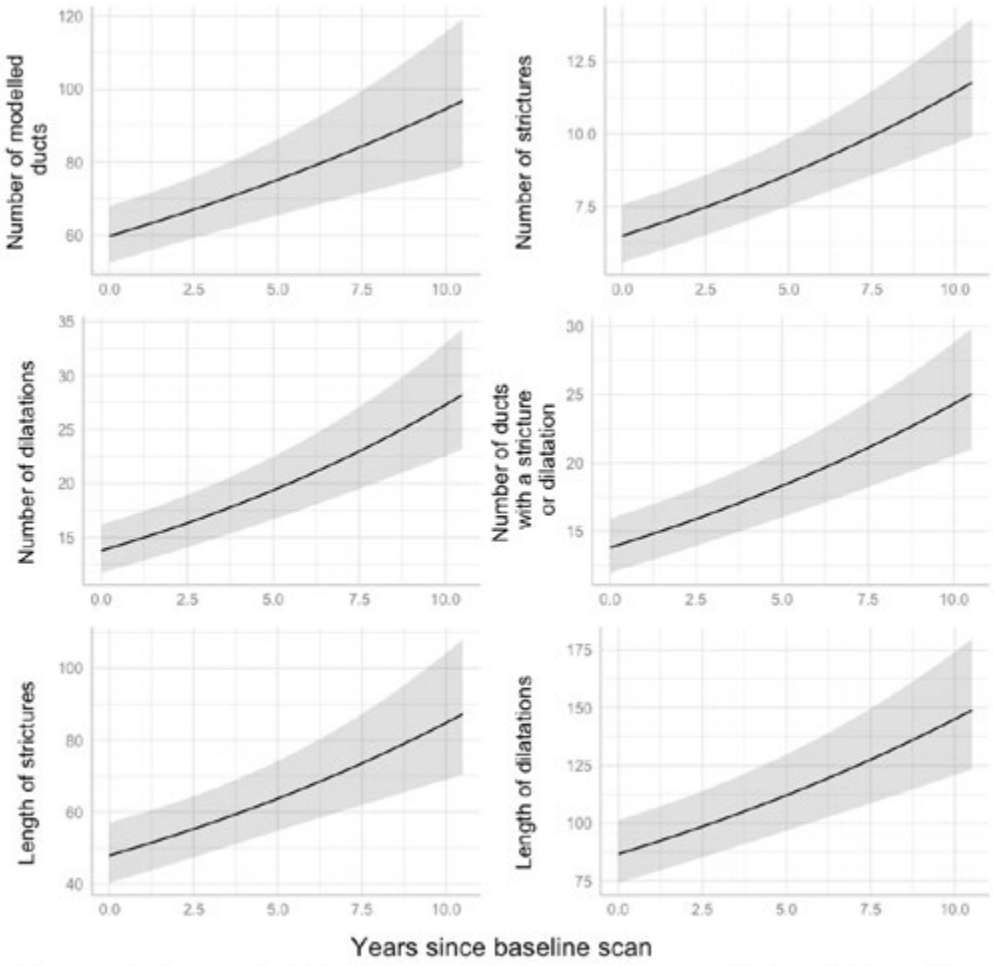

Figure: Change in MRCP+ metrics in adults with PSC followed over a 10-year period

Disclosures: Kartik Jhaveri: Nothing to Disclose, Sarah Finnegan: Nothing to Disclose, Amy Herlihy: Perspectum Ltd: Employee, Elizabeth Shumbayawonda: Perspectum Ltd.: Employee, Tom Davis: Nothing to Disclose, Aliya Gulamhusein: Nothing to Disclose, Gideon Hirschfield: Consultant relationship with Mirum; Has not ended; Consultant relationship with Advanz; Has not ended; Consultant relationship with Chemomab; Has not ended; Consultant relationship with Gilead; Has not ended; Consultant relationship with Kowa; Has not ended; Consultant relationship with Intercept; Has not ended; Consultant relationship with Pliant; Has not ended; Consultant relationship with Falk; Has not ended; Consultant relationship with GSK; Has not ended; Consultant relationship with Ipsen; Has not ended; Consultant relationship with CymaBay; Has not ended

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0134 | SINGLE CELL FIXED RNA PROFILING REVEALS THE INTERACTION OF MACROPHAGE AND HSC VIA SEMAPHORIN 4D-PLXNB2 TO PROMOTE LIVER FIBROSIS ◆

Duc Pham[1] Thi Thanh Thuy Le[2] Hoang Hai[3] Thi Ha Nguyen[2] Norifumi Kawada[2]

[1]Department of Hepatology, Osaka Metropolitan University, [2]Osaka Metropolitan University, [3]Osaka Metropolitan Universiry

Background: Single Cell Fixed RNA Profiling (FLEX) is a novel technology that captures RNA expression in single cells from frozen tissues. Herein, we applied FLEX in the murine model of cirrhosis progression and regression to discover novel targets for anti-fibrotic therapy. **Methods:** Mice were administered for Thioacetamide (TAA) i.p injection at the escalation dose from 50 to 400 mg/kg for 10 weeks, while control mice received saline. Liver fibrosis regression was assessed after termination of TAA administration for 2 weeks. Frozen mouse liver tissues were fixed, then dissociated into single cells (sc), and performed scRNAseq following the 10X genomic protocol. Multiplex flow cytometry, immunoblotting, immunohistochemistry, and proteome cytokine array were used for molecular analysis. **Results:** Using FLEX technology, whole liver cells were preserved and analyzed at single cell resolution and classified into 10 major cell types under the transcriptome of ~40,000 cells which were profiled, integrated, and annotated using signatures of known cell lineage markers. Cellular composition analysis revealed that the number of hepatocytes and LSECs reduced 30-50% while macrophages increased 200% in cirrhotic livers compared to intact liver. Macrophages were clustered andannotated into quiescent Kupffer cells (KUPs), activated KUPs, monocyte-derived macrophages (Momacs), and proliferating macrophages. Gene set enrichment and flow cytometry analysis revealed that the Folr2+ macrophages (Cd45+F4/80+Cd11b-MHCII+Folr2+) denoted quiescent KUPs and were reduced in cirrhosis, while regained in regression phase. They exhibited higher activity of phagocytosis, endocytosis, and expressed antioxidative genes such as Fabp1, Cat, Aldob, and Gsta3 compared with those from controls. Activated KUPs, which were increased in cirrhosis, loss of Folr2 (Cd45+F4/80+Cd11b-MHCII+Folr2-) and secreted pro-inflammatory cytokines and chemokines similarly to MoMacs (Cd45+F4/80-Cd11b+Ly6G-) including MCP-1, Cxcl10, Ccl12, Gdf15, Ccl6, Serpin E1, Tnfa, Il1b, Il10, Osteopontin, and Semaphorin 4D (Sema4d). Interaction analysis showed that the binding of Sema4d to receptor Plexin B1/2 on HSCs occurred in cirrhotic livers but absent in both controls and regression phase. In human and mouse cirrhotic livers, Sema4d+ cells significantly accumulated and accompanied with the upregulation of their receptor Plexin B1/2 in activated HSC. *In vitro*, recombinant human SEMA4D dose-dependently induced type I collagen synthesis in HHSteCs. Neutralization of Sema4d by tail vein injection of VX15/2503 antibody attenuated the development of liver cirrhosis *in vivo* induced by TAA**. Conclusion:** The present work dissected unanticipated aspects of molecular and cellular basics of liver cirrhosis progression/regression and revealed Sema4d as novel targets for antifibrotic therapy.

Disclosures: Duc Pham: Nothing to Disclose, Thi Thanh Thuy Le: Nothing to Disclose, Hoang Hai: Nothing to Disclose, Thi Ha Nguyen: Nothing to Disclose, Norifumi Kawada: Nothing to Disclose

0135 | MULTIMODAL SINGLE-NUCLEI ATLAS OF MASLD PROGRESSION IDENTIFIES A LINK TO INSULIN RESISTANCE

Laura Pikkupeura[1] Rikard Fred[1] Malte Thodberg[1] Thomas Gade Koefoed[1] Benedicte Schultz Kapel[1] Kata Krizic[1] Shanshan He[1] Mikkel Parsberg Werge[2] Sofie Boesgaard Neestrup Hansen[2] Cesar Prada-Medina[3] Elisabeth Douglas Galsgaard[4] Lise Lotte Gluud[2] Torben Hansen[1]

[1]Novo Nordisk Foundation Center for Basic Metabolic Research, University of Copenhagen, Denmark, [2]Gastro Unit, Copenhagen University Hospital–Hvidovre, Copenhagen, Denmark, [3]AI & Digital Research, Research & Early Development, Novo Nordisk Research Centre Oxford, UK, [4]Research & Early Development, Novo Nordisk A/S, Denmark

Background: The course of metabolic dysfunction-associated steatotic liver disease (MASLD) is highly heterogeneous. There is a close link between MASLD and type 2 diabetes (T2DM), which could reflect alterations in glucose production as well as clearance. Hepatic insulin resistance has been associated with hepatocyte steatosis and inflammation. The cellular and genetic underpinnings for disease heterogeneity are poorly characterised. We hypothesised that joined profiling of gene expression and chromatin accessibility at single cell resolution in patients with MASLD and increasing fibrosis would elucidate the distinct cell populations and

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processes associated with disease progression. **Methods:** We therefore generated a large multi-modal single-nuclei atlas of gene regulation with paired snATAC-Seq and snRNA-Seq (10X Multiome) in percutaneous or transjugular liver biopsies. Our analyses included 300.000 cells from 10 healthy controls and 48 patients with MASLD and F0 to F4 fibrosis (F0 n =9, F1 n= 10, F2 n = 10, F3 n=9, and F4 n=10). Based on the analyses, we evaluated disease progression in terms of changes in cell type abundance, transcription and chromatin landscape. The multimodal RNA expression and chromatin accessibility data allowed us to map the activity and interactions of promoters and enhancers in the individual cell types, which were integrated with genome-wide association studies (GWASs) of MASLD and T2DM related traits. **Results:** Our analyses showed that hepatocytes were most affected by MASLD progression and identified a disease progression gradient perpendicular to the porto-central zonation gradient. In particular, we identified a MASLD-associated subpopulation of hepatocytes that were not present in the healthy controls. These MASLD-associated hepatocytes form a bridge between hepatocytes and cholangiocytes and are enriched for tissue regeneration associated transcription factor motifs and pathways, including the Hippo-YAP pathway, as well as pathways linked to hepatocyte senescence and insulin resistance. Furthermore, genetic enrichment analysis revealed that the genetic risk of T2DM is enriched in the accessible chromatin of the MASLD-associated hepatocyte subpopulation. **Conclusion:** Taken together, our atlas provides a unique resource to study cellular and genetic underpinnings of MASLD progression and highlights the changes in hepatocyte composition underlying heterogeneity among MASLD patients.

Disclosures: Laura Pikkupeura: Nothing to Disclose, Rikard Fred: Nothing to Disclose, Malte Thodberg: Nothing to Disclose, Thomas Gade Koefoed: Nothing to Disclose, Benedicte Schultz Kapel: Novo Nordisk A/S: PhD Student, Kata Krizic: Nothing to Disclose, Shanshan He: Nothing to Disclose, Mikkel Parsberg Werge: Nothing to Disclose, Sofie Boesgaard Neestrup Hansen: Nothing to Disclose, Cesar Prada-Medina: Novo Nordisk: Employee, Elisabeth Douglas Galsgaard: Nothing to Disclose, Lise Lotte Gluud: Nothing to Disclose, Torben Hansen: Novo Nordisk: research funding

0136 | CORONARY ARTERY DISEASE RISK AFTER LIVER TRANSPLANTATION IS 2-FOLD HIGHER THAN THE GENERAL POPULATION: A NATIONWIDE SWEDISH COHORT STUDY OF 2925 PATIENTS

Christian Lewinter[1] *Linnea Widman*[2] *Ying Shang*[1] *Axel Wester*[1] *Rickard Strandberg*[1] *Hannes Hagström*[1]

[1]*The Karolinska Institute,* [2]*Karolinska*

Background: The risk of coronary artery disease (CAD) is increased in liver transplant (LT) recipients. But their risk of new-onset CAD has seldom been compared to the general population. It is also unclear if risk cardiovascular disease risk factors are feasible to predict future CAD in LT recipients. **Methods:** We designed a cohort study based on administrative data, identifying all LT recipients in the national Swedish patient registry between 1987 and 2020. Each patient was matched on age, gender, municipality and year of diagnosis with up to 10 controls from the general population. International classification of diseases codes versions 9 and 10 were used to identify liver disease aetiology and cardiovascular disease risk factors. New-onset CAD was a composite of myocardial infarction, revascularized CAD and angina events after liver transplantation.We used Cox regression to compare the incidence of CAD in LT recipients and controls, across subgroups of liver disease aetiologies and cardiovascular disease risk factors. **Results:** A total of 2925 LT recipients were identified, who matched 27,589 controls. Mean age was 54 years and 73% were men. At baseline, previous CAD, hypertension, diabetes, dyslipidaemia, obesity, chronic obstructive lung disease and chronic kidney disease were significantly more common in LT recipients as compared with controls. LT recipients had a more than two-fold higher relative risk of new-onset CAD as the general population; during a median follow-up of 8.0 years (HR, 2.21; 95% [CI]=1.98-2.47).Restricted to controls from the general population: hypertension, dyslipidaemia, diabetes, kidney disease, previous CAD and lung disease were all significantly associated with increased risk of new-onset CAD (Figure 1). In LT recipients, only kidney disease (HR=2.64; 95%CI=1.94-3.60) and previous CAD (HR=7.85; 95%CI=6.10-10.11) were significantly associated with CAD. Apart from the small subgroups of acute liver failure and metabolic dysfunction-associated steatotic liver disease (21 and 26), all the remaining liver aetiologies were strongly associated with new-onset CAD (Figure 1). **Conclusion:** Liver transplant recipients have a more than two-fold higher relative risk of new-onset CAD as compared with the general population independent of liver disease aetiology. Cardiovascular disease risk factors such as hypertension may be less feasible for CAD prediction in LT recipients.

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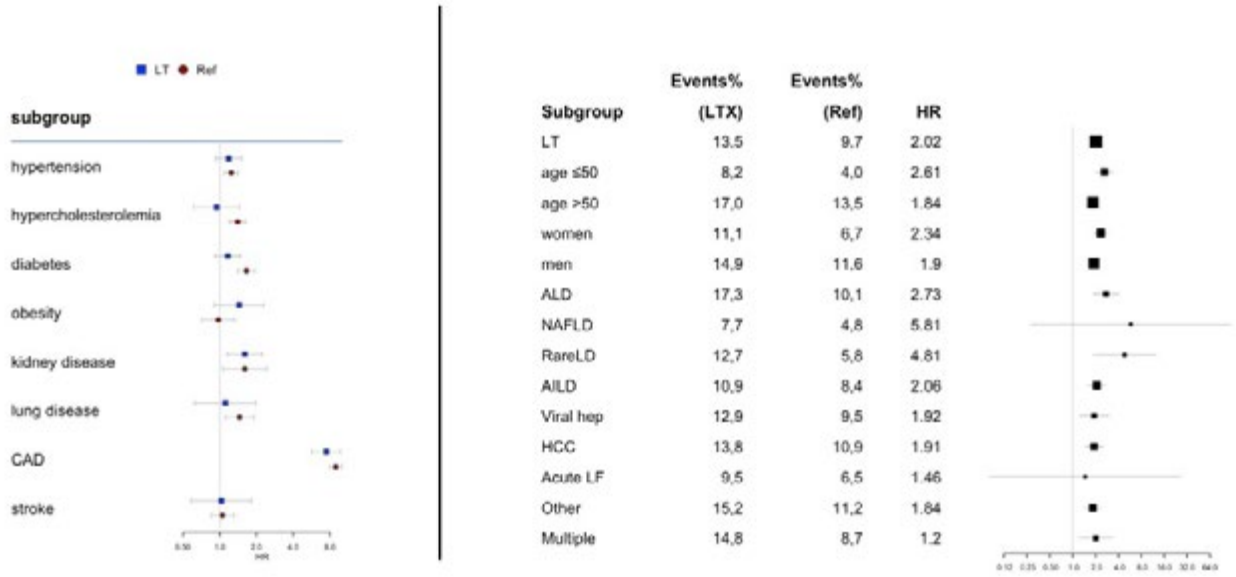

Figure 1 : Forest plots of the incidences of coronary artery disease (CAD) in subgroups of cardiovascular disease risk factors (left) and liver disease aetiologies (right). LT(X), liver transplantation; Ref, controls; HR, hazard ratio; ALD, alcoholic liver disease; NAFLD, metabolic dysfunction-associated steatotic liver disease: LD, liver disease; AILD, autoimmune liver disease; hep, hepatitis; HCC, hepatocellur carcinoma; LF, liver failure.

Disclosures: Christian Lewinter: Nothing to Disclose, Linnea Widman: Nothing to Disclose, Ying Shang: Nothing to Disclose, Axel Wester: Nothing to Disclose, Rickard Strandberg: Nothing to Disclose, Hannes Hagström: Nothing to Disclose

0138 | LIVER CANCER CHEMOPREVENTION BY TARGETING THE HISTAMINE RECEPTOR 2 AND USING PLSEC AS A BIOMARKER

Emilie Crouchet[1] Courtney Katz[2] Naoto Fujiwara[2] Frank Jühling[3] Marine Oudot[3] Sarah Durand[3] Antonio Saviano[4] Jiunn Song[5] Romain Martin[3] Nicolas Brignon[3] Fabio Giannone[4] Patrick Pessaux[4] Catherine Schuster[3] Laurent Mailly[3] Raymond Chung[5] Yujin Hoshida[2] Thomas Baumert[3]

[1]University of Strasbourg, Inserm UMR_S1110 (ITM), [2]UTSouthwestern Medical Center, Dallas, [3]University of Strasbourg, Inserm U1110, [4]Strasbourg University Hospitals, IHU, [5]MGH Harvard Medical School Boston, MA

Background: Given the unsatisfactory therapeutic approaches, there is a major unmet medical need for HCC chemoprevention to improve patient outcomes. The prognostic liver signature (PLS) and the blood-based prognostic liver secretome (PLSec) have been shown to robustly predict progression of liver disease, HCC risk and survival in cohorts with chronic liver disease (Fujiwara et al. Med 2021). Using an *in silico* screen followed by a cell-based assay modeling the PLS, we have identified the FDA-approved histamine 2 receptor (HRH2) antagonist nizatidine as a candidate compound for HCC chemoprevention (Crouchet et al. Nat Comm 2021). Here, we sought to evaluate HRH2 as a therapeutic target for chemoprevention and to investigate the PLSec as a clinically translatable biomarker for a clinical trial design. **Methods:** A *Hrh2* KO mouse model subjected to CDA-HFD was applied to study HRH2 as a genetic driver for MASH-induced HCC. Nizatidine was investigated in a human liver chimeric MASH mouse model. Liver fibrosis progression to HCC and the liquid biomarker PLSec were used as clinical candidate readouts. A US nationwide patient database was studied to investigate the association of the use of H2 blockers with liver fibrosis indices. **Results:** HRH2 was overexpressed and associated with survival in patient cohorts with viral, alcoholic and metabolic liver disease. The use of nizatidine and structurally similar ranitidine was associated with significantly lower FIB-4, APRI and NFS scores compared to nonuse in a US nationwide population analysis. HRH2 loss-of-function in a CDA-HFD mouse model for MASH progressing to HCC revealed a robust and significant effect of *Hrh2* KO on liver tumor burden. The HRH2 blocker nizatidine inhibited liver fibrosis progression in a human liver chimeric MASH mouse model without any detectable adverse effects. Moreover, macroscopic examination of humanized livers revealed reduced liver nodule formation in nizatidine-treated animals. Nizatidine treatment and improvement of liver disease was associated

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with a PLSec reversal associated with HCC risk in the serum of treated mice. **Conclusion:** HRH2 is a driver of hepatocarcinogenesis in liver disease. The HRH2 antagonist nizatidine is a candidate compound for HCC chemoprevention. The reversal of PLSec offers a simple non-invasive biomarker as a readout. Our results pave the way for clinical development of HRH2 inhibitors for HCC chemoprevention using PLSec as a clinical readout.

Disclosures: Emilie Crouchet: Nothing to Disclose, Courtney Katz: Nothing to Disclose, Naoto Fujiwara: Nothing to Disclose, Frank Jühling: Nothing to Disclose, Marine Oudot: Nothing to Disclose, Sarah Durand: Nothing to Disclose, Antonio Saviano: Nothing to Disclose, Jiunn Song: Nothing to Disclose, Romain Martin: Nothing to Disclose, Nicolas Brignon: Nothing to Disclose, Fabio Giannone: Nothing to Disclose, Patrick Pessaux: Nothing to Disclose, Catherine Schuster: Nothing to Disclose, Laurent Mailly: Nothing to Disclose, Raymond Chung: Nothing to Disclose, Yujin Hoshida: Advisor relationship with Espervita Therapeutics; Has not ended; Advisor relationship with Helio Genomics; Has not ended; Stock - privately held company relationship with Alentis Therapeutics; Has not ended; Stock â€“ privately held company relationship with Espervita Therapeutics; Has not ended; Advisor relationship with Elevar Therapeutics; Has ended; Advisor relationship with Roche Diagnostics; Has ended, Thomas Baumert: Nothing to Disclose

0139 | LONG-TERM BULEVIRTIDE MONOTHERAPY IN PATIENTS WITH HDV-RELATED COMPENSATED CIRRHOSIS: EFFECTIVENESS, SAFETY AND CLNICAL OUTCOMES FROM THE RETROSPECTIVE MULTICENTER EUROPEAN STUDY (SAVE-D)

Elisabetta Degasperi[1] Maria Paola Anolli[1] Mathias Jachs[2] Thomas Reiberger[2] Victor Deledinghen[3] Sophie Metivier[4] Gianpiero D'Offizzi[5] Francesco Di Maria[5] Christoph Schramm[6] Hartmut Schmidt[6] Caroline Zöllner[7] Frank Tacke[7] Christopher Dietz-Fricke[8] Heiner Wedemeyer[8] Margarita Papatheodoridi[9] George Papatheodoridis[9] Ivana Carey[10] Kosh Agarwal[10] Florian van Bömmel[11] Maurizia Brunetto[12] Mariana Cardoso[13] Gabriella Verucchi[14] Alessia Ciancio[15] Fabien Zoulim[16] Soo Aleman[17] Nasser Semmo[18] Alessandra Mangia[19] marie noelle HILLERET[20] Alessandro Loglio[21] Uta Merle[22] Teresa Antonia Santantonio[23] Nicola Coppola[24] Adriano Pellicelli[25] Bruno Roche[26] Xavier Causse[27] Louis D'Alteroche[28] Jérôme Dumortier[29] Nathalie Ganne Carrie[30] frederic HELUWAERT[31] Isabelle Hourmand Ollivier[32] Dominique Roulot[33] Alessandro Federico[34] Francesca Pileri[35] Monia Maracci[36] Matteo Tonnini[37] Jean Pierre Arpurt[38] Barange Karl[39] Eric Billaud[40] Stanislas pol[41] Anne Gervais[42] Anne Minello[43] Isabelle Rosa[44] Massimo Puoti[45] Pietro Lampertico[1]

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Background: Bulevirtide (BLV) has been approved for treatment of chronic hepatitis D virus (HDV) infection in Europe in 2020, however, long-term real-life effectiveness and safety data in large cohorts of HDV patients with cirrhosis treated beyond week 48 are lacking. **Methods:** Consecutive HDV patients with cirrhosis starting BLV 2 mg/day sc since September 2019 were included in a retrospective multicenter real-life European study (SAVE-D). Clinical, biochemical, virological features and liver-related events were collected. Virological (HDV-RNA undetectable or ≥2-log decline *vs.* baseline), biochemical (ALT <40 U/L), combined response (biochemical + virological) and adverse events were assessed. HDV-RNA was quantified locally. **Results:** 244 patients treated with BLV monotherapy up to 120 weeks [median follow-up: 92 (range 24-120) weeks] were included: age 49 (IQR 40-58) years, 61% men, ALT 80 (55-130) U/L, liver stiffness measurement (LSM) 18.3 (13.0-26.3) kPa, platelets 94 (67-145) x 10^3/mm^3, 95% CPT score A, 54% with varices, 10% HIV-positive, 15% with a history of ascites, 6% with active HCC, 92% on NUC. Baseline HDV-RNA and HBsAg levels were 5.4 (4.1-6.5) log IU/mL and 3.8 (3.4-4.1) log IU/mL, respectively. Virological responses at W48, W96, W120 were 65%, 79%, and 80%, respectively, while HDV RNA undetectability was achieved by 28%, 48%, and 52% of patients. Biochemical and combined responses were 61%, 64%, 67% and 44%, 54%, 56%, respectively. Patients with <1 log HDV-RNA decline *vs.* baseline declined from 22% at W24 to 10% at W96. AST, GGT, albumin, IgG and LSM values significantly improved throughout treatment (LSM baseline 18.3 kPa à 10.0 kPa W120). Lower baseline HDV-RNA was the only predictor of HDV-RNA undetectability at week 48 (HR 0.74; 95% CI 0.60-0.92, p=0.01). Bile acids significantly increased, 10% patients reported mild and transient pruritus, 3% injection site reactions. The W120 cumulative incidences of de-novo HCC and decompensation was 3.0% (95% CI 2-6%) and 2.8% (95% CI 1-5%), respectively. 14 patients underwent liver transplantation (HCC n=12; decompensation n=2) and 7 patients died due to BLV-unrelated causes. **Conclusion:** BLV 2 mg/day monotherapy up to 120 weeks was safe and effective in patients with HDV-related compensated cirrhosis. Virological and clinical responses continued to increase and only few patients experienced liver-related complications.

Disclosures: Elisabetta Degasperi: Gilead: Speaking and Teaching, Roche: Advisor, Abbvie: Speaking and Teaching, Maria Paola Anolli: Nothing to Disclose, Mathias Jachs: Nothing to Disclose, Thomas Reiberger: Nothing to Disclose, Victor Deledinghen: Nothing to Disclose, Sophie Metivier: Nothing to Disclose, Gianpiero D'Offizzi: Nothing to Disclose, Francesco Di Maria: Nothing to Disclose, Christoph Schramm: Nothing to Disclose, Hartmut Schmidt: Nothing to Disclose, Caroline Zöllner: Nothing to Disclose, Frank Tacke: Gilead: Grant/Research Support, MSD: Grant/Research Support, AstraZeneca: Grant/Research Support, Agomab: Grant/Research Support, NovoNordisk, Boehringer, Gilead, MSD, GSK: Consultant, Pfizer, Sanofi: Advisor, Christopher Dietz-Fricke: Gilead: Grant/Research Support, Gilead: travel support, Heiner Wedemeyer: Nothing to Disclose, Margarita Papatheodoridi: Nothing to Disclose, George Papatheodoridis: Abbvie: Advisor, Abbvie: Speaking and Teaching, Abbvie: Grant/Research Support, Astra Zeneca: Advisor, Astra Zeneca: Speaking and Teaching, Abbvie: Advisor, Abbvie: Speaking and Teaching, Astra Zeneca: Advisor, Astra Zeneca: Speaking and Teaching, Genesis: Advisor, Genesis: Speaking and Teaching, Gilead: Advisor, Gilead: Speaking and Teaching, Gilead: Grant/Research Support, GlaxoSmithKline: Advisor, Ipsen: Advisor, Ipsen: Speaking and Teaching, Novo Nordisk: Advisor, Novo Nordisk: Speaking and Teaching, Roche: Advisor, Roche: Speaking and Teaching, Takeda: Advisor, Ivana Carey: Nothing to Disclose, Kosh Agarwal: Nothing to Disclose, Florian van Bömmel: VIR Biotechnology: Independent Contractor, Maurizia Brunetto: Nothing to Disclose, Mariana Cardoso: Gilead Sciences: Grant/Research Support, Gabriella Verucchi: Nothing to Disclose, Alessia Ciancio: Nothing to Disclose, Fabien Zoulim: Nothing to Disclose, Soo Aleman: Gilead: Speaking and Teaching, Nasser Semmo: Nothing to Disclose, Alessandra Mangia: Nothing to Disclose, marie noelle HILLERET: CHIESI: Consultant, GILEAD: Speaking and Teaching, IPSEN: Consultant, Alessandro Loglio: Nothing to Disclose, Uta Merle: Gilead: Speaking and Teaching, Falk: Speaking and Teaching, Microbiotica: Speaking and Teaching, Teresa Antonia Santantonio: gilead: Advisor, Nicola Coppola: Nothing to Disclose, Adriano Pellicelli: Nothing to Disclose, Bruno Roche:

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0140 | TARGETING THE LIVER CLOCK IMPROVES FIBROSIS BY RESTORATION OF TGF-β SIGNALING

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Background: Liver fibrosis is the major driver for hepatocellular carcinoma and liver disease related death. Approved anti-fibrotic therapies are absent and compounds in development have limited efficacy. Increased TGF-β signaling drives collagen deposition by hepatic stellate cells (HSC)/myofibroblasts. Here, we aimed to dissect the role of the circadian clock (CC) in controlling TGF-β signaling and liver fibrosis. **Methods:** Using CC-mutant mice, enriched HSC obtained from healthy and fibrotic mice in different CC-phases and loss-of-function studies in human hepatocytes and myofibroblasts, we investigated the relationship between CC and TGF-β signaling. We explored hepatocyte-HSC communication through bioinformatic analyses of single nuclei transcriptomes with validation in cell-based models. Using mouse models for MASH fibrosis and spheroids from patients with liver disease, we performed proof-of concept studies to validate pharmacological targetability and clinical translatability. **Results:** We discovered that the CC-oscillator temporally gates TGF-β signaling and this regulation is broken in fibrosis. We demonstrated that HSCs contain a functional CC with rhythmic expression of numerous genes, including fibrogenic genes. Perturbation studies in hepatocytes and HSC revealed a reciprocal relationship between TGF-β-activation and CC perturbation, which was confirmed in patient-derived ex vivo and in vivo models. Remarkably, pharmacological modulation of CC TGF-β signaling inhibited fibrosis in mouse models in vivo as well as patient-derived liver spheroids. **Conclusion:** The CC regulates TGF-β signaling, and the breakdown of this control is associated with liver fibrosis in patients. Pharmacological proof-of-concept studies across different models uncover the CC as a therapeutic target for liver fibrosis – a rising global unmet medical need.

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0142 | LIPID INDUCED ENDOTHELIAL INTERCELLULAR ADHESION MOLECULE 1 (ICAM1) PROMOTES LIVER INFLAMMATION IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS (MASH) ◆ ★

Qianqian Guo[1] Akitoshi Sano[1] Khaled Warasnhe[1] Feda Hamdan[1] Sheng Cao[2] Samar Ibrahim[2]

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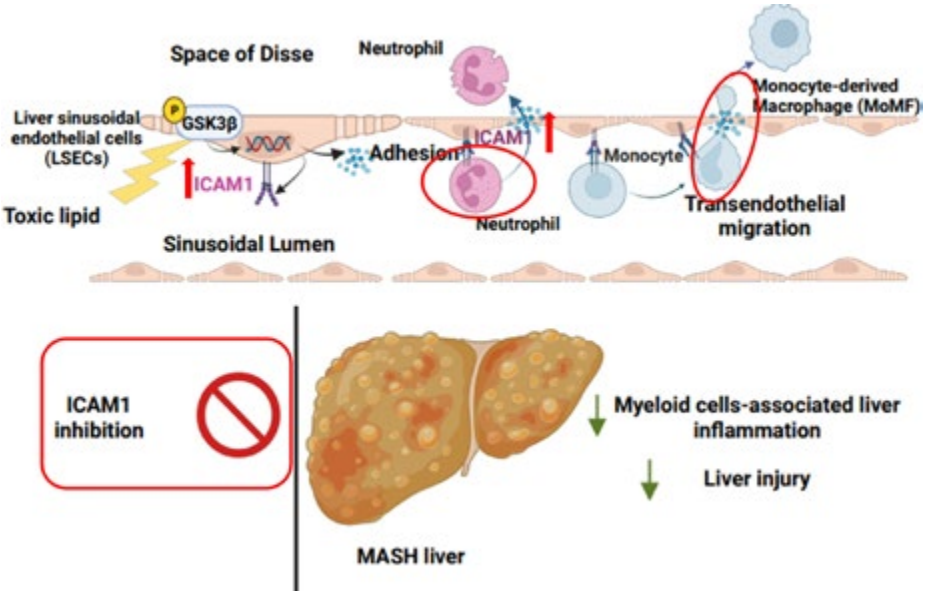
Background: During metabolic dysfunction-associated steatohepatitis (MASH), liver sinusoidal endothelial cells (LSEC) acquire a pro-inflammatory phenotype characterized by increased adhesion molecules expression and myeloid cells associated liver inflammation. We aim to uncover the pathogenic role and the transcriptional regulation of ICAM1, an upregulated LSEC adhesion molecule in MASH and lipotoxicity. **Methods:** Assay for Transposase-Accessible Chromatin with sequencing (ATAC-seq) and Chromatin immunoprecipitation (ChIP) assay on LSEC were used to evaluate the open chromatin regions at the ICAM1 promoter and their enrichment with the active epigenetic mark, H3K27ac in lipotoxicity and MASH. Neutrophils adhesion to LSECs was examined by a functional flow-based adhesion assay. Mice with diet-induced MASH received ICAM1 neutralizing antibody (ICAM1Ab) or isotype control. In a parallel mouse study, ICAM1 expression in LSEC was suppressed using epigenetic editing model CRISPRi-dCas9-KRAB [clustered regularly interspaced short palindromic repeat interference, based on the fusion of nuclease-deactivated Cas9 (dCas9) to the Krüppel-associated box (KRAB)]. Isolated intrahepatic leukocytes (IHL) were analyzed by flowcytometry. ICAM1 immunostaining was performed on liver sections from MASH patient or normal subjects. **Results:** ICAM1 liver immunostaining is increased in patients with different stages of MASH and correlates with disease severity. ChIP assay shows that H3K27ac enrichment at the *ICAM1* promoter region is significantly induced by PA treatment in primary human LSEC. ICAM1 upregulation in lipotoxicity is induced by glycogen synthase kinase 3 (GSK3) activation, and its downstream signaling pathway including JNK and the transcription factor c-Jun. Flow-based adhesion assay shows reduced neutrophil adhesion to PA treated LSEC in the presence of ICAM1 neutralizing antibody. LSEC isolated from dCas9-KRAB/Cdh5PAC-CreERT2 mice shows efficient suppression of ICAM1 expression when transfected with sgRNAs targeting ICAM1 promoter. ICAM1Ab-treated mice in diet-induced MASH models have reduced liver inflammation compared to isotype-treated controls, as assessed by decreased mRNA expressions of proinflammatory genes *Cd68, Tnf-α, Ccr2* and *Il1-β,* reduced immunostaining of the neutrophil marker myeloperoxidase (MPO), and significant reduction of infiltrated proinflammatory monocytes and neutrophils by flowcytometry. **Conclusion:** LSEC ICAM1 is transcriptionally upregulated during lipotoxicity via a GSK3β-C-Jun dependent mechanism and enhances myeloid cells adhesion. ICAM1 inhibition is protective against liver inflammation and injury in murine MASH and might serve as a potential therapeutic target in human MASH.



Disclosures: Qianqian Guo: Nothing to Disclose, Akitoshi Sano: Nothing to Disclose, Khaled Warasnhe: Nothing to Disclose, Feda Hamdan: Nothing to Disclose, Sheng Cao: Nothing to Disclose, Samar Ibrahim: Advisor relationship with Mirum pharmaceutical; Has not ended; Advisor relationship with Albeiro pharma; Has ended

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0143 | THE STEATOSIS-ASSOCIATED FIBROSIS ESTIMATOR (SAFE) SCORE PREDICTS LIVER AND CARDIOVASCULAR OUTCOMES: A UK BIOBANK STUDY

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Background: The Steatosis-Associated Fibrosis Estimator (SAFE) score was developed to distinguish clinically significant (stage 2+) liver fibrosis among subjects with steatotic liver disease. It incorporates additional variables (diabetes, body mass index and serum globulin) to those of the FIB-4 (Fibrosis-4) index. In this study, we interrogated the UK Biobank data to determine the ability of the SAFE score to predict major adverse liver outcomes (MALO), atherosclerotic cardiovascular disease (ASCVD) and all-cause mortality in subjects with or without known metabolic dysfunction-associated steatotic liver disease (MASLD). **Methods:** Data from UK Biobank participants were analyzed (n=414,973). SAFE score and FIB-4 index were calculated in each subject at baseline according to the published formulae. MALO was defined by a diagnosis of cirrhosis, hepatic decompensation or hepatocellular carcinoma and ASCVD by a comprehensive list of cardiac and cerebrovascular disorders. Cox Proportional Hazard models were fitted for the survival across the follow up period with SAFE and FIB-4 as predictors of the future events. The Harrell's C-Index, Akaike's Information Criterion (AIC), and the area under the receiver operating characteristics (AUROC) were used to compare the models. **Results:** The UK biobank population had a mean age of 57 years and included 46% male, 67% overweight (BMI ≥ 25) and 10% diabetes. There were 2,829 MALOs including 557 prevalent and 2,272 incident cases and 64,425 ASCVDs including 30,272 prevalent and 34,153 incident cases. The SAFE score classified 52.9% of individuals as low-risk, 38.5% as intermediate-risk, and 8.6% as high-risk for clinically significant fibrosis. In the Table, the **Results:** of Cox regression analysis predicting MALO, ASCVD and death are shown as hazard ratios and their 95% confidence intervals. Compared to the intermediate risk tier (SAFE: 0-100), low and high risk SAFE score categories were associated with significantly lower and higher risk of all three categories of events, respectively. The FIB-4 index classified 55.6% of the subjects as low-risk, 42.2% as indeterminate-risk, and 2.3% as high-risk for advanced fibrosis. When assessed for their discrimination, SAFE had significantly higher AUROCs than FIB-4 for MALO (SAFE: 0.73 [0.71-0.75] versus FIB-4: 0.66 [0.65-0.68]), ASCVD (SAFE: 0.62 [0.61-0.62] versus FIB-4: 0.56 [0.56-0.57]) and death from all causes (SAFE: 0.64 [0.63-0.64] versus FIB-4: 0.59 [0.59-0.60]). **Conclusion:** In this large population sample, the SAFE score was predictive of liver, cardiovascular and mortality outcomes, which may indicate that the inclusion of metabolic variables affords the SAFE score additional refinement to the prediction by FIB-4. These data provide further validation to the SAFE score as an indicator of clinically significant liver fibrosis, which may be useful in screening for potential candidates for liver-directed therapy for MASLD.

	Liver (MALO)	Cardiovasc. (ASCVD)	Death
Low risk (SAFE<0)	0.45 (0.40-0.50)	0.51 (0.50-0.52)	0.49 (0.48-0.51)
High risk (SAFE>100)	5.90 (5.37-6.48)	1.85 (1.79-1.91)	2.15 (2.08-2.22)

Disclosures: Magdalena Nowak: Perspectum Ltd.: Employee, Blanca Lizaola-Mayo: Nothing to Disclose, Tom Davis: Nothing to Disclose, Arjun Jayaswal: Perspectum: Employee, Andrea Dennis: Perspectum: Employee, Helena Thomaides Brears: Nothing to Disclose, Rajarshi Banerjee: Perspectum: Employee, Perspectum: Executive role, W. Ray Kim: Nothing to Disclose

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0144 | EFFICACY OF CARVEDILOL + IVABRADINE VS CARVEDILOL ALONE FOR LEFT VENTRICULAR DIASTOLIC DYSFUNCTION IN CIRRHOSIS AND IMPACT ON DECOMPENSATION, CARDIAC FUNCTION AND SURVIVAL; AN OPEN LABEL RANDOMIZED CONTROLLED TRIAL

Madhumita Premkumar[1] Kamal Kajal[2] Manhal Izzy[3] Vishesh Kumar[2] Bhupendra Sihag[2] Ajay Bahl[2] Ankur Gupta[2] Ajay Duseja[1] Ashwani Sood[2] Deepy Z[2] Rohit Mehtani[4]

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Background: Left ventricular diastolic dysfunction (LVDD) is associated with adverse outcomes in patients with Cirrhosis and Liver Transplant recipients. Ivabradine, an I_f channel (i.e., pacemaker current channel) inhibitor, lowers heart rate and prolongs diastolic time. We hypothesized that it may improve cirrhotic cardiomyopathy (CCM) and, thus, we aimed to assess changes in cardiac function, decompensation events, and survival following Carvedilol + Ivabradine vs Carvedilol alone over one year. **Methods:** Patients with cirrhosis were screened on transthoracic echocardiography (TTE) with tissue Doppler imaging for presence of LVDD, and those with ischemic heart disease, pacemaker in situ or known arrhythmia, prior use of beta blocker, valvular heart disease, anemia, uncorrected thyroid dysfunction, and hepatocellular carcinoma were excluded. The enrolled patients were randomized to Group A (carvedilol + ivabradine) and Group B (carvedilol alone) &were assessed every 6m for LV systolic and diastolic function per 2020 CCM criteria. Clinical data, TTE, speckle tracking Echo and cardiac imaging, biomarkers (NT-proBNP, aldosterone, norepinephrine), and survival data were prospectively collected at presentation, and at 6 & 12 months. **Results:** Of 506 patients with cirrhosis screened, 153(30.2%) participants had LVDD;91(59.4%) with CCM (i.e., those with grade II-III LVDD). Group A included 77 participants aged 50.2±9.8 years, 65(84.4%) men, MELDNa 14.0±3.5 with median carvedilol dose 6.25mg & ivabradine 7.5mg qd, while Group B included 76 participants aged 50.1±9.6 years, 59(77.6%) men, MELDNa 13.7±3.1 with median carvedilol dose 6.25mg qd. At enrolment, all patients had preserved systolic function & similar baseline characteristics. On follow up, liver decompensation events and adverse events were similar in both groups. (Figure 1) In Group A, 47/77(61%) had CCM at enrolment, of whom 14(29.8%) improved to normal diastolic function and 17(36.2%) improved to Grade I LVDD (i.e., 65.9% of CCM had regression). In Group B,44/76 (57.9%) had CCM at enrolment, of whom 5(11.4%) improved to normal diastolic function, and 12(27.3%) improved to Grade I LVDD (i.e., 38.7% of CCM had regression) (*P*=0.009 for difference in CCM regression in Group A vs B). Reduction in NT-proBNP (62% vs 50.7%; *P*=0.012), norepinephrine (60% vs 44.9%, *P*=0.043), and aldosterone (42.1 % vs 15.8 %; *P*=0.033) was more prominent in Group A vs B. The overall survival in the two groups (85.7% vs 76.3%, *P*=0.079) was similar but in the subgroup analysis for patients with baseline heart rate (HR)>85 bpm (n=37), survival was better in those who received ivabradine (88.9% vs 68.4%, *P*=0.025). (Figure 1 (A) CONSORT Chart (B) Clinical and adverse events (C) Survival) **Conclusion:** Addition of ivabradine to carvedilol was associated with improvement in CCM with equivocal benefit on decompensation events, but shows survival benefit only in those with baseline HR>85 bpm. (NCT04111133)

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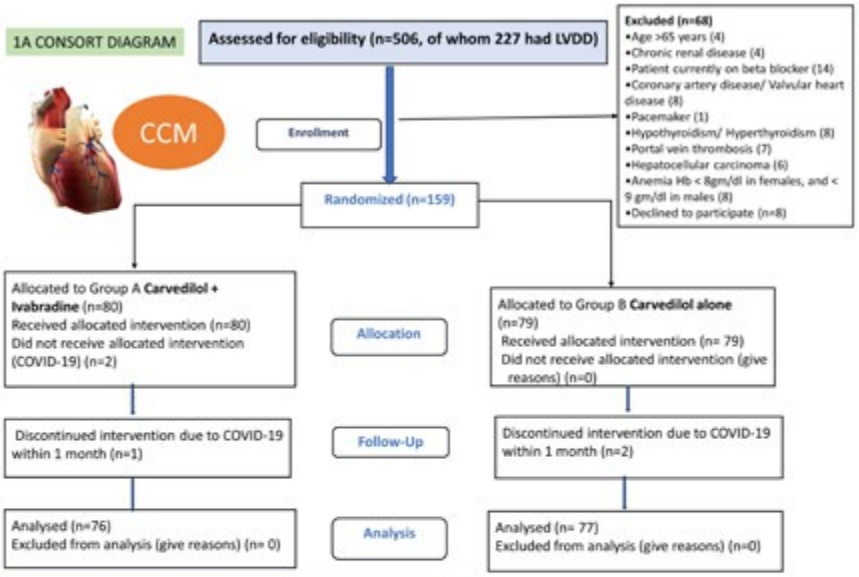
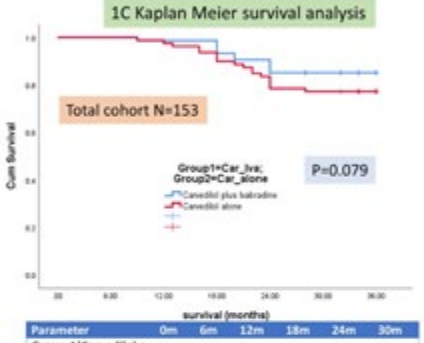
Figure 1: (A)CONSORT diagram (B) Clinical events, deaths and adverse events on follow up. (C) Survival Plots for patients in Gr A (Carvedilol + Ivabradine) vs group B Carvedilol alone and subgroup analysis for patients with baseline HR>85 bpm.



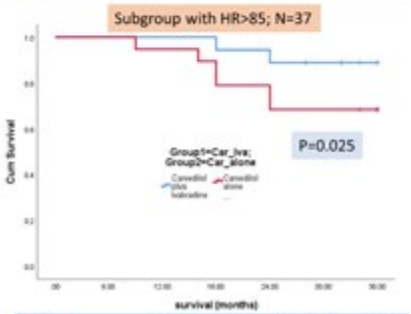
Systolic dysfunction is defined as an ejection fraction (EF) of 50% or less or an absolute value of GLS <18%.

CCM is defined based on presence of 3 of 4 criteria including septal (e')<7 cm/s, E/e'≥15, tricuspid regurgitant jet maximum velocity >2.8m/s and LAVI >34 mL/m²

1C Kaplan Meier survival analysis



Parameter	0m	6m	12m	18m	24m	30m
Group A(Carvedilol + Iva)	77	77	76	72	66	66
Group B (Carvedilol alone)	76	76	74	68	58	58



Parameter	0m	6m	12m	18m	24m	30m
Group A(Carvedilol + Iva)	18	18	18	17	16	16
Group B (Carvedilol alone)	19	19	18	15	13	13

1B Clinical events, deaths and possible adverse events

Indicator	(Ivabradine + Carvedilol) N=77	(Carvedilol) N =76	P value
Episode of HRS-AKI (%)	7(9.1)	8(10.5)	0.765
Episode of Sepsis (%)	4(5.2)	6(7.9)	0.499
Episode of HE (%)	7(9.1)	6(7.9)	0.791
Refractory ascites (%)	3(3.9)	1(1.3)	0.317
Acute variceal bleeding (%)	6(7.8)	6(7.9)	0.981
SBP (%)	1(1.3)	1(1.3)	0.993
Arrhythmia (%)	0(0)	2(2.6)	0.152
Total Mortality	11(14.2)	18(23.7)	0.516
Causes of Death	Alcohol related liver failure (4), COVID-19 related(4), sepsis (2), accident (1)	Alcohol related liver failure (5), COVID-19 related (8), sepsis (5)	

* No episode of syncope /persistent bradycardia/ atrial fibrillation was noted

Disclosures: Madhumita Premkumar: Nothing to Disclose, Kamal Kajal: Nothing to Disclose, Manhal Izzy: Nothing to Disclose, Vishesh Kumar: Nothing to Disclose, Bhupendra Sihag: Nothing to Disclose, Ajay Bahl: Nothing to Disclose, Ankur Gupta: Nothing to Disclose, Ajay Duseja: Nothing to Disclose, Ashwani Sood: Nothing to Disclose, Deepy Z: Nothing to Disclose, Rohit Mehtani: Nothing to Disclose

0145 | ALPHA DIVERSITY ANALYSIS OF HEPATIC TRANSCRIPTOME REVEALS DISTINCT SIGNATURES AND PREDICTS NOVEL PATHWAYS IN ALCOHOL-RELATED HEPATITIS ◆ ★

Sudrishti Chaudhary[1] Silvia Liu[1] Juliane Beier[1] Ramon Bataller[2] Josepmaria Argemi[3] Panayiotis Benos[4] Gavin Arteel[1]

[1]University of Pittsburgh, [2]IDIBAPS, [3]University of Navarra, Spain, [4]University of Florida

Background: Next generation sequencing is a powerful technique to identify novel or cryptic gene expression patterns in disease. Although the dominant form of this analysis is differential gene expression (DEG), pattern recognition (e.g., IPA) and between population diversity (i.e., β-diversity) are also often used to document changes of the total transcriptome. However, within population diversity (i.e., α-diversity) are rarely analyzed, despite the understanding that environmental stresses often impact the totality of gene expression. We investigated the impact alcohol-related liver disease (ALD) on global hepatic gene expression; we compared novel PSD (Percent Shannon diversity) analysis to changes in transcriptome heterogeneity (α-diversity).
Methods: RNA sequencing data were obtained from normal livers (n = 10) and from biopsies of patients with

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early silent ALD (ASH, n = 11), non-severe AH (n = 9), and severe AH (n = 9) (NLM study code phs001807.v1.p1). Indices of α-diversity were calculated using PAST (v. 4.15) software; Percent Shannon Diversity (PSD) was calculated as contribution of each individual gene to the total Shannon entropy (H). Ingenuity pathway analysis (IPA; QIAGEN) was used to identify top canonical and enriched biological pathways determined by DEG and PSD approaches. **Results:** ALD significantly decreased the α-diversity of the hepatic transcriptome versus healthy controls and correlated with an increase in the relative contribution of select genes to overall expression (see Figure). These changes were driven by a net loss of expression of lower abundance genes. IPA of significantly changed genes determined by DEG and PSD showed overlapping genes and canonical pathways by both analyses. However, PSD analysis also identified novel genes and pathways not highlighted by DEG approach. Importantly, novel pathways identified differences between preclinical ALD (ASH), as well as between severe and non-severe AH more effectively than DEG analysis. Moreover, some of these pathways have been established to potentially contribute to ALD. **Conclusion:** Taken together, these data indicate that ALD decreases total hepatic transcriptome heterogeneity (α-diversity), favoring pathways associated with organ damage and/or response to said damage. Preclinical and clinical ALD (ASH vs. AH) led to differential patterns of heterogeneity and may be used to gain new insight into disease. PSD analysis identified enriched pathways not indicated by standard DEG analyses. This novel analysis may yield new insight into disease mechanisms and biomarkers. Supported by R01 AA0288436 and U01 AA026922.

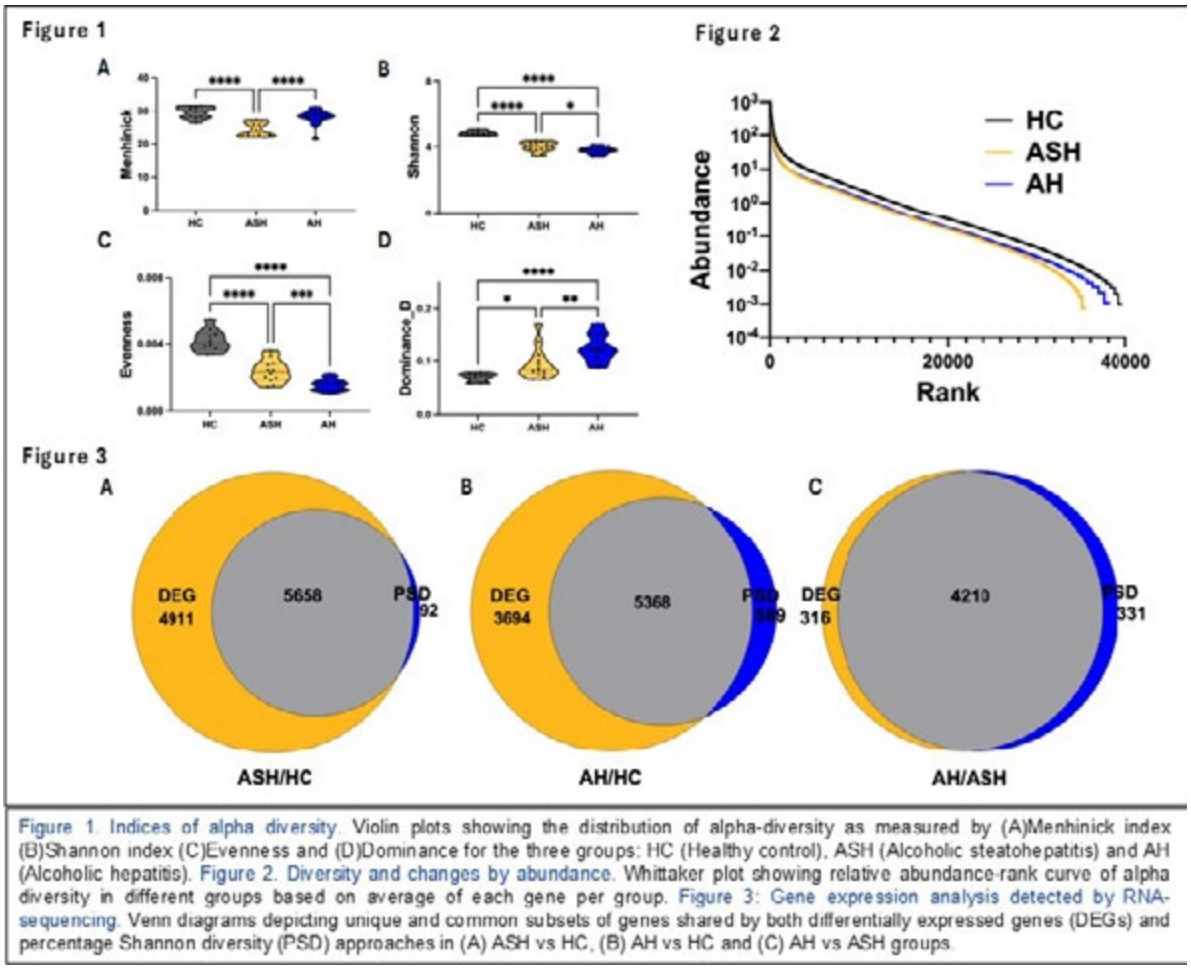

Figure 1. Indices of alpha diversity. Violin plots showing the distribution of alpha-diversity as measured by (A)Menhinick index (B)Shannon index (C)Evenness and (D)Dominance for the three groups: HC (Healthy control), ASH (Alcoholic steatohepatitis) and AH (Alcoholic hepatitis). Figure 2. Diversity and changes by abundance. Whittaker plot showing relative abundance-rank curve of alpha diversity in different groups based on average of each gene per group. Figure 3: Gene expression analysis detected by RNA-sequencing. Venn diagrams depicting unique and common subsets of genes shared by both differentially expressed genes (DEGs) and percentage Shannon diversity (PSD) approaches in (A) ASH vs HC, (B) AH vs HC and (C) AH vs ASH groups.

Disclosures: Sudrishti Chaudhary: Nothing to Disclose, Silvia Liu: Nothing to Disclose, Juliane Beier: Nothing to Disclose, Ramon Bataller: Nothing to Disclose, Josepmaria Argemi: Nothing to Disclose, Panayiotis Benos: Nothing to Disclose, Gavin Arteel: Nothing to Disclose

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0146 | ROLE OF OGT-TFF2 AXIS IN INTRAHEPATIC CROSSTALK AND MASH PATHOGENESIS ◆ ★

Lei Zhang[1] Cuijuan Han[2] Man Shrestha[1] Jiamei Le[1] Max Padian[1] Reina Desrouleaux[3] Eric Wang[2] Xiaoyong Yang[4]

[1]Department of Comparative Medicine, Yale University School of Medicine, [2]The Jackson Laboratory for Genomic Medicine, [3]Department of Cellular and Molecular Physiology, Yale University School of Medicine, [4]Department of Comparative Medicine, Cellular and Molecular Physiology, Yale School of Medicine

Background: Metabolic dysfunction-associated fatty liver disease (MAFLD) is a global metabolic disease that comprises a broad spectrum of liver dysfunction ranging from simple steatosis to metabolic dysfunction-associated steatohepatitis (MASH) with fibrosis. It is largely unknown how the communication between hepatocytes and non-parenchymal cells dictates the disease progression from simple steatosis to MASH and fibrosis. Dysregulation of protein O-GlcNAcylation in hepatocytes has been implicated in a wide range of liver disease. In this study, we demonstrate a novel paracrine factor through which OGlcNAc transferase (OGT) regulates intercellular crosstalk between hepatocytes and immune cells in MASH development. **Methods:** Bioinformatic analysis was conducted to determine hepatocyte-derived secreted proteins uniquely activated in liver-specific *Ogt* knockout mice. Promoter analysis and chromatin immunoprecipitation were employed to identify OGT-targeted transcription factor that mediates the expression of the paracrine factor. The effects of the paracrine factor on inflammation and fibrogenesis was further evaluated in a 3D mouse liver spheroid model of MASH. Flow cytometry was utilized to evaluate the impact of the factor on immune cells. The GalNAc-modified siRNA targeting the paracrine factor was applied in Gubra-Amylin NASH (GAN) diet-fed mice to determine its therapeutic potential in preventing the MASH progression. **Results:** RNA-sequencing analysis of wildtype and liver-specific *Ogt* knockout mice was performed and trefoil factor 2 (TFF2) was identified as one of the highly induced genes encoding secreted proteins in *Ogt*-deficient hepatocytes. Decreased OGT expression and increased TFF2 expression were observed in the liver of MAFLD patients. Mechanically, OGT was found to repress *Tff2* transcription in hepatocytes by modifying forkhead box protein A2 (FOXA2). In the 3D spheroid model of MASH, recombinant TFF2 promoted MASH stimuli-induced triglyceride secretion and expression of pro-inflammatory and fibrogenic genes. Furthermore, secreted TFF2 accelerated hepatic CD4 T cell proliferation and differentiation into Th1 and Th17 cell through CXCR4-STAT1/3 signaling pathway. To test therapeutic potential of the OGT-TFF2 pathway, we found that hepatocyte-specific GalNAc-modified si*Tff2* reduced GAN diet-induced MASH in mice. **Conclusion:** These results identify an OGT-TFF2 axis that mediates the crosstalk between hepatocytes and CD4 T cells during MASH pathogenesis, revealing a potential therapeutic target for the treatment of chronic liver disease.

Disclosures: Lei Zhang: Nothing to Disclose, Cuijuan Han: Nothing to Disclose, Man Shrestha: Nothing to Disclose, Jiamei Le: Nothing to Disclose, Max Padian: Nothing to Disclose, Reina Desrouleaux: Nothing to Disclose, Eric Wang: Nothing to Disclose, Xiaoyong Yang: Nothing to Disclose

0147 | METABOLIC DYSFUNCTION ASSOCIATED STEATOTIC LIVER DISEASE (MASLD) IS SIGNIFICANTLY ASSOCIATED WITH BIOLOGICAL AGE AND ITS ACCELERATION AS ASSESSED BY METHYLATION CLOCK

Naga Chalasani[1] Jie Yao[2] Xiuqing Guo[2] Jingyi Tan[2] Marco Abreu[1] Linus Schwantes-An[1] Stephen Rich[3] Anna Diehl[4] Matthew Budoff[2] Jerome Rotter[2]

[1]Indiana University School of Medicine, Indianapolis, IN, [2]Lundquist Institute, Los Angeles, CA, [3]Virgina School of Medicine, [4]Duke University

Background: Biological age is an important determinant of chronic disease and cancer development and overall mortality. Metabolic comorbidities such as type2 diabetes and obesity are associated with accelerated biological age and these conditions are highly associated with MASLD. We conducted a study to examine the relationship between MASLD and biological age and its acceleration in a cohort of multiethnic adults. **Methods:** This study was conducted on 885 adults participants of the Multi Ethnic Study of Atherosclerosis (MESA) with CT images of the liver and paired methylome of circulating DNA. Methylation was done via Illumina 850K platform, with 865,859 probes (including CpG sites on both X and Y chromosomes). MASLD was defined as liver attenuation < 51 Hounsfield units (L/S ratio <1) with at least 1 metabolic risk factor and the absence of significant alcohol

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consumption or hepatitis B or hepatitis C. Chronical age was assessed via the following methylation clocks: Horvath Clock (353 CpG sites), AgeHannum (71 CPG sites), PhenoAge (513 CPG sites), and GrimAge (1030 CPG sites). Multivariate logistic regression analyses were conducted controlling for chronological age, sex, race, estimated blood cell composition (CD8+ T cells, CD4 T cells, natural killer cells, B lymphocyte cells, monocytes, and granulocytes). **Results:** Study cohort consisted of 885 adults (chronological age 60.1 ± 9.7 years, 52% female, BMI 28.8± 5.1 kg/m2, PNPLA3 genotype: CC 55%, CG 38%, GG 7%) and MASLD was present in 139 (15.7%). The chronological age was not different between individuals with or without MASLD (59.3 ± 8.5 years vs 60.3 ± 9.8 years, p=0.2) After adjusting for co-variates, by AgeHannum methylation clock, there was significant MASLD and biological age by AgeHannum (OR: 1.048; CI 1.004-1.094, p=0.029). In addition, there was significant interaction between *PNPLA3* G-allele and AgeHannum and the risk for (interaction p-value 0.04). Baseline MASLD was significantly associated greater biological age acceleration, as assessed by the AgeHannum, after adjusting for selected co-variates (beta-, 95% CI, p=0.0057). There was an interaction between MASLD and PNPLA3 G-allele and the risk for biological age acceleration (interaction p-value 0.036). **Conclusion:** MASLD is significantly associated with increased biological age and its acceleration. Studies are needed to investigate if MASLD treatment improves biological age.

Disclosures: Naga Chalasani: Madrigal: Consultant, Zydus, Ipsen, Pfizer, Merck, Altimmune, GSK: Consultant, Exact Sciences: Grant/Research Support, NIH: Grant/Research Support, Jie Yao: Nothing to Disclose, Xiuqing Guo: Nothing to Disclose, Jingyi Tan: Nothing to Disclose, Marco Abreu: Nothing to Disclose, Linus Schwantes-An: Nothing to Disclose, Stephen Rich: Nothing to Disclose, Anna Diehl: Nothing to Disclose, Matthew Budoff: Boehringer Ingleheim: Speaking and Teaching, Jerome Rotter: Nothing to Disclose

0148 | VIDEO-BASED MULTI-CENTER COLLABORATION WITH COUNTY PUBLIC HEALTH DEPARTMENT TO ENHANCE DELIVERY OF ALCOHOL-ASSOCIATED LIVER DISEASE CARE BY COMMUNITY PROVIDERS ◆

Tracy Chen[1] Terry Church[1] Stephen Pandol[2] Lourdes Baezconde-Garbanati[1] James Lee[1] Brandy Oeser[3] Thomas Valente[1] Hidekazu Tsukamoto[1] Brian Lee[4]

[1]University of Southern California, [2]Cedars-Sinai Medical Center, [3]UCLA Integrated Substance Abuse Programs, [4]Keck School of Medicine

Background: Alcohol-associated liver disease (ALD) accounts for over 50% of cirrhosis-related deaths in the United States. Yet, only the minority of patients with ALD are seen by hepatologists. Community outreach programs to enhance delivery of ALD-related care by community providers may be beneficial, but are understudied. **Methods:** In this multi-center initiative (University of Southern California, Cedars-Sinai, UCLA) in collaboration with the Los Angeles Department of Public Health, a seminar delivered via remote video platform was organized. Three 25-minute lectures were prepared (TDC, BPL, SJP), focusing on the dangerous effects of alcohol, ALD pathophysiology, practical management for alcohol use disorder and co-morbid conditions (e.g. smoking, pancreatitis), and the role of subspecialty (i.e. gastroenterology/hepatology) care. The lectures were then followed by a 45-minute panel discussion among speakers and the audience. Effectiveness of the seminar was measured by evaluating pre- and post-seminar performance using one-way ANOVA testing of the overall score on a 15-question knowledge-based quiz, and by 4-point Likert scales. **Results:** Among 415 participants who attended the seminar, 298 (20% aged 22-35; 28% aged ≥56; 79% female; 38% Hispanic; 30% non-Hispanic White; 62% Bachelor's degree or higher) completed the pre- and post-seminar quiz to be included in this analysis. The audience consisted mainly of community psychologists, social workers, and addiction counselors, and 82% had heard of the seminar via e-mail from either the Los Angeles Department of Public Health or a colleague. The primary reasons for attending were "to learn" (61%), continuing education credits (20%), and "required for job" (13%). In 4-point Likert scales, 93% rated the seminar as very useful or useful, 84% reported that the seminar exceeded or met expectations, 93% rated the seminar as very interesting or interesting, and 76% rated the content very easy or easy to understand. The mean overall score on the 15-question quiz was higher post- vs. pre-seminar (56% vs 38%, p<0.001). **Conclusion:** This multi-center collaboration with the county department of public health provided a video-based seminar that was well-attended, well-rated, and increased overall scores on a post- vs. pre-seminar knowledge-based quiz among an audience of community substance use providers. This initiative may serve as an example for others as part of community outreach programs to enhance delivery of ALD-related care by community providers.

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Disclosures: Tracy Chen: Nothing to Disclose, Terry Church: Nothing to Disclose, Stephen Pandol: Nothing to Disclose, Lourdes Baezconde-Garbanati: Nothing to Disclose, James Lee: Nothing to Disclose, Brandy Oeser: Nothing to Disclose, Thomas Valente: Nothing to Disclose, Hidekazu Tsukamoto: Nothing to Disclose, Brian Lee: NIAAA: Grant/Research Support, Novo Nordisk: Advisor, GSK: Advisor, DURECT: Advisor, HepaTx: Advisor, CymaBay: Consultant, Ipsen: Consultant, Siemens Healthineers: Grant/Research Support, AltImmune: Advisor

0149 | PHARMACIST-DRIVEN STRATEGIES IMPROVE HEPATITIS C CURES IN A VARIETY OF PRACTICE SETTINGS ◆

Lindsey Sheehan[1] Maribeth Wright[1] Morgan Stacey[1] Christian Rhudy[1] Daniel Moore[2]

[1]University of Kentucky HealthCare, [2]University of Kentucky

Background: Despite existence of hepatitis C (HCV) curative treatments, social and institutional barriers obstruct access and engagement with care for many patients. UK-**CURES** (University of Kentucky - **C**ascade **U**tilizing **R**outinized screening through treatment to **E**liminate **S**yndemics) was created in June 2023 to routinely identify and engage patients with HCV based on AASLD/IDSA simplified treatment guidelines. This model focuses on identifying patients, linkage to care, and retention, with numerous pathways entry and re-entry to treatment. **Methods:** UK-CURES performs identification and workup of HCV and hepatic dysfunction at the patient's point of entry to health system (Figure 1). Non-targeted screening is performed in both emergency department (ED) and ambulatory clinic settings. Patients with HCVAb positivity are evaluated (laboratory values, patient history, transient elastography) by a dedicated team of pharmacists acting on behalf of the patient's provider in a collaborative care agreement (CCA). Based upon workup, the pharmacist and an advanced practice provider (APP) determine if the patient is eligible for simplified treatment under the CCA or requires referral to specialist care. Treatment eligible patients are referred to the institutional specialty pharmacy which performs prior authorizations, benefits investigation, free mail order delivery, proactive refill management, and coordination of systemic virologic response (SVR12) labs. Additionally, patients who fall out of care are followed by a team of social workers to re-engage with the APP in clinic and continue treatment. UK-CURES treatment outcomes at 11 months post-implementation are detailed below. **Results:** Post-implementation, 1,428 patients with HCVAb positivity were evaluated with 485 (34.0%) HCVRNA positive. 50 patients were excluded from simplified treatment due to decompensation/advanced cirrhosis (15), hepatitis B/HIV coinfection (13), incarceration (13), and prior DAA treatment (9). Of 435 eligible for treatment, 285 (65.5%) started treatment with an average attrition between fills of approximately 20%. 152 (53%) initially engaged in care through the ED, while 133 (47%) through telehealth or in-person visit clinic with the APP. 46 (16%) patients achieved SVR12 at time of submission. **Conclusion:** The UK-CURES model illustrates the impact of providing multiple entry points and opportunities to access HCV care. UK-CURES contributed to increases in treatment uptake, adherence, and SVR12 cure compared to pre-program rates.

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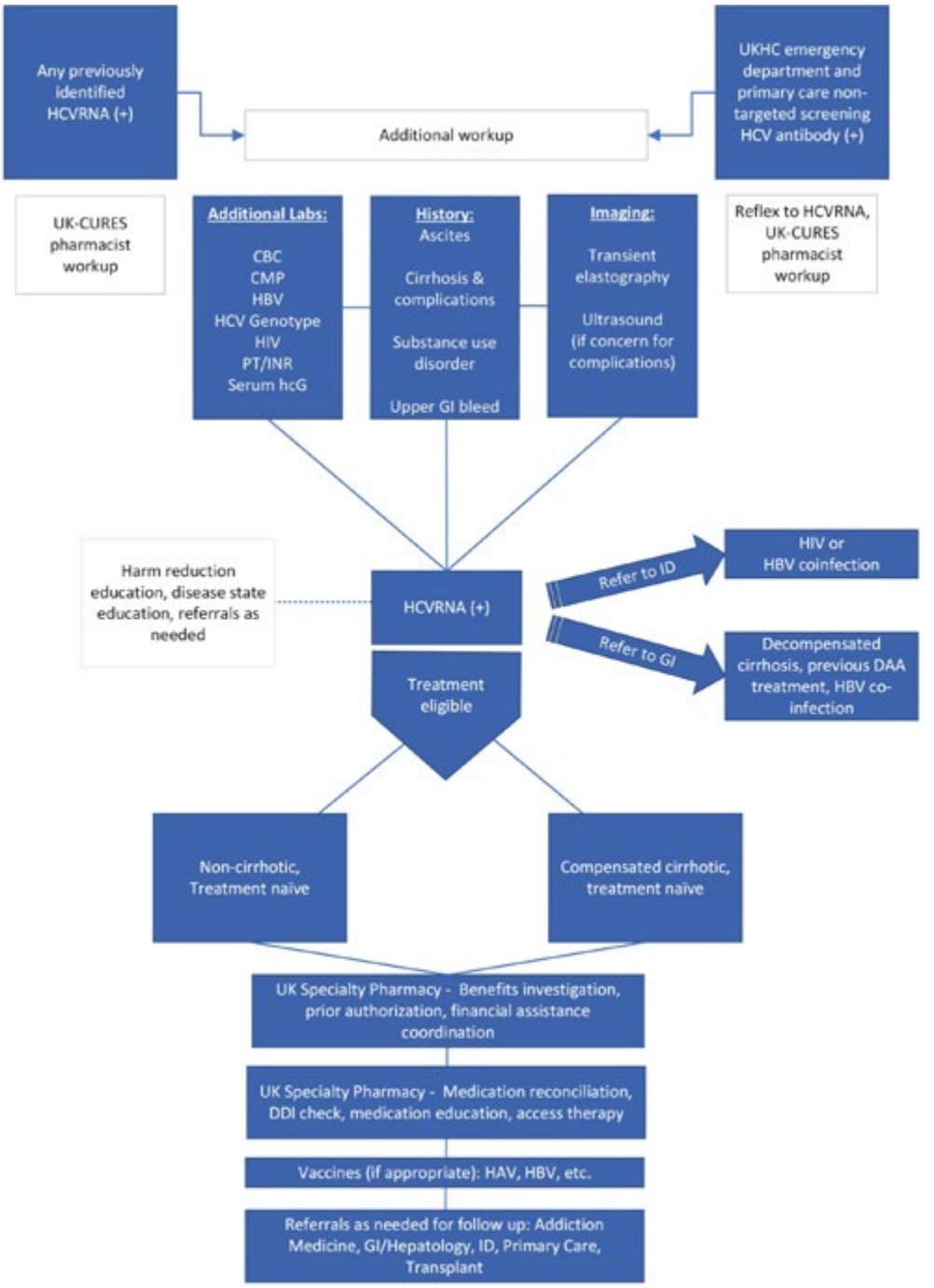

DAA = direct-acting antiviral; DDI = drug-drug interaction; GI = gastrointestinal; HAV = hepatitis A virus; HBV = hepatitis B virus; HCV = hepatitis C virus; HCVRNA = hepatitis C virus ribonucleic acid laboratory test; HIV = human immunodeficiency virus; ID = infectious diseases; UKHC = University of Kentucky Healthcare;

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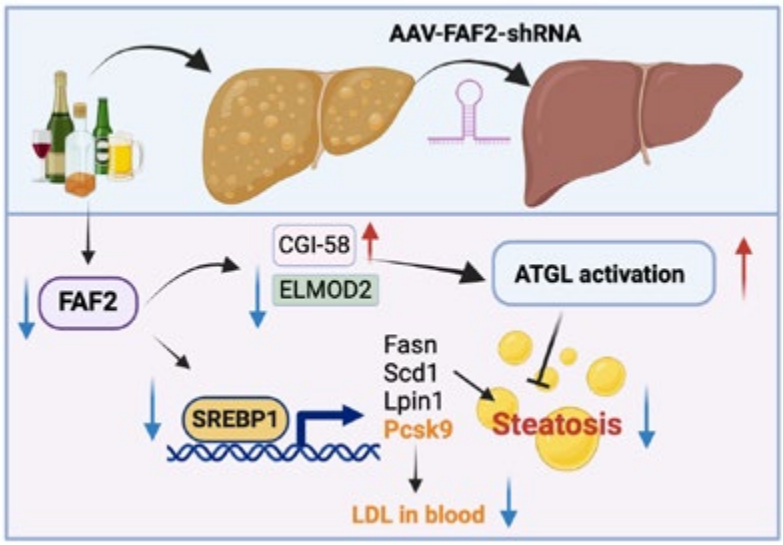
0150 | ROLE OF FAF2, FAS ASSOCIATED FACTOR FAMILY MEMBER 2, IN THE PATHOGENESIS OF ALCOHOL-ASSOCIATED LIVER DISEASE ◆

Nazmul Huda[1] Praveen Kusumanchi[2] Yanchao Jiang[2] Hui Gao[2] THEMIS THOUDAM[2] Ge Zeng[2] Nicholas Skill[3] Zhaoli Sun[4] Suthat Liangpunsakul[2] Jing Ma[2] Zhihong Yang[2]

[1]Indiana University-Purdue University Indianapolis, [2]Indiana University, [3]Louisiana State University Health Science Center, [4]John Hopkins University

Background: The pathogenesis of alcohol-associated liver disease (ALD) is a complex condition characterized by a series of histopathological changes. Fas associated factor family member 2 (FAF2/UBXD8/ETEA) is a ubiquitin ligase adaptor protein that plays a crucial role in the ubiquitin-mediated degradation of misfolded proteins in the endoplasmic reticulum. A recent GWAS study indicated that FAF2 could be associated with ALD, but its exact function in ALD remains to be elucidated. This study aimed to investigate the role of FAF2 in ALD. **Methods:** FAF2 was knocked down using AAV-delivered siRNA in C57/BL6 mice. Mice were subjected to a chronic-plus-single binge ethanol feeding (NIAAA) model. Nine hours post-gavage, liver, blood, and other organs of interest were collected for gene expression and biochemical analyses. **Results:** Hepatic FAF2 mRNA and protein expression were found to be increased in both human patients with ALD and in mice subjected to chronic-plus-single binge ethanol feeding. To investigate the role of FAF2 in alcohol-induced liver damage, siRNA-mediated suppression of FAF2 via AAV injection was performed in mice. This intervention protected the liver from alcohol-induced hepatic steatosis, leading to a reduction in liver triglycerides, although ALT and AST levels remained largely unchanged. Transcriptomic analysis revealed that differentially expressed genes (DEGs) in the livers of FAF2 knockdown (KD) mice, compared to AAV-Null controls, were significantly enriched in fatty acid metabolism pathways. Utilizing the TRRUST transcription factor prediction database, it was predicted that these DEGs are regulated by the transcription factor SREBP1. Validation experiments confirmed the reduction of SREBP1 downstream genes, including FASN, LPIN, and PCSK9, in the livers of FAF2 KD mice. The reduction of PCSK9 in both plasma and liver was associated with decreased plasma LDL levels. Furthermore, FAF2 KD in mouse liver induced ATGL lipolytic activity by upregulating the ATGL activator CGI-58 and downregulating the ATGL transport inhibitor Elmod2. These combined effects contributed to the observed protection against alcoholic steatosis in the livers of FAF2 KD mice. **Conclusion:** Reduction of FAF2 expression ameliorates alcohol-induced liver steatosis by regulating SREBP1-mediated triglyceride synthesis, activating ATGL, and lowering plasma LDL levels through decreased PCSK9 expression. FAF2 is a potential therapeutic target for preventing and treating alcohol-induced liver damage.



Disclosures: Nazmul Huda: Nothing to Disclose, Praveen Kusumanchi: Nothing to Disclose, Yanchao Jiang: Nothing to Disclose, Hui Gao: Nothing to Disclose, THEMIS THOUDAM: Nothing to Disclose, Ge Zeng: Nothing to Disclose, Nicholas Skill: Nothing to Disclose, Zhaoli Sun: Nothing to Disclose, Suthat Liangpunsakul: DURECT: Consultant, Durect Corporation: Consultant, Surrozen: Consultant, Korro Bio: Consultant, Jing Ma: Nothing to Disclose, Zhihong Yang: Nothing to Disclose

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0151 | ASSOCIATIONS BETWEEN BIOMARKERS AND MAGNETIC RESONANCE IMAGING-DERIVED ANALI SCORE IN PATIENTS WITH PRIMARY SCLEROSING CHOLANGITIS: ANALYSIS FROM THE PHASE 3 PRIMIS STUDY

Michael Trauner[1] Jun Xu[2] Xiangyu Liu[3] Kaiyi Zhu[3] Xiaomin Lu[3] Sharlene Lim[3] William Barchuk[3] Lisa Boyette[3] Clare Tempany[4] Zachary Goodman[5] Atsushi Tanaka[6] Douglas Thorburn[7] Cynthia Levy[8] Christopher Bowlus[9]

[1]Medical University of Vienna, [2]Gilead Sciences, Inc., [3]Gilead Sciences Inc., [4]Brigham and Women's Hospital, Harvard University, [5]INOVA Fairfax Hospital, [6]Teikyo University School of Medicine, [7]Royal Free Hospital, [8]University of Miami, [9]University of California, Davis

Background and Aim: Magnetic resonance cholangiopancreatography (MRCP) is the standard diagnostic method for patients with primary sclerosing cholangitis (PSC). Magnetic resonance (MR) risk scoring systems such as ANALI score have been developed to provide risk evaluation and predict disease progression in PSC. To better understand the interrelationship between markers of liver fibrosis, cholestasis and cholangiographic features of biliary disease, we evaluated the baseline (BL) associations between the ANALI score and other biomarkers in the Phase 3 PRIMIS study. **Methods:** 419 patients with large duct non-cirrhotic PSC were enrolled into PRIMIS study and randomized to receive cilofexor or placebo for 96 weeks. MR features and categorical scores were assessed by a central reader. ANALI score without gadolinium was calculated from the intrahepatic dilation, dysmorphy and portal hypertension scores. Liver stiffness measurement (LSM) was assessed by transient elastography and serum biomarkers including ELF score, bile acid (BL) and liver biochemistry were measured individually. Kruskal-Wallis test was used to evaluate the associations between ANALI score and continuous biomarker levels while Pearson's Chi-square test for the categorical parameters, including IBD status and cholangitis event. Wilcoxon test compared the biomarker levels between the dichotomized ANALI groups. **Results:** 388 out of 389 enrolled patients were included in the BL analyses. 285 subjects with both BL and W96 ANALI score had a median increase by one point [1, (0,2)] at W96. At BL, the ANALI score was ≤ 2 (low risk) in 247 and > 2 (high risk) in 141 patients. ELF score and LSM were significantly associated with increases in BL ANALI score (both $p < 0.001$ Figure 1A), while liver enzymes, fecal calprotectin, and BA levels showed a nonsignificant correlation at BL. Patients with BL ANALI score > 2 had significantly higher ELF score, LSM, liver enzymes and BA levels, while the proportion of patients with IBD were similar (Figure 1B). BL ANALI score was significantly correlated with cholangitis events ($p<0.001$ Figure 1A). 15 (10.6%) patients with BL ANALI score > 2 experienced at least one cholangitis event during study, while only 6 (2.4%) patients with BL ANALI ≤ 2 experienced the event ($p<0.001$). **Conclusion:** ANALI score correlates with BL liver fibrosis and cholestasis markers and cholangitis events over the course of the study. The association between ANALI score and other PSC related clinical events requires further exploration in future studies with longer follow up.

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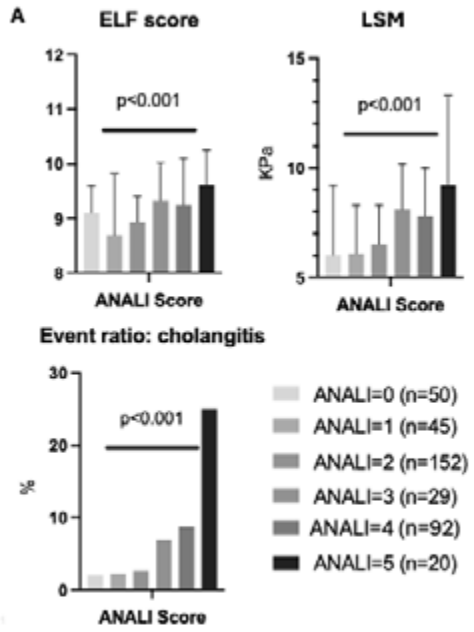
Figure 1: Baseline associations between ANALI score and Non-invasive biomarkers in PRIMIS study



B

	ANALI >2 (n=141)	ANALI ≤2 (n=247)	P value
ELF score	9.33 (8.71, 10.09)	8.91 (8.27, 9.48)	**<0.001**
LSM (KPa)	8.1 (6.1, 10.4)	6.4 (5.0, 8.5)	**<0.001**
IBD n (%)	99 (70.2%)	170 (68.8%)	0.78
Stool calprotectin (µg/g)	104 (29, 336)	62 (29, 235)	0.089
ALT (IU/L)	57 (28, 104)	46 (25, 94)	0.073
AST (IU/L)	43 (27, 74)	36 (24, 63)	**0.032**
GGT (IU/L)	189 (79, 429)	125 (43, 322)	**0.0061**
ALP (IU/L)	190 (128, 344)	156 (98, 271)	**0.0035**
Total BA ng/mL	2376 (1156, 4882)	1565 (697, 4273)	**0.014**
Cholangitis , n (%)	15 (10.6%)	6 (2.4%)	**<0.001**

ELF score: enhanced liver fibrosis score
LSM: liver stiffness measurement
ALT: alanine transaminase
AST: aspartate transferase
ALP: alkaline phosphatase
BA: bile acid

Disclosures: Michael Trauner: Albireo: Grant/Research Support, Alnylam: Grant/Research Support, Cymabay: Grant/Research Support, Falk: Grant/Research Support, Gilead: Grant/Research Support, Intercept: Grant/Research Support, MSD: Grant/Research Support, Takeda: Grant/Research Support, Ultragenyx: Grant/Research Support, Abbvie: Travel Grants, Falk: Travel Grants, Gilead: Travel Grants, Intercept: Travel Grants, Janssen: Travel Grants, Abbvie: Advisor, Albireo: Advisor, BiomX: Advisor, Boehringer Ingelheim: Advisor, Falk Pharma GmbH: Advisor, Genfit: Advisor, Gilead: Advisor, Hightide: Advisor, Intercept: Advisor, Ipsen: Advisor, Janssen: Advisor, MSD: Advisor, Novartis: Advisor, Phenex: Advisor, Pliant: Advisor, Regulus: Advisor, Siemens: Advisor, Shire: Advisor, BMS: Speaking and Teaching, Falk: Speaking and Teaching, Gilead: Speaking and Teaching, Intercept: Speaking and Teaching, Ipsen: Speaking and Teaching, Madrigal: Speaking and Teaching, MSD: Speaking and Teaching, Medical Universities of Graz and Vienna: Co.Inventor of patents for medical use of norUDCA filed by, Genentech: Grant/Research Support, Jun Xu: Gilead Sciences Inc.: Stock owner, Gilead Sciences Inc.: Employee, Xiangyu Liu: Nothing to Disclose, Kaiyi Zhu: Nothing to Disclose, Xiaomin Lu: Nothing to Disclose, Sharlene Lim: Gilead Biosciences, Inc.: Employee, Gilead Sciences, Inc.: Stock – privately held company, William Barchuk: Gilead Sciences, Inc.: Employee, Lisa Boyette: Nothing to Disclose, Clare Tempany: Nothing to Disclose, Zachary Goodman: Nothing to Disclose, Atsushi Tanaka: Nothing to Disclose, Douglas Thorburn: Nothing to Disclose, Cynthia Levy: Consultant relationship with Cymabay; Has ended; Advisor relationship with COur; Has ended; Grant/Research Support relationship with GSK; Has not ended; Grant/Research Support relationship with Ipsen; Has not ended; Consultant relationship with Ipsen; Has ended; Grant/Research Support relationship with Mirum; Has not ended; Consultant relationship with Mirum; Has ended; Grant/Research Support relationship with Zydus; Has not ended; Grant/Research Support relationship with Gilead; Has not ended; Consultant relationship with Gilead; Has ended; Grant/Research Support relationship with Escient; Has not ended; Grant/Research Support relationship with Kowa; Has not ended; Consultant relationship with Kowa; Has ended; Grant/Research Support relationship with Genfit; Has ended; Consultant relationship with Chemomab; Has ended; Consultant relationship with GSK; Has ended; Consultant relationship with Calliditas; Has ended; Grant/Research Support relationship with Calliditas; Has not ended; Consultant relationship with Intercept; Has ended; Grant/Research Support relationship with Cymabay; Has not ended; Grant/Research Support relationship with Intercept; Has not ended, Christopher Bowlus: Calliditas: Grant/Research Support,

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0152 | TUNE-401 IS A NOVEL FIRST-IN-CLASS EPIGENETIC SILENCER DEVELOPED FOR TREATMENT OF CHRONIC HEPATITIS B, WITH PRECLINICAL DATA SHOWING STRONG, DURABLE, AND PRECISE TRANSCRIPTIONAL REPRESSION OF HBV DNA

Brian Cosgrove[1] Aiden Jones[1] Landon Burcham[1] Akiko Seki[1] Matthew Wolpert[1] Lauren Riley[1] Sai An[1] Stuart Sundseth[1] Michael Czerwinski[1] Harry Winters[1] Christina Lee[1] Taylor Bryson[1] Erica Li[1] Ryan Tam[1] Cory Bryant[1] Malathi Chellappan[1] Britta Jones[1] Tyler Goodwin[1] Luis Sanchez-Perez[1] Dilara Sen[1] Jennifer Kwon[1] Jason Dean[1] Tyler Klann[1] Matthew Gemberling[1] Kendra Congdon[1] Derek Jantz[1] Blythe Sather[1]

[1]Tune Therapeutics

Background: Hepatitis B (HBV) viral replication is driven from the cccDNA template, with transcription from cccDNA being heavily regulated through epigenetic mechanisms in chronic infections. Tune-401 is a lipid nanoparticle (LNP) encapsulated nucleic acid therapy that is being developed for the treatment of chronic Hepatitis B. The LNP in Tune-401 packages an mRNA that enables transient protein expression of an epigenetic silencer ("epi-silencer"). This epi-silencer is designed to precisely target and bind a highly conserved HBV DNA sequence with the help of a co-packaged guideRNA. Once bound to HBV DNA targets, the Tune-401 epi-silencer functions to establish a repressive epigenetic state without nicking or cutting DNA. This epigenetic repression results in the durable silencing of HBV transcription from both cccDNA and integrated HBV DNA ("intDNA") following a single dose of Tune-401. **Methods:** The efficacy of Tune-401 was determined using infected PHH to examine cccDNA repression, and Hep3B cell lines for intDNA repression. HBV-infected FRG chimeric liver mice (Fah-/-, Rag2-/-, Il2rg-/-) were utilized to evaluate the performance of Tune-401 in a true *in vivo* HBV infection. A surrogate epi-silencer for a liver gene target (PCSK9) was utilized to understand the durability of epi-silencing in a cynomolgus macaque non-human primate (NHP) model. **Results:** Tune-401 was able to establish as much as 99.99% repression of 3.5 kb HBV RNA from cccDNA (see attached Figure), with similar repression seen in extracellular HBsAg levels. Similarly, Tune-401 dosing resulted in strong repression of Total HBV RNA and extracellular HBsAg from intDNA. Increases in HBV RNA repression following Tune-401 dosing were accompanied by increased methylation of HBV DNA, with durability seen out to 550 days following a single dose. Characterization of the off-target profile with RNA-seq showed precise targeting of HBV with few changes across the human transcriptome. Durable *in vivo* activity of Tune-401 was seen in infected FRG mice, and treatment of NHPs with a PCSK9 surrogate epi-silencer showed repression of PCSK9 at therapeutically relevant levels for over a year following a single transient dose. **Conclusion:** Tune-401 showed strong and durable transcriptional repression from cccDNA and intDNA in a highly precise fashion. Epi-silencing of HBV by Tune-401 represents a new paradigm to potentially achieve functional cure for patients with chronic Hepatitis B, with anticipated clinical readouts beginning in 2025.

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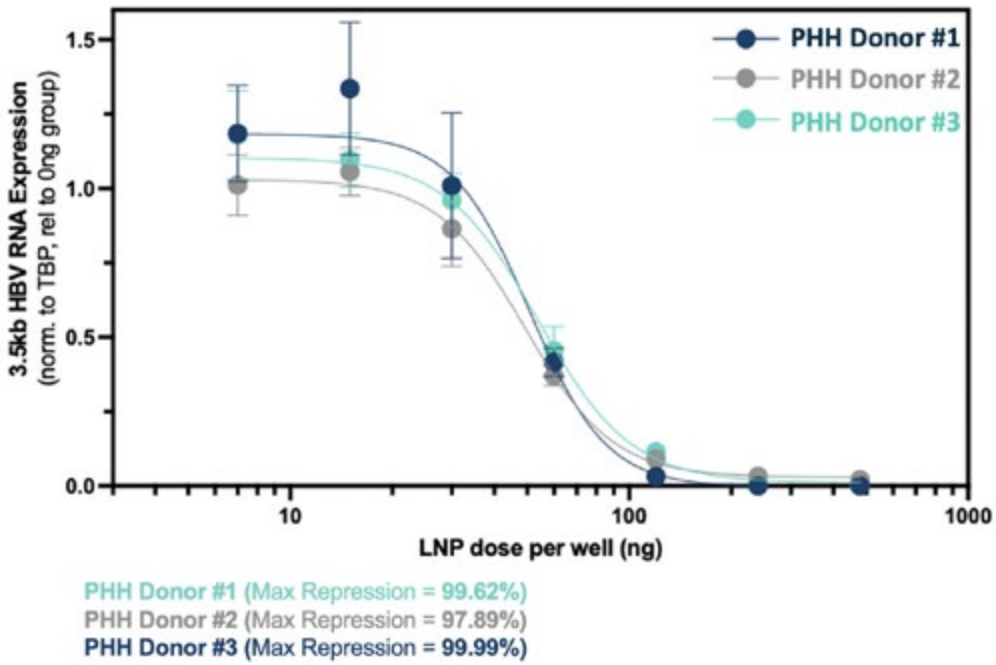

Disclosures: Brian Cosgrove: Tune Therapuetics: Employee, Tune Therapeutics: Stock – privately held company, Tune Therapeutics: Employee, Aiden Jones: Nothing to Disclose, Landon Burcham: Tune Therapeutics: Employee, Tune Therapeutics: Stock – privately held company, Akiko Seki: Tune Therapeutics: Stock – privately held company, Tune Therapeutics: Employee, Matthew Wolpert: Tune Therapeutics: Stock – privately held company, Tune Therapeutics: Employee, Lauren Riley: Nothing to Disclose, Sai An: Nothing to Disclose, Stuart Sundseth: Tune Therapeutics: Employee, Tune Therapeutics: Stock – privately held company, Michael Czerwinski: Tune Therapeutics: Employee, Tune Therapeutics: Stock – privately held company, Harry Winters: Nothing to Disclose, Christina Lee: Tune Therapeutics: Stock – privately held company, Tune Therapeutics: Employee, Taylor Bryson: Nothing to Disclose, Erica Li: Nothing to Disclose, Ryan Tam: Nothing to Disclose, Cory Bryant: Nothing to Disclose, Malathi Chellappan: Nothing to Disclose, Britta Jones: Tune Therapeutics: Employee, Tune Therapeutics: Stock – privately held company, Tyler Goodwin: Nothing to Disclose, Luis Sanchez-Perez: Nothing to Disclose, Dilara Sen: Nothing to Disclose, Jennifer Kwon: Nothing to Disclose, Jason Dean: Nothing to Disclose, Tyler Klann: Nothing to Disclose, Matthew Gemberling: Tune Therapeutics: Stock – privately held company, Tune Therapeutics: Employee, Kendra Congdon: Nothing to Disclose, Derek Jantz: Nothing to Disclose, Blythe Sather: Tune Therapeutics: Holder of Company Stock options, Lyell Immunopharma: Stock - publicly traded company

0153 | A FIRST-IN-CLASS TOOL TO PREDICT FUTURE RISK OF PORTAL HYPERTENSION, LIVER TRANSPLANT AND DEATH IN CHILDREN WITH ALPHA-1-ANTITRYPSIN DEFICIENCY BASED ON PROSPECTIVE DATA FROM THE CHILDHOOD LIVER DISEASE RESEARCH NETWORK

Jeffrey Teckman[1] Catherine Spino[2] Suiyan Huang[2] Gregor Horvath[2] John Magee[3] Philip Rosenthal[4]

[1]Saint Louis University, [2]University of Michigan Hospital, [3]University of Michigan Hospitals and Health Centers, [4]University of California, San Francisco

Background: Children with homozygous ZZ and SZ Alpha-1-antitrypsin deficiency (AATD) exhibit a wide range of liver disease outcomes from asymptomatic without fibrosis to portal hypertension progressing to transplant or death. The course of any individual is not accurately predicted with current tools. **Methods:** The Childhood Liver Disease Research Network (ChiLDReN) is an NIH consortium for the study of pediatric liver diseases, including AATD. ZZ and SZ subjects 0-25 years of age were enrolled at 17 tertiary care sites in the US and Canada. Baseline history, physical exam and standard of care laboratory data were collected and stored in a database. These parameters were then updated at annual prospective follow-up visits and outcomes including development

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of clinically evident portal hypertension (CEPH), liver transplant and death were recorded. We have examined the prospective, standard-of-care data of the AATD participants enrolled with native liver using Cox proportional hazard regression, and new risk prediction techniques, unrelated to past PELD/MELD score development to assign risks of CEPH, liver transplant and death, including confidence intervals. **Results:** Prospective ChiLDReN data from 2007-2023 of 452 AATD participants with native liver were analyzed (60% male, 94% non-Hispanic white, 90% ZZ), with a median of 6.6 years of follow-up and totaling 2,654 patient-years. Twenty-nine subjects underwent liver transplant, plus 3 deaths were observed (all 32 with liver transplant or death had preceding development of CEPH documented) during longitudinal follow-up, and 18 additional participants who entered the study without CEPH with native liver are alive with CEPH and native liver. Clinical parameters significantly associated with liver transplant, death and CEPH were identified from the data set. Newly designed statistical techniques were then used to construct an algorithm and risk predictive nomogram including variables of age, total bilirubin, AST, GGTP, INR, albumin and platelet count for liver transplant and death, and including age, a history of neonatal cholestasis, height Z score, total bilirubin, AST, GGTP, and platelet count for the development of CEPH. **Conclusion:** For the first time, it is possible to assign a predictive risk with confidence intervals, at any age, of future severe liver disease in ZZ and SZ AATD. These data may assist in family counseling, future clinical trial design and in the application of new therapies.

Disclosures: Jeffrey Teckman: Arrowhead Inc: Grant/Research Support, BioMarin: Consultant, Camp4: Grant/Research Support, Congruence Therapeutics: Consultant, Critical Path Institute: Consultant, Inhibrix: Grant/Research Support, KorroBio: Consulting, Takeda: Consultant, UniQure: Independent Contractor, Vertex: Consultant, Intellia: Consultant, Beam Therapeutics: Consultant, Alpha-1 Foundation: Grant recipient, Catherine Spino: Nothing to Disclose, Suiyan Huang: Nothing to Disclose, Gregor Horvath: Nothing to Disclose, John Magee: Nothing to Disclose, Philip Rosenthal: Nothing to Disclose

0154 | CHRONIC HEPACIVIRUS INFECTION IN MICE LEADS TO PROGRESSIVE FIBROSIS AND HCC

Mariana Nogueira Batista[1] Juliano Bordignon[2] Ana Luiza Mosimann[2] Tesia Bobrowski[3] Hsuan-An Chen[1] Gabriel Tobin-Xet[1] Corrine Quirk[1] Luis Chiriboga[4] Neil Theise[4] Troels Scheel[5] Scott Lowe[6] Brad Rosenberg[3] Charles Rice[1]

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Background: Hepatocellular carcinoma (HCC) is the third leading cause of cancer mortality worldwide. Chronic hepatitis C virus (HCV) infection has long been recognized as a major cause of HCC, and although antiviral treatments reduce HCV-associated HCC, cured patients are still at elevated risk of developing HCC. From initial liver damage to HCC development, the oncogenic process of HCC takes decades in humans. There have been many unsuccessful attempts at generating mouse models with the goal of trying to better understand tumorigenesis and tumor vulnerabilities on a shorter timescale. However, to date, there is no murine model where chronic hepatotropic viral infection leads to HCC. We explored the Norway rat hepacivirus (NrHV), an HCV-related virus that recapitulates host factor dependencies and immunological responses of HCV infection in humans, as a surrogate mouse model for hepatitis C pathogenesis. **Methods:** After transient CD4 depletion, we infected 120 mice with the mouse-adapted $NrHV_{SLIS}$ in two independent 18-month experiments and evaluated disease progression over time, collecting serum monthly and organs every 6 months. We characterized disease progression histologically and molecularly. **Results:** Chronic NrHV infection of immunocompetent mice elicits hepatitis with hallmarks of hepatitis C including liver steatosis and lymphoid aggregates. Infection leads to progressive fibrosis, HCC development with high incidence by 18 months, and recapitulates the sexual dimorphism seen in humans. Genes similar to those seen in HCV-infected humans are upregulated in NrHV-infected mice. Tumors are histologically well-differentiated, steatotic, and inflamed. At the transcriptional level, NrHV-elicited tumors are heterogeneous but share upregulated remodeling, inflammatory and proliferation pathways. A subset of NrHV tumors recapitulates the transcriptional signatures seen in mouse tumors harboring mutations in beta-catenin and Tert even without these specific driver mutations. **Conclusion:** Our results establish an experimentally tractable, immunocompetent, and physiologically relevant small animal model for studying hepacivirus-elicited HCC including the impact of comorbidities, such as diet or alcohol, on tumorigenesis.

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Disclosures: Mariana Nogueira Batista: Nothing to Disclose, Juliano Bordignon: Nothing to Disclose, Ana Luiza Mosimann: Nothing to Disclose, Tesia Bobrowski: Nothing to Disclose, Hsuan-An Chen: Nothing to Disclose, Gabriel Tobin-Xet: Nothing to Disclose, Corrine Quirk: Nothing to Disclose, Luis Chiriboga: Nothing to Disclose, Neil Theise: Nothing to Disclose, Troels Scheel: Nothing to Disclose, Scott Lowe: Nothing to Disclose, Brad Rosenberg: Dispatch Biotherapeutics: Advisor, Charles Rice: Vir: Grant/Research Support, Vir: Advisor, Vir: Options, non-excersized will expire in August 2024, Invisishield: Advisor, Invisishield: Stock – privately held company, Apath LLC: Manager, GSK: Grant/Research Support

0155 | NOVEL HOST FACTORS IN HEPATITIS B VIRAL SURFACE ANTIGEN PRODUCTION IDENTIFIED BY GENOME-WIDE CRISPR-CAS9 KNOCKOUT SCREEN★

Chloe Boehm[1] Catherine Freije[1] Ana Pamplona Mosimann[1] Juliano Bordignon[1] Yingpu Yu[1] Jérémie Le Pen[1] H.-Heinrich Hoffmann[1] Xupeng Hong[1] Leon Seifert[1] John Poirier[2] William Schneider[1] Charles Rice[1]

[1]Laboratory of Virology and Infectious Disease, The Rockefeller University, New York, NY, USA, [2]Laura and Isaac Perlmutter Cancer Center, New York University Langone Health, New York, NY, USA

Background: Host-directed antivirals represent a promising avenue in hepatitis B virus (HBV) therapeutics. To identify novel host targets involved in HBV surface antigen production, we performed a full genome CRISPR-Cas9 knockout (KO) screen with RNA launch, a method in which HBV replication is initiated with transfection of pregenomic RNA (pgRNA), an RNA intermediate in HBV's life cycle. Because virus entry is bypassed with RNA launch, later steps in the HBV life cycle, such as genome packaging, reverse transcription, cccDNA formation, and viral antigen production are assessed more readily. **Methods:** A full genome CRISPR-Cas9 KO screen was performed using human hepatoma cells (Huh7.5) and the Brunello library. The cells were then transfected with HBV pgRNA and sorted based on surface antigen (HBsAg) expression. Candidate host targets were determined using MAGECK comparing single-guide RNA (sgRNA) counts between different sorted populations. This analysis guided the selection of 100 genes for arrayed validation representing a combination of known and novel pro- and antiviral host factors. Validation of these 100 genes was performed using Huh7.5 cells stably expressing Cas9 in an arrayed format. In brief, each well received a pool of sgRNAs complementary to a single host factor or a pool of non-targeting sgRNAs. Following Cas9-mediated KO, cells were transfected with HBV pgRNA, HBsAg expression was measured via chemiluminescence immunoassay (CLIA), and cell counts were determined by imaging. **Results:** Arrayed validation of host targets identified by the full genome CRISPR-Cas9 KO screen identified several novel HBV antiviral genes (KO increased HBsAg production) and proviral genes (KO decreased HBsAg production). For proviral hits, there was high concordance between the arrayed and screen **Results:** (92.8% replicated) while antiviral hits showed reduced concordance (51.7% replicated). A small subset of pooled sgRNAs (2%) induced cytotoxicity. **Conclusion:** Arrayed validation of a full genome CRISPR Cas-9 KO screen successfully identified several novel host factors influencing HBsAg production that may represent viable host-directed therapeutic targets. Our validation identified proviral genes involved in viral exocytosis and inter-organelle vesicle transport pathways. Validated antiviral genes include those involved in RNA stability and decay. Generation of KO cell lines followed by measurement of HBV core antigen, HBV DNA levels and cellular HBsAg levels informs the specific steps in which these host factors are acting.

Disclosures: Chloe Boehm: Nothing to Disclose, Catherine Freije: Nothing to Disclose, Ana Pamplona Mosimann: Nothing to Disclose, Juliano Bordignon: Nothing to Disclose, Yingpu Yu: Nothing to Disclose, Jérémie Le Pen: Nothing to Disclose, H.-Heinrich Hoffmann: Nothing to Disclose, Xupeng Hong: Nothing to Disclose, Leon Seifert: Nothing to Disclose, John Poirier: Nothing to Disclose, William Schneider: Nothing to Disclose, Charles Rice: Vir: Grant/Research Support, Vir: Advisor, Vir: Options, non-excersized will expire in August 2024, Invisishield: Advisor, Invisishield: Stock – privately held company, Apath LLC: Manager, GSK: Grant/Research Support

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0156 | THE LIPIDOMIC PROFILE DISCRIMINATES BETWEEN METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE AND COMBINED METABOLIC DYSFUNCTION- AND ALCOHOL-RELATED STEATOTIC LIVER DISEASE ◆

Carolin Victoria Schneider[1] Rohit Loomba[2] Helen Huang[1] Anastasia Raptis[1] Kate Townsend Creasy[3] Jan Clusmann[1] Felix Van Haag[1] Tom Luedde[4] Sven Francque[5] Kai Markus Schneider[6]

[1]RWTH Aachen, [2]University of California, San Diego, [3]University of Pennsylvania, [4]University Hospital Duesseldorf, Heinrich Heine Universität, [5]InflaMed Centre of Excellence, Laboratory for Experimental Medicine and Paediatrics, Translational S, [6]University Hospital Aachen

Background: The recent multi-society Delphi consensus statement revised the nomenclature of steatotic liver disease to replace non-alcoholic fatty liver disease. Based on the new nomenclature, metabolic dysfunction-associated steatotic liver disease (MASLD) and Metabolic Dysfunction and Alcohol-Related Liver Disease (MetALD) represent distinct disease entities. The primary distinguishing feature between the two is often based on self-reported alcohol consumption. However, molecularly discriminating features or biomarkers that define MASLD and MetALD remain largely unknown **Methods:** Using the UK Biobank dataset, 40,534 people with available MRI liver scans at the second follow up (mean six years after baseline) were analyzed. 11,217 (27,7%) cases with a proton density fat fraction (PDFF) ≥5% were identified as having steatotic liver disease (SLD). Among these, following grouping based on the new nomenclature, lipidomic profiles were obtained for 5,539 MASLD, 462 MetALD and 53 alcohol-related liver disease (ALD) cases at baseline and for a subset at the first follow up (mean four years after baseline: 1154 MASLD patients, 97 MetALD and 11 ALD). 250 plasma lipidomic and metabolomic parameters were analyzed and analyses were corrected for age, sex and BMI. **Results:** The top metabolites discriminating MetALD from MASLD were Acetoacetate (OR:1.30, 95%1.21-1.41 p=1,48E-11), 3-Hydroxybutyrate (OR:1.29, 95%1.20-1.39 p=1,72E-11), Phospholipids in Large HDL (OR:1.20, 95%1.16-1.23 p=1,85E-32), Concentration of Large HDL Particles, Free Cholesterol in Large HDL, Cholesterol in Large HDL, Cholesteryl Esters in Large HDL, Total Lipids in Large HDL, Free, Cholesterol in Medium HDL, Cholesterol in Medium HDL. All of these were significantly higher in the MetALD group compared to the MASLD group. Strikingly, the metabolites with the greatest effect sizes are associated with large-sized HDL particles. As a sensitivity analysis, we additionally compared53 cases of patients with proven ALD to MASLD, the effect size was highest for 3-hydroxybutyrate (OR: 1.76, 95%CI 1.44-2.15, p=4,01E-08) and acetoacetate (OR:1.66, 95%1.35-2.06, p=2,2E-06), followed by large HDL related markers. To prove that the lipidomic signature is stable over time, we repeated the analyses comparing MetALD vs. MASLD as well as ALD vs. MASLD. Strikingly, the HDL phenotype, especially concerning large HDL-associated parameters was repeated, but Acetoactetate was not significantly different in MetALD vs MASLD, but in ALD vs. MASLD. **Conclusion:** Our findings indicate that HDL-centric lipidomic markers, particularly those within the larger HDL subfraction as well as acetoacetate, may differentiate MetALD from MASLD. While moderate alcohol consumption is known to raise HDL levels, the underlying mechanisms are still unclear. Further longitudinal and experimental studies are warranted to validate these findings and assess their clinical implications.

Disclosures: Carolin Victoria Schneider: Nothing to Disclose, Rohit Loomba: Eli Lilly and Company: Consultant, 89bio: Consultant, Aardvark Therapeutics: Consultant, Altimmune: Consultant, Alnylam/Regeneron: Consultant, Amgen: Consultant, Arrowhead Pharmaceuticals: Consultant, AstraZeneca: Consultant, Bristol Myers Squibb: Consultant, CohBar: Consultant, Eli Lilly: Consultant, Galmed Pharmaceuticals: Consultant, Gilead: Consultant, Glympse Bio: Consultant, Hightide: Consultant, Inipharma: Consultant, Intercept: Consultant, Inventiva: Consultant, Ionis: Consultant, Janssen, Inc.: Consultant, Madrigal Pharmaceuticals: Consultant, Merck, Metacrine, Inc.: Consultant, NGM Biopharmaceuticals: Consultant, Novartis: Consultant, Novo Nordisk: Consultant, Pfizer: Consultant, Sagimet Biosciences: Consultant, Terns Pharmaceuticals: Consultant, Theratechnologies and Viking Therapeutics: Consultant, 89bio: Stock options, Sagimet Biosciences: Stock options, Arrowhead Pharmaceuticals: Research grant, AstraZeneca: Research grant, Boehringer Ingelheim: Research grant, Bristol Myers Squibb: Research grant, Eli Lilly: Research grant, Galectin Therapeutics: Research grant, Galmed Pharmaceuticals: Research grant, Gilead: Research grant, Hanmi: Research grant, Intercept: Research grant, Inventiva: Research grant, Ionis: Research grant, Janssen, Inc.: Research grant, Madrigal Pharmaceuticals: Research grant, Merck: Research grant, NGM Biopharmaceuticals: Research grant, Novo Nordisk: Research grant, Pfizer: Research grant, Sonic Incytes: Research grant, Terns Pharmaceuticals: Research grant, LipoNexus, Inc.: Co-founder, Helen Huang: Nothing to Disclose, Anastasia Raptis: Nothing to Disclose, Kate Townsend Creasy: Nothing to Disclose, Jan Clusmann: Nothing to Disclose, Felix Van Haag: Nothing to Disclose, Tom Luedde: Nothing to Disclose, Sven Francque: Nothing to Disclose, Kai Markus Schneider: Nothing to Disclose

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0157 | SINGLE-CELL IMAGING MASS CYTOMETRY DEFINES IMMUNE CELL COMPOSITION AND SPATIAL INTERACTIONS WITH APOPTOTIC HEPATOCYTES IN IMMUNE-MEDIATED LIVER INJURY FROM CHECKPOINT INHIBITORS (ILICI) AND AUTOIMMUNE HEPATITIS (AIH) ★

Jacob Bogdanov[1] Neil Zhao[2] Layla Shojaie[1] Helia Alavifard[1] Mahmoud Mohamed[1] Aria Baktash[1] Andrew Stolz[1] Akil Merchant[3] David Kleiner[4] Robert Fontana[2] Jonathan Sexton[2] Lily Dara[1]

[1]University of Southern California, [2]University of Michigan, [3]Cedars-Sinai Medical Center, [4]National Cancer Institute, Bethesda

Background: Rising use of immune checkpoint inhibitors (ICI) targeting the Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1) pathways has transformed oncology. The liver, however, relies on these immunotolerant mechanisms to prevent autoimmunity. Disruption of these mechanisms has led to cases of severe Immune-mediated Liver Injury from Checkpoint Inhibitors (ILICI). In our murine ILICI model, hepatocyte apoptosis was mediated by macrophage and CD8+ cytotoxic T lymphocyte (CTL) cross-talk. Similarly, in autoimmune hepatitis (AIH) the loss of immune tolerance begets aberrant immune activation causing hepatocyte death. In this study we explored the cell death subroutines and mechanisms of immune-mediated injury in liver tissue from patients with ILICI and AIH. **Methods:** Using a 45-plex metal-conjugated antibody panel, Imaging Mass Cytometry (IMC) was performed to phenotype and resolve spatial relationships between >300k cells on FFPE liver biopsies from patients with ILICI (from the Drug-Induced Liver Injury Network), AIH, or healthy controls (n=16,16,3). 184 regions of interest were imaged at 1μm-resolution. Cell segmentation (Cellpose Cyto3) was performed to delineate single cells within the tissue. Cellular intensity and morphometrics (CellProfiler) generated >2,700 per-cell measurements. The k-nearest neighbors (kNN) algorithm was used to assess spatial interactions between different cell types. Machine learning models were then trained on the extracted features to define cellular composition and spatial organization. **Results:** UMAP dimensionality reduction and density-based clustering identified 44 clusters of cells. We evaluated interactions between cleaved Caspase3+ (cC3+) hepatocytes undergoing apoptosis, monocytes/macrophages, and CTLs. Pairwise Euclidian distance plots show macrophages were the nearest cells to cC3+ hepatocytes ($\bar{x}$=41.07μm, p<2.2e-16) and that CTLs were found closer to cC3+ hepatocytes in ILICI when compared to AIH ($\bar{x}$ICI=45.11μm, $\bar{x}$AIH=57.54μm; p<2.2e-16). In contrast, CD20+ B cells were in closer proximity to cC3+ hepatocytes in AIH ($\bar{x}$AIH=54.66μm, $\bar{x}$ICI=63.33μm; p<2.2e-16). **Conclusion:** Single-cell IMC analysis demonstrated that liver biopsies from ILICI patients contain areas of hepatocellular injury enriched in macrophages and CTLs. These data validate prior findings from our murine model and that the mechanism of human ILICI involves the participation of monocytes/macrophages and is separate and distinct from that seen in AIH.

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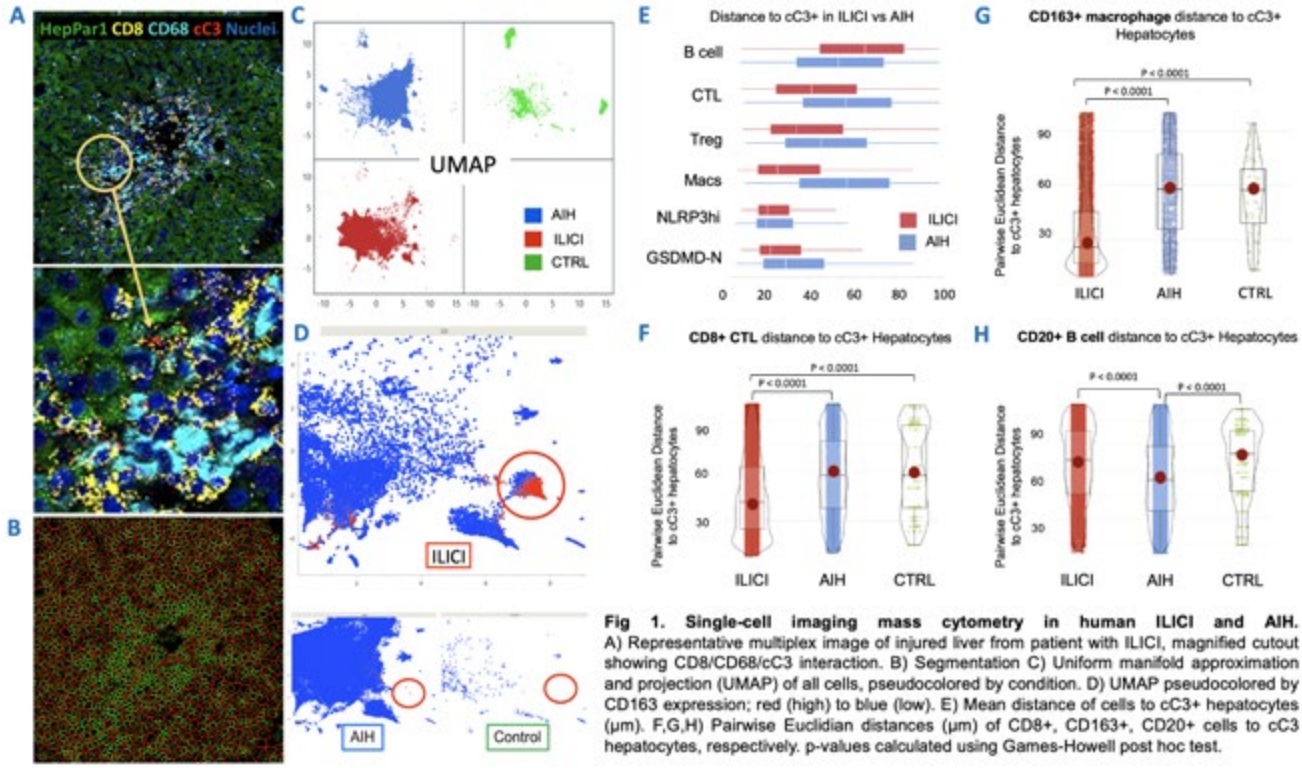

Fig 1. Single-cell imaging mass cytometry in human ILICI and AIH. A) Representative multiplex image of injured liver from patient with ILICI, magnified cutout showing CD8/CD68/cC3 interaction. B) Segmentation C) Uniform manifold approximation and projection (UMAP) of all cells, pseudocolored by condition. D) UMAP pseudocolored by CD163 expression; red (high) to blue (low). E) Mean distance of cells to cC3+ hepatocytes (μm). F,G,H) Pairwise Euclidian distances (μm) of CD8+, CD163+, CD20+ cells to cC3 hepatocytes, respectively. p-values calculated using Games-Howell post hoc test.

Disclosures: Jacob Bogdanov: Nothing to Disclose, Neil Zhao: Nothing to Disclose, Layla Shojaie: Nothing to Disclose, Helia Alavifard: Nothing to Disclose, Mahmoud Mohamed: Nothing to Disclose, Aria Baktash: Nothing to Disclose, Andrew Stolz: Nothing to Disclose, Akil Merchant: Nothing to Disclose, David Kleiner: Nothing to Disclose, Robert Fontana: Grant/Research Support relationship with kezar pharmaceuticals; Has not ended; Consultant relationship with moderna; Has ended; Grant/Research Support relationship with Takeda Pharmaceuticals; Has not ended, Jonathan Sexton: Nothing to Disclose, Lily Dara: Consultant relationship with Intercept Pharmaceuticals; Has not ended; Grant/Research Support relationship with Intercept Pharmaceuticals; Has not ended

0158 | EFRUXIFERMIN SIGNIFICANTLY IMPROVED LIVER FIBROSIS AT WEEK 96 IN THE HARMONY STUDY ACROSS SUBGROUPS AND IMPROVEMENTS WERE ASSOCIATED WITH CHANGES IN BIOMARKERS

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Background: HARMONY, a phase 2b study evaluating the efficacy and safety of efruxifermin (EFX) in subjects with metabolic dysfunction-associated steatohepatitis (MASH), fibrosis stage 2 or 3 (F2–F3), met its primary endpoint of ≥1 stage improvement in fibrosis with no worsening of MASH at Week 24. Here, we describe the expansion (greater response rates) and deepening (reversal by 2 stages) of fibrosis improvement from Weeks 24 to 96 of the study, consistency of histologic response across relevant subgroups, and associations between extent of fibrosis reversal and noninvasive markers of liver injury, fibrosis, and metabolism. **Methods:** Subjects were randomly assigned to groups that received placebo or EFX 28 mg or 50 mg for 96 weeks. Liver biopsies were assessed at baseline and Weeks 24 and 96. Biomarkers of liver injury, fibrosis, and metabolic health were

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measured throughout the study. Associations between changes in these biomarkers and improvements in liver fibrosis were assessed. **Results:** Subjects treated with EFX had sustained and continued improvements in histologic parameters over 96 weeks; response rate for fibrosis improvement by ≥1 stage without worsening of MASH expanded from 40% at Week 24 to 75% at Week 96. Further improvement in extent of fibrosis was evident based on doubling (from 15% at Week 24 to 36% at Week 96) in the proportion of subjects with 2-stage improvement. Consistent fibrosis improvement was observed across subgroups defined by baseline F-stage, NAFLD activity score (NAS), type 2 diabetes status, body mass index (BMI), and *PNPLA3* genotype (see Table). Improvements in noninvasive markers of liver injury and fibrosis and metabolic parameters were associated with histologic response after 96 weeks. **Conclusion:** The anti-fibrotic effects observed at Week 24 in patients with MASH and F2–F3 treated with EFX 28 mg and 50 mg were sustained, expanded, and deepened through Week 96, and were consistent among subgroups. Non-invasive markers of liver injury and fibrosis, as well as metabolic health, corroborated the improvement in histopathology.

Table: Odds Ratios for Proportion of Subjects with Improvement in Fibrosis by ≥1 Stage Without Worsening of MASH after 96 Weeks

	Odds Ratios [OR] for EFX/Placebo	EFX 28 mg	EFX 50 mg
All subjects	N	26	28
	OR (95% CI)	2.9 (0.9, 9.3)	11.9 (3.3, 43.4)
	P value vs placebo	0.07	**<0.001**
Fibrosis stage 2	N	11	9
	OR (95%CI)	1.7 (0.3, 9.2)	9.8 (1, 99)
	P value vs placebo	0.536	**0.040**
Fibrosis Stage 3	N	15	19
	OR (95%CI)	4.9 (0.9,26.4)	13.2 (2.8,62.0)
	P value vs placebo	0.053	**<0.001**
NAS ≤5	N	18	13
	OR (95%CI)	1.9 (0.5,7.2)	30.8 (2.3,413.2)
	P value vs placebo	0.372	**0.002**
NAS >5	N	8	15
	OR (95%CI)	9.2 (0.7,118.1)	7.7 (1.4,42.3)
	P value vs placebo	0.086	**0.016**
Type 2 diabetes at baseline	N	19	21
	OR (95%CI)	1.8 (0.4,7.6)	12.3 (2.7,55.1)
	P value vs placebo	0.401	**<0.001**
No type 2 diabetes at baseline	N	7	7
	OR (95%CI)	9.0 (0.8,97.8)	11.0 (0.9,139.6)
	P value vs placebo	0.053	0.053
BMI ≤ median	N	13	15
	OR (95%CI)	2.0 (0.4,10.6)	5.7 (1.2,26.1)
	P value vs placebo	0.431	**0.032**
BMI > median	N	13	13
	OR (95%CI)	6.7 (0.6,70.0)	Not estimable
	P value vs placebo	0.078	**<0.001**
***PNPLA3* genotype II**	N	7	5
	OR (95%CI)	2.7 (0.3, 15.9)	3.0 (0.4, 22.6)
	P value vs placebo	0.615	0.580
***PNPLA3* genotype IM or MM**	N	19	23
	OR (95%CI)	2.3 (0.6, 8.9)	11.5 (3.0, 41.2)
	P value vs placebo	0.314	**0.0007**

NAS, NAFLD activity score; *PNPLA3*, gene that encodes patatin-like phospholipase domain-containing protein 3

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0159 | ULTRADEEP SEQUENCING OF THE GUT MICROBIOME SHOWS PROGRESSIVE WEAPONIZATION OF ENTEROBACTERIACEAE WITH CIRRHOSIS PROGRESSION THROUGH MOBILE GENETIC ELEMENTS WHICH MAY NOT RECOVER AFTER FMT

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Background: Antibiotic-resistant infections are associated with high mortality in cirrhosis, with the gut being the largest reservoir. Mobile genetic elements (MGE), including plasmids and phage, are major drivers of this resistance. Understanding which bacteria harbor mobile antibiotic resistance (AR) and virulence (VG) genes is critical for the development of targeted treatment strategies against increasingly difficult-to-treat infections. **Methods:** We used proximity ligation metagenomics, which combines ultra-deep shotgun sequencing with formaldehyde cross-linking prior to cell lysis, to establish plasmid- and phage-bacterial host interactions without culturing. We applied this to fecal samples from outpatients with compensated & decompensated cirrhosis and age-matched healthy controls. We developed a Genome Interaction Map Index (GIMI), which incorporates the threat level of chromosomal and mobile ARGs and VGs with knowledge of the microbial hosts of these genes. The GIMI calculation was applied to members of the Enterobacteriaceae given their importance in cirrhosis-related infections. In a parallel analysis, the same methodology was applied to study the enteric resistome in a series of non-cirrhotic patients being treated for recurrent *Clostridioides difficile* infections with fecal microbiota transplantation (FMT). **Results:** We enrolled 54 subjects total (24 initial group with controls & cirrhosis, and 30 with rCDI). Initial group of 24: 4 controls (59 yrs), 6 comp (MELD 8, 60 yrs), 14 decomp pts (61 yrs, all HE controlled on lactulose, 7 also on rifaximin, 7 also with ascites, MELD 15). None were on SBP prophylaxis but 55% of cirrhosis had undergone procedures or had been admitted within 90 days. Enterobacteriaceae spp in controls contained few ARGs and VGs of clinical significance in their genomic DNA or associated plasmids and phages. We observed increased burden of ARGs and VGs in patients with liver cirrhosis (representative image Fig 1). Furthermore, the burden of Enterobacteriaceae-associated ARGs and VGs increased with cirrhosis progression and was driven by MGE. MGE-encoded ARGs and VGs associated with clinically important gram-positive organisms were relatively less prominent. FMT for rCDI (30 subjects, studied pre-FMT and weeks 1 and 4 post-FMT) did not eliminate the ARGs associated with the Enterobacteriaceae spp, although rCDI was prevented.

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Conclusion: Using proximity ligation metagenomics, which allows quantitative assessment of antibiotic resistance & virulence potential of pathobionts, we found that gut microbial Enterobacteriaceae in cirrhosis become more virulent with disease progression through greater association with MGE. In cirrhosis this was related to prior hospital exposure unlike rCDI where chronic antibiotic use produced similar results. Enterobacteriaceae & their MGE were not eliminated by FMT, underlining the need to reduce unnecessary exposure in cirrhosis.

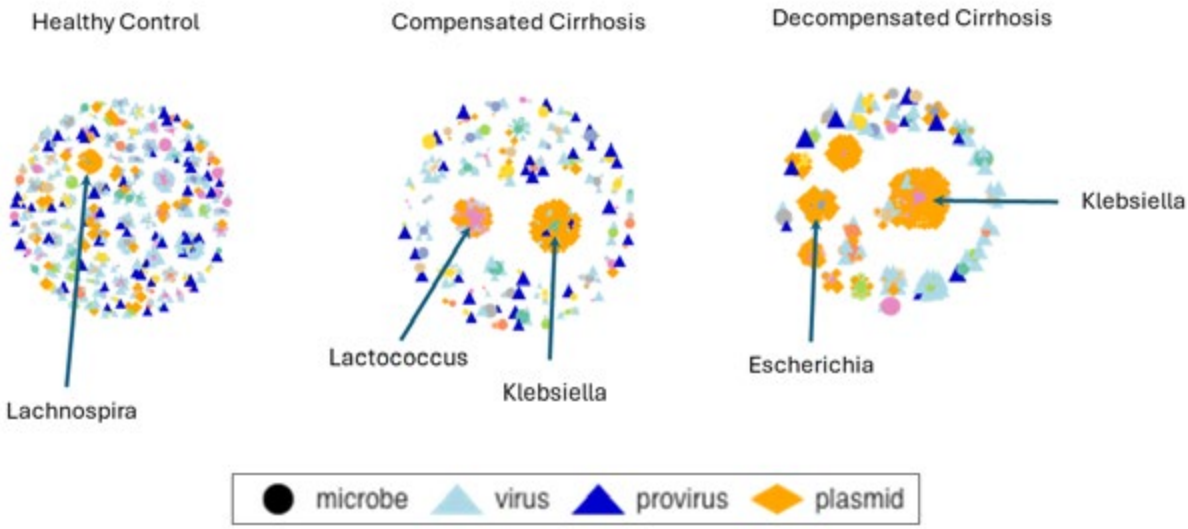

Figure. Representative analyses of fecal samples from healthy (left), compensated cirrhosis (center), and decompensated cirrhosis demonstrate associations of individual bacteria (centers of clusters) with mobile genetic elements.

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0160 | VALIDATION OF POLYGENIC RISK SCORES TO PREDICT MASLD ACTIVITY SCORE (MAS) AND ADVANCED FIBROSIS IN A LARGE COHORT OF PATIENTS WITH BIOPSY-PROVEN MASLD

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Background: MASLD and fibrosis are heritable. While several polygenic scores (PRS) exist, most are from cohorts lacking histological characterization. We therefore investigated selected SLD PRS in a large multiethnic cohort of patients with biopsy-proven MASLD. **Methods:** We included 3,049 biopsy-proven MASLD patients with liver histology and GWAS and whole exome sequencing from the NASH CRN. MAS and fibrosis stage were assessed according to the NASH CRN scoring system. Genotype data were imputed using the latest TOPMed reference panel via TOPMed Imputation Server. Selected SLD and Cirrhosis PRS were derived based on recent publications by Chen et al. (16 SNPs, PMID 37709864), Emdin et al. (12 SNPs, PMID 33310085), Whitfield et al. (3 SNPs, PMID 34656649), Schwantes-An et al. (20 SNPs, PMID 38727677), and Vujkovic et al. (77 SNPs, PMID 35654975). Each PRS was computed by summing the products of SNP risk allele dosages and their reported effect sizes, standardized with mean 0 and standard deviation 1 within each ancestry group. Multivariable regression models, utilizing forward selection by AIC, were applied to identify the PRS showing the strongest associations with both continuous and categorical measures of NAS and fibrosis, after adjusting for ancestry. **Results:** Our cohort comprised 2,149 adults and 900 children, with 55% female and 27% diabetic individuals. The mean BMI was 33.9 ± 6.5 kg/m², with 2010 individuals of European ancestry and 1039 of Ad Mixed American descent. The mean (SD)

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NAS and fibrosis scores were 4.2 (1.7) and 1.5 (1.3), respectively, with 67% having NAS ≥ 4 and 26% with fibrosis stage ≥ 3. Mean (SD) PRS scores were: PRS-Chen 1.18 (0.21), PRS-Emden 2.02 (0.46), PRS – Vujkovic 4.59 (0.39), PRS-Whitfield 1.70 (0.70) and PRS-Schwantes-An 7.45 (1.40). PRS-Chen had the strongest association with MAS (both continuous [β 0.22, SE 0.03, p-val: 3.22E-13] & categorical [OR 1.29, 95% CI 1.20-1.40, p-val: 4.09E-11]) and fibrosis as a continuous variable (β 0.07, SE 0.03, p-val: 1.61E-02) whereas PRS-Schwantes-An showed a strong association with fibrosis (both continuous [β 0.07, SE 0.06, p-val: 3.40E-02] & categorical [OR 1.22, 95% CI 1.12-1.32, p-val: 3.48E-06]) (Table 1). **Conclusion:** The 16-SNP PRS-Chen showed the strongest association with both steatohepatitis and advanced fibrosis. If confirmed by other studies, this PRS could serve as the primary PRS for exploring gene*environmental interplay and informing clinical trial design.

Table 1: Associations between different PRS and MAS and Fibrosis by uni-and- multivariable regression analyses

	Univariate Analysis			Multivariable Analysis		
MAS continuous (0-8)	**Effect Size**	**SE**	**P-value**	**Effect Size**	**SE**	**P-value**
PRS-Chen	0.22	0.03	3.22E-13	0.22	0.03	3.22E-13
PRS-Schwantes-An	0.18	0.03	3.66E-09			
PRS-Vujkovic	0.14	0.03	5.01E-06			
PRS-Emdin	0.15	0.03	2.55E-07			
PRS-Whitfield	0.16	0.03	4.36E-08			
Fibrosis continuous (0-4)	**Effect Size**	**SE**	**P-value**	**Effect Size**	**SE**	**P-value**
PRS-Chen	0.12	0.02	1.61E-07	0.07	0.03	1.61E-02
PRS-Schwantes-An	0.12	0.02	3.14E-07	0.07	0.03	3.40E-02
PRS-Vujkovic	0.05	0.02	2.68E-02			
PRS-Emdin	0.11	0.02	5.47E-07			
PRS-Whitfield	0.11	0.02	2.86E-06			
MAS < 4 vs ≥ 4	**OR**	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**
PRS-Chen	1.29	1.2, 1.4	4.09E-11	1.29	1.20, 1.40	4.09E-11
PRS- Schwantes-An	1.24	1.15, 1.34	3.28E-08			
PRS-Vujkovic	1.17	1.08, 1.25	4.02E-05			
PRS-Emdin	1.23	1.13, 1.32	2.04E-07			
PRS-Whitfield	1.22	1.13, 1.32	2.55E-07			
Fibrosis F0-2 vs F3-4	**OR**	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**
PRS-Schwantes-An	1.22	1.12, 1.32	3.48E-06	1.22	1.12, 1.32	3.48E-06
PRS-Vujkovic	1.04	0.95, 1.12	3.96E-01			
PRS-Emdin	1.19	1.09, 1.29	4.38E-05			
PRS-Chen	1.17	1.08, 1.27	2.27E-04			
PRS-Whitfield	1.16	1.07, 1.26	3.66E-04			

Abbreviations: PRS: Polygenic Risk Score, SE: Standard Error.
References for selected PRS: PRS-Chen: PMID 37709864, PRS-Emdin: PMID 33310085, PRS-Whitfield: PMID 34656649, PRS-Schwantes-An: PMID 38727677, and PRS-Vujkovic: PMID 35654975

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0161 | CLINICAL STATUS AND LIVER HISTOLOGY AT LIVER TRANSPLANTATION IN PROGRESSIVE FAMILIAL INTRAHEPATIC CHOLESTASIS – EXPERIENCES FROM THE CHILDHOOD LIVER DISEASE RESEARCH NETWORK

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Background: FIC1, BSEP, and MDR3 deficiencies (PFIC 1, 2, and 3) are genetic cholestatic liver disorders that typically present in infancy or early childhood. Disease complications that may prompt liver transplant (LT) include decompensated cirrhosis and hepatocellular carcinoma (HCC). LT may also be indicated for other indications, including intractable pruritus, even in the absence of significant hepatic fibrosis or HCC. **Methods:** Children with FIC1, BSEP, or MDR3 deficiency participating in the NIDDK-funded ChiLDReN consortium who received a LT were studied. A pathologist at each participating site retrospectively reviewed pathology reports from explanted livers to extract stage of fibrosis (scale 0 to 4) and presence of hepatic nodules (including HCC). Clinical data were only available for participants enrolled pre-LT. **Results:** Sixty-four participants (pts), including 11 FIC1, 41 BSEP and 12 MDR3, underwent LT at median age of 6.5, 3.5 and 9.9 years respectively. Overall, 81% had stage 3 or 4 fibrosis (FIC1 [55%] BSEP [83%], and MDR3 [100%])(Table). HCC was identified on explant in 7/41 (17%) BSEP (ABCB11 mutations - 4 biallelic missense, 2 biallelic protein-truncating and 1 protein truncating + E297G) and 1/12 (8%) MDR3, with median age at LT 1.7 (0.7-6.3) yrs (BSEP HCC) and at 15.9 yrs (MDR3 HCC). All pts with HCC, except for one BSEP, had stage 3-4 fibrosis. High-grade dysplastic nodules were present in one BSEP, and large regenerative (≥1 cm) nodules were present in half of MDR3s (6/12). Features of decompensated liver disease including INR >2, albumin <3.0 g/dL, and/or platelet ct <110,000/μL were present in ~ 60% of FIC1 and BSEP, and in 88% of MDR3. Severe pruritus (clinician scratch score 3-4) was present in ~50% of pts with FIC1 or BSEP deficiency. **Conclusion:** A majority of children with FIC1, BSEP, and MDR3 deficiency who received LT had advanced hepatic fibrosis with clinical features suggestive of decompensated disease present in most but not all. HCC was most frequently observed in BSEP pts, underscoring the importance of screening and its role as an indication for LT. Notably, LT was performed with mild fibrosis in FIC1 and BSEP deficiency, therefore one should not assume LT equates with liver decompensation and, as such, use of liver transplantation as a marker of disease natural history - especially in clinical trials - is nuanced.

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0162 | PEOPLE OF AFRICAN/AFRICAN AMERICAN ANCESTRY HARBOR FEWER LIVER DISEASE-RELATED RISK ALLELES THAN EUROPEAN (WHITE) ANCESTRY

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Background: African Americans with hepatocellular carcinoma (HCC) tend to have less advanced cirrhosis at diagnosis than other patients but exhibit more aggressive forms of HCC. To investigate if germline single nucleotide polymorphisms (SNPs) play a role in this unique presentation, we compared allele frequencies (AF) of

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liver disease-related SNPs between individuals of African/African American (Black) versus non-Finnish European (White) ancestry. **Methods:** The AF of 52 common SNPs (AF ≥0.01) previously reported to be associated with incident liver disease and cirrhosis/HCC were sourced from the Genome Aggregation Database (gnomAD v3.1.2) and Mount Sinai's Biobank (BioMe). These SNPs were present in both Blacks and Whites but differed between them by at least 0.02 in AF. The Chi-square test was used for comparison, with significance set at p<0.05. We also identified rare deleterious variants (RDVs) (minor AF<0.01; classified as pathogenic/likely pathogenic in ClinVar) in *APOE* in BioMe data and determined their AFs in gnomAD. **Results:** In gnomAD, 38 (73%) out of 52 common SNPs related to liver disease had a higher AF in Whites compared to Blacks (p <0.0001) (**Fig 1A**). Ten of these SNPs had an AF at least 0.20 higher in Whites (marked in pink rectangles). Among these ten, rs12979860-C (red arrow) is associated with accelerated liver fibrosis and *loss* of IFNL4 production. Conversely, the rs12979860-T allele, which is more frequent in Blacks, is associated with IFNL4 production, lower fibrosis risk in chronic hepatitis C patients, and more aggressive disease in men with prostate cancer. Data from BioMe were consistent with the gnomAD findings (**Fig 1B**). Blacks had a lower prevalence of RDVs in *APOE* than Whites (**Fig 1C**). **Conclusion:** The lower prevalence of liver disease risk alleles in Blacks, along with the significant AF differences between Blacks and Whites, suggest that Blacks may have a lower genomic risk for rapid progression to advanced cirrhosis than Whites, contributing to their unique presentation of HCC. Additionally, Blacks may harbor yet to be discovered risk variants. Ironically, a reduced risk for advanced cirrhosis may negatively impact participation in HCC surveillance programs, which primarily target patients with cirrhosis. This could lead to reduced early HCC detection and increased mortality. Additionally, *IFNL4* SNPs that support IFNL4 production may contribute to more aggressive HCC in Blacks (Pfizer, NCI U01CA288425).

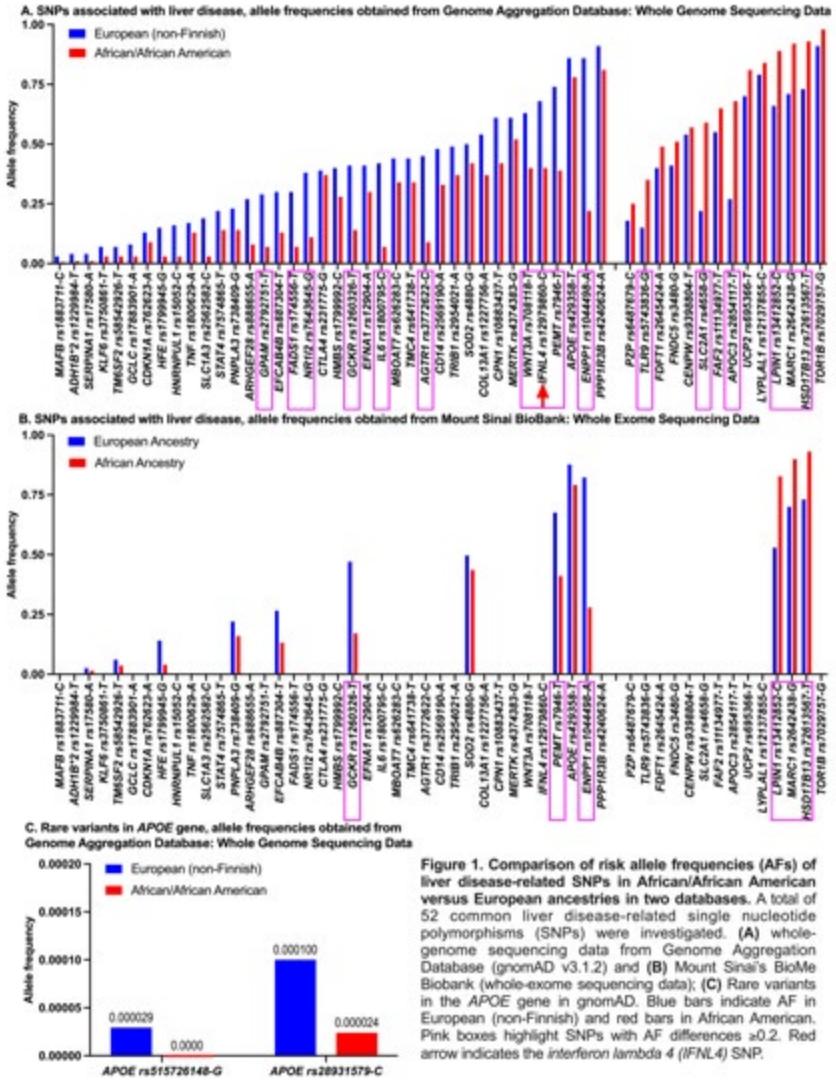

Figure 1. Comparison of risk allele frequencies (AFs) of liver disease-related SNPs in African/African American versus European ancestries in two databases. A total of 52 common liver disease-related single nucleotide polymorphisms (SNPs) were investigated. **(A)** whole-genome sequencing data from Genome Aggregation Database (gnomAD v3.1.2) and **(B)** Mount Sinai's BioMe Biobank (whole-exome sequencing data); **(C)** Rare variants in the *APOE* gene in gnomAD. Blue bars indicate AF in European (non-Finnish) and red bars in African American. Pink boxes highlight SNPs with AF differences ≥0.2. Red arrow indicates the *interferon lambda 4 (IFNL4)* SNP.

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Disclosures: Ning Ma: Nothing to Disclose, Myvizhi Selvan: Nothing to Disclose, Daniela Sia: Nothing to Disclose, Meena Bansal: Advisor relationship with Madrigal; Has not ended; Advisor relationship with Fibronostics; Has not ended; Advisor relationship with NOVO Nordisk; Has not ended; Advisor relationship with GSK; Has not ended; Advisor relationship with Merck; Has not ended; Advisor relationship with Boeheringer-Ingelheim; Has not ended; Advisor relationship with Boston Pharma; Has not ended; Advisor relationship with The Kinetix Group; Has not ended, Richard Sterling: Grant/Research Support relationship with HCV Vax; Has not ended; Grant/Research Support relationship with GSK; Has not ended; Grant/Research Support relationship with Gilead; Has not ended; Grant/Research Support relationship with Roche; Has not ended; Grant/Research Support relationship with AbbVie; Has not ended; Grant/Research Support relationship with Abott; Has not ended; GI Specialty Board relationship with ABIM; Has not ended, Zeynep Gümüş: Nothing to Disclose, Andrea Branch: Gilead Sciences: Research, Pfizer: Research

0163 | ARTIFICIAL INTELLIGENCE-DERIVED GRANULAR HISTOLOGICAL MARKERS OF INFLAMMATION AND FIBROSIS ASSOCIATE WITH PROGRESSION IN PATIENTS WITH ALCOHOL-RELATED STEATOHEPATITIS ◆

Chady Meroueh[1] Vijay Shah[1] Neel Patel[2] Hanna Pulaski[2] Lara Murray[2] Geetika Singh[2] Liz Thomas[2] Resham Ramkissoon[1] Joseph Ahn[1] Camille Kezer[1] Victoria Kusztos[3] Thomas Smith[1] Jason Hipp[1] Hamid Tizhoosh[1] Peyman Nejat[1]

[1]Mayo Clinic Rochester, [2]PathAI, [3]Mayo Clinic, Rochester

Background: There are no current histopathologic markers, which are necessary for adequate treatment, to assess liver-related adverse events (LRE) in Alcohol-associated steatohepatitis (ASH). To close this gap, we leverage AI-derived features of liver histology to detect histologic markers of disease severity and progression in a cohort of ASH subjects. **Methods:** Liver Explore[1], a suite of machine learning models that extract features related to liver cell, tissue, and collagen features, was deployed on 100 H&E WSIs of ASH biopsies (Age range at biopsy 18-73, Male/Female 58/42, Fibrosis stage: F0-1:11, F2:33, F3:15, F4:27). Biopsies were collected at Mayo Clinic and imaged using a Leica Aperio AT2 scanner at 40X magnification. Analysis of the correlation of Liver Explore human interpretable features (HIFs) with several blood-based biomarkers of ASH severity, including Model for End-Stage Liver Disease-Sodium (MELD-Na) and Maddrey's Discriminant Function (MDF) scores was performed; the strength of associations was assessed using Pearson's rho(ρ). The effect of Liver Explore HIFs on progression to LRE (e.g., decompensation, liver transplantation) in ASH patients was assessed using Cox proportional hazards regression. **Results:** Elevated area proportion of pathological fibrosis was significantly associated with higher MELD-Na (ρ = 0.57) and MDF (ρ = 0.47) and faster progression to LRE (HR = 1.75 [1.01-3.04]). Among all the pathological fibrosis subtypes, the relative area fraction of nodular fibrosis (the fibrosis subtype with patterns consistent with cirrhosis), had the strongest association with the ASH biomarkers (MELD-NA ρ = 0.55; MDF ρ = 0.44) and progression to LRE (HR = 1.82 [1.1-3.0]). Two cell-based ratios – the fraction of fibroblasts relative to all cells and the fraction of neutrophils relative to all immune cells in tissue – were positively correlated with ASH severity and progression to LRE. **Conclusion:** Using Liver Explore HIFs, we demonstrated that several histologic features, especially features of advanced pathological fibrosis (e.g., nodular fibrosis) and the presence of fibroblasts and neutrophils in tissue were positively correlated with ASH severity and progression to LRE. While further research will be required to validate these findings, these preliminary **Results:** indicate that there are likely strong histologic predictors of disease progression, which have the potential to inform risk stratification, monitoring, and treatment of patients with ASH. [1]Liver Explore is for research use only. Not for use in diagnostic procedures.

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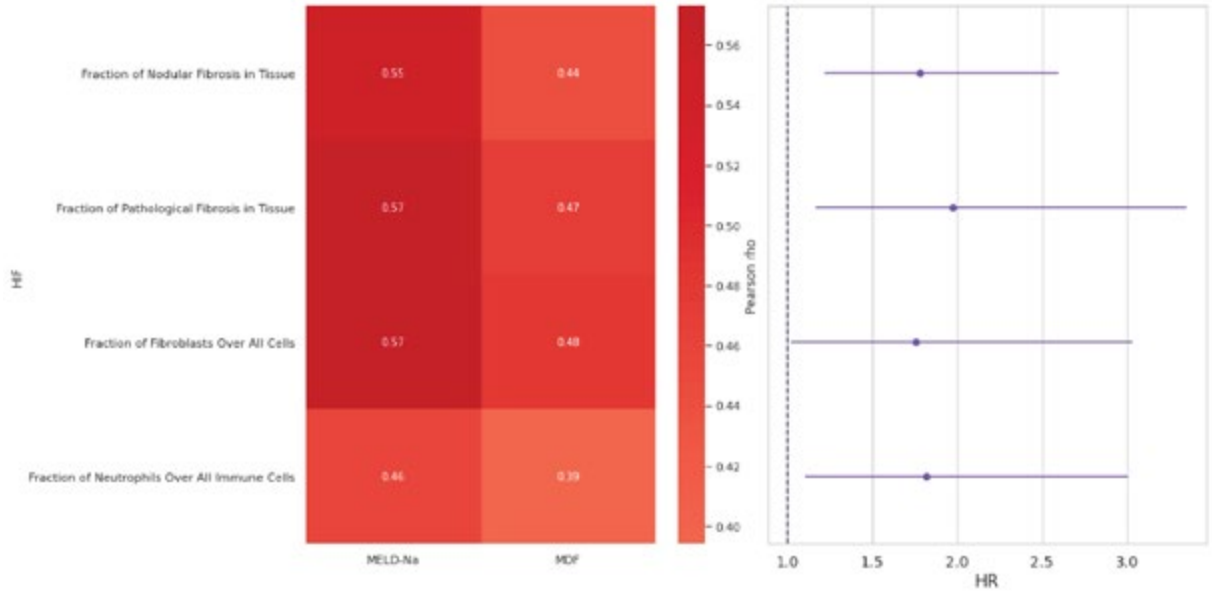

Figure: Select results from Liver Explore analysis of ASH cohort. Pearson's correlation heatmap for select HIFs and ASH biomarkers (left) and corresponding HRs for progression to LRE (right).

Disclosures: Chady Meroueh: Nothing to Disclose, Vijay Shah: Boehringer Ingelheim: Consultant, GSK: Consultant, GENFIT SA: Consultant, Intercept Pharmaceuticals, Inc.: Advisor, Korro Bio, Inc.: Consultant, Mallinckrodt Pharmaceuticals: Advisor, Novo Nordisk A/S: Consultant, Resolution Therapeutics, Ltd.: Advisor, Seal Rock Therapeutics, Ltd.: Consultant, Surrozen: Advisor, Neel Patel: PathAI: Employee, Hanna Pulaski: PathAI, Inc: Employee, Lara Murray: Nothing to Disclose, Geetika Singh: PathAI: Employee, PathAI: Employee, Liz Thomas: Nothing to Disclose, Resham Ramkissoon: Nothing to Disclose, Joseph Ahn: No Relevant Financial Relationships, Camille Kezer: Nothing to Disclose, Victoria Kusztos: Nothing to Disclose, Thomas Smith: Nothing to Disclose, Jason Hipp: Nothing to Disclose, Hamid Tizhoosh: Nothing to Disclose, Peyman Nejat: Nothing to Disclose

0164 | EFFICACY AND SAFETY OF SELADELPAR IN PATIENTS WITH PRIMARY BILIARY CHOLANGITIS AND COMPENSATED CIRRHOSIS IN THE PHASE 3 PLACEBO-CONTROLLED RESPONSE TRIAL

Alejandra Villamil[1] Ziad Younes[2] Christopher Bowlus[3] John Vierling[4] Adam Vasura[5] Andrea Galli[6] Mordechai Rabinovitz[7] Frederik Nevens[8] Susheela Carroll[9] Ke Yang[10] Daria Crittenden[9] Charles McWherter[10] Eric Lawitz[11]

[1]Hospital Italiano de Buenos Aires, Buenos Aires, Argentina, [2]Gastro One, [3]University of California, Davis, [4]Baylor College of Medicine, [5]University of Ostrava, Ostrava, Czech Republic, [6]University of Florence, Florence 50134, Italy, [7]University of Pittsburgh, [8]University Hospital KU Leuven, Belgium, [9]CymaBay Therapeutics Inc, [10]CymaBay Therapeutics, [11]Texas Liver Institute, San Antonio, TX

Background: Patients with primary biliary cholangitis (PBC) and cirrhosis have a high unmet need for second-line therapies. In the phase 3 placebo-controlled RESPONSE trial (NCT04620733), seladelpar, a novel delpar (selective PPAR-delta agonist), significantly improved biomarkers of cholestasis in PBC patients over 12 months compared to placebo. In a prespecified subgroup analysis, a higher percentage of patients with cirrhosis met the composite biochemical endpoint (alkaline phosphatase [ALP] <1.67x upper-limit-of-normal [ULN], ALP decrease ≥15%, and total bilirubin [TB] ≤ULN) in the seladelpar arm (38.9%) vs placebo (22.2%). We now report data on additional biochemical results and safety in patients with or without cirrhosis in RESPONSE. **Methods:** PBC patients with an inadequate response or intolerance to ursodeoxycholic acid, ALP ≥1.67x ULN, and TB ≤2x ULN received daily oral seladelpar 10 mg or placebo (2:1 randomization) for 12 months. Cirrhosis was defined by medical history, liver biopsy, transient elastography (>16.9 kPa), laboratory findings, and/or radiological features. Changes in ALP, gamma glutamyl transferase (GGT), and alanine aminotransferase (ALT) were assessed in patients with and without cirrhosis, as was safety. **Results:** Of 193 enrolled patients, 27 (14.0%) had Child-Pugh A compensated cirrhosis at baseline: 18 received seladelpar and 9 received placebo. Patients with cirrhosis had higher mean liver stiffness (18.8 kPa), ALP (345.8 U/L), and TB (0.97 mg/dL) at baseline vs those without cirrhosis (7.9 kPa, 309.2 U/L, and 0.72 mg/dL,

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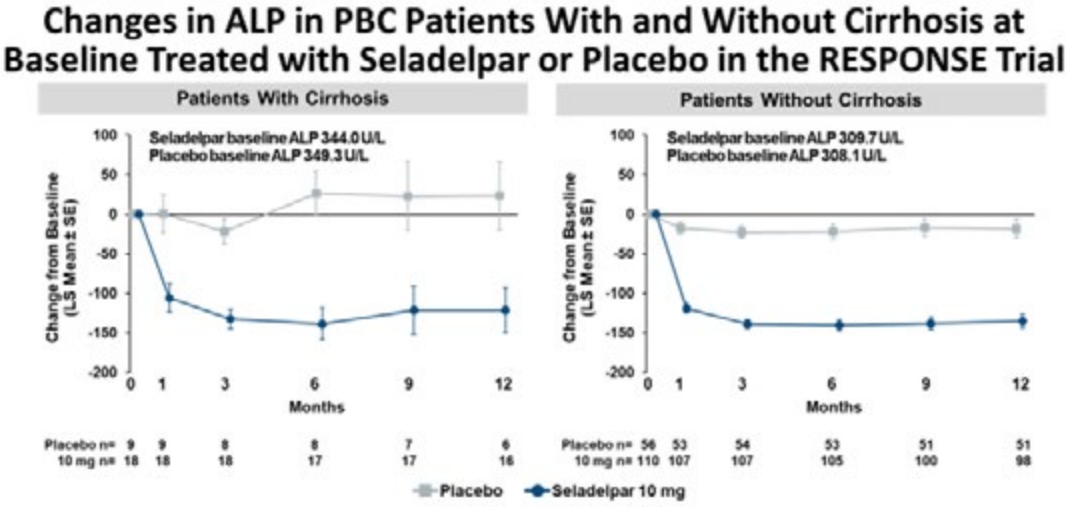
respectively). At Month 12, the mean change from baseline in ALP for patients with cirrhosis on seladelpar was -121.4 U/L vs 23.2 U/L for placebo, and -134.8 U/L for seladelpar vs -18.0 U/L for placebo in patients without cirrhosis. Greater numerical decreases in GGT and ALT were observed with seladelpar vs placebo regardless of cirrhosis status. The type and incidences of AEs with seladelpar were generally similar to placebo in patients with and without cirrhosis. No patients with cirrhosis discontinued seladelpar due to AEs. Elevations in ALT or aspartate aminotransferase of >3x ULN occurred in 1 (5.6%) patient with cirrhosis on seladelpar vs 2 (22.2%) placebo patients. **Conclusion:** Seladelpar reduced biomarkers of cholestasis and liver injury in PBC patients with compensated cirrhosis and in patients without cirrhosis. Seladelpar was overall safe and well tolerated in patients with and without cirrhosis.



Disclosures: Alejandra Villamil: Novartis: Advisor, Intercept: Speaking and Teaching, Gilead: Advisor, Zydus: Advisor, Ziad Younes: Intercept: Grant/Research Support, intercept: Consultant, intercept: Speaking and Teaching, Madrigal: Speaking and Teaching, Madrigal: Consultant, Madrigal: Grant/Research Support, cymabay: Grant/Research Support, cymabay: Consultant, ipsen: Grant/Research Support, Inventiva: Grant/Research Support, Poxel: Grant/Research Support, Altimmune: Grant/Research Support, NST: Grant/Research Support, NGM Bio: Grant/Research Support, 89Bio: Grant/Research Support, Helio: Grant/Research Support, Exact Sciences: Grant/Research Support, Corcept: Grant/Research Support, Galectin: Grant/Research Support, AstraZeneca: Grant/Research Support, Christopher Bowlus: Calliditas: Grant/Research Support, ChemoMab: Grant/Research Support, ChemoMab: Consultant, COUR Phamaceuticals: Grant/Research Support, Cymabay: Grant/Research Support, Cymabay: Consultant, Cymabay: Consultant, Gilead: Grant/Research Support, GSK Pharmaceuticals: Grant/Research Support, GSK Pharmaceuticals: Consultant, Hanmi: Grant/Research Support, Intercept: Grant/Research Support, Invea Therapeutics: Consultant, Ipsen: Grant/Research Support, Ipsen: Consultant, Mirum: Grant/Research Support, NGM Bio: Consultant, Novartis: Grant/Research Support, Novo Nordisk: Grant/Research Support, Pliant Therapeutics: Grant/Research Support, Pliant Therapeutics: Consultant, Viking Therapeutics: Grant/Research Support, Zydus Therapeutics: Grant/Research Support, John Vierling: Nothing to Disclose, Adam Vasura: Nothing to Disclose, Andrea Galli: Nothing to Disclose, Mordechai Rabinovitz: Nothing to Disclose, Frederik Nevens: Nothing to Disclose, Susheela Carroll: CymaBay Therapeutics: Employee, Calithera Biosciences: Employee, Ke Yang: Nothing to Disclose, Daria Crittenden: Nothing to Disclose, Charles McWherter: Nothing to Disclose, Eric Lawitz: Nothing to Disclose

0165 | ENDURANCE EXERCISE PROMOTES FAVORABLE GUT MICROBIOME COMPOSITION DURING HYPERAMMONEMIA

Annette Bellar[1] Nasser Sangwan[1] Avinash Kumar[2] Muaz Alsabbagh Alchirazi[1] Pugazhendhi Kannan[1] Amy Attaway[1] Saurabh Mishra[1] Nicole Welch[1] Srinivasan Dasarathy[1]

[1]Cleveland Clinic, [2]All India Institute of Medical Sciences

Background: Endurance exercise (EE) promotes a favorable gut microbiome (GMB) that includes generation of short chain fatty acid (SCFA). However, during EE circulating ammonia levels increase and are believed to be derived from muscle purine degradation. Since GMB can contribute to ammoniagenesis, we tested if

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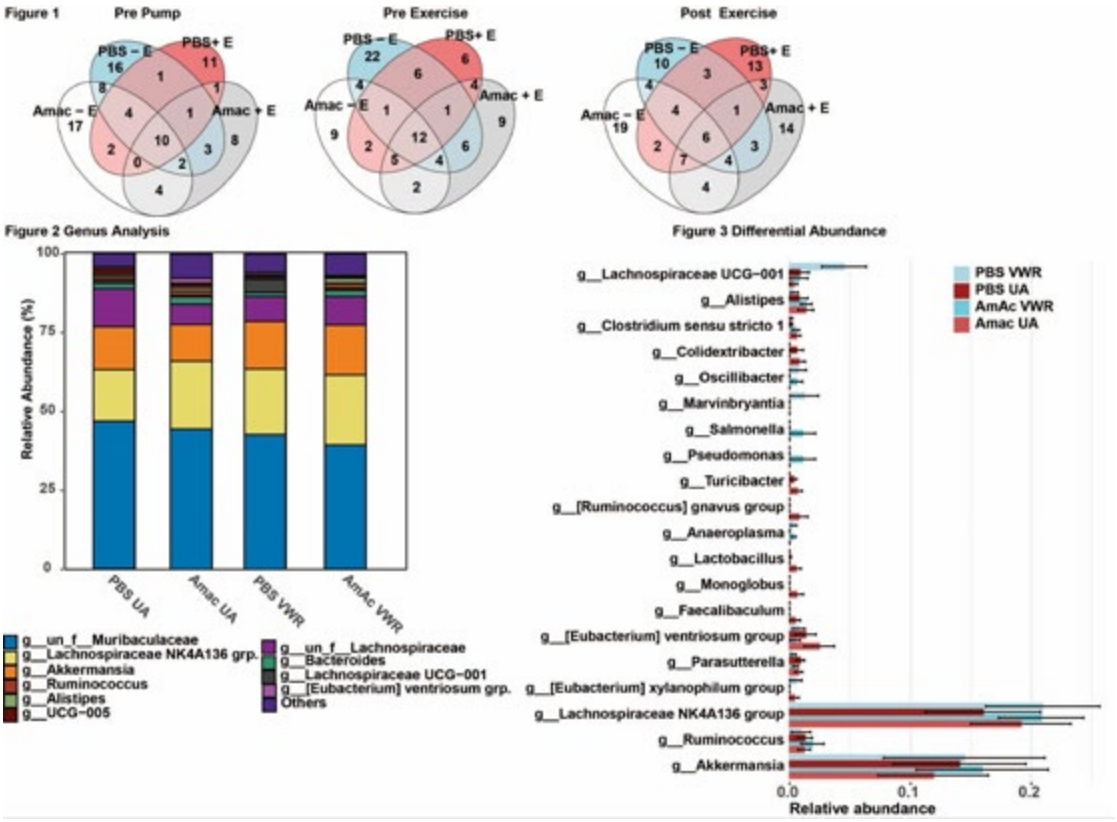
endurance exercise alters the gut microbiome to favor SCFA production and alter ammoniagenic bacteria in ab mouse model of hyperammonemia of liver disease. **Methods:** Male C57/BL6J mice aged 8-9 week (wk) aged with subcutaneous implanted osmotic pump delivering 2.5mmol/kg/d of ammonium acetate (AmAc) or vehicle (PBS) for 6 wk were randomized to either voluntary wheel running (VWR) or usual activity (UA) for 4wk. Baseline, pre-exercise, and post exercise stool 16S sequencing were done. Differential abundance and genus analyses (percent read abundance) were performed. **Results:** Shared and unique taxa in the different groups (pre-pump, pre-exercise and post exercise) are shown in (**Fig.1)**. In order to identify composition of the core microbiome and identify potential differences between groups, genus analyses were performed. We found that in all four groups of mice *Muribaculaceae* (~40%)*, Lachnsopiraceae NK4A136* (~25%), *and Akkremansia* (~25%) comprised 75% of the relative abundance of bacterial taxa across all groups (**Fig.2**). To determine changes at the taxa level, differential abundance analysis was perfomed that showed in PBS UA mice, *Parasutteralla* (part of the core microbiome in mice) succinate producer was most differentially abundant (**Fig.3**). In the PBS VWR group 5 taxa (*Lachnospiraceae, Oscillibacter, Marvinbryantia, Eubacterium xylanophilium, and Lachnospiraceae NK4A136*) that were members of the Firmicutes Phylum and SCFA producers were most abundant. In the AmAc VWR group, 6 taxa that were differentially abundant included *Alistipes, Salmonella, Psuedomonas, Anaeroplasma, Ruminococcus, and Akkremansia*. Of these, *Salmonella and Psuedomonoas,* are urease positive (ammoniagenic) while *Alistipes*, and *Akkermansia* are SCFA producers (beneficial). *Ruminococcus* (SCFA producer and urease positive) provides beneficial and adverse muscle effects. *Anaeroplasma* (TGFb producer) aids gut barrier function but can contribute to sarcopenia. In the AmAc UA mice, 8 most abundant bacterial taxa included *Colstridium sensu stricto, Colidextribacter, Turicibacter, Ruminococcus gnavus, Lactobacillus, Monoglobus, Faecalibacterium, and Eubacterium Ventrios* (phylum Firmicutes). *Clostridium sensu stricto 1* is a known pathogen and decreases SCFA abundance while the others produce SCFA but have unknown urease activity. *Turicibacter* metabolizes bile acid and lipid metabolism also produces SCFA. **Conclusion:** A proinflammatory/pathogenic GMB during hyperammonemia is replaced by SCFA generating bacteria suggesting beneficial effects of EE on the GMB in liver disease.



Disclosures: Annette Bellar: Nothing to Disclose, Nasser Sangwan: Nothing to Disclose, Avinash Kumar: Nothing to Disclose, Muaz Alsabbagh Alchirazi: Nothing to Disclose, Pugazhendhi Kannan: Nothing to Disclose, Amy Attaway: Nothing to Disclose, Saurabh Mishra: Nothing to Disclose, Nicole Welch: Nothing to Disclose, Srinivasan Dasarathy: Nothing to Disclose

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0166 | GLP-1 RECEPTOR AGONISTS HAVE A POTENTIAL TO IMPROVE DISEASE ACTIVITY IN PEDIATRIC METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE ★

Andrea Tou[1] *Jennifer Panganiban*[2]

[1]*Children's Hospital of Philadelphia,* [2]*The Children's Hospital of Philadelphia*

Background: Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) is the most common chronic liver disease in children and is characterized by hepatic steatosis with ≥ 1 cardiometabolic risk factor. In adults, Glucagon-Like-Peptide-1 Receptor Agonists (GLP-1 RAs) are used to not only treat Type 2 Diabetes Mellitus (T2DM) and obesity, but have also been shown to promote histologic resolution of metabolic dysfunction-associated steatohepatitis (MASH). There is a paucity of studies evaluating the use of GLP-1 RAs in pediatric MASLD. Our objective was to determine the effect of GLP-1 RAs in pediatric patients with MASLD by using an alanine aminotransferase (ALT) reduction of ≥ 17 U/L as a marker of improved disease activity per AASLD guidance. Secondary outcomes included changes in body mass index (BMI) z-score, weight, blood pressure, and serum markers of metabolic dysfunction associated co-morbidities. **Methods:** An IRB-approved single center retrospective study was performed in patients < 21 years old who had a diagnosis of NAFLD / MASLD and were started on a GLP-1 RA at the Children's Hospital of Philadelphia from 1/1/2018 – 1/10/2024. ALT and secondary endpoint values were collected at baseline, 6 months into treatment, and at the end of treatment. Demographics and medication start / end dates were also obtained. A Wilcoxon signed-rank test assuming independent observations was used for statistical analysis. **Results:** 111 patients met our inclusion criteria. 51% were male, 40% were White, and median age at GLP-1 RA initiation was 15 years old. Mean treatment duration was 13 months, with Semaglutide (41%) being the most frequently prescribed. Notably, there was a mean reduction in ALT by 18 U/L (p=0.01) post-GLP-1 RA, and by 23 U/L (p =0.02) 6 months into therapy. ALT fully normalized in 58% of patients. BMI z-score decreased by a mean of 0.06 (p<0.01) with no significant changes in weight post-GLP-1 RA, but there were statistically significant improvements in GGT, HbA1c, and triglycerides. When stratifying for patients started on a GLP-1 RA for the indication of obesity (51%) versus T2DM (49%), the T2DM cohort had a significantly greater change in ALT, still without significant weight reduction in either group. **Conclusion:** This is the largest dedicated pediatric study evaluating the effects of GLP-1 RAs on MASLD to date. Our data supports the potential use of GLP-1 RAs in the treatment of pediatric MASLD with the greatest impact in patients with T2DM. The mechanism by which this may occur does not seem exclusive to weight loss given no significant changes in weight, and only minimal changes in BMI z-score post-GLP-1 RA. This is hypothesized to be due to improvements in hepatic and whole-body insulin resistance, among other mechanisms. Further data with standardization of medication dosing and duration, and comparison of serum biomarkers with imaging is required to better understand the impact of GLP-1 RAs on the treatment of pediatric MASLD.

Biomarkers pre- vs post-GLP-1 RA therapy

		N*	Mean pre-GLP-1 RA	Mean post-GLP-1 RA	Mean change*	p value*
Weight (kg)		102	122.7	123.8	+0.16	0.42
BMI z-score		92	2.6	2.6	-0.06	<0.01
ALT		69	78.1	62.4	-18.23	0.01
Initiation for T2DM	6month interval	30	96.2	68.8	-39.0	0.03
	Overall change	38	96.2	68.5	-32.9	0.02
Initiation for Obesity	6month interval	24	58	53.2	-3.95	0.11
	Overall change	31	58	55	-0.19	0.26
AST		66	52.1	44.9	-10.5	0.05
GGT		20	57	64.6	-16	<0.01
HbA1c		65	6.4	6.1	-0.21	<0.01
Platelets		26	308.9	320.6	+7.92	0.43
Vitamin D		63	23.5	24.7	+0.86	0.21
Cholesterol		71	174.5	171	-3.01	0.67
HDL		71	40.1	39.6	+0.38	0.82
LDL		65	102	101.6	+0.20	0.40
Triglycerides		71	188	171.5	-34.2	0.01
BP systolic		96	123.8	122.8	-1.49	0.58
BP diastolic		96	68.3	67.3	-0.74	0.41

**Based on paired comparisons*

(Abbreviations: GLP-1 RA, glucagon-like peptide-1 receptor agonist; kg, kilogram; BMI, body mass index; ALT, alanine aminotransferase; T2DM, type 2 diabetes mellitus; AST, aspartate aminotransferase; GGT, gamma glutamyl transferase; HbA1c, hemoglobin A1c; HDL, high density lipoprotein; LDL, low density lipoprotein; BP, blood pressure)

Disclosures: Andrea Tou: Nothing to Disclose, Jennifer Panganiban: Nothing to Disclose

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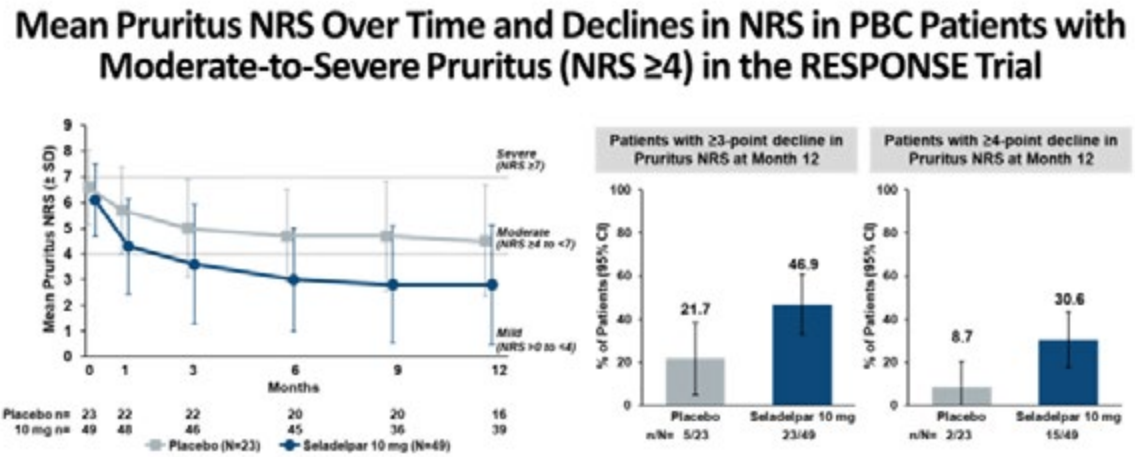
0167 | ATTENUATION, NEAR RESOLUTION, AND PREVENTION OF PRURITUS IN PATIENTS WITH PRIMARY BILIARY CHOLANGITIS TREATED WITH SELADELPAR: A SECONDARY ANALYSIS OF PATTERNS OF PRURITUS CHANGE IN THE RESPONSE TRIAL

Andreas Kremer[1] Cynthia Levy[2] Marlyn Mayo[3] Christopher Bowlus[4] Kris Kowdley[5] Gideon Hirschfield[6] Susheela Carroll[7] Ke Yang[8] Daria Crittenden[7] Charles McWherter[8] David Jones[9]

[1]University Hospital Zürich, Zürich, Switzerland, [2]University of Miami, [3]University of Texas Southwestern Medical Center, [4]University of California, Davis, [5]Liver Institute Northwest, [6]Toronto General Hospital, [7]CymaBay Therapeutics Inc, [8]CymaBay Therapeutics, [9]Newcastle University, UK

Background: Cholestatic pruritus in patients with primary biliary cholangitis (PBC) is frequently debilitating and lacks effective treatments. In the phase 3, RESPONSE trial (NCT04620733), seladelpar, a novel delpar (selective PPAR-delta agonist), significantly decreased pruritus in PBC patients with moderate-to-severe pruritus (numerical rating scale [NRS] ≥4 at baseline) vs placebo. Here, we further evaluated pruritus patterns in RESPONSE. **Methods:** Patients with PBC who received urseodeoxycholic acid (UDCA) for ≥12 months or were UDCA intolerant and had alkaline phosphatase ≥1.67x upper-limit-of-normal (ULN) and total bilirubin ≤2xULN were randomized 2:1 to receive daily oral seladelpar 10 mg or placebo for 12 months. We assessed trends in mean NRS over time and change in pruritus using various thresholds of improvement (eg, ≥3 and ≥4 point reductions in NRS, near resolution of itch [NRS ≤1]) in patients with NRS ≥4 or NRS ≥7 (severe itch) at baseline. Development of pruritus in patients without itch (NRS=0) at baseline and safety by subgroup of baseline NRS (≥4 or <4) were also evaluated. **Results:** 72 of 193 enrolled patients had a baseline NRS ≥4, with 49 randomized to seladelpar and 23 to placebo; 16 seladelpar and 12 placebo patients had NRS ≥7. Among patients with NRS ≥4 at baseline, seladelpar reduced the mean itch intensity from moderate to mild from Month 3 through 12, whereas the mean itch intensity for placebo remained moderate (Figure, left). For patients with baseline NRS ≥4, 46.9% of patients on seladelpar had a ≥3 point NRS decrease vs 21.7% on placebo at Month 12; a ≥4 point NRS decrease was achieved by 30.6% of seladelpar patients vs 8.7% placebo (Figure, right). A higher proportion of patients with baseline NRS ≥4 (26.5%) and NRS ≥7 (18.8%) on seladelpar experienced near resolution of itch at Month 12 vs 0% of patients on placebo. In patients without itch at baseline, 26.7% (4/15) of placebo patients reported pruritus at Month 12 vs 0% (0/30) of seladelpar patients. AEs were reported in 88.9% and 84.3% of patients with baseline NRS ≥4 and NRS <4, respectively, with similar proportions across treatment arms. **Conclusion:** Seladelpar reduced pruritus severity in PBC patients with a durable effect over time and even led to near resolution of itch in some patients, an effect not observed with placebo. Seladelpar mitigated new onset of itch in patients without pruritus and was overall safe and well tolerated regardless of baseline itch.



Disclosures: Andreas Kremer: Abbvie: Advisor, Advanz: Advisor, Alentis: Advisor, AlphaSigma: Speaking and Teaching, AstraZeneca: Advisor, Avior: Advisor, Bayer: Advisor, CymaBay: Advisor, Escient: Advisor, Falk: Speaker, Falk: Speaker, Gilead: Advisor, GSK: Advisor, Intercept: Advisor, Ipsen: Speaking and Teaching, Ipsen: Speaking and Teaching, Mirum: Advisor, Mirum: Advisor, MSD: Advisor, Myr: Advisor, Roche: Advisor, Takeda: Advisor, Viofor: Advisor, Cynthia Levy: Consultant relationship with Cymabay; Has ended; Advisor relationship with COur; Has ended; Grant/Research Support relationship with GSK; Has not ended; Grant/Research Support

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0168 | RAPID HEPATITIS C TEST AND TREAT WITH PEER SUPPORT AT OPIOID TREATMENT PROGRAMS (RAPID HCV): A MULTICENTER RANDOMIZED CONTROL TRIAL

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Background: Strategies to increase HCV treatment uptake among people who use drugs (PWUD) are needed to achieve HCV elimination. Optimization of HCV treatment among PWUD accessing opioid treatment programs (OTPs) may increase HCV treatment reach. The optimal implementation strategy is unknown. **Methods:** The RAPID HCV study is a pragmatic randomized control trial (clinicaltrials.gov NCT04677153) evaluating a strategy of HCV test and treat by OTP staff with patient support provided by peer OTP clients (TT) compared to standard of care offsite specialist referral (SOC) at 5 OTPs in the United States and Canada. OTPs were paired with local specialists to tailor the approach to local context and for ongoing support. OTPs were provided the one-page AASLD/IDSA simplified HCV treatment algorithm and an electronic interactive HCV evaluation and treatment determination tool. PWUD with HCV were enrolled at OTPs and randomized (1:1) to TT or SOC; post-randomization, participants underwent further eligibility assessment for glecaprevir/pibrentasvir (G/P). The primary outcome was HCV treatment initiation within 12 weeks of randomization; secondary outcomes were time-to-HCV treatment initiation, and sustained virologic response (SVR) defined as HCV RNA <15IU/ml measured at study visits 10 or more weeks after end of treatment (EOT). Analyses were conducted within the modified intention-to-treat (mITT, randomized participants eligible for G/P) and per-protocol populations. **Results:** Among 182 participants randomized between August 2021-November 2023 to TT (N=91) or SOC (N=91), 58 were ineligible for G/P (HCV RNA not detected, 38; platelet count <150,000/mm3, 14; missing tests, 6) and 2 were administratively excluded. In the mITT population (n=122), the median age was 49 [interquartile range, IQR:38-58] years, most were white (58%), male (60%), food insecure (62%) and had fentanyl detected in urine at baseline (52%). Overall, 59/66 (89%) in the TT and 12/56 (21%) in the SOC arm initiated treatment [p<0.001]. The median time-to-initiation was 19 days [IQR:11-34] in the TT vs 50 days [IQR:32-57] in the SOC arm [p=<0.001]. Of eligible randomized participants, SVR was confirmed in 40/66 (61%) of PWUD in the TT arm compared to 8/56 (14%) in the SOC arm [p<0.001]. Among those who initiated treatment, SVR was confirmed in 40/59 (68%) in TT and 8/12 (67%) in SOC arms [p >0.05]. Recurrent viremia (11/59 ; 19%) and no follow up SVR testing (8/59; 13%) in the TT arm vs recurrent viremia (1/12; 8%) and no follow up SVR testing (3/12; 25%) in the SOC arm accounted for non-SVR. Among participants who initiated treatment and have SVR assessment available, SVR12 was achieved in 40/51 (78%) in TT and 8/9 (89%) in SOC arm [p=>0.05]. **Conclusion:** Onsite HCV test and treat by OTP staff significantly increased HCV treatment initiation, absence of HCV viremia and population level HCV treatment effectiveness and has potential to accelerate HCV elimination among PWUD accessing OTPs.

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0169 | REGNASE-1 DOWN-REGULATION CONTRIBUTES TO MYELOID CELL INTERMEDIATED ICC DEVELOPMENT ★

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Background: The tumor immune microenvironment (TIME) is a therapeutic target for primary liver cancers. A recent single-cell study found a myeloid cell-rich subtype in intrahepatic cholangiocarcinoma (ICC) with poor prognosis. However, the development process of this TIME subtype remains unclear. We hypothesized that REGNASE-1 (REG1), an endoribonuclease and inflammatory regulator, is involved in ICC development by regulating myeloid

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cells in TIME. **Methods:** We generated liver-specific REG1 knockout (KO) mice, liver-specific REG1/Pten double KO (LDKO), hepatocyte-specific REG1/Pten double KO (HDKO), and cholangiocyte-specific REG1/Pten double KO (CDKO) mice, and crossed them with ROSA-LacZ mice for lineage tracing. Single-cell RNA sequencing (scRNA-seq) and spatial transcriptomics (ST) were performed on the liver of wild-type (WT) and Reg1 KO mice and tumor and non-tumor liver tissue of ICC patients. The association of intratumor REG1 expression, prognosis, and myeloid cells was evaluated in 42 ICC patients. **Results:** Reg1 KO mice showed cholangiocyte hyperplasia with CD11b+ cell infiltration, leading to spontaneous ICC development. Liver-specific Reg1 deletion significantly accelerated ICC formation in the absence of Pten. ICC developed in HDKO but not in CDKO mice. Lineage tracing showed neoplastic cholangiocytes originated from mature hepatocytes. scRNA-seq and ST analysis revealed a predominant intrahepatic immune cell cluster expressing CD11b and CSF1 surrounding proliferative cholangiocytes in Reg1 KO mice but not in WT mice. A similar cluster was found only in tumor sites of ICC patients. Antibody-mediated depletion of CD11b+ cells or CSF1R inhibition suppressed cholangiocyte neoplastic growth in Reg1 KO mice. These results suggested that Reg1 loss promoted hepatocyte-derived ICC formation via oncogenic CSF1+CD11b+ myeloid cells. Mechanistically, RIP-Seq analysis revealed that Reg1 in hepatic cells directly binds to and degrades mRNAs of multiple CXC chemokines important for CD11b+ cell recruitment. Reg1 deletion upregulated their expression in hepatic cells, which induced migration and CSF1 expression in co-cultured CD11b+ cells. CD11b+CSF1+ cells induced transdifferentiation of co-cultured Reg1-deficient hepatocytes into proliferative cholangiocytes. Intratumor Reg1 expression was negatively correlated with the number of infiltrated CD11b+ cells and poor prognosis in ICC patients. **Conclusion:** Regnase-1 down-regulation promotes myeloid cell-mediated ICC development.

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0170 | AI-BASED DIGITAL PATHOLOGY SHOWS THAT DENIFANSTAT IMPROVES MULTIPLE PARAMETERS OF FIBROSIS AND REDUCES PROGRESSION TO CIRRHOSIS IN MASH PATIENTS WITH F2/F3 FIBROSIS –RESULTS OF THE FASCINATE-2 STUDY

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Background: AI-based digital pathology is an advanced tool that complements conventional histopathology by allowing precise and quantitative analysis of histological changes. Denifanstat (TVB-2640), an oral fatty acid synthase (FASN) inhibitor, demonstrated significant MASH resolution and fibrosis improvement in the Ph2b study FASCINATE-2, and decreased liver fat and biomarkers of inflammation and fibrosis. To further investigate how denifanstat improved liver histology, second harmonic generation (SHG) AI-based digital pathology was used to evaluate pre- and post-treatment liver biopsies. **Methods:** 168 patients with biopsy-confirmed MASH and F2/F3 fibrosis were randomized 2:1 to once daily oral denifanstat 50 mg or placebo (PBO) for 52 weeks. Pre- and post-treatment liver biopsy slides were read by an expert central pathologist using NASH CRN criteria. A separate unstained slide was evaluated by SHG AI digital pathology (HistoIndex). All analyses were blinded (PBO n=45 total, F2:22, F3:23; denifanstat n=81 total, F2:34, F3:47). **Results:** Denifanstat significantly improved liver fibrosis by both conventional and AI approaches ($p<0.05$ vs PBO). Significant correlations were shown between central pathologist and AI-generated **Results:** (steatosis pathologist grade vs. qSteatosis continuous value, $r=0.82$, $p<0.001$; fibrosis pathologist stage vs. qFibrosis continuous value, $r=0.67$, $p<0.001$). Denifanstat significantly regressed qFibrosis stage in patients with baseline F3 fibrosis (43% vs. 13% PBO, $p<0.05$). In baseline F3 patients, denifanstat significantly reduced septa area, length and width ($p<0.05$), confirming improvement in liver fibrosis. Denifanstat reduced qSteatosis stage (69% vs. 29% PBO, $p<0.001$). Notably, using steatosis-corrected qFibrosis stage, denifanstat improved fibrosis in patients with baseline F2 (53% vs. 18% PBO, $p<0.05$) or F3 (62% vs. 26% PBO, $p<0.05$). Fibrosis zonal analysis (steatosis-corrected) revealed significant peri-sinusoidal (Zone 2) and peri-portal fibrosis reduction with denifanstat treatment in patients with baseline F2 or F3. In denifanstat treated patients, 5% (4 of 81) progressed from qF3 to qF4 during 52 weeks compared to 13% (6 of 45) PBO patients from qF2/3 to qF4. **Conclusion:** AI digital pathology results support denifanstat's demonstrated efficacy

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reducing liver fibrosis and steatosis in MASH. Denifanstat improved fibrosis in peri-sinusoidal and peri-portal zones, consistent with FASN inhibition. The steatosis-corrected algorithm provides further insight into histological effect on liver fibrosis and denifanstat therapeutic benefit.

Disclosures: Mary Rinella: Consultant relationship with Sagimet; Has not ended; Consultant relationship with Takeda; Has not ended; Consultant relationship with Eli Lilly; Has not ended; Consultant relationship with Novo Nordisk; Has not ended; Consultant relationship with GSK; Has not ended; Consultant relationship with Madrigal; Has not ended; Consultant relationship with Intercept; Has not ended; Consultant relationship with Boehringer Ingelheim; Has not ended; Consultant relationship with 89Bio; Has not ended; Consultant relationship with akero; Has not ended; Consultant relationship with Histoindex; Has not ended; Consultant relationship with Cytodyn; Has not ended; Consultant relationship with Echosens; Has not ended, Wen-Wei Tsai: Sagimet: Stock share holder, Gordian: paid consultant service, Katharine Grimmer: Nothing to Disclose, Eduardo Martins: Sagimet Biosciences: Employee, Sagimet Biosciences: Employee, Sagimet Biosciences: Stock - publicly traded company, Pierre Bedossa: Nothing to Disclose, Kutbuddin Akbary: HistoIndex Pte Ltd: Employee, Dean Tai: Histoindex.com: Employee, Marie O'Farrell: Nothing to Disclose, George Kemble: Sagimet Biosciences: Salary, stock ownership, Rohit Loomba: Eli Lilly and Company: Consultant, 89bio: Consultant, Aardvark Therapeutics: Consultant, Altimmune: Consultant, Alnylam/Regeneron: Consultant, Amgen: Consultant, Arrowhead Pharmaceuticals: Consultant, AstraZeneca: Consultant, Bristol Myers Squibb: Consultant, CohBar: Consultant, Eli Lilly: Consultant, Galmed Pharmaceuticals: Consultant, Gilead: Consultant, Glympse Bio: Consultant, Hightide: Consultant, Inipharma: Consultant, Intercept: Consultant, Inventiva: Consultant, Ionis: Consultant, Janssen, Inc.: Consultant, Madrigal Pharmaceuticals: Consultant, Merck, Metacrine, Inc.: Consultant, NGM Biopharmaceuticals: Consultant, Novartis: Consultant, Novo Nordisk: Consultant, Pfizer: Consultant, Sagimet Biosciences: Consultant, Terns Pharmaceuticals: Consultant, Theratechnologies and Viking Therapeutics: Consultant, 89bio: Stock options, Sagimet Biosciences: Stock options, Arrowhead Pharmaceuticals: Research grant, AstraZeneca: Research grant, Boehringer Ingelheim: Research grant, Bristol Myers Squibb: Research grant, Eli Lilly: Research grant, Galectin Therapeutics: Research grant, Galmed Pharmaceuticals: Research grant, Gilead: Research grant, Hanmi: Research grant, Intercept: Research grant, Inventiva: Research grant, Ionis: Research grant, Janssen, Inc.: Research grant, Madrigal Pharmaceuticals: Research grant, Merck: Research grant, NGM Biopharmaceuticals: Research grant, Novo Nordisk: Research grant, Pfizer: Research grant, Sonic Incytes: Research grant, Terns Pharmaceuticals: Research grant, LipoNexus, Inc.: Co-founder

0171 | AHEAD, A NOVEL VALIDATED MACHINE LEARNING MODEL FOR CLINICAL DIAGNOSIS OF ALCOHOL-ASSOCIATED HEPATITIS ◆ ★

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Background: Alcohol-associated hepatitis (AH) is a unique clinical syndrome, with new onset or worsening of jaundice, with 90-day mortality of up to 90% in most severe forms. The National Institute on Alcohol Abuse and Alcoholism (NIAAA) has proposed clinical criteria for AH diagnosis (AST>50 and <400 IU/L, serum bilirubin [SB] >3 mg/dl, presentation within 60 days from last alcohol use) for management and for enrollment in clinical trials. However, these criteria are not evidence-based. We performed this multicenter study with the aim of validating NIAAA clinical criteria for diagnosis in patients with alcohol associated liver disease (ALD). **Methods:** Seven centers with liver biopsy data for ALD were included in the study. To ensure external validity, centers were randomized into Training and Test Sets, such that each set comprised data from different centers. The outcome of interest was biopsy-proven AH defined by the presence of Mallory-Denk Bodies, lobular inflammation, and ballooning degeneration. Three machine learning algorithms—Random Forest (RF), Gradient Boosting Machine (GBM), and XGBoost (XGB)—were developed using the Training Set (Figure, A-C). The final ensemble model,

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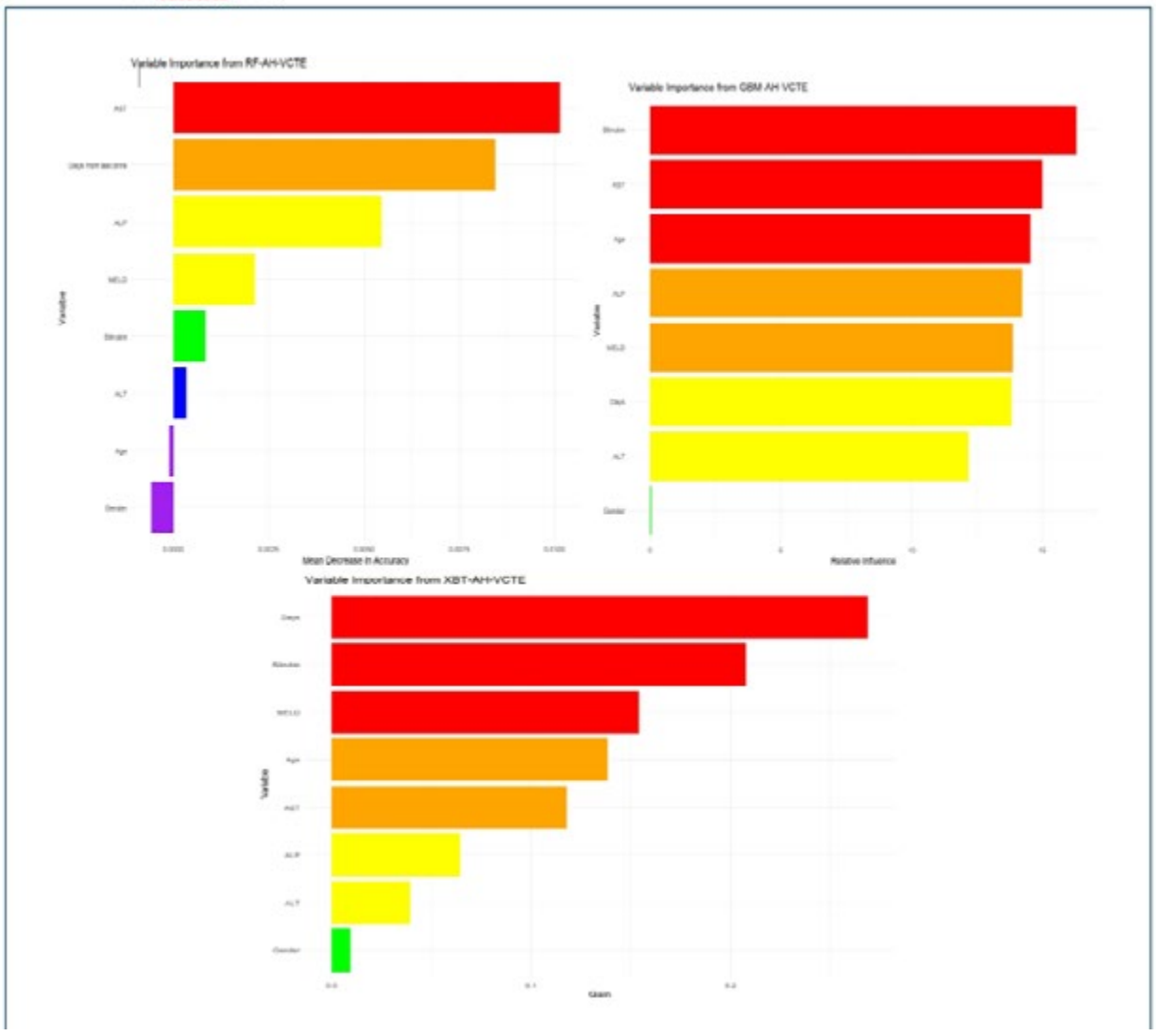
termed the Alcohol Hepatitis Ensemble Algorithm Development (AHEAD), was constructed as the geometric mean of the three individual models. The GME model was compared against the NIAAA criteria. **Results:** The Training Set included 263 patients from 4 centers, with 60 diagnosed with AH. The Test Set comprised 204 patients from 3 centers, with 30 diagnosed with AH. In the Test Set, RF had an AUC of 0.682 (95% CI 0.591–0.773), GBM had an AUC of 0.690 (95% CI 0.597–0.782), and XGB had an AUC of 0.684 (95% CI 0.594–0.774). The AHEAD model achieved an AUC of 0.695 (95% CI 0.608–0.782), demonstrating superior performance compared to the NIAAA model, which had an AUC of 0.590 (95% CI 0.494–0.685) (Bootstrap p = 0.049). Using a 50% probability cutoff, the AHEAD Score achieved a specificity of 61.5% (107 out of 174 non-cases correctly identified) and a sensitivity of 63.3% (19 out of 30 cases correctly identified). In contrast, the NIAAA model showed a specificity of 54.6% (95 out of 174) and the same sensitivity of 63.3% (19 out of 30). The higher specificity of the AHEAD model suggests an improved ability to identify true non-cases compared to the traditional NIAAA criteria. **Conclusion:** AHEAD, a novel validated model based on AST, AST/ALT ratio, and serum bilirubin is more accurate compared to the currently used NIAAA clinical criteria for clinical
diagnosis of AH and for recruitment of patients into clinical trials. Additional variables may further improve the accuracy of the model.

Figure 1, Panel A-C: Three machine learning algorithms—Random Forest (RF), Gradient Boosting Machine (GBM), and XGBoost (XGB)



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0172 | CLINICAL FACTORS IMPACTING THE HEALTH-RELATED QUALITY OF LIFE OF CHILDREN AND YOUNG ADULTS WITH AUTOIMMUNE LIVER DISEASE

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Background: Pediatric autoimmune liver disease (AILD) is a spectrum of rare, chronic liver diseases, ranging from autoimmune hepatitis (AIH) to primary sclerosing cholangitis (PSC). Children and young adults with AILD face unique challenges associated with their disease symptoms and treatment options (or lack thereof). As a result, their health-related quality of life (HRQoL) may be impaired. This study aims to identify clinical factors that impact HRQoL in a large, single-center cohort of pediatric patients with AILD. **Methods:** This prospective cohort study enrolled 91 children and young adults with AILD (51% AIH, 24% PSC, 25% PSC/AIH overlap). Participants and their caregivers completed a Pediatric Quality of Life Inventory™ Version 4.0 Core Short Form, which includes questions regarding the following domains: physical, emotional, social, and school well-being. Forms were scored, with higher scores reflecting better HRQoL. Medical history and laboratory measurements within 3 months of each HRQoL measurement were abstracted from the medical chart. The presence of fatigue was assessed in 70 of the 91 patients (77%) by either a research survey (n = 43) or from clinic notes (n = 27). A Wilcoxon rank-sum test was performed to compare HRQoL scores between subgroups. **Results:** In this cohort, 91 participants (52% female, 90% white, 96% non-Hispanic) and 78 caregivers completed one HRQoL baseline form. The median age was 15 (range 4-24), and median disease duration was 2 (range 0-13). There was no difference in total or domain scores when comparing type of AILD, concurrent IBD, use of steroids or azathioprine, or presence of pruritus. Participants with fatigue had significantly worse physical scores (p = 0.009) and a strong trend toward worse total scores than those without fatigue (p = 0.058). Caregivers of participants with fatigue reported statistically worse scores in all domains. Interestingly, participants with at least one disease complication (ascites, esophageal variceal bleeding, cholangitis, hepatic encephalopathy) had better social and school scores (p = 0.016 and 0.045, respectively) (Table 1). **Conclusion:** Fatigue was associated with a decreased HRQoL in children and young adults with AILD. Therefore, interventions to reduce patient fatigue may improve their quality of life. Patients with more disease complications reported better social and school HRQoL scores. We speculate that these patients may be receiving greater social and school support because of their more complex disease states. Further investigation into the reasons surrounding these findings is needed.

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A	Absence of Fatigue (n = 29)	Presence of Fatigue (n = 41)	p
HRQoL Domain	*Mean Score*		
Physical	92.1	77.3	**0.009**
Emotional	81.9	74.0	0.16
Social	88.8	87.3	0.26
School	79.6	67.2	0.19
Psychosocial	83.2	75.7	0.16
Total	86.0	76.2	**0.058**
B	**No AILD complication (n = 77)**	**≥ 1 AILD complication (n = 14)**	***P***
HRQoL Domain	*Mean Score*		
Physical	83.5	91.4	0.09
Emotional	79.4	79.5	0.84
Social	87.5	97.6	**0.016**
School	72.4	86.3	**0.045**
Psychosocial	79.4	86.8	0.15
Total	80.8	88.3	0.08

Table 1: Comparison of the health-related quality of life total and domain scores of patients with absence of fatigue v. those with fatigue (A) and of patients with no disease complications v. those with complications (B). Higher scores reflect better quality of life.

Disclosures: Rebecca Farr: Nothing to Disclose, Lin Fei: Nothing to Disclose, Rashmi Sahay: Nothing to Disclose, Heidi Kalkwarf: Nothing to Disclose, Kevin Hommel: Nothing to Disclose, Cyd Castro-Rojas: Nothing to Disclose, Mosab Alquraish: Nothing to Disclose, Amy Taylor: Nothing to Disclose, Alexander Miethke: Mirum Pharmaceutical Inc: Grant/Research Support, Mirum Pharmaceutical Inc: Consultant, Ipsen: Speaking and Teaching

0173 | MULTIPLEXED SINGLE-CELL ANALYSIS REVEALS DISTINCT TUMOR-IMMUNE MICROENVIRONMENT LINKED TO PREMETASTATIC NICHE FORMATION IN STEATOTIC LIVER

Jieun Kim[1] *So Yeon Kim*[1] *Jina Kim*[1] *Alexander Xu*[1] *Sungyong You*[1] *Ekihiro Seki*[1]

[1]*Cedars-Sinai Medical Center*

Background: Liver metastasis is a critical determinant of prognosis in patients with colorectal cancer (CRC). We found that steatotic liver creates a premetastatic microenvironment that enhances CRC liver metastasis. The tumor-immune microenvironment (TIME) formed under steatotic liver conditions affects response and resistance to cancer immunotherapy. We used single-cell technologies to determine the complex immune and cancer-associated fibroblast (CAF) compositions, phenotypes, and interactions within tumors with or without steatotic livers, which has not been previously analyzed. **Methods:** We comprehensively analyzed the TIME at the single-cell level in mouse and human CRC liver metastasis with or without steatotic liver using single-cell RNA sequencing (scRNA-seq) and imaging mass cytometry (IMC), respectively. We performed scRNA-seq using a mouse CRC liver metastasis model with mouse CRC MC38 cells. We analyzed IMC using 42 metal-conjugated antibodies on tissue microarrays containing specimens from 30 patients with CRC liver metastasis at single-cell levels. **Results:** Unbiased scRNA-seq identified 25 clusters and immunosuppressive M2 tumor-associated macrophage (TAM) and exhausted PD1+CD8T cell clusters were enriched in steatotic livers. CellChat analysis revealed that increased CAF activity is linked to cell-cell interactions between TAMs, cancer cells, and CD8T cells via PD-1/PD-L1 interaction in steatotic liver compared to non-steatotic liver. These immunosuppressive TIME and CAF phenotypes depend on YAP expression in CRC cells. IMC analysis further supported the role of M2TAM and PD1+CD8T cells in contributing to the immunosuppressive TIME in steatotic livers in humans. Additionally, spatial analysis for IMC data identified that myofibroblastic CAFs are abundant and in close proximity to

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YAP+CD44+CRC cells and CD44+M2TAMs with high PD-L1 expression in the TIME of CRC liver metastasis with steatotic liver. Lastly, we confirmed that anti-PD1 therapy is less effective for CRC liver metastasis with steatotic livers as these tumors had an exhausted TIME. **Conclusion:** ScRNA-seq and single cell IMC determined that steatotic livers have immunosuppressive TIME compared to non-steatotic livers, which is regulated by M2TAMs, T cells, CAFs, and CRC cells with the expression of PD-L1, PD1, CD44, and YAP. Characterizing these complex interactions provides a deeper understanding of prometastatic TIME and the response to immunotherapy in patients with liver metastasis and coexisting steatotic liver.

Disclosures: Jieun Kim: Nothing to Disclose, So Yeon Kim: Nothing to Disclose, Jina Kim: Nothing to Disclose, Alexander Xu: Nothing to Disclose, Sungyong You: Nothing to Disclose, Ekihiro Seki: Nippon Zoki: Research Grant Support, Novonordisc: Consultant

0174 | CURRENT BURDEN AND GEOGRAPHIC DISPARITIES IN LIVER MORTALITY AND ACCESS TO LIVER TRANSPLANTATION

Nicolas Rinella[1] William Charlton[2] Paige McLean Diaz[3] K. Gautham Reddy[4] Michael Charlton[3]

[1]University of Chicago, [2]University of Kentucky, [3]University of Chicago Medical Center, [4]University fo Chicago

Background: Liver disease is a leading cause of mortality in the United States. Liver transplantation can be a life-saving procedure for patients with severe liver disease.
Recent modifications of organ allocation policy for donated livers have sought to reduce geographic disparities in access to transplantation and, thereby, to reduce mortality from liver disease among patients listed for liver transplantation While sequential refinements of organ allocation policy appear to be enhancing some measures of equity, measuring waitlist mortality and transplant rates among waitlisted patients with high MELD scores does not capture or necessarily reduce regional variation in liver-related mortality (LRM) nor regional access to liver transplantation. We studied temporal trends and geographic variance in liver-related mortality and liver transplantation access in the United States**. Methods:** Frequencies and geographic variance of liver related mortality (LRM) were obtained in a cross sectional analysis of the Underlying Cause of Death data available on the CDC's Epidemiologic Research (WONDER) database. The number of livers donated and transplanted according to the state of residence of each donor and recipient were obtained from the United Network for Organ Sharing (UNOS). Main outcomes were Liver related mortality in 2018 and 2021 and liver transplantation rate according to state of residence of recipient and donor. **Results:** Overall LRM in the US was 71,900 in 2021, with a crude rate of LRM of 21.7/100,000, an increase of 26.9% compared to rates seen immediately prior to the COVID-19 pandemic (2018). LRM varies several-fold between states, from 13.7 (New York) – 56.3 (New Mexico) /100,000/yr. The average number of liver-related deaths per transplant from all donor sources (in-state and out-of-state) was 5.7 in the lowest LRM quintile, compared to 15.99 in the highest ($p < 0.0001$; 95% CI: 6.8973 to 13.6827; SE:1.615). Ten states have no liver transplant center. Paradoxically, residents of states with the highest LRM have a much lower rate of liver transplantation (at any location) from organs procured from in-state residents than states with the lowest LRM quintile (11.36 vs 36.12% in-state donors, $p <0.0001$; 95% confidence interval: 17.1% - 39.4%). States in the highest quintile of LRM had lower median household income ($61,871 vs. $78,419.5, $p = 0.0002$), urbanization percentage (57.71% and 13.79%, $p = 0.0002$), and percentage below the poverty (82% and 10.78% respectively, $p = 0.013$), compared to states in the bottom quintile of LRM. **Conclusion:** Liver-related mortality rates have increased dramatically since the COVID-19 pandemic and vary several-fold between states. Rates of liver transplantation are paradoxically *lowest* among residents living in states with the *highest* LRM. These findings highlight apparent geographic disparities in access to liver transplantation that allocation policy cannot address.

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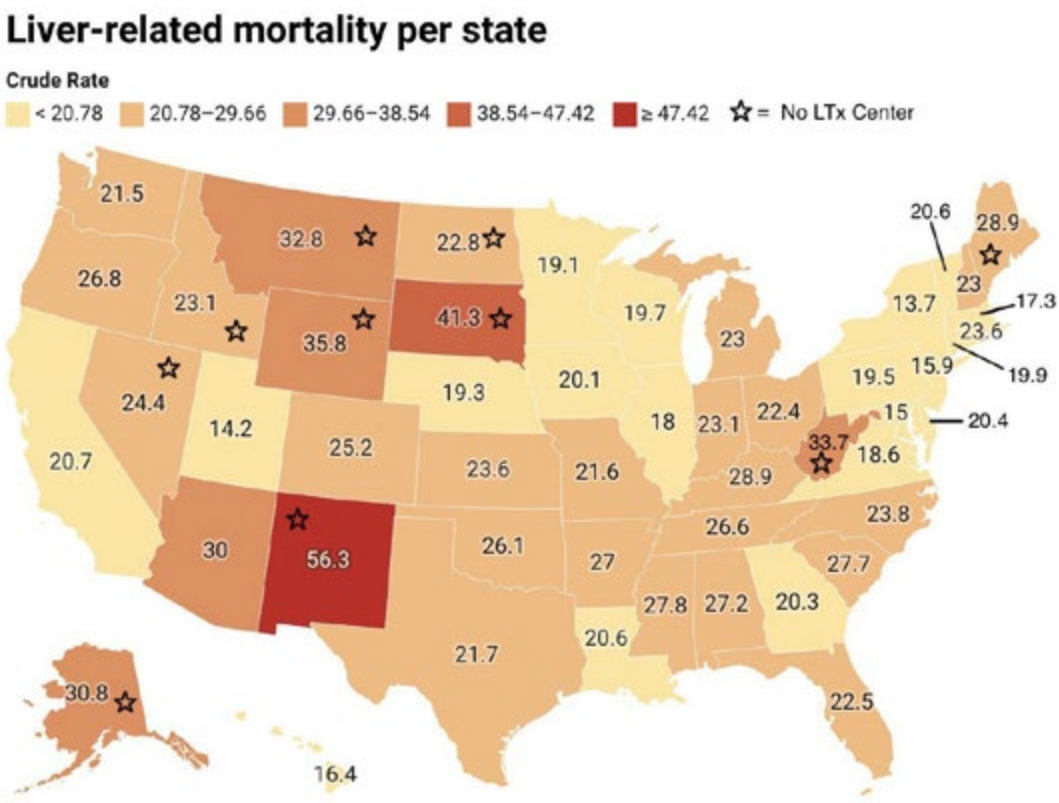

Disclosures: Nicolas Rinella: Nothing to Disclose, William Charlton: Nothing to Disclose, Paige McLean Diaz: Nothing to Disclose, K. Gautham Reddy: CymaBay: Grant/Research Support, CymaBay: Advisor, CymaBay: Speaking and Teaching, Mallinckrodt: Speaking and Teaching, Direct: Grant/Research Support, Durect: Grant/Research Support, Pliant: Grant/Research Support, Cour: Grant/Research Support, Gilead: Grant/Research Support, Gilead: Speaking and Teaching, Michael Charlton: Nothing to Disclose

0175 | INITIATION OF NALTREXONE IS ASSOCIATED WITH LOWER RATES OF AKI, SBP, AND MORTALITY IN PATIENTS WITH DECOMPENSATED ALCOHOL-ASSOCIATED CIRRHOSIS AND ASCITES ◆

Vinay Jahagirdar[1] Katherine Cooper[2] Deepika Devuni[2]

[1]University of Missouri Kansas City School of Medicine, [2]UMass Chan Medical School

Background: Naltrexone is an FDA-approved medication for the treatment of alcohol use disorder (AUD). It has been shown to reduce heavy alcohol consumption and prevent relapse. However, concern for hepatotoxicity in patients with underlying liver disorders is a likely barrier to its widespread use. Data regarding its use in patients with decompensated alcohol-associated cirrhosis (AC) are scarce and emerging. We aimed to compare outcomes in patients with decompensated cirrhosis with or without the use of naltrexone. **Methods:** We queried the TriNetx US Collaborative Network-a research consortium of 60 healthcare organizations, to identify patients with AC with ascites, and ongoing alcohol use. The population was divided into two cohorts – those on naltrexone (Cohort A) and those not on naltrexone or acamprosate (Cohort B). Outcomes were assessed 30 days to 5 years after the initiation of pharmacotherapy or ascites. Propensity Score Matching (PSM) was used to create matched cohorts for age, sex, race and ethnicity. Risk estimate was reported as percentages. Estimates of odds ratios (OR) and 95 % confidence intervals (CI) were used to describe associations. **Results:** A total of 40,623 patients were identified, including 2,274 patients on naltrexone, and 38,349 patients not on naltrexone/acamprosate. After PSM, 2,269 patients were included in each group. A similar proportion of patients with (108/1056, 10%) and without naltrexone therapy (n=16/1486, 11%) developed a new episode of alcohol-associated hepatitis (OR 0.91, 95% CI 0.71, 1.18, p=0.482). Naltrexone was associated with a lower risk of esophageal varices (OR 0.79, 95% CI 0.6-1.0, p=0.050) compared to no naltrexone. Further decompensations including acute kidney injury (AKI) (OR 0.68, 95% CI 0.57-0.81; p<0.001)

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and spontaneous bacterial peritonitis (SBP) (OR 0.57, 95% CI 0.45-0.71], p<0.001) were significantly less common after initiation of naltrexone. Approximately 50% of each group was hospitalized during the follow-up period, with 10 median admissions per patient in each group (p=0.992). One in 4 patients died, and naltrexone was associated with 20% lower odds of death compared to no naltrexone (OR 0.82, 95% CI 0.72-0.94, p=0.005). **Conclusion:** Patients with AC and active drinking have significant healthcare utilization and are at high risk of mortality. In this study, we observed naltrexone to be associated with reduced AKI, SBP, and death in patients with AC and ascites and ongoing alcohol use. These data suggest that naltrexone is not only safe in patients with decompensated liver disease but may also prevent further decompensation and reduce mortality.

Table 1: Propensity score matching of variables and outcomes in patients on naltrexone vs no naltrexone

	Naltrexone (n=2269)	No naltrexone (n=2269)	p-value (Before matching)	p-value (Final cohort)
Age in years	51.6± 11.0	53.7±10.6	<0.001	<0.001
Female sex	855(37.7%)	653 (28.8%)	<0.001	<0.001
White	1,680 (74%)	1,664 (73.3%)	0.125	0.590
Black or African American	219 (9.7%)	205 (9%)	0.890	0.475
Hispanic or Latino	247 (10.9%)	293 (12.9%)	0.077	0.035
Hepatic encephalopathy	369 (16.3%)	275 (12.1%)	<0.001	<0.001
Outcomes				
Event	Risk	Risk	OR (95% CI)	p-value
Alcohol-associated Hepatitis (1st episode)	10.2 %	11.1%	0.91 (0.7, 1.2)	0.482
Variceal bleeding (1st episode)	7.2%	8.9%	0.79 (0.6, 1.001)	0.05
Acute kidney injury (1st episode)	26%	34.1%	0.68 (0.57, 0.80)	0.00
Spontaneous bacterial peritonitis (1st episode)	6.7%	11.2%	0.57 (0.45, 0.71)	0.00
Death	23.4%	27%	0.82 (0.72, 0.94)	0.005

Disclosures: Vinay Jahagirdar: Nothing to Disclose, Katherine Cooper: Nothing to Disclose, Deepika Devuni: Avania Medical: Grant/Research Support, Intercept: Grant/Research Support

0176 | THE OPERATIONAL CHARACTERISTICS OF LIVER TRANSPLANT PROGRAMS DETERMINE GROWTH, AND IMPACT WHERE STATE LEVEL DISPARITIES IN TRANSPLANT ACCESS EXIST

Richard Gilroy[1] Sophie Hansen[1] Jean Botha[1] Michael Hooper[2] Allison Witman[2]

[1]Intermountain Health, [2]University of Utah School of Business

Background: The OPTN has studied, designed, and implemented numerous policies to diminish disparities in organ transplantation. To date, the transplant program's operational characteristics have not been evaluated for their impact upon state transplant rates. Here we examine program level activities for influence over development of programs and the impact upon equity or disparity in liver transplantation at a state level, for US state residents. **Methods:** OPTN data was collected between 01/2017 and 12/2023 for all adult liver transplant programs in the United States doing more than 20 transplants in 2017. Programs were then divided into programs that experienced an increase in transplants per capita and programs that experienced a decline in transplants per capita over the interval of the analysis. Donor and recipient characteristics were used to define each program's operational characteristics and these characteristics compared between low and high performing programs. Differences in means tests compared program operational characteristics between high and low-performing programs. Linear regression analyses with transplant program fixed effects were conducted to determine the association between program operational characteristics and transplant rates overall, by recipient state of residence, and by recipient insurance. **Results:** In 2023 state level transplant rates varied amongst states from 12.3 to 59.5 transplants/ million adult state residents. Between 01/2017 and 12/2023, 69 adult transplant programs grew, and 30 transplant programs did not. Growing programs completed more transplants per capita, had higher offer-acceptance ratios, had

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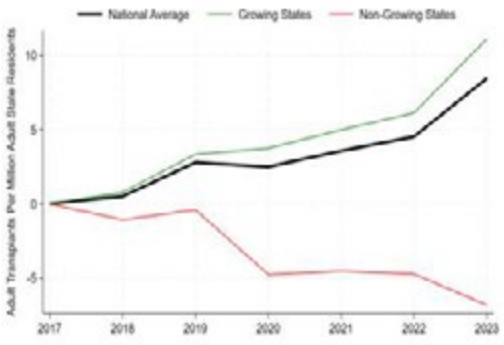
more DCD and living donors, and waitlisted more patients with certain diagnoses. In regression analyses, factors associated with increased transplants included the donor variables of offer-acceptance ratios, DCD utilization, living liver donation, and sourcing out-of-state donors while recipient variables included waitlisting with an alcohol, MASH, PSC, cholangiocarcinoma, or hepatitis C diagnosis. **Conclusion:** Substantial heterogeneity in the operational characteristics of liver transplant programs exists. Modifiable operational characteristics predict transplant rates, suggesting that disparities in access are likely addressable through program-level interventions. States with or adjacent to growing programs more often illustrate state level growth. If OPTN policy design seeks to mitigate disparity in transplant access, irrespective of geography, improving program level operational performance for underperforming programs is prerequisite to future policy design.

Table 2: Impact of Center Performance on Transplants Overall and by State of Residence

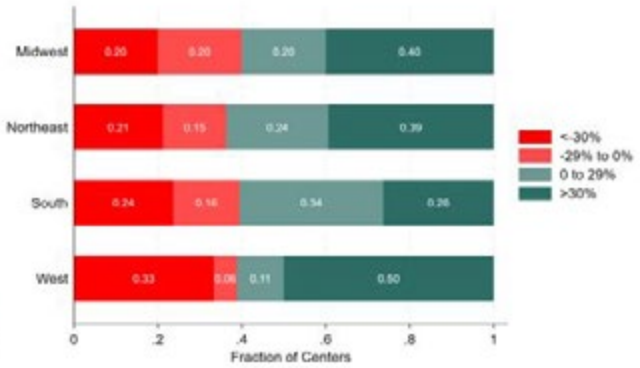
VARIABLES	(1) Ln(Total Transplants Per Capita)	(2) Ln(Resident Transplants Per Capita)	(3) Ln(Nonresident Transplants Per Capita)
Offer/Acceptance Ratio	0.164***	0.159***	0.148**
	(0.0356)	(0.0370)	(0.0567)
Donors: Out-of-State	0.00554***	0.00509***	0.00556***
	(0.000883)	(0.000961)	(0.00183)
Donors: 65+	0.00618**	0.00558*	0.0132**
	(0.00271)	(0.00290)	(0.00593)
Donors: DCD	-0.000944	-0.00139	-0.00281
	(0.000973)	(0.00142)	(0.00185)
Donors: Living	0.00826	0.00349*	0.00710
	(0.00217)	(0.00208)	(0.00547)
Waitlist: Alcohol	0.00439***	0.00381***	0.00281
	(0.00101)	(0.000975)	(0.00206)
Waitlist: NASH/MASH	0.00279**	0.00297**	0.00554**
	(0.00111)	(0.00114)	(0.00278)
Waitlist: Hepatocellular Carcinoma	0.00262**	0.00139	0.00988***
	(0.00119)	(0.00143)	(0.00327)
Waitlist: Cholangiocarcinoma	0.00628*	0.000151	0.0333***
	(0.00378)	(0.00440)	(0.0118)
Waitlist: PSC	0.00600**	0.00310	0.0120
	(0.00257)	(0.00334)	(0.00729)
Waitlist: Hepatitis B	-0.00227	-0.00183	-0.00827
	(0.00494)	(0.00511)	(0.0119)
Waitlist: Hepatitis C	1.356***	1.174***	-0.859***
	(0.0843)	(0.0860)	(0.133)
Constant			
Observations	693	692	608
R-squared	0.524	0.412	0.220
Number of Centers	99	99	98

Note: Table shows coefficients and standard errors from linear regression models with the dependent variable listed in the column title. Dependent variables are natural logged transplant rates per million adult residents in a state. Models include year fixed effects and transplant center fixed effects. Standard errors are clustered at the center level. *** p<0.01, ** p<0.05, * p<0.1

Figure 1. Change in Adult Transplants per Million Adult Residents, 2017 - 2023



Distribution of Growth amongst programs by US Region 2017 – 2023



Disclosures: Richard Gilroy: Abbvie: Speaking and Teaching, Salix: Speaking and Teaching, Sophie Hansen: Nothing to Disclose, Jean Botha: Nothing to Disclose, Michael Hooper: Nothing to Disclose, Allison Witman: Nothing to Disclose

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0177 | DEFINING THE LIVER IMMUNE MICROENVIRONMENT OF INDETERMINATE PEDIATRIC ACUTE LIVER FAILURE WITH SINGLE-CELL TRANSCRIPTOMICS

Harry Sutton[1] Diana Nakib[2] Rachel Edgar[2] Jawaria Atif[3] Blayne Amir Sayed[4] Vicky Ng[1] Amanda Ricciuto[5] Gary Bader[3] Ian McGilvary[2] Binita Kamath[1] Sonya MacParland[2]

[1]The Toronto Hospital for Sick Children, [2]University Health Network, [3]The University of Toronto, [4]The Toronto Hospital of Sick Children, [5]The Hospital for Sick Children

Background: Approximately one-third of children with pediatric acute liver failure (PALF) are classified as indeterminate (IPALF) after a comprehensive diagnostic work-up. Children with IPALF have a higher rates of liver transplant than children with PALF cases where an etiology is diagnosed (Dx-PALF). Although termed "indeterminate" recent research using immunohistochemistry (IHC) and bulk RNA sequencing (RNA-seq) suggests many of these patients share a common immune mediated condition. **Methods:** Using 10x Genomics 5' single-cell RNA-sequencing with T cell receptor (TCR) sequencing and fixed RNA profiling, we examined the cellular composition of ex-planted IPALF livers (n = 3); as well as Dx-PALF livers (n = 2) and healthy pediatric livers (n = 3), for comparison. IHC staining was performed to validate transcriptomic findings. **Results:** Our study population resulted in 63,053 cells from 8 patients, including 37,642 immune cells identified using cell lineage gene markers. Our IPALF cell map (33,440 cells) revealed a CD8+ T cell rich cell population with increased expression of cytotoxic effector proteins (Granzyme B, Perforin) and chemokines associated with T cell migration and activation (CCL4/5). Inferred cell-cell interactions also demonstrated CCL5 produced from CD8+ T cells interacting with all immune cell populations. This marked CD8+ T cell predominate cell environment with high levels of cytotoxic effector proteins and CCL5 expression was not present in our healthy pediatric or Dx-PALF single-cell maps. Through gene set enrichment analysis, we noted that IPALF CD8+ T cells were enriched in pathways related to cell division, while the CD4+ T cells were enriched in pathways related to intra- and inter-cell signalling.
T cell receptor sequencing from one patient with IPALF revealed a hyperexpanded clonal population which expressed CD4, CD28 and CD40 as well as CTLA4, with no hyperexpanded CD8 T cells. **Conclusion:** We present the first single-cell atlas of the liver cellular microenvironment in IPALF. We confirmed a CD8+ T cell rich immune milieu with high expression of granzyme B and perforin. Dense staining for CD8 and granzyme B were also seen on IHC. TCR sequencing revealed a hyperexpanded CD4+ CTLA4+ T cell cluster. CCL5 was identified as highly expressed in IPALF T cells and appears to interact with every other immune subtype. CCL5 may be a rational therapeutic target in the treatment of IPALF.

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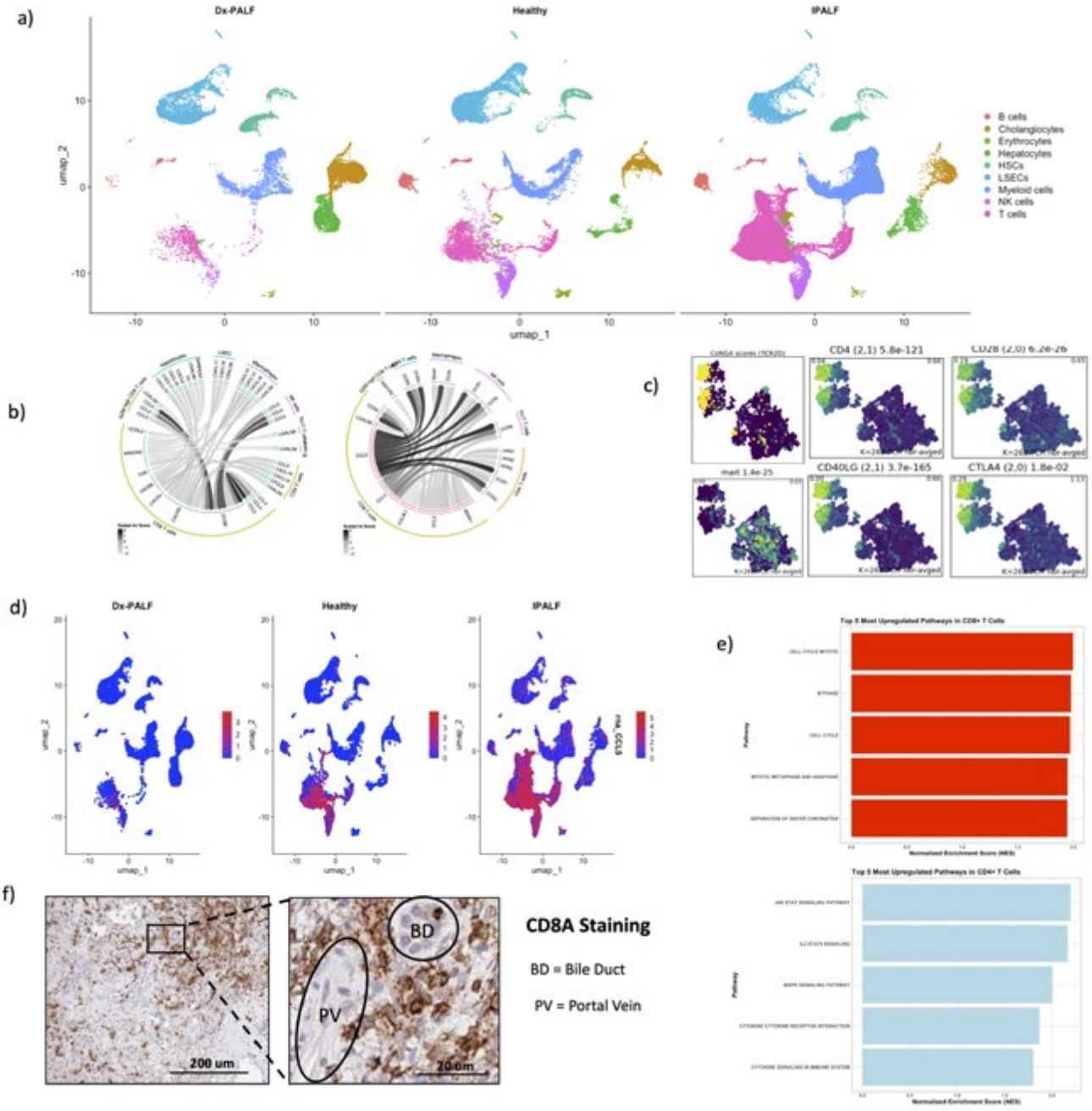

Disclosures: Harry Sutton: Nothing to Disclose, Diana Nakib: Nothing to Disclose, Rachel Edgar: Nothing to Disclose, Jawaria Atif: Nothing to Disclose, Blayne Amir Sayed: Nothing to Disclose, Vicky Ng: Nothing to Disclose, Amanda Ricciuto: Nothing to Disclose, Gary Bader: Nothing to Disclose, Ian McGilvary: Nothing to Disclose, Binita Kamath: Mirum: Consultant, Mirum: Grant/Research Support, Albireo/Ipsen: Consultant, Albireo/Ipsen: Grant/Research Support, Audentes: Consultant, Sonya MacParland: Nothing to Disclose

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0178 | ACCEPTABILITY OF AND EXPERIENCE WITH HEALTH RELATED SOCIAL NEEDS SCREENING AMONG PATIENTS WITH CHRONIC LIVER DISEASE: A QUALITATIVE STUDY

Rebecca Kim[1] April Ballantyne[1] Patrick Galyean[1] Elizabeth Lancaster[1] Susan Zickmund[1] John Inadomi[1] Molly Conroy[1] Jennifer Price[2]

[1]University of Utah, [2]University of California San Francisco

Background: People with chronic liver disease (CLD) and health-related social needs (HRSN) experience poor CLD outcomes. Therefore, screening for and reducing HRSN may lead to improved outcomes. In primary care clinics, patients' acceptability with HRSN screening has varied, and CLD patients' perceptions have not been studied. Using qualitative methods, we aimed to assess patient acceptability of and experience with HRSN screening among those with CLD. **Methods:** From 9/2023-2/2024, 250 adults with CLD completed HRSN screening in liver clinics at an academic health center. Eleven participants were interviewed using a previously published interview guide, adapted for this study, to assess their perception of HRSN screening. Interviews were conducted virtually in English and audio recorded. Participants were given $50. Data were analyzed using Crabtree & Miller's approach creating codes and identifying themes through "open-coding", a process of developing codes for salient concepts as they emerge during the analysis process. We included a co-coding process by two trained analysts to ensure reliability. **Results:** Overall, 82% of participants were women, mean age 57yrs, 73% White, 18% Hispanic, 36% had cirrhosis and 64% had MASLD. Interviews lasted 9-44mins, avg 21mins. Themes that emerged included: 1) patient experience was comfortable or neutral, 2) survey topics were pertinent to health, 3) provider guidance to resources would be useful. The survey was reported to be acceptable; interviewees felt comfortable or neutral answering questions. Literacy was a barrier for one participant who stated reading English was difficult and affected their ability to complete the survey. Most participants indicated close associations with health and HRSN like stress, transportation needs, financial strain, and social isolation. One patient reported losing their social circle to maintain sobriety as advised, leading to an unanticipated consequence of isolation. Interviewees wanted questions about physical activity, diet, and mental health. Some expressed a desire for providers to offer referrals to resources. Specifically, participants requested assistance with transportation, finding more affordable medications, and strategies to cope with alcohol use triggers (e.g., isolation or stress). One person with transportation, financial, and food insecurity was unaware of resources and wanted more provider support. **Conclusion:** In-clinic HRSN screening is pertinent for the CLD patient population. The patient perspective demonstrates that liver clinics provide an invaluable opportunity to help address HRSN.

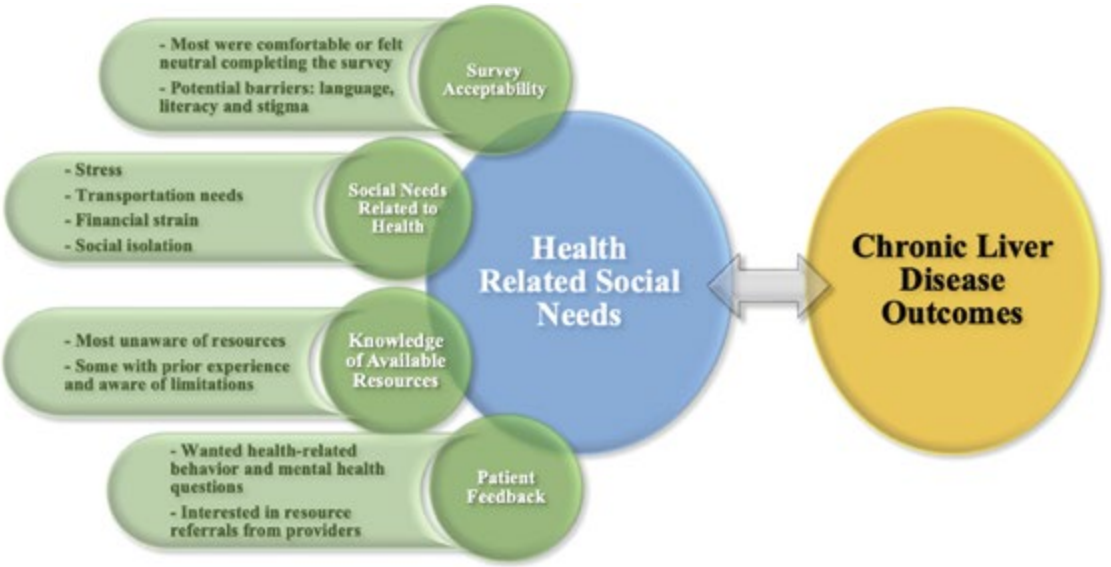

Figure. Patients' experience with and acceptability of health related social needs screening. Themes identified through semi-structured interviews with patients with chronic liver disease.

Disclosures: Rebecca Kim: Nothing to Disclose, April Ballantyne: Nothing to Disclose, Patrick Galyean: Nothing to Disclose, Elizabeth Lancaster: Nothing to Disclose, Susan Zickmund: Nothing to Disclose, John Inadomi: Nothing to Disclose, Molly Conroy: Nothing to Disclose, Jennifer Price: Nothing to Disclose

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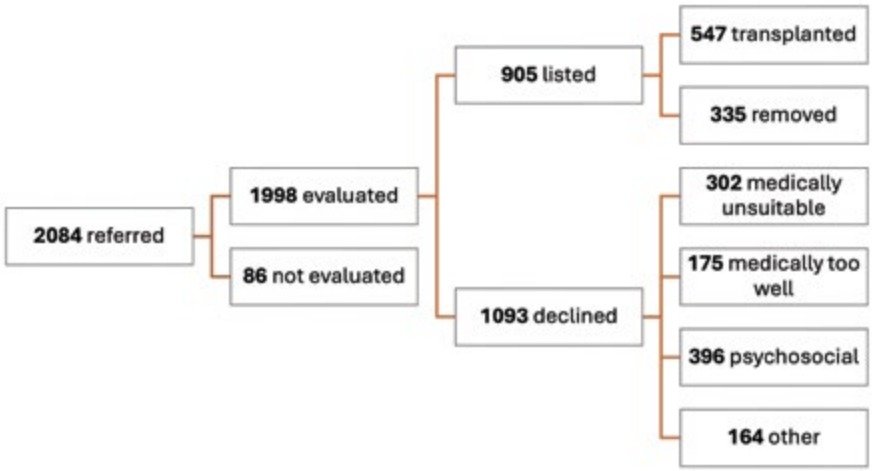
0179 | VARIABLE TREATMENT AND ACCESS TO LIVER TRANSPLANTATION FOR ALCOHOL ASSOCIATED LIVER DISEASE: THE CALIFORNIA LIVER NETWORK ◆ ★

Ashley Jowell[1] Mignote Yilma[2] Shayana Seneviratne[3] Kali Zhou[3] Weiyu Wu[4] Jasleen Singh[5] Steven Wisel[6] Hirsh Trivedi[6] Justin Steggerda[6] Alexander Kuo[6] Aarshi Vipani[7] Tiffany Lim[6] Michie Adjei[6] James Daniels[6] Monica Tincopa[8] Veeral Ajmera[8] Irine Vodkin[8] Chris Freise[2] Neil Mehta[2] Ryutaro Hirose[9] Allison Kwong[10]

[1]Duke University Medical Center, [2]University of California, San Francisco, [3]University of Southern California, [4]Stanford University, Stanford CA, [5]UCLA, [6]Cedars-Sinai, [7]Cedars Sinai, [8]University of California, San Diego, [9]University of Washington, [10]Stanford University Medical Center

Background: Alcohol associated liver disease (ALD) is now the most common indication for liver transplantation (LT), with greater acceptance of LT for alcohol associated hepatitis — however, significant practice variation exists and criteria for transplantation remain non-standard. We evaluated predictors of access to LT for ALD in a large representative state-based cohort. **Methods:** The California Liver Network is a consortium of six major LT centers in California, comprising >75% of the adult liver transplant volume in the state. Sociodemographic, clinical, and outcomes data were retrospectively collected for adults referred for LT at these centers between 2018 and 2020. We evaluated predictors of listing for patients with ALD, using a multivariable mixed effects model with center as a random effect. **Results:** Among 6856 patients referred during the study timeframe, there were 2084 (31%) with a specified indication of ALD. The median age was 55 years (IQR 48-62); 72% male; 40% White, 38% Hispanic; 3% Asian, and 2% Black; 22% reported a primary language other than English; and 34% had private insurance, 40% Medi-cal, and 21% Medicare. Median MELD at referral was 21 (IQR 14-30); 27% met NIAAA criteria for AH or had <6 months of sobriety; and 40% of evaluations were inpatient. Of the patients with AH, 36% were treated with steroid, which varied by center (range 10-58%). Ultimately, 45% were listed (MELD 21, IQR 18-29), and 26% were transplanted (MELD 33, IQR 31-39); 10% had a documented return to alcohol use during the referral/evaluation process. Primary reasons for decline included psychosocial reasons (36%; range 21-49%); medically too sick or unsuitable (28%; range 19-46%); and medically too well (16%; range 3-25%) (Figure). In the mixed effects model, women (p=0.01) and those with public insurance (vs private; p<0.001 for Medi-cal, p=0.001 for Medicare) were less likely to be listed. Adjusted for age, sex, race/ethnicity, insurance, MELD, and HCC status, center remained a significant predictor of listing (p<0.05). results were similar when examining the subgroup of patients with <6 months of sobriety at the time of referral. 126 (6.0%) of patients were also evaluated, and 40 (1.9%) waitlisted, at another US transplant center. **Conclusion:** Referral and selection practices for LT have been suboptimally characterized. This comprehensive study of LT referrals in the state of California, which performs the most liver transplants in the country, highlights the need for standardized medical and psychosocial criteria for ALD to promote and ensure equity in the LT selection process.

Figure: Referral cascade and outcomes for patients with ALD referred for LT.



Disclosures: Ashley Jowell: Nothing to Disclose, Mignote Yilma: Nothing to Disclose, Shayana Seneviratne: Nothing to Disclose, Kali Zhou: Nothing to Disclose, Weiyu Wu: Nothing to Disclose, Jasleen Singh: Nothing to Disclose, Steven Wisel: Nothing to Disclose, Hirsh Trivedi: Nothing to Disclose, Justin Steggerda: Nothing to

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Disclose, Alexander Kuo: Nothing to Disclose, Aarshi Vipani: Nothing to Disclose, Tiffany Lim: Nothing to Disclose, Michie Adjei: Nothing to Disclose, James Daniels: Nothing to Disclose, Monica Tincopa: Nothing to Disclose, Veeral Ajmera: Nothing to Disclose, Irine Vodkin: Nothing to Disclose, Chris Freise: Nothing to Disclose, Neil Mehta: Merck: Consultant, FujiFilm WAKO: Consultant, Ryutaro Hirose: Nothing to Disclose, Allison Kwong: Nothing to Disclose

0180 | THE USC PSYCHOSOCIAL CHECKLIST: A TOOL TO REMOTELY SCREEN POTENTIAL LIVER TRANSPLANT (LT) CANDIDATES WITH ALCOHOL-ASSOCIATED LIVER DISEASE (ALD) PRIOR TO HOSPITAL TRANSFER

Brooke Edwards[1] Samantha Ramirez[1] John Pappas[2] Jennifer Dodge[2] Hyosun Han[3] Jeffrey Kahn[2] Norah Terrault[3] Aaron Ahearn[2] Brian Lee[4]

[1]Keck Medical Center of USC, [2]Keck USC, [3]University of Southern California, [4]Keck School of Medicine

Background: ALD is the #1 indication for LT, leading to a rise in inter-hospital transfer requests for LT evaluation. Standardized, evidence-based tools to assist centers to triage transfer requests for LT for ALD evaluation represent a critical unmet need. We established a novel remote tele-screening tool to assist the LT team to determine the acceptance or denial of the interhospital transfer of patients with ALD for LT evaluation. **Methods:** A multidisciplinary group (social workers, LT administrators, psychiatrists, hepatologists, surgeons, hospital executive leadership) developed the USC Psychosocial Checklist, which is ascertained remotely by a USC social worker, and based on Dallas Consensus criteria and current evidence (FIGURE). None of the responses are an absolute contraindication for transfer. We compared use of no screening tool (Era 1: Oct-Dec 2022) vs. Stanford Integrated Psychosocial Assessment for Transplant (SIPAT) (Era 2: Feb-Jul 2023) vs. USC Psychosocial Checklist (Era 3: Aug 2023-Feb 2024), for 4 metrics: overall LT listing rate for ALD from hospital transfers, transfer acceptance, length of stay among transfers, and changes in transfer decline reasons using Poisson, logistic and linear regression where appropriate. **Results:** Among 390 transfer requests (60% male, median age 47 [IQR 38-57], MELD 33 [IQR 28-39], 69% with <6 months abstinence [similar across 3 eras]), 62 (16%), 153 (39%), 175 (45%) were during Era 1, 2, 3, respectively, and 100 (25%) were transferred. Primary reasons for transfer denial were: psychosocial risk (43%), too sick/co-morbidities (19%), transfer to other LT center (16%), clinical improvement (12%), financial (6%), other (4%). The LT listing rate per month for ALD from hospital transfers was higher in Era 3 (3.2 [95%CI 1.4-4.8]) and Era 2 (3.6 [1.5-5.6]) vs. Era 1 (2.3 [1.8-2.9]), though CIs overlapped. Likelihood of transfer acceptance was similar in Era 3 (27.4%, OR=1.57, p=0.21) and Era 2 (26.1%, OR=1.47, p=0.29) vs. Era 1 (19.3%). Hospital length of stay among transferred patients was similar in Era 3 (9.8±8.6 days, p=0.39) and Era 2 (8.2±7.0 days, p=0.71) vs. Era 1 (7.0±3.2 days). Odds of being declined for psychosocial reasons was lower in Era 3 (34.9%, OR=0.54, p=0.07), but not Era 2 (48.2%, OR=0.93, p=0.83) vs. Era 1 (50.0%), though this did not reach statistical significance. **Conclusion:** Implementing the USC Psychosocial Checklist (vs. no screening tool) was associated with a 35% increase in the rate of LT listings for ALD from hospital transfers, potentially due to lower odds of being declined for psychosocial risk, and without impacting hospital length of stay. Similar results were found using SIPAT, but took longer to administer than the USC Psychosocial Checklist, suggesting general utility of an objective screening tool. If validated in larger cohorts, the USC Psychosocial Checklist may be useful to assist centers to triage transfer requests for LT for ALD.

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FIGURE: USC Psychosocial Checklist for Patients with ALD and Workflow Schematic

Inpatient Transfer Screening Tool for Patients with Alcohol Associated Liver Disease

Purpose: This Screening Tool was established to assist the liver transplant team in determining the acceptance or denial of inpatient transfer for patients with alcohol-associated liver disease. It will be conducted by a social worker and emailed to the attending Hepatologist on-call to help determine transfer candidacy.

None of the responses below are contraindications to transplant.

Screening Tool for Alcohol-Associated Liver Disease:

1. First decompensation of liver disease: ☐Yes or ☐No
2. Patient is currently encephalopathic or intubated, and unable to participate in interview: ☐Yes or ☐No
3. Patient has insight into alcohol as cause of liver failure: ☐Yes or ☐No
4. Patient is agreeable to abstain completely from alcohol indefinitely: ☐Yes or ☐No
5. Patient has stable housing: ☐Yes or ☐No
6. Patient has identified caregiver for post-transplant care: ☐Yes or ☐No
7. Patient has active illicit substance use: ☐Yes or ☐No
8. Patient has hx of uncontrolled psychiatric comorbid disease diagnosis: ☐Yes or ☐No
9. Date of last alcohol use: _____
10. Amount of past formal rehab attempts: _____
11. Past alcohol-related legal issues (e.g. DUI): ☐Yes or ☐No

    If yes, how many? _____
12. Amount of drinks per day at peak: _____
13. SALT Score 0-11: _____



Disclosures: Brooke Edwards: Nothing to Disclose, Samantha Ramirez: Nothing to Disclose, John Pappas: Nothing to Disclose, Jennifer Dodge: Nothing to Disclose, Hyosun Han: Nothing to Disclose, Jeffrey Kahn: Orphalon: Single Advisory Board meeting 11/2023, Malinckrodt: Attended speaker's training session, never spoke, Orphalon: Single advisory board meeting, 2023, Norah Terrault: Grant/Research Support relationship with Eiger Pharmaceuticals; Has ended; Grant/Research Support relationship with GSK; Has not ended; Royalties or patent beneficiary relationship with Elseiver; Has not ended; Grant/Research Support relationship with Helio Health; Has ended; Grant/Research Support relationship with Durect Corp; Has ended; Executive role relationship with AASLD; Has not ended; Board member relationship with HBV Foundation; Has not ended; Grant/Research Support relationship with ImmunoCore; Has ended, Aaron Ahearn: Nothing to Disclose, Brian Lee: NIAAA: Grant/Research Support, Novo Nordisk: Advisor, GSK: Advisor, DURECT: Advisor, HepaTx: Advisor, CymaBay: Consultant, Ipsen: Consultant, Siemens Healthineers: Grant/Research Support, AltImmune: Advisor

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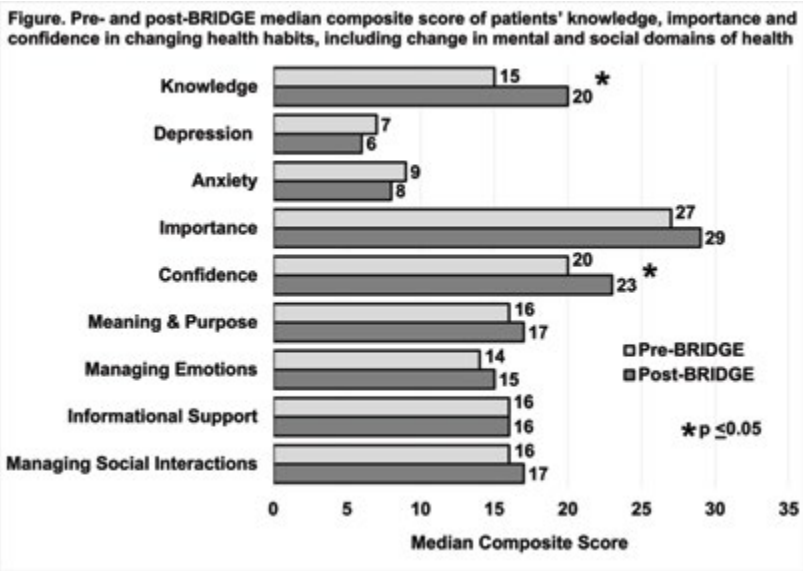
0181 | ENHANCED PATIENT KNOWLEDGE AND CONFIDENCE IN MANAGING METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE THROUGH BEHAVIORAL RESOURCES AND INTERVENTION THROUGH DIGITAL GROUP EDUCATION (BRIDGE): A SHARED MEDICAL APPOINTMENT PROGRAM ◆ ★

Lisa Catalli[1] Nghiem Ha[1] Sara Miller[1] Eliana Agudelo[1] Simone Madan[1] Asal Bastani[1] Riley Tan[1] Danielle Brandman[2] Jennifer Lai[1]

[1]University of California, San Francisco, [2]Weill Cornell Medicine

Background: Managing metabolic dysfunction-associated steatotic liver disease (MASLD) requires lifestyle changes. Integrating education and behavioral health through shared medical appointments (SMA) encourages patients to actively engage in their care through peer-based learning and support. We implemented BRIDGE, a group telehealth SMA program led by advanced practice providers (APPs), to enhance patients' knowledge, confidence, and self-efficacy in managing MASLD. **Methods:** BRIDGE is a video-based, bi-weekly, 6-session (90 min each) psychoeducational program led by APPs. Each session includes didactics, peer discussions, and individual consultations to develop personalized behavioral strategies using motivational interviewing and cognitive behavioral techniques. Participants rated their knowledge, importance, and confidence in making health changes on a 5-point scale. Self-efficacy in managing mental and social health was measured using 6 PROMIS short forms 2 weeks before and after the program **Results:** Included were 44 adults with MASLD who attended 6 (IQR 5-6) BRIDGE sessions between 9/2022-2/2024 and completed pre-/post-surveys. Most were women (77%) with a median age 57 years and obese (89%) with median BMI of 34 kg/m^2. Among them, 34% had diabetes, 55% had hypertension, and 61% had hyperlipidemia. Race/ethnicity included 45% non-Hispanic white, 32% Hispanics, 21% Asian/Native American. Most (91%) had severe steatosis with a median CAP of 332 (IQR 316-356) dB/m, and 25% had advanced fibrosis/cirrhosis. After BRIDGE, patients reported improvements in various life domains, including recognizing the importance of healthy habits, meaning and purpose, managing emotions, mental health, and seeking support, with significant improvements in knowledge and confidence in lifestyle changes in managing MASLD (Figure). Most (77%) achieved weight loss (mean ± SD of 2.2 ± 4.2 kg) and improved their frequency of muscle-strengthening exercises (mean ± SD increased of 1 ± 2 days, p=0.05). Qualitative feedback indicated high satisfaction with the program. **Conclusion:** Our innovative telehealth psychoeducational SMA program significantly improved patients' knowledge, confidence, and understanding of health-related behavioral changes for managing MASLD. It also enhanced mental well-being, social support, and increased the frequency of exercise. Future research should determine the optimal program duration to maximize and sustain lifestyle changes, ultimately leading to improve clinical outcomes.



Disclosures: Lisa Catalli: Madrigal: Advisory board, Nghiem Ha: Nothing to Disclose, Sara Miller: Nothing to Disclose, Eliana Agudelo: Nothing to Disclose, Simone Madan: Nothing to Disclose, Asal Bastani: Nothing to Disclose, Riley Tan: Nothing to Disclose, Danielle Brandman: Consultant relationship with Novo Nordisk; Has ended; Grant/Research Support relationship with Gilead; Has ended; Grant/Research Support relationship

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with Genentech; Has ended, Jennifer Lai: Nestle Nutrition Institute: Grant/Research Support, Novo Nordisk: Consultant, Genfit: Consultant, Boehringer Ingelheim: Advisor

0182 | R0N0 RESECTION FOR PERIHILAR CHOLANGIOCARCINOMA OFFERS SURVIVAL SIMILAR TO TRANSPLANTATION: A MULTICENTRE PAN-EUROPEAN STUDY

Raj Prasad[1] Richard Bell[2] Nawaz Safdar[2] Hauke Lang[3] Alfredo Guglielmi[3] Thomas van Gulik[3] Pim Olthof[3] Raj Prasad[4]

[1]King's College Hospital NHS Foundation Trust, [2]Leeds Teaching Hospitals NHS Trust, [3]Perihilar Cholangiocarcinoma Collaboration Group, Erasmus, Netherlands, [4]Froedtert Memorial Lutheran Hospital & Children's Hospital of Wisconsin

Background: A US multi-institutional study highlighted the improved outcomes with transplantation over resection for de novo perihilar cholangiocarcinoma (pCCA) [Ethun et al., Ann Surg. 2018]. Despite criticisms with small resection volumes (n=234; 1.5 resections/centre/year), this was a practice changing publication, with more centres adopting transplant as first treatment option for pCCA patients. The current study aims to analyse if R0N0 resection (like transplant) offers better overall (OS) and disease-free survival (DFS) compared to those who are margin and/or node positive (non-R0N0). **Methods:** This was a retrospective study of the Perihilar Cholangiocarcinoma Collaboration group database, which is a multicentre international database maintained by IHPBA. All consecutive liver resections for pathologically confirmed pCCA between 2000 and 2019 in 25 centers were included. Median number of resections were 79 (IQR 42-100) per centre. Standard statistical analysis and Kaplan-Meier survival curves for overall survival (OS) and disease-free survival (DFS) was performed. **Results:** Over the 20-year study period, 2226 resections were performed, of which 257 excluded (PSC and no margin or nodal status data). Of the 1969 included, 803 (40.8%) were R0N0 and 1166 (59.2%) were non-R0N0. 88.8% of R0N0 patients underwent major resection (³3 segments), compared to 91.4% in the non-R0N0 group (p=0.048). More patients in the non-R0N0 group needed vascular resection; PV (32.3% vs. 26.5%; p=0.008) and HA (4.5% vs. 2.2%; p=0.011). Histologically, non-R0N0 had higher T3/T4 cancers (42.1% vs. 22.4%; p<0.001), poorly differentiated tumours (27.4% vs. 15.9%; p<0.001) and perineural invasion (74.3% vs. 59.0%; p<0.001). There was no difference between the two groups in terms of Clavien-Dindo grade 3> complications, postoperative stay or 90-day mortality. 1-, 5-, and 10-year OS was much better for R0N0 group (90%, 45%, 20% vs. 85%, 18%, 10%; p<0.001), so was the DFS (92%, 40%, 20% vs. 60%, 15%, 7%; p<0.001). 5-year survival for tumour <3cm/R0N0 group was 50% vs. 40% for tumour >3cm/R0N0 (p=0.025). **Conclusion:** This pan-European multicentre experience with high resection volumes (4.4 cases/centre/year) suggests survival outcomes comparable with transplant outcomes from few centres with stringent selection criteria. An intention to treat analysis (without neoadjuvant therapy), **Results:** of resection are potentially better than transplantation with higher drop-off in de novo patients post-neo-adjuvant chemotherapy. It should be concluded that, transplant should not be a clear indication for pCCA at this point of time.

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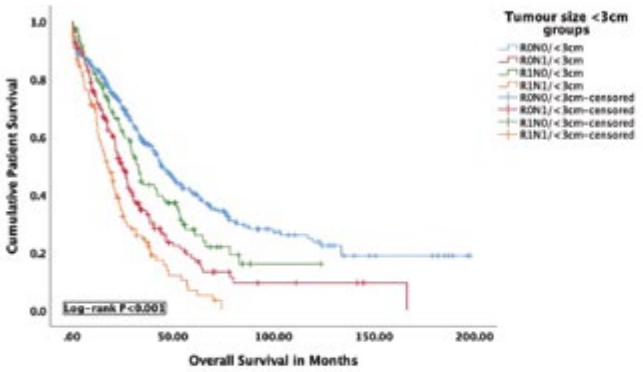
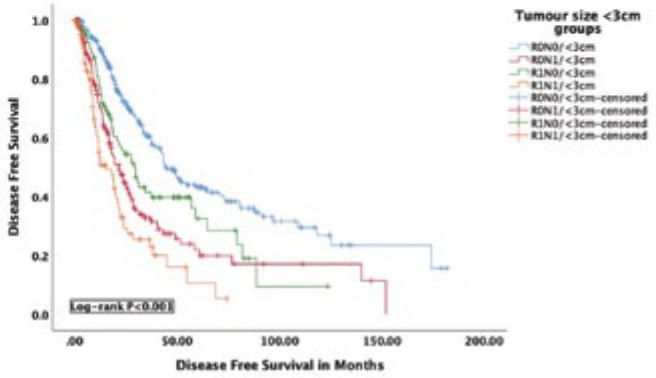
Tumour Size <3cm – Overall Survival



Tumour Size <3cm – Disease Free Survival



Disclosures: Raj Prasad: Nothing to Disclose, Richard Bell: Nothing to Disclose, Nawaz Safdar: Nothing to Disclose, Hauke Lang: Nothing to Disclose, Alfredo Guglielmi: Nothing to Disclose, Thomas van Gulik: Nothing to Disclose, Pim Olthof: Nothing to Disclose, Raj Prasad: Nothing to Disclose, Nothing to Disclose

0183 | A NUCLEOSOME SWITCH PRIMES HEPATITIS B VIRUS INFECTION

Nicholas Prescott[1] Andres Mansisidor[2] Yaron Bram[3] Christine Lim[3] Viviana Risca[2] Yael David[4] Robert Schwartz[5]

[1]Memorial Sloan Kettering Cancer Center, [2]Rockefeller University, [3]Weill Cornell Medicine, [4]MSKCC, [5]Weill Cornell Medical College

Background: Background: Chronic hepatitis B virus (HBV) infection is a global health problem causing significant liver disease and hepatocellular carcinoma. After viral entry, the HBV genome is shuttled into the nucleus and repaired from a partially double-stranded, relaxed circular DNA into a fully double-stranded, covalently closed circular DNA (cccDNA). The cccDNA rapidly becomes populated with host histone octamers and serves as the primary template for viral transcription. The viral protein HBx has a paradoxical relationship to cccDNA transcription during the earliest stages of infection. HBx induces the degradation of the host Smc5/6 complex, which otherwise would transcriptionally silence cccDNA, but is absent from the mature virion and must be expressed *de novo* in freshly infected hepatocytes. HBx is thought to be the earliest-expressed viral gene, with its transcript most abundant in the first 24 hours after HBV infection. Moreover, the interplay between cccDNA chromatin state and viral transcription kinetics remains poorly understood despite its potential importance to the establishment of active chronic infection. Traditional genetic and cell biology approaches lack the temporal and biochemical resolution necessary to characterize this critical intermediate in HBV infection establishment. **Methods:** and **Results:** To surmount these difficulties, we developed a method to generate recombinant cccDNA minichromosomes in a chemically defined system, allowing us to characterize its biophysical properties and map nucleosome occupancy on the chromosome. **Results:** We apply biochemical techniques to demonstrate that chromatin assembly on cccDNA is spatially defined and critical for HBx mRNA expression, but not other viral transcripts. This is further confirmed in native HBV infection using transcriptomic and MNase-seq analysis. Finally, we demonstrate that small molecule-mediated disruption of nucleosome integrity is sufficient to inhibit HBx transcription, cccDNA content, and viral infection in hepatocytes. **Conclusion:** Conclusions: In summary, we show that cccDNA chromatin structure specifically regulates HBV RNA transcription and how when disrupted inhibits and alters HBV infection. Our results shed new light on a long-standing paradox and represent a novel therapeutic avenue for the treatment of chronic HBV.

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Disclosures: Nicholas Prescott: Nothing to Disclose, Andres Mansisidor: Nothing to Disclose, Yaron Bram: Nothing to Disclose, Christine Lim: Nothing to Disclose, Viviana Risca: Nothing to Disclose, Yael David: Nothing to Disclose, Robert Schwartz: Miromatrix Inc: Advisor, Lime Therapeutics: Advisor, Otsuka Inc.: Grant/Research Support, Alnylam Pharmaceuticals: Speaking and Teaching, Alnylam Pharmaceuticals: Consultant

0184 | IMPROVEMENTS IN PRURITUS ARE ASSOCIATED WITH IMPROVEMENTS IN GROWTH IN PATIENTS WITH PROGRESSIVE FAMILIAL INTRAHEPATIC CHOLESTASIS: DATA FROM THE MARCH-ON TRIAL

Alexander Miethke[1] Amal Aqul[2] Chuan-Hao Lin[3] Douglas Mogul[4] Tiago Nunes[4] Jolan Terner-Rosenthal[4] Marshall Baek[4] Pamela Vig[4] Richard Thompson[5]

[1]Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, [2]University of Texas Southwestern Medical Center, Dallas, Texas, [3]Children's Hospital Los Angeles, Los Angeles, California, [4]Mirum Pharmaceuticals, Inc., Foster City, California, [5]King's College London, United Kingdom

Background: Progressive familial intrahepatic cholestasis (PFIC) is a group of disorders resulting in disrupted bile composition and cholestasis leading to debilitating pruritus, growth deficits, vitamin deficiency, and progressive liver damage. MARCH was a 26-week, randomized, placebo-controlled (PBO), Phase 3 trial of maralixibat (MRX), an ileal bile acid transporter (IBAT) inhibitor, that achieved its primary and key secondary endpoints of pruritus and sBA reduction for individuals across the broadest range of PFIC types studied. Long-term maintenance of effect for up to two years was observed in MARCH-ON, an open-label extension. Additionally, sustained improvements in growth were observed in MARCH-ON. We report on the relationship between pruritus response and growth improvements in the MARCH-ON trial. **Methods:** MARCH/MARCH-ON has been previously described. Pruritus response was defined as a participant having ≥1 point reduction in ItchRO(Obs) from baseline to the average of the final 3 week periods of MARCH (Weeks 15-18, 19-22, 23-26). Height and weight Z-scores based on a participant's sex and age at each scheduled trial visit were analyzed. Wilcoxon signed-rank test and rank sum test were used to determine change from baseline (CFB) significance within groups and between groups, respectively. **Results:** We analyzed 60 participants from the All-PFIC cohort (13 FIC1, 28 nt-BSEP, 9 MDR3, 7 TJP2, and 3 MYO5B) that participated in MARCH-ON. Baseline characteristics (eg, age, sBA, pruritus, and liver biochemistries) were well-balanced between groups. Growth (mean [SE]) for the overall PFIC study population was stunted at Baseline (height z-score: -2.11 [0.17]; weight z-score: -1.50 [0.17]). Overall, 32 participants met the pruritus responder criteria in the All-PFIC population and 28 were considered to be non-responders. In MARCH, pruritus responders had a significant improvement in both height (mean CFB [SE]: 0.42 [0.09]; P<0.0001) and weight z-scores (CFB: 0.44 [0.07]; P<0.0001) at Week 26, with these improvements sustained out to 70 weeks of treatment in MARCH-ON (height CFB: 0.51 [0.10]; P<0.0001; weight CFB: 0.55 [0.15]; P=0.0002). No significant improvements in growth were observed in the pruritus non-responder group. Significant differences between pruritus responders and non-responders were sustained out to 70 weeks (height CFB Δ: +0.51; P=0.02; weight CFB Δ: +0.59; P=0.047). **Conclusion:** These consistent trends in growth for participants who received MRX and were pruritus responders indicate a potential disease-modifying effect of MRX treatment in PFIC.

Disclosures: Alexander Miethke: Mirum Pharmaceutical Inc: Grant/Research Support, Mirum Pharmaceutical Inc: Consultant, Ipsen: Speaking and Teaching, Amal Aqul: Nothing to Disclose, Chuan-Hao Lin: Nothing to Disclose, Douglas Mogul: Mirum Pharmaceuticals: Employee, Tiago Nunes: Mirum Pharmaceuticals: Employee, Jolan Terner-Rosenthal: Mirum Pharmaceuticals, Inc.: Employee, Marshall Baek: Mirum Pharmaceuticals, Inc: Employee, Pamela Vig: Nothing to Disclose, Richard Thompson: Generation Bio: Stock - publicly traded company, Generation Bio: Consultant, Rectify: Stock – privately held company, Rectify: Consultant, Mirum: Consultant, Ipsen: Consultant, Alnylam: Consultant, Integra: Stock – privately held company, Glycomine: Consultant, Spruce: Consultant, AIRNA: Consultant

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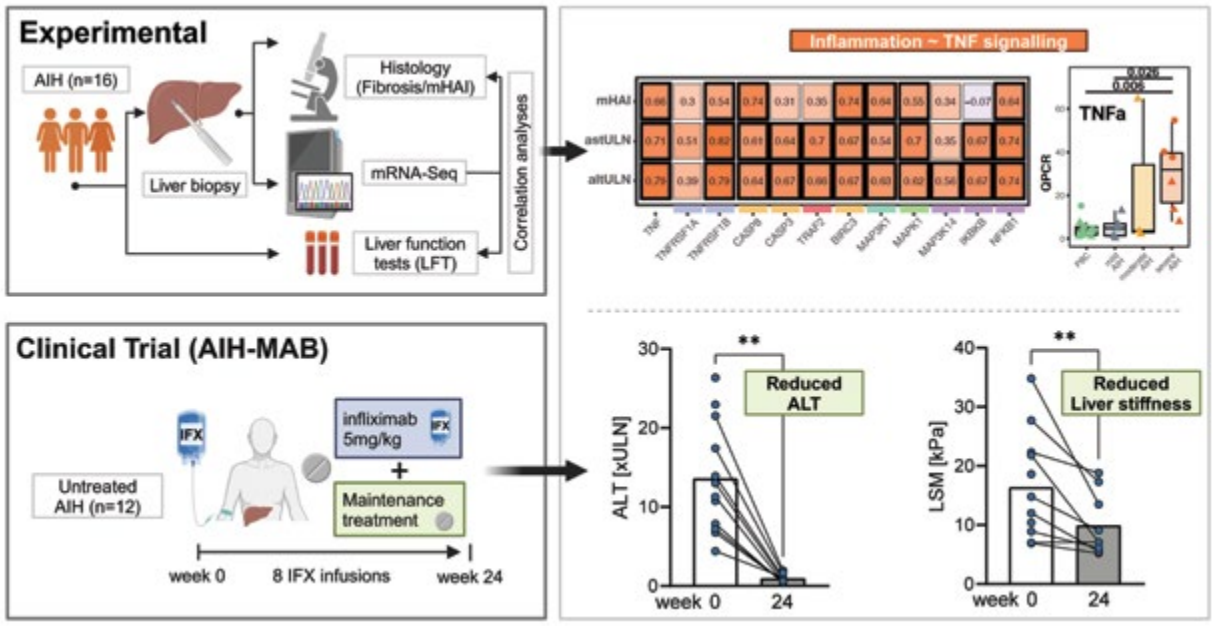
0185 | TNFALPHA AS A KEY INFLAMMATORY MEDIATOR IN AUTOIMMUNE HEPATITIS (AIH): MOLECULAR BASIS AND SUCCESSFUL PROOF-OF-CONCEPT PHASE IIA CLINICAL TRIAL OF INFLIXIMAB INDUCTION THERAPY

Jan Philipp Weltzsch[1] Christoph Kilian[1] Christina Weiler-Normann[1] Alena Laschtowitz[1] Ida Schregel[1] Felix Braun[1] Malte Hermann Wehmeyer[1] Johannes Hartl[1] Johannes Herkel[1] Christoph Schramm[1] Lorenz Adlung[1] Ansgar Wilhelm Lohse[1]

[1]I. Department of Medicine, University Medical Centre Hamburg-Eppendorf

Background: Standard immunotherapy of AIH using high-dose corticosteroids (CS) is non-specific and often leads to relevant side effects. Identifying specific pathways for therapeutic targeting is thus an unmet clinical need in AIH. We previously described the TNF pathway as a possible treatment target, and the anti-TNF antibody infliximab (IFX) as an effective third-line therapy in difficult-to-treat AIH. Here, we aimed to 1) provide further mechanistic proof for targeting the TNF pathway and 2) conduct a phase II clinical trial of CS-free induction therapy in AIH. **Methods:** Liver biopsies from patients with AIH (n=16) and PBC (n=12) were analyzed by mRNA sequencing. Transaminases (TA) and histological features were correlated with gene expression. CS-free induction therapy with IFX (5mg/kg) alongside standard maintenance therapy was assessed in a phase IIA single-arm study of n=12 patients with acute, treatment-naive AIH (*AIH-MAB*, EudraCT: 2017-003311-19). Prospectively collected data (provided by the RLIVER registry) of n=24 patients (matched for sex, fibrosis stage, baseline ALT) receiving standard treatment with CS and maintenance therapeutics served as a comparator for treatment efficacy. **Results:** Activated transcription factor modules like NFKB1/STAT1 and respective pathways (TNF, JAK-STAT) were enriched in the AIH cohort. Spearman correlation showed 20/7% of genes correlated positively/negatively (rho>0.6/rho<-0.6) with TA levels and modified Ishak scores (mHAI). Among positively correlated genes, the KEGG terms TNF and JAK-STAT were overrepresented. Respective cytokines (e.g. TNF, IFNG, IL12A) correlated with disease activity and were confirmed by qPCR. IFX significantly decreased AST (baseline median AST 7.35xULN [3.32-16.71] to 0.76xULN [0.52-1.66], -89.7%, p=0.0078), ALT (12.14xULN [4.4-21.54] to 0.97 xULN [0.6-1.97], -92%, p=0.0078) and liver stiffness (18.3kPa [6.9-34.8] to 8.1kPa [5.2-18.8], -55.7%, p=0.0156) after 24 weeks in the per-protocol analysis (n=8). This was similar to the response rates in the standard of care control group . AST, ALT, and IgG returned to normal values after 24 weeks in 5, 4, and 3/8 patients, respectively. All patients within the per-protocol analysis exhibited transaminase levels <2xULN after 24 weeks of treatment. The strict study protocol led to a drop-out of four patients: two patients with insufficient early treatment response received CS treatment, two patients with severe adverse events did not complete treatment. **Conclusion:** mRNA sequencing of liver biopsies identified TNF and JAK-STAT signalling as key mediators of the inflammatory response in AIH. Targeting TNF with IFX is a viable and effective treatment for acute AIH allowing CS-free therapy. Anti-TNF treatment protocols should be evaluated as primary therapy of AIH.



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Disclosures: Jan Philipp Weltzsch: Nothing to Disclose, Christoph Kilian: Nothing to Disclose, Christina Weiler-Normann: Nothing to Disclose, Alena Laschtowitz: Biontech: Stock – privately held company, Ida Schregel: Nothing to Disclose, Felix Braun: Nothing to Disclose, Malte Hermann Wehmeyer: Nothing to Disclose, Johannes Hartl: Nothing to Disclose, Johannes Herkel: Nothing to Disclose, Christoph Schramm: Nothing to Disclose, Lorenz Adlung: Nothing to Disclose, Ansgar Wilhelm Lohse: Nothing to Disclose

0186 | FIBRATE-OCA (FI-OCA) STUDY – A GLOBAL SNAPSHOT OF PBC PRACTICE AROUND THE GLOBE ★

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Background: The introduction of obeticholic acid (OCA) and the emerging evidence on the efficacy of fibrates and other PPAR-agonists have changed the treatment paradigm for primary biliary cholangitis (PBC) and increased the complexity of disease management, resulting in heterogeneous and diverse PBC practices worldwide. We aimed to define the second-line treatment practice in PBC patients across the Globe. **Methods:** We conducted a retrospective, international, multicentric cohort study involving PBC patients who began second-line treatment with either fibric acid derivatives (fibrates) or OCA in 40 liver centres across Europe, Japan, South America, and North America. We collected clinical, biochemical, and treatment data at diagnosis and at the initiation of second-line treatment. Adverse effects and treatment changes during follow-up were also recorded. **Results:** We accrued data on 1,785 patients, 917 initiated on OCA (901 already on UDCA) and 868 on fibrates (863 on UDCA). Among these, 635 patients started on bezafibrate and 233 on fenofibrate. 296 of the patients on Bezafibrate were from 19 centres with restricted access to OCA, in Japan, Argentina, Netherlands and Belgium. Only 17 patients began bezafibrate and OCA simultaneously. The sex distribution did not differ significantly between the fibrate and OCA groups (female: 87.9% vs 88.9%, p=0.570). Baseline mean ALT, ALP, GGT, and bilirubin (ratios to the upper limit of normal) were 1.47 (±1.29) vs 1.63 (±1.58) (p=0.100), 2.64 (±1.55) vs 2.43 (±2.47) (p=0.070), 5.39 (±4.20) vs 5.06 (±4.79) (p=0.453), and 0.98 (±0.94) vs 0.98 (±0.64) (p=0.986), respectively. Baseline cirrhosis was more frequent in OCA patients (28.3.0%, n=216; vs 19.5%, n=83, p=0.01). Most cirrhotic patients on OCA were Child A (97.7%) compared with 64% on fibrates. The median time from UDCA initiation to second-line treatment was longer for OCA patients (70.7 (28-132) months vs 53 (15-123) months, p< 0.001). During follow-up, 96 OCA patients added a fibrate, while 22 fibrate patients added OCA. OCA was discontinued by 302 patients (33%), primarily due to pruritus (33%). 128 of them switched to fibrates. Fibrates were discontinued by 182 patients (21%) due to increased transaminases (18%) or worsening renal function (10%); 39 switched to OCA. The median time before adding a third medication or switching treatments was 23.5 (12.0-39.8) months for OCA and 27.0 (12.5-53.0) months for fibrates. **Conclusion:** Management of PBC demands dynamic adjustments to second-line treatments, and high discontinuation and change rates underscore the urgent need for better allocation tools.

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0187 | NATURAL HISTORY AND PREDICTORS OF OUTCOMES IN PATIENTS WITH LIVER CIRRHOSIS AFTER INDEX VARICEAL HEMORRHAGE FROM FUNDAL VARICES

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Background: There is limited data on the natural history and outcomes after the first episode of bleeding from fundal varices (FV) in patients with liver cirrhosis, as well as on the predictors of rebleeding, further decompensation and mortality. **Methods:** We prospectively followed patients with liver cirrhosis after index variceal hemorrhage (VH) from large FV (≥2 cm) from January 2017 to January 2024. Baseline demographic, clinical, and endoscopic details were maintained for all patients. Data from computerized tomography scans were available for all patients who underwent imaging. All patients presenting with acute VH received endoscopic cyanoacrylate injection (ECI) for primary hemostasis. Transjugular intrahepatic portosystemic shunt (TIPS) or balloon occluded retrograde transvenous obliteration (BRTO) was offered to patients for secondary prophylaxis. Competing risk analysis was done to assess the risk of rebleeding in patients who had died prior to a rebleeding

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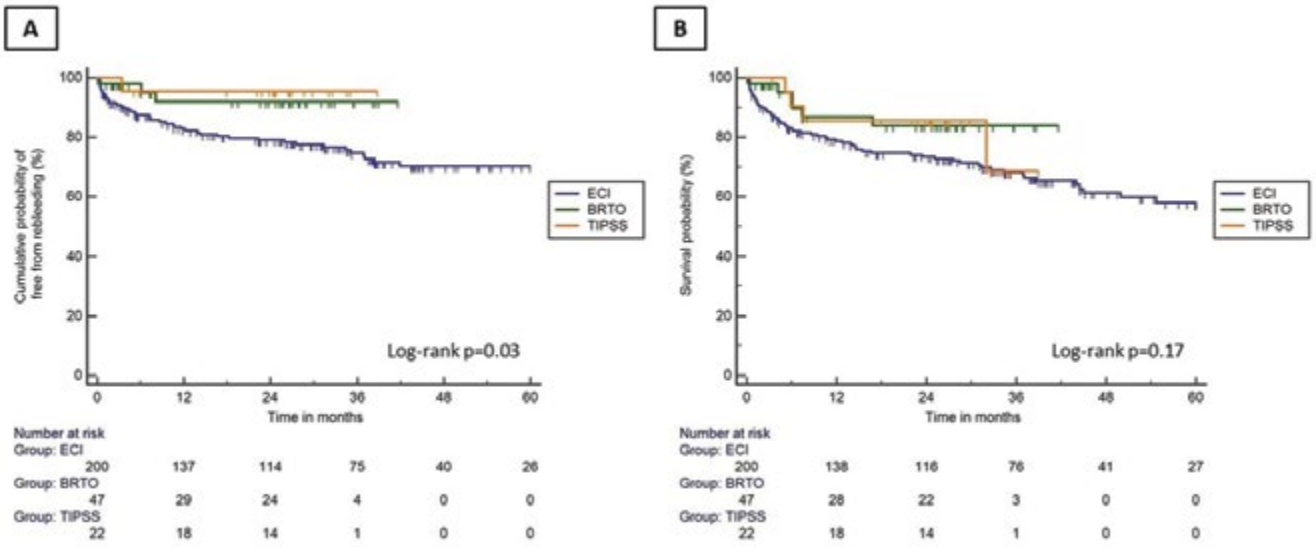
event. **Results:** Two hundred and sixty nine patients with index VH from FV and 47 patients with large non-bleeding FV were recruited during the study period. Alcohol was the leading etiology of cirrhosis in 110 (40.9%) patients with VH. Median baseline Child and MELD score of the cohort was 7 (6-9) and 12.3 (10.2-15.5) respectively. Two hundred patients received endoscopic glue injection (ECI) alone while 47 and 22 patients received BRTO and TIPS respectively. In the ECI group, ascites and hepatic encephalopathy were present at baseline in 110 (55%) and 88 (44%) patients respectively. Over a median follow-up of 870 (214-1319) days, 74 (37%) patients had further decompensation with the most common event being ascites and rebleeding in 23 (31.1%) patients followed by ascites alone in 15 (20.3%). The 1, 3- and 5-year rates of decompensation were 25%, 36.3% and 40% respectively. The 1, 3- and 5-year mortality rates were 21.8%, 32.6% and 45% respectively, with highest mortality rates in patients having rebleeding with ascites [20, 27.8%]. Risk of all-cause rebleeding at 1, 3-and 5-years was 17.8%, 26.3% and 29.7% respectively. In the competing risk analysis, age and size of afferent shunt vessels of FV were independently associated with rebleeding. Patients undergoing BRTO or TIPSS for secondary prophylaxis had significantly lower rebleeding rates than those undergoing ECI alone (log-rank p=0.03) [Figure 1a], although there was no difference in mortality rates among patients of all 3 groups (log-rank p=0.17) [Figure 1b]. Six patients (13%) with non-bleeding FV had index decompensation over a median follow-up period of 480 (133-1088) days with 4 (8.7%) patients having VH. **Conclusion:** Patients with liver cirrhosis who experience an index episode of VH from fundal varices are at high risk of further decompensation. TIPS and BRTO are effective modalities of secondary prophylaxis which reduce the risk of rebleeding in these patients but do not improve overall survival.



Disclosures: Sagnik Biswas: Nothing to Disclose, Sanchita Gupta: Nothing to Disclose, Anuradha Sharma: Nothing to Disclose, Arnav Aggarwal: Nothing to Disclose, Umang Arora: Nothing to Disclose, Shekhar Swaroop: Nothing to Disclose, Rajkumar Bayye: Nothing to Disclose, Amitkumar Chavan: Nothing to Disclose, Swapnil Chaudhary: Nothing to Disclose, Ayush Agarwal: Nothing to Disclose, Anshuman Elhence: Nothing to Disclose, Soumya Mahapatra: Nothing to Disclose, Deepak Gunjan: Nothing to Disclose, Shivanand Gamanagatti: Nothing to Disclose, Dr Shalimar: Nothing to Disclose

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0188 | TOWARDS PRECISION ONCOLOGICAL LIVER SURGERY: LABEL-FREE MULTIPHOTON MICROSCOPY AND MACHINE LEARNING FOR TUMOR RECOGNITION IN HEPATOCELLULAR CARCINOMA

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Background: Complete tumor resection is crucial in oncological liver surgery. Evaluating intraoperative resection margins is essential to prove R0 resection. This can be challenging for hepatocellular carcinoma (HCC) due to the heterogeneity of both tumor and background liver tissue. Intraoperative frozen sections are the gold standard. However, especially low-grade HCC (G1) is even microscopically difficult to detect without specific staining and immunohistochemistry and some resection margins remain unclear during surgery. Moreover, intraoperative histopathological analyses are time-consuming, leading to prolonged operation times. Consequently, new techniques for intraoperative real-time evaluation of resection margins are urgently needed. Label-free multiphoton microscopy (MPM) enables tissue analysis based on endogenous optical signals and has the potential for intraoperative real-time assessment of the resection planes. **Methods:** Matched samples of human HCC and background liver tissue of 76 patients who underwent Surgery in the Department of Visceral, Thoracic and Vascular Surgery, University Hospital Dresden, were imaged with a multimodal approach including coherent anti-Stokes Raman scattering, two-photon autofluorescence, and second harmonic generation, revealing HCC growth patterns as well as steatotic and desmoplastic features. All samples were controlled by conventional histopathological analyses. **Results:** Accurate tumor recognition was achieved by machine learning on low lateral resolution MPM images mimicking the use of endoscopes. A neural network model was trained on approximately 25,000 images (35 patients) to classify a test set of around 27,000 images (38 patients) and create maps that show the tumor border (3 patients). The model achieved a test set correct rate of 97.3% (98.2% for liver and 96.5% for tumor). Analysis of the contribution of the different non-linear optical signals to the classification showed that autofluorescence plays a key role in discriminating between neoplastic and non-neoplastic tissue. **Conclusion:** In conclusion, label-free intraoperative optical histopathology is likely going to play an important role in improving evaluating tumor resection margins to ensure R0 resections. Different imaging modalities can be endoscopically implemented to tailor on-site tissue analysis towards optimization of tumor identification or characterization of background liver tissue.

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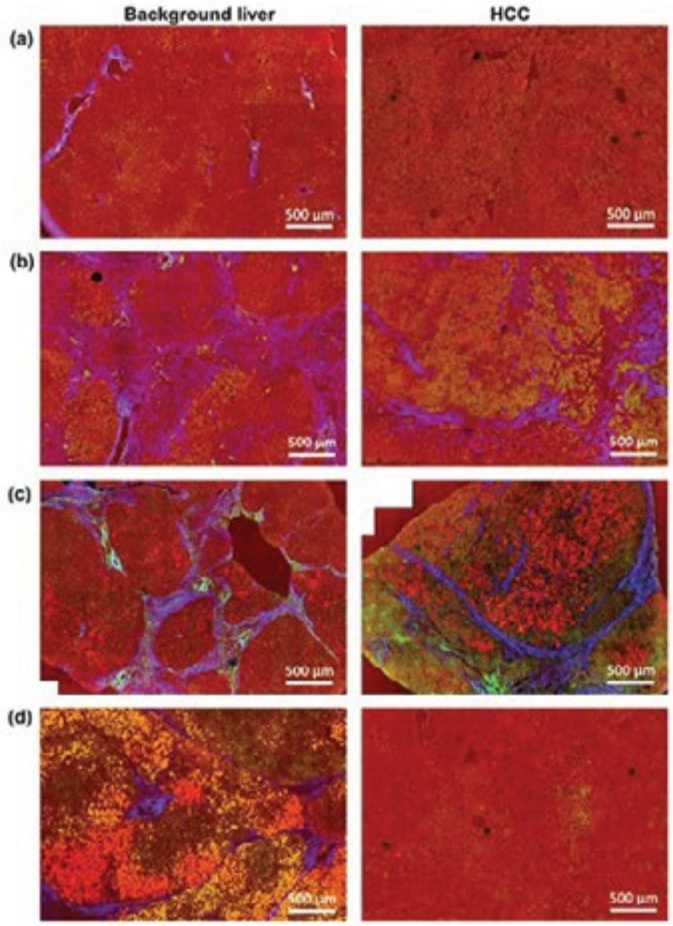

Figure 1. Label-free multimodal multiphoton images showing tissue architecture of background liver and HCC of four selected patients (red: CARS, green: TPEF, blue: SHG). a) Uniform structure lacking fibrosis and fatty changes both in background liver and tumor tissue; (b) background liver tissue with cirrhotic nodules and tumor with fibrosis; c) background liver tissue with cirrhotic nodules and fatty changes, tumor with fibrosis and fatty changes; (d) background liver tissue with marked fatty changes and fibrosis, tumor with homogenous structure lacking of both.

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0189 | CLINICAL OUTCOMES OF INACTIVE HEPATITIS B SURFACE ANTIGEN CARRIERS WITH UNDETECTABLE HBV DNA LEVELS AND LOW-LEVEL VIREMIA

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Background: The difference of clinical outcomes between inactive hepatitis B surface antigen (HBsAg) carriers (IHCs) with undetectable hepatitis B virus (HBV) DNA levels and low-level viremia (LLV) is not yet clear. We

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compared the clinical outcomes between IHCs with undetectable HBV DNA levels and LLV. **Methods:** Four hundred and fifty-six treatment-naïve IHCs characterized by serum hepatitis B e antigen (HBeAg) negativity, HBV DNA < 2,000 IU/mL, and normal alanine aminotransferase (ALT ≤ 40 IU/L), were retrospectively included from three medical centers. Patients were divided into undetectable HBV DNA group (< 20 IU/ml) and LLV group (20 - 2,000 IU/ml) according to baseline HBV DNA levels. Significant liver fibrosis and cirrhosis were identified by aspartate transaminase to platelet ratio index (APRI), fibrosis-4 score (FIB-4), or ultrasonography. **Results:** The median age of patients was 36.0 years and 56.6% patients were male. The proportion of patients with undetectable HBV DNA and LLV were 17.3% and 82.7%, respectively. Patients with undetectable HBV DNA had a higher proportion of HBsAg < 100 IU/mL (51.9% vs. 23.1%, p < 0.001) at baseline, compared to patients with LLV. The APRI (0.25 vs. 0.26, p = 0.948) and FIB-4 (0.87 vs. 0.80, p = 0.426) showed no significant difference between two groups at baseline. After a median follow-up of 24 months (interquartile range: 13 - 38 months), IHCs with undetectable HBV DNA were more likely to achieved spontaneous HBsAg seroclearance compared to LLV group (8.9% vs. 1.3%, p < 0.001), while more patients in LLV group transitioned to HBeAg-negative indeterminate phase (HBV DNA ≥ 2,000 IU/ml, ALT ≤ 40 U/L) than those with undetectable HBV DNA (25.5% vs. 5.1%, p < 0.001). The proportion of IHCs transitioning to HBeAg-negative CHB (HBV DNA > 2,000 IU/ml, ALT > 40 U/L) were comparable between two groups (1.3% vs. 2.1%, p = 0.958). In the multivariate Cox regression analyses, baseline LLV was an independent risk factor of transition to indeterminate phase (hazard ratio [HR]: 4.503, 95%CI: 1.642 - 12.349, p = 0.003) and negatively associated with of HBsAg clearance (HR: 0.247, 95%CI: 0.076 - 0.798, p = 0.019). Only one (1.3%) IHCs with undetectable HBV DNA developed significant liver fibrosis, while three patients (1.2%) with LLV developed liver cirrhosis at the end of follow-up. No IHCs developed hepatocellular carcinoma. **Conclusion:** Compared to undetectable HBV DNA, IHCs with LLV had a significantly higher risk of transition to indeterminate phase and lower probability of HBsAg seroclearance.

Disclosures: Yifan Pan: Nothing to Disclose, Jian Wang: Nothing to Disclose, Shaoqiu Zhang: Nothing to Disclose, Li Zhu: Nothing to Disclose, Zhiyi Zhang: Nothing to Disclose, Yuanyuan Li: Nothing to Disclose, Ye Xiong: Nothing to Disclose, Tao Fan: Nothing to Disclose, Chuanwu Zhu: Nothing to Disclose, Jie Li: Nothing to Disclose, Xingxiang Liu: Nothing to Disclose, Rui Huang: Nothing to Disclose, Wu Chao: Nothing to Disclose

0190 | TARGETING LOWER SERUM ALBUMIN WITH LONG TERM ALBUMIN ADMINISTRATION IMPROVES OUTCOMES OF RECURRENT ASCITES IN PATIENTS WITH DECOMPENSATED CIRRHOSIS- FINAL RESULTS OF THE RANDOMISED CONTROLLED TRIAL

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Background: Long-term albumin (LTA) and targeting serum albumin of 4 gm/dl improves major adverse liver outcomes (MALO) in cirrhosis patients with ascites. We aimed to compare whether a lower target albumin strategy of 3 gm/dl (Alb3.0) could be effective in patients with recurrent ascites (RA). We also aimed to evaluate the mechanisms of benefit of LTA. **Methods:** In a randomized controlled trial, patients received 20% albumin targeting serum albumin>3 gm/dl (Alb3.0) group with standard medical treatment (SMT) compared to SMT alone. Primary outcome was 6-month mortality. Secondary outcomes included MALO assessed as resolution of ascites, development of acute (AKD) or chronic kidney disease (CKD), spontaneous bacterial peritonitis (SBP) or non-SBP infections, hepatic encephalopathy (HE) and 12 -month mortality. **Results:** Patients with RA (Alb3.0; n=61, SMT; n=60), aged 48±10 years, 88% males, 50% alcohol-related, with CTP score 9.7±1.1, liver frailty index (LFI) 5.1±0.5, and serum albumin 2.66±0.32gm/dl were randomized. A significantly higher mortality was seen at 6 months (13.3% vs. 3.3%; p=0.05) and 12 months in SMT compared to the Alb3.0 group [(25% vs. 8.0%); HR 3.07 (1.12-8.45)] respectively. The resolution of ascites was significantly better in Alb3.0 vs. SMT (54%vs.27%; p<0.003), with a reduced incidence of AKD (13%vs.43%;p<0.001), CKD (12% vs. 39%;p<0.001), SBP (8% vs.30%; p=0.003), non-SBP infections (38%vs.62%; p=0.01) and HE (3% vs. 15%; p=0.03) respectively. At 12 months, sarcopenia assessed by CT-scan showed significant worsening from baseline in SMT (p<0.001) while it remained stable or improved in Alb3.0 with an improvement in LFI at 6-months [(5.1±0.5) to (4.4±0.4); p<0.001]].

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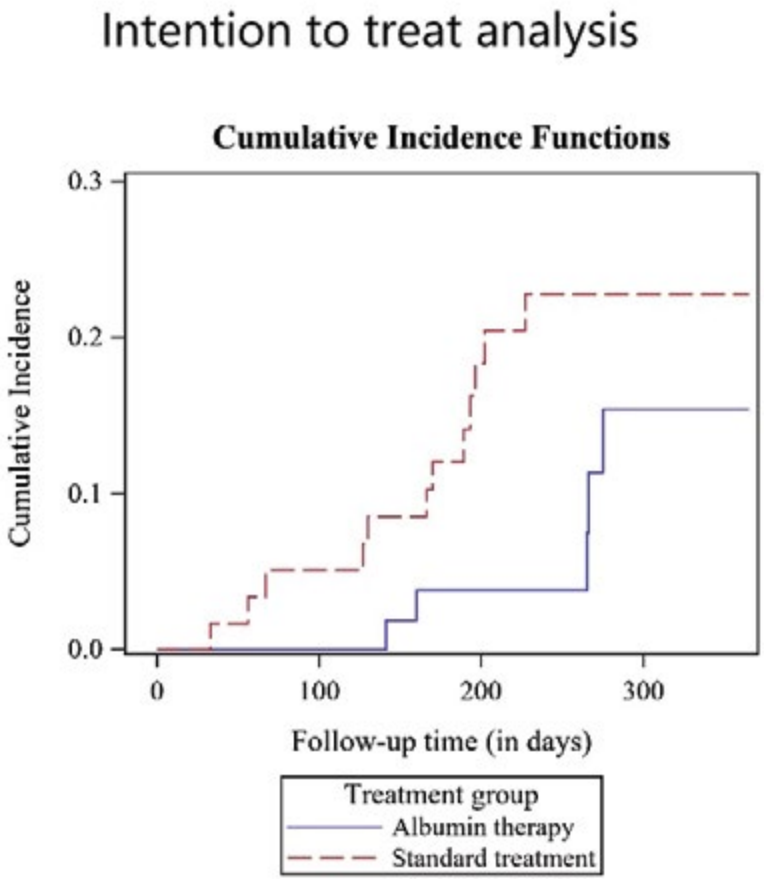
A significantly higher proportion of patients achieved a target albumin of 3.0 gm/dl at 1 month (85% vs. 12%; p<0.001) in Alb3.0 which was an independent predictor of improved survival [HR 0.17, 0.05-0.59] and a reduced incidence of MALO (p<0.05). A significant decrease in the HNA2 and HNA1, renal biomarkers (Cystatin C, IL-18, KIM-1), proinflammatory cytokines (MIP-1B; IL6; IL-2, IFN-, MCP-3, IL-12, TNF-α, IL1B, IL12 and IL-17), an increase in the anti-inflammatory cytokines (IL10, IL-1RA, IL-4) and improvement in monocyte and mitochondrial function was observed in Alb3.0 group vs. SMT. **Conclusion:** An Alb3.0 long-term strategy effectively reduces infections, adverse renal and liver-related outcomes, better ascites control, and improves frailty and long-term survival in patients with recurrent ascites.NCT04679571



Disclosures: Rakhi Maiwall: Nothing to Disclose, Samba Siva Rao Pasupuleti: Nothing to Disclose, Sherin Thomas: Nothing to Disclose, jaswinder singh Maras: Nothing to Disclose, Sukriti Baweja: Nothing to Disclose, Anupam Kumar: Nothing to Disclose, Jaya Benjamin: Nothing to Disclose, Harsh Vardhan Tevethia: Nothing to Disclose, Kanika Jain: Nothing to Disclose, Puja Bhatia Kapoor: Nothing to Disclose, Bindiya Arora: Nothing to Disclose, Varsha Shasthry: Nothing to Disclose, Shiv Kumar Sarin: Nothing to Disclose

0191 | LNP DELIVERED PRIME EDITORS RESTORE GLYCEMIC CONTROL IN HUMANIZED RODENT MODELS OF GLYCOGEN STORAGE DISEASE TYPE 1B (GSD1B)

Vivian Choi[1] Jonathon Winnay[1] Chaitali Dutta[1] Charitha Guruge[1] Chris Hart[1] Daphne Collias[1] Harpreet Turna[1] Celia Chang[1] Justin Darcy[1] Douglas Scott[1] Matt Roy[1] Marine Hatit[1] Seth Alexander[1] Venubabu Kotikam[1] Rowshon Alam[1] Mallikarjuna Putta[1] Li Lai[1] Andrea De Erkenez[1] Jacob Stewart-Ornstein[1] Luis Santos[1] John Hadcock[1] Jeremy Duffield[1]

[1]Prime Medicine

Background: GSD1b is an autosomal recessive disorder caused by mutations in the SLC37A4 gene encoding glucose 6-phosphate translocase (G6PT) which is required for normal glucose-6-phosphate metabolism, including hepatic glycogenolysis. Prime Editing is a next generation gene editing technology that can precisely

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correct >90% of all pathogenic human mutations without the need for double strand breaks and with minimal byproducts at the edit site, minimal off-target activity and minimal risk of large chromosomal alterations. Prime has developed a universal lipid nanoparticle (LNP) targeted to deliver LNP-RNA Prime Editors (PEs) to the liver by a single intravenous (IV) infusion. Our therapeutic approach is to correct two prevalent SLC37A4 mutations, p. G339C and p.L348fs, which are observed in ~50% of GSD1b patients. **Methods:** Potent Prime Editors precisely correcting both mutations were identified by high-throughput screening. **Results:** *In vivo*, IV delivery of the LNP-RNA PE candidates to humanized mice with the human SLC37A4 p.G339C or p.L348fs mutations resulted in average precise correction in 52% and 88% of hepatocytes in the liver, respectively. Precise correction was associated with restoration of SLC37A4 transcript levels and increase in protein expression. p.L348fs and p.G339C homozygous mice die perinatally from hypoglycemia and growth retardation. IV delivery of LNP-RNA PE candidates resulted in increases in body weight and restoration of blood glucose and other metabolic parameters to levels approaching those of healthy mice. Using Prime's suite of biochemical and targeted sequencing assays, initial studies detected no off-target editing in human hepatocytes. A surrogate LNP-RNA Prime Editor for p.L348fs mutation was delivered by single IV infusion to adult cynomolgus monkeys. It was well tolerated, with minimal transient cytokine or LFT changes and no histological changes. The LNP targeting ligand resulted in high levels of biodistribution to liver, that correlated well with levels of editing. On average, 72% of hepatocytes in liver were precisely edited at p.L348 at 14 days. In separate studies, editing was shown to be durable at 4 months (latest timepoint measured). **Conclusion:** These results demonstrate Prime's LNP-RNA Prime Editors are efficiently and safely delivered to primate liver, resulting in durable, efficient and precise correction of two prevalent mutations and reversing hypoglycemia and growth retardation in humanized mice. Additional data will be presented at the conference.

Disclosures: Vivian Choi: Nothing to Disclose, Jonathon Winnay: Prime Medicine: Employee, Chaitali Dutta: Prime medicine: Employee, Charitha Guruge: Prime medicine: Employee, Chris Hart: Prime Medicine Inc.: Employee, Daphne Collias: Prime Medicine: Employee, Harpreet Turna: Nothing to Disclose, Celia Chang: Nothing to Disclose, Justin Darcy: Nothing to Disclose, Douglas Scott: Nothing to Disclose, Matt Roy: Nothing to Disclose, Marine Hatit: Nothing to Disclose, Seth Alexander: Prime Medicine: Employee and Shareholder of Prime Medicine, Venubabu Kotikam: Nothing to Disclose, Rowshon Alam: Nothing to Disclose, Mallikarjuna Putta: Nothing to Disclose, Li Lai: Nothing to Disclose, Andrea De Erkenez: Nothing to Disclose, Jacob Stewart-Ornstein: Nothing to Disclose, Luis Santos: Nothing to Disclose, John Hadcock: Nothing to Disclose, Jeremy Duffield: Nothing to Disclose

0192 | LIVER TRANSPLANTATION FOR METALD RESEMBLES ALD MORE THAN MASLD

Smruti Rath[1] Ashish Bibireddy[2] Ishaan Dharia[2] Thomas Schiano[3] Sander Florman[3] Gene Im[3]

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Background: Steatotic liver disease (SLD) is a new nomenclature that includes alcohol-associated cirrhosis (AC), alcohol-associated hepatitis (AH), metabolic dysfunction-associated liver disease (MASLD), and the newly created metabolic and alcohol-associated liver disease (MetALD). Data regarding LT for MetALD are lacking. The aim of this study is to examine the clinical characteristics and outcomes of patients undergoing LT for MetALD. **Methods:** We performed a retrospective cohort-comparison study of patients who underwent LT for SLD at Mount Sinai Hospital from 1/1/2012-1/1/2023. Demographic and clinical data were analyzed, including alcohol use pre- and post-LT with biomarkers, BMI, and patient survival. For the LT for MetALD group, we reclassfied LT recipients from those originally listed for LT as ALD or MASLD according to the new consensus definition. MetALD and alcohol relapse were defined as per consensus and NIAAA criteria, respectively. **Results:** Over the 11-year study period, 405 LT for SLD were performed at our center, with MetALD being the least common with 28 (7%), followed by AH 114 (28%), ALD 126 (31%), and MASLD 137 (34%). Of the LT for MetALD recipients, 22 (79%) and 6 (21%) were originally classified as ALD and MASLD, respectively. HDL <1.0 mmol/L (96%) and BMI ≥25 kg/m2 (61%) were the top metabolic criteria met by the MetALD group. One-third of the MetALD group met 2 or more metabolic criteria for MetALD. Median drinks per week in the MetALD and ALD groups were 21 [IQR 17-24] and 60 [IQR 42-91], respectively. Median age of the MetALD group (54 years [IQR 50-63]) was similar to ALD (57, p=0.80), lower than MASLD (61, p<0.01), and higher than AH (43, p<0.01). Sex proportions were more equal in MetALD, MASLD, and AH (male sex 54%, 51%, 63%, respectively; all p>0.05) compared to ALD (79%, p<0.01).

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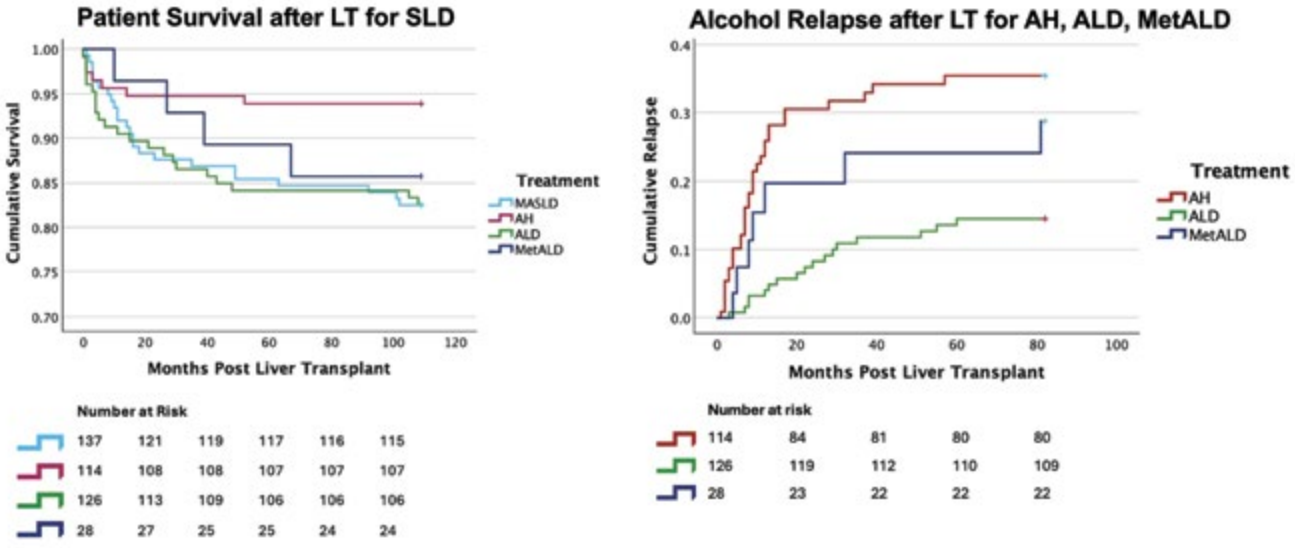
White race was more common in MetALD (82%) compared to ALD and MASLD (52% and 47%, respectively; p<0.01). Median MELD score at LT for MetALD (32 [IQR 28-38]) was similar to ALD (32, p=0.56), higher than MASLD (30, p=0.02), and lower than AH (39, p<0.01). Alcohol biomarker monitoring rates after LT were 100% AH, 70% ALD, 64% MetALD, and 17% MASLD. Despite lower rates of monitoring, the MetALD group had higher numerical rates of alcohol relapse (n=7, 25% at median 1.8 years post-LT) compared to ALD (n=17, 13% at 2.1 years; p=0.13), and similar to AH (n=34, 30% at 0.9 years; p=0.61). Median PEth levels at relapse detection for MetALD and ALD were 97 ng/mL (IQR 60-206) and 106 ng/mL (IQR 74-147), respectively. MetALD and MASLD groups had similar post-LT BMI increases of 4.3 and 4.5, respectively, p=0.71 at 2.4 years follow-up. There were no differences in 1-year (≥90%), 3-year (≥87%), and overall survival (≥87%) rates for MetALD compared to MASLD, ALD, and AH. **Conclusion:** LT for MetALD is an uncommon indication for LT and resembles ALD more than MASLD, with survival rates similar to LT for ALD, MASLD, and AH.



Disclosures: Smruti Rath: Nothing to Disclose, Ashish Bibireddy: Nothing to Disclose, Ishaan Dharia: Nothing to Disclose, Thomas Schiano: eurofins: ad board, Sander Florman: Nothing to Disclose, Gene Im: Consultant relationship with KorroBio; Has not ended; Device support for research relationship with Echosens; Has not ended; Advisor relationship with Novo Nordisk; Has not ended; Consultant relationship with Alimentiv; Has not ended

0193 | ENDOGENOUS DOUBLE-STRANDED RNA DRIVES MACROPHAGE IRF3 ACTIVATION PROMOTING EARLY METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS ◆

Marcelle de Carvalho Ribeiro[1] Yun-Cheng Hsieh[1] Mrigya Babuta[1] Radhika Joshi[1] Jeeval Mehta[1] Christopher Copeland[1] Martí Ortega-Ribera[1] Gyongyi Szabo[2]

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Background: Metabolic dysfunction-associated steatohepatitis (MASH) is associated with increased mitochondrial damage, liver inflammation, and fibrosis. IRF3 (Interferon Regulatory Factor 3) regulates inflammation and it is activated by several upstream signaling pathways, including cGAS/STING, TLR4, and double-stranded RNA (dsRNA) receptors such as TLR3, MDA5, and RIG1. Commonly associated with viral infections, dsRNA also plays a role in sterile inflammation-associated diseases. In this study, we aimed to investigate how dsRNA from macrophages (MØs) and/or hepatocytes contributes to IRF3 activation and its role in promoting the pathogenesis of MASH. **Methods:** Liver samples from MASH patients and healthy controls were analyzed for mitochondrial RNA degrading enzymes (SUV3 and PNPT1) and phosphorylated IRF3. Liver and plasma from WT and IRF3 deficient (IRF3KO) C57BL/6 mice fed a high fat-high cholesterol-high sugar (HF-HC-HSD) or control diet for 16 or 30 weeks (early and late MASH, respectively) were evaluated. Primary hepatocytes and macrophages were treated with Palmitic acid (PA) to investigate the molecular mechanism

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behind IRF3 activation in MASH. **Results:** We found increased hepatic IRF3 phosphorylation in MASH patients' livers and in a mouse model of early MASH compared to controls. IRF3KO mice showed protection from liver damage and fibrosis in early MASH. IRF3 deficiency also attenuated inflammation both in early and late MASH mouse models compared to their controls. We found a significant increase in the expression of dsRNA receptors, TLR3 and MDA5, in early MASH mice livers, along with higher dsRNA expression compared to chow-fed mice. These findings correlated with a decrease in the expression of mitochondrial RNA degrading enzymes SUV3 and PNPT1 in MASH livers in mice. Reduced SUV3 and PNPT1 expression was also observed in MASH patients' livers. Moreover, PA-stimulated hepatocytes and macrophages showed an increase in dsRNA but only macrophages had decreased SUV3 and PNPT1 expression and increased IRF3 phosphorylation. Furthermore, inhibition of mitochondrial RNA polymerase in macrophages significantly decreased PA-stimulated IRF3 phosphorylation, showing that IRF3 activation in macrophages depends on mitochondrial dsRNA. **Conclusion:** Together, our **Results:** demonstrate that dsRNA activates IRF3 promoting early metabolic dysfunction-associated steatohepatitis. Therefore, the dsRNA/IRF3 pathway could be proposed as a new therapeutic target in MASH.

Disclosures: Marcelle de Carvalho Ribeiro: Nothing to Disclose, Yun-Cheng Hsieh: Nothing to Disclose, Mrigya Babuta: Nothing to Disclose, Radhika Joshi: Nothing to Disclose, Jeeval Mehta: Nothing to Disclose, Christopher Copeland: Nothing to Disclose, Martí Ortega-Ribera: Nothing to Disclose, Gyongyi Szabo: Advisor relationship with Glympse Bio, Inc (acquired by Sunbird Bio); Has not ended; Consultant relationship with Terra Firma; Has not ended; Consultant relationship with Pfizer; Has not ended; Consultant relationship with Pandion Therapeutics; Has ended; Consultant relationship with Merck; Has ended; Consultant relationship with Durect Corporation; Has ended; Advisor relationship with Satellite Biosciences; Has not ended; Consultant relationship with Zomagen Bioscience/Ventyx Biosciences; Has ended; Consultant relationship with CYTA Therapeutics; Has ended; Royalties or patent beneficiary relationship with Springer Nature Group; Has not ended; Royalties or patent beneficiary relationship with UpToDate Inc; Has not ended; Consultant relationship with LabCorp; Has not ended; Advisor relationship with Evive; Has not ended; Advisor relationship with Surrozen; Has not ended; Consultant relationship with Takeda; Has ended

0194 | ALCOHOL BEHAVIOR CHANGE IN VETERANS WITH UNHEALTHY ALCOHOL USE: ASSESSING THE SHORT TERM IMPACT OF PERSONALIZED LIVER BIOFEEDBACK USING FIBROSCAN WITH BRIEF INTERVENTION ◆

Ponni Perumalswami[1] Alyssa Meyers[2] Sarosh Irani[1] Arpan Patel[3] Suthat Liangpunsakul[4] Benjamin Szymanski[2] Bridget Mahoney[1] Brittany Cornwell[2] Peter Grau[1] John McCarthy[2]

[1]VA Ann Arbor Healthcare System, [2]VA Serious Mental Illness Treatment Resource and Evaluation Center, Office of Mental Health, [3]VA Greater Los Angeles Healthcare System, [4]VA Indianapolis Healthcare System

Background: Background: For individuals with hazardous alcohol consumption, brief interventions (BI) can lead to decreases in alcohol use for up to 10% of patients. Provision of alcohol-related advice based on liver disease testing may reduce unhealthy alcohol use (UAU). Among Veterans Health Administration (VHA) patients with UAU, we evaluated the impact of noninvasive liver testing, using FibroScan, in Veterans not already engaged in alcohol treatment. FibroScan offers a rapid, noninvasive, and painless tool for identifying liver fibrosis (scarring) and cirrhosis, by measuring liver elasticity. **Methods:** Forty-three Veterans with UAU, as determined by an AUDIT-C score of ≥5 or provider assessment, were invited from primary care to complete a FibroScan and BI delivered by a hepatologist and behavioral health provider (BHP) between December 2022 and January 2024. Detailed, prospective alcohol assessments by the BHP employed a 30-day timeline-follow-back method at baseline, 3 months (short-term), and 6 months (short-term sustained). From these assessments, WHO alcohol risk categories were calculated. Patient characteristics were obtained from chart reviews and VHA administrative data. **Results:** Thirty-one Veterans (72.1%) completed the FibroScan and brief intervention. The mean age was 53.3±15.3 years; 93.6% were male, 87.1% were White, 87.1% had prior mental health diagnoses, and 83.3% had positive AUDIT-C scores, with 56.0% of these scores falling between 8-12. The FibroScan **Results:** indicated liver steatosis (fatty liver) in 29.0% and advanced liver fibrosis in 12.9%. At baseline, 70.0% reported heavy drinking, 16.7% reported daily drinking, and 61.3% were at medium or higher WHO alcohol risk categories. At 3 months (n=25), WHO alcohol risk decreased for 48.0% of participants; remained unchanged for 48.0%; and increased for 4.0%. At 6 months (n=17), WHO alcohol risk decreased from baseline for 52.9% of participants, remained unchanged for 47.1%, and did not increase for any participants. **Conclusion:** Conclusions: In this prospective cohort study, 48% of Veterans with UAU

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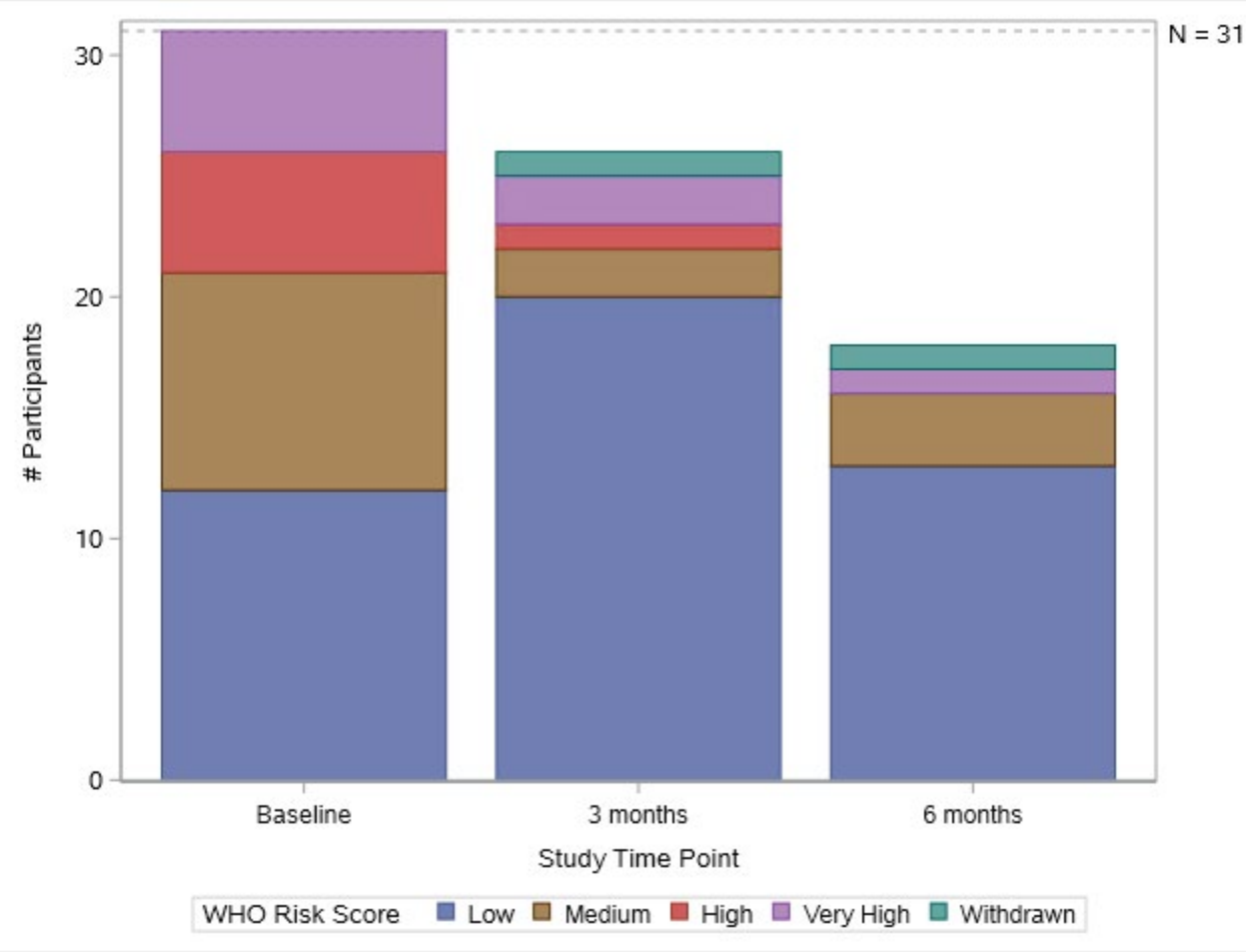
who completed the FibroScan and BI demonstrated decreases in WHO alcohol risk at 3 months. This reduction increased to 52.9% at 6 months. One participant withdrew after baseline, otherwise data on UAU continues to be collected at 6, 9, and 12 months. The combination of FibroScan and BI appears to offer a novel approach for reducing UAU in the short term, with effects that seem to be sustained over time.



Disclosures: Ponni Perumalswami: Nothing to Disclose, Alyssa Meyers: Nothing to Disclose, Sarosh Irani: Nothing to Disclose, Arpan Patel: Nothing to Disclose, Suthat Liangpunsakul: DURECT: Consultant, Durect Corporation: Consultant, Surrozen: Consultant, Korro Bio: Consultant, Benjamin Szymanski: Nothing to Disclose, Bridget Mahoney: Nothing to Disclose, Brittany Cornwell: Nothing to Disclose, Peter Grau: Nothing to Disclose, John McCarthy: Nothing to Disclose

0195 | IMPLEMENTATION OF SYSTEM-WIDE HBSAG TO HDV AB REFLEX TESTING IN A NEW YORK CITY HEALTH SYSTEM

Anna Mageras[1] Demadora Rao Mendu[1] Maria McGuire[1] Lauren Alpert[1] Jimmy Wu[2] Kristie Heiden[2] Michael Fisher[2] Nina Rodriguez[1] Andrea Branch[1] Douglas Dieterich[1] Tatyana Kushner[1]

[1]Icahn School of Medicine at Mount Sinai, [2]Mount Sinai Health System

Background: EASL and APASL recommend HDV Ab testing for all HBsAg-positive patients. Little is known about implementation of HDV reflex testing in U.S. health systems. In the Mount Sinai Health System (MSHS) serving the New York Metropolitan Area, only ~50% of HBsAg-positive specimens were tested for HDV Ab from 2021 to 2023. We evaluated implementation of an HBsAg+ to HDV Ab reflex test at MSHS. **Methods:** We obtained institutional support for reflex testing from laboratory, finance, quality, ambulatory, and compliance stakeholders. As there was no FDA-approved HDV Ab test, our lab team validated International Immunodiagnostics's competitive enzyme immunoassay (ELISA) for total HDV Ab per CLIA/CAP regulations. The reflex was then

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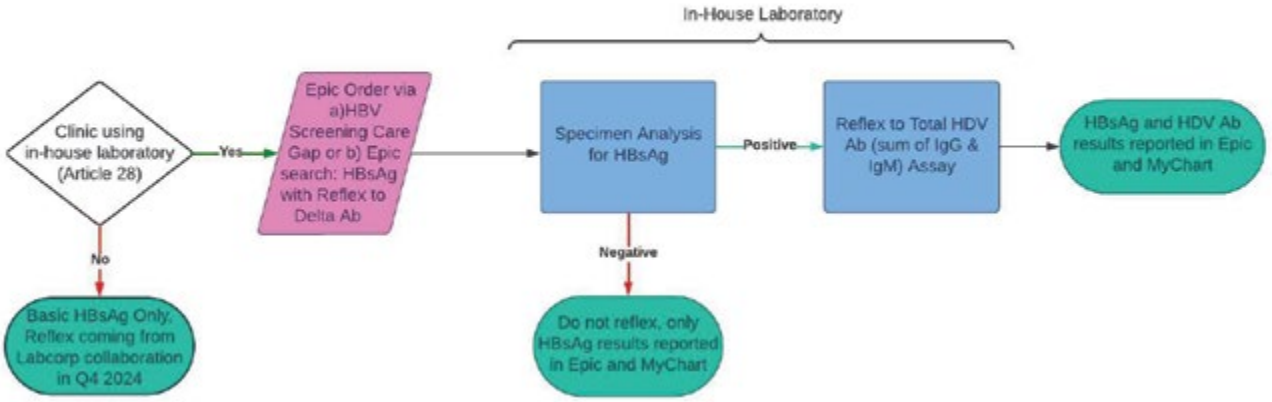
integrated into billing and EMR infrastructures. In our EMR, a “care gap” prompts providers to screen all adults for HBV once. For clinics using our in-house lab, the basic HBsAg test orderable from the care gap was replaced by the reflex test, while the basic HBsAg test was retained at other clinics; this required distinguishing EMR login contexts in the build. We tagged the test with keywords for ordering outside the care gap and circulated a tip sheet to all primary care practices. **Results:** The assay was approved for patient care by the New York State Department of Health on November 1, 2023. Repeat measures of individual specimens differed from each other across 20 days by less than 10%, establishing high precision. Split specimens tested at Mount Sinai and the Mayo Clinic Lab agreed, showing 100% accuracy. Limits of Blank were 0.276, and Limits of Detection were 0.293. No cross-reactivity was observed in the samples derived from non-HBV/HDV viral and autoimmune diseases. There were no instances of carryover or interference. In the first three months after the reflex test became available (2/27/2024 – 5/21/2024), 516 HBsAg to HDV Ab reflex tests were ordered system-wide. Of these, 8 (1.6%) were HBsAg-positive, 100% of which successfully reflexed to HDV Ab. One patient (13%) was HDV Ab positive and was promptly referred by their primary care provider for HDV RNA testing and to liver specialty. This patient was aware of the HBV diagnosis, but HDV was newly discovered due to the reflex. **Conclusion:** Our laboratory successfully established a commercial HDV Ab test for in-house use, enabling reflex testing for HBsAg-positive patients. Reflex tests, especially when automatically prompted, can increase screening rates and reduce provider burden. Future directions include collaboration with Labcorp on a reflex test for clinical practices that send orders out of our health system and implementation of HDV Ab+ to HDV RNA reflex testing. Our implementation may serve as a model to other systems hoping to develop a HBsAg+ to HDV Ab reflex test.

Figure: HBsAg+ to HDV Ab Reflex Logic Diagram



Disclosures: Anna Mageras: The Kinetix Group: Advisor, Novo Nordisk: Speaking and Teaching, Gilead Sciences: Grant/Research Support, Demadora Rao Mendu: Nothing to Disclose, Maria McGuire: Nothing to Disclose, Lauren Alpert: Nothing to Disclose, Jimmy Wu: Nothing to Disclose, Kristie Heiden: Nothing to Disclose, Michael Fisher: Nothing to Disclose, Nina Rodriguez: Nothing to Disclose, Andrea Branch: Gilead Sciences: Research, Pfizer: Research, Douglas Dieterich: Gilead: Consultant, madrigal: Speaking and Teaching, Tatyana Kushner: Advisor relationship with Gilead; Has ended; Advisor relationship with GSK; Has ended; Advisor relationship with Eiger; Has ended; Grant/Research Support relationship with Gilead; Has not ended

0196 | NONINFLAMMATORY MACROPHAGES DRIVE A FIBROGENIC GENE PROGRAM OF PERIDUCTAL FIBROBLASTS IN PEDIATRIC PRIMARY SCLEROSING CHOLANGITIS ★

Yunguan Wang[1] Zi Yang[2] Astha Malik[2] RAMESH KUDIRA[1] Cyd Castro-Rojas[2] Liva Pfuhler[2] Mosab Alquraish[2] Emily Miraldi[2] Alexander Miethke[1]

[1]Cincinnati Children’s Hospital Medical Center, [2]Cincinnati Children Hospital Medical Center

Background: Primary sclerosing cholangitis (PSC) is a cholestatic liver disease characterized by inflammation and fibrosis surrounding interlobular bile ducts. The development of hepatobiliary fibrosis involves several cell types, including cholangiocytes, liver fibroblasts, and macrophages (MP). To gain insights into precise cellular composition in the fibrotic areas and intercellular crosstalk, we performed single-cell spatially resolved

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transcriptomics (SRT) and validated the findings against liver multiome and bulk RNAseq data sets from patients with pediatric onset PSC and/or autoimmune hepatitis (AIH). **Methods:** MERSCOPE SRT using the 400-gene probe set was performed on archived slides from liver biopsies of two patients with new diagnosis PSC. Expression and tissue localization data were subjected to our recently developed “Spacia” algorithm to describe cell-cell communications (CCC). RNA-seq was performed on cryopreserved whole liver tissue samples from diagnostic liver biopsies (PSC, n= 34; AIH, n=33) staged by fibrosis (=F2 late) and 10x Genomics multiome-seq (tandem single-nuclei (sn)RNA-seq and snATAC-seq) on nuclear preparations from cryopreserved liver samples (AIH, n=5; PSC, n=6) **Results:** Noninflammatory macrophages (MP), as opposed to inflammatory MP, were predominantly localized in periductal regions, together with cholangiocytes, hepatic stellate cells (HSCs), and naive-like T cells (Fig. 1a). Four cell niches, defined as tissue regions with similar cell composition and gene expression profiles, were identified. Niche 2 (N2) overlapped with fibrotic periductal regions and was enriched in noninflammatory MP, HSCs, and cholangiocytes (Fig. 1c). The Spacia algorithm revealed cell-cell communications between noninflammatory MP and HSCs and a set of 16 fibrogenic driver genes in MP including *INFGR1*, *NFKB1A,* and the scavenger receptor *MARCO* (Fig. 1d). In silico validation showed that expression of these driver genes positively correlated with advanced fibrosis in the liver bulk RNA-seq and higher expression of fibrogenic genes in HSCs in our snRNA-seq data (Fig. 1e and f). **Conclusion:** SRT on archived liver biopsies and orthogonal validation with liver bulk and snRNAseq data identified the non-inflammatory MP as drivers of periductal fibrosis in pediatric onset PSC.

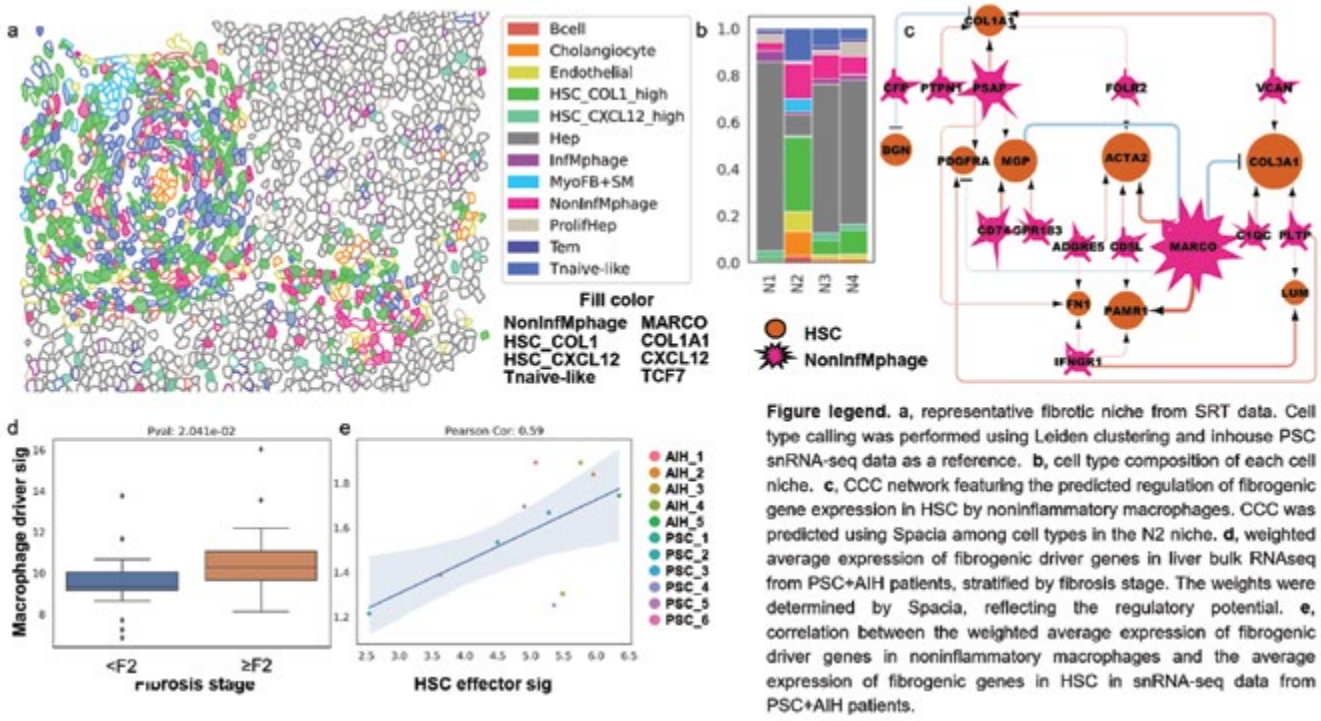

Figure legend. **a**, representative fibrotic niche from SRT data. Cell type calling was performed using Leiden clustering and inhouse PSC snRNA-seq data as a reference. **b**, cell type composition of each cell niche. **c**, CCC network featuring the predicted regulation of fibrogenic gene expression in HSC by noninflammatory macrophages. CCC was predicted using Spacia among cell types in the N2 niche. **d**, weighted average expression of fibrogenic driver genes in liver bulk RNAseq from PSC+AIH patients, stratified by fibrosis stage. The weights were determined by Spacia, reflecting the regulatory potential. **e**, correlation between the weighted average expression of fibrogenic driver genes in noninflammatory macrophages and the average expression of fibrogenic genes in HSC in snRNA-seq data from PSC+AIH patients.

Disclosures: Yunguan Wang: Nothing to Disclose, Zi Yang: Nothing to Disclose, Astha Malik: Nothing to Disclose, RAMESH KUDIRA: Nothing to Disclose, Cyd Castro-Rojas: Nothing to Disclose, Liva Pfuhler: Nothing to Disclose, Mosab Alquraish: Nothing to Disclose, Emily Miraldi: Nothing to Disclose, Alexander Miethke: Mirum Pharmaceutical Inc: Grant/Research Support, Mirum Pharmaceutical Inc: Consultant, Ipsen: Speaking and Teaching

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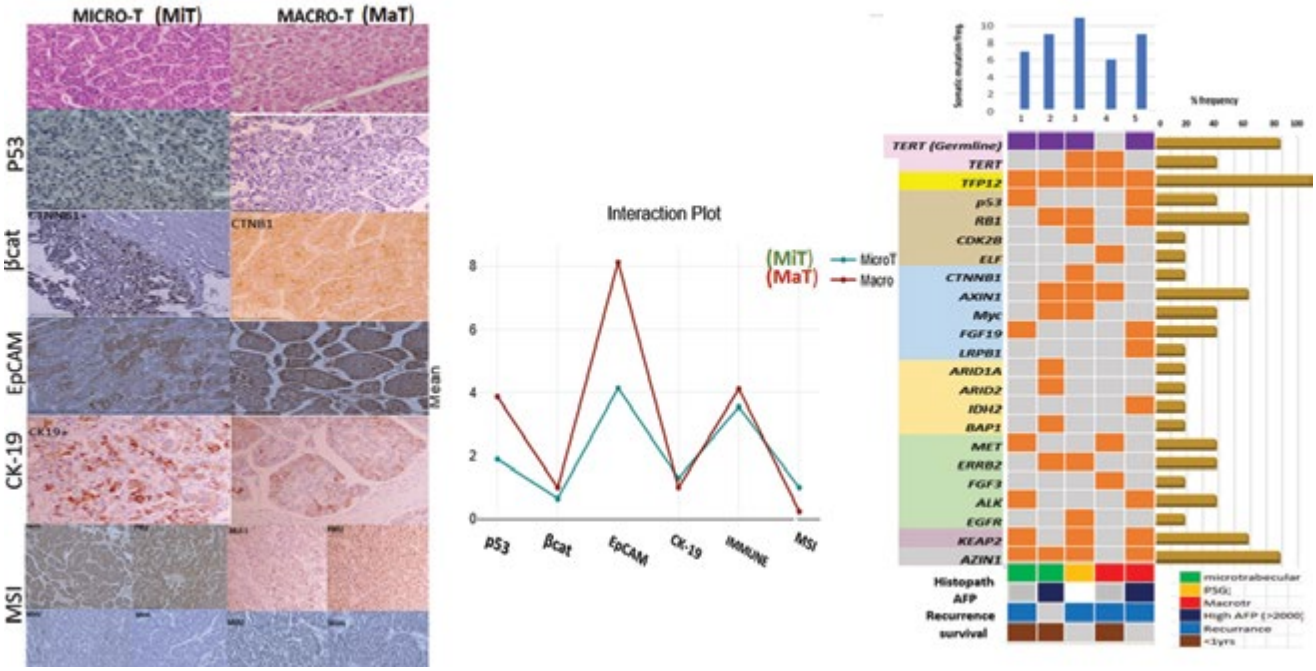
0197 | MOLECULAR CLASSIFICATION OF HEPATOCELLULAR CARCINOMA ON NON-CIRRHOTIC BACKGROUND INTEGRATING IMMUNOHISTOCHEMISTRY PANEL AND GENOMIC ANALYSIS ★

Khushboo Agrawal[1] *Archana Rastogi*[1] *Vipin Yadav*[1] *Gayatri Ramakrishna*[1] *Shiv Sarin*[1]

[1]*Institute of Liver and Biliary Sciences*

Background: Non-cirrhotic hepatocellular carcinoma (NC-HCC) is characterised by unique pathophysiological characteristics and represents 20% of HCC. Unlike the cirrhotic liver, NC-HCC can arise due to direct genetic/ molecular alterations in hepatocytes; however, studies on morpho-molecular characteristics is scarce. The aim of the study was to assess the association of phenotypes with molecular features in NC-HCC **Methods:** Paraffin-embedded tissue blocks of NC-HCC (N=40) resection specimens were assessed for the four histologic patterns. Immunohistochemistry and IRS scoring was performed for the signaling pathways (p53, β-catenin), stem cell markers (EpCAM, CK19), Microsatellite marker panel (MSI), and immune markers (PD1, PDL1, CTLA4). For MSI: nuclear positivity 3-4+/4 markers-considered MSI-stable, and 0-1+/4 MSI unstable. A combined IRS score of PD1 and CTLA4 > 5 was considered hot tumor; 1-4 as cold tumors. DNA from cases with >80% dominance of single histologic pattern was analyzed for targeted somatic mutation analysis by Next Generation Sequencing. **Results:** NASH was most predominant etiology in NC- HCC (23/40: 57.5%) followed by HBV (9/40: 22.5%). Histological pattern dominance (>50%) was recorded: Microtrabecular (MiT) (20/40;50%), Pseudoglandular (PG) (2/40;5%), Macrotrabecular (MaT) (8/40;20%), compact (CT) (8/40;20%).The MiT (15 /20:75%) and CT (6/8: 75%) were more frequent in NASH; while MaT HCC (4/8: 50%) was associated with HBV etiology and had highest AFP levels (>100 mg/L). MaT variant showed higher p53 expression (6/8: 75%), EpCAM positivity (8/8: 100%), and MSI-stable status (7/8: 87.5%); while nuclear β-catenin expression was more predominant in MiT variant (8/20: 40%) and CK19 positivity was most frequent in PG pattern (2/2: 100%). Both CT (4/8: 50%) and MiT variants (9/20: 45%) had high immune scores (IRS>5) compared to MaT variant (5/8: 62.5%, IRS: 1-4). Two-way ANOVA showed significant differences between MaT- and MiT- variants (p=0.02). Genomic landscape of NC-HCC (2 Micro, 2 Macro, 1 PG) showed germline TERT promoter mutation (rs2853669) in 80% of cases; somatic mutation in TFP12 promoter in all; TERT promoter somatic mutation (C228T) in one MaT and PG variant, a novel ELF3 pathogenic mutation was detected in MaT, and AZIN1 pathogenic variant in MiT-HCC. Mutation burden was highest in PG variant. **Conclusion:** NC-HCC had underlying NASH and HBV etiologies with MaT variant more frequent in the HBV. MiT (β Cat+) and CT-HCC (p53+) were hot tumors with exhausted immune markers (PD1, CTLA4). MaT variant (p53+, HBV) had stem cell phenotype and were cold tumors. Germline TERT promoter mutation and somatic TFPI2 promoter mutations were hallmark of NC-HCC. This work has clinical relevance as MaT and MiT variants of NC-HCC may respond better to tyrosine kinase inhibitors and immunotherapy respectively.



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Disclosures: Khushboo Agrawal: Nothing to Disclose, Archana Rastogi: Nothing to Disclose, Vipin Yadav: Nothing to Disclose, Gayatri Ramakrishna: Nothing to Disclose, SHIV SARIN: Nothing to Disclose

0198 | EFFECTS OF TIMELY TREATMENT ON OUTCOMES OF LARSUCOSTEROL FOR SEVERE ALCOHOL-ASSOCIATED HEPATITIS (AHFIRM TRIAL) ◆

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Background: Previously, we reported findings in the Phase 2b AHFIRM trial evaluating efficacy of larsucosterol in patients with severe alcohol-associated hepatitis (sAH). Full data (ex-US+US data) of 90-day death or liver transplant did not meet statistical significance, but US data of larsucosterol vs. Placebo showed p=0.0265 for 30-mg and p=0.1308 for 90-mg groups. Full data showed 90-day mortality was reduced by 41% (p=0.068) in the 30-mg and 35% (p=0.124) in the 90-mg groups. The reduction of 90-day mortality of US data was 57% (p=0.014) and 58% (p=0.008) for 30-mg and 90-mg groups, respectively. Here we report the importance of timely treatment in outcomes of larsucosterol. **Methods:** AHFIRM, a phase 2b randomized, double-blind, placebo-controlled, global study, evaluated the safety and efficacy of larsucosterol in 307 enrolled patients with sAH (MDF ≥32 and MELD 21-30). Patients were randomized 1:1:1 to receive 1 or 2 intravenous infusions (72 hours apart) of 30-mg or 90-mg larsucosterol or Placebo. All patients received standard of care per investigators' discretion. If prescribed, Placebo patients received 32 mg methylprednisolone, while larsucosterol-treated patients received matching placebo capsules. **Results:** In the trial, the median time from hospital admission to the 1st dose (hospitalization-to-treatment days) was 5 days in US, 13 days in EU, 11 days in UK, and 7 days in AU, presenting considerable regional variation. Among all patients, 75% (upper quartile) were treated <10 days of hospitalization. Re-analysis of outcomes of those receiving treatment <10 days of hospitalization showed enhanced efficacy of 30-mg larsucosterol: less 90-day death or transplant from both full and US data (p=0.053 and p=0.015, respectively), and less 90-day mortality from full and US data (p=0.010 and p=0.002, respectively). However, the same re-analysis of timely treatment with the 90-mg group did not improve the efficacy as shown with the 30-mg group. **Conclusion:** AHFIRM showed a compelling signal of mortality reduction with both doses of larsucosterol. Re-analysis of the study outcomes for patients receiving treatment <10 days of hospitalization greatly improved efficacy of mortality reduction by 30-mg larsucosterol, suggesting the importance of timely treatment.

Disclosures: Lance Stein: Abbvie: Speaking and Teaching, Gilead: Speaking and Teaching, GSK: Consultant, Intercept: Speaking and Teaching, Intercept: Consultant, Madrigal: Speaking and Teaching, Ipsen: Speaking and Teaching, Orphalan: Consultant, Mitchell Shiffman: Bio89: Grant/Research Support, CymaBay: Advisor, CymaBay: Grant/Research Support, Durect: Grant/Research Support, Galectin: Grant/Research Support, Genentech: Grant/Research Support, Genentech: Speaking and Teaching, Gilead: Grant/Research Support, Gilead: Advisor, Gilead: Speaking and Teaching, HepQuant: Grant/Research Support, HepQuant: Advisor, Hamni: Grant/Research Support, High Tide: Grant/Research Support, Interept: Grant/Research Support, Interecept: Speaking and Teaching, Intercept: Advisor, Intra-Sana: Advisor, Intra-Sana: Speaking and Teaching, Ipsen: Advisor, Ipsen: Grant/Research Support, Ipsen: Speaking and Teaching, Madrigal: Grant/Research Support, Madrigal: Speaking and Teaching, Mirum: Grant/Research Support, Pliant: Grant/Research Support, Salix: Grant/Research Support, Salix: Advisor, Viking: Grant/Research Support, Aparna Goel: Nothing to Disclose, Allison Kwong: Nothing to Disclose, Ashwini Mehta: Nothing to Disclose, Christophe Moreno: Echosens: Consultant, Surrozen: Consultant, Gilead: Consultant, Julius Clinical: Consultant, Alexandre Louvet: Consultant relationship with Glaxo-Smith-Kline; Has not ended; Consultant relationship with Ipsen; Has not ended; Speaking and Teaching relationship with Astra-Zeneca; Has not ended; Speaking and Teaching relationship with Gilead; Has not ended; Speaking and Teaching relationship with AbbVie; Has not ended, Steven Flamm: Madrigal: Grant/Research Support, Novo: Grant/Research Support, Sanjaya Satapathy: Gilead Sciences: Grant/Research

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0199 | OPIOID AND NON-OPIOID ANALGESIC PRESCRIBING AMONG 398,080 VETERANS WITH CIRRHOSIS: A CONTEMPORARY, NATIONWIDE ANALYSIS

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Background: The opioid epidemic has spurred changes in management algorithms for pain, but questions remain on how this has impacted changes in opioid and non-opioid analgesic prescriptions in patients with cirrhosis—a population with high rates of pain *and* at high risk of analgesic-related adverse effects. **Methods:** We used national data from the US Veterans Health Administration (VA) Corporate Data Warehouse as well as linked Center for Medicare/Medicaid Services data to identify trends in analgesic prescribing among Veterans with cirrhosis from 2010 to 2021, a time period that includes VA's Opioid Safety Initiative (OSI) in late 2013. Cirrhosis and pain were defined using validated sets of ICD-9 and ICD-10 diagnosis codes. VA and non-VA prescription data included analgesic classes: opioids, nonsteroidal anti-inflammatories (NSAID), acetaminophen, gabapentinoids (i.e. gabapentin, pregabalin), and antidepressants (i.e. tricyclics, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors). We used multivariable generalized estimating equation (GEE) logistic regression models to estimate the annual change in the odds of prescribing each analgesic, stratified by the pre-OSI period (2010-2013) and the post-OSI period (2014-2021), adjusting for age, gender, race/ethnicity, and cirrhosis etiology. **Results:** Among 398,080 Veterans with cirrhosis, the prevalence of pain diagnoses increased from 57% to 64% 2010-2021, while overall rates of analgesic prescriptions remained stable by year (Figure 1A). Opioid prescription rates rose until 2014 (21% to 28%, adjusted odds ratio [aOR] for annual change = 1.04, p<0.001), then decreased by half post-OSI (28% to 13%, aOR=0.94, p<0.001). Conversely, acetaminophen and NSAID prescriptions decreased slightly until 2014 (aOR 0.99 and 0.94, respectively, p<0.001), then increased post-OSI (aOR 1.15 and 1.002, respectively, p<0.001) (Figure 1B). Gabapentinoid use increased (13% to 20%, aOR for entire study period = 1.07, p<0.001), and antidepressant use decreased (25% to 23%, aOR 0.99, p<0.001). Among those receiving opioids, the types of opioids prescribed changed from 2010-2021 as well, with increasing rates of oxycodone and decreasing rates of tramadol, morphine, and opioid/acetaminophen combinations (Figure 1C). **Conclusion:** Opioid prescriptions among Veterans with cirrhosis have fallen drastically over the last decade, particularly since 2014, likely due to the OSI and other national policies. Concurrently, rates of other analgesic prescriptions—which may also have risks in cirrhosis patients—have risen slightly, but rates of pain diagnoses continue to rise as well. These findings highlight the urgent need to better understand the risks of opioid and non-opioid analgesics in cirrhosis to improve pain management in this population.

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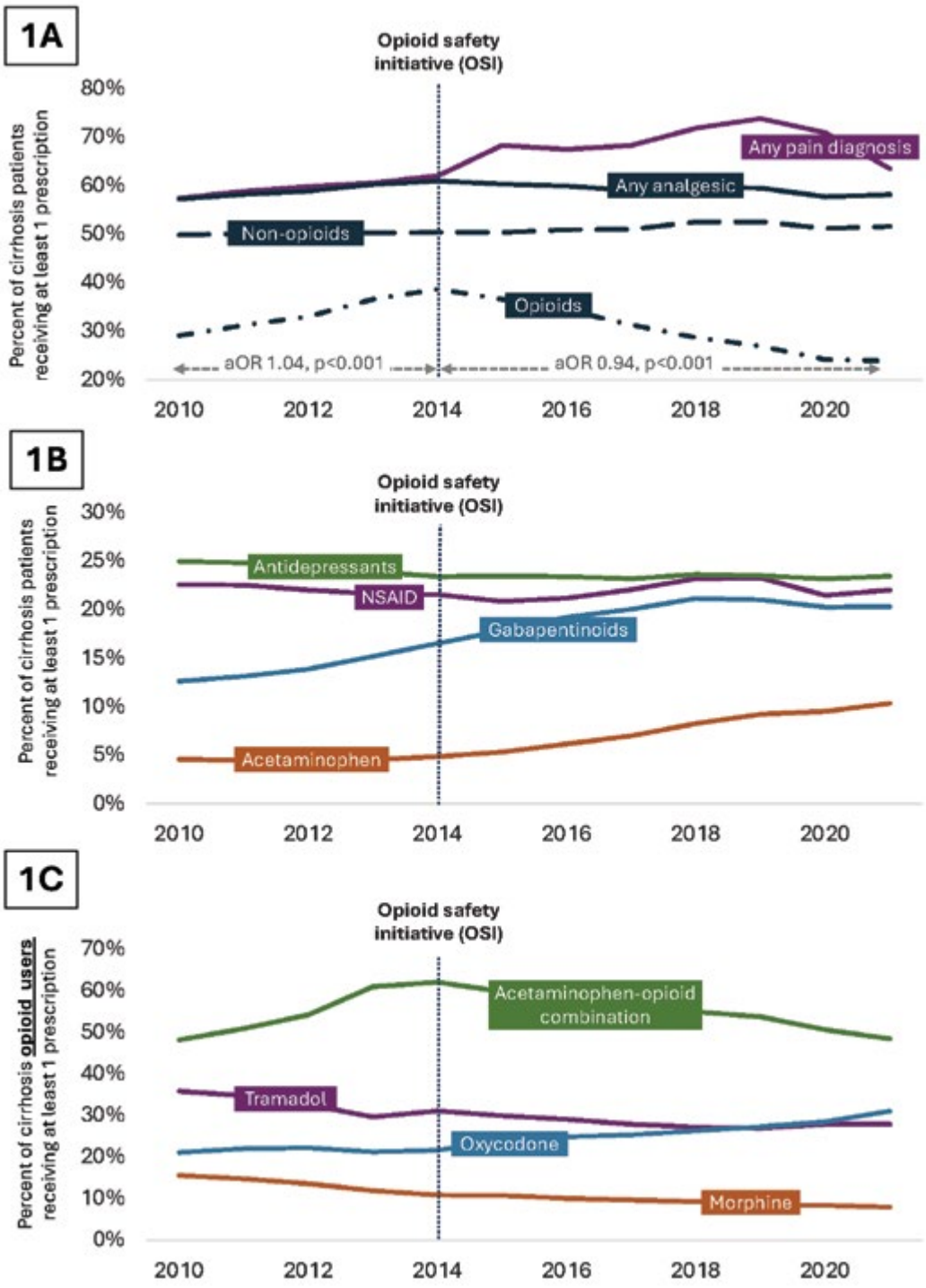

Disclosures: Jessica Rubin: Nothing to Disclose, Rebecca Loeb: Nothing to Disclose, Hui Shen: Nothing to Disclose, Katherine Hoggatt: Nothing to Disclose, Salomeh Keyhani: Nothing to Disclose, Karen Seal: Nothing to Disclose, Jennifer Lai: Nestle Nutrition Institute: Grant/Research Support, Novo Nordisk: Consultant, Genfit: Consultant, Boehringer Ingelheim: Advisor

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0200 | NEOADJUVANT THERAPY PRIOR TO ORTHOTOPIC LIVER TRANSPLANTATION (OLT) FOR HEPATOCELLULAR CARCINOMA (HCC): ABLATION AND RADIATION ASSOCIATED WITH A HIGHER COMPLETE TUMOR NECROSIS RATE THAN CHEMOEMBOLIZATION

Maarouf Hoteit[1] Benjamin Rosenthal[1] Peter Abt[1] Samir Abu-Gazala[1] Therese Bittermann[2]

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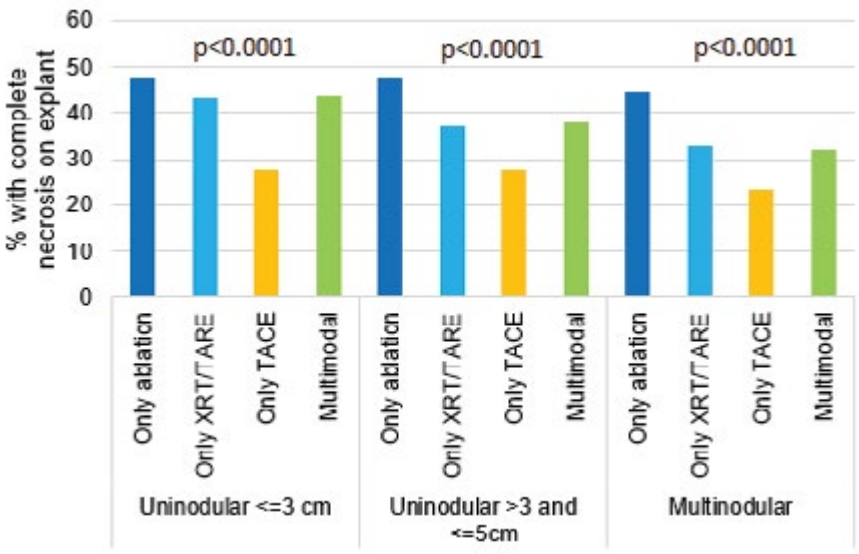
Background: Neoadjuvant liver directed therapy (LDT) is used in the vast majority of OLT candidates for HCC in the US. The specific modality of LDT varies widely among centers. The AASLD does not recommend one LDT modality over another as neoadjuvant therapy. In this study, we evaluated the effectiveness of the different LDT modalities in inducing a complete tumor necrosis (CN) on pathological assessment of the liver explant, as a surrogate measure of a favorable tumor-related transplant outcome. **Methods:** Using the Organ Procurement and Transplantation Network database, all adult OLT recipients between July 2012 and June 2023 with ≥1 approved application for standard T2 MELD exception were identified. Patients with prior HCC resection and those without HCC on explant (necrotic or not) were excluded. Baseline variables were collected at first exception point application. LDT history was assessed up until OLT. Logistic regression evaluated the association of LDT strategy with CN on explant, adjusting for covariates, and predicted probabilities were obtained. **Results:** The cohort included a total of 10,112 patients (76.8% male, 65.2% White, 43.2% HCV and median age 62 years) of whom 8,767 (86.7%) received ≥1 LDT prior to OLT. 92.5% of LDT recipients were Child-Pugh A or B at first exception application. Baseline tumor burden was 58.9% uninodular ≤ 3cm, 19.3% uninodular 3-5 cm, and 21.8% multinodular. Mean AFP was 53.8ng/dL (±374.6). Transarterial Chemoembolization (TACE) alone was the most common modality (44.9%), percutaneous ablation alone was used in 18.9%, radiation-based modalities alone (transarterial radioembolization, or external radotherapy) were used in 13.9%, and multiple modalities were utilized in 22.3%. Overall, 34.0% of explants had CN. Patients with CN had a higher 5 year post transplant survival than patients without CN (82.4% vs 77.9%, p<0.0001). Ablation was associated with a higher rate of CN than other modalities in all tumor burden categories; radiation consistently performed better than TACE (figure). When adjusted for covariates, the predicted probability of achieving CN was 46.0% with ablation, 40.1% with radiation and 26.9% with TACE, and 38.2% when multiple modalities are used. There was no interaction between LDT strategy and baseline tumor burden (p=0.349). **Conclusion:** In this large cohort of OLT recipients, TACE was the most commonly used neoadjuvant modality but was the least effective in inducing a complete tumor necrosis on explant. Since CN is associated with improved post transplant survival, most likely mediated by a low post-transplant HCC recurrence rate, ablation or radiation based modalities should be preferred as neoadjuvant therapies prior to OLT when feasible.



Disclosures: Maarouf Hoteit: HepQuant, LLC: Advisor, Benjamin Rosenthal: Nothing to Disclose, Peter Abt: Nothing to Disclose, Samir Abu-Gazala: Nothing to Disclose, Therese Bittermann: Nothing to Disclose

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0201 | ADVANCES IN PRIME EDITING ENABLE IN VIVO THERAPEUTIC CORRECTION OF THE *ATP7B* P.H1069Q AND P.R778L MUTATIONS CAUSING WILSON'S DISEASE ◆

David Waterman[1] Shivangi Modi[1] Alicia Volmar[1] Michelle O'Connor[1] Celia Chang[1] Justin Darcy[1] Chaitali Dutta[1] Weiyi Li[1] Marine Hatit[1] Rowshon Alam[1] Mallikarjuna Putta[1] Sergii Kyrychenko[1] Jacon Stewart-Ornstein[1] Jonathon Winnay[1] Seth Alexander[1] Andrea De Erkenez[1] Jonathan Levy[1] Andrew Anzalone[1] Vivian Choi[1] John Hadcock[1] Jeremy Duffield[1]

[1]Prime Medicine Inc

Background: Wilson's disease (WD) is a monogenic autosomal recessive disease caused by loss-of-function mutations in the *ATP7B* gene, which encodes a copper-transporting ATPase critical for copper homeostasis. Current therapies are supportive and life-long with side-effects and require intensive management. The *ATP7B* p.H1069Q and p.R778L mutations are highly prevalent, being found in more than 40% of patients. Correcting these mutations by Prime Editing offers a potentially curative and one-time therapeutic strategy to address a significant unmet medical need. **Methods:** We screened Prime Editors that correct the p.H1069Q and p.R778L mutations and identified potent, active, and highly precise editors with minimal unintended edits *in vitro*. To model WD *in vivo*, we developed humanized *ATP7B* mouse models that carry either the p.H1069Q or the p.R778L mutation, which recapitulate WD phenotypes. **Results:** Following a single dose of our universal liver-targeted all-RNA lipid nanoparticle (LNP) formulated with lead Prime Editors, we observed correction in more than 30% of hepatocytes. These editing levels are expected to be therapeutically significant. Using Prime Medicine's suite of biochemical and targeted sequencing assays, no off-target editing was detected in human hepatocytes for either the p.H1069Q or the p.R778L editor.We have recently demonstrated highly efficient Prime Editing of the *SLC37A4* gene in the liver of adult cynomolgus monkeys using our universal liver-targeted LNP delivered by single IV infusion. For nonhuman primate (NHP) studies in WD, we have developed a surrogate Prime Editor that exhibits 40% precise editing at p.H1069 of the *ATP7B gene* in primary cynomolgus monkey hepatocytes. Additional NHP studies using this Prime Editor will be presented. **Conclusion:** These results highlight efficient and safe LNP-mediated delivery of Prime Editor RNA cargo to the liver in preclinical WD models for precise and efficient correction of prevalent pathogenic mutations causing WD. Thus, Prime Editing offers the potential of a one-time safe and effective curative approach for Wilson's disease patients. Updated **Results:** will be provided at the time of the meeting.

Disclosures: David Waterman: Prime Medicine Inc: Emp, Shivangi Modi: Nothing to Disclose, Alicia Volmar: Nothing to Disclose, Michelle O'Connor: Nothing to Disclose, Celia Chang: Nothing to Disclose, Justin Darcy: Nothing to Disclose, Chaitali Dutta: Prime medicine: Employee, Weiyi Li: Nothing to Disclose, Marine Hatit: Nothing to Disclose, Rowshon Alam: Nothing to Disclose, Mallikarjuna Putta: Nothing to Disclose, Sergii Kyrychenko: Prime Medicine, Inc: Employee, Jacon Stewart-Ornstein: Nothing to Disclose, Jonathon Winnay: Prime Medicine: Employee, Seth Alexander: Prime Medicine: Employee and Shareholder of Prime Medicine, Andrea De Erkenez: Nothing to Disclose, Jonathan Levy: Nothing to Disclose, Andrew Anzalone: Nothing to Disclose, Vivian Choi: Nothing to Disclose, John Hadcock: Nothing to Disclose, Jeremy Duffield: Nothing to Disclose

0202 | IMPACT OF HBV INTEGRATION EVENTS IN HBV-RELATED HEPATOCELLULAR CARCINOMA AFTER LONG-TERM ANTIVIRAL THERAPY ON CLINICAL INDICATORS AND HUMAN CHROMOSOMAL STRUCTURE

Bobin Hu[1] Hang Wang[1] Hengkai Liang[1] Rongming Wang[1] Lu Wei[1] Tumei Su[1] Qingmei Li[1] Qianbin Yin[1] Yanfei Feng[1] Minghua Su[1] Jianning Jiang[1]

[1]The First Affiliated Hospital of Guangxi Medical University

Background: Few studies have reported the integrated characteristics of hepatitis B virus (HBV)-related hepatocellular carcinoma (HCC) after long-term antiviral therapy. This study aimed to investigate the HBV integration features in HBV-HCC patients who had undergone long-term antiviral therapy, evaluate their impact on clinical indicators, and analyze the potential mechanisms involved. **Methods:** We utilized genome-wide association study (GWAS) to analyze liver cancer tissues and detect the presence of HBV integration. Seventeen patients with HBV integration were included in the integration (Int) group, while the remaining five patients were included in the non-integration (N-int) group. Clinical indicators were regularly monitored and compared between the two groups. The characteristics of HBV integration patterns were analyzed, and differences between the groups were explored at

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the chromosome and genomic levels. **Results:** After long-term antiviral therapy, although the frequency of HBV integration in HBV-HCC was reduced, residual HBV integration still accelerated the development of HCC. It affected the diagnosis, treatment, and prognosis of patients. HBV integration events led to changes in chromosome structure, which were closely related to HCC. Novel fusion genes were detected at a high frequency and had the potential to be specific detection sites for HBV-HCC. **Conclusion:** HBV integration events are synergistically involved in the human genome and HBV, which can lead to chromosome structural instability, gene rearrangement events closely related to HCC production, and the formation of new specific fusion genes.

Figure.1 HBV essential functional elements and the human genome jointly participate in integration events.

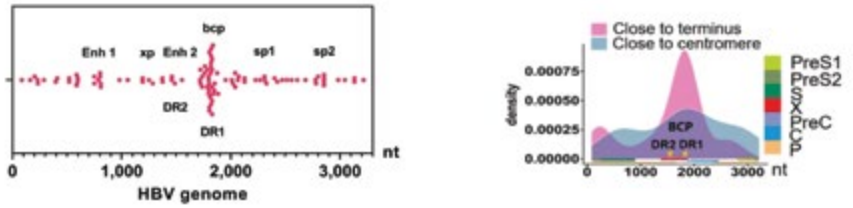


Figure.2 Comparison of clinical indicators between the Integration and N-integration groups.

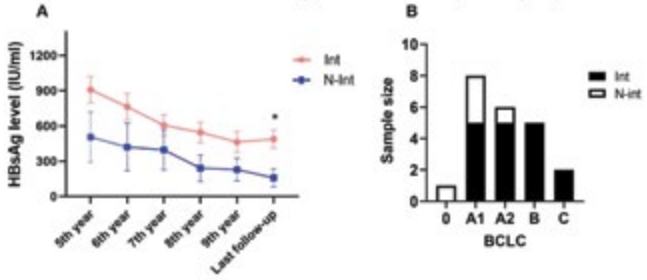
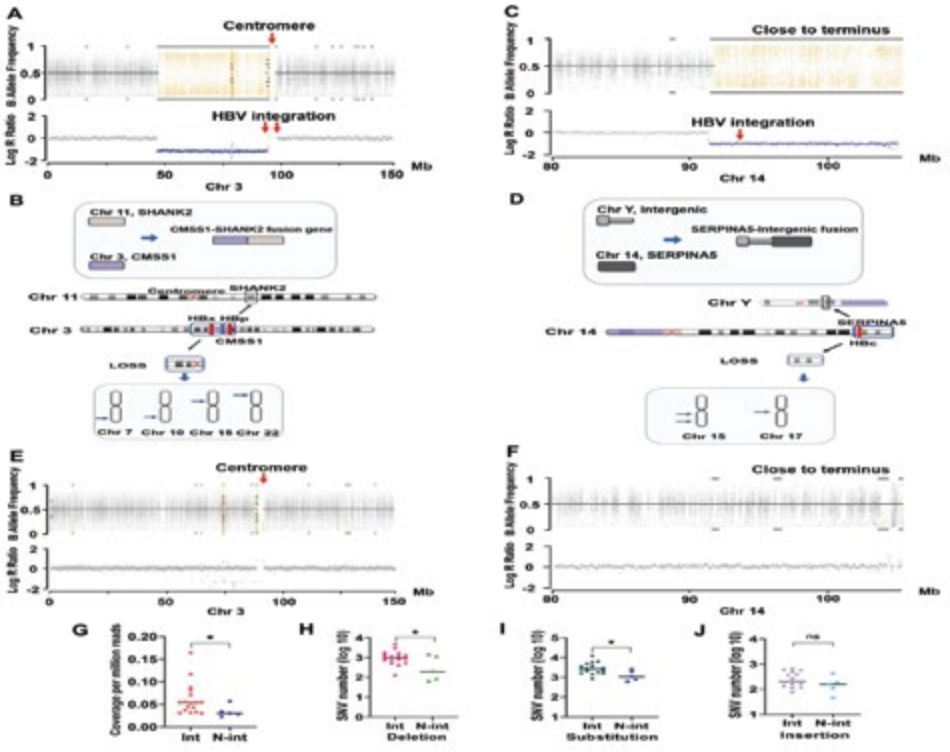


Figure.3 The impact of HBV integration on human chromosome and genomic DNA sequences.



Disclosures: Bobin Hu: Nothing to Disclose, Hang Wang: Nothing to Disclose, Hengkai Liang: Nothing to Disclose, Rongming Wang: Nothing to Disclose, Lu Wei: Nothing to Disclose, Tumei Su: Nothing to Disclose, Qingmei Li: Nothing to Disclose, Qianbin Yin: Nothing to Disclose, Yanfei Feng: Nothing to Disclose, Minghua Su: Nothing to Disclose, Jianning Jiang: Nothing to Disclose

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0203 | USE OF GLUCAGON-LIKE PEPTIDE 1 RECEPTOR AGONISTS (GLP-1 RA) IN PATIENTS WITH MASLD IN A REAL-WORLD SETTING IS ASSOCIATED WITH SLOWER DISEASE PROGRESSION AND LOWER ALL-CAUSE MORTALITY

Alfred Barritt IV[1] Andrea Mospan[2] Breda Munoz[2] Rohit Loomba[3] Michael Fried[4] Brent Neuschwander-Tetri[5] Philip Newsome[6] Kenneth Cusi[7] Arun Sanyal[8]

[1]University of North Carolina, [2]Target RWE, [3]University of California, San Diego, [4]University of North Carolina at Chapel Hill, [5]Saint Louis University, [6]University of Birmingham, [7]University of Florida, [8]Virginia Commonwealth University

Background: GLP-1 RA for the treatment of diabetes (T2DM) and obesity have been widely studied. There is increasing interest in using GLP-1 RA in patients with metabolic dysfunction associated steatotic liver disease (MASLD) although there are limited data in real-world settings. This analysis describes characteristics and disease progression across the spectrum of MASLD patients prescribed GLP-1 RA as part of usual care. **Methods:** Adults enrolled 2016-2023 in the TARGET-NASH US cohort with >6 months of follow up without liver transplant or HCC were included. Previously described TARGET-NASH definitions were used for MASL, MASH, MASH cirrhosis. Minimum GLP-1 RA use was >1 year. Baseline characteristics and competing risk adjusted model **Results:** for progression from compensated to decompensated MASH cirrhosis and all-cause mortality are reported. **Results:** Among 6,603 TARGET-NASH participants, 4,219 met analysis criteria: MASL (n=1,311), MASH (n=1,331), MASH cirrhosis (n=1,577), including 375 GLP-1 RA users: MASL (n=86), MASH (n=74), cirrhosis (n=215) with median duration of use: 2.5, 3.2, 3.3 years, respectively. GLP-1 RA users vs non-users more commonly had T2DM, enrolled at an endocrinology site, greater BMI (p<0.001 for all). Overall, 20 (5%) GLP-1 RA users died and 33 (20%) progressed from compensated to decompensated cirrhosis vs 243 (6%) and 217 (23%) non-users; median time to decompensation was 24.2 vs 21.2 months, respectively. Adjusted Hazard ratios resulted in higher risk for all-cause mortality and progression from compensated to decompensated cirrhosis for GLP-1 RA non-users compared to users (HR=2.28 (1.43-3.60) and 1.69 (1.16-2.46), respectively. Those with T2DM, hypertension (HTN) and >60 years old had a greater risk of all-cause mortality vs those without these risk factors, and those with HTN were at a greater risk of progression to decompensation. **Conclusion:** Significant differences in baseline characteristics and all-cause mortality were noted among GLP-1 RA users vs non-users across the spectrum of MASLD in this real-world setting. Importantly, compared to GLP-1 RA users, non-users had more than twice the risk of all-cause mortality and 1.7 times the risk of progressing from compensated to decompensated MASH cirrhosis. While most patients were likely treated with GLP-1 RA for T2DM, the approval of GLP1 RAs for obesity warrants further investigation into the long-term safety and effectiveness of these medications in patients with MASLD.

Table 1. Competing Risk Adjusted Hazard Ratio Modeling for Progression from Compensated to Decompensated MASH Cirrhosis and All-Cause Mortality Among those with MASL, MASH and MASH Cirrhosis Among Adults Enrolled in the TARGET-NASH Real-world Cohort

Outcome: Progression to decompensated cirrhosis among patients with MASH compensated cirrhosis			
Label	**HR**	**95% lower limit**	**95% Upper limit**
GLP1 non-user vs user	1.69	1.16	2.46
Age: 61+ vs 18-60	0.978	0.762	1.256
NH White vs Other	1.331	0.981	1.805
Sex: Female vs Male	1.309	1.008	1.700
Type 2 diabetes: Yes vs no	1.302	0.972	1.744
Hypertension: Yes vs no	1.347	1.012	1.79
Outcome: All-cause mortality among patients with MASL, MASH and MASH cirrhosis			
Label	**HR**	**95% Lower limit**	**95% Upper limit**
GLP1 non-user vs user	2.28	1.43	3.60
Age: 61+ vs 18-60	1.746	1.341	2.273
NH White vs Other	1.671	1.237	2.256
Sex: Female vs Male	0.915	0.713	1.174
Type 2 diabetes: Yes vs no	2.263	1.689	3.032
Hypertension: Yes vs no	2.229	1.635	3.037

GLP-1 = glucagon-like peptide 1 receptor agonists; MASH = metabolic dysfunction-associated steatohepatitis

All competing risks models were adjusted for sex, age categories, non-Hispanic White, history of type 2 diabetes and history of hypertension.

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Disclosures: Alfred Barritt IV: Merck (Any division): Advisor, Madrigal: Consultant, Life Edit: Consultant, Boehringer Ingelheim: Consultant, Target-RWE: Consultant, Andrea Mospan: Nothing to Disclose, Breda Munoz: Nothing to Disclose, Rohit Loomba: Eli Lilly and Company: Consultant, 89bio: Consultant, Aardvark Therapeutics: Consultant, Altimmune: Consultant, Alnylam/Regeneron: Consultant, Amgen: Consultant, Arrowhead Pharmaceuticals: Consultant, AstraZeneca: Consultant, Bristol Myers Squibb: Consultant, CohBar: Consultant, Eli Lilly: Consultant, Galmed Pharmaceuticals: Consultant, Gilead: Consultant, Glympse Bio: Consultant, Hightide: Consultant, Inipharma: Consultant, Intercept: Consultant, Inventiva: Consultant, Ionis: Consultant, Janssen, Inc.: Consultant, Madrigal Pharmaceuticals: Consultant, Merck, Metacrine, Inc.: Consultant, NGM Biopharmaceuticals: Consultant, Novartis: Consultant, Novo Nordisk: Consultant, Pfizer: Consultant, Sagimet Biosciences: Consultant, Terns Pharmaceuticals: Consultant, Theratechnologies and Viking Therapeutics: Consultant, 89bio: Stock options, Sagimet Biosciences: Stock options, Arrowhead Pharmaceuticals: Research grant, AstraZeneca: Research grant, Boehringer Ingelheim: Research grant, Bristol Myers Squibb: Research grant, Eli Lilly: Research grant, Galectin Therapeutics: Research grant, Galmed Pharmaceuticals: Research grant, Gilead: Research grant, Hanmi: Research grant, Intercept: Research grant, Inventiva: Research grant, Ionis: Research grant, Janssen, Inc.: Research grant, Madrigal Pharmaceuticals: Research grant, Merck: Research grant, NGM Biopharmaceuticals: Research grant, Novo Nordisk: Research grant, Pfizer: Research grant, Sonic Incytes: Research grant, Terns Pharmaceuticals: Research grant, LipoNexus, Inc.: Co-founder, Michael Fried: Nothing to Disclose, Brent Neuschwander-Tetri: Akero: Consultant, Aligos: Consultant, Arrowhead: Consultant, Corcept: Consultant, GSK: Consultant, Hepion: Consultant, HIstoIndex: Consultant, Madrigal: Consultant, Madrigal: Grant/Research Support, Merck: Consultant, Mirum: Consultant, Sagimet: Consultant, Senseion: Consultant, HepGene: Stock – privately held company, HeptaBio: Stock – privately held company, Philip Newsome: Novo Nordisk: Consultant, B Ingelheim: Consultant, Madrigal: Consultant, 89 Bio: Consultant, Sagimet: Consultant, Echosens: Speaking and Teaching, Eli Lilly: Speaking and Teaching, Zydus Therapeutics: Consultant, Abbott: Speaking and Teaching, Kenneth Cusi: Nothing to Disclose, Arun Sanyal: Genfit, Akarna, Tiziana, Durect, Inversago, Hemoshear, North: Stock - publicly traded company, Astra Zeneca (60K), Boston Pharmaceutical

0204 | A RANDOMIZED CONTROLLED TRIAL OF TENOFOVIR ALAFENAMIDE PROPHYLAXIS IN HBSAG-POSITIVE RHEUMATIC PATIENTS TREATED WITH BIOLOGICS

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Background: Many novel biologic disease-modifying antirheumatic drugs (bDMARDs) are being developed for the treatment of rheumatic diseases, but the risk of hepatitis B virus (HBV) reactivation in hepatitis B surface antigen (HBsAg)-positive patients and the role of NA prophylaxis is unknown. We conducted a randomized controlled trial (RCT) to delineate this issue. **Methods:** HBsAg-positive patients with inflammatory arthritis (IA) receiving first-line bDMARDs (other than anti-CD20) were randomized in a 1:1 ratio to prophylactic tenofovir alafenamide (TAF) or observation. For prophylactic arm, TAF had been provided for 3 years since the onset of biologic agents. For the control group, liver function and HBV viral load were closely monitored every three months for 48 weeks, and TAF was initiated once the 2018 AASLD criteria for HBV reactivation (HBVr) were met. TAF will be provided to all cases observed after 48 weeks in the control group. **Results:** There were 30 cases in each arm in this RCT. The median age was 63 y/o in the control arm and 65 y/o in the TAF arm. Both were predominantly female, with 25 (83.3%) in the control group and 22 (73.3%) in the TAF group. The median HBV viral load was 319 IU/ml (ranged 91 to 2802) in the control arm, and 191 IU/ml (ranged 30 to 557) in the TAF arm. TNF-blocker (12 in control, 8 in TAF arm), abatacept (9 in control, 10 in TAF arm), and JAK inhibitor (4 in control, 5 in TAF arm) were the most common biologics in this study. Other bDMARDs included tocilizumab (2 vs 5), IL-17 blocker (2 vs 2) and dual IL-4 & IL13 inhibitor (1 vs 0). After a median follow-up period of 45.3 weeks (ranged 35.3 to 48.0 weeks), 7 cases (23.3%) in the control arm (2 tocilizumab, 2 abatacept, 2 TNF-b and 1 JAK inhibitor, and none case in the TAF experienced HBVr (p=0.011). The

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cumulative incidence of HBVr in the control arm was 14.4% at week 24, and 42.2% at week 48 (p=0.035). Additional 2 cases in the control arm (both were certolizumab treated) met the Taiwan National Health Insurance criteria for chronic hepatitis B treatment due to a persistent ALT > 2 x ULN for more than 3 months. **Conclusion:** The risk of HBVr within 48 weeks in HBsAg-positive patients treated with biologics (other than rituximab) is 23.3%. The role of NA prophylaxis for biologics (other than rituximab) is confirmed in this RCT.

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0205 | X-BOX BINDING PROTEIN 1 (XBP1) TRANSCRIPTIONALLY REGULATES SMALL HETERODIMER PARTNER (SHP) EXPRESSION IN THE LIVER

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Background: Small heterodimer partner (SHP) is an orphan nuclear receptor that regulates several genes in bile acid synthesis and transport. Bile acids induce *Shp* gene expression via farnesoid X receptor (FXR) signaling. Hydrophobic bile acids can induce ER stress and activate the adaptive unfolded protein response (UPR). We have shown that X-box binding protein 1 (XBP1), a key protein in the UPR pathway, regulates bile acid metabolism. Furthermore, it has been demonstrated that the promoter region of *Shp* contains a putative XBP1 binding site. In this study, we examined the role of XBP1 in regulating hepatic *Shp* gene expression. **Methods:** Liver-specific *Xbp1* knockout (*Xbp1*^{LKO}) mice and flox controls (*Xbp1*$^{f/f}$) were fed 0.5% cholic acid (CA) for 10 weeks since birth, or 0.3% deoxycholic acid (DCA) for 3 days in 15-week-old mice. Hepatic gene expression was measured by qPCR. WT C57BL/6 mice were treated with the XBP1 agonist IXA4 (50 mg/kg, ip) or vehicle for 2 hrs. XBP1 ChIP-seq and ATAC-seq were performed on whole liver tissues and analyzed with HOMER. Hepa 1-6 cells, AML12 cells, and AML12 cells with either CRISPR-deleted FXR or XBP1 (AML12-FXRKO or AML12-XBP1KO) were transfected with a -2kb mouse *Shp* promoter luciferase reporter construct and plasmids overexpressing XBP1s, FXR, RXR, and/or treated with the FXR agonist GW4064 (1 uM, 24h). **Results:** After CA or DCA feeding, *Xbp1*^{LKO} mice had lower hepatic *Shp* gene expression compared to *Xbp1*$^{f/f}$ mice (CA: 40% lower, p=0.03; DCA: 55% lower, p=0.001). Liver XBP1 ChIP-seq identified significant XBP1 protein:DNA binding at the *Shp* promoter region in IXA4-treated, but not vehicle-treated mice. ATAC-seq demonstrated similar chromosomal accessibility at the *Shp* promoter region in both groups. *In vitro*, XBP1 overexpression significantly increased mShp promoter activity in Hepa 1-6 and AML12 cells. When co-transfected with FXR/RXR, XBP1 further increased FXR/RXR-induced mShp promoter activity. In AML12-FXRKO cells, XBP1 maintained the ability to increase mShp promoter activities. In contrast, AML12-XBP1KO cells had reduced basal mShp promoter activities compared to WT AML12 cells, but GW4064 still increased mShp promoter activities in AML12-XBP1KO cells. **Conclusion:** Bile acid-induced hepatic *Shp* gene expression is decreased in mice with liver XBP1 deficiency. XBP1 binds to the mShp promoter *in vivo* and increases its *in vitro* activity independent of FXR/RXR. Moreover, XBP1 is not required for FXR induction of mShp promoter activity, but loss of XBP1 reduces basal mShp promoter activity. These data indicate that ER stress can regulate bile acid metabolism via an XBP1/SHP axis.

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0206 | ALCOHOL-ASSOCIATED HEPATITIS REMAINS A HIGHLY FATAL CONDITION: RESULTS FROM A CONTEMPORARY PROSPECTIVE MULTICENTER COHORT STUDY FROM THE UNITED STATES ◆

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Background: Despite recent data on the increased incidence of alcohol-associated hepatitis (AH), there is limited data on the contemporary natural history of AH in the United States. **Methods:** A multicenter, prospective observational study of well-characterized patients with AH was conducted at 8 sites across the United States (AlcHepNet NCT 3850899) to identify the natural course and associations with disease severity and outcomes in a cohort of 709 patients with AH. 550 (78.8%) patients had severe AH (sAH) defined as MELD≥20. Clinical and laboratory findings, as well as outcomes, were documented at baseline, and on days 30, 90, and 180. Univariate and Cox proportional hazard analyses were performed to examine 90- and 180-day mortality and their correlates. **Results:** The mean age of patients with AH was 45±10.7yr; a majority of patients were male (59.1%) and had a college education (58.8%). Among the 709 patients with AH, 167 died within 180 days (23.6%), and 80 had liver transplants (11.3%). Mortality (%) in moderate AH (mAH) and sAH was 0.7 vs 16.4 (30d), 3.4 vs 25.1 (90d), and 7.4 vs 28.4 (180d) respectively. Over a third (37.1%) of patients had a prior hospitalization for AH. Cox regression analysis showed that higher baseline MELD (HR=1.1, 95% CI:[1.066, 1.137]; p<0.0001) and higher white blood cell count (WBC, HR=1.036, 95% CI:[1.011, 1.061]; p=0.0045), were associated with increased 90-day mortality; higher mean arterial pressure (MAP, HR=0.97, 95% CI:[0.947, 0.994]; p=0.014), colleague education (HR=0.527, 95% CI:[0.331, 0.84]; p=0.007), and higher alkaline phosphatase (Alk.PO4ase, HR=0.996, 95% CI:[0.992, 0.999]; p=0.0132) were associated with lower 90-day mortality. Patient characteristics associated with 180-day mortality mirrored those with 90-day mortality (Table). Primary causes of death were decompensation/multiorgan failure (46.9%); renal failure (7.2%); infection/septic shock (8.7%), respiratory causes (3.4%); GI bleed (2.9%) and unspecified (30.4%). **Conclusion:** AH mortality remains considerable at 90 and 180 days, even in patients with mAH. Patients with more severe disease and lower education are at significantly higher risk for death. The study highlights the importance of developing effective interventions to target systemic organ injury including multiorgan failure and to better understand the impact of social determinants of health on AH mortality.

Table 1. Factors associated with 90- and 180-day mortality among patients with AH.

	90-day survival				180-day survival			
	P value	HR	Lower CL	Upper CL	P value	HR	Lower CL	Upper CL
Age	0.064	1.021	0.999	1.043	0.0236	1.023	1.003	1.044
Male sex	0.284	0.737	0.421	1.289	0.3768	0.8	0.488	1.312
White race	0.2124	0.649	0.33	1.28	0.0403	0.552	0.313	0.974
Body mass index	0.7174	1.006	0.975	1.037	0.7918	0.996	0.968	1.025
College education	0.0071	0.527	0.331	0.84	0.0037	0.541	0.357	0.819
Married	0.3746	1.236	0.774	1.972	0.5235	1.145	0.755	1.737
Start drinking age	0.4963	1.012	0.978	1.048	0.4419	1.013	0.98	1.046
Baseline drink	0.6486	1.151	0.629	2.106	0.5009	1.211	0.693	2.117
Ever on steroids	0.5694	0.854	0.496	1.47	0.3694	0.798	0.488	1.306
MELD	<.0001	1.101	1.066	1.137	<.0001	1.089	1.058	1.122
Serum albumin	0.7722	1.063	0.703	1.609	0.9032	1.023	0.706	1.484
ALT	0.135	1.007	0.998	1.016	0.0791	1.007	0.999	1.015
AST	0.4379	1.002	0.998	1.005	0.5898	1.001	0.997	1.005
Alk. PO4ase	0.0132	0.996	0.992	0.999	0.0142	0.996	0.993	0.999
Total protein	0.6031	0.928	0.702	1.228	0.5423	0.926	0.724	1.185
Hemoglobin	0.4654	1.058	0.909	1.233	0.6339	1.033	0.904	1.181
WBC count	0.0045	1.036	1.011	1.061	0.0037	1.034	1.011	1.057
Platelet count	0.3335	0.999	0.996	1.002	0.0478	0.997	0.994	1
MCV	0.0997	0.978	0.953	1.004	0.1303	0.982	0.96	1.005
Mean art. press.	0.0139	0.97	0.947	0.994	0.0956	0.982	0.962	1.003

Alk PO4ase alkaline phosphatase; ALT alanine aminotransferase; AST aspartate aminotransferase; MELD model for end-stage liver disease; MCV mean red blood cell corpuscular volume; WBC white blood cell count in circulation.

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0207 | RACIAL DISPARITIES IN ACCESS AND OUTCOMES OF LIVER TRANSPLANT IN THE UNITED STATES: AN UPDATE

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Background: Liver transplantation (LT) is the treatment of choice for fulminant hepatic failure, decompensated liver cirrhosis, and hepatocellular carcinoma. Efforts have been made to address racial disparities in LT, including the implementation of the MELD score, community outreach & support programs, physician bias reduction training, and ongoing research to identify barriers. Despite these measures, recent studies indicate that non-Hispanic Blacks are disproportionately affected in terms of access and outcomes. This study aims to update the literature on racial differences in access and outcomes among LT patients in U.S. hospitals. **Methods:** This is a retrospective longitudinal study of hospitalized patients undergoing LT. Data were obtained from the 2016 to 2020 Nationwide Inpatient Sample databases using International Classification of Disease codes (tenth revision, ICD-10). Univariable and multivariable regression analyses were performed to compare the likelihood of undergoing LT and the outcomes (mortality, morbidity, length of stay, total healthcare charges) of LT among races in the U.S. T-test and Chi-square tests were performed to assess baseline patient characteristics. **Results:** A total of 35,220 adults were hospitalized for LT from 2016 to 2020. The majority (68.3%) (N=24,050) were non-Hispanic Whites, with 7,8% (N=2,750) non-Hispanic Blacks, 15.5% (N=5,455) Hispanics, and 8.4% (N= 2,965) Others. Non-Hispanic Blacks were more likely to be in the lowest income quartile (43% Blacks vs. 21% Whites, p<0.001), and had less comorbid conditions as compared to other racial groups (Charlson Comorbidity Index Score ≥ 3 in 95% Whites vs. 90% Blacks vs. 96% Hispanics vs. 94% Others, p<0.001) (Table 1). On multivariable regression analysis, we found that non-Hispanic Blacks were less likely to undergo LT as compared to non-Hispanic Whites (aOR = 0.37, 95%CI: 0.32 – 0.42), while there were no signicant differences with Hispanics and Others. Pertaining to outcomes, we found no significant difference in mortality between racial groups (p=0.170). However, non-Hispanic Blacks had significantly higher rates of transplant rejection (p=0.001) and transplant failure (p=0.008) as compared to the other racial groups (Table 2). Hispanics had higher rates of sepsis (p<0.001), longer stays (p<0.001), and higher healthcare expenditures (p<0.001) (Table 2). **Conclusion:** Despite prior efforts to mitigate racial disparities in LT in the U.S., our analysis showed that non-Hispanic Blacks remained less likely to undergo LT from 2016 to 2020 and suffered worse outcomes as compared to other races. Given that non-Hispanic Blacks appear to have less comorbidities, the current disparity may be due to social factors &/or physician bias. Therefore, adopting a multidimensional approach,

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including reducing social disparities and promoting awareness among providers are necessary steps to improve access and outcomes of LT among racial minorities.

Table 2. Outcomes of liver transplant among races. There were no significant differences in mortality among races. Non-Hispanic Blacks had higher rates of transplant rejection, transplant failure, and sepsis as compared to non- Hispanic Whites, Hispanics, and Others (**A**). Hispanics had significantly longer stays, and higher total expenditures as compared to other races (**B**).

	Non-Hispanic White Percentage (No.)	Non-Hispanic Black Percentage (No.)	Hispanic Percentage (No.)	Others Percentage (No.)	p-value
LT hospitalizations	100% (24,050)	100% (2,750)	100% (5,455)	100% (2,965)	-
A Mortality	2.6% (635)	4.2% (115)	3.2% (175)	2.9% (85)	0.170
Transplant rejection	4.1% (995)	8% (220)	4.3% (235)	4.6% (135)	0.001
Transplant failure	2.2% (525)	4.6% (125)	2.8% (155)	2.9% (85)	0.008
Sepsis	13.7% (3,285)	17.3% (475)	18.8% (1,025)	15.9% (470)	<0.001

	Non-Hispanic White Percentage (No.)	Non-Hispanic Black Percentage (No.)	Hispanic Percentage (No.)	Others Percentage (No.)	p-value
Total charges (Mean)	$568,273	$600,223	$777,144	$707,090	<0.001
B Length of Stay (Mean)	19.3 days	21.6 days	22.4 days	21.2 days	<0.001

Disclosures: Yassine Kilani: Nothing to Disclose, Mahmoud Madi: Nothing to Disclose, Daniel Alejandro Gonzalez Mosquera: Nothing to Disclose, Saqr Alsakarneh: Nothing to Disclose, Kym Yves Sirilan: Nothing to Disclose, Fouad Jaber: Nothing to Disclose, Kamran Qureshi: Phathom Pharmaceuticals: Speaking and Teaching, Intercept Pharmaceuticals: Speaking and Teaching, Gilead Sciences: Speaking and Teaching, Salix Pharmaceuticals: Speaking and Teaching, Madrigal Pharmaceuticals: Speaking and Teaching, Wing-Kin Syn: Zydus: to University, Merck: Consultant, Merck: Consultant, Merck: Consultant

0208 | KINETICS OF HEPATITIS B SURFACE ANTIGEN LOSS FOLLOWING 8 YEARS OF TENOFOVIR-BASED TREATMENT IN HEPATITIS B E ANTIGEN-NEGATIVE AND HEPATITIS B E ANTIGEN-POSITIVE PATIENTS WITH CHRONIC HEPATITIS B

Jeong Heo[1] Scott Fung[2] Maria Buti[3] Roberto Mateo[4] Tahmineh Yazdi[4] Frida Abramov[4] John Flaherty[4] Thomas Aeschbacher[4] Yu Hu[4] Silvia Chang[4] Hongyuan Wang[4] Hongmei Mo[4] Young-Suk Lim[5] Edward Gane[6] Kosh Agarwal[7]

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Background: Sustained hepatitis B surface antigen (HBsAg) loss is a marker of hepatitis B virus (HBV) functional cure and remains the goal of antiviral treatment for patients with chronic HBV infection (CHB). We sought to characterize patients with CHB achieving HBsAg loss after long-term antiviral treatment enrolled in 2 large, recently completed, Phase 3 studies of tenofovir alafenamide (TAF). **Methods:** In 2 studies (GS-US-320-0108/0110), hepatitis B e antigen (HBeAg)-negative (Study 108; n=425) and -positive (Study 110; n=873) patients with CHB were treated with TAF or tenofovir disoproxil fumarate followed by TAF for up to 8 years. HBsAg levels were measured using the Abbott Architect assay (quantification limit ≤0.05 IU/mL); HBsAg loss was defined as a change from HBsAg positive at baseline (BL) to negative at a post-BL visit with anti-HBs negative/missing at BL. HBsAg seroconversion was defined as HBsAg loss plus a change from anti-HBs negative/missing at BL to positive at a post-BL visit. The rapid-phase kinetics of HBsAg loss were calculated as the time required for a negative HBsAg result, starting from a constant rate of decline of at least 0.12 $\log_{10}$ IU/mL/month. **Results:** Median (IQR) BL HBsAg levels were 3.51 (3.14, 3.85) and 4.22 $\log_{10}$ IU/mL (3.68, 4.64) for Studies 108 and 110, respectively. At year 8, the median (IQR) decline in HBsAg level was 0.60 (−1.16, −0.19) $\log_{10}$ IU/mL from BL, with 2%–3% of patients experiencing HBsAg loss. Both HBeAg-negative (10/425; 2%) and -positive patients (29/873; 3%) had similar HBsAg loss rates, with longer median

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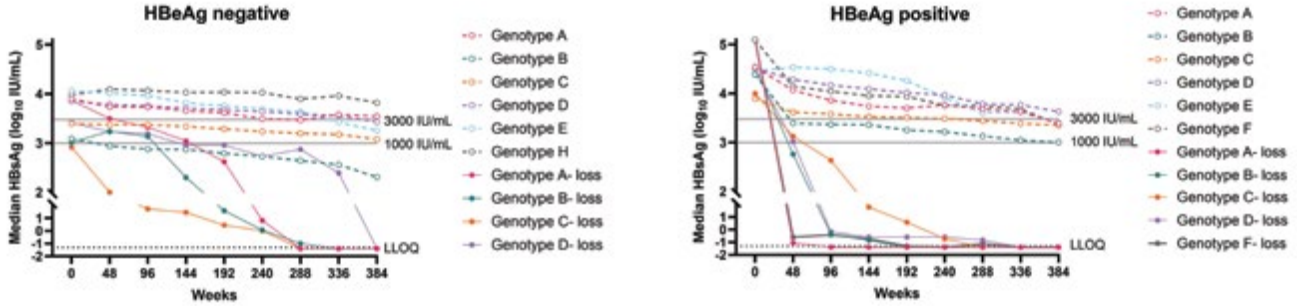
duration in HBeAg-negative patients than HBeAg-positive patients (300 vs 126 weeks, respectively; *P* = .02; Figure). Seventy percent (7/10; Study 108) and 83% (24/29; Study 110) of patients experiencing HBsAg loss also achieved anti-HBs seroconversion during the study. The median duration of the rapid phase of HBsAg loss was 96 weeks for both groups. HBV genotype (GT) affected HBsAg loss rates, with the highest in GT F (2/5; 40%), followed by GT A (9/85; 11%; Figure). Despite GT C being the most common (48%), its HBsAg loss rate was 2% (11/618), and GTs B and D had 2% (6/248) and 3% (11/330) loss rates, respectively. **Conclusion:** Long-term tenofovir-based treatment resulted in low rates of HBsAg loss, consistent with prior long-term studies. Although proportions of HBsAg loss were similar for HBeAg-negative/-positive patients, HBeAg-positive patients required less time to achieve HBsAg loss. GTs A and F had higher rates of HBsAg loss.



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0209 | DIFFERENTIAL IMPACTS OF GLP1R GENE VARIANTS ON DISEASE RISK AND TREATMENT EFFICACY IN AFRICAN AMERICANS

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Background: Previous studies in European cohorts have established associations between single nucleotide polymorphisms (SNPs) in the glucagon-like peptide 1 receptor gene (GLP1R) and both obesity and type 2 diabetes (T2D), conditions characterized by a fundamental insulin resistance. The advent of GLP-1R agonists, or incretin mimetics, has revolutionized T2D management worldwide, demonstrating efficacy in glycemic control, weight management and liver fat reduction. However, individual responses to these treatments vary widely, necessitating a deeper examination of the factors influencing therapeutic efficacy, particularly genetic variations. Genetic factors are increasingly recognized for their role in disease pathogenesis and treatment outcomes. This study seeks to elucidate the relationships between a specific GLP-1R gene variant and obesity, T2D, and associated cardiometabolic parameters, with a focus on the African American population. This demographic focus is crucial for understanding the potential variable efficacy of GLP1-agonist treatments due to genetic diversity. **Methods:** We extracted data concerning SNP variants in GLP1R and liver disease diagnoses, analyzing these in relation to metabolic, hepatic, and clinical phenotypes using the Penn Medicine Biobank, UK Biobank, and All of Us database. Covariates including the first ten principal components (PC1-10), age, sex, and BMI were adjusted for to mitigate potential confounding factors. **Results:** Our analysis identified a rare and deleterious missense GLP1R gene variant (rs10305510) with a minor allele frequency of 0.5% in the general population, which

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increases to 2% among African Americans. In the UK Biobank, this variant was significantly associated with lower plasma levels of triglycerides, vitamin D, and urea, alongside higher levels of lipoprotein(a) and HbA1c. Further investigation in the Penn Medicine Biobank revealed that rs10305510 correlates with increased BMI and a higher risk of hepatocellular carcinoma (OR=2.3; 95%CI 1.1, 5.1; p=0.03). Additionally, in the African American subset, significant associations were noted between this variant and elevated BMI and T2D risk. Preliminary **Results:** from the All of Us database indicate that this GLP1R variant may affect the initial BMI response to GLP1R agonist treatment (β= 1.6; SE 0.6; p=0.01) in the African American population. **Conclusion:** The GLP1R variant rs10305510, predominantly identified in the African American population, exhibits significant associations with key metabolic alterations relevant to dysmetabolic syndromes and cardiovascular diseases, as well as an elevated risk of hepatocellular carcinoma. Notably, this variant also influences the initial BMI response to GLP1R agonist treatments in African American population, underscoring its potential impact on GLP-1 therapeutic efficacy. Future research should prioritize evaluating the impact of this variant on the response to GLP1 agonist therapies. Additionally, studies should aim to further elucidate its role in modulating the risks of obesity and type 2 diabetes specifically within African American cohorts. These investigations are crucial for developing tailored clinical interventions and advancing the field of personalized medicine.

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0210 | THERAPEUTIC EFFICACY OF VARENICLINE TARTRATE IN ATTENUATING ALCOHOL CRAVING IN PATIENTS SUFFERING FROM ALCOHOL USE DISORDER AND MET-ALD ◆

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Background: Recent consensus on steatotic liver disease (SLD) describes it as a spectrum of liver diseases clarifying metabolic dysfunction associated-steatotic liver disease (MASLD) and MetALD (MASLD and increased alcohol intake). Met-ALD is a new terminology that defines weekly intake of 140–350 g for females and 210–420 g for males, in addition to the contributing metabolic factors. We investigated if treatment with Varenicline could alleviate craving in Met-ALD patients. **Methods:** Thirtyone adult male and female AUD patients who met criteria for Met-ALD with ALD predominant status were treated with varenicline tartrate 1 mg BID for 3 months. All patients had elevated ALT at admission. Based on the improvement in alanine transaminase (ALT) value to non-clinical levels at the treatment-end, participants were categorized into responders (Group 1, n=20) and non-responders (Group 2, n=11) to therapy. Clinical data on drinking was collected for craving (Penn Alcohol Craving Scale [PACS]) and Timeline Followback (TLFB); and liver enzymes at admission and treatment-end (3-months). Baseline TLFB was collected for the past 90 days (Total Drinks in the past 90 days: TD90, Heavy Drinking Days in the past 90 days: HDD90, Average Drinks Per Day in the past 90 days: AvgDPD90, Number of Drinking Days in the past 90 days: NDD90) and for 1-month prior to the treatment-end (Total drinks: TD3M, heavy drinking days: HDD3M, average drinks: AvgDPD3M, number of drinking days: NDD90). **Results:** The responders showed a statistically significant decline ($p<0.001$, $pEta^2=0.721$) in craving overtime (at treatment-end from sub-threshold to non-clinical levels). At treatment-end, the responders also showed a statistically significant drop in the levels of craving (p=0.015) and drinking markers, TD3M (p=0.005), HDD3M (p<0.001), and AvgDPD3M (p=0.005) vs. the non-responders. Yet, the drop in heavy drinking markers among the responders met the heavy drinking marginally regardless of recovery from craving, with observed alleviation in liver injury markers. Baseline TD90 and PACS were closely associated, p=0.021 at $R^2=0.262$. A corresponding relationship was also observed at treatment-end between TD3M and PACS, p=0.003, $R^2=0.389$. **Conclusion:** Met-ALD patients who showed alleviation in liver injury with varenicline who showed recovery in liver injury, also showed robust lowering of craving along with substantial recovery from heavy drinking. Importantly, the responders showed an earlier positive response in the reward mechanism than the recovery in clinical phenotypes of drinking, suggesting that alleviation of liver injury may be regulated by varenicline directly therapeutic-mechanistic mechanisms as well as indirectly by the lowering of excessive alcohol intake.

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Table 1

Measures	Group 1 (Responders)			Group 2 (Non-Responders)			Between-group p-value
	Males (n=18; 90%)	Females (n=2; 10%)	Total (n=20; 60.60%)	Males (n=8; 72.72%)	Females (n=3; 27.27%)	Total (n=11; 33.33%)	
Demographics							
Age (years)	45.44 ± 10.51	51.5 ± 6.36	46.05 ± 10.22	48.13 ± 8.74	34.33 ± 11.37	44.36 ±10.99	NS
BMI	32.90 ± 6.87	36.02	33.13 ± 6.66	30.89 ± 5.94	34.93	31.40 ± 5.68	NS
Baseline Drinking History							
TD90	932.11 ± 455.78	785.5 ± 156.27	917.45 ± 434.96	1571.63 ± 670.78	1850 ± 531.06	1647.55 ± 623.11	0.003
HDD90	77.28 ± 16.09	87 ± 4.24	78.25 ± 15.54	86 ± 5.61	88 ± 3.46	86.55 ± 5.03	0.04
AvgDPD90	10.36 ± 5.06	8.73 ± 1.74	10.19 ± 4.83	17.46 ± 7.45	20.56 ± 5.90	18.31 ± 6.92	0.003
NDD90	82.78 ± 12.79	87 ± 4.24	83.2 ± 12.21	87.13 ± 5.46	88 ± 3.46	87.36 ± 4.84	NS
Three Month Drinking Status							
TD3M	93.11 ± 100.63	95 ± 10	93.3 ± 95.22	212.88 ± 164.35	364.67 ± 300.76	254.27 ± 205	0.03
HDD3M	7.11 ± 8.35	6.5 ± 0.71	7.05 ± 7.90	20.13 ± 9.39	17.33 ± 13.50	19.36 ± 10	0.003
AvgDPD3M	3 ± 3.25	3.06 ± 0.32	3 ± 3.07	6.87 ± 5.30	11.76 ± 9.70	8.20 ± 6.61	0.03
NDD3M	15.89 ± 10.45	18.5 ± 17.68	16.15 ± 10.72	24.88 ± 7.81	18.67 ± 13.65	23.18 ± 9.4	NS
Baseline Clinical Determinants of AUD							
PACS	14.89 ± 6.10	18 ± 12.73	15.2 ± 6.53	18.75 ± 4.74	22.67 ± 3.06	19.82 ± 4.58	0.03
Three Month Clinical Determinants of AUD							
PACS	7.72 ± 6.71	7.5 ± 10.61	7.7 ± 6.80	11.5 ± 5.90	22 ± 2	14.36 ± 7.02	0.02
Baseline Liver Injury Markers							
ALT (IU/L)	45.22 ± 8.02	63.5 ± 7.78	47.05 ± 9.61	84.13 ± 60.06	77 ± 49.67	82.18 ± 55.04	NS
AST (IU/L)	35.72 ± 9.38	53.5 ± 26.16	37.5 ± 12.03	60.88 ± 28.09	67.67 ± 57.45	62.73 ± 34.97	0.04
AST: ALT	0.80 ± 0.22	0.82 ± 0.31	0.80 ± 0.22	0.80 ± 0.19	0.81 ± 0.18	0.81 ± 0.18	NS
Three Month Liver Injury Markers							
ALT (IU/L)	27.72 ± 5.80	26 ± 5.66	27.55 ± 5.66	91.32 ± 62.46	121.67 ± 39.55	99.64 ± 56.96	0.002
AST (IU/L)	25.67 ± 5.49	23.5 ± 2.12	25.45 ± 5.26	65.63 ± 37.77	86.33 ± 47.61	71.27 ± 39.31	0.003
AST: ALT	0.95 ± 0.24	0.93 ± 0.28	0.95 ± 0.23	0.79 ± 0.22	0.73 ± 0.32	0.78 ± 0.23	NS
Candidate Blood Cell Measures							
WBC (K/µL)	7.06 ± 1.95	7.45 ± 0.78	7.1 ± 1.86	6.34 ± 0.69	6.9 ± 1.57	6.49 ± 0.95	NS
ALC (K/µL)	1.88 ± 0.47	1.8 ± 0.28	1.87 ± 0.45	1.61 ± 0.35	1.78 ± 0.49	1.65 ± 0.38	NS
ANC (K/µL)	4.37 ± 1.87	5.08 ± 1.02	4.44 ± 1.8	3.93 ± 0.59	4.43 ± 1.17	4.07 ± 0.76	NS

Table Legends

ALC=Absolute Lymphocyte Count, ALT=Alanine Transaminase, ANC=Absolute Neutrophil Count, AST=Aspartate Transaminase, AST: ALT=Ratio of AST to ALT, AvgDPD3M=Average Drinks Per Day 3 Months into Study, AvgDPD90=Average Drinks Per Day in the past 90 days, BMI=Body Mass Index, HDD3M=Heavy Drinking Days 3 Months into Study, HDD90=Heavy Drinking Days in the past 90 days, n=number, NS=Not Significant, NDD3M=Number of Drinking Days 3 Months into Study, NDD90=Number of Drinking Days in the past 90 days, PACS=Penn Alcohol Craving Scale, p-value=Statistical probability value, TD3M=Total Drinks 3 Months into Study, TD90=Total Drinks in the past 90 days, WBC=White Blood Cells.

Units: IU/L=International Units per liter, K/µL=thousands per microliter, kg=kilograms.

Statistically significant difference between only males of Gr.1 and Gr.2, Statistically significant difference between only females of Gr.1 and Gr.2, Statistically significant difference between males and females of Gr.1, and Statistically significant difference between males and females of Gr.2. Data are presented as Mean ± Standard Deviation [SD]. Statistical significance was set at p<0.05.

Disclosures: Vatsalya Vatsalya: Nothing to Disclose, Aditya Shah: Nothing to Disclose, Dev Tyagi: Nothing to Disclose, Aula Said: Nothing to Disclose, Maiying Kong: Nothing to Disclose, Walter Watson: Nothing to Disclose, Chris Stewart: Nothing to Disclose, Matthew Cave: Nothing to Disclose, Zhongbin Deng: Nothing to Disclose, Ashwani Singal: Advisor relationship with CLD Foundation; Has not ended; Speaking and Teaching relationship with Medical Speaker's Network; Has not ended; Speaking and Teaching relationship with Madrigal; Has not ended; Stock â€“ privately held company relationship with Pleiogenix; Has not ended; Consultant relationship with Pleiogenix; Has not ended; Advisor relationship with Durect; Has ended; Royalties or patent beneficiary relationship with Up-to-Date; Has not ended; Executive role relationship with Gastro Endo News; Has not ended; Grant/Research Support relationship with NIAAA; Has not ended; Employee relationship with Avera Medical Group; Has ended; Grant/Research Support relationship with GSK; Has not ended; Employee relationship with University of Louisville School of Medicine; Has not ended; Speaking and Teaching relationship with Medscape; Has not ended, Craig McClain: Novo Nordisk: Grant/Research Support, Intercept Pharmaceuticals: Grant/Research Support, Altimmune: Grant/Research Support, Target Pharma Solutions: Grant/Research Support, NIH: Grant/Research Support, VAMC: Grant/Research Support

0211 | CARRIAGE OF THE Z ALLELE OF THE *SERPINA1* GENE AS A PREDISPOSING FACTOR FOR THE DEVELOPMENT OF HEPATORENAL SYNDROME IN PATIENTS WITH DECOMPENSATED LIVER CIRRHOSIS

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Background: Hepatorenal syndrome (HRS) significantly affects mortality in patients with advanced liver cirrhosis. The strongest predictor of HRS is the severity of hepatic dysfunction. The association of HRS with variants in *NOS3* and with TNF-alpha levels has been described in small animal cohorts. The aim of our study was to validate the role of variants in *NOS3*, *TNFA* and *SERPINA1* genes in the predisposition to HRS. **Methods:** The cohort consisted of 1063 adult liver transplant candidates with decompensated cirrhosis. The median age was 55.8 years (18-75), and the median MELD score at waitlisting was 15 (6-40). The etiology of liver cirrhosis was alcoholic (375), autoimmune or cholestatic (147), viral (156), cryptogenic and NASH (305), and metabolic (80). Clinical records were retrospectively reviewed identifying patients fulfilling HRS criteria. Patients were genotyped for: NOS3_786, C/T (rs2070744), NOS3_894, G/T (rs179998), TNFA, G/A (rs361525) and SERPINA1, M/Z,

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(rs28929474). **Results:** A total of 127 patients with HRS (HRS group) were identified and compared with the remaining 936 patients (non-HRS group). HRS group had a significantly higher MELD score than the non-HRS group (median, range); 17 (6-40) vs. 15 (6-40). However, regarding MELD score components, the two groups differed only in creatinine 103 µmol/l (45-729) vs. 72 µmol/l (18-698), p=0.0001, but not in other MELD components: bilirubin 53 µmol/l (9-739) vs. 54 µmol/l (3-1168), p=0.688, and INR 1.42 (0.96-3.63) vs. 1.40 (0.9-6.7), p=0.094. The association of *NOS3* and *TNFA* variants with the occurrence of HRS was demonstrated neither in the allelic nor in the recessive model. Regarding *SERPINA1,* there were significantly more Z allele carriers in the HRS than in the non-HRS group. The distribution of *SERPINA1* genotypes in the non-HRS and HRS groups was MM 887 (94.8%), MZ 42 (4.3%) and ZZ 7 (0.9%), respectively, and MM 87 (68.5%, MZ 12 (9.4%) and 1 ZZ (0.1%), p=0.0166 in the allelic model, Bonferroni correction for 3 loci). In multivariate analysis, at least one Z allele *SERPINA1* carriage (OR 2.37, CI 95% 1.17–4.5) and age (OR 1.03 per one-year increment, CI 95% 1.01-1.06) were independent predictors of HRS development. **Conclusion:** Z allele carriage represents a risk factor for HRS development. One of the functions of alpha-1-antitrypsin is to bind circulating TNF-alpha; TNF-alpha levels are higher in *SERPINA1* Z allele carriers, which could contribute to the development of HRS.

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0212 | EXPECTED EIGHT-WEEK VERSUS TWELVE-WEEK TENOFOVIR ALAFENAMIDE TO PREVENT MOTHER-TO-CHILD TRANSMISSION OF HEPATITIS B (TAF-HBV-MTCT): A MULTICENTER, OPEN-LABEL, RANDOMIZED CONTROLLED TRIAL

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Background: The course of maternal antiviral prophylaxis to prevent mother-to-child transmission of hepatitis B virus (HBV-MTCT) varies greatly. We aimed to investigate the safety and efficacy of short-course tenofovir alafenamide fumarate (TAF) prophylaxis to prevent HBV-MTCT. **Methods:** In this multicenter, open-label, randomized controlled trial, eligible pregnant women with HBV DNA of 5.3-9.0 $\log_{10}$ IU/mL who received TAF from the first day of 33 gestational weeks to delivery (expected eight-week) or to 4-week postpartum (expected twelve-week) were randomly enrolled at a 1:1 ratio and followed until 6-month postpartum. All infants received standard immunoprophylaxis. The primary endpoint was the safety of mothers and infants. The secondary endpoint was infants' HBV-MTCT rate at 7 months of age. **Results:** Among 119 and 120 intention-to-treat pregnant women, 115 and 116 women were followed until delivery, and 110 and 112 per-protocol mother-infant dyads in two groups completed the study. Overall, TAF was well tolerated, no one discontinued therapy due to adverse events (0/231), and no per-protocol infant had congenital defects or malformations at delivery (0/231). The infants' physical development at birth (n=231) and at 7 months (n=222) were normal. Furthermore, 97.0% (224/231) of the intention-to-treat women achieved HBV DNA <5.3 $\log_{10}$ IU/mL at delivery. The per-protocol infants' HBV-MTCT rate was 0% (0/222) at 7 months of age. Comparatively, 15.1% (18/119) vs 18.3% (22/120) of women in the two groups had mildly elevated alanine aminotransferase levels at 3-month and 6-month postpartum, respectively (*P*=0.507); notably, no one experienced alanine aminotransferase flare. **Conclusion:** Maternal TAF prophylaxis to prevent HBV-MTCT is generally safe and effective, and expected eight-week duration is feasible.

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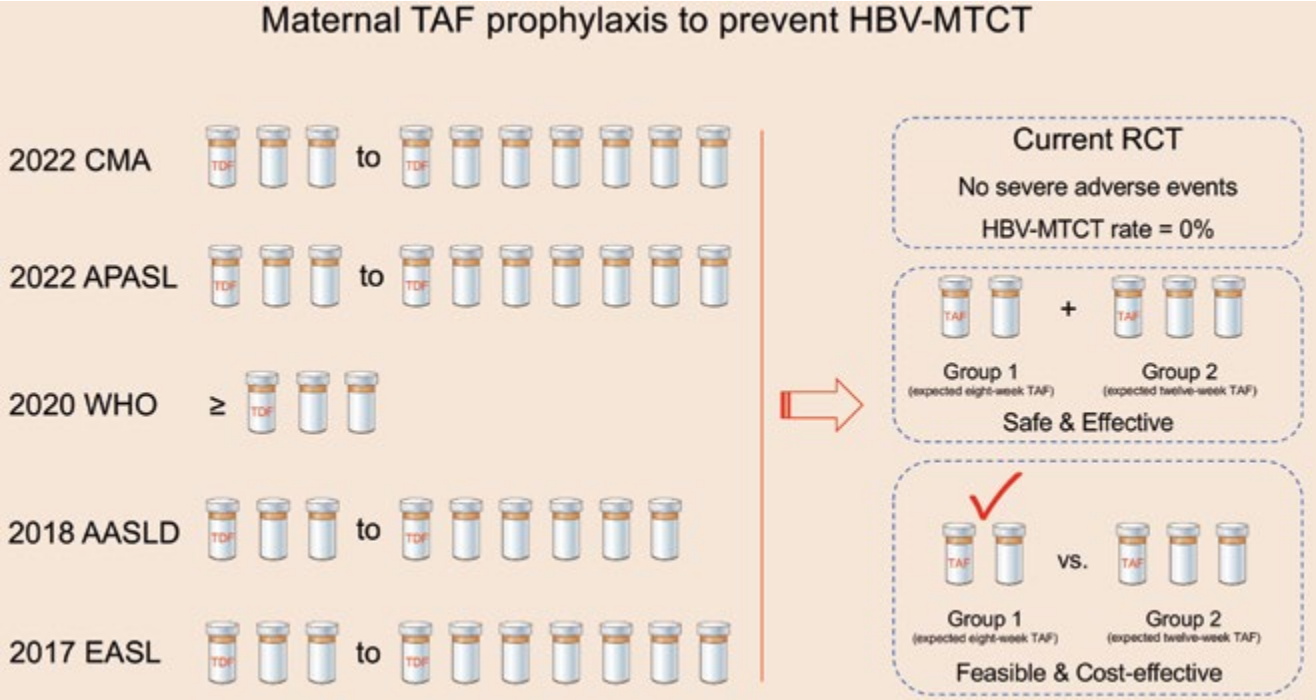

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0213 | HBS ISOFORMS AS INNOVATIVE BIOMARKERS IN PREDICTING VIROLOGICAL RESPONSE TO BULEVIRTIDE MONOTHERAPY IN PATIENTS WITH CHRONIC HEPATITIS DELTA

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Background: HDV exploits HBV surface protein (HBsAg) for its morphogenesis and entry into hepatocytes. HBsAg consists of 3 isoforms: Large- (L-HBs, predominantly present in virions and mediating binding to NTCP-receptor), Middle- (M-HBs) and Small-HBsAg (S-HBs). Here, we investigated the still unknown kinetics of HBs-isoforms under bulevirtide-treatment (BLV). **Methods:** 36 consecutive patients with HDV-related compensated cirrhosis starting BLV 2mg/day were enrolled in this retrospective/longitudinal study, all under effective NUC treatment at entry. L-HBs, M-HBs and S-HBs were quantified by *ad-hoc* ELISAs in baseline and week 48 (W48) samples (Beacle). HDV-RNA was quantified by Robogene 2.0. Virological response was defined as HDV-RNA undetectable or >2log decline compared to baseline. **Results:** At baseline, median (IQR) serum HDV-RNA, HBsAg and ALT were 5.1 (4.3-5.7) log IU/ml, 3.7 (3.4-4.0) log IU/ml and 102 (65-152) U/l, respectively. Pre-treatment median (IQR) levels of S-HBs, M-HBs and L-HBs were 3681 (1240-7184), 813 (260-2262) and 5 (1-12) ng/ml, respectively. At W48, serum HDV-RNA declined by 3.1(1.6-3.7) log IU/ml while virological response and ALT normalization were observed in 69% and 67% of patients, respectively. A >10% decrease of S-HBs, M-HBs and L-HBs levels was observed in 53%, 53% and 31% of pts (median [IQR] decline: 1323 [731-3712], 327 [79-589] and 10 [4-14] ng/ml, respectively). Baseline HDV-RNA <5 log IU/ml was associated with HDV-RNA <100 IU/ml at W48 (71% with vs 32% without, P=0.04). A similar correlation was observed for baseline L-HBs <9 ng/ml (63% vs. 17%, P=0.01). The combination of pre-treatment L-HBs <9 ng/ml + HDV-RNA <5 log IU/ml was the best predictor for achieving HDV-RNA <100 IU/ml (PPV:77%, NPV:65%). A different scenario was observed for M-HBs. Indeed, patients with baseline M-HBs >500 ng/ml had a significantly greater HDV-RNA decline than those

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with baseline M-HBs <500 ng/ml (3.5 [2.6-4.1] vs. 1.4 [0.5-3.1] log IU/ml, P=0.002). Furthermore, baseline M-HBs >500 ng/ml predicted the achievement of virological response at W48 of BLV (PPV:91%, NPV:64%) also with ALT normalization (PPV:68%, NPV:71%). **Conclusion:** Quantification of L-HBs and M-HBs along with HDV-RNA may better reflect the burden of circulating infectious virions in HBV/HDV co-infection, providing a promising tool to identify patients more likely to respond to BLV.

Disclosures: Stefano D'Anna: Nothing to Disclose, Romina Salpini: Nothing to Disclose, Elisabetta Degasperi: Gilead: Speaking and Teaching, Roche: Advisor, Abbvie: Speaking and Teaching, Leonardo Duca: Nothing to Disclose, Maria Paola Anolli: Nothing to Disclose, Lorenzo Piermatteo: Nothing to Disclose, Dana Sambarino: Nothing to Disclose, Marta Borghi: Nothing to Disclose, Francesca Ceccherini Silberstein: Nothing to Disclose, Floriana Facchetti: Nothing to Disclose, Riccardo Perbellini: Nothing to Disclose, valentina svicher: Nothing to Disclose, Pietro Lampertico: ROCHE PHARMA/DIAGNOSTICS, GILEAD SCIENCES, GSK, ABBVIE, JANS: Advisor

0214 | ALANINE AMINOTRANSFERASE FLARES DURING PREGNANCY OR POSTPARTUM PREDICT INCREASED HBEAG SEROCLEARANCE IN HIGHLY VIREMIC HBV-INFECTED WOMEN ★

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Background: Since 2020, WHO has recommended that HBV-infected pregnant women with an HBV DNA ≥ 200,000 IU/mL receive antiviral prophylaxis during pregnancy to prevent mother-to-child transmission, a key step toward global hepatitis elimination. However, data on the long-term maternal outcomes, such as hepatitis B e antigen (HBeAg) seroclearance, of these highly viremic HBV-infected women are lacking. **Methods:** This study included mothers from our open-label, non-randomized controlled trials on maternal use of tenofovir disoproxil fumarate (TDF) (ClinicalTrials.gov identifier, NCT 01312012) or tenofovir alafenamide (TAF) (NCT 03695029) from the 3rd trimester until 2-4 weeks postpartum to prevent mother-to-child transmission. At baseline, all pregnant women were HBeAg-positive and had a viral load above 6.0 log10 IU/mL. Serum alanine aminotransferase (ALT) and HBV DNA were measured at baseline, delivery, 1, 2, 4, and 6 months postpartum. HBeAg was checked at delivery, 6, and 12 months postpartum, and subsequently at 12-month intervals. A group-based trajectory model was used to analyze ALT patterns from baseline to 6 months postpartum, with the best model selected based on the minimum Bayesian information criterion. Hazard ratios (HR) for HBeAg seroclearance with 95% confidence intervals (CI) were determined using a Cox proportional hazards model adjusted with multiple covariates. **Results:** The analysis included 293 women, including 127 in TDF group, 77 in TAF group and 89 in control group. Four ALT trajectory patterns were identified: stable, moderate, or severe postpartum flares, or prepartum flares. The majority (85.7%) of women had stable ALT from late pregnancy to 6 months postpartum. The median follow-up time after delivery was 26.3 months (range, 12 to 142 months). During follow-up, 46 women (15.7%) cleared HBeAg, with a median seroclearance time of 31.3 months postpartum (range, 0 to 116 months). After adjusting for maternal age, HBV genotype, TDF/TAF treatment during pregnancy, antiviral treatment during postpartum follow-up, and HBV DNA <6.0 log10 IU/mL at delivery, women with ALT flares either prepartum or within 6 months postpartum were more likely to clear HBeAg compared to those with stable ALT (HR, 11.2; 95% CI, 5.9 to 21.5; *P* < 0.001). **Conclusion:** Women experiencing ALT flares during late pregnancy and the postpartum period are more likely to clear HBeAg. ALT flares in this timeframe predict increased HBeAg seroclearance in highly viremic HBV-infected women.

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0215 | HUMAN DISEASE IS RECAPITULATED BY A NOVEL BILIARY ATRESIA THROUGH TARGETED ENDOTHELIAL DESTRUCTION SYSTEM

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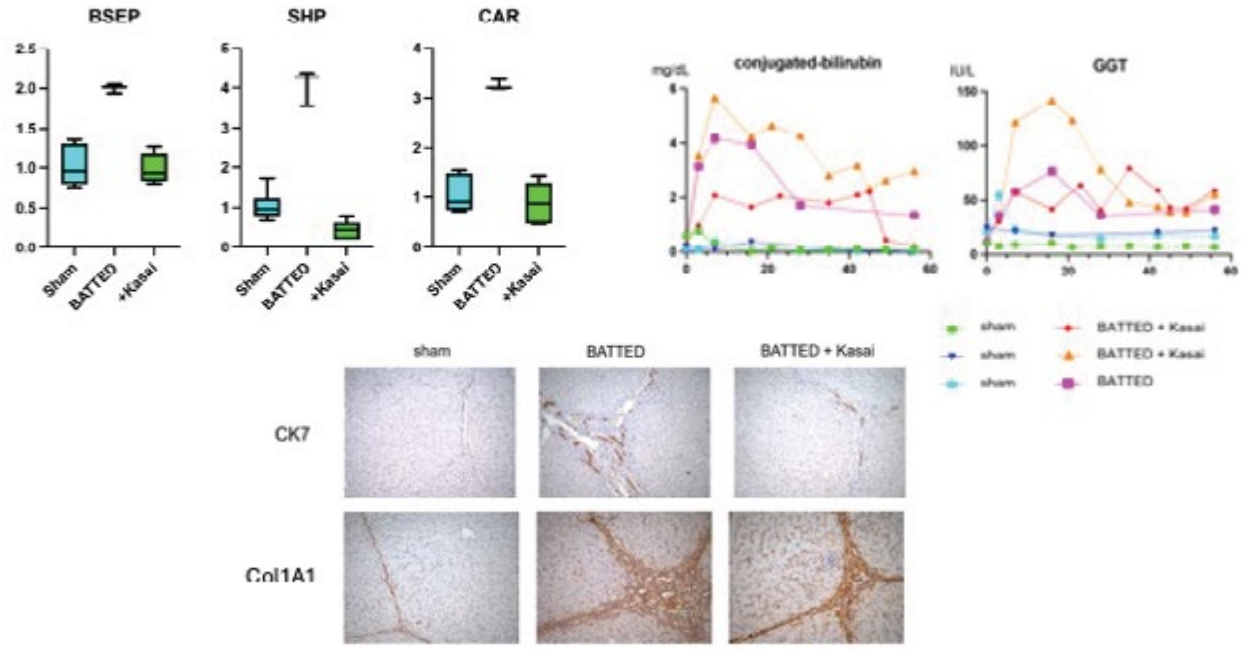
Background: Hepato-portoenterostomy (HPE) is routinely performed for biliary atresia (BA) patients, but a majority eventually require liver transplantation. The mechanisms driving the pathogenesis of BA remains elusive and not recapitulated in current models that rely on bile duct ligation. Addressing prevailing lacunae, we hypothesized that extra and intra hepatic bile duct destruction through an endothelial irritant would recapitulate human BA. We thus developed a novel neonatal piglet BA model called, BATTED – Biliary Atresia Through Targeted Endothelial Destruction. Piglets have liver and gastro-intestinal homology to infants providing a robust platform for BATTED and HPE. **Methods:** 7–10-day old piglets were randomized to BATTED (US provisional Patent US63/603,995) or sham. BATTED included cholecystectomy, common bile, and hepatic duct injection of sclerosing agent and a retainer suture for continued intrahepatic injury. Vascular access ports were placed and scheduled ultrasound guided liver biopsies performed. Six-weeks post-BATTED piglets underwent HPE and were euthanized at 8 weeks. Serology, histology, gene expression and immunohistochemistry were performed. **Results:** Serological evaluation revealed a surge in conjugated bilirubin and bile acids, 6 weeks post BATTED from baseline (mean Δ 0.39mg/dL to 3.88mg/dL) and Gamma-glutamyl transferase (GGT) increased by several folds (mean: Δ 16.3IU to 89.5IU) vs Sham (conjugated bilirubin: Δ 0.39mg/dL to 0.98mg/dL, GGT: Δ 9.2IU to 10.4IU). Sirius red staining demonstrated significant periportal and diffuse hepatic fibrosis (16-fold increase) and bile duct proliferation marker CK-7 increased 9-fold with BATTED. Piglets in the BATTED group demonstrated enhanced CD-3 (7-fold), alpha-SMA (8.85-fold), COL1A1 (11.7-fold) and CYP7A1 (7-fold), vs sham, Figure 1. Successful HPE was accomplished with reduction in conjugated bilirubin (Δ 4.89mg/dL to 2.11mg/dL), GGT and bile acids. BSEP, SHP and CAR expression was restored with BATTED. **Conclusion:** BATTED recapitulated BA features, including hyperbilirubinemia, GGT elevation, significant hepatic fibrosis, bile duct proliferation, and inflammatory infiltration with subsequent successful HPE. This model offers substantial opportunities to elucidate mechanism underlying BA and adaptation post HPE, paving the path for development of diagnostics and therapeutics.

Figure 1



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Disclosures: Ajay Jain: Mirum Camp 4 Gilead: Consultant, Kento Kurashima: Nothing to Disclose, Arun Verma: Nothing to Disclose, Si-Min Park: Nothing to Disclose, Marzena Swiderska-Syn: Nothing to Disclose, Shaurya Mehta: Nothing to Disclose, Austin Sims: Nothing to Disclose, Katherine DeSanti: Nothing to Disclose, Madeline Johnson: Nothing to Disclose, Mustafa Nazzal: Nothing to Disclose, John Long: Nothing to Disclose, Chandrashekhara Manithody: Nothing to Disclose, Jeffery Teckman: Nothing to Disclose, Shin Miyata: Nothing to Disclose

0216 | LONG-TERM OUTCOMES OF BARIATRIC SURGERY IN PATIENTS WITH COMBINED METABOLIC DYSFUNCTION AND INCREASED ALCOHOL CONSUMPTION (METALD) ◆ ★

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Background: Bariatric surgery is an effective intervention to improve hepatic steatosis and fibrosis in patients with metabolic dysfunction-associated fatty liver disease (MASLD). However, several reports raised concern on increased alcohol consumption after bariatric surgery in patients with risk factors for alcohol use disorder (AUD). Thus, the safety and efficacy of bariatric surgery in patients with dual risk factors of metabolic dysfunction and increased alcohol use (MetALD) is uncertain. In this study, we aimed to evaluate major liver-related outcomes in patients with met-ALD who underwent bariatric surgery. **Methods:** This is a retrospective cohort of patients with steatotic liver disease due to MetALD. Data is based on the National Eversana database. MetALD was defined based on presence of steatotic liver disease and a history of both metabolic dysfunction and excessive alcohol use. Metabolic dysfunction was defined as the presence of at least one out of five cardiometabolic risk factors. Patients with a history of cirrhosis or decompensated liver disease were excluded at the time of entry to the study. Patients were categorized into intervention group who underwent any type of bariatric surgery including gastric bypass or gastric sleeve surgeries versus non-surgical therapies. Patients were followed for incidence of decompensated liver disease or death. Basic and propensity score (PS) matching were performed to limit confounding factors. **Results:** We identified 388 MetALD patients who underwent bariatric surgery and 7,6449 MetALD patients with no surgical intervention. Patients in bariatric group were younger (47.1 vs. 55 yrs), predominantly female (74% vs. 31%), and had higher body mass index (BMI), compared to non-surgical group. Patients who underwent bariatric surgery had higher rate of comorbid conditions including diabetes (36% vs. 21.4%). After PS matching demographic and comorbid conditions were balanced between intervention and control groups. As expected, bariatric group achieved significant weight loss, compared to control group (delta-BMI: -3.3 vs. -0.1, E, 2.8, p <0.01). In unmatched time-to-event analysis, patients in bariatric group had lower risk of incident decompensated cirrhosis (HR, 0.4; 95% CI, 0.27-0.62; E, 2.6; p <0.01). However, after PS matching, the beneficial effect of bariatric surgery lost significance (HR, 0.6; 95%CI, 0.3-1.3; p, 0.2). Regardless of the type of matching, bariatric surgery resulted in decline in overall mortality (HR, 0.16; 95% CI, 0.05-0.48; E, 3.6; p <0.01).**Conclusion:** In patients with MetALD, bariatric surgery is an effective intervention to reduce BMI and is associated with reduction in overall mortality. However, our findings did not show improvement in liver-related outcomes in patients with MetALD in matched analysis. Additional studies are warranted to assess the safety and efficacy of bariatric surgery in patients with MetALD.

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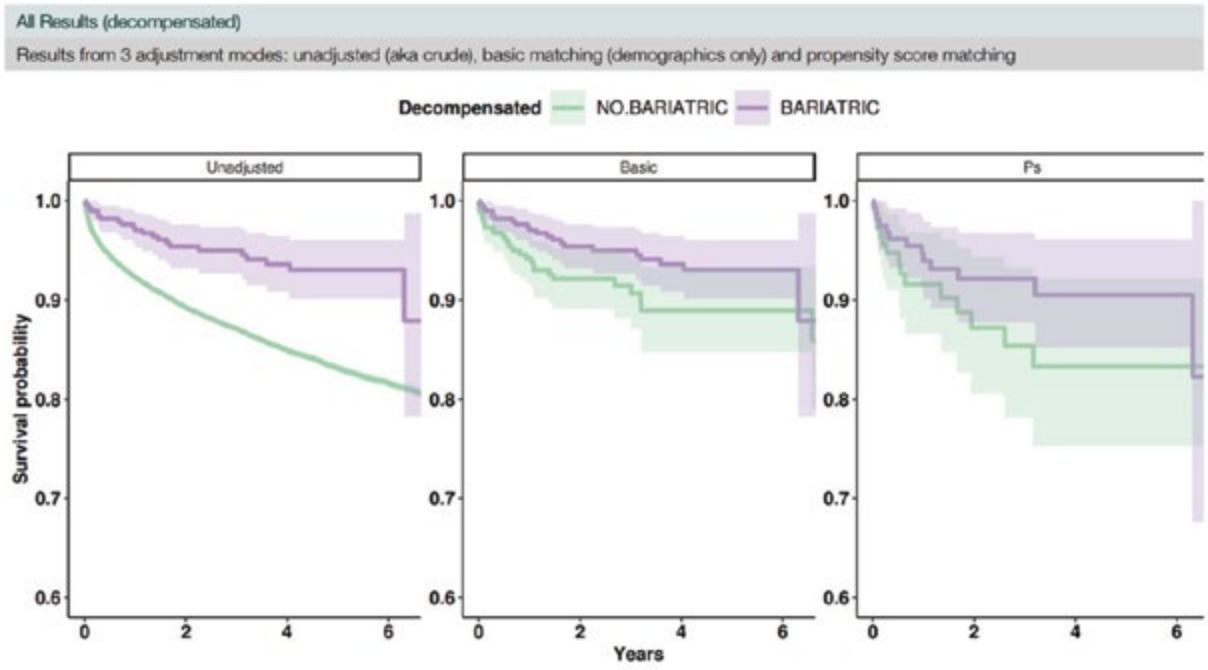

Disclosures: Seyedbabak Mirminachi: Nothing to Disclose, C. William Pike: Nothing to Disclose, Gavin Hui: Nothing to Disclose, Saurabh Gombar: Nothing to Disclose, Paul Kwo: Nothing to Disclose, Amir Hossein Gougol: Nothing to Disclose

0217 | CHANGES IN HEPATITIS C VIRUS INFECTIONS AFTER IMPLEMENTATION OF AN EXPANDED TREATMENT PROGRAM IN NEW MEXICO STATE PRISONS

Paulina Deming[1] Juan Ceniceros[1] Laura Tomedi[1] Karla Thornton[1]

[1]University of New Mexico

Background: Tracking trends in hepatitis C virus (HCV) prevalence over time is crucial to understanding HCV elimination projects. The prevalence of HCV infection among incarcerated populations is up to 10 times higher than the general US population. In 2009, the NM Corrections Department (NMCD) implemented universal opt-out HCV testing. NM prisons have one of the highest prevalence rates of HCV in the U.S.. Project ECHO® (ECHO) uses telementoring to increase access to care and partners with the NMCD to treat HCV in prison. In 2020, NMCD significantly expanded HCV treatment in New Mexico state prisons. **Methods:** From 2/1/21 to 4/28/24, ECHO received the number of entrants coming into the NM prison system each week split by HCV antibody (AB) and HCV RNA (RNA) test result. Demographic and clinical details were only available for the entrants who are AB and RNA positive, so we were unable to adjust our models for any covariates. Poisson and Quasi-Poisson regression models were done to assess changes in the RNA positivity rates among AB positive entrants, RNA positivity rates among the total entrant population, and AB positivity among the total entrant population. **Results:** From 2/1/21 – 4/28/24, there were 6,966 entrants, 3,482 were AB positive, and 2,205 were AB and RNA positive. The total AB positivity was 50.0%, the total RNA positivity among all entrants was 31.7%, and the total RNA positivity among AB positive entrants was 62.9%. RNA positivity among AB positive entrants decreased significantly over time (Poisson rate ratio (RR): 0.9988, CI: 0.998 – 0.999, p = 0.007). RNA positivity among all entrants also decreased significantly over time (Quasi-Poisson RR: 0.9987, CI: 0.998 – 0.999, p = 0.02). AB positivity among the total entrant population stayed the same over time (Poisson RR: 1.0, CI: 0.999 - 1.00, p = 0.91). **Conclusion:** RNA positivity has decreased among entrants of NM state prisons, but AB positivity has not changed. Around 1,800 people have been treated in NMCD since the start of the treatment ramp-up in 2020. Other factors could be influencing the decrease in RNA positivity, including community treatment and shifting patterns in injection drug use, but it is likely that the expansion of treatment in carceral settings among high-risk populations is contributing to the decline in HCV RNA positivity in prisons statewide. We contend that the collaboration between NMCD and Project ECHO has been a primary driver of the decreased RNA positivity rates

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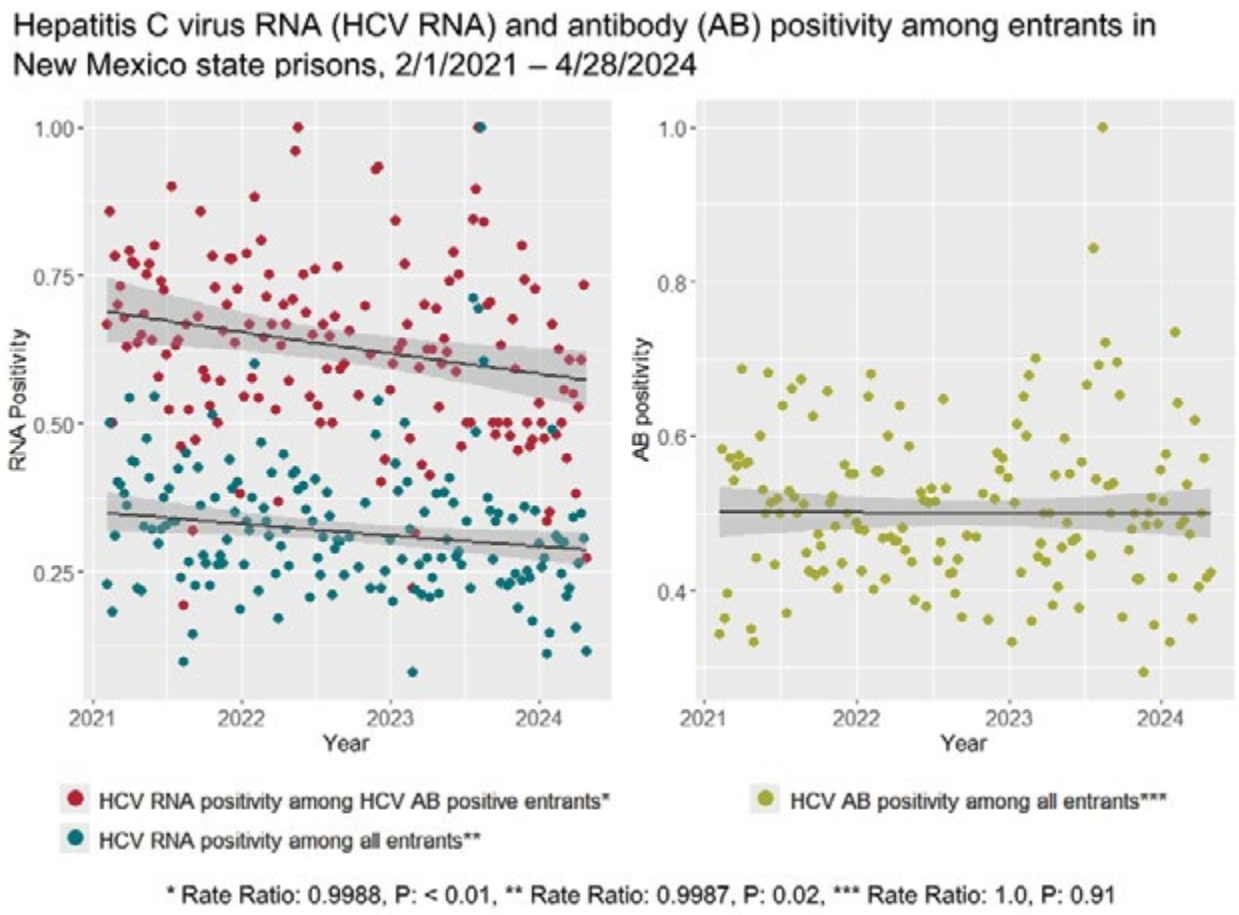
among people entering prison in New Mexico. Continued and accelerated treatment ramp-up among incarcerated populations is key to reducing HCV prevalence in the US and achieving HCV elimination.



Disclosures: Paulina Deming: Nothing to Disclose, Juan Ceniceros: Nothing to Disclose, Laura Tomedi: Nothing to Disclose, Karla Thornton: Nothing to Disclose

0218 | CONJUGATED, SULFATED, AND AMPHIPATHIC BILE ACIDS ARE ASSOCIATED WITH ACUTE KIDNEY INJURY RECOVERY IN PATIENTS WITH DECOMPENSATED CIRRHOSIS: AN UNTARGETED METABOLOMICS STUDY

Giuseppe Cullaro[1] *Kavish Patidar*[2] *Andrew Allegretti*[3] *Elizabeth Verna*[1] *Jennifer Lai*[4]

[1]*Columbia University,* [2]*Baylor College of Medicine,* [3]*MGH,* [4]*University of California, San Francisco*

Background: Bile acids (BAs), which are elevated among all patients with cirrhosis, but particularly those with elevated total bilirubin (Tbili) levels, are known to be toxic to the kidney proximal tubular epithelial cell. Given there are several mechanisms to target BA synthesis and reabsorption, we performed untargeted metabolomics to determine the association between BA concentration and composition and AKI recovery (AKI-R). **Methods:** We studied 73 decompensated cirrhosis patients hospitalized with acute kidney injury (AKI) at our center. We measured 42 different BAs and generated BA factor scores to quantify both BA concentration and composition. This was done through principal component analysis, examining eigenvalues > 1, and utilizing a scree plot to choose a 5-factor model. Factor analysis and rotation then generated 5 BA factor scores (BA1-BA5). Using ANCOVA and adjusting for confounders, we analyzed the association between each BA score and full AKI-R, defined as a decrease in serum creatinine (sCr) to within 0.3 mg/dL of baseline. Linear regression identified factors associated with elevated BA1 scores, while logistic regression determined factors associated with full AKI-R. **Results:** Among the 73 hospitalized decompensated cirrhosis patients with AKI and a median MELD

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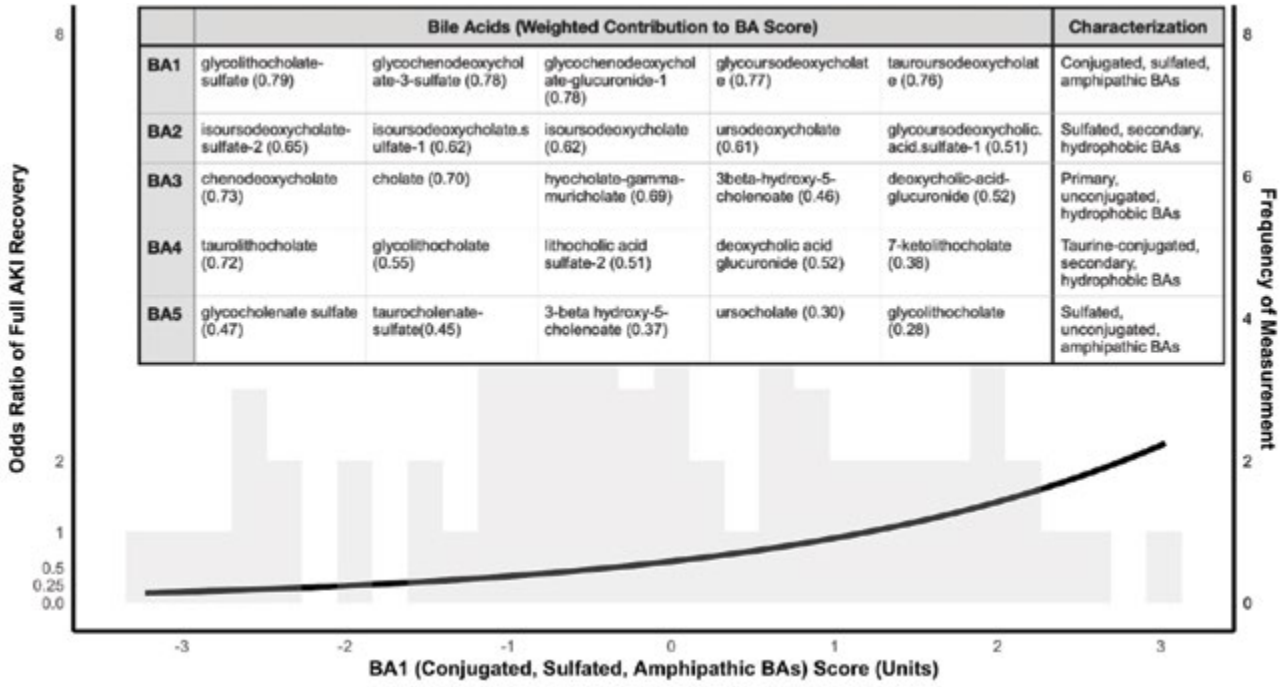
3.0 score of 34 (30 – 39) at the time of biospecimen collection, 68% had ≥ Stage 2 AKI, 45% had HRS-AKI, and 37% had full AKI recovery. The five bile acids (BAs) contributing most to each BA score are displayed in Figure 1. In ANCOVA analyses, after adjusting for age, MELD 3.0, baseline sCr, ascites status, and HE status, we found that those with AKI-R had 0.88 units higher BA1 score (p=0.003). In multivariable linear regression models, female sex (B 0.76, 95 CI 0.17 - 1.3), total bilirubin (B 0.03, 95CI 0.01 - 0.06), serum albumin (B -0.52, 95CI -0.86 - -0.17), serum sodium (B -0.06, 95CI -0.11 - -0.01), and the presence of HE (B 0.91, 95CI 0.29 - 1.50) were each significantly associated with BA1 scores. In multivariable logistic regression, each 1-point increase in BA1 was associated with 1.95x (95 CI 1.20 - 3.47) the odds of AKI-R, even after controlling for sCr, total bilirubin, serum albumin, sex, and HE status. We demonstrate the odds of AKI-R with increasing levels of BA1 in Figure 1. **Conclusion:** Our data demonstrate that not all bile acids are associated with AKI recovery equally, with conjugated, sulfated, amphipathic bile acids (i.e., BA1) being higher in those with AKI recovery. These data support further exploration of therapies that target bile acid composition and concentration to promote AKI recovery among hospitalized patients with decompensated cirrhosis.



	Bile Acids (Weighted Contribution to BA Score)					Characterization
BA1	glycolithocholate-sulfate (0.79)	glycochenodeoxycholate-3-sulfate (0.78)	glycochenodeoxycholate-glucuronide-1 (0.78)	glycoursodeoxycholate (0.77)	tauroursodeoxycholate (0.76)	Conjugated, sulfated, amphipathic BAs
BA2	isoursodeoxycholate-sulfate-2 (0.65)	isoursodeoxycholate.sulfate-1 (0.62)	isoursodeoxycholate (0.62)	ursodeoxycholate (0.61)	glycoursodeoxycholic.acid.sulfate-1 (0.51)	Sulfated, secondary, hydrophobic BAs
BA3	chenodeoxycholate (0.73)	cholate (0.70)	hyocholate-gamma-muricholate (0.69)	3beta-hydroxy-5-cholenoate (0.46)	deoxycholic-acid-glucuronide (0.52)	Primary, unconjugated, hydrophobic BAs
BA4	taurolithocholate (0.72)	glycolithocholate (0.55)	lithocholic acid sulfate-2 (0.51)	deoxycholic acid glucuronide (0.52)	7-ketolithocholate (0.38)	Taurine-conjugated, secondary, hydrophobic BAs
BA5	glycocholenate sulfate (0.47)	taurocholenate-sulfate(0.45)	3-beta hydroxy-5-cholenoate (0.37)	ursocholate (0.30)	glycolithocholate (0.28)	Sulfated, unconjugated, amphipathic BAs

Disclosures: Giuseppe Cullaro: Nothing to Disclose, Kavish Patidar: Nothing to Disclose, Andrew Allegretti: Nothing to Disclose, Elizabeth Verna: Salix: Grant/Research Support, Jennifer Lai: Nestle Nutrition Institute: Grant/Research Support, Novo Nordisk: Consultant, Genfit: Consultant, Boehringer Ingelheim: Advisor

0219 | THE EFFECT OF OBETICHOLIC ACID ON INFLAMMATORY MARKERS AND FIBROSIS SCORES IN POISE INCOMPLETE RESPONDERS: A RETROSPECTIVE REVIEW OF POISE, A PHASE 3 TRIAL OF OBETICHOLIC ACID FOR THE TREATMENT OF PRIMARY BILIARY CHOLANGITIS

David Victor[1] Jing Li[2] Radhika Nair[2] Darren Wheeler[2] Kris Kowdley[3]

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Background: In the phase 3 POISE trial (NCT01473524) of obeticholic acid (OCA) for primary biliary cholangitis (PBC), responders and incomplete responders were defined as patients who did or did not achieve alkaline phosphatase (ALP) <1.67× upper limit of normal (ULN) with ≥15% reduction from baseline and total bilirubin (TB) ≤ULN at 12 months, respectively. Here, we report the effect of OCA on incomplete responders using other efficacy assessments including a marker of farnesoid x receptor activation (fibroblast growth factor 19 [FGF19]), a marker of hepatocyte injury (cleaved cytokeratin-18 [CK-18]), inflammatory immune markers (eg, C-reactive

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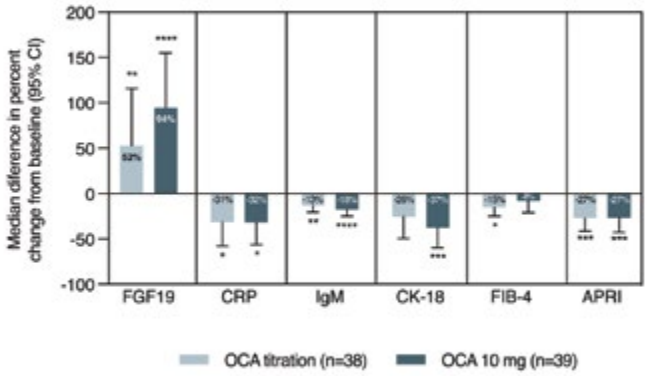
protein [CRP], immunoglobulin M [IgM]), and hepatic fibrosis scores (eg, fibrosis-4 [FIB-4] and aspartate-to-platelet ratio index [APRI]). **Methods:** This was a retrospective evaluation of incomplete responders in the POISE study. The median percent changes from baseline (% CFB) for placebo, OCA 5 to 10 mg titration, and OCA 10 mg were assessed for FGF19, CRP, IgM, CK-18, FIB-4, and APRI. The difference in median % CFB and 95% CI were calculated using Hodges-Lehmann estimates. *P* values for comparing OCA vs placebo were calculated using the Wilcoxon rank-sum test. **Results:** At month 12, the median % CFB [95% CI] in FGF19 was significantly increased for OCA titration (52 [15, 116], *P*<0.01) and OCA 10 mg (94 [61, 155], *P*<0.0001). Significant decreases in the median % CFB [95% CI] of CRP occurred for OCA titration (−31 [−58, −3], *P*<0.05) and OCA 10 mg (−32 [−56, −4], *P*<0.05). The median % CFB [95% CI] in IgM was significantly decreased for OCA titration (−13 [−21, −5], *P*<0.01) and OCA 10 mg (−18 [−25, −9], *P*<0.0001). Substantial decreases in the median % CFB [95% CI] of CK-18 occurred for OCA titration (−26 [−50, 0.1], *P*=0.05) and OCA 10 mg (−37 [−60, −16], *P*<0.001). A significant reduction in the median % CFB [95% CI] of FIB-4 occurred only in the OCA titration (−15 [−25, −4], *P*<0.05) group. The median % CFB [95% CI] in APRI was significantly decreased for OCA titration (−27 [−42, −14], *P*<0.001) and OCA 10 mg (−27 [−43, −15], *P*<0.001). **Conclusion:** OCA-treated patients had lower fibrosis scores and reduced CRP, CK-18, and IgM, which is a key prognostic marker for worse clinical outcomes in PBC, regardless of whether they met the primary POISE endpoint. Patients who do not achieve the composite endpoint for ALP and TB may still benefit from OCA in terms of lower inflammation and reduced fibrosis progression.

Figure 1. Median difference for OCA vs placebo in percent change from baseline in hepatic biomarker levels and fibrosis scores in POISE incomplete responders



*P<0.05, **P<0.01, ***P<0.001, ****P<0.0001 OCA vs placebo using Wilcoxon rank-sum test.

Abbreviations: APRI, aspartate-to-platelet ratio index; CK-18, cytokeratin-18; CRP, C-reactive protein; FGF19, fibroblast growth factor 19; FIB-4, fibrosis-4; IgM, immunoglobulin M; OCA, obeticholic acid.

Disclosures: David Victor: Nothing to Disclose, Jing Li: Nothing to Disclose, Radhika Nair: Intercept Pharma: Employee, Sanofi: Employee, Darren Wheeler: Nothing to Disclose, Kris Kowdley: Boston Scientific: Grant/Research Support, Corcept: Grant/Research Support, CymaBay: Grant/Research Support, Genfit: Grant/Research Support, Gilead: Grant/Research Support, GSK: Grant/Research Support, Hanmi: Grant/Research Support, Intercept: Grant/Research Support, Ipsen: Grant/Research Support, Janssen: Grant/Research Support, Madrigal: Grant/Research Support, Mirum: Grant/Research Support, Novo Nordisk: Grant/Research Support, NGM: Grant/Research Support, Pfizer: Grant/Research Support, Pliant Therapeutics: Grant/Research Support, Terns: Grant/Research Support, Viking: Grant/Research Support, Zydus: Grant/Research Support, 89bio Inc: Grant/Research Support, UpToDate: Royalties or patent beneficiary, CymaBay: Consultant, Enanta: Consultant, Genfit: Consultant, Gilead: Consultant, HighTide: Consultant, Inipharm: Consultant, Intercept: Consultant, Ipsen: Consultant, Madrigal: Consultant, Mirum: Consultant, NGM: Consultant, Pliant Therapeutics: Consultant, Pfizer: Consultant, Protagonist: Consultant, Zydus: Consultant, 89bio Inc: Consultant, AbbVie: Payment or honoraria, Gilead: Payment or honoraria, Intercept: Payment or honoraria, US Department of Justice: Payment for expert testimony, CTI: Advisor, Medpace: Advisor, Labcorp: Advisor, Worldwide Clinical Trials: Advisor, Inipharm: Stock – privately held company, Velacur: Received equipment, materials, drugs, medical writing, gifts

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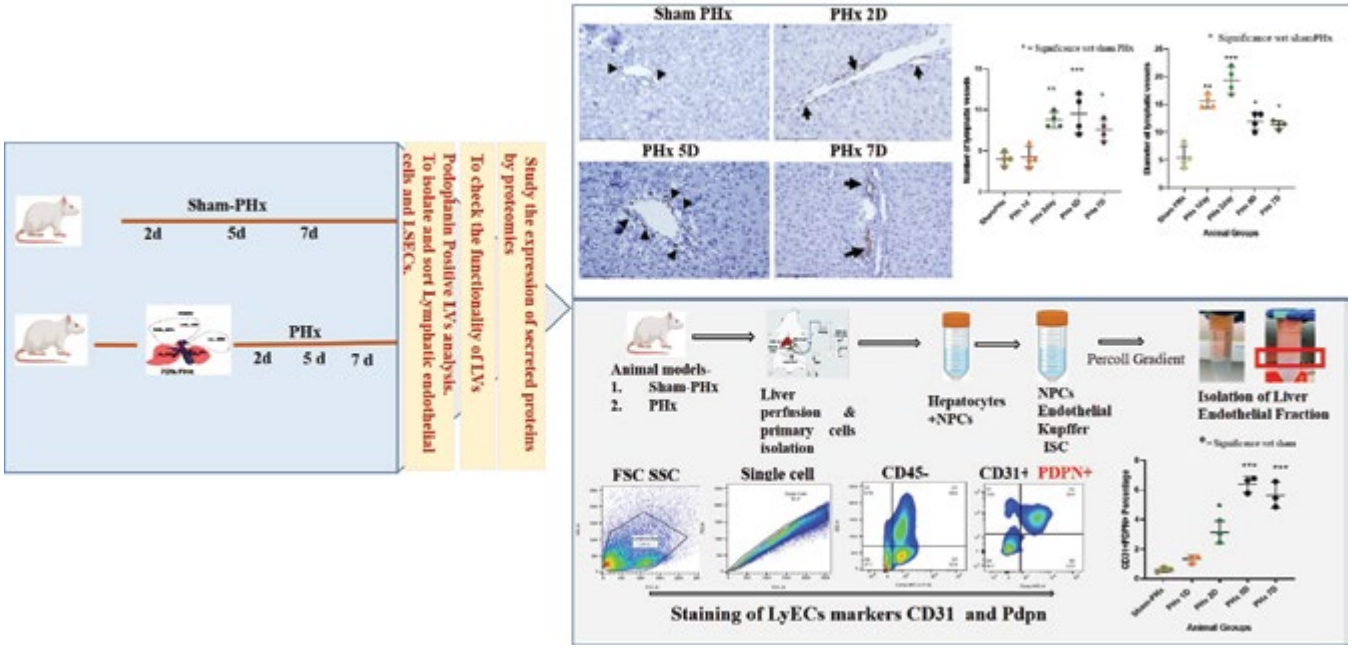
0220 | HEPATIC LYMPHANGIOGENESIS REGULATES BILIARY CELL PROLIFERATION DURING LIVER REGENERATION AFTER PARTIAL HEPATECTOMY ★

Aarti Sharma[1] Pinky Juneja[1] Jayesh Kumar Sevak[1] Ashwini Vasudevan[1] DEEPIKA JAKHAR[1] Impreet Kaur[1] Shiv Kumar Sarin[1] Dinesh Mani Tripathi[2] Savneet kaur[1]

[1]Institute Of Liver And Biliary Sciences,New Delhi, [2]Institute of Liver and Biliary Sciences

Background: Background: Two thirds partial hepatectomy (PHx) triggers a systematic sequelae of multicellular events for liver regeneration. The kinetics of liver sinusoidal endothelial cells (LSEC) after PHx is well-known. Liver also contains a network of lymphatic capillaries lined by lymphatic endothelial cells (LyEC), which remain less studied. We investigated LyEC kinetics and their proteome profile after PHx. **Methods:** 70%-PHx rat models were developed and compared with sham at 1, 2, 5 and 7 days (D) post-PHx (n=4 each). FACS analysis and imaging of hepatic LyECs and lymphatics were done. Lymphatic functionality was assessed by FITC dextran. Primary LSEC and LyEC were sorted using CD31+ and PDPN+CD31+ for proteome analysis at D2 post-PHx. Co-cultures of cholangiocytes-organoids (Chol-org) were done in presence of LyEC-CM (conditioned Media). Studies were done in which lymphangiogenesis was inhibited by i.p. injection of VEGFR-3 inhibitor (MAZ51:10mg/kg) for 3 days along with PHx. **Results:** Proliferating hepatocytes (Ki67+HNF4?+) were maximally observed at D1 and D2 post-PHx. An increase in intrahepatic CK19+ cholangiocytes was seen between D2 3 post-PHx in portal areas. Increased percentage of LSEC [D2: 6.5% ($p<0.005$), D5:14% ($p=0.001$)] and LyEC [D2: 3% ($p=0.0024$), D5: 7% ($p<0.0001$] was observed at 2 and 5D post-PHx compared to sham. LyEC were prominently localized in portal areas in zone 1. Hepatic lymphatic drainage was increased by 20% ($p=0.03$) in D2 PHx compared to sham. In proteome analysis, about 500 significant differentially expressed proteins were identified. Compared to sham, pathways like MAPK and Hedgehog were upregulated in PHx-LSEC while AMPK, MAPK, and IL17 were upregulated in PHx-LyEC. Among secreted proteins, PHx-LSEC showed increased expression of hepatocyte mitogen proteins, Wnt2 and oncostatin-M and in LyEC, Wnt7a and FGF20 factors, involved in cholangiocytes proliferation were increased. Chol-org treated with LyEC-CM showed a considerable increase in numbers compared to untreated controls (12.6+1.5 vs 6+2, $p=0.01$). Furthermore, MAZ51 treatment, significantly decreased intrahepatic CK19+ cells at D2 PHx as compared to untreated ones ($p<0.05$). **Conclusion:** Conclusion: Hepatic lymphangiogenesis is a characteristic feature after PHx. We identified secretory proteins like Wnt7a and pathways like IL-17 in hepatic LyEC, facilitating biliary cells proliferation in portal areas. Our study highlights a novel contribution of hepatic lymphatic vessels during liver regeneration.



Disclosures: Aarti Sharma: Nothing to Disclose, Pinky Juneja: Nothing to Disclose, Jayesh Kumar Sevak: Nothing to Disclose, Ashwini Vasudevan: Nothing to Disclose, DEEPIKA JAKHAR: Nothing to Disclose, Impreet

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Kaur: Nothing to Disclose, Shiv Kumar Sarin: Nothing to Disclose, Dinesh Mani Tripathi: Nothing to Disclose, Savneet kaur: Nothing to Disclose

0221 | HEALTH SYSTEM AND PATIENT PREDICTORS OF POST-TRANSPLANT SHORT-TERM MORTALITY AND LENGTH OF STAY AMONG LIVER TRANSPLANT RECIPIENTS

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[1]UMass Chan Medical School, [2]University of Pennsylvania Health System, [3]University of Pennsylvania, Perelman School of Medicine

Background: Previous efforts to study post-liver transplantation outcomes have focused on mortality or graft failure. However, futility of transplant is understudied. We applied a novel two-stage approach to determine predictors of (i) the probability of death during the immediate post-transplant period and (ii) length-of-post-stay post-transplant among those surviving to hospital discharge. **Methods:** The study population was derived from United Network for Organ Sharing (UNOS). Our study cohort consisted of n=67,311 adult (age ≥18) patients receiving a deceased donor liver transplant during 2010-22. We excluded multi-organ, repeat transplant, and status 1 patients. Candidate predictors included in the model fitting but not selected for in either model include recipient, donor, and health system variables (eg. blood type, Race=Asian, Race=Other, Region=6, transplant volume >60 per year, donor age, donor sex, donor Hispanic, donor Asian, and partial/split liver). Our end point has two dimensions: (i) in-hospital mortality (IHM) (ii) post-transplant length-of-say (LOS) among patients discharged. We use logistic regression for in-hospital morality and the generalized estimating equations (GEE) version of linear regression for LOS given discharged. For both models, predictors were determined using stepwise regression. **Results:** There were a total of 1755 in-hospital deaths (2.6%). Among the 66,518 patients discharged, median LOS was 9 days. Only ~1% of patients had LOS >90 day, so we capped LOS at 90 days for the regression modeling. The in-hospital death model had moderate-good risk discrimination (C=0.70). Odds ratios (OR) and differences-in-means for significant predictors of either in-hospital and/or post-discharge length-of-stay are provided in Table 1. Variables most strongly predictive of early post-LT mortality and LOS include mechanical ventilation (OR 1.84 for IHM and mean LOS difference of 9.25 days), dialysis (OR 1.31 for IHM and mean LOS difference of 6.91 days), center volume < 10 transplants per year (OR 2.50 for IHM and mean LOS difference 6.13 days), pre-transplant ICU hospitalization (OR 1.97 for IHM and mean LOS difference of 4.96 days), and Region 9 (OR 1.57 for IHM and mean LOS difference of 3.88 days) (all p< 0.001). **Conclusion:** A non-negligible percentage of patients die in-hospital in the immediate post-transplant period. We developed a model of in-hospital mortality and length-of-stay with reasonable risk discrimination that highlights important geographic and center-volume differences. Despite the functional relationship between the outcomes, there was considerable non-overlap in the risk factors for mortality and LOS, suggesting different approaches to patient selection and clinical care are needed to reduce immediate post-LT mortality and LOS.

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Table 1. Odds ratios (OR) and difference in means (β) for significant predictors of eit or post-transplant length of stay, respectively

Source	Predictor	OR	β
Recipient	Age (per 5 years)	1.15	0.48
	Sex: female	1.21	0.59
	Race: Black	●	0.51
	Race: Hispanic	●	0.46
	Blood group: A	●	0.23
	Diagnosis: HCV	0.81	-0.54
	Diagnosis: AHN	●	-1.06
	Diagnosis: Non-cholestatic cirrhosis	0.89	0.29
	Diagnosis: HCC	●	-1.06
	Dialysis	1.31	6.91
	Ventilator	1.84	9.25
	Center volume <10 per year	2.50	6.13
	Creatinine (not on dialysis)	1.12	0.40
	Creatinine (on dialysis)	1.08	-1.18
	Albumin	0.88	-0.45
	Bilirubin	●	0.09
	INR	●	0.10
	Diabetes	1.18	0.39
	Hospitalized: ICU	1.97	4.96
	Hospitalized: not ICU	1.30	2.55
	Pre-LT years on WL	1.08	0.23
	Functional status (per 10 points)	0.88	-0.54
	Working for income	0.74	-1.30
	Region 1	1.47	1.08
	Region 2	●	1.47
	Region 3	●	-0.96
	Region 4	0.75	-1.45
	Region 7	1.21	●
	Region 9	1.57	3.88
	Region 11	●	-1.39
	Year of transplant	0.97	●
Donor	Weight (per 5 kg)	1.02	●
	Height (per 10 cm)	●	-0.18
	Diabetes	1.17	0.84
	Donation after circulatory death (DCD)	1.29	●
	Bilirubin	1.05	0.18
	Creatinine	●	0.06
	Cause of death: stroke	1.24	●
	Cause of death: Anoxia	●	-0.47
	Smoking	●	-0.26
	Cytomegalovirus (CMV): D+ / R-	●	-0.27
	Race: Black	●	0.33

Disclosures: Joyce Tien: Nothing to Disclose, Marina Serper: Grant/Research Support relationship with Grifols; Has not ended; Grant/Research Support relationship with Eurofins; Has not ended; Grant/Research Support relationship with Transplant Genomics; Has not ended, Douglas Schaubel: Nothing to Disclose

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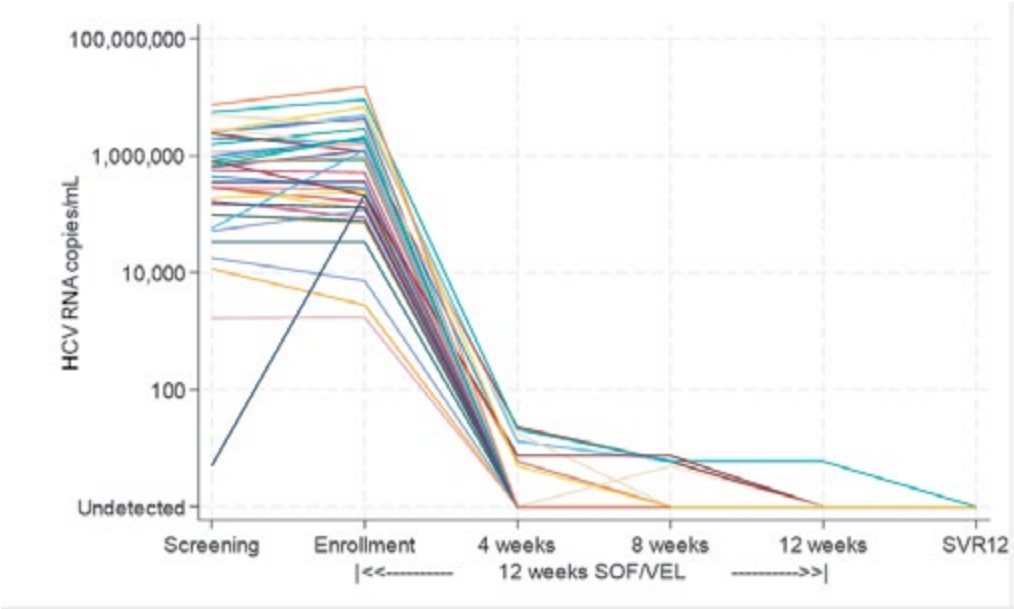
0222 | SAFETY, TOLERABILITY, AND OUTCOMES OF SOFOSBUVIR/VELPATASVIR IN TREATMENT OF CHRONIC HEPATITIS C VIRUS DURING PREGNANCY: INTERIM RESULTS FROM THE STORC STUDY

Catherine Chappell[1] Jasmin Charles[2] Marcela Smid[2] Kara Rood[3] John Cafardi[4] Tatyana Kushner[5] Mia Biondi[6] Jordan Feld[7] Mark Yudin[8] Genevieve Eastabrook[9] Sarah Osmundson[10] Todd Davies[11] Meyn Leslie[1] Cathleen Letterio[12] Kyung min Kwon[12] Bruce Kreter[13] Sharon Hillier[1]

[1]University of Pittsburgh, [2]University of Utah, [3]Ohio State University, [4]The Christ Hospital, [5]Mount Sinai Medical Center, [6]University Health Network, [7]Toronto General Hospital, [8]Unity Health Toronto, [9]London Health Sciences Centre, [10]Vanderbilt University, [11]Marshall University, [12]Gilead Sciences, [13]Gilead Sciences, Inc.

Background: Hepatitis C virus (HCV) prevalence is increasing among pregnant people, yet postpartum treatment rates are less than 10%. Use of direct acting antivirals during pregnancy could cure HCV infection during a time of high healthcare engagement, reduce HCV-associated maternal morbidity and prevent perinatal transmission. However, limited safety and efficacy data exist for this population. The STORC study is an international, multi-center study evaluating the safety and efficacy of sofosbuvir/velpatasvir (SOF/VEL) in pregnant people. **Methods:** In this phase 4, open-label, single-arm study, pregnant persons with HCV infection were enrolled between 20+0- and 30+0-weeks' gestation and treated with a 12-week course of SOF/VEL. HCV RNA testing was performed at screening, enrollment, 4, 8 and 12 weeks after SOF/VEL initiation, at delivery and 12 weeks after SOF/VEL completion (SVR12). The primary outcomes were gestational age at delivery and SVR12. Infants were followed for one year. **Results:** From July 2022 to May 2024, 51 pregnant people with HCV were screened and 41 were enrolled. The enrolled participants had a median age of 31 (range 18, 40). 33 (80%) identified as White, 8 (15%) identified as other races, including Black, Native American, Asian and multiracial and 6 (11.5%) identified as Hispanic. One participant discontinued treatment after one dose due to vomiting. Participants enrolled with median HCV RNA of 5.81 (range 3.23, 7.18) log copies/mL. After initiation of SOF/VEL, 28/36 (78%) at 4 weeks, 28/33 (85%) at 8 weeks and 27/28 (96%) at 12 weeks of treatment had undetectable HCV RNA (Figure). All participants with HCV RNA obtained at delivery (n=25) and at the SVR12 (n=27) visit were undetectable. The maternal retention rate at the SVR12 visit was 27/31 (87%). Of the 32 participants who have delivered, median gestational age was 38+2 weeks (range 33+5, 41+1) and 5 (16%) had preterm delivery < 37 weeks' gestation. 19 (53%) participants completed treatment prior to delivery. All adverse events related to SOF/VEL were ≤grade 2. Of 27 infants tested for HCV RNA, all were undetectable at 2 months and/or 6 months of age. Infant retention was 29/32 (91%), 14/18 (78%), and 5/12 (42%) at the 2-month, 6-month and 12-month visits. **Conclusion:** The interim data from the STORC study provides preliminary reassurance regarding the safety and efficacy of SOF/VEL administration after 20 weeks' gestation. Recruitment for the STORC study is ongoing.



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Disclosures: Catherine Chappell: Gilead Sciences: Grant/Research Support, Gilead Sciences: Advisor, Organon: Grant/Research Support, Jasmin Charles: Gilead Science: Member of a Medical Advisory Board, Marcela Smid: Nothing to Disclose, Kara Rood: Nothing to Disclose, John Cafardi: Nothing to Disclose, Tatyana Kushner: Advisor relationship with Gilead; Has ended; Advisor relationship with GSK; Has ended; Advisor relationship with Eiger; Has ended; Grant/Research Support relationship with Gilead; Has not ended, Mia Biondi: Gilead Sciences: Grant/Research Support, Gilead Sciences: Speaking and Teaching, AbbVie: Speaking and Teaching, AbbVie: Grant/Research Support, Cepheid: Grant/Research Support, Jordan Feld: Mirum: Consultant, AbbVie, Bluejays, Gilead, Janssen, GSK, Roche, VIR Roche: Consultant, Bluejays: Consultant, Gilead: Consultant, Janssen: Consultant, GSK: Consultant, Roche: Consultant, VIR Biotechnology: Consultant, Altimmune, AbbVie, Gilead, Jannsen, GSK, Roche, VIR Bio: Grant/Research Support, Mark Yudin: Nothing to Disclose, Genevieve Eastabrook: Nothing to Disclose, Sarah Osmundson: Nothing to Disclose, Todd Davies: Nothing to Disclose, Meyn Leslie: Nothing to Disclose, Cathleen Letterio: Nothing to Disclose, Kyung min Kwon: Nothing to Disclose, Bruce Kreter: Gilead Sciences: Employee, Gilead Sciences: Stock - publicly traded company, Akero Therapeutics: Stock - publicly traded company, Bristol-Myers Squibb: Stock - publicly traded company, Eli Lilly and Company: Stock - publicly traded company, Merck and Company: Stock - publicly traded company, Novo Nordisk A/S: Stock - publicly traded company, Pfizer Inc: Stock - publicly traded company, Sharon Hillier: Nothing to Disclose

0223 | TARGETING LIVER LYMPHATIC DRAINAGE: A NOVEL APPROACH TO TREAT LIVER CIRRHOSIS AND PORTAL HYPERTENSION

JAIN JEONG[1] Shao-Jung Hsu[2] Daiki Horikami[1] Teruo Utsumi[1] Yilin Yang[1] Xuchen Zhang[1] James Boyer[1] James Boyer[1] Matthew McConnell[1] Hui-Chun Huang[3] Yasuko Iwakiri[1]

[1]Yale University, [2]National Yang-Ming University, [3]Taipei Veterans General Hospital

Background: Liver lymphatic vascular system is crucial for maintaining fluid balance and removing toxic metabolites from the liver. Thus, efficient removal of lymph produced within the liver (i.e., lymphatic drainage) helps to reduce inflammation and maintain constant intrahepatic vascular resistance (IHR). However, the impact of altered liver lymphatic drainage function on liver pathophysiology is largely unknown. We hypothesized that enhancing liver lymphatic drainage could reduce liver injury, fibrosis and portal hypertension (PH) in liver cirrhosis. **Methods:** Bile duct ligation (BDL) was performed on mice and rats to study liver injury, inflammation, fibrosis, lymphatic drainage, and hemodynamic changes. Lymphatic drainage was blocked by surgically removing regional lymph nodes and occluding connecting lymphatic vessel (LV) or administration of MAZ51 (a VEGFR3 blocker) to block LV function. Vascular endothelial growth factor (VEGF)-C, the most potent lymph-angiogenic factor (new LV formation), was overexpressed in the liver using adeno-associated virus 8 (AAV8)-VEGF-C. Lymphatic drainage was measured by the Evans blue content in the portal lymph node. Additionally, liver samples from healthy individuals and patients with primary sclerotic cholangitis (PSC) were analyzed. **Results:** Blocking liver lymphatic drainage in normal mice led to increased liver and spleen weights (1.1-fold & $p<0.05$, 1.3-fold & $p<0.01$, respectively), CD45+ lymphocyte accumulation (1.4-fold, $p<0.05$), and fibrotic area (Sirius Red+ area, ~16-fold, $p<0.05$). In cholestatic mice, decreased lymphatic drainage (2.5-fold, $p<0.05$) due to MAZ51 treatment worsened liver fibrosis (Sirius Red+ area, 1.4-fold increase, $p<0.05$; hydroxyproline, 1.9-fold increase, $p<0.05$), and increased MPO-positive neutrophils (2.8-fold, $p<0.05$), compared to vehicle-treated cholestatic mice, indicating that reduced lymphatic drainage induces liver fibrosis. Conversely, VEGF-C overexpression in the liver via AAV8-VEGF-C increased LV numbers (1.5-fold, $p<0.01$), improved lymphatic drainage (2.5-fold, $p<0.05$), and decreased liver fibrosis (1.4-fold reduction in Sirius Red+ area, $p<0.05$; hydroxyproline, 1.4-fold, $p<0.05$). VEGF-C-driven lymphatic drainage also reduced splenomegaly (1.4-fold, $p<0.05$), suggesting decreased portal pressure. In cholestatic rats, VEGF-C overexpression reduced IHR and portal pressure by 20% ($p<0.05$ and $p<0.01$, respectively) without affecting cardiac index or mean arterial pressures. Analysis of PSC patient livers showed a 2.5-fold decrease LV numbers in decompensated cirrhotic patients ($p<0.05$), compared to compensated PSC cohorts, suggesting decreased lymphatic function advances cirrhosis and PH. **Conclusion:** Enhancing liver lymphatic drainage via VEGF-C overexpression could be a novel therapeutic strategy for reducing liver fibrosis/cirrhosis and ameliorating portal hypertension.

Disclosures: JAIN JEONG: Nothing to Disclose, Shao-Jung Hsu: Nothing to Disclose, Daiki Horikami: Nothing to Disclose, Teruo Utsumi: Nothing to Disclose, Yilin Yang: Nothing to Disclose, Xuchen Zhang: Nothing to Disclose, James Boyer: IPSEN: Clinical Evenets Committee for clinical trial, James Boyer: Mirum Pharmaceuticals: grant

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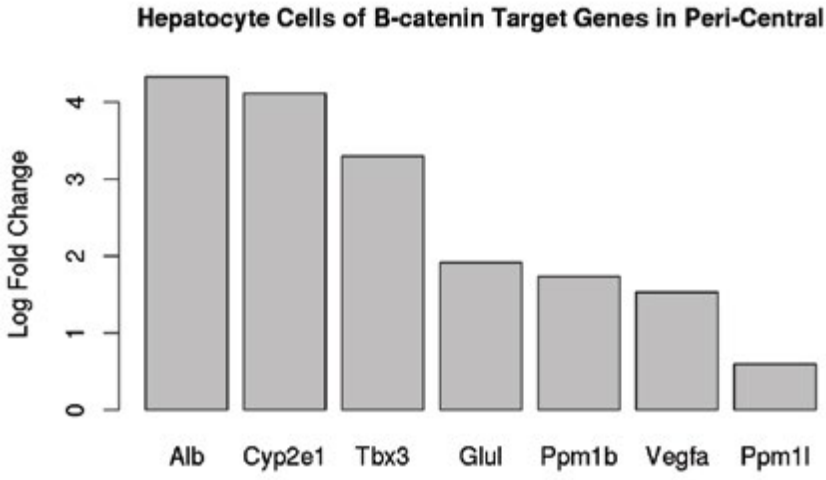
recipient, Matthew McConnell: Nothing to Disclose, Hui-Chun Huang: Nothing to Disclose, Yasuko Iwakiri: Nothing to Disclose

0224 | LIVER SINUSOIDAL ENDOTHELIAL CELL RESPONSES TO HEPATIC CONGESTION INSTIGATE B-CATENIN DEPENDENT PROLIFERATIVE RESPONSES IN PERI-CENTRAL HEPATOCYTES

Papawee Sutthirat[1] Nidhi Jalan-Sakrikar[1] Maarouf Hoteit[2] Vijay Shah[1] Moira Hilscher[3]

[1]Mayo Clinic Rochester, [2]University of Pennsylvania, [3]Penn Medicine

Background: Liver masses are common in patients with congestive hepatopathy (CH) and may be benign or malignant. CH is characterized by aberrant mechanical forces in the liver sinusoid which affect neighboring cell populations. In this study, we examine the impact of congestion on interactions between liver sinusoidal endothelial cells (LSECs) and hepatocytes. We hypothesize that LSEC responses to congestion instigate proliferative responses in hepatocytes which lead to the formation of liver masses. **Methods:** Single cell RNA-sequencing was performed on primary cells isolated from wild type mice 6 weeks after partial inferior vena cava ligation (pIVCL), a murine model of CH, and sham procedures. Mechanistic studies utilized RT-PCR analysis on LSECs stretched using Flexcell. Immunofluorescence (IF) was also performed on liver tissues for β-catenin pathway and proliferation analysis. Mutational analysis was done on tumors from patients with hepatocellular carcinoma (HCC). **Results:** We identified 3 subpopulations of LSECs and hepatocytes: peri-central, middle, and peri-portal. Cell chat analysis revealed interaction between Wnt2 released from peri-central LSECs with the Fzd8_LRP5/6 coreceptor complex in peri-central hepatocytes. Congruently, expression of glutamine synthase (GS), an effector molecule of the β-catenin pathway which is expressed by peri-central hepatocytes, increased significantly by IF in pIVCL mice livers compared to sham (fold change 1.85, p value < 0.05). Furthermore, Cyclin d1, a marker of proliferation, is also significantly upregulated after pIVCL (fold change 5.34, p value < 0.05). Mechanistically, LSEC exposed to cyclic stretch in vitro to mimic the mechanical forces in CH transcriptionally upregulated Wnt2 (fold change 3.51, p value < 0.05). We then analyzed liver tissue obtained from patients with hepatocellular carcinoma in the setting of Fontan associated liver disease (n=6). Tumor mutation analysis revealed mutations in the β-catenin pathway in 3 of these tumors, supporting the role of β-catenin in promoting liver masses in CH. **Conclusion:** The mechanical milieu created by CH impacts signaling between LSECs and hepatocytes in the peri-central region of the sinusoid. These changes instigate proliferative responses in hepatocytes which may contribute to the development of liver masses.



Disclosures: Papawee Sutthirat: Nothing to Disclose, Nidhi Jalan-Sakrikar: Nothing to Disclose, Maarouf Hoteit: HepQuant, LLC: Advisor, Vijay Shah: Boehringer Ingelheim: Consultant, GSK: Consultant, GENFIT SA: Consultant, Intercept Pharmaceuticals, Inc.: Advisor, Korro Bio, Inc.: Consultant, Mallinckrodt Pharmaceuticals: Advisor, Novo Nordisk A/S: Consultant, Resolution Therapeutics, Ltd.: Advisor, Seal Rock Therapeutics, Ltd.: Consultant, Surrozen: Advisor, Moira Hilscher: Nothing to Disclose

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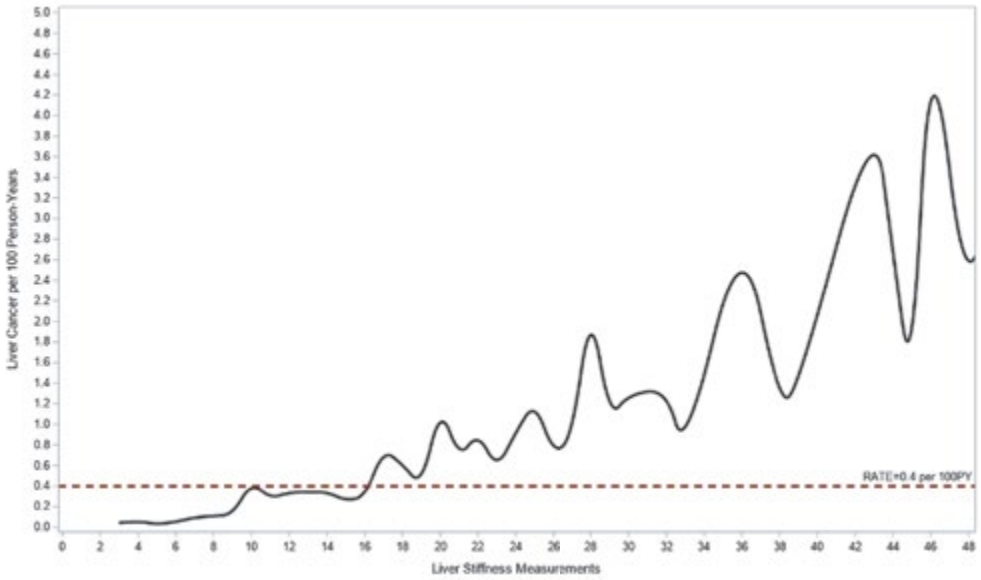
0225 | LIVER STIFFNESS MEASUREMENT AND HEPATOCELLULAR CARCINOMA RISK IN METABOLIC DYSFUNCTION ASSOCIATED STEATOTIC LIVER DISEASE

Binu John[1] Yangyang Deng[2] Amit Singal[3] Bassam Dahman[4]

[1]University of Miami, [2]JohnsHopkins University, [3]University of Texas Southwestern, [4]Virginia Commonwealth University

Background: Metabolic Dysfunction Associated Steatotic Liver Disease (MASLD) is the fastest rising cause of Hepatocellular Carcinoma (HCC), and patients with MASLD develop HCC in the absence of cirrhosis. However, tools to predict MASLD HCC are lacking. Liver Stiffness Measurement (LSM) on transient elastography (TE) is associated with hepatic decompensation and liver-related death. This study aimed to assess if LSM is associated with MASLD HCC, and can be used to inform need for surveillance. **Methods:** This was a retrospective cohort study of Veterans assembled from 130 VA medical centers in the United States from the Veterans Health Administration (VHA) Corporate Data Warehouse (CDW). Participants with MASLD who underwent TE between 5/27/2014 and 1/5/2023 and fulfilled criteria for MASLD were included. LE with less than ten documented valid LSM measurements, those with an IQR>30%, and veterans for whom LSM was obtained after HCC diagnosis were excluded. Only the first valid study was included in participants with multiple exams. Participants were followed until HCC, death, or 6/1/23. To validate the predictive capability of the LSM groups, the sample data were 70:30 split into training and testing datasets and the training proportional hazard model was used to predict the risk of HCC for the external testing sample. The predicted risk scores for the testing sample were used to classify the participants into high-risk and low-risk groups based on the median predicted risk score, then we estimated the two-group hazard ratio from a Cox model for time to HCC. **Results:** We included 30,414 participants with MASLD, followed up over 69,974 person-years. The rate of HCC increased by 19% with every 5 kPa increase in LSM (aHR 1.19, 95% CI 1.15-1.24, p<0.0001). The adjusted annual rate of HCC was 0.05% for participants with LSM <5 kPa (reference group), 0.07% with LSM 5-9.9 kPa (adjusted Hazard Ratio [aHR] vs. reference 1.34, 95% CI 0.60-3.02, p=0.48), 0.37% with LSM 10-14.9 (aHR 6.26, 95% CI 2.82-13.92, p<0.0001), 0.49% with LSM 15-19.9 (aHR 7.10, 95% CI 2.89-17.47, p<0.0001), 0.88% with LSM 20-24.9 (aHR 12.27, 95% CI 5.18-29.05, p<0.0001), and 1.12% with LSM ≥ 25 kPa (aHR 15.45, 95% CI 7.00-34.07, p<0.0001). Annual HCC risk was <0.4% for patients with LSM below 16.2 kPa. In the testing dataset, the high-risk group from the predictive model had a higher risk of HCC compared to the low-risk group, with the hazard ratio for the high-risk to the low-risk group of 10.20 (95% CI: 3.65-28.47, p<0.0001), showing strong separation in the predictive risk on the external dataset. **Conclusion:** LSM on elastography is associated with HCC risk in patients with MASLD, and is useful to identify patients at higher risk of HCC, to target for surveillance. Annual HCC risk appears to be higher than 0.4% in patients with LSM >16.2 kPa, and surveillance may be cost effective in these patients.



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0226 | SELECTIVE ABLATION OF FXR IN NEURONS IS NEUROPROTECTIVE IN A MOUSE MODEL OF ACUTE LIVER FAILURE

Kathryn Rhodes[1] Juliet Venter[1] Patrick Mireles[1] Gabriel Frampton[1] Matthew McMillin[2] Sharon DeMorrow[1]

[1]University of Texas at Austin, [2]Baylor College of Medicine, Temple

Background: Hepatic encephalopathy (HE) describes a spectrum of neurological and cognitive disturbances due to acute and chronic liver disease. Associated with HE is a buildup of ammonia, astrocyte swelling and neuroinflammation, however our understanding of the pathogenic mechanisms of HE is limited. We have demonstrated that the nuclear receptor, FXR, is activated in the frontal cortex in a mouse model of Type A HE and that strategies to block FXR in this region attenuated HE. However, whether FXR is activated in other brain regions impaired in HE and whether neuron-specific ablation of FXR signaling is also protective is unclear and thus are the aims of this study. **Methods:** Male and female C57/Bl6 (WT), floxed FXR (FXRfl/fl) and neuron-specific FXR knockout mice (FXRΔneu) were injected with azoxymethane (AOM) to induce acute liver failure (ALF) and HE. Cognitive impairment was monitored by reflex response assessment at various time points. Neuromuscular deficits were assessed using a grip strength meter and rotarod and a digigait analysis system was utilized to measure ataxia. The expression and nuclear translocation of FXR was assessed in the frontal cortex, hippocampus and cerebellum by qPCR, and immunofluorescence. Liver damage was assessed by hematoxylin and eosin staining and serum chemistry. Ammonia accumulation in the liver and brain was assessed by Nessler staining. Microglia were stained with IBA1 and field staining and cell morphology were assessed. Proinflammatory cytokine expression was assessed by immunoblotting, immunohistochemistry and/or qPCR. **Results:** FXR expression and nuclear translocation were increased in all brain regions studied in AOM-treated male and female WT and FXRfl/fl mice, which correlated with neurological and neuromuscular deficits associated with HE. While similar liver damage was observed in AOM-treated FXRΔneu mice, the neurological and neuromuscular deficits were attenuated when compared to AOM-treated FXRfl/fl control mice. This protective phenotype of FXRΔneu mice was not associated with alterations in ammonia, as brain ammonia increased to a similar degree in all mouse strains. However, neuron-specific FXR knockout mice had reduced AOM-induced microgliosis in all brain regions assessed and reduced percentage of reactive microglia based on cell morphological analysis and decreased proinflammatory cytokine expression. **Conclusion:** These data suggest that neuronal ablation of FXR expression in neurons attenuated the neurological and neuromuscular deficits and neuroinflammation associated with Type A HE, without altering the underlying liver damage and ammonia accumulation in the brain.

Disclosures: Kathryn Rhodes: Nothing to Disclose, Juliet Venter: Nothing to Disclose, Patrick Mireles: Nothing to Disclose, Gabriel Frampton: Nothing to Disclose, Matthew McMillin: Nothing to Disclose, Sharon DeMorrow: Nothing to Disclose

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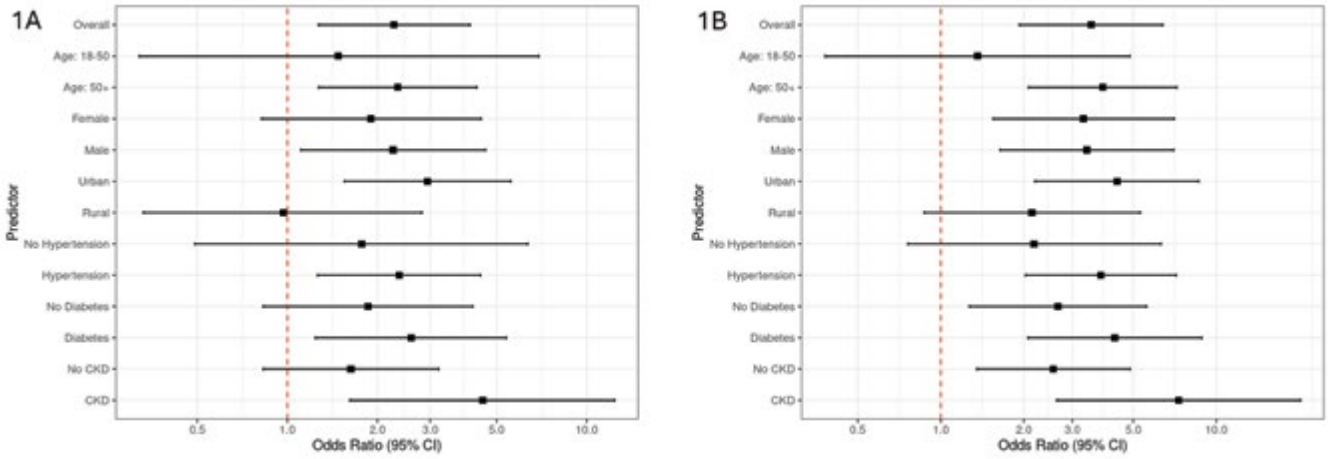
0227 | DETECTION OF UNDIAGNOSED LIVER CIRRHOSIS VIA ARTIFICIAL INTELLIGENCE-ENABLED ELECTROCARDIOGRAM (DULCE): A PRAGMATIC, CLUSTER-RANDOMIZED CLINICAL TRIAL

Douglas Simonetto[1] David Rushlow[2] Alberto Calleri[2] Puru Rattan[2] Joseph Ahn[2] Blake Kassmeyer[2] Ryan Lennon[2] Kan Liu[2] Itzhak Attia[2] Amy Olofson[2] Xiaoxi Yao[2] Alina Allen[1] Paul Friedman[2] Peter Noseworthy[2] Vijay Shah[1]

[1]Mayo Clinic Rochester, [2]Mayo Clinic

Background: It is estimated that 1-2% of general population have undiagnosed advanced chronic liver disease (ACLD). Thus, novel noninvasive and accessible screening tools are needed in primary care settings. Artificial intelligence-enabled models demonstrate potential but have not yet been investigated in clinical trials. We conducted a pragmatic clinical trial to assess whether an electrocardiogram (ECG)-based convoluted neural network allows for early detection of ACLD in primary care. **Methods:** In this trial (NCT05782283), 98 primary care teams from 45 clinics or hospitals were cluster-randomized to intervention (access to DULCE results; 123 clinicians), or usual care (122 clinicians). Randomization was stratified by region and patient volume. Clinicians in the intervention arm were notified of a DULCE-positive ECG, indicating a higher risk of ACLD. Patients with prior diagnosis of ACLD were excluded. Primary endpoint was new diagnosis of ACLD within 180 days of ECG, as determined by clinically available noninvasive liver disease assessment (NILDA). Analysis of the primary outcome was conducted using a mixed-effects model with a logit link to test differences in the incidence between the study arms. **Results:** A total of 15,596 adults underwent 12-lead ECGs as part of their routine care during the study period and met inclusion criteria (N=8,034 intervention; N=7,562 control). Baseline demographics were similar between the groups. The overall cohort included 53.6% women, mean age 63.4 (SD 18.3), mean BMI 35.3 (SD 12.4), and 37% of subjects had diabetes. The intervention significantly increased the new diagnoses of ACLD in the overall cohort (0.6% in the intervention arm, 0.3% in the control arm; odds ratio [OR] 2.27; 95% CI 1.27-4.07; p = .006) (Figure 1A). Among those identified as high risk based on a positive DULCE score, ACLD was more frequent in the intervention arm (3.0% versus 0.8%; OR 4.53; 95% CI 1.86- 11.03; p < .001). The intervention also increased the detection of any liver fibrosis (mild/severe) in the overall cohort (1.3% versus 0.4%; OR 3.51 (1.93-6.39; p < .001) (Figure 1B) and among those with positive DULCE score (6.3% versus 0.8%; OR 8.82 (3.59-21.68; p < .001). Completion of NILDA or liver biopsy was significantly greater (p < .001) in the intervention group (2.9%) compared to the control arm (1.3%). **Conclusion:** The results of this pragmatic trial demonstrate that a machine learning algorithm based on 12-lead ECG may aid in the early diagnosis of advanced chronic liver disease in routine primary care settings.



Disclosures: Douglas Simonetto: Consultant relationship with BioVie; Has ended; Consultant relationship with Iota; Has ended; Consultant relationship with Mallinckrodt; Has ended; Consultant relationship with Resolution Therapeutics; Has ended; Consultant relationship with Evive; Has ended, David Rushlow: Anumana: inventor of [an unrelated] technology licensed to Anumana, Alberto Calleri: Nothing to Disclose, Puru Rattan: Nothing to Disclose, Joseph Ahn: No Relevant Financial Relationships, Blake Kassmeyer: Nothing to Disclose, Ryan Lennon: Nothing to Disclose, Kan Liu: Nothing to Disclose, Itzhak Attia: Nothing to Disclose, Amy Olofson: Nothing to Disclose, Xiaoxi Yao: Nothing to Disclose, Alina Allen: Grant/Research Support relationship with

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Astra Zeneca; Has not ended; Grant/Research Support relationship with Oncoustics; Has not ended; Grant/Research Support relationship with Escopics; Has not ended; Advisor relationship with GSK; Has ended; Advisor relationship with Madrigal; Has not ended; Advisor relationship with Boehringer Ingelheim; Has not ended; Grant/Research Support relationship with Pfizer; Has ended; Grant/Research Support relationship with Target Pharma; Has not ended; Advisor relationship with Novo Nordisk; Has not ended; Grant/Research Support relationship with Novo Nordisk; Has not ended, Paul Friedman: Nothing to Disclose, Peter Noseworthy: Nothing to Disclose, Vijay Shah: Boehringer Ingelheim: Consultant, GSK: Consultant, GENFIT SA: Consultant, Intercept Pharmaceuticals, Inc.: Advisor, Korro Bio, Inc.: Consultant, Mallinckrodt Pharmaceuticals: Advisor, Novo Nordisk A/S: Consultant, Resolution Therapeutics, Ltd.: Advisor, Seal Rock Therapeutics, Ltd.: Consultant, Surrozen: Advisor

0228 | VALUE-BASED PRICING OF RESMETIROM FOR THE TREATMENT OF METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE: A COST-EFFECTIVENESS ANALYSIS

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Background: Resmetirom can slow fibrosis progression and improve resolution of metabolic dysfunction-associated steatohepatitis (MASH), but drug cost could impede uptake. We estimated the cost-effectiveness of resmetirom vs. no treatment and determined a price at which resmetirom would be cost-effective. **Methods:** We developed an agent-based state transition model with a yearly cycle to follow 100,000 patients with MASH and F2/F3 for life. The model included 16 distinct histologically defined health states: no steatosis, metabolic dysfunction-associated steatotic liver (MASL) or F0, MASH, fibrosis F1-F3 with or without MASH, cirrhosis (F4), decompensated cirrhosis, liver cancer, transplant, and liver-related and other-cause death. Compared to no treatment, resmetirom group hastened fibrosis regression and MASH resolution and slowed fibrosis progression. Treatment was assumed for life unless patients entered F4 or more advanced states or discontinued for other reasons (20% annually in base-case, ranging 0%-20% in sensitivity analysis). Model inputs were derived from published data. Outcomes included costs (in 2023$) and quality-adjusted life years (QALYs). Incremental cost-effectiveness ratio (ICER) was calculated as incremental costs divided by incremental QALYs. Base-case drug price was $19,011/year; maximum price was determined based on willingness-to-pay of $100,000 and $150,000 per QALY. The analysis was conducted from health system perspective. Outcomes were discounted at 3% annually. **Results:** Compared to no treatment, resmetirom led to a gain of 0.3183 QALY/patient. The drug cost $58,844 and treatment saved $20,679 in MASLD-related medical costs for a total incremental cost of $38,164/patient and ICER of $119,893/QALY. To be cost-effective at $100,000 and $150,000 per QALY, resmetirom's annual price could not exceed $16,965 and $22,107, respectively. The lower the discontinuation rate, the greater the effectiveness and savings from medical costs, but also the higher the total treatment costs. Without discontinuation, the ICER would be $286,441/QALY, supporting a price between $8,736 and $11,498 per year. **Conclusion:** In the base-case, resmetirom was cost-effective at $150,000/QALY threshold. Depending on the discontinuation rate and willingness-to-pay, the cost-effective annual price ranged from $8,736 to $22,107. Model assumptions could have significant impacts on the cost-effectiveness, but our study provided estimates for resource allocation for MASH therapy.

Disclosures: Phuc Le: Nothing to Disclose, Srinivasan Dasarathy: Nothing to Disclose, William Herman: Merck Sharp & Dohme: Advisor, Rivus Pharmaceuticals: Advisor, Wen Ye: Nothing to Disclose, Nicole Welch: Nothing to Disclose, Victoria Criswell: Nothing to Disclose, Michael Rothberg: Moderna: Stock - publicly traded company

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0229 | PLASMA LIPIDOMIC AND FUNGAL PEPTIDE-BASED COMMUNITY ANALYSIS IDENTIFIES DISTINCT SIGNATURES OF EARLY MORTALITY IN ACUTE LIVER FAILURE

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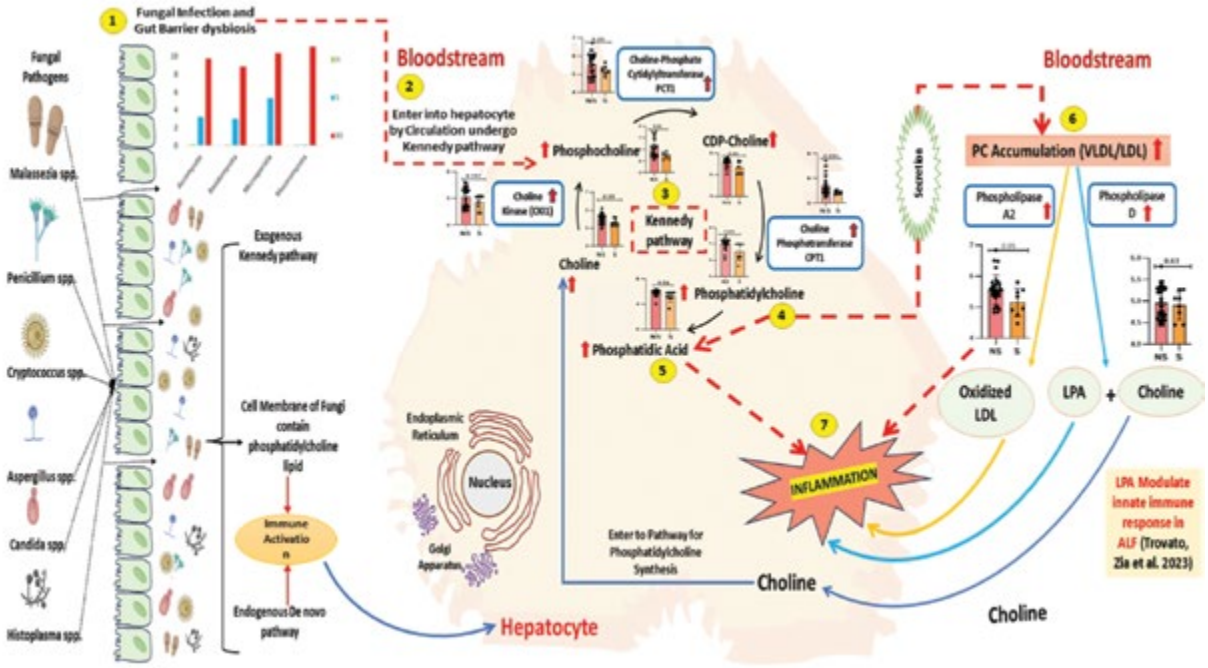
Background: Acute liver failure (ALF) is a rapidly progressive disease with high mortality. Severe hepatocellular injury disrupts metabolism, weakens immunity, and can compromise the gut barrier, raising susceptibility to infections. Lipidomic changes and fungal infections are known to be correlated, and can influence outcome of ALF **Methods:** We studied lipidome landscape and fungal peptide-based community analysis (mycobiome) in the plasma samples of 270-ALF and 30-healthy subjects [40 and 5 in the derivative and 230 (146 non-survivors and 84 survivors) and 25 in the validation cohort]. High-resolution-mass-spectrometry-(HRMS) followed by artificial neural networking (ANN), machine learning-(ML), weighted lipid/fungal correlation network analysis (WL/FCNA) was done to correlate with disease severity and outcome. **Results:** Untargeted lipidomics identified 2,013 lipid species and lipid-like metabolites across 8 lipid groups in plasma. Among these, 5 lipid species [Phosphatidylcholine; PC(15:0/17:0), PC(20:1/14:1), PC(26:4/10:0), PC(32:0), and TG(4:0/10:0/23:6)] significantly differentiated ALF non-survivors (FC>10, p<0.05, FDR<0.01). Fungal peptide-based diversity (Alpha/Beta diversity) was significantly higher and showed 4 phyla and >20 species significantly dysregulated in non-survivors (p<0.05). Fungal peptide specific in non-survivors were linked with lipid-metabolism, fatty acid elongation in endoplasmic reticulum and others (p<0.05). Non-survivors showed strong correlation between Shannon-lipid and Shannon-fungal diversity profile (r^2>0.7, p<0.05). Multi Modular Correlation Network (MMCN) analysis showed striking associations between lipid, fungal-peptides modules, functionality and clinical parameters distinct in non-survivors(p<0.05). Increased Basidiomycota; *Trametes pubescens*, *Cryptococcus amylolentus CBS6039*, Ascomycota; *Penicillium oxalicum1142*, *Cladophialophora bantiana CBS173.52* and their functionality directly correlated with lipid classes such as phosphatidylcholine and triglyceridesin non-survivors S(r^2>0.85, p<0.05). Probability of Detection (POD)-lipid showed direct association with hepatic encephalopathy whereas POD-fungus was associated with infection, necrosis and multi-organ-failure (Beta>1.2, p<0.05). POD-Lipid (AUC=0.969) superseded POD-Mycobiome with HR=1.5(1.021-1.844) for early mortality. Finally, POD-lipid >25% along with increased phosphatidylcholine (15:0/17:0) level showed highest normalized importance and predicted early mortality with >95% accuracy/sensitivity/specificity using ANN and machine learning. **Conclusion:** Plasma lipidome and mycobiome profile are markedly dysregulated in ALF patients. Increased plasma level of phosphatidylcholine is an early predictor of mortality and need for urgent liver transplant in ALF patients.



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0230 | LIVER-DIRECTED GENE THERAPY NORMALIZES TOXIC BILE ACID METABOLITE LEVELS IN THE BLOOD AND BRAIN OF MICE WITH CEREBROTENDINOUS XANTHOMATOSIS

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Background: Cerebrotendinous xanthomatosis (CTX) is an autosomal recessive disease caused by mutations in the *CYP27A1* gene, that encodes for the sterol 27-hydroxylase, essential for the conversion of cholesterol to bile acids. Loss-of-function mutations in *CYP27A1* lead to the accumulation of toxic precursors, such as 7 alpha-hydroxy-4-cholesten-3-one (7αC4) and cholestanol, in blood, eyes, tendons and brain, resulting in the formation of cataracts, xanthomas and neurodegeneration. The standard treatment is chenodeoxycholic acid, which reduces the levels of toxic metabolites but does not always prevent neurodegeneration leaving an unmet medical need. Liver-directed gene therapy is a valuable alternative for CTX patients, since published data showed a correction of disease biomarkers upon *CYP27A1* gene supplementation using an adeno-associated virus (AAV) serotype 8 in CTX mice. **Methods:** To develop an AAV vector with high potency and low immunogenicity, several optimized *CYP27A1* expression cassettes containing a liver-specific promoter were designed with a) three codon-optimized transgene sequences depleted of CpG motifs to avoid the potential activation of an innate immune response and b) addition of regulatory elements: minute virus of mice small intron (MVM) and Woodchuck Hepatitis Virus post-transcriptional regulatory element (WPRE). The optimized expression cassettes were tested *in vitro* and AAV8 vectors were generated with the selected sequences and tested *in vivo*. **Results:** Transfection of Huh7 cells with the different plasmids allowed to select the best two candidates. Next, the therapeutic efficacy of the selected candidates AAV8-CYP27A1co1 and AAV8-MVM-CYP27A1co1-WPRE was tested at different doses and compared to an AAV8 vector carrying the WT sequence of *CYP27A1,* in CTX mice. Inclusion of the regulatory elements to enhance expression did not bring any benefit *in vivo*. However, both *in vitro* and *in vivo* results showed higher CYP27A1 expression with VTX-806(8), candidate bearing the codon-optimized version of the transgene. Treatment with VTX-806(8) restored normal levels of circulating 7αC4, expression of hepatic bile acid synthesis-related genes and corrected hepatomegaly. Most importantly, normal levels of 7αC4 in the brain of CTX mice were restored. **Conclusion:** These results showed for the first time that liver-directed AAV gene therapy can normalize the levels of toxic metabolites in the brain of CTX mice and thus may offer an effective curative treatment option for CTX patients.

Disclosures: Gloria Gonzalez-Aseguinolaza: Vivet therapeutics: Executive role, Vivet therapeutics: Stock – privately held company, Angie Molina: Nothing to Disclose, LAIA Trigueros-Motos: Nothing to Disclose, Guiomar Perez: Nothing to Disclose, Manuela Molina: Nothing to Disclose, Irene Marcilla-Garcia: Nothing to Disclose, Leire Neri Valencia: Nothing to Disclose, Anne Douar: Vivet therapeutics: Employee, Jean-Philippe Combal: Nothing to Disclose, Blanche Tamarit: Vivet Therapeutics: Employee, Pranvera Krasniqi: Nothing to Disclose, Antonin Lamaziere: Nothing to Disclose, Ruben Hernandez-Alcoceba: Nothing to Disclose

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0231 | SPLEEN STIFFNESS IS RELIABLE IN ASSESSING HEMODYNAMIC RESPONSE AND PREDICTION OF REBLEEDING ON BETA-BLOCKER THERAPY FOR SECONDARY PROPHYLAXIS OF VARICEAL BLEED-BETA-RESPONSE STUDY

Akhil Deshmukh[1] Manoj Kumar[1] Ashok Kumar Choudhury[1] CHITRANSHU VASHISHTHA[1] Ankur Jindal[1] Vishnu Girish[1] Tushar Madke[1] Rahul khajuria[1] Shiv Kumar Sarin[1]

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Background: Prevention of variceal rebleed after acute variceal bleeding (AVB) is achieved by the reduction in portal pressure by nonselective beta-blocker (NSBB) therapy. Response to NSBB is assessed by hepatic vein pressure gradient (HVPG) measurement (≤ 12 mmHg or reduction by ≥20% from baseline). We evaluated the efficacy of non-invasive tests (NITs), namely liver and spleen stiffness (LS, SS) post-AVB using transient elastography, as non-invasive correlates of HVPG for treatment response and rebleed. **Methods:** 220 cirrhotic patients with AVB were prospectively assessed using HVPG, LS, and SS within 5 days post-bleed when carvedilol (starting at 6.25 mg/day and escalated to achieve a target heart rate of 55-60bpm) therapy was started. LS and SS were measured at 0, 3, and 6 weeks, while HVPG, at 0, 6 weeks. Rebleed was recorded for up to 90 days. Our primary objective was to determine the diagnostic accuracy of NITs in predicting NSBB response at 6 weeks. The secondary objectives were to correlate NIT and HVPG response, & correlation with rebleed, clinical outcomes, and mortality. Drug compliance was closely monitored. **Results:** The study population [age 49.56 ± 10.34 years, 91.4% male, dominantly ethanol (45%) and NAFLD (40%)] had a mean MELD score of 15.13 **±** 2.75. The mean dose of carvedilol used was 11.91±2.03mg per day. At 6 weeks, there were 86 (39%) HVPG responders. The predictive accuracy of SS for HVPG response at 6 weeks was higher (AUROC 0.84) than LS (AUROC 0.78). In fact, at 3 weeks, SS was highly reliable in predicting HVPG response (AUROC 0.81). Rebleeding occurred in 31 (14.36%) patients, dominantly in HVPG non-responders than responders (18.6% vs 7.1%; P=0.027). Furthermore, an increase in SS by 8% (5.5Kpa) from baseline at 6 weeks predicted rebleed. None of the patients with HVPG ≤12 mm of Hg at 6 weeks rebled within follow-up period. **Conclusion:** Spleen stiffness post-AVB offers a valuable tool to assess response to carvedilol therapy; and can be used as an alternative to HVPG measurement. SS had high predictive ability to identify carvedilol non-responders. Serial SS measurements offer an opportunity to know NSBB response at 3 weeks and can guide to increase the dose or add additional agents to reduce portal pressure.

Table 1: Performance characteristics of NITs for assessing HVPG response to carvedilol.

Statistical method	LSM(3wks)	SSM(3wks)	LSM(6wks)	SSM(6wks)	LSPS	SSPS	APRI	Platelet	Forn Index
Co-efficient(B)(Kpa)	1.39	1.69	1.68	2.14	0.52	0.69	0.08	1.96	0.097
R	0.21	0.38	0.23	0.47	0.22	0.21	0.12	0.4	0.14
r^2	0.04	0.14	0.05	0.22	0.05	0.04	0.01	0.22	0.02
Value cutoff(Kpa)	0.26	2.65	2.85	9.5	0.7	1.35	0.15	1	0.15
Cut-off(%)	0.93	3.07	4.6	10.27	10.05	12.11	8.04	1	3.15
AUROC	0.76	0.81	0.78	0.84	0.67	0.68	0.59	0.6	0.61
Sensitivity	73	75	75	73	52	53	56	53.5	60
Specificity	77	82	74	80	40	38	57	59	62
PPV	66	72	64	69	35	35	44	44.5	51
NPV	82	84	83	82.5	58	57	67.5	67	71
Accuracy	75	79	74.5	77	45	44	56	57	0.56
Youden Index	0.5	0.57	0.49	0.53	0.08	-0.9	0.13	0.12	0.22

Abbreviations: LSM: Liver Stiffness Measurement; SSM: Spleen Stiffness Measurement; LSPS: Liver Stiffness to Platelet Ratio Score; SSPS: Spleen Stiffness to Platelet Ratio Score; APRI: AST to Platelet Ratio Index; PPV: Positive Predictive Value; NPV: Negative Predictive Value; AUROC: Area Under the Receiver Operating Characteristic; r: Correlation Coefficient; r^2: Coefficient of Determination

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0232 | AN ULTRASOUND APPROACH TO VISUALIZE THE &LDQUO;DUCT AT THE HILUM&RDQUO; IN INFANTS UNDERGOING EVALUATION FOR BILIARY ATRESIA ★

Ashley Upton[1] J. Alberto Hernandez[1] Benjamin Shneider[1] Sridevi Devaraj[1] Kalyani Patel[1] Sanjeev Vasudevan[1] Adam Vogel[1] Sanjiv Harpavat[1]

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Background: Clinicians often use fasting ultrasound exams to evaluate infants for biliary atresia. However, ultrasound findings can be inconclusive and often do not prevent the need for more invasive diagnostic tests. To address this problem, we asked if another ultrasound finding—absence of the extrahepatic bile duct at the liver hilum (the "duct at the hilum")—could be useful. **Methods:** Ultrasound exams were reviewed from infants evaluated for biliary atresia at Texas Children's Hospital during 2 periods. First, exams performed before 2021 were reviewed, to develop a systematic approach to visualize the duct at the hilum. Second, exams performed during a subsequent 26 month period were reviewed, to assess the approach's diagnostic performance. All ultrasounds in the second period were performed by a single sonographer (AU) using a General Electric LOGIQ E10 machine with standard probes. **Results:** We first reviewed earlier ultrasound exams to develop a 4 step approach to visualize the duct at the hilum (Figure). This approach includes locating the pancreatic head to ensure an extrahepatic position (step 2), visualizing the duct lengthwise rather than in cross-section to avoid artifacts (step 4), and feeding infants to make the duct more prominent. We next assessed the approach on 64 sequential infants undergoing evaluation for biliary atresia. They were 39.1% female (n=25), 57.8% white (n=37), and 46.9% Hispanic (n=30), with a median age and weight of 25 days (range 0-170) and 3.2 kg (range 1.0-6.3), respectively. When performed during or immediately after feeding, the approach identified all 12 infants eventually diagnosed with biliary atresia. The approach excluded 49 of 52 infants eventually found not to have biliary atresia, including patients with Alagille Syndrome (n=5), alpha-1 antitrypsin deficiency (n=1), panhypopituitarism (n=2), and a portosystemic shunt (n=1). In 75.5% of cases without biliary atresia (n=37), the approach was completed in less than 5 minutes. **Conclusion:** We present a systematic approach to visualize the duct at the hilum, which has 3 major advantages compared to current ultrasound protocols: (i) it does not require fasting; (ii) it quickly identifies infants who may have biliary atresia, which can help avoid delays in treatment; and (iii) it efficiently excludes many infants without biliary atresia, which can prevent the need for more invasive testing. Future multi-site studies are needed to test how the approach performs in larger populations and in different healthcare settings.



Disclosures: Ashley Upton: Nothing to Disclose, J. Alberto Hernandez: Nothing to Disclose, Benjamin Shneider: Nothing to Disclose, Sridevi Devaraj: Nothing to Disclose, Kalyani Patel: Nothing to Disclose, Sanjeev Vasudevan: Nothing to Disclose, Adam Vogel: Nothing to Disclose, Sanjiv Harpavat: Syneos Health: I sit on a Data Safety Monitoring Board

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0233 | DECODING AND TARGETING HEPATOCYTE SENESCENCE IN MASLD: FROM IDENTIFICATION TO TREATMENT ◆

Kuo Du[1] Liuyang Wang[2] Rajesh Dutta[2] Ji Hye Jun[2] Seh-Hoon Oh[1] Anna Mae Diehl[1]

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Background: Senescent hepatocytes accumulate in MASLD livers and correlate with adverse outcomes. However, identifying and characterizing these cells, particularly at the single-cell level, is challenging due to the heterogeneous nature of senescent cells and the lack of specific and reliable markers. Consequently, the characteristics of senescent hepatocytes remain undefined, and their impact on MASLD progression is unclear. This study aims to identify, characterize, and target senescent hepatocytes for MASLD treatment. **Methods:** Hepatocyte senescence was induced in Huh7 cells using a CDK4/6 inhibitor and in primary hepatocytes through selective Kras overexpression via hydrodynamic tail vein injection of NRASG12V in mice. By overlapping the transcriptomes of these datasets, we identified a senescent hepatocyte gene signature (SenDuke) comprising 100 DEGs. Deconvolution analyses using SenDuke were performed on diverse bulk MASLD RNA-seq datasets to examine its association and prognostic potential in MASLD progression, as well as on mouse and human snRNA-seq datasets to identify and characterize senescent hepatocytes at the single-cell level. The paracrine effects of senescent hepatocytes were studied by applying conditioned medium to proliferating hepatocytes, HSCs, macrophages, and LSECs. A bioactive chemical library screening was conducted to identify novel senolytic hits, which were further validated in vitro and in mouse MASLD models **Results:** SenDuke strongly associates with MASLD severity across diverse patient cohorts and tracks with clinical intervention outcomes such as bariatric surgery and statin treatment. SenDuke reliably identified senescent hepatocytes at the single-cell level, revealing that ~6% of hepatocytes are senescent in fibrotic MASLD liver, compared to less than 0.1% in healthy controls. These senescent hepatocytes lost mature functions and exhibited a pro-inflammatory and pro-fibrogenic SASP phenotype. The conditioned medium from senescent hepatocytes induced secondary senescence in proliferating hepatocytes and promoted HSC fibrogenesis, macrophage activation, and LSEC capillarization. Bioactive chemical library screening identified several senolytic candidates that successfully reduced senescent cell burden and decreased liver inflammation and fibrosis in mouse MASLD models. **Conclusion:** Hepatocyte senescence is a central pathogenic mechanism in MASLD development. SenDuke is a potentially clinically applicable panel for monitoring MASLD development and clinical intervention outcomes. Our novel senolytics alleviate senescent hepatocyte burden and improve MASLD in mice. These findings lay the groundwork for future studies to exploit cellular senescence as both a prognostic marker and therapeutic strategy for treating liver diseases, including MASLD.

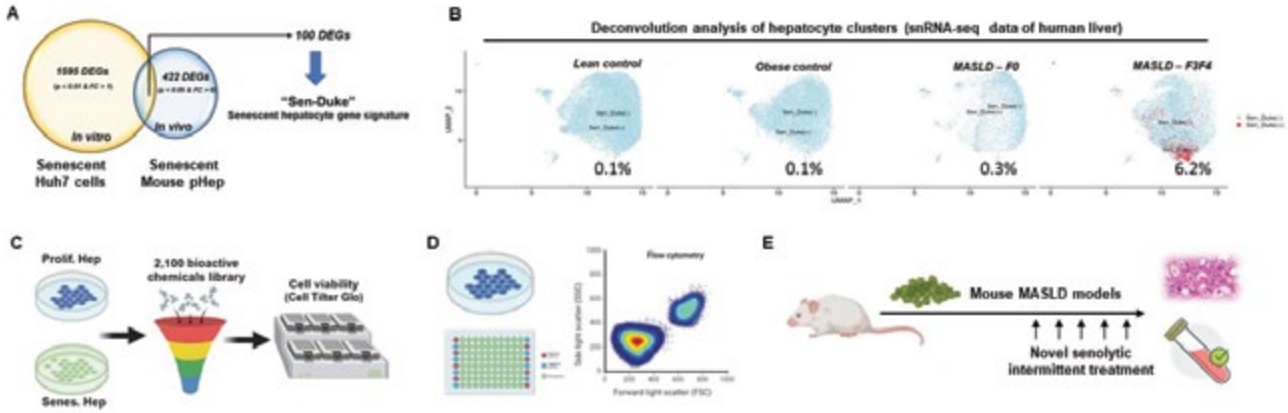

Fig.1 Work flow. **A.** Construction of senescent hepatocyte gene signature (SenDuke); **B.** Identification and characterization of senescent hepatocytes from MASLD liver; **C.** Bioactive chemical screening for novel senolytics. **D.** *In vitro* validation of senolytic effects; **E.** Validation of senolytics in mouse MASLD models.

Disclosures: Kuo Du: Nothing to Disclose, Liuyang Wang: Nothing to Disclose, Rajesh Dutta: Nothing to Disclose, Ji Hye Jun: Nothing to Disclose, Seh-Hoon Oh: Nothing to Disclose, Anna Mae Diehl: >$10,000 relationship with Tune Therapeutics; Has not ended; <$10,000 relationship with Boehringer Ingelheim; Has not ended; Associate Editor, < $10,000 relationship with EASL - Journal of Hepatology; Has not ended; >$10,000 relationship with HeptaBio; Has not ended

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0234 | THE ROLE OF SIRT2 AND DOWNSTREAM SIGNALING IN HEPATOCELLULAR CARCINOMA PROGRESSION ★

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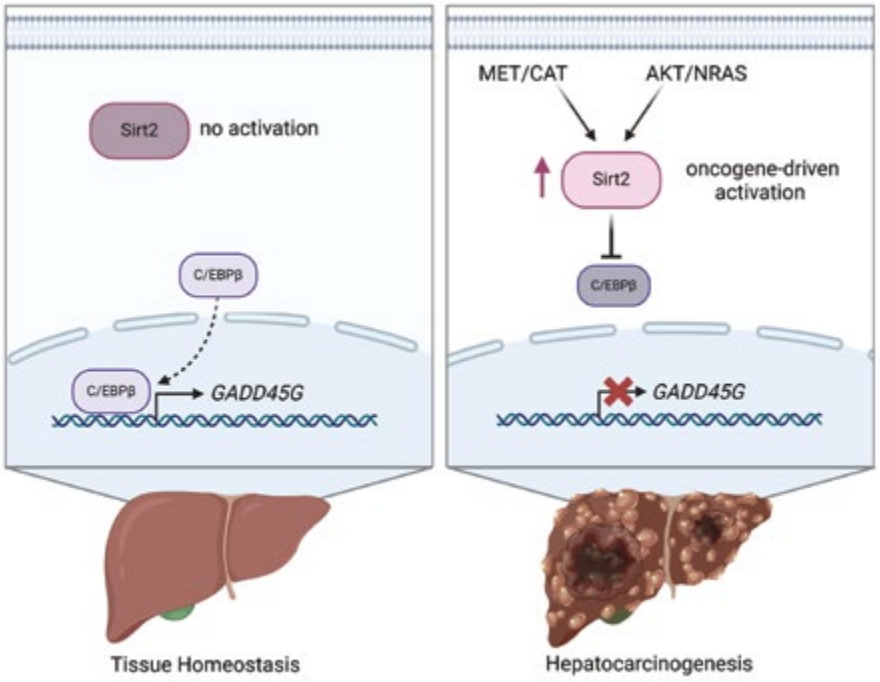
Background: There is a significant gap in our understanding of mechanisms underlying the promotion of hepatocellular carcinoma (HCC), and this greatly limits our ability to treat HCC in the clinic. In particular, the lack of targetable protein drivers prevents us from practicing personalized medicine in HCC. NAD-dependent deacetylase sirtuin 2 (Sirt2), is a deacetylase that functions to remove acetyl marks from proteins, which can have varied downstream effects including enhancing protein activation and suppressing gene transcription in the liver. In TCGA HCC samples, Sirt2 levels are increased compared to normal liver tissue, and this increase is associated with a significantly worse prognosis. Other groups have reported Sirt2 as a driver of HCC, but the role of Sirt2 in hepatocarcinogenesis *in vivo* and the downstream mechanisms remain poorly understood. **Methods:** To assess the role of Sirt2 in hepatocarcinogenesis, we used a liver-specific knockout of Sirt2 compared to Sirt2 WT controls. We employed two plasmid overexpression HCC models: MET/CAT and AKT/Nras. Subsequent RNA-sequencing of mouse liver tissue was performed, and mechanistic findings were confirmed using IHC, qPCR, western blot, and CCK-8 assays. **Results:** Using the MET/CAT and AKT/Nras overexpression-driven model of HCC, we found that Sirt2 is a significant mediator of liver tumorigenesis, with the liver-specific knockout of Sirt2 delaying the growth of tumors. RNA-sequencing of tumor tissue driven by MET/CAT overexpression showed an increase in GADD45g in liver-specific Sirt2 knockout mice compared to WT. GADD45g, or growth arrest and DNA-damage-inducible protein gamma, is a known tumor suppressor in HCC, but the regulation of GADD45g by Sirt2 has not been shown. C/EBP family proteins have been shown to regulate GADD45g expression, and we found that C/EBPb expression was increased in *Sirt2* knockout livers and Sirt2 knockdown HCC cells. In addition, C/EBPb knockdown reversed the increased expression of GADD45g and cell growth suppression expected following Sirt2 inhibition. Furthermore, C/EBPb overexpression significantly suppressed MET/CAT-induced HCC development. **Conclusion:** In conclusion, Sirt2 is a potent tumor promotor in HCC that negatively regulates the expression of GADD45g through regulating C/EBPb. The characterization of the Sirt2-C/EBPb-GADD45g pathway in HCC helps us to better understand underlying mechanisms in HCC and establishes that targeting Sirt2 may be a viable personalized therapeutic option for patients with HCC.



Disclosures: Claudia Rose Keating: Nothing to Disclose, Fang Wang: Nothing to Disclose, Wei Qiu: Nothing to Disclose

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0235 | WITH NO LYSINE KINASE 1 (WNK1)-MEDIATED METABOLISM PROMOTES HEPATIC STELLATE CELL ACTIVATION IN A SPATIAL MANNER DURING *IN VIVO* LIVER FIBROSIS

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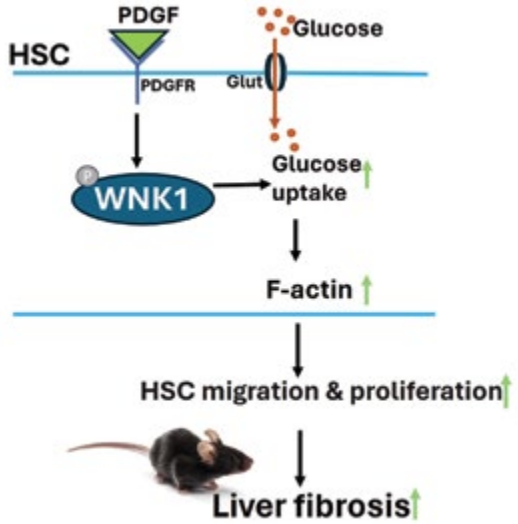
Background: Hepatic stellate cell (HSC) proliferation and migration, induced by platelet-derived growth factor B (PDGF), are hallmarks of liver fibrosis. HSC activation correlates with an increase in glycolysis. However, the kinase signaling leading to glycolysis in HSCs remains unknown. Thus, the aim of this study is to unveil new PDGF signaling targets that drive HSC metabolism and liver fibrosis. **Methods:** *In vitro,* human phospho-kinase proteomic array, glucose-glo™ assay, transwell migration assay, siRNA transfection, KI67 immunofluorescence (IF), qPCR and western blot (WB) were performed utilizing primary human HSCs. *In vivo,* liver fibrosis was induced by carbon tetrachloride (CCl_4). With no lysine kinase 1 (WNK1) was pharmacologically inhibited with WNK-IN-11 or WNK463. Livers were analyzed by spatial transcriptomics (ST, GSE259363) and WB. **Results:** To identify novel kinases involved in HSC activation, human phospho-kinase array was performed. In addition to the canonical kinases, PDGF increased the phosphorylation of WNK1 4-fold (n=4, p<0.05). Since glycolysis is increased in activated HSCs, we examined the role of WNK1 on glucose consumption. WNK1 inhibitor, WNK-IN-11, decreased PDGF-mediated glucose consumption (Glucose-Glo™, n=5, p<0.05), suggesting that WNK1 promotes glucose uptake in HSCs. Functionally, WNK1 inhibition by WNK-IN-11 or siRNA significantly decreased PDGF-induced HSC proliferation (KI67 IF, 2-fold n=3 p<0.005 and 1.9-fold n=3 p<0.05, respectively) and migration (transwell assay, 2.1-fold n=3 p<0.005 and 2.5-fold n=3 p<0.05, respectively). To understand how WNK1 promotes HSC migration, actin polymerization was examined. WNK-IN-11 significantly decreased PDGF-mediated phalloidin levels 1.5-fold (n=5, p<0.05) and F to G-actin ratio 2-fold (WB, n= 5, p<0.05). Actin polymerization was also reduced 1.7-fold when glucose transporters (GLUTs) were inhibited in HSCs (n=6, p<0.05). These data suggest that WNK1 and GLUTs are involved in actin polymerization in HSCs. *In vivo*, WNK1 expression was 1.5-fold upregulated in the collagen-high areas in CCl_4-treated fibrotic livers as compared to healthy condition (ST, adj.p=5.25E-36). In addition, CCl_4-mediated Sirius red staining, COL1α1 and αSMA protein levels (5.2-fold p<0.001, 3.4-fold p<0.05, 4.8-fold p<0.05, respectively) were significantly reduced by WNK1 inhibitors (5-10 mice/group, p<0.01). **Conclusion:** As a conclusion, WNK1 is a novel PDGF downstream kinase promoting glucose consumption, HSC proliferation and migration in a spatial manner during liver fibrosis.



Disclosures: Shalil Khanal: Nothing to Disclose, Abdul Aziz Timbilla: Nothing to Disclose, Lulu Lyu: Nothing to Disclose, Alexander Washington: Nothing to Disclose, Vijay Shah: Boehringer Ingelheim: Consultant, GSK: Consultant, GENFIT SA: Consultant, Intercept Pharmaceuticals, Inc.: Advisor, Korro Bio, Inc.: Consultant, Mallinckrodt Pharmaceuticals: Advisor, Novo Nordisk A/S: Consultant, Resolution Therapeutics, Ltd.: Advisor, Seal Rock Therapeutics, Ltd.: Consultant, Surrozen: Advisor, Enis Kostallari: Nothing to Disclose

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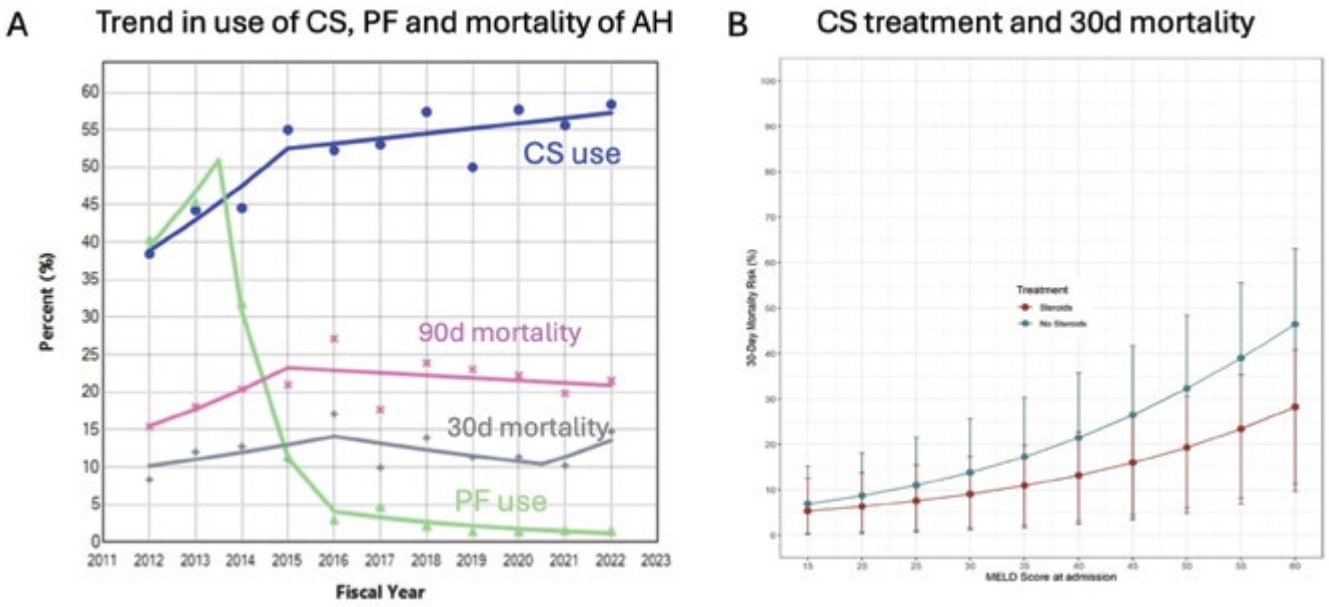
0236 | USE OF PHARMACOLOGICAL THERAPIES FOR ALCOHOL-ASSOCIATED HEPATITIS IN ALBERTA: IMPACT OF SHIFTING EVIDENCE AND GUIDELINE-BASED RECOMMENDATIONS ◆

Abdel Shaheen[1] Meng Wang[2] Juan Abraldes[3]

[1]University of Calgary, [2]Alberta Health Services, [3]University of Alberta

Background: Corticosteroids (CS) have been the standard treatment of Alcohol-Associated hepatitis (AH) for over 40 years. Limited evidence resulted in the common use of pentoxifylline (PF), especially in patients with contraindications for CS. While the STOPAH trial provided unequivocal evidence for lack of efficacy of PF, the non significant decrease in 1-month mortality with CS offered different interpretations. How those findings impacted AH management is not well known. Alberta is a single-payer healthcare system that could address this question. We aimed at evaluating the use of CS and PF for AH between 2012 and 2023, and to assess the impact of real-world use of CS treatment on 30d and 90d mortality. **Methods:** We examined all adult (≥18 years) patients who were hospitalized with AH between 2012-2023 and fulfilled the NIAAA criteria in Alberta, Canada. Discharge Abstract Database (DAD) was linked to the provincial laboratory database and the inpatient and outpatient pharmaceutical databases. Demographics, clinical and laboratory variables including MELD score were reported on admission date. Temporal trends were assessed using Joinpoint analysis. To assess the effect of real-word use of CS on 30d and 90d mortality, adjusted Cox regression models with CS use as a time-varying variable were used. **Results:** We identified 2706 admissions with AH between 2012-2023. In our cohort, 68% had a MELD ≥20. Joinpoint analysis identified two inflection points in the use of PF, a sharp decrease starting in 2014 (inflection point) with a residual use after 2016. For CS, there was an upward trend up to 2015 (inflection point), with a slight subsequent slow increase from 2016 onwards (Fig A). Both 30d and 90d mortality had a slow trend down from 2016 onward. Only 30-d mortality increased after the onset of COVID-19 pandemic. Patients treated with CS were younger, more frequently female, and had higher MELD than patients not treated with CS. After adjusting for disease severity and patient characteristics, patients treated with CS had a lower 30d (Fig B) and 90d mortality. There was an interaction between MELD and CS effect on mortality. Therefore, both in relative and absolute terms, the effect of CS was greater with greater severity of the disease. **Conclusion:** We report that after the release of the STOPAH trial **Results:** PF use diminished and CS continued to increase. In this large cohort of AH patients using real-world data, short-term mortality at 30d and 90d improved among patients using CS. Finally, the benefit from CS increases with the severity of the episode of AH.



Disclosures: Abdel Shaheen: Nothing to Disclose, Meng Wang: Nothing to Disclose, Juan Abraldes: Gilead: Grant/Research Support, 89bio: Consultant, Boston Pharmaceuticals: Consultant, Novo Nordisk: Consultant, Boehringer Ingelheim: Consultant, Astra Zeneca: Consultant, Agomab: Consultant, Terumo: Speaking and Teaching, Cook: Grant/Research Support

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0237 | IN VIVO SCREENING FOR TARGETS TO BLOCK IMMUNE ESCAPE IN HEPATOCELLULAR CARCINOMA ★

Chunmiao Cai[1] Dingzi Yin[1] Salah Adlat[1] Markcus Lee[1] Kirk Wangensteen[1] David Stokoe[2] Ari Firestone[2] Agnes Holczbauer[3]

[1]Mayo Clinic, [2]Calico Life Sciences, [3]University of Pennsylvania

Background: The advent of PD1-inhibitors has led to an incremental survival benefit in hepatocellular carcinoma. While only a subset of tumors respond to anti-PD-1 treatment alone, combination therapy targeting additional pathways can improve response rates. We aimed to leverage in vivo genetic screening to identify synergistic targets that can prevent immune escape by HCC. **Methods:** We built a CRISPR inhibition (CRISPRi) screening library targeting 2,773 genes that are expressed in cirrhosis, the precursor to HCC. We inserted gRNA sequences into a Sleeping Beauty transposon plasmid containing Fah to mediate liver repopulation and Myc to drive cell hyperproliferation, to mimic the cancer state. We hydrodynamicly injected through the tail vein the library of gRNA-expressing plasmids into Fah-/-;dCas9+ mice. We high-throughput sequenced gRNAs at the **Conclusion:** of the assay to identify genes that (1) gRNAs are significantly depleted (genes are essential for cell proliferation) within an activated immune system and (2) are novel, cancer-relevant, druggable and (3) the expression correlated with worse survival in tumors with high immune infiltration, through analysis on liver tumor samples extracted from The Cancer Genome Atlas Program (TCGA). **Results:** We hydrodynamicly injected a gRNA library that generated a transduction of up to one million unique hepatocytes (~1% of total). Four weeks later, the livers were 90% repopulated with dysplastic clusters of cells derived from the transduced hepatocytes. Whole liver tissue DNA was collected from mice for high throughput sequencing. By comparing to input and IgG treatment, we identified 461 significant depleted genes in immune-activated cohort treated with anti-PD-1 antibody. In an enhanced immune-activated cohort by adding Ova antigen, we identified 391 depleted genes, 92 of which overlap with the first cohort ($p < 0.0001$), indicating a reliable screening result. We further tested the screening by combining treatment of anti-PD-1 antibody with anti-CTLA4 antibody or GM-CSF, and identified 842 and 868 depleted genes respectively, with 173 ($p < 0.001$) and 186 ($p < 0.0001$) genes overlapping with the first cohort. We finalized a list of 28 depleted genes that do not have essential role in the in vitro screening of DepMap project and are cancer relevant. Among them, YBX1, IL1RAP and PHB1 are correlated with poor survival in tumors with high immune infiltration, but not in tumors with low immune infiltration. For the ongoing in vivo validation, we generated a mouse HCC model by injecting plasmid containing MYC, gRNA for mouse Trp53, and a single gRNA targeting each candidate gene. **Conclusion:** We herein established a reliable *in vivo* CRISPRi screening and discovered novel immune escape targets in mice HCC model by applying different combinations of immune therapies. The potential targets found in this study will advance the development of new combinatorial immune therapies for precision medicine.

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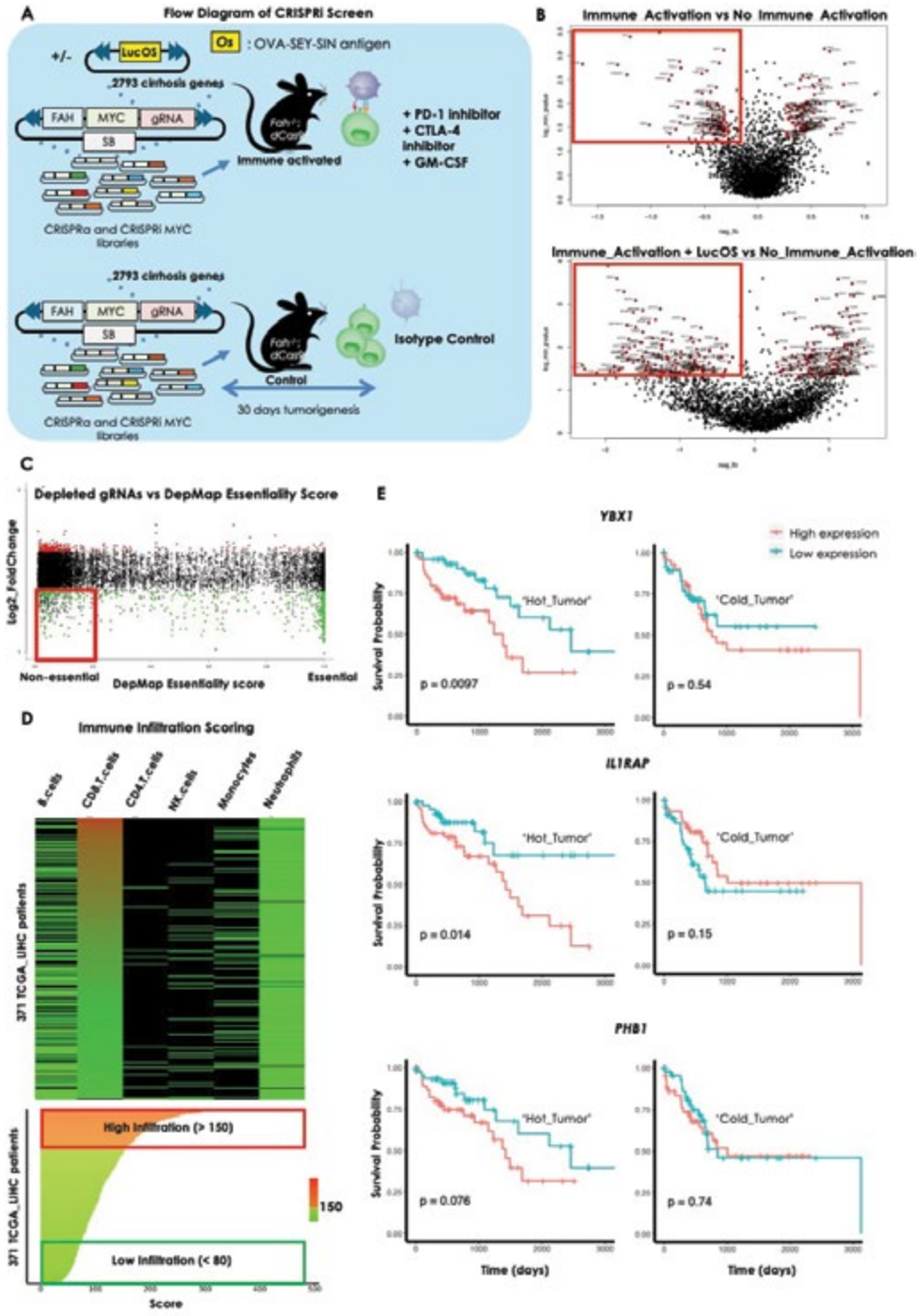

Disclosures: Chunmiao Cai: Nothing to Disclose, Dingzi Yin: Nothing to Disclose, Salah Adlat: Nothing to Disclose, Markcus Lee: Nothing to Disclose, Kirk Wangensteen: Nothing to Disclose, David Stokoe: CalicoLabs LLC: Employee, Ari Firestone: Nothing to Disclose, Agnes Holczbauer: Nothing to Disclose

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0238 | NOTCH SIGNALING DISRUPTION AND CELLULAR CROSSTALK: DISSECTING THE PATHOPHYSIOLOGY OF BILE DUCT PAUCITY IN ALAGILLE SYNDROME USING HUMAN LIVER ORGANOIDS

Marie-Agnès M'CALLUM[1] Quang Toan PHAM[1] Kristen Vieira-Lomasney[1] Eytan Haddad[1] Silvia Selleri[1] Massimiliano Paganelli[1]

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Background: Alagille syndrome (ALGS) is a multisystemic genetic disorder resulting in severe liver disease characterized by intrahepatic bile duct paucity. Studying the pathophysiology of ALGS has been challenging given its multisystemic nature and the pivotal role of the Notch signaling pathway in intercellular communication. Existing models fail to recreate the involvement of several cell types, the complexity of interacting pathways, and their effects on macroscopic structures. Here we aimed at clarifying ALGS pathophysiology and understand the role of non-parenchymal liver cells in determining disease phenotype. **Methods:** We recently developed an *in vitro* human model capable of recreating the crosstalk between liver cells within a structure preserving gradients of paracrine signals. Here we used such iPSC-derived complex liver organoids to assess the specific impact of ALGS-causing mutations on parenchymal and non-parenchymal liver cells, their role on bile duct formation and survival, and the interactions between signaling pathways suspected to play a role in ALGS pathophysiology. **Results:** We generated a representative human model of ALGS reproducing ductopenia in a controlled and reproducible experimental environment. Using isogeneic controls, we showed how Jagged1 haploinsufficiency affects the formation of the ductal plate and bile ducts. We demonstrated that defective Notch signaling affects biliary morphogenesis during liver development mainly through its the downregulation of SOX9 in bipotent hepatoblasts. Using hybrid organoids, we also demonstrated a pivotal role of ductal plate cells and differentiating cholangiocytes in stimulating biliary differentiation of adjacent hepatoblasts. We then unveiled how the mutation affects endothelial progenitor cells and impacts angiogenesis and endothelial stability, revealing how the liver niche plays a significant role in ALGS-related liver disease and explaining some of the systemic manifestations of the syndrome. The organoids allowed us to study the interplay between Notch, VEGF, Hippo and Wnt pathways and to show how Jagged1 haploinsufficiency results in liver fibrosis and inflammation. **Conclusion:** Our human complex liver organoids showed significant promise as a representative human model to study ALGS. Thanks to an isogeneic approach and the unique potential of hybrid configurations, they constitute an invaluable tool to study how the crosstalk within an organ microenvironment determines disease phenotype.

Disclosures: Marie-Agnès M'CALLUM: Nothing to Disclose, Quang Toan PHAM: Nothing to Disclose, Kristen Vieira-Lomasney: Nothing to Disclose, Eytan Haddad: Nothing to Disclose, Silvia Selleri: Abcellera Biologics: Employee, Massimiliano Paganelli: Morphocell Technologies: Executive role

0239 | BJT-778, ANTI-HBSAG MONOCLONAL ANTIBODY, ACHIEVED 100% VIROLOGIC RESPONSE IN SUBJECTS WITH CHRONIC HEPATITIS D (CHD): PHASE 2 STUDY RESULTS

Kosh Agarwal[1] Marta Dobryanska[2] Alina Jucov[3] Patrick Kennedy[4] Edward Gane[5] Man-Fung Yuen[6] Grace Wong[7] Simone Strasser[8] Jacinta Holmes[9] Stuart Roberts[10] Hassan Javanbakht[11] Nancy Shulman[11] Jenny Stanton[11]

[1]Kings College Hospital, [2]ARENSIA Exploratory Medicine, Kyiv, Ukraine, [3]ARENSIA Exploratory Medicine, Chisinau, Moldova, [4]Barts and The London SMD, [5]New Zealand Clinical Research, [6]The University of Hong Kong, [7]The Chinese University of Hong Kong, [8]University of Sydney, [9]St. Vincent's Hospital, [10]The Alfred Hospital, [11]Bluejay Therapeutics, INC.

Background: BJT-778 is a fully human anti-HBsAg monoclonal antibody that exhibits potent antiviral activity against HBV and HDV in vitro. BJT-778 is currently being evaluated in a Phase 1/2 study, BJT-778-001, for the treatment of chronic hepatitis B and CHD. We report the ongoing Phase 2 safety and efficacy results, where BJT-778 is administered subcutaneously (SC) for a duration of up to 48 weeks in subjects with CHD. **Methods:** Up to ~20 subjects per arm could be enrolled into: Arm 1: BJT-778 300 mg SC once weekly (QW); Arm 2: BJT-778 600 mg SC QW for 12 weeks followed by Q2W; and Arm 3: BJT-778 900 mg SC Q2W for 4 weeks followed by Q4W. Primary endpoints are safety and tolerability. Efficacy endpoints include absolute reductions and changes from baseline (BL) in HDV RNA and ALT levels, and the proportion of subjects achieving (i) virologic response defined as ≥2 log10 HDV RNA IU/mL reduction from BL or below the limit of detection (BLD, 5 IU/mL),

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(ii) ALT normalization (defined as ≤ULN in subjects with >ULN at BL), and (iii) composite response (defined as virologic response and ALT normalization). Eligible patients have quantifiable HDV RNA, HBV DNA <100 IU/ml on nucleos(t)ides and have compensated liver disease. Here, we provide 28-wk treatment **Results:** from the first 10 subjects in Arm 1 and 12-wk treatment **Results:** from 11 subjects in Arm 2. Limited efficacy data is available for Arm 3. Comprehensive data from all arms will be presented. **Results:** 10 subjects have been enrolled into Arm 1, 11 into Arm 2, and 11 into Arm 3. BL demographics and characteristics of the 32 subjects: Median (range) age of 41 years (31 to 47), ALT of 54 U/L (19 to 117), HDV RNA of 5.2 (2.4 to 7.4) log10 IU/mL, HBsAg of 4.3 (2.4 to 5.1) log10 IU/mL, 19% have cirrhosis, 56% men, 94% Caucasian, and 97% HDV GT1. Table summarizes the 28-wk and 12-wk treatment response in Arm 1 and 2, respectively. In Arm 1, all subjects had a reduction in ALT from BL, including a subject with normal ALT at BL. Across all treatment arms, BJT-778 at doses ≤900mg have been safe and well tolerated, with no reported serious or Grade 3/4 adverse events, and no treatment discontinuations due to adverse events. **Conclusion:** Monotherapy with BJT-778 ≤900mg has been safe and well-tolerated. BJT-778 300mg QW achieved 100% virologic response and a decline in ALT in all subjects with CHD, with a combined response of 67% by Week 28. These promising **Results:** warrant further development of BJT-778 for chronic HDV.

	Arm 1 300 mg QW		Arm 2 600mg QW
	Week 12	Week 28	Week 12
Virologic Response	7/10 (**70%**)	10/10 (**100%**)	8/10 (**80%**)
HDV RNA BLQ (<10 IU/ml)	1/10 (**10%**)	6/10 (**60%**)	3/10 (**30%**)
ALT normalization*	5/9 (**56%**)	6/9 (**67%**)	3/4 (**75%**)
Virologic Response + ALT normalization*	5/9 (**56%**)	6/9 (**67%**)	2/4 (**50%**)
Median HDV RNA reduction from baseline	-2.6	-3.5	-2.4

* In subjects with abnormal ALT at baseline

Disclosures: Kosh Agarwal: Nothing to Disclose, Marta Dobryanska: Nothing to Disclose, Alina Jucov: Nothing to Disclose, Patrick Kennedy: Nothing to Disclose, Edward Gane: Aligos Therapeutics: Advisor, Assembly Biosciences: Advisor, AbbVie: Speaking and Teaching, Intellia Therapeutics: Advisor, Tune Therapeutics: Consultant, Precision Bio: Advisor, Virion Therapeutics: Advisor, Gilead Sciences: Advisor, GSK: Advisor, Man-Fung Yuen: Speaking and Teaching relationship with Fujirebio Incorporation, Gilead Sciences, Roche, Sysmex Corp; Has not ended; Consultant relationship with Clear B Therapeutics, Dicerna Pharmaceuticals; Has not ended; Consultant relationship with AbbVie, Abbott Diagnotics, Aligos Therapeutics; Has not ended; Consultant relationship with Arbutus Biopharma, Arrowhead Pharmaceuticals, Assembly Biosc; Has not ended; Consultant relationship with Immunocore, Janssen, Precision BioSciences; Has not ended; Consultant relationship with Fujirebio Incorporation, GlaxoSmithKline, Gilead Sciences; Has not ended; Grant/Research Support relationship with Fujirebio Incorporation, Gilead Sciences, Immunocore; Has not ended; Grant/Research Support relationship with AbbVie, Assembly Biosciences, Arrowhead Pharmaceuticals; Has not ended; Consultant relationship with Vir Biotechnology and Visirna Therapeutics; Has not ended; Consultant relationship with Roche, Sysmex Corporation, Tune Therapeutics; Has not ended; Grant/Research Support relationship with Sysmex Corporation and Roche; Has not ended, Grace Wong: AstraZeneca: Advisor, Gilead Sciences: Advisor, Gilead Sciences: Speaking and Teaching, Janssen: Advisor, GSK: Advisor, GSK: Speaking and Teaching, Abbott: Speaking and Teaching, AbbVie: Speaking and Teaching, AstraZeneca, Gilead Sciences, GlaxoSmithKline and Janssen,: Advisor, Abbott, AbbVie, Ascletis, Bristol-Myers Squibb, Echosens, Gi: Speaking and Teaching, Gilead Sciences: Grant/Research Support, AstraZeneca, Gilead Sciences, GlaxoSmithKline and Janssen: Consultant, Abbott, AbbVie, Ascletis, Bristol-Myers Squibb, Echosens, Gi: Speaking and Teaching, AstraZeneca, Gilead Sciences, GlaxoSmithKline Pharmaceutical: Consultant, Gilead Sciences: Independent Contractor, AstraZeneca, Gilead Sciences, GSK and Janssen,: Advisor, Abbott, AbbVie, BMS, Gilead Sciences, GSK, Janssen, Roche: Speaking and Teaching, Gilead Sciences: Grant/Research Support, Simone Strasser: Chiesi: Advisor, Roche Diagnostics: Advisor, Roche Therapeutics: Advisor, Norgine: Speaking and Teaching, Abbott Diagnostics: Advisor, CSL Behring: Advisor, Novo Nordisk: Advisor, Astra Zeneca: Advisor, Sirtex: Speaking and Teaching, Eisai: Speaking and Teaching, Jacinta Holmes: Nothing to Disclose, Stuart Roberts: Nothing to Disclose, Hassan Javanbakht: Nothing to Disclose, Nancy Shulman: Bluejay Therapeutics, INC: Salary and equity, Jenny Stanton: Nothing to Disclose

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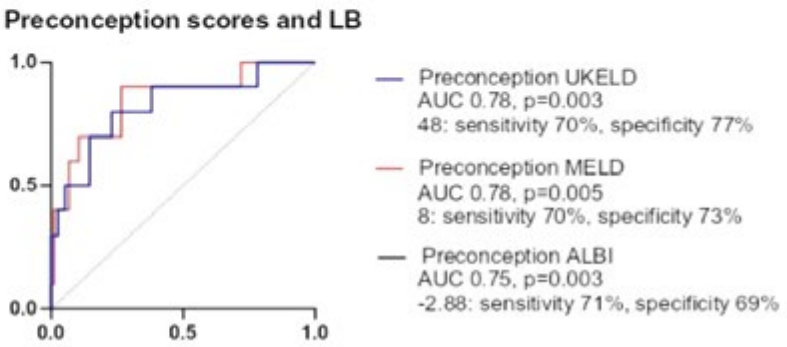
0240 | PREDICTING OUTCOMES IN AUTOIMMUNE HEPATITIS PREGNANCY

Yooyun Chung Lara Budwig[1] Lisa Long[1] Enoka Gonsalkorala[2] Michael Heneghan[1]

[1]King's College Hospital, [2]Royal Brisbane and Women's Hospital

Background: The prevalence of autoimmune hepatitis (AIH) among women of reproductive age is increasing. Population data has shown reasonable pregnancy outcomes in AIH with the exception of preterm births (PTB) and post-partum loss of biochemical remission (LOBR). However, there lacks preconception risk stratification to allow personalised management strategies. **Methods:** Pregnancy outcomes in women with AIH at King's College Hospital (KCH) were gathered from a prospective database of self-reported pregnancies. **Results:** There were 158 pregnancies from 83 women with AIH between 1972 – 2023 at KCH. Of these 66 pregnancies were in women with cirrhosis. The median age of conception was 29 years (IQR 24-33). Majority of women were receiving thiopurine and/or corticosteroids during pregnancy. The live birth (LB) rate with the exclusion of termination of pregnancy (n=15) was 87% (n=127), miscarriage occurred in 11% (n=16), stillbirth in 1% (n=2) and ectopic in 1% (n=1). Pre-eclampsia and intrahepatic cholestasis appeared in 5% and 6% respectively. The rate of PTB was 26% (n=30) of LB. Post-partum LOBR occurred in 25% compared to 3% intrapartum. The rate of hepatic decompensation was 8% (n=5) in women with cirrhosis. There were no significant difference in LB, PTB and mode of delivery between women with and without cirrhosis. Previous data from our group demonstrated the preconception albumin-bilirubin (ALBI) and model for end stage liver disease (MELD) scores to predict LB in chronic liver disease. In this data of women with AIH, the preconception ALBI score predicted LB with area under the receiver operator curve (AUROC) of 0.747 (p=0.003), MELD score had AUROC of 0.775 (p=0.005) and in addition, the United Kingdon model for end stage liver disease (UKELD) score demonstrated AUROC of 0.784 (p=0.004) (Figure 1). The preconception creatinine and ALBI score was predictive of pre-eclampsia with AUROC of 0.761 (p=0.05) and 0.942 (p=0.001) respectively, though due to the low statistical power, this requires validation. **Conclusion:** There is a need for more robust prognostic tools to determine pregnancy outcomes in AIH. The ALBI, MELD and UKELD scores may be useful for predicting LB. A collaborative effort is required to validate these and other prognostic markers.

Figure 1. Preconception UKELD, MELD and ALBI scores and live birth rate.



Disclosures: Yooyun Chung: Nothing to Disclose, Lara Budwig: Nothing to Disclose, Lisa Long: Nothing to Disclose, Enoka Gonsalkorala: Nothing to Disclose, Michael Heneghan: Advanz: Speaking and Teaching

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0241 | HEPATOCYTE-SPECIFIC DELETIONS OF AUTOPHAGY-INITIATING GENES RESULT IN PRONOUNCED HEPATOMEGALY AND PATHOLOGY

Shengxiang Sun[1] Jennifer Frein[1] Amanda Foster[1] Changqing Ma[1] Ta-Chiang Liu[2]

[1]Washington University, [2]Washington University in St. Louis

Background: Canonical autophagy is a multi-step process and involves initiation (mediated by *Fip200*, *Ulk1*, *etc.*), phagophore nucleation (*Atg14*, *Becn1, etc.*), followed by autophagosome formation (*Atg16l1*, *Atg5*, *Atg7*, *etc.*), and completes with autolysosome digestion. Autophagy protects the liver against injury and disease. Previous studies showed that hepatocyte conditional knockout (cKO) of *Atg5* or *Atg7* genes in autophagosome formation, resulted in hepatomegaly. However, it is unclear whether genes in the upstream autophagy process such as *Fip200* or *Atg14* are involved in modulating liver size and pathology. **Methods:** We generated *Fip200*, *Atg14*, *Atg16l1*, and *Atg7* hepatocyte cKO mice. *Fip200* and *Atg14* cKO mice were additionally crossed with *p62* or *Yap* KO mice. Hepatocyte size, cell death, proliferation, and Kupffer cell infiltration were defined by using beta-catenin, cleaved caspase-3, Ki67, and F4/80 immunostaining, respectively. Transcriptomics was performed by bulk RNAseq, and transmission electron microscopy (TEM) was used to examine hepatocyte ultrastructure. Cell death inhibition was performed by administering inhibitors for apoptosis (Z-VAD-FMK), necroptosis (necrostatin-1), and pyroptosis (Ac-FCTD-CMK). Anti-CSF1R and anti-Ly6G antibodies were administrated to deplete macrophages and neutrophils. **Results:** *Fip200* and *Atg14* cKO mice showed more accelerated and profound hepatomegaly compared to the *Atg16l1* and *Atg7* cKO mice. Hepatomegaly was not due to developmental defects, as the phenotype was induced after these genes were deleted post-weaning. Hepatic *Fip200* and *Atg14* cKO mice increased hepatocyte size, hepatocyte proliferation and death, and Kupffer cell infiltration. In contrast, livers from the *Atg16l1* and *Atg7* cKO mice showed relatively unremarkable histology. *Fip200* cKO livers showed enhanced inflammasome signature with upregulations of type I interferon (IFN) genes, however type I IFN blockade did not rescue liver pathology. TEM showed reduced autophagosome and lysosome numbers, with frequent mitochondria abnormalities. Liver histologic changes in *Atg14* cKO mice were not rescued by either cell death inhibition or depletion of macrophages and neutrophils. Furthermore, in contrast to previous studies where concomitant deletion of either *Yap* or *p62* was able to reverse hepatomegaly and liver pathology in *Atg7* or *Atg5* cKO mice, in the *Fip200* and *Atg14* cKO mice, deletion of *Yap* did not rescue liver size or pathology, while *p62* deletion rescued liver size but only partially rescued histology changes. **Conclusion:** Compared to *Atg16l1* and *Atg7* cKO, *Fip200* and *Atg14* cKO result in aggravated hepatomegaly, accompanied by increases in hepatocyte proliferation and death, and Kupffer cell infiltration. Phenotypes associated with the *Fip200* and *Atg14* cKO mice are only partially rescued by concomitant *p62* KO but not by *Yap* KO. Our results suggest that genes involved in autophagy initiation have more profound effects on liver pathophysiology compared to genes associated with autophagosome formation.

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0242 | TAP-LT: A PILOT RANDOMIZED CONTROLLED TRIAL OF A TRANSPORTATION ASSISTANCE PROGRAM IN LIVER TRANSPLANT CANDIDATES

Kali Zhou Christopher Wong[1] Aaron Ahearn[1] Jeffrey Kahn[1] Norah Terrault[1]

[1]University of Southern California

Background: Access to transportation is a key social determinant of health outcomes and typically a required component of liver transplant (LT) eligibility. In this pilot interventional randomized controlled trial, we assessed feasibility, acceptability, and preliminary effectiveness of a transportation assistance program (TAP) provided during the evaluation process among at-risk LT candidates. **Methods:** Adult participants were recruited from a single urban high-volume transplant center at an initial LT evaluation clinic visit in 2022. Included participants either reported transportation barriers on a screening survey or were Medicaid-insured. Exclusion criteria included ineligible for LT or hospitalized at first visit, distance from center ≥60 miles, no telephone access, or unable to provide consent. Participants were randomized 1:1 to TAP intervention (Lyft rideshares to any healthcare-related visit) or control (usual care) arms with study end at time of listing decision. Outcomes included intervention uptake and patient reported outcomes. **Results:** 42 LT candidates were enrolled in the TAP-LT trial (N=21 per arm).

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Median age was 56 years (IQR 47-62), 62% were male, 76% Hispanic, and 79% had Medicaid. 52% had alcohol-associated liver disease, 17% with hepatocellular carcinoma, and median MELD was 18 (11-22). Demographic/clinical characteristics were similar, though the TAP arm had more foreign-born (82% vs 53%) and non-English speaking (77% vs 47%). Median time to listing decision was 147 days (66-245) and did not differ by study arm (P=0.88). 9 (43%) of 21 TAP participants completed a Lyft ride for a total of 103 rides. The median number of rides per rider was 8 (4-18), median cost/ride was $33 ($24-62), and median distance/ride was 17 miles (12-25). 8 in the TAP vs 6 in the control arm were listed (P=0.37); 3 vs 1 were transplanted (P=0.39). Mortality differed with 1 death (5%) in the TAP compared to 7 deaths (33%) in the control arm (P=0.03). Median RAND Patient Satisfaction Questionnaire (PSQ-18) scores were high (>4) for all 7 subscales except for communication (3) and were similar across arms. 100% of intervention participants reported being more likely to attend medical visits because of the TAP-LT program. **Conclusion:** Our pilot data demonstrates transportation assistance through Lyft rideshares to be feasible and highly acceptable to LT candidates. A larger trial is warranted to examine efficacy of the TAP-LT intervention on transplant outcomes.

Disclosures: Kali Zhou: Nothing to Disclose, Christopher Wong: Nothing to Disclose, Aaron Ahearn: Nothing to Disclose, Jeffrey Kahn: Orphalon: Single Advisory Board meeting 11/2023, Malinckrodt: Attended speaker's training session, never spoke, Orphalon: Single advisory board meeting, 2023, Norah Terrault: Grant/Research Support relationship with Eiger Pharmaceuticals; Has ended; Grant/Research Support relationship with GSK; Has not ended; Royalties or patent beneficiary relationship with Elseiver; Has not ended; Grant/Research Support relationship with Helio Health; Has ended; Grant/Research Support relationship with Durect Corp; Has ended; Executive role relationship with AASLD; Has not ended; Board member relationship with HBV Foundation; Has not ended; Grant/Research Support relationship with ImmunoCore; Has ended

0243 | INDIVIDUAL NUTRITION SUPPORT IN PATIENTS WITH HBV-ACLF AT NUTRITION RISK: PRELIMINARY RESULTS OF A RANDOMIZED CONTROLLED CLINICAL TRIAL

Li Zhipeng[1] *Liang Peng*[1]

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Background: Malnutrition is a common complication of hepatitis B virus-related acute-on-chronic liver failure (HBV-ACLF) and is closely associated with poor prognosis. However, the benefits of nutritional interventions in these populations have not been proven. This study aimed to evaluate the safety and efficacy of a new nutrition intervention method for patients with HBV-ACLF. **Methods:** In this open-label, randomized controlled clinical trial (NCT 06128421), HBV-ACLF patients at nutrition risk (NRS 2002 score ≥ 3) were randomly allocated to either the nutritional support group (Intervention Group: 1.2 times REE/day, 1.2 grams of protein/kg/day) or the control group (standard hospital meals) for 10 days. REE was based on the gold standard of metabolic indirect calorimetry. The primary outcome was the liver transplant-free mortality rate. The secondary indicators included the incidence of clinical adverse outcomes and changes in indicators such as muscle mass, muscle strength, physical function, and quality of life (EQ-5D scale). **Results:** As of May 2024, 20 patients enrolled were evaluable for the primary and key secondary outcomes at 30 days: intervention group (n=9) and control group (n=11). Baseline characteristics were similar between two groups. However, there was no significant difference 30-day liver transplant-free mortality in the intervention group as compared to the control group (11.1% vs 18.2%, p=1) (Table 1). The 30-day incidence of clinical adverse outcomes was comparable between the intervention group vs control group (11.1% vs 36.4%, p=0.642). By the end of 30 days,15 of the 20 patients could be assessed for other secondary outcomes, changes in mid-arm circumference (MAC) between intervention group (n=8) and control group (n=7) were -0.03±0.91 and -1.89±1.2, p = 0.003. There were no incidences of severe adverse events during nutrition intervention, and adverse events related to nutrition intervention were similar. **Conclusion:** Individual nutrition support decreased 30-day liver transplant-free mortality and 30-day incidence rate of clinical adverse outcomes in patients with HBV-ACLF, while there was no significant difference. Individual nutrition support significantly improved MAC as compared to control group. More **Results:** will be reported in future.

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Table 1. Change from baseline to day 30 in key outcomes

	Intervention group	Control group	P-value
Primary Outcome			
Liver transplant-free mortality rate	11.1%	18.2%	1
Secondary Outcome			
Clinical adverse outcomes incidence rate	11.1%	36.4%	0.642
△-MAC	-0.03±0.91	-1.89±1.20	0.003
△MAMC	4.38±5.11	0.55±5.80	0.183
△Grip	4.98±6.04	0.18±4.81	0.1
△SPPB	1.5±3.21	1.13±0.83	0.754
△EQ-5D	19.38±21.62	10.63±16.35	0.377
△MELD	-1.82±8.57	-3.22±8.5	0.733
△COSSH	-0.7±0.98	-0.92±0.92	0.633

MAC, mid-arm circumference; MAMC, mid-arm muscle circumference; SPPB, short physical performance battery; MELD, model for end-stage liver disease ; COSSH, score of Chinese group on the study of severe hepatitis B.

Disclosures: Li Zhipeng: Nothing to Disclose, Liang Peng: Nothing to Disclose

0244 | RAPID START-UP OF A FIELD-BASED HEPATITIS C ELIMINATION PROGRAM ENABLED BY STATE FUNDED 340B INITIATIVE ◆

Dylan Moore[1] Ann Moore[1] Brennin Palfrey[1] Karen Arendt[1] Mark Bailey[1] Richard Manch[1] Anita Kohli[1] Rudy Lizarraga[1] Colleen Hopkins[1] Tiffany Hendrix[1]

[1]Arizona Liver Health

Background: 90,000 individuals in Arizona (AZ) are living with HCV. Arizona Liver Health is a private hepatology practice and largest treater of HCV in AZ. In 2021 AZ Department of Health and Human Services granted ALH limited 340B status, with funds to be used to eliminate HCV in AZ. Despite a robust clinical and tele-mentoring program, ALH historically treated only about 150 HCV patients/yr with an additional 100/yr via tele-mentoring collaborations. A new and scalable strategy was necessary. **Methods:** ALH developed a 340B funded HCV outreach program in July 2024 focused on three populations: people who use drugs, are incarcerated or unsheltered. ALH targeted high prevalence areas in urban and remote areas. A specialized mobile outreach and street medicine team with lived experience was trained and partnerships established with organizations supporting high-risk groups. A consistent presence at sites was established and maintained. Testing and treatment services occur in public spaces, by home visit, and via partnering organizations. Prior authorization specialists expedited prescription delivery and case management team provided patient support, addressing barriers including lack of phone service and housing through specific intake processes and follow-up. **Results:** Since July 2023 884 patients with HCV have been identified and prescribed direct acting antivirals, 433 (49.0%) in traditional clinic and 451 (51.0%) via mobile units/outreach teams. 253 patients/month are screened for HCV with 11.9% HCV Ab positive rate, with significant differences in HCV Ab positivity by testing site (Table 1).
Since Jan 2024 ALH prescribed DAAs to an average of 102.5 patients/month, 67% of whom were treated by the outreach team. 67.1% (593/884) of patients prescribed DAAs since July 2023 have initiated DAAs. 62.0% of patients who completed treatment are at or beyond 12 weeks post completion and 63% (107/170) of these patients have completed SVR12 labs with no detectable HCV RNA. 58% (31/48) outreach vs 60% (76/126) clinic, p>0.05)). Other patients are being actively contacted to obtain SVR12 confirmation. 5.3% (23/433) vs

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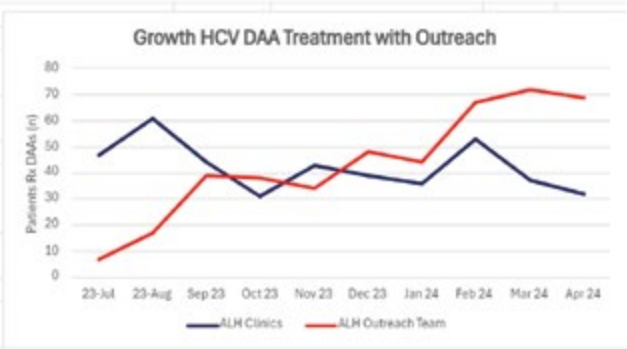
8.9% (40/451) of clinic vs outreach patients were lost to follow up (p<0.05). 3/170 (1.76%) patients relapsed. No reported reinfections. **Conclusion:** ALH developed a scalable and replicable and successful 340B funded HCV elimination model that can be implemented across the United States. Outreach programs targeting at-risk populations are successful and equivalent to clinic-based care and necessary to address the complexities of HCV treatment access. Our experience highlights a unique collaboration between a state health department and a hepatology practice to develop an effective HCV elimination strategy

Significant Variation in HCV POC Testing Positivity by Outreach Site Type* (1/24-5/24)			
Testing Site Type	**Total Tests**	**HCB Ab Reactive**	**% Reactive**
Directed Street Testing	273	51	18.68%
Re-Entry Programs	112	16	14.29%
Recovery Centers	221	29	13.12%
Unsheltered/ Community Service Programs	264	34	12.88%
Harm Reduction (SSP)	69	4	5.80%
MAT Facilities	42	1	2.38%
Community Events	137	2	1.46%



Disclosures: Dylan Moore: Nothing to Disclose, Ann Moore: Abbvie: Speaking and Teaching, Gilead: Speaking and Teaching, Brennin Palfrey: Nothing to Disclose, Karen Arendt: Nothing to Disclose, Mark Bailey: Nothing to Disclose, Richard Manch: Gilead: Speaking and Teaching, AbbVie: Speaking and Teaching, Intercept: Speaking and Teaching, Madrigal: Speaking and Teaching, Anita Kohli: Nothing to Disclose, Rudy Lizarraga: Nothing to Disclose, Colleen Hopkins: Nothing to Disclose, Tiffany Hendrix: Nothing to Disclose

0245 | THE COMPETING ROLE OF HEPATIC X-BOX BINDING PROTEIN 1 (XBP1) IN BILE ACID METABOLISM AND BILE-ACID INDUCED INJURY IN MURINE CHRONIC CHOLESTASIS

Alyssa Kriegermeier[1] *Brian LeCuyer*[2] *Angela Hyon*[1] *Mahmoud Khalafalla*[3] *Xiaoying Liu*[3] *Richard Green*[2]

[1]*Ann and Robert H. Lurie Children's Hospital of Chicago,* [2]*Northwestern University,* [3]*Northwestern University Feinberg School of Medicine*

Background: Cholestasis causes endoplasmic reticulum (ER) stress and the unfolded protein response (UPR), including Xbp1, is a protective molecular response designed to decrease ER stress. Mice with impaired or deleted hepatic Xbp1 function cannot resolve ER stress appropriately and have increased liver injury. Additionally, Xbp1 is known to regulate bile acid metabolism. The purpose of this study is to determine the effects of hepatic Xbp1 on liver injury in murine models of cholestasis including bile acid feeding and Mdr2$^{-/-}$ mice. **Methods:** Liver-specific Xbp1 knock out (LS-Xbp1$^{-/-}$) and floxed control (Xbp1$^{fl/fl}$) mice were fed a diet supplemented with 0.5% cholic acid (CA) from birth. We developed LS-Xbp1$^{-/-}$/Mdr2$^{-/-}$ double knock out (DKO) mice and Xbp1$^{fl/fl}$/Mdr2$^{-/-}$ single knock-out (SKO) controls. SKO and DKO mice were fed chow or a diet containing 1.25% cholesterol from birth. Ten-week-old male mice were used to measure serum liver chemistries, serum C4 (Mayo, MN), and hepatic RNA-seq. Total hepatic bile acids were quantified via spectrophotometric assay and hepatic bile acid species were quantified via mass spectrometry (Duke Metabolomics). **Results:** After CA feeding, LS-Xbp1$^{-/-}$ mice had significantly increased ALT (292±123 vs 144±57 U/L, p=0.04) and alkaline phosphatase (ALP) (260±89 vs 142±5 U/L, p=0.02) compared to Xbp1$^{fl/fl}$ mice. There was no difference in serum bile acids and hepatic bile acids were lower in LS-Xbp1$^{-/-}$ mice, although this did not reach significance (446±92 vs 556±111 nmol/gm, p=0.1). Paradoxically, in the Mdr2$^{-/-}$ model of cholestasis, chow fed DKO mice had improved serum ALT and hepatic fibrosis compared to SKO mice. Serum C4 levels were significantly lower in DKO vs SKO mice (14±3 vs 36±13, p=0.005), indicating reduced Cyp7a1 activity. Total hepatic bile acids were also decreased in DKO vs SKO mice (35±5 vs 121±44 nmol/gm, p=0.009) with significant decreases in taurine conjugates of CA and muricholic acids. There was no difference in hepatic gene expression of *Cyp7a1, Cyp8b1, Cyp27a1, Fxr, Shp, Abcb11* or *Ntcp* between SKO and DKO mice. After cholesterol feeding, hepatic bile acid concentrations between DKO and SKO mice were similar (87±25 vs 98±42 nmol/gm, p=0.7), the genotype-specific improvement in ALT in DKO vs SKO mice was lost (179±49 vs 224±66 U/L, p=0.2), and there was a significant increase in ALP in DKO vs SKO mice (307±91 vs 197±53 U/L, p=0.02). **Conclusion:** LS-Xbp1$^{-/-}$ mice fed CA had more liver injury than controls but Mdr2$^{-/-}$ mice lacking hepatic

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Xbp1 seemingly paradoxically were protected from cholestatic injury. The lower ALT elevation in the Mdr2-DKO mice is associated with a lower bile acid pool. The genotype-specific changes in liver injury were ameliorated by cholesterol feeding which equalized the bile acid pool. These data indicate that the hepatic Xbp1 signaling pathway may be protective during cholestasis but XBP1 regulation of bile acid metabolism can have competing effects on injury.

Disclosures: Alyssa Kriegermeier: Nothing to Disclose, Brian LeCuyer: Nothing to Disclose, Angela Hyon: Nothing to Disclose, Mahmoud Khalafalla: Nothing to Disclose, Xiaoying Liu: Nothing to Disclose, Richard Green: Nothing to Disclose

0246 | LOW SHEAR INDUCED HEPATIC KALLIKREIN-KININ SYSTEM ACTIVATION REGULATES INTRAHEPATIC VASCULAR ADHESION AND DEVELOPS PRO-THROMBOTIC MICROENVIRONMENT

Rajni Yadav[1] Dinesh Mani Tripathi[1] vaibhav tiwari[2] Shiv Kumar Sarin[2] Savneet kaur[2] Aishwarya bhatnagar[2] parul singh[2] himanshi himanshi[2]

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Background: Physiological shear stress regulates liver sinusoidal endothelial cells (LSEC) mediated hepatic vascular homeostasis, while aberrant/low blood flow promotes hepatic microvascular remodelling, further leading to vascular complications. Sparse knowledge on LSEC specific cellular mechanisms and its pathological involvement in portal dynamics limits its therapeutic potential. We aimed to identify LSEC specific underlying cellular mechanisms in response to low shear. **Methods:** Experimentally, intra-hepatic low shear model was developed by 60% portal vein constriction (PVC). Shear flow was evaluated by transonic flow probe and quantification of Rhodamine-6G-fluorophore-stained platelet by intra-vital imaging at 24 and 48hrs post PVC. Hepatic hemodynamic was monitored followed by molecular, cellular and histological analysis. Proteomics analysis of hepatic tissue was also done. **Results:** Hemodynamic studies revealed that intrahepatic shear was markedly decreased by 50% and 56.2% at 24hrs and 48hrs, respectively post PVC and was further confirmed with intravital imaging. Histologically, intrahepatic sinusoidal dilatation with mild hepatic congestion and immune cells infiltration was observed. Pathway analysis of proteomic data revealed significant upregulation of complement and coagulation cascade, neutrophil degranulation, platelet aggregation, and endothelial activation. Proteins such as S100A8 and S100A9 were upregulated (Log2FC= -1to+1, $p<0.05$) indicating endothelial damage. Coagulation markers including leukocyte elastase inhibitor, serine protease inhibitor, plasma protease C1 inhibitor, prothrombin and factors IX and XII, were also upregulated. Adhesion proteins like integrins α-1 and β-1, ICAM1, VCAM1, and cadherin-1, which promote inflammatory cell chemotaxis and adhesion were elevated ($p<0.05$). Notably, T-kininogen induced bradykinin 2 receptor promotes “kallikrein-kinin” system activation and was observed along with increased expression of its secondary messenger PIP2, NO, and PKC. Further, activation of RhoA mediated downregulation of cytoskeleton proteins F-Actin, MLC, B-catenin, phosphorylation and internalization of junction protein- Cadherin and demsoplakin-plakoglobin promoting destabilization of the vascular barrier and permeability were observed. Gene expression also confirmed significant upregulation of endothelial remodelling markers, including PECAM-1, vWF, IL-6, and Notch. **Conclusion:** Intrahepatic low shear activates complement and coagulation cascade, cell adhesion molecules, DAMPs, and the kallikrein-kinin system. This leads to bradykinin-mediated loss of vascular permeability, contributing to hepatic vascular dysfunction and pro-thrombotic microenvironment.

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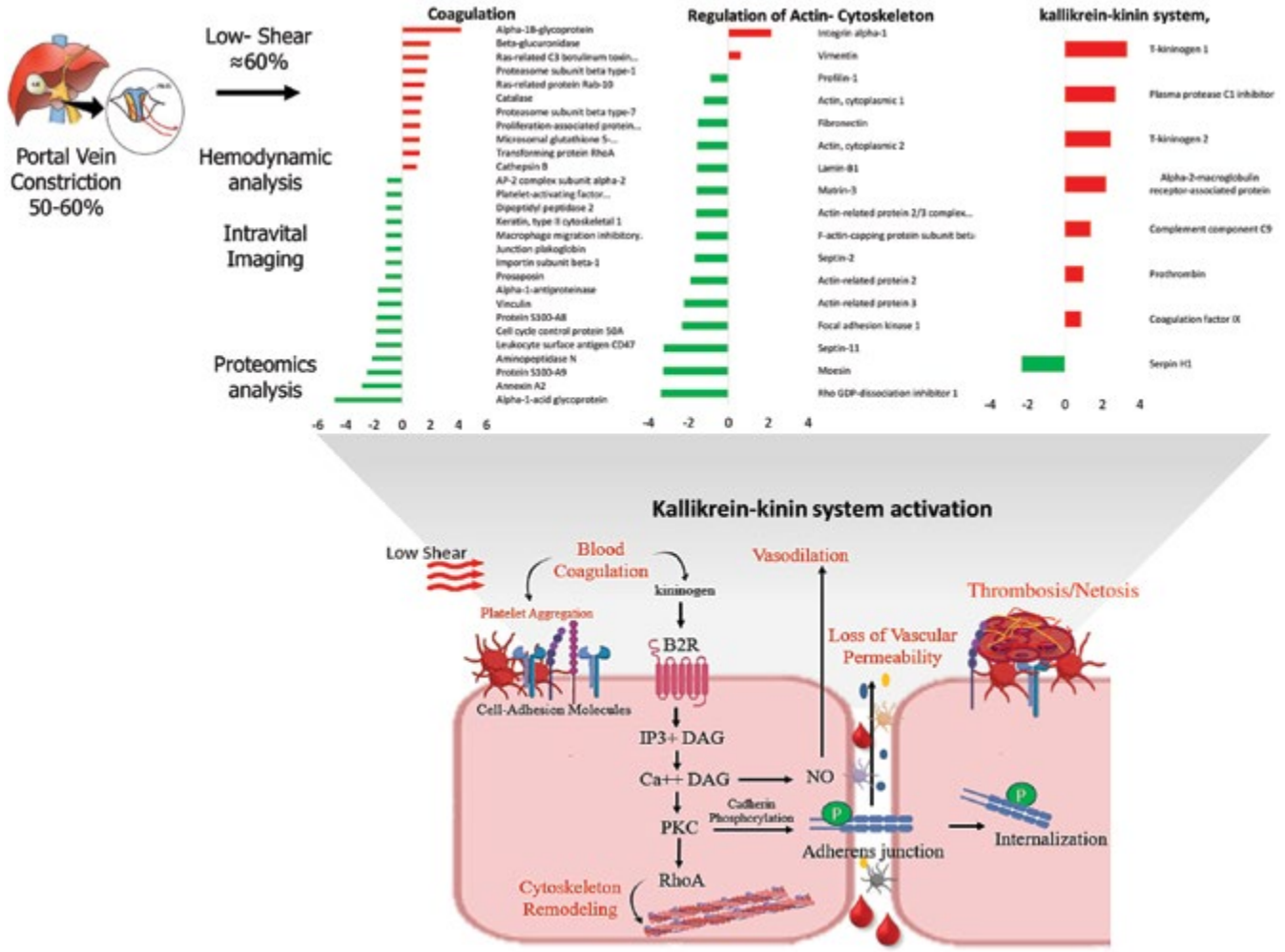

Disclosures: Rajni Yadav: Nothing to Disclose, Dinesh Mani Tripathi: Nothing to Disclose, vaibhav tiwari: Nothing to Disclose, Shiv Kumar Sarin: Nothing to Disclose, Savneet kaur: Nothing to Disclose, Aishwarya bhatnagar: Nothing to Disclose, parul singh: Nothing to Disclose, himanshi himanshi: Nothing to Disclose

1002 | MECHANOSENSITIVE REGULATION OF LXR BY YAP/TAZ DETERMINES HEPATIC CHOLESTEROL ACCUMULATION

Na Young Lee[1] *Ja Hyun Koo*[1]

[1]*Seoul National University*

Background: Liver cirrhosis is defined by an abnormal increase in stiffness. However, little is known about how stiffness determines hepatocyte functions, although matrix stiffness impacts diverse cellular functions. Hippo signaling pathway and its effector proteins, namely yes-associated protein (YAP) and the transcriptional coactivator with PDZ-binding motif (TAZ), play pivotal roles in intracellular mechanostransduction. This study investigates the relationship between liver stiffness and cholesterol metabolism, focusing on the mechanosensitive regulation of liver X receptor (LXR) by matrix stiffness. **Methods:** We compared cells cultured on matrices of 1 kPa and 20 kPa stiffness and conducted in vivo studies using hepatocyte-specific Yap/Taz knockout mice to assess the effects of mechanical stiffness on cholesterol metabolism and liver fibrosis. Hepatocyte-specific Yap/Taz knockout mice were used to examine mechanism of cholesterol regulation by altered stiffness. **Results:** We demonstrate that matrix stiffness enhances YAP activity to inhibit LXR and results in suppressed cholesterol efflux. Hepatocyte-specific Yap/Taz knockout mice were protected from cholesterol accumulation and cholesterol-induced hepatic fibrosis development. Mechanistically, the expression of active mutant YAP suppressed the expression of LXR target genes. Moreover, LXR suppression still occurred when YAP-TEAD interaction was abolished, indicating that the

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LXR regulation by YAP does not require classical YAP transactivation. An inverse correlation between LXR and YAP was observed in the livers of patients with cirrhosis. **Conclusion:** Our results suggest a novel physiological input for metabolic dysregulation during chronic liver disease progression and provide new insights how mechanotransduction affects hepatocyte functions. Moreover, these findings suggest that targeting YAP/TAZ could be a potential therapeutic strategy for treating liver fibrosis and related metabolic complications.

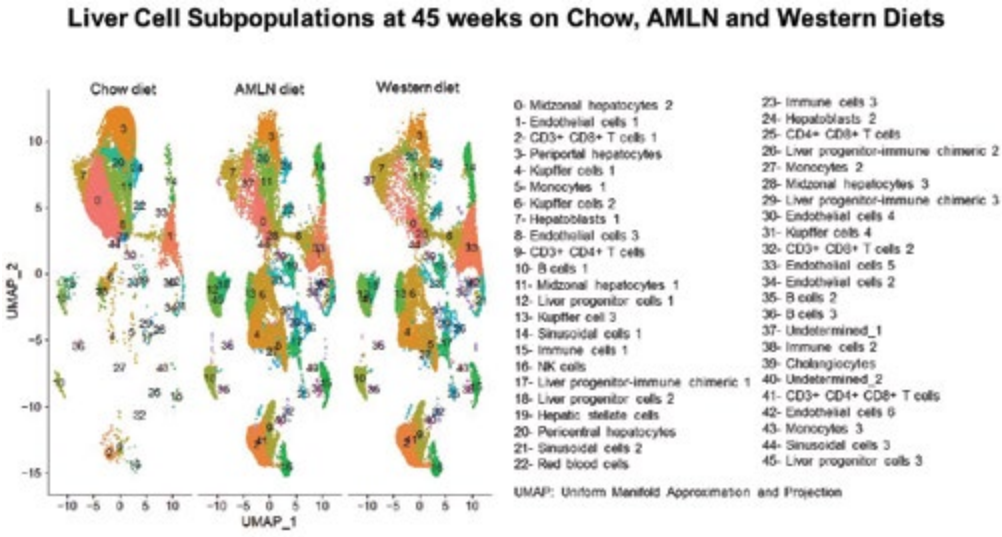
Disclosures: Na Young Lee: Nothing to Disclose, Ja Hyun Koo: Nothing to Disclose

1003 | LIVER SINGLE-CELL RNA TRANSCRIPTOME EVOLUTION IN RESPONSE TO DIET-INDUCED MASH/FIBROSIS

Simeng Wang[1]

[1]*UT Southwestern Medical Center*

Background: MASH involves perturbations of hepatocytes, non-parenchymal liver cells (NPCs) and their interactions that result from insulin resistance. Here, we used single-cell sequencing (scRNA-seq) of hepatocytes and NPCs to determine the time-dependent gene expression changes in gene expression induced by two distinct MASH diets. **Methods:** Mice (n=9) fed Chow, Western (40% fat, 29% sucrose, 0.14% cholesterol), or AMLN diets (40% fat, 20% fructose, 9% sucrose, 2% cholesterol) for 24, 34, or 45 weeks. Mice were subjected to a partial hepatectomy for histology followed by liver perfusion for scRNA-seq. Analysis of scRNA-seq utilized Seurat, RNA velocity, and Cellrank. **Results:** 324,827 high-yield single-cell transcriptomes were analyzed. After 45 weeks, liver collagen increased 22-fold and 15-fold on AMLN and Western diets, respectively. Histology sections revealed more prominent liver fibrosis in mice fed AMLN. Genes associated with the actin cytoskeleton, myofibroblast differentiation, and fatty acid catabolism were significantly induced in stellate cells (HSCs), with greater changes on the AMLN diet. Embryonically-derived and circulating monocyte-derived Kupffer cells (KCs) were markedly increased on the AMLN diet. Both diets significantly induced the differentiation of circulating monocytes to KCs at 34 weeks.At 34 weeks, AMLN diet promoted hepatocyte de-differentiation, apoptosis through TNF-α signaling, and induced extracellular matrix formation and cell migration. The Western diet induced genes involved in intrinsic DNA damage via alternative splicing defect pathways along with extrinsic apoptosis via MAPK, p75 NTR receptor-mediated signaling, and NF-kB signaling. Both diets similarly induced ferroptosis and pyroptosis, but there was no evidence of necroptosis. Liver progenitor cell (LPC) proliferation and differentiation of cholangiocytes into myofibroblasts were induced by both diets with greater changes induced by the AMLN diet. **Conclusion:** Our study provides the first time-dependent nonparenchymal and hepatocyte single-cell sequencing transcriptome response to two commonly used MASH diets. The AMLN diet induced HSC activation and proliferation to a greater extent than the Western diet. Both diets induced LPC differentiation into cholangiocytes then to myofibroblasts. Pericentral and midzonal hepatocytes closest to pericentral region appear to be differentiating hepatocytes replacing hepatocytes that have undergone cell death.



Disclosures: Simeng Wang: Nothing to Disclose

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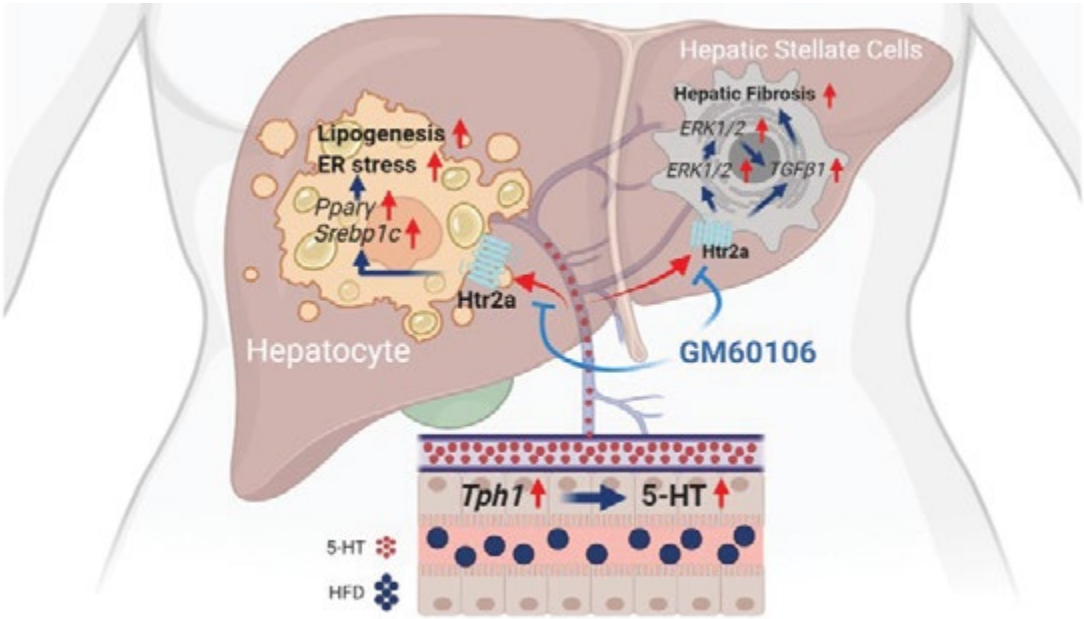
1004 | A NOVEL HTR2A ANTAGONIST FOR THE TREATMENT OF METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE

WON-IL CHOI[1] Sungmin Song[2] Won Hee Lee[3] Byung-Kwan Jeong[4] Peter Goughnour[2] Hee Jong Lee[2] Wonsuk Choi[5] Jun Yong Park[6] Jin Hee Ahn[7] Hail Kim[3]

[1]KAIST (Korea Advanced Institute of Science and Technology), [2]JD Bioscience Inc., [3]KAIST, [4]Asan Medical Center, [5]University of California Irvine, [6]Yonsei University College of Medicine, [7]GIST

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is now a global health concern. Current treatments have limited efficacy, highlighting the need for innovative therapeutic strategies. This study investigates the safety and tolerability of GM-60106, a peripheral serotonin receptor 2A (HTR2A) antagonist, in healthy adults and individuals with elevated MASLD markers in a Phase 1 trial (NCT05517564). **Methods:** Building upon recent findings linking peripheral serotonin synthesis to hepatic steatosis, we investigated targeting HTR2A as a potential therapeutic approach. Using both genetic and pharmacological interventions, we assessed the impact of HTR2A inhibition on MASLD/MASH and liver fibrosis in murine models, including STZHFD, CCL4-induced, and bile duct ligation models. The Phase 1 trial of GM-60106 is a randomized, double-blind, placebo-controlled study assessing single and multiple ascending doses in healthy adults and individuals with elevated MASLD markers. The trial consists of three parts: Part A (single ascending dose, SAD) included 64 healthy participants across 8 cohorts; Part B (multiple ascending dose, MAD), once daily for 14 days, involved 24 participants across 3 cohorts; and Part C (MAD), once daily for 28 days, involved 8 participants with NAFLD markers. **Results:** Our research showed elevated expression of HTR2A during hepatic stellate cell activation, further potentiated by peripheral serotonin. Genetically depleting HTR2A in hepatocyte or hepatic stellate cells reduced steatosis and/or liver fibrosis in various murine models. GM-60106 effectively mitigated fatty liver and liver fibrosis in diverse MASLD/MASH murine models. In the completed Phase 1 trial, adverse events (AEs) following the administration of single or multiple doses of GM-60106 were mostly mild to moderate, with minimal impact on a high-fat meal. Pharmacokinetic (PK) data showed dose-proportional absorption ranging from 2.5 mg to 160 mg dosing in the SAD study and from 20 mg to 60 mg in the MAD study. **Conclusion:** HTR2A knockout in hepatocytes reduced lipid accumulation, inflammation, and hepatocyte ballooning, while HTR2A knockout in hepatic stellate cells decreased fibrosis across several mouse models. In a preclinical study, GM-60106, a novel HTR2A antagonist, reduced MASLD progression at multiple levels and effectively reduced hepatic fibrosis. In the phase 1 clinical trial, GM-60106 was found to be safe and well-tolerated, with optimal PK profiles for oral administration. This study has been completed to assess the safety, PK, and pharmacodynamics of GM-60106, paving the way for further long-term toxicity assessments and human proof-of-concept studies. These results aim to establish the potential of GM-60106 as a promising treatment for MASLD.



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Disclosures: WON-IL CHOI: Nothing to Disclose, Sungmin Song: Nothing to Disclose, Won Hee Lee: Nothing to Disclose, Byung-Kwan Jeong: Nothing to Disclose, Peter Goughnour: Nothing to Disclose, Hee Jong Lee: Nothing to Disclose, Wonsuk Choi: Nothing to Disclose, Jun Yong Park: Nothing to Disclose, Jin Hee Ahn: Nothing to Disclose, Hail Kim: Nothing to Disclose

1005 | SOLUBLE SIGLEC-9 IMPROVES INTESTINAL BARRIER FUNCTION IN A MOUSE MODEL OF METABOLIC-DYSFUNCTION ASSOCIATED STEATOHEPATITIS (MASH)

Hisanori Muto[1] Fumitaka Mizuno[1] Shinya Yokoyama[1] Taku Tanaka[1] Kenta Yamamoto[1] Takanori Ito[1] yoji ishizu[1] Takashi Honda[1] Masatoshi Ishigami[1]

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Background: In a promising preclinical study of metabolic-dysfunction associated steatohepatitis (MASH), we have previously reported that injection of serum-free conditioned medium from stem cells derived from human exfoliated deciduous teeth (SHED-CM) provides therapeutic benefit in a mouse model. This therapeutic benefit is multifaceted, including hepatoprotective, macrophage-mediated anti-inflammatory, and intestinal barrier protective effects. We are particularly interested in the therapeutic potential of soluble siglec-9 (sSiglec-9), one of the proteins in SHED-CM, because it induces anti-inflammatory macrophages and a recent study showed that sSiglec-9 exerts a protective effect on intestinal epithelium. In the present study, we found that sSiglec-9 protects the intestinal barrier function in MASH mice. **Methods:** Initially, the ability of sSiglec-9 to preserve intestinal barrier function was investigated *in vitro* using a Caco-2 cell monolayer as a model. Then, for *in vivo* studies, we used the MASH mouse model in which male C57BL/6J mice were given a Western diet and high-sugar solution orally and, to induce liver injury, CCl_4 intraperitoneally once a week for 12 weeks. These mice were also treated with 10 ng/g sSiglec-9 or PBS once a week. Intestinal permeability was evaluated by measuring blood levels of 4kD-FITC dextran after oral administration. Finally, mice were sacrificed for transcriptomic analysis of intestinal tissues and histological evaluation of the liver. **Results:** In Caco-2 monolayers injured with TNFα and INFγ, treatment with either sSiglec-9 or SHED-CM was protective as shown by a decreased permeability for FITC-dextran. In MASH mice, sSiglec-9 treatment also significantly suppressed the MASH-typical increase in intestinal permeability (p=0.016). RNA sequencing of intestinal tissue identified 34 differentially expressed genes, including the innate immunity genes *Olfm4*, *CD177 and defensin α*. GO analysis revealed significant enrichment in sets of genes related to intestinal mucosal immunity, including “membrane disruption in another organism” and “innate immune response in mucosa.” In liver tissue, sSiglec-9 treatment showed a tendency to reduce inflammation in the portal area. **Conclusion:** In MASH, sSiglec-9 treatment may help protect the intestinal barrier function by reducing mucosal inflammation as suggested in our mouse model. sSiglec-9 treatment may become a new therapy for treating MASH via the gut-liver axis.

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1006 | A NEW THERAPEUTIC APPROACH FOR MASLD/MASH TREATMENT

Takashi Tsuchiya[1] So Yeon Kim[1] Vijay Pandyarajan[2] Michitaka Matsuda[3] Mitsuru Naiki[4] Ekihiro Seki[1]

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Background: The prevalence of metabolic dysfunction–associated steatotic liver disease (MASLD) has been increasing over the last decade, with 20 to 25% of the cases developing to metabolic dysfunction–associated steatohepatitis (MASH). Thanks to many clinical trials, the Food and Drug Administration (FDA) has approved the first medication called Rezdiffra (resmetirom) recently. However, a different drug for MASLD/MASH is still highly sought-after. Existing drugs, with safety data available, could be repurposed for new indications, thereby saving time and cost for development. We investigated in an animal model if the analgesic Neurotropin (NTP) can be

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used for MASLD treatment. **Methods:** C57BL/6 WT mice were divided into two groups in terms of feeding: (1) normal chow diet plus normal drinking water (ND/NW) (2) high-fat diet plus high fructose/glucose drinking water (HFD/HFGW), and four treatment groups: (1) vehicle control, (2) Obeticholic acid (OCA), (3) NTP (Low dose), and (4) NTP (High dose). They were fed for a total of 12 weeks. The drugs were administered daily for six weeks by oral gavage following six weeks of feeding. **Results:** NTP treatment decreased serum ALT and AST levels, protecting the liver against high-fat diet-induced hepatocellular damage. NTP also inhibited liver steatosis as assessed by serum and liver lipids, Oil Red O, and H&E staining. Moreover, F4/80 staining indicated that NTP reduced the diet-induced hepatic inflammation. Western blot analysis supported these findings by confirming the decreased protein expression of p-JNK, p-ERK, p-p38 in the NTP-treated mice liver. NTP suppressed primary hepatic stellate cells activation in vitro, and reticulin staining revealed that NTP ameliorated liver fibrosis in vivo. In keeping with this observation, mRNA levels of Cxcl1, Ccl2, Tnf, Timp1, Col1a1, Col3a1, Col4a1, Scd, and Dgat 1&2 were downregulated in the liver by NTP treatment. Mitoplex analysis showed that NTP upregulated the expression of mitochondrial proteins for maintaining mitochondria functions via AMPK activation. Consistent with this data, mRNA levels of Ppargac1b, Ogg1, and Cox8c and protein levels of PGC-1β and p-AMPK were recovered by NTP administration. Notably, NTP inhibited free fatty acid (FFA)-induced lipid accumulation, and improved mitochondrial dysfunction in human primary hepatocytes, as revealed by Oil Red O staining and Seahorse assay. Also, we found distinct signatures in our gut microbiome analysis data; NTP reduced total bacteria DNA levels in the stool, and abundance of Clostridia bacteria which is related to wound infection. **Conclusion:** NTP has beneficial effect on multiple cell types and protective function against hepatic steatosis and injury in the liver. Therefore, NTP can be a useful intervention for treating MASLD/MASH. Widely used for over 50 years in Japan and China without significant side effect, NTP can be an effective and safe medication for MASLD/MASH management.

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1007 | 11β-HSD1 INHIBITION ON NON-ALCOHOLIC FATTY LIVER DISEASE: INVESTIGATING IMMUNE CELL DYNAMICS VIA SINGLE-CELL MASS CYTOMETRY

Dae Won Jun[1] Eileen Yoon[1] Ji Hyun An[1] HA IL KIM[1] Joo Hyun Sohn[1] Bo-Kyeong Kang[1] Chul-Min Lee[1] Hyo Young Lee[2] Hyun Woo Oh[3] Hye-Lin Kim[4] Sang Bong Ahn[5] Joo Hyun Oh[5]

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Background: Metabolic dysfunction associated steatosis liver disease (MASLD) affecting one-fourth of the world's population. However, non-invasive diagnostic tools and effective drug treatments for patients with MASLD are still lacking. Systemic immune dysregulation, such as inflammation, plays a pivotal role in MASLD development, indicating the possibility of utilizing quantitative and phenotypic changes in the peripheral immune cells to diagnose and treat MASLD. **Methods:** We compared the immune cell populations in samples of healthy patients and patients with MASLD using high-dimensional mass cytometry at the single-cell level. Using a multi-parametric mass cytometry approach, we analyzed peripheral blood mononuclear cells (PBMCs) from MASLD, healthy, and drug-treated groups. Isolated PBMCs were stained with 29 markers, and 15 cell types were identified. **Results:** Comparison of manually gated immune cell percentages in total leukocytes revealed elevated frequencies of total $CD8^+$ T cells, early NK cells, and monocytes, and decreased T_H2, late NK, T_H1, and Treg cells in patients with MASLD. Automated clustering was used to identify subsets of NK and phagocytic cells. These subsets were further investigated for specific marker expression. We demonstrated that an 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) inhibitor significantly downregulated inflammatory cytokines in late NK cells and pDCs, suggesting its potential therapeutic efficacy in MASLD treatment. **Conclusion:** Our findings illuminate the complex immune landscape of MASLD and suggest that 11β-HSD1 inhibition may offer a novel therapeutic strategy. These insights contribute to our understanding of the immunological dimensions of MASLD and propose a targeted approach for future interventions.

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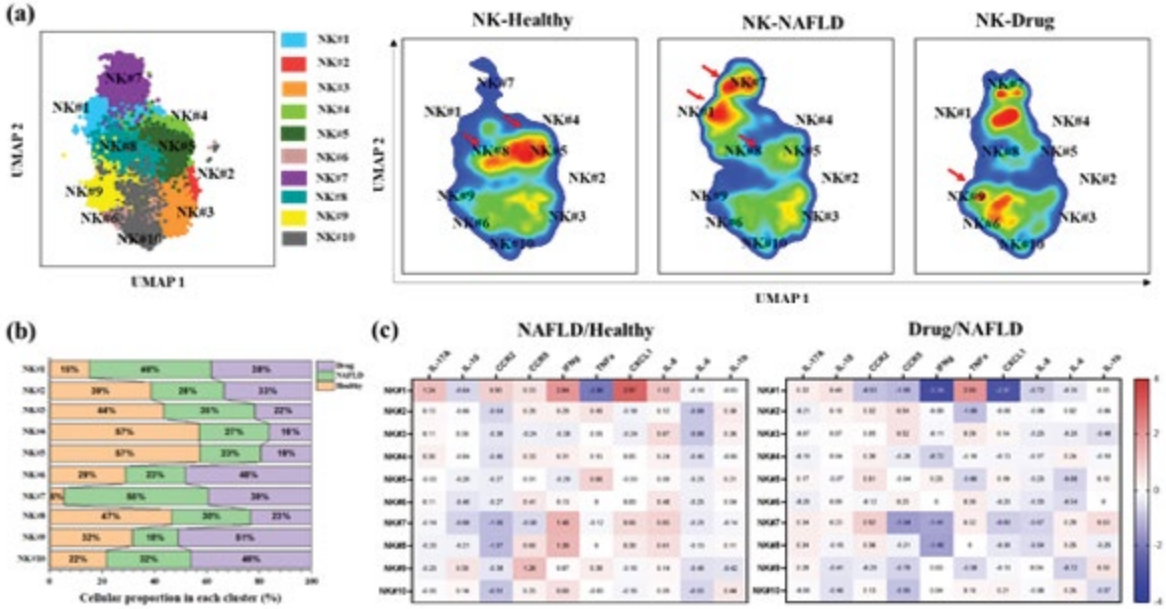

Disclosures: Dae Won Jun: Nothing to Disclose, Eileen Yoon: Nothing to Disclose, Ji Hyun An: Nothing to Disclose, HA IL KIM: Nothing to Disclose, Joo Hyun Sohn: Nothing to Disclose, Bo-Kyeong Kang: Nothing to Disclose, Chul-Min Lee: Nothing to Disclose, Hyo Young Lee: Nothing to Disclose, Hyun Woo Oh: Nothing to Disclose, Hye-Lin Kim: Nothing to Disclose, Sang Bong Ahn: Nothing to Disclose, Joo Hyun Oh: Nothing to Disclose

1008 | DGAT2 INHIBITION BLOCKS ACTIVATION OF SREBP-1 AND IMPROVES HEPATIC STEATOSIS BY INCREASING ER PHOSPHATIDYLETHANOLAMINE

Shunxing Rong[1] Mingfeng Xia[2] Goncalo Vale[1] Simeng Wang[1] Chai-Wan Kim[1] Shili Li[1] Jeffrey McDonald[1] Arun Radhakrishnan[1] Jay Horton[1]

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Background: Diacylglycerol acyltransferase (DGAT)-2 catalyzes the final step of triglyceride (TG) synthesis by adding acyl-CoAs to diacylglycerol (DAG). Deletion of DGAT2 in mice dramatically reduces liver TG level. Recent clinical trial studies demonstrate DGAT2 inhibition significantly improves hepatic steatosis in individuals with metabolic dysfunction-associated steatotic liver disease (MASLD). Here, we further characterized the molecular mechanism by which DGAT2 inhibition reduces *de novo* lipogenesis and improves hepatic steatosis. **Methods:** A DGAT2 inhibitor was mixed in diet and fed to C57Bl/6J mice, *ob/ob* mice and human SREBP-1c transgenic (TghSREBP-1c) rats for 7 days. Cholesterol and TG levels in both plasma and liver were measured. Total RNA was prepared from liver and lipogenesis gene expression was quantified by qPCR. Membrane and nuclear forms of SREBPs were detected by immunoblot analysis. ER fractions from the livers were prepared and subjected to lipid profiling measurements with LC-MS/MS. In cultured cells, phosphatidylethanolamine (PE) was enriched in the ER by incubating cells with either PE enriched liposomes or ethanolamine and activation of SREBPs was analyzed. To determine whether Insigs were required for the regulation of SREBP-1 by PE, Insigs were knocked out in both human fibroblast cells and in mice. PE levels were modified by supplementing ethanolamine to cells or deleting DGAT2 in hepatocytes of mice. **Results:** In all animal models, when DGAT2 was inhibited or knocked out, the PE content in the ER increased, which blocked SREBP-1 exit from the ER to Golgi for cleavage and activation, resulting in reduced fatty acid synthesis and lowered TG accumulation in liver. PE enrichment of the ER in cultured cells also suppressed SREBP-1 cleavage suggesting that PE was responsible for the regulation. Finally, we show the PE regulation of SREBP activation does not require Insigs, critical retention proteins that prevent the activation of SREBPs by sterols. **Conclusion:** Here we show that not only does blocking DGAT2 inhibit the conversion of DAGs to TGs, but it also shunts DAGs into phospholipid synthesis, increasing the PE content of the ER, resulting in reduced SREBP-1 cleavage and less hepatic steatosis. These studies reveal a previously unrecognized mechanism that regulates SREBP-1 activation in mammals that is independent of the usual SREBP regulatory machinery by sterols and Insigs.

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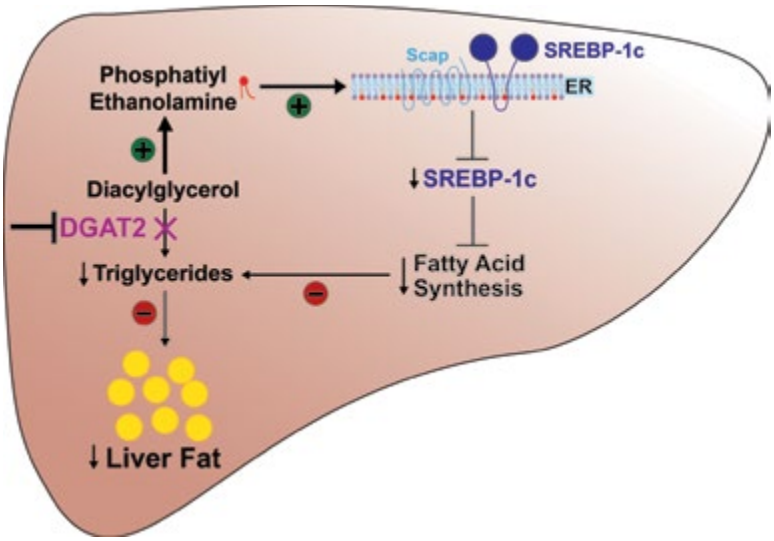

Disclosures: Shunxing Rong: Nothing to Disclose, Mingfeng Xia: Nothing to Disclose, Goncalo Vale: Nothing to Disclose, Simeng Wang: Nothing to Disclose, Chai-Wan Kim: Nothing to Disclose, Shili Li: Nothing to Disclose, Jeffrey McDonald: Nothing to Disclose, Arun Radhakrishnan: Nothing to Disclose, Jay Horton: Pfizer: Consultant, Merck: Consultant, Regeneron: Consultant

1009 | CYTOPLASMIC EXPORT OF CIRCPOLD1 PROMOTES METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS LIVER DISEASE THROUGH INTERACTION WITH HUR ◆

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Background: The increasing prevalence of metabolic dysfunction–associated steatohepatitis liver disease (MASLD) due to obesity highlights the need for early biomarkers and targeted therapies. Circular RNA (circRNA), known for its stability in bodily fluids, holds potential as an early diagnostic and prognostic biomarker. However, the mechanism of circRNA nuclear export and its interactions with RNA-binding proteins (RBPs) in MASLD remains unclear. This study aims to explore the regulatory role of circPOLD1 on HuR in MASLD pathogenesis. **Methods:** Liver tissues from healthy controls and MASLD patients were analyzed using RNA-sequencing and bioinformatics to identify differentially expressed circRNAs. In vitro and in vivo experiments were performed to study the role of circRNA in MASLD. RT-qPCR and western blot assays were used to measure mRNA and protein levels. Predicted circRNA-RBPs interactions were validated through RNA-FISH, RNA pull-down, and RNA immunoprecipitation assays. **Results:** We identified that circPOLD1, derived from the POLD1 gene, was upregulated in MASLD patients and models. Knockdown of circPOLD1 increased hepatic lipid transport and decreased hepatic lipid accumulation, while overexpression of circPOLD1 has the opposite effect. Mechanistically, we found that circPOLD1 interacted with HuR, an RBP, facilitating its translocation from the nucleus to the cytoplasm. This led to increased cytoplasmic HuR levels, activating Akt and FoxO1 phosphorylation. Consequently, FoxO1 was excluded from the nucleus, suppressing microsomal triglyceride transfer protein expression and inhibiting lipid transport. We further found that SUMOylation of DDX39A, a key regulator of circRNA nuclear-cytoplasmic transport, controlled the nuclear retention of circPOLD1. SUMOylated DDX39A facilitates the nuclear export of circPOLD1, which drags HuR out of the nucleus, enhancing the inhibitory effect of circPOLD1 on lipid transport and leading to increased hepatic lipid accumulation. Clinically, we observed a significant upregulation in serum circPOLD1 levels in MASLD patients. **Conclusion:** Our study identifies circPOLD1 as a novel factor involved in MASLD and reveals its role in regulating HuR/AKT/FOXO1 signaling and lipid transport through SUMOylation-mediated nuclear export. These findings highlight the potential of circPOLD1 as a promising therapeutic target for patients with MASLD.

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1010 | MRC2 DEFICIENCY ALLEVIATES THE DEVELOPMENT OF HFD-INDUCED NAFLD VIA DOWNREGULATING CD147-MEDIATED TNF-α PRODUCTION IN MACROPHAGE

Hui-Ru Kuo[1] Kwei-Yan Liu[2] Hsin-Ying Clair Chiou[3] Yu-Fen Chung[2] Li-Ting Wang[4] Chih-Wen Wang[1] Shih-Hsien Hsu[1] Shau-Ku Huang[2] Ming-Hong Lin[1]

[1]Kaohsiung Medical University, [2]National Health Research Institutes, [3]Kaohsiung Chang Gung Memorial Hospital, [4]National Taiwan Normal University

Background: NAFLD is becoming the most common chronic liver disease worldwide, while its mechanism remains unclear and there are still no effective drugs in the clinic. MRC2 is a transmembrane glycoprotein involved in the internalization and lysosomal degradation of collagen and has been suggested to play a role in hepatocellular carcinoma (HCC), but its regulatory role in the development and progression of NAFLD is still unknown. **Methods:** We fed WT and *Mrc2*$^{-/-}$ mice with a high-fat diet (HFD) for 8 weeks to observe the effects of *Mrc2* on NAFLD. We also isolated mouse primary hepatocytes (MPHs) and bone marrow-derived macrophages (BMDMs) for *in vitro* study and used palmitic acid (PA) to simulate the HFD effect. **Results:** Analysis of the NAFLD dataset from the GEO database showed a positive correlation between hepatic MRC2 levels and NAFLD severity. Increased *Mrc2* level was observed in the liver of HFD-fed WT mice, but, surprisingly, *Mrc2*$^{-/-}$ mice showed significantly reduced levels of HFD-induced weight gain and fatty liver compared with WT mice. Besides, *Mrc2* was mainly expressed in hepatic nonparenchymal cells but rare in mouse hepatocytes. Conditioned medium (CM) collected from WT-BMDMs increased PA-induced steatosis in MPHs, such effect was ameliorated by CM collected from *Mrc2*$^{-/-}$-deficient BMDMs, and the addition of TNF-α neutralizing antibody or TNFR antagonist in the co-culture. Moreover, the disruption of the MRC2-CD147 complex on the cell membrane affected CD147-mediated NF-κB signaling and reduced the release of TNF-α in BMDMs, thereby leading to a reduction in steatosis in MPHs. **Conclusion:** Conclusively, Macrophage MRC2 prompted HFD-mediated steatosis in hepatocytes by, at least in part, stabilizing CD147 on the membrane, and its subsequent NF-κB signaling and TNF-α release, suggesting the potential role of the MRC2-CD147 complex in NAFLD and its promise as a therapeutic target for NAFLD.

Disclosures: Hui-Ru Kuo: Nothing to Disclose, Kwei-Yan Liu: Nothing to Disclose, Hsin-Ying Clair Chiou: Nothing to Disclose, Yu-Fen Chung: Nothing to Disclose, Li-Ting Wang: Nothing to Disclose, Chih-Wen Wang: Nothing to Disclose, Shih-Hsien Hsu: Nothing to Disclose, Shau-Ku Huang: Nothing to Disclose, Ming-Hong Lin: Nothing to Disclose

1011 | LIPROXSTATIN-1 MITIGATES LIVER DAMAGE BY INHIBITING FERROPTOSIS IN A MASLD MOUSE MODEL

Wei Wang[1] Hongsong Chen[1] Feng Liu[1] Huiying Rao[1]

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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) represents a growing public health concern worldwide. The central role of oxidative stress and dysregulation of lipid metabolism in MASLD pathogenesis positions ferroptosis as an attractive target for novel therapeutic approaches. The purpose of this study is to evaluate the therapeutic potential of the ferroptosis inhibitor, Liproxstatin-1, in methionine-choline deficient (MCD)-diet induced mice as a MASLD mouse model. **Methods:** Various stages of MASLD mouse model were established by feeding male C57BL/6 mice a MCD-diet. Then the mice were randomly divided into two groups. The mice in experimental group were intraperitoneally injected with 10mg/kg Liproxstatin-1 twice a week. The control group was not received Liproxstatin-1 treatment. There was also a group of mice fed by normal food for comparison. Serum biochemical markers of liver function were measured at multiple time points, specifically at 4-, 8-, and 12-weeks post-induction of the model. The content of malondialdehyde (MDA), a key marker of lipid peroxidation, was quantitatively analyzed in liver tissues at corresponding time points. Liver Activity Score (NAS) was determined based on liver histopathological evaluation, with scores ranging from 0 to 8. **Results:** Mice in the MCD-diet group exhibited significantly elevated levels of ALT, AST, ALP, TBIL and BIL compared to those on a normal diet. Upon administration of Liproxstatin-1, a downward trend in these biochemical markers was observed, with the most significant differences occurring at the 12-week interval, suggesting a substantial improvement

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in liver function due to the therapeutic intervention. MDA levels were significantly elevated in the MCD-induced model at each experimental point. Liproxstatin-1 treatment significantly decreased hepatic MDA levels at weeks 8 and 12, with the difference being especially notable at week 12. Liver histopathology results showed an increase in NAS values of the MCD-diet mice over time; however, administration of Liproxstatin-1 initiated a reduction in NAS values commencing at week 8. **Conclusion:** Liproxstatin-1 showed a promising candidate for reducing liver damage and antioxidative effects through ferroptosis inhibition, offering potential therapeutic strategies for managing MASLD.

Disclosures: Wei Wang: Nothing to Disclose, Hongsong Chen: Nothing to Disclose, Feng Liu: Nothing to Disclose, Huiying Rao: Nothing to Disclose

1012 | HEPATIC CHENODEOXYCHOLIC ACID PROMOTES MASH WITH HCC IN HIGH-FAT/HIGH-SUCROSE DIET-FED MICE WITH HUMAN-LIKE BILE ACID COMPOSITION

Hajime Ueda[1] *Akira Honda*[1] *Teruo Miyazaki*[1] *Tadashi Ikegami*[1]

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Background: Metabolic dysfunction-associated steatohepatitis (MASH) is a significant risk factor for developing hepatocellular carcinoma (HCC); however, the mechanisms remain unclear. Feeding wild-type (WT) mice a high-fat/high-sucrose diet (HFHSD), without cholesterol loading or a carcinogen, rarely results in MASH with HCC. At the last Liver Meeting, we reported that a conventional HFHSD caused a high rate of MASH with HCC, in Cyp2a12/Cyp2c70 double knockout (DKO) mice with human-like bile acid (BA) composition. Therefore, this study explored the role of two essential factors—HFHSD and hydrophobic BAs—in developing MASH with HCC. **Methods:** Eleven-week-old WT and DKO mice were divided into two groups, including: one which was fed a normal chow diet, and one which was fed an HFHSD. Samples were collected after 15, 30, 47, and 58 weeks for histological, biochemical, and immunological analyses. **Results:** No differences in body weight gain were observed between WT and DKO mice after being fed an HFHSD. DKO mice showed less severe hepatic steatosis and insulin resistance than WT mice. However, they had markedly accelerated liver inflammation, fibrosis, and carcinogenesis when compared with WT mice. In HFHSD-fed DKO mice, tumor incidence was 70% after 47 weeks, and reached 100% after 58 weeks. In both genotypes, HFHSD upregulated lipogenesis and downregulated fatty acid β- and ω-oxidation, which increased liver lipid accumulation and consequently lipotoxicity. However, this abnormal lipid metabolism alone could not explain the increased reactive oxygen species (ROS) production and carcinogenesis in DKO mice when compared with WT mice. For BA metabolism, DKO mice not only had a higher hydrophobicity index, but were also characterized by an age-associated increase in the proportion of chenodeoxycholic acid (CDCA) due to inhibited CYP8B1 activity. HFHSD further downregulated CYP8B1, presumably by suppressing the retinoid-related orphan receptor (ROR) via the activation of the Liver X receptor (LXR). Accumulated CDCA in the liver was associated with increased inflammation, ROS production, and the induction of fibroblast growth factor 15 (FGF15) in hepatocytes. Moreover, HFHSD tended to activate the oncogenic transcription factor STAT3 in noncancerous liver tissue, with a high CDCA environment further enhancing this activation. **Conclusion:** We generated a new mouse model of MASH with HCC under human-like conditions. HFHSD and elevated hepatic CDCA synergistically increased the risk of MASH with HCC in this mouse model.

Disclosures: Hajime Ueda: Nothing to Disclose, Akira Honda: Nothing to Disclose, Teruo Miyazaki: Nothing to Disclose, Tadashi Ikegami: Nothing to Disclose

1013 | A NOVEL MASLD MODEL EVALUATES DIET AND ALCOHOL INDUCED PATHOLOGY AND BEHAVIOR

Josiah Hardesty[1] *Rui Treves*[1] *Tyler Gripshover*[1]

[1]*University of Louisville*

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is a disease associated with many modifying factors such as diet and alcohol consumption. Because humans are on a continuum of exposures

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based on unique behavior patterns, it has been difficult to develop models to monitor dietary and alcohol preferences. The objective of this study was to analyze the metabolic and behavioral impact of high fat diet (HFD) feeding with concurrent alcohol (EtOH) consumption in a MASLD mouse model. We hypothesize that differing dietary consumption patterns will uniquely impact pre-clinical markers of alcohol-related metabolism disruption and injury. **Methods:** 10-12 week old, male C57Bl/6J mice (n=9 per group) were fed either a control diet (CD), HFD, or both along with only H_2O, 10% EtOH, or both. A full choice group was provided all diet and liquids for the duration of study. An intervention group was provided full choice for the first 6 weeks, but were switched to CD and H_2O only from week 7 to 13. Mice and diets were measured weekly. A glucose tolerance test was performed at week 12. Blood lipids, cytokeratin-18 (KRT18), endotoxin, and hepatic cytokines were assessed. Data were analyzed via one-way ANOVA with Tukey's post-hoc test for a a=0.05. **Results:** Mice that were provided both CD and HFD consumed more HFD than CD, and mice provided H_2O and EtOH consumed more H_2O than EtOH. All mice that had access to HFD developed dyslipidemia, enhanced body weight, glucose intolerance, hepatic steatosis, and increased white adipose tissue weight. Mice that had access to EtOH had reduced fasting glucose levels and improved glucose tolerance, even when provided a HFD. Mice that only had access to HFD had elevated plasma KRT18 and endotoxin, while mice that had access to both diets had lower levels. Endotoxemia was exacerbated in HFD fed mice, but mice that had concurrent access to CD were protected. Liver TNFa levels were elevated in mice that had access to an HFD. By week 13, the intervention mice body weight, dyslipidemia, glucose tolerance, and hepatic steatosis returned to CD+H_2O mice levels. **Conclusion:** While mice that were exclusively provided a HFD had exacerbated MASLD endpoints, mice that had access to both CD and HFD were protected against endotoxemia and hepatic necrosis. This suggests that a balanced diet is protective even when most calories are from fat. Balanced dietary choices and alcohol cessation is an initial, effective way to mitigate alcohol-related metabolism disruption and injury.

Disclosures: Josiah Hardesty: Nothing to Disclose, Rui Treves: Nothing to Disclose, Tyler Gripshover: Nothing to Disclose

1014 | FUMARATE SUPPLEMENTATION AMELIORATES MASH PATHOLOGY IN A MURINE MODEL OF MASLD BY TARGETING THE TCA CYCLE

Masaaki Mino[1] Eiji Kakazu[1] Akitoshi Sano[2] Taiji Yamazoe[3] Michitaka Matsuda[3] Taizo Mori[3] Sachiyo Yoshio[1] Jun Inoue[4] Tatsuya Kanto[1]

[1]National Center for Global Health and Medicine, [2]Mayo Clinic, Rochester, [3]National Center for Global Health and Me, [4]Tohoku University

Background: Metabolic dysregulation, characterized by imbalances in free fatty acids, amino acids (AAs) and carbohydrates, is crucial for the development of steatosis and fibrosis in MASH. Fumarate, an intermediate of the tricarboxylic acid (TCA) cycle, plays a key role in protecting against MASH-associated lipotoxicity. The aim of this study is to elucidate the therapeutic effect of targeting fumarate in the TCA cycle in MASH mice. **Methods:** Eight-week-old male C57BL/6 mice were assigned to the following groups: a normal chow (NC) group, a high-fat, high-fructose, high-cholesterol diet (FFC) group, and FFC group supplemented with five types of esterified compounds with cell membrane permeability targeting fumarate: dimethyl fumarate (DMF), dimethyl malate (DMM), dimethyl succinate (DMS), dimethyl maleate (DMME) and dimethyl malonate (DMMO). We assessed body weight, various blood biochemical parameters, and performed histopathological examinations. In the NC, FFC and DMF groups, lipoprotein fraction analyses in blood, metabolomics, lipidomics and RNA-seq analyses of liver and adipose tissue were performed. **Results:** The FFC group showed significant increases in body weight, liver weight, and liver damage compared to the NC group, with pathological changes characteristic of MASH. This was associated with a decrease in the large VLDL fraction in the blood and a significant reduction in glucogenic AAs, as well as in TCA cycle intermediates fumarate and succinate. Additionally, the NADH/NAD ratio increased, suggesting mitochondrial dysfunction. Among the five groups, the DMF group showed significant improvement in body weight, liver damage and MASH-like pathological changes observed in the FFC group. The DMM group showed a tendency for improvement in liver damage and MASH pathology, while the DMS, DMME and DMMO groups did not show these improvements. In the DMF group fumarate in the TCA cycle and glucogenic AAs in the liver increased compared to the FFC group, and the NADH/NAD ratio improved. Furthermore, the reduced large VLDL fraction in the blood improved. RNA-seq and lipidomics analyses also showed that DMF suppresses the upregulated lipogenesis in the liver induced by the FFC diet, suggesting that DMF has the potential to ameliorate MASH pathogenesis by improving dysfunctional VLDL secretion. Interestingly, in the DMS group, which includes

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a precursor of succinate, and in the DMME group, which is the geometric isomer of DMF, neither body weight nor liver weight increased, nor was liver damage suppressed. Pathologically, there were no improvements in MASH-like changes. These findings suggest that intermediate metabolites in the TCA cycle, specifically from fumarate to malate, might play a crucial role in the progression of MASH. **Conclusion:** Targeting fumarate within the TCA cycle in the liver with DMF improves MASH pathology in a murine model of MASH.

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1015 | THE ROLE OF BH3-ONLY PROTEIN NOXA IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE

SHINNOSUKE KUDO[1] *Hayato Hikita*[1] *Yoshinobu Saito*[1] *Takahiro Kodama*[1] *Tomohide Tatsumi*[1] *Tetsuo Takehara*[1]

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Background: Continuous hepatocyte apoptosis with the activation of pro-apoptotic Bcl-2 family proteins, Bak/Bax, is observed in various chronic liver diseases including metabolic dysfunction-associated steatotic liver disease (MASLD) and viral hepatitis. BH3-only proteins, upstream of the core Bcl-2 family proteins, can activate Bak and Bax, and the activation of these BH3-only proteins is involved in various chronic liver diseases. We previously reported that BH3-only proteins, Bid and Bim, were involved in regulating hepatocyte apoptosis. In the present study, we aimed to reveal the role of another BH3-only protein, Noxa, in hepatocyte apoptosis and the pathophysiology of MASLD. **Methods:** As a model of chronic liver injury with Bak/Bax activation, we generated hepatocyte-specific Mcl-1 knockout (KO) mice. We crossed these mice with Noxa KO mice to clarify the role of BH3-only protein, Noxa. To examine the role of Noxa in apoptosis related chronic liver disease, MASLD, C57BL/6J mice were fed a Western Diet (WD) or a normal diet (ND) for 12 weeks. Noxa KO mice and control mice were fed a Western Diet for 12 weeks and analyzed. Human liver tissue samples for histological analyses were obtained from 27 patients with MASLD who underwent liver biopsy at Osaka University Hospital from 2016 to 2019. **Results:** Hepatocyte-specific Mcl-1 knockout (KO) mice showed hepatocyte apoptosis and elevation of serum ALT levels at the age of 6 weeks. Mcl-1/Noxa double KO mice showed significantly lower levels of serum ALT and smaller number of TUNEL positive hepatocytes than Mcl-1 KO mice. These findings showed that Noxa had a role of inducing hepatocyte apoptosis. We next examined the role of Noxa in MASLD. Serum ALT levels of WD-fed C57BL/6J mice were significantly higher than those of ND-fed mice. Liver tissues from the mice fed with WD displayed extensive steatosis, and the significant increase in TUNEL positive hepatocytes compared to ND-fed group. Noxa expressions were significantly upregulated in WD-fed mouse liver. WD-fed Noxa KO mice demonstrated significant reduction of liver weight to body weight ratio, serum ALT levels, and the number of TUNEL positive hepatocytes than WD-fed control mice. Noxa KO mice also showed significant improvement of liver steatosis as evidenced by Oil Red O staining. The clinical relevance of Noxa was further investigated in human MASLD. Noxa expression in resected liver tissues of MASLD patients were increased compared to samples of normal liver. In addition, expression levels of Noxa in the liver biopsy samples from MASLD patients exhibited a positive correlation with serum ALT levels, and Noxa expressions were significantly increased in accordance with the grade of steatosis. **Conclusion:** BH3-only protein Noxa participates in Bak/Bax dependent hepatocyte apoptosis, and the activation of Noxa in hepatocyte may be associated with the pathophysiology of MASLD.

Disclosures: SHINNOSUKE KUDO: Nothing to Disclose, Hayato Hikita: Nothing to Disclose, Yoshinobu Saito: Nothing to Disclose, Takahiro Kodama: Chugai Pharmaceuticals: Speaking and Teaching, Astrazeneca: Speaking and Teaching, Eisai Co Ltd: Speaking and Teaching, Tomohide Tatsumi: Nothing to Disclose, Tetsuo Takehara: Nothing to Disclose

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1016 | THE INCREASED IL-1β SECRETION OF MACROPHAGES ACCOMPANYING AUTOPHAGY DYSFUNCTION ENHANCES THE INFLAMMATORY CHEMOKINE EXPRESSION OF LSECS, CONTRIBUTING TO THE PROGRESSION OF MASH PATHOLOGY

Kenji Fukumoto[1] Hayato Hikita[1] Yoshinobu Saito[1] Kazumasa Soma[1] Seiya Kato[1] Yoichi Sasaki[1] Kazuhiro Murai[1] Takahiro Kodama[1] Tomohide Tatsumi[1] Tetsuo Takehara[1]

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Background: In the pathogenesis of chronic liver diseases, the various roles of non-parenchymal cells in the hepatic microenvironment have been highlighted. The aim of this study is to elucidate the pathogenic mechanisms of MASH progression through cell-cell interactions, with liver macrophages as the starting point. **Methods:** For in vitro studies, the human monocytic cell line THP-1 and the human liver sinusoidal endothelial cell (LSEC) line TMNK-1 were utilized. Western Diet (WD) was administered to create a MASH mouse model, and intraperitoneal injection of LPS was performed for acute hepatitis mouse model. Clinical specimens consisted of RNA sequencing analysis using liver biopsy samples from 98 MASLD patients, including those with MASH. Single-cell RNA sequencing analysis was performed using liver samples from three donor patients and surgical specimens from two MASH patients. **Results:** In liver tissues of MASH mice and hepatic macrophages, impaired autophagy with diminished TFEB and enhanced IL-1β secretion were observed. Furthermore, induction of autophagy impairment via palmitic acid administration or Atg7 KO augmented IL-1β secretion in THP-1 macrophages. Analysis of Single cell RNA sequencing of liver tissues and MACS-isolated cells revealed upregulation of inflammatory chemokine gene expression, such as CXCL10 and CCL2, in LSECs of the WD group compared to the normal diet group. Furthermore, the **Results:** of the single-cell RNA sequencing analysis revealed that the IL1R1 gene was highly expressed in endothelial cells in both mouse liver tissues and liver tissues from MASH patients. IL-1β in the culture supernatant of Atg7 KO THP-1 macrophages activated JNK, thereby enhancing inflammatory chemokine expression in TMNK-1 cells. In the intraperitoneal LPS injection model, bone marrow-specific Atg7 KO mice exhibited increased secretion of IL-1β protein and upregulated inflammatory chemokine expression in LSECs compared to wild-type mice. Endothelial cell-specific IL1R1 KO and systemic CXCL10 KO in MASH models led to decreased expression of inflammatory chemokines and monocyte-macrophage-related genes in liver tissues, accompanied by improvement in hepatic damage and fibrosis compared to wild-type mice. RNA sequencing of liver tissues from MASLD patients revealed significantly increased CXCL10 gene expression in the MASH group compared to the non-MASH group, correlating positively with the NAS score. CXCL10 gene expression showed a strong positive correlation with IL1B expression and expression of monocyte-macrophage-related genes. **Conclusion:** The increased IL-1β secretion from hepatic macrophages due to autophagy impairment potentially contributes to the progression of MASH by enhancing infiltration of inflammatory cells such as monocytes, mediated through chemokine induction in LSECs.

Disclosures: Kenji Fukumoto: Nothing to Disclose, Hayato Hikita: Nothing to Disclose, Yoshinobu Saito: Nothing to Disclose, Kazumasa Soma: Nothing to Disclose, Seiya Kato: Nothing to Disclose, Yoichi Sasaki: Nothing to Disclose, Kazuhiro Murai: Nothing to Disclose, Takahiro Kodama: Chugai Pharmaceuticals: Speaking and Teaching, Astrazeneca: Speaking and Teaching, Eisai Co Ltd: Speaking and Teaching, Tomohide Tatsumi: Nothing to Disclose, Tetsuo Takehara: Nothing to Disclose

1017 | AUTOMATED SHEAR WAVE ELASTOGRAPHY CAPTURES MASLD ONSET IN C57BL/6NTAC MICE PRECONDITIONED ON A MODIFIED AMYLIN LIVER NASH DIET

Laura Griffin[1] Sri Radhakrishnan[2] Steven Yeung[2] Tomek Czernuszewicz[3] Christopher Moore[3] Juan Rojas[3] Brian Velasco[4] Paul Dayton[4]

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Background: C57BL/6 mice on a modified Amylin liver NASH (GAN) diet demonstrate SLD and more closely recapitulate human MASLD compared to other preclinical models. While translatable, this model is characterized by variation which historically could only be addressed through liver biopsies to assess disease stage. While non-invasive techniques like liver elastography for humans exist, a need exists for comparable technology for preclinical models. The study goal was to determine whether a non-invasive, automated shear wave elastography (SWE) imaging instrument could accurately determine progression of SLD in GAN diet-fed C57BL/6NTac (NASH

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B6) mice. **Methods:** Commercially available NASH B6 mice conditioned on GAN diet for 15, 26, or 37 weeks (*n*=8/group) and age-matched controls (*n*=4/group) were shipped from vendor to study site. Following acclimation, liver stiffness, volume, and echogenicity was assessed via 3D B-mode and SWE imaging. Livers were segmented from 3D image datasets using novel AI-assisted segmentation software. Median stiffness and echogenicity were quantified per mouse. A separate cohort of NASH B6 mice (*n*=8; 12 weeks on diet) and age-matched controls were shipped to the study site for longitudinal assessment every 3 weeks for 4 months. SWE measurements from all cohorts were compared to histological and blood chemistry data to assess correlation. Results are reported as mean ± std. **Results:** Liver volume significantly increased over time in cross-sectional and longitudinal NASH B6 cohorts compared to controls, indicating increased liver weight due to NASH diet conditioning (3.6±0.5 cm^3 vs 1.5±0.4 cm^3 at 37 wks, p≤0.01). Liver echogenicity also significantly increased over time in the cross-sectional and longitudinal NASH B6 cohorts (63±14 a.u at 15 wks vs. 94±5 a.u. at 37 wks, p≤0.01) indicating the onset of liver steatosis. Liver stiffness was only marginally increased in NASH B6 mice from the cross-sectional cohort, despite diet conditioning beyond 8 months (4.9±0.6 kPa vs. 4.3±0.6 kPa at 37 weeks, p=n.s.). This observation highlights the utility of noninvasive screening technology for phenotype assessment and subject recruitment in preclinical studies. **Conclusion:** Our data present the potential of automated ultrasound to assess SLD progression in a clinically translatable preclinical model non-invasively. This allows for an improved study design targeting specific SLD stages and reduced study variability in the pursuit of SLD drug discovery.

Disclosures: Laura Griffin: Nothing to Disclose, Sri Radhakrishnan: Nothing to Disclose, Steven Yeung: Nothing to Disclose, Tomek Czernuszewicz: Revvity, Inc.: Employee, Christopher Moore: Revvity, Inc.: Employee, Juan Rojas: Nothing to Disclose, Brian Velasco: Nothing to Disclose, Paul Dayton: Nothing to Disclose

1018 | TMEM41B AS A THERAPEUTIC TARGET TO ENHANCE VLDL SECRETION IN MASLD/MASH TREATMENT◆

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Background: Transmembrane Protein 41B (TMEM41B) is an endoplasmic reticulum (ER)-resident scramblases with important roles in autophagy and VLDL secretion. Hepatic loss of TMEM41B leads to defective autophagy and rapid development of metabolic-associated steatohepatitis (MASH) in mice. Previous studies showed that overexpression of a homologous protein, vacuolar membrane protein 1 (VMP1), alleviates MASH in mice fed with choline-deficient amino acid-defined high-fat diet (CDAHFD). However, mechanisms of scramblase deficiency-related MASH and the potential of targeting TMEM41B as a therapeutic approach need further study. **Methods:** Liver-specific TMEM41B knockout (L-TMEM41B KO) mice were generated by crossing with Albumin-Cre mice and mice were monitored for 1 month. 2-month-old flox-STOP-flox-*Tmem41b-Flag* (H-*Tmem41b* KI) mice were placed on CDAHFD for 6 weeks to induce MASH. A single dose of AAV8-TBG-Cre was administered IV at 2 weeks to induce TMEM41B overexpression. Serum and liver were analyzed. **Results:** L-TMEM41B KO resulted in microvesicular pattern of steatohepatitis at 1 month with decreased VLDL secretion. Lipidomics and Western Blot indicate a possible role of phospholipid deficiency and decreased COPII associated with steatohepatitis in L-TMEM41B KO mice. Cell fractionation experiments showed decreased localization of phosphatidylethanolamine N-methyltransferase (PEMT), a critical mitochondrial-associated ER membrane (MAM) protein involved in phospholipid synthesis (PL) to MAM fraction in TMEM41B KO mouse livers, indicating reduced phospholipid biotransformation at MAM sites. With VMP1 KO, levels of TMEM41B at MAM sites were also decreased, possibly indicating importance of interaction between TMEM41B and VMP1 within the cell.
Importantly, TMEM41B levels were found to be decreased in human liver samples with MASH and MASLD as well as in CDAHFD fed mouse livers compared to controls. CDAHFD feeding resulted in increased liver triglyceride content, liver lipid droplet deposition, and increased ALT. VLDL secretion increased in H-Tmem41b KI mice fed with CDAHFD. CDAHFD fed H-Tmem41b KI successfully reduced steatosis and lipid droplet size but had no effect on ALT compared with WT mice fed with CDAHFD. **Conclusion:** Loss of scramblase results in reduced PEMT and homologous scramblase localization to MAM sites, implicating phospholipid deficiency as a potential mechanism for impaired VLDL secretion and MASH development. TMEM41B KI can partially ameliorate hepatic steatosis of CDAHFD-fed mice by restoring VLDL secretion. However, parsing of hepatic steatosis and liver injury within this model needs further exploration.

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Disclosures: Allen Chen: Nothing to Disclose, Wen-Xing Ding: Nothing to Disclose, Hong-Min Ni: Nothing to Disclose

1019 | EXTRACELLULAR VESICLES DERIVED FROM THE IPS-DERIVED MESENCHYMAL STEM CELLS AMELIORATED LIVER FIBROSIS AND FATTY DEPOSITION IN MASLD-RELATED CIRRHOTIC MICE

Tsuyoshi Fujioka[1] Toshihiko Matsumoto[2] Ami Enomoto[2] Kazuma Takahashi[3] Daiki Kawamoto[1] Kaori Hamamoto[2] Shuhei Shinoda[2] Koichi Fujisawa[2] Naoki Yamamoto[1] Taro Takami[1]

[1]Yamaguchi University Graduate School of Medicine, [2]Yamaguchi University Graduate School, [3]Ajinomoto co., inc.

Background: The prevalence of metabolic dysfunction-associated steatotic liver disease (MASLD) has increased in recent years. MASLD could be defined with steatotic liver and metabolic syndrome and cause severe liver cirrhosis, hepatocellular carcinoma and portal hypertension-related complications. However, fundamental treatments for the disease have not yet been developed. We developed the iPS-derived mesenchymal stem cells (iMSC), which were higher quality MSCs induced from undifferentiated iPS cells. The aim of this study is to investigate therapeutic effects of iMSC-derived extracellular vesicles (EVs) on MASLD and the mechanisms of ameliorating fatty deposition and fibrosis in liver. **Methods:** C57BL/6 mice were fed by the Gubra-Amylin-NASH (GAN) diet and with carbon tetrachloride by once intraperitoneal administration at 4weeks. We divided the MASLD model mice into two groups, GAN diet only group (GAN group) and GAN diet with the iMSC-derived EVs intravenous injection group (iMSC-EV group), at 20 weeks. The iMSC-EV group mice received EV injection once a week for 4 weeks. We analyzed blood and liver samples by serum biochemistry test, Sirius–red and Oil-red-O staining. The oxidative stress was analyzed by hepatic 8-OHdG content. We used a serial analysis of gene expression and ingenuity pathway analysis to perform a comprehensive analysis of mRNA expression profiles and compared gene expression profiles in liver of GAN mice and iMSC-EV mice. **Results:** Compared to GAN group, iMSC-EV group showed amelioration of liver injury (AST, ALT), dyslipidemia (T.chol, LDL-C) and hypoalbuminemia($p<0.05$). Histological examination also showed the significant decrease of fatty deposition and fibrotic area in the liver of iMSC-EV group ($p<0.05$). Administration of iMSC-EVs inhibited expression of fibrosis-related genes (TGF-β, αSMA, Collagen I) and inflammatory genes (MCP-1, TNF-α, IL-6) in the iMSC-EV group($p<0.05$). iMSC-EV group significantly decreased levels of 8-OHdG ($p<0.05$). Gene expression analysis revealed that the pathway of LPS/IL-1 mediated inhibition of retinoid X receptor (RXR) function was suppressed in the iMSC-EV group. **Conclusion:** The iMSC-EV suppress the expression of inflammatory cytokines and fibrosis-related genes and may improve liver steatosis by activation of RXR pathway. Our iMSC-EVs will be the new treatment for MASLD related cirrhotic patients.

Disclosures: Tsuyoshi Fujioka: Nothing to Disclose, Toshihiko Matsumoto: Nothing to Disclose, Ami Enomoto: Nothing to Disclose, Kazuma Takahashi: Nothing to Disclose, Daiki Kawamoto: Nothing to Disclose, Kaori Hamamoto: Nothing to Disclose, Shuhei Shinoda: Nothing to Disclose, Koichi Fujisawa: Nothing to Disclose, Naoki Yamamoto: Nothing to Disclose, Taro Takami: Nothing to Disclose

1020 | A LONGITUDINAL STUDY OF MASH PATHOGENESIS IN A NON-HUMAN PRIMATE MODEL AT SINGLE NUCLEUS RESOLUTION

Joanne Hsieh[1] Heather Burkart[2] Susan Appt[2] Vinay Kartha[1] Hikaru Miyazaki[1] Caroline Duwaerts[1] Dimitry Popov[1] Smitha Shambhu[1] Chris Towne[1] Francisco LePort[1] Kylie Kavanagh[3] Martin Borch Jensen[1]

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Background: Rodent models of MASH are widely used but no single mouse model fully recapitulates the multiple aspects of human disease, including the fibrosis zonation pattern and metabolic comorbidities. Differences in liver physiology, such as bile acid composition, *de novo* lipogenesis and lipoprotein metabolism, impede accurate predictions of clinical outcomes. Therefore, we aim to develop non-human primate (NHP) models. **Methods:** Male

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middle-aged *Chlorocebus aethiops sabaeus* were selected for signs of metabolic dysfunction. The NHPs were fed a diet high in fat, cholesterol, and fructose, with additional fructose enrichment starting on week 36. Comprehensive bloodwork was conducted at regular intervals with liver biopsies done at weeks 20 and 54. Single nucleus RNA-Seq was performed on 22 distinct NHP liver samples, yielding over 50,000 analyzable single-nucleus transcriptomes spanning all animals. The vervets' response to the diet showed high phenotypic heterogeneity, enabling us to correlate gene expression with various biomarkers. **Results:** Within 20 weeks of diet, serum ALT at least doubled in every animal then remained elevated through 54 weeks. Total cholesterol levels rose between 74% - 422% of baseline and 4 of the 11 NHPs had elevated glucose at 54 weeks. Between 20 weeks and 54 weeks on diet, there was a relative depletion of zone 1 hepatocytes, consistent with the portal inflammation observed in these animals. An expansion of the immune cell population, featuring increased *CD9*+, *IL1B*+, *LGALS3*+, and *PDGFB*+ cells are reminiscent of the scar-associated macrophage population described in human cirrhotic liver. The endothelial cell population showed a time-dependent increase in *PLVAP*+ subclusters, which have been described to populate the human liver fibrotic niche. Every NHP had at least F1a fibrosis. Three of the 11 animals reached F2, with *COL1A2* upregulation in the fibrogenic mesenchymal population. Mesenchymal *RBP1* and *COL4A1* expression, genes described to mark activated hepatic stellate cells in human MASH, increased specifically in one animal with emerging porto-portal fibrosis. Serum ALT inversely correlated with hepatocyte transcriptional of pathways involved in high density lipoprotein metabolism and coagulation. HbA1c inversely correlated with FOXO-dependent transcription and positive regulation of glucose metabolism. Low density lipoprotein (LDL)-cholesterol correlated expression of genes linked with glucagon response and the urea cycle. One animal had one of the lowest LDL-cholesterol values but the highest degree of steatosis. This pattern of low LDL despite steatosis resembles the metabolic profile of patients with variants such as *TM6SF2* E167K. **Conclusion:** NHPs fed a MASH-inducing diet exhibit many cellular and transcriptional changes that resemble human disease. The individual differences of each NHP may be harnessed for drug discovery targeted to subsets of the MASH patient population.

Disclosures: Joanne Hsieh: Gordian Biotechnology: Employee, Heather Burkart: Gordian Biotechnology: Preclinical Research Study, Susan Appt: Nothing to Disclose, Vinay Kartha: Nothing to Disclose, Hikaru Miyazaki: Nothing to Disclose, Caroline Duwaerts: Gordian Biotechnology: Employee, Dimitry Popov: Nothing to Disclose, Smitha Shambhu: Nothing to Disclose, Chris Towne: Nothing to Disclose, Francisco LePort: Nothing to Disclose, Kylie Kavanagh: Nothing to Disclose, Martin Borch Jensen: Nothing to Disclose

1021 | GENERATING HEPATIC CELLS EXPRESSING THE VARIOUS PNPLA3-I148M VARIANTS BY PRIME EDITING

Takuro Uchida[1] Mitsuki Inomata[1] Naoki Wakita[2] Mitsumasa Takenaga[3] Tetsushi Sakuma[2] Tomoko Tokumaru[1] Tomoko Saito[1] Masao Iwao[1] mie arakawa[1] Mizuki Endo[1] Kazuhiro Mizukami[1]

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Background: Genomic studies have revealed a strong association between NAFLD progression and the I148M variant in patatin-like phospholipase domain-containing protein 3 (PNPLA3). However, the pathogenesis of MASLD has not yet been fully elucidated, and the importance of genetic factors has only recently been appreciated. Regarding cell models, hepatic cell lines such as Huh7 and HepG2 are not ideal for studying the function of the PNPLA3-I148M variant, as both cell lines are homozygous for the variant allele. In present study, we attempted to generate in vitro experimental model for steatotic liver disease with all the type of PNPLA3-I148M (rs738409) variants including heterozygous by prime editing. **Methods:** We designed prime editing system for the installing PNPLA3-I148M variant and tested the efficiency of the system, and introduced the genome editing on the rs738409 genome in hepatoma cells. Then, we analyzed the effects of PNPLA3 mutations on steatosis and lipid-induced stress between homozygous 148M variant allele carriers (G/G), noncarriers (C/C), and heterozygous (G/C) under free fatty acid treatment. **Results:** We generated the all-in-one prime editing system for PNPLA3-I148M, which carries all the elements for prime editing such as prime editor (modified PEmax), pegRNA, and ngRNA. In addition, The EGFP gene was fused to the prime editor with an intervening autocleavage site and served as a convenient means to measure prime editor expression. All-in-one prime editing system was transduced into hepatoma cells, and GFP+ cells were sorted using a fluorescence-activated cell sorter 2 days after transfection and expanded for a week. A G-to-C conversion on target site was detected in GFP-sorted cells in both HepG2 and Huh7 cells. We then selected single clones from the GFP-sorted cells and screened them for the I148M variant. We were able to identify several clones with homozygous and heterozygous variants on PNPA3-I148M from both hepatoma cell lines. The *PNPLA3* mRNA levels were comparable among

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the various clones and the unedited parental cells. For lipid accumulation under fatty acid treatment, The CC cells accumulated the fewest lipid droplets, and the PNPLA3-I148M cells (G/G and G/C) exhibited more lipid droplets. **Conclusion:** We successfully introduced the PNPLA3-I148M variant in genetically edited HepG2 and Huh7 cells. The clones with both homozygous and heterozygous variants were identified after prime editing. This model would be helpful to assess the pathogenesis of MASLD.

Disclosures: Takuro Uchida: Nothing to Disclose, Mitsuki Inomata: Nothing to Disclose, Naoki Wakita: Nothing to Disclose, Mitsumasa Takenaga: Nothing to Disclose, Tetsushi Sakuma: Nothing to Disclose, Tomoko Tokumaru: Nothing to Disclose, Tomoko Saito: Nothing to Disclose, Masao Iwao: Nothing to Disclose, mie arakawa: Nothing to Disclose, Mizuki Endo: Nothing to Disclose, Kazuhiro Mizukami: Nothing to Disclose

1022 | STEATOTIC AND FIBROTIC LIVER-DERIVED TNF-ALPHA EXACERBATES SKELETAL MUSCLE ATROPHY IN SENESCENCE-ACCELERATED MICE

Yohei Shirakami[1] Hiroyasu Sakai[2] Daisuke Taguchi[1] Toshihide Maeda[1] Masahito Shimizu[1]

[1]Gifu University, [2]Gifu Universtiy

Background: In recent years, the loss of skeletal muscle mass, known as sarcopenia, has attracted significant attention due to its relation with a poor prognosis for various diseases. Although skeletal muscle atrophy is one of the major complications of chronic liver disease, including metabolic dysfunction-associated steatohepatitis (MASH), the mechanism behind their association has not been fully elucidated. In this study, the effects of aging and MASH on the skeletal muscle and the interaction between the liver and muscle were investigated using a diet-induced MASH model in senescence-accelerated mice. **Methods:** A total of four groups of senescence-accelerated mice and the control mice were fed either an MASH-inducing or control diet, and their livers, serum, and skeletal muscles (tibialis anterior and gastrocnemius) were removed for analyses, including histopathology, gene expressions, and protein levels. Metabolome analysis of the skeletal muscle was also performed to investigate changes in the metabolites under the condition of muscle atrophy. **Results:** In the senescence-accelerated/MASH-diet group, serum level of alanine aminotransferase was markedly elevated and histopathology of MASH was significant. The markers for inflammation, fibrosis, and oxidative stress in the liver were also elevated, suggesting an exacerbation of steatohepatitis with aging. Skeletal muscles were significantly atrophied in the MASH-diet groups. The expression of the ubiquitin ligase *Murf1* in the muscle was significantly increased with muscle atrophy, while that of *Tnfa* was not significantly different. In contrast, the hepatic *Tnfa* expression and serum TNF-alpha levels were significantly increased in the MASH-diet groups compared to the respective control groups. These results suggested that liver-derived TNF-alpha might promote muscle atrophy associated with steatohepatitis and aging through Murf-1. The metabolomic analysis of skeletal muscle showed similar metabolic changes in the senescence-accelerated and the MASH-diet groups in principal component analysis and hierarchical clustering. The analysis also indicated higher spermidine and lower tryptophan levels in the senescence-accelerated and MASH-diet groups, respectively. **Conclusion:** The present study indicated that senescent liver is susceptible to steatosis and fibrosis due to enhanced oxidative stress, and that TNF-alpha released from steatotic and fibrotic liver might induce MASH-associated skeletal muscle atrophy. The findings revealed an aspect of liver-muscle interaction, which might be a potential target for prevention and treatment of sarcopenia associated with liver diseases.

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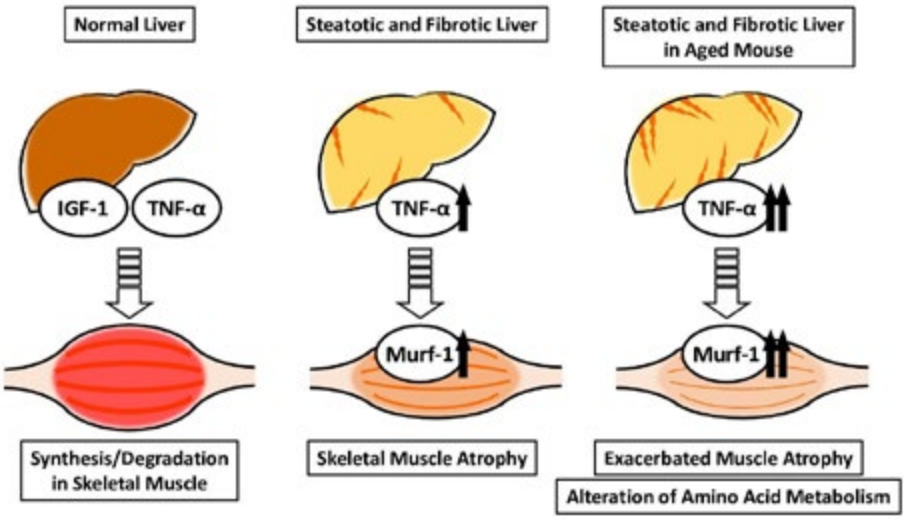

Disclosures: Yohei Shirakami: Nothing to Disclose, Hiroyasu Sakai: Nothing to Disclose, Daisuke Taguchi: Nothing to Disclose, Toshihide Maeda: Nothing to Disclose, Masahito Shimizu: Nothing to Disclose

1023 | VALIDATION OF AND MECHANISTIC INSIGHTS ON A BILE ACID SIGNATURE OF FIBROSIS PROGRESSION IN METABOLIC DYSFUNCTION ASSOCIATED STEATOHEPATITIS

Ekaterina Smirnova[1] Jason Kang[1] Yusuf Yilmaz[2] Fatih Eren[3] Huiping Zhou[1] Faridoddin Mirshahi[1] Phillip Hylemon[1] Arun Sanyal[1]

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Background: The mechanisms underlying fibrosis progression to cirrhosis in metabolic dysfunction associated steatotic liver disease (MASLD) are not fully understood. We have recently demonstrated increased serum and fecal deoxycholic acid (DCA) derivatives with increasing fibrosis in MASLD. The mechanistic basis for this and whether these findings are generalizable were not known. **AIMS:** (1) To validate the bile acid (BA) changes noted in Western populations in a histologically defined cohort of patients with MASLD from Turkey. (2) To define the mechanistic basis for the observed changes in DCA. **Methods:** A cohort of biopsy-proven MASLD from a single center in Turkey was studied. Bile acid profiles in serum and stool were defined using mass spectrometry. 3α-Hydroxysteroid dehydrogenase (hdhA) and bile acid inducible operon CD gene (baiCD) mRNAs were measured by qPCR and relative gene copy estimated. DCA generation was evaluated in stool incubated under N_2 anaerobic conditions. Statistical comparisons were performed with pairwise t-tests adjusted with Holm procedure for multiple comparisons correction. Significance was set at 0.05. **Results:** A total of 166 MASLD patients (fibrosis stage 0-1 (n=66); stage 2 (n = 50); stage 3 (n=60); stage 4(n=22) and 8 healthy controls were studied. Serum TCA (p=0.006 for ≥ stage 2.; p=0.001 ≥ Stage 3), GCA (p=0.005; p<0.001), TDCA (p=0.019 ≥ stage 2; p=0.001 ≥ stage 3), GDCA (p=0.010 ≥stage 2; p<0.001 ≥stage 3), CDCA-3-S (p=0.018 ≥ stage 2; 0.017 ≥stage 3) were increased with increasing fibrosis. In stool, the following sulfated BA were increased with increasing fibrosis: CDCA-3-S (p=0.003 ≥ stage 2; 0.047 ≥stage 3), DCA-3-S (p=0.019 ≥ stage 2), UDCA-3-S (p=0.012 ≥ stage 2) and TUDCA (p=0.022 ≥ stage 2) were increased in patients with clinically significant and advanced fibrosis. baiCD and hdhA expression was increased with advanced fibrosis, particularly in cirrhosis. DCA, 7-oxo-DCA, isoDCA, 12-oxo-DCA were all produced in excess in MASH with advanced fibrosis compared to healthy controls. **Conclusion:** (1) Increasing liver fibrosis is associated with greater DCA and its derivatives as well as serum conjugated cholic acid in a Turkish cohort, confirming the generalizability of the DCA signature associated with increased fibrosis, (2) Generation of DCA metabolites are increased in MASH with increased fibrosis and related to an increase in the gut bacteria bai operon responsible for DCA synthesis from cholic acid.

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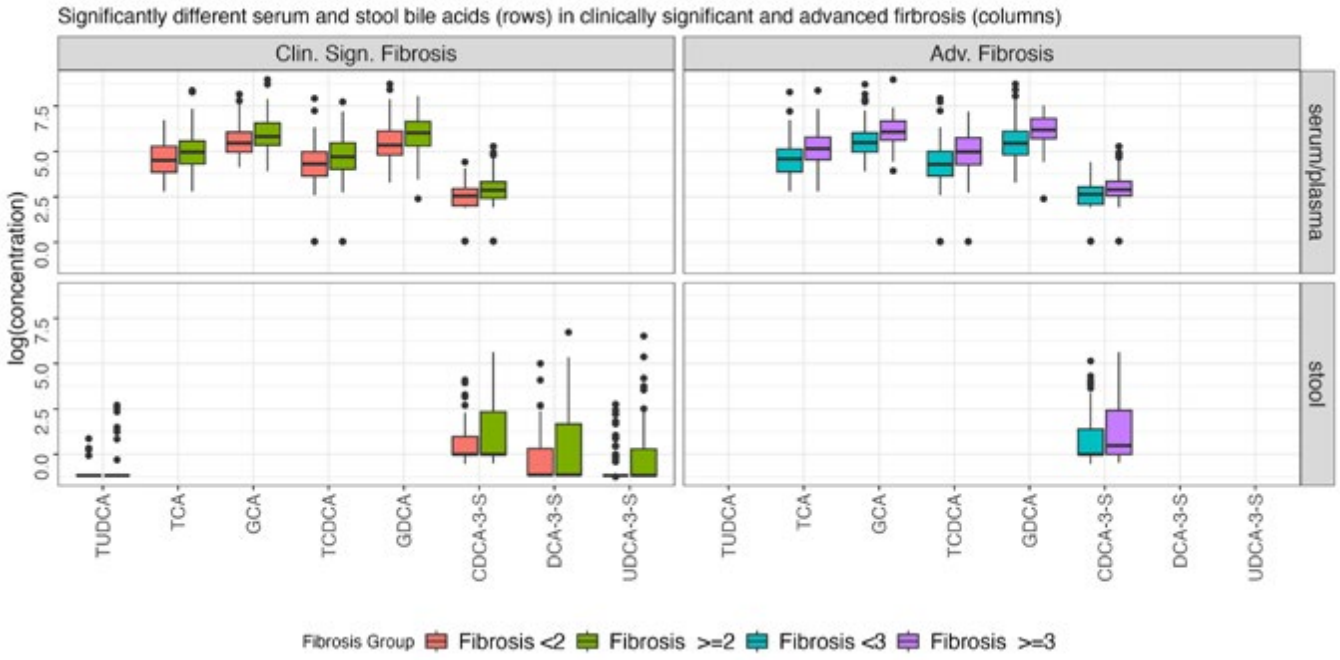

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1024 | MURINE MASH LIVERS DISPLAY BIAS TOWARDS A HYPERTROPHIC MECHANISM OF REGENERATION FOLLOWING PARTIAL HEPATECTOMY

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Background: The mammalian liver has the unique potential to regenerate to its original mass and restore normal functions after injury or surgical resection (partial hepatectomy). Using the partial hepatectomy mouse model, previous studies uncovered two distinct regenerative strategies adopted by hepatocytes: proliferation and hypertrophy (increase in size without division). In chronic liver injury, including MASH (metabolic dysfunction-associated steatohepatitis), the liver's extraordinary regenerative capacity breaks down, which leads to a dangerous reduction in vital functions performed by the liver that ultimately manifests as liver failure. Our goal is to understand why the MASH liver fails to regenerate. **Methods:** Control or MASH (FAT-MASH, *Tsuchida 2018 J. Hepatol.*) mice were subjected to 2/3 partial hepatectomy surgery and the liver was collected at 0, 4, 24, 48, 96, 168 hours post-surgery. Liver-to-body-weight ratio was used as a global readout of liver regeneration. Ki67, DAPI, and phalloidin staining were used to measure cell proliferation, nuclear size, and cell size with quantification by IMARIS software. Single-nuclei RNA sequencing (snRNA-seq) was performed using the Parse Evercode™ technology and analyzed using Seurat (*Hao 2024 Nat. Biotechnol.*). **Results:** Overall regeneration kinetics, as measured by liver-to-body-weight ratios, was the same between control and MASH mice following 70% partial hepatectomy surgery, with complete recovery of liver mass by 7 days post-surgery. Hepatocytes in MASH livers demonstrated slightly higher proliferation (Ki67+ nuclei) compared to control at baseline but dramatically reduced proliferation at 48 hours post-surgery, a timepoint that corresponds to peak liver regeneration. In line with clinical observations, lipid-laden MASH hepatocytes display larger cell size compared to controls, as measured by phalloidin staining of cell membrane. Surprisingly, MASH hepatocytes underwent further expansion of cell size at 24 hours post-surgery, whereas control hepatocytes also increased in cell size but to a lesser extent. In ongoing studies, we are using snRNA-seq to understand this altered regenerative response in MASH mice. **Conclusion:** Our results suggest that MASH hepatocytes preferentially use hypertrophy rather than proliferation to regenerate liver mass, understanding which may lead to novel strategies to improve liver regeneration in MASH patients.

Disclosures: Maylene Yu: Nothing to Disclose, Shuang Wang: Nothing to Disclose

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1025 | ENDOTHELIAL-STELLATE CELL CROSSTALK UNDERLIES FIBROSIS RESOLUTION IN LIVER ◆

Kenneth Li[1] Chittampalli Yashaswini[1] Maylene Yu[1] Bruno Cogliati[2] Scott Friedman[1] Shuang Wang[1]

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Background: Advanced hepatic fibrosis is the strongest predictor of mortality in metabolic dysfunction-associated steatohepatitis (MASH); however, there are no approved anti-fibrotic therapies. Although fibrosis in MASH can resolve and liver function typically improves (e.g, after bariatric surgery), the underlying molecular mechanisms are obscure. Here we use single-cell and spatial RNA sequencing technology to identify molecular and cellular drivers of fibrosis resolution in mice following discontinuation of MASH. **Methods:** We employed two mouse models of fibrosis regression, using either an established MASH model (the "FAT-MASH" model [1]) or high dose CCl_4 (0.5ml/kg body weight, twice a week) for 6 weeks, then discontinued. Livers were analyzed at 6 weeks ("Peak Fibrosis") and then 2 and 6 weeks following model discontinuation ("Regression" timepoints). Analyses included serum biochemistries, histopathology, qPCR, and ELISA-based assays. Single-cell, single-nucleus, and spatial sequencing were performed on freshly-isolated liver cells, flash-frozen liver tissue, and formalin-fixed paraffin-embedded liver sections, respectively. Informatics **Methods:** were used to define changes in cellular composition and cell-cell communication. **Results:** Histopathological and transcriptomic indicators of fibrosis were attenuated within 2 weeks after model discontinuation with similar kinetics (FAT-MASH or CCl_4), with maximum fibrosis resolution at 2 weeks of regression. Single-cell and single-nucleus transcriptomics captured different liver cell types at varying efficiencies, as expected. Changes in cellular composition with fibrosis regression were remarkably similar in both models, with a gradual decrease in immune cell numbers and expansion of resident liver cells, including hepatocytes and endothelial cells. Based on cell-cell interaction analyses, intercellular communication was globally downregulated during fibrosis regression. However, crosstalk between a specific subset of endothelial cells and hepatic stellate cells was amplified concurrent with increased endo-HSC contacts by IHC. This interaction may contribute to fibrosis regression through regulation of matrix turnover and stellate cell activation. These findings are being further validated using spatial RNA sequencing and *in vivo* perturbation studies. **Conclusion:** Resolution of hepatic fibrosis harnesses the liver's innate ability to resolve fibrosis. Using two different mouse models of fibrosis regression, we report an endothelial-mesenchymal cell (ie., activated HSCs) crosstalk that may represent a key driver of regression and a potential antifibrotic drug target. Tsuchida, T., et al., *A simple diet- and chemical-induced murine NASH model with rapid progression of steatohepatitis, fibrosis and liver cancer.* Journal of Hepatology, 2018. **69**(2): p. 385-395.

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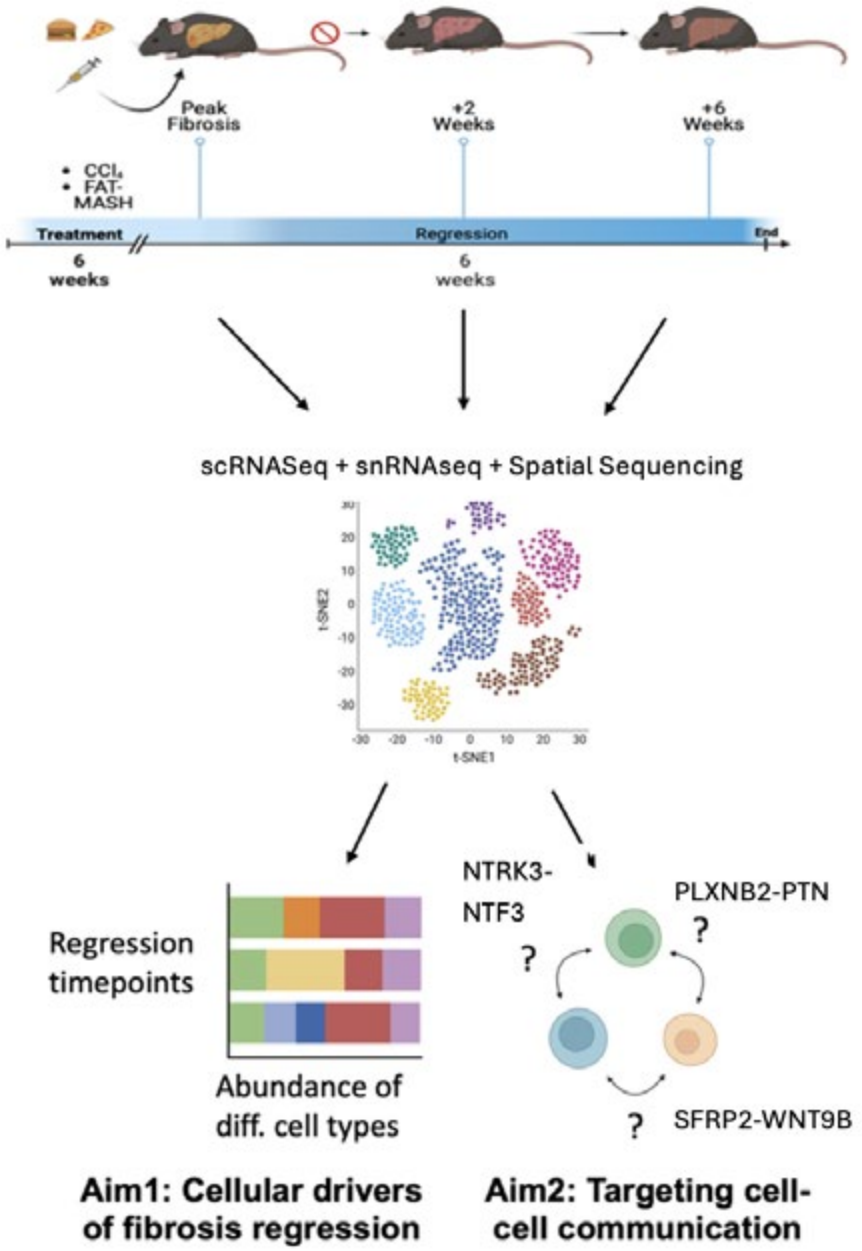

Disclosures: Kenneth Li: Nothing to Disclose, Chittampalli Yashaswini: Nothing to Disclose, Maylene Yu: Nothing to Disclose, Bruno Cogliati: Nothing to Disclose, Scott Friedman: 89 Bio: Consultant, Boehringer Ingelheim: Consultant, Boston Pharmaceutical: Consultant, Bristol Myers Squibb: Consultant, Merck: Consultant, Glycotest: Consultant, Morphic Therapeutics: Consultant, HepGene: Consultant, North Sea Therapeutics: Consultant, Pfizer Pharmaceuticals: Consultant, Sagimet: Consultant, Scholar Rock: Consultant, Prosciento: Consultant, Seal Rock: Consultant, Surrozen: Consultant, Takeda Pharmaceuticals: Consultant, Junevity: Consultant, Therasid Bio: Consultant, Merck: Consultant, Ochre Bio: Consultant, Gordian Biotechnology: Consultant, Abalone Bio: Grant/ Research Support, Prosciento: Consultant, Shuang Wang: Nothing to Disclose

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1026 | A GENOME-WIDE CRISPR-CAS9 SCREEN IDENTIFIES MODIFIERS OF CELLULAR CHOLESTEROL UPTAKE

Aaron Hakim[1] Shi Fang[2] Zhenghui Jiang[1] Gavin Schnitzler[3] Rajat Gupta[3]

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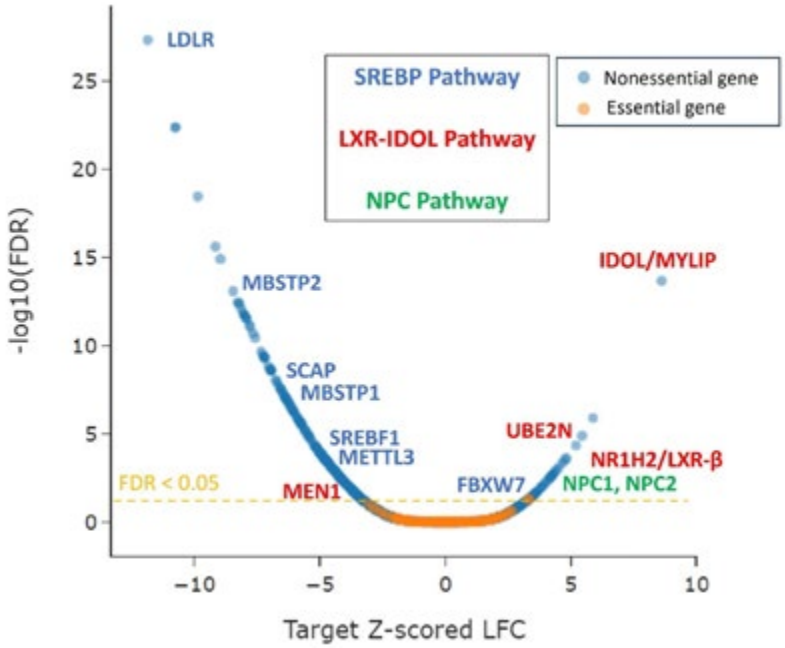
Background: Disturbances in cholesterol homeostasis are associated with metabolic dysfunction-associated steatotic liver disease (MASLD) as well as atherosclerosis. Cholesterol is an essential component of mammalian lipid membranes and is taken up into cells as low-density lipoprotein (LDL) particles. To identify genes and pathways critical for cholesterol uptake and uncover shared mechanisms underlying MASLD and atherosclerosis, we undertook a pooled genome wide knockout CRISPR screen in telomerase-immortalized human aortic endothelial cells (TeloHAEC) and compared results to prior LDL uptake screens in hepatocytes. **Methods:** We engineered TeloHAEC to express Cas9 and transduced 240 million cells with a genome-wide CRISPR lentiviral library (40,964 unique sgRNA; 2 sgRNA/gene); cells were exposed to fluorescently conjugated LDL and sorted by flow cytometry into bins of LDL-high (top 20%) and LDL-low (bottom 20%). Massively parallel sequencing was performed to assess the relative enrichment of each guide RNA sequence in either bin. We compared results to prior genome-wide LDL uptake screens in hepatocytes. A subset of hits was confirmed using individual sgRNAs. We used genome-wide CRISPR cell essentiality screen datasets (DepMap) to cluster identified genes with similar functions. **Results:** We identified 339 genes associated with decreased LDL uptake and 42 genes associated with increased LDL uptake in TeloHAEC (false discovery rate <5%). We observed modest but appreciable correlation between our results and prior hepatocyte LDL uptake screens ($r = 0.21$, $p = 6.9 \times 10^{-13}$). We identified multiple regulators of LDL uptake from the SREBP, LXR-IDOL, and NPC/mTOR pathways (Figure); many of these hits were cell-type independent. Additional hits could be grouped into categories that reflect successive stages of LDL import including (i) protein folding and N-linked glycosylation, (ii) early secretory pathway, (iii) clathrin-mediated endocytosis, (iv) endosomal acidification, (v) endosomal trafficking, and (vi) cholesterol lysosomal export. Our screen identified the involvement of the TRAPP complex, the Exocyst complex, the COG complex (and co-dependent gene UNC50), and the GARP complex (and co-dependent gene JTB) in cholesterol uptake; we also demonstrate a novel role for the electron carrier CYB5B in cholesterol metabolism and its co-dependency with multiple genes in the SCAP/SREBP pathway. **Conclusion:** Our cholesterol uptake screen provides unique insight into factors essential for LDL uptake and potential shared and distinct mechanisms underlying MASLD and atherosclerosis.



Disclosures: Aaron Hakim: Olix Pharmaceuticals: Advisor, Deep Track Capital, LP: Consultant, Shi Fang: Nothing to Disclose, Zhenghui Jiang: Nothing to Disclose, Gavin Schnitzler: Nothing to Disclose, Rajat Gupta: Nothing to Disclose

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1027 | IMPACT OF ADULT-ONSET, HEPATOCYTE-SPECIFIC, LOSS OF THE GROWTH HORMONE RECEPTOR ON MASH PROGRESSION

Mercedes del Rio-Moreno[1] Mari Vazquez-Borrego[1] Jose Cordoba Chacon[1] David J. Waxman[2] Rhonda Kineman[1]

[1]University of Illinois at Chicago, [2]Boston University

Background: A reduction in growth hormone (GH) is associated with MASH. We previously reported chow-fed male mice with adult-onset, hepatocyte-specific, GH receptor knockdown (aHepGHRkd = GHRkd) develop liver steatosis, and with age a mild MASH-like phenotype, suggesting GH acts directly on the hepatocyte to prevent MASH. **Methods:** To determine if GHRkd accelerates steatosis and liver injury in the context of diet-induced obesity, GHR-intact control and GHRkd male mice were fed a translationally relevant diet consisting of 60% fat, high in saturation, and provided glucose and fructose in the drinking water to achieve concentrations that occur in sucrose containing beverages (HFS diet). Since GHR signals through the transcription factor STAT5b, and STAT5b is required to sustain hepatocyte insulin-like growth factor 1 (IGF1) production, a subset of GHRkd mice were treated with AAVs that express IGF1 or a constitutively active STAT5b (STAT5bCA) in hepatocytes. **Results:** After 3 months of HFS diet, GHRkd did not alter liver weight or total hepatic triglyceride content compared to GHR-intact mice. However, there were changes in lipid composition, in part corrected by expression of STAT5CA, but not IGF1. Control mice showed microsteatosis in the pericentral area and variable levels of macrosteatosis in the periportal region. In GHRkd livers, without or with IGF1 replacement, macrosteatosis dominated and was evenly distributed across zones, and STAT5bCA partially shifted this pattern back towards that observed in control livers. GHRkd increased hepatic $CD8^+$ lymphocytes and F4/80+ macrophages forming crown-like structures (hCLS; marking dying hepatocytes), as well as periportal and invasive ductular reaction (DR, Krt19+ cells) associated with fibrosis, all features not observed in GHR-intact controls. In addition, GHRkd increased hepatic bile acid content, without impacting bile acid composition. STAT5bCA, but not IGF1, reduced DR and fibrosis in GHRkd livers, without impacting $CD8^+$ lymphocytes, hCLS or bile acids. RNA-seq analysis revealed genes related to hepatocyte regeneration (Lifr, E2f8, Onecut1/HNF6) and detoxification (Cyp4a10/12a/12b/14 and UGT2b37/38) were decreased by GHRkd and increased by STAT5bCA. **Conclusion:** The protective actions of hepatocyte GHR against MASH progression can be observed independent of the absolute level of steatosis, and may include regulation of hepatocyte detoxification, repair and/or regeneration, in part mediated by STAT5b.

Disclosures: Mercedes del Rio-Moreno: Nothing to Disclose, Mari Vazquez-Borrego: Nothing to Disclose, Jose Cordoba Chacon: Nothing to Disclose, David J. Waxman: Nothing to Disclose, Rhonda Kineman: Nothing to Disclose

1028 | OXIDIZED LDL'S ROLE IN MASLD: INSIGHTS FROM LIVER SPHEROID TRANSCRIPTOMICS

Ana Maretti-Mira[1] Matthew Salomon[1] Chikako Matsuba[1] Yufen Wang[1] Lucy Golden-Mason[1]

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Background: Free cholesterol, especially low-density lipoprotein (LDL), plays a central role in metabolic dysfunction-associated steatotic liver disease (MASLD). High cholesterol intake increases internal cholesterol oxidation, and oxidized LDL (oxLDL) has been linked to steatohepatitis, fibrosis, and cirrhosis. However, the underlying mechanisms by which oxLDL contributes to MASLD progression are poorly understood. Given the likelihood of oxLDL contribution to MASLD severity and that cholesterol is a modifiable risk factor, we explored the role of LDL oxidation in MASLD development using a novel in vitro/in silico framework based on a complex 3D liver spheroid model and single-cell transcriptomics (scRNAseq). **Methods:** We exposed the multi-donor 3D InSight™ Human Liver Model (InSphero), composed of primary hepatocytes, Kupffer cells, and other non-parenchymal cells (NPCs), to 50µg/mL highly oxLDL (HoxLDL) in low glucose media for 7 days. Spheroid transcriptomics was analyzed by scRNA-seq (Chromium Next GEM Single Cell 3' Kit, 10X Genomics). Lipid accumulation was detected by Nile Red staining. Unstimulated spheroids were used as controls. **Results:** Our data demonstrated that 3D liver spheroids exposed to HoxLDL upregulated several MASLD-related pathways, such as hepatic steatosis and liver inflammation. Specifically, HoxLDL upregulated: (i) *Oxidative phosphorylation*, a key process involved in fatty acid oxidation and bile acid synthesis; (ii) *IL-1 Mediated Inhibition of RXR Function*,

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involved in cholesterol uptake and efflux; and (iii) *Neutrophil Extracellular Trap Signaling Pathway*, critical for inflammation progression in MASLD. Confocal imaging confirmed lipid accumulation in liver spheroids exposed to HoxLDL**.** Analysis of transcriptomic changes in individual cell clusters demonstrated that hepatocytes are the cell type most affected by HoxLDL exposure, showing the highest number of differentially expressed genes (DEGs). T cells, Kupffer cells, and NK cells show fewer DEGs, while LSECs and B cells were not significantly disturbed by HoxLDL. **Conclusion:** Our study suggests that HoxLDL disrupts lipid metabolism and inflammation in 3D liver spheroids, similar to in vivo and human studies findings. These results support that 3D spheroid is a good model for characterizing the intricate molecular and cellular mechanisms whereby oxLDL favors MASLD progression and identifying and validating possible therapeutic targets.

Disclosures: Ana Maretti-Mira: Nothing to Disclose, Matthew Salomon: Nothing to Disclose, Chikako Matsuba: Nothing to Disclose, Yufen Wang: Nothing to Disclose, Lucy Golden-Mason: Nothing to Disclose

1029 | CIRCULATING AND LIVER TISSUES EMILIN1 LEVELS ARE REDUCED AND ASSOCIATED WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE IN PATIENTS AND MICE MODELS

Xiaomei Wang Huifan Ji[1] Junqi Niu[1]

[1]The First Hospital of Jilin University

Background: Metabolic dysfunction-associated steatohepatitis (MASH) increases the risk for the development of cirrhosis, liver failure, and hepatocellular carcinoma. Elastin microfibrillar interface protein 1 (EMILIN1) is an extracellular matrix glycoprotein, whose function has been linked to cancer and metastasis. However, EMILIN1's role during metabolic dysfunction-associated steatotic liver disease (MASLD) development has never been investigated. Herein, the level of EMILIN1 in the liver and serum were explored in the progression of MASLD. **Methods:** Serum was collected from 81 patients with magnetic resonance imaging proton density fat fraction (MRI-PDFF) proven MASLD and 40 healthy controls. MASLD patients were divided into mild steatosis(n=39) and moderate-severe steatosis (n=42) groups. Serum EMILIN1 expression was measured with ELISA kits. Metabolic-associated fatty liver (MAFL) mice models fed with a high-fat diet and MASH mice models fed with choline-deficient, L-amino acid-defined, high-fat diet (CDAHFD) for 12 weeks were established. The expression of EMILIN1 in the mice liver was detected with immunofluorescence and Western blot. **Results:** Compared to healthy controls, both mild steatosis patients and moderate-severe steatosis group exhibited diminished levels of serum EMILIN1. In addition, serum EMILIN1 was significantly reduced in the moderate-severe steatosis group than in the mild steatosis group. The protein level of EMILIN1 in mice liver decreased in MAFL mice compared with normal diet-feeding mice. As expected, MASH mice had lower hepatic expression of EMILIN1 than MAFL mice. EMILIN1 level exhibited a negative correlation with the NAS score of mice liver. **Conclusion:** EMILIN1 levels are significantly reduced in MASLD patients and mice models and exhibited a negative correlation with NAS score, proposing its potential as a biomarker in the pathogenesis of MASLD.

Disclosures: Xiaomei Wang: Nothing to Disclose, Huifan Ji: Nothing to Disclose, Junqi Niu: Nothing to Disclose

1030 | WFDC2 PROMOTES MASH-DRIVEN HCC DEVELOPMENT BY RESTRAINING INTRACELLULAR FATTY ACID FLUX IN HYPOXIA

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Background: The prevalence of Metabolic dysfunction associated with steatohepatitis (MASH)-driven hepatocellular carcinoma (HCC) is rising rapidly, yet its underlying mechanisms remain unclear. Herein, we aim to determine the role of whey acidic protein (WAP) four-disulfide core domain protease inhibitor 2 (WFDC2) in MASH-driven HCC. **Methods:** The clinical significance of WFDC2 was assessed in human MASH-driven HCC specimens by immunohistochemistry and transcriptomics analyses. The oncogenic effect of WFDC2 was assessed in human HCC cells and in 3D epithelial spheroids upon exposure to free fatty acids and either normoxia or hypoxia. Lipidomics profiling of wild-type and WFDC2 knockout HCC cells was assessed via shotgun

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and targeted approaches. Wild-type ($Wfdc2^{fl/fl}$) and hepatocyte-specific Hilpda knockout ($Wfdc2^{\Delta Hep}$) mice were fed a Western diet and high sugar in drinking water while receiving carbon tetrachloride to induce MASH-driven HCC. **Results:** In patients with MASH-driven HCC, upregulated WFDC2 expression is strongly associated with poor survival. In oxygen-deprived and lipid-loaded culture conditions, WFDC2 promotes viability of human hepatoma cells and growth of 3D epithelial spheroids. Lack of WFDC2 triggered flux of polyunsaturated fatty acids to membrane phospholipids and of saturated fatty acids to ceramide synthesis, exacerbating lipid peroxidation and apoptosis in hypoxia. The apoptosis induced by WFDC2 deficiency was reversed by pharmacological inhibition of ceramide synthesis. In our experimental mouse model of MASH-driven HCC, $Wfdc2^{\Delta Hep}$ exhibited reduced hepatic steatosis and tumorigenesis but increased oxidative stress in the liver. Single-cell analysis supports a dual role of hepatic WFDC2 in protecting HCC cells and facilitating the establishment of a pro-tumorigenic immune microenvironment in MASH. **Conclusion:** Collectively, our **Results:** indicate that WFDC2 drives MASH to HCC and therefore can be a potential therapeutic target for HCC.

Disclosures: Peiyu Wu: Nothing to Disclose, Xiaosong Mu: Nothing to Disclose

1031 | IDENTIFYING NEUROGENIC MECHANISMS FOR METABOLIC DYSFUNCTION ASSOCIATED STEATOHEPATITIS (MASH) AFTER SPINAL CORD INJURY

Dorsin Chang[1] *Richard Bruno*[1] *Dana McTigue*[1]

[1]*The Ohio State University*

Background: We report that spinal cord injury (SCI) in a non-obese rodent model rapidly induces a phenotype we coined neurogenic MASH (nMASH) that may help explain the heightened cardiometabolic risks for individuals with SCI. The objective of this study is to use our clinically translatable model of SCI in combination with a high-fat diet (HFD) to examine the independent and additive effects of dysregulated spinal circuitry and an obesogenic diet on MASH-associated hepatic injury. **Methods:** In a 2x2 factorial design, male Sprague Dawley rats (n = 24; 3-mo old) were provided a low-fat diet (LFD; 10% energy from fat) or a HFD (45% fat) for 3-wk before receiving a sham laminectomy (LAM) or a thoracic contusion injury (200 kD at level T8) with weekly assessment of hindlimb locomotor recovery. At study termination (28 days post-injury; dpi), white matter sparing of the spinal cord was assessed immunohistochemically. Serum was collected to assess biochemical markers for lipids and liver function. Liver steatosis and inflammation were assessed histologically, hepatic lipid peroxidation (malondialdehyde) by HPLC, and mRNA expression of hepatic genes involved in lipid uptake, lipogenesis, oxidation, and secretion as well as inflammation by qPCR. **Results:** HFD+SCI increased intraspinal pathology compared with LFD+SCI ($P<0.05$) although locomotor recovery following SCI was unaffected by diet. Body mass only increased over time by HFD+SCI ($P_{time \times diet}<0.05$) and was higher 28-dpi in HFD+SCI compared with LFD+SCI ($P_{time \times injury}<0.05$). Serum triglyceride was lower in HFD+LAM but increased in HFD+SCI. ALT increased after SCI regardless of diet, but not in HFD alone. Oil Red O and Clec4f (Kupffer cell marker) staining of liver sections increased in LFD+SCI and HFD+LAM, and was exacerbated in HFD+SCI. Hepatic mRNA expression of *Cd36* was increased in LFD+SCI and HFD+LAM, and potentiated by HFD+SCI. *Srebp1c* was unaffected among all groups and *Fasn* and *Scd1* mRNA were increased only in LFD+SCI, whereas *Dgat1* was increased in HFD+LAM and further upregulated in HFD+SCI. *Cpt1a* mRNA increased to a similar extent in all groups whereas *Mttp* was only increased in HFD+SCI as with pro-inflammatory mediators *Tnfα* and *Trem2* and concentrations of hepatic malondialdehyde. Hepatic iron accumulation based on Perls staining was increased in LFD+SCI and HFD+LAM, but unaffected in HFD+SCI, whereas immunolabeling of ferritin was increased in LFD+SCI and unaffected in HFD regardless of SCI. **Conclusion:** SCI or an obesogenic diet induce MASH but likely through different mechanisms. The independent and combined contribution of neurogenic and obesogenic mechanisms highlight the cross-talk of functional central nervous system circuitry on hepatic metabolic health, which is expected to provide an innovative framework for continued investigation to improve cardiometabolic health of the SCI population and potential new insights for alleviating obesogenic MASH.

Disclosures: Dorsin Chang: Nothing to Disclose, Richard Bruno: Nothing to Disclose, Dana McTigue: Nothing to Disclose

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1032 | HEPATIC PNPLA3I148M ASSOCIATES WITH SKELETAL FRAGILITY WITHOUT HIGH-FAT DIET EXPOSURE IN DIAMOND MICE

Galen Goldscheitter[1] *Mulugeta Seneshaw*[1] *Faridoddin Mirshahi*[1] *Evan Buettmann*[1] *Henry Donahue*[1] *Arun Sanyal*[1]

[1]*Virginia Commonwealth University*

Background: Obesity is associated with greater bone density but increased risk of fractures due to poorer quality bone (Gkastaris et al, JMNI 2020). There is a paucity of experimental evidence to evaluate the impact of metabolic dysfunction associated steatohepatitis (MASH) in the setting of obesity on bone quality. **AIMS:** (1) To evaluate the impact of diet-induced obesity on functional, structural and cellular markers of bone quality, and (2) to determine if steatohepatitis affected bone quality above and beyond the effects of background obesity. **Methods:** 8-week-old DIAMOND mice (s129/C57Bl6) isogenic cross mice (n=59), a validated model of MASH, were studied. Mice were injected with AAV- containing luciferase (Luc) or human PNPLA3 wild-type ($PNPLA3^{WT}$) or containing the I148M mutation ($PNPLA3^{MT}$). Each group were randomized to get chow diet (CD) or a high-fat Western diet (WD) for 36 weeks. The rationale for introducing AAV-PNPLA3 was to accelerate the development of steatohepatitis without impacting background obesity or insulin resistance, as shown previously (Banini et al, Hepatology 2021). Bone strength was assessed by 3-point bending to failure by fracture. Bone geometry and marrow adiposity (BMA) were measured using micro-CT with and without osmium contrast. Osteocyte counts were performed on H&E-stained sections. Gene expression was quantified via RT-qPCR. Significance was set at $p<0.05$. **Results: Aim 1:** Compared to mice on chow diet, AAV-luc and $PNPLA3^{WT}$ mice on WD developed diet-induced obesity and moderate steatohepatitis with stage 2 or 3 fibrosis. In contrast. $PNPLA3^{MT}$ had more severe steatohepatitis and stage 3 and early stage 4 fibrosis. WD intake decreased ultimate load, cortical thickness (Ct. Th), and osteocyte number (Ot.N/B.Ar) in Luc and $PNPLA3^{WT}$ mice. (Figure 1A, B, D) **Aim 2:** Compared to AAV-luc on CD, $PNPLA3^{MT}$ mice on CD had lower cortical thickness, load bearing, osteocyte number and *tnfsf11* relative to *tnfrsf11b* (a marker of bone turnover). On WD, many of these differences were not seen. Compared to AAV-luc, $PNPLA3^{MT}$ had similar cortical thickness, load bearing, and osteocyte number but increased t*nfsf11:tnfrsf11b*. (Figure 1A-D) BMA was 5-fold higher in WD mice than CD mice ($p<0.0001$) with no differences among genotype groups. (Figure 1E) **Conclusion:** Diet-induced obesity and MASLD are associated with worsening of multiple markers of bone quality and an increase in bone marrow adiposity. Hepatic $PNPLA3^{MT}$ expression was associated with decreased bone quality even under conditions of chow diet. These data provide a rationale to evaluate $PNPLA3^{MT}$ as a risk factor for fractures.

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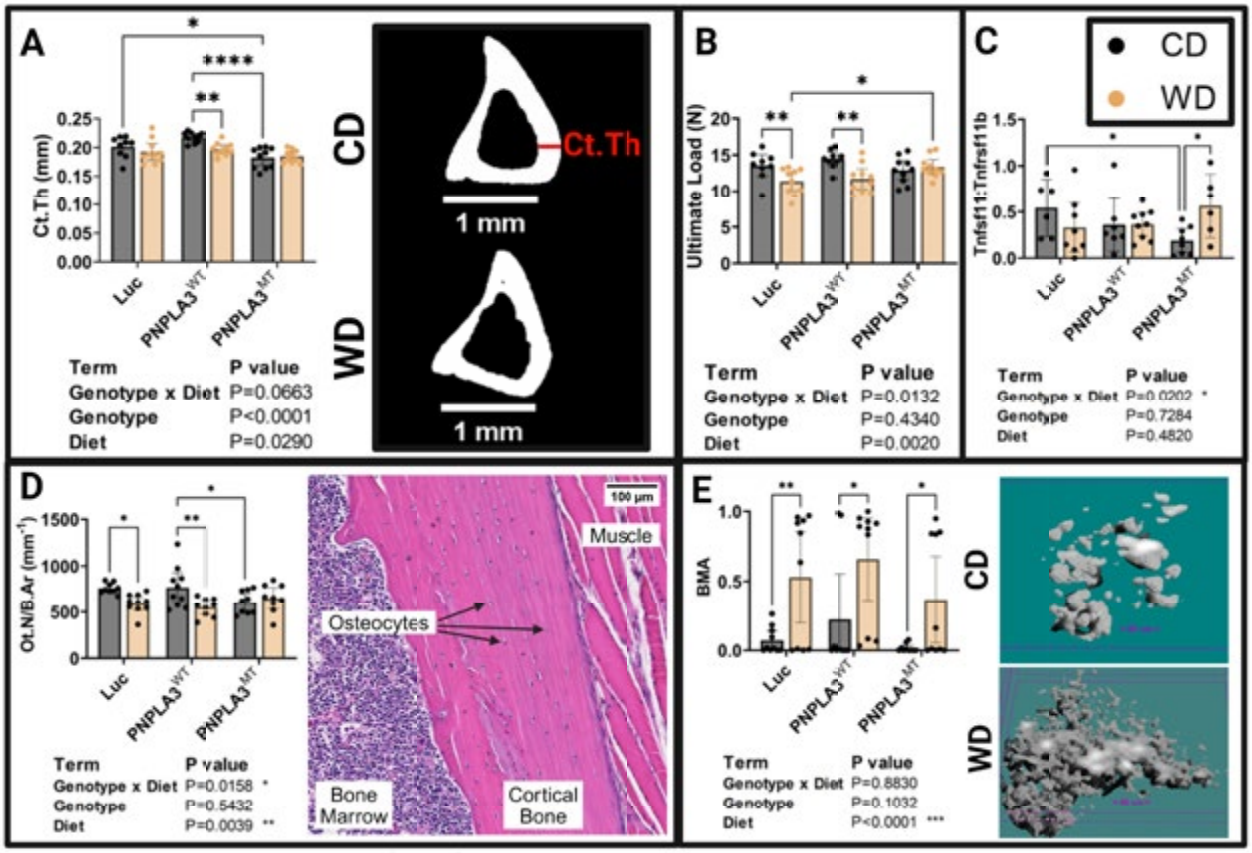

Figure 1: (A) Cortical thickness (Ct.Th) measured at the mid-diaphysis of the tibia via microCT. **(B)** Ultimate load achieved before failure in 3-point bending of the tibia. **(C)** Expression of Tnfsf11 (RANKL) relative to Tnfrsf11b (OPG) in femoral cortical bone osteocytes via qPCR. **(D)** Area-normalized osteocyte number (Ot.N/B.Ar) assessed on femoral H&E Sections. **(E)** Tibial bone marrow adiposity measured via osmium-contrast microCT.

Disclosures: Galen Goldscheitter: Nothing to Disclose, Mulugeta Seneshaw: Nothing to Disclose, Faridoddin Mirshahi: Nothing to Disclose, Evan Buettmann: Nothing to Disclose, Henry Donahue: Nothing to Disclose, Arun Sanyal: Genfit, Akarna, Tiziana, Durect, Inversago, Hemoshear, North: Stock - publicly traded company, Astra Zeneca (60K), Boston Pharmaceutical

1034 | ROLE OF STARD1 IN HEPATIC MITOCHONDRIAL-DERIVED OXYSTEROLS IN THE DEVELOPMENT OF CARDIOVASCULAR DYSFUNCTION IN MASH

Sandra Torres[1] Eduardo Garcia[2] Susana Nuñez[3] Vicent Ribas[4] Leire Goicoechea[4] Hala Jaara[1] Mariana Acevedo Roldan[4] Ana Garcia Alvarez[5] Ana Cenarro[6] Emma Muñoz[7] Naira Rico[8] Ana Paula Dantas[5] Francisco Rafael Jimenez-Trinidad[5] Eduard Guasch[9] Xavier Lopez[7] Montserrat Rigoll[7] Josefina Casas[10] Vicenta Llorente-Cortes[2] Carmen Garcia-Ruiz[1]

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Background: Metabolic dysfunction-associated fatty liver disease (MAFLD) is associated with multiple extrahepatic diseases. Several studies indicated the association between MAFLD and cardiovascular disease (CVD), sharing common risk factors,with a negative impact on patients' outcome. The direct causal relationship between them has not yet been firmly established. Cholesterol, and particularly its transport and accumulation in hepatic mitochondria by StARD1, contributes to the progression of MASH driven hepatocellular carcinoma due to the stimulation of the alternative mitochondrial bile acid synthesis pathway. 27-hydroxycholesterol (27-OHC) is the most abundant circulating oxysterol and is derived from the metabolism of mitochondrial cholesterol

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by CYP27A1, an ubiquitous enzyme localized in mitochondrial matrix. Thus, the aims of this study were to evaluate the impact of the hepatic StARD1 in the progression of MAFLD and cardiovascular events, and to examine the role of 27-OHC in the interplay between MAFLD and CVD. **Methods:** Hepatocyte-specific StARD1 deletion (StARD1$^{\Delta Hep}$) male mice were fed with normal chow (Ctrl) or HFHC diet containing 60% calories from fat and added 0.5% cholesterol up to 10 months. Liver damage, fibrosis and steatosis were examined. Cardiac fibrosis and MRI functional assay were performed in hearts. Levels of cholesterol ester (CE), triglycerides (TG), ceramides and 27-OHC were determined in the cardiac tissue. Expression of cardiac remodeling markers, such as cathepsin D (CatD) and LRP-1, were examined in cardiac tissue and in 27-OHC exposed human cardiac myocytes. **Results:** Compared to StARD1$^{f/f}$ mice, StARD1$^{\Delta Hep}$ mice fed HFHC diet developed less liver injury and hepatocyte ballooning, and exhibited decreased fibrosis and expression of inflammatory markers, confirming the role of STARD1 in MASH development. Expression of LRP-1 and CatD was lower in hearts from HFHC-fed StARD1$^{\Delta Hep}$ mice compared to StARD1$^{f/f}$ mice, indicating the contribution of hepatic StARD1 to cardiac remodelling and fibrosis. MRI analysis indicated a preserved functional cardiac output in HFHC-fed StARD1$^{\Delta Hep}$ mice compared to StARD1$^{f/f}$ mice with preserved ejection fraction and cardiac output. Serum ceramide levels and heart CE and TG content increased upon HFHC feeding with a similar levels in either StARD1$^{\Delta Hep}$ and StARD1$^{f/f}$ mice. However, mass spectrometry analysis indicated that hepatic levels of 27-OHC were barely detected in HFHC-fed StARD1$^{\Delta Hep}$, while hepatocyte StARD1 deletion reduced by half the content of 27-OHC in heart tissue, indicating that a significant amount of heart 27-OHC derived from the liver and was dependent on StARD1 expression. Incubation of human cardiac myocytes with increasing doses of 27-OHC resulted in decreased viability and enhanced expression of LRP-1 and CatD. **Conclusion:** These findings indicate that hepatic StARD1-dependent 27-OHC links MASH development with CVD onset.

Disclosures: Sandra Torres: Nothing to Disclose, Eduardo Garcia: Nothing to Disclose, Susana Nuñez: Nothing to Disclose, Vicent Ribas: Nothing to Disclose, Leire Goicoechea: Nothing to Disclose, Hala Jaara: Nothing to Disclose, Mariana Acevedo Roldan: Nothing to Disclose, Ana Garcia Alvarez: Nothing to Disclose, Ana Cenarro: Nothing to Disclose, Emma Muñoz: Nothing to Disclose, Naira Rico: Nothing to Disclose, Ana Paula Dantas: Nothing to Disclose, Francisco Rafael Jimenez-Trinidad: Nothing to Disclose, Eduard Guasch: Nothing to Disclose, Xavier Lopez: Nothing to Disclose, Montserrat Rigoll: Nothing to Disclose, Josefina Casas: Nothing to Disclose, Vicenta Llorente-Cortes: Nothing to Disclose, Carmen Garcia-Ruiz: Nothing to Disclose

1035 | HEPATOCYTE ARGINASE-2 PROTECTS FROM METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS BY REGULATING MITOCHONDRIAL FATTY ACID OXIDATION

Hui Han[1] Chao Wang[1] Nithyananthan Subramaniyam[1] Sai Santosh Babu Komakula[2] Xiaodong Ge[2] Abid Anwar[1] Dan Lantvit[1] Natalia Nieto[2]

[1]University of Illinois Chicago, [2]University of Illinois at Chicago

Background: Arginase-2 (ARG2) is a mitochondrial protein involved in cell respiration. We have previously reported that induction of ARG2 in hepatocytes mediated the protective effect of *Spp1*^{high} macrophages in metabolic dysfunction-associated steatohepatitis (MASH). However, the molecular mechanism involved remained unknown. **Methods:** To study this, we generated mice with ablation of *Arg2* in hepatocytes (*Arg2*$^{\Delta Hep}$) by breeding *Arg2*$^{fl/fl}$ with *Alb.Cre* mice and fed *Arg2*$^{\Delta Hep}$ and control (*Alb.Cre*) mice with a high fat, fructose, and cholesterol diet to induce MASH or an isocaloric control diet for six months. We analyzed mitochondrial fatty acid oxidation (FAO) using the Seahorse XF palmitate oxidation stress test. **Results:** Male and female *Arg2*$^{\Delta Hep}$ mice had elevated baseline levels of glucose and insulin and displayed worse MASH, shown by increased liver inflammation, ductular reaction, and fibrosis, compared to control mice. Ablation of *Arg2* in hepatocytes decreased basal respiration, maximal respiratory capacity, spare respiratory capacity, and ATP production in the presence of palmitic acid as an energy source. To investigate the role of ARG2 in mitochondrial FAO, the oxygen consumption rate was measured in freshly isolated mitochondria with palmitoyl-CoA as substrate. Liver mitochondria from *Arg2*$^{\Delta Hep}$ mice with MASH showed a significant reduction in basal and maximal respiratory capacity and ATP production compared to WT mice with MASH, suggesting decreased FAO. To rule out the effect of changes in the acyl-carnitine shuttle, FAO was measured in the presence of palmitoyl-CoA or palmitoyl-L-carnitine as substrates, but no differences were observed. We previously showed that *Spp1*$^{KI\ Mye}$ mice have increased urea cycle byproducts, including fumarate that feeds into the TCA cycle. Treatment of mitochondria from WT with fumarate,

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increased FAO, however it decreased in mitochondria from *Arg2*$^{\Delta Hep}$ mice. **Conclusion:** Hepatocyte ARG2 is involved in the protective effects of *Spp1*^{high} macrophages. Loss of ARG2 from hepatocytes worsens MASH by reducing the availability of fumarate for the TCA cycle.

Disclosures: Hui Han: Nothing to Disclose, Chao Wang: Nothing to Disclose, Nithyananthan Subramaniyam: Nothing to Disclose, Sai Santosh Babu Komakula: Nothing to Disclose, Xiaodong Ge: Nothing to Disclose, Abid Anwar: Nothing to Disclose, Dan Lantvit: Nothing to Disclose, Natalia Nieto: Nothing to Disclose

1036 | REGULATORY T CELL: FRIEND OR FOE IN THE PROGRESSION FROM MASH TO HCC?

Han Wang[1] *Yu Lei*[2] *Shuhui Wang*[2] *Yu Chen*[2] *Dean Tian*[2] *Mei Liu*[2]

[1]*Tongji Hospital, Tongji Medical College,* [2]*Tongji Hospital, Tongji Medical College*

Background: Metabolic-dysfunction-associated steatotic liver disease (MASLD) affects a significant proportion of the US population and is regarded as a metabolic predisposition to hepatocellular carcinoma (HCC). Metabolic-dysfunction-associated steatohepatitis (MASH) represents a progressive and inflammatory subset of MASLD, featured by exacerbated intrahepatic inflammation, intensified steatosis, and hepatocellular damage. Our recent investigations have revealed that regulatory T cells (Tregs) in conjunction with neutrophils facilitate the initiation of HCC in the context of MASH. Conventionally, Tregs have been perceived as protectors against extensive inflammation in MASH. Nevertheless, accumulating evidence suggests that Tregs may have detrimental effects on disease progression. Here we aim to delineate the dual roles of Tregs throughout the different stages from simple steatosis to MASH-HCC. **Methods:** MASH murine models were generated by exposing C57Bl/6 mice to streptozotocin, while FoxP3-DTR/EGFP mice were utilized to delete Tregs.10x Genomics RNA sequencing (RNA-seq) and SMART RNA-seq were conducted to analyze the hepatic CD45$^+$ lymphocytes and Tregs. The metabolic function of Tregs during various stages of MASLD-HCC was assessed using Seahorse. **Results:** Flow cytometry analysis indicates an increase in hepatic Tregs from simple steatosis to MASH-HCC. Treg depletion led to enhanced infiltration of CD4$^+$T and CD8$^+$ T cells in MASH, whereas Treg adoptive transfer promoted steatosis and HCC development. Utilizing 10x Genomics and SMART RNA-seq, we observed that Treg behavior varies across disease stages, with upregulation of surface markers LAG3, PD-1, and TIGIT in advanced stage of MASH, thereby enhancing their functional potency. Metabolic analysis suggests that these mechanisms may be linked to the metabolic reprogramming of hepatic Tregs during the progression from MASLD to HCC. **Conclusion:**
● Tregs exhibit dual roles in the progression from MASLD to HCC. Tregs inhibit effector T cell infiltration while simultaneously promoting steatosis and HCC development in the MASH liver.
● Treg depletion presents a potential therapeutic strategy to hinder the onset of MASH-HCC; however, determining the optimal timing for such intervention requires further investigation.

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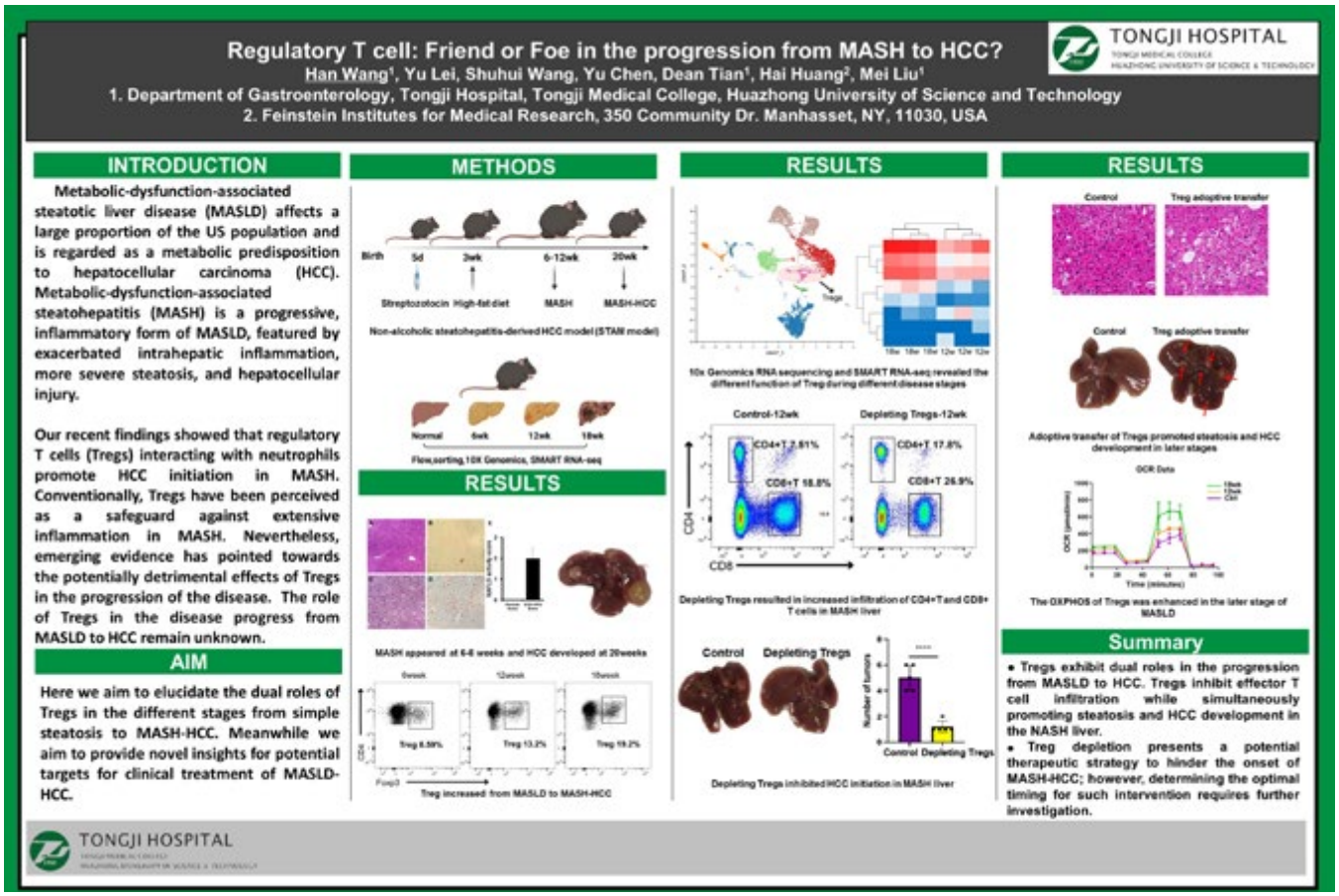

Disclosures: Han Wang: Nothing to Disclose, Yu Lei: Nothing to Disclose, Shuhui Wang: Nothing to Disclose, Yu Chen: Nothing to Disclose, Dean Tian: Nothing to Disclose, Mei Liu: Nothing to Disclose

1037 | THE PAN-PPAR AGONIST LANIFIBRANOR IMPROVES LIVER INFLAMMATION, BALLOONING, AND FIBROSIS IN A DIET-INDUCED OBESE MASH HAMSTER MODEL OF BINGE DRINKING

Francois Briand[1] *Estelle Grasset*[1] *Natalia Breyner*[1] *Thierry Sulpice*[1]

[1]*Physiogenex*

Background: We aimed to validate an animal model to evaluate the efficacy of drugs targeting MASH in a context of moderate to heavy alcohol use, which may aggravate liver lesions in patients with MASH. Because mouse and rat are not convenient models to study the effects of alcohol, we previously characterized a diet-induced obese MASH hamster model that spontaneously shows a high preference for alcohol. Here we further optimized our model to evaluate the effects of the pan-PPAR agonist lanifibranor (LANI) on liver lesions induced by binge drinking. **Methods:** Obesity and MASH were first induced with a free choice diet, which presents golden Syrian hamsters with a choice between control chow or high fat/cholesterol diet, and normal water or 10% fructose water. After a 20-week diet induction, animals were maintained on the same diet with the 10% fructose water supplemented with 5% alcohol, without (control) or with alcohol binge drinking (40% alcohol at 5mL/kg p.o., 3 times per week), and hamsters were simultaneously treated with vehicle or LANI 30mg/kg p.o. QD for 5 weeks. **Results:** Compared to control, binge drinking in obese MASH hamsters led to higher plasma triglycerides levels, hepatic inflammation and ballooning scores and greater liver fibrosis, as measured with % Sirius Red labelling (all $p<0.05$). Binge drinking reduced the hepatic expression of genes involved in alcohol metabolism (Cyp2e1 and ADH1) and significantly raised the expression of genes involved in lipogenesis (ACC and SCD1), inflammation (IL-1b, IL-6, and MCP-1), cell death (caspase 3) and fibrosis (a-SMA, Col1a1, Col3a1 and TIMP1). Compared to hamsters treated with both binge drinking and vehicle, LANI significantly lowered total cholesterol,

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LDL-cholesterol levels, and triglycerides plasma levels. Liver triglycerides content, hepatic inflammation and ballooning scores, as well as liver fibrosis were all reduced with LANI (all p<0.05 vs. vehicle). Additionally, LANI significantly reduced the hepatic expression of genes involved in inflammation and fibrosis. **Conclusion:** LANI significantly improved dyslipidemia and liver lesions in a diet-induced obese MASH hamster model of binge drinking. This preclinical model will help to evaluate drugs targeting MASH in a context of moderate to heavy alcohol use and their potential benefits in humans.

Disclosures: Francois Briand: Physiogenex: Employee, Physiogenex: Stock – privately held company, Estelle Grasset: Nothing to Disclose, Natalia Breyner: Nothing to Disclose, Thierry Sulpice: Nothing to Disclose

1038 | NEUTROPHIL DEPLETION ATTENUATED NLRP3-INDUCED LIVER INFLAMMATION AND FIBROSIS IN NASH

Lin Kui[1] Sharon Ka Pui Yau[1] Janset Onyuru[1] Michael Carbone[1] Hal Hoffman[1] Ariel Feldstein[2]

[1]UC San Diego, [2]University of California, San Diego

Background: Chronic inflammation is a key driver of disease progression in Nonalcoholic Steatohepatitis (NASH). In our previous study, we demonstrated that BRP39 deficiency in NLRP3-induced inflammation improved liver inflammation and fibrosis by reducing neutrophil infiltration into the liver (CMGH 2024). In this study, we investigated the role of neutrophils in NLRP3-induced liver inflammation and evaluated the effectiveness of a neutrophil-depletion strategy in this context. **Methods:** Using tamoxifen-inducible Nlrp3 knock-in ($Nlrp3^{A350V}$ CRT) mice, we assessed the significance of neutrophil depletion employing a double antibody-based strategy with anti-Ly6G (1A8) and anti-rat *kappa* light chain (MAR 18.5) masking antibodies. **Results:** Neutrophil-depleted $Nlrp3^{A350V}$ CRT mice showed improved overall survival and body weight compared to those given isotype-control. Additionally, liver inflammation, fibrosis, and cellular infiltration were reduced, evidenced by decreased Sirius red signals, and fewer CD68+ Osteopontin (OPN)+ lipid-associated macrophages and Ly6G+ citrullinated histone H3 (H3Cit) + activated neutrophils in liver biopsies of neutrophils-depleted $Nlrp3^{A350V}$ CRT mice. Flow cytometry analysis showed a reduction in Siglec F- CD45+ CD11b+ Ly6G- Ly6C++ monocytes in the bone marrow and spleen of neutrophil-depleted $Nlrp3^{A350V}$ CRT mice compared to isotype-control. Confocal microscopy of $Nlrp3^{A350V}$ CRT mice liver biopsies revealed that infiltrating neutrophils closely interacted with hepatic stellate cells. **Conclusion:** Our current data suggested that neutrophils play a crucial role in orchestrating NLRP3-induced liver inflammation and fibrosis, potentially mediated by interactions with hepatic stellate cells. Furthermore, a neutrophil-depletion strategy could improve survival outcomes in NLRP3-induced liver inflammation.

Disclosures: Lin Kui: Nothing to Disclose, Sharon Ka Pui Yau: Nothing to Disclose, Janset Onyuru: Nothing to Disclose, Michael Carbone: Nothing to Disclose, Hal Hoffman: Nothing to Disclose, Ariel Feldstein: Nothing to Disclose

1039 | A NOVEL STEATOHEPATITIS MODEL IN THE FAH-DEFICIENT SWINE

Silvana Wilken[1] Philipp Felgendreff[1] Anna Minshew[1] Boyukkhanim Ahmadzada[1] Byoung Uk Park[1] Ameya Patil[1] Bruce Amiot[1] Ahmer Sultan[1] Kamal Hussein[1] Julio Cisneros Correa[1] Harmeet Malhi[1] Roger Moreira[1] Scott Nyberg[1]

[1]Mayo Clinic, Rochester, MN

Background: Metabolic dysfunction-associated steatohepatitis (MASH) is a rising healthcare burden. The grade of fibrosis is the principal prognostic factor of MASH patients. Employing appropriate animal models mimicking the main MASH characteristics of steatosis, inflammation and hepatocyte damage alongside progression of fibrosis are imperative for the development of new treatment strategies. Robust large animal models comprising all above-mentioned features are currently lacking. We developed a steatohepatitis model in the fumarylacetoacetate hydroxylase deficient (FAH-/-) swine by combining steatosis-inducing diet and subtherapeutic doses of nitisinone (NTBC) to induce hepatocyte damage, inflammation and fibrosis. **Methods:** FAH-/- swine (n=4) were generated by CRIPR/Cas9 system and somatic nuclear transfer. After reaching one month of age the animals received a choline-deficient, L-amino acid-defined high-fat diet (CDAHFD) and subtherapeutic doses of NTBC. The animals were followed up for 3 months of treatment. Liver biopsies (ultrasound-guided percutaneous biopsies or at endpoint necropsy) were obtained before, one, two and three months after beginning of treatment. The liver

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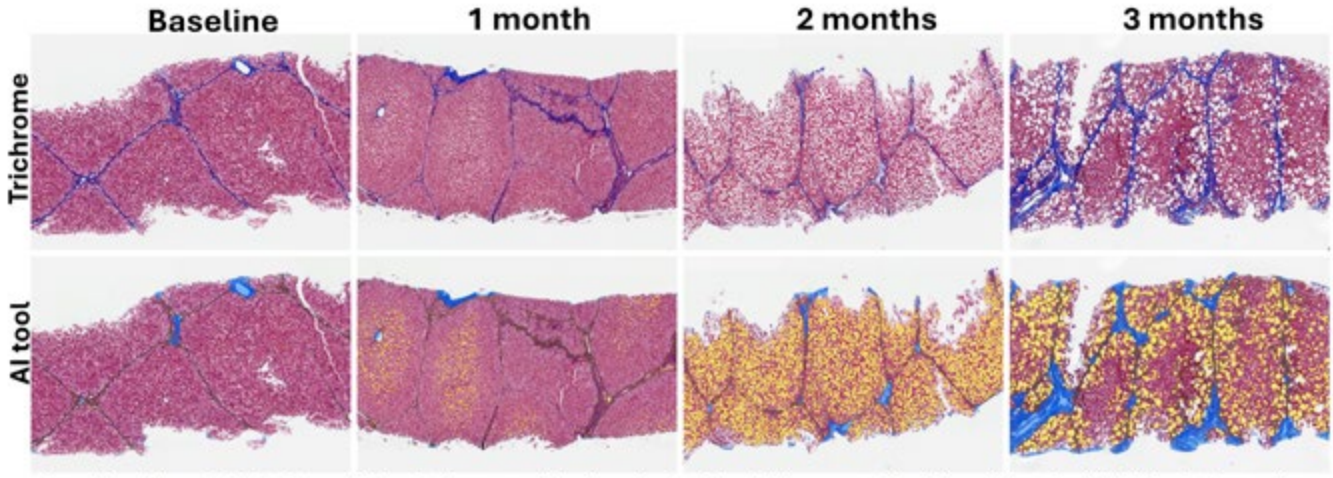
tissue was stained for H&E, Sirius red and trichrome. Steatosis, inflammation and fibrosis were evaluated by a blinded hepatologist according to the NAFLD Activity Score (NAS). The amount of steatosis (ratio of area of lipid droplets to total area of hepatic lobules) and fibrosis (collagen proportionate area) were quantified by an AI machine learning software. Native CT scans were performed at eight weeks and were analyzed with ImageJ for absolute Hounsfield units (HU) in ten regions of interest in the liver and spleen. **Results:** Severe steatosis was observed already at two months of treatment. There was a significant increase in the steatosis grade according to the NAS score from baseline to 2 months and 3 months ($p<0.05$, Mann-Whitney-U test), as well as according to the AI-based quantification of steatosis ($p=0.0001$, one-way ANOVA). The development of steatosis was also confirmed by CT scans, in which the average of HU of the liver was 1.41 [-9.59;+25.53] and the average difference in HU between liver and spleen was 64.29 (±2.67). The grade of inflammation increased significantly after 3 months of treatment ($p<0.05$, Mann-Whitney-U test). The histology showed distinct development of periportal and perisinusoidal fibrosis after 3 months. The grade of fibrosis according to the NAS score, as well as the proportionate collagen in the tissue showed an increase from baseline to 3 months, however, the difference was not significant. There was no balooning observed in the liver specimens. **Conclusion:** We successfully developed a novel model of steatohepatitis within three months, combining all major histological MASH characteristics. The model warrants further evaluation in mechanistic studies and preclinical trials of novel MASH therapies.



Quantification of steatosis and fibrosis by a machine learning tool on trichrome stained liver biopsies (lipid droplets – yellow; collagen – blue and brown).

Disclosures: Silvana Wilken: Nothing to Disclose, Philipp Felgendreff: Nothing to Disclose, Anna Minshew: Nothing to Disclose, Boyukkhanim Ahmadzada: Nothing to Disclose, Byoung Uk Park: Nothing to Disclose, Ameya Patil: Nothing to Disclose, Bruce Amiot: Nothing to Disclose, Ahmer Sultan: Nothing to Disclose, Kamal Hussein: Nothing to Disclose, Julio Cisneros Correa: Nothing to Disclose, Harmeet Malhi: Nothing to Disclose, Roger Moreira: Nothing to Disclose, Scott Nyberg: Nothing to Disclose

1040 | THE EXERCISE-INDUCED METABOKINE BETA-AMINOISOBUTYRIC ACID REGULATES HEPATIC LIPID METABOLISM AND REDUCES HEPATIC METABOLIC DYSFUNCTION AND FATTY LIVER IN A DIETARY OBESE MOUSE MODEL

Shaimaa Gad[1] Helene Daou[1] Amanda Maccannell[1] Nicole Watt[1] Laeticia Lichtenstein[1] David Beech[1] Scott Bowen[1] Lee Roberts[1]

[1]University of Leeds

Background: Obesity is a common pathology arising from energy disbalance which increases the risk of metabolic and cardiovascular disease. Exercise is an effective intervention, decreasing obesity and associated cardiometabolic risks. Beta-aminoisobutyric acid (BAIBA), a skeletal muscle metabokine regulated by exercise and the transcriptional coregulator Pgc1α (peroxisome proliferator-activated receptor-gamma coactivator-1alpha) mediates muscle-liver-adipose crosstalk. BAIBA enhances hepatic fatty acid beta oxidation (FaβO) and browning

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of fat. The effects and signals of BAIBA on hepatic tissue are poorly elucidated. We hypothesize that BAIBA regulates and can improve hepatic metabolism to treat dietary obesity induced fatty liver. **Methods:** 8-week-old male C57BL/6J mice were either fed chow diet {CD} +/- BAIBA (100mg/kg/day water-added) for 6 weeks (A), 14 weeks (B) or high fat diet {HFD} +/- BAIBA for 14 weeks (C) (n=10/group). We investigated hepatic 1) Metabolism: mitochondrial density (citrate synthase {CS} assay) and function (carnitine palmitoyl transferase {CPT} activity and high resolution mitochondrial respirometry analysis); 2) Molecular phenotype: gene (RT-qPCR) and protein (immunoblotting) expression for FaβO, mitochondrial, lipid and carbohydrate metabolic markers; 3) Histomorphological analysis. Nominal Significance, $p<0.05$ using GraphPad Prism software. **Results:** Hepatic tissue from CD 6-week BAIBA treated mice (A) was characterised by significantly: 1) lower acetyl CoA carboxylase alpha (Acaca) gene and protein expression. 2) greater expression of Cpt1a gene and protein as well as peroxisome proliferator activated receptor alpha (Ppara) gene and protein. 3) increased mitochondrial density, total CPT activity and CPT1 activity (identifying increased fatty acid oxidation). 4) enhanced mitochondrial FaβO. 5) higher gene expression of fatty acid transporter 2, hepatic and monoacylglycerol lipases and fasting induced adipose factor with lower triglycerides. Analysis of hepatic tissue from 14-week BAIBA treated mice under CD (B) and HFD (C) revealed significantly: 1) raised total CPT functional activity. 2) enhanced Acaca protein expression driven by HFD which was reduced with BAIBA treatment. 3) higher expression of Cpt1a, Ppara and gluconeogenic genes with BAIBA treatment under chow conditions. 4) reduced the expression of HFD-induced denovo lipogenesis (DNL) genes including Acaca, diacylglycerol acyltransferase2, stearoyl CoA desaturase1 and elongas6 lipogenic genes. 5) decreased plasma cholesterol in both CD and HFD fed mice. 6) decreased hepatic fat accumulation and decreased fibrosis (collagen I) (n=5) in BAIBA-treated mice. **Conclusion:** BAIBA has beneficial metabolic effects in the livers of lean and obese mice, enhancing hepatic FaβO, mitochondrial energetics and decreasing DNL leading to reduced hepatic fat accumulation and fibrosis.

Disclosures: Shaimaa Gad: Nothing to Disclose, Helene Daou: Nothing to Disclose, Amanda Maccannell: Nothing to Disclose, Nicole Watt: Nothing to Disclose, Laeticia Lichtenstein: Nothing to Disclose, David Beech: Nothing to Disclose, Scott Bowen: Nothing to Disclose, Lee Roberts: Nothing to Disclose

1041 | PHARMACOLOGICAL CHARACTERIZATION OF EA3571: A NOVEL DUAL INHIBITOR OF ENTEROPEPTIDASE AND TRYPSIN WITH LUMINAL ACTION FOR METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS

Ayatoshi Andou[1] *Yui Yamaura*[1] *Masahiko Kaneko*[1] *Sen Takeshita*[1]

[1]*EA Pharma Co., Ltd.*

Background: EA3571 is a novel dual inhibitor of enteropeptidase and trypsin with luminal action. EA3571 has the potential to embody the effects of gastric bypass surgery by preventing the digestion of dietary nutrients in the small intestine of obese metabolic dysfunction-associated steatohepatitis (MASH) patients. The objective of the following studies is to demonstrate the effectiveness of EA3571 for MASH and to elucidate its pharmacological properties and mode of action (MoA). **Methods:** The *in vitro* inhibitory activity of EA3571 against human enteropeptidase and trypsin activity was determined. To elucidate the MoA of EA3571, single oral dose studies were performed in normal mice to confirm the degradation of dietary proteins and changes in hormones, GLP-1 and FGF-21. The effects of repeated oral doses of EA3571 were investigated in a high-fat, high-fructose and high-cholesterol diet-induced mouse MASH model. **Results:** The 50% inhibitory concentration values of EA3571 against human enteropeptidase, trypsin 1, trypsin 2 and trypsin 3 were 0.38±0.04, 0.37±0.09, 0.29±0.05 and 0.13±0.02 nmol/L, respectively. The inhibitory constant values were further calculated to be 0.083±0.019, 0.15±0.02, 0.15±0.02 and 0.056±0.004 nmol/L, respectively. The effect of EA3571 on elevated plasma hydroxyproline levels in normal mice following oral dose of gelatin was assessed, confirming that luminal exposure of EA3571 inhibited intestinal degradation of dietary protein. Furthermore, dose of EA3571 significantly increased plasma levels of GLP-1 and FGF-21, hormones with potential therapeutic effects on MASH. Finally, repeated doses of EA3571 showed an ameliorative effect on various pathological parameters such as liver steatosis, inflammation and fibrosis (Figure), as well as on blood ALT, obesity and insulin resistance in the mouse MASH model. **Conclusion:** *In vitro* studies show that EA3571 is a highly potent dual inhibitor of enteropeptidase and trypsin. EA3571 inhibited luminal proteolysis, allowing dietary proteins to reach the lower small intestine and promoting the secretion of hormones such as GLP-1 from the intestine. EA3571 also mimicked the ‘effects of a

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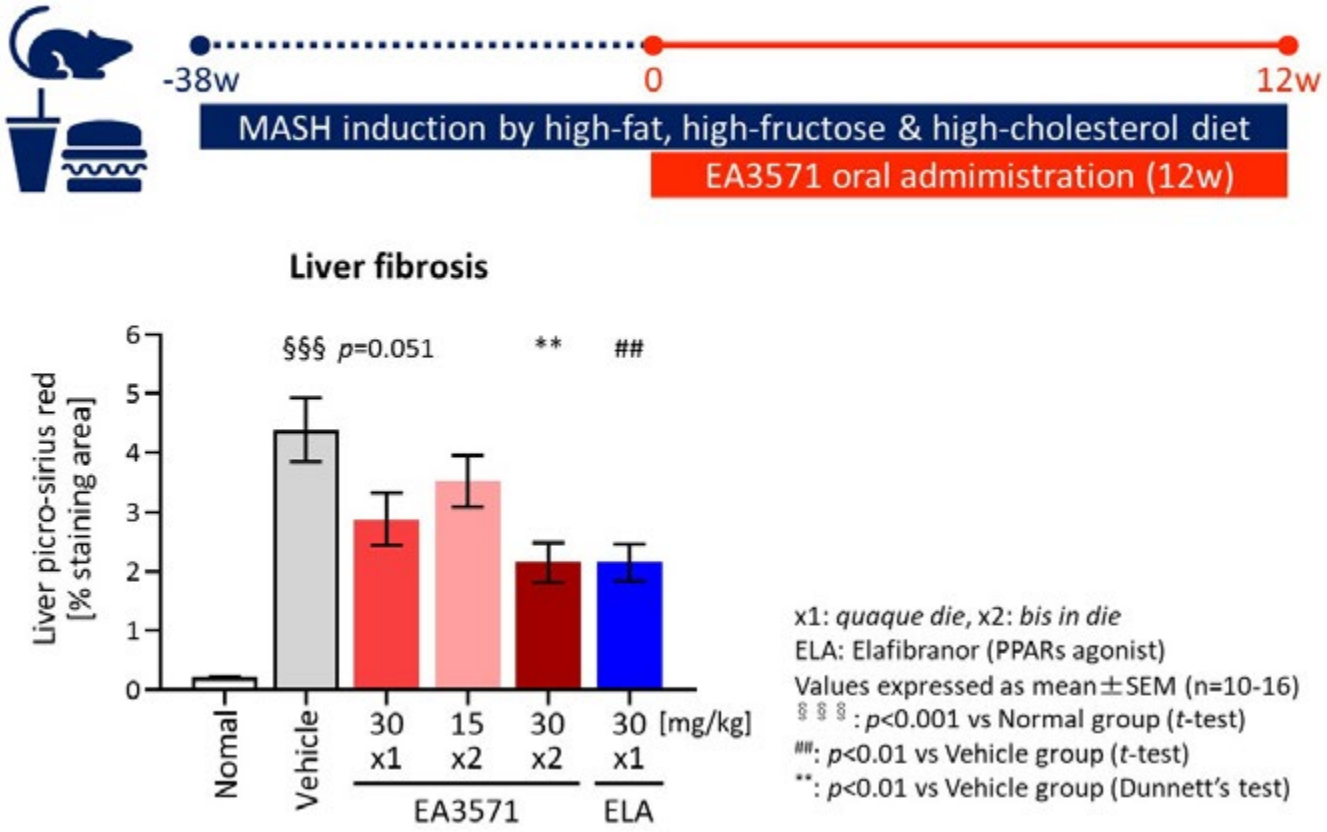
protein-restricted diet' and promoted FGF-21 secretion from the liver, which may have anti-insulin resistance and fat-burning properties. EA3571 completed a Phase 1 clinical trial for a new oral treatment for MASH.



Disclosures: Ayatoshi Andou: Nothing to Disclose, Yui Yamaura: Nothing to Disclose, Masahiko Kaneko: Nothing to Disclose, Sen Takeshita: Nothing to Disclose

1042 | HEPATOCYTE-SPECIFIC DELETION OF THE NOVEL HEXOKINASE, HKDC1, PROTECTS AGAINST MASH-INDUCED FIBROSIS IN FEMALE MICE

Irene Corona-Avila[1] Zeenat Farooq[1] Kai Xu[1] Medha Priyadarshini[1] Md. Wasim Khan[1]

[1]University of Illinois at Chicago

Background: The inflammatory advanced stage of MASLD, **metabolic-associated steatohepatitis (MASH)**, is closely associated with the global obesity epidemic and often leads to fibrosis, cirrhosis, and an increased risk of hepatocellular carcinoma. The prevalence of MASLD varies by sex, with a higher prevalence in men (22–42%) than in women (13–24%). However, a meta-analysis of 17 population-based studies found that women had a 37% higher prevalence of advanced fibrosis than men. The intricate interplay between glucose and lipid metabolism plays a central role in the development and progression of MASH. The concept of **glucotoxicity** and **lipotoxicity**, or the presence of hepatocellular injury due to dysregulation of glucose and fat metabolism, remains critical in uncovering the drivers that precipitate MASH; thus, targeting metabolic pathways provides an attractive option to halt the progression of MASH. Our target, Hexokinase domain containing 1 (**HKDC1**), is a novel protein involved in glucose and lipid metabolism of the pathological liver. We have previously shown that HKDC1 is overexpressed in human MASLD, and now we have critical data showing that HKDC1 is also significantly overexpressed in the livers of MASH (female) patients. **Methods:** We have used our novel mouse model of liver-specific knockout (LKO) of HKDC1 by crossing our HKDC1 floxed mice ($HKDC1^{fl/fl)}$ with the Albumin Cre mice to generate early-onset knockout of HKDC1 ($eHKDC1^{LKO}$). Littermates HKDC1 floxed mice served as controls for this study. When these **female** mice were eight weeks old, we fed them the classical Western Diet for 28 weeks. **Results:** Our data

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shows that HKDC1 deletion significantly inhibits weight gain and overall adiposity compared to HKDC1$^{fl/fl}$ mice with no changes in food intake or energy expenditure. In addition, eHKDC1^{LKO} mice have better glucose tolerance and insulin sensitivity than control mice. eHKDC1^{LKO} mice had smaller livers, better liver health parameters (lower ALT and AST), lower NAS activity, and fibrosis scores than HKDC1$^{fl/fl}$ mice. Furthermore, eHKDC1^{LKO} mice had significantly low proinflammatory and profibrogenic gene expression. MASH progression is known to perturb the expression of genes involved in lipids and cholesterol metabolism; we did not see any changes in serum triglyceride and NEFA levels in 4h-fasted mice. However, we observed significant changes in the expression of important lipid and cholesterol metabolism pathway regulators where HKDC1 ablation corrected the aberrant expression of these genes. **Conclusion:** Our data suggest a promising protective role of HKDC1 deletion against diet-induced obesity and MASH progression in female mice. Targeting HKDC1 in MASH is highly significant as it *is highly expressed in MASH liver but has negligible expression in normal hepatocytes.*

Disclosures: Irene Corona-Avila: Nothing to Disclose, Zeenat Farooq: Nothing to Disclose, Kai Xu: Nothing to Disclose, Medha Priyadarshini: Nothing to Disclose, Md. Wasim Khan: Nothing to Disclose

1043 | ADIPOCYTE ACTIVATING TRANSCRIPTION FACTOR 3 IS A GATEKEEPER IN PREVENTING NON-ALCOHOLIC STEATOHEPATITIS

Shuwei Hu[1] Fathima N Cassim Bawa[1] Yingdong Zhu[1] Yanyong Xu[1] Xiaoli Pan[1] Hui Wang[1] Raja Gopoju[1] Yanqiao Zhang[1]

[1]NORTHEAST OHIO MEDICAL UNIVERSITY

Background: The crosstalk between adipose tissue and the liver is finely controlled to maintain metabolic health. Yet, how adipose tissue regulates the development of metabolic dysfunction-associated steatohepatitis (MASH) under physiological and pathological conditions is not well understood. Hepatic activating transcription factor 3 (ATF3) plays an important role in lipid metabolism. However, the role of adipocyte ATF3 in the development of MASH is completely unknown. **Methods:** Adipocyte-specific *Atf3*$^{-/-}$ (*Atf3*$^{Adi-/-}$) mice and their control mice were fed a chow diet, a high fat diet (HFD), or a high fat/high cholesterol (HFHC) diet to investigate the effect of adipocyte ATF3 inactivation on the development of metabolic dysfunction-associated steatotic liver disease (MASLD) and obesity. The contributions of the AMPK pathway and fatty acid flux were investigated using AICAR or overexpression AMPKα. Adipocyte lipolysis and lipogenesis were analyzed using 3T3-L1 cells and small adipose depots. An adipocyte/hepatocyte co-culture study was performed. **Results:** Here we show that adipocyte activating transcription factor 3 (ATF3) was induced in obesity and by palmitic acid. Mechanistically, adipocyte ATF3 inhibited lipolysis via adipose triglyceride lipase (ATGL), thus preventing hepatocytic lipogenesis and damage. Adipocyte ATF3 also inhibited adipogenesis and inflammation and induced thermogenesis, hence attenuating obesity and insulin resistance. **Conclusion:** Our data demonstrate that adipocyte ATF3 is a gatekeeper in counteracting the development of NASH under both physiological and pathological conditions.

Disclosures: Shuwei Hu: Nothing to Disclose, Fathima N Cassim Bawa: Nothing to Disclose, Yingdong Zhu: Nothing to Disclose, Yanyong Xu: Nothing to Disclose, Xiaoli Pan: Nothing to Disclose, Hui Wang: Nothing to Disclose, Raja Gopoju: Nothing to Disclose, Yanqiao Zhang: Nothing to Disclose

1044 | C/EBPB-VCAM1 AXIS IN KUPFFER CELLS PROMOTES HEPATIC INFLAMMATION IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS ◆

Yang Xie[1] Yu-Qing Cheng[1] Rui Xue[1] Yin-Shi Su[2] Mingxi Liu[3] Yuanwen Chen[4] Jiangao Fan[1]

[1]Shanghai Xin Hua Hospital, [2]Huadong Hospital, [3]Nanjing Medical University, [4]Huadong Hospital, Fudan university

Background: Kupffer cell (KC) participates in hepatic inflammation and fibrosis in metabolic dysfunction-associated steatohepatitis (MASH), but underlying molecular mechanisms are not fully resolved. Transcription factor CCAAT/enhancer binding protein β (C/EBPβ) has been implicated in both metabolic and immune dysregulations. In this study, we aimed to investigate the role of C/EBPβ in Kupffer cells under the context of MASH pathogenesis. **Methods:** A 12-week high-fat and high-cholesterol diet (HFHCD) model was used in wild-type or KC-specific Cebpb heterozygous knockout mice (*Cebpb*$^{fl/+}$;Clec4f-iCre), followed by evaluation of

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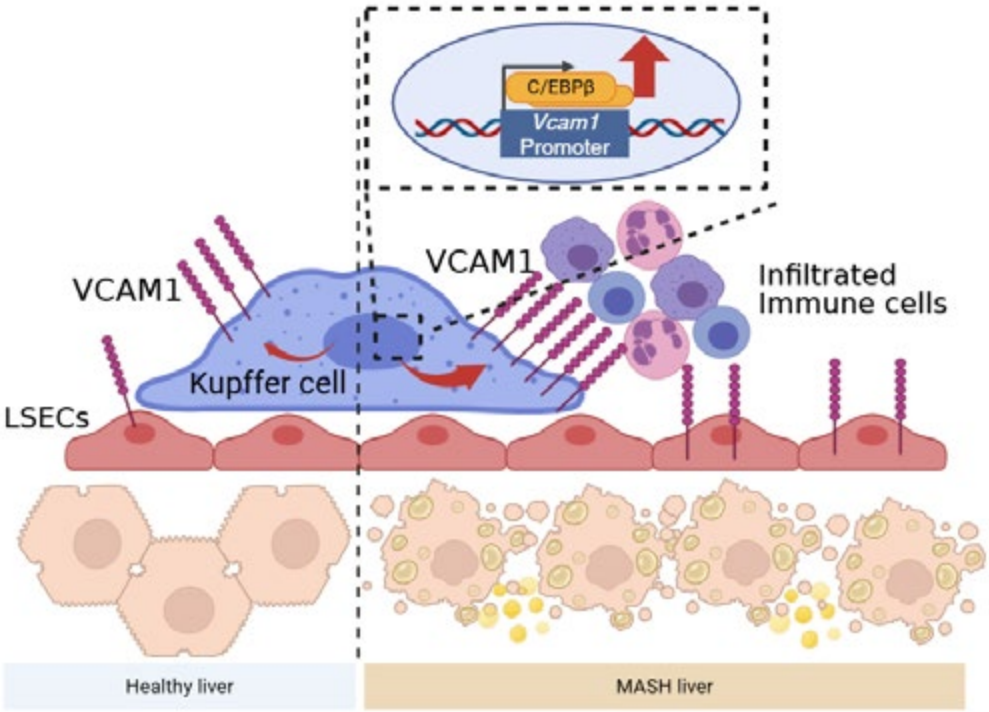
liver using histopathology, analytical flow cytometry and RNA-seq. FACS-sorted KCs of HFHCD-treated mice were used for C/EBPβ CUT&Tag-seq. **Results:** We found that HFHCD in wild-type mice induced significant inflammatory immune cell infiltration, including increased proportion of monocyte-derived macrophages (MoMFs), accompanied with concomitant increase in C/EBPβ protein level in KCs. KC-specific Cebpb heterozygous knockout significantly reduced HFHCD-induced immune cell (including MoMFs, neutrophils and CD8+ T cells) infiltration and inflammation-related gene expression in liver, although hepatic steatosis and hepatocellular ballooning were not significantly changed. Combined analysis of RNA-seq and CUT&Tag-seq identified *Vcam1* (encoding vascular cell adhesion molecule 1, VCAM1) as a key downstream gene of C/EBPβ in KCs of murine MASH liver: C/EBPβ CUT&Tag-seq revealed prominent distribution of C/EBPβ in *Vcam1* promoter in KCs from MASH mice, while VCAM1 expression were significantly downregulated in murine MASH liver and Kupffer cells. The activating effect of C/EBPβ on *Vcam1* promoter was further verified by dual luciferase reporter assay. In both murine liver and MASH patients, VCAM1 was predominantly expressed in Kupffer cells. Its expression in liver was significantly increased after MASH onset, and it was involved in promoting immune cell infiltration in MASH. **Conclusion:** In MASH pathogenesis, increased C/EBPβ in KCs has a direct transcriptional activation effect on *Vcam1* promoter, leading to abnormal elevation in VCAM1 expression in KCs and subsequent immune cell infiltration. Our findings suggest that C/EBPβ in KCs can be a potential therapeutic target for MASH inflammation.



Disclosures: Yang Xie: Nothing to Disclose, Yu-Qing Cheng: Nothing to Disclose, Rui Xue: Nothing to Disclose, Yin-Shi Su: Nothing to Disclose, Mingxi Liu: Nothing to Disclose, Yuanwen Chen: Nothing to Disclose, Jiangao Fan: Nothing to Disclose

1045 | INHIBITION OF VISCERAL ADIPOSE TISSUE-DERIVED PATHOGENIC SIGNALS BY ACTIVATION OF ADENOSINE A_{2A}R IMPROVES CARDIAC DYSFUNCTION OF NASH MICE

Ying-Ying Yang *Roger Lin*[1] *Tsai-Ling Liao*[2] *Han-Chieh Lin*[1]

[1]*Taipei Veterans General Hospital,* [2]*Taichung Veterans General Hospital*

Background: A_{2A}R-disrupted mice is characterized by severe systemic and visceral adipose tissue (VAT) inflammation. Increasing adenosine cyclase (AC), cAMP and protein kinase A (PKA) formation through A_{2A}R activation suppress systemic/VAT inflammation in obese mice. **Methods:** This study explores the effects of four-weeks A_{2A}R agonist PSB0777 treatment on the VAT-driven pathogenic signals in cardiac dysfunction of non-alcoholic steatohepatitis (NASH) obese mice. **Results:** Among NASH mice with cardiac dysfunction,

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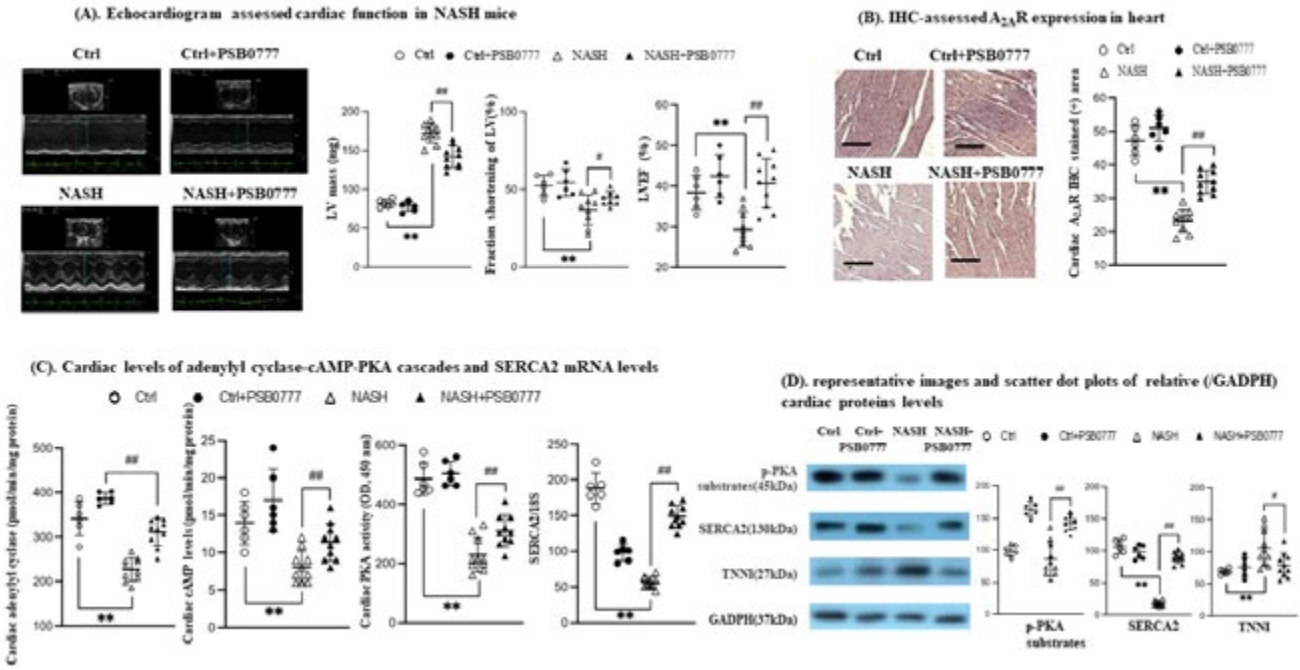
simultaneous decrease in the $A_{2A}R$, AC, cAMP and PKA levels were observed in VAT, liver, and heart. PSB0777 treatment significantly restores AC, cAMP, PKA, *HSL* levels, decreased *SREBP-1/FASN*, MCP-1 and CD68 levels, reduces infiltrated $CD11b^{+}F4/80^{+}$ cells and adipogenesis in VAT of NASH+PSB0777 mice. The changes in VAT were accompanied by the suppression of cardiac lipogenic/inflammatory/injury/apoptotic/fibrotic markers, the normalization of cardiac contractile [sarco/endoplasmic reticulum Ca^{2+}ATPase (SERCA2)] marker, and cardiac dysfunction **Conclusion:** This study revealed that, $A_{2A}R$ agonists are potential agent to inhibit the effects of VAT inflammation-driven pathogenic signals on the cardiac lipogenesis, inflammation, injury, apoptosis, fibrosis, hypo-contractility, and subsequently improve cardiac dysfunction in NASH mice.



Disclosures: Ying-Ying Yang: Nothing to Disclose, Roger Lin: Nothing to Disclose, Tsai-Ling Liao: Nothing to Disclose, Han-Chieh Lin: Nothing to Disclose

1046 | THE GENE EXPRESSION CHARACTERISTIC IN MASLD-HCC PROGRESSION WITH DIET-INDUCED METABOLIC SHIFTS

yuyun song[1] *Ke Yin*[1] *Yin Ai*[2] *Huiying Rao*[2] *Xiaoxiao Wang*[2] *Feng Liu*[2]

[1]*Peking University People's Hospital,* [2]*Peking University People's Hospital*

Background: The role of metabolic factors in the progression and regression of metabolic dysfunction-associated steatotic liver disease associated hepatocellular carcinoma (MASLD-HCC) is still unclear. In this study, we investigated the metabolic effects on MASLD-HCC progression by evaluating the dynamic changes of genes in the MASLD-HCC model induced by high-fat, high-cholesterol diet and its withdrawal post-tumorigenesis. **Methods:** C57BL/6J mice were fed WD (western diet) (containing high-fat, high-cholesterol) supplemented with a fructose-glucose solution (F) and administered carbon tetrachloride (CCl4) via intraperitoneal injection. After MASLD-HCC model were established, mice returned to normal diet for 8 weeks. Single-cell RNA sequencing (scRNA-seq) was conducted on liver tissues of normal diet controls (ND), tumor nodules of MASLD-HCC and post-normal diet resumption (HCC-PND). **Results:** Compared with ND group, scRNA-seq revealed monocytes and macrophages were more abundant in HCC and HCC-PND groups. Endothelial cells were less prevalent in the HCC group but significantly increased in the HCC-PND group. The differentially expressed genes (DEG) between Group A (HCC vs. ND) and Group B (HCC-PND vs. HCC) showed 792 shared genes (Figure),which demonstrated significant differences primarily in inflammatory responses, lipid binding, positive regulation of cell proliferation, and apoptosis by enrichment analysis. 408 shared genes were upregulated in HCC compared to ND group, and downregulated in HCC-PND compared to HCC, involveing in inflammatory responses (S100a8, S100a9, Tnfrsf1b, Cxcl2, Ccr5), cell proliferation (Hdac4, Bcl2, Thbs1, Tpd52, Hipk1), and apoptosis (Fasl, Bcl2,

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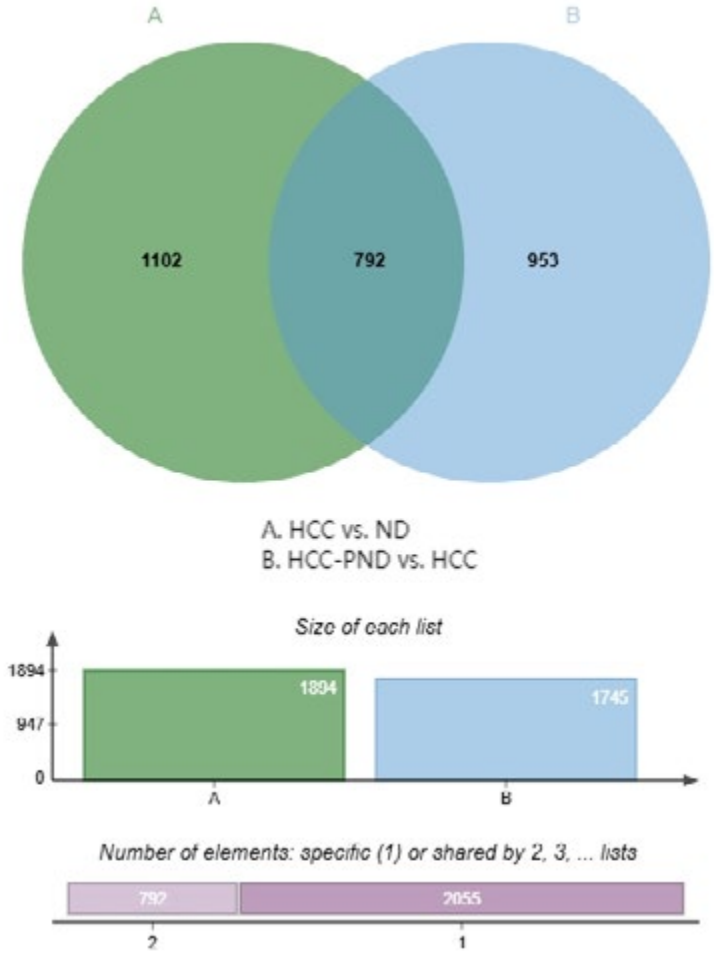
Jun, Kras, Birc2). 138 shared genes were downregulated in HCC compared to ND group, and upregulated in HCC-PND, and mainly enriched into lipid binding (Alb, Cd55, Apoa2, Dbi, Ap2a2). The change of these shared genes suggest that dietary might impacts on gene expression. **Conclusion:** A high-fat, high-cholesterol diet influences DEGs associated with MASLD-HCC progression. Post-tumorigenesis, switching to a normal diet might reduce inflammation, cell proliferation, and apoptosis activities while boosting lipid metabolism, possibly normalizing cellular states, underlining the key role of metabolic factors in MASLD-HCC development.



Disclosures: yuyun song: Nothing to Disclose, Ke Yin: Nothing to Disclose, Yin Ai: Nothing to Disclose, Huiying Rao: Nothing to Disclose, Xiaoxiao Wang: Nothing to Disclose, Feng Liu: Nothing to Disclose

1047 | MICROVASCULARIZED LIVER MICROPHYSIOLOCAL SYSTEM MODELS KEY FEATURES OF HUMAN INSULIN RESISTANCE

Erin Tevonian[1] Ellen Kan[1] Alex Wang[1] Kairav Maniar[1] Roger Kamm[1] Douglas Lauffenburger[1] Linda Griffith[1]

[1]Massachusetts Institute of Technology

Background: Modeling the interplay between molecular and cellular cues driving hepatic insulin resistance (IR) is crucial for understanding the mechanisms of disease and ultimately therapeutic development. 3D cell culture models, such as microphysiological systems (MPS), serve as a valuable tool for better investigation of human biology, however these models can be limited in their ability to recapitulate this disease state, often using supraphysiological levels of nutrients and hormones or neglecting to incorporate relevant interacting cell types. **Methods:** We established a vascularized liver spheroid model, first generating multicellular spheroids composed of primary human hepatocytes, Kupffer cells, stellate cells, and endothelial cells (HUVECs). Seeding these spheroids into microfluidic devices alongside additional HUVECS and fibroblasts established a vascularized liver model,

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which further enabled perfusion of PBMC derived CD14+ monocytes for investigation of immune cell trafficking. This platform was applied to model hepatic IR through overload of nutrients and insulin within a physiologically relevant range. Characterization of hepatic function, insulin resistance, and inflammation was assayed from media supernatant in physiological and IR conditions, and altered immune cell recruitment was measured via flow cytometry and microscopy. **Results:** Our results demonstrate that our co-culture platform is supportive of vascularized hepatic spheroids, with images showing extensive interactions between spheroids and endothelial networks. Culture in IR conditions demonstrated reduced insulin clearance, dysregulated gluconeogenesis, and elevated cytokine release. Microvascular networks themselves further showed a disease phenotype with narrowing of the networks and increased permeability over time in the IR media compared to the physiological baseline condition. Perfusion testing revealed these self-organized networks have open lumens allowing transport directly into the hepatic spheroids. CD14+ Monocytes were then added to the co-culture resulting in increased CD14+ cell frequency in IR conditions, aligning with clinical observations. **Conclusion:** This study establishes an *in vitro* vascularized liver model incorporating primary local and circulating immune populations, alongside liver resident cell types. This enables independent tuning of molecular or cellular parameters and investigations of cell-cell interactions for better mechanistic understanding of disease pathology. Furthermore, this system is adaptable to a range of applications as a tool for therapeutic development and validation.

Disclosures: Erin Tevonian: Nothing to Disclose, Ellen Kan: Nothing to Disclose, Alex Wang: Nothing to Disclose, Kairav Maniar: Nothing to Disclose, Roger Kamm: Nothing to Disclose, Douglas Lauffenburger: Nothing to Disclose, Linda Griffith: Nothing to Disclose

1048 | CARRIAGE OF MULTIPLE GENETIC RISK FACTORS FOR MASH STIMULATES AN ALTERED INFLAMMATORY SECRETOME IN A HUMAN STEM CELL-BASED *IN VITRO* MODEL

Alexandra Gatzios[1] Matthias Rombaut[1] Joery De Kock[1] Dinja De Win[1] Anja Heymans[1] Vera Rogiers[1] Robim Rodrigues[1] Joost Boeckmans[1] Tamara Vanhaecke[1]

[1]Vrije Universiteit Brussel

Background: Genetics play an important role in the development of metabolic dysfunction-associated steatohepatitis (MASH). Specifically, a combination of single nucleotide polymorphisms in known MASH-modifying genes - *PNPLA3* (rs738409 C>G), *TM6SF2* (rs58542926 C>T), *GCKR* (rs1260326 C>T), and *MBOAT7* (rs641738 C>T) - has been integrated into a polygenic risk score for hepatic fat content (PRS-HFC). However, the impact of this polygenic risk on the hepatocyte-specific inflammatory secretome is unclear. Here, we aimed to identify inflammatory proteins related to an increased polygenic risk for MASH using a human stem cell-based *in vitro* model representing genetic variability in the MASH population. **Methods:** 90 human skin-derived precursor (hSKP) cell lines were genotyped and classified according to their PRS-HFC. Five cell lines were selected from the low (RC_{low}) and high (RC_{high}) risk categories and differentiated to hepatic cells (hSKP-HPCs) over 24 days. These cultures were then exposed for 24 hours to a mix consisting of fatty acids, fructose, lipopolysaccharide and TNF-alpha, mimicking a 'MASH' phenotype, or vehicle-matched control medium. Intracellular lipids were quantified using flow cytometry following BODIPY™ 493/503 staining for neutral lipids to validate the PRS-HFC in this *in vitro* system. Protein biomarkers were determined in the cell culture supernatant using the Olink® multiplex analysis platform. **Results:** MASH-induced hSKP-HPC RC_{high} cultures exhibited a 3.5-fold increase in lipid load compared to RC_{low} cultures ($p = 0,0004$). RC_{high} cultures secreted remarkably more interleukin 6 (IL6) than RC_{low} cultures (5.2-fold, $p < 0.0001$) in response to the 'MASH' mix. While RC_{low} and RC_{high} cultures secreted similar amounts of CC motif chemokine ligand (CCL) 2 ($p = 0.053$) and CXC motif chemokine ligand (CXCL) 10 ($p = 0.56$), an increased secretion in RC_{high} was also found for CCL7 (1.5-fold, $p = 0.0058$), CCL8 (7.1-fold, $p < 0.0001$), CCL19 (3.8-fold, $p < 0.0001$), CXCL8 (1.8-fold, $p = 0.0007$), and colony stimulating factor 3 (CSF3) (2.4-fold, $p < 0.0001$). **Conclusion:** This *in vitro* study suggests that carriage of multiple genetic risk factors for MASH stimulates an altered inflammatory secretome involving at least IL6, CCL7, CCL8, CCL19, CXCL8, and CSF3. Employing pathway analysis and sequencing techniques will further uncover the underlying mechanisms responsible for the altered secretion of inflammatory proteins.

Disclosures: Alexandra Gatzios: Nothing to Disclose, Matthias Rombaut: Nothing to Disclose, Joery De Kock: Nothing to Disclose, Dinja De Win: Nothing to Disclose, Anja Heymans: Nothing to Disclose, Vera Rogiers:

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Nothing to Disclose, Robim Rodrigues: Nothing to Disclose, Joost Boeckmans: Nothing to Disclose, Tamara Vanhaecke: Nothing to Disclose

1049 | *FAM172A* GENE KNOCKDOWN AGGRAVATES HEPATOCYTE LIPOTOXIC INJURY THROUGH ACTIVATING THE ERK PATHWAY

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Background: As research progresses, the understanding of the pathogenesis of nonalcoholic fatty liver disease (NAFLD) has improved, yet many questions remain unanswered. The *Fam172a* gene, also known as C5orf21, has been poor studied, with most research focusing on its role in cancer. In our previous study, wefound that *Fam172a* gene knockout mice exhibited abnormal liver function and lipid metabolism disorders without any induction, but the specific mechanisms were not elucidated. Therefore, in the present study, we further explored the potential mechanisms by which *Fam172a* gene knockout leads to spontaneous lipotoxicity. **Methods:** Wild-type (WT) and *Fam172a* gene knockout (*Fam172a*$^{-/-}$) mice were used. Serum ALT and AST levels were measured. Hematoxylin-eosin staining and Oil Red O staining were used to assess lipid accumulation and inflammation levels in mouse liver tissues. The relative mRNA expression levels of the inflammatory cytokines in liver tissues were detected by real-time fluorescence quantitative PCR. *Fam172a* gene knockdown HepG2 cell line was used. The relative protein expression levels of pERK/ERK, intracellular triglyceride content, and the relative mRNA expression levels of the inflammatory cytokines, using the aforementioned experimental methods. **Results:** Compared with WT mice, *Fam172a*$^{-/-}$ mice showed more severe structural damage, more lipid accumulation, and inflammation in the liver (Fig. 1A). Serum ALT and AST levels were more significantly elevated in (Fig. 1B). The relative mRNA expression of the inflammatory factor TNF-α in liver histiocytes was markedly increased in *Fam172a*$^{-/-}$ mice (Fig. 1C). Similarly, The pERK/ERK relative protein expression levels were more significantly up-regulated in *Fam172a*$^{-/-}$ mice (Fig. 1D). Consistent with the results in vivo In HepG2 cells, the intracellular triglyceride content, the levels of the inflammatory cytokines and pERK/ERK relative protein were more significantly increased after *Fam172a* gene knockdown (Fig. 1E-G). However, hepatocyte lipotoxic injury caused by *Fam172a* gene knockdown was attenuated after the application of ERK inhibitors (Fig. 1H-1J). We have also analyzed the information of HCC and normal human samples in TCGA database, showing that the low-expression FAM172A group in HCC samples has a lower disease specific survival, and the area under the receiver operating characteristic curve is 0.85 ($P < 0.0001$, data not showed). **Conclusion:** Simple *Fam172a* gene knockout could spontaneously induce lipotoxic damage of hepatocytes by activating the ERK pathway. Inhibition of ERK activity could reverse above damage. More importantly, since ERK is an important molecule regulating tumor occurrence and development, and Fam172a gene is closely related to tumors, we speculate that Fam172a gene knockout may promote the development of NAFLD to liver cancer via the ERK pathway, but this needs further verification.

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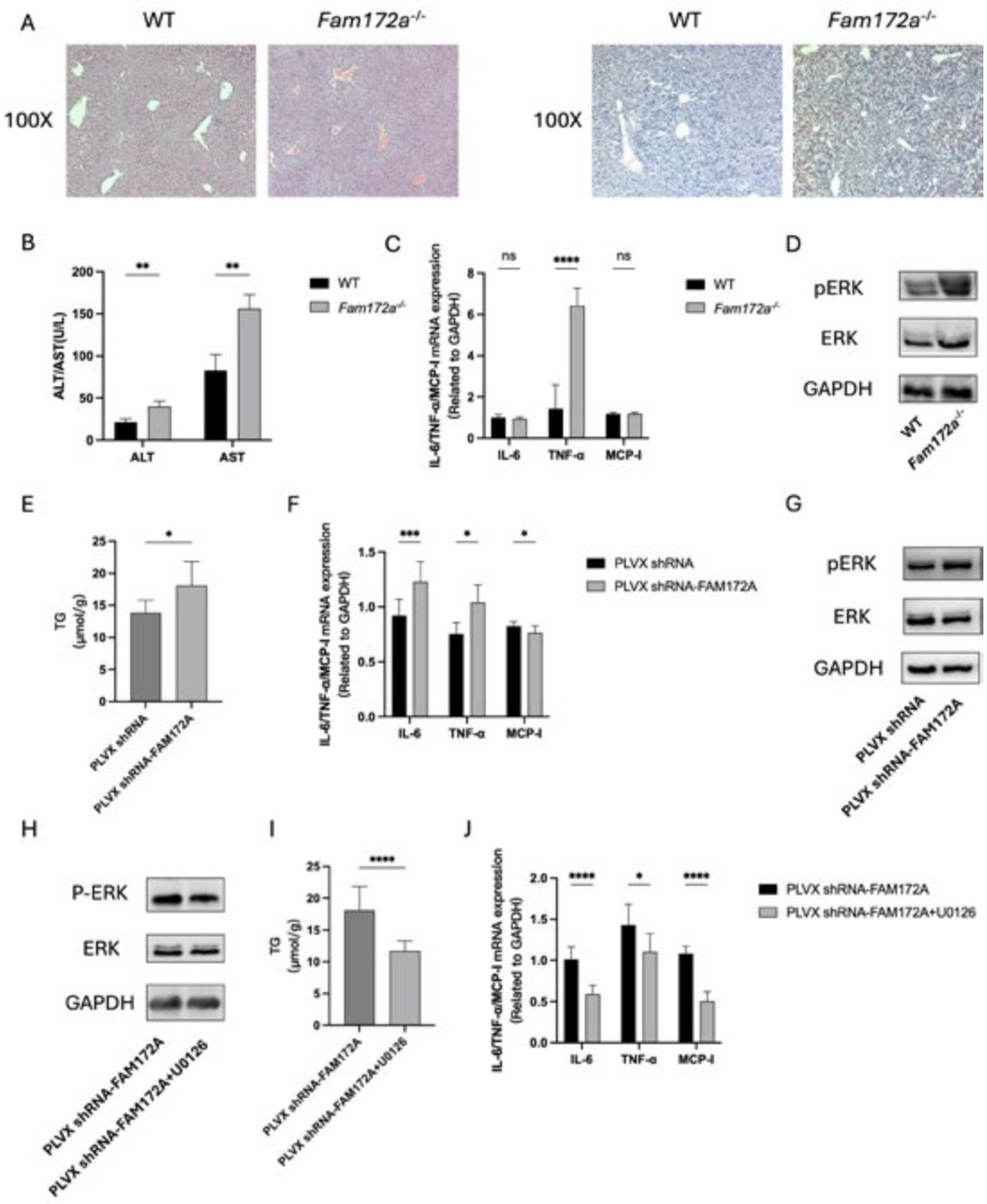

Disclosures: Mengqi Li: Nothing to Disclose, Hongshan Wei: Nothing to Disclose, Fan Xiao: Nothing to Disclose

1050 | MASH AND FIBROSIS RELATED-HCC MODEL MOUSE FOR IMMUNE-ONCOLOGY

Taishi Hashiguchi[1]

[1]*SMC Laboratories,Inc*

Background: Metabolic dysfunction-associated steatohepatitis (MASH) is a is linked to type II-diabetes and marked by steatosis, steatohepatitis, fibrosis and eventually HCC. The number of patients with MASH and fibrosis related-HCC is increasing worldwide. Currently, the first line of cancer treatment drugs are immune checkpoint inhibitors (ICIs). Although ICIs have been approved by the FDA for various cancers, it has been reported that the response rate for HCC is low, and the development of new therapeutic drugs including ICIs for HCC is

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expected. Therefore, a mouse model for evaluating MASH-derived liver cancer is needed for drug discovery against HCC. In this study, in order to examine whether the STAM mouse, a MASH/fibrosis-HCC model mouse, can be used for the evaluation of ICIs, we conducted an analysis of immunohistochemistry and RNA-seq related to the immuno-oncology (IO) of HCC derived from STAM mice. **Methods:** MASH was induced in male mice by a single subcutaneous injection of 200 μg streptozotocin solution 2 days after birth and feeding with high fat diet after 4 weeks of age. The mice were sacrificed and livers collected at 6, 8, 10, 12, 16, 20 and 24 weeks of age. For RNA-seq analysis, total RNA from the left lateral lobe was isolated using RNeasy mini kit. Liver specimens were stored at -80°C embedded in Optimal Cutting Temperature compound for immunohistochemistry (IHC). IHC for CD3, CD4, CD8, FOXP3, PD-1, PD-L1, alpha-SMA and FAP was performed. **Results:** Expression analysis of IO-related genes was performed. Increased expression was observed in CCl5, CD4, CD8a, CD274, CXCR4, CXCR10 and PDCD1. Additionally, mutations were observed in some genes. As a result of IHC, CD3, CD4, CD8, PD-1, a-SMA and FAP-positive signals were detected in the peri-tumor region. Furthermore, CD8-positive signals were also detected in the intra-tumor region. **Conclusion:** STAM mouse model, is the model that allows the evaluation of drugs that genetic mutations, immune cells, and tumor microenvironment in addition to molecular targeted drugs.

Disclosures: Taishi Hashiguchi: Nothing to Disclose

1051 | THE EFFECTS OF CSE DEFICIENCY ON HIGH-FAT DIET-INDUCED NONALCOHOLIC FATTY LIVER

Min Ji Kim[1] Gibong Jang[1] Kwon Moo Park[2]

[1]The Graduate School of Medicine, Kyungpook National University, [2]The Graduate School of Medicine, Kyungpook National University, Kyungpook National University

Background: Cystathionine γ-lyase (CSE), a key enzyme in the transsulfuration pathway, is involved in the production of glutathione (GSH), which regulates redox balance and acts as an important antioxidant molecule. Impairment of the GSH-mediated antioxidant system is associated with the exacerbation of non-alcoholic fatty liver disease (NAFLD), which is characterized by fatty liver, steatohepatitis, and liver fibrosis. NAFLD is associated with increased oxidative stress. Therefore, we investigated the association of CSE with the development of prolonged high-fat diet-induced NAFLD. **Methods:** Eight-to-nine-week *cse* gene-deleted male mice ($cse^{-/-}$) and wild-type male mice ($cse^{+/+}$) were fed either a normal diet (ND, 10% calories from fat) or a high-fat diet (HFD, 60% calories from fat) for 16 weeks. Plasma alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were used to estimate liver injury. Fatty liver was determined with oil red o staining and the level of hepatic triglycerides. Hepatic histological damage was evaluated with hematoxylin & eosin staining, F4/80 immunohistochemistry, and sirius red. **Results:** The high-fat diet in $cse^{+/+}$ mice reduced the expression of CSE in the liver and consequently reduced GSH levels with increased oxidative stress in the liver. Deficiency of CSE lowered GSH levels in the liver. CSE deficiency exacerbated HFD-induced fatty liver; increases collagen deposition, α-smooth muscle actin expression, and inflammatory cell infiltration. Furthermore, CSE deficiency exacerbated HFD-induced decrease of phosphatase and tensin homolog (PTEN) which is known as a negative regulator of NAFLD. Decrease in GSH levels after HFD was positively correlated with the decrease of PTEN in the fatty liver. **Conclusion:** HFD causes fatty liver in the mice and this fatty liver is exacerbated by CSE deletion with increased oxidative stress and decreased GSH level in the liver. These data suggest that CSE-associated antioxidant system could be considered as a target for NAFLD treatment.

Disclosures: Min Ji Kim: Nothing to Disclose, Gibong Jang: Nothing to Disclose, Kwon Moo Park: Nothing to Disclose

1052 | HEPATIC MITOCHONDRIAL QUALITY CONTROL REGULATES SKELETAL MUSCLE ADAPTATION TO EXERCISE THROUGH SELENOPROTEIN P IN MASH-RELATED HEPATOCARCINOGENIC MICE

Keisuke Hino[1] Kyo Sasaki[2] YUICHI HARA[2] Sohji Nishina[2]

[1]Shunan Memorial Hospital, [2]Kawasaki Medical School

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Background: Although exercise is a critical therapeutic intervention for metabolic dysfunction-associated steatotic liver disease (MASH), the response to exercise varies among individuals. The hepatokine, selenoprotein P (SeP) is reported to cause “exercise resistance” through reduced ROS production in skeletal muscle, and to be elevated in serum in MASH patients. Meanwhile, dysregulated mitochondrial quality control (mitophagy) is closely associated with pathogenesis of MASH. We aimed to examine if hepatic mitochondrial quality control regulates skeletal muscle adaptation to exercise by downregulating SeP production in the liver. **Methods:** Iron chelator, deferiprone (DFP) was used as mitophagy trigger via mitochondrial ferritin (FTMT) induction, as reported previously (EMBO Rep 2020). The 7,12-dimethylbenz[a] anthracene (DMBA)-treated mice fed a high fat diet was used as an obesity-related HCC mouse model (MASH-HCC mice). Responsiveness to exercise was assessed by running endurance test after running endurance exercise for 4 weeks in MASH-HCC mice treated with/without DFP. **Results:** The levels of *sep* mRNA was repressed with DFP treatment in a dose dependent manner but was independent of iron concentration, and its reduction was abrogated by FTMT knockdown in hepatoma cell lines. Similarly, hepatic *sep* mRNA and serum SeP levels were significantly lower in MASH-HCC mice with DFP treatment than in those without. Treatment with SeP repressed mitochondrial basal and maximal respiration in mouse myoblast cell line, C2C12 cells, in a dose dependent manner. Production of 2-thiobarbituric reactive substances in skeletal muscle were significantly greater in the exercised MASH-HCC mice with DFP treatment than in those without. Grip strength was significantly greater in the exercised MASH-HCC mice with DFP treatment than in nonexercised mice without DFP treatment, even though skeletal muscle volume did not increase with exercise and DFP treatment. Electron microscopic analysis demonstrated that the number of mitophagosome-like structures in the liver and mitochondrial area/μm^2 in skeletal muscle were significantly greater in the exercised MASH-HCC mice with DFP treatment than in those without. Consequently, running distance in endurance test was significantly longer in the exercised MASH-HCC mice with DFP treatment than in those without. **Conclusion:** Mitophagy induction in the liver ameliorates responsiveness to exercise through downregulation of SeP production in NASH-HCC mice. Liver-muscle axis via SeP is a critical regulator of resistance to exercise in MASH.

Disclosures: Keisuke Hino: Nothing to Disclose, Kyo Sasaki: Nothing to Disclose, YUICHI HARA: Nothing to Disclose, Sohji Nishina: Nothing to Disclose

1053 | POLYCYCLIC AROMATIC HYDROCARBONS (PAHS) AGGRAVATE HFD-INDUCED NAFLD THROUGH INCREASING HEPATOCYTE SPHINGOSINE-1-PHOSPHATE

Kwei-Yan Liu[1] *Hui-Ru Kuo*[2] *Yu-Fen Chung*[1] *Shau-Ku Huang*[1]

[1]*National Health Research Institute,* [2]*Kaohsiung Medical University*

Background: Nonalcoholic fatty liver disease (NAFLD) has become the most common chronic liver disease worldwide and exposure to environmental pollutants, including polycyclic aromatic hydrocarbons (PAHs), is suggested to be a risk factor for NAFLD; however, the regulatory mechanisms remain to be elucidated. Sphingolipid dysregulation has been linked to NAFLD development and we have previously demonstrated that exposure to PAH significantly induced oxidation of sphingosine-1-phosphate (S1P) lyase (SGPL1), resulting in reduced lyase activity and increased levels of S1P, a bioactive sphingolipid metabolite. Thus, we aimed to investigate the mechanistic impact of PAH, mostly derived from air pollution and processed food, on NAFLD progression and explored whether SGPL1 and S1P were critically involved. **Methods:** Wild-type (WT) and mutant *Sgpl1*^{C317A} knock-in (C to A mutant at position 317 rendering resistance to oxidation) mice were fed with a high-fat diet (HFD, 60% fat calories) for 8 weeks to induce NAFLD, and indeno[1,2,3-cd]pyrene (IP) was administered by oral gavage every three days during this period to examine the effects of PAH on NAFLD progression. Mouse primary hepatocytes (MPHs) were also isolated using classic two-step collagenase perfusion method for *in vitro* study. **Results:** Reduced levels of weight gain, fatty liver, and serum S1P were observed in *Sgpl1* KI mice compared to those of WT mice upon HFD and IP treatments. Increased lipid accumulation and upregulated S1P levels were found in WT MPH upon IP treatment, while inhibition of SGPL1 increased lipid accumulation and S1P levels in MPH derived from *Sgpl1* KI mice. Also, pharmacological inhibition of SPHK1, but not SPHK2, decreased IP-induced S1P levels and lipid accumulation in MPH derived from WT mice, indicating that IP upregulated S1P through both SPHK1- and SGPL1-mediated pathways, which, in turn, increased intracellular lipid deposition in hepatocytes. **Conclusion:** PAH upregulated hepatocyte S1P by inducing SPHK1 activation and suppressing

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SGPL1 activity, thereby promoting HFD-induced NAFLD. Collectively, these results suggested the importance of SGPL1 in regulating S1P levels in NAFLD under the influence of environmental pollutants, such as PAHs.

Disclosures: Kwei-Yan Liu: Nothing to Disclose, Hui-Ru Kuo: Nothing to Disclose, Yu-Fen Chung: Nothing to Disclose, Shau-Ku Huang: Nothing to Disclose

1054 | REAL-TIME, NON-INVASIVE PROFILING OF LIVE CELL BEHAVIOUR IN HUMAN HEPATIC HEALTH-TO-DISEASE (MASLD-MASH) TRANSITION MODELS USING ELECTRIC CELL-SUBSTRATE IMPEDANCE SENSING (ECIS)

Callum Rafferty[1] *Anabel Martinez Lyons*[1] *Debbie Neill*[1] *Stephen Mitchell*[1] *Justyna Cholewa-Waclaw*[1] *Pierre Bagnaninchi*[1] *Leonard Nelson*[1]

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Background: Tight junctions (TJs) maintain cell polarity, bidirectional signalling, and organ homeostasis by forming semipermeable barriers. Disruption of intestinal TJs has been observed in murine metabolic dysfunction-associated steatotic liver disease (MASLD)-metabolic dysfunction-associated steatohepatitis (MASH) disease models, but the underlying causes and mechanisms responsible are unknown. Investigating TJ disruption in the human MASLD-MASH transition may offer a novel approach for better mechanistic understanding and biomarker discovery. We aimed to define health-to-disease (MASLD-MASH) transition events using label-free ECIS monitoring of hepatic cell behaviour (TJs; cell adhesion; membrane integrity) with human HepaRG-based modelling. **Methods:** Human HepaRG116 (intrinsic hepatocyte:cholangiocyte co-culture) were cultured alone, or in combination with endothelial and immune cells, on ECIS microelectrode plates. Cultures were treated with either basal medium (untreated controls) to emulate 'healthy liver', oleate (MASLD: simple steatosis) or lactate, pyruvate, octanoate and ammonia (LPON; MASH: steatosis + inflammation). Impedance (Z), of live cells was measured at multiple AC frequencies (250Hz-64KHz) every 300s for 72h using the ECIS-Z?? platform (Applied Biophysics). Specific parameters including TJ integrity (Rb), membrane integrity (Cm), and cell-substrate adhesion (α) were assessed. Barrier function was performed by TEER assay. Biochemical assays for ATP (Promega) and ALT (ELISA) levels, immunofluorescent (IF) staining using confocal, and ultrastructural (TEM) imaging were performed to phenotype transitional stages, including quantification of TJs (ZO-1, Occludin), mitochondrial, and ER stress (XBP1) protein with In-Cell Westerns. **Results:** ECIS (Z)-spectra modelling revealed dose-/time-dependent TJ disruption in LPON-treated HepaRG-based multicellular systems (from 48 Hrs; $P<0.05$). Elevated ALT levels with reduced ATP content associated cell injury with changes in (Z) in the LPON/MASH *vs* Oleate/MASLD or Controls. IF staining (e.g., Perilipin-2, XBP1) and TEM revealed increased lipid droplet (LD) formation (BODIPY staining) in LPON-treated cells, along with apparent hyper-fission events of the mitochondrial network adjacent to LDs. ZO-1 and Occludin IF staining showed heterogeneous disruption of TJs in both Oleate- and LPON-treated cells. Mitochondrial-LD interactions and ER stress was ascertained for correlation with Oleate and LPON-treatment. **Conclusion:** Our liver biochip provides a novel *in vitro* platform to profile MASLD-MASH cellular/biophysical transitional changes in real-time. These data demonstrated exposure to Oleate or LPON triggers increased LD formation *vs* untreated cells, whilst LPON-treatment caused significant TJ complex disruption with cellular injury and perturbation of mitochondrial and ER-associated pathways.

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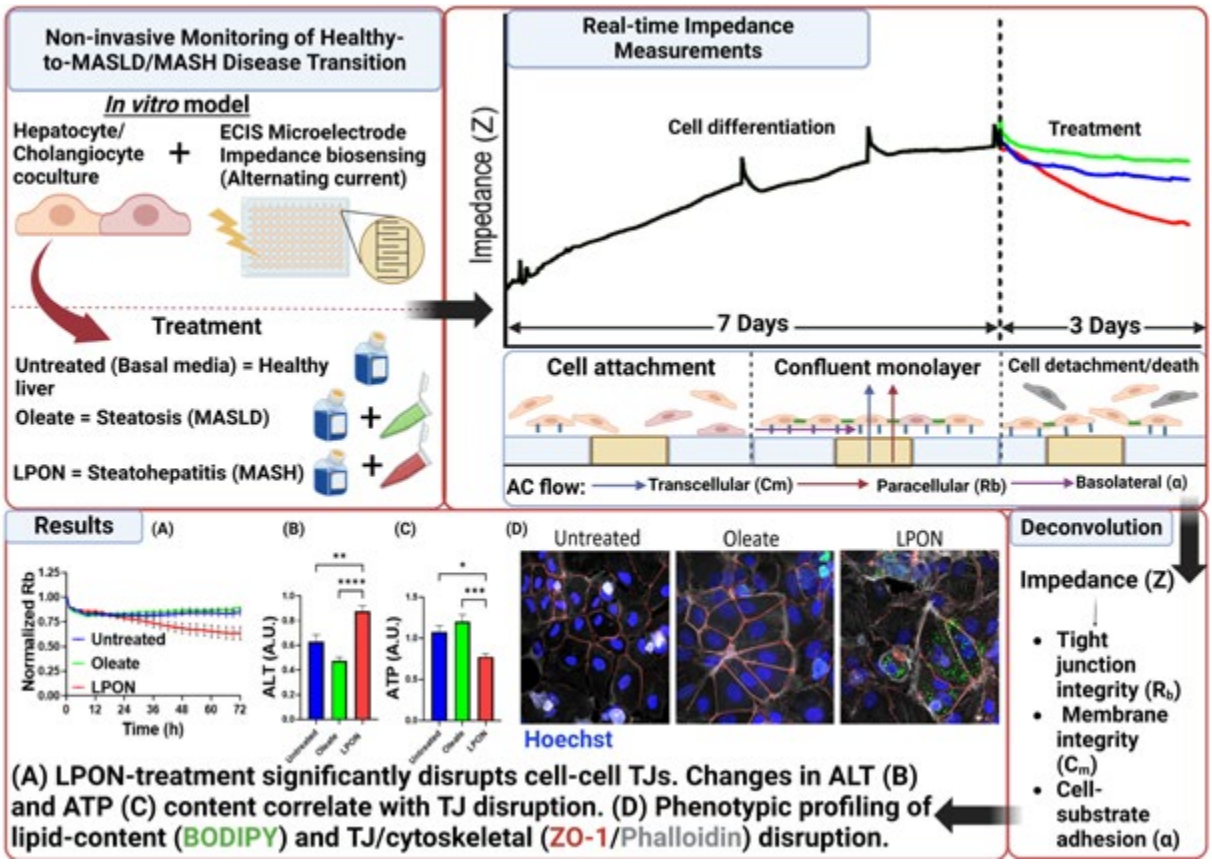

Disclosures: Callum Rafferty: Nothing to Disclose, Anabel Martinez Lyons: Nothing to Disclose, Debbie Neill: Nothing to Disclose, Stephen Mitchell: Nothing to Disclose, Justyna Cholewa-Waclaw: Nothing to Disclose, Pierre Bagnaninchi: Nothing to Disclose, Leonard Nelson: Nothing to Disclose

1055 | HEPATIC R-SPONDIN 2 IS A KEY SUPPRESSOR OF HEPATOSTEATOSIS ◆ ★

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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD), characterized by hepatic steatosis primarily **Results:** from dysregulated lipid metabolism in hepatocytes. However, our understanding of the mechanisms regulating hepatic lipid metabolism remains limited. Our preliminary experiments demonstrated elevated expression of R-spondin 2 (RSPO2), a matricellular protein, in murine steatotic livers. Therefore, the present study was designed to investigate the role of RSPO2 in the pathogenesis of hepatosteatosis and potential underlying mechanisms. **Methods:** Comprehensive methods, including *in vivo* assessments in mice and rigorous *in vitro* studies were performed to investigate the role of RSPO2 in hepatosteatosis. Unbiased transcriptomic analyses of hepatic RNA samples were conducted to elucidate the molecular mechanisms regulated by RSPO2. To examine the role of *Rspo2* in hepatosteatosis *in vivo*, hepatocyte-specific *Rspo2* deficient mice and *Rspo2*-overexpressing AAV in mice were utilized. **Results:** Western blotting data demonstrated increased RSPO2 expression in steatotic livers of high-fat diet-fed wild-type and Western diet-fed *Apoe*$^{-/-}$ mice. Interestingly, hepatocyte-specific *Rspo2* deletion in *Rspo2* floxed mice using *TBG*-Cre-AAV8 injection (postnatal) and via breeding with *Alb*-Cre mice (embryonic) promoted diet-induced hepatic steatosis and fibrosis, as determined by Oil Red O and Sirius red staining, suggesting protective effects of RSPO2 against MASLD. Additionally, AAV8-mediated *Rspo2* overexpression in mice reduced hepatic lipid deposition and decreased hepatic levels of triglycerides and non-esterified fatty acids compared with control mice following feeding a fat-rich diet. Furthermore, *Rspo2* overexpression inhibited hepatic fibrosis and macrophage accumulation. Mechanistic studies conducted using RNA-sequencing and other techniques suggested improved lipid metabolism, increased

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AMPK-ACC signaling, reduced inflammation, and suppressed apoptosis in the liver with *Rspo2* overexpression. *In vitro* experiments also revealed the anti-steatotic effects of recombinant RSPO2 treatment in hepatocytes. **Conclusion:** These findings suggest that RSPO2 plays a crucial role in the suppression of hepatosteatosis, therefore, targeting RSPO2 may be a promising therapeutic approach for the treatment of MASLD.

Disclosures: Bhupesh Singla: Nothing to Disclose, Ravi Aithabathula: Nothing to Disclose, Naveed Pervaiz: Nothing to Disclose, Ishita Kathuria: Nothing to Disclose, BalKrishan Sharma: Nothing to Disclose, Malvin Ofosu-Boateng: Nothing to Disclose, Maxwell Gyamfi: Nothing to Disclose, Britney-Thuy Le: Nothing to Disclose, Ki-Suk Kim: Nothing to Disclose, Udai Singh: Nothing to Disclose

1056 | MANIPULATION OF MIR-15A/16 IN EMBRYONIC KUPFFER CELLS PROMOTES HEPATIC STEATOSIS AND INFLAMMATION BY RECRUITING MONOCYTE-DERIVED KUPFFER CELLS

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Background: Metabolic dysfunction-associated fatty liver disease (MAFLD) is an immune disease that mobilize a vast network of immune cells, leading to advanced fibrosis, cirrhosis and its complications, including hepatocellular carcinoma (HCC). Kupffer cells (KCs) comprise the largest population of liver resident macrophages. However, the role of KCs in modulating the onset and progression of MAFLD is poorly described. The study is aimed to investigate the role miR-15a/16-manipulated KCs in hepatosteatosis and its transition to metabolic dysfunction-associated steatohepatitis (MASH). **Methods:** A high fat high carbohydrate diet was used to induce MAFLD/MASH. RNA-Seq was used to analyze miRome alteration in livers of HFHC-treated mice and blood of MAFLD patients. Clec4f-Cre-tdTomato knock-in mice expressing Cre recombinase and tdTomato-NLS under direction of the C-type lectin domain family 4, member f (Clec4f) promoter in embryonic KCs (EmKCs) were used to manipulate expression of miR-15a/16 in EmKCs. Liquid chromatography–tandem mass spectrometry (LC–MS/MS) was used to analyze secretome of miR-15a/16-manipulated EmKCs. **Results:** miRome analysis revealed that miR-15a/16 were the most upregulated miRNAs in hepatosteatotic livers of HFHC-treated mice. Their levels were also significantly reduced in blood of MAFLD patients. EmKCs-specific expression of miR-15a/16 induced hepatosteatosis, M1 polarization of KCs, and MASH progression in HFHC-treated mice. Immune profiling revealed that miR-15a/16 manipulation promoted death of EmKCs and generation of monocyte-derived KCs (MoKCs) that maintains KC numbers. Mechanistically, secretome analysis revealed that miR-15a/16-manipulated EmKCs overproduced proinflammatory CCL2, TNFα and GM-CSF (granulocyte-macrophage colony-stimulating factor). It is know that TNFα promotes nuclear translocation of p65 that drives transcription of *Csf2* encoding GM-CSF. GM-CSF can promote differentiation of monocytes into macrophages with distinct phenotypes and unique functional abilities, while CCL2 plays a crucial role in the chemotaxis of macrophages. As expected, EmKC-specific expression of miR-15a/16 promoted hepatic enrichment of MoKCs, which maintained KC pool in HFHC-treated mice. TNFa overproduction promoted transcription of *Srebp1c*, *de novo* lipogenesis and hepatosteatosis. **Conclusion:** miR-15a/16 manipulation in EmKCs maintains KC pool via promoting hepatic enrichment of proinflamantory MoKCs, which promoted hepatosteatosis and MASH.

Disclosures: Guisheng Song: Nothing to Disclose, Bo Sun: Nothing to Disclose, Hongtao Shi: Nothing to Disclose

1057 | WESTERN DIET THROUGH GALECTIN-1-DEPENDENT MANNERS AFFECTING MASH-HCC DEVELOPMENT

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Background: Hepatocellular carcinoma (HCC) rises from metabolic dysfunction-associated steatohepatitis (MASH) poses a clinical challenge because of the prevalence of the Western diet (WD). How diet affects the tumor environment remains to be elucidated. Galectin-1 (Gal-1) is an HCC biomarker and essential for liver

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tumorigenesis. Our published data showed that silencing Gal-1 treats HCC in mouse models. The effects of WD intake on Gal-1 signaling during HCC development are unknown. The current study addresses the knowledge gaps. **Methods:** We established a novel mouse MASH-HCC model. The impacts of a WD on the liver and tumor environment were characterized by transcriptomic profiling and multiplex immunohistochemistry. By silencing and overexpressing Gal-1, we established the effects of WD intake on Gal-1 signaling based on location using spatial transcriptomics. **Results:** Rho signaling, extracellular matrix (ECM) remodeling, and senescence-associated secretory phenotypes (SASP) were the top pathways in WD-induced metabolic dysfunction-associated fatty liver disease (MAFLD) and MASH-HCC in comparison with their respective controls. Furthermore, Rho GTPase effectors, signaling by Rho GTPases, ECM remodeling, neutrophil degranulation, cellular stress, and cell cycle pathways were commonly enriched in human and mouse MASH-HCC. Spatially, those pathways were enriched in the tumor and tumor margin of mouse MASH-HCC. Additionally, a progressive increase in CD11c and PD-L1-positive cells from non-tumor tissues to the tumor margin and tumor in MASH-HCC were observed, suggesting compromised immune surveillance influenced by WD. Furthermore, MASH-HCC had marked induction of Gal-1 in N-Cadherin-positive location, indicating heightened epithelial-to-mesenchymal transition (EMT). Silencing and overexpressing Gal-1 in MASH-HCC unveiled Gal-1-specific effects on regulating Rho and SASP at the tumor margin and non-tumor tissues. **Conclusion:** WD intake impacts cellular processes critical for Gal-1-mediated signaling, including Rho and ECM remodeling, in the tumor environment, thereby contributing to carcinogenesis in MASH-HCC.

Disclosures: Tahereh Setayesh: Nothing to Disclose, Ying Hu: Nothing to Disclose, Yu-Jui Wan: Nothing to Disclose

1058 | AN ORAL INHIBITOR OF CBP/β-CATENIN SIGNALING, C-82, IMPROVES LIVER STEATOSIS, FUNCTION, INFLAMMATION AND FIBROSIS IN THE GAN DIET-INDUCED OBESE MOUSE MODEL OF MASH

Kenzaburo Yamaji[1] Yuko Tokunaga[1] Tomoko Honda[1] Sakiko Toyama[1] Risa Kono[1] Daisuke Yamane[1] Sadahiro Iwabuchi[2] Shinichi Hashimoto[2] Kiminori Kimura[3] Takeshi Okanoue[4] Kyoko Tsukiyama-Kohara[5] Michinori Kohara[1]

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Background: Metabolic dysfunction-associated steatohepatitis (MASH) is an aggressive liver disease, which is marked by liver inflammation and may progress to advanced fibrosis and failure. However, there are still no effective therapeutic strategies available. We previously reported the efficacy of PRI-724, a second-generation specific CBP/β-catenin antagonist, for HCV/HBV cirrhosis. PRI-724-treated CDAHFD (choline-deficient, L-amino acid-defined, high-fat diet)-fed mice recovered from liver fibrosis and hepatic inflammation. However, PRI-724 needs to be administered intravenously. PRI-724 is a prodrug and is rapidly hydrolyzed to its active form, C-82, *in vivo.* In the present study, we examined the C-82 efficacy to treat MASH-animal model and characterized the mechanism of action. **Methods:** Mice were fed a GAN (Gubra-Amylin NASH) diet for 28 or 46 weeks to establish obese mouse model of MASH. C-82 was administered orally in GAN diet-fed mice once daily for 6 or 9 weeks. The efficacy of C-82 was assessed by analyzing the recovery of hepatic steatosis, liver function and inflammation and improvement of liver fibrosis. To investigate glucose metabolism, the glucose tolerance test was performed. **Results:** GAN diet-fed mice exhibited obesity, hypercholesterolemia and liver fibrosis that is characterized by steatosis, lobular inflammation, hepatocellular injury, and collagen fibrils. Prothrombin time (PT) did not change after 28 weeks of feeding GAN diet, but decreased significantly at 46 weeks. After administering C-82 in GAN diet-fed mice, body weight and serum levels of total cholesterol were significantly decreased. PT improved from 44.9 ± 7.3% to 72.5 ± 9.6%. Serum ALT levels, which increased in MASH model mice, significantly decreased. Moreover, glucose-AUC levels were significantly decreased, signifying improvement of impaired glucose tolerance. In addition, liver lipid droplets and hepatic expression of pyruvate dehydrogenase kinase 4, a key enzyme involved in the regulation of glucose and fatty acid metabolism and homeostasis and hepatic mRNA expression levels of type I and type III collagens, liver fibrosis markers, were significantly decreased. **Conclusion:** C-82 treatment improves not only MASH-like liver disorders (steatosis, function and inflammation) but also liver fibrosis. C-82, an oral inhibitor of CBP/β-catenin signaling, shows a potent therapeutic effect on MASH-related liver fibrosis and steatosis.

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Disclosures: Kenzaburo Yamaji: Nothing to Disclose, Yuko Tokunaga: Nothing to Disclose, Tomoko Honda: Nothing to Disclose, Sakiko Toyama: Nothing to Disclose, Risa Kono: Nothing to Disclose, Daisuke Yamane: Nothing to Disclose, Sadahiro Iwabuchi: Nothing to Disclose, Shinichi Hashimoto: Nothing to Disclose, Kiminori Kimura: Nothing to Disclose, Takeshi Okanoue: Nothing to Disclose, Kyoko Tsukiyama-Kohara: Nothing to Disclose, Michinori Kohara: Nothing to Disclose

1059 | THERAPEUTIC IMPLICATIONS OF DNA METHYLATION IN MASLD PROGRESSION

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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) represents a well-recognized liver pathology marked by lipid accumulation and inflammation, impacting roughly 25% of the global population and exhibiting growing links to contemporary metabolic syndromes. Approximately 30% of MASLD instances transition to inflammatory metabolic dysfunction-associated steatohepatitis (MASH), a progression that exacerbates fibrosis and heightens susceptibility to cirrhosis and hepatocellular carcinoma. Despite these grave implications, effective therapeutic strategies for MASLD remain elusive, and investigations into epigenetic modifications in both human subjects and animal models remain relatively constrained. **Methods:** We performed methylation analysis utilizing the 850K methylation array and RNA sequencing on liver tissues from 130 patients in the MASLD cohort. Our study aimed to elucidate the regulatory effects of DNA methylation on gene expression in MASLD patients, focusing on epigenetic modulation. Furthermore, we assessed the therapeutic potential of targeting DNA methylation by employing a diet-induced mouse model. **Results:** Our genome-wide DNA methylome analysis revealed extensive differential methylation changes, with the MASLD patient group showing a higher prevalence of hypermethylated CpG sites compared to hypomethylated sites relative to the normal group. KEGG pathway analysis indicated that genes involved in inflammation and lipid metabolism were significantly affected by these methylation changes. Transcriptome analysis from the same patient cohort demonstrated a proportional increase in the expression of various epigenetic regulators as MASLD progressed. Notably, DNMT1, a key enzyme in DNA methylation, exhibited a significant rise in expression correlating with the severity of MASLD. Furthermore, pharmacological inhibition of DNMT1 in a diet-induced mouse model of MASLD attenuated disease progression by reducing lipid accumulation and inflammation. **Conclusion:** Our study reveals that MASLD progression is associated with dynamic changes in methylation and the expression of related epigenetic genes. Specifically, DNMT1, a major DNA methyltransferase in the liver, plays a pivotal role in regulating the progression of MASLD, highlighting its potential as a therapeutic target for MASLD treatment.

Disclosures: Hyunahm Sohn: Nothing to Disclose, Mirang Kim: Nothing to Disclose

1060 | THE BENEFICIAL EFFECT OF RESMETIROM ON TUMORIGENESIS ASSOCIATED WITH MASH IN STAM MICE

Atsutaka Masuda[1] *Toru Nakamura*[1] *Hiroyuki Suzuki*[1] *Hideki Iwamoto*[1] *Toshimitsu Tanaka*[1] *Takahiko Sakaue*[1] *Hironori Koga*[1] *Takumi Kawaguchi*[1]

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Background: Recently, resmetirom, a thyroid hormone receptor beta (THRβ) activator, was reported to improve hepatic steatosis and fibrosis in a phase III trial for metabolic dysfunction-associated steatohepatitis (MASH). However, the direct effect of resmetirom on hepatocellular carcinoma (HCC) is unknown. We aimed to investigate the effect of resmetirom on the proliferation of human HCC cell lines and hepato-carcinogenesis in a mice model of MASH. **Methods:** *In vitro* study: We evaluated the expression of THRα/β in 11 HCC cell lines (HAK-1A, HAK-1B, HAK5, HepG2, HuH7, KYN-1, KYN-2, PLC, KMCH-1, KMCH-2, HLF) using real-time PCR. In addition, cell proliferation assays with various concentrations of resmetirom (0 to 5,000 nmol/L) were performed using HCC cell lines with high and low THRβ expression. *In vivo* study: We employed STAM mice, a mouse model of MASH-related HCC. Male C57BL/6J mice were subjected to a single subcutaneous injection of streptozotocin at 2 days of age and fed a high-fat diet (HFD32) from the weaning period (4 weeks of age). Six mice were fed a normal diet as a control. At 6 weeks, HFD32-fed mice were randomly assigned to three groups and orally treated with either vehicle control (vehicle) or resmetirom (3 mg/kg [Low-dose] or 5 mg/kg [high-dose] treatment) for 10 weeks.

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Tumor number and size were compared to the vehicle group at 16 weeks. **Results:** Both THRα and β were highly expressed in KYN-1, HepG2, and HAK5 cell lines. Whereas, the THRβ expression was low in HLF, KMCH-1, and KMCH-2 cell lines. In KYN-1 cell lines, resmetirom had a dose-independent cell proliferation-promoting effect ($P<0.05$), while in HLF cell line, resmetirom at 5,000 nmol/L had an approximately 20% proliferation-inhibitory effect. In HAK5 and KMCH-1 cells, resmetirom had no effect on cell proliferation. *In vivo*, the high-dose of resmetirom treatment significantly reduces hepatomegaly (liver/body weight ratio) and plasma total cholesterol levels ($p<0.05$). In background liver, the high-dose of resmetirom treatment clearly eliminated lipid accumulation. Furthermore, the incidence of tumorigenesis, the number of tumors, and the total length of all tumors tended to be reduced in the high-dose group compared to the vehicle group. **Conclusion:** *In vitro* experiments revealed that resmetirom may affect HCC growth regardless of THRβ expression. We further revealed that resmetirom has a potential to exert an anti-carcinogenic effect in a mice model of MASH.

Disclosures: Atsutaka Masuda: Nothing to Disclose, Toru Nakamura: Nothing to Disclose, Hiroyuki Suzuki: Nothing to Disclose, Hideki Iwamoto: Nothing to Disclose, Toshimitsu Tanaka: Nothing to Disclose, Takahiko Sakaue: Nothing to Disclose, Hironori Koga: Nothing to Disclose, Takumi Kawaguchi: ASKA Pharmaceutical Co., Ltd.: Speaking and Teaching, Taisho Pharmaceutical Co., Ltd.: Speaking and Teaching, Kowa Company, Ltd.: Speaking and Teaching, AbbVie GK.: Speaking and Teaching, Eisai Co., Ltd.: Speaking and Teaching, Novo Nordisk Pharma Ltd.: Speaking and Teaching, Janssen Pharmaceutical K.K.: Speaking and Teaching, Janssen Pharmaceutical K.K.: Speaking and Teaching, Otsuka Pharmaceutical Co., Ltd.: Speaking and Teaching, EA Pharma Co.,Ltd.: Speaking and Teaching

1061 | HUMAN HEPATIC 3D SPHEROIDS AS A MODEL FOR METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD)

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Background: Non-alcoholic fatty liver disease (NAFLD) is a major contributor to chronic liver injury globally. Recently, with an evolving understanding of the pathogenesis of NAFLD, the term NAFLD has shifted to metabolic dysfunction-associated steatotic liver disease (MASLD), while NASH was redefined as metabolic dysfunction-associated steatohepatitis (MASH). Despite the widespread distribution and high prevalence of MASLD, the mechanisms underlying MASLD are still not fully elucidated. Thus, there is a need to develop sophisticated human cell models to study therapeutic responses and disease mechanisms. In this study, we developed three-dimensional (3D) liver cell models that recapitulate critical liver characteristics of MASLD phenotypes. **Methods:** Hepatocytes (HepaRG) and stellate cells (LX-2) were co-cultured in microtissue-based 3D system to reproduce the liver microenvironment. Treatments with fatty acid and TNFα led to a MASLD phenotype. To induce hepatic steatosis and MASH, 3D cell models were treated with free fatty acid (FFA) and co-treated with TNFα, respectively. Clinical-like characteristics of the 3D spheroid model undergoing steatotic liver disease (SLD) were investigated by assessing fat accumulation, cell ballooning, and molecular markers. **Results:** Hepatic steatosis and metabolic dysfunction-associated steatohepatitis (MASH) were cultured in 3D microtissue-based 3D system for up to 2 weeks, retaining key functions and markers. Importantly, supplementation of culture medium with FFA and TNFα induced steatosis and lipotoxicity in 3D spheroid models. Furthermore, fat-loaded 3D cell models ex exhibited fat accumulation and cell ballooning, and regulated the expression of inflammation and liver function related genes. Finally, reversible effects in 3D MASLD models were observed by incubating spheroids with different drugs currently in clinical trials for the treatment of MASH. **Conclusion:** Our hepatic 3D spheroids platform provides a valuable model for understanding molecular mechanisms associated with NASLD and identifying novel drug targets for therapeutic development.

Disclosures: Choi Mi-Sun: Nothing to Disclose, Soojin Kim: Nothing to Disclose, Hyun Jegal: Nothing to Disclose, Ga-Won Lee: Nothing to Disclose, Jungh-Hwa Oh: Nothing to Disclose

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1062 | PUM1 KNOCKDOWN AGGRAVATES LIPID DEPOSITION IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE

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Background: Abnormal lipid deposition accelerates progression of metabolic dysfunction-associated steatotic liver disease (MASLD), the role of PUMILIO (an RNA-binding protein) in this process are unclear. **Methods:** Tissue samples from livers of patients with MASLD were collected. Additionally, we generated two sets of MASLD model mice via a western diet combined with intraperitoneal injection of carbon tetrachloride (WD+CCl4) and a choline-deficient, L-amino acid-defined, high-fat diet (CDAHFD). PUM1 knockdown experiments were performed with adeno-associated virus type 8 carrying Pum1-targeting shRNA. Liver histopathological analysis, immunofluorescence histochemistry experiment, western blot, RT-qPCR, and enzyme-linked immunosorbent assay were also performed. **Results:** The expression of PUM1, not PUM2, was down-regulated in the livers of MASLD patients and two MASLD model mice. Besides, the expression of PUM1 was significantly negatively correlated with liver weight, liver index, and the NAFLD activity score (NAS). Western blot experiments confirmed that PUM1 was successfully knocked down in the liver of the two MASLD model mice. With PUM1 knockdown, not only the liver weight and liver index increased, but also their NAS scores increased significantly. Importantly, H&E staining and Oil Red O staining suggested that two MASLD model mice knocking down PUM1 had more severe steatosis and lipid deposition in the liver. After knocking down PUM1, the expressions of sterol regulatory element-binding protein1 (SREBP1), acetyl-coenzyme A carboxylase 1 (ACC1) and fatty acid synthase (FAS) in the livers of both MASLD model mice were significantly increased. Knockdown of PUM1 also inhibited the expression of fatty acid β-oxidation-related genes in the liver. Moveover, the serum alanine aminotransferase, asparate aminotransferase concentrations and liver triglyceride content of the two MASLD model mice significantly increased with the knockdown of PUM1. **Conclusion:** The expression of PUM1 is down-regulated during MASLD, and knocking down PUM1 aggravates the lipid deposition in MASLD.

Disclosures: Zhiping Wan: Nothing to Disclose, Xiang Cai: Nothing to Disclose, Xiaoquan Liu: Nothing to Disclose, Xiaoan Yang: Nothing to Disclose, Haoqi Chen: Nothing to Disclose, Hong Deng: Nothing to Disclose

1063 | INTESTINE-SPECIFIC FAF2 DEPLETION AMELIORATES METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE BY IMPAIRING LIPID ABSORPTION

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Background: Fas-associated factor family member 2 (Faf2), a protein localized in both the endoplasmic reticulum and lipid droplets, plays a critical role in proteasome-mediated apolipoprotein B degradation in hepatocytes. Hepatocyte-specific Faf2 deletion suppresses very low-density lipoprotein secretion in mice fed a high fat diet (HFD). Because Faf2 is also expressed in the intestine, we hypothesized that it plays a key regulatory role in the assimilation of dietary lipids. This study aimed to elucidate the role of Faf2 in intestinal lipid metabolism and contribution to hepatic steatosis. **Methods:** Intestine-specific Faf2 knockout (Faf2-IKO) mice were generated by crossing mice carrying the *Faf2*$^{flox/flox}$ allele with *Villin-Cre* transgenic mice. Male and female Faf2-IKO and littermate control mice were fed either chow or a HFD (60% kcal fat) for 13 w. Glucose metabolism was assessed using tolerance tests. Energy balance was evaluated using an individual metabolic monitoring system. Chylomicron formation in the jejunum was evaluated using electron microscopy. Hepatic steatosis was assessed by histopathology. **Results:** Faf2-IKO male and female mice fed both chow and high-fat diets exhibited reduced body weight (bw) relative to controls. Although ratios of skeletal muscle-to-bw did not differ, ratios of white adipose tissue-to-bw were markedly reduced in Faf2-IKO mice compared to control mice. For both sexes, we observed longer small intestines and villi in Faf2-IKO mice. Chow-fed Faf2-IKO mice demonstrated significantly lower serum triglyceride and total cholesterol concentrations than controls for both sexes. Faf2-IKO mice exhibited a trend toward increased food intake and increased energy expenditure, but there were no alterations in the respiratory

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exchange ratios. Notably, energy absorption was decreased in the absence of intestinal Faf2 expression, and this was associated with reductions in the size and abundance of chylomicrons in intestinal epithelial cells and lacteals. Without differences in insulin sensitivity, HFD–fed Faf2-IKO mice exhibited improved glucose tolerance. Moreover, HFD–fed Faf2-IKO mice were protected against hepatic steatosis, which was exhibited by control mice. **Conclusion:** Faf2 depletion in the intestine reduces lipid absorption by limiting chylomicron formation. This improves glucose tolerance and ameliorates hepatic steatosis in the setting of overnutrition. Intestinal Faf2 is proposed as a potential therapeutic target for metabolic dysfunction-associated steatotic liver disease.

Disclosures: Jingjing ZHANG: Nothing to Disclose, Norihiro Imai: Nothing to Disclose, Shinya Yokoyama: Nothing to Disclose, Kenta Yamamoto: Nothing to Disclose, Takanori Ito: Chugai Pharmaceutical Co., Ltd.: Grant/Research Support, Chugai Pharmaceutical Co., Ltd. and AstraZeneca: Speaking and Teaching, yoji ishizu: Nothing to Disclose, Takashi Honda: Nothing to Disclose, Akiko Sugiyama: Nothing to Disclose, David Cohen: Nothing to Disclose, Hiroki Kawashima: Nothing to Disclose

1064 | SYSTEMIC IGA ACCUMULATION DUE TO DYSFUNCTIONAL PIGR ENFORCES NEUTROPHIL-MEDIATED INFLAMMATION DURING STEATOHEPATITIS

Dragana Rajčić[1] Constanze Hoebinger[1] Sonja Lang[2] Münevver Demir[3] Tim Hendrikx[4]

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Background: Intestinal dysbiosis and increased gut permeability have been implicated in the inflammatory processes during metabolically-associated steatotic liver disease (MASLD). While immunoglobulin type A (IgA) is the predominant antibody in the gut where it maintains intestinal homeostasis and generates immune protection against invading pathogens, increased systemic IgA titers have been shown to propagate MASLD. Yet, the mechanism that contributes to increased circulatory IgA during SLD is incompletely understood. Given that IgA levels are regulated by the polymeric immunoglobulin receptor (pIgR), transporting dimeric IgA across intestinal epithelium and hepatic canaliculi into the gut, our aim was to elucidate the function of pIgR-dependent IgA secretion in the context of steatohepatitis. **Methods:** Systemic and intestinal IgA titers were assessed in a biopsy-proven MASLD cohort and mouse models of steatohepatitis. Wildtype and *pIgR*-deficient (*pIgR*$^{-/-}$) littermates were subjected to 4 weeks of methionine- and choline-deficient (MCD) diet, with or without antibiotics-mediated microbiome depletion, to induce fibrotic steatohepatitis. Further, wildtype and *IgA*-deficient bone marrow was transplanted into *pIgR*$^{-/-}$ recipients receiving MCD diet to study the role of IgA accumulation during pIgR-deficiency in liver disease. **Results:** In addition to elevated plasma IgA titers, MASLD patients had higher fecal IgA levels, which positively correlated with histological liver fibrosis staging. Similarly, fecal IgA levels were increased during steatohepatitis in various murine models, which associated with increased *pIgR* in the colonic epithelium. In contrast, *pIgR* expression was diminished in the liver, indicating site-specific *pIgR* regulation and suggesting aberrant hepatic IgA secretion into the small intestine via the enterohepatic circulation, thereby promoting MASLD. In line, systemic IgA accumulation in *pIgR*$^{-/-}$ mice resulted in more hepatic inflammation and injury after 4 weeks of MCD diet compared with wildtype littermates, independent of alterations in the intestinal microbiome in *pIgR*-deficient mice. Mice lacking *pIgR* demonstrated increased hepatic neutrophil infiltration and neutrophil elastase after MCD diet, suggesting elevated NETosis. Importantly, IgA-deficient bone marrow transplantation prevented aggravated liver injury, steatohepatitis and hepatic neutrophil infiltration in *pIgR*$^{-/-}$ mice upon MCD diet feeding. **Conclusion:** Our study identifies pIgR-dependent regulation and maintenance of systemic IgA antibody levels as an important immunological mediator to prevent MASLD progression.

Disclosures: Dragana Rajčić: Nothing to Disclose, Constanze Hoebinger: Nothing to Disclose, Sonja Lang: Nothing to Disclose, Münevver Demir: Nothing to Disclose, Tim Hendrikx: Nothing to Disclose

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1065 | HISTONE METHYLTRANSFERASE G9A: KEY REGULATOR IN HEPATIC STEATOSIS PATHOGENESIS AND POTENTIAL THERAPEUTIC TARGET BEYOND EPIGENETICS

Keisuke Mabuchi[1] *Yotaro Kudo*[1] *Takuma Nakatsuka*[1] *Ryosuke Tateishi*[1] *Mitsuhiro Fujishiro*[1]

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Background: Hepatic steatosis is a leading cause of chronic liver disease worldwide, driven by the obesity pandemic. Despite its prevalence, effective pharmacological treatments targeting the disease's underlying mechanisms are lacking. While genetic factors contribute to the development of steatosis, epigenetic modifications also play a crucial role. We have previously demonstrated the significance of histone methyltransferase G9a in liver tumor initiation (Nakatsuka, T. et al. Cell Death Dis. 2021). Here, we investigate the role of G9a in hepatic lipid metabolism and its potential as a therapeutic target for steatosis. **Methods:** Hepatocyte-specific G9a knockout (G9aΔhep) mice were used. Mice were fed a high-fat diet (HFD) to induce fatty liver. The livers of these mice were histologically examined, including Oil Red O staining, to assess lipid accumulation. Comprehensive transcriptome and proteome analyses were conducted to explore the molecular mechanisms underlying the observed phenotypes. Additionally, cultured cells were used to investigate the potential role of G9a in hepatocytes in a cell-autonomous manner. **Results:** G9aΔhep mice exhibited a marked improvement in steatosis under HFD conditions. This improvement was evidenced by histological analysis showing reduced lipid accumulation in Oil Red O staining, and significantly lower serum ALT levels compared to wild-type mice. Under normal diet conditions, G9a deficiency resulted in no significant phenotypic differences. Transcriptome and proteome analyses revealed that G9a deletion modulated the activity of the peroxisome proliferator-activated receptor (PPAR), a key regulator of lipid metabolism, suggesting that G9a affects lipid metabolism through PPAR-dependent pathways. Notably, cultured cell analyses indicated that G9a regulates PPAR activity independently of its known histone methylation activity, highlighting a novel mechanism of G9a in controlling steatosis. **Conclusion:** Our findings highlight the critical role of G9a in the pathogenesis of diet-induced hepatic steatosis. G9a deficiency leads to a marked improvement in steatosis, likely through the modulation of PPAR activity independent of its histone methylation function. These results suggest that targeting G9a could be a novel therapeutic strategy for steatosis. Further research is warranted to explore the potential of G9a inhibitors in clinical settings.

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1066 | THE INFLUENCE AND MECHANISM OF VITAMIN C ON PM2.5 EXPOSURE METABOLIC DYSFUNCTION ASSOCIATED FATTY LIVER DISEASE

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Background: To analyze the effects of vitamin C (VC) intervention treatment on PM2.5 exposure MAFLD and discuss whether VC intervention treatment can alleviate the progression of PM2.5 exposure-induced MAFLD, and explore the potential therapeutic mechanism. **Methods:** 44 male C57BL/6 mice (6-8 weeks old) were randomly divided into 5 groups (n= 8 individuals/group): normal control group (NC group), high-fat model group (HF group), HFD fed and using VC treatment group (HF+VC group), HFD fed and PM2.5 exposure group (HF+PM2.5 group), HFD fed and PM2.5 exposure and using VC treatment group (HF+PM2.5 +VC group). The therapeutic dose of VC was 30mg/kg/d by gavage; The exposure dose of PM2.5 was 415.1 μg/mL at an actual atmospheric concentration and was administered through nasal drops. Body weight was recorded weekly for 12 weeks total. Parameters compared among groups included: body weight, liver weight and index, perirenal fat weight and index, blood biochemistry for liver function, blood lipids, insulin level, inflammatory factors; gross liver morphology, liver lipid deposition, oxidative stress and liver histopathology. **Results:** HF and HF+PM2.5 groups showed increased body weight, body weight percentage, liver wet weight and index, perirenal fat weight and index, homeostasis model assessment of insulin resistance (HOMA-IR); decreased insulin sensitivity index (ISI). Inflammatory factors in blood (TNF-α, IL-1β and IL-6) were significantly elevated. Abnormal levels of MDA, SOD and GPx proteins in liver tissues.HE and oil red O staining revealed hepatocyte steatosis and ballooning degeneration. These changes were more significant in the HF+PM2.5 group compared to the HF and HF+PM2.5 groups. After VC treatment, the

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HF+VC and HF+PM2.5+VC groups showed decreased body weight, body weight percentage, liver wet weight and index, perirenal fat weight and index, ALT, AST, serum TC, TG, LDL-C, FBG, FINS, HOMA-IR, blood inflammatory factors, and increased ISI. Abnormalities in hepatic MDA, SOD, GPx were ameliorated. Gross observation still showed yellowish-white color and full shape of mice livers, while HE and oil red O staining revealed alleviated hepatocyte steatosis and ballooning degeneration. **Conclusion:** VC antioxidant treatment improved inflammation, oxidative stress, dysregulated glucose/lipid metabolism, IR, and reduced lipid deposition in hepatocytes, thereby alleviating PM2.5 exposure MAFLD progression.

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1067 | TARGETING BRD4 MITIGATES HEPATOCELLULAR LIPOTOXICITY BY SUPPRESSING THE NLRP3 INFLAMMASOME ACTIVATION AND GSDMD-MEDIATED HEPATOCYTES PYROPTOSIS

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Background: The epigenetic reader bromodomain-containing protein 4 (BRD4) was reported to mediate lipid metabolism, liver fibrosis, and hepatocellular carcinoma. But the mechanism underlying the role of the BRD4 in metabolic dysfunction-associated steatohepatitis (MASH) remains incompletely understood. This study aimed to investigate if and how BRD4 regulated the activation of Nod-like receptor family pyrin-containing protein 3 (NLRP3) inflammasome and promoted gasdermin D (GSDMD)-mediated pyrotosis during MASH progression. **Methods:** Primary mouse hepatocytes or AML12 cells induced by palmitic acid (PA) served as an in vitro model of hepatosteatosis to test the effects of the BRD4 on lipid deposition, NLRP3 inflammasome activation, hepatocytes pyroptosis, and the oligomerization of voltage-dependent anion channel 1 (VDAC1). ChIP sequence analysis was used to explore the epigenetic regulatory function of BRD4. The expression and cellular distribution of BRD4 in nonalcoholic fatty liver disease (NAFLD) livers from human and mice samples were assessed by immunostaining. **Results:** Targeting BRD4 by genetic knockdown or specific BRD4 inhibitor MS417 protected against hepatocellular lipotoxicity; and this protective effect was attributed to inhibiting the NLRP3 inflammasome activation and reducing the expression of Caspase-1, GSDMD, and interleukin-1β (IL-1β). Moreover, targeting BRD4 inhibited the voltage-dependent anion channel-1 (VDAC1) expression and oligomerization in hepatocytes stimulated by palmitic acid, therefore suppressing the activation of NLRP3 inflammasome. Mechanistically, BRD4 was upregulated during hepatocellular lipotoxicity that in turn modulated the active epigenetic mark H3K27ac at the promoter regions of the VDAC and GSDMD genes, thereby enhancing expression of VDAC and GSDMD. Additionally, the levels of BRD4, VDAC1 and NLRP3 proteins expression was higher in MASH livers from both humans and mice as compared with normal healthy control. **Conclusion:** Our study provides novel insights into epigenetic mechanisms underlying BRD4 activating the NLRP3 inflammasome and promoting GSDMD-mediated pyrotosis in hepatocellular lipotoxicity. Thus, BRD4 might serve as novel therapeutic target for MASH.

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1068 | KETOHEXOKINASE DEFICIENCY MITIGATES MASH/HCC PROGRESSION

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Background: Ketohexokinase (KHK) is a key enzyme that is specific for fructose metabolism and fructose metabolism is regulated by hypoxia-inducible factor (HIF). Given that fructose is a risk factor of MASH and MASH is a major cause of hepatocellular carcinoma (HCC), the aim of this study is to determine whether KHK deficiency prevents MASH/HCC progression and explore the underlying mechanisms. **Methods:** Male and female WT and *Khk KO (Khk$^{-/-}$)* mice were subjected to two MASH/HCC models, i.e., STAM [(STZ+high-fat diet (HF)] and DEN/HF. Liver transcriptome was assessed by bulk RNA-seq. ODD-luc mice (HIF-α luciferase reporter

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mice) were used to examine intestine HIF-α stability by *ex vivo* bioluminescence imaging (BLI). To determine the KHK-dependency on HIF-α stability, ODD-luc mice were crossed with *Khk*$^{-/-}$ mice or WT littermates to generate *Khk*$^{-/-}$/ODD-luc and WT/ODD-luc mice, respectively. Two mice models of HIF-2α-dependent intestine iron hyperabsorption, i.e., low-iron diet- and phenylhydrazine (PhZ)-induced anemia, were used to determine HIF-2α-dependent iron absorption in WT and *Khk*$^{-/-}$ mice. Complete blood count (CBC), plasma iron, and duodenum HIF-2α were evaluated. **Results:** KHK deficiency markedly mitigates MASH/HCC progression in two murine models. While dietary fructose stabilizes intestinal HIF-α, *Khk*$^{-/-}$/ODD-luc mice exhibit markedly reduced intestinal HIF-α luciferase activity compared to the controls, and that was rescued by pyruvate kinase M2 (PKM2) inhibitor, suggesting that KHK-dependent HIF-α stabilization is mediated by PKM2. High-fructose diet increases plasma iron level and that was abrogated by KHK deficiency. Conversely, *Khk*$^{-/-}$ mice spontaneously develop mild hypochromic anemia with iron-sufficient diet. Hepatic *Hamp* (hepcidin) mRNA was downregulated as shown by liver RNA-seq and RT-PCR. CBC analysis revealed markedly reduced hemoglobin, neutrophil numbers in the blood of *Khk*$^{-/-}$ mice, suggesting that KHK deficiency leads to systemic iron deficiency and reduced neutropoiesis. Mechanistically, KHK deficiency inhibits iron absorption in a HIF-2α-dependent manner as shown by low-iron diet- and Phz-induced anemia models. **Conclusion:** Our data provide evidence that fructose facilitates iron absorption and KHK deficiency inhibits MASH/HCC progression through reduced iron absorption mediated by KHK/PKM2/HIF-2α axis, leading to suppression of systemic inflammation and pro-tumorigenic liver microenvironments due to iron-dependent neutropoiesis.

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1069 | HEPATIC FOXA3 OVEREXPRESSION ALLEVIATES DIET-INDUCED METABOLIC DYSFUNCTION ASSOICIATED STEATOHEPATITIS AND OBESITY IN MICE VIA TGR5

Raja Gopoju Jiayou Wang[1] Shuwei Hu[1]

[1]Northeast Ohio Medical University

Background: Metabolic dysfunction–associated steatotic liver disease (MASLD) is an emerging healthcare issue and a major chronic liver disease worldwide. Disruption of hepatic fatty acid/TG homeostasis may cause lipotoxicity and the development of metabolic dysfunction–associated steatohepatitis (MASH). MASH is an advanced form of MASLD and is characterized by steatosis, hepatocyte ballooning, lobular inflammation, and fibrosis. Forkhead transcription factor 3 (FOXA3) has been shown to regulate metabolism and development. Hepatic FOXA3 is reduced in obesity and fatty liver disease. However, the role of hepatic FOXA3 in regulating obesity or steatohepatitis remains to be investigated. **Methods:** In this work, C57BL/6 mice were i.v. injected with AAV8-ALB-FOXA3 or the control virus. The mice were then fed a chow or Western diet for 16 weeks. The role of hepatic FOXA3 in energy metabolism and steatohepatitis was investigated. Plasma bile acid composition and the role of Takeda G protein-coupled receptor 5 (TGR5) in mediating the metabolic effects of FOXA3 were determined. **Results:** Overexpression of hepatic FOXA3 reduced hepatic steatosis in chow-fed mice and attenuated Western diet-induced obesity and steatohepatitis. FOXA3 induced lipolysis and inhibited hepatic genes involved in bile acid uptake, resulting in elevated plasma bile acids. The beneficial effects of hepatic FOXA3 overexpression on Western diet-induced obesity and steatohepatitis were abolished in Tgr5$^{-/-}$ mice. **Conclusion:** Our data demonstrate that overexpression of hepatic FOXA3 prevents Western diet-induced obesity and steatohepatitis via activation of TGR5.

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1070 | COAGULATION PROTEASE-ACTIVATED RECEPTOR-2 (PAR2) PROMOTES DYSLIPIDEMIA, OBESITY AND MAFLD THROUGH SUPPRESSION OF A HEPATIC PIONEER FACTOR ◆

Athan Kuliopulos[1] Regina Chen[1] Nga Nguyen[2] Yanling Wang[2] Manal Abdelmalek[3] Lidija Covic[4]

[1]Tufts University School of Medicine, [2]Tufts Medical Center, [3]Mayo Clinic Rochester, [4]Oasis Pharmaceuticals

Background: Metabolic-associated fatty liver disease (MAFLD) has been rising in incidence in parallel with the epidemic of type 2 diabetes, obesity, and dyslipidemia in the US and worldwide. For reasons that are not well understood, MAFLD and its more severe version, metabolic-associated steatohepatitis (MASH), are also associated with atherothrombotic disease and hypercoagulability. PAR2, a receptor activated by proteases that are dysregulated in inflammatory and fibrotic diseases, is emerging as a new drug target for MASH. We recently showed that the severity of MASH and/or diabetes significantly correlated with liver PAR2 expression in patients and mice. However, it is not yet understood whether hepatocyte PAR2 plays a direct role in liver metabolism and which liver cell types contribute to specific aspects of PAR2-driven pathology. **Methods:** To address the contribution of hepatocyte PAR2 to progression of MAFLD, we fed hepatocyte-specific PAR2 knockout mice ($PAR2^{\Delta Hep}$), whole-body PAR2 KO, and control floxed (fl/fl) WT mice high-fat diet for 12 weeks and conducted metatabolic, biochemical and molecular analyses using RNAseq. **Results:** After high-fat diet for 12 weeks, $PAR2^{\Delta Hep}$ mice had 30% lower liver cholesterol (p=0.029), a 23% reduction in plasma cholesterol (p=0.016), 26% lower liver triglycerides (p=0.028), and a 38% reduction in plasma triglycerides (p=0.038) compared to WT. $PAR2^{\Delta Hep}$ mice were also protected from obesity, weighing 24% less than WT mice. Both liver weight (p<0.0001) and body weight (p=0.0002) were significantly correlated with liver *Par2* mRNA expression. RNA-seq revealed that PAR2 deletion in whole-body KO or in $PAR2^{\Delta Hep}$ mice resulted in significant changes in fatty acid, cholesterol, and glucose metabolism, inflammation, and extracellular matrix pathways in liver. Using iRegulon analysis, the PAR2-mediated changes were consistent with suppression of a hepatic pioneer transcription factor that functions as a master regulator of metabolism. Mechanistic studies revealed that coagulation factor Xa activates PAR2-JNK1/2 and ERK1/2 pathways to suppress expression of this transcription factor through cJun and CEBPα, respectively, which has global effects on liver fatty acid and cholesterol metabolism including suppression of revere cholesterol transport. **Conclusion:** These data provide support that targeting hepatic PAR2 may potentially provide broad metabolic benefits to patients with MAFLD and MASH.

Disclosures: Athan Kuliopulos: Oasis Pharmaceuticals: Executive role, Regina Chen: Nothing to Disclose, Nga Nguyen: Nothing to Disclose, Yanling Wang: Nothing to Disclose, Manal Abdelmalek: Madrigal: Advisor, Madrigal, Gilead, Inventiva, Hanmi, Oasis, 89BIo: Grant/Research Support, Madrigal, Inventiva, Novo Nordisk, 89Bio, Intercept: Advisor, Hanmi: Consultant, 89BIo: Advisor, Lidija Covic: Nothing to Disclose

1071 | NOVEL HEPATIC LIPID-INDUCED ENHANCER ACTIVATION MODULATES STEATOHEPATITIS VIA S100A11 ◆ ★

P. Vineeth Daniel[1] Feda H. Hamdan[2] Amy Mauer[3] Yasuhiko Nakao[4] Daheui Choi[3] Gyanendra Puri[3] Yeriel (Yewon) Yoon[3] Alexander Revzin[3] Harmeet Malhi[4]

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Background: Metabolic dysfunction associated steatohepatitis (MASH) is a complex liver disease in which endoplasmic reticulum (ER) stress and the release of endogenous alarmins are key mediators. Studies indicate that epigenetic regulation governs individual susceptibility and risk of MASH progression. Yet, the crosstalk between lipotoxic ER stress and epigenetic regulation is understudied. **Methods:** Extracellular vesicles (EVs) were isolated by differential ultracentrifugation from palmitate treated hepatocytes. Proteomics was performed by mass spectroscopy. Mice were fed Choline-deficient, Amino acid-defined high-fat diet (CDAHFD) to induce steatohepatitis and high Fat, Fructose, and Cholesterol (FFC) diet to induce MASH. Chromatin immunoprecipitation (ChIP), histone acetylation studies, and dCas9-KRAB mice were employed to determine the functional consequences of the Lipid Influenced Enhancer (LIE) domain. **Results:** Proteomics of hepatocyte-derived lipotoxic EVs identified S100A11 enrichment. Bulk-RNA sequencing of FFC-fed mouse livers demonstrated a 3-fold increase and qPCR of MASH livers a 2-fold increase in S100A11 mRNA relative to controls. Correspondingly, S100A11-enriched EVs were significantly increased in MASH patient sera. Examination

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of the genomic location of S100A11 indicated clustering of several S100 family genes; however, only S100A11 was upregulated in lipotoxicity. Interrogation of publically available human liver ChIP-Seq GEO datasets identified a putative H3K27acetylated region, upstream to the promoter. ChIP-qPCR studies demonstrated a direct correlation between lipotoxic ER stress and H3K27acetylation, which we termed LIE. dCas9-KRAB mediated repression of LIE activation in Huh7 cells alleviated palmitate-induced S100A11 upregulation. Transient LIE repression in thapsigargin treated Huh7 cells showed no attenuation of S100A11 transcripts, demonstrating LIE specificity to lipotoxicity. We employed two steatohepatitis models; 3 weeks of CDAHFD (rapid disease model) and 6 weeks of FFC diet (recapitulates human MASH) to test murine LIE activation. Overexpression of murine LIE-sgRNAs in dCas9-KRAB expressing mice, fed with either of the diets demonstrated significant reduction of S100A11 transcripts and inflammatory foci within the liver of LIE-sgRNA injected mice. **Conclusion:** Our studies define a novel LIE and demonstrate lipotoxicity dependent epigenetically upregulated hepatic-S100A11 signalling as a potential therapeutic target in MASH.

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1072 | TOLL-LIKE RECEPTOR (TLR)5 MEDIATES DELETERIOUS EFFECTS OF LIPID INJURY AND FIBROGENIC RESPONSES IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS (MASH) AND CLINICAL OUTCOMES

Wenhao Li[1] John Loy[2] Kalpana Devalia[3] James Boot[4] Chaz Mein[4] Jonathan Fallowfield[5] Tim Kendall[5] Maria Jimenez Ramos[5] William Alazawi[6]

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Background: Metabolic dysfunction-associated steatohepatitis (MASH) is a progressive inflammatory liver condition characterised by hepatocyte lipotoxicity, infiltration of inflammatory and immune cells and stellate cell activation leading to fibrosis. The gastrointestinal tract is an important source of inflammatory mediators which activate hepatic Toll-like receptor (TLR) signalling. Stool from patients with MASH have increased proportions of flagellated bacteria (Firmicutes and Proteobacteria phyla). Flagellin is a direct agonist of TLR5 and we test the hypothesis that activation of TLR5 mediates the pathology observed in MASH and fibrosis. **Methods:** Plasma flagellin and stool *Flic* gene load (shotgun metagenomics sequencing) were measured in samples from 69 MASLD patients and 11 controls. Lipotoxicity was modelled in vitro using oleic (1mM) and palmitic (0.5mM) acid in primary hepatocytes and stellate (LX2) cells. Hepatic TLR5 mRNA expression and linked healthcare outcomes were extracted from SteatoSITE [1] (n=668 MASLD, 39 controls). **Results:** Compared to controls, plasma flagellin is increased in advanced MASH fibrosis (F3-4) but not earlier stages of disease ((538.3v 745.8pg/ml,p<0.01) or in hepatitis B virus infection) which normalises in samples taken median 83 days following bariatric surgery (n=20, p<0.01). Stool *Flic* gene expression and hepatic *TLR5* (but not *TLR2* or *TLR4*) expression are increased in MASH, along with markers of intestinal permeability (FABP2, D-lactate). In vitro, TLR5 inhibition does not alter lipid accumulation (BODIPY) or beta oxidation, but attenuates lipotoxicity-mediated IL8 protein expression (p<0.01, vs control) in primary hepatocytes. TLR5 is not expressed in stellate cells and flagellin does not activate LX2 cells (nor do toxic lipids). However lipid-injured hepatocyte-conditioned media induces 1.4-fold increase in TGFb1 gene expression in LX2 cells compared to control (p=0.01), and Th1 cell differentiation; both of which are reduced through TLR5 inhibition on the hepatocytes prior to media transfer (1.6-fold,p<0.01). High hepatic TLR5 expression is associated with greater hepatic decompensation events and all-cause mortality (Figure 1, Kaplan–Meier time-to-event analysis with log-rank test, P<0.01 for both). **Conclusion:** TLR5 mediates key pathology in the progression of human MASH and fibrosis, reverses following bariatric surgery and is associated with mechanisms of lipid-mediated inflammation and stellate cell activation. This pathway has potential as a novel therapeutic target in MASH fibrosis.

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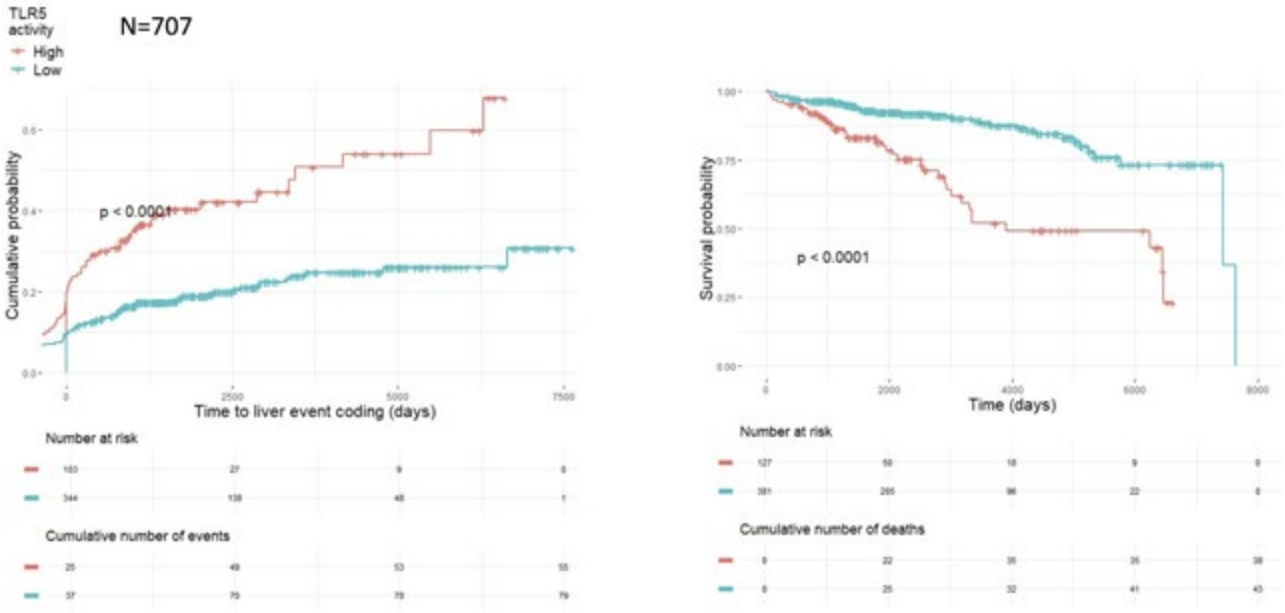

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1073 | FATTY ACID SYNTHASE (FASN) INHIBITOR REDUCES ATHEROSCLEROSIS DEVELOPMENT IN DIET-INDUCED DYSLIPIDAEMIA LDL RECEPTOR KNOCKOUT MICE WITH MASH

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Background: Increased *de novo* lipogenesis (DNL) drives the development of MASH, and FASN is the rate-limiting enzyme in the DNL pathway. In preclinical studies, denifanstat (TVB-2640) directly blocks endogenous FASN in stellate cells, immune cells and hepatocytes, thereby directly inhibiting fibrosis, inflammation and steatosis. Denifanstat, an oral FASN inhibitor, demonstrated significant MASH resolution and fibrosis improvement in the Ph2b MASH study, FASCINATE-2, as well as decreased liver fat and biomarkers of inflammation and fibrosis. Additionally, denifanstat decreased LDL-cholesterol and increased polyunsaturated triglycerides in both Ph2a (FACINATE-1) and Ph2b studies, suggesting potential cardiovascular benefits. We hypothesized that FASN inhibitor could prevent atherosclerosis through reduction of circulating cholesterol in the context of MASH. This study was to evaluate the effect of FASN inhibitor on plasma lipids and atherosclerosis in LDL receptor knockout (Ldlr-/-) dyslipidaemia and MASH mice. **Methods:** Male Ldlr-/-.Leiden mice were fed with fast-food diet (FFD) for 18 weeks to induce dyslipidaemia, atherosclerosis and MASH features and treated with TVB-3664 (a surrogate FASN inhibitor for denifanstat, 5 mg/kg, PO, QD) for 10 weeks. Endpoints included plasma lipids, lipoprotein profile and histological analysis of atherosclerosis in the aortic root (lesion area and severity according to the AHA score in 4 cross sections, *TNO, Netherlands*). **Results:** FFD feeding significantly increased plasma total cholesterol and triglycerides in Ldlr-/- mice. Treatment with TVB-3664 rapidly reduced plasma cholesterol and triglycerides within 4 weeks treatment, and these reductions were sustained until end of the study (10 weeks). Lipoprotein profile analysis showed that atherogenic LDL-C and VLDL-C, which were elevated by the FFD, were reduced by TVB-3664. After 28 weeks of FFD feeding, the Ldlr-/- mice developed severe type V plaque lesions

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and increased atherosclerotic lesion area in the aortic root. TVB-3664 treatment significantly reduced lesion size of the most severe type V lesions and reduced total atherosclerotic lesion area per cross-section of aortic root. Additionally, FFD feeding induced MASH features, including increased fat accumulation, immune cell infiltrates and fibrosis in the liver, in Ldlr-/- mice and TVB-3664 effectively reversed these features. **Conclusion:** Denifanstat has shown promise on LDL-C lowering and histological improvements in MASH patients. FASN inhibition not only reduced circulating cholesterol but also decreased the development of atherosclerosis and improved liver histology in a mouse model of dyslipidaemia and MASH. These results suggest that denifanstat could provide benefits in both cardiovascular and liver health and support its future clinical evaluation for long term outcomes in MASH patients.

Disclosures: Wen-Wei Tsai: Sagimet: Stock share holder, Gordian: paid consultant service, Eveline Gart: Sagimet: Independent Contractor, Mead Johnson: Independent Contractor, Martine Morrison: Nothing to Disclose, Eduardo Martins: Sagimet Biosciences: Employee, Sagimet Biosciences: Employee, Sagimet Biosciences: Stock - publicly traded company, George Kemble: Sagimet Biosciences: Salary, stock ownership, Marie O'Farrell: Nothing to Disclose

1074 | A PNPLA3-DEFICIENT IPSC-DERIVED HEPATOCYTE SCREEN IDENTIFIES PATHWAYS TO POTENTIALLY REDUCE STEATOSIS IN METABOLIC DYSFUNCTION-ASSOCIATED FATTY LIVER DISEASE

Caren Doueiry[1] *Christiana Kappler*[1] *Carla Martinez Morant*[1] *Stephen Duncan*[1]

[1]*Medical University of South Carolina*

Background: Background: The incidence of metabolic dysfunction-associated fatty liver disease (MAFLD), or nonalcoholic fatty liver disease (NAFLD), is dramatically increasing in adults and children, while effective pharmacological treatments remain unavailable. MAFLD can progress from lipid accumulation in the liver to more severe inflammation, cirrhosis, and cancer. It is the most common cause of chronic liver disease and is projected to be the leading cause of end-stage liver disease in the next decade.Many etiologies contribute to MAFLD. A polymorphism in the Patatin-like Phospholipase Domain Containing Protein (PNPLA3 I148M) has the most significant association with the disease and all stages of its progression. A roadblock to identifying potential treatments for PNPLA3-induced MAFLD is the scarcity of a cellular platform that recapitulates PNPLA3 I148M-mediated onset of steatosis in human hepatocytes. We used hepatocytes generated from our PNPLA3 I148M induced Pluripotent Stem Cells (iPSCs) to model the effect of the polymorphism on lipid content and lipid droplet accumulation, providing a platform to identify pathways with potential therapeutic value using an established high-throughput screening platform. **Methods:** We generated *PNPLA3* I148M and PNPLA3 -/- iPSCs using CRISPR-Cas9. Using established protocols, we differentiated the resulting cells into hepatocytes and measured the efficiency of differentiation. Using BODIPY 493/503 staining, we measured lipid accumulation in our iPSC-derived hepatocytes. We then used a small molecule screen to identify lead compounds that reduce lipid accumulation. **Results:** Both our PNPLA3 I148M and PNPLA3 -/- iPSC-induced hepatocytes showed hepatic marker expression as well as significant increase in lipid content compared to wildtype iPSC-induced hepatocytes. Our small molecule screen resulted in lead compounds that give insight to pathways involved in PNPLA3-mediated lipid accumulation. **Conclusion:** Conclusion: We conclude that human iPSC-derived hepatocytes can be used to effectively model the onset of MAFLD in the presence of the PNPLA3 I148M variant, which we show acts through a loss of function. Our model also provides a platform to identify small molecules with potential therapeutic value. Lead compounds were used to find common pathways that could play a role in PNPLA3-mediated lipid accumulation.

Disclosures: Caren Doueiry: Nothing to Disclose, Christiana Kappler: Nothing to Disclose, Carla Martinez Morant: Nothing to Disclose, Stephen Duncan: Nothing to Disclose

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1075 | POTENTIAL OF NOVEL REGULATORY BILE ACID, 3β-SULFATE-5-CHOLESTENOIC ACID (3SCA) IN MASLD THERAPY

Yaping Wang[1] Michael Fuchs[2] Shunlin Ren[1]

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Background: 3β-Sulfate-5-Cholestenoic Acid (3SCA) is a metabolite of cholestenoic acid (CA), synthesized and secreted from hepatocytes. Previous studies have demonstrated its ability to downregulate inflammatory responses induced by LPS in human macrophages. Metabolic dysfunction-associated steatotic liver diseases (MASLD) is characterized by lipid accumulation inflammation in liver tissues. Currently there is no highly effective FDA-approved treatment. This study aims to explore the potential of 3SCA for treating MASLD. **Methods:** 3SCA was chemically synthesized using sulfur trioxide–trimethylamine complex in anhydrous pyridine, purified by HPLC. The chemical structure was determined by LC-MS-MS analysis. Human hepatocytes cultured in high-glucose medium were served as an in vitro MASLD model. C57BL/6J mice were fed a western diet and high glucose/fructose water for 12 weeks to establish an in vivo MASLD model. MASLD mice were treated with the purified 3SCA (10 mg/kg) via IV injection once every two days for two weeks. Liver function was evaluated by measuring serum enzyme activities including AST, ALT, and ALK. Cholesterol and cholesterol ester levels in liver tissues were determined using biochemical kits. Gene expression involved in lipid metabolism and inflammation responses were determined by RT-qPCR. **Results:** Chemical synthesis yielded 98% pure 3SCA in white powder form as confirmed by HPLC. Treatment of 20 μM of 3SCA exhibited time- and dose-dependent downregulation of lipid biosynthesis genes (Hmgr, Fas, Acc, and Pcsk9), along with upregulation of PGC1a and CREB5 genes. In animal experiments, 3SCA significantly improved liver function, reducing ALT levels by 40%, AST levels by 6%, and ALK levels by 43%. Moreover, it markedly decreased liver total cholesterol levels by 22.7% and cholesterol ester levels by 21.8%. **Conclusion:** The results demonstrate that 3SCA, biosynthesized and secreted by human hepatocytes, possesses anti-inflammatory properties in human macrophages. Its ability to mitigate lipid accumulation in both in vitro and in vivo MASLD models suggests its potential as a therapeutic agent for MASLD recovery.

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1076 | A FRUCTOSE-ENRICHED DIET CONSUMPTION PROMOTES A SPECIFIC TRANSCRIPTOMIC SIGNATURE DEFINING AN AGGRESSIVE PHENOTYPE

Lisette Chávez Rodríguez[1] Oscar Alejandro Escobedo Calvario[1] Arturo Simoni Nieves[2] Monserrat Gerardo-Ramírez[3] Verena Jendrossek[4] Johann Matschke[4] Diego Calvisi[5] Jens Marquardt[6] Darko Castven[6] Concepcion Gutierrez Ruiz[1] María Elizabeth Tejero[7] Luis Gomez Quiroz[1]

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Background: Fructose-enriched diet consumption has increased over the years. Fructose is a highly lipogenic compound related to Metabolic-associated Steatotic Liver Disease (MASLD) and progression to Hepatocellular Carcinoma (HCC). Although many authors have tried to understand the role of fructose metabolism in HCC development and progression, the specific MASLD/HCC signature induced by fructose remains unknown. In the present work, we report the specific gene expression signature of 31 genes induced by fructose-enriched diet consumption related to HCC progression and aggressiveness of MASLD/HCC tumors. **Methods:** We fed the 15-day-old C57BL6/j male mice with a control chow diet (Chow 5001) and a high-fructose diet (33% of fructose in the drinking water ad libitum). Two days later, mice were injected with a single dose of N-diethylnitrosamine

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(DEN, 10µg/kg i.p.), and the treatments were continued for 32 weeks. mRNA-Seq was performed from the liver sections and was run using Illumina HiSeq4000. All data analysis was performed using R programming language and related packages. The comparative genomic was performed with MASLD/HCC tumors from patients with HCC. The chorioallantoic membrane (CAM) model was used to prove the aggressive phenotype induced by fructose. Ten eggs per group were grafted with NT or Fructose-treated (1mM) Huh-7 cells and treated with 100 µM of CisPlatin (CDDP) on two consecutive days before the end of the assay. **Results:** Mice treated with fructose developed MASLD after 32 weeks of treatments judged by steatosis and triglyceride accumulation; glucose and total cholesterol levels in serum were increased. mRNA-Seq results showed a specific gene profile induced by fructose specifically related to complement activation, lipid metabolism, response to insulin, biological oxidations, and biotransformation phase I and II, among others. Ingenuity pathway analysis highlighted a hyperproliferative and hyperplastic phenotype triggered by STAT3 activation. These results were substantiated by immunostaining of ki67 and ck19 with higher levels in the supplemented group. The comparative genomics analysis showed 31 genes shared with MASLD/HCC tumors. Interestingly, most of the genes were downregulated and mainly represented by immune modulation to favor aggressiveness and poor survival of the patients. To prove the aggressive phenotype induced by fructose, we used the CAM model with Huh-7 cells untreated or treated with 1mM of fructose, and two days before the end of the assay, we added CDDP (100 µM). Fructose treatment increased tumor volume compared to the volume of NT tumors and promoted an earlier therapy failure in the eggs treated with Fructose + CDDP compared to CDDP alone. **Conclusion:** Fructose-enriched diet consumption promotes a subtype of HCC with highly aggressive features and poor prognosis. *In vivo* analysis using the CAM model proved that fructose treatment enhances therapy failure in liver cancer cells.

Disclosures: Lisette Chávez Rodríguez: Nothing to Disclose, Oscar Alejandro Escobedo Calvario: Nothing to Disclose, Arturo Simoni Nieves: Nothing to Disclose, Monserrat Gerardo-Ramírez: Nothing to Disclose, Verena Jendrossek: Nothing to Disclose, Johann Matschke: Nothing to Disclose, Diego Calvisi: Nothing to Disclose, Jens Marquardt: Nothing to Disclose, Darko Castven: Nothing to Disclose, Concepcion Gutierrez Ruiz: Nothing to Disclose, María Elizabeth Tejero: Nothing to Disclose, Luis Gomez Quiroz: Nothing to Disclose

1077 | LUTEIN MITIGATES LIPID ACCUMULATION IN HEPATIC CELLS VIA TFEB ACTIVATION: A POTENTIAL THERAPEUTIC APPROACH FOR MASLD

elisa balboa[1] *Faride Saud*[1]

[1]*Universidad Finis terrae*

Background: The global prevalence of Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) is increasing, now affecting 25-30% of the population worldwide. MASLD, characterized by hepatic steatosis, results from an imbalance in lipid metabolism, leading to oxidative stress, lipoperoxidation, and inflammation. The activation of autophagy, particularly lipophagy, alleviates hepatic steatosis by regulating intracellular lipid levels. Lutein, a carotenoid with antioxidant and anti-inflammatory properties, protects against liver damage, and individuals who consume high amounts of lutein have a lower risk of developing MASLD. Evidence suggests that lutein could modulate cellular clearance pathways, such as autophagy, by the master gene transcription factor EB (TFEB), which regulates lysosomal biogenesis and function. TFEB plays a crucial role in regulating lipid homeostasis by linking autophagy to energy metabolism at the transcriptional level, making TFEB a potential target against MASLD. **Methods:** We propose that lutein decreases lipid accumulation via TFEB activation, increasing lipid droplet autophagy and lysosomal exocytosis in hepatocyte models of MASLD. In HepG2 cells treated with free fatty acids (FFA) and lutein, we measured: i) Lipid droplets (LD) by Bodipy; ii) TFEB and Lamp-1 by IF; iii) Autophagy markers like LC3B, P62 by western blot; and iv) exocytosis by electron microscopy. **Results:** In HepG2 cells treated with FFA and lutein: i) there was a decrease in the number of lipid droplets; ii) TFEB translocation to the nucleus increased; iii) the number of perinuclear lysosomes increased; iv) changes in autophagy-related proteins were induced; and v) LD excretion through lysosomal exocytosis increased. **Conclusion:** Our study demonstrates that lutein effectively decreases lipid accumulation in HepG2 cells treated with free fatty acids. This effect is mediated through the activation of TFEB, which enhances autophagy and lysosomal exocytosis. The findings suggest that lutein could be a promising therapeutic agent for preventing and treating MASLD by targeting lipid metabolism pathways and promoting cellular mechanisms that alleviate hepatic steatosis. Further research is needed to confirm these results in vivo and explore lutein's potential clinical applications in managing MASLD.

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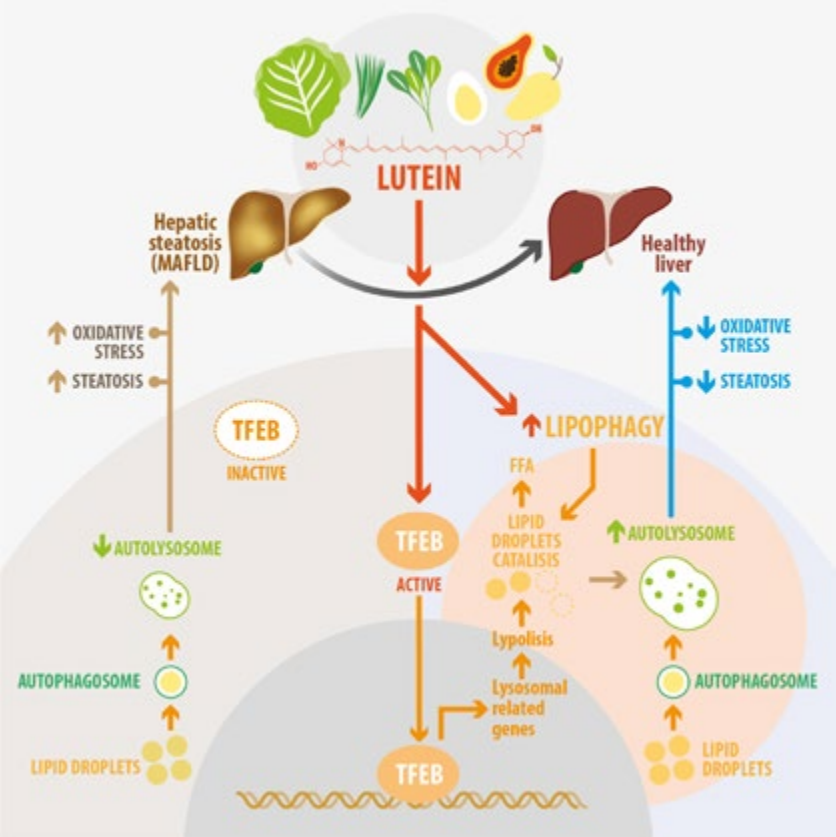

Disclosures: elisa balboa: Nothing to Disclose, Faride Saud: Nothing to Disclose

1078 | *IN VITRO* CELLULAR STUDIES IMPLICATE HSD17B13 IN LIPID AND IMMUNE ASSOCIATED PATHWAYS IN CULTURED PRIMARY HUMAN HEPATOCYTES

Wensheng Xie[1] Felix Frauhammer[1] Prerak Desai[1] Maggie Truong[1] Christian Schwoyer[1] Zoey Zheng[1] Christopher Traini[1] Wendy Halsey[1] Guillaume Heger[1] Forrest Gulden[1] Mathieu Bray[1] Stephen Atkinson[1] Mark Harpel[1]

[1]GlaxoSmithKline

Background: Steatohepatitis is characterized by hepatic steatosis, hepatocyte ballooning, and inflammation, which leads to fibrosis and progressive liver disease. A loss of function SNP (rs72613567) in the hydroxysteroid 17β-dehydrogenase 13 (HSD17B13) gene protects against the development of progressive steatotic liver disease, particularly inflammation and fibrosis. Although this allele results in lower HSD17B13 protein level and loss of enzymatic activity, the biological function of HSD17B13 and mechanisms of protection remain unclear. **Methods:** Primary human hepatocytes (PHH) were cultured in an *in vitro* model using murine fibroblasts as a supportive matrix (Hepatopac, BioIVT, MA, USA). On day 0, cells were transfected with one of three siRNAs targeting *HSD17B13* or an RNAiMAX control. On day 17, media was changed to either: i) low glucose; ii) high glucose and fructose; or iii) palmitic acid supplement. Four days later, cells were stained for lipid and HSD17B13 protein or harvested for RNA isolation and RNAseq analysis. PHH-specific gene signatures that correlated with siRNA treatments or HSD17B13 levels were identified with mixed effect linear models. Hypergeometric tests were used to identify overrepresentation of signature genes across multiple pathway databases and gene ontologies. **Results:** siRNA treatment resulted in 35-42% knockdown of *HSD17B13* transcript and 50-70% knockdown of HSD17B13 protein at end of culture time. RNAseq analysis defined a signature comprising 266 genes (1% false discovery rate) that were coordinately downregulated with *HSD17B13* knockdown. The most significantly enriched pathways included cholesterol biosynthesis/metabolism, lipid mobilization, complement and coagulation cascades, and xenobiotic/bile acid metabolism (Fig. 1). **Conclusion:** Pathway enrichment with the *HSD17B13* siRNA gene signature evokes potential roles of HSD17B13 in steatotic liver disease. In particular, enrichment of cholesterol and other lipid pathways, combined with complement and coagulation cascades, suggests that

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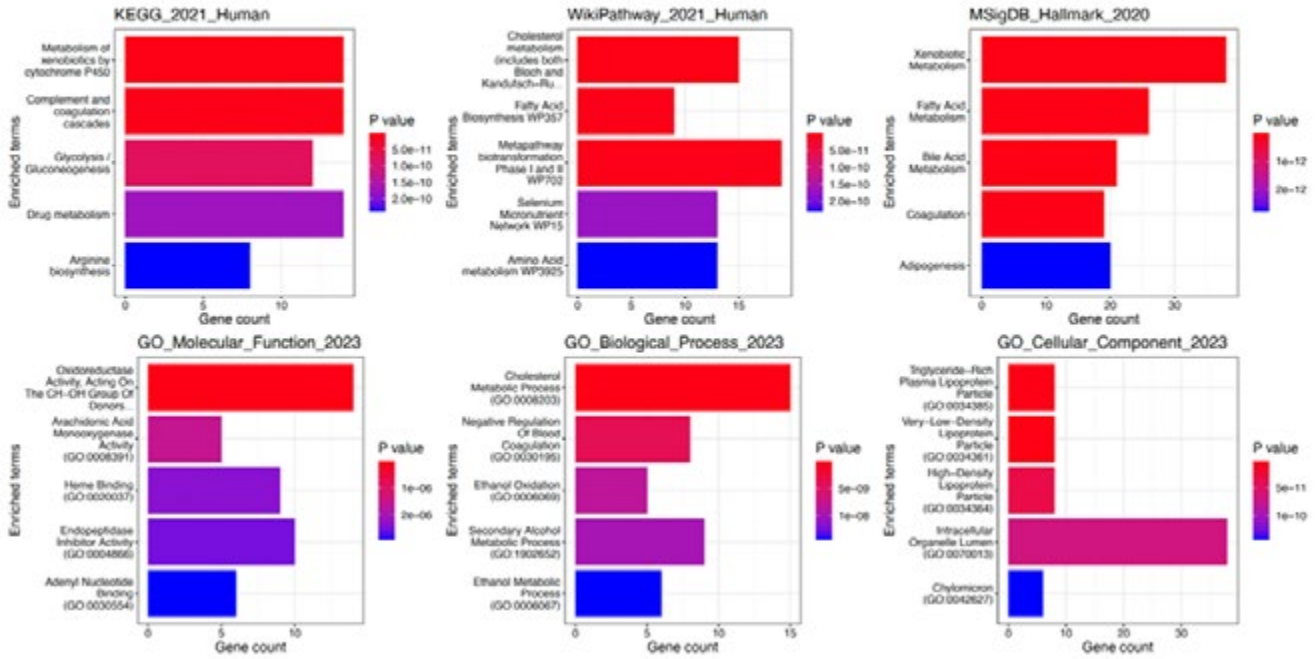
HSD17B13 may contribute to lipid remodeling, lipotoxicity, and the switch to inflammatory steatohepatitis. These results help explain the protective effect of the *HSD17B13* loss of function variant against progressive inflammation and fibrosis and support a hypothesis whereby *HSD17B13* knockdown may protect the liver as a treatment for steatotic liver diseases by attenuating lipotoxicity and steatohepatitis.

Figure 1: Enrichment analysis of genes downregulated in the Hepatopac model following HSD17B13 siRNA treatment.



Disclosures: Wensheng Xie: Nothing to Disclose, Felix Frauhammer: GlaxoSmithKline: Employee, Prerak Desai: Nothing to Disclose, Maggie Truong: Nothing to Disclose, Christian Schwoyer: GSK: Employee, Zoey Zheng: Nothing to Disclose, Christopher Traini: Nothing to Disclose, Wendy Halsey: Nothing to Disclose, Guillaume Heger: Nothing to Disclose, Forrest Gulden: Nothing to Disclose, Mathieu Bray: GSK: Employee, Stephen Atkinson: Nothing to Disclose, Mark Harpel: GSK: Employee

1079 | ELUCIDATING NOVEL THERAPEUTIC TARGETS FOR METABOLIC DISEASE THROUGH HIGH RESOLUTION EPIGENETIC PROFILING OF PRIMARY HUMAN ADIPOCYTES

Rigel Kishton[1] Siddhartha Bagaria[1] Alexander Campbell[1] Sam Gross[1] Pedro Mendez[1] Sanjay Pandey[1] Paul Cohen[2] Arash Jamshidi[1] Justin Valley[1] Alex Aravanis[1]

[1]Moonwalk Biosciences, [2]The Rockefeller University

Background: Metabolic diseases are the end result of multi-system dysfunction arising due to prolonged alterations in caloric intake, energy expenditure and endocrine signaling pathways. While obesity itself is associated with poor health outcomes, increased adiposity can also directly drive worsening liver pathogenesis in MASH through white adipose tissue endocrine activity and additional mechanisms. Consequently, a deep understanding of the biological mechanisms underlying white adipose tissue dysfunction in metabolic disease can result in novel biological insights along with therapeutic targets for metabolically-associated liver dysfunction. **Methods:** Here we describe the generation of an epigenetic atlas of primary human adipocytes by utilizing our EpiRead™ epigenetic sequencing and informatics platform. EpiRead provides genome-wide, single-cell level DNA methylation profiling and can be utilized to identify differentially methylated regions (DMRs) of the chromatin that correspond to differences in cell state. For our adipocyte atlas, we have profiled a variety of primary human adipose tissue subtypes. In the current study, we performed EpiRead epigenetic mapping analysis of primary white adipocytes isolated from the subcutaneous adipose tissue of healthy weight (BMI < 25), overweight (BMI between 25 and 29.9) and obese (BMI > 30) human donors. **Results:** Analysis of genome-wide DNA

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methylation data revealed that DMRs between healthy BMI and obese BMI adipose tissue donors are observed in gene coding regions, annotated regulatory regions, and unannotated segments of DNA. Interestingly, the absolute number of DMRs between healthy and obese donor adipocytes was relatively restricted, with 47 DMRs corresponding to 49 gene targets identified. Our computational algorithms determined that a number of DMRs represent druggable targets, either as de novo targets entirely or from settings other than metabolic disease. **Conclusion:** DMRs between healthy and obese donor adipocytes reflect a novel source of putative targets for cardiometabolic therapeutic interventions utilizing epigenetic editing modalities such as EpiWrite™, our programmable epigenetic engineering platform that can specifically target discrete DNA sequences and drive desired DNA methylation or demethylation at desired sites to suppress or activate gene expression in order to ameliorate disease. In addition, these targets may be potentially addressed with traditional modalities such as small molecules or biologics. Ongoing work focuses on validating the causal nature of identified DMRs through epigenetic editing.

Disclosures: Rigel Kishton: Nothing to Disclose, Siddhartha Bagaria: Nothing to Disclose, Alexander Campbell: Nothing to Disclose, Sam Gross: Nothing to Disclose, Pedro Mendez: Nothing to Disclose, Sanjay Pandey: Nothing to Disclose, Paul Cohen: Nothing to Disclose, Arash Jamshidi: Nothing to Disclose, Justin Valley: Nothing to Disclose, Alex Aravanis: Nothing to Disclose

1080 | LIVER-DERIVED EXTRACELLULAR MATRIX HYDROGELS AUGMENT THE SURVIVAL AND FUNCTION OF PRIMARY RAT LIVER SINUSOIDAL ENDOTHELIAL CELLS

Junyu Wang[1] *Fenghua Zhao*[1] *Linda Brouwer*[1] *Manon Buist-Homan*[1] *Han Moshage*[1] *Martin Harmsen*[1]

[1]*University Medical Center Groningen*

Background: Liver sinusoidal endothelial cells (LSECs) have great potential as target cells for novel therapeutic strategies aimed at preventing or reversing metabolic dysfunction-associated steatotic liver disease (MASLD). However, isolating and culturing primary LSECs is notoriously difficult as they rapidly dedifferentiate, losing their specific phenotype and function. The extracellular matrix (ECM), including its composition, 3-dimensional structure, and mechanical properties, likely plays a crucial role in maintaining the fate and function of LSECs. In traditional 2D culture models, LSECs dedifferentiate into vascular-type endothelial cells, losing their specific functions quickly. In this study, we aim to explore the effects of liver-derived ECM (L-ECM) hydrogels on LSECs and develop culture conditions that maintain the differentiated function of LSECs for prolonged periods in vitro. **Methods:** The L-ECM was isolated from porcine liver and made into hydrogels to culture primary rat LSECs in vitro. Biochemical and mechanical properties of L-ECM hydrogels were measured. Ultrastructure of L-ECM hydrogels was performed by scanning electron microscopy (SEM). Primary rat LSECs were isolated from male Wistar rats. The viability of LSECs was analyzed by the uptake of fluorescein diacetate/propidium iodide. Gene expression was determined by qPCR and protein expression was determined by immunofluorescence and the determination of fenestrae and sieve plates by SEM. **Results:** L-ECM hydrogels showed a protein content of 34.9% and the presence of glycosaminoglycans (0.045%) with a low residual DNA level (41.2 ng/mg). The proteomic analysis and molecular weight distribution of proteins of solubilized L-ECM hydrogels revealed ECM core matrisome components, abundant presence of collagens and, unexpectedly, liver-specific function proteins. L-ECM hydrogels had a stiffness of 2.1 ± 1.1 kPa and 87.9% stress relaxation after 100 seconds. The hydrogels reduced cell death of LSECs. LSECs cultured on L-ECM hydrogels presented higher expression of the LSEC-specific mRNAs Stab-2, Nos3, LYVE1, lower expression of Mmp9, CD31, and more abundant fenestrae compared to non-coated tissue-culture polystyrene (TCPS) and collagen type I coated TCPS. **Conclusion:** L-ECM hydrogels enhanced the cell viability of LSECs, and slowed down the dedifferentiation of LSECs compared to traditional culture models. Our results suggest that L-ECM hydrogels create a better environment for sustaining differentiated LSEC function, offering the potential for therapeutic interventions against metabolic liver diseases.

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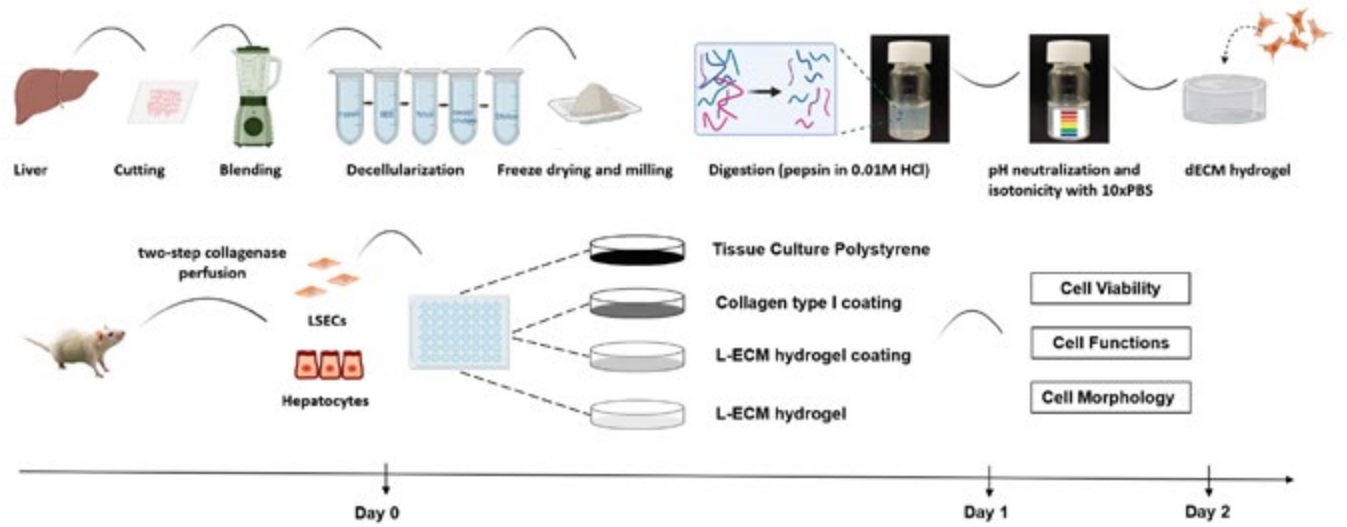

Disclosures: Junyu Wang: Nothing to Disclose, Fenghua Zhao: Nothing to Disclose, Linda Brouwer: Nothing to Disclose, Manon Buist-Homan: Nothing to Disclose, Han Moshage: Nothing to Disclose, Martin Harmsen: Nothing to Disclose

1081 | CARD9 DEFICIENCY EXACERBATES DIET-INDUCED STEATOTIC LIVER DISEASE

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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD), is characterized by excessive lipid accumulation in the liver and affects nearly 40% of the world's population. Despite this, few pharmaceutical therapies exist. To develop new therapies a deeper understanding of MASLD's pathophysiology is needed. The gut microbiome is emerging as a significant risk factor in MASLD progression. While gut bacteria have been the primary focus, gut fungi are also present in significant quantities. Caspase recruitment domain protein-9 (CARD9) is a crucial protein in myeloid cells for signaling from cell-surface fungal pattern recognition receptors. CARD9 is implicated in inflammatory bowel disease and mutations lead to severe CNS fungal infections. We hypothesize that CARD9 loss significantly impacts gut barrier function. Our objective therefore was to examine the effect of CARD9 deficiency-induced fungal dysbiosis in a mouse model of MASLD. **Methods:** C57/BL6J or CARD9 knockout (CARD9KO) mice were fed a high-fat high-sugar (HFHS) diet for 6 months. After the feeding period, livers, blood, stool and intestines were collected. Liver architecture, lipid content and fibrosis were examined using histology. Blood was analyzed for liver injury markers and stool DNA was used for next-generation sequencing studies. Intestinal samples were analyzed for anti-microbial peptides using PCR and immunohistochemistry. Additionally, human stool samples from MASLD patients were used for next-generation sequencing. **Results:** CARD9KO mice on a high-fat high sugar diet exhibited significant liver injury, evidenced by elevated ALT levels and increased amounts of fibrosis. Additionally, CARDKO mice showed notable bacterial and fungal dysbiosis with a significant reduction in the Penicillium genus. We confirmed a similar reduction of Penicillium in our human cohort of data. Examination of the intestines in CARD9KO mice revealed no significant changes in architecture. However, there was a significant reduction in cells positive for antimicrobial peptides Peptide-YY and lysozyme in the small intestine. **Conclusion:** Our results indicate that fungal dysbiosis significantly impacts MASLD progression. CARD9KO mice showed increased liver injury and fibrosis. The Penicillium genus was notably reduced in CARD9KO mice, a finding we confirmed in MASLD patients. Given the Penicillium genus' known interactions with bacteria and other fungi, we propose it may ameliorate MASLD, warranting further study. In the small intestine, reductions in PYY and lysozyme, proteins active against fungi, were observed, suggesting these deficiencies lead to fungal dysbiosis. These findings imply that targeting gut mycobiota could be a promising novel treatment for MASLD.

Disclosures: Vijay Pandyarajan: Nothing to Disclose, Ekihiro Seki: Nippon Zoki: Research Grant Support, Novonordisc: Consultant

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1082 | IMPACT OF EX-VIVO EXPANDED CD34-POSITIVE CELLS ON TUMOR FORMATION IN HEPATOCARCINOGENIC MICE WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS

Toru Nakamura[1] Atsutaka Masuda[1] Hideki Iwamoto[1] Hiroyuki Suzuki[1] Takahiko Sakaue[1] Toshimitsu Tanaka[1] Hironori Koga[1] Takumi Kawaguchi[1]

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Background: We previously reported the efficacy and safety of autologous peripheral blood CD34⁺ cell transplantation in patients with decompensated cirrhosis without hepatocellular carcinoma (HCC) in a multicenter clinical trial. Since liver cirrhosis is highly carcinogenic, it is very important to evaluate the effect of CD34⁺ cell transplantation on hepatocarcinogenesis. However, the possibility that CD34⁺ cells directly proliferate HCC has not been examined. Therefore, the aim of this study was to investigate whether CD34⁺ cell transplantation suppresses liver fibrosis and effects on hepatocarcinogenesis in spontaneous hepatocarcinogenesis mice (STAM model mice). **Methods:** Mouse CD34⁺ cells were harvested from healthy mouse bone marrow and cultured for one week. To establish STAM mice, male C57BL/6J mice were subjected to a single subcutaneous injection of streptozotocin on 2 days of age and fed a high-fat diet (HFD32) from the weaning period (4 weeks of age). Additionally, two types of metabolic dysfunction-associated steatohepatitis (MASH) model mice were created. (i) a liver fibrosis model fed until 12 weeks of age (STAM-fibrosis model) and (ii) a HCC model fed until 16 weeks of age in which HCC develops spontaneously (STAM-HCC model). In both models, CD34⁺ cells (CD34o group, $5x10^6$/kg) or saline (Control group) were administered via the spleen at 8 weeks of age. In the STAM-fibrosis model, a twice-treatment group (CD34t group) was also created. In the STAM-fibrosis model, the anti-fibrotic effect was evaluated by Sirius-red staining and immunohistochemistry against αSMA; in the STAM-HCC model, tumor number and size were compared to the control group. **Results:** In the STAM-fibrosis model, the Sirius-red positive areas were 1.18 ± 0.17% in the control group and 0.97 ± 0.18% in the CD34o group, although there was no significant difference. However, the CD34t group (0.59 ± 0.06%) showed a significant improvement compared to the control group ($p<0.05$). Immunohistochemical staining for αSMA positive areas was significantly decreased in the CD34t group ($p<0.05$). In the STAM-HCC model, the number of visible tumors tended to be fewer in the CD34o group compared to the control group (Control, 4.1 ± 0.9; CD34o, 1.4 ± 1.0). The maximum tumor diameter tended to be smaller in the CD34o group compared to the control group (Control, 5.1 ± 1.4 mm; CD34o, 4.0 ± 1.7 mm), and the sum of tumor diameter tended to be smaller in the CD34o group compared to the control group (Control, 14.6 ± 3.5 mm; CD34o, 4.8 ± 4.1 mm). In background liver, the CD34o group showed less lipid accumulation and significantly reduced plasma total cholesterol and triglycerides levels ($p<0.05$). **Conclusion:** CD34⁺ cell transplantation ameliorates MASH liver fibrosis and did not affect progressively for HCC. These results suggest that CD34⁺ cell transplantation may be a potentially safe cell therapy for patients with cirrhosis.

Disclosures: Toru Nakamura: Nothing to Disclose, Atsutaka Masuda: Nothing to Disclose, Hideki Iwamoto: Nothing to Disclose, Hiroyuki Suzuki: Nothing to Disclose, Takahiko Sakaue: Nothing to Disclose, Toshimitsu Tanaka: Nothing to Disclose, Hironori Koga: Nothing to Disclose, Takumi Kawaguchi: ASKA Pharmaceutical Co., Ltd.: Speaking and Teaching, Taisho Pharmaceutical Co., Ltd.: Speaking and Teaching, Kowa Company, Ltd.: Speaking and Teaching, AbbVie GK.: Speaking and Teaching, Eisai Co., Ltd.: Speaking and Teaching, Novo Nordisk Pharma Ltd.: Speaking and Teaching, Janssen Pharmaceutical K.K.: Speaking and Teaching, Janssen Pharmaceutical K.K.: Speaking and Teaching, Otsuka Pharmaceutical Co., Ltd.: Speaking and Teaching, EA Pharma Co.,Ltd.: Speaking and Teaching

1083 | ROLE OF BILE ACIDS IN PATHOGENIC INTESTINAL PERMEABILITY AND FIBROSIS IN A CO-CULTURE MODEL

James Reed[1] Yongtao Wang[2] Liz Jones[3] Min Xu[2] Wenyu Lin[2] Charlotte Warner[2] Sloan Devlin[3] Raymond Chung[2]

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Background: Pathogenic intestinal permeability (PIP) contributes to development of metabolic dysfunction-associated steatotic liver disease (MASLD). Prior therapies have not completely addressed the role of bile acids (BAs) in PIP and MASLD. We previously demonstrated that unconjugated BAs (UBA) increased epithelial permeability *in vitro* while conjugated BAs (CBA) ameliorated the effect by inhibiting deconjugation and preventing

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hepatic inflammation in rats given a choline-deficient high-fat diet (Li, Sci Adv 2022). This study investigated how BAs regulate the intestinal barrier and participate in liver injury using cell co-culture models. **Methods:** Caco-2 cells differentiated in transwells into enterocyte-like cells while trans-epithelial electrical resistance (TEER) was assessed to confirm maturity prior to exposure to BAs and co-culture with LX2 hepatic stellate cells. Different concentrations and mixtures UBAs and CBAs (with the 3:1 glyco:tauro ratio found in humans) were applied to the co-cultures for 48 hours, prior to measuring TEER and harvesting RNA for qPCR. **Results:** UBAs applied in the absence of CBAs increased Caco-2 epithelial permeability and induced expression of Claudin-1 and Occludin. In co-cultured LX2 cells, UBAs upregulated pro-fibrogenic Yes associated protein (YAP) downstream targets. Applying CBAs alone resulted in no perturbation of TEER. When CBAs were added to UBAs, we observed rescue of TEER; as well as modulated transcription of tight junction genes, TGR5, and FXR target genes in Caco-2 cells, and YAP downstream targets in LX2 cells. **Conclusion:** This work provides evidence that BA pools alter intestinal permeability and contribute to regulation of pro-fibrogenic genes in hepatic stellate cells. Additional study regarding the interactions between the BA-exposed stellate cells and hepatocytes is warranted to elucidate the mechanism of their interaction. These findings suggest that manipulating the BA pool, potentially through microbiota-directed inhibitors, could be a therapeutic target for fibrosis in MASLD.

Disclosures: James Reed: Nothing to Disclose, Yongtao Wang: Nothing to Disclose, Liz Jones: Nothing to Disclose, Min Xu: Nothing to Disclose, Wenyu Lin: Nothing to Disclose, Charlotte Warner: Nothing to Disclose, Sloan Devlin: Nothing to Disclose, Raymond Chung: Nothing to Disclose

1084 | GLUCAGON ENGAGEMENT IS ESSENTIAL FOR THE DIRECT ANTI-INFLAMMATION AND ANTI-FIBROSIS EFFECT OF EFOCIPEGTRUTIDE IN TAA-INDUCED MOUSE MODEL OF LIVER INJURY AND FIBROSIS

yohan kim[1] Jung Kuk Kim[1] Eun Jin Park[1] Hyunjoo Kwon[1] Jeong A Kim[1] Sang Hyun Park[1] Sungmin Bae[1] Daejin Kim[1] Sang Hyun Lee[1] In Young Choi[1]

[1]Hanmi pharmaceutical

Background: Nowadays, potential benefits of incretin such as glucagon (GCG), GIP, and GLP-1 beyond metabolism have been proposed, particularly in inflammation and fibrosis. A long-acting GCG/GIP/GLP-1 triple agonist, efocipegtrutide (also known as HM15211), was developed for MASH and demonstrated consistent treatment benefits in various animal models of MASH and/or fibrosis. Considering its unique activity profile, GCG action of efocipegtrutide might play an important role in the improvement effect on inflammation and fibrosis. To demonstrate this hypothesis, potential effect of GCG engagement was investigated in a TAA (thioacetamide)-induced liver injury and fibrosis mouse model. **Methods:** TAA was i.p. injected into mice for 12 weeks to induce liver injury and fibrosis, and efocipegtrutide was administered during the last 10 weeks. Tirzepatide (GLP-1/GIP) was included as comparative control. Efpegerglucagon, which has a same structure with efocipegtrutide but only exhibits GCG activity, was also included. At the end of the treatment, hepatic hydroxyproline content and pro-collagen 1α1 level were measured, and the liver tissues were subjected to H&E and Sirius Red staining followed by histological grading. **Results:** Efocipegtrutide treatment significantly reduced hepatic hydroxyproline content (178.46 nmol/g; $p<0.0001$) compared to the TAA vehicle group (243.73 nmol/g). Similar reduction was observed with efpegerglucagon, while tirzepatide (230.68 nmol/g) had only marginal effect. Similarly, efocipegtrutide significantly reduced pro-collagen 1α1 content (0.47 mg/g; $p<0.001$) compared to the TAA vehicle group (0.88 mg/g), and efpegerglucaon also showed a significant reduction, whereas tirzepatide (0.89 mg/g) had no reduction effect. H&E and Sirius red staining demonstrated that efocipegtrutide exhibited greater reduction in portal inflammation and fibrosis scores (1.00; $p<0.0001$, 0.86; $p<0.0001$) compared to the TAA vehicle group (2.29, 3.29). Notably, efpegerglucagon showed similar histological improvement. In contrast, tirzepatide had no improvement effects. Consistent with these histological findings, hepatic expression of *collagen 1α1* and blood level of TIMP-1 was significantly reduced by efocipegtrutide or efpegerglucagon, but not by tirzepatide. **Conclusion:** In TAA mice, efocipegtrutide (GCG/GIP/GLP-1 triple) and efpegerglucagon (GCG mono) showed similar anti-inflammatory and anti-fibrosis benefits while tirzepatide (GIP/GLP-1 dual) had relatively little effect. These result demonstrate that GCG engagement could play a crucial role in managing hepatic inflammation and fibrosis. P2b study in biopsy confirmed MASH patients is currently ongoing to assess the clinical relevance of these findings.

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Disclosures: yohan kim: Nothing to Disclose, Jung Kuk Kim: Nothing to Disclose, Eun Jin Park: Nothing to Disclose, Hyunjoo Kwon: Nothing to Disclose, Jeong A Kim: Nothing to Disclose, Sang Hyun Park: Nothing to Disclose, Sungmin Bae: Nothing to Disclose, Daejin Kim: Nothing to Disclose, Sang Hyun Lee: Nothing to Disclose, In Young Choi: Nothing to Disclose

1085 | SULFONATED ALBUMIN ACTIVATES HEPATIC STELLATE CELLS TO ACCELERATE NASH LIVER FIBROSIS

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Background: Albumin undergoes post-translational modification (PTMs) during liver injury, and sulfonated albumin is one of the important modified components. Since oxidative stress plays an important role in the development of NASH and can promote the sulfonated modification of albumin, but the effect of sulfonated albumin on the progression of NASH liver fibrosis is unclear. **Methods:** Serum samples of normal and NASH people were obtained. NASH models induced by high fat diet (HFD) and methionine choline deficient diet (MCD) were constructed. Human hepatic stellate cell line LX2 were used for in vitro studies. The role and specific mechanisms underlying sulfonated modified albumin in the progression in NASH liver fibrosis was explored. **Results:** Sulfonated albumin was significantly increased in human NASH and mouse NASH serum samples. Intraperitoneal injection of sulfonated albumin aggravated liver fibrosis in mice. Next, we further confirmed that sulfonated albumin can promote the pro-fibrotic activation of hepatic stellate cells (HSCs). Meanwhile, mechanism exploration showed that sulfonated albumin activated the endoplasmic reticulum stress pathway of HSCs, and inhibition of endoplasmic reticulum stress could inhibit the activation of HSCs. In addition, we found that the pro-fibrotic effect of sulfonated albumin was mediated by GAL3 signaling in HSCs. **Conclusion:** Sulfonated albumin promotes the progression of NASH by regulating endoplasmic reticulum stress to activate hepatic stellate cells. Therefore, our results suggest that sulfonated albumin may be a new target for the treatment of NASH liver fibrosis.

Disclosures: Tiantian Liu: Nothing to Disclose, Jianni Qi: Nothing to Disclose, Qiang Zhu: Nothing to Disclose

1086 | PHOCAEICOLA COPROCOLA ALLEVIATES METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE BY MODULATING LIPOGENESIS

JeongHa Park[1] seol hee Song[2] JEONG SU KIM[2] Young Seok Kown[2] Dong Joon Kim[3]

[1]Hallym University/ graduate student, [2]Hallym University, [3]Hallym University Medical Center

Background: Metabolic dysfunction–associated steatotic liver disease (MASLD) is one of the most common chronic liver diseases globally. This study aimed to elucidate the underlying mechanisms of gut-microbiota in MASLD and explore the effects of Phocaeicola coprocola on the gut-microbiota profiles perspective. **Methods:** To identify distinctive microbiota in MASLD, 151 stool samples were divided into healthy control (n=54), MASLD (n=78), and MASLD associated cirrhosis (n=19) group. Five weeks old C57BL/6J mice were fed the Western diet for 18 weeks for the MASLD model and fibrosis model was induced by thioacetamide (200 mg/L drinking water) and 0.05% 3,5-diethoxycarbonyl-1,4-dihydro-collidine diet. P. coprocola was administered 3 times/week at a concentration of 4.0×10^9 CFU. We compared liver/body weight ratio (L/B ratio), NAFLD activity score (NAS), liver function tests with serum, histopathological examination, markers for inflammation and lipogenesis in the liver. **Results:** Abundance of P. coprocola species were suppressed according to liver disease progressed (healthy, 2.90%; MASLD, 1.06%; cirrhosis, 0.00%). P. coprocola group shows significant improvement in biochemistry parameters (AST 106.0±28.2, ALT 142.7±70.6, TC 249.6±40.4), L/B ratio (6.4±1.1) and NAS (5.1±2.3) compared with Western diet group (AST 175.3±87.9, ALT 293.0±155.3, TC 299.2 ±46.0, L/B ratio 8.6±1.5, NAS 7.4±0.8). The expression of inflammation biomarkers (TNF-α) and fatty acid uptake genes (CD36, PPAR-γ, Srebp-1c, and FAS) was down regulated in the P. coprocola group. In the fibrosis model, strain group shows significant improvement in histological (fibrosis 3.6±0.5, inflammation 2.3±0.5, ballooning 1.0±0.5, and fibrosis area 20.7%) compared with DDC+TAA diet group (fibrosis 4.0±0.0, inflammation 3.0±0.0, ballooning 2.0±0.0, and fibrosis area 35.7%). **Conclusion:** P. coprocola administration showed a preventive effect in MASLD and fibrosis by regulating

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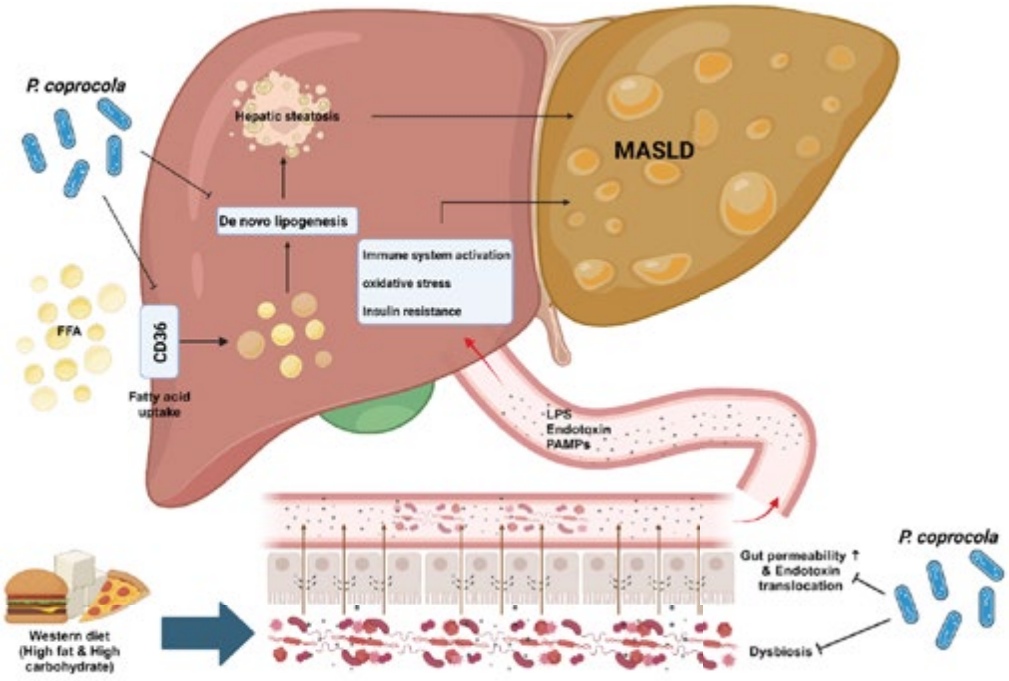
lipid accumulation as well as reducing inflammation in the liver. Therefore, our study suggests that P. coprocola may be a potential preventive treatment for MASLD.



Disclosures: JeongHa Park: Nothing to Disclose, seol hee Song: Nothing to Disclose, JEONG SU KIM: Nothing to Disclose, Young Seok Kown: Nothing to Disclose, Dong Joon Kim: Nothing to Disclose

1087 | AN EX-VIVO APPROACH TO MODEL METABOLIC DYSFUNCTION ASSOCIATED STEATOHEPATITIS (MASH) USING PATIENT-DERIVED INDUCED PLURIPOTENT STEM CELLS

Ekta Minocha[1] Andrew Benintende[2] Ashwani Gupta[1] Nate Schmidt[1] John Purdy[1] Richard Green[2] Jason Wertheim[1]

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Background: Metabolic dysfunction associated steatohepatitis (MASH) which is characterized by excessive steatosis, inflammation and progressive fibrosis, is projected to become the leading indication for liver transplantation with high risk of disease recurrence. There are few medical treatments available for MASH, but the major limiting factor for drug development is the lack of suitable human models that mimic the disease accurately. Therefore, the primary focus of this study was to develop a patient-based induced pluripotent stem cells (iPSCs) platform to determine the pathophysiology of the disease. **Methods:** Peripheral blood mononuclear cells from patients with MASH, who had progressed to cirrhosis and end-stage liver disease, were reprogrammed to iPSCs. Additionally, iPSCs were also obtained from CDI-CIRM Bank, that were derived from patients with MASH or without liver disease (controls). Both iPSC populations were differentiated into iPSC-hepatocytes and assessed for morphological and functional properties. Bodipy staining examined lipid droplets and LC-MS/MS lipidomic analysis was done to define the lipidome. Quantitative PCR was performed to analyze the gene expression of endoplasmic reticulum (ER) stress/unfolded protein response (UPR) and Farnesoid X receptor (FXR) downstream genes. **Results:** iPSC-hepatocytes from MASH/Cirrhosis patients displayed histological features of hepatocyte ballooning and macro-steatosis, and lower gene expression levels of albumin and A1AT, compared to controls. Bodipy staining indicated that iPSC-hepatocytes from MASH/Cirrhosis donors accumulate more intracellular lipid droplets than controls. Lipidomic analysis showed that MASH/Cirrhosis iPSC-hepatocytes exhibited higher levels of phospholipids with 6-double bonds polyunsaturated fatty acid (PUFA) tails and lower levels of phospholipids with 5-double bonds PUFA tails, reflecting differences in metabolizing these lipids. qPCR revealed increased expression of UPR genes: IRE1α, XBP1s, EDEM, ATF6, ATF4 and CHOP in the MASH/cirrhosis group compared to controls. Additionally, they had reduced FXR signaling with lower levels of FXR and SHP, although higher levels of Cyp27A1 and NTCP compared to controls. **Conclusion:** This study demonstrates that iPSC-hepatocytes derived from MASH/Cirrhosis patients recapitulate several disease-relevant features seen in the patients.

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Thus, they can serve as a valuable patient-specific ex-vivo platform to investigate disease mechanisms and enable high-throughput personalized drug-screening.

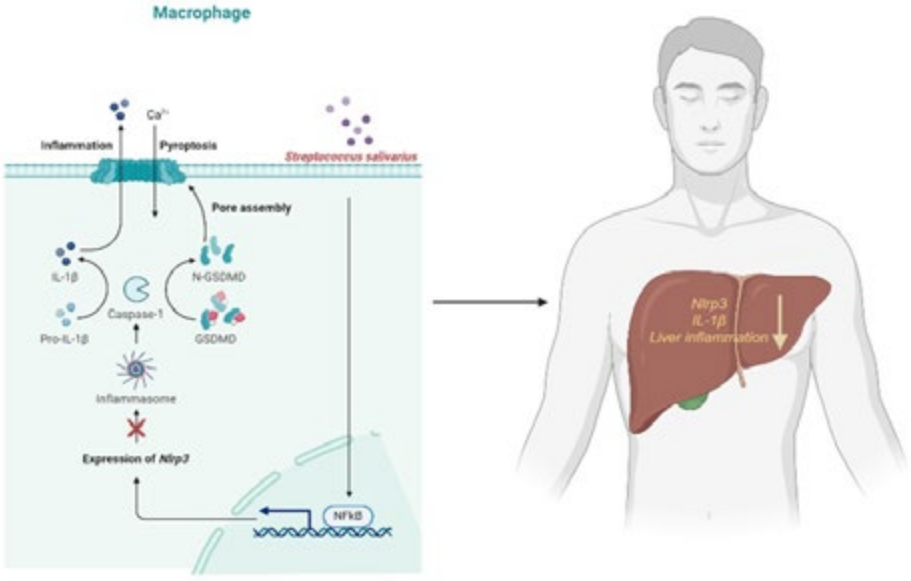
Disclosures: Ekta Minocha: Nothing to Disclose, Andrew Benintende: Nothing to Disclose, Ashwani Gupta: Nothing to Disclose, Nate Schmidt: Nothing to Disclose, John Purdy: Nothing to Disclose, Richard Green: Nothing to Disclose, Jason Wertheim: Nothing to Disclose

1088 | STREPTOCOCCUS SALIVARIUS MITIGATES METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE BY MODULATING NLRP3 INFLAMMASOME PATHWAY

JEONG SU KIM[1] seol hee Song[1] JeongHa Park[1] Young Seok Kwon[1] Dong Joon Kim[2]

[1]Hallym University College of Medicine, [2]Hallym University Medical Center

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is one of the most prevalent liver diseases worldwide. Definitive medical treatments have not been established apart from lifestyle modifications. There is a substantial body of research indicating an association between the microbiome and MASLD. Therapeutic strategies employing the microbiome for MASLD are emerging. This study aimed to demonstrate the role of gut microbiome in the MASLD and explore the effects of Streptococcus salivarius in the prevention of MASLD. **Methods:** To identify distinctive microbiota in MASLD, 76 patients' stools (healthy controls [HC, n=19], MASLD (n=16), MASH (metabolic dysfunction-associated steatohepatitis, n=24), and MASLD-associated cirrhosis (MAC, n=17) were analyzed by 16s-rRNA sequencing. To substantiate the effects of the identified strain from human data, six weeks old C57BL/6N mice were fed the Western diet with/without S. salivarius for 9 weeks (4 times/week) with a concentration of 1×109 CFU/day. We compared liver/body weight ratio (L/B ratio), NAFLD activity score (NAS), liver function tests, histopathology, fecal analysis, and markers for inflammation in the liver. **Results:** In the human microbiota analysis, the species abundance of S. salivarius increased in MAC group (HC; 0.2%, MASLD; 0.7%, MASH; 0.6%, and MAC; 1.6%). In the animal study, S. salivarius groups revealed significant improvement in liver enzymes (AST 78.3±8.6), L/B ratio (5.0±0.5), and NAS (2.6±1.4) compared with the Western diet group (AST 105.7±32.1; L/B ratio 5.6±0.5; NAS 5.8±1.5). S. salivarius supplementation significantly downregulated the expression of inflammation biomarkers (il-1β, nlrp3, gasdermin D and caspase1). **Conclusion:** S. salivarius supplementation ameliorates MASLD progression and dysbiosis through modulation of gut microbiota in improving hepatic inflammation and NLRP3 inflammasome pathway.



Disclosures: JEONG SU KIM: Nothing to Disclose, seol hee Song: Nothing to Disclose, JeongHa Park: Nothing to Disclose, Young Seok Kwon: Nothing to Disclose, Dong Joon Kim: Nothing to Disclose

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1089 | REPRODUCIBLE THERAPEUTIC EFFECTS OF SEMAGLUTIDE IN THE GAN DIET-INDUCED OBESE AND BIOPSY-CONFIRMED MOUSE MODEL OF MASH

Malte Nielsen[1] Henrik Hansen[1] Jacob Nøhr-Meldgaard[1] Susanne Pors[1] Michael Feigh[1]

[1]Gubra

Background: The glucagon-like-peptide (GLP)-1 analogue semaglutide is currently approved for the treatment of type 2 diabetes and obesity. Semaglutide has recently been reported to promote NASH resolution (Newsome et al., NEJM, 2020) and is currently in phase 3 clinical trial (ESSENCE) for NASH. The present study aimed to evaluate robustness of therapeutic outcomes following treatment with semaglutide in the translational GAN diet-induced obese (DIO) mouse model of biopsy-confirmed MASH and fibrosis. **Methods:** Semaglutide was characterized in 8 individual studies. C57BL/6JRj mice were fed the GAN diet high in saturated fat, fructose, and cholesterol for 34-40 weeks before treatment start. Only animals with biopsy-confirmed MASH (NAFLD Activity Score, NAS≥5) and fibrosis (stage ≥F1) were included, randomized and stratified into treatment groups. GAN DIO-MASH mice (n=14-18 per group) received semaglutide (30 nmol/kg, SC) or vehicle (Veh, SC) once daily for 12 weeks. Vehicle-dosed chow-fed controls served as healthy controls. Within-subject comparisons (pre- vs. post-treatment) were performed for NAS and fibrosis stage. Terminal quantitative endpoints included plasma/liver biochemistry and AI-based quantitative liver histology. **Results:** For all studies in GAN DIO-MASH mice, semaglutide consistently improved body weight, hepatomegaly, plasma transaminases and hypercholesterolemia. Semaglutide promoted a ≥2-point significant improvement in NAS, primarily driven by reduced steatosis. Benefits on NAS were supported by quantitative liver histology on steatosis (% lipid-laden hepatocytes) and inflammation (% area of galectin-3). Semaglutide had no effect on fibrosis score and fibrosis histomorphometry (% area of PSR, Col1a1) but improved α-SMA levels, a marker of fibrogenesis. **Conclusion:** Semaglutide consistently improved NAS as well as metabolic, biochemical and liver histological markers of steatosis, but not fibrosis, in the GAN DIO-MASH mouse. The highly reproducible therapeutic effects of semaglutide highlights the translatability, robustness and applicability of the GAN DIO-MASH mouse model in preclinical drug discovery.

Disclosures: Malte Nielsen: Nothing to Disclose, Henrik Hansen: Nothing to Disclose, Jacob Nøhr-Meldgaard: Nothing to Disclose, Susanne Pors: Nothing to Disclose, Michael Feigh: Nothing to Disclose

1090 | REPRODUCIBLE THERAPEUTIC EFFECTS OF RESMETIROM IN THE GAN DIET-INDUCED OBESE AND BIOPSY-CONFIRMED MOUSE MODEL OF MASH

Malte Nielsen[1] Michael Feigh[1] Jacob Nøhr-Meldgaard[1] Susanne Pors[1] Henrik Hansen[1]

[1]Gubra

Background: Resmetirom, a selective THR-β agonist, has been demonstrated to improve NAFLD Activity Score (NAS) and fibrosis stage in a recent phase-3 clinical trial (MAESTRO-NASH) in patients with metabolic dysfunction-associated steatohepatitis (MASH). FDA has recently granted accelerated approval of resmetirom (Rezdiffra®) as the first drug therapy for MASH with fibrosis. The present study aimed to evaluate robustness of therapeutic outcomes following treatment with resmetirom in the translational GAN diet-induced obese (DIO) mouse model of biopsy-confirmed MASH and fibrosis. **Methods:** Resmetirom was characterized in 6 individual studies. C57BL/6JRj mice were fed the GAN diet high in saturated fat, fructose, and cholesterol for 34-40 weeks before treatment start. Only animals with biopsy-confirmed MASH (NAS≥5) and fibrosis (stage ≥F1) were included and stratified into treatment groups. GAN DIO-MASH mice (n=15-18 per group) received resmetirom (3 mg/kg, PO) or vehicle (PO) once daily for 12 weeks. Vehicle-dosed chow-fed controls served as healthy controls. Within-subject comparisons (pre- vs. post-treatment) were performed for NAS and fibrosis stage. Terminal quantitative endpoints included plasma/liver biochemistry and AI-based quantitative liver histology. **Results:** For all individual studies in GAN DIO-MASH mice, resmetirom was weight-neutral and consistently improved hepatomegaly, plasma transaminases and hypercholesterolemia. Resmetirom promoted a ≥2-point significant improvement in NAS, primarily by reducing steatosis scores. Benefits on NAS were supported by quantitative liver histology on steatosis (% lipid-laden hepatocytes). Resmetirom had no effect on quantitative histological markers of inflammation (inflammatory foci, galectin-3). Resmetirom showed inconsistent effects on histological markers of fibrosis (fibrosis score, % area of PSR) and fibrogenesis (α-SMA). **Conclusion:** Resmetirom reproducibly improved metabolic, biochemical and liver histological

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markers in the GAN DIO-MASH mouse but showed no consistent effect on fibrosis. The highly reproducible therapeutic effects of resmetirom highlights the robustness and applicability of the GAN DIO-MASH mouse model in preclinical drug discovery. Extended treatment intervention may potentially be required to observe antifibrotic effects of resmetirom in the model.

Disclosures: Malte Nielsen: Nothing to Disclose, Michael Feigh: Nothing to Disclose, Jacob Nøhr-Meldgaard: Nothing to Disclose, Susanne Pors: Nothing to Disclose, Henrik Hansen: Nothing to Disclose

1091 | ESTROGEN-RELATED RECEPTOR-ALPHA PLAYS A ROLE IN ROS PRODUCTION BY REGULATING LIPID METABOLISM IN THE LIVER

Diala Alhousari[1] Dante Dikeman[2] Jingyu Chen[2] Chenxi Xu[2] Brittney Hua Hua[2] Ebony Flowers[2] Joshua Chen[2] Handan Hong[2] Lina He[2] Bangyan Stiles[2]

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Background: Estrogen-related receptor alpha (ERR) is an orphan nuclear receptor that is predominately expressed in the liver. ERR-alpha plays a critical role in regulating the expression of genes encoding mitochondrial complexes and metabolic enzymes involved in glucose and lipid metabolism. Our lab reported previously that ERR-alpha is regulated by PI3K/AKT signaling pathway and is responsible for the elevated oxidative oxygen species (ROS) associated with the activation of this pathway. **Methods:** To address the functional role of ERR-alpha, we developed a small molecule inhibitor for ERR-alpha (ERR-PA). In the mouse model (LiPten) of steatohepatitis (MASH), fibrosis, cirrhosis, and hepatocellular carcinoma established by the loss of phosphatase PTEN that negatively regulates PI3K/AKT signal. **Results:** In LiPten hepatocytes, we observed a decrease in lipid accumulation and lipid peroxidation products upon treatment with PA-ERR-alpha. To explore this phenotype further, we isolated hepatocytes from the LiPten livers and showed that PTEN loss induces both endogenous and exogenous fatty acid β-oxidation. This observed increase in fatty acid oxidation is due to the upregulation of fatty acid β-oxidation enzymes such as CPT1a, MCAD, and CACT, upon Pten deletion. We also observed increased ROS production in Pten-null hepatocytes compared to WT-hepatocytes. This suggests that Pten deletion led to elevated ROS by increasing exogenous fatty acid oxidation and uncoupling of mitochondria-mediated by fatty acids. To investigate the role of ERR-alpha in fatty acid oxidation, we utilized the genetic knockdown of shERR-alpha in Huh7 cell lines. We discovered that inhibiting ERR-alpha led to a reduction in exogenous fatty acid oxidation, but not in endogenous oxidation. **Conclusion:** This suggests that ERR-alpha plays a role in regulating fatty acid oxidation. To elucidate the role of ERR-alpha in fatty acid oxidation and ROS production regulated by the PTEN/AKT pathway, we are manipulating ERR-alpha in Pten-null hepatocytes. Furthermore, using chip-sequencing analysis, we are investigating the molecular mechanism of ERR-alpha regulation of fatty acid oxidation genes under various metabolic conditions. In summary, our study highlights the potential role of ERR-alpha on ROS production by regulating lipid metabolism.

Disclosures: Diala Alhousari: Nothing to Disclose, Dante Dikeman: Nothing to Disclose, Jingyu Chen: Nothing to Disclose, Chenxi Xu: Nothing to Disclose, Brittney Hua Hua: Nothing to Disclose, Ebony Flowers: Nothing to Disclose, Joshua Chen: Nothing to Disclose, Handan Hong: Nothing to Disclose, Lina He: Nothing to Disclose, Bangyan Stiles: Nothing to Disclose

1092 | NSRP70 DEFICIENCY WORSENS METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS BY REGULATING LIPOGENESIS

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Background: Nuclear speckle-related protein 70 (NSrp70) regulates alternative processing of various mRNA splicing factors. NSrp70 is known to be expressed in tissues related to immune function, and its role in breast cancer was recently reported. We aimed to investigate the impact of NSrp70 deficiency in metabolic dysfunction-associated steatohepatitis (MASH), a global liver disease for which no clear treatment has yet been reported.

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Methods: Conditional Knock-out mice, which can conditionally delete the NSrp70 gene only in hepatocytes using the Cre-loxP system, were used in this study. Mice were fed a western diet (WD; 40 kcal% fat, 20 kcal% fructose, and 2% cholesterol) and high fructose-glucose water ad libitum for 16 weeks to induce MASH. **Results:** Hepatocyte-specific NSrp70 deficiency significantly increased the liver/body weight ratio in mice, which was increased by WD intake. Level of alanine aminotransferase, an indicator of liver damage, was significantly increased in the WD-induced MASH model and worsened by NSrp70 deficiency. As a result of hematoxylin & eosin staining of liver tissue, it was confirmed that MASH-specific lesions such as microvesicular steatosis, lobular inflammation, and ballooning degeneration were worsened by the absence of NSrp70 in hepatocytes. These results were similarly confirmed in Terminal deoxynucleotidyl transferase dUTP nick end labeling staining, Oil Red O staining, and Sirius Red staining. Interestingly, NSrp70 deficiency in hepatocytes significantly regulated the expression of mRNA and proteins including acetyl-CoA carboxylase 1 and sterol regulatory element-binding protein 1 related with lipid synthesis. The total cholesterol level increased by WD intake was significantly increased by NSrp70 deficiency in hepatocytes. As a result of mRNA sequencing of liver tissue, it was confirmed that the expression of Cytochrome P450 46A1, which is known to regulate cholesterol expression in the brain, was decreased due to NSrp70 deficiency in hepatocytes. **Conclusion:** Hepatocyte-specific deficiency of NSrp70 exacerbated WD intake-induced MASH. In particular, the absence of NSrp70 in hepatocytes regulated the expression of factors that modulate lipid biosynthesis and the expression of CYP enzymes related to cholesterol metabolism. These results show that NSrp70 can be considered as a new target factor for MASH treatment.

Disclosures: Daram Yang: Nothing to Disclose, Hyuneui Jeong: Nothing to Disclose, Sang-Ik Oh: Nothing to Disclose, Bumseok Kim: Nothing to Disclose

1093 | UNRAVELLING MASLD HETEROGENEITY AT SINGLE CELL LEVEL IN THE SWITCHING TOWARDS PROGRESSIVE DISEASE

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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) embraces different conditions, including metabolic dysfunction-associated steatohepatitis (MASH), fibrosis, cirrhosis and hepatocarcinoma. The cellular abnormalities occurring in the different stages of MASLD as well as the processes which drives its evolution are not completely clarified. Therefore, we aimed to investigate cell population heterogeneity involved in progressive MASLD at single cell resolution, in the attempt to define the role of hepatic cell types in the disease transition. **Methods:** C57Bl6 male mice were fed standard or high fat high fructose (referred to Amylin liver NASH-AMLN) diets for 14 (steatosis), 22 (MASH) and 28 (MASH-fibrosis) weeks to resemble human MASLD. Single cell RNA-sequencing has been applied to decipher cell populations, cell differentiation and genes/pathways guiding MASLD progression. **Results:** Overall, 29753 single-cell transcriptomes across all MASLD stages were analyzed. By considering gene expression similarity and the canonical markers, we classified a total of 32 clusters (Cls), including hepatocytes (HEPs), hepatic stellate cells (HSCs), endothelial cells (Endo), Kupffer cells (KCs), and immune cells (Mo/MoMF, N, DCs, T, NKs, B cells). We observed changes in HEPs Cls across disease severity, with a mixed pericentral/periportal localization in steatosis and a periportal one in MASH and MASH-fibrosis, reflecting the advanced damage in this area. The latter conditions were featured by Endo Cls which induced the expression of vascular angiogenesis and ECM molecules whereas endothelial mesenchymal transition (EndMT) markers gradually appeared during the disease. Among KCs we found Cls of resident cells and others including immune cells recruited from the circulation with a M1 phenotype which increased throughout diet exposure. Regarding HSCs, MASH-fibrosis was featured by Cls with mesenchymal markers. Finally, among the 32 Cls, we identified 4 chimeric populations named HSCs/Endo (Cl 21), HEPs/Endo (Cl 15), KCs/Endo (Cl 26) and HEPs/KCs (Cl 10). Trajectory inference across cell clusters by exploiting RNA-velocity tool enabled to characterize the directions of cell differentiation, which was more pronounced in the MASH-fibrosis time point. **Conclusion:** In

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sum, we observed an evolution of cellular heterogeneity during MASLD and identified chimeric populations in the advanced stages thus suggesting their involvement in disease progression.

Disclosures: Paola Dongiovanni: Nothing to Disclose, Marica Meroni: Nothing to Disclose, Erika Paolini: Nothing to Disclose, Miriam Longo: Nothing to Disclose, MIchele Battistin: Nothing to Disclose, Paride Pelucchi: Nothing to Disclose, Alice Chiodi: Nothing to Disclose, Ada Sula: Nothing to Disclose, Elena Trombetta: Nothing to Disclose, Daniele Dondossola: Nothing to Disclose, Ettore Mosca: Nothing to Disclose, Stefano Gatti: Nothing to Disclose

1094 | HIGH FREQUENCY ULTRASOUND SHEAR WAVE ELASTOGRAPHY FOR PRECLINICAL LIVER INVESTIGATION: A PILOT STUDY ON AN OGT MOUSE MODEL

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Background: Measurement of stiffness in preclinical models is a key parameter to study tumor stoma development of liver pathologies, but in ultrasound (US) is still limited to dedicated clinical or research programmable scanners. Both systems do provide such information, but make it necessary to use a high-resolution US scanner for conventional preclinical measurements and then switch to a dedicated machine for elasticity measurement with poorer image resolution or specific methodological developments. Such limitations impair the use of shear wave elastography (SWE) imaging in preclinical studies when follow-up of large animal cohorts is needed. There is a need for an integrated solution combining conventional high-resolution imaging modes together with SWE imaging mode for the phenotyping of mouse models, more specifically in mouse models of liver fibrosis. **Methods:** *In vivo* experiments were carried out on a genetic mouse model of spontaneous liver fibrosis induced by constitutive hepatocyte-specific deletion of the gene coding for O-GlcNAc transferase (OGT^{LKO}), or its littermate as control (Ortega, J HEP Reports 2023). This model shows a progressive fibrosis initiated as early as 4 weeks with a maximum extent at 7-8 weeks. SWE non-invasive follow-up was performed and at end point histologic analysis was correlated with SWE. For SWE, experiments were conducted on an ultrafast high frequency US scanner (VevoF2, UHF29x array, Fujifilm Visualsonics). The elastography sequences were programmed trough the VADA option available on the VevoF2 to quantify shear modulus maps. Measurements were confronted to those obtained by using a reference SWE US imaging device (Aixplorer, SLH20-6 array, Supersonic Imagine). Expression of key genes of inflammation and fibrosis was measured by qPCR analysis. **Results:** Our results show that OGT^{LKO} mice present, as expected, a progressive increase in liver stiffness from weeks 4 to weeks 7 (Aixplorer: from 2.32±0.71 kPa to 3.39±1.33 kPa and, VevoF2: from 2.24±0.87 kPa to 2.77±0.88 kPa (mean over all mice)). It also shows a variable stiffness increase from one mouse to another, reflecting the biological variability associated to the model. Confrontation of the shear modulus quantified with both devices shows a very good correlation (Pearson 0.94, $p=5.8e^{-14}$). Confrontation with qPCR analysis of genes involved in inflammation and fibrosis confirmed increased levels in OGT KO mice. High resolution US images showed modifications of the liver structure with early detection and progressive development of regenerative nodules. **Conclusion:** These results show that SWE measurement of stiffness and high frequency US images can be integrated seamlessly in routine examination of mouse models of liver pathology in a single preclinical ultrafast US device. This extends the range of measurable parameters in pre-clinical routine allowing non-invasive follow-up of large cohorts of mouse models of liver pathology.

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1095 | NEW STEPS FORWARD IN LEARNING ABOUT THE USE OF DGAT1 AND DGAT2 INHIBITORS FOR METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD) MANAGEMENT: BENEFITS FOR THEIR SINGLE OR COMBINED APPLICATION

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Background: Restricted therapeutic options for MASLD remain a current challenge. Blocking DGAT1 and DGAT2 enzymes (i-DGAT1, i-DGAT2), involved in triglycerides (TG) synthesis, has shown a certain efficacy in reducing fat accumulation in clinical trials. However, their potential synergism in MASLD progressive forms has been poorly explored. Moreover, their use is limited by lipotoxic effects due to excessive release of free fatty acids (FFAs), not neutralized in TG structures or by mitochondrial (mt-) β-oxidation. We investigated i-DGAT1 and i-DGAT2 efficacy, alone or combined (i-DGAT1/2), on: 1) fat accumulation and hepatocellular damage in human HepG2 cells; 2) hepatic stellate cells (HSCs) activation, mediating fibrogenesis, by exploiting immortalized human LX2 cells. Then, we assessed if the addition of Mitoquinone mesylate (MitoQ) antioxidant to i-DGAT1/2 may empower their effects. **Methods:** Steatotic and MASH conditions were reproduced by exposing HepG2 cells to palmitic/oleic acids (PAOA) alone (steatotic medium), or combined to LPS, fructose and glucose (MASH medium). LX2 cells were treated with conditioned steatotic and MASH media for 24 hours. **Results:** i-DGAT1 and i-DGAT2 reduced lipid content and TG synthesis in HepG2 cells exposed to steatotic medium, showing the greatest efficacy when supplemented together. Markers of endoplasmic reticulum stress (ATF4, XBP1), oxidative damage (ROS, MDA) and inflammation (TNFα, IL6) were slightly decreased after i-DGAT1 or i-DGAT2 supplementation. Conversely, i-DGAT1/2 combination improved hepatocellular injury and enhanced the TCA activity, ATP synthase and total ATP production, thus resulting the best strategy to counteract cell damage and rescue mt-bioenergetics. In HepG2 cells exposed to MASH medium, which exacerbated hepatocellular damage compared to steatotic one, only the i-DGAT1/2 co-administration resulted effective in ameliorating TG synthesis, oxidative stress, and inflammation, with a parallel improvement of energetic balance. LX2 cells, challenged with steatotic/MASH media, showed less proliferative, contractile and migration capacity in response to i-DGAT1/2 drugs. MitoQ combined to i-DGAT1/2 reduced FFAs release, increased *PPAR-α* and *CPT1* mRNA levels, involved in β-oxidation, and improved cell viability. **Conclusion:** The combined use of i-DGAT1/2 improves fat accumulation, mt-activity and dampens fibrogenesis thus opening new perspectives for the treatment of MASLD and its severe manifestations.

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1096 | AKT ISOFORM SPECIFIC REGULATION OF HEPATIC STEATOSIS INDUCED BY BIOACTIVE LIPIDS

Mario Alba[1] Ielyzaveta Slarve[1] Qi Tang[1] Dante Dikemen[1] Jared Khan[1] Yiren Zhou[1] Yunyi Jia[1] Aditi Ashish Datta[1] Zixin Zong[1] Brandon Ebright[1] Elizabeth Elton[2] Whitaker Cohn[3] Taojian Tu[1] Handan Hong[1] Pranav Pammidimukkala[1] Phillip Nguyen[1] Lina He[1] Guo Zhang[1] Karam Ashouri[4] Anastasia Martynova[4] Christina Nakhoul[4] Jonathan Katz[2] Anthony El-Khoueiry[4] Julian Whitelegge[3] Stan Louie[1] Bangyan Stiles[1]

[1]USC Alfred E Mann School of Pharmacy, [2]Ellison Institute of Technology, [3]UCLA, [4]Division of Medical Oncology, Keck School of Medicine, Norris Comprehensive Cancer Center

Background: Despite the clinical advancement of immune checkpoint inhibitors, HCC median survival continues to be less than twenty months and most patients develop resistance. The rate of liver cancer continues to rise, which is coupled to the high prevalence of steatosis and steatohepatitis in the general population. Pathologically, 80% of liver cancer occurs in patients with an underlying liver disease that displays liver steatosis. Thus, it is paramount to better characterize the transition from steatosis to HCC. **Methods:** Utilizing a PTEN genetic knockout model that recapitulates HCC progression, protein and lipid fractions were analyzed. Global untargeted differential proteomics was done using a nano-LC-MS/MS qExactive. Targeted lipidomics of eicosanoids was done using a Sciex QTRAP. Genetic k/o hepatocyte cell lines of each AKT isoform and PTEN-AKT isoform specific double genetic k/o mice were also generated and subjected to the same workflow. Immunotherapy treated recurrent human HCC patient serum was analyzed using our lipidomic workflow. **Results:** The PTEN regulated PI3K/AKT signal is induced in 54% of all liver cancers and represents the dominant signaling pathway

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regulating liver cancer progression. To understand the molecular signals driving the progression from steatosis to HCC, we performed untargeted differential proteomics to analyze the changes in protein expression longitudinally throughout disease progression from a PTEN k/o model. Our analysis revealed significant dysregulation in eicosanoid metabolism among the top enriched pathways when the phenotype progressed from steatosis to HCC. To validate these initial proteomic findings agnostic of PTEN deletion, patient data was analyzed using the NCI Proteomic Data Commons and found to also be consistent. Our analysis using targeted lipidomics further validates significant increases in prostaglandin synthesis and decreases in resolving metabolism during disease progression. Phosphoproteomic analysis of AKT isoform specific genetic k/o hepatocytes revealed distinct signaling cascades regulating eicosanoid metabolism. Proteomic and lipidomic analysis of double k/o PTEN-AKT isoform specific mice further validated isoform specific regulatory roles in eicosanoid metabolism and steatosis. Analysis of immunotherapy treated recurrent HCC patient serum also revealed correlations between resolving eicosanoid metabolite levels and stable disease duration. **Conclusion:** Multiomic analysis reveals significant dysregulation of eicosanoid metabolism in liver disease progression as the balance between pro-resolving and pro-inflammatory eicosanoid synthesis is lost. Hepatic eicosanoid biosynthesis is AKT isoform specific in regulation. Higher levels of resolving eicosanoid metabolites are associated with increased duration of stable disease in immunotherapy treatment, demonstrating the clinical significance of these bioactive lipids.

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1097 | TREATMENT WITH THE CCR2/CCR5 ANTAGONIST CENICRIVIROC DOES NOT AFFECT MASH AND FIBROSIS DEVELOPMENT IN LDLR-/-.LEIDEN MICE, TRANSLATIONAL TO CLINICAL PHASE 3 TRIAL RESULTS

Martine Morrison[1] Eveline Gart[1] Wim van Duyvenvoorde[1] Jessica Snabel[1] Aswin Menke[1] Anita van den Hoek[1] Robert Kleemann[1]

[1]TNO Metabolic Health Research

Background: Cenicriviroc (CVC) is a dual CCR2/CCR5 antagonist that was developed for the treatment of metabolic dysfunction-associated steatohepatitis (MASH) and associated fibrosis. While it showed antifibrotic potential in the phase 2B CENTAUR trial, the phase 3 AURORA trial was terminated at the 1-year interim analysis due to lack of efficacy on improvement of fibrosis. In contrast with these results in humans, many preclinical studies have shown anti-inflammatory and anti-fibrotic efficacy of CVC – which brings into question the translational value of these models for human MASH. Here we studied the effects of CVC treatment in the Ldlr-/-.Leiden mouse model for obesity-associated MASH and liver fibrosis, to investigate if this model can more accurately predict treatment effects in MASH patients. **Methods:** Male Ldlr-/-.Leiden mice were fed a MASH and fibrosis-inducing high-fat diet (HFD) for 20 weeks, after which the 14-week treatment with CVC (20 mg/kg BW, provided as dietary admix) was started in one group of mice (HFD+CVC) and another group of mice was kept on HFD as an untreated control. A chow-fed group was included as an aging reference. All mice were terminated at t=34 weeks for histological and biochemical analysis of MASH and fibrosis development as well as analysis of MASH and fibrosis-related biomarkers. Target engagement was assessed by measurement of plasma levels of CCR2 and CCR5 ligands. **Results:** Twenty weeks of HFD feeding induced obesity, hyperinsulinemia and atherogenic hyperlipidemia with increased plasma LDL cholesterol and triglyceride levels relative to chow. CVC treatment showed target engagement as observed in clinical trials. Treatment with CVC did not affect body weight or food intake. CVC significantly lowered fasting blood glucose with a concomitant increase in plasma insulin towards the end of the study. Fasting plasma cholesterol was not affected by CVC treatment while fasting plasma triglycerides were significantly increased. Histologically, CVC treatment did not affect macrovesicular or microvesicular steatosis in the liver. In addition, CVC had no effect on hepatic

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inflammation or fibrosis as measured histologically. This lack of anti-fibrotic effect was further corroborated by biochemical analysis of hepatic collagen content and the plasma markers PIIINP, TIMP-1 and CK18-M30, none of which were reduced by CVC treatment. **Conclusion:** While many preclinical models have shown efficacy of CVC that contrasts clinical observations, CVC treatment (at a translational dose that did show efficacy in other preclinical models) in the HFD-fed Ldlr-/-.Leiden mouse did not reduce hepatic fibrosis – in line with the outcome of the phase 3 AURORA trial. These findings underline the importance for validation of preclinical MASH models not only with treatments that have been found to have clinical efficacy, but also with treatments that have failed clinically.

Disclosures: Martine Morrison: Nothing to Disclose, Eveline Gart: Sagimet: Independent Contractor, Mead Johnson: Independent Contractor, Wim van Duyvenvoorde: Nothing to Disclose, Jessica Snabel: Nothing to Disclose, Aswin Menke: Nothing to Disclose, Anita van den Hoek: ProQR: Independent Contractor, Yoxlo: Independent Contractor, E-Therapeutics: Independent Contractor, Abbott: Independent Contractor, Amarin Corporations: Independent Contractor, Enveda Biosciences: Independent Contractor, NorthSea Therapeutics: Independent Contractor, Calico: Grant/Research Support, Reckitt: Grant/Research Support, Robert Kleemann: Nothing to Disclose

1098 | LIVER FIBROSIS INDUCED BY CDAHFD AND SURFACTANT POLYSORBATE 80

Masaki Yamamoto[1] Ryo Tofukuji[1] Keiko Iwaisako[2]

[1]Graduate School of Life and Medical Sciences, Doshisha University, [2]Faculty of Life and Medical Sciences, Doshisha University

Background: The incidence of metabolic steatohepatitis has increased worldwide in recent years. However, the mechanisms underlying the progression from simple steatosis to steatohepatitis, fibrosis and cirrhosis remain unclear. To elucidate this pathological mechanism and to develop therapeutic strategies, a mouse model with characteristics similar to human metabolic dysfunction-associated steatohepatitis (MASH) is needed. The problems with previously used diet-induced mouse models are that they require a long period of time (20 weeks or more) to generate and that they show only mild fibrosis. To overcome these problems, we focused on the possibility that the complication of enteritis or colitis may exacerbate steatohepatitis and attempted to induce enteritis or colitis in a diet (choline-deficient, L-amino acid-defined, high-fat diet: CDAHFD)-induced steatohepatitis model by administering polysorbate 80, a surfactant widely used as a food emulsifier. **Methods:** Male 8-week-old BALB/c mice were treated with CDAHFD and 1%, 2%, and 5% polysorbate 80 water for 4 weeks; body weights were measured weekly, and liver, intestine, and peripheral blood samples were collected after 4 weeks. Livers and intestines were subjected to histopathological analysis. Liver fibrosis was quantified by image analysis with Sirius Red staining. Plasma biochemical analysis and insulin quantification were performed. **Results:** Administration of CDAHFD and 5% polysolabate 80 was discontinued after 1 week because of watery diarrhea and weight loss of -6.2 ± 2.6%. In contrast,CDAHFD and 1% or 2% Polysolabate 80 showed little weight loss, and after 4 weeks, CDAHFD and 2% Polysolabate 80 showed liver fibrosis along with lymphocyte infiltration and ballooning. Fecal water content tended to be higher than in the control group, but there was no intestinal mucosal sloughing and limited intestinal inflammation. **Conclusion:** Feeding CDAHFD and polysorbate 80 water to BALB/c mice induced liver fibrosis in a shorter period (4 weeks) than in the conventional CDAHFD alone model. In addition, the mice consistently gained weight without weight loss, a result consistent with the characteristics of weight changes in human MASH. Peripheral blood liver enzymes were elevated (300-700 IU/L) and histopathology showed hepatitis. The combination of a high-fat diet and polysorbate 80, used as a food emulsifier, induces steatosis and hepatic fibrosis more rapidly than conventional diet-induced fatty liver models and may be useful in MASH research.

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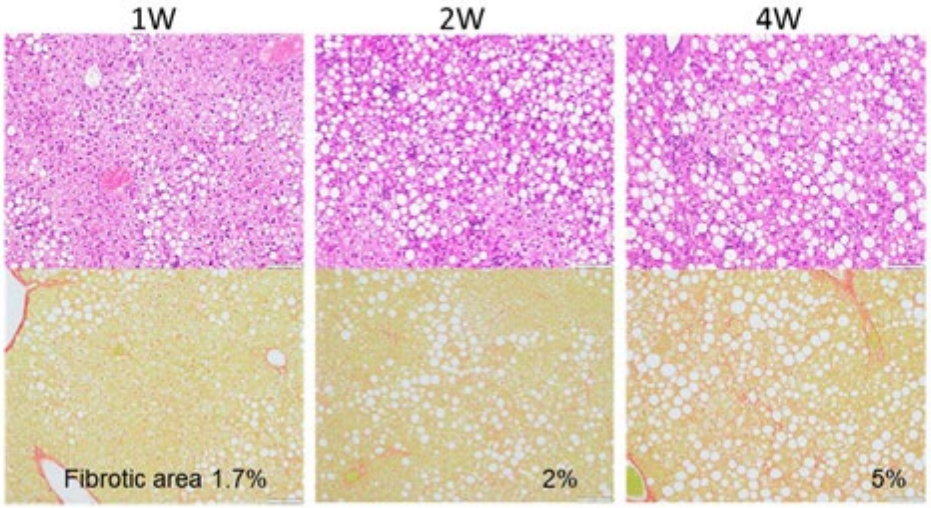
Histological changes in the liver induced by 2% Polysorbate 80 and CDAHFD



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1100 | HIGHLY SENSITIVE METABOLIC FLUX ANALYSIS USING 14C-MICROTRACERS COMBINED WITH ACCELERATOR MASS SPECTROMETRY - A PROOF OF CONCEPT STUDY ON *DE NOVO* LIPOGENESIS

Martine Morrison[1] Lianne Stevens[1] Robert Kleemann[1] Elwin Verheij[1] Wouter Vaes[1]

[1]TNO Metabolic Health Research

Background: Metabolic flux measurements play an important role in advancing our understanding of (patho) physiology, disease mechanisms and the development of new therapeutics. By incorporating stable or radioactive isotopes into specific molecules (tracers), the distribution and fate of the isotope can be followed – thereby providing insight into the movement and metabolic transformation of biomolecules. An isotope that is frequently used for such analyses is ^{13}C, which is analysed by isotope ratio mass spectrometry. The high natural abundance of ^{13}C (~1%) requires the use of large amounts of labelled substrates, especially in clinical studies. An alternative isotope is ^{14}C, which has an extremely low natural abundance (1 in 10^{12}). In combination with analysis by extremely sensitive accelerator mass spectrometry (AMS), this enables the detection of very small amounts of ^{14}C-labeled product/biomarker formed at very low (microtrace) amounts of labelled substrate administration. Here we provide proof of concept for this ^{14}C microtracer approach to assess activity of the de novo lipogenesis (DNL) pathway, an important metabolic pathway that is deregulated in various disease states, including metabolic dysfunction-associated steatotic liver disease (MASLD). **Methods:** De novo lipogenesis activity was assessed in Ldlr-/-.Leiden MASLD mice fed a standard chow or a MASH-inducing high-fat diet (HFD) with/without the DNL inhibitor firsocostat (ACCi), as well as in an ex vivo porcine liver perfusion model. Incorporation of ^{14}C from ^{14}C-acetate into total lipid extracts (from plasma and liver samples), bile, fatty acids and cholesterol was assessed by LC/MS and AMS. **Results:** Using this method, we show that DNL activity is significantly higher in HFD-fed Ldlr-/-.Leiden MASH mice than in chow-fed controls. This is demonstrated by increased incorporation of ^{14}C into total lipid extracts, which we confirmed to be DNL by demonstrating incorporation into fatty acids profiled by LC/MS. Treatment with the DNL inhibitor firsocostat significantly reduced DNL activity as expected. In the ex vivo liver perfusion model we similarly demonstrate that ^{14}C from acetate is incorporated into total lipids and fatty acids. In addition, we show in this model that this method can also be used for assessment of de novo synthesised cholesterol using the same labelling protocol. **Conclusion:** We show here that this ^{14}C microtracer approach combined with AMS analysis can be used for assessment of metabolic fluxes in various experimental models at much lower amounts of tracer used than in conventional tracer methodologies. This allows study of

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metabolic pathways without disrupting the pathway of interest by adding large quantities of precursor and opens up opportunities to study the activity of other (metabolic) pathways in which only very small amounts of product are produced.

Disclosures: Martine Morrison: Nothing to Disclose, Lianne Stevens: Nothing to Disclose, Robert Kleemann: Nothing to Disclose, Elwin Verheij: Nothing to Disclose, Wouter Vaes: Nothing to Disclose

1101 | HEPATOPROTECTIVE EFFECTS OF LONGER-TERM TREATMENT INTERVENTION WITH SEMAGLUTIDE AND TIRZEPATIDE IN THE GAN DIET-INDUCED OBESE AND BIOPSY-CONFIRMED MOUSE MODEL OF MASH

Jacob Nøhr-Meldgaard[1] Michael Feigh[2] Susanne Pors[1] Tobias Kroon[3] Anna Lindblom[3] Henrik Hansen[1] Linnea Österberg[3]

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Background: Semaglutide (glucagon-like peptide-1 receptor (GLP-1R) agonist) and tirzepatide (GLP-1R and glucose-dependent insulinotropic polypeptide (GIP) receptor co-agonist) are both in late-stage clinical development for the treatment of metabolic dysfunction-associated steatohepatitis (MASH). The present study aimed to compare metabolic, biochemical and histopathological effects of semaglutide and tirzepatide longer-term monotherapy in the translational Gubra Amylin NASH (GAN) diet-induced obese and biopsy-confirmed mouse model of MASH with liver fibrosis. **Methods:** Male C57BL/6 mice were fed the GAN diet high in fat, fructose and cholesterol for 34 weeks prior to study start. A liver biopsy was sampled 4 weeks before treatment start. Only GAN DIO-MASH mice with biopsy-confirmed NAFLD Activity Score (NAS≥5) and fibrosis stage ≥F1 were included and stratified into treatment groups (n=18 per group). Mice were administered (QD) vehicle (SC), semaglutide (10 nmol/kg, SC) or tirzepatide (10 nmol/kg, SC) for 16 weeks. Histopathological pre-to-post individual assessment of NAS and fibrosis stage was performed. Other terminal endpoints included quantitative liver histology, blood and liver biochemistry. **Results:** GAN DIO-MASH mice demonstrated robust weight loss after semaglutide (17%) and tirzepatide (25%) monotherapy. Treatments equally improved adiposity, hepatomegaly, plasma transaminases, plasma total cholesterol and plasma/liver triglyceride levels. Both semaglutide and tirzepatide promoted a ≥2-point significant improvement in NAS. Whereas tirzepatide demonstrated greater efficacy on steatosis scores, only semaglutide significantly improved lobular inflammation scores. Benefits on NAS were supported by quantitative liver histology on steatosis (% lipid-laden hepatocytes, lipid droplet size) and marker of inflammation (galectin-3). Treatments did not improve fibrosis stage, however reduced total levels of fibrosis histological markers (PSR, and collagen 1a1) and fibrogenesis (α-SMA) as well as total hydroxyproline content. **Conclusion:** Semaglutide and tirzepatide longer-term monotherapy markedly improved metabolic, biochemical, and histopathological parameters in addition to NAFLD Activity Score in the translational GAN DIO-MASH mouse model.

Disclosures: Jacob Nøhr-Meldgaard: Nothing to Disclose, Michael Feigh: Nothing to Disclose, Susanne Pors: Nothing to Disclose, Tobias Kroon: Nothing to Disclose, Anna Lindblom: AstraZeneca R&D: Employee, AstraZeneca R&D: Employee, Henrik Hansen: Nothing to Disclose, Linnea Österberg: Nothing to Disclose

1102 | SYNERGISTIC HEPATOPROTECTIVE EFFECTS OF SEMAGLUTIDE AND RESMETIROM COMBINATION THERAPY IN THE GAN DIET-INDUCED OBESE AND BIOPSY-CONFIRMED MOUSE MODEL OF MASH

Jacob Nøhr-Meldgaard[1] Sanne Veidal[2] Jenny Norlin[2] Line Wendt Nilsson[1] Henrik Hansen[1] Michael Feigh[3] Malte Nielsen[1]

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Background: Semaglutide (glucagon-like receptor-1 (GLP-1R) agonist) and resmetirom (THR-β receptor agonist) are both in late-stage clinical development for treatment of metabolic dysfunction-associated steatohepatitis (MASH). The present study aimed to compare metabolic, biochemical, and histological effects of semaglutide and resmetirom as mono- and combination treatment in a translational GAN diet-induced obese and biopsy-confirmed mouse model of MASH with liver fibrosis. **Methods:** C57BL/6JRj mice were fed the GAN diet high in saturated fat,

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fructose, and cholesterol for 38 weeks before treatment start. Only animals with biopsy-confirmed MASH (NAFLD Activity Score, NAS≥5) and moderate fibrosis (stage ≥F2) were included and stratified into treatment groups. GAN DIO-MASH mice (n=17-18 per group) received vehicle (SC), semaglutide (30 nmol/kg, SC), resmetirom (3 mg/kg, PO) or resmetirom (3 mg/kg, PO) + semaglutide (30 nmol/kg, SC) once daily for 12 weeks. Vehicle-dosed (SC) chow-fed controls (n=10) served as healthy controls. Within-subject comparisons (pre- vs. post-treatment) were performed for NAS and fibrosis stage. Terminal quantitative endpoints included plasma/liver biochemistry and quantitative liver histology. **Results:** While resmetirom was weight-neutral, semaglutide significantly reduced body weight (28%) and combination treatment led to further weight loss (37%) in GAN DIO-MASH mice. Both monotherapies and combination treatment reduced plasma transaminases and plasma/liver markers of inflammation (MCP-1) and fibrogenesis (TIMP-1). Combination treatment improved hepatomegaly and liver lipid levels greater than individual monotherapies. NAS (pre-post) was significantly improved by semaglutide (≥2-point, 28% of mice) and resmetirom (≥2-point, 17% of mice) and combination treatment led to synergistic reductions in NAS (≥2-point, 71% of mice) largely driven by improved steatosis scores, being further supported by quantitative histology. Only semaglutide significantly reduced quantitative histological markers of inflammation (galectin-3) and fibrogenesis (α-SMA). Treatments did not improve fibrosis stage and quantitative histological markers of fibrosis (PSR, Col1a1). **Conclusion:** Both semaglutide and resmetirom improve biochemical and histological hallmarks of MASH in GAN DIO-MASH mice. Further therapeutic benefits are achieved by combination treatment, demonstrating the feasibility of combined stimulation of GLP-1R and THR-β receptor function to improve outcomes in MASH.

Disclosures: Jacob Nøhr-Meldgaard: Nothing to Disclose, Sanne Veidal: Nothing to Disclose, Jenny Norlin: Novo Nordisk: Employee, Novo Nordisk: Stock - publicly traded company, Line Wendt Nilsson: Nothing to Disclose, Henrik Hansen: Nothing to Disclose, Michael Feigh: Nothing to Disclose, Malte Nielsen: Nothing to Disclose

1103 | TREATMENT WITH RETINOIC ACID IMPROVES DIET-INDUCED MASLD IN MALE MICE

Katharina Burger[1] *Anja Baumann*[1] *Annette Brandt*[1] *Ina Bergheim*[1]

[1]*University of Vienna*

Background: Studies suggest that vitamin A (retinol, ROH) metabolism is altered in livers affected by metabolic dysfunction-associated steatotic liver disease (MASLD). Moreover, the activity of alcohol dehydrogenase (ADH), being not only the key enzyme in ethanol elimination but also critical in the oxidation of retinol to retinal, has been shown to be lower in livers of MASLD patients. Starting from this background, the aim of the present study was to investigate whether an impact of impaired hepatic ADH activity is related to a lower bioavailability of retinoic acid (RA) in mice with MASLD and if supplementing RA may improve a pre-existing diet-induced MASLD in mice. **Methods:** Male C57BL/6J mice (6-8 weeks old) were fed ad libitum a control (C) or sucrose-, fat- and cholesterol-rich diet (SFC) for 8 weeks to induce early signs of metabolic dysfunction-associated steatohepatitis. Some mice (n=3-4) received once orally ROH (50 mg/kg bw) or vehicle and were killed 1, 2 and 4 hours thereafter, while others (n=7-8) being continually fed the respective diet were then treated with RA (15 mg/ kg bw) or vehicle for 10 days. Glucose tolerance was assessed 3 days prior to sacrifice. Markers of liver damage and inflammation, TLR4 ligands in portal plasma as well as hepatic ADH activity and RA levels were determined. **Results:** The significantly lower ADH activity in liver tissue was related to lower RA levels in mice with diet-induced MASLD. Moreover, synthesis of RA was also significantly lower in SFC-fed mice compared to C-fed animals. In SFC-fed mice treated with RA for 10 days signs of inflammation i.e., numbers of neutrophils and numbers of Ly6G positive cells of SFC-fed mice were significantly lower compared to SFC-fed mice treated with vehicle. The 10-day treatment with RA had no effect on fat and triglyceride accumulation in livers of SFC-fed mice. Furthermore, while concentration of TLR4 ligands in portal plasma were unaffected by the RA treatment, NO_x concentration in liver tissue was significantly lower in SFC-fed mice treated with RA compared to SFC-fed mice treated with vehicle. **Conclusion:** Taken together, results of the present study suggest that a treatment with retinoic acid abolished inflammatory alterations in the development of MASLD and that the impaired ADH activity herein also plays a role in vitamin A metabolism.

Disclosures: Katharina Burger: Nothing to Disclose, Anja Baumann: Nothing to Disclose, Annette Brandt: Nothing to Disclose, Ina Bergheim: Nothing to Disclose

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1104 | LIVER-SPECIFIC CAPN4 KNOCKDOWN PROTECTS THE LIVER FROM DIET-INDUCED MASH IN MICE

Jiang Li[1] Charis-Marie Vanderpuye[2] Pooja Muddasani[1] Sudrishti Chaudhary[1] Sam Taborski[1] Lorien Walker[1] Juliane Beier[1] Ian Sipula[1] Michael Jurczak[1] Michael Merchant[3] Gavin Arteel[1]

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Background: The pattern of degraded proteins in plasma samples from experimental and human MASH fibrosis has been shown to differ dramatically from healthy livers; informatic analysis suggested that robust elevated calpain-mediated cleavage of target proteins was involved in the pathogenic process of MASH fibrosis (PMID: 36778394). Calpain proteases, with Calpain 1/2 being the most ubiquitous isoforms, are activated by stress and Ca2+ overload. They are implicated in tissue remodeling and disease models in other organs and have not been thoroughly investigated in MASH. The purpose of the current study was to investigate the impact of liver-specific targeted disruption of hepatic Calpain 1/2 activity in a preclinical mouse model of MASH. **Methods:** 4 wks old C57Bl6/J mice were injected with recombinant adeno-associated virus type 8 vectors (rAAV8; 1×1011 PFU/mouse, i.v.) encoding shRNA against Capn4 (Capns1) driven by albumin promoter, or control scrambled rAAV8 vectors. After 4 wks, mice were fed ad libitum either a low-fat control diet (CD: 13% saturated fat) or a 'Western'-style high-fat, high-fructose diet (WD: 42% saturated fat) for 12 wks. Liver tissue portions were frozen immediately in liquid nitrogen or preserved for FFPE or frozen tissue sectioning. Major endpoints were assessed by histology, biochemical analyses and/or gene expression. **Results:** rAAV8-mediated liver-specific knockdown of Capn4 mediated a robust and stable suppression of hepatic Capns1 expression. As expected, WD caused obesity and insulin resistance (HOMA-IR) under these conditions. WD also caused severe fatty liver, as determined by histological assessment and biochemical analysis. Interestingly, knocking down Capn4 significantly delayed body weight gain and fat deposition at the 6 wks timepoint. Knocking down hepatic Capn4 also attenuated liver damage caused by 12 weeks WD feeding, as indicated by biochemical and histological assessment. **Conclusion:** Taken together, these results indicate that blocking calpain activity by targeting a key regulatory protein (Capn4) protects against liver damage caused by WD, in part by against the development of hepatic inflammation. Moreover, these results suggest a loss-of-function Capn4 impairs MASH initiation rather than progression and attenuates whole body adiposity. These data indicate that hepatic Capn1/2 activity is critically associated with the development of MASH. Supported, in part by, P30 DK120531 and R01 DK130294.

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1105 | UNDERSTANDING HOW HMGCS2-DERIVED KETONE BODY METABOLITES IMPACT MASLD PROGRESSION ◆

Jessica Shay[1] Constantine Tzouanas[2] Marc Sherman[1] Wolfram Goessling[1] Alex Shalek[2] Omer Yilmaz[3]

[1]Massachusetts General Hospital, [2]Broad Institute of MIT and Harvard, [3]Koch Institute for Integrative Cancer Research at MIT

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is becoming a leading cause of liver disease, contributing to cirrhosis, hepatocellular carcinoma and the need for liver transplantation. Our understanding of how diet and nutritional metabolites influence hepatocyte biology and tissue dysfunction remains incomplete. **Methods:** C57BL/6 mice maintained on an obesogenic high-fat diet (HFD) for six months develop obesity, insulin resistance, hypercholesterolemia, and evidence of steatosis. When maintained on HFD for 12 and 15 months, mice develop features of steatohepatitis/fibrosis and HCC, respectively. To understand longitudinal adaptations to chronic metabolic stress, we performed immune-biased live tissue single-cell RNA sequencing (scRNA-seq) and epithelial-biased frozen tissue snRNA-seq for HFD and control diet (CD) mice at each timepoint (6M, 12M, 15M) to identify key modulators of hepatocyte dysregulation during longitudinal adaptation to chronic nutrient-driven stress. **Results:** Initial analysis identified four expression programs that encompassed temporally coordinated gene expression in response to diet-induced metabolic stress. As part of the *Longitudinal Decrease*

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program, progressive decreases in 3-hydroxy-3-methylglutaryl-CoA synthetase 2 (HMGCS2), the rate-limiting enzyme of ketogenesis. *Hmgcs2* is upregulated at six months but progressively downregulated at 12 and 15 months. Similar findings are seen when interrogating nascent single nucleus RNA sequencing (snRNA-seq) from human liver samples across the spectrum of MASLD. To study this further, we crossed Albumin-Cre mice (Jackson Laboratory #003574) to Hmgcs2$^{fl/fl}$ mice (created in-house). These mice are born in expected Mendelian ratios without any obvious growth defects. A 24-hour fast strongly induces fatty acid oxidation and ketone body production in adult mice; however, hepatocyte-specific loss of HMGCS2 eliminates fasting-induced increases in circulating ketone bodies. To investigate the effects of HMGCS2 loss on liver adaptations under chronic metabolic stress, we conducted snRNA-seq at the 6-month timepoint across HMGCS2 genotypes and diet conditions (N = 8 mice, n = 27,119 cells). To understand how loss of HMGCS2 influences hepatocyte phenotypes, we mapped gene expression profiles of WT and HepKO hepatocytes to the natural progression of chronic metabolic stress. Loss of HMGCS2 associated with over twice as many hepatocytes mapped to the 12-month HFD condition (63%) as to the 6-month HFD condition (30%). **Conclusion:** We identified the rate-limiting enzyme in ketogenesis, HMGCS2, as a critical metabolic modulator of progressive hepatocyte dysfunction in a longitudinal mouse model of HFD exposure and nutrient-driven chronic stress. Future work will focus on assessing how HMGCS2-mediated metabolic flux and ketone body metabolites influence hepatocyte responses to chronic nutrient stress.

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1106 | TOLL-LIKE RECEPTOR LIGANDS PATTERN IN ALCOHOL-RELATED LIVER DISEASE AND METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE PATIENTS

Raphaela Staltner[1] Katharina Staufer[2] Michael Trauner[3] Sebastian Mueller[4] Ina Bergheim[1]

[1]University Of Vienna, [2]GENFIT, [3]Medical University of Vienna, [4]University of Heidelberg

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) and alcohol-related liver disease (ALD) are two of the world's leading liver diseases. Alteration of intestinal microbiota composition and intestinal barrier dysfunction and subsequently an increased translocation of pathogen-associated molecular patterns and the induction of certain Toll-like receptors (TLRs) in the liver have been related to the development of both diseases. Here, we determined and compared TLR ligand patterns (= 'ligandomics') in ALD and MASLD patients. **Methods:** Fasting blood samples were obtained from 20 ALD patients (age 50 ± 3 years) and from 12 age-matched healthy controls (age 48 ± 2 years). ALD was diagnosed by ultrasound and Fibroscan. In addition, fasting blood was collected from MASLD patients (n= 33, age 48 ± 3 years) and age-matched healthy controls (n= 20, age 49 ± 3 years). MASLD was diagnosed by ultrasound and liver biopsy, respectively. Concentration of TLR1-9 ligands (TLR2-1: TLR1 in combination with TLR2 and TLR2-6: TLR6 in combination with TLR2) in the serum samples of both studies were measured using SEAP reporter HEK293 cell-based assays which are activated by ligands. **Results:** In serum of ALD patients, concentrations of all TLR ligands (TLR1-9) were significantly higher compared to age-matched healthy controls. Furthermore, activity of alanine aminotransferase was significantly positive related with TLR4, TLR5 and TLR7 ligand concentrations in ALD patients. In contrast, in MASLD patients, concentration of TLR1, TLR2, TLR4, TLR5 as well as TLR6 ligands were significantly higher compared to healthy controls, while concentrations of TLR3, TLR8 and TLR9 were at the level of controls. **Conclusion:** In summary, **Results:** of our data suggest that in both ALD and MASLD patients several TLR ligands besides TLR4 (= bacterial endotoxin) are higher than in controls but that the blood TLR 'ligandom' may markedly differ between ALD and MASLD patients.

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Teaching, Falk: Speaking and Teaching, Gilead: Speaking and Teaching, Intercept: Speaking and Teaching, Ipsen: Speaking and Teaching, Madrigal: Speaking and Teaching, MSD: Speaking and Teaching, Medical Universities of Graz and Vienna: Co.Inventor of patents for medical use of norUDCA filed by, Genentech: Grant/Research Support, Sebastian Mueller: Nothing to Disclose, Ina Bergheim: Nothing to Disclose

1107 | TENOFOVIR DISOPROXIL FUMARATE REDUCES HEPATIC DE NOVO LIPOGENESIS BY DOWNREGULATING THE CHREBP/SCD1 PATHWAY

Jing Tang[1] Zhiwei Chen[1] Yan Han[1] Peng Hu[1]

[1]Second Affiliated Hospital, Chongqing Medical University

Background: Tenofovir disoproxil fumarate (TDF) is a first-line antiviral agent for the treatment of HBV and HIV infections. Previous clinical studies have demonstrated that TDF exerts beneficial effects on lipid profiles in patients with HBV or HIV infections; however, the underlying mechanisms remain incompletely elucidated. **Methods:** TDF, with or without free fatty acids, were administered to L02, HepG2, HepG2.2.15, and AD38 cells for a duration of 48 hours. The presence of hepatocyte lipid deposition was assessed through oil red O staining, while triglyceride (TG) levels were quantified using ELISA. C57BL/6 mice received TDF treatment at a dosage of 45.5 mg/kg/day for a period of four months. RNA-Seq and metabolomics analysis were conducted on the liver samples to investigate the impact of TDF on lipid metabolism. The expression levels of key adipogenic genes were determined using qRT-PCR and western blotting. **Results:** The lipid droplet and TG levels were significantly reduced in both TDF-treated L02 and HepG2 cells. FFA-treated HepG2.2.15 and AD38 cells exhibited excessive lipogenesis and TG secretion, whereas TDF-treated HepG2.2.15 and AD38 cells showed decreased lipogenesis and TG secretion. Additionally, we observed a significant decrease in several fatty acids, including adipic acid, ricinoleic acid, DHA, and EPA, in mice (all $P<0.05$). RNA-Seq analysis revealed the downregulation of hepatic de novo lipogenesis pathway genes (ACC, FAS, and SCD1) in TDF-treated mice. And then we verified these key genes in all four cell lines, and found that the mRNA and protein expression levels of SCD1 were downregulated in TDF treated groups, regardless of FFA status. The intracellular TG content exhibited a significant increase in the TDF-treated groups following SCD1 overexpression. Further screening of upstream molecules, we identified a dramatic decrease in ChREBP, a critical transcription factor regulating lipogenesis, in TDF-treated groups. **Conclusion:** TDF may improve the lipid profile by down-regulation of the ChREBP/ SCD1 pathway. Our findings suggest that TDF holds promise as a potential therapeutic agent for NAFLD, particularly in individuals with HBV or HIV infection.

Disclosures: Jing Tang: Nothing to Disclose, Zhiwei Chen: Nothing to Disclose, Yan Han: Nothing to Disclose, Peng Hu: Nothing to Disclose

1108 | NEUTRALIZING THE OX40L-OX40 AXIS ATTENUATES FIBROSIS AND RECRUITMENT OF MONOCYTE-DERIVED MACROPHAGES IN MURINE METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS ◆

Lucia Valenzuela Perez[1] Hyun Se Kim Lee[1] Malaz Sidahmed[1] Edward Ssali[1] Wale Bamidele[1] Petra Hirsova[1]

[1]Mayo Clinic Rochester

Background: Metabolic dysfunction-associated steatohepatitis (MASH) is a progressive disease characterized by liver inflammation and varying degrees of fibrosis. Emerging evidence implicates T cells in the disease pathogenesis. Our unpublished scRNAseq data revealed an enrichment of effector $CD4^+$ T cell expressing OX40, a costimulatory receptor, in murine MASH livers. Therefore, we aimed to explore the role of OX40 signaling in MASH reversal. **Methods:** C57BL/6J mice were fed a chow or MASH-inducing diet high in fat, fructose, and cholesterol (FFC) for 26 weeks. Chow mice were treated with vehicle, whereas FFC mice were treated with either control IgG or monoclonal antibody against OX40L, the only known ligand for OX40. At the end of the treatment, steatosis, liver injury, and fibrosis were evaluated. Intrahepatic leukocytes were isolated for immunophenotyping by mass cytometry (CyTOF) or flow cytometry. **Results:** Our single-cell transcriptomic analysis of intrahepatic CD4 T cells revealed enrichment of OX40-expressing effector CD4 T cells in MASH versus normal liver. In addition, OX40 was also found to be the top 5 upregulated gene when pseudo-bulk differential gene expression was compared between MASH and normal $CD4^+$ T cells. Next, we confirmed by flow cytometry that the OX40

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receptor is mainly expressed in CD4⁺ T cells but not in CD8⁺ T cells or other leukocytes, especially in FFC-fed mice. After collecting tissue samples from the treatment study, we did not observe differences in body and liver weights. While mice treated with OX40L antibody did not show improvement in either liver steatosis (measured by triglyceride levels) or liver injury (assessed by plasma alanine aminotransferase), OX40L inhibition significantly reversed hepatic collagen deposition (quantified by liver hydroxyproline assay and Sirius red staining). Intrahepatic leukocytes were isolated for immunophenotyping by mass cytometry (CyTOF) and flow cytometry analyses. Blocking OX40L in FFC-fed mice decreases Ly6C⁺ monocyte-derived macrophage (MoMF) recruitment to the liver, indicating that the OX40L-OX40 axis is relevant to the interaction between T cells and myeloid cells in MASH. **Conclusion:** Targeting a CD4⁺ T cell-expressed costimulatory receptor significantly reduces hepatic fibrosis and MoMF recruitment in MASH, thus improving disease severity. These findings indicate that the OX40L-OX40 axis is a plausible therapeutic target for MASH.

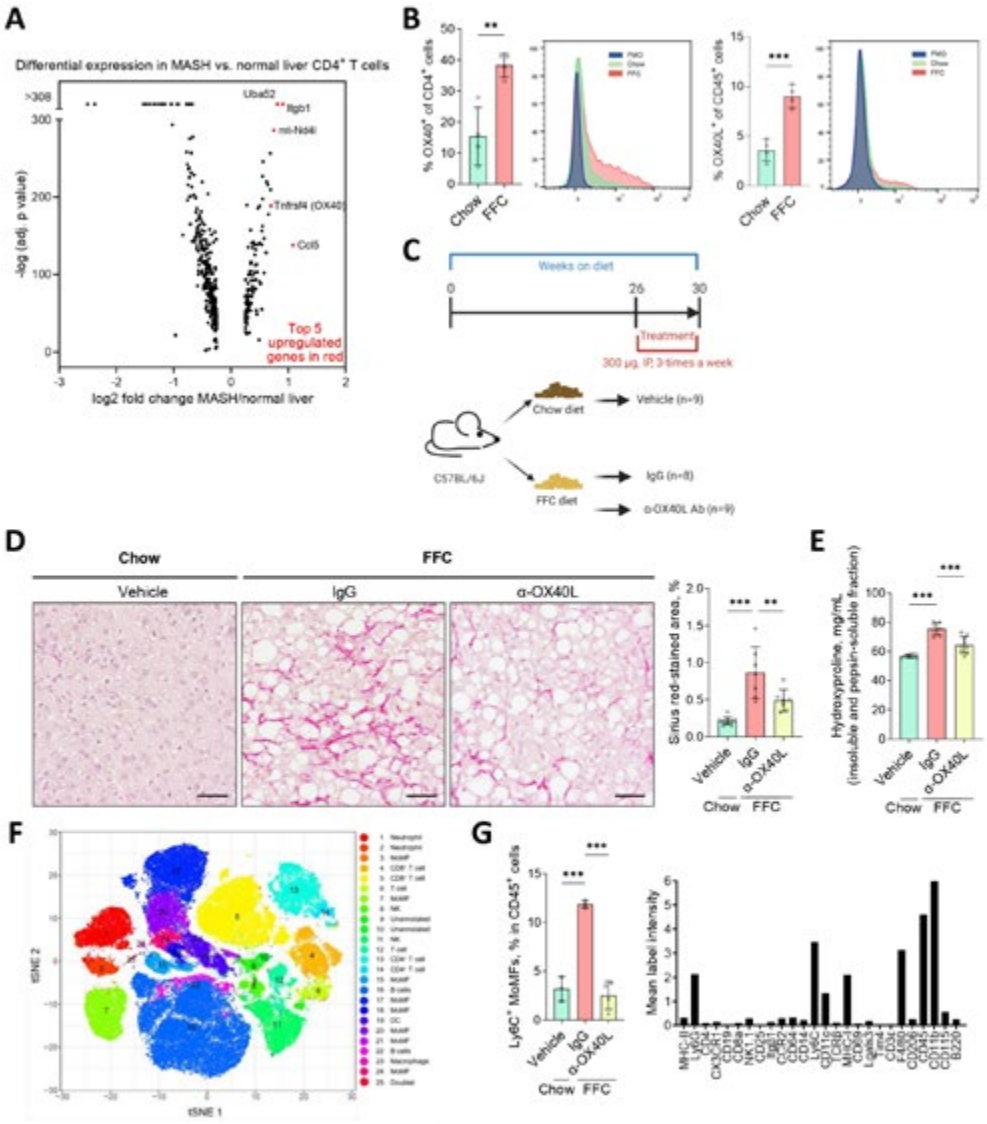

Figure 1. OX40L-OX40 axis blockade reduces fibrosis and MoMF recruitment in MASH livers.
(A) Pseudo-bulk scRNA-seq for liver CD4⁺ T cell showing the five most upregulated genes in MASH versus normal livers. **(B)** Percentage of CD4⁺ T cells and CD45⁺ cells expressing OX40 and OX40L, respectively. **(C)** Experimental design for OX40L Ab treatment. **(D)** Sirius red staining for liver collagen deposition and quantification **(E)** Hydroxyproline assay for quantifying liver collagen content. **(F)** Intrahepatic leukocyte immunoprofiling showing 25 different clusters. **(G)** Relative abundance and mean label intensity for Ly6C⁺ monocyte-derived macrophage cluster.

Disclosures: Lucia Valenzuela Perez: Nothing to Disclose, Hyun Se Kim Lee: Nothing to Disclose, Malaz Sidahmed: Nothing to Disclose, Edward Ssali: Nothing to Disclose, Wale Bamidele: Nothing to Disclose, Petra Hirsova: Nothing to Disclose

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1109 | MAP1LC3B PROTEIN INTERACTOME IN A HEPATOCYTE MITOCHONDRIAL INJURY MODEL IDENTIFIES NOVEL TARGETS RELEVANT TO STEATOTIC LIVER DISEASES

Prithvi Reddy Akepati[1] *Ruheena Javed*[2] *Michelle Salemi*[3] *Brett Phinney*[3] *Vojo Deretic*[2]

[1]*University of New Mexico Hospital and Health Sciences Center,* [2]*University of New Mexico Health Sciences Center,* [3]*University of California, Davis.*

Background: Steatotic liver diseases (MASLD, ALD, and MetALD) are prevalent in the US and constitute the most common indication for liver transplantation. Sub-cellularly, these diseases are characterized by mitochondrial injury in hepatocytes. This produces reactive oxygen species which cause DNA damage and leakage of pro-apoptotic factors into the cytoplasm. To counter this, hepatocytes employ homeostatic mechanisms such as mitophagy, mitochondrial biogenesis, DNA repair, etc. MAP1LC3B protein (LC3B) is a critical mediator of mitophagy through its covalent conjugation to the autophagosomal double membrane and non-covalent interactions with effector proteins. Recently, LC3B has also been shown to covalently conjugate with single membranes and individual proteins. This suggests the possibility of unexplored roles for LC3B in mitophagy and restoring cellular homeostasis. Here, we explore these roles via a protein interactome approach. We establish a comprehensive list of LC3B interactions with cellular proteins to serve as a road map for mechanistic studies into hepatocyte responses to mitochondrial injury. **Methods:** To mimic mitochondrial injury in hepatocytes, a Huh7 cell line expressing the fusion protein HaloTag-LC3B was treated with Carbonyl cyanide m-chlorophenyl hydrazone (CCCP), an ionophore that disrupts mitochondrial membrane potential. Dimethyl sulfoxide (DMSO, diluent of CCCP) was used as the control reagent. After cell lysis, the HaloTag (HT) allowed for affinity purification of LC3B and its interacting protein partners (Panel A). The purified proteins were subjected to mass-spectrometric (MS) analysis to compile a list of LC3B interacting proteins along with the fold change (FC) of the amount of each interacting protein in CCCP over DMSO. The interactors with an FC ≥ 2 were subjected to Gene Ontology (G.O.) analysis on Metascape. **Results:** MS analysis identified proteins potentially interacting with LC3B (Panel B). In the background of mitochondrial injury, we identified increased interaction of LC3B with protein networks involved in DNA repair, mitochondrial translation initiation, and apoptotic signaling pathways (Panel C). For instance, LC3B increasingly interacts with MRPS31 of the mitochondrial protein translation network and XPC of the DNA repair network (Panel D). **Conclusion:** This study reveals novel interactions of LC3B protein, a classic mediator of mitophagy, with proteins from other homeostatic processes such as DNA repair, mitochondrial translation initiation, and apoptotic signaling. LC3B may thus play a broader role in hepatocyte homeostasis beyond mitophagy. The findings suggest a concerted effort from diverse cellular homeostatic pathways to minimize hepatocyte injury. Studying the mechanisms by which these newly discovered protein-protein interactions affect cellular homeostasis may provide novel prognostic and therapeutic targets for steatotic liver diseases.

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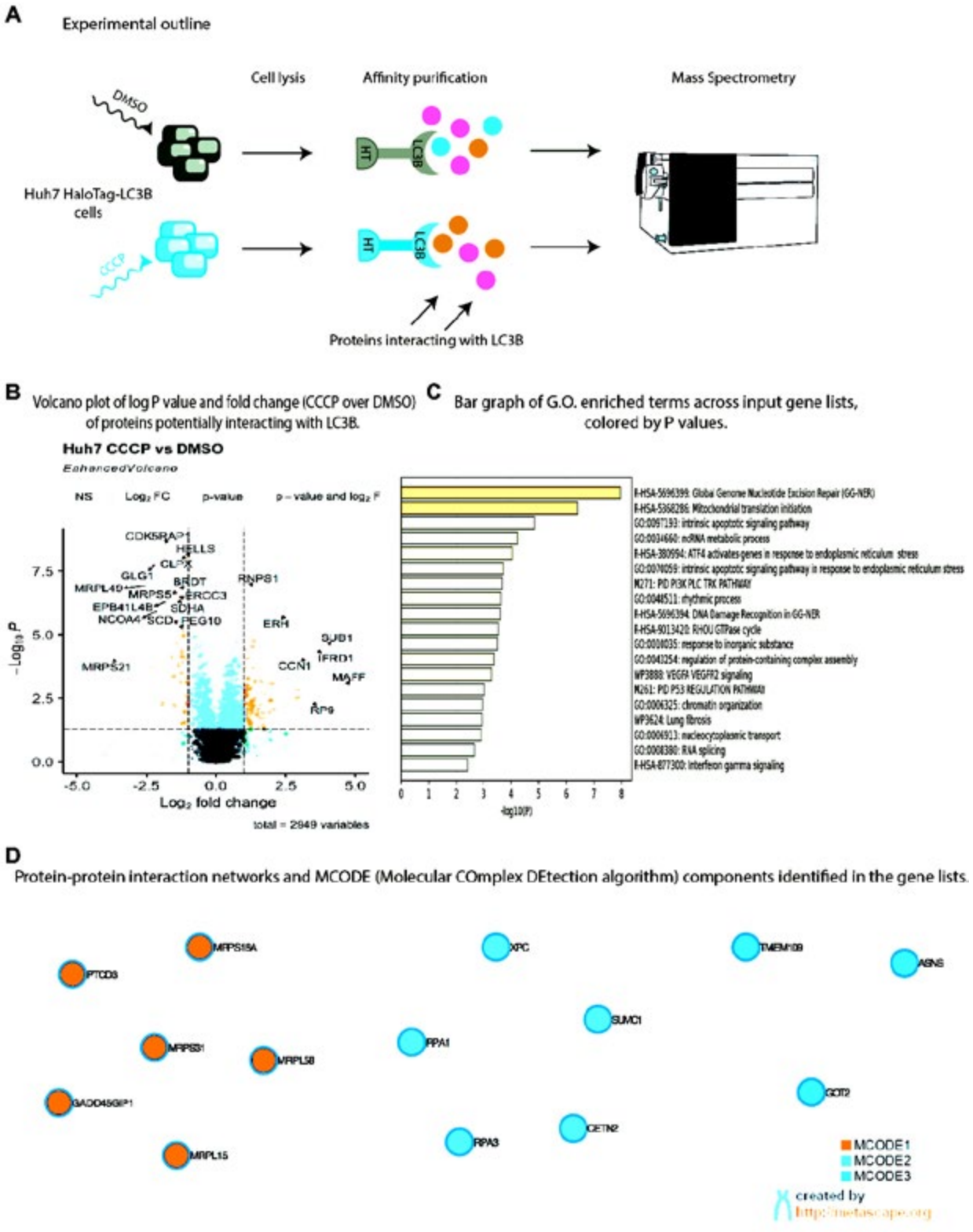

Disclosures: Prithvi Reddy Akepati: Nothing to Disclose, Ruheena Javed: Nothing to Disclose, Michelle Salemi: Nothing to Disclose, Brett Phinney: Nothing to Disclose, Vojo Deretic: Nothing to Disclose

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1110 | EPHA2 PROMOTES INFLAMMATION AND ALTERS HEPATOCYTE METABOLISM TO ENHANCE METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE

Brenna Pearson-Gallion[1] Alexandra Finney[1] Elizabeth Cockerham[1] Eshika Tandon[1] Dhananjay Kumar[1] SUMIT KUMAR ANAND[1] Matthew Scott[2] Cyrine Ben Dhaou[1] Kelley Nunez[3] Zhipeng Liu[4] Wanqing Liu[5] Paul Thevenot[3] Ari Cohen[3] James Traylor[1] Arif Yurdagul[1] Oren Rom[1] Anthony Orr[1]

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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) **Results:** from diet-induced hepatic steatosis, which can lead to inflammation and fibrosis driving metabolic dysfunction associated steatohepatitis (MASH). GWAS studies have linked the receptor tyrosine kinase EphA2 and its ephrinA1 ligand to circulating transaminase levels and MASLD development, and we demonstrated altered plasma lipid levels in EphA2 KO mice. While Eph receptors affect inflammation and fibrosis in other model systems, the potential role of EphA2 in MASLD remains unknown. **Methods:** Global EphA2 KO and hepatocyte-specific EphA2 KO mice were fed the FPC diet for 8 or 16 weeks followed by histological and molecular analyses. EphA2 and ephrinA1 expression were assessed in mouse MASLD/MASH and human MASH samples. The effect of EphA2 signaling on hepatocyte function was assessed in primary hepatocytes isolated from global EphA2 KO mice and in HuH7 cells and primary human hepatocytes treated with EphA2 siRNA. **Results:** Global EphA2 KO mice show reduced indices of MASLD following FPC diet feeding (steatosis, transaminases, inflammation), and RNA sequencing of EphA2 KO livers demonstrates enhanced expression of fatty acid metabolism and mitochondrial b-oxidation genes and reduced expression of proinflammatory genes. While EphA2 expression is unaffected in mouse models of MASH or in human liver samples from MASH patients, ephrinA1 expression is significantly reduced. Consistent with this, EphA2 expression positively correlates with hepatic steatosis in liver transplantation donors, whereas ephrinA1 shows a negative correlation. Data adapted from published scRNA-Seq of normal human livers shows preferential expression of EphA2 and ephrinA1 in the hepatocyte and endothelial cell subpopulations. To assess EphA2's role in hepatocytes, we developed EphA2 conditional knockout mice and showed that hepatocyte-specific EphA2 deletion similarly reduces hepatic steatosis and MASLD development. EphA2 deletion in primary hepatocytes and EphA2 knockdown Huh7 cells reduces lipid accumulation following palmitic acid treatment. While lipid accumulation and inflammatory gene expression are interrelated, RNASeq analysis of EphA2 knockdown in the absence of lipid loading shows similar trends for enhanced metabolic pathways and reduced proinflammatory gene expression. **Conclusion:** Taken together, our data demonstrate that EphA2 promotes inflammation and alters hepatocyte metabolism to enhance steatosis during MASLD progression.

Disclosures: Brenna Pearson-Gallion: Nothing to Disclose, Alexandra Finney: Nothing to Disclose, Elizabeth Cockerham: Nothing to Disclose, Eshika Tandon: Nothing to Disclose, Dhananjay Kumar: Nothing to Disclose, SUMIT KUMAR ANAND: Nothing to Disclose, Matthew Scott: Nothing to Disclose, Cyrine Ben Dhaou: Nothing to Disclose, Kelley Nunez: Nothing to Disclose, Zhipeng Liu: Nothing to Disclose, Wanqing Liu: Nothing to Disclose, Paul Thevenot: Boston Scientific: Grant/Research Support, FUJIFILM: Grant/Research Support, Helio Genomics: Grant/Research Support, Ari Cohen: Nothing to Disclose, James Traylor: Nothing to Disclose, Arif Yurdagul: Nothing to Disclose, Oren Rom: Diapin Therapeutics: Scientific Advisor, Anthony Orr: Nothing to Disclose

1111 | GLYCOGEN SYNTHASE KINASE 3β HEPATOCYTE DELETION AMELIORATES MURINE METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS

Khaled Warasnhe[1] Qianqian Guo[1] Akitoshi Sano[2] Peyton Classon[3] Chady Meroueh[1] Wale Bamidele[3] Hyun Se Kim Lee[1] Lucia Valenzuela Perez[1] Petra Hirsova[3] Davide Povero[3] Samar Ibrahim[3]

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Background: Metabolic dysfunction-associated steatohepatitis (MASH) is a growing public health problem characterized by toxic lipid-induced cellular stress (lipotoxicity) and sterile inflammatory response. We have reported that pharmacological inhibition of GSK3 ameliorates murine MASH. However, the role of GSK3β in hepatocyte lipotoxic injury and fibro-inflammatory response in MASH remains obscure. **Methods:** We generated hepatocyte specific GSK3β knockout ($GSK3\beta^{\triangle Hep}$) mice by crossing $GSK3\beta^{fl/fl}$ with albumin-Cre mice. Mice were fed either a choline-deficient high-fat diet (CDHFD) or high fat, fructose, and cholesterol (FFC) diet to induce

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MASH. **Results:** Metabolic parameters were similar in FFC-fed GSK3β$^{\triangle Hep}$ and GSK3β$^{fl/fl}$ mice. GSK3β$^{\triangle Hep}$ mice with MASH showed reduced lipid droplet size in the pericentral area. Liver tissue lipidomics revealed similar composition of non-esterified fatty acids in GSK3β$^{fl/fl}$ and GSK3β$^{\triangle Hep}$ mice. NanoString Metabolic Pathways Panel on liver tissues showed upregulation of *G6pc* and differential expression of AMPK and glycolysis pathways in the FFC fed GSK3β$^{\triangle Hep}$ mice, implicating GSK3β in mitochondrial dysfunction. Liver injury (plasma ALT), cell death (ApopTag positive cells), and ferroptosis (*Ptgs2, Fth1, Acsl4* mRNA expression) were reduced in the GSK3β$^{\triangle Hep}$ mice with MASH. Likewise, the expression of *Cxcl2,* a chemokine released by ferroptotic hepatocyte was reduced. Furthermore, GSK3β$^{\triangle Hep}$ mice with MASH had reduced liver inflammation as assessed by decreased expression of proinflammatory genes (*Ccr2* and *Mcp1)* and reduced hepatic macrophage and neutrophil infiltration (assessed by F4/80 and MPO immunostaining). Interestingly, GSK3β$^{\triangle Hep}$ mice with MASH had significant reduction of fibrosis evident by reduced *Col1a1* mRNA expression, Sirius red and α-smooth muscle actin (αSMA) staining. NanoString Fibrosis Panel on liver tissues identified downregulation of hypoxia, programmed cell death and TGFβ pathways, supporting the role of GSK3β in mitochondrial dysfunction, ferroptosis and fibrogenesis in MASH. The human relevance of this observation was confirmed by increased activated phosphorylation of GSK3α/β (Y279/216) in patients with MASH versus patients with steatosis and normal subjects. **Conclusion:** Hepatocyte specific GSK3β deletion attenuates liver injury, inflammation, and fibrosis in murine MASH, likely by attenuating mitochondrial dysfunction and ferroptosis. Hence, GSK3 may serve as a potential therapeutic target in human MASH.

Disclosures: Khaled Warasnhe: Nothing to Disclose, Qianqian Guo: Nothing to Disclose, Akitoshi Sano: Nothing to Disclose, Peyton Classon: Nothing to Disclose, Chady Meroueh: Nothing to Disclose, Wale Bamidele: Nothing to Disclose, Hyun Se Kim Lee: Nothing to Disclose, Lucia Valenzuela Perez: Nothing to Disclose, Petra Hirsova: Nothing to Disclose, Davide Povero: Nothing to Disclose, Samar Ibrahim: Advisor relationship with Mirum pharmaceutical; Has not ended; Advisor relationship with Albeiro pharma; Has ended

1112 | GENETIC CONTROL OF THE MASLD/MASH TRANSITION ◆

Jean-David Morel[1] *Giorgia Benegiamo*[1] *Johan Auwerx*[1]

[1]*EPFL*

Background: MASLD represents a spectrum of liver diseases that can vary from steatosis to the more severe Metabolic dysfunction-associated steatohepatitis (MASH); however, the mechanisms governing the transition from MASLD to MASH are still poorly understood. To understand to what extent genetic differences affect MASH development, our lab recently profiled western diet and thermoneutrality-induced MASH susceptibility in mice from 7 different genetic backgrounds from three distinct Mus musculus subspecies [PMID: 36787127]. Out of the 7 tested strains, the PWK/PhJ were most sensitive, the only strain to develop fibrosis, and their liver transcript signature was most similar to human MASH. Conversely, the CAST/EiJ mice were fully resistant to liver damage, weight gain and any other effects of the WD. This combination of a resistant strain (CAST/EiJ) and a strain reproducing human MASH (PWK/PhJ), inspired us to create a new genetic reference population focused on uncovering the genetic basis of resistance and sensitivity to MASH. **Methods:** We designed a second generation (F2) cross population of 500 mice (250 males and 250 females), which would be suitably powered to detect QTLs with meaningful effects as well as assess sexual dimorphism (Figure 1A). To induce liver disease, mice were housed at thermoneutrality starting at 6 wks of age and were fed a western diet or a matched control diet from 7 wks of age for 17 wks.Mice were evaluated for metabolic function (CLAMS at 7 and 20 wks of age), body composition (EchoMRI at 6, 14, 22 wks of age) and body weight (bi-weekly) (Figure 1B). Mice were sacrificed at 24 weeks of age after a four-hour fast, and we performed liver histology, as well as RNAseq of liver and kidneys. **Results:** The analysis of the phenotypes (Figure 1C) and the transcriptome of the F2 mice show that they cluster into groups, with the more severe group showing severe MASH, including fibrosis, like their PWK/PhJ progenitor, while another group shows complete resistance to diet-induced obesity and MASLD, taking after their CAST/EiJ progenitor. This range of responses enabled quantitative trait locus (QTL) mapping, and we found many genetic loci associated with obesity and liver disease (Figure 1D). To assess the human relevance of these associations, we are performing genome-wide association analysis and mendelian randomization in the human populations of the UK Biobank, Estonian biobank, Million veterans program and Finngen. **Conclusion:** The F2 mouse population that we generated in this study covers a very wide range of genetic susceptibility to resistance to MASH, making it an ideal tool to discover causative genes of both susceptibility to MASLD and the transition to MASH. Our research will hence contribute to a better understanding of the mechanisms of MASLD/MASH in

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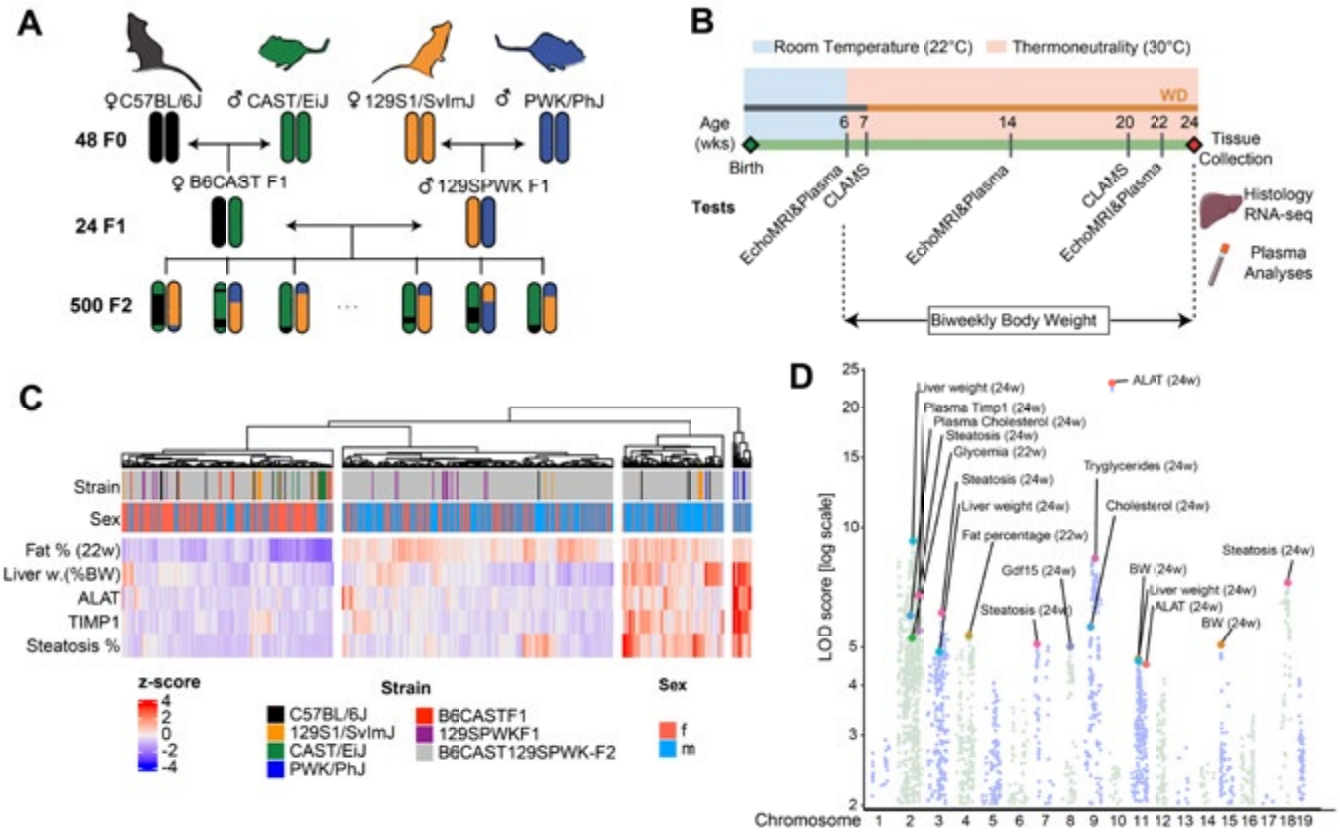
generalizable animal models, and assess their translational potential through human genetics, which we expect to be leveraged for the development of new human therapies.



A. The selected 4-way cross. At any autosomal locus, the F2 mice will have the following possible haplotypes: B6J/129S1, B6J/PWK, or CAST/129S1, 129S1/PWK, in an expected 1:1:1:1 ratio. **B.** in-life phenotyping pipeline. Mice were housed at thermoneutrality starting at 6 wks of age and were fed a western diet starting at 7 wks of age. Phenotypes (Body weight, EchoMRI, plasma and CLAMS) were collected at the indicated timepoints. **C**: Heatmap of some of the main liver disease-related phenotypes. The genetic diversity of the F2 population creates 4 clusters, including the rightmost one with severe disease markers, with gradually less severe disease as we move to the left. In addition, to having no measureable liver disease, the leftmost group of mice also gains no extra weight under western diet. **D**. Manhattan plot of the preliminary genetic mapping results of the males of the F2 population, showing genetic sites assocated with obesity and liver disease related phenotypes.

Disclosures: Jean-David Morel: Nothing to Disclose, Giorgia Benegiamo: Nothing to Disclose, Johan Auwerx: Nothing to Disclose

1113 | JIGUCAO CAPSULE ALLEVIATES METABOLIC DYSFUNCTION-ASSOCIATED FATTY LIVER DISEASE BY REGULATING THE GUT MICROBIOTA AND LIPID METABOLISM

Wenying Qi[1] Yue Chen[1] Xu Cao[1] Hening Chen[1] Ningyi Zhang[1] Ruijia Liu[1] Wei Wang[1] Yong'An Ye[1] Xiaobin Zao[2]

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Background: The pathogenesis of metabolic dysfunction-associated fatty liver disease (MAFLD) is not fully elucidated, and the current treatment is still limited. The JiGuCao capsule (JGC) is a commonly used traditional Chinese medicine already on the market for the treatment of acute and chronic hepatitis. However, the role and mechanism of JGC in the prevention and treatment of MAFLD is not clear and needs further study. **Methods:**

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The C57BL/6J mice MAFLD model was established by feeding with a high-fat diet (HFD) and 5% fructose water for 16 weeks. From the 9th week, the model mice were treated with JGC by gavage. The therapeutic effect of JGC on MAFLD was determined by serum detection of liver function, blood lipid, andhistopathological examination of hematoxylin-eosin (HE) and oil red (OR) staining for liver and intestin tissues. Meanwhile, the transcriptome sequencing of liver tissue and 16s ribosomal RNA sequencing (16S-seq) of the gut microbiota were performed. The differently expressed genes (DEGs) between the model and the JGC groups were screed out to perform further enrichment analyses including the Gene Ontology (GO) and the Kyoto Encyclopedia of Genes and Genomes (KEGG). **Results:** Compared with HFD, the JGC treatment significantly decreased the mice's body weight, Lee's index, fat content, and liver weight (Figure B). Meanwhile, the levels of serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), triglyceride (TG), cholesterol (CHO), low-density lipoprotein (LDL), and total bile acid (TBA) were decreased after JGC treatment (Figure D). The HE and OR stainings showed that the HFD significantly increased hepatocyte steatosis, hepatocyte balloon degeneration, and inflammatory cell infiltration in the model group (Figure C). At the same time, the villi of the small intestine were dispersed, the cells fell off, and the glands of the small intestine increased in the model group. Compared with HFD, JGC treatment reduced hepatic steatosis and restored the integrity of intestinal structure (Figure C). The GO analysis of DEGs showed that JGC may affect the process of lipid metabolic process, lipid binding, and so on (Figure E). The KEGG analysis of DEGs showed that JGC could regulate the Glutathione metabolism and PPAR signaling pathways (Figure F). The results of 16S-seq showed that the JGC treatment increased the abundance of Lactobacillus and reduced the abundance of Colidextribacter at the genus level (Figure G) . Association analysis between bacterial abundance and biochemical indicators showed that Colidextribacter was closely related to the increase of ALT, AST, CHO, and LDL (Figure H) . **Conclusion:** JGC has a good preventive and therapeutic effect on MAFLD by effectively relieving liver inflammation and restoring the normal function of the gut-liver axis. The mechanism of JGC in treating MAFLD is correlated to regulating liver lipid metabolism and the ecological structure of the gut microbiota.

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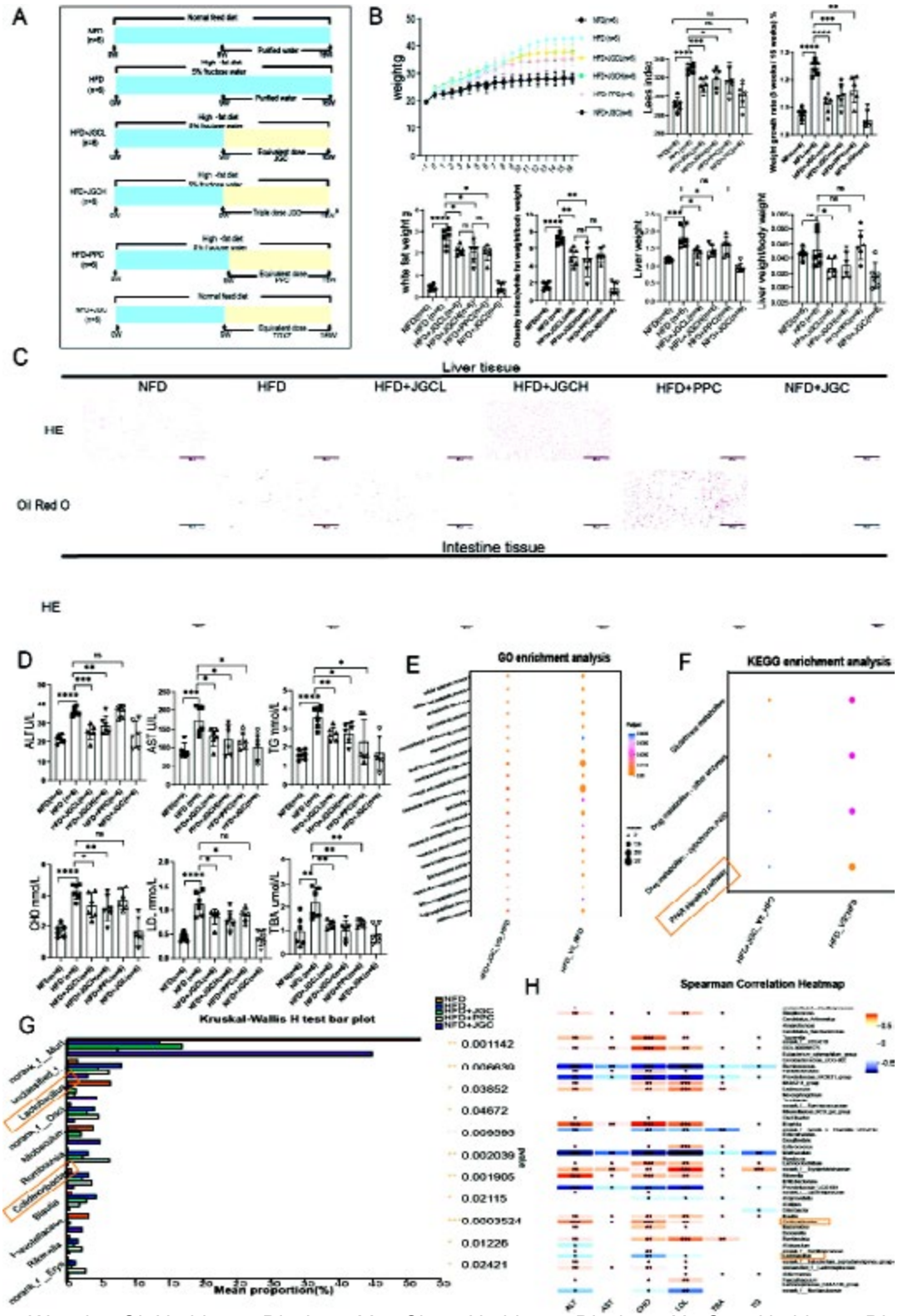

Disclosures: Wenying Qi: Nothing to Disclose, Yue Chen: Nothing to Disclose, Xu Cao: Nothing to Disclose, Hening Chen: Nothing to Disclose, Ningyi Zhang: Nothing to Disclose, Ruijia Liu: Nothing to Disclose, Wei Wang: Nothing to Disclose, Yong'An Ye: Nothing to Disclose, Xiaobin Zao: Nothing to Disclose

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1114 | THE EFFECTS OF HYDROXYNONENAL ON HEPATOCYTES AND ITS ASSOCIATION WITH THE PATHOGENESIS OF NAFLD

Masahiro Yanagi[1] Hidenori Kido[2] Shihui Li[1] Eishiro Mizukoshi[1] Tetsumori Yamashima[3] Taro Yamashita[4]

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Background: Hydroxynonenal (HNE) is a lipid peroxide derived from linoleic acid, which is involved in the development of various lifestyle-related diseases such as Alzheimer's disease and diabetes, cardiovascular disease, and cancer. We previously reported that the degree of HNE deposition in liver tissue is correlated with the histopathological findings of human NAFLD (Seike T, et al. Cell Mol Gastroenterol Hepatol 2022: 14: 925-944). In the present study, a larger sample size of NAFLD liver tissue was analyzed and confirmed the mechanism of action of HNE in the pathogenesis of NAFLD. To further investigate the direct effects of HNE on hepatocytes, the non-human primate model (Japanese macaque monkey) was used for HNE-administration experiment. **Methods:** 1) HNE deposition in liver tissue of 190 patients with NAFLD who underwent liver biopsy was detected by immunohistochemical staining. The degree of HNE deposition was evaluated and scored in three levels, and the relationship with histopathological findings of NAFLD was analyzed. The morphology of lysosomes and mitochondria in hepatocytes of NAFLD liver was observed by electron microscopy. 2) Six Japanese macaque monkeys (5-6 years old) were treated with intravenous or intramuscular injections of 5 mg of synthetic HNE once a week for 24 weeks. The morphology of lysosomes and mitochondria in hepatocytes after HNE exposure was observed by electron microscopy using liver tissues obtained by serial liver biopsies of monkeys. **Results:** Liver tissues with higher HNE grade showed more advanced inflammation, hepatocyte ballooning, and fibrosis, as well as higher NAFLD activity score. In the hepatocyte of NAFLD liver tissue, the membrane of lysosomes was disrupted and their contents were leaking out. In addition, the cristae of mitochondria were disorganized, the membranes were disrupted and strongly degenerated. Similar electron microscopic findings were observed in the hepatocyte of Japanese macaque monkeys treated with HNE. **Conclusion:** It was suggested that HNE is involved in the pathogenesis of NAFLD by damaging lysosomes and mitochondria in the hepatocytes.

Disclosures: Masahiro Yanagi: Nothing to Disclose, Hidenori Kido: Nothing to Disclose, Shihui Li: Nothing to Disclose, Eishiro Mizukoshi: Nothing to Disclose, Tetsumori Yamashima: Nothing to Disclose, Taro Yamashita: Nothing to Disclose

1115 | MODELLING HEALTH-TO-DISEASE TRANSITION IN MASLD-MASH: DEVELOPMENT OF A DYNAMIC MICROFLUIDIC HUMAN LIVER-ON-CHIP SYSTEM

Debbie Neill Anabel Martinez Lyons[1] Callum Rafferty[1] Justyna Cholewa-Waclaw[1] Leonard Nelson[1] Shaden Melhem[1]

[1]University of Edinburgh

Background: Metabolic dysfunction-associate steatotic liver disease (MASLD) is an umbrella term for a spectrum of metabolic liver disorders ranging from simple steatotic liver disease (SLD) to inflammation-driven metabolic dysfunction-associated steatohepatitis (MASH). Mechanisms underlying healthy-SLD-MASH progression remain poorly understood, in part due to conventional 2D cell culture approaches lacking in tissue complexity, which is crucial for recapitulating hepatic phenotypes. To address this gap, we applied a 3D multicellular human liver organ-on-chip (OoC) model that promotes cell-cell/cell-matrix interactions and recapitulates the Health-SLD-MASH transition. We aimed to use these organotypic models to better understand the pathogenic transition pathways underlying SLD/MASH, and to uncover novel biomarkers for early diagnosis and treatment. **Methods:** HepaRG116 cells and non-parenchymal cells were cultured within the Human Emulation System™ OoC (Emulate) alongside comparator HepaRG-based 2D and 3D Transwell® multicellular models and cultured for 7 days. Models were then exposed to Oleate (SLD model), or a lipogenic and immunogenic cocktail containing lactate, pyruvate, octanoate and ammonia (LPON; MASH model) for 72h. Immunofluorescence (IF) microscopy for (e.g., HNF4α; HIF1α) and lipid droplet (LD) BODIPY staining (**Fig. A**) was performed. The Proteome Profiler Human 105 Cytokine Array was used to assess the inflammatory signature for LPON-treated 2D HepaRG cells (**Fig. B**). Phenotypic profiling of cell health/viability was performed using a panel of ELISA assays (**Fig. C**) **Results:** Enhanced LD deposition was evident in both Oleate-SLD and LPON-MASH 2D and 3D Transwell

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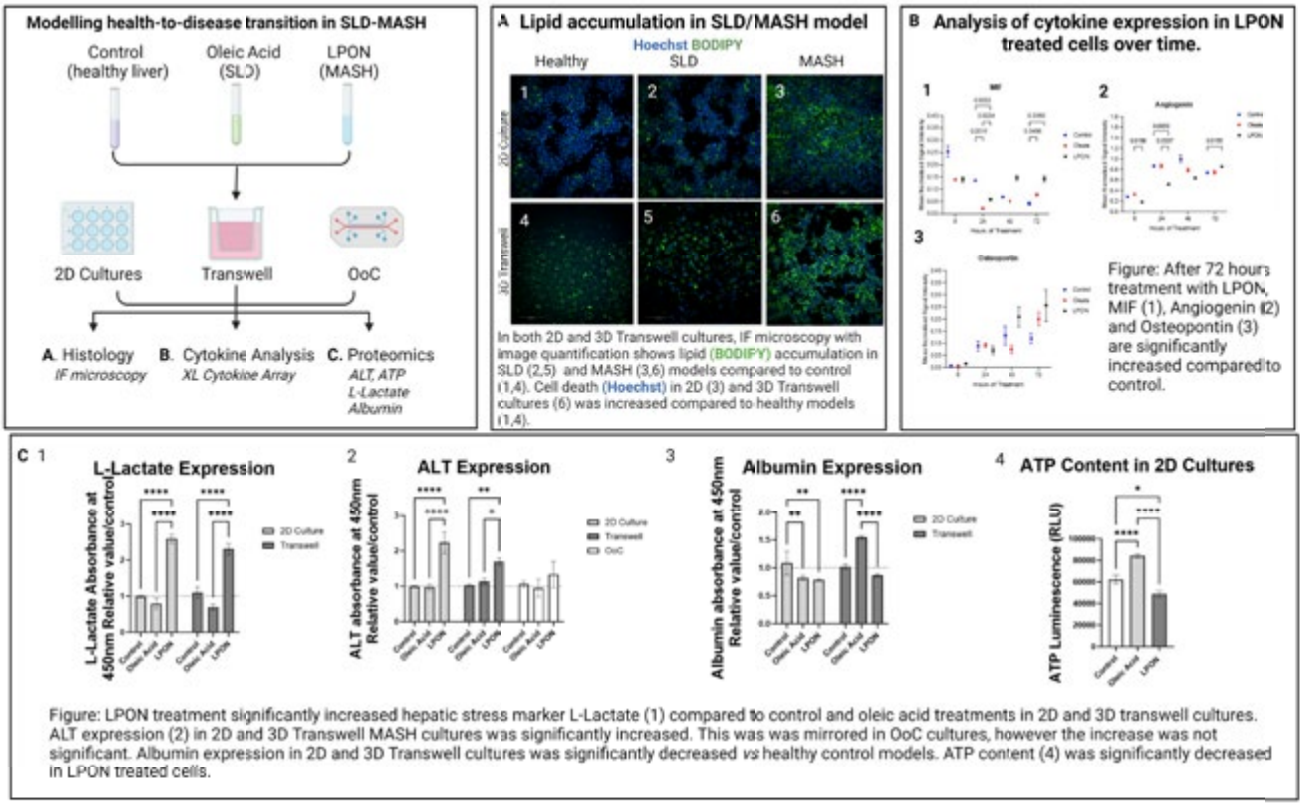
models vs HepaRG controls. At least 6 Cytokines were significantly upregulated in 2D MASH model vs control or SLD models after 72h of LPON treatment (**Fig. B**), whilst the latter in all platforms increased ALT and L-Lactate expression vs controls. Both albumin expression and ATP content was significantly decreased in 2D and 3D Transwell MASH models (observed also in MASH patients). **Conclusion:** Here, we have established a prototype human liver chip model of healthy-SLD-MASH pathogenic transition with comparator human HepaRG-based 2D co-culture and 3D multicellular Transwell systems. Lipid accumulation, increased ALT and L-Lactate expression, with decreased albumin expression and ATP content are features of pathogenic hepatic dysfunction, stress and/or cell death due to excessive lipid accumulation/inflammation in our LPON-MASH model. In addition this model displays enhanced expression of pro-inflammatory (lipogenic and immunogenic) markers. Given these preliminary results, we aim to further refine and characterize our liver-chip model to investigate the role of inflammatory cytokines in the development and progression in the healthy-SLD-MASH transition.



Disclosures: Debbie Neill: Nothing to Disclose, Anabel Martinez Lyons: Nothing to Disclose, Callum Rafferty: Nothing to Disclose, Justyna Cholewa-Waclaw: Nothing to Disclose, Leonard Nelson: Nothing to Disclose, Shaden Melhem: Nothing to Disclose

1116 | BLOCKADE OF CXCR3 ATTENUATES CD4 T CELL-MEDIATED LIVER INJURY IN MURINE METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS

Hyun Se Kim Lee[1] *Lucia Valenzuela Perez*[1] *Adna Hassan*[1] *Margaret Dick*[1] *Petra Hirsova*[1]

[1]*Mayo Clinic Rochester*

Background: The role of CD4 T cell-mediated immune response during the pathogenesis of metabolic dysfunction-associated steatohepatitis (MASH) has been largely unexplored. Our single-cell transcriptomic analysis of intrahepatic CD4 T cells revealed enrichment of CXCR3 chemokine receptor-expressing Th1 and cytotoxic cell clusters in MASH versus healthy livers. Also, CXCR3-deficient mice are protected from MASH. Therefore, we aimed to examine the effect of pharmacologic CXCR3 inhibition on reversal of established MASH. **Methods:** C57BL/6J mice with established MASH (by a 26-week feeding with FFC, a diet high in fat, fructose, and cholesterol) were treated with a CXCR3 antagonist AMG-487 for 4 weeks. After completion of the treatment, the liver phenotype was

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evaluated. Expression of CXCR3 was measured in isolated intrahepatic leukocytes via flow cytometry, while liver immune cell composition was assessed via mass cytometry (CyTOF). **Results:** Flow cytometry analysis showed an increase in CXCR3⁺ CD4 T cells in FFC (MASH) versus chow (healthy) mouse livers, confirming the transcriptomic data. Treatment with AMG-487 did not affect body weight, liver/body weight ratio, or steatosis. Mass cytometry (CyTOF) on isolated intrahepatic leukocytes revealed no striking changes in immune cell type composition in AMG-487-treated FFC mice compared to FFC controls. However, flow cytometry analysis showed a reduced frequency of CXCR3-expressing hepatic CD4 T cells in FFC-fed mice treated with AMG-487. Interestingly, this reduction was exclusive to CD4 T cells and not observed among CXCR3⁺ CD8 T, NKT, and CD11b⁺ cells. Plasma alanine transaminase and aspartate aminotransferase levels were measured to assess liver injury. FFC-fed mice treated with AMG-487 exhibited a significant reduction in liver damage markers compared to FFC mice treated with vehicle. Despite this improvement in liver injury, blockade of CXCR3 during the 4-week treatment period was insufficient to reverse liver fibrosis as assessed by Sirius red staining and hepatic hydroxyproline levels. **Conclusion:** Pharmacologic inhibition of chemokine receptor CXCR3 in mice with established MASH results in exclusive reduction of intrahepatic CXCR3⁺ CD4 T cells and attenuated liver injury. These data indicate that CXCR3⁺ CD4 T cells contribute to liver damage during MASH, thus promoting disease pathogenesis.

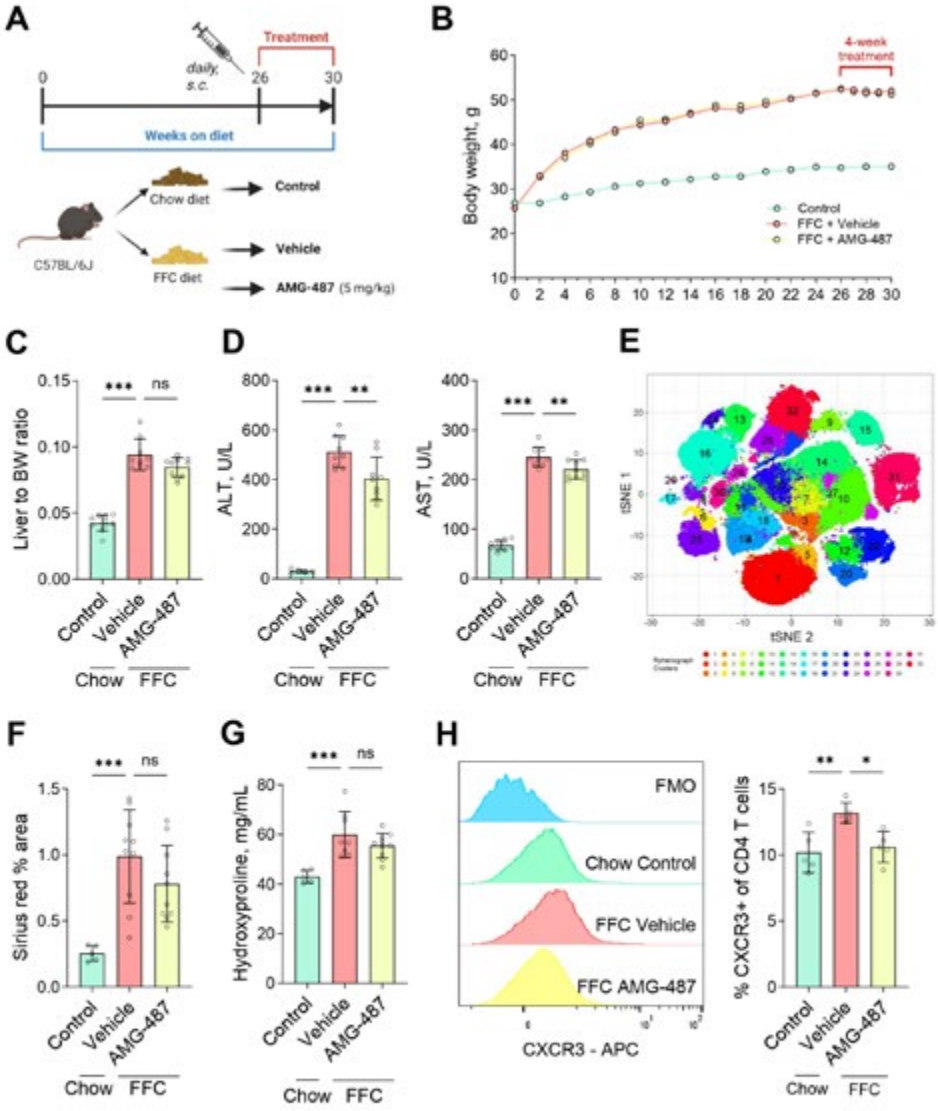

Figure. Blockade of CXCR3 attenuates CD4 T cell-mediated liver injury during diet-induced murine MASH. **(A)** C57BL/6J mice were fed chow or FFC diet for 30 weeks, during which treatment with either vehicle or AMG-487 began at week 26. **(B)** Body weight time course. **(C)** Liver to body weight ratio. **(D)** Plasma biochemistry; ALT: alanine transaminase; AST: aspartate transaminase. **(E)** Liver immune landscape represented using an R-phenograph clustering algorithm (CyTOF). **(F)** Sirius red staining quantification. **(G)** Liver hydroxyproline levels. **(H)** CXCR3+ CD4 T cells quantified via flow cytometry. *p<.05, **p<.01, ***p<.001

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Disclosures: Hyun Se Kim Lee: Nothing to Disclose, Lucia Valenzuela Perez: Nothing to Disclose, Adna Hassan: Nothing to Disclose, Margaret Dick: Nothing to Disclose, Petra Hirsova: Nothing to Disclose

1117 | HEPATOCYTE-SPECIFIC (PRO)RENIN RECEPTOR KNOCKOUT ATTENUATED DIET-INDUCED STEATOSIS IN MICE WITH IMPROVED INSULIN RESISTANCE AND METABOLIC RATES

Yun-Cheng Hsieh[1] Atsuhiro Ichihara[2] Han-Chieh Lin[1] Kuei-Chuan Lee[3]

[1]Taipei Veterans General Hospital, [2]Tokyo Women's Medical University, Shinjuku, Tokyo, Japan., [3]Taipei Veterans General Hospital, Taipei, Taiwan

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD), defined as steatosis in the presence of cardiometabolic risk factors, is the most common cause of chronic liver disease and is the leading cause of liver-related morbidity and mortality. (Pro)renin receptor (PRR) is reportedly involved in lipid metabolism and PRR knockdown protects mice against hepatosteatosis and inflammation. However, the impact of hepatocyte-specific PRR knockout on MASLD remain unclear. **Methods:** Hepatocyte-specific PRR knockout (PRRhepKO) mice were generated by crossing PRR floxed mice with albumin-Cre transgenic mice. MASLD was generated by high fat diet (HFD) feeding for 12 weeks. Primary hepatocytes isolated from wild-type (WT) and PRRhepKO mice were used for proteome analysis. **Results:** PRRhepKO mice had decreased body weight and reduced total body fat weight on an HFD. In addition, PRRhepKO mice also displayed improved insulin resistance and increased metabolic rates. Hepatic steatosis was also attenuated by hepatocyte PRR knockout. The expressions of peroxisome proliferator-activated receptor-alpha (PPARα), peroxisomal acyl-coenzyme A oxidase 1 (ACOX1) and cytochrome p450 4A14 (CYP4a14) were upregulated in PRRhepKO mice livers. In vitro, primary hepatocytes from PRRhepKO mice showed increased abundance of proteins regulating fatty acids oxidation in both proteomics and western blots. However, hepatocyte-specific PRR knockout mice showed increased hepatic inflammation on both normal diet and HFD, including increased liver enzymes, inflammatory cell recruitment, and proinflammatory cytokines expression with autophagy impairment. **Conclusion:** Our findings revealed that PRR knockout in hepatocytes attenuated steatosis and improved metabolism in mice with MASLD but caused liver inflammation on both normal diet and HFD by autophagy impairment. Accordingly, targeting PRR signaling in MASLD should be cautious.

Disclosures: Yun-Cheng Hsieh: Nothing to Disclose, Atsuhiro Ichihara: Nothing to Disclose, Han-Chieh Lin: Nothing to Disclose, Kuei-Chuan Lee: Nothing to Disclose

1118 | PERIPHERAL BLOCKADE OF CB1 SIGNALING IMPROVES LIVER FIBROSIS

Kei Ishizuka[1] Souradipta Ganguly[2] Barun Das[3] Malika Nindra[3] Aryaman Bhattacharya[3] Tatiana Kisseleva[2] Kenichi Ikejima[4] David Brenner[5] Debanjan Dhar[6]

[1]Juntendo University Graduate School of Medicine, [2]University of California, San Diego, [3]University of California San Diego, [4]Juntendo University School of Medicine, [5]Sanford Burnham Prebys Medical Discovery Institute, [6]Sanford Burnham Prebys Medical Discovery Institute

Background: Cannabinoid 1 receptor (CB1R) belongs to the endocannabinoid system that plays an important role in the pathogenesis of MASH and liver fibrosis. CB1R antagonism is a clinically proven strategy to treat obesity. Unfortunately, the first-in-class brain-penetrant CB1R antagonist Rimonabant, initially approved for the management of obesity and related cardiometabolic risks, was withdrawn because of CNS-mediated neuropsychiatric side effects. However, peripherally-restricted CB1 antagonists with limited brain penetrance have the potential to be efficacious without neuropsychiatric side effects. The role of CB1 in hepatic stellate cell (HSC) activation and fibrosis also remains poorly understood. As a proof-of-concept, we generated mice that lacked *CB1* in peripheral tissues while retaining *CB1* expression in the brain or had an HSC specific *CB1* deletion. Using these mice in multiple pre-clinical models of chronic liver disease and liver fibrosis, we investigate whether HSC specific CB1 deletion or CB1 deletion in peripheral tissues have any beneficial effects on MASH, cholestatic liver injury and liver fibrosis. **Methods:** $CB1^{F/F}$ mice was crossed with Lrat-cre mice to generate HSC specific CB1 deleted mice ($CB1^{DHSC}$). To generate mice that lacks peripheral CB1 while sparing the gene in the brain,

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CB1$^{F/F}$ mice was crossed with MX1-cre mice (*CB1*^{DMX1}). *CB1*^{DMX1} mice when injected with poly (I:C) recombines and deletes CB1 in peripheral tissues with little to no recombination in the brain. Three distinct preclinical models were used: (1) MASH (Fructose+Western Diet), (2) bile duct ligation (BDL) induced cholestatic injury and (3) CCl_4 induced liver fibrosis. Hepatic gene expression was determined by qRT-PCR. Fibrosis was evaluated by Sirius red staining. IHC staining was performed to evaluate asmooth muscle actin (αSMA) and F4/80 expression. **Results:** Poly (I:C)-treated *CB1*^{DMX1} mice reduced *CB1* in peripheral tissues such as liver, kidney and adipose tissue but did not affect the *CB1* in the brain. The peripheral absence of CB1 had overall protection towards MASH development including liver steatosis, fibrosis, inflammation and liver damage. Importantly, while the peripheral absence of CB1 did not affect body weight gain on MASH diet, the liver weight and liver:body weight ratio was significantly reduced in *CB1*^{DMX1} mice. *CB1*^{DMX1} mice were also protected from cholestatic liver injury and CCl_4 induced liver fibrosis. *CB1*^{DHSC} mice, on the other hand, that lacked *CB1* expression specifically in the HSC compartment were not protected from MASH, cholestatic injury, or liver fibrosis. **Conclusion:** This study provides genetic foundational and proof-of-concept studies indicating that peripheral CB1 antagonists (sparing the CNS and the brain) have potential therapeutic applications in multiple liver diseases. However, deletion of CB1 specifically in HSC did not have a protective effect in our models of liver disease.

Disclosures: Kei Ishizuka: Nothing to Disclose, Souradipta Ganguly: Nothing to Disclose, Barun Das: Nothing to Disclose, Malika Nindra: Nothing to Disclose, Aryaman Bhattacharya: Nothing to Disclose, Tatiana Kisseleva: Nothing to Disclose, Kenichi Ikejima: Nothing to Disclose, David Brenner: Nothing to Disclose, Debanjan Dhar: Nothing to Disclose

1119 | TARGETING EFHD1 TO REDUCE LIVER DAMAGE IN MASH

David Eberhardt[1] *Dipayan Chaudhuri*[1]

[1]*University of Utah*

Background: New treatments for liver disease may arise by examining genes identified in genome-wide association studies (GWAS). Variation in one such gene, *EF-hand domain family member D1* (*EFHD1*), has been associated with liver injury biomarkers in multiple GWAS analyses. In these studies, higher serum biomarkers correlate with increased EFHD1 expression. EFHD1 is a poorly studied mitochondrial Ca^{2+}-binding protein, and how it regulates liver function is unknown. We sought to assess whether inhibiting hepatic EFHD1 could represent a novel therapy for treating metabolic liver disease. In human and mouse livers, EFHD1 is expressed at low levels preferentially in hepatocytes, with little to no expression in other cell types. It is found primarily on the outer mitochondrial membrane and inter-membrane space. **Methods:** To study the effects of EFHD1 inhibition on liver injury, we subject wild-type (WT) and EFHD1 whole body knockout (*Efhd1*$^{-/-}$) mice to diets which induced MASLD. We found that *EFHD1*$^{-/-}$ mice with MASLD exhibited lower levels of serum AST and ALT compared with WT which corresponded with reduced inflammation and fibrosis in *EFHD1*$^{-/-}$ livers. Moreover, RNA sequencing of *Efhd1*$^{-/-}$ livers from mice with MASLD revealed a significant reduction in genes associated with inflammation and fibrosis, relative to WT animals. To confirm that this was a liver-specific response, we treated mice suffering from MASLD with a liver-targeting AAV containing a short-hairpin RNAi against EFHD1 (shEFHD1). We found that the mice treated with shEFHD1 exhibited significantly lower liver damage and lower AST and ALT levels compared to control animals. **Results:** Mitochondria continuously undergo fission and fusion, and increased fission has been correlated with liver injury. We found EFHD1 was present at sites of ER-mitochondrial contact on the outer membrane, where fission and fusion occur. We found that mitochondria in *Efhd1*$^{-/-}$ hepatocytes were around 100.03±0.32% larger than controls and showed less remodeling after activating cytoplasmic Ca^{2+} signals. Thus, reducing fission by deleting EFHD1 may prevent mitochondrial damage and subsequent liver injury, representing a potential mechanism whereby EFHD1 ablation is protective in liver injury. **Conclusion:** These findings demonstrate that EFHD1 inhibition may be a promising therapy for liver injury.

Disclosures: David Eberhardt: Nothing to Disclose, Dipayan Chaudhuri: Nothing to Disclose

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1120 | EXPRESSION OF HEPATIC DRUG METABOLIZING ENZYMES IS ALTERED BY CONCOMITANT OBESOGENIC LIPIDS AND ETHANOL IN MICE AND ADULT HUMAN HEPATIC ORGANOIDS

Joseph Dempsey[1] Inkyung Kang[1] Julia Harkin[1] Susovon Bayen[1] Samira Abdirahim[1] Kelly Stevens[1] Rotonya Carr[1]

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Background: MetALD is the subtype of steatotic liver disease (SLD) that develops from metabolic dysfunction-associated SLD and ethanol (EtOH). Previously, we showed that mice given concomitant high fat, fructose, and cholesterol (FFC) and EtOH had greater steatosis and dyslipidemia compared to FFC or EtOH alone. FFC-EtOH mice also had downregulated hepatic insulin signaling. Previous studies have also shown that diet or EtOH alter the RNA expression of genes that metabolize xenobiotics, including drugs that manage insulin resistance in MetALD patients, such as TZDs. However, how the concomitant exposure of obesogenic lipids and ethanol alters the expression of hepatic xenobiotic metabolizing genes is not fully known. Furthermore, there are no reports of in vitro models of MetALD. We hypothesize that concomitant obesogenic lipids and EtOH will have a synergistic effect on the RNA expression of xenobiotic metabolizing genes in mouse liver and human hepatocytes. **Methods:** For our MetALD mouse model, we fed C57BL6/J male mice a chow (Chow) or FFC diet and co-administered either saline or EtOH for four experimental groups: Chow, EtOH, FFC, and FFC-EtOH for 12 weeks. Biomarkers for MetALD were taken, and the hepatic transcriptome was sequenced. We developed a new in vitro SLD model using adult human hepatocyte organoids (AHHOs) exposed to EtOH (100 mM), oleate (1 mM), or EtOH and oleate. Steatosis in AHHOs was determined by immunostaining for lipid droplets, and RNA was isolated for RT-qPCR. **Results:** In mice, gene set enrichment analysis of the hepatic transcriptome showed that FFC-EtOH, compared to EtOH alone, led to dysregulated biological pathways related to xenobiotic metabolism, oxidative stress, and lipid metabolism. Among 330 Phase I (oxidation) enzymes, the expression of 114 genes was decreased by either FFC or FFC-EtOH, including the cytochrome P450s (Cyp) 2b10, 2c's, and 3a11. Among 97 Phase II (conjugation) enzymes, expression of 37 genes, including glutathione-s-transferases, were altered by at least one diet. Immunostaining of AHHOs exposed to EtOH-oleate showed increased lipid droplets and lipid droplet protein perilipin 2 (PLIN2) compared to EtOH or oleate alone. PLIN2 RNA expression was increased by oleate and EtOH-oleate. EtOH increased the expression of CYP2B6, whereas oleate and oleate-EtOH decreased the expression of CYP2C8 and CYP3A4. Expression of the xenobiotic and lipid metabolism regulating nuclear receptor CAR was decreased by oleate and EtOH-oleate, which may be responsible for the decreased expression of CYP2C8 and CYP3A4. **Conclusion:** This study provides evidence of the potential effects of obesogenic diet, EtOH, and MetALD on xenobiotic metabolism in mouse liver and human hepatocytes. Obesogenic lipids alter the expression of xenobiotic metabolizing genes more than EtOH. Identifying the changes to enzymes that metabolize therapeutics may help improve treatment of metabolic diseases.

Disclosures: Joseph Dempsey: Nothing to Disclose, Inkyung Kang: Nothing to Disclose, Julia Harkin: Nothing to Disclose, Susovon Bayen: Nothing to Disclose, Samira Abdirahim: Nothing to Disclose, Kelly Stevens: Nothing to Disclose, Rotonya Carr: Grant/Research Support relationship with Merck; Has ended; Consultant relationship with Intercept; Has not ended; Consultant relationship with Astra Zeneca; Has ended

1121 | MODULATION OF GUT MICROBIOTA AND METABOLIC AND HISTOLOGICAL IMPROVEMENTS THROUGH METHYL GROUP DONOR SUPPLEMENTATION IN A METALD MODEL

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Background: *Metabolic and alcohol-related liver disease* (MetALD) describes patients who have *Metabolic dysfunction-associated steatotic liver disease* (MASLD) alongside alcohol consumption. This combination

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leads to intestinal barrier dysfunction, gut dysbiosis, and bacterial translocation which promotes liver inflammation; resulting in steatosis and fibrosis. Emerging therapeutic approaches, such as methyl group donor supplementation, may modulate epigenetic alterations and thereby exerting a beneficial effect on disease progression. **Methods:** Male C57BL/6J mice (10 wks old, 25 g) were randomly assigned to three experimental groups (8 mice/group): 1) Control group (ND); 2) MetALD (20% ethanol in water + 45% fat diet to induce liver damage); 3) MetALD + MetMix (MetALD diet + daily gavage of methionine, betaine, zinc sulfate, choline, B9, B6 and B12). Each group was maintained on its respective diet for 20 weeks. Body weight and body composition was monitored. Biochemical assays were conducted to measure liver enzymes, lipid profile, and hormones. Histopathological evaluation was performed on liver, adipose and colon tissues. Gene expression of proinflammatory markers was analyzed using qPCR, while 16S rRNA gene sequencing assessed gut microbiota. **Results:** Supplementation with methyl group donors led to a significant decrease ($p<0.05$) in body and fat weight, as well as in cholesterol, HDL, and LDL levels. Additionally, there was a trend towards reduction in AST, ALT, TG, VLDL, the hormones insulin, leptin, glucagon, and resistin and the mRNA of IL-6 and TNF-α. Histological analysis revealed a significant decrease ($p<0.05$) in hepatic steatosis and adipocyte area in the MetALD + MetMix group. Moreover, the length of the intestinal crypts tended to be restored to similar measure to those in the control group. The microbiota composition showed an enrichment of Firmicutes, resulting in a tendency to reestablish the Firmicutes/Bacteroidetes ratio, along with a trend towards increased alpha diversity in the supplemented group. Beta diversity was similar between groups. **Conclusion:** Methyl donor treatment improved body composition, lipid profile parameters and reduced the percentage of steatosis and adipocyte area while also showing a trend towards enhancing the abundance and diversity of the intestinal microbiota.

Disclosures: Carolina Diaz Canul: Nothing to Disclose, Ángel Omar Vázquez-Esqueda: Nothing to Disclose, Rebeca Rosas-Campos: Nothing to Disclose, Rebeca Escutia-Gutierrez: Nothing to Disclose, Natalia Gómez-Gómez: Nothing to Disclose, Mónica Alejandra Ibarra-Hernández: Nothing to Disclose, Marina Galicia-Moreno: Nothing to Disclose, Juan Armendariz-Borunda: Nothing to Disclose, Ana Sandoval-Rodriguez: Nothing to Disclose

1122 | THE ROLE OF MICRORNA-122 IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE

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Background: Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD), formerly known as nonalcoholic fatty liver disease is a major health problem. Worldwide, 25% of people have MASLD. MASLD is characterized by fat accumulation in more than 5% of the hepatocytes' macrovesicles and is not caused by alcohol or drugs. MASLD can present initially as acute steatohepatitis but can progress to fibrosis, cirrhosis, and liver failure. Despite being the leading cause of chronic liver disease worldwide, the general understanding of the disease remains limited. MicroRNAs are small non-coding RNAs that play a critical role in regulating post-transcriptional regulation of gene expression. Specifically, MicroRNA-122 (miR-122) makes up more than 70% of the total microRNAs in the liver and plays a major role in liver physiology, metabolism, and disease. miR-122 has been linked to various liver diseases including liver fibrosis, hepatocellular carcinoma, hepatitis C, cholestasis, and MASLD in adults. In previous studies, circulating miR-122 was found to be elevated in pre-pubertal obese children. However, there are *few* studies investigating the utility of miR-122 in patients with MASLD and its role in metabolic processes. **Methods:** We utilized miR-122 knockout mice and wildtype mice. The mice will be divided in four groups: 1.) miR-122 knockout mice with regular chow diet, 2.) wildtype mice with regular chow diet, 3.) miR-122 knockout mice with high-fat high-cholesterol diet, and 4.) wildtype mice with high-fat high-cholesterol diet. Euthanasia is induced at 7 months old. Serum and hepatic miRNA-122 are measured before euthanasia and liver autopsy will be performed to evaluate and compare histological differences. The samples will undergo staining procedures to detect fatty infiltration and fibrosis. Liver function and other metabolic process evaluation are also assessed utilizing aspartate transaminase (AST), alanine transaminase (ALT), bilirubin, glucose tolerance test (GTT) and insulin tolerance test (ITT). Body fat composition and body weight are also compared across different groups over time. **Results:** At 18 weeks, utilizing ANOVA models with post-hoc test, we observed a statically significant difference in weight progression across these 4 groups ($p<0.05$). The high-fat high-cholesterol diet miR-122 knock-out mice group showed the most impressive weight gain, followed by the miR-122 knock-out mice with regular chow diet. In addition, miR-122 knock-out mice maintain a higher basal glucose state with

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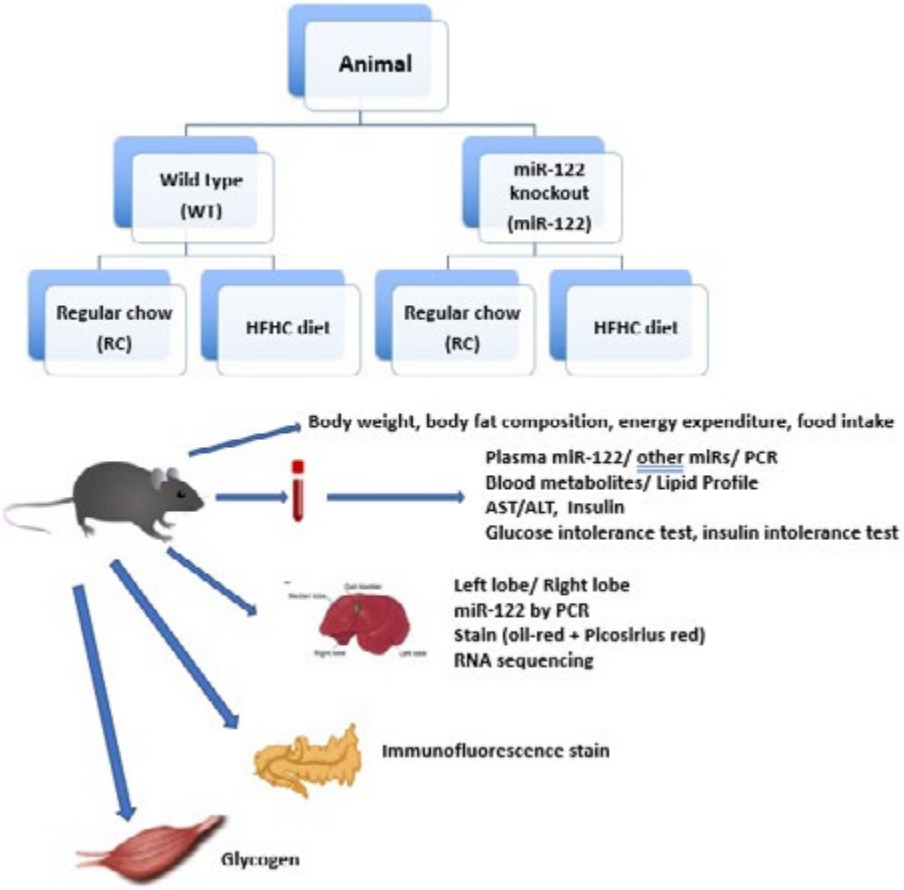
worse glucose tolerance than their wildtype counterparts (p <0.05). **Conclusion:** miR-122 plays a regulatory role in lipolysis and lipid metabolism. In addition, miR-122 also plays an important role and can potentially be investigated as a biomarker for liver steatosis, steatohepatitis, and fibrosis.



Disclosures: Khang Tran: Nothing to Disclose, Sherin Devaskar: Nothing to Disclose, Shubhamoy Ghosh: Nothing to Disclose, Kara Calkins: Nothing to Disclose

1123 | RETATRUTIDE IMPROVES STEATOHEPATITIS IN A NEW ACCELERATED MOUSE MODEL OF DIET-INDUCED STEATOHEPATITIS WITH A FRUCTOSE BINGE

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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is associated with significant mortality and morbidity, and related to fructose consumption. Retatrutide is a triple glucagon-like peptide 1 (GLP-1), glucose-dependent insulinotropic polypeptide (GIP), and glucagon receptor agonist that has been shown to reduce body weight and improve hepatic steatosis in adults with obesity. We aimed to create a novel shortened diet-induced steatohepatitis mouse model employing fructose to exacerbate disease and then evaluate whether retatrutide could abrogate the development of steatohepatitis in this mouse model. **Methods:** For the acute fructose-induced liver injury model, female and male mice were submitted to a single binge of fructose [10 mg/g body weight] dissolved in water 3, 6 and 9 hours prior to sacrifice. For the chronic diet-induced steatohepatitis model, female and male mice were placed on a western diet and on 23.1 g/L fructose and 18.9 g/L sucrose in the drinking water for 31 days, and were given a single fructose binge 6 hours before sacrifice. To evaluate the effectiveness of retatrutide in that chronic model, female mice were treated with subcutaneous retatrutide injections [30nmol/kg body weight] every 2-3 days during the last 2 weeks of the 31-day long model. **Results:** Females showed significantly increased liver weight-to-body weight ratio, plasma alanine aminotransferase (ALT) levels and hepatic triglycerides 6 hours after a single binge in the acute model. In treated male mice however,

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only plasma ALT levels but not steatosis were increased compared to controls. Both female and male mice showed elevated plasma ALT levels, hepatic triglycerides and cholesterol, and expression of hepatic inflammatory markers in the chronic model of diet-induced steatohepatitis. Both treated female and male groups showed higher body weights, total mesenteric, subcutaneous and gonadal fat compared to their chow-fed controls. Finally, an intervention with retatrutide over the last 2 weeks of the 31-day feeding model led to decreased body and liver weights, plasma ALT levels, and hepatic triglycerides and cholesterol in female mice. **Conclusion:** Female mice are more prone to acute fructose-induced liver injury than males, whereas both female and male mice develop robust steatohepatitis in a novel chronic diet-induced steatohepatitis model over 31 days with a final fructose binge. Retatrutide improves diet-induced steatohepatitis in mice.

Disclosures: Greta Viebahn: Nothing to Disclose, Amit Khurana: Nothing to Disclose, Bernd Schnabl: Grant/Research Support relationship with Prodigy Biotech; Has not ended; Grant/Research Support relationship with CymaBay Therapeutics; Has ended; Consultant relationship with Surrozen; Has ended; Grant/Research Support relationship with Intercept Pharmaceuticals; Has not ended; Stock â€“ privately held company relationship with Nterica Bio; Has not ended; Grant/Research Support relationship with Axial Biotherapeutics; Has ended; Consultant relationship with Ambys Medicines; Has ended; Grant/Research Support relationship with ChromoLogic; Has not ended; Consultant relationship with Mabwell Therapeutics; Has not ended, Phillipp Hartmann: Nothing to Disclose

1124 | INSIGHT TO THE EFFICACY OF CLINICAL ANTI-FIBROTIC COMPOUNDS USING DIGITAL PATHOLOGY WITH ARTIFICIAL INTELLIGENCE ANALYSIS IN A 3D MULTICELLULAR PRIMARY HUMAN MASH MODEL

Susan Grepper[1] Radina Kostadinova[1] Mathieu Petitjean[2]

[1]InSphero, [2]Pharmanest

Background: Metabolic dysfunction-associated steatohepatitis (MASH) is a severe liver disease characterized by lipid accumulation, inflammation and fibrosis. The development of MASH therapies has been hindered by the lack of human translational models and limitations of analysis techniques for fibrosis. Here we aimed to establish an algorithm for automated phenotypic quantification of fibrosis of Sirius Red stained histology sections of InSphero's 3D InSight™ Human liver MASH (MASH LiMT) model using a digital pathology quantitative single-fiber artificial intelligence FibroNest image analysis platform. **Methods:** The MASH hLiMT model consists of primary human hepatocytes, Kupffer cells, liver endothelial cells and hepatic stellate cells. Upon exposure to defined lipotoxic and inflammatory stimuli such as free fatty acids and LPS in media containing high levels of sugar and insulin the 3D MASH model displayed key disease pathophysiological features within 10 days of treatment. Quantifiable markers were established for drug efficacy testing such as secretion of pro-collagen type I/III and TIMPs/MMPs as well as quantification of fibrosis using FibroNest platform based on the Sirius Red staining of histology slides. Next generation sequencing was used for the assessment of the gene expression changes. **Results:** The FibroNest algorithm for MASH hLiMTs was validated using anti-fibrotic reference compounds with different therapeutic modalities: ALK5i and anti-TGF-beta antibody. The phenotypic quantification of fibrosis demonstrated that both reference compounds decreased the deposition of fibrillated collagen in alignment with effects on the secretion of pro-collagen type I/III, tissue inhibitor of metalloproteinases-1 and matrix metalloproteinase-3 and pro-fibrotic gene expression. In contrast, several clinical MASH compounds, alone and in combination, showed strong anti-fibrotic effects on the deposition of collagen fibers, however less pronounced on the secretion of pro-fibrotic biomarkers. **Conclusion:** In summary, the phenotypic quantification of fibrosis of MASH hLiMTs combined with secretion of pro-fibrotic biomarkers and transcriptomics represents a promising drug discovery tool for assessing anti-fibrotic compounds.

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1125 | CDS2 DELETION LEADS TO SREBP DYSREGULATION AND FATTY LIVER INDUCTION

Matthew Mitsche *Chai-Wan Kim*[1]

[1]*University of Texas Southwestern Medical Center*

Background: Recent studies in both human genetics and mouse models have highlighted the significance of phosphatidylinositol (PI) in the progression of fatty liver disease (FLD). Despite this, the precise mechanisms underlying PI's role remain elusive. This study aimed to elucidate the involvement of PI in FLD by disrupting hepatic PI biosynthesis through modulation of CDP-diacylglycerol synthase 2 (CDS2) expression, the primary enzyme in PI biosynthesis. **Methods:** We generated liver-specific knockouts of CDS2 and SCAP (SREBP cleavage-activating protein) using adeno-associated virus (AAV) expressing sgRNA against each gene. Phospholipid species were analyzed and quantified by LC/MS. **Results:** CDS2 liver-specific knockout mice exhibited a pronounced development of fatty liver, characterized by elevated triglyceride and cholesterol levels. Notably, liver PI levels were significantly reduced in CDS2 knockout mice, accompanied by dysregulated activation of sterol regulatory element-binding protein (SREBP) even during fasting conditions, leading to increased de novo lipogenesis. Intraperitoneal administration of exogenous PI effectively normalized SREBP cleavage, highlighting PI's critical role in SREBP regulation. Furthermore, simultaneous knockout of SCAP with CDS2 restored the normal liver phenotype, implicating SREBP activation as a central mechanism underlying fatty liver development in CDS2 knockout mice. **Conclusion:** Deletion of CDS2 in the liver reduced PI levels, subsequently inducing significant fatty liver due to dysregulated SREBP activation. This study underscores the importance of CDS2 in maintaining PI homeostasis, which in turn regulates SREBP activity and lipid metabolism. Our findings provide valuable insights into the pathogenesis of metabolic disorders and offer potential therapeutic strategies for targeting FLD.

Disclosures: Matthew Mitsche: Nothing to Disclose, Chai-Wan Kim: Nothing to Disclose

1126 | DIFFERENTIAL ROLE OF *SERPINE1* IN HEPATOCYTES AND HEPATIC STELLATE CELLS IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS ◆

Hyun Young Kim[1] *Sara Brin Rosenthal*[1] *Wonseok Lee*[1] *Xiao Liu*[1] *Haeum Jang*[1] *Karin Diggle*[1] *David Brenner*[2] *Tatiana Kisseleva*[1]

[1]*University of California, San Diego,* [2]*Sanford Burnham Prebys Medical Discovery Institute*

Background: *SERPINE1*, the gene encoding PAI-1 protein (Plasminogen Activator Inhibitor-1), inhibits fibrinolysis in the coagulation process and is involved in atherosclerosis, obesity, and metabolic liver disease, ranging from steatosis to metabolic dysfunction-associated steatohepatitis (MASH) and fibrosis. Hepatocytes serve a significant source of plasma PAI-1, which regulates fibrinolysis in obese mice. Despite extensive studies, the cellular source and function of PAI-1 in MASH remain poorly understood. Here, we investigated PAI-1 expression in human MASH livers and dissected the role of PAI-1 using cell-type-specific *Serpine1* knockout mice fed with Western diet. **Methods:** Hepatic Stellate Cell (HSC)-specific knockout ($HSC^{\Delta Serpine1}$) mice were generated by crossing $Lrat^{Cre}$ mice with *Serpine1*-floxed mice (*Serpine1*$^{f/f}$ mice). Hepatocyte-specific knockout ($Hepatocyte^{\Delta Serpine1}$) mice were generated by crossing Alb^{Cre} mice with *Serpine1*$^{f/f}$ mice. HSC and hepatocyte double knockout ($HSC^{\Delta Serpine1}Hepatocyte^{\Delta Serpine1}$) mice were generated by crossing $HSC^{\Delta Serpine1}$ females with $Hepatocyte^{\Delta Serpine1}$ males. Mice were fed with Western diet (AIN-76A diet with 30 % fructose water) for 24 weeks to induce MASH. **Results:** Based on single nucleus (sn)RNA-sequencing analysis of livers from NORMAL (n=5), MASL (n=4), and MASH (n=9, fibrosis stage 2-4) donors, *SERPINE1* was mainly expressed in HSCs and hepatocytes. *SERPINE1* was identified as one of the most highly induced genes in MASH HSCs (compared to NORMAL and MASL HSCs). To investigate the role of *Seprine1* in MASH, MASH was induced in $HSC^{\Delta Serpine1}$, $Hepatocyte^{\Delta Serpine1}$, and $HSC^{\Delta Serpine1}Hepatocyte^{\Delta Serpine1}$ mice. Deletion of *Serpine1* in HSCs or hepatocytes significantly reduced *Serpine1* transcript in whole liver tissues, as well as PAI-1 secreted to plasma. Remarkably, $HSC^{\Delta Serpine1}$ mice were strongly protected from MASH-induced steatosis and liver fibrosis, while MASH-induced $Hepatocyte^{\Delta Serpine1}$ and $HSC^{\Delta Serpine1}Hepatocyte^{\Delta Serpine1}$ mice exhibited a phenotype similar to that observed in *Serpine1*$^{f/f}$ mice. To further explore the functions of PAI-1 in HSCs, *SERPINE1* was knocked down in TGFβ1-stimulated human HSCs. Knockdown of PAI-1 significantly decreased TGFβ1-mediated HSC activation and migration. **Conclusion:**

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SERPINE1 is expressed in HSCs and hepatocytes of MASH livers. Our findings on cell-type-specific *Serpine1* knockout mice suggest that targeting of *Serpine1* in HSCs may ameliorate MASH-induced liver fibrosis.

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1127 | CHARACTERIZATION OF HUMAN LIVER SPHEROIDS USING STABLE ISOTOPE TRACING

Samuel Kerk[1] Kanani Hokutan[2] Wonseok Lee[2] Sadatsugu Sakane[2] Karin Diggle[2] Tatiana Kisseleva[2] Christian Metallo[1] David Brenner[3]

[1]Salk Institute for Biological Studies, [2]University of California, San Diego, [3]Sanford Burnham Prebys Medical Discovery Institute

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) progresses from simple steatosis to metabolic dysfunction-associated steatohepatitis (MASH) and liver fibrosis. Dysregulation of lipid and glucose metabolism is a major factor in the development of MASH. However, progress in target discovery and drug development for MASH is limited by the available methodologies to mimic metabolically injured human livers. We developed a technique to generate human 3D liver spheroids to study 'liver in a dish' and induced metabolic liver injury in the spheroids using a MASH-cocktail containing glucose, palmitate, and oleate. We identified significant lipid accumulation in MASH spheroids, which led us to investigate the source of lipids. **Methods:** We incubated human liver spheroids with stable isotope-labeled MASH-cocktail components to identify the lipid source. Human liver spheroids were generated using a total of 5,300 primary human liver cells containing 60% hepatocytes and 40% non-parenchymal cells including Hepatic Stellate Cells (HSCs). Upon formation, spheroids were incubated with DMEM supplemented with each of the isotope-labeled MASH cocktail components that can be a source for intracellular lipid synthesis; U-^{13}C-glucose, $^{13}C_2$-acetate (β-oxidation of palmitate generate acetyl-coA), or $^{13}C_{18}$-BSA-oleate. Spheroids and supernatant were collected after 2 days and analyzed for isotope enrichment using gas chromatography-mass spectrometry and liquid chromatography with tandem mass spectrometry. **Results:** Isotope-labeled glucose, acetate, and oleate are catabolized in the tricarboxylic acid cycle (TCA cycle) of human liver spheroids. In lipidomic analysis, we found that $^{13}C_{18}$-BSA-oleate is substantially incorporated into diacylglycerols (DGs), triacylglycerols (TGs), phosphatidylethanolamines (PEs), and phosphatidylcholines (PCs). Human liver spheroids produced M+3 glycerol-3P from U-^{13}C-glucose that was incorporated into lipid head groups (hydrophilic backbone of lipids). Minor $^{13}C_2$-acetate was incorporated into DGs, TGs, PEs, and PCs, indicating that these specific culture conditions facilitate the uptake of exogenous oleate by human liver spheroids but do not simulate *de novo* lipogenesis. **Conclusion:** Our human liver spheroids can uptake exogenous fatty acids and use them for the synthesis of complex lipids. Human liver spheroids recapitulate metabolism in the human liver and can be a useful tool for translational research.

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1128 | THE ROLE OF SMOOTHENED (SMO) IN HEPATOCYTE SENESCENCE AND FERROPTOSIS IN MASLD

Rajesh Dutta[1] Kuo Du[1] Ji Hye Jun[1] Seh-Hoon Oh[1] Anna Mae Diehl[1]

[1]Duke University

Background: Smoothened (SMO), a key component of the Hedgehog signaling pathway, plays a crucial role in regulating liver function and maintaining cellular homeostasis. Disruption of SMO in mouse hepatocytes dramatically accelerates their aging and promotes senescence. Aging generally increases the risk for ferroptosis and inhibiting ferroptosis was reported to improve metabolic-associated steatotic liver disease (MASLD) in mice. This study investigates the association of SMO expression with senescence and aging in hepatocytes of humans

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with MASLD. **Methods:** Single-nuclei RNA sequencing (snRNA-seq) was performed on liver samples from control and MASLD patients at various fibrosis stages. Data were analyzed using the Seurat (v5.0.3) package in R. Senescence and aging gene signatures were applied to the snRNA-seq data to identify senescent and aging hepatocyte populations. SMO expression was assessed, and cells were classified as SMO positive if the normalized expression of SMO was greater than zero and SMO negative if less than zero. The association between SMO expression and ferroptosis was examined using a previously established ferroptosis gene signature and validated by immunostaining. **Results:** We found that hepatocyte SMO expression decreases in MASLD in parallel with advancing fibrosis stages. Application of a senescence gene signature revealed a dramatic 20-fold increase in the percentage of senescent hepatocytes in F3-F4 fibrosis stages compared to F0. Further analysis showed that 95% of the senescent hepatocyte population was negative for SMO expression and exhibited decreased expression of Hedgehog pathway genes. Additionally, the aging gene signature indicated a significant increase in the aging hepatocyte population within the MASLD group, with 91.8% of aging hepatocytes being SMO negative. Importantly, we observed a substantial increase in the ferroptosis score among SMO-negative hepatocytes in the MASLD group, with a six-fold increase compared to a 1.07-fold increase in the control group. Immunostained liver sections confirmed that ferroptosis markers increased in hepatocytes as fibrosis severity worsened. **Conclusion:** Our findings suggest that SMO expression is inversely related to fibrosis progression, cellular senescence, and aging of hepatocytes in MASLD. Furthermore, the elevated ferroptosis scores in SMO-negative cells underscore that the loss of SMO is a key factor in the induction of ferroptosis in MASLD.

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1129 | ENTPD1/CD39 REGULATES INFLAMMATORY PROCESS IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD)

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Background: Extracellular ATP (eATP) is a damage-associated molecule that triggers the inflammatory response, leading to immune cell infiltration and cytokine release. ENTPD1/CD39 is an ectonucleotidase which is responsible for metabolizing ATP, decreasing circulating ATP levels, allowing a regulation of inflammation. The aim of this study was to determine the role of ENTPD1 in the early stages Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) progression. **Methods:** Thirty-six male C57BL/6J mice were fed a High Fat High Carbohydrate and Cholesterol (HFHCC) diet (5TJT Test Diet) (n=29) or chow (n=7) for 52 weeks and thirty male C5BL/6J mice were fed a CDAC-HFD diet (Teklad Rodent Maintenance 2014) (n=20) or chow (n=10) diet for 8 weeks. *Entpd1* gene and protein expression were assessed by PCR and IHC assays. Moreover, one-hundred three biopsy-proven MASLD patients were included and classified according to SAF and NAS Score as bland steatosis (n=42) or MASH (N=61). Patients with at least 1 point in each parameter of SAF score and NAS Score > 4 were classified as MASH. Serum CD39 levels were measured by ELISA. **Results:** In mice fed a HFHCC diet for 52 weeks 5 times higher levels of *Entpd1* were observed compared to controls (p<0.0001) (Figure 1A). Moreover, in mice fed with a CDAC-HFD diet, an increase of *Entpd1* levels were observed (fold change of 1 ± 0.37 vs 4.3 ± 2.08; p<0.0001) (Figure 1B). In the IHC of Entpd1, wider expression of this protein was detected in more damaged liver sections. Patients with MASH (1368 ±1094 pg/ml) had increased ENTPD1 levels compared to patients with bland steatosis (925 ± 474 pg/ml) (p=0.006). Based on inflammation, an increase in ENTPD1 serum levels were observed as inflammation increased [none (n=19), 879 ± 484 pg/ml; mild (n=56), 1164 ±757 pg/ml; moderate (n=28), 1444 ±1312 pg/ml; p= 0.112] (Figure 1C). In addition, a correlation between ENTPD1 levels and SAF Score's activity was found (p = 0.03). ENTPD1 levels were not significant in fibrosis [F0 (n=22), 947 ± 563 pg/ml; F1 (n=22), 1404 ±1536 pg/ml; F2 (n=17), 1263 ±656 pg/ml; F3 (n=33), 1227 ±749 pg/ml; F4 (n=9), 960 ±490 pg/ml; p= 0.491] (Figure 1D). **Conclusion:** mRNA and protein levels of *Entpd1* were found raised as the disease progresses in mice. In patients with MASH, ENTPD1 seems to participate in early process to develop

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steatosis and the transition to steatohepatitis. ENTPD1 could be a new therapeutic target to address MASLD progression.

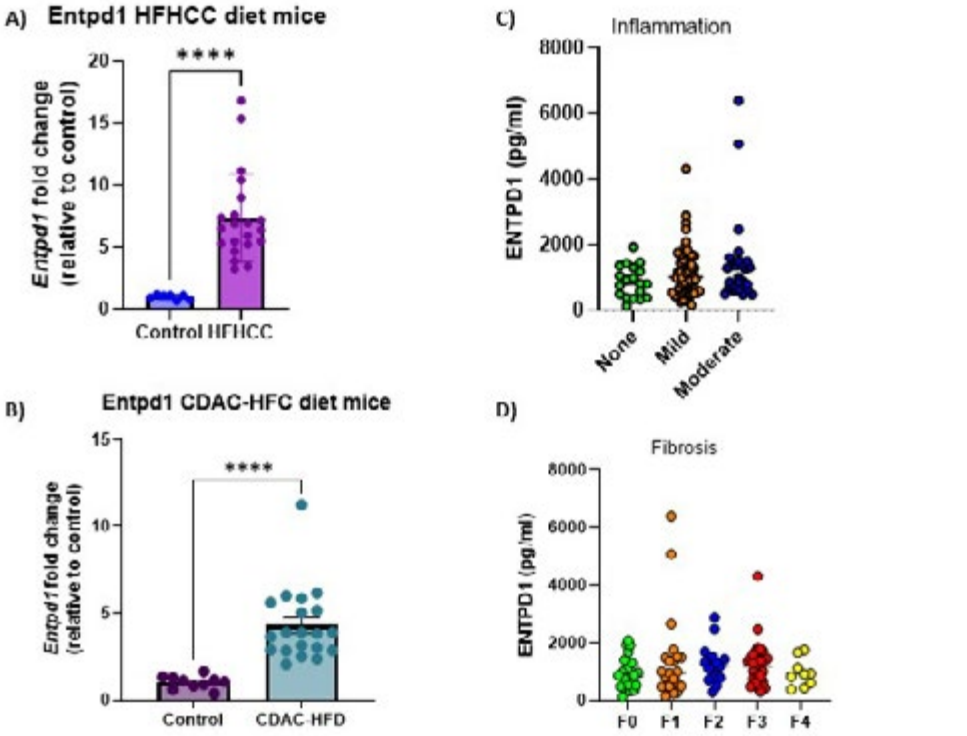

Figure 1. A) Relative *Entpd1* expression in mice fed with a HFHCC diet. **B)** Relative *Entpd1* expression in mice fed with a CDAC-HFC diet. **C)** ENTPD1 levels in serum of patients classified in none, mild or moderate inflammation. **D)** ENTPD1 levels in serum of patients classified based on the fibrosis stage.

Disclosures: Vanessa Garcia-Fernandez: Nothing to Disclose, Antonio Gil-Gómez: Nothing to Disclose, Rocío Muñoz Hernández: Nothing to Disclose, Angela Rojas: Nothing to Disclose, Sheila Gato-Zambrano: Nothing to Disclose, Rocio Montero-Vallejo: Nothing to Disclose, Rocio Gallego-Duran: Nothing to Disclose, Douglas Maya Miles: Nothing to Disclose, Maria Del Carmen Rico: Nothing to Disclose, Javier Ampuero Herrojo: Nothing to Disclose, Manuel Romero-Gómez: Nothing to Disclose

1130 | SINGLE NUCLEI RNA-SEQ ANALYSIS SUGGESTS THAT HUMAN MASLD IS A CILIOPATHY ◆

Rajesh Dutta[1] *Raquel Maeso-Diaz*[2] *Kuo Du*[1] *Ji Hye Jun*[1] *Seh-Hoon Oh*[1] *Anna Mae Diehl*[1]

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Background: Primary nonmotile cilia (PC) are a hub for signal transduction and critically regulate metabolism. Ciliopathies, such as Alstrom Syndrome (ALMS), exhibit severe insulin resistance, obesity, steatotic liver disease (SLD) and liver fibrosis. Hedgehog (Hh) is the most well-known signaling system that is coordinated by PC. Smoothened (Smo), a pivotal component of the Hh pathway, must traffic onto PC to activate signaling that regulates Hh target genes, and genetic manipulations that abrogate ciliogenesis block Hh signaling. We reported that conditional deletion of Smo in adult hepatocytes (Heps) rapidly evokes insulin resistance and induces SLD and liver fibrogenesis in young chow-fed mice. However, adult Heps are thought to rarely (if ever) exhibit PC. **Methods:** To resolve this paradox we conducted single-nucleus RNA sequencing (snRNA-seq) on 48, 059 Heps from liver samples of control subjects (n=6) and patients with MASLD at various stages of fibrosis (F0-1, F3-4 n=3/group) to evaluate co-expression of Smo and PC markers. Data were analyzed using the Seurat package (version 5.0.3) in R. Smo expression levels were quantified, with cells classified as Smo-positive if the normalized expression of Smo exceeded zero. To investigate the relationship between Smo expression and ciliary components, we used the FindMarkers function in Seurat to

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calculate a composite “cilia_score” based on expression levels of 303 genes from the SYSCILIA gold standard (SCGS) which contains a comprehensive list of genes associated with ciliary function. High resolution confocal microscopy was used to assess co-localization of cilia markers (Ift88, Arl13b) and Smo in primary Hep isolates from healthy adult mice. **Results:** SnRNA-seq analysis showed that 35% of the Hep population in human livers is Smo(+) (versus <10% Smo(+) cells in other populations). Eighty-five percent of the Smo(+) Heps have a positive cilia score. Immunocytochemistry confirmed that Smo protein co-localizes with Ift88 and Arl13b. Smo(-) Heps express lower levels of genes that are mutated and dysfunctional in ALMS and other ciliopathies. Smo(-) Heps also have significantly lower cilia_scores than SMO(+) Heps, showing that expression of ciliary gene transcripts declines when Smo is absent. Compared to controls, human MASLD livers have significantly fewer Smo(+) Heps and Hep populations become progressively depleted of Smo(+) cells as fibrosis stage increases. **Conclusion:** Subpopulations of Heps in adult human livers co-express Smo and signatures of PC. Hep expression of Smo is decreased in human MASLD and livers become enriched with Smo(-) Heps with low cilia signatures. These Smo(-)/low PC Heps have decreased expression of genes that are inactivated by mutations in ALMS and other ciliopathies that cause systemic metabolic dysfunction, SLD and liver fibrosis. These results suggest that human MASLD is a ciliopathy.

Disclosures: Rajesh Dutta: Nothing to Disclose, Raquel Maeso-Diaz: Nothing to Disclose, Kuo Du: Nothing to Disclose, Ji Hye Jun: Nothing to Disclose, Seh-Hoon Oh: Nothing to Disclose, Anna Mae Diehl: >$10,000 relationship with Tune Therapeutics; Has not ended; <$10,000 relationship with Boehringer Ingelheim; Has not ended; Associate Editor, < $10,000 relationship with EASL - Journal of Hepatology; Has not ended; >$10,000 relationship with HeptaBio; Has not ended

1131 | MACHINE LEARNING ON MULTIPLE MODALITIES OF CLINICAL AND CELLULAR DATASETS OF LIVER AND HEPATOCYTE FAT CONTENT REVEALS UNIQUE TARGETS, SUBSEQUENTLY VALIDATED IN PRECLINICAL MODELS

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[1]insitro

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is characterized by steatosis (≥ 5% fat accumulation) in the absence of other known causes for liver disease. Though MASLD is widely recognized to be polygenic, genome-wide association studies (GWASs) have to date identified only a handful of loci (< 20), primarily due to the need for accurate and scalable phenotyping. **Methods:** We employed machine learning (ML) to predict liver fat content using each of three different data modalities available in the UK Biobank (UKB): dual-energy X-ray absorptiometry (DXA; n = 46,461 participants), plasma metabolites (n = 82,138), blood-based biomarkers (BMx; n = 262,927) and conducted GWASs, separately, within each modality. To credential the hits, we employed pooled optical screening in human HepG2 cells using CRISPR-cas9 technology at a druggable genome scale (~2000 genes), with ML-based lipid droplet and cellular analysis as the phenotypic readout to identify high dimensional revertants. We selected five genes with large effect size and knocked them down using siRNA in diet-induced obese (DIO) mice, to assess their impact on hepatic lipid content. **Results:** GWASs of ML-predicted liver fat from the three modalities (DXA, metabolites and BMx) identified 15, 55, and 314 loci,respectively, totalling 321 unique independent loci. In addition to replicating 9 of the 14 known MASLD loci at genome-wide significance, we identified 17 novel genes involved in de novo lipogenesis, highlighting its causal role in MASLD pathogenesis. Cellular CRISPR-cas9 screening efforts yielded ~150 novel hits, validating many of our GWAS genes including novel high dimensional revertants as well as drivers. Of our five genes selected for in vivo testing, four significantly decreased hepatic fat content in DIO mice, with two showing comparable results to DGAT2, an enzyme that regulates triglyceride synthesis, with programs currently in clinical trials. **Conclusion:** Our work shows the ability of ML-enabled statistical genetics to uncover novel genetic modulators of MASLD, with four of five tested targets validating in a translatable animal model.

Disclosures: santhosh satapati: Nothing to Disclose, Hari Somineni: Nothing to Disclose, Summit Mukherjee: Nothing to Disclose, Colm O’Dushlaine: Nothing to Disclose, Max Salick: Nothing to Disclose, Saradha Venkatachalapathy: Nothing to Disclose, Tima Dehghani: Nothing to Disclose, Vaishaali Natarajan: Nothing to Disclose, Tanaya Walimbe: Nothing to Disclose, Ariel Kauss: Nothing to Disclose, Kaitlin Flynn: Nothing to

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Disclose, Philip Tagari: Nothing to Disclose, Daphne Koller: insitro: Employee, insitro: Stock – privately held company, insitro: Executive role, David Lloyd: Nothing to Disclose

1132 | LONGITUDINAL TRACKING OF RESPONSE TO THERAPY IN A DIET-REVERSAL MASH MOUSE MODEL

Tomek Czernuszewicz[1] Juan Rojas[1] Thomas Kierski[1] Brian Velasco[2] Phillip Durham[2] Paul Dayton[2] Ryan Gessner[1]

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Background: Automated small-animal ultrasound using a Vega™ imager has recently been proposed as a valuable noninvasive tool for staging liver disease in mouse models. The device can provide longitudinal readouts in mice of liver stiffness (LS), echogenicity (LE), and volume (LV) that have been shown to correlate with histological endpoints such as steatosis, fibrosis, and hepatomegaly. While most studies to date have focused on monitoring the progression of disease, few have focused on regression in response to therapy. The purpose of this study was to evaluate the ability of Vega to monitor disease regression using a diet-reversal study design, validated with histology. **Methods:** 12-wk-old C57Bl/6 female mice (N=40) were split into 5 groups (N=8 per group). Mice were fed one of three diets for 18 weeks: choline-deficient high fat diet ("CDAHFD", Research Diets, A06071302); choline-normal high fat diet ("HFD", A06071306); or standard diet ("SD"). After 8 wks, half of CDAHFD mice were switched to HFD, and half on HFD were switched to CDAHFD. Imaging was performed every 2 wks including (1) a wide-field 3D B-mode scan and (2) a 3D shear wave elastography (SWE) scan covering the liver. Scans were analyzed in 3D by manually outlining the border of the liver to produce 3 readouts: median LS, median LE, and LV. At the final timepoint, livers were harvested for histological workup. H&E and picrosirius red (PSR) slides were quantified using automated disease scoring (RevealBio) to measure readouts such as fibrosis and steatosis. In vivo parameters were compared against ex vivo to determine level of agreement (Pearson correlation, r). **Results:** Imaging revealed significant increases in LS, LE, and LV in CDAHFD compared to both SD and HFD. At baseline, LS was 4.1 ± 0.4 kPa and LE was 27.6 ± 3.0 a.u. By 8 wks, LS had increased by 1.8-fold to 8.0 ± 0.4 kPa, and LE by 3.8-fold to 103.0 ± 3.5 a.u. Following diet switch, a sharp reversal was observed, with LS regressing to 5.5 ± 0.4 kPa and LE to 77.1 ± 5.6 a.u after only 2 wks, and returning nearly back to baseline after 10 more wks. Histology confirmed substantial regression of steatosis (18.9 ± 2.7% vs. 4.3 ± 1.2%) and liver weight (1.8 ± 0.2 g vs. 1.2 ± 0.2 g) both of which were non-significant compared to SD controls. Fibrosis also decreased considerably after diet reversal (13.4 ± 2.8% vs. 8.0 ± 1.6%) but was still significantly elevated over SD (2.9 ± 0.6%). In vivo and ex vivo parameters were all significantly correlated; LE and steatosis (r = 0.97), LV and weight (r = 0.85), and LS and fibrosis (r = 0.74). **Conclusion:** Results indicate Vega can be used to track the progression and regression of liver disease in MASH mouse models. LE and LV were highly correlated with steatosis and liver weight in this model. LS, while still well correlated, indicated more regression in fibrosis than histology, suggesting fibrosis was not the only parameter influencing LS modulation. Future studies will evaluate imaging in the context of pharmaceutical therapies.

Disclosures: Tomek Czernuszewicz: Revvity, Inc.: Employee, Juan Rojas: Nothing to Disclose, Thomas Kierski: Nothing to Disclose, Brian Velasco: Nothing to Disclose, Phillip Durham: Nothing to Disclose, Paul Dayton: Nothing to Disclose, Ryan Gessner: Nothing to Disclose

1133 | EXAMINATION OF PREDICTORS OF METABOLIC STEATOTIC LIVER DISEASE (MASH/MASLD) AMONG WOMEN ON ORAL CONTRACEPTIVES (OCPS) USING THE NATIONAL INPATIENT SAMPLE: A 10-YEAR RETROSPECTIVE ANALYSIS

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[1]Piedmont Athens Regional, [2]Piedmont Healthcare, [3]Beth Israel Lahey Hospital, [4]More House School of Medicine

Background: The prevalence of metabolic associated steatotic liver disease is an increasing concern globally. Oral contraceptive pills (OCPs) are widely used for birth control and hormonal regulation. They have been associated with increased prevalence of focal nodular hyperplasia. However, little is known about the relationship with other hepatic diseases such as MASH/MALD. Through a retrospective analysis, we seek to identify potential associations and contributing factors of MASH/MALD in relation to the use of OCPs with a

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goal of providing crucial insights for healthcare providers managing women's health and informing future clinical guidelines. **Methods:** The 2010-2020 US National Inpatient Sample (NIS) Database were utilized. Adult women 21-45 years of age, hospitalized between 2010–2020 in the US, were assessed for a diagnosis of MASLD. Patients with MASLD were matched with patients without MASLD for age, race, socio-economic status and geographic location using propensity score matching. Baseline patient characteristics and outcomes of interest were compared in the matched cohort. Univariate logistic regression was used to estimate the adjusted odds ratio for the study outcomes in the study group compared to control. Multivariate logistic regression was used to determine the independent predictors of increased prevalence of MASLD among female patient with OCP use. The odds ratio was calculated for each association, and the level of significance used for retention was 0.05. International Classification for Diseases (ICD) 9 and 10 codes were used. Data analysis was performed using SPSS software version 22 **Results:** 531,125 adult females aged 21-45 years diagnosed with MASH/ MASLD were identified nationwide in a cohort of admitted patients between 2010-2020. 57.8% were whites. The univariate analysis indicated statistically significant prevalence of MASH/ MASLD across different races, urban-rural locations, and income quartiles.The use of OCPs and comorbid conditions such as Polycystic Ovary Syndrome (PCOS), obesity, hypertension, chronic kidney disease, tobacco use, alcohol use, hyperlipidemia, metabolic syndrome, endometriosis, dysmenorrhea demonstrated significant associations with MASH/MAFLD . Following the multivariate logistic regression adjusting for confounding variables and comorbidities revealed race alcohol use disorder, tobacco use disorder, MASH cirrhosis, chronic liver disease PCOS, metabolic syndrome, hyperlipidemia, obesity, diabetes hypertension, CKD and endometriosis were associated with increased odds of developing MASH/MASLD. Additionally, OCP use revealed an increased odds of developing MASH/MASLD which was statistically significant. **Conclusion:** Our study revealed a significant association between OCP use and an increased prevalence of MASLD, highlighting the need for healthcare providers to consider liver health when prescribing OCPs. Additionally, comorbid conditions highlighted above were also significantly associated with MASLD, further emphasizing the multifactorial nature of this disease. The findings demonstrate substantial variations in MASLD prevalence across different demographic groups and a notably higher prevalence among white and Asian Pacific women. These findings are crucial for the development of tailored clinical guidelines and preventative strategies, ensuring comprehensive care for women at risk of MASLD. Further prospective studies are warranted to explore the underlying mechanisms and causal relationships, ultimately improving patient outcomes, and guiding public health interventions.

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Table 2: Multivariate logistic Regression

Variables	Odds Ratio (CI)	P- value
Race		0.000
White	0.168 (0.161 – 0.176)	0.000
Black	0.337 (0.058 – 0.064)	0.000
Hispanic	0.061 (0.058 – 0.064)	0.000
Asian Pacific	0.042 (0.040 – 0.045)	0.000
Native American	0.075 (0.072 – 0.079)	0.000
Others	Reference group	-
Patient Location		
Central countries of metro area of > 1 million	0.681 (0.653 – 0.711)	0.000
Fringe countries of metro area ≥ 1 million.	0.480 (0.460 – 0.501)	0.000
Countries in Metro area of 250,000-999,999	0.199 (0.190 – 0.209)	0.000
Countries in metro area of 50,000-249,999	0.189 (0.179 – 0.199)	0.000
Micropolitan, countries	0.144 (0.136 – 0.153)	0.000
Not metropolitan or micropolitan countries	Reference group	-
Median Household Income (National Quartile for patient zip)		
40,999 – 51,999	0.716 (0.689 – 0.744)	0.000
41,000 – 70,999	0.597 (0.573 – 0.621)	0.000
51,000 – 93,999	0.520 (0.497 – 0.544)	0.000
Tobacco use disorder	1.675 (1.604 - 1.750)	0.000
Alcohol use disorder	3.916 (3.547 - 4.323)	0.000
MASH cirrhosis	10.784 (8.489 – 13.714)	0.000
Chronic Liver Disease	14.663 (9.306 – 23.103)	0.000
PCOS	3.467 (2.964 – 4.054)	0.000
Metabolic Syndrome	5.213 (3.330 – 8.162)	0.001
Hyperlipidemia	2.390 (2.230 – 2.562)	0.000
Obesity	5.963 (5.733 – 6.203)	0.000
Diabetes	2.283 (2.172 – 2.400)	0.000
Hypertension	2.272 (2.178 – 2.369)	0.000
CKD	1.289 (1.153 – 1.441)	0.000
Endometriosis	1.031 (0.888 – 1.197)	0.687
Dysmenorrhea	0.418 (0.357 – 0.489)	0.000
OCP	2.722 (1.690 – 4.385)	0.000

Disclosures: Elizabeth Soladoye: Nothing to Disclose, kikelomo Olaosebikan: Nothing to Disclose, Dominic Amakye: Nothing to Disclose, Chineye (Brenda) Amuchi: Nothing to Disclose, Chibuzo Eze: Nothing to Disclose, Raissa Nana Sede Mbakop Forlemu: Nothing to Disclose

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1134 | IN VIVO EXPERIMENTS AND NETWORK PHARMACOLOGY TO INVESTIGATE MECHANISMS OF JIGUCAO CAPSULE FOR METABOLIC-ASSOCIATED FATTY LIVER DISEASE

Wenying Qi[1] Yue Chen[1] Xu Cao[2] Hening Chen[2] Niingyi Zhang[2] Ruijia Liu[2] Wei Wang[2] Yong'An Ye[2] Xiaobin Zao[3]

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Background: The JiGuCao capsule (JGC) is a commonly used traditional Chinese medicine already on the market for the treatment of acute and chronic hepatitis. Current research has confirmed that JGC has the function of regulating liver lipid metabolism. However, whether JGC could be used to treat metabolic-associated fatty liver disease (MAFLD) and the mechanism of action is not yet clear. **Methods:** The C57BL/6J mice MAFLD model was established by a high-fat diet (HFD) and the therapeutic effect was evaluated after treatment with JGC aqueous solution. The transcriptome sequencing of the liver tissue, 16s ribosomal RNA sequencing (16S-seq) of the gut microbiota, and lipidomics of the gut microbiota were performed and further analyzed. The effective chemical components of JGC were detected by mass spectrometry. The DisGeNET and GeneCards databases were used to obtain target genes related to MAFLD. The Cytoscape3.7.2 software and STRING platform were used to construct the protein-protein interaction network and the topological structure was analyzed. The Gene Ontology (GO) and the Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis were performed for the target genes. **Results:** Network pharmacology analysis predicted 139 potential targets of JGC on MAFLD (Figure D), and liver transcriptome analysis showed 97 differently expressed genes related to JGC in treating MAFLD (Figure E). And we finally obtained 236 target genes. The GO and KEGG analysis of the target genes showed that the main pathways involved are Lipid metabolism, Signal transduction, Endocrine system, Transport and catabolism, and so on (Figure F-G). The 16S-seq results showed that The lipidomics results showed that HFD disturbs the peptide chain length and double bond numbers of lipid metabolism such as diacylglycerol, triacylglycerol, and ceramide, while JGC treatment could rebalance these lipids(Figure J). Furthermore, multi-omic and PCR verification of the liver tissue showed that the mechanism of JGC in treating metabolic-related steatohepatitis was related to the down-regulation of the AMPK signaling pathway and PPAR signaling pathway(Figure K-O) . **Conclusion:** The mechanism of JGC in regulating lipid metabolism may be related to regulating of AMPK signaling pathway and PPAR signaling pathway, which alleviates lipid metabolism disorders caused by a high-fat diet.

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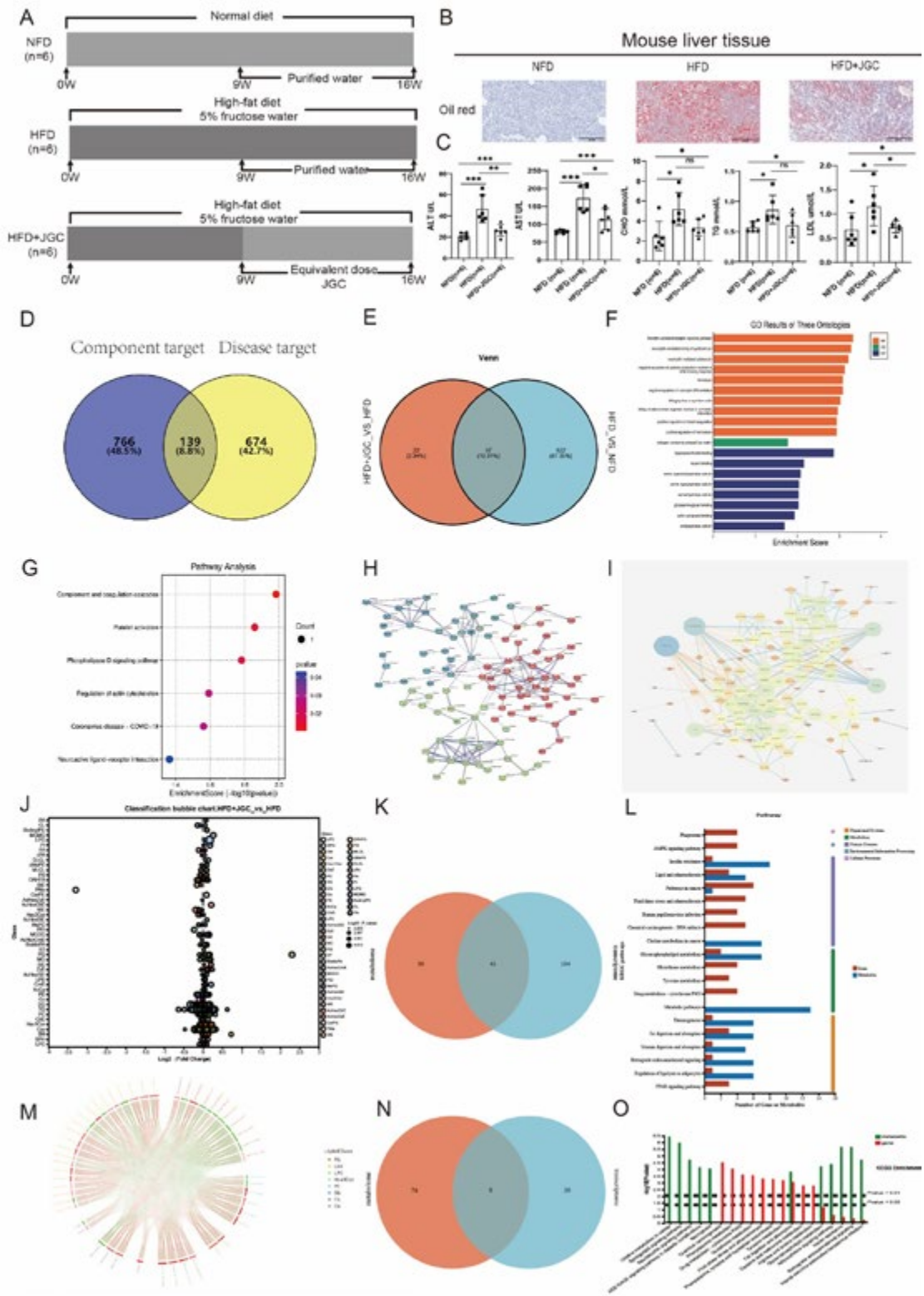

Disclosures: Wenying Qi: Nothing to Disclose, Yue Chen: Nothing to Disclose, Xu Cao: Nothing to Disclose, Hening Chen: Nothing to Disclose, Niingyi Zhang: Nothing to Disclose, Ruijia Liu: Nothing to Disclose, Wei Wang: Nothing to Disclose, Yong'An Ye: Nothing to Disclose, Xiaobin Zao: Nothing to Disclose

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1135 | REDUCED HNF4A EXPRESSION IN MASLD IPSC-DERIVED HEPATOCYTES AND ASSOCIATED EPIGENETIC MODIFICATIONS

Dounia Le Guillou[1] Kevin Siao[1] Chris Her[1] Caroline Duwaerts[1] Jacquelyn Maher[1]

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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is characterized by complex molecular changes, such as the dysregulation of key transcription factors crucial for hepatic function and lipid metabolism. We recently showed that MASLD iPSC-derived hepatocytes (iPSC-Heps) display a disease-specific gene expression profile with altered lipid metabolism, inflammation, and increased basal triglyceride content. In this study, we aimed to explore the underlying mechanisms contributing to the MASLD phenotype in our iPSC-Heps. **Methods:** iPSCs from control and MASLD patients were differentiated into iPSC-Heps using a standard protocol. iPSC-Heps were harvested at various stages for RNA sequencing (RNA-Seq), DNA methylation analysis, and ATAC sequencing (ATAC-Seq) to investigate gene expression, DNA methylation, and chromatin accessibility, respectively. **Results:** IPA of RNA-Seq data revealed marked downregulation of HNF4A in MASLD vs. control iPSC-Heps (Z-score = -3.94, P = 4.4e-4). HNF4α mRNA and protein expression were also significantly reduced in MASLD vs. control iPSC-Heps (mRNA fold-change -1.38, P = 0.001). GSEA further demonstrated a significant reduction in the expression of HNF4α target genes, many of which regulate lipid metabolism, in MASLD vs. control iPSC-Heps. HNF4α mRNA expression correlated inversely with triglyceride content in iPSC-Heps (r = -0.406 P = 0.040). HNF4A is regulated by two promoters (P1 and P2). DNA methylation analysis (EPIC Array) revealed enhanced methylation of both promoters in MASLD vs control iPSC-Heps, suggesting an epigenetic mechanism for reduced HNF4α expression in the MASLD group. Additionally, hydroxymethylation of the P1 promoter, which precedes and is required for promoter demethylation, was decreased in MASLD iPSC-Heps compared to controls at day 10 of differentiation. ATAC-Seq in iPSC-Heps at day 10 of differentiation identified reduced availability of DNA binding sites for the pioneer factor FOXA2, a critical upstream regulator of HNF4α during hepatocyte differentiation, in MASLD vs. control cells (P = 0.01). **Conclusion:** HNF4α and its transcriptional targets are significantly suppressed in MASLD vs. control iPSC-Heps. Reduced HNF4α expression correlates with altered lipid metabolism in MASLD iPSC-Heps and may explain the disease phenotype. Epigenetic modifications pertinent to HNF4A, including enhanced promoter methylation and reduced chromatin accessibility of upstream regulators, may be important factors underlying HNF4α suppression.

Disclosures: Dounia Le Guillou: Nothing to Disclose, Kevin Siao: Nothing to Disclose, Chris Her: Nothing to Disclose, Caroline Duwaerts: Gordian Biotechnology: Employee, Jacquelyn Maher: Nothing to Disclose

1136 | FRATAXIN DEFICIENCY INDUCES HEPATOCYTE FERROPTOSIS AND LIVER INJURY IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE

Somesh Banerjee[1] Hui Tao[1] Irene Wang[1] Peijian He[1]

[1]Emory University

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most common liver disease. While mitochondrial dysfunction plays a crucial role in the pathogenesis of MASLD, the cause of mitochondrial abnormalities remains not well understood. Iron is essential for cell metabolism by supporting citric acid cycle and mitochondrial respiration. Herein, we determined an important role of the perturbed mitochondrial iron metabolism in the development of mitochondrial dysfunction and liver injury in MASLD. **Methods:** WT and hepatocyte-specific frataxin knockout (FXN-hepKO) mice, were fed a regular chow, Western diet (WD) or *choline-deficient* L-amino-defined (CDAA) diet. Mice were infected with AAV8-TBG-FXN to overexpress FXN in the hepatocytes. Hepatic death was determined by propidium iodide (PI) and TUNEL staining. Microstructural changes of the hepatocytes were assessed by transmissive electron microscopy (TEM), and mitochondrial labile iron was labelled with Mito-FerroGreen. Hepatic inflammation and liver fibrosis were evaluated by qPCR and Sirius red staining, respectively. **Results:** Mice on a WD for 30 weeks displayed ferroptosis in a prominent number of hepatic cells, correlating with increased lipid peroxidation, mitochondrial damage, and mitochondrial free iron overload (MFIO). In seeking for the mechanism of MFIO, we identified the expression of FXN, an essential mitochondrial iron chaperone, was markedly decreased in advanced MASLD in mice and humans. Cultured FXN-hepKO hepatocytes exhibited MFIO, massive mitochondrial damage, and extensive lipid

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accumulation. Moreover, FXN-hepKO hepatocytes underwent spontaneous ferroptosis, whereas ectopic FXN expression protected hepatocytes against RSL3 induced ferroptosis. Compared to WT mice, FXN-hepKO mice fed on a CDAA diet developed increased hepatic death and inflammation, while FXN overexpression alleviated liver injury. Endoplasmic reticulum stress is a hallmark change associated with MASLD. We further showed that ER stress is responsible for the downregulated expression of FXN in the hepatocytes by utilizing pharmacological and genetic models of ER stress in vitro and in vivo. **Conclusion:** Our study demonstrates that ER stress induced downregulation of FXN causes MFIO-dependent mitochondrial damage and hepatocyte ferroptosis, promoting MASLD-associated liver injury.

Disclosures: Somesh Banerjee: Nothing to Disclose, Hui Tao: Nothing to Disclose, Irene Wang: Nothing to Disclose, Peijian He: Nothing to Disclose

1137 | RAP1A ACTIVATION SUPPRESSES MASLD AND MASH DEVELOPMENT VIA REGULATING THE AMINO ACID MEDIATED MTORC1 ACTIVATION

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Background: In patients with type 2 diabetes (T2D), insulin fails to inhibit hepatic glucose production; however, its ability to stimulate lipid synthesis and storage is unimpaired. This selective insulin resistance, which is characterized by hyperglycemia and metabolic dysfunction-associated steatotic liver disease (MASLD) of T2D, can progress to a more severe form of liver disease referred to as metabolic dysfunction-associated steatohepatitis (MASH). Recently, we showed that hepatic activation of a small G protein of the Ras family, Rap1a, is suppressed in obesity, contributing to glucose intolerance; however, Rap1a's role in MASLD or MASH is unknown. **Methods:** To explore the role of Rap1a in hepatic TG accumulation, liver-specific Rap1a deficient and liver-specific Rap1a overexpressing mice were used. Hepatic triglyceride (TG) accumulation, plasma ALT levels, fatty acid oxidation and lipogenic gene expression, immunoblotting, hematoxylin and eosin, Picrosirius Red, and Col1a1 staining were used. **Results:** We show that the GTP-bound, active Rap1a levels are significantly decreased in obese mice with MASLD, and restoring Rap1a activity lowers liver steatosis and plasma ALT in obese mice. Rap1a activation decreases hepatic TG accumulation by decreasing the mature form of the master lipogenic transcription factor, *sterol regulatory element-binding protein 1* (Srebp1), via inhibiting mTORC1, which cleaves Srebp1. The mechanism linking Rap1a activation to the suppression of mTORC1 involves lowering membrane-bound amino acid transporters, which reduced hepatocyte amino acid uptake, decreased intracellular amino acid levels, and inhibited amino acid-mediated mTORC1 activation. Furthermore, we observed that active-Rap1a levels were also lowered in mice fed with MASH-provoking diets and liver extracts from subjects with MASH. Accordingly, restoration of Rap1a activity lowered plasma ALT and liver fibrotic gene expression and prevented fibrosis formation, while Rap1a silencing promoted the progression of MASH. **Conclusion:** Hepatic Rap1a serves as a signaling molecule that suppresses both hepatic glucose production and steatosis, and inhibition of its activity in the liver contributes to the pathogenesis of glucose intolerance and MASLD/MASH development.

Disclosures: Heena Agarwal: Nothing to Disclose, Yating Wang: Nothing to Disclose, Brea Tinsley: Nothing to Disclose, Lale Ozcan: Nothing to Disclose

1138 | MANIPULATING BILE ACID POOL SIZE TO TARGET DIETARY FAT ABSORPTION IN MASLD

Alvin Chan[1] Kelsey Jarrett[1] Rochelle Lai[1] Madelaine Brearley-Sholto[1] Andrew Lau[1] Angela Cheng[1] Maria Taveras[1] Anne Iwata[1] Michelle Steel[1] Elizabeth Tarling[1] Thomas Vallim[1]

[1]University of California, Los Angeles

Background: The growing obesity epidemic has fueled a surge in metabolic dysfunction-associated steatotic liver disease (MASLD), making it the leading cause of chronic liver disease worldwide. A major risk factor for MASLD progression is dietary fat. Saturated fat and polyunsaturated fat are known to have opposite effects on

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the liver, suggesting a potential role for targeting pathways that interfere with their absorption. Bile acids are critical for the absorption of dietary fats and thus make attractive targets. In this study, we manipulate the bile acid pool size to selectively alter fatty acid absorption for MASLD management. **Methods:** To reduce the bile acid pool, we disrupted cholesterol 7 alpha-hydroxylase (*Cyp7a1*), the first and rate-limiting enzyme in bile acid synthesis, using liver-directed adeno-associated virus (AAV) Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)/Cas9. *Cyp7a1* disruption resulted in a decrease of all bile acids, and a 70% reduction of the total bile acid pool size. For comparative purposes, we pursued a separate strategy to alter dietary fat absorption and incorporated tetrahydrolipstatin (orlistat) into the diet to reduce lipase activity. We performed parallel experiments in *Cyp7a1* CRISPR mice as well as orlistat-treated mice on Western diet for 8 weeks to induce MASLD. **Results:** Decreasing bile acid levels with loss of CYP7A1 protected mice from diet-induced steatosis due to impairments in total fatty acid absorption. Remarkably, a smaller bile acid pool disproportionately reduced the absorption of saturated fatty acids but preserved the absorption of key polyunsaturated fatty acids. We then determined that specific bile acids, particularly conjugated cholic acid, preferentially solubilized polyunsaturated fatty acids into mixed micelles, thus providing a mechanism for the enhanced uptake of these fatty acids. We further showed that these select changes in absorption produced important downstream consequences in both the liver and the gut. The preferential absorption of polyunsaturated fatty acids enhanced uptake into the liver inhibiting hepatic lipogenesis, while the unabsorbed fatty acids in the intestine stimulated gut hormone secretion (GLP-1, PYY) to induce satiety. In contrast to reduced bile acids, lipase inhibition only slightly attenuated hepatic steatosis, indiscriminately decreased absorption of all fatty acids, induced lipogenesis, and increased food intake. **Conclusion:** Taken together, our studies unveil a natural selectivity in the absorption of fatty acids by bile acids—a physiological phenomenon that gets magnified when bile acids are reduced. Importantly, this work highlights the therapeutic potential of bile acid modulation to control the intestinal absorption of different fatty acids for MASLD.

Disclosures: Alvin Chan: Nothing to Disclose, Kelsey Jarrett: Nothing to Disclose, Rochelle Lai: Nothing to Disclose, Madelaine Brearley-Sholto: Nothing to Disclose, Andrew Lau: Nothing to Disclose, Angela Cheng: Nothing to Disclose, Maria Taveras: Nothing to Disclose, Anne Iwata: Nothing to Disclose, Michelle Steel: Nothing to Disclose, Elizabeth Tarling: Nothing to Disclose, Thomas Vallim: Nothing to Disclose

1139 | UNLOCKING S-PINDOLOL'S POTENTIAL FOR MASLD: BENEFICIAL EFFECTS ON MUSCLE MASS AND FUNCTION AND LIVER HISTOLOGY IN WESTERN-DIET FED MICE

Daniel Cabrera Loreto Aguilar[1] Faride Saud[2] Lisbell Estrada[3] Marcelo Andia[4] Catterina Ferreccio[5] Marco Arrese[5] Juan Pablo Arab[6] Luis Antonio Díaz[5] Francisco Barrera[5] Rene Baudrand[5] Claudio Cabello-Verrugio[7]

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Background: Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) is linked to sarcopenia, which worsens disease's prognosis. The complex liver-muscle crosstalk open the possibility that improvements in muscle quantity and quality may be directly beneficial for MASLD. This study investigates the effects of s-pindolol, a beta-blocker known for its anabolic properties, on both muscle mass and function as well as on MASLD progression in mice. **Methods:** Male C57BL6 mice were subjected to a western diet (WD) for 20 weeks to induce MASLD and then mice were randomly grouped and treated with 3 mg/kg s-pindolol twice a week or left untreated. Assessments included grip and isolated muscle strength, body composition via bioimpedance spectroscopy, Abdominal MRI, liver histology, serum analyses, gene expression profiling, and exercise performance via a treadmill challenge. **Results:** S-pindolol reduced liver steatosis and inflammation and was associated with lower levels of MCP-1, IL-10, TGF-β, and ACACA (Acetyl-CoA Carboxylase Alpha). S-pindolol also counteracted IGF-1 serum levels reduction seen in WD-fed mice. In addition, S-pindolol treatment led to an increase in muscle mass as confirmed by bioimpedance spectroscopy and MRI techniques. While exercise performance remained unchanged, grip strength improved together with a reduction in myosteatosis suggesting enhanced muscle quality. This was supported by an increase in muscle fiber diameter, indicating muscular hypertrophy independent of exercise. **Conclusion:** S-pindolol treatment ameliorates MASLD and enhances muscle quality in WD-fed mice. It may be hypothesized that pindolol's positive effects on muscle mass and function could play a role on its

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beneficial effects on MASLD through improvement of secretion of various salutary myokines. The present data underscore S-pindolol's therapeutic potential in MASLD.

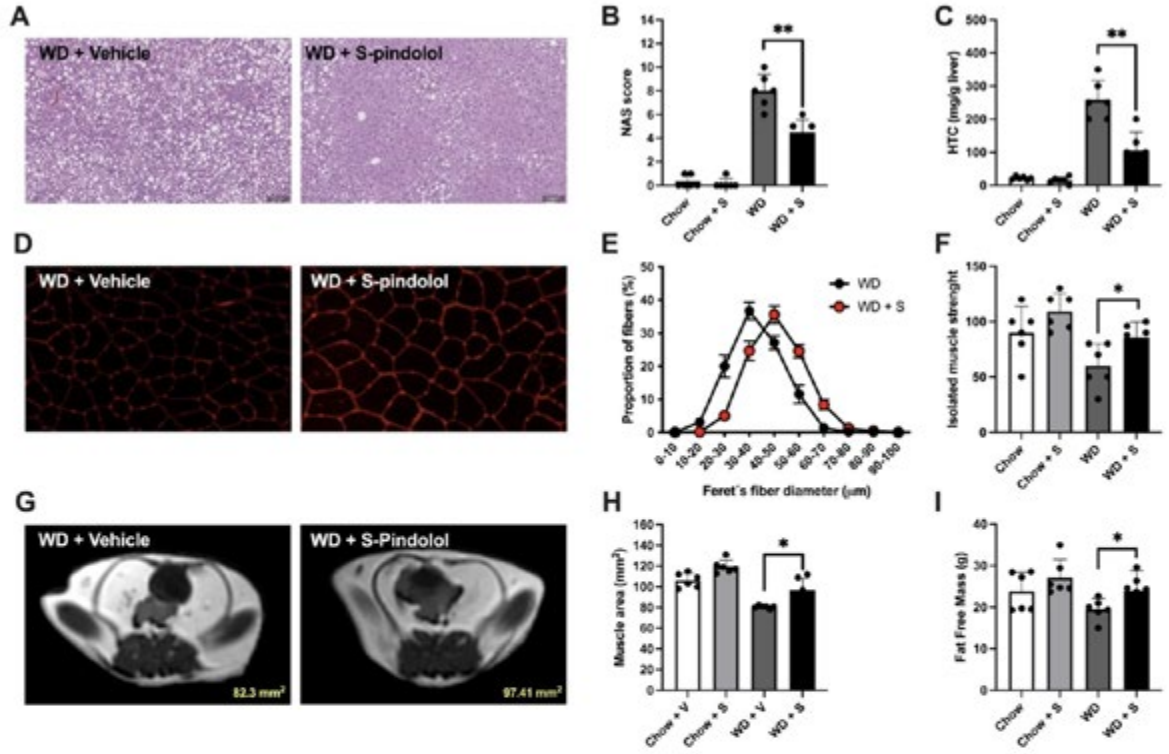

Figure 1: S-pindolol promotes muscle hypertrophy and reduces liver pathology in MASLD mice. Panel A displays hematoxylin and eosin-stained liver sections, where s-pindolol treated mice exhibit markedly reduced steatosis compared to vehicle controls. Panel B shows the NAFLD Activity Score (NAS) with statistically significant improvements in inflammation and ballooning scores (**p<0.01**) in the treated group. Panel C quantifies hepatic triglyceride content, revealing a significant decrease in s-pindolol treated mice (**p<0.01**). Panel D illustrates enhanced muscle fiber cross sectional area in s-pindolol treated mice via wheat germ agglutinin staining. Panel E analyzes the distribution of muscle fiber cross-sectional areas, indicating a significant increase in larger diameter fibers in treated mice, suggesting muscle hypertrophy (**p<0.05**). Panel F presents electrophysiological measurements of tetanic strength from isolated tibialis anterior muscles,

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1140 | REGULATION OF *TM6SF2* BY MICRORNA-432: A POTENTIAL THERAPEUTIC TARGET

Shahrbanoo Keshavarz Aziziraftar[1] Mohammad Mehraban[1] Caitlin Peaslee[1] Medha Somayaji[1] Caroline Duwaerts[2] Dounia Le Guillou[3] Jacquelyn Maher[3] Aras Mattis[4]

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Background: Individual liver disease risk factors in metabolic dysfunction-associated steatotic liver disease (MASLD) including cirrhosis and hepatocellular carcinoma are correlated to genetic variants in metabolic genes. A single nucleotide polymorphism (SNP) in transmembrane 6 superfamily member 2 (*TM6SF2*; rs58542926) was previously discovered through GWAS to be strongly associated with hepatic steatosis, fibrosis, inflammation, and liver cancer while being inversely associated with serum cholesterol and triglycerides. Previous studies with synthetic vector constructs in liver tumor cell lines suggested that rs58542926 resulted in the degradation of TM6SF2 protein despite stable RNA. **Methods:** We tested the stability of natively expressed *TM6SF2* RNA in iPSC-derived hepatocytes (iHeps) from patients with MASLD who are heterozygous for rs58542926. Furthermore, we tested the effects on steatosis in iHep cell lines with anti-sense oligonucleotide (ASOs) targeting miR-432. **Results:** Quantification of *TM6SF2* RNA levels in the patient-derived rs58542926 carrier iHeps showed approximately half the level of available RNA versus those measured in control iHeps available for translation into protein. Prompted by these findings, we set out to establish the cause for this RNA instability in iHeps harboring the rs58542926 variant. Our studies led to the discovery that rs58542926 leads to the introduction of a novel but unusual microRNA-432 (miR-432-5p) binding site in the coding sequence of TM6SF2. ASO studies quenching miR-432-5p rescued the stability of the variant *TM6SF2* mRNA, restoring its function, and normalizing hepatocyte functions including reducing steatosis. **Conclusion:** Our studies demonstrate that the fate of the rs58542926 variant *TM6SF2* mRNA is distinctly different in iHeps than published synthetic expression constructs. We hypothesize that in human liver, the rs58542926 variant and miR-432-5p combine to inhibit the normal expression and function of TM6SF2. This interaction may be central to the risk of rs58542926 for hepatic steatosis, inflammation, fibrosis, and hepatocellular carcinoma within this unique patient cohort and this axis is therefore a potential therapeutic target for patients carrying this SNP.

Disclosures: Shahrbanoo Keshavarz Aziziraftar: Nothing to Disclose, Mohammad Mehraban: Nothing to Disclose, Caitlin Peaslee: Nothing to Disclose, Medha Somayaji: Nothing to Disclose, Caroline Duwaerts: Gordian Biotechnology: Employee, Dounia Le Guillou: Nothing to Disclose, Jacquelyn Maher: Nothing to Disclose, Aras Mattis: BioMarin Pharmaceuticals: Consultant, Pliant Therapeutics: Consultant, Regeneron Phamaceuticals: Consultant, HepaTx: Consultant, Pharmanest: Consultant

1141 | ENHANCED MUSCLE MASS MITIGATES MASLD IN MYOSTATIN KNOCKOUT MICE WITHOUT IMPACTING EXERCISE PERFORMANCE

Daniel Cabrera Faride Saud[1] Loreto Aguilar Barría[1] Marco Arrese[2] Luis Antonio Díaz[2] Juan Pablo Arab[3] Lisbell Estrada[4] Claudio Cabello-Verrugio[5] Francisco Barrera[2] Marcelo Andia[2]

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Background: Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) is a prevalent condition linked with sarcopenia and exacerbated by obesity. Interestingly, individuals with higher relative skeletal muscle mass are protected against incident MASLD, or more likely to experience resolution of baseline MASLD, regardless of demographic and health-related factors. This study explores the effects of muscle mass enhancement independent of exercise on MASLD progression using myostatin knockout (Mstn-KO) mice, which are genetically modified to exhibit increased muscle mass due to myostatin deficiency. **Methods:** 11-week-old Mstn-KO mice and their wild-type counterparts were fed a Western diet (WD) for 24 weeks to induce MASLD. Parameters assessed included liver steatosis through histological analysis, muscle mass via MRI and histological cross-sectional area, exercise performance through treadmill tests and muscle strength measured by electrophysiology. **Results:** Mstn-KO mice demonstrated significantly reduced (-20%) liver steatosis and increased muscle mass by 30%

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compared to wild-type controls. Additionally, liver pro-inflammatory cytokines such as IL-1β and TNF-α were decreased in Mstn-KO mice, alongside lower expression of lipogenesis-related genes, indicating a protective effect against the progression of MASLD. Histological assessments showed less hepatic lipid accumulation and inflammation in Mstn-KO mice, correlating with a decrease in myosteatosis and an enhanced cross-sectional area of muscle fibers evaluated by wheat germ agglutinin fluorescence staining. Muscle mass was measured by bioimpedance analysis, and paravertebral muscles area were evaluated by using MRI. All the results suggested an improvement in muscle quality from Mstn-KO compared to WT mice. Histological assessments revealed less lipid accumulation and inflammation in Mstn-KO mice, correlating with an increased cross-sectional area (CSA) of muscle fibers evaluated by fluorescein staining with wheat germ agglutinin. Electrophysiological measures indicated increased tetanic strenght in Mstn-KO mice. Despite these physiological improvements, treadmill test results did not show any significant differences in exercise performance between Mstn-KO and wild-type groups, suggesting that muscle mass improvement did not translate into enhanced exercise capacity. These results indicates that Mstn-KO mice are protected against muscle atrophy and the progression of MASLD. **Conclusion:** Our findings suggest that increased muscle mass, independent of exercise performance, can significantly ameliorate MASLD histology. Mstn-KO mice serve as a valuable model for exploring and harnessing muscle-liver crosstalk in liver diseases, indicating potential pathways for treatment that do not rely on exercise enhancement.

Disclosures: Daniel Cabrera: Nothing to Disclose, Faride Saud: Nothing to Disclose, Loreto Aguilar Barría: Nothing to Disclose, Marco Arrese: Aztra Seneca: Steering Commitee, Inventiva: Consultant, Luis Antonio Díaz: Nothing to Disclose, Juan Pablo Arab: Nothing to Disclose, Lisbell Estrada: Nothing to Disclose, Claudio Cabello-Verrugio: Nothing to Disclose, Francisco Barrera: Nothing to Disclose, Marcelo Andia: Nothing to Disclose

1142 | NUCLEAR SEQUESTRATION OF Y BOX-BINDING PROTEIN 1 REPROGRAMS HEPATOCYTES FOR ADIPOGENICITY

James Jordan[1] Fahrettin Haczeyni[1] Zeynep Ugurlu[1] Baran Ersoy[2]

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Background: Y box-binding protein 1 (Ybx1) is a nucleic acid-binding protein that is primarily linked to early development, innate immunity, adipogenesis, and cancer. We have previously shown that Ybx1 becomes activated within the liver in response to overnutrition and that mice with hepatocyte-specific deletion of Ybx1 are protected against diet-induced pathogenesis of MASLD and MASH. We further elucidated that the maladaptive appearance of Ybx1 within the liver directly transcriptionally regulates the adipogenic master switch PPARγ and its target genes, via direct interactions with C/EBPα, leading to excessive lipid accumulation. The mechanisms underlying nutrition-induced expression and nuclear localization of Ybx1 remains unclear. This study aims to elucidate how hepatic Ybx1 is regulated in obesity and how it turns on adipogenic gene expression to promote deleterious lipid accumulation. **Methods:** 1) The role of mTORC1 in driving total Ybx1 expression was determined using rapamycin in hepatocytes. 2) To test whether lipid exposure and insulin resistance led to Ybx1 expression and nuclear localization, hepatocytes were treated with palmitate, insulin, or PI3K inhibitors. Cytosolic and nuclear compartments were then fractionated and analyzed with immunoblotting. Diet-induced phosphorylation state of nuclear Ybx1 was determined by mass spectrometry. 3) To determine how Ybx1 drives adipogenic gene expression within hepatocytes, Ybx1-bound protein complex was identified by proteomics analysis of co-immunoprecipitated (co-IP'd) proteins from liver nuclei. The contributions of Ybx1-bound factors in lipid accumulation were determined by BODIPY staining. **Results:** 1) Palmitate, which activates mTORC1, increased total Ybx1 expression. This was neutralized by rapamycin, indicating that mTORC1 drives diet-induced expression of Ybx1 in hepatocytes. 2) Palmitate treatment also promoted the nuclear localization of Ybx1 whereas insulin stimulation resulted in its cytosolic retention. This was associated with insulin stimulated phosphorylation of Ybx1 at S102, which was inhibited by the pre-treatment of hepatocytes with palmitate. Inhibiting insulin signaling using PI3K inhibitors also resulted in the nuclear sequestration of Ybx1. 3) Ybx1 coIP'd with SMARCD2 and SMARCE1, which are components of the SWI/SNF chromatin remodeling complex that drive adipogenesis in pre-adipocytes. Ybx1 interacted with both SWI/SNF subunits to profoundly influence lipid accumulation in palmitate-exposed hepatocytes. **Conclusion:** Overall, our findings indicate that obesity-induced mTORC1 activity and insulin resistance results in the increased expression and nuclear localization of Ybx1 where it directly stimulates a canonical adipogenic SWI/SNF:C/EBPα:PPARγ regulatory axis to promote lipotoxic lipid accumulation within the liver. Given these findings, Ybx1 emerges as a potential therapeutic target for MASLD and MASH.

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Disclosures: James Jordan: Nothing to Disclose, Fahrettin Haczeyni: Nothing to Disclose, Zeynep Ugurlu: Nothing to Disclose, Baran Ersoy: Nothing to Disclose

1143 | SYPHILITIC HEPATITIS: A RARE CASE OF HEPATIC INJURY FROM A COMMONLY TRANSMITTED VENEREAL DISEASE

Karthic Drishna Perumal[1] *Omar Brijawi*[1] *Matthew Holcomb*[1]

[1]*Mount Carmel Health*

Background: Syphilis is a sexually transmitted disease caused by a non-hepatotropic spirochete Treponema pallidum. Syphilitic hepatitis (SH) in adults is a rare and often misdiagnosed condition that can mimic other infectious or noninfectious pathologies in patients with abnormal liver function tests. Most patients usually recover with a single injection of Benzathine penicillin G, but some may not tolerate this treatment due to severe allergies to penicillin. To this end, we have investigated a case of syphilitic hepatitis amendable to alternative treatment strategies. **Methods:** N/A **Results:** A 43-year-old Caucasian female with a past medical history of ectopic pregnancy status post hysterectomy, appendectomy, and chronic constipation presented to the emergency department for worsening abdominal pain and fever. On admission, she was normotensive, tachycardic, and afebrile. She reported symptoms of night sweats, fevers up to 101-102.4 °F, worsening nausea, decreased appetite, and lightheadedness. On physical exam, she had a diffuse, macular, pruritic rash on the torso and extremities including the palms and soles; tenderness over the right upper and left lower quadrants; and bilateral tender inguinal lymph nodes, approximately 3 cm in size. Labs showed a significant cholestatic pattern of liver injury, positive treponema palladium antibody, and rapid plasma reagin (RPR) quantitative study yielding 1:128. Gastroenterology was consulted and performed an esophagogastroduodenoscopy (EGD) and colonoscopy that were unremarkable. Due to severe allergic reactions to penicillin, an infectious disease consult recommended starting doxycycline 100 mg twice daily for 14 days. The patient's symptoms on admission had reduced by the end of her stay, along with significant improvement in her rash and inguinal lymphadenopathy. A repeat outpatient quantitative RPR demonstrated a 16-fold decrease (1:8), ALP at 133, and near normalization of aminotransferases as well. **Conclusion:** Our patient was classified in the secondary stage of infection and presented with a cholestatic pattern of liver injury with negative viral hepatitis serologies and other infectious workups, non-acute ultrasound, and CT imaging, but through positive treponema palladium antibody and RPR values, we arrived at our diagnosis of syphilitic hepatitis. Our patient also had a history of severe penicillin allergy. Thus, our patient underwent an unorthodox treatment strategy with doxycycline. SH may occur in an estimated 3% of secondary syphilis cases and given the increasing incidence of syphilis, SH should be considered an important differential when working up a cholestatic pattern of liver injury that is not the result of biliary pathology. Penicillin remains the mainstay treatment for all stages of syphilis, but patients who experience severe drug reactions to penicillins can undergo alternative treatment with doxycycline.

Lab Parameters	Admission	Day 1	Day 2	Day 3	Day 4	Follow-up Visit (5 weeks)
ALP (32-91 unit/L)	533 unit/L	416 unit/L	411 unit/L	364 unit/L	430 unit/L	133 unit/L
AST (15-41 unit/L)	42 unit/L	36 unit/L	34 unit/L	35 unit/L	69 unit/L	34 unit/L
ALT (7-52 unit/L)	119 unit/L	89 unit/L	75 unit/L	67 unit/L	82 unit/L	42 unit/L
GGT (7-50 unit/L)	352 unit/L	-	-	-	-	-
Total Bilirubin (0.3-1.2 mg/dL)	2.2 mg/dL	2.8 mg/dL	1.2 mg/dL	2.9 mg/dL	3.2 mg/dL	0.5 mg/dL
WBC (4.6-10.2 K/mcL)	14.6 K/mcL	14.3 K/mcL	11.3 K/mcL	8.5 K/mcL	8.3 K/mcL	7.7 K/mcL

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Disclosures: Karthic Drishna Perumal: Nothing to Disclose, Omar Brijawi: Nothing to Disclose, Matthew Holcomb: Nothing to Disclose

1144 | CLINICAL UTILITY OF TWO-STEP HEPATITIS E VIRUS IGM ANTIBODY TESTING IN A LOW-PREVALENCE SETTING: A 10-YEAR RETROSPECTIVE MULTICENTER STUDY

Chia-Yu Chiu Raymund Razonable[1] Joseph Yao[1] Kymberly Watt[1] Supavit Chesdachai[1]

[1]Mayo Clinic

Background: Diagnosis of hepatitis E (HEV) infection involves epidemiologic exposure and clinical history supported by serological and molecular methods. However, diagnostic uncertainty may be caused by the low positive predictive value of HEV-specific IgM antibody (Ab) testing in a low-prevalence setting. We investigated the utility of a two-step HEV IgM Ab testing approach for the diagnosis of HEV infection at our institution. **Methods:** We conducted a retrospective review of all patients 18 years or older who underwent HEV IgM Ab and/or HEV RNA testing from July 2013 through June 2023 at the Mayo Clinic in Arizona, Florida, and Minnesota. Two-step HEV IgM testing involved initial testing using recomWell HEV IgM ELISA (Mikrogen, Neuried, Germany), with reflex to recomLine HEV IgM Strip (Mikrogen) on all recomWell HEV IgM-reactive or -equivocal specimens, as recomLine HEV IgM has higher specificity than recomWell HEV IgM but is more labor-intensive. True-positive HEV IgM Ab results were those that were reactive with both tests, whereas false-positive HEV IgM Ab results were those that were reactive with the first test but non-reactive with the second test. A laboratory-developed HEV RNA assay was available for routine clinical use. **Results:** A total of 1,640 patients had HEV IgM Ab or HEV RNA testing, including 1,293 (79%) with only HEV IgM Ab testing, 213 (13%) with only HEV RNA testing, and 134 (8%) with both HEV IgM Ab and HEV RNA testing (see Figure 1 on (A) immunocompromised and (B) immunocompetent groups). Eighteen HEV infections were diagnosed with acute (N = 16) and chronic (N = 2) infections. Two-step IgM Ab testing did not identify 2 solid organ transplant recipients with chronic HEV infection (Figure 1A). In acute HEV infection with HEV viremia, 3 out of 4 patients (2 solid organ transplant recipients and 1 patient with Guillain-Barre syndrome) were treated with ribavirin. **Conclusion:** A two-step HEV IgM Ab test may accurately diagnose acute HEV infection in immunocompetent persons. However, such testing approach may fail to identify chronic HEV infection in immunocompromised individuals, who would need HEV RNA testing to establish the diagnosis.

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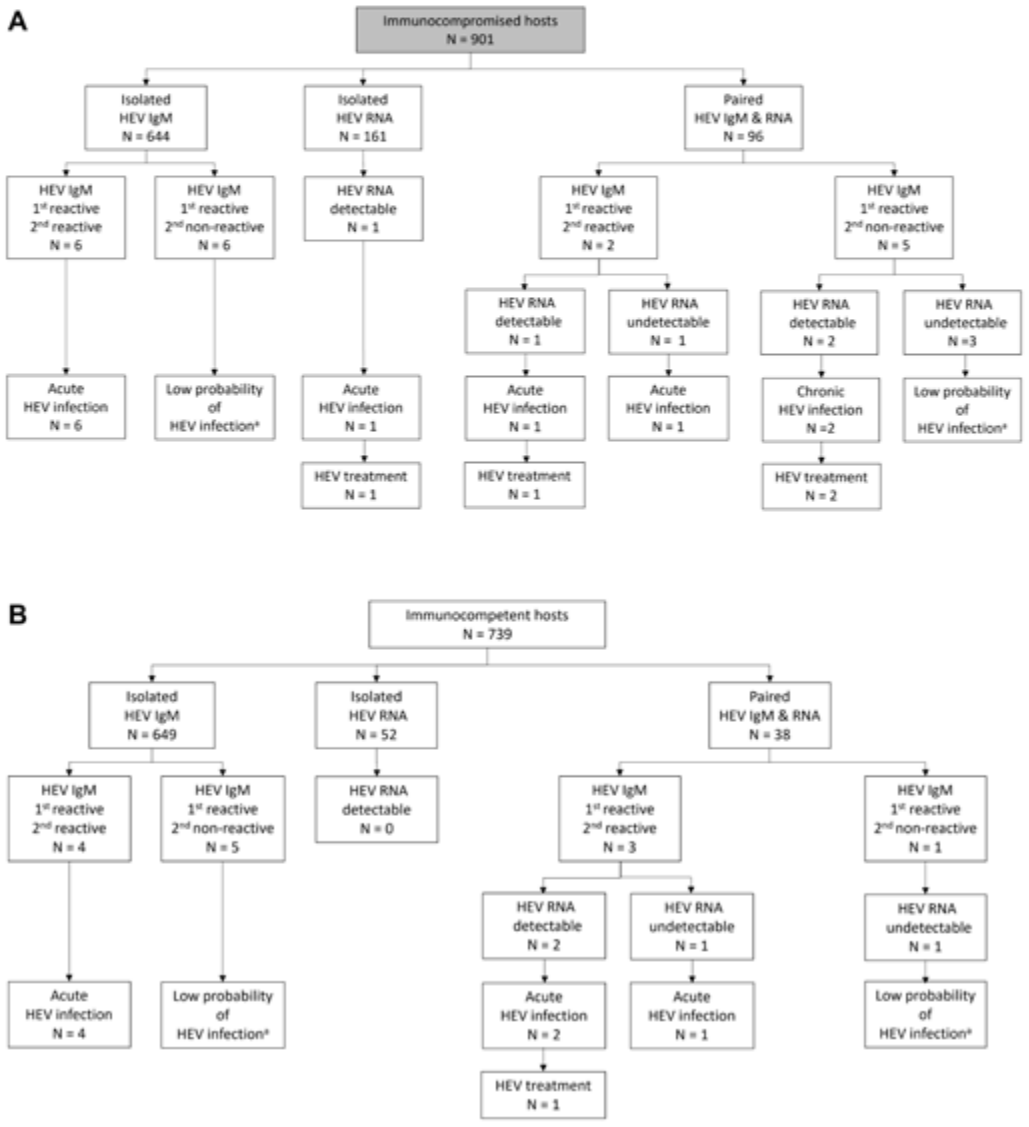
Footnote:
Isolated HEV IgM was defined as patients tested for HEV IgM Ab alone but not HEV RNA. Isolated HEV RNA was defined as patients tested for HEV RNA alone without HEV IgM Ab testing. Paired HEV IgM and HEV RNA was defined as having HEV IgM Ab and HEV RNA testing within 1 week. According to the European Association for the Study of the Liver guideline, acute HEV infection was defined by (i) the presence of HEV antibodies (IgM ± IgG), or (ii) detectable HEV RNA in serum or plasma. Chronic HEV infection was defined as the detectable HEV RNA for at least 3 months.
a. A low probability of HEV infection was defined as a false-positive HEV IgM Ab and an alternative diagnosis was identified.



Disclosures: Chia-Yu Chiu: Nothing to Disclose, Raymund Razonable: Regeneron: Grant/Research Support, Roche: Grant/Research Support, Gilead: Grant/Research Support, Invivyd: Consultant, Novartis: Consultant, Joseph Yao: Nothing to Disclose, Kymberly Watt: Madrigal: Stock - publicly traded company, Viking: Stock - publicly traded company, Supavit Chesdachai: Nothing to Disclose

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1145 | SUCCESSFUL DEVELOPMENT OF A LOOP-MEDIATED ISOTHERMAL AMPLIFICATION ASSAY (LAMP-PCR) FOR DETECTION HDV-RNA ★

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Background: Hepatitis delta virus (HDV) is a significant cause of liver disease-related mortality in many countries. Early detection of HDV infection is crucial for successful treatment and elimination of HDV endemicity. However, in many cases, HDV-infected individuals are often diagnosed at advanced stages of the disease, and therefore, reflex testing of HDV infection in all HbsAg-positive patients is mandatory. The current standard diagnostic assay, RT-PCR, requires specialized equipment and is not easily accessible in resource-limited settings. The development and utilization of a rapid, user-friendly, and sensitive diagnostic method for HDV detection could be an important addition to the reduction of HDV global prevalence. In this study, we have developed and characterized a LAMP-PCR assay for detecting HDV-RNA in blood serum. **Methods:** Using an online tool, five primer sets were designed on a highly conserved region of the HDV genotype 1 sequence. The LAMP assay was performed using the WarmStart Colorimetric and Fluorescent LAMP 2X Master Mix kits. RNA extraction was carried out using a viral RNA isolation kit. Serum samples from 13 HDV-RNA-positive patients and 15 healthy people (a total of 28 people) were used to compare primer sets and determine the specificity of the assay. A serially diluted plasmid construct containing the genomic sequence of HDV was employed to determine the limit of detection (LOD) for colorimetric and fluorescence LAMP assay. For quantification analysis, WHO reference material (7657/12) was used as a standard to express **Results:** by IU/mL. The amplified PCR products were confirmed using agarose gel electrophoresis and dissociation curve analysis in the case of fluorescence assay. **Results:** Among the primer sets tested, primer set-5 showed the highest specificity and was selected for further analysis. The HDV-LAMP assay using primer set-5 exhibited a sensitivity of 100% and a specificity of 94.4%. The optimal reaction temperature for the colorimetric LAMP-PCR was determined to be 65°C, while for the fluorescence LAMP-PCR, it was 68°C. The limit of detection (LOD) for the HDV-LAMP assay was found to be 57 IU/mL, indicating excellent sensitivity. The optimal reaction time was 50-60 minutes for the colorimetric assay and 40-50 minutes for the fluorescence assay. Prolonged incubation time increased the likelihood of false positive results. **Conclusion:** The HDV-LAMP assay is a rapid, user-friendly, and sensitive diagnostic tool for detecting HDV-RNA in blood samples. It offers advantages over the standard RT-PCR method, including ease of use and no need for specialized equipment.This makes it suitable for resource-limited settings like primary hospitals, mobile labs, and point-of-care units.It could contribute to the effective elimination of HDV infection. Further optimization and validation of this novel assay must be done using a large number of sample sets.

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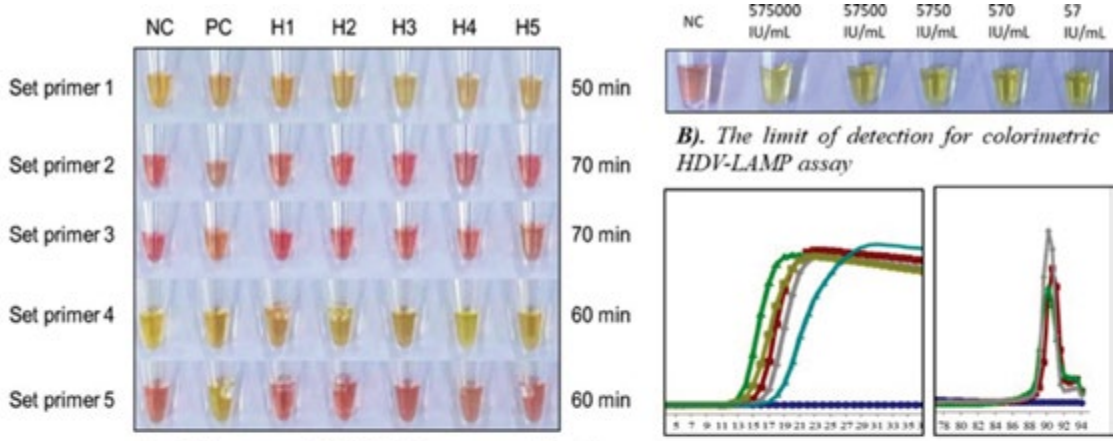

A). Colorimetric HDV-LAMP assay results of HDV primer sets: pink indicates no infection, yellow indicates HDV infection.

B). The limit of detection for colorimetric HDV-LAMP assay

C). The amplification curve and dissociation curve of the fluorescent HDV-LAMP assay



D). The most optimal primer set shown on the highly homology region of the HDV genotype 1 sequence.

Disclosures: Saruul Enkhjargal: Nothing to Disclose, Maral Enkhtur: Nothing to Disclose, Nomin Ariungerel: Nothing to Disclose, Khaliunaa Otgonbaatar: Nothing to Disclose, Ulziigerel Erdembileg: Nothing to Disclose, Purevjargal Bat-Ulzii: Nothing to Disclose, Byambasuren Ochirsum: Nothing to Disclose, Naranjargal Dashdorj: Nothing to Disclose, Odgerel Oidovsambuu: Nothing to Disclose

1146 | PERFORMANCE CHARACTERISTICS OF A NEW OPEN-SOURCE CASE-FINDING ALGORITHM FOR HDV AND A SURVEY OF PROVIDER KNOWLEDGE

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Background: Hepatitis delta virus (HDV) uses HBsAg to form an infectious particle that contains HDV RNA and HDV Ag, causing life-threatening acute and chronic disease. EASL and AASLD recommend HDV screening for all (EASL) or high risk (AASLD) HBsAg+ patients. Rates of HDV screening and linkage to care are suboptimal. We created an HDV case-finding algorithm to monitor screening and conducted a survey to evaluate provider knowledge. **Methods:** An algorithm was developed using SQL coding and applied to records of 4,095,070 individuals with clinical laboratory data in the Mount Sinai Data Warehouse (2010-2023) to identify HBsAg+ and HDV Ab+ patients and any additional individuals with HBV DNA and/or HDV RNA tests (Fig, Top Panel). Manual chart review was used to validate and refine the algorithm, which considered 116 tests and panels (Fig, Bottom Panel). An online survey was completed by 60 medical students, trainees, and primary care providers. **Results:** We first determined the percentage of HBsAg+ patients who were tested for HDV Ab: 1,913 (28.8%) of 6,633 HBsAg+ living adults received HDV Ab testing; 89 (4.7%) were positive. We then examined the percentage of HDV Ab+ patients who had HDV RNA testing: 43 (48.3%) of 89 HDV Ab+ patients had RNA testing; 10 (23.3%)

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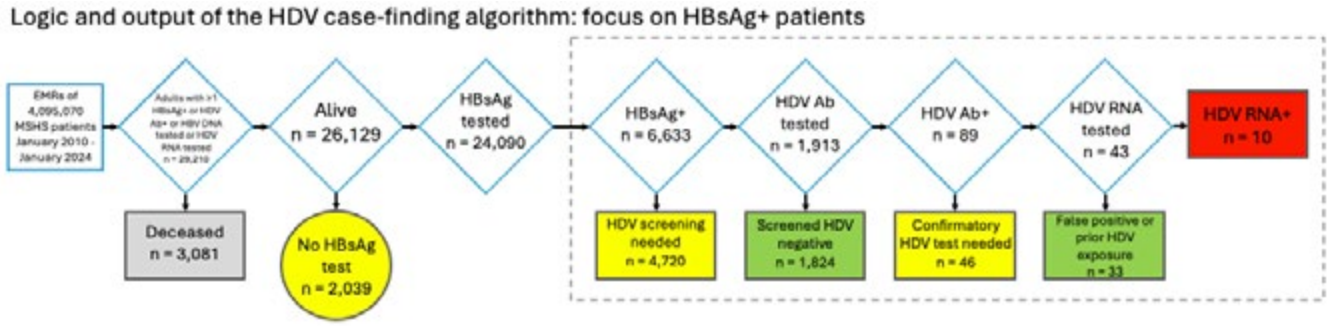
were positive (Fig, Middle Panel). Two additional HDV RNA+ patients were found among 2,039 patients who did not have an HBsAg test on record, showing the complexity of HDV case finding in the real world where it is critical to cast a wide net. Chart review of 200 HBsAg+ patients showed that the algorithm had a 91% accuracy for correctly classifying HDV Ab status but missed 20 patients with HDV tests ordered as part of an archaic panel (which will be added). The survey revealed that 43% of responders were unsure of HDV screening guidelines; 62% reported lack of knowledge about HDV; 72% were unsure about HDV treatment options. **Conclusion:** Phenotyping algorithms are useful tools for case finding and quality control monitoring. Our HDV case-finding algorithm is 91% accurate and will be made freely available on GitHub once sensitivity is further optimized. The algorithm revealed that <30% of HBsAg+ patients were tested for HDV Ab and <50% of HDV Ab+ patients were tested for HDV RNA. Now that this declining cascade of care has been documented, the underlying problems can be addressed. Future efforts will focus on provider education and the introduction of reflex testing for HDV Ab in HBsAg+ patients.





HBV and HDV tests considered by the algorithm

Procedure Key	Lab Name	Procedure Key	Lab Name	Procedure Key	Lab Name	Procedure Key	Lab Name	Procedure Key	Lab Name
87	HEPATITIS BS AG	1075	HEP. B SURFACE AG.	2424	HEP. B SURFACE AG.	11063	HEPATITIS BS AG	39263	HEP. B SURFACE AG.
88	HEP. B SURFACE AG.	1099	HEP. B SURFACE AG.	2445	HEPATITIS BS AG	11126	HEPATITIS BS AG	39310	HEP. B SURFACE AG.
176	HEP. B SURFACE AG.	1254	HEP. B SURFACE AG.	2451	HEPATITIS BE AB	11215	HEPATITIS BS AG	39596	HEPATITIS BS AG
377	HEP. B SURFACE AG.	1273	HEPATITIS BS AG	2602	HEP. B SURFACE AG.	11606	HEPATITIS BS AG	44873	HEPATITIS BS AG
452	HEPATITIS BS AG	1372	Hepatitis B Surf Ag	2615	HEP. B SURFACE AG.	11618	HEPATITIS BS AG	55579	HEPATITIS BS AG
467	HEP B SURF AG	1413	HEPATITIS BS AG	2714	HEP. B SURFACE AG.	11631	HEPATITIS BS AG	55678	HEPATITIS BS AG
491	HEPATITIS BS AG(INS)	1554	HEP. B SURFACE AG.	2755	HEPATITIS BS AG	11654	HEPATITIS BS AG	72781	HEPATITIS BS AG
492	HEP. B SURFACE AG.	1717	HEP. B SURFACE AG.	2876	HEP. B SURFACE AG.	11671	HEPATITIS BS AG	73581	HEPATITIS BS AG
510	HEP. B SURFACE AG.	1728	HEP. B SURFACE AG.	2916	HEP. B SURFACE AG.	11714	HEPATITIS BS AG	513920	HEPATITIS BS AG
544	HEP. B SURFACE AG.	1834	HEPATITIS BS AG	2492	HEPATITIS BS AG	11715	HEPATITIS BS AG	555790	HEPATITIS BS AG
547	HEP. B SURFACE AG.	1843	HEP. B SURFACE AG.	3550	HEPATITIS BS AG	11734	HEPATITIS BS AG	555937	HEPATITIS BS AG
581	HEP. B SURFACE AG.	1888	HEP. B SURFACE AG.	3654	Hepatitis B Surf Ag	11815	HEPATITIS BS AG	555941	HEP BE AG
643	HEP. B SURFACE AG.	1898	HEP BE AG	3647	HEP. B SURFACE AG.	11837	HEPATITIS BS AG	555937	HEP B SURF AG
648	HEP. B SURFACE AG.	1912	HEP. B SURFACE AG.	3682	HEPATITIS BS AG	11865	HEPATITIS BS AG	767060	Hepatitis B Surface Antigen
713	HEP. B SURFACE AG.	1961	HEPATITIS BS AG	3681	HEPATITIS BS AG	11901	HEPATITIS BS AG	767062	Hepatitis B Surface Antigen
714	HEP. B SURFACE AG.	1969	HEP. B SURFACE AG.	3682	HEPATITIS BS AG	11906	HEPATITIS BS AG	802142	HEPATITIS BS AG
730	HEPATITIS BS AG	2073	HEPATITIS BS AG	3701	HEPATITIS BS AG	11915	HEPATITIS BS AG	802945	HEPATITIS BS AG
792	HEP. B SURFACE AG.	2138	HEP. B SURFACE AG.	3726	HEPATITIS BS AG	11963	HEP.BS AG CONFIRM	807523	Hep B Surface Antigen Quant
846	HEP. B SURFACE AG.	2157	HEP. B SURFACE AG.	3845	HEPATITIS BS AG	12016	HEP. B SURFACE AG.		
903	HEPATITIS BS AG	2261	HEP. B SURFACE AG.	3854	HEPATITIS BS AG	12029	HEPATITIS BS AG		
985	HEPATITIS BS AG	2344	HEPATITIS BS AG	3880	HEP. B SURFACE AG.	28095	HEP. B SURFACE AG.		
1044	HEP. B SURFACE AG.	2363	HEPATITIS BS AG	11050	HEPATITIS BS AG	38441	HEPATITIS BS AG		

Procedure Key	Lab Name	Procedure Name
72775	HEPATITIS D ANTIGEN	HEPATITIS D ANTIGEN
40743	HDV QRT-PCR (PLASMA)	HEPATITIS D QRT-PCR (PLASMA)
40742	HDV QRT-PCR (SERUM)	HEPATITIS D QRT-PCR (SERUM)
1474	HEPATITIS D RNA,QL,RT-PCR	HEPATITIS D RNA,QL,RT-PCR
1363	HEPATITIS D RNA,QL,RT-PCR	HEPATITIS D RNA,QL,RT-PCR
1011	HEPATITIS DELTA, AB	HEPATITIS D VIRUS (HDV) TOTAL
1011	Hepatitis D Antigen	HEPATITIS D VIRUS (HDV) TOTAL
1011	HDV AB	HEPATITIS D VIRUS (HDV) TOTAL
1011	Hepatitis D Ab	HEPATITIS D VIRUS (HDV) TOTAL
1011	HEPATITIS D AB TOTAL	HEPATITIS D VIRUS (HDV) TOTAL

Disclosures: Nathaniel Ash: Nothing to Disclose, Brooke Wyatt: Nothing to Disclose, Brandon Mui: Nothing to Disclose, Anna Mageras: The Kinetix Group: Advisor, Novo Nordisk: Speaking and Teaching, Gilead Sciences: Grant/Research Support, Francina Collado: Nothing to Disclose, Alyson Harty: Nothing to Disclose, Mark Miller: Nothing to Disclose, Lauren Alpert: Nothing to Disclose, Tatyana Kushner: Advisor relationship with Gilead; Has ended; Advisor relationship with GSK; Has ended; Advisor relationship with Eiger; Has ended; Grant/Research Support relationship with Gilead; Has not ended, Douglas Dieterich: Gilead: Consultant, madrigal: Speaking and Teaching, Andrea Branch: Gilead Sciences: Research, Pfizer: Research

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1147 | EFFICACY AND SAFETY OF BLV MONOTHERAPY FOR CHRONIC HEPATITIS DELTA: POST TREATMENT RESULTS THROUGH 48 WEEKS AFTER THE END OF TREATMENT FROM AN INTERIM ANALYSIS OF A RANDOMIZED PHASE 3 STUDY MYR301

Grace Chee[1] Soo Aleman[2] Maurizia Brunetto[3] Antje Blank[4] Pietro Andreone[5] Pavel Bogomolov[6] Vladimir Chulanov[7] Nina Mamonova[7] Natalia Geyvandova[8] Morozov Viacheslav[9] Olga Sagalova[10] Tatyana Stepanova[11] Dmitry Manuilov[12] Sarah Arterburn[12] Audrey Lau[12] Anu Osinusi[12] Florence Christian-Cox[12] Frank Duff[12] Julian Schulze Zur Wiesch[13] Markus Cornberg[14] Stefan Zeuzem[15] Heiner Wedemeyer[14] Pietro Lampertico[16]

[1]Gilead Sciences, [2]Karolinska University Hospital/Karolinsk, [3]University of Pisa, [4]Heidelberg University Medical Faculty, [5]University of Modena and Reggio Emilia, [6]State Budgetary Institution of Health Care of Moscow Region "Moscow Regional Research Clinical Insti, [7]Sechenov University, Moscow, Russian Federation, [8]Stavropol Regional Hospital, Stavropol, Russian Federation, [9]LLC Medical Company "Hepatolog", Samara, Russian Federation, [10]Federal State-Funded Institution of Higher Education "South Ural State Medical University of Minis, [11]Limited Liability Company "Clinic of Modern Medicine", Moscow, Russian Federation, [12]Gilead Sciences, Inc., Foster City, United States, [13]Universitätsklinikum Hamburg-Eppendorf, Medizinische Klinik Studienambulanz Hepatologie, Hannover, [14]Medizinische Hochschule Hannover, Klinik für Gastroenterologie, Hepatologie, Infektiologie und End, [15]Department of Medicine, University Hospital, Goethe-University, Frankfurt, Germany, [16]University of Milan

Background: Bulevirtide (BLV, Hepcludex®) is a first-in-class entry inhibitor approved in Europe for chronic hepatitis delta (CHD). **Results:** from MYR301 (NCT03852719), a phase 3 randomized study, showed monotherapy with BLV 2 mg/day (d) or 10 mg/d was found to be efficacious and safe through 144 weeks (w) of treatment. Here we present results from MYR301 through 48 weeks after end of treatment (FU48). **Methods:** 150 CHD patients were randomized (stratification by presence/absence of compensated cirrhosis) in a 1:1:1 ratio to Arm A: no active anti-HDV treatment for 48 weeks followed by BLV 10 mg/d for 96 weeks (n=51), Arm B: BLV 2 mg/d (n=49) or Arm C: BLV 10 mg/d (n=50) for 144W. Patients will continue to be followed for 96 weeks after the end of treatment (EOT). Endpoints include: combined response (CR) defined as virologic response (VR; undetectable HDV RNA or a decrease by ≥2 $\log_{10}$ IU/mL from baseline) and ALT normalization, VR, ALT normalization, undetectable HDV RNA, liver stiffness (LS), and liver related outcomes. **Results:** Demographic and baseline (BL) characteristics were similar across groups and included: mean (SD) age 42 (8.4) years, 57% males, 83% White, 47% with compensated cirrhosis, mean (SD) HDV RNA 5.04 (1.34) $\log_{10}$ IU/mL, ALT 111 (69.0) U/L, LS 14.7 (8.8) kPa and 61% were on concomitant nucleos(t)ide analogues (NA) therapy. 72% of participants remained in the study at FU48. Efficacy and safety results are summarized below (figure). All response rates decreased after treatment was stopped due to viral relapses or rebounds, which mainly occurred over the first 24 weeks after EOT. CR and ALT normalization rates were similar regardless of dose and duration. Viral response and undetectable HDV RNA rates post EOT were numerically higher with BLV 10 mg compared to BLV 2 mg or DT. Only 2 liver related events were reported after EOT: ascites (Arm A) and esophageal variceal bleed (Arm B), both in patients with cirrhosis at BL. Two patients first experienced HBsAg loss during the post treatment period, not associated with increase in ALT. Safety during the post treatment period was similar between Arms B and C, with slightly higher rates of patients with reported SAEs and grade ≥ 3 AE in Arm A. Previously reported death in Arm A due to plasma cell myeloma after patient discontinued study drug, unrelated to BLV. Of the 13 patients who reported an SAE that started after EOT, 9/13 had post treatment flare with increases in ALT and HDV RNA, 4/9 were noncirrhotic, 5/9 were cirrhotic, at least 4/9 started commercial BLV with no reports of liver failure. **Conclusion:** A subset of patients treated with BLV monotherapy for 2-3 years maintained virological and biochemical responses one year after stopping BLV. Rates of liver related events one year after completing BLV monotherapy were low. Assessment of durability of response at 96 weeks after EOT is planned.

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Efficacy and Safety From EOT to FU48

Number of patients, n (%)	DT to BLV 10 mg N=50			BLV 2 mg N=49			BLV 10 mg N=50		
	EOT 96 weeks of BLV	FU24	FU48	EOT 144 weeks of BLV	FU24	FU48	EOT 144 weeks of BLV	FU24	FU48
Combined Response	28 (56)	10 (20)	9 (18)	28 (57)	11 (22)	11 (22)	27 (54)	16 (32)	10 (20)
ALT Normalization	29 (58)	13 (26)	12 (24)	29 (59)	12 (25)	13 (27)	30 (60)	18 (36)	14 (28)
Virologic Response	46 (92)	22 (44)	14 (28)	36 (74)	19 (39)	14 (29)	38 (76)	23 (46)	20 (40)
Undetectable HDV RNA	26 (52)	9 (18)	8 (16)	14 (29)	9 (18)	8 (16)	25 (50)	13 (26)	12 (24)
Mean change in liver stiffness (kPa) from BL (SD)+	-4.66 (7.458)	N/A	-2.36 (7.203)	-4.94 (7.301)	N/A	-3.54 (7.249)	-4.05 (5.044)	N/A	-3.91 (4.050)
HBsAg Loss	1 (2)	1 (2)	1 (2)	0	1 (2)	1 (2)	0	0	1 (2)
Safety in the post treatment period*									
Any Adverse Events	N/A		30/49 (61)	N/A		31/46 (67)	N/A		34/47 (72)
Grade ≥ 3 AE			11/49 (22)			6/46 (13)			6/47 (13)
SAE			6/49 (12)			3/46 (7)			4/47 (9)

* Safety in the post treatment period included patients who have at least 1 post treatment visit; + liver stiffness not conducted at FU24. M = F analysis for binary endpoints; observed cases for continuous endpoints

Disclosures: Grace Chee: Gilead Sciences: Employee, Soo Aleman: Gilead: Speaking and Teaching, Maurizia Brunetto: Nothing to Disclose, Antje Blank: Gilead: Contract for study conduct of Myr301 with Gilead Sciences, Myr GmbH: Research support and provision of documents for bulevirtide, Pietro Andreone: Nothing to Disclose, Pavel Bogomolov: Nothing to Disclose, Vladimir Chulanov: Nothing to Disclose, Nina Mamonova: Nothing to Disclose, Natalia Geyvandova: Nothing to Disclose, Morozov Viacheslav: Nothing to Disclose, Olga Sagalova: Hepatera, R-Pharm: Speaking and Teaching, Tatyana Stepanova: Nothing to Disclose, Dmitry Manuilov: Nothing to Disclose, Sarah Arterburn: Gilead Sciences Inc: Employee, Gilead Sciences Inc: Stock – privately held company, Gilead Sciences Inc.: Stock - publicly traded company, Audrey Lau: Nothing to Disclose, Anu Osinusi: Nothing to Disclose, Florence Christian-Cox: Gilead Sciences INTL: Employee, Frank Duff: Nothing to Disclose, Julian Schulze Zur Wiesch: Nothing to Disclose, Markus Cornberg: Nothing to Disclose, Stefan Zeuzem: Nothing to Disclose, Heiner Wedemeyer: Nothing to Disclose, Pietro Lampertico: ROCHE PHARMA/DIAGNOSTICS, GILEAD SCIENCES, GSK, ABBVIE, JANS: Advisor

1148 | THE VIRAL ENVELOPE GLYCOPROTEIN GP120 FACILITATES A PROFIBROTIC PROGRAM FOLLOWING HIV EXPOSURE IN THE LIVER

Volney Spalding[1] Shadi Salloum[1] Raymond Chung[2] Brian Fellenstein[1] Min Xu[1] Charlotte Warner[1] Nadia Alatrakchi[1] Wenyu Lin[2]

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Background: *Background:* The successful implementation of antiretroviral therapy (ART) has shifted the focus of HIV-1 research towards the long-term effects of persistent, controlled infections. Recent evidence has suggested that HIV infection is a driver of hepatic fibrogenesis itself, in addition to accelerating liver fibrosis

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in other etiologies. We and others have demonstrated the critical role of Yes-Associated Protein 1 (YAP1) in regulating liver fibrosis in MAFLD and HIV. However, the mechanisms for these processes remain poorly understood. The aim of this work is to further define how the HIV gp120 interacts with the liver environment to drive fibrosis. **Methods:** qRT-PCR and western blot were used to determine the response of Huh7 cells exposed to various HIV envelope proteins. Primary hepatocytes (pHH), primary hepatic stellate cells (pHSC), and a 3D spheroid system combining pHSC with Huh7 cells were also used to investigate this mechanism in vitro. *In vivo* samples were sourced from mice treated with gp120 over 12 weeks. **Results:** Compared to DMSO, REV, and GAG; gp120 protein had a significant upregulation of YAP-related mRNA and protein in Huh7 cells. These effects are consistent across several gp120 tropisms. A colony formation assay of Huh7 cells showed that proliferation increased by 33% post gp120 exposure. gp120 exposure in Huh7 cells also significantly upregulated lipid droplet formation pathways (ADM2, LDLR, PLIN2), which was reflected in extensive lipid droplet staining. pHSC directly exposed to gp120 produced no alterations in the expression of benchmark fibrosis genes (CTGF, αSMA, COL1A1). However, in a spheroid model where crosstalk with hepatocytes is facilitated, we observed substantial coregulation of both fibrogenic and YAP-related genes, in some cases stronger than that seen with full virus infection. pHH and mice exposed to gp120 generated moderate increases in the expression of YAP-related genes. **Conclusion:** *Conclusion:* Early data from multiple lines of investigation suggest a compelling relationship between gp120 and YAP-related hepatic fibrogenesis post HIV infection. This novel mechanistic insight suggests new pharmacologic targets for treatment of liver fibrosis in persons living with HIV.

Disclosures: Volney Spalding: Nothing to Disclose, Shadi Salloum: Nothing to Disclose, Raymond Chung: Nothing to Disclose, Brian Fellenstein: Nothing to Disclose, Min Xu: Nothing to Disclose, Charlotte Warner: Nothing to Disclose, Nadia Alatrakchi: Nothing to Disclose, Wenyu Lin: Nothing to Disclose

1149 | THE PREVALENCE AND CLINICAL CHARACTERISTICS OF CONCURRENT HEPATITIS D INFECTION IN CHRONIC HEPATITIS B PATIENTS IN XINJIANG REGION: A MULTICENTER, RETROSPECTIVE, CROSS-SECTIONAL STUDY

WEI SUN[1] *Zhuanguo Wang*[2]

[1]*The Fourth Clinical Medical College of Xinjiang Medical University, Urumqi, China.,* [2]*Department of Hepatology, Hospital of Traditional Chinese Medicine of Xinjiang Autonomous Region*

Background: This study aimed to investigate the prevalence and clinical characteristics of concurrent hepatitis D virus (HDV) infection in patients with chronic hepatitis B in the Xinjiang region. **Methods:** A multicenter, retrospective, cross-sectional study was conducted, involving 1550 HBsAg-positive patients who sought medical care at the Fourth Clinical Medical College of Xinjiang Medical University and the First People's Hospital of Kashgar in Xinjiang between December 15, 2022, and December 30, 2023. All patients underwent HDV antibody and HDV RNA testing, with HDV antibodies (HDV-IgM, HDV-IgG) detected using ELISA and HDV RNA using RT-PCR. **Results:** Among the 1550 HBsAg-positive patients, 38 (2.45%) were found to have concurrent HDV infection, with 16 males (42.11%) and 22 females (57.89%), and an average age of (41.60±7.50) years. Serologically, 38 (2.45%) were positive for HDV-IgG, 15 (1.10%) were positive for HDV-IgM, and 22 (1.74%) were positive for HDV RNA, all belonging to genotype 1. Clinical analysis revealed that 28 patients (73.68%) presented with concurrent liver function abnormalities, 25 patients (65.79%) had progressive liver disease, including 18 with compensated cirrhosis (47.37%), 6 with decompensated cirrhosis (15.79%), and 1 with liver cancer (2.63%). Additionally, 6 patients (15.79%) had concurrent autoimmune liver disease, including 5 with autoimmune hepatitis (13.16%) and 1 with primary biliary cholangitis (2.63%). **Conclusion:** In Xinjiang, the seropositivity rates for HDV antibodies and HDV RNA among patients with chronic hepatitis B were 2.45% and 1.74%, respectively, all belonging to genotype 1. Concurrent HDV infection was associated with a higher likelihood of liver function abnormalities and disease progression, emphasizing the importance of screening and diagnosing such patients in clinical practice.

Disclosures: WEI SUN: Nothing to Disclose, Zhuanguo Wang: Nothing to Disclose

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1150 | CHARACTERISTICS AND ANTIVIRAL TREATMENT PATTERNS AMONG US ADULTS WITH LABORATORY-CONFIRMED HEPATITIS DELTA VIRUS VS HEPATITIS B VIRUS MONOINFECTION

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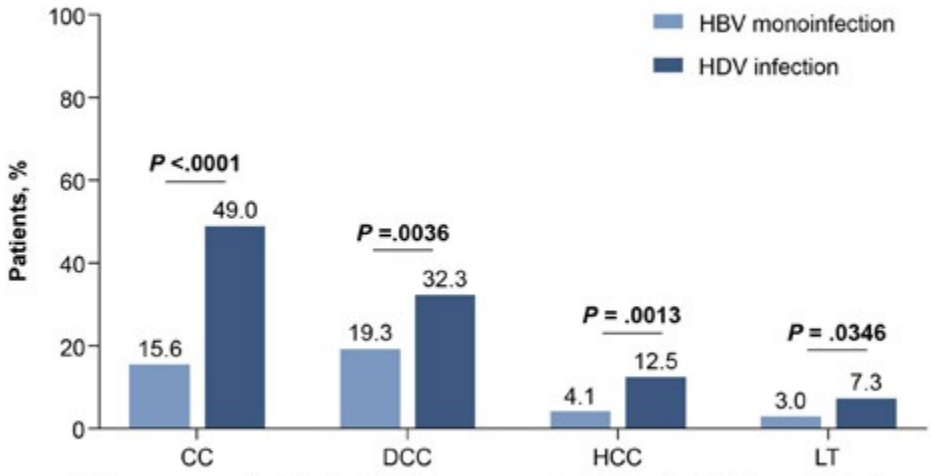
Background: Patients with hepatitis delta virus (HDV) infection are at greater risk of liver disease progression compared to patients with hepatitis B virus monoinfection (HBV only). We evaluated real-world patient characteristics and treatment utilization patterns among US adults with HDV vs HBV only. **Methods:** This retrospective cohort study used the US HealthVerity database to identify adults with HDV or HBV only from 2015–2021. HDV diagnosis was based on detectable HDV RNA, whereas HBV diagnosis was based on *ICD-9/10-CM* claims codes; the index date for calculating follow-up time was based on the earlier date of diagnosis via laboratory test or *ICD-9/10-CM* claims code. HDV laboratory data, HBV treatment utilization, and physician specialities were captured pre- and post-index. **Results:** We identified lab-confirmed patients with HDV (n=96) or HBV only (n=1,138), with mean ages of 47.4 and 46.6 years, respectively. A significantly greater proportion of patients with HDV were male vs HBV only (72.9% vs 55.1%; *P*<.001). Compared with patients with HBV only, significantly greater proportions of patients with HDV had compensated cirrhosis (49.0% vs 15.6%; *P*<.001), decompensated cirrhosis (32.3% vs 19.3%; *P*<.01), hepatocellular carcinoma (12.5% vs 4.1%; *P*<.01), and liver transplant (7.3% vs 3.0%; *P*=.03) at any time during the study (Figure). Mean baseline (BL; first measured) alanine aminotransferase (ALT) levels were significantly higher in patients with HDV vs HBV only (85.5 IU/L vs. 57.3 IU/L; *P*<.0001). Among patients with HDV, mean (SD) BL HDV RNA level was 19.5 (37.4) $\log_{10}$ IU/mL; 8/32 patients (25%) with 2 RNA measurements achieved undetectable RNA or a ≥2-fold $\log_{10}$ IU/mL decrease and ALT normalization post-index. Patients with HDV were more likely to have been treated with HBV antiviral therapy vs HBV only (55.2% vs 37.2%; *P*<0.001), including tenofovir disoproxil fumarate (35.4% vs 22.5%; *P*<0.01), tenofovir alafenamide (20.8% vs 9.5%; *P*<0.01), and pegylated interferon (11.5% vs 0.1%; *P*<.001). There were no differences in the proportions of patients with HDV vs HBV only who received care from gastroenterologists or hepatologists. **Conclusion:** Among US adults with lab-confirmed HDV and/or HBV diagnosis, patients with HDV had significantly higher rates of advanced liver disease and liver-related complications compared to patients with HBV only. While patients with HDV were more likely to receive HBV antiviral therapy, it is concerning that 45% of patients with HBV/HDV were not receiving HBV treatment.

Figure. Liver-Related Events in Patients With HDV vs HBV Monoinfection



CC, compensated cirrhosis; DCC, decompensated cirrhosis; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HDV, hepatitis delta virus; LT, liver transplant.

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Disclosures: Robert Wong: Theratechnologies: Grant/Research Support, Durect: Grant/Research Support, Gilead Sciences: Grant/Research Support, Exact Sciences: Grant/Research Support, Theratechnologies: Grant/Research Support, Durect Corporation: Grant/Research Support, Robert Gish: Nothing to Disclose, Ira Jacobson: Nothing to Disclose, Joseph Lim: Nothing to Disclose, Marvin Rock: Nothing to Disclose, Gary Leung: Gilead sciences: Employee, Chong Hoon Kim: Gilead Sciences, Inc.: Employee

1151 | SUMMARY OF CLINICAL FEATURES OF 1800 CASES OF BACTERIAL LIVER ABSCESSES

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Background: Liver abscess is a common infectious disease in clinical practice, and bacteria are the most important causative organisms of liver abscess..This study provides an overview of the clinical and epidemiological characteristics of bacterial liver abscess (BLA) patients in the First Hospital of Jilin University in the past 5 years. **Methods:** This study included 1800 patients diagnosed with BLA at the First Hospital of Jilin University from January 1, 2019, to December 31, 2023, collected their clinical data, outlined their clinical characteristics. They were divided into two groups according to whether PLA was combined with extrahepatic metastatic infection(EMI), and the clinical characteristics and prognosis of the two groups were compared. **Results:** The basic characteristics were as follows: There were 1180 male patients (65.56%), with an mean age of 60.00(51.00,68.00)years . A total of 1371 patients (76.17%) underwent ultrasound-guided abscess drainage. Of the underlying diseases, diabetes was the most common systemic disease, with 818 patients having diabetes (45.44%). Fever was the main clinical symptom in 1520 patients (84.44%). The average hospital stay for BLA patients in this study was 9.00 (5.00,16.00)days. The laboratory results of 1800 BLA patients were as follows: WBC: 11.50(8.59, 15.40)×10^9/L, NE : 0.84 (0.77,0.90), CRP: 182.52(110.38,257.64) mg/L, PCT: 4.24(0.63,27.94) ng/mL, AST:42.20(25.5,80.8)U/L;ALT:52.75(30.3,95.38) U/L;blood cultures were performed in 1021 patients: 17 (1.67%) patients had cultures of Escherichia coli, 253 (24.78%) cultures of Klebsiella pneumoniae. Pus cultures were performed in 1338 patients: 81 (6.05%) patients had culture **Results:** of Escherichia coli, 916 (68.46%) patients had culture **Results:** of Klebsiella pneumoniae.1167 (64.83%) patients had imaging suggestive of right lobe abscess. 1227 (68.17%) patients had a single liver abscess. The mean size of PLA was 61.00(43.00,80.00) cm. During disease progression, 76 (4.22%) patients were combined with lung abscess, 7 (0.39%) patients were combined with brain abscess, 2 (0.11%) patients were combined with splenic abscess, 11 (0.61%) patients were combined with renal abscess, and 37 patients (2.06%) were combined with endophthalmitis. Out of 1800 patients with BLA, 1731 (96.17%) improved after prompt treatment, 30 (1.67%) patients died during hospitalization. Clinical characteristics of BLA patients with combined extrahepatic migratory infection (EMI) and uncomplicated EMI: 1,800 BLA patients were divided into two groups of combined EMI and uncomplicated EMI. It was found that compared to patients without EMI, those with EMI tended to be younger($Z = -4.564, P < 0.001$), had longer hospital stays($Z = -7.454, P < 0.001$), and had a higher proportion of patients with underlying conditions such as diabetes and cerebrovascular disease($P < 0.05$). In terms of laboratory tests, BLA patients with EMI had elevated levels of WBC($Z=-3.190, P=0.001$), NE($Z=-3.788$,P **Conclusion:** In this study, we found that BLA was mainly observed in middle-aged to elderly men, often presenting as solitary abscesses in the right lobe. Diabetes mellitus was the most common underlying disease in BLA patients. The majority of patients showed improvement to recovery with effective antibiotic treatment and ultrasound-guided percutaneous drainage of the liver abscess. Compared to BLA patients without EMI, BLA patients with EMI tended to be younger on average, had longer hospital stays, had a significantly higher proportion of underlying diseases such as diabetes and cerebrovascular diseases, and had smaller abscesses. In BLA patients with EMI often had a worse prognosis.

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The Pus Culture and Imaging Examination Results Of PLA Patient

		positive numbers	composition ratio
blood culture	aseptic growth	702	68.76
	Klebsiella pneumoniae	253	24.78
	Escherichia coli	17	1.67
	Enterococcus faecalis	49	4.80
Pus Culture	aseptic growth	173	12.93
	Klebsiella pneumoniae	916	68.46
	Escherichia coli	81	6.05
	Enterococcus faecalis	25	1.87
	Other bacteria	143	10.69
abscess location	Right lobe	1167	64.83
	Left lobe	323	17.94
	Both in the left and right lobes	226	12.56
	The boundary between the left and right lobes	84	4.67
Number of abscesses	Solitary	1227	68.17
	Multiple	573	31.83
Size of abscesses	d ≤ 30mm	166	9.22
	30mm < d ≤ 50mm	436	24.22
	50mm < d ≤ 100mm	898	49.89
	d > 100mm	167	9.28
	Unknown	133	7.39
Prognosis	Recovery	1731	96.17
	Death	30	1.67
	Lost to follow-up	39	2.17

Disclosures: diandian Hao: Nothing to Disclose, Yu Tian: Nothing to Disclose, JiaLin Du: Nothing to Disclose, Hui Wang: Nothing to Disclose, Xiao yu Wen: Nothing to Disclose

1152 | BARODELTA STUDY : REAL WORLD DATA (RWD) OF 498 UNIQUE PATIENTS WITH CHRONIC HEPATITIS DELTA TREATED WITH BULEVIRTIDE (BLV) 2 MG. ANALYSIS FROM THE FRENCH NATIONAL HEALTH DATA SYSTEM (SNDS)

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Background: Bulevirtide (BLV) 2 mg, an entry inhibitor for the treatment of chronic Hepatitis Delta Virus (HDV) infection in patients with compensated liver disease, received European Medicine Agency conditionnal approval in 2020 and full authorization in July 2023. Patients received a daily subcutaneous injection as long as associated with clinical benefit. In France, BLV was available since September 2019 through an early access program. Barodelta, a retrospective cohort, assesed the adherence, persistence, and empowerment of all the patients with chronic HDV infection treated with BLV 2 mg in France and identified in the SNDS claims database.
Methods: All patients identified in the SNDS database with BLV initiation from September 2019 to December 2022 were included. Patients characteristics include age, gender, precarious status through health insurance type, comorbidities (diabetes, HIV, hypertension, obesity) and the treatment option: BLV monotherapy or in

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association with pegylated interferon (peg-IFN). SNDS does not provide qualitative data as clinical, biological and virological characteristics.BLV adherence and persistence were analyzed. Adherence was estimated by the Medication Possession Ratio (MPR) and treatment discontinuation was defined as permanent (definitive stop), or temporary (stop followed by reinitiation). Persistence was defined by the absence of treatment discontinuation over time and was estimated using the Kaplan Meier Method. The correlation between persistence and different sociodemographic criteria, comorbidities and comedications was assesed through univariate analysis. **Results:** From September 2019 to December 2022, 551 BLV treatments were initiated: 498 unique patients were included, 51 patients were reinitiated after more than 3-month discontinuations and 2 patients were reinitiated twice. The mean age was 42.5 years (± 11.4 years), 69.5% were male, 76.7% had universal medical coverage or state medical aid, suggesting patients with limited income and ressources, 12% were HIV coinfected, 18% had hypertension and 8% were current or former drug users. 60% received nucleo(s)tide analogues (NUC), 46% received peg-IFN concomitantly to BLV and 22% received neither NUC nor peg-IFN. Adherence rate reached 91% at 6 months, 89% at 12 months and 87% at 24 months. Persistence rate went up to 87.7% at 6 months, 75.5% at 12 months and 54% at 24 months. No significant correlation between persistence and sociodemographic criteria, comorbidities or comedications were identified. At day 15, 62% of patients were empowered to manage BLV treatment. **Conclusion:** During the first 24-month follow-up presented here, Barodelta demonstrated high rates of BLV adherence (87%), persistence (54%) and patient empowerment (62%) considering the specificities of BLV administration and HDV patients characteristics. Additional qualitative real world data need to be generated to discuss the persistence rate.

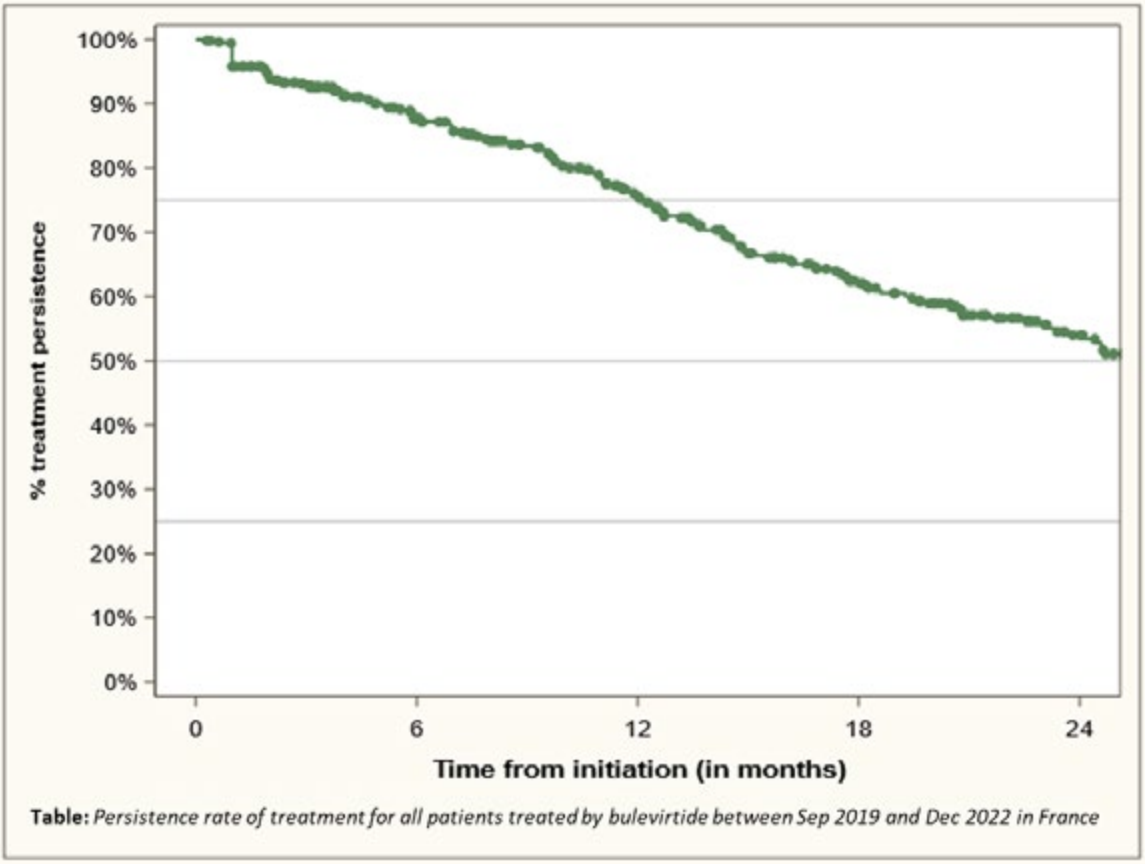

Table: *Persistence rate of treatment for all patients treated by bulevirtide between Sep 2019 and Dec 2022 in France*

Disclosures: Tarik Asselah: Nothing to Disclose, Veronique Loustaud-Ratti: GILEAD: Consultant, abbvie: Speaking and Teaching, GSK: Consultant, Jean-Pierre Bronowicki: Nothing to Disclose, Emmanuel Gordien:

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Gilead: Eurobio, Eurobio: Consultant, Gilead: Eurobio, Eurobio; Gilead: Consultant, Estelle Maugain: Nothing to Disclose, Audrey Le Blevec: Nothing to Disclose, Claire Idelovici-Marchal: Nothing to Disclose, Clémentine Lacueille: Nothing to Disclose, Magali Lemaitre: Nothing to Disclose, Fabienne Bazin: Nothing to Disclose, Charlotte COLOMBI: Gilead sciences: Employee

1153 | HEALTHCARE RESOURCE UTILIZATION AND COSTS ACROSS VARYING DISEASE STATES AMONG ADULTS WITH HEPATITIS DELTA VIRUS OR HEPATITIS B VIRUS MONOINFECTION IN THE INPATIENT AND OUTPATIENT SETTING IN ITALY

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Background: Hepatitis delta virus (HDV) infection increases the risk of liver-related morbidity and mortality compared to hepatitis B virus monoinfection (HBV only). In this study, healthcare resource utilization (HCRU) and costs were compared between adult patients with HDV vs HBV only across levels of disease severity in the inpatient and outpatient setting in Italy. **Methods:** Administrative databases of local health units in Italy (covering nearly 12 million individuals) were screened for adult patients with an inpatient or outpatient claim (*ICD-9-CM* or exemption code, respectively) between 1/1/2009 and 6/30/2022. Included patients had an HDV or HBV only diagnosis between 1/1/2010 and 6/30/2021, no prior diagnosis, and at least 12 months of continuous capture before and after diagnosis. Baseline characteristics were assessed over the 12-month period before each patient's first diagnosis. Inverse probability of treatment weighting (IPTW) was calculated using a propensity score (the probability of having HDV vs HBV only, given the covariates at baseline) to generate weights. The mean per-patient-per-year (PPPY) all-cause HCRU and costs between subgroups of liver disease severity (compensated cirrhosis [CC], decompensated cirrhosis [DCC], hepatocellular carcinoma [HCC], liver transplant [LT]) were compared via Mann-Whitney U test; descriptive statistics were summarized. **Results:** Of 16,172 patients confirmed to have HDV and/or HBV, 11,187 were included (HDV, n = 686; HBV only, n = 10,501). There were no differences in age, number of males, or Quan-Charlson Comorbidity Index scores in IPTW HDV vs HBV only patients (standardized difference = 0.001, 0.01, and 0.01, respectively). Mean (95% CI) number of inpatient visits PPPY was significantly greater for patients with HDV vs HBV only among those with CC (1.01 [0.97–1.06] vs 0.80 [0.76–0.85]; *P* <.001), DCC (1.59 [1.52-1.66] vs 1.33 [1.25-1.40]; *P* <.001), and HCC (1.88 [1.79-1.98] vs 1.68 [1.56-1.80]; *P* = .037). In patients with HDV vs HBV only, mean total costs PPPY were significantly higher for DCC (*P* = .001), and inpatient costs PPPY were significantly higher for DCC (*P* <.001) and HCC (*P* = .045) (Table). **Conclusion:** In Italy, inpatient length of stay and costs from liver-related morbidities (CC, DCC, HCC, and LT) were high overall, but were significantly greater for patients with HDV vs HBV only, depending on liver disease severity. This information highlights the need for advancement in screening and treatment measures to reduce disease burden.

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Table. IPTW All-Cause Healthcare and Disease-Related HCRU and Costs by Disease State

Variables	HBV Only	HDV	*P*-value
Average time in disease state, months			
No cirrhosis	64.5 (63.6–65.3)	69.9 (69.0–70.9)	**.014**
CC	43.4 (41.4–45.4)	38.8 (37.1–40.5)	.524
DCC	31.5 (29.6–33.4)	25.7 (24.2–27.3)	.302
HCC	24.7 (22.2–27.3)	20.2 (18.7–21.7)	.616
LT	62.7 (56.3–69.1)	60.7 (58.4–63.1)	.886
Inpatient LOS PPPY, days			
No cirrhosis	22.8 (21.6–24.1)	21.9 (20.6–23.2)	.062
CC	49.0 (43.4–54.7)	94.4 (87.1–101.8)	**<.001**
DCC	57.4 (50.5–64.2)	97.0 (85.6–108.4)	.105
HCC	80.7 (66.7–94.8)	90.9 (79.8–102.0)	.570
LT	195.8 (160.0–231.6)	222.6 (206.8–238.3)	.593
Total costs PPPY, £			
No cirrhosis	8,143.9 (7,625.0–8,662.8)	6,061.4 (5,872.9–6,249.8)	.372
CC	15,220.3 (13,701.3–16,739.2)	12,501.7 (11,767.3–13,236.0)	.683
DCC	25,528.9 (23,096.5–27,961.3)	39,845.3 (33,959.2–45,731.4)	**.001**
HCC	36,068.6 (32,681.4–39,455.8)	43,246.7 (40,441.3–46,052.1)	.182
LT	46,869.0 (40,005.4–53,732.6)	57,829.5 (54,687.4–60,971.7)	.388
Inpatient costs PPPY, £			
No cirrhosis	3,276.5 (3,137.2–3,415.8)	2,404.0 (2,313.3–2,494.6)	.068
CC	7,200.1 (6,649.0–7,751.1)	9,169.0 (8,536.9–9,801.1)	.067
DCC	14,059.0 (13,054.5–15,063.6)	26,022.9 (24,249.5–27,796.3)	**<.001**
HCC	24,702.4 (22,133.9–27,270.9)	43,876.8 (40,501.5–47,252.1)	**.045**
LT	25,509.1 (21,966.2–29,051.9)	32,880.2 (31,305.5–34,454.9)	.077

Data are reported as mean (95% CI) unless otherwise noted. **Bold** *P* values indicate statistical significance.
CC, compensated cirrhosis; **CI**, confidence interval; **DCC**, decompensated cirrhosis; **HBV**, hepatitis B virus; **HCC**, hepatocellular carcinoma; **HCRU**, healthcare resource utilization; **HDV**, hepatitis delta virus; **IPTW**, inverse probability of treatment weighting; **LOS**, length of stay; **LT**, liver transplant; **PPPY**, per-patient-per-year.

Disclosures: Pietro Lampertico: ROCHE PHARMA/DIAGNOSTICS, GILEAD SCIENCES, GSK, ABBVIE, JANS: Advisor, Valentina Perrone: Nothing to Disclose, Luca Degli Esposti: Nothing to Disclose, Melania Leogrande: Nothing to Disclose, Chong Hoon Kim: Gilead Sciences, Inc.: Employee, Marvin Rock: Nothing to Disclose

1154 | PHARMACOKINETICS, PHARMACODYNAMICS, AND SAFETY OF BULEVIRTIDE 2 MG ONCE-DAILY FOR 6 DAYS IN PARTICIPANTS WITH MODERATE AND SEVERE HEPATIC IMPAIRMENT AND IN MATCHED CONTROL PARTICIPANTS WITH NORMAL HEPATIC FUNCTION

Parag Kumar[1] Renee-Claude Mercier[1] Wildaliz Nieves[1] David Pan[1] Steve Tseng[1] Grace Chee[1] Xu Zhang[1] Yehong Wang[1] Ann Qin[1] Carrie Nielson[1] Teckla Akinyi[1] Helen Winter[1]

[1]Gilead Sciences

Background: Bulevirtide (BLV, Hepcludex®) is a 47-amino acid (AA) lipopeptide, hepatitis delta virus (HDV) entry inhibitor that binds to the sodium taurocholate co-transporting polypeptide (NTCP) receptor and received its first full approval in the EU for the treatment of adults with chronic HDV and compensated liver disease. BLV is expected to be catabolized by peptidases to smaller peptides and AAs, with no active metabolites. By inhibiting NTCP, BLV treatment results in asymptomatic and transient elevations of bile acids (BAs). This study evaluated the influence of moderate and severe hepatic impairment (HI) on the pharmacokinetics (PK), pharmacodynamics (PD), and safety of BLV. **Methods:** This was a Phase 1 open-label, parallel-group, multiple-dose study in HDV-uninfected participants with moderate HI (Child-Pugh Turcotte [CPT] Class B, n=11), severe HI (CPT Class C, n=8), and controls with normal hepatic function (n=19) (matched for age [± 10 years], sex, and BMI [± 20%]) who received BLV 2 mg subcutaneously (SC) once-daily (QD) for 6 days, with intensive serial sampling for BLV PK and PD (total BAs). Geometric mean ratios (GMR) and 90% confidence intervals (CI) of maximum plasma concentration (C_{max}; ng/mL) and area under the time-vs-concentration curve over 24 hours (AUC_{τ}; ng*h/mL) were evaluated for PK and BAs. Safety was assessed by clinical laboratory tests and evaluation of adverse events (AEs). **Results:** Moderate HI vs matched controls: BLV PK on Day 6 was similar in both groups (Figure 1a): GMR (90% CI): C_{max}: 1.17 (0.671, 2.05); AUC_{τ}: 0.872 (0.494, 1.54). Total BAs on Day 6 were also similar between the groups: GMR (90% CI): C_{max}: 1.07 (0.48, 2.37); AUC_{τ}: 1.17 (0.56, 2.44). Severe HI vs matched controls: BLV PK exposure on Day 6 was increased in severe HI versus controls (Figure 1b): GMR (90% CI): C_{max}: 4.01 (2.71, 5.93); AUC_{τ}: 1.97 (1.38, 2.81), with an corresponding reduction in the observed mean apparent volume of distribution (severe HI: 34.4 liters; vs controls:

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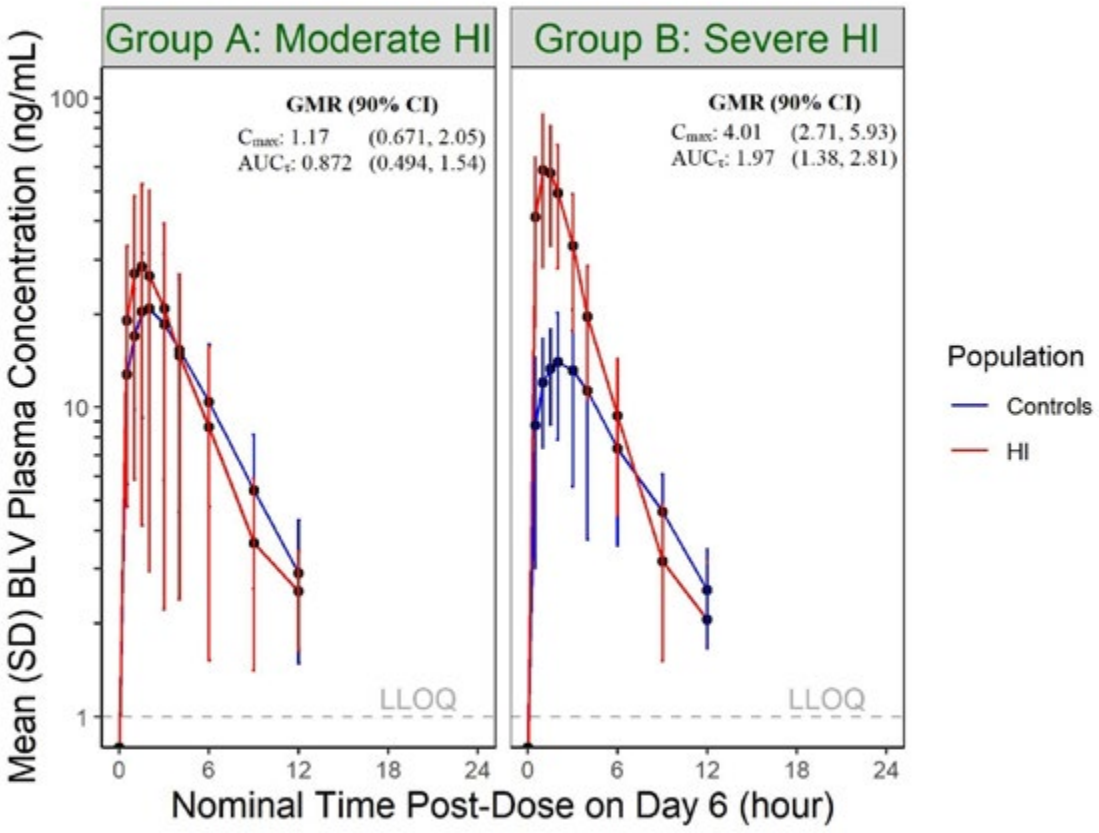
148 liters) Total BAs were elevated in severe HI versus controls at baseline (predose Day 1): GMR (90% CI): 60.38 (32.58, 111.91) as well as on Day 6 of dosing: GMR (90% CI): C_{max}: 5.89 (3.70, 9.38); AUC_{τ}: 8.83 (5.40, 14.44), but remained asymptomatic. Median BLV half-life (hours) was similar in all groups on Day 6 (Moderate HI: 2.6, matched controls: 2.7; Severe HI: 2.2, matched controls: 4.8), indicating that HI did not prolong BLV elimination. There were no Grade ≥ 3 treatment-emergent (TE) AEs or laboratory abnormalities, serious AEs, or AEs leading to BLV discontinuation. The TEAEs were generally mild and with no increased severity versus controls. **Conclusion:** There was no clinically meaningful impact of moderate HI on BLV steady state PK following BLV 2 mg SC QD dosing for 6 days, while increased BLV PK (by ~ 2 - 4-fold) was observed in severe HI compared to matched controls. BLV was generally safe and well tolerated in all groups.

Figure 1: Semi-log Plot of Mean (SD) Plasma Concentrations of Bulevirtide on Day 6 Following 2 mg Subcutaneous Once-Daily Dosing in (A) Participants with Moderate Hepatic Impairment and Matched Control Participants and in (B) Participants with Severe Hepatic Impairment and Matched Control Participants



AUC_{τ} = Area under the time-concentration plasma curve over 24 hours; BLV = bulevirtide; CI = confidence interval; C_{max} = maximum plasma concentration; Controls = matched healthy control participants; GMR = geometric mean ratio; HI =hepatic impairment; LLOQ = lower limit of quantification (1 ng/mL); SD = standard deviation.
PK sampling relative to BLV dose was taken on Day 6 at predose (≤ 30 minutes before dose), 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12, 24 (Day 7), and 48 (Day 8) hours postdose. All participants had BLV concentrations below the LLOQ at the 24 and 48 hour timepoints.

Disclosures: Parag Kumar: Gilead Sciences, Inc.: Employee, Gilead Sciences, Inc.: Stock - publicly traded company, Renee-Claude Mercier: Nothing to Disclose, Wildaliz Nieves: Gilead Sciences, Inc.: Employee, David Pan: Nothing to Disclose, Steve Tseng: Gilead Sciences, Inc.: Employee, Grace Chee: Gilead Sciences: Employee, Xu Zhang: Nothing to Disclose, Yehong Wang: Nothing to Disclose, Ann Qin: Nothing to Disclose, Carrie Nielson: Gilead Sciences: Employee, Gilead Sciences: Stock - publicly traded company, Teckla Akinyi: Gilead Sciences: Employee, Helen Winter: Gilead Sciences: Employee

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1155 | REAL WORLD OUTCOMES OF HEPATITIS DELTA PATIENTS WITH MILD OR MODERATE FIBROSIS

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Background: Hepatitis Delta is considered the most severe form of viral hepatitis. New therapeutic options are now available and, in some countries, therapy prioritization is recommended. We aimed to evaluate the real world outcomes of HDV-infected patients with mild or moderate fibrosis in order to identify risk factors for fibrosis progression. **Methods:** Multicenter international retrospective study of adult patients with active HDV infection (HDV-RNA+) and absence of advanced fibrosis at diagnosis. Baseline demographical, clinical and virological variables were collected. Cirrhosis development and liver-related events (decompensation, HCC) were recorded. Patients were followed until last follow-up (FU) visit, liver transplantation (LT) or death. **Results:** The cohort included 170 adult patients with mild/moderate fibrosis assessed histologically (45%) and/or non-invasively [median (IQR) age at first visit: 37 (31-45) years, males:53%]. Most patients were Caucasians (55%) or Asians (21%), <5% were coinfected with HIV or HCV and <15% had comorbidities (obesity, diabetes, hypertension). At baseline, only 36% of patients had ALT>2xULN. In 102 cases with LSM within year-1, median (IQR) values were 7.6 (6-9) kPa. During the study period, 33% of patients received Interferon, 36% NA and only 8% bulevirtide therapy. After a median (IQR) follow-up of 62 (21-108) months, 31 (18%) patients developed cirrhosis; of them, 5 developed liver decompensation and 2 HCC. One patient underwent LT and one patient with HCC died. Median LSM (IQR) of patients at cirrhosis diagnosis was 16 (10-17) kPa. By multivariate analysis, higher LSM at baseline (model 1) and albumin and platelet levels (model 2 excluding LSM) were the only independent predictors for cirrhosis development. The best cut-off for LSM value at baseline for cirrhosis development was 7.6 kPa (Se 84%). Neither baseline qHDV-RNA levels nor ALT influenced on cirrhosis development. In addition, 17 (10%) patients achieved HDV-RNA clearance during FU (6 after IFN therapy and 11 spontaneously) with only 1/17 patients developing cirrhosis during FU. **Conclusion:** Some patients with active HDV replication and mild-moderate fibrosis may have a benign course, but up to 18% of such patients progress to cirrhosis within 5 years having increased risk for liver-related complications. LSM seems to be a reliable non-invasive predictor, as patients with LSM<7.6 kPa have a low probability of progression to cirrhosis. Dissecting the factors associated with fibrosis progression may be useful to prioritize the need of new antiviral therapies.

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1156 | UTILITY OF THE FUNGAL BIOMARKER BETA-D-GLUCAN (BDG) FOR DIAGNOSIS OF INVASIVE FUNGAL INFECTIONS, ANTIFUNGAL PRESCRIPTION AND CORRELATION WITH MORTALITY FOR CRITICALLY ILL PATIENTS IN A LIVER INTENSIVE CARE UNIT

Anita Verma[1] Sameer Patel[2] Pervez Khan[2] Tasneem Pirani[2] Georg Auzinger[2] Vandana Jain[2] Abid Suddle[2] Wayel Jassem[2] Robert Loveridge[2]

[1]King's College Hospital NHS Trust, [2]King's College Hospital NHS Foundation T

Background: The risk of invasive fungal infections (IFI) in critically ill liver patients admitted to intensive care unit (ICU) increases significantly because of cumulative exposure to the risk factors. Early diagnosis and prompt antifungal therapy are key to improve outcomes. **Methods:** To evaluate the utility of fungal biomarker beta-D-glucan (BDG) for the diagnosis of IFI and antifungal use in liver patients with risk factors for IFI. We also analysed the correlation of BDG levels with mortality. Institutional approval was obtained for this study. **Results:** During the 15 month period, 1355 patients were admitted to liver ICU. 23% (312/1355) of patients had high risk factors for IFI and BDG was done. More than 30% (108/312) of patients had ≥2 positive BDG of >80pg/ml. The incidence of IFI was 28% (87/312). Infections with *Candida* spp. was 75%, non-*Candida* yeast was >12% and invasive aspergillosis (IA) was 10%. Patients with acute liver failure (ALF), acute on chronic liver failure (AOCLF) and decompensated liver disease (DLD) had highest rates of IFI in comparison to patients with hepatobiliary (HPB) and chronic liver disease (CLD). The sensitivity and specificity of BDG for ≥2 samples at cut off value of >80pg/ml was 94% and 92% respectively and negative predictive value (NPV) was 98%. White Blood Cell (WBC) and C-reactive protein had a poor predictive value to predict IFI (Figure 1) . However on multivariate logistic regression WBC and BDG remained independently associated with IFI with an adjusted odds ratio of 1.048 (10.40-1.057) for BDG (p = <0.001) and 1.035 (1.008-1.063) for WCC (p = 0.009). Antifungals were stopped in 81% of patients when BDG value was below <80pg/ml, which resulted in significant reduction in duration and cost of antifungals. Ninety-day all cause mortality was 47% and associated with high SOFA score. However IFI associated mortality was <10%. Increasing or persistently high BDG >80pg/ml whilst on antifungals were associated with significantly higher mortality. The significant risk factors for IFI were; SOFA score >7, >2-week stay in ICU, colonisation with fungi, renal failure requiring renal support > 1week, ALF, AOCLF, bowel and biliary complications. **Conclusion:** Our data suggests that the incorporation of BDG and risk factors into a diagnostic algorithm has good diagnostic accuracy for early diagnoses of IFI. BDG also demonstrated a high NPV to stopping the use of antifungals. Increasing or persistently higher values of BDG whilst on antifungals were associated with significantly higher mortality. Further studies are needed to better understand the prognostic value of BDG in subgroups of liver patients.

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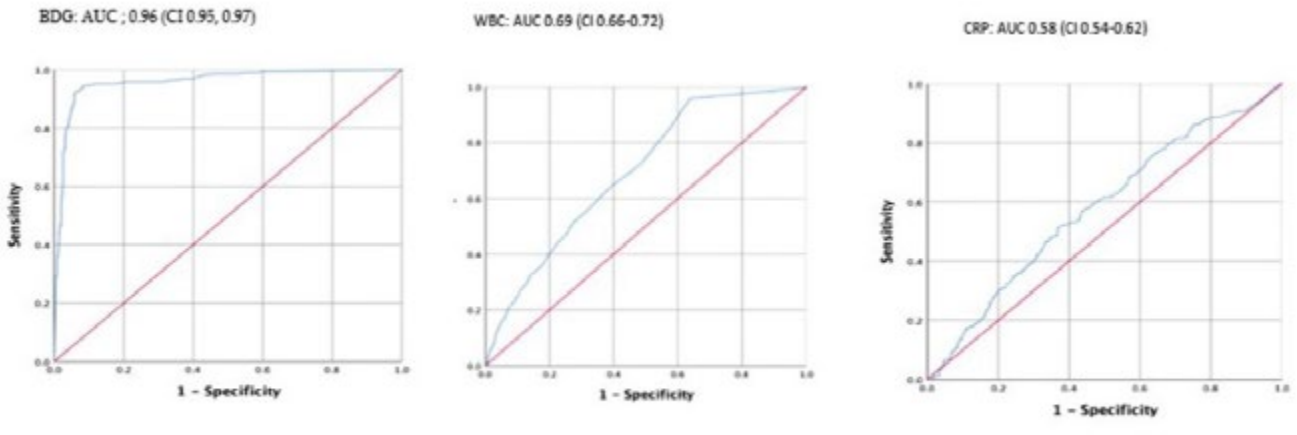

Figure: Receiver-operating characteristic curve for BDG, WBC and CRP as a predictor of IFI

Disclosures: Anita Verma: Nothing to Disclose, Sameer Patel: Nothing to Disclose, Pervez Khan: Nothing to Disclose, Tasneem Pirani: Nothing to Disclose, Georg Auzinger: Nothing to Disclose, Vandana Jain: Nothing to Disclose, Abid Suddle: Nothing to Disclose, Wayel Jassem: Nothing to Disclose, Robert Loveridge: Nothing to Disclose

1157 | RECENT SEROPREVALENCE AND EPIDEMIOLOGICAL CHARACTERISTICS OF HDV INFECTION AMONG HBSAG-POSITIVE INPATIENTS IN CHINA

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Background: Hepatitis D virus (HDV), a defective virus occurs as a coinfection with hepatitis B virus (HBV) and increases the risk of severe viral hepatitis. Despite an estimated 43.3 million HBV infections in China in 2021, the recent burden of HDV/HBV coinfections remains unknown. Reliable estimates of the prevalence of HDV infection and disease burden are essential to develop strategies in order to manage co-infected individuals more effectively and efficiently. **Methods:** We screened HBsAg-positive inpatients between 2023 and 2024 across 6 centers in northeastern, eastern, and southwestern China. HDV antibodies (both IgM and IgG) in serum were tested by ELISA, and seropositive samples were further assessed by HDV RNA PCR to identify the HDV genotype. Available clinical information was collected and analyzed. **Results:** After excluding patients without properly stored serums and appropriate clinical information, 9028 patients with HBsAg positive were included. Of these, anti-HDV antibodies were detected in 0.66% of patients (0.34% for IgM; 0.37% for IgG). And the serological prevalence of HDV varied among regions, from 0% to 0.96% (p=0.023) in Fujian and Guizhou, respectively. The seroprevalence of HDV was higher in HBcAb-negative patients (1.4% vs 0.6%) and HBV/HCV (1.52% vs 0.58%) or HBV/TP (0.89% vs 0.53%) co-infected patients. Patients with anti-HDV positivity were significantly older (57 years old vs 52 years old, p=0.005), and demonstrated significantly lower lymphocytes ratio (1.10% vs 1.44%, p=0.010), longer prothrombin time (12.8s vs 12.2s, p=0.017) and lower Fib (2.38 g/L vs 2.62 g/L, p=0.033) in peripheral serum compared to anti-HDV-negative patients. HBsAg-positive patients with anti-HDV positivity had significantly higher HBsAg S/CO levels (340.1 COI vs 250.1 COI, p=0.005) while lower HBV DNA load (26.8 IU/mL vs 49.9 IU/mL, p=0.216) than those with anti-HDV negativity, although the difference in HBV DNA load was not yet significant due to insufficient data. **Conclusion:** This multi-center study highlights the current HDV epidemic in China, and the seroprevalence of anti-HDV was much lower than previously reported in published studies. The results identify geographical difference and high-risk populations of HDV infection, especially HBsAg-positive patients with undetectable HBV DNA, which provide insights for improving surveillance of HDV-related diseases and mitigating the spread of HDV.

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1158 | ESTABLISHMENT AND APPLICATION OF A NEW METHOD FOR DUAL DETECTION OF HDV RNA AND HBV DNA BASED ON CRISPR TECHNOLOGY

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Background: Hepatitis D virus (HDV) is a defective virus that is dependent on hepatitis B virus (HBV) for infection and replication, and co-infection with HDV and HBV exacerbates the development of viral hepatitis. In this study, we used the clustered regularly interspaced short palindromic repeats-CRISPR-associated proteins (CRISPR-Cas) system to establish a method for the detection of HDV RNA and HBV DNA, as well as dual detection. **Methods:** We constructed HDV and HBV plasmids by comparing conserved sequence regions; and we designed and screened RT-RAA primer pairs to amplify the HDV plasmid and RAA primers to amplify the HBV plasmid, as well as corresponding crRNAs (CRISPR-derived RNAs), respectively; the conditions of the assay were optimized, leading to the establishment of a new CRISPR-Cas13a/Cas12a-based assay. Then the sensitivity and specificity of the new method was evaluated by fluorescence and lateral flow test strip method of the “line elimination method”. The established new assay was validated by collecting HDV- and HBV-related clinical samples in comparison with RT-qPCR and RT-ddPCR methods. **Results:** RT-RAA-CRISPR-Cas13a/RAA-CRISPR-Cas12a fluorescence and “line elimination” lateral flow test strip assays were established for HDV RNA detection and HBV DNA detection, respectively. The sensitivities of RT-RAA-CRISPR-Cas13a for detecting HDV plasmids and positive samples were both 10 copies/μL, and the sensitivities of RAA-CRISPR-Cas12a for detecting HBV plasmids and positive samples were both 1 copy/μL. Moreover, we established a RT-RAA-CRISPR-Cas13a/Cas12a dual fluorescence and “line elimination” lateral flow test strip assays for HDV RNA and HBV DNA. The sensitivity for detecting HDV and HBV plasmids and positive samples was 10 copies/μL, and there was no cross-reactivity between the detection of HDV and HBV and other related viruses; the RT-RAA-CRISPR-Cas13a/Cas12a dual fluorescence and lateral flow test strip assays showed a detection rate of 70% and 65.7% for HDV RNA and HBV DNA, respectively. **Conclusion:** We developed a novel CRISPR-Cas13a/Cas12a-based assay for accurate, convenient, highly sensitive and specific detection of HDV RNA and HBV DNA, providing a more effective alternative for early detection and treatment of HDV and HBV infections, as well as for the guidance of medication administration and the evaluation of clinical therapeutic effects.

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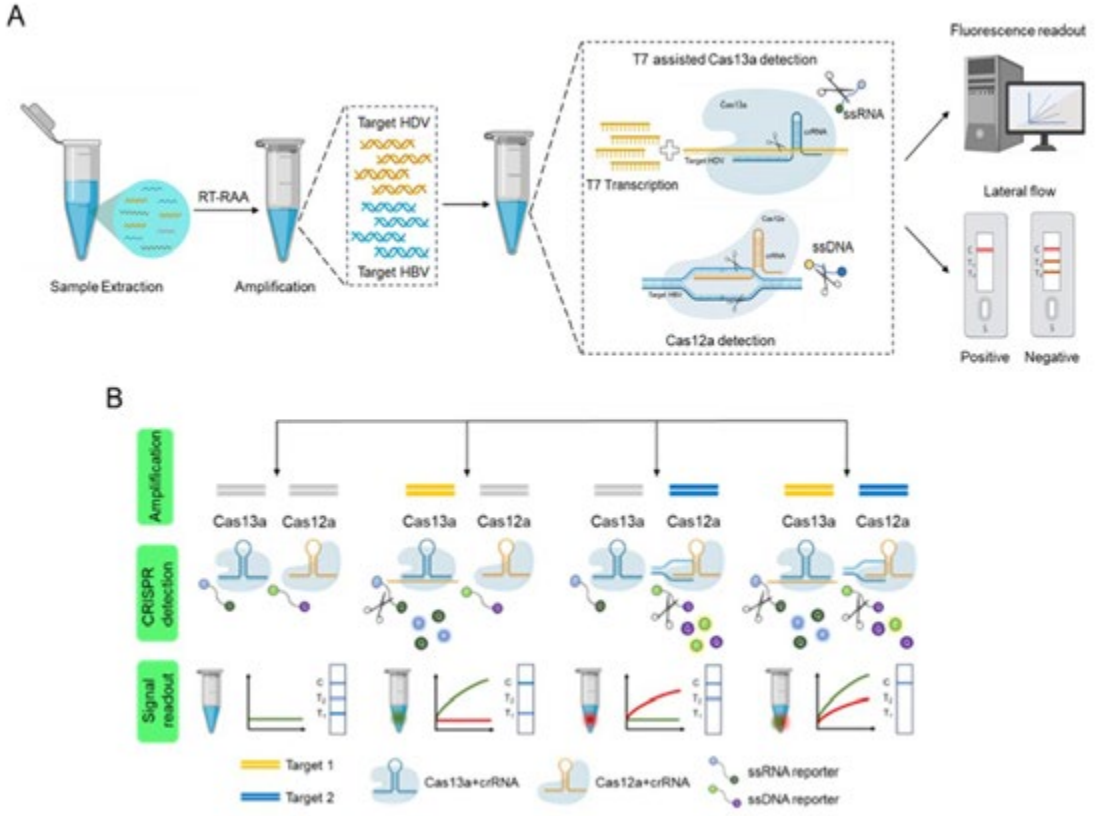

Schematic diagram of dual detection method by RT-RAA-CRISPR-Cas13a/Cas12a for HBV DNA and HDV RNA

Disclosures: Feng Ren: Nothing to Disclose, Xiangying Zhang: Nothing to Disclose, Yuan Tian: Nothing to Disclose, Ling Xu: Nothing to Disclose, Zihao Fan: Nothing to Disclose

1159 | A NOVEL SPR ASSAY DETECTS SPECIFICALLY ANTI-HDV IN HUMAN SERUM SAMPLES

Nomin Ariungerel[1] Batzul Ganbold[1] Badmaarag Munkhjin[1] Nomin-Erdene Erdenebat[1] Maral Enkhtur[2] Galbadrakh Ragchaa[1] Davaasambuu Jav[1] Naranjargal Dashdorj[3] Odgerel Oidovsambuu[1]

[1]National University of Mongolia, [2]Hobby school, Mongolia, [3]Onom foundation, Mongolia

Background: The hepatitis delta virus (HDV) is a defective RNA virus that causes severe liver disease. Despite its endemicity in a few countries, the worldwide prevalence of HDV is unequally distributed. SPR (surface plasmon resonance) is an optical phenomenon that develops label-free, rapid, highly sensitive, and real-time sensing devices. SPR detection can be applied to various bioanalytical applications, and a wide range of immobilization methods have been developed. The serological diagnostic option is limited by only a few numbers of ELISA kits, and rapid diagnostic tests or full automatic serological tests are not yet developed for this virus. In this work, we have developed a biosensor for detecting HDV-antibody using a thin gold film and a laser detection setup based on Kretschman's configuration. **Methods:** In this biosensor assembly, Au thin films (50 nm) were vapor-deposited onto microscope slides. The Au thin film surface was immersed with a piranha solution, and the surface was modified using 10mM 11-Mercaptoundecanoic acid (MUA) solution in ethanol for at least 24h. The NHS ester was formed via exposure of the MUA to 75 mM EDC and 15 mM NHS for 1 h. MUA NHS ester monolayers were reacted for 1 h with a solution of S-HDAg in pH=10.6 carbonate-bicarbonate buffer. The modified SPR sensor is blocked by non-infected human serum for 30 min, and t 1% BSA for 30 min subsequently. To determine the characteristics of the assay, serum samples from 31 people, including 15 patients with HDV/HBV chronic infection (HDV-RNA and HBsAg positive) and 16 healthy people (Anti-HCV and HBsAg negative) were analyzed using the experimental setup according to the Kretschmann configuration. The SPR data was collected from 4 types of measurement, including blank-NT (only Au deposited, non-treated), negative-NT

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(S-HDAg immobilized, non-treated), negative-T (S-HDAg immobilized, treated with negative serum samples) positive-T (S-HDAg immobilized treated with positive serum samples). The total time duration of the assay is 30 min. **Results:** S-HDAg was successfully immobilized on the Au thin film slide (data not shown). The average SPR angle values were 45.8^0 for blank-NT, 48.4^0 for negative-NT, 49.7^0 for negative-T and 52.4^0 for positive-T (*Figure1, Table1*). These results indicate that the SPR diagnostic setup can differentiate anti-HDV-positive samples from healthy people samples. **Conclusion:** The results showed that a newly developed SPR-based biosensor can quickly and specifically detect anti-HDV in human serum samples without probe or conjugate.

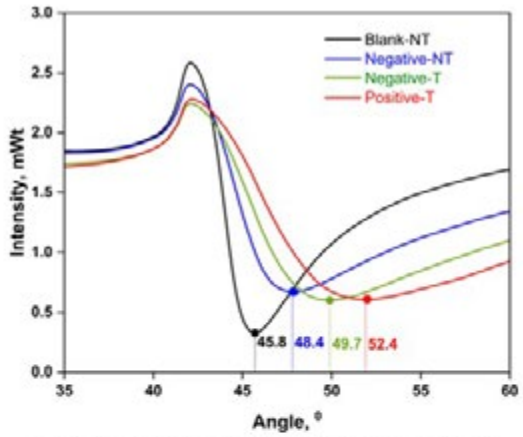

***Figure 1**. SPR graphic curve of blank-NT, negative-NT, negative-T and positive-T*

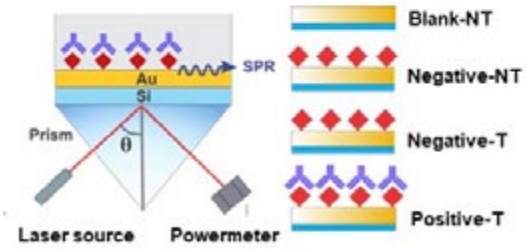

***Figure 2**. General scheme of SPR based assay and assembly of biosensor*

№	Blank-NT		Negative-NT		Negative-T		Positive-T	
	SPR angle	Intensity, mWt	SPR angle	Intensity, mWt	SPR angle	Intensity, mWt	SPR angle	Intensity, mWt
1	44.9	0.1248	47	0.5457	49.2	0.9908	52.4	0.8605
2	45.6	0.5301	49	0.9869	47.5	0.6064	49.3	0.3235
3	45.3	0.3646	45.3	0.3646	49.4	0.6935	52.8	0.8178
4	46.9	0.3138	46.2	0.3308	48.9	0.4502	52.9	0.8018
5	46.6	0.0927	51.3	0.7563	50.3	0.2961	51.7	0.6678
6	46.4	0.0924	48.8	0.4632	50.2	0.5109	56.9	0.8330
7	45.3	0.1072	49.4	0.3721	49.5	0.3123	50.2	0.3237
8	45.3	0.1229	46.5	0.5422	49.9	0.3196	50.1	0.7037
9	46.5	0.0537	47.1	0.2021	48.9	0.3396	54.5	0.5074
10	45.7	0.3258	51.2	0.5551	50.1	0.4283	53.1	0.5034
11	-	-	50.3	0.56974	49.7	0.5364	54.3	0.5771
12	-	-	-	-	48	0.3073	54.5	0.5074
13	-	-	-	-	51.8	0.3457	51.2	0.5601
14	-	-	-	-	51.8	0.4040	51.9	0.2642
15	-	-	-	-	50.9	0.4340	50.5	0.3580
16	-	-	-	-	49.9	0.3787	-	-

***Table 1**. SPR angle and the intensity value of blank-NT, negative-NT, negative-T and positive-T*

Disclosures: Nomin Ariungerel: Nothing to Disclose, Batzul Ganbold: Nothing to Disclose, Badmaarag Munkhjin: Nothing to Disclose, Nomin-Erdene Erdenebat: Nothing to Disclose, Maral Enkhtur: Nothing to Disclose, Galbadrakh Ragchaa: Nothing to Disclose, Davaasambuu Jav: Nothing to Disclose, Naranjargal Dashdorj: Nothing to Disclose, Odgerel Oidovsambuu: Nothing to Disclose

1160 | EFFECT OF SEX STEROID HORMONES ON HEV REPLICATION – CLINICAL IMPLICATION

Premashis Kar[1]

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Background: Pregnant women are highly susceptible to HEV infection particularly in north India. High incidence and mortality rate of HEV infection in pregnancy is believed to be secondary to the associated increase in sex steroid hormones estrogen, progesterone and human Chorionic gonadotropin(hCG) hormone. In this experimental study we analysed the role sex steroid hormone on replication of HEV on hepatic cell lines. **Methods:** Hepatic cell line S10-3 were infected with HEV-1 clone pSK-HEV1 which is tagged with luciferase enzymes (Renila). Before transfection of HEV plasmid was linearized with restriction enzyme having *Bgl II* site located immediately downstream of the poly (A) tract. Linear plasmid was in vitro-transcription into HEV 1 capped RNA transcripts using mMessage mMachine T7 ultra kit (Ambion). For each experiment, cells were grown up to 60–70%

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confluence in 24-well cell culture plates in DMEM media and 5% FBS. Cells were transfected with HEV1 RNA transcripts (2 µg of psK-HEV1 RNA per 24 well plate) in Opti-MEM using DMRIE-C reagent. Confluent cells were then introduced with serial dilution of estrogen, progesterone and hCG hormones in the range of 0 pg/ml to 10000 pg/ml, 5 to 50 ng/ml and 5 miu/ml to 50 miu/ml respectively which are the physiological concentrations typically seen in the first- to third-trimester during pregnancy Dual luciferase assay was used to measure the luciferase activity of HEV replicon. Replication of HEV was measured on luminometer as RLU unit. **Results:** Pre-treatment of S10-3 cells with estrogen at lower concentration below 2500 pg/ml had little effect on replication of HEV. However as the concentration increase from 2500 pg/ml to 3000 pg/ml, 5000 pg/ml, 10000 pg/ml significantly high replication of HEV was observed which are the physiological concentrations seen in first- to third-trimester during pregnancy, Similarly pre-treatment of S10-3 cells with progesterone has no significant impact on replication of HEV clones on lower dose progesterone (5 ng/ml to 40 ng/ml) however as the concentration increases form 40 ng/ml to 60 ng/ml significant high efficiency (p=0.0313) in replication of HEV clone was observed. Treatment of hepatic cell lines with hCG at the range of 5 miu/ml to 50 miu/ml has significant difference on replication efficiency of HEV clone even at lower dose i.e., 5 miu/ml and 25 miu/ml (p=0.02 and 0.009). However, as the concentration of hCG increases from 25 miu/ml to 50 miu/ml it showed lower expression of HEV clone than it has at 25 miu. This could be due toxic effect of hCG at higher dose. **Conclusion:** This study experimentally proved that sex steroid hormones have significant impact on HEV replication on hepatic cell lines. It was also observed that as the concentration of estrogen and progesterone increases, significant impact is noted at higher doses which is usually seen in second and third trimester of pregnancy.

Disclosures: Premashis Kar: Nothing to Disclose

1161 | DELTA DESCRIBE, THE FRENCH COLLABORATIVE PROJECT: PROFILE AND MANAGEMENT OF HEPATITS DELTA PATIENTS IN METROPOLITAN FRANCE

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Background: Chronic hepatitis delta patients are at high risk of cirrhosis and liver cancer. We already presented the inadequacy of Hepatitis Delta Virus (HDV) screening in mainland France in the first part of our Delta Describe study (AASLD 2023 1208-C). In this second part, we aim to describe epidemiological characteristics, management and treatments of HDV patients. **Methods:** We identified patients who tested positive for HDV RNA at least once in 2019 by extracting data from 7 public laboratories and the 2 main groups of private laboratories testing HDV RNA in the national territory. Patients informed and not opposed to the study were contacted by phone to collect the following data: age, country of birth, HIV and/or HCV co-infections, frequency of follow-up by a specialist, **Results:** of additional examinations, treatments. **Results:** We present here intermediate **Results:** which will be updated for the congress. The data collected concern 123 patients, 64.2% were men, with a median age of 45 years. 53.3% of the patients were natives of Africa and 23.6% of Eastern Europe and 16.7% admitted to using or having used drugs. 88.6% known the year of their delta hepatitis diagnosis. 18.3% declared HIV co-infection and 6.6% HCV co-infection. Medical follow-up was mainly carried out by a hepato-gastroenterologist or an infectious disease specialist for 91.8% of patients, with quarterly (33.3%) or six-monthly (47.7%) follow-up. 82.9% indicated having already had a FibroScan®, with 26.2% of patients having cirrhosis. 26.9% indicated having or having had liver related complications of their disease. Of the 123 patients, 5.6% presented cirrhosis decompensation, 3.2% developed HCC and 6.5% received a liver transplant. Out of 103 patients whose HDV RNA could be collected, 51.3% currently had an undetectable HDV viral load. Likewise, out of 76 patients whose HBV DNA could be collected, 61.8% had an undetectable HBV viral load. 73.5% of patients benefited from current treatment against hepatitis B and/or D: nucleotide(s)ide analogue (NUC) alone (44.2%), bulevirtide (BLV)+NUC

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(24%), BLV alone (5.8%), BLV+NUC+pegylated interferon (peg-IFN) (5.8%). Of the 123 patients, 9.8% had previously received BLV +/- peg-IFN and 18.7% peg-IFN with discontinuation of treatment. **Conclusion:** HDV patients, who were able to enter a care pathway in mainland France with at least one positive HDV RNA result in 2019, had an expected severity profile. The care pathway can improve but patients have or had significant access to specific treatment: 37% for bulevirtide and 70.7% for HBV analogues.

Disclosures: Veronique Loustaud-Ratti: GILEAD: Consultant, abbvie: Speaking and Teaching, GSK: Consultant, Marie Bosselut: Nothing to Disclose, Paul Carrier: Nothing to Disclose, Marilyne Debette-Gratien: Nothing to Disclose, Segolene Brichler: Nothing to Disclose, Caroline Scholtes: Gilead: Speaking and Teaching, Roche Diagnostics: Independent Contractor, anne-marie roque-afonso: Nothing to Disclose, Sonia Burrel: Nothing to Disclose, Pascale TRIMOULET: Nothing to Disclose, Aurélie Guigon: Nothing to Disclose, Marianne Coste-Burel: Nothing to Disclose, Eric Billaud: Nothing to Disclose, Jacques Izopet: Nothing to Disclose, Karine Sauné: Nothing to Disclose, Stephane Chevaliez: Nothing to Disclose, Benoit Visseaux: Nothing to Disclose, Anaïs Soares: Nothing to Disclose, Anaïs Labrunie: Nothing to Disclose, Céline Rigaud: Nothing to Disclose, Sandrine Francois: Nothing to Disclose

1162 | NATURAL HISTORY AND LIVER RELATED OUTCOMES DUE TO CHRONIC HEPATITIS DELTA VIRUS FROM NORTH AMERICA

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Background: Hepatitis delta virus (HDV) is one of the most severe forms of chronic viral hepatitis with rapid progression to cirrhosis and associated complications. While previous studies on the natural history of HDV have predominantly originated from Europe, there is a notable absence of similar studies from North America. Therefore, this study aims to explore the natural history of HDV from North America. **Methods:** We included 174 patients with chronic HDV who were prospectively followed for at least 6 months at the National Institutes of Health from May 1992 to April 2024 (NCT00001971). Patients with positive anti-HDV antibody along with either positive HDV RNA PCR or liver biopsy with positive HDAg staining were included. Primary outcome was development of cirrhosis, hepatocellular carcinoma (HCC) or liver-related death in patients without baseline cirrhosis. For those with cirrhosis at presentation, the primary outcome included decompensation, HCC or liver-related death. **Results:** Median age of the cohort was 38 years (range:18-68), with 65% males, and median duration of follow-up was 5.8 years. Risk factors included birth in endemic region (59%), high-risk sexual behavior (15%) and intravenous drug use (14%). There was predominance of Asians (43%), followed by White (34%), and Black (21%) race. Median HDV RNA level was 5.1 $\log_{10}$ genome equivalents/mL and 14% had HBeAg positive. Twenty-five (14%) had cirrhosis at presentation. Among these patients, 12 (48%) developed primary outcome over a medial follow up of 3 years, with 4 patients developing HCC. In those without cirrhosis, 23% developed primary outcome, while 9 (6%) subjects cleared HBsAg - 7 due to treatment and 2 spontaneously. Among those without baseline cirrhosis, significant differences (all $p < 0.01$) were observed in platelet count (150 vs 204 x 10^9/L), albumin (3.8 vs 4.2 g/dL), INR (1.2 vs 1.1), spleen size (12.5 vs 10 cm) and liver stiffness measurement (LSM) by transient elastography (13.5 vs 7.6 kPa) between those with and without primary outcome. Multivariable logistic regression showed platelet count and LSM were significant predictors of outcome. **Conclusion:** In this North American study of HDV's natural history, almost half of patients with cirrhosis at presentation and one-fourth without baseline cirrhosis developed liver-related complications within 6 years of follow up. Notably, in non-cirrhotic patients, platelet count and LSM can serve as predictors for identifying those at risk of liver-related outcomes.

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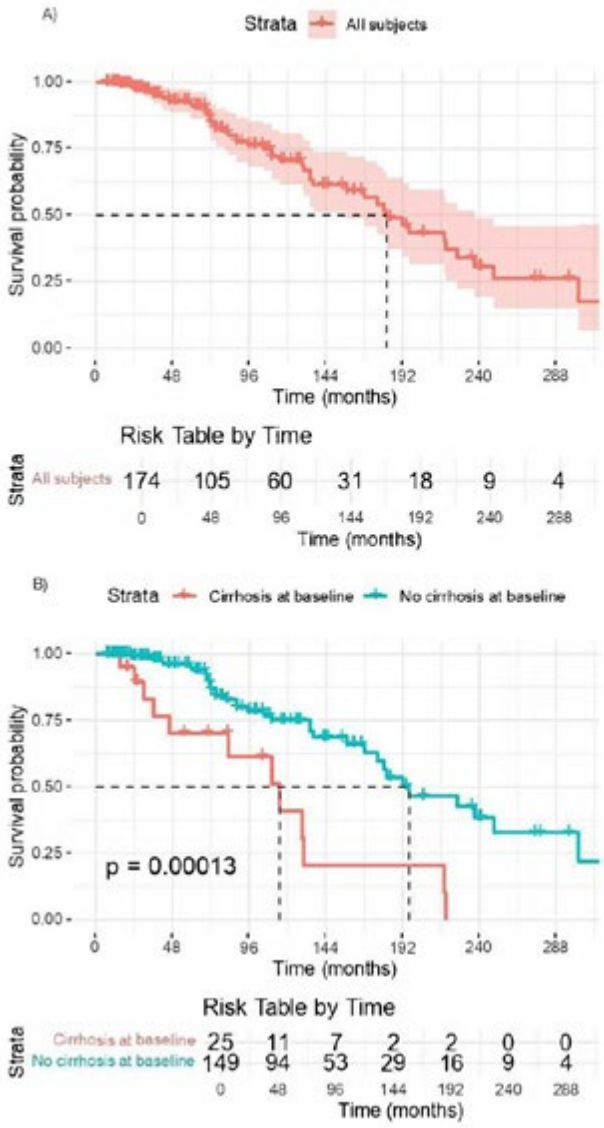
Kaplan-Meier survival plot showing probability of developing primary outcome in the A) overall cohort B) stratified by presence or absence of cirrhosis at initial presentation



Disclosures: Harish Gopalakrishna: Nothing to Disclose, Maria Mironova: Nothing to Disclose, Cinthya Aviles: Nothing to Disclose, Elizabeth Townsend: Nothing to Disclose, Gayatri Nair: Nothing to Disclose, Gian Rodriguez Franco: Nothing to Disclose, Asif Hitawala: Nothing to Disclose, David Kleiner: Nothing to Disclose, Christopher Koh: Nothing to Disclose, Theo Heller: Nothing to Disclose

1163 | SERO-PREVALENCE AND GENOTYPE DISTRIBUTION OF HDV AMONG 67 HBSAG-POSITIVE PREGNANT WOMEN IN SIEM REAP, CAMBODIA, USING IN-HOUSE DIRECT ELISA TEST METHOD

Golda Akuffo[1] Ko Ko[1] Bunthen E[2] Serge Ouoba[3] Ulugbek Mirzaev[1] Chanroth Chhoung[1] ZAYAR PHYO[1] Aya Sugiyama[1] Tomoyuki Akita[1] Shingo Fukuma[1] Kazuaki Takahashi[1] Junko Tanaka[1]

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Background: Hepatitis Delta virus (HDV), which co-infects with hepatitis B (HBV), affects about 48 to 60 million people and is a major cause of increased mortality from viral liver disease. Its prevalence is poorly documented in low-income regions, such as Cambodia, due to the high cost and limited accessibility of standardized tests. The

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WHO recommends the development of accurate and affordable diagnostic methods for HDV to improve access to testing, especially with new treatments available, to meet the 2030 goal of reducing viral hepatitis mortality by 65%. In response, an affordable direct enzyme immunoassay (ELISA) was developed. It was then used to estimate anti-HDV prevalence and HDV genotype distribution among 67 HBsAg-positive pregnant women in Siem Reap, Cambodia. The results will provide essential baseline data for HDV in Cambodia and support the use of this diagnostic method in other low-income countries. **Methods:** This study followed up on previous research that identified 67 HBsAg-positive pregnant women out of 1565 in Cambodia. In our study, we developed a direct ELISA method and evaluated its performance against a commercial HDV assay using 108 samples from various regions. The in-house ELISA was then used to assess the anti-HDV status of the 67 HBsAg-positive pregnant women. HDV RNA was analyzed, and genotypes were identified. The test's performance was evaluated using ROC analysis with JMP 17.0. **Results:** The sensitivity and specificity of the in-house direct ELISA compared with the commercial ELISA were 96.6% (95% CI: 82.2–99.9) and 82.3% (95% CI: 70.6–89.0), respectively. With an agreement of 81.9% (95% CI: 73.4–88.7) and a Kappa coefficient of 0.67 (95% CI: 0.53-0.81),. Utilizing the newly developed ELISA method, the prevalence of anti-HDV was 5.97% (95% CI: 1.65–14.59) (4/67) among HBSAg+ Cambodian pregnant women. However, among the general population of 1565 Cambodian pregnant women, the prevalence of anti-HDV was 0.26% (95% CI: 0.07–0.65) (4/1565). Of the four anti-HDV-positive samples, 2 (2/4) had detectable HDV RNA. Both were found to be HDV genotype 1. And was closely related to strains from Nigeria and Ivory Coast. **Conclusion:** Our in-house direct ELISA proved effective as a screening method, with implications for the diagnosis and treatment of HDV in low-income settings. The prevalence of anti-HDV among 67 HBsAg-positive Cambodian pregnant women was 5.97%, with genotype 1 being the predominant strain.

Disclosures: Golda Akuffo: Nothing to Disclose, Ko Ko: Nothing to Disclose, Bunthen E: Nothing to Disclose, Serge Ouoba: Nothing to Disclose, Ulugbek Mirzaev: Nothing to Disclose, Chanroth Chhoung: Nothing to Disclose, ZAYAR PHYO: Nothing to Disclose, Aya Sugiyama: Nothing to Disclose, Tomoyuki Akita: Nothing to Disclose, Shingo Fukuma: Nothing to Disclose, Kazuaki Takahashi: Nothing to Disclose, Junko Tanaka: Nothing to Disclose

1164 | ESTABLISHMENT OF BALB/CAJCL-NU/NU MICE XENOGRAFT MODEL AND DRUG SCREENING PLATFORM FOR ACUTE HEPATITIS A

Reina Sasaki-Tanaka[1] Tatsuo Kanda[1] Ryota Masuzaki[2] Hiroyuki Abe[1] Tomoaki Yoshida[1] Yusuke Watanabe[1] Naruhiro Kimura[1] Kazunao Hayashi[1] Takeshi Yokoo[1] Akira Sakamaki[1] Hiroteru Kamimura[1] Atsunori Tsuchiya[1] Hiroaki Okamoto[3] Shuji Terai[1]

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Background: Although no potent anti-HAV drugs are available in clinical situations, hepatitis A caused by Hepatitis A virus (HAV) infection is a major cause of acute viral hepatitis worldwide. Moreover, there is no easily obtainable and useful HAV *in vivo* models, especially HAV genotype (GT)-Ⅲ. In this study, we developed a HAV GT-ⅢA *in vivo* models using BALB/cAJcl-nu/nu (nude) xenograft mice, and treated with masitinib which is a highly selective oral tyrosine kinase inhibitor, an antineoplastic agent. Masitinib has been reported as a useful anti-HAV drug *in vitro* experiments. **Methods:** 1) Human hepatoma cell lines Huh7 or HepG2 were infected with HAV GT-IB or GT-IIIA and then transplanted into the back of nude mice as xenografts. 2) HAV RNA were measured by real-time RT-PCR in liver and intestinal tissues, feces, sera and tumors of the mice. 3) Tissues were evaluated by hematoxylin and eosin staining. 4) Serum aminotransferase levels were measured by ELISA. 5) The characteristics of gut microbiota was determined using Illumina Miseq for the V3-V4 region of the 16S rRNA gene. 6) HAV infected Huh7 cells were injected into the back of nude mice as xenografts and treated with masitinib. 7) HAV RNA were measured by real-time RT-PCR in liver and intestinal tissues, feces, sera and tumors of the mice. **Results:** 1) No difference in the body weight of HAV infected and uninfected mice. Mice transplanted with HepG2 cells and mice transplanted with Huh7 cells were sacrificed after 13 days and after 32 days of transplantation, respectively. 2) Mice transplanted with HAV infected HepG2 cells; HAV RNA were detected in tumors only. 3) Mice transplanted with HAV GT-IB infected Huh7 cells; no tumor and no HAV RNA were detected. 4) Mice transplanted with HAV GT-IIIA infected Huh7 cells; HAV RNA was detected in liver and intestinal tissues, feces, sera, and tumors. Hepatic necroinflammation was observed in the liver with a slight elevation of serum aminotransferase levels. Submucosal inflammation was partly observed in the intestinal tissues. 5) HAV GT-IIIA induced gut microecological dysregulation in Huh7 cell-derived xenografts. 6) Masitinib in the loads of this study did not inhibit quantitative HAV RNA in liver and intestinal tissues, feces, sera and tumors of the mice. However, submucosal

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inflammation was improved in the intestinal tissues and serum aminotransferase levels tended to improve in masitinib treatment. **Conclusion:** We have established and unitized easily obtainable and useful an HAV GT-IIIA *in vivo* model for anti-HAV drugs screening. In this model, inflammation was histopathologically observed in the liver and intestinal tissues where HAV RNA was detected. In addition, HAV GT-IIIA induces gut microecological dysregulation in Huh7 cell-derived xenografts. Masitinib did not inhibit quantitative HAV RNA in our protocol, further studies are needed at this point.

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1165 | CLINICAL CHARACTERISTICS AND PROGNOSIS OF HEV HEPATITIS: A RETROSPECTIVE STUDY OF 628 CHINESE PATIENTS

Wen An[1] *Hongshan Wei*[1]

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Background: Infection with hepatitis E virus is a significant cause of morbidity and mortality, representing a serious global health problem. The aim of the present study was to characterize the clinical features and therapeutic response of patients with HEV hepatitis and identify risk factors for poor prognosis. **Methods:** In a retrospective study from 01/01/2014 to 01/01/2022, we collected baseline data of all eligible patients for HEV hepatitis and followed up all patients by interview and review of medical records. We explored the clinical feature in Chinese HEV infection patients. The follow-up data of patients who did not combined with more one liver other liver disease or liver cirrhosis were used to identify risk factors for poor prognosis. **Results:** Totally 628 HEV infection patients fulfilled the inclusion criteria and did not meet the exclusion criteria. Among them, 452 were males and 176 were females (M: F=2.57:1). The median age at diagnosis was 57.0 years (interquartile range: 46–64 years). There were average 79 laboratory-confirmed infections with HEV every year. As seen in figure 1, the number of Annual HEV infection is not increasing. The imaging feature of patients with HEV infection demonstrated injury of liver, gallbladder. Diffuse liver injury can be seen in 204 patients. Thickening of the gallbladder wall were seen in 382 patients. In our cohort, 343 patients without other liver disease, 69 patients with liver cirrhosis, 19 patients combined with two kind of liver disease. 90, 66, 41 patients combined with NAFLD, alcoholic liver disease, HBV hepatitis, respectively. Compared with patients without other liver disease, patients with liver cirrhosis shown lower baseline ALT, AST level, poorer coagulation index and higher MELD score. Compared with patients without other liver disease, patients with one or two other liver disease shown no difference between baseline ALT, AST, coagulation index and MELD score. Out of the 628 patients, 596 patients recovered from HEV hepatitis, 21 patients died because of liver failure, 8 patients did not remission in 3 months, 3 patients turned to liver transplantation. 540 patients did not combined with more one other liver disease or liver cirrhosis. Among them,519 patients recovered within 3 months, another 21 patients had poor prognosis. On multivariate analysis, patients combined with other liver disease, higher TBIL, lower PTA were independent predictors for poor prognosis of HEV infection. **Conclusion:** Compared with healthy patients, HEV hepatitis patients combined with other liver disease or liver cirrhosis reflect differences in demographics and serological features. The risk factors of poor prognosis were patients combined with other liver disease, higher TBIL level, lower PTA level.

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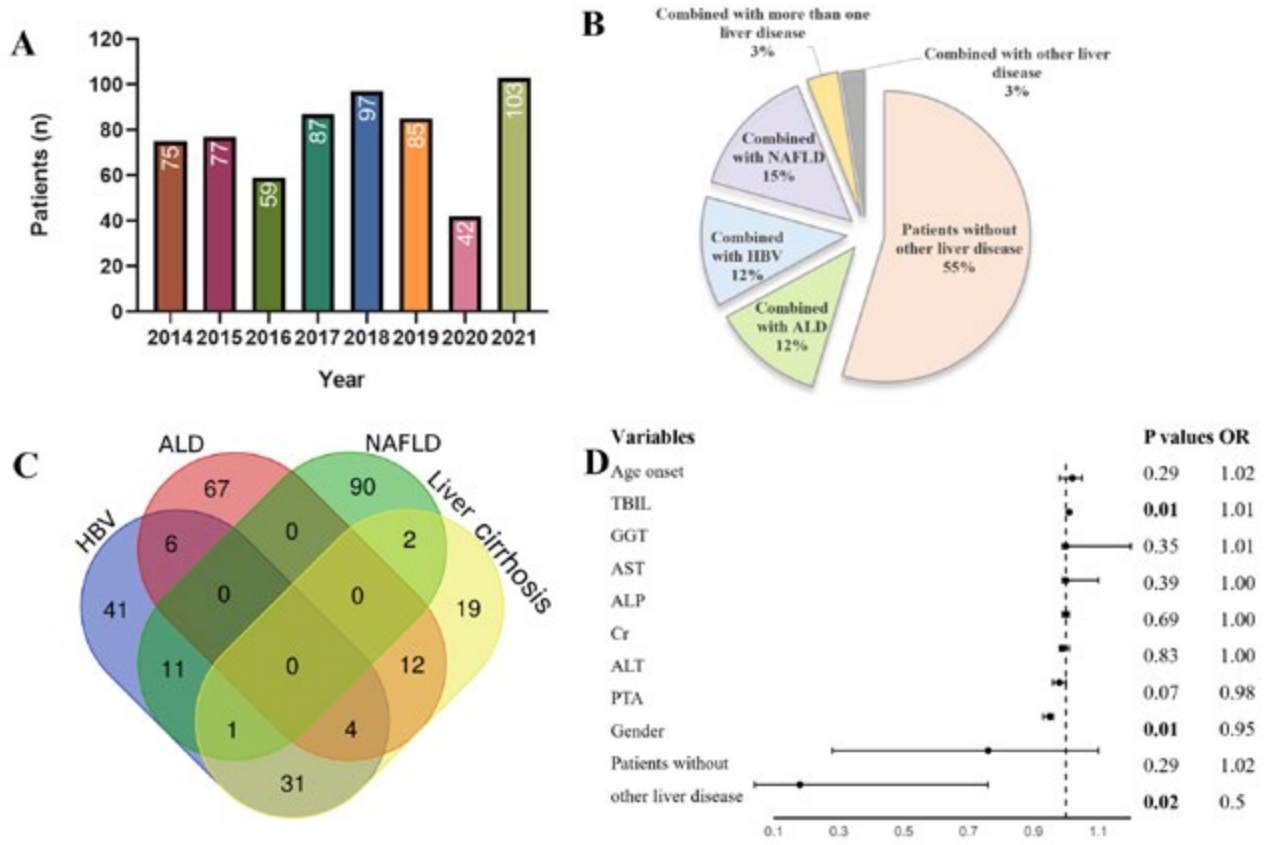

A Annual morbidity number for HEV hepatits in 2014-2021 B The composition and structure of patients with hepatitis E
C Venn chart for HEV hepatitis patients combined with other liver disease D Predictors for poor prognosis of HEV hepatitis patients

Disclosures: Wen An: Nothing to Disclose, Hongshan Wei: Nothing to Disclose

1166 | BULEVIRTIDE MONOTHERAPY MAY REDUCE LIVER DECOMPENSATION IN PATIENTS WITH HDV-RELATED COMPENSATED CIRRHOSIS: A CASE CONTROL STUDY WITH PROPENSITY SCORE WEIGHTED ANALYSIS

Elisabetta Degasperi[1] Annalisa De Silvestri[2] Maria Paola Anolli[1] Dana Sambarino[1] Marta Borghi[1] Riccardo Perbellini[1] Floriana Facchetti[1] Roberta Soffredini[1] Sara Monico[1] Victor de Ledinghen[3] Sophie Metivier[4] Mathias Jachs[5] Thomas Reiberger[5] Gianpiero Doffizi[6] Christopher Dietz-Fricke[7] George Papatheodoridis[8] Maurizia Brunetto[9] Gabriella Verucchi[10] Alessia Ciancio[11] Fabien Zoulim[12] Alessandra Mangia[13] marie noelle HILLERET[14] Teresa Antonia Santantonio[15] Nicola Coppola[16] Adriano Pellicelli[17] Bruno Roche[18] Xavier Causse[19] Louis D'Alteroche[20] Jérôme Dumortier[21] Nathalie Ganne Carrie[22] frederic HELUWAERT[23] Isabelle Hourmand Ollivier[24] Alessandro Loglio[25] Mauro Viganò[26] Alessandro Federico[27] Francesca Pileri[28] Monia Maracci[29] Matteo Tonnini[30] Jean Pierre Arpurt[31] Barange Karl[32] Eric Billaud[33] Stanislas pol[34] Anne Gervais[35] Anne Minello[36] Isabelle Rosa[37] Massimo Puoti[38] Pietro Lampertico[39]

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Background: Bulevirtide (BLV) monotherapy yields high rates of virological and biochemical response in patients with cirrhosis due hepatitis Delta virus (HDV), however clinical benefits on hard outcomes remain unknown. **Methods:** Consecutive patients with HDV-related cirrhosis treated with BLV monotherapy in a retrospective multicenter European study (SAVE-D) were compared with untreated HDV cirrhotic patients enrolled in a natural history single-center cohort study (Romeo, Gastroenterology 2009). Liver-related events (LRE: hepatocellular carcinoma [HCC], decompensation) and mortality were compared by inverse probability treatment weighting analysis. Follow-up was censored at LRE, liver transplantation, death or 24 months. **Results:** The BLV-treated cohort included 176 HDV cirrhotic patients with the following baseline features (median and IQR): age 49 (39-59) years, 59% men, ALT 77 (53-127) U/L, albumin 4.0 (3.7-4.4) g/dL, 100% CPT score A, 55% with varices. The untreated cohort included 140 HDV cirrhotic patients (features at study entry): age 40 (34-49) years, 78% men, ALT 102 (57-176) U/L, albumin 3.9 (3.6-4.3) g/dL, 100% CPT score A, 46% with varices. Overall, the 2-year cumulative probabilities of LRE were 7.3% (95% CI 3-13%) in the BLV-treated cohort *vs.* 15.6% (95% CI 9-22%) in untreated patients (p=0.05): 4.0% (95% CI 1-7%) *vs.* 6.6% (95% CI 3-11%) for de-novo HCC (p=0.34) and 3.6% (95% CI 1-6%) *vs.* 9.1% (95% CI 3-13%) for decompensation (p=0.06), respectively. The 2-year cumulative probability of mortality was 2.7% (95% CI 1-6%) *vs.* 3% (95% CI 1-6%) in BLV-treated *vs.* untreated patients (p=0.34). By inverse probability treatment weighting analysis adjusted for confounding baseline factors and competing mortality risks, the BLV-treated cohort had a significantly decreased risk of all-type liver-related events (HR 0.38; 95% CI 0.23-0.62, p<0.0001), decompensation (HR 0.32; 95% CI 0.16-0.63, p<0.0001) compared to untreated patients. Conversely, the HCC risk was similar in the two cohorts (HR 0.50; 95% CI 0.24-1.06, p=0.07). **Conclusion:** In patients with HDV-related compensated cirrhosis, a 2-year course of BLV monotherapy may reduce the risk of liver decompensation, but not HCC, compared to untreated patients.

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1167 | EPIDEMIOLOGIC AND CLINICAL CHARACTERISTICS OF ACUTE VIRAL HEPATITIS IN SOUTH KOREA: A PROSPECTIVE, NATIONWIDE MULTICENTER STUDY

In Hee Kim[1] Chang Hun Lee[1] Hoon Gil Jo[2] Eun Young Cho[2] Ju Yeon Cho[3] Jae hyun Yoon[4] Sung Bum Cho[5] Ki Tae Suk[6] Seok Hyun Kim[7] Hyuk Soo Eun[7] Byung Seok Lee[7] Jeong-Ju Yoo[8] Young Seok Kim[8] Woo Jin Chung[9] Youn-Jae Lee[10] Jun Sik Yoon[10] Hyun-Jin Cho[11] Neung Hwa Park[12] Moon-Young Kim[13] Seul Ki Han[13] Dae Hee Choi[14] Tae Suk Kim[14] Kyung-Ah Kim[15] Gwang Hyeon Choi[16] Eun Sun Jang[16] Sook-Hyang Jeong[16]

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Background: This study aims to examine the epidemiology and clinico-epidemiological characteristics of acute viral hepatitis (AVH) in South Korea. **Methods:** From 2020 to March 2024, participants were recruited from 17 centers, specifically targeting patients who met the criteria for acute hepatitis. We evaluated the etiology, clinical characteristics, and progression of the disease. **Results:** After excluding patients with non-hepatic causes, we enrolled a total of 1,102 patients. Of these, 348 (31.6%) were diagnosed with acute viral hepatitis (AVH) based on specific serologic markers. The predominant etiology was hepatitis A virus (HAV, 68.1%), followed by hepatitis E virus (HEV, 10.1%), Epstein-Barr virus (EBV, 10.1%), hepatitis B virus (6.6%), hepatitis C virus (2.6%), cytomegalovirus (0.6%), herpes simplex virus (0.3%), and other pathogens (1.7%). When comparing viral and non-viral causes, male predominance was observed among patients with AVH, with an average age of 43.8 ± 12.4 years, significantly younger than those with non-viral causes (50.1 ± 17.6, $p < 0.001$). AVH patients also showed higher levels of platelets, alkaline phosphatase, gamma-glutamyl transferase, aspartate aminotransferase, alanine aminotransferase, and lactate dehydrogenase. However, bilirubin, albumin, and prothrombin time did not differ significantly. Regarding prognosis, there were no significant differences between the viral and non-viral groups in terms of intensive care unit admissions, dialysis, liver transplants, or mortality. **Conclusion:** AVH accounts for approximately 30% of acute hepatitis cases in South Korea, with HAV, HEV, and EBV infections being the most prevalent. Understanding the characteristics of AVH may contribute to improved management and prevention strategies.

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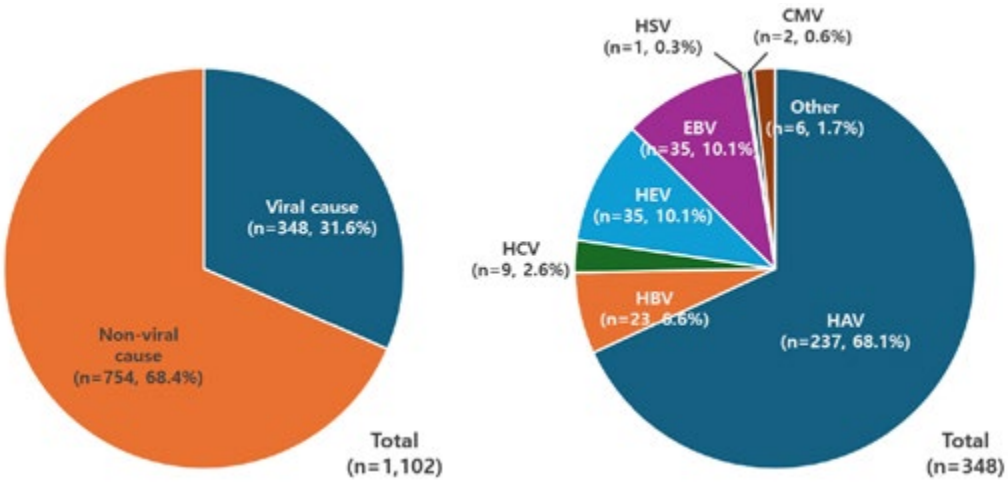

Disclosures: In Hee Kim: Nothing to Disclose, Chang Hun Lee: Nothing to Disclose, Hoon Gil Jo: Nothing to Disclose, Eun Young Cho: Nothing to Disclose, Ju Yeon Cho: Nothing to Disclose, Jae hyun Yoon: Nothing to Disclose, Sung Bum Cho: Nothing to Disclose, Ki Tae Suk: Nothing to Disclose, Seok Hyun Kim: Nothing to Disclose, Hyuk Soo Eun: Nothing to Disclose, Byung Seok Lee: Nothing to Disclose, Jeong-Ju Yoo: Nothing to Disclose, Young Seok Kim: Nothing to Disclose, Woo Jin Chung: Nothing to Disclose, Youn-Jae Lee: Nothing to Disclose, Jun Sik Yoon: Nothing to Disclose, Hyun-Jin Cho: Nothing to Disclose, Neung Hwa Park: Nothing to Disclose, Moon-Young Kim: Nothing to Disclose, Seul Ki Han: Nothing to Disclose, Dae Hee Choi: Nothing to Disclose, Tae Suk Kim: Nothing to Disclose, Kyung-Ah Kim: Nothing to Disclose, Gwang Hyeon Choi: Nothing to Disclose, Eun Sun Jang: Nothing to Disclose, Sook-Hyang Jeong: Nothing to Disclose

1168 | HEPATITIS B SURFACE ANTIGEN (HBSAG) RESPONSE IN PATIENTS WITH CHRONIC HEPATITIS DELTA RECEIVING BULEVIRTIDE WITH OR WITHOUT PEGYLATED INTERFERON ALFA-2A IN MYR204

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Background: Bulevirtide (BLV) is an entry inhibitor approved for the treatment of compensated chronic hepatitis D (CHD) in the EU while interferon therapy is associated with variable rates of hepatitis B surface antigen (HBsAg) loss in different subsets of patients with chronic hepatitis B (CHB). Here, we assessed HBsAg response in patients with CHD receiving BLV with or without pegylated interferon alfa-2a (PegIFN) in a phase 2b study MYR204 (NCT03852433). **Methods:** A total of 174 patients with CHD were randomized (1:2:2:2) to receive (A) PegIFN for 48 weeks (W); (B) BLV 2mg+PegIFN for 48W; (C) BLV 10mg+PegIFN for 48W, then BLV 2mg (B) or 10mg (C) monotherapy for 48W; or (D) BLV 10mg for 96W. Participants were followed for 48W after end of treatment. HBsAg response was defined as ≥1$\log_{10}$ IU/mL decline in HBsAg from baseline (BL) and HBsAg <100 IU/mL at follow-up Week 48 (FU48). **Results:** Demographics and BL characteristics including HBsAg and HDV RNA levels were similar across arms. In total, 17 of 174 (9.8%) patients achieved HBsAg response. The proportion of patients achieving HBsAg response in the BLV 10mg monotherapy arm (Arm D) (1/50, 2%) was lower than those in the PegIFN-containing treatment arms (Arm A: 2/24, 8.3%; Arm B: 8/50, 16%; Arm C: 6/50, 12%) (Table 1). All 17 achieved undetectable HDV RNA, while 15 and 16 achieved undetectable HBV DNA and ALT normalization respectively. Of the 17 patients, 14 were HBV/HDV genotypes D/1, representing the most prevalent HBV/HDV genotypes D/1 (137/174, 78%) in this study. Notably, patients with HBsAg response had significantly lower HBsAg (p=0.0304) and HDV RNA (p=0.0290) at BL compared to patients without significant HBsAg response. Eight of the 17 patients with HBsAg response achieved HBsAg loss, with 6 also achieving anti-HBs seroconversion. The majority of patients (7/8, 88%) developing HBsAg loss were from BLV+PegIFN groups (Arms B and C) and none from PegIFN only group (Arm A). **Conclusion:** In MYR204, the majority of the CHD patients (14 of 17) achieving HBsAg response through FU48, particularly HBsAg loss, were in the BLV+PegIFN

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arms, suggesting that combination therapy with BLV and PegIFN improves the chance of HBsAg loss in patients with CHD compared to either monotherapy. As expected, patients with HBsAg response achieved undetectable HBV DNA and HDV RNA as well as ALT normalization. Lower HBsAg and HDV RNA at BL were associated with HBsAg response in CHD patients treated with BLV+PegIFN.

Treatment Group	Arm A, PegIFN (n=24)	Arm B, BLV 2mg+PegIFN (n=50)	Arm C, BLV 10mg+PegIFN (n=50)	Arm D, BLV 10mg (n=50)
Total HBsAg response	2/24 (8.3%)	8/50 (16%)	6/50 (12%)	1/50 (2%)
HBsAg loss	0/24 (0%)	5/50 (10%)	2/50 (4%)	1/50 (2%)

Disclosures: yang liu: Nothing to Disclose, Jiani Li: Nothing to Disclose, Silvia Chang: Nothing to Disclose, Yu Hu: Nothing to Disclose, simin xu: Nothing to Disclose, Ross Martin: Gilead Sciences: Employee, Dmitry Manuilov: Nothing to Disclose, Renee-Claude Mercier: Nothing to Disclose, Audrey Lau: Nothing to Disclose, Tarik Asselah: Nothing to Disclose, Fabien Zoulim: Nothing to Disclose, Vladimir Chulanov: Roche: Speaking and Teaching, AstraZeneca: Speaking and Teaching, Gilead: Speaking and Teaching, R-Pharm: Speaking and Teaching, AbbVie: Speaking and Teaching, Hongmei Mo: Nothing to Disclose, Evguenia Maiorova: Nothing to Disclose

1169 | EFFECT OF BULEVIRTIDE TREATMENT ON THE HDV INDUCED ANTIVIRAL STATE AND CELL DAMAGE IN INFECTED HUMANIZED MICE AND PATIENTS WITH CHRONIC HEPATITIS D

Maura Dandri[1] Tassilo Volz[1] Lena Allweiss[1] Dmitry Manuilov[2] Simon Fletcher[3] Meghan Holdorf[2] Robert Muench[2] Bryan Downie[2] Jeffrey Wallin[2]

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Background: Hepatitis D virus (HDV) causes the most severe form of viral hepatitis, with patients at increased risks of cirrhosis and liver cancer compared to hepatitis B virus (HBV) mono-infection. HDV-mediated enhancement of innate-immunity-related genes has been observed in chronic hepatitis D (CHD) patients (*Allweiss, J. Hepatol 2024*) as well as in humanized chimeric mice (*Giersch, J. Hepatol 2015*). However, it is unclear to what extent HDV infection directly contributes to hepatocyte damage, both in co- and mono-infected cells, and whether blocking new HDV infection events limits the enhancement of innate and inflammatory genes. Aim: This study aimed to investigate the impact of HDV on innate responses and hepatocyte damage following bulevirtide (BLV)-mediated blockade of infection in CHD patients and HBV/HDV-infected immunodeficient humanized mice. **Methods:** RNAseq analysis was performed in a subgroup of paired liver biopsies (BL & 48 weeks) available from the MYR301 clinical trial. Among these, 15 patients received BLV 10mg, 6 BLV 2mg and 6 were in control arm. Interferon-stimulated genes (ISG), cell death and proliferation were investigated by qPCR, RNA in-situ hybridization and immunofluorescence in mice that either had high levels of HDV mono-infected human hepatocytes (A) or were infected with HBV and superinfected with HDV (B). Some mice in group B received BLV for 8 weeks. **Results:** In both groups of mice, ISG expression was induced in human hepatocytes during the ramp-up phase of HDV viremia with a strong correlation observed between ALT and HDV viremia, and between the percent of HDV+ cells and the human cellular proliferation marker Ki67. Although 8 weeks of treatment with BLV did not reduce the numbers of HDV+ cells substantially, ISG induction appeared lower in BLV-treated mice than in controls. Cell turnover was most pronounced in a setting where HDV largely persisted without HBV (A). In liver biopsies from CHD patients treated with BLV, a substantial decrease in genes associated with apoptotic and inflammatory pathways as well as cell cycle markers were observed compared to the control group. **Conclusion:** BLV administration in both CHD patients and humanized mice reduce the expression of genes associated with innate immune and cell death/proliferation pathways, suggesting that HDV infection can directly contribute to cell damage and innate immune activation. This could explain why some patients with delayed/poor virological response to BLV still experience a reduction in ALT.

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1170 | ASSOCIATION OF SOCIOECONOMIC STATUS ON THE PREVALENCE OF HEPATITIS D CO-INFECTION IN PATIENTS WITH CHRONIC HEPATITIS B IN SAN DIEGO COUNTY

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Background: Hepatitis Delta Virus (HDV) is a virus that can uniquely affect patients with Chronic Hepatitis B (CHB), causing rapid progression of hepatocellular carcinoma and liver-related death. Currently global society guidelines differ in their recommendations for HDV screening. The American Association for the Study of Liver Diseases (AASLD) recommends screening CHB patients with high risk factors. In comparison, European and Asian society guidelines recommend testing for Hepatitis D co-infection in all patients with CHB. This difference is likely due to differing perceptions of HDV prevalence in the US compared to Europe and Asia. Previous data has proposed HDV prevalence of about 5% in the US, however, the actual prevalence in the US is still not clearly defined, and newer studies suggest it may be lower. The aim of our study is to assess and compare the prevalence of HDV in patients of varying socioeconomic status in San Diego County (SDC). **Methods:** A retrospective cohort study of CHB patients tested for HDV in SDC from April 2017- December 2023 was performed. We identified two populations of differing socioeconomic status (SES): La Maestra clinic, comprising patients with lower SES and select Scripps Clinics comprising patients with higher SES. Our main outcome was the prevalence of HDV antibody (Ab) and viremia. A Fisher's exact test was used to compare the prevalence of HDV Ab and viral load in both groups. **Results:** In La Maestra, 118 patients out of 312 CHB patients were screened for HDV. At Scripps, 593 patients out of 2441 CHB patients were screened for HDV. From the 118 patients in La Maestra, 3 patients tested positive for HDV Ab with 0 patients having positive viremia. Amongst the 593 patients in Scripps, 14 patients tested positive for HDV Ab with 2 patients having positive viremia. The prevalence of delta antibody positivity in both groups was found to be less than 3%. There was no statistically significant difference in prevalence of HDV Ab or viremia in either group. **Conclusion:** The prevalence of HDV in SDC appears to be lower than the previous expected national average and more congruent with recent studies. Additionally, prevalence is comparable between the two SES groups. Interestingly, prevalence of viremia was below expected average. Whilst possibly impacted by the small sample size, overall these **Results:** potentially challenge current AASLD guidelines. A prospective study has been initiated at Scripps to screen the balance of CHB patients without risk factors for delta antibody after being consented for inclusion.

Disclosures: Karine Moussa: Nothing to Disclose, Robert Gish: Nothing to Disclose, Danyal Imam: Nothing to Disclose

1171 | HEPATITIS D VIRUS (HDV) SCREENING PROGRAM IN A SINGLE TERTIARY LIVER CENTER IN THE UNITED STATES

Rohullah Rasikh[1] Fatima Usama[1] Mansoor Rahman[1] Ashraf Ullah[1] Syed Bilal Shah[1] Khawaja Hassam[1] Adderly Toribio[1] Daryl Lau[1]

[1]Beth Israel Deaconess Medical Center

Background: Hepatitis delta virus (HDV) infection affects about 12 to 20 million individuals globally and is the most severe form of viral hepatitis. The prevalence of HDV is variable in different geographic regions. It is recommended that patients with chronic hepatitis B (CHB) should have anti-HDV screening. We aimed to evaluate the HDV screening patterns and the clinical characteristics of chronic hepatitis D among our CHB patients in a tertiary liver center. **Methods:** This is a cross-sectional study in a single center. CHB patients who visited liver clinics between January 2021 and December 2023 were included. Systematic chart review was performed to capture the demographics and anti-HDV tests status. For those tested anti-HDV positive, detailed review of their medical records was done to identify the risks of viral transmission, HBV profiles, disease severity and complications. Anti-HDV tests were performed at Quest Diagnostics. **Results:** A total of 1337 (M= 525, F=812) unique CHB patients were included in this analysis. The countries of birth were available on 1302. The majority, 1247(93.3%), were foreign born. In this cohort, there were 1002 (74.9%) Asians, 165 (12.3%) Blacks, 121 (9.1%) Whites, 17 (1.3%) Hispanics and 32 (2.3%) were unknown. Among the Asians, most were from China (80.7%), Vietnam (7.9%) and Korea (2.7%). 668 (50%) patients had anti-HDV screening at least once after their first liver clinic. The US-born patients (n=55) were older (62.6 yrs vs. 52.9 yrs, p=0.0005) and had a lower rate of

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anti-HDV testing compared to the foreign-borns (36% vs.50.8%, p= 0.036). Among the foreign-born subjects, the frequencies of HDV screening were similar, about 50% across the different racial groups. Subjects aged 18-40 yrs had the highest screening rate (58%) compared to those >40-60 yrs (49.8%) and >60 yrs (46%), p=0.02. HDV tests were more frequently performed for the Asian males (57%) compared to Asian females (42%) [p=0.0008]. For non-Asians, there was no gender difference in screening rate. 9 (1.35%) of the tested subjects (M=4, F=5) were anti-HDV (+) [Table]. All but one were foreign-born with ages ranged from 41 to 71 years. 6 (66.7%) were HBeAg (-). All had low HBV DNA levels and 5 had cirrhosis at the time of HDV diagnosis. Two patients also had HCV coinfection and one developed HCC. **Conclusion:** Our tertiary Liver Center has predominantly foreign-born CHB patients. The HDV screening rate was 50%; those between age 18 and 40 were more frequently tested. Among Asians, males had a higher rate of HDV screening. Anti-HDV(+) was identified in 1.35% of the tested subjects; they had a wide age range with similar number of males and females. It is, therefore, important to perform HDV screening on CHB patients regardless of their age and gender. HBeAg (-) CHB with low HBV DNA levels and advanced fibrosis should alert to HDV coinfection. As HDV therapy becomes available, it is even more important to identify these challenging patients.

Table. CHB Patients With Anti-HDV Positive Test

Anti-HDV (+)	Country of birth	Age (yrs)	Sex	HBeAg status	*HBV DNA (log IU/ml)	*HDV RNA	*Hepatic fibrosis	Risk Factors
Pt.1	Hungary	71	F	Neg	<1.55	Pos	Stage 2	Occupation exposure
Pt.2	Cape Verde	55	F	Neg	Undetected	Pos	Stage 2	Uncertain
Pt.3	China	52	M	Neg	<1.03	Pos	Cirrhosis	IVDU
Pt.4	USA	53	F	Neg	Undetected	Pos	Cirrhosis	Sexual contacts
Pt.5	Liberia	41	M	Pos	<1.6	Pos	Stage 2	Uncertain
Pt.6	China	55	M	Pos	<1	Pos	Stage 2	IVDU
Pt.7	Russia	44	F	Pos	1.9	Pos	Cirrhosis	Shared needle during childhood vaccination
Pt.8	Liberia	46	M	Neg	1.1	Pos	Cirrhosis	MSM, Occupation
Pt.9	Mongolia	41	F	NA	1.4	Pos	Stage 2	?Exposure in Mongolia Day Care center

*at the time of HDV diagnosis.

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1172 | SIMILAR RATES OF BIOCHEMICAL RESPONSE ARE OBSERVED ACROSS VIROLOGIC RESPONSE CATEGORIES OVER 96 WEEKS OF BULEVIRTIDE MONOTHERAPY IN PATIENTS WITH CHRONIC HEPATITIS DELTA

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Background: Bulevirtide (BLV), a novel entry inhibitor of hepatitis delta virus (HDV), is the only approved treatment for chronic hepatitis delta (CHD) in Europe. Unlike nucleos(t)ide analogues for hepatitis B virus, BLV is

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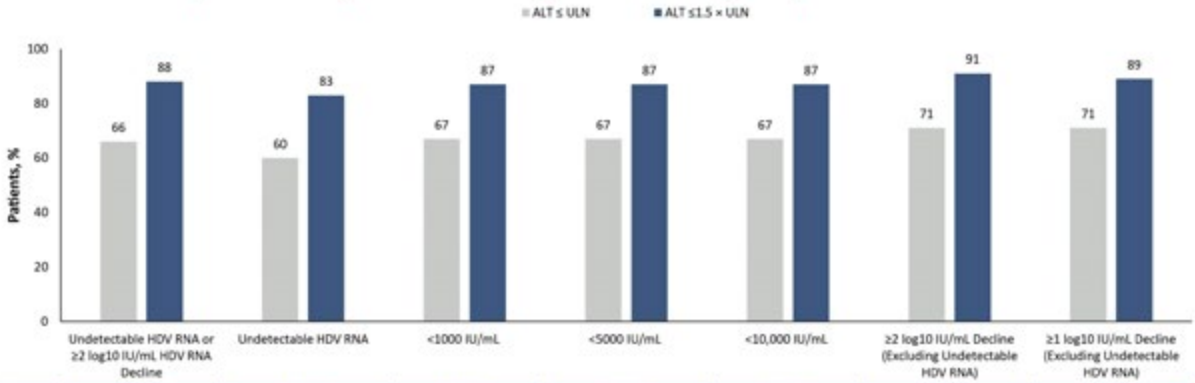
not a direct antiviral but prevents liver spreading of HDV; biochemical response (BR; alanine aminotransferase [ALT] normalization) can be observed independently of virologic response (VR) likely due to the prevention of de novo infection of hepatocytes. Previous analyses using 48-week treatment data described similar rates of BR across multiple HDV RNA response cutoffs. We now further explore this relationship to evaluate if this effect persists beyond 48 weeks with BLV monotherapy. **Methods:** A pooled analysis of data from patients who completed 96 weeks of monotherapy with BLV 2 mg/day or 10 mg/day in the Phase 2 study MYR204 and the Phase 3 study MYR301 was performed. VR categories included $\log_{10}$ declines from baseline (BL), undetectable HDV RNA, and absolute value HDV RNA cutoffs ranging from 1000 to 10,000 IU/mL. ALT response, defined as ALT ≤ upper limit of normal (ULN) or ALT ≤1.5 × ULN, was evaluated in each VR category. **Results:** We included 190 patients with CHD: 47 on BLV 2 mg, 143 on 10 mg; 63% male, 84% White, and 44% with compensated cirrhosis. At BL, mean (SD) age and HDV RNA levels were 42 (8.3) years and 5.2 (1.3) $\log_{10}$ IU/mL. Median (Q1, Q3) ALT and liver stiffness were 89 (60, 130) U/L and 11.8 (8.8, 16.8) kPa; 25% had ALT ≤1.5 × ULN. After 96 weeks of BLV monotherapy, 34% to 90% of patients achieved VR, depending on VR criteria (Figure); 85% (161/190) had VR, defined as HDV RNA undetectable or ≥2 $\log_{10}$ decline from BL in HDV RNA. ALT ≤ULN or ≤1.5 × ULN was achieved by 64% (122/190) and 83% (158/190) patients, respectively. Proportions of those achieving VR were similar: 88% (107/122) of patients with ALT ≤ULN and 89% (141/158) with ALT ≤1.5 × ULN. HDV RNA <10,000 IU/mL was the most inclusive metric for detecting ALT response, capturing 94% (115/122) of those with ALT ≤ULN and 94% (149/158) of those with ALT ≤1.5 × ULN. The proportions of patients with VR with or without BR were similar regardless of the VR cutoff. **Conclusion:** The use of a less stringent cutoff for VR (ie, HDV RNA <10,000 IU/mL) over the standard VR definition can capture additional cases of ALT response. Consistent with previously reported findings, similar rates of ALT responses were observed across the evaluated VR subgroups after 96 weeks of BLV monotherapy.

Figure. Biochemical Responses Among Patients Achieving Different Virologic Response Criteria at Week 96



Patients achieving each virologic response category for total cohort, % (n/N)	85% (161/190)	34% (65/190)	82% (156/190)	89% (169/190)	90% (171/190)	51% (96/190)	59% (112/190)

ALT, alanine aminotransferase; HDV, hepatitis delta virus; ULN, upper limit of normal.

Disclosures: Pietro Lampertico: ROCHE PHARMA/DIAGNOSTICS, GILEAD SCIENCES, GSK, ABBVIE, JANS: Advisor, Tarik Asselah: Nothing to Disclose, Vladimir Chulanov: Roche: Speaking and Teaching, AstraZeneca: Speaking and Teaching, Gilead: Speaking and Teaching, R-Pharm: Speaking and Teaching, AbbVie: Speaking and Teaching, Pavel Bogomolov: Nothing to Disclose, Tatyana Stepanova: Nothing to Disclose, Markus Cornberg: Nothing to Disclose, Dmitry Manuilov: Nothing to Disclose, Mingyang Li: Nothing to Disclose, Audrey Lau: Nothing to Disclose, Ben Da: Nothing to Disclose, DANA TEDESCO: Gilead Sciences, Inc.: Employee, Grace Chee: Gilead Sciences: Employee, Maurizia Brunetto: Nothing to Disclose, Stefan Zeuzem: Nothing to Disclose, Fabien Zoulim: Nothing to Disclose, Heiner Wedemeyer: Nothing to Disclose, Soo Aleman: Gilead: Speaking and Teaching

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1173 | DAY 3 MELD SCORE AS A RELIABLE GUIDE FOR EARLY LIVER TRANSPLANT IN AUTOIMMUNE HEPATITIS - A PROSPECTIVE STUDY

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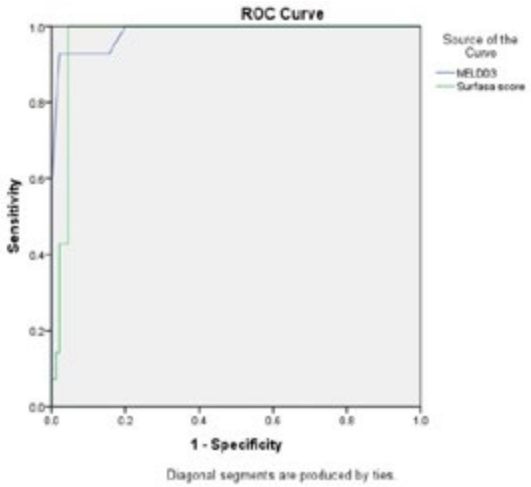
Background: In Autoimmune Hepatitis (AIH), patients' response to corticosteroids and optimal timing of liver transplantation (LT) is still a clinical dilemma. Recently, a SURFASA score was introduced to identify patients who are corticosteroid non-responders at day 3 and should be advised early LT. We conducted this study to assess factors predicting early response to corticosteroids and 90-day transplant-free survival in Indian AIH patients. **Methods:** We conducted a prospective, single-centre study (2021 – 2023) of histologically proven AIH patients. Patients were divided into i) Acute AIH, ii) Acute severe (AS-AIH), iii) Acute on chronic liver failure (ACLF) AIH (according to APASL guidelines), and iv) Decompensated AIH patients. All patients received corticosteroids and were followed with various clinical and laboratory parameters on days 3, 7, 14, 28 and 90 after starting steroids. **Results:** A total of 104 patients were included, with a mean age of 46.1 ± 14.3 years; & 77 % were females. Transplant-free survival was 86.53% from the start of the steroid to the end of 90 days. Out of 14 patients who succumbed, 10 belonged to the ACLF group and 4 belonged to the decompensated AIH group. On univariate analysis for predicting mortality, higher age, presence of diabetes mellitus, encephalopathy, fibrosis, presence of varices, low serum albumin at day 3, MELD score at day 3, increment in MELD score at day 3 and day 7, SURFASA score were found statistically significant (P value <0.005). On multivariate analysis, the MELD score at day 3 (OR 2.108; 95% CI {1.131-3.928}; p 0.019) was alone found to be statistically significant. MELD score at day 3 was strongly predictive of mortality (AUC = 0.984) (100% sensitivity and 80% specificity) with a cut-off point of ≥ 22.5. In contrast, the SURFASA score had 100% sensitivity with only 56% specificity (AUC = 0.967) at a cut-off point of ≥ -2.95 (figure 1). **Conclusion:** After starting steroids, an increase in the day 3 MELD score by 4 points and the day 7 MELD score by 5 points were predictive of mortality. The MELD score on day 3 outperformed the SURFASA score in predicting mortality and response to steroids in patients with autoimmune hepatitis. We suggest using the day 3 MELD score for early referral for a liver transplant.



Area Under the Curve

Test Result Variable(s)	Area
MELDD3	.984
SURFASA score	.967

Figure1. Area under the curve comparing MELD at day 3 vs SURFASA score

Disclosures: Shubham Jain: Nothing to Disclose, Harsh Gandhi: Nothing to Disclose, Sanjay Chandnani: Nothing to Disclose, Rima Kamat: Nothing to Disclose, Pravin Rathi: Nothing to Disclose

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1174 | REVIEW OF EVIDENCE TO SUPPORT THE USE OF SURROGATE ENDPOINTS AND FIBROSCAN IN HEPATITIS D INFECTION

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Background: Hepatitis D virus (HDV) infection is associated with higher risk of adverse clinical outcomes including cirrhosis, hepatocellular carcinoma (HCC) and mortality compared to chronic hepatitis B. To support the development of new therapies it is important to understand evidence on the use of surrogate endpoints, and the benefits/limitations of non-invasive methods such as vibration-controlled transient elastography (VCTE) versus traditional biopsy to assess fibrosis/cirrhosis and define treatment eligible patients. A targeted review was carried out to identify key evidence. **Methods:** Articles utilizing surrogate endpoints (HDV RNA reduction or ≥2 log10 decrease less than the lower level of quantification [LLOQ] with/without alanine transaminase [ALT] normalization), and VCTE for staging and detecting clinical outcomes in patients with HDV were sought using a protocol-driven targeted literature review. Literature searches in Medline, Embase and several grey literature sources (October 2023) identified key articles which were selected based on recency and level of evidence. **Results:** 16 unique records were included (12 primary studies, 2 guidelines, 1 systematic review [SLR], 1 FDA regulatory document). 14 records reported on surrogate endpoints while 2 conference abstracts reported on VCTE (Table 1). The FDA has approved treatments using both HDV surrogate endpoints, though US and European guidelines questioned the added value of ALT normalization beyond RNA reduction. Evidence from several primary studies and a recent SLR showed that HDV RNA negativity/ HDV RNA <LLOQ was associated with reduced risk of clinical outcomes including cirrhosis, HCC, liver transplant and/or death. However, no statistically significant correlations were reported between ≥2 log decrease in HDV RNA and clinical outcomes in patients with long-term follow-up in 2 studies. 2 retrospective studies reported VCTE offered advantages over biopsy with good diagnostic performance for identifying patients with cirrhosis but may not perform as well in patients with significant (F2) fibrosis. **Conclusion:** Despite some evidence of the utility of VCTE and that the early reduction and stabilization of RNA levels in patients with HDV can reduce long term adverse clinical outcomes, confirmation is needed in further studies. Questions still remain as to the additional benefit of ALT normalization beyond RNA reduction and how to improve the performance of non-invasive tests like VCTE in some patients.

Table 1. Number and type of studies reporting on surrogate endpoints for clinical outcomes in patients with HBV and HDV co-infection

		Clinical Outcome			
		Cirrhosis (any type)	HCC	Liver Transplant and Mortality	Composite of Clinical Outcomes
		Type of Study (# of Studies)			
HDV surrogate endpoints	HDV RNA < LLOQ	Primary (4)[1-4] SLR (1)[5] FDA guidance (1)[7] Guidelines^ (2)[6,8]	Primary (5)[4, 12-15] SLR (1)[5] FDA guidance (1)[7] Guidelines^ (2)[6,8]	Primary (4)[13-16] SLR (1)[5] FDA guidance (1)[7] Guidelines^ (2)[6,8]	Primary (2*)[14,17]
	≥2 log decrease in HDV-RNA and ALT normalization	FDA guidance (1)[7] Guidelines^ (2)[6,8]	FDA guidance (1)[7] Guidelines^ (2)[6,8]	FDA guidance (1)[7] Guidelines^ (2)[6,8]	-
	≥2 log decrease in HDV-RNA	Primary (1)[9] Guidelines^ (2)[6,8]	Primary (1)[9] Guidelines^ (2)[6,8]	Guidelines^ (2)[6,8]	Primary (2*)[9,17]
VCTE	Performance of VCTE vs. biopsy for monitoring of fibrosis/cirrhosis	Primary (2)[10,11]	-	-	-

*** Composite of hepatic decompensation, hepatocellular carcinoma, mortality, or liver transplantation**
^ Includes literature of evidence to support guideline statements

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1175 | ASSOCIATIONS BETWEEN LIVER BIOMARKERS AND CLINICAL EVENTS IN PATIENTS WITH HEPATITIS D VIRUS INFECTION: A RETROSPECTIVE REAL-WORLD STUDY ◆

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[1]*Gilead Sciences*

Background: Worldwide, around 12 million people are chronically infected with hepatitis delta virus (HDV). Chronic hepatitis D (CHD) is the most severe form of viral hepatitis with fast progression to liver fibrosis, cirrhosis, and hepatocellular carcinoma (HCC). We explored associations between liver biomarkers and clinical events in a cohort of CHD patients in the United States. **Methods:** Patients (≥18 years) with ≥1 HDV ICD code or ≥1 positive HDV lab test results between 2010 and 2022 were identified from the nationwide TriNetX Research Database and those with history of hepatitis C, moderate/severe liver disease, malignancies, or those who were pregnant during the study period were excluded. Liver biomarkers (ALT, AST, platelet count, total bilirubin, albumin, and FIB4 score) at baseline and during follow-up period (6-12 months prior to the event) were evaluated for their association with cirrhosis and HCC. Cox proportional hazards (PH) models for the baseline biomarkers, and logistic regressions for the follow-up biomarkers were used. Respectively, adjusted hazard ratios (aHR) and adjust odds ratios (aOR) with 95% confidential intervals (CI) by quartiles of biomarker levels were reported. FIB4 was categorized as L1: <1.30, L2: 1.30-2.67, L3: >2.67. **Results:** HDV patients (N=2249) were mostly 35-64 years (67%, mean: 50 ±14 years), and male (59%) with a mean follow-up of 6.1 years. Asian (36%), white (27%), and black (21%) patients primarily constitute the cohort. Most patients (88%) had one or no known baseline comorbidities. In adjusted models (Table 1), baseline AST level was associated (aHR [95% CI]) with both HCC (Q4 vs. Q1: 8.4[1.7-42.1]) and cirrhosis (Q4 vs. Q1: 4.2[1.4-13.1]). Baseline FIB4 score was also associated (aHR [95% CI]) with HCC (L2 vs. L1: 3.4[1.4-7.9], L3 vs L1: 5.5[2.3-13.3]). AST levels at follow-up was associated (aOR [95% CI]) with HCC (Q4 vs. Q1: 10.7[1.5-76.3]), whereas follow-up serum albumin was associated (aOR [95% CI]) with cirrhosis (Q1 vs. Q4: 6.7[1.6-28.6]). A 10% increase in albumin from baseline to follow-up was significantly associated with a 45% decrease in the odds of having HCC. **Conclusion:** In this large cohort of CHD patients, liver biomarkers at baseline and their changes during follow-up were associated with cirrhosis and HCC. Additional research is required to establish prognostic thresholds for these biomarkers, and to define their clinical relevance for better management of patients.

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Table 1. Association of baseline and follow-up biomarkers with clinical outcomes

Biomarker	Cirrhosis		Hepatocellular Carcinoma	
	Baseline aHR (95% CI)*	Follow-up aOR (95% CI)**	Baseline aHR (95% CI)*	Follow-up aOR (95% CI)**
Platelet Count				
Q4	Reference	Reference	Reference	Reference
Q3	1.31 (0.62, 2.8)	0.68 (0.18, 2.5)	0.90 (0.28, 2.9)	1.12 (0.25, 5.1)
Q2	1.40 (0.66, 3.0)	0.50 (0.12, 2.0)	1.26 (0.43, 3.6)	1.46 (0.35, 6.1)
Q1	1.85 (0.95, 3.6)	2.37 (0.64, 8.7)	1.85 (0.68, 5.0)	2.30 (0.52, 10.2)
ALT				
Q1	Reference	Reference	Reference	Reference
Q2	0.91 (0.39, 2.2)	0.81 (0.18, 3.6)	0.77 (0.25, 2.3)	1.16 (0.27, 5.0)
Q3	0.80 (0.32, 2.0)	2.43 (0.52, 11.3)	0.75 (0.23, 2.5)	0.43 (0.07, 2.6)
Q4	0.89 (0.31, 2.6)	5.23 (0.85, 32.3)	0.52 (0.12, 2.2)	0.30 (0.04, 2.2)
AST				
Q1	Reference	Reference	Reference	Reference
Q2	1.37 (0.54, 3.5)	0.62 (0.15, 2.6)	2.76 (0.81, 9.5)	1.28 (0.27, 6.0)
Q3	2.32 (0.90, 6.0)	1.73 (0.39, 7.6)	1.90 (0.42, 8.5)	3.56 (0.73, 17.3)
Q4	**4.21 (1.35, 13.1)**	1.35 (0.24, 7.5)	**8.40 (1.68, 42.1)**	**10.7 (1.50, 76.3)**
Total Bilirubin				
Q1	Reference	Reference	Reference	Reference
Q2	1.05 (0.50, 2.2)	3.05 (0.91, 10.3)	0.92 (0.32, 2.6)	1.01 (0.30, 3.4)
Q3	1.22 (0.60, 2.4)	5.49 (1.27, 23.7)	1.25 (0.47, 3.3)	0.56 (0.14, 2.2)
Q4	1.54 (0.76, 3.1)	3.48 (0.98, 12.4)	0.56 (0.18, 1.8)	0.68 (0.19, 2.5)
Albumin				
Q4	Reference	Reference	Reference	Reference
Q3	0.48 (0.18, 1.3)	0.57 (0.15, 2.2)	0.33 (0.10, 1.1)	0.91 (0.20, 4.2)
Q2	1.35 (0.68, 2.7)	3.49 (0.91, 13.4)	0.90 (0.37, 2.2)	1.70 (0.42, 7.0)
Q1	1.89 (0.96, 3.7)	**6.66 (1.55, 28.6)**	0.62 (0.25, 1.6)	3.09 (0.76, 12.5)
FIB4				
L1 (<1.45)	N/A	N/A	Reference	Reference
L2 (1.45-2.67)			**3.37 (1.44, 7.9)**	**7.34 (2.53, 21.3)**
L3 (>2.67)			**5.47 (2.26, 13.3)**	**11.2 (3.19, 39.3)**

*Adusted for age group, gender and race
** Adjusted for age group, gender and race
ALT = Alanine Aminotransferase, AST = Aspartate Transaminase

Disclosures: Yunhao Liu: Gilead Sciences: Employee, Wildaliz Nieves: Gilead Sciences, Inc.: Employee, Jeffrey Wallin: Nothing to Disclose, Shahed Iqbal: Gilead Sciences, Inc.: Stockholder, Gilead Sciences, Inc.: Stock - publicly traded company, Gilead Sciences, Inc.: Employee

1176 | PREVALENCE AND CLINICAL CHARACTERISTICS OF HEPATITIS DELTA VIRUS (HDV) INFECTED INDIVIDUALS IN BRITISH COLUMBIA AND ONTARIO: A MULTI-CENTRE UPDATE

Valeriya Zaborska[1] *David Wong*[2] *Hin Hin Ko*[3] *Edward Tam*[4] *Julia MacIsaac*[4] *Alnoor Ramji*[3]

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Background: Globally, Hepatitis Delta Virus (HDV) is reported in 4.5-13% of persons with chronic hepatitis B (CHB). Early case identification is crucial as HBV-HDV co-infected patients have increased risks of cirrhosis, hepatocellular carcinoma (HCC) and liver-related mortality, compared to HBV mono-infected patients. In Canada, reported HDV prevalence is likely overestimated due to selection bias, as testing occurs only in HBsAg+ patients at high risk of HDV infection. The purpose of the current study is to report prevalence and clinical characteristics of HDV infection among patients from two large Canadian tertiary care centers in Ontario and British Columbia, where the clinical practice of universal HDV screening among HBsAg+ patients has recently been adopted. **Methods:** Retrospective study of HBsAg-positive patients ≥18 years of age tested for HDV Ab between 2013-2023 in BC and 1996-2024 in ON. Data collected include HDV Ab status and viral load, patient demographics, clinical characteristics, comorbidities, alcohol use, fibrosis stage, and therapies utilized. HDV-HBV co-infected and HBV mono-infected populations were compared. **Results:** Among 1686 HBsAg-positive patients tested for HDV Ab in BC and ON, 1.8% (95% CI 1.15 - 2.41) were HDV Ab+, with 75% (21/28, CI 59 - 91%) of those HDV RNA +. Of the 30 HDV Ab+ individuals, 24 (80%) were male, 8 (27%) consumed >3 units alcohol/week, 5 (17%) had evidence of decompensated liver disease and 5 (17%) had hepatocellular carcinoma (HCC). Nine (33%) had liver stiffness measurement by transient elastography >9.0kPa. At the time of HDV Ab result, for HDV Ab+ patients,

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mean ALT was 94 (CI 65.4 - 121.9) versus 57 (CI 39.2 - 74.0) on their recent labs, and 12 (40%) had detectable (≥20 IU/mL) HBV DNA at time of HDV diagnosis. When comparing HDV co-infected individuals to HBV mono-infected individuals, the HDV Ab+ group was more likely to be male (80% vs 57%, p=0.01), White or Middle Eastern (p<0.01) and more likely to have a concurrent diagnosis of HCC (17% vs 4%, p<0.01). Interestingly, the prevalence of HDV Ab positive status was 6.9% (CI 3.3 - 10.5) in White, 9.8% (CI 0.7 - 18.8) in Middle Eastern, and 0.5% (CI 0.1 - 0.9) in East/Southeast Asian patients. **Conclusion:** HDV Ab prevalence was 1.8% in our cohort where broad HDV Ab screening practices have been adopted. This estimate is significantly lower than reported in other Canadian datasets. The difference may be attributable to variable HDV Ab screening practices. While the majority of HBV affected individuals in this cohort are of East or Southeast Asian origin, the HDV Ab prevalence in this population is low. Given the clinical importance of HDV case identification, universal screening of HBsAg+ patients for HDV remains important, particularly given the emerging availability of HDV-specific antiviral therapies. Further efforts to characterize the epidemiology of the HDV/HBV co-infected population in Canada will allow for more refined screening practices.

Table 1.0: Comparison of demographics of HBV/HDV Ab+ individuals and HBV+/HDV Ab- individuals across two Canadian tertiary care centers in Ontario (ON) and British Columbia (BC)

	HBV+ HDV+ (n=30)	HBV+ HDV- (n=1656)	p=value
Demographics			
M	24 (80%)	949 (57%)	**0.01**
F	6 (20%)	707 (43%)	**0.01**
Age (mean)	57.8 (31-79)	54.5 (18-101)	
Ethnicity			
Asian (East/Southeast)	6 (20%)	1240/1616 (77%)	**<0.01**
White	13 (43%)	176/1616 (11%)	**<0.01**
Middle Eastern	4 (13%)	37/1616 (2%)	**<0.01**
South Asian	2 (7%)	53/1616 (3%)	0.31
Black/African/Caribbean	4 (13%)	97/1616 (6%)	0.1
Hispanic	1 (3%)	13/1616 (1%)	0.14
Comorbidities			
HIV+	2/26 (8%)	31/1480 (2%)	0.05
HCC	5 (17%)	68 (4%)	**<0.01**
Current Medications			
Entecavir	4 (13%)	279 (17%)	0.6
Tenofovir	6 (20%)	486 (29%)	0.26
Lamivudine	1 (3%)	66 (4%)	0.86
Continuous data are shown as mean (range). Categorical data are shown as n/n known (mean %). Chi-square tests were done for categorical data.			

Disclosures: Valeriya Zaborska: Nothing to Disclose, David Wong: Nothing to Disclose, Hin Hin Ko: Nothing to Disclose, Edward Tam: Nothing to Disclose, Julia MacIsaac: Nothing to Disclose, Alnoor Ramji: Nothing to Disclose

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1177 | EVIDENCE FOR AN ONCOGENIC ROLE OF THE SMALL HEPATITIS DELTA ANTIGEN IN HEPATOCELLULAR CARCINOMA (HCC)

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Background: The mechanism whereby HDV promotes hepatocarcinogenesis remains elusive. Our goal was to investigate whether the small (S-) and large (L-) HDAg play a role in the pathogenesis of HCC using *in vivo* and *in vitro* approaches. **Methods:** We studied 18 patients, 10 with HDV-HCC and 8 with non-HCC HDV cirrhosis. Paired tumor/nontumor and cirrhosis liver specimens were obtained at the time of liver transplantation. We performed full-length HDV sequencing (NGS), transcriptomics (RNAseq), mutational landscape analysis by whole exome sequencing (WES), HDV RNA by PCR and *in situ* hybridization, immunohistopathology and confocal microscopy. To dissect the role of the two HDAg isoforms, we established an *in vitro* model in Huh7 cells transfected with plasmids encoding the S-HDAg (pDL444) or the L-HDAg (pDL445). RNAseq and confocal microscopy were performed on 42 samples from 7 time points (Day 0, 1, 2, 3, 4, 6 and 8), each in duplicate, for S-HDAg, L-HDAg, and controls. **Results:** All patients had HDV genotype 1. Phylogenetic analysis showed that HDV strains derived from HCC do not form a separate cluster. NGS demonstrated a dominance (>80%) of unedited genomes, encoding the S-HDAg, in all liver compartments. The S-HDAg dominance was confirmed at the protein level by confocal microscopy using two new in-house generated antibodies, one of which identifies only the L-HDAg. Our *in vitro* mechanistic studies demonstrated that the S-HDAg plays a central role in HDV pathogenesis. By analyzing the kinetics of the changes induced by the two HDAg isoforms, we found that the S-HDAg triggers: (i) early and strong proinflammatory response; (ii) early induction of oxidative stress; (iii) early upregulation of several proto-oncogenes, including *FOS* and *JUN,* required for cell cycle progression; (iv) exuberant expression of genes involved in cell cycle regulation and mitotic progression, leading to cell proliferation; (v) upregulation of DNA repair genes induced in response to DNA damage, critical for maintaining genome integrity. These effects were also elicited by the L-HDAg, but to a much lesser extent. Changes induced by the S-HDAg were validated by RNAseq and immunohistochemistry using tumor tissue from patients with HDV HCC. By WES, we detected impactful mutations in genes belonging to the WNT, TP53 and RTK-RAS pathways, commonly detected in other HCC, along with mutated genes in pathways that are less represented in other HCC (PI3K, cell cycle, NRF2). **Conclusion:** Our study corroborates the oncogenic role of HDV in hepatocarcinogenesis and identifies the S-HDAg as a key potential oncogenic factor, with direct implications for future strategies of prevention, surveillance, and therapeutics.

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Kleiner: Nothing to Disclose, Fausto Zamboni: Nothing to Disclose, David McGivern: Nothing to Disclose, Patrizia Farci: Nothing to Disclose

1178 | DEFINING THE DATA REQUIREMENT TO IMPROVE HEPATITIS D CO-INFECTION DETECTION IN THE UNITED KINGDOM: THE SOMERSET LIVER IMPROVEMENT PROJECT

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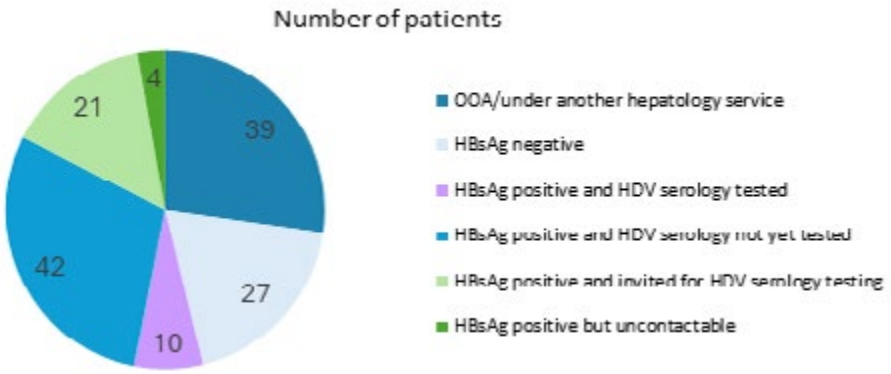
Background: Hepatitis D virus (HDV) is increasingly recognized as a critical worldwide public health issue. Co-infection in hepatitis B accelerates the progression of chronic liver disease. At least 12-15 million individuals are estimated to be infected globally, which is likely an underestimate due to a paucity of screening. The World Health Organization global health sector strategy for 2022-2030 asserts the importance of anti-HDV antibody reflex testing in all hepatitis B surface antigen (HBsAg) positive individuals to increase detection and early diagnosis. Using a novel case finding database in Somerset (609,474 individuals), the Somerset Liver Improvement Project aimed to identify all persistently HBsAg positive individuals yet to be tested for HDV who may require treatment. **Methods:** The database was configured to identify all HBsAg positive adult individuals lacking anti-HDV testing. Clinical records were reviewed to determine if individuals remained HBsAg positive and were (or had ever been) under a hepatology service. **Results:** Overall, 143 living individuals were identified - 69 (48.3%) male, 74 (51.7%) female. 39 (27.3%) were out of area (OOA) or under another hepatology service and 27 (18.9%) were now HBsAg negative, leaving 77 HBsAg positive individuals in area for review. Of those, 10 (13%) individuals had subsequently received anti-HDV testing but, concerningly, six (7.8%) individuals under regular hepatology follow up had not. The team has already invited 21 (27.3%) individuals for anti-HDV testing and four (5.2%) were uncontactable, meaning 42 individuals (54.5%) remain in need of invite (Figure 1). However, seven (16.7%) of those had previously disengaged from hepatology follow up. **Conclusion:** Our data suggests that detecting cases of HDV co-infection can now be achieved using a systematic longitudinal approach to a) ensure all relevant individuals are screened, b) ensure that data is available across multiple geographies (as the missing **Results:** may be accessible elsewhere); and c) ensure a regular data refresh and an iterative approach. The latter is crucial as, while there may have been successful prior initiatives, new untreated populations arise. Work is now underway to invite the relevant individuals in Somerset for further investigation and/or treatment. A proactive approach has the potential to identify individuals quicker than standard clinical care and should be seen as an adjunct to reflexive testing.



Disclosures: Emma Saunsbury: Grifols: Advisor, Christina Owen: Nothing to Disclose, Timothy Jobson: Predictive Health Intelligence Ltd: Executive role, Predictive Health Intelligence Ltd: Stock – privately held company

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1179 | SEROPREVALENCE AND GENOTYPE DISTRIBUTION OF HEPATITIS A AND E VIRUSES AMONG GENERAL RESIDENTS IN BINH THUAN PROVINCE, SOUTHERN VIETNAM

Chanroth Chhoung[1] Ko Ko[1] ZAYAR PHYO[1] Golda Akuffo[1] Mirzaev Ulugbek[1] Suzuki Ryosuke[2] Do Huy Son[3] Aya Sugiyama[1] Tomoyuki Akita[1] Shingo Fukuma[4] Kazuaki Takahashi[1] Junko Tanaka[1]

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Background: Hepatitis A virus (HAV) and hepatitis E virus (HEV), transmitted primarily by fecal-oral route, are common in low- and middle-income countries with poor sanitary conditions and hygienic practices. A recent meta-analysis revealed that between 2004 to 2022, 61.4% and 27.3% of global HEV outbreak cases were reported in Africa and Southeast Asia, respectively, while food-borne HAV outbreaks were reported in India in 2017. Though Vietnam is a developing country in Southeast Asia, the reports on HAV and HEV infection are limited. Therefore, this study aimed to estimate the seroprevalence and genotype distribution of HAV and HEV using stocked serum samples of the general residents in Binh Thuan province, Vietnam. **Methods:** A total of 504 stocked serum samples collected from residents in Southern Vietnam by a multi-stage random sampling in 2012 was used to detect total anti-HAV and anti-HEV IgG using the in-house ELISA method. HAV and HEV RNA screening was done by RT-PCR using a universal primer set targeting nonstructural protein 2A, 2B of HAV, and ORF1 of HEV. The genotyping was done by phylogenetic tree analysis. **Results:** The overall seroprevalence of total anti-HAV was 93.8%(473/504) and that of anti-HEV IgG was 31.3%(158/504) with no significant difference by sex [male Vs female; total anti-HAV: 93.8% Vs 93.9% (p=0.989) and anti-HEV IgG: 32.6% Vs 31.4% (p=0.584)]. However, the seroprevalence of both HAV and HEV was significantly increased by age (from 85.3% in 20-29 yrs to 97.2% in >50 yrs for HAV and from 20.2% in 20-29 yrs to 40% in >50 yrs for HEV, p< 0.05). HAV RNA was detected in 27/473 anti-HAV positives (5.7%) with a mean viral load of 6.3 $x10^3$ copies/mL while no HEV RNA was detected in 158 anti-HEV positives. By phylogenetic tree analysis, all HAV strains were sub-genotype IA and close to HAV strains from China and Japan. **Conclusion:** Our study revealed that over 90% of residents were immune to HAV while 31.9% were immune to HEV, especially in young adults <40 years old. Having herd immunity of HAV, a prevention measure, and improved sanitation are required to prevent the potential sporadic outbreak of HEV infection in Vietnam.

Disclosures: Chanroth Chhoung: Nothing to Disclose, Ko Ko: Nothing to Disclose, ZAYAR PHYO: Nothing to Disclose, Golda Akuffo: Nothing to Disclose, Mirzaev Ulugbek: Nothing to Disclose, Suzuki Ryosuke: Nothing to Disclose, Do Huy Son: Nothing to Disclose, Aya Sugiyama: Nothing to Disclose, Tomoyuki Akita: Nothing to Disclose, Shingo Fukuma: Nothing to Disclose, Kazuaki Takahashi: Nothing to Disclose, Junko Tanaka: Nothing to Disclose

1180 | A SYSTEMATIC REVIEW AND META-ANALYSIS ASSESSING THE SAFETY AND EFFICACY OF HEPATITIS E VIRUS VACCINE

Islam Mohamed[1] Hazem Abosheaishaa[2] Anna Boda[1] Felix Yang[1] Emily Kamali[1] Regina Scott[1] Kate Huntress[3] Tejas Saravanan[3] Ahmed Salem[4] Fouad Jaber[1] Yazan Abboud[5] Dushyant Dahiya[6] Laura Alba[1] Nikki Duong[7]

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Background: Hepatitis E virus (HEV) is a global cause of viral hepatitis. While genotypes 1 and 2 cause acute hepatitis in Asia and Africa, genotypes 3 and 4 lead to sporadic acute or chronic hepatitis in America and Europe. Pregnant women, immunosuppressed individuals, and those with chronic liver disease face a higher risk of severe outcomes. Hecolin, an HEV recombinant vaccine, is approved for outbreak use in China but awaits FDA approval in the USA. **Methods:** We conducted a systematic search in Medline, Cochrane, Scopus, and Embase, employing specific terms for the recombinant HEV vaccine. Eligibility criteria involved all-age individuals receiving recombinant HEV vaccine in randomized controlled trials. Covidence software was used to screen studies, and data extraction encompassed study characteristics, baseline data, and efficacy outcomes by four reviewers. Bias

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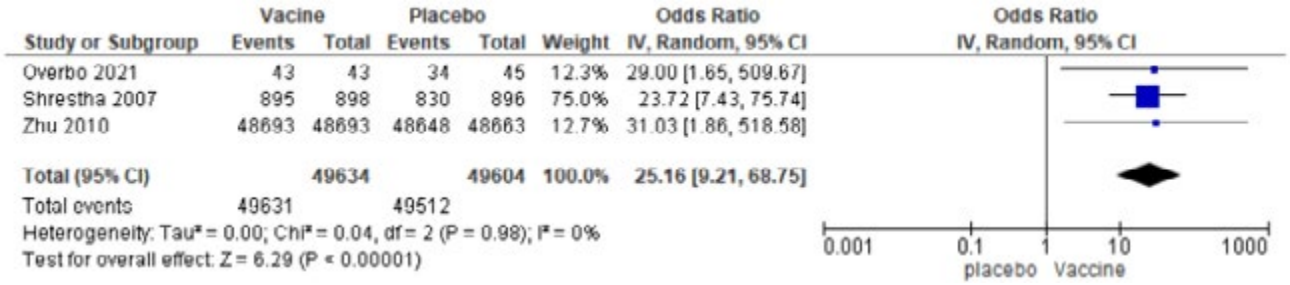
evaluation used Cochrane's RoB 2 tool. Statistical analysis utilized Revman v5.4 with a random effect model, considering P < 0.05 as statistically significant. Heterogeneity was assessed using the I2 test. **Results:** The analysis revealed a statistically significant difference in Hepatitis E vaccine efficacy compared to placebo (OR: 25.16, 95% CI [9.21, 68.75], P < 0.00001) with a substantial reduction in Hepatitis E cases (OR: 0.04, 95% CI [0.01, 0.11], P < 0.00001). In terms of safety, the HEV vaccine exhibited a significant increase in injection pain (OR: 1.56, 95% CI [1.03, 2.36], P = 0.04) and injection bruising (OR: 3.62, 95% CI [1.76, 7.48], P = 0.0005). No statistically significant differences were observed in fever (OR: 1.03, 95% CI [0.86, 1.23], P = 0.76) or headache (OR: 1.15, 95% CI [0.72, 1.84], P = 0.56). Local events significantly increased with the vaccine (OR: 1.50, 95% CI [1.38, 1.63], P < 0.00001). There were no significant differences in systemic events (OR: 1.06, 95% CI [0.86, 1.31], P = 0.59) or serious adverse events (OR: 0.58, 95% CI [0.16, 2.07], P = 0.40). **Conclusion:** In conclusion, our systematic review and meta-analysis demonstrate the significant and favorable impact of the recombinant HEV vaccine on the reduction of Hepatitis E cases. However, safety considerations are notable, as the vaccine is associated with a significant increase in injection-related pain and bruising. While localized adverse events were more frequent with the vaccine, there were no statistically significant differences in systemic events, serious adverse events, fever, or headache compared to placebo. These findings emphasize the overall effectiveness of the Hepatitis E vaccine in preventing HEV infections but highlight the need for careful monitoring and consideration of potential localized side effects.



Disclosures: Islam Mohamed: Nothing to Disclose, Hazem Abosheaishaa: Nothing to Disclose, Anna Boda: Nothing to Disclose, Felix Yang: Nothing to Disclose, Emily Kamali: Nothing to Disclose, Regina Scott: Nothing to Disclose, Kate Huntress: Nothing to Disclose, Tejas Saravanan: Nothing to Disclose, Ahmed Salem: Nothing to Disclose, Fouad Jaber: Nothing to Disclose, Yazan Abboud: Nothing to Disclose, Dushyant Dahiya: Nothing to Disclose, Laura Alba: Nothing to Disclose, Nikki Duong: Nothing to Disclose

1181 | ZINC ACETATE INHIBITS HEPATITIS A VIRUS REPLICATION *IN VITRO*

Tatsuo Kanda[1] Reina Sasaki-Tanaka[2] Hiroyuki Abe[3] Naruhiro Kimura[3] Msaki Mito[4] Moeno Sugita[4] Yoshihisa Arao[4] Satoshi Abe[4] Hiroteru Kamimura[3] Kazunao Hayashi[3] Takeshi Yokoo[3] Atsunori Tsuchiya[3] Takeshi Suda[4] Hiroaki Okamoto[5] Shuji Terai[3]

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Background: Japanese rice-koji miso extracts could inhibit HAV replication in association with the unfolded protein response. Zinc sulfate and zinc chloride could suppress HAV replication. Patients with ALF type A and diabetes is occasionally observed. We examined the mechanism of Japanese rice-koji miso extracts on the mRNA expression of human hepatocytes using RNA-Seq, and the effects on zinc acetate on HAV replication of low glucose or high glucose condition *in vitro*. **Methods:** Human hepatoma cell line Huh7 cells were treated with Japanese rice-koji miso, Kurasaigetsuusujiomiso and Igoumiso, which are made from rice, soy, and salt with special Yurara yeast, at 5% concentration for 24 hours. With next-generation sequencer technology, RNA-Seq analysis was performed on an Illumina HiSeq1500. Huh7 or African green monkey kidney GL37 cells were treated with low glucose (1000 mg/dL) or high glucose medium (4500 mg/dL), and infected with HAV HA11-1299 genotype IIIA at a multiplicity of infection (MOI) of 0.01. Twenty-four hours after infection, the cells were treated with zinc acetate at 10 and 20 microM. At 48 hours post-infection, total cellular RNA was extracted for further HAV RNA analysis. HAV RNA levels were measured by real-time RT-PCR. Data was analyzed by the ddCt method

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or the standard curve method. Dimethylthiazol carboxymethoxyphenyl sulfophenyl tetrazolium (MTS) assay was performed for the evaluation of cell viabilities. **Results:** (1) In Huh7 cells, Kurasaigetsuusujiomiso up-regulated the gene expressions of LOC100129931, LOC101929125, REL, GPR82, NUN5P2, MT1A, EIF5A2, LIF and AP4S1 (more than 1-LFC) and down-regulated the gene expressions of LOC729218, TRIM78P, LOC100130074, RPS28, MT1E, RN7SL1, HIST1H3C, ELF2P4 and MT1L (less than -1-LFC). (2) In Huh7 cells, Igoumiso up-regulated the gene expressions of NPIPA5, CERS6-AS1, PIR-FIGF, LOC100129931, MED4-AS1, RPL39P19, ZC2HC1B, LOC101929125, NSUN5P2, GPR82, LIF, NPPB, PTMAP3, EPO, LOC3893322, TMSB4X, TLR9, C8orf58, TRNAI2, KIAA1984, MT1A, LOC78755, LOC100128979, NEDD9 and LOC100133150 (more than 2-LFC) and down-regulated the gene expressions of LOC100130074, RN7SL1, MT1G, MT1E, LOC729218 and HIST1H3C (less than -1-LFC). Then we focused on the Zinc. (3) In Huh7 cells treated with low glucose (1000 mg/dL) or high glucose medium (4500 mg/dL), zinc acetate at 10 and 20 microM, inhibits HAV replication to 69.1% and 51.0%; or 57.4% and 52.8%, respectively. (4) In GL37 cells treated with low or high glucose medium, zinc acetate at 10 and 20 microM, inhibits HAV replication to 87.0% and 17.5%; or 64.3% and 32.5%, respectively. (5) Zinc acetate had no effects on Huh7 or GL37 cell viabilities at 0-100 microM for 48 hours. **Conclusion:** Japanese rice-koji miso extracts had altered the gene expression of zinc-associated genes in human hepatocytes. Zinc acetate inhibits HAV replication *in vitro*. Zinc acetate could be useful for the treatment of hepatitis A patients with diabetes.

Disclosures: Tatsuo Kanda: Nothing to Disclose, Reina Sasaki-Tanaka: Nothing to Disclose, Hiroyuki Abe: Nothing to Disclose, Naruhiro Kimura: Nothing to Disclose, Msaki Mito: Nothing to Disclose, Moeno Sugita: Nothing to Disclose, Yoshihisa Arao: Nothing to Disclose, Satoshi Abe: Nothing to Disclose, Hiroteru Kamimura: Nothing to Disclose, Kazunao Hayashi: Nothing to Disclose, Takeshi Yokoo: Nothing to Disclose, Atsunori Tsuchiya: Nothing to Disclose, Takeshi Suda: Nothing to Disclose, Hiroaki Okamoto: Nothing to Disclose, Shuji Terai: Nothing to Disclose

1182 | AUTOIMMUNE HEPATITIS TRIGGERED BY ACUTE HEPATITIS A INFECTION

David Aguirre-Villarreal[1] Ignacio García Juárez[1] Luis Alejandro Rosales Renteria[2] Jose-David Prieto-Nava[2] Mario Orlando Santana Montes[1] Leticia Montserrat Martínez-Martínez[3] Jonathan Aguirre[4] Victor Manuel Paez Zayas[5] Francisco García-Juárez[6] Fátima Manzo-Santana[1] Mauricio Lisker-Melman[7]

[1]Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán Mexico City, Mexico., [2]Centro Médico Issemym, Metepec, Edomex. Toluca., [3]Hospital Central "Dr. Ignacio Morones Prieto", San Luis Potosí, SLP, México., [4]Hospital Angeles Pedregal, Mexico City, Mexico, [5]Hospital General de México Dr. Eduardo Liceaga, Ciudad de México, México., [6]Centro Medico Nacional 20 de Noviembre, ISSSTE. Mexico City, Mexico, [7]Washington University in St. Louis

Background: The pathogenesis of autoimmune hepatitis (AIH) is complex and viral infections may play a role in it. Hepatitis A virus (HAV) causing AIH has been previously reported but its incidence, prevalence, and natural history are largely unknown. In a large cohort of patients with acute HAV (aHAV), we describe a group of patients that developed AIH. **Methods:** This is a case-control study that involves patients diagnosed with AIH weeks after a confirmed aHAV (positive IgM anti-HAV) infection. AIH was defined by abnormal liver chemistry (LC), hyperglobulinemia, positive autoimmune serologies and a liver biopsy with interface hepatitis with portal and lobular lymphoplasmacytic infiltrates and hepatocyte necrosis. We explored the possibility of AIH in patients with prolonged aHAV (≥3 months with intermittent elevation of >1,000 U/L of ALT or constant elevation of ALT). Patients were matched by sex and age (3:1) to patients with aHAV infection that underwent complete resolution (classic aHAV). We collected demographics, medical history, clinical presentation, LC, serology and biopsy results. Finally, we recorded steroid and immunosuppressant use. **Results:** In a cohort of 553 patients with confirmed aHAV infection, 19 (3.4%) were diagnosed with AIH (all with a liver biopsy). In those patients, the aHAV behaved with intermittent elevations of ALT in 15, and with constant elevation of ALT in 4. Median time to diagnosis of AIH after initial symptoms of aHAV was 66 days. The median time to normalization of LC in the classic aHAV group was 45 days. Median age was 40 years (IQR 12.5) and 53% were male. Biochemical (ALT and TB) progression of aHAV to AIH is shown in Figure 1. All patients had positive ANA titers (median 1:320) and 11 had positive ASMA titers (median 1:160). Median IgG levels were 2454 g/dL. All cases of AIH received prednisone (PDN) for a median duration of 119 days (58-283), 11/19 patients PDN + azathioprine and 1/19 PDN + mycophenolate mofetil. Of the 19 patients treated, 18 completely normalized LC, 1 patient had a partial improvement in LC and 4 patients are currently receiving treatment. **Conclusion:** In our cohort, the

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diagnosis of AIH after aHAV remains infrequent (3.4%). In most patients with aHAV that progressed to AIH, the clinical course was prolonged and with intermittent elevations of ALT. A brief course of steroids combined with immunosuppressants normalized the LC. The natural history of AIH post-aHAV remains to be fully characterized.

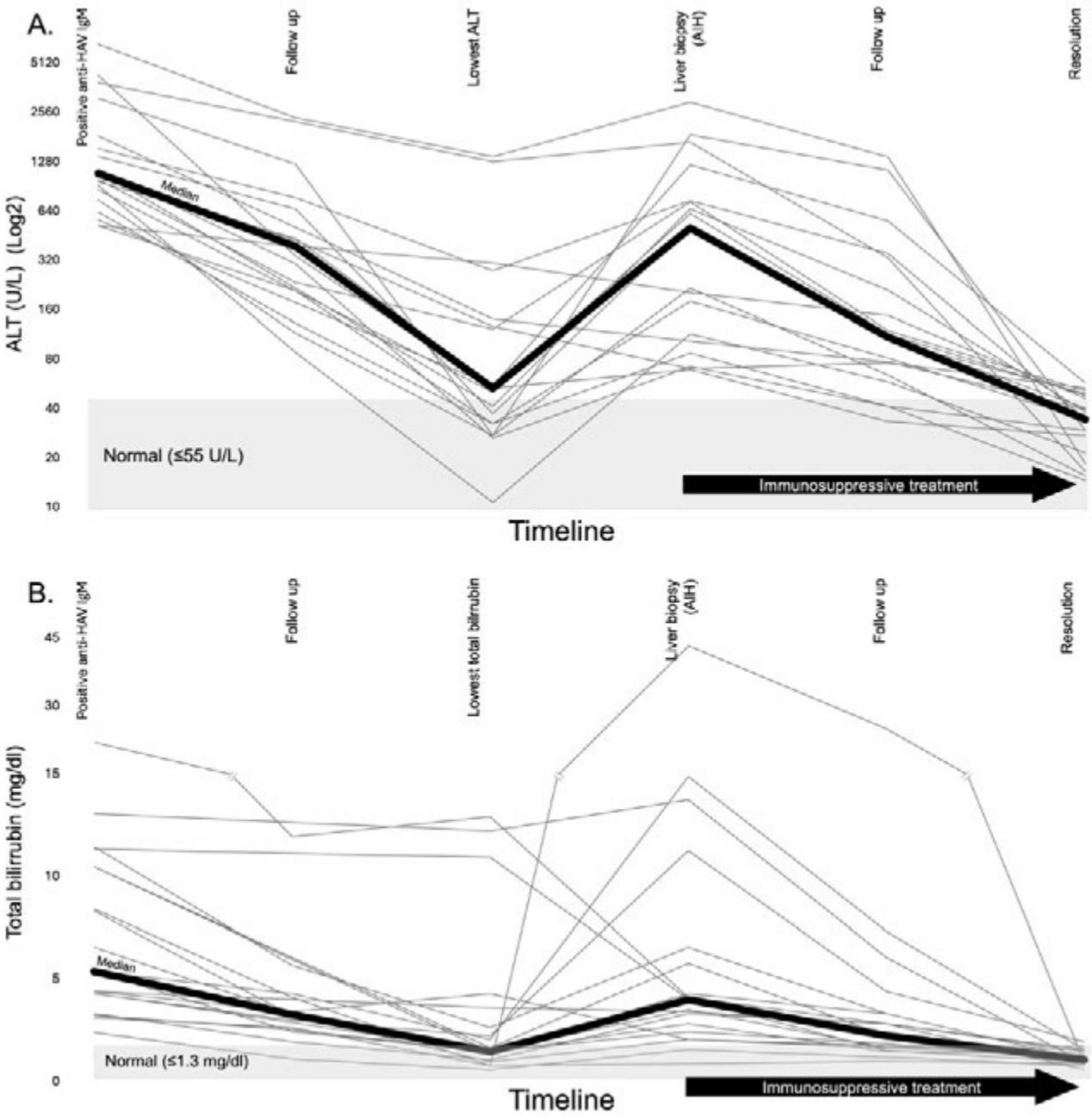

Figure 1. Biochemical changes in ALT (A) an TB (B) across time in patients with aHAV-associated AIH.

Disclosures: David Aguirre-Villarreal: Nothing to Disclose, Ignacio García Juárez: Nothing to Disclose, Luis Alejandro Rosales Renteria: Nothing to Disclose, Jose-David Prieto-Nava: Nothing to Disclose, Mario Orlando Santana Montes: Nothing to Disclose, Leticia Montserrat Martínez-Martínez: Nothing to Disclose, Jonathan Aguirre: Nothing to Disclose, Victor Manuel Paez Zayas: Nothing to Disclose, Francisco García-Juárez: Nothing to Disclose, Fátima Manzo-Santana: Nothing to Disclose, Mauricio Lisker-Melman: Abbvie: Speaking and Teaching

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1183 | DEVELOPMENT AND IMPLEMENTATION OF AN HEPATITIS D DETECTION AND LINKAGE TO CARE PROGRAM IN CATALONIA. PRELIMINARY RESULTS

Adriana Palom[1] ARIADNA RANDO-SEGURA[2] Laura Calatayud-Samper[3] Gema Fernandez-Rivas[4] Alicia Sellés[5] Saray Mormeneo Bayo[6] Dúnia Perez del Campo[7] Mar Olga Perez Moreno[8] Josefina Ayats Ardite[9] David Tabernero[10] José Castellote[3] Rosa Maria Morillas[11] Adrià Rodríguez Castellano[5] Carles Aracil Blanch[6] Carmen López[7] Darly Salazar[8] Andrés Marco[12] Maria Buti[10]

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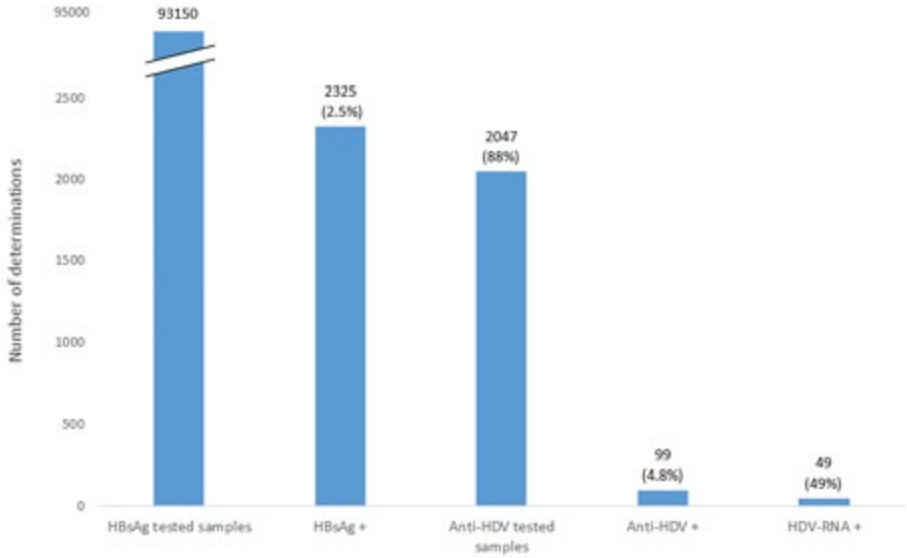
Background: HDV (hepatitis D virus) infection still remains underdiagnosed, although most guidelines recommend anti-HDV testing in all HBsAg-positive individuals. In Spain, HBsAg estimated prevalence in the general population is 0.22%, from which 7.7% are anti-HDV+. This project aims to develop and implement an hepatitis D detection program for all HBsAg-positive samples that are collected in public healthcare centers of Catalonia (>95% population coverage). **Methods:** Prospective study including all HBsAg+ samples collected in 7 laboratories of the Catalan healthcare system. Double anti-HDV reflex testing was conducted, including a centralized HDV-RNA quantification. Medical records of anti-HDV positive patients were examined and registered in a digital platform (demographics, epidemiology, clinical data, lab data, and linkage to care status). Linkage to care was ensured for all HDV-RNA positive individuals. **Results:** From 01/2024 to 04/2024, HBsAg was tested in 93.150 samples and 2.325(2.5%) were HBsAg+. Anti-HDV was tested in 2.047 (88%) of HBsAg+ samples; a total of 99 (4.8%) were anti-HDV positive, and 49 (49%) were HDV-RNA positive (Figure). Anti-HDV+ subjects were mainly male (62%), with a median age of 53 (42-58) years, and foreign (55%). Risk factors were reported in 34% of individuals, (22% parenteral transmission, from which 11% were PWID, 7% sexual risk behavior), with median ALT levels of 70 (41-112) IU/ml. Regarding liver disease, 29% had liver cirrhosis, 7% had history of liver-related decompensation, and 3% had history of hepatocellular carcinoma.The program allowed testing 940 (46%) HBsAg+ samples not previously tested for anti-HDV, and detected 28 (3%) new cases of anti-HDV+, 6 (21%) of them being HDV-RNA positive. All of them have been linked to care and are now under evaluation for treatment. **Conclusion:** The development and implementation of a regional hepatitis D program has proven to be feasible and has a wide acceptance amongst all microbiology and liver units. Our preliminary results show that hepatitis D detection programs linked to the general healthcare system are crucial for optimal diagnosis and linkage to care of these patients.



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1184 | DIFFERENTIAL PLACENTAL ESTROGEN RECEPTOR EXPRESSION IS RESPONSIBLE FOR THE ADVERSE CLINICAL OUTCOMES IN HEPATITIS E VIRUS AND COVID-19 INFECTED PREGNANT WOMEN

Maryam Javed[1] Anoushka Saxena[1] Prabhjyoti Pahwa[1] Sandhya Hora[1] Rashmi Kaul[2] Nirupma Trehanpati[3]

[1]Institute of Liver and Biliary Sciences, [2]Oklahoma State University-Centre for Health Sciences, [3]Institue of Liver and Biliary Sciences

Background: Viral infections during pregnancy are known to be associated with adverse pregnancy outcomes. During pregnancy, there is a higher secretion of steroid hormones which promotes viral replication. The severity of infection in Hepatitis E virus (HEV) and COVID-19 positive pregnant females varies significantly, possibly due to altered estrogen levels during pregnancy. The expression of estrogen receptors in placenta facilitates binding of estrogen and regulate host or viral gene expression during viral infection. We hypothesized that placental estrogen receptors (ER) ESR-1, ESR-2 and GPER-1 expression may dictate how the placenta responds to and withstands the stresses of viral infections during pregnancy. **Methods:** Placental samples from COVID-19+ pregnant women (Gr.1, n=23, age 30±5 yr. SARS CoV-2 IgG+) and HEV infected pregnant women (Gr.2, n=9, age 25±5 yr. HEV IgM+) were collected at the time of delivery. Expression of estrogen receptors ESR-1, ESR-2 and GPER-1 were determined using RT-PCR and immunohistochemistry (IHC). Healthy pregnant females (n=5) served as control (HC). **Results:** Comparison of HCs to patients for RT-PCR data revealed an increased expression of ESR-1 in Gr.1(p=0.0015) and Gr.2 (p=0.44) while expression of ESR-2 was markedly reduced in Gr.2 compared to Gr.1, but not significantly. GPER-1 showed no significant decrease (p=0.50) in Gr.1 but was significantly increased in Gr.2 (p=00110) compared to healthy. Moreover, a comparative analysis between Gr.1 and Gr.2 showed significantly decreased expression of ESR-1 (0.0039) and ESR-2 (p=0.0002) and increased expression of GPER-1 (0.0328) in Gr.2. Immunohistochemistry (IHC) data further corroborated the RT-PCR data, demonstrating significantly increased expression of GPER-1 and ESR-1 in both Gr.1 and Gr.2 compared to HC. However, ESR-2 expression was decreased in Gr.1 and Gr.2, compared to HC, with no statistical significance. **Conclusion:** Our work is the first to identify differential levels of placental ER subtype expression in HEV versus COVID-19 infected pregnant. The two RNA viruses may have diverse role in activating ERs to break the tolerogenic immune environment at the maternal-fetal interface resulting in higher morbidity and mortality observed in HEV infected pregnant women than COVID-19 infected pregnant women.

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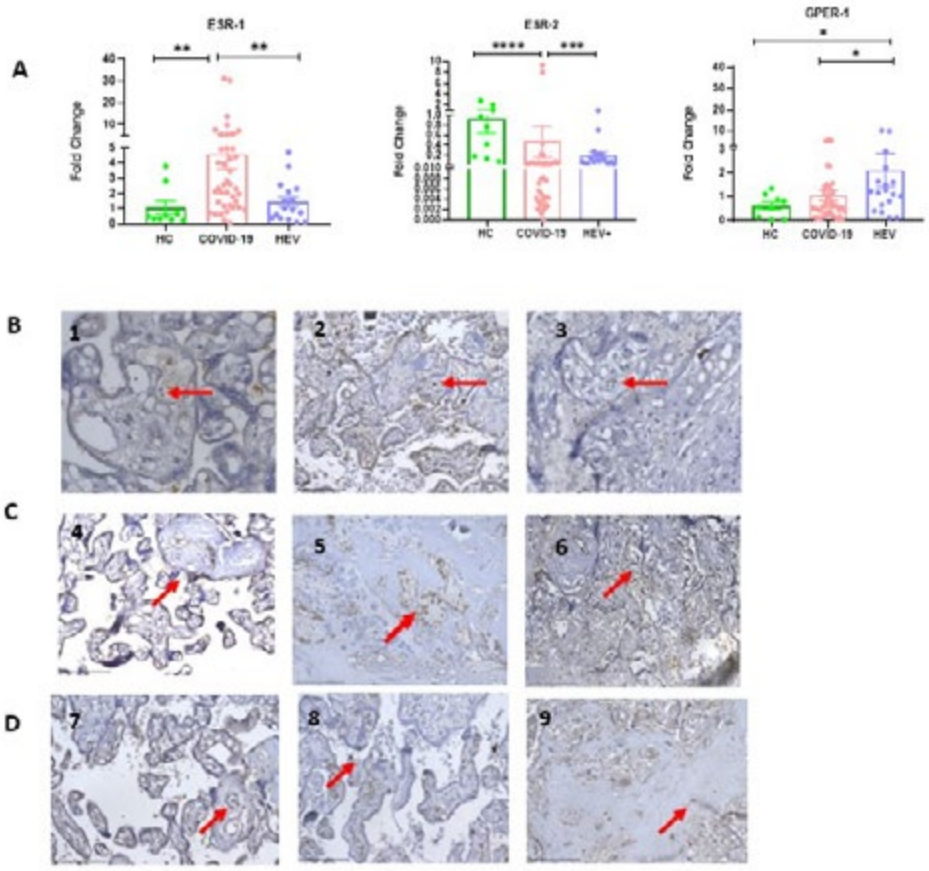

Figure: **(A)** Fold change in gene expression levels of ESR-1, ESR-2 and GPER-1 between HC, COVID-19, and HEV infected placenta assessed by RT-PCR **(B)** and **(C)** Representative immunohistochemical staining of ESR-1 (1-3), GPER-1 (4-6), ESR-2 (7-9) in HC, COVID-19, and HEV infected placentas at 40X.

Disclosures: Maryam Javed: Nothing to Disclose, Anoushka Saxena: Nothing to Disclose, Prabhjyoti Pahwa: Nothing to Disclose, Sandhya Hora: Nothing to Disclose, Rashmi Kaul: Nothing to Disclose, Nirupma Trehanpati: Nothing to Disclose

1185 | BULEVIRTIDE FOR PATIENTS WITH CHRONIC HEPATITIS D (CHD) IN ITALY: A MULTICENTER PROSPECTIVE NATIONWIDE REAL-LIFE STUDY (D-SHIELD)

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Background: Bulevirtide (BLV) is the only approved drug for patients with chronic hepatitis delta (CHD) in EU. In Italy this drug has been available since May 2023, but no studies so far have addressed the demographic, virological and clinical features of patients treated with BLV as well as they response to treatment. **Methods:** Consecutive HDV patients with chronic hepatitis Delta (CHD) starting BLV 2 mg/day as monotherapy or in combination with pegIFNα were included in a multicenter real-life Italian study (D-SHIELD). Patients' characteristics before and during BLV treatment were collected. Virological, biochemical, clinical features were assessed. **Results:** 301 patients with CHD from 27 centers were enrolled in this ongoing study. 99% received BLV 2 mg/day monotherapy: median age 54 (28-82) years, 55% men, 96% of European origin, 79% with cirrhosis, 7% HIV-coinfected. Among patients with cirrhosis, 30% had varices, 9% had a history of HCC (active in 67%), 9% had a history of ascites (50% persistent), 2% with previous varices hemorrhage, 6% had decompensated (CPT-B) cirrhosis. At BLV start, median ALT were 75 (16-1,074) U/L, liver stiffness measurement (LSM) 13.6 (3.6-68.1) kPa, platelets 116 (14-377)10^3/mm^3, 97% patients were on NUC therapy, 89% HBeAg negative. Median HDV RNA was 5.3 (1.5-8.2) log IU/mL and HBsAg 3.7 (0.6-4.7) log IU/mL. As of May 2024, 124 patients have reached week 32 of treatment. ALT and HDV RNA levels significantly declined: ALT from 75 (16-1,074) at baseline to 37 (11-173) at week 24 and 36 (12-213) U/L at week 32 and HDV RNA from 5.3 (1.5-8.2) to 3.3 (0.3-7.0) and 2.7 (0.2-7.2) Log IU/mL, respectively ($p<0.0001$). Virological, biochemical and combined response were achieved by 46%, 62% and 33% of patients at week 24 of treatment, respectively. At week 32, these responses were achieved by 62%, 64% and 40% of patients, respectively. Among patients not achieving a virological response, 58% and 50% achieved a partial virological response (HDV RNA decline >1 but <2 Log IU/mL, compared to baseline) at week 24 and 32, respectively. Moreover, 13% and 19% of patients achieved HDV RNA undetectable at week 24 and 32, respectively. **Conclusion:** D-SHIELD is the largest single country study on BLV treatment for CHD in Europe. Almost all Italian patients started BLV as monotherapy.. Virological, biochemical and combined response rates at week 32 compare favorably with previous small retrospective studies.

Disclosures: Maria Paola Anolli: Nothing to Disclose, Elisabetta Degasperi: Gilead: Speaking and Teaching, Roche: Advisor, Abbvie: Speaking and Teaching, Gianpiero Doffizi: Nothing to Disclose, Alessia Rianda: Nothing to Disclose, Alessandro Loglio: Nothing to Disclose, Mauro Viganò: Nothing to Disclose, Alessia Ciancio: Nothing to Disclose, Yulia Troshina: Nothing to Disclose, Maurizia Brunetto: Nothing to Disclose, Barbara Coco: Nothing to Disclose, Serena Zaltron: Nothing to Disclose, Michele Milella: Nothing to Disclose, Pierluigi Toniutto: Nothing to Disclose, Letizia Marinaro: Nothing to Disclose, Andrea Gori: Nothing to Disclose, Alessandro Federico: Nothing to Disclose, Teresa Antonia Santantonio: gilead: Advisor, Gabriella Verucchi: Nothing to Disclose, Filomena Morisco: Nothing to Disclose, Alessandra Mangia: Nothing to Disclose, Stella De Nicola: Nothing to Disclose, Monia Maracci: Nothing to Disclose, Antonietta Romano: Nothing to Disclose, Pietro Gatti: Nothing to Disclose, Rosa Zampino: Nothing to Disclose, Marcello Persico: Nothing to Disclose, Pietro Pozzoni: Nothing to Disclose, Adriano Pellicelli: Nothing to Disclose, Nicola Coppola: Nothing to Disclose, Francesca Pileri: Nothing to Disclose, Matteo Tonnini: Nothing to Disclose, Massimo Puoti: Nothing to Disclose, Pietro Lampertico: ROCHE PHARMA/DIAGNOSTICS, GILEAD SCIENCES, GSK, ABBVIE, JANS: Advisor

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1186 | HBCRAG MIRRORS HDV RNA DECLINE AND ALT NORMALISATION DURING BULEVIRTIDE THERAPY IN PATIENTS WITH CHRONIC HEPATITIS DELTA

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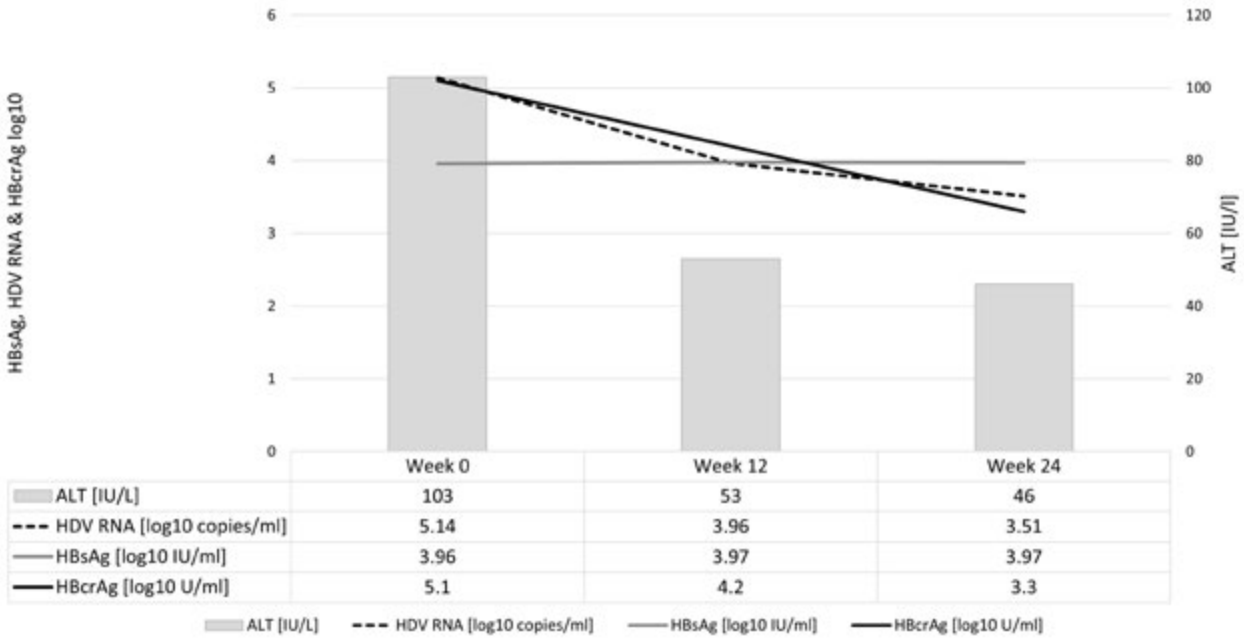
Background: The HBV envelope comprises LHBS, MHBS and SHBS proteins. Large HBsAg mediates HBV attachment to the NTCP receptor and entry into hepatocytes and is critical to the propagation of hepatitis delta virus (HDV). LHBS originates from both covalently closed circular DNA (cccDNA) and integrated HBV DNA. Hepatitis B core-related antigen (HBcrAg) reflects cccDNA transcriptional activity and higher levels of HBcrAg were noted in HDV RNA positive patients vs anti-HDV positive patients with undetectable HDV RNA. Bulevirtide (BLV) mimics a pre-S1 LHBS protein and blocks viral entry to hepatocytes. While HBsAg concentrations are not affected during antiviral therapy with BLV, there is only limited data comparing changes in HBcrAg during BLV antiviral therapy. We aimed to compare levels of HBV serological markers (HBsAg, HBcrAg) during antiviral therapy with BLV and assess their changes in relation to HDV RNA decline and/or ALT normalisation. **Methods:** Blood samples were collected from 14 HBV/HDV co-infected patients treated with BLV (all HDV RNA positive, median age 45 years, males n=8, 79% compensated cirrhosis). Plasma was collected at three time points (baseline, week 12 & 24), and the following serological & virological biomarkers were measured: HBsAg (Abbott Architect® assay, IU/ml), HBcrAg (CLEIA, Fujirebio, $\log_{10}$ U/ml), HDV RNA (in-house real-time qPCR, LLoQ 640 copies/ml). Up-to-date, 10 patients have completed 24 weeks of BLV therapy. **Results:** Baseline vs treatment week 12: 3 patients (30%) achieved HDV RNA decline >2 $\log_{10}$ vs 7 patients (70%) with a slow HDV RNA decline <1 $\log_{10}$; 4 (40%) patients had normal ALT. There was a marked reduction in ALT (-38 IU/L, p=0.02), HDV RNA (-0.94 $\log_{10}$ copies/ml, p<0.01) and HBcrAg (-0.8 $\log_{10}$ U/ml, p<0.01), but no significant change in HBsAg (9082 vs 9434 IU/ml, p=0.8). Baseline vs treatment week 24: 3 (30%) patients achieved >2 $\log_{10}$ HDV RNA decline, 4 (40%) patients had HDV RNA decline 1-2 $\log_{10}$ vs 3 (30%) patients with a slow decline of <1 $\log_{10}$; 5 (50%) patients had normal ALT. There was a significant reduction in ALT (-46 IU/L, p<0.01), HDV RNA (-1.64 $\log_{10}$ copies/ml, p<0.01) and HBcrAg (-1.1 $\log_{10}$U/ml, p<0.01), but HBsAg levels were similar (9082 vs. 9389 IU/ml, p=0.67) (Figure 1). Baseline levels of HBcrAg, HBsAg, HDV RNA and ALT were not predictive of a sharp HDV RNA decline (>2 $\log_{10}$) or ALT normalisation at week 12 and/or 24. HBcrAg titres <3.5 $\log_{10}$ U/ml at week 24 coincided with normalisation of ALT and sharp HDV RNA decline at the same time point. **Conclusion:** In contrast to HBsAg, HBcrAg levels mirrored changes in HDV RNA during BLV therapy. The meaning of lower HBcrAg during BLV therapy is unexplained, but could mirror relative differences in expression of LHBS from residual cccDNA versus integrated genomes, affecting HDV propagation, as BLV is not a HDV replication or assembly inhibitor. Larger studies assessing the predictive role of this serological biomarker with BLV HDV treatment are required.



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Disclosures: Ivana Carey: Gilead: Speaking and Teaching, Zillah Cargill: Nothing to Disclose, Sital Shah: Gilead Sciences: Speaking and Teaching, James Lok: Nothing to Disclose, Geoffrey Dusheiko: Nothing to Disclose, Kaushik Agarwal: Nothing to Disclose

1187 | VIBRATION-CONTROLLED TRANSIENT ELASTOGRAPHY-BASED SCORES IN AUTOIMMUNE HEPATITIS FOR PREDICTING LIVER FIBROSIS STAGE AND LIVER-RELATED EVENTS

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Background: Monitoring fibrosis progression in autoimmune hepatitis (AIH) is crucial. Recently, vibration-controlled transient elastography (VCTE)-based scores has been developed for monitoring fibrosis in metabolic dysfunction-associated steatotic liver disease. However, the predictive performance of these scores in AIH has not been explored. **Methods:** This study included 308 patients diagnosed with autoimmune hepatitis. We compared area under the receiver operating curve (AUROC) of liver stiffness measurement (LSM), Agile 3+, Agile 4, and serologic scores for predicting fibrosis stage. We also compared the concordance index (c-index) and AUROC for 3-year and 5-year liver related events (LREs). **Results:** Overall, VCTE-based scores performed better in predicting fibrosis stage or LREs, compared to serologic scoring systems. For predicting fibrosis stage 3 (F3), the AUROC of LSM, Agile 3+, Agile 4 was 0.864 (95% CI 0.818-0.910), 0.870 (95% CI 0.823-0.918), and 0.866 (95% CI 0.817-0.916), which was higher than that of FIB-4 (0.709, 95% CI 0.640-0.779), NFS (0.766, 95% CI 0.704-0.829), AST/ALT ratio (0.640, 95% CI 0.568-0.712), BARD (0.710, 95% CI 0.646-0.773), or APRI (0.559, 95% CI 0.484-0.635). The AUROC of LSM, Agile 3+, Agile 4 for predicting 5-year LREs was 0.854 (95% CI 0.796-0.912), 0.867 (95% CI 0.806-0.928), 0.868 (95% CI 0.806-0.930), which was higher than that of FIB-4 (0.749, 95% CI 0.668-0.830), NFS (0.789, 95% CI 0.710-0.868), AST/ALT ratio (0.789, 95% CI 0.710-0.868), BARD (0.712, 95% CI 0.629-0.794), or APRI (0.602, 95% CI 0.511-0.694). **Conclusion:** VCTE-based scores are effective for predicting fibrosis stages and LREs in AIH and should be considered for clinical use.

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1188 | QUANTIFICATION OF PLASMA HDV RNA IN UNTREATED AND BULEVIRTIDE-TREATED PATIENTS WITH CHD: A COMPARISON BETWEEN ROBOGENE 2.0, EUROBIOPLEX AND ALTOSTAR

Maria Paola Anolli[1] Sara Colonia Uceda Renteria[1] Elisabetta Degasperi[1] Floriana Facchetti[1] Dana Sambarino[1] Marta Borghi[1] Riccardo Perbellini[1] Roberta Soffredini[1] Sara Monico[1] Annapaola Callegaro[1] Pietro Lampertico[1]

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Background: Accurate HDV-RNA quantification is crucial for diagnosis and management of chronic hepatitis Delta (CHD), yet a significant variability between assays exists. We compared three methods to quantify HDV-RNA levels in untreated and Bulevirtide (BLV)-treated CHD patients. **Methods:** Frozen plasma from untreated and BLV–treated CHD patients were tested in a single-center retrospective study by 3 different assays: Robogene HDV-RNA Quantification Kit 2.0 (Roboscreen GmbH; LOD 6 IU/mL on 7500 Fast Real-Time PCR System [Applied Byosystem]), EurobioPlex HDV PCR quantitative (Eurobio Scientific, LOD 100 IU/m) on CFX96™ real-time PCR detection system [Bio-Rad]) and AltoStar HDV RT-PCR RUO Kit 1.5 (Altona Diagnostics, estimated LOD <10 IU/mL) on the AltoStar®AM16 . **Results:** Overall, 431 plasma samples from 130 CHD (69 untreated and 61 BLV-treated) patients were studied. Compared to Robogene, EurobioPlex reported higher HDV RNA levels [3.78 (0.70-7.99) vs. 4.69 (2.00-8.19) Log IU/mL, p<0.0001], with viremia higher than >0.5 Log in 160 (69%). Likewise, HDV RNA levels were higher with Altostar than with Robogene 2.0 [3.32 (0.70-7.37) *vs*. 3.91 (0.19-7.54) Log IU/mL, p<0.0001], with AltoStar reporting HDV-RNA levels >0.5 Log in 127 (52%). Although virological response rates (≥2 log decline *vs.* baseline) at week 24 (Robogene 2.0 *vs.* EurobioPlex and AltoStar) and 48 (Robogene 2.0 *vs.* AltoStar) were similar across assays, rates of HDV RNA undetectability significantly differed between the three assays at week 24 and 72 (p=0.003 and p=0.02) **Conclusion:** HDV-RNA levels quantified by EurobioPlex and

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Altostar were 1 and 0.5 logs higher than Robogene 2.0, respectively. HDV-RNA undetectability rates during BLV treatment were assay-dependent.

Disclosures: Maria Paola Anolli: Nothing to Disclose, Sara Colonia Uceda Renteria: Nothing to Disclose, Elisabetta Degasperi: Gilead: Speaking and Teaching, Roche: Advisor, Abbvie: Speaking and Teaching, Floriana Facchetti: Nothing to Disclose, Dana Sambarino: Nothing to Disclose, Marta Borghi: Nothing to Disclose, Riccardo Perbellini: Nothing to Disclose, Roberta Soffredini: Nothing to Disclose, Sara Monico: Nothing to Disclose, Annapaola Callegaro: Nothing to Disclose, Pietro Lampertico: ROCHE PHARMA/DIAGNOSTICS, GILEAD SCIENCES, GSK, ABBVIE, JANS: Advisor

1189 | PATIENT CHARACTERISTICS AND DISEASE PROGRESSION IN ADULTS WITH HEPATITIS DELTA VIRUS IN THE INPATIENT AND OUTPATIENT SETTING IN ITALY

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Background: Hepatitis delta virus (HDV) is the most severe form of viral hepatitis and affects nearly 5% of people living with chronic hepatitis B virus (HBV) infection. Chronic HDV infection results in more rapid progression to cirrhosis, hepatocellular carcinoma (HCC), and ultimately liver disease–related death compared with HBV monoinfection (HBV only). This retrospective study compared rates of disease progression between adult patients with HDV infection and HBV only in Italy. **Methods:** Administrative databases from local health units in Italy, covering nearly 12 million individuals, were screened for patients aged 18 years or older with an inpatient or outpatient claim (using *ICD-9-CM* or exemption codes, respectively) between 1/1/2009 and 6/30/2022. Patients with an HDV or HBV only diagnosis between 1/1/2010 and 6/30/2021 (identification period), no prior diagnosis, and at least 12 months of continuous capture before and after diagnosis were identified; the date of a patients' first diagnosis was their index date. Inverse probability of treatment weighting was calculated based on propensity scores (probability of having HDV vs HBV only, considering baseline demographics and clinical characteristics). The risks of disease progression between cohorts from noncirrhotic disease (NCD) to compensated cirrhosis (CC), CC to decompensated cirrhosis (DC), DC to HCC, HCC to liver transplantation (LT), and LT to death were compared using Cox proportional hazard regression and Kaplan-Meier curves. **Results:** Among 17,670 patients, 11,187 were included (HDV, n = 686; HBV only, n = 10,501). The mean (SD) age was similar between cohorts (HDV, 55.7 [16.2]; HBV only, 55.8 [16.4]; *P* = .845), as was the male to female ratio (approximately 2:1). Patients with HDV were more likely to progress from NCD to CC (hazard ratio [HR], 1.47; 95% CI, 1.08–1.98; *P* = .014), CC to DC (HR, 3.53; 95% CI, 1.60–7.75; *P* = .002), DC to HCC (HR, 2.79; 95% CI, 1.15–6.74; *P* = .023), and HCC to LT (HR, 6.23; 95% CI, 2.34–16.60; *P* <.001) compared to patients with HBV only; progression from LT to death was similar between patients with HDV and HBV only (HR, 1.32; 95% CI, 0.42–4.18; *P* = .637; Table). **Conclusion:** In Italy, patients with HDV have a significantly increased risk of progressing to greater liver disease severity compared to patients with HBV only, emphasizing the need for early screening, diagnosis, and treatment of HDV to slow disease progression.

Table. Cox Proportional Hazard Regression Results of Comparing Disease Progression Among Patients With HDV Infection vs HBV Monoinfection

Baseline State	Transition State				
	CC	DC	HCC	LT	Death
NCD	1.47 (1.08–1.98)	1.20 (0.80–1.79)	1.82 (0.98–3.40)	3.42 (1.12–10.43)	0.97 (0.77–1.21)
CC		3.53 (1.60–7.75)	1.54 (0.36–6.55)	9.61 (2.21–41.79)	1.79 (1.08–2.94)
DC			2.79 (1.15–6.74)	4.65 (2.04–10.64)	1.24 (0.71–2.15)
HCC				6.23 (2.34–16.60)	1.14 (0.83–1.58)
LT					1.32 (0.42–4.18)

Data are reported as hazard ratio (95% CI).
CC, compensated cirrhosis; **DC**, decompensated cirrhosis; **HBV**, hepatitis B virus; **HCC**, hepatocellular carcinoma; **HDV**, hepatitis delta virus; **LT**, liver transplant; **NCD**, noncirrhotic disease.

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Disclosures: Pietro Lampertico: ROCHE PHARMA/DIAGNOSTICS, GILEAD SCIENCES, GSK, ABBVIE, JANS: Advisor, Valentina Perrone: Nothing to Disclose, Luca Degli Esposti: Nothing to Disclose, Melania Leogrande: Nothing to Disclose, Chong Hoon Kim: Gilead Sciences, Inc.: Employee, Marvin Rock: Nothing to Disclose

1190 | PATIENTS WITH HEPATITIS DELTA VIRUS HAVE A HIGHER RISK OF DISEASE PROGRESSION THAN PATIENTS WITH HEPATITIS B VIRUS MONOINFECTION: RESULTS FROM A LARGE HEALTHCARE PROVIDER IN ISRAEL

Rawi Hazzan[1] Marvin Rock[2] Odelia Tassa-Liani[3] Yonatan Green[3] Clara Weil[4] Moshe Hoshen[4] Sivan Gazit[4] Chong Hoon Kim[2]

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Background: Patients with hepatitis delta virus (HDV) infection have a greater risk of liver disease progression compared to patients with hepatitis B virus monoinfection (HBV only). This study compared the rates of disease progression in adult patients with HDV vs HBV only using a large healthcare provider database in Israel. **Methods:** This retrospective cohort study used anonymized data from Maccabi Healthcare Services covering 2.7 million patients. Diagnosis (Dx) and laboratory data were used to identify patients with HDV or HBV only from 2005–2021. Adult patients (18 years or older) with chronic HBV (via *ICD-9* or positive laboratory test) who also had a Dx or positive HDV test result were included in the HDV cohort (index date = earliest of HDV Dx or positive test result). Patients who had an HBV Dx (*ICD-9* claims code), tested negative for HDV, and also did not have a prior HDV-positive test result were included in the HBV cohort (index date = date of first HDV-negative test result). Patient characteristics and disease state (noncirrhotic liver disease [NC], compensated cirrhosis, decompensated cirrhosis, liver cancer, liver transplant) at index were described. Post-index progression to a more advanced disease state or death was adjusted for baseline characteristics. **Results:** Of 1.8 million adult patients, 168 with HDV and 2,580 with HBV only were included. Median (IQR) age at index was 42.9 (33.3, 55.1) years for patients with HDV and 45.2 (34.4, 56.4) years for patients with HBV only. Overall, 54.8% and 58.8% of patients with HDV and HBV only, respectively, were male. Patients with HDV had a relatively lower socioeconomic status and higher baseline (BL) prevalence rate for HIV (4.2% vs 0.8%), hepatitis C virus (HCV) RNA+ (5.4% vs 1.6%), drug dependence (6.5% vs 1.6%), and alcohol abuse (6.0% vs 2.4%) vs HBV only. The risk of progression from NC (HDV, n = 42; HBV only, n = 152) was significantly higher in patients with HDV vs HBV only (adjusted HR: 4.4; 95% CI: 3.1, 6.4; P <.001; Figure). The risk of all-cause mortality from NC was significantly greater for patients with HDV vs HBV only (adjusted HR: 3.3; 95% CI: 1.9, 5.7; P <.001). **Conclusion:** In Israel, patients with HDV infection had higher BL prevalence of substance abuse and infection with HIV and HCV; they also had a higher risk of (1) disease progression and/or death, and (2) death alone, vs those with HBV only. These findings underscore the need for early screening, diagnosis, and eventual treatment of HDV to mitigate future disease progression.

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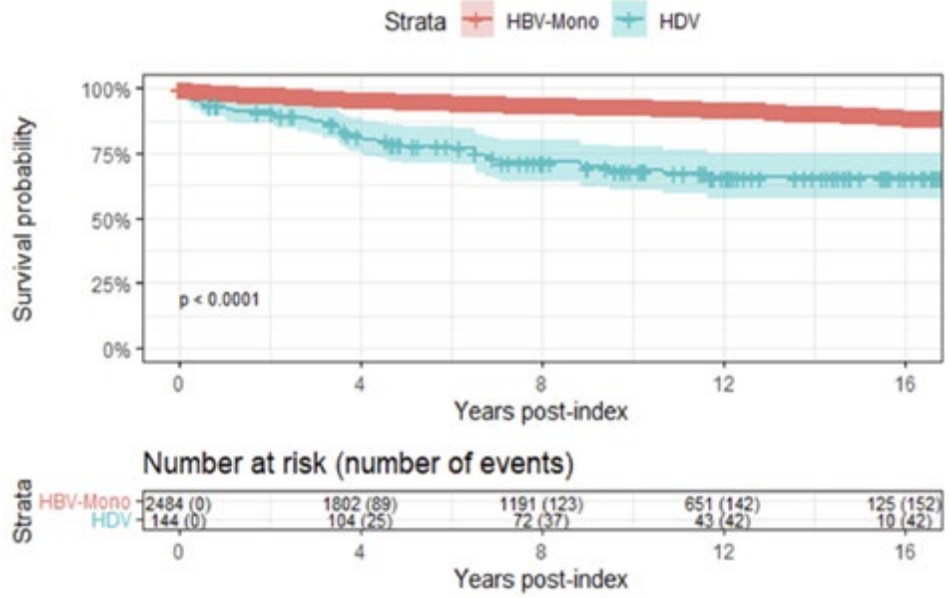

HBV-mono, hepatitis B virus monoinfection; HDV, hepatitis delta virus.

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1191 | EVALUATION OF COVID-19-RELATED DECOMPENSATION AND LONG-TERM ASSESSMENT OF POST COVID CONDITION IN PATIENTS WITH CIRRHOSIS (EVA-LONG COVID STUDY)

Madhumita Premkumar[1] Prerna Sharma[2] Rashmi Guru[2] Anchal Sandhu[2] Sahaj Rathi[2] Arka De[2] Nipun Verma[2] SUNIL TANEJA[2] Ajay Duseja[1] Virendra Singh[2] Kamal Kajal[2]

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Background: Patients with cirrhosis have worse outcomes after SARS-Cov-2 infection, including decompensation events [acute variceal bleeding (AVB), hepatic encephalopathy, & ascites] or death. Survivors of COVID-19 may experience long COVID or post-COVID condition (PCC), defined by the WHO as “the persistence or development of new symptoms after infection with SARS-CoV-2, with symptoms including cardiovascular, neuropsychiatric, musculoskeletal complications, and other health problems for over 2-3 months”. **Methods:** We enrolled consecutive patients with cirrhosis and COVID-19 managed at the specialized COVID-unit between January 2021 and January 2023. Following discharge, patients were longitudinally assessed for PCC and cirrhosis related decompensation events or deaths based on MELDNa and COVID-19 severity. Clinical data, scores for physical activity, depression, anxiety & PCC sequelae were documented using an electronic World Health Organization case record form for PCC from the Global COVID-19 Clinical Platform. Predictors of development of PCC, or risk of death were assessed. **Results:** We enrolled 252 patients had cirrhosis and COVID-19 (73% men, mean age 48.9±13.7 years, 35% alcohol associated, 34.5% MASLD related). Severity of COVID-19 was moderate (29.4%), severe (49.9%), and critical (27.8%). Of them 72 (28.6%) died during hospitalization and 180 (71.4%) were discharged following COVID-19 recovery. Of the 180 COVID survivors, only 79 were alive at 6 months post discharge. Over 1 year, 60(33.3%) met criteria for PCC, 19 (10.5%) had no sequelae and 101(56.1%) patients died(N=45) or were lost to follow up(N=56).Causes of death (N=45) were sepsis(16), progressive liver failure (20), AVB (2), hepatocellular carcinoma(7). On PCC tests, 47.1% patients scored ≤ 4 on the WHO physical function scale, 37.7% scored ≥ 1 on the MRC scale; 39.6% scored ≥ 5 on the GAD-7 scale, which corresponds to mild to moderate impairment. Patients with PCC were aged 47.6 years,

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63.3% men, alcohol associated-25%, MASLD-38.3% 18.3% viral hepatitis, and 33.3%, 23.3% and 43.3% with Child Pugh Class A, B and C respectively. Over 71% patients were fully vaccinated, 25% never received any COVID-19 vaccine, &3.3% reported getting only 1 dose. Patients with PCC had higher Charlson Comorbidity Index > 3 (28.3%) and >4(51.7%), with 45% having diabetes, and 56.7% with hypertension. Over a fourth of patients smoked or consumed tobacco. (Table 1) On multivariable Cox Proportional Hazards analysis, predictors of PCC were baseline MELDNa (HR 1.12, 95%CI:1.05-1.17, P<0.001), and age (HR 0.9, 95%CI 0.91-0.99, P=0.012). Predictors of mortality following COVID-19 recovery were MELDNa (HR 1.03, 95%CI:1.01-1.05, P=0.008), hypertension (HR 1.63, 95%CI 1.07-2.49, P=0.025) and age (HR 1.2, 95%CI 1.1-1.5, P=0.002) **Conclusion:** Patients with cirrhosis who survive COVID-19 remain at risk of decompensation, liver related deaths and Post COVID Condition.

Table 1: Prospective Evaluation for Patients with Cirrhosis following recovery from COVID-19

Parameters	Total N=180	Post Covid Condition (N=60)	No sequelae post COVID (N=19)	Deaths or lost to follow up (N=101)	P value
Age (years)	49.6 (47.6-51.7)	47.6 (44.3-50.8)	42.2 (35.7-48.7)	52.3 (49.5-55)	**0.005**
Male	127 (70.6%)	38 (63.3%)	14 (73.7%)	75 (74.3%)	0.323
Hypertension	78 (43.3%)	34 (56.7%)	10 (52.6%)	34 (33.7%)	**0.012**
Diabetes	58 (32.2%)	27 (45%)	4 (21.1%)	27 (26.7%)	**0.031**
Charlson Comorbidity index					**0.046**
1	19 (10.6)	6(10)	3(15.8)	10(9.8)	
2	35 (19.4)	6 (10)	8 (42.1)	21(20.8)	
3	48 (26.7)	17(28.3)	5 (26.3)	26 (25.7)	
≥ 4	78 (43.3)	31(51.7)	3(15.8)	44(43.6)	
Alcohol	73 (40.6%)	24 (40%)	11 (57.9%)	38 (37.6%)	0.254
Smoking	46 (25.6%)	15 (25%)	7 (26.8%)	24 (23.8%)	0.484
DISEASE ETIOLOGY					0.404
Alcohol associated	51 (28.3%)	15 (25%)	8 (42.1%)	28 (27.7%)	
MASLD	71 (39.4%)	23 (38.3%)	6 (31.6%)	42 (41.6%)	
Bilirubin (Total) mg/dl	10.6 (8.8-12.3)	8.5 (4.9-12)	11.2 (5.6-16.8)	11.6 (9.5-13.8)	0.270
Albumin g/dl	2.8 (2.7-2.9)	3 (2.8-3.2)	3.1 (2.8-3.5)	2.6 (2.4-2.8)	**0.004**
AST IU/L	128 (105.3-150.8)	115.6 (66.4-164.9)	99.5 (41.9-157.2)	140.6 (113.5-167.7)	0.428
ALT IU/L	86.5 (67.5-105.6)	82.8 (35.7-130)	66.2 (20-112.4)	92.5 (73.5-111.5)	0.691
INR	1.9 (1.6-2.2)	1.7 (1.4-2)	1.8 (1.3-2.4)	2 (1.6-2.5)	0.506
Creatinine mg/dl	1.3 (1.1-1.4)	1.2 (1-1.4)	1.4 (0.6-2.3)	1.3 (1.1-1.5)	0.627
Severity of first COVID episode					0.219
Moderate	67(37.2)	23(38.3)	4 (21.1)	40 (39.6)	
Severe	106(58.9)	36 (60)	15 (78.9)	55 (54.5)	
Critical	7 (3.9)	1(1.7)	0	6(5.9)	
Second Episode of COVID-19	51 (28.3%)	32 (53.3%)	1 (5.3%)	18 (17.8%)	**<0.001**
Child Pugh Score					**0.013**
A	35 (19.4%)	20 (33.3%)	2 (10%)	13 (12.9%)	
B	40 (22.2%)	14 (23.3%)	5 (26.3%)	21 (20.8%)	
C	105 (58.3%)	26 (43.3%)	12 (63.2%)	67 (66.3%)	
MELD-Na					**0.030**
MELD-Na 10-15	75 (41.7%)	34 (56.7%)	7 (36.8%)	34 (33.7%)	
MELD-Na 16-20	19 (10.6%)	4 (6.7%)	4 (21.1%)	11 (10.9%)	
MELD-Na>21	86 (47.8%)	22 (36.7%)	8 (42.1%)	56 (55.4%)	

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to Disclose, Nipun Verma: Nothing to Disclose, SUNIL TANEJA: Nothing to Disclose, Ajay Duseja: Nothing to Disclose, Virendra Singh: Nothing to Disclose, Kamal Kajal: Nothing to Disclose

1192 | THE ASYMMETRY OF THE LIVER AND SPLEEN STIFFNESS MEASURES BETWEEN PATIENTS WITH CHRONIC HEPATITIS B AND D REFLECTS IMPORTANT CLINIC-PATHOLOGIC DIFFERENCES

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Background: Chronic HDV infection causes an additional pathologic burden in patients (pts) with chronic HBV infection that accounts for their worse clinical outcome. We studied the relative differences in liver (LSM) and spleen stiffness measurements (SSM) in a single center cohort of pts with chronic hepatitis B (CHB) and D (CHD), in order to point out potential added values of the SSM in this clinical setting **Methods:** We studied 119 HBsAg+ pts, 71 CHB and 48 CHD [30(42.3%) and 27(56.3%) with cirrhosis, respectively] undergoing regular follow-up at the Hepatology Unit of Pisa University Hospital. Fifty-two (73.2%) CHB were on NUC and 15 (31.3%) CHD pts on Bulevirtide (BLV) therapy. Physical examination, ultrasound scan (US), LSM and SSM (FibroScan®, Echosens, France) were performed on the same day, liver biochemistry and virological assays within one week **Results:** Table 1 shows the comparison of demographic, clinical and laboratory characteristics in CHB and CHD pts. Median LSM was lower in CHB than in CHD pts [6.2(2.8-71) vs 8.1(2.8-33.1) kPa (p=0.004)], whereas SSM was similar [25.6(9.3-87.6) vs 26.8 (4.8-100) kPa (p=0.569)]; accordingly, median SSM/LSM ratio was lower in CHD than in CHB [2.98(1.00-9.64) vs 3.88 (1.09-16.25), p=0.003). Median spleen diameter (SD) was 11.0 (7.0-18.0) cm in CHB and 12.0 (6.5-23.0) cm in CHD (p=0.079). CHD pts showed a significantly lower SD/LSM ratio [1.33(0.36-3.89) vs 1.78(0.21-4.08), p=0.007], but similar SD/SSM ratio [0.44 (0.14-2.06) vs 0.43 (0.14-1.07), p=0.688]. Also among pts diagnosed with cirrhosis, median LSM was significantly lower in CHB than in CHD [9.7(3.7-71) vs 13.3 (5.6-33.1) kPa, p=0.022], whereas SSM was similar [34.0(9.9-87.6) vs 33.3(14.5-100) kPa, p=0.842]. The SD/LSM ratio showed a trend to be lower in cirrhotic CHD [0.92 (0.36-2.09) vs 1.20 (0.21-2.89), p=0.054]. In CHD, as compared to CHB pts, SSM correlated better with LSM, overall (r=0.761 vs r=0.465) and in cirrhotics (r=0.799 vs r=0.432); with SD overall (r=0.643 vs r=0.489) and in cirrhotics (r=0.647 vs r=524) and with platelets count overall (r=-0.617 vs r=-0.498) and in cirrhotics (r=-0.726 vs r=-0.638). **Conclusion:** The combined measure of liver and spleen stiffness provides a useful differential clinic pathologic characterization of liver disease in patients with chronic HBV and HDV infection. The significantly lower SD/LSM ratio found in CHD pts, suggests underlines the specific role of HDV induced necro-inflammation as a driver of disease progression with splenomegaly and platelet count reduction. Longer follow up in CHD treated patients are needed to define the curative impact of the current antivirals.

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Variables		HDV N=48	HBV N=71	p
Age	yrs	47.8 (20.2-74.8)	58.9 (28.9-86.4)	**<0.001**
Gender	F M	21 (43.8) 27 (56.3)	17 (23.9) 54 (76.1)	**0.038**
Country	Italy Other	18 (37.5) 30 (62.5)	52 (73.2) 19 (26.8)	**<0.001**
BMI	Kg/m^2	24.6 (17.3-43.1)	24.9 (18.8-51.8)	0.497
Cofactors	MASLD HCV (SVR) Alcohol	21 (43.8) 5 (10.4) 5 (10.4)	22 (31.0) 4 (5.6) 9 (12.7)	0.220 0.539 0.932
Cirrhosis	Yes No	27 (56.3) 21 (43.8)	30 (42.3) 41 (57.7)	0.189
HBV Genotype	D Non D	18 (90.0) 2 (10.0)	43 (72.9) 16 (27.1)	0.204
HBV DNA	Log IU/mL	1.00 (0.70-4.38)	0.70 (0.70-8.30)	0.951
HBsAg	Log IU/mL	3.65 (-0.70 / 4.75)	2.61 (-0.70 / 5.07)	**<0.001**
NUC Therapy	Yes No	34 (70.8) 14 (29.2)	51 (71.8) 20 (28.2)	1.000
AST	U/L	28 (11 - 155)	24 (11 - 218)	**0.014**
ALT	U/L	27 (9 - 160)	19 (5 - 219)	**0.001**
gGT	U/L	24 (11 - 152)	20 (8 - 290)	*0.082*
ALP	U/L	87 (36 - 141)	76 (39 - 161)	**0.044**
Albumin	g/dL	4.3 (3.2 - 4.9)	4.5 (2.8 - 5.1)	**0.002**
PLTs	n/mmc	176 (33 - 341)	187 (20 - 489)	*0.066*
INR		1.06 (0.90 - 1.49)	1.04 (0.87 - 2.84)	0.476
AFP	ng/mL	3.3 (0.9 - 60.9)	2.3 (0.9 - 79.4)	**0.005**
Bilirubin	mg/dL	0.66 (0.13 - 3.05)	0.59 (0.18 - 2.58)	0.358

Disclosures: Francesco Damone: Nothing to Disclose, Piero Colombatto: Gilead Sciences: Speaking and Teaching, Abbvie: Consultant, Ipsen: Consultant, Andrea Pinna: Nothing to Disclose, Gabriele Ricco: Nothing to Disclose, Daniela Cavallone: Nothing to Disclose, Giovanni Petralli: Nothing to Disclose, Lorenzo De Stefano: Nothing to Disclose, Barbara Coco: Nothing to Disclose, Lidia Surace: Nothing to Disclose, Filippo Oliveri: Nothing to Disclose, Ferruccio Bonino: Nothing to Disclose, Maurizia Brunetto: Nothing to Disclose

1193 | PATIENT-REPORTED OUTCOMES AMONG PATIENTS WITH CHRONIC HEPATITIS DELTA TREATED WITH BULEVIRTIDE 2 MG: A LONG-TERM ANALYSIS OF THE PHASE 3 MYR301 TRIAL AT 144 WEEKS

Maria Buti[1] Heiner Wedemeyer[2] Soo Aleman[3] Vladimir Chulanov[4] Viacheslav Morozov[5] Olga Sagalova[6] Tatyana Stepanova[7] Robert Gish[8] Andrew Lloyd[9] Vithika Suri[10] Dmitry Manuilov[10] Grace Chee[10] Audrey Lau[10] Anu Osinusi[10] John Flaherty[10] Marvin Rock[10] Chong Hoon Kim[10] Shubhram Pandey[11] Barinder Singh[11] Pietro Lampertico[12]

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Background: Patients with chronic hepatitis delta (CHD) are at significant risk of developing cirrhosis, hepatic decompensation, and hepatocellular carcinoma.[1] Bulevirtide (BLV) monotherapy improved health-related quality of life in patients with CHD at 24 and 48 weeks (W) compared to a control group who did not receive treatment for CHD.[2,3] This presentation specifically focuses on an exploratory analysis of Hepatitis Quality of Life Questionnaire (HQLQ) outcomes among patients with CHD who received 144W of treatment with BLV 2 mg as part of an ongoing trial. **Methods:** In MYR301 (NCT03852719), a Phase 3, randomized, multicenter, open-label,

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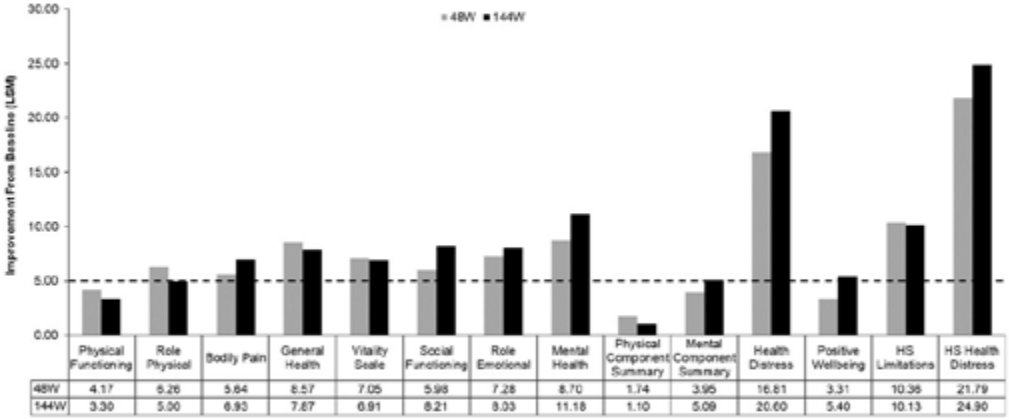
parallel-group trial, 150 patients with CHD were randomized (1:1:1) to 3 treatments: BLV 2 mg (n = 49) or BLV 10 mg (n = 50) for 144W or delayed treatment (DT; n = 51) for 48W followed by BLV 10 mg for 96W. This presentation focuses on BLV 2 mg, the dose approved for use in the EU. Patients completed the HQLQ, comprising the 36-Item Short Form Health Survey questionnaire and 4 hepatitis-specific (HS) health domain scores (15 supplemental items), on their own at key time points, including baseline (BL), 24W, 48W, 96W, and 144W. Higher scores on the HQLQ (range 0–100) indicate better health-related quality of life. **Results:** At BL, demographic characteristics and HQLQ domain scores were similar across groups. By 144W, 4 patients each dropped out of the BLV 2 mg and DT groups and were excluded, which may have introduced potential bias. In comparison to their BL scores, mean HQLQ outcomes for those who received BLV 2 mg were improved in all domains at 144W, except for the physical component summary (Figure). The mean score improvements from BL were ≥5 points for 12 of 14 domains, and substantial mean score improvements (>10 points) were reported for the 2 HS health domains—HS limitations and HS health distress. The HQLQ improvements observed at 24W and 48W with BLV 2 mg were sustained or further improved at 144W. **Conclusion:** Patients with CHD treated with BLV 2 mg for 144W showed improvements across nearly all domains of the HQLQ, including 2 HS health domains, which were maintained or enhanced vs earlier findings, thus demonstrating the long-term benefits of BLV 2 mg monotherapy.
References:1. Lampertico P, Roulot D, Wedemeyer H. *J Hepatol*. 2022;77(5):1422-30; 2. Buti M, Wedemeyer H, Aleman S, et al. *J Hepatol*. 2022;77(Supp 1):S013; 3. Wedemeyer H, Aleman S, Chulanov V, et al. Presented at: AASLD The Liver Meeting. November 12-16, 2021. https://www.natap.org/2021/AASLD/AASLD.htm

Figure. Mean Improvement From Baseline to 144 Weeks in HQLQ Domain Scores Among Patients With CHD Treated With BLV 2 mg



BLV, bulevirtide; CHD, chronic hepatitis delta; HQLQ, Hepatitis Quality of Life Questionnaire; HS, hepatitis-specific; LSM, least squares mean; W, week.

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1194 | PHARMACOKINETICS, PHARMACODYNAMICS, AND SAFETY OF BULEVIRTIDE 2 MG ONCE-DAILY FOR 6 DAYS IN PARTICIPANTS WITH NORMAL AND SEVERELY IMPAIRED RENAL FUNCTION

Yehong Wang[1] Renee-Claude Mercier[2] Wildaliz Nieves[1] David Pan[1] Steve Tseng[2] Xu Zhang[2] Carrie Nielson[2] Ann Qin[2] Parag Kumar[2]

[1]Gilead Sciences, Inc, [2]Gilead Sciences, Inc.

Background: Bulevirtide (BLV, Hepcludex®) is a 47-amino acid lipopeptide approved in the EU for the treatment of hepatitis delta virus (HDV) infection that acts by binding to the sodium taurocholate co-transporting polypeptide (NTCP) receptor and blocking entry of HDV into hepatocytes. By inhibiting NTCP, BLV causes asymptomatic and transient elevations of bile acids (BAs). Despite having a low molecular weight (~5 kDa) that could theoretically undergo glomerular filtration, BLV is unlikely renally eliminated due to very high plasma protein binding (> 99 %). Clinical data on the use of BLV in renal impairment (RI) population is currently limited to HDV patients with mild RI. This study assessed the pharmacokinetics (PK), pharmacodynamics (PD), and safety of multiple doses of BLV in participants with severe renal impairment (RI) compared to matched controls with normal renal function. **Methods:** This was a Phase 1, open-label, multicenter, multiple-dose study in HDV-uninfected participants with severe RI (eGFR ≥15 to ≤ 29 mL/min/1.73 m², n=10) and matched controls (matched for age [± 10 years], sex, and BMI [± 20%]) with normal renal function (n=10) treated with BLV 2 mg subcutaneously (SC) daily for 6 days. Intensive plasma BLV PK and PD (BA) samples were assessed on Day 1 and at steady state on Day 6. Maximum plasma concentration (C_{max}) and area under the time-vs-concentration curve over 24 hours (AUC_{τ}) were evaluated and geometric mean ratios (GMR) with 90% confidence intervals (CI) were calculated. Safety was assessed by clinical laboratory tests and evaluation of adverse events (AEs). **Results:** After daily dosing for 6 days, BLV showed no accumulation in C_{max} and mild accumulation (~70%) in AUC_{τ} on Day 6 compared to Day 1 in both severe RI and control groups. On Day 6, slightly faster apparent clearance and increased apparent volume of distribution were observed in severe RI than controls, but the mean BLV half-life (hours) were similar (severe RI: 4.7, matched controls: 4.5). GMR (90% CI) of PK exposures on Day 6 demonstrated similar drug exposures between the two groups: C_{max}: 1.06 (0.64 – 1.75); AUC_{τ}: 0.84 (0.6 – 1.19). Total BAs showed similar trends of transient elevations after dosing on Day 6 for both groups and returned to near baseline values after 24 hours post-treatment. The frequency of treatment-emergent (TE) AEs and laboratory abnormalities were numerically similar between both groups and there were no serious AEs, AEs leading to BLV discontinuation, or Grade ≥ 3 TEAEs related to BLV. **Conclusion:** Following 6 days of BLV 2 mg SC daily dosing, there were no differences in BLV PK exposures and total BA change from baseline between participants with severe RI and matched controls. BLV was generally safe in severe RI participants. The results of this study support the use of BLV without dose adjustment in the RI population from the approved 2 mg daily SC dosing.

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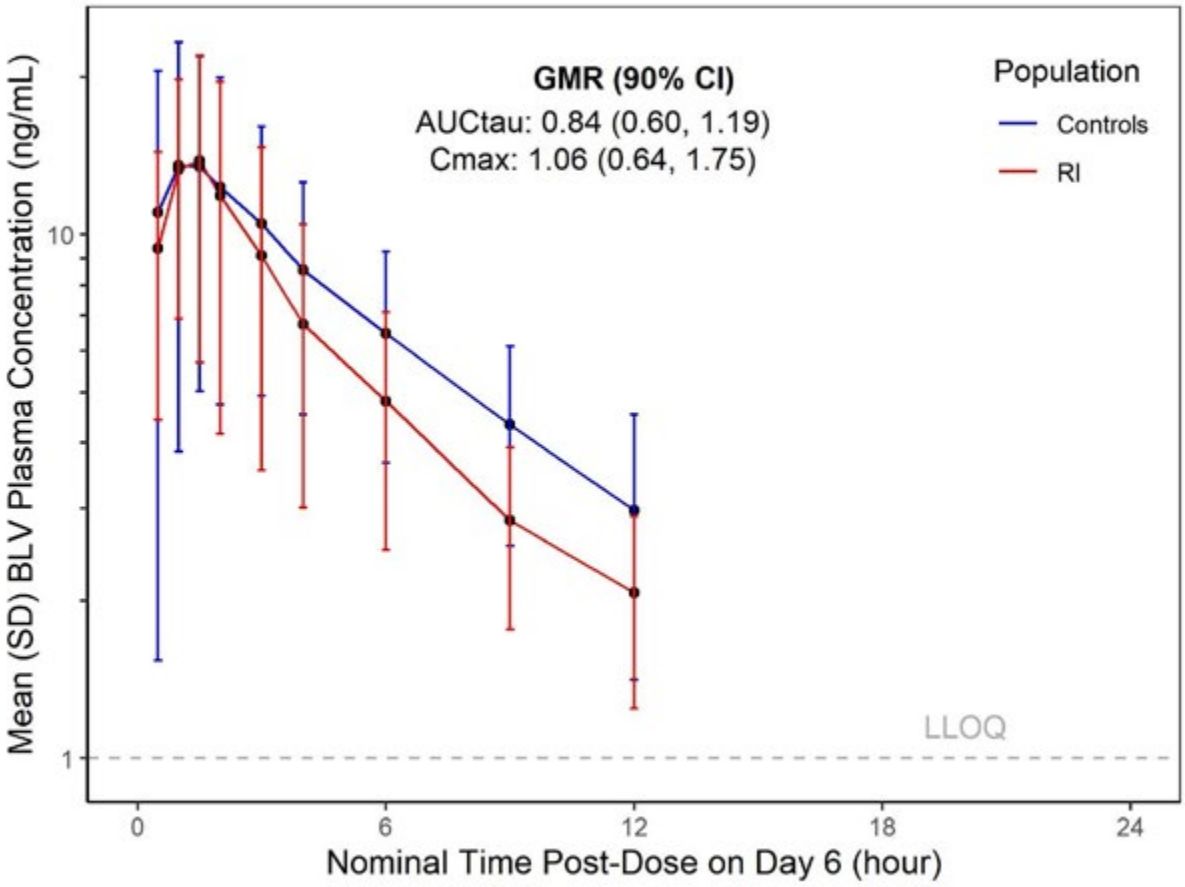
Figure 1: Semi-log Plot of Mean (SD) Plasma Concentrations of Bulevirtide on Day 6 Following 2 mg Subcutaneous Once-Daily Dosing in Participants with Severe RI and Matched Controls



AUCτ: Area under the time-concentration plasma curve over 24 hours; BLV: bulevirtide; CI:confidence interval; Cmax: maximum plasma concentration; Controls: matched healthy control participants; GMR; geometric mean ratio; LLOQ: lowest limit of quantification; RI: renal impairment; SD: standard deviation. PK sampling on Day 6 includes timepoints at predose (≤ 30 minutes before dose), 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12, 24, and 48 hours postdose. No data point is shown at 24 hours postdose due to concentrations below the limit of quantification.

Disclosures: Yehong Wang: Nothing to Disclose, Renee-Claude Mercier: Nothing to Disclose, Wildaliz Nieves: Gilead Sciences, Inc.: Employee, David Pan: Nothing to Disclose, Steve Tseng: Gilead Sciences, Inc.: Employee, Xu Zhang: Nothing to Disclose, Carrie Nielson: Gilead Sciences: Employee, Gilead Sciences: Stock - publicly traded company, Ann Qin: Nothing to Disclose, Parag Kumar: Gilead Sciences, Inc.: Employee, Gilead Sciences, Inc.: Stock - publicly traded company

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1195 | HEPATITIS A INFECTION DECREASES AMINO ACID AND SCFA METABOLISM BY GUT BACTERIA, COMPROMISING GUT BARRIER INTEGRITY AND CONTRIBUTING TO ACUTE LIVER FAILURE

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Background: Acute hepatitis A virus (AVH-A) infection is typically self-resolving but can rarely cause acute liver failure (ALF). As an enteric virus, HAV may alter gut microbiota and metabolites to influence the disease pathogenesis. This study aims to characterize the metagenomic and metabolomic shifts in acute HAV and ALF-A. **Methods:** Seventy subjects (24±4 yrs, bilirubin >2 mg/dL) with i) acute viral hepatitis (AVH), IgM HAV positive (AVH-A, n=27, ALT/AST>5xULN), ii) acute liver failure (ALF-A, n=23, ALT/AST>10xULN) and healthy (HC, n=20). Stool was assessed for gut microbiota via 16S rRNA sequencing and plasma was subject to untargeted metabolomics. **Results:** Alpha diversity analysis showed decrease in Shannon index from HC to AVH-A and ALF-A ($p<0.0001$). Bray-Curtis dissimilarity indicated distinct clustering, reflecting significant differences in microbial community structure. Random forest analysis revealed that beneficial bacteria, *Dorea* ($p=0.0016$,$p=0.007$), *Prevotella* ($p=0.0016$,$p=0.007$), and *Romboutsia* ($p=0.0016$,$p=0.0043$) progressively decreased from HC to AVH-A and ALF-A, with significant reductions at each stage. *Streptococcus* ($p=0.0016$,$p=0.007$) and *Faecalibacterium* ($p=0.0031$,$p=0.007$) increased from HC to AVH-A but significantly decreased in ALF-A. There was marked elevation of pathogenic *Enterococcus* in ALF-A in comparison to AVH-A ($p=0.0007$) and HC ($p=0.0043$). Pathway analysis of bacteria-associated clusters, identified through correlation clustering, revealed histidine, butanoate, and tryptophan metabolism were the most impacted. Metabolite levels indicated reduced histamine degradation, decreased tryptophan metabolism and butanoate production in ALF-A compared to AVH-A. **Conclusion:** HAV infection alters gut microbiota, increasing pathobionts in ALF, while beneficial bacteria progressively decrease from HC to AVH-A to ALF-A. These changes in bacterial composition affect tryptophan and histidine metabolism which impacts immune response, serotonin production, antioxidant defenses and butanoate metabolism (crucial for maintaining gut lining integrity and reducing inflammation). Restoring gut dysbiosis could be a therapeutic target in patients with ALF due to HAV.

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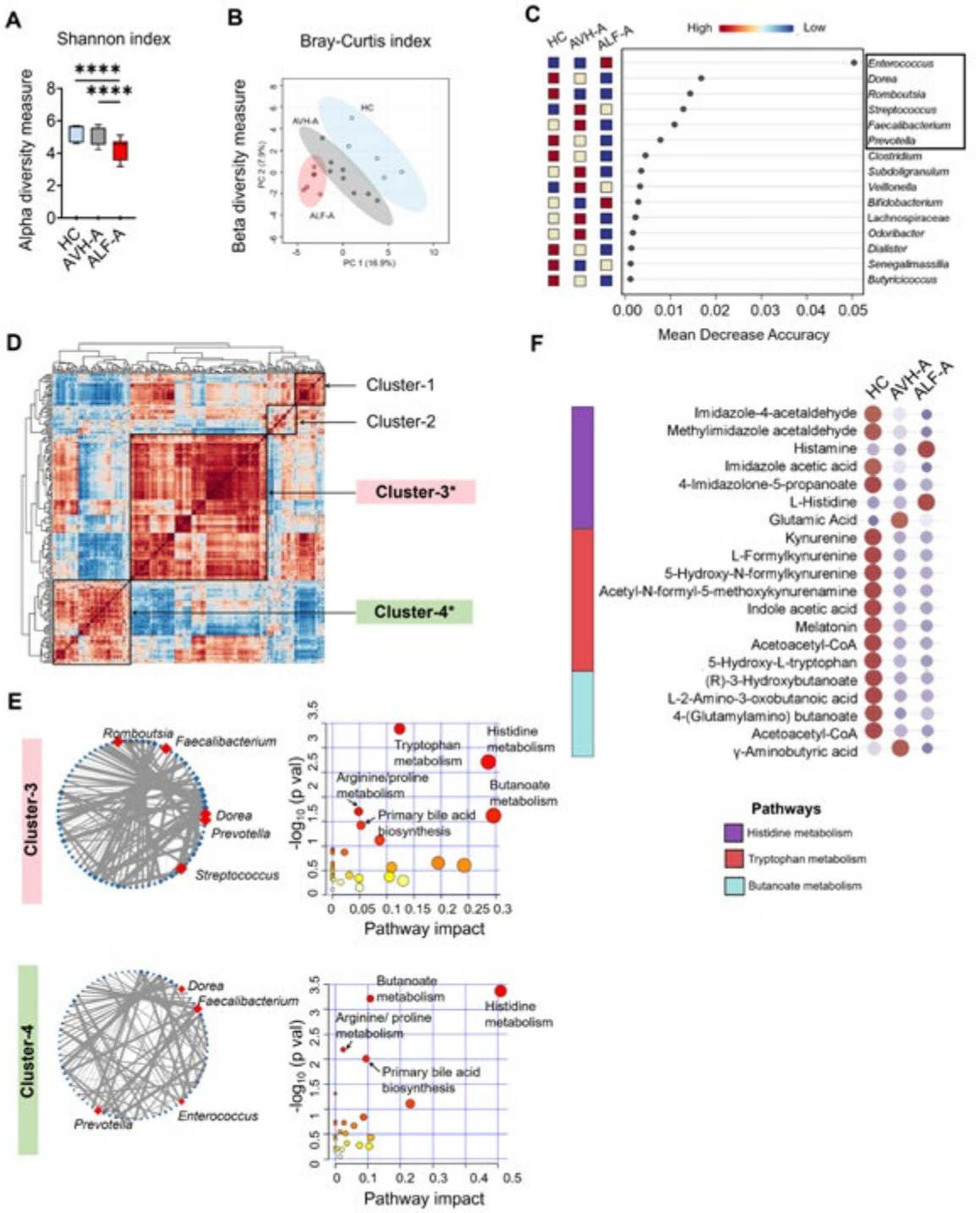

Figure (A) Shannon index, an alpha diversity measure, evaluated for healthy controls (HC), patients with acute hepatitis A (AVH-A), and patients with hepatitis A-induced acute liver failure (ALF-A). (B) Beta diversity assessed using the Bray-Curtis dissimilarity index, depicted through principal coordinates analysis (PCoA) for separation among HC, AVH-A, and ALF-A groups. (C) Importance of bacterial taxa determined by mean decrease accuracy in a random forest classification model differentiating between the groups. (D) Heatmap with hierarchical clustering of bacteria and metabolites distinguishing four primary clusters. Asterisks (*) indicate clusters containing significant bacterial correlations. (E) Bacterial-metabolite network analysis for Cluster-3 and Cluster-4; Bubble plot of pathway impact analysis for HC, AVH-A, and ALF-A groups. The x-axis represents pathway impact, while the y-axis represents the -log$_{10}$(p-value). Larger and darker circles represent pathways with higher impact and significance. (F) Balloon plot showing the normalized values of key metabolites across the HC, AVH-A, and ALF-A groups. Metabolites are listed on the left, and pathways are color-coded. The color gradient indicates the normalized value of each metabolite, with darker shades representing higher concentrations.

Disclosures: Anoushka Saxena: Nothing to Disclose, Rakhi Maiwall: Nothing to Disclose, Jaswinder Maras: Nothing to Disclose, Shiv Kumar Sarin: Nothing to Disclose, Nirupma Trehanpati: Nothing to Disclose

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1196 | HEPATITIS E VIRUS INDUCED METABOLOMIC AND IMMUNE SHIFT IN ACUTE LIVER FAILURE IS ASSOCIATED WITH OBSTETRIC COMPLICATIONS DURING PREGNANCY

Anoushka Saxena[1] Minal .[2] Prabhjyoti Pahwa[3] Jaswinder Maras[1] Hamda Siddiqui[1] Jayesh Kumar Sevak[3] Y.M. Mala[2] Shakun Tyagi[2] Shiv Kumar Sarin[1] Nirupma Trehanpati[1]

[1]Institute of Liver and Biliary Sciences, India, [2]Maulana Azad Medical College, India, [3]Institute of Liver and Biliary Sciences

Background: Hepatitis E virus (HEV) induced liver failure during pregnancy leads to maternal and fetal complications. This study investigates the HEV associated metabolomic and immunological changes to elucidate worsening obstetric outcomes. **Methods:** Seventy six pregnant women (24±2 yrs, bilirubin >2 mg/dL) with i) acute viral hepatitis (AVH), IgM HEV positive (AVH-E, n=31, ALT/AST>5xULN, Gr.I), ii) acute liver failure (ALF-E, n=15, Gr.II), iii) acute hepatitis negative for HBsAg, HEV, HAV, CMV (non-HEV, n=30, ALT/AST>2xULN, Gr.III), and healthy pregnant women (HC, n=21, Gr.IV) were evaluated at delivery for untargeted plasma metabolomics, cytokine and immune profiling supported by multivariate statistics. **Results:** Patients with AVH-E demonstrated a T_H1 milieu with low levels of choline, proline, but elevated pro-inflammatory cytokines, contributing to onset of pre-term spontaneous labor, eclampsia, disseminated intravascular coagulation (DIC), pre-term premature rupture of membranes (PT-PROM), and mortality. In patients with acute hepatitis (Gr.III) increased levels of choline, proline and T_H2 dominance at delivery posed a higher risk of induced labor, small-for-gestational-age infants with low birth weight. In ALF-E (Gr.II) patients, low choline, phosphocholine, palmitoyl carnitine, along with increased taurocholic acid, impaired plasmablast and memory T cell formation, correlated with pre-term spontaneous labor, eclampsia, DIC, PT-PROM, higher maternal mortality, increased rates of intrauterine death and abortion. The metabolic and immune alterations in Gr.II were distinctly different with Gr.I patients and can help in predicting the outcome of AVH-E in pregnancy. **Conclusion:** In HEV infection, choline, phosphocholine, and palmitoyl carnitine decrease from AVH-E to ALF-E, while taurocholic acid increases. These alterations in the plasma metabolome further impair immune responses, causing severe obstetric complications, including increased pre-term spontaneous labor, intrauterine death, and higher maternal mortality in ALF-E.

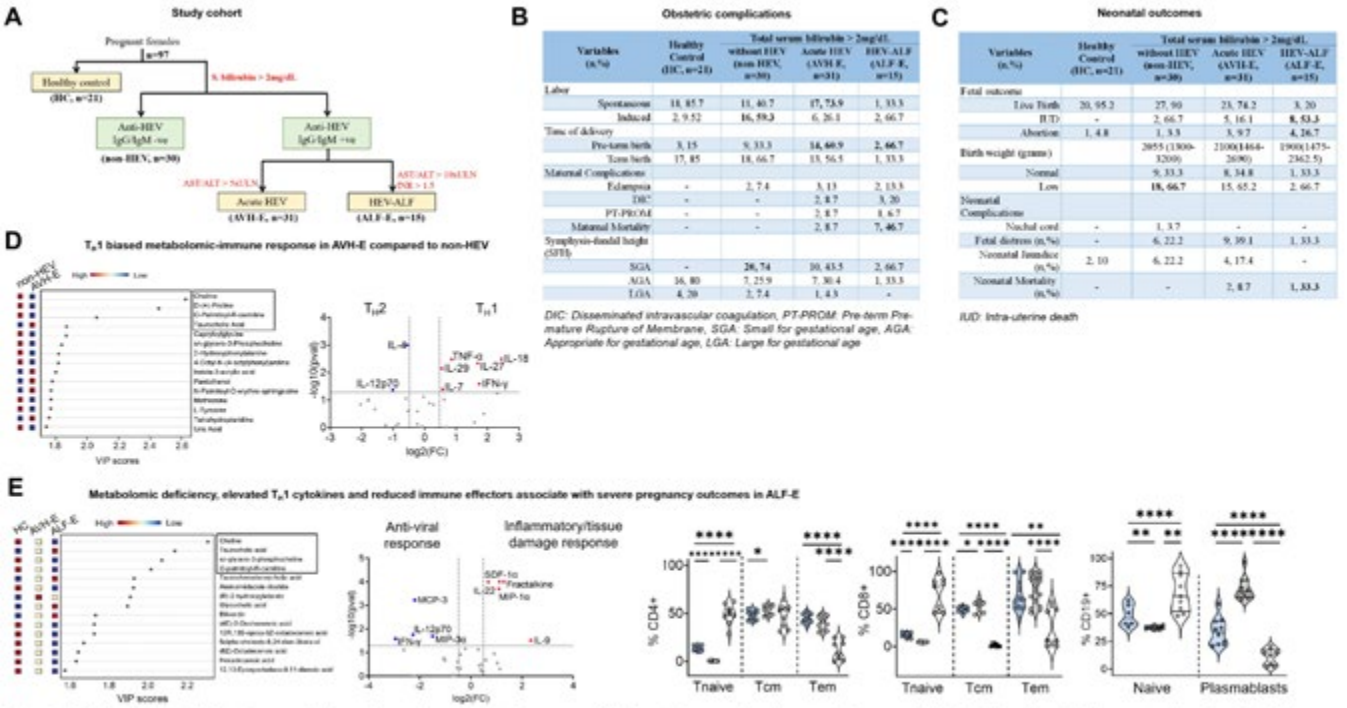

Figure (A) Cohort design. (B) Obstetric complications observed across the study groups. (C) Neonatal outcomes in different study groups. (D) Visualization of variable importance in projection (VIP) scores, highlighting metabolites with significant differential expression between AVH-E and non-HEV. (VIP score>2.0 are considered). Colored boxes on the left indicate the relative concentration of corresponding metabolite; Volcano plot showing significant cytokine variations between AVH-E and non-HEV, displayed by log_2 FC and $-log_{10}$(p-value). (E) VIP scores derived from the partial least squares-discriminant analysis (PLS-DA) highlight metabolites with significant differential expression across groups; Volcano plot showing differential cytokine levels between ALF-E and AVH-E, highlighting significantly altered cytokines; Proportion of CD4+, CD8+, CD19+ subsets

Disclosures: Anoushka Saxena: Nothing to Disclose, Minal .: Nothing to Disclose, Prabhjyoti Pahwa: Nothing to Disclose, Jaswinder Maras: Nothing to Disclose, Hamda Siddiqui: Nothing to Disclose, Jayesh Kumar Sevak:

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Nothing to Disclose, Y.M. Mala: Nothing to Disclose, Shakun Tyagi: Nothing to Disclose, Shiv Kumar Sarin: Nothing to Disclose, Nirupma Trehanpati: Nothing to Disclose

1197 | PYOGENIC LIVER ABSCESS: NATIONAL FINDINGS ON DEMOGRAPHICS, INTERVENTIONS, AND OUTCOMES

Faris Shweikeh[1] Naga Venkata Rama Krishna Vura[2] Yaritza Torres[3] Neha Sharma[2] Anthony Leung[1] Anamay Sharma[4]

[1]Cleveland Clinic Akron General, [2]UT San Antonio, [3]Northeast Ohio Medical University, [4]University Hospitals Cleveland Medical Center/Case Western Reserve University

Background: About 80% of liver abscess (LA) cases in the Western world have a bacterial etiology. Underlying hepatobiliary conditions can result in higher risk for development and it is associated with significant morbidity and mortality. Treatment includes antibiotics and abscess drainage, either percutaneously or surgically. Our aim was to report on epidemiological characteristics and compare treatments for LA based on a national database. **Methods:** The study utilized the National Inpatient Sample between 2017 - 2020. The subpopulation, comorbidities, and procedure variables were defined by ICD-10 codes. The differences in patient and hospital characteristics were compared using the Chi-square or Fisher's exact test for categorical variables and unpaired t-test for continuous variables. Logistic univariate and multivariate regression analyses adjusted for age, sex, race, insurance status, median household income, hospital location, and teaching status. **Results:** Approximately 20,055 admissions for LA occurred. Compared to all hospitalizations, LA had higher age (61.1 vs. 49.9 years), more likely in males (60.5% vs. 44.1%) and more associated with private insurance (34.0% vs. 29.2%) ($p<0.001$). Comorbidities included gallbladder/biliary disease (12.6%), chronic liver disease (12.5%), chronic kidney disease (11.1%), and inflammatory bowel disease (IBD) (2.2%). Treatments were 7,780 (38.8%) with percutaneous catheter drainage (PCD), 2,705 (13.5%) percutaneous needle aspiration (PNA), 1,345 (6.7%) with surgery, 7,070 (35.3%) with medical management only (MMO), and 1,155 (5.7%) with a combination. Comorbidities of hepatobiliary malignancy and IBD had higher likelihoods of MMO ($p<0.001$). PCD with higher length of stay than PNA (7.8 vs 6.6 days, $p < 0.001$). Roughly 55.3% of PNA were discharged routinely (i.e. to home) vs.43.3% of PCD and 46.4% of MMO ($p<0.001$). More Hispanics with surgery (9.3% vs. 6.9%, $p =0.005$) and Blacks with MMO (39.7% vs. 37.1%, $p<0.001$). Overall, mortality at 3.3%. **Conclusion:** We report on several national disparities in LA, particularly in Hispanics and Blacks. It is more likely in males and private insurance reimbursement, although it is in significantly older patients. PCD was more likely utilized, although an overwhelming number received MMO. Concurrent malignancy and IBD are linked to higher MMO. Given better clinical outcomes profile, PNA may be a sounder choice over PCD. Finally, mortality rate is much lower than historically reported.

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1198 | HEPATITIS DELTA VIRUS AWARENESS AND SCREENING AMONG IMMIGRANTS IN THE METROPOLITAN-DC AREA

Christine Lin[1] Angeline Nguyen[2] Chooson Byambaa[2] Hai Chi Le[2] Jennifer Galdamez[2] Sandra Marrero-Ashford[2] Lydia Tang[1]

[1]University of Maryland, Baltimore, [2]Health Betterment Initiative

Background: Hepatitis delta virus (HDV) is the most aggressive form of human viral hepatitis and co-infects people with chronic hepatitis B (HBV), tripling the risk of liver cancer. HDV screening, however, is not routinely done. In Metropolitan-DC, 5% of African, Asian, and Latin American immigrants have HBV (10x the national average) and are at risk of HDV. These communities would benefit from increased HDV education and screening. Health Betterment Initiative (HBI) provides HBV screening and linkage-to-care in Metropolitan-DC. HBI community health workers (CHWs) have diagnosed over 500 people (90% immigrants) with HBV since 2017. This project aims to evaluate HDV screening among HBV-positive immigrants. **Methods:** HD-METRO is a CHW-led education intervention aimed at increasing HDV screening among people with HBV implemented in May 2023. People

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diagnosed with HBV by HBI from 2017 to May 2023 were invited to participate in a survey to determine pre-intervention HDV testing. Association between participant characteristics and HDV testing was done with logistic regression or χ2-test. **Results:** As of May 2024, HBI has contacted 160 people, and 49 have participated. Most participants were from Mongolia (40%) and Vietnam (21%), and 24 (41%) were from African countries. All but 2 surveys were in a language other than English. Sixty-seven percent had seen a doctor for HBV (45% with hepatology or infectious diseases). Fifty-five percent had not heard of HDV and did not know that people with HDV were at risk of HDV. Forty-four percent reported HDV testing, and of these, 89% knew their results. Report of HDV testing was strongly associated with follow up with a specialist compared to follow up with primary care ($p<0.001$). There was no association between age, length of time in US, insurance, nor having a primary care doctor with HDV testing. **Conclusion:** Findings indicate good linkage-to-care for HBV, but low HDV screening with a greater likelihood for screening if seen by a specialist. Outreach to primary care providers may improve HDV screening rates among this at-risk population.

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1199 | SPECTRUM OF HEPATITIS A VIRAL INFECTION AND RELATED MORTALITY FROM A TERTIARY CARE CENTRE IN SOUTH EAST ASIA REGION : TIME FOR A NEW ERA

Manasa Alla[1] Anand Kulkarni[2] Mithun Sharma[3] Shantan Venishetty[1] Sowmya T R[1] Nagaraja Rao Padaki[1] Nageshwar Reddy Duvvur[1]

[1]AIG Hospitals, [2]Asian Institute of Gastroenterology, [3]ASIAN INSTITUTE OF GASTROENTROLOGY PVT LTD

Background: Viral Hepatitis A is an important public health problem and burden in South East Asia region and a significant challenge to the health care system. With economic development, the burden of disease has decreased in developing nations like India and the presentation shifted to adolescents and older population over the decades. Severity of disease, hospitalization and the associated mortality has been shown to be higher with later exposure to the virus. This segment of population remains vulnerable due to lack in target vaccination drive. **Methods:** The primary objective of the study is to assess the HAV related acute liver failure (ALF) in a tertiary care referral centre in South India. The secondary objectives are to assess HAV related hospitalizations, the spectrum of liver disease, duration of hospital stay and morbidity and mortality associated with it. Patients presenting with symptoms of acute hepatitis to a tertiary care referral centre in South India from December 2022 - September 2023 have been screened and analysed. They have been grouped as self-limited hepatitis in outpatient clinic and inpatients. Inpatients have further been grouped as those with and without signs of hepatic encephalopathy (HE) as per west Haven criteria **Results:** Out of 16,353 patients screened, 3235 (19.7%) tested positive for IgM HAV. Mean age was 24.53 ± 8.23 years with a male to female ratio of 1.2:1. 39.1% (911/3235) were managed as outpatients with self-limited hepatitis and 71.8%(2324/3235) needed hospitalization. 64.08% (1490/3235) were hospitalized with hepatitis A complicating other underlying illness and 25.7% (834/3235) were hospitalized with various spectrums of liver disease presentation. 22.8% (174/834) had features of impending or early stages of HE (grade 1-2 as per West Haven criteria) and admitted in ICU. Presentation or progression to acute liver failure (ALF grade 3-4 HE) was seen in 2% (17/834) patients. Total patients needing ICU admissions were 22.6%(189/834). The mean duration of hospitalization was 6.45 ± 2.72 vs 13.75 ± 5.36 days ($p< 0.01$) in those with Non ICU vs ICU admission. Plasma exchange as a rescue therapy was done in 6% (12/189) ALF patients. Inpatient mortality was noted 6.8%(13/189) patients with varying grades of HE and out of which 76.4%(13/17) patients were with ALF presentation. Only one patient underwent liver transplant. **Conclusion:** In an era with an available vaccine for HAV, health care related costs, morbidity, acute liver failure and related mortality are preventable if an effective vaccination program for hepatitis A is in place. Considering the epidemiological transition of the virus, we propose for more vaccine drives to be undertaken by the government especially targeting the adolescents, high risk groups and for HAV vaccination be incorporated as part of national immunization schedule, and with that we are one step ahead in preventing a segment of non-communicable disease related deaths.

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Disclosures: Manasa Alla: Nothing to Disclose, Anand Kulkarni: Nothing to Disclose, Mithun Sharma: Nothing to Disclose, Shantan Venishetty: Nothing to Disclose, Sowmya T R: Nothing to Disclose, Nagaraja Rao Padaki: Nothing to Disclose, Nageshwar Reddy Duvvur: Nothing to Disclose

1200 | MANAGEMENT AND CARE OF PATIENTS WITH HDV DIFFERS ACROSS SPECIALTIES

Faisal Abaalkhail[1] Faisal Sanai[2] Duna Barakeh[1] Ahmed Saati[2] Majed Almaghrabi[2] Asma Alnajjar[3] Abdulmohsen Alshammari[3] Habeeb Razack[4] Muath Najmi[3] Fatima Ahmed[2] Saad Aldosari[2] Maram Almutairi[2] Hani Tamim[5] Saleh Alqahtani[1]

[1]King Faisal Specialist Hospital and Research Center, [2]King Abdulaziz Medical City, King Abdullah International Medical Research Center, Jeddah, [3]King Faisal Specialist Hospital and Research Center, Riyadh, [4]King Saud University, [5]Alfaisal University

Background: Testing rates of hepatitis D virus (HDV) remain low globally. Management and care of patients with HDV may differ across specialties; however, not many studies reported the gaps in testing and managing comorbidities between specialists like hepatologists (HEP)/gastroenterologists (GES) and non-specialists. The present study aimed to analyze and compare the HDV testing rates, comorbidities, and liver disease stages in patients with HDV managed by different specialties. **Methods:** This retrospective study involved the chart review of consecutive adult or adolescent (> 14 years) patients with chronic hepatitis B virus infection (HBV, >6 months HBsAg) in two tertiary care centers in Saudi Arabia between 2000 and 2023. Both centers have anti-HDV testing routinely available. We evaluated comorbidities, liver biochemistry, and fibrosis stages (by transient elastography) and compared them across specialties (HEP, GES, and non-specialists). **Results:** Overall, 845 chronic HBV patients (male, 61.7%) with a mean age of 54.8±13.1 years were evaluated during the study period (<2011, 81 [9.9%], 2011-2020, 653 [79.7%] and >2020, 85 [10.4%]). Overall, 572 (67.7%) received anti-HDV testing. HEP performed anti-HDV testing (76.6%) most frequently, followed by GES (62.3%), and least by other non-specialists (35.3%, p<0.001). Testing rates were similar between specialties during the three time periods (p=0.475). Anti-HDV positivity did not significantly differ across specialties (p=0.145). The presence of dyslipidemia (p=0.047) and renal disease (p=0.023) was higher in HBV patients managed by HEP. HEP managed a higher proportion of patients with compensated cirrhosis, decompensated cirrhosis and hepatocellular carcinoma than others (p<0.05 for all). HEP were more likely to order transient elastography (p<0.001) than GES and others. HEP and GES had more patients with severe steatosis (S3) (p=0.044). None of the HDV-infected patients received treatment for HDV. **Conclusion:** Wide differences exist in HBV-infected patients undergoing anti-HDV testing rates, assessment of liver disease severity, presence of comorbid conditions, and managing patients with severe disease across specialties. HEP managed more sicker patients and performed more comprehensive evaluations. Anti-HDV positivity rates did not differ amongst the various specialties managing HBV patients, suggesting uniformity in outcomes irrespective of the specialties.

Disclosures: Faisal Abaalkhail: Nothing to Disclose, Faisal Sanai: Nothing to Disclose, Duna Barakeh: Nothing to Disclose, Ahmed Saati: Nothing to Disclose, Majed Almaghrabi: Nothing to Disclose, Asma Alnajjar: Nothing to Disclose, Abdulmohsen Alshammari: Nothing to Disclose, Habeeb Razack: Nothing to Disclose, Muath Najmi: Nothing to Disclose, Fatima Ahmed: Nothing to Disclose, Saad Aldosari: Nothing to Disclose, Maram Almutairi: Nothing to Disclose, Hani Tamim: Nothing to Disclose, Saleh Alqahtani: Nothing to Disclose

1201 | DURATION OF NUCLEOS(T)IDE ANALOGUE (NA) TREATMENTS IN PATIENTS WITH CHRONIC HEPATITIS B (CHB) VIRUS INFECTION IN THE UNITED STATES (US)

Seth Anderson[1] Vera Gielen[2] Laura Clark[3] Chris Bell[3] Shay Salehi[2] Renee Gennarelli[4] Eileen Farrelly[5] Dana Stafkey[6] Robert Gish[7]

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Background: In 2022, it was estimated that 254 million people were living with CHB virus infection (WHO, 2024). NAs are the current standard of care for CHB infection. Most patients will require long-term NA treatment

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to inhibit viral replication; however, treatment does not eradicate the virus or achieve a functional cure We describe the duration and adherence to 2nd generation NAs among adult patients with CHB infection from the US. **Methods:** This retrospective cohort study used administrative claims data from the Merative MarketScan Research Databases (study identification period: Jan 1 2007–March 31 2023). Included patients were ≥18 years, diagnosed with CHB infection, started treatment with 2nd generation NAs (index defined as date of first NA pharmacy claim), and had ≥12 months of continuous medical/pharmacy eligibility prior to index and ≥4 months of follow-up after index date. Patients with human immunodeficiency virus, hepatitis c or delta virus were excluded. Outcomes included patient demographics, clinical characteristics, and measures of NA adherence (e.g., time to discontinuation of NAs, proportion of days covered [PDC]). **Results:** In total, 6696 patients were eligible to be included in the final sample. Mean (SD) age was 47.2 (11.5) years, 2787 (41.6%) were female, 6371 (95.1%) had commercial coverage and 325 (4.9%) had Medicare coverage. Mean (SD) modified Charlson Comorbidity Index (CCI) score was 0.6 (1.5). Index NA treatment was predominantly tenofovir alafenamide (n=3247, 48.5%) or entecavir (n=2792, 41.7%). Overall, 2721 (40.6%) patients discontinued NAs (Table). Median time to discontinuation of NAs was 45 months. A total of 1243 (45.7%) patients restarted NAs (after >90 days' discontinuation). From index date to end of follow-up, mean PDC was 0.91 and rate of adherent patients (PDC >80%) was 86.5%. Significant predictors of adherence (p<0.0001) included age at index, CCI score, index treatment of tenofovir alafenamide, and follow-up duration. Predictors of persistence were similar to those of adherence. **Conclusion:** Our study highlights one of the inherent challenges of long-term NA therapy in patients with CHB infection; variable adherence, with patients starting/stopping treatment. An unmet need in the management of CHB infection is alternative treatments of shorter and finite durations that offer an opportunity to achieve functional cure and the potential to reduce the risks of CHB liver progression.
Funding: GSK (Study 218719)

Table

	Overall (n=6696)
Treatment discontinuation	
Discontinued 2nd generation NA therapy, n (%)	2721 (40.6)
Duration of 2nd generation NA treatment in months, among patients that discontinued, mean (SD)	12.8 (17.8)
Time to discontinuation in months, median (95% CI)	45 (41, 49)
Adherence to treatment[a]	
PDC from index date to end of follow-up, mean (SD)	0.91 (0.12)
Rate of adherent patients (PDC >80%) from index date to, n (%):[b]	
End of follow-up	5791 (86.5)
6 months	4253 (87.3)
12 months	3112 (90.4)
24 months	1855 (91.5)
36 months	1236 (94.6)

[a]end of follow-up defined as the earlier of date of treatment discontinuation, the date of onset of co-infections, the date of the end of continuous medical and pharmacy enrolment, date of skilled nursing facility or hospice admission, or date of data cutoff; [b]evaluated only among patients who have follow-up through the timepoint of interest

Disclosures: Seth Anderson: Nothing to Disclose, Vera Gielen: GSK: Employee, Laura Clark: Nothing to Disclose, Chris Bell: GSK: Employee, Shay Salehi: GSK: Employee, Renee Gennarelli: Nothing to Disclose, Eileen Farrelly: Nothing to Disclose, Dana Stafkey: Nothing to Disclose, Robert Gish: Nothing to Disclose

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1202 | STIMULATING STING PATHWAY LEADS TO INHIBITION OF HBV REPLICATION: INSIGHTS INTO KUPFFER CELL

Mingyuan Zhang[1] Jie Zhou[1] Xiaomei Wang[1] Hongqin Xu[1] YANHANG GAO[2] Junqi Niu[1]

[1]first hospital of jilin university, [2]First hosptial of Jilin University

Background: Host immune system activation is a promising strategy for the treatment of hepatitis B. The stimulator of interferon genes (STING) signaling pathway serves as an innate immune sensor of pathogen DNA. We aimed to investigate the potential of STING activation in inhibiting HBV replication and to elucidate its underlying immunological mechanisms. **Methods:** Peripheral blood mononuclear cells (PBMCs) and liver biopsy specimens obtained from patients with chronic hepatitis B (CHB) infection were used to evaluate the expression of STING. A chronic HBV infection model was established through transinfection with rAAV8-HBV 1.3. Subsequently, in vivo depletion of macrophages by clodronate liposomes was conducted to investigate the roles of macrophages in the antiviral effects of the STING agonist (DMXAA). Blood samples were collected from the mice via the retroorbital plexus for the detection of serum HBV virological markers. Following euthanasia, the mice livers were utilized for immunohistochemical staining and quantitative polymerase chain reaction analysis(qPCR). **Results:** STING expression in CHB patients was higher during the immune-active phase than during the inactive phase and in the healthy control group, indicating a potential association between elevated STING expression and immune activation. In AAV-HBV transinfectd mice model, repeated administration of DMXAA resulted in dose-dependent reductions in the serum levels of HBV DNA, HBsAg, and HBeAg, accompanied by an elevated hepatic immune response. Additionally, in Kupffer cell-deficient mice model, immunohistochemical analysis of liver tissue using STING staining revealed a reduction in intrahepatic STING expression after the depletion of macrophages, suggesting a prominent role of STING in Kupffer cells. Assessment of serum HBV virological markers at 48 hours post-DMXAA treatment showed a diminished suppression of HBV replication following the clearance of macrophages, particularly affecting HBV DNA replication. To delve deeper into the immunological alterations triggered by DMXAA therapy, mice were euthanized 4 hours after the second dose of DMXAA to harvest liver tissues for RNA extraction and qPCR analysis. The group treated with DMXAA showed markedly increased expression levels of anti-viral and proinflammatory genes, such as OAS-1, OAS-3, viperin, and ISG15, in comparison to the control group. Subsequent to the elimination of macrophages, the stimulatory effect of the STING agonist on OAS family genes was significantly reduced. **Conclusion:** Activation of the STING pathway enhances the immune response against hepatitis B virus by upregulating the expression of immune-related genes, with Kupffer cells playing a crucial role in mediating this process.

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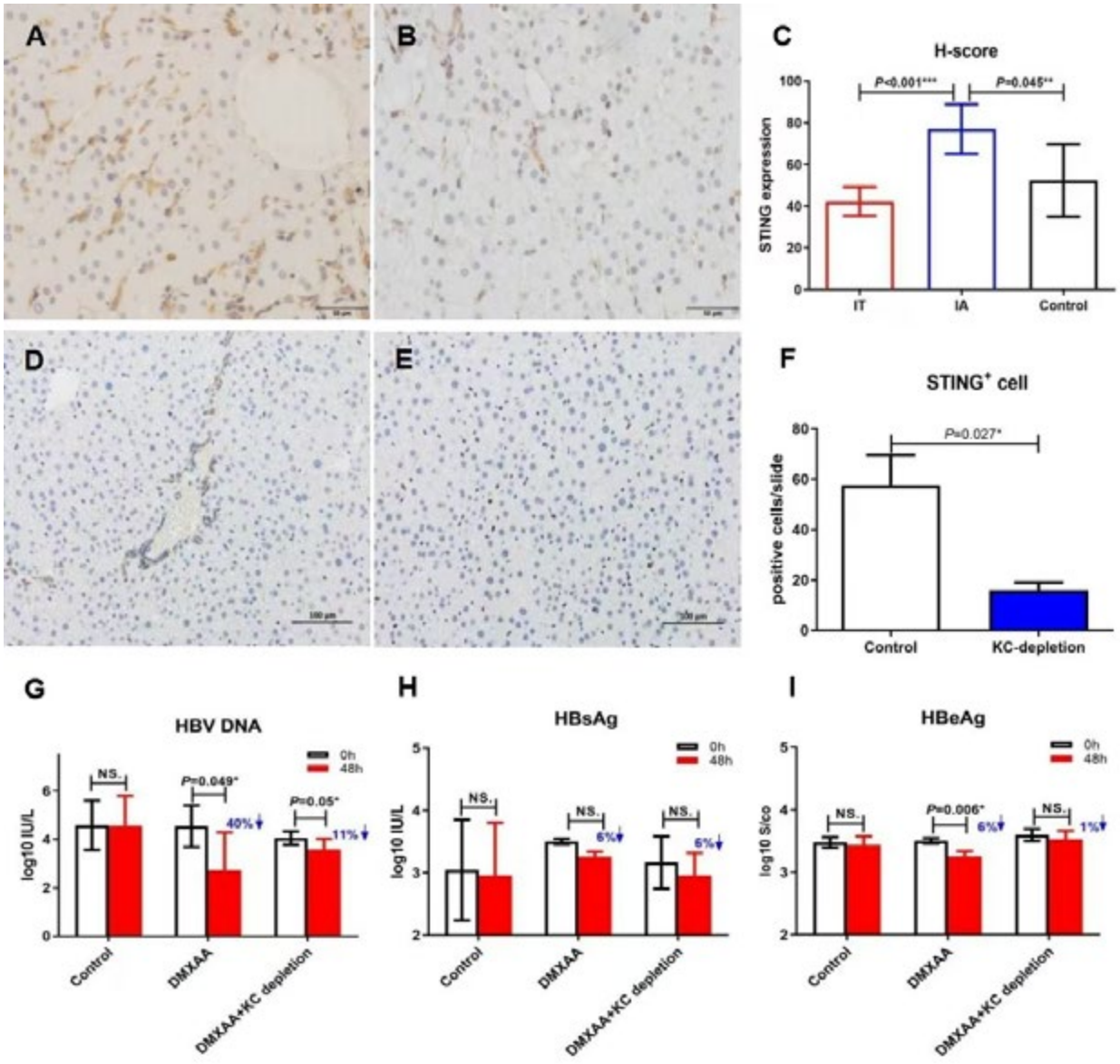

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1203 | THE ROLE OF NUCLEOPORIN 214 IN HEPATITIS B VIRUS REPLICATION

WEI-LUN TSAI[1] *wei-chih sun*[1] *Chih-Wen Shu*[2] *Chia-Ming Lu*[1]

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Background: Chronic hepatitis B virus (HBV) infection is the leading cause of cirrhosis or hepatocellular carcinoma (HCC) in Taiwan. However, there remained no effective therapy to cure HBV. Nuclear transport is essential for the replication of many DNA virus or retrovirus in their life cycles. But the role of nuclear transport inhibition in HBV replication remained unclear. The aim of the study is to investigate the association of Nup214 with replication of HBV. **Methods:** The HepG2.2.15cells (cells with HBV expression and replication), HBV infected HepG2-hNTCP-C4 were used in the experiments. Short hairpin RNA (shRNA) or siRNA mediated knock-down of Nup214 will be done. Quantification of supernatant HBsAg, and HBV DNA and intracellular cccDNA, will be performed. Immunofluorescence assay (IFA) will be conducted. **Results:** We screened many molecules associated with nuclear transport in hepatocytes and investigated their impacts on HBV replication. We found that shRNA mediated knock-down of Nup214 associated with nuclear transport significantly reduced HBsAg and

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HBV DNA secretion and cellular cccDNA in HepG2.2.15 cells. Reduced HBsAg secretion and cellular cccDNA were also noted in HBV infected HepG2-hNTCP-C4 cells after knockdown of Nup214 with siRNA. Knock-down efficiency of Nup214 was ideal and cell viability was not influenced. IFA of HepG2-hNTCP-C4 cells transfected with siRNA (si-Nup214) for 24h and then HBV infection for 48h found that siRNA treatments against Nup214 significantly decreased nuclear accumulation of HBc protein. **Conclusion:** Inhibition of Nup214 significantly reduced HBsAg secretion and cellular cccDNA and
significantly decreased nuclear accumulation of HBc protein in HBV infected
HepG2-hNTCP-C4 cells. Our data is promising and Nup214 may be a new
therapeutic target for future anti-HBV treatment.

Disclosures: WEI-LUN TSAI: Nothing to Disclose, wei-chih sun: Nothing to Disclose, Chih-Wen Shu: Nothing to Disclose, Chia-Ming Lu: Nothing to Disclose

1204 | NON-LINEAR ASSOCIATION BETWEEN LIVER FIBROSIS SCORES AND VIRAL LOAD IN PATIENTS WITH CHRONIC HEPATITIS B

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Background: Serum hepatitis B virus (HBV) DNA levels and non-invasive liver fibrosis scores are significantly associated with hepatocellular carcinoma (HCC) risk in chronic hepatitis B (CHB) patients. Nonetheless, the relationship between HBV DNA levels and liver fibrosis scores is unclear. **Methods:** A historical cohort comprising 6,949 non-cirrhotic Korean CHB patients without significant alanine aminotransferase elevation was investigated. The association of HBV DNA levels with the aspartate aminotransferase to platelet ratio index (APRI) and fibrosis (FIB)-4 score at baseline was analyzed using general linear models. **Results:** In HBeAg-negative patients (n=4,868), HBV DNA levels correlated linearly with both APRI and FIB-4 scores. In contrast, in HBeAg-positive patients (n=2,081), HBV DNA levels correlated inversely with both APRI and FIB-4 scores. Across the entire cohort, a significant non-linear parabolic relationship was identified between HBV DNA levels and fibrosis scores, independent of age and other covariates. Notably, moderate viral loads (6–7 $\log_{10}$ IU/mL) corresponded to the highest APRI and FIB-4 scores (P<0.001). Over a median 10-year follow-up, 435 patients (6.3%) developed HCC. Higher APRI scores ≥0.5 and FIB-4 scores ≥1.45 were significantly associated with elevated HCC risk (P<0.001 for both). HBV DNA level remained a significant predictive factor for HCC development, even after adjusting for APRI or FIB-4 scores. **Conclusion:** HBV viral load is significantly correlated with APRI and FIB-4 scores, and is also associated with HCC risk independent of those scores in CHB patients. These findings suggest that HBV DNA level is associated with hepatocarcinogenesis through both direct and indirect pathways.

Disclosures: Gi-Ae Kim: Nothing to Disclose, Young-Suk Lim: Nothing to Disclose, Seungbong Han: Nothing to Disclose, Seung Won Choi: Nothing to Disclose

1205 | POST-TRANSPLANT HBV VACCINE COMPLIANCE AND SEROPROTECTION IN THORACIC ORGAN TRANSPLANT RECIPIENTS

Chia-Yu Chiu Priya Sampathkumar[1] Lisa Brumble[1] Holenarasipur Vikram[1] Kymberly Watt[1] Elena Beam[1]

[1]Mayo Clinic

Background: Vaccination is crucial to solid organ transplant (SOT) recipients to reduce vaccine-preventable diseases. However, data on post-transplant hepatitis B virus (HBV) vaccination compliance and vaccine-induced seroprotection from conventional recombinant hepatitis B vaccine (Recombivax HB) versus CpG-adjuvanted recombinant hepatitis B vaccine (Heplisav-B) are lacking. This study aims to examine the rate of post-transplant HBV vaccine compliance and vaccine-induced seroprotection in thoracic organ transplant recipients. **Methods:** We conducted a retrospective study of adult thoracic organ (heart and lung) transplant recipients at Mayo Clinic sites in Minnesota, Arizona, and Florida between January 2018 and August 2023. Recombivax HB (40 mcg/mL, 3-dose series at 0, 1, 6 months) was used before 2020, and Heplisav-B (2-dose series at 0, 1 month)

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was preferred after 2020. Recipients with post-transplant hepatitis B surface antibody (HBsAb) <10 IU/L were eligible for the HBV vaccine. Our study collected HBsAb data 1 ─ 6 months after HBV vaccine completion. HBV seroprotection was defined as an HBsAb ≥10 IU/L. **Results:** A total of 1,116 recipients who underwent post-transplant HBsAb testing were evaluated. The median time from transplantation to the HBsAb testing was 3 months (IQR 1 – 6 months). Of these, 751 (67%) had an HBsAb level <10 IU/L and were thus eligible for post-transplant HBV vaccination. Of the eligible recipients, 117 (16%) completed the HBV vaccine series during the study period. Among these 117 recipients, 40 (34%) had their HBsAb titers rechecked after completing the vaccine series, with a seroprotection rate of 37.5% (15/40). There was no statistically significant difference in the seroprotection rates between Heplisav-B and Recombivax HB vaccines (39% [13/33] vs. 29% [2/7]; p = 0.691). **Conclusion:** We observed suboptimal post-transplant HBV vaccine compliance and poor vaccine-induced seroprotection in thoracic organ transplant recipients, regardless of the vaccine used. This study's findings emphasize the need to explore alternative post-transplant HBV vaccination strategies to improve both compliance and seroprotection.

Table 1. Demographic and Clinical Characteristics of Thoracic Organ Transplant Recipients with Post-Transplant Hepatitis B Surface Antibody Level < 10 IU/L

	Post-Transplant HBsAb ≤ 10 IU/L	Post-transplant HBV vaccine completion	Post-transplant HBV vaccine completion with HBsAb testing			
	Total N = 751	Total N = 117	Total N = 40	HBsAb < 10 IU/L N = 25	HBs Ab ≥ 10 IU/L N = 15	P value [a]
Characteristic						
Age, median year (IQR)	56 (50 – 65)	59 (51 – 66)	56 (50 – 66)	58 (49 – 66)	61 (57 – 67)	0.409
Male	503 (67)	79 (68)	26 (65)	15 (58)	11 (42)	0.502
Race						0.648
White	593 (79)	94 (80)	30 (75)	19 (63)	11 (37)	
African American or Black	113 (15)	15 (13)	9 (23)	6 (67)	3 (33)	
Others	45 (6)	8 (7)	1 (2)	0 (0)	1 (100)	
Organ of transplantation						1.000
Heart	450 (60)	71 (61)	26 (65)	16 (62)	10 (38)	
Lung	301 (40)	46 (39)	14 (35)	9 (64)	5 (36)	
BMI ≥ 30 kg/m²	225 (30)	34 (29)	13 (33)	9 (69)	4 (31)	0.730
Pre-transplant HBV vaccine completion [b,c]	115 (15)	34 (29)	12 (30)	10 (83)	2 (17)	0.152
Pre-transplant HBsAb ≥ 10 IU/L	75 (10) [d]	17 (15) [e]	8 (20)	7 (88)	1 (12)	0.219
HBV vaccine after transplantation						0.691
Heplisav-B	N/A	98 (84)	33 (83)	20 (61)	13 (39)	
Recombivax HB	N/A	19 (16)	7 (17)	5 (71)	2 (29)	
From transplantation to HBsAb level testing, median months (IQR)	N/A	3 (1 – 6)	3 (1 – 6)	3 (1 – 6)	3 (1 – 7)	0.713
From transplantation to receiving the first dose HBV vaccine, median months (IQR)	N/A	11 (4 – 14)	10 (5 – 14)	11 (6 – 13)	8 (4 – 15)	0.556
First dose of HBV vaccine administration (post-transplant)						0.273
3 – 6 months post-transplant	N/A	36 (31)	11 (27.5)	5 (45)	6 (55)	
> 6 months post-transplant	N/A	81 (69)	29 (72.5)	20 (69)	9 (31)	
From transplantation to the completion of HBV vaccine series, median months (IQR)	N/A	13 (8 – 18)	12 (7 – 16)	12 (9 – 17)	9 (7 – 16)	0.263
From vaccine completion to HBsAb level testing, median month (IQR)	N/A	N/A	2 (1 – 5)	2 (1 – 6)	2 (1 – 4)	0.819
Induction regimen						0.233
Anti-thymocyte globulin	376 (50)	57 (49)	21 (53)	15 (71)	6 (29)	
Basiliximab	240 (32)	42 (36)	15 (38)	9 (60)	6 (40)	
Methylprednisolone	113 (15)	13 (11)	4 (10)	1 (25)	3 (75)	

Abbreviations: CMV, cytomegalovirus; HBsAb, hepatitis B surface antibody; HBV, hepatitis B virus; IQR, interquartile range; N/A, not applicable.

a. P value compared HBsAb < 10 IU/L group and HBsAb ≥ 10 IU/L group.

b. Completed 2-dose Heplisav-B series or 3-dose Recombivax HB.

c. Completed HBV vaccine series pre-transplant did not guarantee pre-transplant HBsAb ≥ 10 IU/L.

d. 75 patients with pre-transplant HBsAb levels ≥ 10 IU/L had decreased levels < 10 IU/L post-transplant, making them eligible for post-transplant HBV vaccination. 40 patients did not have documentation of the HBV vaccine received pre-transplant, 18 completed pre-transplant Heplisav-B, 12 completed pre-transplant Recombivax HB.

e. None of these 17 patients had documentation of the HBV vaccine received pre-transplant.

Disclosures: Chia-Yu Chiu: Nothing to Disclose, Priya Sampathkumar: Nothing to Disclose, Lisa Brumble: Nothing to Disclose, Holenarasipur Vikram: Nothing to Disclose, Kymberly Watt: Madrigal: Stock - publicly traded company, Viking: Stock - publicly traded company, Elena Beam: Nothing to Disclose

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1206 | OPTIMIZING HEPATITIS B VIRUS SEROPROTECTION IN THORACIC ORGAN TRANSPLANTATION: THE ROLE OF HEPLISAV-B VACCINATION SCHEDULE

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Background: Heplisav-B, a CpG-adjuvanted recombinant hepatitis B virus (HBV) vaccine, is more immunogenic compared to the conventional HBV vaccine. However, solid organ transplant recipients may not complete the required 2-dose Heplisav-B vaccine series pre-transplantation in real-world practice. This study aims to compare seroprotection rates across 3 different Heplisav-B vaccination schedules and identify predictors of HBV seroprotection post-transplantation in thoracic organ transplant recipients. **Methods:** We conducted a retrospective study of adult thoracic organ (heart and lung) transplant recipients at Mayo Clinic sites in Minnesota, Arizona, and Florida between January 2020 and August 2023. Patients who completed the Heplisav-B series were classified into three strategies: strategy A (completed 2 doses of Heplisav-B pre-transplantation and achieved seroprotection pre-transplantation), strategy B (received first dose of Heplisav-B pre-transplantation and second dose of Heplisav-B post-transplantation), and strategy C (completed 2 doses of Heplisav-B post-transplantation). HBV seroprotection was defined as hepatitis B surface antibody (HBsAb) ≥10 IU/L. **Results:** A total of 154 thoracic organ transplant recipients completed the Heplisav-B vaccine series. Post-transplant seroprotection was highest in strategy A, followed by strategy B and strategy C (54/76 [71%] vs. 18/39 [46%] vs. 14/39 [36%]; $p < 0.001$). Multivariate logistic regression analysis identified two independent factors predicting lack of HBV seroprotection post-transplantation; both were related to the Heplisav-B schedule: strategy B (adjusted odds ratio [aOR], 2.482; 95% confidence interval [CI] 1.085 ─ 5.679; $p = 0.031$), and strategy C (aOR 4.963; 95% CI 2.106 ─ 11.697; $p <0.001$). **Conclusion:** The vaccine schedule significantly predicts HBV seroprotection in thoracic organ transplant recipients. Completion of two doses of Heplisav-B vaccine pre-transplantation to achieve HBsAb ≥10 IU/L is crucial to achieve seroprotection post-transplantation. If it is not feasible to complete two doses of Heplisav-B pre-transplantation, initiating the first dose pre-transplantation followed by the second dose post-transplantation (strategy B) is preferable to administering both doses post-transplantation (strategy C) for achieving HBV seroprotection post-transplant.

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Table 1. Risk assessment for post-transplant HBsAb <10 IU/L in thoracic organ transplant recipients.

	No. (%)			Univariate Analysis		Multivariate Analysis	
	Total N = 154	HBsAb ≥ 10 IU/L N = 86	HBsAb < 10 IU/L N = 68	OR (95% CI)	P value	Adjusted OR (95% CI)	P value
Age ≥ 60 years	83 (54)	45 (52)	38 (56)	1.154 (0.609 – 2.190)	0.660		
Sex					0.310		
Male	102 (66)	54 (63)	48 (71)	Reference			
Female	52 (34)	32 (37)	20 (29)	0.703 (0.356 – 1.390)			
Race					0.986		
White	129 (84)	72 (84)	57 (84)	Reference			
African American or Black	25 (16)	14 (16)	11 (16)	0.992 (0.419 – 2.350)			
Obesity	41 (27)	21 (24)	20 (29)	1.290 (0.630 – 2.640)	0.487		
Diabetes mellitus	33 (21)	17 (20)	16 (24)	1.249 (0.577 – 2.700)	0.572		
Organ of transplantation					0.170		
Heart	73 (47)	45 (52)	28 (41)	Reference		Reference	
Lung	81 (53)	41 (48)	40 (59)	1.568 (0.825 – 2.980)		1.708 (0.834 – 3.497)	0.143
Pre-Transplant mechanical circulatory support	42 (27)	25 (29)	17 (25)	0.813 (0.396 – 1.670)	0.574		
Heplisav-B vaccine schedule							
Strategy A [a]	76 (49)	54 (63)	22 (32)	Reference		Reference	
Strategy B [b]	39 (25)	18 (21)	21 (31)	2.864 (1.285 – 6.381)	0.010	2.482 (1.085 – 5.679)	0.031
Strategy C [c]	39 (25)	14 (16)	25 (37)	4.383 (1.929 – 9.960)	<0.001	4.963 (2.106 – 11.697)	<0.001
Lymphopenia at first dose of Heplisav-B	52 (34)	28 (33)	24 (35)	1.130 (0.577 – 2.210)	0.722		
Lymphopenia at second dose of Heplisav-B	64 (42)	33 (38)	31 (46)	1.346 (0.706 – 2.570)	0.367		
Induction regimens							
Anti-thymocyte globulin	71 (46)	43 (50)	28 (41)	Reference		Reference	
Alemtuzumab	12 (8)	7 (8)	5 (7)	1.097 (0.317 – 3.800)	0.884	0.894 (0.241 – 3.316)	0.866
Basiliximab	71 (46)	36 (42)	35 (52)	1.493 (0.767 – 2.900)	0.238	1.376 (0.656 – 2.886)	0.398
Rituximab	5 (3)	2 (2)	3 (4)	1.938 (0.315 – 11.940)	0.476		
Post-transplant Complication							
Acute rejection	37 (24)	19 (22)	18 (27)	1.269 (0.605 – 2.660)	0.528		
CMV viremia	50 (33)	24 (28)	26 (38)	1.599 (0.811 – 3.150)	0.175	1.386 (0.672 – 2.858)	0.377
Dialysis	50 (33)	29 (34)	21 (31)	0.878 (0.444 – 1.740)	0.709		

Abbreviation: BMI, body mass index; CI, confidence interval; CMV, cytomegalovirus; HbsAb, hepatitis B surface antibody; OR, odds ratio; Tx, transplantation.

a. Strategy A: Recipients who completed two doses of Heplisav-B vaccine pre-transplantation and achieved seroprotection (i.e., HBsAb levels ≥ 10 IU/L) pre-transplantation.

b. Strategy B: recipients who received the first dose of Heplisav-B at least 2 weeks before transplantation and the second dose at least 3 months after transplantation.

c. Strategy C: recipients who completed 2 doses of Heplisav-B vaccine post-transplantation, with the first dose given at least 3 months post-transplantation.

Disclosures: Chia-Yu Chiu: Nothing to Disclose, Priya Sampathkumar: Nothing to Disclose, Lisa Brumble: Nothing to Disclose, Holenarasipur Vikram: Nothing to Disclose, Kymberly Watt: Madrigal: Stock - publicly traded company, Viking: Stock - publicly traded company, Elena Beam: Nothing to Disclose

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1207 | FUZHENG HUAYU FOMULA AGAINST HBV-INDUCED LIVER FIBROSIS VIA PROMOTING RECRUITMENT AND PHENOTYPE POLARIZATION OF CX3CR1+ RESTORATIVE BMDMS

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Background: The Fuzheng Huayu Fomula (FZHY) is a widely utilized traditional Chinese medicine (TCM) prescription in medical practice for the treatment of liver fibrosis. Our previous experiments have demonstrated that FZHY can prevent and treat CCl4-induced mice liver fibrosis by recruiting and polarizing liver restorative macrophages. However, it's still unclear whether FZHY can have a therapeutic effect on hepatitis B virus (HBV)-induced liver fibrosis by recruiting and polarizing these restorative macrophages in the liver. Additionally, further clarification is needed regarding the main phenotypic molecules of the restorative macrophages that are affected by FZHY. The objective of this study was to explore the mechanism of FZHY against HBV-induced liver fibrosis by detecting its effect on the recruitment and polarization of restorative macrophages in the liver. **Methods:** Multiplex fluorescence immunohistochemistry experiments were conducted to evaluate changes in the proportions of pro-inflammatory and restorative macrophages in the liver biopsy samples from patients with HBV-induced liver fibrosis, treated with FZHY+entecavir (ETV) or ETV alone. Additionally, CCl4-induced liver fibrosis models were established in HBV-Tg mice and CX3CR1-/- mice, followed by administration of FZHY. Flow cytometry was employed to assess the proportion of different macrophage phenotypes in each group. Immunohistochemical experiments were performed to analyze the expression changes of α-SMA and CX3CL1 proteins in liver tissue, while biochemical experiments and ELISA were conducted to measure the levels of serum transaminases, inflammatory factors, and pro-fibrotic factors. HE staining and Sirius red staining were used to evaluate liver tissue damage degree and liver tissue fibrosis extent respectively. In vitro experiments, mouse bone marrow-derived macrophages (BMDMs) were stimulated with LPS and treated with FZHY. The expression levels of TNF-α and TGF-β in the cell culture supernatants were measured using ELISA. The proportions of Ly6ChighCCR2+ pro-inflammatory BMDMs and Ly6ClowCX3CR1+ restorative BMDMs were determined employing flow cytometry. **Results:** Clinical experiments demonstrated that FZHY+ETV significantly increased the proportion of restorative macrophages in liver tissues, thereby enhancing the anti-HBV-induced liver fibrosis effect of ETV. In vivo experiments discovered that, FZHY+ETV effectively reduced the proportion of pro-inflammatory macrophages (Ly6ChighCCR2+) and increased the proportion of restorative macrophages (Ly6ClowCX3CR1+) in HBV-induced liver fibrosis mice. Additionally, FZHY increased the expression of the CX3CL1 protein in both CCl4-induced liver fibrosis wild-type and CX3CR1-/- mice. Furthermore, FZHY significantly reduced the severity of liver tissue injury and fibrosis in wild-type liver fibrosis mice, as well as decreased the levels of inflammatory factors (IL-6, TNF-α, and CCL2) and pro-fibrotic factors (TGF-β and PDGF) in the serum. However, FZHY did not demonstrate any pharmacological effects in CX3CR1-/- liver fibrosis mice. In vitro experiments revealed that FZHY effectively suppressed the gene expression of TNF-α and TGF-β in pro-inflammatory BMDMs, thereby reducing the proportion of pro-inflammatory BMDMs and increasing the proportion of restorative BMDMs (Ly6ClowCX3CR1+). **Conclusion:** FZHY enhances the recruitment of restorative BMDMs expressing CX3CR1 by upregulating the expression of CX3CL1 protein in liver tissue. Meanwhile, FZHY facilitates the transition of pro-inflammatory BMDMs expressing CCR2 to restorative BMDMs expressing CX3CR1, thereby exerting its anti-HBV-induced liver fibrosis effects.

Disclosures: Lu Xing: Nothing to Disclose

1208 | THE PROPORTION OF SERUM HBSAG-NEGATIVE PATIENTS IN HEPATITIS B VIRUS-ASSOCIATED GLOMERULONEPHRITIS WAS AS HIGH AS 70%——A RETROSPECTIVE COHORT STUDY FROM CHINA

Tongtong Ji[1] *yanyan yu*[1] *Jinghang Xu*[1]

[1]*Peking University First Hospital*

Background: Hepatitis B virus-associated glomerulonephritis (HBV-GN) is a common form of secondary glomerulonephritis in China, most patients with HBV-GN are serum HBsAg positive, however, recent studies have

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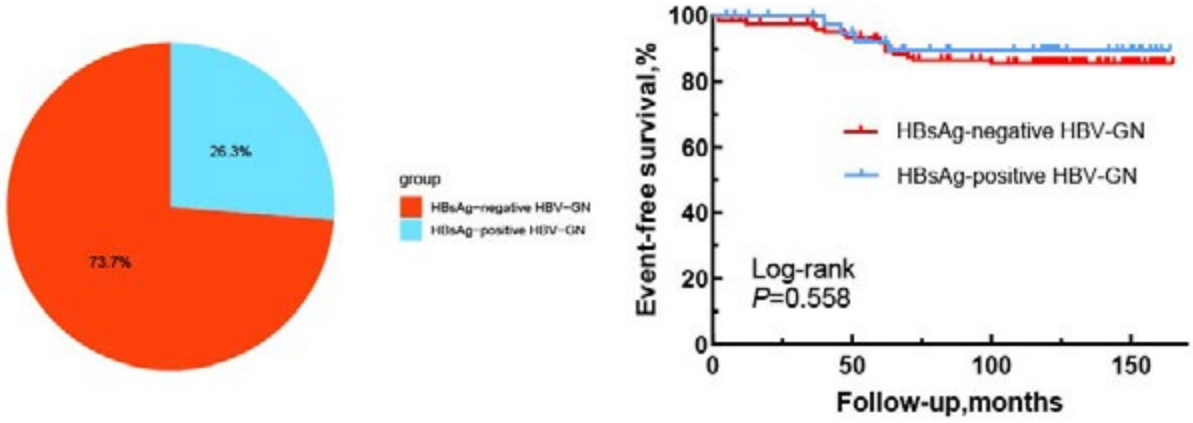
found that around 13% to 37% of HBV-GN patients are serum HBsAg negative. The clinicopathologic features and prognosis of HBV-GN with different serum HBsAg status have not been fully clarified. **Methods:** Patients diagnosed with HBV-GN by renal biopsy at Peking University First Hospital from 2010 to 2020 were included. The patients were grouped based on their serum HBsAg status. The clinicopathologic features and the risk of end-stage renal disease (ESRD) were compared between HBsAg-negative and positive HBV-GN patients. **Results:** A total of 175 patients with HBV-GN were enrolled, of which 62.9% were male, and the median age was 47 years (IQR 32 - 61). Among the patients, 74.9% had clinical presentation of nephrotic syndrome, and 97.1% showed pathological evidence of membranous nephropathy. Additionally, 7.4% had abnormal liver function, and 10.9% had elevated serum creatinine levels (>133 μmol/L). The distribution according to chronic kidney disease (CKD) stages showed that 64.0% had stage 1, followed by stage 2 (21.7%), stage 3 (11.4%), and stage 4 (2.9%). 73.7% of patients were serum HBsAg-negative, while 26.3% were serum HBsAg-positive. 13.1% of patients were HBeAg positive, and 14.3% were positive for HBV DNA. Compared with the HBsAg negative group, the HBsAg positive group had higher levels of ALT, AST, IgG, and IgA, and lower levels of complement C3. However, there were no significant differences in serum creatinine and estimated glomerular filtration rate (eGFR) levels between the two groups. A higher proportion of the HBsAg-positive group received anti-HBV therapy (78.3% vs. 6.2%, $P < 0.001$), and a lower proportion received glucocorticoid therapy (21.7% vs 48.1%, $P=0.002$). With a median follow-up of 120 months (IQR 63 - 142), 21 cases (12.0%) progressed to ESRD, including 17 cases in the HBsAg-negative group and 4 cases in the HBsAg-positive group. Kaplan-Meier analysis showed that there was no significant difference in the risk of ESRD between serum HBsAg-negative and positive HBV-GN ($P=0.558$). **Conclusion:** HBV-GN is more common in males, the clinical manifestations are mostly nephrotic syndrome, and the pathological manifestations are mostly membranous nephropathy. Most patients had normal liver function, and renal function was mostly in CKD stage 1-2. The proportion of serum HBsAg-negative patients in HBV-GN was as high as 73.7%. For HBsAg-negative patients who develop renal damage, the possibility of HBV-GN also needs to be considered for early diagnosis and intervention. The group of HBsAg-positive HBV-GN had worse liver function, while there was no significant difference in baseline renal function between the two groups. Serum HBsAg status was not found to be associated with the risk of ESRD.



Disclosures: Tongtong Ji: Nothing to Disclose, yanyan yu: Nothing to Disclose, Jinghang Xu: Nothing to Disclose

1209 | SERUM TOTAL CHOLESTEROL IS A PREDICTOR OF END-STAGE RENAL DISEASE IN PATIENTS WITH HEPATITIS B VIRUS-ASSOCIATED GLOMERULONEPHRITIS: A RETROSPECTIVE COHORT STUDY FROM CHINA

Tongtong Ji[1] *yanyan yu*[1] *Jinghang Xu*[1]

[1]*Peking University First Hospital*

Background: Hepatitis B virus-associated glomerulonephritis (HBV-GN) is a common form of secondary glomerulonephritis in China, and there are still few studies on the long-term prognosis of HBV-GN. **Methods:** Patients diagnosed with HBV-GN by renal biopsy at Peking University First Hospital from 2010 to 2020 were

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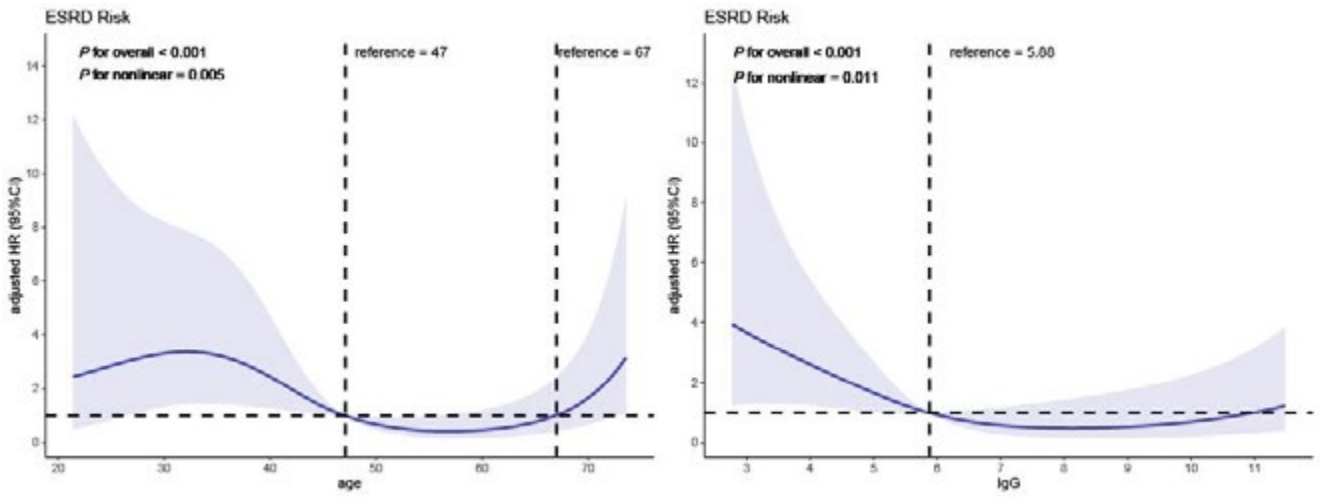
enrolled, and the study endpoint was end-stage renal disease(ESRD), Univariate and multivariate Cox regression modeling was used to explore the predictors of ESRD in patients with HBV-GN, and restricted cubic spline modeling was used to to investigate the nonlinear relationship between continuous variables and ESRD. **Results:** A total of 175 patients with HBV-GN were enrolled, 37.1% were female, and the median age was 47 years (range: 18 - 84 years). During a median follow-up of 120 months (range: 2 - 165 months), 21 (12.0%) patients progressed to ESRD. Multivariate Cox regression analysis revealed that eGFR (HR = 0.972, 95% CI: 0.959 - 0.985, *P* < 0.001) and TCHO (HR = 1.352, 95% CI: 1.130 - 1.617, *P* < 0.001) were independent predictors of ESRD. The risk of ESRD was found to be unaffected by the presence or absence of serum HBsAg and HBeAg. The restricted cubic spline model analysis showed that age and IgG have a non-linear relationship with the risk of ESRD (*P* for nonlinearity < 0.05). The risk of ESRD is lowest when the age is between 47 to 67 years, However, the risk of ESRD is higher when the age is < 47 years or > 67 years. When IgG < 5.88g/L, the risk of ESRD is significantly increased with the decrease of IgG, Conversely, when IgG > 5.88g/L, there is no significant relationship between IgG and the risk of ESRD. **Conclusion:** The prognosis of HBV-GN was poor, with 12.0% of patients progressing to ESRD during follow-up. Serum HBsAg and HBeAg status is not associated with the risk of ESRD, reduced eGFR and elevated TCHO are independent predictors of ESRD. Age and IgG have a non-linear relationship with the risk of ESRD, the risk of ESRD is higher when the age is < 47 years or > 67 years. When IgG < 5.88g/L, the risk of ESRD increased significantly with the decrease of IgG.



Disclosures: Tongtong Ji: Nothing to Disclose, yanyan yu: Nothing to Disclose, Jinghang Xu: Nothing to Disclose

1210 | SAFETY OF TENOFOVIR ALAFENAMIDE IN THE CONTEXT OF HYPERLIPIDEMIA AND CARDIOVASCULAR DISEASES: A NATIONWIDE ANALYSIS

Young Seok Kim[1]

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Background: Despite numerous small-scale studies, correlation between tenofovir alafenamide fumarate (TAF) and hyperlipidemia remains still limited. This study aims to evaluate the safety of TAF regarding hyperlipidemia and cardiovascular diseases using a nationwide cohort. **Methods:** We conducted a retrospective analysis of claims data from the Health Insurance Review and Assessment Service, comparing incidence rates of hyperlipidemia and major adverse cardiovascular events (MACE) using 1:1 propensity score matching between TAF and tenofovir disoproxil fumarate (TDF) users. **Results:** The incidence of hyperlipidemia among TAF users was 21.53 per 1,000 person-years, compared to 10.15 among TDF users. The incidence rate ratio (IRR) was 2.12 (95% confidence interval [CI] 1.92 - 2.35), indicating a significantly higher incidence in TAF users compared to TDF users (*P* < 0.001). After adjusting for other factors, Cox regression analysis showed that TAF was significantly associated with hyperlipidemia compared to TDF (hazard ratio [HR] 1.83, 95% CI 1.66 - 2.02, *P* < 0.001). There was no significant difference in the incidence of MACE between TDF and TAF users (2.26 per 1,000 person-years for both groups, IRR 1.00, 95% CI 0.77 - 1.28, *P* = 0.978), with Cox regression analysis showing no disparity between the groups (HR 1.02, 95% CI 0.78 - 1.33, *P* = 0.906). **Conclusion:** TAF is associated with

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a higher incidence of hyperlipidemia than TDF. While the incidence of MACE in the TAF group has not shown a significant increase compared to the TDF group, further investigation into long-term outcomes is warranted.

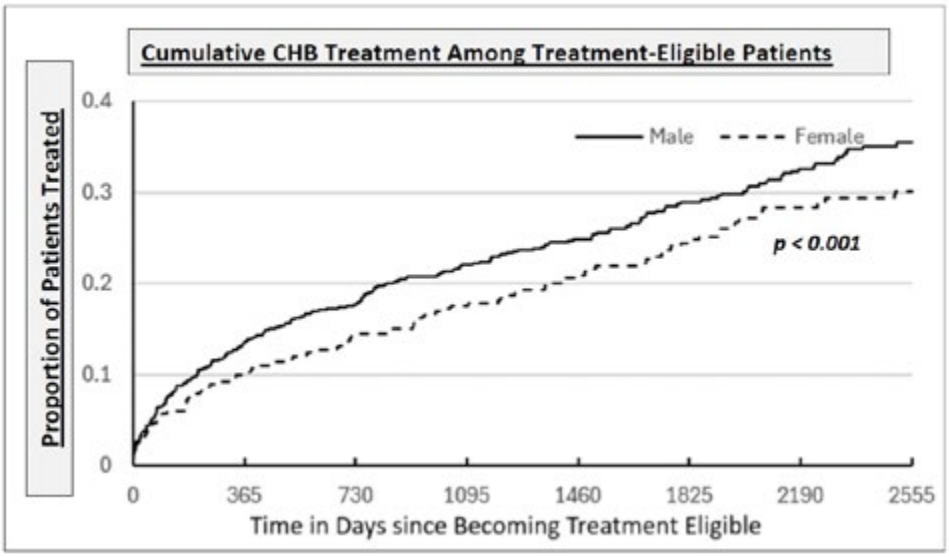
Disclosures: Young Seok Kim: Nothing to Disclose

1211 | GENDER-SPECIFIC DISPARITIES IN RECEIVING ANTIVIRAL THERAPY AMONG TREATMENT-ELIGIBLE ADULTS WITH CHRONIC HEPATITIS B INFECTION ACROSS THREE SAFETY-NET HEALTH SYSTEMS IN THE UNITED STATES ◆

Robert Wong[1] Mamta Jain[2] Bolin Niu[3] George Therapondos[4] Onkar Kshirsagar[5] Mae Thamer[5]

[1]VA Palo Alto Healthcare System, [2]UT Southwestern, [3]MetroHealth Medical Center, [4]Ochsner Health System, [5]Medical Technology and Pratice Patterns

Background: Timely antiviral therapy in chronic hepatitis B (CHB) reduces long-term risks of cirrhosis and hepatocellular carcinoma. Gaps and disparities in timely treatment persists, especially among underserved safety-net populations. We aim to evaluate gender-specific disparities in timely access to CHB treatment among a multi-center U.S. safety-net cohort of CHB patients. **Methods:** Adults with treatment-naïve CHB identified from 2010 to 2018 across 3 safety-net health systems were evaluated for treatment eligibility (TxElig) using longitudinal assessment of alanine aminotransferase, HBV DNA, hepatitis B e antigen, and liver disease severity, based on AASLD CHB guidelines. Patients with HIV co-infection were excluded. Among TxElig patients, the proportion that received CHB treatment in men vs. women was compared using chi-square methods. Adjusted Cox Proportional Hazards models evaluated the predictors of receiving CHB treatment over time among TxElig patients. **Results:** Among 3,749 patients with treatment-naïve CHB (51.5% women, 38.7% white, 33.7% African American, 19.6% Asian, 38.2% Medicaid/indigent care, 32.9% commercial insurance, 18.1% Medicare, 24.6% with baseline cirrhosis), 30.0% (n=1,126) were TxElig during follow-up. Men were more likely to be TxElig vs. women (39.7% vs. 20.9%, p<0.01). Among TxElig patients, only 31.0% received CHB treatment during follow up; men were more likely to be treated vs. women (33.5% vs. 26.6%, p<0.01) (Figure). This gender disparity in treatment was particularly pronounced among patients who were white (29.3% treated in men vs. 16.0% in women, p<0.01), had Medicaid (29.7% in men vs. 22.8% in women, p<0.01), or had commercial insurance (34.7% in men vs. 24.4% in women, p<0.01). On adjusted regression models, additional treatment disparities were noted. Asians were more likely to be treated vs. whites (aHR 1.55, 95% CI 1.14-2.11). Lower likelihood of CHB treatment was observed in those with Medicare vs. commercial insurance (aHR 0.62, 95% CI 0.45-0.85) and in patients with concurrent metabolic dysfunction associated steatotic liver disease (aHR 0.56, 95% CI 0.42-0.74). **Conclusion:** Among an ethnically diverse multi-center safety-net cohort of CHB patients, less than one-third of TxElig patients received CHB treatment. Better understanding the patient, provider, and health system level barriers contributing to these low treatment rates, particularly among women, is urgently needed to improve CHB patient care.



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Disclosures: Robert Wong: Theratechnologies: Grant/Research Support, Durect: Grant/Research Support, Gilead Sciences: Grant/Research Support, Exact Sciences: Grant/Research Support, Theratechnologies: Grant/Research Support, Durect Corporation: Grant/Research Support, Mamta Jain: Gilead Sciences: Grant/Research Support, Laurent: Grant/Research Support, Abbvie: Grant/Research Support, Bolin Niu: Nothing to Disclose, George Therapondos: Nothing to Disclose, Onkar Kshirsagar: Nothing to Disclose, Mae Thamer: Gilead Sciences: Grant/Research Support

1212 | GAPS IN HEPATITIS B LABORATORY MONITORING AMONG AN ETHNICALLY DIVERSE COHORT OF ADULTS WITH TREATMENT-NA&IUML;VE CHRONIC HEPATITIS B INFECTION IN THE UNITED STATES

Robert Wong[1] Bolin Niu[2] George Therapondos[3] Mamta Jain[4] Onkar Kshirsagar[5] Mae Thamer[6]

[1]VA Palo Alto Healthcare System, [2]MetroHealth Medical Center, [3]Ochsner Health System, [4]UT Southwestern, [5]Medical Technology Pratice Patterns, [6]Medical Technology and Practice Patterns

Background: Delays in timely treatment of chronic hepatitis B (CHB) contributes to increased risks of hepatocellular carcinoma and liver-related mortality. While reasons for delays in treatment are multi-factorial, gaps in CHB laboratory monitoring prevent timely assessment of treatment-eligibility to guide treatment decisions. We aim to evaluate gaps and disparities in CHB monitoring among a multi-center cohort of CHB patients in the U.S. **Methods:** Longitudinal follow-up data among adults with treatment-naïve CHB identified from 2010 to 2018 across 3 safety-net health systems were evaluated to determine the proportion of patients that completed laboratory monitoring with HBV DNA and alanine aminotransferase (ALT) within the first year of CHB diagnosis (*LabMonitor1*). The proportion of CHB patients who completed *LabMonitor1* was stratified by gender, age, race/ethnicity, insurance status, and presence of cirrhosis, and compared using chi-square testing. Adjusted multivariable logistic regression models evaluated predictors of *LabMonitor1*. **Results:** Among 3,749 patients with treatment-naïve CHB (51.5% women, 38.7% white, 33.7% African American, 19.6% Asian, 38.2% Medicaid/indigent care, 32.9% commercial insurance, 18.1% Medicare, 24.6% with baseline cirrhosis), 36.9% (n=1,382) completed *LabMonitor1*. Lower rates of completing *LabMonitor1* was observed in men vs. women (36.1% vs. 37.6%, p<0.01) and in older patients age ≥65y vs age < 45y (32.4% vs. 40.1%, p<0.01) (Figure). *LabMonitor1* was highest in Asians (49.7%) and lowest in Hispanics (30.0%). CHB patients with Medicaid or indigent care had greater proportion completing *LabMonitor1* vs. Medicare (43.3% vs. 32.3%, p<0.01). While cirrhosis patients were more likely to have completed *LabMonitor1* vs. non-cirrhotics (46.5% vs. 33.7%, p<0.01), the observation that less than half of patients with CHB cirrhosis completed *LabMonitor1* is alarming. On multivariable regression, Asian CHB patients (vs. whites) were more likely to have completed *LabMonitor1* (aOR 1.60, 95% CI 1.32-1.95, p<0.01) and patients with cirrhosis were more likely to have completed *LabMonitor1* (aOR 1.74, 95% CI 1.43-2.11, p<0.01). **Conclusion:** Among a large multi-center cohort of predominantly non-Asian CHB patients, only 36.9% completed ALT and HBV DNA monitoring within the first year CHB diagnosis. Even more alarming, less than half of patients with CHB cirrhosis had ALT and HBV DNA monitoring within the first year of diagnosis.

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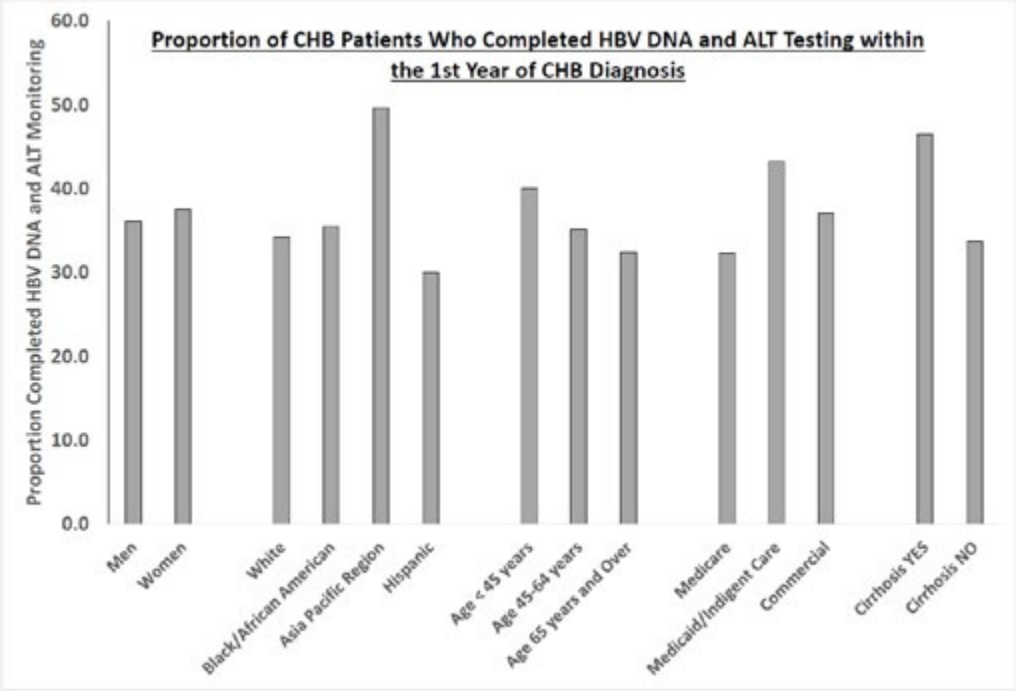

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1213 | MONOTHERAPY WITH THE CAPSID ASSEMBLY MODULATOR, ALG-000184, RESULTS IN HIGH VIRAL SUPPRESSION RATES IN UNTREATED HBEAG+ AND HBEAG- SUBJECTS WITH CHRONIC HEPATITIS B OR CHRONIC HEPATITIS B VIRUS INFECTION

Man-Fung Yuen[1] Edward Gane[2] Christian Schwabe[3] Alina Jucov[4] Alexei Haceatrean[4] Min Wu[5] Kha Le[5] Jennifer Rito[5] Maida Maderazo[5] Lawrence Blatt[5] Sushmita Chanda[5] Tse-I Lin[5] Matthew McClure[6] Kosh Agarwal[7]

[1]The University of Hong Kong, [2]The University of Auckland, [3]Auckland Clinical Studies Ltd, [4]ARENSIA Exploratory Medicine GmbH, [5]Aligos Therapeutics, Inc., [6]Aligos Therapeutics, [7]Kings College Hospital

Background: ALG-000184 is a prodrug of ALG-001075, a highly potent capsid assembly modulator-empty (CAM-E) that, in vitro, inhibits both hepatitis B virus (HBV) replication and cccDNA establishment. **Methods:** ALG-000184-201 is a multi-part, multi-center, randomized clinical trial evaluating the safety, PK, and antiviral activity of ALG-000184 in healthy volunteers and subjects with untreated chronic HBV infection (NCT04536337). We previously reported favorable results from cohorts receiving ALG-000184 ± entecavir for ≤ 64 weeks. Here we report safety and antiviral activity data in untreated HBeAg+ and HBeAg- CHB subjects that received 300 mg ALG-000184 monotherapy for ≤ 72 weeks. **Results:** 21 subjects (N=10 HBeAg+, N=11 HBeAg-) were enrolled and have received 300 mg ALG-000184 monotherapy for up to 72 weeks. Baseline disease characteristics were typical for each HBeAg+ or - patient population, including younger age and higher baseline viral marker levels in HBeAg+ subjects. The mean (SEM) HBV DNA levels were 8.0 (0.2) and 4.3 (0.2) $\log_{10}$ IU/mL for HBeAg+ and HBeAg- subject, respectively. By Week 48 and 72, 60% and 90%, respectively, of HBeAg+ subjects achieved HBV DNA < 10 IU/mL (LLOQ); for HBeAg- subjects, by Week 48, 100% of subjects achieved HBV DNA < 10 IU/mL. All HBeAg+ and HBeAg- subjects had detectable HBV RNA at baseline and with their levels < LLOQ (10 copies/mL) by Week 48. No viral breakthrough has been observed. In addition, multi-$\log_{10}$ declines have been observed for all HBV antigens including HBsAg, HBeAg and HBcrAg in HBeAg+ subjects and for HBcrAg in HBeAg- subjects. Treatment has been well tolerated with no serious adverse events (AEs) reported and no

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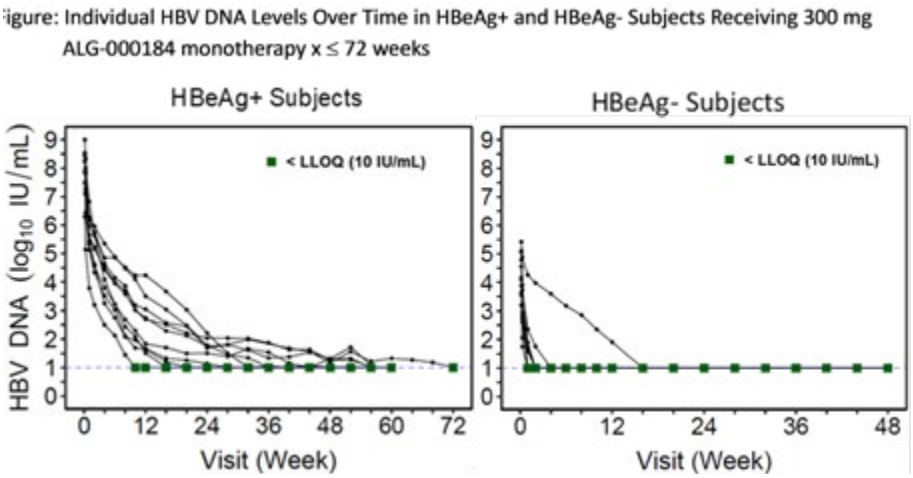
discontinuations due to AEs. Grade 3 TEAEs were reported in 4 subjects: ALT elevations (HBeAg+: n=3; HBeAg–:n=1) and cholesterol/triglycerides increase (n=1). All events have resolved or are improving with continued dosing and all ALT flare events were asymptomatic, without associated synthetic dysfunction, and assessed by the study's safety oversight committee as not related to study drug toxicity. **Conclusion:** 300 mg ALG-000184 monotherapy has resulted in rapid, profound and sustained HBV DNA and HBV RNA viral suppression in untreated CHB subjects. These viral suppressive magnitudes exceed those described by nucleos(t)ide analogs, and suggest ALG-000184 monotherapy could become a long-term treatment for chronic suppression in patient with chronic hepatitis B. Longer dosing in this cohort is currently ongoing.



Disclosures: Man-Fung Yuen: Speaking and Teaching relationship with Fujirebio Incorporation, Gilead Sciences, Roche, Sysmex Corp; Has not ended; Consultant relationship with Clear B Therapeutics, Dicerna Pharmaceuticals; Has not ended; Consultant relationship with AbbVie, Abbott Diagnotics, Aligos Therapeutics; Has not ended; Consultant relationship with Arbutus Biopharma, Arrowhead Pharmaceuticals, Assembly Biosc; Has not ended; Consultant relationship with Immunocore, Janssen, Precision BioSciences; Has not ended; Consultant relationship with Fujirebio Incorporation, GlaxoSmithKline, Gilead Sciences; Has not ended; Grant/Research Support relationship with Fujirebio Incorporation, Gilead Sciences, Immunocore; Has not ended; Grant/Research Support relationship with AbbVie, Assembly Biosciences, Arrowhead Pharmaceuticals; Has not ended; Consultant relationship with Vir Biotechnology and Visirna Therapeutics; Has not ended; Consultant relationship with Roche, Sysmex Corporation, Tune Therapeutics; Has not ended; Grant/Research Support relationship with Sysmex Corporation and Roche; Has not ended, Edward Gane: Aligos Therapeutics: Advisor, Assembly Biosciences: Advisor, AbbVie: Speaking and Teaching, Intellia Therapeutics: Advisor, Tune Therapeutics: Consultant, Precision Bio: Advisor, Virion Therapeutics: Advisor, Gilead Sciences: Advisor, GSK: Advisor, Christian Schwabe: Nothing to Disclose, Alina Jucov: Nothing to Disclose, Alexei Haceatrean: Nothing to Disclose, Min Wu: Nothing to Disclose, Kha Le: Nothing to Disclose, Jennifer Rito: Nothing to Disclose, Maida Maderazo: Nothing to Disclose, Lawrence Blatt: Nothing to Disclose, Sushmita Chanda: Nothing to Disclose, Tse-I Lin: Nothing to Disclose, Matthew McClure: Nothing to Disclose, Kosh Agarwal: Nothing to Disclose

1214 | THE EFFICACY AND SAFETY ANALYSIS OF TDF FOR PREVENTING MOTHER-TO-CHILD TRANSMISSION OF HEPATITIS B VIRUS IN DIFFERENT GESTATIONAL WEEKS

Xiaohong Gao

Background: At present, there is no agreement on the timing of the initiation of the treatment in using antiviral drugs to prevent the mother-to-child transmission (MTCT) of hepatitis B virus (HBV) during pregnancy.There has different advices between physicians of infectious disease and obstetricians, aslo in various regions at home and abroad.Therefore, for the start of antiviral drugs for preventing MTCT at 24-28 weeks of gestation or 28-32 weeks of gestation, the effect between the two and the impact on mothers and babies still needs more data to provide clinical evidence. Analyzing the efficacy and safety of tenofovir dipivoxil fumarate (TDF) for preventing MTCT in pregnant women with high hepatitis B virus load at different gestational weeks in the middle and late stages of pregnancy. **Methods:** Retrospective data collection was performed on pregnant women who received TDF for

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preventing MCTC of HBV during the middle and late stages of pregnancy who were admitted to the Infection and Obstetrics department of the Affiliated Hospital of Yan 'an University from February 2017 to May 2020.A total of 76 cases were included in this study according to the inclusion and exclusion criteria. All included subjects were hepatitis B virus deoxidation nucleic acid (HBV DNA) ≥200000 IU/ml before preventing, and have signed informed consent. They were divided into two groups according to the gestational weeks at which TDF was used. Analyze the antiviral effects of TDF at different gestational weeks and the success rate of maternal and infant blockade; observe the maternal and infant outcomes and the safety at different gestational weeks. **Results:** 1. The HBV DNA level of pregnant who started taking TDF at 24~27+6 weeks of pregnancy was lower than that at 28~32 weeks of pregnancy.2. The success rate of preventing mother-to-child transmission of HBV by taking TDF from 28~32 weeks of gestation is equivalent to that of 24~27+6 weeks of gestation. **Conclusion:** During 24-27+6 weeks or 28-32 weeks of gestation taking TDF are all well tolerated and be generally safe for both mothers and infants.

Disclosures: Xiaohong Gao: Nothing to Disclose

1215 | TENOFOVIR ALAFENAMIDE VERSUS TENOFOVIR DISOPROXIL FUMARATE IN CHRONIC HEPATITIS B: LIVER-RELATED CLINICAL OUTCOMES AND SUBGROUP ANALYSIS BY LIVER CIRRHOSIS STATUS ◆

Soon Sun Kim[1] Gi Hyeon Seo[2] Ji Eun Han[1] Hyo Jung Cho[1] Eunju Kim[3] Eileen Yoon[4] Eun Sun Jang[5] Jong-In Chang[3] Young Youn Cho[6] Hyung Woong Lee[7] Jae Youn Cheong[1] Hyung Joon Kim[6]

[1]Ajou University School of Medicine, [2]Health Insurance Review and Assessment, [3]Chung-Ang University Gwangmyeong Hospita, [4]Hanyang University College of Medicine, [5]Seoul National University College of Med, [6]Chung-Ang University College of Medicine, [7]Yonsei University College of Medicine

Background: This study evaluates the differential impacts of tenofovir alafenamide (TAF) versus tenofovir disoproxil fumarate (TDF) on liver-related clinical outcomes in patients with chronic hepatitis B (CHB), with a particular focus on subgroup analyses according to the presence of liver cirrhosis. **Methods:** A total of 23,074 patients with CHB treated with either TAF (n = 11,537) or TDF (n = 11,537) were analyzed after propensity score matching (PSM) for age, sex, liver cirrhosis, diabetes mellitus, hypertension, and the quarter of the year when treatment was initiated. Of these patients, 24.8% had liver cirrhosis. Liver-related clinical outcomes (hepatocellular carcinoma [HCC], decompensation, and liver transplantation [LT] or death) were followed for a mean of 34.8 months. **Results:** The incidence of HCC was lower in the TAF group (0.72 per 100 person-years) than in the TDF group (0.93 per 100 person-years), with a hazard ratio (HR) for HCC development in the TAF group of 0.77 (95% CI: 0.65–0.92, *P* = 0.003). The incidence of decompensation was lower in patients receiving TAF than in those on TDF (0.84 vs. 1.14 per 100 person-years; HR: 0.74, 95% CI: 0.63–0.86, *P*< 0.001). TAF treatment was associated with a reduced risk of LT or death compared to TDF treatment (incidence: 0.12 vs. 0.29 per 100 person-years; HR: 0.43, 95% CI: 0.30–0.62, *P*< 0.001). Subgroup analysis revealed that among patients without liver cirrhosis, TAF treatment significantly reduced the risk of HCC (HR: 0.69, 95% CI: 0.52–0.92, P = 0.012), decompensation (HR: 0.73, 95% CI: 0.59–0.90, *P* = 0.003), and LT or death (HR: 0.30, 95% CI: 0.16–0.54, *P* < 0.001) compared to TDF treatment. In contrast, among patients with liver cirrhosis, TAF treatment significantly reduced the risk of LT or death (HR: 0.55, 95% CI: 0.35–0.88, *P* = 0.012), although the difference in the reduction of HCC incidence between TAF and TDF did not reach statistical significance (*P* = 0.063). **Conclusion:** TAF treatment in patients with CHB was associated with significantly lower risks of HCC, LT or death, and decompensation compared to TDF treatment. In patients without cirrhosis, treatment with TAF decreases the risks of HCC, decompensation, and LT or death. However, for those with cirrhosis, although TAF reduces the likelihood of decompensation and LT or death, it does not significantly alter the risk of HCC when compared to the TDF group. These findings suggest the potential of TAF as a preferred treatment option in CHB management, regardless of the presence of liver cirrhosis.

Disclosures: Soon Sun Kim: Nothing to Disclose, Gi Hyeon Seo: Nothing to Disclose, Ji Eun Han: Nothing to Disclose, Hyo Jung Cho: Nothing to Disclose, Eunju Kim: Nothing to Disclose, Eileen Yoon: Nothing to Disclose, Eun Sun Jang: Nothing to Disclose, Jong-In Chang: Nothing to Disclose, Young Youn Cho: Nothing to Disclose, Hyung Woong Lee: Nothing to Disclose, Jae Youn Cheong: Nothing to Disclose, Hyung Joon Kim: Nothing to Disclose

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1216 | HEPATITIS B VIRUS SUBVIRAL PARTICLE BIOGENESIS RELIES ON FUNCTIONAL UBIQUITIN AND PROTEASOME PATHWAYS

Sisi Yang[1] Jiyang Chen[1] Lin Zheng[1] Yida Yang[1] Ju-tao Guo[2]

[1]Zhejiang University, [2]Baruch S. Blumberg Institute

Background: The high level of HBV surface antigen (HBsAg), or HBV subviral particle (SVP) in the blood is the driving force for the development of immune tolerance towards chronic hepatitis B (CHB). Our recent study indicated that S protein was degraded by 20S proteasome in an ubiquitin-independent manner, interestingly, both the intracellular and secreted SVP were significantly reduced following treatment with RA190, a 26S proteasome inhibitor. These findings suggested that ubiquitin and proteasome pathways may play a crucial role in SVP biogenesis. **Methods:** A high throughput assay was established with the HepG2-3GS11 cell lines, designed for the screening of a small molecule compound library targeting the ubiquitin-proteasome pathway (Catalog No. HY-L050, MCE). The plasmids were reported previously (Yang et al., 2021) Both the HepG2 cell lines and Huh 7 cell lines were used for transfection and compound treatment for further mechanism exploring. Experiments for knock-down and over-expression were conducted specifically with HepG2 cell lines. Intracellular and secreted SVP was detected by Particle gel assay and ELISA respectively. **Results:** In HepG2-3GS11 cell lines, 136 small molecular compounds targeting the ubiquitin-proteasome pathway were screened by a high throughput assay, and most inhibitors of E3 ubiquitin ligase MDM2, adenosine triphosphatase VCP/p97 and 26S proteasome were found can inhibit SVP secretion. Specifically, the EC50 and CC50 of RG7112 (MDM2 inhibitor), DBeQ (VCP/p97 inhibitor), RA190 (26S proteasome inhibitor), MG-132 (20S proteasome inhibitor) were found to be 10.59μM and >100μM, 10.34μM and 25.89μM, 1.40μM and >50μM, 5.01μM and >100μM, respectively. And the inhibitory effect of the selected compounds on SVP secretion was dose-dependent. Furthermore, siRNA-mediated knockdown of MDM2, VCP, and ADRM1 expressions in HepG2 cell lines led to a significant reduction in both secreted and intracellular SVP. Additionally, MDM2 inhibitors had a similar inhibition effect on SVP in both Huh7 cell lines (namely p53 Mut cell lines) and HepG2 cell lines (namely p53 WT cell lines). To investigate whether S protein polyubiquitination is required for SVP biogenesis, all four lysine (K) residues of S protein were replaced with alanine (A) or arginine (R) in WT S protein to prevent ubiquitination and intracellular and secreted SVP could still be detected in cells with arginine substitutions. **Conclusion:** In summary, our study elucidated that SVP assembly and secretion was regulated by MDM2-ubiquitin-26S proteasome pathway through an unknown host factor other than P53, and further study was supposed to be conducted to identify the unknown host factor, which will provide a theoretical basis for new target on HBV drug discovery.

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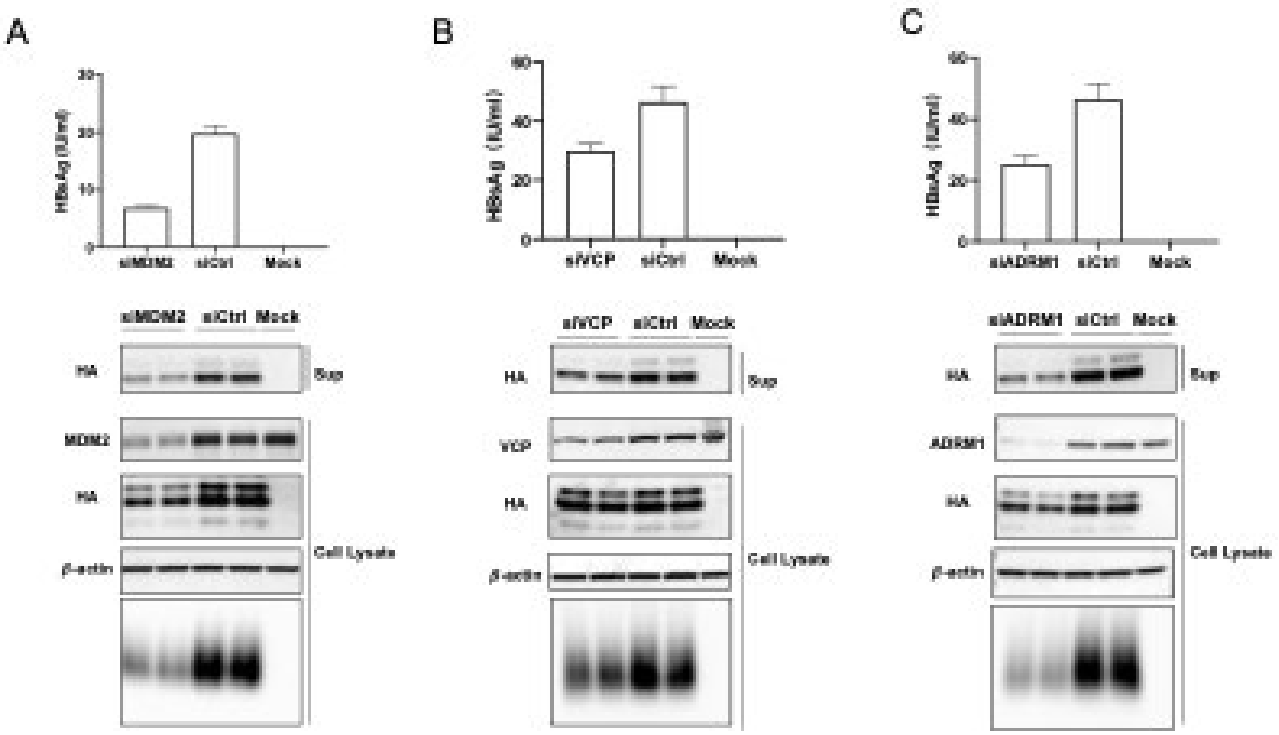

Disclosures: Sisi Yang: Nothing to Disclose, Jiyang Chen: Nothing to Disclose, Lin Zheng: Nothing to Disclose, Yida Yang: Nothing to Disclose, Ju-tao Guo: Nothing to Disclose

1217 | HBEAG-POSITIVE PREGNANT MOTHERS WITH HIGHER HBV DNA DECLINE RATE FROM MID-PREGNANCY TO DELIVERY ARE MORE LIKELY TO ACHIEVE HBEAG SEROCONVERSION AFTER DELIVERY WITHOUT POSTPARTUM CESSATION OF NUCLEOS(T)IDE ANALOGS THERAPY

Wenting Zhong[1] Jie Zheng[1] Naijuan Yao[1] Lei Shi[1] Yingli He[2] Tianyan Chen[1]

[1]Xi'an Jiaotong University, [2]Xi'an Jiatong University

Background: There is still controversy about whether to continue nucleos(t)ide analogs(NAs) after delivery,especially for pregnant women in the immune tolerance(IT) phase.In this study,a retrospective cohort study was conducted to explore the relationship between HBV DNA decline rate from mid-pregnancy to delivery and HBeAg seroconversion postpartum among patients using NAs to prevent mother-to-child transmission(MTCT),with the goal of identifying the ideal candidates for postpartum NAs continuation. **Methods:** In this retrospective study,postpartum women who received NAs at mid-pregnancy to prevent MTCT and continue NAs for at least 96 weeks after delivery in the first Affiliated Hospital of Xi'an Jiaotong University from 2014 to 2020 were included.They were defined as HBsAg positive,HBeAg positive,HBV DNA load>5.3log10 IU/ml at mid-pregnancy and alanine aminotransferase(ALT) level during pregnancy < 2ULN.Univariate and multivariable logistic regression analyses were conducted to assess the association between the HBV DNA decline rate and HBeAg seroconversion postpartum.Receiver operating characteristic(ROC) analysis was utilized to evaluate the predictive capacity of the HBeAg decline rate and determine the optimal cut-off point. **Results:** Our study included 151 cases,among which 27.15%(41/151) of patients achieved HBeAg seroconversion after delivery.The univariate analysis revealed a significant association between the HBV decline rate (%) and HBeAg seroconversion postpartum (OR 1.054, 95% CI: 1.024-1.085, P < 0.001).In the multivariate regression analysis,adjusting for age,HBsAg titer at mid-pregnancy and HBsAg decline rate from mid-pregnancy to delivery,the HBV DNA decline rate remained significantly associated with HBeAg seroconversion postpartum (OR 1.038, 95% CI: 1.009-1.072, P = 0.014).Then HBV DNA decline rate was treated as a categorical variable(tertiles) for sensitivity analysis.In the three distinct models,taking Tertile1 as a reference,women in Tertile3 still had a 4.276-fold(OR 4.276, 95% CI:1.374-13.308, P=0.012) higher risk of developing HBeAg seroconversion (P for trend <0.05) after adjusting

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above covariates.The area under the curve(AUC) was 0.702 (95% CI: 0.616-0.788).The optimal cut-off value was 63.27%,with a sensitivity of 0.610,specificity of 0.736,and Youden's index of 0.346. **Conclusion:** A higher HBV DNA decline rate(%) from mid-pregnancy to delivery independently correlated with an increased risk of HBeAg seroconversion postpartum.Pregnant women with HBV DNA decline rate(%)>63.27% from mid-pregnancy to delivery were more likely to achieve HBeAg seroconversion without postpartum cessation of NAs.

Table Relationship between HBV DNA decline rate (%) from mid-pregnancy to delivery with HBeAg seroconversion after delivery in different models

	Crude Model		Model I		Model II	
	OR (95%CI)	P-value	OR (95%CI)	P-value	OR (95%CI)	P-value
HBV DNA decline rate(%)	1.054(1.024,1.085)	<0.001	1.054(1.026,1.087)	<0.001	1.038(1.009,1.072)	0.014
Tertile1	Reference		Reference		Reference	
Tertile2	3.943(1.308,11.886)	0.015	3.931(1.303,11.857)	0.015	3.934(1.259,12.298)	0.019
Tertile3	6.662(2.262,19.625)	0.001	6.714(2.275,19.810)	0.001	4.276(1.374,13.308)	0.012
P for trend	2.397(1.471,3.908)	<0.001	2.411(1.476,3.937)	<0.001	1.914(1.146,3.197)	0.013

Abbreviations: OR, odds ratio; CI, confidence interval; HBeAg, hepatitis B e antigen.
Model I adjusted for age.
Model II adjusted for age,HBsAg titer(log10 IU/mL) at mid-pregnancy,HBsAg decline rate(%) from mid-pregnancy to delivery.

Disclosures: Wenting Zhong: Nothing to Disclose, Jie Zheng: Nothing to Disclose, Naijuan Yao: Nothing to Disclose, Lei Shi: Nothing to Disclose, Yingli He: Nothing to Disclose, Tianyan Chen: Nothing to Disclose

1218 | HIGH FUNCTIONAL CURE RATE INDUCED BY PEG IFN ALPHA-2B IN HBV POSTPARTUM WOMEN WITH HBEAG NEGATIVE: AN EXPLORATIONAL STUDY

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Background: There is a lack of data supporting the idea that postpartum women with hepatitis B virus(HBV) are an advantageous population for functional cure with pegylated interferon(Peg-IFN) alpha-2b due to the hormonal changes and the restoration of immune function after delivery.Our goal was to assess the effectiveness and safety of Peg-IFN alpha-2b in HBV postpartum women with HBeAg negative and identify factors linked to functional cure. **Methods:** In this retrospective study,HBeAg-negative postpartum women(12-72 weeks post-delivery) with HBsAg≤3000IU/mL and HBV DNA≤2000IU/ml in the first Affiliated Hospital of Xi'an Jiaotong University from 2018 to 2022 were included.They were divided into 2 groups depending on whether they used Peg-IFN alpha-2b or not.Propensity score matching(PSM) was used to equalize the baseline imbalance between two groups. Patients were followed for at least 48 weeks.The primary endpoints were hepatitis B surface antigen(HBsAg) loss and HBsAg seroconversion at 48 weeks.Logistic regression analysis was used to assess factors associated with HBsAg loss at 48 weeks. **Results:** Our study included 150 cases,among which 47 patients received Peg-IFNa-2b[Peg-IFN(+) group] and the other 103 patients didn't receive it[Peg-IFN(-) group].At week 48,the HBsAg loss and seroconversion rate in Peg-IFN(+) group were 51.06%(24/47) and 40.43%(19/47),respectively. Even after PSM,Peg-IFN(+) group still showed higher HBsAg loss rate(50.00% vs 7.14%,p<0.001) and higher HBsAg seroconversion rate(38.10% vs 2.38%,p<0.001).Baseline HBsAg levels (OR:0.051,95%CI:0.003-0.273,P:0.010),HBsAg at week24 (OR:0.214,95%CI:0.033-0.616,P:0.022),HBsAg decline at week24 (OR:4.682,95%CI:1.624-30.198,P:0.022) and postpartum flare (OR:21.181,95%CI:1.872-633.801,P:0.030) significantly associated with HBsAg loss at week48 after Peg-IFN alpha-2b therapy.Furthermore, the receiver operating characteristic curve(ROC) showed baseline HBsAg<182 IU/mL(AUC:0.924,P=0.001),HBsAg at week24 < 4 IU/mL(AUC:0.969,P<0.001) and HBsAg decline at week24>12IU/mL(AUC:0.863,P<0.001) provided good

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predictions for HBsAg loss.No serious adverse events were reported. **Conclusion:** Peg-IFN alpha-2b leads to a high rate of HBsAg loss and seroconversion in HBeAg-negative postpartum women with reliable safety, particularly for patients who experienced postpartum flare and had low baseline HBsAg levels.

Baseline and outcomes of patients before and after PSM

Variables	Before PSM			After PSM		
	Peg-IFN (-) N=103	Peg-IFN (+) N=47	P	Peg-IFN (-) N=42	Peg-IFN (+) N=42	P
Baseline						
use of NAs（%）	64(62.14)	28(59.57)	0.765	28(66.67)	27(64.29)	1.000
Age（years）	29.80±3.56	31.49±3.38	0.007	31.43±3.74	31.52±3.49	0.891
Postpartum flare,N（%）	13(12.62)	11(24.44)	0.073	16(38.10)	15(35.71)	1.000
Time from delivery to study enrollment(months)	11.30(7.80,14.43)	11.93(8.27,14.37)	0.741	11.97(8.10,14.70)	12.17(8.10,14.37)	0.960
ALT(U/L)	18.96±8.08	17.87±8.90	0.465	19.18±7.55	17.62±9.06	0.400
AST(U/L)	21.36±6.17	20.94±8.30	0.732	21.65±5.37	20.31±6.35	0.302
HBsAg(log10 IU/mL)	2.98(2.38,3.22)	2.55(1.95,2.99)	0.006	2.69(2.09,3.02)	2.55(1.45,3.01)	0.288
HBV DNA(log10 IU/mL)	1.30(1.30,2.00)	1.30(1.30,1.30)	0.107	1.30(1.30,2.00)	1.30(1.30,1.30)	0.527
HBsAg reduction from mid-pregnancy to delivery(log10 IU/mL)	0.05(-0.07,0.21)	0.09(-0.04,0.52)	0.087	0.07(-0.04,0.25)	0.09(-0.04,0.52)	0.339
Outcomes at week24						
HBsAg reduction from baseline, log10 IU/mL	0.03(-0.10,0.14)	1.08(0.53,2.55)	<0.001	0.04(-0.07,0.25)	1.03(0.47,2.69)	<0.001
HBsAg loss, n (%)	1(0.97)	14(29.79)	<0.001	1(2.38)	13(30.95)	<0.001
HBsAg seroconversion, n (%)	1(0.97)	10(21.28)	<0.001	1(2.38)	9(21.43)	0.008
HBV DNA undetectable, n (%)	67(65.05)	38(80.85)	0.050	30(71.43)	34(80.95)	0.454
Outcomes at week48						
HBsAg reduction from baseline, log10 IU/mL	0.07(-0.09,0.21)	1.85(1.13,3.25)	<0.001	0.07(-0.09,0.24)	1.61(1.07,3.21)	<0.001
HBsAg loss, n (%)	3(2.91)	24(51.06)	<0.001	3(7.14)	21(50.00)	<0.001
HBsAg seroconversion, n (%)	1(0.97)	19(40.43)	<0.001	1(2.38)	16(38.10)	<0.001
HBV DNA undetectable, n (%)	67(65.05)	45(95.75)	<0.001	30(71.43)	40(95.24)	0.013

Abbreviations:PSM,propensity score matching; Peg-IFN alpha-2b,pegylated interferon alpha-2b; NAs,nucleos(t)ide analogs; AST,aspartate aminotransferase; ALT,alanine aminotransferase; HBV, hepatitis B virus;HBsAg,hepatitis B surface antigen.

P<0.05 was considered statistically significant.

Disclosures: Wenting Zhong: Nothing to Disclose, Lanzhi Yan: Nothing to Disclose, Yage Zhu: Nothing to Disclose, Lei Shi: Nothing to Disclose, Yingli He: Nothing to Disclose, Tianyan Chen: Nothing to Disclose, Jie Zheng: Nothing to Disclose

1219 | DISMANTLING BARRIERS TO HEPATITIS B AND DELTA SCREENING, PREVENTION, AND LINKAGE TO CARE AMONG THE PWUD COMMUNITY IN PHILADELPHIA

Beatrice Zovich[1] Catherine Freeland[1] Holly Moore[1] Kara Sapp[1] Anousha Qureshi[1] Chari Cohen[1] Rachel Holbert[2] Jason Zambrano[1] Daljinder Bhangoo[3] Richard Hass[3] Amy Jessop[2]

[1]Hepatitis B Foundation, [2]HepTREC at Prevention Point Philadelphia, [3]Thomas Jefferson University

Background: Despite the serious effects of unmanaged hepatitis B and delta virus infections (HBV and HDV), knowledge about disease prevalence and efforts to ensure diagnosis and connection to care among people who use drugs (PWUD) remain limited. This study assessed HBV and HDV prevalence and facilitated linkage to vaccination or care at a Philadelphia, PA (USA) harm reduction organization (HRO). **Methods:** Participants

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completed a demographic/risk factors survey and blood draw to assess HBV immunity and infection, with reflex testing for HDV if HBV surface antigen (current infection) or isolated core antibody (previous exposure) were present. Participants were incentivized for testing and to return to review results with study staff, where linkage to immunization and care were attempted. Fisher's exact tests and regression were used to identify relationships between risk factors and HBV blood markers. **Results:** Of the 498 participants, 126 (25.3%) were susceptible to HBV, 52.6% were vaccinated, and 17.9% had recovered from past infection. Eleven (2.2%) tested positive for isolated HBV core antibody, 10 (2.0%) for HBV surface antigen, and one (10% of those with HBV) for HDV antibody. History of incarceration was associated with current HBV infection, while transactional sex and experiences of homelessness were associated with previous HBV exposure. **Conclusion:** This study found high rates of current and past HBV infection, and a 10% HBV/HDV co-infection rate. Despite availability of vaccine, 25% remained vulnerable to infection. Linking participants to immunization and care was complicated by provider restrictions and logistical challenges. These results demonstrate the need to improve low-threshold HBV/HDV screening, vaccination, and linkage to care among PWUD, and how tools like point-of-care diagnostics and increased support for HROs can fill gaps in the HBV/HDV care cascade.

Disclosures: Beatrice Zovich: Nothing to Disclose, Catherine Freeland: Nothing to Disclose, Holly Moore: Nothing to Disclose, Kara Sapp: Nothing to Disclose, Anousha Qureshi: Nothing to Disclose, Chari Cohen: Gilead Sciences: Grant/Research Support, VBI Vaccines: Grant/Research Support, GSK: Grant/Research Support, Roche: Grant/Research Support, Rachel Holbert: Nothing to Disclose, Jason Zambrano: Nothing to Disclose, Daljinder Bhangoo: Nothing to Disclose, Richard Hass: Nothing to Disclose, Amy Jessop: Nothing to Disclose

1220 | SERUM HBSAG RATHER THAN HBV DNA REFLECTS LIVER HBV TRANSCRIPT LEVELS OF HEPATITIS B PATIENTS TREATED BY NUCLEOSIDE ANALOGUES

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[1]Gansu Wuwei Tumour Hospital, Wuwei, China, [2]The 4th People's Hospital of Qinghai Province, Xining, China, [3]Jumei Doctor Group Medical (Shenzhen) Co., Ltd, Shenzhen, China, [4]Beijjing Institute of Hepatology/Beijing Youan Hospital

Background: The therapeutic goal of CHB is to achieve a "functional" cure, which is characterized by sustained HBsAg loss and HBV DNA levels below the lower limit of detection.However,it is almost impossible to achieve sustained HBsAg loss with nucleoside analogues (NAs) treatment. It is poor treatment efficacy and low HBsAg conversion rate for antiviral treatment of CHB patients with high HBsAg levels, although serum HBV DNA levels were below the lower limit of detection or undetectable. Here, we evaluated serum HBsAg and serum HBV DNA, which is better for evaluating HBV transcriptional activity in liver tissue of hepatitis B patients treated by NAs. **Methods:** This study was derived from the "Excellence" project-HBV cohort, which consisted of 20 CHB patients(male/11,female/9)with NAs (ETV/TDF/TAF) treatment for a median interquartile range (IQR) of 36 (4-240) months,whose aged 27–58 years and admitted to the hospital from May 2023 to October 2023 . Liver histologic biopsy was performed immediately after admission. Intrahepatic HBV covalent closed loop DNA (cccDNA) was quantified by droplet digital PCR (ddPCR), and intrahepatic HBV DNA was quantified by quantitative real-time PCR (qRT-PCR). Intrahepatic HBV cccDNA and HBV DNA parameters were analyzed in relation to serum HBsAg and HBV DNA levels, respectively. **Results:** Serum HBsAg levels of all CHB patients with antiviral treatmentwere greater than 1500IU/mL, but serum HBV DNA were already at very low or undetectable levels. Interestingly, for CHB patients with no HBV DNA detection in serum, their liver tissues have high levels of HBV DNA (4.880±0.894,log10 IU/mL,) and HBV cccDNA (3.967±0.695, log10copies/μL,) with significantly positively correlation(r=0.772,P<0.0001). Serum HBsAg level was positively correlated with intrahepatic HBV cccDNA level (r=0.673,P=0.0011), and positively correlated with intrahepatic HBV DNA level (r=0.728,P=0.0003). The serum HBsAg and serum HBeAg level had good correlation (r=0.618, P=0.0037), however, serum HBV DNA and serum HBeAg level were no correlated with intrahepatic HBV ccc DNA level and intrahepatic HBV DNA level. **Conclusion:** In CHB patients with NAs treatment, serum HBsAg rather than HBV DNA reflects liver HBV transcript levels of hepatitis B patients. It is serum HBsAg level, not HBV DNA level that may comprehensively reflect HBV replication activity and help evaluation of antiviral therapeutic efficacy.

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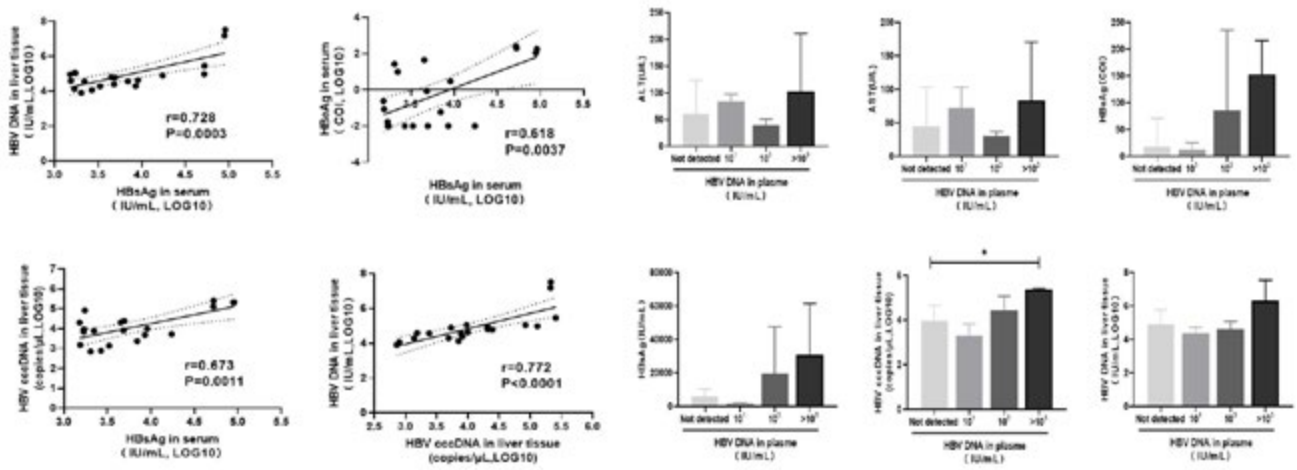

Disclosures: Wenhua Zhang: Nothing to Disclose, Haitao Tang: Nothing to Disclose, Qinghua Lu: Nothing to Disclose, Tingxia Chao: Nothing to Disclose, Haifang Cao: Nothing to Disclose, Hongfei Zhang: Nothing to Disclose, Feng Ren: Nothing to Disclose

1221 | PROGNOSTIC AND THERPEUTIC POTENTIAL OF IMBALANCE BETWEEN PD-1+CD8 AND ICOS+REGULATORY T CELLS IN ADVANCED HBV-HCC

Yan Fengna

Background: Over 50% of patients with Hepatitis B virus-associated hepatocellular carcinoma (HBV-HCC) are diagnosed at an advanced stage, which characterized by immune imbalance between CD8+T cells and regulatory T (Treg) cells accelerates disease progression, but there was no imbalance indicator to predicted clincal outcomes. **Methods:** Flow cytometry was used to analyzed the peripheral anti-tumor immune response with healthy control, HBV-cirrhosis, advanced HBV-HCC patients. **Results:** We show that the proportion of CD8+T cells decreased and Treg cells increased in advanced HBV-HCC patients. During this stage, CD8+T cells and Treg cells expressed the co-inhibitory molecule PD-1 and the co-stimulatory molecule ICOS, respectively. Additionally, the ratio between PD-1+CD8 and ICOS+Tregs showed significant changes. Patients were further divided into high and low ratio : PD-1+CD8 and ICOS+Tregs high (PD-1/ICOShigh) and low ratio (PD-1/ICOSlow) groups according to ratio median. Compared with PD-1/ICOSlow patients, PD-1/ICOShigh group had better clinical prognosis, weaker CD8+T cells exhaustion, T cell killing and proliferation function is more conservative. More surprisingly, the small sample analysis found that PD-1/ICOShigh patients exhibited a higher proportion of tissue-resident memory T-cells (TRM) cells and have more stable killing capacity and lower apoptosis capacity than PD-1/ICOSlow advanced HBV-HCC patients treated with immune checkpoint inhibitors (ICI). **Conclusion:** The ratio between PD-1+CD8 and ICOS+Tregs was associated with extreme immune imbalance and poor prognosis in advanced HBV-HCC.

Disclosures: Yan Fengna: Nothing to Disclose

1222 | ANTI-HBS IMMUNE COMPLEX LEVELS: A NOVEL BIOMARKER OF HEPATITIS FLARE IN PATIENTS WITH HBEAG-NEGATIVE CHRONIC HEPATITIS B WHO STOP NUCLEOS(T)IDE ANALOGUE THERAPY

Simon Hume[1] Samuel Hall[1] Gareth Burns[2] Kathy Jackson[3] Peter Revill[3] Margaret Littlejohn[3] Kaylene Cheng[1] Darren Wong[4] Sara Vogrin[5] Jacinta Holmes[6] Kumar Visvanathan[1] Alexander Thompson[1] Nadia Warner[3]

[1]St Vincent's Hospital Melbourne, [2]Western Health, [3]VIDRL, [4]Austin Health, [5]University of Melbourne, [6]St.Vincent's University Hospital

Background: The saturation of HBsAg by the formation of Anti-HBs immune complexes (HBsAg-IC) has made it challenging to study the humoral immune response in chronic hepatitis B (CHB). We have previously optimised an

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immune complex assay for quantifying anti-HBs in the presence of HBsAg. We have previously observed that on treatment ALT flares leading to HBsAg loss are associated with an increase in HBsAg-IC (Xu et al., JHEP, 2022). The role of HBsAg-IC in the pathophysiology of hepatitis flare warrants further study. **Methods:** HBsAg-IC levels were evaluated amongst 34 patients previously enrolled in a prospective study of nucleos(t)ide analogue (NA) discontinuation with 96 weeks of follow-up (all patients were non-cirrhotic with HBeAg-negative CHB). Patients with available stored sera were selected (21 cases of ALT > 10 x ULN, 5 cases ALT 2-10 x ULN and 8 controls with no ALT flare). HBsAg-IC was isolated using an established polyethylene glycol precipitation method with quantification subsequently performed using the Roche Elecsys system. End-of-treatment (EOT; at NA cessation) and longitudinal HBsAg-IC levels were used to predict clinical outcomes including hepatitis flare (ALT>5xULN with HBV DNA>2000 IU/mL) and major flare (ALT>10xULN with HBV DNA>2000 IU/mL). **Results:** At EOT, the median age was 54 years, 62% were male, 79% were Asian and the median EOT HBsAg titre was 547 IU/mL. HBsAg-IC level was detectable at EOT in 33/34 participants with a median level of 9.78 IU/mL. A high EOT HBsAg-IC (≥39 IU/mL or 75th centile) was associated with a reduced risk of major flare (22% vs 76%, p=.01) and a trend towards a lower risk of hepatitis flare (44% vs 83%, p=.05). Amongst participants who experienced a flare, peak flare was associated with an increase in HBsAg-IC levels (Figure 1) and occurred at the time of peak ALT in 92% of patients. No significant change in HBsAg-IC levels were observed over time in the patients without flare. **Conclusion:** This is the first study to demonstrate that higher EOT HBsAg-IC levels are associated with a lower risk of flare amongst individuals who stop NA therapy and therefore may be a marker of immune control. Amongst those who experienced a hepatitis flare off-treatment, a rapid rise in HBsAg-IC level was observed at time of peak ALT. This suggests that the humoral immune system may play an important role in the pathophysiology of hepatitis flare.

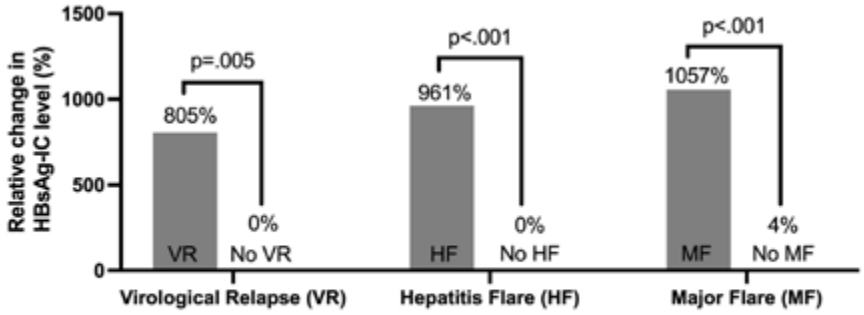

Figure 1. Median relative increase in HBsAg-IC off-treatment [(peak - EOT) / EOT]

Disclosures: Simon Hume: Nothing to Disclose, Samuel Hall: Nothing to Disclose, Gareth Burns: Nothing to Disclose, Kathy Jackson: Nothing to Disclose, Peter Revill: Nothing to Disclose, Margaret Littlejohn: Nothing to Disclose, Kaylene Cheng: Nothing to Disclose, Darren Wong: Nothing to Disclose, Sara Vogrin: Nothing to Disclose, Jacinta Holmes: Nothing to Disclose, Kumar Visvanathan: Nothing to Disclose, Alexander Thompson: Gilead Sciences: Consultant, Gilead Sciences: Speaking and Teaching, Abbvie: Consultant, Abbvie: Speaking and Teaching, Immunocore: Advisor, Nadia Warner: Nothing to Disclose

1223 | THE IMPACT OF TENOFOVIR AMIBUFENAMIDE (TMF) ON BLOOD LIPIDS DURING THE PROCESS OF ANTI-HEPATITIS B VIRUS TREATMENT – A REAL WORLD PROSPECTIVE STUDY

Yang Ling[1] Yang Ling[1] Huikuan Chu[1] Jin Ye[1] Fan Du[1] Yang Ling[2]

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Background: Tenofovir amibufenamide (TMF), a second-generation of tenofovir, is a widely used antiviral drug for chronic hepatitis B. However, it remains unclear whether long-term use of TMF would affect blood lipid metabolism. As the prevalence of metabolism-related diseases continues to rise, there is an increasingly demand for maintaining appropriate blood lipid levels. Therefore, a real-world prospective study was designed and carried out aiming at clarifying the influence of TMF on blood lipid spectrum by comparing the changes of blood lipid profiles before and after antiviral treatment. **Methods:** A total of 209 chronic hepatitis B (CHB) patients with

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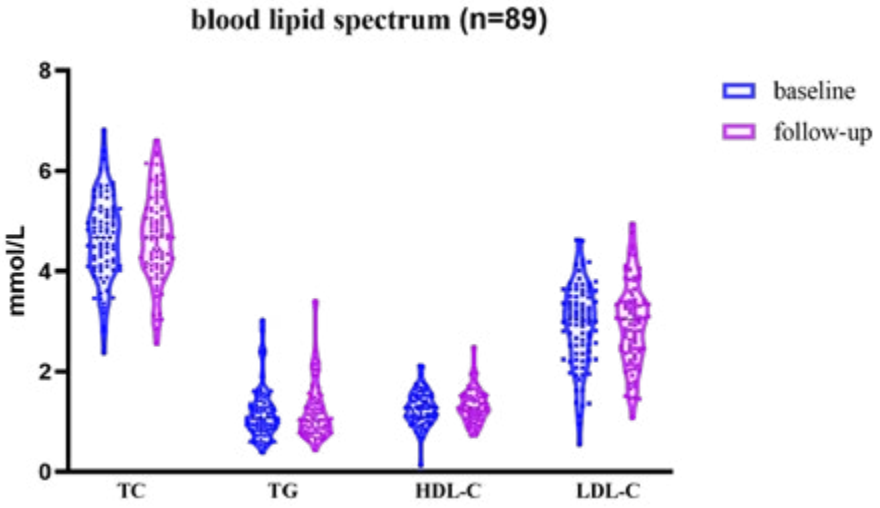
TMF treatment were enrolled in this study. Among which, 19 patients were found to be receiving lipid-lowering medication treatment, and 38 patients are excluded for combining other liver disease and incomplete data. Finally, 89 patients were recorded to have complete data before and after TMF treatment, with 43 patients having normal baseline blood lipids normal group) and 46 patients having disordered blood lipids (abnormal group) before TMF intervention. During the follow-up period, lipid profiles, including total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C), were used to analyze the effects of TMF on blood lipids (Using Wilcoxon matched-pairs signed rank test). (ClinicalTrials.gov number, NCT05398393.) **Results:** Compared to baseline, the levels of lipid indices after a median follow-up of 370 (304~452) days in patients accepting TMF (n=89) were not changed significantly [TC: 4.67 vs. 4.69 (p=0.16), TG: 1.07 vs. 1.04 (p=0.31), HDL-C: 1.27 vs. 1.27 (p=0.25), LDL-C: 3.02 vs. 3.03 (p=0.41)]. In the abnormal group(n=46), the changes in blood lipid profiles before and after TMF treatment were not significant, either [TC: 5.2 vs. 4.98 (p=0.98), TG: 1.22 vs.1.19 (p=0.84), HDL-C: 1.13 vs.1.21 (p=0.59), LDL-C: 3.49 vs. 3.33 (p=0.89)]. And in the normal group (n=43), the levels of blood spectrums remained relatively stable [TC: 4.29 vs. 4.38 (p=0.06), TG: 0.92 vs. 0.91 (p=0.09), HDL-C: 1.30 vs. 1.32 (p=0.43), LDL-C: 2.54 vs. 2.63 (p=0.33)]. **Conclusion:** TMF showed no significantly lipid-raising effect during one year follow-up of antiviral treatment.



Disclosures: Yang Ling: Nothing to Disclose, Huikuan Chu: Nothing to Disclose, Jin Ye: Nothing to Disclose, Fan Du: Nothing to Disclose, Nothing to Disclose

1224 | LARGE REDUCTIONS OF HBV INTEGRATIONS AND VIRAL TRANSCRIPTS IN LIVER BIOPSIES FROM FUNCTIONALLY-CURED CHB PATIENTS

Cameron Soulette[1]

[1]*Gilead Science, Inc*

Background: Novel therapeutic strategies for chronic hepatitis B (CHB) aim to achieve functional cure (FC), defined by sustained off-treatment loss of HBV surface antigen (HBsAg). Integrated HBV DNA (iDNA) is thought to be an important barrier to FC given that iDNA acts as a reservoir for HBsAg production, yet iDNA burden has not been well defined after achieving FC. Here, we utilized a long-read sequencing approach to provide a high-resolution snapshot of the intrahepatic viral burden from individuals achieving FC. **Methods:** Liver biopsies were collected from 17 individuals; n=12 from CHB patients (n=3 virally suppressed, n=9 treatment naïve) and n=5 from individuals who were previously chronically infected but achieved FC 1-7 years prior to biopsy. Of the FC cohort, n=1 patient spontaneously cleared infection and n=4 achieved HBsAg loss while on PEG-IFN-α2b + NUC treatment. RNA and DNA extraction were processed by our long-read sequencing method to identify VirAL Integrations ANd Translocations (VALIANT). **Results:** Intrahepatic levels of iDNA were >100-fold lower in biopsies from FC patients relative to biopsies from the CHB cohort ($p<0.05$), and non-integrated HBV DNA was detected in only a single FC biopsy at very low abundance. iDNA detected from the FC cohort were typically short,

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truncated fragments of the HBV genome, lacking a complete HBsAg encoding region. Nevertheless, VALIANT detected some intrahepatic viral transcripts from both iDNA and cccDNA in the FC cohort. Transcripts encoding HBsAg were rare; n=3 patients contained at least one sequenced read spanning the entire S-HBs open reading frame, and only a single patient had >5 S-HBs transcripts. Export and escape mutations associated with HBsAg 'a'-determinant region were not observed in s-encoded transcripts . The overall abundance of HBV transcripts was >500-fold lower in liver biopsies from FC vs CHB patients ($p<0.05$). **Conclusion:** iDNA and HBV RNA are present at very low levels in patients achieving FC relative to CHB patients. The remaining iDNA were typically short fragments lacking the HBsAg coding region, indicating that FC requires elimination of nearly all HBsAg producing integrations. These results suggest that therapeutic strategies aimed toward eliminating iDNA as well as cccDNA may be key to achieving FC.

Disclosures: Cameron Soulette: Gilead Sciences, Inc.: Employee

1225 | ROLE OF HEALTHCARE PROVIDERS IN RECRUITMENT OF MINORITY POPULATIONS LIVING WITH HEPATITIS B IN CLINICAL TRIALS

Chari Cohen[1] *Tanya Machado*[1] *Yasmin Ibrahim*[1] *Fiona Borondy-Jenkins*[1]

[1]*Hepatitis B Foundation*

Background: Clinical trials investigating therapies for chronic hepatitis B (CHB) lack adequate representation of diverse racial backgrounds, impeding accurate assessment of treatment efficacy and safety for these communities. Identifying specific barriers among minority groups in the United States, such as Asians, Native Hawaiians, Pacific Islanders, and Africans, is essential to enhance inclusivity in these trials. This study investigated patients' perspectives and recommendations to foster diverse representation in future CHB clinical trials. The results in this poster focus on the perceived role of healthcare providers in clinical trial participation. **Methods:** A qualitative study, with six focus groups and five in-depth interviews, representing Vietnamese, West African, Somalian, Korean, Chinese, and Caucasian communities. All participants were people living with CHB. Focus groups and interviews were conducted in different languages when needed; languages included Korean, Vietnamese, Chuukese, Somali, and French. The inquiries centered on current perceptions of clinical trials, barriers to participation, factors affecting willingness to participate, and suggestions for enhancing inclusivity among diverse populations in future clinical trial recruitment. All focus groups and interviews were recorded, transcribed and translated into English. Grounded theory analysis was used to formulate hypotheses around the influence of healthcare providers on participants' willingness to join clinical trials. **Results:** According to participants, providers play three key roles in patient recruitment: bridging knowledge gaps surrounding clinical trials, nurturing patient relationships (particularly with ethnic minorities), and fostering trust in clinical trial participation by providing clear information and maintaining transparency. Future recruitment efforts should involve forging collaborations between medical providers and community partners, emphasizing the need to educate providers at the primary care level about gaps in clinical trial knowledge among potential participants, to ultimately increase willingness to participate. **Conclusion:** Healthcare providers hold a distinct level of trust within minority populations, underscoring their pivotal role in imparting information about clinical trials and addressing knowledge gaps. Their involvement is integral to ensuring inclusivity among diverse populations in clinical trial participation.

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1226 | CYTOKINES SECRETED BY MACROPHAGES MEDIATES THE INTERACTION BETWEEN HEPATITIS B AND C VIRUSES

Fan Zhang[1] Yuanyuan Zhao[1] Lu Bian[1] Xianfang Wu[1]

[1]Cleveland Clinic

Background: The shared transmission routes of hepatitis B virus (HBV) and hepatitis C virus (HCV) lead to coinfections that accelerate and worsen liver disease. This clinical impact is heightened in the era of direct-acting antivirals (DAAs) against HCV, as reports of HBV reactivation post-DAA treatment in coinfected patients have surfaced. Beyond an HCV-induced canonical interferon (IFN) response, the mechanisms through which HCV suppresses HBV remain poorly understood. **Methods:** Here, we employ a multicellular liver culture system, co-culturing human-induced pluripotent stem cells (hiPSCs)-derived hepatocytes, hepatic stellate cells and macrophages, that supports productive HCV and HBV infection and replicates clinical coinfection dynamics. **Results:** We demonstrate that specific cytokines secreted from macrophages activated by HCV modulates host factors involved in HBV infection independent of IFN signaling. By combining bioinformatic predictions with reporter assay validation, we identified two critical transcriptional mediators of these changes. Finally, we show that a modified treatment protocol combining DAA with an HBV entry inhibitor effectively prevents HBV reactivation. **Conclusion:** These findings underscore the pivotal role of an external signal mediated by macrophages in orchestrating the complex interplay between coexisting hepatitis viruses within hepatocytes. Targeting this signal may provide promising therapeutic avenues for addressing HBV reactivation in the context of HBV and HCV coinfections, offering valuable insights for the development of targeted interventions in clinical practice.

Disclosures: Fan Zhang: Nothing to Disclose, Yuanyuan Zhao: Nothing to Disclose, Lu Bian: Nothing to Disclose, Xianfang Wu: Nothing to Disclose

1227 | HBV INDUCES LIVER FIBROSIS THROUGH THE GENERATION OF ROS IN A PYRUVATE-PPAR&ALPHA;-DEPENDENT PATHWAY

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Background: Chronic hepatitis B (CHB) is a major cause of cirrhosis and hepatocellular carcinoma (HCC). We previously found that pyruvate, a key intermediate in many metabolic pathways, increases HBV replication and liver fibrosis. However, the mechanism by which pyruvate mediates HBV-induced liver fibrosis is not well characterized. We hypothesize that HBV induces liver fibrosis through a pyruvate-peroxisome proliferator-activated receptor α (PPARα) - reactive oxygen species (ROS) pathway. **Methods:** We evaluated HBV-induced fibrogenesis in HBV HepAD38, HBV-infected NTCP-HepG2 cells, and hepatic stellate cell lines (HSC, LX2) in mono- and co-culture models, as well as in sera from CHB patients, an HBV carrier mouse model, and a human precision-cut liver slice (PCLS) model. Cells were cultured in medium without pyruvate. Infectious HBV viral particles (HBVvp) were purified from HepAD38 supernatant (HBVsup). The HBV carrier mouse model was generated by hydrodynamic injection of pAAV/HBV1.2 plasmid through the tail vein into wild-type C57BL/6 mice. We evaluated the effects of the PPARα agonist fenofibrate and of the PPARα antagonist GW6471, PPARa RNAi knockdown, as well as the ROS inhibitor diphenyliodonium chloride (DPI), on HBV-induced liver fibrosis. HBV replication and the expression of pyruvate, PPARα, TGF-β1, and liver fibrosis-related genes were monitored by qRT-PCR, Western blot, or ELISA. **Results:** We found that HBV increased pyruvate levels and fibrosis-related gene expression in both HBV-infected hepatocytes and sera from CHB patients. The supernatants from HBV-infected cell lines (HBVsup) and pyruvate supplementation independently and additively increased the expression of liver fibrosis-related genes (TGF-β1, TIMP1, COL1A1, and α-SMA), activated ROS production, and inhibited PPARα expression. Notably, PPARα inhibition and siRNA knockdown each increased ROS production and profibrogenic gene expression, while activation of PPARα blocked HBVsup- and pyruvate- induced ROS generation and fibrogenesis. ROS generation was confirmed to be downstream of PPARα-related fibrogenesis, as

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inhibition of ROS production abrogated HBVsup-, pyruvate supplementation-, or PPARα inhibition-induced liver fibrosis. **Conclusion:** HBV infection promoted liver fibrosis through pyruvate production, which in turn inhibited PPARα expression and activated ROS generation and liver fibrogenesis. These findings suggest that targeting the pyruvate-PPARα pathway can block liver fibrogenesis for antifibrotic therapeutic development.

Disclosures: Xiaoqiong Duan: Nothing to Disclose, Shasha Li: Nothing to Disclose, Qingyuan Li: Nothing to Disclose, Wenxian Wen: Nothing to Disclose, Charlotte Warner: Nothing to Disclose, Min Xu: Nothing to Disclose, Andre Jeyarajan: Nothing to Disclose, Yujia Li: Nothing to Disclose, Yaoqiong Shi: Nothing to Disclose, Ning Jiang: Nothing to Disclose, Wenting Li: Nothing to Disclose, Chunhui Yang: Nothing to Disclose, Youmin Yang: Nothing to Disclose, Jing Xu: Nothing to Disclose, Min Xu: Nothing to Disclose, He Xie: Nothing to Disclose, Shilin Li: Nothing to Disclose, Xianding Wang: Nothing to Disclose, Raymond Chung: Nothing to Disclose, Limin Chen: Nothing to Disclose

1228 | OUTCOMES OF NUCLEOS(T)IDE ANALOGUE DISCONTINUATION IN CHRONIC HEPATITIS B PARTICIPANTS TREATED WITH XALNESIRAN WITH AND WITHOUT AN IMMUNOMODULATOR: 48 WEEKS OF FOLLOW-UP RESULTS FROM THE PHASE 2, RANDOMIZED, CONTROLLED, ADAPTIVE, OPEN-LABEL PLATFORM STUDY PIRANGA ◆

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Background: Withdrawal of nucleos(t)ide analogue (NA) treatment is a requirement for a finite functional cure for chronic HBV (CHB) but carries potential safety risks. The efficacy and safety of xalnesiran (a small interfering ribonucleic acid targeting the HBsAg coding region of the HBV genome) with and without an immunomodulator were evaluated in the Piranga phase 2 platform study (NCT04225715). This analysis reports the **Results:** of the NA discontinuation outcomes up to 48 weeks of follow-up. **Methods:** 159 virologically-suppressed CHB participants (pts) on established NA therapy (entecavir, tenofovir alafenamide/disoproxil fumarate) were randomized into one of 4 xalnesiran arms (see table) or the NA control arm for 48 weeks (wks) of treatment and 48 wks of follow-up. All pts continued NA until NA stopping criteria were met at the end of the treatment or during the follow-up period. Pts who stopped NA were monitored rigorously and NA was restarted if restarting criteria were met (See table footnote for the definitions of NA stopping and restarting criteria). HBsAg rebound was defined post-hoc as either HBsAg ≥ 0.05 IU/mL or > 1.5 fold of the HBsAg level when NA stopping criteria were met for pts who had or did not have HBsAg loss (< 0.05 IU/mL) at this time point, respectively. **Results:** Across 124 pts in the xalnesiran arms, 58 (47%) met the NA stopping criteria, of whom 40 (32%) stopped NA. Of these 40 pts, 19 (48%), 3 (8%), and 16 (40%) pts had virological relapse (VR), clinical relapse (CR), and restarted NA, respectively. VR occurred only in 2 of the 9 pts who had HBsAg loss when they met the NA stopping criteria vs. 17 of the 31 pts who did not have HBsAg loss when they met the NA stopping criteria. The 2 VR cases from pts who had HBsAg loss when they met the NA stopping criteria occurred at 4 and 6 months after NA withdrawal and did not qualify as CR. All 3 CR cases were associated with preserved liver functions and resolved without sequelae. Of the 40 pts who stopped NA, 26 (65%) had HBsAg rebound after stopping NA, with a comparable duration of observation after NA discontinuation to those who did not have HBsAg rebound. The rate of HBsAg rebound was 22% (2/9) and 77% (24/31) among pts who had and did not have HBsAg loss when NA stopping criteria were met, respectively. Furthermore, the median (range) of HBsAg level when pts met the NA stopping criteria was 12 (0.05-98) and 0.06 (0.05-13) IU/mL in pts who had and did not have HBsAg rebound, respectively. Finally, 5 pts had HBsAg loss and HBV DNA **Conclusion:** The Piranga study demonstrated that stopping NA can be safely managed with pre-specified stopping and restarting criteria, together with rigorous safety monitoring.

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Further studies evaluating predictors of NA discontinuation outcomes will be essential to improve the success of NA management in finite functional cures.

Table: NA discontinuation events and clinical and virological-related outcomes (safety population).

Arm, n (%)	1 (n=30)	2 (n=30)	3 (n=34)	4 (n=30)	1-4 (n=124)	5 (n=35)
Met NA stopping criteria#	12 (40)	14 (47)	21 (62)	11 (37)	58 (47)	2 (6)¶
Discontinued NA	7 (23)	8 (27)	17 (50)	8 (27)	40 (32)	2 (6)
HBsAg status when NA stopping criteria were met:						
- HBsAg loss^	0	0	5 (29)	4 (50)	9(23)	0¶
- quantifiable HBsAg <100 IU/mL with ≥1 log10 IU/mL decline from baseline^	7 (100)	8 (100)	12 (71)	4 (50)	31(78)	0¶
HBsAg status at the end of the study:						
- HBsAg rebound#^	6 (86)	4 (50)	12 (71)	4 (50)	26(65)#	0
- No HBsAg rebound^	1(14)	4 (50)	5 (29)	4 (50)	14(35)#	2 (100)
Virological relapse#^	6 (86)	1 (13)	10 (59)	2 (25)	19 (48)	2 (100)
Clinical relapse#^	1 (14)	0	2 (12)	0	3 (8)	1 (50)
Met restarting criteria#^	6 (86)	1 (13)	8 (47)	2 (25)	17 (43)	2 (100)¶
Restarted NA^	5 (71)*	1 (13)	8 (47)	2 (25)	16 (40)	2 (100)
Remained off NA until the end of the study^	2 (29)	7 (88)	9 (53)	6 (75)	24 (60)	0
- with quantifiable HBsAg and quantifiable HBV DNA <2000 IU/mL^	2 (29)	2 (25)	4 (24)	3 (38)	11 (28)	0
- with quantifiable HBsAg and HBV DNA <LLOQ^	0	5 (63)	1 (6)	0	6 (15)	0
- with HBsAg loss and quantifiable HBV DNA^	0	0	2 (12)	0	2 (5)	0
- with HBsAg loss and HBV DNA <LLOQ^	0	0	2 (12)	3 (38)	5 (13)	0

Arm 1: xalnesiran 100 mg + NA, Arm 2: xalnesiran 200 mg + NA, Arm 3: xalnesiran 200 mg + ruzotolimod 150 mg + NA, Arm 4: xalnesiran 200 mg + pegylated-interferon-α-2a 180 µg + NA, Arm 5: NA. LLOQ, lower limit of quantification; NA: nucleos(t)ide analogues; Safety population: All pts randomized to a treatment regimen who received at least one dose of any drug for their assigned treatment regimen, whether prematurely withdrawn from the study or not, were included in the safety population.

 # NA stopping criteria is defined by the protocol as ALT<1.25 x baseline value, AND HBV DNA<20 IU/mL, AND negative HBeAg, AND HBsAg loss or HBsAg <100 IU/mL with ≥1 log10 IU/mL decline from baseline. Pts who discontinued NA therapy were required to be followed up every 2 weeks for the first 12 weeks, and 4 weekly thereafter. In addition, pts with HBV DNA levels >20 and >2,000 IU/mL were required to be followed up every 2 weeks and weekly. **NA therapy should have been restarted if**: HBV DNA >20,000 IU/mL; OR HBV DNA >2,000 IU/mL and ALT >1.5 upper limit of normal (ULN); OR HBV DNA >2,000 IU/mL and ALT ≤1.5ULN and if retest within 7 days confirmed HBV DNA >2,000 IU/mL; OR clinically significant signs of decreasing liver function (based on laboratory findings or clinical assessments). **Virological relapse** was defined as HBV DNA >2000 IU/mL. **Clinical relapse** was defined as HBV DNA >2000 IU/mL and ALT >2 × ULN. **HBsAg rebound** was defined as either HBsAg ≥ 0.05 IU/mL or > 1.5 fold of the HBsAg level when NA stopping criteria were met for pts who had or did not have HBsAg loss (< 0.05 IU/mL) at this time point, respectively.
^ These percentages of pts are calculated using the number of pts who discontinued NA as the denominator.
* One pt in group 1 refused to restart NA treatment despite meeting restarting criteria.
¶ Two pts in group 5 met the previous version of NA stopping and restarting criteria, both pts only achieved quantifiable HBsAg <100 IU/mL but without ≥1 log10 IU/mL decline from baseline when they met stopping criteria.

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1229 | STRATIFICATION OF HBEAG-NEGATIVE CHRONIC HEPATITIS B PATIENTS THROUGH LONGITUDINAL MONITORING OF HBV DNA LEVELS

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Background: The international guideline states that the disease phase of chronic hepatitis B (CHB) cannot be determined by a single assessment due to the continuous interaction between viral activity and the host immune response. In this study, we longitudinally monitored HBV DNA levels over a 2-year period in HBeAg-negative patients not initially indicated for antiviral treatment (AVT), with the aim of allocating them to a more precise disease phase and differentiating prognoses. **Methods:** A total of 2,032 patients diagnosed with CHB between 2008 and 2019 were enrolled from the medical centers of The Catholic University of Korea. Clinical prognoses were compared among patient groups categorized based on their HBV DNA level patterns during the 2-year period. **Results:** During the 2-year period, HBV DNA level was persistently low in 53.0% of the patients (<2,000 IU/mL, low-level viremia (LLV) group), elevated in 15.2% (≥2,000 IU/mL during >75% of tests, high-level viremia (HLV) group), and fluctuated in 31.8% (remaining patients, intermittently high-level viremia (IHV) group). Alanine aminotransferase level remained <=40 IU/L in 65.3%, 51.7%, and 32.4% of the patients in the LLV, IHV, and HLV groups, respectively. AVT was initiated in 5.2% of the LLV group, 24.1% of the IHV group, and 55.7% of the HLV group, indicating a transition to a chronic hepatitis phase during the follow-up period. The estimated annual incidence rate of HBsAg seroclearance, stratified by HBV DNA group, revealed rates of 3.2%, 1.8%, and 0.6% in the LLV, IHV, and HLV groups, respectively (P <0.001). When censoring patients at the initiation of AVT, the estimated annual incidence rate of hepatocellular carcinoma development, also stratified by HBV DNA group, showed rates of 0.39%, 0.37%, and 0.79% in the LLV, IHV, and HLV groups, respectively (P=0.03). **Conclusion:** Precise stratification of HBeAg-negative CHB patients holds significant promise in guiding clinicians to establish personalized treatment approaches using current potent AVT, as well as forthcoming novel therapeutic strategies.

Disclosures: Hae Lim Lee: Nothing to Disclose, Sung Won Lee: Nothing to Disclose, Jeong Won Jang: Nothing to Disclose, Hyun Yang: Nothing to Disclose, Heechul Nam: Nothing to Disclose, Pil Soo Sung: Nothing to Disclose, Do Seon Song: Nothing to Disclose, Jung Hyun Kwon: Nothing to Disclose, SI HYUN BAE: Nothing to Disclose, Jong Young Choi: Nothing to Disclose, Seung Kew Yoon: Nothing to Disclose

1230 | HIGH-THROUGHPUT SCREENING FOR ANTIVIRAL COMPOUNDS USING A RECOMBINANT HEPATITIS B VIRUS REVEALED THE POTENT ENTRY INHIBITOR, SKIMMIANINE

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Background: For the development of antiviral agents to eliminate HBV, it is essential to establish an HBV cell culture system that can easily monitor HBV infection. However, it was thought to be difficult to insert a foreign gene into the HBV genome and produce recombinant HBV without impairing the infectivity. We developed a novel recombinant HBV infection-monitoring system using a luminescent, 11-amino acid reporter (HiBiT) to overcome these difficulties. After inoculation of the recombinant HBV(HiBiT-HBV) with human hepatocytes (PXB cells), HiBiT-HBV was able to replicate, produce infectious virus and re-infect PXB cells. We performed high-throughput antiviral screening using this system with the aim of identifying anti-HBV compounds. **Methods:** We constructed HBV genome-containing plasmids by inserting the HiBiT-coding sequence. pUC1.2×HBV-C/HiBiT encodes a 1.2-fold HBV genotype C genome with insertion of the HiBiT coding sequence into the N-terminus of preS1, and pCMV HBV-D/HiBiT, which is regulated by a CMV promoter and encodes genotype D pregenomic RNA with insertion of the HiBiT coding sequence into the C-terminus of the NTCP-binding site of preS1. We

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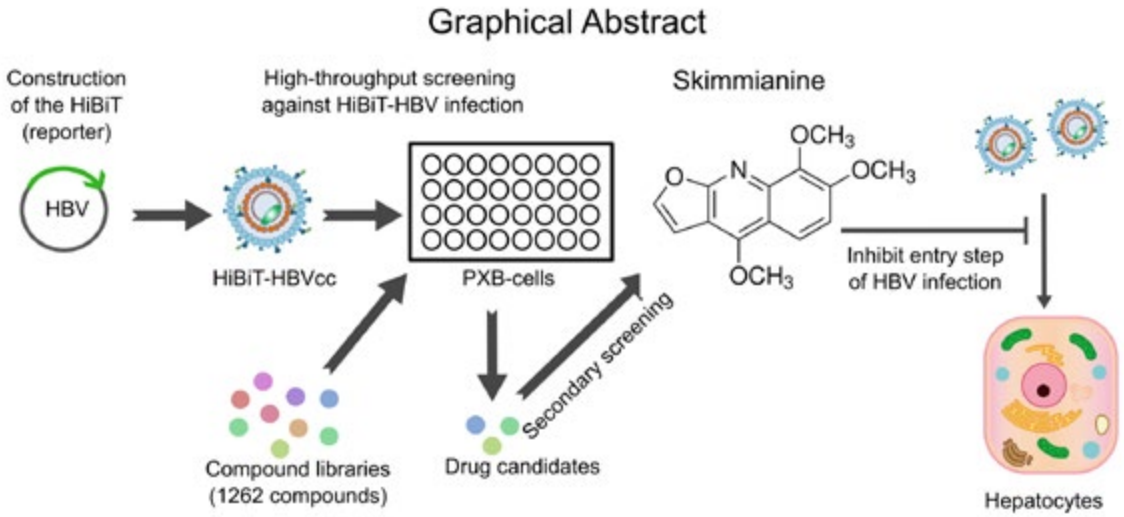
utilized them to prepare the cell culture-derived recombinant virus HiBiT-HBV. After inoculation of primary human hepatocytes with HiBiT-HBV, 1,262 compounds were tested in a screening and antiviral activity was examined using extracellular HiBiT activity. **Results:** Following the screening, we focused on the compound skimmianine, furoquinoline alkaloid, which showed the most prominent antiviral effect. We focused on this drug to investigate the mechanism of the reduction of infection. When skimmianine was added at the same time as HiBiT-HBV infection, skimmianine inhibited HiBiT activity with an EC50 of 0.36 pM, CC50 of 1.67 μM and selectivity index (CC50:EC50 ratio) of 5,100,000. When skimmianine was added 72 h after HiBiT-HBV infection, the EC50, CC50 and selectivity index were 0.19 μM, 1.87 μM and 8.79 respectively. Time-lapse fluorescence imaging analysis using another recombinant virus, ReAsH-TC155HBV, with insertion of tetra-cysteine within the HBV capsid revealed that Skimmianine inhibited the entry step of this virus into hepatocytes. These results indicate that Skimmianine inhibits the HBV entry step. **Conclusion:** This study demonstrates usefulness of the recently developed recombinant HiBiT-HBV for the high-throughput screening of anti-HBV compounds. Our High-throughput screening system revealed Skimmianine have a potential to inhibit the entry of HBV.



Disclosures: Masaya Funaki: Nothing to Disclose, Tetsuro Shimakami: Nothing to Disclose, Taro Yamashita: Nothing to Disclose

1231 | HEPATOCELLULAR CARCINOMA RISK REDUCTION ASSOCIATED WITH ANTIVIRAL TREATMENT IN NON-CIRRHOTIC CHRONIC HEPATITIS B PATIENTS: A COMPARATIVE META-ANALYSIS

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Background: Chronic hepatitis B (CHB) affects nearly 300 million people globally and is responsible for over half of hepatocellular carcinoma (HCC) cases. Antiviral therapy with nucleo(s/t)ide analogs (NAs) reduces HCC risk in CHB patients and may be most effective when prescribed earlier in the disease course and for significant duration. A systematic literature review (SLR) and meta-analysis (MA) were conducted to estimate HCC risk reduction for non-cirrhotic CHB patients who were treated with NAs vs untreated patients. **Methods:** An SLR conducted in February 2023 identified studies reporting on HCC incidence in CHB patients who were non-cirrhotic and treatment-naïve at baseline, in which treated patients were treated for ≥three years on average. Following a heterogeneity assessment of patient and study characteristics, an MA generated an unadjusted estimate of the incidence rate ratio (IRR) of HCC between treated and untreated patients among papers reporting on both groups. **Results:** Among 50 studies identified in the SLR, four cohort studies reporting on both treated and

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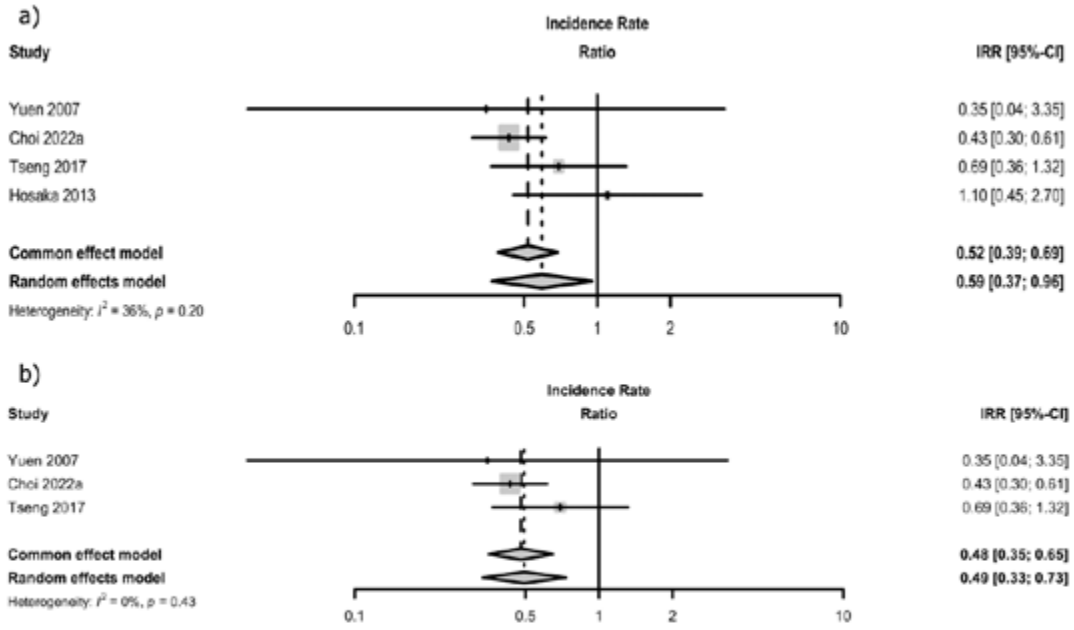
untreated patients were included in analyses. These studies included a total of 5,546 patients in Asian countries, with average follow-up ≥five years in both groups. There was moderate between-study heterogeneity in sample size, NAs used, baseline patient age, HBV DNA levels, and HBeAg positivity. Two studies employed propensity score matching and had relatively balanced patient characteristics between untreated and treated cohorts, while two studies did not and had substantial differences between arms. A random effects MA found an IRR of 0.59 (95% CI: 0.37, 0.96), indicating that treated populations experienced a 41% reduction in HCC risk compared to untreated populations (Figure 1a). The I^2 value of 36% indicates moderate between-study heterogeneity. Further analysis identified Hosaka 2013 as a potential outlier; re-analyzing the data without this study increased risk reduction to 51% (IRR 0.49, 95% CI: 0.33, 0.73) and reduced heterogeneity (I^2= 0%) (Figure 1b). **Conclusion:** This MA suggests that long-term treatment with NAs in non-cirrhotic CHB patients reduces HCC risk compared to no treatment. In the context of exclusively non-cirrhotic and treatment-naïve patients, who are likely to be earlier in the CHB disease course and have lower cumulative HBV DNA exposure, these findings support earlier treatment initiation. This study adds to a growing body of research on the cumulative effects of HBV DNA exposure on HCC risk.

Figure 1: Unadjusted comparative meta-analysis of HCC incidence in treated vs. untreated populations



Footnote: HCC incidence is estimated per 100 person-years. The dashed and dotted vertical lines visually represent the pooled estimates of HCC incidence according to the common and random effects models, respectively. Section a) displays the overall MA results. Section b) displays the results of the sensitivity analysis in which Hosaka 2013 was removed.

Abbreviations: CI, confidence interval; HCC, hepatocellular carcinoma; IRR, incidence rate ratio.

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1232 | THERAPEUTIC EVALUATION OF TENOFOVIR ALAFENAMIDE IN THE TREATMENT OF CHRONIC HEPATITIS B PATIENTS WITH NORMAL ALANINE TRANSAMINASE AND POSITIVE HEPATITIS B VIRUS DNA: A 48-WEEK MULTICENTER RETROSPECTIVE STUDY FROM CHINA

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Background: The Chinese Hepatitis guidelines recommends antiviral treatment for patients aged over 30 with positive hepatitis B virus DNA. Meanwhile some studies confirmed that there is a significant proportion of patients with gray areas or an indeterminate phase in chronic hepatitis B (CHB), and part of them exhibit inflammation and fibrosis. However, there is insufficient evidence regarding the efficacy and benefits of antiviral treatment in patients with normal alanine aminotransferase (ALT) levels. This study aims to evaluate the early efficacy and benefits of antiviral treatment in these patients. **Methods:** From August 2022 onwards, a total of 528 treatment-naive patients with positive HBV-DNA and normal ALT levels were recruited from six medical institutions to receive tenofovir alafenamide (TAF) antiviral therapy. As of now, 265 patients have completed the 48-week follow-up and clinical data collection. Changes in blood routine, liver and kidney function, HBV DNA,GPR, APRI, and FIB-4, were assessed at baseline, 12, 24, and 48 weeks. The primary efficacy endpoint was achieving a complete virologic response (CVR), while secondary endpoints included improvements in GPR, APRI, and FIB- 4. **Results:** After TAF antiviral therapy, the rates of achieving HBV-DNA < 20 IU/mL at week 12, 24, and 48 were respectively 62.3 % (203 / 326), 76.3 % (219/ 287), and 86.0 % (228 / 265), the difference between groups was statistically significant (p **Conclusion:** TAF antiviral therapy effectively reduces HBV-DNA levels and significantly improves inflammatory liver fibrosis in CHB patients with normal ALT and HBV-DNA positive.

Table: Efficacy assessment after 48-week treatment

	Baseline	48week	p-value
CVR in%, n/N		228/265(86.0%)	
HBeAg clearance in%, n/N		15/57(26.3%)	
Serologic transformation of HBeAb in%, n/N		5/49(10.2%)	
ALT in U/L	32.0(19.0,45.0)	22.0(16.0,28.75)	<0.001
AST in U/L	25.0(20.0,30.0)	21.0(19.0,26.0)	<0.001
GGT in U/L	20.0(14.0,28.0)	18.0(13.0,24.0)	0.092
GPR	0.17(0.12,0.26)	0.15(0.11,0.22)	0.062
APRI	0.32(0.24,0.46)	0.26(0.20,0.31)	<0.001
FIB-4	1.06(0.72,1.47)	0.95(0.72,1.32)	0.304

*CVR, complete virological response, HBV-DNA is below the detection limit (20 IU/mL). Data are represented as medians (P25, P75) because of without normal distribution.

Disclosures: Yida Yang: Nothing to Disclose, jiangshan Lian: Nothing to Disclose, Jin Ye: Nothing to Disclose, Qirui Song: Nothing to Disclose, Yang Ling: Nothing to Disclose, Jie Li: Nothing to Disclose, Qinzhi Deng: Nothing to Disclose, Fan Du: Nothing to Disclose, Jianjun Lou: Nothing to Disclose, Jianfeng Zhong: Nothing to Disclose, Zhaowei Tong: Nothing to Disclose

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1233 | RISK FACTORS ASSOCIATED WITH HEPATOCELLULAR CARCINOMA OCCURRENCE IN CHRONIC HEPATITIS B PATIENTS ON LONG-TERM NUCLEOS(T)IDE ANALOGUES

Kazuhiro Murai[1] Hayato Hikita[1] RYOKO YAMADA[1] Takayuki Miyake[1] Emi Sometani[1] Shinji Kuriki[1] Jihyun Sung[1] Akiyoshi Shimoda[1] Satoshi Shigeno[1] Yuki Tahata[1] Yoshinobu Saito[1] Takahiro Kodama[1] Tomohide Tatsumi[1] Tetsuo Takehara[1]

[1]Osaka University Graduate School of Medicine

Background: Nucleos(t)ide analogues (NUCs) are current treatments for chronic hepatitis B (CHB), reducing hepatocellular carcinoma (HCC) occurrence, but not completely. The effect of long-term administration of NUCs on the occurrence of HCC in CHB patients is unclear. We aimed to clarify the risk factors associated with HCC occurrence in CHB patients on long-term NUCs and the suppressive effect of long-term NUC administration on HCC occurrence. **Methods:** We analyzed CHB patients who received initial treatment with NUCs from July 2000 to March 2019. Patients with a history of HCC, patients with HCC before and within one year of starting treatment, patients within one year of starting NUC treatment, patients with HBV DNA below detection sensitivity at the start of NUC treatment, patients receiving concomitant interferon (IFN) at the start of NUC treatment, and patients with other liver diseases (hepatitis C virus (HCV) or human immunodeficiency virus (HIV) infection, autoimmune diseases, or post liver transplant) were excluded. **Results:** Total 703 CHB patients including 143 cirrhotic patients received initial treatment with NUCs. During median follow-up 106.2 months, 110 patients developed HCC. The cumulative HCC occurrence after initiation of NUC treatment was 9.5% at 5 years and 13.6% at 7 years. By using cox proportional hazard model, the presence of cirrhosis, higher age, and higher γ-GTP at NUCs initiation were independent risk factors for HCC occurrence. The cumulative HCC occurrence rate after NUC treatment was significantly higher in cirrhotic patients than in the non-cirrhotic patients (cirrhotic patients 3 years: 20.6%, 5 years: 33.1%, 7 years: 39.8%, 9 years: 45.6%; non-cirrhotic patients 3 years: 1.7%, 5 years: 3.2%, 7 years: 6.6%, 9 years: 8.3%). The cumulative HCC occurrence rate increased steadily in non-cirrhotic patients, whereas in cirrhotic patients, the cumulative HCC occurrence rate increased slower after 5 years of NUC treatment than after less than 5 years of NUC treatment. The proportional hazards assumption was held in less than 5years of NUC treatment for HCC occurrence between cirrhotic and non-cirrhotic patients, while not after 5 years of NUC treatment (p=0.0017). It was suggested that HCC occurrence was suppressed in cirrhotic patients after 5 years of NUC initiation. **Conclusion:** Cirrhosis, higher age, and higher γ-GTP increased HCC risk. Long-term NUC administration suppressed HCC occurrence in patients with hepatitis B virus-related cirrhosis.

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1234 | PREVALENCE OF HEPATITIS DELTA VIRUS INFECTION AMONG HEPATITIS B POSITIVE INDIVIDUALS IN GEORGIA: FINDINGS FROM THE NATIONAL SEROPREVALENCE SURVEY, 2021

Nazibrola Chitadze[1] Maia Alkhazashvili[2] Maia Tsereteli[2] Irina Tskhomelidze[3] Nino Khetsuriani[4] Francisco Averhoff[5] Mary Rodgers[5] Abbas Hadji[6] Mark Anderson[5] Abbas Hadji[6] Gavin Cloherty[6] Sophia Surguladze[3] Jan Drobeniuc[7]

[1]National Center for Disease Control and Public Health (NCDC), [2]National Center for Disease Control, [3]The Task Force for Global Health, [4]CDC, [5]Abbott Diagnostics, Abbott Park, IL, USA, [6]Abbott, [7]Centers for Disease Control and Prevention

Background: Hepatitis delta virus (HDV) infection can cause severe acute and chronic liver disease in patients infected with the hepatitis B virus (HBV). The burden of HDV infection in Georgia is low. This study aims to update previous estimates of the prevalence of HDV infection among HBV infected persons in Georgia. **Methods:** A cross-sectional, nationwide survey among persons aged ≥5 years was conducted in 2021 using a stratified, multi-stage cluster design with random sampling. All blood samples were tested for total antibody to hepatitis B core

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antigen (total anti-HBc) and, if positive, for hepatitis B surface antigen (HBsAg). The HBsAg-positive samples were tested for the presence of immunoglobulin G (IgG) class antibody to HDV (anti-HDV) by a research-use-only (RUO) chemiluminescent microparticle immunoassay (CMIA, ARCHITECT IgG Anti-HDV); anti-HDV positive samples were tested for HDV RNA by a high throughput RUO Nucleic Acid Test (RealTime, m2000). **Results:** A total of 8,710 persons (7,237 adults and 1,473 children, age 5 – 18 years), had their serum samples tested for markers of HBV infection. The prevalence of total anti-HBc among adults was 21.7% (95% CI: 20.4% – 23.2%) and among children 0.7% (95% CI: 0.3% – 1.6%). HBsAg positivity was 2.7% (95% CI: 2.2 – 3.4) among adults and 0.03% (95% CI: 0% – 0.19%) among children. Among 163 HBsAg-positive samples anti-HDV was detected in 6 adults (3.7%), among whom 4 had detectable HDV RNA. There was no geographic clustering observed. **Conclusion:** These findings confirm previous studies that the prevalence of HDV infection among HBV-infected persons is very low in Georgia. Prevention of HBV infection through vaccination will further reduce/eliminate HDV infection in the country.

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1235 | A PHASE 1, DOUBLE-BLINDED, RANDOMIZED, PLACEBO-CONTROLLED, MULTICENTER GLOBAL STUDY EVALUATING THE SAFETY, TOLERABILITY, ANTIVIRAL ACTIVITY AND PHARMACODYNAMIC RESPONSES OF DF-006 IN CHRONIC HEPATITIS B, VIROLOGICALLY-SUPPRESSED SUBJECTS

Edward Gane[1] Dr. Eshwari Kovoor[2] Alina Jucov[3] Igor Anastasiy[3] Marta Dobryanska[4] Susan Parker[2] Carl Cook[2] Sicong Geng[5] Shuai Zhang[6] Qiguang Xia[5] Cong Xu[5] Tian Xu[2] Henri Lichenstein[2] Jeysen Yogaratnam[2]

[1]University of Auckland, New Zealand, [2]Drug Farm, Inc., [3]Arensia Exploratory Medicine, [4]Kyiv City Clinical Hospital #12, [5]Shanghai Yao Yuan Biotechnology Ltd, [6]Zhejiang Yao Yuan Biotechnology Ltd

Background: DF-006, an oral (PO), small molecule prodrug, activates alpha-protein kinase 1 (ALPK1) and stimulates host immune response in the liver. The completed Phase 1 DF-006-1001 study evaluated the safety, efficacy, and pharmacodynamics (PD) of DF-006 in virologically-suppressed (VS) hepatitis B e antigen (HBeAg)-negative chronic hepatitis B (CHB) subjects. Here, we present the preliminary blinded PD data from 2 completed cohorts. **Methods:** The study consisted of 3 CHB cohorts: Cohort 1 (0.4 mcg DF-006 /placebo [PBO]) and Cohort 2 (0.7 mcg DF-006 /PBO) have been completed; Cohort 3 (1 mcg DF-006 /PBO) analysis is ongoing. DF-006 or PBO (randomized 6:2) was administered PO once weekly (QW) for 4 weeks on Days 1, 8, 15, and 22 in combination with a nucleotide reverse transcriptase inhibitor (NrtI). After the last dose, subjects were followed up for 4 weeks on Days 29, 36, 43, and 50. PD blood samples for interleukin (IL)-1b, IL-6, IL-8, IL-17a, IL-18, interferon-beta (IFN-β), interferon-gamma (IFN-γ), macrophage inflammatory protein-1b (MIP-1b), monocyte chemoattractant protein-1 (MCP-1), tumor necrosis factor-alpha (TNF-α) and serum amyloid A (SAA) assessments were collected predose on Day 1, 2 hours post dose Day 1, Day 4, predose Day 8, Day 11, and predose Day 15. Of the 16 subjects randomized to Cohort 1 and Cohort 2, 2 subjects from Cohort 1 were excluded from PD analysis due to a protocol deviation prior to the first dose. **Results:** Across all cohorts, there were no serious adverse events (SAEs), Grade 3-4 treatment emergent adverse events (TEAEs), or clinically significant vital sign, electrocardiogram (ECG), or urinalysis abnormalities. Across all doses and all time points, elevations were seen in the following PD biomarkers: IL-17a, DF-006 (7/11, 64%) vs. PBO (1/3; 33%); IL-8, DF-006 (9/11, 82%) vs. PBO (2/3, 67%); MIP-1b, DF-006 (11/11, 100%) vs. PBO (1/3; 33%); and TNF-α, DF-006 (10/11, 91%) vs. PBO (2/3, 67%). The maximum increase for those biomarkers were: IL-17a, 2.19-fold in DF-006 vs. 1.56-fold in PBO; IL-8, 4.42-fold in DF-006 vs. 1.46-fold in PBO; MIP-1b, 2.23-fold in DF-006 vs. 1.04-fold in PBO; and TNF-α, 12.45-fold in DF-006 vs. 1.41-fold in PBO. In subjects dosed with DF-006 at either 0.4 or 0.7 mcg who were observed to have elevations in IL-17a, IL-8, MIP-1b, or TNF-α, there were also on- and/or off-treatment HBsAg reductions from baseline ranging from 0.02 $\log_{10}$ IU/mL to 0.38 $\log_{10}$ IU/mL. In some of these subjects, the HBsAg reductions from baseline were associated with minor, transient elevations in alanine

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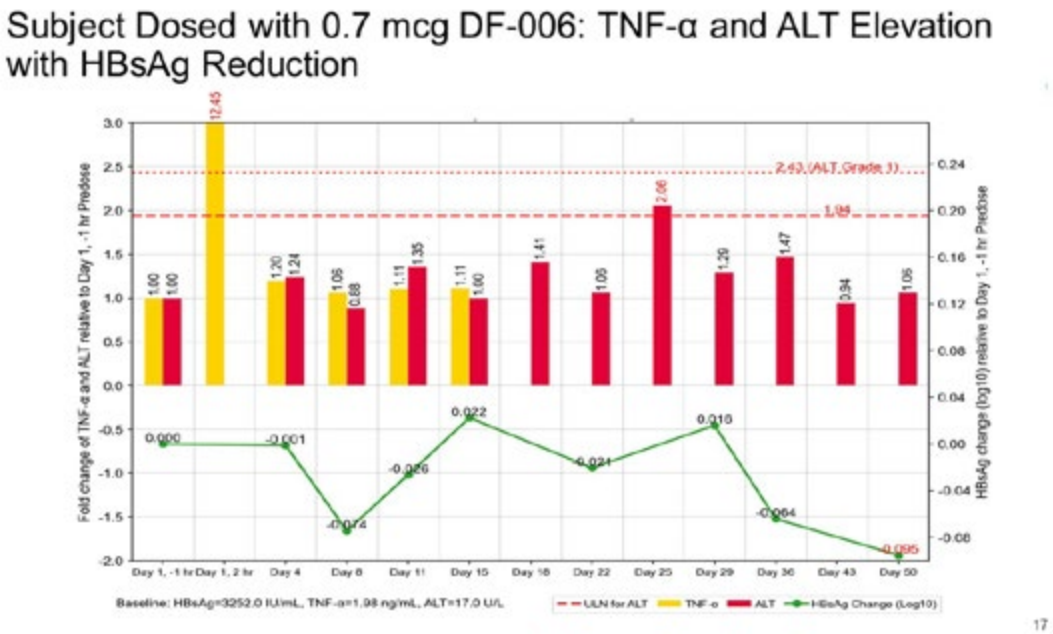
aminotransferase (ALT). **Conclusion:** DF-006 is safe and well tolerated in VS HBeAg-negative subjects after 4 weeks of PO QW dosing up to 1 mcg. The PD data suggests that DF-006-induced on-treatment immune activation may have led to HBsAg reduction.



Disclosures: Edward Gane: Aligos Therapeutics: Advisor, Assembly Biosciences: Advisor, AbbVie: Speaking and Teaching, Intellia Therapeutics: Advisor, Tune Therapeutics: Consultant, Precision Bio: Advisor, Virion Therapeutics: Advisor, Gilead Sciences: Advisor, GSK: Advisor, Dr. Eshwari Kovoor: Nothing to Disclose, Alina Jucov: Nothing to Disclose, Igor Anastasiy: Nothing to Disclose, Marta Dobryanska: Nothing to Disclose, Susan Parker: Nothing to Disclose, Carl Cook: Nothing to Disclose, Sicong Geng: Nothing to Disclose, Shuai Zhang: Nothing to Disclose, Qiguang Xia: Nothing to Disclose, Cong Xu: Nothing to Disclose, Tian Xu: Nothing to Disclose, Henri Lichenstein: Nothing to Disclose, Jeysen Yogaratnam: Nothing to Disclose

1236 | CAN PRIMARY CARE HEALTH CENTERS MANAGE CHRONIC HEPATITIS B? CLINICAL CARE CHARACTERISTICS OF HEPATITIS B REGISTRY PATIENTS AT A FEDERALLY QUALIFIED HEALTH CENTER IN THE SAN FRANCISCO BAY AREA

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Background: Community health centers (CHCs) are primary care medical homes for some of the most vulnerable populations and are therefore high-impact settings for hepatitis B virus (HBV) identification and care management. An estimated 880,000 people have chronic HBV in the United States (U.S.), with 70% born outside of the U.S. In 2022, Federally Qualified Health Centers (FQHCs) cared for almost 45,000 people with chronic HBV, but little is known about HBV care in these settings. North East Medical Services (NEMS) is an FQHC in the San Francisco Bay Area with a large Asian and immigrant population and an HBV registry-based care management program. We aimed to describe the demographic and clinical care characteristics of patients receiving primary care-based HBV management in this setting. **Methods:** We performed a retrospective descriptive analysis of HBV registry patients with at least one primary care medical visit at the FQHC between 1/1/22 to 12/31/23. Demographic and clinical data were extracted from the FQHC's electronic health records. HBV registry patients had a positive HBV surface antigen result, detectable HBV DNA, or chronic HBV ICD-code. **Results:** Of the 3457 chronic HBV patients who received primary care at the FQHC between 2022 to 2023, 2902 (84%) were aged 40-79 years, 3047 (88%) had Chinese as their preferred language, 3293 (95%) were non-U.S.-born, and 2904 (84%) had Medicaid insurance (Table 1). Further, 913 (26%) were prescribed HBV antiviral treatment, 2497 (72%) completed an HBV e antigen (HBeAg) test of which 193 (8%) were HBeAg positive, 687

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(20%) were screened for hepatitis delta virus (HDV) of which 3 had a positive HDV antibody and detectable HDV RNA, 109 (3%) had cirrhosis, and 51 (1%) had a hepatocellular carcinoma (HCC) diagnosis. During the study period, 2696 (78%) had ≥ one HBV DNA test, 2975 (86%) had ≥ one ALT test, and 1979 (74%) of 2688 eligible high HCC risk patients (per AASLD criteria) completed HCC surveillance liver ultrasounds. **Conclusion:** CHCs are crucial in the nation's viral hepatitis elimination plan as they provide longitudinal care to low-income immigrant populations. In our analysis, ≥74% of HBV registry patients received primary care-based HBV lab monitoring and HCC surveillance, and more than a quarter were prescribed treatment which is higher than rates described in the literature. HBV registries can aid in population health management and should be used by CHCs with high-risk populations to improve HBV care delivery in the primary care setting.

Table 1. Characteristics of Hepatitis B Registry Patients Receiving Primary Care at a Federally Qualified Health Center in the San Francisco Bay Area, Patients with Active Primary Medical Care Visits Between 2022 to 2023

	Hepatitis B Registry Patients, N (%)
Total Registry Patients	3457
Sex	
Female	1715 (50%)
Male	1742 (50%)
Age	
0-9	1 (<1%)
10-19	13 (<1%)
20-29	57 (2%)
30-39	323 (9%)
40-49	630 (18%)
50-59	814 (24%)
60-69	882 (26%)
70-79	576 (17%)
80-89	134 (4%)
90-99	26 (<1%)
100+	1 (<1%)
Preferred Language / Dialect (Top 5)	
Chinese (Cantonese)	2567 (74%)
Chinese (Mandarin)	459 (13%)
English	223 (6%)
Vietnamese	140 (4%)
Chinese (Toishanese)	21 (1%)
Place of Birth	
United States of America	47 (1%)
Non-U.S. (Top 5)	
China	2737 (79%)
Vietnam	269 (8%)
Hong Kong	80 (2%)
Taiwan	44 (1%)
Myanmar	39 (1%)
Other	124 (3%)
Declined / No Info	117 (3%)
Insurance Status	
Medicaid (includes dual coverage with Medicare)	2904 (84%)
Medicare Only	37 (1%)
Public Option	102 (3%)
Self-Pay	124 (4%)
Private	270 (8%)
Other / Unknown	20 (1%)
HBV Antiviral Ever Prescribed	913 (26%)
HBeAg Status Screened	2497 (72%)
Positive*	193 (8%)
Negative*	2304 (92%)
HDV Status Screened	687 (20%)
HDV Ab Positive*	13 (2%)
HDV RNA Detected**	3 (23%)
Cirrhosis^	109 (3%)
Hepatocellular Carcinoma^^	51 (1%)

HBV = Hepatitis B Virus; HBeAg = Hepatitis B e Antigen; HDV = Hepatitis Delta Virus; Ab = Antibody
*Proportion of those screened
**Proportion of HDV Ab Positive
^Determined by ICD code, FIB-4 > 3.25, and F4 fibrosis stage result
^^Determined by ICD code

Disclosures: Zinnia Dong: Nothing to Disclose, Su Wang: Gilead Sciences: Grant/Research Support, Amy Tang: Nothing to Disclose

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1237 | A COMPARATIVE ANALYSIS OF ADVERSE EVENT INCIDENCE RATES BETWEEN INTERMITTENT AND CONTINUOUS REGIMEN OF PEGINTERFERON ALPHA-2B BASED ON EXPOSURE-RESPONSE ANALYSIS

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Background: Peginterferon alpha (PegIFNα) has been shown to promote functional cure in patients with chronic hepatitis B (CHB). However, continuous treatment with PegIFNα may cause adverse events (AEs) such as thrombocytopenia (tcp) and neutropenia (ntp) in some subjects. To mitigate AEs, the dosing regimen was optimized to an intermittent schedule of 8 weeks on followed by 4 weeks off in a phase III trial (NCT04846491) of PegIFNα-2b (40kD, Y shape, Pegbing®) combined with tenofovir disoproxil fumarate (TDF) for the treatment of CHB. In this study, we compared the incidence rates of major AEs under different schedules of PegIFNα-2b based on the exposure-response (E-R) analysis. **Methods:** Data for analysis were from three clinical trials. Trial 1 (NCT01143662) and Trial 2 (NCT01760122) were phase II/III studies in which treatment-naïve CHB patients received continuous PegIFNα-2b therapy. Trial 3 was the phase III study NCT04846491. E-R modeling was conducted using logistic regression. The dose of PegIFNα-2b was used as the exposure indicator. In this study, ntp and tcp, which were the most common AEs of PegIFNα-2b, were selected as safety indicators. A covariate model was used to examine the impact of dosing regimen on the safety outcomes. **Results:** The study enrolled 1163 subjects (Trial 1 = 154; Trial 2 = 570; Trial 3 = 472). Baseline characteristics of demographics and blood routine were similar between groups. The observed incidence rates of Grade I and III ntp and tcp in the intermittent group were not higher than those in the continuous groups (Figure 1). The E-R relationships were significant for Grade I ntp ($p < 2\times10^{-16}$), Grade III ntp ($p = 5.46\times10^{-8}$) and Grade I tcp ($p = 3.74\times10^{-15}$), except for Grade I tcp ($p = 0.07682$). Intermittent/continuous schedule was identified as a significant covariate in all of the above E-R relationships ($p = 0.00789$, 1.61×10^{-6}, 0.00134, and 0.00542, respectively), indicating that the incidence rate of AEs in the intermittent group was significantly lower than that in the continuous group. **Conclusion:** During the same 48-week treatment period, patients with CHB receiving PegIFNα-2b intermittent therapy had lower incidence rates of ntp and tcp compared to continuous therapy.

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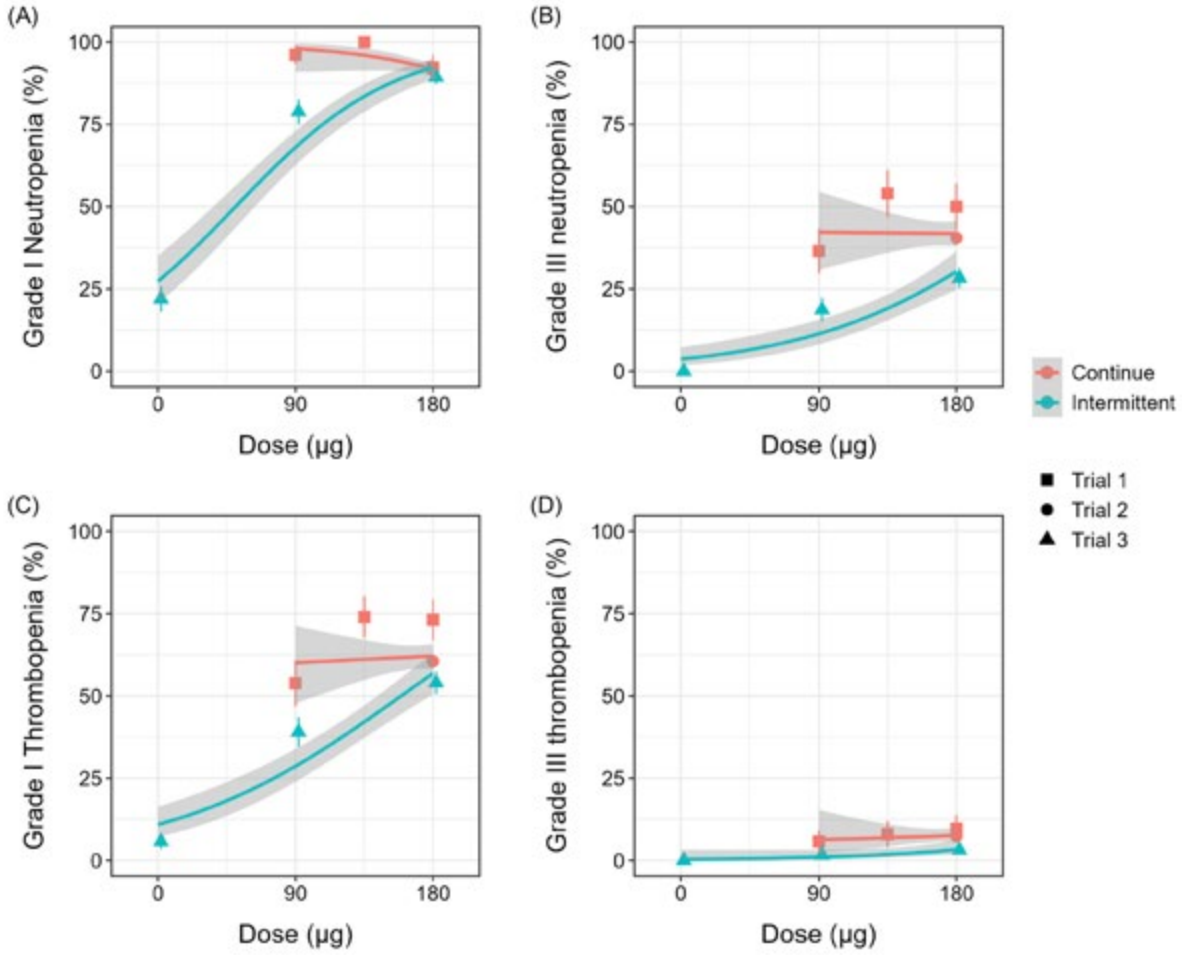

Figure 1. E-R relationship between PegIFNα-2b dose and adverse events. (A) Grade I neutropenia; (B) Grade III neutropenia; (C) Grade I thrombocytopenia; (D) Grade III thrombocytopenia. The solid line represents median predicted incidence rates, and the shaded area represents 95% confidence intervals of the predicted response. The dots and error bars represent median and 95% confidence intervals of observed incidence rates. The orange and blue colours represent continuous and intermittent regimen of PegIFNα-2b. The shape of dots represents different clinical trials. According to the Common Terminology Criteria for Adverse Events (CTCAE) 5.0 standard, Grade I neutropenia is defined as a neutrophil count lower than 2.0×10^9/L during the 48-week period from the start of treatment in this study, and lower than 1.0×10^9/L for Grade III neutropenia. As for the Grade I and III thrombocytopenia, thresholds of platelet were 100×10^9/L and 50×10^9/L, respectively.

Disclosures: Weizhe Jian: Nothing to Disclose, Yalin Yin: Nothing to Disclose, Junsheng Xue: Nothing to Disclose, Ruoyi He: Nothing to Disclose, Tianyan Zhou: Nothing to Disclose

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1238 | HBV PROMOTES HEPATOCYTE BINUCLEATED POLYPLOID FORMATION THROUGH DOWN-REGULATION OF HDAC6 TO MAINTAIN THE STABILITY OF THE CCCDNA POOL AND PROMOTE VIRAL REPLICATION

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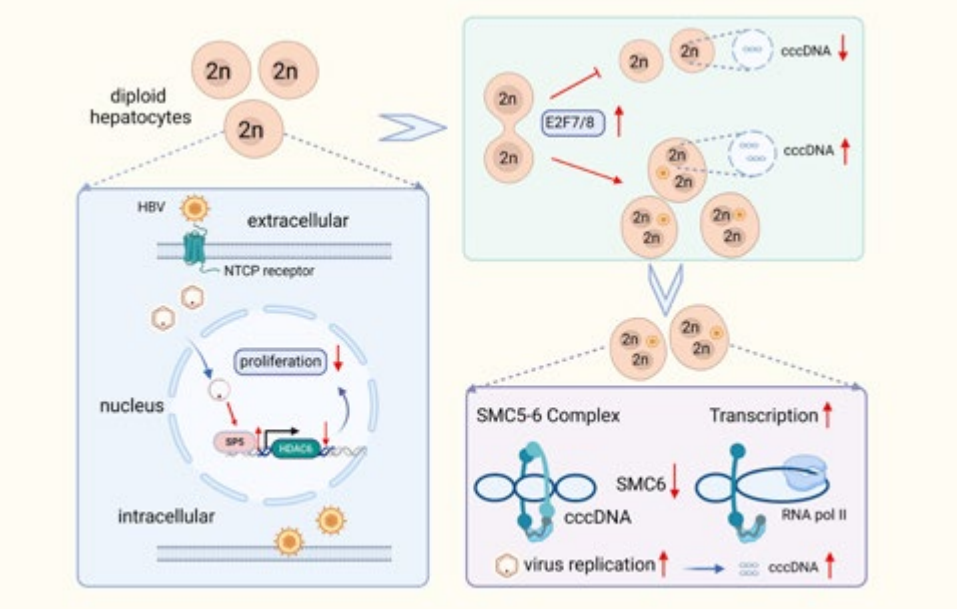
[1]Third Affiliated Hospital of Sun Yat-Sen University, [2]Sun Yat-sen University

Background: Covalently closed circular DNA (cccDNA) clearance is the difficulty in achieving clinical cure with antiviral in chronic hepatitis B (CHB). It is diluted in the context of hepatocyte proliferation. Previous studies suggest a close association between HBV infection and an increased proportion of binucleated polyploids in the liver. Slower proliferation of polyploid hepatocytes compared to diploid hepatocytes may favour maintenance of viral infection, and the exact mechanism remains to be elucidated. **Methods:** The proportion of binucleated hepatocytes and cccDNA levels were examined in patients with CHB (n=120) at different disease stages as well as in healthy controls (n=10). HepG2, Huh7, HepG2.2.15, NTCP-hepG2 and HepAD38 cell lines were used for mechanism validation. The expression levels of target genes were verified using RT-qPCR and Western Blot. Hepatocyte ploidy and cell proliferation levels were examined using methods such as flow cytometric analysis techniques and EDU staining. **Results:** The higher the serum HBV DNA load and HBsAg level, the higher the proportion of intrahepatic binucleated polyploidy in patients with CHB. After antiviral therapy, the proportion of intrahepatic binucleated polyploidy declined progressively, and the intrahepatic cccDNA level decreased. HBV significantly upregulates the proportion of hepatocyte polyploidy and down-regulated the level of histone deacetylase 6 (HDAC6), a gene associated with proliferation. The lower the serum HBsAg level, the higher the level of HDAC6 expression in the liver, and the proportion of binucleated polyploidy in the liver was negatively correlated with the expression level of HDAC6. Overexpression of HDAC6 significantly promoted hepatocyte proliferation and down-regulated the proportion of hepatocyte polyploidy. It is the level of HBV DNA rather than HBV-associated antigens HBsAg (large, medium, and small), HBeAg, HBx, and HBcAg that are directly involved in down-regulating HDAC6 expression. HBV DNA represses HDAC6 transcription by upregulating the transcriptional repressor SP5 of HDAC6 and thereby repressing HDAC6 transcription, and SP5 expression is downregulated after HBV DNA inhibition. HBV significantly up-regulated E2F7/8, two genes that inhibit cytoplasmic division, to promote binucleate hepatocyte formation, and E2F7/8 levels decreased after HDAC6 overexpression. The expression levels of HDAC6 and SMC6 were positively correlated, sequencing data from hepatocyte polyploids revealed that the expression levels of HDAC6 and SMC6 declined progressively with the increase in nuclear ploidy of hepatocytes. Overexpression of HDAC6 decreases cccDNA levels in Hep AD38 cells and inhibits cccDNA transcription by up-regulating SMC6 levels. **Conclusion:** HBV promotes hepatocyte binucleated polyploid formation through down-regulation of HDAC6 to maintain the stability of the cccDNA pool and promote viral replication.



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Disclosures: Lili Wu: Nothing to Disclose, Huiying Yu: Nothing to Disclose, Zhiliang Gao: Nothing to Disclose, Bingliang Lin: Nothing to Disclose

1239 | SAFETY AND EFFICACY ASSESSMENT OF TENOFOVIR ALAFENAMIDE (TAF) ANTIVIRAL THERAPY COMMENCED PRECONCEPTION OR DURING EARLY/MID-TRIMESTER OF PREGNANCY IN HEPATITIS B VIRUS (HBV) INFECTION

Keshu Shen[1] Hui Chen[1] Chong Zhao[1] Jing Zhao[1] Bo Wang[1] Yan Zheng[1] Xin Shi[1]

[1]Jilin Hepatobiliary Hospital

Background: Tenofovir Alafenamide (TAF) is recommended as the primary antiviral agent for managing chronic hepatitis B virus (HBV) infection according to international guidelines. While real-world evidence supports its efficacy and safety in preventing vertical transmission during late pregnancy, there is limited data on its use in pregnant women with active chronic HBV and its impact on infants. This study aims to evaluate the safety and efficacy of TAF antiviral therapy initiated preconception or during early/mid-trimester of pregnancy. **Methods:** This retrospective, single-center study recruited women with chronic HBV infection who underwent TAF 25mg antiviral therapy initiated preconception or during early/mid-trimester of pregnancy. Follow-up was conducted until postpartum month 7, and infants received immunoprophylaxis. The primary endpoint assessed safety for both mothers and infants, while the secondary endpoint evaluated the hepatitis B surface antigen (HBsAg)-positive rate in infants at 7 months. **Results:** Total of 27 women were enrolled, resulting in the birth of 26 infants. The median age and gestational age at TAF initiation were 32 years old (range: 26 to 43 weeks) and preconception to 21 weeks, respectively. TAF treatment was initiated preconception in 77.78% and during early/mid-trimester in 22.22% of cases. At the first visit with median gestational age of 26 weeks (range: 4 to 29 weeks), 65.38% (17 out of 26) of infants were HBV e antigen (HBeAg) positive. Furthermore, 57.14% (12 out of 21) and 92.31% (24 out of 26) achieved virological response (HBV DNA<5*102IU/ML) and ALT normalization (ALT <40U/L), respectively. TAF was well tolerated, with only one instance of induced abortion for nonmedical reasons. No abnormalities were observed in renal function markers during pregnancy. At postpartum month 2 (median time: 1 to 7), 76.9% (10 out of 13) and 78.57% (11 out of 14) of patients achieved virological response and ALT normalization, respectively. No infants exhibited birth defects or malformations. All infants displayed normal growth parameters and tested negative for HBsAg at 7 months. **Conclusion:** Initiating TAF antiviral therapy preconception or during early/mid-trimester of pregnancy in active chronic HBV infection appears to be both safe and effective for pregnant women and infants.

Disclosures: Keshu Shen: Nothing to Disclose, Hui Chen: Nothing to Disclose, Chong Zhao: Nothing to Disclose, Jing Zhao: Nothing to Disclose, Bo Wang: Nothing to Disclose, Yan Zheng: Nothing to Disclose, Xin Shi: Nothing to Disclose

1240 | SHORT-TERM EFFICACY AND SAFETY AFTER SWITCHING FROM ENTECAVIR TO TENOFOVIR ALAFERAMIDE FOR CHRONIC HEPATITIS B PATIENTS WITH SUBOPTIMAL RESPONSE OR INTOLERANT TO ENTECAVIR

Fei Kong[1] Ying Dai[2] Xiqiu Zeng[3] Hongxin Piao[4] Xianbo Wang[5] Dongmei Wei[6] Lei Yu[7] Chenxin Meng[8] Junqi Niu[1] YANHANG GAO[1]

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Background: Entecavir (ETV) is the first-line therapy for chronic hepatitis B (CHB) patients. However, some patients may exhibit persistent viremia after prolonged ETV monotherapy, and long term ETV treatment has been reported associated with decline in renal function. Tenofovir alaferamide (TAF) may be preferable to ETV in specific circumstances such as in patients with risk of renal complications, elderly patients or those with suboptimal response to ETV. The aim of the present study was to evaluate the efficacy and safety of switching to TAF treatment in CHB patients with suboptimal response or intolerant to ETV. **Methods:** This ongoing single-arm study was conduct at 8 clinical sites in China. In this prospective trial, patients who showed partial response

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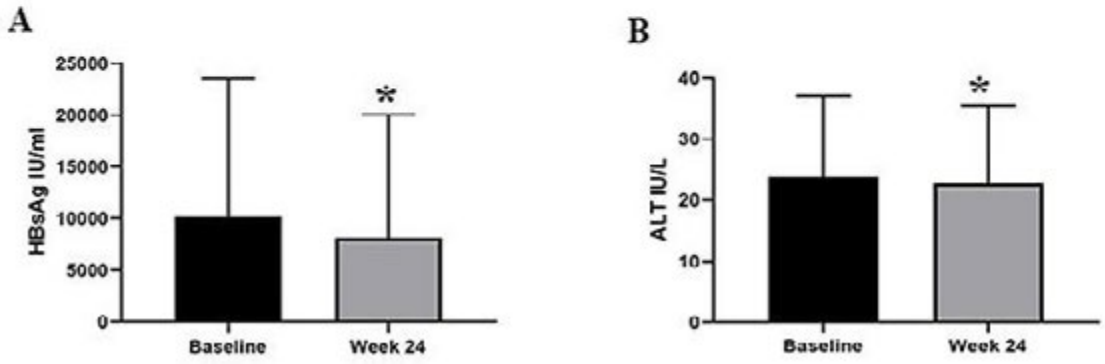
(defined as serum HBV DNA >20 IU/mL after 0.5mg daily ETV monotherapy for at least 48 weeks for CHB patients or 24-72 weeks for patients with cirrhosis) or intolerant to ETV therapy were treated with TAF 25mg, once daily. The primary efficacy endpoint was the proportion of patients with viral suppression (HBV DNA < 20 IU/mL) at week 24. **Results:** Overall, 121 patients enrolled in this study, including 105 patients with suboptimal response to ETV and 16 patients with intolerant to ETV. The mean age was 45.6 years, 57.0% were male, 10.7% had cirrhosis and 83.5% were positive for hepatitis B e antigen (HBeAg). Among patients with suboptimal response to ETV, HBV DNA < 20 IU/mL was achieved by 28 out of 105 (26.7%, 95%CI, [18.1%, 35.3%]) patients at week 24. The alanine aminotransferase (ALT) normalisation rate increased from 76.9% at baseline to 85.6% at week 24 (P=0.035). Among patients with intolerant to ETV, all the 16 (100%, 95%CI, [100%, 100%]) patients maintain HBV DNA < 20 IU/mL at week 24. The levels of serum hepatitis B surface antigen (HBsAg) significantly decreased from baseline after 24 weeks (10137.6[3252.6-23603.2] to 8151.3[1859.9-20073.2] IU/ml, P **Conclusion:** At 24 weeks after switch to TAF, virological and biochemical outcomes improved significantly in patients exhibiting suboptimal responses to ETV therapy, while renal and bone safety remained stable. Further study in a larger cohort with a longer observation period is ongoing to evaluate the actual merit of switching from ETV to TAF.

Table 1 Virological responses after switch to TAF

Characteristics	Suboptimal response group (n=105)	Intolerant group (n=16)
HBV DNA < 20 IU/ml	28/105 (26.7% [18.1%, 35.3%])	16/16 (100%, [100%, 100%])
HBeAg loss	2/104 (1.9% [-0.8%, 4.7%])	0/16 (0%, [0%, 0%])
HBeAg seroconversion	1/104 (1.0% [-1.0%, 2.1%])	0/16 (0%, [0%, 0%])

Figure 1. Mean reduction or improvement from baseline to 24 weeks after switch to TAF (*P<0.05)



Disclosures: Fei Kong: Nothing to Disclose, Ying Dai: Nothing to Disclose, Xiqiu Zeng: Nothing to Disclose, Hongxin Piao: Nothing to Disclose, Xianbo Wang: Nothing to Disclose, Dongmei Wei: Nothing to Disclose, Lei Yu: Nothing to Disclose, Chenxin Meng: Nothing to Disclose, Junqi Niu: Nothing to Disclose, YANHANG GAO: Nothing to Disclose

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1241 | FACTORS ASSOCIATED WITH MASLD AND LIVER FIBROSIS IN FOREIGN-BORN ASIAN-AMERICANS WITH CHRONIC HEPATITIS B SEEN IN TWO NON-ACADEMIC HEPATOLOGY CLINICS IN SOUTHERN CALIFORNIA: IMPACT OF METABOLIC FEATURES, MASLD AND TIME SPENT LIVING IN THE US

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Background: Asians with chronic hepatitis B (CHB) are at risk of liver fibrosis. MASLD also leads to fibrosis. Risk factors for MASLD in Asians are not clearly delineated. Our aim was to identify metabolic features associated with MASLD and progressive disease in a cohort of foreign-born Asian-Americans (FBAA) seen for CHB in 2 "real-world", non-academic Hepatology practices in Southern California. **Methods:** Retrospective study of FBAA with CHB and protocolized testing of HBV serologies, liver biochemistry, metabolic syndrome, liver steatosis and fibrosis [Fibroscan® CAP (dB/m) and stiffness (kPa)], and InBody® measures of fat distribution. **Results:** 115 FBAA were included, seen from 2020-2023: 52.2% were women, median age was 53y(21-79) immigrating primarily from Taiwan (30%), Vietnam (26%), and China (25%). Patients had lived in the US for 36y(6-59); 50% arrived below the age of 20y, 48% between 20y-40y. 74.8% were HBeAb+, 58.3% were treated for 9.9y(0.2-20.6) and undetectable viremia in 50.5%. Alcohol use was insignificant. CAP was 250(15-400); 36.5% had a CAP ≥268 (steatosis threshold). Stiffness was 5(2.1-11.4); 28.7% had liver stiffness ≥ 6 (fibrosis threshold). Median BMI was 24.4(15.6-39.0). Patients with a BMI ≥23 (68.7%) had higher triglycerides (mg/dL) [108(49-348) vs 73(42-178), p=0.0008], CAP [260(181-353) vs 224.5(151-350), p<0.0001], and lower HDL (mg/dL) [51(30-155) vs 64(42-156), p=0.0003]. Patients with a CAP ≥268 had significantly higher BMI, liver stiffness, prevalence of MS, ALP, HbA1c and triglycerides, and significantly lower AST/ALT ratios and HDL. A CAP ≥268 was associated with higher liver stiffness [6.1(3.3-11.4) vs 4.5 (2.1-11), p<0.0001], % body fat [34.1(15.9-47.8) vs [29.3(11.3-42.9), p=0.0032], and lower % skeletal muscle mass [36.1(28.2-47.9) vs. 38.4(29.2-50.4), p=0.0178]. Multivariate analysis adjusted for age and gender found BMI as the only variable independently associated with CAP ≥268 (p=0.0014). Patients with stiffness ≥6 had significantly higher BMI, prevalence of MS and increased number of components (in particular HTN), ALP, HbA1c, ALT, and CAP ≥268 (63.6% vs 25.6%, p=0.0002). Acculturation: those who immigrated young had an increased risk of both elevated BMI and steatosis with time lived in the US, independently of age alone. Male gender and time in the US adjusted for age were independently associated with a BMI ≥23. **Conclusion:** FBAA with CHB patients and a BMI ≥23 are at increased risk for MS, which is associated with high risk of MASLD and fibrosis. Time spent living in the US is a risk factor for MASLD in this cohort.

Disclosures: Michelle Gunawan: Nothing to Disclose, Brian Xu: Nothing to Disclose, Micaela Wong: Nothing to Disclose, Michel Mendler: Nothing to Disclose, Tse-Ling Fong: Nothing to Disclose, Edward Mena: Nothing to Disclose

1242 | IMATINIB PROMOTES HBV REACTIVATION THROUGH OXIDATIVE STRESS-INDUCED BLOCKAGE OF AUTOPHAGIC FLUX

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Background: Imatinib is a milestone drug in molecular targeted therapy against cancer. However, it is with high risk of hepatitis B virus (HBV) reactivation and the underlying mechanism remains to be clarified. Previous studies indicated that oxidative stress was involved in imatinib induced HBV reactivation in liver cells. Therefore, we conduct the current study to explore the detailed role and future mechanism. **Methods:** HBV cell lines (hepG2.2.15 and hepAD38) were treated with imatinib for 72 hours. ELISA and Southern blot were applied to detect the level of viral protein expression and HBV replication. Fluorescence staining was used to detect reactive oxygen species (ROS) and malondialdehyde (MDA) levels. Quantitative real-time PCR and Western blot were used to evaluate oxidative stress response and autophagy related mRNA transcription and protein expression. Oxidative stress inhibitor, acetylcysteine, was further applied to validate the regulatory

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mechanism from imatinib induced oxidative stress to related cytokine pathways. **Results:** Imatinib treatment increased the level of intracellular HBV replication intermediates and supernatant HBeAg. Fluorescence staining demonstrated that imatinib treatment up-regulated intracellular ROS and MDA, indicating oxidative stress was induced in cells. Oxidative stress triggered host response and downregulated the autophagy inhibitors, m-TOR and p-mTOR. Sequentially, the expression of autophagy initiation markers, Beclin-1 and LC3B, increased, which means increased formation of autophagosomes. Meanwhile, the expression of p62, a marker for autophagy degradation, increased, indicating that the degradation of autophagosomes was reduced. Collectively, these **Results:** reveal the blockage of autophagic flux and accumulation of autophagosomes in cells. Acetylcysteine treatment attenuated the promoting effect of imatinib on HBV protein expression and HBV DNA replication. As a result, the level of p-mTOR increased and the autophagic flux partially recovered. **Conclusion:** Imatinib treatment would trigger HBV reactivation and induce oxidative stress to block autophagic flux, leading to accumulation of autophagosomes. Acetylcysteine treatment could attenuate HBV reactivation caused by imatinib and partially recover autophagic flux through inhibiting oxidative stress. Taken together,imatinib might induce HBV reactivation via triggering oxidative stress and sequential host response of autophagy.

Disclosures: Weixiu Li: Nothing to Disclose, Lingyao Du: Nothing to Disclose, hong Tang: Nothing to Disclose

1243 | NUCLEOTIDE ANALOGS REDUCED 3-YEAR RECURRENCE RATE AFTER CURATIVE RADIOFREQUENCY ABLATION THERAPY IN HBV-RELATED HCC PATIENTS

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Background: Sustained viral suppression after radical treatment is important to reduce HCC recurrence. Whether there is a difference of recurrence between nucleoside analogs and nucleotide analogs post curative radiofrequency ablation therapy of hepatocellular carcinoma is currently unclear. This retrospective study aimed to compare the 3-year recurrence and survival rates among HCC patients receiving nucleotide analogs (TDF or TAF) and nucleoside analog (ETV) post-RFA. **Methods:** This study consecutively collected patients with hepatitis B cirrhosis who were initially diagnosed with hepatocellular carcinoma at the Tianjin Third Central Hospital between August 2018 and December 2020. We compared the recurrence rates of HCC in patients receiving nucleoside analog (ETV group) and nucleotide analogs (TDF and TAF groups) during 3-year regular follow-up period after radiofrequency treatment. After controlling for age and gender, the weights were determined using the inverse probability weighting (IPTW)method, multiple regression equations were developed and recurrence-free survival curves were plotted. **Results:** A total of 270 patients with hepatitis B cirrhosis who were initially diagnosed with hepatocellular carcinoma were enrolled in this study. Among them, 177 HCC patients treated with RFA were divided into the ETV group (n = 112), the TDF group(n=41) and the TAF group (n=24) according to the postoperative administration of oral antiviral drugs. The 3-year RFS rates in the ETV, TDF, and TAF groups were 57.14%, 51.22% and 25.00%, respectively. In comparison to the nucleoside analog (ETV group), nucleotide analogs group (TDF and TAF) had a lower recurrence rate of HCC at 1 year,2 year and 3 year (1-year:HR=0.69, 95% CI 0.31-1.54,P<0.0001; 2-year HR=0.55, 95% CI 0.31-0.97,P<0.0001; 3-year HR=0.61,95% CI 0.37-1.02, P<0.0001). In HCC patients after RFA treatment, nucleotide analogue therapy is associated with higher 2-and 3-year recurrence-free survival compared with nucleoside analogue therapy (2-year 66.15% vs 47.32% P=0.015; 3-year 58.46% vs 42.86% p=0.045).There was no difference in 3-year overall survival between the two groups after radiofrequency treatment. **Conclusion:** Receiving nucleotide analog treatment was associated with higher 2-and 3-year recurrence-free survival than nucleoside analogs in HCC patients after radiofrequency ablation treatment.

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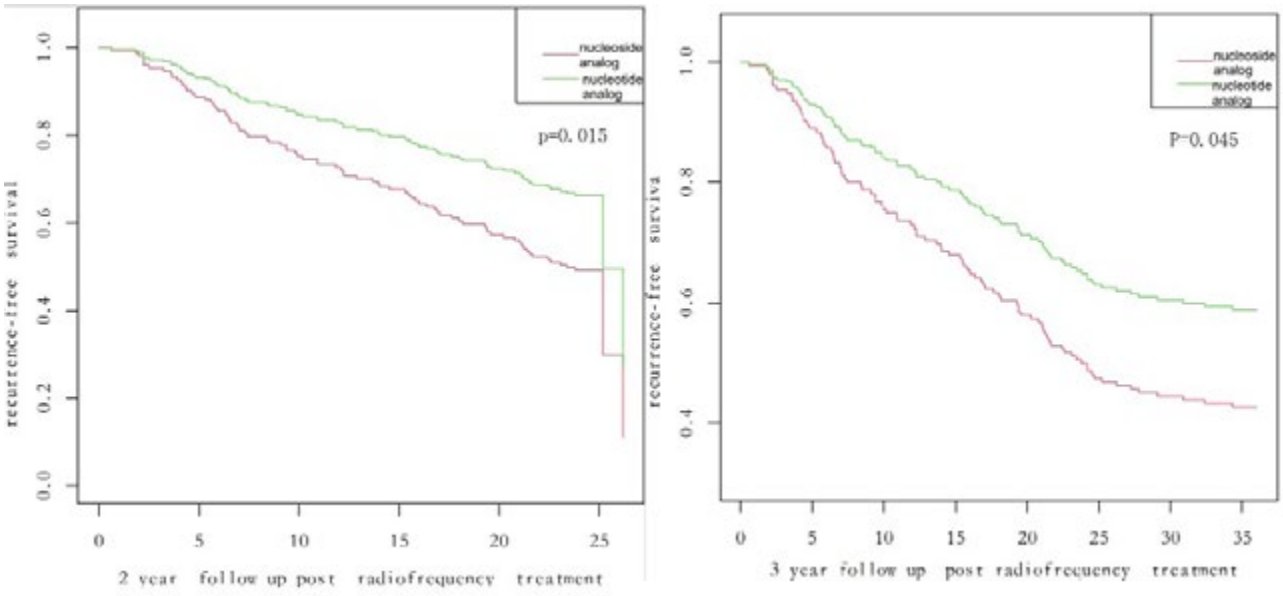

Disclosures: Jing Liang: Nothing to Disclose, BAIGUO XU: Nothing to Disclose, Xue Zhang: Nothing to Disclose

1244 | THE EFFICACY AND SAFETY OF PROPHYLACTIC TENOFOVIR ALAFENAMIDE TO PREVENT HBSAG-POSITIVE CANCER PATIENTS UNDERGOING CHEMOTHERAPY FROM HBV REACTIVATION- AN INTERIM REPORT OF A PROSPECTIVE TRIAL

Po-Yueh Chen[1] Ching-Chu Lo[2] Jow-Jyh Huang[2] Kuo-Chih Tseng[3] Chi-Wei Tseng[4] Jyh-Jou Chen[5] Hung-DA Tung[5] Chi-Yi Chen[6]

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Background: Hepatitis B reactivation had been noted in HBsAg-positive patients undergoing chemotherapy and could cause hepatic decompensation or even mortality. Prophylactic use of nucleos(t)ide analogues (NUCs) had been proved to lower the incidence of HBV reactivation in patients receiving highly risky immunosuppressants. We aim to prospectively evaluate the efficacy and safety of prophylactic tenofovir alafenamide (TAF) in HBsAg-positive cancer patients undergoing chemotherapy. **Methods:** This prospective trial was conducted in middle-south part of Taiwan and we aimed to enroll 150 patients. Individuals aged 20 years or more with positive HBsAg would be enrolled when scheduled systemic chemotherapy was confirmed. All participants would receive 25mg TAF daily for 48 weeks and the first dose would be given less than 7 days prior to start of chemotherapy. The HBV DNA level would be checked at baseline, week 4, 12, 24, 36, and 48 after TAF use. The primary endpoint is the rate of HBV reactivation during prophylactic use of TAF. HBV reactivation is defined as either HBV DNA increase 2 logs compared to the baseline level or 3 log of HBV DNA in patient with previously undetectable level. **Results:** One hundred and twenty-eight patients were screened from Jun 2021 to Dec 2023 and 102 patients were enrolled. The mean age of all patients was 56.5 years old and 50 (49%) patients were male. The baseline mean HBV DNA level was 3.48 (log IU/ml) and the mean value of liver stiffness was 7.57 kPa. Among the 102 patients, the most common cancer type was breast cancer (33.3%, 34/102). Cisplatin-containing regimens were prescribed in 26 patients (25.5%, 26/102) and 7 patients (6.9%, 7/102) ever received rituximab. Of 102 patients with a mean follow-up of 10.1 months, two (1.9%, 2/102) had experience of virologic HBV reactivation. Three patients (2.9%, 3/102) had hepatitis flares (ALT > 5.0 x upper limited normal), but their HBV DNA level decreased and drug induced liver injury was considered. Among 74 patients with complete 48-weeks of TAF prophylaxis, 59 patients (79.7%, 59/74) were with HBV DNA < 20 IU/ml and decreased liver stiffness from baseline to 48th week was also found (7.57 kPa to 7.01 kPa). The eGFR level and serum phosphate were stationary from baseline to 48th week of TAF treatment. The safety profiled show that 43 patients (42.2%, 43/102) had adverse effects. Ten patients were expired due to progression of underlying malignancies. Serious adverse effects were found in 19 patients (18.6%, 19/102), however, none was resulted from TAF. No adverse effect induced drug discontinuity or

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death was found. The most common adverse effects were nausea (30.4%, 31/102) and vomit (17.6%, 18/102). **Conclusion:** Tenofovir alafenamide (TAF) is an effective and tolerable antiviral agent to prevent HBV reactivation in cancer patients with positive HBsAg undergoing chemotherapy.

Disclosures: Po-Yueh Chen: Nothing to Disclose, Ching-Chu Lo: Nothing to Disclose, Jow-Jyh Huang: Nothing to Disclose, Kuo-Chih Tseng: Nothing to Disclose, Chi-Wei Tseng: Nothing to Disclose, Jyh-Jou Chen: Nothing to Disclose, Hung-DA Tung: Nothing to Disclose, Chi-Yi Chen: Nothing to Disclose

1245 | IMMUNOLOGICAL CORRELATES OF RAPID HBSAG DECLINE IN CHRONIC HBV HEPATITIS PATIENTS UNDERGOING TENOFOVIR AMIBUFENAMIDE TREATMENT ◆

Shue Xiong[1] Hang Jia[1] Xu Quan[1] Bo Liang[1] Si Lu[1] Hua Wang[1] Han Li[1] Yi Cheng[1] Tian Xiang[1] Jia Liu[1] Xin Zheng[1]

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Background: While most chronic viral hepatitis B (CHB) patients undergoing Tenofovir Amibufenamide (TMF) antiviral therapy experience a rapid decline in HBV DNA levels, the same is not observed for HBsAg decline in all patients, highlighting unclear immunological mechanisms. This study aims to dynamically observe changes in immunological function and its correlation with clinical indicators during the initial stages of TMF antiviral treatment through a prospective, single-center clinical study. **Methods:** A total of 31 CHB patients receiving antiviral treatment were included, comprising 15 HBeAg positive and 16 HBeAg negative individuals. Changes in virological indicators were monitored over 24 weeks post-TMF treatment. Peripheral blood samples from 11 HBeAg-positive and 10 HBeAg-negative patients were collected at baseline and at 4, 8, 12, and 24 weeks. Peripheral blood mononuclear cells (PBMCs) were analyzed to detect the phenotypes of B cells, dendritic cells (DCs), monocytes, T cells, and HBV-specific T cell functions. **Results:** The study found significantly higher baseline levels of HBV-DNA, HBV RNA, and HBsAg in the HBeAg-positive CHB group compared to the HBeAg-negative group. After TMF antiviral treatment, HBV DNA and RNA levels decreased rapidly, particularly within the first 4 weeks, in all CHB patients. Notably, the group of HBeAg-positive hepatitis patients (ALT>2ULN at baseline) exhibited a significant decline in HBsAg levels within the first 4 weeks, followed by prompt ALT normalization. In contrast, the HBsAg levels remained at baseline levels in HBeAg-positive infection patients (ALT<2ULN at baseline) and HBeAg-negative patients. Immunological marker monitoring revealed elevated frequencies of B cells and CD8 T cells, as well as increased expression of HLA-DR on CD4 T cells in the HBeAg-positive group, both at baseline and during treatment. Additionally, monocyte frequency and the expression levels of CD86, CD80, HLA-DR and PD-L1 on B cells after 4 or 8 weeks TMF antiviral treatment were significantly increased, while the expression levels of CD100 and Foxp3 on CD4 and CD8 T cells decreased after 4 weeks of TMF antiviral treatment. Dynamic analysis of HBV-specific T cell function showed an early increase of HBsAg-specific CD4+ T cell responses post-TMF therapy, particularly during weeks 4-8, in the group of HBeAg-positive hepatitis patients compare to the group of HBeAg-positive infection patients. **Conclusion:** TMF antiviral treatment leads to rapid declines in HBV DNA and RNA levels in CHB patients, with more pronounced HBsAg reduction observed in treatment naïve HBeAg-positive hepatitis patients. This reduction coincides with activation of peripheral B and T cell immune functions, as well as early increased HBsAg-specific CD4+ T cell responses in this group of patients. Our results suggest a potential immunological mechanism underlying TMF's antiviral effect during early treatment stages.

Disclosures: Shue Xiong: Nothing to Disclose, Hang Jia: Nothing to Disclose, Xu Quan: Nothing to Disclose, Bo Liang: Nothing to Disclose, Si Lu: Nothing to Disclose, Hua Wang: Nothing to Disclose, Han Li: Nothing to Disclose, Yi Cheng: Nothing to Disclose, Tian Xiang: Nothing to Disclose, Jia Liu: Nothing to Disclose, Xin Zheng: Nothing to Disclose

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1246 | COMPARATIVE ANALYSIS OF HEPATOCELLULAR CARCINOMA RISK IN CHRONIC HEPATITIS B PATIENTS TREATED WITH TENOFOVIR ALAFENAMIDE (TAF), TENOFOVIR DISOPROXIL FUMARATE (TDF), AND ENTECAVIR (ETV): A SYSTEMATIC REVIEW AND META-ANALYSIS WITH GRADE ASSESSMENT ◆

Natchaya Polpichai[1] Sakditad Saowapa[2] Aunchalee Jaroenlapnopparat[3] Phuuwadith Wattanachayakul[4] Pojsakorn Danpanichkul[5] Angkawipa Trongtorsak[6] Pimsiri Sripongpun Sripongpun[7] Naichaya Chamroonkul[7] Pisit Tangkijvanich[8] Suthat Liangpunsakul[9] Teerha Piratvisuth[10] Apichat Kaewdech[7]

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Background: Chronic hepatitis B (CHB) is a significant risk factor for the development of hepatocellular carcinoma (HCC), necessitating effective antiviral therapy. While nucleotide analogs such as Tenofovir Alafenamide (TAF), Tenofovir Disoproxil Fumarate (TDF), and Entecavir (ETV) are recommended for CHB, their impacts on HCC risk remain uncertain. This study aims to assess the risks of HCC in CHB patients receiving these antiviral agents. **Methods:** A comprehensive literature search up to March 31, 2024, was conducted to identify studies comparing HCC incidence among CHB patients treated with TAF, TDF, or ETV. Data extraction and quality assessment adhered to PRISMA guidelines, and Review Manager was used for statistical analyses. The quality appraisal was conducted using the Newcastle Ottawa Scale and the Cochrane Risk of Bias tool. **Results:** Twenty-seven studies involving 93,236 CHB patients met the eligibility criteria. The meta-analysis revealed a significantly lower incidence of HCC in patients treated with TAF compared to those treated with TDF (Risk Ratio (RR) 0.40; 95% CI: 0.27–0.57; p < 0.00001) and ETV (RR 0.55; 95% CI: 0.31–0.96; p = 0.03). TDF-treated patients also had lower HCC incidences compared to those treated with ETV (RR: 0.60; 95% CI: 0.49–0.74; p < 0.00001) (Figure 1A,1B and 1C). GRADE assessment was utilized to evaluate the quality of evidence. **Conclusion:** Patients with CHB receiving TAF experienced a reduced incidence of HCC compared to those treated with TDF and ETV, with TDF also showing advantages over ETV. Further research is needed to understand the mechanisms and refine treatments for CHB.

Figure 1A: Forest plot comparing the cumulative incidence of HCC in patients receiving TAF or TDF

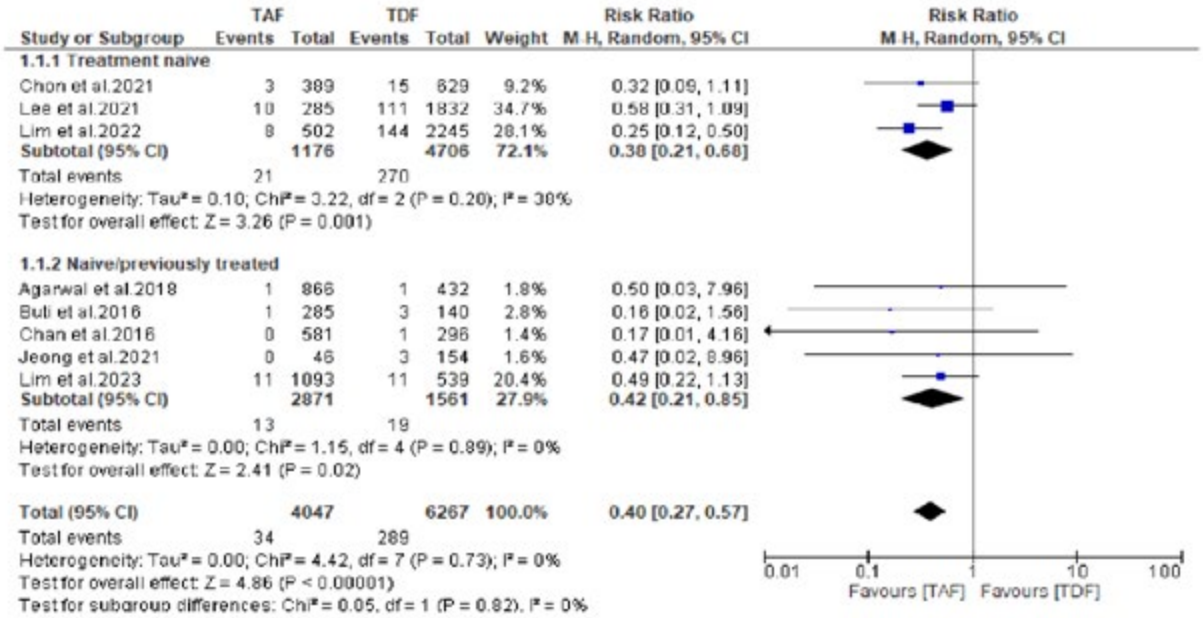

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Figure 1B: Forest plot comparing the cumulative incidence of HCC in patients receiving TAF or ETV

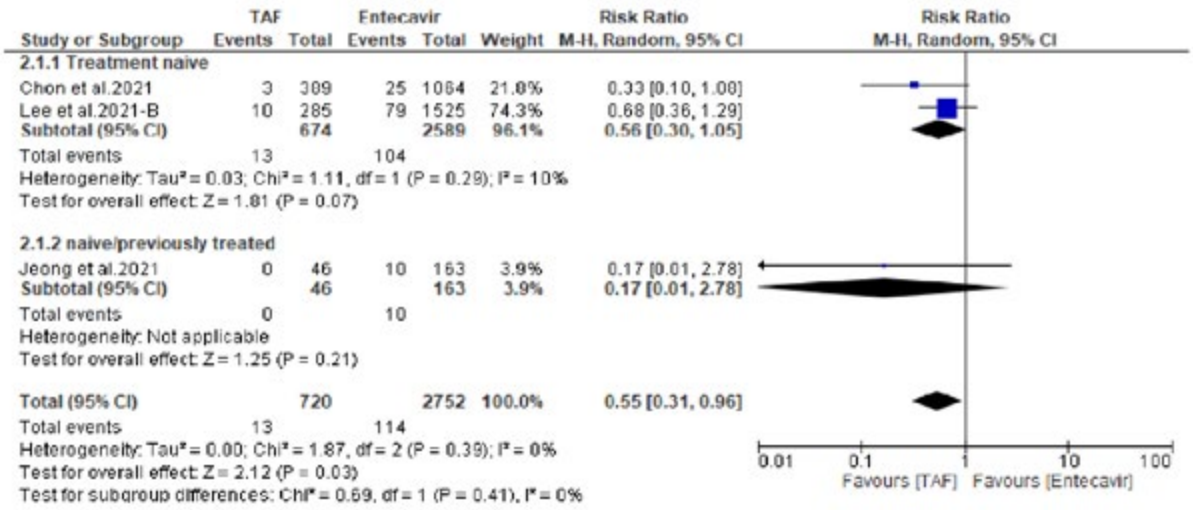
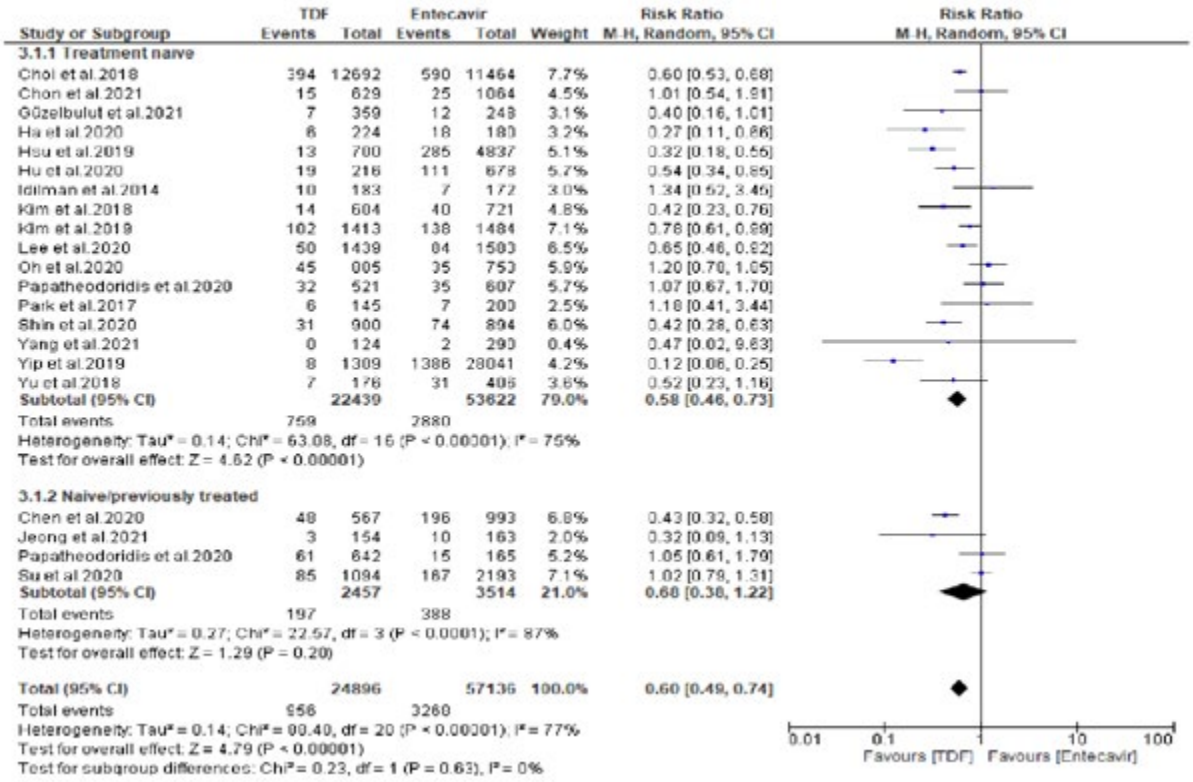


Figure 1C: Forest plot comparing the cumulative incidence of HCC in patients receiving TDF or ETV



Disclosures: Natchaya Polpichai: Nothing to Disclose, Sakditad Saowapa: Nothing to Disclose, Aunchalee Jaroenlapnopparat: Nothing to Disclose, Phuuwadith Wattanachayakul: Nothing to Disclose, Pojsakorn Danpanichkul: Nothing to Disclose, Angkawipa Trongtorsak: Nothing to Disclose, Pimsiri Sripongpun Sripongpun: Nothing to Disclose, Naichaya Chamroonkul: Nothing to Disclose, Pisit Tangkijvanich: Nothing to Disclose, Suthat Liangpunsakul: DURECT: Consultant, Durect Corporation: Consultant, Surrozen: Consultant, Korro Bio: Consultant, Teerha Piratvisuth: Nothing to Disclose, Apichat Kaewdech: Nothing to Disclose

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1247 | LONGITUDINAL PROFILE OF SERUM HBV RNA IN PATIENTS WITH CHRONIC HEPATITIS B INFECTION ON LONG-TERM NUCLEOSIDE ANALOGUES

Lung Yi Mak[1] Mark Anderson[2] Michael Stec[2] Danny Wong[1] Rex Wan-Hin Hui[1] Wai-Kay Seto[1] Gavin Cloherty[3] Man-Fung Yuen[1]

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Background: Serum hepatitis B virus RNA (HBV RNA) is a novel biomarker in chronic hepatitis B infection (CHB). We aimed to describe the longitudinal profile of HBV RNA and factors influencing its levels in CHB patients on nucleoside analogue (NUC) therapy. **Methods:** Serial samples from 1354 CHB patients started on first-line NUC were evaluated. Time of NUC initiation was taken as baseline (year 0), followed by 1-year, 3-year and 5-year of NUC therapy. HBV RNA was measured by Research Use Only RealTi*m*e HBV RNA v2.0 (0.2 mL) (Abbott Diagnostics) which has a lower limit of detection and quantification (LLOQ) of 0.8 log U/mL (~20 copies/mL). HBV DNA measurements were performed by Cobas Taqman assay (Roche Diagnostics) with a lower limit of detection (LLOD) of 20 IU/ml. Levels were log transformed and expressed in $\log_{10}$ U/mL. **Results:** Among 1354 subjects, median age at baseline was 49.8 (interquartile range [IQR] 40.2-57.3) years, with 65.2% male. By FIB-4 criteria (i.e., >3.25), 9.9% were cirrhotic. Baseline median HBV RNA and DNA were 3.68 (IQR 2.42-5.19) log IU/mL and 5.76 (IQR 3.54-7.17) log U/mL, respectively. Upon NUC therapy, median serum HBV RNA levels were 2.45 (IQR 1.82-3.62), 2.23 (IQR 1.67-3.05) and 2.14 (IQR 1.48-2.86) log U/mL at 1-year, 3-year and 5-year respectively, with corresponding log U/mL reductions of 0.82, 1.20 and 1.54. In contrast, median HBV DNA declined to 1 (IQR 1-2.23) log IU/mL at 1-year and remained to be 1 (IQR 1-1) at 3-year and 5-year (Figure 1A). Undetectable HBV RNA was achieved in 13.5% (1-year), 15.9% (3-year) and 20.1% (5-year), compared to 69.2% (1-year), 88.9% (3-year) and 93.0% (5-year) achieving undetectable HBV DNA. The correlation between RNA and DNA diminished with increasing duration of NUC (r=0.553, r=0.257, r=0.276, r=0.224 for baseline, 1-year, 3-year and 5-year, respectively). Cirrhosis was associated with lower serum HBV RNA although not statistically significant (Figure 1B). Age was negatively correlated with RNA (r=-0.277) and DNA (r=-0.206). Older age was associated with higher chance of RNA undetectability (Figure 1C). **Conclusion:** Serum HBV RNA declines much slower than DNA upon NUC therapy supporting the notion of indirect action of NUC through gradual reduction of infected hepatocytes in liver. As only 20% patients will achieve undetectable serum HBV RNA at 5 years of NUC therapy, it may serve as a biomarker for disease and treatment monitoring of different novel agents acting on cccDNA transcription even in patients taking long-term NUC.

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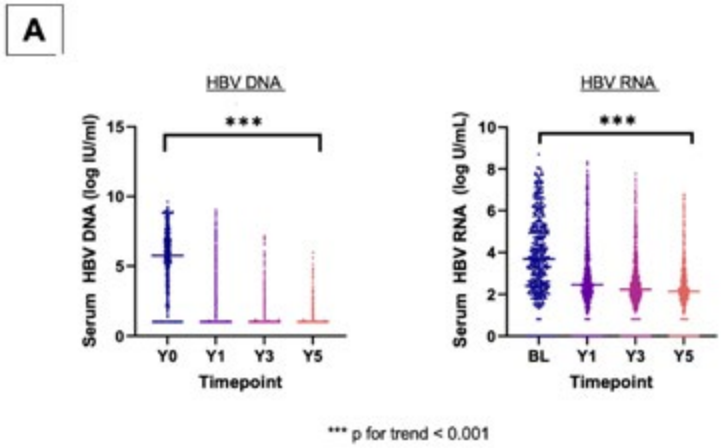

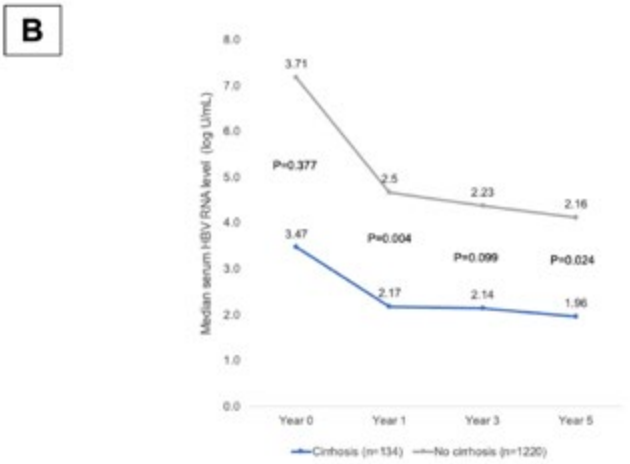

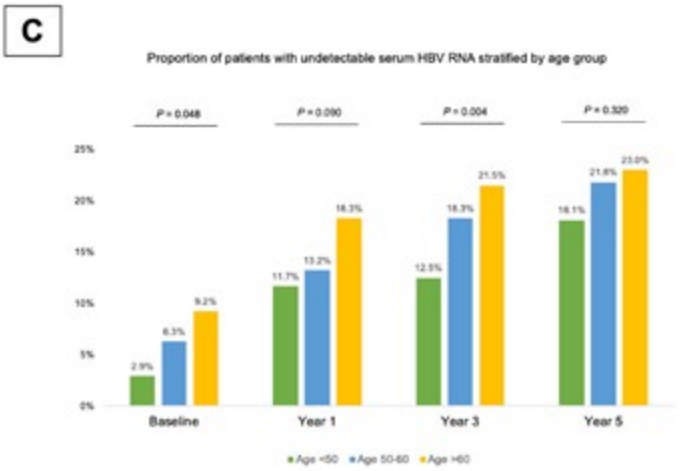

Disclosures: Lung Yi Mak: Nothing to Disclose, Mark Anderson: Abbott Laboratories: Employee, Abbott Laboratories: Stock - publicly traded company, Michael Stec: Nothing to Disclose, Danny Wong: Nothing to Disclose, Rex Wan-Hin Hui: Nothing to Disclose, Wai-Kay Seto: Nothing to Disclose, Gavin Cloherty: Abbott: Shareholder, Abbott: Head of Infectious Disease Research, Man-Fung Yuen: Speaking and Teaching relationship with Fujirebio Incorporation, Gilead Sciences, Roche, Sysmex Corp; Has not ended; Consultant relationship with

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1248 | LONGITUDINAL PROFILE OF HBSAG ISOFORMS AND HBSAG-ANTIBODY IMMUNE COMPLEX IN NATURAL HISTORY OF CHRONIC HEPATITIS B INFECTION

Lung Yi Mak[1] Mark Anderson[2] Tiffany Fortney[2] Danny Wong[1] Rex Wan-Hin Hui[1] Wai-Kay Seto[1] Gavin Cloherty[3] Man-Fung Yuen[1]

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Background: Hepatitis B surface antigen (HBsAg) consists of three isoforms: large (LHBs), middle (MHBs), and small (SHBs) surface proteins. The composition of HBsAg has been demonstrated to differentiate the disease stage and predict treatment response in chronic hepatitis B infection (CHB). We aimed to characterize the longitudinal profile of HBsAg isoforms and HBsAg-antibody immune complexes in the natural history of CHB. **Methods:** Serial samples of 80 CHB patients (**Part A** [n=40]: hepatitis B e antigen [HBeAg]-positive patients with documented time of HBeAg seroclearance [ESC]; **Part B** [n=40]: HBeAg-negative patients with documented time of HBsAg seroclearance [n=20] and without subsequent HBsAg seroclearance [n=20]) were evaluated. Large (LHBs), Medium (MHBs), and Total-S (THBs) isoforms of HBsAg were detected using prototype Research Use Only (RUO) assays (Abbott Diagnostics) performed on the fully-automated ARCHITECT platform. Assay results were reported as $\log_{10}$ signal-to-noise (S/N). The level of small HBsAg (SHBs) was arbitrarily calculated by subtracting LHBs and MHBs from THBs. An RUO Immune complex assay (Abbott Diagnostics) was performed on an ARCHITECT instrument. **Results:** In **Part A**, samples were available at -5years, -3years, time of ESC, +1year and +3years. SHBs was the most abundant isoform at all timepoints, followed by MHBs and LHBs being the least abundant. The levels and compositions of HBsAg remained static before and after ESC, irrespective of whether serum alanine aminotransferase was elevated after ESC (Figure 1A). HBsAg-Ab immune complexes declined with time leading to ESC but remained static afterwards. In **Part B**, samples were available at -5 to -10years, -3 to -5years, -1 to -3years, and 0 to -1years before HBsAg seroclearance in 20 subjects and 20 age-matched subjects without subsequent HBsAg seroclearance with matched index timepoints. In the subgroup with HBsAg seroclearance, all 3 HBsAg isoforms declined over the years leading to HBsAg seroclearance. In contrast, patients without subsequent HBsAg seroclearance demonstrated static HBsAg isoforms (Figure 1B). At the time of HBsAg seroclearance (timepoint 0 to 1-years), HBsAg isoforms could still be detected in 15/20 (75%) subjects. HBsAg-Ab immune complexes remained static over the years regardless of subsequent HBsAg seroclearance (Figure 1C). **Conclusion:** Composition and levels of HBsAg isoforms are stable before or after ESC, but decline together preceding HBsAg seroclearance. Immune complexes remained stable in HBeAg-negative phase despite decline in HBsAg levels.

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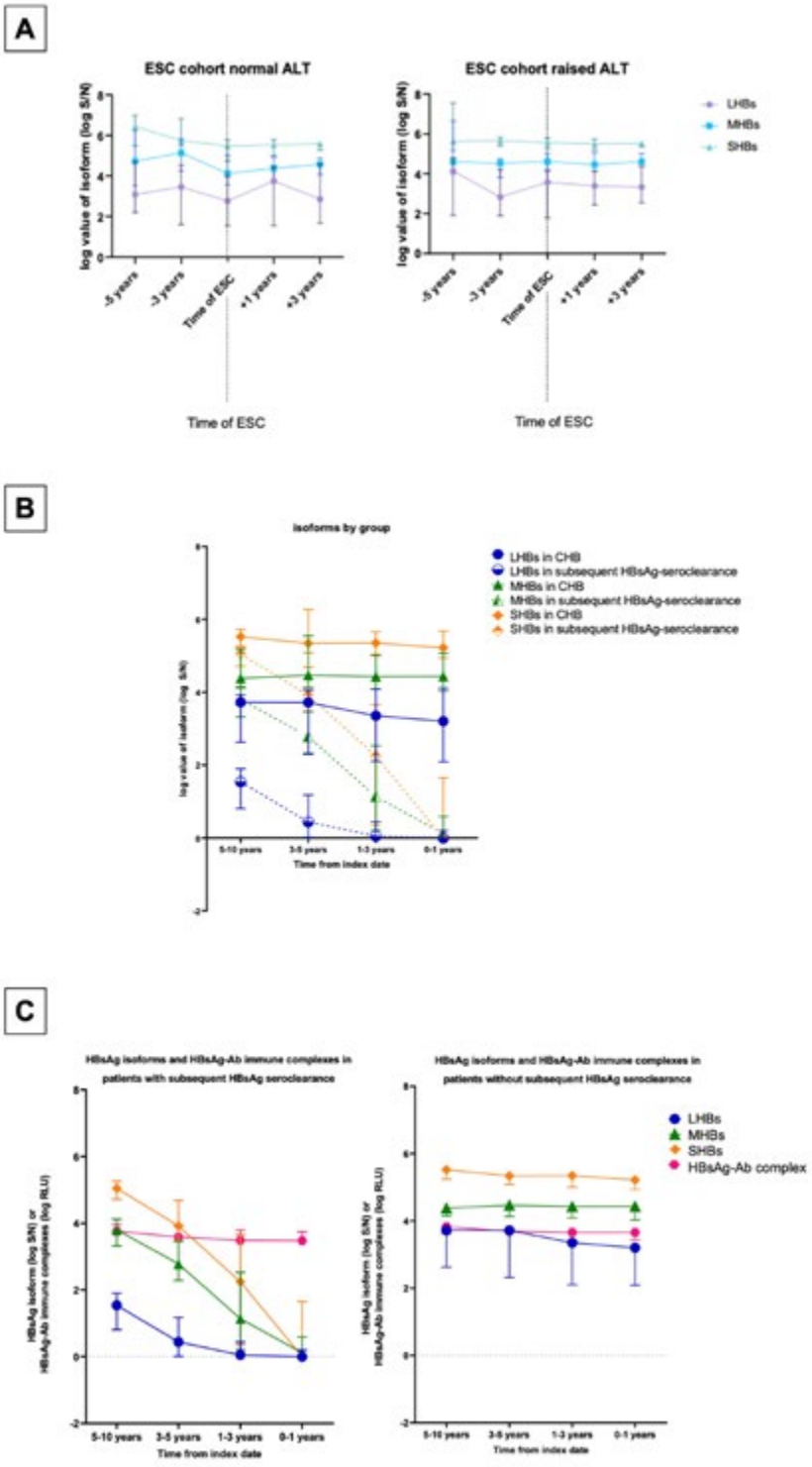

Disclosures: Lung Yi Mak: Nothing to Disclose, Mark Anderson: Abbott Laboratories: Employee, Abbott Laboratories: Stock - publicly traded company, Tiffany Fortney: Abbott Laboratories: Employee, Danny Wong: Nothing to Disclose, Rex Wan-Hin Hui: Nothing to Disclose, Wai-Kay Seto: Nothing to Disclose, Gavin Cloherty: Abbott: Shareholder, Abbott: Head of Infectious Disease Research, Man-Fung Yuen: Speaking and Teaching relationship with Fujirebio Incorporation, Gilead Sciences, Roche, Sysmex Corp; Has not ended; Consultant relationship with Clear B Therapeutics, Dicerna Pharmaceuticals; Has not ended; Consultant relationship with AbbVie, Abbott Diagnotics, Aligos Therapeutics; Has not ended; Consultant relationship with Arbutus Biopharma, Arrowhead Pharmaceuticals, Assembly Biosc; Has not ended; Consultant relationship with Immunocore, Janssen,

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Precision BioSciences; Has not ended; Consultant relationship with Fujirebio Incorporation, GlaxoSmithKline, Gilead Sciences; Has not ended; Grant/Research Support relationship with Fujirebio Incorporation, Gilead Sciences, Immunocore; Has not ended; Grant/Research Support relationship with AbbVie, Assembly Biosciences, Arrowhead Pharmaceuticals; Has not ended; Consultant relationship with Vir Biotechnology and Visirna Therapeutics; Has not ended; Consultant relationship with Roche, Sysmex Corporation, Tune Therapeutics; Has not ended; Grant/Research Support relationship with Sysmex Corporation and Roche; Has not ended

1249 | CUSTOMIZED SCREENING STRATEGY FOR HEPATOCELLULAR CARCINOMA DEMONSTRATES GOOD COST-EFFECTIVENESS IN PATIENTS WITH HBSAG-POSITIVE IN CHINA ◆

Xin Hao[1] Lei Zhang[2] Hongyan Liu[3] Xiaohuan Lai[4] Qing Yang[5] Xiuhua Li[6] Jubing Luo[7] Songtao Tang[8] Ronglong Jiang[9] Zhihong Diao[10] Songmei He[11] Xiaotian Lin[12] Rong Fan[1] Jinlin Hou[1]

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Background: Hepatocellular Carcinoma (HCC) screening is recommended for high-risk populations worldwide to enhance early diagnosis. aMAP score has been developed as an effective tool for assessing the risk of HCC occurrence. We aim to determine the cost-effectiveness of standard HCC screening strategy (Strategy A: US+AFP/6M) and stratified screening strategy based on aMAP score (Strategy B: US+AFP/12M, 6M, 3M for aMAP low-, medium-, and high-risk group respectively) for HBsAg-positive patients in China. **Methods:** We developed a Markov decision analysis model to assess the cost and health outcomes of the two screening strategies in a real-world cohort of 44,852 HBsAg-positive patients in 10 hospitals across China over the next 30 years. Epidemiological, clinical manifestations, health utility, and cost data were obtained from literature and actual data. We also analyzed parameter uncertainty through deterministic and probability sensitivity analyses (DSA and PSA). We evaluated from a healthcare provider's perspective with a 3.5% discounting rate and a willingness-to-pay (WTP) threshold of 3 times China's GDP (US$37,500). **Results:** The customized screening strategy B incurred lower costs ($2,002 per person over 30 years) and could generate higher quality-adjusted life years (6.82 QALYs per person over 30 years) compared to strategy A. Precisely, the Net Monetary Benefits (NMB) of strategy B were calculated to be $338,846, compared to $336,865 for strategy A, further supporting the cost-effectiveness of the customized approach. Our cost-effectiveness analysis indicated that, compared with strategy A, strategy B has a 97% likelihood to be cost-effective. **Conclusion:** Our real-world multi-center study in China shows that the customized HCC screening strategy based on aMAP score was more cost-effective than the standard screening strategy. The findings underscore the potential of the individualized approach to optimize healthcare resources for HCC screening.

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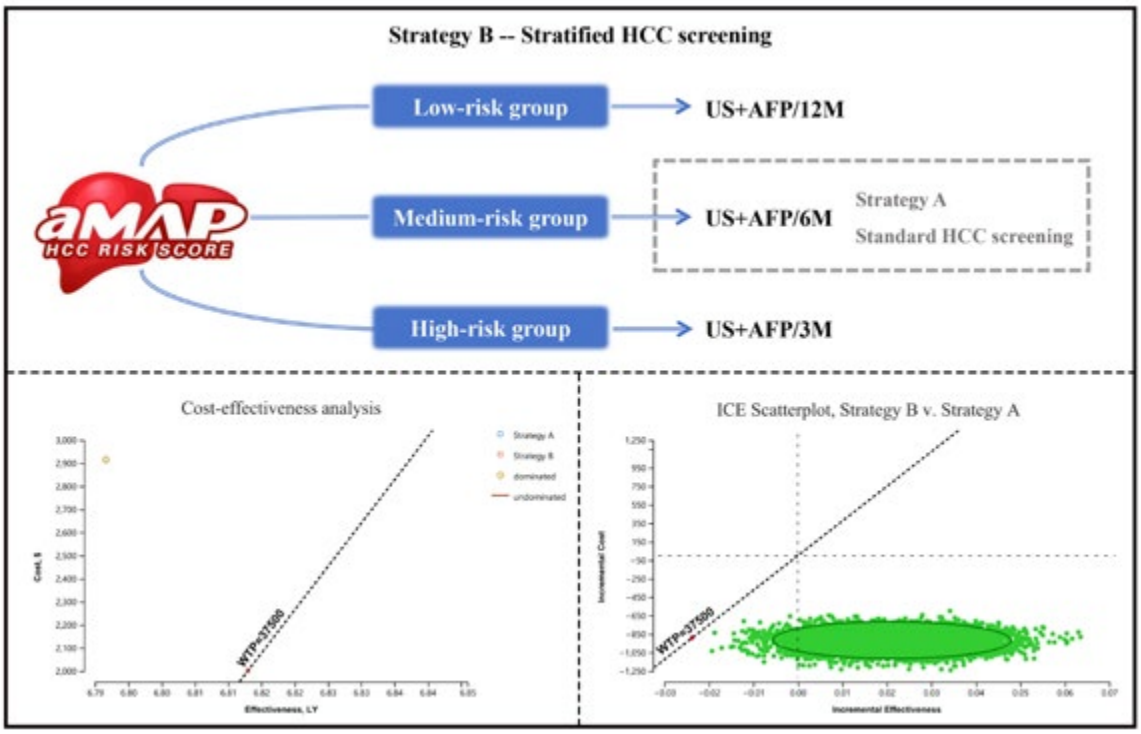

Disclosures: Xin Hao: Nothing to Disclose, Lei Zhang: Nothing to Disclose, Hongyan Liu: Nothing to Disclose, Xiaohuan Lai: Nothing to Disclose, Qing Yang: Nothing to Disclose, Xiuhua Li: Nothing to Disclose, Jubing Luo: Nothing to Disclose, Songtao Tang: Nothing to Disclose, Ronglong Jiang: Nothing to Disclose, Zhihong Diao: Nothing to Disclose, Songmei He: Nothing to Disclose, Xiaotian Lin: Nothing to Disclose, Rong Fan: Nothing to Disclose, Jinlin Hou: Nothing to Disclose

1250 | CURRENT MANAGEMENT AND TREATMENT INDICATIONS OF BASELINE GREY-ZONE (GZ) PATIENTS WITH HBEAG-NEGATIVE CHRONIC HEPATITIS B VIRUS INFECTION (CHBVE-) IN GREECE

Margarita Papatheodoridi[1] Sofia Paraskevopoulou[2] Panagiota Ioannidou[2] Paraskevi Fytili[2] Dimitrios Karagiannakis[3] Evangelos Cholongitas[2] Ioannis Vlachogiannakos[2] George Papatheodoridis[2]

[1]Medical School of Athens University, [2]General Hospital of Athens "Laiko", [3]General Hospital of Athens "Laiko", Depa

Background: The incidence of treatment indications and the optimal management of GZ CHBVe- patients (pts) remain controversial and thus their approach differs among different physicians and countries. In this study, we assessed the current management and treatment indications of such pts in Greece. **Methods:** All CHBVe- pts with ≥1 visit between 2010-2019 were included if they had baseline a) HBV DNA ≤20,000 IU/ml or b) HBV DNA >20,000 and ALT ≤2xULN. Patients with HCV/HDV/HIV coinfection, immunosuppression, decompensation or HCC, alcohol abuse or other liver injury were excluded. Epidemiological, clinical and laboratory parameters based on a predefined CRF were collected. Typical CHBVe- pts had baseline ALT≤ULN and HBV DNA <2000 and GZ pts had baseline ALT>ULN ± HBV DNA ≥2000. Typical treatment indications included a) HBV DNA >20,000 and ALT >2xULN, b) HBV DNA >2000 and advanced fibrosis [Ishak's stage 3-4 or liver stiffness (LS) 9.1-12/12.1-15 kPa in case of ALT ≤/>ULN] or c) detectable HBV DNA and cirrhosis (Ishak's stage 5-6 or LS >12/>15 kPa in case of ALT ≤/>ULN). **Results:** Of 2012 chronic HBV pts, 1501 (75%) (M 60%, age:44±15 years, born in Greece 57%, BMI 26±4 kg/m^2, follow-up 6.0±4.6 years) fulfilled the inclusion/exclusion criteria; of them, 690 (46%) were typical CHBVe- and 811 (54%) GZ pts. GZ vs typical CHBVe- pts did not differ in age, country of birth (Greece or abroad) or BMI, but they were more frequently males (64% vs 56%, P=0.002) and had higher ALT, AST and HBV DNA, lower platelets and more frequently typical treatment indications at baseline (165/811 or 20% vs 11/690 or 2%, P<0.001) and/or during follow-up (cumulative 3/5/10-year rate: 33/35/38% vs 3/4.5/5%, log-rank P<0.001) (Table 1). Similarly, baseline GZ pts were treated more

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frequently than typical CHBVe- pts (cumulative 1/5/10-year rate: 49/68/77% vs 1/10/15%, log-rank P<0.001). Treatment was initiated in 297/306 (97%) pts who developed typical treatment indications, 257/602 (43%) pts who remained as GZ pts and 25/593 (4%) patients who remained typical CHBVe- pts throughout follow-up (P<0.001). **Conclusion:** GZ pts by baseline ALT and HBV DNA represent a large proportion of CHBVe- cases seen at Greek tertiary liver centers. Treatment indications may be found in 20% of such pts by baseline LS and/or histology and develop in up to 40% of them over 10 years. In real life, therapy is given to almost all CHBVe- pts with typical treatment indications and >40% of pts remaining as GZ cases.

Table 1. Main characteristics of HBeAg-negative grey-zone (HBeAg- GZ) patients (pts) and typical pts with HBeAg-negative chronic HBV infection (CHBVe-)

	Total (N=1501)	HBeAg- GZ pts (n=811)	CHBVe- pts (n=690)	P
Age, years	45±14	45±14	45±14	0.788
Sex, males (%)	908 (60)	521 (64)	387 (56)	0.002
Place of birth, Greece (%)	860 (57)	472 (58)	388 (56)	0.474
BMI, kg/m^2	25.8±3.5	25.8±3.5	25.7±3.4	0.628
Diabetes, n (%)	72 (4.8)	28 (4.1)	44 (5.4)	0.265
ALT, IU/L	38±28	49±33	23±8	<0.001
AST, IU/L	29±17	35±20	21±6	<0.001
Platelets, x10^3/mm^3	218±47	212±48	227±44	<0.001
HBV DNA, IU/ml 1880 (0-210x10^6)		11700 (0-210x10^6)	235 (0-1980)	<0.001
Follow-up, years	6.0±4.6	6.8±4.8	5.1±4.2	<0.001
Treatment indications, %				<0.001
Year 0	12	20	1.6	
Year 5	21	35	4.5	
Year 10	23	38	5	
Treatment, %				<0.001
Year 1	27	48	2.5	
Year 5	42	68	10	
Year 10	50	77	15	

Disclosures: Margarita Papatheodoridi: Nothing to Disclose, Sofia Paraskevopoulou: Nothing to Disclose, Panagiota Ioannidou: Nothing to Disclose, Paraskevi Fytili: Nothing to Disclose, Dimitrios Karagiannakis: Nothing to Disclose, Evangelos Cholongitas: Nothing to Disclose, Ioannis Vlachogiannakos: Nothing to Disclose, George Papatheodoridis: Abbvie: Advisor, Abbvie: Speaking and Teaching, Abbvie: Grant/Research Support, Astra Zeneca: Advisor, Astra Zeneca: Speaking and Teaching, Abbvie: Advisor, Abbvie: Speaking and Teaching, Astra Zeneca: Advisor, Astra Zeneca: Speaking and Teaching, Genesis: Advisor, Genesis: Speaking and Teaching, Gilead: Advisor, Gilead: Speaking and Teaching, Gilead: Grant/Research Support, GlaxoSmithKline: Advisor, Ipsen: Advisor, Ipsen: Speaking and Teaching, Novo Nordisk: Advisor, Novo Nordisk: Speaking and Teaching, Roche: Advisor, Roche: Speaking and Teaching, Takeda: Advisor, Abbvie: Advisor, Abbvie: Speaking and Teaching, Abbvie: Grant/Research Support, Astra Zeneca: Advisor, Astra Zeneca: Speaking and Teaching, Abbvie: Advisor, Abbvie: Speaking and Teaching, Astra Zeneca: Advisor, Astra Zeneca: Speaking and Teaching, Genesis: Advisor, Genesis: Speaking and Teaching, Gilead: Advisor, Gilead: Speaking and Teaching, Gilead: Grant/Research Support, GlaxoSmithKline: Advisor, Ipsen: Advisor, Ipsen: Speaking and Teaching, Novo Nordisk: Advisor, Novo Nordisk: Speaking and Teaching, Roche: Advisor, Roche: Speaking and Teaching, Takeda: Advisor

1251 | LONG-TERM OUTCOMES OF BASELINE GREY-ZONE (GZ) PATIENTS WITH HBEAG-NEGATIVE CHRONIC HEPATITIS B VIRUS INFECTION (CHBVE-) IN GREECE ◆

Margarita Papatheodoridi[1] Sofia Paraskevopoulou[2] Panagiota Ioannidou[2] Paraskevi Fytili[2] Dimitrios Karagiannakis[2] Evangelos Cholongitas[2] Ioannis Vlachogiannakos[2] George Papatheodoridis[2]

[1]Medical School of Athens University, [2]General Hospital of Athens "Laiko"

Background: The outcomes of GZ CHBVe- patients (pts) remain debatable and their management differs among different physicians and countries. In this study, we assessed the long-term outcomes of such pts in Greece. **Methods:** All CHBVe- pts with ≥1 visit between 2010-2019 were included if they had a) baseline HBV DNA ≤20,000 IU/ml or b) baseline HBV DNA >20,000 and ALT ≤2xULN. Patients with HCV/HDV/HIV coinfection, immunosuppression, decompensation or HCC at baseline, alcohol abuse or other liver injury were excluded. Typical CHBVe- pts had ALT≤ULN and HBV DNA <2000 and GZ pts had ALT>ULN ± HBV DNA ≥2000 at baseline. Outcomes were HBsAg loss, hepatocellular carcinoma (HCC) and any negative event (HCC/decompensation/liver related death). **Results:** In total, 1501 pts [males 60%, age 44±15 years (yrs), BMI 26±4 kg/m^2, follow-up

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6.0±4.6 yrs] were included: 690 (46%) typical CHBVe and 811 (54%) GZ pts. GZ and CHBVe- pts did not differ in age or BMI, but they were more frequently males (64% vs 56%, P=0.002) and had higher ALT/AST/HBV DNA and lower platelets (all P<0.001). Therapy was initiated more frequently in baseline GZ than CHBVe- pts (1/10-yr cumulative rate: 49/77% vs 1/15%, log-rank P<0.001). HBsAg loss was observed in 19/811 (2.3%) GZ and 24/690 (3.5%) typical CHBe- pts with 1/5/10-yr cumulative rates 0.1/1/4.2% vs 1/3/8%, log-rank P=0.012). HBsAg loss was independently associated with greater BMI [HR/kg/m^2:1.13 (1.05-1.22), P=0.001] and baseline typical CHBVe- state [HR:2.26 (1.22-4.17), P=0.014]. HCC was diagnosed only in GZ pts (32/811 or 4%) with 1/5/10-yr cumulative rates 1/3/5% (log-rank P<0.001 vs typical CHBVe-). HCC development was independently associated with older age [HR/yr:1.10 (1.06-1.15), P<0.001], male gender [HR:3.29 (1.39-8.91), P=0.006], lower baseline platelets [HR/10^3/mm^3: 0.98 (0.97-0.99), P<0.001] and baseline GZ state [HR:36.47 (4.30-4790)]. Any negative event developed in 36/811 (4.4%) GZ (1/5/10-yr cumulative rates 1/4/6%) and 1/690 (0.1%) typical CHBe- pts (log-rank P<0.001). Development of any negative event was independently associated with older age [HR/yr:1.09 (1.05-1.13), P<0.001], lower platelets [HR/10^3/mm^3: 0.985 (0.98-0.99), P<0.001] and baseline GZ state [HR:16.07 (1.96-132), P=0.010]. **Conclusion:** In CHBVe- patients seen at Greek tertiary liver centers, GZ state by baseline ALT and HBV DNA, compared to typical CHBVe- state, is associated with significantly worse long-term outcomes including HCC despite frequent treatment initiation during follow-up. Thus, immediate onset of treatment in CHBVe- GZ patients may be warranted.

Disclosures: Margarita Papatheodoridi: Nothing to Disclose, Sofia Paraskevopoulou: Nothing to Disclose, Panagiota Ioannidou: Nothing to Disclose, Paraskevi Fytili: Nothing to Disclose, Dimitrios Karagiannakis: Nothing to Disclose, Evangelos Cholongitas: Nothing to Disclose, Ioannis Vlachogiannakos: Nothing to Disclose, George Papatheodoridis: Abbvie: Advisor, Abbvie: Speaking and Teaching, Abbvie: Grant/Research Support, Astra Zeneca: Advisor, Astra Zeneca: Speaking and Teaching, Abbvie: Advisor, Abbvie: Speaking and Teaching, Astra Zeneca: Advisor, Astra Zeneca: Speaking and Teaching, Genesis: Advisor, Genesis: Speaking and Teaching, Gilead: Advisor, Gilead: Speaking and Teaching, Gilead: Grant/Research Support, GlaxoSmithKline: Advisor, Ipsen: Advisor, Ipsen: Speaking and Teaching, Novo Nordisk: Advisor, Novo Nordisk: Speaking and Teaching, Roche: Advisor, Roche: Speaking and Teaching, Takeda: Advisor, Abbvie: Advisor, Abbvie: Speaking and Teaching, Abbvie: Grant/Research Support, Astra Zeneca: Advisor, Astra Zeneca: Speaking and Teaching, Abbvie: Advisor, Abbvie: Speaking and Teaching, Astra Zeneca: Advisor, Astra Zeneca: Speaking and Teaching, Genesis: Advisor, Genesis: Speaking and Teaching, Gilead: Advisor, Gilead: Speaking and Teaching, Gilead: Grant/Research Support, GlaxoSmithKline: Advisor, Ipsen: Advisor, Ipsen: Speaking and Teaching, Novo Nordisk: Advisor, Novo Nordisk: Speaking and Teaching, Roche: Advisor, Roche: Speaking and Teaching, Takeda: Advisor

1252 | EFFECTIVENESS AND SAFETY OF TENOFOVIR ALAFENAMIDE IN CHRONIC HEPATITIS B PATIENTS WITH SUBOPTIMAL RESPONSE TO ANTIVIRAL THERAPY

Wen Xie[1] Lihua Cao[2] Shuangsuo Dang[3] Liying Zhu[4] Dongliang Yang[5] Yueyong Zhu[6] Xiaoguang Dou[7] Zhiliang Gao[8] Binbin Chen[9] Xinxin Zhang[10] Yuming Wang[11] Yan Liu[12] Ting Zhang[1] Tingdan Ye[1] Ke Mi[1] Calvin Pan[13]

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Background: In patients with chronic hepatitis B (CHB), a suboptimal response (SOR) to entecavir or second-line therapy is associated with an increased risk of resistance and treatment failure. This study aimed to elucidate the efficacy and safety of switching to tenofovir alafenamide (TAF) therapy in these patients. **Methods:** We conducted a prospective, national cohort study across 11 sites of the Hepatitis B Research Network in China. Adult patients who met the 2017 EASL guideline definition for SOR were screened from September 2021 to March 2023. Additional criteria included adherence to antiviral therapy and HBV DNA levels >300 IU/mL without genotypic resistance. Patients on tenofovir disoproxil fumarate therapy, those with severe comorbidities, liver decompensation, or co-infections of HCV, HDV, or HIV were excluded. The primary outcome was the proportion

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of patients achieving a complete virological response (CVR, i.e., HBV DNA <20 IU/mL) at week 48 after switching to TAF therapy. Secondary outcomes were HBeAg/HBsAg loss, ALT normalization, and safety of TAF therapy. **Results:** Among 109 patients enrolled, the mean age was 40 years, with 66% male and 95% on entecavir for over one year. Additionally, 91% (99/109) were HBeAg-positive, and 23% (25/109) had elevated ALT levels. The median (IQR) HBV DNA was 2,050 (844, 11,565) IU/mL (Table 1). At 48 weeks post-switch to TAF therapy, 34% (37/109) of patients achieved CVR; 4% (4/99) achieved HBeAg negativity; and 82% (89/109) had normal ALT levels (a 5% increase compared to baseline). Comparing baseline variables between CVR achievers and non-achievers showed high albumin levels and female gender as independent predictors of achieving CVR. Although 72 patients did not achieve CVR at week 48, there was a significant reduction from baseline in median (IQR) HBV DNA [3,170 (1,098, 22,525) vs. 93 (44, 653) IU/mL, p<0.01] and HBeAg levels [1,105 (313, 1,376) vs. 752 (191, 1,157) IU/mL, p=0.047]. TAF therapy was well tolerated. Safety parameters were similar when comparing baseline and 48-week measurements, including the median (IQR) creatinine clearance [113 (95, 140) vs. 111 (100, 131), p=0.70] and BMI [23 (21, 26) vs. 23 (21, 26), p=0.78]. **Conclusion:** In CHB patients with SOR on entecavir or second-line therapy, switching to TAF therapy for 48 weeks resulted in 34% of patients achieving CVR and should be recommended. The therapy is safe, with the benefits of achieving HBeAg negativity and ALT normalization.

Table 1. Baseline characteristics of study patients

Variables presented as mean ± SD, median (IQR), or specified	Baseline n = 109
Age - year	40.2 ± 10.1
Male - No. (%)	72/109 (66.1)
History of NAFLD - No. (%)	6/109 (5.5)
History of Diabetes - No. (%)	1/109 (0.9)
BMI - kg/m^2	23.1 (20.9, 26.0)
HBV DNA - Log10 IU/ml	3.3 (2.9, 4.1)
HBsAg - IU/ml	5704.0 (448.1, 26171.0)
HBeAg positivity - No. (%)	99/109 (90.8)
HBeAg - IU/ml	794.8 (135.0, 1323.0)
Alanine transaminase - U/L	27.4 (20.0, 39.0)
Aspartate aminotransferase - U/L	22.5 (19.0, 27.8)
Total bilirubin -μmol/L	12.5 (9.1, 16.2)
Albumin - g/L	46.0 ± 2.9
Total protein - g/L	74.0 ± 4.4
Platelet count - 10^9/L	219.5 ± 48.6
Creatinine clearance rate - ml/min	112.5 (95.2, 140.3)
Alpha-fetoprotein - ng/ml	3.0 (2.1, 9.4)
APRI score	0.3 (0.2, 0.4)
FIB-4 score	0.8 (0.6, 1.2)
Fibroscan LSM - kPa	5.4 (4.3, 6.6)
Receiving entecavir - No. (%)	104/109 (95.4)
Receiving adefovir dipivoxil - No. (%)	2/109 (1.8)
Receiving telbivudine - No. (%)	1/109 (0.9)
Receiving lamivudine - No. (%)	2/109 (1.8)

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Disclosures: Wen Xie: Nothing to Disclose, Lihua Cao: Nothing to Disclose, Shuangsuo Dang: Nothing to Disclose, Liying Zhu: Nothing to Disclose, Dongliang Yang: Nothing to Disclose, Yueyong Zhu: Nothing to Disclose, Xiaoguang Dou: Nothing to Disclose, Zhiliang Gao: Nothing to Disclose, Binbin Chen: Nothing to Disclose, Xinxin Zhang: Nothing to Disclose, Yuming Wang: Nothing to Disclose, Yan Liu: Nothing to Disclose, Ting Zhang: Nothing to Disclose, Tingdan Ye: Nothing to Disclose, Ke Mi: Nothing to Disclose, Calvin Pan: Nothing to Disclose

1253 | THE IMPACT OF SUPERIMPOSED METABOLIC-DYSFUNCTION ASSOCIATED STEATOTIC LIVER DISEASE (MASLD) ON CLINICAL AND PATIENT-REPORTED OUTCOMES (PROS) PROFILE OF PATIENTS WITH CHRONIC HEPATITIS B (CHB) AND C (CHC)

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Background: CHB, CHC and MASLD are common causes of liver disease. We aimed to assess clinical and PRO profiles of patients with CHB and CHC with and without superimposed MASLD using the Global Liver Registry™. **Methods:** Clinical and PRO (FACIT-F, CLDQ, WPAI) data were analyzed from CHB and CHC patients from GLR. Superimposed MASLD was defined as Hepatic Steatosis Index (HSI) ≥36 and presence of ≥1 cardio-metabolic risk factor (overweight, type 2 diabetes, hypertension, hyperlipidemia). **Results:** We included 4,649 subjects: 2,063 CHB (48±13 years, 57% male, 11% advanced fibrosis) and 2,586 CHC subjects (56±14 years, 47% male, 18% advanced fibrosis). Among CHB, 49% had superimposed MASLD. CHB patients with and without MASLD were similar in age, sex, and had similar rates of advanced fibrosis (defined as FIB-4 ≥2.67 or liver stiffness ≥12 kPa), biopsy-proven cirrhosis, and non-cardio-metabolic comorbidities (all p>0.05). Despite this, CHB patients with MASLD had significantly lower PRO scores in the domains of Physical Well-Being and Fatigue of FACIT-F, and all six domains of CLDQ (all p<0.01); the greatest impairment was observed in the Fatigue domain of CLDQ (-6% of the score range size). In multivariate analysis, the presence of superimposed MASLD in CHB was independently associated with lower scores in these domains after adjustment for confounders (p<0.05). Among CHC, 47% had superimposed MASLD. CHC patients with MASLD were younger and more commonly female (p<0.01). However, they had similar rates of advanced fibrosis, biopsy-proven cirrhosis, and non-cardio-metabolic comorbidities (all p>0.05). CHC patients with MASLD had lower PRO scores in Physical Well-Being domain of FACIT-F and all four domains of CLDQ-HCV (all p<0.01); the greatest impairment was observed in Systemic Symptoms and Worry domains of CLDQ-HCV (-6% of the score range size). In multivariate analysis, presence of superimposed MASLD in CHC was independently associated with lower scores in CLDQ-HCV domains after adjustment for confounders (p<0.05). In comparison to CHC+MASLD, CHB+MASLD were younger (48 vs. 54 years), more commonly male (58% vs. 39%) with lower rates of advanced fibrosis (10% vs. 18%) and select non-hepatic comorbidities, and had higher PRO scores in most domains (3/5 domains of FACIT-F, work productivity and activity impairment by WPAI) (p<0.05). **Conclusion:** Almost half of the patients with CHC or CHB had superimposed MASLD. The clinical profile between those with viral hepatitis with or without MASLD is similar but those with superimposed MASLD reported a significant impairment in their patient-reported outcomes.

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1254 | HIV COINFECTION DESTABILIZES INTRAHEPATIC IMMUNITY AT THE SINGLE-CELL LEVEL IN ZAMBIAN ADULTS STARTING TREATMENT FOR CHRONIC HBV INFECTION

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Background: HBV/HIV coinfection affects 3 million people globally. HIV-related immune dysfunction provides opportunities to better define mechanisms of HBV persistence in humans. We compared the intrahepatic immune milieu between adults with HBV/HIV and chronic HBV alone starting antivirals in Zambia. **Methods:** Zambian adults with chronic HBV, with/without HIV coinfection, and eligibility to start antiviral therapy underwent liver fine needle aspirations (FNAs), which were loaded fresh onto a transportable microwell array (HIVE single-cell solution). Following cDNA library preparation and sequencing, high-quality single-cell gene expression was compared by HBV clinical parameters, HIV status, and HIV infection severity based on CD4 count. **Results:** Among 42 participants, including 26 with HBV/HIV, median age was 35 years, 31 (73.8%) were men, and median HBV DNA was 44,550 IU/mL. In HBV/HIV, median CD4 count was 112 cells/mm^3 (range: 19-641) and median HIV RNA was 250,445 copies/mL. Transcriptomic analysis revealed that HBV/HIV was associated with decreased frequencies of CD4+ T cells, mucosal-associated invariant T cells, and immunoregulatory CD56bright natural killer (NK) cells, and increased frequencies of CD8+ T cells, cytotoxic CD56dim NK cells, and macrophages compared to HBV alone. Interferon-gamma, a key player in antiviral adaptive immunity, was increased in HBV/HIV in CD56dim NK and CD8+ T cells but was not associated with control of HBV replication in either infection group. In these cells, we extracted genes and KEGG pathways that correlated strongly with viral loads and CD4 counts. In HBV/HIV, genes/pathways involved in T/NK effector functions were linked with low HBV DNA and HIV RNA, suggesting some viral control, but this faded with reduced CD4. Interferon stimulated genes (ISGs), another pillar of antiviral defense, were increased in HBV/HIV compared to HBV alone and surprisingly displayed an opposite pattern: In HBV/HIV, high ISGs were associated with higher HBV DNA and lower CD4. **Conclusion:** At a single-cell level, marked pre/early-treatment differences in the intrahepatic milieu between adults with HBV/HIV and HBV alone were observed. Higher ISG tone in HBV/HIV correlated with impaired functional mechanisms of HBV control. HIV-associated disrupted effector mechanisms in T and NK cells, possibly driven by an increased ISG milieu and consequent immune activation, may reveal unique mechanisms by which HIV promotes HBV persistence in the liver.

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1255 | HIV COINFECTION ACCELERATES HBV-INDUCED LIVER FIBROGENESIS THROUGH AN EXOSOME AND MIR-103A-3P DEPENDENT PATHWAY

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Background: Approximately 4 million people worldwide are co-infected with chronic HBV (CHB) and HIV due to shared transmission routes. The progression of CHB to cirrhosis and HCC is accelerated by HIV coinfection compared to HBV mono-infection. The mechanisms underlying this accelerated natural history are not well characterized. Exosomes are cell-derived extracellular vesicles present in cell culture supernatants and patient serum and have been shown to transfer functional molecules including miRNA, pre-mRNA, lncRNAs, and proteins between cells as a means of cell-to-cell communication. HIV infection has been reported to increase miR-103a-3p expression. We sought to investigate whether and the mechanism by which miR-103a-3p regulates HBV-induced liver fibrogenesis in hepatocytes. **Methods:** Infectious HBV viral particles (HBVvp) were purified from the HBV supernatant (HBVsup) of HepAD38 cells. HIV NL4-3 strain viral particles (HIVvp) and exosomes were isolated from HIV-infected (HIVexo) or uninfected supernatants (U937exo) of cultured U937 macrophages. NTCP-HepG2 and LX-2 cells were directly incubated with HIVsup, HIVvp, HIVexo or U937exo in mono- or coculture models. Putative targets of miR-103a-3p were explored by searching the miRNet 2.0 database. Cells were also treated by either mimics or inhibitors of miRNA-103a-3p. **Results:** miR-103a-3p levels were significantly increased in HIV-infected U937 cells and HIVexo compared with uninfected controls. Incubation with the HIVexo or synthetic miR-103a-3p mimic further significantly increased the HBVsup-induced fibrotic gene expression in NTCP HepG2 and LX-2 cells. Among the 453 miR103-regulated genes predicted by bioinformatics analysis, the TGFβ1 pathway negative regulator SMAD7 and HIF-1α pathway negative regulator DNA-binding protein 2 (ID2) were significantly down-regulated by the synthetic miR-103a-3p mimic. Furthermore, the upregulation of fibrotic gene expression mediated by exposure to both HIV- and HBV-positive supernatants was abrogated by treatment with synthetic miR-103a-3p inhibitor this effect was reversed with siRNA mediated knockdown of SMAD7. **Conclusion:** HIV coinfection exacerbates HBV-induced liver fibrogenesis through miR-103a-3p induction, leading to inhibition of ID2 and SMAD7, which have previously been shown to upregulate HIF-1α to increase HBV-induced TGF-β1 and profibrogenic gene expression in hepatocytes and HSCs. These data suggest that miR-103a-3p as a novel target for antifibrotic therapeutic development in HBV/HIV coinfection.

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1256 | EFFICACY AND SAFETY OF TENOFOVIR AMIBUFENAMIDE IN CHRONIC HEPATITIS B VIRUS INFECTION PATIENTS WITH NORMAL ALANINE AMINOTRANSFERASE: A MULTICENTER, OPEN-LABEL, RANDOMIZED CONTROLLED TRIAL

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Background: Antiviral therapy may be beneficial for chronic hepatitis B (CHB) patients (pts) with normal ALT. Tenofovir amibufenamide (TMF) is a novel nucleotide analog reverse transcriptase inhibitor recommended as a first-line treatment for CHB in mainland China. The PROMOTE study aims to evaluate the efficacy and safety of TMF in CHB pts with normal ALT. **Methods:** The PROMOTE study (Registration No. NCT05797714) is a multicenter, open-label, randomized controlled trial that enrolled pts with untreated chronic HBV infection, who had normal ALT levels and serum HBV DNA > 20 IU/mL. Pts were randomly assigned 1:1 to group A (oral TMF

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25 mg once daily for 48 weeks) or group B (no antiviral treatment). The primary endpoint was the proportion of pts with serum HBV DNA < 20 IU/mL at week 48. **Results:** A total of 211 pts were randomized and 193 were included in the full analysis set (FAS), with 93 in group A and 100 in group B. Seven pts in group B had crossover to TMF due to elevated ALT. Baseline characteristics were generally balanced between groups. At week 48, in the FAS, the proportion of pts with HBV DNA < 20 IU/mL in group A was 74.2%, compared to 9.0% in group B. The proportion difference was 65.2% (95% CI: 54.7-75.7%, P<0.001). In the per-protocol set (PPS), the proportion difference was 68.3% (95% CI: 58.0-78.7%, P<0.001), further supporting the better efficacy of group A. In the FAS, the median reduction in HBV DNA at week 48 was 2.63 log10 IU/mL in group A and 0.22 log10 IU/ml in group B, with a significant difference (P<0.001). A greater reduction in HBsAg in group A was observed as compared to group B (0.07 vs. 0.04 log10 IU/mL, P=0.02) at week 48. The findings of these secondary efficacy endpoints in the PPS consistently suggested better efficacy in group A. No significant differences were observed in the changes of serum creatinine (1.00 vs. 1.50 umol/L, P=0.856) and eGFR (-1.60 vs. -1.65 mL/min, P=0.461) from baseline between group A and group B. The change of blood lipid parameters from baseline also showed no statistical significance between two groups (P>0.05 for all). **Conclusion:** In conclusion, the PROMOTE study demonstrates the significant clinical benefit of TMF in CHB pts with normal ALT, showing substantial improvement in the proportion of pts with HBV DNA < 20 IU/mL, HBV DNA reduction, HBsAg reduction, with favorable renal and lipids safety. The follow-up of PROMOTE study is ongoing, and the report of long-term TMF treatment is forthcoming.

Table. Summary of treatment efficacy at week 48 analysis-Full Analysis Set

	Group A (TMF group)	Group B (blank control group)	P of difference
No. of pts	93	100	NA
Pts with HBV DNA < 20 IU/mL n (%) 95% CI	 69 (74.2%) 64.1% to 82.7%	 9 (9.0%) 4.2% to 16.4%	<0.001
Pts with HBV DNA < 10 IU/mL n (%)	68 (73.1%)	8 (8.0%)	<0.001
HBV DNA, log10 IU/mL Median Median change from baseline (95% CI)	 1.00 -2.63 (-4.71 to -1.88)	 3.41 -0.22 (-0.71 to 0.02)	 <0.001 <0.001
HBsAg, log10 IU/mL Median Median change from baseline (95% CI)	 3.34 -0.07 (-0.16 to -0.01)	 3.23 -0.04 (-0.09 to 0.01)	 0.672 0.020
FIB4 Median Median change from baseline (%)	 0.99 -0.13 (-11.09, 10.97)	 0.90 0.36 (-10.09, 16.18)	 0.126 0.745
HBeAg and HBeAb assessments: No. of pts with positive HBeAg at baseline, n HBeAg seroclearance at week 48, n (%) HBeAg seroconversion at week 48, n (%)	 23 0 (0) 0 (0)	 25 1 (4.0%) 1 (4.0%)	 >0.999 >0.999

Abbreviations: FAS, full analysis set; TMF, tenofovir amibufenamide; pts, patients; NA, not applicable; FIB4, fibrosis-4 score.

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1257 | ANTI-PD-1 ANTIBODY COMBINED WITH ETV AND PEG-IFN-α SAFELY ENHANCES ANTI-HBV EFFICACY AND T CELL RESPONSE IN AAV-HBV MICE

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Background: This study aimed to explore the safety, efficacy and mechanism of therapeutic strategies based on anti-PD-1 antibody (αPD-1), entecavir (ETV) and pegylated interferon-alpha (Peg-IFN-α) in an adeno-associated virus (AAV)-hepatitis B virus (HBV) mouse model. **Methods:** Various biochemical/virological/immune

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indicators were compared between model control (MC), ETV, ETV+αPD-1, ETV+Peg-IFN-α, triple-drug sequential combination (ETV+αPD-1/Peg-IFN-α [EA/P] and ETV+Peg-IFN-α/αPD-1) and triple-drug initial combination (ETV+αPD-1+Peg-IFN-α [EAP]) groups. **Results:** No death, joint swelling/deformation and bloody stools were observed. All groups had stable weight, alanine aminotransferase and aspartate transaminase levels. Liver necroinflammatory activity, liver and spleen weights and serum creatinine, glucose and cardiac troponin I levels were similar between groups (P>0.05). After 4-week treatment, plasma HBsAg decreased more in triple-drug combination groups, with a significant difference between EA/P and MC groups (mean HBsAg levels: 3.99 log10 vs. 4.36 log10, P=0.023), with no significant difference between initial combination and sequential combination groups. Plasma HBV DNA and HBeAg, and hepatocyte HBcAg positivity rates significantly decreased, with no statistically significant difference between groups. Myeloid, NK, B and T cell responses were detected. Notably, after 4-week treatment, frequencies of HBV surface-specific IL-4+/IL-21+/IFN-γ+/TNF-α+ CD8+T cells increased significantly in liver and blood in EA/P group (P<0.05); Frequencies of PD-1+CD8+ T cells in liver and CD8+ effector memory T (TEM) cells in spleen increased significantly in EA/P group, and the former positively correlated with frequencies of CD38+CD8+ T cells (P<0.05); Frequencies of circulating T follicular helper 1 (cTfh1) cells increased more in EA/P and EAP groups. Furthermore, HBsAg decrease value correlated with frequencies of above surface-specific IL-21+CD8+, PD-1+CD8+, CD8+ TEM and cTfh1 cells (P<0.05). RNA-seq data analysis of liver non-parenchymal cells showed that, compared with MC group, negative regulation of T cell proliferation/activation pathways were downregulated in EA/P group, and some genes (Arg1, Arg2, Cebpb, etc.) in these pathways had been shown to negatively regulate T cell proliferation/activation. **Conclusion:** EA/P sequential combination therapy reduces HBsAg levels safely and more effectively, whose efficacy may be related to enhanced T cell response.

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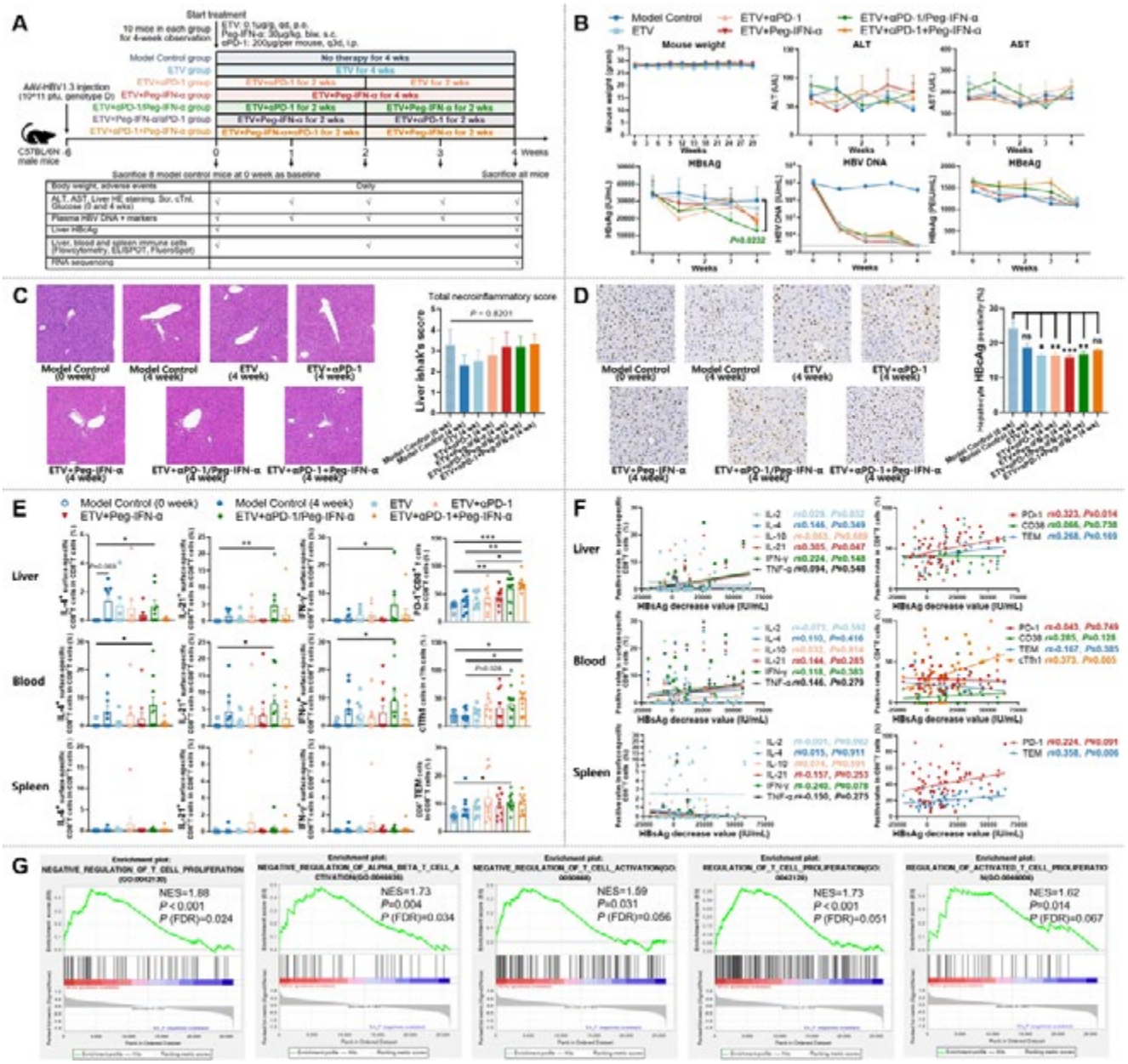

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1258 | METABOLIC DYSFUNCTION-ASSOCIATED FATTY LIVER DISEASE IMPROVES RESPONSE TO PEGINTERFERON ALPHA-2B THERAPY IN PATIENTS WITH CHRONIC HEPATITIS B

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Background: More than 30% of patients with chronic hepatitis B (CHB) have metabolic dysfunction-associated fatty liver disease (MAFLD), and the antiviral efficacy of this population needs further exploration. **Methods:** Patients aged 18-60 years with CHB were included in this study and were categorized into CHB group or CHB+MASLD group based on the presence of MASLD. All patients were treated with nucleos(t)ide analogues

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sequential or combined with peginterferon alpha-2b (PegIFNα-2b) for 48 weeks, and patients in the CHB+MASLD group were concurrently treated with anti-MASLD therapy. **Results:** A total of 90 patients were enrolled so far (CHB group, n=48; CHB+MASLD group, n=42). The average age was 44.8 ± 8.7 years, 66.7% were male, and the mean baseline HBsAg and pgRNA levels were 2.64 ± 0.93 $\log_{10}$ IU/mL and 2.18 ± 1.40 $\log_{10}$ copies/mL. The CHB+MASLD group had higher baseline alanine transaminase (ALT) and gamma glutamyl transpeptidase (GGT) levels than the CHB group. 49, 39, and 26 patients completed 12, 24, and 48 weeks of treatment, respectively, with complete data available. By week 48, 26.9% (7/26) of patients achieved HBsAg loss and 57.7% (15/26) achieved pgRNA undetectable. HBsAg and pgRNA levels in both groups decreased gradually with prolonged treatment, and the proportion of patients in the CHB+MASLD group with declines ≥ 0.5 log at week 12 (HBsAg: 68% vs. 37.5%; pgRNA: 72% vs. 41.7%), ≥ 1 log at week 24 (HBsAg: 65% vs. 31.6%; pgRNA: 65% vs. 26.3%) and ≥ 2 log at week 48 (HBsAg: 75% vs. 30%; pgRNA: 68.8% vs. 20%) were significantly higher than in the CHB group (all *P* values < 0.05, Figure 1). At week 12, 24 and 48, 44%, 60% and 81.2% of patients in the CHB+MASLD group achieved liver fibrosis reduction ≥1 stage, compared with 16.7%, 26.3%, and 40% in the CHB group (all *P* values < 0.05). Correlation analysis showed that controlled attenuation parameter (CAP) value was negatively correlated with serum pgRNA and HBsAg (*P* < 0.05); and uric acid (UA) was negatively correlated with serum pgRNA (*P* < 0.05). Bioinformatics analysis showed that EGR1, FOS, JUN, ATF3, EGR2, BTG2, ZFP36, CCN1, KLF4 and RHOB were the key genes related to CHB and MASLD. **Conclusion:** Compared with non-MASLD population, CHB patients with MASLD had more significant decreases in HBsAg, pgRNA and improvement in liver fibrosis after PegIFNα-2b therapy. MASLD may inhibit HBV replication by promoting the expression of AP-1, EGR1 and ATF3, to induce immune activation and inhibit mitophagy.

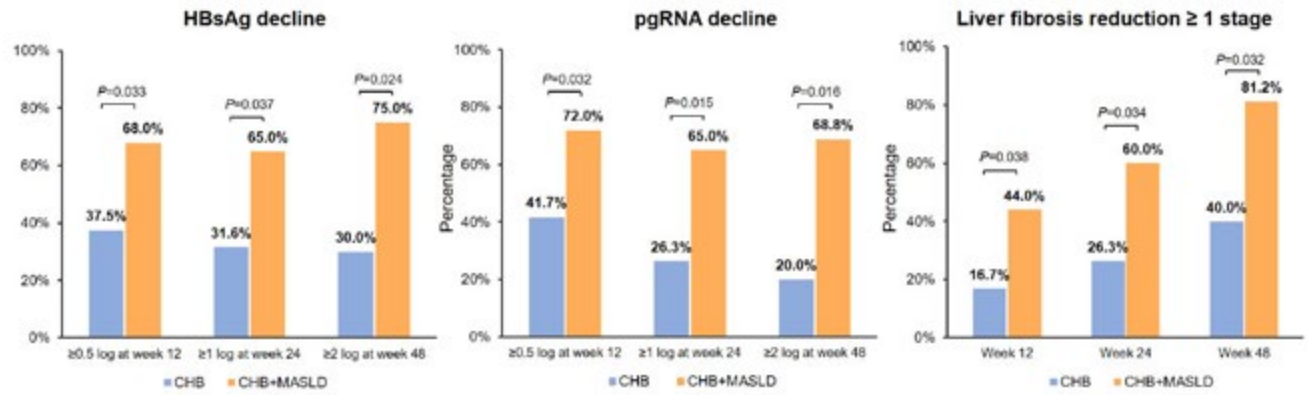

Figure 1. Proportion of patients achieving different HBsAg and pgRNA declines and liver fibrosis reduction ≥ 1 stage in the CHB and CHB+MASLD groups.

Disclosures: Ying Zhu: Nothing to Disclose, Sitong Yi: Nothing to Disclose, Guanghui Ren: Nothing to Disclose, Shi Yin: Nothing to Disclose

1259 | EFFECTIVENESS OF ADOPTIVE CELL TRANSFER OF ANTIGEN-SPECIFIC T CELLS IN MOUSE MODELS OF HBV INFECTION

Toshikatsu Tamai[1] *Eishiro Mizukoshi*[1] *Hikari Okada*[1] *Shihui Li*[1] *Taro Yamashita*[1] *Makoto Kurachi*[1]

[1]*Kanazawa University*

Background: Hepatitis B virus (HBV) is converted to covalently closed circular DNA (cccDNA) after infection of hepatocytes and persists for a long period of time. It is difficult to eliminate cccDNA completely with existing therapies. In the present study, we examined the efficacy of adoptive cell transfer using hepatitis B model mice. **Methods:** First, a mouse model of persistent HBV replication was created by infecting wild-type mice with adeno-associated virus (AAV)8-HBV viral vectors. Splenic CD8-T cells from transgenic mice with T cell receptor (TCR) of CD8-T cells recognizing epitopes 93-100 of HBV nucleocapsid protein (core93) were then adoptively transferred into AAV8-HBV infected mice as donor cells. Peripheral blood was obtained over time and lymphocytes from the liver, spleen, and hepatic lymph nodes at 7, 28, and 80 days after adoptive transfer. Serum ALT and HBV-related proteins/genes of the acquired samples and phenotypes of the transferred core93 cells were analyzed. Immunohistochemistry of liver tissue was performed using antibodies for HBs and HBc antigens. Mice infected

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with AAV8-Empty viral vector were used as a control group. **Results:** First, we observed elevated blood HBs antigen (Ag) and intrahepatic cccDNA in AAV8-HBV infected mice. Adoptive transfer of naive core93 cells into AAV8-HBV infected mice caused hepatitis, and peak serum ALT was observed 7 days after transfer. Blood HBV-DNA was below detection sensitivity after 7 days of adoptive transfer, and blood HBsAg and intrahepatic cccDNA were almost eliminated after 28 days. Immunohistochemistry of liver tissue showed that HBs and HBc-antigen positive cells decreased over time in mice transferred with core93 cells. Analysis of the transferred core93 cells revealed an increased percentage of CD44-positive effector cells in the peripheral blood, spleen, liver, and hepatic lymph nodes. Especially in the liver, the percentage of CD62L-negative CD44-positive cells was higher than in other organs. PD-1, LAG-3, TIM-3, and TIGIT expression in core93 cells was elevated 28 days after adoptive transfer. **Conclusion:** In a mouse model of persistent HBV replication, adoptive transfer of HBV-specific T cells almost eliminated hepatic cccDNA and other HBV-related proteins and genes. Adoptive cell therapy has been shown to be a potential option for the treatment of HBV.

Disclosures: Toshikatsu Tamai: Nothing to Disclose, Eishiro Mizukoshi: Nothing to Disclose, Hikari Okada: Nothing to Disclose, Shihui Li: Nothing to Disclose, Taro Yamashita: Nothing to Disclose, Makoto Kurachi: Nothing to Disclose

1260 | RISK OF ADVANCED LIVER DISEASE AMONG INDIVIDUALS WITH HEPATITIS B VIRUS INFECTION WITH LOW LEVEL VIREMIA COMPARED TO INDIVIDUALS WITH NO EVIDENCE OF HEPATITIS B VIRUS INFECTION

Su Wang[1] Laura Telep[2] Leland Yee[2] Betty Chiang[2] Sarjita Naik[2] Catherine Frenette[2] Amanda Singer[2] Anand Chokkalingam[2] Ching-Yi Chuo[2] Camilla Graham[3] Paul Kwo[4]

[1]Saint Barnabas Medical Center, [2]Gilead Sciences, [3]Beth Israel Deaconess Medical Center, [4]Stanford University Medical Center

Background: Current hepatitis B virus (HBV) treatment guidelines do not recommend antiviral therapy for individuals with low level viremia (LLV; defined as HBV DNA ≤ 2,000 IU/mL) unless cirrhosis has been diagnosed; however, the association between LLV and advanced liver disease (ALD) is unclear. In this study we examine United States (US) electronic medical record (EMR) data to describe the characteristics of individuals with LLV compared to those with no evidence of HBV, and to evaluate the risk of cirrhosis and of ALD – defined as a composite outcome of cirrhosis, decompensation, hepatocellular carcinoma (HCC), and liver transplant – in these two groups. **Methods:** Using HealthVerity EMR and administrative claims data from October 2015 – December 2023, we identified the first HBV DNA laboratory result ≤ 2,000 IU/mL in adults (18+ years at index) and a cohort of individuals with no evidence of HBV. Chronic HBV infection was defined as at least two lab **Results:** (HBsAg or HBV DNA) at least six months apart. Those with < 365 days of continuous insurance enrollment prior to index, nucleot(s)ide analogue (NA) treatment in the six months prior to index, or baseline evidence of any ALD, hepatitis C or D, or HIV were excluded. Absolute rates per 100 person-years (PY) and corresponding exact Poisson 95% confidence intervals (CIs) were calculated for each cohort, and Cox proportional hazards methods were used to estimate the risk of cirrhosis or of any ALD among those with LLV vs. no evidence of HBV after adjusting for demographic factors and baseline health conditions. **Results:** We identified 1,897 individuals with HBV with LLV, and 240,657 individuals with no evidence of HBV. Those with LLV were older, more likely to be Asian, and had significantly higher rates of diabetes, hypertension, anemia, MASH, and ALD (see Table). After restricting the cohort to chronically infected individuals and excluding those with any evidence of ALD at baseline (n=758), the absolute rate of incident cirrhosis in those with LLV was markedly higher than in those without evidence of HBV: 0.88 (95% CI: 0.54 – 1.35) vs 0.15 (0.14 – 0.16) per 100 PY. After adjustment for age, sex, race, and baseline health conditions, HBV infection with LLV was associated with a significant increased risk of cirrhosis compared to no evidence of HBV (HR: 8.39, 95% CI: 5.28 – 13.34). An increased risk of the composite outcome was also observed (HR: 2.68, 1.82 -3.93). The risk of cirrhosis and of any ALD remained elevated in a subgroup analysis including only individuals with no evidence of NA treatment or recorded HBV DNA > 2,000 during the follow up period (71.5% of the original cohort; cirrhosis HR: 6.72 (3.86 – 11.71); ALD HR: 2.10 (1.31 – 3.38)). **Conclusion:** In this analysis of US EMR and claims data, individuals with HBV DNA ≤ 2,000 had a significant increased risk of ALD relative to those with no evidence of HBV. Antiviral therapy may be a mechanism for mitigating the ALD risk associated with LLV.

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Table 1. Baseline characteristics, follow up time, and hazard ratios characterizing the risk of cirrhosis and advanced liver disease, stratified by HBV infection status

	Low Level HBV Cohort (n = 1,897)	Control Cohort (no HBV) (n = 240,657)
Category	**n (%)**	**n (%)**
Demographic information		
Age: Mean (SD)	49.5 (12.9)	43.8 (17.4)
Sex (Male)	885 (46.7)	106,355 (44.2)
Race		
Asian	829 (43.7)	9,584 (4.0)
Black	154 (18.1)	24,587 (10.2)
Hispanic	50 (2.6)	23,013 (9.6)
White	124 (6.5)	71,741 (29.8)
Other	153 (8.1)	11,256 (4.7)
Missing	587 (30.9)	100,485 (41.8)
Baseline liver status		
Cirrhosis	109 (5.7)	1,545 (0.6)
Decompensated cirrhosis (DC)	33 (1.7)	3,032 (1.3)
Hepatocellular carcinoma (HCC)	17 (0.9)	200 (0.1)
Liver transplant (LTx)	2 (0.1)	98 (0.0)
Baseline comorbidities		
Hepatitis C virus	133 (7.0)	3,103 (1.3)
Human immunodeficiency virus	49 (2.6)	1,498 (0.6)
Diabetes	286 (15.1)	26,670 (11.1)
Hypertension	550 (29.0)	54,581 (22.7)
Hyperlipidemia	647 (34.1)	47,125 (19.6)
Chronic renal insufficiency	67 (3.5)	8,056 (3.3)
MASH/MASLD	224 (11.8)	6,098 (2.5)
Additional baseline risk factors		
Smoking	148 (7.8)	30,340 (12.6)
Alcohol use	31(1.6)	5,435 (2.3)
Substance abuse	132 (7.0)	28,650 (11.9)
Overweight/Obese	202 (10.6)	31,898 (13.3)
Follow-up, days of person time		
Median (Q1, Q3)	721 (340, 1,270)	568 (250, 1,050)
Mean (SD)	868 (642)	722 (589)
Adjusted HR (95% CI) during follow up period		
Cirrhosis	1.00 (ref)	8.39 (5.28 – 13.34)
ALD (cirrhosis, DC, HCC, LTx)	1.00 (ref)	2.68 (1.82 – 3.93)
Sensitivity analysis: Adjust HR with no NA treatment or HBV DNA > 2,000 during follow up		
Cirrhosis	1.00 (ref)	6.72 (3.86 – 11.71)
ALD (cirrhosis, DC, HCC, LTx)	1.00 (ref)	2.10 (1.31 – 3.38)

* Comorbidities and additional baseline risk factors are defined using ICD-10-CM codes found in HealthVerity administrative claims data.

ALD: advanced liver disease; DC: decompensated cirrhosis; HBV: hepatitis B virus; HCC: hepatocellular carcinoma; HR: hazard ratio; TX: liver transplant; MASH: metabolic dysfunction-associated steatohepatitis; MASLD: metabolic dysfunction-associated steatotic liver disease; NA: nucleot(s)ide analogue; SD: standard deviation

Disclosures: Su Wang: Gilead Sciences: Grant/Research Support, Laura Telep: Gilead Sciences, LLC: Employee, Gilead Sciences, LLC: Stock - publicly traded company, Leland Yee: Gilead Sciences: Employee, Betty Chiang: Nothing to Disclose, Sarjita Naik: Gilead Sciences: Employee, Gilead Sciences: Stock – privately held company, Catherine Frenette: Gilead Sciences, Inc.: Employee, Gilead Sciences, Inc.: Stock - publicly traded company, Amanda Singer: Gilead Sciences: Employee, Gilead Sciences: Stock - publicly traded company, Anand Chokkalingam: Nothing to Disclose, Ching-Yi Chuo: Nothing to Disclose, Camilla Graham: Nothing to Disclose, Paul Kwo: Nothing to Disclose

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1261 | EFFECTS OF DIFFERENT ANTIVIRAL TREATMENTS ON LIVER INFLAMMATION AND FIBROSIS IN PATIENTS WITH CHRONIC HEPATITIS B

Huiqing Liang[1] Xiaoting Zheng[1] Yaoyi Liu[1] Qianguo Mao[1] Chuncheng Wu[1] Yue Chen[1] Manying Zhang[1] Shaodong Chen[2]

[1]Hepatology Unit, Xiamen Hospital of Traditional Chinese Medicine, Xiamen, China, [2]School of Medicine, Xiamen University, Xiamen, China

Background: Oral nucleotide analogues (NAs) and peginterferon-α injection are commonly used for treatment of patients with chronic hepatitis B (CHB). This study aims to evaluate the effects of different antiviral therapies on the degree of liver inflammation and fibrosis in CHB patients. **Methods:** This was a retrospective cohort study. A total of 101 CHB patients were admitted to the Liver Center of Xiamen Hospital of Traditional Chinese Medicine from 2017 to 2021, and were divided into three groups for different antiviral treatments: NAs therapy group (n = 36), peginterferon-α therapy group (n = 38) and non-antiviral therapy group (n = 27). The differences in degrees of liver inflammation and liver fibrosis between two histopathologic biopsies before and after treatment were analyzed and compared to evaluate the efficacy of different treatments. **Results:** The degrees of liver inflammation and liver fibrosis were improved after NAs or peginterferon-α therapy (Figure 1). In terms of improving the degree of liver inflammation, peginterferon-α therapy (74%) and NAs therapy (44%) were better than non-antiviral therapy (11%, $P < 0.05$), although no significant difference was showed between peginterferon-α therapy and NAs therapy ($P = 0.974$). For liver fibrosis improvement, peginterferon-α therapy showed significantly better efficacy than NAs therapy (68% vs. 33%, $P = 0.044$), while NAs therapy was better than non-antiviral therapy (33% vs. 11%, $P = 0.028$). Further correlation factor analysis showed that both NAs therapy (OR = 8.861, 95% CI: 1.974-39.766, $P = 0.004$) and peginterferon-α therapy (OR = 7.088, 95% CI: 1.588-31.633, $P = 0.010$) had a significant impact on liver inflammation; and NAs therapy (OR = 8.770, 95% CI: 1.831-41.996, $P = 0.007$) and peginterferon-α therapy (OR = 43.268, 95% CI: 8.489-220.54, $P < 0.001$) were also significant factors associated with the improvement of liver fibrosis. **Conclusion:** Peginterferon-α and NAs can significantly improve the degrees of liver inflammation and liver fibrosis in CHB patients. Peginterferon-α is superior to NAs in delaying and reversing liver fibrosis. This study provides a new basis for peginterferon-α therapy to prevent progression of fibrosis in CHB patients.

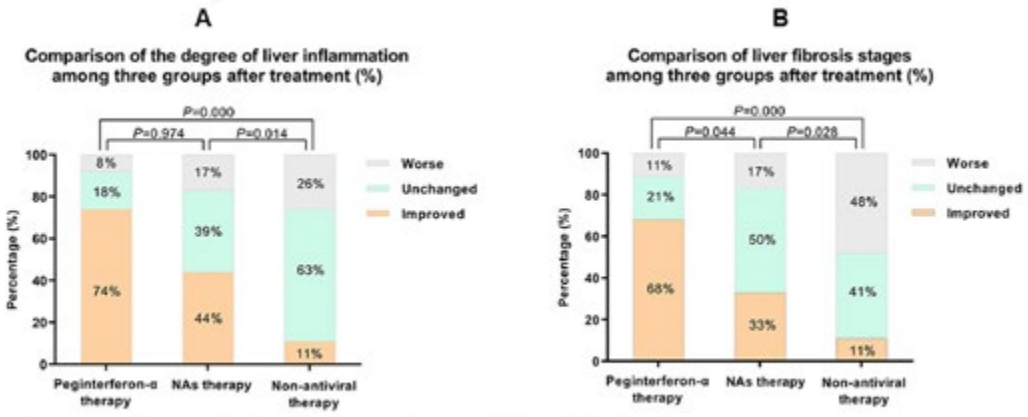

Figure 1. Changes in liver inflammation and fibrosis in the three groups.

Disclosures: Huiqing Liang: Nothing to Disclose, Xiaoting Zheng: Nothing to Disclose, Yaoyi Liu: Nothing to Disclose, Qianguo Mao: Nothing to Disclose, Chuncheng Wu: Nothing to Disclose, Yue Chen: Nothing to Disclose, Manying Zhang: Nothing to Disclose, Shaodong Chen: Nothing to Disclose

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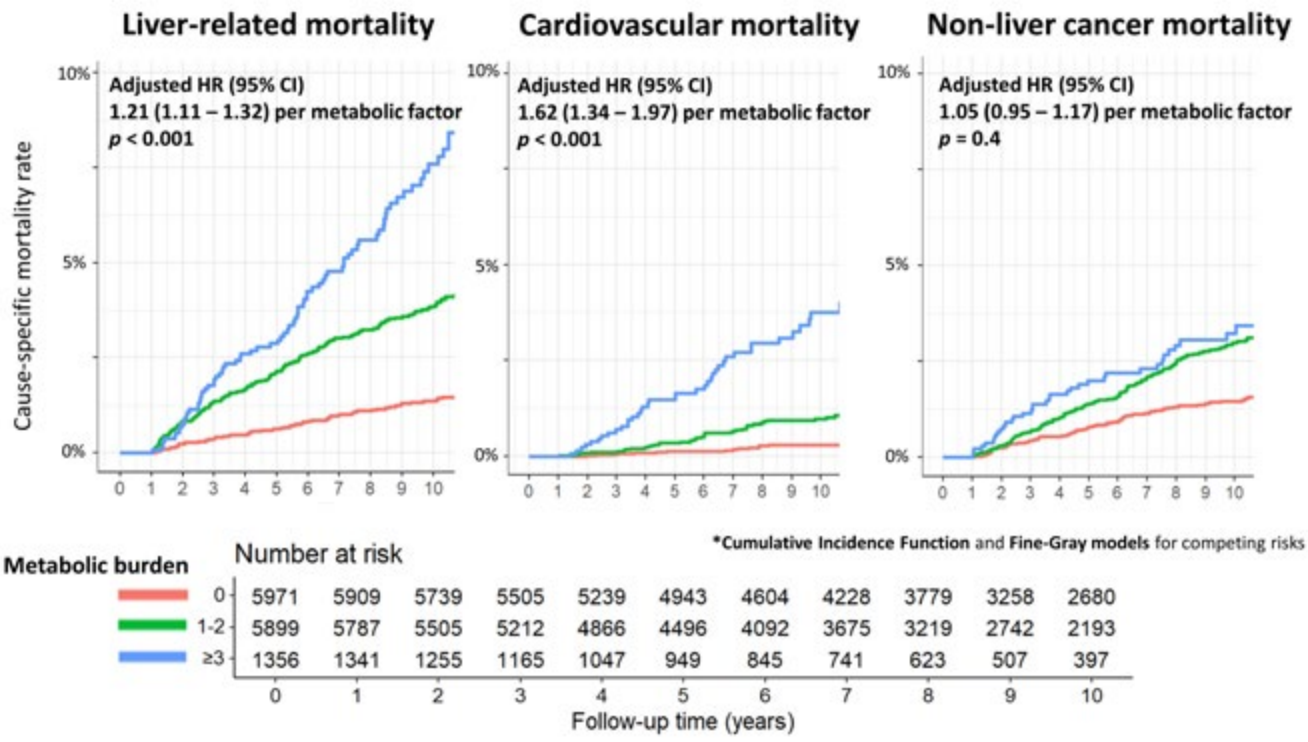
1262 | ALL-CAUSE AND CAUSE-SPECIFIC MORTALITY IN NON-STEATOTIC CHRONIC HEPATITIS B PATIENTS WITH CARDIOMETABOLIC RISK FACTORS

Shang-Chin Huang[1] Tung-Hung Su[1] Tai-Chung Tseng[1] Shih-Jer Hsu[1] Chun-Ming Hong[2] Chen-Hua Liu[1] Hung-Chih Yang[1] Chun Jen Liu[1] Pei-Jer Chen[1] Jia-Horng Kao[1]

[1]National Taiwan University Hospital, [2]National Taiwan University

Background: Cardiometabolic risk factors (CMRF) have been reported to increase the risks of adverse liver outcomes in chronic hepatitis B (CHB) patients with metabolic dysfunction-associated steatotic liver disease (MASLD). However, the impacts of CMRF on long-term mortality risks of non-steatotic CHB patients are unknown. **Methods:** Non-steatotic CHB patients were consecutively enrolled in a tertiary center with longitudinal follow-up. The CMRF was defined according to the MASLD criteria, including hyperglycemia, hypertension, high BMI, and dyslipidemia. The metabolic burden was calculated by the number of fulfilled CMRF. Cumulative incidences of all-cause and cause-specific mortality were compared after adjustment for competing risks. **Results:** From 2006 to 2021, 13226 non-steatotic CHB patients were included. At baseline, CHB patients with CMRF (n = 7,255) were older and had a lower proportion of HBeAg positivity and lower HBV DNA levels than non-CMRF patients (n = 5,971). After a median follow-up time of 8.9 years, patients with CMRF had a higher risk of all-cause mortality than those without CMRF after adjustment for age, sex, cirrhosis, HBeAg, ALT levels, and anti-viral therapy (adjusted hazard ratio [aHR]: 1.75, 95% confidence interval [CI]: 1.48–2.06, p < 0.001). Furthermore, cumulative CMRF increased the risks of all-cause, liver-related, and cardiovascular mortality in a dose-dependent manner (all p < 0.001). During the study period, incident diabetes mellitus (aHR: 2.31, 95% CI: 1.91–2.79) and incident hypertension (aHR: 1.79, 95% CI: 1.49–2.16) further aggravates the risks of all-cause and liver-related mortality (all p < 0.001). **Conclusion:** Cumulative metabolic burden increases the risks of all-cause, liver-related, and cardiovascular mortality in non-steatotic CHB patients, and new-onset CMRF further aggravates the risks. Routine monitoring and aggressively identifying CMRF in CHB patients, even for those without concurrent MASLD, is required for risk stratification and early intervention.



Disclosures: Shang-Chin Huang: Nothing to Disclose, Tung-Hung Su: Nothing to Disclose, Tai-Chung Tseng: Nothing to Disclose, Shih-Jer Hsu: Nothing to Disclose, Chun-Ming Hong: Nothing to Disclose, Chen-Hua Liu: Nothing to Disclose, Hung-Chih Yang: Nothing to Disclose, Chun Jen Liu: Nothing to Disclose, Pei-Jer Chen: Nothing to Disclose, Jia-Horng Kao: Nothing to Disclose

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1263 | "BENEG-DO": A STUDY OF CLINICAL OUTCOMES, IMMUNOLOGIC CORRELATES AND GENETIC PREDICTORS AFTER NUC TREATMENT WITHDRAWAL IN E-ANTIGEN NEGATIVE CHRONIC HEPATITIS B

Jiajing Li[1] Lia Avanesyan[2] Stewart Cooper[2] Jody Baron[3]

[1]Sutter Health - California Pacific Medical Center, [2]California Pacific Medical Center, [3]University of California, San Francisco

Background: Seroclearance of HBV surface antigen (HBsAg), defines clinical cure but is a rare outcome with nucleos(t)ide analogue (NA) antiviral therapies. European studies suggest that discontinuation of NA after ≥192 weeks can safely induce high rates of HBsAg loss in non-cirrhotic patients with HBeAg-negative CHB. "BeNEG-DO" is a two-center NIH-sponsored prospective, case-control study in the San Francisco Bay Area, of safety and clinical outcomes, HBsAg seroclearance rates, immune responses, genetic predictors and virologic features in non-cirrhotic adult human subjects with HBeAg-negative CHB who either continue (controls) or stop (cases) NA therapy given for ≥192 weeks. **Methods:** HBsAg-positive patients, HBeAg-negative when NA started, were enrolled from UCSF and Sutter Health clinics. After liver biopsies in cases, and historical reviews, 76 cases stopped NA and 30 became controls. Baseline (BL) clinical labs were drawn ≤1 month before stopping NA. Per-protocol clinical and research follow-up is shown in Figure 1. Diagnostically surplus *biopsy tissue* was studied by flow cytometry and used for RNA isolation. Bulk RNA sequencing was performed on an Illumina NovaSeq 6000. For immune-targeted liver gene expression analysis, Nanostring™ nCounter Human Immunology V2 panel was used. FFPE tissue is used for spatial transcriptomic analyses (Imaging mass cytometry, NanoString® CosMx™ and 10X Genomics Xenium). Longitudinal *peripheral blood* samples collected into sterile EDTA vacutainer tubes are centrally processed and stored. Lab monitoring frequency exceeded protocol during ALT flares at the discretion of the managing hepatologist. In-person, video or telephonic visits followed each set of clinical labs. Serum HBsAg was quantified by ARCHITECT/Alinity *i* HBsAg NEXT assay. Serum HBV RNA was measured with dual-target RT-qPCR High Sensitivity Qualitative HBV RNA Assay on the Abbott m2000sp/rt system. CITE-seq is performed using Chromium Single Cell 3' v3.1 Reagent Kits (10X Genomics) and TotalSeq™-A Panel (Biolegend). Cytometry by time of flight (CyTOF) and Spectral Flow are used to study peripheral immune cell phenotypes and function. Participant safety is assessed by symptom questionnaires, the number and severity of adverse events, the number of cases re-treated and by APRI scores and elastography. **Results:** We present the BeNEG-DO study framework, participant and virologic characteristics, and analytical methods. HBsAg loss in >20% cases to date, ensures that we are powered to conduct comparative analyses using the BL characteristics and methods proposed. **Conclusion:** In a CHB population that has a high global disease burden, the BeNEG-DO trial is evaluating safety and benefit of finite NA therapy, finding significant rates of HBsAg loss in cases, seeking viral and host factors predictive of outcome, and aims to identify targetable immune pathways leading to HBsAg seroclearance after unleashed HBV replication.

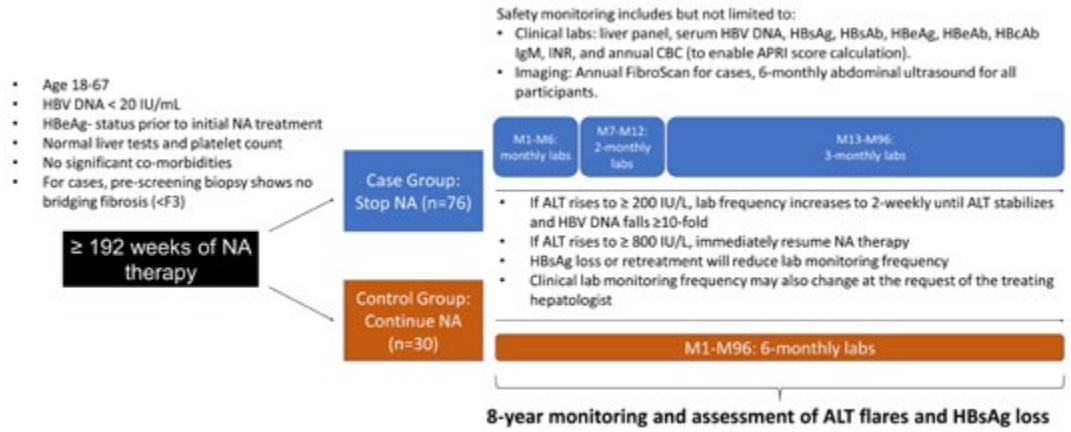

Figure 1. Study schematic

Disclosures: Jiajing Li: Nothing to Disclose, Lia Avanesyan: Nothing to Disclose, Stewart Cooper: Nothing to Disclose, Jody Baron: Nothing to Disclose

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1264 | EFFICACY AND SAFETY OF PD-L1 ANTIBODY ASC22 (ENVAFOLIMAB) IN PATIENTS WITH LOW BASELINE HBSAG LEVELS: A RANDOMIZED PHASE IIB EXPANSION COHORT

Jinzi Jason Wu[1] Guiqiang Wang[2] Guoxin Hu[3] Lei Fu[4] Jiajie Lu[5] Yong-ping Chen[6] Qing Xie[7] Yao Xie[8] Guizhou Zou[9] Xiaolin Guo[10] Jinlin Hou[11] Yongfeng Yang[12] Qianguo Mao[13] Yuemei Yan[1]

[1]Ascletis BioScience Co., Ltd., [2]Peking University First Hospital, [3]Peking university Shenzhen hospital, [4]Xiangya Hospital of Central South Univ., [5]West China Hospital of Sichuan Uni., [6]1st Affil. Hosp. of Wenzhou Med. Univ., [7]Ruijin Hospital, [8]Beijing Ditan Hospital, [9]2nd Affil. Hosp. of Anhui Med. Univ., [10]The first hospital of Jilin University, [11]Nanfang Hospital of Southern Med. Univ., [12]Nanjing Second Hospital, [13]Xiamen Hospital of Trad. Chinese Medi.

Background: A phase 2b study demonstrated the potential of subcutaneously injected PD-L1 antibody ASC22 to reduce HBsAg in patients with chronic hepatitis B (CHB), particularly notable in patients with low baseline (BL) HBsAg ≤100 IU/mL, 43% (3/7, per-protocol set) achieved functional cure. An expansion cohort has been devised to validate the efficacy and safety profile of ASC22 in the specific subpopulation of patients with low BL HBsAg levels. **Methods:** Eligible patients were HBeAg-negative, HBV-DNA suppressed patients with BL HBsAg ≤100 IU/mL, and were randomized at a ratio of 4:1 to receive either 1.0 mg/kg ASC22 Q2W + Nucleot(s)ide analogues (NAs) or placebo (PBO) Q2W+NAs for 24-week treatment. During 24-week follow-up, NAs will be discontinued for the patients who achieve HBsAg loss at the end of 24-week treatment and other patients will continue on NAs. The primary efficacy endpoint was the reduction of HBsAg levels and the proportion of patients with a reduction of HBsAg ≥0.5 $\log_{10}$ IU/mL at each scheduled visit. **Results:** Forty-nine patients were included in the study (Table 1). The mean (SD) reduction in HBsAg levels from BL and the patients achieving a reduction of HBsAg ≥0.5 $\log_{10}$ IU/mL at week 24 were -0.86 (0.76) $\log_{10}$ IU/mL and 19 (55.9%), respectively, in the ASC22 group. In contrast, the corresponding values in the PBO group were -0.10 (0.16) and 0. Specifically, six patients in the ASC22 group achieved HBsAg loss at week 24. The incidence of ALT flare in the ASC22 group was recorded at 12.5%, whereas no ALT flare were observed in the PBO group. Among ALT flare patients, there was a notable decrease of 1.5 $\log_{10}$ IU/mL in HBsAg levels. Among six patients withdrew from the study in ASC22 group, two patients withdrew voluntarily, one due to an adverse event (AE) unrelated to the study drug, and three due to study drug related AE. The main AEs are elevated ALT, AST, abnormal thyroid function, itching and rash, etc. **Conclusion:** ASC22 monotherapy with background NAs showed statistically significant HBsAg reduction and 6(17.6%) HBsAg loss after 24-week treatment. Together with the acceptable safety profile and convenient subcutaneous injections, ASC22 demonstrated potential as a promising immune-therapy for CHB with low BL HBsAg levels.

Table 1. Baseline characteristics and trial results

Characteristics	ASC22+NAs (n=40)	PBO+NAs (n=9)	Total (N=49)
Male, n(%)	33(82.5%)	6(66.7%)	39(79.6%)
Age, Median(range)	46.0(36.8,52.0)	47.0(38.0,53.0)	46.0(37.0,52.0)
BMI (kg/m^2), Mean(SD)	23.6(2.6)	24.5(1.9)	23.8(2.5)
ALT (U/L), Mean(SD)	22.6(10.6)	22.9(14.5)	22.7(11.3)
AST (U/L), Mean(SD)	23.7(7.2)	22.1(3.2)	23.4(6.7)
HBsAg(IU/L), Mean(SD)	28.9(28.3)	22.9(26.0)	27.8(27.7)
Results	**ASC22+NAs (n=34)**	**PBO+NAs (n=9)**	***p***
Mean(SD) HBsAg reduction, $\log_{10}$ IU/mL	-0.86(0.76)	-0.10(0.16)	0.0025
HBsAg reduction≥1 $\log_{10}$ IU/mL, n(%)	13(38.2%)	0	0.0391
HBsAg reduction≥0.5 $\log_{10}$ IU/mL, n(%)	19(55.9%)	0	0.0025
HBsAg loss, n(%)	6(17.6%)	0	0.3154

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Disclosures: Jinzi Jason Wu: Ascletis Pharma Inc.: an employee and stockholder of Ascletis Pharma Inc., Guiqiang Wang: Nothing to Disclose, Guoxin Hu: Nothing to Disclose, Lei Fu: Nothing to Disclose, Jiajie Lu: Nothing to Disclose, Yong-ping Chen: Nothing to Disclose, Qing Xie: Nothing to Disclose, Yao Xie: Nothing to Disclose, Guizhou Zou: Nothing to Disclose, Xiaolin Guo: Nothing to Disclose, Jinlin Hou: Nothing to Disclose, Yongfeng Yang: Nothing to Disclose, Qianguo Mao: Nothing to Disclose, Yuemei Yan: Ascletis BioScience Co., Ltd: an employee and stockholder of Ascletis BioScience Co., Ltd

1265 | EFFICACY OF PROPHYLACTIC ANTIVIRAL THERAPY IN PREVENTING HEPATITIS B REACTIVATION IN PATIENTS WITH ANTI-HBC ANTIBODY UNDERGOING DARATUMUMAB TREATMENT ◆

Jaejun Lee[1] *Pil Soo Sung*[1] *Ji Won Han*[1] *Soon Kyu Lee*[1]

[1]*Catholic university of Korea*

Background: Daratumumab, a monoclonal antibody targeting CD38, is currently used as a first-line therapy in patients with multiple myeloma. This study aims to investigate the risk of HBR in patients with the anti-HBc antibody and to evaluate the efficacy of prophylactic antiviral therapy in this population. **Methods:** Data from 345 multiple myeloma patients treated with daratumumab between 2014 and 2024 were retrospectively collected. Patients with the anti-HBc antibody were included in the study, while those with positive HBsAg prior to daratumumab treatment were excluded. HBR was defined as HBsAg seroconversion or detection of HBV DNA until subsequent chemotherapy or 12 months after cessation of daratumumab if no subsequent chemotherapy was performed. **Results:** Among the 345 patients, 109 had the anti-HBc antibody and were included in the analysis. The mean age was 64.6 years, and males were predominant (56.0%). The median duration of daratumumab treatment was 101 days, during which ten patients received prophylactic antiviral therapy (9 with entecavir and 1 with tenofovir alafenamide). Overall, 9 patients (8.3%) experienced HBR, with 3 suffering from severe hepatitis (ALT exceeding 200U/L) due to HBR, resulting in one mortality. No patient who received prophylactic antiviral therapy experienced HBR. The cumulative incidence rates of HBR in the non-antiviral treatment group were 8.0% at 12 months and 12.3% at 24 months after the start of daratumumab, while the antiviral treatment group had a cumulative incidence of 0.0%. When restricted mean survival time (RMST) was employed to compare the area under the Kaplan-Meier curve of HBR-free survival in both groups, the antiviral treatment group was significantly higher than the non-antiviral treatment group (Difference in RMST = 2.00, p = 0.002; Ratio of RMST = 1.09, p = 0.002). HBsAb titers less than 100 IU/L (odds ratio 7.527, p = 0.057) and anti-HBc antibody titer (odds ratio 1.234, p = 0.156) showed a tendency towards an increased incidence of HBR. **Conclusion:** There is a considerable risk of HBR in multiple myeloma patients with the anti-HBc antibody undergoing daratumumab treatment. The use of antiviral therapy for a sufficient duration may prevent HBR in these at-risk patients.

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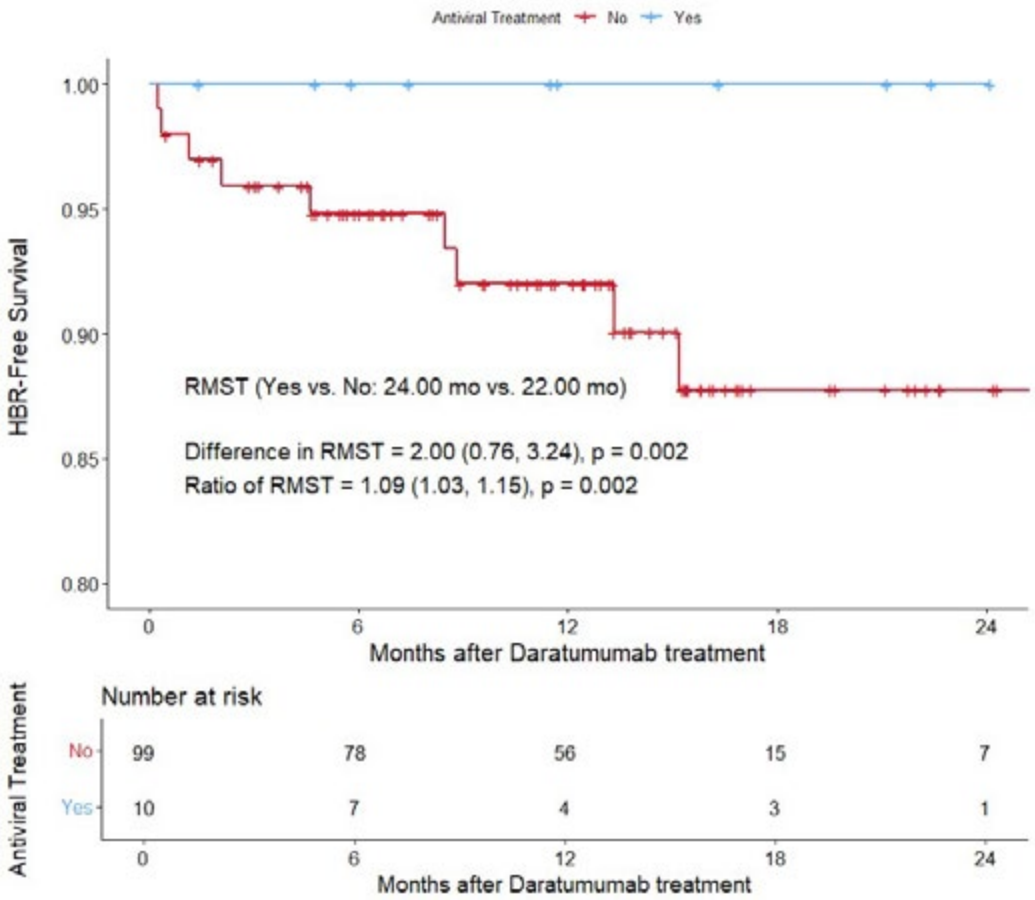

Disclosures: Jaejun Lee: Nothing to Disclose, Pil Soo Sung: Nothing to Disclose, Ji Won Han: Nothing to Disclose, Soon Kyu Lee: Nothing to Disclose

1266 | CAPSID ASSEMBLY MODULATORS SUCH AS ALG-001075 INDUCE PROFOUND HBV DNA KNOCKDOWN AND DIRECTLY TARGET HBEAG IN VITRO

Cheng Liu[1] Jordi Verheyen[2] Dieudonné Buh Kum[1] Hannah Vanrusselt[2] Tse-I Lin[2] Julian Symons[3] Lawrence Blatt[1] Andreas Jekle[1] Yannick Debing[2]

[1]Aligos Therapeutics, Inc., [2]Aligos Belgium BV, [3]Aligos Therapeutics

Background: The hepatitis B virus (HBV) capsid assembly process has emerged as a key target for the treatment of chronic hepatitis B (CHB). ALG-000184 is a prodrug of ALG-001075, a novel capsid assembly modulator leading to the formation of empty capsids (CAM-E). ALG-000184 has demonstrated best-in-class reductions of HBV DNA, RNA, HBsAg and HBeAg in CHB patients. Here, we reproduce the superior HBV DNA reductions over the nucleoside analog entecavir in vitro and show that CAMs directly target HBeAg. **Methods:** HBV DNA knockdown was assessed in HBV-expressing HepG2.117 cells with additional DNase digestion steps to remove non-encapsidated HBV DNA, allowing for the determination of EC_{90}, EC_{99} and $EC_{99.9}$ values. Cellular effects on HBeAg expression were studied using transient HBeAg expression in Huh7 cells and stably transfected HepG2 cells, with a plasmid encoding either wild-type or T33N-mutated HBeAg. Interactions between CAMs and purified HBeAg were further investigated using microscale thermophoresis (MST), spectral shift, and size exclusion chromatography with multi-angle light scattering (SEC-MALS). **Results:** ALG-001075 induced pronounced HBV DNA reductions with EC_{90}, EC_{99} and $EC_{99.9}$ values of 2.65, 6.99 and 22.3 nM, compared to 8.56, 1480 and 26,700 nM for entecavir, respectively. ALG-001075 and other CAMs also strongly reduced the levels of secreted HBeAg in the absence of other HBV proteins, suggesting a direct effect on HBeAg. EC_{50} values for HBeAg inhibition where generally ~100 fold higher than for HBV DNA inhibition, but became higher for most CAMs upon introduction of the T33N mutation into HBeAg, indicating that the HBeAg binding site is similar to

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the HBV core protein binding site. Biophysical analysis through MST and spectral shift confirmed direct binding to HBeAg for different CAMs but not for entecavir. Finally, SEC-MALS analysis revealed notable differences between CAM-A- and CAM-E-treated HBeAg. **Conclusion:** ALG-001075 demonstrated highly pronounced in vitro reductions in HBV DNA and HBeAg, in line with clinical observations for its prodrug ALG-000184, further confirming its best-in-class properties.

Disclosures: Cheng Liu: Nothing to Disclose, Jordi Verheyen: Aligos Therapeutics: Employee, Dieudonné Buh Kum: Nothing to Disclose, Hannah Vanrusselt: Nothing to Disclose, Tse-I Lin: Nothing to Disclose, Julian Symons: Nothing to Disclose, Lawrence Blatt: Nothing to Disclose, Andreas Jekle: Nothing to Disclose, Yannick Debing: Aligos Therapeutics, Inc.: Employee, Aligos Therapeutics, Inc.: Stock - publicly traded company

1267 | FDA APPROVED DRUG LIBRARY SCREENING TO IDENTIFY COMPOUNDS THAT REDUCE HBS ANTIGEN

Akiyoshi Shimoda[1] Hayato Hikita[2] Kazuhiro Murai[1] Takayuki Miyake[1] Shinji Kuriki[1] Emi Sometani[1] Jihyun Sung[3] Satoshi Shigeno[1] Kumiko Shirai[1] Yuki Tahata[3] Yoshinobu Saito[1] Takahiro Kodama[3] Tomohide Tatsumi[3] Hiroshi Suemizu[4] Tetsuo Takehara[3]

[1]The University of Osaka, [2]Osaka University Graduate School of Medicine, [3]Osaka University, [4]Central Institute for Experimental Medic

Background: Hepatitis B surface antigen (HBsAg), a protein of hepatitis B virus (HBV), is linked to hepatocellular carcinoma and immune exhaustion, contributing to persistent infection. Current anti-HBV therapy, nucleos(t)ide analogue (NUC) have little effect on HBsAg. This study aims to find novel treatments to reduce HBsAg using an FDA-approved drug library and to elucidate the mechanisms involved. **Methods:** A library of 1134 FDA-approved drugs was screened on HepG2.2.15.7 cells, HBV genome integrated cells, at 9.9μM for 7 days. After 7 days incubation, the level of HBsAg in the supernatant and cell viability were measured. Compounds that reduced cell viability by more than 1 standard deviation (SD) were excluded. The compounds that decreased the level of HBsAg in the supernatant by more than 1.5 SD were selected as candidate compounds. The candidates were validated at concentrations of 5 and 0.5 μM with the same time course. Compounds that significantly reduced the supernatant HBsAg at both concentrations were selected as final candidates. To elucidate the mechanism of HBsAg reduction, HepG2.2.15.7 cells and HBV-inoculated (1000 genome equivalent/cell) primary human hepatocytes isolated from humanized liver chimeric TK-NOG mice (HepaSH cells) were treated with final candidates. **Results:** A total of 126 compounds were excluded due to reduced cell viability below 1 SD. From the remaining 1008 compounds, 6 compounds were identified as candidate compounds with HBsAg levels decreased by more than 1.5 SD. Among them, only ethacridine and auranofin significantly decreased HBsAg at the both concentrations of 5 and 0.5 μM. Using HepaSH cells, while ethacridine did not decrease HBsAg, auranofin decreased HBsAg. Hepatitis B envelope antigen (HBeAg), HBV-DNA in the supernatant or pregenomic RNA (pgRNA) was not decreased by auranofin. In addition, Western blotting did not show a change in intracellular HBsAg by auranofin. In a transmission electron microscopy image, many vesicles in the endosome were detectable in auranofin-treated HepaSH cells, but not in untreated HepaSH cells. Western blotting showed that auranofin treatment enhanced protein expression of galectin3, a marker of damaged lysosomes, suggesting that the vesicles increased by auranofin treatment are damaged lysosomes and that damaged lysosomes are responsible for the decrease in HBsAg. **Conclusion:** FDA approved drug library screening identified auranofin which suppresses HBsAg levels.

Disclosures: Akiyoshi Shimoda: Nothing to Disclose, Hayato Hikita: Nothing to Disclose, Kazuhiro Murai: Nothing to Disclose, Takayuki Miyake: Nothing to Disclose, Shinji Kuriki: Nothing to Disclose, Emi Sometani: Nothing to Disclose, Jihyun Sung: Nothing to Disclose, Satoshi Shigeno: Nothing to Disclose, Kumiko Shirai: Nothing to Disclose, Yuki Tahata: Nothing to Disclose, Yoshinobu Saito: Nothing to Disclose, Takahiro Kodama: Chugai Pharmaceuticals: Speaking and Teaching, Astrazeneca: Speaking and Teaching, Eisai Co Ltd: Speaking and Teaching, Tomohide Tatsumi: Nothing to Disclose, Hiroshi Suemizu: Nothing to Disclose, Tetsuo Takehara: Nothing to Disclose

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1268 | HIGHER RISK OF DISEASE PROGRESSION IN THE GREY ZONE RELATIVE TO INACTIVE CHRONIC HEPATITIS B

YunLing Xue[1] Xiaoqing Liu[1] Peng Hu[1]

[1]Chongqing Medical University

Background: Inactive Chronic hepatitis B (IC) is the commonest immune state in CHB. However, there are also HBeAg-negative, ALT-normal patients with CHB who are not definitively in stage IC, and are therefore referred to as the gray zone corresponding to stage IC. There is still confusion about the evolution of disease progression in the GZIC. So we aimed to study the natural history and antiviral treatment of IC and GZIC. **Methods:** This was a retrospective cohort study that included 386 patients with stage IC and GZIC. Conversion to HBeAg-negative immune-active CHB (IA) and IA corresponding grey zone (GZIA), initiation of antiviral therapy, and occurrence of end-stage liver disease events were defined as outcome events. The cumulative incidence of outcome events in the IC and GZIC groups was compared. **Results:** Of the 386 patients, 32.4% (125/386) were in GZIC status. Of these, 13.8% (36/261) of IC patients were converted to IA or GZIA, while 36.8% (46/261) of GZIC patients underwent this change in immune status. In addition, 37.6% (47/125) and 4.8% (6/125) of GZIC patients initiated antiviral therapy and developed end-stage liver disease, both of which were higher than the proportion of IC patients with both outcomes (18.8%,49/261; 1.5%,4/261). Meanwhile, the cumulative event rates of conversion to IA or GZIA, initiation of antiviral therapy and development of end-stage liver disease were higher in patients with GZIC than in those with IC (all P values <0.05). **Conclusion:** Patients with GZIC have a higher risk of disease progression than those with IC.

Disclosures: YunLing Xue: Nothing to Disclose, Xiaoqing Liu: Nothing to Disclose, Peng Hu: Nothing to Disclose

1269 | A SIMPLE MODEL FOR PREDICTING HBSAG LOSS USING BASELINE HBSAG IN CHRONIC HEPATITIS B PATIENTS WHO RECEIVED PEG-IFNα-2B THERAPY

fei yan[1] Jiayin Wang[2] Jing Chen[3] Jing Liang[2] Jun Li[2] Fang Wang[2] Qing Ye[2] Yanying Gao[2] Weili Yin[2] Fei Tang[2] Huiling Xiang[2]

[1]The Third Central Clinical College of Tianjin Medical University, [2]Tianjin Third Central Hospital, [3]Tianjin Medical University

Background: Although interferon (IFN) therapy for chronic hepatitis B has garnered increasing attention, determining the optimal treatment course remains elusive. This research aimed to develop a straightforward model for predicting IFN treatment duration using baseline data to provide clinicians and patients with valuable references. **Methods:** Patients with chronic hepatitis B, undergoing pegylated interferon α-2b (PEG-IFNα-2b) monotherapy or combined with NAs (nucleoside/nucleotide analogs), were recruited from January 2018 to December 2023 at Tianjin Third Central Hospital. All patients achieved HBsAg loss post-treatment. Baseline data including routine blood tests, liver function, HBsAg, HBeAg, HBV DNA, and liver stiffness measures (LSM) were collected. Linear regression analysis was employed to assess the association between IFN therapy and baseline HBsAg. **Results:** The study included 176 chronic hepatitis B patients with or without compensatory cirrhosis (117 males and 59 females), with an average age of 41.68 ± 8.83 years. The median duration of IFN treatment was 35.54 ± 25.49 weeks (median 25.00; Q1-Q3 17.00-46.00). The median baseline HBsAg level was 45.38 (Q1-Q3: 2.62-440.03) IU/mL. Correlation analysis revealed a significant relationship between baseline HBsAg and IFN therapy ($rs = 0.577$, $p < 0.05$). Univariable and multivariable analyses demonstrated that baseline HBsAg significantly influenced IFN therapy. Even after adjusting for confounding factors, HBsAg remained a significant predictor of IFN therapy ($\beta = 10.05$, 95% CI: 6.16, 13.94; $p < 0.05$). Upon above analyses, a prediction formula based on baseline HBsAg levels can be initially established and has good performance in predicting IFN treatment. **Conclusion:** The duration of IFN treatment required for functional cure in chronic hepatitis B individuals correlates positively with baseline HBsAg levels. A linear model was established which can be conveniently used in the individualized prediction.

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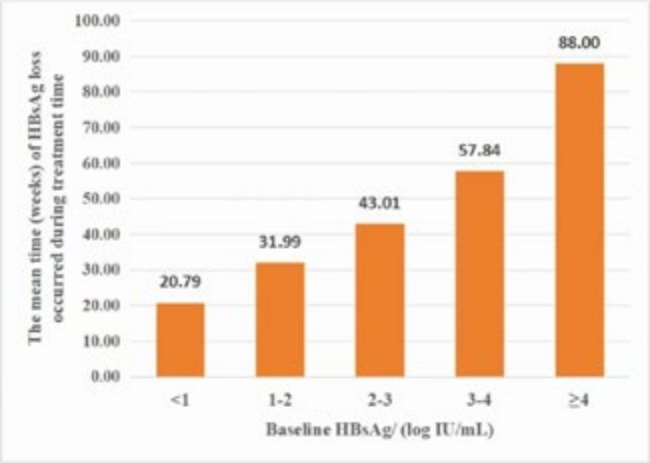

Figure 1. The median time (weeks) of HBsAg loss under different baseline HBsAg levels. When HBsAg<1 log IU/mL, the median time of HBsAg loss is 20.79, which was the shortest; when HBsAg≥4 log IU/mL, the median time is 88.00, indicating that the lower the baseline HBsAg, the shorter the median time required for clinical cure.

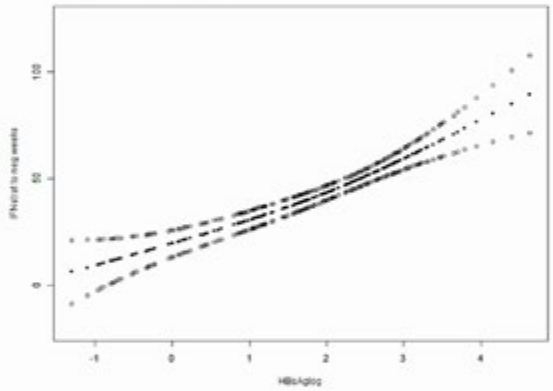

Figure 2. The curve fitting and correlation analysis between IFN treatment and baseline HBsAg. The curve fitting showed an approximate linear trend.Spearman correlation analysis indicated that there was a significant positive correlation between the two variables (rs=0.577,p<0.001)

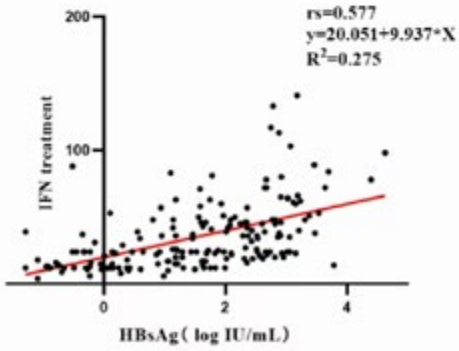

Figure 4. The curve of linear model predicting IFN treatment. a prediction model for IFN treatment was established: IFN treatment=20.051+9.937*Log (baseline HBsAg), R^2=0.275

Disclosures: fei yan: Nothing to Disclose, Jiayin Wang: Nothing to Disclose, Jing Chen: Nothing to Disclose, Jing Liang: Nothing to Disclose, Jun Li: Nothing to Disclose, Fang Wang: Nothing to Disclose, Qing Ye: Nothing to Disclose, Yanying Gao: Nothing to Disclose, Weili Yin: Nothing to Disclose, Fei Tang: Nothing to Disclose, Huiling Xiang: Nothing to Disclose

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1270 | PHARMACOKINETICS, SAFETY, AND TOLERABILITY OF THE SIRNA TQA3038 IN HEALTHY CHINESE VOLUNTEERS

Dong Liu[1] Zhelong Liu[1] Xiuhua Ren[1] Yinian Fang[1] Xingxing Qi[1] Donglin Zhang[1] Hengyi Yu[1] Yongfang Lei[1] Zheng He[1] Qin Zuo[1] Chang Liu[1] zhongnan xu[2] Wen Wang[2]

[1]Huazhong University of Sci and Tech, [2]Chia Tai Tianqing Pharmaceutical

Background: TQA3038 is a novel N-acetylgalactosamine (GalNAc)-conjugated small interfering RNA (siRNA) developing for chronic hepatitis B virus (HBV) infection. TQA3038 could target all HBV transcripts reducing all viral proteins, and has shown favorable safety and antiviral activity in nonclinical studies. **Methods:** This was a phase I, single center, randomized, double-blind, placebo-controlled study(NCT06085053). All the volunteers were given 1 subcutaneous injection of TQA3038(50-800mg) or placebo to investigate the pharmacokinetics, safety, and tolerability of TQA3038. Plasma pharmacokinetic parameters were determined for each volunteer up to 48 hours after dosing. Safety assessments were collected throughout the study conduct. **Results:** To date, dosing of all cohorts is complete and still blinded. Fifty-four volunteers were enrolled in this study. Four sentinel volunteers were randomized 3:1 to TQA3038(50mg) or placebo. Ten volunteers in each remaining cohort were randomized 8:2 to TQA3038 (100–800mg) or placebo. All treatment-emergent adverse events (AEs) were mild and resolved by study end. An unrelated grade 3 AE of lung infection was observed in the 200mg cohort. There were no severe adverse events and drug-related grade 3 AEs reported. No dose-related trends in types or incidence of AEs were observed across the dose cohorts. TQA3038 was rapidly absorbed with a median time to maximum concentration ranged from 4-7 hours and eliminated from the systemic circulation with plasma concentrations declining below LLOQ beyond 48 hours in any subject which is consistent with rapid GalNAc-mediated uptake into the liver. The plasma exposures increased in a slightly greater-than-dose-proportional manner across the dose range with low variability. **Conclusion:** Single dose of up to 800mg TQA3038 was safe and well tolerated in healthy volunteers. Plasma pharmacokinetic variables were well defined. These data are supportive to continue development in patients with chronic HBV infection.

Disclosures: Dong Liu: Nothing to Disclose, Zhelong Liu: Nothing to Disclose, Xiuhua Ren: Nothing to Disclose, Yinian Fang: Nothing to Disclose, Xingxing Qi: Nothing to Disclose, Donglin Zhang: Nothing to Disclose, Hengyi Yu: Nothing to Disclose, Yongfang Lei: Nothing to Disclose, Zheng He: Nothing to Disclose, Qin Zuo: Nothing to Disclose, Chang Liu: Nothing to Disclose, zhongnan xu: Nothing to Disclose, Wen Wang: Nothing to Disclose

1271 | THE RELATIONSHIP BETWEEN REPRODUCTIVE HISTORY AND CLINICAL CHARACTERISTICS IN HBEAG-NEGATIVE CHRONIC HBV-INFECTED WOMEN OF CHILDBEARING AGE

Shimin Yin[1] Xueru Yin[1] Xiaohuan Jiang[1] Jingran Wu[1] Jialin Li[1] Yunfei Gao[1] Zhihua Liu[1]

[1]Nanfang Hospital, Southern Medical University

Background: The prevalence of Hepatitis B surface antigen (HBsAg) is high among women of childbearing age in China. Pregnancy is a unique physiological process that brings about various changes in women's physiology and metabolism. It is not clear how the process of pregnancy may affect the process of chronic Hepatitis B Virus (HBV) infection. This study was conducted to describe the clinical characteristics of Hepatitis B E antigen(HBeAg)-negative chronic HBV-infected women of childbearing age, and to analyze the correlation between their reproductive histories and clinical characteristics. **Methods:** The study subjects were HBeAg-negative chronic HBV-infected women of childbearing age, who had not received antiviral treatment and were in the non-pregnant period. They were selected from the clinic of liver disease at Nanfang Hospital from August 2022 to September 2023. The study subjects were divided into group 1 (no reproductive history group) and group 2 (reproductive history group) according to reproductive history. The clinical characteristics were compared between group 1 and group 2. Logistic regression analysis was applied to identify the influencing factors for qHBsAg. **Results:** A total of 556 HBeAg-negative chronic HBV-infected women of childbearing age were enrolled, and the number of births was 0, 1, 2, 3, and 4 in 231 (41.55%), 86 (15.47%), 68 (12.23%), 12 (2.16%), and 2 (0.36%), respectively; and the remaining 157 cases (28.24%) had an unknown reproductive history. Among them, 59.53% were HBV DNA positive and 4.74% of the total population had abnormal liver function. Compared with the HBV DNA-negative group, the HBV DNA-positive group had a higher rate of abnormalities in qHBsAg, ALT, AST, AFP, LSM

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levels, APRI scores, and steatosis (p<0.05). There were statistically significant differences in age, qHBsAg, ALB, LSM levels and FIB-4 scores between the group 1 and group 2 (p< 0.05). After stratified analysis by age, among patients of age ≥26 years, there was significant difference in the qHBsAg level between the two groups (p<0.05). Univariate and multivariate regression analysis showed that reproductive history was independent risk factor influencing qHBsAg level of HBeAg-negative women of childbearing age (OR=0.52, p<0.05). **Conclusion:** HBeAg-negative chronic HBV-infected women of childbearing age with a reproductive history have lower qHBsAg levels. Reproductive history may be a risk factor influencing qHBsAg level.

Table1 Logistic regression analysis on risk factors of qHBsAg＞1500IU/ml in HBeAg-negative chronic HBV-infected women of childbearing age

Variables	Univariate logistic		Multivariate logistic	
	OR (95%CI)	*p*	OR (95%CI)	*p*
Age(years)	0.96 (0.90,1.03)	0.306		
Parity				
0				
⩾1	0.51 (0.31,0.86)	0.012	0.52 (0.30,0.91)	0.022
LSM(kpa)	1.55 (1.19,2.03)	0.001	1.43 (1.04,1.97)	0.030
HBV DNA(log_{10}IU/ml)	1.48 (1.15,1.91)	0.002	1.30 (0.97,1.74)	0.081
AFP(ng/ml)	1.18 (1.00,1.39)	0.053	1.11 (0.93,1.33)	0.252
ALT(U/L)	1.02 (1.00,1.04)	0.072	0.99 (0.95,1.04)	0.757
AST(U/L)	1.04 (1.00,1.09)	0.042	1.02 (0.95,1.11)	0.556
TBIL(μmol/L)	1.00 (0.95,1.05)	0.967		
IBIL(μmol/L)	1.00 (0.93,1.07)	0.952		
DBIL(μmol/L)	1.02 (0.87,1.20)	0.793		
ALB(g/L)	0.93 (0.87,1.01)	0.079	0.93 (0.85,1.03)	0.165
GLB(g/L)	1.06 (1.00,1.13)	0.042	1.02 (0.95,1.11)	0.573

Disclosures: Shimin Yin: Nothing to Disclose, Xueru Yin: Nothing to Disclose, Xiaohuan Jiang: Nothing to Disclose, Jingran Wu: Nothing to Disclose, Jialin Li: Nothing to Disclose, Yunfei Gao: Nothing to Disclose, Zhihua Liu: Nothing to Disclose

1272 | MANAGEMENT AND OUTCOME OF BASELINE GREY-ZONE (GZ) PATIENTS AMONG THE FRENCH HEPATHER COHORT: IS IT DIFFERENT FROM HBEAG NEGATIVE CHRONIC HEPATITIS B INFECTION (CHBVE-) OR HBEAG NEGATIVE CHRONIC HEPATITIS (CHBVHE-)?

Lucia Parlati[1] Clovis Lusivika[2] Jérôme Nicol[2] Fabrice Carrat[2] Vincent Leroy[3] Marc Bourliere[4]

[1]Hepatology Departement, Cochin Hospital, [2]IPLESP, UMR-S 1136 INSERM Paris, [3]Hepatology Departement, Mondor Hospital, [4]Hopital Saint Joseph

Background: The optimal management and outcomes of GZ CHBVe- patients remain controversial and may be different according to different region worldwide. We assessed the current management and outcomes of such patients among the French HEPATHER cohort. **Methods:** All CHBVe patients with available follow-up enrolled in the cohort between 2012 and 2014 were included if they had a) baseline HBV DNA ≤ 20,000 UI/ml or b) baseline HBV DNA > 20,000 and ALT ≤ 2 x ULN. Patients with HCV and/or HIV coinfection, immunosuppressive therapy, HCC or decompensated cirrhosis at baseline, alcohol use disorders or any other cause of liver disease were excluded. GZ patients were defined by baseline ALT > ULN and/or HBV DNA ≥ 2,000 UI/ml, whereas the remaining were considered as typical CHBVe-pts (baseline ALT ≤ ULN and HBV DNA < 2,000 UI/ml. Treatment

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indication was based on EASL guidelines: a) HBV DNA > 20,000 and ALT > 2 x ULN, b) HBV DNA > 2,000 UI/ml and advanced fibrosis or c) detectable HBV DNA and cirrhosis. CHBVHe-were HBeAg- patients on treatment with NAs at baseline. **Results:** Of 5,944 chronic HBV patients, 1,499 were CHBVHe- and 1,881 patients fulfilled the inclusion criteria. Of them 741 (39.4%) were classified as baseline GZ with a median follow-up of 5.8 years (3.7-7.6) and 1,140 (60.6%) as typical CHBVe- patients with a median follow-up of 5.9 years (4.0-7.5). GZ compared to CHBVe- patients were younger 38.5 vs 41.2 and more frequently male (65.7%vs 48.9% (p<0.0001)). During follow-up GZ patients were more frequently treated than CHBVe- patients 17% vs 6% (p<0.0001). Among GZ patients there were 10 deaths, 1 HCC, no decompensated cirrhosis and no LT. Crude incidence ratio (95%CI) of death and HCC for GZ patients vs CHBVe- was 0.98 (0.45-2.16) (p=0.96), 0.78 (0.07-8.64) (p=0.84) respectively. The hazard ratio (HR) of HBsAg loss adjusted on age, sex, geographical origin, fibrosis scoring, ALT, AST and arterial hypertension for GZ vs CHBVe- patients was 0.32 (0.17-0.60) (p=0.0004). GZ patients, compared to CHBVHe- patients, were younger 38.5 vs 48.4 years (p<0.0001), had less frequently advanced fibrosis (7.3% vs 25.5% (p<0.0001)), arterial hypertension (11.4% vs 20.4%) and diabetes (5% vs 9.6% (p<0.001)). The HR of deaths, HCC, and HBsAg loss adjusted on age, sex, geographical origin, fibrosis score, ALT, AST and arterial hypertension for GZ vs CHBVHe- were 0.58 (0.28-1.17) (p=0.13), 0.20(0.03-1.58) (0.13) and 0.59 (0.32-1.09) (0.09) respectively. **Conclusion:** GZ patients at baseline represent 40% of the CHBVe- cases in the HEPATHER Cohort. GZ patients had a higher probability to be treated and a lower chance of HBsAg loss without increased risk of HCC and death.

Disclosures: Lucia Parlati: Nothing to Disclose, Clovis Lusivika: Nothing to Disclose, Jérôme Nicol: Nothing to Disclose, Fabrice Carrat: Nothing to Disclose, Vincent Leroy: Nothing to Disclose, Marc Bourliere: Nothing to Disclose

1273 | THE UPREGULATION OF GRP78 BY HBV PROMOTES THE PROGRESSION OF HEPATOCELLULAR CARCINOGENESIS THROUGH THE MODULATION OF GLUCOSE UPTAKE IN HOST CELLS ◆

Miao Liu[1] *Lingyao Du*[2] *hong Tang*[2]

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Background: HBV infection can cause endoplasmic reticulum stress (ERS). Glucose-regulated protein 78 (GRP78), a major molecular chaperone predominantly located within the ER, plays a vital role in ERS. Our previous research indicated that GRP78 plays a crucial role in the development of HBV-HCC, and highlighted the correlation between GRP78 expression level and the carcinogenicity of the virus strains. ERS can affect intracellular material and energy metabolism, enhance glucose uptake and alter glucose metabolism in cells. The potential involvement of HBV-induced GRP78 in HCC pathogenesis through modulation of host cell glucose uptake and cellular energy metabolism warrants further investigation. **Methods:** Human hepatocyte L02, HBV replicative hepatocytes L02-pHBV4.1 and L02-pHBV4.1* were used in this study. In vitro, the protein levels of GRP78 and GLUT1 were detected with western blot. Glucose uptake and lactate production were measured by glucose uptake kits and lactate detection kits, respectively. Then we employed L02-pHBV4.1* cells and their GLUT1-knockout counterparts to evaluate cellular proliferation through a colony formation assay. Additionally, subcutaneous tumorigenesis models were established in nude mice for in vivo analysis. **Results:** In this study we found that overexpression of GRP78 elevated glucose uptake levels and lactate production by upregulating of GLUT1. In vitro, GLUT1-knockout in cells decreased glucose uptake, lactate production and even cellular proliferation. In vivo, PET/CT imaging showed that GLUT1-knockout decreased glucose uptake in the subcutaneous tumor and inhibited the formation of subcutaneous tumors in nude mice. Furthermore, western blot indicated that HBV can upregulate GRP78-GLUT1 pathway. HBV can increase glucose uptake and lactate production of host cells. These findings above suggest that HBV may enhance cellular glucose uptake and glycolysis via GRP78-GLUT1 pathway. Besides, PET/CT imaging showed increased glucose uptake and larger tumor size in L02-pHBV4.1 xenografts compared to L02. Expression levels of GRP78, GLUT1, and Ki67 were significantly higher in L02-pHBV4.1 tumor tissues compared to L02. **Conclusion:** The upregulation of GRP78-GLUT1 by HBV may increase host cell glucose uptake and promotes cell proliferation, thus promoting hepatocellular carcinoma.

Disclosures: Miao Liu: Nothing to Disclose, Lingyao Du: Nothing to Disclose, hong Tang: Nothing to Disclose

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1274 | FIRST-IN-HUMAN STUDY TO ASSESS THE SAFETY, TOLERABILITY AND PHARMACOKINETICS OF AN ORAL TOLL-LIKE RECEPTOR 8 AGONIST IN HEALTHY SUBJECTS

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Background: TQA3810 is a novel, oral, selective Toll-like receptor 8 (TLR8) agonist in development for the treatment of chronic hepatitis B (CHB). This phase 1 study was conducted aiming to assess the safety, tolerability and pharmacokinetics (PK) of TQA3810 in healthy Chinese subjects. **Methods:** This study was designed into four parts. PartA/B was a randomized, double-blind, placebo-controlled, single/multiple dose escalation(SAD/MAD) study. Forty subjects were randomized 4:1 to TQA3810(0.1/0.3/0.5/1.0mg) or placebo in SAD. Seven cohorts with different doses and intervals were constructed in MAD. Sixteen subjects were enrolled for food effect study in PartC. PartD was a drug-drug interaction (DDI) study to evaluate PK interactions between TQA3810 and Entecavir(ETV). **Results:** TQA3810 was well tolerated and no serious adverse events (SAEs) or deaths were reported. A total of 103 treatment-related adverse events (TRAEs) were reported in 27 of 40 subjects (67.5%) in SAD and one subject in 1.0mg group experienced a grade 3 AE of neutrophil count decreased. In MAD, 567 TRAEs were reported in 41 of 50 subjects (82%) and six grade 3 AEs occurred without a dose-related trend. No grade 3 AEs were observed in both food effect and DDI study. The incidence and severity of AEs were comparable between the fasting and fed subjects. Moreover, administering with ETV did not increase the incidence of AEs. Collectively, the most common and dose-related TEAEs included gastrointestinal disorders (such as nausea, vomiting, abdominal pain and diarrhea), abnormalities in blood cell counts and fever. The plasma exposure of TQA3810 increased in a dose-dependent manner. TQA3810 was rapidly absorbed with a median time to peak concentration of 0.33-0.50 hours and had a short mean half-life of 1.39-2.33 hours after single dosing. No significant accumulation was observed after multiple dosing. A high-fat and high-calorie diet caused slight changes in the PK profile of TQA3810. Taking with ETV did not significantly affect the PK of either TQA3810 or ETV in this study. **Conclusion:** TQA3810 was safe and well tolerated. TQA3810 can be taken with or without food. No DDI was observed between TQA3810 and ETV. These data indicate that TQA3810 is a promising candidate for further development in CHB patients.

Disclosures: Bei Cao: Nothing to Disclose, Lei Huang: Nothing to Disclose, Tingting Ma: Nothing to Disclose, Hui Lin: Nothing to Disclose, Sha Wu: Nothing to Disclose, Yuanxun Yang: Nothing to Disclose, Yu Zhao: Nothing to Disclose, zhongnan xu: Nothing to Disclose, Juan Li: Nothing to Disclose

1275 | THE ROLE OF STEATOSIS AND FIBROSIS PARAMETERS IN PREDICTING HEPATOCELLULAR CARCINOMA RECURRENCE IN CHRONIC HEPATITIS B PATIENTS

Ke Yin[1] yuyun song[1] Rui Jin[1] Baiyi Liu[1] Zilong Wang[1] Yayun Ren[2] Elaine Chng[2] Jiaojiao Li[3] Huiying Rao[1] Xiaoxiao Wang[1] Feng Liu[1]

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Background: The relationship between metabolic dysfunction-associated steatotic liver disease (MASLD), hepatitis B virus (HBV) infection, and their contributions to progressive fibrosis, cirrhosis, and hepatocellular carcinoma (HCC) remains unclear. This study aims to analyze the characteristics of steatosis and fibrosis in HCC and adjacent tissues in patients with Chronic Hepatitis B (CHB) to evaluate their impact on HCC prognosis using Second Harmonic Generation/Two Photon Excitation (SHG/TPE) microscopy. **Methods:** SHG/TPEF microscopy images were acquired on unstained sections of 3 tissue types (tumor tissue, normal adjacent tissue within 1 cm [NAT1] from 37 patients with HBV-induced HCC. Among these, 5 patients experienced HCC recurrence within 4 years. A machine learning (ML)-based algorithm quantitatively analyzed liver fibrosis and steatosis, with parameters quantified in five regions: portal tract (PT), periportal (PP), zone 2, pericentral (PC) and central vein (CV). Disease-free survival curves were calculated using the Kaplan–Meier method, and compared using the log-rank test. **Results:** Steatosis parameters demonstrated a stronger correlation with HCC recurrence than fibrosis parameters across 3 tissue parts. In tumor tissues, the most significant parameters were macrovescular steatosis percentage (HR:8.04, p=0.026) and collagen area percentage (HR:11.74, p=0.006). In NAT1 tissues, important parameters were microvescular steatosis percentage (HR:8.37, p=0.040) and the number of thin, aggregated

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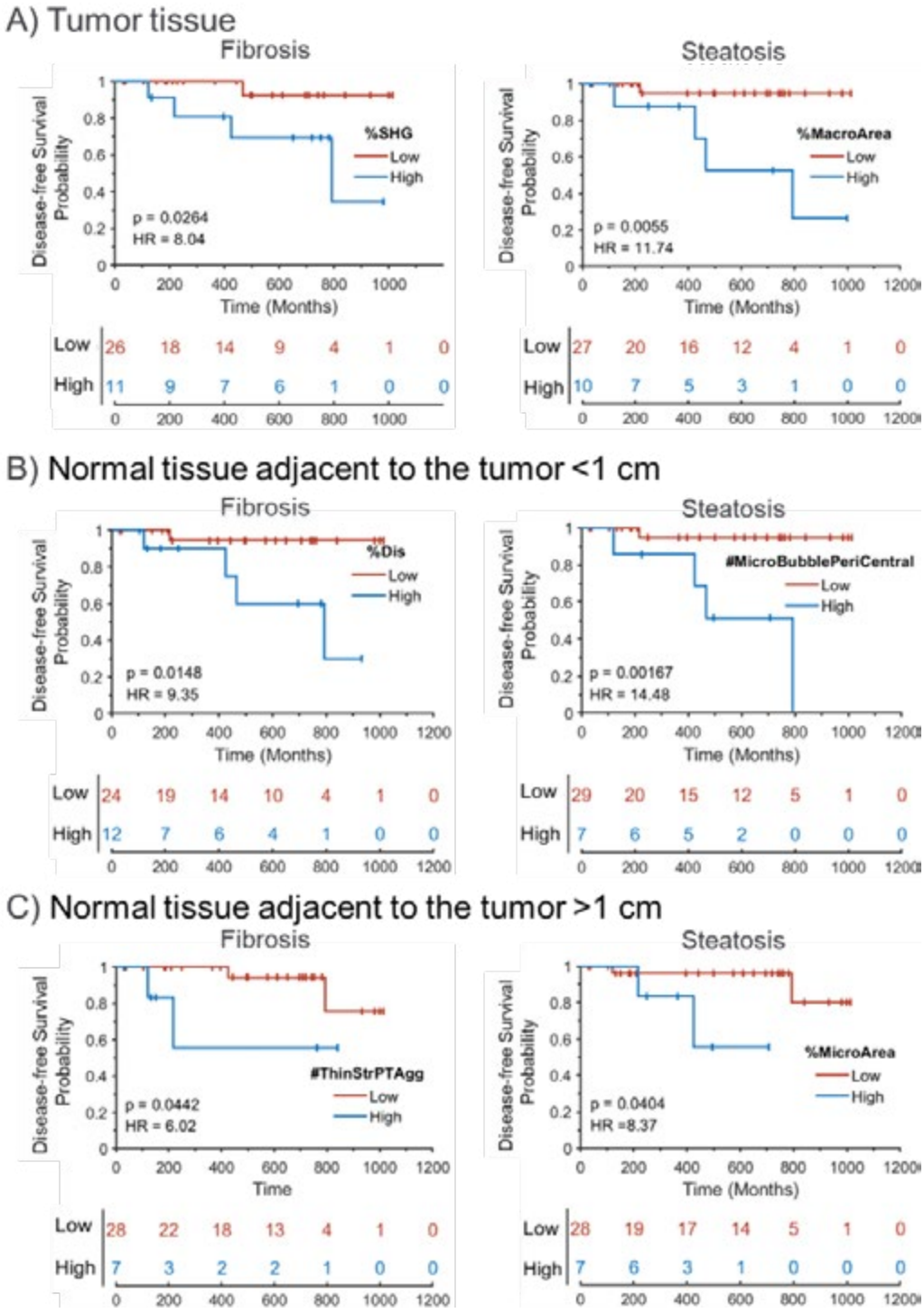
collagen strings in the PT region (HR:6.02, p=0.044). Parameters from NAT **Conclusion:** Steatosis and fibrosis parameters in tumor and NAT tissues from patients with HBV-induced HCC effectively predict HCC recurrence. The ML-based quantitative method may serve as a valuable prognostic tool for HCC.



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1276 | THE IMPACT OF HEPATITIS B VIRUS INFECTION ON ASSISTED REPRODUCTIVE TECHNOLOGY OUTCOMES A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: The impact of hepatitis B virus (HBV) infection on the outcomes of assisted reproductive technology (ART) has been a topic of considerable debate within the field of reproductive medicine. There is a lack of clear guidance and treatment recommendations for this issue. This meta-analysis was conducted to evaluate the impact of different biparental HBV infection conditions on couples undergoing ART treatment. **Methods:** PubMed, Web of Science, Cochrane Library, EMBASE, CNKI, and Wangfang databases were systematically searched for eligible studies from the inception of the databases until December 2023. Summary odds ratio (OR) with 95% confidence interval (CI) was applied to assess the relationship using a random-effects model. **Results:** A total of 39 retrospective cohort studies were included, involving 60,352 ART treatment cycles. Couples with paternal and/or maternal hepatitis B surface antigen (HBsAg) positive were categorized as the HBV infection group for a total of 11,437 cycles. Couples who were both HBsAg negative composed the control group for a total of 48,915 cycles. Fertilization rates were significantly higher in couples with paternal and/or maternal HBV infection (OR = 0.78, 95% CI: 0.62–0.97; p = 0.03) or with maternal infection only (OR = 0.71, 95% CI: 0.52–0.98; p = 0.03), compared to couples where neither partner was infected. However, dual pronuclear (2PN) fertilization rates were not significantly increased in couples with paternal and/or maternal HBV infection. Miscarriage rates were significantly higher in couples with paternal and/or maternal HBV infection, compared to couples where neither partner was infected (OR = 1.38, 95% CI: 1.02–1.86; p = 0.03). The prevalence of intrahepatic cholestasis of pregnancy (ICP) was higher in couples with paternal and/or maternal HBV infection (OR = 2.44, 95% CI: 1.66–3.56; p < 0.01), as well as in couples with maternal infection only (OR = 2.41, 95% CI: 1.63–3.55; p < 0.01), compared to couples where neither partner was infected.There were no statistical differences in the cleavage rate, high-quality embryo rate, implantation rate, clinical pregnancy rate, early miscarriage rate, live birth rate, and the prevalence of gestational diabetes mellitus (GDM). **Conclusion:** Overall, the fertilization rate in the HBV group was significantly increased, but there was no significant difference in the 2PN fertilization rate. Therefore, HBV infection may increase the abnormal fertilization rate during ART treatment. Furthermore, HBV infection may be associated with a higher risk of ICP for pregnant women who underwent ART.

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1277 | LONG-TERM FOLLOW UP IDENTIFIES A HIGHER INCIDENCE OF FUNCTIONAL CURE FOLLOWING NUCLEOS(T)IDE ANALOGUE DISCONTINUATION IN HBEAG-NEGATIVE CHRONIC HEPATITIS B

Simon Hume[1] Samuel Hall[1] Gareth Burns[2] Daniel Tassone[1] Paul Desmond[1] Dilip Ratnam[3] Marie Sinclair[4] William Sievert[5] Miriam Levy[6] Rohit Sawhney[4] Amanda Nicoll[7] Zina Valaydon[2] Simone Strasser[8] Meng Ngu[9] Christopher Meredith[10] Gail Matthews[11] Kumar Visvanathan[1] Jacinta Holmes[12] Alexander Thompson[1]

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Background: Discontinuation of nucleos(t)ide analogue (NA) therapy has been associated with favourable outcomes including functional cure (HBsAg loss) amongst patients with chronic hepatitis B (CHB). A higher incidence of HBsAg loss has been reported in studies with longer follow up. **Methods:** This is a prespecified analysis of the longer-term outcomes of participants enrolled in a prospective multicentre study of NA discontinuation (all patients were non-cirrhotic with HBeAg-negative CHB at enrolment; 85% were Asian). Following 96 weeks of follow up (outcomes previously reported), participants returned to standard of care and were reviewed 6 monthly and managed at the discretion of their treating practitioner. Key efficacy (including HBsAg loss) and safety outcomes [including ALT flare (ALT>2x upper limit of normal) and HCC (hepatocellular carcinoma)] were assessed. **Results:** Data collection is ongoing with complete data expected

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by July 2024. Results are currently available for 81/110 participants with a median follow up of 6.8 years from NA discontinuation. Overall, treatment was recommenced for 67% of participants. 33% remained stable in the immune control phase. Beyond 96 weeks, an additional 7 patients achieved HBsAg loss to date, with a frequency of HBsAg loss of 7.8% at 4 years and 16.7% at 6 years (Figure 1). Early HBsAg loss (<96 weeks) was associated with very low end of treatment (EOT) HBsAg levels and was observed in the absence of ALT flares. In contrast, participants who achieved late HBsAg loss (>96 weeks) had higher EOT HBsAg levels (median 680 IU/mL vs 3.1 IU/mL, p<.05) and were more likely to have experienced a hepatitis flare (6/7 vs 0/7, p<0.05). Overall, 65 patients experienced an ALT flare. Of the seven patients who lost HBsAg beyond 96 weeks, four participants were re-treated with NA at the time of ALT flare. The median time from ALT flare to HBsAg loss was 155 weeks. No episodes of hepatic decompensation, liver transplant of death occurred. HCC was identified in three participants, all of whom were treated with curative intent and no patient has active disease at time of writing. **Conclusion:** A higher incidence of functional cure was observed with longer follow up. Late HBsAg loss (>96 weeks) was associated with ALT flares suggesting that a subset of flares may be therapeutic.

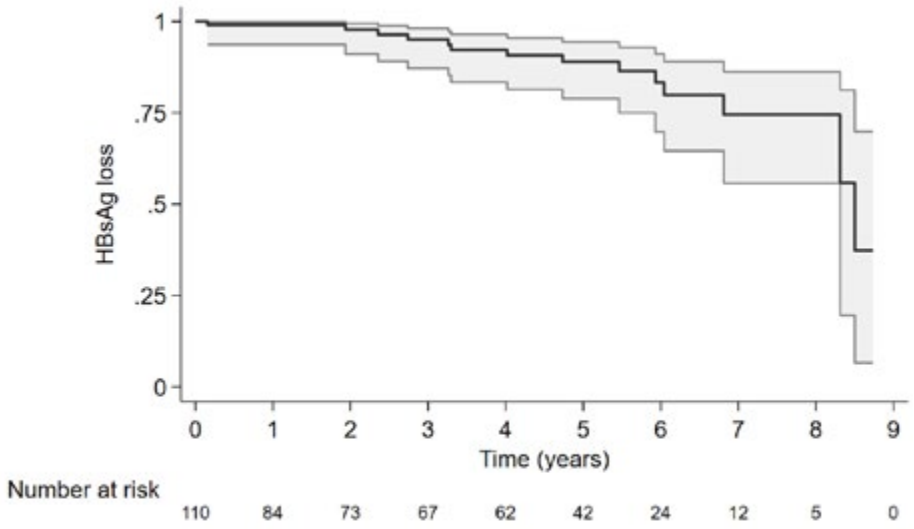

Figure 1. Time to HBsAg loss from EOT to end of follow up

Disclosures: Simon Hume: Nothing to Disclose, Samuel Hall: Nothing to Disclose, Gareth Burns: Nothing to Disclose, Daniel Tassone: Nothing to Disclose, Paul Desmond: Nothing to Disclose, Dilip Ratnam: Nothing to Disclose, Marie Sinclair: Nothing to Disclose, William Sievert: Nothing to Disclose, Miriam Levy: Nothing to Disclose, Rohit Sawhney: Nothing to Disclose, Amanda Nicoll: Nothing to Disclose, Zina Valaydon: Nothing to Disclose, Simone Strasser: Chiesi: Advisor, Roche Diagnostics: Advisor, Roche Therapeutics: Advisor, Norgine: Speaking and Teaching, Abbott Diagnostics: Advisor, CSL Behring: Advisor, Novo Nordisk: Advisor, Astra Zeneca: Advisor, Sirtex: Speaking and Teaching, Eisai: Speaking and Teaching, Meng Ngu: Nothing to Disclose, Christopher Meredith: Nothing to Disclose, Gail Matthews: Nothing to Disclose, Kumar Visvanathan: Nothing to Disclose, Jacinta Holmes: Nothing to Disclose, Alexander Thompson: Gilead Sciences: Consultant, Gilead Sciences: Speaking and Teaching, Abbvie: Consultant, Abbvie: Speaking and Teaching, Immunocore: Advisor

1278 | SAFETY OF PEGIFN&ALPHA;-2B IN PATIENTS WITH COMPENSATED HEPATITIS B CIRRHOSIS

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Background: This study aimed to assess the safety of pegylated interferon-alpha (PegIFNα-2b) in treating patients with compensated hepatitis B cirrhosis. **Methods:** We analyzed subjective adverse reaction symptoms, liver-related mortality, incidence of decompensation events, and changes in laboratory parameters among 354 patients with compensated hepatitis B cirrhosis who underwent PegIFNα-2b therapy within the CHESS2306 cohort. These were compared to 505 non-cirrhotic patients from the same cohort who also received PegIFNα-2b treatment. Patients were further categorized into four groups for comparison: cirrhosis + IFN, non-cirrhosis + IFN; cirrhosis + IFN + NAs (nucleoside analogs), non-cirrhosis + IFN + NAs. The standard dosage of PegIFNα-2b was 180 μg per week, with a treatment duration of 48 weeks and a follow-up period of 48 weeks. **Results:** No deaths occurred in any groups. The incidence of decompensation was similar among the groups. Among PegIFNα-2b recipients, flu-like symptoms were observed in 281 individuals (79.2%), gastrointestinal reactions in 27 patients (7.6%), hair loss in 20 patients (5.6%), and rashes in 19 patients (5.4%). In the cirrhosis + IFN group, the incidence of severe adverse reactions (NEUT < 0.5×10^9/L, PLT < 30×10^9/L, ALT > 10ULN, TBIL > 2ULN) and mild adverse reactions(0.5×10^9/L≤NEUT <1.0×10^9/L, 30×10^9/L≤PLT<100×10^9/L, 5ULN≤ALT **Conclusion:** Compensated hepatitis B cirrhosis patients receiving PegIFNα-2b monotherapy showed a similar incidence rate of adverse reactions compared to non-cirrhotic chronic hepatitis B patients. However, patients receiving combination therapy of PegIFNα-2b and nucleoside analogs might have a higher incidence rate of mild thrombocytopenia and bilirubin elevation compared to the non-cirrhotic control group, underscoring the need for more frequent monitoring of blood routine and liver function in such patients.

Table 1 Incidence of Adverse Events in four groups

		Cirrhosis+IFN	Non-Cirrhosis+IFN	*p* value	Cirrhosis+IFN+NAs	Non-Cirrhosis+IFN+NAs	*p* value
Duration of Peg-IFN-α (week)		42.9±11.0	40.7±11.8	0.084	41.4±11.8	42.1±11.5	0.515
liver-related mortality		0/120(0%)	0/305(0%)	1.000	0/234(0%)	0/200(0%)	1.000
Decompensation		0/120(0%)	0/305(0%)	1.000	1/234(0.4%)	0/200(0%)	1.000
HCC		1/120(0.8%)	0/305(0%)	0.628	0/234(0%)	0/200(0%)	1.000
Neutrophil	<0.5 *10^9/L	0/107(0%)	2/281(0.7%)	0.958	1/221(0.4%)	1/193(0.5%)	1.000
	>0.5 & <1.0 *10^9/L	11/107(10.3%)	40/281((14.2%)	0.389	51/221(23.1%)	41/193(21.2%)	0.742
Platelet	<30 *10^9/L	0/108(0%)	0/281(0%)	1.000	4/221(1.8%)	0/193(0%)	0.127
	>30 & <100 *10^9/L	57/108(52.8%)	118/281(42.0%)	0.072	150/221(67.9%)	95/193(49.2%)	<0.001
ALT	> 10ULN (400 U/L)	1/100(1.0%)	2/290(0.7%)	1.000	1/214(0.5%)	2/195(1.0%)	0.936
	< 5ULN & > 10ULN (200 U/L)	4/100(4.0%)	9/290(3.1%)	0.914	12/214(5.6%)	11/195(5.6%)	1.000
TBiL	> 2ULN (42 μmol/L)	0/79(0%)	5/290(1.7%)	0.540	5/164(3.0%)	1/195(0.5%)	0.097
	<2ULN & > ULN (21 μmol/L)	15/79(19.0%)	48/290(16.6%)	0.733	41/164(25.0%)	26/195(13.3%)	0.007

Disclosures: Taoran Geng: Nothing to Disclose, Ying Guo: Nothing to Disclose, Haifang Cao: Nothing to Disclose, Wenhua Zhang: Nothing to Disclose, Huiling Xiang: Nothing to Disclose, Jianqi Lian: Nothing to Disclose, Rui Zhao: Nothing to Disclose, Guohong Ge: Nothing to Disclose, Jia Shang: Nothing to Disclose, Ming Liang: Nothing to Disclose, Yanbin Wang: Nothing to Disclose, Lihua Zhong: Nothing to Disclose, Qiran Zhang: Nothing to Disclose, Ruirui You: Nothing to Disclose, Qun Zhang: Nothing to Disclose, Xiaolong Qi: Nothing to Disclose

1279 | PERFORMANCE OF HEPATOCELLULAR CARCINOMA PREDICTIVE SCORES IN AN AUSTRALIAN COHORT WITH CHRONIC HEPATITIS B INFECTION

Thisuri Jayawardena[1] Luis Calzadilla Bertot[2] Joanne Bunney[1] Joanne Vallve[1] Zein Salim[1] Leon Adams[2] Gary Jeffrey[1] Gerry MacQuillan[1]

[1]Sir Charles Gairdner Hospital, Australia, [2]University of Western Australia

Background: Several hepatocellular carcinoma (HCC) predictive scores have been developed in international settings to rationalize cancer surveillance in patients with chronic hepatitis B (CHB). This study assessed the performance of HCC predictive scores in a large Australian CHB cohort for the first time. **Methods:** Patients with CHB attending a tertiary hospital liver clinic and undergoing HCC surveillance from 1st January 2017 to 30th June 2023 were identified. Patients with prior HCC, liver transplant or lost to follow-up were excluded. The PAGE-B,

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modified PAGE-B, REACH-B, modified REACH-B and Hepascore were calculated at baseline, and patients followed for the development of liver cancer. Patients were classified into low risk (not requiring screening), intermediate and high risk (requiring screening) based on previously validated cut-offs. The primary outcome was the validity of each score (sensitivity, specificity, and predictive values). **Results:** 535 patients underwent HCC surveillance with a median follow up of 4.96 years. The median age was 49 years, 55% were male, 61% were of Asian ethnicity, 19% were of African ethnicity, 6.2% were Caucasian, 8.4% were cirrhotic and 47% received antivirals. Thirteen patients (2.4%) developed HCC during the study period (incidence 0.46 per 1000 person-years). Key results are reported in table 1. Data were available to calculate the time-dependent area under the curve at 3 years for the PAGE-B and modified PAGE-B scores which were 0.77 and 0.82 respectively. Both showed good overall accuracy (Integrated Brier Score 0.04 and 0.02 respectively) and discrimination (Gonen and Heller's k-statistic 0.73 and 0.76 respectively). The cumulative incidence of HCC at 3 years for those classified as low, intermediate and high risk was 0%, 2.6% and 4.7% respectively for PAGE-B and 0.42%, 1% and 7.5% for modified PAGE-B. **Conclusion:** PAGE-B, modified PAGE-B, modified REACH-B and Hepascore have a high sensitivity and negative predictive value with respect to HCC risk stratification. The modified PAGE-B score performed better overall compared to the PAGE-B score in our cohort of diverse ethnicity, cirrhosis, and treatment status. Our study adds to international evidence that CHB patients classified as low risk using scores such as the modified PAGE-B may safely avoid HCC surveillance.

Figure: *Performance of HCC predictive scores in an Australian cohort of patients with CHB*

Predictive score (number of patients with data available to calculate score; HCC cases)	PAGE-B (531 patients; 13 HCC cases)	Modified PAGE-B (530 patients; 13 HCC cases)	REACH-B (406 patients; 11 HCC cases)	Modified REACH-B (159 patients; 3 HCC cases)	Hepascore-5-year HCC liver outcome (169 patients; 4 HCC cases)
Cut-off for screening	≥10	≥9	≥9	≥9	≥1% 5-year risk
Sensitivity	92.3%	92.3%	45.5%	100%	100%
Specificity	46.5%	46.2%	72.9%	79.5%	60.6%
Positive predictive value	4.2%	4.1%	4.5%	8.6%	5.8%
Negative predictive value	99.6%	99.6%	98.0%	100%	100%
% of patients screened	54.4%	54.7%	27.6%	22.0%	40.8%

Disclosures: Thisuri Jayawardena: Nothing to Disclose, Luis Calzadilla Bertot: Nothing to Disclose, Joanne Bunney: Nothing to Disclose, Joanne Vallve: Nothing to Disclose, Zein Salim: Nothing to Disclose, Leon Adams: Novo Nordisk: Advisor, SCL Behring: Advisor, Pfizer: Advisor, Gary Jeffrey: Nothing to Disclose, Gerry MacQuillan: Nothing to Disclose

1280 | HEPATITIS B SCREENING AND VACCINATION RATES AT RUSH HEPATOLOGY CLINIC: A RETROSPECTIVE REVIEW

Caroline Wang[1] Dauris Rosario[1] Nitika Agrawal[1] Jessica Strzepka[1] Anuhya Gampa[2]

[1]Rush University Medical Center, [2]Rush University Mecial Center

Background: Hepatitis B is viral infection that puts patients at risk of developing liver cirrhosis, hepatocellular cancer and acute liver failure. Current guidelines for hepatitis B screening and vaccination target screening both symptomatic patients and asymptomatic patients at high risk for the infection. Despite this, up to 60% of hepatitis B infected persons remain unaware of their infection and up to 25% will die prematurely from related complications. This project aims to determine hepatitis B screening and vaccination rates at Rush Hepatology Clinic to identify areas for improvement in the primary prevention of this disease. **Methods:** We determined hepatitis B screening and vaccination rates of 357 new patients at Rush Hepatology Clinic from September 2022 to March 2023 and investigated correlation of these rates with hepatologist, liver disease diagnosis, severity of liver disease, and/or patient demographics. **Results:** 37% of all new patients were screened at the initial office visit while 27% did not undergo screening and 32% had been screened prior to their new patient visit. Of all patients screened, 28% were immune while 49% were non-immune. About 9% had active hepatitis B infection and 14% had unknown hepatitis B immunity. Only 18% of non-immune patients were immunized at follow-up visits. Less than 3% of patients obtained screening serologies at subsequent follow-up visits. The biggest factor

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correlated with screening and immunization rates was the provider. Similar rates of screening and vaccination appeared irrespective of liver disease diagnosis, severity of liver disease and patient age, sex, race and primary language. **Conclusion:** About one third of patients did not undergo screening; of those screened, roughly half were non immune. More than 80% of these non-immune patients moreover did not undergo immunization at follow-up visits. Additionally, 14% of patients had unknown immunity status despite having other hepatitis B serologies ordered, and chances of screening at followup visits was low. This study underscores gaps in care in the primary prevention of hepatitis B and will guide future interventions in increasing screening and immunization rates for all new patients at Rush Hepatology Clinic.

Disclosures: Caroline Wang: Nothing to Disclose, Dauris Rosario: Nothing to Disclose, Nitika Agrawal: Nothing to Disclose, Jessica Strzepka: Nothing to Disclose, Anuhya Gampa: Nothing to Disclose

1281 | PEGINTERFERON ALPHA-2B BASED ANTIVIRAL THERAPY AS AN EFFECTIVE TREATMENT OPTION FOR FUNCTIONAL CURE IN INACTIVE HEPATITIS B SURFACE ANTIGEN CARRIERS: A PROSPECTIVE, MULTICENTER, RANDOMIZED CONTROLLED TRIAL

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Background: The aim of this study was to investigate the efficacy and safety of peginterferon alpha-2b (PegIFNα-2b) based treatment for inactive hepatitis B surface antigen carriers (IHCs), and explore the factors associated with HBsAg loss. **Methods:** This was a prospective, multicenter, randomized controlled trial (ChiCTR2200059576). 240 IHCs were randomized (2:1:1) into three groups, where group 1 received continuous treatment with PegIFNα-2b monotherapy or combined with TAF, group 2 received intermittent treatment with PegIFNα-2b monotherapy or combined with TAF, and group 3 was a control group without antiviral therapy. The treatment period was 96 weeks and the primary outcome was HBsAg loss rate. **Results:** By April 2024, 261 patients had been screened and 242 were enrolled. The average age was 42 years and 59.5% were male. The median baseline HBsAg and HBV DNA levels were 80 and 214 IU/mL, respectively. 26.4% had undetectable HBV DNA and 27.3% also had steatohepatitis. Baseline hepatic histopathological examination was completed in 54 IHCs, of which 3 (5.6%) had an inflammation degree (G) ≥ 2, and 5 (9.3%) had a fibrosis stage (F) ≥ 2. A total of 69 IHCs completed 48 weeks of treatment. In group 3, only 1 patient achieved virological response (VR, HBV DNA < 10 IU/mL) at week 48, and no patient achieved HBsAg loss. Group 1 and 2 achieved an overall VR of 94.83% (55/58) and a cumulative HBsAg loss rate of 38.8% (26/67) at week 48. Although the cumulative HBsAg loss rate at week 48 was higher in group 1 than group 2, the difference was not statistically significant (41.7% vs. 31.6%, $P > 0.05$). IHCs with baseline HBV DNA<10 IU/mL treated with PegIFNα-2b monotherapy had higher cumulative HBsAg loss rates at weeks 24 and 48 than IHCs with baseline HBV DNA ≥ 10 IU/mL treated with PegIFNα-2b+TAF (week 24: 35.7% vs. 19.3%, $P = 0.076$; week 48: 55.6% vs. 32.7%, $P = 0.080$). Lasso regression analysis identified baseline HBsAg levels as independent predictors of HBsAg loss at weeks 24 and 48. Patients with baseline HBsAg < 100 IU/mL and ≥ 100 IU/mL had HBsAg loss rates of 36.8% and 9.3% ($P < 0.001$) at week 24, and 55.6% and 19.4% ($P = 0.002$) at week 48, respectively. **Conclusion:** High HBsAg loss rates can be achieved through PegIFNα-2b based therapies, whether continuous or intermittent for IHCs, with an overall cumulative HBsAg loss rate of 38.8% after 48 weeks of treatment. Patients with baseline HBsAg < 100 IU/mL achieved HBsAg loss more frequently compared to those ≥ 100 IU/mL.

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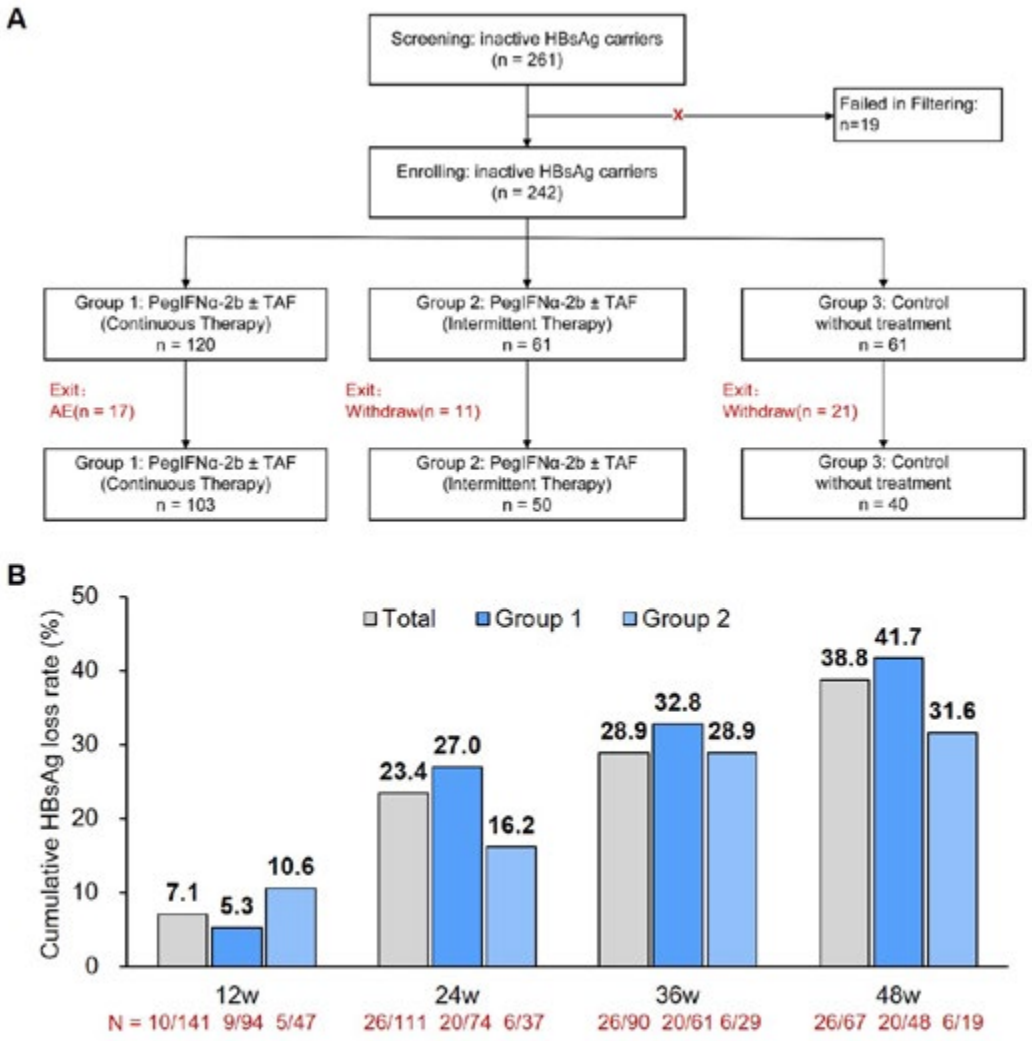

Figure 1. A: Study design and flow chart; B: Cumulative HBsAg loss rates at different time points among IHCs with treatment of PegIFNα-2b±TAF. Group 1: PegIFNα-2b±TAF continuous therapy; Group 2: PegIFNα-2b±TAF intermittent therapy; Total: Group 1 + Group 2.

Disclosures: Shan Ren: Nothing to Disclose, Sujun Zheng: Nothing to Disclose, Jing ZHAO: Nothing to Disclose, Yao Xie: Nothing to Disclose, Minghui Li: Nothing to Disclose, Junliang Fu: Nothing to Disclose, Xinyue Chen: Nothing to Disclose

1282 | HIGHER CIRCULATING CCR7LOPD-1HI FOLLICULAR HELPER T CELLS AND LOWER HBCRAG INDICATE DURABLE CLINICAL CURE AFTER PEGIFN&ALPHA;-2B-BASED THERAPY IN PATIENTS WITH CHB

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Background: In this study, we aimed to identify biomarkers associated with recurrent after clinical cure based on PegIFNα-2b therapy in patients with CHB. **Methods:** A bidirectional cohort of 358 clinical cure patients was established. HBV markers, plasma cytokines and immunological biomarkers were examined dynamically at time of treatment cessation (EOT) and during follow-up (EOF). Recurrence (R) was defined as the reappearance of HBsAg, HBV DNA, or both during EOF. Non-recurrence (NR) was defined as sustained HBsAg loss. **Results:** Out of 358 patients, 39 (10.89%) had experienced recurrent during EOF, with patients in R group being older

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(43.00±11.67 vs. 33.93±9.49, P < 0.001). After 1:2 propensity score matching (PSM), 16 in R and 32 in NR group were included. The level of anti-HBs at EOT was significantly higher in the NR group (2.97 log_{10} IU/mL vs. 2.42 log_{10} IU/mL, P=0.03), while the HBcrAg level in the R group was higher (3.45±0.94 log_{10} U/mL vs 2.63±0.80 log_{10} U/mL, P=0.003). Of the 48 patients, 35 had anti-HBs levels □ 100 IU/mL. Among these, 8 patients with HBcrAg>2.78 log_{10} U/mL experienced a 100% recurrent rate (8/8). Conversely, none of the patients with anti-HBs □ 100 IU/mL and HBcrAg □ 2.78 log_{10} U/mL had a recurrence, resulting in a 0% recurrent rate (0/27) (Figure 1A). The levels of sCTLA-4, sPD-1, and sTIM-3 were significantly higher in R group both at EOT and EOF (P<0.005), HBcrAg showed a significant positive correlation with sCTLA-4, sPD-1 at EOT (r=0.452, P=0.001; r=0.375, P=0.009). Compared to R patients, these NR patients showed maintained higher proportions of follicular helper T cells (EOT: 12.52 vs. 8.78, P=0.008; EOF:11.38 vs. 8.29, P=0.008), a markedly higher proportion of CCR7^{lo}PD-1^{hi} follicular helper T Cells at EOT (9.4% vs. 4.5%, P=0.009), and a significantly increased expression of IL-21 on CCR7^{lo}PD-1^{hi} Tfh cells in NR patients from 42.86% at EOT to 62.5% at EOF (p=0.017) (Figure 1B). Among all the patients, the frequency of CCR7^{lo}PD-1^{hi} Tfh cells at EOT was significantly positively correlated with the levels of anti-HBs and anti-HBc (P=0.015, r=0.392; P=0.049, r=0.322). **Conclusion:** Higher circulating CCR7^{lo}PD-1^{hi} Tfh cells and lower HBcrAg indicate durable clinical cure after PegIFNα-2b-based therapy in CHB patients. Notably, serum HBcrAg levels showed a significant positive correlation with sCTLA-4 and sPD-1. Additionally, patients who experienced a recurrence had insufficient production of IL-21 by CCR7^{lo}PD-1^{hi} Tfh cells.

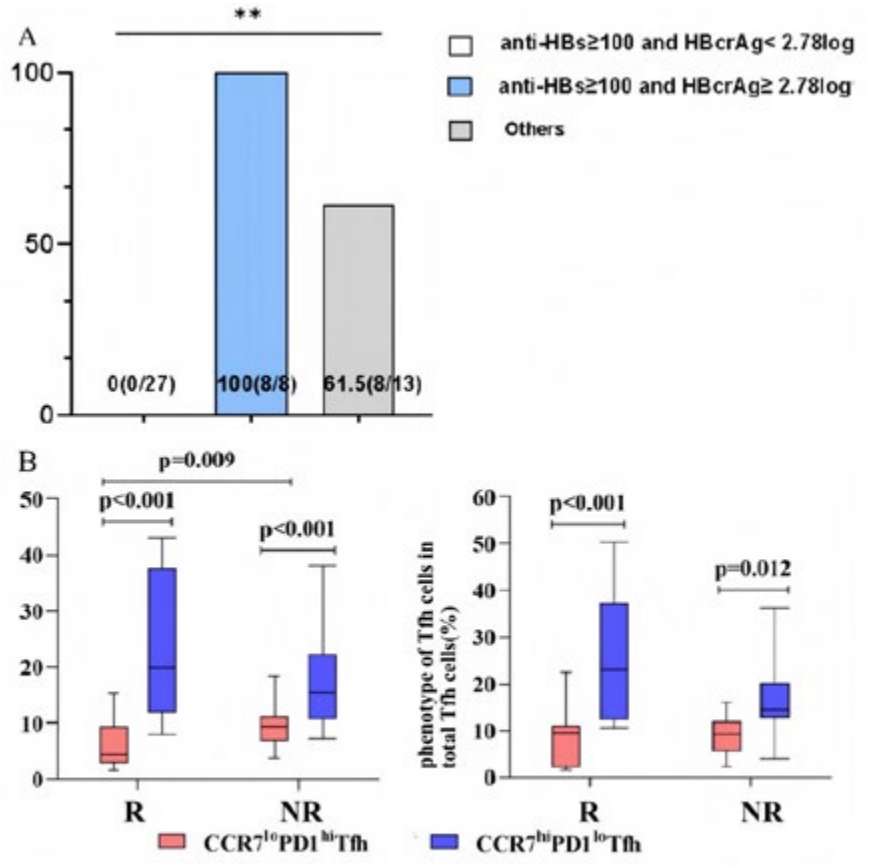

Figure 1. A: The recurrent rate among all patients with different anti-HBs and HBcrAg. B: The percentage of CCR7^{lo}PD-1^{hi} Tfh cells and CCR7^{hi}PD-1^{lo} Tfh cells in Tfh cells among two groups at EOT and EOF.

Disclosures: Shan Ren: Nothing to Disclose, Xiao Lin: Nothing to Disclose, Sujun Zheng: Nothing to Disclose, Xinyue Chen: Nothing to Disclose

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1283 | LITTLE LIVER DISEASE PROGRESSION AFTER LONG-TERM DRUG WITHDRAWAL IN HBEAG POSITIVE POSTPARTUM WOMEN

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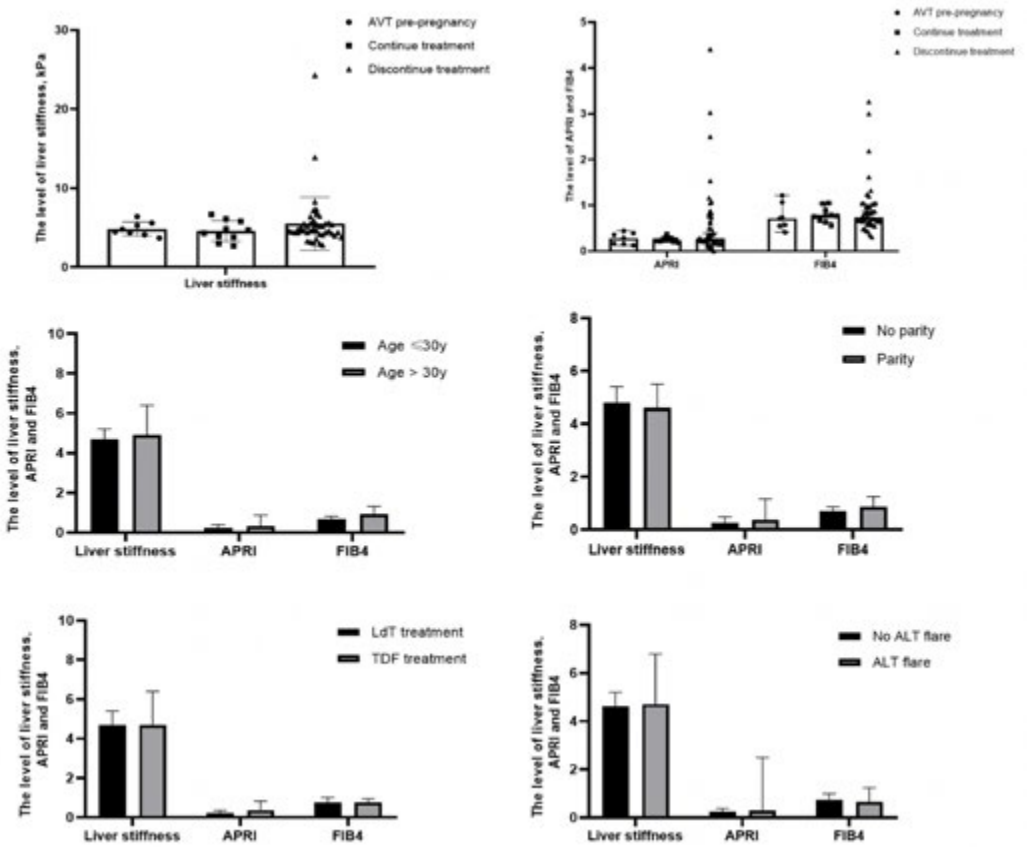
[1]*Chongqing Medical University*

Background: Previous studies have provided fewer data on the effects of prophylactic antiviral intervention on the mother in pregnant women with CHB. The discontinuation of treatment postpartum remains controversial and data on the progression of liver disease after treatment discontinuation postpartum are very lacking. **Methods:** We conducted a retrospective-prospective real-world study to explore the progression of liver disease in HBeAg positive postpartum women. Finally, sixty HBeAg positive postpartum women discontinuing treatment for more than six months, 10 HBeAg positive postpartum women continuing treatment after delivery and 12 HBeAg positive postpartum women received NAs treatment pre-pregnancy were eventually included. **Results:** The baseline characteristics between three groups are comparable in terms of age, platelets count, APRI and FIB-4. The median follow-up time for postpartum women discontinuing treatment was 28.8 months (6.0 - 89.2), which was comparable with the 27.6 months (6.6 - 111.7) for postpartum women continuing treatment after delivery and 33.0 months (6.0 - 75.5, p = 0.963) for postpartum women received NAs treatment pre-pregnancy. No postpartum women developed to liver cirrhosis or hepatocellular carcinoma in three groups and only 2 patients developed to liver fibrosis in patients discontinuing treatment postpartum. The liver stiffness value was 4.75 kPa (2.8 - 24.3) in postpartum women discontinuing treatment, 4.1 kPa (2.7 - 6.7) in postpartum women continuing treatment after delivery and 4.65 (3.7 - 6.4) in postpartum women received NAs treatment pre-pregnancy, which was comparable in three groups (p = 0.360). Moreover, APRI and FIB-4 were comparable in three groups (p > 0.05). Subgroup analysis indicated that the liver stiffness, APRI and FIB were also comparable regarding age, labour history, treatment regimen and ALT flare in patients discontinuing treatment postpartum. **Conclusion:** It is relatively safe for HBeAg positive postpartum women to discontinue NAs treatment after delivery, and age over 30 years and postpartum hepatitis did not increase the risk of liver disease progression.



Disclosures: Qiao Tang: Nothing to Disclose, Chunrui Wang: Nothing to Disclose, Xiaoqing Liu: Nothing to Disclose, Peng Hu: Nothing to Disclose

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1284 | FUNCTIONAL CURE AND PREDICTION ANALYSIS OF PEGYLATED INTERFERON ALPHA-2B IN HBEAG NEGATIVE CHRONIC HEPATITIS B PATIENTS WITH NORMAL ALT (ICE-BREAKING PROJECT IN CHINA): AN INTERIM ANALYSIS UPDATE

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Background: In China, the proportion of Hepatitis B e antigen (HBeAg) negative chronic hepatitis B (CHB) patients is gradually increasing, which is related to the pre-C region mutation of long-term HBV infection. The disease progression of HBeAg negative CHB patients is fast, a large proportion of them have moderate or advanced liver inflammation or fibrosis, even if alanine aminotransferase (ALT) is normal, which requires timely antiviral treatment. The purpose of this study was to analyse the efficacy of pegylated interferon alpha-2b (PegIFNα-2b) in HBeAg negative CHB patients with normal ALT, and to explore the predictive factors of virological and serological responses. **Methods:** This is a multi-center, prospective, non-interventive, real-world clinical study conducted in China, involving 20 hospitals in 12 provinces or municipalities, which enrolled CHB patients with age of 18-60 years, Hepatitis B surface antigen (HBsAg) positive for more than 6 months, HBeAg negative, HBV DNA > 20 IU/mL and normal ALT, without antivirus treatment history. PegIFN α-2b 180 μg/week was applied on a voluntary basis. Examinations were performed every 12 weeks during treatment to monitor antiviral efficacy and adverse effects. The treatment strategy is adjusted according to the virological and serological response every 24 weeks, the total treatment course is not exceeded 96 weeks. **Results:** A total of 249 patients were currently enrolled, and statistical analysis only be performed on 120 patients who completed PegIFNα-2b treatment. 72 (60.0%) were male, with an average age of 39.76 ± 8.28 years (21 - 60 years). The median baseline HBV DNA and HBsAg were 6.87×10^2 IU/mL (1.00×10^1 ~ 7.62×10^6) and 297.91 IU/mL (0.12 ~ 32828.22) respectively. The mean duration of PegIFNα-2b treatment was 12.78 months. 43 patients (35.83%) achieved HBsAg loss, and their baseline HBsAg levels were significantly lower than those who did not achieve HBsAg loss (381.29 ± 827.18 vs. 1872.31 ± 4102.32, p < 0.001). 23 patients achieved HBsAg loss after a short course of 6 - 9 months, with lower baseline HBsAg levels compared to those achieved HBsAg loss after a course of ≥ 12 months (96.34 ± 141.54 vs. 708.98 ± 1130.47, p < 0.001) (Figure 1). Furthermore, HBsAg loss rate increased to52.38% in patients with baseline HBV DNA < 1000 IU/mL and HBsAg < 500 IU/mL, and 66.67% in those with baseline HBV DNA < 100 IU/mL and HBsAg < 100 IU/mL. These patients all experienced functional cure with a short course of PegIFNα-2b treatment. **Conclusion:** HBeAg negative CHB patients with normal ALT can achieve a high rate of functional cure by PegIFNα-2b therapy, especially for those with low baseline HBV DNA and HBsAg levels, only a short course of PegIFNα-2b treatment is required.

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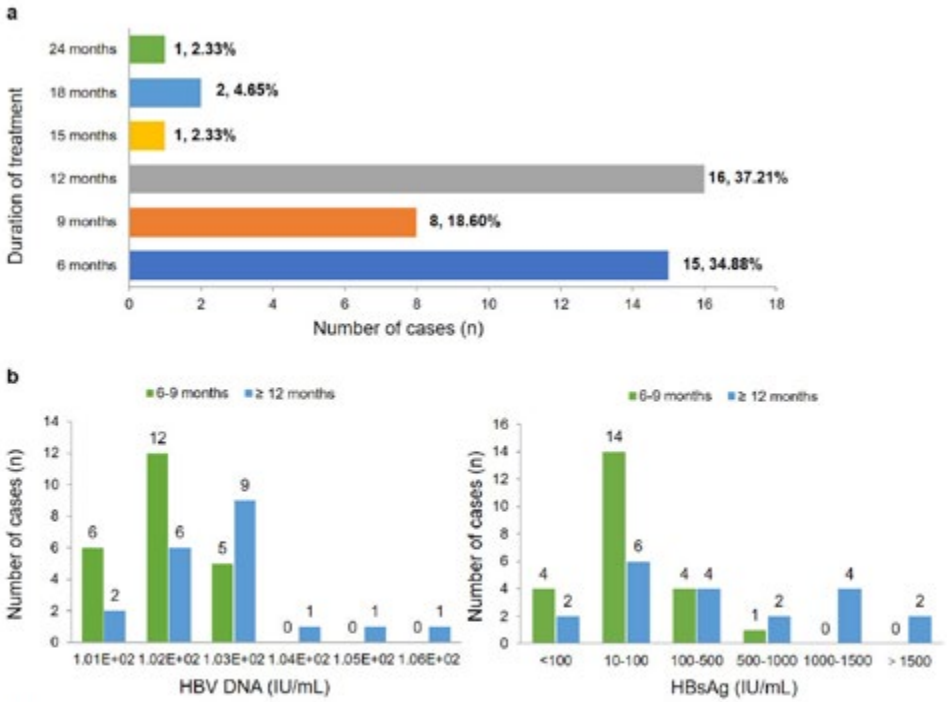

Figure 1.
a. Duration of PegIFNα-2b treatment in patients achieved HBsAg loss.
b. Baseline HBV DNA and HBsAg distribution in patients achieved HBsAg loss after different courses of treatment.

Disclosures: Chong Zhang: Nothing to Disclose, Dawu Zeng: Nothing to Disclose, Dachuan Cai: Nothing to Disclose, Xiulan Xue: Nothing to Disclose, Lingyi Zhang: Nothing to Disclose, Baojun Song: Nothing to Disclose, Yufeng Gao: Nothing to Disclose, Yan Huang: Nothing to Disclose, Jia Shang: Nothing to Disclose, Xiaofeng Wu: Nothing to Disclose, Ying Zhang: Nothing to Disclose, Hua Jin: Nothing to Disclose, Hui Chen: Nothing to Disclose, hong Tang: Nothing to Disclose, Xiaobo Lu: Nothing to Disclose, Yujuan Guan: Nothing to Disclose, Feng Min: Nothing to Disclose, Liang Xu: Nothing to Disclose, Gang Li: Nothing to Disclose, Zhenguang Wang: Nothing to Disclose, Xiaoguang Dou: Nothing to Disclose

1285 | ASSESSMENT OF CLINICAL OUTCOMES IN HBSAG POSITIVE INDIVIDUALS COMPARED TO PATIENTS WHO ACHIEVED HBSAG LOSS AS DETERMINED BY CONVENTIONAL OR ULTRASENSITIVE TESTING FOR HBSAG

Golasa Samadi Kochaksaraei[1] Emma Lee[2] Carla Osiowy[3] Lindsey Lamboo[2] Karen Doucette[4] Curtis Cooper[5] Magdy Elkhashab[6] Hin Hin Ko[7] Alnoor Ramji[7] Edward Tam[8] David Wong[9] Scott Fung[9] Pam Crotty[1] Stephen Congly[1] Carla Coffin[1]

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Background: Individuals with chronic hepatitis B (CHB) who achieve hepatitis B surface antigen (HBsAg) loss (i.e., a functional cure) show improved clinical outcomes. Quantitative HBsAg (qHBsAg) is used to inform treatment decisions; more recently developed ultrasensitive HBsAg assays are proposed as a cost-effective prognostic biomarker. Occult HBV infection (OBI) is defined as presence of replication competent HBV DNA (episomal cccDNA in liver) and/or HBV DNA in blood in persons who test HBsAg negative by standard commercial assays, but OBI diagnosis relies on HBsAg assay sensitivity. In this multi-site study, we recruited HBeAg negative subjects who were HBsAg positive, or who had recently cleared HBsAg (functional cure) and evaluated for demographic, clinical, and virological outcomes, including ultrasensitive HBsAg assays.
Methods: Individuals with low level HBsAg (<500 IU/ml) or after HBsAg loss were prospectively enrolled across 6 participating clinics in Canada. Clinical outcomes including liver fibrosis using FibroScan was collected and

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available serum was tested for HBsAg with standard (lower limit of detection LLOD 5 mIU/ml, Elecsys II) and ultrasensitive qualitative (NEXT assay, >10 fold limit of detection), with confirmation ongoing. HBV genotype was determined by PCR and Sanger sequencing. **Results:** In 107 subjects enrolled, 97 provided blood for research (1-3 time-points ~6-12 months apart, n=172 samples). Based on conventional HBsAg assays, 80% (86/107) subjects were HBsAg negative (in those with seroconversion, the median antibody to HBsAg titers was 42.06 IU/mL, IQR: 5.6-118.4) and 19.6% (21/107) were HBsAg positive (median qHBsAg levels 61 IU/mL, IQR: 4.8-302.7). Compared to the HBsAg negative group (n=86), the HBsAg positive group (n=21) were younger (median 59.0 vs. 51.0 years, p=0.01) but no differences were found in gender, ethnicity, Canadian-born status, prior HBV treatment (38.9% vs. 28.4% p=0.4), ALT (18.5 IU/mL [14-24] vs 21 IU/ml [IQR 17-30], p=0.2), and FibroScan (4.9 [4-6.2]) vs 4.8 kPa [4.0-6.1]). In 21.6 % (21/97; or 24/133 samples) who tested HBsAg negative by standard assay (Elecsys II Quant) were positive using ultrasensitive NEXT assay (median qHBsAg S/CO of 1.78 [IQR 1.3-2.6]). **Conclusion:** In 107 individuals followed for 1-3 years, either with low qHBsAg levels or HBsAg clearance, there was no significant differences in clinical outcomes. Notably, 21.6% of individuals with resolved HBV infection, were positive by ultrasensitive HBsAg test. The data is potentially useful in diagnosis of OBI and counselling after functional cure, including reactivation risk with potent immunosuppression.

Disclosures: Golasa Samadi Kochaksaraei: Nothing to Disclose, Emma Lee: Nothing to Disclose, Carla Osiowy: Nothing to Disclose, Lindsey Lamboo: Nothing to Disclose, Karen Doucette: Roche: Grant/Research Support, GSK: Grant/Research Support, Altimmune: Grant/Research Support, Curtis Cooper: Nothing to Disclose, Magdy Elkhashab: Nothing to Disclose, Hin Hin Ko: Nothing to Disclose, Alnoor Ramji: Nothing to Disclose, Edward Tam: Nothing to Disclose, David Wong: Nothing to Disclose, Scott Fung: Nothing to Disclose, Pam Crotty: Nothing to Disclose, Stephen Congly: Nothing to Disclose, Carla Coffin: Grant/Research Support relationship with Gilead Sciences; Has not ended; Grant/Research Support relationship with Janssen Pharmaceuticals; Has ended; Funds paid to the University of Calgary relationship with GSK; Has not ended; Grant/Research Support relationship with Riche Pharmaceuticals; Has not ended; Fund paid to the University of Calgary relationship with Altimmune Pharmacueticals; Has ended; Speaking and Teaching relationship with GSK; Has ended

1286 | EARLY OFF-TREATMENT HBCRAG AND ANTI-HBC LEVELS IDENTIFY PATIENTS AT HIGH RISK OF SEVERE ALT FLARES AFTER NUCLEOS(T)IDE ANALOGUE WITHDRAWAL – A POOLED ANALYSIS OF TWO PROSPECTIVE STUDIES

Edo Dongelmans[1] Jordan Feld[2] Andre Boonstra[1] Sylvia Brakenhoff[1] David Wong[2] Colina Yim[2] Mark Claassen[3] Pieter Honkoop[4] Bettina Hansen[1] Robert De Man[1] Scott Fung[2] Thomas Berg[5] Florian van Bömmel[5] Harry Janssen[6] Milan Sonneveld[1]

[1]Erasmus University Medical Center, [2]Toronto General Hospital, [3]Rijnstate Hospital, [4]Albert Schweitzer Hospital, [5]Leipzig University Medical Center, [6]Erasmus University Medical Centre

Background: Severe flares (ALT ≥10xULN) are a well-recognised adverse outcome after nucleos(t)ide analogue (NA) cessation and may precipitate liver failure. Identification of patients at risk for severe flares is therefore of major importance. The aim of our study was to assess the association between HBcrAg and anti-HBc levels with severe flares after NA withdrawal. **Methods:** We used data from two prospective studies of NA cessation conducted in the Netherlands and Canada. Patients were eligible for NA withdrawal based on EASL criteria. We measured HBcrAg and anti-HBc levels at end of treatment (EOT) and follow-up week 6 (FUW6) and assessed associations with severe ALT flares during follow-up. **Results:** We analysed 78 patients with a mean age of 49 (±9.7) years, 16 (21%) were Caucasian and most were treated with Tenofovir (TDF) (65%). At EOT, mean HBsAg-, HBcrAg- and anti-HBc levels were 2.88 (±0.75), 3.36 (±0.86) and 2.38 (±0.50) log IU/mL, respectively. During follow-up, 22 patients (28%) developed a severe flare, and 29 (37%) patients were retreated. At EOT, higher HBcrAg levels (aOR:1.97, p=0.05; 47% severe flare if ≥4log, 19% if <3log, p=0.036), lower anti-HBc (aOR:0.29, p=0.036; 50% if <2log, 11% if ≥3log, p=0.033) and HBcrAg/anti-HBc ratio (aOR:3.17, p=0.015; 58% if ≥2.0, 14% if <1.5, p<0.001) were associated with an increased risk of severe flares, adjusted for HBsAg. At FUW6, mean HBcrAg and anti-HBc levels were 3.72 (±1.10) and 2.59 (±0.61) log IU/mL. Higher HBcrAg (aOR:2.91, p=0.035; 83% if ≥5log, 4% if <3log, p<0.001), lower anti-HBc (aOR:0.46, p=0.29; 50% if <2log, 0% if ≥3log, p=0.003) and higher HBcrAg/anti-HBc ratio (aOR:2.19, p=0.048; 52% if ≥1.75, 8% if <1.75, p<0.001) were associated with an increased risk of severe flares, adjusted for HBV DNA and ALT. **Conclusion:** Both HBcrAg and anti-HBc levels are promising new biomarkers for the prediction of severe flares after NA withdrawal. HBcrAg level

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≥5log, anti-HBc levels <2log and HBcrAg/anti-HBc ratio ≥1.75 at FUW6 identify patients with such a high risk of severe flares that early retreatment should be considered.

Disclosures: Edo Dongelmans: Nothing to Disclose, Jordan Feld: Mirum: Consultant, AbbVie, Bluejays, Gilead, Janssen, GSK, Roche, VIR Roche: Consultant, Bluejays: Consultant, Gilead: Consultant, Janssen: Consultant, GSK: Consultant, Roche: Consultant, VIR Biotechnology: Consultant, Altimmune, AbbVie, Gilead, Jannsen, GSK, Roche, VIR Bio: Grant/Research Support, Andre Boonstra: Gilead: Grant/Research Support, Janssen Pharma: Grant/Research Support, GSK: Grant/Research Support, Fujirebio: Grant/Research Support, Sylvia Brakenhoff: Nothing to Disclose, David Wong: Nothing to Disclose, Colina Yim: Gilead Canada: Speaking and Teaching, Abbvie Canada: Consultant, Mark Claassen: Nothing to Disclose, Pieter Honkoop: Nothing to Disclose, Bettina Hansen: Nothing to Disclose, Robert De Man: roche diagnostics: Grant/Research Support, Scott Fung: Nothing to Disclose, Thomas Berg: Nothing to Disclose, Florian van Bömmel: VIR Biotechnology: Independent Contractor, Harry Janssen: Gilead Sciences: and consultant, Gilead Sciences: Grant/Research Support, GlaxoSmithKline: Grant/Research Support, Janssen: Grant/Research Support, Roche: Grant/Research Support, Vir Biotechnology Inc.: Grant/Research Support, Aligos: Consultant, Gilead Sciences: Consultant, GlaxoSmithKline: Consultant, Grifols: Consultant, Roche: Consultant, Vir Biotechnology Inc: Consultant, Precision Biosciences: Consultant, Milan Sonneveld: Nothing to Disclose

1287 | PLASMA HEPCIDIN AND HAPTOGLOBIN CONCENTRATION PREDICTS PEGYLATED INTERFERON A-2B TREATMENT RESPONSE IN HBEAG-NEGATIVE CHRONIC HEPATITIS B PATIENTS ◆

Jing Liang[1] *Fei Tang*[1] *Fengmei Wang*[1]

[1]*Tianjin Third Central Hospital*

Background: Studies have shown that nucleoside (acid) analogs sequenced with interferon can improve HBsAg elimination, while how to improve the efficacy of PEG-IFN is still not completely clear. By combining proteomic studies of chronic hepatitis B (CHB) patients, we aim to search for serum differential proteins in patients of CHB functional cure, explore early predictive markers of functional cure of CHB patients, and provide better predictive indicators for functional cure of CHB. **Methods:** A cohort study was conducted on 278 patients with HBeAg-negative chronic hepatitis B treated with pegylated interferon a-2b combined with nucleos(t)ide analogs (NAs)) for 48 weeks. After 48 weeks of treatment, 65 patients achieved functional cure and 213 cases did not. Plasma samples were randomly selected from 40 CHB patients who were cured with interferon a-2b and 40 patients who were not cured. The serum levels of Hepcidin and Haptoglobin in patients were measured and logistic regression analysis was conducted to examine the influence of baseline HBsAg, plasma Hepcidin and haptoglobin on HBsAg clearance. Utilizing ROC curve analysis, a treatment equation was formulated to predict HBsAg clearance, and baseline plasma samples from 10 cured and uncured patients were selected for subsequent validation. **Results:** The baseline plasma Hepcidin concentration in cured patients was higher than that in patients with uncured(35.64 ng/mL vs 16.05 ng/mL,P < 0.001).The mean baseline plasma Haptoglobin concentration in cured patients was lower than that in patients with uncured (5.58 ng/mL vs 8.57ng/mL,P<0.001).Based on the baseline plasma concentrations of Hepcidin and Haptoglobin in CHB patients, and combined with the corresponding baseline HBsAg levels, a regression equation was formulated.(Logit (X)=7.038+2.004 × Hepcidin 0.192 × Haptoglobin 1.668 × baseline HBsAg). The accuracy of predicting cure was 97.6%, the accuracy of predicting uncured was 94.3%. A test dataset comprising plasma samples from 10 chronic hepatitis B patients, both CHB cured and uncured was selected. The baseline levels of HBsAg, hepcidin, and haptoglobin in these patients were inserted into the formula(Logit (X) = 7.038 + 2.004 ×Hepcidin - 0.192 × haptoglobin - 1.668 × baseline HBsAg). **Conclusion:** The baseline plasma levels of Hepcidin and Haptoglobin in CHB patients treated with NAs can serve as early predictive indicators of sequential PEG-IFN treatment efficacy. The regression equation based on baseline Hepcidin, Haptoglobin and HBsAg levels has the potential to enhance the predictive accuracy of CHB functional cure in patients treated with NAs combined with PEG-IFN.

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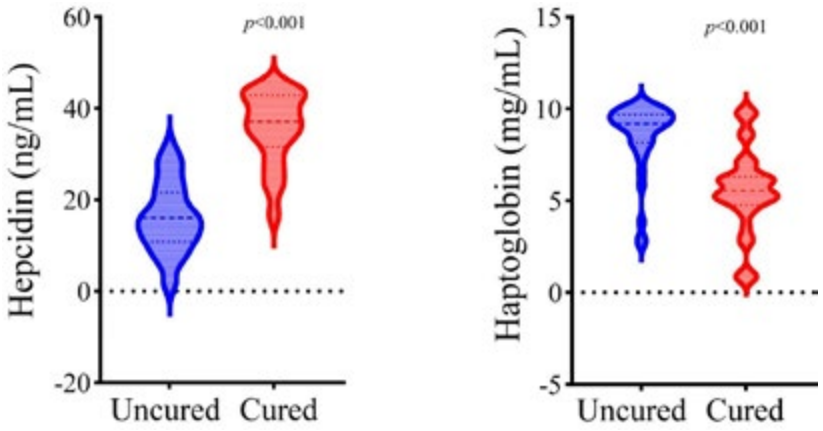

Disclosures: Jing Liang: Nothing to Disclose, Fei Tang: Nothing to Disclose, Fengmei Wang: Nothing to Disclose

1288 | PHARMACOKINETIC/PHARMACODYNAMIC MODELLING OF RG6084 EFFECTS ON HEPATITIS B SURFACE ANTIGEN AND ALANINE TRANSAMINASE TO INFORM PHASE 2 DOSING REGIMEN SELECTION

Sijie Lu[1] Sylvie Retout[2] Vedran Pavlovic[3] Gregory Hooper[3] Gemma Attley[4] Annabelle Lemenuel-Diot[5]

[1]China Innovation Centre of Roche (CICOR), [2]Roche pRED, [3]Roche Products, [4]Hoffmann-La Roche Inc, [5]F. Hoffman-La Roche AG.

Background: RG6084 is a liver-directed locked nucleic acid oligonucleotide that induces RNaseH-mediated degradation of PD-L1 mRNA. In the Phase 1 study, RG6084 induced reductions in hepatitis B surface antigen (HBsAg) were often accompanied by parallel transient increases in alanine aminotransferase (ALT), which indicated suboptimal tolerability towards the highest explored regimen. Optimization of the dosing regimen was desirable, and a pharmacokinetic/pharmacodynamic (PK/PD) model was developed to simulate HBsAg and ALT for candidate Phase 2 dosing regimens. **Methods:** The population PK model was used to describe the plasma concentration and predict liver concentration time-course profiles. The PK/PD model estimated the effect of the liver concentration on HBsAg and ALT as two separate mechanisms of action. For the effect on HBsAg, a viral kinetic approach was utilised to describe the production of HBsAg and the RG6084 effect was tested on the HBsAg production/elimination. For the effect on ALT, an empirical PK/PD approach was utilised and the RG6084 effect was tested on the ALT production/elimination. Using this PK/PD model, HBsAg and ALT time profiles were simulated for 10,000 virtual subjects under each dosing regimen. **Results:** RG6084 liver exposure simulations were performed for 7 candidate dosing regimens, and 3 regimens were selected for further assessment. PK/PD model accurately captured the individual time course of HBsAg and ALT. RG6084 effect was included via a faster clearance of the infected hepatocytes and an increase of ALT production. The estimated ALT EC50 was found to be greater than the HBsAg EC50, which enabled identification of an optimised dosing regimen. Further, HBsAg and ALT probability simulation confirmed the appropriateness of the identified dosing regimen. The candidate dosing regimen was predicted to result in a clinically meaningful reduction[1] [2] in the proportion of subjects that exceed the ALT > 5x ULN threshold, and still ensured an appreciable proportion of subjects achieve > 0.5 log10 IU/mL decline in HBsAg levels. **Conclusion:** The developed PK and PK/PD model identifies separate exposure-response curves for ALT and HBsAg, and predicts the proportion of subjects that will exceed a defined ALT and HBsAg threshold. The model was successfully utilised in RG6084 Phase 2 dosing regimen selection[1] [2], whereby the chosen regimen is anticipated to meaningfully reduce the ALT liability without overtly impacting the HBsAg response.

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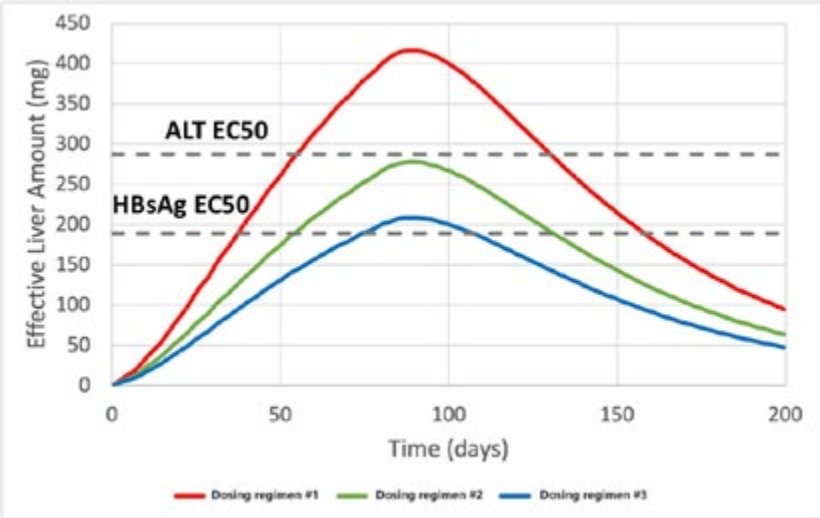

Disclosures: Sijie Lu: Nothing to Disclose, Sylvie Retout: Nothing to Disclose, Vedran Pavlovic: Nothing to Disclose, Gregory Hooper: Roche Products Limited: Employee, Gemma Attley: Hoffmann-La Roche Inc: Employee, Annabelle Lemenuel-Diot: Nothing to Disclose

1289 | CORE BIOMARKERS FOR EARLY DETECTION OF PRIMARY LIVER CANCER

Hien Thi Thu Nguyen[1] Duy Nguyen[2] Vang Le-Quy[3] Jakob Thomsen[1] Xuan Hoan Nghiem[4] Inge Pedersen[1] Henrik Krarup[1]

[1]Aalborg University Hospital, [2]Grinnell College, [3]Novodan ApS, [4]108 Military Central Hospital

Background: Primary liver cancer, predominantly, hepatocellular carcinoma (HCC) stands as the third leading cause of global cancer-related deaths. Despite this, no effective blood or urine tests exists for early detection and diagnosis. While many studies have reported on metabolomics-based clinical investigations to identify biomarkers of HCC, the clinical utility of these biomarkers often remains unclear. Therefore, we performed an unbiased system review and meta-analysis of published biomarkers to identify a core set with the highest performance for detection of HCC. We also conducted a prospective cohort metabolomic study to validate the findings. **Methods:** The HCCs-related metabolome profiles from human fluid samples were selected in a comprehensive search. Amanida package in R software was utilized for performing the meta-analysis. Sub-type analyses generated a consensus list of metabolites in each category was obtained. To identify the most affected pathways, metabolite set enrichment analysis (MSEA) was performed with MetaboAnalystR. Validation was done for selected metabolites using data sets from five published studies from Austria, China, Egypt, and USA; and from a metabolomic study of a cohort combining patients from Denmark and Vietnam by using four machine learning algorithms. **Results:** Out of 3526 searched studies, 74 eligible studies were identified, collectively reporting 3353 differential metabolites in HCC. Among these, 93 metabolites were dysregulated in HCCs versus controls from 52 studies; and 46 metabolites were dysregulated in HCCs versus cirrhosis (LC) from 40 studies. We selected top twenty-five dysregulated metabolites based on their performance scores. The enrichment analyses **Results:** revealed their involvement in different biological pathways such as the TCA cycle and amino acid metabolisms in the pathogenesis of HCC. **Conclusion:** This is a comprehensive metabolomic study of primary liver cancer to date where candidate biomarkers were selected from meta-analysis and validated with experimental data. Our findings suggest this metabolite panels could be used for early non-invasive diagnosis of HCC sub-types and explaining pathological pathways of HCC.

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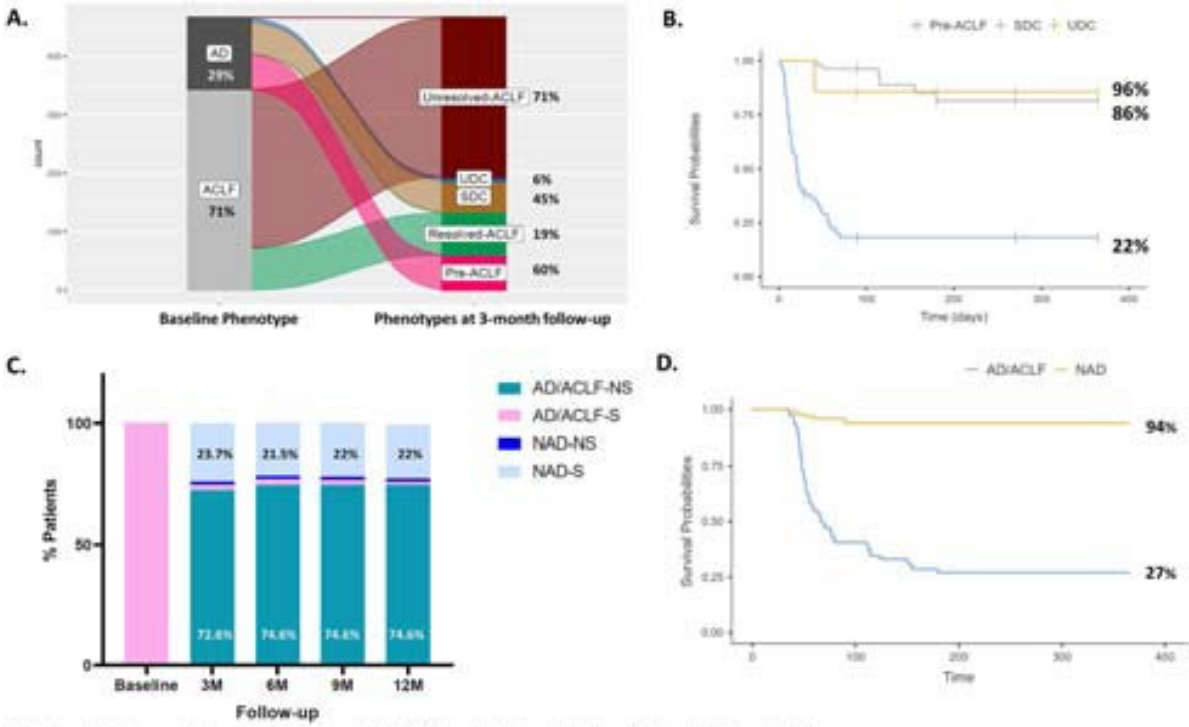

A: Sankey plot demonstrating the phenotypes of AD/ACLF patients transitioning at the end of 3-month follow-up
B: Kaplan Meier demonstrating the survival probabilities of Pre-ACLF, SDC and UDC phenotypes of AD non-ACLF patients at the end of 1-year follow-up. Interestingly, the cumulative 1-year mortality of pre-ACLF group was similar to the overall mortality observed in patients presenting with ACLF at baseline.
C: Bar plot showing the proportions of phenotypes and death during each follow-up timeframe during 1 year follow up in AD/ACLF patients
D. Kaplan Meier demonstrating the survival probabilities at end of 1-year, in patients who developed any episode of AD/ACLF compared to those who had no episode of AD [non- AD patients (NAD)] during the follow-up

Disclosures: Hien Thi Thu Nguyen: Nothing to Disclose, Duy Nguyen: Nothing to Disclose, Vang Le-Quy: Nothing to Disclose, Jakob Thomsen: Nothing to Disclose, Xuan Hoan Nghiem: Nothing to Disclose, Inge Pedersen: Nothing to Disclose, Henrik Krarup: Nothing to Disclose

1290 | COMBINATION THERAPY WITH TLR7 AGONIST TQ-A3334 AND ANTI-PD-L1 TQ-B2450 ENHANCE HBSAG DECLINE IN VIRALLY-SUPPRESSED PATIENTS WITH CHRONIC HEPATITIS B: OCEANCURE05 STUDY

Di Wu[1] Yuying Chen[2] Da Huang[2] Zhize Yuan[2] Wenyu Wu[2] Wei Yuan[2] wang peng[2] zhongnan xu[3] Shuna Wang[3] Dandan Huo[3] Man-Fung Yuen[4] Weiming Yan[2] Meifang Han[2] Qin Ning[5]

[1]Tongji Hospital, [2]Tongji Hospital, Tongji Medical College, [3]Chia Tai Tianqing Company, [4]The University of Hong Kong, [5]Huazhong University of Science and Technology

Background: TQ-A3334, a selective toll-like receptor-7 (TLR-7) agonist, can activate innate immunity against hepatitis B virus (HBV). TQ-B2450, a humanized programmed death ligand 1 (PD-L1) antibody, can restore T cells function. This study aimed to assess the safety and efficacy of the combination of nucleos(t)ide analogues (NUCs) and TQ-A3334 with or without TQ-B2450 in patients with chronic hepatitis B (CHB). **Methods:** In the OCEANcure05 study, 24 NUC-treated CHB patients were randomized to either continued NUC monotherapy (n=6), dual therapy with NUC + TQ-A3334 (1.2mg or 1.5mg once weekly) (n=9), or triple therapy with NUC + TQ-A3334 + TQ-B2450 (400mg every 3 weeks) (n=9) for 24 weeks, and followed for additional 24 weeks post-treatment. The primary endpoint was hepatitis B surface antigen (HBsAg) reduction. This trial was registered at ClinicalTrials.gov, NCT 04202653. **Results:** At the end of treatment (EOT), triple therapy resulted in numerically greater HBsAg reduction (0.45 ± 0.55 log10 IU/ml), compared to dual therapy (0.03 ± 0.16 log10 IU/ml, p=0.068) and monotherapy (0.04 ± 0.08 log10 IU/ml, p=0.094,Figure A). Similar trends were observed in the reduction of

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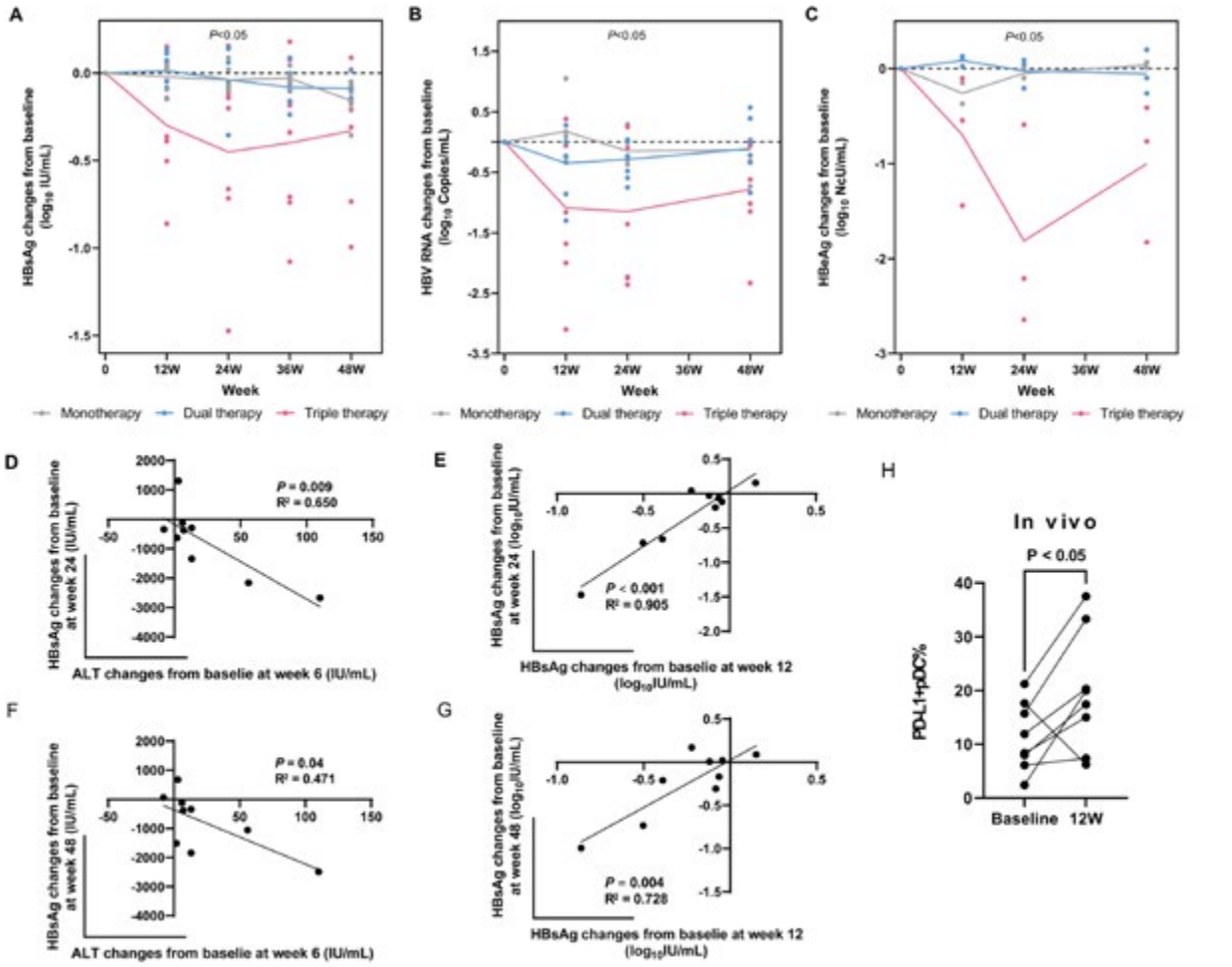
HBV RNA (1.15 ± 1.18 log10 copies/ml vs. 0.29 ± 0.32 and -0.15 ± 0.25 log10 copies/ml, respectively, Figure B) and HBeAg levels (1.81 ± 1.08 log10 national clinical unit(NcU)/ml vs. 0.02 ± 0.16 and 0.05 ± 0.07 log10 NcU/ml, respectively, Figure C). In the triple therapy group, ALT elevation at week 6 and HBsAg decline at week 12 were significantly correlated with the reduction in HBsAg levels at EOT (p=0.009 and p<0.001, respectively,Figure D-E) and at the end of follow-up (EOF) (p=0.04 and p=0.004, respectively,Figure F-G). PD-L1 expression on plasmacytoid dendritic cells was significantly increased by the TQ-A3334-containing dual therapy at week 12 (19.64%) compared to baseline(14.41%, p=0.04, Figure H). No severe adverse events occurred and combination therapy was well tolerated. **Conclusion:** The addition of PD-L1 antibody to the combination of NUC and TLR7 agonist enhanced HBsAg decline in virally-suppressed CHB patients. This effect might be attributed to the ability to counteract the upregulation of PD-L1 associated with TLR7 agonist. Early ALT elevation and HBsAg decline may predict sustained reduction in HBsAg after the triple therapy.



Mean changes of HBsAg (A), HBeAg(B) and HBV RNA (C) from baseling; ALT elevation at week 6 (D) and HBsAg decline at week 12 (E) correlated with reduction in HBsAg levels at EOT; ALT elevation at week 6 (F) and HBsAg decline at week 12 (G) correlated with reduction in HBsAg levels at EOF; (H) Increse in frquency of PD-L1 positive pDC in dual therapy group at week 12 (E). hepatitis B surface antigen, HBsAg; hepatitis B e antigen, HBeAg; programmed death ligand 1, PD-L1; end of treatment (week 24), EOT; end of follow-up (week 48), EOF;plasmacytoid dendritic cells, pDCs.

Disclosures: Di Wu: Nothing to Disclose, Yuying Chen: Nothing to Disclose, Da Huang: Nothing to Disclose, Zhize Yuan: Nothing to Disclose, Wenyu Wu: Nothing to Disclose, Wei Yuan: Nothing to Disclose, wang peng: Nothing to Disclose, zhongnan xu: Nothing to Disclose, Shuna Wang: Nothing to Disclose, Dandan Huo: Nothing to Disclose, Man-Fung Yuen: Speaking and Teaching relationship with Fujirebio Incorporation, Gilead Sciences, Roche, Sysmex Corp; Has not ended; Consultant relationship with Clear B Therapeutics, Dicerna Pharmaceuticals; Has not ended; Consultant relationship with AbbVie, Abbott Diagnotics, Aligos Therapeutics; Has not ended; Consultant relationship with Arbutus Biopharma, Arrowhead Pharmaceuticals, Assembly Biosc; Has not ended; Consultant relationship with Immunocore, Janssen, Precision BioSciences; Has not ended; Consultant relationship with Fujirebio Incorporation, GlaxoSmithKline, Gilead Sciences; Has not ended; Grant/

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1291 | RELATIONSHIP BETWEEN THE CLINICAL EFFICACY AND LYMPHOCYTE SUBSETS IN THE CLINICAL CURE ADVANAGE POPULATION OF CHRONIC HEPATITIS B WITH PEGYLATED INTERFERON ALPHA

Dan Duan[1] Lunli Zhang[1] Xiaopeng Li[1] Wang Liang[1] Qian Yang[1]

[1]Jiangxi Medical Center for Critical Public Health Events, The First Affiliated Hospital, Jiangxi Medical College, Nanchang University, Nanchang, China

Background: Pegylated interferon alpha-2b (PegIFNα-2b) serves first-line antiviral drug for treating chronic hepatitis B (CHB), functioning through the modulation of the body's immune response. Lymphocyte subsets can reflect the immune status of patients and the strength of their ability to clear the virus. We aimed to identify relevant indicators that can predict the clinical efficacy of PegIFNα-2b by comprehensively analyzing lymphocyte subsets in different patients. **Methods:** Between January 2020 and December 2023, a retrospective investigation and analysis were conducted on 67 patients diagnosed with CHB. Patients were divided into effective and ineffective groups based on whether HBsAg loss or decreased >1 $\log_{10}$ IU/ml after 24 weeks of PegIFNα-2b treatment. Lymphocyte subsets were detected by flow cytometer. Logistics regression analysis was used to identify the independent influencing factors of HBsAg loss. The receiver operating characteristic curve (ROC) was constructed, and the area under the ROC curve (AUC) was compared to analyze the predictive value of each lymphocyte subset on HBsAg loss. **Results:** A total of 67 patients with treatment advantages for CHB were included in this study. According to the definition of the effective group, there were 47 effective patients, so the clinical response rate of PegIFNα-2b treatment in this study was 70.15% (47/67). The absolute values of CD3(+) cells, CD3(+) CD4(+) cells, CD56(+) CD16(+) CD3(-) cells and CD19(+) CD3(-) cells in the effective group were higher than those in the ineffective group (P<0.05), and the percentage of Treg cells was lower than that in the ineffective group (*P*<0.05). The proportions of CD3(+), CD3(+) CD4(+) and CD3(+) CD8(+) in the effective group were lower than those in the ineffective group, but the differences were not statistically significant (*P*>0.05). Through the analysis of binary logistic regression model, the percentage of Treg cells was the factor influencing HBsAg loss after 24 weeks of PegIFNα-2b treatment (OR=0.441, 95%CI 0.289-0.672, *P*<0.05). The ROC curve showed that the AUC value of Treg cell percentage was 0.896, and the optimal cut-off value was 8.97%, with statistical significance (*P*<0.001). The sensitivity was 72.3% and the specificity was 95%. AUC>0.7, indicating that Treg cell percentage has a good predictive value for the efficacy of PegIFNα-2b treatment in advantageous population. **Conclusion:** The percentage of Treg cells is an independent factor of HBsAg loss after 24 weeks of PegIFNα-2b treatment in the chronic hepatitis B clinical cure advantage population, and it also has a good predictive value for the clinical efficacy of this population.

Disclosures: Dan Duan: Nothing to Disclose, Lunli Zhang: Nothing to Disclose, Xiaopeng Li: Nothing to Disclose, Wang Liang: Nothing to Disclose, Qian Yang: Nothing to Disclose

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1292 | EFFECTIVENESS AND SAFETY OF TENOFOVIR ALAFENAMIDE FOR CHRONIC HEPATITIS B PATIENTS WITH DECOMPENSATED CIRRHOSIS: A REAL-WORLD STUDY IN CHINA

Jing Dou[1] Feng Guo[1] Zhonghui Ning[1] Xiaobo Wang[1] Qiang Xu[1] Fanpu Ji[2] Yonghong Yue[1] Zhuanguo Wang[1] Shuangsuo Dang[2] Hongfeng Wang[1] Qiang Fu[1] Shengtao Zeng[3] Weize Zuo[4] Xinhua Zhang[5] Xiaozhong Wang[1]

[1]新疆医科大学附属中医医院, [2]西安交通大学第二附属医院, [3]伊犁州新华医院, [4]石河子大学第一附属医院, [5]伊犁州友谊医院

Background: Tenofovir alafenamide fumarate(TAF) has a favorable efficacy and safety profile in chronic hepatitis B (CHB), but there are limited data from studies in CHB patients with decompensated cirrhosis. The aim of this study was to investigate the efficacy and safety of TAF in the treatment of CHB patients with decompensated cirrhosis. **Methods:** This was a retrospective and prospective, multicenter, real-world study. TAF was administered at a dose of 25mg per day. Follow-up was planned to be at least 48 weeks. The primary endpoint was the proportion of patients with undetectable (<20 IU/ml) HBV DNA at week 12. Other endpoints included the rate of ALT normalization (40 U/L), change in HBV DNA levels, and changes in Child-Pugh (CTP) and Model for End-Stage Liver Disease (MELD) scores from baseline. Safety outcomes, including drug-related adverse events (AEs) or serious adverse events (SAEs), as well as clinical outcomes, such as liver transplantation, hepatocellular carcinoma (HCC), death, renal function, or dyslipidemia were also analyzed. **Results:** A total of 74 patients (22 females and 52 males) with a mean age of 53.14±9.15 years from 6 medical centers were included in this study before 18th April,2024. The median HBV DNA and ALT at baseline were 5.06 lg IU/mL and 27.65 U/L, respectively. 49 patients (66.22%) had a CTP score of B/C at baseline. 25 patients completed 24 weeks of follow-up and 33 patients completed 48 weeks of follow-up. After 48 weeks of TAF treatment, HBV DNA was undetectable in 96.97% (32/33) of patients, higher than at baseline (58.1%, 43/74). ALT levels were significantly lower than at baseline (P=0.019), and the rate of ALT normalization was higher (72.73%, 24/33) than at baseline (47.30%, 35/74). The proportion of patients with CTP-B/C was significantly lower than at baseline (66.22%, 49/74 vs 28.30%, 10/33, P=0.010). HCC occurred in 1 patient during follow-up, and no drug-related AEs or SAEs, as well as liver transplantation or death were observed. Patients' renal functions such as serum creatinine (sCr), β2-microglobulin (β2-MG), and eGFR, as well as lipid profile, were stable during the 48-week treatment period. **Conclusion:** TAF has good effectiveness and safety in the treatment of patients with CHB with decompensated cirrhosis patients in a real-world setting.

Disclosures: Jing Dou: Nothing to Disclose, Feng Guo: Nothing to Disclose, Zhonghui Ning: Nothing to Disclose, Xiaobo Wang: Nothing to Disclose, Qiang Xu: Nothing to Disclose, Fanpu Ji: Nothing to Disclose, Yonghong Yue: Nothing to Disclose, Zhuanguo Wang: Nothing to Disclose, Shuangsuo Dang: Nothing to Disclose, Hongfeng Wang: Nothing to Disclose, Qiang Fu: Nothing to Disclose, Shengtao Zeng: Nothing to Disclose, Weize Zuo: Nothing to Disclose, Xinhua Zhang: Nothing to Disclose, Xiaozhong Wang: Nothing to Disclose

1293 | IMPACT AND COST-EFFECTIVENESS OF A HOSPITAL-BASED HEPATITIS B SCREENING AND MANAGEMENT PROGRAM IN CHINA: A MATHEMATICAL MODELLING PREDICTION

Jia Chen[1] Qiumin Luo[1] Hanting Liu[1] Bo Zhang[1] Jinghua Li[1] Liang Peng[1]

[1]Sun Yat-sen University

Background: The burden of hepatitis B in China remains substantial, accounting for approximately 29% of global cases. To improve hepatitis B virus(HBV) diagnosis and treatment rates, the Third Affiliated Hospital of Sun Yat-sen University launched an integrated hospital-based hepatitis B screening and management program(the Hot wave project) in 2022, which encompasses patient education, screening, diagnosis, treatment, and follow-up. Following the implementation of this project, HBV screening rates, HBsAg-positive patient referral rates, and antiviral treatment rates increased from 7.95%, 11.23%, and 57.18% in 2021 to 8.36%, 19.32%, and 62.48% in 2022. **Methods:** Assuming widespread implementation of the Hot wave project across comprehensive hospitals in Guangzhou, a deterministic compartmental model was constructed to predict the impact and cost-effectiveness of this project on HBV prevalence from 2023 to 2030. The study simulated scenarios for 18,734,100 individuals

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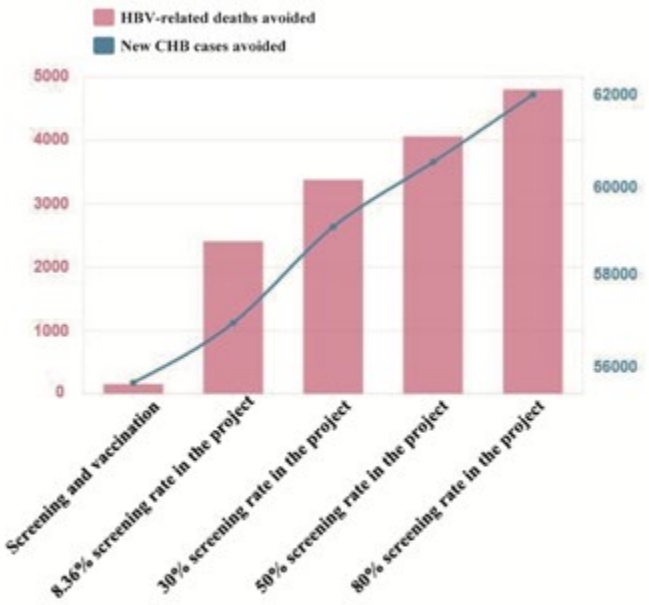
(50% of Guangzhou's resident population in 2022) under six conditions: screening rates of 8.36%, 30%, 50%, and 80%, screening and vaccination, and the status quo(i.e., no implementation of the Hot wave project). Incremental cost effectiveness ratios (ICERs) were calculated by comparing different scenarios with the status quo, using the willingness-to-pay(WTP) threshold based on Guangzhou's 2022 per capita GDP. **Results:** For the status quo, it is projected that there will be an accumulation of 118,060 new cases and 123,258 HBV-related deaths in the cohort between 2023 to 2030. Compared to the status quo, the screening and vaccination strategy can prevent 55745 new cases and 149 HBV-related deaths during 2023-2030, with an ICER of $10754 per quality-adjusted life year(QALY). If the Hot wave project is widely implemented at Guangzhou, and the HBsAg screening rate is 8.36%, it could prevent 57,063 new cases and 2,405 HBV- related deaths. The additional medical cost required for each QALY would be $14,769. As the screening rate in the Hot wave project increases to 30%, 50%, and 80%, it is expected that more new cases and HBV-related deaths can be prevented. The additional medical cost required for each QALY is also decreasing, which save total medical costs for the public health system. **Conclusion:** The hospital-based hepatitis B screening and management program can accelerate the elimination of hepatitis B in China while being cost-effective and cost-saving. In the future, it is essential to promote the extensive adoption of this program within hospitals across China.



scenarios	Intervention Cost($) per person	QALY per person	Average CER vs. status quo ($/QALY)	Saved medical care cost($) per person	Total saved medical care cost($)
Status quo	16.88	4.8156	-	-	
Screening and vaccination	23.92	4.8162	10754	1.66	31.10M
8.36% screening rate in the project	57.33	4.81832	14769	3.01	56.39M
30% screening rate in the project	62.57	4.8196	11411	4.1	76.81M
50% screening rate in the project	66.28	4.8205	10094	4.87	91.24M
80% screening rate in the project	70.82	4.8214	9232	5.7	106.78M

Figure1. (A) Epidemiological impact of the Hot wave project, 2023-2030.
(B) Benefits, costs, and savings in healthcare costs of the project, 2023–2030.

Disclosures: Jia Chen: Nothing to Disclose, Qiumin Luo: Nothing to Disclose, Hanting Liu: Nothing to Disclose, Bo Zhang: Nothing to Disclose, Jinghua Li: Nothing to Disclose, Liang Peng: Nothing to Disclose

1294 | HBV ANTIGEN-GUIDED SWITCHING STRATEGY FROM NUCLEOS(T)IDE ANALOGUE TO INTERFERON: AVOID VIROLOGIC BREAKTHROUGH AND IMPROVE FUNCTIONAL CURE

Da Huang[1] *Di Wu*[1] *Weiming Yan*[1] *Qin Ning*[2]

[1]*Tongji Hospital,* [2]*Huazhong University of Science and Technology*

Background: This study aims to determine the factors associated with virologic breakthrough (VBT) after switching from nucleos(t)ide analogue (NA) to pegylated interferon alpha (Peg-IFN-α) and explore the optimized strategy to improve functional cure of chronic hepatitis B (CHB). **Methods:** Of 257 NA suppressed CHB patients enrolled in Anchor study (NCT02327416), 80 patients who received Peg-IFN-α and NA combination therapy for 48 weeks followed by Peg-IFN-α monotherapy for additional 48 weeks between March 2014 and June 2019 were included in this pilot study. Virologic and immunological biomarkers were dynamically evaluated. **Results:**

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Twelve (15.0%) patients experienced VBT after switching to Peg-IFN-α and exhibited significantly lower rates of HBsAg loss after therapy completion (0% vs. 35.3%, *P*=0.014). HBcrAg and HBsAg levels at the time of NA cessation were independently associated with VBT after stopping NA. The patients with HBcrAg≥5 $\log_{10}$U/mL and HBsAg≥100 IU/mL had the highest risk of VBT and failed to achieve subsequent HBsAg clearance. Intrahepatic cccDNA level was significantly higher in patients with HBcrAg≥5 $\log_{10}$U/mL than those with HBcrAg<5 $\log_{10}$U/mL. Notably, in contrast to patients with HBcrAg<5 $\log_{10}$U/mL or with HBsAg<100 IU/mL who had obviously restored HBV-specific $CD8^+$T cell, Tfh or B cell responses before NA cessation, those with HBcrAg≥5 $\log_{10}$U/mL or with HBsAg≥100 IU/mL exhibited lackluster immunities before NA cessation and notable diminished immune responses thereafter. **Conclusion:** Monitoring HBcrAg and HBsAg levels, which correlated with poor immune responses during sequential Peg-IFN-α strategy, may help to avoid VBT and improve functional cure of CHB.

Disclosures: Da Huang: Nothing to Disclose, Di Wu: Nothing to Disclose, Weiming Yan: Nothing to Disclose, Qin Ning: Nothing to Disclose

1295 | SEMI-MECHANISTIC PK/PD MODELING AND SIMULATION OF SEQUENTIAL SIRNA AND BEPIROVIRSEN TREATMENT PREDICTS ADDED BENEFIT IN HBSAG RESPONSE IN SUPPORT OF PHASE 2B DOSE SELECTION

Nadia Noormohamed[1] Mohamed Ismail[2] Mindy Magee[1] Susan Dixon[3] Maximilian Lee[1] Melanie Paff[1] Ahmed Nader[1]

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Background: Daplusiran/tomligisiran (DAP/TOM, formerly JNJ-3989) is a fixed combination siRNA that has shown marked declines in HBsAg irrespective of baseline HBsAg but is unlikely to achieve functional cure (FC) alone. Bepirovirsen is an antisense oligonucleotide in development for treatment of CHB and has shown sustained HBsAg loss in a proportion of patients with a baseline HBsAg ≤3000 IU/mL. Whether lowering of HBsAg by DAP/TOM before administration of bepirovirsen could potentially increase the proportion of patients achieving FC will be assessed in a Phase 2b study. To inform dose selection, pharmacokinetic (PK)/pharmacodynamic (PD) model-based simulations were used to characterize HBsAg response after sequential therapy. **Methods:** A semi-mechanistic PK/PD model was previously developed to describe the full time-course of bepirovirsen exposures and HBsAg changes (PK-HBsAg) after administration and was updated to include the PK/PD of DAP/TOM. Clinical trial simulations were conducted at two DAP/TOM doses of interest (50 mg every 4 weeks and 200 mg every 4 weeks) for 24 weeks followed by bepirovirsen 300 mg weekly for 24 weeks plus loading doses in a virally suppressed population. Bepirovirsen plus standard of care (SOC) alone was simulated as a control arm. Simulations were conducted in participants with baseline HBsAg >3000 and ≤3000 IU/mL, and an overall population. The proportion of participants to achieve HBsAg <LLOQ was summarized for each regimen. **Results:** The PK-HBsAg model demonstrated good agreement between predicted and observed PK and PD data for both DAP/TOM and bepirovirsen. Simulation results showed a greater proportion of participants achieving HBsAg <LLOQ with sequential therapy at both doses simulated (28.4% and 30.5% for 50 mg and 200 mg every 4 weeks, respectively) than with bepirovirsen plus SOC alone (15.2%) in the overall population. An increased response is predicted in the ≤3000 population, with 39.2% achieving HBsAg <LLOQ, versus 17.2% in the >3000 population with the 200 mg dose; similar findings are predicted with the 50 mg dose. Simulation results depicting HBsAg over time are presented in the figure. **Conclusion:** The PK-HBsAg model-based simulation results predict an added benefit of sequential DAP/TOM followed by bepirovirsen therapy versus bepirovirsen plus SOC alone due to lowering HBsAg levels with siRNA before starting bepirovirsen treatment. These results support the evaluation of this sequential regimen in a Phase 2b study. **Funding** GSK (218309)

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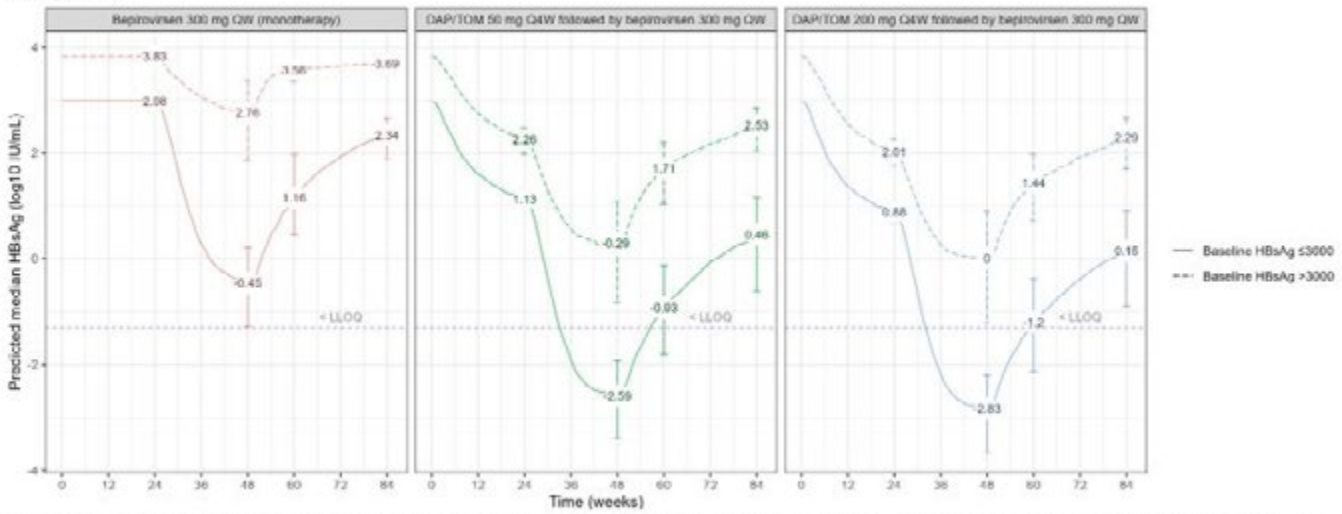
Figure: PK/PD Analysis of HBsAg over time during DAP/TOM and bepirovirsen sequential therapy versus bepirovirsen plus SOC by baseline HBsAg levels



CI, confidence interval; DAP/TOM, daplusiran/tomligisiran; HBsAg, hepatitis B surface antigen; LLOQ, lower limit of quantification; PK/PD, pharmacokinetic/pharmacodynamic; Q4W, once every 4 weeks; QW, once weekly SOC, standard of care. Error bars represent the 90% CI of the median.

Disclosures: Nadia Noormohamed: GSK: Employee, GSK: Stock - publicly traded company, Mohamed Ismail: Nothing to Disclose, Mindy Magee: Nothing to Disclose, Susan Dixon: Nothing to Disclose, Maximilian Lee: GSK: Employee, Melanie Paff: Nothing to Disclose, Ahmed Nader: Nothing to Disclose

1296 | NK CELLS FUNCTION DVDFTRECREASES, WHAT IS THE CAUSE OF LLV OCCURRENCE?

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Background: Low level viremia(LLV)is closely related to the progression of Chronic hepatitis B liver fibrosis, occurrence of decompensated cirrhosis, risk of hepatocellular carcinoma, and decreased long-term survival rate. Natural killer cells has antiviral effects, what role does it play in LLV? **Methods:** HBV DNA can still be detected using a highly sensitive quantitative PCR method with an antiviral treatment time of ≥ 48 weeks, but LLV is defined as<2000 IU/mL. A retrospective study was conducted on 273 hospitalized patients with chronic HBV infection who used Entecavir or Tenofovir alafenamide Fumarate alone. They were divided into LLV group and a complete virological response group (CVR group). The peripheral blood NK cells count, perforin, and granzyme B data were collected. **Results:** 36 cases of LLV and 77 cases of CVR, there is no difference in ALT,AST, ALB, and disease staging indicators.There is a difference in gender, age, and antiviral medication use between the two groups, P<0.05. There was no difference in the peripheral blood NK cells count and perforin expression between the LLV group and the CVR group, P>0.05; the peripheral blood NK cells ratio and granular enzyme B in the LLV group were lower than those in the CVR group, P **Conclusion:** The decrease in the proportion and function of NK cells may be an immune factor contributing to the development of LLV in chronic HBV infected individuals. Therefore, starting with NK cells may be a feasible measure for future LLV treatment. There are differences in the average medication time and disease stage between the population taking Entecavir and Tenofovir alafenamide Fumarate, and the relationship between the two and LLV needs to be further validated of time.

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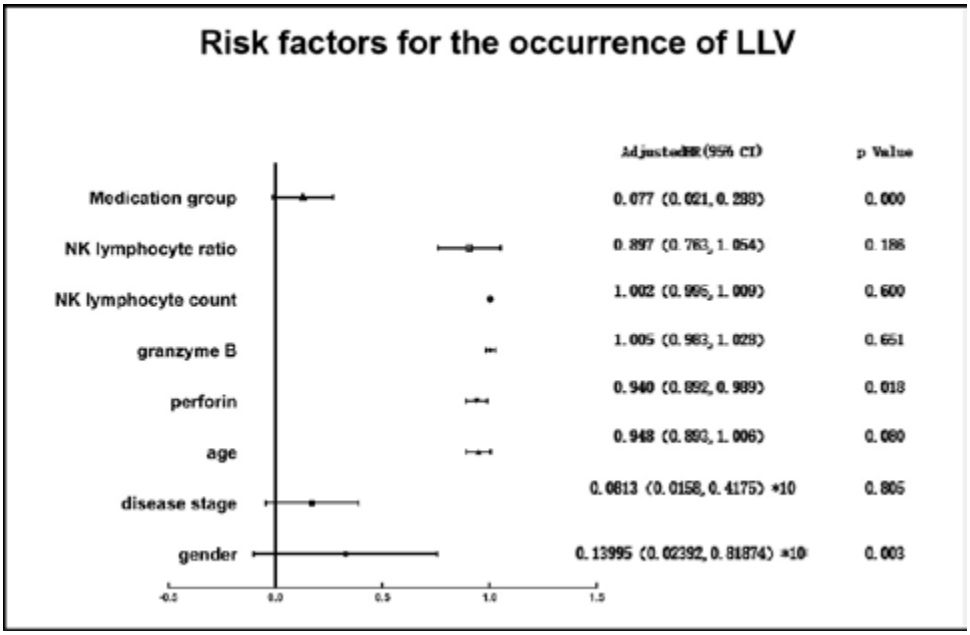

Disclosures: Guo Liying: Nothing to Disclose, Hui SUN: Nothing to Disclose, Jianwei JIA: Nothing to Disclose, Jie ZHAO: Nothing to Disclose, Xiliang WU: Nothing to Disclose, Jing MIAO: Nothing to Disclose

1297 | COMPARATIVE ANALYSIS OF CLINICAL EFFICACY AND SAFETY OF COMBINED PEGYLATED INTERFERON A-2B IN 489 PATIENTS WITH CHRONIC HEPATITIS B

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Background: To evaluate the efficacy and safety of pegylated interferon α-2b combined with pegylated interferon α-2b alone in treated or untreated chronic viral hepatitis B (CHB) patients with low HBsAg expression (**Methods:** In this study, 489 patients with CHB who were hospitalized or outpatients of infectious liver disease department in our hospital were randomly divided into 3 groups: nucleoside analogue treatment group (nucleoside group,n=166); Pegylated interferon α-2b group (interferon group,n=163); Nucleoside analogues combined with pegylated interferon α-2b group (combined group,n=160). Hepatitis B virus surface antigen (HBsAg) level, negative conversion rate and serological conversion rate were observed at baseline, 24, 48 and 72 weeks, respectively. The effects of different HBsAg baseline levels on HBsAg decline and negative conversion rate under multi-target intervention were analyzed. **Results:** There were no significant differences in HBsAg levels in the nucleoside group at 24, 48 and 72 weeks compared with the baseline value (P > 0.05 for all), while the levels in the interferon group and the combination group were significantly lower than the baseline value at 24 weeks (P < 0.05 for all), and the differences were more significant in the combination group compared with the nucleoside group and the interferon group. At 72 weeks, the decrease rate of HBsAg, negative conversion rate of HBsAg and serological conversion rate of the combined group were also significantly higher than those of the nucleoside group (all P < 0.05);In the group with baseline HBsAg≤1 500 IU/ml, the proportion of patients with low level HBsAg(≤10 IU/ml) and the negative conversion rate of HBsAg at 48 weeks were higher than those in the group with HBsAg > 1 500 IU/ml;There were some common adverse reactions of interferon, such as fever, leucocytocytopenia and thrombocytopenia, and alanine aminotransferase (ALT) increase, and the incidence of HCC and decompensated cirrhosis were decreased in the interferon group and the combined group, and there was no statistical significance between the two groups (all P > 0.05). **Conclusion:** Nucleoside combined with pegylated interferon α-2b can significantly improve the negative conversion rate and serological conversion rate of HBsAg. Patients with HBsAg≤1 500 IU/ml should choose multi-target combined intervention for antiviral efficacy.

Disclosures: weihua Ju: Nothing to Disclose

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1298 | STUDY ON THE CORRELATION BETWEEN HLA-DR+CD38+CD8+ T CELL CHANGES AND EFFICACY IN THE TREATMENT OF HEPATITIS B VIRUS WITH INTERFERON

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Background: Interferon (IFN) plays a dual role of direct antiviral and immune regulation in anti-hepatitis B virus (HBV) therapy. Some patients can obtain early hepatitis B surface antigen (HBsAg) response in the early stage of IFN treatment, but the decline of HBsAg level stagnates in the later stage, and the antiviral effect cannot be continued even if IFN treatment is continued. Currently, how to further explain the cause of this phenomenon from the immunological level is still a problem to be solved. Thus, we aim to investigate changes in phenotype and function of CD8+ T lymphocytes in chronic hepatitis B (CHB) patients undergoing IFN and correlation with clinical response. **Methods:** CHB patients were divided into three groups according to antiviral treatment. PegIFNα was then administered to Naïve group and nucleos (t) ide analogues (NAs)-treated group. For Plateau group, whose HBsAg decline reached a plateau, IFN therapy was stopped and was resumed after an interval. Peripheral blood samples were collected to detect clinical indexs, and T lymphocyte related phenotypes and functions using flow cytometry at corresponding detection points of three groups. **Results:** A prospective cohort of 151 CHB patients participated in this study. During IFN treatment, HLA-DR+CD38dim subset of CD8+ T cells increased and then markedly decreased, while the HLA-DR+CD38hi subgroup increased significantly in both Naïve and NAs-treated groups (p all < 0.0001). For Plateau group, the HLA-DR+CD38dimCD8+ T cells increased significantly and the HLA-DR+CD38hiCD8+ T cells greatly decreased after IFN intermittent treatment (p all < 0.0001). The changes of HLA-DR+CD38dim and HLA-DR+CD38hi subsets during IFN intermittent treatment were strongly positively correlated with the changes of HBsAg during IFN retreatment, respectively (r = 0.4843, p = 0.0066; r = 0.4588, p = 0.0315). Compared with activated HLA-DR+CD38dimCD8+ T cells, HLA-DR+CD38hi subgroup expressed lower level of co-stimulatory molecules and killing ability. **Conclusion:** IFN treatment made activated HLA-DR+CD38dimCD8+ T cells gradually differentiated into HLA-DR+CD38hi subset that indicated impaired killing function. IFN intermittent therapy can reverse this trend and help restore antiviral efficacy of IFN.

Disclosures: Yanjie Lin: Nothing to Disclose, Shiyu Wang: Nothing to Disclose, Liu Yang: Nothing to Disclose, Xiaoyue Bi: Nothing to Disclose, Wen Deng: Nothing to Disclose, Xinxin Li: Nothing to Disclose, Ziyu Zhang: Nothing to Disclose, Yao Xie: Nothing to Disclose, Minghui Li: Nothing to Disclose

1299 | TENOFOVIR ALAFENAMIDE TO PREVENT HEPATITIS B VIRUS REACTIVATION IN PATIENTS WITH RESOLVED INFECTION RECEIVING RITUXIMAB-BASED CHEMOTHERAPY: A RANDOMIZED CONTROLLED TRIAL

Grishma Hirode[1] Sanam Tabataba Vakili[2] Atif Zahoor[2] Ahreni Saunthar[2] Joshua Feld[2] Bettina Hansen[3] Ambreen Syeda[2] David Wong[2] Harry Janssen[3] Vishal Kukreti[4] John Kuruvilla[4] Anca Prica[4] Matthew Cheung[5] Rena Buckstein[5] Martina Trinkaus[6] Carla Coffin[7] Patricia Disperati[8] Kelvin Chan[5] Lisa Hicks[6] Michael Crump[4] Jordan Feld[1]

[1]Toronto General Hospital; Viral Hepatitis Care Network (VIRCAN), [2]Toronto General Hospital, [3]Toronto General Hospital; Erasmus University Medical Centre, [4]Princess Margaret Cancer Centre, [5]Sunnybrook Odette Cancer Centre, University of Toronto, [6]St. Michael's Hospital, [7]Cumming School of Medicine, University of Calgary, [8]Michael Garron Hospital

Background: Potent immunosuppressive therapy can cause hepatitis B virus (HBV) reactivation leading to severe or fatal outcomes even in patients who have cleared hepatitis B surface antigen (HBsAg) but remain hepatitis B core antibody (anti-HBc) positive. This multi-center randomized placebo-controlled trial assessed the efficacy of pre-emptive antiviral therapy with tenofovir alafenamide (TAF) in HBsAg negative, anti-HBc positive patients receiving rituximab-based chemotherapy for non-Hodgkin's lymphoma (NHL). **Methods:** Patients randomized 1:1 to TAF/placebo had 3 follow-up phases: chemotherapy plus TAF/placebo, TAF/placebo only post-chemotherapy, and follow-up after cessation of all therapy. The primary endpoint was HBsAg seroreversion with HBsAg assessments every 3 months up to 12 months post-chemotherapy. Open label entecavir (ETV) was initiated upon HBsAg reversion. HBV DNA was measured post-hoc from stored samples. Patients were grouped by low-grade and high-grade lymphoma due to differences in treatment regimens. **Results:** Of 42 patients (20 TAF, 22 placebo), 22 (52%) were male, 18 (43%) White, 19 (45%) Asian, 20 (48%) had low-grade and 22 (52%) had high-grade NHL. At

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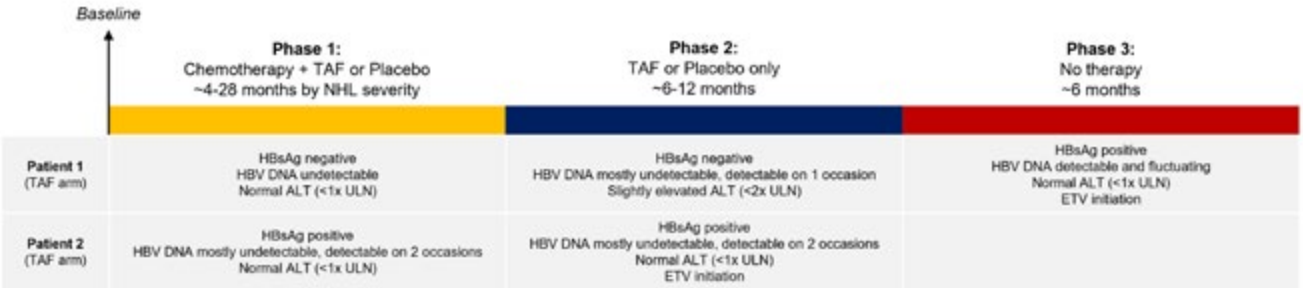
baseline, mean age was 64±11 years, 29 (69%) were hepatitis B surface antibody (anti-HBs) positive, and median alanine aminotransferase (ALT) was 0.5x (IQR:0.4-0.7x) upper limit of normal (ULN). Median follow-up was 69 weeks (IQR:62-165) with 6 weeks (IQR:5-8) between visits. During follow-up, 2 patients in the TAF arm (both Asian females), but none receiving placebo, had HBsAg reversions. Patient 1 was a 57-year-old with high-grade NHL. HBV DNA became detectable (251 IU/mL) post-chemotherapy but during TAF at 40 weeks from baseline, continued to fluctuate between 11-225 IU/mL until HBsAg reversion which occurred after TAF cessation at 62 weeks from baseline, with a peak HBV DNA of 2720 IU/mL ~2 weeks later – prior to ETV initiation. In patient 2, a 69-year-old with low-grade NHL, HBV DNA became detectable (<130 IU/mL) but was then serially undetectable prior to HBsAg reversion that occurred during chemotherapy at 20 weeks from baseline. Neither patient experienced ALT >2x ULN or other sequelae. **Conclusion:** In patients with "resolved" HBV receiving rituximab-based chemotherapy, pre-emptive treatment with TAF did not result in a lower risk of HBsAg seroreversion. The study highlights the need for careful HBsAg monitoring even in treated patients and the importance of close follow-up after antiviral withdrawal.



Disclosures: Grishma Hirode: Nothing to Disclose, Sanam Tabataba Vakili: Nothing to Disclose, Atif Zahoor: Nothing to Disclose, Ahreni Saunthar: Nothing to Disclose, Joshua Feld: Nothing to Disclose, Bettina Hansen: Nothing to Disclose, Ambreen Syeda: Nothing to Disclose, David Wong: Nothing to Disclose, Harry Janssen: Gilead Sciences: and consultant, Gilead Sciences: Grant/Research Support, GlaxoSmithKline: Grant/Research Support, Janssen: Grant/Research Support, Roche: Grant/Research Support, Vir Biotechnology Inc.: Grant/Research Support, Aligos: Consultant, Gilead Sciences: Consultant, GlaxoSmithKline: Consultant, Grifols: Consultant, Roche: Consultant, Vir Biotechnology Inc: Consultant, Precision Biosciences: Consultant, Vishal Kukreti: Nothing to Disclose, John Kuruvilla: Nothing to Disclose, Anca Prica: Nothing to Disclose, Matthew Cheung: Nothing to Disclose, Rena Buckstein: Nothing to Disclose, Martina Trinkaus: Nothing to Disclose, Carla Coffin: Grant/Research Support relationship with Gilead Sciences; Has not ended; Grant/Research Support relationship with Janssen Pharmaceuticals; Has ended; Funds paid to the University of Calgary relationship with GSK; Has not ended; Grant/Research Support relationship with Riche Pharmaceuticals; Has not ended; Fund paid to the University of Calgary relationship with Altimmune Pharmacueticals; Has ended; Speaking and Teaching relationship with GSK; Has ended, Patricia Disperati: Nothing to Disclose, Kelvin Chan: Nothing to Disclose, Lisa Hicks: Nothing to Disclose, Michael Crump: Nothing to Disclose, Jordan Feld: Mirum: Consultant, AbbVie, Bluejays, Gilead, Janssen, GSK, Roche, VIR Roche: Consultant, Bluejays: Consultant, Gilead: Consultant, Janssen: Consultant, GSK: Consultant, Roche: Consultant, VIR Biotechnology: Consultant, Altimmune, AbbVie, Gilead, Jannsen, GSK, Roche, VIR Bio: Grant/Research Support

1300 | RESIDUAL HEPATITIS B VIREMIA DETECTED BY A HIGH-SENSITIVITY DROPLET DIGITAL-PCR ASSAY PREDICTS HEPATOCELLULAR CARCINOMA RISK AND PROGNOSIS IN PATIENTS ON ANTIVIRAL THERAPY

Rex Wan-Hin Hui[1] *Danny Wong*[1] *Lung Yi Mak*[1] *James Yan Yue Fung*[1] *Wai-Kay Seto*[1] *Man-Fung Yuen*[1]

[1]*The University of Hong Kong*

Background: Nucleos(t)ide analogues (NUCs) are effective in suppressing hepatitis B virus (HBV) DNA levels and reducing the risk of hepatocellular carcinoma (HCC) in chronic hepatitis B (CHB). Nonetheless, it cannot completely eliminate viral replication. We hypothesize that residual HBV viremia may predict HCC risks and prognosis in NUC-treated CHB patients. **Methods:** We recruited NUC-treated CHB patients with unquantifiable HBV DNA by the Cobas Taqman assay (Roche, lower limit of quantification [LLOQ] 20.0 IU/ml). Patients who developed HCC were matched in a 1:1 ratio with non-HCC CHB controls by age, sex, type of NUCs, and cirrhosis

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status. Archived patient sera at the time of HCC diagnosis, 1 year, and 2 years prior to HCC were tested. Sera at the same time points from last follow-up were tested in controls. Patient sera was tested by an in-house high-sensitivity droplet digital PCR (ddPCR) assay for HBV DNA with lower limit of detection (LLOD) of 1.6 IU/ml and LLOQ of 9.4 IU/ml respectively. **Results:** Among 208 patients (104 HCC vs 104 controls; 80.8% male; mean age 63.1 years; mean age at starting NUCs 55.7 years; 29.3% cirrhosis; 85.6% on entecavir, 10.1% on tenofovir, 4.3% on other NUCs), 65.9% patients had ≥1 incidences of detectable HBV DNA by the ddPCR assay within the 2-year assessment period. HCC patients, when compared with controls, were significantly more likely to have detectable HBV DNA at HCC diagnosis (48.1% vs 16.3%, p<0.001), at 1 year prior to diagnosis (52.9% vs 24.0%, p<0.001), and at 2 years prior to diagnosis (39.4% vs 25.0%, p<0.001). Detectable HBV DNA at any time point within the 2-year pre-diagnosis period independently predicted HCC occurrence (OR 7.92, 95%CI 2.95-21.24, p<0.001). Among HCC patients, detectable HBV DNA within 2 years was associated with more advanced tumor staging (OR 3.53 for Barcelona-Clinic Liver Cancer [BCLC] stage A or higher vs BCLC-0, 95%CI 1.23-10.13, p=0.019), while no associations with chance of curative treatment or histological grading were demonstrable (all p>0.05). The HCC patients were further followed up for a mean duration of 4.6 years, and detectable HBV DNA within the 2-year pre-diagnosis period independently predicted liver-related mortality (HR 5.75, 95%CI 1.08-30.3, p=0.040). **Conclusion:** Residual viremia predicts risk and outcome of HCC in NUC-treated CHB patients, supporting the use of high-sensitivity HBV DNA assays for disease monitoring. Novel antivirals enabling more profound viral suppression may further reduce HCC risks in NUC-treated patients.

Disclosures: Rex Wan-Hin Hui: Nothing to Disclose, Danny Wong: Nothing to Disclose, Lung Yi Mak: Nothing to Disclose, James Yan Yue Fung: Nothing to Disclose, Wai-Kay Seto: Nothing to Disclose, Man-Fung Yuen: Speaking and Teaching relationship with Fujirebio Incorporation, Gilead Sciences, Roche, Sysmex Corp; Has not ended; Consultant relationship with Clear B Therapeutics, Dicerna Pharmaceuticals; Has not ended; Consultant relationship with AbbVie, Abbott Diagnotics, Aligos Therapeutics; Has not ended; Consultant relationship with Arbutus Biopharma, Arrowhead Pharmaceuticals, Assembly Biosc; Has not ended; Consultant relationship with Immunocore, Janssen, Precision BioSciences; Has not ended; Consultant relationship with Fujirebio Incorporation, GlaxoSmithKline, Gilead Sciences; Has not ended; Grant/Research Support relationship with Fujirebio Incorporation, Gilead Sciences, Immunocore; Has not ended; Grant/Research Support relationship with AbbVie, Assembly Biosciences, Arrowhead Pharmaceuticals; Has not ended; Consultant relationship with Vir Biotechnology and Visirna Therapeutics; Has not ended; Consultant relationship with Roche, Sysmex Corporation, Tune Therapeutics; Has not ended; Grant/Research Support relationship with Sysmex Corporation and Roche; Has not ended

1301 | HEPATITIS B VIRUS GENOTYPE INFLUENCES QUANTITATIVE SURFACE ANTIGEN LEVEL

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[1]University of Ottawa, [2]Ottawa Hospital Research Institute, [3]The Ottawa Hospital

Background: Recommendations for hepatitis B virus (HBV) infection antiviral treatment are guided by HBV DNA levels, liver enzyme values, and fibrosis score. Quantitative hepatitis B surface antigen (qHBsAg) may represent a more cost-effective and less labour-intensive surrogate for HBV DNA. However, studies have reported inconsistent results with weakly positive, negative, or no correlation between HBV DNA and qHBsAg levels. The influence of HBV genotype on qHBsAg has not been considered. We explore the relationship between HBV DNA and qHBsAg and whether this is influenced by HBV genotype. **Methods:** Baseline genotype, HBV DNA and qHBsAg levels for 138 consenting patients followed at The Ottawa Hospital Viral Hepatitis Program were assessed. Correlations between HBV DNA, qHBsAg and the ratio between these two variables as a function of HBV genotype were evaluated. **Results:** The mean age was 44.5 years, 52.2% were male, 52.3% Asian and 34.9% Black. The overall median HBV DNA was 2557 IU/mL. The highest median baseline HBV DNA was recorded in genotypes B (7899 IU/mL) and C (39900 IU/mL) and the lowest was in genotype E (684 IU/mL) (p = 0.14). The median qHBsAg overall was 2000 IU/mL. The highest median baseline qHBsAg was noted in genotype E (9665 IU/mL) and the lowest values were in genotype B (300 IU/mL) and C (1913 IU/mL) (p<0.0001). The HBV DNA:qHBsAg ratio differed in direction and magnitude by genotype (p<0.0001). HBV DNA and qHBsAg are moderately positively correlated for genotype A, B, and D (p=0.04, 0.007, 0.0007, respectively), but not correlated for genotype C and E (p=0.15, 0.21, respectively). Age, HBeAg status and genotype independently predicted HBsAg level and log10 HBV DNA: log10 qHBsAg ratio by multivariable median regression analysis. **Conclusion:**

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The median amounts and correlations between HBV DNA and qHBsAg differ in magnitude and direction depending on genotype. This knowledge may be relevant to HBV antiviral treatment guidelines.

Disclosures: Leon He: Nothing to Disclose, Alexa Keeshan: Nothing to Disclose, Curtis Cooper: Nothing to Disclose

1302 | ALTERNATIVE HBV VACCINATION STRATEGIES FOR BOTH COMPENSATED AND DECOMPENSATED CIRRHOTICS ◆

Brian Pearlman[1] Michael Perrys[2] andrew hinds[3] carole Ehleben[4]

[1]Hamilton/Emory/Medical College of Georgia, [2]Medical College of Georgia, [3]Wellstar, [4]Wellstar/Medical College of Georgia

Background: Patients with cirrhosis, particularly those with decompensated disease, have reduced seroprotection rates with traditional HBV vaccines (alum adjuvant). The aim of this study was to investigate if alternative HBV vaccination strategies could effect improved immunogenicity in a cirrhotic population. **Methods:** HBV-vaccine naive cirrhotic subjects, aged 18-75, at two hepatology clinics were stratified into those with a history of decompensation versus those without a history of the same, and each group was randomized 1:2:2 to *SD*-standard dose-3 doses of 20 mcg of Engerix-B (alum adjuvant; GlaxoSmithKlein) at 0,1 and 6 months; *HD*-high dose-4 doses of 40 mcg of Engerix-B at 0, 1, 2, and 6 months; and *HS*-Heplisav- 2 doses of Heplisav-B (Dynavax) at 0 and 1 months, respectively. The FDA approved, two-dose Heplisav-B, combines 20 mcg of recombinant HBsAg with 3000 mcg CpG adjuvant which binds to a toll-like receptor (TLR9) and provokes innnate immune responses. The primary end point was the peak seroprotection rates (SPR=proportion of anti-HBs ≥ 10 mIU/ml) measured at 24-28 weeks after vaccine initiation. Secondary end points were safety and adverse events. **Results:** 379 subjects with cirrhosis (189 compensated; 190 decompensated) had baseline characteristics that did not significantly statistically differ across therapy arms, including factors historically associated with reduced SPR rates (male gender, race, age > 60 years, tobacco use, BMI ≥ 30, type 2 diabetes, serum albumin < 3.5 mg/dl, higher CPT scores). MASLD and ALD were the most common cirrhosis etiologies. SPR rates were highest in the HS arms, relative to those in the HD and SD arms, in both compensated and decompensated groups (Table); overall SPR rates in patients receiving HS were significantly highest. All vaccine strategies were relatively well-tolerated with the severity and rate of adverse events being similar across all six groups. **Conclusion:** Seroprotection rates following HBV vaccination may be maximized in both compensated and decompensated cirrhotic patients by utilizing alternative vaccine strategies such as 4 doses of double strength standard HBV, or 2 doses of standard strength Heplisav-B with no compromise in safety. The percentage of patients achieving seroprotection was statistically highest in the group receiving HS, regardless of compensation status.

TABLE: Seroprotection Rates

	SD	HD	HS
Overall (a)	43/76 (57%)	97/152 (64%)	118/151 (78%)
Compensated (b)	26/38 (68%)	52/75 (69%)	66/76 (87%)
Decompensated (c)	17/38 (45%)	45/77 (58%)	52/75 (69%)

Significant Differences:
a: SD vs HS, p=0.001; HS vs HD, p=0.007
b: SD vs HS, p=0.016; HS vs HD, p=0.008
c: SD vs HS, p=0.01

Disclosures: Brian Pearlman: Abbvie: Speaking and Teaching, Mallinckrodt: Speaking and Teaching, Ipsen: Advisor, Michael Perrys: Nothing to Disclose, andrew hinds: Nothing to Disclose, carole Ehleben: Nothing to Disclose

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1303 | PATIENTS WITH CHRONIC HBV INFECTION EXHIBITING SIGNIFICANT INFLAMMATION AND FIBROSIS SHOULD PAY PARTICULAR ATTENTION TO THE STATUS OF MASLD DURING ANTIVIRAL THERAPY

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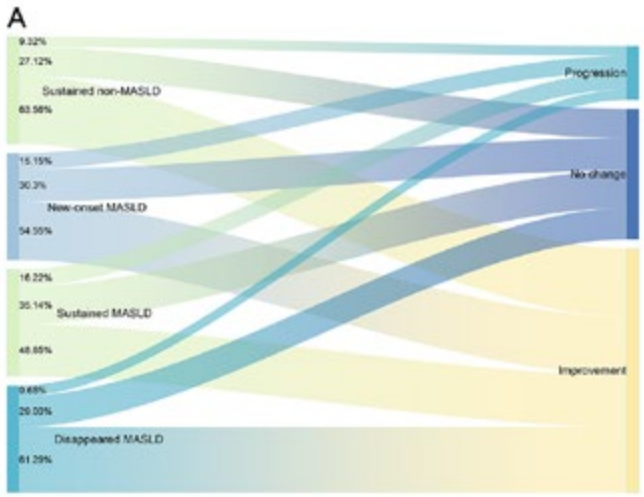
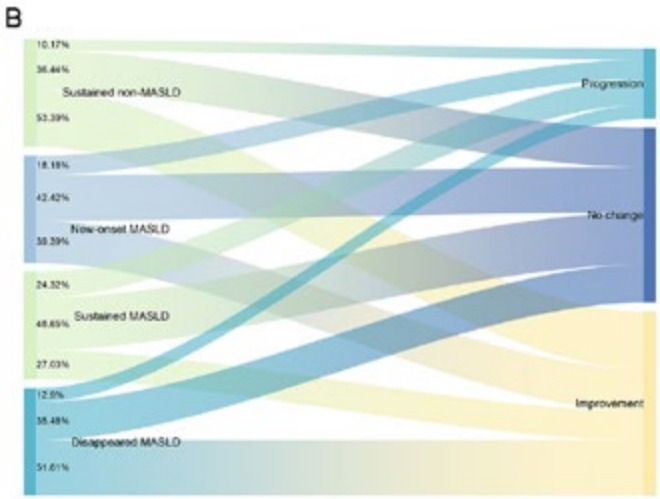
Background: There is a scarcity of data regarding the dynamic changes that occur in patients with chronic hepatitis B (CHB) and metabolic dysfunction-associated steatohepatitis (MASLD) while undergoing antiviral therapy. The objective of our study is to examine the influence of various statuses of MASLD on histological results in CHB patients with varied levels of hepatitis and fibrosis. Additionally, we will analyze the impacts on HBV virological clearance and biochemical improvement. **Methods:** The study retrospectively included CHB patients who underwent antiviral treatment and paired liver biopsies before and after treatment. The severity of liver inflammation and fibrosis was determined by evaluating histological findings using the Scheuer grading system. The presence of steatosis was evaluated using the nonalcoholic fatty liver disease activity score. A comparison was made between the liver biochemical markers and histological abnormalities before and after treatment. Logistic regression analysis was employed to assess the characteristics linked to the improvement in hepatic significant inflammation (G≥2), significant fibrosis (S≥2), and the persistence of MASLD. **Results:** We observed differences in the improvement of significant liver fibrosis post-treatment among the four groups: the highest improvement rate was in the sustained non-MASLD group (53.39%), while the lowest was in the sustained MASLD group (27.03%, p=0.031). There were also differences in the improvement of significant hepatitis among the four groups: the highest improvement was seen in the sustained non-MASLD group (75.31%) and the lowest in the sustained MASLD group (42.31%, p=0.008). Multivariate logistic regression suggested that sustained MASLD is a significant risk factor for poor improvement in significant hepatitis and significant liver fibrosis. Furthermore, the sustained MASLD group had the lowest improvement rate in liver enzyme indicators post-treatment. **Conclusion:** Our study strongly suggests that the persistent presence of MASLD during antiviral therapy in patients with significant hepatitis and fibrosis may impede the improvement of inflammation and fibrosis and is more likely to result in abnormal biochemical indices after treatment.



A. Liver inflammatory changes among subgroups based on different MASLD distributions



B. Liver fibrosis changes among subgroups based on different MASLD distributions

Disclosures: Bingqing Yang: Nothing to Disclose, Tianyuan Yang: Nothing to Disclose

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1304 | IMMUNOMODULATORS REINVIGORATE INTRAHEPATIC EXHAUSTED ANTIVIRAL IMMUNITY IN AN IMMUNOCOMPETENT MOUSE MODEL OF CHRONIC HEPATITIS B

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Background: Targeting exhausted immune systems would be a promising therapeutic strategy to achieve a functional cure for HBV infection in chronic hepatitis B (CHB) patients. However, animal models recapitulating the immunokinetics of CHB are very limited. We aimed to develop an immunocompetent mouse model of CHB for intrahepatic immune profiling. **Methods:** FAH cDNA with or without the1.24-mer overall length of HBV genome were tandemly cloned into a single Sleeping Beauty transposon vector (SB-FAH and SB-HBV-FAH). Via hydrodynamic tail vein injection (HTVi), SB-HBV-FAH and SB transposase-expressing vectors were introduced into the hepatocytes of Fumarylacetoacetate hydrolase (FAH) knockout (KO) mice that cannot avoid lethal hepatic damage without nitisinone drinking. After HTVi and nitisinone withdrawal, only hepatocytes expressing HBV and FAH from genome-integrated SB-HBV-FAH could compensate for FAH deficiency and repopulate the liver, resulting in persistent expression of HBV (CHB mouse). Control mice were created by introducing SB-FAH vector in FAH KO mice. We profiled the viral and intrahepatic immune kinetics in CHB mice with or without treatment with recombinant IFNα or the hepatotropic Toll-like receptor 7 agonist SA-5 using single-cell RNA-seq. **Results:** CHB mice exhibited sustained HBV viremia and persistent hepatitis for more than 6 months. They showed intrahepatic expansion of exhausted CD8T cells, the frequency of which was positively associated with viral load. Hepatitis B surface and core antigen-specific CTLs were detected in the CHB mice. HBV-specific CD8T cells showed significantly higher PD-1 expression and lower IFNγ production compared to non-specific CD8T cells. Recruited macrophages increased in number but impaired inflammatory responses in the liver. The number and cytotoxicity of mature NK cells also increased in CHB mice. IFNα and SA-5 treatment both resulted in viral suppression with mild hepatic flares in CHB mice. While both treatments activated NK cells, only SA-5 could revitalize the impaired function of Tex cells and macrophages recruited in the liver. **Conclusion:** Our novel CHB mouse model recapitulated the intrahepatic exhausted antiviral immunity in CHB patients, which might be able to be reinvigorated by a hepatotropic TLR7 agonist.

Disclosures: Satoshi Shigeno: Nothing to Disclose, Takahiro Kodama: Chugai Pharmaceuticals: Speaking and Teaching, Astrazeneca: Speaking and Teaching, Eisai Co Ltd: Speaking and Teaching, Kazuhiro Murai: Nothing to Disclose, Fukushima Akihisa: Nothing to Disclose, Hayato Hikita: Nothing to Disclose, Tomohide Tatsumi: Nothing to Disclose, Tatsuya Kanto: Nothing to Disclose, Tetsuo Takehara: Nothing to Disclose

1305 | CLB-405 AND CLB-505 COMBINED WITH A SAPONIN BASED ADJUVANT TQL-1055 EXHIBITS A STRONG ANTIVIRAL AND ENHANCED IMMUNE RESPONSES IN A MOUSE MODEL OF PERSISTENT HEPATITIS B INFECTION

Aditi Deshpande[1] Hans Netter[2] Renae Walsh[2] Stephen Locarnini[3] Lei Qiugang[4] Sun Ya[5] Bharat Dixit[1] Aileen Rubio[1]

[1]ClearB Therapeutics, [2]Melbourne Health, [3]Victorian Infectious Diseases Reference, [4]WuXi AppTec, [5]Wuxi AppTech

Background: It is hypothesized that a robust humoral and cellular immune response is essential to achieve functional cure in patients with chronic Hepatitis B infection (CHB) [Zheng, P. et al, Front. Cell. Infect. Microbiol. 13:1206720]. We have previously reported anti-viral activity and robust antibody response after treatment with two modified Hepatitis B surface antigen (HBsAg) variants, CLB-405 and CLB-505, adjuvanted to Alhydrogel in the Hydrodynamic tail vein injection (HDI) murine model of persistent Hepatitis B infection [EASL 2021 poster 853]. Saponin based adjuvants are known to provide a balanced Th1/Th2 response which may be beneficial in the situation of CHB [Zhu, D. et al, Nat Prod Chem Res. 2016 Apr; 3(4): e113]. In this study, efficacy in the HDI model was evaluated using CLB-405 and CLB-505 combined with a novel, semi-synthetic saponin-based adjuvant, TQL-1055, to invoke both a cellular and humoral immune response. **Methods:** HBV genotype A2 adw plasmid was injected via tail vein into male CBA/CaJ mice to establish persistent infection of ~3 log IU/mL HBsAg [Chou H-H et al 2015. PNAS 112(7) pp2175]. CHB mice were administered CLB-405 and CLB-405 combined with

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40 µg TQL-1055 adjuvant by subcutaneous (SC) injection. The mice were monitored over time for serological HBsAg, HBV DNA, anti-CLB-405 and anti-CLB-505 levels. At termination, liver (Hepatitis B core antigen) HBcAg and HBsAg immunohistochemistry was performed and splenocytes were isolated to assess cellular immune response by ELISPOT. **Results:** Treatment of CHB mice in the HDI model displayed dose-dependent reductions in HBsAg) of up to 2.7 log IU/ml by two weeks post the third dose. In addition, development of anti-CLB-405 and anti-CLB-505 antibodies, seroconversion to anti-HBs and clearance of HBsAg and HBcAg positive cells from the liver was achieved. Splenocytes isolated from CLB-405 and CLB-505 treated mice had higher numbers of IFN-γ secreting cells post ex vivo stimulation with HBsAg overlapping peptides compared to placebo treated mice. **Conclusion:** CLB-405 and CLB-505 combined with TQL-1055 adjuvant was highly efficacious in a murine model of persistent HBV infection with a dose-dependent decline in serum HBsAg, clearance of infected hepatocytes, development of anti-CLB-405 and anti-CLB-505 antibodies and a robust T cell response. These findings further support the development of a therapeutic vaccine with both Th1 and Th2 immune response for CHB patients.

Disclosures: Aditi Deshpande: Nothing to Disclose, Hans Netter: Nothing to Disclose, Renae Walsh: Nothing to Disclose, Stephen Locarnini: Nothing to Disclose, Lei Qiugang: Nothing to Disclose, Sun Ya: Nothing to Disclose, Bharat Dixit: Nothing to Disclose, Aileen Rubio: Nothing to Disclose

1306 | FACTORS PREDICTIVE OF IMPROVEMENT OF RENAL FUNCTION AFTER SWITCHING TO TENOFOVIR ALAFENAMIDE FROM TENOFOVIR DISOPROXIL FUMARATE IN PATIENTS WITH CHRONIC HEPATITIS B

Hyeyeon Hong[1] Won-Mook Choi[1] Danbi Lee[1] Ju Hyun Shim[1] Kang Mo Kim[1] Young-Suk Lim[1] Han Chu Lee[1] Jonggi Choi[2]

[1]Asan Medical Center, [2]University of Ulsan, Asan Medical Center

Background: Switching from Tenofovir disoproxil fumarate (TDF) to Tenofovir alafenamide (TAF) is known to improve renal function in chronic hepatitis B (CHB) patients. However, the factors influencing this improvement remain unclear. We aimed to identify predictors of renal function improvement after switching. **Methods:** We retrospectively analyzed 942 CHB patients who switched from TDF to TAF between 2017 and 2024 at Asan Medical Center, Seoul, Republic of Korea. The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. The primary outcome was an improvement of eGFR ≥5% from baseline at 6 months post-switch. Multivariable logistic regression analysis assessed predictive factors. Longitudinal changes in eGFR after the switch were also assessed. **Results:** Mean age was 58.4 years and 504 (53.5%) were male. The baseline eGFR was 69.8 ml/min/1.73m^2. Reasons of switching from TDF to TAF were low eGFR <60 ml/min/1.73m^2 (45.4%), osteoporosis (30.5%), and other causes (24.1%), such as partial virologic response or switching from combination to single therapy. Median eGFR increase post-switch: 2.0 ml/min/1.73m^2 (interquartile range: -2 – 7). 372 (39.5%) patients showed ≥5% eGFR improvement; 251 (26.6%) had ≥10% eGFR improvement at 6 months post-switch. Baseline eGFR <60 ml/min/1.73m^2 (adjusted odds ratio: 3.80, 95% confidence interval: 2.73–5.29, p<0.001) was significantly associated with eGFR improvement post-switch. Serial eGFR changes indicated significant improvement post-switch in patients with baseline low eGFR, age ≥60 years, and diabetes. **Conclusion:** In the present study, baseline low eGFR <60 ml/min/1.73m^2 was a predictive factor for renal function improvement post-switch from TDF to TAF in patients with CHB. Older age and diabetes may also indicate greater benefit from the switch.

Disclosures: Hyeyeon Hong: Nothing to Disclose, Won-Mook Choi: Nothing to Disclose, Danbi Lee: Nothing to Disclose, Ju Hyun Shim: Nothing to Disclose, Kang Mo Kim: Nothing to Disclose, Young-Suk Lim: Nothing to Disclose, Han Chu Lee: Nothing to Disclose, Jonggi Choi: GILEAD SCIENCE: Grant/Research Support

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1307 | SEQUENTIAL ADMINISTRATION OF SIRNA WITH CLB-405 AND CLB-505 HBSAG VARIANTS ENCODING CLEARANCE PROFILE EPITOPES, COMBINED WITH A NOVEL ADJUVANT TQL-1055 EXHIBITS SIGNIFICANT ANTI-VIRAL AND T CELL ACTIVITY IN AN AAV/HBV MOUSE MODEL

Aditi Deshpande[1] *Lei Qiugang*[2] *Sun Ya*[2] *Bharat Dixit*[1] *Aileen Rubio*[1]

[1]*ClearB Therapeutics,* [2]*Wuxi Apptech*

Background: A therapeutic vaccine comprised of two modified HBsAg variants, CLB-405 and CLB-505 encoding functional cure epitopes, combined with a novel semi-synthetic saponin-based adjuvant TQL-1055, demonstrated robust anti-viral activity along with development of a humoral and cellular immune response in mice from the Hydrodynamic tail vein injection (HDI) model of persistent Hepatitis B infection (AASLD 2024 abstract submission ID 227461). Since lowering viral antigen expression first has been shown to increase the effectiveness of therapeutic vaccines in high-titer HBsAg expressing AAV/HBV mice (Michler, T., et al. 2020. Gastroenterology 158, pp1762–1775), we evaluated the efficacy of the vaccine in combination with siRNA AD66810 (WO2018/195165; which targets the X gene expression in the HBV genome) in the AAV/HBV model. **Methods:** Male C57BL/6 mice were infected with 5×10^{10} viral genome equivalents of AAV8 carrying HBV genotype D ayw to establish a stable infection of ~4 log IU/mL HBsAg (Yang D, et al 2014 Cell Mol Immunol 11 pp718). Mice were treated with Placebo, siRNA monotherapy (10 mg/Kg on day 0), or combination of siRNA given on day 0, followed by intramuscular (IM) injection of CLB-405 and CLB-405 combined with 40 µg TQL-1055 given on days 7, 21 and 35. The mice were monitored over time for serological markers of HBsAg and HBV DNA. The cellular immune response by ELISPOT was assessed at the end of study. **Results:** Mice in the AAV/HBV model treated with siRNA followed by vaccine lowered HBsAg levels 4.3 log IU/ml one-week post-last dose compared to baseline. The mice treated with siRNA monotherapy resulted in a transient 2.3 log IU/ml HBsAg reduction. HBV DNA levels followed similar trends. The mice in the placebo group resulted in no significant change in plasma HBsAg and HBV DNA levels over the study duration. Significantly higher IFN-γ levels were observed from splenocytes harvested from the combination treated group compared to the siRNA monotherapy group. **Conclusion:** Sequential administration of a single dose of siRNA AD66810 followed by therapeutic vaccination using CLB-405 and CLB-505 encoding two modified HBsAg sequences combined with a novel semi-synthetic saponin adjuvant TQL-1055 was highly efficacious in an AAV/HBV murine model compared to siRNA monotherapy. These findings further support the development of combination therapy of anti-viral siRNA and therapeutic vaccination in Chronic Hepatitis B patients.

Disclosures: Aditi Deshpande: Nothing to Disclose, Lei Qiugang: Nothing to Disclose, Sun Ya: Nothing to Disclose, Bharat Dixit: Nothing to Disclose, Aileen Rubio: Nothing to Disclose

1308 | TOLERABILITY AND IMMUNOGENICITY OF HBSAG VARIANTS, CLB-405 AND CLB-505, COMBINED WITH A NOVEL SEMI-SYNTHETIC SAPONIN ADJUVANT TQL-1055, IN NEW ZEALAND WHITE RABBITS

Aditi Deshpande[1] *Laurie Iciek*[2] *Bharat Dixit*[1] *Aileen Rubio*[1]

[1]*ClearB Therapeutics,* [2]*Biologics Consulting Group*

Background: CLB-405 and CLB-505 are HBsAg variants designed to display functional cure (FC) associated epitopes and were identified from antibody responses of FC Chronic Hepatitis B (CHB) patients (Walsh, R et al 2019. Liver Int 39(11) pp2066). We have shown that CLB-405 and CLB-505 when combined with a novel semi-synthetic saponin, TQL-1055, can provide both antigen-specific humoral and cellular immune responses, hypothesized to be essential for eliminating circulating HBsAg and infected hepatocytes (AASLD 2024 abstract submission ID 227461). The main objective of this study was to evaluate the safety, tolerability and humoral and cellular immune responses in NZW rabbits following repeat intramuscular (IM) injection of CLB-405 and CLB-505 adjuvanted with TQL-1055. **Methods:** Female NZW rabbits were dosed with either Placebo or CLB-405 and CLB-505 (500 µg total dose), combined with 800 µg TQL-1055. A total of 6 doses were administered IM on Days 1, 22, 43, 64, 85 and 106. Serum samples were taken periodically to measure production of anti-CLB-405 or anti-CLB-505 antibodies using a direct ELISA assay format. PBMCs were also collected to evaluate the cellular response by ELISPOT for detection of HBsAg-specific production of IFN-γ. **Results:** All animals

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survived to the day of euthanasia (Day 127), with no test article related clinical observations. Both CLB-405 and CLB-505 elicited a strong immune response in NZW rabbits as seen by significantly higher anti-CLB-405 and anti-CLB-505 geometric mean titers (GMT) compared to the placebo group animals. PBMC samples from animals treated with CLB-405 and CLB-505 had a higher IFN-γ response compared to placebo animals and unstimulated media control PBMC samples. **Conclusion:** CLB-405 and CLB-505 at a total dose of 500 µg combined with 800 µg of TQL-1055 adjuvant at 800µg dose was well-tolerated with no test article-related adverse effects on local tolerance. The vaccine stimulated both a humoral (anti-CLB-405 and anti-CLB-505 antibody) and cellular (ex vivo IFN-γ) response in female NZW rabbits. These findings further support the development of a vaccine with a balanced Th1/Th2 immune response for the potential treatment of CHB patients.

Disclosures: Aditi Deshpande: Nothing to Disclose, Laurie Iciek: Bristol Myers Squibb: Stock - publicly traded company, Abbott (AbbVie): Stock - publicly traded company, AstraZeneca (MedImmune): Stock - publicly traded company, ClearB: Consultant, Other Pharmaceutical Companies: Consultant, Bharat Dixit: Nothing to Disclose, Aileen Rubio: Nothing to Disclose

1309 | LOWER ALANINE AMINOTRANSFERASE NORMALIZATION DURING ANTIVIRAL TREATMENT IS ASSOCIATED WITH LOWER RISK OF HEPATOCELLULAR CARCINOMA IN CHRONIC HEPATITIS B

Hyunjun Park[1] Won-Mook Choi[2] Danbi Lee[2] Ju Hyun Shim[2] Kang Mo Kim[2] Young-Suk Lim[2] Han Chu Lee[2] Jonggi Choi[3]

[1]Asan Medical Center, University of Ulsan, [2]Asan Medical Center, [3]University of Ulsan, Asan Medical Center

Background: The occurrence of Hepatocellular Carcinoma (HCC) poses a significant concern in patients with Chronic Hepatitis B (CHB). Previous studies underscore the risk-lowering effects of Tenofovir Disoproxil Fumarate (TDF) and Entecavir (ETC) in CHB patients. Additionally, early normalization of Alanine Aminotransferase (ALT) levels has been associated with a decreased HCC risk. However, varying ALT criteria exist, necessitating a comprehensive investigation into the risk of HCC across different thresholds. This study seeks to assess the association between diverse ALT normalization criteria and the subsequent reduction in HCC risk. our goal is to determine whether lower thresholds can effectively reduce the risk of HCC in CHB patients. **Methods:** Between 2007 and 2017, a total of 4640 treatment- naïve patients with CHB who received treatment with ETV or TDF at Asan Medical Center, Seoul, Republic of Korea were retrospectively analyzed. The primary outcome under investigation was the incidence of newly diagnosed HCC. To assess Alanine Aminotransferase (ALT) normalization, two sets of criteria were employed. The first set considered ALT normalization as ≤40 U/L, while the second set utilized the following thresholds: ≤35 U/L for men and 25 U/L for women. A landmark analysis was conducted to explore the differences in the incidence of HCC across each ALT range. Following patients were excluded: patients with baseline ALT under 40, Patients who developed HCC within 1 year **Results:** During a median 5.4 years of treatment, 387 patients(10.3%) developed HCC. In the 1-year follow-up ALT analysis, the cohort comprised 934 individuals with ALT levels exceeding 40 U/L, 453 individuals with ALT levels ranging from 35 to less than 40 U/L for men and 25 to less than 40 U/L for women, and 2374 individuals with ALT levels below 35 U/L for men and below 25 U/L for women. When comparing the <35 U/L for men & <25 U/L for women group with the 35≤ <40 U/L for men and 25≤ <40 U/L for women group, the hazard was 1.7 times higher, while the >40 U/L group exhibited a hazard 2.1535 times higher. **Conclusion:** This study suggests that maintaining lower Alanine Aminotransferase (ALT) thresholds, specifically ≤35 U/L for men and ≤25 U/L for women, is associated with a significant reduction in the risk of Hepatocellular Carcinoma (HCC) in treatment-naïve patients with Chronic Hepatitis B (CHB) receiving Entecavir (ETV) or Tenofovir Disoproxil Fumarate (TDF)

Disclosures: Hyunjun Park: Nothing to Disclose, Won-Mook Choi: Nothing to Disclose, Danbi Lee: Nothing to Disclose, Ju Hyun Shim: Nothing to Disclose, Kang Mo Kim: Nothing to Disclose, Young-Suk Lim: Nothing to Disclose, Han Chu Lee: Nothing to Disclose, Jonggi Choi: GILEAD SCIENCE: Grant/Research Support

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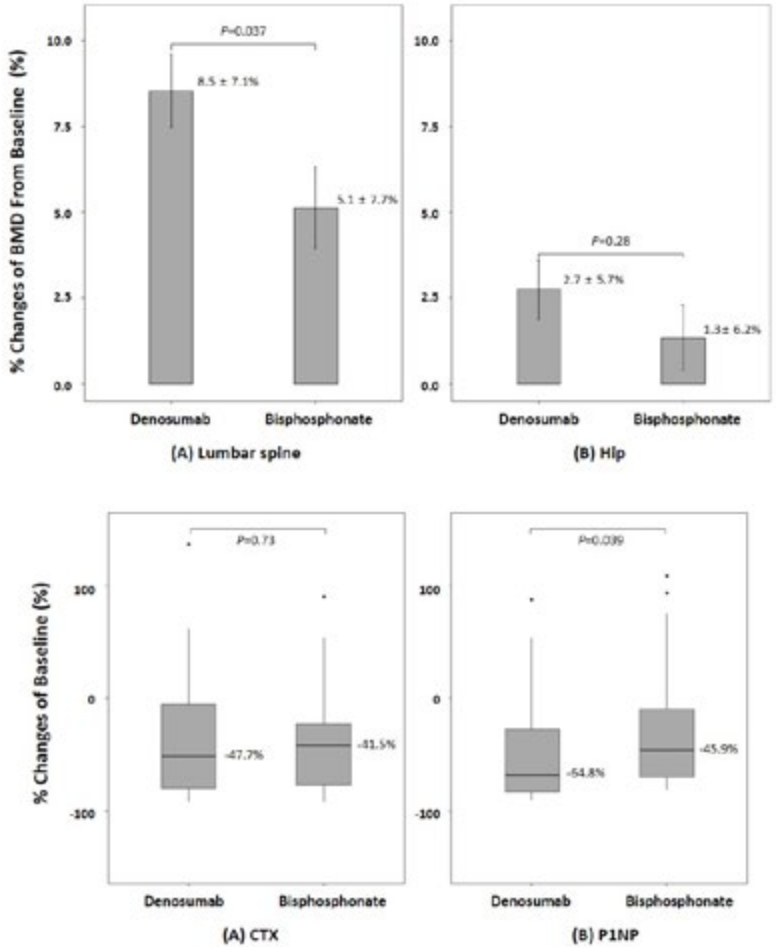
1310 | COMPARISON OF DENOSUMAB AND BISPHOSPHONATES FOR TENOFOVIR-INDUCED OSTEOPOROSIS IN PATIENTS WITH CHRONIC HEPATITIS B

Yunmi Ko[1] *Moon Haeng Hur*[1] *Jeong-Hoon Lee*[1]

[1]*Seoul National University Hospital*

Background: Tenofovir disoproxil fumarate (TDF), a first-line antiviral drug for chronic hepatitis B (CHB), is a risk factor for osteoporosis. This study aimed to compare the effectiveness of denosumab and bisphosphonates for TDF-induced osteoporosis in CHB patients. **Methods:** CHB patients who were treated with either denosumab or bisphosphonates for newly diagnosed osteoporosis during >1 year of TDF treatment between 2010 and 2022 were included from two tertiary centers in Korea. The primary outcome was bone mineral density (BMD) change at year 1. Secondary outcomes included changes in two bone turnover markers, procollagen type 1 N-terminal propeptide (P1NP) and C-telopeptide of type 1 collagen (CTX). **Results:** A total of 125 patients were included: 50 received denosumab and 75 received bisphosphonates. The median time to the diagnosis of osteoporosis from the TDF initiation was 4.6 (interquartile range=2.9–6.5) years. After balancing baseline characteristics using propensity score matching, the denosumab group showed a significantly greater increase in the lumbar spine BMD (denosumab vs. bisphosphonate: 8.5% vs. 5.1%, *P*=0.037), but comparable change in the hip (2.7% vs. 1.3%, *P*=0.28) at year 1. The denosumab group showed a significantly greater reduction in P1NP levels at year 1 (-64.8% vs. -45.9%, *P*=0.039), with no significant difference in CTX changes (-47.7% vs. -41.5%, *P*=0.73) compared to the bisphosphonates group. **Conclusion:** In CHB patients with TDF-induced osteoporosis, denosumab outperformed bisphosphonates in the lumbar spine BMD recovery but was comparable in the hip at year 1. The reduction in P1NP level was also more prominent in the denosumab group.



Disclosures: Yunmi Ko: Nothing to Disclose, Moon Haeng Hur: Nothing to Disclose, Jeong-Hoon Lee: Nothing to Disclose

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1311 | GENOME-WIDE OFF-TARGET ASSESSMENT OF EPIGENETIC MODULATION IN HUMAN PRIMARY HEPATOCYTES AND HBV TRANSGENIC MICE

Leilei Wu[1] Wenbo Peng[1] Junzheng Zhao[1] Shaoshuai Mao[1] Junjian Liu[1] Yifan Wang[1] Jing Sun[1] Di Sun[1] Ruimin Lv[1] Pinzheng Huang[1] Yingqi Li[1] Qi Zhu[1] Baohong Zhang[1] Yidi Sun[2] Changyang Zhou[3]

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Background: The persistence of hepatitis B virus (HBV) pose a major obstacle to eradicating chronic HBV infection. EPIREG® is a CRISPR-based epigenetic modulation tech using inactivated Cas9 fused with epigenetic modulator. It efficiently, specifically, and durably silences target genes, avoiding genomic safety issues from Cas9 cleavage. EPI-003, an anti-HBV preclinical development candidate discovered by EPIREG®,was designed for blocking HBV transcriptions by targeting HBV genome. To assess off-target effects of epigenetic modulation, we profiled DNA methylation, gene expressions, and histone modifications in HBV-infected primary human hepatocytes (PHHs) and transgenic (Tg) mice treated with EPI-003. **Methods:** Whole-genome bisulfite sequencing (WGBS) used for evaluation of off-target effect of CpG methylation whereas RNA sequencing (RNA-Seq) used for evaluation of gene expression levels were conducted in HBV-infected PHHs and HBV Tg mice treated with a saturating dose of EPI-003 for maximal HBsAg inhibition. Additionally, cleavage under Targets and Tagmentation (CUT&Tag) used for investigation histone modifications. An internally-created computational algorithm analyzed and merged genomic and transcriptomic data to delineate sgRNA-dependent and independent off-target effects. **Results:** Comparing transcriptome-wide gene expression in EPI-003-treated HBV Tg mice and PHHs with control groups, no significant differences were observed except for a downregulation of HBV encoded genes. WGBS revealed a significant increase in methylation levels at the regulatory region of HBV genome, accompanied by a marginal increase (0.7%) in genome-wide methylation which was not significantly different when compared EPI-003-treated with control groups for most of CpG sites. The CUT&Tag analysis demonstrated a marked decrease in H3K4me3, H3K9ac, and H3K27ac, as well as a significant increase in H3K9me3 only at the regulatory region of HBV genome, with no detectable changes in the host genomes in both systems. In addition, we integrated all three omics data and found no overlap between differentially expressed genes from RNA-seq and differential methylated regions (DMRs) from WGBS or differential abundant peaks from CUT&Tag analysis, except for the targeted sites on the HBV genome. We also performed sequence alignment of DMRs and differential abundant peaks using *in silico* to predict sgRNA-dependent off-target sites, and found minimal sequence similarity. **Conclusion:** Through multi-omics sequencing and in-house developed algorithm, we have established a rigorous yet applicable genome-wide assessment methodology in order for off-target evaluations for epigenetic drug discovery both *in vitro* and *in vivo*. It not only underscores the potential of epigenetic modulation as a potential therapeutic strategy but also sets a precedent for the meticulous evaluation of off-target effects in future epigenetic interventions.

Disclosures: Leilei Wu: Nothing to Disclose, Wenbo Peng: Nothing to Disclose, Junzheng Zhao: Nothing to Disclose, Shaoshuai Mao: Nothing to Disclose, Junjian Liu: Nothing to Disclose, Yifan Wang: Nothing to Disclose, Jing Sun: Nothing to Disclose, Di Sun: Nothing to Disclose, Ruimin Lv: Nothing to Disclose, Pinzheng Huang: Nothing to Disclose, Yingqi Li: Nothing to Disclose, Qi Zhu: Nothing to Disclose, Baohong Zhang: Nothing to Disclose, Yidi Sun: Nothing to Disclose, Changyang Zhou: Nothing to Disclose

1312 | EFFICACY OF PEG-IFNα-2B IN COMBINATION WITH NAS IN THE TREATMENT OF CHRONIC HEPATITIS B PATIENTS WITH/WITHOUT NON-ALCOHOLIC FATTY LIVER DISEASE: A MULTICENTER STUDY ◆

Jing Dou Xiaozhong Wang[1] Xin Da[2] Zhuangguo Wang[1] Yonghong Yue[1] Xiaobo Lu[3] Zhonghui Ning[1] Xiaobo Wang[1] Qiang Xu[1] Feng Guo[1] Min Chen[4] Shengtao Zeng[5] Yanqin Wu[6] Yongping Zhang[7] Huxi baiheti[1] Maimaitijiang Aishan Wubuli[8] Maimaitiaili Tuerxun[9]

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Background: Currently, studies on antiviral efficacy in chronic hepatitis B (CHB) combined with non-alcoholic fatty liver disease (NAFLD) are controversial, so the aim of this study is to evaluate the difference in efficacy of Peg IFNα-2b combined with NAs regimen in CHB patients combined with NAFLD or without NAFLD to provide a

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reference point for clinical treatment. **Methods:** This is a prospective, multicenter, real-world study that enrolled patients diagnosed with CHB with or without NAFLD and treated with NAs for more than 6 months. All participants were HBeAg negative, HBsAg ≤1500 IU/ml, and ALT <5 ULN. All subjects were treated with Peg-IFNα-2b in combination with NAs for 48 weeks. The primary endpoint was the difference in antiviral efficacy between CHB patients with NAFLD and CHB patients without NAFLD. Other endpoints included evaluation of the proportion of CHB patients with NAFLD who achieved HBsAg clearance or a decline of >1 log over 48 weeks of treatment with Peg-IFNα-2b in combination with NAs. **Results:** A total of 67 CHB patients with or without NAFLD from six medical centers from December 2022 to January 2024 were included in this study, of whom 54 patients were followed up to 24 weeks and 40 patients were followed up to 48 weeks. The proportion of undetectable HBV DNA in CHB patients without NAFLD was higher than that in CHB patients with NAFLD at 48 weeks of treatment compared to baseline (100.00%, 24/24 vs. 87.50%, 14/16) (P<0.05). HBsAg decreased significantly in CHB patients without NAFLD at 24 and 48 weeks of treatment (P<0.05), whereas in the group of CHB patients with NAFLD, the decrease in HBsAg did not reach statistical significance at 24 and 48 weeks of treatment (P>0.05). After 48 weeks of treatment, the proportion of patients with HBsAg decrease >1 log or who experienced clearance was higher in CHB patients without NAFLD than in CHB patients with NAFLD (37.50%, 9/24 vs. 15.00%, 6/16) (P>0.05). ALT increased significantly at 24 weeks and decreased at 48 weeks in both groups, with no significant difference between the groups. After 48 weeks of treatment, the weight of patients in both groups decreased, and the levels of white blood cells (WBC), neutrophils, platelets, and lymphocytes decreased significantly (P<0.05), but there was no significant difference between the groups. During the follow-up period, 1 patient developed fatty liver, 1 patient developed a skin rash, and all patients had no abnormalities in renal function and thyroid function. **Conclusion:** In CHB patients, the combination of NAFLD may be a negative influencing factor for Peg-IFNα-2b in combination with NAs antiviral therapy and HBsAg clearance.

Disclosures: Jing Dou: Nothing to Disclose, Xiaozhong Wang: Nothing to Disclose, Xin Da: Nothing to Disclose, Zhuangguo Wang: Nothing to Disclose, Yonghong Yue: Nothing to Disclose, Xiaobo Lu: Nothing to Disclose, Zhonghui Ning: Nothing to Disclose, Xiaobo Wang: Nothing to Disclose, Qiang Xu: Nothing to Disclose, Feng Guo: Nothing to Disclose, Min Chen: Nothing to Disclose, Shengtao Zeng: Nothing to Disclose, Yanqin Wu: Nothing to Disclose, Yongping Zhang: Nothing to Disclose, Huxi baiheti: Nothing to Disclose, Maimaitijiang Aishan Wubuli: Nothing to Disclose, Maimaitiaili Tuerxun: Nothing to Disclose

1313 | VIROLOGIC OUTCOME OF PEGINTERFERON FOR HBEAG-POSITIVE CHRONIC HEPATITIS B – A 20-YEAR FOLLOW-UP, ENTECAVIR-MATCHED STUDY

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Background: Functional cure of chronic hepatitis B (CHB) virus infection significantly reduces risk of hepatic events. Peginterferon treatment had a high rate of virologic response including hepatitis B surface antigen (HBsAg) seroclearance, in hepatitis B e antigen (HBeAg)-positive patients from previous studies. Direct comparison with oral antiviral agents in long-term follow-up is lacking. We aimed to study the virologic outcomes of patients with HBeAg-positive CHB who received peginterferon alfa-2b, compared to entecavir-treated patients. **Methods:** We included HBeAg-positive CHB patients who received peginterferon alfa-2b 1.5 μg/kg/week for 32 weeks and lamivudine 100mg/day for 52 or 104 weeks in years 2000-2004 from two randomized controlled trials, and compared them with those receiving entecavir treatment by 1:5 matching with age, sex, platelet count, serum alanine transaminase level and cirrhosis status. Patients were censored upon retreatment. The cumulative incidence of virologic response, including functional cure (*i.e.,* HBsAg seroclearance), HBeAg seroconversion and serum hepatitis B virus (HBV) DNA suppression, were analysed. **Results:** 85 HBeAg-positive patients in peginterferon group were followed for a median (interquartile range) of 13.8 (3.7 – 19.9) years, compared to 9.2 (6.0 – 12.2) years in 425 patients in entecavir group. Eight and 12 patients (9.4% *vs.* 2.8%) in the peginterferon and entecavir groups achieved HBsAg seroclearance. The cumulative incidences of HBsAg seroclearance were 1.2% and 1.7% at 5 years, 5.0% and 3.4% at 10 years, and 11.3% and 5.2% respectively (p=0.121) (Fig. 1A). 70 patients (82.4%) in peginterferon group achieved HBeAg seroconversion, compared to 134 patients (31.5%) in entecavir group. The cumulative incidences of HBeAg seroconversion were 59.1% and 28.7% at 5 years, and 65.7% and 36.6% at 10 years and 15 years respectively (p<0.001) (Fig. 1B). 55 (65%) and 33 (39%) patients in the peginterferon group had sustained HBeAg seroconversion and HBV DNA < 2,000 IU/mL throughout. 50

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(48.8%) peginterferon-treatment patients received oral antiviral retreatment at a mean of 8.0 years. Genotype B (compared to genotype C) (adjusted odds ratio [aOR] 11.05, 95% confidence interval [CI] 3.13-38.96; p<0.001) and undetectable HBV DNA at the end of peginterferon treatment (aOR 9.98, 95% CI 3.04-32.72; p<0.001) were factors associated with sustained virologic response. **Conclusion:** Peginterferon treatment is associated with more HBeAg seroclearance but not HBsAg seroclearance over time compared with entecavir treatment in patients with positive HBeAg. Further analysis on virologic outcomes on the peginterferon group without censoring will reveal its role in achieving functional cure.

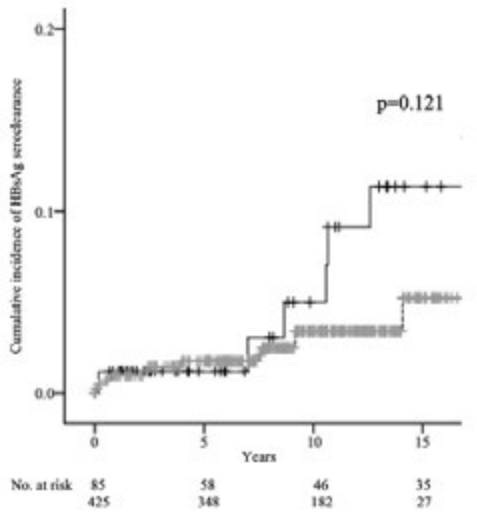

Fig. 1A Cumulative incidence of HBsAg seroclearance in HBeAg-positive patients

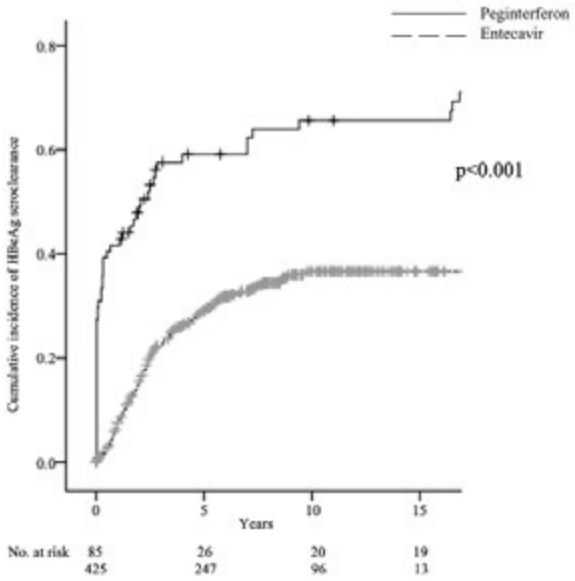

Fig. 1B Cumulative incidence of HBeAg seroclearance in HBeAg-positive patients

Disclosures: Che To Jimmy Lai: Nothing to Disclose, Vincent Wong: Abbott: Speaking and Teaching, AbbVie: Advisor, AbbVie: Speaking and Teaching, Boehringer Ingelheim: Advisor, Echosens: Advisor, Echosens: Speaking and Teaching, Gilead Sciences: Advisor, Gilead Sciences: Speaking and Teaching, Gilead Sciences: Grant/Research Support, Intercept: Advisor, Inventiva: Advisor, Novo Nordisk: Advisor, Novo Nordisk: Speaking and Teaching, Pfizer: Advisor, Sagimet: Advisor, TARGET PharmaSolutions: Advisor, Unilab: Speaking and Teaching, Visirna: Consultant, Illuminatio Medical Technology: Stock – privately held company, Vicki Hui: Nothing to Disclose, Yee-Kit TSE: Nothing to Disclose, Terry Cheuk-Fung Yip: Gilead Sciences: Consultant, Gilead Sciences: Advisor, Gilead Sciences: Speaking and Teaching, Henry Lik Yuen Chan: Aligos: Advisor, Arbutus: Advisor, GSK: Advisor, Roche: Advisor, Vaccitech: Advisor, Virion Therapeutics: Advisor, Precision BioSciences: Advisor, Grace Wong: AstraZeneca: Advisor, Gilead Sciences: Advisor, Gilead Sciences: Speaking and Teaching, Janssen: Advisor, GSK: Advisor, GSK: Speaking and Teaching, Abbott: Speaking and Teaching, AbbVie: Speaking and Teaching, AstraZeneca, Gilead Sciences, GlaxoSmithKline and Janssen,: Advisor, Abbott, AbbVie, Ascletis, Bristol-Myers Squibb, Echosens, Gi: Speaking and Teaching, Gilead Sciences: Grant/Research Support, AstraZeneca, Gilead Sciences, GlaxoSmithKline and Janssen: Consultant, Abbott, AbbVie, Ascletis, Bristol-Myers Squibb, Echosens, Gi: Speaking and Teaching, AstraZeneca, Gilead Sciences, GlaxoSmithKline Pharmaceutical: Consultant, Gilead Sciences: Independent Contractor, AstraZeneca, Gilead Sciences, GSK and Janssen,: Advisor, Abbott, AbbVie, BMS, Gilead Sciences, GSK, Janssen, Roche: Speaking and Teaching, Gilead Sciences: Grant/Research Support

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1314 | HLA GENOTYPE REGULATES HEPATITIS B VIRUS MUTATIONS ASSOCIATED WITH HEPATOCELLULAR CARCINOMA

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Background: Several viral mutations have been reported to predict the risk of developing hepatocellular carcinoma (HCC) in chronic hepatitis B. In particular, the C1653T and A1762T/G1764A mutations in the core promoter region have been widely reported, but these mutations may not be reproducible between studies. The reasons for the uncertain reproducibility remain unclear, partly because it is unclear whether this is due to differences in patient populations between studies. On the other hand, genetic polymorphisms in the HLA-DPB1 region have been reported in patients with HCC in GWAS-based analyses, highlighting the importance of HLA genotypes. In this study, patients were classified according to their HLA-DPB1 genotype and the pattern of HBV mutations associated with liver carcinogenesis was analysed. **Methods:** A total of 2996 cases were enrolled in this multicentre study in Japan. These included 408 cases of CHB, 307 cases of HCC and 2281 healthy subjects. In this study, among the HLA-DPB1 genotypes, we focused on HLA-DPB1*05:01 (about 40%) and HLA-DPB1*02:01 (about 20%), which are commonly carried by Japanese, and established four groups of homo- and heterozygotes of each. Within these four groups, HBV sequence comparisons were made between CHB and HCC matched for age, sex and HBV genotype. **Results:** In the analysis of the patient carrying HLA-DPB1*05:01 as homozygote, the A1762T/G1764A mutation in the core promoter region was significantly detected in the HCC population compared to the CHB population ($p < 0.001$, OR=8.8: 95%CI 4.4-17.8). In addition, the C1653T mutation was significantly detected in the HCC population with heterozygous HLA-DPB1*05:01 compared to the CHB population ($p < 0.001$, OR=4.4: 95%CI 2.0-9.6). In contrast, analysis of the homozygous HLA-DPB1*02:01 population revealed a significant C129T mutation in the PreS2 region ($p < 0.02$, OR=23.8: 95%CI 4.5-119.8). Similarly, analysis of the HLA-DPB1*02:01 heterozygote population revealed a significant C129T mutation in the PreS2 region ($p < 0.01$, OR=33.1: 95%CI 11.3-96.5). The C129T mutation of the HBV genome in the PreS2 region was novel. **Conclusion:** The pattern of HBV mutations associated with HCC development varies according to HLA genotype. Stratification using human disease-related genes partly explains why viral mutations differ between individuals. This stratification approach to risk assessment may lead to useful prognostication.

Disclosures: Masaya Sugiyama: Nothing to Disclose, Nao Nishida: Nothing to Disclose, Aiko Sakai: Nothing to Disclose, Katsushi Tokunaga: Nothing to Disclose

1315 | RENAL FUNCTION COMPARISON BETWEEN ENTECAVIR AND TENOFOVIR ALAFENAMIDE IN TREATMENT-NA&IUML;VE CHRONIC HEPATITIS B

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Background: Limited studies have directly compared the renal safety profiles between Entecavir (ETV) and tenofovir alafenamide (TAF). Therefore, we conducted a comparative analysis to assess the risk of renal function decline among treatment-naïve chronic hepatitis B (CHB) patients treated with these two regimens. **Methods:** This retrospective study enrolled treatment naïve CHB patients treated with ETV or TAF for at least 48 weeks between September 2019 and November 2023. Post-treatment estimated glomerular filtration rate (eGFR) and incidence of abnormal renal function (eGFR < 90 ml/min/1.73 m^2) were compared between the two groups at week 48. **Results:** A total 190 patients were recruited (ETV group, n=112; TAF group, n=78) and 1: 1 propensity score matching (PSM) resulted in 76 patients in each group. After PSM, baseline characteristics were balanced between the two groups. After 36 weeks of treatment, the mean eGFR was 109.93 ml/min/1.73 m^2 vs. 115.12 ml/min/1.73 m^2 in the ETV and TAF groups respectively, with a significant statistical difference ($p<0.05$). Multivariable Logistic regression analysis showed that baseline eGFR (OR 0.87, 0.80~0.94, $p<0.001$) and the antiviral regimen (ETV/TAF) (OR 0.21, 0.05~0.90, $p=0.035$) were independently associated with renal abnormalities. 7 (9.21%) patients in the ETV group were switched to TAF due to eGFR abnormality at week 48, the eGFR values in the ETV to TAF group increased from 87.84 ml/min/1.73m^2 to 92.02 ml/min/1.73m^2. **Conclusion:** Compared with TAF-treated patients, ETV treatment in treatment-naïve CHB was associated with a higher risk of renal function

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decline. In ETV-treated patients with eGFR abnormalities, there was a substantial improvement in renal function after switching to TAF.

Disclosures: Wang Liang: Nothing to Disclose, Shipeng Ma: Nothing to Disclose, Liping Liu: Nothing to Disclose, Xin Wan: Nothing to Disclose, Yujing Zhang: Nothing to Disclose, Shanfei Ge: Nothing to Disclose

1316 | NEW TRANSIENT ELASTOGRAPHY (TE) DEVICE HEPATUS® SHOWS SUPERIOR EFFICIENCY AND STRONG COMPARABLE TO A CONVENTIONAL TE DEVICE IN LIVER STIFFNESS MEASUREMENT FOR CHB AND NAFLD PATIENTS

Shuyan Chen[1] Tongtong Meng[2] Mengyang Zhang[2] Chenglin Sun[2] Xiaojuan Ou[2] Xiaoning Wu[2] Jingjie Zhao[2] Bingqiong Wang[2] Xiaowei Ai[2] Siru Wu[2] Hua Li[3] Xinyan Zhao[2] Xiaoqian Xu[2] Yuanyuan Kong[2] Jidong Jia[2] Yameng Sun[2] Hong You[2]

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Background: Transient elastography has been widely used in clinical practice and clinical trials to assess the liver fibrosis stage. Recently, a new transient elastography device, Hepatus®, can assess liver fibrosis using real-time two-dimensional ultrasound guidance. This study investigates the correlation of fibrosis assessment between Hepatus® and FibroScan®502. **Methods:** Hepatus® has one probe for ultrasound visual guidance and quantitative detection, making the quantitative evaluation of liver fibrosis under the visual guidance of real-time 2D ultrasound. Ten groups of adequate data can be automatically continuously acquired and intelligently screened by pressing one button (mode of continuous detection). We conducted a prospective single-center study of CHB and NAFLD patients. All patients performed three times of fibrosis assessments, including manual localization by FibroScan®502, the same point with single detection mode and continuous detection mode of Hepatus®. **Results:** A total of 423 patients were enrolled. Of those, 18% (n = 76) were compensated cirrhosis. The median values of liver stiffness of all patients were 6.1 (4.9, 8.8) kPa in FibroScan®502, 6.8 (5.7, 9.7) kPa and 6.8 (5.6, 9.5) kPa in the same point with single detection mode and continuous detection mode of Hepatus® respectively. The liver stiffness values based on FibroScan®502 were significantly correlated with both the detections undergoing the same point with single detection mode and continuous detection mode of Hepatus®, respectively ($r > 0.9$, $P < 0.001$). The median rates of successful detection were both 100% (100%, 100%) in the two times detections of Hepatus® and 100% (91%, 100%) in FibroScan®502 ($P < 0.001$). The median time of the total detection based on Hepatus® (single detection mode: 40.9s; continuous detection mode: 21.2s) was significantly less than that by FibroScan®502 (98.2s; $P < 0.001$). The same results were also shown in the subgroup analysis of cirrhosis and non-cirrhosis patients. **Conclusion:** Hepatus® demonstrated excellent correlation with FibroScan®502 for liver stiffness measurement and required less time in patients with CHB and NAFLD.

Disclosures: Shuyan Chen: Nothing to Disclose, Tongtong Meng: Nothing to Disclose, Mengyang Zhang: Nothing to Disclose, Chenglin Sun: Nothing to Disclose, Xiaojuan Ou: Nothing to Disclose, Xiaoning Wu: Nothing to Disclose, Jingjie Zhao: Nothing to Disclose, Bingqiong Wang: Nothing to Disclose, Xiaowei Ai: Nothing to Disclose, Siru Wu: Nothing to Disclose, Hua Li: Nothing to Disclose, Xinyan Zhao: Nothing to Disclose, Xiaoqian Xu: Nothing to Disclose, Yuanyuan Kong: Nothing to Disclose, Jidong Jia: Nothing to Disclose, Yameng Sun: Nothing to Disclose, Hong You: Nothing to Disclose

1317 | LONG-TERM EFFICACY OF THE HEPATITIS B VACCINE: A 24-YEAR FOLLOW-UP STUDY OF 6,645 VACCINATED INDIVIDUALS

Saad Alghamdi[1] Abdulrahman Ibn Awadh[1] Khulud Alanazi[1] Dimitri Raptis[1] Saleh Alqahtani[1] Dieter Broering[1] Waleed Al Hamoudi[2]

[1]King Faisal Specialist Hospital, [2]King Saud University/KKUH

Background: Hepatitis B is a significant global health concern; it is a leading cause of cirrhosis and hepatocellular carcinoma. The hepatitis B vaccine has played a major role in preventing HBV infection and reducing the prevalence of the disease in many countries. In 1989, the Saudi government launched a mass vaccination program

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against HBV. The aim of this study is to evaluate the durability and efficacy of the vaccine in a large cohort of healthy individuals over a long period of time. **Methods:** Data were obtained from a prospectively maintained registry at our center. Demographic data and anti-hepatitis B surface antigen antibody (anti-HBsAb) levels of all consecutive individuals evaluated for living liver donation were analyzed. Anti-HBsAb ≥10 IU/L were considered as seroprotective. Statistical analysis was performed on R. **Results:** Data from 6,645 healthy individuals who received vaccination at birth were included. The median age at time of Anti-HBsAb level quantification was 33 (IQR 28-38) years, 29% were females, with a median BMI of 25.1 (IQR 22.3-17.5). Only 36% maintained a protective Anti-HBsAb ≥10 IU/L. The median age of individuals with protective levels was 34 (29-37) while for those with Anti-HBsAb ≥10 IU/L was 32 (IQR 27-39), p=0.230. None of the vaccinated individuals developed HBV infection irrespective of the Anti-HBsAb levels. **Conclusion:** Given that none of the vaccinated individuals developed HBV infection regardless of antibody titers above or below the traditional 10 mIU/mL threshold, and considering emerging evidence on the protective role of memory B cells and the potential adequacy of lower antibody levels, the efficacy of this cutoff in predicting long-term immunity warrants further investigation.

Disclosures: Saad Alghamdi: Nothing to Disclose, Abdulrahman Ibn Awadh: Nothing to Disclose, Khulud Alanazi: Nothing to Disclose, Dimitri Raptis: Nothing to Disclose, Saleh Alqahtani: Nothing to Disclose, Dieter Broering: Nothing to Disclose, Waleed Al Hamoudi: Nothing to Disclose

1318 | KINETICS AND PREDICTION OF HBSAG SEROCLEARANCE DURING LONG-TERM TREATMENT WITH NUCLEOS(T)IDE ANALOGUES IN PATIENTS WITH CHRONIC HEPATITIS B

Yim Sun Young[1] Sarah Hyun[2] Seoyoung Song[2] YEON SEOK SEO[2] Young-Sun Lee[2] Hyung Joon Yim[2] Ji Hoon Kim[2] Young Kul Jung[2] Seong Hee Kang[2] Taehyung Kim[3] Jong Eun Yeon[2] Eunho Choi[2]

[1]Korea University Anam Hospital, [2]Korea University Hospital, [3]Hallym University Hospital

Background: Serum Hepatitis B Surface Antigen (HBsAg) seroclearance is the ultimate goal in the treatment of chronic hepatitis B (CHB) patients, but is a rare event. The factors influencing HBsAg seroclearance remain unclear. This study aims to investigate the long-term kinetics of HBsAg levels according to different nucleos(t)ide analogues (NUCs) and identify predictors of functional cure (HBsAg seroclearance). **Methods:** We conducted a retrospective observational study of patients treated with one of the following NUCs: entecavir (ETV), tenofovir disoproxil fumarate (TDF), tenofovir alafenamide fumarate (TAF), or besifovir (BSV). The patients were enrolled from 2007 to 2023 and were followed-up for at least one year and HBsAg levels were quantified every 6-12 months. **Results:** A total of 539 CHB patients treated with first-line NAs were included, with a follow-up duration of 61.5 months. Baseline HBV DNA and HBsAg level were significantly higher in HBeAg patients compared to HBeAg negative patients (3.72 ± 0.81 vs 3.02 ± 0.99 IU/mL). During follow-up, 24 patients (4.4%) achieved functional cure within 44 months and 33 patients (6.1%) achieved significant HBsAg reduction (>2 $\log_{10}$ IU/mL). The first-year mean HBsAg log reduction was 0.21 log IU/mL, significantly higher than reductions in the second (0.10 $\log_{10}$IU/mL, p=0.017) and third (0.06 log IU/mL, p=0.004) years. All four NA groups showed consistent reductions in HBsAg levels throughout without significant difference within 3 years of treatment but a significant decrease was observed in TAF treated patient after 3 years of treatment compared to other types of NUCs. The first-year HBsAg reduction rate was positively associated with baseline HBsAg levels (p=0.013). Key predictors for functional cure included lower baseline HBsAg levels (<3 log IU/mL) and a higher first-year HBsAg reduction rate of ≥1 log IU/mL (both, p<0.001). The estimated time for functional cure in TAF, TDF and ETV treated patients were 67.3, 71.4, 94.3 months, respectively. None of the patients who achieved functional cure developed hepatocellular carcinoma (HCC), while 34 patients (8.1%) among those who did not achieved functional cure progressed to HCC. **Conclusion:** Consistent HBsAg reduction was observed throughout treatment with no significant differences among the four NUCs. However, further decrease in HBsAg level can be expected in TAF treated patients after a prolonged treatment duration compared to other treatment groups. Low baseline HBsAg levels and higher reduction rates of HBsAg in the first year of treatment, may be reliable factors in predicting HBsAg seroclearance.

Disclosures: Yim Sun Young: Nothing to Disclose, Sarah Hyun: Nothing to Disclose, Seoyoung Song: Nothing to Disclose, YEON SEOK SEO: Nothing to Disclose, Young-Sun Lee: Nothing to Disclose, Hyung Joon Yim: Nothing to Disclose, Ji Hoon Kim: Nothing to Disclose, Young Kul Jung: Nothing to Disclose, Seong Hee Kang: Nothing to Disclose, Taehyung Kim: Nothing to Disclose, Jong Eun Yeon: Nothing to Disclose, Eunho Choi: Nothing to Disclose

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1319 | SIGNIFICANT INCREASE IN RISK OF HEPATIC FURTHER DECOMPENSATION FROM EXCESSIVE ALCOHOL USE IN PATIENTS WITH CHRONIC HEPATITIS B-RELATED DECOMPENSATED CIRRHOSIS

Vicki Wing-Ki Hui[1] Zeyuan Yang[2] Che To Jimmy Lai[1] Ramsey Cheung[3] Terry Cheuk-Fung Yip[1] Vincent Wai-Sun Wong[4] Grace Wong[4] Robert Wong[5]

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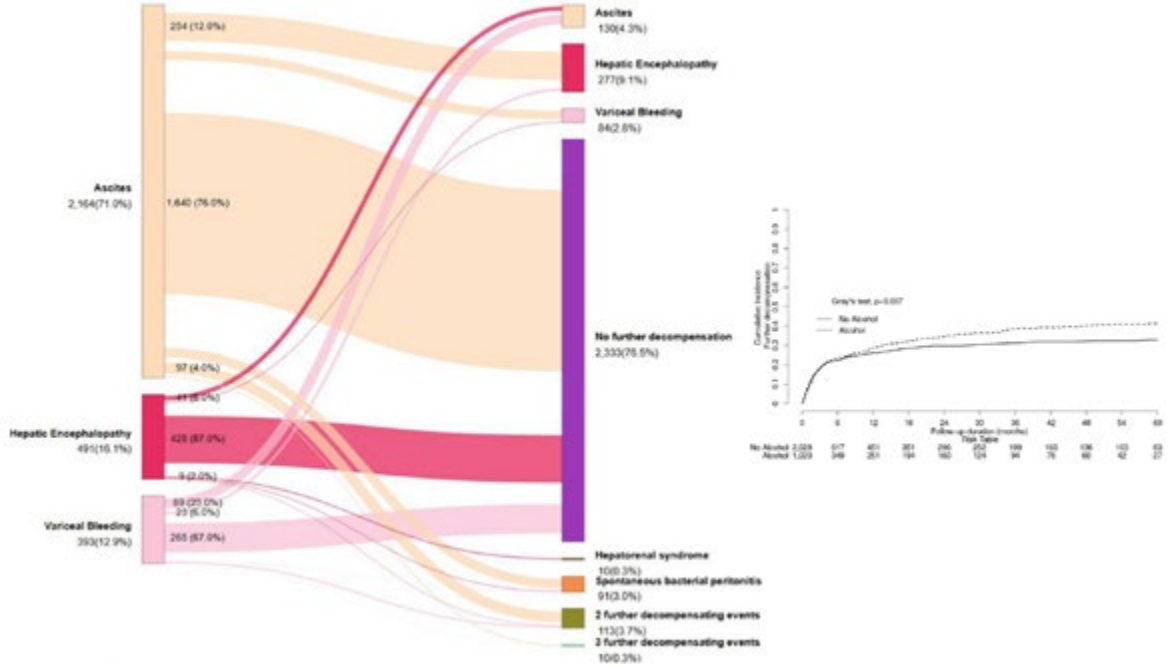
Background: While long-term antiviral therapy with nucleos(t)ide analogues (NA) effectively reduces the risk of hepatic decompensation in patients with chronic hepatitis B (CHB)-related cirrhosis, research on the impact of alcohol consumption is limited. Individuals with excessive alcohol use are often excluded from clinical trials for NA therapy. This study aimed to assess the impact of self-reported excessive alcohol consumption on the rate of further decompensation in patients with CHB-related decompensated cirrhosis receiving NA therapy. **Methods:** Patients who were treated with entecavir or tenofovir with CHB-related decompensated cirrhosis from 2017 to 2023 were identified from a Hong Kong territory-wide database. Excessive alcohol consumption was determined using a combination of ICD-9/10 codes based on drinking status and alcohol consumption levels (i.e. pure alcohol use amount >50 ml/day). First decompensation was defined as the development of ascites, hepatic encephalopathy, and variceal bleeding. Further decompensation was defined as non-duplicate decompensating events including ascites, hepatic encephalopathy, variceal bleeding, jaundice, hepatorenal syndrome, and repeated paracentesis, that occurred after the first decompensating event as specified by the Baveno VII consensus. Patients were followed until further decompensation, death, or for a period of 5 years, whichever earlier. **Results:** We identified 3,048 patients with CHB-related Baveno VII-defined decompensated cirrhosis (mean age 65 years, 73% male), among whom 1,020 (33%) reported excessive alcohol consumption. Overall, 715 (23.5%) patients developed further decompensation and 445 (14.6%) died during follow-up. Of 715 patients who had further decompensation, 123 (17.2%) had multiple further decompensating events. The most common further decompensating event was hepatic encephalopathy (277, 38.7%). The median [IQR] time to further decompensation was 1.8 [0.8, 5.2] months in those who never consumed alcohol, and 2.6 [1.0, 10.5] months in those who had consumed excessive alcohol. The incidence of further decompensation over time was significantly higher in patients with excessive alcohol consumption than those without (41.3% [37.1%, 45.3%] vs. 32.8% [30.1%, 35.4%] at 5 years, p=0.007). **Conclusion:** Excessive alcohol consumption significantly increases the risk of further decompensation in CHB-related cirrhotic patients treated with NA. The findings highlight the importance of considering alcohol use history in clinical decision-making to optimize treatment outcomes for these patients.



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Disclosures: Vicki Wing-Ki Hui: Nothing to Disclose, Zeyuan Yang: Nothing to Disclose, Che To Jimmy Lai: Nothing to Disclose, Ramsey Cheung: Nothing to Disclose, Terry Cheuk-Fung Yip: Gilead Sciences: Consultant, Gilead Sciences: Advisor, Gilead Sciences: Speaking and Teaching, Vincent Wai-Sun Wong: Nothing to Disclose, Grace Wong: AstraZeneca: Advisor, Gilead Sciences: Advisor, Gilead Sciences: Speaking and Teaching, Janssen: Advisor, GSK: Advisor, GSK: Speaking and Teaching, Abbott: Speaking and Teaching, AbbVie: Speaking and Teaching, AstraZeneca, Gilead Sciences, GlaxoSmithKline and Janssen,: Advisor, Abbott, AbbVie, Ascletis, Bristol-Myers Squibb, Echosens, Gi: Speaking and Teaching, Gilead Sciences: Grant/Research Support, AstraZeneca, Gilead Sciences, GlaxoSmithKline and Janssen: Consultant, Abbott, AbbVie, Ascletis, Bristol-Myers Squibb, Echosens, Gi: Speaking and Teaching, AstraZeneca, Gilead Sciences, GlaxoSmithKline Pharmaceutical: Consultant, Gilead Sciences: Independent Contractor, AstraZeneca, Gilead Sciences, GSK and Janssen,: Advisor, Abbott, AbbVie, BMS, Gilead Sciences, GSK, Janssen, Roche: Speaking and Teaching, Gilead Sciences: Grant/Research Support, Robert Wong: Theratechnologies: Grant/Research Support, Durect: Grant/Research Support, Gilead Sciences: Grant/Research Support, Exact Sciences: Grant/Research Support, Theratechnologies: Grant/Research Support, Durect Corporation: Grant/Research Support

1320 | SINGLE-CELL PROFILING OF HBV-ASSOCIATED HEPATOCELLULAR CARCINOMA REVEALS NOVEL HBV-RELATED TUMOR-IMMUNE INTERACTION

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Background: While the tumor microenvironment (TME) associated with HBV-related hepatocellular carcinoma (HCC) and its role in tumor progression has been studied, the mechanisms by which HBV shapes the immune profile to facilitate tumor immune escape remain unclear. This study aims to elucidate how HBV alters immune checkpoint ligand expression on HCC, thereby facilitating immune escape. **Methods:** Advanced techniques such as single-cell RNA sequencing, bulk RNA sequencing, NanoString GeoMx Digital Spatial Profiler (DSP) analysis and multiplex immunohistochemistry were employed to delineate tumor heterogeneity in patients with HBV-associated HCC. **Results:** Our findings revealed that HBV-positive and HBV-negative HCC cells expressed differential immune checkpoint ligands, mediating various interactions with both $CD8^+$ and $CD4^+$ T cells, particularly regulatory T cells (Tregs). Additionally, we utilized *in vitro* and *in vivo* models to investigate the functional consequences of HBV-induced changes in immune cell behavior and tumor immune escape. **Conclusion:** Our findings suggest that HBV plays a pivotal role in reprogramming the immune profile of the TME by regulating immune checkpoint ligand expression on HCC cells. Understanding these mechanisms provides crucial insights into potential prognostic markers and therapeutic targets to restore anti-tumor immunity in patients with HBV-related HCC.

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Single-cell profiling of HBV-associated hepatocellular carcinoma reveals novel HBV-related tumor-immune interaction

Pei-Ching Chang[1], Jiunn-Chang Lin[2], Kai-Ting Yu[1], Yung-Chih Hong[1], Tze-Yun Hu[1], Kai-Hsiang Hsu[1], Kate Hua[1], Chih-Sin Hsu[1], Tai-Ming Ko[1], Li-Ling Wu[1], Chun-Ying Wu[1], Yan-Hwa Wu Lee[1]

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While the tumor microenvironment (TME) associated with HBV-related hepatocellular carcinoma (HCC) and its role in tumor progression has been studied, the mechanisms by which HBV shapes the immune profile to facilitate tumor immune escape remain unclear. This study aims to elucidate how HBV alters immune checkpoint ligand expression on HCC, thereby facilitating immune escape. Advanced techniques such as single-cell RNA sequencing, bulk RNA sequencing, NanoString GeoMx Digital Spatial Profiler (DSP) analysis and multiplex immunohistochemistry were employed to delineate tumor heterogeneity in patients with HBV-associated HCC. Our findings revealed that HBV-positive and HBV-negative HCC cells expressed differential immune checkpoint ligands, mediating various interactions with both $CD8^+$ and $CD4^+$ T cells, particularly regulatory T cells (Tregs). Additionally, we utilized *in vitro* and *in vivo* models to investigate the functional consequences of HBV-induced changes in immune cell behavior and tumor immune escape. Our findings suggest that HBV plays a pivotal role in reprogramming the immune profile of the TME by regulating immune checkpoint ligand expression on HCC cells. Understanding these mechanisms provides crucial insights into potential prognostic markers and therapeutic targets to restore anti-tumor immunity in patients with HBV-related HCC.

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1322 | EFFECT OF AGE AND DEVELOPMENT OF LIVER AND OTHER ORGAN CANCERS ON HBS ANTIGEN LOSS IN HEPATITIS B PATIENTS

Takashi Honda[1] Kazuyuki Mizuno[1] Shinya Yokoyama[2] Kenta Yamamoto[3] Takanori Ito[3] Norihiro Imai[1] yoji ishizu[3] Yoshiki Murakami[4] Tetsuya Ishikawa[3] Hiroki Kawashima[3]

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Background: The goal of hepatitis B treatment is HBs antigen loss (functional cure: FC). Factors affecting FC are unclear. We encountered a patient who achieved FC during nucleic acid analogue treatment as HBs antigen decreased rapidly with the development of cancer including hepatocellular carcinoma (HCC). **Methods:** 102 patients with seroclearance from HBs antigen positive to negative (FC) were examined. Factors affecting FC, including gender, IFN treatment history, acute exacerbation, presence or absence of steatotic liver disease (SLD), and the cancer within 3 years prior to FC were compared. Survival curves were calculated by Kaplan-Meier at around 50, 60, and 70 years of age, and the Log Rank test was performed to test for differences. **Results:** When achieving FC, the median age was 59 years, ALT 17 U/L, Alb 4.2 g/dL, and platelet level 18.8 x 10^4/μL. There were 12 patients with cirrhosis; 10 patients had previous IFN treatment, 9 had acute exacerbation, and 22 had SLD. Six patients had HCC within three years prior to FC, and six developed other cancers. Comparison of patient backgrounds at the time of FC between the cancer (n=12) and non-cancer (n=90) groups showed significantly lower Alb in the cancer group. Comparing the younger group (n=27, aged <50 years) and the older group (n=24, aged ≥70 years), the younger group had a significantly higher incidence of acute exacerbation ($P<0.05$). No cirrhosis or new hepatocarcinogenesis has been observed in the 27 patients who achieved FC before 50 years of age. There were no deaths among those who achieved FC before 50 years of age, with a 10-year survival rate

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of 72.6% among those who achieved FC after 50 years of age. The prognosis was significantly better in patients with FC before 60 years of age (94.4% at 10 years) compared to patients with FC after 60 years of age (64.9% at 10 years) (P=0.020). **Conclusion:** Achievement of FC in young patients was associated with acute exacerbation. The absence of cirrhosis at FC before 50 years of age was associated with a better prognosis than FC after 60 years of age, with no subsequent cirrhosis or HCC. The low Alb levels in patients with carcinoma at the time of FC suggested the need for follow-up with imaging tests, including for occult cancer, even in patients with low or no detectable HBsAg.

Disclosures: Takashi Honda: Nothing to Disclose, Kazuyuki Mizuno: Nothing to Disclose, Shinya Yokoyama: Nothing to Disclose, Kenta Yamamoto: Nothing to Disclose, Takanori Ito: Chugai Pharmaceutical Co., Ltd.: Grant/Research Support, Chugai Pharmaceutical Co., Ltd. and AstraZeneca: Speaking and Teaching, Norihiro Imai: Nothing to Disclose, yoji ishizu: Nothing to Disclose, Yoshiki Murakami: Nothing to Disclose, Tetsuya Ishikawa: Nothing to Disclose, Hiroki Kawashima: Nothing to Disclose

1323 | INCREASED HEPATITIS D VIRUS (HDV) DETECTION IN HEPATITIS B VIRUS (HBV) PATIENTS UTILIZING A MODIFIED HDV REFLEX TESTING PROTOCOL

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Background: Hepatitis Delta Virus (HDV) testing practices within the Hepatitis B Virus (HBV) patient population are limited, with studies indicating that fewer than 25% of HBV patients are tested for HDV. As a rare infectious disease, HDV exacerbates liver disease, cirrhosis, and hepatocellular carcinoma when co-infected with HBV. The current AASLD testing guidelines recommend HDV testing only for HBV patients with known risk factors, starting with HDV antibody (HDV-Ab) and, if positive, proceeding with HDV-RNA testing. The reported limited testing for HDV hinders the identification of co-infected patients, establishing essential linkage to care and initiation of therapeutic treatments. This study was designed to implement a modified reflex testing in the HBV patient population to identify the prevalence of HDV and to assess newly reported HDV-RNA positivity in the absence of HDV antibody. **Methods:** All HBV surface antigen-positive (HBsAg+) plasma samples were acquired from the University of Utah UHealth patient population (12/2023-5/2024) and tested at ARUP National Reference Lab. Plasma samples were tested for HDV-Ab (IgM, IgG total antibody) and HDV-RNA, regardless of HDV-Ab status. Electronic health records were evaluated to define the overall demographics and comorbidities of the tested samples. Statistical analyses included Student's t-test, Fisher's exact test, and Chi-squared test. **Results:** This study evaluated HBsAg(+) plasma samples (n=128) and performed reflex testing for HDV. Among the HBsAg(+) samples evaluated, 51% were from females. 50% of HDV(+) samples were from females. The average age of the HBsAg(+) cohort was 47.0 ± 15.1 years, while the HDV(+) cohort was 52.0 ± 15.9 years. Of the HBsAg(+) samples, 6.3% (8/128) tested positive for HDV, with 87.5% (7/8) positive for HDV-Ab and 25.0% (2/8) positive for both HDV-Ab and HDV-RNA. The modified reflex testing protocol of testing for HDV-RNA and HDV-Ab identified 12.5% (1/8) positive for HDV-RNA but negative for detectible HDV-Ab. **Conclusion:** Reflex testing of HBsAg(+) patients for HDV identified more cases that may otherwise be overlooked. The detection of HDV-RNA in the absence of HDV antibody suggests that the current AASLD testing guidelines might miss certain clinical phenotypes. This study, along with similar reports, underscores the need for implementing reflex testing for HDV in all HBV patients to ensure comprehensive identification and appropriate clinical management.

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1324 | FINAL RESULTS OF GATE STUDY: A PROGRAM TO NARROW GAP BETWEEN IN ACCORDANCE WITH GUIDELINES AND CONSENT TO TREAT CHB POPULATION IN EAST OF CHINA ◆

Shaoqiu Zhang[1] Jian Wang[1] Yifan Pan[2] Yuanyuan Li[2] Tao Fan[3] Ye Xiong[3] Chao Jiang[4] Xiaomin Yan[1] Li Wang[1] Zhaoping Zhang[1] Sufang Lu[1] Jie Li[1] Rui Huang[1] Chao Wu[1]

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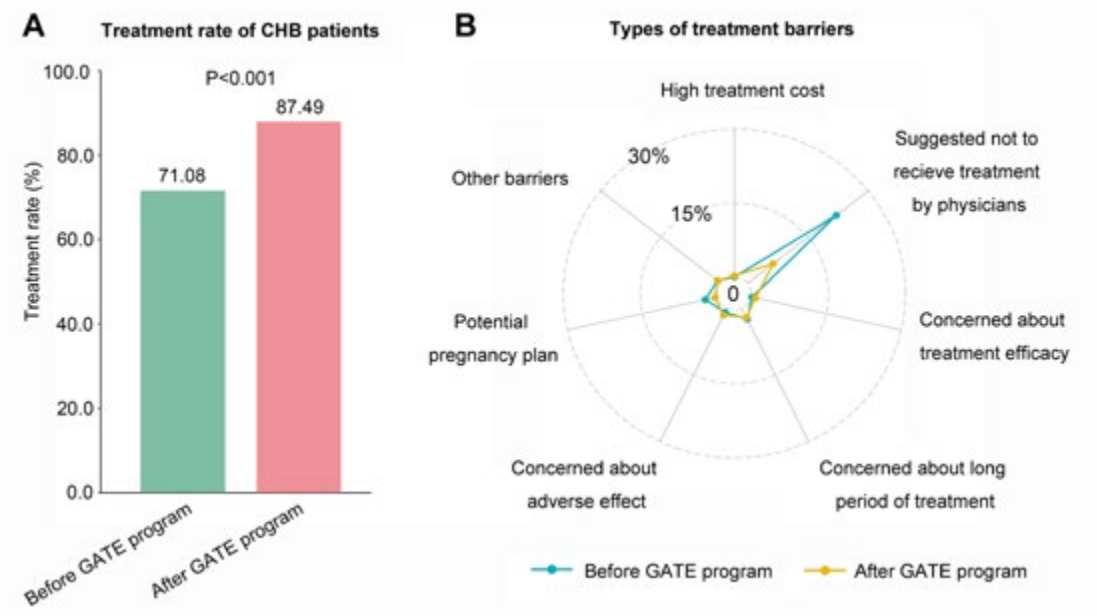
Background: Antiviral treatment can delay the disease progression and reduce the incidence of hepatocellular carcinoma (HCC) in patients with chronic hepatitis (CHB). However, the treatment rate is low for patients with CHB and a major treatment gap remains. We investigated the barriers to antiviral treatment and conducted a program to increase the treatment rate of patients with CHB who met the treatment criteria. **Methods:** We established a retrospective cohort and a prospective cohort of treatment-naïve CHB patients from January 2019 to October 2021 and from November 2021 to May 2024, respectively. Treatment-naïve CHB patients who fulfilled with indications for antiviral treatment according to Chinese 2019 CHB guidelines were regarded as treatment-eligible and included. A standardized questionnaire survey was conducted to evaluate the treatment status of patients and explore the possible treatment barriers. A program with integrated intervention strategies, including medical education and follow-up alert, was implemented to narrow the Gap between in Accordance with guidelines and consent to Treat CHB population in East of China (GATE) and improve the treatment uptake. **Results:** Before the integrated intervention strategies, 1134 treatment-eligible CHB patients were included, whereas 911 patients were enrolled after the implementation of the GATE program. The major treatment barriers including physicians' suggestions not to treatment (22.05%) and patients' varying concerns, including concerns about long period of treatment (2.47%). After the implement of integrated strategies, the rate of antiviral treatment significantly increased from 71.08% to 87.49% (P<0.001). There was a significant decrease (from 22.05% to 6.37%, P<0.001) in proportion of patients not suggested to receive treatment by their physicians. **Conclusion:** The inadequate adherence to guidelines for CHB treatment in physicians is one of the major treatment barriers. The integrated intervention strategies including the physician education significantly increase the treatment rate of indicated-but-not-treated CHB patients. This approach could contribute to overcoming the barriers in hepatitis B treatment and improving treatment uptake.



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Nothing to Disclose, Sufang Lu: Nothing to Disclose, Jie Li: Nothing to Disclose, Rui Huang: Nothing to Disclose, Chao Wu: Nothing to Disclose

1325 | HBV/HIV COINFECTION BEFORE AND DURING TENOFOVIR-BASED THERAPY ALTERS SOLUBLE IMMUNE PROFILES COMPARED TO HBV OR HIV ALONE AMONG ADULTS IN ZAMBIA

Taonga Musonda[1] Hailey Patel[2] Dennis Ngosa[3] Ruth Phiri[4] Annie Kanunga[3] Carolyn Chibundi[3] Sydney Mpisa[5] Enock Syabbalo[5] Bright Nsokolo[6] Samuel Bosomprah[3] Paul Kelly[7] Georg Lauer[2] Raymond Chung[2] Guy Muula[3] Edford Sinkala[8] Nadia Alatrakchi[2] Michael Vinikoor[9]

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Background: Chronic hepatitis B virus (HBV) infection and HIV have overlapping epidemiology in Africa and coinfection of the two is common. In the pre-tenofovir era, coinfection had higher liver-related mortality than either infection alone. While tenofovir-based therapy suppresses both viruses in HBV/HIV, HBV-related liver disease may persist for unclear reasons. We compared soluble immune profiles in the setting of HBV/HIV to HBV and HIV alone before and on therapy **Methods:** We enrolled adults living with HBV/HIV, HBV alone, or HIV alone and starting tenofovir-based therapy in Lusaka, Zambia, and a healthy control (HC) group (HIV-negative and both HBsAg- and cAb-negative) who had requested HBV vaccination. In plasma, we measured 18 soluble markers of pro- and anti-inflammation, 2 of monocyte/macrophage activation and soluble PD-1 using ELISA and Luminex platforms.We compared pre-treatment biomarker concentrations in each infection state to HC using t-test, and compared longitudinal levels in HBV/HIV with HIV and HBV alone with a random effects log-normal regression model adjusted for age and sex. P<0.05 was considered significant. **Results:** Among 119 individuals analyzed, 33 each had HBV/HIV, HBV, and HIV, and 20 were HC. The median age was 32 years (range, 18-61); 73 (61%) were men. For participants with HBV/HIV or HIV (n=66), median CD4 count was 211 cells/mm^3 (range, 10-648). Compared to HC, multiple biomarkers of pro-inflammation (e.g., TNF-a and CXCL10) and monocyte/macrophage activation (e.g., CD163) as well as PD-1 were significantly increased in HIV and HBV/HIV. IL-6 and CXCL10 were also higher in HBV alone versus HC. Initiation of tenofovir-based therapy led to significant declines in most markers. Compared to HBV, biomarker levels were increased with HBV/HIV, including CD14 (adjusted geometric mean ratio [aGMR] 1.22), TNF-a (aGMR, 1.82), and CXCL10 (aGMR, 1.85; all P<0.05) but decreased compared to HIV alone, including CD14 (aGMR, 0.78), IL-6 (aGMR, 0.34), and IL-2 (aGMR, 0.31). Anti-inflammatory markers (IL-4 and IL-10) were not different by infection state. **Conclusion:** While chronic HBV and HIV alone were linked to elevated inflammatory and activation markers, HBV/HIV had heterogenous differences in these markers, with patterns of inflammation in coinfection tracking more closely with those seen in HIV than HBV. The finding of lower inflammatory markers in HBV/HIV versus HIV alone raises the possibility that HBV coinfection can attenuate immune responses in the context of HIV.

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Table showing results of the cross sectional and longitudinal analysis of the immune markers (P<0.05 considered significant)								
	Cross sectional analysis at baseline				Random effects model analysis (adjusted for age &sex)			
	HBV/HIV vs	HBV/HIV vs	HBV vs HC	HIV vs HC	HBV/HIV vs HBV		HBV/HIV vs HIV	
Marker	P -value	P -value	P -value	P -value	GMC ratio (95% CI)	P -value	GMC ratio (95% CI)	P -value
CD163	0.227	0.0106	0.0929	0.0026	1.13 (0.87, 1.47)	0.363	1.16 (0.91, 1.46)	0.227
CD14	0.002	0.0756	0.6725	<0.0001	1.22 (1.04, 1.44)	0.017	0.78 (0.67, 0.91)	0.002
PD-1	0.722	<0.0001	0.8448	<0.0001	2.05 (1.60, 2.62)	<0.001	1.05 (0.80, 1.38)	0.722
TNF-a	0.244	<0.0001	0.0276	<0.0001	1.82 (1.31, 2.53)	<0.001	0.85 (0.65, 1.11)	0.244
IL-6	<0.001	0.0768	<0.0001	<0.0001	0.75 (0.43, 1.30)	0.299	0.34 (0.19, 0.59)	<0.001
IL-33	<0.001	0.019	0.0847	<0.0001	0.35 (0.09, 1.35)	0.126	0.01 (0.00, 0.05)	<0.001
IL-3	<0.001	0.9472	0.1233	0.0008	0.55 (0.29, 1.03)	0.061	0.16 (0.07, 0.35)	<0.001
CXCL10	0.243	<0.0001	<0.0001	<0.0001	1.85 (1.42, 2.41)	<0.001	0.85 (0.65, 1.12)	0.243
IL-10	0.174	<0.0001	<0.0001	<0.0001	1.14 (0.61, 2.12)	0.689	0.50 (0.19, 1.36)	0.174
CXCL13	0.201	<0.0001	<0.0001	<0.0001	1.68 (1.24, 2.28)	0.001	0.78 (0.54, 1.14)	0.201
IFN-γ	<0.001	0.045	0.1733	<0.0001	1.64 (0.88, 3.04)	0.117	0.22 (0.13, 0.38)	<0.001
IL-4	0.96	0.0009	0.3585	0.0093	1.13 (0.64, 2.01)	0.674	1.02 (0.48, 2.16)	0.96
IL-17	0.127	0.6138	0.9733	0.2601	0.64 (0.31, 1.33)	0.233	0.49 (0.19, 1.23)	0.127
IL-2	<0.001	0.4416	0.4416	0.0016	1.02 (0.86, 1.21)	0.834	0.31 (0.17, 0.56)	<0.001
GM-CSF	<0.001	<0.0001	<0.0001	<0.0001	1.82 (0.51, 6.45)	0.353	0.06 (0.02, 0.17)	<0.001
CXCL9	<0.001	0.0038	0.0003	<0.0001	1.43 (0.88, 2.33)	0.147	0.29 (0.19, 0.44)	<0.001
IL-5	<0.001	0.0079	0.0864	0.002	2.64 (1.57, 4.45)	<0.001	4.71 (2.56, 8.65)	<0.001
IL-1b	0.025	0.6513	0.6565	0.0646	0.92 (0.71, 1.18)	0.492	0.63 (0.42, 0.94)	0.025
IFN-a	0.007	0.0026	0.1502	0.7301	1.10 (0.50, 2.42)	0.82	2.55)1.29, 5,03)	0.007
IL-21	0.014	0.7136	0.3834	0.1502	0.83 (0.55, 1.26)	0.389	0.47 (0.26, 0.86)	0.014
IL-12	0.001	0.0011	<0.0001	<0.0001	0.72 (0.23, 2.20)	0.56	0.17 90.06, 0.50)	0.001

Disclosures: Taonga Musonda: Nothing to Disclose, Hailey Patel: Nothing to Disclose, Dennis Ngosa: Nothing to Disclose, Ruth Phiri: Nothing to Disclose, Annie Kanunga: Nothing to Disclose, Carolyn Chibundi: Nothing to Disclose, Sydney Mpisa: Nothing to Disclose, Enock Syabbalo: Nothing to Disclose, Bright Nsokolo: Nothing to Disclose, Samuel Bosomprah: Nothing to Disclose, Paul Kelly: Nothing to Disclose, Georg Lauer: GSK: Grant/ Research Support, GSK: Consultant, Raymond Chung: Nothing to Disclose, Guy Muula: Nothing to Disclose, Edford Sinkala: Nothing to Disclose, Nadia Alatrakchi: Nothing to Disclose, Michael Vinikoor: Abbott Diagnostics: Speaking and Teaching

1326 | COMPLETE DETERMINATION OF HEPATITIS B VIRUS GENOTYPE IN ALL PARTICIPANTS WITH CHRONIC HBV INFECTION RECEIVING NUCLEOS(T)IDE ANALOG THERAPY USING MULTI-METHOD ANALYSIS TO BETTER UNDERSTAND CLINICAL OUTCOMES: PHASE 2B B-CLEAR STUDY

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Background: Comprehensive hepatitis B virus (HBV) genotype (GT) information is critical to better understand clinical outcomes and develop therapeutics, but difficult to obtain in virally suppressed participants (pts). The Phase 2b B-Clear study (NCT04449029) assessed the efficacy and safety of 12 and 24 weeks of 150–300 mg bepirovirsen treatment in pts with chronic HBV infection on or not on nucleos(t)ide analog (NA) therapy. The HBV GT of B-Clear pts was previously assessed using a two-tiered methodology of HBV DNA and RNA sequencing and/or investigator report. However, 93/226 (41%) had undetermined GT in virally suppressed pts.[1] Here we present the results of a post hoc re-analysis of the on-NA B-Clear population using a three-tiered GT methodology. **Methods:** An enzyme immunoassay targeting four hepatitis B surface antigen (HBsAg) GT-specific epitopes (IMMUNIS HBV Genotype EIA) was added to the tiered GT methodology. When investigator-reported GT was missing, GT was assigned using HBV sequencing data; when HBV sequencing was missing, GT was assigned using immunoassay data. **Results:** There were 226 on-NA pts included in the analyses. The three-tiered methodology successfully determined GT in all on-NA pts (Table). The majority of pts were GT-C (n=93/226 [41%]), followed by GT-D (n=61/226 [27%]), GT-A (n=34/226 [15%]), GT-B (n=26/226 [12%]) and other (constituting of GT-E, -H, -F and unclassified; n=12/226 [5%]). There was a high degree of concordance between each of the three methods (83–91%). Predominant GTs included GT-C in Asia (n=82/114 [72%]), GT-D in Europe (n=48/85 [56%]) and GT-A in Americas (n=9/27 [33%]). GT-A had the highest and GT-B the lowest mean

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HBsAg at baseline. HBsAg reductions were seen in all GTs by end of treatment (EOT) and 24 weeks after EOT. **Conclusion:** The addition of the immunoassay method to the workflow successfully determined HBV GT in all virally suppressed B-Clear pts on NA. HBsAg reductions were observed across all major GTs. This new analysis of GT in virally suppressed pts allows for a comprehensive assessment of the association between GT, disease heterogeneity and treatment response in trials for novel HBV therapies. **Funding:** GSK (209668)

Reference:

1. Bouquet J et al. Analysis of HBV genotype association to bepirovirsen treatment response in patients with chronic HBV infection (Phase 2b B-Clear study). AASLD 2023 (Poster #SAT-176).

Table: HBV genotype results by individual method determination

B-Clear on-NA population (n=226)				
Genotype	Investigator reported n (%)	Sequence predicted n (%)	Immunoassay predicted n (%)	Final GT result* n (%)
Available	64 (28.3)	90 (39.8)	226 (100)	226 (100)
A	10 (15.6)	11 (12.2)	36 (15.9)	34 (15.0)
B	8 (12.5)	13 (14.4)	18 (8.0)	26 (11.5)
C	34 (53.1)	50 (55.6)	90 (39.8)	93 (41.2)
D	11 (17.2)	10 (11.1)	71 (31.4)	61 (27.0)
Other†	1 (1.6)	6 (6.7)	11 (4.9)	12 (5.3)
Missing	162 (71.7)	136 (60.2)	0 (0)	0 (0)

Percentages for individual genotypes are calculated based on available data. *When investigator reported genotype is missing, genotype was assigned using HBV sequencing data; when HBV sequencing is missing, genotype was assigned using immunoassay data. †Other constituted genotypes E, H, F and unclassified.

Disclosures: Jerome Bouquet: GSK: Employee, GSK: Stock - publicly traded company, Rob Elston: Nothing to Disclose, Scott Speer: Nothing to Disclose, Phillip Yates: Nothing to Disclose, Shihyun You: Nothing to Disclose, Lauren Maynard: GSK: Employee, GSK: Stock - publicly traded company, Melanie Paff: Nothing to Disclose, Dickens Theodore: GSK: Employee, GSK: Stock - publicly traded company

1327 | IMPACT OF HEPATITIS B SURFACE ANTIGEN LEVELS ON REGULATORY T LYMPHOCYTE FREQUENCY: POOLED ANALYSIS FROM SINGLE CELL RNA SEQUENCING DATASETS

Fengge Zhu[1] Liqiong Yang[1] Wai-Kay Seto[1] Man-Fung Yuen[1] Lung Yi Mak[1]

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Background: Suppressive immune cells are a critical component in finetuning the pathogenesis of chronic hepatitis B (CHB), but the exact mechanism is not clear. We tested the frequency of regulatory T lymphocytes (Treg) in a cross-sectional study with CHB with varying hepatitis B surface antigen (HBsAg) and assessed for correlation between Treg and HBsAg levels in 2 open datasets. **Methods:** Flow cytometry was performed on peripheral blood mononuclear cells from a local cohort of patients with CHB (n=99) and healthy controls (n=26). Two additional single cell RNA sequencing (scRNA-seq) datasets GSE182159, GSE247322 were obtained from Gene Expression Omnibus (GEO) database. scRNA-seq data is analysed with Partek Flow (United States). Treg cells are annotated based on a manual feature list (IL2RA, IKZF2, CD69, CTLA4, ICOS, CCR4, and TNFRSF18). We also mapped and determined the phenotype of Th17 cells which are known to trans-differentiate into Treg cells. Multiple linear regression and Pearson correlation analysis are performed with GraphPad Prism 10. **Results:** Peripheral $CD25^{+}CD127^{-}FoxP3^{+}$ Treg cell frequency by flow cytometry is significantly increased in CHB patients compared to healthy donors (4.93% vs 4.06%, p=0.04), but no significant difference between CHB (n=50) and patients who achieved HBsAg seroclearance (n=49) (4.93% vs 5.48%, p=0.36) (Figure a). There was no linear correlation between serum HBsAg levels with frequency of peripheral blood Tregs (r=-0.11, p=0.46). From the datasets, multiple linear regression analysis reveals a predictive model containing intrahepatic Treg proportion that predicts serum HBsAg concentration at R^2=0.9773 (GSE182159, Figure b). Peripheral blood Treg proportion showed similar result though at lower R^2=0.7108 (Figure c). Treg cells were observed to be enriched in the liver compared to peripheral blood in patients with HBeAg-positive CHB infection, but not in acute resolved patients (Figure d). Intrahepatic Treg cell frequency was significantly higher in HBeAg-positive CHB infection compared

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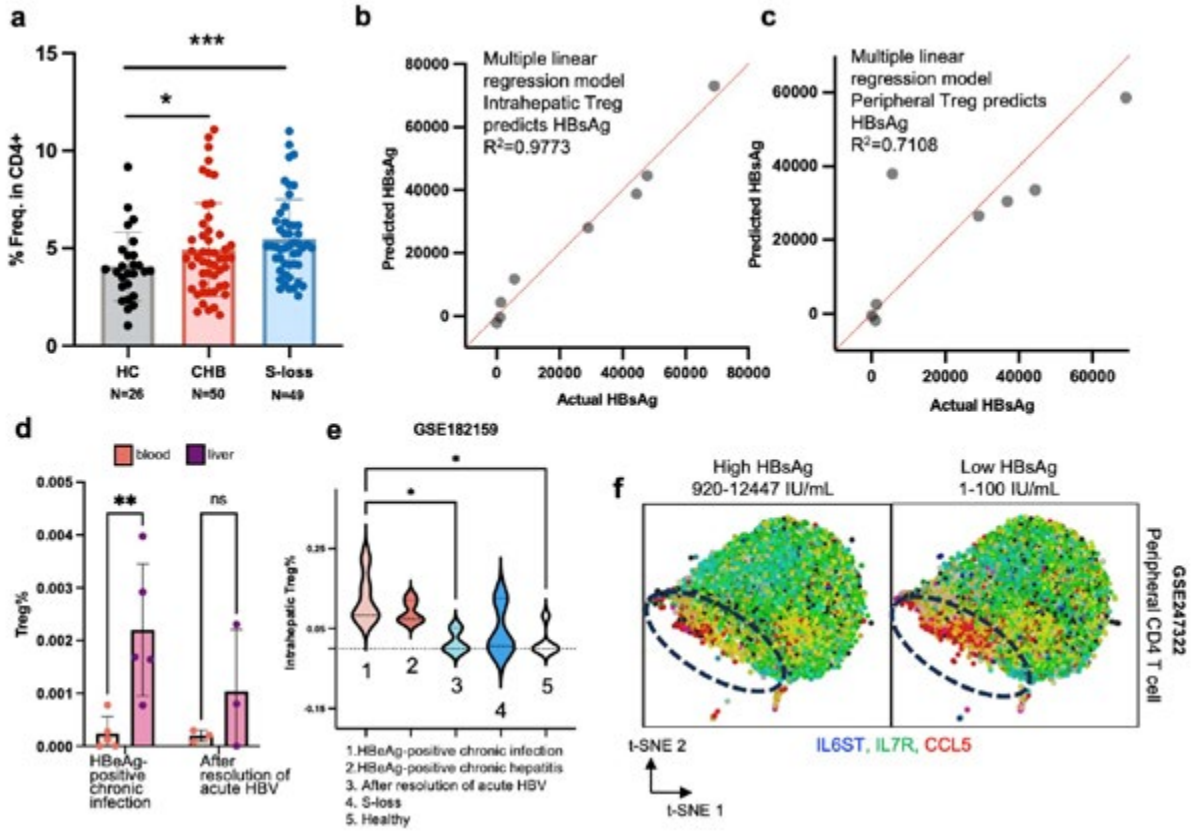
with acute resolved and healthy control (Figure e). Among peripheral CD4⁺ T cells, we mapped an increased Th17 pro-pathogenic phenotype (featured by IL7R, CXCL3 and CCL5) in patients with low HBsAg (defined as HBsAg ≤100 IU/mL; GSE247322, Figure f) compared to patients with higher HBsAg, with enhanced expression of CCL5. **Conclusion:** Our results revealed a potential correlation between Treg cell frequency with higher HBsAg concentration and a potential protective role of CCL5 expressing Th17 cells in chronic hepatitis B. Intrahepatic compartment changes on Treg population cannot be fully represented by peripheral blood.



Disclosures: Fengge Zhu: Nothing to Disclose, Liqiong Yang: Nothing to Disclose, Wai-Kay Seto: Nothing to Disclose, Man-Fung Yuen: Speaking and Teaching relationship with Fujirebio Incorporation, Gilead Sciences, Roche, Sysmex Corp; Has not ended; Consultant relationship with Clear B Therapeutics, Dicerna Pharmaceuticals; Has not ended; Consultant relationship with AbbVie, Abbott Diagnotics, Aligos Therapeutics; Has not ended; Consultant relationship with Arbutus Biopharma, Arrowhead Pharmaceuticals, Assembly Biosc; Has not ended; Consultant relationship with Immunocore, Janssen, Precision BioSciences; Has not ended; Consultant relationship with Fujirebio Incorporation, GlaxoSmithKline, Gilead Sciences; Has not ended; Grant/ Research Support relationship with Fujirebio Incorporation, Gilead Sciences, Immunocore; Has not ended; Grant/ Research Support relationship with AbbVie, Assembly Biosciences, Arrowhead Pharmaceuticals; Has not ended; Consultant relationship with Vir Biotechnology and Visirna Therapeutics; Has not ended; Consultant relationship with Roche, Sysmex Corporation, Tune Therapeutics; Has not ended; Grant/Research Support relationship with Sysmex Corporation and Roche; Has not ended, Lung Yi Mak: Nothing to Disclose

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1328 | A PHASE 1B, OPEN-LABEL STUDY TO EVALUATE THE SAFETY AND EFFICACY OF NOVEL HEPATITIS B VIRUS COMBINATION THERAPIES IN PATIENTS LIVING WITH CHRONIC HEPATITIS B

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Background: Current treatments for chronic hepatitis B virus infection (CHB) are effective at inhibiting viral replication, but rarely achieve functional cure. Cure may require combination treatment to suppress viral antigen production and stimulate host immunity by multiple mechanisms. Here we present results from a Phase 1b study that evaluated the following novel agents in combination regimens in patients with CHB: nivolumab (NIVO, anti–programmed death-1 monoclonal antibody); selgantolimod (SLGN; toll-like receptor 8 agonist); and/or GS-4224 (a novel small molecule programmed death ligand-1 inhibitor). Suppression of HBsAg was previously observed in HBV/HCV coinfected patients treated with ledipasvir/sofosbuvir (LDV/SOF). In this study, we also evaluated LDV/SOF combined with NIVO. **Methods:** This open-label, multicenter study (ACTRN12618001843246p) enrolled nucleos(t)ide-suppressed, HBeAg-negative patients into 4 cohorts (C): C1 received NIVO (0.3 mg/kg IV every 4 weeks [Q4W]) x12 weeks (w); C2 received LDV/SOF (90/400 mg oral daily [QD]) for 24w plus NIVO Q4W x12w starting at w12; C3 received SLGN (3 mg oral QW) with NIVO Q4W x12w; C4 received SLGN (3 mg oral QW) with GS-4224 (500 mg oral QD) x12w. The primary efficacy endpoint was the proportion of patients with ≥0.5 log10 IU/mL decline in serum HBsAg from baseline (BL) to W8 post-treatment (FU W8). Safety, including adverse events (AEs) and laboratory parameters, pharmacokinetics, and pharmacodynamics (PD) were assessed over the study period. **Results:** Fifty-one patients were enrolled (median age, 50 years; 80% male; 49% Asian). Table 1 provides key efficacy and safety results. The primary endpoint was met by one patient each in C2 (9%) and C3 (8%). Minimal changes from BL in mean serum HBsAg levels were observed in the treatment groups with no observed HBsAg loss. PD evaluation of T cell proliferation showed increases from BL in all cohorts except C4, while inflammatory cytokines had the most significant elevations in C1 and C3. All AEs reported in the study were Grade ≤2 in severity, except for 1 patient with a serious Grade 3 AE of anemia considered unrelated to study treatment. Three treatment emergent (TE) serious AEs were reported, and none were considered related. One patient in C4 (8%) prematurely discontinued study treatment due to multiple gastrointestinal AEs (all Grade 1). There were no TE ALT flares. **Conclusion:** Novel treatments and combinations for HBV cure in this trial were generally safe and well tolerated; however, only a few patients achieved a ≥0.5 log10 IU/mL decline from BL in HBsAg at FU W8 and no patient experienced HBsAg loss.

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Table 1: Efficacy & Safety Outcomes by Treatment Cohort

	Cohort 1 (NIVO) (n=13)	Cohort 2 (LDV/SOF + NIVO) (n=12)	Cohort 3 (SLGN +NIVO) (n=14)	Cohort 4 (SLGN + GS-4224) (n=12)
Efficacy Results				
≥0.5 log_{10} decline from BL in HBsAg at W8 post-treatment (FU W8), n (%) (95% CI)	0 (0) (0.0, 24.7)	1 (9) (0.2, 41.3)	1 (8) (0.2, 36.0)	0 (0) (0.0, 26.5)
HBsAg Loss overall during study, n (%)	0	0	0	0
Mean (SD) Change from BL in HBsAg (log_{10} IU/mL)				
EOT	-0.06 (0.083)	-0.44 (0.286)	-0.03 (0.104)	-0.02 (0.163)
FU W8	0.06 (0.101)	0.10 (0.251)	0.05 (0.283)	0.02 (0.094)
FU W24	-0.07 (0.108)	0.01 (0.145)	-0.04 (0.240)	0.03 (0.092)
Safety Results				
Any TEAE, n (%)	12 (92)	10 (83)	13 (93)	9 (75)
Grade 3 or 4 TEAE, n (%)[a]	0	0	0	1 (8)
Serious TEAE, n (%)[b]	1 (8)	1 (8)	0	1 (8)
TEAE leading to study drug d/c, n (%)[c]	0	0	0	1 (8)
Deaths, n (%)	0	0	0	0
Grade 3 or 4 TE lab abnormalities, n (%)[d]	0	2 (17)	1 (7)	1 (8)
TE ALT Flares [ALT > 2x BL & ≥ 5x ULN][e]	0	0	0	0

[a] anemia [not related to study treatment] in one participant also reported as an SAE with a Grade 4 hemoglobin decrease

[b] chondrocalcinosis [C1], pancreatitis [C2], anemia [C4] [none were related to study treatment]

[c] Grade 1 AEs of nausea, abdominal discomfort, diarrhea, abdominal distension, and decreased appetite [all AEs were considered related to GS-4224]

[d] Grade 3 creatine kinase [C2], Grade 3 LDL [C2], Grade 4 lipase [C3]; Grade 4 hemoglobin decreased [C4]

[e] Central lab ULN [34 U/L for female and 43 U/L for male]

ALT, alanine aminotransferase; BL, baseline; d/c, discontinuation; EOT, end of treatment; FU, follow up; LDV, ledipasvir; NIVO, nivolumab; SLGN, selgantolimod; SOF, sofosbuvir; TE, treatment emergent; TEAE, treatment emergent adverse event; ULN, upper limit of normal; W, week

Disclosures: Edward Gane: Aligos Therapeutics: Advisor, Assembly Biosciences: Advisor, AbbVie: Speaking and Teaching, Intellia Therapeutics: Advisor, Tune Therapeutics: Consultant, Precision Bio: Advisor, Virion Therapeutics: Advisor, Gilead Sciences: Advisor, GSK: Advisor, Tien Huey Lim: Nothing to Disclose, Jing Hieng Ngu: Nothing to Disclose, DANA TEDESCO: Gilead Sciences, Inc.: Employee, Ran Duan: Gilead Sciences, Inc: Employee, David Pan: Nothing to Disclose, Irina Botros: Nothing to Disclose, Naveed Shaik: Nothing to Disclose, Roberto Mateo: Gilead Sciences, Inc.: Employee, Scott Balsitis: Gilead Sciences: Employee, Jeffrey Wallin: Nothing to Disclose, Frida Abramov: Gilead Sciences, Inc: Employee, Gilead Sciences, Inc: Stock - publicly traded company, Audrey Lau: Nothing to Disclose, Grace Wong: AstraZeneca: Advisor, Gilead Sciences: Advisor, Gilead Sciences: Speaking and Teaching, Janssen: Advisor, GSK: Advisor, GSK: Speaking and Teaching, Abbott: Speaking and Teaching, AbbVie: Speaking and Teaching, AstraZeneca, Gilead Sciences, GlaxoSmithKline and Janssen,: Advisor, Abbott, AbbVie, Ascletis, Bristol-Myers Squibb, Echosens, Gi: Speaking and Teaching, Gilead Sciences: Grant/Research Support, AstraZeneca, Gilead Sciences, GlaxoSmithKline and Janssen: Consultant, Abbott, AbbVie, Ascletis, Bristol-Myers Squibb, Echosens, Gi: Speaking and Teaching, AstraZeneca, Gilead Sciences, GlaxoSmithKline Pharmaceutical: Consultant, Gilead Sciences: Independent Contractor, AstraZeneca, Gilead Sciences, GSK and Janssen,: Advisor, Abbott, AbbVie, BMS, Gilead Sciences, GSK, Janssen, Roche: Speaking and Teaching, Gilead Sciences: Grant/Research Support

1329 | ACCURATE HBSAG TESTING IS ASSOCIATED WITH HBSAG SEROREVERSION OUTCOMES

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Background: The sensitivity of HBsAg assays are different which may lead to controversial 'HBsAg seroclearance'. Furthermore, its association with subsequent HBsAg seroreversion outcomes is unclear. We aim to use two HBsAg assays from Roche diagnostics to evaluate serum HBsAg loss and further explore predictors in HBsAg seroreversion outcomes. **Methods:** Patients with serum HBsAg < 0.05 IU/mL were enrolled and completed at least 96 weeks follow-up. HBsAg was detected using Elecsys HBsAg II (Roche Diagnostics; lower

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limit of quantitation (LLOQ):1 COI) and Elecsys HBsAg II Quant reagent kits (Roche Diagnostics;LLOQ:0.05 IU/mL). A multivariate logistic regression analysis was used to determine the factors associated with HBsAg seroreversion. **Results:** In total, 179 patients achieving serum HBsAg < 0.05 IU/mL who received PEG-IFN based therapy before were enrolled in this study. The positive serum HBsAg level (HBsAg > 1COI) was detected in 14/179 (7.8%) patients with Elecsys HBsAg II assay. Notably, 10/14 (71.4%) patients with HBsAg >1 COI experienced HBsAg seroreversion during the follow-up. There were no significant difference of age, gender, and nucleos(t)ide analogs consolidation between the HBsAg seroreversion group and none-HBsAg seroreversion group. HBsAg seroreversion group had higher proportion of serum HBsAg level > 1COI (24.4% vs. 2.9%, P < 0.001) and proportion of detectable HBV DNA (10% vs. 0%, P = 0.002) than none-HBsAg seroreversion group. The serum HBsAb titer was less abundant in the HBsAg seroreversion group than in the non-HBsAg seroreversion group (1.37 [0.63–1.74] vs. 2.09 [1.27–2.55]; P 1COI (odds ratio, 4.733, 95% confidence interval: 1.215–18.434, P =0.025) and serum hepatitis B surface antibody titer (odds ratio, 0.462, 95% confidence interval: 0.291–0.733, P =0.001) were found to be associated with HBsAg seroreversion. **Conclusion:** Higher sensitivity of HBsAg assays contribute to define HBsAg seroclearance and it is involved in less HBsAg seroreversion after cessation of PEG-IFN.

Table 1. Multivariable logistic analysis for predictors of HBsAg seroreversion

	Univariable analysis			Multivariable logistic analysis		
	HBsAg seroreversion group (n=41)	Non-HBsAg seroreversion group (n=138)	*P*-value	OR	95% CI	*P*-value
Age (years)	39.88±7.28	41.34±8.81	0.337	—	—	—
Sex, male (n, %)	35 (85.4%)	112 (81.2%)	0.537	—	—	—
Detectable HBsAg level (COI)	10 (24.4%)	4 (2.9%)	<0.001	4.733	1.215–18.434	0.025
Serum HBsAb level (Log mIU/mL)	1.37 (0.63, 1.74)	2.09 (1.27, 2.55)	<0.001	0.462	0.291–0.733	0.001
Serum ALT level (IU/mL)	52.00 (33.50, 73.00)	37.50 (25.00, 57.00)	0.003	—	—	—
NUCs consolidation (n%)	12 (29.3%)	22 (15.9%)	0.056	—	—	—
Detectable HBV DNA level (IU/mL) [1]	4 (10%)	0 (0%)	0.002	—	—	—

[1] HBV DNA detection was missing for one patient in none HBsAg seroreversion group and for one patient in HBsAg seroreversion group.

"—" stands for factors ruled out in multivariable logistic analysis.

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1330 | SWITCHING TENOFOVIR-BASED ANTIVIRAL TO ENTECAVIR >12 WEEKS BY END OF THERAPY IN HBEAG-NEGATIVE PATIENTS: A PROOF-OF-CONCEPT STUDY

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Background: Our earlier study showed a much earlier clinical relapse (CR) after end of therapy (EOT) of tenofovir disoproxil fumarate (TDF) than those after entecavir (ETV) (58 vs 2.3% within 3 months; 87 vs 26% within 6 months) in HBeAg-negative chronic hepatitis B patients[1]. The earlier onset of CR is associated with more severe flare (ALT >=20x ULN, 26.3 vs 16.3%). Another small retrospective study found a significantly lower 24-week incidence of off-treatment CR (17.5%) in 40 non-ETV treated patients (only 3 TDF-treated) who had switched to ETV >3 months before EOT. We conducted a pilot prospective study in more TDF/tenofovir alafenamide (TAF)-treated patients to confirm or refute this ETV-switching strategy in reducing the early 24-week CR rate. **Methods:** The inclusion criteria included (1). HBeAg-negative patients treated with TDF/TAF; (2). treatment for >=2 years with undetectable HBV DNA >=1 year; (3). had switched to ETV for >=12 weeks before EOT. Patients with evidence of other liver diseases or prophylactic antiviral therapy before chemotherapy were excluded. By the end of April 2024, 15 patients have been followed-up every 1-3

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months for >6 months after the end of ETV treatment. Virological relapse (VR) and CR were defined as HBV DNA >2000 IU/mL and combined VR with ALT >=2x ULN, respectively. **Results:** The median age of the 15 patients (10 males, 3 cirrhotic) was 64 years. Baseline median (range) levels of serum ALT, HBV DNA and HBsAg were 223 (42-1318) U/L, 6.73 (3.29-8.78) log IU/mL, and 3.44 (1.94-3.98) log IU/mL, respectively. Total median treatment duration was 160 weeks including consolidation therapy of 133 weeks and switching to ETV for 13.3 weeks. During follow-up period of 54.7 (17-146) weeks after EOT, VR occurred in 14 (93.3%) patients at 22.6 (8.3-50.7) weeks after EOT. CR (median ALT 146 U/L) occurred in 9 (60%) patients at 28 (12.7-97) weeks after EOT, none occurred within 12 weeks and 3 (20%) within 24 weeks. Of the 9 patients with CR, 4 (44.4%) showed ALT levels >5x ULN and one (11.1%) >10x ULN. None developed hepatic decompensation. **Conclusion:** Compared with our earlier study[1], the ETV-switching strategy before EOT reduced CR within 12 weeks (0 vs 58%) and 24 weeks (20 vs 87%), with ALT levels less often >10x ULN (11.1 vs 57.9%) in HBeAg-negative patients with tenofovir-based treatment. Based on this, a planned randomized controlled study is currently going to start. Jeng WJ, et al. CGH 2016;14:1813-1820.

Disclosures: Yi-Cheng Chen: Nothing to Disclose, Rachel Wen-Juei Jeng: Nothing to Disclose, Rong-Nan Chien: Nothing to Disclose, Yun-Fan Liaw: Nothing to Disclose

1331 | EVALUATION OF PAGE-B SCORE AND MACHINE LEARNING ENHANCED PREDICTION OF HEPATOCELLULAR CARCINOMA DEVELOPMENT IN CHRONIC HEPATITIS B PATIENTS USING CONDITIONAL SURVIVAL FOREST: A MULTICENTER STUDY

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Background: Hepatocellular carcinoma (HCC) remains a critical concern in patients with chronic hepatitis B (CHB) even in those virally suppressed with NUCs. PAGE-B is a recognized score for HCC risk stratification. This study extends the evaluation of the PAGE-B score versus a Conditional Survival Forest Model (CSFM) in a large, multicenter cohort, aiming to enhance predictive performance regarding HCC development. **Methods:** We retrospectively analyzed data from 11 medical centers. According to the TRIPOD-AI guidelines and following data science (DS) methodology we randomly split the 1713 total patients into train and test sets with 90/10 ratio. The PAGE-B score was calculated for each patient, including age, gender, and platelet count. In the Cox Proportional Hazards model (CoxPH) only the PAGE-B score was used. The CSFM included PAGE-B's score individual parameters {PAGE_age, Page_age, Page_plt}, as well as the age, gender and platelet count, and the presence of cirrhosis at baseline. The initial training set data spanned up to 15.9 years of follow-up, and the test set up to 13.6 years. We applied 10 fold cross validation (10CV) on the train set in order to evaluate PAGE-B's performance and its prognostic power using CoxPH, and to tune the CSFM. The following hyper-parameters had been used: n_estimators=50, min_samples_split=2, min_samples_leaf=29, random_state=17 while for all the other we used the default values. We used Pandas 2.2.0, NumPy 1.26.3, scikit-survival 0.22.2, scikit-learn 1.3.2 and python 3.10.13. **Results:** On the 10CV the mean c-index +/- standard deviation (std) for the CoxPH using PAGE-B score was: 0.79 +/- 0.03 while the CSFM: 0.83 +/- 0.03. Trained both on the 90% and applied on the 10% resulted in the following performance: on the train and on the test CoxPH achieved a c-index of 0.79, 0.80 while the CSFM: 0.86, 0.85. **Conclusion:** Evaluating the PAGE-B score with 10CV using TRIPOD-AI guidelines verified its prognostic power. Integrating patient parameters, including cirrhosis status, into the CSFM outperformed the traditional PAGE-B score in predicting HCC risk among HCB patients. This improvement highlights CSFM's ability to capture complex non-linear associations between parameters and risk factors. This multicenter study demonstrates the potential of advanced machine learning techniques in refining risk assessment tools, offering a more nuanced approach to patient management and surveillance in HCC.

Disclosures: Athanasios Angelakis: Nothing to Disclose, Pietro Lampertico: ROCHE PHARMA/DIAGNOSTICS, GILEAD SCIENCES, GSK, ABBVIE, JANS: Advisor, Vana Sypsa: Nothing to Disclose, George Dalekos: Nothing

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to Disclose, Cihan Yurdaydin: Gilead Biopharma: Grant/Research Support, Roche Diagnostics: Advisor, Eiger Biopharma: Advisor, Thomas Berg: Nothing to Disclose, IOANNIS GOULIS: Nothing to Disclose, Jose Luis Calleja: Nothing to Disclose, Harry Janssen: Gilead Sciences: and consultant, Gilead Sciences: Grant/Research Support, GlaxoSmithKline: Grant/Research Support, Janssen: Grant/Research Support, Roche: Grant/Research Support, Vir Biotechnology Inc.: Grant/Research Support, Aligos: Consultant, Gilead Sciences: Consultant, GlaxoSmithKline: Consultant, Grifols: Consultant, Roche: Consultant, Vir Biotechnology Inc: Consultant, Precision Biosciences: Consultant, Maria Buti: Nothing to Disclose, George Papatheodoridis: Abbvie: Advisor, Abbvie: Speaking and Teaching, Abbvie: Grant/Research Support, Astra Zeneca: Advisor, Astra Zeneca: Speaking and Teaching, Abbvie: Advisor, Abbvie: Speaking and Teaching, Astra Zeneca: Advisor, Astra Zeneca: Speaking and Teaching, Genesis: Advisor, Genesis: Speaking and Teaching, Gilead: Advisor, Gilead: Speaking and Teaching, Gilead: Grant/Research Support, GlaxoSmithKline: Advisor, Ipsen: Advisor, Ipsen: Speaking and Teaching, Novo Nordisk: Advisor, Novo Nordisk: Speaking and Teaching, Roche: Advisor, Roche: Speaking and Teaching, Takeda: Advisor

1332 | IMMUNE-RELATED ADVERSE EVENTS WITH LOW-DOSE NIVOLUMAB IN PATIENTS WITH CHRONIC HEPATITIS B: EXPERIENCE FROM 3 CLINICAL STUDIES

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Background: Anti–programmed death-1/programmed death ligand-1 (PD-1/PD-L1) monoclonal antibodies (mAbs) are being investigated at low doses for finite treatment of chronic hepatitis B (CHB) virus infection. Immune-related adverse events (irAEs) are a known class effect of anti–PD-1/PD-L1 mAbs, although safety data at lower doses in non-oncological indications are limited. This analysis aimed to assess the occurrence of irAEs with low-dose nivolumab (NIVO), an anti–PD-1 mAb, in patients with CHB. **Methods:** Safety data from 3 clinical studies (2 completed Phase 1 studies, GS-US-330-1938 [Study 1938] and GS-US-493-5342 [Study 5342]; and 1 ongoing Phase 2 study, GS-US-465-4439 [Study 4439]) were analyzed. A single intravenous (IV) dose of NIVO (0.1 mg/kg or 0.3 mg/kg) was administered in Study 1938 (n = 24, virally suppressed), 3 IV doses of NIVO (0.3 mg/kg) were administered every 4 weeks (Q4W) in Study 5342 (n = 39, virally suppressed), and up to 6 IV doses of NIVO (0.3 mg/kg) were administered Q4W in Study 4439 (n = 42 virally suppressed, n = 58 viremic), alone or in combination with antivirals or immunomodulators. **Results:** Overall, 163 patients with CHB received at least 1 dose of NIVO (0.1 mg/kg [n = 2]; 0.3 mg/kg [n = 161]). Of these patients, 7/163 (4.3%; n = 3 virally suppressed and n = 4 viremic patients with CHB, all from ongoing Study 4439) experienced irAEs (Table). Two patients experienced serious irAEs (Grade 3: type 1 diabetes mellitus and immune-mediated hepatitis, n = 1 each). The remaining 5 patients experienced nonserious irAEs (Grade 2: psoriasis, thyroiditis, and hypothyroidism, n = 1 each; and Grade 1: hypothyroidism and optic neuropathy, n = 1 each). Onset of irAEs ranged from after 3–6 doses of NIVO (median: after 4 doses), with 3 irAEs occurring after the last dose of NIVO; irAEs led to discontinuation of NIVO in the remaining 4 patients. All irAEs except for optic neuropathy required treatment; 2 irAEs have resolved, with additional longer-term follow-up ongoing for the remaining cases. **Conclusion:** The emerging safety profile of low-dose anti–PD-1 mAbs in the setting of CHB is consistent with the known profile in the oncology setting. This is demonstrated by clinically significant irAEs, including some requiring lifelong management, observed in patients with CHB treated with low-dose NIVO in our analysis.

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Table 1. Immune-Related Adverse Events With Low-Dose Nivolumab in Patients With CHB

irAE	CHB Status	Regimen	Severity Grade[a]	SAE	TTO (After # NIVO Doses)	Action Taken With NIVO	Intervention and Other Treatment	Status[b]
Type 1 diabetes mellitus	Viremic	NIVO + SLGN	G3	Y	6	n/a[c]	Insulin	SAE and treatment ongoing
Immune-mediated hepatitis	Viremic	NIVO + SLGN + VIR-2218	G3	Y	3	n/a[d]	Corticosteroids (prednisolone, ~2.5 mo) / TAF started	SAE resolved, corticosteroids stopped
Psoriasis	Viremic	NIVO + SLGN	G2[e]	N	3	d/c	Corticosteroids (prednisone, ~1 mo) Cyclosporine / TAF started	AE ongoing, failed corticosteroid taper, currently on cyclosporine (50 mg, ongoing)
Thyroiditis	Virally suppressed	NIVO + SLGN + VIR-2218	G2	N	4	d/c	Thyroid hormone replacement, carbimazole, hydrocortisone (oral)	AE resolved, all supportive treatment stopped
Hypothyroidism	Virally suppressed	NIVO + SLGN + VIR-2218	G2	N	5	d/c	Thyroid hormone replacement	AE and treatment ongoing
Hypothyroidism	Virally suppressed	NIVO + SLGN + VIR-2218	G1	N	6	n/a[c]	Thyroid hormone replacement	AE and treatment ongoing
Optic neuropathy	Viremic	NIVO + SLGN	G1	N	4	d/c	No treatment	AE ongoing

Safety data are from 3 Gilead-sponsored clinical studies (Studies GS-US-330-1938 [Study 1938, ACTRN12615001133527], GS-US-493-5342 [Study 5342, ACTRN12618001843246p], and GS-US-465-4439 [Study 4439, NCT04891770]). All 7 irAEs occurred in Study 4439.
[a]Per Gilead Sciences, Inc., toxicity grading scale in the protocol. [b]As of May 7, 2024. [c]Reported after the end of treatment. [d]Reported after NIVO was permanently discontinued by the sponsor across cohorts in Study 4439. [e]G2 per protocol by Gilead Sciences, Inc., toxicity grading, but G3 by Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 grading.
AE, adverse event; CHB, chronic hepatitis B virus infection; d/c, discontinued/discontinuation; G, grade; irAE, immune-related adverse event; mo, month; N, no; n/a, not applicable; NIVO, nivolumab; SAE, serious adverse event; SLGN, selgantolimod (a toll-like receptor 8 agonist); TAF, tenofovir alafenamide; TTO, time to onset; VIR-2218, a small interfering RNA against hepatitis B virus; Y, yes.

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1333 | DETECTION AND MONITORING OF INFANT DRUG EXPOSURE: A STUDY ON TFV CONCENTRATION IN TDF AND TAF

Chengjing Tao

Background: A few studies have observed the Tenofovir (TFV) concentration of Tenofovir Disoproxil Fumara (TDF) and Tenofovir Alafenamide Fumarate (TAF) in the blood, milk, and amniotic fluid of pregnant women, but few have investigated the concentration of TFV in infant blood and urine, which could aid in detecting and monitoring infant drug exposure. **Methods:** From March 2019 to December 2020, pregnant women with HBeAg positivity and HBV DNA levels ≥ 2 x 10^5 IU/mL were recruited at Hangzhou Xixi Hospital and Maternal and Child Health Hospital of Tonglu. These patients were administered TDF for prevention of mother-to-child transmission during the middle and late stages of pregnancy. TDF was discontinued on the day of delivery, and blood samples were collected from the infants at birth. Urine samples were collected from the infants 24-72 hours after birth. Drug concentration was determined using LCMS/MS analysis, with serum concentration < 1 ng/ml and urine concentration < 10 ng/ml considered the lower limits of quantification, consistent with methods and limits of quantification used in the Australian studies. Mann-Whitney U test was employed to compare the differences in TFV concentration between TAF and TDF infant urine samples. **Results:** A total of 37 infant serum samples were collected, with a mean TFV concentration of 11.81±10.98 ng/ml. There were 49 infant urine samples collected, surprisingly with a mean TFV concentration of 1912.51±2057.07 ng/ml, which is 162 times higher than that in

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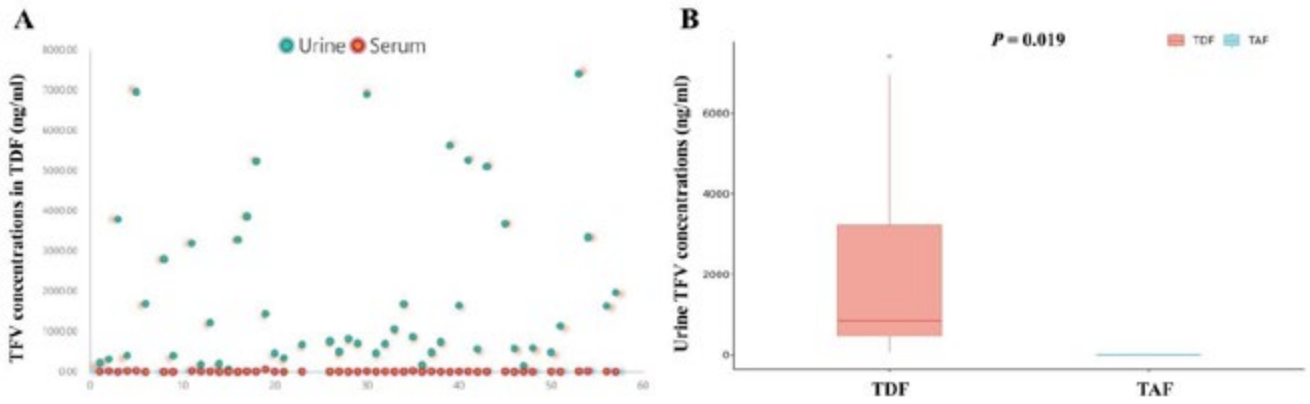
infant serum (Figure A). In Australian studies, infants born to mothers continuously taking TAF and with urine collection at 0 and 8 hours had a mean urine TFV concentration of only 11.57±9.20 ng/ml. In this study, TDF was discontinued at delivery, and urine collection occurred 24-72 hours postpartum, which is 165 times higher than that in TAF, resulting in a statistically significant difference in urine TFV concentration between the TDF and TAF (P=0.019) (Figure B). **Conclusion:** Infant drug exposure of TFV in urine from the TDF is significantly higher than in TAF.



Disclosures: Chengjing Tao: Nothing to Disclose

1334 | IMMUNOLOGIC BIOMARKER DYNAMICS IN CHRONIC HEPATITIS B: INSIGHTS FROM A PHASE 2A OPEN-LABEL STUDY ON COMBINATION THERAPIES WITH SMALL INTERFERING RNA, SELGANTOLIMOD, AND NIVOLUMAB

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Background: Novel therapeutic strategies for chronic hepatitis B (CHB) aim to achieve functional cure. A Phase 2a open-label study was conducted in patients with CHB to evaluate the safety and efficacy of combination therapies with VIR-2218 (a small interfering RNA [siRNA] targeting the HBx region of the HBV genome), selgantolimod (SLGN; an oral TLR8 agonist), and nivolumab (NIVO; an anti–PD-1 monoclonal antibody). To better understand the immunologic impact of this combination, we assessed longitudinal changes in peripheral cytokines, whole blood transcriptome, and cellular immune responses. **Methods:** Biomarker samples were collected longitudinally from Study GS-US-465-4439 patients (NCT04891770). Cohort 1 (C1; virally suppressed, received tenofovir alafenamide during study treatment, n = 42) and cohort 2A (C2A; viremic, n = 40) received VIR-2218 (200 mg SQ, every 4 weeks [Q4W]) for 24 weeks (W). At W12, SLGN (3 mg PO, weekly) and NIVO (0.3 mg/kg IV, Q4W) were added for an additional 24W. Cohort 2B (C2B; viremic, n = 20) received only SLGN and NIVO for 24W. Plasma cytokines were analyzed by singleplex ELISA and whole blood was evaluated by RNAseq. Peripheral blood mononuclear cells were immunophenotyped with cytometry by time of flight, while HBV-specific T cell responses were quantified using a 2-color Fluorospot (IFNg/granzyme B). For all analyses, changes from baseline and differences between cohorts were evaluated using the nonparametric Wilcoxon rank-sum test. **Results:** Transient increases in TLR8-associated cytokines and redistribution of innate and adaptive immune cells were observed 4h after SLGN dosing in all cohorts, consistent with prior studies. While no changes in peripheral blood gene expression were observed after siRNA lead-in, a transient increase in inflammatory and antiviral gene pathways was identified 24h after SLGN + NIVO dosing in all cohorts. A significant increase from baseline in the frequency of proliferating CD4+ and CD8+ T cells was observed after siRNA lead-in (C1; $P<0.05$) or 2W after SLGN + NIVO dosing (C2A and C2B; $P<0.01$). No consistent increases in HBV-specific T cell responses were observed in any cohort. **Conclusion:** A comprehensive biomarker assessment of novel HBV cure combination strategies revealed minimal immunologic changes during/after siRNA lead-in, limited increases in HBV-specific T

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cell responses, and expected shifts in biomarkers associated with immune modulation. These insights may guide the data-driven design of subsequent combination approaches.

Disclosures: David Pan: Nothing to Disclose, Nikita Kolhatkar: Gilead Sciences: Employee, Leonard Sowah: Nothing to Disclose, Andre Arizpe: Vir Biotechnology: Employee, Vir Biotechnology: Stock - publicly traded company, Daniel Cloutier: Nothing to Disclose, P. Rod Dunbar: Nothing to Disclose, Daniel Verdon: Nothing to Disclose, Bryan Downie: Gilead Sciences, Inc: Employee, Gilead Sciences, Inc: Stock - publicly traded company, Jeffrey Wallin: Nothing to Disclose, Frida Abramov: Gilead Sciences, Inc: Employee, Gilead Sciences, Inc: Stock - publicly traded company, Audrey Lau: Nothing to Disclose, Pamela Odorizzi: Gilead Sciences, Inc.: Employee

1335 | FACTORS ASSOCIATED WITH HIGH TITER RESPONSE TO HBV VACCINE IN PRIOR VACCINE NON-RESPONDERS WITH HIV: THE BEEHIVE TRIAL ◆

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Background: Persons with HIV (PWH) have a high rate of non-response to standard hepatitis B vaccine regimens. Prior data suggest that a CpG 1018 adjuvanted vaccine may improve response and achieve higher antibody titers which have historically been associated with greater vaccine durability. We conducted an international trial in PWH to evaluate a HepB-CpG vaccine and predictors of vaccine response in prior vaccine non-responders. **Methods:** ACTG A5379 BEeHIVe (B-Enhancement of HBV Vaccination in PWH) trial included a 3-arm, open-label, 1:1:1 randomization comparing recombinant HepB-CpG (HEPLISAV-B®, Dynavax Technologies Corporation) using a 2- or 3-dose regimen to a 3-dose HepB-Alum vaccine (Engerix-B®, SKF) in PWH who failed to mount a response to prior non-CpG adjuvanted vaccines. Participants received intramuscular (IM) regimens at Week 0, 4 (2-dose) or Week 0, 4, 24 (3-dose) and were assessed for seroprotective response (SPR: Hepatitis B surface antibody ≥10 mIU/mL) at 8 (2-dose) and 4 (3-dose) weeks after the series. Host factors associated with quantitative titers >1000 mIU/mL (ULQ) were assessed in logistic regression models. **Results:** 561 participants enrolled at 41 sites in 10 countries. The majority were male (64%). The median age was 46 years, median CD4+ T cell count was 638 cells/mm^3 and most (94%) had HIV RNA <40 copies/mL. SPR was 99% in 3-dose HepB-CpG, 93% in 2-dose HepB-CpG, and 81% in 3-dose HepB-Alum (9% missing data). In 3-dose HepB-CpG, 78% achieved titers >1,000 mIU/mL, 26% in 2-dose HepB-CpG, and 35% in 3-dose HepB-Alum. In the univariate analyses adjusted for study arm, participants who were younger, female, in the Asia or Africa region, Asian or Black, had no history of smoking, or had lower BMI were more likely to achieve >1000 mIU/mL titer (Figure). Stepwise variable selection led to study arm, race and age remaining as key factors associated with high titer response. **Conclusion:** In a study of PWH with prior HBV vaccine non-response, a 3-dose regimen of HepB-CpG yielded high seroprotection titers independent of most known factors associated with lower vaccine response. Black and Asian races and younger age were predictive of high titers thought to predict HBV vaccine durability, which will be evaluated after trial completion.

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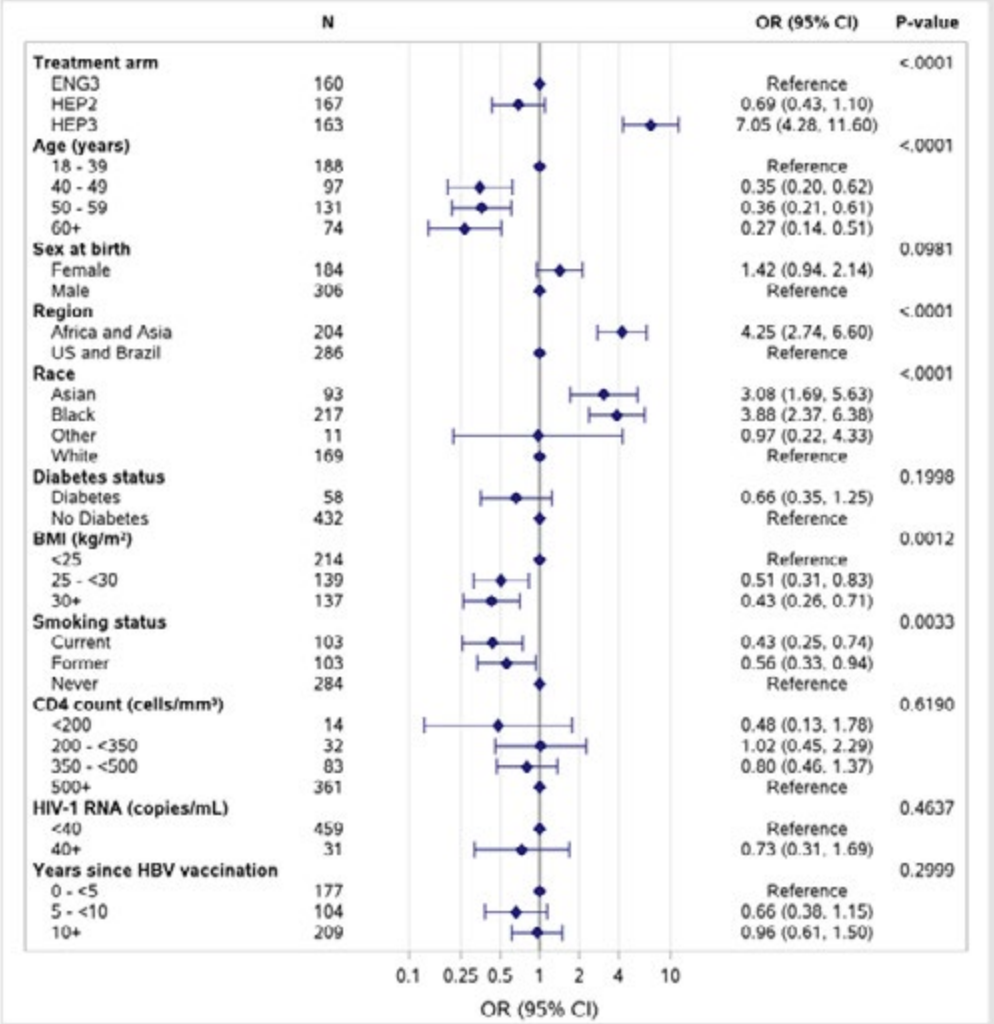
Figure: Associations with HBsAb>1000 mIU/mL in Univariate Analyses Adjusting for Treatment Arm



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1336 | ROLE OF AIR POLLUTION IN THE DEVELOPMENT OF HEPATOCELLULAR CARCINOMA AMONG CHRONIC HEPATITIS B PATIENTS TREATED WITH NUCLEOTIDE/NUCLEOSIDE ANALOGUES

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Background: Hepatitis B virus (HBV) infection is the major cause of hepatocellular carcinoma (HCC). Air pollution can cause multiple organ damage such as cardiovascular, lung, cerebrovascular disease and kidney disease, and it also increases the occurrence of cancers. The association between air pollution and the development of HCC is uncertain. The present study aimed to investigate the association between air pollution and HCC among patients with infection of chronic hepatitis B (CHB) virus treated by nucleotide/nucleoside analogues (NAs).

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Methods: A total of 1,298 CHB patients treated with NAs were enrolled and the incidence and risk factors of HCC development were analyzed in a tertiary medical center in southern Taiwan. Daily estimates of air pollutants (particulate matter ≤ 2.5 μm in diameter ($PM_{2.5}$)), (particulate matter ≤ 10 μm in diameter (PM_{10}), nitrogen dioxide (NO_2) and ozone (O_3)) were estimated since the previous year based on the date of enrolment. **Results:** The annual incidence of HCC was 2.1 per 100 person-years after a follow-up period of over 4840.5 person-years. Factors with the strongest association with HCC development were liver cirrhosis (hazard ratio [HR]/95% confidence interval: 3.00/1.55-5.81, *P*=0.001), followed by male gender (: 2.98/1.51-5.90, *P*=0.02), BMI (HR: 1.11, CI: 1.04–1.18, *P*=0.002) and age (HR: 1.06, CI: 1.04–1.09, *P*<0.001). Among cirrhotic patients, the factors associated with HCC development were male gender (2.10/1.00-4.25, *P*=0.04) and NO_2 (per one-unit increment, ppb) (HR: 1.07, CI: 1.01–1.13, *P*=0.01). Compared to patients with lowest quartile level of annual NO_2 exposure, those with highest quartile level of annual NO_2 exposure had more than three-fold risk ((HR: 3.26, CI: 1.34–7.93, *P*=0.01)) of HCC development in cirrhotic patients. Among non-cirrhotic patients, the strongest factors associated with HCC development was male gender (HR/CI: 5.86/1.79-19.23, *P*=0.004), followed by age (HR/CI: 1.12/1.07-1.17, *P*<0.001) and platelet count (HR/CI: 0.99/ 0.98-1.00, *P*=0.04). **Conclusion:** Air pollution played a potential role in HCC development in CHB patients who underwent NA therapy. Long-term NO_2 exposure might accelerate HCC development in CHB cirrhotic patients receiving NAs treatment.

Disclosures: Chia-Yen Dai: Nothing to Disclose, Tyng-yuan Jang: Nothing to Disclose, Chih-Wen Wang: Nothing to Disclose, Chung-Feng Huang: Gilead Sience: Grant/Research Support, Ming-Lung Yu: Abbvie, Gilead and Roche diagnostics.: Grant/Research Support, Abbott, Abbvie, Gilead, Roche and Roche diagnostics: Consultant, Abbvie, BMS, Gilead, Roche and Roche diagnostics: Speaking and Teaching

1337 | CHARACTERIZATION OF CHANGES IN NONINVASIVE FIBROSIS MARKERS OVER 8 YEARS OF TENOFOVIR-BASED TREATMENT IN PATIENTS WITH CHRONIC HEPATITIS B ENROLLED IN TWO PHASE 3 TRIALS

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Background: Blood-based noninvasive tests (NITs) are frequently used to assess liver fibrosis severity or monitor fibrosis progression. However, limited data exist on the evolution of these markers in the context of patients with chronic hepatitis B (CHB) receiving long-term nucleos(t)ide analogue therapy. We serially evaluated 3 blood-based NITs to characterize changes in fibrosis over 8 years in patients with CHB receiving tenofovir-based therapy. **Methods:** In 2 similarly designed Phase 3 studies (GS-US-320-0108/0110) evaluating tenofovir alafenamide (TAF), HBeAg-positive and -negative patients were randomized 2:1 to double-blind treatment with TAF 25 mg once daily (QD) or tenofovir disoproxil fumarate (TDF) 300 mg QD for up to 144 weeks followed by open-label TAF (i.e., TAF and TDF→TAF groups). Patients were assessed through 384 weeks (8 years). Three blood-based NITs were evaluated: FibroTest (BioPredictive SAS), aspartate aminotransferase–to-platelet ratio index (APRI), and fibrosis index based on 4 factors (FIB-4), all performed at baseline (BL) and annually thereafter. The FibroTest cutoff for no to mild fibrosis was <0.49; moderate to severe, 0.49–0.74; and cirrhosis, >0.74. Respective cutoffs to rule out or rule in advanced fibrosis or cirrhosis were FIB-4 ≤0.7 and >3.25 or APRI ≤0.45 and >2. Differences in blood-based NITs were evaluated using descriptive statistics of absolute values and change from BL through year 8. **Results:** Overall, 1632 patients were included in this pooled analysis. The mean (SD) absolute values for FibroTest, APRI, and FIB-4 at BL and changes from BL through year 8 were comparable across treatment groups, with the greatest mean declines observed at week 48 (Table). At year 8, 95% of TAF- and 88% of TDF→TAF–treated patients with available FibroTest data with a BL fibrosis category of no or minimal fibrosis remained in that fibrosis category (Table). Similar trends were observed for APRI and FIB-4. For patients with FibroTest values suggestive of cirrhosis at BL, 75% showed improvement at year 8. Similarly, 99% and 83% of patients with advanced fibrosis/cirrhosis at BL by APRI and FIB-4, respectively, improved by year 8. Overall, few low/intermediate-category patients moved to a higher fibrosis category at year 8. **Conclusion:** Improvements in FibroTest, FIB-4, and APRI scores were observed over

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8 years of tenofovir-based treatment. Early declines may be due to reduced necroinflammation. The significance of these dynamic long-term changes in fibrosis markers requires further investigation.

Table. Changes From Baseline in FibroTest, APRI, and FIB-4 Scores by Treatment Group

Mean (SD) Change From Baseline in FibroTest, APRI, and FIB-4						
	FibroTest		APRI		FIB-4	
	TAF (n = 1070)	TDF→TAF (n = 524)	TAF (n = 1085)	TDF→TAF (n = 539)	TAF (n = 1085)	TDF→TAF (n = 539)
BL, mean (SD)	0.38 (0.23)	0.38 (0.24)	1.22 (1.38)	1.37 (1.87)	1.63 (1.53)	1.76 (1.56)
W 48, mean (SD)	–0.07 (0.12)	–0.04 (0.13)	–0.77 (1.29)	–0.86 (1.75)	–0.43 (0.99)	–0.43 (0.96)
W 96, mean (SD)	–0.06 (0.13)	–0.03 (0.14)	–0.83 (1.31)	–0.88 (1.76)	–0.50 (1.05)	–0.48 (1.03)
W 144, mean (SD)	–0.06 (0.14)	–0.02 (0.15)	–0.82 (1.33)	–0.88 (1.74)	–0.47 (1.08)	–0.40 (1.24)
W 240, mean (SD)	–0.06 (0.14)	–0.04 (0.16)	–0.87 (1.37)	–0.93 (1.86)	–0.52 (1.17)	–0.47 (1.53)
W 384, mean (SD)	–0.06 (0.15)	–0.04 (0.17)	–0.87 (1.35)	–0.97 (1.87)	–0.49 (1.19)	–0.46 (1.18)

Categorical Shift in Fibrosis Stage From Baseline								
	TAF				TDF→TAF			
FibroTest BL	0.00–0.48 (n = 747)	0.49–0.74 (n = 223)	0.75–1.00 (n = 100)	Missing (n = 23)	0.00–0.48 (n = 356)	0.49–0.74 (n = 113)	0.75–1.00 (n = 55)	Missing (n = 15)
W 384								
0.00–0.48	500 (95%)	98 (59%)	15 (23%)	16	214 (88%)	39 (47%)	8 (20%)	4
0.49–0.74	26 (5%)	61 (37%)	37 (56%)	1	27 (11%)	36 (43%)	20 (50%)	1
0.75–1.00	2 (0.4%)	6 (4%)	14 (21%)	1	1 (0.4%)	8 (10%)	12 (30%)	2
Missing	219	58	34	5	114	30	15	8
APRI BL	≤0.45 (n = 178)	>0.45–≤2 (n = 757)	>2 (n = 150)	Missing (n = 8)	≤0.45 (n = 89)	>0.45–≤2 (n = 368)	>2 (n = 82)	Missing (n = 0)
W 384								
≤0.45	118 (96%)	443 (84%)	73 (72%)	6	56 (93%)	200 (81%)	35 (70%)	0
>0.45–≤2	5 (4%)	85 (16%)	28 (28%)	1	4 (7%)	46 (19%)	13 (26%)	0
>2	0	1 (0.2%)	0	0	0	2 (1%)	2 (4%)	0
Missing	55	228	49	1	29	120	32	0
FIB-4 BL	≤0.7 (n = 208)	>0.7–≤3.25 (n = 785)	>3.25 (n = 92)	Missing (n = 8)	≤0.7 (n = 80)	>0.7–≤3.25 (n = 402)	>3.25 (n = 57)	Missing (n = 0)
W 384								
≤0.7	85 (71%)	81 (14%)	2 (3%)	1	32 (74%)	37 (13%)	0	0
>0.7–≤3.25	35 (29%)	481 (85%)	55 (85%)	6	11 (26%)	239 (86%)	27 (75%)	0
>3.25	0	5 (1%)	8 (12%)	0	0	3 (1%)	9 (25%)	0
Missing	88	218	27	1	37	123	21	0

Data are shown as n (%) unless otherwise indicated.
APRI, AST-to-platelet ratio index; **AST**, aspartate aminotransferase; **BL**, baseline; **FIB-4**, fibrosis index based on 4 factors; **TAF**, tenofovir alafenamide; **TDF**, tenofovir disoproxil fumarate; **W**, week.

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1338 | PRESENCE OF METABOLIC COMORBIDITIES INCREASES THE RISK OF HEPATOCELLULAR CARCINOMA IN SUB-SAHARAN AFRICAN INDIVIDUALS LIVING WITH CHRONIC HEPATITIS B

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Background: Recent studies have identified metabolic comorbidities (MC) as risk factors for hepatocellular carcinoma (HCC) in individuals with chronic hepatitis B (CHB). However, individuals from sub-Saharan Africa (SSA) were underrepresented or excluded in these studies. We therefore aimed to study the association between presence of metabolic comorbidities with the risk of HCC in this population. **Methods:** We conducted an international multicenter retrospective cohort study of all consecutive mono-infected CHB individuals with SSA or Afro-Surinamese ethnicity managed at sites in the Netherlands, the United Kingdom and Spain. The presence of diabetes mellitus, hypertension and dyslipidemia were assessed based on chart review. We studied the association between metabolic comorbidities and HCC development using Cox regression. Metabolic comorbidities were combined to assess the cumulative risk effect in the overall study population and in subsets of individuals at increased risk based on presence of advanced fibrosis (METAVIR ≥F3 based on biopsy or liver stiffness measurement >9 kPa) and/or intermediate-high PAGE-B scores. **Results:** We analyzed 1473 individuals; the majority of whom were male (59.7%) with a median age of 38 years (interquartile range [IQR] 29-46) and 12.7% had advanced fibrosis at baseline. In total 20.5% of the individuals had one or more metabolic comorbidity (16.8% hypertension, 7.8% diabetes, 4.1% dyslipidemia). During a median follow-up of 8 years (IQR 3.9 – 11.4), 34 individuals developed HCC. In univariable analysis, diabetes mellitus (hazard ratio [HR] 6.4, p<0.001), hypertension (HR 3.4, p<0.001) and dyslipidemia (HR 3.3, p=0.014) were significantly associated with HCC development. Presence of multiple comorbidities was associated with an additive risk of HCC (1 MC: HR 4.1, ≥2 MCs: HR 7.2, p<0.001). Findings were consistent in individuals without advanced fibrosis at baseline (n=1260, 1 MC: HR 3.8, ≥2 MCs: HR 17.5, p=0.004), individuals with intermediate or high PAGE-B scores (n=654, 1 MCs: HR 3.2, ≥2 MCs:HR 4.5, p=0.003) and in multivariable analysis adjusting for age, platelet count, albumin (1 MC: adjusted HR [aHR] 3.6, MC ≥ 2 aHR 4.1, p=0.003). **Conclusion:** Presence of metabolic comorbidities is associated with an increased risk of HCC in Sub-Saharan African and Afro-Surinamese individuals with CHB, with the highest risk observed in individuals with multiple metabolic comorbidities. Findings were consistent among individuals with advanced fibrosis at baseline and in those with intermediate or high PAGE-B scores.

Disclosures: Lesley Patmore: Gilead Sciences: Consultant, Kirsi van Eekhout: Nothing to Disclose, Maria Buti: Nothing to Disclose, Özgür Muhammet Koc: Nothing to Disclose, Kosh Agarwal: Nothing to Disclose, Robert De Knegt: AbbVie: Speaking and Teaching, Gilead: Advisor, Gilead: Grant/Research Support, Johnson: Independent Contractor, Echosens: Independent Contractor, Echosens: Advisor, Echosens: Speaking and Teaching, Bracco: Consultant, GSK: Independent Contractor, Harry Janssen: Gilead Sciences: and consultant, Gilead Sciences: Grant/Research Support, GlaxoSmithKline: Grant/Research Support, Janssen: Grant/Research Support, Roche: Grant/Research Support, Vir Biotechnology Inc.: Grant/Research Support, Aligos: Consultant, Gilead Sciences: Consultant, GlaxoSmithKline: Consultant, Grifols: Consultant, Roche: Consultant, Vir Biotechnology Inc: Consultant, Precision Biosciences: Consultant, Marc van der Valk: MSD: Grant/Research Support, MSD: Advisor, gilead: Grant/Research Support, gilead: Advisor, ViiV healthcare: Grant/Research Support, ViiV healthcare: Advisor, Faydra Lieveld: Nothing to Disclose, Matthijs Kramer: Dr Falk: Sponsoring of educational meetings, Joep de Bruijne: Nothing to Disclose, Mark Claassen: Nothing to Disclose, Colette Smit: Nothing to Disclose, Robert De Man: roche diagnostics: Grant/Research Support, Bart Takkenberg: Nothing to Disclose, Ivana Carey: Nothing to Disclose, Milan Sonneveld: Nothing to Disclose

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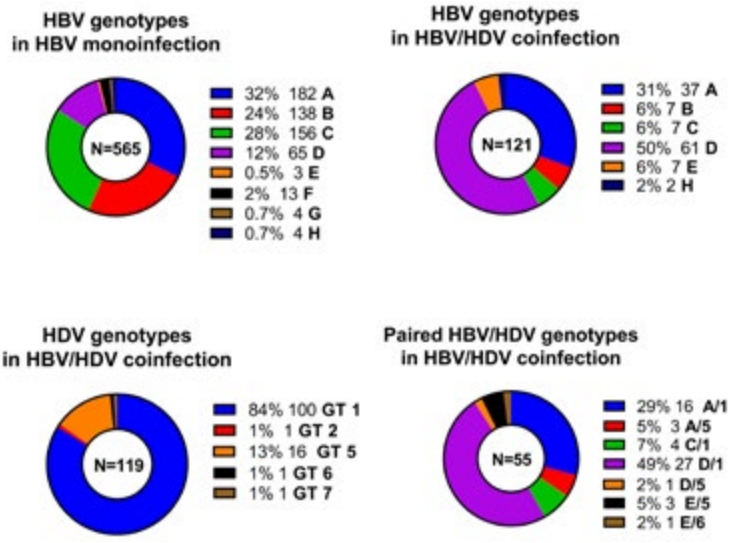
1339 | HBV/HDV GENOTYPES IN HBV/HDV CO-INFECTED PATIENTS IN THE UNITED STATES

Andrew Lopez[1] Beth Marlowe[2] William Meyer[2] Brooke Swanson[2] Roberto Mateo[1] yang liu[1] Ross Martin[1] Grace Chee[1] Savrina Manhas[1] Silvia Chang[1] Harish Gopalakrishna[3] Hongmei Mo[1] Theo Heller[3] Evguenia Maiorova[1] Christopher Koh[3]

[1]Gilead science Inc, [2]Quest Diagnostics, [3]National Institutes of Health

Background: Hepatitis D virus (HDV) is classified into 8 major genotypes (GT1 to GT8) and Hepatitis B virus (HBV) also consists of 8 confirmed genotypes (GTA to GTH). HDV GT1 is the most predominant genotype (GT) globally. The predominant HBV GT in Europe is GTD (88%), and the predominant HBV/HDV GT combination is GT D/1 (88%). In the US, HBV mono-infected patients are primarily genotypes A (32%), C (28%), B (24%), and D (12%). However, HBV/HDV GTs in Chronic hepatitis D (CHD) patients in the US remains unknown. We aim to determine HBV/HDV GTs for patients infected with HDV in the US. **Methods:** Samples were obtained from 232 patients positive for both HBV surface antigen and HDV antibody, 178/232 samples from patients followed prospectively at the NIH (NCT00001971) and 54/232 from Quest Diagnostics. Total nucleic acid was extracted from serum and used to amplify fragments of the HBsAg coding region and HDV full genome. Amplicon-based next generation sequencing was performed and consensus HBV and HDV sequences were used to determine GT. Additionally, an ELISA-based HBV genotyping assay (Cosmo Bio) was used to supplement HBV GT data. **Results:** Out of 232 samples, 92 and 129 were PCR positive for HBV and HDV, respectively. Then, 80 and 119 were genotyped for HBV and HDV based on sequence, respectively. An additional 41 HBV GTs were determined via EIA. HBV and HDV genotypes were determined for 121 and 119 patients, respectively. Of these, HBV GTs were: 61/121 (50%) GTD, 37/121 (31%) GTA, 7 /121 (6%) GTB, 7/121 (6%) GTC, 7/121 (6%) GT E and 2/121 (2%) GTH (see Figure). HDV GTs were: 100/119 (84%) GT1, 16/119 (13%) GT5, 1/119 (1%) GT2, 1/119 (1%) GT6 and 1/119 (1%) GT7. Paired HBV/HDV genotypes were available for 55 patients and were: 27/55 (49%) D/1, 16/55 (29%) A/1, 4/55 (7%) C/1, 3/55 (5%) A/5, 3/55 (5%) E5, 1/55 (2%) D/5, and 1/55 (2%) E/6. Mean age of NIH cohort was 44 ± 13 years with 59% males, 41% were Asians, 32% Whites and 23% Blacks. Majority (75%) were from states in southern region, 10% from midwest, 9% from northeast and 6% from west region. HDV RNA PCR was positive in 104 (58%) patients. Those with positive HDV PCR had significantly higher alanine aminotransferase (124 vs 57 U/L, p<0.01) and significantly lower platelet count (167 vs 212 x10^9/L, p<0.01) compared to those who were PCR negative. **Conclusion:** In the US, HBV/HDV GT D/1 (49%) is the predominant paired genotype, followed by A/1 (29%) in CHD patients, which is different with HBV mono-infection.



Disclosures: Andrew Lopez: Gilead Sciences: Stocks, Beth Marlowe: Quest Diagnostic: I own Stock in Quest Diagnostics, William Meyer: Nothing to Disclose, Brooke Swanson: Nothing to Disclose, Roberto Mateo: Gilead Sciences, Inc.: Employee, yang liu: Nothing to Disclose, Ross Martin: Gilead Sciences: Employee, Grace Chee: Gilead Sciences: Employee, Savrina Manhas: Gilead Sciences: Employee, Silvia Chang: Nothing to Disclose, Harish Gopalakrishna: Nothing to Disclose, Hongmei Mo: Nothing to Disclose, Theo Heller: Nothing to Disclose, Evguenia Maiorova: Nothing to Disclose, Christopher Koh: Nothing to Disclose

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1340 | PHARMACOKINETICS AND SAFETY OF A SINGLE DOSE OF ELEBSIRAN (VIR-2218, SIRNA) SUBCUTANEOUSLY ADMINISTERED IN ADULT PARTICIPANTS WITH MODERATE RENAL IMPAIRMENT

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[1]Vir Biotechnology, Inc.

Background: Elebsiran (VIR-2218) is a N-acetylgalactosamine (GalNAc)–conjugated, double-stranded RNA interference (RNAi) investigational therapeutic that targets the X region of the hepatitis B virus (HBV) genome that is common to all HBV viral RNA transcripts. Elebsiran is in clinical development for the treatment of chronic HBV (CHB) and hepatitis delta virus infections (CHD). In CHB and CHD studies, elebsiran 200 mg in combination with tobevibart 300 mg administered subcutaneously (SC) showed antiviral activity evident of reductions in HBsAg and HDV RNA[1,2]. Here, we report the pharmacokinetics (PK) and safety of elebsiran 200mg SC, after single-dose administration in participants with moderate renal impairment (RI) (eGFR 30-59 mL/min/1.73m^2 based on Modification of Diet in Renal Disease (MDRD) equation) and in matched healthy volunteers (HV). **Methods:** VIR-2218-V108 (NCT05844228) is a Phase 1, open-label, single-dose parallel-group study conducted in adult participants with RI and demographically matched HV. Each participant received a single SC dose of elebsiran 200 mg on Day 1. Blood samples for PK analysis were collected up to 5 days post-dose and urine samples were collected over 96 hours. The concentrations of elebsiran and its major metabolite AS(N-1)3'VIR-2218 in blood and urine were measured using validated LC-MS methods. **Results:** Eight (8) participants with moderate RI and 8 matched HV were enrolled. The geometric mean ratios (GMR) (90%CI) of C_{max} and AUC_{inf} of elebsiran in participants with moderate RI versus HV were 0.82 (0.66-1.01), and 1.14 (0.85-1.52), respectively. Similarly, the GMR (90% CI) of C_{max} and AUC_{inf} of AS(N-1)3'VIR-2218 in participants with moderate RI versus HV were 0.90 (0.66-1.24) and 1.16 (0.50-2.71), respectively. The fraction of unchanged drug excreted in urine (%fe) for elebsiran was 9.66% in participants with moderate RI versus 13.2% in HV participants. There were 4 adverse events (AE) (peripheral oedema, urinary tract infection, hyperglycemia and crystalluria) of Grade 1 and 2 reported in 2 RI participants and none were considered related to elebsiran. **Conclusion:** Following a single SC dose of elebsiran 200 mg, elebsiran PK exposures and renal excretion were similar in participants with moderate RI and HV. No drug related AEs were observed in participants with moderate RI. The collective PK and safety data supports continued evaluation of elebsiran 200mg in patients with CHB and CHD with up to moderate renal impairment.

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Disclosures: Li Wang: Vir Biotechnology, Inc.: Employee, Vir Biotechnology, Inc.: Stock - publicly traded company, Asma El-zailik: Nothing to Disclose, Keith Boundy: Nothing to Disclose, Shenghua Mao: Nothing to Disclose, Madhukar Aryal: Nothing to Disclose, Sneha Gupta: Nothing to Disclose, Maribel Reyes: Nothing to Disclose

1341 | IMAGING FOLLOW-UP FOR HBV PATIENTS WITH ADVANCED FIBROSIS AND/OR PAGE -B SCORE ≥10 FOR HCC SCREENING IN THE HEPATHER FRENCH COHORT; IS THE JOB WELL DONE? ◆

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Background: International guidelines (EASL, AASLD, APASL) recommend imaging follow-up (FU) by ultrasound for HBV patients (pts) with advanced fibrosis (AF) and/or Page-B score ≥10 (PBS ≥ 10). Are these recommendations

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tracked over time and do they allow HCC early detection and curative HCC treatment? We aimed to evaluate these points in the French cohort ANRS CO 22 HEPATHER. **Methods:** All chronic HBV-pts enrolled in the cohort between 2012-2014, with available FU both within the cohort study and within the French National Health Data System (SNDS) were included if they had baseline AF and/or PBS ≥ 10. Pts with HDV, HCV and /or HIV coinfection, HCC or decompensated cirrhosis at baseline or any other cause of liver injury were excluded. We defined 3 pts groups: I) pts with AF and PBS <10, II) pts with AF and PBS ≥ 10, III) pts without AF and PBS ≥ 10. Pts follow-up by imaging surveillance by ultrasound (or CT scan or MRI when appropriate) was divided into 4 groups a) regular FU every 6 months (RFU6), b) regular FU every year (RFU12), c) irregular FU less than annually (IFU), d) no FU. **Results:** Of 5,944 chronic HBV pts, 1,935 pts fulfilled the inclusion criteria. They were 76 (3.9%) in group I, 343 (17.7%) pts in group II and 1,516 (78.3%) in group III. The median follow-up was 99 months (IQR: 89-109). Table 1 shows the baseline demographic, clinical characteristics and HCC incidence of each group. Pts FU by imaging surveillance was RFU6 (1.6%) RFU12 (20.1%), IFU (74%) and no FU (4.3%). Group I and II pts had a more frequent RFU 6 or 12 (42%) than group III pts (16.1%) and less IFU 55.8% versus 79% respectively (p<0.0001). During the FU, 45 pts (2.3%) developed HCC, one pt (1.3%) in group I, 31 pts (9%) in group II and 13 pts (0.9%) in group III (p<0.0001). Of the 45 HCCs, 10 (22.2%) were diagnosed in patients with RFU6, 23 (51.1%) with RFU12 and 12 (36.7%) with IFU. 54.6% of HCCs had curative treatment and 45.5% had palliative treatment. Data were lacking in 12 pts, 6 patients who died after HCC diagnosis and 6 patients without available data on HCC treatment. Pts with RFU6 -12 more frequently had curative treatment than patients with IFU (60.0 vs 35.5%; p=0.05). **Conclusion:** In the HEPATHER cohort with extended follow-up, HBV patient imaging surveillance is generally performed, although often irregular. The occurrence of HCC in the AF group justifies monitoring, which allows curative treatment. HCC is rare in patients without AF and with a PAGE-B score ≥ 10, raising the question of the necessity of monitoring these patients in the absence of associated liver risk factors.

Table 1. Baseline demographic, clinical characteristics and HCC incidence of each group

	Group I (n=76) (AF and PBS<10	Group II (n=343) (AF and PBS≥10)	Group III (n=1,516) (no AF and PBS≥10)	p-value
Median age (IQR)	37.1 (29.5-51.8)	55.1 (45.1-64.3)	47.6 (41-57.8)	<0.0001
Female sex-n (%)	41 (54%)	31 (10.5%)	167 (11%)	<0.0001
Origin-n (%)				<0.0001
Caucasian	18 (23.7)	166 (48.8)	547 (36.4)	
African	33 (43.4)	108 (31.8)	627 (41.7)	
Asian	15 (19.7)	41 (12.1)	216 (14.4)	
HBV treatment-n (%)	56 (73.7%)	305 (88.9)	877 (57.9)	<0.0001
No Alcohol- n (%)	49 (64.5)	176 (51.8)	734 (48.6)	0.003
Diabetes-n (%)	9 (11.8)	51 (14.9)	116 (7.7)	0.0001
Hypertension-n (%)	11 (14.5)	108 (31.5)	303 (20)	<0.0001
HCC -n (%)	1 (1.3)	31 (9.0)	13 (0.9)	<0.0001

Incidences of HCC by group			
Group	N	n evt/P-Y (Persons Years)	Incidence per 100 P-Y [95%CI]
I	76	1/582	0,17 [0,00 – 0,96]
II	343	31/2480	1,25 [0,85 – 1,77]
III	1516	13/11822	0,11 [0,06 – 0,19]

Disclosures: Lucia Parlati: Nothing to Disclose, Paul Burgat: Nothing to Disclose, Clovis Lusivika: Nothing to Disclose, Jérôme Nicol: Nothing to Disclose, Jean Pierre Bronowicki: Nothing to Disclose, Georges-Philippe Pageaux: Nothing to Disclose, Vincent Leroy: Nothing to Disclose, Stanislas Pol: Nothing to Disclose, Fabrice Carrat: Nothing to Disclose, Marc Bourliere: Nothing to Disclose

1342 | IMPLEMENTATION OF THE HEPATITIS B "TRIPLE PANEL" IN THE OBSTETRIC CARE SETTING: PREVALENCE AND PREDICTORS OF TESTING, EXPOSURE, AND VACCINE IMMUNITY

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Background: In 2023, the CDC and ACOG released new HBV guidelines, recommending screening with the triple panel (HBsAg, HBsAb, and HBcAb) during each pregnancy. We evaluated the rates and predictors of HBV

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screening and positivity in pregnancy at our academic center, where one obstetrics practice site sequentially included all three tests into their prenatal lab order set, with HBcAb added in 2/2024. **Methods:** We conducted a retrospective chart review of women over age 18 with at least one documented pregnancy encounter and HBV test result at a single academic center between August 2021 and March 2024 (i.e. 2 years pre- and 2 months post triple panel implementation), and evaluated testing rates for HBsAg, HBcAb, and HBsAb before and after implementation, as well as trends in test results. T-test or Chi-squared test were used to evaluate predictive factors for HBV results. **Results:** We identified 19499 individuals with at least one pregnancy encounter; median age was 34 (IQR 30, 38); 40% were White, 24% Hispanic, 15% Black, and 12% Asian. HBV testing among pregnant individuals significantly increased following sequential implementation of triple screening with HBsAb in 8/2022, followed by the addition of HbcAb to one site's prenatal panel on 2/7/24 (Figure 1). Overall, 1566 women (8%) had a complete triple panel test, with the highest rates seen among Black (13%), followed by Hispanic (10%), and Asian (6%) individuals, ($p<0.01$). Higher rates of triple panel tests were seen among Medicaid patients, compared to other insurance types (11% vs 7%, $p<0.01$). In regards to individual test results 5038 (26%) were tested for HBsAb; among those tested, 1430 (28%) were non-reactive. Highest rates of non-reactive HBsAb were seen among Hispanic (33%) and Black women (32%), compared to Asian (21%), and White (18%) ($p<0.01$). A total of 19495 (99%) were tested for HBsAg; 80 (0.4%) had a reactive HBsAg, with highest rates among Asian women compared to all other races (1.4% vs 0.3%, $p<0.01$). Of 1779 (9%) who were tested for HBcAb, 95 (5%) had a reactive HBcAb result, with higher rates seen among Black (12%) and Asian women (10%), compared to White (1.5%) and Hispanic (1.4%) individuals ($p<0.01$). **Conclusion:** Incorporating HBV triple panel into prenatal visits offers an important opportunity to increase overall rates of HBV screening, identify those who are non-immune (almost 30% were not immune in our cohort), and encourage vaccination, which is recommended in pregnancy. Lower rates of immunity were seen in Hispanic and Black women in our cohort, highlighting potential target communities for HBV vaccine efforts. There is also an educational opportunity regarding counseling and management of patients who test positive for HBcAb. Adding triple screening to a prenatal order set, as has been done at one of our sites, is an effective way to improve testing for HBsAb and HBcAb among women, and should be adopted by other sites in the future in order to improve adherence to CDC/ACOG guidance.

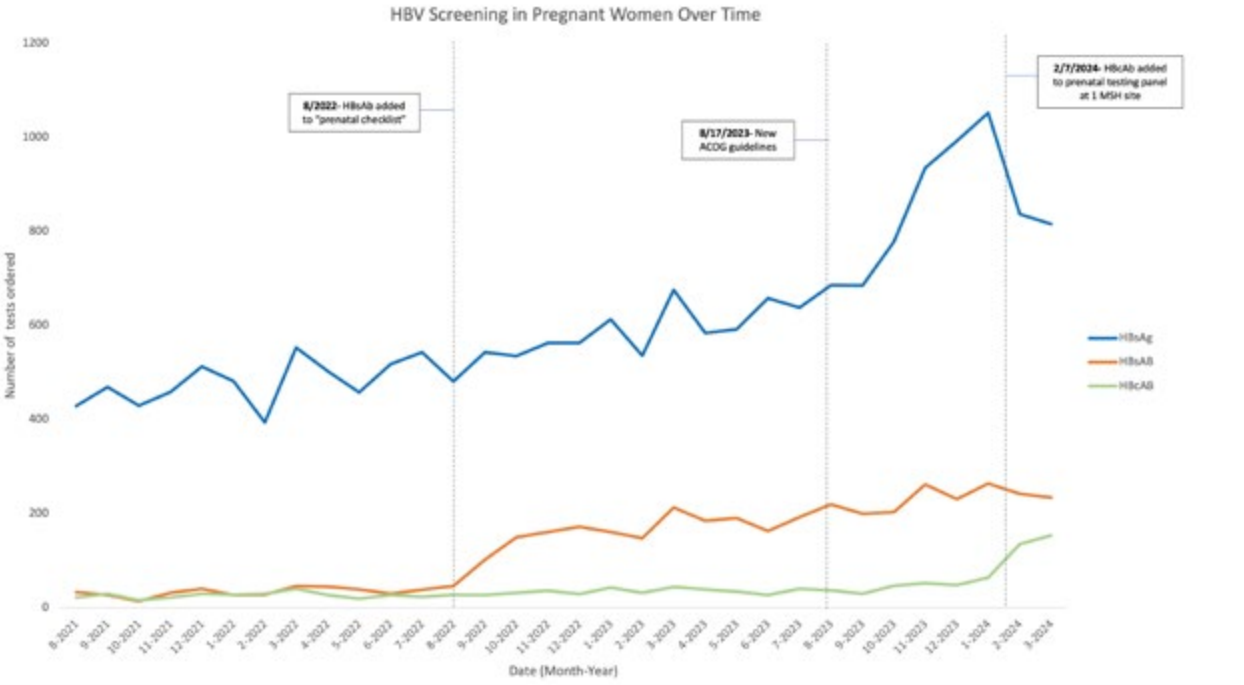

Figure 1: Most recent HBsAg, HBsAb, and HBcAb test performed between 8/2021 and 3/2024 for women who had at least one pregnancy encounter during this time period across all Mount Sinai prenatal clinics, plotted over time. Dashed lines indicate 3 time points: (1) Addition of HBsAb to a "prenatal checklist" at one hospital center (2) ACOG releases new triple screen guidelines (3) Addition of all 3 HBV tests to a prenatal lab order set at a single MSH clinic site

Disclosures: Natalia Schmidt: Nothing to Disclose, Jeanette Rios: Nothing to Disclose, Lauren Alpert: Nothing to Disclose, Anna Mageras: The Kinetix Group: Advisor, Novo Nordisk: Speaking and Teaching, Gilead Sciences: Grant/Research Support, Rachel Meislin: Nothing to Disclose, Whitney Lieb: Nothing to Disclose, Tatyana Kushner: Advisor relationship with Gilead; Has ended; Advisor relationship with GSK; Has ended; Advisor relationship with Eiger; Has ended; Grant/Research Support relationship with Gilead; Has not ended

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1343 | HEPATITIS B VIRUS REACTIVATION IN CANCER PATIENTS RECEIVING JANUS KINASE INHIBITORS

Khalis Mustafayev[1] Nicholas Short[1] Kelly Chien[1] Naval Daver[1] Fareed Khawaja[1] Harrys Torres[1]

[1]The University of Texas MD Anderson Cancer Center

Background: Janus kinase inhibitors (JAKis), which suppress cytokine overproduction by inhibiting the JAK/STAT pathway, are used to treat myelofibrosis, polycythemia vera, refractory graft-versus-host disease, and chronic inflammatory diseases. Low-quality data show that, among non-cancer patients receiving JAKis, the risk of hepatitis B virus reactivation (HBVr) is as high as 14% in those with past HBV infection but HBVr remains unknown in those with chronic HBV infection. In this study, we sought to determine the risk of HBVr in cancer patients with past or chronic HBV infection receiving JAKis. **Methods:** We retrospectively analyzed all consecutive cancer patients with past HBV infection (non-reactive HBV surface antigen [HBsAg], reactive HBV core antibody [anti-HBc]) or chronic HBV infection (reactive HBsAg, reactive anti-HBc) receiving JAKis (ruxolitinib, momelotinib, or tofacitinib) at MD Anderson Cancer Center from April 1, 2015, through May 1, 2024. HBVr was defined per the 2018 American Association for the Study of Liver Diseases guidelines. The risk of HBVr was categorized as low (<1%), intermediate (1%–10%), or high (>10%). Descriptive *p* values at a 2-sided significance level of 0.05 were reported. **Results:** We identified 71 patients with HBV (68 with past HBV and 3 with chronic HBV) (Figure 1). The median age was 68 years (interquartile range, 63–77 years). Most patients were men (53; 75%), were white (45; 63%), had myelofibrosis (28; 39%), and received ruxolitinib (65; 92%). Only 1 patient (1%) developed HBVr. That patient, who had past HBV infection while not on antiviral prophylaxis, developed HBVr after 8 months of ruxolitinib therapy (Figure 2). He did not develop HBV-associated hepatitis or liver failure, and HBVr resolved after antivirals were started. All 3 patients with chronic HBV infection received antiviral prophylaxis before starting JAKis (ruxolitinib), and none developed HBVr. Among the patients with past HBV infection, 1 of the 43 (2%) who did not receive antiviral prophylaxis developed HBVr, whereas none of the 25 (0%) who received antiviral prophylaxis had HBVr (p=0.44). Of the 28 patients who received an antiviral, 27 (96%) received entecavir. **Conclusion:** JAKis pose a low to intermediate risk of HBVr in cancer patients with past HBV. On the basis of our preliminary results, patients with past HBV infection should be monitored for HBVr while on JAKis, and antiviral therapy should be started promptly if HBVr occurs.

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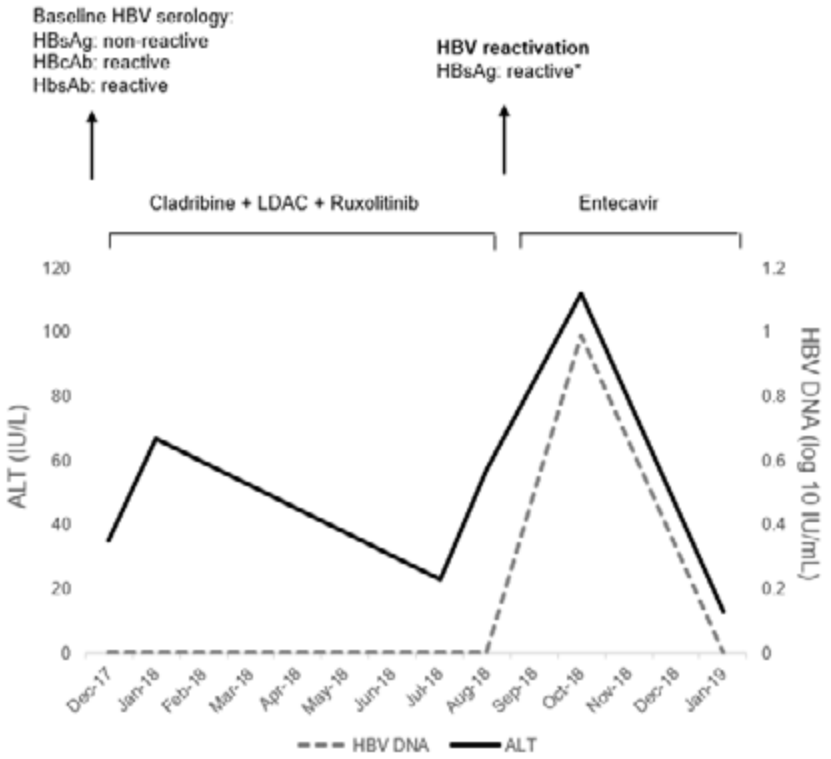
Figure 2. HBV reactivation in a patient with past HBV infection who received ruxolitinib.



*Reverse HbsAg seroconversion as type of HBVr. Abbreviations: HBcAb, hepatitis B core antibody; HbsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; LDAC, low dose cytarabine.

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1344 | IMPACT OF COVID-19 PANDEMIC ON TREATMENT FOR HEPATITIS B IN BRITISH COLUMBIA, CANADA: AN INTERRUPTED TIME SERIES ANALYSIS

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Background: Previous research suggests the COVID-19 pandemic was associated with reduced treatment for hepatitis B (HBV) early in the pandemic. However, impacts of the pandemic on HBV treatment over a longer time period are not well understood. We investigated the impact of the pandemic and related policies on HBV treatment initiation, continuation > 1 year, and discontinuation in British Columbia (BC) from 2020 to 2022. **Methods:** We used data from the BC COVID-19 Cohort, which integrates data from provincial registries and databases. We conducted interrupted time series analyses of the impact of the pandemic on the number of individuals initiating HBV treatment, the proportion of initiators who continued HBV therapy >1 year, and the proportion of treated individuals who discontinued therapy in BC. The study included a pre-policy period (January 2017–Feb 2020), a transition

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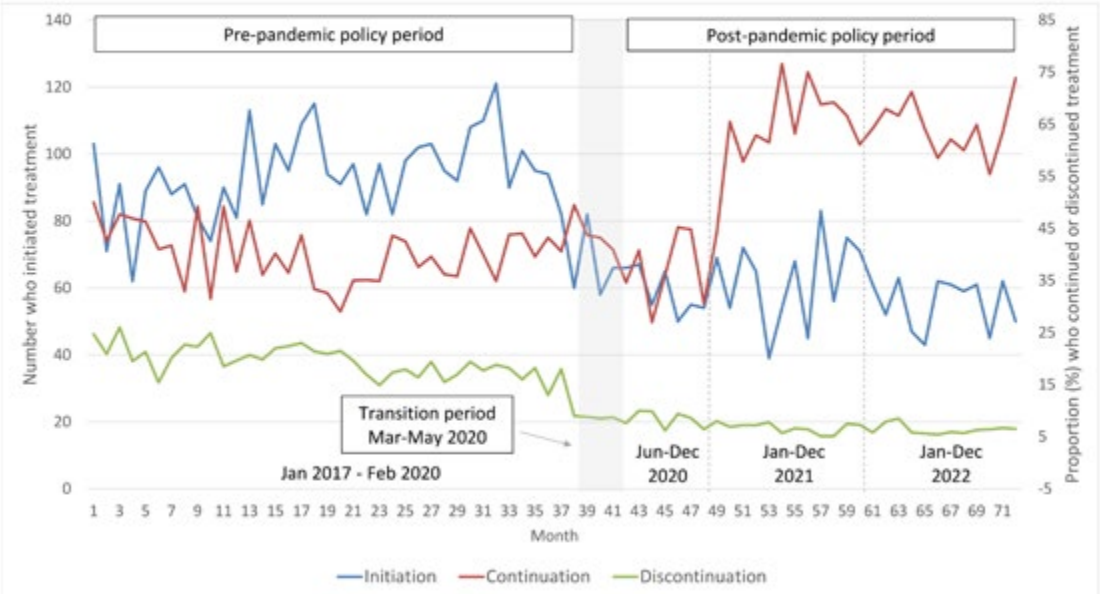
period (March–May 2020), and three post-policy periods (June–December 2020, January–December 2021, and January–December 2022). We calculated absolute and relative changes, relative to counterfactual estimates. **Results:** During the pre-policy period, a median of 94 individuals initiated HBV treatment, a median of 40.4% of initiators continued treatment >1 year, and a median of 19.6% of treated individuals discontinued treatment monthly. During June–December 2020, 43 (95% CI 31 to 53) fewer individuals than expected initiated treatment monthly, and treatment initiation remained lower than expected in 2021 and 2022. We found the proportion of initiators who continued treatment >1 year did not change in 2020 (-0.2%; 95% CI -4.8 to 4.5), but the absolute increase in the proportion who continued treatment was 26.8% in 2021 and 27.7% in 2022. We found an absolute decrease in the proportion who discontinued treatment of 7.0% (95% CI 5.0 to 9.0) in June-Dec 2020, and discontinuation remained below expectation in 2021 and 2022. People who inject drugs experienced a greater relative impact on treatment initiation, and individuals under 45 years of age experienced greater relative impacts on HBV treatment initiation, continuation >1 year, and discontinuation. **Conclusion:** After the introduction of COVID-19 pandemic–related policies, HBV treatment initiation and discontinuation decreased and remained lower than expected from 2020 to 2022 in BC. However, HBV treatment continuation >1 year was higher than expected in 2021 and 2022. Impacts on HBV treatment varied by age and history of injection drug use.

Figure. Pre- and post-pandemic policy trends in the number of individuals who initiate hepatitis B treatment, the proportion of initiators who continue treatment >1 year, and the proportion of treated individuals who discontinue treatment in British Columbia, Canada.



Disclosures: Richard Morrow: Nothing to Disclose, Dahn Jeong: Nothing to Disclose, Jean Makuza: Nothing to Disclose, Michael Irvine: Nothing to Disclose, Alnoor Ramji: Nothing to Disclose, Hin Hin Ko: Nothing to Disclose, Mel Krajden: Nothing to Disclose, Sofia Bartlett: Nothing to Disclose, Stanley Wong: Nothing to Disclose, Amanda Yu: Nothing to Disclose, JASON WONG: Nothing to Disclose, Julia Li: Nothing to Disclose, Naveed Janjua: Nothing to Disclose

1345 | HEPATITIS B TREATMENT OUTCOMES AND FACTORS ASSOCIATED WITH HBV TREATMENT SUCCESS: A POPULATION-BASED STUDY IN RWANDA

Jean Damascene Makuza[1] Dahn Jeong[2] Atul Aravindakshan[3] Richard Morrow[3] Prince Adu[4] Marie Paul Nisingizwe[3] Georgine Cua[4] Héctor Velásquez García[4] Janvier Serumondo[5] Albert Tuyishime[5] Joseph Puyat[3] Joseph Puyat[3] Alnoor Ramji[2] Michael Law[3] Naveed Janjua[4]

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Background: Timely treatment of chronic hepatitis B virus (HBV) infection reduces complications such as cirrhosis and hepatocellular carcinoma and improves overall survival. In Sub-Saharan Africa, data on HBV

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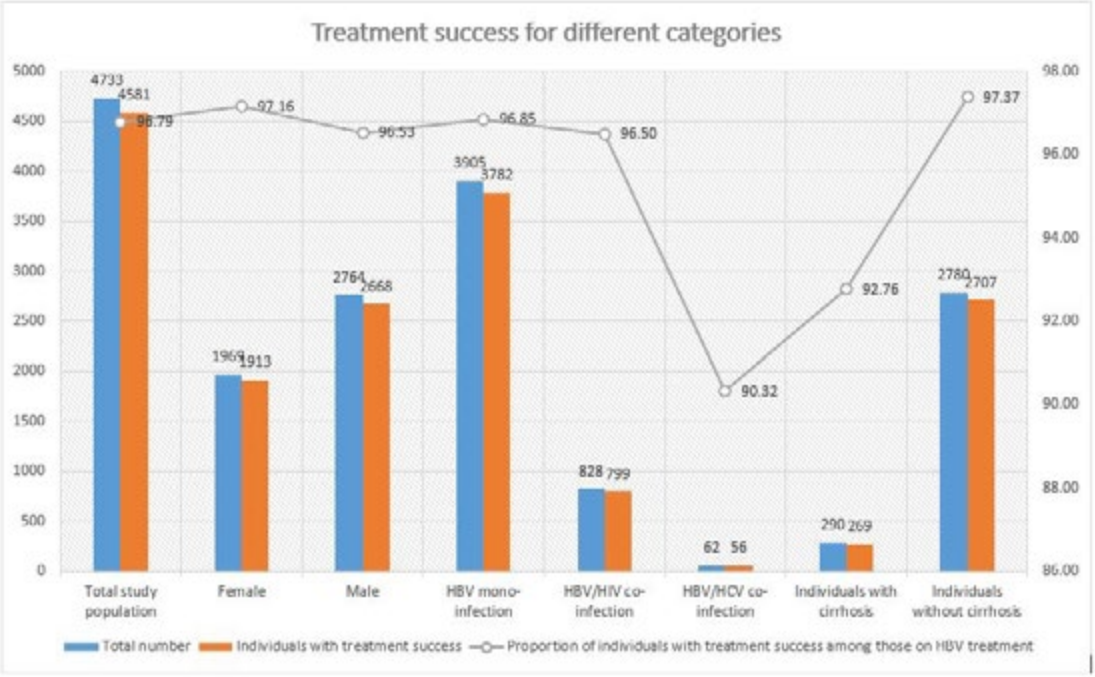
treatment success are limited in the general population, as well as among people living with HIV. We assessed the success of HBV treatment and associated factors among people diagnosed with HBV mono-infection and HIV co-infection. **Methods:** We used data from the updated District Health Information System 2 (DHIS2), which included information on 4.6 million individuals screened for HBV in Rwanda, from January 2016 to June 2023. DHIS2 includes data on screening, diagnosis, treatment, follow-up, comorbidities, demographic characteristics, and outcomes such as death. Patients were included if they had received HBV therapy for at least 12 months. We defined HBV treatment success as undetectable HBV DNA or normal ALT at 12 months. Individuals with chronic HBV infection, age ≥ 2 years, who received a highly potent anti-viral treatment (tenofovir-based, entecavir-based, or other) during the study period were considered in the analysis. We computed treatment success proportion and assessed risk factors associated with HBV treatment success using multilevel logistic regression that accounts for clustering by hospital. **Results:** Overall, 4,733 people received HBV treatment during the study period. The median age 39 years, and 58.4% were males. During the study period, 4,581 (96.8%) individuals had HBV treatment success. People with HBV mono-infection and those with HBV/HIV co-infection had similar proportions of treatment success [3,782 (96.8%) vs. 799 (96.5%)]. In the multivariable hierarchical model, HCV co-infection (aOR: 0.33; 95%CI: 0.12, 0.85), follow-up at provincial or referral hospital (aOR: 0.26; 95%CI: 0.08, 0.86) and cirrhosis (aOR: 0.36; 95%CI: 0.20, 0.63) were associated with a lower likelihood of HBV treatment success. Compared to those with HBV mono-infection, individuals with triple infection HBV/HCV/HIV were less likely to experience HBV treatment success (aOR: 0.14; 95%CI: 0.02, 0.93). **Conclusion:** The study showed a very high treatment success rate among people who initiated HBV treatment in Rwanda. However, it also showed that individuals with HBV/HCV coinfection or cirrhosis were less likely to experience treatment success. The study emphasizes the significance of early detection and timely treatment of HBV in people with triple viral infection HBV/HCV/HIV. It also underscores the importance of closely monitoring people with advanced liver diseases to effectively suppress HBV.



Disclosures: Jean Damascene Makuza: Nothing to Disclose, Dahn Jeong: Nothing to Disclose, Atul Aravindakshan: Nothing to Disclose, Richard Morrow: Nothing to Disclose, Prince Adu: Nothing to Disclose, Marie Paul Nisingizwe: Nothing to Disclose, Georgine Cua: Nothing to Disclose, Héctor Velásquez García: Nothing to Disclose, Janvier Serumondo: Nothing to Disclose, Albert Tuyishime: Nothing to Disclose, Joseph Puyat: Nothing to Disclose, Joseph Puyat: Nothing to Disclose, Alnoor Ramji: Nothing to Disclose, Michael Law: Nothing to Disclose, Naveed Janjua: Nothing to Disclose

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1346 | ESTABLISHMENT OF HBX RESPONSIVE QUANTITATIVE CELL CULTURE REPORTER SYSTEM FOR MONITORING HBV INFECTION

Muhammad Atif Zahoor[1] Nahla Fadlelmawla[2] Adrian Kuipery[3] Joshua Feld[2] Alexander Mosa[2] Adam Gehring[4] Jordan Feld[5]

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Background: Chronic hepatitis B virus (HBV) is a major risk factor for developing liver fibrosis, cirrhosis, and hepatocellular carcinoma. Current therapy with nucleot(s)ide analogues (NAs) and/or interferon alpha (IFNα) improve outcomes but fail to eliminate covalently closed circular DNA (cccDNA) and rarely lead to functional cure. HBV model systems are required to identify new potential therapeutic agents. Development of a cell-based quantifiable reporter system is highly desirable. Leveraging the ability of HBx to activate CREB [cyclic adenosine monophosphate (cAMP) response element binding protein] signaling, we aimed to develop a cell-based system to reliably identify the presence of HBx and thus HBV replication for the purpose of screening compounds for anti-HBV activity. **Methods:** We established a HBx-responsive cell line stably expressing nano-luciferase under the control of viral CREB-response element (vCRE) derived from human T-cell leukemia virus-1 core promoter and investigated the effect of HBV replication as well as various drug inhibitors in HBV-infected cells. HBx function was confirmed by assessment of derepression of the SMC6 by Western Blot. **Results:** We confirmed the responsiveness of vCRE-nLuc towards HBx using pHBV1.3mer (wild type), pHBx or pHBV1.2*7ΔX. Further, HBV infection with cell culture or patient-derived clinical isolates yielded enhanced luciferase activity. Inhibitors of HBx production (siRNA), specific HBx inhibitors, and IFNα inhibited luciferase production, whereas antivirals with no effect on protein production (tenofovir) had no effect. Finally, HepG2.2.15 cells with pre-existing HBV transduced with vCRE-nLuc confirmed the suitability of vCRE-nLuc cassette in monitoring HBV infection. **Conclusion:** We successfully established a vCRE-nLuc driven HBx-responsive cell line for quantitative monitoring of HBV infection as well as evaluation of antiviral drugs. We believe this system may aid in identifying new anti-HBV agents as well as enhance our current understanding of HBV replication.

Disclosures: Muhammad Atif Zahoor: Nothing to Disclose, Nahla Fadlelmawla: Nothing to Disclose, Adrian Kuipery: Nothing to Disclose, Joshua Feld: Nothing to Disclose, Alexander Mosa: Nothing to Disclose, Adam Gehring: Nothing to Disclose, Jordan Feld: Mirum: Consultant, AbbVie, Bluejays, Gilead, Janssen, GSK, Roche, VIR Roche: Consultant, Bluejays: Consultant, Gilead: Consultant, Janssen: Consultant, GSK: Consultant, Roche: Consultant, VIR Biotechnology: Consultant, Altimmune, AbbVie, Gilead, Jannsen, GSK, Roche, VIR Bio: Grant/ Research Support

1347 | TENOFOVIR ALAFENAMIDE FUMARATE IN TREATMENT-NAÏVE CHRONIC HEPATITIS B PATIENTS WITH LIVER FIBROSIS: A PRELIMINARY NON-INVASIVE RESULTS OF 96 WEEKS

Jialing Zhou[1] Xiaoning Wu[1] Chuanwu Zhu[2] Jiming Zhang[3] Ping Li[4] Tao Han[5] huiguo ding[6] Chenghai Liu[7] Wen Xie[8] Qing Xie[9] Yali Zong[10] Hong You[11] Jidong Jia[12]

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Background: To investigate the antifibrotic efficacy and safety of tenofovir alafenamide (TAF) in treatment-naïve chronic hepatitis B (CHB) with liver fibrosis. **Methods:** Treatment-naïve CHB patients with histologically confirmed liver fibrosis were prospectively recruited from 10 tertiary hospitals in China (NCT04939441). They received TAF for 96 weeks. Virological response (VR, HBVDNA< 20 IU/ml), alanine aminotransferase (ALT) normalization (≤40 IU/L) were used to assess the virological and biochemical effect, respectively. Noninvasive tests including LSM, aspartate aminotransferase-to-platelet ratio index (APRI) and Fibrosis 4 Score (FIB-4) were used to assess liver

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fibrosis every 24 weeks during treatment. Safety profiles including estimated glomerular filtration rate (eGFR), bone mineral density and lipid profiles were evaluated every 48 weeks. **Results:** A total of 100 CHB patients (61% HBeAg positive) were enrolled. Before treatment, 47, 30 and 23 patients were staged at F2, F3 and F4 respectively according to Metavir score system. Among the 89 patients who completed 96 weeks of follow-up, the mean of HBV DNA declined from 5.81 to 0.26 log IU/ml, resulting VR rates of 75% and 86% for week 48 and 96, respectively. ALT normalization rate was 84% at week 96. The mean of LSM rapidly decreased from 11.4 at baseline to 7.8 kPa at week 48, then slowly declined to 7.5 kPa at week 96. There were 45 patients (45/88, 51%) had more than 30% decline in LSM at 96 weeks. In patients with F2, F3, and F4, the mean of LSM decreased from 8.3, 12.1 and 16.8 at baseline to 5.9, 8.0 and 10.3 kPa at week 96, respectively ($p<0.005$). **Conclusion:** 96 weeks of TAF treatment resulted in good virological and biochemical response, and more importantly, significantly reverse liver fibrosis as evaluated by non-invasive tests. The safety in terms of renal function, bone mineral density and lipids profiles were favorable.

Disclosures: Jialing Zhou: Nothing to Disclose, Xiaoning Wu: Nothing to Disclose, Chuanwu Zhu: Nothing to Disclose, Jiming Zhang: Nothing to Disclose, Ping Li: Nothing to Disclose, Tao Han: Nothing to Disclose, huiguo ding: Nothing to Disclose, Chenghai Liu: Nothing to Disclose, Wen Xie: Nothing to Disclose, Qing Xie: Nothing to Disclose, Yali Zong: Nothing to Disclose, Hong You: Nothing to Disclose, Jidong Jia: Nothing to Disclose

1348 | LATE DIAGNOSIS OF CHRONIC HEPATITIS B IS ASSOCIATED WITH INCREASED LIVER-RELATED COMPLICATIONS – A POPULATION-BASED, RETROSPECTIVE COHORT STUDY

Michael Le[1] Joanne Liu[2] Ramsey Cheung[2] Mindie Nguyen[2]

[1]University of Vermont, [2]Stanford University Medical Center

Background: The WHO has called for global elimination of chronic viral hepatitis by 2030. However, up to 90% of people with chronic hepatitis B (CHB) may be undiagnosed globally. This study aimed to identify the trends and liver-related complications associated with late diagnosis of CHB. **Methods:** This is a retrospective analysis of patients in the Truven MarketScan database (1/2007-12/2021), a claims database for more than 250 million persons in the USA with private insurance. Liver complications included cirrhosis, hepatocellular carcinoma, and liver transplant. Late diagnosis of CHB was defined as a diagnosis of CHB after or within 2 years of the patient's first presentation of liver complication. All adults age ≥18 years with a diagnosis of CHB with at least 12 months of insurance coverage prior to the first liver complication were included. Patients with >3 months break of insurance coverage within the 12 months before first liver complication, who received a non-liver transplant within 5 years of their first liver complication, or with CHB diagnosis after insurance coverage ended were excluded. The index date was the date of the patient's first liver complication. **Results:** Of the 78,764 patients diagnosed with CHB, 2,608 met inclusion criteria with 1999 (77%) having a late diagnosis of CHB. In trends analysis, the prevalence of late diagnosis of CHB remained stable at 73.8% in 2009, 85.6% in 2014, and 74.2% in 2017 *(p=0.904).* 60% of persons with a late diagnosis of CHB developed their first liver complication within 6 months of their CHB diagnosis and 11% of persons with a liver complication received their CHB diagnosis at least 1 year after their first liver complication (figure). For patients who received a diagnosis of CHB >3 years after their first liver complication, 32 (46%) patients were diagnosed with another liver disease within 12 months of that complication. Complications developed included cirrhosis (n=1820, 91.0%), decompensated cirrhosis (n=1630, 81.5%), HCC (n=615, 30.8%), and liver transplant (n=288, 14.4%). **Conclusion:** In the United States, the majority of patients presenting with a liver complication had a late diagnosis of CHB. Additionally, the prevalence of late diagnosis of CHB did not improve between 2009 and 2017. Increased screening efforts must be made to meet the WHO goals of viral hepatitis elimination.

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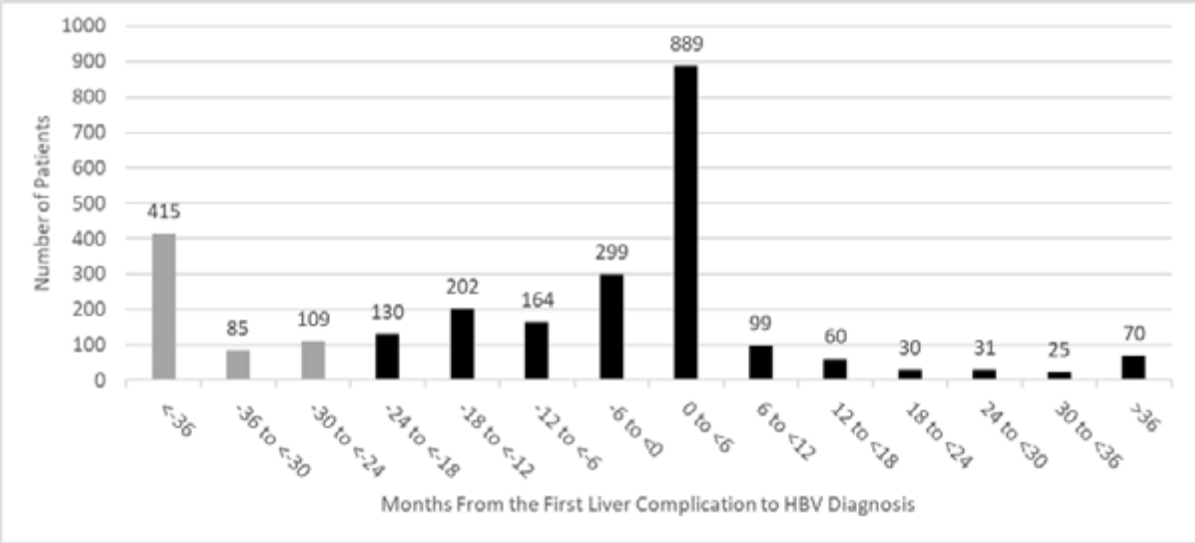

Disclosures: Michael Le: Nothing to Disclose, Joanne Liu: Nothing to Disclose, Ramsey Cheung: Nothing to Disclose, Mindie Nguyen: Nothing to Disclose

1349 | DIFFERENCES IN HEPATITIS B CHARACTERISTICS, TREATMENT ELIGIBILITY, AND OUTCOMES BETWEEN FOREIGN-BORN AND US-BORN BLACKS IN THE UNITED STATES

Mohamad Elgozair[1] Sanjana Rao[2] Spenser Hood[3] Vishal Shah[1] Michelle Van Hee[1] Fowsiyo Ahmed[1] Mohammed Youssef[1] Matthew Akiyama[4] Kenneth Rothstein[5] Daryl Lau[6] Ibrahim Hanouneh[7] Kevin Rank[7] Anupama Nookala[3] Patricia Jones[2] Lewis Roberts[1]

[1]Mayo Clinic Rochester, [2]University of Miami, [3]Health Partners, [4]albert einstein college of medicine, [5]PennMedicine/University of Pennsylvania, [6]Beth Israel Deaconess Medical Center, [7]MNGI Digestive Health

Background: Chronic Hepatitis B (CHB) affects over 250 million people worldwide, causing complications including cirrhosis and hepatocellular carcinoma (HCC). In the US, Black individuals have unique disease characteristics and face significant healthcare challenges. This study compares CHB progression in foreign-born Black individuals (FBB) versus US-born Black individuals (USB), highlighting healthcare disparities. **Methods:** Black adults with CHB seen from January 2000 to December 2020 at three tertiary care centers were categorized as FBB or USB. Data on demographics, comorbidities, lab results, imaging, and treatment were abstracted. The sample included individuals born in diverse regions: America, the Caribbean, East/Southern Africa, and West/Central Africa. Descriptive statistics, Pearson's chi-square and Linear Model ANOVA tests were used for analysis. **Results:** Of 888 Black adults with CHB (mean age 54.1 years (SD 14.4; range 18-100), 53% males, 93% non-Hispanic), 82% were FBB and 18% USB. USB had higher rates of diabetes (24% vs. 14%), hypertension (49% vs. 30%), hyperlipidemia (29% vs. 16%), and metabolic syndrome - reported as MASLD (12% vs. 4.4%). USB also showed higher alcohol use (29% vs. 15%), smoking (13% vs. 3.8%), drug use (24% vs. 1.6%), HIV infection (17% vs. 3%), and blood transfusions (23% vs. 9%). FBB were more likely to have a family history of HBV (10% vs. 3.5%). HBV genotype A was more common in USB (19% vs. 8.9%), who also had higher $\log_{10}$ DNA levels (mean: 3.8(SD: 2) vs 3.4(SD: 1.8) and treatment rates (62% vs. 30%) but lower vaccination rates (4.9% vs. 19%). USB had higher rates of hepatic complications, including decompensated cirrhosis (22% vs. 9.8%), ascites (13% vs. 5.3%), portal hypertension (9% vs. 4.4%), esophageal varices (8.3% vs. 4.1%), and liver transplant (5.6% vs. 1.5%). The two groups had similar HCC incidence, but USB had higher HCC screening rates at 6 and 12 months (62.5% and 63.9% vs. 55.8% and 49.3%). All differences were statistically significant ($P < 0.001$). **Conclusion:** USB with CHB had higher rates of comorbidities, risk behaviors, and hepatic complications compared to FBB, who had higher HBV vaccination rates and family history of HBV but lower HCC screening rates. Despite having equivalent HCC incidence to USB, FBB were less likely to be candidates for treatment. These disparities highlight the need for tailored healthcare strategies to improve outcomes for Black individuals with CHB.

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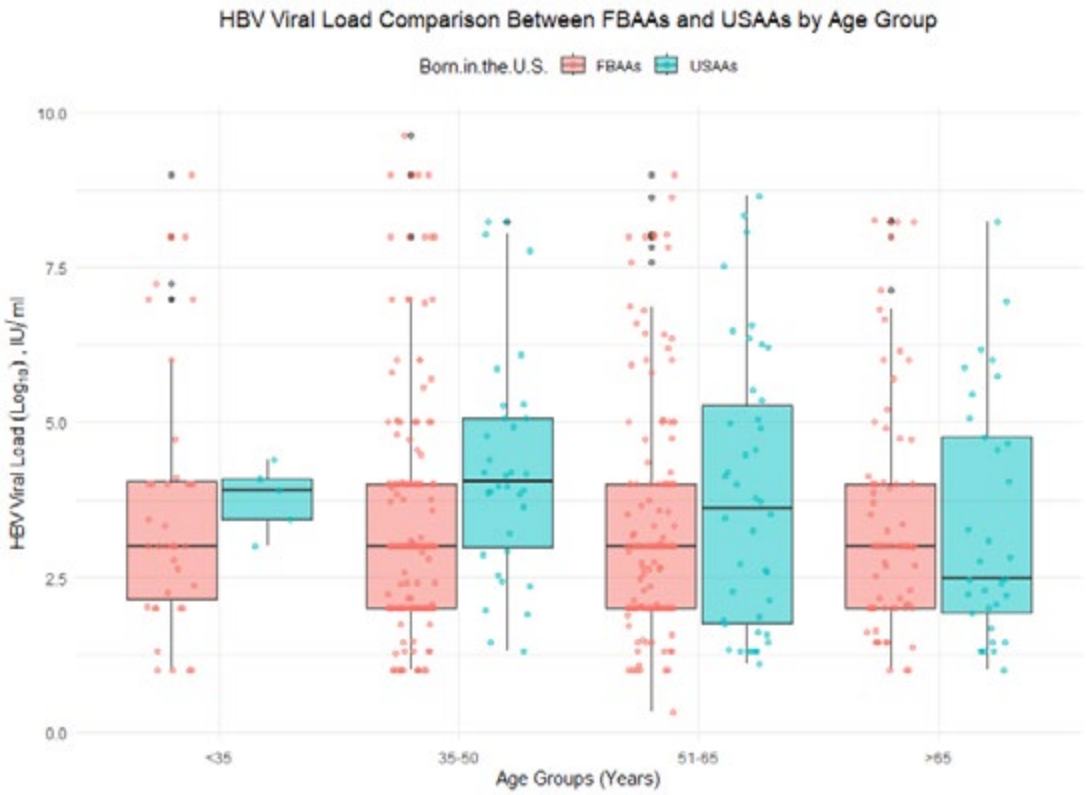

Disclosures: Mohamad Elgozair: Nothing to Disclose, Sanjana Rao: Nothing to Disclose, Spenser Hood: Nothing to Disclose, Vishal Shah: Nothing to Disclose, Michelle Van Hee: Nothing to Disclose, Fowsiyo Ahmed: Nothing to Disclose, Mohammed Youssef: Nothing to Disclose, Matthew Akiyama: Nothing to Disclose, Kenneth Rothstein: Alexion: other, Orphalan: other, Daryl Lau: Gilead: Grant/Research Support, GSK: Consultant, Abbott Laboratories: Consultant, Ibrahim Hanouneh: Nothing to Disclose, Kevin Rank: Nothing to Disclose, Anupama Nookala: Intercept Pharmaceuticals: Speaking and Teaching, Curio Sciences: Advisor, Patricia Jones: Gilead: Grant/Research Support, Lewis Roberts: Nothing to Disclose

1350 | OUTCOMES OF NUCLEOS(T)IDE ANALOG DISCONTINUATION IN HBEAG-POSITIVE CHRONIC HEPATITIS B PATIENTS WITHOUT ACHIEVING HBEAG LOSS

CHIEN-WEI PENG[1] *Yen-Chun Liu*[1] *Rachel Wen-Juei Jeng*[2] *Rong-Nan Chien*[1]

[1]*Linkou Chang Gung Memorial Hospital,* [2]*Chang Gung Medical Foundation*

Background: Patients with hepatitis B e antigen (HBeAg)-positive chronic hepatitis B (CHB) who fail to achieve HBeAg loss after two years on nucleos(t)ide analog (Nuc) therapy have only a 10% annual chance of subsequent HBeAg loss. Given this low likelihood and the challenges of long-term medication adherence, some patients opt to discontinue Nuc therapy. The clinical outcomes of this decision, which are not well-documented, require thorough investigation. **Methods:** In an HBeAg-positive Nuc treated cohort, we followed 63 patients who stopped Nuc therapy after 2 years without achieving HBeAg loss. Off-Nuc outcomes and complications were analyzed using descriptive statistics and survival analysis, with events categorized as virological relapse (VR: serum HBV DNA levels of ≥2000 IU/mL), clinical relapse (CR: ALT level ≥2 times(x) the upper normal limit (ULN) plus serum HBV DNA levels of ≥2000 IU/mL), hepatitis flare (ALT ≥5x ULN), severe hepatitis flare (ALT >1000 U/L or flare with ALT <1000 U/L plus total bilirubin (T.Bil) >2.0 mg/dL), and hepatic decompensation (T.Bil >2.0 mg/dL and INR > 1.5). **Results:** Of the 63 patients, the mean age was 49 years, 65% were male, 17% were cirrhotic, 67% were treated with ETV, and the median treatment duration was 3 years. Over 96 weeks after Nuc cessation, cumulative incidence of VR and CR were 88.9% and 84.1%, respectively. Hepatitis flares occurred in 70.4% of patients, with severe flares in 24.4%. Importantly, no liver decompensation or mortality was observed. Among the 53 (84%) Nuc retreated patients, all patients had CR prior re-treatment and 12 patients were with severe flare. These 12 patients with severe flares also all lost HBeAg within 2 years. Over 5 years, the cumulative incidence of HBeAg loss during

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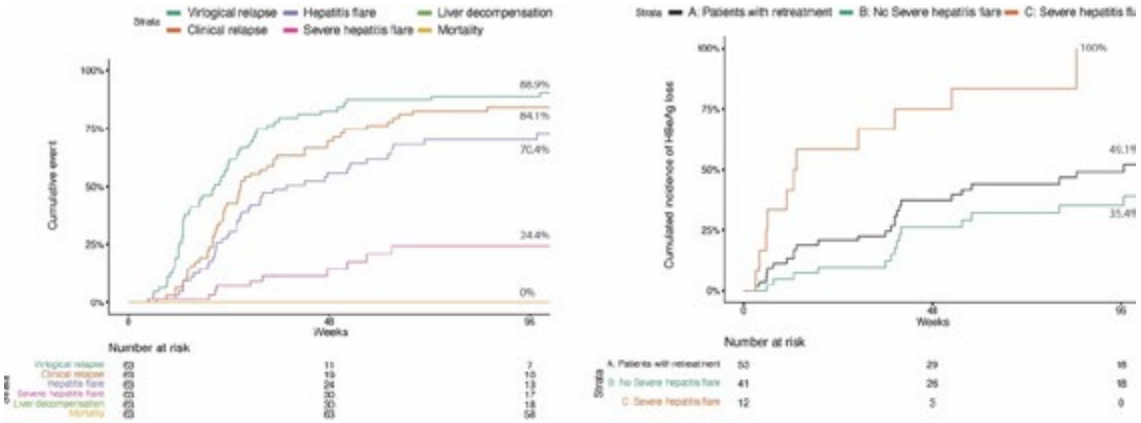
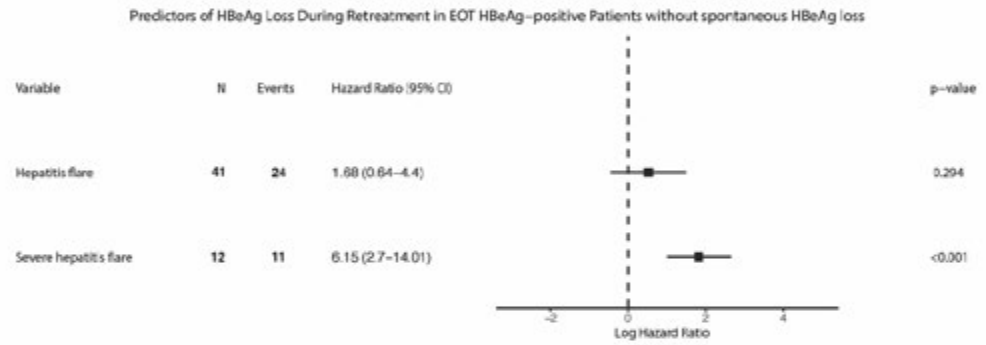
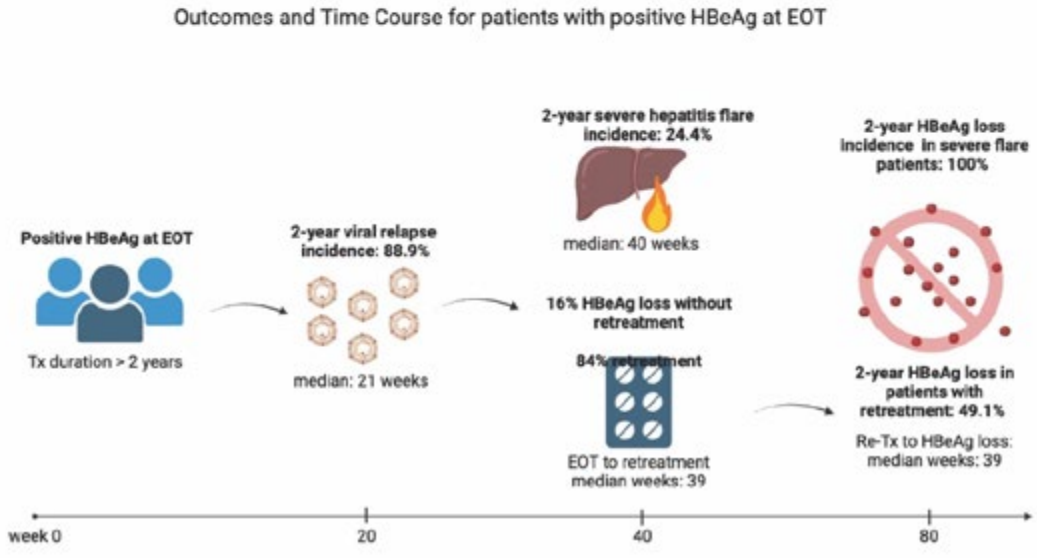
retreatment was 49.6%. Among the retreated patients, severe flares is the only predictor for HBeAg loss [rate ratio: 6.15 (95% CI: 2.7-14.01, p<0.001), underscoring its potential role as an indicator for immune reconstitution and therapeutic intervention. Among the 10 non-retreated patients, all achieved HBeAg loss after Nuc cessation with a median of 32 (11-241) weeks after EOT; 7 of these patients had documented CR (6 with hepatitis flare including 1 with severe flare) prior to HBeAg loss. **Conclusion:** In HBeAg-positive CHB patients, stopping nucleos(t)ide analogs without HBeAg loss led to a high retreatment rate. However, HBeAg seroconversion was high during or without retreatment, and re-treatment should be considered for severe ALT flares.







Disclosures: CHIEN-WEI PENG: Nothing to Disclose, Yen-Chun Liu: Nothing to Disclose, Rachel Wen-Juei Jeng: Nothing to Disclose, Rong-Nan Chien: Nothing to Disclose

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1351 | MALE SEX, HIGH β-GTF, HIGH AFP, HIGH GDF15 AND HIGH FIB-4 INDEX WERE HIGH RISK FACTORS FOR THE OCCURRENCE OF PRIMARY HCC IN CHB PATIENTS UNDER NUC TREATMENT

Kazuhiro Murai[1] Hayato Hikita[1] Emi Sometani[1] Satoshi Tanaka[2] Takayuki Miyake[1] Shinji Kuriki[1] Jihyun Sung[1] Akiyoshi Shimoda[1] Satoshi Shigeno[1] Kumiko Shirai[1] Yoshinobu Saito[1] Takahiro Kodama[1] Ryotaro Sakamori[2] Tomohide Tatsumi[1] Hidenori Toyoda[3] Akihiro Umezawa[4] Tetsuo Takehara[1]

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Background: Although treatment with nucleos(t)ide analogues (NUCs) for chronic hepatitis B (CHB) reduces the risk of developing hepatocellular carcinoma (HCC), it does not completely suppress the development of HCC. The clinical characteristics of CHB patients who developed primary HCC under NUC treatment are not clear. It has also been reported that serum GDF15 levels can be a potential biomarker for the diagnosis of cirrhosis and HCC. Elevated levels of HBV RNA have been reported to increase the risk of HCC in patients treated with NUC. The aim of this study was to identify high-risk groups for primary HCC in CHB patients under NUC treatment by retrospective analysis of biomarkers including serum GDF15 and HBV RNA. **Methods:** Two hundred forty-two CHB patients for whom stored sera were available, who had been treated with NUC for at least 1 year at the time of stored serum collection, whose serum HBV DNA levels were less than 3.0 log IU/mL, and who had no history of HCC were included. The stored sera were used to measure GDF15 by ELISA and HBV RNA by RT-PCR. The lower limit of quantification (LLOQ) for HBV RNA was 400 copies/mL (2.60 log copies/mL). **Results:** The median age of the patient cohort was 55 years, and 144 patients (60.0%) were male. The median follow-up was 123.1 months. Seventy-three (30.3%) were hepatitis B e antigen (HBeAg) positive. The median hepatitis B surface antigen (HBsAg) level was 3.2 log U/mL. HBV RNA was quantified in 57 patients (23.6%). GDF15 was quantified in 241 patients (99.6%) with a median of 0.86 ng/mL. During the observation period, 44 patients (18.2%) developed primary HCC, of which 13 were HBeAg positive. In multivariate analysis, gender (HR: 2.65 [1.18-5.96]), γ-GTP (HR: 1.01 per 1IU/L increase [1.003-1.011]), AFP (HR: 1.06 per 1ng/mL increase [1.02-1.09]), GDF15 (HR: 1.53 per 1ng/mL increase [1.04-2.12]), and FIB-4 index (HR: 1. 27 per 1ng/mL increase [1.10-1.43]) were significant factors in the Cox proportional hazards model for factors associated with the occurrence of primary HCC, whereas HBsAg, HBeAg, HBV DNA, and HBV RNA were not significant. When the median was defined as the cut-off value (0.858ng/mL), the cumulative HCC incidence rate at 5/10 years was 12.4%/23.1% and 6.7%/9.2% in the high and low GDF15 groups, respectively. **Conclusion:** Male sex, high γ-GTP, high AFP, high GDF15 and fibrosis progression were high risk factors for the occurrence of primary HCC in CHB patients under NUC treatment.

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1352 | TRACKING B CELL IMMUNITY DURING PERTURBATION OF HEPATITIS B INFECTION INDUCED BY TREATMENT WITHDRAWAL OF PROLONGED NUCLEOS(T)IDE ANALOGUE (NA) TREATMENT CAN RESULT IN HBSAG LOSS IN SOME SUBJECTS WITH CHRONIC HEPATITIS B (CHB), POTENTIALLY REVEALING IMMUNE CORRELATES OF FUNCTIONAL CURE. WE AIMED TO ASSESS WHETHER THERE WAS ANY RECOVERY OF DEFECTIVE HUMORAL IMMUNITY IN THOSE WITH LOSS OF HBSAG, WITH OR WITHOUT DEVELOPMENT OF ANTI-HBS ANTIBODIES, IN THIS SETTING

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Background: Withdrawal of prolonged nucleos(t)ide analogue (NA) treatment can result in HBsAg loss in some subjects with chronic hepatitis B (CHB), potentially revealing immune correlates of functional cure. We aimed to assess whether there was any recovery of defective humoral immunity in those with loss of HBsAg, with or without development of anti-HBs antibodies, in this setting. **Methods:** Global memory B cells (MBC) and T follicular helper cells (Tfh) were quantified and phenotyped by flow cytometry. HBsAg/HBcAg-MBC were quantified by *ex vivo* bait staining and function assessed by cultured ELISpots. Immune parameters were assessed at end-of-treatment (EOT), 12 and 48 weeks after treatment withdrawal and correlated with baseline intrahepatic and longitudinal serum viral markers and ALT. **Results:** After a median follow-up of 34 months (IQR 26-37), 16 (76%) patients remained off-therapy, with 5 (24% of the total cohort) losing HBsAg, whilst 5 (24%) required NA reintroduction. In contrast to previous reports in untreated CHB, individuals on prolonged NA had comparable frequencies of HBcAg-MBC and HBsAg-MBC, although the latter remained PD-1^{hi} and functionally defective. Following treatment withdrawal, increases in class-switched HBcAg-MBC were frequently temporally linked with hepatic flares. In subjects achieving HBsAg loss, there was an increase in activated MBC that was detectable at EOT and further increased at week 48. In those with HBsAg seroconversion, the function of HBsAg-MBC increased in tandem with a decrease in their PD-1 expression, together with an increase in activated circulating Tfh and plasmablasts. **Conclusion:** We demonstrate that coordinated recovery of B cell immunity associates with HBsAg loss with or without seroconversion following withdrawal of prolonged NA treatment. Furthermore, frequencies of activated and class-switched MBC may be predictive of functional cure. Our results underscore the need to further explore the potential of B cell targets for monitoring and enhancing HBV functional cure in this and other novel therapeutic approaches.

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1353 | CIRCULAR RNA CIRCSMAD2 INHIBITS AUTOPHAGY VIA TARGETING MIR-629/PDCD4 AXIS IN HEPATITIS B VIRUS INFECTION

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Background: Circular RNAs (circRNA), a non–coding RNA class, are involved in modulating various cellular processes and infections. They can regulate cellular autophagy, apoptosis and cell proliferation by sponging miRNAs or interacting with RNA-binding proteins. Hepatitis B virus (HBV) is a double-stranded DNA virus that causes persistent infection via forming covalently closed circular DNA (cccDNA). It induces the cellular recycling mechanism autophagy for its survival and replication via modulating the expression of various non-coding RNAs. Recently, a study reported that circSMAD2 (hsa_circ_0000847) is upregulated in Hepatocellular carcinoma (HCC) via sponging miR-629-5p. Further, another study showed that miR-629-5p has been upregulated in HBV-induced HCC patient serum samples. In this study, we aimed to investigate the role of circular RNA

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circSMAD2 in HBV-induced autophagy. **Methods:** Circular RNA circSMAD2 plasmid was designed and cloned in pcDNA3.1(+). CircSMAD2, HBV, and HBx plasmids were transfected into HepG2.2.15 and HepG2 cells using Lipofectamine-2000 reagent. MiR-629-5p mimics were transfected in HepG2 cells using SiPORT NeoFX transfection reagents. After 48 hours and 72 hours of transfections, cells were collected for RNA and protein isolation, respectively. CircSMAD2 and miR-629-5p expression were analysed by real-time PCR. PDCD4 and autophagy markers, such as ATG5 and Beclin1 expression, were analysed by Western blots. **Results:** The expression of circSMAD2 and PDCD4 were significantly downregulated, whereas miR-629-5p expression was upregulated in HepG2.2.15 cells compared to HepG2 cells ($p \leq 0.05$). Similarly, transfection of HBV and HBx plasmids to HepG2 resulted in significant downregulation of circSMAD2 and PDCD4, while the expression of miR-629-5p was upregulated ($p \leq 0.05$). Overexpression miR-629-5p significantly downregulated the expression of PDCD4. Further, overexpression of circular RNA circSMAD2 in HepG2.2.15 cells led to downregulation of miR-629-5p expression andupregulated the levels of PDCD4 and autophagy markers ATG5 and Beclin1 ($p \leq 0.05$). **Conclusion:** The data suggested that HBV might be enhancing autophagy, at least in part, via inhibiting the expression of circular RNA circSMAD2, thereby increasing miR-629-5p expression, resulting inhibition of PDCD4.

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1354 | IMPACT OF CONCURRENT FATTY LIVER (FL) AND CHRONIC HEPATITIS B (CHB) ON VIROLOGIC (VR), BIOCHEMICAL (BR), AND COMPLETE RESPONSE (CR) AMONG PATIENTS TREATED WITH NUCLEOS(T)IDE ANALOGS (NA): A REAL-B STUDY

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Background: Nucleos(t)ide analog (NA) therapy for chronic hepatitis B (CHB) is known to reduce viral replication and normalize liver enzymes. However, data is limited regarding treatment outcomes among patients with

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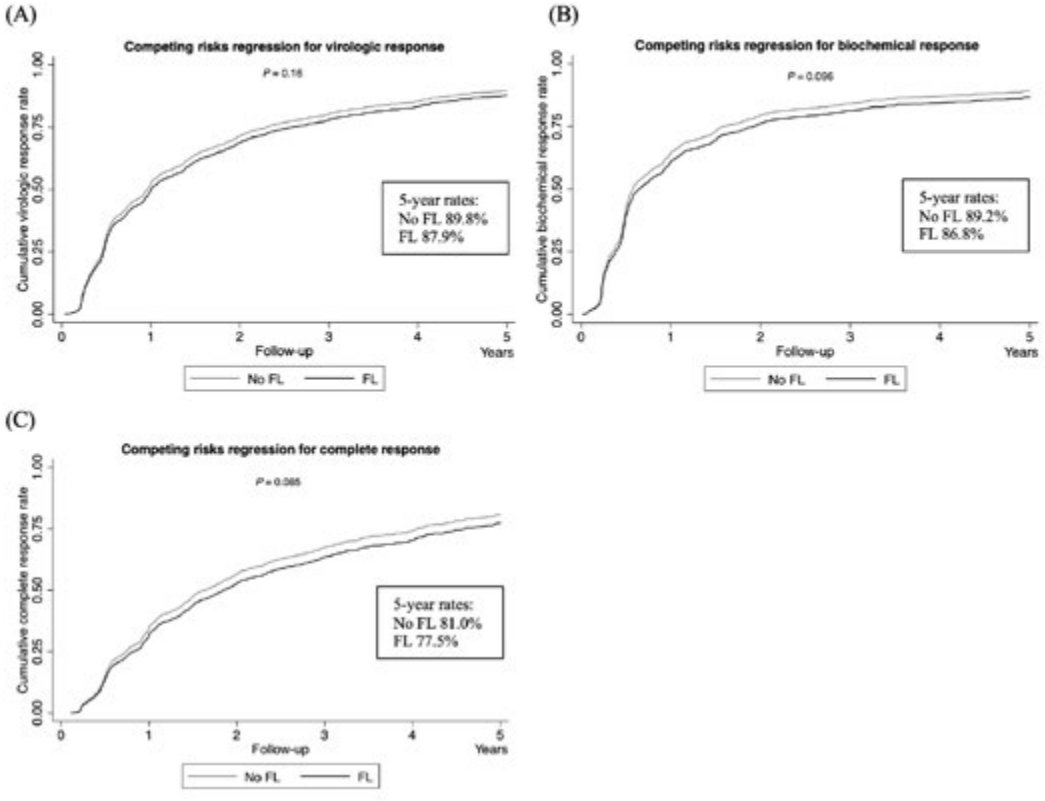
concurrent fatty liver (FL) and CHB, including virologic response (VR), biochemical response (BR), and complete response (CR) rates. Thus, we compared the outcomes of NA therapy between patients with concurrent FL and CHB (FL-CHB) and patients with CHB but not FL (non-FL CHB). **Methods:** A retrospective real-world cohort study of adult CHB patients treated with ETV, TDF, or TAF from 28 sites (United States, Taiwan, Japan, Korea, China, Singapore, Argentina) was conducted. FL was diagnosed by imaging. Propensity score matching (PSM) was used to balance the FL-CHB and non-FL CHB groups. Fine–Gray competing-risks regression analysis was used on the matched cohort to compare incidence and sub-distribution hazard ratios (SHRs) of VR, BR, and CR, between the FL-CHB and non-FL CHB groups. **Results:** We analyzed 4600 adult CHB patients (1227 FL-CHB; 3373 non-FL CHB). The mean (± SD) follow-up was 5.3 (± 3.8) years before PSM and 5.1 (± 3.6) years after PSM. At baseline before PSM, FL-CHB patients were younger (49.4 vs. 50.9 years, *P*<0.001) and more likely to be male (68.0% vs. 61.6%, *P*<0.001) and from the West (24.9% vs. 19.3%, *P*<0.001). FL-CHB patients had higher BMI (25.3 vs. 23.5, *P*<0.001) and baseline platelet count (194.7 vs. 173.9, *P*<0.001), and were more likely to have diabetes mellitus (14.3% vs. 10.6%, *P*=0.001) but less likely to have a high FIB-4 score of >3.25 (22.6% vs. 35.9%, *P*<0.001). Baseline characteristics between the FL and non-FL CHB groups became balanced after matching for age, sex, study region, BMI, diabetes mellitus, baseline ALT, baseline AST, and baseline platelet count. On follow-up after PSM, FL and non-FL CHB patients had similar 5-year cumulative VR (87.9% vs. 89.8%, *P*=0.16), BR (86.8% vs. 89.2%, *P*=0.096), and CR rates (77.5% vs. 81.0%, *P*=0.085) (Figure 1). After multivariable analysis adjusting for age, sex, diabetes mellitus, baseline HBV DNA, and baseline ALT, there was no statistically significant association between FL and VR (SHR=0.93, CI: 0.83-1.03, *P*=0.14), BR (SHR=0.91, CI: 0.81-1.01, *P*=0.085), or CR (SHR=0.90, CI: 0.79-1.01, *P*=0.077) in the PS-matched cohort. **Conclusion:** Among real-world CHB patients treated with NA therapy from both the East and West, FL did not independently affect the VR, BR, or CR to NA therapy.

Figure 1. Competing risks regression for virologic (A), biochemical (B), and complete response (C) in CHB patients with and without fatty liver in PS-matched cohort.



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1355 | DEVELOPMENT OF A LOW-COST DIAGNOSTICS PLATFORM FOR THE IDENTIFICATION OF HBV DNA USING CRISPR/CAS13A SYSTEM

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Background: Chronic hepatitis B virus (HBV) is one of the major burdens, and screening tests are not widely performed among high-risk populations. CRISPR-based detection platforms have shown to be a novel low-cost technology with high sensitivity and specificity. They mainly employ the trans-cleavage activities of specific cas proteins against single-stranded nucleic acids, including DNA-targeting Cas12 and RNA-targeting Cas13. In the presence of target nucleic acids, Cas12a and Cas13a molecule is activated to trans-cleave the fluorophore quencher (FQ)-labeled ssDNA/ssRNA reporter, respectively, and illuminate detectable fluorescent signals. **Methods:** Leptotrichia wadei (Lwa) cas13a was expressed and purified. Recombinase Polymerase Amplification (RPA) was implemented to produce T7 RNA polymerase appended amplicons of conserved regions of HBV at 37□. Corresponding crRNAs have been designed against amplified regions and produced using in-vitro transcription (IVT). With T7 RNA polymerase, the RPA-amplified HBV templates are transcribed into ssRNAs, which are further used in detection assay containing expressed cas protein, crRNA, and fluorescent probes. This detection was performed in the microplate reader in kinetic format and lateral flow strip in endpoint format. **Results:** LwaCas13a was expressed in Rosetta2(DE3)pLysS strain and was purified using the strep tag. Conserved regions among HBV genomes are selected as targets of detection. RPA was performed using primers against conjunct region of HBV polymerase and surface antigen. CRISPR RNAs were produced using T7 RNA polymerase. The detection assay was performed from randomly selected 45 HBV positive samples and 5 healthy human samples, and the detection assay could accurately reproduce 45 samples as HBV positive and 5 samples as healthy samples. **Conclusion:** This approach can be a better alternative to be used in rural India and at the same time with high sensitivity, for a rapid detection of HBV, which could be used as a novel a low-cost diagnostics platform for identification of HBV DNA.

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1356 | A TWENTY YEARS TAILORED TREATMENT HISTORY OF AN ITALIAN COHORT PATIENTS WITH HBV/HDV CHRONIC HEPATITIS: FROM MULTIPLE PEGYLATED INTERFERON-ALPHA (PEG-IFN) CYCLES THROUGH ENTECAVIR/TENOFOVIR TO BULEVIRTIDE TREATMENT ◆

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Background: Hepatitis D virus (HDV) causes the most severe form of viral chronic liver disease. The estimated global number of HDV infected people variably ranges from 72 million to 12 million. In countries where HBV vaccination has been introduced, such as Italy, the prevalence of HDV cases is drastically reduced accounting about 7% of HBV infected patients. Peg-IFNa, which has been used for the treatment of HDV infection since the'90s leading to a 10%-20% rate of sustained HDV clearance and a 10% rate of HBsAg clearance, is still recommended by the EASL HDV guidelines 2023. Bulevirtide, recently approved, is changing the HDV treatment paradigm. We describe the changing therapeutic scenario in a native Italian patients (pts.) cohort in the last 20 years. **Methods:** We describe clinical ad virologic outcome of 15 pts. with HBV/HDV infection who received multiple Peg-IFN 48-weeks treatment cycles followed by entecavir or tenofovir switch in cases of HDV-RNA clearance. Quantitative HBV-DNA, HDV-RNA and HBsAg were measured at baseline and at the end of each treatment cycle. At the first evaluation pts. started Peg-IFN for 48 weeks. If they had presented decline of HDV-RNA without clearance at the end of treatment, they started a new Peg-IFN cycle after 6-12 months. If HDV-RNA became undetectable at discontinuation of Peg-IFN, they started long term entecavir or tenofovir therapy. Non responder pts. to Peg-IFN recently started bulevirtide therapy **Results:** 15 pts. (M/F: 10/5; median age: 62 yrs.) were evaluated. Nine pts. presented chronic hepatitis (CH) and 6 cirrhosis. Baseline virologic patterns were the following: 9 pts. HBV-DNA pos/HDV-RNA pos; 5 pts. HBV-DNA neg/HDV-RNA pos; 1 HBV-DNA pos/HDV-RNA neg. Eight of 15 pts. started Peg-IFN. Among those: 3 pts. received one cycle, 1 pt. two cycles, 2 pts. three cycles, 2 pts. four cycles. Two pts. stopped Peg-IFN because occurrence of HCC and severe thrombocytopenia. One of 15 received entecavir at baseline because HDV-RNA negative. At the last follow-up: 1) two pts cleared HBsAg; 2) HBV-DNA was non detectable in 8 pts; 3) HDV-RNA was not detectable in 6 pts.. Median platelets number decreased from the baseline value 135 to 171 x 10^3/ul ($p < 0.05$). At the last Fibroscan control median KPa was 8 and median CAP 228. Four pts. started bulevirtide/entecavir combination and 3 bulevirtide/tenofovir. Median HDV-RNA declined from baseline 105000 I.U/ml to 419 I.U./ml at 6th month; one pt.became HDV-RNA negative; four pts. normalized ALT values. Both IFN and bulevirtide treatment were well tolerated and no relevant side effects occurred. **Conclusion:** Peg-IFN, despite the occurrence of known side effects, still demonstrates some efficacy on HBV/HDV infection treatment and in some case can lead to functional cure. Bulevirtide is an effective and safe promising drug. However, as recent studies demonstrated, the combination with PEG-IFN is advisable and further clinical trials need.

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1357 | THE IMPACT OF HIV INFECTION ON ALL-CAUSE MORTALITY AMONG INDIVIDUALS TREATED FOR HBV IN RWANDA: A POPULATION-BASED COHORT STUDY ◆

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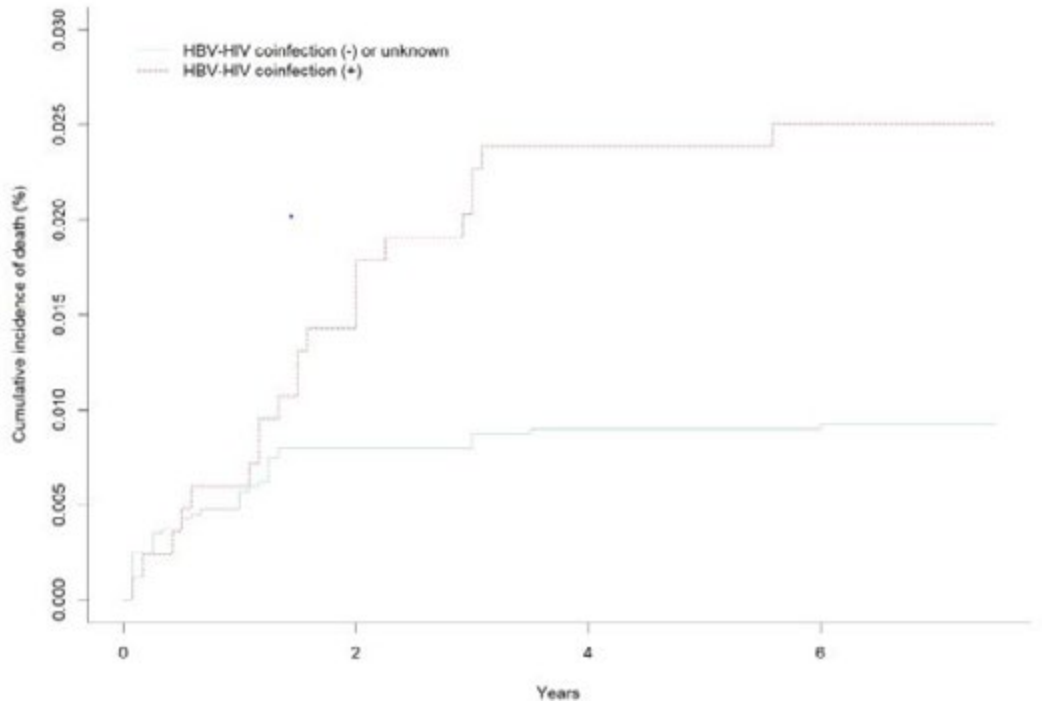
Background: Chronic hepatitis B virus (HBV) infection increases the risk of severe liver diseases such as cirrhosis, hepatocellular carcinoma, non-liver complications, and mortality. HIV co-infection contributes to the acceleration of liver disease progression, leading to greater mortality risk compared to HBV mono-infection. We evaluated the crude all-cause mortality rates among people with chronic HBV on treatment and assessed the impact of HBV/HIV co-infection on all-cause mortality. **Methods:** A retrospective cohort study was conducted using data extracted from the Rwandan District Health Information System 2, which includes information on HBV screening, diagnosis, treatment, follow-up, and treatment outcomes. Rwandans diagnosed with HBV infection, age ≥ 2 years, who received treatment between January 2016 and June 2023 were considered in the analysis. Individuals were followed from the HBV testing date until death or end of the study period (June 30, 2023). We computed crude mortality rates and used multilevel Cox proportional hazard regression accounting for clustering by hospital adjusting for socio-demographic, and clinical characteristics to assess the impact of HBV/HIV co-infection on all-cause mortality. **Results:** Overall, 4,849 people received HBV treatment during the study period (4,011 with HBV mono-infection and 838 with HBV/HIV co-infection) and were followed for a median of 3.8 (interquartile range 2.8) years. During follow-up, 58 deaths occurred, yielding an overall crude mortality rate of 2.76 per 1,000 person-years (PY). The mortality rate for people with HBV/HIV co-infection was higher than that for those with HBV mono-infection (4.30 vs 2.30 per 1,000 PY, respectively). In the multilevel model, HBV/HIV co-infection was associated with a higher hazard of all-cause mortality (adjusted hazard ratio 2.00, 95% confidence interval: 1.02, 3.92). **Conclusion:** Among people in Rwanda who received HBV treatment, HBV/HIV co-infection was associated with mortality risk. Moreover, HIV co-infection was associated with increased mortality risk. These findings underscore the critical importance of closer follow-up of individuals with HBV/HIV co-infection. Further studies could explore the role of HIV viral load suppression on all-cause mortality among individuals with HBV/HIV co-infection.



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1358 | ELIMINATING VIRAL HEPATITIS ONE ISLAND AT A TIME – THE HAINAN EXPERIENCE

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Background: Hainan Island presents the highest incidence of hepatocellular carcinoma (HCC) in China, predominantly associated with hepatitis B viral (HBV)and hepatitis C viral (HCV). However, low screening and treatment rates in Hainan pose a significant challenge to achieving the World Health Organization's targets for viral hepatitis elimination by 2030. **Methods:** In response, the Hainan provincial government established viral hepatitis elimination task forces to work with health commissions, medical institutions, media and community centers. A comprehensive public health education campaign was conducted, focusing on raising awareness among healthcare workers and the general public. HBV screening was initiated for the population (age >=20 years), and HCV screening focused on special population. To support this, a patient database management system was developed to track screening, diagnosis and treatment outcomes. **Results:** From January 2021 to May 2024, the screening rate for HBV in the population (age >=20 years) was 63.9% (4.841 million / 7.573 million). The HBsAg positive rate was 3.36%, with 252,600 positive cases identified. The diagnosis rate was 56.9% and the treatment rate was 49.4%. For HCV, 1.869 million people were screened, with 4,016 HCV antibodies (HCV-Ab) postive. Of these, 1,301 had detectable HCV RNA, resulting in a diagnosis rate of 71.3% and a treatment rate of 60.3%. **Conclusion:** Hainan model of cross-sector collaboration has been successful and could help achieve the global goal of viral hepatitis elimination by 2030.

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1359 | 32.2% OF INACTIVE HBSAG CARRIERS ACHIEVED CLINICAL CURE AT 48 WEEKS WITH PEGYLATED INTERFERON ALPHA-2B THERAPY: A MULTICENTER REAL-WORLD STUDY (STARHB PROJECT IN CHINA) - 2-YEAR DATA UPDATE ◆

Jing ZHAO[1] Shan Ren[1] Sujun Zheng[1] Bingliang Lin[2] Yongfang Jiang[3] Qingfa Ruan[4] Yan Huang[5] Yilan Zeng[6] Jiawei Geng[7] Haifang Cao[8] Wenhua Zhang[9] Ying Guo[10] Xiaorong Mao[11] Zhiliang Gao[2] Tianyuan Shi[12] Yueyong Zhu[13] Zujiang Yu[14] Xiaoping Wu[15] Qing Mao[16] Xiulan Xue[17] Yingli He[18] Jia Shang[19] Shuangsuo Dang[20] Haidong Zhao[21] Rongshan Fan[22] Jiangling Yang[23] Jianqi Lian[24] Haibing Gao[25] Xinyue Chen[1]

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Background: This study aimed to investigate the efficacy and safety of achieving functional cure (HBsAg loss) using Pegylated Interferon alpha-2b (PEG IFNα-2b) treatment in inactive HBsAg carriers (IHC). **Methods:** The STARHB Project (The STUDY ON TREATMENT FOR INACTIVE CARRIERS OF HEPATITIS B) is a multicenter real-world study in China focused on the functional cure of IHC, aiming to onboard approximately 25,000 patients (ChiCTR2200061541). Based on patient preferences, participants were assigned to a control group (without antiviral treatment) or treatment groups (NAs group and PEG IFNα-2b ± NAs group). The basic treatment duration was 48 weeks, extendable to 96 weeks as needed. **Results:** As of May 2024, 10,028 individuals were screened, and 6,593 eligible IHC patients were included in the mITT population baseline analysis. This cohort was 64.9% male with a mean age of 43.1 years; 8.5% were under 30 years old, and 5.5% had fatty liver. The mean HBsAg level was 223 IU/ml, with 81.8% below 500 IU/ml. The mean HBV DNA level was 256 IU/ml, with 62.1% having undetectable HBV DNA at baseline. The mean ALT was 22 U/L. Liver biopsies were performed on 48 patients at baseline, with 41.7% showing significant liver necroinflammation and/or fibrosis (≥ G2 and/or ≥ S2). At present, 372 patients have completed the 48-week follow-up. In the control group (n=6), 2 achieved virological response (VR), with no HBsAg loss. In the NAs group, the VR rate at 48 weeks was 100% (5/5), with no HBsAg loss. Among those treated with PEG IFNα-2b ± NAs, the VR rate at 48 weeks was 89.1% (245/275), with an HBsAg loss rate of 32.2% (116/360), corresponding to a cumulative HBsAg loss rate of 71.6% (482/673). ROC analysis indicated that baseline HBsAg levels, 12-week and 24-week HBsAg levels, and 12-week AST levels could predict HBsAg loss at 48 weeks. **Conclusion:** PEG IFNα-2b therapy can effectively achieve functional cure in IHC patients, with a 48-week HBsAg loss rate of 32.2% and a cumulative loss rate of 71.6%. Lower baseline, 12-week, and 24-week HBsAg levels, along with higher 12-week AST levels, are predictors of functional cure at 48 weeks. Thus, the IHC population is a favorable group for pursuing clinical cure for hepatitis B.

Table 1. Baseline Characteristics of the Participants

	Total N=6593	Treatment Groups			Control N= 284	*P*
		PEG IFNα-2b N= 2848	PEG IFNα-2b+ NAs N= 3033	NAs N= 428		
Age (years)	43.1 ± 0.6	42.6 ± 0.2[b]	43.1 ± 0.2[b]	45.9 ± 0.4[a]	43.1 ± 0.6[b]	<0.001
Male （n,%）	4280(64.9%)	1834(64.4%)[a]	2025(66.8%)[a]	272(63.6%)[a]	149(52.5%)[b]	<0.001
BMI (Kg/m²)	23.3 ± 0.04	23.2 ± 0.06[a]	23.3 ± 0.05[a,b]	23.5 ± 0.22[a,b]	23.9 ± 0.37[b]	0.02
ALT (U/L)	21.7 ± 0.1	21.9 ± 0.1	21.4 ± 0.1	22.4 ± 0.4	21.8 ± 0.5	0.08
HBV DNA (IU/mL)	256 ± 4.7	253 ± 7.3[b]	242 ± 6.8[b]	320 ± 18.2[a]	341 ± 24.1[a]	<0.001
HBV DNA undetectable (n,%)	4093(62.1%)	1729(60.7%)[b]	1965(64.8%)[c]	253(59.1%)[a,b,c]	146(51.4%)[a]	<0.001
HBsAg (IU/mL)	223 ± 3.4	196 ± 4.9[b]	250 ± 5.2[a]	245 ± 13.4[a]	175 ± 14.6[b]	<0.001
Fibroscan CAP(db/m²)	238 ± 2.3	234 ± 3.4	239 ± 3.7	234 ± 6.4	246 ± 5.6	0.57
Fatty liver diagnosed by ultrasond （n,%）	364(5.5%)	123(4.3%)[b]	184(6.1%)[a]	34(7.9%)[a]	23(8.1%)[a]	<0.001

Continuous variables presented as mean ± SE; categorical variables presented as number (percentage).
a, b, c: with the same letter indicates no difference between groups.

Disclosures: Jing ZHAO: Nothing to Disclose, Shan Ren: Nothing to Disclose, Sujun Zheng: Nothing to Disclose, Bingliang Lin: Nothing to Disclose, Yongfang Jiang: Nothing to Disclose, Qingfa Ruan: Nothing to Disclose, Yan Huang: Nothing to Disclose, Yilan Zeng: Nothing to Disclose, Jiawei Geng: Nothing to Disclose, Haifang Cao: Nothing to Disclose, Wenhua Zhang: Nothing to Disclose, Ying Guo: Nothing to Disclose, Xiaorong Mao: Nothing to Disclose, Zhiliang Gao: Nothing to Disclose, Tianyuan Shi: Nothing to Disclose, Yueyong Zhu: Nothing to Disclose, Zujiang Yu: Nothing to Disclose, Xiaoping Wu: Nothing to Disclose, Qing Mao: Nothing to Disclose, Xiulan Xue: Nothing to Disclose, Yingli He: Nothing to Disclose, Jia Shang: Nothing to Disclose, Shuangsuo Dang: Nothing to Disclose, Haidong Zhao: Nothing to Disclose, Rongshan Fan: Nothing to Disclose, Jiangling Yang: Nothing to Disclose, Jianqi Lian: Nothing to Disclose, Haibing Gao: Nothing to Disclose, Xinyue Chen: Nothing to Disclose

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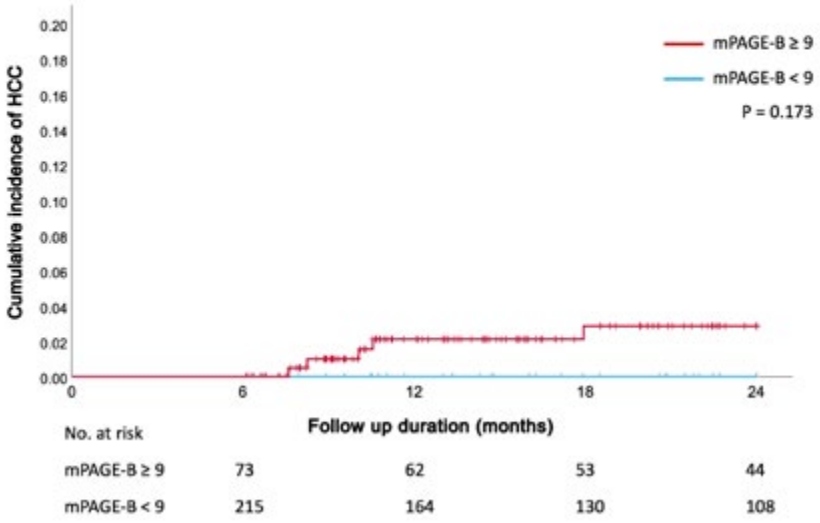
1360 | THE EFFECT OF TENOFOVIR ALAFENAMIDE ON THE RISK OF HEPATOCELLULAR CARCINOMA IN DIFFERENT RISK GROUPS DEFINED BY MPAGE-B SCORE

Lilian Yan Liang[1] Terry Cheuk-Fung Yip[1] Vincent Wong[1] Grace Wong[1]

[1]The Chinese University of Hong Kong

Background: The mPAGE-B score has shown to be a reliable predictor of hepatocellular carcinoma (HCC) risk among various populations of chronic hepatitis B (CHB) patients receiving antiviral therapy. We aimed to evaluate the effect of tenofovir alafenamide (TAF) on the HCC development in different risk groups defined by mPAGE-B score. **Methods:** This is a retrospective cohort study in Hong Kong. CHB patients who initially received TAF as antiviral treatment for at least six months were included. The baseline was defined as the start date of TAF treatment. The primary endpoint was the cumulative incidence of HCC. The Kapan-Meier method was used to compare the HCC risk in different risk groups defined by mPAGE-B score. Patients who developed HCC before or within six months of baseline were excluded. **Results:** This study included 288 CHB patients treated with TAF who had an mPAGE-B score available at baseline. Their average age was 57 years and 54.9% of them were males. By using the cutoff value of 9, 215 (74.7%) and 73 (25.3%) patients were classified as low- and high-risk of developing HCC at baseline. The Kaplan-Meier curve showed a trend towards higher HCC incidence in the high-risk group, but the differences between the two groups were not statistically significant among these TAF-treated CHB patients (P = 0.173) (Figure). The corresponding cumulative incidences of HCC in these two groups were 0 and 2.9% at 24 months. **Conclusion:** TAF reduce the risk of HCC development in high-risk CHB patients defined by mPAGE-B score.

Figure. Cumulative incidences of HCC in TAF-treated CHB patients with different mPAGE-B levels



Disclosures: Lilian Yan Liang: Nothing to Disclose, Terry Cheuk-Fung Yip: Gilead Sciences: Consultant, Gilead Sciences: Advisor, Gilead Sciences: Speaking and Teaching, Vincent Wong: Abbott: Speaking and Teaching, AbbVie: Advisor, AbbVie: Speaking and Teaching, Boehringer Ingelheim: Advisor, Echosens: Advisor, Echosens: Speaking and Teaching, Gilead Sciences: Advisor, Gilead Sciences: Speaking and Teaching, Gilead Sciences: Grant/Research Support, Intercept: Advisor, Inventiva: Advisor, Novo Nordisk: Advisor, Novo Nordisk: Speaking and Teaching, Pfizer: Advisor, Sagimet: Advisor, TARGET PharmaSolutions: Advisor, Unilab: Speaking and Teaching, Visirna: Consultant, Illuminatio Medical Technology: Stock – privately held company, Grace Wong: AstraZeneca: Advisor, Gilead Sciences: Advisor, Gilead Sciences: Speaking and Teaching, Janssen: Advisor, GSK: Advisor, GSK: Speaking and Teaching, Abbott: Speaking and Teaching, AbbVie: Speaking and Teaching, AstraZeneca, Gilead Sciences, GlaxoSmithKline and Janssen,: Advisor, Abbott, AbbVie, Ascletis, Bristol-Myers Squibb, Echosens, Gi: Speaking and Teaching, Gilead Sciences: Grant/Research Support, AstraZeneca, Gilead Sciences, GlaxoSmithKline and Janssen: Consultant, Abbott, AbbVie, Ascletis, Bristol-Myers Squibb, Echosens, Gi: Speaking and Teaching, AstraZeneca, Gilead Sciences, GlaxoSmithKline Pharmaceutical: Consultant, Gilead

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Sciences: Independent Contractor, AstraZeneca, Gilead Sciences, GSK and Janssen,: Advisor, Abbott, AbbVie, BMS, Gilead Sciences, GSK, Janssen, Roche: Speaking and Teaching, Gilead Sciences: Grant/Research Support

1361 | THE PREVALENCE AND NATURAL HISTORY OF DIVERSE SUBTYPES OF INDETERMINATE PHASE CHRONIC HEPATITIS B: RESULTS OF THE INTERNATIONAL REAL-B COHORT

Ai-Thien Do[1] Ming-Lung Yu[2] Hidenori Toyoda[3] Seng Gee Lim[4] Ramsey Cheung[5] Man-Fung Yuen[6] Yasuhito Tanaka[7] Wan Long Chuang[2] Chao Wu[8] Maria Buti[9] Adrian Gadano[10] Ming-Lun Yeh[2] Chung-Feng Huang[11] Rui Huang[12] Jee-Fu Huang[2] Chia-Yen Dai[2] Mayumi Maeda[5] Kaori Inoue[13] Chul-Jin Lee[14] Cheng-Hao Tseng[15] Ana Barreira[16] Rex Wan-Hin Hui[6] Kwan-Lung Ko[6] Yoko Yoshimaru[17] Takanori Suzuki[7] Irina Sandra[18] Raluca Marin[18] Vy Nguyen[5] Yao-Chun Hsu[19] Huy Trinh[20] Jiayi Li[21] jianqing zhang[22] Eiichi Ogawa[23] Dong Hyun Lee[14] Takanori Ito[24] Tsunamasa Watanabe[25] Masaru Enomoto[26] Carmen Preda[18] Masanori Atsukawa[27] Sebastián Marciano[10] Son Do[28] Daniel Huang[29] Christopher Wong[30] Haruki Uojima[31] Hirokazu Takahashi[13] Htet Htet Toe Wai Khine[32] Takashi Honda[24] Norio Itokawa[33] Min Seok Go[14]

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Background: Many patients with chronic hepatitis B (CHB) are in the indeterminate phase, but they make up a diverse cohort with likely different natural history and outcome. We aimed to characterize the subgroups of patients with indeterminate CHB phenotypes according to their HBeAg, HBV DNA, and ALT levels, including their prevalence and phase transition probabilities. **Methods:** Our study cohort included 6,261 adult treatment-naïve CHB patients without viral coinfection or advanced fibrosis/cirrhosis enrolled retrospectively from 26 centers (North America, South America, Europe, and Asia). Indeterminate patients were defined as per the AASLD 2018 guidance. Follow-up was censored at the date of the last follow-up, antiviral receipt or once the patient transitioned to a different immune phase from indeterminate, whichever came first. **Results:** The study cohort comprised 55.9% male, 95.3% Asian, 23.5% HBeAg positive and with mean age of 47.4 years. At baseline, 3,008 (48.0%) patients were in the indeterminate phase (mean age 46.9 years, median ALT 35.0 U/L, mean HBV DNA 4.1 $\log_{10}$IU/mL, 18.2% HBeAg-positivity). We subclassified the indeterminate patients into ten groups according the HBeAg status, ALT and HBV DNA levels (Figure). The most prevalent subtype of patients with HBeAg-positivity was subtype 2 (ALT 1-2xULN and HBV DNA>=20,000 IU/mL) which accounted of 12.0% of indeterminate patients. The most prevalent HBeAg-negative subtype was subtype 6 (ALT=2,000 IU/mL) accounting for 26.8% of indeterminate patients, followed by subtype 7 (ALT 1-2xULN with HBV DNA>=2,000 IU/mL) and subtype 8 (ALT 1-2xULN with HBV DNA<2,000 IU/mL) accounting for 24.0% and 21.9%, respectively. 809 indeterminate patients were followed for a median of 3.2 years (IQR, 1.2-6.9 years), during which 37.7% remained indeterminate, 16.4% transitioned to immune active phase and 42.5% to inactive phase. As high as 43.3% of patients in subtype 2 transitioned to immune active phase, while only 7.7% of subtype 8 transitioned to immune active phase. **Conclusion:** Indeterminate CHB patients can be classified into diverse subtypes with the most prevalent group being those with HBeAg-negative, HBV DNA>=2,000 IU/mL with ALT=20,000 IU/mL subtype were most likely to transition to immune active phase (43.3%). The monitoring and management of indeterminate CHB patients should be individualized according to their subtypes.

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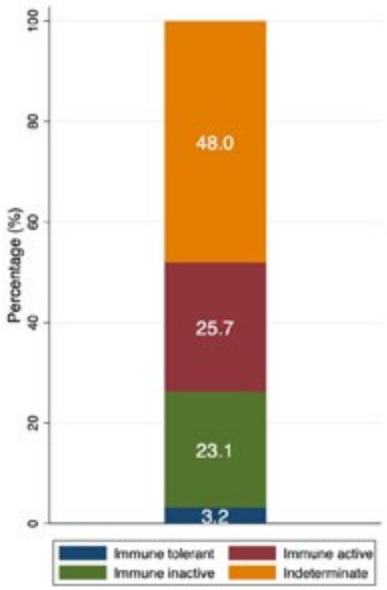

B

Subtypes	HBeAg	ALT	HBV DNA (IU/mL)	Cases	Proportions of indeterminate patients (%)
1	Positive	< 1× ULN	20,000-10^6	31	1.0
2		1-2 × ULN	≥20,000	362	12.0
3		1-2 × ULN	<20,000	62	2.1
4		>2 × ULN	<20,000	33	1.1
5		<1× ULN	<20,000	59	2.0
6	Negative	<1 × ULN	≥2,000	806	26.8
7		1-2 × ULN	≥2,000	722	24.0
8		1-2 × ULN	< 2,000	658	21.9
9		>2 × ULN	<2,000	209	6.9
10		<1 × ULN*	<2,000	66	2.2

* With moderate to severe inflammation and/or with significant fibrosis
ULN: upper limit of normal (35 U/L for males, 25 U/L for females)

Disclosures: Ai-Thien Do: Nothing to Disclose, Ming-Lung Yu: Abbvie, Gilead and Roche diagnostics.: Grant/Research Support, Abbott, Abbvie, Gilead, Roche and Roche diagnostics: Consultant, Abbvie, BMS, Gilead, Roche and Roche diagnostics: Speaking and Teaching, Hidenori Toyoda: Nothing to Disclose, Seng Gee Lim: Nothing to Disclose, Ramsey Cheung: Nothing to Disclose, Man-Fung Yuen: Speaking and Teaching relationship with Fujirebio Incorporation, Gilead Sciences, Roche, Sysmex Corp; Has not ended; Consultant relationship with Clear B Therapeutics, Dicerna Pharmaceuticals; Has not ended; Consultant relationship with AbbVie, Abbott Diagnotics, Aligos Therapeutics; Has not ended; Consultant relationship with Arbutus Biopharma, Arrowhead Pharmaceuticals, Assembly Biosc; Has not ended; Consultant relationship with Immunocore, Janssen, Precision BioSciences; Has not ended; Consultant relationship with Fujirebio Incorporation, GlaxoSmithKline, Gilead Sciences; Has not ended; Grant/Research Support relationship with Fujirebio Incorporation, Gilead Sciences, Immunocore; Has not ended; Grant/Research Support relationship with AbbVie, Assembly Biosciences, Arrowhead Pharmaceuticals; Has not ended; Consultant relationship with Vir Biotechnology and Visirna Therapeutics; Has not ended; Consultant relationship with Roche, Sysmex Corporation, Tune Therapeutics; Has not ended; Grant/Research Support relationship with Sysmex Corporation and Roche; Has not ended, Yasuhito Tanaka: Nothing to Disclose, Wan Long Chuang: Gilead: Speaking and Teaching, AbbVie: Speaking and Teaching, BMS: Speaking and Teaching, Vaccitech: Consultant, PharmaEssentia: Consultant, Chao Wu: Nothing to Disclose, Maria Buti: Nothing to Disclose, Adrian Gadano: Nothing to Disclose, Ming-Lun Yeh: Nothing to Disclose, Chung-Feng Huang: Gilead Sience: Grant/Research Support, Rui Huang: Nothing to Disclose, Jee-Fu Huang: Roche: Consultant, Gilead: Consultant, Sysmex: Consultant, Aligos: Consultant, Abbvie: Speaking and Teaching, Gilead: Speaking and Teaching, Merck: Speaking and Teaching, Sysmex: Speaking and Teaching, Novo Nordisk: Speaking and Teaching, Chia-Yen Dai: Nothing to Disclose, Mayumi Maeda: Nothing to Disclose, Kaori Inoue: Nothing to Disclose, Chul-Jin Lee: Nothing to Disclose, Cheng-Hao Tseng: Nothing to Disclose, Ana Barreira: Nothing to Disclose, Rex Wan-Hin Hui: Nothing to Disclose, Kwan-Lung Ko: Nothing to Disclose, Yoko Yoshimaru: Nothing to Disclose, Takanori Suzuki: Nothing to Disclose, Irina Sandra: Nothing to Disclose, Raluca Marin: Nothing to Disclose, Vy Nguyen: Nothing to Disclose, Yao-Chun Hsu: Gilead Sciences: Grant/Research Support, Gilead Sciences: Advisor, Sysmex: Advisor, Abbvie: Speaking and Teaching, Bristol Myers Squibb: Speaking and Teaching, Gilead Sciences: Speaking and Teaching, Roch: Speaking and Teaching, Huy Trinh: Nothing to Disclose, Jiayi Li: Nothing to Disclose, jianqing zhang: Nothing to Disclose, Eiichi Ogawa: Gilead Sciences: Grant/Research Support, Dong Hyun Lee: Nothing to Disclose, Takanori Ito: Chugai Pharmaceutical Co., Ltd.: Grant/Research Support, Chugai Pharmaceutical Co., Ltd. and AstraZeneca: Speaking and Teaching, Tsunamasa Watanabe: Nothing to Disclose, Masaru Enomoto: Nothing to Disclose, Carmen Preda: Nothing to Disclose, Masanori Atsukawa: Nothing to Disclose, Sebastián Marciano: Nothing to Disclose, Son Do: Nothing to Disclose, Daniel Huang: Nothing to Disclose, Christopher Wong: Nothing to Disclose, Haruki Uojima: Nothing to Disclose, Hirokazu Takahashi: Sysmex: Grant/Research Support, Novo Nordisk: Speaking and Teaching, Kowa:

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Speaking and Teaching, Taisho: Speaking and Teaching, Takeda: Grant/Research Support, Htet Htet Toe Wai Khine: Nothing to Disclose, Takashi Honda: Nothing to Disclose, Norio Itokawa: Nothing to Disclose, Min Seok Go: Nothing to Disclose

1362 | FACTORS AND PREDICTION MODEL OF HBSAG RELAPSE AFTER ACHIEVING CLINICAL CURE IN CHB PATIENTS WITH PEG IFNα-2B

Jing Chen[1] fei yan[1] Jiayin Wang[2] Jing Liang[2] Jun Li[2] Fang Wang[2] Qing Ye[2] Yanying Gao[2] Weili Yin[2] Fei Tang[2] Huiling Xiang[2]

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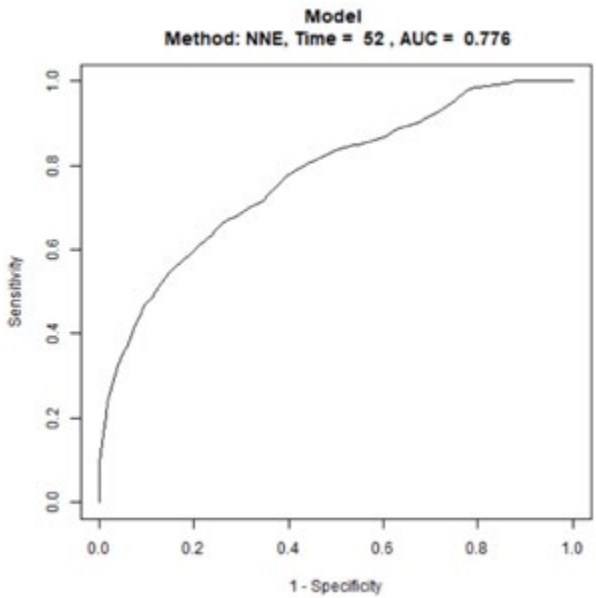
Background: Due to the existence of cccDNA in hepatocytes, there is still a portion of patients with HBsAg relapse after HBsAg seroclearance with interferon, and the predictive factors of whether HBsAg is recurrent are still in the exploratory stage. This study aims to investigate the factors affecting HBsAg relapse and develop a prediction model through long-term follow-up, which provides advice for optimal clinical management after functional cure. **Methods:** Patients with pegylated interferon α-2b monotherapy or combined with nucleoside (acid) analogs (NAs), were enrolled from January 2018 to May 2024 at Tianjin Third Central Hospital. Every participant achieved clinical cure after treatment.Patients were assessed for hepatitis B viral markers and biochemical indicators every 3 months during the follow-up.The endpoint was HBsAg relapse, defined as HBsAg > 0.05 IU/ml. **Results:** A total of 183 patients who met the criteria were included, with a median follow-up period of 67.50 (12.00, 268.90) weeks. The overall relapsed rate during the follow-up was 14.2% (26/183), and the patients who relapsed within 48 weeks accounted for 61.54% (16/26). Based on whether HBsAg relapse or not, 183 subjects was divided into relapsed and non-relapsed group. In the relapsed group, the mean time to relapse was 42.72±27.59 weeks, and the median baseline HBsAg level was 1.64 (-1.29, 4.63) log IU/ml. There were significant differences between the two groups($p<0.05$) respect to gender, HBsAg, HBsAb, LSM, and whether to prolong the treatment. Further analysis revealed that baseline LSM, whether treatment was prolonged (≥12 weeks), whether the highest HBsAb level was >100 IU/ml during the follow-up, and whether hepatitis B vaccination was administered after HBsAg conversion were identified as independent risk factors for HBsAg recurrence($p<0.05$). This novel model for predicting HBsAg relapse includes the above four indicators(AUC=0.775), with sensitivity and specificity of 62.87%, 77.12% respectively. and C-index was 0.8 (0.7035, 0.8965), which showed good performance of the model in predicting whether HBsAg recurrence. **Conclusion:** Patients with chronic hepatitis B still have risk of HBsAg relapse after clinical cure, and the risk within 48 weeks is significantly high. Moreover, extending treatment beyond 12 weeks, HBsAb level greater than 100 IU/ml during the follow-up and hepatitis B vaccination is a protective factor for HBsAg recurrence, and baseline LSM is a risk factor. Based on the above independent factors, the model can be developed for predicting HBsAg recurrence(C-index = 0.8).



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Disclosures: Jing Chen: Nothing to Disclose, fei yan: Nothing to Disclose, Jiayin Wang: Nothing to Disclose, Jing Liang: Nothing to Disclose, Jun Li: Nothing to Disclose, Fang Wang: Nothing to Disclose, Qing Ye: Nothing to Disclose, Yanying Gao: Nothing to Disclose, Weili Yin: Nothing to Disclose, Fei Tang: Nothing to Disclose, Huiling Xiang: Nothing to Disclose

1363 | REVELATION OF UNKNOWN CONFOUNDING FACTORS IN FUNCTIONAL HBV CURE: A SYSTEMIC REVIEW AND META-ANALYSIS

George Lau[1] Jing Chen[2] Dong Ji[3] Hui Zhuang[4] Xinxin Zhang[5] Fusheng Wang[6] Wenhong Zhang[7] Xiaoguang Dou[8] Tawesak Tanwandee[9] Shiv Kumar Sarin[10] Rakhi Maiwall[11] Manoj Kumar[12] Ming-Lung Yu[13] Jacob George[14] George Boon-Bee Goh[15] Hasmik GHAZINYAN[16] Anuchit CHUTAPTTI15[17] Pei-Jer Chen[18] Hong You[19] Masao Omata[20] George Lau[21]

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Background: The preferred primary endpoint for CHB phase II/III trials is a “functional” cure, defined as sustained HBsAg loss and HBV DNA below the LLOQ for 24 weeks off-treatment. Many new therapies targeting various stages of the hepatitis B virus lifecycle are in clinical development for this purpose. This review evaluates the efficacy and safety of these novel antiviral treatments, and identifies the barriers in achieving HBV functional cure. **Methods:** A systematic search of clinicaltrials.gov from January 2018 to December 2023 found 244 trials related to HBV. After screening, 90 trials investigating 42 unique compounds were selected. Additional searches in Pubmed and Google identified relevant published trials on these compounds. Primary outcomes included EOF functional cure rates, with secondary outcomes covering changes in HBsAg quantification, rates of HBsAg loss, HBV DNA rebound, and adverse events (AEs). Meta-analysis was conducted using Stata. **Results:** A meta-analysis of 19 studies involving 15 compounds for non-cirrhotic CHB patients showed minimal functional cure rates (0·0%, 95%CI 0·0 – 0·4%, p=0·99) and HBsAg loss (EOT 0·9%, 95%CI 0·0 – 3·1%, p=0.064; EOF 0·1%, 95%CI 0 – 0·8%, p=0·36). While there was an observed decline in HBsAg at the end of treatment (EOT), it was not sustained, with significant rebound observed at EOF (EOT: -1.20 log10 IU/mL, 95%CI -1.44 to -0.96, p<0.001, and EOF: -0·64 log10 IU/mL (95%CI -0·73 to -0·56, p<0·001 among studies with both reported negative EOT and EOF change from baseline). Novel treatments did not significantly improve outcomes compared to NA-treated control groups. Virological relapse occurred in 20.5% of cases off-tx. Novel treatments were well-tolerated but had higher adverse event rates compared to NA-treated groups (OR=1.77, 95%CI 1.26 – 2.48, p<0.001). The presence of unknown confounding factors emerged as a significant barrier in pursuit of a functional cure. For instance, the phase 2 B-CLEAR study on bepivrovirsen highlighted the impact of these confounding factors. **Conclusion:** The novel antiviral treatment showed limited effectiveness in desired therapeutic endpoints, including functional cure, HBsAg loss and reduction, without demonstrating superiority over NA-treated control groups. The HBsAg loss and reduction generally is not durable. The deciphering of the unknown confounding factors revealed in our review might facilitate the development of effective therapy to achieve “functional’ cure.

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1364 | SINGLE CELL RNA SEQUENCING REVEALS EXHAUSTED ADAPTIVE IMMUNITY *IN UTERO* TO HBV EXPOSED NEONATES BORN TO MOTHERS WITH HIGH HBSAG TITRES PERSISTING DESPITE VACCINATION ◆

Prabhjyoti Pahwa[1] Ravinder Singh[1] Partha Chattopadhyay[2] Priyanka Mehta[2] Sharda Patra[3] Rajesh Pandey[2] Shakun Tyagi[4] Shiv Kumar Sarin[1] Nirupma Trehanpati[1]

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Background: High levels of HBV DNA and HBsAg titres increase the risk of mother-to-child transmission. Though, HBV vaccination does protect from HBV exposure, there remains a gap in understanding how immunity varies in neonates born to mothers with high and low HBsAg levels. We analysed immune responses before and after HBV vaccination in infants born to high and low HBsAg titres in mothers using single-cell RNA sequencing (scRNAseq). **Methods:** scRNAseq was conducted in infants born to mothers with low (Gr.1, n=3, HBsAg $3.186x10^3$IU/ml) and high HBsAg titres (Gr.2, n=3, HBsAg $1.0708x10^4$IU/ml) at birth (prior to HBV vaccination) and after the 14th week dose of HBV vaccination. Analysis was done using Seurat R package and cell type identification with SingleR. Validation of single-cell data was performed through immunophenotyping in Gr.1 (n=8) and Gr.2 (n=8) cohorts. **Results:** scRNAseq revealed that, before HBV vaccination, new born in Gr.2 showed increased expression of immune-exhaustion and metabolic markers like thymocyte selection associated high mobility group box (TOX, p<0.0001), CTLA-4 (p<0.0001), TIGIT (p=0.07), HK2, POGLUT1, and decreased expression of CD45RO (p=0.01), CD69 (p=0.07) and mTOR (p=0.03) in CD8$^+$T cells, compared to Gr.1 (FigA-B). Additionally, there was elevated expression of CCR2 (p=0.001) and CX3CR1(p<0.0001) on monocytes and NK cells in Gr.2 compared to Gr.1. Post vaccination, Gr.2 showed persistently high expression of exhaustion with significantly higher levels of TOX (p<0.0001) and LDHA (p=0.02) compared to Gr.1 (FigB). Both Gr.1 and Gr.2 neonates exhibited anti-HBs titre ≥ 10 IU/mL post 14th week HBV vaccination. Immunophenotyping data also confirmed the scRNAseq findings, indicating higher expression of exhaustion markers like Tim-3 (p=0.003), TIGIT (p=0.03), and BTLA (p<0.0001) on CD8$^+$T cells before vaccination. Also, there was a higher percentage of total monocytes (p=0.05) and HLA-DR expressing neutrophils (p=0.03) in Gr.2 compared to Gr.1 (FigC). Post-vaccination, CD8$^+$T cells displayed higher expression of Tim-3 (p=0.04) and TIGIT, along with reduced frequency of total monocytes (p=0.008) and HLA-DR expressing neutrophils (p=0.02) in Gr.2 compared to Gr.1 (FigC). **Conclusion:** *In utero* HBV exposure in infants born to mothers with high HBsAg titres showed heightened expression of HLA on monocytes and neutrophils, but compromised adaptive immunity with CD8$^+$T cell exhaustion and metabolic dysregulations. Despite vaccination, immune exhaustion persisted in these neonates with increased expression of TOX.

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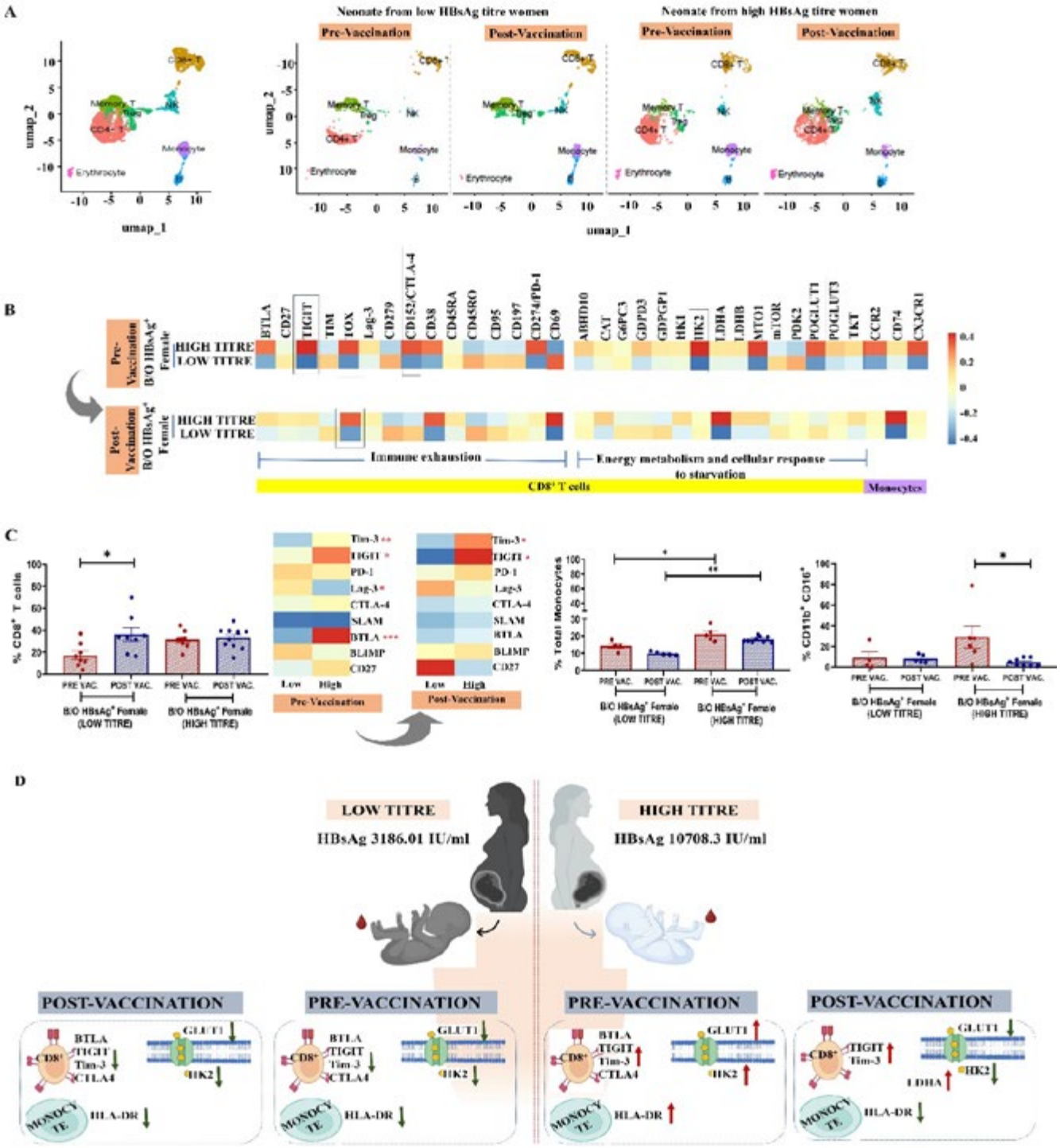

Disclosures: Prabhjyoti Pahwa: Nothing to Disclose, Ravinder Singh: Nothing to Disclose, Partha Chattopadhyay: Nothing to Disclose, Priyanka Mehta: Nothing to Disclose, Sharda Patra: Nothing to Disclose, Rajesh Pandey: Nothing to Disclose, Shakun Tyagi: Nothing to Disclose, Shiv Kumar Sarin: Nothing to Disclose, Nirupma Trehanpati: Nothing to Disclose

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1365 | COMPARABLE OUTCOMES BETWEEN BESIFOVIR AND OTHER ANTIVIRAL THERAPIES IN HEPATOCELLULAR CARCINOMA DEVELOPMENT AMONG PATIENTS WITH CHRONIC HEPATITIS B

Jae Seung Lee[1] Sung Won Lee[2] Sang Gyune Kim[3] Yeon Seok Seo[4] Su Jong Yu[5] Hyung Joon Yim[6] Hye Won Lee[1] Mi Na Kim[1] Beom Kyung Kim[1] Jun Yong Park[1] Do Young Kim[1] Sang Hoon Ahn[1] Seung Up Kim[1]

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Background: Besifovir dipivoxil maleate (BSV), an acyclic nucleotide phosphonate, has potent antiviral efficacy against chronic hepatitis B (CHB), similar to other antiviral agents, such as entecavir (ETV), tenofovir disoproxil fumarate (TDF), and tenofovir alafenamide (TAF). This study compares outcomes between BSV and the other antiviral agents in hepatocellular carcinoma (HCC) development among patients with CHB. **Methods:** We conducted a retrospective cohort of 2,684 treatment-naïve patients with CHB who started their first-line antiviral therapy (AVT) between May 2017 and April 2022 with ETV (n=840), TAF (n=706), TDF (n=666), or BSV (n=472) at six tertiary medical institutions in South Korea. The incidence and hazard ratio (HR) were calculated using Kaplan-Meier and Cox regression analyses, respectively. Selection bias was minimized using inverse probability of treatment weighting (IPTW) and propensity score matching (PSM). **Results:** Compared to the patients with other antiviral agents, BSV users showed a higher proportion of male patients (61.2% vs. 50.1–56.2%), alcohol intake >20g/day (12.1% vs. 5.5–11.2%), and cirrhosis (37.9% vs. 30.5–34.3%). The incidence of HCC in BSV users (n=6, 4.4 per 1000 person-years [PYs]) was similar to that in TAF users (8.5 per 1000 PYs, log-rank *P*=0.111, HR 2.098, 95% confidence interval [CI] 0.827–5.324), however, significantly lower than those in ETV (n=38, 12.7 per 1000 PYs, log-rank *P*=0.026, HR 2.603, 95% CI 1.087–6.233) and TDF users (12.7 per 1000PYs, log-rank *P*=0.035, HR 2.539, 95% CI 1.034–6.234). After applying 1:1:1:1 IPTW, the incidence of HCC in BSV users (n=7 of 591, 3.8 per 1000 PYs) was similar to that in TAF users (n=17 of 713, 8.6 per 1000 PYs, adjusted HR [aHR] 2.324, 95% CI 0.894–6.043), however, significantly lower than in ETV (n=32 of 706, 12.4 per 1000 PYs, aHR 2.795 (95% CI 1.138–6.866, E-value 5.035) and TDF users (n=34 of 674, 14.6 per 1000 PYs, aHR 3.322 (95% CI 1.334–8.274, E- value 6.099). Following separated 1:1 PSM (all 472 pairs), the incidence of HCC in BSV users (n=6, 4.4 per 1000 PYs) was similar to that in TAF users (n=12, 8.6 per 1000 PYs, log-rank *P*=0.782, aHR 1.167, 95% CI 0.392–3.471), however, significantly lower than in ETV (n=27, 15.2 per 1000 PYs, log-rank P=0.025, aHR 2.978, 95% CI 1.024 – 8.659, E-value 5.404), and TDF users (n=27, 16.6 per 1000 PYs, log-rank P=0.025, aHR 3.000, 95% CI 1.090–8.254, E-value 5.449). **Conclusion:** BSV showed comparable outcomes in HCC development among patients with CHB compared to TAF, ETV, and TDF. Given the small number of events and the relatively short follow-up duration observed in BSV users, further long-term analysis is warranted.

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Table. Comparisons of cumulative incidence of HCC after 1:1:1:1 IPTW and each 1:1 PSM

IPTW	n	HCC (%)	Follow-up (PYs)	Incidence rate*	logrank *P* value	Cox regression		E value (lower)
						Adjusted HR† (95% CI)	*P* value†	
BSV	591	7 (1.1)	1698.7	3.8	0.005	Reference	-	-
ETV	706	32 (4.5)	2593.0	12.4		2.795 (1.138, 6.866)	0.025	5.035 (1.534)
TAF	713	17 (2.4)	2029.2	8.6		2.324 (0.894, 6.043)	0.084	Not applicable
TDF	674	34 (5.0)	2330.8	14.6		3.322 (1.334, 8.274)	0.010	6.099 (2.001)
1:1 PSM	Pairs**	HCC (%)	Follow-up (PYs)	Incidence rate*	logrank *P* value	Cox regression		E value (lower)
						Adjusted HR (95% CI)	*P* value	
BSV	472	6 (1.3)	1374.2	4.4	-	Reference	-	-
ETV	472	27 (5.7)	1779.9	15.2	0.025	2.978 (1.024, 8.659)	0.045‡	5.404 (1.180)
TAF	472	12 (2.5)	1399.9	8.6	0.782	1.167 (0.392, 3.471)	0.782	Not applicable
TDF	472	27 (5.7)	1628.7	16.6	0.025	3.000 (1.090, 8.254)	0.033	5.449 (1.404)

*Incidence rate, per 1000 person-years

**For every 1:1 PSM, 472 pairs were yielded.

†IPTW-adjusted HR, adjusted with hypertension, chronic kidney disease, and HBV DNA

‡PSM-adjusted HR, adjusted with serum albumin

Abbreviations: IPTW, inverse probability treatment weighting; PSM, propensity-score matching; n, number; HCC, hepatocellular carcinoma; PYs, person-years; HR, hazard ratio; CI, confidence interval; BSV, besifovir dipivoxil maleate; ETV, entecavir; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

Disclosures: Jae Seung Lee: Nothing to Disclose, Sung Won Lee: Nothing to Disclose, Sang Gyune Kim: Nothing to Disclose, Yeon Seok Seo: Nothing to Disclose, Su Jong Yu: Nothing to Disclose, Hyung Joon Yim: Nothing to Disclose, Hye Won Lee: Nothing to Disclose, Mi Na Kim: Nothing to Disclose, Beom Kyung Kim: Nothing to Disclose, Jun Yong Park: Nothing to Disclose, Do Young Kim: Nothing to Disclose, Sang Hoon Ahn: Nothing to Disclose, Seung Up Kim: Nothing to Disclose

1366 | FUNCTIONAL ANALYSIS OF FUMARYLACETOACETATE HYDROLASE AS A HEPATOCYTE HOST FACTOR GENE REGULATING HEPATITIS B VIRUS REPLICATION AND HEPATOCARCINOGENESIS

Shouichi Namikawa[1] *Takuto Nosaka*[1] *Yosuke Murata*[1] *Tomoko Tanaka*[1] *Yu Akazawa*[1] *Kazuto Takahashi*[1] *Tatsushi Naito*[1] *Masahiro Ohtani*[1] *Yasunari Nakamoto*[1]

[1]*University of Fukui*

Background: Recent molecular biological analyses have highlighted the importance of host factors in anti-viral and/or anti-tumor effects. We established a hepatitis B virus (HBV) infection assay system using primary human hepatocytes and extracted fumarylacetoacetate hydrolase (FAH) as a host factor gene that regulates viral life cycle by RNA microarray analysis (in submission). In this study, we investigated the anti-HBV and anti-tumor effects of FAH using resected hepatocellular carcinoma (HCC) tissue and HBV stable transfected HCC cell lines. **Methods:** In 60 resected HCC specimens, the intensity of immunohistological staining of FAH in tumor and non-tumor areas was determined by H-score using inform (akoya), and the correlation with prognosis was analyzed. The FAH index was calculated by H-score of tumor/non-tumor area. The 1.3 mer HBV genome of genotype C2 with basic core promoter and/or pre-core mutation (wt/wt; Low transcription, mu/mu; High t.) was transfected into HepG2 cells and HepG2.1-E10 (Low t.) and HepG2.D11 (High t.) were established. FAH vector and siRNA were transfected and MTT assay, apoptosis assay, and sphere formation assay were performed. The HBsAg was standardized by cell count (HBsAg index). RNA expression was analyzed for 205 anti-tumor and anti-viral related genes using TaqMan custom array plates. **Results:** The H-score of FAH in resected HCC specimens was significantly lower in tumor areas compared to non-tumor areas (tumor/non-tumor areas: 143/165). Recurrence and survival rates were worse in the patient group with lower FAH index ($p < 0.05$). In HepG2.D11 and HepG2.1-E10, the viability index and HBsAg index were increased in the FAH knockdown and decreased in the FAH vector transduction experiments compared to controls. Furthermore, FAH overexpression in HepG2.D11 and HepG2.1-E10 induced apoptosis and decreased the number of spheres. In FAH overexpression, the expression

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of CCKN2B and CHEK1 (cell cycle) were elevated, NANOG and SALL4 (stem cell function) were decreased, and anti-HBV related genes, APOBEC3B and IRF7, were increased. **Conclusion:** Evaluation of FAH expression in HCC tissues and the functional analysis in HBV-transfected HepG2 cells suggest that the FAH gene may contribute to HBV reduction, inhibition of cell proliferation, and induction of cell apoptosis. Hepatocyte host factor FAH is shown to have the potential to exhibit both anti-tumor and anti-HBV effects, and may be a candidate for a new therapeutic strategy of viral carcinogenesis.

Disclosures: Shouichi Namikawa: Nothing to Disclose, Takuto Nosaka: Nothing to Disclose, Yosuke Murata: Nothing to Disclose, Tomoko Tanaka: Nothing to Disclose, Yu Akazawa: Nothing to Disclose, Kazuto Takahashi: Nothing to Disclose, Tatsushi Naito: Nothing to Disclose, Masahiro Ohtani: Nothing to Disclose, Yasunari Nakamoto: Nothing to Disclose

1367 | APPLY HBV RNA AND HBCRAG TO FOLLOW-UP OF PATIENTS WITH CHRONIC HEPATITIS B RECEIVING NUCLEOS(T)IDE ANALOGS

Mingyang Feng[1] Kehui Liu[1] Wanqing Chi[2] Baoyan An[1] Lanyi Lin[1] Yezhou Ding[1] Yumin Xu[1] Hui Wang[1]

[1]Department of Infectious Diseases, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, [2]Yale University School of Public Health, Epidemiology of Microbial Disease

Background: Some patients with chronic hepatitis B (CHB) may still experience low-level viremia (LLV) despite receiving first-line oral antiviral agents for more than 48 weeks, which can lead to disease progression and unfavorable clinical outcomes, such as an increased risk of hepatocellular carcinoma (HCC) and liver cirrhosis. **Methods:** This single-center retrospective study analyzed clinical data from 270 patients with CHB who were treated with first-line nucleos(t)ide analogs (NAs) > 48 weeks at the Outpatient Department of Infectious Diseases of a tertiary hospital. CHB patients were divided into two groups: those achieving a maintained virological response (MVR) with HBV DNA within the lower limit of detection (10 IU/mL) and those with LLV, whose HBV DNA was detectable but lower than 2000 IU/mL. We analyzed the demographic and clinical characteristics of these patients and the factors associated with LLV. Furthermore, levels of HBV RNA and HBcrAg were evaluated. **Results:** In this cohort, 90 patients achieved MVR, and 180 patients developed LLV. The percentage of CHB patients who were first-line NA-naïve was 79.5% in the MVR group and 66.8% in the LLV group (p=0.031). Patients with LLV had higher levels of ALT, AST, and bile acid, but lower levels of total protein, albumin, and serum calcium compared to those with MVR (p<0.05 for all). LLV patients also had higher levels of HBV S protein, HBeAg and HBeAb, but lower levels of HBsAb compared to MVR patients (p<0.05 for all). Risk factors for LLV included positive HBeAg, positive HBeAb, positivity for both HBeAg and HBeAb, and the use of non-first-line drugs during treatment. LLV patients consistently maintained higher levels of HBV RNA and HBcrAg compared to those who achieved MVR, from baseline through the 96-week follow-up period. Even in LLV patients who eventually achieved MVR, their HBV RNA and HBcrAg levels remained higher than those of patients who maintained MVR after over 48 weeks of NA treatment. Our findings showed that HBV RNA levels in MVR patients significantly decreased from 12 weeks to 48 weeks, while a moderate decline in HBV RNA levels was observed in LLV patients during the same period. **Conclusion:** These results indicate that it is necessary to continuously monitor HBV RNA and HBcrAg levels during the disease assessment and long-term follow-up of CHB patients, to enable early detection and intervention of LLV.

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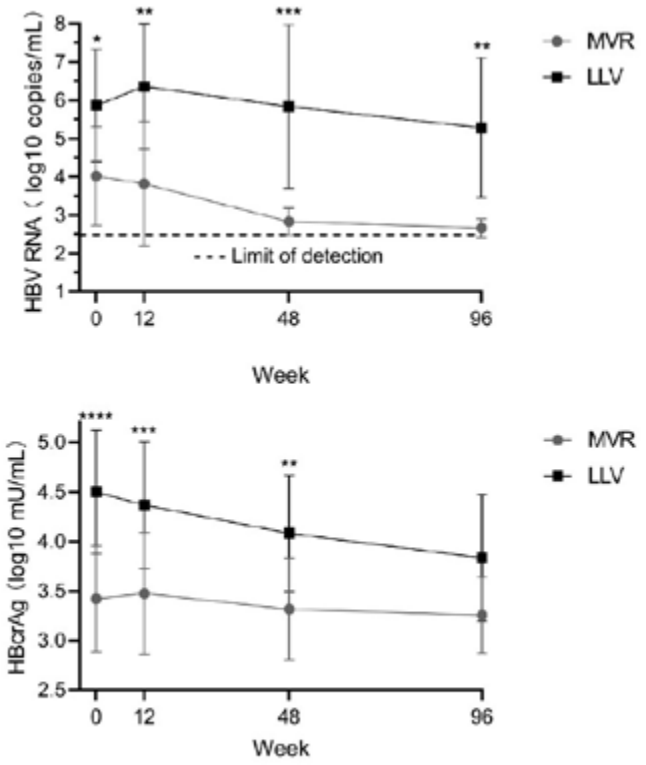

Figure: Dynamic changes of HBV RNA and HBcrAg
*p < 0.05, **p < 0.01, ***p < 0.001 and ****p < 0.0001

Disclosures: Mingyang Feng: Nothing to Disclose, Kehui Liu: Nothing to Disclose, Wanqing Chi: Nothing to Disclose, Baoyan An: Nothing to Disclose, Lanyi Lin: Nothing to Disclose, Yezhou Ding: Nothing to Disclose, Yumin Xu: Nothing to Disclose, Hui Wang: Nothing to Disclose

1368 | TREATMENT ELIGIBILITY OF PATIENTS WITH CHRONIC HEPATITIS B IN THE INDETERMINATE PHASE

Jian Wang[1] Zhiyi Zhang[2] Juan Xia[1] Bei Jia[1] Yue Yang[1] Guiyang Wang[1] Weihua Wu[1] Yali Xiong[1] Xiaomin Yan[1] Jie Li[1] Xingxiang Liu[3] Chuanwu Zhu[4] Chao Wu[1] Rui Huang[1]

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Background: A substantial proportion of chronic hepatitis B (CHB) patients fall outside the traditional natural phases and are classified as indeterminate phase. The proportion of CHB patients eligible for treatment and the associated factors with treatment in the indeterminate phase remains unclear. **Methods:** This is a multi-center and retrospective cohort study. The immune phases of CHB patients were classified according to the definitions of immune phases of AASLD 2018 Guidance. The indeterminate phase was further classified into indeterminate phase 1 (HBeAg positive, ALT ≤1 × ULN, HBV DNA ≤10^6 IU/ml) and indeterminate phase 2 (HBeAg positive, ALT >1 × ULN, HBV DNA ≤2 × 10^4 IU/ml), indeterminate phase 3 (HBeAg negative, ALT ≤1 × ULN, HBV DNA ≥2 × 10^3 IU/ml) and indeterminate phase 4 (HBeAg negative, ALT >1 × ULN, HBV DNA ≤2 × 10^3 IU/ml). Liver fibrosis was evaluated by liver biopsy or transient elastography. The antiviral treatment criteria were based on AASLD 2018 Guidance and WHO 2024 hepatitis B Guidelines, respectively. **Results:** Of 748 CHB patients with indeterminate phase, the median age was 39.0 years and 60.9% of patients were male. The proportions of indeterminate phase 1, 2, 3, and 4 were 5.6%, 3.2%, 48.0%, and 43.2%, respectively. Based on AASLD 2018 Guidance, 17.9% of patients were eligible for antiviral treatment, including 21 (21/42, 50.0%) patients in the indeterminate phase 1 and 113 (113/359, 31.5%) patients in the indeterminate phase 3, while no patient was eligible for treatment in the

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indeterminate phase 2 and 4. However, a larger proportion of patients (72.6%) met treatment criteria of WHO 2024 hepatitis B Guidelines. Age >40 years (OR 1.787, P=0.008), platelet ≤180 × 10^9/L (OR 1.808, P=0.006), AST ≤1 × ULN (OR 4.063, P <0.001), albumin ≤40 g/L (OR 2.396, P =0.009), and HBV DNA >2 × 10^4 IU/ml (OR 4.855, P <0.001) were independently associated with treatment eligibility. A simple integer point range from 0 point to 13 points was established based on these parameters. The proportions of treatment eligibility were 2.7%, 16.1%, 40.0%, and 85.7% in patients with 0-3 points, 4-7 points, 8-11 points, and ≥12 points, respectively. Moreover, after excluding patients with significant liver fibrosis or inflammation, 68.1% of patients remain meet the treatment criteria according to the WHO 2024 hepatitis B Guidelines. **Conclusion:** As high as 17.9% and 72.6% of patients in the indeterminate phase met treatment criteria of AASLD 2018 Guidance and WHO 2024 Guidelines, respectively.

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1369 | PROTECTIVE EFFECTS OF MASLD IN CHRONIC HEPATITIS B PATIENTS ON THE RISK FOR HEPATOCELLULAR CARCINOMA, HEPATIC DECOMPENSATION, AND MORTALITY

Hye Won Lee[1] Sang Hoon Ahn[1] Kunhee Kim[1] Hyeyeon Hong[2] Jonggi Choi[3]

[1]Yonsei University College of Medicine, [2]Asan Medical Center, [3]University of Ulsan, Asan Medical Center

Background: Both metabolic dysfunction-associated steatotic liver disease (MASLD) and chronic hepatitis B (CHB) can proceed to hepatocellular carcinoma (HCC), hepatic decompensation (DCC), and mortality. However, the role of MASLD in CHB patients in this process remains controversial. **Methods:** This study included 5,614 treatment-naive CHB patients with or without MASLD between 2007 and 2021. We compared the incidence rates and cumulative incidences of HCC, DCC, and mortality between MASLD and non-MASLD patients. To adjust for confounding variables, the inverse probability of treatment weighting (IPTW) was used. Furthermore, patients were stratified by PAGE-B scores to compare the HCC cumulative incidence between MASLD and non-MASLD patients. **Results:** MASLD patients (n=1,001) had lower incidence rates of DCC (5.4 per 1,000 person-years, hazard ratio [HR] 0.379), HCC (6.8 per 1,000 person-year, HR 0.418), and mortality (1.4 per 1,000 person-year, HR 0.199) compared to non-MASLD patients (n=4,613; 14.3, 16.1, and 7.1 per 1,000 person-years for DCC, HCC, and mortality, respectively). In the analysis after IPTW, the respective adjusted HRs of MASLD were 0.532 (95% confidence interval [CI] 0.288-0.982, p=0.043), 0.522 (95% CI 0.306-0.893, p=0.018), and 0.432 (95% CI 0.185-1.009, p=0.052) for DCC, HCC, and mortality. The results remained consistent even after stratification by PAGE-B. Furthermore, an increase in cardiometabolic risk factors was associated with increased incidences of DCC, HCC, and mortality, with or without stratification by PAGE-B. **Conclusion:** We explore the effect of newly defined MASLD in the progression of CHB patients to HCC, DCC, and mortality. Concurrent MASLD in CHB patients was associated with a lower risk of DCC, HCC, and mortality in CHB patients after adjustment by IPTW and stratification by PAGE-B. Therefore, different criteria for HCC surveillance could be applied in CHB patients with MASLD.

Disclosures: Hye Won Lee: Nothing to Disclose, Sang Hoon Ahn: Nothing to Disclose, Kunhee Kim: Nothing to Disclose, Hyeyeon Hong: Nothing to Disclose, Jonggi Choi: GILEAD SCIENCE: Grant/Research Support

1370 | CLINICAL PROGNOSIS OF HBEAG-NEGATIVE PATIENTS WITH CHRONIC HEPATITIS B WITH LOW HBSAG

Jian Wang[1] Li Zhu[2] Zhiyi Zhang[3] Shengxia Yin[1] Shaoqiu Zhang[1] Tao Fan[3] Ye Xiong[3] Chao Jiang[4] Xingxiang Liu[5] Jie Li[1] Chuanwu Zhu[2] Chao Wu[1] Rui Huang[1]

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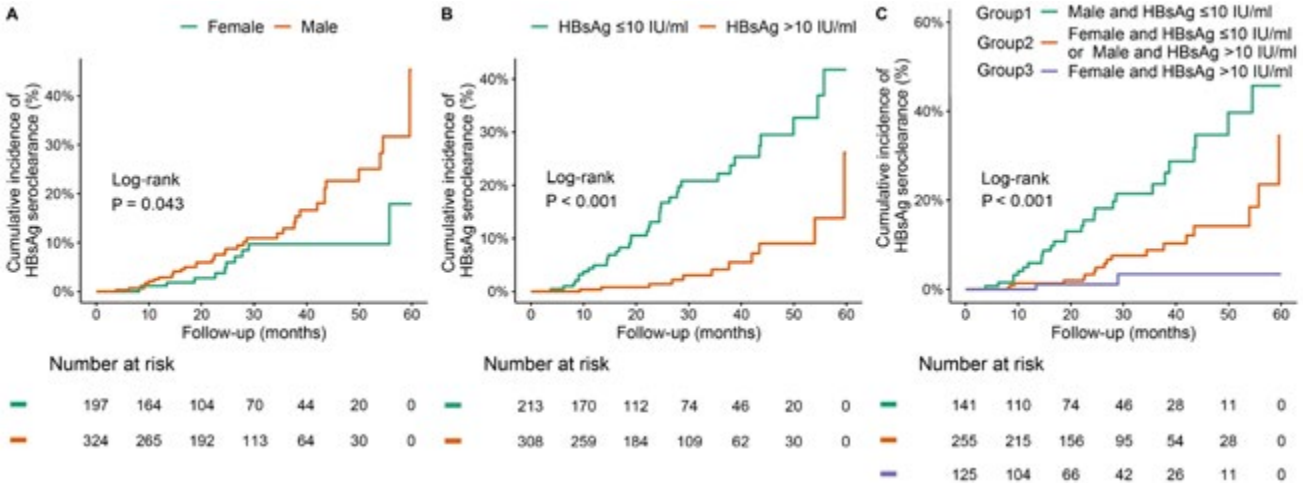
Chinese Medicine, [4]Nanjing Drum Tower Hospital Clinical College of Jiangsu University, [5]Huai'an No. 4 People's Hospital

Background: Serum HBsAg <100 IU/mL has been regarded as a criterion of " partial cure " in patients with chronic hepatitis B virus (HBV) infection. We evaluated the prognosis of untreated HBeAg-negative patients with HBsAg <100 IU/ml and normal alanine aminotransferase (ALT). **Methods:** Five hundred and twenty-one untreated patients with HBeAg negativity, HBsAg <100 IU/ml, and normal ALT were included from three hospitals. Spontaneous HBsAg seroclearance, immune phase transition, fibrosis progression, and hepatocellular carcinoma (HCC) development of patients during follow-up were analyzed. **Results:** The median age of patients was 43.0 years and a median follow-up period was 23.3 months. During follow-up, 47 (9.0%) patients achieved spontaneous HBsAg seroclearance with an annual HBsAg seroclearance rate of 4.2%. Patients with male gender (aHR =2.099, P =0.040) and baseline HBsAg ≤10 IU/ml (adjusted HR =4.264, P <0.001) were more likely to achieve HBsAg seroclearance. 6 (1.2%) and 23 (4.8%) of patients transitioned to immune active phase and HBeAg-negative indeterminate phase, respectively. Baseline serum HBsAg >10 IU/ml (aHR =5.837, P =0.019) and detectable HBV DNA (aHR =3.004, P =0.010) were independent factors associated with transition to HBeAg-negative indeterminate phase. No significant change of APRI, FIB-4, and liver stiffness values was found from baseline to the end of follow-up regardless of HBsAg seroclearance. No patients developed HCC during follow-up. **Conclusion:** HBeAg-negative patients with HBsAg <100 IU/ml and normal ALT had a favorable prognosis. Baseline serum HBsAg ≤10 IU/ml and male gender were associated with higher chance of HBsAg seroclearance.



Disclosures: Jian Wang: Nothing to Disclose, Li Zhu: Nothing to Disclose, Zhiyi Zhang: Nothing to Disclose, Shengxia Yin: Nothing to Disclose, Shaoqiu Zhang: Nothing to Disclose, Tao Fan: Nothing to Disclose, Ye Xiong: Nothing to Disclose, Chao Jiang: Nothing to Disclose, Xingxiang Liu: Nothing to Disclose, Jie Li: Nothing to Disclose, Chuanwu Zhu: Nothing to Disclose, Chao Wu: Nothing to Disclose, Rui Huang: Nothing to Disclose

1371 | EFFECTS OF TENOFOVIR ALAFENAMIDE FUMARATE VERSUS TENOFOVIR DISOPROXIL FUMARATE ON SERUM LIPID PROFILES IN PATIENTS WITH CHRONIC HEPATITIS B

Fei Cao[1] Tao Fan[1] Xue Jiang[2] Jian Wang[3] Ye Xiong[1] Shaoqiu Zhang[3] Zhiyi Zhang[1] Xingxiang Liu[2] Chuanwu Zhu[4] Jie Li[3] Rui Huang[3] Chao Wu[3]

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Background: The effect of lipid profiles in patients with chronic hepatitis B (CHB) during tenofovir alafenamide fumarate (TAF) treatment remains unclear. We aimed to compare the impact of TAF versus tenofovir disoproxil fumarate (TDF) on the serum lipid profiles in patients with CHB. **Methods:** A total of 430 patients with CHB were retrospectively included from 3 hospitals, including 158 patients treated with TAF and 272 patients treated with

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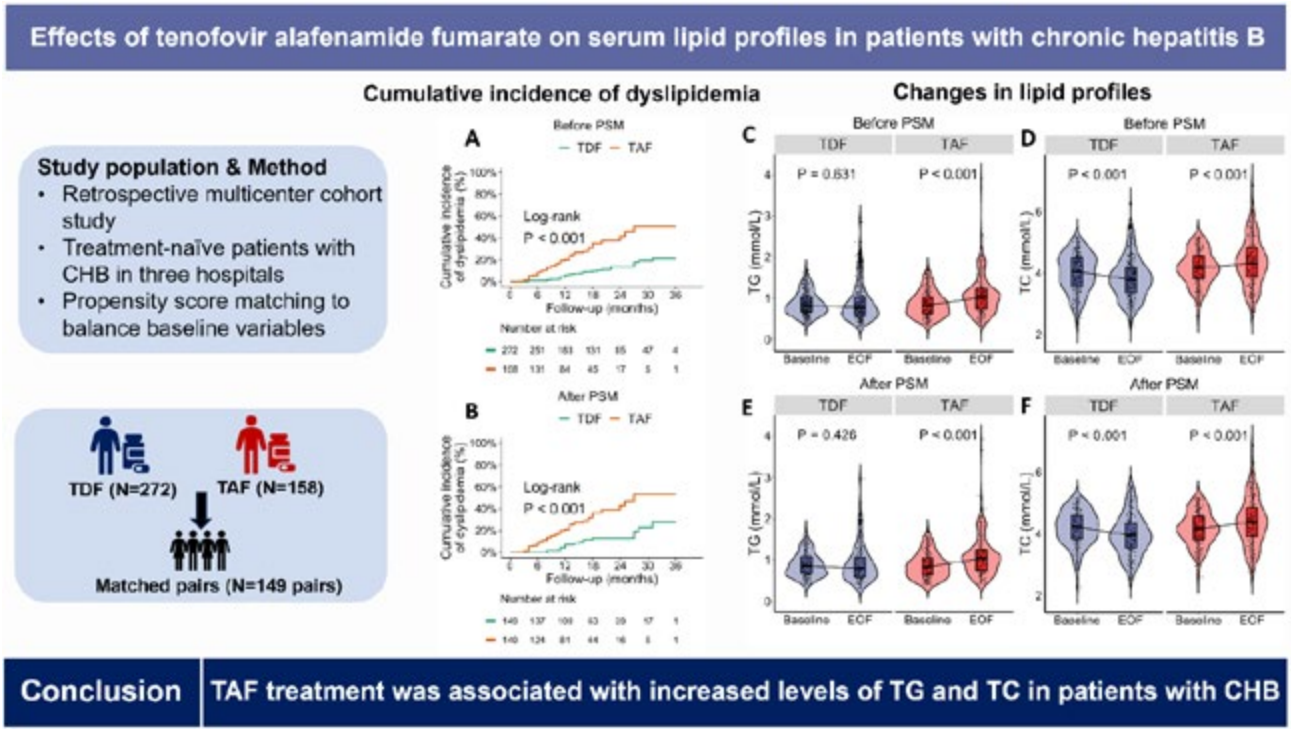
tenofovir disoproxil fumarate (TDF) and were followed for a median of 16.0 months and 18.0 months, respectively. The changes of serum lipid profiles during treatment were compared between TDF and TAF groups. **Results:** In this multi-center real-world retrospective cohort, the cumulative incidence of dyslipidemia was significantly higher in the TAF group compared to TDF group (P < 0.001). After TAF treatment, a significant increase of serum TG levels (from 0.83 mmol/L to 1.02 mmol/L, P < 0.001) and TC levels (from 4.16 mmol/L to 4.32 mmol/L, P < 0.001) was observed. After propensity score matching (PSM), the TAF group remain had a relatively higher incidence of dyslipidemia (P < 0.001) compared to TDF group. The TG levels (from 0.83 mmol/L to 1.04 mmol/L, P < 0.001) and TC levels (from 4.16 mmol/L to 4.38 mmol/L, P < 0.001) were both increased significantly compared to the baseline levels in the PSM cohort. The TAF treatment was an independent factor for elevated TG levels (HR = 3.042, 95% CI: 1.486-6.231, P = 0.002) and TC levels (HR = 9.488, 95% CI: 4.111-21.902, P < 0.001) after treatment. **Conclusion:** Compared to TDF treatment, the TAF treatment was associated with higher incidence of dyslipidemia in patients with CHB. Thus, close monitoring of lipid profiles is needed in patients with CHB who received TAF treatment.



Disclosures: Fei Cao: Nothing to Disclose, Tao Fan: Nothing to Disclose, Xue Jiang: Nothing to Disclose, Jian Wang: Nothing to Disclose, Ye Xiong: Nothing to Disclose, Shaoqiu Zhang: Nothing to Disclose, Zhiyi Zhang: Nothing to Disclose, Xingxiang Liu: Nothing to Disclose, Chuanwu Zhu: Nothing to Disclose, Jie Li: Nothing to Disclose, Rui Huang: Nothing to Disclose, Chao Wu: Nothing to Disclose

1372 | NOVEL THERAPEUTIC HEPATITIS B VIRUS VACCINE USING PLASMID-LAUNCHED LIVE ATTENUATED FLAVIVIRUS VECTOR IMMUNIZATION GENERATES ROBUST CD8 T CELL RESPONSES THAT CORRELATE WITH EFFICACY IN A CHRONIC HEPATITIS B MODEL

Frederik Pauwels[1] Goele Bosmans[1] Liese Aerts[1] Véronique Bodo[1] Thomas Vercruysse[1] Joeri Auwerx[1] Gregory Fanning[1] Mathieu Peeters[1] Wilfried Dalemans[1] Hanne Callewaert[1]

[1]AstriVax NV

Background: AVX70371, a novel therapeutic vaccine using a plasmid-launched live attenuated flavivirus as vector, was developed to elicit hepatitis B virus (HBV)-specific T cell responses against the HBV core (HBc) antigen. The functionality of T cells induced by AVX70371 was characterized in two preclinical animal models. Furthermore, the live-attenuated virus (LAV) vector was tested in a mouse model of chronic hepatitis B. **Methods:**

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A dose range of AVX70371 was administered to naïve interferon receptor type I knock-out mice (*ifnar*$^{-/-}$) and Syrian hamsters, two preclinical animal models permissive for replication of the yellow fever live attenuated viral vector. Immunogenicity was evaluated by *ex vivo* peptide stimulation of splenocytes using cytokine readouts by ELISpot or FluoroSpot. *In vivo* efficacy of vaccine-derived LAVs was tested in *ifnar*$^{-/-}$ mice inoculated with different titers of recombinant adeno-associated virus (rAAV)-HBV vector to monitor the effect at different baseline levels of HBV surface antigen (HBsAg). **Results:** AVX70371 was shown to induce HBc-specific T cells in *ifnar*$^{-/-}$ mice that were able to produce IFN-gamma, IL-2 and TNF-alpha upon stimulation with an HBc peptide pool. Immunization of rAAV-HBV transduced *ifnar*$^{-/-}$ mice with the HBc-expressing LAV resulted in reductions of surface antigen when baseline levels of HBsAg were low. These responses correlated with the presence of HBc-specific intrahepatic T cells. In addition, we demonstrated that the immune response in the immunocompetent hamster model was comparable in magnitude to the responses induced in *ifnar*$^{-/-}$ mice. **Conclusion:** HBV specific T cells induced by AVX70371 vaccination were confirmed in two animal models and were shown to be polyfunctional, present in the liver and able to reduce surface antigen in mice with low baseline levels of HBsAg. These results complement the previous preliminary data on preclinical efficacy using adoptive transfer and support the continued preclinical and clinical development of AVX70371 for HBV cure.

Disclosures: Frederik Pauwels: Johnson & Johnson: Employee, AstriVax NV: Employee, Goele Bosmans: Nothing to Disclose, Liese Aerts: Nothing to Disclose, Véronique Bodo: AstriVax: Employee, Aelin Therapeutics: Employee, Thomas Vercruysse: Nothing to Disclose, Joeri Auwerx: Nothing to Disclose, Gregory Fanning: AstriVax: Consultant, Mathieu Peeters: Nothing to Disclose, Wilfried Dalemans: AstriVax NV: Consultant, Hanne Callewaert: Nothing to Disclose

1373 | SERUM ESPL1 PROTEIN AS AN EARLY WARNING BIOMARKER FOR THE INITIAL OCCURRENCE AND RECURRENCE OF HEPATITIS B VIRUS-RELATED HEPATOCELLULAR CARCINOMA

Bobin Hu[1] *Deli Deng*[1] *Hengkai Liang*[1] *Rongming Wang*[1] *Lu Wei*[1] *Tumei Su*[1] *Qingmei Li*[1] *Qianbin Yin*[1] *Yanfei Feng*[1] *Minghua Su*[1] *Jianning Jiang*[1]

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Background: This study aims to assess the potential of serum Extra Spindle Pole Bodies-like 1 (ESPL1) protein as a biomarker for the effective early warning of Hepatitis B Virus (HBV)-related hepatocellular carcinoma (HCC). **Methods:** A cross-sectional study was conducted, including 119 patients who were classified into three groups: chronic hepatitis B (CHB), HBV-related liver cirrhosis (LC), and HBV-HCC. Additionally, a longitudinal study included 49 patients in a non-recurrent (N-Rec) group with first occurrence of HBV-HCC and a recurrent (Rec) group with multiple HCC recurrences. Serum ESPL1 levels were measured using enzyme-linked immunosorbent assay. Differences in serum ESPL1 levels among the CHB, HBV-LC, and HBV-HCC groups and alpha-fetoprotein (AFP) levels among these groups were compared. The dynamic changes of serum ESPL1 and AFP levels were analyzed in the N-Rec group before and after the hepatectomy and in the Rec group before and after each HCC recurrence. **Results:** Serum ESPL1 levels showed a gradual increase in the CHB, HBV-LC, and HBV-HCC groups ($P<0.05$). In the N-Rec group, serum ESPL1 levels exhibited a continuous upward trend in the 5 years before the hepatectomy, followed by a consistent decline over the subsequent 5 years. In the Rec group, serum ESPL1 levels demonstrated a fluctuating pattern of increase and decrease before and after each liver cancer resection. Conversely, the changes in serum AFP levels did not follow a consistent pattern. **Conclusion:** Serum ESPL1 has potential as a biomarker for effective early warning of initial and recurrent HBV-related HCC.

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Figure1. Comparison of serum ESPL1 and AFP levels in CHB, HBV-LC, and HBV-HCC groups.

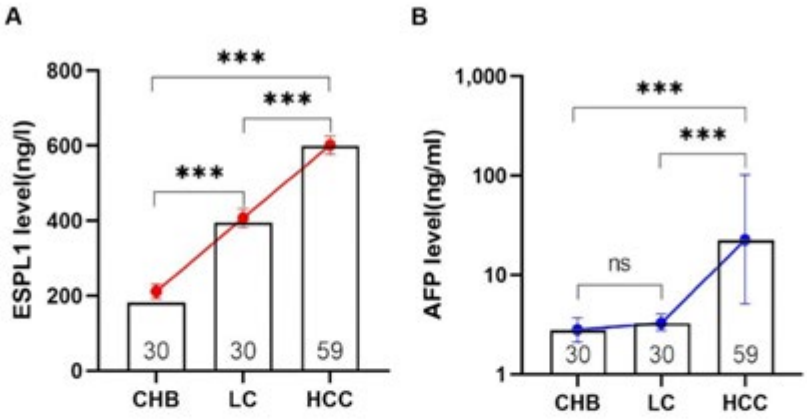
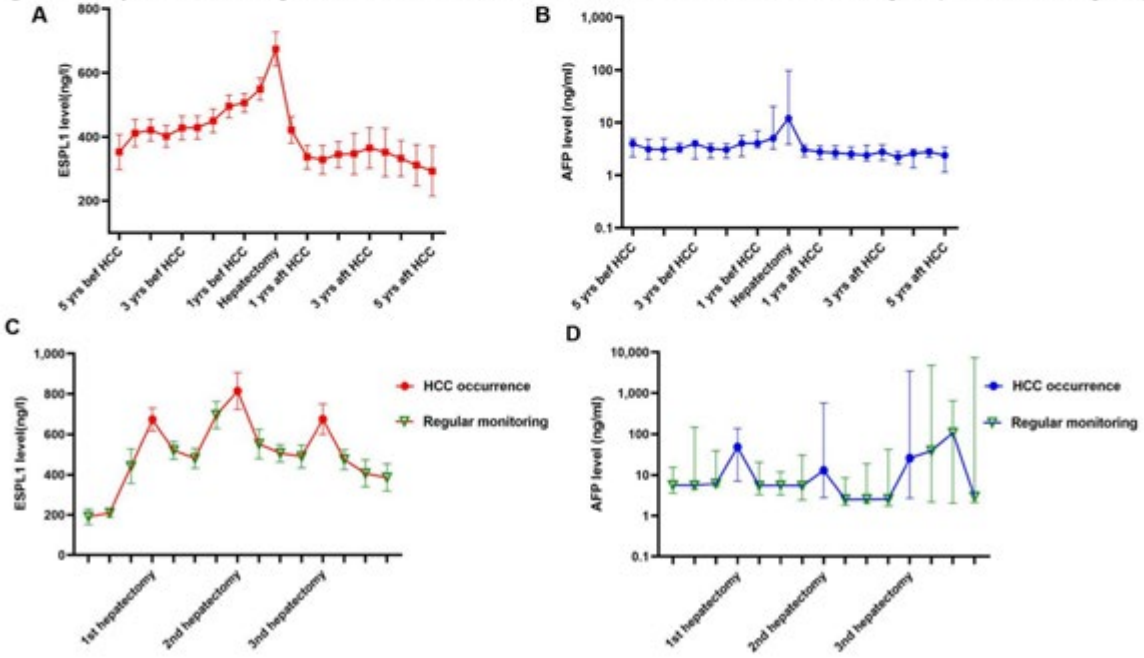


Figure2. Dynamic changes of serum ESPL1 and AFP levels in N-Rec group and Rec group.



Disclosures: Bobin Hu: Nothing to Disclose, Deli Deng: Nothing to Disclose, Hengkai Liang: Nothing to Disclose, Rongming Wang: Nothing to Disclose, Lu Wei: Nothing to Disclose, Tumei Su: Nothing to Disclose, Qingmei Li: Nothing to Disclose, Qianbin Yin: Nothing to Disclose, Yanfei Feng: Nothing to Disclose, Minghua Su: Nothing to Disclose, Jianning Jiang: Nothing to Disclose

1374 | CHARACTERIZATION OF THE DIRECT ANTIVIRAL EFFECT OF REP 2139 IN 2D AND 3D HDV INFECTION MODELS

Simone Fonte[1] Marie Laure Plissonnier[1] Maud Michelet[2] Matthieu Blanchet[3] Patrick Labonté[4] Andrew Vaillant[5] Massimo Levrero[6]

[1]IHU Lyon - Lyon Hepatology Institute, INSERM U1052, Lyon, France, [2]IHU Lyon - Lyon Institute of Hepatology, INSERM U1052, Lyon, France, [3]Replicor Inc, Montreal, Canada, [4]INRS – Institut Armand Frappier, Institut National de la Recherche Scientifique, Laval, Canada, [5]Replicor Inc., Montreal, Canada, [6]INSERM U1054, CHU Lyon and University Claude Bernard Lyon 1

Background: The nucleic acid polymer (NAP) REP 2139 has been shown to: i) target the HSP40 DNAJB12 chaperone to block HBV subviral particles assembly/secretion and HDV ribonucloprotein (HDV RNP)

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envelopment/secretion; ii) to directly bind S-HDAg and L-HDAg. Building upon this latter observation and the robust and early HDV RNA response compared to HBsAg observed in the phase II study and the REP 2139 compassionate use in HBV/HDV infection, we have shown that REP2139 has a direct antiviral activity in cell models *in vitro*. Here we further investigate and characterize the mechanisms underlying REP 2139 antiviral activity in relevant 2D and 3D and HDV infection models. **Methods:** REP 2139-Mg (lot FAB-22-0001) was used for dosing in HDV stably replicating Huh7-END cells (10 ge/cell), HDV-infected HepG2-NTCP cells and primary human hepatocytes (PHH) (10 ge/cell) and Precision Cut Liver Cuts (PCLS) (100 ge/cell), a 3D liver model that includes hepatocytes and non-hepatocytic liver cells and displays conserved hepatocytes polarization and cell-cell interactions. Intracellular HDV RNA levels were assessed by qRT-PCR and ddPCR. HDV RNA and HDAg association to form the HDV RNP was monitored by anti-HDAg RNA immunoprecipitation (RIP) followed by HDV qRT-PCR. **Results:** A single dose of REP 2139-Mg reduces intracellular genomic and anti-genomic HDV RNA levels by ~1 log10 in HepG2-NTCP cells, PHH and HuH7-END cells (that supports a complete HDV viral cycle and secretes HDV infectious virions) and a ~1.5 log10 dose dependent decrease in *de novo* HDV RNA synthesis. In HBV-HDV coinfected PHHs REP 2139 also inhibits HBsAg secretion without affecting intracellular pgRNA levels or HBeAg secretion. In these 2D cell models, REP 2139 endosomal release was restored by UNC 7938. Of note, REP 2139 treatment of HDV-infected PCLS results in a >1.5 log10 decrease in HDV RNA without UNC 7938, thus limiting cell toxicity and allowing repeated dosing. Finally, RIP experiments with multiple anti-HDAg antibodies have shown that REP 2139-Mg reduces the intranuclear association of HDV RNA with HDAg in both HepG2-NTCP cells and PHHs without affecting HDAg protein levels. **Conclusion: Conclusions.** REP 2139 has a direct antiviral effect against HDV RNA replication that involves a block of HDV RNA interaction with HDAg during the morphogenesis of the HDV RNP. The establishment of the 3D PCLS model paves the way to further mechanistic studies and the investigation of REP 2139 in combination therapies.

Disclosures: Simone Fonte: Nothing to Disclose, Marie Laure Plissonnier: Nothing to Disclose, Maud Michelet: Nothing to Disclose, Matthieu Blanchet: Nothing to Disclose, Patrick Labonté: Nothing to Disclose, Andrew Vaillant: Replicor Inc.: Employee, Replicor Inc.: Stock – privately held company, Massimo Levrero: CLS Behring: Speaking and Teaching, Roche: Grant/Research Support, Ipsen: Grant/Research Support, Gilead: Speaking and Teaching, Gilead: Travel grant, Abbvie: Travel Grant, Inventiva: Travel grant, MSD: Travel grant

1375 | SAFETY PROFILE OF TOBEVIBART (VIR-3434) AND ELEBSIRAN (VIR-2218) FOR THE TREATMENT OF CHRONIC HEPATITIS B AND DELTA (CHB AND CHD)

Alina Jucov[1] Edward Gane[2] Man-Fung Yuen[3] Kosh Agarwal[4] Anca Streinu-Cercel[5] Young-Suk Lim[6] Keith Boundy[7] Cara Pilowa[7] Michael Chattergoon[7] Andre Arizpe[7] Vaidehi Thanawala[7] Shuli Yu[7] Pan Wu[7] Yimeng Lu[7] Todd Correll[7] Tarik Asselah[8]

[1]ARENSIA Exploratory Medicine GmbH, [2]Auckland Clinical Studies, [3]The University of Hong Kong, [4]King's College Hospital, [5]National Institute for Infectious Diseases, [6]Asan Medical Center, [7]Vir Biotechnology, Inc., [8]Hôpital Beaujon

Background: Tobevibart (VIR-3434) is an investigational fragment crystallizable (Fc)-engineered human monoclonal antibody that binds to the antigenic loop present in all forms of hepatitis B surface antigen (HBsAg). Elebsiran (VIR-2218) is an investigational RNA interference (RNAi) therapeutic that targets the X region of the hepatitis B virus (HBV) genome that is common to all HBV viral RNA transcripts. Tobevibart and elebsiran are in development for the treatment of chronic hepatitis B virus (CHB) and hepatitis D virus (CHD) infections and have been shown to potently reduce HBsAg and HDV RNA. **Methods:** This analysis includes data from participants who have received at least 24 weeks (≥ 6 doses) of tobevibart 300 mg and elebsiran 200 mg subcutaneously every 4 weeks (Q4W) and are on nucleoside reverse transcriptase inhibitors in the ongoing MARCH, STRIVE, and THRIVE studies in participants with CHB (NCT04856085 and NCT05612581) and the SOLSTICE study in participants with CHD (NCT05461170). On-treatment safety outcomes, including treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs), are presented herein. **Results:** This analysis across 4 trials includes 121 participants (100 CHB, 21 CHD) who received a median of 10 doses each of tobevibart and elebsiran Q4W. The median age was 45 years, 66.1% were male, and 83.5% were HBeAg-negative. The majority of TEAEs were grade 1 (40.5%) or grade 2 (31.4%), 2.5% of participants reported grade ≥3 TEAEs, and 1.7% of participants reported grade ≥3 tobevibart- or elebsiran-related TEAEs. The most common study drug-related TEAEs were influenza-like illness (12.4% tobevibart- and 11.6% elebsiran-related), chills (10.7% and 9.1%), and headache (10.7% and 9.9%). SAEs were reported in 2 participants (1.7%); 1 participant in THRIVE experienced

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an SAE of neutropenia that was considered related to tobevibart, and 1 participant in MARCH experienced unrelated SAEs of coronary artery disease and acute cholecystitis. No TEAEs led to tobevibart or elebsiran discontinuation or death. **Conclusion:** Aggregate safety outcomes across 4 global clinical studies suggest that the safety profile of the combination of tobevibart and elebsiran observed to date is generally consistent with the reported class effects of RNAi therapeutics and monoclonal antibodies. These data support the continued clinical development of tobevibart and elebsiran for the treatment of CHB and CHD.

Disclosures: Alina Jucov: Nothing to Disclose, Edward Gane: Aligos Therapeutics: Advisor, Assembly Biosciences: Advisor, AbbVie: Speaking and Teaching, Intellia Therapeutics: Advisor, Tune Therapeutics: Consultant, Precision Bio: Advisor, Virion Therapeutics: Advisor, Gilead Sciences: Advisor, GSK: Advisor, Man-Fung Yuen: Speaking and Teaching relationship with Fujirebio Incorporation, Gilead Sciences, Roche, Sysmex Corp; Has not ended; Consultant relationship with Clear B Therapeutics, Dicerna Pharmaceuticals; Has not ended; Consultant relationship with AbbVie, Abbott Diagnotics, Aligos Therapeutics; Has not ended; Consultant relationship with Arbutus Biopharma, Arrowhead Pharmaceuticals, Assembly Biosc; Has not ended; Consultant relationship with Immunocore, Janssen, Precision BioSciences; Has not ended; Consultant relationship with Fujirebio Incorporation, GlaxoSmithKline, Gilead Sciences; Has not ended; Grant/Research Support relationship with Fujirebio Incorporation, Gilead Sciences, Immunocore; Has not ended; Grant/Research Support relationship with AbbVie, Assembly Biosciences, Arrowhead Pharmaceuticals; Has not ended; Consultant relationship with Vir Biotechnology and Visirna Therapeutics; Has not ended; Consultant relationship with Roche, Sysmex Corporation, Tune Therapeutics; Has not ended; Grant/Research Support relationship with Sysmex Corporation and Roche; Has not ended, Kosh Agarwal: Nothing to Disclose, Anca Streinu-Cercel: Nothing to Disclose, Young-Suk Lim: Nothing to Disclose, Keith Boundy: Nothing to Disclose, Cara Pilowa: Nothing to Disclose, Michael Chattergoon: Nothing to Disclose, Andre Arizpe: Vir Biotechnology: Employee, Vir Biotechnology: Stock - publicly traded company, Vaidehi Thanawala: Nothing to Disclose, Shuli Yu: Nothing to Disclose, Pan Wu: Nothing to Disclose, Yimeng Lu: Nothing to Disclose, Todd Correll: Nothing to Disclose, Tarik Asselah: Nothing to Disclose

1376 | THE IMPACT OF STEATOTIC LIVER DISEASE ON HBV INTEGRATION IN PATIENTS WITH CHRONIC HEPATITIS B VIRUS INFECTION

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Background: Steatotic liver disease (SLD) was associated with an increased risk of HCC among patients with chronic hepatitis B virus infection (CHB) but with a higher chance of achieving an HBsAg loss. The role of HBV integration in this effect remains unclear. **Methods:** We recruited 52 patients with CHB who underwent liver resection at our hospital, including 15 with SLD and 37 without SLD. Clinical information and liver tissues were collected, and a probe-based capture strategy was employed to analyze HBV integration. **Results:** Among the 52 patients with CHB, 41 had HCC while 11 did not. Tumor tissues were collected from 28 patients, whereas non-tumor tissues were collected from 49 patients. Regarding the non-tumor tissues, the average number of HBV integration sites in patients with SLD was found to be lower at 43.2 (561/13), compared to those without SLD who exhibited an average of 77.5 integration sites (2790/36). Specifically, HBV integration was reduced in both SLD and non-SLD groups with lower levels of HBsAg and cirrhosis subgroups. However, it was more frequently detected in male, younger age, and lower HBV-DNA levels subgroups among patients with SLD; conversely, this trend was opposite for patients without SLD. Notably, for tumor tissues, the average number of HBV integration sites was higher in patients with SLD compared to those without SLD (66.6 [533/8] vs. 37.9 [758/20]). A similar trend of HBV integration was also observed when subgroup analysis was performed on tumor tissues. Furthermore, the HBV integration sites exhibited a random distribution across the chromosome and were found to be enriched in specific regions of the HBV genome, namely 1822-827nt and 3203-3215nt. In patients with SLD, these integration sites predominantly occurred in intergenic regions (52.7%), followed by introns (43.7%) and exons (3.7%), which was consistent with observations in patients without SLD. Notably, ALB, NONO, DOCK5, USP6NL etc., were identified as specific genes targeted for HBV integration in patients with SLD. **Conclusion:** The occurrence of HBV integration was less frequently observed in non-tumor tissues from patients with SLD, whereas it exhibited a higher frequency in tumor tissues from patients with SLD. Our findings provide novel insights into the intricate relationship between HBV and SLD through the process of HBV integration.

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Disclosures: Zhiwei Chen: Nothing to Disclose, Yan Han: Nothing to Disclose, Na Wu: Nothing to Disclose, Jing Tang: Nothing to Disclose, Peng Hu: Nothing to Disclose, Hong Ren: Nothing to Disclose

1377 | THE RAPID REDUCTION RATE WAS SIGNIFICANTLY LOWER IN GREY ZONE HBEAG-NEGATIVE PATIENTS WHO STARTED ANTIVIRAL THERAPY COMPARED TO THOSE WITH ACTIVE HEPATITIS ◆

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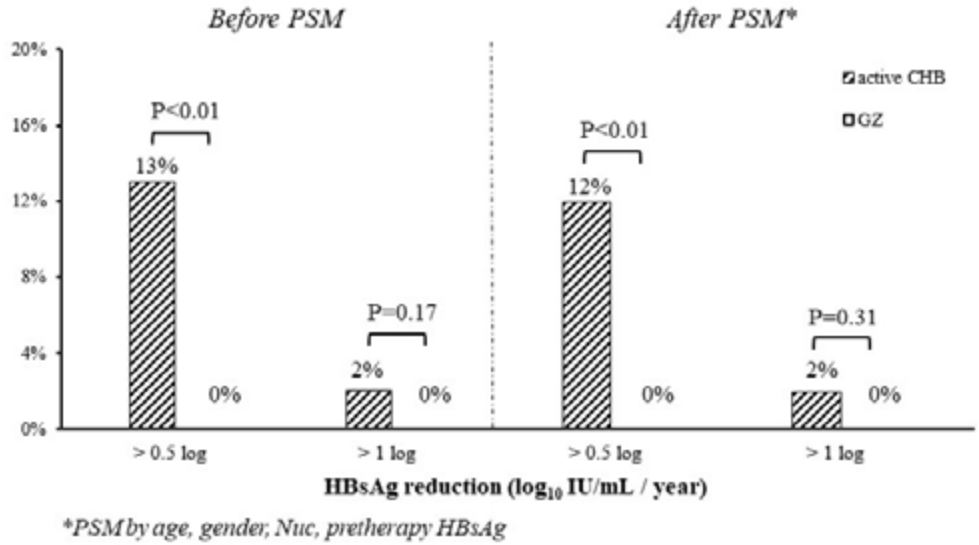
Background: HBsAg seroclearance in active hepatitis B treatment may take >3-4 decades. Little is known about HBsAg kinetics during treatment in grey zone HBeAg-negative patients (GZ), crucial due to longer treatments leading to adherence and follow-up challenges. This study compares on-treatment HBsAg kinetics in GZ HBeAg-negative CHB patients (GZ group) to those with active HBeAg-negative hepatitis (Active CHB group) receiving Nuc treatment. **Methods:** Non-cirrhotic HBeAg-negative CHB patients on Nuc therapy >1 year with consecutive HBsAg assessments were enrolled, excluding those on prophylactic Nuc therapy for cancer or immunosuppressive agents, or with HCV, HDV, or HIV coinfection. The “grey zone” was defined as HBV DNA <2000 IU/mL + ALT >=1 time (x) upper limit of normal (ULN) or HBV DNA >=2000 IU/mL + ALT < 2x ULN. The active CHB group was defined as HBV DNA >=2000 IU/mL + ALT >=2x ULN. Phenotype was based on >=2 consecutive assessment. HBsAg kinetics was calculated as the average reduction per year: (log reduction of last HBsAg level – pretherapy HBsAg level)/(assessment interval in years). Rapid HBsAg decline was defined as a reduction > 0.5 $\log_{10}$ IU/mL per year. A 2:1 Propensity Score Matching (PSM) adjusted age, gender, Nuc types, pretherapy HBsAg level was used for sensitivity analysis. **Results:** Among 1793 HBeAg-negative patients, 115 were in GZ group. The GZ group had lower pretherapy HBV DNA (4.8 vs. 6.3 $\log_{10}$ IU/mL), HBsAg (2.9 vs. 3.1 $\log_{10}$ IU/mL) and ALT levels (44 vs. 177 U/L) compared to the active CHB group (all P <0.01). The proportion treated with high genetic barrier Nucs (ETV or TDF) was comparable. The treatment duration was longer in the active CHB group (median: 3 vs. 2.7 years, P<0.01). The annual HBsAg reduction was less in GZ group then active CHB group (GZ vs. active: median: -0.06 vs. -0.15 $\log_{10}$ IU/mL/year, P<0.01). In the active CHB group, 13% achieved rapid HBsAg reduction while none in GZ group (figure, P<0.01). After PSM, there were 230 in active CHB and 115 in GZ group. Annual HBsAg reduction remained lower in the GZ group (median: -0.06 vs. -0.13 $\log_{10}$ IU/mL/year, P<0.01), with 12% of the active CHB group achieving rapid HBsAg decline compared to none in GZ group (P<0.01). **Conclusion:** The significantly lower HBsAg reduction in the GZ group suggests they need much longer treatment compared to the active CHB group to achieve HBsAg loss. This raises concerns about the potential need for lifelong therapy in GZ HBeAg-negative patients, given the debatable benefits.



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1378 | CCR2 OF CD4+CD8+CXCR5+ T CELL REGULATED IL-21 AND TNF-α SECRETION IN CHB PATIENTS

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Background: Follicular helper T cells (Tfh), which high express C-X-C chemokine receptor type 5 (CXCR5), can assist the function of B cells. There are multiple subtypes of CXCR5+ T cells and they are found to have influence to the progress of HBV. The aim of this study is to find the difference between subtypes of CXCR5+ T cells in CHB patients and investigate their surface protein features and potential role. **Methods:** We collected peripheral blood from CHB patients without antiviral therapy and healthy controls, and performed single-cell RNA sequencing of CXCR5+ T cells. Peripheral blood mononuclear cells (PBMCs) in peripheral blood of 67 CHB patients in 4 different phases and 12 healthy controls were collected and we analyzed the surface protein features of CXCR5+ T cells and HBsAg-special B cells by flow cytometry. We collected CD4+CD8+CXCR5+ T cells from peripheral blood of CHB patients and were treated with or without 200nM CCR2 inhibitor, and assessed IL-21 and TNF-α at 48 hours. **Results:** In the single-cell RNA sequencing, we found a group of CD4+CD8intCXCR5+ T cells. The percentage of CD4+CD8intCXCR5+ T cell in CHB patients was higher than healthy controls (7.64% vs 0.96%). Analyzed by flow cytometry, it was found that the expression of CC chemokine receptor 2 (CCR2) in CD4+CD8+CXCR5+ T cells was significant higher than CD4+CD8-CXCR5+ T cells and CD4-CD8+CXCR5+ T cells, respectively (58.83% vs 26.35%, P<0.001; 58.83% vs 31.00%, P<0.001). Further analysis revealed that CCR2 had a positive correlation with HBsAg+ B cells (P=0.030, r=0.256). For patients in different CHB phases, the patients in immune tolerant phase and inactive HBV carrier state had higher expression of CCR2 than healthy controls respectively (72.18% vs 40.50%, P=0.0125; 65.01% vs 40.50%, P=0.0429). After inhibited CCR2 for 48 hours, the treated group had higher levels of IL-21 (598.6 vs 792.9 pg/ml, P=0.017) and TNF-α (571.4 vs 1676 pg/ml, P=0.04) than control group. **Conclusion:** Our study found that CCR2 was up regulated in CD4+CD8+CXCR5+ T cells of CHB patients and the expression of IL-21 and TNF-α increased significantly after inhibited CCR2. That might provide a new direction of HBV therapy.

Disclosures: Qi Gu: Nothing to Disclose, Shengxia Yin: Nothing to Disclose, Chao Wu: Nothing to Disclose, Jie Li: Nothing to Disclose

1379 | SUPERIOR DIAGNOSTIC EFFICACY OF PRO-C3 AND GP73 COMPARED WITH FIB-4, FAST, AGILE 3+, AND LSM FOR DETECTION OF FIBROSIS IN CHRONIC HEPATITIS B ◆

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Background: Significant liver fibrosis is an indication of antiviral therapy for chronic hepatitis B (CHB). Using liver histology as the gold standard, we evaluated the diagnostic efficacy of N-terminal propeptide of type III collagen (PRO-C3), Golgi protein 73 (GP73) and their combination for liver fibrosis, and compared their performance with fibrosis-4 index (FIB-4), Agile 3+, FibroScan-aspartate aminotransferase (FAST), liver elastography (liver stiffness measurement [LSM]). **Methods:** Treatment-naïve CHB patients with liver biopsies and blood tests on the same day at two centers were enrolled with serum PRO-C3 and GP73 levels assessed using enzyme-linked immunosorbent assay and liver histology using the Scheuer system (S0-S4). **Methods:** Treatment-naïve CHB patients with liver biopsies and blood tests on the same day at two centers were enrolled with serum PRO-C3 and GP73 levels assessed using enzyme-linked immunosorbent assay and liver histology using the Scheuer system (S0-S4). **Results:** 324 patients were enrolled (median age 39, 63.5% male) with 167 (51.5%) with S2-4 (significant fibrosis) and 83 (25.6%) with S3-4 (advanced fibrosis) on liver histology. PRO-C3 level was higher in those with S2-4 [41.64 (22.50, 59.94)] and S3-4 [50.82 (33.88, 66.96)] compared to S0-1 [16.26 (11.38, 42.01)] and S0-2 [19.51 (12.14, 35.70)], respectively (both P<0.001), with similar finding for GP73. On multivariable

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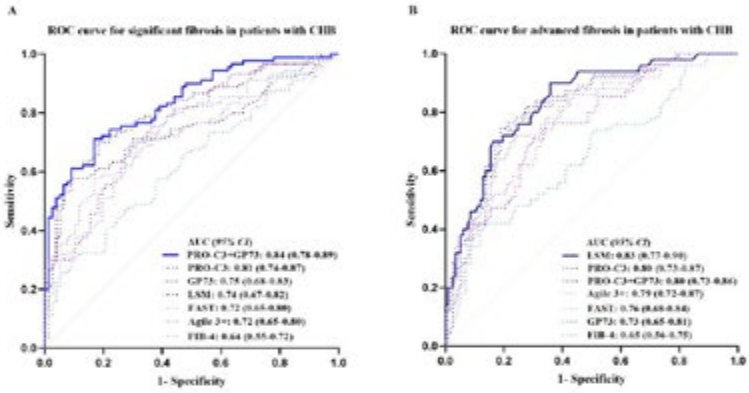
analyses, PRO-C3 and GP73 were independently associated with S2-4 (OR 4.67 95% CI: 2.74-7.96 and OR 2.82 95% CI: 1.64-4.85, respectively) and S3-4 (OR 8.37 95% CI: 4.17-16.78 and OR 3.91 95% CI: 2.04-7.49, respectively). The area under the curves (AUCs) of PRO-C3 for S2-4 and S3-4 fibrosis were 0.81 (0.74-0.86) and 0.80 (0.73-0.86), and that of GP73 was 0.75 (0.68-0.82) and 0.73 (0.66-0.80), respectively. PRO-C3 and GP73 combination had superior performance compared to FIB-4 for S2-4 (AUC=0.84 [0.78-0.89] vs. 0.64 [0.55-0.72]) and S3-4 (AUC=0.80 [0.73-0.86] vs. 0.65 [0.56-0.75]), with similar findings for LSM (AUC=0.74 [0.67-0.82]), FAST (AUC=0.72 [0.65-0.80]), and Agile 3+ (AUC=0.72 [0.65-0.80]) for S2-4. **Conclusion:** PRO-C3, especially in combination with GP73, is an excellent blood-based tool for liver fibrosis detection among CHB patients and is superior to FIB-4, FAST, Agile 3+, and LSM.

Figure 1 Comparison of diagnostic efficacy for identifying fibrosis in CHB patients. Receiver operating characteristic curves for identifying significant fibrosis (S2-4) (A) and advanced fibrosis (S3-4) (B). (C) Delong test for the differences between AUC of the different makers. a, significant fibrosis; b, advanced fibrosis. Logistic regression was performed to calculate predicted values of PRO-C3+GP73. Abbreviation: CHB, chronic hepatitis B; ROC curve, receiver operating characteristic curve; AUC, area under the curve; PRO-C3, N-terminal type III collagen propeptide; GP73, Golgi protein 73; LSM, liver stiffness measurement; FAST, FibroScan-aspartate aminotransferase; FIB-4, fibrosis-4 index.



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Delong test for the comparison of AUCs

	P-value compared to PRO-C3	*P*-value compared to GP73	*P*-value compared to PRO-C3 + GP73	*P*-value compared to LSM	*P*-value compared to FAST	*P*-value compared to Agile 3+	*P*-value compared to FIB-4
PRO-C3	1	0.16[a]	1.00[a]	0.54[a]	0.35[a]	0.88[a]	0.01[a]
GP73	0.28[a]	1	0.16[a]	0.03[a]	0.62[a]	0.23[a]	0.15[a]
PRO-C3 + GP73	0.12[a]	0.02[a]	1	0.54[a]	0.35[a]	0.88[a]	0.01[a]
LSM	0.20[a]	0.84[a]	0.049[a]	1	0.01[a]	0.21[a]	<0.001[a]
FAST	0.60[a]	0.35[a]	0.01[a]	0.54[a]	1	0.42[a]	0.03[a]
Agile 3+	0.12[a]	0.56[a]	0.02[a]	0.55[a]	0.99[a]	1	<0.001[a]
FIB-4	<0.01[a]	0.02[a]	<0.001[a]	0.03[a]	0.05[a]	0.01[a]	1

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1380 | RESULTS FROM A PHASE 2A, OPEN-LABEL STUDY TO EVALUATE THE SAFETY AND EFFICACY OF NOVEL COMBINATION THERAPIES CONTAINING VIR-2218, SELGANTOLIMOD, AND NIVOLUMAB FOR THE TREATMENT OF CHRONIC HEPATITIS B

Grace Wong[1] Seng-Gee Lim[2] Kosh Agarwal[3] Anchalee Avihingsanon[4] Young-Suk Lim[5] Leonard Sowah[6] Ran Duan[6] Irina Botros[6] Savrina Manhas[6] Andre Arizpe[7] Daniel Cloutier[7] Frida Abramov[6] Audrey Lau[6] Tawesak Tanwandee[8] Man-Fung Yuen[9] Edward Gane[10]

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Background: Current approved therapies for chronic hepatitis B (CHB) rarely achieve functional cure. Novel combinations that target hepatitis B virus (HBV) replication and boost the host immune response may offer added benefits. Here, we present **Results:** from a Phase 2a study evaluating the safety and efficacy of VIR-2218, a small interfering RNA, nivolumab (NIVO; an anti–PD-1 mAb), and selgantolimod (SLGN; a TLR8 agonist). **Methods:** This multicenter study (NCT04891770) included patients with virally suppressed (Cohort [C] 1) and viremic (C2) CHB. C1 received VIR-2218 (200 mg SQ, every 4 weeks [Q4W]) for 24 weeks (W) with tenofovir alafenamide administered during study treatment. At W12, SLGN (3 mg oral, QW) and NIVO (0.3 mg/kg IV, Q4W) were added for 24W. C2 patients were randomized 2:1 (stratified by HBsAg level) to receive VIR-2218+SLGN+NIVO ([C2A] per C1 schedule) or SLGN+NIVO for 24W (C2B). The primary efficacy analysis was the proportion of patients achieving functional cure, defined as HBsAg loss and HBV DNA < lower limit of quantitation (LLOQ) at 24W post-treatment (ie, follow-up [FU] W24). Safety, including treatment-emergent adverse events (TEAEs) and laboratory parameters, was assessed throughout the study period. **Results:** In total, 102 patients were enrolled and treated (C1 n = 42, C2A n = 40, C2B n = 20). Overall, the median age was 45 years, 50% were male, 94% were Asian, 61% were HBeAg negative, and most had genotype C (56%). Key efficacy and safety results are summarized in the Table. Only 1 patient (C2A) achieved HBsAg loss and HBV DNA **Conclusion:** Combinations of VIR-2218, NIVO, and SLGN for HBV cure led to low rates of HBsAg loss in this trial. The use of NIVO was associated with the emergence of irAEs in this CHB patient population.

Table. Efficacy and Safety Outcomes by Treatment Cohort

	Cohort 1 (VIR-2218+ SLGN+NIVO+TAF) (n = 42)	Cohort 2A (VIR-2218+ SLGN+NIVO) (n = 40)	Cohort 2B (SLGN+NIVO) (n = 20)
Efficacy Results			
HBsAg loss and HBV DNA <LLOQ at FU W24, n (%)[a]	1 (2)	1 (3)	0 (0)
(95% CI)	(0, 13)	(0, 13)	(0, 17)
HBsAg loss at FU W24, n (%)[a]	2 (5)	1 (3)	0 (0)
(95% CI)	(1, 16)	(0, 13)	(0, 17)
Change from BL in HBsAg, log_{10} IU/mL, mean (SD)			
W12	−1.55 (0.60)	−1.53 (0.55)	−0.18 (0.47)
W24 (EOT for C2B)	−2.01 (0.56)	−1.90 (0.73)	−0.03 (0.36)
W36 (EOT for C1 and C2A)	−1.71 (0.45)	−1.54 (0.69)	-
FU W12	−1.38 (0.51)	−1.21 (0.70)	−0.21 (0.62)
FU W24	−1.16 (0.83)	−0.98 (0.72)	−0.22 (0.63)
HBeAg loss at FU W24, n/N (%)[b]	1/18 (6)	2/16 (13)	0/6 (0)
HBV DNA <LLOQ at FU W24, n (%)[c]	27 (64)	6 (15)	3 (15)
Patients off NUC at FU W24, n (%)[c]	6 (14)	23 (64)	16 (80)
Safety Results			
Any TEAE, n (%)	39 (93)	40 (100)	19 (95)
Grade 3 or 4 TEAE, n (%)	5 (12)	11 (28)	7 (35)
Grade 3 or 4 TEAE related to study drug, n (%)	2 (5)	5 (13)	5 (25)
Serious TEAE, n (%)[d]	2 (5)	5 (13)	3 (15)
Serious TEAE related to study drug, n (%)	0	1 (3)	3 (15)
TEAE leading to study drug discontinuation, n (%)	7 (17)	6 (15)	2 (10)
Death, n (%)	0	0	0
Grade 3 or 4 TE laboratory abnormality, n (%)	9 (21)	18 (45)	11 (55)
TE ALT flare (ALT >2 × BL & ≥5 × ULN)[e]	0	8 (20%)	5 (25%)

[a]The 2 patients in C1 who achieved HBsAg loss had HBsAg <1.5 log_{10} IU/mL and did not meet study HBsAg inclusion criteria, but were included via protocol deviation. No patient had anti-HBs seroconversion.
[b]Two patients in C2A achieved HBeAg seroconversion.
[c]Some C1 patients stopped TAF at the end of study treatment at the investigator's discretion after meeting prespecified criteria. Some C2 patients initiated NUCs for safety reasons.
[d]ALT increased (n = 2, one of which was related to study treatment), malaise (related), immune-mediated hepatitis (related), type 1 diabetes mellitus (related), COVID-19, dehydration, upper limb fracture, adenomyosis, and chronic hepatitis B (1 each).
[e]Central lab ULN (34 U/L for female and 43 U/L for male); ALT flare was defined as elevated ALT at 2 consecutive visits.
ALT, alanine aminotransferase; BL, baseline; C1, cohort 1; C2A, cohort 2A; C2B, cohort 2B; EOT, end of treatment; FU, follow-up; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; LLOQ, lower limit of quantitation; NIVO, nivolumab; NUC, nucleos(t)ide analogue; SLGN, selgantolimod; TAF, tenofovir alafenamide; TE, treatment-emergent; TEAE, treatment-emergent adverse event; ULN, upper limit of normal; W, week.

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Disclosures: Grace Wong: AstraZeneca: Advisor, Gilead Sciences: Advisor, Gilead Sciences: Speaking and Teaching, Janssen: Advisor, GSK: Advisor, GSK: Speaking and Teaching, Abbott: Speaking and Teaching, AbbVie: Speaking and Teaching, AstraZeneca, Gilead Sciences, GlaxoSmithKline and Janssen,: Advisor, Abbott, AbbVie, Ascletis, Bristol-Myers Squibb, Echosens, Gi: Speaking and Teaching, Gilead Sciences: Grant/Research Support, AstraZeneca, Gilead Sciences, GlaxoSmithKline and Janssen: Consultant, Abbott, AbbVie, Ascletis, Bristol-Myers Squibb, Echosens, Gi: Speaking and Teaching, AstraZeneca, Gilead Sciences, GlaxoSmithKline Pharmaceutical: Consultant, Gilead Sciences: Independent Contractor, AstraZeneca, Gilead Sciences, GSK and Janssen,: Advisor, Abbott, AbbVie, BMS, Gilead Sciences, GSK, Janssen, Roche: Speaking and Teaching, Gilead Sciences: Grant/Research Support, Seng-Gee Lim: Nothing to Disclose, Kosh Agarwal: Nothing to Disclose, Anchalee Avihingsanon: Gilead Science, ViiV/GSK, Roche, MSD,: Grant/Research Support, Gilead Science: travel support to present abstract, Young-Suk Lim: Nothing to Disclose, Leonard Sowah: Nothing to Disclose, Ran Duan: Gilead Sciences, Inc: Employee, Irina Botros: Nothing to Disclose, Savrina Manhas: Gilead Sciences: Employee, Andre Arizpe: Vir Biotechnology: Employee, Vir Biotechnology: Stock - publicly traded company, Daniel Cloutier: Nothing to Disclose, Frida Abramov: Gilead Sciences, Inc: Employee, Gilead Sciences, Inc: Stock - publicly traded company, Audrey Lau: Nothing to Disclose, Tawesak Tanwandee: Roche: Grant/Research Support, MSD: Grant/Research Support, Altimune: Grant/Research Support, Gilead: Grant/Research Support, Vir Biotech: Grant/Research Support, Man-Fung Yuen: Speaking and Teaching relationship with Fujirebio Incorporation, Gilead Sciences, Roche, Sysmex Corp; Has not ended; Consultant relationship with Clear B Therapeutics, Dicerna Pharmaceuticals; Has not ended; Consultant relationship with AbbVie, Abbott Diagnotics, Aligos Therapeutics; Has not ended; Consultant relationship with Arbutus Biopharma, Arrowhead Pharmaceuticals, Assembly Biosc; Has not ended; Consultant relationship with Immunocore, Janssen, Precision BioSciences; Has not ended; Consultant relationship with Fujirebio Incorporation, GlaxoSmithKline, Gilead Sciences; Has not ended; Grant/Research Support relationship with Fujirebio Incorporation, Gilead Sciences, Immunocore; Has not ended; Grant/Research Support relationship with AbbVie, Assembly Biosciences, Arrowhead Pharmaceuticals; Has not ended; Consultant relationship with Vir Biotechnology and Visirna Therapeutics; Has not ended; Consultant relationship with Roche, Sysmex Corporation, Tune Therapeutics; Has not ended; Grant/Research Support relationship with Sysmex Corporation and Roche; Has not ended, Edward Gane: Aligos Therapeutics: Advisor, Assembly Biosciences: Advisor, AbbVie: Speaking and Teaching, Intellia Therapeutics: Advisor, Tune Therapeutics: Consultant, Precision Bio: Advisor, Virion Therapeutics: Advisor, Gilead Sciences: Advisor, GSK: Advisor

1381 | LEVERAGING *IN SILICO* CLINICAL TRIALS OF THE EVEREST STUDY TO OBTAIN MECHANISTIC INSIGHTS INTO DETERMINANTS OF FUNCTIONAL CURE WITH STANDARD-OF-CARE THERAPIES IN CHRONICALLY INFECTED HEPATITIS B PATIENTS

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Background: The therapeutic goal with chronically infected patients with Hepatitis B virus (HBV) is functional cure (FC), defined as undetectable serum virological biomarkers (HBV DNA and HBsAg) at 6 months after stopping all treatment. The Everest clinical trial (NCT04035837) aims to evaluate HBsAg loss (a surrogate for FC) with add-on or switch-to interferon (IFN) therapy in previously nucleot(s)ide analogue (NA)-treated patients and raises many questions: (i) How much additional FC does switch-to or add-on IFN yield in NA-suppressed patients? (ii) Does the duration of IFN treatment impact FC? (iii) Why do patients with lower baseline HBsAg exhibit higher FC? Virtual (*in silico*) clinical trial simulations using Quantitative Systems Pharmacology (QSP) models of HBV disease progression are a powerful tool to address these questions, and we develop and leverage an HBV-QSP model to yield mechanistic insights. **Methods:** We develop a QSP HBV model to capture observations from the Everest trial. The model is calibrated using individual-level data from both untreated patients and those treated with NA/IFN. A cohort with ~100,000 virtual patients mirroring baseline characteristics of patients in the Everest study is used for *in silico* clinical trials similar to the Everest treatment protocols. Correlations between FC and biomarkers such as HBsAg before, during, and after IFN treatment are evaluated, and differences in mechanistic pathways between responders vs non-responders assessed via statistical and global sensitivity analysis to gain insights into optimizing FC. **Results:** Retrospectively simulated *in silico* trials of the Everest study show agreement with the reported clinical endpoints. Prospective QSP *in silico* clinical trials with 24-96 weeks of IFN treatment show marginal differences in FC rates, but increased FC compared to NA monotherapy which is attributed to pleitropic

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(antiviral + immunomodulatory) pharmacodynamic effects of IFN. *In silico* trials also quantify the correlation between the surrogate clinical endpoint – HBsAg loss at the end of treatment – with FC, as a function of baseline HBsAg. Responder vs. non-responder stratification identifies mechanistic drug/dose-regimen and host/virus-related effects that could underly differential FC rates observed in patients with low and high baseline HBsAg. **Conclusion:** *In silico* trials of the Everest study highlight the interplay between host-virus dynamics and treatment parameters influencing FC with NA and/or Peg-IFN therapies, and make testable predictions for how IFN dosing regimens influence FC thus opening avenues for optimizing of standard-of-care therapies.

Disclosures: Rajat Desikan: GSK: Employee, Javiera Cortés-Ríos: Nothing to Disclose, Nathan Hanan: Nothing to Disclose, Anna Sher: Nothing to Disclose, Ahmed Nader: Nothing to Disclose, Mindy Magee: Nothing to Disclose, William Jusko: Nothing to Disclose

1382 | RISKS OF DISCONTINUATION AND BENEFITS OF CONTINUATION OF TDF AFTER INTERRUPTION OF MOTHER-TO-CHILD TRANSMISSION IN IMMUNOTOLERANT PREGNANT WOMEN

Huan Liang[1] *Bobin Hu*[1] *Hang Wang*[1] *Hengkai Liang*[1] *Rongming Wang*[1] *Lu Wei*[1] *Tumei Su*[1] *Qingmei Li*[1] *Qianbin Yin*[1] *Yanfei Feng*[1] *Minghua Su*[1] *Jianning Jiang*[1]

[1]*The First Affiliated Hospital of Guangxi Medical University*

Background: It is still controversial whether to stop TDF mother-to-child blocking therapy in immune-tolerant pregnant women after delivery. This study aims at investigate the risks of stopping TDF mother-to-child blocking therapy in immune-tolerant pregnant women after delivery and the benefits of continuing TDF treatment until 48 weeks after delivery. **Methods:** This study belongs to the retrospective study, the research object from January 2012 to December 2023, establishes the real world of maternal and child block queue, all criteria according to the included 275 cases of early pregnancy using TDF antiviral cure of chronic HBV infection in pregnant women, including 118 patients using TDF to block immune tolerance phase of pregnant women, the control group was 157 cases of TDF of Chronic Hepatitis B viral hepatitis(CHB) treated first pregnant women, compared two groups of rebound in the postpartum withdrawal of virology and biochemistry bounce rate, time and level, the efficacy of antiviral therapy, changes in renal eGFR and serum phosphorus levels, and virological breakthrough rate were analyzed. **Results:** 1.Among 275 pregnant women with chronic HBV infection who were initially treated with TDF, the median course of antiviral therapy before labor was 16.50 (14.00-39.00) weeks, and 76% of pregnant women achieved low viral load (HBV DNA ≤2×105IU/ml) before labor. The success rate of preventing mother-to-child transmission was 100%. 2. 25.4% (70/275) at the beginning of TDF cure of chronic HBV infection in maternal postpartum withdrawal followed up to 48 weeks, cumulative virology bounce rate is higher than biochemistry recovery rate (P < 0.05), immune tolerance with CHB pregnant women pregnant women stops drug withdrawal, withdrawal and postpartum postpartum 4 ~ 12 weeks immediately stop drug, age and whether the risk of drug withdrawal rather less than 30 years old. 3.A total of 69 immunotolerant parturient women continued TDF therapy until 48 weeks after delivery, 100% (69/69) of the parturient women's HBVDNA level could be reduced to low viral load level, and 88.41% (61/69) of them achieved virological response(HBV DNA≤500IU/ml).The virological response rate and HBeAg seroconversion rate at 48 weeks postpartum was significantly higher than those before labor(*P* **Conclusion:** There is a high risk of rebound when TDF is stopped after delivery in pregnant women with immune tolerance. It is effective and safe to continue TDF treatment for 48 weeks after delivery.

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Figure 1 Research Roadmap

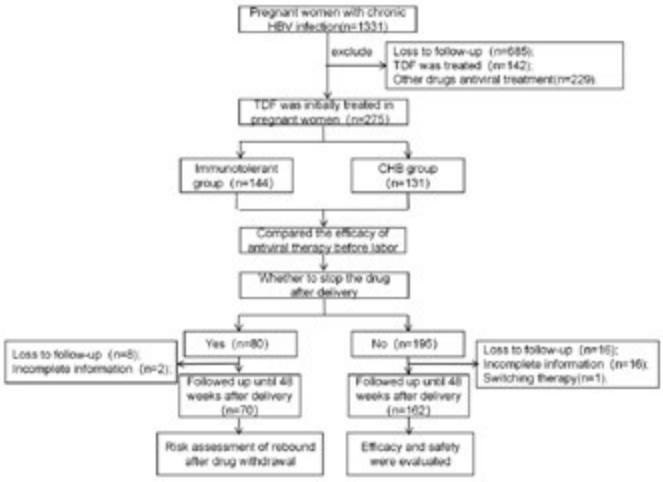
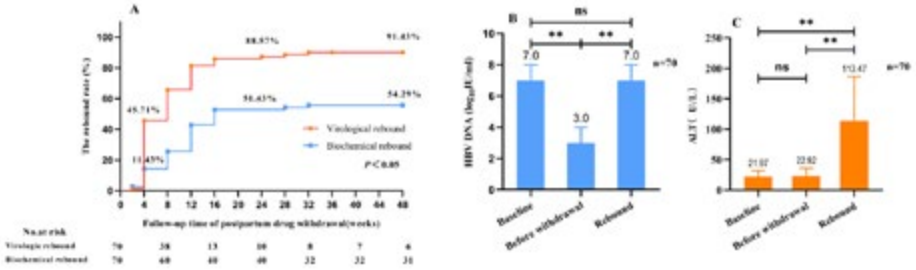


Figure 2 Risk of rebound from TDF withdrawal to 48 weeks postpartum in women with chronic HBV infection

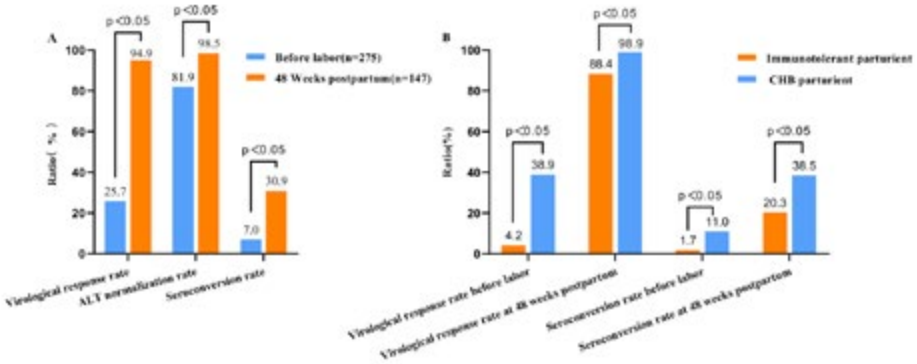


A:Cumulative virological and biochemical rebound rate of 70 parturients after withdrawal of TDF;

B:Comparison of the level of virological rebound after discontinuation of TDF in 70 pregnant women;

C:Comparison of the level of biochemical rebound after discontinuation of TDF in 70 pregnant women

Figure 2 Evaluation of therapeutic effect of TDF in the initial treatment of pregnant women with chronic HBV infection.



Disclosures: Huan Liang: Nothing to Disclose, Bobin Hu: Nothing to Disclose, Hang Wang: Nothing to Disclose, Hengkai Liang: Nothing to Disclose, Rongming Wang: Nothing to Disclose, Lu Wei: Nothing to Disclose, Tumei Su: Nothing to Disclose, Qingmei Li: Nothing to Disclose, Qianbin Yin: Nothing to Disclose, Yanfei Feng: Nothing to Disclose, Minghua Su: Nothing to Disclose, Jianning Jiang: Nothing to Disclose

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1383 | SOLUBLE IMMUNE BIOMARKER PROFILING OF CHRONIC HEPATITIS B SUBJECTS TREATED WITH IMDUSIRAN IN COMBINATION WITH PEGYLATED INTERFERON ALFA REVEALS PHASES OF IMMUNE ACTIVATION

Christine Espiritu[1] Sharie Ganchua[1] Timothy Eley[1] Kevin Gray[1] Man-Fung Yuen[2] Jeong Heo[3] Ronald Nahass[4] Grace Wong[5] Tatiana Burda[6] Kalyan Ram Bhamidimarri[7] Tsung-Hui Hu[8] Tuan T Nguyen[9] Young-Suk Lim[10] Chi-Yi Chen[11] Stuart Gordon[12] Jacinta Holmes[13] Wan Long Chuang[14] Anita Kohli[15] Naim Alkhouri[15] Angela Lam[1] Michael Sofia[1] Karen Sims[1] Emily Thi[1]

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Background: Functional cure of chronic hepatitis B (CHB) requires suppression of viral replication, reduction of HBV antigens and induction of anti-HBV immune response. Pegylated interferon alfa-2a (IFN) is a standard of care immunomodulator with limited efficacy against HBV. Imdusiran (AB-729, IDR) is an *N*-Acetylgalactosamine-conjugated single trigger siRNA targeting all HBV RNA transcripts, resulting in suppression of all viral antigens including HBsAg. In an ongoing Phase 2a study assessing IDR as lead-in (24 weeks) followed by 12 or 24 weeks of IFN ± additional IDR doses in HBeAg-negative CHB subjects virally suppressed on nucleos(t)ide analog (NA) therapy (AB-729-201, IM-PROVE I), soluble immune biomarkers were profiled and association with HBsAg response assessed. **Methods:** Longitudinal plasma samples were collected from 43 subjects during the 24-week IDR lead-in, IFN treatment and follow-up periods. Soluble immune biomarkers were assessed using Luminex multiplex panels (58 analytes). **Results:** Transient increases ≥3 to 31-fold from baseline in immune biomarkers associated with immune activation (sCD40, sCD28, sCD80, sCD86), Th1 cell-mediated response (IL-6, IL-12 p40, IL-12 p70, IL-7, IL-10), inflammation regulation (GROa, PDGF-AA, PDGF-AB, VEGF), and immune checkpoint proteins (PD-1, PD-L1, CTLA-4, LAG-3, BTLA) were observed during IDR lead-in, with peaks occurring during the plateau of HBsAg reduction in assessed subjects to date. Elevations occurred again during IFN treatment, during which time increase in the Th2 cytokine IL-5 was also observed. At 24 weeks post IFN treatment, 6 subjects achieved HBsAg loss and HBsAg seroconversion. 5/6 subjects with HBsAg loss had greater Th1/inflammation-related responses during IDR lead-in or IFN treatment compared to those without HBsAg loss. Further increases in Th2 cytokines IL-4 and IL-13 after end of IFN treatment were associated with HBsAg seroconversion. **Conclusion:** IDR treatment in combination with IFN was associated with distinct phases of soluble immune biomarker signatures. Immune biomarkers associated with Th1 immune activation and regulation of inflammation were observed in subjects during IDR lead-in, coinciding with the establishment of a plateau in HBsAg reduction. Secondary transient elevations of these immune biomarkers were observed to occur during IFN treatment and were followed by appearance of Th2 immune biomarker signatures that were associated with HBsAg seroconversion.

Disclosures: Christine Espiritu: Arbutus Biopharma Corp: Employee, Sharie Ganchua: Arbutus Biopharma Inc.: Employee, Timothy Eley: Arbutus Biopharma: Employee, Arbutus Biopharma: Stock - publicly traded company, Kevin Gray: Nothing to Disclose, Man-Fung Yuen: Speaking and Teaching relationship with Fujirebio Incorporation, Gilead Sciences, Roche, Sysmex Corp; Has not ended; Consultant relationship with Clear B Therapeutics, Dicerna Pharmaceuticals; Has not ended; Consultant relationship with AbbVie, Abbott Diagnotics, Aligos Therapeutics; Has not ended; Consultant relationship with Arbutus Biopharma, Arrowhead Pharmaceuticals, Assembly Biosc; Has not ended; Consultant relationship with Immunocore, Janssen, Precision BioSciences; Has not ended; Consultant relationship with Fujirebio Incorporation, GlaxoSmithKline, Gilead Sciences; Has not ended; Grant/Research Support relationship with Fujirebio Incorporation, Gilead Sciences, Immunocore; Has not ended; Grant/Research Support relationship with AbbVie, Assembly Biosciences, Arrowhead Pharmaceuticals; Has not ended; Consultant relationship with Vir Biotechnology and Visirna Therapeutics; Has not ended; Consultant relationship with Roche, Sysmex Corporation, Tune Therapeutics; Has not ended; Grant/Research Support relationship with Sysmex Corporation and Roche; Has not ended,

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1384 | THE IMPACT OF CONCURRENT CHRONIC HEPATITIS B INFECTION ON THE DIAGNOSTIC ACCURACY OF FIB-4 IN INDIVIDUALS WITH METABOLIC-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD)

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Background: A main difference between the definition of (NAFLD) and metabolic-associated steatotic liver disease (MASLD) is the inclusion of chronic hepatitis B (CHB). While recent studies did not show a significant difference between NAFLD and MASLD, these studies were limited by not including individuals with CHB. Given the escalating prevalence of concurrent CHB and MASLD globally, we aimed to compare the accuracy of the FIB-4 index in diagnosing fibrosis in individuals with MASLD, with and without CHB. **Methods:** A multicenter cohort study was conducted, including patients with biopsy-proven CHB, MASLD, and MASLD combined with CHB from 11 medical centers. MASLD was defined as biopsy-proven hepatic steatosis in combination with any cardiometabolic risk factors (CMRFs). Propensity score matching based on age, sex, and the 5 CMRFs was performed to ensure comparability between the MASLD-only and MASLD+CHB groups. For the comparison

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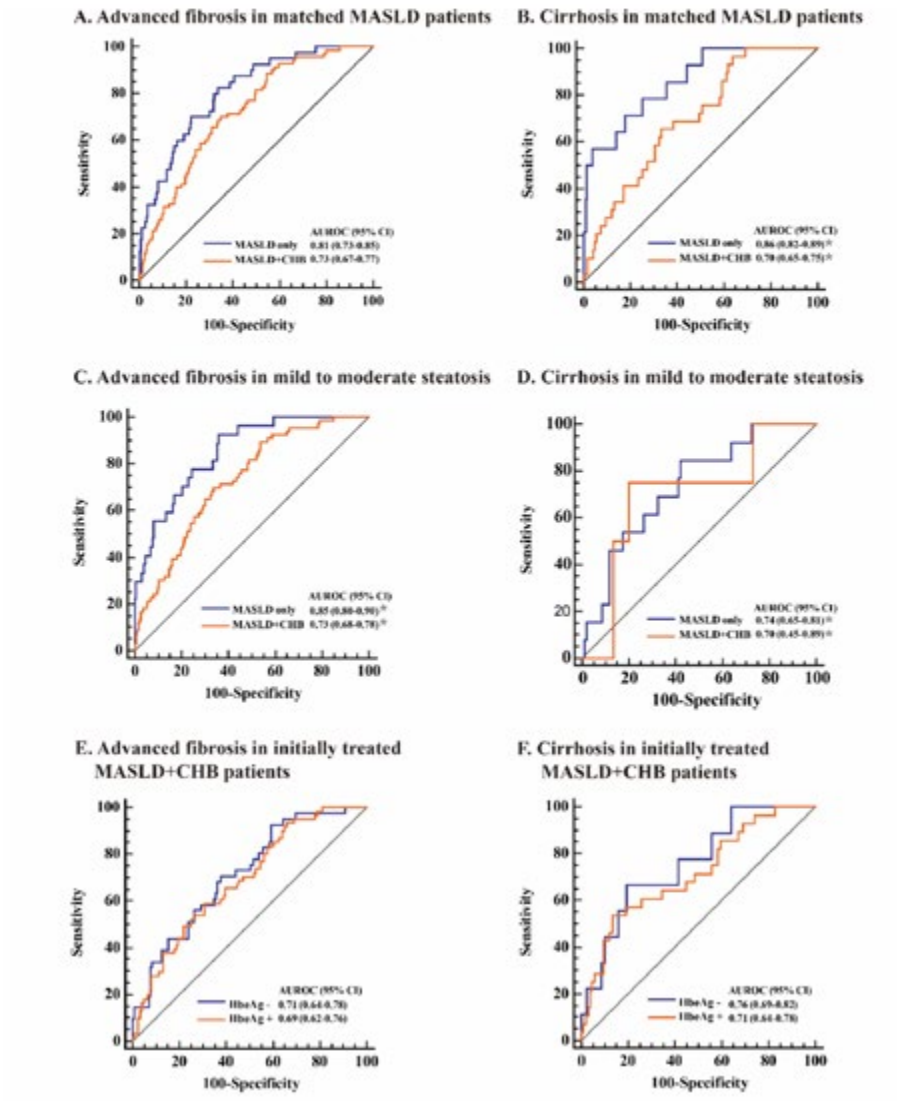
between CHB-only and CHB+MASLD groups, matching variables included age, gender, and CHB-related markers. The diagnostic accuracy of the FIB-4 index was assessed using the AUROC, with the DeLong test employed for comparing AUROCs. **Results:** Of 1609 MASLD cases, 536 were MASLD-only and 1073 MASLD+CHB. Among the 1770 CHB cases, 708 were CHB-only. After matching, the AUROCs of FIB-4 for diagnosing advanced fibrosis (0.73, 95%CI 0.67-0.77) and cirrhosis (0.70, 95%CI 0.65-0.75) in MASLD+CHB patients were significantly lower than in MASLD-only patients (advanced fibrosis: 0.81 95%CI 0.76-0.85, *P*=0.068; cirrhosis: 0.86, 95%CI 0.82-0.89, *P*=0.017). In patients with mild to moderate steatosis, the AUROCs of FIB-4 for diagnosing advanced fibrosis (0.73, 95%CI 0.68-0.78) and cirrhosis (0.71, 95%CI 0.66-0.76) in MASLD+CHB patients were significantly lower than those in MASLD-only patients (advanced fibrosis: 0.85, 95%CI 0.80-0.90; cirrhosis: 0.88, 95%CI 0.83-0.92) (all *P*<0.05). To investigate the reasons for the decreased performance of the FIB-4 index in MASLD+CHB patients, our further analysis revealed that the FIB-4 index had a higher AUROC for diagnosing fibrosis in HBeAg-negative individuals compared to HBeAg-positive patients (all *P*>0.05). However, the DeLong test did not show a significant difference due to the limited sample size. **Conclusion:** The presence of CHB is associated with a reduced diagnostic performance of the FIB-4 index in patients with MASLD. More reliable diagnostic tools for fibrosis are needed in patients with concurrent MASLD and CHB.

Figure. The diagnostic efficacy of FIB-4 in identifying significant fibrosis, advanced fibrosis, and cirrhosis in populations with MASLD only and CHB+MASLD.
***: DeLong test determined that there is a significant difference in AUROC between the two groups.**



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1385 | CHARACTERIZATION OF HDV RNA AND HBSAG DURING PEGYLATED INTERFERON-ALPHA AND RITONAVIR-BOOSTED LONAFARNIB COMBINATION THERAPY: THE D-LIVR STUDY

Leeor Hershkovich[1] Harel Dahari[1] Scott Cotler[2] Theo Heller[3] Christopher Koh[3] Jeffrey Glenn[4] Tarik Asselah[5] Saeed Hamid[6] Ohad Etzion[7]

[1]Loyola University Chicago, [2]Loyola University Health System, [3]Liver Disease Branch, NIDDK, NIH, [4]Stanford School of Medicine, [5]Hôpital Beaujon, [6]Aga Khan University, [7]Soroka University Medical Center

Background: Understanding of the kinetic profiles of hepatitis D virus (HDV) and hepatitis B surface antigen (HBsAg) during pegylated-interferon-α-2a (pegIFN) and ritonavir-boosted lonafarnib (LNF) therapy is lacking. We analyzed data from the Phase 3 D-LIVR study to characterize HDV and HBsAg kinetics in patients treated with pegIFN and LNF. **Methods:** 125 participants in the D-LIVR study (NCT03719313) were treated with pegIFN and LNF for 48 weeks. HDV RNA was measured by Quest laboratories (lower limit of quantification, LLoQ <40 IU/mL; target not detected, TND <4 IU/mL) and HBsAg by Abbott Diagnostics at baseline, Weeks 1, 2, and 4 of therapy, and then every 4 weeks until end of therapy (EOT) and at 24 weeks of follow up (EOFU). We defined monophasic (MP) pattern as a single HDV decline, biphasic (BP) pattern as an initial rapid decline followed by a slower decline, and triphasic (TP) pattern as two decline phases separated by an intermediary plateau. MP, BP, or TP patterns that were followed by a plateau (≥LLoQ) were termed flat partial response (FPR), biphasic FPR (BFPR), and staircase, respectively. A ≥2-fold change in slope was used to distinguish between decline phases. **Results:** 37 of 125 patients were excluded from analysis: 22 discontinued therapy, 10 had poor adherence or dose reductions, and 5 were non-responders (<1.6 log decline from baseline). For the remaining 88, we identified 6 HDV RNA decline kinetic patterns. Three patterns, MP(n=10), BP(n=7), and TP(n=11) were associated with reaching TND. FPR(n=14), BFPR (n=19), and staircase(n=27) plateaued above TND. 47 (53%) patients had HDV rebound (>1.5 log IU/mL increase from nadir) after MP (n=2/10), BP (n=2/7), TP (n=2/11), FPR (n=9/14), BFPR(n=14/19), and staircase (n=18/27), 18±9 weeks into therapy. The prevalence of HDV rebounds was significantly (p=0.004) higher in FPR, BFPR, and staircase patterns compared to MP, BP, and TP. While HBsAg remained at baseline levels for most patients, 3 patients experienced a >1.5 log decline from baseline, all of whom achieved sustained HDV TND at EOFU. 17 patients had HDV TND at EOT. In total, 12 participants achieved HDV TND at EOFU, of whom 10 were TND at EOT. HDV TND at EOT had a positive predictive value of 59% and a negative predictive value (NPV) of 97% for TND at EOFU. **Conclusion:** The MP, BP, and TP kinetic profiles were associated with reaching on treatment HDV TND. Not reaching HDV TND at EOT had a 97% NPV for sustained HDV TND. Lastly, a >1.5 log decline in HBsAg was associated with sustained HDV TND.

Disclosures: Leeor Hershkovich: Nothing to Disclose, Harel Dahari: Nothing to Disclose, Scott Cotler: Nothing to Disclose, Theo Heller: Nothing to Disclose, Christopher Koh: Nothing to Disclose, Jeffrey Glenn: Nothing to Disclose, Tarik Asselah: Nothing to Disclose, Saeed Hamid: Nothing to Disclose, Ohad Etzion: Nothing to Disclose

1386 | HIGHER SUSTAINED RESPONSE RATE AND PARTIAL CURE IN NUC EXPERIENCED PEGYLATED INTERFERON-TREATED PATIENTS COMPARED TO NUC NAIVE PEGYLATED INTERFERON MONOTHERAPY PATIENTS

Rachel Wen-Juei Jeng[1] Yu-Ting Kao[2] Yen-Chun Liu[2] Rong-Nan Chien[2]

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Background: Our previous study showed that patients with off-Nuc clinical relapse (CR) retreated with pegylated interferon (Peg-IFN) also had a higher functional cure rate than NUC-naïve Peg-IFN patients (10-year: 49.2% vs. 0.1%). It is unclear if this is due to off-Peg-IFN or off NUC following Peg-IFN sustained response prior to HBsAg

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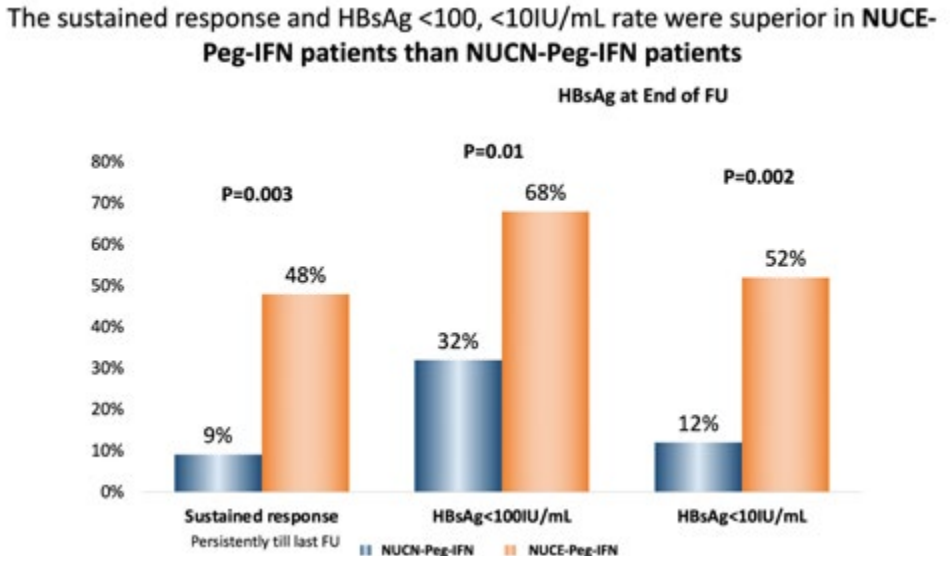
loss. This study aims to clarify this by comparing propensity score-matched finite NUC experienced off-Peg-IFN patients (NUCE-Peg-IFN) to NUC-naive off-Peg-IFN patients (NUCN-Peg-IFN). **Methods:** From the CGMH off-Nuc cohort, 25 HBeAg-negative CHB patients with CR retreated with Peg-IFN were included (NUCE-Peg-IFN). Only HBeAg-negative CHB patients treated with Peg-IFN monotherapy for 48-52 weeks were included in the NUCN Peg-IFN arm. Propensity score matching (PSM) based on age, gender, ALT, HBV DNA, and HBsAg levels at the start of Peg-IFN treatment was performed at a 1:1 ratio. Events after 1 year of Peg-IFN treatment were compared. Sustained response was defined as normal ALT levels (<36 U/L) after stopping Peg-IFN until the end of follow-up. Partial cure was defined as normal ALT levels with HBsAg levels < 100 IU/mL. Chi-square or Fisher's exact test compared categorical outcomes. A two-tailed P < 0.05 was considered statistically significant. **Results:** After PSM, each group had 25 patients. Baseline characteristics were comparable: mean age (49.8 vs. 49.9 years, P=0.97), median ALT (156 vs. 130 U/L, P=0.14), HBV DNA (5.68 vs. 5.3 $\log_{10}$IU/mL, P=0.13), and HBsAg levels (2.78 vs. 3.1 $\log_{10}$IU/mL, P=0.13). Follow-up duration was longer in the NUCN-Peg-IFN group (130 vs. 82 months, P<0.001). HBsAg reduction was greater in the NUCE-Peg-IFN group (median: -1.14 vs. -0.13 $\log_{10}$IU/mL, P<0.001), resulting in lower end-of-treatment HBsAg levels (1.58 vs. 2.72 $\log_{10}$IU/mL, P<0.001). Sustained response rates were higher in the NUCE -Peg-IFN group (48% vs. 8%, P=0.003). More NUCN-Peg-IFN patients required retreatment (72% vs. 40%, P=0.02). By the end of follow-up, 68% and 52% of the NUCE-Peg-IFN group achieved HBsAg <100 IU/mL (Partial cure) and <10 IU/mL, respectively, versus 32% and 12% in the NUCN-Peg-IFN group (P=0.001 and 0.002). Among 12 patients with HBsAg loss, 83.3% did not experience clinical relapse before HBsAg loss. **Conclusion:** The higher sustained response, partial cure, and functional cure rates in NUCE-Peg-IFN patients compared to NUCN-Peg-IFN patients suggest that previous finite NUC therapy significantly influences the host immune response rather than Peg-IFN itself.



Disclosures: Rachel Wen-Juei Jeng: Nothing to Disclose, Yu-Ting Kao: Nothing to Disclose, Yen-Chun Liu: Nothing to Disclose, Rong-Nan Chien: Nothing to Disclose

1387 | EVALUATION OF HEPATITIS B VACCINATION UPTAKE AND AWARENESS OF LIVER CANCER RISK FACTORS AMONG STATE FAIR-GOERS IN MINNESOTA: A CROSS-SECTIONAL STUDY

Amir Sultan Seid[1] *Erin Mann*[1] *Jose Debes*[1]

[1]*University of Minnesota*

Background: Hepatitis B virus (HBV) vaccination is crucial for preventing HBV infection and its sequelae, including hepatocellular carcinoma (HCC). This study aimed to investigate the differences in HBV vaccination status and uptake among adults in Minnesota and identify associated demographic factors and knowledge of HCC risk factors. **Methods:** A cross-sectional structured survey was conducted among 481 adults (61.5% female, 83.0% White) attending the 2023 Minnesota State Fair. This is the largest in the state attended by comers

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from all backgrounds and ages. Participants were categorized as younger (age <40, 48.4%) or older (age ≥40, 51.6%) adults. Vaccination status, demographic factors, and knowledge of HCC risk factors were assessed. Knowledge scores were categorized as low (0-2 correct) or high (3-4 correct). Chi-square tests were used to compare vaccination status and uptake between age groups and evaluate associations with demographics and HCC knowledge. **Results:** Among the participants, 55.7% reported being vaccinated against HBV, while 44.3% were unvaccinated or unsure. Vaccination rates were significantly higher in younger adults compared to older adults (64.4% vs. 52.0%, p=0.006). However, older adults had significantly higher knowledge of risk factors for HCC than younger adults (46.8% vs. 37.3%, p=0.036). U.S.-born participants had lower reported vaccination rates than foreign-born participants (57.2% vs. 89.2%, p=0.012). Participants with higher knowledge of HCC risk factors were more likely to know the availability of a vaccine against HBV (89.2% vs. 78.4%, p=0.002 and more likely to be vaccinated (63.5% vs. 53.8%, p=0.035). No difference in knowledge of risk factor rates was found based on gender, race, or metropolitan status. Significant factors reported as reasons for non-vaccination among older adults (compared to younger adults) included lack of recommendation by healthcare providers (27.7% vs. 4.8%, p<0.001), lack of belief about being at risk for HBV (14.3% vs. 3.6%, p=0.01), and lack of awareness of the presence of a vaccine (16.0% vs. 4.8%, p=0.01). **Conclusion:** Discussion: This study reveals disparities in HBV vaccination rates and knowledge of HCC risk factors between younger and older adults in Minnesota. Despite higher knowledge among older adults, vaccination rates were lower, highlighting the need for targeted interventions. Healthcare providers play a crucial role in recommending HBV vaccination, particularly for older adults, as lack of provider recommendation was reported as a major reason for non-vaccination.

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1388 | EFFECTIVENESS AND SAFETY OF 48-WEEK TENOFOVIR AMIBUFENAMIDE VS TENOFOVIR ALAFENAMIDE FUMARATE FOR PATIENTS WITH CHRONIC HEPATITIS B: A RETROSPECTIVE REAL-WORLD STUDY

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Background: Few comparison data are existed on the effectiveness and safety of tenofovir amibufenamide (TMF) vs tenofovir alafenamide fumarate (TAF) for patients with chronic hepatitis B (CHB) in real-world settings. The aim of this study was to evaluate the 48-week real-life effectiveness and safety profiles of TMF vs TAF for patients with CHB. **Methods:** This retrospective single-arm study recruited treatment-naive CHB patients who undergone TMF or TAF therapy at 25 mg daily at The First Affiliated Hospital of Zhengzhou University, China, from January 2021 to May 2024. The primary effectiveness outcome was HBV DNA undetectable (less than 20 IU/mL) rate at week 48. The key secondary outcomes were ALT normalization rate, hepatitis B e antigen (HBeAg) seroconversion rate, renal function, renal tubular function parameters, and lipid dynamic levels at week 48. **Results:** A total of 130 CHB patients were enrolled, thereinto, 72 and 58 patients were treated with TMF and TAF, respectively (Table 1). The baseline HBV DNA levels in the TMF and TAF groups were 4.8 ± 2.69 vs 4.5 ± 2.74 $\log_{10}$ IU/mL (p=0.521). At 48 weeks of treatment, the HBV DNA undetectable rates were 81.9% (59/72) vs 84.5% (49/58) (p=0.701) in TMF and TAF groups. ALT normalization rates were 83.8% (31/37) vs 75.0% (15/20) (p=0.423), and the HBeAg seroconversion rates were 22.0% (9/41) vs 15.6% (5/32) (p=0.496) in TMF and TAF groups, respectively. In terms of safety, no severe adverse events were occurred and no one discontinued therapy due to adverse events during treatment. Furthermore, there were no significant differences in renal function and renal tubular function parameters between two groups at 48 weeks of treatment (all p>0.05); and there were no significant differences were observed in lipid profile parameters between two groups at 48 weeks of treatment (all p>0.05). **Conclusion:** TMF and TAF exhibited similar 48-week effectiveness and safety profiles for CHB patients in real-world settings. Future prospective, long-term validation studies are warranted.

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Table 1. Laboratory parameters at baseline and 48 weeks for patients with chronic hepatitis B treated with TMF and TAF

	Baseline Characteristics			48 weeks		
Parameters	TMF group (n=72)	TAF group (n=58)	*p* value	TMF group (n=72)	TAF group (n=58)	*p* value
Male/Female	46/26	31/27	0.029	-	-	-
Age, years	36.0 (31.0, 41.0)	34.5 (31.0, 41.0)	0.230	37.0 (32.0, 42.0)	35.5 (32.0, 42.0)	0.482
HBV DNA, log_{10} IU/mL	4.8 ± 2.69	4.5 ± 2.74	0.521	0.4 ± 0.97	0.3 ± 0.82	0.646
HBeAg positive (%)	41/72 (56.9)	32/58 (55.2)	0.229	32/72 (44.4)	27/58 (46.6)	0.205
HBeAg, PEIU/mL	202.2 ± 194.80	250.9 ± 214.50	0.209	131.8 ± 201. 04	192.6 ± 267.72	0.315
HBsAg, log_{10} IU/mL	3.6 ± 0.84	3.6 ± 0.86	0.773	3.3 ± 0.98	3.2 ± 1.40	0.720
Alanine aminotransferase, U/L	43.0 (27.0, 80.0)	31.0 (21.0, 58.0)	0.046	24.0 (16.0, 34.0)	25 (18.0, 34.0)	0.300
Platelet, 10^9/L	205.9 ± 8.10	214.5 ± 8.53	0.465	209.0 (156.0, 260)	194.0 (142.0 241.0)	0.130
Liver Stiffness Measure, kPa	7.3 (5.9, 10.9)	7.5 (6.8, 111.4)	0.379	7.2 (6.5, 9.6)	6.7 (5.6, 8.7)	0.137
Creatinine, μ mol/L	64.8 ± 12.5	64.0 ± 13.0	0.758	67.2 ± 13.8	65.5 ± 12.0	0.706
Urinary α1-microglobulin, mg/L	5.4 (4.1, 8.6)	4.9 (3.4, 6.9)	0.144	7.4 (3.9, 12.5)	6.3 (3.3, 8.2)	0.103
Urinary β2-microglobulin, mg/L	0.2 (0.1, 0.3)	0.2 (0.1, 0.4)	0.585	0.2 (0.1, 0.3)	0.2 (0.1, 0.3)	0.187
Urinary retinol binding protein, mg/L	0.2 (0.5, 0.3)	0.1 (0, 0.3)	0.275	0.2 (0.1, 0.3)	0.2 (0.1, 0.2)	0.199
Urinary N-acetyl-β-D-glucosaminidase, U/L	10.2 (6.9, 20.6)	6.8 (4.3, 10.4)	0.003	10.3 (7.2, 14.7)	9.1 (6.8, 11.0)	0.105
eGFR, mL/min/1.73m²	116.2 (108.5, 120.6)	116.0 (111.1, 123.5)	0.250	110.8 (105.3, 115.7)	112.9 (106.2, 119.3)	0.366
Total cholesterol, mmol/L	4.5 (4.0, 5.0)	4.9 (4.0, 5.2)	0.202	4.5 ± 0.80	4.5 ± 0.90	0.921
Triglycerides, mmol/L	1.0 (0.8, 1.4)	1.3 (0.7, 1.9)	0.350	1.1 (0.7,1.4)	1.1 (0.9, 1.7)	0.401
High density lipoprotein, mmol/L	1.4 (1.2, 1.6)	1.4 (1.2, 1.8)	0.238	1.4 ± 0.43	1.4 ± 0.44	0.663
Low density lipoprotein, mmol/L	2.5 (2.2, 3.1)	2.7 (2.2, 3.1)	0.350	2.7 ± 0.77	2.6 ± 0.71	0.644

Disclosures: Qing-Lei Zeng: Nothing to Disclose, Ru-Yue Chen: Nothing to Disclose, Xue-Yan Lv: Nothing to Disclose

1389 | INNATE IMMUNITY PLAYS AN IMPORTANT ROLE IN THE INACTIVE CHRONIC HBV CARRIERS WITH POSITIVE HBEAG AND HIGH HBV DNA DURING TAF TREATMENT

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Background: The innate immune mechanisms that affect the efficacy of TAF treatment in chronic HBV carriers with normal ALT and high HBV DNA load deserve more exploration. **Methods:** Patients with HBeAg-positive, high HBV DNA load, and normal ALT received TAF antiviral therapy for 48 weeks. Three patients with posttreatment HBV DNA<20 IU/ml were enrolled in the VR group, while three patients with HBV DNA 20~2000 IU/ml were included in the LLV group. Peripheral blood was collected from the patients and PBMC were extracted for single-cell transcriptome sequencing. The characteristics of peripheral immunocytes were compared between the two groups by dimensionality reduction clustering, differentially expressed genes, Gene Ontology (GO) Enrichment Analysis. **Results:** NK and NKT cells had distributional advantages in the VR group, accounting for 19.62% and 15.9%. While in the LLV group, these cells accounted for 11.78% and 10.15%, respectively. Compared with the LLV group, the Ro/e values of NK_FCER1G, NK_KLRF1, NK_XCL1, and NKT_FCGR3A clusters in the VR group were 1.24, 1.32, 1.21 and 1.23, respectively (Figure A). Fifteen genes were over-representation in all the above NK and NKT cell clusters, which were more significant in the VR group, including the lipid metabolism-related gene SLC27A4, the transcription-related gene PTMA, and the protein translation-related genes RPS3A and RPL39. Among them, SLC27A4 gene was highly expressed in the above four cell clusters in the VR group (Figure B-E). GO analysis showed that the up-regulated genes of NK and NKT cells in VR group were mainly enriched

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in the cytoplasmic translation pathway and energy metabolism-related pathways. **Conclusion:** Innate immunity plays an important and positive role in the TAF treatment in chronic HBV infected patients with positive HBeAg, high HBV DNA and normal ALT. But the in-depth mechanism needs to be further investigated.

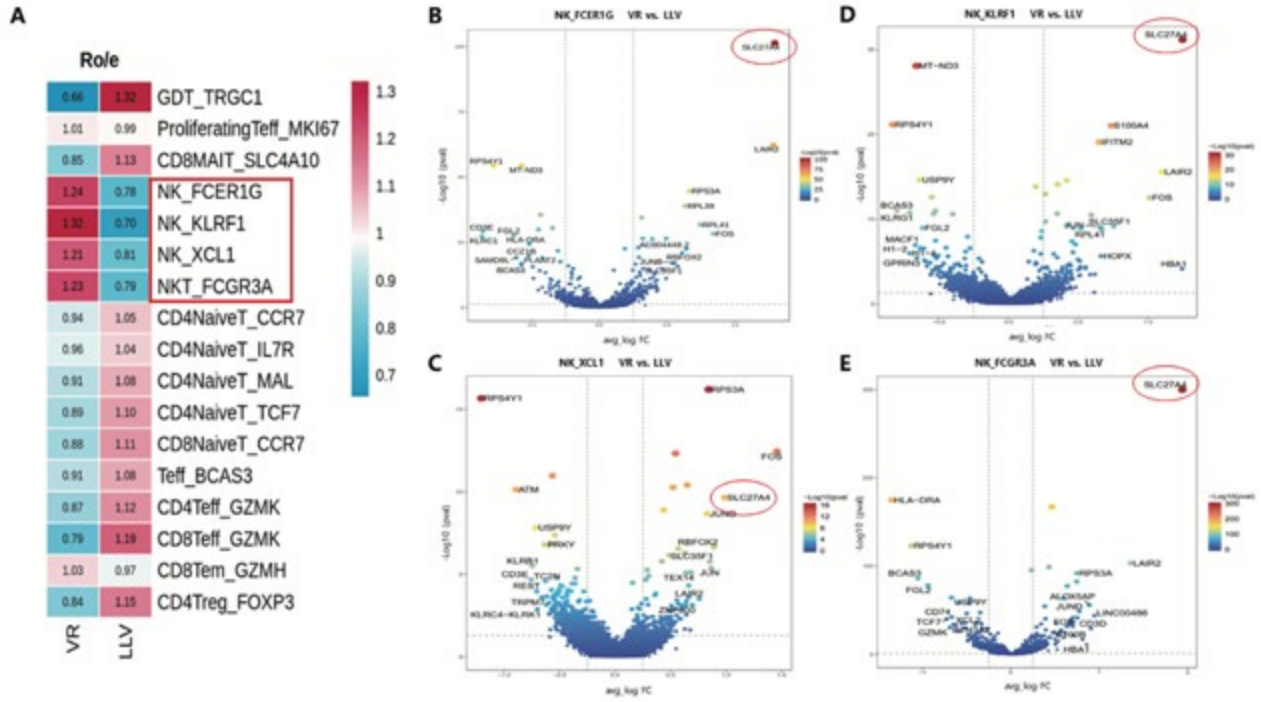

Figure 1. Distribution of cell clusters and the top 10 DEGs between VR group and LLV group

Disclosures: Qiumin Luo: Nothing to Disclose, Wenxiong Xu: Nothing to Disclose, Yeqiong Zhang: Nothing to Disclose, Chan Xie: Nothing to Disclose, Liang Peng: Nothing to Disclose

1390 | SECOND LINE TREATMENT WITH BULEVIRTIDE IN HDV PATIENTS FROM THE ANRS-MIE FRENCH MULTICENTRE REAL-LIFE COHORT ANRS HD EP01 BULEDELTA ◆

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Background: Bulevertide (BLV) has been approved for the treatment of patients with chronic HDV hepatitis (CHD). However, treatment duration and stopping rules in current clinical practice have not yet been defined. *Virological response* is currently defined either as HDV RNA undetectability or as a >2 log decrease in HDV RNA; *biological response* by a normalisation of ALT and the *combined response* by the association of both. The rate of primary non-response or relapse after a first line of treatment with BLV±PegIFNα is high. The aim of this analysis is to provide data on the efficacy of BLV±PegIFNα as a second line treatment in BLV-experienced patients from the ANRS-MIE French multicentre real-life cohort BULEDELTA.**Methods:** 286 patients treated with 2 mg/day

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BLV ± PegIFNα were included. In 109 patients, the first line (L1) of treatment was discontinued due to: i) lack of *virological response*; ii) achievement of *virological* or *biochemical response*; iii) patient or clinician decision; iv) social problems; v) loss to follow-up. 20 patients were treated with a second line treatment (L2) and among them, 11 received 2 mg/day BLV ± PegIFNα with a follow-up (FU) >6 months. Their baseline characteristics at D0 of L1 were: 90.9% cirrhosis; 33.3% portal hypertension; HDV RNA positive in all (median 5.6±1.7 $\log_{10}$ IU/mL); HBeAg+ve 30%; no HIV coinfection. In L1, 5 (45.5 %) patients received BLV 2 mg QD ± PegIFNα QW for 53.4±18.5 weeks. L1 discontinuation was due to *virological* or *biochemical response* in 3/11 patients, *lack of virological response* in 4/11 and other reasons in the remaining 4 patients. 3/11 patients (27.3%) had undetectable HDV-RNA and 6/11 patients (72.7%) had ALT < ULN at the end of L1. **Results:** L2 patients included both non-responders to L1 and relapsers after L1 discontinuation. The mean interval between L1 and L2 was 35.6 ± 26.1 weeks. At D0 of L2, HDV RNA was quantifiable in all (mean 5.8±1.4 $\log_{10}$ IU/mL), HBV DNA in 5 (mean 1.7±0.9 $\log_{10}$ IU/mL), mean ALT values 123,9±59.4 (>ULN 9/11, 81.8%). Patients in L2 received BLV 2 mg QD alone (7/11) or in combination with PegIFNα QW (4/11 patients, 36.4%). Mean duration of BLV in L2 was 67.6±42.0 weeks. A *virological response (*HDV RNA decrease > 2 $\log_{10}$) and HDV RNA *undetectability* were observed in 5/11 (45.4%) and 4/11 (36.4%) patients, respectively. L2 BLV was stopped in 3/11 (27.3%) non responder patients and in 2 responders (one of them had a virological relapse during the FU). **Conclusion:** A second line treatment with BLV±PegIFNα can be considered in selected patients and can achieve a virological response in up to 45% of CHD patients with advanced disease and high biochemical and virological activity. Larger studies are needed to identify baseline or on-treatment predictive factors.

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1391 | HBV TARGET SITE FOR THE RNA INTERFERENCE THERAPEUTIC IMDUSIRAN IS HIGHLY CONSERVED IN CHRONIC HEPATITIS B SUBJECTS

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Background: Imdusiran (AB-729, IDR) is an *N*-Acetylgalactosamine-conjugated small interfering RNA (siRNA) currently being investigated in multiple combination studies, including pegylated interferon-alfa 2a (AB-729-201, IM-PROVE I) and the immunotherapeutic VTP-300 (AB-729-202, IM-PROVE II) for the treatment of chronic hepatitis B (CHB). Previously, we reported target site variants identified in sequences from an HBV database and in CHB subjects enrolled in the Phase 1a/b study of IDR in combination with nucleos(t)ide analogs (AB-729-001). Here we expand our analysis to subjects enrolled in the Phase 2a studies IM-PROVE I and IM-PROVE II and provide comprehensive IDR target site sequence and HBV genotype analysis from over 100 subjects at baseline. **Methods:** CHB subjects were enrolled in clinical studies AB-729-001, IM-PROVE I, or IM-PROVE II. At baseline, prior to IDR administration, HBV RNA extracted from plasma was reverse transcribed and subjected to PCR amplification and ultra deep sequencing (UDS) of the HBx region. To determine the impact of identified IDR target site variants on viral fitness and IDR activity, point mutations were introduced into an HBV plasmid by site-directed-mutagenesis and transfected into HepG2 cells. Viral fitness and antiviral activity were determined by comparing inhibitory activity in variants versus wildtype. HBV genotype was determined by comparing consensus sequences against genotype reference sequences. **Results:** UDS analysis at baseline showed IDR target site conservation in 98 out of 103 subjects (95.2%). In 5 subjects, single nucleotide polymorphisms (SNPs) at >15% read count frequency were observed at positions 1587, 1590 or 1593. *In vitro* analysis confirmed maintenance of IDR activity against these variants. HBV genotypes A to E were identified in IDR clinical studies assessed to date, with genotype B (34%) and C (46%) being the most prevalent, followed by genotype D (16%). Imdusiran activity was similar across subjects with HBV genotypes A-E (HBsAg mean 1.3-1.8 $\log_{10}$ reduction from baseline). **Conclusion:** The IDR target site is highly conserved in baseline samples from CHB subjects enrolled in IDR clinical studies assessed to date. *In vitro* testing in an HBV cell-based model confirmed retention of IDR activity

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against tested variants, suggesting that these SNPs have no apparent influence on HBsAg declines in subjects treated with IDR. Imdusiran has demonstrated clinical activity against HBV genotypes A-E.

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1392 | IMPACT OF METABOLIC DISEASE ON TREATMENT RESPONSE IN CHRONIC HEPATITIS B PATIENTS WITH NUCLEOS(T)IDE ANALOGUES THERAPY: A MULTICENTER REAL-B STUDY

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Background: The prevalence of metabolic diseases is increasing in patients with chronic hepatitis B (CHB). We investigated the impact of metabolic diseases on the treatment responses of CHB patients with first-line nucleos(t)ide analogues (NAs) therapy in an international consortium of CHB patients. **Methods:** We compared the biochemical response (BR), virologic response (VR) and complete response (CR) between previously treatment-naïve CHB patients with and without metabolic disease (diabetes, obesity, dyslipidemia, and hypertension) who initiated NAs from 32 centers from 7 countries/regions (the U.S., Mainland China, Japan, Korea, Singapore, Argentina and Taiwan). Patients with HCC or viral co-infection or less than 6 month follow-up were excluded. We used propensity-score matching (PSM) on sex, age, HBeAg status, baseline HBV DNA, platelets, albumin, total bilirubin and alanine transaminase levels, ethnicity, alcohol intake, cirrhosis, fatty liver and NA type (entecavir, tenofovir DF or AF) to balance background characteristics between groups. **Results:** We analyzed 4507 eligible patients (62.9% male, 97.4% Asian, mean age 50.7 years). More than half (54.8%) had at least one metabolic disease; and among those, 60.8%, 27.3% and 11.9% had 1, 2 and ≥3 metabolic diseases, respectively. Patients with metabolic disease (vs. no metabolic disease) were older (52.8±12.6 years vs. 48.1±12.7 years) and more likely male (58.3% vs. 41.7%), both P<0.001. After PSM, relevant characteristics became balanced between the two study groups. In the PSM cohort, patients with metabolic disease (vs. no metabolic disease) had significantly

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lower cumulative 5-year BR (91.3 % vs. 95.8 %; P<0.001) and CR rates (81.8% vs. 87.4%; P=0.008), but similar VR rates (93.5% vs. 94.1%; P=0.647). Patients with metabolic disease overall were less likely to achieve BR (adjusted hazard ratio [aHR], 0.73, 95%CI: 0.65-0.82, P<0.001) and CR (aHR, 0.79, 95% CI: 0.69-0.91, P=0.001), with the lowest likelihood observed in patients with ≥3 metabolic diseases (aHR, 0.55, 95% CI: 0.41-0.73 for BR; aHR, 0.53, 95% CI: 0.38-0.76 for CR, both P<0.001) (Figure). **Conclusion:** More than half of CHB patients have at least one metabolic disease, and the presence and number of metabolic disease was significantly and incrementally associated with lower BR and CR. Metabolic disease should be taken into account in the management and monitoring of patients with CHB receiving NA therapies.

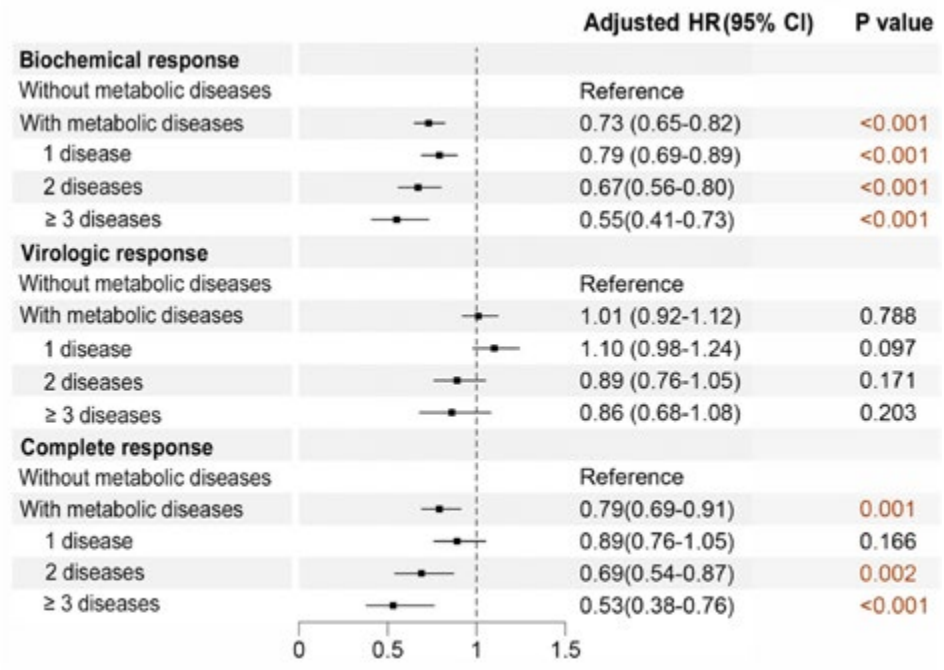

Figure. Cox proportional hazards regression of antiviral treatment responses between CHB patients with and without metabolic diseases.

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Consultant, Ramsey Cheung: Nothing to Disclose, Chao Wu: Nothing to Disclose, Ming-Lung Yu: Abbvie, Gilead and Roche diagnostics.: Grant/Research Support, Abbott, Abbvie, Gilead, Roche and Roche diagnostics: Consultant, Abbvie, BMS, Gilead, Roche and Roche diagnostics: Speaking and Teaching, Mindie Nguyen: Nothing to Disclose

1393 | BULEVIRTIDE MONOTHERAPY IN PATIENTS WITH COMPENSATED CIRRHOSIS AND CSPH: A 96-WEEK INTERIM KINETIC ANALYSIS OF REAL-LIFE SETTING ◆

Ori Wasserman[1] Scott Cotler[2] Louis Shekhtman[1] Elisabetta Degasperi[3] Maria Anolli[3] Sara Colonia Uceda Renteria[3] Dana Sambarino[3] Marta Borghi[3] Riccardo Perbellini[3] Floriana Facchetti[3] Ferruccio Ceriotti[3] Harel Dahari[1] Pietro Lampertico[4]

[1]Loyola University Chicago, [2]Loyola University Health System, [3]Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, [4]University of Milan

Background: Bulevirtide (BLV) was recently approved for treatment of hepatitis D in Europe. We aim to characterize HDV, HBsAg and ALT kinetics under BLV monotherapy in patients with compensated cirrhosis and clinically significant portal hypertension (CSPH). **Methods:** Thirty-eight patients with HDV-related compensated cirrhosis and CSPH were treated with BLV 2 mg/day monotherapy. All patients received TDF or ETV for HBV. Blood samples were collected at treatment initiation, weeks 4, 8, 16, 24, 32, 40, 48 and every 12 weeks thereafter. Fifteen (39%) patients did not reach 96 weeks of therapy: 3 had liver transplantation (week 48, 60, or 72), 1 stopped treatment (week 48), and 11 are still ongoing (range: week 60-84). HDV RNA was measured using Robogene 2.0 (lower limit of detection, LLD= 6 IU/mL). ALT normalization was defined as 41 U/L and 59 U/L for women and men, respectively. **Results:** Mean baseline HDV RNA, HBsAg and ALT levels were 4.89 ± 1.23 log IU/mL, 3.55 ± 0.67 log IU/mL, and 114.4 ± 76.5 U/L respectively. Five (13%) patients were non-responders (<1.6 log IU/ml decline from baseline throughout treatment). All responders (n=33) experienced an initial rapid viral decline (0.19 ± 0.12 log/wk) followed by: (i) flat partial response with viral plateau (FPR) (n=19, Fig.1a), (ii) FPR and breakthrough (B) (n=3, Fig.1b), (iii) FPR and viral decline (n=3, Fig.1c), (iv) second slower phase, biphasic (BP) (n=2, Fig.1e), (v) BP + B (n=4, Fig.1d), or (vi) transient increase, TP (n=2, Fig.1f). ALT normalization was achieved in 28 (76%) patients at 7.9 ± 6.5 weeks (Fig.1). HBsAg remained at pre-treatment levels (Fig.1). **Conclusion:** Interim analysis finds that 22 patients (67% of responders) reached a low viral plateau (3.2 ± 1.1 log IU/mL below baseline) that lasted 56.4 ± 11.2 weeks (i.e., FPR in Fig.1 a, b & c), of whom 3 patients had a further decline (Fig.1c).Thus far, 7 (18%) of responders had viral breakthrough (Fig.1 b & e), 2 patients had a sustained 2nd decline phase (Fig.1d), and only 3 patients (8%) achieved sustainable HDV RNA TND (≥24 weeks) at the end of week 96 (Fig.1 c & f).

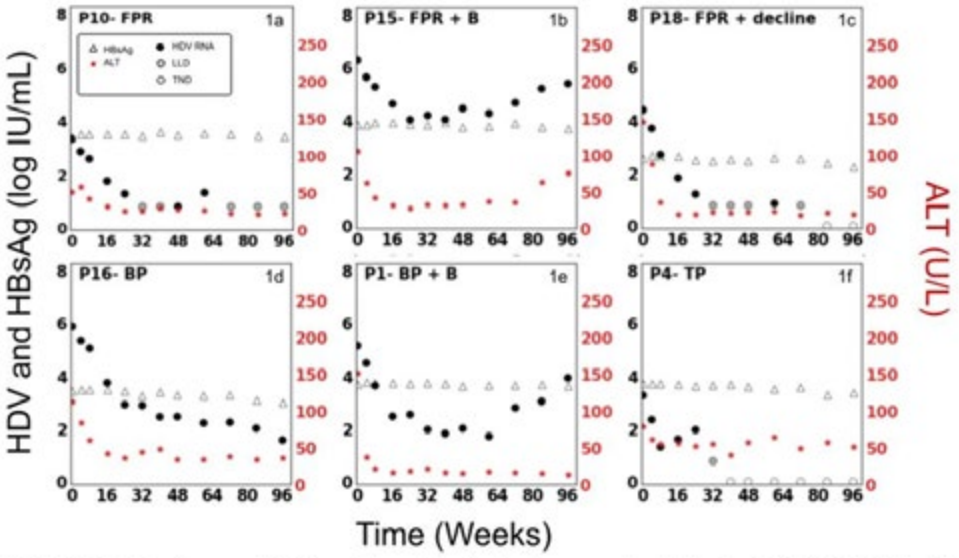

Fig. 1. HDV kinetic patterns under BLV monotherapy in patients with compensated cirrhosis and CSPH. FPR, flat-partial response; BP, biphasic; B, viral breakthrough (>1.6 log IU/ml from nadir viral load); TP, triphasic; LLD, lower limit of detection; TND, target not detected. Filled circles, quantifiable HDV RNA.

Disclosures: Ori Wasserman: Nothing to Disclose, Scott Cotler: Nothing to Disclose, Louis Shekhtman: Nothing to Disclose, Elisabetta Degasperi: Gilead: Speaking and Teaching, Roche: Advisor, Abbvie: Speaking and

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1394 | TEMPORAL CHANGES IN DEMOGRAPHICS AND COMPLICATIONS/COMORBIDITIES OF PATIENT WITH CHRONIC HEPATITIS B: RESULTS OF A REAL-WORLD U.S. COHORT

Mindie Nguyen[1] Hiroki Ono[1] Xinrong Zhang[1] Ramsey Cheung[1]

[1]Stanford University Medical Center

Background: Real-world demographic characteristics and complications/comorbidities data in chronic hepatitis B (CHB) patients are limited. This study aimed to determine the updates and temporal changes of demographic characteristics and complications/comorbidities in CHB patients, using a nationwide real-world database in the United States. **Methods:** This study included 71,916 patients aged ≥18 years with a diagnosis of CHB during 1/1/2007-12/31/2020. Demographic characteristics, liver complications/comorbidities and non-liver comorbidities, Deyo-Charlson Comorbidity Index (DCCI), hepatitis B virus (HBV) antivirals, selected metabolic medications (anti-diabetic medications including sodium-glucose cotransporter-2 inhibitors [SGLT2-Is], glucagon-like peptide-1 receptor agonists [GLP-1 RA], and metformin and statin) were analyzed. **Results:** The mean age of patients with CHB increased from 46.7 ± 11.5 years in 2007 to 47.7 ± 11.4 years in 2020 (p=0.016; Table), while the proportion of males decreased from 61.8% in 2007 to 55.3% in 2020 ($p < 0.001$). From 2007 to 2020, the proportions of CHB patients with liver complications/comorbidities decreased including cirrhosis (18.8% to 9.2%), liver decompensation (5.7% to 4.1%), hepatocellular carcinoma (3.5% to 1.7%), and liver transplantation (3.3% to 1.5%), though the proportion of patients with receipt of HBV antivirals also decreased (37.6% to 33.6%) (all $p < 0.001$). The proportion of obese patients increased more than 2-fold from 3.5% in 2007 to 8.4% in 2020 ($p < 0.001$). But the proportion of diabetes (16.5% to 12.6%, $p = 0.003$) decreased, whereas the proportion of cardiovascular disease (CVD) (3.6% to 5.6%, $p < 0.001$) increased from 2007 to 2020. **Conclusion:** Patients with CHB are becoming older, more likely female, more likely obese, more likely to have CVD between 2007 and 2020. The proportions of patients with a liver complications/comorbidities also decreased over time, which may be due to availability of first-line HBV antivirals since 2005. Unfortunately, the proportion of patients receiving HBV antivirals also decreased over time, and further efforts to improve HBV diagnosis and treatment are needed.

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Table. Changes in demographic characteristics and complications/comorbidities of CHB patients over time (2007, 2010, 2015, vs. 2020)

Demographic Characteristics	CHB (2007) (n = 6746)	CHB (2010) (n=5782)	CHB (2015) (n=3642)	CHB (2020) (n = 1243)	p
Age (years)					
mean (SD)	46.7 (11.5)	47.4 (12.3)	47.5 (12.3)	47.7 (11.4)	0.016
Median	47 (38-55)	47 (38-56)	47 (38-56)	48 (39-56)	
Sex (n, %)					
Male	4172 (61.8)	3345 (57.9)	2078 (57.1)	687 (55.3)	<0.001
Female	2574 (38.2)	2437 (42.1)	1564 (42.9)	556 (44.7)	
Obesity (n, %)	239 (3.5)	256 (4.4)	348 (9.6)	105 (8.4)	<0.001
Clinical Characteristics					
Liver complications/comorbidities (n, %)					
Cirrhosis	1266 (18.8)	961 (16.6)	441 (12.1)	114 (9.2)	<0.001
HCC	236 (3.5)	171 (3.0)	81 (2.2)	21 (1.7)	<0.001
Liver transplant	221 (3.3)	145 (2.5)	52 (1.4)	19 (1.5)	<0.001
Steatotic liver disease	647 (9.5)	522 (9.0)	410 (11.3)	109 (8.8)	0.002
Infectious liver disease	1021 (15.1)	814 (14.1)	443 (12.2)	136 (10.9)	<0.001
HBV antivirals (n, %)	2539 (37.6)	1898 (32.8)	1382 (37.9)	418 (33.6)	<0.001
Mean DCCI (SD)	3.78 (2.72)	3.93 (2.88)	3.87 (2.83)	3.68 (2.83)	0.005
Non-liver comorbidities (n, %)					
non-liver cancer	609 (9.0)	515 (8.9)	302 (8.3)	85 (6.8)	0.060
CVD	245 (3.6)	288 (5.0)	240 (6.6)	70 (5.6)	<0.001
CKD	430 (6.4)	366 (6.3)	264 (7.2)	65 (5.2)	0.009
Diabetes	1115 (16.5)	907 (15.7)	614 (16.9)	157 (12.6)	0.003
Selected metabolic medications (n, %)					
All antidiabetic medications	615 (9.1)	497 (8.6)	428 (11.8)	113 (9.1)	<0.001
SGLT2-Is	26 (0.4)	23 (0.4)	54 (1.5)	19 (1.5)	<0.001
GLP-1 RA	17 (0.3)	12 (0.2)	17 (0.5)	19 (1.5)	<0.001
Metformin	326 (4.8)	267 (4.6)	293 (8.0)	72 (5.8)	<0.001
Statin	1029 (15.3)	847 (14.6)	710 (19.5)	223 (17.9)	<0.001

Disclosures: Mindie Nguyen: Nothing to Disclose, Hiroki Ono: Nothing to Disclose, Xinrong Zhang: Nothing to Disclose, Ramsey Cheung: Nothing to Disclose

1395 | PREVALENCE OF DELTA HEPATITIS IDENTIFIED WITH HEPATITIS B INFECTION THROUGH EMERGENCY DEPARTMENT BLOOD-BORNE VIRUS SCREENING

Shivaali Karelia[1] *Andrea Cartier*[1] *Neil Turner*[1] *Lauren Bull*[1] *Ann Sullivan*[1] *Matthew Foxton*[1]

[1]*Chelsea and Westminster Hospital*

Background: Hepatitis D virus (HDV) is associated with increased mortality and morbidity in patients with chronic hepatitis B virus (HBV) infection. HDV hastens the development of liver fibrosis and decompensated liver disease and increases the risk of cancer. The aim of this study was to assess the prevalence of HDV infection in the population identified with HBV through universal blood-borne virus (BBV) screening in those attending the emergency department. **Methods:** All patients attending the ED department were offered opt-out BBV testing. Those positive for HBsAg were contacted and offered clinic appointments. Comprehensive risk stratification at these clinics included HBV DNA testing and HDV testing. Data was collected from Patient Healthcare Records. **Results:** Between April 2022 and December 2023, 29411 people attending the emergency department were tested for HBsAg. There were 349 positive tests (1.19%). 41.5% (145/349) of the HBV population were tested for HDV. 1.4% (2/145) tested positive for HDV. 68.9% of the population testing positive for HBV were already known to hepatology at either our Trust or other hospitals; 31.6% of the population were a new diagnosis. 72.4% of HBV positive patients linked to a consultant were tested for HDV. No HDV testing occurred outside of specialist clinics. **Conclusion:** Testing of the population attending the emergency department highlighted the high prevalence of chronic HBV infection, with 31% having a new diagnosis of HBV. Nearly three quarters of the HBV positive population already known to hepatology were tested for HDV. In majority of cases, HDV testing was occurring only after being known to a hepatologist or infectious disease team. More money should be invested to facilitate linkage to care testing for HDV rather than reflex testing given its association with worse prognosis and outcomes.

Disclosures: Shivaali Karelia: Nothing to Disclose, Andrea Cartier: Nothing to Disclose, Neil Turner: Nothing to Disclose, Lauren Bull: Nothing to Disclose, Ann Sullivan: Nothing to Disclose, Matthew Foxton: Nothing to Disclose

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1396 | HEPATOCELLULAR CARCINOMA IN WESTERN KENYA: RISK FACTORS, DIAGNOSIS & SURGICAL MANAGEMENT ★

Mercy Karoney[1] Evangeline Njiru[1] Sarah Obuya[2] Aidah Kenseko[2] Ronald Tonui[1] Daniel Chepsiror[2] Samwel Toroitich[1] Kibet Keitany[2] Gabriel Kigen[1] Andrew Wandera[1] Fatuma Some[1]

[1]Moi University School of Medicine, [2]Moi Teaching and Referral Hospital

Background: Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer globally, accounting for 75-85% of all liver cancer cases with a prevalence of 16 to 32 times higher in developing countries than in developed countries. HCC is an asymptomatic malignancy with a particularly grave prognosis in black Africans. In Kenya HCC is the 13th prevalent cancer in Kenya, and 9th cause of cancer mortality. The cancer burden is greatest in areas where viral Hepatitis B or C prevalence is 8% or more. Surveillance should be tailored to those at risk as it leads to early detection of lesions while they are still amenable to surgery. We describe the clinical profile of patients with chronic liver disease and HCC in a western Kenya multidisciplinary collaborative project. **Methods:** The HepWek project was carried out in Western Kenya to study risk factors and to improve diagnostic capability and surgical management of HCC. This was a prospective study of patients known to have chronic liver disease or uncharacterized liver lesions requiring further workup. Chronic liver disease was defined either by follow up in the liver clinic or presence of abnormal liver function for more than 6 months. **Results:** A total of 200 patients were included in the final analysis. The majority were male 110/200 (55%), mean age was 47 (SD 16) years. The commonest etiology for liver disease was Hepatitis B with 90/200 (45%) cases, 30% of the patients (59/200) were diagnosed to have HCC. Risk factors for HCC were older age Odds Ratio (OR) 1.03 (95% CI 1.01 to 1.06), Hepatitis B; OR 2.66 (95% CI 1.28 to 5.51) and liver cirrhosis OR 2.41 (95% CI 1.21 to 4.81). Median alpha-fetoprotein (AFP) level was 111 (range 1 to 1000) ng/ml in HCC patients and majority of them had albumin-bilirubin score of 3 (78%). Most patients (88%), presented with advanced stages of HCC, only 2 patients were amenable to Hepatic resection which they underwent successfully. Thirty-five (74%) out of the 59 patients with HCC died within 1 year. **Conclusion:** Hepatocellular carcinoma patients in western Kenya present with advanced stage of the disease that is unresectable. Hepatitis B virus infection and cirrhosis from all causes remains the most common risk factor.

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1397 | IMMUNE CHECKPOINT INHIBITOR (ICI) TREATMENT AND IMMUNE-RELATED ADVERSE EVENTS (IRAES): LESSONS LEARNED FROM ONCOLOGY FOR ITS POTENTIAL USE FOR CHRONIC HEPATITIS B (CHB) PATIENTS

Mitchell Leus[1] Agustina Crespi[2] Veronica Miller[1] Sue Currie[3] Adam Gehring[2]

[1]Forum for Collaborative Research, [2]University Health Network, [3]Virion Therapeutics

Background: ICIs targeting PD-1/PD-L1 have changed treatment strategies for cancers. Their potential to restore HBV-specific T & B cell magnitude and function in CHB patients makes them attractive agents, but the risk of IrAEs is a potential barrier to use. Early studies (pre-2019) of PD-1/PD-L1 drugs to treat cancers suggested high rates of IrAEs, but these studies included patients with advanced cancers, multiple lines of treatments, and addon therapies that may have contributed to IrAEs. Thus, we conducted a literature review to identify the incidence, type, and severity of IrAEs in cancer patients treated with ICIs as first-line therapy. The objective was to understand the potential risks of IrAEs in less advanced patients to better inform the risks of PD-1/PD-L1 treatments in CHB patients. **Methods:** Given the changes to IrAE surveillance and increased harmonization on IrAE definitions and reporting, our search criteria focused on studies between 2019-2024, examining ICIs targeting PD-1 or PD-L1 as first-line monotherapy in cancer patients. Patient population and IrAE data were extracted and pooled to obtain composite values. All IrAEs were graded using the Common Terminology Criteria for Adverse Events (CTCAE) system. **Results:** The search yielded 10 original research papers, with a total of 5540 patients, of which 2378 patients were treated with PD-1/PD-L1 therapy (see Table 1). IrAEs of any grade

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were reported in 765 patients (32.2%), with 191 patients (8.0%) discontinuing treatment due to experiencing an IrAE. Among those treated with PD-1/PD-L1 therapy, Grade 1-2 IrAEs were reported in 622 patients (26.2%) and Grade ≥ 3 IrAEs were reported in 143 patients (6.0%). **Conclusion:** Among cancer patients receiving PD-1/PD-L1 therapy as first-line treatment, the majority (67.8%) did not experience an IrAE. However, more granular data are needed on IrAEs of interest to a CHB patient population, including data on hepatic and thyroid toxicities. Our findings support the need to continue assessing the risk-benefit of ICIs for CHB patients and the need to expand IrAE standardized reporting from oncology to ensure that IrAEs of interest to CHB, including PD-1/PD-L1-mediated hepatitis and thyroidism, are included.

TABLE 1. Immune-related adverse events (IrAEs) among first-line cancer patients treated with anti-PD-1 or anti-PD-L1 monotherapy, n = 2,378 (2019 - 2024 from 10 studies)

Immune-related adverse event (IrAE), No. (%)	Grade 1 - 2	Grade ≥ 3	Any Grade
Any IrAE	622 (26.2)	143 (6.0)	765 (32.2)
IrAE leading to discontinuation*	NA	NA	191 (8.0)
IrAE by category			
Thyroidism[a]	336 (14.1)	4 (0.2)	340 (14.3)
Rash/Skin involvement[b]	105 (4.4)	29 (1.2)	134 (5.6)
Pneumonitis	51 (2.1)	26 (1.1)	77 (3.2)
Diarrhea/Gut involvment[c]	51 (2.1)	21 (0.9)	72 (3.0)
Hepatitis	45 (1.9)	33 (1.4)	78 (3.3)
Infusion reaction	8 (0.3)	3 (0.1)	11 (0.5)
Nephritis	7 (0.3)	10 (0.4)	17 (0.7)
Adrenal insufficiency	5 (0.2)	4 (0.2)	9 (0.4)
Anaphylactic reaction	5 (0.2)	0	5 (0.2)
Pancreatitis	3 (0.1)	2 (0.1)	5 (0.2)
Hypophysitis	3 (0.1)	2 (0.1)	5 (0.2)
Myositis	2 (0.1)	1 (0.04)	3 (0.1)
Uveitis	1 (0.04)	0	1 (0.04)
Myocarditis	0	2 (0.1)	2 (0.1)
Encephalitis	0	1 (0.04)	1 (0.04)
Peripheral neuropathy	0	1 (0.04)	1 (0.04)
Mysathenia gravis	0	1 (0.04)	1 (0.04)
Autoimmune arthritis	0	1 (0.04)	1 (0.04)
Guillan-Barre Syndrome	0	1 (0.04)	1 (0.04)
Stevens-Johnson Syndrome	0	1 (0.04)	1 (0.04)

* NA values are given because IrAEs leading to discontinuation were not stratified by grade across all studies

[a] Thyroidism is a composite category including hypothyroidism, hyperthyroidism, or increased blood TSH

[b] Rash/Skin involvement is a composite category including rash and pruritus unrelated to an infusion reaction

[c] Diarrhea/Gut involvement is a composite category including diarrhea, colitis, nausea, vomiting, and constipation

Disclosures: Mitchell Leus: Nothing to Disclose, Agustina Crespi: Nothing to Disclose, Veronica Miller: Nothing to Disclose, Sue Currie: Virion Therapeutics LLC: Executive role, Adam Gehring: Nothing to Disclose

1398 | THE CURRENT BURDEN OF HEPATITIS B IN THE UNITED STATES: A STATE, TERRITORIAL, AND COUNTY ANALYSIS –THE IMPACT OF IMMIGRATION, 2021

Devin Razavi-Shearer[1] *Ivane Gamkrelidze*[1] *Samantha Hall*[1] *Kathryn Razavi-Shearer*[1] *Alexis Voeller*[1] *Carolyn Wallace*[1] *Homie Razavi*[1]

[1]*Center for Disease Analysis Foundation*

Background: The burden of hepatitis B virus (HBV) in the United States (US) remains uncertain due to the large impact of immigration. Several groups have used immigration patterns and prevalence of HBV in the home-country to estimate the number of HBV infections in the US. There is a strong need for more localized estimates so that state and local governments can better understand the current burden of HBV and develop targeted strategies. This will allow local health systems to better respond to a burden which falls disproportionally upon immigrant communities. **Methods:** Using previously validated and published population-based country level Markov models, the prevalence of HBV among immigrants in the US by country of birth was estimated in 2021. These estimates were applied to the 2018-2022 American Community Survey (ACS) estimates for the number of foreign-born individuals by country of birth for each county. For non-foreign-born individuals, the National Health and Nutrition Examination Survey prevalence of 0.12% for this group was applied to each county's population

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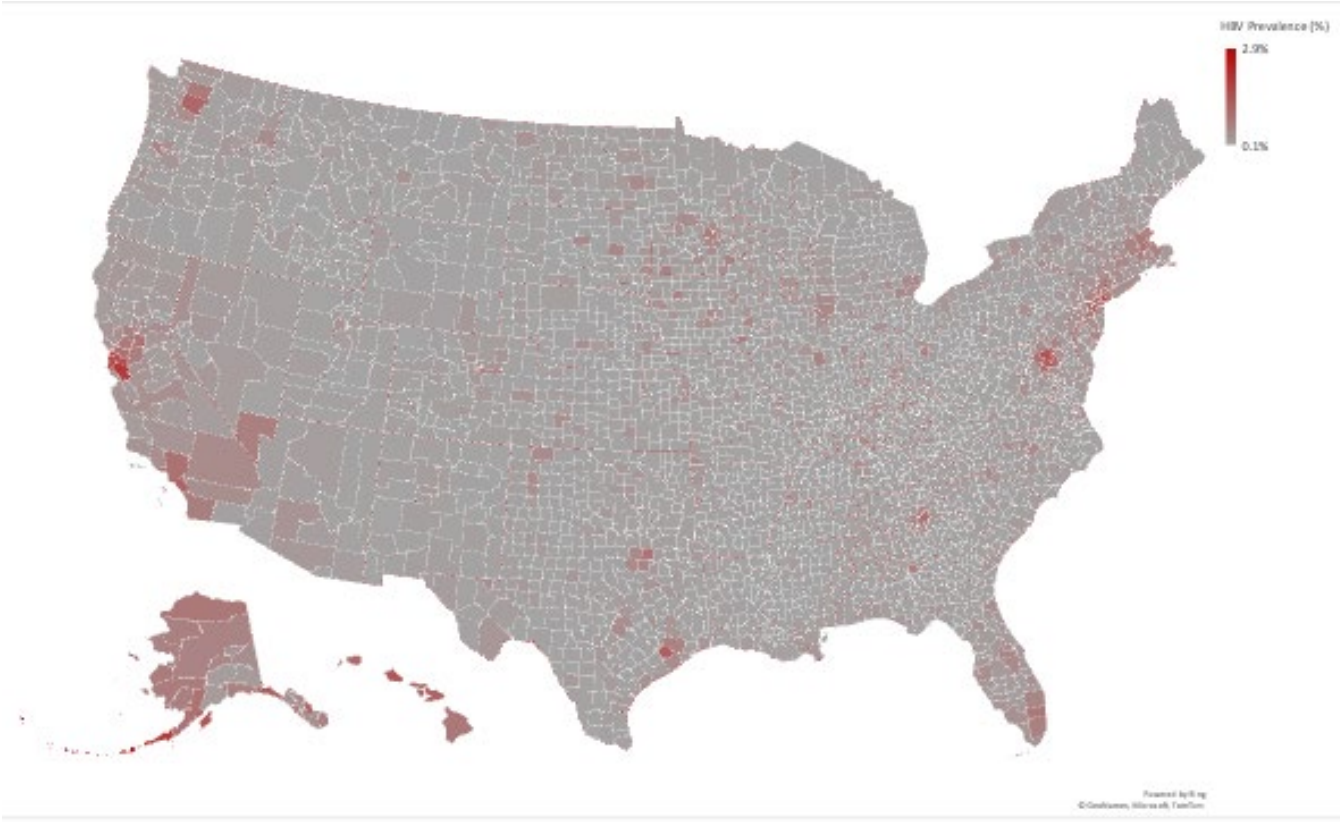
with two exceptions. Alaskan Natives residing in Alaska and non-foreign-born Asian and Pacific Islanders in all counties were estimated to have HBV prevalence of 0.80% and 0.69% respectively. This resulted in new county, state, territorial (Puerto Rico and Washington D.C.) and national level HBV prevalence estimates. **Results:** 119 country models were compatible with ACS data resulting in an estimated 1.7 million (795,000 – 4.1 million) people living with HBV (PLWHBV) in the US. Nationally, 76% of PLWHBV were foreign-born, with a range of 30% in West Virginia to 87% in New York. The highest prevalence was found in Hawaii 1.3% (UI:0.5-4.0%). Over 50% of all infections in the US were estimated to be in 5 states: California, New York, Texas, Florida, and New Jersey. The highest prevalence by county was found in Aleutians West Census Area, Alaska 2.9% (UI: 0.8%-9.7%) (Figure 1). Los Angeles County was found to have the highest absolute number of cases in the US, 96,700 (UI: 54,800-190,600). 31% of all HBV infections in the US are estimated to be among first generation immigrants from mainland China, the Philippines and Viet Nam. However, there is great heterogeneity at the local level. In California, the largest number of PLWHBV are from the Philippines, in New York, Mainland China, in Texas, Vietnam, in Florida, Jamaica, and in New Jersey, India. **Conclusion:** There is vast heterogeneity in the burden of HBV in the US at both state and county levels. This is compounded by counties with different sized compositions of immigrant communities most impacted. These data provide evidence for policy makers to better understand the burden their community faces by showing the local hotspots of HBV prevalence. By providing estimates of the immigrant communities most impacted by HBV at the county level, local organizations can be better poised to develop culturally appropriate materials and outreach.



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1399 | INVESTIGATION OF THE REFERENCE VALUE OF ALT FOR THE INITIATION OF NUCLEIC ACID ANALOGS FOR CHRONIC HEPATITIS B

Taisei Keitoku[1] *Nobuharu Tamaki*[1] *Masayuki Kurosaki*[1]

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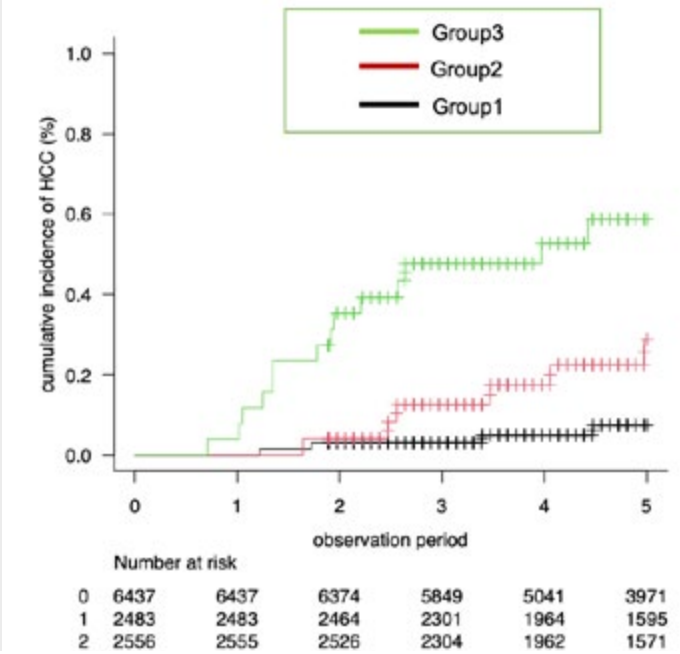
Background: The criteria of ALT value for initiation of nucleic acid analog (NA) therapy are different in AASLD2018 and EASL2017: ALT > 2ULN and ALT > ULN. In Japan, ALT level of ≥31U/L and HBV-DNA≥3.3 log IU/ml (2000IU/ml) is considered as a criterion, regardless of HBeAg positive/negative status. As mentioned above, the criteria differ from country to country, and there is no clear consensus on the ALT level. Patients who do not receive NA even if their ALT is above the threshold are considered to be in the so-called “Gray zone”. In this study, we focused on the carcinogenesis of chronic hepatitis B patients by ALT level. **Methods:** In Study 1, we used a large database integrating health insurance claims and health checkup results of subscribers to a health insurance union in Japan. We analyzed development of HCC in 110594 patients with chronic hepatitis B or liver cirrhosis without a history of HCC in the past. In Study 2, We studied 851 patients diagnosed with chronic hepatitis B at Musashino Red Cross Hospital, excluding those who were 1) under 18 years old, 2) had a history of HCC, 3) followed for 30 days or less, 4) developed HCC within 6 months, and 5) had ALT >30 IU/L and HBV-DNA≥3.3 log IU/ml (2000 IU/ml) at the start of observation but not treated with NA. **Results:** Study 1: Patient background: observation period (median): 5.2 years, age(median): 52 (45-58), male were 8242 cases (71%), 2556 patients (22%) were taking NA, and the average ALT during the observation period (median) was 23 (20-29) U/L. They were classified into three groups as follows. Group 1 (6437 cases): NA-naïve patients with average ALT ≤30U/L, Group 2 (2483 cases): NA-naïve patients with average ALT >30 U/L, and Group 3 (2556 cases): NA group. 3-year cumulative incidence of HCC was 0% vs. 0.1% vs. 0.5%, respectively (Group1 vs Group 2: p=0.07, Group 2 vs Group 3: p=0.1, Group1 vs Group3: p<0.001, Bonferroni). Study 2: Patient background: observation period (median): 3.9 years, age(median): 58 (46-68), male were 413 cases (49%), 126 (14.8%) patients were taking NA and the average ALT during the observation period (median): 21 (16-27) U/L. They were classified into three groups as follows. Group1 (346 patients): NA-naïve patients with average ALT ≤30IU/L and HBV-DNA <3.3logIU/ml, Group2 (379 cases): NA-naïve patients with average ALT >30IU/L or HBV-DNA ≥3.3logIU/ml, and Group3 (126 cases): NA group. 3-year cumulative incidence of HCC was 1.1% vs 2.0% vs 3.0%, respectively. (Group1 vs Group 2: p=1, Group 2 vs Group 3: p=0.02, Group1 vs Group3: p=0.01, Bonferroni)There was no significant difference compared to the group with ALT ≤ 30U/L, since NA is relatively introduced at ALT levels > 30 U/L according to the criteria for initiation of treatment in Japan. **Conclusion:** A cutoff of 30 U/l for the reference value of ALT may deter carcinogenesis in patients with chronic hepatitis B.



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Disclosures: Taisei Keitoku: Nothing to Disclose, Nobuharu Tamaki: Nothing to Disclose, Masayuki Kurosaki: Nothing to Disclose

1400 | IMMUNO-METABOLIC DRIVEN HEPATITIS B SURFACE ANTIGEN SEROCONVERSION IN MILD AND SEVERE HEPATITIS B REACTIVATION ◆ ★

Jayesh Kumar Sevak[1] MOJAHIDUL ISLAM[1] Gayantika Verma[1] Anoushka Saxena[1] Manoj Sharma[1] Ankur Jindal[1] Varsha Shasthry[1] Syed Naqui Kazim[2] Shiv Kumar Sarin[1] Nirupma Trehanpati[1]

[1]Institute of Liver and Biliary Sciences, [2]Jamia Milia Islamia

Background: HBV mediated loss of immune control is the primary cause of HBV reactivation. Metabolic reprograming of immune cells can drive the seroconversion or lead to ACLF progression. Therefore, our aim was to investigate global metabolic changes in immune cells during HBV reactivation (rHBV). **Methods:** Altogether 39 rHBV patients (age 42± 13) with raised ALT (>5XULN) and HBV DNA>log10^{4}IU/ml categorized on the basis of INR levels as mild (n = 18, INR <1.5), severe (n = 11, INR >1.5, bilirubin >2.5XULN) and acute on chronic liver failure (ACLF, n=10) were subjected to immune metabolic profiling, plasma metabolomics, and cytokine analysis using mass spectrometry, flow-cytometry and cytokine bead array at baseline, week 12 and 24. **Results:** 17 patients (10/18 (55.55%) mild, 7/11(63.63%) severe, none from ACLF) achieved HBsAg seroconversion. At baseline, soluble inhibitory molecules such as TIM3, LAG3, PDL2 and CD80, along with PD1-expressing CD4, CD8, and Tregs, were significantly ($p<0.05$) lower in mild and severe patients compared to ACLF patients. Glut1, HK2, and mTOR enriched T effector memory (TEM) and TEMRA cells were increased ($p<0.05$) in mild patients compared to severe and ACLF patients. Plasma metabolomics also revealed increased levels of phenylalanine and thymidine in mild and severe rHBV. In ACLF patients, methionine and gliclazide metabolites suggestive of Tregs differentiation were observed. At week 12 and 24, elevated levels of gliclazide, methionine, methyl palmitate, and inosine ($p<0.05$) suggested immune suppression and inhibition in ACLF. Increased levels of inhibitory molecules in ACLF cause immune exhaustion, which contributes to a low survival rate. By 24-week, only 2 (20%) patients survived in ACLF. However, the reduction of these metabolites was associated with significant differentiation of TEM, Tfh, and B cells ($p<0.05$) in mild and severe patients compared to ACLF patients, indicating immune regulation in these patients. Additionally, NAD+ and L-cysteine were also found significantly upregulated ($p<0.05$) in mild and severe patients compared to ACLF indicating availability of cellular energy. **Conclusion:** Our results reveal that amino acids (Phenylalanine, tyrosine and cysteine) and available energy sources (NAD+ and NMN) to TEM cells contributes to HBsAg seroconversion in both mild and severe patients. Additionally, increased inhibitory markers in ACLF lead to lack of HBsAg clearance and immune metabolic dysfunction.

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Figure 1a

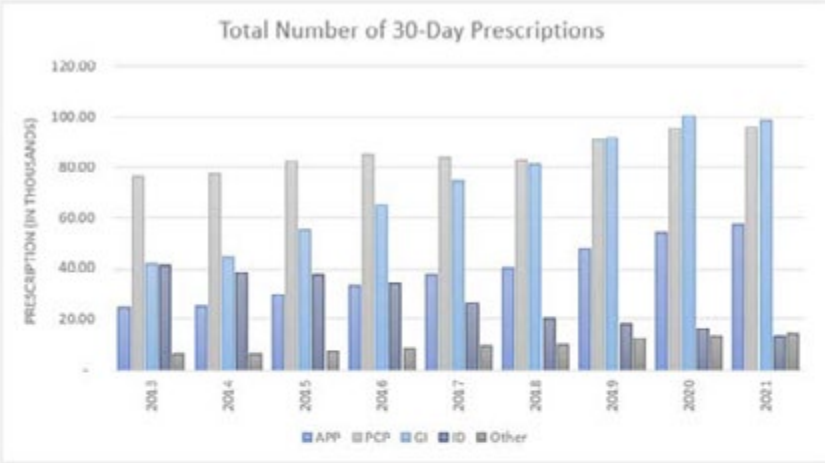
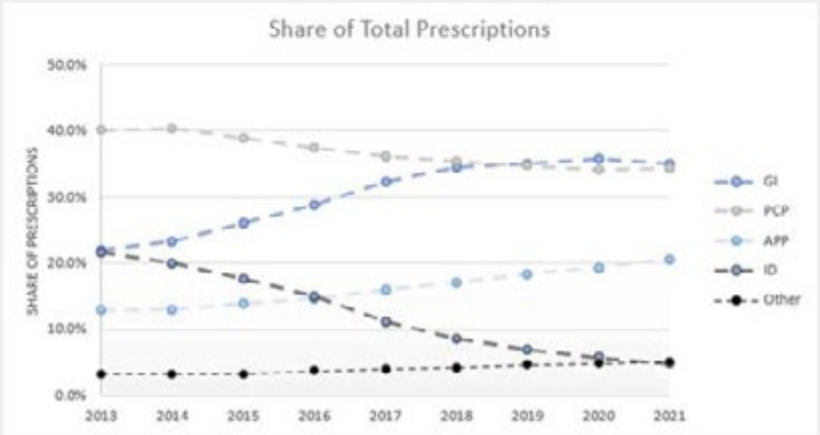


Figure 1b



Disclosures: Jayesh Kumar Sevak: Nothing to Disclose, MOJAHIDUL ISLAM: Nothing to Disclose, Gayantika Verma: Nothing to Disclose, Anoushka Saxena: Nothing to Disclose, Manoj Sharma: Nothing to Disclose, Ankur Jindal: Nothing to Disclose, Varsha Shasthry: Nothing to Disclose, Syed Naqui Kazim: Nothing to Disclose, Shiv Kumar Sarin: Nothing to Disclose, Nirupma Trehanpati: Nothing to Disclose

1401 | PREVALENCE OF HDV VIRUS IN A COHORT OF HBV INFECTED PATIENTS IN SOUTH-BAY SAN DIEGO

Jasmine Ahmed[1] Deanna Oliver[1] Yaseen Kady[2] Julian Diaz-Moreno[1] James Johnson[1] Eric Storey[1] Maryam Yasso[1] Anna Hefner[1] Tarek Hassanein[1]

[1]Southern California Liver Centers, [2]None

Background: HDV is an RNA virus, which is dependent on the presence of HBs Ag, hence it occurs as a coinfection or a superinfection in patients harboring HBV infection. Much attention to HDV diagnosis is underway because of new HDV therapies which could alter the course of liver injury in patients with chronic HBV/HDV infections. Aim We embarked on estimating the prevalence of HDV infection in our population with chronic HBV infections (HBs Ag positive) patients seen in the liver clinics. **Methods:** From our center's database of about 13,500 patients with chronic liver disease seen between January 2017 and November 2022, 293 have chronic HBV (2% of patients). All patients were ordered labs to check for HDV co-infection. **Results:** Age ranged from 32 to 84 years old with a mean of 57.85 ± 1.59. 47% were female and 53% were male. Ethnic distribution was 52% Asian descent, 4% Hispanic, 32% White, and 12% Black. Duration of HBV infection ranged from childhood to 84 years of age. HBs Ag was positive in 100%. HBV-DNA was <2000 in 73%, >1 million in 27%. Their mean ALT 31 ± 4.2, AST 35.6 ± 6, and platelet count 235,000 ± 10.9. HBe Ag was detected in 9.5% of patients. HDV-Ab was

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detected in 0.25% of patients. These 3 patients were tested for HDV-RNA titer. None of the 3 patients had active viruses. **Conclusion:** Active HDV is rarely detected in our cohort of patients in Southern California. Further efforts to screen HBV positive patients of other ethnic groups is underway.

Disclosures: Jasmine Ahmed: Nothing to Disclose, Deanna Oliver: Nothing to Disclose, Yaseen Kady: Nothing to Disclose, Julian Diaz-Moreno: Nothing to Disclose, James Johnson: Nothing to Disclose, Eric Storey: Nothing to Disclose, Maryam Yasso: Nothing to Disclose, Anna Hefner: Nothing to Disclose, Tarek Hassanein: Nothing to Disclose

1402 | INCIDENCE OF HEPATITIS DELTA VIRUS SUPER-INFECTION IN HBSAG POSITIVE PATIENTS FROM FRANCE AND THE GAMBIA (THE INCI-D COHORT STUDY)

Patrick INGILIZ[1] Erwan Vo Quang[2] Maud Lemoine[3] Amie Ceesay[4] Gibril Ndow[5] Marie-Noelle Hilleret[6] Laure Bordy[7] Thomas Decaens[6] Anne-Laure Mazialivoua[8] Yusuke Shimakava[9] Alhagie Bakoteh[5] Jean-Michel Pawlotsky[10] Isabelle CHEMIN[4] Stephane Chevaliez[11] Vincent Leroy[8]

[1]APHP Henri-Mondor University Hospital, [2]INSERM U955, Créteil, France, MRC The Gambia Unit@London School of Hygiene and Tropical Medicine, F, [3]Imperial College London, London, UK, [4]Cancer Research Centre, INSERM, Lyon, France, [5]MRC The Gambia Unit@London School of Hygiene and Tropical Medicine, Fajara, The Gambia, [6]University Hospital Grenoble-Alpes, Hepatology Department, Grenoble, France, [7]MNHilleret@chu-grenoble.fr, [8]APHP Henri-Mondor University Hospital, Hepatology Department, Créteil, France, [9]Unité d'Épidémiologie des Maladies Émergentes, Institut Pasteur, Paris, France, [10]INSERM U955, Créteil, France, [11]INSERM U955

Background: Super-infection with the hepatitis D virus (HDV) leads to a more aggressive form of chronic hepatitis in patients infected with the hepatitis B virus (HBV). While around 5% of HBsAg-positive individuals are estimated to be HBV-HDV dually infected globally, the timepoint of super-infection is unknown and longitudinal repeated HDV testing is not yet supported by international guidelines. Inci-D is a collaborative multicenter and longitudinal cohort study that aims to evaluate the incidence of HDV super-infection in HBsAg chronic carriers from West Africa and Europe. **Methods:** The Inci-D cohort consists of two distinct HBV cohorts of clinical meta-data and stored clinical specimens including plasma or dried-blood spots (DBS). Cohort A is a West African cohort derived from the PROLIFICA population-based study in The Gambia. Cohort B is a French cohort including out-patients seen in two university hospitals (Grenoble Alpes and Henri Mondor APHP). The HBsAg positive patients' first available stored blood sample was used to calculate the baseline prevalence. HDV-antibody (HDVAb) levels were detected using the Diasorin serology kit (Italy). **Results:** For cohort A, 942 blood samples (915 plasma, 27 DBS) of HBsAg-positive individuals were available at baseline. The median age was 35 years (interquartile range (IQR): 31-43), 592/942 (63%) were male. At baseline, 14/942 individuals (1.5%) were HDVAb-positive. Among HDVAb-negative patients at baseline, 566 individuals had a follow-up sample available (520 plasma, 46 DBS) with an overall follow-up time of 3363 patient-years. After a median follow-up time of 6.0 years (IQR: 5.5-6.8), 16 individuals were detected to be newly HDVAb- positive, representing an incidence rate of 4.3/1000 patient-years. For cohort B, 391 HBsAg-positive samples were available at baseline, the median age was 47 years (IQR 34-59), and 7/391 samples were HDVAb-positive (1.8%). Among HDVAb-negative patients, 379 had a follow-up sample available with an overall follow-up time of 813 patient-years. After a median follow-up time of 2.2 years (IQR: 1.42-3.06), 3 individuals were newly detected HDVAb-positive, representing an incidence rate of 3.69/1000 patient-years. **Conclusion:** Hepatitis delta superinfection increases considerably in HBsAg-positive carriers in The Gambia as well as in France putting patients at risk for advanced liver disease and death. In order to identify individuals with need for treatment or surveillance, repeated HDV serology testing should be implemented by international guidelines.

Disclosures: Patrick INGILIZ: GILEAD: Speaking and Teaching, Abbvie: Speaking and Teaching, ViiV: Speaking and Teaching, Erwan Vo Quang: Nothing to Disclose, Maud Lemoine: Nothing to Disclose, Amie Ceesay: Nothing to Disclose, Gibril Ndow: Nothing to Disclose, Marie-Noelle Hilleret: Nothing to Disclose, Laure Bordy: Nothing to Disclose, Thomas Decaens: Nothing to Disclose, Anne-Laure Mazialivoua: Nothing to Disclose, Yusuke Shimakava: Nothing to Disclose, Alhagie Bakoteh: Nothing to Disclose, Jean-Michel Pawlotsky: Abbvie: Speaker, Abbott: Advisor, Gilead: Speaking and Teaching, GSK: Advisor, Isabelle CHEMIN: Nothing to Disclose, Stephane Chevaliez: Nothing to Disclose, Vincent Leroy: Nothing to Disclose

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1403 | HEPATIC STEATOSIS IS ASSOCIATED WITH HBSAG CLEARANCE IN PATIENTS WITH CHRONIC HEPATITIS B VIRUS INFECTION

Emin Bodakci[1] Saba Kiremitçi[1] Serkan Duman[1] Zeynep Melekoglu Ellik[1] Mesut Gumussoy[1] Sevinc Tuğçe Guvenir[1] Volkan YILMAZ[1] ramazan erdem er[1] Fatih Karakaya[1] Hale Gokcan[1] Atilla Elhan[1] Berna Savas[1] Ramazan Idilman[1]

[1]Ankara University

Background: The present study aimed to determine the effect of hepatic steatosis detected by liver biopsy on HBsAg seroclearance and disease outcome in hepatitis B virus (HBV)-infected patients. **Methods:** This is a single-center, cross-sectional study. Between January 2005 and January 2021, patients with chronic HBV infection and patients with chronic hepatitis B (CHB) from an existing cohort of HBV-infected patients were enrolled. At the end of the follow-up period, the FIB-4 score was calculated, and transient elastography (VCTE) was performed. A Multivariable Cox Proportional Hazard model was used for statistical analysis. **Results:** This study included 296 HBV-infected patients: 186 with chronic HBV infection and 110 with CHB. At the diagnosis, the median age of HBV-infected patients was 56.9 years, and their gender was predominantly female (52%). The median BMI was 27.7 kg/m^2. Ninety and two percent of them were HBeAg negative. At baseline liver biopsy, 93 (31.4%) patients had hepatosteatosis: 81% had mild, and the remaining 19% had moderate/severe hepatosteatosis. No significant difference in hepatosteatosis between patients with chronic HBV infection and patients with CHB was observed (p= 0.780). Thirty-two patients (11%) achieved HBsAg loss during the follow-up period; 23 had HBsAg seroconversion to anti-HBs. Among these 32 patients, 30 had chronic HBV infection, while only two had CHB (11.4% vs. 1.8%, p < 0.001). HBsAg seroconversion to anti-HBs more commonly occurred in patients with HBV infection than in patients with CHB (11.4% vs. 1.8%, p= 0.003). HBsAg clearance commonly occurred in patients with hepatosteatosis compared to patients without hepatosteatosis (20.4% vs. 6.4%; p < 0.001). There was a significant association between hepatosteatosis grading and HBsAg loss (p < 0.001). Multivariable Cox regression showed the phase of HBV disease (Chronic HBV infection vs CHB) (Hazard Ratio [HR]: 6.385, Confidence Interval [CI]: 1.513-26.941 p = 0.012) and grading of hepatosteatosis at baseline liver biopsy (HR: 4.699, CI: 1.662-13.286 p = 0.004) were predictors of HBsAg loss in HBV-infected patients. At the end of the follow-up period, among patients with CHB who were on antiviral therapy, the fibrosis score detected by VCTE was significantly higher in patients with hepatosteatosis than that of patients without hepatosteatosis (median 6.8 kPa vs 5.1kPa, p< 0.001). **Conclusion:** Hepatosteatosis was associated with HBsAg seroclerance in patients with chronic HBV infection; however, hepatosteatosis causes disease progression in patients with CHB.

Disclosures: Emin Bodakci: Nothing to Disclose, Saba Kiremitçi: Nothing to Disclose, Serkan Duman: Nothing to Disclose, Zeynep Melekoglu Ellik: Nothing to Disclose, Mesut Gumussoy: Nothing to Disclose, Sevinc Tuğçe Guvenir: Nothing to Disclose, Volkan YILMAZ: Nothing to Disclose, ramazan erdem er: Nothing to Disclose, Fatih Karakaya: Nothing to Disclose, Hale Gokcan: Nothing to Disclose, Atilla Elhan: Nothing to Disclose, Berna Savas: Nothing to Disclose, Ramazan Idilman: Nothing to Disclose

1404 | SINGLE CELL SEQUENCING REVEALS RISE IN INTRAHEPATIC CXCL8, CCL4, AND SELL EXPRESSION WITH INCREASED FIBROSIS IN NAIVE CHRONIC HEPATITIS B PATIENTS WITH LOW HBSAG LEVELS

Ravinder Singh[1] Pramod Gautam[1] Manoj Sharma[1] EkTA Gupta[1] Archana Rastogi[1] Shiv Kumar Sarin[1] Nirupma Trehanpati[1]

[1]Institute of Liver and Biliary Sciences

Background: Chronic Hepatitis B (CHB) infection-mediated immune responses induce liver fibrosis. However, association of HBsAg levels and the severity of liver disease in CHB patients is not well understood. Therefore, with single-cell RNA sequencing (scRNA Seq), we have analysed the intrahepatic and peripheral immune cells in treatment-naive CHB (nCHB) patients. **Methods:** 36 nCHBV patients with HBsAg levels; Group I (HBsAg < 2000 IU/mL, HBsAg^{lo}, n=9) and Group II (HBsAg > 2000 IU/mL, HBsAg^{hi}, n=27) HBV DNA < and >2,000 IU/mL and ALT/AST ≥ 1.2 x ULN, liver biopsies, and blood were assessed using cytokine bead array, scRNA-Seq and histopathological analysis for fibrosis. **Results:** HBsAg^{lo} patients had significantly higher circulatory IL-8 (p=0.027) levels. scRNA seq of peripheral immune cells showed significantly (p<0.05) high, CCL4, CXCL8, and

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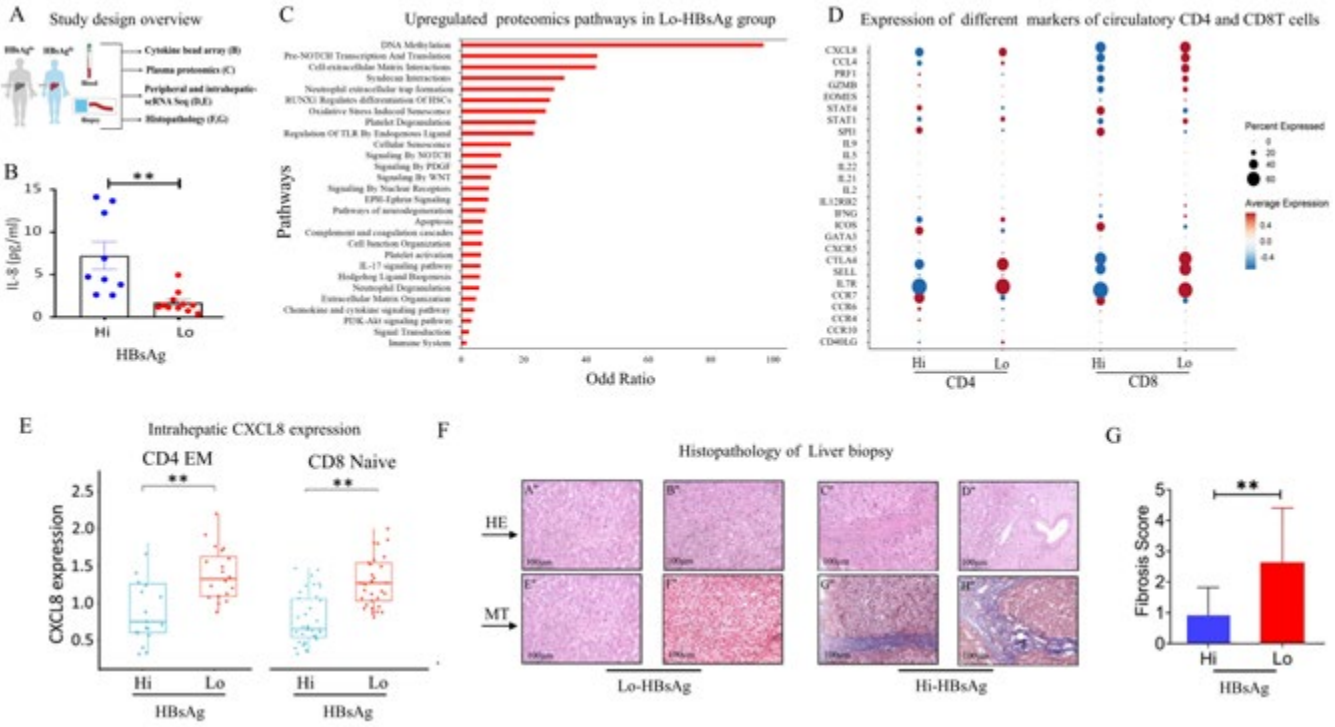
SELL in CD4 and CD8 compared to HBsAg^{hi} patients. Further, scRNA sequencing of liver biopsies in HBsAg^{lo} patients also revealed elevated CXCL8 expression (p=0.007) associated with intrahepatic CD4 effector memory (p=0.038) and CD8 naive (p=0.017) cells, compared to HBsAg^{hi} patients. In addition, HBsAg^{lo} patients exhibited a correlation between high expression of IL-8, CXCL8, and a higher fibrosis score (p=0.008). These patients also showed a stronger association between high levels of CXCL8, CCL4, and SELL with advanced fibrosis stages compared to HBsAg^{hi} patients. **Conclusion:** This study highlights that naive CHB patients with low HBsAg levels are more susceptible to fibrosis mediated by high circulatory and intrahepatic levels of CXCL8, and CCL4, alongside increased intrahepatic expression of the adhesion molecule SELL. These findings suggest that targeting these chemokines and adhesion molecules could offer new therapeutic avenues for managing fibrosis in CHB patients, particularly those with low HBsAg levels.



Disclosures: Ravinder Singh: Nothing to Disclose, Pramod Gautam: Nothing to Disclose, Manoj Sharma: Nothing to Disclose, EkTA Gupta: Nothing to Disclose, Archana Rastogi: Nothing to Disclose, Shiv Kumar Sarin: Nothing to Disclose, Nirupma Trehanpati: Nothing to Disclose

1405 | CHARACTERIZATION OF INTRAHEPATIC IMMUNE MICROENVIRONMENT IN LIVER BIOPSIES ACROSS DIFFERENT PHASES OF UNTREATED HBEAG-NEGATIVE PATIENTS

Maria Stella Franzè[1] Pascale MAILLE[2] Stefano Caruso[2] Julien Calderaro[2] Yasmine Bouda[3] Anna Sessa[2] Stephane Chevaliez[2] Patrick Ingiliz[4] Teresa Pollicino[5] Giovanni Raimondo[5] Jean-Michel Pawlotsky[2] Vincent Leroy[2] Giuliana Amaddeo[2]

[1]Team 18 INSERM U955; Université Paris-Est Créteil, France; University of Messina, Italy, [2]Team 18 INSERM U955; Université Paris-Est Créteil; Henri Mondor University Hospital, Créteil, France, [3]Team 18 INSERM U955; Université Paris-Est Créteil; Créteil, France, [4]Team 18 INSERM U955; Henri Mondor University Hospital, Créteil, France, [5]University of Messina, Messina, Italy

Background: Chronic hepatitis B virus (HBV) infection involves complex interplays between the virus and the host immune response, leading to distinct clinical phases defined arbitrarily. Some patients who do not meet the staging criteria of these phases fall into a “grey zone (GZ)”. We aimed to characterize the intrahepatic immune microenvironment by evaluating different genes expressions in a large cohort of untreated HBeAg negative (HBeAg-) patients to decipher their immune activation profiles. **Methods:** Ninety-six HBsAg positive HBeAg-patients who underwent liver biopsy at Henri Mondor Hospital between 2005 and 2020 were included. Data were

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collected for each patient at time of biopsy and during follow-up. Patients were classified as HBeAg- chronic low viremia infection (CI-LV), HBeAg- chronic hepatitis B (CHB), and GZ. RNA sequencing was performed for each case. **Results:** Seventy-four patients (77.1%) were male, with a median age of 40 (33-52) years. Fifteen subjects (15.6%) had a CI-LV (HBV DNA<2,000 IU/ml), 53 (55.2%) a CHB, and 28 were in a GZ (GZ1: 23 with HBV DNA>2,000 IU/ml but <20,000 IU/ml and normal ALT; GZ2: 5 with HBV DNA<2,000 IU/ml, but ALT>ULN). Fibrosis staging was F0/F1 in 83 patients (86.4%), F2/F3 in 10 (10.4%), F4 in 3 (3.1%). Histological activity was A0/A1 in 74 cases (77%) and A2/3 in 22 (23%). RNA-sequencing analysis showed two patient clusters (51 C1A, 45 C2A) with differently expressed genes (DEGs) profiles. C2A had higher histological activity grades (p=0.024) and ALT levels (p=0.035) than C1A. Intrahepatic immune infiltrate of C2A compared to C1A was enriched with monocytes, B, and $CD8^+$ T cells, and gene set pathways were mainly involved in immune responses. By excluding the 5 GZ2 patients, unsupervised hierarchical clustering identified two other patient groups (16 C1B, 75 C2B). C1B showed higher fibrosis (p=0.005), activity (p<0.001), HBV DNA (p<0.001), and ALT (p=0.003) than C2B. MCP-counter analysis showed an immune infiltrate enriched with fibroblasts, monocytes, cytotoxic lymphocytes, and endothelial, myeloid dendritic, B, T, CD8+T cells in C1B vs C2B. Supervised DEGs analysis revealed 841 and 374 genes significantly down- and up-regulated in C2B vs C1B. Gene set enrichment analysis with MSigDB indicated that C1B was associated with gene sets pathways mainly involved in immune response. A sensitivity analysis was performed in a subgroup of 71 cases (F0/1-A0/1) identified again 2 clusters, differing in monocytic and CD8+ T cells immune infiltrate and related pathways activation. **Conclusion:** These results reveal differences in gene expression profiles across different phases of HBeAg- patients, suggesting the need to characterize those at risk of liver disease progression well and thus requiring early antiviral treatment.

Disclosures: Maria Stella Franzè: Nothing to Disclose, Pascale MAILLE: Nothing to Disclose, Stefano Caruso: Nothing to Disclose, Julien Calderaro: Nothing to Disclose, Yasmine Bouda: Nothing to Disclose, Anna Sessa: Nothing to Disclose, Stephane Chevaliez: Nothing to Disclose, Patrick Ingiliz: Nothing to Disclose, Teresa Pollicino: Nothing to Disclose, Giovanni Raimondo: Nothing to Disclose, Jean-Michel Pawlotsky: Abbvie: Speaker, Abbott: Advisor, Gilead: Speaking and Teaching, GSK: Advisor, Vincent Leroy: Nothing to Disclose, Giuliana Amaddeo: Nothing to Disclose

1406 | UPTAKE AND T CELL STIMULATION BY BJT-778-HBSAG IMMUNE COMPLEXES: INSIGHTS INTO ANTI-HBS MONOCLONAL ANTIBODY FUNCTION ◆

Loghman Salimzadeh[1] Stuti Shah[1] Danie La[1] Hilario Ramos[2] Nancy Shulman[2] Hassan Javanbakht[2] Adam Gehring[1]

[1]University Health Network, [2]Bluejay Therapeutics

Background: In chronic hepatitis B (CHB) patients, the persistent high levels of hepatitis B virus surface antigen (HBsAg) contributes to the exhaustion of HBV-specific T and B cell responses. BJT-778, a fully human IgG1 monoclonal antibody targeting the antigenic loop of HBsAg, is currently in clinical development for CHB and Hepatitis Delta. This study investigated the uptake of BJT-778-HBsAg immune complexes (ICs) by antigen-presenting cells and the impact on recombinant and serum-derived HBsAg presentation to HBs-specific CD4 T cells. **Methods:** ICs were produced by combining BJT-778 with DyLight-550-labeled recombinant HBsAg (rHBsAg) or serum HBsAg (sHBsAg) from CHB patients. Flow cytometry was utilized to examine the uptake kinetics of ICs in seven distinct antigen presenting cell populations in PBMCs from healthy individuals and CHB patients. Fc-dependent uptake was confirmed by blocking Fc receptors. The expression profile of FcγRI, FcγRII and FcγRIII was assessed on PBMC samples using flowcytometry and correlated with HBsAg-IC uptake and binding affinity measured via Biacore. Antigen presentation was studied by loading CD14+ cells with BJT-778-rHBsAg or sHBsAg-ICs, followed by co-culture with an HBsAg-specific CD4+ T cell clone then measuring T cell activation through IFN-γ production. **Results:** BJT-778 significantly increased the uptake of HBsAg compared to an isotype control Ab or HBsAg alone. There was a distinct hierarchy of IC uptake that was blocked by inhibiting Fc receptors: classical monocytes (cMono; 99.50%) > intermediate monocytes (iMono; 87.2%) > Non-classical monocytes (ncMono; 64.8%) > myeloid dendritic cells (mDC; 30.2%). CD141+ DCs, plasmacytoid DCs, or B cells did not show significant enhancement of HBsAg uptake with ICs. Notably, cMono and mDCs from CHB patients exhibited significantly slower uptake of ICs compared to healthy donors. BJT-778 showed the highest binding affinity to FcRI and FcγRIIIa which was correlated with expression on cMono, iMono, and mDCs. Enhanced uptake of both rHBsAg-ICs and sHBsAg-ICs by CD14+ monocytes enhanced activation of HBsAg-specific CD4 T cells. **Conclusion:** These data identify the likely in vivo targets of BJT-778-HBsAg ICs and demonstrate that BJT-778 ICs lead to enhanced HBsAg uptake in professional antigen presenting cells. Enhanced uptake of HBsAg

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resulted in increased HBV-specific CD4 T cell activation, supporting a dual mechanism of action through removal of circulating HBsAg and stimulation of HBV-specific T cell immunity.

Disclosures: Loghman Salimzadeh: Nothing to Disclose, Stuti Shah: Nothing to Disclose, Danie La: Nothing to Disclose, Hilario Ramos: Bluejay Therapeutics: Employee, Bluejay Therapeutics: Stock – privately held company, Nancy Shulman: Bluejay Therapeutics, INC: Salary and equity, Hassan Javanbakht: Nothing to Disclose, Adam Gehring: Nothing to Disclose

1407 | PRECLINICAL PHARMACOKINETICS OF EDP-514, AN ORAL, ONCE-DAILY ANTIVIRAL TREATMENT FOR HEPATITIS B VIRUS

Meng Huang[1] Khanh Hoang[1] Jonathan Kibel[1] Shucha Zhang[1] Lisha Xu[1] Yang Li[1] Indy Zang[1] Daniel Leonard[1] Siu-Lung Chan[1] Joshua Klaene[1] Yat Sun Or[1] Li-Juan Jiang[1]

[1]Enanta Pharmaceuticals

Background: Hepatitis B virus (HBV) is a global public health threat that causes approximately 1.5 million new infections every year. Chronic infection with HBV leads to increased risk of cirrhosis and hepatocellular carcinoma. Current treatments for HBV infection are rarely curative but urgently needed. Here, we describe the preclinical pharmacokinetics (PK) of EDP-514, a potent and selective class II core assembly modulator, with Fast Track designation from the FDA. In a randomized, double-blind, placebo-controlled clinical proof of concept study with chronic HBV patients, EDP-514 was safe and well-tolerated. Once-daily dosing reduced HBV DNA up to 3.5 logs (placebo=0.2 log reduction). **Methods:** Human oral absorption and metabolic stability were tested using Caco-2 cells and human liver microsomes, respectively. To determine the PK profile, mice were orally dosed with 10 or 25 mg/kg of EDP-514 and plasma and tissue drug levels were analyzed by high performance liquid chromatography and tandem mass spectrometry (HPLC-MS/MS). Allometric scaling was applied to predict human PK. **Results:** EDP-514 was readily absorbed with 12.6 x 10^{-6} cm/s A-B permeability in the Caco-2 assay. Consistent with *in vitro* data, oral bioavailability was high in the murine model (male: 49.6%, female: 80.1%) and plasma exposure increased linearly with dose from 25 mg/kg to 400 mg/kg in males; a similar trend was later observed in the clinic. The target organ of HBV, the liver, incurred a high distribution of EDP-514 (male: 7.5, female: 7.3), while distribution to the brain was exceedingly low. Allometric scaling projected a long half-life of 16.1 hours with an efficacious once-daily dose of 200 mg in humans, consistent with the half-life reported in clinical studies. **Conclusion:** EDP-514 has a favorable PK profile and excellent target tissue penetration. The impressive combination of potent antiviral activity, high target tissue distribution, and clinical efficacy demonstrated from once-daily oral dosing, makes EDP-514 the ideal candidate for continued development in a combination regimen.

Compound	Caco-2 permeability (x 10^{-6} cm/s)	Mouse PK			Human PK	
		Gender	F (%)	Liver over Plasma Ratio	Predicted $t_{1/2}$ (h)	Observed $t_{1/2}$ (h)
EDP-514	12.6	M	49.6	7.5	16.1	15.6
		F	80.1	7.3		

Disclosures: Meng Huang: Enanta Pharmaceuticals: Employee, Khanh Hoang: Nothing to Disclose, Jonathan Kibel: Nothing to Disclose, Shucha Zhang: Nothing to Disclose, Lisha Xu: Nothing to Disclose, Yang Li: Nothing to Disclose, Indy Zang: Nothing to Disclose, Daniel Leonard: Nothing to Disclose, Siu-Lung Chan: Nothing to Disclose, Joshua Klaene: Nothing to Disclose, Yat Sun Or: Nothing to Disclose, Li-Juan Jiang: Nothing to Disclose

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1408 | INCREASING RISK OF METABOLIC COMORBIDITIES IN PATIENTS WITH HBV MONOINFECTION, HBV/HCV COINFECTION, AND HBV/HIV COINFECTION: A NATIONWIDE POPULATION-BASED STUDY

Jae Yoon Jeong[1] Won Sohn[2] Hyun Woo Oh[2] Hyo Young Lee[3] Na Ryung Choi[1] Yeonjae Kim[4] Jung Hee Kim[5]

[1]Ewha Womans University Mokdong Hospital, College of Medicine, Ewha Womans University, [2]Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, [3]Inje University Sanggye Paik Hospital, [4]National Medical Center, [5]Dongtan Sacred Heart Hospital of Hallym University Medical Center

Background: The use of antiviral therapy in patients with chronic hepatitis B (CHB) has consistently improved survival rates and a positive impact on metabolic comorbidities. However, increased longevity resulting from these improved survival rates has led to a rising prevalence of metabolic comorbidities among elderly CHB patients. Additionally, it is known that both hepatitis C virus (HCV) and human immunodeficiency virus (HIV) infections contribute to an increased risk of metabolic comorbidities. This study aimed to assess the changes in metabolic comorbidities among patients with HBV monoinfection, HBV/HCV coinfection, and HBV/HIV coinfection in South Korea. **Methods:** A retrospective, cross-sectional study was conducted using nationwide claims data obtained from the Health Insurance Review and Assessment Service (HIRA), covering the period from 2014 to 2021 in South Korea. Subjects were stratified into HBV monoinfection, HBV/HCV coinfection, and HBV/HIV coinfection groups, with annual intergroup comparisons conducted. **Results:** The number of chronic hepatitis B patients increased annually from 327,041 in 2014 to 473,811 in 2021. HBV monoinfection cases rose from 324,335 in 2014 to 469,834 in 2021. HBV/HCV coinfection cases increased from 2,505 in 2014 to 4,503 in 2019, and HBV/HIV coinfection cases from 180 in 2014 to 308 in 2020. The proportion of patients aged 60 years and older also increased annually across all groups: HBV monoinfection (19.9% in 2014 to 35.3% in 2021), HBV/HCV coinfection (37.0% in 2014 to 54.1% in 2021), and HBV/HIV coinfection (11.1% in 2014 to 26.9% in 2021). The prevalence of metabolic comorbidities such as hypertension, diabetes, and hyperlipidemia increased annually among HBV patients. Comparatively, HBV/HCV coinfection patients exhibited a higher prevalence of these metabolic comorbidities than those with HBV monoinfection and HBV/HIV coinfection ($P<0.001$ in all years). Over time, the difference in the prevalence of metabolic comorbidities between HBV monoinfection and HBV/HIV coinfection patients diminished (Figure 1). **Conclusion:** In South Korea, the aging population of chronic hepatitis B patients is accompanied by an increasing prevalence of metabolic comorbidities. Patients with HBV/HCV coinfection exhibit a higher prevalence of metabolic comorbidities compared to those with HBV monoinfection and HBV/HIV coinfection. However, the prevalence of metabolic comorbidities between HBV monoinfection and HBV/HIV coinfection patients is becoming increasingly similar over time.

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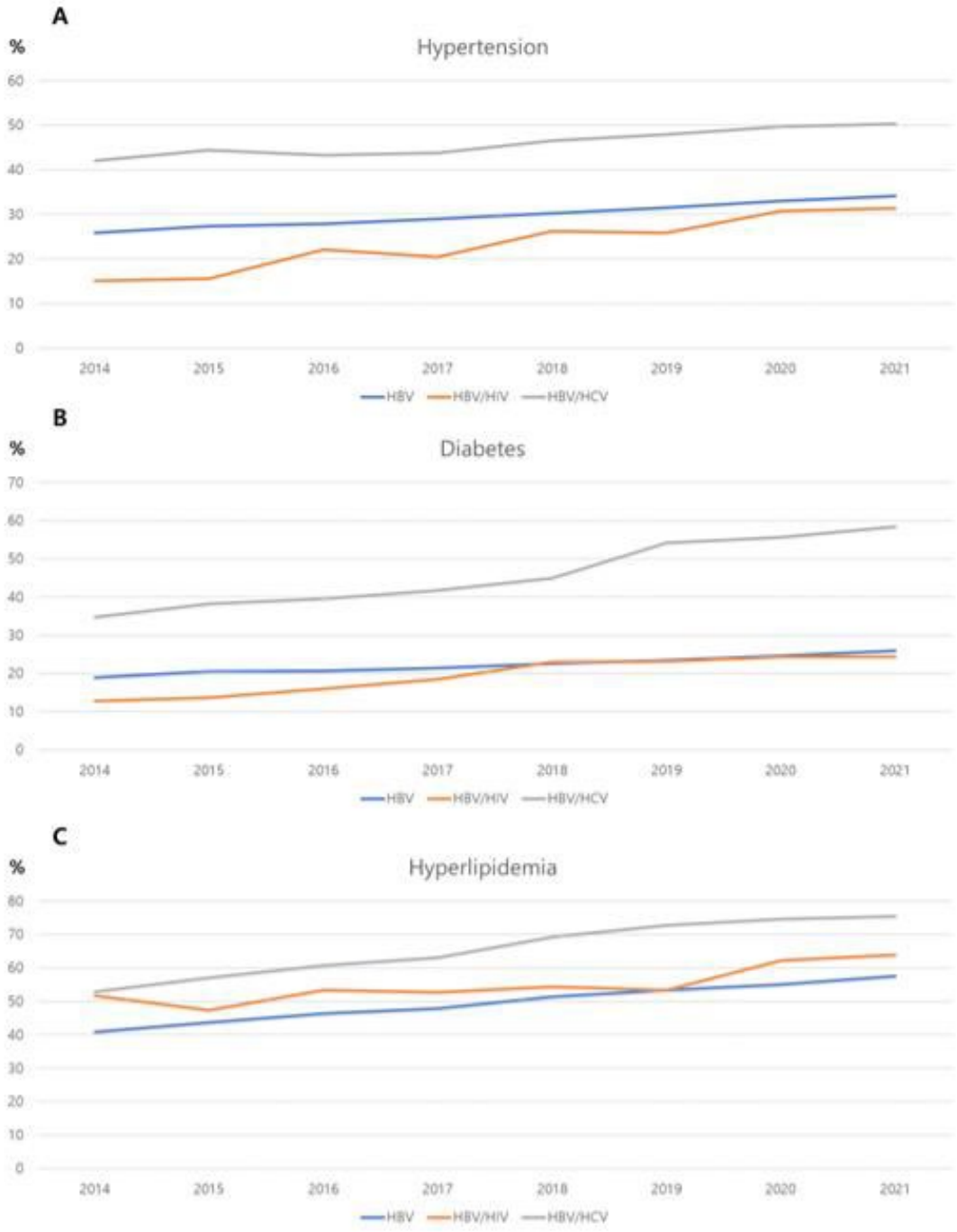
Figure 1. Change of prevalence of hypertension (A), diabetes (B) and hyperlipidemia (C) according to group from 2014 to 2021



Disclosures: Jae Yoon Jeong: Nothing to Disclose, Won Sohn: Nothing to Disclose, Hyun Woo Oh: Nothing to Disclose, Hyo Young Lee: Nothing to Disclose, Na Ryung Choi: Nothing to Disclose, Yeonjae Kim: Nothing to Disclose, Jung Hee Kim: Nothing to Disclose

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1409 | DOSE-DEPENDENT EFFECTS OF NEUTRALIZING ANTI-HBS MONOCLONAL ANTIBODY VIR-3434 ON HEPATITIS B SURFACE ANTIGEN COMPOSITION

Maria Pfefferkorn[1] Gregory Camus[2] Andrea Cathcart[2] Jonathan Seltmann[3] Thomas Berg[3] Hasan Imam[2] Andre Arizpe[2] Madlen Matz-Soja[4] Florian van Bömmel[3]

[1]Division of Hepatology, Department of Medicine II, Leipzig University Medical Center, Leipzig, [2]Vir Biotechnology, Inc., San Francisco, CA, USA, [3]Division of Hepatology, Department of Medicine II, Leipzig University Medical Center, [4]Rudolf-Schönheimer-Institute for Biochemistry, Leipzig University, Germany

Background: Tobevibart (VIR-3434) is an investigational Fc-engineered human monoclonal antibody (mAb) targeting the conserved antigenic loop of HBsAg in development for the treatment of chronic hepatitis B (CHB). Recently, a decrease in large (L) and medium (M) HBsAg components during treatment with nucleos(t)ide analogues (NA) was found to be associated with subsequent HBsAg loss, indicating a likely association of MHBs and LHBs with cccDNA transcriptional activity. We analyzed the effect of tobevibart, alone or in combination with NA, on the composition of HBsAg in the serum of patients with chronic hepatitis B (CHB). **Methods:** Sera of 69 mostly HBeAg-negative patients from the prospective randomized VIR-3434-1002 phase I trial were retrospectively analyzed. Patients were divided in 3 cohorts: Part B (n=30; NA treatment ≥ 2 months prior to study + BL HBsAg levels <3000 IU/mL), Part C (n=23; NA treatment ≥ 2 months prior to study + BL HBsAg levels ≥3000 IU/mL) and Part D (n=16; not on NA, BL HBV DNA ≥ 1000 IU/mL, any HBsAg level) and received a single dose subcutaneous injection of either 6, 18, 75, or 300 mg of tobevibart at day 1 (BL). Serum HBsAg components were quantified on an automated platform (DiaSorin) with well-defined mAbs (LHBs [Ma18/7]; MHBs [Q19/10]; total HBsAg: [DiaSorin, Enzygnost HBsAg 6.0]) in sera of days 1, 8 and 57. **Results:** At BL, levels of total HBsAg, MHBs, and LHBs were significantly lower in Part B compared to Part C or D, respectively (p<0.001). At day 8, levels of LHBs and MHBs decreased in all groups independent of the tobevibart dose, with Part B showing the strongest decline. However, the ratio of MHBs only decreased significantly in Part B from 3.8% at BL to 0% at day 8 (p<0.001) and slightly re-increased to 0.7% at day 57. In Part C and D, MHBs also decreased from 3.9 and 3.4% at BL to 1.4 and 2.1% after 8 days but re-increased to 4.3 and 6.1% at day 57 (p=n.s.). Moreover, treatment in Part B showed a dose-dependent effect on the decrease of LHBs and MHBs levels, with a single dose of 300 mg causing the strongest decrease in ratios of LHBs and MHBs. **Conclusion:** A single dose of tobevibart added to NA treatment significantly suppressed LHBs and MHBs components in patients with baseline HBsAg levels below 3.000 IU/mL. Further investigation is needed to determine if this suppression indicates reduced cccDNA transcriptional activity, potentially predicting a functional cure with long-term tobevibart treatment.

Disclosures: Maria Pfefferkorn: Nothing to Disclose, Gregory Camus: Nothing to Disclose, Andrea Cathcart: VIR Biotechnology: Employee, Jonathan Seltmann: Nothing to Disclose, Thomas Berg: Nothing to Disclose, Hasan Imam: Nothing to Disclose, Andre Arizpe: Vir Biotechnology: Employee, Madlen Matz-Soja: Nothing to Disclose, Florian van Bömmel: VIR Biotechnology: Independent Contractor

1410 | GLOBAL PREVALENCE AND OUTCOME OF CHB PATIENTS WITH INDETERMINATE PHASE: A SYSTEMATIC REVIEW AND META-ANALYSIS OF 35 STUDIES AND 27,529 PATIENTS

Jie Li Xiaoming Xu[1] Ming Li[1] Jiacheng Liu[1] Rahma Issa[1] Leslie Kam[2] Fajuan Rui[1] Wenjing Ni[1] Yixuan Zhu[1] Xiaoyan Ma[1] Qi Gu[1] Yifan Pan[1] Chao Wu[1] Mindie Nguyen[3]

[1]Department of Infectious Diseases, Nanjing Drum Tower Hospital, [2]Division of Gastroenterology and Hepatology, Stanford University Medical Center, [3]Stanford University Medical Center

Background: Although current guidelines classify chronic hepatitis B (CHB) into several immune phases, a substantial proportion of patients fall into an uncertain phenotype which is known as indeterminate phase. Therefore, we performed a meta-analysis to systematically evaluate the prevalence and outcomes of indeterminate CHB patients. **Methods:** PubMed, Embase, WOS, and Cochrane library were searched for eligible studies from inception to 22nd Oct 2023. Primary outcomes were the prevalence of indeterminate CHB patients defined by the American Association for the Study of Liver Diseases (AASLD) 2018 guidelines within the CHB group, and pooled occurrence rate of adverse liver events in indeterminate CHB population. **Results:** We identified 35 eligible studies, covering 27,529 participants from 12 countries or regions, we found that the

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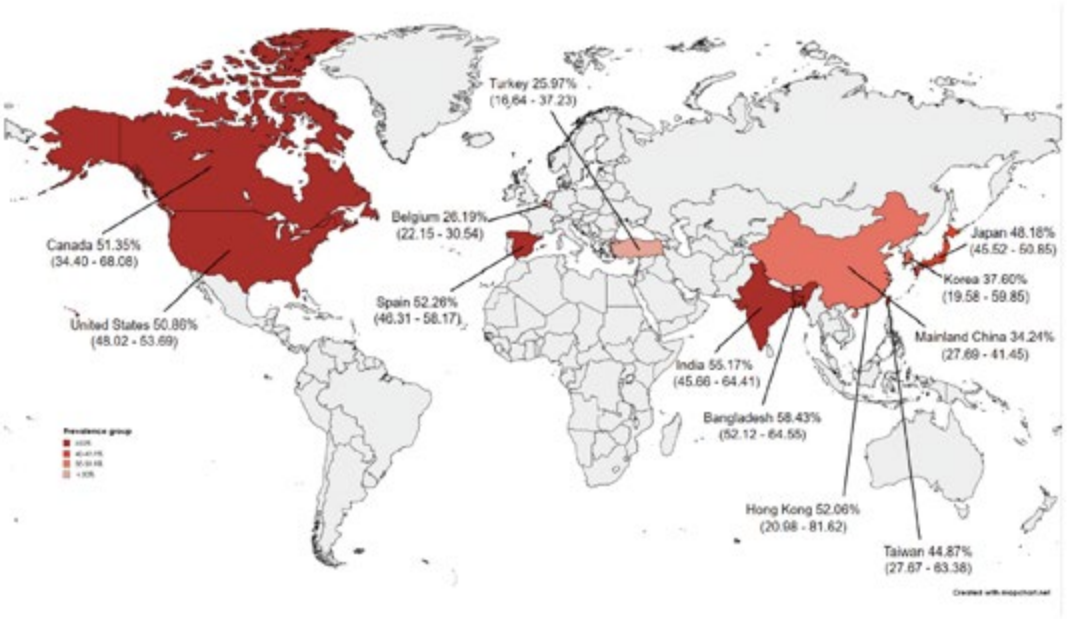
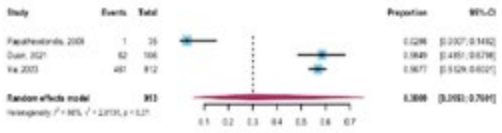
global prevalence of indeterminate CHB among the CHB population was 41.12% (95% CI: 34.58 - 48.00). Among countries/regions with at least two studies, Hong Kong had the highest prevalence of indeterminate CHB, at 52.06% (95% CI 20.98 - 81.62; I^2=99%), while Chinese mainland had the lowest, at 34.24% (95% CI 27.69 - 41.45; I^2=99%). The prevalence was 37.73% (95% CI 30.76 - 45.24; I^2=99%) and 34.99% (95% CI 27.35 - 43.49; I^2=98%) in male and female, respectively. In HBeAg-positive and negative patients, the prevalence were 30.61% (95% CI 18.60 - 45.99; I^2=99%) and 43.88% (95% CI 36.20 - 51.88; I^2=99%), respectively. Notably, the prevalence of indeterminate CHB in the ALT ≥ ULN and HBV DNA ≥ 2000 IU/mL populations were 80.61% and 91.80%, respectively, which differed significantly compared with the population of HBV DNA < 2000 IU/mL and ALT < ULN. Among indeterminate CHB patients, the pooled occurrence rates of significant inflammation, significant fibrosis, HCC, and summary liver related events among the included studies were 46.55% (95% CI 27.03 - 67.19; I^2=96%), 7.16% (95% CI 2.06 - 22.10; I^2=88%), 2.64 %(95% CI 0.97 - 7.02; I^2=91%), and 0. 77% (95% CI 0.05 - 11.36; I^2=61%), respectively. **Conclusion:** Indeterminate CHB accounts for a substantial proportion of the untreated CHB cases and carry high rates of adverse liver events. The evaluation of patients with indeterminate CHB should be individualized and high-risk patients should be considered for antiviral therapies.

A. The global prevalence of indeterminate CHB

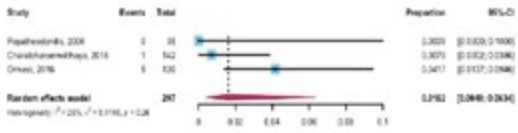


B. Pooled occurrence rate of adverse liver events in indeterminate CHB population

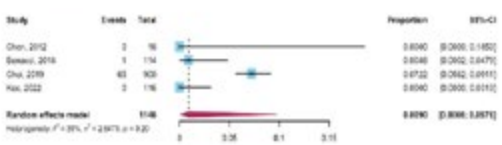
a. Significant inflammation



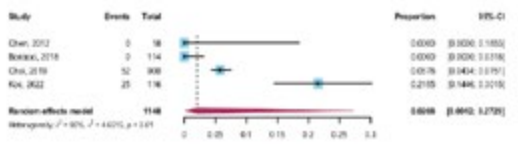
b. Significant fibrosis



c. HCC



d. Liver related events



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Disclosures: Jie Li: Nothing to Disclose, Xiaoming Xu: Nothing to Disclose, Ming Li: Nothing to Disclose, Jiacheng Liu: Nothing to Disclose, Rahma Issa: Nothing to Disclose, Leslie Kam: Nothing to Disclose, Fajuan Rui: Nothing to Disclose, Wenjing Ni: Nothing to Disclose, Yixuan Zhu: Nothing to Disclose, Xiaoyan Ma: Nothing to Disclose, Qi Gu: Nothing to Disclose, Yifan Pan: Nothing to Disclose, Chao Wu: Nothing to Disclose, Mindie Nguyen: Nothing to Disclose

1411 | PREDICTORS OF HBSAG LOSS IN HIV-HBV COINFECTED PATIENTS RECEIVING ANTIRETROVIRAL THERAPY: A SYSTEMATIC REVIEW ◆

Mansoor Rahman[1] FNU Khalil Ur Rehman[1] Fatima Usama[1] Khawaja Hassam[1] Rohullah Rasikh[1] Syed Bilal Shah[1] Ashraf Ullah[1] Zabeeh Ullah[2] Abu baker Khan[3] Daryl Lau[1]

[1]Beth Israel Deaconess Medical Center, [2]Khyber Teaching Hospital, [3]Ayub Medical Complex

Background: There were reports that patients with HIV-HBV coinfection achieved higher rates of HBsAg loss, or functional cure, in response to therapy compared to those with HBV monoinfection. This systematic review aimed to identify the factors associated with functional cure in HIV-HBV coninfected patients from various geographical regions on HAART treatment. **Methods:** A literature search was performed in PubMed, Embase, and Web of Science databases to retrieve studies published in English on HBsAg and HBeAg loss in HIV-HBV coinfected patients who received anti-HBV containing HAART therapy. **Results:** Out of the 2852 citations, 36 studies met the inclusion criteria; that included 3 clinical trials and 33 observational studies with 15 retrospective, 18 prospective cohorts. Among these studies, 17 were conducted in Europe, 11 in Asia, 5 in Africa, and 3 in North America. 6675 subjects were included: 3639 (54.5%) from Europe, 1879 (28%) from Asia, 914 (13.7%) from Africa, and 243 (3.6%) from North America. There was a broad baseline pretreatment CD4+ T cell count from 25-605 cells/µl across the studies with variable follow-up observations from 0.9-9.9 years. In all the continents, the rates of HBeAg loss was higher than HBsAg loss during the study periods. For HBeAg loss, the rates were 28.6%, 29.1%, 33.6% and 30.5% for studies from Asia, Europe, North America and Africa, respectively. There was no significant corelation between baseline CD4 count and HBeAg loss (p= 0.13). The rates of HBsAg loss were 8.7%, 10.7%, 10.2% and 13% for studies from Asia, Europe, North America and Africa, respectively. Median baseline CD4 count was found to have a significant inverse correlation with HBsAg loss (r=-0.30, p=0.044) [Figure]. This inverse relationship of CD4+ T cells and functional cure was strongest among the African studies (r=-0.7, p=0.04). Other key variables assocaied with HBsAg loss were CD4 count increase on therapy, baseline HBsAg and the reduction of HBsAg during treatment. Significant odds ratios (OR, 95%CI) of achieving HBsAg loss in patients with a CD4 increase were reported by studies from North America OR 1.004 (1.001-1.006), p=0.007) and Africa OR 4.94(1.02-23.80), p<0.05). Many studies from Europe found that a low HBsAg count of <1000 IU/ml or >2 log reduction in HBsAg titers during the initial 6 months of therapy were associated with functional cure. **Conclusion:** In this analysis, low pretreatment CD4 count was found to be associated with functional cure especially among the studies conducted in Africa. This supported the hypothesis that the rigorous recovery of immune function secondary to HAART can also facilitate the HBV specific immune response leading to HBsAg clearance. There are, however, other predictors that may be preferentially contributing to functional cure in selective populations. More in-depth understanding of the mechanisms of immune reconstitution would be important for the development of novel therapeutic agents.

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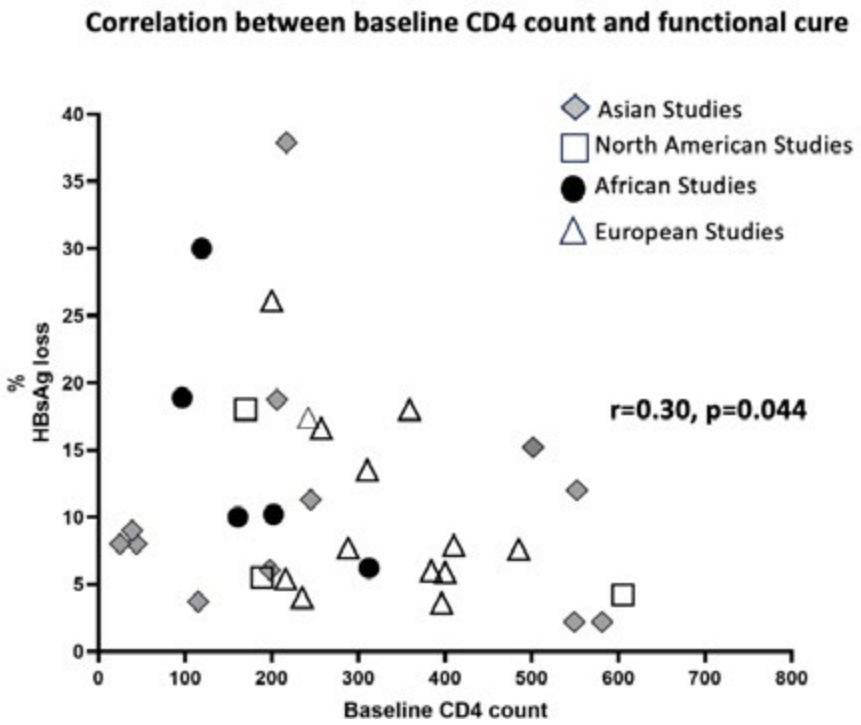

Disclosures: Mansoor Rahman: Nothing to Disclose, FNU Khalil Ur Rehman: Nothing to Disclose, Fatima Usama: Nothing to Disclose, Khawaja Hassam: Nothing to Disclose, Rohullah Rasikh: Nothing to Disclose, Syed Bilal Shah: Nothing to Disclose, Ashraf Ullah: Nothing to Disclose, Zabeeh Ullah: Nothing to Disclose, Abu baker Khan: Nothing to Disclose, Daryl Lau: Gilead: Grant/Research Support, GSK: Consultant, Abbott Laboratories: Consultant

1412 | DISTRIBUTION OF CIRCULATING T FOLLICULAR HELPER 17 CELL SUBSETS ALTERED IN CHB PATIENTS

Shengxia Yin[1] *Qi Gu*[1] *Minxin Mao*[1] *Chao Wu*[1] *Jie Li*[1]

[1]*Nanjing Drum Tower Hospital, Affiliated Hospital of Medical School, Nanjing University*

Background: Hepatitis B virus (HBV)-specific B cell dysfunction is associated with failure of functional cure in chronic hepatitis B (CHB). Tfh cells play a key role in the production of antibody-secreting B cells. **Methods:** We analysed the subgroup frequencies and surface protein features of follicular T helper cells (Tfh) and HBsAg-specific B cells by flow cytometry, using samples from peripheral blood mononuclear cells (PBMCs) of CHB patients and healthy individuals treated with untreated nucleoside analogues and/or Peg-IFN-α. To detect the frequency and number of Tfh cells secreted by HBsAg-specific IL21, PBMCs were resuscitated in RPMI 1640 complete medium with 10 μg/ml HBsAg peptide pools for 3 days. **Results:** Compared to healthy individuals, patients with chronic hepatitis B had significantly more Tfh cells (P <0.0001), significantly more Tfh17 cells (P =0.0082), and significantly more PD-1 expression in cTfh17 (P <0.0001). Further analysis revealed a decrease in the frequency of actived Tfh17 cells and IL-21+ Tfh17 cells during the HBeAg-negative chronic hepatitis (ENH) phase; an increase in the frequency of Tfh17 cells and quiescent Tfh17 cells (all P <0.05). The frequencies of actived Tfh17 cells had a positive correlation with HBsAg+ B cells (P =0.0006, r=0.4245), but the frequencies of quiescent Tfh17 cells had a negatived correlation with HBsAg+ B cells (P =0.004, r=-0.3604). The frequency of quiescent Tfh17 cells was positively correlated with total IgG (P =0.0014, r=0.5473). Further analysis revealed that the frequency of quiescent Tfh17 cells was positively correlated with IgG1 (P =0.0059, r=0.4758) and IgG3 (P =0.0070, r=0.4896). **Conclusion:** Our study suggested that Tfh17 frequency and IL-21+ cTfh cell frequency differ in different immune stages of patients with chronic HBV infection and that Tfh17 may play an important role in regulating the immune response to chronic HBV infection.

Disclosures: Shengxia Yin: Nothing to Disclose, Qi Gu: Nothing to Disclose, Minxin Mao: Nothing to Disclose, Chao Wu: Nothing to Disclose, Jie Li: Nothing to Disclose

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1413 | DIFFERENTIAL HBV REPLICATIVE MARKERS AND COVALENTLY CLOSED CIRCULAR DNA TRANSCRIPTION IN IMMUNE-ACTIVE CHRONIC HEPATITIS B WITH AND WITHOUT HBEAG

Hye Seon Kim[1] Soon Kyu Lee[2] Ji Won Han[2] Heechul Nam[2] Pil Soo Sung[2] Sung Won Lee[2] Jung Hyun Kwon[2] SI HYUN BAE[2] Jong Young Choi[2] Seung Kew Yoon[2] Jeong Won Jang[2]

[1]The Catholic University Liver Research Center, The Catholic University of Korea, [2]Department of Internal Medicine, The Catholic University of Korea

Background: Molecular processes driving immune-active chronic hepatitis B (CHB) with and without HBeAg remain incompletely understood. This study aimed to investigate expression profiles of serum and intrahepatic HBV markers and replicative activity of HBV in CHB patients with or without HBeAg. **Methods:** This study recruited 111 untreated immune-active CHB (60 HBeAg-positive and 51 HBeAg-negative) patients and quantified intrahepatic covalently closed circular DNA (cccDNA), pre-genomic RNA (pgRNA), total HBV DNA (tDNA), and replicative intermediates as well as serum HBV markers (HBV DNA, HBsAg, HBcrAg). Correlations between HBV markers and clinico-virological factors influencing expression levels of HBV markers were analyzed. **Results:** Levels of all serum markers and intrahepatic cccDNA/tDNA as well as cccDNA transcriptional activity and virion productivity were significantly reduced in HBeAg-negative patients compared to those in HBeAg-positive patients. Additionally, correlations between intrahepatic cccDNA/pgRNA and serum markers were impaired in HBeAg-negative individuals. Aminotransferase levels were positively correlated with cccDNA transcriptional activity in HBeAg-positive patients, but not in HBeAg-negative patients. Notably, among HBeAg-positive patients, there was a progressive decline in pgRNA level, transcriptional activity, and serum HBV markers as liver fibrosis advanced, which was not observed in HBeAg-negative patients. **Conclusion:** HBeAg loss is correlated with diminished intrahepatic HBV reservoirs and cccDNA transcription, leading to decreased serum HBV marker levels. Circulating HBV markers are not reliable indicators of intrahepatic HBV replicative activity for HBeAg-negative patients. Our findings reveal distinct disease phenotypes between immune-active CHB with and without HBeAg, highlighting the need to establish optimal surrogate biomarkers that can accurately mirror intrahepatic viral activity to aid in decision-making for antiviral therapy for immune-active CHB.

Disclosures: Hye Seon Kim: Nothing to Disclose, Soon Kyu Lee: Nothing to Disclose, Ji Won Han: Nothing to Disclose, Heechul Nam: Nothing to Disclose, Pil Soo Sung: Nothing to Disclose, Sung Won Lee: Nothing to Disclose, Jung Hyun Kwon: Nothing to Disclose, SI HYUN BAE: Nothing to Disclose, Jong Young Choi: Nothing to Disclose, Seung Kew Yoon: Nothing to Disclose, Jeong Won Jang: Nothing to Disclose

1414 | PRE-CLINICAL CHARACTERIZATION OF CAVROTOLIMOD, A TLR9 AGONIST FOR THE TREATMENT OF CHRONIC HEPATITIS B

Hilario Ramos[1] Jerome Deval[1] Jenny Stanton[1] Nancy Shulman[1] Hassan Javanbakht[1]

[1]Bluejay Therapeutics

Background: Cavrotolimod (CAVRO), a novel spherical nucleic acid (SNA) configuration of a Toll-Like Receptor 9 (TLR9) agonist oligonucleotide, is designed to activate both innate and adaptive immune responses, potentially enhancing antiviral immunity in patients with chronic hepatitis B (CHB). The safety and pharmacokinetic (PK) properties of CAVRO have been evaluated in a first-in-human Ph 1 study in healthy subjects (Daniel et al., 2022) demonstrating its safety and tolerability across various doses. Consequently, CAVRO shows promise in safely activating antiviral immunity and improving functional cure rates in CHB. In this study, the pharmacologic activity of CAVRO was assessed through a series of in vitro and in vivo experiments. **Methods:** In vitro studies were conducted to demonstrate the potency and selectivity of CAVRO. The impact of treatment on human peripheral blood mononuclear cells (PBMCs) was evaluated, alongside a study assessing the PD effects of subcutaneously administered CAVRO in cynomolgus monkeys across a range of doses. Assessments included immune cell activation measured by flow cytometry and cytokine and chemokine concentrations in serum. **Results:** CAVRO selectively activated TLR9 without impacting other TLRs such as TLR3, TLR7, or TLR8 in engineered HEK cells. It effectively induced the production of key Th1-type cytokines in human PBMCs, including IFNγ, IL-6, IL-10, IL-12p40, IP-10, and TNFα. In non-human primates, CAVRO administration prompted a dose-dependent activation of immune cells, notably B cells and plasmacytoid dendritic cells (pDC), which predominantly express

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TLR9. Additional immune cells, such as T cells, NK cells, and myeloid dendritic cells, were also activated, reflecting the cascading effects of B cell and pDC activation. Th1-type cytokine and chemokine responses were dose-dependent, peaking between 8 and 16 hrs post-dose. All measured cytokine and chemokine levels returned to baseline levels within 7 days. The cytokine responses to repeated dosing remained stable over time, showing no significant fluctuations in pharmacodynamic responses. **Conclusion:** Cavro has demonstrated the ability to induce a strong cellular and humoral immune response in pre-clinical studies, which may result in sustained control of HBV infection. A Phase 1b study has initiated to evaluate CAVRO in patients with CHB.

Disclosures: Hilario Ramos: Bluejay Therapeutics: Employee, Bluejay Therapeutics: Stock – privately held company, Jerome Deval: Nothing to Disclose, Jenny Stanton: Nothing to Disclose, Nancy Shulman: Bluejay Therapeutics, INC: Salary and equity, Hassan Javanbakht: Nothing to Disclose

1415 | MATHEMATICAL MODELING OF ACUTE HBV INFECTION IN HUMANIZED MICE TREATED WITH HBS ANTIBODIES

Ashish Goyal[1] Harel Dahari[2] Yuji Ishida[3] Hiromi Abe-Chayama[4] Ophir Dahari[2] Chise Tateno[3] Kazuaki Chayama[5]

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Background: A novel HBs antibody (Ab) was tested in different doses and at different times post HBV inoculation in humanized mice. We aim to provide insights into the mechanism of action (MOA) of the Ab against HBV dynamics using a mathematical modeling approach. **Methods:** Eighteen uPA/SCID humanized mice were inoculated with HBV DNA (6.0 log cp/ml). Serum HBV DNA levels were frequently measured. Of all mice, 3 mice received no Ab, 7 mice received one dose of Ab (33 mpk or 66 mpk) and 8 mice received a second dose of Ab (66 mpk or 100 mpk). First dose was administrated at week 2,4, or 5 and second dose at week 3,5 or 6 post HBV inoculation. We developed multiscale mathematical models and simulated two Ab MOA (i) enhancement of viral clearance from blood, and/or (ii) reduces viral infection. We fixed the natural half-life of HBV ($t_{1/2}$) in humanized mice at ~60 mins as previously estimated [Hepatology 2018, 68(2): 473-484]. We fit the models with measured data using a population, nonlinear mixed-effects approach. Akaike Information criterion (AIC, lower AIC have better support by the data) was used to identify the best models. **Results:** Model selection indicates that the main MOA of Ab is to enhance viral clearance (AIC=363.5) rather than solely reducing viral infection (AIC= 436.3). Modeling suggests HBV $t_{1/2}$ reduces by 147-fold (~49 sec), 24000-fold (~0.3 sec) and 2400000-fold (~3 msec) after administration of 33 mpk, 66 mpk and 100 mpk, respectively. A negative correlation between the time of administration of Ab and the magnitude of the enhancement in the viral clearance was found. This suggests that the administration of Ab at earlier time points post-infection, which is also associated with the lower levels of viremia, could induce faster clearance. The best model also assumes a waning efficacy at a rate of 0.04-0.5/day which suggests large variation across mice. **Conclusion:** Modeling suggests that the main MOA of the novel Ab is enhancing viral clearance in a dose-dependent manner.

Disclosures: Ashish Goyal: Nothing to Disclose, Harel Dahari: Nothing to Disclose, Yuji Ishida: Nothing to Disclose, Hiromi Abe-Chayama: Nothing to Disclose, Ophir Dahari: Nothing to Disclose, Chise Tateno: Nothing to Disclose, Kazuaki Chayama: Nothing to Disclose

1416 | TREATMENT RESPONSE OF IFN AND NUC IN CHB PATIENTS WITH SEVERE LIVER FIBROSIS OR CIRRHOSIS (OASIS SUBGROUP ANALYSIS)

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Background: Patients with severe liver fibrosis or cirrhosis associated with CHB often exhibit a series of structural and functional changes in the liver. The available clinical evidence regarding the treatment response to IFN in patients with severe liver fibrosis or cirrhosis was insufficient. This analysis aimed to explore the treatment response of patients with severe liver fibrosis/cirrhosis after antiviral therapy with IFN or Nuc. **Methods:** This analysis was conducted in the data from a multicenter, prospective real-world study (OASIS project) in China. Participants were assigned to receive either IFN-based therapy (including IFN alone and IFN combined with Nuc)

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or Nuc therapy (Nuc alone). This analysis focused on the subgroup of patients with severe fibrosis or cirrhosis. The treatment response, including HBeAg loss, HBeAg seroconversion, HBsAg loss, and HBsAg seroconversion, was compared between patients with severe liver fibrosis/cirrhosis and those without liver fibrosis at week 48 and week 96 of follow-up under both treatment regimens. **Results:** A total of 1819 patients with severe liver fibrosis/cirrhosis (2116 in IFN group, 971 in Nuc group) and 3087 patients without liver fibrosis (958 in IFN group, 861 in Nuc group) were included. Compared to non-fibrotic patients, severe fibrotic/cirrhotic patients treated with IFN exhibited significantly lower rates of HBsAg loss and seroconversion at 48 weeks (HBsAg loss: 6.18% vs 11.93%, P<0.0001; HBsAg seroconversion: 4.23% vs 8.47%, P<0.0001) and 96 weeks (HBsAg loss: 0.47% vs 13.27%, P=0.0003; HBsAg seroconversion: 7.55% vs 11.77%, P=0.0006). There was no statistical difference in HBsAg seroconversion rates at 48 and 96 weeks and HBsAg loss rate at 96 weeks. As for HBeAg, regardless of IFN or Nuc treatment, patients with severe liver fibrosis/cirrhosis had significantly higher rates of HBeAg loss at 48 weeks (IFN: 27.68% vs 18.63%, P=0.002; Nuc: 33.21% vs 24.04%, P=0.004) and 96 weeks (IFN: 20.00% vs 10.80%, P=0.0006; Nuc: 13.35% vs 27.35%, P < 0.0001) than those without liver fibrosis. There was no statistical difference in the rate of HBeAg seroconversion at 48 and 96 weeks in either IFN or Nuc group between non-fibrotic patients and severe fibrotic/cirrhotic patients. **Conclusion:** Compared to patients without liver fibrosis, patients with severe liver fibrosis/cirrhosis exhibited significantly lower rates of HBsAg loss and HBsAg seroconversion, but a higher rate of HBeAg loss following IFN or Nuc treatment.



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1417 | ANTIVIRAL EFFICACY OF TENOFOVIR ALAFENAMIDE VERSUS ENTECAVIR IN TREATMENT-NA&IUML;VE CHRONIC HEPATITIS B: A MULTICENTER LONGITUDINAL STUDY

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Background: While both tenofovir alafenamide (TAF) and entecavir (ETV) have been recommended as first-line anti-HBV therapies according to current clinical practice guidelines, data on their comparative efficacy in achieving surrogate virologic response (VR), biochemical response (BR) and complete response (CR) among chronic hepatitis B (CHB) patients remain limited. The objective of our study was to compare the efficacy of these two antivirals. **Methods:** Treatment-naïve chronic hepatitis B (CHB) patients who with either TAF or ETV across 24 sites in Argentina, South Korea, Japan, the mainland of China, Taiwan, and the United States were enrolled in this retrospective study. Competing-risks regression analysis was used to evaluate incidence and hazard ratios (HRs) for VR, BR and CR. **Results:** A total of 3,068 patients were included (700 TAF and 2,368 ETV patients). The mean age was 50.2 years for TAF and 49.9 years for ETV patients, with a slight male predominance in the ETV group (63.1% vs. 56.6%, *P* =0.002). Compared to TAF patients, ETV patients had higher baseline HBV DNA (5.8 vs. 5.5 log10 IU/mL, *P* =0.001) and ALT (89 vs. 47 IU/L, *P* <0.001). In the overall cohort, TAF demonstrated a superior 5-year rate of VR (97.4% vs. 82.9%, *P* <0.001) and CR (92.3% vs. 77.5%, *P* <0.001) compared to ETV, while the BR rate did not reach significant difference between the two groups (90.4% vs. 91.2%, *P* =0.48). When stratified by alanine aminotransferase (ALT) levels, both subgroups treated with TAF demonstrated significantly higher VR (96.4% vs. 77.2% for ALT <2×upper limit of normal [ULN]; 97.3% vs. 86.8% for ALT ³2×ULN, all *P* <0.001) and CR (90.3% vs. 70.4% for ALT <2×ULN; 93.2% vs. 79.9% for ALT ³2×ULN, all *P* <0.001) rates over those treated with ETV. Multivariate analysis confirmed the advantages of TAF over ETV after adjusting for potential confounders. The HR for TAF versus ETV was 0.44 (*P* <0.001) for the overall VR and 0.52 (*P* <0.001) for the overall CR, indicating significantly better outcomes with TAF. In patients with ALT < 2×ULN, the TAF group demonstrated a HR of 0.39 (*P* <0.001) for VR and 0.52 (*P* <0.001) for CR compared to the ETV group. Likewise, in patients with ALT ≥ 2×ULN, the TAF group obtained HRs of 0.49 (*P* <0.001) for VR and 0.48 (*P* <0.001) for CR compared to the ETV group, thereby substantiating the superiority of TAF in these cohorts. **Conclusion:** TAF exhibits enhanced efficacy compared to ETV in CHB patients, with a notable advantage in achieving VR and CR.

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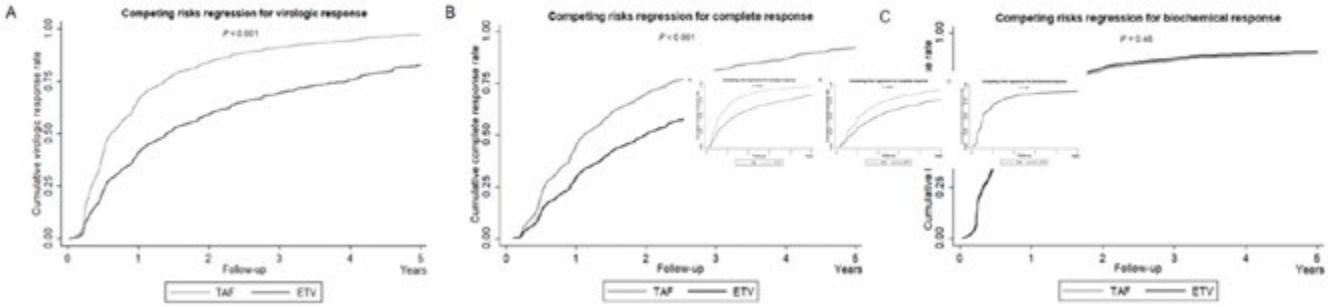
Figure 1. Competing risks regression for virologic response (A), complete response (B) and biochemical response (C) in TAF- and ETV- treated patients in overall cohort. Note: TAF, tenofovir alafenamide; ETV, entecavir.



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1418 | RISK OF CIRRHOSIS AND HCC IN CHB PATIENTS DURING IFN OR NUC TREATMENT (OASIS SUBGROUP ANALYSIS)

Ruirui You[1] Qiran Zhang[1] Yiqi Yu[1] Feng Sun[1] Yuxian Huang[1] Jiming Zhang[1] Chao Qiu[1] Wenhong Zhang[1]

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Background: There is still some controversy about whether IFN can improve the long-term prognosis and reduce the incidence of adverse events of CHB patients, especially those with compensated cirrhosis. This study aimed to analyze the incidence of liver cirrhosis in non-cirrhotic patients and the incidence of HCC in compensated cirrhotic patients in a prospective real-world cohort. We aimed to compare the effectiveness of IFN and Nuc in reducing the incidence of these adverse clinical events. **Methods:** This analysis was conducted in the data from a multicenter, prospective real-world study (OASIS project) in China. Participants were assigned to receive either IFN-based therapy (including IFN alone and IFN combined with Nuc) or Nuc therapy (Nuc alone). This analysis involved two sub-cohorts, namely the non-cirrhotic cohort and cirrhotic cohort. Kaplan-Meier curves were utilized to compare the incidence of cirrhosis (only

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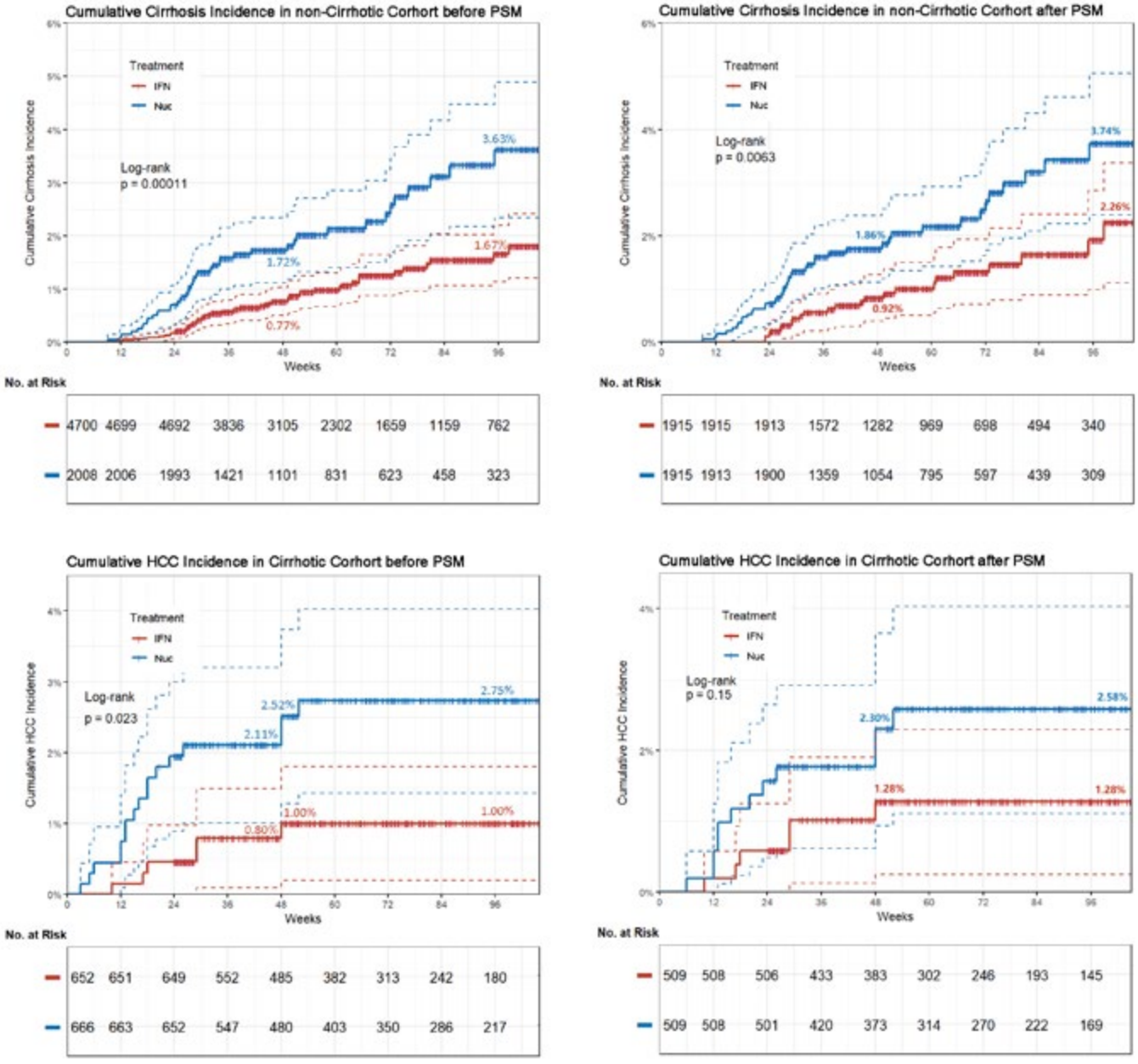
in the non-cirrhotic cohort) and HCC (only in the cirrhotic cohort) at 96 weeks between the IFN group and Nuc group. Propensity score matching (PSM) was used to balance the differences between the baseline characteristics of the two groups. PSM was performed using the nearest-neighbor matching at a 1:1 ratio. **Results:** A total of 6708 patients were included in the non-cirrhotic cohort, with 4700 in IFN group and 2008 in Nuc group. A total of 1314 patients were included in the cirrhotic cohort, with 652 in IFN group and 662 in Nuc group. In the non-cirrhotic cohort, the cumulative incidence of cirrhosis at 96 weeks was significantly lower in the IFN group compared to the Nuc group, both before and after PSM. (before PSM: Log Rank P = 0.0001; after PSM: Log Rank P = 0.0063). In the compensated cirrhosis cohort, before PSM, the cumulative incidence of HCC at 96 weeks was significantly lower in the IFN group compared to the Nuc group (Log Rank P = 0.036). However, after PSM, there was no longer a significant difference in the risk of HCC incidence between the two groups ((Log Rank P = 0.15). **Conclusion:** IFN is superior to Nuc in reducing the risk of the incidence of cirrhosis in non-cirrhotic patients. In terms of reducing the incidence of HCC, no statistical difference was observed between the two groups in the current data after PSM yet.



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1419 | SURVEILLANCE OF HEPATOCELLULAR CARCINOMA IS COST-EFFECTIVE IN CHRONIC VIRAL HEPATITIS PATIENTS IN KOREA

Hyung Joon Kim[1] Eunju Kim[2] Hye-Lin Kim[3] Gi Hyeon Seo[4]

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Background: Biannual hepatocellular carcinoma (HCC) surveillance of ultrasound (US) and alpha-fetoprotein (AFP) is recommended for chronic viral hepatitis and liver cirrhosis. However, there are little evidence supporting HCC surveillance in chronic hepatitis patients. In Korea, US was reimbursed in April 2018. After reimbursement, nationwide cost of the HCC surveillance program could be analyzed. This study aimed to check whether the HCC surveillance program was cost-effective using the nationwide cohort data. **Methods:** We designed a Markov model to compare the expected costs and quality-adjusted live-years (QALYs), between biannual and annual surveillance compared to no surveillance, with a 20-year time horizon. The starting age of the cohort was set to 40 or 50 years. Transition probabilities and costs were obtained mainly from the National Health Insurance database. An incremental cost-effectiveness ratio (ICER) was calculated. Early HCC was defined by treatment methods. **Results:** In liver cirrhosis patients, with starting age of 40, biannual and annual surveillance resulted in ICERs of $17,911 and $12,739 per QALY, respectively. When surveillance was restricted to chronic viral hepatitis patients without cirrhosis, with starting age of 40, biannual surveillance was marginally cost effective. Biannual and annual surveillance resulted with ICERs of $20,597 and $16,253 per QALY, respectively. After increasing the starting age to 50, both biannual and annual surveillance was cost effective, with ICERs of $12,288 and $9,742 per QALY respectively. **Conclusion:** In Korea, HCC surveillance program was cost effective in most clinical scenarios for liver cirrhosis and chronic viral hepatitis patients.

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1420 | ASSOCIATION OF PROTON PUMP INHIBITORS AND THE RISK OF HEPATOCELLULAR CARCINOMA IN CHRONIC HEPATITIS B PATIENTS: A KOREAN NATIONWIDE COHORT STUDY

Hyung Joon Kim[1] Eunju Kim[2] Jong-In Chang[2]

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Background: Long term proton pump inhibitors (PPI) can be associated with various gastrointestinal cancers. Association of PPI use and hepatocellular carcinoma (HCC) was controversial in previous studies. **Methods:** We analyzed 12,544 chronic hepatitis B (CHB) patients in the Korean National Health Insurance Service database from 2009 to 2012. Patients using H2-receptor antagonist were excluded. Multivariable cox regression and 1:5 propensity score (PS) matching were performed. **Results:** In the total cohort 975 patients were included in the PPI group, 11,569 patients were included in the non-user group. After mean 7.4 years of follow up, 60 (6.15%) patients developed HCC in the PPI group, and 840 (7.26%) patients developed HCC in the non-user group. PPI was not associated with HCC development in the multivariable analysis (adjusted hazard ratio (HR), 1.169; 95% confidence interval (CI), 0.897–1.524; P value= 0.248). In the PS matched cohort, PPI was still not associated with HCC development (HR, 1.129; 95% CI, 0.855–1.49; P value=0.392). **Conclusion:** In our study, PPI use was not associated with HCC development in CHB patients.

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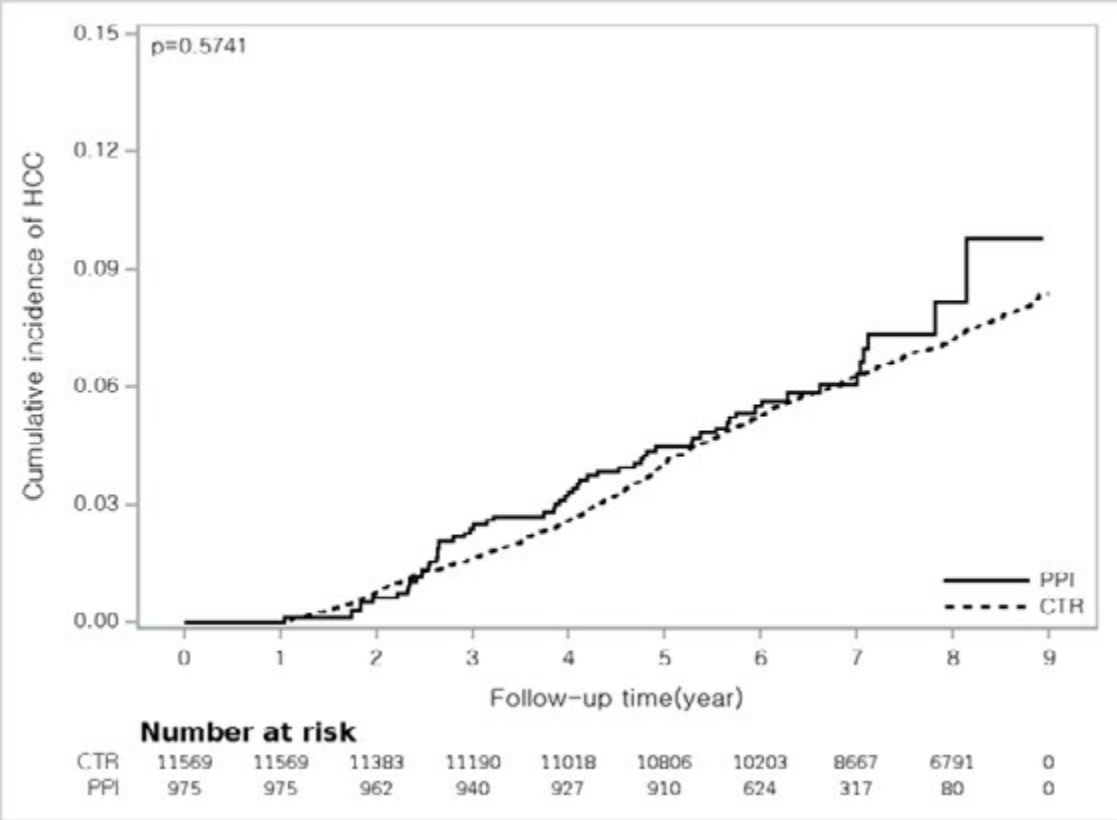

Disclosures: Hyung Joon Kim: Nothing to Disclose, Eunju Kim: Nothing to Disclose, Jong-In Chang: Nothing to Disclose

1421 | BEHAVIOUR, ASPIRATIONS AND TREATMENT NEEDS OF PEOPLE LIVING WITH HEPATITIS B (BEAT-B): A MIXED METHODS STUDY IN HEPATITIS B PATIENTS FROM FIVE COUNTRIES IN SOUTH ASIA

Manya Prasad[1] Shiv Kumar Sarin[1] Tawesak Tanwandee[2] Sudhamshu KC[3] Zaigham Abbas[4] MOHAMMAD GOLAM AZAM[5] Dr.Priyanka Aggarwal[1] Bharat Bhushan Rewari[1]

[1]Institute of Liver and Biliary Sciences, New Delhi, [2]Siriraj Hospital/Mahidol University, [3]Norvic International Hospital, [4]Ziauddin University Hospital, [5]BIRDEM Academy

Background: This multicentric study explores the socio-cultural environment, healthcare worker inaction, and patient values and preferences affecting chronic hepatitis B testing and treatment, aiming for Hepatitis elimination by 2030. **Methods:** We conducted a mixed-methods study. The quantitative cross-sectional component included HBV-infected subjects from India, Thailand, Nepal, Pakistan and Bangladesh. Data collection involved a pre-tested online proforma covering demographics, knowledge, attitudes, practices, health related quality of life (using SF-12) and open ended questions on perceptions about hepatitis B and treatment barriers. The qualitative component included focused group discussions and in-depth interviews, using purposive sampling until data saturation. Data were analyzed using a grounded theory approach, focusing on treatment experiences, barriers, and facilitators. **Results:** A total of 515 chronically HBV-infected subjects were enrolled from the five country sites. The mean age of participants was 47.9 ± 14.5 years, 73% being male. 39.8% had a family history of hepatitis B. 381 (74%) participants were taking treatment for Hepatitis B, out of which 343 (90%) reported taking the medication regularly. Key barriers to uptake of treatment included lack of knowledge (32%, n=165), high costs (48%, n=247), and access difficulties (30%, n=155). Catalysts for treatment adherence included concern about complications (62%, n=319), family support and familial impact (56%, n=288) and trust in healthcare providers (50%, n=256). Thematic analysis revealed core categories related to treatment motivation, including “trust in healthcare,” “financial burden,” “social support” and “reducing risk of complications and transmission”, and that patients desired deeper involvement and counselling in making treatment decisions for their disease.

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Knowledge about transmission rates and vaccine was good; however, only 106 (20.5%) understood the chronic nature of the disease. HRQoL showed mean Physical Component Summary (PCS) and Mental Component Summary (MCS) scores of 52.1 ± 8.3 and 50.3 ± 9.7, respectively, indicating moderate impairment in quality of life. Participants not on treatment reported significantly higher barriers related to cost and access. **Conclusion:** The study underscores the multifaceted nature of treatment uptake and adherence in HBV patients, highlighting critical areas for intervention such as enhancing knowledge, reducing financial barriers, and fostering supportive healthcare environments.

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1422 | LONG-TERM CLINICAL OUTCOMES AFTER HCV ELIMINATION BY DIRECT-ACTING ANTIVIRALS IN PATIENTS WITH CHRONIC HEPATITIS C: A LARGE-SCALE, MULTICENTER COHORT STUDY

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Background: Treatment of hepatitis C with direct-acting antivirals (DAAs) results in sustained virological response (SVR) in the vast majority of patients with chronic hepatitis C (CHC). Many reports have shown that SVR is associated with a significant reduction of liver morbidity and mortality for up to approximately five years. The aim of this study was to assess long-term clinical outcomes and mortality after SVR by DAA treatment. **Methods:** This multicenter, retrospective cohort study consisted of 3,024 consecutive adult CHC patients without decompensated cirrhosis who have achieved SVR with all-oral DAAs. The index date was the end of DAA treatment. Primary endpoints were the occurrence or recurrence of hepatocellular carcinoma (HCC), mortality, and the causes and related factors of death. **Results:** The median follow-up durations were 6.6 (range 0.3-8.9) and 6.3 (range 0.3-8.9) years for the non-HCC (n=2,691) and HCC experienced groups (n=333), respectively. Although the cumulative de novo HCC incidence rates were longitudinally increased (3-year, 4.0%: 5-year, 5.6%: 8-year, 7.0%), those of the recurrence rates reached a plateau in 3-5 years (3-year, 50.4%: 5-year, 59.1%: 8-year, 62.0%). None of the patients aged under 50 (n=377) developed de novo HCC. In contrast, for patients with cirrhosis aged 50 and over (n=536), the cumulative de novo HCC incidence rates were high (3-year, 11.2%: 5-year, 15.6%: 8-year, 18.9%). Even in patients without cirrhosis, the 8-year cumulative de novo HCC incidence increased with age (age 50-59, 1.8%: age≥60, 5.5%: age≥75, 8.7%) (log-rank test: P<0.001). The 3-year, 5-year, and 8-year survival rates for patients with HCC were 85.2%, 74.6%, and 67.4%, respectively. 74% of the deaths were caused by liver-related complications, mainly HCC recurrence. For patients in the non-HCC group, 72% of the deaths were caused by non-liver-related complications (43% non-liver cancer, 20% cerebral/cardiovascular disease). Diabetes at baseline and ALT levels after SVR were not associated with the mortality in the non-HCC group. **Conclusion:** DAA treatment improves liver-related morbidity and survival irrespective of HCC experience; however, our data attributes the causes of death in the non-HCC group in large part to non-liver-related complications. In addition, non-cirrhotic patients aged over 60 should be considered for long-term HCC surveillance.

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to Disclose, Norihiro Furusyo: Nothing to Disclose, Eiji Kajiwara: Nothing to Disclose, Koichi Azuma: Nothing to Disclose, Yasunori Ichiki: Nothing to Disclose, Rie Sugimoto: Nothing to Disclose, Hiromasa Amagase: Nothing to Disclose, Takeshi Senju: Nothing to Disclose, Chie Morita: Nothing to Disclose, Masatake Tanaka: Nothing to Disclose, Makoto Nakamuta: Nothing to Disclose, Hideyuki Nomura: Nothing to Disclose, Jun Hayashi: Nothing to Disclose

1423 | HIGH GGT LEVELS IS A RISK FACTOR FOR HCC DEVELOPMENT HAVING POTENTIAL TO REFLECT MITOCHONDRIAL DYSFUNCTION AFTER HCV ERADICATION

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Background: As HCV infection itself causes oxidative stress, we clarified the influence of overlapping metabolic diseases on the association between Gamma-glutamyltransferase (GGT) and hepatocarcinogenesis and survival after achieving sustained viral response (SVR) particularly in patients without drinking habits or diabetes. **Methods:** This is a prospective, multicenter and observational study from Sep. 2014 to Aug. 2023 using the database of 1,085 patients after HCV eradication with direct-acting antiviral agents (DAA). The association of GGT levels at SVR and metabolic diseases with cumulative HCC development was examined in a multivariate analysis. The genetic predisposition related to GGT levels were also analyzed by using STATA 16 (StataCorp LP, College Station, TX, USA) **Results:** The median follow-up days for developing HCC was 1338 days (range 4–3294days), and 52 patients (4.8%) developed HCC. High GGT levels at SVR, male gender, older age, and the presence of hypovascular nodules were associated with HCC development after adjustment for alcohol consumption, diabetes, dyslipidemia, and obesity. Multivariate analysis among the patients with neither alcohol consumption nor DM (n=557) showed that older age, hypovascular nodules, and high GGT levels at SVR were associated with HCC development [age (HR 6.16, 95% CI 1.90, 19.92), hypovascular nodule (HR 15.50, 95% CI 4.94, 48.67), GGT at SVR (HR 10.69, 95% CI 2.90, 39.43)] GGT levels were correlated with growth differentiation factor 15 (GDF15) levels and single nucleotide polymorphisms of HNF1a, ZNF1a, and GDF15 were associated with high GGT levels after adjustment for metabolic factors. The mortality rate among post-SVR patients without a history of HCC was 3.1%, and more deaths due to cardiovascular events or cancer of other organs were found than those from liver associated death. In post-SVR patients under 70 years, elevated GGT and diabetes are independent prognostic factors for patient' survival. **Conclusion:** High GGT levels at SVR was associated with carcinogenesis after HCV eradication in patients without alcohol consumption or diabetes. GGT levels are influenced by genetic predisposition and reflect mitochondrial dysfunction after HCV eradication.

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1424 | SCANVIR: AN IDEAL CONCEPT FOR ELIMINATING HEPATITIS C

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Background: Hepatitis C virus elimination means getting closer to at-risk individuals outside conventional care structures, with an "all-inclusive" approach. The Scanvir project aims to "create the event on dedicated days" to optimize screening efficiency, initiation of treatment and patient's return to the care pathway. **Methods:** We organized dedicated monthly screening days to bring together in each structure (Limousin and Périgueux, France) the multidisciplinary staff involving hepatologist/infectiologist, addictologist, nurses and social workers, and the screening tools (HCV, HBV, HIV RDTs, FibroScan®, Point-of-Care molecular testing (GeneXpert) for HCV

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RNA detection, in a joint action. A risk prevention, addiction and psychosocial management was proposed. The recruitment of patients for the event was carried out ahead by the staff of the facilities, through the dissemination of information via cross-functional networks. **Results:** Since May 2017, 116 dedicated days have been scheduled and 861 patients (74% men, median age 46) taken care of. 12% were active injectors, 29% had substitution treatment, 66% excessive alcohol consumption, and 73% smoked. 98.9% of patients accepted FibroScan®. 19.2% were suspected to have advanced fibrosis (FS > 8 kPa) and severe fibrosis (FS >12kPa) was very likely in 11.1% of the participants. RDT were accepted by 77% of the participants with 1.1% AgHBs+ and 2% HIV Ab+ (status already known). 23.8% (205 patients) were HCV Ab+; 56% had a replicative profile. 82% initiated treatment, of which 80% were cured, others are still under treatment. 18% remain untreated today. Among the 180 patients in whom CAP was available with FS, 18% had severe steatosis (CAP>300 dB/m). **Conclusion:** The Scanvir project is an innovative pathway promoting the “Test, Treat and Prevent” strategy for eliminating HCV. This is an innovative concept that makes diagnostic testing more cost-effective for high-risk patients who are far from healthcare structures. Thanks to the collaboration of multi-disciplinary teams, we cured and followed up 80% of our patients. The educational role played by FibroScan® in attracting patients who refused RDT is essential. Its use demonstrates the growing interest in screening for fibrosis and steatosis, a consequence of alcoholic and metabolic liver diseases increasingly prevalent in this population. The Scanvir model is a registered concept, applicable nationwide.

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1425 | MENDELIAN RANDOMIZATION ANALYSIS REVEALS HEPATITIS C INFECTION IS CAUSALLY ASSOCIATED WITH EXTRAHEPATIC CANCER

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Background: Hepatitis C virus (HCV) infection is prevalent worldwide. Observational studies have shown that HCV infection is associated with extrahepatic cancer. However, the results are inconsistent and causality remains to be established. **Methods:** A two-sample Mendelian randomization (MR) was conducted to explore whether HCV infection is causally associated with extrahepatic cancers. Based on the summary-level genome-wide association studies (GWAS) data from a publicly available database, the variance weighted inverse (IVW) was applied as the primary method to estimate causality, and other estimators were used as complementary methods. **Results:** A total of 14 extrahepatic cancer were included in this study and 4 single nucleotide polymorphisms (SNPs) were used as instrumental variables (IVs) for HCV infection. The results of IVW method indicated that genetic liabilities of HCV infection were strongly associated with colorectal cancer (OR: 1.353, P = 4.05e-06) and lung cancer (OR: 1.341, P = 7.03e-04). Also, we found that the genetic liability of HCV infection was suggestively causally associated with gastric cancer (OR: 1.224, P = 0.017). However, HCV infection was not significantly associated with ovarian, cervical cancer, biliary cancer, pancreatic cancer, ovarian cancer, esophageal cancer, pharyngeal and laryngeal cancer, skin cancer, thyroid cancer, endometrial cancer, and breast cancer. And no pleiotropy was observed. **Conclusion:** HCV infection have causal effect on extrahepatic cancers including colorectal and lung cancers. Enhanced screening for extrahepatic cancers in chronically HCV-infected individuals for early detection of cancer is recommended.

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1426 | HISTOLOGICAL IMPROVEMENT OF FIBROSIS IN PATIENTS WITH HEPATITIS C WHO EXHIBIT FOR 5 YEARS A SUSTAINED VIROLOGICAL RESPONSE TO ANTIVIRAL TREATMENT WITH DIRECT-ACTING ANTIVIRALS

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Background: The histological improvement of liver fibrosis in patients with hepatitis C who achieved sustained virological response (SVR) to direct-acting antiviral treatment (DAA) has not been investigated comprehensively. Therefore, we aimed to assess the histological changes in liver fibrosis among patients with hepatitis C who underwent long-term follow-up after achieving SVR to antiviral treatment with DAA. **Methods:** This retrospective study enrolled 71 patients with hepatitis C who achieved SVR to antiviral treatment with DAA. Changes in histological liver fibrosis and fibrosis biomarkers (hyaluronic acid, type 4 collagen 7S, Mac-2 binding protein glycosylation isomer, autotaxin, and Fibrosis-4 index) were assessed before and 5 years after treatment. Transient elastography using the FibroScan® device was performed 5 years after treatment. Advanced fibrosis and cirrhosis were defined as Ishak fibrosis scores of ≥4 and ≥5, respectively. **Results:** Histological liver fibrosis regressed significantly after SVR. Fibrosis biomarkers had significantly reduced values after SVR. The transient elastography was the most helpful after evaluating the predictive performance of advanced fibrosis and cirrhosis after SVR, with an area under the receiver operating characteristic curve of 0.965 and a cut-off value of 6.75 kPa. The cut-off values of serum fibrosis biomarkers identifying advanced fibrosis and cirrhosis after SVR were lower than those before treatment. **Conclusion:** Long-term SVR to antiviral treatment with DAA ameliorated histological liver fibrosis. Noninvasive tests helped predict the degree of liver fibrosis after SVR, but their cut-off values need to be redefined to avoid underestimation of liver fibrosis after SVR.

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1427 | SUSTAINED VIROLOGIC RESPONSE AND POSTTREATMENT LIVER FUNCTION ARE ASSOCIATED WITH 5-YEAR SURVIVAL AFTER DIRECT-ACTING ANTIVIRAL TREATMENT IN DECOMPENSATED CIRRHOTIC PATIENTS WITH HEPATITIS C VIRUS: A LONG-TERM FOLLOW UP STUDY OF JAPANESE CLINICAL TRIAL COHORT ◆

Yuki Tahata[1] Hayato Hikita[2] Akinobu Takaki[3] Masayuki Kurosaki[4] Kentaro Matsuura[5] Hiroshi Yatsuhashi[6] HIDEKATSU KURODA[7] Yoshiyuki Ueno[8] Takahiro Kodama[1] Ryotaro Sakamori[9] Tomohide Tatsumi[1] Tetsuo Takehara[1]

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Background: Sustained virologic response (SVR) can be achieved in approximately 90% of decompensated cirrhotic patients with chronic hepatitis C virus (HCV) infection by direct-acting antiviral (DAA) treatment. However, the impact of SVR on long-term prognosis of decompensated cirrhotic patients treated with DAA is unclear. **Methods:** Among 102 patients who were enrolled in the Japanese phase 3 clinical trial of sofosbuvir and velpatasvir (SOF/VEL) with or without ribavirin (RBV) treatment to decompensated cirrhotic patients with HCV, 99 patients who agreed to a long-term follow up study were included in this study. All patients were treated with SOF/VEL with or without RBV for 12 weeks between January 2017 and August 2017 at 32 Japanese hospitals. The definition of decompensated cirrhosis was Child-Pugh B or Child-Pugh C at screening. We collected clinical data at the timing of baseline, end of the treatment (EOT), 12 weeks after the EOT, 24 weeks after the EOT, 1 year after the EOT and every 1 year thereafter, which were examined at each hospital. The observation period started from when DAA was initiated, and the last observation period was the date of death or liver transplantation (LT) or last visit, whichever came first. The median observation period of this study was 60.2 months from DAA initiation. Factors associated with LT-free survival after DAA were examined by Cox proportional hazard analysis. **Results:** The median age was 67 years, and 7% of patients had HCC history before DAA. The baseline percentage of

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patients with Child-Pugh A, Child-Pugh B and Child-Pugh C were 12%, 77%, and 10%, respectively. The SVR rate was 88.9% in an intention-to-treat analysis. During the observation period, 21 patients died (8 liver failure, 6 hepatocellular carcinoma, 1 varix rupture, 1 spontaneous bacterial peritonitis, 5 non-liver causes), and one patient underwent LT. The 5-year LT-free survival rate was 76.1%. In multivariate analysis, Child-Pugh C at 12 weeks after the EOT (hazard ratio (HR): 15.669, p=0.001) and virologic failure (HR: 6.356, p=0.002) were significantly associated with LT-free survival after DAA. The 5-year LT-free survival rates were 80.6% in patients with SVR and 33.3% in those with virologic failure (p<0.001). The 4-year LT-free survival rates were 96.2%, 86.4% and 41.7% for patients with Child-Pugh A, Child-Pugh B and Child-Pugh C at 12 weeks after the EOT, respectively (Child-Pugh A vs. Child-Pugh B; p=0.104, Child-Pugh A vs. Child-Pugh C; p<0.001, Child-Pugh B vs. Child-Pugh C; p=0.004). **Conclusion:** In decompensated cirrhotic patients with HCV enrolled in follow up study of Japanese clinical trial, the 5-year LT-free survival rate after DAA was 76.1%. SVR and posttreatment liver function are associated with long-term prognosis in decompensated cirrhotic patients with HCV after DAA.

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1428 | HCV AB TITER AND ALT MARK OCCULT HEPATITIS C VIRUS INFECTION IN TREATMENT-NA&IUML;VE HCV AB-POSITIVE AND -NEGATIVE PATIENTS, RESPECTIVELY: A 3-YEAR PROSPECTIVE COHORT STUDY

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Background: The prevalence and phenotype of occult hepatitis C virus (HCV) infection (OCI) in anti-HCV treatment-naïve patients in Taiwan have remained elusive. **Methods:** A prospective 3-year cohort study of anti-HCV treatment-naïve patients was conducted. OCI was defined as positive HCV RNA in the peripheral blood mononuclear cells (PBMCs) of patients with negative serum HCV RNA. **Results:** Of the 128 HCV Ab-positive patients, 15 (11.7%) had OCI (mean and median viral loads: 1046 IU and 28.38 IU in 10^7 PBMCs); of the 90 HCV Ab-negative patients, 5 (5.6%) had OCI (mean and median viral loads: 2356 IU and 111.7 IU in 10^7 PBMCs). HCV viral loads were similar between HCV Ab-positive and HCV Ab-negative OCI patients. Among HCV Ab-positive patients, higher HCV Ab titers were noted in patients with than without OCI (84.25±64.76 vs. 46.60±46.07 ng/ml, *p*=0.006); with a cutoff value: >53.2 ng/ml, HCV Ab titer might mark OCI (AUROC: 0.701). Among HCV Ab-negative patients, alanine aminotransferase level was higher in patients with than without OCI (114.4±71.6 vs. 67.2±87.4 U/L, *p*=0.035). Among HCV Ab-positive patients, the cumulative incidence (CI) of cardiovascular events was higher in patients with than without OCI (84% vs. 46.4%, *p*=0.043). Among HCV Ab-negative patients, a higher autoimmune disease CI was noted in patients with than without OCI (20% vs. 1.2%, *p*=0.006). **Conclusion:** Among anti-HCV treatment-naïve patients, the prevalence rates of OCI were 11.7% for HCV Ab-positive patients and 5.6% for HCV Ab-negative patients. High HCV titers in HCV Ab-positive patients demand caution about OCI and cardiovascular events, and cryptogenic hepatitis warrants suspicion of OCI and autoimmune diseases.

Disclosures: Ming-Ling Chang: Nothing to Disclose

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1429 | A RARE CASE OF DIFFUSE LARGE B-CELL LYMPHOMA THAT DEVELOPED AFTER SOFOSBUVIR-LEDIPASVIR TREATMENT FOR CHRONIC HEPATITIS C

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Background: Treatments for chronic hepatitis C virus (HCV) infection have been dramatically improved by the development of direct-acting antiviral agents (DAAs) and almost all patients with HCV can complete antiviral treatment without apparent adverse events. Malignant lymphoma, particularly B-cell non-Hodgkin's lymphoma (NHL), is one of the extrahepatic manifestations associated with chronic HCV infection. The effectiveness of anti-HCV therapy with DAAs for B-cell NHL has been demonstrated in recent reports, whereas late-onset B-cell NHL after HCV eradication with DAAs has rarely been reported. Thus far, only seven cases of the late-onset of B-cell NHLs have been reported since 2016; however, the underlying mechanisms have remained unclear. **Methods:** A 61-year-old man was diagnosed with chronic hepatitis C in April 2000 and treated by conventional interferon (IFN) monotherapy for 24 weeks from August 2000 to January 2001. However, he did not achieve sustained virologic response (SVR) and was subsequently treated with ursodeoxycholic acid at a local clinic. He had been followed up every 3 months and serum alanine aminotransferase levels remained normal for 15 years. In February 2016, when the patient was 77 years of age, he was admitted to our hospital to evaluate the indication of IFN-free DAA treatment. **Results:** He had received sofosbuvir-ledipasvir treatment for 12 weeks. Two months after the end of antiviral therapy, he had achieved SVR for 8 weeks. However, the patient occasionally found swelling of the right cervical lymph nodes without any subjective symptoms. Lymph node biopsy revealed diffuse large B-cell lymphoma and whole-body ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography with computed tomography showed increased FDG uptake in the right cervical, right submandibular, mediastinal, and mesenteric lymph nodes. The patient received six courses of R-CHOP chemotherapy and achieved complete response at 8 months after initiation of the chemotherapy. **Conclusion:** The development of lymphoid malignancies may arise, even after HCV eradication with DAAs. Therefore, clinicians should be aware of such risks during and after antiviral treatment with DAAs. In this study, we will discuss the possible underlying mechanisms by reviewing previous reteratures.

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1430 | HEPATIC STEATOSIS IN CHRONIC HEPATITIS C AFFECTS THE RISK OF HEPATOCELLULAR CARCINOMA MAINLY IN WOMEN

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Background: The risk of hepatocellular carcinoma (HCC) in patients with chronic hepatitis C (HCV) is higher in the elderly and those with advanced fibrosis even after a sustained virological response (SVR). Although there have been reports on the relationship between hepatic steatosis and HCC, it is not known which patients with hepatic steatosis are at increased risk of carcinogenesis. This study investigated the relationship between hepatic steatosis and HCC in patients with HCV after an SVR. **Methods:** A search of our electronic records from 2004 to 2021 identified 1602 patients who achieved an SVR following interferon-based and direct-acting antiviral therapy and had no history of HCC; 1040 of these patients underwent liver biopsy before treatment and were included in the study. All patients had been assessed by laboratory and imaging examinations every 3–6 months. The relationship between HCC and various factors, including the amount of fat in liver tissue at the start of antiviral therapy, was investigated. Risk factors for HCC were identified by Cox proportional hazards regression analysis. The cumulative incidence of HCC was examined according to extent of hepatic steatosis using the log-rank test. **Results:** The median follow-up after initiation of antiviral therapy was 6.0 years. Fifty-seven (5.5%) of the 1040 patients developed HCC. The respective 3-year, 5-year, and 10-year cumulative rates of HCC were 4.3%, 5.8%, and 8.4%. Multivariate analysis identified age (HR 1.097, 95% CI 1.057–1.1308; P<0.001), platelet count (HR 0.873, 95% CI 0.826–0.922; P<0.001), alfa-fetoprotein at SVR (HR 1.227, 95% CI 1.137–1.324; P<0.001), gamma-glutamyl transpeptidase (HR 1.005, 95% CI 1.002–1.009; P=0.003), and sex (HR 0.530, 95% CI 0.302–0.928; P=0.026) to be independently associated with the incidence of HCC. Hepatic steatosis of >5%, >10%, and

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>30% was observed in 308 (29.6%), 137 (13.2%), and 28 (2.7%) patients, respectively; HCC was significantly more common in patients with >30% hepatic steatosis (*P*=0.038). When the data were analyzed by sex, hepatic steatosis rates of >5%, >10%, and >30% were significantly associated with HCC in women (*P*=0.003, *P*=0.002, and *P*=0.010, respectively), but there was no significant difference in the incidence of HCC according to the extent of hepatic steatosis in men. Multivariate analysis showed that >10% hepatic steatosis was an independent risk factor for HCC in women (HR 7.635, 95% CI 2.736–21.302; *P*<0.001), along with age, platelet count, alfa-fetoprotein at SVR, and gamma-glutamyl transpeptidase. Hepatic steatosis was not an independent risk factor in men. **Conclusion:** Hepatic steatosis may affect the risk of HCC even after elimination of HCV, particularly in women. Sex-related differences in the risk of HCC after an SVR in patients with HCV require further investigation.

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1431 | FATIGUE IN CHRONIC HEPATITIS B (CHB) AND C (CHC) IS ASSOCIATED WITH IMPAIRMENT OF PATIENT-REPORTED OUTCOMES (PROS) AND WORK PRODUCTIVITY

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Background: CHB and CHC infections are linked to impaired PROs. We sought to identify factors associated with fatigue and PROs in CHB and CHC. **Methods:** We analyzed clinical, demographic, and PRO data (FACIT-F, CLDQ or CLDQ-HCV, WPAI) from CHB and CHC patients enrolled in the Global Liver Registry™. Clinically overt fatigue was defined as a Fatigue Scale (FS) score of less than 30 on a 0-52 scale. **Results:** We included 2,888 patients: 1,561 CHB (age 47±13 years, 60% male, 26% obese, 12% type 2 diabetes, 13% advanced fibrosis, 13% history of depression, 21% fatigue) and 1,327 CHC (age 50±13 years, 47% male, 30% obese, 16% type 2 diabetes, 21% advanced fibrosis, 18% depression, 39% fatigue), recruited from 19 countries. Patients with CHB and fatigue were younger, more likely female, and more commonly obese, with higher rates of anxiety and depression (all p<0.01). They also reported significant impairment in all PRO domains, with mean total CLDQ score (range 1-7) 4.14 (SD 0.90) vs. 5.77 (0.86), total FACIT (4 generic domains of FACIT-F, not including FS, range 0-108) 67.6 (14.5) vs. 87.7 (13.7), work productivity impairment (WPI) (range 0-1) 0.33 (0.29) vs. 0.11 (0.22) (all p<0.0001). Multivariable analysis revealed that the association between lower PRO scores and fatigue in CHB remained significant, with an impairment magnitude of up to -23% of the PRO range size (all p<0.01). Similarly to CHB, CHC patients with fatigue were more commonly female, obese, and had higher rates of type 2 diabetes, anxiety, and depression (all p<0.05). They reported substantial impairment in PRO scores, with mean total CLDQ-HCV scores of 3.76 (SD 1.03) vs. 5.46 (0.99), mean total FACIT scores of 61.8 (14.1) vs. 85.6 (14.5), and mean WPI of 0.49 (0.32) vs. 0.17 (0.25) (all p<0.0001). Multivariable analysis showed that the association between lower PRO scores and fatigue in CHC was significant for all PROs, with an impairment magnitude of up to -33% (all p<0.01). Other predictors of lower PRO scores in both CHB and CHC included age, female sex, advanced fibrosis, non-hepatic comorbidities, and lack of regular exercise (p<0.05). In the combined CHB and CHC sample, having CHB (reference: CHC) was independently associated with higher PRO scores in all but one domain and the total score of FACIT (up to +5%, p<0.01). **Conclusion:** Our study highlights the significant burden of fatigue experienced in both CHB and CHC, which is associated with substantial impairment of PROs and work productivity.

Disclosures: Yusuf Yilmaz: Nothing to Disclose, Ming-Lung Yu: Abbvie, Gilead and Roche diagnostics.: Grant/Research Support, Abbott, Abbvie, Gilead, Roche and Roche diagnostics: Consultant, Abbvie, BMS, Gilead,

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Roche and Roche diagnostics: Speaking and Teaching, Khalid Alswat: Nothing to Disclose, Mohamed El-Kassas: Nothing to Disclose, Maria Buti: Nothing to Disclose, George Papatheodoridis: Abbvie: Advisor, Abbvie: Speaking and Teaching, Abbvie: Grant/Research Support, Astra Zeneca: Advisor, Astra Zeneca: Speaking and Teaching, Abbvie: Advisor, Abbvie: Speaking and Teaching, Astra Zeneca: Advisor, Astra Zeneca: Speaking and Teaching, Genesis: Advisor, Genesis: Speaking and Teaching, Gilead: Advisor, Gilead: Speaking and Teaching, Gilead: Grant/Research Support, GlaxoSmithKline: Advisor, Ipsen: Advisor, Ipsen: Speaking and Teaching, Novo Nordisk: Advisor, Novo Nordisk: Speaking and Teaching, Roche: Advisor, Roche: Speaking and Teaching, Takeda: Advisor, Marlen Ivon Castellanos Fernandez: Nothing to Disclose, Yuichiro Eguchi: Nothing to Disclose, Ajay Duseja: Nothing to Disclose, Caglayan Keklikkiran: Nothing to Disclose, Saeed Hamid: Nothing to Disclose, Wah Kheong Chan: Nothing to Disclose, Stuart Gordon: Nothing to Disclose, Gamal ESMAT: Nothing to Disclose, Vasily Isakov: Nothing to Disclose, Stuart Roberts: Nothing to Disclose, NAHUM NAHUM MENDEZ-SANCHEZ: Nothing to Disclose, Jian-Gao Fan: Nothing to Disclose, Manuel Romero Gomez: Nothing to Disclose, Jacob George: Nothing to Disclose, Ashwani Singal: Nothing to Disclose, Aijaz Ahmed: Nothing to Disclose, Brian Lam: Madrigal: Speaking and Teaching, Fatema Nader: Nothing to Disclose, Linda Henry: Nothing to Disclose, Maria Stepanova: Nothing to Disclose, Saleh Alqahtani: Nothing to Disclose

1432 | CLOSE PARTNERSHIP WITH NGOS INCREASES ATTENDANCE AND DAA TREATMENT UPTAKE IN PEOPLE WHO PREVIOUSLY INJECTED DRUGS (EX-PWID) WITH CHRONIC HEPATITIS C

Grace Wong[1] Bonnie Siu[1] Jimmy Lai[1] Angel Chim[1] Adam Ng[1] Angel Ma[1] Olive Yau[1] Rashid Lui[1] Vincent Wong[1]

[1]The Chinese University of Hong Kong

Background: Chronic hepatitis C virus (HCV) infection is highly prevalent among people who inject drugs (PWID). We aimed to report the outcomes of a targeted care program for ex-PWID, with a special focus on recent treatment uptake rates after the generalized availability of direct-acting antivirals (DAAs) to all viraemic patients since 2020, with or without close partnership with non-governmental organisations (NGOs). **Methods:** Consecutive ex-PWID referred from various NGOs received care under a streamlined program with point-of-care rapid anti-HCV testing, followed by HCV RNA testing, education talks and comprehensive liver assessments. Patients with detectable HCV RNA were offered DAA treatment. The treatment uptake rates before (2020-2021) and after (2022-2024) the launch of this personalized care model (with appointments arranged according to individual needs and accompanied by social workers) offered by NGOs were compared. **Results:** 365 (138 in 2020-2021, 227 in 2022-2024) ex-PWIDs were referred for DAA treatment. 47 (34.1%) in 2020-2021 and 36 (15.9%) in 2022-2024 did not show up during the first scheduled appointment; 23 (48.9%) and 31 (86.1%) agreed to attend after rescheduling, hence the overall attendance rate was 114/138 (82.6%) and 222/227 (97.8%) in the two periods, respectively. 102/138 (73.9%) and 218/227 (96.0%) of attended ex-PWIDs agreed to receive DAA, and 97/138 (70.3%) and 215/227 (94.7%) completed DAA treatment. Sustained virologic response was achieved in all but one patient who had completed DAA treatment. With an intention-to-treat analysis, the sustained virologic response rate was 96/138 (69.6%) in 2020-2021 and 215/227 (94.7%) in 2022-2024 (Figure). **Conclusion:** Close partnership with NGOs with a personalized care model increases attendance and DAA treatment uptake in ex-PWID with chronic hepatitis C, which brings the hope of HCV cure to more patients.
Figure. Attendance and DAA treatment uptake rates in people who previously injected drugs (ex-PWID) with chronic hepatitis C, before (in 2020-2021) and after (in 2022-2024) the launch of the personalised care model offered by non-governmental organisations. ITT = intention-to-treat analysis, SVR = sustained virologic response.

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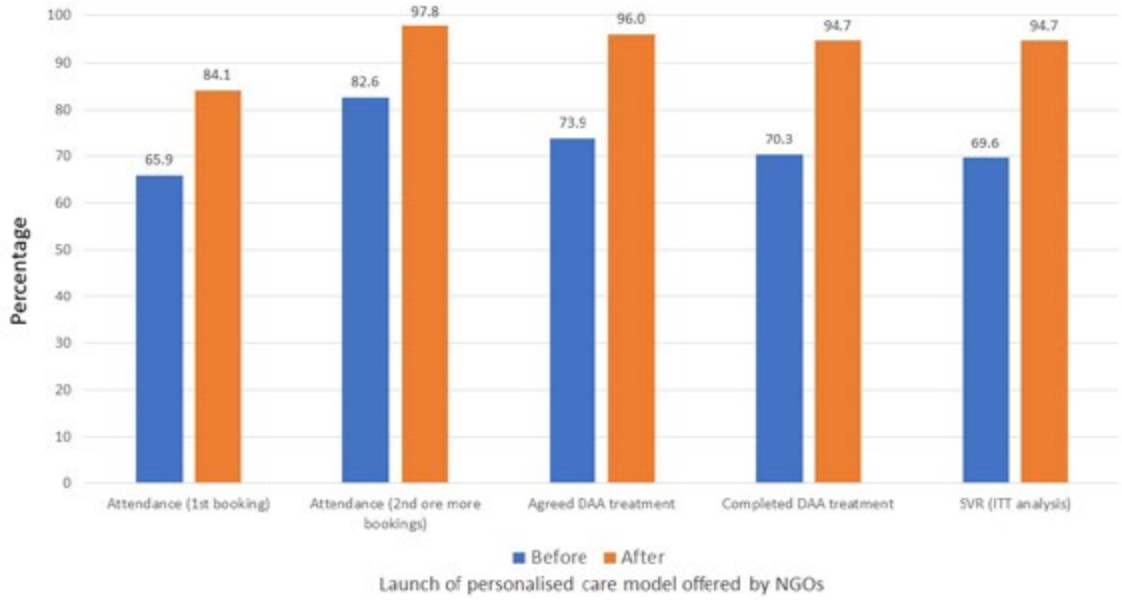

Disclosures: Grace Wong: AstraZeneca: Advisor, Gilead Sciences: Advisor, Gilead Sciences: Speaking and Teaching, Janssen: Advisor, GSK: Advisor, GSK: Speaking and Teaching, Abbott: Speaking and Teaching, AbbVie: Speaking and Teaching, AstraZeneca, Gilead Sciences, GlaxoSmithKline and Janssen,: Advisor, Abbott, AbbVie, Ascletis, Bristol-Myers Squibb, Echosens, Gi: Speaking and Teaching, Gilead Sciences: Grant/Research Support, AstraZeneca, Gilead Sciences, GlaxoSmithKline and Janssen: Consultant, Abbott, AbbVie, Ascletis, Bristol-Myers Squibb, Echosens, Gi: Speaking and Teaching, AstraZeneca, Gilead Sciences, GlaxoSmithKline Pharmaceutical: Consultant, Gilead Sciences: Independent Contractor, AstraZeneca, Gilead Sciences, GSK and Janssen,: Advisor, Abbott, AbbVie, BMS, Gilead Sciences, GSK, Janssen, Roche: Speaking and Teaching, Gilead Sciences: Grant/Research Support, Bonnie Siu: Nothing to Disclose, Jimmy Lai: Nothing to Disclose, Angel Chim: Nothing to Disclose, Adam Ng: Nothing to Disclose, Angel Ma: Nothing to Disclose, Olive Yau: Nothing to Disclose, Rashid Lui: Nothing to Disclose, Vincent Wong: Abbott: Speaking and Teaching, AbbVie: Advisor, AbbVie: Speaking and Teaching, Boehringer Ingelheim: Advisor, Echosens: Advisor, Echosens: Speaking and Teaching, Gilead Sciences: Advisor, Gilead Sciences: Speaking and Teaching, Gilead Sciences: Grant/Research Support, Intercept: Advisor, Inventiva: Advisor, Novo Nordisk: Advisor, Novo Nordisk: Speaking and Teaching, Pfizer: Advisor, Sagimet: Advisor, TARGET PharmaSolutions: Advisor, Unilab: Speaking and Teaching, Visirna: Consultant, Illuminatio Medical Technology: Stock – privately held company

1433 | SERVICE EVALUATION OF CHILDREN WITH HCV AND NEURODEVELOPMENT DELAY; INCIDENTAL FINDING OF HIGH RATES OF LEARNING AND BEHAVIOURAL DIFFICULTIES IN UK CHILDREN LIVING WITH HCV

Carla Lloyd[1] Deirdre Kelly[2] Caroline Jane Foster[3] Dhamyanthi Thangarajah[4]

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Background: Directly acting antivirals (DAAs) for UK children & young people (CYAP) living with HCV (CYAPHCV) are approved through a national Paediatric Operational Delivery Network (PODN)[1]. Whilst central nervous system manifestations of HCV are well recognised in adults less is known for children, although sparse data suggests possible impairments in psychosocial and neurocognitive functioning. Anecdotal observation of an excess in reported learning difficulties (LD) in PODN referrals prompted an audit of LD and treatment outcomes. **Methods:** Retrospective review of e-referrals to HCV PODN between January 2021 and April 2024. In addition to clinical HCV data there is a free text request for information on "co-morbidities". Data extracted included presence/absence of learning or behavioural difficulties, DAA recommendation and outcomes. **Results:** 132 CYAP HCV referrals for DAA approval, median(range) age 8.5years (3-16.); 69(52%) female; ethnicity: Caucasian 75(57%), Asian 22(17%) and other/unknown 35. HCV genotype: (G)1=62(47%); G2=5(4%); G3=60(45%)

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and G4=5(4%). 23/132 (17%) were documented to have one or more learning +/- behavioural difficulty most frequently; autistic spectrum disorder (ASD 10/23[43%]), fetal alcohol syndrome/maternal substance use (FAS 13/23[57%]) & attention deficit hyperactivity disorder (ADHD 10/23[43%]). Three had confirmed chromosomal abnormalities associated with developmental delay. 12/23(52%) in foster care or adopted. DAAs approved (tablets/granules); ledipasvir/sofosbuvir (6/6)& sofosbuvir/velpatasvir (7/4). Despite DAA approval & granular formulations available, 5/23(22%) remain untreated due to severe oral sensory issues associated with ASD/FAS. 18 children started treatment with documented viral clearance (12), data missing (5) and unable to obtain blood due to LD (1). **Conclusion:** Rates of learning & behavioural difficulties in UK school age are estimated at 2.5-4%[2]. Even excluding children with FAS, LD rates were more than twice expected and delayed HCV treatment in more than 20%. Maternal systemic inflammatory disorders +/- infections in pregnancy are associated with an increased risk of neurodevelopmental disorders in childhood. The potential role of maternal-infant HCV infection on neurocognitive outcomes requires elucidation for optimal timing of HCV therapy, currently not licensed until age 3+ years and to determine the risk benefit of maternal HCV clearance in pregnancy. Ref 1. Kelly DA, et al.Eliminating HepC in Children ; Care Closer to Home. Hepatology Vol 78 (Suppl 1) October 2023 S719
Ref 2 Lisa A Croen, Jennifer L Ames et al Inflammatory Conditions During Pregnancy and Risk of Autism and Other Neurodevelopmental Disorders Biol Psychiatry Glob Open Sci 2023 Oct 11;4(1):39-50. eCollection 2 Jan 2024 Acknowledgments to Steering Group and referrers

Referral demographics	
Median age (range) yrs	8.5 (3-16)
Gender n(%)	69 (25)
Ethnicity n(%):	
• Caucasian	75 (57)
• Asian	22 (17)
• Other/Unknown	35 (26)
Genotype n(%):	
• 1	62 (47)
• 2	5 (4)
• 3	60 (45)
• 4	23 (17)
Learning +/- behavioural difficulty n(%)	
• Autistic Spectrum Disorder (ASD)	10/23 (43)
• Fetal Alcohol Syndrome (FAS)/Maternal substance abuse	13/23 (57)
• Attention Deficit Hyperactivity disorder (ADHD)	10/23 (43)
• Associated Chromosomal abnormalities	3/23 (13)
Foster care or adopted n(%)	12/23 (52)
Untreated due to Sensory/oral aversion associated with ASD/FAS)	5/23 (22)

Disclosures: Carla Lloyd: Nothing to Disclose, Deirdre Kelly: Nothing to Disclose, Caroline Jane Foster: Nothing to Disclose, Dhamyanthi Thangarajah: Nothing to Disclose

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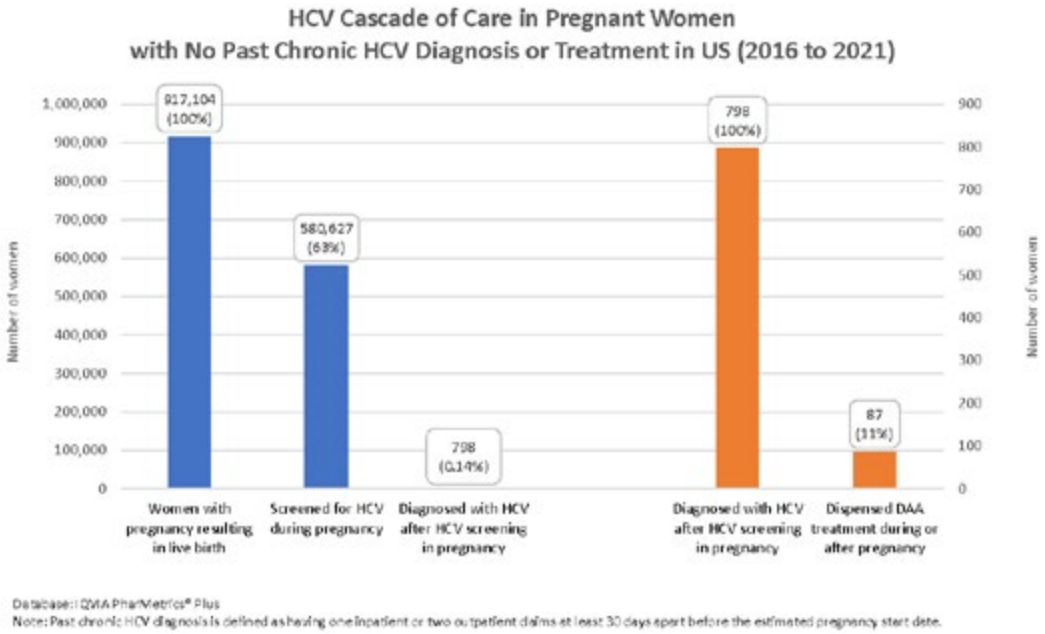
1434 | DELINEATING GAPS IN THE CASCADE OF CARE AMONG PREGNANT WOMEN WITH HCV: AN OBSERVATIONAL RETROSPECTIVE ANALYSIS OF REAL WORLD DATA ON A COMMERCIALLY INSURED COHORT IN THE US

Lauren Liu Wenyi Wang[1] Harriet Dickinson[1] Amanda Singer[1] Laura Telep[1] Alice Stead[1] Katy Schwarz[1] Stacey Federman[1] Annalisa Rubino[1] Tatyana Kushner[2]

[1]Gilead Sciences, Inc, [2]Icahn School of Medicine at Mount Sinai

Background: Hepatitis C virus (HCV) prevalence in pregnancy increased from 0.05% to 0.49% in the US (2000 to 2019). In 2021, the proportion of women with commercial insurance screened for HCV during pregnancy was ~41% despite recommendations for universal HCV screening in each pregnancy. Currently there are no clear guidelines for direct-acting antiviral (DAA) use in pregnancy. To explore potential gaps in the HCV care cascade in this population, we sought to characterize HCV testing, diagnosis, and treatment among commercially insured pregnant women in the US. **Methods:** This observational retrospective cohort study utilized US administrative claims data (IQVIA PharMetrics® Plus) to characterize the HCV care cascade in a cohort of women with a pregnancy resulting in live birth between 2016 and 2021. We assessed the proportion of women screened for HCV during pregnancy, the proportion of women subsequently diagnosed with HCV among those screened, and the frequency of dispensed DAA treatment during/after pregnancy among those diagnosed with HCV. **Results:** The study cohort included 917,891 women; 917,104 (99%) had no past chronic HCV diagnosis or treatment before pregnancy. In their first pregnancy within the study period, 580,627 (63%) women were screened for HCV; among those, 798 (0.14%) received an initial HCV diagnosis. Among diagnosed women, the mean (standard deviation) age was 29.7 (5.7) years, and women were from the Southern (42%), Eastern (23%), Midwestern (22%), and Western (13%) US regions. DAA treatment was dispensed to 87 (11%) women either during pregnancy (n=2) or after pregnancy through the end of their observational time in the database (n=85). The 711 (89%) women not dispensed DAA treatment after pregnancy had a median (Q1, Q3) of 317 (114, 781) days of observation postpartum within the database. **Conclusion:** In a US administrative claims database, more than 35% of women were not screened for HCV during pregnancy between 2016 and 2021. Prevalence of detected HCV was lower than earlier reported in broader nationwide samples, suggesting a commercially insured population appears to be at lower risk of HCV. Despite insurance coverage, however, dispensing of DAA treatment to pregnant women with HCV was limited during pregnancy and during a 10-month postpartum period. Further investigations on the impact of lack of treatment are needed to inform best practices to ensure all patients diagnosed with HCV during pregnancy receive adequate linkage to care.



Disclosures: Lauren Liu: Gilead Sciences Inc.: Employee, Wenyi Wang: Nothing to Disclose, Harriet Dickinson: Nothing to Disclose, Amanda Singer: Gilead Sciences: Employee, Gilead Sciences: Stock - publicly traded

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company, Laura Telep: Gilead Sciences, LLC: Employee, Gilead Sciences, LLC: Stock - publicly traded company, Alice Stead: Gilead Sciences: Employee, Katy Schwarz: Nothing to Disclose, Stacey Federman: Gilead Sciences: Employee, Annalisa Rubino: Gilead Sciences: Employee, Tatyana Kushner: Advisor relationship with Gilead; Has ended; Advisor relationship with GSK; Has ended; Advisor relationship with Eiger; Has ended; Grant/Research Support relationship with Gilead; Has not ended

1435 | FACTORS ASSOCIATED WITH THE AGGRAVATION OF GASTROESOPHAGEAL VARIX IN COMPENSATED AND DECOMPENSATED CIRRHOTIC PATIENTS DUE TO CHRONIC HEPATITIS C VIRUS INFECTION AFTER DIRECT-ACTING ANTIVIRAL THERAPY

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Background: The aggravation of gastroesophageal varix is observed in some cirrhotic patients after direct-acting antiviral (DAA) therapy. However, the incidence rate of and factors associated with the aggravation of gastroesophageal varix after DAA in hepatitis C virus (HCV) cirrhotic patients, including decompensated cirrhosis, are unclear. **Methods:** This study prospectively enrolled 478 HCV cirrhotic patients who started DAA therapy between February 2019 and December 2021 at 33 Japanese institutions. Decompensated cirrhosis was defined as patients with Child-Pugh class B or C when considering DAA therapy, or patients with Child-Pugh class A with a history of decompensation when considering DAA therapy. Gastroesophageal varix was classified as F1 (small-caliber), F2 (moderately enlarged), and F3 (markedly enlarged) according to Japanese criteria (Tajiri T, et al. 2010;22:1-9). Patients without varix or with F1 without red color sign were defined as low-risk varix, and patients with F2 or more, or with red color sign or with a history of varix rupture were defined as high-risk varix. Aggravation of varix was defined as a prophylactic treatment or rupture of gastroesophageal varix. We examined the cumulative incidence rate and the factors associated with aggravation of gastroesophageal varix after DAA therapy. The sustained virologic response (SVR) was defined as serum HCV-RNA undetectable at 12 or 24 weeks after the end of therapy. **Results:** The median age was 70 years, 43% were decompensated cirrhosis, and 16% had high-risk varix (13% in compensated and 33% in decompensated, p<0.001). The SVR rates were 94.9% in compensated cirrhosis and 91.3% in decompensated cirrhosis (p=0.120). During 35.7 months from the initiation of DAA, 25 patients received prophylactic treatment, and four experienced varix rupture. The cumulative aggravation rate of varix at 3 years was 6.2% (3.5% in compensated and 9.9% in decompensated, p=0.001). In multivariate Cox hazard analysis, high-risk varix (p<0.001), higher baseline gamma-glutamyl transpeptidase (GGT) levels (p=0.001), and virologic failure (p=0.018) were significantly associated with the aggravation of varix. The aggravation rates of varix were 22.8% in patients with high-risk varix, 3.9% in those with low-risk varix, and 11.3% in patients with GGT of 75U/l or more and 4.5% in those with GGT less than 75U/l, and 46.7% in patients with virologic failure and 5.9% in those with SVR, respectively. **Conclusion:** The cumulative aggravation rates of varix at 3 years were 9.9% in decompensated cirrhosis and 3.5% in compensated cirrhosis, respectively, and which was significantly higher in decompensated cirrhosis than in compensated cirrhosis. As risk factors of the aggravation of varix in HCV cirrhotic patients treated with DAA, baseline status of varix, baseline GGT levels, and virologic response were identified.

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1436 | CLOSING THE GAP: IMPLEMENTING HEPATITIS C REFLEX TESTING WITHIN UNM HEALTH SYSTEM

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Background: This academic health system micro-elimination (UNM-HCEP) aims to eliminate hepatitis C (HCV) within the University of New Mexico (UNM) patient population. The goal is that every patient receives treatment, leaving no cases of untreated HCV. In the U.S. HCV care follows 5 stages: 1) antibody ([AB] screening, 2) confirmatory testing, 3) linkage to care, 4) medication, and 5) cure. HCV testing was a 2-step process, with blood tests on different dates. This causes a loss of patients, with 25% of HCV AB+ individuals lost (Terrault N. 2019. Hepatitis C elimination: challenges with under-diagnosis and under-treatment). **Methods:** UNM-HCEP began HCV reflex testing in Dec. 2021 and in 2022 was integrated into Electronic Medical Record (EMR). The Caresets and Powerplans containing HCV AB-only tests were identified and AB-only tests were replaced with the reflex test. Analysis included: 1) the uptake of HCV DX reflex testing, 2) increase in confirmatory testing, and 3) estimated viremia. **Results:** reflect 2023 data from the EMR across the UNM health system only. UNM system improved confirmatory testing for 100% of AB+ results. Inclusion and automation of HCV DX caused uptake and sustained use of the test most often. The Hep Panel represents 25% of all screens. In 2023 there was a total of 973 AB+ tests and 193 people did not receive a confirmatory test (20%). Reflex testing predicts viremia rates better, enabling prediction of patient volume. AB-only tests persist, leading to incomplete diagnosis. **Conclusion:** UNM-HCEP demonstrates benefits of integrating automated reflex testing within an EMR and include: sustained use of this test, improved quality of care, decreased clinical uncertainty for providers, and provide patient-centered experience. Collaboration with existing stakeholders remains vital and will include advocacy to replace the contracted lab HCV AB-only tests. UNM-HCEP next steps 1) Assess and address provider concerns and rationale for continued use of AB-only tests 2) Identify clinic-specific standing orders and paper order forms that perpetuate

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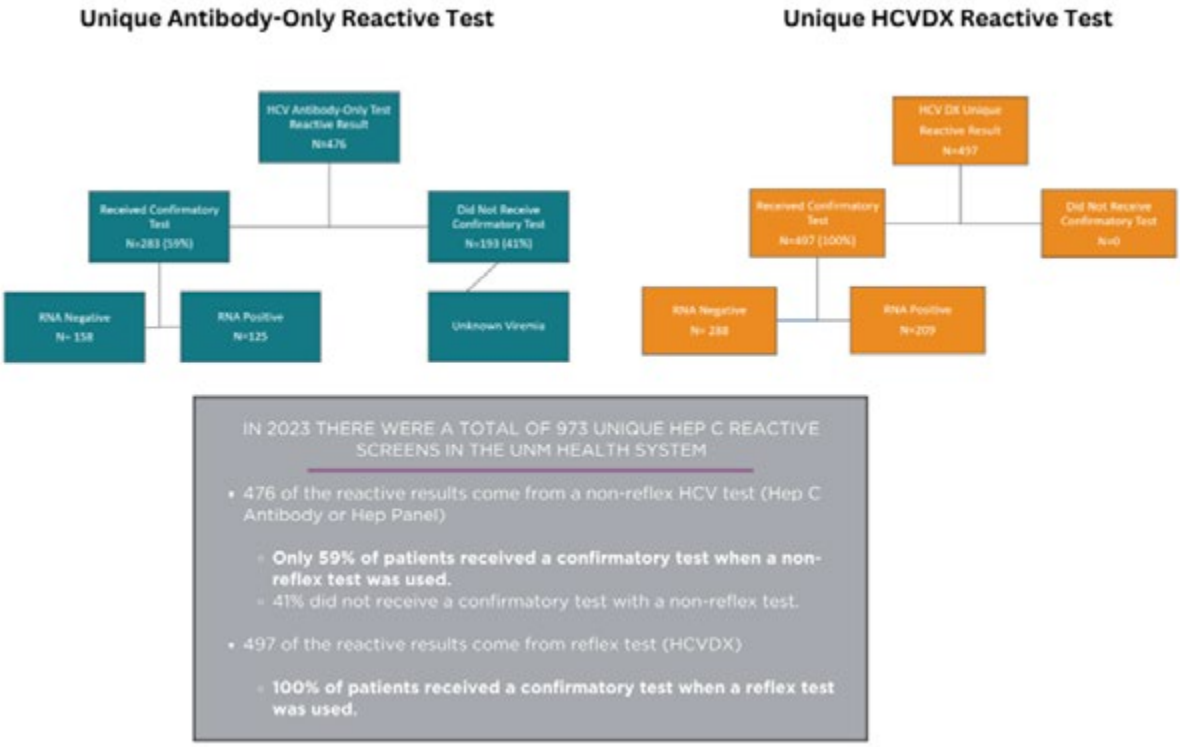
AB-only tests and 3) Analyze which patients do not receive HCV DX test and evaluate trends in testing locations or patient demographics. This will further the vision of the UNM Hepatitis C Elimination Project.



Disclosures: Colleen Chávez: Nothing to Disclose, Aaron Skiles: Nothing to Disclose

1437 | ALTERATIONS IN THE TRYPTOPHAN PATHWAY DURING HEPATITIS C VIRUS INFECTION DEMONSTRATES A SHIFT TOWARDS A PRO-INFLAMMATORY STATE

Jenna Oringher[1] Rownock Afruza[1] Moumita Chakraborty[1] Rabab Ali[1] Kareen Akiva[1] Grace Zhang[1] Elizabeth Townsend[1] Gabriella Quinn[1] Lisa Scheuing[1] Matthew Menkart[1] David Kleiner[2] Ohad Etzion[1] Elliott Levy[3] Christopher Koh[1] Theo Heller[1]

[1]NIDDK, [2]National Cancer Institute, Bethesda, [3]NIH CC

Background: Tryptophan catabolism is controlled by the liver, gut, and gut microbiome, integrated within the gut-liver axis. Tryptophan feeds into three distinct pathways, kynurenine, serotonin, and indole production, resulting in pro-inflammatory intermediates. This investigation aimed to characterize perturbations in the tryptophan pathway during and post Hepatitis C Virus infection (HCVi) and elucidate the relationship of tryptophan metabolites to the microbiome to better understand mechanistic role of the tryptophan pathway in liver disease. **Methods:** Peripheral and portal blood, liver biopsy and stool were collected before (n=24) and after DAA therapy (n=19) (NCT02400216). Tryptophan metabolites measured via metabolon global metabolomics assays. Immune cells quantified via flow cytometry. The microbiome was assessed using 16S rRNA sequencing. The liver transcriptome determined using RNAseq. Ishak fibrosis (IF) and hepatic activity index (HAI) used to score fibrosis and inflammation. Statistical testing: Wilcoxon paired t-test, Spearman's nonparametric correlation, and DESeq2. **Results:** In peripheral blood of HCVi patients, tryptophan and kynurenine were increased and indolelactate and xanthurenate were decreased ($p<0.05$). Portal blood had an increased amount of kynurenine and decreased indoleacetate and xanthurenate during infection ($p<0.05$). Four genes in the tryptophan pathway were upregulated in the liver during infection: IDO1, TDO2, INMT and CYP1B1 (adjP<0.1 & Log2FC>|0.5|). Kynurenine in peripheral blood negatively correlated with Bacillota, Clostridia, Eubacteriales, Lachnospiraceae, *Dorea,* and *Dorea longicatena* (rho>-0.5, $p<0.05$). Lachnospiraceae and Clostridia are known to be depleted in HCVi, and these findings suggest a connection between dysbiosis in HCV and the tryptophan pathway. *Qiania dongpingenesis* negatively correlated with tryptophan in the portal venous system at the genus and species

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level (rho>-0.7, p<0.05). Peripheral tryptophan correlated to HAI score (rho>0.45, p<0.05). Portal tryptophan and kynurenine correlated with eosinophils (rho>0.45, p<0.05). **Conclusion:** Alterations in tryptophan pathway metabolites and differential liver transcription of key enzymes in the pathway demonstrates a virus induced shift. Correlations to the microbiome demonstrates a connection to the gut-liver axis. Lastly, correlations to HAI and eosinophils suggest a mechanistic relationship to disease progression and a pro-inflammatory state.

Disclosures: Jenna Oringher: Nothing to Disclose, Rownock Afruza: Nothing to Disclose, Moumita Chakraborty: Nothing to Disclose, Rabab Ali: Nothing to Disclose, Kareen Akiva: Nothing to Disclose, Grace Zhang: Nothing to Disclose, Elizabeth Townsend: Nothing to Disclose, Gabriella Quinn: Nothing to Disclose, Lisa Scheuing: Nothing to Disclose, Matthew Menkart: Nothing to Disclose, David Kleiner: Nothing to Disclose, Ohad Etzion: Nothing to Disclose, Elliott Levy: Nothing to Disclose, Christopher Koh: Nothing to Disclose, Theo Heller: Nothing to Disclose

1438 | INCIDENCE OF LIVER DISEASE PROGRESSION IN PATIENTS WITH HEPATITIS C VIRUS GENOTYPE 3 AFTER SVR FOLLOWING DAA THERAPY

Dachuan Cai[1] *Ying Wang*[1]

[1]*Dept of inf dis,2nd affil hosp of CQMU*

Background: HCV genotype (GT) 3 is associated with rapid liver disease progression. However, the liver disease progression and its risk factors in patients with HCV GT 3 infection after sustained virological response (SVR) following direct-acting antivirals (DAAs) remain unclear. Therefore, this study aimed to investigate the liver disease progression of patients with HCV GT3 after DAA. **Methods:** This was a retrospective cohort study of patients with HCV infection who achieved SVR by DAAs. The overall liver disease progression (OLDP) was defined as newly diagnosed compensated liver cirrhosis, decompensated liver cirrhosis, or hepatocellular carcinoma. The incidence of OLDP was evaluated by Kaplan–Meier analysis. Cox regression analysis identified the risk factors for OLDP. **Results:** A total of 409 patients (46.9% GT3) were followed for 43.7 (32.9, 58.7) months. Patients with HCV GT 3 had a lower baseline age (45 vs 49; P<0.001), and a higher proportion of cirrhosis (43.2% vs 29.5%; P=0.002) than patients with HCV non-GT 3. The incidence of OLDP was higher in patients with GT 3 (4.63/100PY) than non-GT 3 (0.60/100PY; P<0.001). The incidence of OLPD in patients without cirrhosis or with liver fibrosis was similar between the GT 3 group and the non-GT 3 group. Cox univariate analysis results suggested that male, diabetes, HCV recurrence, FIB-4>3.25, PLT < 100×10^9/L, and ALB<0.001) and FIB-4>3.25 (HR 16.40, 95% CI 1.03 - 39.81; P = 0.046) at baseline according to Cox multivariate analysis. **Conclusion:** HCV GT 3-infected patients remain at a higher risk of OLDP even after achieving SVR by DAAs, especially patients with advanced liver fibrosis and at high risk for reinfection or virological late relapse.

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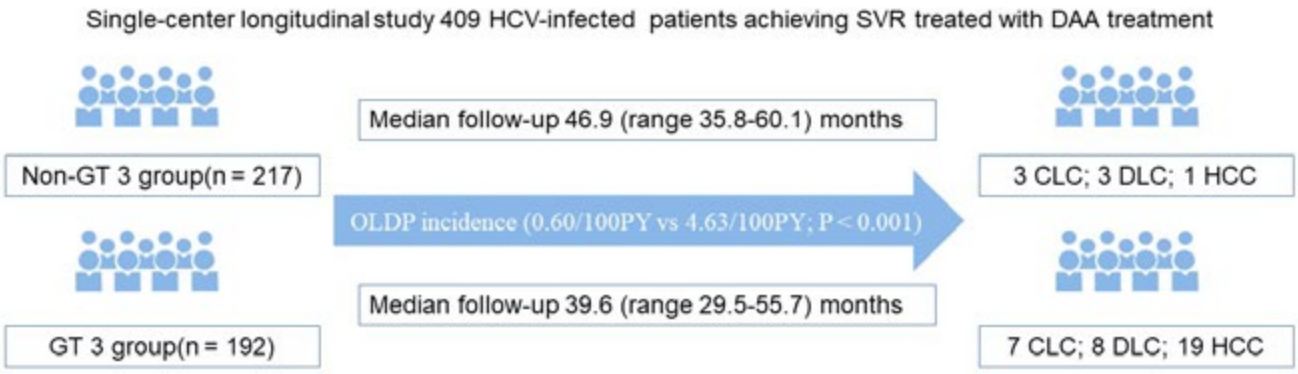

	Univariate analysis		Multivariate analysis	
	p value	HR (95%CI)	*p* value	HR (95%CI)
HCV Recurrence				
No		1.00 (Reference)		1.00 (Reference)
Yes	<.001	8.97 (3.37 - 23.87)	<.001	12.15 (3.18 - 46.46)
FIB-4 index				
≤ 3.25		1.00 (Reference)		1.00 (Reference)
> 3.25	0.006	7.65 (1.80 - 32.58)	0.046	6.40 (1.03 - 39.81)

HCV: hepatitis C virus; SVR: Sustained virological response; DAA: direct-acting antivirals; GT: Genotype; OLDP: Overall liver disease progression; CLC: Compensated liver cirrhosis; HCC: Hepatocellular carcinoma; DLC: Decompensated liver cirrhosis; FIB-4: Fibrosis-4; HR: Hazard ratio.

Disclosures: Dachuan Cai: Nothing to Disclose, Ying Wang: Nothing to Disclose

1439 | CHARACTERISTICS AND TREATMENT PATTERNS OF TRANSGENDER MEN AND WOMEN LIVING WITH HEPATITIS C IN THE UNITED STATES

Alice Stead[1] Catherine Frenette[1] Laura Telep[1] Wenyi Wang[1] Anand Chokkalingam[1] Stacey Federman[1] Amanda Singer[1]

[1]Gilead Sciences

Background: Few studies have described the characteristics of transgender (TG) individuals living with Hepatitis C virus (HCV) infection. The TG population may have a higher prevalence of risk factors for HCV infection and be less likely to access health services due to stigma. This study describes characteristics and treatment patterns of TG individuals with HCV infection in the United States (US). **Methods:** Health Verity administrative claims data were used to identify adults (≥18 years) between 2017-2022 with evidence of HCV and continuous enrollment ≥365 days prior to first HCV diagnosis (index date); individuals could not have evidence of prior direct-acting antiviral (DAA) treatment, HIV, or Hepatitis B infection. TG individuals were identified using an algorithm developed from published literature utilizing diagnoses, procedures, and medications. Treatment initiation was defined as ≥1 dispensing claim for DAAs after index date, and treatment completion was identified by ≥8 weeks of dispensed treatment. Descriptive analyses examined demographic characteristics, prevalence of injection drug use (IDU) and mental health disorders (MHDs), and the proportion of individuals initiating and completing HCV treatment by age, race, and gender. **Results:** In this cohort of 405,833 individuals with HCV, 280 TG men (TGM) (0.07%) and 386 TG women (TGW) (0.10%) were identified. Both TGM and TGW were predominantly White (50% and 43.5%, respectively), though race data was missing for approximately 33%. Nearly one-third of TGM and TGW had a history of IDU (194/666; 29.1%), and a large proportion (463/666; 69.5%) had a history of MHDs. Compared to individuals with HCV infection not classified as TG, TGM and TGW were more likely to be younger than 35 years old. Overall, 26 (9.3%) TGM and 64 (16.6%) TGW initiated DAA treatment; by comparison, 18.1% of individuals in the HCV cohort overall initiated DAA treatment. There was particularly low treatment uptake among Black and Hispanic TGM and TGW. Overall and among the subgroups of individuals with a history of IDU or MHDs, most TG persons who were dispensed DAAs completed ≥8 weeks of treatment (75-85%). **Conclusion:** Utilizing an algorithm to identify TG individuals in US claims data provides insight into a population of TG individuals who have not previously been well described. Although these findings suggest that TGM and TGW represent a small proportion of the HCV-infected population, they may warrant specific outreach for HCV care and treatment.

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Proportion of Transgender Men and Women with HCV Infection Initiating and Completing Treatment Overall, and among Subgroups of Individuals with a History of Injection Drug Use and/or Mental Health Disorders

	HCV Infections n (%)	Initiated Treatment n (%)	Completed ≥ 8 Weeks Treatment[1] n (%)
Transgender Men			
HCV Overall	280 (100)	26 (9.3)	20/25 (80.0)
History of IDU	93 (33.2)	16 (17.2)	12/16 (75.0)
History of MHD	205 (73.2)	21 (9.8)	17/21 (81.0)
Transgender Women			
HCV Overall	386 (100)	64 (16.6)	50/61 (82.0)
History of IDU	101 (26.2)	22 (21.8)	17/20 (85.0)
History of MHD	258 (66.8)	43 (16.7)	33/41 (80.5)

1. The denominator for treatment completion is the total number of individuals with at least 9 weeks of follow-up after treatment initiation.
HCV=Hepatitis C Virus, IDU=injection drug use, MHD=mental health disorders

Disclosures: Alice Stead: Gilead Sciences: Employee, Catherine Frenette: Gilead Sciences, Inc.: Employee, Gilead Sciences, Inc.: Stock - publicly traded company, Laura Telep: Gilead Sciences, LLC: Employee, Gilead Sciences, LLC: Stock - publicly traded company, Wenyi Wang: Nothing to Disclose, Anand Chokkalingam: Nothing to Disclose, Stacey Federman: Gilead Sciences: Employee, Amanda Singer: Gilead Sciences: Employee, Gilead Sciences: Stock - publicly traded company

1440 | CHANGES IN HEPATITIS C VIRUS SCREENING AND TREATMENT RATES IN PREGNANT INDIVIDUALS BEFORE AND AFTER IMPLEMENTATION OF UNIVERSAL SCREENING GUIDELINES

Chandler Shapiro[1] *Sheena Gillani*[1] *Nancy Reau*[1] *Samantha de los Reyes*[1]

[1]*Rush University Medical Center*

Background: Hepatitis C virus (HCV) incidence has doubled since 2013 due to injection drug use among those of reproductive age, leading to higher rates of HCV during pregnancy. Consequently, in Aug 2017 the Society of Maternal Fetal-Medicine (sMFM) recommended HCV screening in high-risk pregnancies. Both the United States Preventive Services Task Force (USPSTF) and American College of Obstetricians and Gynecologists (ACOG) then recommended universal HCV screening during pregnancy in March 2020 and May 2021, respectively. Universal screening did improve HCV identification during pregnancy, but only 6-9% of positive patients were linked to care within a year postpartum. The purpose of this study is to determine if universal HCV screening recommendations during pregnancy were followed and if this led to improved treatment rates within a year postpartum at our tertiary care center. **Methods:** We conducted a retrospective analysis of pregnant adult patients who received their first prenatal visit at two centers at our institution from Jan 1, 2013 - Oct 1, 2023. HCV screening was defined as HCV-antibody (Ab) testing. De-identified HCV-Ab and viral load data were extracted from the electronic medical record. Patients were categorized into three screening phases (SP) based on timing of the test: SP 1 – before risk screening (Jan 1 2013 – Aug 1 2017), SP 2- after sMFM risk screening recommendation but prior to ACOG universal screening (Aug 2 2017 – May 1 2021), and SP 3 – after ACOG universal screening (May 2 2021- Oct 1 2023). Of those with positive HCV-Ab and viral loads, charts were manually reviewed to see if treatment was prescribed within a year postpartum or later. **Results:** Of the 31,927 patients, 6,713 had an HCV-Ab test completed (21%). 1% (111/11,414) were screened in SP1, 16.6% (2,085/12,594) in SP2, and 57% (4,517/7,919) in SP3. In total, 40 patients had a positive HCV-Ab (0.6%). Of those 40, 35 (87.5%) had quantitative HCV RNA testing with 5 having a positive viral load. 100% (5/5) were linked to an HCV provider, however none received treatment within 1 year of delivery. 1/5 was treated after this period. **Conclusion:** HCV screening increased with each SP though remains inadequate. HCV-Ab prevalence was higher in SP 2 and 3 suggesting that universal HCV screening guidelines promoted improved surveillance and identification early in pregnancies. Patients found to have detectable HCV viral loads were appropriately linked to care, though that rarely resulted in treatment.

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Table 1. HCV Antibody Screening, Hepatology Referral, and Treatment Completion Trends During Each Screening Phase

	Number of Prenatal Visits	Number of Prenatal Visits with HCV-Ab Testing		Number of Prenatal Visits with Positive HCV-Ab		Number of Prenatal Visits with Positive HCV-Ab Testing and Positive Viral Load	Number Referred to Hepatologist for Treatment	Number of Patients Who Completed Treatment for Active HCV Within 1 Year Postpartum
	n (%)	n (%)	%: # of HCV-Ab tests completed compared to # of prenatal visits	n (%)	%: # of HCV-Ab positive tests compared to # of prenatal visits with Hep C-Ab screening	n (%)	n (%)	n (%)
All Patients	31,927	6,713	21%	40	0.6%	5	5	0
Screening Phase 1 (Before Risk Screening)	11,414 (33.8%)	111 (1.6%)	1.0%	5 (12.5%)	4.5%	2 (40%)	2 (40%)	0
Screening Phase 2 (After Risk Screening, Before Universal Guideline)	12,594 (37.3%)	2,085 (31%)	16.6%	19 (47.5%)	0.91%	3 (60%)	3 (60%)	0
Screening Phase 3 (After Universal Guideline)	7,919 (23.5%)	4,517 (67%)	57.0%	16 (40%)	0.35%	0	N/A	N/A

Disclosures: Chandler Shapiro: Nothing to Disclose, Sheena Gillani: Nothing to Disclose, Nancy Reau: Gilead: Grant/Research Support, eiger: Grant/Research Support, abbott: Consultant, Arbutus: Consultant, Gilead: Consultant, VIR: Consultant, Salix: Consultant, Salix: Grant/Research Support, AbbVie: Grant/Research Support, Samantha de los Reyes: Nothing to Disclose

1441 | IMPACT OF SUSTAINED VIROLOGICAL RESPONSE ON LONG-TERM OUTCOMES AFTER CURATIVE RESECTION IN PATIENTS WITH OF HEPATITIS-C-VIRUS-RELATED HEPATOCELLULAR CARCINOMA IN THE ERA OF DIRECT-ACTING ANTIVIRAL THERAPY

Hayato Abe[1] *Yukiyasu Okamura*[1]

[1]*Nihon University School of Medicine*

Background: There is controversy over the impact of sustained virologic response (SVR) for hepatitis C virus (HCV) infection on surgical outcomes for hepatocellular carcinoma (HCC) in the era of direct-acting antiviral (DAA) therapy. The aim of the present study was to clarify the long-term outcomes after curative resection for HCV-related HCC in the patients with SVR by antiviral therapy and patients without SVR. **Methods:** This single-center retrospective cohort study included 216 patients with HCV-related HCC who underwent primary curative resection. Overall survival (OS) and recurrence-free survival (RFS) rates following HCC treatment were determined according to Kaplan–Meier method and compared using the log-rank test. Potential associations of achievement of SVR, and other clinicopathological and surgical variables with OS and RFS were analyzed in multivariate Cox proportional hazards analysis. This analysis to reduce selection bias was performed using propensity score (PS) matching method and adjusting with the confounding factors. Analyzed patients were divided into preoperative achieved SVR (Pre-SVR: 108 patients), postoperative achieved SVR (Post-SVR: 28 patients) and not achieved SVR (Non-SVR: 80 patients). Finally, study population was divided into SVR (n = 136) and Non-SVR groups. **Results:** Patients with Pre-SVR had better liver function and less liver fibrosis compared to patients with Post-SVR and without SVR. In multivariate analysis, Pre- or Post-SVR (hazard ratio (HR), 0.13; 95% confidence interval (CI), 0.03-0.38; P <0.001) was the only independent predictor of OS. For RFS, Pre- or Post-SVR (HR, 0.36; 95% CI, 0.18-0.64; P = 0.001) was one of several independent predictors. Propensity score-matched OS and RFS were significantly better in SVR group (n = 53) than Non-SVR group (n = 53) (P <0.001 and P = 0.012, respectively). In addition, OS rate of SVR achieved by DAA were significantly better than that of SVR achieved by interferon (P = 0.019). **Conclusion:** Obtaining an SVR by DAA either before or after curative resection was associated with the suppression of recurrence and the prevention of death in patients with HCV-related HCC.

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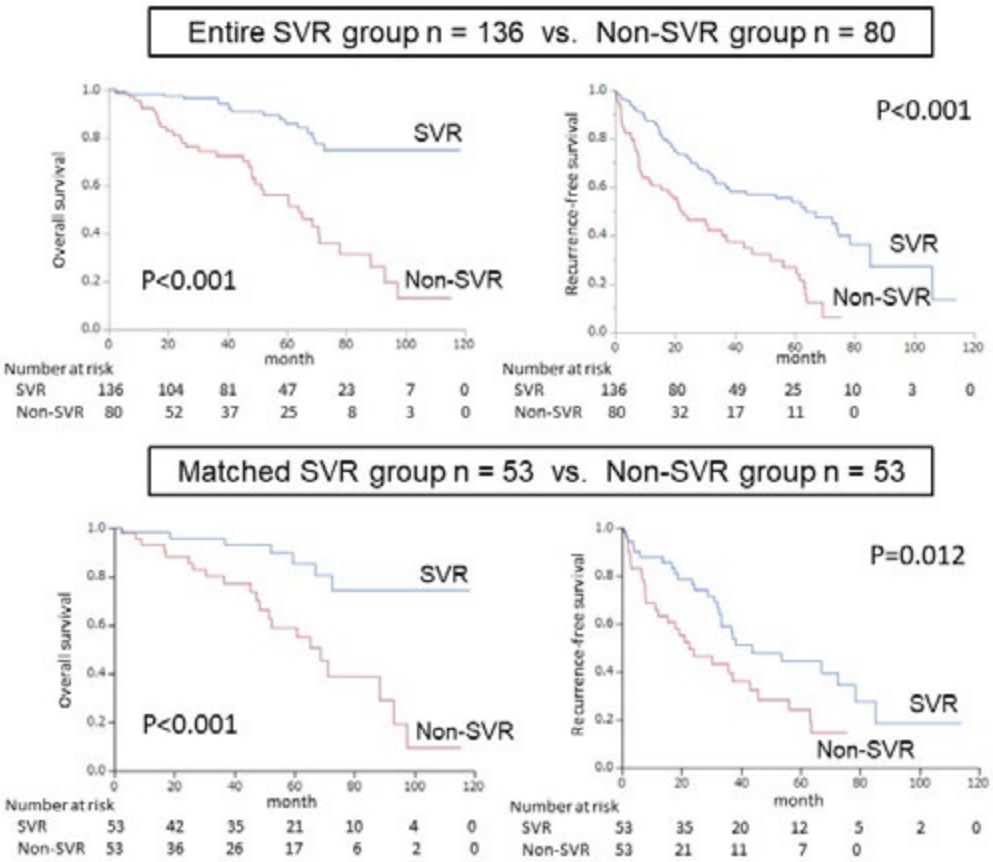

Disclosures: Hayato Abe: Nothing to Disclose, Yukiyasu Okamura: Nothing to Disclose

1442 | TELEHEALTH TO INCREASE HEALTHCARE ACCESS; PERSPECTIVES OF PEOPLE WHO USE DRUGS

Zoi Papalamprakopoulou[1] Elisavet Ntagianta[2] Vasiliki Triantafyllou[2] George Kalamitsis[2] Arpan Dharia[1] Suzanne Dickerson[1] Angelos Hatzakis[3] Andrew Talal[1]

[1]University at Buffalo, [2]Hellenic Liver Patient Association, [3]University of Athens

Background: Hepatitis C virus (HCV) elimination plans prioritize treatment of high-risk individuals, such as people who use drugs (PWUD). However, PWUD often face barriers accessing the highly effective HCV treatment, largely due to stigma, healthcare system mistrust, and geographical obstacles. Telehealth, through the transcendence of geographical and temporal barriers, presents an innovative approach to expand HCV treatment to PWUD, addressing many healthcare access barriers. We explored PWUDs' perceptions towards telehealth as a healthcare delivery modality. **Methods:** Between May and September 2023, we conducted nine focus group discussions (FGDs) (N = 57) employing purposive sampling for PWUD recruitment. Inclusion criteria required participants to be at least 18 years old, have a history of injection drug use, and have current internet access. We used a semi-structured interview guide, and the FGDs were audio-recorded, transcribed verbatim, and subsequently translated into English and analyzed using thematic analysis. **Results:** Participants' mean (standard deviation) age was 47.9 (8.9) years, 89.5% (51/57) were male, 91.2% (52/57) were of Greek origin, and 61.4% (35/57) had attended at least 10 years of school. Three main themes emerged from the FGDs: (1) high internet utilization for healthcare-related activities among PWUD, (2) highlighting telehealth benefits despite access obstacles and PWUD concerns about diagnostic accuracy, and (3) approaches to overcome access obstacles and build digital trust. Our participants, largely telehealth-inexperienced, frequently used the internet for healthcare interactions and viewed telehealth positively. While most recognized telehealth benefits, such as convenience and trust in the digital environment, a few participants expressed diagnostic accuracy concerns without physical examination. To address technology accessibility barriers and improve digital trust, they

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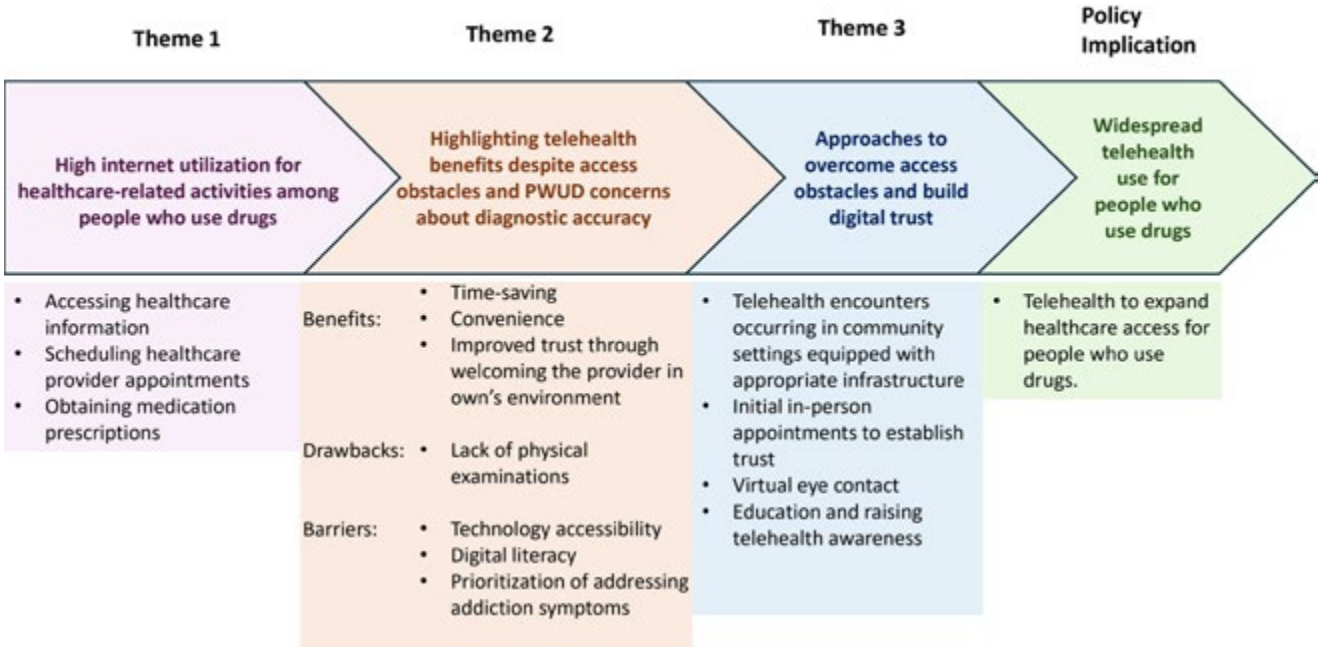
suggested partnering with community organizations equipped with telehealth infrastructure, scheduling an initial in-person provider appointment, and promoting virtual eye contact. **Conclusion:** Participants' suggestions for telehealth improvement, including an initial in-person appointment and partnering with community organizations, offer practical steps for intervention design. Policymakers seeking to expand HCV treatment should consider these findings to enhance PWUD service delivery, aligning with elimination goals.

Figure 1. Building digital trust among people who use drugs: Themes identified through focus group discussions among 57 people who use drugs related to perceptions of telehealth as a healthcare delivery modality.



Disclosures: Zoi Papalamprakopoulou: Nothing to Disclose, Elisavet Ntagianta: Nothing to Disclose, Vasiliki Triantafyllou: Nothing to Disclose, George Kalamitsis: Nothing to Disclose, Arpan Dharia: Nothing to Disclose, Suzanne Dickerson: Nothing to Disclose, Angelos Hatzakis: Nothing to Disclose, Andrew Talal: Gilead Sciences: Grant/Research Support, AbbVie: Consultant, Abbott Laboratories: Grant/Research Support, Novo Nordisk: Advisor, Astra Zeneca: Grant/Research Support, Novo Nordisk: Grant/Research Support

1443 | STABILITY OF CAPILLARY WHOLE BLOOD (CWB) IN MICROTAINER, AND LIMIT OF DETECTION (LOD) FOR HEPATITIS C VIRUS (HCV) (GENOTYPES 1-6) IN CWB VERSUS VENOUS WB (VWB) USING CEPHEID XPERT® HCV RUO SYSTEM

Anuradha Rao[1] Kaleb McLendon[2] Tiffany Edwards[3] Leda Bassit[2] Mahi Patel[2] Evelyn Morales[2] Heather Bowers[2] Courtney Sabino[2] Zianya Solis[2] Hayden Smith[3] Kelsey M Badger[3] Aidan Wilson[3] Karen Peltier[3] Nathan Garza[3] Yun Wang[4] Emily Kennedy[5] Gail Radcliffe[6] Carlos Aparicio[7] Pamela Miller[8] Eric Lai[9] Julie Sullivan[2] Wilbur Lam[2]

[1]Emory University School of Medicine, [2]Emory University, [3]MRIGlobal, [4]Emory University and Grady Memorial, [5]OOMVELT, [6]Radcliffe Consulting, Inc., [7]CLAS Consulting, Inc., [8]Echo Bay Consulting, [9]Personalized Science

Background: As part of the US National Hepatitis C Elimination Initiative and WHO goal of HCV elimination by 2030, there is an impetus to develop a Point-of-Care (POC) test in a CLIA waived setting for HCV detection that does not require venous blood draw by an on-site phlebotomist. A test yielding results in a short time (~1 hour) using CWB from a fingerstick (FS) would be ideal to allow patients to leave with medication the same day, obviating the need for a repeat visit. We have been working closely with Cepheid to obtain FDA clearance for the Xpert® HCV test with the GeneXpert Xpress System. This will be the first US device for HCV detection in a POC setting. We describe here results from two laboratory studies that were performed to support clinical development. Aim 1: Establish stability for storage of CWB in a microtainer to identify a time window for sample testing in a clinical setting. Aim 2: Conduct a laboratory based analytical study to determine the LoD for 6 HCV genotypes (Gts) in CWB, ideally with

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similar sensitivity to detection in VWB. **Methods:** For Aim 1, we collected CWB from 6 HCV negative donors in BD Microtainers. Five samples were spiked with HCV Gt 1a, while one was unspiked. All samples were incubated at 2°C and 30°C for 2, 4 and 5 hours. At each time point and temperature, samples were tested. For Aim 2, CWB and VWB from HCV negative donors were used for LoD range finding (replicates of 5) and LOD confirmation (replicates of 20, minimum of three concentrations) for all 6 Gts. Totals of 884 and 1170 data points for CWB and VWB respectively were analyzed. LoD was calculated using Probit analysis with Analyse-it® for Microsoft® Excel. **Results:** The sample stability study indicated CWB spiked with 150 and 210 International Units (IU)/ml of HCV Gt 1a was detectable at all time points when stored at 2°C and 30°C. Probit analysis showed similar LoD for detection of HCV in VWB and CWB. Data for three Gts out of 6 are indicated in the table below. **Conclusion:** The Xpert® HCV test run on the GeneXpert Xpress System can detect low concentrations of HCV in CWB for up to 5 hours. This will have significant clinical utility in the field, especially in low resource settings, where samples often cannot be tested immediately after collection. Secondly, similar LoD results were obtained for all HCV Gts in CWB and VWB indicating comparable analytic sensitivity. This analytical data supports use of Cepheid Xpert® HCV in a CLIA waived setting.

Genotype	Probit LoD in IU/ml (Confidence Interval), Datapoints used for LoD calculation	
	CWB	VWB
Gt 1a	35.0 (22.3 - 54.9), 90	74.2 (39.9 - 138.0), 85
Gt 1b	41.5 (29.8 – 57.9), 95	43.8 (30.3 – 63.2), 110
Gt 2b	89.2 (47.7 – 166.8), 100	66.72 (41.1 – 108.3), 120
Gt 3a	58.2 (39.0 – 86.7), 125	75.3 (50.6 - 112), 125

Table 1. Probit Limit of Detection (LoD) for HCV genotypes in capillary whole blood (CWB) and venous whole blood (VWB). International units (IU)/ml. Datapoints used for each LoD are indicated.

Disclosures: Anuradha Rao: Nothing to Disclose, Kaleb McLendon: Nothing to Disclose, Tiffany Edwards: Nothing to Disclose, Leda Bassit: Nothing to Disclose, Mahi Patel: Nothing to Disclose, Evelyn Morales: Nothing to Disclose, Heather Bowers: Nothing to Disclose, Courtney Sabino: Nothing to Disclose, Zianya Solis: Nothing to Disclose, Hayden Smith: Nothing to Disclose, Kelsey M Badger: Nothing to Disclose, Aidan Wilson: Nothing to Disclose, Karen Peltier: Nothing to Disclose, Nathan Garza: Nothing to Disclose, Yun Wang: Nothing to Disclose, Emily Kennedy: Nothing to Disclose, Gail Radcliffe: Nothing to Disclose, Carlos Aparicio: Nothing to Disclose, Pamela Miller: Nothing to Disclose, Eric Lai: Nothing to Disclose, Julie Sullivan: Nothing to Disclose, Wilbur Lam: Sanguina Inc: Executive role

1444 | COMPARING BASELINE FIB-4 VERSUS POST-SVR12 FIB-4 TO PREDICT HCC OCCURRENCE FOLLOWING DIRECT-ACTING ANTIVIRAL ATTAINED SVR12

Mustafa Al-Karaghouli[1] Kai Le Ashley Tiong[2] Pooja Devan[2] Jean Ee Neo[2] Wei Xuan Tay[3] Yi-Lyn Jessica Tan[3] Carlos Moctezuma-Velazquez[1] Rahul Kumar[4] YU JUN WONG[1]

[1]University of Alberta, [2]Yong Loo Lin School of Medicine, [3]Changi General Hospital, [4]Changi General Hospital,

Background: Direct-acting antiviral (DAA) has cured millions of patients with chronic hepatitis C (CHC). The occurrence of HCC and the need for hepatocellular carcinoma (HCC) surveillance after DAA-attained SVR12 among non-cirrhotic CHC patients remained a matter of debate. We sought to compare the performance of baseline and FIB-4 at SVR12 to predict the HCC occurrence in CHC patients after DAA-attained SVR12. **Methods:** This is a post-hoc analysis of consecutive CHC patients treated with DAA between 2018-2019 in our institution and followed-up for the occurrence of post-SVR12 HCC. Primary predictor was FIB-4 at baseline, post-SVR12 along with change in FIB-4. Primary outcome was the occurrence of de-novo HCC. **Results:** A total of 762 patients were studied. Over 53 months of follow-up, 2.4% developed new HCC. Patients with De-novo HCC were older (58 vs 52, p-value= 0.003), exclusively male, with higher FIB-4 for both baseline and post SVR12. FIB-4 had good performance to predict HCC after SVR12, but the optimal threshold for HCC prediction differs [Baseline FIB-4:2.91; post-SVR FIB-4: 2.39] as FIB-4 value decreases after SVR12 [2.89 (± 3.6) vs 2.1 (± 2.6), p-value= 0.043]. The performance was similar between baseline and post-SVR12 FIB-4 (AUROC: 0.909 vs 0.881, p-value= 0.279). Change in FIB-4 was not predictive of HCC post-SVR12. **Conclusion:** Both baseline FIB-4 and post-SVR12 FIB4 had similar performance in predicting post-SVR12 HCC, however the optimal threshold differs as FIB-4 decreases following SVR12.

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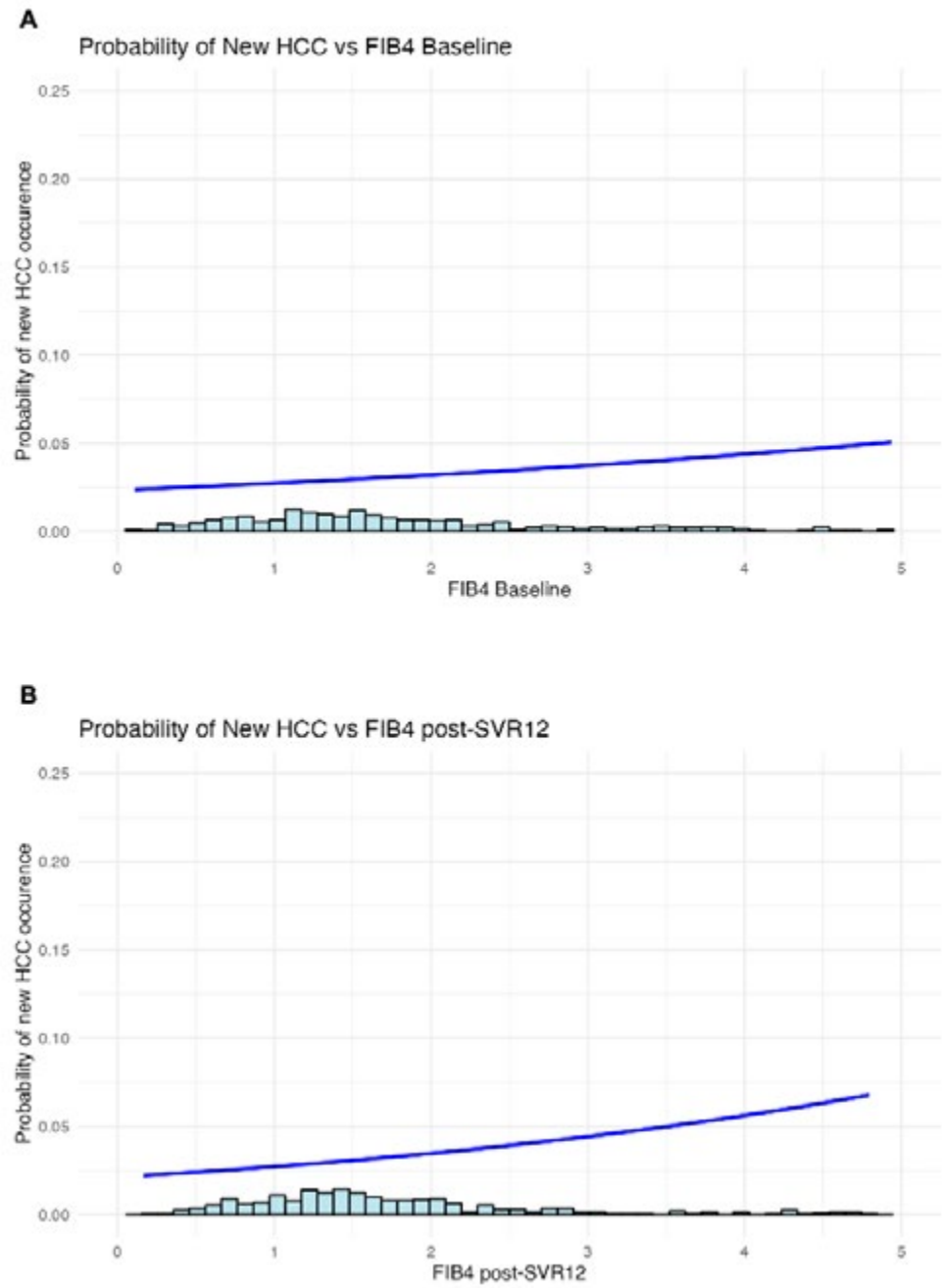

Disclosures: Mustafa Al-Karaghouli: Nothing to Disclose, Kai Le Ashley Tiong: Nothing to Disclose, Pooja Devan: Nothing to Disclose, Jean Ee Neo: Nothing to Disclose, Wei Xuan Tay: Nothing to Disclose, Yi-Lyn Jessica Tan: Nothing to Disclose, Carlos Moctezuma-Velazquez: Nothing to Disclose, Rahul Kumar: Nothing to Disclose, YU JUN WONG: Nothing to Disclose

1445 | THREE FOR TWO OR ONE FOR THREE: EVALUATING HCV TREATMENT REGIMENS, COMPLIANCE, AND SUBPOPULATIONS

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Background: The advent of potent pan-genotypic direct-acting antivirals (DAAs) has revolutionized HCV management, making sustained virologic response (SVR) achievable. Among these, Maviret (glecaprevir/

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pibrentasvir) and Epclusa (sofosbuvir/velpatasvir) are prominent regimens that differ in pill number and treatment duration. This study aims to compare treatment adherence and SVR rates between these regimens, considering patient demographics, medical histories, medications, habits, and various HCV subpopulations. **Methods:** A retrospective cohort study was conducted utilizing data from the Leumit Health Services (LHS) database, a major HMO in Israel, spanning five years. The cohort included HCV patients identified via ICD-9-CM codes and serological confirmation. Data included demographics, social and marital status, education, habits (smoking, alcohol, drug use), medication history, comorbidities, liver-related outcomes, mortality, and laboratory results. HCV-specific variables such as genotype, RNA levels, fibrosis stage, treatment status, and response were documented. Adherence was assessed by monitoring dispensed medications and refill frequencies, supplemented by electronic visit records. Comparative and multivariate analyses were conducted to identify predictors of poor adherence. **Results:** The study included 395 patients treated with Epclusa and 345 with Maviret. Patients on Epclusa were older (54.4±12.6 vs. 49.7±11.9, P<0.01), but no significant differences were noted in gender, ethnicity, marital status, education, social status, or BMI. SVR rates for Epclusa and Maviret were similar in the overall cohort (95.7% vs. 95.4%; P=0.12) and among cirrhotic patients (93.7% vs. 93.1%; P=0.23). Mortality (8.1% vs. 6.4%) and hepatocellular carcinoma (HCC) incidences (2.1% vs. 1.8%) were comparable. Overall, treatment adherence was robust, with 85% considered high compliance (≥80%). SVR rates were lower among patients with moderate-low compliance than those with higher compliance (82.1% vs. 98.2%; P<0.01). The SVR rates among people who inject drugs (PWIDs) (87.5%) and those with alcohol use disorder (88.4%) were lower, primarily due to reduced adherence. Multivariate analysis identified PWID status, polypharmacy, and severe comorbidities as significant predictors of poor adherence, while treatment type did not influence adherence. **Conclusion:** This study underscores the high efficacy and comparable SVR rates of Epclusa and Maviret across diverse HCV populations. Adherence remains a critical determinant of SVR, particularly among PWIDs and those with alcohol use disorder, highlighting the need for targeted interventions to enhance compliance in these groups. The findings advocate for tailored strategies addressing adherence barriers, thereby optimizing treatment outcomes in HCV management.

Disclosures: Fadi Abu Baker: Nothing to Disclose, Rawi Hazzan: Nothing to Disclose, Tarek Saadi: Nothing to Disclose, Saif Abu Mouch: Nothing to Disclose, Ariel Israel: Nothing to Disclose

1446 | SEX AND RACE DISPARITIES IN LIVER LISTINGS AND TRANSPLANTS FOR HEPATOCELLULAR CARCINOMA IN THE UNITED STATES ◆

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Background: Alcohol-associated liver disease (ALD) and metabolic dysfunction-associated steatohepatitis (MASH) are emerging as major indications for liver transplant (LT) in the US. Although hepatitis C virus (HCV) infection-related LT has decreased markedly since the availability of effective HCV drugs in 2013, it remains a prevalent cause for hepatocellular carcinoma (HCC) related LT. The aim of this study is to examine etiology-based trends on listing for and receiving LT for HCC indication in the US. **Methods:** The United Network for Organ Sharing (UNOS) database was used to extract a retrospective cohort (2011-2023) of adults who were listed for or received the first LT for HCC indication due to ALD, MASH, and HCV etiology. **Results:** Of 16,190 HCC listings (Fig. 1, Upper Panel), MASH led since 2022 with 37.7% listings in 2023 and an increase of 377% since 2011 (407% in males and 249% in females). In males, MASH led in Caucasians with 35.1% of listings in 2023, and ALD led in Hispanics with over 40% of listings in 2023. In females, MASH led in both Caucasians and Hispanics, with 48.1% and 60.6% listings in 2023, respectively. HCV led in blacks (77.5% in males and 66.7% in females in 2023) despite a 1489% increase for ALD in males and a 788% increase for MASH in females. Of 9913 LT for HCC (Fig. 1, Lower Panel), MASH led since 2021 with 37.1% transplants in 2023 and an increase of 347% since 2011 (331% in females and 289% in males). In males, MASH led in Caucasians (35.6%), ALD in Hispanics (44.6%), and HCV in blacks (66.7%) in 2023, despite a 592% increase in MASH in blacks. In females, MASH led in Caucasians and Hispanics (48.1% and 58.7%, respectively), while all 15 LT for HCC in 2023 in black females were due to HCV. **Conclusion:** MASH has emerged as a leading indication for HCC-related listings and LT in Caucasians. ALD led for HCC listings while MASH was the leading indication for receiving HCC related LT in Hispanics. Among blacks, despite the highest increase for MASH, HCV remains a leading indication for liver

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listings and transplants for HCC. These trends are relevant in developing strategies and policy implementation for the control of HCC in the US.

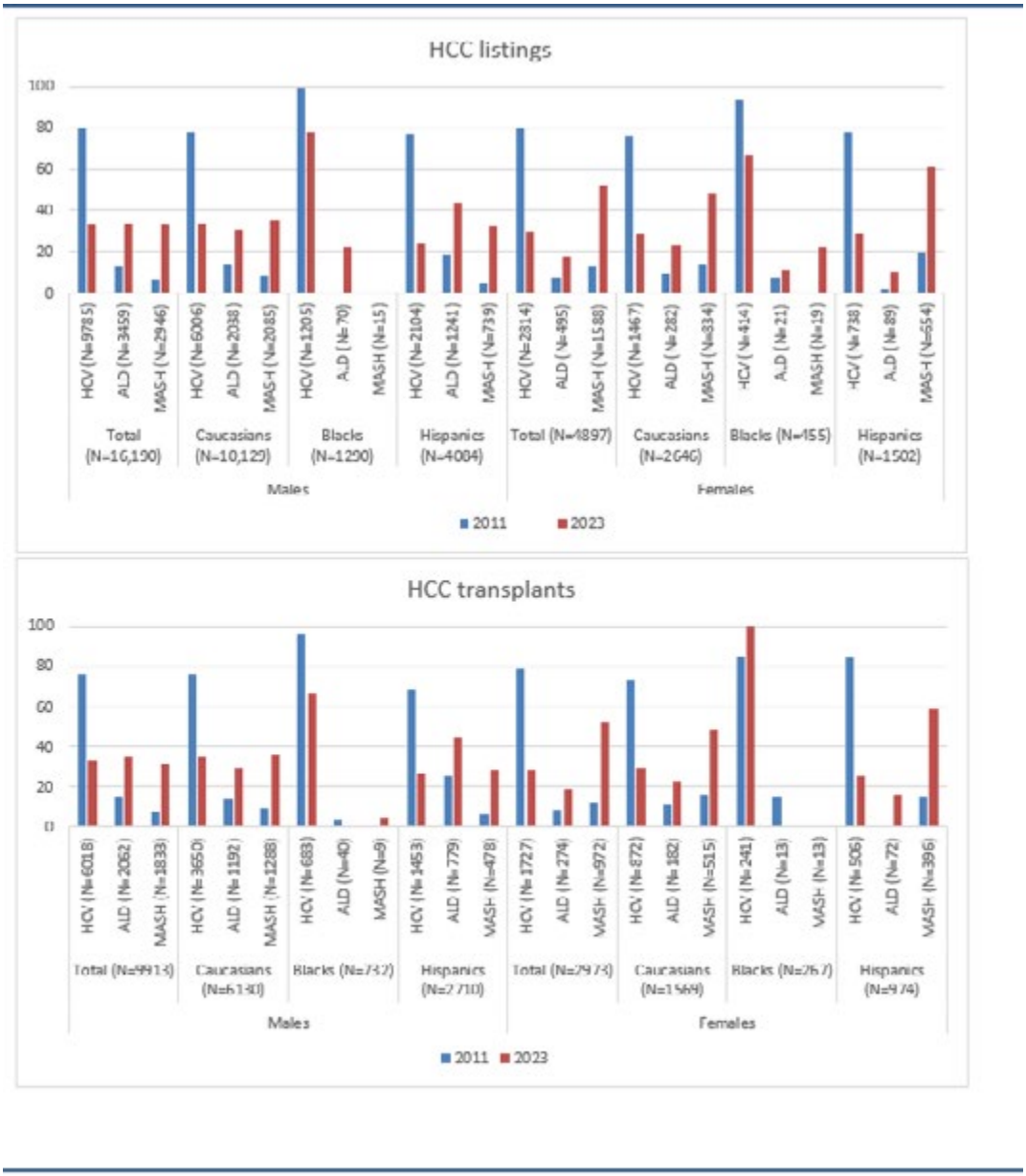

Figure 1 *Upper Panel: Trends in liver transplant listings for hepatocellular carcinoma (HCC) (2011-2023) for hepatitis C virus (HCV), alcohol associated liver disease (ALD), and non alcoholic steatohepatitis (MASH)*

Lower Panel: Trends in receiving liver transplants for HCC (2011-2023) for HCV, ALD, and MASH.

Disclosures: Abdellatif Ismail: Nothing to Disclose, Mohanad Awadalla: Nothing to Disclose, Prabha Bhandari: Nothing to Disclose, shaikhoon mohammed: Nothing to Disclose, Robert Wong: Theratechnologies: Grant/Research Support, Durect: Grant/Research Support, Gilead Sciences: Grant/Research Support, Exact Sciences: Grant/Research Support, Theratechnologies: Grant/Research Support, Durect Corporation: Grant/Research Support, Zobair Younossi: Nothing to Disclose, Ashwani Singal: Advisor relationship with CLD Foundation; Has not ended; Speaking and Teaching relationship with Medical Speaker's Network; Has not ended; Speaking and Teaching relationship with Madrigal; Has not ended; Stock â€“ privately held company relationship with Pleiogenix; Has not ended; Consultant relationship with Pleiogenix; Has not ended; Advisor relationship with Durect; Has ended; Royalties or patent beneficiary relationship with Up-to-Date; Has not ended; Executive role relationship with Gastro Endo News; Has not ended; Grant/Research Support relationship with NIAAA; Has not

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1447 | LONG-TERM GLYCEMIC CONTROL IN PATIENTS ACHIEVING SUSTAINED VIROLOGIC RESPONSE WITH DIRECT-ACTING ANTIVIRALS FOR HEPATITIS C VIRUS INFECTION

Chen-Hua Liu[1] Yu-Ping Chang[1] Ji-Yuh Lee[1] Chi-Yi Chen[2] Wei-Yu Kao[3] Chih-Lin Lin[4] Sheng-Shun Yang[5] Yu-Lueng Shih[6] Cheng Yuan Peng[7] Fu-Jen Lee[8] Ming-Chang Tsai[9] Shang-Chin Huang[1] Tung-Hung Su[1] Tai-Chung Tseng[1] Chun Jen Liu[1] Pei-Jer Chen[1] Jia-Horng Kao[1]

[1]National Taiwan University Hospital, [2]Chiayi Christian Hospital, [3]Taipei Medical University Hospital, [4]Taipei City Hospital Ren-Ai Branch, [5]Taichung Veterans General Hospital, [6]Tri-Service General Hospital, [7]China Medical University Hospital, [8]Fu Jen Catholic University Hospital, [9]Chung Shan Medical University Hospital

Background: Assessment of long-term glycemic dynamics among patients with hepatitis C virus (HCV) who achieve sustained virologic response (SVR_{12}) using direct-acting antivirals (DAAs) remains limited. **Methods:** A total of 1417 eligible patients with a median post-SVR_{12} follow-up of 5.5 years were enrolled. We demonstrated the age-standardized incidence rates (ASIRs) of type 2 diabetes (T2D) and prediabetes. Factors associated with new-onset T2D and prediabetes were assessed using the Cox regression analysis. The time-dependent evolution of glycosylated hemoglobin (HbA1c) for patients with different glycemic status was compared using the generalized estimating equation (GEE). **Results:** The ASIRs of T2D and prediabetes were 1.04 and 6.83 per 100 person-years of follow-up (PYFU). Age < 60 years (hazard ration [HR]: 0.51; 95% confidence interval [CI]: 0.31-0.83, p = 0.007), body mass index (BMI) < 23 kg/m^2 (HR:0.26; 95% CI: 0.11-0.63, p = 0.003), and absence of dyslipidemia (HR: 0.50; 95% CI: 0.30-0.84, p = 0.008) were associated with a lower risk of new-onset T2D. Age < 60 years (HR: 0.68; 95% CI: 0.54-0.86, p = 0.001) was associated with a lower risk of new-onset prediabetes. There were no slope coefficient differences for HbA1c among patients with T2D, prediabetes, and normoglycemia (normoglycemia vs. T2D, 0.012 %/year, p = 0.38; prediabetes vs. T2D, 0.008 %/year, p = 0.59). **Conclusion:** The incidence rates of T2D and prediabetes among patients with HCV remain significant despite viral eradication. Age, BMI, and dyslipidemia are associated with risks of new-onset T2D and prediabetes. The trend of post-SVR_{12} glycemic evolution is similar regardless of glycemic status.

Disclosures: Chen-Hua Liu: Nothing to Disclose, Yu-Ping Chang: Nothing to Disclose, Ji-Yuh Lee: Nothing to Disclose, Chi-Yi Chen: Nothing to Disclose, Wei-Yu Kao: Nothing to Disclose, Chih-Lin Lin: Nothing to Disclose, Sheng-Shun Yang: Nothing to Disclose, Yu-Lueng Shih: Nothing to Disclose, Cheng Yuan Peng: Nothing to Disclose, Fu-Jen Lee: Nothing to Disclose, Ming-Chang Tsai: Nothing to Disclose, Shang-Chin Huang: Nothing to Disclose, Tung-Hung Su: Nothing to Disclose, Tai-Chung Tseng: Nothing to Disclose, Chun Jen Liu: Nothing to Disclose, Pei-Jer Chen: Nothing to Disclose, Jia-Horng Kao: Nothing to Disclose

1448 | SUSTAINED VIROLOGIC RESPONSE (SVR) IN HCV-INFECTED PATIENTS WITH HEPATOCELLULAR CARCINOMA (HCC): REAL-WORLD OUTCOMES AND PREDICTORS OF SUCCESS

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Background: Chronic hepatitis C infection is a leading cause of cirrhosis and hepatocellular carcinoma (HCC). Many times, patients are unaware they are infected with the hepatitis C virus (HCV) and present with HCC. **Methods:** This retrospective data collection study included 61 patients with staged and treated HCC. Patients received 12-24 weeks of HCV direct-acting antiviral (DAA) therapy between JUL18-JAN24. Patients were from South TX and HCV care was done by a specialty HCV team. The primary endpoint was sustained virologic response (SVR). Patients who died during HCV therapy/follow up were not included. **Results:** The patient

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population was predominantly white (92.5%), Hispanic (74%) males (86.9%). Median age was 63. Current tobacco use was reported in 28.6%, past use in 30.6% and no use in 40.8%. Using the BCLC staging system at HCC diagnosis, most patients were Stage A (early) (44.3%) or Stage B (intermediate) (34.4%); 19.7% were Stage C (advanced). Mean number of tumors was 2.23 (range 1-11) and mean size of the largest tumor was 3.5 cm (range 1.2-11.5 cm). Interventions depended on stage of HCC; 55.7% underwent TACE, 39.3% microwave ablation, 32.8% Y90 radioembolization or TARE, 34.3% systemic therapy and 29.5% transplant. Only 4.9% underwent resection. Treatments were started prior to or contemporaneously with HCV therapy. All patients were cirrhotic and most were decompensated (72.1%). The majority were HCV treatment naïve (68.9%), however, 29.5% were previously treated with DAAs. Most common HCV genotypes were 1a (62.3%) and 3 (24.6%). SVR was achieved in 72.1% (44/61). Those who failed DAA therapy were men with more advanced HCC, who used tobacco and were infected with HCV genotype 3 (Table 1). Portal vein tumor thrombus was present in 23.5% of non-SVR patients and could in part be responsible for inadequate hepatic exposure to DAAs. All patients who underwent liver transplant (18/18) had detectable HCV RNA post-transplant and achieved SVR following DAA treatment.
Conclusion: SVR was achieved in 72.1% treated post-HCC diagnosis which is lower than the >95% SVR rate achieved in our overall HCV population; similar SVR rates in US HCC patients were reported in a recent meta-analysis. The benefits of SVR, including the possibility of liver function improvement to allow future HCC therapies and to decrease the risk of metachronous lesions, outweigh the risk of treatment failure and possible development of resistance associated variants. Past DAA failure and genotype 3 portended the lowest rate rates.

Table 1.	SVR	Non-SVR
Overall	**72.1% (44/61)**	**27.9% (17/61)**
Race		
White	69.4% (34/49)	30.6% (15/49)
Black	66.7% (2/3)	33.3% (1/3)
Ethnicity		
Hispanic/Latinx	75% (30/40)	25% (10/40)
Non-Hispanic/Latinx	64.3% (9/14)	35.7% (5/14)
Gender		
Male	67.9% (36/53)	30.2% (17/53)
Female	100% (8/8)	0% (0/8)
Cirrhosis at HCC Diagnosis		
Compensated	47.1% (8/17)	41.2% (7/17)
Decompensated	81.8% (36/44)	18.2% (8/44)
Stage		
A (Early Stage)	77.8% (21/27)	22.2% (6/27)
B (Intermediate Stage)	76.2% (16/21)	23.8% (23.8%)
C (Advanced Stage)	50% (6/12)	50% (6/12)
Intervention		
Microwave Ablation	75% (18/24)	25% (6/24)
Y90 Radioembolization or TARE	65% (13/20)	35% (7/20)
TACE	73.5% (25/34)	25.5% (9/34)
Resection	66.7% (2/3)	33.3% (1/3)
Systemic Therapy	57.1% (12/21)	42.9% (9/21)
Transplant	100% (18/18)	0% (0/18)
HCV Genotype		
1a	81.6% (31/38)	18.4% (7/38)
1b	100% (4/4)	0% (0/4)
2	100% (3/3)	0% (0/3)
3	40% (6/15)	60% (9/15)
Tobacco Use		
Current	35.7% (5/14)	64.3% (9/14)
Ex-Smoker	80% (12/15)	20% (3/15)
Never Used	85% (17/20)	15% (3/20)
HCV Treatment		
Epclusa x 12 Weeks	73.7% (14/19)	26.3% (5/19)
Epclusa x 24 Weeks	72.7% (16/22)	27.3% (6/22)
Harvoni x 12 Weeks	50% (2/4)	50% (2/4)
Harvoni x 24 Weeks	100% (3/3)	0% (0/3)
Mavyret x 12 Weeks	100% (3/3)	0% (0/3)
Mavyret x 16 Weeks	100% (2/2)	0% (0/2)
Vosevi x 12 Weeks	50% (4/8)	50% (4/8)

Disclosures: David Twitchell: Nothing to Disclose, Dakota Bigham: Nothing to Disclose, Rodolfo Singleterry: Nothing to Disclose, Owais Syed: Nothing to Disclose, Eugenia Tsai: Nothing to Disclose, Fabian Rodas: Nothing to Disclose, Carmen Landaverde: Nothing to Disclose, Jan Petrasek: Nothing to Disclose, Eric Lawitz: Nothing to Disclose, Andres Gomez-Aldana: Nothing to Disclose, Emma Pham: Nothing to Disclose, Amanda Matthews:

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Nothing to Disclose, Jamiel Ramos: Nothing to Disclose, Kelly Velasquez: Nothing to Disclose, ELIZABETH CALDERA: Nothing to Disclose, Jonathan Inskeep: Nothing to Disclose, Clarissa Vaughn: Nothing to Disclose, Lisa Pedicone: Nothing to Disclose, Fred Poordad: Nothing to Disclose

1449 | AVOIDING PHLEBOTOMY ENTIRELY: VALIDATION OF A POINT-OF-CARE MEASURE OF APRI & FIB4 FROM FINGER-PRICK BLOOD

David Smookler[1] Sarah Tran[2] Bethany Barber[2] Ahreni Saunthar[2] Magdalena Kuczynski[2] Andrew Mendlowitz[2] Aaron Vanderhoff[2] Mia Biondi[2] Camelia Capraru[2] Jordan Feld[3]

[1]Toronto Centre for Liver Disease, [2]VIRCAN/Toronto Centre for Liver Disease, [3]Toronto General Hospital

Background: Achieving the World Health Organization's viral hepatitis elimination goals requires decentralized treatment. Point-of-care (POC) testing for all stages of work-up, including fibrosis assessment, would expand treatment for marginalized/remote populations. Cirrhosis can be excluded with the APRI (AST-platelet ratio index) or FIB-4 tests, however both require a lab/hospital visit for venipuncture. We evaluated two FDA/Health Canada-approved bench-top devices which together could determine APRI and FIB-4 using finger-prick blood. **Methods:** OLO (Sight Diagnostics) provides complete blood count and Piccolo (Abaxis) can quantify AST, ALT, creatinine, bilirubin and albumin. Participants were recruited from visiting patients at the Toronto Centre for Liver Disease Clinic undergoing transient elastography (TE) that day or who had established cirrhosis. Participants provided finger-prick blood, analyzed by OLO and Piccolo (FP); and venipuncture blood, analyzed by the core lab, for calculation of APRI and FIB-4. Cut-offs for APRI were: <1.0 low risk for cirrhosis; >2 high risk; 1.0-2.0 - mid-risk. For FIB-4: <1.45 low risk; >3.25 high risk; 1.45-3.25 mid-risk. **Results:** 60 participants (32 female, 28 male, mean age 56) provided results.There was strong association between FP and core lab results, with Pearson correlation coefficients of 0.96 for ALT, 0.93 for AST, & 0.95 for platelets; with mean differences of 0 ALT (p >0.9), +4 AST (p<0.001) and -27 platelets (p<0.001). Lower platelets in FP led to higher mean APRI (1.08 vs 0.94, p=0.001), and FIB4 (3.66 vs 2.94, p<0.001) scores. However, overall categorization into low, intermediate and high risk compared with TE was very similar using FP or core lab.36/60 scored low/intermediate by TE. Using APRI: 0/36 of the FP and 0/36 of the core lab calculations rated these as high risk. Using FIB4: 5/36 FP and 3/36 core lab calculations rated these high risk.24/60 had high TE scores or known cirrhosis: APRI: 7/24 FP and 6/24 core lab results rated these as high risk. FIB-4: 19/24 FP and 19/24 core lab results rated these as high risk.Ruling out cirrhosis via FIB-4 (<1.45) showed the largest differences: 25/60 (42%) core lab vs 15/60 (25%) FP, due to lower platelet values in FP FIB-4, pushing scores above the low cut-off value, compared to core FIB-4.FP provided results within ~20 minutes with some training required for OLO. There was high acceptability by participants and staff. **Conclusion:** FP was well-tolerated and as sensitive as the core lab at predicting cirrhosis. For APRI, FP results closely matched core lab regarding ruling out cirrhosis. For FIB-4, the FP ruled out cirrhosis in fewer cases, primarily due to 15% lower platelet count. Combining this tool with other POC methods could entirely avoid the need for phlebotomy and greatly enable same-day treatment starts for hepatitis C; as well as potentially providing a quick and a simple test for ruling out cirrhosis in patients at risk for MASLD**.**

Disclosures: David Smookler: Nothing to Disclose, Sarah Tran: Nothing to Disclose, Bethany Barber: Nothing to Disclose, Ahreni Saunthar: Nothing to Disclose, Magdalena Kuczynski: Nothing to Disclose, Andrew Mendlowitz: Nothing to Disclose, Aaron Vanderhoff: Nothing to Disclose, Mia Biondi: Gilead Sciences: Grant/Research Support, Gilead Sciences: Speaking and Teaching, AbbVie: Speaking and Teaching, AbbVie: Grant/Research Support, Cepheid: Grant/Research Support, Camelia Capraru: Nothing to Disclose, Jordan Feld: Mirum: Consultant, AbbVie, Bluejays, Gilead, Janssen, GSK, Roche, VIR Roche: Consultant, Bluejays: Consultant, Gilead: Consultant, Janssen: Consultant, GSK: Consultant, Roche: Consultant, VIR Biotechnology: Consultant, Altimmune, AbbVie, Gilead, Jannsen, GSK, Roche, VIR Bio: Grant/Research Support

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1450 | SOFOSBUVIR/VELPATASVIR EFFECTIVENESS IN TREATING CHRONIC HEPATITIS C GENOTYPE 3: A REAL-WORLD STUDY IN XINJIANG, CHINA

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Background: To observe the effectiveness of the combination of sofosbuvir/velpatasvir (SOF/VEL) with or without ribavirin (RBV) in the real-world treatment of patients with chronic hepatitis C (CHC) genotype 3 (GT3). **Methods:** Select 258 cases of GT3-type chronic hepatitis C patients who were treated at the Xinjiang Uygur Autonomous Region Hospital of Traditional Chinese Medicine and Hotan Prefecture Infectious Disease Hospital from June 2018 to November 2023. Patients were treated based on their individual condition with either SOF/VEL monotherapy or a combination RBV regimen for a duration of 12-24 weeks. Laboratory indicators such as high-sensitivity HCV RNA were tested, with the primary outcome being the sustained virologic response (SVR) at 12 weeks after the completion of treatment (SVR12). **Results:** 1.A total of 258 cases of GT3-type chronic hepatitis C patients were included in this study, with an average age of 44.02±10.50 years. Among them, 68.22% were male (176/258). Of the cases, 153 (59.30%) were GT3a and 105 (40.70%) were GT3b. Additionally, 192 cases (74.42%) were classified as chronic hepatitis C (CHC), 49 cases (18.99%) had compensated cirrhosis (CC), and 17 cases (6.59%) had decompensated cirrhosis (DCC). Moreover, 252 cases (97.67%) were treatment-naïve patients, while 6 cases (2.33%) had received prior treatment. 2.Among the overall patients, 220 cases had HCV monoinfection, 8 cases had HBV/HCV coinfection, 36 cases had HCV/HIV coinfection, and 10 cases had triple infection of HBV/HCV/HIV. 3.Treatment Regimen: Patients with chronic hepatitis C (CHC) and compensated cirrhosis (CC) were treated with SOF/VEL for 12 weeks. Patients with previous direct-acting antiviral (DAA) treatment failure, intolerance to ribavirin, and decompensated cirrhosis (DCC) were treated with SOF/VEL monotherapy for 24 weeks or a combination of SOF/VEL and ribavirin for 12 weeks. In this study, 193 cases (74.81%) received SOF/VEL monotherapy, while 65 cases (25.19%) were treated with a combination of SOF/VEL and ribavirin. 4.Treatment Response and Safety: (1) The overall SVR12 for all patients was 98.84% (255/258), with SVR12 rates of 99.35% (152/153) for GT3a and 98.10% (103/105) for GT3b patients, respectively. (2)The SVR12 rates for CHC, CC, and DCC patients were 99.48% (191/192), 97.96% (48/49), and 94.12% (16/17), respectively. Among all patients, the SVR12 rates for HCV monoinfection, HCV/HIV, HBV/HCV, and HBV/HCV/HIV were 98.64% (217/220), 100% (7/7), 100% (3/3), and 100% (1/1) respectively. (3)During DAA treatment, no patients discontinued treatment due to adverse drug reactions, and the safety profile was good. (4)Relapse: Three patients experienced relapse due to irregular DAA medication adherence. **Conclusion:** The virological response rate is high and the safety profile is good when treating patients with genotype 3 chronic hepatitis C and cirrhosis using SOF/VEL monotherapy or in combination with RBV.

Disclosures: WEI SUN: Nothing to Disclose, Maimaiti Aliturson: Nothing to Disclose

1451 | IMPLEMENTATION OF GLECAPREVIR-PIBRENTASVIR TREATMENT FOR CHILDREN AGED 3-12 YEARS WITH CHRONIC HEPATITIS C: MULTICENTER REAL-WORLD DATA

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Background: Glecaprevir-pibrentasvir (GLE/PIB), a pangenotypic direct-acting antiviral (DAA) treatment for hepatitis C virus (HCV), is a first-line therapy for the pediatric population, showing high efficacy and safety in clinical trials. While real-world data has shown promising results in adults and adolescents treated with GLE-PIB, data for children aged 3-12 years is still emerging. This age group faces challenges with treatment adherence due to palatability and administration difficulties. Therefore, we conducted a national, multicenter study, including the first experience of children aged 3-12 years treated with GLE/PIB, to asses real-world data of sustained viral response (SVR), compliance, and adverse events. **Methods:** We conducted a multicenter retrospective analysis of children aged 3-12 years with chronic HCV infection treated with GLE/PIB between 2022-2023. Data collected included demographics, comorbidities, HCV genotype, viral load, and liver assessments before and after treatment (Table 1). We also analyzed documented adverse events, side effects, and treatment adherence. **Results:** Data were

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collected on ten children (five males, five females) with a median age of 6.8 years (IQR 4.9-8.2). Genotype 1b was the most common, affecting five children (50%). None had HIV or hepatitis B co-infection, liver cirrhosis, or liver-related symptoms. The median pretreatment viral load was 621,616 (IQR 89,643 – 870,000) IU/mL. Median pretreatment aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels were 60 (IQR 32-64) and 58 (IQR 45-100) U/L, respectively. All patients had normal bilirubin, albumin, and INR levels. Of the nine children who underwent pretreatment sonographic evaluation, two showed mild steatosis, and one showed mild fibrosis. GLE/PIB was administered as first-line therapy for all patients in an 8-week regimen, using oral sachets on a weight-based dosage. One patient had a high fever and malaise for two days due to Covid-19 infection during treatment. Nevertheless, treatment was not discontinued. No other adverse events were reported. Blood HCV virion levels were taken on all patients 12 weeks post-treatment, showing SVR with undetectable levels. **Conclusion:** Our real-world data supports previous clinical trials, indicating that the Pangenotypal GLE-PIB treatment was highly effective and well tolerated for children aged 3-12 years with chronic HCV infection, and treatment adherence can be achieved. Providing therapy early in life may help prevent future liver damage and reduce transmission rates.

Table 1: Demographical, clinical and laboratory assessment Pre and- post Glecaprevir-Pibrentasvir treatment of studied patients

Variable	N=10 patients, n (%) or median (IQR)
Demographic parameters	
Female	5 (50%)
Age (years)	6.8 (IQR 4.9-8.2)
Time from first HCV detection to treatment (years)	6.3 (IQR 5.7-7.2)
Pre-treatment laboratory findings	
HCV Genotype	
1a	3 (30%)
1b	5 (50%)
3	2 (20%)
HCV RNA,IU/L	621,616 (IQR 89,643 – 870,000)
HCV RNA ≥ 800,000 IU/L	5 (50%)
AST, IU/L	60 (32-64)
ALT, IU/L	58 (45-100)
ALKP, IU/L	259 (214-359)
GGT, IU/L	13.5 (11-18)
Albumin, g/dL	4.2 (4-4.4)
Bilirubin, mg/dL	0.8 (0.4-1)
Platelets count, 10^9/L	289 (230-372)
Hemoglobin, g/dL	12.9 (12.7-13.2)
INR	0.98 (0.9-1)
Liver complications and associated comorbidities	
HBV/HIV coinfection	None
Positive sonographic findings (N=9)	3 (33%)
Hepatocellular carcinoma	None
Liver transplantation	None
Other comorbidities or chronic conditions*	1 (10%)
SVR 12 weeks post-treatment	10 (100%)

* One patient had fetal alcohol syndrome as a known comorbidity.

AST – aspartate transaminase ALT- Alanine transaminase. ALKP – Alkaline phosphatase. GGT- Gamma-glutamyl transferase. HBV – Hepatitis B virus. HCV – Hepatitis C virus. HIV – Human immunodeficiency virus, INR – International normalized ratio. SVR- sustained viral response.

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1452 | MULTISTEP HEPATOCARCINOGENESIS IN PRENEOPLASTIC NODULES ON EOB-MRI AFTER LONG-TERM SUSTAINED VIROLOGIC RESPONSE IN PATIENTS WITH CHRONIC HEPATITIS C

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[1]University of Fukui

Background: Preneoplastic nodules with hypointensity in the hepatobiliary phase (HBP) of Gd-EOB-DTPA-enhanced MRI (EOB-MRI) is a risk factor for hepatocellular carcinoma (HCC) after sustained virologic response (SVR). However, de novo hepatocarcinogenesis has been observed in some cases, and the pathogenesis of hepatocarcinogenesis after SVR remains unclear. We evaluated HCC after SVR and investigated factors involved in hepatocarcinogenesis. **Methods:** We studied 112 patients with chronic hepatitis C who achieved SVR and underwent multiple follow-up EOB-MRI scans, resulting in 64 hypervascular HCCs, which were retrospectively reviewed. We investigated the characteristics of hepatocarcinogenesis after SVR. Additionally, we identified 73 hypovascular nodules. Of these, we investigated 57 nodules observed after SVR to determine whether the temporal relationship between the appearance of preneoplastic nodules and SVR was associated with incident HCC. **Results:** Among the 112 patients, 64 newly developed HCCs were observed in 39 patients. In the 64 HCC cases, the multistep group, which showed preneoplastic nodules before hypervascularization, included 26 nodules in 21 patients. The de novo group, which did not show preneoplastic nodules, included 38 nodules in 17 patients. In contrast to the 64 HCC cases, 47 preneoplastic nodules that appeared before or after SVR showed no changes in hypervascularization during the follow-up period. A lower FIB-4 index, higher total bilirubin and protein induced by vitamin K absence II levels, larger tumor size, and hyperintensity on diffusion-weighted imaging at SVR were significantly more frequent in the de novo group. In the de novo group, 23/38 (60.5%) nodules appeared within 3 years of SVR, and 13/38 (34.2%) nodules appeared after 3 years of SVR. The cumulative incidences of hypervascularization from SVR at 1, 3, and 5 years were 4.8%, 2.7%, and 16.7%, respectively, whereas the cumulative incidences from the appearance of the nodule were 19.6%, 29.4%, and 1.4%, respectively, decreasing after the third year. **Conclusion:** In HCC cases, after achieving HCV SVR, hypervascularization from preneoplastic nodules in the HBP hypointensity was observed in approximately 40% of the patients, suggesting that multistep hepatocarcinogenesis may still occur after long-term SVR. Close follow-up are recommended for hypervascularization occurring 3 years after the appearance of preneoplastic nodules.

Disclosures: Tomoko Tanaka: Nothing to Disclose, Takuto Nosaka: Nothing to Disclose, Yosuke Murata: Nothing to Disclose, RYOTARO SUGATA: Nothing to Disclose, Yu Akazawa: Nothing to Disclose, Tatsushi Naito: Nothing to Disclose, Kazuto Takahashi: Nothing to Disclose, Masahiro Ohtani: Nothing to Disclose, Yasunari Nakamoto: Nothing to Disclose

1453 | PREVALENCE AND TRENDS OF HEPATITIS C INFECTION IN PREGNANT WOMEN IN XI'AN, CHINA: A 10-YEAR RETROSPECTIVE STUDY

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Background: This study was to understand the prevalence of hepatitis C virus (HCV) infection in pregnant women in China, and to provide data basis for the formulation of HCV prevention and control strategies in pregnant women. **Methods:** We selected the Obstetrics and Gynecology Specialized Hospital of Xi'an and reviewed the data of pregnant women who were hospitalized in the hospital during the period from January 2014 to December 2023. All patients underwent either quantitative or qualitative anti-HCV detection, and HCV RNA detection was performed on those who were anti-HCV positive. We described the 10-year prevalence of HCV antibody and HCV RNA positivity. **Results:** A total of 116,171 pregnant women were screened, of which 621 were positive for anti-HCV, with a median age of 30 years (IQR 27.5,32). The anti-HCV positive rate showed a significant increase (P = 0.047) from 0.49% (264 cases) in the first five years (2014-2018) to 0.57% (357 cases) in the second five years (2019-2023). Of the 621 anti-HCV-positive patients, the rate of HCV RNA test was 66.50% (413/621),69 (16.71%) (69/413) were HCV RNA positive, with a median age of 29 years (IQR 27,32). In contrast to the increasing anti-HCV trend, the HCV RNA positive rate showed a significant decrease (P = 0.001) from

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23.429% (41/175) in the first five years to 11.765% (28/238) in the second five years. **Conclusion:** This study represents the largest known domestic screening for HCV infection among pregnant women in China. We found a 0.54% prevalence of anti-HCV antibodies in pregnant women in western China, which is comparable to the prevalence reported in the general population during the same period. While the anti-HCV positive rate appears to be increasing, the HCV RNA positive rate is decreasing. This suggests potential improvements in screening and treatment rates for hepatitis C patients in China. However, a significant number of cases (208, 33.50%) remain undiagnosed due to the lack of HCV RNA testing following a positive anti-HCV test. To address this issue and support the action plan to eliminate hepatitis C in Shaanxi Province, we plan to implement a recall program for both anti-HCV-positive and HCV RNA-positive patients. This initiative will facilitate diagnosis and treatment with Direct-Acting Antivirals (DAA), ultimately improving overall diagnosis and treatment rates.

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1454 | ANALYSIS OF INFLUENCE FACTORS ON ANTIVIRAL EFFICACY IN PATIENTS WITH CHRONIC HEPATITIS C VIRUS INFECTION IN TIANJIN AREA

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Background: To explore the influence factors of sustained virological response 12 weeks (SVR12) rates in patients with chronic hepatitis C virus (HCV) infection after completion of therapy. **Methods:** Clinical data of 84 patients with chronic HCV infection treated at the hepatitis C outpatient of Tianjin Second People's Hospital from September 2020 to April 2022 were retrospectively collected. Based on sustained virological response at 12 weeks, patients were divided into SVR 12 group and Non-SVR 12 group. The effects of gender, age, intravenous drug addiction, liver function, platelet count, genotype, baseline viral load, and cirrhosis on SVR12 were analyzed. **Results:** All patients completed treatment and follow-up, with 48 cases of chronic hepatitis C (CHC) and 36 cases of cirrhosis. There were 4 cases of HCV genotype 3 CHC (SOF/VEL 12-weeks regimen), 14 cases of genotype 3 cirrhosis (6 cases of SOF/VEL+RBV 12-weeks regimen, 8 cases of SOF/VEL 24-weeks regimen alone). Overall SVR12 rate was 88%. Intravenous drug addiction, genotype 3 and platelet count are related to SVR12 rate (P=0.016, P = 0.005 and P = 0.044). Further analysis revealed that 19% of patients with intravenous drug addiction had genotype 3, and 60% of genotype 3 patients with intravenous drug addiction did not reach SVR12. The logistic multiple regression analysis of HCV genotype 3 and platelet count showed that, genotype 3 was an independent risk factor for SVR12 in patients with chronic HCV infection (OR=1.717, 95% CI=0.039-0.831, P = 0.028). There were no serious adverse events in this cohort. **Conclusion:** SVR12 in patients with chronic HCV infection is susceptible to intravenous drug addiction, HCV genotype 3 and platelet count. The CHC patients with intravenous drug addict are susceptible to genotype 3 HCV infection and have poor compliance, that may be one of the reasons for SVR12 rate decrease.

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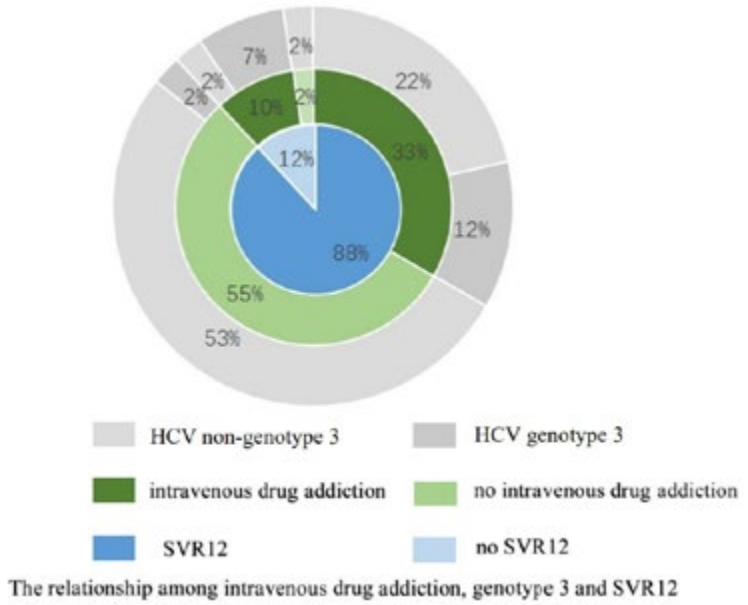

The relationship among intravenous drug addiction, genotype 3 and SVR12

Disclosures: Peng Chen: Nothing to Disclose, Lan wang: Nothing to Disclose, Wentao Kuai: Nothing to Disclose

1455 | THE SVR10K STUDY: A REAL-WORLD DATA WITH PANGENOTYPIC DIRECT-ACTING ANTIVIRALS ACROSS MULTIPLE DIVERSE REGIONS

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Background: A previous real-world data analysis demonstrated high effectiveness of sofosbuvir/velpatasvir (SOF/VEL) without ribavirin (RBV) in > 6,000 HCV patients from 12 clinical cohorts across Australia, Canada, Europe & USA. Expanding this research to include even more patients from additional geographical areas will allow assessing SOF/VEL (without RBV) effectiveness across multiple diverse populations and the evaluation of HCV patient characteristics across Western countries, Asia, Middle Eastern and Latin-American (LATAM) regions (the ongoing SVR10K study). **Methods:** This real-world analysis includes patients ≥ 18 years treated with SOF/VEL without RBV for 12 weeks, as decided by the treating HCP, from 10 sites across Brazil, Hong Kong, Mexico, Singapore, Sweden, Spain, Taiwan, and the United Arab Emirates, grouped into five regions for analysis purposes: LATAM, Asian, Nordic, Southern-Europe and Middle East. Age, sex, whether treatment experienced (TE), cirrhosis stage (F4, no decompensated), genotype, coinfections were described, and time to treatment initiation (TTI) from HCV diagnosis, and overall SVR at any time, were assessed. **Results:** Overall, 6,633 patients were included, with Asian region contributing more than half of cases, LATAM sites with 496 patients (Table). Median age in the overall population was 55 years [IQR 46-64]; highest in Asian sites (57 yo); lowest in the Middle Eastern site (31 yo). Patients over 50 yo represented two thirds (65%) of the overall population, with the highest percentage in Asian and Southern-Europe sites (71%%) and lowest in the Middle Eastern site (28%). Cirrhosis was reported in 20% [18%-24%] of the overall population, with the highest rate in LATAM. Regarding HCV genotypes, overall GT 3 and 1 were the most prevalent (31% and 30%, respectively); GT 3 genotype was particularly prevalent in Nordic (57%), GT1 - in Middle East (49%). The TTI was available in 72% (n=4,772) of the sample, with 13% [4%-40%] treated in ≤30 days. Overall SVR was achieved in 99% [97.1%-100%] of the treated population. **Conclusion:** Real-world efficacy of SOF/VEL is consistency high across a diverse population of HCV patients. There is still a significant room for improvement in the time to treatment initiation for all the regions. Further work should focus improve timely treatment initiation to achieve the WHO goal of HCV elimination by 2030.

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Table: Key demographics, Time to Treatment initiation, and SVR rate of patients by region

	Overall	LATAM	Asia	Nordics	Southern-Europe	Middle East
# patients	6,633	496	3,804	1,357	857	119
Median age, y	55	51	57	51	55	31
Male, %	66	48	68	65	69	69
≥50 y, % (male and female)	65	54	71	53	71	28
≥50 y male, %	41	28	45	35	46	7
≥50 y female, %	24	26	25	18	25	21
Genotype 3, %	31	28	26	57	21	28
Cirrhosis stage, %	20	24	20	18	21	22
Time to Treatment < 1 month, %*	13	40	18	4	28	22
Overall SVR (%) in effectiveness population**	99%	100%	99%	97%	98%	100%

**For Southern-Europe data available for TT was available from 2 of the 5 sites; **Excludes patients who did not have a valid SVR status because of non-virological reasons or unknown reasons*

Disclosures: Grace Wong: AstraZeneca: Advisor, Gilead Sciences: Advisor, Gilead Sciences: Speaking and Teaching, Janssen: Advisor, GSK: Advisor, GSK: Speaking and Teaching, Abbott: Speaking and Teaching, AbbVie: Speaking and Teaching, AstraZeneca, Gilead Sciences, GlaxoSmithKline and Janssen,: Advisor, Abbott, AbbVie, Ascletis, Bristol-Myers Squibb, Echosens, Gi: Speaking and Teaching, Gilead Sciences: Grant/Research Support, AstraZeneca, Gilead Sciences, GlaxoSmithKline and Janssen: Consultant, Abbott, AbbVie, Ascletis, Bristol-Myers Squibb, Echosens, Gi: Speaking and Teaching, AstraZeneca, Gilead Sciences, GlaxoSmithKline Pharmaceutical: Consultant, Gilead Sciences: Independent Contractor, AstraZeneca, Gilead Sciences, GSK and Janssen,: Advisor, Abbott, AbbVie, BMS, Gilead Sciences, GSK, Janssen, Roche: Speaking and Teaching, Gilead Sciences: Grant/Research Support, Mario Alvares-da-Silva: Nothing to Disclose, Fatima Higuera-de-la-Tijera: Nothing to Disclose, Ming-Lung Yu: Abbvie, Gilead and Roche diagnostics.: Grant/Research Support, Abbott, Abbvie, Gilead, Roche and Roche diagnostics: Consultant, Abbvie, BMS, Gilead, Roche and Roche diagnostics: Speaking and Teaching, Soo Aleman: Gilead: Speaking and Teaching, Francisco Javier García-Samaniego Rey: Gilead; Abbvie: Speaking and Teaching, JOAQUIN CABEZAS: Gilead: Advisor, Gilead: Speaking and Teaching, Abbvie: Speaking and Teaching, MARTA CASADO MARTIN: Nothing to Disclose, Mohamed Alzaabi: Nothing to Disclose, Aastha Chandak: Certara: Employee, Certara: Stock - publicly traded company, Gilead Sciences: My institution (Certara) was contracted by Gilead for study, Marta Martinez: Nothing to Disclose, Artak Khachatryan: Nothing to Disclose, Linda Chen: Nothing to Disclose, Candido Hernandez: Gilead Sciences: Employee, YU JUN WONG: Nothing to Disclose

1456 | EVALUATION OF HEPATITIS C TREATMENT AND CARE MODEL IN PRIMARY HEALTHCARE CENTERS IN THE COUNTRY OF GEORGIA

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Background: Georgia launched the world's first hepatitis C elimination program in April 2015, in partnership with Gilead Sciences and with technical assistance from the US Centers for Disease Control and Prevention. By the end of March 2024, more than 86,000 patients with current hepatitis C virus (HCV) infection initiated treatment, with 99% cure rates among those tested for sustained virologic response (SVR). Broad access to direct acting antivirals (DAAs) resulted in rapid increase in treatment uptake in 2016, which has since declined due to barriers in diagnosis and linkage to care. To address this issue, Georgia initiated service decentralization in 2018 by integrating HCV screening and treatment in primary healthcare centers (PHCs). We report preliminary **Results:** of an integrated model of hepatitis C care in PHCs. **Methods:** By March 31, 2024, a total of 10 PHCs were providing hepatitis C care services throughout the country. The integrated model was based on a "one stop shop" approach, where patients receive all HCV screening, treatment, and care services in selected PHCs. PHCs provided care

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to HCV treatment-naïve patients with no or mild fibrosis (FIB-4 score<1.45) using simplified diagnostics and a treatment monitoring approach, while persons with advanced liver fibrosis/cirrhosis were referred to specialized clinics. Patients were treated with Sofosbuvir/Ledipasvir and/or Sofosbuvir/Velpatasvir for 12 weeks. SVR was defined as undetectable HCV RNA at 12-24 weeks after end of therapy. The Extension for Community Healthcare Outcomes (ECHO) telemedicine model was used to train and support primary healthcare providers. Regular teleECHO videoconferencing was conducted to provide primary care providers with advice and clinical mentoring. **Results:** Overall, 1,982 persons with current HCV infection were evaluated for FIB-4 score at PHCs as of March 31, 2024. A total of 1,298 initiated treatment, and of them 1,204 (92.7%) had completed treatment at the time of analysis. Of 1,179 persons eligible for SVR testing (12-24 weeks post treatment completion), 922 (78.2%) had been tested, and 906 (98.3%) achieved SVR. **Conclusion:** Our analysis shows the effectiveness of integrating a simplified HCV diagnosis and treatment model in PHCs. Countrywide expansion of this model is warranted to bridge the gaps in the hepatitis C care continuum and ensure high rates of treatment uptake, enabling Georgia to achieve hepatitis C elimination.

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1457 | PREVALENCE AND RISK FACTORS FOR HEPATOCELLULAR CARCINOMA (HCC) AMONG PATIENTS WITH CURRENT AND PRIOR HEPATITIS C VIRUS (HCV) INFECTION IN A REAL-WORLD COHORT IN THE POST-DAA ERA

Mai Sedki[1] Jennifer Price[2] Gina Intinarelli[2] Michael Helle, NRP/CCP, FP-C, MHA, MBA[2] Tasha Toliver[2] Rena Fox[3]

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Background: Since the 1990s, HCV has been the most common cause of HCC in the U.S. Direct-acting antivirals (DAAs) have reduced this risk, though about 1/3 of chronic HCV patients remain untreated. Meanwhile, MASLD now affects 30% of adults and is raising HCC incidence. With these changing risk factors, we aimed to determine the prevalence and predictors of HCC in real-world HCV patients in the post-DAA era. **Methods:** Using the electronic medical record at a large urban tertiary health system, we identified patients seen between 2016-2023 with evidence of current or prior HCV (reactive HCV Ab, detectable HCV RNA, HCV medication prescription, and/or chronic HCV ICD 9/10 code). We extracted demographic, laboratory, radiology, ICD codes for comorbidities, and visit data. Patients were categorized by HCC status (ICD code C22 or 155) and HCV/treatment status: treated (HCV medication prescription and undetectable HCV RNA post-treatment), viremic (quantifiable recent HCV RNA), and untreated (detectable recent HCV RNA without medication prescription). We computed FIB-4 scores and categorized by established cutoffs. Descriptive statistics for baseline characteristics were calculated, and comparisons were made between patients with and without HCC. Univariate and multivariate logistic regression were used to identify factors independently associated with HCC presence. **Results:** We found 12,424 patients with current or prior HCV, and 10% (n=1,213) had HCC (Table 1). HCC patients were older than those without HCC (68 vs 61 years, p<0.001). The cohort was diverse: 19% White, 13% Black, 16% Latinx, and 11% Asian. HCC rates were higher among Latinx (15%) and Asian (12%) patients compared to White (9%) and Black (7%) patients. Of the 1,410 patients who died within the 7 years, 23% had HCC. Receiving prior HCV treatment showed a borderline association with HCC (OR 1.17, 95% CI 1.02-1.35), but treatment without SVR had a stronger association (OR 2.36, 95% CI 1.54-3.62). Significant predictors of HCC in multivariate analysis included being non-White, having indeterminate/high FIB-4, hypertension, alcohol use disorder, or MASH, while having a primary care provider (PCP) was strongly protective (OR 0.23, 95% CI 0.18-0.29). **Conclusion:** In a large cohort of patients with current or prior HCV, 10% had HCC, and 23% of those who died in the past 7 years had HCC. This study's healthcare setting offers liver transplantation, but is also the provider of care to a major U.S. city, indicating that HCC persists as a common complication for HCV patients. In this study, we cannot confirm that DAA treatment is protective against HCC, as treatment could have been before or after HCC diagnosis, but treatment without SVR was associated with HCC. Asian or Latinx ethnicity, comorbid MASH, and lack of a PCP increased HCC risk. As the post-DAA era continues, with rising metabolic liver disease, improving access to PCPs and increasing HCV treatment linkage may enhance HCC prevention.

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Table 1. Univariate and multivariate logistic regression analysis of predictors of hepatocellular carcinoma (HCC)

	No HCC n=11211 (90%)	HCC n=1213 (10%)	Univariate logistic regression OR (95% CI)	*Multivariate logistic regression OR (95% CI)
Age	61.1 +/- 14.8	68.4 +/- 7.3	1.05 (1.04 – 1.05)	---
Race/ethnicity			1.02 (0.977 – 1.06)	1.09 (1.04 – 1.15)
White	5524 (91%)	557 (9%)		
Black/AA	1527 (93%)	115 (7%)		
Latinx	1665 (85%)	287 (15%)		
Asian	1165 (88%)	154 (12%)		
Other	910 (92%)	139 (8%)		
Unknown/declined	420 (96%)	17 (4%)		
Sex			0.456 (0.399 – 0.523)	0.537 (0.454 – 0.636)
Male	6489 (88%)	910 (12%)		
Female	4719 (94%)	302 (6%)		
Prior treatment	2328 (89%)	285 (11%)	1.17 (1.02 – 1.35)	---
Chronic untreated	1599 (91%)	155 (8%)	0.881 (0.738 – 1.05)	---
Treated with SVR	1514 (88%)	205 (12%)	1.30 (1.11 – 1.53)	---
Treated without SVR	107 (80%)	27 (20%)	2.36 (1.54 – 3.62)	---
Ever PCP	2606 (96%)	110 (4%)	0.330 (0.269 – 0.403)	
Ever hepatology	3522 (31%)	978 (81%)	9.09 (7.84 – 10.5)	---
Ever seen in ED in 7 years	2701 (94%)	162 (6%)	0.486 (0.409 – 0.576)	---
Ever inpatient in the last 7 years	2816 (91%)	263 (9%)	0.825 (0.715 – 0.952)	---
FIB 4 category			4.05 (3.39 – 4.83)	3.32 (2.76 – 4.00)
Low	3055 (95%)	161 (5%)		
Intermediate/High	3511 (82%)	749 (18%)		
Decompensation	719 (54%)	602 (46%)	14.4 (12.6 – 16.5)	---
Diabetic	2077 (86%)	348 (14%)	1.77 (1.55 – 2.02)	1.04 (0.873 – 1.24)
Hyperlipidemia	1768 (86%)	281 (14%)	1.61 (1.40 – 1.86)	0.789 (0.652 – 0.953)
Hypertension	3706 (83%)	741 (17%)	3.18 (2.81 – 3.59)	2.59 (2.19 – 3.07)
Alcohol Abuse	624 (84%)	123 (16%)	1.91 (1.56 – 2.35)	1.69 (1.30 – 2.21)
NASH	156 (71%)	64 (29%)	3.95 (2.93 – 5.31)	2.25 (1.58 – 3.20)
Obesity	2601 (89%)	337 (11%)	1.04 (0.910 – 1.19)	0.973 (0.821 – 1.52)
Hemodialysis	565 (93%)	44 (7%)	0.709 (0.519 – 0.970)	---
Death (all cause)	1082 (77%)	328 (23%)	3.47 (2.01 – 4.00)	---

*Multivariate logistic regression analysis included the following variables: ever seen by PCP, categorical binary fib4 score (low and intermediate/high), race, sex, diabetes mellitus, hypertension, hyperlipidemia, alcohol use disorder, nonalcoholic steatohepatitis (NASH), obesity

Disclosures: Mai Sedki: Nothing to Disclose, Jennifer Price: Nothing to Disclose, Gina Intinarelli: Nothing to Disclose, Michael Helle, NRP/CCP, FP-C, MHA, MBA: Nothing to Disclose, Tasha Toliver: Nothing to Disclose, Rena Fox: Nothing to Disclose

1458 | TRENDS IN CARE UTILIZATION IN TWO LARGE NATIONALLY REPRESENTATIVE DATASETS REVEAL IMPORTANT DISPARITIES IN HEPATITIS C ACCESS TO SCREENING AND TREATMENT

Brian McSteen Yihan Liu[1] Himel Mallick[1] Mark Unruh[1] Robert Brown[1] Adam Buckholz[2]

[1]Weill Cornell Medicine, [2]New York Presbyterian Hospital Program

Background: Adequate screening is a major barrier to identifying those with Hepatitis C virus (HCV) infection, as up to half of those with hepatitis C are unaware of their status. Given the United States Preventative Services Task Force recommendation for universal HCV screening in 2020, we sought to study recent nationwide trends in HCV testing and care. **Methods:** To gain a nationwide perspective on HCV testing and care utilization, we analyzed data from the 2010-2021 NAMCS/NHAMS survey – an annual, national probability sample of ambulatory care visits. ICD-9-CM or ICD-10-CM codes corresponding to HCV and related complications were used to identify encounters. The two primary outcomes were HCV at the time of visit and utilization of HCV testing. Inverse probability allowed for nationwide estimates using weighted multivariable logistic regression adjusting for gender, age, region, race and insurance status. **Results:** Between 2010 and 2021, there were 23.63 million visits for HCV identified with 22.24 million in the office setting. HCV testing was performed at 1.24% of new preventive care primary care visits, with rates similar among all demographic groups, except Black patients (OR 2.43 95%CI 1.43-4.14). Visits increased sharply after WHO screening recommendations (2012) and direct-acting

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antiviral treatment were implemented (2014), with a recent decrease among privately insured and White patients (Figure 1A,1B). HCV care utilization was highest in male patients, people born between 1945-1965, Black patients, those insured by Medicare or Medicaid, and those in the West region (Table). Of people with HCV, those with Medicaid (OR = 0.30, 95% CI 0.25-0.37) and people born after 1965 (OR 0.59, 95% CI 0.49-0.71) were less likely to utilize the office setting vs the emergency room (ER) for care. Rates of Medicaid insurance was highest among Black (OR = 1.56, 95% CI 1.34-1.8) and Hispanic patients (OR = 1.58, 95% CI 1.35-1.85). **Conclusion:** This study found that patients born after 1965 and patients with Medicaid insurance (who were more likely to be Black or Hispanic) were more likely to utilize the ER for HCV-related care. These results suggest a potential emerging disparity given trends in HCV prevalence, where patients born after 1965 and/or insured by Medicaid have reduced care and testing access related to their visit patterns compared to patients who are more likely to utilize the office for care (White, born 1945-1965, privately insured). This work indicates universal HCV screening in the ER may help address this care gap. Further, screening recommendations have been effective at identifying HCV cases amongst birth cohort 1945-1965, underscoring the importance of educating ambulatory providers on updated screening recommendations. These findings may be particularly important in the context of the ongoing opioid epidemic where screening and care efforts should take into consideration where and how at-risk individuals present for care.

Figure 1

Table: Estimated adjusted odds ratios for factors associated with Hepatitis C Visits.

Variable	OR for HCV+	95% CI	p value
Male	1.87	1.43 - 2.45	<0.001
Birth Cohort			
Before 1945	1 (Reference)	n/a	n/a
1945-1965	9.12	4.92 - 16.92	<0.001
After 1965	1.89	0.93 - 3.81	0.077
Region			
Northeast	1 (Reference)	n/a	n/a
Midwest	1.26	0.71 - 2.22	0.435
South	1.03	0.66 - 1.6	0.909
West	2.39	1.45 - 3.93	<0.001
Race/Ethnicity			
Non-Hispanic White	1 (Reference)	n/a	n/a
Non-Hispanic Black	1.70	1.19 - 2.43	0.004
Hispanic	1.29	0.77 - 2.16	0.324
Other	1.25	0.45 - 3.46	0.674
Insurance Type			
Private	1 (Reference)	n/a	n/a
Medicaid	1.93	1.32 - 2.82	<0.001
Medicare	2.10	1.43 - 3.09	0.001
Non-MSA	0.72	0.43 - 1.19	0.195

A multivariable logistic regression model was used to estimate odds ratios (OR) adjusting for gender, age, region, race and insurance status; all factors in column 1 were included as dummy variables. ORs are calculated with respect to the reference group for each factor. Reference groups are indicated in the parentheses.

Abbreviations: CI, confidence interval; HCV, hepatitis C virus; MSA, metropolitan statistical area

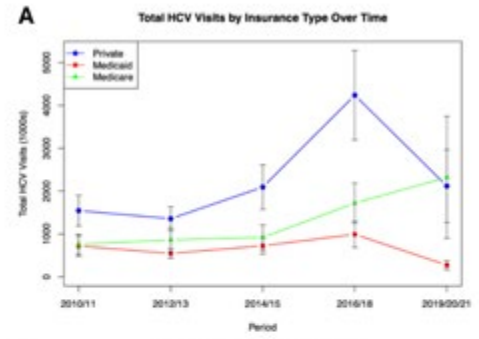

Figure 1A: Total HCV Visits (1000s) by Insurance Type Over Time

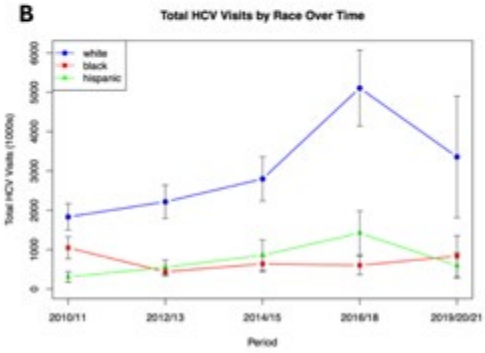

Figure 1B: Total HCV Visits (1000s) by Race Over Time

Disclosures: Brian McSteen: Nothing to Disclose, Yihan Liu: Nothing to Disclose, Himel Mallick: Nothing to Disclose, Mark Unruh: Nothing to Disclose, Robert Brown: Consultant relationship with Intercept; Has not ended; Consultant relationship with Gilead; Has not ended; Consultant relationship with Abbvie; Has not ended; Consultant relationship with Madrigal; Has not ended; Consultant relationship with GSK; Has not ended; Consultant relationship with eGenesis; Has not ended; Consultant relationship with mirum; Has not ended, Adam Buckholz: Nothing to Disclose

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1459 | GLECAPREVIR/PIBRENTASVIR IN CHRONIC HCV: AN INTEGRATED ANALYSIS OF PATIENTS ON MULTIPLE CONCOMITANT MEDICATIONS

Shweta Raina[1] Curtis Cooper[2] Jordan Feld[3] Lisa Johnson[1] Ashley Brown[4] Anthony Martinez[5] Brian Conway[6] Stuart Gordon[7] Tarik Asselah[8] Liz Uribe[1] Moming Li[1] Alexandru Iacob[9] John Marcinak[10] Jatinder Kaur[1] Dimitri Semizarov[1] Stanislas Pol[11]

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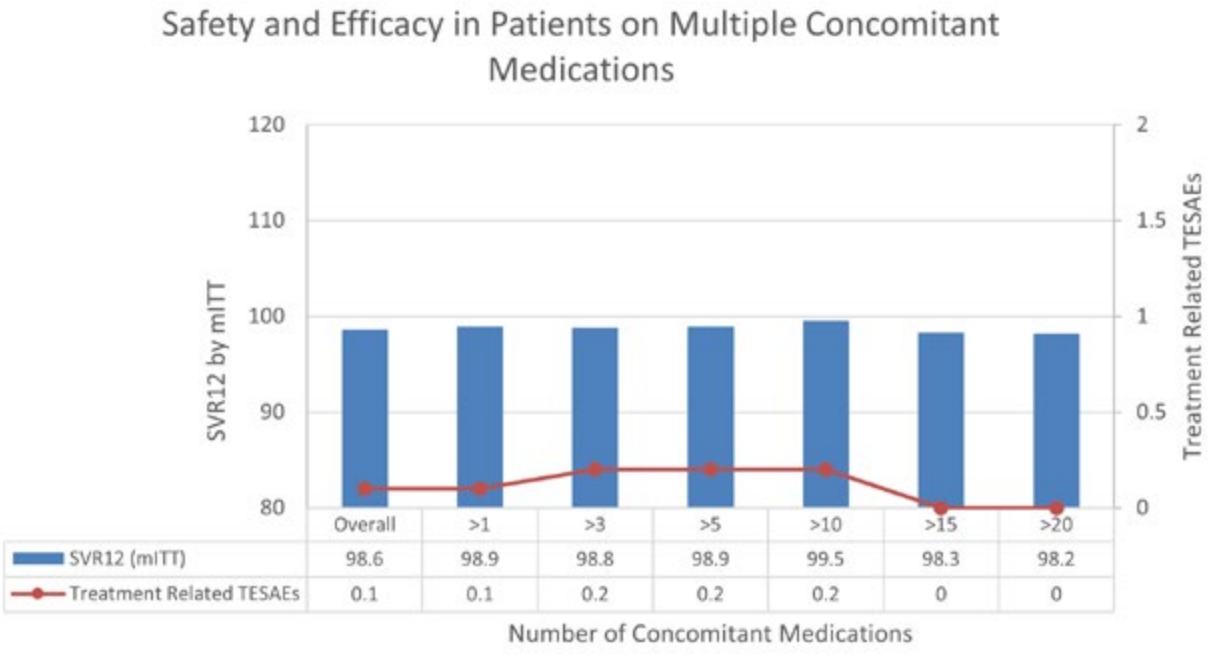
Background: The safety of direct acting antivirals (DAAs) can be impacted by drug-drug interactions (DDIs). This integrated analysis of phase 2 and phase 3 studies uses the pangenotypic DAA regimen of glecaprevir and pibrentasvir (G/P) to analyze the efficacy and safety of glecaprevir/pibrentasvir (G/P) in the presence of multiple co-morbidities and concomitant medications. **Methods:** An integrated pooled analysis was carried out across twenty-one (21) randomized controlled clinical trials in patients with chronic HCV genotype 1-6 infection with or without compensated cirrhosis receiving G/P for 8, 12 or 16 weeks that were on concomitant medications. Primary analyses assessed safety and efficacy (sustained virologic response at post-treatment week 12; SVR12). Patients were stratified for analysis by number of concomitant medications, age >65yrs, having a co-morbidity and use of injectable and other drugs (PWUD). **Results:** Among 6569 patients in this analysis, 1170 (17.8%) were age >65yrs, 2049 (31.2%) had a psychiatric disorder, 300 (4.6%) had a cardiovascular disorder, 1786 (27.2%) had HIV-HCV co-infection, and 2049 (31.2%) were PWUD. 2705 patients were on >3, 1638 patients were on >5, 439 patients were on >10, 138 patients were on >15 and 59 patients were on >20 concomitant medications. High efficacy of G/P (mITT SVR12) was observed overall (98.6%) including in patients on >20 (98.2%) concomitant medications. Treatment emergent serious adverse events (TESAEs) occurred at low rates (overall 2.5%, range (2.4-5.1%) across all patient populations, with the most frequently reported SAE being infections, injuries/procedural complications and neoplasms. The majority of the TESAEs were considered unrelated to G/P with only 0.1% possibly related to G/P. Treatment related TESAEs in patients on >1 concomitant medication were rare (0.1%, range0-0.2%). Grade 3 elevations in alanine aminotransferase (ALT) or bilirubin were uncommon (0.5%, 0.1%) in the overall population as well as in patients >65yrs of age (0.2, 0.4%), those with psychiatric comorbidities (0.5, 0.2%), cardiovascular comorbidities (0.7. 0.4%), HIV-HCV co-infection (0.4, 0.1%), and PWUD (0.6, 0.1%). There were no patients with both Grade 3 ALT and Grade 3 bilirubin elevations. **Conclusion:** This integrated pooled analysis confirms the safety, tolerability and high efficacy of G/P in chronic HCV patients on as many as >20 multiple concomitant medications, >65 years of age, those with comorbidities and PWUD.



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Disclosures: Shweta Raina: Nothing to Disclose, Curtis Cooper: Nothing to Disclose, Jordan Feld: Mirum: Consultant, AbbVie, Bluejays, Gilead, Janssen, GSK, Roche, VIR Roche: Consultant, Bluejays: Consultant, Gilead: Consultant, Janssen: Consultant, GSK: Consultant, Roche: Consultant, VIR Biotechnology: Consultant, Altimmune, AbbVie, Gilead, Jannsen, GSK, Roche, VIR Bio: Grant/Research Support, Lisa Johnson: Nothing to Disclose, Ashley Brown: Nothing to Disclose, Anthony Martinez: Gilead: Consultant, Gilead: Speaking and Teaching, Abbvie: Consultant, Abbvie: Speaking and Teaching, Arbutus: Consultant, Braeburn: Speaking and Teaching, Sirtex: Consultant, Roche: Consultant, Syneos/VBI: Consultant, Madrigal: Speaking and Teaching, Altimune: Consultant, Brian Conway: Nothing to Disclose, Stuart Gordon: Nothing to Disclose, Tarik Asselah: Nothing to Disclose, Liz Uribe: Nothing to Disclose, Moming Li: Nothing to Disclose, Alexandru Iacob: Nothing to Disclose, John Marcinak: AbbVie: Employee, Jatinder Kaur: AbbVie: Employee, Dimitri Semizarov: Nothing to Disclose, Stanislas Pol: Nothing to Disclose

1460 | METHIONINE SULFOXIDE, METHIONINE, AND ORNITHINE AS BIOMARKERS FOR PREDICTING DEVELOPMENT OF HEPATOCELLULAR CARCINOMA AFTER HEPATITIS C VIRUS ELIMINATION

Takeshi Chida[1] Masahiko Ito[1] Kazuyoshi Ohta[1] Hidenao Noritake[1] Kazuhito Kawata[2] Tetsuro Suzuki[1]

[1]Hamamatsu University School of Medicine, [2]Hamamatsu University

Background: Hepatitis C virus (HCV) infection leads to inflammatory responses in the liver, resulting in fibrosis and hepatocellular carcinoma (HCC). Simultaneously, HCV perturbs crucial metabolic pathways, involving glucose, lipid, and amino acids. Despite the achievement of sustained virological response (SVR) with antiviral therapy, the risk of HCC still remains, necessitating strategies to identify high-risk group. This study aimed to explore predictive factors for HCC, with a focus on identifying serum metabolites that changed following HCV clearance. **Methods:** Multicenter retrospective study. Study 1: A comprehensive analysis of serum metabolites was conducted using capillary electrophoresis time-of-flight mass spectrometry (CE-TOFMS) in 8 SVR and 3 non-SVR patients treated with interferon-based direct-acting antiviral (DAA). Metabolites exhibiting quantitative changes after SVR were extracted.
Study 2: The metabolites extracted in Study 1 were analyzed to predict HCC after SVR in patients treated with interferon-free DAA. Twenty-nine cases developed HCC after SVR (HCC group), and 58 age- and sex-matched cases without HCC were selected (non-HCC group). The metabolites were quantified using liquid chromatography-tandem mass spectrometry. **Results:** CE-TOFMS identified 185 metabolites. In multivariate analysis, eight metabolites with significant impact on the alteration of serum metabolic profile were extracted. In study 2, in the non-HCC group, levels of Methionine (Met, μg/mL) changed from 2.64 to 3.59, Methionine sulfoxide (MetO, x10² ng/mL) from 3.63 to 1.63, and Ornithine (Orn, μg/mL) from 18.98 to 16.50 (pre-treatment; pre-Tx to post-treatment; post-Tx). Univariate analysis identified pre-Tx Met, Orn, and post-Tx MetO, Orn, in addition to known markers AFP and FIB-4. Multivariate analysis identified the combinations of post-Tx MetO, Orn, and FIB-4, as independent predictive factors. Combining three post-Tx factors provides a predictive model that identifies the high-risk group with cumulative HCC rates (%) of 25.2, 58.8, and 80.8 at 1, 3, and 5 years, respectively. The intermediate-risk group has rates of 5.3, 13.7, and 24.1, and the low-risk group has rates of 0, 0, and 5.6. This demonstrates that the combination model is a potent tool for stratifying patients into different HCC risk categories, and is more effective than using each factor alone. **Conclusion:** A comprehensive analysis identified Met, MetO, and Orn as predictive factors for HCC after SVR. Utilizing the combination of these metabolites with known markers enables more accurate predictions.

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1461 | DIRECTLY OBSERVED DAA THERAPY COMPRISING EXTENDED DISPENSATION INTERVALS AS A UNIQUE APPROACH TO STREAMLINED HCV MICROELIMINATION FOR PWID

Caroline Schwarz[1] Angelika Schütz[2] David Bauer[1] Enisa Gutic[1] Thomas Reiberger[3] Hans Haltmayer[2] Michael Gschwantler[1]

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Background: Directly observed therapy (DOT) with direct-acting antivirals (DAA) alongside opioid agonist therapy (OAT) is an effective hepatitis C (HCV) microelimination strategy for people who inject drugs (PWID). The traditional concept of DOT was based on DAA prescription via a low-threshold facility (LTF) and daily supervised DAA ingestion alongside OAT at the LTF or a pharmacy. In PWID with excellent adherence, DOT intervals may be extended from daily up to once weekly, yet the effect of these adapted DOT schedules on sustained virologic response (SVR) rates has not been investigated. **Methods:** Due to social distancing requirements during the COVID19 pandemic, DOT intervals were bound to be extended in a Viennese cohort of PWID starting 03/15/2020. We compared SVR rates, DOT distribution schedules, and socioeconomic factors between 278 PWID starting DAA DOT between 03/15/2020 and 05/02/2023 ("Extended DOT", EDOT) and 441 PWID undergoing DAA DOT between 09/26/2014 and 03/14/2020 ("Traditional DOT", TDOT). **Results:** During the TDOT era, most PWID underwent daily DOT (348 [78.9%] vs. 19 [4.3%] with 2-3x/week and 74 [16.8%] with 1x/week OAT/DAA dispensation). By comparison, in the EDOT period, only 86 (30.9%) PWID remained with daily DOT while in 67 (24.1%) and 125 (45.0%) individuals, OAT/DAA dispensation intervals were extended to 2-3x/week and 1x/week, respectively (p<0.001). However, both approaches resulted in comparably high SVR rates (EDOT: 194/194, 100% vs. TDOT: 401/402, 99.38% according to modified intention-to-treat analysis; p=1).
Of note, socioeconomic status was equal or lower in the EDOT group (homelessness: 39.3% vs. 44.5%, p=0.223; unemployment: 84.6% vs. 85.3%, p=0.889; habitual alcohol consumption: 28.1% vs. 15.4%, p<0.001; ongoing intravenous drug use: 64.0% vs. 57.8%, p<0.001). Nevertheless, no treatment interruptions or COVID19-related deaths were registered. **Conclusion:** TDOT was originally designed to account for problematic adherence among PWID related to their underlying substance use disorder and socioeconomic factors largely associated with it. However, our data suggest that the success of DAA DOT may not be a direct result of strict surveillance but rather of the streamlined approach to DAA treatment provided through a single visit at an LTF and the bypassing of bureaucratic and socioeconomic barriers.

Disclosures: Caroline Schwarz: Abbvie, Gilead, Gebro, Galapagos: travel support, Abbvie, Gilead: Speaking and Teaching, Gilead: Consultant, Angelika Schütz: Nothing to Disclose, David Bauer: Nothing to Disclose, Enisa Gutic: Nothing to Disclose, Thomas Reiberger: Nothing to Disclose, Hans Haltmayer: Nothing to Disclose, Michael Gschwantler: Nothing to Disclose

1462 | INCLUDING UNDERSERVED POPULATIONS IN THE GLOBAL EFFORTS AGAINST VIRAL HEPATITIS – AN AUSTRIAN APPROACH TO HCV ELIMINATION AMONG HOMELESS PEOPLE WITHOUT HEALTH INSURANCE

Caroline Schwarz[1] Bernadette Becsi[2] Stephan Leick[2] Stephan Gretel[2] Lena Wien[3] Enisa Gutic[1] Thomas Reiberger[4] Hans Haltmayer[5] Michael Gschwantler[1]

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Background: In people experiencing homelessness (PH) and/or lack of health insurance (PI) the risk for hepatitis C virus (HCV) infection is increased. Yet, due to manifold barriers in reaching this population, linking them to care, and coverage of treatment costs, specific HCV elimination strategies are lacking. **Methods:** Through a cooperation between a tertiary care center and a low-threshold facility (LTF) providing social support, medical care, and housing for >5.000 PH and PI annually in Vienna, this project aiming to provide HCV care for PH and PI was initiated. Starting in 03/2020, serum antiHCV screening was offered to clients attending the LTF or one of its housing facilities. In case of antiHCV(+), the respective blood samples were further analyzed by HCV-RNA PCR ("reflex testing"). Individuals with HCV-RNA(+) received DAA treatment through a hepatitis outpatient clinic

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integrated in the LTF and staffed in cooperation with the tertiary care center. During HCV therapy, PH were given housing opportunities by the LTF and PI were provided with DAA by Gilead® and Abbvie®. Social workers and the respective housing institutions assisted patients in the adherence to DAA therapy. **Results:** Serologic screening for HCV was performed in 601 individuals 03/2020-07/2023. Among them, 116 (19.3%) were antiHCV(+), 24 (20.7%) of whom showed HCV-RNA(-), indicative of resolved HCV infection. Of the 92 (79.3%) antiHCV(+) who showed persisting HCV viremia, 36 (39.1%) were started on DAA treatment. By 07/2023, 21/36 (58.3%) patients had completed DAA therapy, none of whom had experienced treatment interruptions. In 17/21 (81.0%), sustained virologic response (SVR) could be documented while 4 (19.0%) patients had not presented for SVR verification. **Conclusion:** Though restrictions associated with the COVID19 pandemic limited the number of people reached by this project, we achieved to provide a relevant number of PH and PI with HCV testing. The high prevalence of HCV-RNA viremia at 15.3% of the study cohort emphasizes the need for targeted HCV care for this underserved population.
According to our data, DAA therapy is highly effective among PH and PI, however, a streamlined approach encompassing support by social workers and provision of housing for during treatment are essential for this success.
Due to the high prevalence of HCV viremia and the effectiveness of DAA in PH and PI, these underserved populations need to be included in future HCV elimination efforts.

Disclosures: Caroline Schwarz: Abbvie, Gilead, Gebro, Galapagos: travel support, Abbvie, Gilead: Speaking and Teaching, Gilead: Consultant, Bernadette Becsi: Nothing to Disclose, Stephan Leick: Nothing to Disclose, Stephan Gretel: Nothing to Disclose, Lena Wien: Nothing to Disclose, Enisa Gutic: Nothing to Disclose, Thomas Reiberger: Nothing to Disclose, Hans Haltmayer: Nothing to Disclose, Michael Gschwantler: Nothing to Disclose

1463 | PROGRESS TOWARDS ACHIEVING HEPATITIS C ELIMINATION IN THE COUNTRY OF GEORGIA, April 2015 – March 2024

Tengiz Tsertsvadze[1] Akaki Abutidze[1] Lali Sharvadze[2] Maia Butsashvili[3] Jaba Zarkua[4] Rania Tohme[5] Shaun Shadaker[5] Ekaterine Adamia[6] Tamar Gabunia[7]

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Background: The country of Georgia launched the world's first national hepatitis C elimination program in April 2015. Key strategies include nationwide screening, active case finding, linkage to care, decentralized care, and provision of treatment for all persons with hepatitis C virus (HCV) infection, along with effective prevention interventions. The elimination program aims to achieve the following targets: a) diagnose 90% of persons with HCV infection, b) treat 95% of those diagnosed, and c) cure 95% of those treated. We report progress toward those targets. **Methods:** Based on population-based national seroprevalence surveys conducted in 2015 and 2021, the estimated number of adults with HCV infection in Georgia is approximately 130,000 persons. We analyzed data in the national HCV screening and treatment databases for the period April 2015-March 2024. **Results:** As of March 31, 2024, 164,352 adults screened positive for HCV antibodies. Of those, 138,058 (84.0%) received HCV RNA or core antigen testing, of whom 107,121 (77.6%) had current HCV infection, and 86,682 (80.9%) initiated treatment. Of 60,728 persons who were evaluated for sustained virologic response (SVR), 60,112 (99.0%) had no detectable HCV RNA. Based on the 90-95-95 program goals, Georgia has diagnosed 91.6% of the target 117,000 (90% of the estimated 130,000 adults with current HCV infection), treated 78.0% of the target 111,150 (95% of 117,000), and cured 56.9% of the target 105,593 (95% of 111,150). Treatment effectiveness was comparable among persons with advanced fibrosis (elastography score F3- F4 or FIB-4 > 3.25) with 98.4% achieving SVR, and among patients with mild or no liver fibrosis (elastography score≤ F2 or FIB-4 < 1.25), SVR= 99.2%, p<.0001. **Conclusion:** Georgia has made substantial progress towards eliminating hepatitis C. Over 80% of persons with current HCV infection have been diagnosed, and most have initiated treatment and experienced high cure rates regardless of fibrosis status. Challenges remain in identifying persons with current HCV infection not yet linked to care and treatment in Georgia. Expansion of a national integrated, decentralized model of HCV treatment, currently implemented in some locations, will be critical to improve linkage to care and close gaps in the HCV cascade of care.

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1464 | MULTI-COLLABORATION CONTRIBUTES TO HCV DBU RELINK IN GUANGDONG,CHINA (FIRST REPORT)

Yue Wu[1] Aiqi Lu[1] Jinfeng Liu[2] Lingjie Wu[3] Runqi Luo[4] Zeng Pang[5] Xi He[6] Lan Zhou[7] Guangming Zhu[1] Ganqiu Lin[1] Qiqi Shi[1] Biao Zheng[1] Jianping Li[1] Yujuan Guan[1]

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Background: To meet the WHO 2030 target, from April 2024, we've organized a well-trained HCV Relink team including HCV hepatologists, call-back specialists and nurses, and we are now relinking diagnosed but untreated (DBU) HCV patients in Guangdong. **Methods:** Firstly, we prepared the relink list from the CDC database in the area covered by the team, including part of Guangzhou, Foshan, Qingyuan, Shantou, Shaoguan, Yunfu and Zhanjiang from 2021-2023. Second, we reviewed the preliminary data in Baiyun District to get some insights for the relink project. This is the first report of this project. **Results:** From Jan. 2021 to Dec.2023, there were 8197 records of DBU HCV patients. 340 cases were deceased,7651 cases were alive with phone numbers (Fig.1A) (417 records were fixed-line numbers and 7234 records were mobile phone numbers). 5673 cases (74.1%) were male and 90.18% of patients were aged 30-69 years (Fig.1B). The top 3 groups of people were: household and non-working, farmers, and commercial services. Guangzhou Eighth People's Hospital, Guangzhou Medical University had called the 2021-2023 HCV DBU list in Baiyun Districts for 1st try. In total, 2270 patients were enrolled. 51 cases were deceased (information from family member), 380 cases had wrong numbers, 485 cases didn't answer. In 1354 people who were successfully reached, 1145 cases had been treated or are under treatment, 7 cases were pregnant. In 202 people who were eligible for recall, 137 people intended to return to the hospital for examination and treatment after communication with the relink team by phone call. 65 people refused or are pending return to the hospital. Based on these preliminary results, we expect that 100 HCV DBU patients in Baiyun District will be recalled in a short period of time. The team has sent messages to the refused or pending people and will follow up with them a month later. Preliminary mapping shows that at least 20% of people didn't answer the phone, which indicates that there is still room for improvement in the team's contact methods, we plan to use a phone number that can display the name of the hospital, and at the same time send text messages with the hospital's address and information about the doctor who they would see to increase trust. **Conclusion:** The HCV-DBU Relink project in Guangdong has started. The professional HCV relink team is currently optimizing the process so that more HCV-DBU patients can be diagnosed and followed up as early as possible in a standardized way.

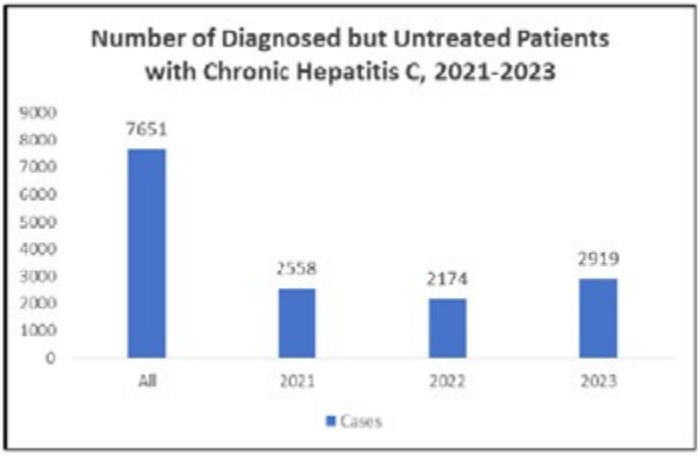

Fig.1A Number of Diagnosed but Untreated Patients with Chronic Hepatitis C, 2021-2023

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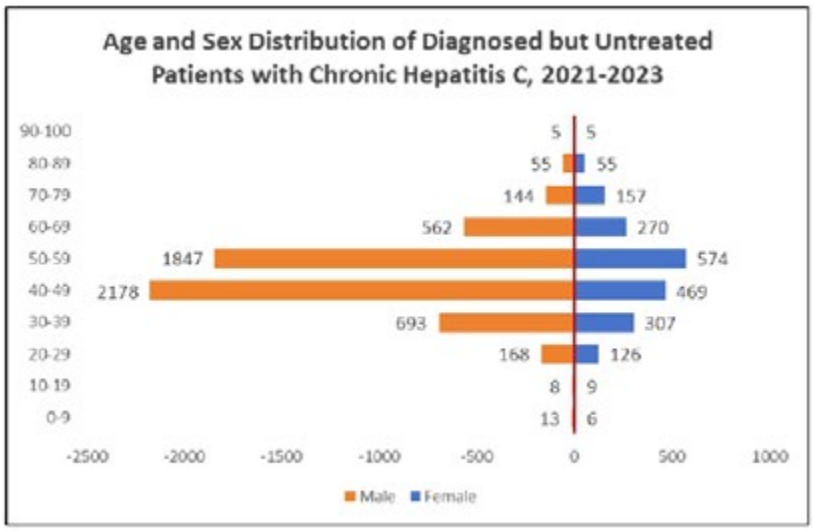

Fig.1B Age and Sex Distribution of Diagnosed but Untreated Patients with Chronic Hepatitis C, 2021-2023

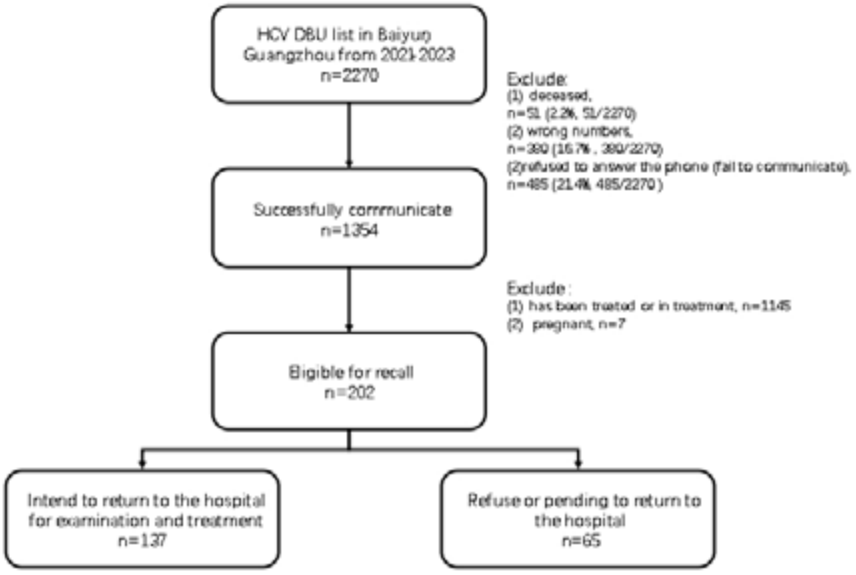

Fig. 1C The HCV Relink Team's initial telephone contact results in Baiyun District (prework)

Disclosures: Yue Wu: Nothing to Disclose, Aiqi Lu: Nothing to Disclose, Jinfeng Liu: Nothing to Disclose, Lingjie Wu: Nothing to Disclose, Runqi Luo: Nothing to Disclose, Zeng Pang: Nothing to Disclose, Xi He: Nothing to Disclose, Lan Zhou: Nothing to Disclose, Guangming Zhu: Nothing to Disclose, Ganqiu Lin: Nothing to Disclose, Qiqi Shi: Nothing to Disclose, Biao Zheng: Nothing to Disclose, Jianping Li: Gilead Science: Grant/Research Support, Yujuan Guan: Nothing to Disclose

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1465 | A REVIEW OF PHASE 1 & 2 OF THE JOINT UNITED KINGDOM HEALTH SECURITY AGENCY (UKHSA) & NATIONAL HEPATITIS C PAEDIATRIC MULTI-DISCIPLINARY OPERATIONAL DELIVERY NETWORK (PMDT ODN) NATIONAL HEPATITIS C PAEDIATRIC TRACKING PROJECT

Carla Lloyd[1] Rachel Cockayne[1] Maxine Brown[1] Simmons Ruth[2] SEma Mandal[2] Aneesha Noonan[2] Sarah Tizzard[3] John Corcoran[2] Paddy McMaster[4] Deirdre Kelly[1] William Irving[5]

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Background: Hepatitis C virus(HCV) infection is a major global health problem in adults & young people (and can cause serious, potentially life-threatening damage to the liver[1]. HCV Global Elimination by 2030 remains a target for the World Health Organisation(WHO) and NHS England (NHSE). HCV is treated by Direct Acting Anti-viral therapies(DAAs) achieving cure rates of 99% in adults and adolescents. DAAs were licensed for children ≥3yrs of age in 2020. In 2021, a specialised National Paediatric Multidisciplinary Team Operational Delivery Network(MDT ODN)[2,3] supported by NHSE hosted at Birmingham Women's and Children's, was established to receive referrals; assess, & approve treatment for HCV RNA positive children and young people(C&YP). **Methods:** Laboratory **Results:** reported to Public Health England (now the UK Health Security Agency (UKHSA) from 2019 identified 1086 C&YP nationally who had tested positive. No further follow up was known. In 2022 the pMDT ODN established a joint project sub-group with UKHSA to track these patients who may be at risk of HCV and determine their current HCV status.

Phase 1

- March 2022: UKHSA rechecked 1086 patients identified, those with a known HCV status were removed
- July 2022: 481/1086 patient details, whose HCV status was unknown, were shared with the subgroup, including their primary care physician (PCP) details
- Letters were sent to their physician requesting information on current HCV status. Where status was unknown, HCV antibody and HCV RNA tests were requested. **Results: See Table 1 for outcomes (March 2022-April 2024) for 481 patient records shared by UKHSA**

Phase 2 November 2023

- 605/1086 records reviewed
- 459/605 no further action required
- 146/605 HCV RNA+/Ab+ to be followed up

A primary care champion has joined the project assisting with access to primary care records to support the tracking of patients, improving communication and engagement with PCPs. **Conclusion:** Communication and engagement with PCPs have been strengthened to ensure they engage with requests for information, understand long-term risks of HCV infection, and the need for testing.

Phase 1 of the project has been successful in determining the HCV status of 381/431 (88%) children, providing treatment for 53 children ensuring equity of treatment and care closer to home.

Phase 2 will build on the successes of Phase 1 and continue to follow up the 196 outstanding patients whose HCV status is unknown.

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n	Current Status	Action
50/ 481	>18 years, referred to adult ODN	Referred to adult ODNs

381/431	No further action required:
	• 215 re-tested negative for HCV (Ab or RNA)
	• 64 treated
	  • 53 through pMDT ODN
	  • 11 in trials before 2021
	• 1 awaiting referral
	• 98 required UKHSA advice:
	  • 16 Lab tests miscoded
	  • 82 Confirmed HCV Ab-ve
	• 2 returned to home country
	• 1 spontaneously cleared virus
		No further action

Status not confirmed n=50		
15/50	• 3 parent/guardian issues • 1 refusing to re-test*	UKHSA checking lab results
	• 2 not responding	GPs asked to keep trying
	• 7 not known to GP	New GP to be identified
	• 5 Data confirmation required • NHS Number/D.o.B	UKHSA checking records
15/35	RNA +ve	Following up
10/20	HCV Ab +ve	Following up
10	GP requesting retesting	Following up

Disclosures: Carla Lloyd: Nothing to Disclose, Rachel Cockayne: Nothing to Disclose, Maxine Brown: Nothing to Disclose, Simmons Ruth: Nothing to Disclose, SEma Mandal: Nothing to Disclose, Aneesha Noonan: Nothing to Disclose, Sarah Tizzard: Nothing to Disclose, John Corcoran: Nothing to Disclose, Paddy McMaster: Nothing to Disclose, Deirdre Kelly: Nothing to Disclose, William Irving: Gilead Sciences: Grant/Research Support

1466 | BEMNIFOSBUVIR DOES NOT ALTER CARDIAC REPOLARIZATION IN HEALTHY PARTICIPANTS: RESULTS FROM A THOROUGH QT STUDY

Xiao-Jian Zhou[1] Borje Darpo[2] Hongqi Xue[2] Gaetano Morelli[3] Maureen Montrond[1] Keith Pietropaolo[1] Bruce Belanger[1] Shannan Lynch[1] Dayle James[1] Arantxa Horga[1] Janet Hammond[1]

[1]Atea Pharmaceuticals, Inc., [2]Clario, [3]Altasciences

Background: Bemnifosbuvir (BEM, AT-527) is an oral double prodrug of a guanosine nucleotide analog with potent activities against coronaviruses and flaviviruses including hepatitis C virus and SARS-CoV-2 and is under clinical development for the treatment of COVID-19 (phase 3) and chronic hepatitis C (phase 2). We report results from a thorough QT (TQT) study of bemnifosbuvir in healthy participants. **Methods:** 36 eligible healthy participants 18-55 years of age were randomized to receive a single oral dose of BEM 550 mg (QTc population n=32), 1100 mg (n=33), matching placebo (n=30), and open-label moxifloxacin 400 mg (n=34), in a four-way crossover design. Continuous ECG recorders were applied pre- and post-dose up to 48h during each period, and 12-lead ECGs were extracted at PK-matched time points. **Results:** BEM at the studied doses did not have a clinically relevant effect on heart rate or cardiac conduction, i.e., the PR and QRS intervals. In the by-time point analysis of the QT-interval, least-square mean (LSM) change-from-baseline QTcF (ΔQTcF) on BEM closely followed the placebo pattern across post-dose time points. LSM placebo-corrected ΔQTcF (ΔΔQTcF) on BEM varied from -2.5ms (at 5h post-dose in the 550 mg dose group) to 4.5ms (at 0.75h post-dose in the 1100 mg dose group), without an indication of dose-dependency. The upper bound of the 90% CI of ΔΔQTcF was below 10 ms across all post-dose time points on both BEM doses, whereas LSM ΔΔQTcF peaked at 13ms at 2 and 3 h post-dose for the positive control, moxifloxacin. In the concentration-QTc (C-QTc) analysis, a linear-mixed effects model including BEM and its 3 metabolites (AT-551, AT-229, and AT-273) as the explanatory variables was initially fitted, and a model selection procedure was performed. The individual model with the metabolite, AT-229

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as the only analyte was selected the primary model per the pre-specified criteria. The estimated slope of plasma AT-229 C-QTc relationship was shallow and significant: 0.0028 ms per ng/mL (90% CI: 0.00179 to 0.00378; P = < 0.0001), with a not statistically significant treatment effect-specific intercept of -0.51ms. An effect on ΔΔQTcF exceeding 10 ms can be excluded within the full observed range of AT-229 plasma concentrations up to ~2700 ng/mL. The predicted effect on ΔΔQTcF with C-QTc models with BEM and other metabolites, alone were similar to those from the primary model, and all concluded that an effect on ΔΔQTcF exceeding 10ms can be excluded within the observed plasma concentration ranges of BEM, AT-551 and AT-273 up to ~10100, ~2120 and ~496 ng/mL, respectively. **Conclusion:** BEM had no clinically relevant effects on cardiac repolarization, heart rate, PR interval, or QRS duration. An QTc effect exceeding 10 ms, the established threshold of concern, can be excluded across the observed plasma concentration ranges of BEM and its metabolites expected to exceed high clinical exposure scenarios.

Disclosures: Xiao-Jian Zhou: Nothing to Disclose, Borje Darpo: Nothing to Disclose, Hongqi Xue: Nothing to Disclose, Gaetano Morelli: Nothing to Disclose, Maureen Montrond: Nothing to Disclose, Keith Pietropaolo: Atea Pharmaceuticals, Inc.: Employee, Bruce Belanger: Nothing to Disclose, Shannan Lynch: Nothing to Disclose, Dayle James: Nothing to Disclose, Arantxa Horga: Nothing to Disclose, Janet Hammond: Nothing to Disclose.

1467 | MULTISCALE MODELING OF LEAD-IN RESULTS FROM A PHASE 2 STUDY OF AN 8-WEEK COMBINATION REGIMEN OF BEMNIFOSBUVIR AND RUZASVIR IN PATIENTS WITH CHRONIC HEPATITIS C VIRUS INFECTION

Carolin Zitzmann[1] Ruy Ribeiro[1] Sergey Izmailyan[2] Keith Pietropaolo[2] Arantxa Horga[2] Xiao-Jian Zhou[2] Janet Hammond[2] Alan Perelson[1]

[1]Los Alamos National Laboratory, [2]Atea Pharmaceuticals, Inc.

Background: Bemnifosbuvir (BEM) and ruzasvir (RZR) are potent, pan-genotypic inhibitors of the HCV NS5B polymerase and the NS5A protein, respectively. The novel combination of BEM/RZR is being assessed for safety and efficacy in a phase 2 open-label study targeting 280 HCV-infected individuals including those with compensated cirrhosis (NCT05904470). Previously we developed a multiscale model of HCV infection and treatment to estimate the in vivo effectiveness of daclatasvir in blocking HCV replication and viral assembly/secretion. Here we use the same approach to evaluate the BEM/RZR combination in a lead-in cohort from the on-going phase 2 trial. **Methods:** In this single arm study, a lead-in cohort (n=60) of treatment-naïve, non-cirrhotic individuals with chronic HCV (CHC) (any genotype) received 550 mg BEM once daily (QD) + 180 mg RZR QD for 8 weeks. Plasma HCV RNA was evaluated frequently using the Roche Cobas® HCV quantitative nucleic acid test, with a lower limit of quantitation (LLOQ) of 15 IU/mL. The previously developed multiscale model was fit to the plasma viral load (VL) and the ALT data from all 60 subjects simultaneously via population fitting. **Results:** The 60 lead-in participants were infected with GT1 (n=45), GT2 (n=2) or GT3 (n=13), and 17% had F3 fibrosis. 57% were male, 95% were Caucasian, with a median age of 47 (range 25-79) years. All completed the 8-weeks of treatment. After treatment initiation, the VL decreased in a triphasic manner, with a very rapid first phase lasting < 12 h, followed by a slower 2nd phase and an even slower 3rd phase. The model fit both the VL and ALT data well. The population estimate of the time to reach the LLOQ was 19.7 days. The population estimate of the effectiveness of the combination in blocking viral assembly/secretion was extremely high at 0.9993 [95%CI 0.9990, 0.9995], while the population estimate of the effectiveness in blocking viral replication was 0.992 [95% CI 0.981, 0.997]. As shown in Fig. 1, this therapy was equally effective for GT1,2 and 3 and for individuals with F0-F3 fibrosis. The therapy was also equally effective in males and females and in all age groups represented. **Conclusion:** BEM/RZR for 8 weeks was highly effective in blocking both viral replication and viral assembly/secretion in HCV-infected patients independent of genotype, age, sex or fibrosis stage. This analysis supports the shortened 8 weeks of treatment with BEM/RZR for CHC.

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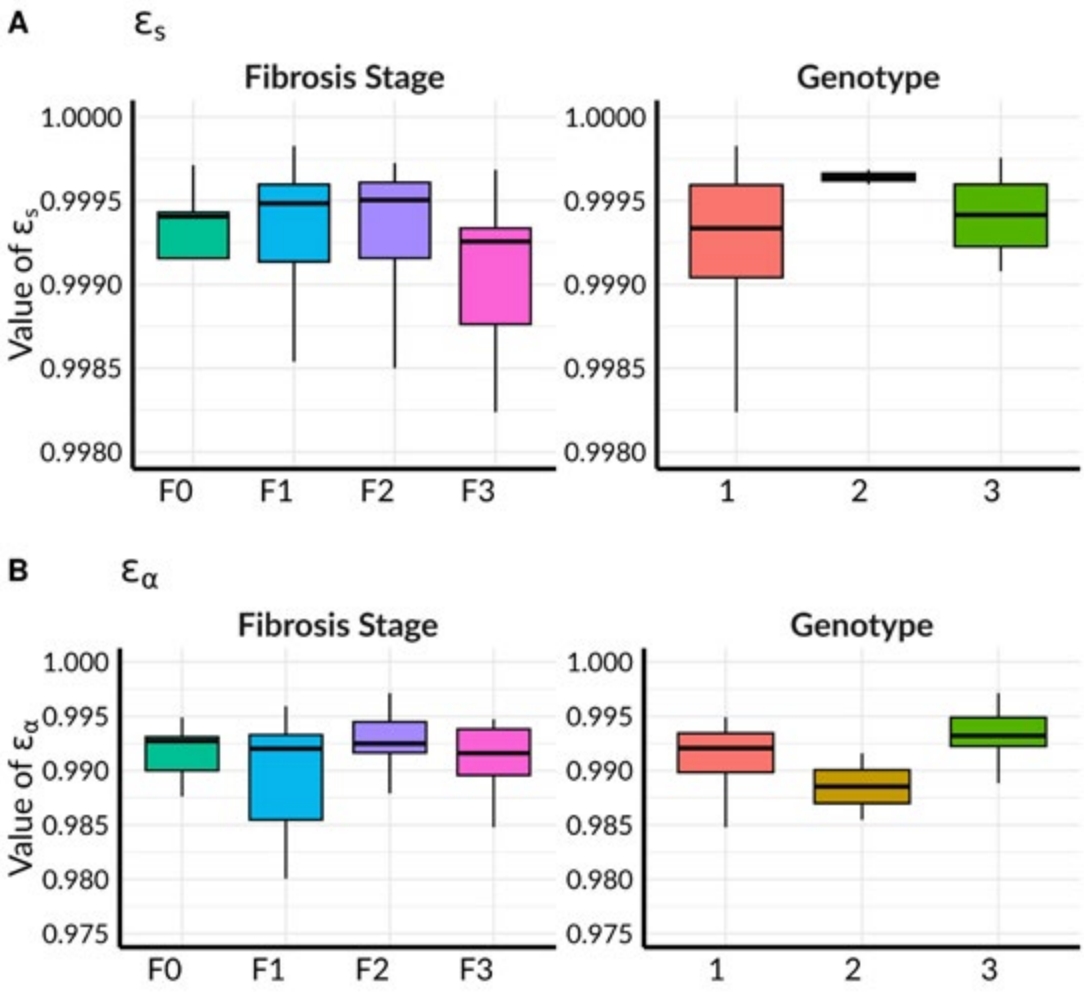

Fig. 1: The model predicted effectiveness of BEM and RZR in blocking viral assembly/secretion, ε_s, and in blocking HCV RNA replication, ε_α, for participants with different levels of fibrosis and infected with different genotypes.

Disclosures: Carolin Zitzmann: Nothing to Disclose, Ruy Ribeiro: Atea Pharmaceuticals: I have grant support, but I am not the PI of that grant., Sergey Izmailyan: Nothing to Disclose, Keith Pietropaolo: Atea Pharmaceuticals, Inc.: Employee, Arantxa Horga: Nothing to Disclose, Xiao-Jian Zhou: Nothing to Disclose, Janet Hammond: Nothing to Disclose, Alan Perelson: Atea Pharmaceuticals: Have a research contract with the company

1468 | STRATEGIC APPROACHES FOR HCV MICRO-ELIMINATION IN HEMODIALYSIS POPULATION IN SHANGHAI

Bing Dai[1] Shuqin Mei[1] Cheng Xue[1] Zhiguo Mao[1] Na Liu[2] Weijie Yuan[3] Xiaonong Chen[4] Chen Yu[5] Bibo Wu[6] Xiujuan Zang[7] Jing Qian[8] Shunjie Chen[9] Ji Fang[10] Jianying Niu[11] Changlin Mei[12]

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Background: The prevalence of anti-HCV among hemodialysis patients is significantly higher than in the general population, presenting a significant healthcare challenge. We explored effective approaches to achieve HCV elimination among dialysis patients by the end of 2025. **Methods:** The Chinese Non-Government Medical Institutions Association initiated "Zero by 2025," with the aim of eradicating HCV infection within the hemodialysis population. The action plans comprise the following strategies: 1. Screening HCV infection in patients with chronic kidney disease before commencing dialysis, ensuring prompt treatment for positive cases to achieve cure prior to hemodialysis initiation. 2. Implementing tests for HCV antibodies biannually in hemodialysis patients with a target screening rate of 100%. 3. Timely and complete diagnosis of HCV infections among incident and maintenance hemodialysis patients. 4. Adopting proactive treatment measures with a cure rate more than 95%. 5. Providing comprehensive training for nephrologists on hepatitis C, aiming for a training rate of 100%. 6. Educating hemodialysis patients to dispel misconceptions and discrimination against those with HCV. **Results:** Since November 2022, totally 3,730 hemodialysis patients from 10 hemodialysis centers in Shanghai have been screened and more than 8,900 HCV antibody tests have been performed. Among patients screened, 122 individuals tested positive for HCV antibodies, yielding a 3.28% positive rate, much higher than that in Chinese general population which was 0.60%. All of them underwent further confirmatory HCV RNA testing. 26 patients tested positive for HCV RNA, comprising 25 treatment-naive cases and 1 patient failed to DAA treatment previously. Notably, 14 of the HCV RNA positive patients have initiated treatment with 12-week Sofosbuvir/Velpatasvir (SOF/VEL) regimen and 4 patients are in the process of starting DAA treatment. 1 individual is currently enrolled in an alternative clinical trial. For two patients in advanced disease stages, treatment initiation has been deferred based on clinical evaluation. Additionally, two patients refused therapy, believing it unnecessary. The only patient with prior DAA plus ribavirin (RBV) discontinued treatment due to intolerance to RBV and is currently under evaluation for switching to a tailored 24-week SOF/VEL regimen. Furthermore, in total 44 HCV educational lectures were held by 400 hemodialysis healthcare professionals. Additionally, over 440 individuals undergoing hemodialysis participated in 26 HCV awareness promotion meetings. **Conclusion:** The initiative demonstrates promising progress in HCV elimination among hemodialysis patients. Despite modest treatment rates, early screening, prompt diagnosis, and targeted education have been proven highly efficacious in China. Consistent dedication to these strategies is essential for achieving goal of HCV elimination.

Disclosures: Bing Dai: Nothing to Disclose, Shuqin Mei: Nothing to Disclose, Cheng Xue: Nothing to Disclose, Zhiguo Mao: Nothing to Disclose, Na Liu: Nothing to Disclose, Weijie Yuan: Nothing to Disclose, Xiaonong Chen: Nothing to Disclose, Chen Yu: Nothing to Disclose, Bibo Wu: Nothing to Disclose, Xiujuan Zang: Nothing to Disclose, Jing Qian: Nothing to Disclose, Shunjie Chen: Nothing to Disclose, Ji Fang: Nothing to Disclose, Jianying Niu: Nothing to Disclose, Changlin Mei: Nothing to Disclose

1469 | EPIDEMIOLOGICAL INSIGHTS INTO HEPATITIS B AND C THROUGH BLOOD SAMPLES FROM THE KOREA NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEY

Chang Hun Lee[1] Hwa Young Choi[2] Gwang Hyeon Choi[3] Sojung Han[4] Won-Mook Choi[5] Gi-Ae Kim[6] Ji-Hyun Ahn[7] Kyung-Ah Kim[8] Moran Ki[2] Sook-Hyang Jeong[3] In Hee Kim[1]

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Background: As indicators for viral hepatitis elimination, the World Health Organization defines hepatitis C virus (HCV) infection as the presence of HCV RNA and calculates the treatment rate for hepatitis B virus (HBV) infection based on the number of patients requiring treatment. Our aim was to assess the current status of HBV and HCV infections in Korea. **Methods:** We analyzed a total of 159 blood samples positive for HCV antibodies collected from 2016 to 2020, and 137 samples positive for HBV surface antigen collected in 2020 from participants of the Korea National Health and Nutrition Examination Survey (KNHANES), all stored at the National Biobank of Korea. **Results:** The analysis of HCV samples revealed a 15.7% HCV RNA positivity rate, reflecting a 52.54% decline from the 33.5% rate documented in the 2012-2015 KNHANES results. Positivity rates were

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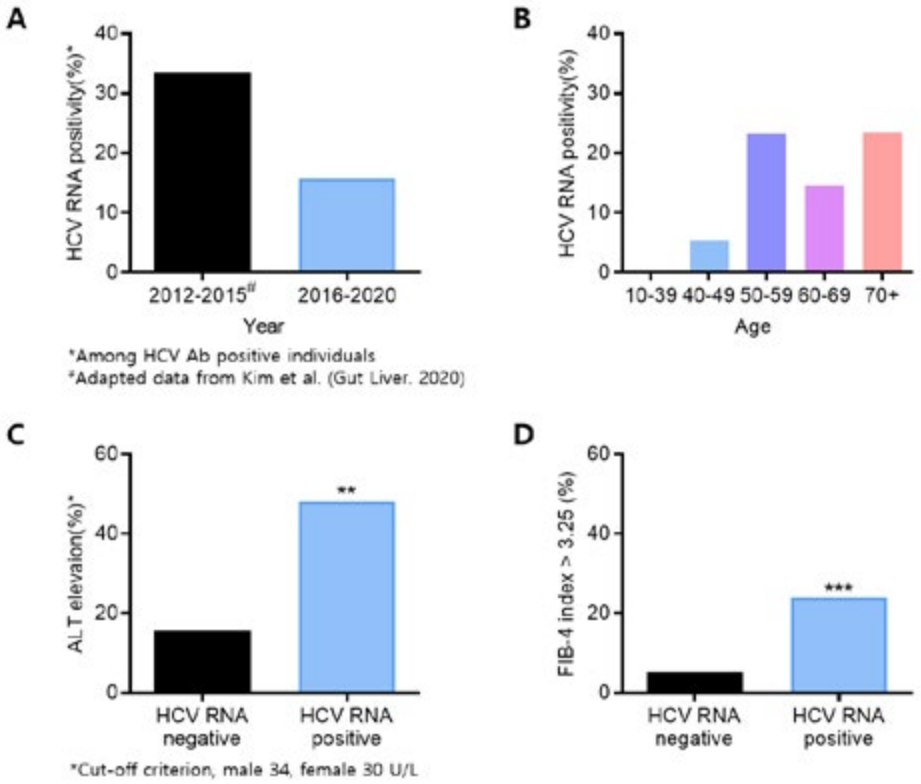
similar between genders, and HCV RNA-positive individuals had a higher average age (65.9 years) compared to those testing negative (56.8 years). The age group over 70 showed the highest positivity rate at 23.4%. HCV RNA-positive individuals exhibited higher levels of AST and ALT, and a greater proportion had a FIB-4 index above 3.25 (24.0% vs. 5.2%, p<0.001). The analysis of HBV samples revealed detectable HBV DNA levels in 62% of cases. The prevalence of detectable HBV DNA was highest among individuals aged 10 to 39 years and decreased with age. Among those with detectable HBV DNA, 12 individuals were receiving hepatitis B treatment. According to domestic medical reimbursement criteria, 12.4% required antiviral therapy, with a treatment rate of 70.6%. Elevated AST, ALT, and FIB-4 index levels were more common in participants with undetectable HBV DNA or levels between 10^5 and 10^8 IU/ml. **Conclusion:** Analysis of KNHANES blood samples collected between 2016 and 2020 indicates a 15.7% HCV RNA positivity rate among individuals with HCV antibodies. HCV RNA-positive individuals exhibited elevated levels of AST, ALT, and FIB-4 index. In the 2020 KNHANES blood sample analysis, approximately 12% of patients required hepatitis B treatment, with a treatment rate of 70%.



Disclosures: Chang Hun Lee: Nothing to Disclose, Hwa Young Choi: Nothing to Disclose, Gwang Hyeon Choi: Nothing to Disclose, Sojung Han: Nothing to Disclose, Won-Mook Choi: Nothing to Disclose, Gi-Ae Kim: Nothing to Disclose, Ji-Hyun Ahn: Nothing to Disclose, Kyung-Ah Kim: Nothing to Disclose, Moran Ki: Nothing to Disclose, Sook-Hyang Jeong: Nothing to Disclose, In Hee Kim: Nothing to Disclose

1470 | A MULTICENTER REAL WORLD STUDY OF SOFOSBUVIR/VELPATASVIR FOR HIV/HCV COINFECTED PATIENTS

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[1]*The Second People's Hospital of Yining, Yining, China,* [2]*The Specialized Hospital for Infectious Disease of Hetian District, Hetian, China*

Background: This study aimed to assess the efficacy and safety of the sofosbuvir/velpatasvir(SOF/VEL) in a real world clinical setting. **Methods:** 79 patients presenting with HIV/HCV coinfection were recruited from the second people's hospital of Yining and the specialized hospital for infectious diseases of Hetian District in Xinjiang between November 2021 and September 2023.The treatment involved a 12-weeks course of SOF/VEL,either as

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monotherapy or in combination with RBV based on individual patient conditions.Routine assessments included high-sensitivity HCV RNA, hepatitis C genotyping,high sensitivity HIV RNA,HIV genotyping,liver and kidney function,abdominal ultrasound.The primary endpoint was sustained virologic response at post-treatment week 12(SVR12). **Results:** A total of 79 HIV/HCV coinfected patients enrolled, alll of them were HCV treatment naive patients with a mean age of 45.61±8.12 years, predominantly male 82.28%.Genotype distribution revealed that 32 cases(40.51%) were GT3a, 30 cases(37.97%) were GT3b, 17 cases(21.52%) were GT1b;12 cases (15.19%) had cirrhosis.HIV genotyping indicated that all were HIV type 1 with a mean HIV RNA level of 14694.82±41256IU/ml and mean CD4+ T-cell count of 379.35±233cells/ul.Patients with GT3b and cirrhosis received SOF/VEL+RBV for 12 weeks, others were treated with SOF/VEL alone for 12 weeks.Patients with HIV are given nucleoside reverse transcriptase inhibitors (NRTIs): TDF+3TC-based ART regimens. Overall SVR12 was 98.73%(78/79), with 100%(32/32), 96.67%(29/30), 100%(17/17) SVR12 for GT3a, GT3b, and GT1b, respectively. SVR12 rates for chronic hepatitis C and cirrhotic patients were 98.51%(66/67)and 100%(12/12) respectively.One patient with GT3b experienced relapse due to the poor adherence.No treatment discontinuation occurred due to adverse events or drug-drug interaction, affirming the safe and tolerability of the regeimen, with stable liver and renal function throughout treatment and follow up. **Conclusion:** sofosbuvir/velpatasvir(SOF/VEL),either as monotherapy or in combination with ribavirin(RBV),exhibited robust virologic response and favorable safety outcomes in the treatment of HIV/HCV coinfected patients.

Disclosures: Jing Chen: Nothing to Disclose, Maimaitijiang Wubuliaishan: Nothing to Disclose

1471 | EXAMINATION OF FACTORS PREDICTING HEPATIC DECOMPENSATION AFTER ELIMINATION OF HCV IN PATIENTS WITH LIVER CIRRHOSIS

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Background: With the development of direct-acting antiviral drugs (DAA), many patients can now eliminate hepatitis C virus at a high rate. However, in some patients, liver disease progresses even after the virus has been eradicated. This study investigates predictors of hepatic decompensation in cirrhotic patients after HCV elimination. **Methods:** We analyzed 102 patients with hepatitis C virus-induced liver cirrhosis who achieved sustained virologic response at week 24 (SVR24) between February 2012 and July 2021. Patient characteristics: age 69.8 ± 8.7 years, male/female = 48/54, Child-Pugh class A/B/C = 94/8/0, history of hepatocellular carcinoma (HCC) treatment: 37 cases, history of esophagogastric varices treatment: 13 cases. **Results:** The median observation period after achieving SVR was 6 years and 10 months, and 37 patients (36.3%) developed HCC (cumulative incidence rate of 1 year/3 years/5 years = 7.8/21.5/32.1%). In addition, complications related to portal hypertension occurred in 23 patients (22.5%) (gastrointestinal varices/ascites/other = 14/7/2, cumulative incidence rate 1 year/3 year/5 year = 1.9/ 10.8/18.6%). Multivariate analysis of factors predicting decompensation using parameters at SVR24 revealed that serum albumin (odds ratio [OR], 8.16; p=0.018), platelet count (OR, 1.33; p=0.031) and γ-GTP (OR, 0.97; p=0.049) were significant independent factors. ROC curve analysis was performed and the cut off values were serum albumin: 4.1g/dL(area under the ROC[AUROC], 0.722; 95% confidence interval[CI], 0.591-0.852, p<0.001), platelets: 99,000/μL(AUROC, 0.792; 95%CI, 0.675-0.909, p<0.001) and γ-GTP: 38 U/L (AUROC, 0.795; 95%CI,0.679-0.912, p<0.001). Among the patients analyzed in this study, those in the albumin <4.1g/dL group had poor liver function and were more likely to develop HCC within 3 years after SVR. The platelet <99,000/μL group is a case of progressing portal hypertension, and HCC is likely to develop after 5 years after SVR. γ-GTP>38U/L group is more likely to develop portal hypertension-related complications and hepatocellular carcinoma after 3 years or more after SVR. **Conclusion:** We identified factors that predict decompensation in cirrhosis patients who have achieved HCV eradication. Patients with these factors require careful follow-up because their liver disease progresses even after HCV has been eliminated.

Disclosures: Ryo Sasaki: Nothing to Disclose, Tsuyoshi Ishikawa: Nothing to Disclose, Taro Takami: Nothing to Disclose

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1472 | METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE IS ASSOCIATED WITH LIVER FIBROSIS IN HEPATITIS C

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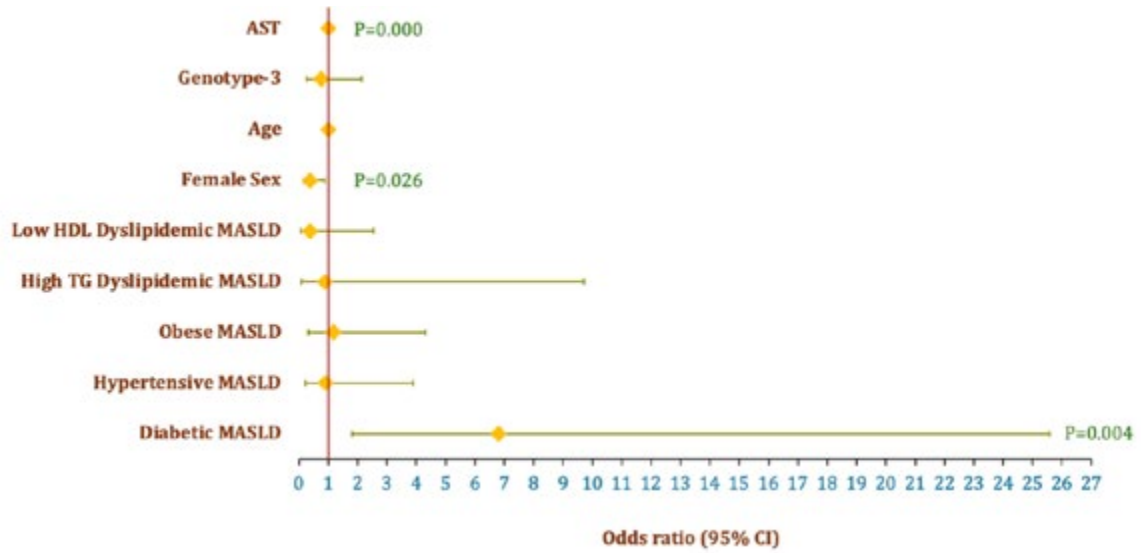
Background: Hepatitis C virus (HCV) remains a major cause of chronic liver disease worldwide. About 45-55% of HCV patients develop hepatic steatosis (HS). The term “steatotic liver disease (SLD)” has replaced “nonalcoholic fatty liver disease (NAFLD)”. SLD with cardiometabolic risk factors is defined as “metabolic dysfunction-associated steatotic liver disease (MASLD)”. The new nomenclature emphasizes the metabolic nature of HS and allows its coexistence with other conditions, such as HCV. We aimed to investigate the effect of MASLD and HCV coexistence on liver fibrosis. **Methods:** This was a retrospective cross-sectional study of people with HCV without other chronic liver diseases. Between 2015 and 2023, we recruited from 2 centers: McGill University Health Center and The Ottawa Hospital. MASLD was defined as the presence of HS by controlled attenuation parameter ≥275 dB/m plus ≥1 cardiometabolic conditions: increased body mass index and waist circumference; prediabetes or diabetes; hypertension; dyslipidemia. Significant liver fibrosis was defined as a liver stiffness measurement ≥7.1 kPa. Cofactors of liver fibrosis were investigated using multivariable analysis by change-in-estimate method supported by stepwise regression. All models were cross-validated by LASSO models (10-fold validation) to select confounders. All MASLD phenotypes (overweight, diabetic, hypertensive, and dyslipidemic MASLD) were integrated into the model. **Results:** We included 590 people with HCV monoinfection (mean age 51, 39% female). SLD was found in 36% of patients (MASLD 31% and HCV-related steatosis 5%). The prevalence of liver fibrosis was significantly higher in the MASLD group compared to no SLD (58% vs. 39%, p=<0.001), while no difference was observed between HCV-related steatosis and no SLD (45% vs. 39%). After adjusting for potential confounders, multivariable regression analysis showed that MASLD was associated with a 2-fold higher odds of significant liver fibrosis (adjusted odds ratio [aOR] 2.3, 95% confidence interval [CI] 1.07-4.87; p=0.031). Additionally, upon examining the association of MASLD phenotypes and significant liver fibrosis, only the diabetic phenotype was associated with significant liver fibrosis (aOR 6.8, 95% CI 1.81-25.58; p=0.004) (see Figure). **Conclusion:** MASLD is associated with a higher prevalence of fibrosis in people with HCV. Beyond pursuing a virological cure, healthcare practitioners should target metabolic conditions, especially diabetes.



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Disclosures: Wesal Elgretli: Nothing to Disclose, Mohamed Shengir: Nothing to Disclose, Solomon Sasson: Nothing to Disclose, Ramanakumar Agnihotram V: Nothing to Disclose, Luz Esther Ramos Ballesteros: Nothing to Disclose, Marc Deschenes: Nothing to Disclose, Philip Wong: Nothing to Disclose, Tianyan Chen: Nothing to Disclose, Nadine Kronfli: Nothing to Disclose, Alexa Keeshan: Nothing to Disclose, Saniya Tandon: Nothing to Disclose, Curtis Cooper: Nothing to Disclose, Giada Sebastiani: Novo Nordisk: Consultant, Abbvie: Speaking and Teaching, Merck: Consultant, Gilead: Speaking and Teaching, Theratechnologies Inc.: Grant/Research Support

1473 | THE POWER OF THE COMMUNITY POP-UP CLINIC: CASCADE OF CARE AND HCV TREATMENT AMONG VANCOUVER'S INNER-CITY POPULATIONS AS A PATH TOWARDS ELIMINATION

Shana Yi[1] Shawn Sharma[1] Rossitta Yung[1] Brian Conway[2]

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Background: Several strategies have been proposed to identify HCV-infected inner-city residents, engage them in care, provide them with antiviral therapy, establish conditions to maximize treatment completion and achievement and cure. Elimination of HCV infection as a public health concern by the end of this decade will require a concerted effort in all target populations, including vulnerable inner-city populations, many of whom are actively using drugs and are facing other issues more challenging that HCV infection: housing and financial insecurity, untreated mental illness, and active untreated addiction. **Methods:** This study aims to assess the effectiveness of a formal program of community pop-up clinics (CPCs) to identify HCV-infected individual, engage them in care and provide them with antiviral therapy. CPC events were held once weekly at identified places of residence in Vancouver's inner city. The primary outcome is achievement of SVR12 following the initiation of therapy. Additional analyses of HCV reinfection events and opioid-related mortality. **Results:** From January 2021 – November (35 months), we conducted 124 CPCs and evaluated 1567 individuals. Of these, 620 (31.5%) were found to carry HCV antibodies. Of whom 474 (76.5%) were found to be viremic. Engagement in HCV care has been secured in 387 cases (81.6%). 326 (84.2%) individuals have started treatment and 60 are in the pre-treatment phase, and 1 had died of an overdose in the pre-treatment phase. The median time from CPC attendance to HCV treatment initiation was 6 weeks. Of 326, 302 have completed treatment, 18 are currently on treatment and 1 died of an overdose during treatment. Of 302 subjects who have completed treatment, 286 are confirmed as cured (SVR 12), 16 are awaiting SVR 4, 2 with documented virologic relapse and 1 documented to be reinfected, a rate of 0.31/100 person-years. 3 patients withdrew from treatment prematurely. By mITT, the cure rate is 286/288 (99.3%). Overall, in this vulnerable population taken from a neighborhood with 6-7 opioid overdose deaths/day, we only documented 2 overdose deaths over 326 PY of follow-up. **Conclusion:** Taken together, the data we present validates the development of multidisciplinary programs such as ours aimed at treating HCV in vulnerable inner-city populations that must be engaged in care for HCV elimination to become a reality. This report also documents additional societal benefits that could be achieved from such a program including lowered overdose death rates and a low rate of HCV reinfection.

Disclosures: Shana Yi: Nothing to Disclose, Shawn Sharma: Nothing to Disclose, Rossitta Yung: Nothing to Disclose, Brian Conway: Nothing to Disclose

1474 | A COMPARISON OF SOFOSBUVIR/VELPATASVIR (S/V) AND GLECAPREVIR/PIBRENTASVIR (G/P) FOR THE TREATMENT OF HCV INFECTION AMONG HCV-INFECTED PEOPLE WHO USE DRUGS (PWUDS)

Shana Yi[1] Rossitta Yung[1] Shawn Sharma[1] Brian Conway[1]

[1]Vancouver Infectious Diseases Centre

Background: To eliminate HCV infection as a public health concern by 2030, there is a need to develop comprehensive programs among key populations such as PWUD. Two highly effective regimens are available for initial therapy: S/V given as 1 tablet/day for 12 weeks; G/P given as 3 tablets/day for 8 weeks. Data evaluating the safety, efficacy and factors determining a choice of one regimen over another in a population of PWUD is limited. **Methods:** Viremic HCV-infected PWUD were identified in the community and offered antiviral therapy delivered

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within a multidisciplinary program to address medical, social, mental health and addiction-related concerns. All participants (except those with decompensated cirrhosis) were offered either S/V or G/P in an equal fashion, and their selection of therapy was honored. Programs to enhance adherence were put in place, with the standard being weekly delivery to the place of residence, with daily observed therapy available when clinically necessary. Outreach programs were also in place to address potential loss to follow up. For this analysis, we identified the last 120 individuals who received S/V or G/P, with the endpoints being safety, efficacy (achievement of SVR12), loss to follow up and mortality. **Results:** Among 240 subjects enrolled, the median age was 47 for both treatment groups. We note 37.5% female, 24% Indigenous, 98.2% active drug use, 93.5% opiates/fentanyl, and 68% unstable housing. Overall, 119 and 117 patients completed therapy on S/V and G/P. A total of 1 and 3 patients stopped therapy prematurely on S/V and G/P respectively (including one opiate overdose-related death on each of S/V and G/P). Excluding these individuals, SVR12 was achieved in 115/119 (96.6%) and 114/117 (97.4%) subjects on S/V and G/P, with all non-SVR12 events being due to virologic relapse. **Conclusion:** We have evaluated two highly effective regimens in a group of inner-city PWUD. By mITT, 97% of participants were cured, with no difference between treatments. Our data supports the offer of both treatments within the setting of this program for the treatment of HCV-infected PWUD, irrespective of the level of stability.

Disclosures: Shana Yi: Nothing to Disclose, Rossitta Yung: Nothing to Disclose, Shawn Sharma: Nothing to Disclose, Brian Conway: Nothing to Disclose

1475 | HEPATITIS C MANAGEMENT OF WOMEN IN THE THIRD TRIMESTER OF PREGNANCY IN LA BODEGA

Anthony Martinez[1] Scott Springer[2] Ali Aijaz[1] Nariman Hossein-Javaheri[1] Tricia Formato[2] Michelle Clark[2]

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Background: The World Health Organization aims to eliminate HCV by 2030, but the U.S. is projected to reach this goal by 2037. An estimated 2.7-3.9 million Americans are chronically infected, with 1 in 3 treated and only 1 in 4 under age 40. HCV prevalence among pregnant women increased 16-fold from 1998-2018 and 31-fold among women aged 21-30. La Bodega has treated around 5000 people, with over 1200 active People Who Use Drugs (PWUD), achieving a 91% adherence rate and a 95% SVR rate. New York State Medicaid now allows same-day HCV treatment starts without restrictions or prior authorization, while Medicare and commercial plans require prior authorization but have no restrictions. La Bodega combines hepatology and addiction medicine with on-site phlebotomy and pharmacy, facilitating same-day treatment starts. **Methods:** Patients come from addiction centers, syringe exchanges, high-risk obstetrics, Planned Parenthood, incarceration systems, drug courts, and referrals. Telemedicine is used for rural patients. Case managers and social workers schedule appointments within three days. Patients choose their HCV regimen unless co-morbidities dictate otherwise. Additional services include addiction therapy, medically assisted therapy (MAT), PrEP, and HIV management. Patients are grouped into same-day start, Medicare next-day rapid start, and next-day telemedicine start. Active drug use is defined as use within the past six months. **Results:** Thirteen women were evaluated in the third trimester; two treated with ledipasvir/sofosbuvir achieved SVR. Nine began sofosbuvir/velpatisvir; six achieved SVR, three remain on treatment, two were lost to follow-up, one before and another after starting therapy. The overall SVR rate is 100% among those with available data. Six women treated with sofosbuvir/velpatisvir began therapy the same day using a test and treat model; three achieved SVR, three are pending. Two women were on MAT, and four started buprenorphine with HCV treatment while actively using narcotics. No cases of vertical transmission have been reported, and all women self-reported complete adherence. **Conclusion:** Treatment with sofosbuvir-based regimens in the third trimester results in high SVR rates among high-risk women with HCV. Using a test and treat model for pregnant women actively using drugs improves HCV treatment starts, SVR rates, and reduces vertical transmission. Third-trimester HCV therapy can also help initiate MAT for those actively using substances.

Disclosures: Anthony Martinez: Gilead: Consultant, Gilead: Speaking and Teaching, Abbvie: Consultant, Abbvie: Speaking and Teaching, Arbutus: Consultant, Braeburn: Speaking and Teaching, Sirtex: Consultant, Roche: Consultant, Syneos/VBI: Consultant, Madrigal: Speaking and Teaching, Altimune: Consultant, Scott Springer: AbbVie: Advisory board, Speaker bureau, GIlead Sciences: Advisory board, Speaker bureau, Ali Aijaz: Nothing to Disclose, Nariman Hossein-Javaheri: Nothing to Disclose, Tricia Formato: Nothing to Disclose, Michelle Clark: Nothing to Disclose

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1476 | HEPATITIS C TREATMENT UPTAKE DIFFERS BY GENDER AMONG A COMMERCIALLY INSURED POPULATION IN THE UNITED STATES

Alice Stead[1] Catherine Frenette[1] Stacey Federman[1] Wenyi Wang[1] Laura Telep[1] Anand Chokkalingam[1] Amanda Singer[1] Nadege Gunn[2]

[1]Gilead Sciences, [2]Impact Research Institute

Background: Despite the availability of curative direct-acting antivirals (DAAs) for Hepatitis C virus (HCV) infection, observational studies show mixed results around treatment uptake by gender, particularly among people who inject drugs (PWID) or people with mental health disorders (MHDs). This analysis examines differences in DAA initiation and completion rates among individuals with HCV infection in the United States. **Methods:** IQVIA PharMetrics Plus administrative claims data were used to identify adults (≥18 years) between 01Jan2017 and 31Dec2022 with evidence of HCV and no evidence of prior DAA treatment, HIV, or Hepatitis B infection. Continuous enrollment (CE) was required for 365 days prior to first HCV diagnosis (index date), during which PWID and MHD status were assessed. Treatment initiation was defined as evidence of DAA dispensing after index date; treatment completion was defined as evidence of ≥8 weeks of treatment among individuals with ≥9 weeks of CE after treatment initiation. Unadjusted incidence rates (IRs) of treatment initiation per 100-person years with 95% confidence intervals (CIs) were calculated, stratified by age and gender. **Results:** Among 223,211 individuals identified with HCV, 91,632 (41.1%) were women and a majority (56.3%) were ≥55 years old. A total of 28,430 (12.7%) individuals were identified as PWID, of which nearly 40% were between the ages of 18 and 34. Additionally, 73,794 (33.1%) individuals had a history of MHDs. Overall, 24.4% of women and 28.6% of men started treatment during the study period. DAA initiation rates were lower among women than men in all three groups, particularly among PWID (IRR 0.75, 95% CI 0.71 – 0.80). By age, 18-34-year-old female PWID were 35% less likely to initiate treatment compared to male PWID of the same age (IRR 0.65, 95% CI 0.59 – 0.71); similar results were evident across all age groups of PWID <65 years old. Females with a history of MHDs had lower treatment initiation rates across all age groups <65 years old, with lowest rates among 35-44-year-olds (IRR 0.64, 95% CI: 0.58 – 0.71). Of the 57,285 individuals with adequate follow-up after treatment initiation, 86.9% completed ≥8 weeks of treatment, with no notable differences by gender. **Conclusion:** Women with HCV are initiating DAA treatment less frequently than men, most notably among younger age groups. These data highlight a need for gender-specific efforts to engage women, particularly younger women, in HCV treatment.

Treatment Initiation Rates of Females Compared to Males Among HCV Overall and Among PWID and MHD Subgroups

Cohort	Sex	HCV Infection n	Initiated Treatment n (%)	Total FU (PY) After Treatment Initiation	N Individuals Initiating Treatment/100 PY	IRR (95% CI)
HCV	Total	223,211	59,958 (26.9)			
	Female	91,632	22,385 (24.4)	239,353	9.4	0.83 (0.81 – 0.84)
	Male	131,579	37,573 (28.6)	332,264	11.3	ref
HCV/PWID	Total	28,430	6,107 (21.5)			
	Female	12,172	2,231 (18.3)	23,512	9.5	0.75 (0.71 – 0.80)
	Male	16,258	3,876 (23.8)	30,762	12.6	ref
HCV/MHD	Total	73,794	16,979 (23.0)			
	Female	35,214	7,568 (21.5)	79,311	9.5	0.83 (0.80 – 0.86)
	Male	38,580	9,411 (24.4)	82,154	11.5	ref

CI=confidence interval, FU=follow-up, HCV=Hepatitis C Virus, IRR=incidence rate ratio, MHD=mental health disorder, PWID= person who injects drugs, PY=person-year

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1477 | TRANSIENT ELASTOGRAPHY IN THE ED ENHANCES TRIAGE OF HEPATITIS C VIRUS PATIENTS COMPARED TO FIB-4

Morgan Stacey[1] Jordan Arnold[1] Maribeth Wright[1] Lindsey Sheehan[1] Christian Rhudy[1] Daniel Moore[2]

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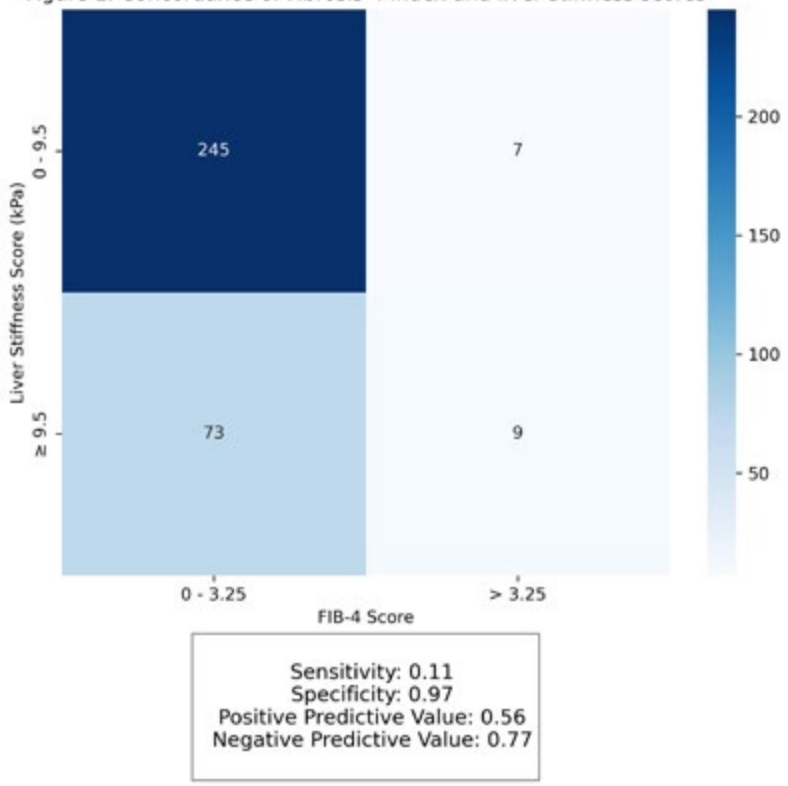
Background: National guidelines use non-invasive fibrosis assessment tools including Fibrosis-4 (FIB-4) and transient elastography (TE) to define criteria for specialist referral for patients infected with hepatitis C virus (HCV). This study is the first to examine concordance of FIB-4 results with TE in the detection of advanced fibrosis of HCV patients in an Emergency Department (ED) setting. **Methods:** This retrospective study examined the concordance of FIB-4 with TE in patients evaluated within a novel, pharmacy-led HCV model of care at an academic ED between June 1, 2023 and May 1, 2024. Patients were excluded if they did not have both a TE and FIB-4 evaluation within 30 days, if the TE study was interpreted as unreliable, had an alanine aminotransferase lab value greater than five times the upper limit of normal, or if the patient had eaten/drank within three hours prior to the TE study. Patient demographics and clinical data were collected from TE procedure documentation. Concordance was evaluated by accuracy, sensitivity, specificity, and positive/negative predictive values (PPV/NPV) of FIB-4 as compared to TE results. FIB-4 indices > 3.25 were considered predictive of advanced fibrosis, while TE liver stiffness score values ≥ 9.5 kPa defined advanced fibrosis. **Results:** 423 patients met inclusion criteria, and 89 patients were excluded. Of 357 patients reviewed, median age was 43, with 70.3% (n = 235) below the age of 50. Demographics were predominantly male (60.8%; n = 203), non-Hispanic white (94.6%, n = 316), and insured by Medicaid (72.4%; n = 242). Median BMI was 26.16 kg/m^2, 82.9% (n = 277) had detectable HCV RNA and 72.5% (n = 242) had a history of injection drug use. The median FIB-4 was 1.01 and the median liver stiffness score was 7 kPa. 16 patients (4.8%) had a FIB-4 index > 3.25 (vs. 318, 95.2%, FIB-4 ≤ 3.25), while 82 (24.6%) had a liver stiffness score ≥ 9.5 kPa (vs. 252, 75.4%, kPa < 9.5). FIB-4 had a sensitivity of 11%, specificity of 97%, NPV of 77%, PPV of 56%, and overall accuracy of 76% in prediction of advanced fibrosis status observed on TE (Figure 1). **Conclusion:** Combining TE with FIB-4 in an ED-based cohort triages the majority of HCV patients to a simplified model of care while also enhancing the sensitivity in identifying patients in need of specialist referral.

Figure 1. Concordance of Fibrosis-4 index and liver stiffness scores



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1478 | COSTS AND OUTCOMES OF A ONE-STEP HEPATITIS C VIRUS RNA POINT-OF-CARE DIAGNOSTIC STRATEGY AMONG PEOPLE WHO INJECT DRUGS IN THE U.S.

Emily Kahn[1] Neda Al Rawashdh[1] Cheryl Ferrufino[1] Mindy Cheng[2]

[1]IQVIA, [2]Cepheid

Background: The U.S. Department of Health and Human Services estimates 2.4M people in the U.S. are infected with hepatitis C virus (HCV), >50% unaware of their infection status. Injection drug use is the most common risk factor, accounting for 60% of infections. The standard HCV diagnostic algorithm (SOC) includes an antibody (AB) test followed by a confirmatory HCV RNA test for those with HCV AB detected. SOC is associated with high rates of patients lost to follow-up (LTFU) and low diagnosis and treatment (Tx) rates, especially among high-risk populations. This study examines costs and outcomes of a one-step HCV RNA point-of-care (POC) diagnostic strategy (POC_RNA) compared to SOC among people who inject drugs (PWID). **Methods:** A decision tree model projected costs and outcomes associated with POC_RNA and SOC from the Medicaid perspective given expanded coverage of many PWID. The model assumed HCV testing in outpatient settings; each person was tracked through Tx initiation. Model inputs included HCV AB and RNA prevalence, test performance, linkage to care (LTC) rates, Tx initiation, clinic visit and testing costs. All model inputs were sourced from published literature. Clinical outcomes included the proportions of correctly diagnosed HCV cases, LTC, LTFU (1-LTC), Tx initiation, and cases averted through reduced transmission. Incremental cost effectiveness ratios were calculated for key outcome measures. **Results:** Among the model cohort with active HCV infection, POC_RNA identified 100.0% of cases compared to 98.0% with SOC. Among those correctly diagnosed, 100.0% in POC_RNA were LTC (0% LTFU) and 56.9% were Tx initiated vs. 23.0% LTC (77.0% LTFU) and 4.1% Tx initiated in SOC. The POC_RNA strategy was projected to reduce first generation transmitted cases by 42.6% compared to SOC. The total testing cost per Medicaid beneficiary was $187.70 for SOC vs. $113.60 for POC_RNA. POC_RNA was the dominant testing strategy, yielding lower costs and improved outcomes. **Conclusion:** A POC_RNA testing strategy was estimated to diagnose more active HCV infections resulting in immediate linkage to care and increase in Tx initiation among PWID when compared to SOC. The total cost per Medicaid beneficiary of POC_RNA was lower than SOC. Combined with additional cost-savings expected from reduced disease transmission, this study suggests that a one-step HCV RNA POC diagnostic strategy is optimal for high-risk populations and critical to support U.S. HCV elimination goals.

Disclosures: Emily Kahn: Cepheid: IQVIA received funding from Cepheid to perform the analysis, Neda Al Rawashdh: Nothing to Disclose, Cheryl Ferrufino: Cepheid: IQVIA received funding from Cepheid to perform analysis, Mindy Cheng: Nothing to Disclose

1479 | TRENDS IN HCV SCREENING, FOLLOW-UP TESTING, AND TREATMENT IN PREGNANT PEOPLE AND INFANTS IN A TERTIARY CARE CENTER

Randeep Kaur[1] Jennifer Price[1] Jasmine Gamez[1] Emily Perito[1] Annie Luetkemeyer[1] Dominika Seidman[1] Monika Sarkar[1]

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Background: Hepatitis C virus (HCV) screening is universally recommended in pregnancy, though uptake of screening, performance of confirmatory viral load testing, or receipt of antiviral therapy during the peripartum period are not well described. **Methods:** This was a retrospective chart review of birthing parents and infants who delivered at an urban academic medical center from 1/1/2014 to 3/9/2023. **Results:** From 1/2014-3/2023, we identified 25,241 pregnant people with deliveries at our center, of whom 6,944 received HCV Ab screening (27.5%). HCV screening rates increased over time from 4% in 2014 to 66% in 2022 (p <0.001) (Figure). 58 (0.84%) tested positive for HCV Ab of whom 52 (89.7%) received follow-up HCV RNA testing during pregnancy, while 5 had viral load testing postpartum, prior to hospital discharge. Of the 32/57 (56.1%) with confirmed HCV

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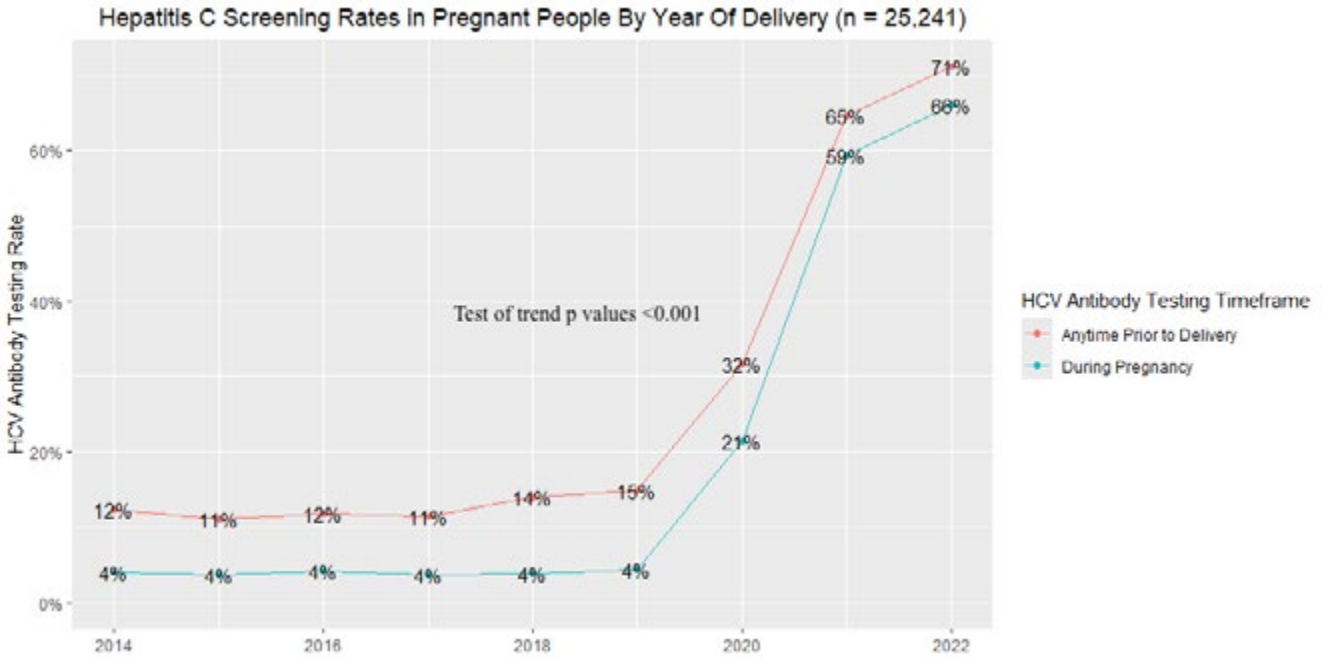
viremia, 21 (65.6%) were referred to outpatient hepatology and 2 (6.3%) also had inpatient consults. Of the 11 without HCV-related consults, 7 (77.8%) were advised on discharge summaries to follow-up with primary care for HCV management. Of the 32 with viremia, none received antiviral therapy during pregnancy; 9 (28.1%) received postpartum antiviral therapy (3 with ledipasvir-sofosbuvir, 1 with daclatasvir-sofosbuvir, 1 with elbasvir-grazoprevir, 1 with velpatasvir-sofosbuvir, 3 with unknown regimens). The remainder (23/32; 71.9%) were lost to follow-up. Thirty-six infants were exposed to maternal HCV in utero, of whom 15 (41.7%) were pre-term (< 37 weeks). Median birthweight was 6.6 lbs (IQR 5.2-7.0), and 9 (25.0%) were small-for-gestational age. At 1- and 5- minutes post birth, APGAR scores indicated 5 (14.0%) and 3 (8.3%) with moderate distress, and 1 (2.8%) had severe distress at both timepoints. Fifteen infants (42.0%) had available post-discharge data, of whom 8 (53.3%) received HCV screening at a median age of 21.5 months (IQR 19.0-24.3). Of these, 2 were HCV Ab positive, and both received follow-up HCV RNA testing. One had detectable virus, was referred to hepatology, and spontaneously cleared HCV at age 19 months. **Conclusion:** From 2014-2023, HCV screening in pregnancy improved to 66%, but remained much lower than universal screening recommendations. HCV viremia was < 1%, with no identified perinatal transmission. However, 58% of babies and 72% of mothers were lost to follow-up, supporting the need for improved screening as well as referral during pregnancy, postpartum, and for pediatric care.



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1480 | SUCCESSFUL PERFORMANCE OF THE XPERT® HCV TEST FOR POINT OF CARE DETECTION OF HCV RNA IN A CLIA-WAIVED SETTING

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Background: A key pillar of the US National Hepatitis C Elimination Program is improvement in HCV diagnostic testing. Point of Care (POC) HCV tests offer an advantage over current standard of care (SOC) tests, which

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require venipuncture and can take days to result. We performed a prospective study to evaluate the accuracy and ease of use of a POC RNA test using a capillary whole blood (CWB) sample obtained via fingerstick in a CLIA-waived clinical setting. **Methods:** The Xpert® HCV test, performed on the GeneXpert® Xpress System, is an automated qualitative *in vitro* reverse transcription polymerase chain reaction (RT-PCR) test for the detection of HCV RNA using CWB. We performed a prospective study comparing POC HCV RNA testing on the Xpress system to testing on the Cobas 6800 platform. Adult subjects were enrolled from the Grady Health System (Atlanta, GA, USA) Primary Care Center and Liver Clinic. Study staff collected between 250-500 microliter CWB sample via fingerstick and a venous blood sample from each subject. CWB samples were pipetted into Xpert HCV cartridges and run on the Xpress system, which allows up to four samples to be run concurrently and provides results in approximately 1 hour. results were reported as HCV detected, HCV not detected, or error. Venous blood samples were tested for HCV RNA on the Cobas platform and results were compared. **Results:** Of the 109 subjects enrolled in the study, 89 had both valid Xpress and Cobas comparator results and were included in the final analysis. The majority of subjects were male and Black (65% and 82% respectively). On the Xpress system, 16 out of 89 (18%) subjects had an HCV RNA detected result, and 73 (82%) had an HCV RNA not detected result. On the Cobas assay,17 out of 89 (19%) had HCV RNA detected and the remaining 72 (81%) had HCV RNA not detected. Only one sample was detectable on the Cobas assay but not on the Xpress system, yielding a sensitivity of 94% and specificity of 100%. Operators found the device easy to use. **Conclusion:** This is one of the first US studies to assess the accuracy and clinical utility of the Xpert® HCV test. We found that the test provided accurate results and was easy to use in a clinical setting. POC HCV RNA testing can radically improve the HCV care cascade, allowing for accurate HCV diagnosis in a fraction of the time compared to current SOC, thereby facilitating rapid treatment starts. POC HCV testing promises to be a critical tool in US HCV elimination efforts.

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1481 | EFFICACY AND SAFETY OF FOUR-WEEK GLECAPREVIR/PIBRENTASVIR TREATMENT IN KIDNEY TRANSPLANTS FROM HEPATITIS C VIRUS POSITIVE DONORS TO NEGATIVE RECIPIENTS

Allison Carroll[1] *Meghan Sise*[1] *ann mini*[1] *Jenna Gustafson*[1] *Elias Nahel*[1] *Raymond Chung*[1]

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Background: Approximately 93,000 patients in the U.S. are on the waitlist for a kidney transplant (KT). [1] The number of hepatitis C virus (HCV) positive donor to HCV negative recipient KTs have increased, with recipient acceptance growing twenty-fold from 2015 to 2022. [2] A previous multi-center trial demonstrated a 100% sustained virological response rate (SVR) and excellent patient and graft outcomes at one year post-KT with an 8-week course of glecaprevir/pibrentasvir (G/P). [3] However, the efficacy and safety of shorter G/P courses post-transplant have not been thoroughly studied. **Methods:** In this open-label, single-center, interventional clinical trial, 18 HCV negative patients agreed to receive KT from HCV RNA-positive donors. Two patients underwent KT from an HCV-infected donor and began G/P (300mg/120mg) within 24 hours post-KT and received once daily dosing for four weeks. Post-KT monitoring included vital signs, liver function tests (LFTs), HCV antibodies and RNA at two- and four-weeks post-KT, and at 12 weeks, one year, and two years post-treatment. Key outcomes were death, graft failure, acute rejection, delayed graft function, and LFT abnormalities. **Results:** Patient 1: 32-year-old Asian, non-Hispanic female (CMV+/EBV+) with ESKD from chronic glomerulonephritis who was on hemodialysis (HD) and waitlist for 6 years before KT. She received an HCV Ab+/PCR+/CMV-/EBV+ KT (KPDI 50). She had undetectable HCV viremia at all timepoints 2 years post-KT. She experienced biopsy-confirmed antibody mediated rejection and active cellular rejection at 96- and 108-weeks post-transplant treated with IVIG/Rituximab and intravenous solumedrol, respectively. This was deemed by investigators to be unrelated to receipt of her HCV-infected KT. eGFR at 2 years was 62 mL/min per 1.73m2. Patient 2: 78-year-old white, non-Hispanic female (CMV+/EBV+) with ESKD from hypertension on HD for 2 years, on the waitlist for 5 years prior to KT. She received an HCV Ab+/PCR+/CMV+/EBV+ KT (KPDI 42). She had undetectable HCV viremia at all timepoints

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2 years post-KT. Patient 2 did not encounter any complications related to G/P treatment, LFT abnormalities, rejection or graft failure; eGFR at 2 years was 38 mL/min per 1.73m2. **Conclusion:** This study contributes to the expanding data on the successful use of a shorter, four-week pre-emptive G/P treatment regimen in high quality KT from HCV positive donors to negative recipients.

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Disclosures: Allison Carroll: Nothing to Disclose, Meghan Sise: Nothing to Disclose, ann mini: Nothing to Disclose, Jenna Gustafson: Nothing to Disclose, Elias Nahel: Nothing to Disclose, Raymond Chung: Nothing to Disclose

1482 | UNCOVERING ONCOGENIC EFFECTS OF HCV IN NON-CIRRHOTIC HEPATOCELLULAR CARCINOMA: NEW MOLECULAR MARKERS AND GENETIC PREDISPOSITIONS IDENTIFIED BY WHOLE EXOME SEQUENCING ◆

Yongjun Liu[1] Duncan Hussey[2] Angela Zou[3] Matthew Yeh[2] Yajuan Liu[2]

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Background: Hepatitis C virus (HCV) infection is the leading cause of hepatocellular carcinoma (HCC) in the United States. While HCV is traditionally linked to oncogenesis through inflammation and subsequent cirrhosis, recent evidence, including our studies, suggests that some HCV-associated HCC cases arise in non-cirrhotic livers. This suggests HCV may directly contribute to oncogenesis in certain patients. This study aims to explore genetic predispositions to HCV-related non-cirrhotic HCC and identify abnormal tumor mutations in this patient population. **Methods:** Formalin-fixed-paraffin-embedded blocks of surgically resected HCC and background liver tissue were subjected to DNA extraction and whole-exome sequencing from 9 non-cirrhotic and 5 cirrhotic HCV-related HCC patients. All the patients were confirmed negative for aflatoxin exposure and hepatitis B coinfection. The deleterious nature of genetic variants were assessed using known allele frequencies in the general population (gnomAD), CADD (Combined Annotation Dependent Depletion), and PolyPhen scores. **Results:** Analysis of tumor samples revealed no significant differences in somatic mutations between non-cirrhotic and cirrhotic HCC samples. CTNNB1 was the most commonly mutated gene, consistent with its known role in HCC oncogenesis. Additionally, recurrent mutations in *CDC27, HERC2, GRID2, PABPC1*, and *SCN9A* were found, although these are not commonly reported in the literature. Sequencing non-neoplastic tissues revealed mutations enriched in non-cirrhotic samples, including ERAP2, NEB, DNAH10, DNAH2, DCDC2C, SPEG, ZFHX4, and SPERT. Notably, mutations in ERAP2 were identified in non-neoplastic tissues from 4 non-cirrhotic HCC patients (Table 1). ERAP2 encodes an endoplasmic reticulum aminopeptidase involved in the antigen presentation pathway, responsible for presentating viral polypeptides on MHC-I receptors. Mutations in other genes within the antigen presentation pathway, ERAP1 and TAP1, were identified in non-neoplastic tissues from an additional 2 non-cirrhotic HCC patients (Table 1). **Conclusion:** Although there is no significant difference in tumor somatic gene mutations between non-cirrhotic and cirrhotic HCC samples, enriched germline mutations (particularly ERAP2) were found in non-neoplastic tissue in non-cirrhotic samples. These findings suggest that altered antigen presentation might affect immune recognition and viral response, potentially contributing to HCV-related carcinogenesis - a mechanism not previously recognized. Our findings may have clinical implications for patient surveillance and management. Gene sequencing in additional non-cirrhotic HCV-related HCC samples will be pursued to further investigate the role of the antigen presentation pathway in HCC oncogenesis.

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Table 1.

Patient	Gene	g.[hg38]	HGVS.c	HGVS.p	CADD[a]	PolyPhen[b]	gnomAD_AF
NL-01	ERAP2	g.96,892,368	c.1040C>T	Thr347Met	23.8	0.993	0.03
NL-03	ERAP2	g.96,883,857	c.641C>T	Pro214Leu	25.2	0.998	0.01
NL-07	ERAP2	g.96,892,368	c.1040C>T	Thr347Met	23.8	0.993	0.03
NL-08	ERAP2	g.96,883,857	c.641C>T	Pro214Leu	25.2	0.998	0.01
	ERAP2	g.96,903,554	c.2006T>A	Leu669Gln	25.4	0.985	0.05
NL-09	ERAP1	g.96,800,974	c.551C>G	Pro184Arg	27.7	0.997	0.0005
NL-06	TAP1	g.32,845,703	c.2123A>G	Gln708Arg	20.3	1	ND

Note:
[a]The Combined Annotation Dependent Depletion (CADD) scores >20 indicates the top 1% of deleterious SNVs and insertion/deletion variants.

[b]The PolyPhen-2 score ranges from 0.0 (tolerated) to 1.0 (deleterious). Variants with scores of 0.0-0.15 are predicted to be benign. Values closer to 1.0 are more confidently predicted to be damaging.

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1483 | LONG TERM OUTCOME FOLLOWING HCV TREATMENT WITH GLECAPREVIR/PIBRENTASVIR IN PEOPLE WHO USE DRUGS

Shana Yi[1] *Rossitta Yung*[1] *Shawn Sharma*[1] *Brian Conway*[1]

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Background: Several studies, including the recently published GRAND PLAN study from our centre, have demonstrated the efficacy of HCV therapy among active drug users, including those facing significant addiction-related and social challenges. In GRAND PLAN, we documented SVR12 in 108/117 (92.3%) participants (108/111 (mITT) 97.3% SVR12) receiving an 8-week course of Glecaprevir/Pibrentasvir, with almost all using fentanyl and over half being unstably housed. Data on the maintenance of such a positive outcome in the long term in such a population with a significant risk of reinfection are limited. We hypothesized that the offer of ongoing multidisciplinary care after SVR12 was achieved would reduce the likelihood of loss to follow up, HCV reinfection/death and consolidate the gains achieved by initial engagement in care to diagnose and treat HCV infection. **Methods:** The inception cohort for this analysis was the 108 individuals achieving a cure of HCV infection within the study. All were offered the opportunity to continue to receive care at our centre. This is a multidisciplinary model of care to address medical, mental health, social and addiction-related concerns. This included opiate agonist and safe supply therapy, usually provided by the pharmacy adjacent to our inner-city campus. Among those choosing to be retained in care, the endpoint of this analysis was loss to follow up, mortality and HCV reinfection and their correlates. Reinfection was ascertained by repat HCV RNA testing every 6 months, more frequently if clinically indicated. **Results:** Of the 108 individuals making up the inception cohort for this analysis, all chose to remain in care at our center. We note: median age 47 (22-75) years, 28% female, 21.3% identifying as Indigenous, with 90.8% F0-F2, slightly more than half with unstable housing. We recorded a 20% decrease in fentanyl users among those who were cured compared to the baseline evaluation of the overall study cohort (73.5% vs 94.9%, $p < 0.000001$) . Among the cured participants, 104 (96.3%) remained alive, while 4 individuals died of opioid overdoses over time. Out of the 104 patients, 99 (95.2%) remained HCV-free, while 5 (4.8%) were re-infected. All five have recently initiated repeat HCV therapy at our center, 2 of whom are cured and the other 3 awaiting therapy. **Conclusion:** Among a population of vulnerable inner-city residents cured of HCV infection within a multidisciplinary program of care at our center, all accepted the offer to remain in long-term follow up, with a statistically significant reduction in fentanyl use over time. In the setting of an ongoing opioid crisis where 3 deaths/day are recorded in the neighborhood where the study population resides, we documented only 4 deaths. Reinfections occurred at a very modest rate, with maintenance in care allowing prompt re-treatment, with a cure already being documented in 2/5 cases, with the other 3 individuals remaining in care at our center.

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Disclosures: Shana Yi: Nothing to Disclose, Rossitta Yung: Nothing to Disclose, Shawn Sharma: Nothing to Disclose, Brian Conway: Nothing to Disclose

1484 | VIROLOGIC EFFECT AND HEPATOTOXICITY OF BCR-ABL TYROSINE KINASE INHIBITORS IN CANCER PATIENTS WITH CHRONIC HEPATITIS C VIRUS INFECTION: A PROSPECTIVE STUDY

Khalis Mustafayev[1] Eduardo Yepez Guevara[1] Courtney DiNardo[1] Elias Jabbour[1] Issa Ghayas[1] Ravin Ratan[1] Naveen Pemmaraju[1] Harrys Torres[1]

[1]The University of Texas MD Anderson Cancer Center

Background: Tyrosine kinase inhibitors (TKIs) that target BCR-ABL, such as dasatinib, imatinib, nilotinib, bosutinib, and ponatinib, have revolutionized the treatment of chronic myeloid leukemia (CML), Philadelphia chromosome–positive acute lymphoblastic leukemia (Ph+ALL), and gastrointestinal stromal tumor (GIST). *In vitro*, TKIs inhibit hepatitis C virus (HCV) infection at the entry step of the HCV into hepatocytes and disrupt c-Kit signaling in HCV-associated hepatocellular carcinoma. However, clinical data on the virologic changes of HCV infection following TKIs are limited. We examined the impact of these agents on HCV replication in patients with cancer and chronic infection. **Methods:** Cancer patients with HCV infection who were treated with TKIs at The University of Texas MD Anderson Cancer Center between January 31, 2015, and December 31, 2023, were enrolled in a prospective observational study. Changes in HCV viremia were analysed. In general, patients' serum HCV RNA levels are chronically stable, varying only within 0.5 log IU/mL. Therefore, HCV inhibition was defined as a decrease in HCV RNA level <1 log IU/mL from baseline following treatment with TKIs. HCV reactivation was defined as an increase in HCV RNA level ≥1 log IU/mL over baseline following treatment with TKIs. **Results:** We identified 37 HCV-infected patients with Ph+ALL, CML, or GIST who received Abl TKIs during the study period. Thirty-two patients were excluded because they did not receive therapy and follow up at our institution (26 patients) or had undetectable HCV RNA after antiviral treatment (6 patients). Five patients with viremia were further analyzed (Table 1). The median follow-up period was 24 months (interquartile range [IQR], 13-35 months). Two patients (40%) were treated with direct-acting antivirals (DAA), both concomitantly with TKIs. One achieved a sustained virologic response at week 12, and the other achieved SVR4 but died due to cancer progression. The other 3 patients with viremia were monitored while taking TKIs without DAAs, no cases of HCV reactivation, or HCV-associated liver failure occurred; two patients developed ponatinib-induced grade 2 hepatotoxicity. One patient experienced a decrease in HCV replication during BCR-ABL TKI therapy in the absence of DAA therapy, but without evidence of HCV inhibition (Figure 1C). **Conclusion:** This is the first study to prospectively analyze the impact of BCR-ABL TKIs on HCV. Our preliminary findings suggest that patients with chronic HCV do not develop significant changes in HCV viremia while on BCR-ABL TKIs, but larger studies should be conducted to address the impact of these antineoplastic agents on HCV viremia.

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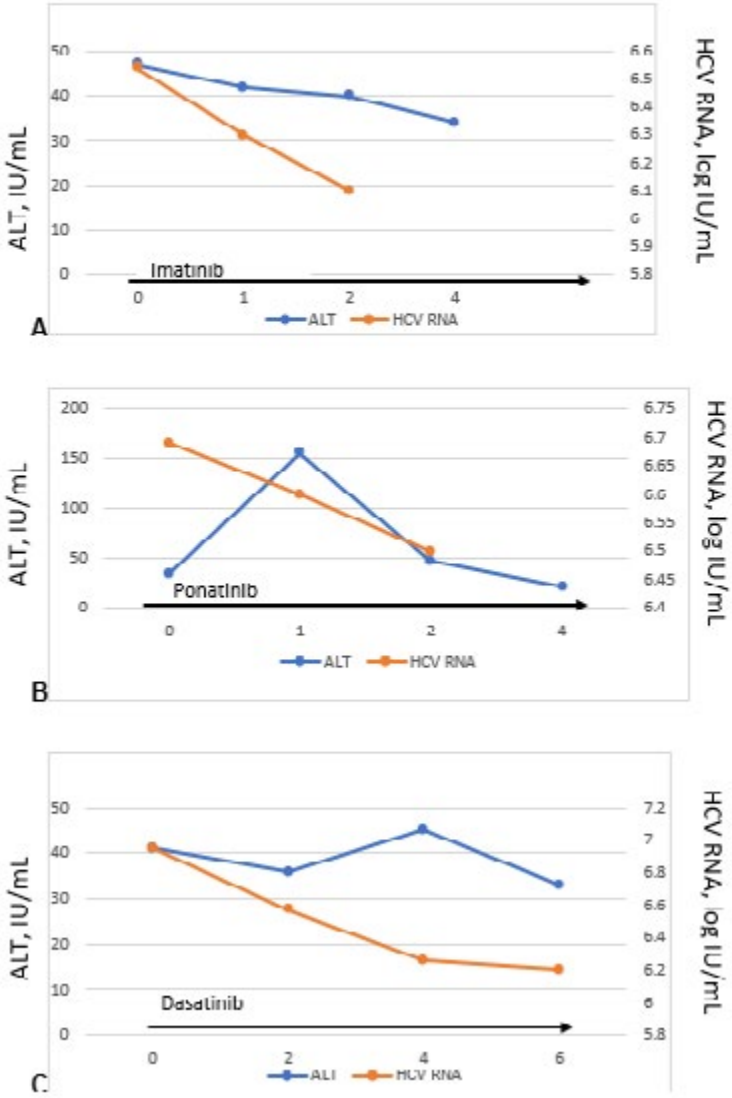
Figure 1. Changes over time in alanine aminotransferase (ALT) level and hepatitis C virus (HCV) viremia in patients with chronic HCV infection with viremia treated with BCR-ABL tyrosine kinase inhibitors. (A) Patient 1. (B) Patient 2. (C) Patient 3.



Disclosures: Khalis Mustafayev: Nothing to Disclose, Eduardo Yepez Guevara: Nothing to Disclose, Courtney DiNardo: Nothing to Disclose, Elias Jabbour: Nothing to Disclose, Issa Ghayas: Nothing to Disclose, Ravin Ratan: Nothing to Disclose, Naveen Pemmaraju: Nothing to Disclose, Harrys Torres: Principal Investigator relationship with Merck; Has ended; Principal Investigator relationship with Gilead; Has not ended

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1485 | ATTEMPT TO PREDICT OUTCOMES IN DAA-TREATED PATIENTS USING MACHINE LEARNING WITH HEPATITIS C VIRUS AND HUMAN GENETIC INFORMATION

Hiroaki Haga[1] Hidenori Sato[1] Kyoko Hoshikawa[1] Tomohiro Katsumi[1] Keita Maki[1] Fumiya Suzuki[1] Fumi Uchiyama[1] Yoshiyuki Ueno[1]

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Background: In the field of disease genome analysis, recent advancements have been made in using machine learning for gene selection (dimensionality reduction) to uncover novel relationships between clinical phenotypes and genes. We explored the potential of this approach using machine learning-based gene selection. **Methods:** Following ethical guidelines for human genome analysis and obtaining informed consent, we analyzed exome data from 35 individuals and whole genome sequencing (WGS) data of serum-derived HCV genomes. We calculated the total functional variants for each gene, resulting in normalized data for 12,948 genes (12,937 human genes and 10 HCV genes) from 158,232 variants. We evaluated three gene selection methods embedded methods, filter methods, and wrapper methods. For each selected gene, we performed OPLS analysis and NMF analysis to identify genes contributing to platelet (PLT) changes one year after DAA treatment (cutoff value 1.0 x 10^4). We assessed the importance of the identified genes using machine learning and compared these results with traditional gene enrichment analysis. **Results:** Enrichment analysis of all genes (12,948 genes) did not identify any significant genes. Gene selection methods identified 374 genes using the filter method and 140 genes using the wrapper method. OPLS-DA analysis of all genes did not show significant differences, but significant differences were observed in genes selected through gene selection. NMF analysis produced basis components that classified the PLT change groups similarly. Machine learning models showed high discriminative ability with gene sets selected through gene selection methods, particularly with svmRadial, rf, pls, mlp, and kknn. Genes evaluated as important by 12 machine learning models exhibited some variation in ranking based on gene selection methods but largely overlapped. Genes with functional variants in both PLT improvement and non-improvement groups were identified, many of which were related to liver disease and fibrosis. **Conclusion:** While enrichment analysis influenced by multiple testing P-values did not yield significant results in group comparisons, gene combinations obtained through machine learning-based gene selection revealed multiple genes associated with liver dysfunction. This suggests that gene selection is effective in genome-wide genetic analysis.

Disclosures: Hiroaki Haga: Nothing to Disclose, Hidenori Sato: Nothing to Disclose, Kyoko Hoshikawa: Nothing to Disclose, Tomohiro Katsumi: Nothing to Disclose, Keita Maki: Nothing to Disclose, Fumiya Suzuki: Nothing to Disclose, Fumi Uchiyama: Nothing to Disclose, Yoshiyuki Ueno: Nothing to Disclose

1486 | A DISAGGREAGTED GENDER-BASED APPROACH TO UNDERSTANDING HCV AMONG WOMEN: DESCRIPTIVE ANALYSIS OF THE CANADIAN NETWORK UNDERTAKING AGAINST HEPATITIS C (CANUHC) COHORT FROM 2015 TO 2023

Mia Biondi[1] Haris Imsirovic[2] Jordan Feld[3] Hongqun Q Liu[4] Samuel Lee[4] Curtis Cooper[5]

[1]York University, [2]Ottawa Hospital Research Institute, [3]Toronto General Hospital, [4]University of Calgary, [5]The Ottawa Hospital

Background: There are 15,000,000 women of childbearing potential living with HCV globally, and a 20% increase among women in high-income countries in the last 25 years. As a result, there has been a call for a gender-based approach to HCV elimination in line with country-level indicators, yet few studies have described disaggregated data for cis and trans women cross-sectionally. **Methods:** The Canadian Network Undertaking against Hepatitis C (CANUHC) cohort contains prospectively collected, patient-level data including demographic, lifestyle, fibrosis staging, co-morbidities, and treatment, from 17 HCV clinics in Canada from 2015 to 2023. We describe a cohort of individuals whose biological sex was identified as female; whose biological sex was identified as male but gender as trans; or with self-identified gender as woman. Patients were followed from their index assessment until SVR assessment date. **Results:** 1,167 were included which was 36% of the complete CANUHC cohort. Ages ranged from 17-89 years (mean 48.8 (14.0 SD)); most identified as Caucasian (64%); 15 (1.3%) self-identified as trans; and 73% had children. While 72% had a history of injection drugs, 74% were not on opiate agonist therapy (OAT); 37% had a psychiatric diagnosis; and 11% had housing insecurity. Notably, 68% did not use alcohol. Mean APRI score was 0.8 (1.1), and 17% were cirrhotic. Within the cirrhosis group, the mean age was 10.4 years higher than

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overall, and 13% had decompensation. Newcomers and immigrants (7.1% difference), those with diabetes (7.2% difference), and those using drugs (15% difference) were overrepresented in the cirrhosis group. In the overall cohort, 6% were reinfected, with the greatest overrepresentation among those living with HIV (9.2% difference), a psychiatric diagnosis (17% difference), incarceration (18% difference), drug use (15% difference), high risk sexual activities (18% difference). 1,040 (89%) initiated DAA treatment, with 99% SVR (available data). **Conclusion:** This cohort describes cis and trans women with HCV and has the potential for clinical implications. In terms of liver disease, fibrosis scores were low, and women rarely used alcohol. This finding may support rapid treatment starts even in the absence of a comprehensive work-up among women. From a harm reduction perspective, strikingly, despite high HCV treatment initiation rates, OAT uptake was poor, an observation which may support co-localizing HCV treatment with OAT initiation to prevent drug use relapse and reinfection.

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1487 | DEFAULT HEPATITIS C SCREENING AND PROACTIVE LINKAGE TO CARE AMONG HOSPITALIZED ADULTS

Lina Yagan[1] Rebecca Russell[2] Siquette Williams[3] Julia Gasior[3] Matty Zimmerman[4] Jean O'Neal[4] Alexis Schwartz[2] Dena Carbonari[3] Vincent Lo Re[3] Jessie Torgersen[3]

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Background: Hepatitis C virus (HCV) is the most common bloodborne infection in the US yet remains underdiagnosed. Expansion of HCV screening to all adults 18-79 years old has been recommended since 2020; however, best practices for implementing such screening and linking to HCV treatment within hospital settings are not well defined. **Methods:** We conducted a retrospective cohort study to identify factors associated with successful care engagement, defined as attending ≥1 HCV provider appointment following an inpatient HCV diagnosis. Admitted patients born between 18-79 years old without prior HCV diagnosis or documentation of HCV screening had a default order for HCV antibody testing with reflex to confirmatory RNA testing embedded in the admission order set. This quality improvement initiative began October 16, 2023 across six academic hospitals in Southeastern Pennsylvania and New Jersey within the Penn Medicine health system. Results from the default order were automatically routed to the Hepatitis Linkage Team and viremic patients were then proactively contacted by a Nurse Navigator to link to outpatient care. Patients screened through January 20, 2024 and followed through May 19, 2024 were included. Data collected from the time of hospital admission included age, gender, race, insurance status, presence of substance use disorder (SUD), length of stay, polypharmacy, having a primary care provider, and discharge disposition. Prescription of a direct acting antiviral (DAA) before end of follow-up was abstracted from chart review. Comparison of variables by HCV care engagement status were completed using chi2 and Fisher exact tests for binary or categorical variables and Wilcoxon rank sum for continuous variables. **Results:** During the first three months, 7,539 patients were screened across the six hospitals, identifying 221 (2.9%) with reactive HCV antibody. Of 213 patients with sufficient sample for confirmatory viral load, 64 (30.0%) had HCV viremia. Of these 64 patients, 39 (60.9%) were linked to a HCV-treating provider, 17 (26.5%) were lost to follow-up before linkage, 5 (7.8%) were not linked due to terminal illness, and 3 (4.5%) deferred linkage. Of the 39 patients linked to care, 16 (41.0%) attended ≥1 appointment with an HCV provider. Patients who engaged in care were older, had a primary care provider, were more commonly discharged home, and less likely to have SUD or Medicaid insurance (Table 1). Of those engaged in care, 14 (87.5%) were initiated on DAAs with SVR12 documented in two patients. **Conclusion:** Default HCV screening for all adults can increase diagnosis of HCV infection and offers an opportunity to link patients to curative treatment in real time. Early engagement and robust care transitions services are needed to decrease barriers to HCV curative

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treatment. Further work is needed to investigate optimal approaches to facilitate care engagement following hospital discharge among people with SUD.

Table 1: Characteristics of patients with HCV viremia identified by inpatient screening program, by status of care engagement following linkage to HCV-treating provider.

Characteristic*	Engaged in HCV Care (n=16)	Not Engaged in HCV Care (n=23)	*P*
Median age, years (IQR)	63.5 (58.5, 67)	48 (33, 58)	**0.005**
Male	12 (75%)	12 (52.2%)	0.15
Marital Status			0.09
Single	8 (50.0%)	19 (82.6%)	
Married/Partner	5 (31.3%)	2 (8.7%)	
Divorced/Widowed/Separated	3 (18.8%)	2 (8.7%)	
Race			0.27
Black/African American	8 (50.0%)	8 (34.8%)	
White	8 (50.0%)	12 (52.2%)	
Other	--	3 (13.0%)	
Employment Status			0.14
Employed	4 (25.0%)	3 (13.1%)	
Unemployed	3 (18.8%)	10 (43.5%)	
Retired	5 (31.3%)	2 (8.7%)	
Disabled/Not Listed	4 (25.0%)	8 (34.8%)	
Had a Primary Care Provider	14 (87.5%)	9 (39.1%)	**0.003**
Median length of stay, days (IQR)	5 (2, 7.5)	5 (3, 13)	0.35
Polypharmacy†	12 (75.0%)	16 (69.6%)	0.71
Discharge Disposition			**0.02**
Home	11 (68.8%)	8 (34.8%)	
Skilled nursing facility/Rehab	4 (25.0%)	9 (39.1%)	
Shelter/Supportive Housing	--	6 (26.1%)	
Patient Directed Discharge	1 (6.3%)	--	
Current substance use disorder‡	3 (18.8%)	19 (82.6%)	**<0.001**
Insurance status			**0.006**
Medicare	9 (56.3%)	5 (21.7%)	
Medicaid	5 (31.3%)	18 (78.3%)	
Commercial/Other	2 (12.5%)	--	
Median time to first scheduled HCV visit, days (IQR)¶	21.5 (9, 34.5)	23.5 (14, 36)	0.52

Abbreviations: HCV, hepatitis C virus; IQR, interquartile range
*Percentages presented in parentheses unless otherwise stated.
†Defined as ≥5 prescribed medications at time of hospital discharge; co-formulated medications counted as single medication.
‡Defined by substance use disorder diagnosis with substance use reported in prior 12 months.
¶Data missing on one person linked to out-of-state HCV provider.

Disclosures: Lina Yagan: Nothing to Disclose, Rebecca Russell: Nothing to Disclose, Siquette Williams: Nothing to Disclose, Julia Gasior: Nothing to Disclose, Matty Zimmerman: Nothing to Disclose, Jean O'Neal: Nothing to Disclose, Alexis Schwartz: Nothing to Disclose, Dena Carbonari: Nothing to Disclose, Vincent Lo Re: Urovant Sciences: Consultant, Entasis: Consultant, Jessie Torgersen: Nothing to Disclose

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1488 | ENGAGING COMMUNITY PHARMACIES WITHIN HEPATITIS C (HCV) TEST AND TREAT NETWORKS TO ENHANCE ACCESS TO CARE FOR KEY POPULATIONS LIVING WITH HCV: EXPERIENCE FROM ALBERTA, CANADA

Jenny Godley[1] Christine Hughes[2] Cari Egan[3] Helena Atkinson[4] Klaudia Zabrzenski[5] Colter Young[6] Jaanek Grewal[7] Chinedu Diribe[1] Daniyal Khan[1] Mark Swain[1]

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Background: A significant challenge facing HCV elimination programs involves finding and linking to care people living with HCV within underserved populations that do not/cannot regularly access healthcare, including the unhoused and those with active/historical injection drug use. The Alberta LiveRx study was co-designed with people with lived experience of HCV to reduce these health disparities by increasing equitable access to trained community pharmacists that test (using point-of-care testing/dried blood spot; POCT/DBS) and prescribe HCV treatment for viremic individuals in urban centers across Alberta, Canada. **Methods:** Upon enrollment, pharmacies were encouraged to engage with other LiveRx pharmacies and relationships were facilitated with local community-based organizations (CBOs). Social network analysis was employed to measure how pharmacies' HCV client referral and information gathering networks have changed since engaging with the LiveRx project. Pharmacist HCV training included customized HCV e-modules and in-person/virtual webinars co-developed by LiveRx and INSHU, hands-on POCT/DBS training, and ongoing support by LiveRx consultants. Each pharmacy reported the number of clients screened, viremic HCV patients identified, and percent of cases successfully linked to HCV treatment. **Results:** Pharmacists' HCV patient referral and information sharing networks diversified after enrolling in LiveRx, with more pharmacies receiving HCV referrals from CBOs, Public Health, and physicians and more pharmacies sharing information with CBOs, Public Health and other pharmacies. All pharmacists reported that their knowledge about HCV increased (Table 1). To date, 13 of 21 pharmacies (62%) have screened 327 patients for HCV with POCT/DBS testing, 60 of whom (18%) were viremic. An additional 28 viremic cases were identified through LiveRx supported in-pharmacy case finding programs. Over 50% of identified HCV viremic cases (45/88) have started direct acting antiviral (DAA) treatment, and 42% of those who started DAA's (19/45) have completed treatment to date. **Conclusion:** Engaging community pharmacists with HCV-related training and cultivating intersectoral collaboration with CBOs and Public Health fosters a wrap-around care model for underserved populations. The LiveRx project is ongoing, and future work will examine the relationship between the pharmacists' referral and information sharing networks and their ability to conduct HCV testing and successfully retain and treat patients.

Table 1: Pharmacists referral and information networks and knowledge about HCV, before and after LiveRx (N = 21 pharmacies)

	Before LiveRx		Since LiveRx	
Patient referrals	Number	Percent	Number	Percent
CBOs	7	33	10	48
Public Health	2	10	7	33
Physicians	4	19	9	43
Corrections	1	5	1	5
Sharing information about HepC				
CBOs	1	6	7	38
Public Health	0	0	5	24
Other Pharmacies	0	0	2	10
Knowledge about HCV (0-10)				
Mean	4.9*		8.4*	
SD	2.0		.82	
Range	0-8		7-10	

*Difference significant at p <.001 (paired sample t-test)

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Disclosures: Jenny Godley: Nothing to Disclose, Christine Hughes: Nothing to Disclose, Cari Egan: Nothing to Disclose, Helena Atkinson: Nothing to Disclose, Klaudia Zabrzenski: Nothing to Disclose, Colter Young: Nothing to Disclose, Jaanek Grewal: Nothing to Disclose, Chinedu Diribe: Nothing to Disclose, Daniyal Khan: Nothing to Disclose, Mark Swain: Ipsen: Advisor, Abbott: Advisor, Advanz: Advisor, Novo Nordisk: Advisor, GSK: Advisor, Ipsen: clinical trial research grant support, Novo Nordisk: clinical trial research grant support, Madrigal: clinical trial research grant support, Kowa: clinical trial research grant support, Gilead: clinical trial research grant support, Abbvie: clinical trial research grant support, Merck: clinical trial research grant support, Galectin: clinical trial research grant support

1489 | CURRENT STATUS OF HEPATITIS C VIRUS INFECTION AND TREATMENT IN HEMODIALYSIS CENTERS IN SICHUAN PROVINCE, CHINA

Xiaoxia Geng[1] Xiaoxia Geng[2] Daqing Hong[1] Yao Cao[3] Ting Feng[1] Jingyu Yang[1] Hengjian Du[1] Rongzhen Tang[1] Guisen Li[1] Li Wang[4]

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Background: It is necessary to prevent hepatitis C virus infection among hemodialysis patients. This study aims to analyze the status of HCV screening and treatment among patients from 22 hemodialysis centers in Sichuan province, China. **Methods:** Standard survey was provided to hemodialysis patients to assess the awareness of hepatitis C. Screening and treatment status of each center and the clinical characteristics of patients would be analyzed. **Results:** 1. A total of 7095 hemodialysis patients from 22 hemodialysis centers in Sichuan Province were included (Figure 1A). Current rate of HCV antibody(+), HCV-RNA screening, HCV-RNA (+) and treatment rate were 2.65%(187/7095), 85.03%(159/187), 90.57%(144/159) and 55.56%(80/144).
2.Totally 3532 patients completed the survey. Only 9.48%(335/3532) of patients had a general knowledge of hepatitis C (Figure 1B). 44.74%(1580/3532) of patients were unaware that HCV infection was a high risk factor of cirrhosis and HCC. 59.62%(2106/3532) of patients didn't know hepatitis C could be cured. The survey results showed that the primary reasons for rejecting treatment were financial problems(78.26%), fear of AE(34.78%) and believing the virus would clear spontaneously (8.7%). Additionally, logistic regression analysis revealed that the presence or absence of medical insurance was a significant factor influencing the decision to receive treatment. 3. Characteristics between treated(n=35) and untreated(n=51) patients who completed 48 weeks follow-up were compared (Figure 1C). For patients who completed follow-up post-treatment, 100%(16/16) of patients achieved SVR12 after DAAs treatment. With a mean follow-up duration of 48 weeks, significant improvements were observed in ALT, AST, GGT, FIB-4 and APRI ($P<0.05$) in treated patients, while eGFR remained stable. Conversely, untreated patients showed a significant decrease in eGFR(from mean 6.77 to 5.94 (min·1.73 m2), $P<0.05$) and no significant improvement in ALT, AST, GGT and APRI during the follow-up period. **Conclusion:** Liver and renal function could be improved after DAAs treatment. But a low treatment rate is observed among hemodialysis patients with HCV infection, primarily due to lack of disease awareness and financial problem. A comprehensive elimination plan(ZERO-HD project) will increase the diagnosis and treatment rate of hepatitis C in hemodialysis patients.

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Figure 1A Distribution map of 22 Hemodialysis centers in Sichuan Province which the total area is 486,000 square kilometers



Figure 1B Hepatitis C awareness rate of 3532 Hemodialysis patients

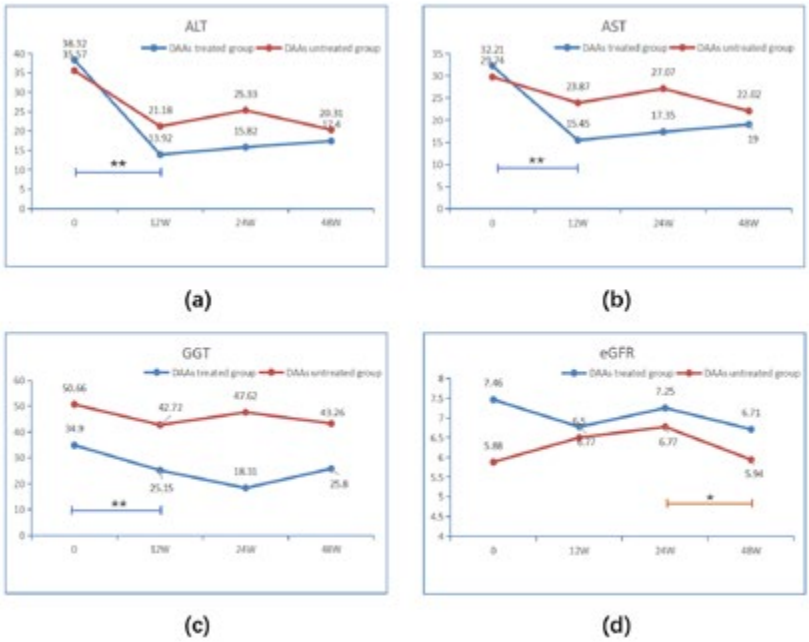

Figure 1C Changes in hepatic function and eGFR from baseline to 48 weeks in DAAs treated group(n=35) and DAAs untreated group(n=51) (a) ALT, (b) AST,(c)GGT,(d) eGFR. * P<0.05, ** P<0.001.

Disclosures: Xiaoxia Geng: Nothing to Disclose, Xiaoxia Geng: Nothing to Disclose, Daqing Hong: Nothing to Disclose, Yao Cao: Nothing to Disclose, Ting Feng: Nothing to Disclose, Jingyu Yang: Nothing to Disclose, Hengjian Du: Nothing to Disclose, Rongzhen Tang: Nothing to Disclose, Guisen Li: Nothing to Disclose, Li Wang: Nothing to Disclose

1490 | A GOVERNMENT-LEADING MULTI-ORGANIZATION COLLABORATIVE MODEL FOR HCV ELIMINATION IN CHENGMAI COUNTY, HAINAN PROVINCE

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Background: To achieve the goal of HCV elimination in Hainan province by 2025 (screening rate >90%, treatment rate >80%). The government of Chengmai county initiated this model to screen, diagnose, and treat the population (age≥20yrs). **Methods:** The model involves collaboration between the government, disease control center, community, health insurance department, civil affairs department, and designated treatment hospitals. Community outreach teams conduct rapid HCV antibody (HCV-Ab) screening for the populations (age≥20yrs) in community health centers. The disease control center performs HCV-RNA testing on HCV-Ab (+) cases and shares data with the designated treatment hospitals. Infection specialists at the designated hospitals provide face-to-face counselling and free treatment assessments and DAA treatment for HCV RNA positive patients, with simplified treatment protocols and follow-up. **Results:** During the project period from September 1, 2023 to February 30, 2024, a total of 38,680 people were screened, with 94 HCV-Ab(+), 72 HCV-RNA(+), and 67 HCV-RNA(+) patients treated with SOF/VEL, all achieving SVR12. Treatment baseline included 47 males, 20 females, ALT 7-176 IU/L, AST 12-360 IU/L, HCV RNA $1.2*10^{3}$-$1.6*10^{7}$ IU/L. All treated patients had no adverse reactions. Reasons for declining treatment included lack of HCV knowledge, fear of discrimination, and being away working. **Conclusion:** The program is still going on. The model will contribute to achieving the goal of HCV elimination in Hainan Province.

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1491 | VALIDATION OF AN ARTIFICIAL INTELLIGENCE MODEL FOR PREDICTION OF HEPATOCELLULAR CARCINOMA RISK AFTER ORAL ANTIVIRAL THERAPY IN PATIENTS WITH CHRONIC HEPATITIS C

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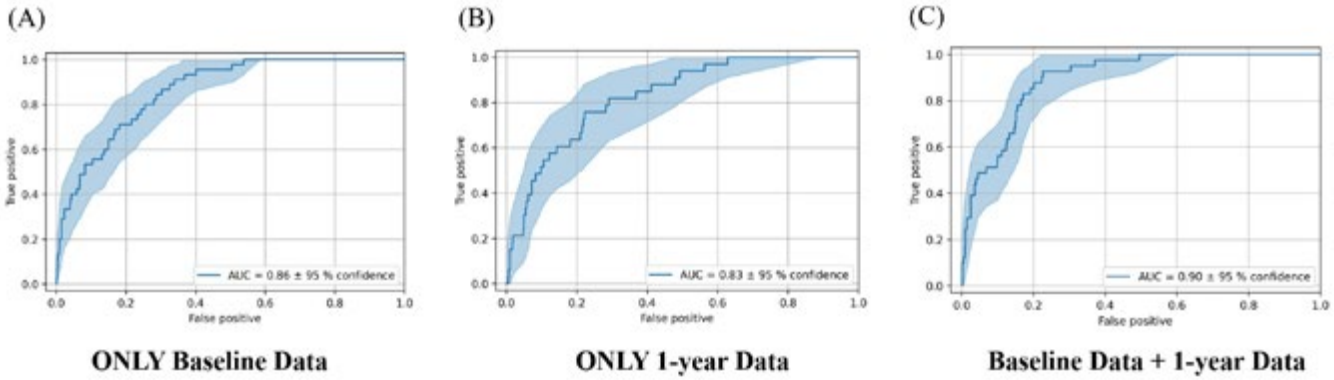
Background: Hepatocellular carcinoma (HCC) can still occur after achieving a sustained virologic response (SVR) to direct-acting antiviral (DAA) therapy in patients with hepatitis C. Prediction models have been developed to effectively select high-risk patients who need HCC surveillance. We previously developed an AI-assisted HCC prediction model in patients with chronic hepatitis C who have achieved SVR. In this study, we validated an AI-assisted HCC prediction model in patients with chronic hepatitis C who have achieved SVR. **Methods:** A total of 3,489 HCV patients who treated with DAAs and had achieved SVR from ten hospitals in South Korea were included in the derivation cohort. The external validation cohorts were recruited from a nationwide multicenter at 29 university-affiliated hospitals in Korea between 2014 to 2022. Developed machine learning algorithms using random forest were employed for HCC prediction. All possible variables for the development of new models were collected at the time of the initiation of DAAs and 1 year after SVR. **Results:** Age, platelet, AST, ALT, bilirubin, and albumin at baseline and 1 year after treatment were determined to be important factors predicting HCC risk. When using parameters at both baseline and 1 year after treatment, Prediction model showed best predictive abilities. Longitudinal inputs with machine learning algorithms improve the prediction performance. Prediction models using these parameters at baseline and 1 year after treatment was showed good predictive abilities in both internal and external validation cohort (internal validation cohort : Harrell's c-index 0.886, 5 year AUROC 0.903, external validation cohort : Harrell's c-index 0.796, 5 year AUROC 0.820). This model showed significantly better discrimination than previous models. **Conclusion:** HCC risk prediction models using machine learning with longitudinal inputs accurately predicted the risk of HCC in patients with chronic hepatitis C who have achieved SVR with DAAs.

Figure. ROC curves of prediction models for HCC development using Random forest (A) ROC curves of prediction models using parameters at baseline (B) ROC curves of prediction models using parameters at 1 year after treatment (C) ROC curves of prediction models using age, platelet, AST, ALT, bilirubin, and albumin at baseline and 1 year after treatment



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1492 | CHRONO-OPTIMAL TREATMENTS FOR HIV/HCV CO-INFECTION YIELD COMPARABLE SURVIVAL OUTCOMES WITH HCV MONO-INFECTION

Jeayeon Park[1] Jae Yoon Jeong[2] Soon Sun Kim[3] Jae hyun Yoon[4] Hyuk Soo Eun[5] Jonggi Choi[6] Ki Tae Yoon[7] Young Kul Jung[8] Soo Young Park[9] Geum-Youn Gwak[10] Do Young Kim[11] Ji Hoon Kim[12] Jin-Woo Lee[13] Tae Yeob Kim[14] Jeong Won Jang[15] Su Jong Yu[1]

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Background: Over the past decades, the treatment of human immunodeficiency virus (HIV)/hepatitis C virus (HCV) co-infection has significantly advanced. Previous studies have shown that HIV accelerates HCV progression, leading to increased liver-related complications and mortality. With advances in treatments for HIV/HCV co-infection, our study aims to re assess the effectiveness of various HCV treatments by comparing outcomes between patients with HIV/HCV co-infection and those with HCV mono-infection. **Methods:** We retrospectively included consecutive patients who were diagnosed and treated for HIV and/or HCV at 12 tertiary referral centers from January 2009 to December 2020. The primary endpoint was overall survival (OS). Secondary endpoints included achievement of a sustained virologic response (SVR), and the incidence of hepatocellular carcinoma (HCC). **Results:** A total of 908 patients were included: 114 (103 males, mean age of 46.0 ± 13.1 years) were HIV/HCV co-infected, and 794 (341 males, mean age of 58.4 ± 12.2 years) had HCV mono-infection. In the HIV/HCV co-infection group, 97 (85.1%) had received HIV treatment prior to inclusion in the study. In the HIV/HCV co-infection group, 26 (22.8%) were untreated, 30 (26.3%) received pegylated interferon plus ribavirin, and 58 (50.9%) received direct-acting antivirals (DAAs), compared to 52 (6.4%), 213 (26.8%), and 530 (66.8%) respectively in the HCV mono-infection group. The median follow-up duration was 58.2 months in the treated group receiving pegylated interferon plus ribavirin or DAAs. There was no statistically significant difference in OS between the treated HIV/HCV co-infection group and the treated HCV mono-infection group even after inverse probability of treatment weighting (IPTW) (adjusted hazard ratio [aHR], 1.20; 95% confidence interval [CI], 0.25–5.64; P=0.82; Figure 1A). SVR 12 was achieved significantly less in the HIV/HCV co-infection group (79.5%) compared to the HCV mono-infection group (93.1%) (P<0.001). The incidence of HCC was 1 (1.14%) in the treated HIV/HCV co-infection group and 48 (6.46%) in the treated HCV mono-infection group, with no statistically significant difference observed after IPTW (aHR 0.32, 95% CI 0.05–2.04, P=0.23; Figure 1B). **Conclusion:** With the establishment of optimal treatment regimens for HIV/HCV co-infection, the risk of HCC occurrence and mortality in patients with HIV/HCV co-infection have become comparable to those in patients with HCV mono-infection.

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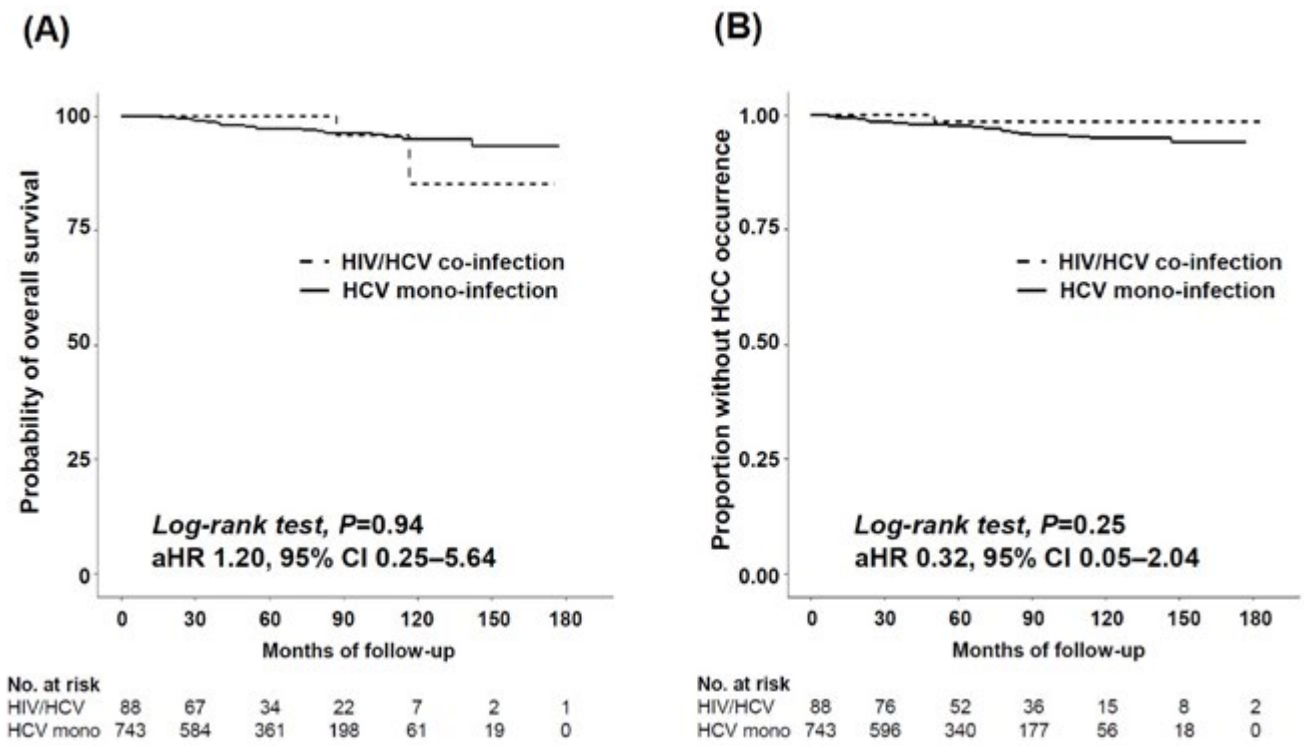

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1493 | SEIZING THE MOMENT: OPPORTUNISTIC SCREENING IMPACT ON VIRAL HEPATITIS PREVALENCE IN THE EMERGENCY DEPARTMENT OVER FOUR YEARS

Juan Carlos Ruiz Cobo[1] JORDI LLANERAS ARTIGUES[1] ARIADNA RANDO-SEGURA[2] Adriana Palom[1] Elena Vargas-Accarino[1] Francisco Rodriguez-Frias[1] MARIA DEL MAR RIVEIRO BARCIELA[1] Judit Romero[1] Rafael Esteban-Mur[1] Maria Buti[1]

[1]Hospital Vall D'Hebron, [2]Hospital Vall D´Hebron

Background: Several viral hepatitis screening studies at Emergency Departments (ED) have been reported in recent years. However, they have mainly focused on hepatitis C and patients with known risk factors, and included data from screening periods of less than 2 years. Our objective was to assess if maintaining an opportunistic screening in the ED over 4 years decreased the prevalence of hepatitis B, C and Delta. **Methods:** Prospective study of HCV and HBV systematic screening in adults who visited the ED and required a blood test from Jan/20 to Apr/24. Without additional sample collection, HBsAg and anti-HCV screening were conducted. In positive cases, reflex testing for HCV-RNA and anti-HDV was performed, respectively. Patients were evaluated and, when appropriate, linked to care. Since May/23, the process was automated by the central laboratory to avoid the need for ED physicians to request the screening. Prior to automation, we analyzed our data and made some changes to maximize cost-effectiveness. We excluded screening for patients >80 years old as they exhibited a low HBV prevalence (<0.3%) and only 15% (12/78) of HCV viremic patients were considered for treatment due to low life expectancy in most cases. **Results:** From Jan/20, 33783 patients have been screened, with 188 (0.56%) testing positive for HCV-RNA, 207 (0.61%) for HBsAg, and 8 for anti-HDV. Comparing patients ≤80 years old in the period prior to automated screening (Jan/20-Apr/23, n=15260) to the period after (May/23-Apr/24, n=11907), we noticed a decrease in HCV prevalence from 0.54% to 0.23% (p<0.01) (Figure 1A). There was a trend towards lower HBV prevalence (0.81% vs 0.61%), but this was not statistically significant (p=0.06)

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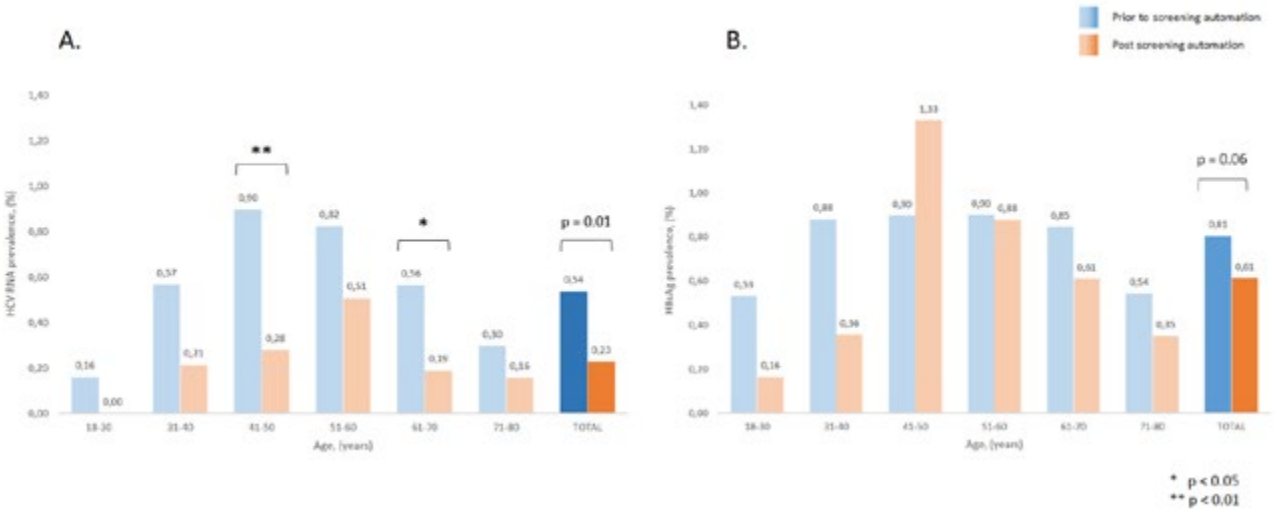
(Figure 1B). Regarding HCV patients, 93 (49.5%) were considered suitable for linkage, and 80 were treated. Of the 207 patients infected with HBV, 114 were considered suitable for linkage, 93 linked to care, and 14 required treatment. **Conclusion:** Maintaining opportunistic and systematic screening of viral hepatitis in the ED had a significant impact on HCV prevalence at our center, with rates decreasing by more than half among patients ≤80 over 4 years. Although it did not significantly reduce HBV prevalence, there was a trend towards lower HBV rates. Therefore, ED screening is an effective intervention for the elimination of viral hepatitis as public health threat.



Disclosures: Juan Carlos Ruiz Cobo: Gilead Sciences SL: Speaking and Teaching, JORDI LLANERAS ARTIGUES: Nothing to Disclose, ARIADNA RANDO-SEGURA: Nothing to Disclose, Adriana Palom: Nothing to Disclose, Elena Vargas-Accarino: Nothing to Disclose, Francisco Rodriguez-Frias: Nothing to Disclose, MARIA DEL MAR RIVEIRO BARCIELA: Nothing to Disclose, Judit Romero: Nothing to Disclose, Rafael Esteban-Mur: Nothing to Disclose, Maria Buti: Nothing to Disclose

1494 | EXPLORATION OF INFLUENCING FACTORS AND PREDICTIVE MODELS FOR THE DECREASE OF NON-INVASIVE LIVER FIBROSIS INDICATORS IN PATIENTS WITH HCV INFECTION TREATED WITH DAA

Xiaoxia Geng[1] *Yao Cao*[2] *Ting Feng*[1] *Jingyu Yang*[1] *Hengjian Du*[1] *Rongzhen Tang*[1]

[1]*Sichuan Provincial People's Hospital,* [2]*University of Electronic Science and Technology of China*

Background: Exploring the influencing factors of non-invasive liver fibrosis indexes(FIB-4 and APRI) recovery in HCV infected patients after direct antiviral agents (DAAs), and constructing a predictive model **Methods:** We conducted a retrospective analysis on the change of noninvasive liver fibrosis indexes in 197 HCV-infected patients treated with DAAs. Among them, 80 patients with baseline FIB-4 > 3.25 and APRI > 2 were categorized into two groups based on whether they achieved the standard (FIB-4 < 3.25 and APRI < 2) post-treatment. Factors influencing the degree of decrease in non-invasive liver fibrosis indexes (FIB-4, APRI) were analyzed. Additionally, we developed a column chart model for individualized assessment of the likelihood of decrease in non-invasive liver fibrosis indicators in HCV-infected patients following DAAs treatment. **Results:** FIB-4 and APRI of HCV-infected patients were rapidly and significantly decreased after treatment with DAAs (Z = -8.428, -10.702, P value<0.05). Whether those patients achieved FIB-4<3.25 and APRI<2 after DAAs treatment was used as the dependent variable (assigned value 0=no, 1=yes). The results of binary logistic regression showed that age (P=0.038, regression coefficient of -0.442, OR=0.643, 95% CI: 0.424~0.975), baseline HGB (P=0.044, regression coefficient of 0.171, OR=1.187, 95% CI: 1.004~1.402), and PLT (P=0.011, regression coefficient of 0.147, OR=1.158, 95% CI: 1.035~1.296) were independent predictors of achieving FIB-4<3.25 and APRI<2 after DAAs treatment. The column-line graph model (Figure 1A) constructed based on the above indicators had a well-fitting calibration curve (Figure 1B) and DCA curve (Figure 1C). The results of ROC curves showed that the AUCs of age, HGB, and PLT were 0.723, 0.742, and 0.862, respectively, with good diagnostic performance. **Conclusion:** DAAs treatment can significantly decrease the FIB-4 and APRI indexes of HCV-infected patients. Age, baseline

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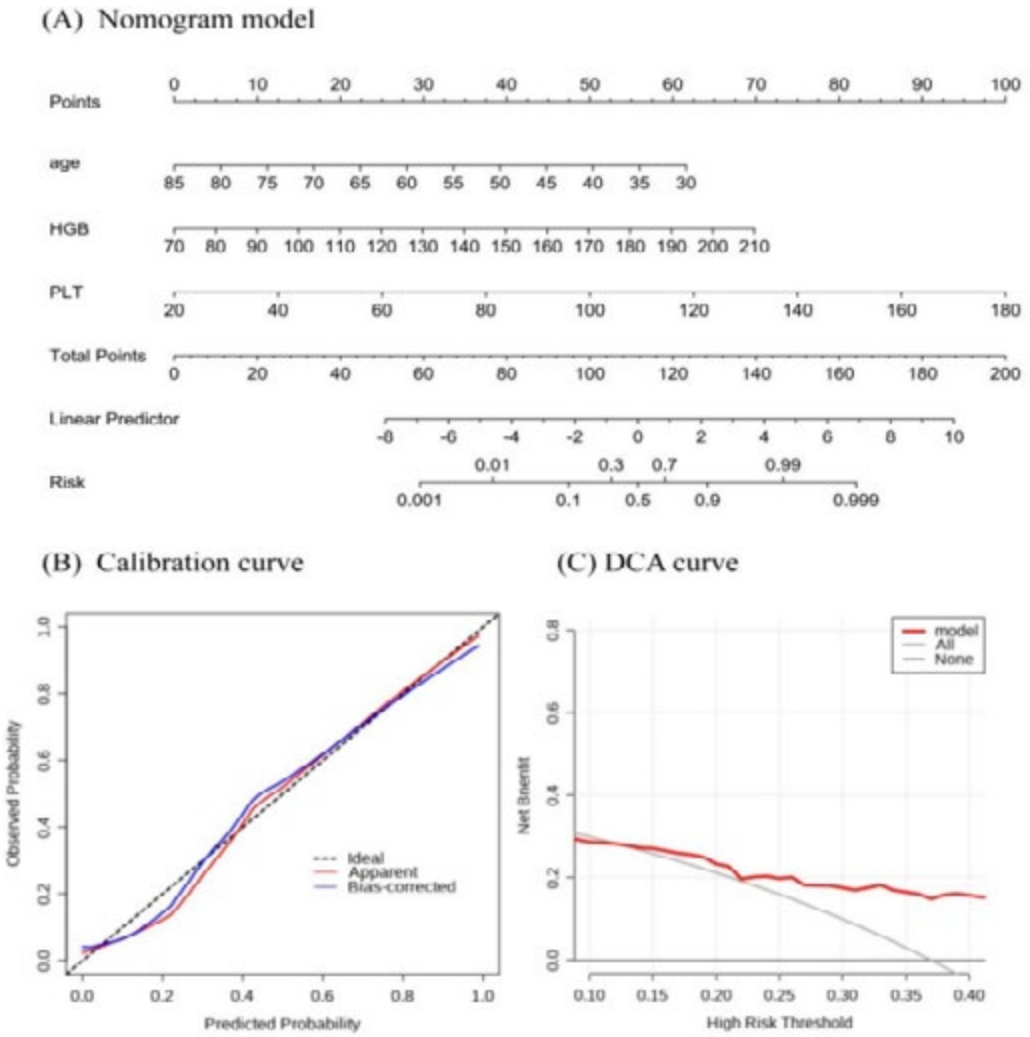
HGB, and PLT were independent predictors of achieving FIB-4<3.25 and APRI<2 after DAA treatment. The column-line graph model constructed based on the above indicators has good predictive performance and clinical application value.



Disclosures: Xiaoxia Geng: Nothing to Disclose, Yao Cao: Nothing to Disclose, Ting Feng: Nothing to Disclose, Jingyu Yang: Nothing to Disclose, Hengjian Du: Nothing to Disclose, Rongzhen Tang: Nothing to Disclose

1495 | CHANGES IN PORTAL INSULIN AND INSULIN HOMEOSTASIS IN PATIENTS DURING AND AFTER CHRONIC HEPATITIS C INFECTION

Matthew Menkart[1] James Haddad[1] Moumita Chakraborty[1] Rownock Afruza[1] Jenna Oringher[1] Gabriella Quinn[1] Elizabeth Townsend[1] Kareen Akiva[1] Lisa Scheuing[1] Rabab Ali[1] Christopher Koh[1] Regina Umarova[1] Elliott Levy[2] Etzion Ohad[1] David Kleiner[3] Theo Heller[1]

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Background: Insulin resistance is a common extrahepatic manifestation of Hepatitis C virus (HCV) infection, though its mechanism and the study of insulin homeostasis in the setting of HCV infection remain unclear. This explores changes in portal and peripheral insulin during infection and after treatment and its correlations with cytokines, metabolites, immune cells, hepatic gene expression, and the gut microbiome. **Methods:** HCV patients underwent a liver biopsy, portal vein cannulation, peripheral blood phlebotomy, and stool sampling, in a fasting state, before (HCVi, n=29), and 1 year after initiating direct-acting antiviral (DAA) therapy (SVR, n=23) (NCT02400216). Glucose, insulin, metabolites, cytokines, and PBMCs were measured in the blood, 16S

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rRNA and metatranscriptome sequencing was performed using stool samples. Wilcoxon signed-rank tests ($p < 0.05$) and Spearman's test ($\rho > 0.4$, $p < 0.05$) were used to evaluate differences in blood measurements and correlations between cytokines and metabolites with insulin levels respectively. Differential Gene Expression and pathway analysis was conducted using R, and pathways and modules were taken from the Kyoto Encyclopedia of Genes and Genomes. **Results:** HCVi patients had significantly reduced levels of portal insulin ($p = 0.02$) when compared to SVR levels. Portal glucose and peripheral values were not significantly different ($p > 0.05$) when corrected for BMI. HCVi patients also had a significantly reduced portal:peripheral insulin ratio ($p = 0.03$), a measure of insulin extraction, compared to SVR. Neither portal insulin nor the portal:peripheral ratio differed across cirrhosis status. Portal insulin significantly correlated with portal and peripheral TNFα, thrombomodulin, and sICAM-3 as well as peripheral sICAM-1 and sVCAM-1 ($p < 0.05$). Portal insulin further negatively correlated with peripheral CD8/CD62L/CD45RA/CD3 cells, portal and peripheral nucleotides, and the relative abundance of *Christensenlla minuta*. Portal insulin correlated with various immune and amino acid synthesis pathways from the liver transcriptome (FDR > 0.1), but no pathways from the metatranscriptome. **Conclusion:** Portal insulin and the portal:peripheral insulin ratio were significantly reduced in HCV-infected patients compared to after DAA, indicating a reduction in insulin secretion and decreased hepatic insulin extraction. Correlations of TNFα, cytotoxic T cells, and immune system pathways with portal insulin suggest the reduction in portal insulin may be immune mediated.

Disclosures: Matthew Menkart: Nothing to Disclose, James Haddad: Nothing to Disclose, Moumita Chakraborty: Nothing to Disclose, Rownock Afruza: Nothing to Disclose, Jenna Oringher: Nothing to Disclose, Gabriella Quinn: Nothing to Disclose, Elizabeth Townsend: Nothing to Disclose, Kareen Akiva: Nothing to Disclose, Lisa Scheuing: Nothing to Disclose, Rabab Ali: Nothing to Disclose, Christopher Koh: Nothing to Disclose, Regina Umarova: Nothing to Disclose, Elliott Levy: Nothing to Disclose, Etzion Ohad: Nothing to Disclose, David Kleiner: Nothing to Disclose, Theo Heller: Nothing to Disclose

1496 | TAILORING HCC RISK STRATIFICATION IN CHRONIC HEPATITIS C PATIENTS FOLLOWING VIRAL ERADICATION: A SIMPLE ALGORITHM UTILIZING ALPHA-FETOPROTEIN

Yen-Chun Liu[1] Yu-Ting Kao[1] Ya-Ting Cheng[1] Yi-Cheng Chen[1] Yi-Chung Hsieh[1] Rachel Wen-Juei Jeng[1] Wei-Ting Chen[1] Chun-Yen Lin[1] Rong-Nan Chien[1] Dar-In Tai[1] I-Shyan Sheen[1]

[1]Chang Gung Memorial Hospital, Linkou branch

Background: Guidelines recommend hepatocellular carcinoma (HCC) surveillance for chronic hepatitis C (CHC) patients with advanced liver fibrosis (ACLD) who achieve sustained virological response (SVR) due to an annual HCC incidence ≥ 1%. However, relying solely on ACLD may overlook non-ACLD subjects at high HCC risks. Existing scoring systems often require impractical components like liver stiffness measurement (LSM) or genetic testing. This study examines whether alpha fetoprotein (AFP), widely used in Asia for HCC surveillance, improve risk assessment. **Methods:** CHC patients who achieved SVR with DAA and had AFP levels measured before (SOT) and after (EOT) treatment were enrolled. The ACLD was defined as LSM ≥10 kPa and/or FIB-4 ≥3.25 and/or ultrasound signs of cirrhosis. Patients were categorized by ACLD status and AFP levels, with optimal cutoffs determined by the Youden Index. Multivariate Cox regression identified HCC risk factors in CHC-SVR patients, also stratified by ACLD status. Cumulative HCC incidences were analyzed using the Kaplan-Meier method and log-rank test. **Results:** During a median follow-up of 42 months, 92 out of 2,484 CHC-SVR patients developed HCC. SOT and EOT AFP levels had similar predictive accuracy for HCC (AUROCs: 0.72 vs. 0.74, $p > 0.1$). Multivariate Cox regression identified male gender and AFP levels (SOT ≥6 ng/mL or EOT ≥3 ng/mL) as independent HCC predictors. The 4-year cumulative incidence of HCC was highest in ACLD patients with SOT AFP ≥6 ng/mL, followed by ACLD patients with SOT AFP <6, non-ACLD patients with SOT AFP ≥6 and non-ACLD patients with SOT AFP <6 (13.3% vs. 4.3% vs. 3.1% vs, 0.2%, log-rank $P<0.01$). Stratified by EOT AFP levels, ACLD patients with EOT AFP ≥3 ng/mL had the highest 4-year incidence, followed by ACLD with EOT AFP <3, non-ACLD with EOT AFP ≥3 ng/mL, and non-ACLD with EOT AFP <3 (14.4% vs. 2.2% vs. 1.3% vs. 0.4%, log-rank $P<0.01$). Combining SOT and EOT AFP levels with ACLD status, 189 of 1,151 ACLD patients were classified as low risk (annual incidence: 0.4%), and 165 of 1,333 non-ACLD patients had an annual HCC incidence of 1% (Figure), warranting HCC surveillance. **Conclusion:** Incorporating SOT and EOT AFP levels with ACLD criteria improve HCC risk stratification. ACLD patients with both SOT and EOT AFP < 6 ng/mL and 3 ng/mL, respectively,

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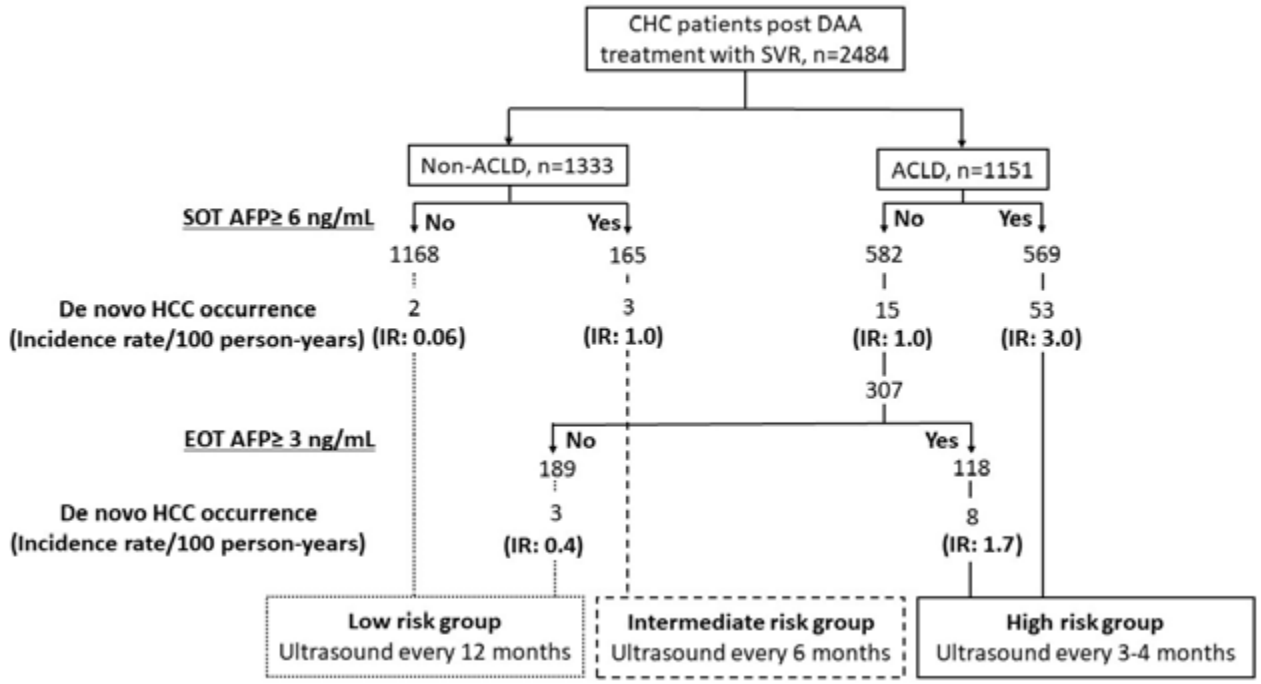
may not require HCC surveillance due to the low incidence. However, non-ACLD patients with SOT AFP >6 ng/mL should undergo HCC surveillance.



Disclosures: Yen-Chun Liu: Nothing to Disclose, Yu-Ting Kao: Nothing to Disclose, Ya-Ting Cheng: Nothing to Disclose, Yi-Cheng Chen: Nothing to Disclose, Yi-Chung Hsieh: Nothing to Disclose, Rachel Wen-Juei Jeng: Nothing to Disclose, Wei-Ting Chen: Nothing to Disclose, Chun-Yen Lin: Roche: Speaking and Teaching, Rong-Nan Chien: Nothing to Disclose, Dar-In Tai: Nothing to Disclose, I-Shyan Sheen: Nothing to Disclose

1497 | POSITIVE ANTI-HBC IGG IS AN INDEPENDENT RISK FACTOR FOR HEPATOCELLULAR CARCINOMA IN A COHORT OF CHRONIC HEPATITIS C PATIENTS

Mario Pessoa[1] Alexandre Trazzi[1] Marcus Acevedo[1] Eduardo Pombo[1] Betania Rocha[1] Rosa Marcusso[2] Patricia Zitelli[1]

[1]University of São Paulo School of Medicine, [2]Institute of Infectology Emílio Ribas

Background: Chronic infection with hepatitis C virus (HCV) still affects millions of people around the world despite the recent development of very effective direct acting antiviral (DAA) treatment. Even after a high cure rate, patients with advanced fibrosis should remain under surveillance due to the high risk of development hepatocellular carcinoma. **AIMS:** To evaluate the prevalence and risk factors for hepatocellular carcinoma development in previously treated chronic HCV patients in an outpatient hepatology clinic at “Hospital das Clinicas” of University of São Paulo School of Medicine, São Paulo, Brazil. **Methods:** This is a retrospective and prospective, observational, and descriptive study in a series of cases in which 402 HCV patients, treated with three different antiviral regiments: Interferon plus Ribavirin (INF + RBV) or Protease Inhibitors (PI) or DAA, were followed for up to ten years (2011-2021). Demographic, clinical and laboratory data were obtained to electronic medical records. **Results:** The total sample of this study consists of 402 patients, mean age was 59.8 years, 49% female. Table 1 shows the patient demographic and clinical data. Of the 35 patients who developed HCC, 25 (71.4%) had F4 degree fibrosis, 5 (14.3%) had F3 and, interestingly, 2 (5.7%) and 3 (8.6%) of patients had F1 and F2 degree fibrosis, respectively. Logistic regression model was performed with the following variables: BMI>25 (p=0.057) with OR 7.046, positive anti-HBC IgG (p=0.035) with OR 4.760 and female gender (p=0.007) with OR 2.834. **Conclusion:** In our cohort, female gender, overweight and positive anti-HBc IgG were significantly associated with a high risk developing of HCC. Type of antiviral treatment (IFN or DAA-based) was not associated with risk of HCC.

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Table 1. Frequency of demographic, laboratory, and clinical characteristics of patients with Hepatitis C virus

		HCC		
	Variable	No	Yes	p value
Gender	Male	182 (49.6%)	23 (65.7%)	0.049
	Female	185 (50.4%)	12 (34.3%)	
	Diabetes (yes)	81 (22.1%)	12 (34.3%)	0.080
	Overweight (BMI>25)	52(14.2%)	12 (34.3%)	0.004
	Smoke (yes)	48 (13.1%)	5 (14.3%)	0.502
Genotype of HCV	Genotype 1	273 (75.4%)	21 (60.0%)	0.218
	Genotype 2	7 (1.9%)	1 (2.9%)	
	Genotype 3	80 (22.1%)	13 (37.1%)	
	Genotype 4	2 (0.6%)	0.00%	
Grade of Fibrosis	F0	6 (1.6%)	0.00%	<0.001
	F1	59 (16.1%)	2 (5.7%)	
	F2	98 (26.8%)	3 (8.6%)	
	F3	77 (21.0%)	5 (14.3%)	
	F4	126 (34.4%)	25 (71.4%)	
Child	Child A	111 (87.4%)	18 (72.0%)	0.047
	Child B	13 (10.2%)	4 (16.0%)	
	Child C	3 (2.4%)	3 (12.0%)	

Abbreviation: HCV. Hepatitis C virus. HCC. Hepatocellular carcinoma.

Disclosures: Mario Pessoa: Nothing to Disclose, Alexandre Trazzi: Nothing to Disclose, Marcus Acevedo: Nothing to Disclose, Eduardo Pombo: Nothing to Disclose, Betania Rocha: Nothing to Disclose, Rosa Marcusso: Nothing to Disclose, Patricia Zitelli: Nothing to Disclose

1498 | HCV PROMOTES AGING IN HIV-INFECTED INDIVIDUALS: EVALUATING IMMUNE SENESCENCE USING TELOMERE LENGTH AND DNA METHYLATION

Jacob Ciricillo[1] Susan Rouster[1] Heidi Meeds[1] Jason Blackard[1] Marianna Baum[2] Kenneth Sherman[3]

[1]University of Cincinnati, [2]Florida International University, [3]University of Cincinnati, Massachusetts General Hospital-Harvard Medical School

Background: Purpose: Explore telomere length (TL) and DNA Methylation as markers of immune senescence in HIV- and/or HCV-infected individuals. **Methods:** This study utilized peripheral blood mononuclear cell (PBMC) samples from the Miami Adult Studies on HIV (MASH) cohort. PBMC TL assays were performed using a qPCR method with an oligonucleotide quantitation standard. DNA methylation was measured using global DNA methylation (5-mC) ELISA. HIV- and/or HCV-infected individuals and controls were compared by age, ethnicity, HIV viral load (VL), CD4+ T cell count, ALT, and Enhanced Liver Fibrosis (ELF) score. **Results:** TL was measured for 149 total participants including 103 with HIV mono-infection, 6 with HCV mono-infection, 14 with HIV/HCV co-infection, and 26 uninfected controls. Mean ages: HIV mono-infected was 53 years, HIV/HCV co-infected was 55 years, uninfected was 50 years. 59% were male while 62% were black, non-Hispanic. Overall TL ranged from 3,790 to 220,000 kb with a mean of 22,803 (SE 1772) and a median of 16,900. Average TL length (in kilobases) for each group was Healthy controls – 27760 kb, HIV mono-infected – 23686, HIV/HCV co-infected 11,975, and HCV mono-infected 37,550. HIV/HCV co-infected samples had lower average TL (p=0.001), while differences between other groups were not significant. Those with ELF>9.8 (N=6) had lower average TL (15,263 vs 24,207, p=0.38), higher mean HIV VL (34,976 versus 16,719 copies/mL; p=0.73), lower CD4+ T cell counts (382 versus 654 cells/mm^3; p=0.09), and higher age (63.2 versus 52.4 years; p=0.002) compared to ELF<9.8 (N=97). Subset regression modeling of factors potentially affecting TL demonstrated the best model fit included age, ELF, and CD4+ T cell count. Subsequent linear regression modeling identified age and ELF as significantly affecting

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TL (p=0.02 and p=0.03, respectively). A subset of this group (N= 27) was analyzed for DNA methylation. After controlling for fibrosis and viral load, HIV mono-infected and HIV/HCV co-infected samples had similar levels of methylation, with mean 5-mC % of 0.097% and 0.114% respectively (p=0.7). **Conclusion:** Hepatic fibrosis, age, and possibly CD4+ T cell count can influence immune senescence as measured by telomere shortening. Further studies should explore a larger database to analyze the effect of HCV on aging in HIV-infected individuals.

Disclosures: Jacob Ciricillo: Nothing to Disclose, Susan Rouster: Nothing to Disclose, Heidi Meeds: Nothing to Disclose, Jason Blackard: Nothing to Disclose, Marianna Baum: Nothing to Disclose, Kenneth Sherman: AbbVie: Grant/Research Support, Gilead: Grant/Research Support, Helio: Grant/Research Support, Intercept: Grant/Research Support, Zydus: Grant/Research Support, NovoNordisk: Advisor, MedPace: Consultant, Pliant: Consultant, Horizon/Amgen: Consultant

1499 | PREVALENCE OF HBV AND HIV INFECTION IN ANTI-HCV POSITIVE INDIVIDUALS WITH A HISTORY OF DRUG USE

CHARIKLEIA KRANIDIOTI[1] Pinelopi Antonakaki[2] Anestis Goulas[2] Sofia Vasileiadi[2] Maria Manolakopoulou[2] MARIA MELANIE DEUTSCH[2] Olga Anagnostou[3] Spilios Manolakopoulos[2]

[1]Hippocratio General Hospital of Athens, Greece, [2]Liver-Gi Unit, 2nd Academic Department of Internal Medicine, Hippocratio General Hospital of Athens, [3]Greek Organisation Against Drugs (OKANA), Athens

Background: Persons who use drugs (PWUD) are at high risk for blood – borne infections such as hepatitis C Virus (HCV), hepatitis B virus (HBV) and human immunodeficiency virus (HIV). Monitoring HCV, HBV and HIV profile in this vulnerable population reflects the public health harm reduction policies. In Greece, according to clinical guidelines and the National plan for HCV elimination all anti-HCV PWUD are candidates for DAA therapy; testing for coinfections is necessary at anti-HCV treatment initiation. The aim of the study was to determine HCV viremia and HBV and HIV seroprevalence rates in a cohort of anti-HCV positive PWUD. **Methods:** We retrospectively analyzed serum HCV RNA, HBV and HIV serology data of anti-HCV (+) PWUD during 2022 to 2024. **Results:** 657 PWUD (mean age was 48.6±9 years, 85% males) were enrolled in the study. 585/657 (89%) had an available serum HCV RNA result. Among them, 488/585 (83%) had HCV RNA detectable and 439/488 started DAA treatment. Thirty-two (5%) individuals were anti-HIV (+) (29 males, 49±10 years old), while 16 (2.4%) were found HBsAg (+). In 303/657 (46%) PWUD none of the tested serological markers for HBV was found positive. 192/657 (29.2%) had evidence of past HBV infection [HBsAg (-), anti-HBc (+)]. PWUD with indication of past HBV infection were older than those negative for HBV markers and vaccinated ones (52±8 vs 47±9, p $<10^{-3}$). Serology indicating vaccination was observed in 146/657 (22%) [isolated anti-HBs (+)]. There was a trend for higher vaccination coverage in urban areas (rural vs urban: 19% vs 24.5%, p=0,07). Vaccinated individuals were younger (45±10 vs 49±8, p $<10^{-3}$). 2.7% of HCV RNA (+) individuals were HBsAg (+) vs 1% of those HCV RNA (-) (p=ns). **Conclusion:** Our data have shown that 4 out of 5 anti-HCV (+) PWUD had viremia. HIV and HBV co-infection rates were low, while only one out of 5 has been vaccinated against HBV. Closer screening for infectious diseases among PWUD is necessary in order to assess prevalence trends. Harm reduction policies, HBV vaccination and early HCV / HIV / HBV treatment will help to reduce new transmissions.

Disclosures: CHARIKLEIA KRANIDIOTI: Nothing to Disclose, Pinelopi Antonakaki: Nothing to Disclose, Anestis Goulas: Nothing to Disclose, Sofia Vasileiadi: Nothing to Disclose, Maria Manolakopoulou: Nothing to Disclose, MARIA MELANIE DEUTSCH: Nothing to Disclose, Olga Anagnostou: Nothing to Disclose, Spilios Manolakopoulos: Nothing to Disclose

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1500 | BRIDGING THE GAP BETWEEN CONTROLLED HUMAN INFECTION MODELS AND REAL-WORD TESTING USING COMPUTATIONAL MODELING OF RANDOMIZED HEPATITIS C VACCINE TRIALS

Mary Ellen Mackesy-Amiti[1] Alexander Gutfraind[2] Eric Tatara[3] Nicholson Collier[3] Scott Cotler[4] Kimberly Page[5] Jonathan Ozik[3] Basmattee Boodram[6] Marian Major[7] Harel Dahari[2]

[1]University of Illinois at Chicago, Chicago, IL, USA, [2]Loyola University Chicago, [3]University of Chicago & Argonne National Laboratory, [4]Loyola University Health System, [5]University of New Mexico, [6]University of Illinois at Chicago, [7]Food and Drug Administration

Background: Global elimination of chronic hepatitis C (CHC) will remain difficult without an effective vaccine. Since injection drug use is the leading cause of hepatitis C virus (HCV) transmission in Western Europe and North America, people who inject drugs (PWID) are an important population for testing the effectiveness of HCV vaccines in randomized-clinical trials (RCTs). However, RCTs in PWID are inherently challenging. Discussions are ongoing regarding the use of a controlled human infection (CHI) model for further development of a vaccine to prevent CHC. To bridge the gap between CHI models and real-world testing, we developed an agent-based model (ABM) to simulate vaccines to prevent CHC in PWID. **Methods:** The ABM was designed to simulate HCV vaccine trials in PWID with the capacity to test the robustness of different vaccine regimens and vaccine efficacies with variable parameters. The ABM, representing 32,000 PWID in metropolitan Chicago, accounts for networks and HCV infections. In this study we simulated a two-dose vaccine trial to prevent CHC. We ran 1000 trial simulations under 50% and 75% assumed-vaccine efficacy (aVE) and sampled HCV infection status of recruited *in silico* PWID. **Results:** The mean estimated vaccine efficacy (eVE) for 50% and 75% aVE was 48% (standard deviation (SD ±12)) and 72% (SD±11), respectively (**Fig. 1**). For both simulation conditions, the majority of trials (~71%) resulted in eVEs within 1SD of the mean, demonstrating a robust trial design. Trials that resulted in eVEs >1SD from the mean (lowest eVEs of 3% and 35% for 50% and 75% aVE, respectively), were associated with post-randomization imbalances in acute infection rates across trial arms. **Conclusion:** Modeling indicates robust trial design and high success rates of finding vaccines to be effective in real-life trials in PWID. However, with less effective vaccines (aVEs~50%) there remains a higher risk of concluding poor vaccine efficacy due to post-randomization imbalances. Our model contributes to the use of the CHI model for vaccine development by indicating that vaccines with both moderate and high efficacy could successfully complete later-phase trials. However, a vaccine tested in a CHI model should show > 50% effectiveness in order to avoid the risk of being found ineffective in a real-world study assessing vaccine efficacy in at-risk populations such as PWID.

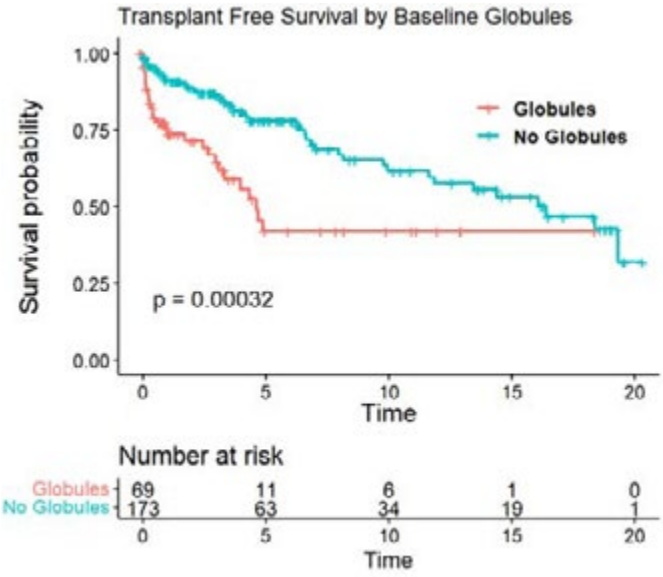

Figure 1: Kaplan Meier Curve illustrating transplant-free survival amongst individuals with PAS-D Globules on baseline biopsies compared to those without. p-value represents results from log-rank testing.

Disclosures: Mary Ellen Mackesy-Amiti: Nothing to Disclose, Alexander Gutfraind: Nothing to Disclose, Eric Tatara: Nothing to Disclose, Nicholson Collier: Nothing to Disclose, Scott Cotler: Nothing to Disclose, Kimberly

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Page: Nothing to Disclose, Jonathan Ozik: Nothing to Disclose, Basmattee Boodram: Nothing to Disclose, Marian Major: Nothing to Disclose, Harel Dahari: Nothing to Disclose

1501 | BEMNIFOSBUVIR POSES HIGH BARRIER FOR RESISTANCE IN BOTH PRECLINICAL AND PHASE 1B MONOTHERAPY STUDIES

Qi Huang[1] Dawei Cai[1] Shannan Lynch[1] Keith Pietropaolo[1] Xiao-Jian Zhou[1] Nancy Agrawal[1] Jean-Pierre Sommadossi[2]

[1]Atea Pharmaceuticals, Inc., [2]Atea Pharmaceuticals, Inc

Background: Bemnifosbuvir (BEM), an oral prodrug of a guanosine analog, has potent pan-genotypic, best-in-class *in vitro* and clinical antiviral activities against all HCV genotypes tested. We performed *de novo* resistance studies with HCV replicons and NGS analysis of samples from BEM monotherapy clinical studies (NCT03219957) to establish BEM's resistance profile. **Methods:** *In vitro* resistance selection was conducted in the presence of G418 and gradually increasing concentrations of AT-511 (free base of BEM). Emerged NS5B substitutions were phenotyped in transient replicon assays. For the analysis of BEM resistant substitutions in the Phase I study, NGS was performed for 42 HCV-infected patients treated with BEM. Baseline RASs and on-treatment NS5B substitution analyses were conducted using Athvena NGS analysis pipeline with a 1% cutoff. **Results:** Previous studies showed that AT-511 retained high potency against identified clinical SOF HCV RASs *in vitro*, including S282T. AT-511 resistance selection study in HCV GT1a and GT1b replicons with up to 22 passages/209 days identified several amino acid changes, including S46N, F54I, E237G, C223H and T344I in GT1b and C316F in GT1a. Subsequent phenotyping studies showed that C223H is the key BEM RAS yet it needs additional linked mutations to confer meaningful resistance (~8 fold). In the clinical study, 9/40 HCV-infected patients had SOF RASs L159F and C316N at baseline; NS5B substitutions were detected in some on-treatment samples and only a few are known HCV nucleoside inhibitor (NI) RASs such as S15R, F162L/Y162F, F289L/S. Neither S282T nor C223H was detected at baseline or emerged on-treatment. The frequency of these treatment emergent substitutions was very low (<2%), indicating they existed at undetectable levels at baseline and are likely associated with poor fitness, and consequently may confer minimal resistance with no significant impact on clinical efficacy. **Conclusion:** BEM has demonstrated a strong capacity to inhibit HCV replication *in vitro* and *in vivo*, without the rapid development of viral resistance**.** Given the highly potent pan-genotypic antiviral activity and high resistance barrier of BEM, it is currently being developed in combination with ruzasvir (RZR), a picomolar potent pan-genotypic NS5A inhibitor, for the treatment of HCV infections in a Phase 2 clinical trial (NCT05904470). The combination of BEM/RZR should have a more compelling antiviral profile against all genotypes than current SOCs.

Disclosures: Qi Huang: Nothing to Disclose, Dawei Cai: Nothing to Disclose, Shannan Lynch: Nothing to Disclose, Keith Pietropaolo: Atea Pharmaceuticals, Inc.: Employee, Xiao-Jian Zhou: Nothing to Disclose, Nancy Agrawal: Nothing to Disclose, Jean-Pierre Sommadossi: Nothing to Disclose

1502 | TRANSFORMING HEPATITIS C TREATMENT: THE POWER OF LARGE LANGUAGE MODEL-BASED INTELLIGENT AGENTS IN CLINICAL DECISION SUPPORT

Mauro Giuffre[1] Simone Kresevic[1] Lory Crocè[2] Dennis Shung[1]

[1]Section of Digestive Disease (Department of Internal Medicine), Yale School of Medicine, [2]Department of Medical, Surgical, and Health Sciences - University of Trieste

Background: Large Language Models (LLMs) may be useful for clinical tasks that require reasoning over different information sources. LLMs could be regarded as intelligent "agents" with internal planning abilities, enabling them to engage in multi-step reasoning and interacting with other agents or external users. Hepatitis C Virus (HCV) management is a potential area where LLM-enabled agents could be useful, since treatment decisions are made by considering genotype evaluation, previous treatment history, liver fibrosis extent, and potential drug-drug interactions. **Methods:** We developed 50 clinical cases with the task of prescribing the most appropriate therapeutic regimen given the following conditions: genotype, prior treatment with interferon or other DAAs, fibrosis/hepatic decompensation degree, and concurrent medications at treatment initiation. LLM agents

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were engineered using a fine-tuned version of GPT-3.5 with HCV treatment guidelines. Each agent had access to a specific section of the guidelines based on its task, extracted relevant information from the clinical case, and provided with a task-based recommendation to the final agent, referred to as “the prescriber.” Different agent configurations were tested and compared to a baseline fine-tuned model: a single agent, multi-agent, and specialized multi-agent. For the single agent, one LLM extracted all critical data elements. The multi-agent configuration had three LLM agents: one agent focused on genotype and previous therapy extraction, another handled disease status and current therapy, and the third was a prescriber agent. The specialized multi-agent configuration used one for genotype, one for therapy history, one for fibrosis status, one for current therapy, and one as a prescriber agent. **Results:** The baseline scenario had an accuracy of correctly prescribed treatment of 24%. The single agent configuration had accuracy of 50% (p=0.007), the multi-agent configuration had accuracy of 76% (p<0.001), and the specialized multi-agent configuration had accuracy of 89% (p<0.001). **Conclusion:** The introduction of specialized multi-agent LLMs in decision-making significantly improves the accuracy of treatment recommendations for HCV. Validation in real-world settings is needed to test the promise of employing LLM-based intelligent agents to optimize clinical decision-support systems.

Disclosures: Mauro Giuffre: Nothing to Disclose, Simone Kresevic: Nothing to Disclose, Lory Crocè: Nothing to Disclose, Dennis Shung: Nothing to Disclose

1503 | HCV REINFECTION AMONG PEOPLE WHO USE DRUGS (PWUD) TREATED FOR HCV INFECTION: A LONG-TERM VIEW

Shana Yi[1] Rossitta Yung[1] Shawn Sharma[1] Brian Conway[1]

[1]Vancouver Infectious Diseases Centre

Background: Comprehensive programs of care for priority populations such as PWUD are needed to eliminate HCV infection as a public health concern by 2030. A primary challenge associated with such initiatives is the need for effective strategies to mitigate the risk of reinfection. Meta-analyses suggest a reinfection rate of approximately 5 per 100 person-years (py) among key populations, especially those who continue to inject drugs. The objective of this study is to assess reinfection rates among populations of PWUD successfully treated for HCV infection and maintained in long-term follow-up within a multidisciplinary program of care following cure. **Methods:** In our program, we provide HCV therapy to PWUD within the context of a multidisciplinary program addressing all medical, social, mental health, and addiction-related needs in the context of HCV therapy with strategies designed to maximize adherence and successful completion of therapy. Once HCV cure has been documented, patients continue to be offered the opportunity to remain integrated in longitudinal care. HCV RNA testing is repeated annually, or more frequently if clinically indicated. We conducted an ongoing, prospective evaluation of the last 304 successful HCV therapy administered to PWUD in our center to determine the rate of HCV reinfection and its correlates. **Results:** All participants were cured of HCV infection between 03/19-08/23. We document median age 48.5 (22-83) years, 29% female, 19.7% identifying as indigenous, 55.7% unstably housed, and 95.4% continuing active drug use (mostly fentanyl). Since 2019, we documented 11 cases of reinfection. This represents a rate of 0.88 cases per 100 PY. Of these 11 individuals, we note median age 38 (27-63) years, 2 female, 2 identifying as indigenous, and all experiencing unstable housing and ongoing drug use. All were maintained in care and offered re-treatment of HCV infection, with 1 getting glecaprevir/pibrentasvir (G/P) and 4 sofosbuvir/velpatasvir (S/V) according to their preference, and 6 still awaiting treatment. Of those who received repeat treatment 4/5 are cured and one had a virologic relapse on S/V. This patient is scheduled to receive S/V/voxilaprevir. **Conclusion:** To our knowledge, this is the largest single center longitudinal evaluation of HCV reinfection rates among active PWUD enriched for factors of instability (high rates of fentanyl use and unstable housing). We demonstrate that a comprehensive, multidisciplinary approach to HCV therapy with maintenance in follow up after cure is associated with rates of reinfection below 1/100 py. Those who experienced reinfection appear to disengage from ongoing follow up more frequently prior to the reinfection being documented. Our robust structure allows for a near-immediate offer of repeat therapy, with largely successful outcomes to date, being able to offer second line therapy in a timely manner to the one individual who did not respond to therapy.

Disclosures: Shana Yi: Nothing to Disclose, Rossitta Yung: Nothing to Disclose, Shawn Sharma: Nothing to Disclose, Brian Conway: Nothing to Disclose

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1504 | IMPLEMENTING A NOVEL IN-HOSPITAL HEPATITIS C MANAGEMENT MODEL: ADVANCING TOWARDS THE WORLD HEALTH ORGANIZATION'S 2030 ELIMINATION GOAL

YongFang Jiang[1] *Wan Hu*[1] *Jing Ma*[1]

[1]*the Second XiangYa Hospital*

Background: As the 2030 global hepatitis C elimination goal proposed by the World Health Organization approaches, China still faces significant public health challenges. The Second Xiangya Hospital has designed an in-hospital hepatitis C management model to improve the efficiency of screening, diagnosis, and treatment. This not only enhances disease management efficiency but also optimizes the use of resources, offering high cost-effectiveness and contributing to the global goal of eliminating hepatitis C. **Methods:** This work began in March 2021, led by the Department of Infectious Diseases of the Second Xiangya Hospital, and involved collaboration across departments, including the laboratory, blood transfusion department, hemodialysis center, surgery, medical affairs, and other related clinical departments. the model was developed and implemented with the cooperation of all departments, focusing on comprehensive screening, accurate diagnosis and effective treatment. Standardised procedures ensure that all inpatients and high-risk outpatients are screened for HCV antibodies. An immediate notification system and referral strategy was adopted to direct individuals who screened positive to confirmatory HCV RNA testing. Patients diagnosed as RNA-positive are assigned a case manager who is responsible for coordinating the treatment pathway and ensuring that the patient receives guideline-recommended antiviral therapy. In addition, the case management team is responsible for subsequent patient follow-up to monitor treatment outcomes and adherence. Through this multidisciplinary and process-oriented approach, we aim to establish an efficient and sustainable hepatitis C management system to provide continuous follow-up and care for hepatitis C patients from screening to treatment. **Results:** During the study period from January 2021 to December 2023, the Second Xiangya Hospital conducted comprehensive HCV antibody screening for hospitalized patients. A total of 375252 HCV antibody tests were carried out during this time (averaging 125084 per year), achieving a screening coverage rate of 74%. Among the antibody-positive patients, the proportion undergoing confirmatory HCV RNA testing significantly increased from 48.27% to 71.02%. Furthermore, the treatment rate for hepatitis C diagnosed in infectious patients is more than 75%, while the treatment rate for hepatitis C diagnosed in non-infectious patients is more than 50%. **Conclusion:** The management model implemented by the Second Xiangya Hospital has significantly improved the rates of hepatitis C screening, diagnosis, and treatment, marking an important step forward in the management of the disease. This model can also be widely promoted in other medical institutions in China and in developing countries, and to contribute to the World Health Organization's goal of eliminating hepatitis C by 2030.

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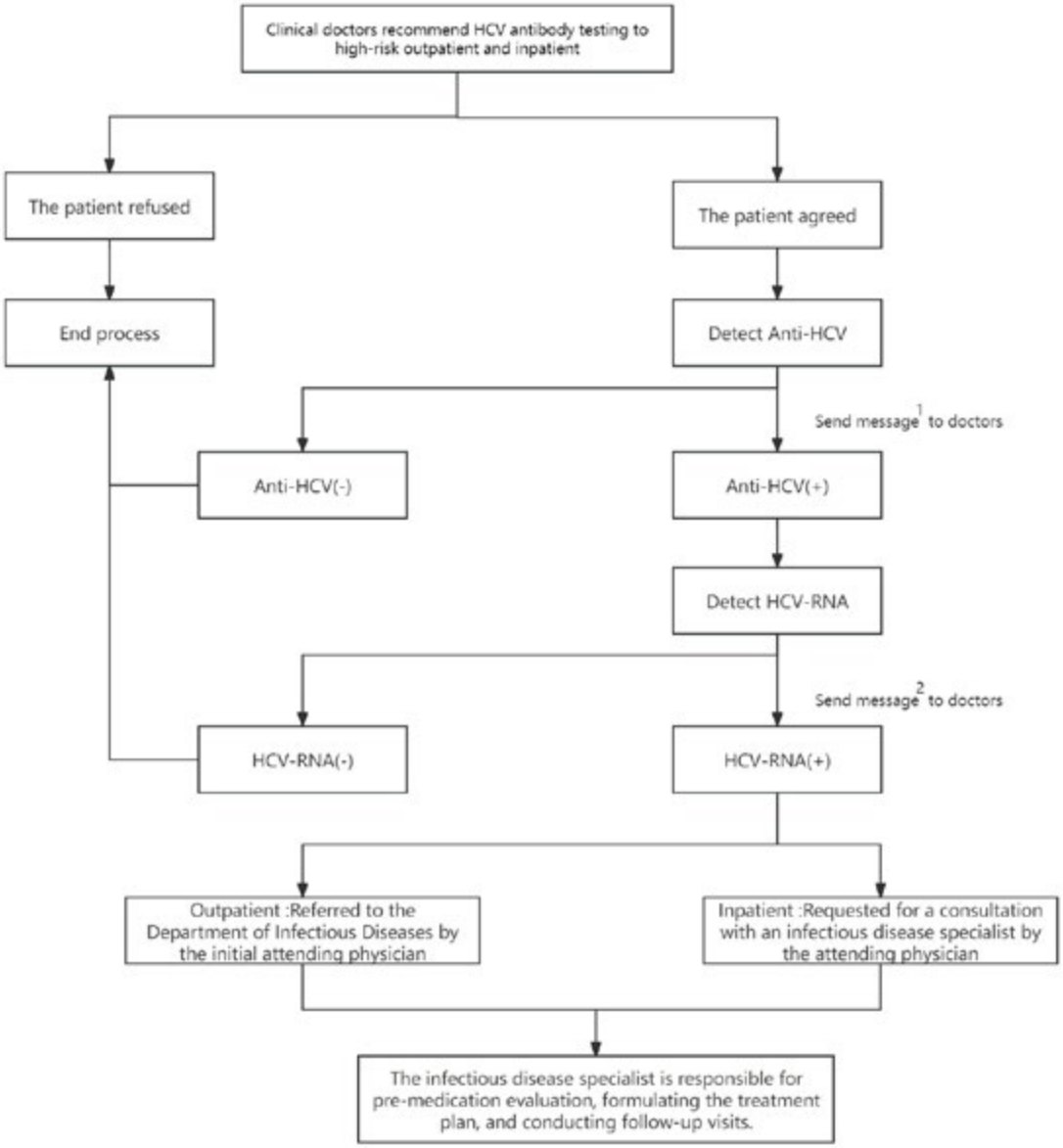

[1]Fig. Screening, diagnosis, and referral process of hepatitis C cases in the hospital.
[1]Dr. XXX, the hepatitis C virus antibody test result for your patient XXX (patient ID XXXXXX) is positive;please complete the Hepatitis C Virus Nucleic Acid Test to confirm the diagnosis of Hepatitis C.
[2]Dr. XXX, the hepatitis C virus antibody test result for your patient XXX (patient ID XXXXXX) is positive;please report the infectious disease card, and request a consultation with the infectious disease specialist to formulate the treatment plan.

Disclosures: YongFang Jiang: Nothing to Disclose, Wan Hu: Nothing to Disclose, Jing Ma: Nothing to Disclose

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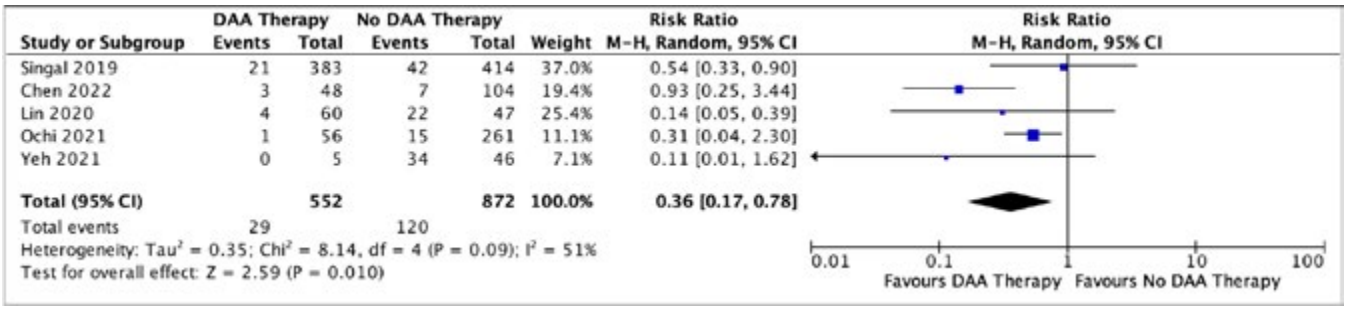
1505 | DIRECT ACTING ANTIVIRAL THERAPY IS ASSOCIATED WITH INCREASED ONE-YEAR OVERALL SURVIVAL IN PATIENTS WITH HEPATITIS C RELATED HEPATOCELLULAR CARCINOMA

Sarah Huang[1] Alan Zakko[1] Joshua Harroch[1] Kevin Pain[2] Brandon Swed[1] Ilan Weisberg[1]

[1]NewYork-Presbyterian Brooklyn Methodist Hospital, [2]Weill Cornell Medicine Samuel J. Wood Library & C.V. Starr Biomedical Information Center

Background: The AASLD recommends universal treatment of Hepatitis C (HCV) with direct acting antiviral (DAA) therapy except in those with shortened life expectancy which would not improve with HCV treatment. It is not known whether treating patients with HCV related hepatocellular carcinoma (HCC) with DAA therapy improves their outcomes or life expectancy. Our primary objective was to determine whether patients with HCV related HCC had improved overall survival with DAA therapy. **Methods:** We performed a systematic search of PubMed, Ovid Embase, Cochrane Library, Scopus, CINAHL, and Web of Science Core Collection databases. Inclusion criteria were adult patients with a diagnosis of chronic HCV and HCC who received DAA therapy with a comparator of no DAA therapy. Our primary endpoint was 1-year overall survival. We used this outcome data to determine the 1-year mortality to perform a meta-analysis with random effects model. Methodological quality was assessed with the Newcastle-Ottawa Scale. **Results:** Our search identified 2870 citations with 12 studies meeting our inclusion criteria. Five of these studies were included in the meta-analysis for our primary endpoint. Direct acting antiviral therapy lowered the risk of death at 1-year: RR 0.36 (95% CI, 0.17-0.78) with moderate heterogeneity (I2=51%). The number-needed-to treat was 11 (95% CI 9-33). All included studies had methodologic limitations. **Conclusion:** Direct acting antiviral therapy was associated with a decreased risk of death, and thus increased 1-year overall survival, in patients with HCV related HCC in our systematic review and meta-analysis. Higher quality studies are needed to improve the certainty of the estimated effect size.



Disclosures: Sarah Huang: Nothing to Disclose, Alan Zakko: Nothing to Disclose, Joshua Harroch: Nothing to Disclose, Kevin Pain: Nothing to Disclose, Brandon Swed: Nothing to Disclose, Ilan Weisberg: Nothing to Disclose

1507 | EXPERT EVALUATION OF GUIDELINE-BASED RETRIEVAL AUGMENTED GENERATION VS. SUPERVISED FINE-TUNING FOR LARGE LANGUAGE MODEL OUTPUTS: A CASE STUDY IN HEPATITIS C VIRAL INFECTION MANAGEMENT

Mauro Giuffre Nicola Pugliese[1] Simone Kresevic[2] Francesco Negro[3] Massimo Puoti[4] Xavier Forns[5] Jean-Michel Pawlotsky[6] Alessio Aghemo[1] Dennis Shung[2]

[1]Department of Biomedical Sciences, Humanitas University, Pieve Emanuele (MI), Italy, [2]Department of Internal Medicine (Section of Digestive Diseases), Yale School of Medicine, [3]Division of Gastroenterology, University Hospitals of Geneva, Geneva, Switzerland, [4]Niguarda Ca Granda, [5]Liver Unit, Hospital Clínic, University of Barcelona, IDIBAPS, Barcelona, Spain, [6]Université Paris Est Créteil, INSERM, IMRB, Créteil, F-94010, France

Background: Advances in artificial intelligence, particularly large language models (LLMs), hold the potential for transforming chronic disease management, such as Hepatitis C Virus (HCV) infection. LLMs currently have variable accuracy in digestive diseases, with reported accuracy ranging from 6.4 to 91.4%. Ensuring the accuracy and completeness of the information generated is critical in clinical practice, where over-reliance on inaccurate LLM-generated recommendations could lead to patient harm. This study evaluates the impact of

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domain-knowledge infusion frameworks, such as retrieval augmented generation (RAG) with guidelines and supervised fine-tuning (SFT), on LLM-generated response accuracy and clarity. **Methods:** We used OpenAI's GPT-4 Turbo (baseline and RAG) and GPT-3.5 Turbo for SFT, enhanced with HCV guidelines. Fifteen questions reflecting general, patient, and physician perspectives were reviewed by a lead guideline author. Answers were scored on a 10-point accuracy scale and binary evaluations for accuracy and clarity, graded by four experts (European guidelines main authors and chair). Experiments were conducted in a local Python environment using the OpenAI API with a temperature setting of 0.8. Queries were generated without specific length constraints, and heuristic prompt engineering was applied. For RAG, the European guidelines on HCV were used as the reference text. SFT was carried out on OpenAI's fine-tuning platform and involved two fine-tuning stages: the first with HCV guidelines text and the second (i.e., instruction fine-tuning) with curated Q/A pairs to align the model's outputs with expert knowledge. **Results:** The RAG-enhanced GPT-4 Turbo model had higher accuracy compared to baseline GPT-4 Turbo (83.3% vs 36.6%; P<0.001) and higher perceived clarity (91.6% vs. 46.6%; P<0.001). Compared to baseline, the SFT GPT-3.5 also had higher accuracy (80% vs 36.6%; P<0.001) and higher perceived clarity (86.6% vs. 46.6%; P<0.001). Inter-grader agreement for the 10-point scale showed an ICC of 0.76 for the baseline, 0.82 for RAG, and 0.86 for SFT. Binary accuracy grading ICCs were 0.50, 0.65, and 0.66, respectively. On the 10-point scale, RAG-enhanced GPT-4 Turbo achieved a mean accuracy of 9.1 (±1.4), SFT GPT-3.5 achieved 8.8 (±2.1), and baseline GPT-4 Turbo achieved 6.4 (±2.3). The RAG and SFT models demonstrated significantly improved accuracy and clarity of HCV management recommendations compared to the baseline. **Conclusion:** RAG and SFT significantly improve the accuracy and perceived clarity of HCV management recommendations compared to the baseline. Using RAG with guidelines and SFT enhances LLM output quality, supporting their clinical decision-making potential. The involvement of experts in creation and scoring underscores the results' reliability and clinical relevance. Establishing rigorous evaluation criteria is important for safe LLM integration in healthcare.

Disclosures: Mauro Giuffre: Nothing to Disclose, Nicola Pugliese: Nothing to Disclose, Simone Kresevic: Nothing to Disclose, Francesco Negro: Gilead: Consultant, Massimo Puoti: Nothing to Disclose, Xavier Forns: Nothing to Disclose, Jean-Michel Pawlotsky: Abbvie: Speaker, Abbott: Advisor, Gilead: Speaking and Teaching, GSK: Advisor, Alessio Aghemo: Nothing to Disclose, Dennis Shung: Nothing to Disclose

1508 | SEX DISPARITIES IN THE RATE OF DELAYED HEPATITIS C DIAGNOSIS IN PATIENTS WITH A LIVER COMPLICATION–RESULTS OF A POPULATION-BASED ANALYSIS

Charles Levesley[1] Xinrong Zhang[1] Leslie Kam[1] Richie Manikat[1] Ramsey Cheung[1] Mindie Nguyen[1]

[1]Stanford University Medical Center

Background: Despite universal hepatitis C virus (HCV) screening recommendations in the U.S. and available effective direct-acting antiviral (DAA) therapies, HCV infection remains underdiagnosed, and affected patients remain undertreated. However, it is unclear if there are significant differences in the rates of delayed HCV diagnosis between males and females. We aimed to compare the proportion of delayed HCV diagnosis in patients with a liver complication, as well as their associated factors, between males and females in a nationwide real-world cohort in the U.S. **Methods:** We conducted a retrospective cohort study of adults with chronic hepatitis C (CHC) and a liver complication using Merative™ Marketscan® Research Databases (1/2007-12/2021). Delayed HCV diagnosis was defined as HCV diagnosis occurring within 2 years prior to or any time after occurrence of a liver complication such as cirrhosis, hepatocellular carcinoma (HCC), or liver transplant. **Results:** Our study included 69,989 patients with CHC and at least one liver complication (mean age 55.8 years and 65.9% male). Patients with delayed diagnosis were more likely to be male (66.4% vs. 62.5%). The study included 40,264 males and 20,364 females with delayed diagnosis. Males with delayed diagnosis were more likely than females to be alcohol users (25.1% vs. 16.1%), to receive DAA treatment (17.7% vs. 16.3%), and to have diabetes (35.1% vs. 29.6%) (Table 1). The two groups had similar mean age, distribution of insurance types and Charlton Comorbidity Index. The percentage of delayed diagnoses was highest (47.7%) within the 6 months leading to the first liver complication and decreased with every 6-month interval thereafter for both males and females. A greater proportion of females than males received a diagnosis between 6 and 24 months before a complication (17.4% vs. 16.4%). However, a greater proportion of females than males received a diagnosis 6 months or more after developing a liver complication (13.8% vs. 12.4%). More males than females received a diagnosis within

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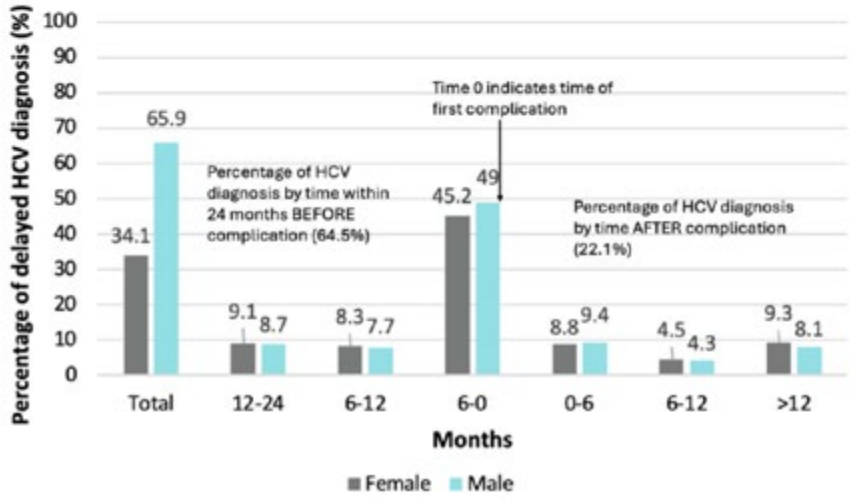
6 months either before or after the occurrence of a liver complication (58.4% vs. 54%) (Figure 1). **Conclusion:** Males with delayed diagnosis were more likely than females to be alcohol users and to receive DAA treatment. Targeted intervention is needed to address the higher rates of alcohol use in males and the lower DAA treatment rates in females.

Table 1. Delayed Diagnosis Patients Characteristics by Sex

Variables	Male n= 40,264	P value	Female n= 20,364	P value
Age (SD), y	55.35 (8.69)	<0.001	55.69 (11.10)	<0.001
Geographic region (%)		0.002		<0.001
Northeast	7,960 (19.8)		3,488 (17.1)	
North central	6,632 (16.5)		3,612 (17.7)	
South	15,788 (39.2)		8,363 (41.1)	
West	7,310 (18.2)		3,595 (17.7)	
Unknown	2,574 (6.4)		1,306 (6.4)	
Insurance type (%)		<0.001		<0.001
HMO	5,773 (14.3)		2,851 (14.0)	
PPO	23,722 (58.9)		11,682 (57.4)	
HMO/PPO hybrid[a]	3,880 (9.6)		1,920 (9.4)	
Other[b]	6,889 (17.1)		3,911 (19.2)	
Year of index date (%)		<0.001		<0.001
Pre-2015	34,168 (84.9)		17,220 (84.6)	
2015-2021	6,096 (15.1)		3,144 (15.4)	
DAA use (%)	7,112 (17.7)	<0.001	3,329 (16.3)	<0.001
Alcohol use (%)	10,093 (25.1)	<0.001	3,278 (16.1)	<0.001
Illicit drug use (%)	4,018 (10.0)	<0.001	1,999 (9.8)	0.005
Mental health visits (%)	659 (1.6)	0.076	297 (1.5)	0.317
Diabetes mellitus (%)	14,149 (35.1)	<0.001	6,025 (29.6)	0.088
Hypertension (%)	25,158 (62.5)	<0.001	12,321 (60.5)	<0.001
Hyperlipidemia (%)	13,034 (32.4)	<0.001	5,809 (28.5)	<0.001
Houselessness (%)	86 (0.2)	0.309	35 (0.2)	0.387
Charlson Comorbidity Index (SD)	3.87 (1.90)	<0.001	3.90 (1.89)	<0.001

Continuous variables are expressed as mean ± standard deviation. Categorical variables were presented as numbers (percentage). [a]Includes EPO, POS, and POS with capitation. [b]Includes basic/major medical, comprehensive, CDHP, HDHP, and unknown.

Figure 1. Percentage of Patients with Liver Complications and Delayed HCV Diagnosis, Total and by Time Before and After Complications (in months) by Sex



Disclosures: Charles Levesley: Nothing to Disclose, Xinrong Zhang: Nothing to Disclose, Leslie Kam: Nothing to Disclose, Richie Manikat: Nothing to Disclose, Ramsey Cheung: Nothing to Disclose, Mindie Nguyen: Nothing to Disclose

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1509 | AUTOMATED SCREENING OUTCOMES FOR HEPATITIS B AND C IN THE PREANESTHESIA UNIT: A HOSPITAL-BASED STUDY

Carlos Alventosa-Mateu[1] María Dolores Ocete Mochón[2] Juan Catalá Bauset[3] Javier Hernández Felices[2] Juan José Urquijo Ponce[4] Mercedes Latorre Sánchez[4] Inmaculada Castelló Miralles[4] Concepción Cardona Gimeno[5] Moisés Diago[4]

[1]General University Hospital Consortium of Valencia, [2]Microbiology Department. Consortium General Universitary Hospital of Valencia., [3]Preanesthetic Unit. Consortium General Universitary Hospital of Valencia., [4]Hepatology Unit. General University Hospital Consortium of Valencia, [5]Microbiology Department. General University Hospital Consortium of Valencia

Background: To achieve the goal of hepatitis C (HCV) elimination and control hepatitis B (VHB), screening strategies that identify new patients and link them to the healthcare system for treatment are necessary. Herein, we present the outcomes of universal HBV and HCV screening in our preanesthesia unit. **Methods:** We analyzed the **Results:** of our fully automated screening system for HBV and HCV in patients undergoing preanesthetic assessment at our hospital from 1/1/2023 to 5/25/2024. Our system routinely determined anti-HCV and anti-HBc antibodies and, if positive, measured HCV core antigen and HBsAg, respectively. In cases of confirmed active infection, the system sent an encrypted alert to Hepatology Unit to connect the diagnosis with specialized care. These physicians assessed the patient and determined the indication for antiviral treatment. We recorded the prevalence of both viruses and the characteristics of the diagnosed patients. **Results:** A total of 11,023 tests were performed, ranging from 1-99 years. The prevalence of anti-HCV was 3.04 % (335/11023), and HCV core Ag was 0.12 % (13/11023). For HBV, HBsAg prevalence was 0.25 % (28/11023). Prevalences by age groups are shown in the table, highlighting that HCV core Ag was higher at > 80 years old. Patients with active HCV infection were primarily Spanish, with an average age of 80.5 ± 11.5 (range 61-98), and 61.5 % (8/13) were women. The main originating service was orthopedics (61.5 %, 8/13). Most of new diagnosis (84.6 %, 11/13) were unaware of the disease. 61.5% (8/13) received treatment, all with F0-F2 fibrosis. The remaining 38.5 % (5/13) were not treated due to advanced age combined with severe comorbidities. For HBsAg, the average age was 60.93 ± 11.36, with a male predominance (67.9 %, 19/28). The majority were Spanish (78.6 %, 22/28), followed by Eastern Europe (10.7 %, 3/28). The main originating services were orthopedics (35.7 %, 10/28) and general surgery (25 %, 7/28). 57.1 % (16/28) had positive HBV DNA, and 35.7 % (10/28) had an indication for antiviral treatment, with 9 of these 10 patients having F3-F4 fibrosis, including one patient with advanced hepatocellular carcinoma. **Conclusion:** Preanesthesia screening enables the identification of new patients with HCV and HBV. The prevalence of anti-HCV is high in our area (3%), but active infection is very low (0.12%), concentrated in those >60 years. Half of the patients with active HCV infection were not candidates for treatment due to advanced age and severe comorbidities. Our automated alert system facilitates access to specialized care for patients and prevents loss in the care continuum.

	Anti-HCV	HCVcAg	HBs Ag
0-20 years (n = 594)	2.18 % (n = 13)	0 %	0 %
21-40 years (n = 1884)	7.38 % (n = 136)	0 %	0.05 % (n= 1)
41-60 years (n = 3147)	4.83 % (n = 89)	0 %	0.32 % (n = 10)
61-80 years (n = 4443(	2.00% (n = 89)	0.12 % (n = 6)	0.34 (n = 15)
>80 years (n = 995)	2.91% (n = 29)	0.70 % (n = 7)	0.20 % (n = 2)

Disclosures: Carlos Alventosa-Mateu: Nothing to Disclose, María Dolores Ocete Mochón: Nothing to Disclose, Juan Catalá Bauset: Nothing to Disclose, Javier Hernández Felices: Nothing to Disclose, Juan José Urquijo Ponce: Nothing to Disclose, Mercedes Latorre Sánchez: Nothing to Disclose, Inmaculada Castelló Miralles: Nothing to Disclose, Concepción Cardona Gimeno: Nothing to Disclose, Moisés Diago: Nothing to Disclose

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1510 | THE IMPACT OF HOMELESSNESS ON THE OUTCOMES OF PATIENTS WITH HEPATITIS C: AN ANALYSIS OF A NATIONAL DATABASE

David Lee[1] Mohammed Shaik[1] Sharmitha Yerneni[2] Nishat Anjum Shaik[1] Youngjae Cha[1] Ki Jung Lee[2] Gregory Fan[2] Nathalie Urrunaga[1]

[1]University of Maryland School of Medicine, [2]Tufts School of Medicine

Background: Homelessness and housing instability have been linked to higher rates of injection drug use and consequent Hepatitis C virus (HCV) acquisition. This study investigates the impact of homelessness on outcomes in patients hospitalized with HCV. **Methods:** Using the National Inpatient Sample from 2012-2017, patients admitted with HCV were selected and classified based on homelessness status. Homeless individuals were matched to their non-homeless counterparts using propensity score matching and then compared using Cox regression analysis. Primary endpoints included mortality, length of stay (LOS), and hospitalization costs, while secondary endpoints consisted of hepatic complications such as ascites, hepatic encephalopathy, varices, and sepsis. Further sub analyses were performed for specific needs, such as inadequate housing or lack of material resources. **Results:** Our study comprised 481,710 patients with HCV, with 445,049 (92.39%) being non-homeless and 36,661 (7.61%) being homeless. Each homeless patient was matched with a non-homeless counterpart, resulting in 36,661 matched pairs. Homeless patients with HCV demonstrated lower mortality (aHR 0.28, 95% CI 0.24-0.33, p<0.001) and hospitalization costs (aHR 0.85, 95%CI 0.85-0.85, p<0.001), but longer LOS (aHR 1.19, 95% CI 1.19-1.20, p<0.001). In terms of hepatic complications, homeless patients had lower rates of ascites (aHR 0.44, 95% CI 0.40-0.49, p<0.001), varices (aHR: 0.34, 95% CI 0.31-0.37, p<0.001), hepatic encephalopathy (aHR: 0.56, 95% CI 0.51-0.62, p<0.001), and sepsis (aHR: 0.89, 95% CI 0.84-0.94, p<0.001) compared to non-homeless patients. Further sub analyses showed that those with inadequate housing and lack of material resources did not demonstrate any significant difference in the primary endpoints or hepatic complications compared to their matched counterparts. The exception was the LOS, which was longer across all these strata. **Conclusion:** Despite the stigma of being socially complex and resource-intensive, homeless patients with HCV showed lower mortality and hospitalization costs, likely due to fewer hepatic complications. Longer length of stay was expected due to social complexities and discharge challenges. There is a need for a longitudinal study to better understand these findings in this patient population.

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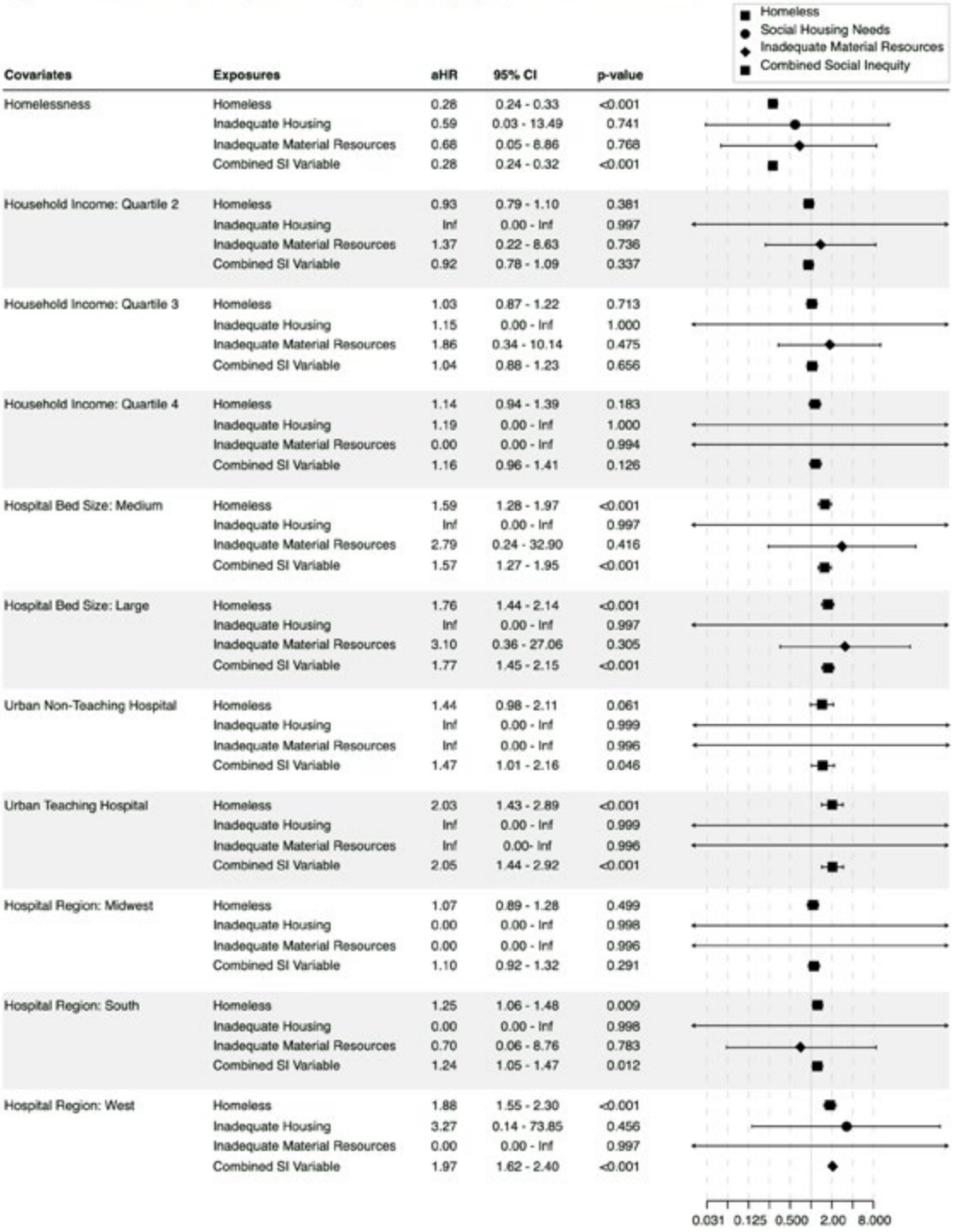
Figure 1: The multivariate forest plot using all-cause mortality as the primary endpoint, with homeless status as the exposure variable



Covariates	Exposures	aHR	95% CI	p-value
Homelessness	Homeless	0.28	0.24 - 0.33	<0.001
	Inadequate Housing	0.59	0.03 - 13.49	0.741
	Inadequate Material Resources	0.68	0.05 - 8.86	0.768
	Combined SI Variable	0.28	0.24 - 0.32	<0.001
Household Income: Quartile 2	Homeless	0.93	0.79 - 1.10	0.381
	Inadequate Housing	Inf	0.00 - Inf	0.997
	Inadequate Material Resources	1.37	0.22 - 8.63	0.736
	Combined SI Variable	0.92	0.78 - 1.09	0.337
Household Income: Quartile 3	Homeless	1.03	0.87 - 1.22	0.713
	Inadequate Housing	1.15	0.00 - Inf	1.000
	Inadequate Material Resources	1.86	0.34 - 10.14	0.475
	Combined SI Variable	1.04	0.88 - 1.23	0.656
Household Income: Quartile 4	Homeless	1.14	0.94 - 1.39	0.183
	Inadequate Housing	1.19	0.00 - Inf	1.000
	Inadequate Material Resources	0.00	0.00 - Inf	0.994
	Combined SI Variable	1.16	0.96 - 1.41	0.126
Hospital Bed Size: Medium	Homeless	1.59	1.28 - 1.97	<0.001
	Inadequate Housing	Inf	0.00 - Inf	0.997
	Inadequate Material Resources	2.79	0.24 - 32.90	0.416
	Combined SI Variable	1.57	1.27 - 1.95	<0.001
Hospital Bed Size: Large	Homeless	1.76	1.44 - 2.14	<0.001
	Inadequate Housing	Inf	0.00 - Inf	0.997
	Inadequate Material Resources	3.10	0.36 - 27.06	0.305
	Combined SI Variable	1.77	1.45 - 2.15	<0.001
Urban Non-Teaching Hospital	Homeless	1.44	0.98 - 2.11	0.061
	Inadequate Housing	Inf	0.00 - Inf	0.999
	Inadequate Material Resources	Inf	0.00 - Inf	0.996
	Combined SI Variable	1.47	1.01 - 2.16	0.046
Urban Teaching Hospital	Homeless	2.03	1.43 - 2.89	<0.001
	Inadequate Housing	Inf	0.00 - Inf	0.999
	Inadequate Material Resources	Inf	0.00- Inf	0.996
	Combined SI Variable	2.05	1.44 - 2.92	<0.001
Hospital Region: Midwest	Homeless	1.07	0.89 - 1.28	0.499
	Inadequate Housing	0.00	0.00 - Inf	0.998
	Inadequate Material Resources	0.00	0.00 - Inf	0.996
	Combined SI Variable	1.10	0.92 - 1.32	0.291
Hospital Region: South	Homeless	1.25	1.06 - 1.48	0.009
	Inadequate Housing	0.00	0.00 - Inf	0.998
	Inadequate Material Resources	0.70	0.06 - 8.76	0.783
	Combined SI Variable	1.24	1.05 - 1.47	0.012
Hospital Region: West	Homeless	1.88	1.55 - 2.30	<0.001
	Inadequate Housing	3.27	0.14 - 73.85	0.456
	Inadequate Material Resources	0.00	0.00 - Inf	0.997
	Combined SI Variable	1.97	1.62 - 2.40	<0.001

Disclosures: David Lee: Nothing to Disclose, Mohammed Shaik: Nothing to Disclose, Sharmitha Yerneni: Nothing to Disclose, Nishat Anjum Shaik: Nothing to Disclose, Youngjae Cha: Nothing to Disclose, Ki Jung Lee: Nothing to Disclose, Gregory Fan: Nothing to Disclose, Nathalie Urrunaga: Nothing to Disclose

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1511 | ANALYSIS OF THE INFLUENCING FACTORS OF DIAGNOSED BUT UNTREATED HCV INFECTED PATIENTS IN YUNNAN PROVINCE, CHINA

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Background: To explore the possible influencing factors that may lead to low diagnosis and treatment rate of hepatitis C in China, and to propose improvement measures to enhance the diagnosis and treatment level of hepatitis C. **Methods:** A total of 5506 HCV antibody positive and/or HCV RNA positive cases from 11 regions in Yunnan Province between 2004 and 2021 were included, of which 2006 cases received treatment, while 3500 cases not. A statistical model of logistic regression analysis for 2 outcomes binomial was established by jamovi statistical analysis software (version 2.3.28). **Results:** The dependent variable of the statistical model is whether treatment is received, while independent variables including age, area, urban-rural, gender, educational background, income, marital status, exposure factors 1 and 2, needle-sharing behavior among drug abusers and awareness of HCV infection. Based on the requirements of logistic regression analysis for 2 outcomes binomial, six independent variables, including age, area, urban-rural, marital status, needle-sharing behavior, and HCV infection awareness, were statistically significant and included in the statistical model (see Table 1). Model coefficients-outcomes (see Table 2) indicate the following results Specifically, those under 20 years old were 1.798 times more likely to refuse treatment compared to those over 60. Those age between 20 to 30 years old was 1.311 times more likely to refuse treatment than those over 60 years old. Urban residents were 1.676 times more likely to refuse treatment than rural residents. Individuals unaware of their HCV infection were 1.729 times more likely to refuse treatment. Non-needle sharing drug users were 1.318 times more likely to refuse treatment than those who shared needles. Unmarried individuals were 23% more likely to refuse treatment than married individuals. Compared with area D, the probability of rejecting treatment in regions O, A and L was 1.54, 1.574 and 1.419 times higher than that of area D, respectively. The risk of rejecting treatment in B, G, N, J, E, I, and H regions decreased by 63%, 37%, 26%, 68%, 51.8%, and 37.6%, respectively. The predictive indicators of the model (see Table 3, Figures 1 and 2) show that the accuracy of correctly classifying the dependent variable by the six variables entering the model is 65.9%, sensitivity is 85.9%, and specificity is 31.1%, The area under the ROC curve is 66.9%. **Conclusion:** By establishing a binary logistic regression analysis model, possible factors and risks leading to untreated HCV infected individuals in Yunnan Province, China were predicted. Although the model has low specificity, its 85.9% sensitivity helps to identify HCV infected individuals with low or unwilling treatment intentions. In clinical practice, providing health education to these individuals and to raise awareness of the risks associated with HCV infection can effectively improve treatment rate.

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Table 1. Model Fit Measure

Model	Deviance	AIC	BIC	R^2_{McF}	R^2_{CS}	R^2_N	R^2_T	Overall Model Test		
								χ^2	df	p
1	7138	7150	7190	0.0107	0.0140	0.0191	0.0133	77.4	5	< .001
2	7078	7092	7138	0.0192	0.0248	0.0340	0.0243	138.4	6	< .001
3	7032	7048	7101	0.0255	0.0329	0.0450	0.0324	183.9	7	< .001
4	7002	7020	7080	0.0296	0.0381	0.0521	0.0379	213.5	8	< .001
5	6997	7019	7092	0.0303	0.0389	0.0533	0.0387	218.4	10	< .001
6	6757	6801	6946	0.0636	0.0801	0.1096	0.0805	459.2	21	< .001

Table 2. Model coefficient-outcome

Predictor	Estimate	95% Confidence Interval		SE	Z	p	Odds ratio	95% Confidence Interval	
		Lower	Upper					Lower	Upper
Intercept	0.7959	0.4849	1.1068	0.1586	5.017	< .001	2.216	1.624	3.025
Age:									
2 - 0	0.5868	−0.1339	1.3074	0.3677	1.596	0.111	1.798	0.875	3.697
3 - 0	0.2711	−0.1028	0.6449	0.1907	1.421	0.155	1.311	0.902	1.906
4 - 0	−0.1071	−0.3220	0.1079	0.1097	−0.976	0.329	0.898	0.725	1.114
5 - 0	−0.3782	−0.5662	−0.1901	0.0960	−3.941	< .001	0.685	0.568	0.827
6 - 0	−0.3696	−0.5673	−0.1719	0.1009	−3.664	< .001	0.691	0.567	0.842
rural-urban:									
1 - 2	0.5147	0.3763	0.6571	0.0716	7.214	< .001	1.676	1.457	1.929
known or not:									
2 - 1	0.5473	0.4088	0.6857	0.0707	7.746	< .001	1.729	1.505	1.985
needlesharing:									
2 - 1	0.2763	0.1278	0.4247	0.0757	3.648	< .001	1.318	1.136	1.529
marital status:									
2 - 1	−0.2601	−0.4632	−0.0570	0.1036	−2.510	0.012	0.771	0.629	0.945
3 - 1	−0.0806	−0.3313	0.1700	0.1279	−0.631	0.528	0.923	0.718	1.185
area:									
G - D	−0.4710	−0.6870	−0.2550	0.1102	−4.274	< .001	0.624	0.503	0.775
B - D	−1.0040	−1.2723	−0.7356	0.1369	−7.333	< .001	0.366	0.280	0.479
N - D	−0.3016	−0.5702	−0.0451	0.1368	−2.295	0.022	0.735	0.565	0.956
K - D	−0.2283	−0.5716	0.1171	0.1762	−1.296	0.195	0.796	0.563	1.124
O - D	0.4318	0.1787	0.6849	0.1292	3.343	< .001	1.540	1.196	1.984
J - D	−1.1769	−1.5802	−0.7736	0.2058	−5.719	< .001	0.308	0.206	0.461
E - D	−0.7280	−0.9327	−0.5251	0.1040	−7.010	< .001	0.482	0.393	0.591
A - D	0.4535	0.0497	0.8574	0.2060	2.201	0.028	1.574	1.051	2.357
I - D	−0.2140	−0.4923	0.0642	0.1420	−1.508	0.132	0.807	0.611	1.066
H - D	−0.4716	−0.8299	−0.1132	0.1829	−2.579	0.010	0.624	0.436	0.893
L - D	0.3502	0.0882	0.6122	0.1337	2.620	0.009	1.419	1.092	1.845

Table 3. Predictive Measures

Accuracy	Specificity	Sensitivity	AUC
0.659	0.311	0.859	0.669

Note. The cut-off value is set to 0.5

Figure 1. Cut-off plot

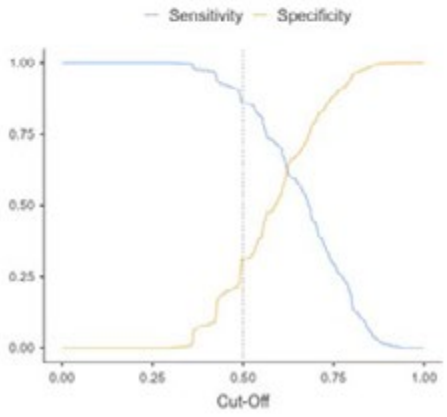
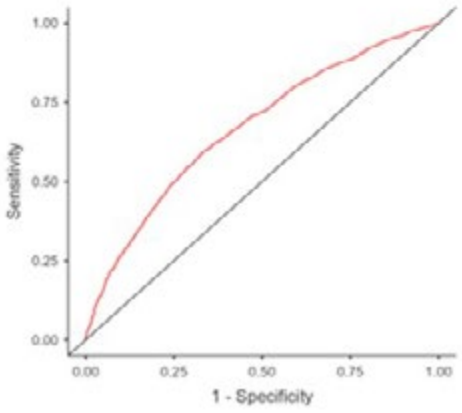


Figure 2. ROC curve



Disclosures: jia wei: Nothing to Disclose, Yuhua Shi: Nothing to Disclose, Hui Li: Nothing to Disclose, Xiaobin Zhang: Nothing to Disclose, Changhui Wu: Nothing to Disclose, Chuntao Liu: Nothing to Disclose, Yan Guo: Nothing to Disclose

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1512 | ACCESS TO A PRIMARY CARE PROVIDER (PCP) BOTH REDUCES THE RISK OF UNTREATED VIREMIA AND OF INCOMPLETE DIAGNOSIS AMONG PATIENTS WITH HEPATITIS C VIRUS (HCV)

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Background: Despite the success of direct acting antivirals (DAA) for HCV, the CDC reports persistent incomplete diagnostic testing and inadequate treatment in the U.S. Without a HEDIS measure for HCV, most healthcare systems do not address their HCV metrics independently. We aimed to identify specific gaps in HCV care within a real-world health system and determine the predictors of treatment with sustained virologic response (SVR), compared to untreated viremia and partial diagnosis. **Methods:** Using the electronic medical record (EMR) at a large urban tertiary health system, we identified all patients with current or prior HCV over 7 years (2016-2023). Inclusion required at least one of: reactive HCV Ab, detectable HCV RNA, HCV medication prescription, or chronic HCV ICD code. We extracted sociodemographic, laboratory, radiology, ICD codes for comorbidities, and visit data. HCV status categories were defined: 1) Treated with SVR, if HCV medication prescribed and undetectable RNA post-prescription; 2) Viremic, if most recent RNA was quantifiable; 3) Partially diagnosed, if reactive HCV Ab without RNA testing. Annual FIB-4 scores were computed for each patient with available lab data, categorized by risk for advanced fibrosis, using age-based cutoffs. Univariate and multivariate multinomial logistic regression was used to determine factors associated with achieving SVR. **Results:** We identified 12,424 patients in the HCV cohort: 1,719 treated with SVR, 2,113 viremic, and 2,069 partially diagnosed. Partially diagnosed patients were younger than treated and viremic patients (57 vs. 65 and 63). The cohort was diverse: 19% White, 13% Black, 16% Latinx, and 11% Asian; viremic patients had more Black (18%) and fewer Asian patients (5%). Women were less likely to be untreated and viremic but more likely to be incompletely diagnosed. Seeing a PCP was more common among patients with SVR than viremic or partially diagnosed (37% vs. 16% and 11%, $p<0.001$); and among SVR patients, 92% had seen hepatology. Among viremic patients, 62% had intermediate or high FIB-4 scores. On multivariate multinomial regression analysis seeing a PCP was shown to reduce the likelihood of untreated viremia and partial diagnosis by about 2/3 to 3/4 (Table 1). **Conclusion:** In this large real-world cohort of current/prior HCV patients in the post-DAA era, we found high rates of incomplete diagnosis and untreated viremia, with Black patients especially at risk. These findings illustrate how the EMR can provide extensive information for targeted outreach to patients needing RNA testing, treatment, evaluation for cirrhosis and HCC screening if cirrhotic. Seeing a PCP was the sole factor that both reduced the likelihood of viremia and incomplete diagnosis, suggesting that gaps in HCV care may be improved with better overall healthcare access.

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Table 1. Univariate and multivariate multinomial logistic regression analysis comparing viremia and partial diagnosis to treated with SVR.

	Treated with SVR n = 1719 (29%)	Viremic n = 2113 (36%)	Univariate OR (95% CI)	Multivariate OR (95% CI)	Partially Diagnosed n = 2069 (35%)	Univariate OR (95% CI)	Multivariate OR (95% CI)
Age			0.900 (0.849 – 0.950)	---		0.639 (0.604 – 0.677)	---
< 50	178 (15%)	337 (28%)			691 (57%)		
50 – 59	265 (30%)	309 (35%)			318 (365%)		
60 – 69	659 (33%)	785 (39%)			565 (28%)		
70 – 79	529 (35%)	569 (38%)			419 (28%)		
>80	88 (32%)	113 (41%)			76 (27%)		
Race/ethnicity			0.914 (0.875 – 0.956)	---		1.08 (1.03 – 1.12)	---
White	817 (28%)	1119 (39%)			959 (33%)		
Black/AA	265 (30%)	377 (43%)			230 (26%)		
Latinx	315 (33%)	301 (31%)			340 (36%)		
Asian	145 (27%)	118 (22%)			270 (51%)		
Other	128 (18%)	139 (20%)			203 (28%)		
Unknown/declined	49 (28%)	59 (30%)			67 (38%)		
Gender			0.793 (0.694 – 0.905)	---		1.37 (1.20 – 1.56)	---
Male	1057 (30%)	1411 (39%)			1113 (31%)		
Female	662 (29%)	702 (30%)			956 (41%)		
Ever PCP	640 (54%)	330 (28%)	0.312 (0.268 – 0.364)	0.301 (0.256 – 0.353)	224 (19%)	0.205 (0.173 – 0.243)	0.229 (0.192 – 0.273)
Ever hepatology	1584 (57%)	785 (28%)	0.050 (0.041 – 0.061)	---	431 (15%)	0.022 (0.018 – 0.028)	---
Ever seen in ED in 7 years	498 (37%)	535 (40%)	0.831 (0.720 – 0.959)	1.12 (0.952 – 1.31)	308 (23%)	0.429 (0.366 – 0.503)	0.656 (0.551 – 0.781)
Ever inpatient in the last 7 years	405 (28%)	673 (48%)	1.52 (1.31 – 1.75)	---	331 (23%)	0.618 (0.526 – 0.727)	---
FIB 4 category			1.16 (1.04 – 1.28)	---		0.890 (0.799 – 0.992)	---
Low risk (<1.45)	482 (32%)	457 (31%)			547 (37%)		
Intermediate risk (1.45-3.25)	544 (42%)	461 (36%)			299 (23%)		
High risk /cirrhosis (>3.25)	209 (28%)	293 (40%)			236 (32%)		
Decompensation	271 (42%)	225 (35%)	0.637 (0.527 – 0.770)	---	143 (22%)	0.397 (0.320 – 0.492)	---
Liver cancer	205 (34%)	214 (36%)	0.832 (0.584 – 0.900)	---	184 (31%)	0.721 (0.584 – 0.890)	---
Diabetic	346 (30%)	422 (37%)	0.990 (0.845 – 1.16)	0.957 (0.811 – 1.13)	378 (33%)	0.887 (0.754 – 1.04)	0.796 (0.670 – 0.945)
Prediabetic	166 (32%)	180 (35%)	0.871 (0.698 – 1.09)	---	167 (33%)	0.821 (0.656 – 1.03)	---
Hyperlipidemia	340 (44%)	233 (30%)	0.503 (0.420 – 0.602)	---	195 (25%)	0.422 (0.349 – 0.510)	---
Hypertension	762 (40%)	729 (38%)	0.662 (0.580 – 0.754)	---	438 (23%)	0.337 (0.293 – 0.389)	---
Alcohol use disorder	106 (28%)	195 (51%)	1.55 (1.21 – 1.98)	1.52 (1.18 – 1.97)	83 (21%)	0.636 (0.474 – 0.854)	0.738 (0.541 – 1.01)
NASH	28 (37%)	23 (30%)	0.665 (0.381 – 1.16)	---	25 (33%)	0.739 (0.429 – 1.27)	---
Obesity	496 (11%)	423 (54%)	0.799 (0.686 – 0.932)	---	467 (35%)	0.827 (0.712 – 0.960)	---
Hemodialysis	76 (26%)	111 (37%)	1.20 (0.889 – 1.62)	1.19 (0.807 – 1.50)	111 (37%)	1.23 (0.909 – 1.65)	1.18 (0.860 – 1.61)
Death	183 (25%)	313 (43%)	1.46 (1.29 – 1.77)	---	233 (32%)	1.07 (0.87 – 1.31)	---

Multivariate multinomial logistic regression model included the following variables: ever seen by PCP, ever seen in the ED in 7 years, diabetes, alcohol use disorder, and hemodialysis
OR = odds ratio, CI = confidence interval, ED = emergency department, SVR = sustained virologic response, PCP = primary care provider, AA = African American, NASH = nonalcoholic steatohepatitis

Disclosures: Mai Sedki: Nothing to Disclose, Jennifer Price: Nothing to Disclose, Gina Intinarelli: Nothing to Disclose, Michael Helle: Nothing to Disclose, Tasha Toliver: Nothing to Disclose, Rena Fox: Nothing to Disclose

1513 | A DESCRIPTIVE ANALYSIS OF INJECTION-RELATED INFECTIONS AMONG PEOPLE LIVING WITH HEPATITIS C FOR DIRECT ACTING ANTIVIRAL (DAA) TREATMENT RECEIVED AND NAIIVE INDIVIDUALS ACROSS PRE- AND POST-TREATMENT PHASES

Ji Hyun Choi[1] Stanley Wong[2] Hector Velasquez[2] Dahn Jeong[1] Sofia Bartlett[1] Nicholas Crier[3] James McLeod[3] Samona Marsh[3] Julie Chapman[3] Naveed Janjua[2]

[1]University of British Columbia, [2]BC Centre for Disease Control, [3]The Downtown Eastside Community Research Ethics Workshop Group

Background: Injection drug use (IDU) is one the major risk factor for HCV in developed countries, including Canada. Unsafe IDU practices are associated with a high risk of injection-related infections (IRIs), which can lead to serious complications if untreated. Introduction of direct-acting antiviral (DAA) drugs has expanded treatment reach and enabled outreach efforts to engage people living with HCV in care. We examined the relationship of engagement with DAA treatment and injection-related infections among people living with HCV. **Methods:** Using the BC Hepatitis Testers Cohort (BC-HTC), which integrates data on HCV testing with medical visits, hospitalizations, prescription drugs, and death records, we have created a matched cohort comprising a group

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treated with DAA and a group not treated with DAA. HCV testing in this cohort includes data from 1990 to 2015, with infection incident data up to March 31st, 2021. The cohorts were matched based on time of diagnosis, demographic data, and the local health area. We examined different levels of IRIs, such as skin and soft tissue infection, sepsis, endocarditis, osteomyelitis, and bacteremia. We assessed the annual rate of infection per person before the initial visit with the DAA prescribing doctor, during the workup period (between the initial visit with the DAA prescribing doctor and the first date of DAA treatment), during DAA treatment, and after DAA treatment periods. Additionally, we recorded infection incidents per year for the group who did not receive DAA treatment. **Results:** The study included a total of 8062 individuals for analysis, comprising 4031 individuals treated with DAA and a matched counterpart of 4031 individuals not receiving DAA treatment. Among them, 5948 individuals had experienced injection-related infections. Regarding the most common serious complication, sepsis, the untreated group had a mean of 106.2 rate per 1000 per year while the treated group had 51.53 before treatment, 19.49 during the workup period, 3.464 during DAA treatment, and 36.81 after DAA treatment. **Conclusion:** This preliminary analysis shows a trend towards decreasing injecting related infections following engagement in the HCV treatment. Further investigations with robust design and control for confounding is warranted.

Table 1. Means (rate x 1000) and standard deviations of Infection events per year for treated and not treated with DAA, and each period for the treated group

	Not treated with DAA	Treated with DAA			
		Before treatment period	Workup period	During DAA treatment period	After DAA treatment period
	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)
Skin and soft tissue infection	322.9 (9.2)	271.4 (9.5)	56.65 (4.02)	8.407 (1.545)	81.20 (4.28)
Injection-related infections	472.6 (11)	350.5 (10.8)	87.23 (4.98)	14.40 (2.01)	131.4 (5.4)
Sepsis	106.2 (5.2)	51.53 (4.16)	19.49 (2.37)	3.464 (0.999)	36.81(2.89)
Bacteremia	5.978 (1.259)	3.781 (1.143)	1.176 (0.596)	0.595 (3.262)	2.422 (0.752)
Osteomyelitis	22.00 (2.4)	10.52 (1.89)	5.602 (1.277)	1.804 (0.726)	8.361 (1.384)
Endocarditis	26.78 (2.65)	19.08 (2.54)	5.768 (1.294)	0.5052 (0.3944)	5.486 (1.124)

Disclosures: Ji Hyun Choi: Nothing to Disclose, Stanley Wong: Nothing to Disclose, Hector Velasquez: Nothing to Disclose, Dahn Jeong: Nothing to Disclose, Sofia Bartlett: Nothing to Disclose, Nicholas Crier: Nothing to Disclose, James McLeod: Nothing to Disclose, Samona Marsh: Nothing to Disclose, Julie Chapman: Nothing to Disclose, Naveed Janjua: Nothing to Disclose

1514 | THE IMPACT OF PRE-TRANSPLANT PORTAL VEIN THROMBOSIS ON POST-TRANSPLANT PATIENT SURVIVAL

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Background: Non-tumoral bland portal vein thrombosis (PVT) is present in 2-26% of patients on the waitlist for liver transplantation (LT). Increased need for blood product transfusions, longer intensive care and hospital stay, and inability to perform LT have been implicated with the impaired prognosis or survival in patients with extensive portomesenteric thrombosis. Controversial findings exist on whether post-LT mortality is equivalent or not in patients with pre-LT PVT compared to those without. **Methods:** An analysis of all adult patients who underwent LT at our center between 2013-2023 was performed. Clinical, laboratory, histological, and follow-up data were collected. The presence of PVT was determined via imaging or assessed during LT through direct or pathological examination of the explant. Categorical variables are presented as numbers and percentages, and continuous variables are presented as means and standard deviation or median with interquartile range. Kaplan-Meier curves

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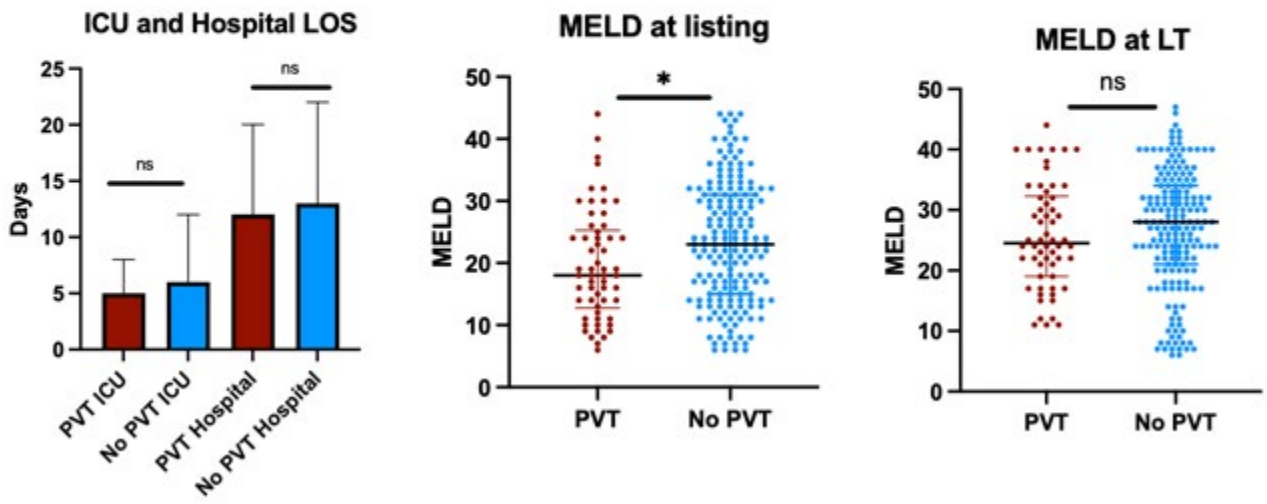
with Log-rank test were used to compare survival outcomes. **Results:** Out of the 239 patients who underwent LT, 58 (24.3%) had pre-LT PVT. Post-LT PVT recurrence was seen in 12 (5.0%) patients, with no significant difference between patients with and without pre-LT PVT. However, significant differences were noted for male gender (79.3% vs 64.1%, *p*=0.03), lower MELD at listing [18 (13-25) vs 23 (15-31), *p*=0.01], presence of esophageal varices (91.4% vs 69.6%, *p*=0.001), esophageal variceal bleeding (51.7% vs 29.3%, *p*=0.002), and TIPS (27.6% vs 10.5%, *p*=0.001) in patients with pre-LT PVT compared to those without PVT. Patients with pre-LT PVT also experienced longer waitlist times [218 (15-428) vs 43 (8-199) days, *p*=0.0001]. ICU and hospital length of stay did not significantly differ between the two groups (Figure 1). Post-LT hepatic artery thrombosis (HAT) was more prevelant in patients with pre-LT PVT (6.9% vs 1.1%, *p*=0.02). Overall mortality among patients with PVT was 19%, compared to 18.2% among those without PVT (*p*=0.9), with no significant difference in post-LT survival (*p*=0.9). The 1-year survival rate post-LT was 94.7% in patients with pre-LT PVT, compared to 95.5% in those without PVT; 3-year survival rates were 88.6% in patients with pre-LT PVT, compared to 92.3% in those without PVT; and 5-year survival rates were 81.8% in patients with pre-LT PVT, compared to 78.1% in those without PVT. **Conclusion:** PVT is a well-recognized complication of cirrhosis, and remains controversial for LT. In our study, patients with pre-LT PVT had significant differences for gender, MELD at listing, decompensation events with variceal bleeding compared to patients without PVT. TIPS and post-LT HAT were more commonly present in patients with pre-LT PVT. ICU and hospital length of stay, and post-LT mortality were comparable between both groups. Notably, the presence of pre-LT PVT was not associated with worse overall survival.

Figure 1. Median LOS post-LT, MELD at listing and at LT in patients with pre-LT PVT compared to without PVT



Disclosures: Nazli Begum Ozturk: Nothing to Disclose, Ewelina Niedzialkowska: Nothing to Disclose, Tatjana Blazin: Nothing to Disclose, Ahmed Aref: Nothing to Disclose, Usman Bin Hameed: Nothing to Disclose, Laith Jamil: Nothing to Disclose

1515 | PRESENTATION AND MALFORMATIONS ASSOCIATED WITH EXTRAHEPATIC CONGENITAL PORTOSYSTEMIC SHUNTS

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Background: Extrahepatic congenital portosystemic shunts (EH CPSS) are accepted to be associated with more severe signs and symptoms than intrahepatic (IH) shunts. There is a broad spectrum of anatomical subtypes of EH CPSS, and their frequency is unknown. Whether anatomical subtype or congenital malformations are associated with severity of signs and symptoms at diagnosis would help orient management and follow up. To

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this end, we analyzed the frequency of anatomical subtypes, associated congenital malformations, and signs and symptoms at time of diagnosis using the International Registry of Congenital Portosystemic Shunts (IRCPSS). **Methods:** Congenital malformations (CM), signs and symptoms (S&S) at time of diagnosis were extracted from the IRCPSS (PMID: 35854389). Anatomical subtypes were defined using the Bicêtre classification (PMID: 29730740). S&S were defined as follows: 'liver' (nodules, cholestasis), 'cardiopulmonary' (pulmonary vascular disease or high output heart failure), 'neurological' (any neuropsychological manifestations compatible with hepatic encephalopathy) 'metabolic' (hypoglycemia, hyperammonemia), and renal or endocrine abnormalities. Severe S&S included liver nodules or pulmonary vascular disease. We tested whether anatomical subtypes and the presence of CM were associated with the severity of S&S using Fisher exact tests. For all extracted variables, missing or unknown information were considered as missing data and descriptive statistics were computed on available data. **Results:** In May 2024, of 295 patients in IRCPSS, 133 were identified as having an EH CPSS anatomical type (Table 1). Associated CM were reported in 80/123 patients (65%). Among 51/129 patients (38%) with cardiac malformations, atrial septal defect and ventricular septal defect were recorded in 18 and 20 patients respectively, and 7 patients displayed situs abnormalities. No association was detected between the severity of S&S and shunt anatomy (p=0.391) or associated CM (p=0.672). **Conclusion:** In patients referred to expert centers for EH CPSS management, associated CM, especially cardiac malformations, were very common and seemingly unrelated to severity of S&S at presentation. Likewise, anatomical type of EH CPSS was not associated with S&S. These results suggest that patients with CPSS should be screened for other malformations, and that EH CPSS may be underestimated in children with congenital malformations.

Table 1

Variable	Modality	EH (n=133) n (%)	Missing
Shunt type	3	53(40)	
	4	69 (52)	
	5	11 (8)	
Females		70 (53)	
Age at diagnosis	>1 year	65 (52)	9
Severity at diagnosis	Severe	57 (43)	
	Non severe	74 (56)	
	No signs & symptoms	2 (2)	
Signs and symptoms at diagnosis	Metabolic	89 (74)	12
	Cardiopulmonary	67 (54)	10
	Liver	55 (44)	7
	Neuropsychological	48 (44)	24
	Renal and endocrine	12 (9)	16
Associated congenital malformations	Any	80 (65)	10
	Cardiac	51 (40)	4
	Urological	16 (12)	4
	Gastrointestinal	10 (8)	5
	Brain	3 (2)	11
	Vascular	27 (23)	15

Disclosures: Valerie McLin: Mirum: Consultant, Ipsen: Speaking and Teaching, Astra Zeneca: Advisor, Isaline Chabbey: Nothing to Disclose, Julie Wacker: Nothing to Disclose, Laurent Savale: Nothing to Disclose, Riccardo Superina: Nothing to Disclose, Anne-Laure Rougemont: Nothing to Disclose, Valeria Casotti: Alexion: Speaking and Teaching, Antoine Poncet: Nothing to Disclose, Simona Korff: Nothing to Disclose, Dominique Debray: Nothing to Disclose

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1516 | HEMATOLOGICAL LONG-TERM COMPLICATIONS OF COVID-19 IN PATIENTS WITH COMPENSATED CIRRHOSIS: A U.S. BASED ANALYSIS

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Background: COVID-19 infection is associated with a wide array of manifestations. Patients with cirrhosis are a particularly susceptible population. There is available data that patients with cirrhosis have an increased mortality rate and decompensation events with COVID-19 infection. COVID-19 is also associated with a hypercoagulable state promoting clot formation. Patients with cirrhosis have an imbalanced coagulation profile. Our study aims to analyze the hematological long-term effect of COVID-19 in patients with compensated cirrhosis. **Methods:** We queried the US Collaborative Network (contains 63 healthcare organizations) of TriNetX deidentified research database. Patients with compensated cirrhosis from 2020 to 2024 were divided into 2 cohorts; patients with a positive COVID-19 test and patients without COVID-19. We excluded patients with any prior decompensation event, prosthetic heart valve, atrial fibrillation, prior portal vein thrombosis (PVT), deep vein thrombosis (DVT), or pulmonary embolism (PE). Two well-matched cohorts were created using a 1:1 propensity-scored matching (PSM) model between cohorts. PSM was based on baseline patients' characteristics, comorbidities, and medications. We compared the rates PVT, DVT, and PE between the two cohorts at 6 months, 1- and 3- years. **Results:** A total of 330,521 patients with compensated cirrhosis were identified. Of those, 27% (n=89,227) tested positive for COVID-19 and 73% (n=241,294) did not. After PSM, both cohorts included 74,738 patients. Patients with compensated cirrhosis who tested positive for COVID-19 infection had a statistically higher rate of PVT when compared to those without at 6 months (0.63% vs 0.5%, p<0.05), at 1 year (0.8% vs 0.6%, p<0.05), and at 3 years (1% vs 0.7%, p<0.05). They also had a statistically higher rate of DVT at 6 months (0.8% vs 0.4%, p<0.05), 1 year (1% vs 0.5%, p<0.05), and at 3 years (1.4% vs 0.8%, p<0.05). Furthermore, the rate of PE was also significantly higher in patients with compensated cirrhosis who tested positive for COVID-19 infection when compared to those without at 6 months (0.6% vs 0.3%, p<0.05), 1 year (0.7% vs 0.4%, p<0.05), and 3 years (1% vs 0.6%, p<0.05). **Conclusion:** Presence of COVID-19 infection in patients with compensated cirrhosis was associated with higher rate of PVT, DVT, and PE at 6 months, 1- and 3- years.

	PVT			DVT			PE		
	COVID-19 N=74,738	No COVID-19 N=74,738	P-value	COVID-19 N=74,738	No COVID-19 N=74,738	P-value	COVID-19 N=74,738	No COVID-19 N=74,738	P-value
6 months	470 (0.63%)	372 (0.50%)	0.001	592 (0.79%)	297 (0.40%)	<0.001	418 (0.56%)	187 (0.25%)	<0.001
1 year	577 (0.77%)	454 (0.61%)	<0.001	739 (0.99%)	397 (0.53%)	<0.001	533 (0.71%)	258 (0.35%)	<0.001
3 years	732 (1.0%)	553 (0.74%)	0.000	1,027 (1.37%)	630 (0.84%)	0.000	749 (1.0%)	413 (0.55%)	0.000

Disclosures: Mark Ayoub: Nothing to Disclose, Carol Faris: Nothing to Disclose, Tajana Juranovic: Nothing to Disclose, Rafi Aibani: Nothing to Disclose, Harleen Chela: Nothing to Disclose, Nadeem Anwar: Nothing to Disclose, Ebubekir Daglilar: Nothing to Disclose

1517 | URSODEOXYCHOLIC ACID IMPROVES LIVER ENZYMES IN PATIENTS WITH OBLITERATIVE PORTAL VENOPATHY - A PILOT STUDY

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[1]Mount Sinai Hospital

Background: Obliterative portal venopathy (OPV) is a histopathologic lesion on liver biopsy representing a type of idiopathic noncirrhotic portal hypertension (INCPH) or porto-sinusoidal vascular disease (PVSD). Currently, there is no independent, liver-specific treatment for OPV or other forms of PSVD. However, there are anecdotal reports that ursodeoxycholic acid (UDCA) may have a beneficial effect. The aim of this study was to evaluate the potential effect of UDCA on liver enzymes in patients with OPV. **Methods:** In this pilot study, consecutive patients seen in a hepatology practice with a diagnosis with OPV on liver biopsy and abnormal liver enzymes were prescribed weight-based UDCA and followed for drug safety and response. An unmatched control group of

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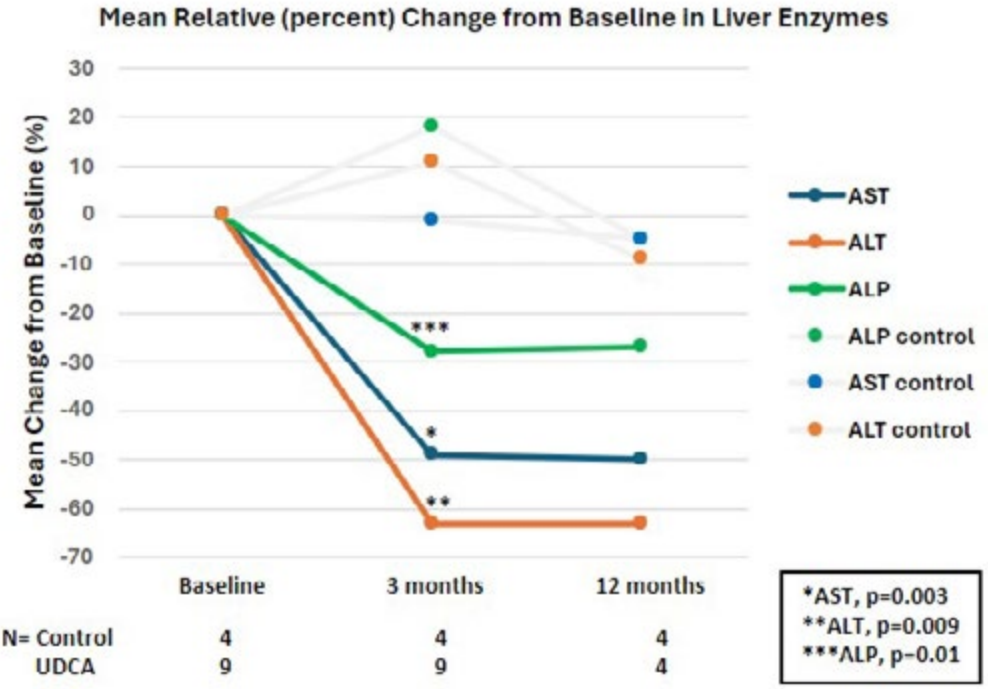
patients with OPV without treatment was used for comparison. The primary outcome of analysis was improvement of liver enzymes from baseline and compared to controls, namely AST, ALT and ALP. Secondary outcomes examined were normalization of liver enzymes and treatment-related adverse events. **Results:** From 2018-2024, 11 patients with biopsy-proven OPV were identified. Patient characteristics were median age 57 years (IQR 46-64), 55% female with diverse race (27% African [Caribbean], 27% Hispanic, 27% White, 18% Asian). The primary indication for liver biopsy was portal hypertension evaluation (55%) and abnormal liver enzymes (45%). Nine out of 11 (82%) patients had at least one abnormal liver enzyme at the time of diagnosis. Eight out of 11 (73%) patients had elevated ALP and 7/11 (64%) had AST and/or ALT elevations. While autoimmune serologies were negative in all except one patient (+AMA), 6/10 (56%) had elevated IgA. Concomitant NRH was noted on biopsy in 4/11 (36%). Potential OPV risk factors identified were portal vein thrombosis (n=2), autoimmune disorders (n=2), DILI (n=2), and latent tuberculosis (n=1). No risk factors were identified in 55%. Nine patients with OPV and abnormal liver enzymes were treated with UDCA at a median dose 13 mg/kg (IQR 12.3-13.7) with follow-up and repeat laboratory assessment at a median 98 days from treatment initiation. Overall, baseline median AST, ALT, and ALP levels were 56 U/L (IQR 38-97), 58 U/L (IQR 39-141), 214 U/L (IQR 167-354), respectively. Mean changes from baseline after UDCA in AST, ALT, and ALP were -49% (SD 16), -53% (22), -29% (17), respectively. All were significantly improved compared to untreated controls (n=4), $p<0.01$ for all (Figure 1). In 4 patients with 1-year follow-up on UDCA, AST and ALT normalization occurred in 100%, but 0% for ALP. One patient with initial improvement in liver enzymes who later self-discontinued UDCA had recurrent elevations. No treatment-related adverse events were seen. **Conclusion:** UDCA improves liver enzymes in patients with OPV, particularly the aminotransferases. While the therapeutic mechanism is unclear, UDCA warrants further study as the first potential liver-specific treatment for OPV.



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1518 | PORTO-SINUSOIDAL VASCULAR DISORDER AND SINUSOIDAL OBSTRUCTIVE SYNDROME IN PATIENTS TREATED WITH THIOPURINES: A SYSTEMATIC ANALYSIS

Erica Nicola Lynch[1] Armando Curto[2] Simona Parisse[3] Università Careggi[1]

[1]University of Florence, [2]Unversity of Florence, [3]Sapienza University of Rome

Background: Porto-sinusoidal vascular disorder (PSVD) is a new term that encompasses a spectrum of liver vascular abnormalities that can eventually lead to non-cirrhotic portal hypertension. The most specific pathological alterations are obliterative portal venopathy (also defined as portal stenosis) and nodular regenerative hyperplasia (NRH). Thiopurine (including 6-mercaptopurine – 6-MP, azathioprine – AZA, and 6-thioguanine – 6-TG) use has been associated with the development of PSVD but also sinusoidal obstructive syndrome (SOS), a more acute liver vascular disease, considered a separate entity from PSVD. The extent of the association between PSVD and thiopurine use across different diseases is currently unknown. **Methods:** A comprehensive search was conducted in EMBASE, MEDLINE, Web of Science, the Cochrane database, and SCOPUS. Two separate reviewers were involved in the process of article selection and evaluation. All case reports, case series, published clinical trials, retrospective, and prospective studies which reported PSVD (including all previous terminology) and SOS in patients treated with thiopurines were included in the analysis. Cases which were identified with previous terminology were considered PSVD when current diagnostic criteria were met. **Results:** After duplicate removal and appropriate screening, from a total of 762, 130 articles were included in the study. Seventeen studies concerned haematological patients, 6 rheumatic patients, 53 inflammatory bowel disease patients, 41 transplant recipients, and 13 were miscellaneous. A total of 20 cases of PSVD appeared to be clearly related to 6-MP. Lower doses of AZA (<1 mg/kg) were associated with PSVD in 10 cases. No evidence of PSVD in autoimmune hepatitis treated with thiopurines has ever been recorded. Early identification of PSVD with active surveillance (including liver biopsy) in patients treated with thiopurines was associated with resolution of the disease. Thiopurines were associated with both SOS and PSVD. 6-TG is clearly associated with SOS as demonstrated in haematological clinical trials, whereas only sporadic cases of SOS are reported in patients treated with AZA or 6-MP. **Conclusion:** 6-MP and low daily dosage of AZA (<1 mg/kg) appear be associated with a lower risk of PSVD and SOS. Active surveillance for PSVD in patients treated with thiopurines may enable timely treatment interruption and vascular disease regression before full-blown portal hypertension is established. PSVD and SOS were both associated with thiopurine therapy. SOS should not probably be considered a separate disease entity but a more acute and severe manifestation of PSVD.

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TITLE	
1. Title:	Porto-sinusoidal vascular disorder and sinusoidal obstructive syndrome in patients treated with thiopurines: a systematic analysis
BACKGROUND	
2. Objectives:	Define disease characteristics of PSVD and SOS in patients treated with thiopurines
METHODS	
3. Eligibility criteria:	All available case reports, case series, published clinical trials, retrospective, and prospective studies which reported PSVD (including all previous terminology) and SOS in patients treated with thiopurines
4. Information sources	EMBASE, MEDLINE, Web of Science, the Cochrane database, and SCOPUS
5. Risk of bias:	All cases of PSVD were considered as such when fitting the current definition of PSVD
RESULTS	
6. Included studies	130 articles: 17 about haematological patients, 6 about rheumatic patients, 53 about inflammatory bowel disease patients, and 41 about transplant recipients, and 13 were miscellaneous
7. Synthesis of results:	Low incidence of PSVD and no evidence of SOS in low-dose AZA and 6-MP. No evidence of liver vascular disease in autoimmune hepatitis treated with thiopurines. Active surveillance and timely diagnosis of PSVD lead to favourable outcomes
DISCUSSION	
8. Strengths and Limitations of evidence:	No comprehensive analysis of incidence and prevalence of PSVD and SOS was performed as only studies which specifically included reports of liver vascular disease where included.
9. Interpretation:	SOS and PSVD probably should not be considered separate entities but different manifestations of a single disease
OTHER	
10. Funding:	No funding source

Disclosures: Erica Nicola Lynch: Nothing to Disclose, Armando Curto: Nothing to Disclose, Simona Parisse: Nothing to Disclose, Università Careggi: Nothing to Disclose

1519 | DEFIBROTIDE AND ITS ROLE IN THROMBIN INDUCED PLATELET ACTIVATION AND ENDOTHELIAL CELL PROTECTION VIA PAR-1

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Background: Sinusoidal obstruction syndrome (SOS), or veno-occlusive disease (VOD), is a severe disease that **Results:** from toxic injury to hepatic endothelial cells (ECs), including inflammation, EC activation, widening of EC gaps, and platelet aggregation. Defibrotide (DF) is a large mixture of single stranded phosphodiester oligonucleotides and an effective FDA-approved treatment for adult and pediatric SOS. It has a wide number of known and proposed actions, including anti-inflammatory, anti-thrombotic, and fibrinolytic capabilities as well as endothelial cell (EC) protection; however, its precise mechanisms are unknown.[1] Protease activated receptors (PARs) are G protein coupled receptors (GPCR). PAR-1 is the primary mediator of thrombin-stimulated platelet aggregation and EC activation. PAR-1 can be cleaved by numerous serine proteases to cause downstream proinflammatory effects and vascular leak.[2] We aim to better define the impact of DF on platelet and EC activation by testing the hypothesis that DF acts via PAR-1. **Methods:** Human washed platelets were incubated with DF (1mg/ml) and stimulated with thrombin and PAR-agonist peptides for use in flow cytometry. Antibodies specific for platelet activation (PAC1) and PAR-1 (WEDE15 which binds to the cleaved and uncleaved receptor and SPAN12 which only binds to the uncleaved receptor) were employed to analyze the effect of DF as well as potential binding sites. We have shown that EA.hy926 cells, an immortalized endothelial cell line, express PAR-1. We are currently using CRISPR CAS9 technology to knock out PAR-1 and PAR-4 from these cells, with the goal of measuring the impact of DF treatment on GPCR Gq activation and monolayer retraction. **Results:** DF inhibited thrombin induced platelet activation by 88±6% ($p<0.001$). A minimal inhibitory effect of DF was seen for PAR-1 (10±4%) and PAR-4 (8±7%) agonists alone or in combination (3±2%). These findings were confirmed with platelet aggregometry. Furthermore, with or without thrombin stimulation, there was decreased WEDE15 (but not

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SPAN12) binding to PAR-1 in the presence of DF, identifying an association between DF and PAR-1 ($p<0.05$). **Conclusion:** DF inhibits thrombin's ability to act on PAR-1. DF does not directly interact with the downstream pathways as it did not inhibit PAR-peptide agonist signaling. A decrease in WEDE15 binding in the presence of DF suggests a common binding site of interaction between the two compounds. Further research is needed, particularly on the impact of DF's interactions with PAR-1 on ECs. Additional investigation is ongoing.

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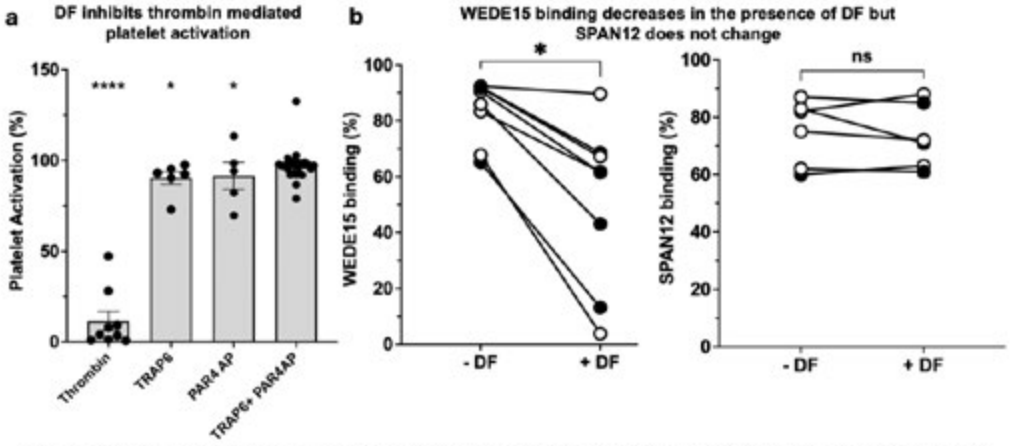

Figure 1: a) Defibrotide (1mg/ml) inhibits thrombin (0.1-1U/ml) induced platelet activation as measured by % of platelets positive for PAC1 (activated glycoprotein IIb/IIIa) versus control ($p=0.0002$). This decrease in platelet activation was minimal for TRAP6, PAR4AP, and TRAP6 and PAR4AP in combination at various concentrations. b) WEDE15 antibody shows decreased binding in the presence of defibrotide with and without the presence of thrombin where black dots= 0.1U/ml thrombin and white dots= no thrombin ($p=0.02$) but SPAN12 antibody binding does not change.

Disclosures: Shelley Choudhury: Nothing to Disclose, Kristin Maher: Nothing to Disclose, Thomas Girard: Nothing to Disclose, Jorge Di Paola: Alnylam Pharmaceuticals: Consultant

1520 | HEPATIC CONGESTION PROMOTES LIVER PATHOGENESIS THROUGH THE ACTIVATION OF INTEGRIN αV-YAP/TAZ-CTGF AXIS IN LSECS

Seiya Kato[1] Hayato Hikita[1] Kazuhiro Murai[2] Yuki Tahata[3] Yoshinobu Saito[1] Takahiro Kodama[3] Tomohide Tatsumi[3] Tetsuo Takehara[3]

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Background: The detailed mechanism of pathogenesis in congestive hepatopathy, such as right-sided heart failure, post-Fontan surgery, and Budd-Chiari syndrome, remains unclear. We aimed to elucidate it by focusing on the mechanotransduction of liver sinusoidal endothelial cells (LSECs). **Methods:** Partial IVC ligation (pIVCL) was performed to induce hepatic congestion in mice. Single-cell RNA sequencing (scRNA-seq) was performed on murine livers after pIVCL. Primary murine LSECs or TMNK-1 cells, a human liver endothelial cell line, were subjected to hydrostatic pressure stimulation (HPS). Spatial transcriptomics was performed on human livers from patients with Fontan-associated liver disease (FALD) using the CosMx Spatial Molecular Imager. **Results:** Portal venous pressure was significantly elevated 2 weeks after pIVCL, and liver fibrosis was observed mainly in Zone 3, developing without ALT elevation. Liver tumors were observed in some of the mice at 48 weeks after pIVCL. The scRNA-seq analysis showed that in Zone 3 LSECs after pIVCL, the Integrin signaling pathway and YAP/TAZ were activated. The most upregulated gene in Zone 3 LSECs was connective tissue growth factor (CTGF). HPS activated YAP/TAZ through Integrin αV in LSECs. HPS-induced CTGF upregulation in TMNK-1 cells was suppressed by siRNA-induced silencing of YAP/TAZ, a YAP inhibitor, or an Integrin αV inhibitor. By adding to CTGF, YAP/TAZ activity in TMNK-1 cells was increased via Integrin αV. We generated tamoxifen-inducible endothelial cell-specific CTGF knockout mice (Cdh5-CreERT2; $CTGF^{fl/fl}$), followed by pIVCL. pIVCL-induced liver fibrosis was reduced, portal hypertension was attenuated, and liver tumorigenesis was suppressed by CTGF

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knockout in endothelial cells. Treatment with an Integrin αV inhibitor also improved pIVCL-induced liver fibrosis and portal hypertension. Spatial transcriptomic analysis of the FALD liver revealed that Integrin αV was expressed in LSECs and that CTGF was upregulated in LSECs in areas of hepatic congestion and perisinusoidal fibrosis. **Conclusion:** In congestive hepatopathy, mechanostress in the liver sinusoids activates YAP/TAZ in LSECs through Integrin αV and promotes CTGF secretion, which is responsible for the progression of liver fibrosis and portal hypertension.

Disclosures: Seiya Kato: Nothing to Disclose, Hayato Hikita: Nothing to Disclose, Kazuhiro Murai: Nothing to Disclose, Yuki Tahata: Nothing to Disclose, Yoshinobu Saito: Nothing to Disclose, Takahiro Kodama: Chugai Pharmaceuticals: Speaking and Teaching, Astrazeneca: Speaking and Teaching, Eisai Co Ltd: Speaking and Teaching, Tomohide Tatsumi: Nothing to Disclose, Tetsuo Takehara: Nothing to Disclose

1521 | LIVER NODULES INCLUDING HEPATOCELLULAR CANCER RATHER THAN IMPAIRED LIVER FUNCTION ARE THE PRIMARY CLINICAL CHALLENGE IN MANAGEMENT OF PATIENTS WITH FONTAN ASSOCIATED LIVER DISEASE

Aliya Gulamhusein[1] *Zaman Khan*[2] *Shani Nagler*[2] *Guillermo Agorrody*[2] *Rafa Alonso*[2]

[1]*University of Toronto, University Health Network,* [2]*University Health Network*

Background: Fontan Associated Liver Disease (FALD) is an increasingly common complication of patients with complex congenital heart disease undergoing Fontan palliation in childhood. **Methods:** Clinical characteristics of patients followed at the Toronto Centre for Liver Disease with FALD were reviewed. Descriptive statistics were used to define the characteristics of the cohort. Qualitative variables were summarized as proportions and continuous variables as means with standard deviations and medians with interquartile ranges. **Results:** 110 patients with post Fontan palliation who were followed at the Toronto Centre for Liver Disease were included. Original cardiac anomaly was most commonly tricuspid atresia or hypoplastic left ventricle (Table 1). The majority of patients underwent Fontan palliation between 2-5 years of age with a lateral tunnel or extracardiac conduit. Median follow-up time was 25.0 (IQR 21-29) years and 45.5% (n=50) were female. Over the follow-up period, 4.5% (n=5) patients died, 7.2% (n=8) underwent heart transplant and 0.9% (n=1) had heart-liver transplant. Cirrhotic morphology on ultrasound was frequent with heterogeneity (48.2%, n=53), contour nodularity (72.7%, n=80) and, lobar redistribution (76.4%, n=84) being commonly reported. Splenomegaly ≥12 cm was noted in 59.1% (n=65) and steatosis in 10.0% (n=11). Clinical manifestations of portal hypertension were infrequent with esophageal varices in 11.8% (n=13/57) though all varices were small (</= grade 2) and ascites in 19.1% (n=21) though this was most commonly trace/small volume. Liver nodules were seen in the majority (68.2%, n=75) and biopsy proven hepatocellular carcinoma diagnosed in 3.6% (n=4). Of those who died, 2 had liver dysfunction (one post heart-liver and one heart alone). The remainder of deaths were related to cardiac failure. Liver tests were largely normal with median AST 25 IU/L (IQR 20-34), ALT 24 IU/L (IQR 16-37), platelets 151 10^9/L (IQR 106-212), total bilirubin 18 umol/L(12-28), and albumin g/L of 43 (IQR 43-46). Median liver stiffness was 19.9 (SD10.8) and CAP 235 (IQR 203.5-282.5). **Conclusion:** Cirrhosis is a common complication of FALD but most patients have preserved liver function without complications of portal hypertension. Liver nodules including HCC remain an important clinical challenge.

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Table 1	Total Cohort n=110
Demographics	**n (%)**
Median years of FU (IQR)	25.0 (21-29)
Transplant and Death	
Heart	8 (7.2)
Heart and Liver Transplant	1 (0.9)
Death	5 (4.5)
Caval-Pulmonary Characteristics	
AtrioPulmonary Connection	14 (14.3)
Lateral Tunnel	32 (32.3)
Extracardiac Conduit	55 (55.6)
Other	9 (8.2)
Systolic Function	**n (%)**
Grade 1 50-70%	79 (74.5)
Grade 2 41-49%	22 (20.8)
Grade 3 ≤ 40	5 (4.7)
Liver Characteristics	
Mean Liver Stiffness kPA (SD)	19.9 (10.8)
Ultrasound detected nodules	75 (68.2)
Mean number of nodules	3.3 (2.5)
Gastroscopies performed	57 (51.8)
Esophageal varices	13 (11.8)
Ascites	21 (19.1)
Trace/small	13 (11.8)
Mild-moderate	6 (5.5)
Large/Severe	2 (1.8)
Splenomegaly (≥12cm)	65 (59.1)

Disclosures: Aliya Gulamhusein: Advanz: Consultant, Cymabay: Consultant, Zaman Khan: Nothing to Disclose, Shani Nagler: Nothing to Disclose, Guillermo Agorrody: Nothing to Disclose, Rafa Alonso: Nothing to Disclose

1522 | THROMBOEMBOLIC EVENT RISK FACTORS IN PATIENTS WITH LIVER ABSCESSES: DEVELOPMENT OF A PREDICTIVE NOMOGRAM

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Background: Thromboembolism, a serious complication in patients with liver abscesses, can lead to organ deterioration if left untreated. However, factors associated with thromboembolism in these patients remain poorly understood. We aimed to identify the factors associated with thromboembolism in patients with liver abscesses. **Methods:** Data from 325 patients diagnosed with liver abscesses between March 2019 and June 2023 were retrospectively collected. Clinical and laboratory variables associated with thromboembolic events and metastatic infections were analyzed using logistic regression. A nomogram for predicting thromboembolism was constructed using significant predictors. **Results:** Among the 325 patients, the median age was 68.0 years, and included 129 women. Fifty patients experienced thromboembolic events and 44 had metastatic infections. Among the thromboembolic events, the hepatobiliary vessels were most commonly affected, with 28 out of 50 cases involving these vessels, specifically nine cases in the portal vein and 19 in the hepatic veins. Brain embolisms were the second most common (nine cases), followed by pulmonary vein or artery embolisms (eight cases), iliac vessels

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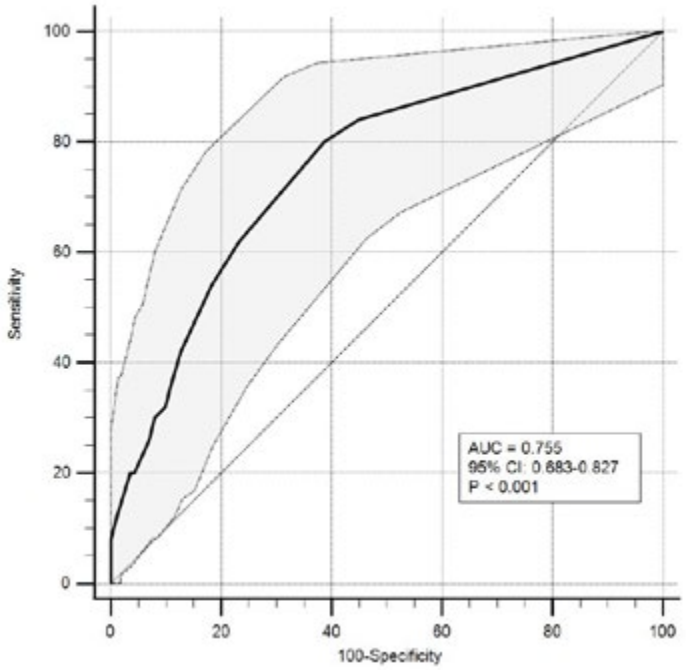
(five cases), inferior vena cava (two cases), and renal vein (one case). Significant predictors for thromboembolic events included white blood cell (WBC) ≥20 000/μL (odds ratio [OR] 3.401, p = 0.002), platelet count <100 000/μL (OR 3.291, p = 0.004), and abscess septation (OR 2.704, p = 0.007). Age ≥65 years (OR 0.457, p = 0.040), WBC ≥20 000/μL (OR 3.340, p = 0.005), and abscess septation (OR 2.909, p = 0.008) were identified as factors associated with metastatic infections. A nomogram was constructed to predict thromboembolism using the following four variables: WBC ≥20 000/μL, platelet count <100 000/μL, albumin <2.8 g/dL, and abscess septation, and demonstrated an AUROC of 0.755. **Conclusion:** High WBC count, low platelet count, and abscess septation were identified as risk factors for thromboembolic events in patients with liver abscesses. The nomogram established for thromboembolism prediction will allow clinicians to identify at-risk patients.



Disclosures: Jaejun Lee: Nothing to Disclose, Soon Kyu Lee: Nothing to Disclose, Jung Hyun Kwon: Nothing to Disclose

1523 | PORTO-SINUSOIDAL VASCULAR DISEASE:A NEW NOMENCLATURE DIFFERENT FROM IDIOPATHIC NON-CIRRHOTIC PORTAL HYPERTENSION

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Background: Porto-sinusoidal vascular disease (PSVD) as a novel clinical conception was modified on the basis of idiopathic non-cirrhotic portal hypertension (INCPH). We aimed to compare the difference between PSVD and INCPH. **Methods:** 65 patients were screened and were grouped according to two different definitions of PSVD and INCPH. The clinical, pathological and prognosis differences between the two groups were compared. **Results:** Sixty-five patients were diagnosed with PSVD of which 31 (47.69%) also fulfilled INCPH criteria (PSVD+/INCPH+). PSVD+/INCPH- showed higher LSM levels (11.45(6.38, 18.08)vs. 7.90 (6.70, 13.00), P = 0.039) and a lower prevalence of liver related complications (14.71% vs 70.96%, P = 0.001). The LSM was higher in the group with other liver diseases than control groups (P = 0.033). Patients with PSVD+/INCPH+ and specific clinical signs had a higher cumulative incidence of liver disease-related complications than control groups (86.95% vs 35.71%, log-rank P. **Conclusion:** It should be warned that patients with other liver diseases in PSVD may cause interference to diagnosis.Clinical course of PSVD is more favorable than INCPH. Importantly, specific clinical signs are associated with liver disease-related complications.

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Table 1. Baseline characteristics of PSVD+/INCPH+ and PSVD+/INCPH-

	PSVD（65）	PSVD+/INCPH+(n=31, 47.69%)	PSVD+/INCPH-（n=34, 52.3%）	P
Age(y)	51.28±12.58	50.00±14.73	52.44±10.33	0.447
Male Sex,n(%)	30（46.15%）	16(51.61%)	14（41.18%）	0.276
ALT(U/L)	25.50（16.70, 37.00）	23 (13.50, 34.05)	26.70 (16.93, 43.03)	0.444
AST(U/L)	27(19.60, 41.80)	24 (17.50, 37.25)	33.70 (19.95, 43.03)	0.195
ALP(U/L)	76(51.3, 116)	72.35 (50.13 , 115.33)	79.00 (51.50, 134.93)	0.594
GGT(U/L)	37.15(16.13, 90.18)	35.15 (19.10, 95.85)	43.30 (14.55, 74.25)	0.694
WBC (109/L)	3.99(2.67, 6.14)	3.81 (2.73, 5.23)	4.54 (2.66, 6.32)	0.511
HGB (1012/L)	123(101, 136)	123 (98.00, 135.00)	127.50 (102.75, 137.00)	0.304
PLT (109/L)	121(88, 155)	82.00 (54.00 , 132.00)	115 (79.25 , 213.25)	0.064
Blood ammonia(umol/L)	18.20(10.70, 31.15)	17.30 (11.30 , 27.90)	21.60 (9.23 , 35.93)	0.553
LSM (kPa)	9.30（6.60, 14.95）	7.90（6.70, 13.00）	11.45（6.38, 18.08）	0.039
CAP（dB/m）	246（195, 243）	202.50 (176.00 , 229.00)	216.50 (199.75 , 236.00)	0.495
ARFI (m/s)	2（1, 3）	1 (1.00 , .50)	2 (1.50 , 3.50)	0.130
CHE(U/L)	5408 (4401, 7572)	5135 (4619 ,7572)	5728.50 (4366.50 ,7401.75)	0.940
ALB(g/L)	40.90(36.80, 46.63)	40.90 (34.80 , 46.30)	40.90 (36.95 , 47.05)	0.675
PT(s)	11.30（10.50, 14.50）	12.70 (11.50, 13.90)	11.00 (9.30, 12.40)	0.158
D-dimer(mg/L)	0.58（0.38, 1.06）	0.48 (0.26, 0.99)	0.71 (0.33, 1.72)	0.511
PVT, n(%)	8	-	8	-
TB(μmol/L)	15.40(12.40, 22.98)	14.70 (11.60 , 24.40)	16.40 (13.15 , 22.65)	0.560
Spleen size（mm）	139（120, 160）	143.00 (121.25 , 165.50)	137.00 (120.00, 151.00)	0.206
liver related complications,n(%)	27（41.50%）	22（70.96%）	5（14.71%）	0.001
Ascites,n(%)	12 (18.46%)	9 (29.03%)	3 (8.82%)	0.037
Hepatic encephalopathy,n(%)	2	2	-	-
Esophageal and gastric varices with PH,n(%)	13(20%)	11(35.48%)	2(6.25%)	0.003
Varices				
Mild,n(%)	29 (44.62%)	27 (87.10%)	12 (35.29%)	0.146
HRV,n(%)	23 (35.38%)	15 (48.39%)	8 (23.53%)	0.033
MAFLD,n(%)	3 (4.62%)	-	3 (8.82%)	-
CHB,n(%)	7 (10.77%)	-	7 (20.59%)	-
CHC,n(%)	3 (4.62%)	-	3 (8.82%)	-
Chief complaint				
ascites	5 (7.69%)	2 (6.45%)	3 (8.82%)	
gastrointestinal hemorrhage	13(20.00%)	11(35.48%)	2 (5.88%)	
splenomegalia	4(6.15%)	2(6.45%)	2(5.88%)	
liver nodules	18(16.92%)	10(32.26%)	1(2.94%)	
thrombocytopenia	2(3.08%)	1(3.23%)	1(2.94%)	
elevated alanine transaminase	16(24.62%)	6(19.35%)	10(29.41%)	

PSVD, porto-sinusoidal vascular disease; INCPH, idiopathic non-cirrhotic portal pertension; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, g-glutamyl transpeptidase; WBC, white blood cell count; HGB, hemoglobin; PLT, platelet count, LSM, liver stiffness measurement; CAP, controlled attenuation parameter; ARFI, acoustic radiation force impuls; CHE, cholinesterase; ALB, albumin; PT, prothrombin time; PVT, portal vein thrombosis; TB, total bilirubin; HRV, high-risk varices; MAFLD, metabolic-associated fatty liver disease; CHB, chronic hepatitis B; CHC, chronic hepatitis C.

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Table 2. Histological and clinical evaluation of PSVD+/INCPH+ and PSVD+/INCPH-

	PSVD n=65	PSVD+ /INCPH + (n= 31, 47.69%)	PSVD+/INCPH- (n= 34，52.3%)	P
Specific histological signs				
Obliterative portal venopathy (thickening of vessel wall,occlusion of the lumen, and vanishing of portal veins)	5(7.69%)	6(19.37%)	19(55.88%)	0.003
Nodular regenerative hyperplasmia	13(20.00%)	2(6.45%)	3(8.82%)	0.545
Incomplete septal fibrosis or cirrhosis	13(20.00%)	5(16.13%)	8(23.53%)	0.333
Unspecific histological signs				
Portal tract abnormalities (multiplication, dilation of arteries, periportal vascular channels, and aberrant vessels)	20(30.77%)	6(19.35%)	14(41.18%)	0.05
Portal tract abnormalities (multiplication, dilation of arteries, periportal vascular channels, and aberrant vessels)	15(23.08%)	1(3.23%)	14(41.18%)	<0.001
Non-zonal sinusoidal dilation	12(18.46%)	7(22.58%)	5(14.71%)	0.309
Mild perisinusoidal fibrosis	42(64.62%)	21(67.74%)	21(61.76%)	0.404
Specific clinical signs				
Gastric oesophageal, or ectopic varices	52(80.00%)	30(96.77%)	22(64.71%)	0.001
Portal hypertensive bleeding	13(20.00%)	11(35.48%)	2(5.88%)	0.003
Porto-systemic collaterals at imaging	9(13.85%)	4(12.90%)	5(14.71%)	0.561
Unspecific clinical signs				
Spleen size ≥13 cm in the largest axis	33(50.77%)	23(74.19%)	10(29.41%)	<0.001
Ascites	12(18.46%)	9(29.03%)	3(8.82%)	0.037
Platelet count <150 000 per μL	27(41.54%)	15(48.39%)	12(35.29%)	0.207
Number of specific histological criteria				
0	34(52.31%)	21(67.74%)	13(38.24%)	
1	19(29.23%)	7(22.58%)	12(35.29%)	
2	12(18.46%)	3(9.68%)	9(26.47%)	
Number of unspecific histological criteria				
0	6(9.23%)	3(9.68%)	3(8.82%)	
1	42(64.62%)	22(70.97%)	20(58.82%)	
2	16(24.62%)	5(16.13%)	11(32.35%)	
3	1(1.54%)	1(3.23%)	0	
Number of specific clinical criteria				
0	15(23.08%)	1(3.23%)	14(41.18%)	
1	29(44.62%)	17(54.84%)	12(35.29%)	
2	15(23.08%)	9(29.03%)	6(17.65%)	
3	4(6.15%)	2(6.45%)	2(5.88%)	
Number of unspecific clinical criteria				
0	24(36.92%)	6(19.35%)	18(52.94%)	
1	15(23.08%)	7(22.58%)	8(23.53%)	
2	17(26.15%)	12(38.71%)	5(14.71%)	
3	7(10.77%)	4(12.90%)	3(8.82%)	

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PSVD,porto-sinusoidal vascular disease; INCPH,idiopathic non-cirrhotic portal pertension.

Table 3. Comparison of LSM among different subgroups

PSVD+/INCPH-	LSM	P
Other liver diseases+	15.9（7.85，23.00）	
Other liver diseases-	9.60（6.25，14.45）	0.033
PVT+	11.30（8.10，19.40）	
PVT-	10.40（6.40，15.00）	0.253
PH+	13.25（8.80，21.45）	
PH-	7.70（5.95，16.25）	0.111

PSVD,porto-sinusoidal vascular disease; INCPH, idiopathic non-cirrhotic portal pertension; PVT, portal vein thrombosis; PH, portal hypertension.

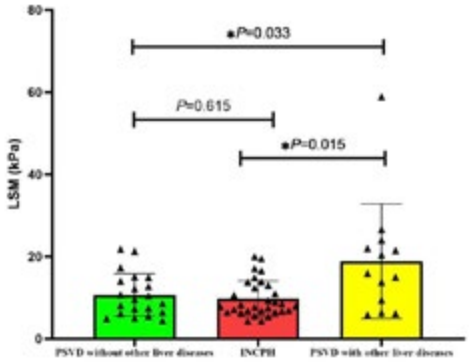

Figure 1. Comparison of LSM in PSVD with and without other liver diseases

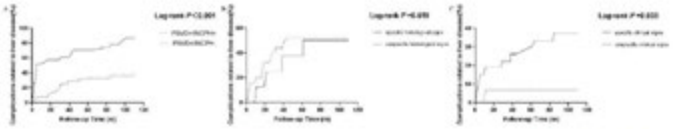

Figure 2. Cumulative incidence of complications related to liver disease between (A)PSVD+/INCPH+ vs PSVD+/INCPH-; (B)with specific histological signs vs without; (C)with specific clinical signs vs without.

Disclosures: Jie Liu: Nothing to Disclose, Qian Zhang: Nothing to Disclose

1524 | MACHINE LEARNING OF CT IMAGES FOR NONINVASIVE DISCRIMINATION OF PORTO-SINUSOIDAL VASCULAR DISEASE FROM CIRRHOSIS IN PATIENTS WITH PORTAL HYPERTENSION ◆ ★

Yanna Liu[1] *Qian Yu*[2] *Yanglan He*[1] *Hui Liu*[1] *Chunlei Fan*[1] *Huiguo Ding*[1]

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Background: Porto-sinusoidal vascular liver disease (PSVD) is still often misdiagnosed as cirrhosis. This study aims to evaluate the accuracy of the machine learning model using CT images for discriminating PSVD from cirrhosis in patients with signs of portal hypertension. **Methods:** Patients diagnosed with PSVD according to the VALDIG criteria were retrospectively recruited from our center from January 2012 to December 2021. The control cohort included patients with cirrhotic portal hypertension recruiting consecutively during the same period with a matching ratio of 1:2. All patients had undergone upper abdominal contrast-enhanced CT scanning. Patients were randomly divided into the training cohort and the test cohort at a ratio of 8:2. We developed an auto-machine-learning CT radiomics quantitative model, termed PSVD score, and then we validated the model in the internal test datasets by the area under the receiver operating characteristic curves (AUC) for differentiating PSVD from cirrhosis (Figure 1A). **Results:** A total of 291 patients were included, of which 97 were PSVD patients and 194 were cirrhosis patients. PSVD score was developed based on the CT images in the training cohort consisted of 232 patients. As a result, a total of 31 features were final included in the model, of which 16 were from liver and 15 from spleen (Figure 1B). The diagnostic performance was validated in the internal test dataset including 59

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patients. PSVD score showed a good performance in differentiation of PSVD with the AUCs of 0.913 and 0.819 in the training and test dataset, respectively (Figure 1C). **Conclusion:** Machine learning models based on CT images achieved promising accuracy in noninvasive discrimination of PSVD from cirrhosis in patients with signs of portal hypertension.

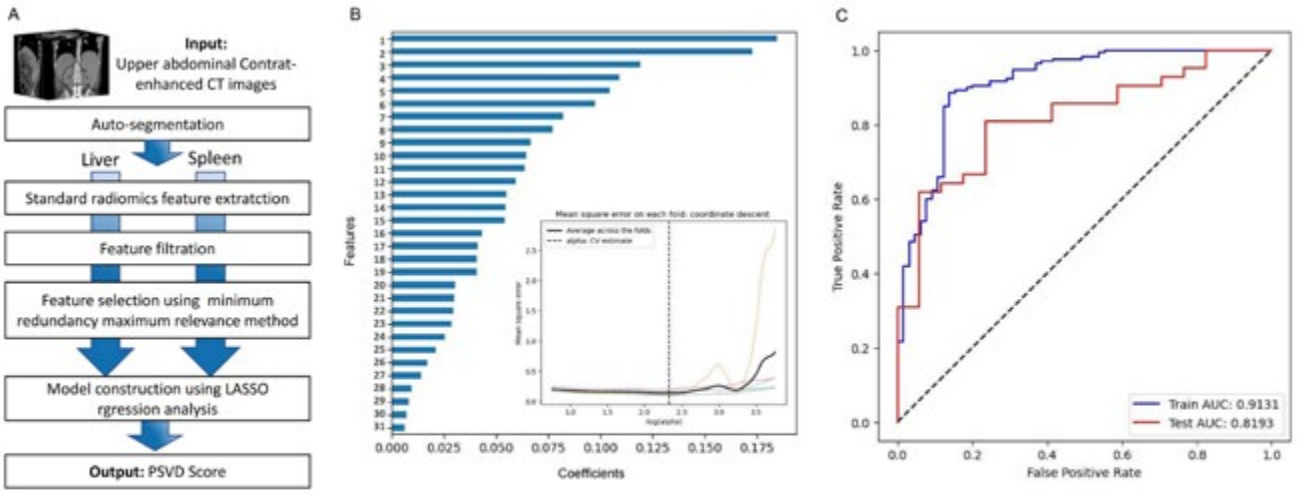

Figure 1. A.Development workflow of the machine learning-based model, termed PSVD score. B. Selection of the tuning parameter (alpha) in the LASSO regression model and coefficients of the included features in the model. D. Receiver operating characteristic curves of the PSVD score for discriminating PSVD from cirrhosis in training (red line) and internal test sets (blue line). PSVD, porto-sinusoidal vascular liver disease; LASSO, least absolute shrinkage and selection operator; AUC, area under the ROC curve.

Disclosures: Yanna Liu: Nothing to Disclose, Qian Yu: Nothing to Disclose, Yanglan He: Nothing to Disclose, Hui Liu: Nothing to Disclose, Chunlei Fan: Nothing to Disclose, Huiguo Ding: Nothing to Disclose

1525 | ASSESSMENT OF THROMBIN GENERATION IN CIRRHOSIS PATIENTS BEFORE AND AFTER LIVER TRANSPLANTATION: IMPACT OF CLINICAL PARAMETERS ON ENDOGENOUS THROMBIN POTENTIAL

Yadana Khin[1] Kaleb Ardoin[1] Andrew Tiu[1] Ellie Hummel[1] Serenity Budd[1] Amol Rangnekar[1] Arul Thomas[1] Craig Kessler[1]

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Background: Cirrhosis involves various pathophysiologic states that can lead to either hyper- or hypocoagulability. This complexity is compounded by systemic inflammation, infection, and reduced blood flow from portal hypertension, which traditional coagulation tests (PT, aPTT, INR) fail to accurately reflect. Thrombin generation assays (TGA) offer a better representation by capturing both thrombin formation and inactivation dynamically with thrombomodulin substrate. The Thrombogram, showing thrombin concentration over time, highlights the endogenous thrombin potential (ETP), the area under the curve. Previous TGAs had limitations due to poor standardization, interlaboratory variation, and cross-sectional study designs. Adhering to recommendations from the International Society on Thrombosis and Haemostasis, this study analyzes the impact of demographics, liver disease etiology, and clinical parameters on ETP in cirrhosis patients before and after liver transplantation. **Methods:** This prospective observational study began on September 7, 2023, at a single academic transplant center and will conclude in 2025. We collected 115 serial blood samples from 35 patients with cirrhosis, 14 of whom underwent liver transplant as of May 15, 2024. Platelet-poor plasma was obtained via double centrifugation, snap-frozen at -80°C, and later thawed at 37°C for testing using the ST Genesia Machine for quantitative thrombin generation determination via a fluorogenic method. The STG® - ThromboScreen +/- TM reagents, containing phospholipids and tissue factor, initiated the coagulation system in plasma. Data were analyzed using linear mixed models and likelihood ratio tests. **Results:** Patient demographics (age, sex, race, BMI) did not significantly affect ETP values (age: X^2 = 0.4, p = 0.554; sex: X^2 = 3.4, p = 0.066; race: X^2= 0.7, p = 0.714; BMI: X^2= 1.7, p = 0.195). Similarly, liver cirrhosis etiology (X^2= 4.0, p = 0.263), creatinine levels (X^2= 0.5, p = 0.463), and prophylactic anticoagulation (X^2= 0.1, p = 0.753) had no significant impact. However,

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MELD 3.0 (X^2= 26.3, p < 0.001) and total bilirubin (X^2= 23.0, p < 0.001) were inversely related to ETP values. Post-liver transplant status significantly affected ETP (X^2= 7.7, p = 0.006). Specifically, a one-point increase in MELD 3.0 score and total bilirubin led to ETP decreases by 24 points (95% CI: [15, 32]) and 21 points (95% CI: [13, 30]), respectively, while post-liver transplant patients showed an ETP increase of 213 points (95% CI: [64, 362]). **Conclusion:** Demographics, liver cirrhosis etiology, creatinine, and prophylactic anticoagulation did not significantly impact ETP. However, MELD 3.0 and total bilirubin increases were associated with decreased ETP, while liver transplantation increased ETP. TGA holds promise as a clinical tool for real-time assessment of global coagulation in cirrhosis patients.

	Lab Draws N = 115	p value based on absolute ETP
Liver Transplant, n (%)		
Pre transplant	76 (66%)	
Post transplant	39 (34%)	**0.006**
Age, mean (SD)	53 (12)	0.554
Sex, n (%)		
Male	58 (50%)	0.066
Female	57 (50%)	
Race, n (%)		
White	69 (71%)	
Black	17 (18%)	0.714
Other	11 (11%)	
Unknown	18	
BMI, mean (SD)	27.9 (5.9)	0.195
Unknown	3	
Etiology of Cirrhosis, n (%)		
Alcohol	36 (51%)	
MASH	19 (27%)	0.263
Combination	8 (11%)	
Other	7 (10%)	
Unknown	6	
MELD 3.0, mean (SD)	24 (8)	**< 0.001**
Unknown	4	
Total Bilirubin, mean (SD)	8 (8)	**< 0.001**
Unknown	1	
Creatinine, mean (SD)	1.52 (1.11)	0.463
Prophylactic anticoagulation, n (%)		
No	58 (55%)	0.753
Yes	47 (45%)	

Table 1. Characteristics of lab draws and p value based on absolute ETP.

Disclosures: Yadana Khin: Nothing to Disclose, Kaleb Ardoin: Nothing to Disclose, Andrew Tiu: Nothing to Disclose, Ellie Hummel: Nothing to Disclose, Serenity Budd: Nothing to Disclose, Amol Rangnekar: Nothing to Disclose, Arul Thomas: Nothing to Disclose, Craig Kessler: Nothing to Disclose

1526 | ASSOCIATION OF HEMOSTATIC STATUS WITH PORTAL VENOUS SYSTEM THROMBOSIS IN PORTO-SINUSOIDAL VASCULAR DISEASE

Yanglan He[1] Yanna Liu[2] Chunlei Fan[2] Hui Liu[2] Huiguo Ding[2]

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Background: Porto-sinusoidal vascular disease (PSVD) is a common non-cirrhotic portal hypertension disease, often accompanied by portal venous system thrombosis (PT). According to Virchow triad, PVT may be associated with hypercoagulability. Data on the hemostatic status of PVT in PSVD are lacking. **Methods:** We continuously included patients who were histologically proven PSVD according to the VALDIG criteria and received enhanced

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CT or MRI. Exclusion criteria included patients who had previously undergone hepatectomy, splenectomy, splenic embolization, or trans-jugular intrahepatic portosystemic shunts (TIPS). PVT referred to thrombosis in the portal vein, splenic, and superior mesenteric veins or intrahepatic portal vein branches, eavaluated by entranced CT or MRI. The coagulation status was evaluated by conventional coagulation test and thromboelastography (TEG). Continuous variables were presented by median and compared by Mann-Whitney U tests. **Results:** We included 189 potentially eligible patients without any history of hepatectomy, splenectomy, splenic embolization, or TIPS. Of them, 141 patients were without PVT and 48 patients were with PVT. There were 182 (with and without PVT: 134:48) patients who underwent PT, INR, PTA and APTT tests, 132 patients (with and without PVT: 96:36) who underwent Fibrinogen, D-Dimers, fibrinogen degradation products (FDP), and antithrombin (AT) tests, and 64 patients (with and without PVT: 44:20) who underwent TEG. Compared to patients without PVT, patients with PVT had significantly higher levels of PT/INR (12.05 vs 13.25, p<0.001), D-dimer (144.00 vs 293.50, p=0.007) and FDP (1.03 vs 2.50, p<0.001), and lower levels of PTA (81.55 vs 77.00, p<0.001), fibrinogen (2.29 vs 1.97, p=0.001) and AT (85.00 vs 74.00, p=0.018). TEG parameters, including R, K, Angle, MA, LY30 and CI, were not significantly different between PSVD with and without PVT (p>0.1). Additionally, patients with PVT had lower levels of WBC (p=0.013), RBC (p=0.015), PLT (p=0.061), and cholinesterase (p=0.02). **Conclusion:** Hypercoagulable status indicated by TEG might not be the main risk factors of PVT in PSVD. Compared to patients without PVT, PSVD patients with PVT might have poorer liver function and severer portal hypertension.

Disclosures: Yanglan He: Nothing to Disclose, Yanna Liu: Nothing to Disclose, Chunlei Fan: Nothing to Disclose, Hui Liu: Nothing to Disclose, Huiguo Ding: Nothing to Disclose

1527 | SARS-COV-2 INFECTED LIVER PERICYTES STIMULATE VWF EXPRESSION BY PORTAL ENDOTHELIAL CELLS AND AN ANGIOGENIC RESPONSE IN THE PULMONARY ENDOTHELIUM

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Background: Severe SARS-CoV-2 infection can lead to the formation of systemic microthrombosis with alterations in the vascular component of several organs, including liver. The involvement of hepatic portal vasculature may be associated with the development of intrapulmonary vascular dilatations (IPVD) and worsening of hypoxemia, featuring hepatopulmonary syndrome. Previous studies indicate that pulmonary circulation alterations develop in COVID-19 patients with persistent hypoxemia. We hypothesized that liver pericytes, mesenchymal cells intimately associated with the endothelium, infected by SARS-CoV-2 induce a pro-coagulant phenotype sustaining an angiogenic response of the pulmonary circulation. **Methods:** Immunofluorescence of archival liver specimens from COVID-19 autopsies (n=16) and controls (n=17) was used to study SARS-CoV-2 spike (SP) or nuclear (NP) proteins coexpression with von Willebrand Factor (vWF) and PDGFR-β (pericyte marker). Expression levels of viral SP/NP were also evaluated in endothelial cells (ECs) and pericytes. Supernatant from cell cultures of pericytes infected with SARS-CoV-2 was used to infect human umbilical vein ECs (HUVEC) and human pulmonary microvascular ECs (HPMECs) to assess vWF expression. Tubulisation of HPMECs was assessed with Angiogenesis Analyser software patch for ImageJ following treatment with recombinant human (rh) vWF protein. **Results:** In the liver, PDGFR-β$^+$ pericytes co-expressed significantly more SP and NP than ECs lining the portal vasculature, which were instead more intensely decorated by vWF and contained extensive microthrombi compared to controls. Conditioned medium harvested from infected pericytes induced significant up-regulation of vWF in HUVEC (60.99±12.67 vs 27.57±11.06) and HPMEC (72.96±23.19 vs 18.85±10.75) as respect to untreated controls. Cultured 3D-HPMECs treated with rh-vWF significantly increased their tubule size as respect to untreated controls (1.5x). **Conclusion:** SARS-CoV-2 infection of the liver leads to a local procoagulant response by up-regulating vWF in ECs contributing to portal microthrombosis. Moreover, vWF induced the expansion of HPMEC 3D tubules, consistent its vasodilatory effect relevant to IPVD found in COVID-19 patients with severe hypoxemia. Thus, vWF released by portal ECs may behave as a putative molecular effector linking hepatic lesions with pulmonary vascular perturbations in hepatopulmonary syndrome.

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Disclosures: Luca Fabris: Nothing to Disclose, Camilla Venturin: Nothing to Disclose, Yahima Friòn-Herrera: Nothing to Disclose, Massimiliano Cadamuro: Nothing to Disclose, Claudia Maria Radu: Nothing to Disclose, Arianna Calistri: Nothing to Disclose, Cristina Parolin: Nothing to Disclose, Mario Strazzabosco: Nothing to Disclose, Paolo Simioni: Nothing to Disclose

1528 | SAFETY AND OUTCOMES OF AN ON-DEMAND TRANSFUSION STRATEGY VERSUS PROPHYLACTIC TRANSFUSION OF PLATELETS IN PATIENTS WITH LIVER CIRRHOSIS AND SEVERE THROMBOCYTOPENIA UNDERGOING HIGH-RISK INVASIVE PROCEDURES

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Background: There is limited data on the safety and efficacy of performing high-risk procedures in patients with liver cirrhosis and severe thrombocytopenia (platelet counts <50x10^9/L) without prophylactic platelet transfusions as advocated by the AASLD compared to the conventional practice of prophylactic platelet transfusion at a threshold value of 50 x 10^9/L. **Methods:** We combined prospective data from two prior randomized controlled trials (CTRI/2017/12/010822, and CTRI/2021/05/033464) on high-risk invasive procedures in patients with liver cirrhosis. We included patients with platelet counts <50 x 10^9/L while excluding patients with acute-on-chronic liver failure, renal dysfunction and those on antiplatelet agents or anticoagulants. Patients were divided into two groups: (i) Standard-of-care (SOC): patients received 3 units of random donor platelets (RDP) as prophylactic transfusions prior to the procedure, and (ii) On-demand: patients underwent the allocated procedure without any prophylactic transfusion, with platelets being given only if post-procedural bleeding occured. Outcome measures included major bleeding within 5- and 28 days of the procedure, requirement of blood transfusion and procedural bleeding-related mortality. **Results:** Fifty patients were allocated to the SOC arm while 68 patients received on-demand transfusions. Baseline demographics were well matched between the two groups. The median Child and MELD score of the cohort was 6 (5-7) and 12 (10-14.3) respectively. Median platelet count of the entire cohort was 35.5 (28.0-44.3) x 10^9/L. Percutaneous liver biopsy was the most commonly performed procedure (75 patients, 63.6%) followed by transjugular intrahepatic portosystemic shunt (TIPS) in 14 (11.9%) patients. There were no major bleeding episodes or any bleeding related mortality in either group within 28 days of the procedure. Five (4.2%) patients in the entire cohort had minor bleeding (WHO Grade 1) which did not require any packed red blood cell transfusion. One patient (2%) belonged to the SOC arm while 4 (5.8%) belonged to the on-demand arm. All bleeding in the on-demand arm were from the local puncture site in the form of persistent ooze, while the patient in the SOC arm had increase in perihepatic fluid after 30 minutes of liver biopsy without any hemoperitoneum and underwent prophylactic embolization of the branch of the hepatic artery supplying the area of biopsy. Overall, only 5 (7.4%) patients in the on-demand arm received platelet transfusions (17 units) as compared to all 50 patients (150 units) in the SOC arm. No patient in the SOC arm required post procedure platelet transfusions. **Conclusion:** High-risk invasive procedures can be performed safely in a select group of patients of liver cirrhosis and severe thrombocytopenia without prophylactic platelet transfusions. Adoption of the AASLD recommendations would reduce empirical and irrational transfusion practices in these patients.

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Variables	Standard-of-care (n=50)	On-demand transfusion (n=68)	p value
Baseline demographics			
Age (yrs)	33.5 (23.8-46.2)	37.0 (25.0- 49.0)	0.32
Body mass index (kg/m^2)	20.1 (18.5 – 23.1)	20.9 (17.9-23.7)	0.92
Child score	6.0 (5.0-7.0)	6.0 (5.0-7.0)	0.59
Model for end-stage liver disease	12.0 (10.0-15.0)	12 (9.0-14.0)	0.51
Hemoglobin (g/dL)	10.3 (8.6-12.2)	11.1 (8.4-12.5)	0.72
Platelet count (x10^9/L)	33.5 (28.8-40.0)	33.0 (27.3- 47.0)	0.19
International normalized ratio	1.3 (1.4-1.5)	1.3 (1.2-1.5)	0.09
Activated partial thromboplastin time (APTT) (secs)	34.0 (31.4-36.1)	31.9 (29.4 – 36.6)	0.08
Fibrinogen (mg/dL)	247.0 (201.2-282.1)	245.1 (187.5-310.4)	0.77
Creatinine (mg/dl)	0.7 (0.5 – 0.8)	0.7 (0.6 – 0.8)	0.28
Bilirubin (mg/dl)	1.5 (1.1 – 2.5)	1.6 (1.0 – 2.4)	0.57
Albumin (g/dL)	4.1 (3.2 – 4.3)	3.9 (3.4-4.4)	0.84
Sodium (meq/L)	139.0 (136.0-142.3)	139.5 (137.0-142.0)	0.81
Procedure type			0.49
Percutaneous liver biopsy	33 (66.0%)	42 (61.8%)	
Transarterial chemoembolization	8 (16.0%)	6 (8.8%)	
Transjugular intrahepatic portosystemic shunt (TIPSS)	5 (10.0%)	8 (11.8%)	
Balloon occluded retrograde transvenous obliteration (BRTO)	1 (2.0%)	7 (10.3%)	
Percutaneous ablation of hepatocellular carcinoma	2 (4.0%)	3 (4.4%)	
Splenic artery embolization	1 (2.0%)	2 (2.9%)	
Study outcomes			
Procedural bleeding within 5-days	1 (2%)	4 (5.9%)	0.394
Packed red cell transfusion within 5 days	0	1 (1.5)*	0.389
Procedure related mortality	0	0	-

Data provided as median (IQR: Q1-Q3) or n (%) as appropriate.

*This patient received packed red blood cell transfusion for the management of anemia due to symptomatic hypersplenism. There was no procedural bleeding in this patient.

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1529 | THE LIVER AND SPLEEN STIFFNESS MEASURE BY TRANSIENT ELASTOGRAGHY A PROMISING TOOL FOR THE CLINICAL MANAGEMENT OF PATIENTS AFTER FONTAN-TYPE SURGERY CIRCULATION

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Background: Haemodynamic changes after Fontan palliation in infant patients with univentricular heart promote progressive liver damage (Fontan-associated-liver-disease, FALD). FALD is not adequately monitored by traditional liver clinical scores (VAST score; non-advanced/advanced compensated FALD) representing just the mere sequence of clinic-pathologic events and progression risk biomarkers are missing. Liver and spleen stiffness (LSM and SSM) measured by transient elastography might be useful tools. *Aim of the study was* the correlations among LSM, SSM and FALD stage in adult post-Fontan patients. **Methods:** 32 consecutive patients with compensated FALD (median age 27 y, 23.1-37.7 y; 8 F) were studied. We recorded liver morphology/structure by ultrasound-scan, LSM and SSM (Fibroscan©, Echosens, Paris), biochemical liver tests, radiologic and/or upper endoscopic signs of portal hypertension and cardiological functional parameters. **Results:** Median LSM and SSM were 16.8 (13.7-24.1) kPa and 30.4 (24.4-42.1) kPa respectively and significantly correlated (r=0.492, *p*=0.0058). Both correlated with g-GT levels (*r=0.452, p*=0.0139) and caudate lobe hypertrophy (*r=0.449; p*=0.0127). Patients with advanced liver involvement had significantly higher LSM: 18.5 (16.6-38.8) kPa in VAST > 1 vs 15.2 (13.1-20.8) kPa in VAST </= 1 pts (*p*=0.0472) and 18.7 (16.6-29.7) kPa in advanced compensated FALD vs 15.1 (12.8-17.8) kPa in non-advanced FALD (*p*=0.0078). LSM correlated with FALD stage (*r*=0.647, *p*=0.0020) and VAST-score >1 (*r*=0.429, *p*=0.0136) with 0.750 AUROC and 16.4 kPa/cut-off with 100%/88% sensitivity and 50%/72% specificity respectively. SSM was not correlated with FALD stage; 30.1 kPa-cut-off showed 69% sensitivity and 64% specificity for advanced compensated FALD. Both LSM and SSM correlated with NHYA class (*p*=0.0005 and *p*<0.0001 respectively). Moreover, SSM was higher in patients on beta-blockers (34.0 *vs* 26.7 kPa, *p*=0.0144) or diuretics (39.1 *vs* 26.7 kPa, *p*=0.0225) reflecting a worse hemodynamic conditions. **Conclusion:** LSM and SSM appear promising tools for the clinical management of paients with Fontan circulation. LSM >16.4 kPa predicted with high sensitivity advanced FALD. SSM is significantly higher in patients requiring on diuretics, suggesting its potential role in the prognostic stratification of this challenging population. These preliminary results prompt prospective studies on larger cohorts of patients after Fontan's surgery.

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1530 | S100A8/9 IS UPREGULATED IN PLATELETS AND PLATELET-DERIVED MICROPARTICLES IN ALCOHOL-ASSOCIATED HEPATITIS AND CAN MEDIATE ENDOTHELIAL INFLAMMATION

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Background: Platelets have emerged as playing a pathological role in a variety of liver diseases, but their specific role in alcohol-associated hepatitis (AH) remains unknown. **Methods:** Pure platelets were isolated from hospitalized patients with alcohol-associated hepatitis (AH) (n=8), alcohol-associated cirrhosis (AC) (n=9), and healthy donors (HD) (n=7) for RNAseq. Pure washed platelets were isolated from hospitalized patients with AH (n=10), AC (n=12), and HD (n=8) for proteomics. Matching plasma was isolated from these patients and analyzed for platelet-derived microparticles (CD61+) by nanoscale flow cytometry. Human liver tissue was analyzed by immunohistochemistry for platelet marker CD61. Human megakaryocytic cell line (MEG01-cells) and

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primary human liver sinusoidal endothelial cells (LSECs) were used for *in vitro* experiments. **Results:** RNAseq identified proinflammatory mediators S100A8 (4.56-fold) and S100A9 (3.18-fold) as uniquely upregulated in AH. Platelet proteomics revealed 1090 differentially abundant proteins (DAPs) (FDR<0.05) between AC vs HD, and 1055 DAPs (FDR<0.05) between AH vs HD, with S100A8 and S100A9 in the top 10 unique DAPs in AH. Using molecules for which both RNA and protein were detected in platelets, Ingenuity Pathway Analysis (IPA) revealed significant (FDR p<0.05) effects on S100A8/9-containing pathways for regulation and accumulation of neutrophils and inflammation of endothelial cells, key pathological processes in AH. Pathway analysis of the RNAseq data identified TP63 (FDR p<0.05) as a potential upstream regulator of S100A8/9. TNF-alpha, a key cytokine in AH, significantly upregulated gene expression of S100A8 (2.885 fold-change vs control, p<0.0001), S100A9 (1.641 fold-change vs control, p<0.0001) and TP63 (9.791 fold-change vs control, p<0.0001) and S100A8/9 protein by flow cytometry (mean fluorescence intensity 1176 vs 1054, p<0.01) in MEG-01 cells. Immunohistochemistry for platelet marker CD61 revealed fewer intact platelets in the liver in AH vs healthy controls (215.3 vs 71.7, p<0.05), so we hypothesized that platelet-derived microparticles rather than intact platelets may mediate platelet signaling to the liver in AH. Nanoscale flow cytometry revealed microparticles double-positive for platelet marker CD61 and S100A8/9 were significantly increased in AH vs HD ($2.23x10^7$ vs $6.31x10^6$ microparticles/mL, p<0.05). LSECs are likely targets of these microparticles due to their scavenger function, and LSECs treated with recombinant S100A8/9 showed significant upregulation of VCAM1 (1.427 fold-change vs control, p=0.0025), ICAM1 (1.301 fold-change vs control, p=0.0208), and CXCL8 (1.296 fold-change vs control, p=0.0061). **Conclusion:** Platelets in AH upregulate RNA and protein for inflammatory mediator S100A8/9, which is packaged into platelet-derived microparticles and can cause endothelial inflammation in the liver.

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1531 | RELIABILITY OF SPLENIC STIFFNESS IN PREDICTION OF VARICEAL BLEEDING AND HIGH-RISK VARICES IN NON-CIRRHOTIC PORTAL FIBROSIS (NCPF)

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Background: Splenic stiffness measurement (SSM) value is predictive of presence of high-risk varices in cirrhosis. Data on clinical utility of SSM in non-cirrhotic portal hypertension is scarce and ambiguous.
In this study, we aim to investigate whether SSM values can be used to predict variceal bleeding (AVB) and high-risk varices (HRV) in patients with NCPF. We also explored the utility of a unique variable, SSM-platelet count ratio for predicting variceal bleeding in NCPF. **Methods:** A total of 54 consecutive patients with histologically proven NCPF were enrolled. LSM and SSM were measured on FibroScan 630 expert (Echosens) machine. Upper gastrointestinal endoscopy was done for all patients at presentation and HRV was defined as per Baveno consensus. SSM (kPa)-Platelet count ($X10^3$/microL) ratio was calculated for each patient.
Point biserial correlation and Logistic regression analysis were used to determine relationship between SSM values, SSM-platelet count ratio and variceal bleeding. **Results:** Of the 54 patients, 28 (51.9%) presented with acute variceal bleeding and 35 (64.8%) had HRV on index endoscopy. High risk varices were seen in 8 of 26 (30.8%) patients who did not have variceal bleed. Mean SSM was 65.8 (±20.4) kPa, mean spleen size was 20.1 (±3.4) cm and mean SSM/Platelet ratio was 1.31 (±0.93). 19 (35.2%) patients had portal vein thrombosis (PVT). There was no correlation between SSM/platelet ratio and variceal bleeding (r_{pb} = 0.09, p = 0.503).
Multivariate logistic regression analysis of factors influencing variceal bleeding showed that presence of PVT was the only significant variable (p=0.01, OR 6.29 [95% CI 1.57-25.26]). Predictive model was created with forward selection of variables to predict AVB. PVT and SSM/platelet ratio were included as variables. The odds ratio of model was 4.63, with p= 0.03 and AUROC 0.734. The area under ROC was higher with this model compared to PVT alone [AUROC 0.65] **Conclusion:** SSM does not predict variceal bleeding or presence of HRV in NCPF. Presence of PVT is associated with variceal bleeding in patients with NCPF. Non-invasive tools need to be developed for predicting presence of HRV in NCPF.

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Table 1-Multivariate analysis of factors influencing variceal bleeding

Variable	Coefficient B	Standard error	z	p	Odds Ratio	95% conf. interval
Platelet count	0	0	0.64	0.52	1	1-1
SSM-platelet count ratio	-0.21	0.43	0.48	0.632	0.81	0.35 - 1.89
Spleen size	-0.14	0.11	1.34	0.181	0.87	0.7 - 1.07
SSM	0.02	0.02	0.91	0.362	1.02	0.98 - 1.07
PVT	1.84	0.71	2.59	0.01	6.29	1.57 - 25.26
SSM:LSM ratio	0.01	0.16	0.08	0.937	1.01	0.75- 1.37

PVT- portal vein thrombosis, SSM -Splenic stiffness measurement, LSM- liver stiffness measurement

Disclosures: Akash Shukla: Nothing to Disclose, Ankita Singh: Nothing to Disclose, Saurav Panda: Nothing to Disclose, Kashmira Datta: Nothing to Disclose, Prajakta Mane: Nothing to Disclose

1532 | GALECTIN-3 BINDING PROTEIN MAY ACT VIA PLATELET-DERIVED MICROPARTICLES TO PROMOTE HEPATIC STELLATE CELL-MONOCYTE CROSSTALK LEADING TO DISEASE PROGRESSION IN ALCOHOL-ASSOCIATED CIRRHOSIS ◆

Ainsley Baker[1] Rolando Garcia-Milian[2] Yohan Kim[3] Fabrice Lucien-Matteoni[3] John Hwa[4] Enis Kostallari[3] Yasuko Iwakiri[2] Matthew McConnell[1]

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Background: Platelets have been suggested to play a key role in liver fibrosis and inflammation, but the detailed mechanisms by which they do so remain poorly defined. **Methods:** Platelets from hospitalized patients with alcohol-associated cirrhosis (AC) (n = 17) and healthy donors (HD) (n = 7) were isolated for RNAseq. Immunohistochemistry was performed for platelet marker CD61. Nanoscale flow cytometry was utilized on patient plasma to examine platelet-derived microparticles ($CD61^+$). Human hepatic stellate cell (HSC) line (LX-2) and human monocytic cell line (THP-1) were utilized for *in vitro* experiments. **Results:** RNAseq of platelets from AC patients vs HD revealed LGALS3BP, the gene for galectin-3 binding protein (Gal3BP) as one of the top upregulated genes in AC (9.23 fold-increase, $p_{adj} = 1.21x10^{-20}$). Although platelet number was lower in the livers of AC patients by immunohistochemistry (208.9 vs 102.5 cells/hpf, $p<0.05$), platelets produce extracellular vesicles termed “platelet-derived microparticles” (PMPs), through which they may communicate with the liver. Nanoscale flow cytometric analysis of plasma from AC patients (n = 12) vs. HD (n = 8) revealed significantly increased PMPs (defined as $CD61^+$ extracellular vesicles (EVs)) positive for Gal3BP (1.15×10^7 EVs/mL vs 3.97×10^6 EVs/mL, $p<0.05$). which strongly correlated with MELD score (r-squared = 0.59, $p<0.01$), suggesting a role in disease progression. Gal3BP binds multiple C-type lectins, including galectin-3 (LGALS3) and endosialin (CD248). Evaluation of RNA expression in LX-2 cells, primary human liver sinusoidal endothelial cells, primary human umbilical vein endothelial cells, and HepG2 cells showed significantly higher levels of these receptors in LX-2 cells than the other cell types (LGALS3: 3.77 fold-change, $p<0.0001$; CD248: 251.1 fold-change, $p<0.0001$). Treatment of LX-2 cells with Gal3BP did not upregulate profibrotic genes COL1A1 or ACTA2, but did lead to the upregulation of molecules implicated in HSC-monocyte crosstalk such as CSF1 (1.52 fold-change, $p<0.0001$), VCAM1 (1.28

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fold-change, p=0.0016), ICAM1 (1.82 fold-change, p<0.0001), CXCL1 (2.01 fold-change, p<0.0001), CCL2 (1.89 fold-change, p<0.0001), and IL-6 (1.47 fold-change, p<0.0001). IL-6 secretion from LX-2 cells was also confirmed to be increased by Gal3BP (474.7 pg/mL vs. 275.5 pg/mL, p=0.036). HSC-monocyte crosstalk was further examined by culturing THP-1 cells with conditioned medium from Gal3BP-treated LX-2 cells, which induced a profibrotic M2-type phenotype in the THP-1 monocytic cells (TGFB1: 1.55 fold-change, p=0.0001; IL-10: 14.48 fold-change, p=0.0002). **Conclusion:** Platelets upregulate Gal3BP in AC, packaging it into PMPs. Gal3BP may signal to HSCs and promote crosstalk with monocytes to enhance liver fibrosis and progression of disease, and may represent a new therapeutic target in chronic liver disease.

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1533 | PREPROCEDURAL THROMBOELASTOGRAPHY DECREASES NEED FOR BLOOD PRODUCT TRANSFUSION PRIOR TO ENDOSCOPY FOR UPPER GASTROINTESTINAL BLEEDING IN CIRRHOTICS: A RETROSPECTIVE REVIEW

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Background: Thromboelastography (TEG) is a diagnostic tool that assesses the viscoelastic properties of blood clot formation and dissolution in real-time, providing a comprehensive evaluation of hemostasis. Randomized controlled trials have shown benefits in TEG-guided transfusion protocols over standard transfusion protocols for cirrhotic patients undergoing liver transplantation, acute variceal bleeding, and prior to minor procedures. This study aims to assess how utilization of TEG affected blood product usage prior to endoscopy for patients with cirrhosis and upper gastrointestinal (GI) bleeding. **Methods:** Retrospective chart review was conducted for cirrhotic patients who received a TEG within 24 hours prior to endoscopy at a tertiary care center. Demographics, TEG data, and transfusion details were collected. Blood product usage within six hours after TEG was compared to the expected usage based on standard management protocols. Cutoff values of INR ≥ 2.0, platelets <50,000, and fibrinogen <150 mg/dL were used to determine the expected usage of fresh frozen plasma (FFP), platelets, and cryoprecipitate, respectively. Wilkson's signed rank test was used to determine statistical significance between the observed transfusions after TEG and the expected based on standard transfusion cutoffs. **Results:** Sixty-two patients (age 53.8 ± 12.2 years) with cirrhosis who presented with upper GI bleed and underwent upper endoscopy were included in the analysis. 66.1% of endoscopies occurred in the intensive care unit, and variceal banding was performed in 46.7% of cases. Pre-procedure laboratory values showed a mean INR of 2.5 ± 1.3, mean platelet count of 83.2 ± 49.0 K/μL, and mean fibrinogen of 141 ± 74 mg/dL. 19.3% of patients received platelets compared to 29.0% expected to be transfused with standard transfusion cutoffs (OR=0.67, p=0.117), 22.7% received cryoprecipitate vs. 63.6% expected (OR=0.357, p<0.01), and 19.3% received fresh frozen plasma vs. 54.8% expected (OR=0.35, p<0.01). **Conclusion:** Our findings reveal a statistically significant reduction in the use of cryoprecipitate and FFP transfusions when guided by TEG, suggesting that TEG may provide a more precise assessment of coagulopathy in these patients compared to traditional parameters. This adds to the body of evidence in support of TEG-guided protocols prior to procedures for patients with cirrhosis. Larger randomized controlled trials are needed with patient-oriented outcomes to establish standardized guidelines for the use of TEG in managing coagulopathy prior to endoscopy.

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1534 | PORTAL VEIN THROMBOSIS IN CIRRHOSIS, ETIOLOGICAL SPECTRUM, RISK PROFILE, AND OUTCOME

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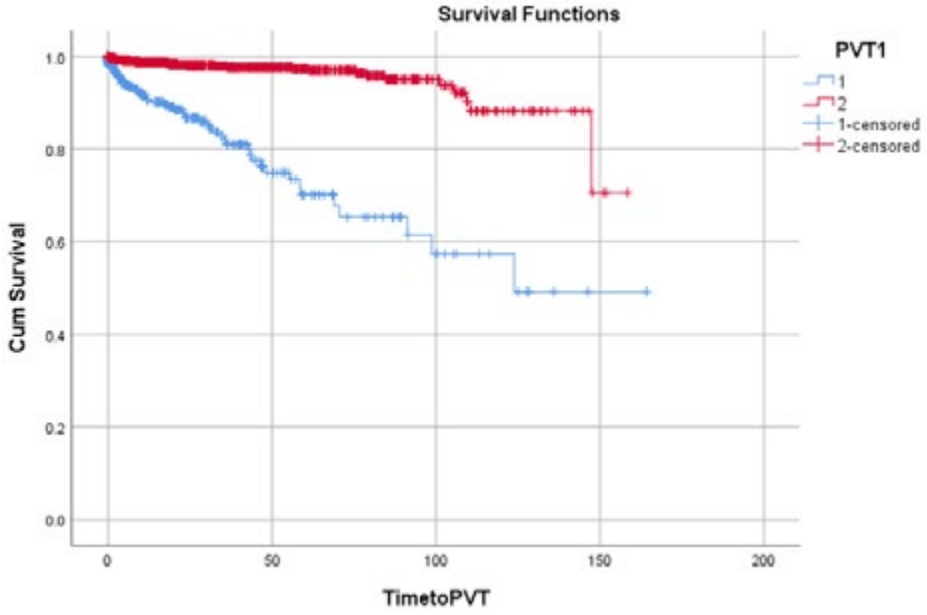
Background: Portal vein thrombosis (PVT) frequently occurs in cirrhosis. Many risk factors have been reported for PVT, e.g., higher CTP class, decreased portal blood flow, collateral circulation, and beta-blocker use. However, these risk factors are derived from small studies and do not precisely predict the occurrence of PVT. **Methods:** The current study aimed to evaluate the incidence and risk factors for non-tumoral PVT development in a large prospective cohort of patients with cirrhosis and to create a model that predicts PVT in cirrhosis. We analysed our electronic data and exhaustively evaluated clinical and biochemical profiles in patients with cirrhosis without PVT who underwent serial imaging. Doppler ultrasound was performed at baseline and every six months or whenever clinically indicated. PVT was confirmed by a computed tomography scan. Serum alfa-fetoprotein and PIVKA II were done whenever required. **Results:** We screened 2776 cirrhosis patients. Out of these, 274(9.8%) developed non-tumoral PVT over the serial follow-up, with an incidence of CTP-A (16%), CTP-B (15.4%) and CTP-C (14.3%), respectively. Seventy-eight per cent were males, and the median age was 48 years (39-57). Ethanol(42.7%) NASH cirrhosis(44.1%), cryptogenic(6.25) and hepatitis B(5.7%) were the main causes of cirrhosis. Univariate analysis showed that a CTP score >9.3(OR 2.74), a history of variceal bleeding(OR 15.6), advanced age(>47.6years, OR 4.6), and portosystemic collaterals(OR 5.9) were the risk factors for PVT. PVT development is associated with lower survival; in the PVT group, 15.9% of the patients died, whereas in the non-PVT group, only 1.7% of the patients died. **Conclusion:** In patients with cirrhosis, the factors predictive of PVT development were mainly those related to the severity of portal hypertension. Our results support age, variceal bleeding, and portosystemic collaterals but not higher CTP class as the risk factors for developing PVT in cirrhosis patients. Occurrence of PVT in one of the risk factor for death.



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Disclosures: Babu Lal Meena: Nothing to Disclose, Shiv Kumar Sarin: Nothing to Disclose, Deepti Sharma: Nothing to Disclose

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1535 | FIRST-IN-HUMAN PHASE 1 STUDY OF EA3571, WHICH IS A NOVEL DUAL INHIBITOR OF ENTEROPEPTIDASE AND TRYPSIN WITH LUMINAL ACTION, IN HEALTHY ADULT PARTICIPANTS ◆

Atsushi Umeda[1] Yasuko Owada[2] Kenichi Furihata[3] Shuichi Tsuruoka[4] Atsushi Nakajima[5] Ryosuke Mikami[6] Masakaze Oaku[1] Takuya Yamamoto[1] Tetsuo Yano[1] Yuji Kumagai[7]

[1]EA Pharma Co., Ltd., [2]OPHAC Hospital, [3]P-one Clinic, [4]Tajirigaoka Hospital, [5]Yokohama City University, [6]EA Pharma Co., Ltd, [7]Kitasato Institute Hospital

Background: EA3571 is a novel dual inhibitor of enteropeptidase and trypsin with luminal action. EA3571 has the potential to embody the effects of gastric bypass surgery by preventing the digestion of dietary nutrients in the small intestine of obese metabolic dysfunction-associated steatohepatitis (MASH) patients. EA3571 significantly improved liver fibrosis and obesity in a high-fat, high-fructose and high-cholesterol diet-induced MASH mouse model at 12 weeks. We assessed safety, pharmacokinetics and pharmacodynamics (PD) of EA3571 in a first-in-human phase 1 study in healthy adult participants (jRCT2051220036). **Methods:** This study consisted of single ascending dose (SAD) parts, multiple ascending dose (MAD) parts and gelatin load test parts. In SAD parts, healthy adult participants received oral EA3571 (10 mg to 1200 mg) or placebo in fasted condition. In MAD parts, healthy adult participants received a single (Day 1) and repeated dose (Day 4 to 10, three times a day) of oral EA3571 (50 mg to 200 mg) or placebo. In the gelatin load test parts, the PD effect of EA3571 was assessed by measuring plasma hydroxyproline (Hyp) concentration as an indicator after oral administration of EA3571 and gelatin which has an amino acid composition with high content of Hyp. **Results:** In the three parts, no serious TEAEs, severe TEAEs, or TEAEs leading to discontinuation of investigational products were observed. Moreover, there were no apparent dose- or treatment-related trends or clinically significant findings in clinical laboratory evaluations or 12-lead ECGs after single or multiple doses of EA3571. The plasma EA3571 concentrations decreased with $t_{1/2}$ less than 1.0 hour after reaching the peak concentration in SAD parts. No abnormal accumulation of EA3571 was observed in MAD parts. The elevation of plasma Hyp level by gelatin loading was suppressed by EA3571 in a dose-dependent manner. EA3571 administered in the morning continuously suppressed the elevation of plasma Hyp level by gelatin loading at lunch as well as that at breakfast (Fig. 1). These results in gelatin load test parts suggested that EA3571 inhibited enteropeptidase/trypsin on the luminal side and that the inhibitory effect of EA3571 was sustained. In MAD parts, plasma total GLP-1 concentrations increased to higher levels after lunch and dinner in the EA3571 groups, and the increase was maintained longer compared to placebo group. **Conclusion:** The results suggest that EA3571 has well-tolerated favorable safety profile and improves MASH by enhanced GLP-1 level due to inhibiting enteropeptidase/trypsin on the luminal side in patients with MASH.

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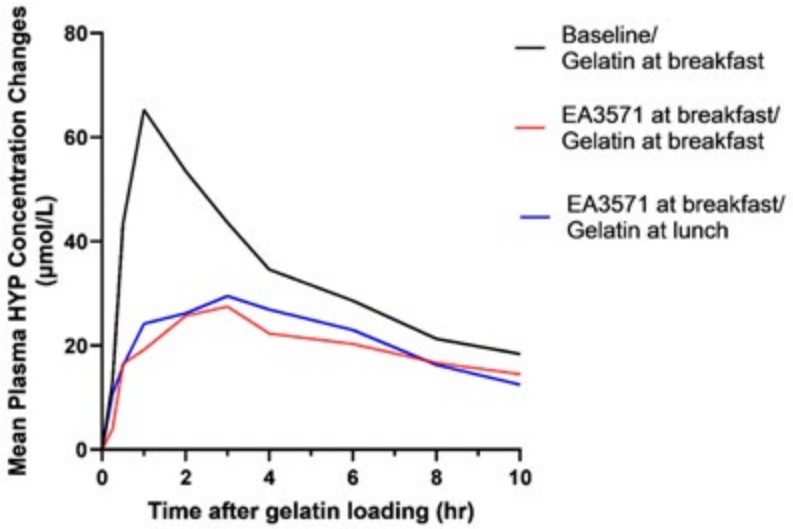

Fig.1 Mean plasma hydroxyproline (Hyp) concentration changes from the value before gelatin loading in Caucasian healthy adult participants.

6 Caucasian healthy adult participants ingested gelatin on Day -4 (at breakfast), Day 1 (at breakfast) and Day 6 (at lunch) and orally received EA3571 at breakfast on Day 1 and Day 6.

Disclosures: ATSUSHI UMEDA: EA Pharma Co., Ltd.: Employee, YASUKO OWADA: Nothing to Disclose, KENICHI FURIHATA: Kissei Pharmaceutical Company: Advisor, SHUICHI TSURUOKA: Nothing to Disclose, Atsushi Nakajima: Nothing to Disclose, RYOSUKE MIKAMI: Nothing to Disclose, MASAKAZE OAKU: Nothing to Disclose, TAKUYA YAMAMOTO: Nothing to Disclose, TETSUO YANO: Nothing to Disclose, YUJI KUMAGAI: Nothing to Disclose

1536 | DNA METHYLOME ANALYSIS REVEALS EPIGENETIC ALTERATION OF COMPLEMENT GENES IN ADVANCED MASLD

Won Kim[1] *Young Ho So*[1] *YONG JIN JUNG*[1] *Sae Kyung Joo*[1]

[1]*Boramae Medical Center*

Background: Blocking the complement system presents a promising strategy to impede the progression of metabolic dysfunction-associated steatotic liver disease (MASLD). Nevertheless, our comprehension of the interplay between complement and MASLD remains nascent. To advance this understanding, we conducted an extensive analysis, integrating DNA methylome and transcriptome studies. This comprehensive approach aims to elucidate the potential association between complement dysregulation and the severity of MASLD. **Methods:** Liver biopsy specimens were procured from a cohort comprising 106 Korean individuals, which included 31 controls, 17 metabolic dysfunction-associated steatotic liver (MASL), and 58 metabolic dysfunction-associated steatohepatitis (MASH). Utilizing the Infinium Methylation EPIC array, a thorough analysis of methylation alterations in 61 complement genes was conducted. **Results:** Our examination of DNA methylome and transcriptome data from liver biopsies of Korean patients reveals a consistent pattern: specific genes such as C1R, C1S, C3, C6, regulation and hepatic pathophysiology. C4BPA, and SERPING1 exhibit hypermethylation and downregulation, while others such as C5AR1, C7, and CD59 display hypomethylation and upregulation. Furthermore, analysis of methylation and expression profiles across various ethnic groups underscores the widespread occurrence of these epigenetic alterations. Additionally, by integrating publicly available single

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nucleus RNA sequencing datasets, we unveil a correlation between complement gene expression and liver zonation, shedding light on the intricate interplay between complemen **Conclusion:** Our research presents compelling evidence of epigenetic alterations in complement genes associated with MASLD. This study provides valuable insights into the underlying mechanisms driving MASLD progression and proposes potential precision-targeted therapeutic strategies involving complement inhibitors for MASLD.

Disclosures: Won Kim: Nothing to Disclose, Young Ho So: Nothing to Disclose, YONG JIN JUNG: Nothing to Disclose, Sae Kyung Joo: Nothing to Disclose

1537 | EFFECTS OF VARIOUS GENETIC POLYMORPHISMS IN F METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE IN JAPAN AND THEIR APPROPRIATE USE IN RISK ASSESSMENT OF LIVER-RELATED EVENTS

Yuya Seko[1] Kanji Yamaguchi[1] Toshihide Shima[2] Michihiro Iwaki[3] Hirokazu Takahashi[4] Miwa Kawanaka[5] Saiyu Tanaka[6] Yasuhide Mitsumoto[2] Masato Yoneda[3] Atsushi Nakajima[7] Takeshi Okanoue[2] Yoshito Itoh[1]

[1]Kyoto Prefectural University of Medicine, [2]Saiseikai Suita Hospital, [3]Yokohama City University Graduate School, [4]Saga University Hospital, [5]Kawasaki Medical School, [6]Nara City Hospital, [7]National Hospital Organization Yokohama Medical Center

Background: *PNPLA3* rs738409, *TM6SF2* rs58542926, and *HSD17B13* rs72613567 have been associated with an increased risk of liver-related events (LRE) in patients with metabolic dysfunction-associated steatotic liver disease (MASLD). In this study, we investigated the combined effects of these variants on LRE in Japan. **Methods:** The longitudinal multicenter cohort study enrolled 1178 patients with biopsy-proven MASLD. We calculated the genetic risk of LRE according to the impact of these variants. Next, we divided the patients into 3 groups according to the FIB-4 index and *PNPLA3* and *TM6SF2* genotypes. **Results:** Multivariate analysis revealed that *PNPLA3* and *TM6SF2*, but not *HSD17B13*, were significantly associated with LRE development. The hazard ratio (HR) of the genetic high-risk group based on *PNPLA3* and *TM6SF2* for LRE was 1.91 (95% CI 1.20–3.04). The higher risk of LRE development in the genetic high-risk group was also seen in patients with F ≥ 3 or FIB-4 index > 2.67. The HRs of the genetic high-risk group for LRE were greater in patients without obesity, without diabetes, and of younger age compared with patients with obesity, with diabetes, or of older age, respectively. The LRE development rate in low/intermediate/high-risk groups based on FIB-4 index and genetic risk was 2.2%/31.9%/53.5% respectively, at 10 years ($p < 0.01$). Overall survival in each group was 98.6%/85.3%/72.4%, respectively, at 10 years (p<0.01). **Conclusion:** This combination of genetic variants of *PNPLA3* and *TM6SF2* is useful for predicting LRE in Japanese patients with MASLD. The approach of measuring the FIB-4 index first followed by assessment of genetic polymorphisms efficiently detected patients at high risk of developing LRE. Therefore, this two-step strategy could be used as a screening method in large populations of patients with MASLD.

Disclosures: Yuya Seko: AbbVie GK: Speaking and Teaching, Novo Nordisk Pharma Ltd: Speaking and Teaching, Merck & Co., Inc.: Speaking and Teaching, Gilead Sciences, Inc.: Speaking and Teaching, Mitsubishi Tanabe Pharma Corporation: Speaking and Teaching, Kanji Yamaguchi: Nothing to Disclose, Toshihide Shima: Nothing to Disclose, Michihiro Iwaki: Nothing to Disclose, Hirokazu Takahashi: Nothing to Disclose, Miwa Kawanaka: Nothing to Disclose, Saiyu Tanaka: Nothing to Disclose, Yasuhide Mitsumoto: Nothing to Disclose, Masato Yoneda: Gilead Sciences: Grant/Research Support, Gilead Siences inc.: Grant/Research Support, Atsushi Nakajima: Nothing to Disclose, Takeshi Okanoue: Nothing to Disclose, Yoshito Itoh: Novo Nordisk Pharma LTD: Speaking and Teaching, ZERIA PHARMACEUTICAL CO., LTD.: Speaking and Teaching, Otsuka Pharmaceutical Co., Ltd.: Speaking and Teaching, Viatris Inc.: Speaking and Teaching, ASKA Pharmaceutical Co., Ltd.: Speaking and Teaching, Astelas Pharma Inc.: Speaking and Teaching, AstraZeneca K.K.: Speaking and Teaching, Gilead Sciences Inc.: Speaking and Teaching, Mitsubishi Tanabe Pharma Corporation: Speaking and Teaching, EA Pharma Co. Ltd.: Speaking and Teaching, Kowa Company Ltd.: Speaking and Teaching, CHUGAI PHARMACEUTICAL CO., LTD.: Speaking and Teaching, Takeda Pharmaceutical Company Limited.: Speaking and Teaching, ONO PHARMACEUTICAL CO., LTD.: Speaking and Teaching, AbbVie Inc.: Speaking and Teaching, Novartis Pharma Inc.: Speaking and Teaching, MYYARISAN Phramaceutocal Co.: Speaking and Teaching, Eli Lilly and Co.: Speaking and Teaching, Olympus Co.: Speaking and Teaching, AbbVie Inc.: Grant/Research Support, Otsuka Pharmaceutical Co., Ltd.: Grant/Research Support, CHUGAI PHARMACEUTICAL

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1538 | NAFLD DOES NOT AFFECT THE EFFECTIVENESS OF TENOFOVIR ALAFENAMIDE IN PATIENTS WITH CHRONIC HBV INFECTION AFTER EXPANDING THE ANTIVIRAL INDICATIONS: A REAL-WORLD MULTICENTER, RETROSPECTIVE COHORT STUDY FROM EASTERN AND CENTRAL CHINA

Yang Ling[1] Yang Ling[1] Qirui Song[2] Weiwei Pan[2] Yanyun Shu[3] Qinzhi Deng[4] Jianjun Lou[5] Jie Li[6] Jianfeng Zhong[7] Zhaowei Tong[7] Zhonglin Li[1] Lilin Hu[1] Huikuan Chu[1] Jin Ye[1] Fan Du[1] jiangshan Lian[2] Yang Ling[8]

[1]Union hospital, Tongji Medical College, [2]Zhejiang University, [3]The Central Hospital of Wuhan, [4]Ningbo No. 2 Hospital, [5]Yuyao people's hospital of Zhejiang, [6]Wenzhou Medical University, [7]Huzhou central hospital, [8]Huazhong University of Science and Technology

Background: An increasing number of patients with chronic hepatitis B virus infection (CHB) also suffer non-alcoholic fatty liver disease (NAFLD). Whether NAFLD affects the antiviral effectiveness in CHB remains controversial. This study assessed the antiviral effectiveness of tenofovir alafenamide (TAF) in CHB patients meeting the expanded antiviral indications in China with or without NAFLD. **Methods:** The inclusion criteria: 1) age≥ 18 years, 2) diagnosed with chronic HBV infection (HBsAg positive> 6 months) and HBV DNA ≥20 IU/mL, 3) received TAF treatment, 4) underwent the abdominal ultrasound examination or elastography to determine the presence or absence of NAFLD. All patients were followed every 3~6 months and had regular medication during follow-up period. According to the severity of fatty liver, NAFLD patients were further divided into the mild group (CAP<265dB/m) and the moderate-to-severe group (CAP≥265dB/m) based on the values of controlled attenuation parameter (CAP). The primary endpoint was the cumulative rate of complete viral suppression (CVS, defined as HBV DNA< 20-30 IU/mL). The second endpoint were the changes of HBsAg, HBeAg, liver stiffness measurement (LSM), in the NAFLD and the non-NAFLD group before and after 48-week follow-up. **Results:** Totally, 390 patients with CHB (nNAFLD=149, nnon-NAFLD=241) treated with TAF from 2019 to 2023 were prospectively enrolled from different regions of China. Compared to the non-NAFLD group, the variables significantly increased in the NAFLD group were male [51.3% vs. 79.2%, p<0.001], GGT [17.1(13.0-27.0) vs. 23.0(18.8-38.3) U/L, p<0.001], TC [4.45(3.88-4.99) vs. 4.61(4.15-5.29) mmol/L, p=0.016], TG [0.91(0.69-1.34 vs. 1.44(0.99-2.03) mmol/L, p<0.001], LDL [2.48(1.92-2.99) vs. 2.87(2.37-3.49) mmol/L, p<0.001], and CAP [225(213-231) vs. 255(245-274) dB/m, p<0.001], which were consistent with precious reports. There was no statistical difference in the cumulative rates of CVS between the non-NAFLD group and the NAFLD group (72.6% vs. 79.2%, log-rank p=0.142), and between the mild NAFLD group and the moderate-to-severe NAFLD group (86.7% vs. 80.6%, log-rank p=0.634). After 48-week treatment, the decreasing degree of LSM in the non-NAFLD group was similar to that of the NAFLD group [1.0 (0.2-1.7) vs. 1.35(0.5-2.2) kPa, p=0.697]. No patients achieved seroconversion of HBsAg and HBeAg in the two groups. The multivariate Cox regression suggested the variables affecting the probability of achieving CVS at baseline were AST (HR: 0.970, 95%CI: 0.944~0.996, p=0.023), HBeAg (positive vs. negative: 0.112, 95%CI: 0.039~0.318, p<0.001), and Log10(HBV DNA) (HR: 0.761, 95%CI: 0.645~0.899, p=0.001), respectively. **Conclusion:** NAFLD, regardless of mild or moderate-to-severe, had no adverse impact on the effectiveness of TAF in patients eligible for expanded antiviral indications.

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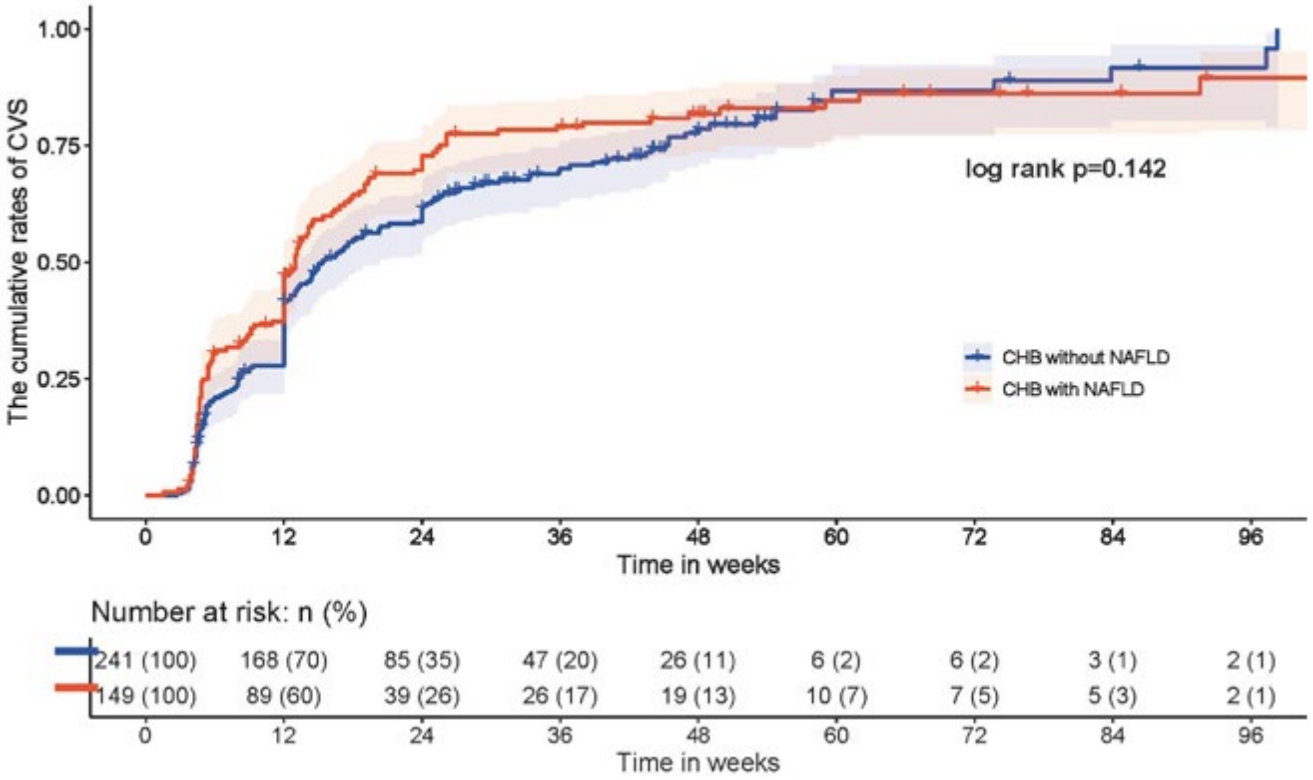

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1539 | IMPACT OF GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS ON METABOLIC HEALTH IN LIVER TRANSPLANT RECIPIENTS

Joseph Spengler[1] Madison Nguyen[1] Rehan Rezzaq[1] Geneva Roche[1] Vaishali Patel[1] Mohammad Siddiqui[1] Kavish Patidar[2]

[1]Virginia Commonwealth University Health, [2]Baylor College of Medicine

Background: The burden of metabolic diseases is high after liver transplantation (LT) and there are limited therapeutic options available that have proven to be effective. Glucagon like peptide-1 (GLP-1) receptor agonist (RA) initially approved for management of diabetes have demonstrated a wide range of metabolic benefit. However, there is limited data with GLP-1RA in LT recipients. Thus, the aim of the present analysis was to determine the metabolic impact of GLP-1RA following LT. **Methods:** The study is a retrospective analysis of adult patients who received a LT at author's institution. Inclusion criteria included LT recipients with type 2 diabetes mellitus (T2DM) who received either GLP-1RA (experimental group) or insulin (controls) following LT with baseline defined as initiation of T2DM therapy. Patients were excluded if they consumed alcohol following LT, had non-dermatological malignancy, life expectancy < 6 months, or graft dysfunction. Patients receiving GLP-1RA were propensity matched 1:1 to those receiving insulin therapy with regards to age, gender, ethnicity, MASH, and immunosuppression as these are factors that can affect metabolic health post-LT. **Results:** A total of 76 patients met study criteria (n=38 for GLP-1RA & n=38 for insulin). The two groups were similar at baseline with regards to clinical characteristics and laboratory values with the exception of time from LT was greater in patients who were on GLP-1RA. LT recipients who received GLP-1RA were significantly more likely to lose weight over 12-month period when compared to weight gain observed in patients who received insulin therapy (Figure 1A). After 12 month of therapy, patients who received GLP-1RA had significantly lower controlled attenuation parameter value

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(Figure 1B) and lower likelihood of having occurrence of post-LT MASLD (Figure 1C). The medications were well tolerated and no significant changes in indices of renal function (i.e. creatinine, eGFR) were noted. Serum bilirubin was similar between two groups from baseline to 12 months post-therapy and serum aminotransferases were significantly lower in GLP-1RA group after 12 months therapy compared to baseline values (GLP-1RA baseline 36±21 vs. 31±16 IU vs. insulin 29±16 vs. 50±46 IU/L, p<0.01). **Conclusion:** GLP-1RA therapy had metabolic benefits in LT recipients and was well tolerated. The results from this retrospective study provide reassuring data and are currently being validated in a prospective double-blinded randomized controlled trial.

Figure 1A: Liver transplant (LT) recipients receiving glucagon like peptide-1 receptor agonist (GLP-1RA) were more likely to lose weight when compared to patients receiving insulin therapy

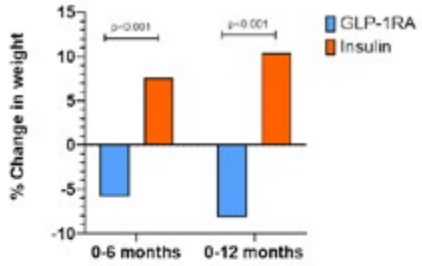


Figure 1B: Controlled attenuation parameter, a surrogate for hepatic fat content, was significantly lower after 12 months of therapy in LT recipients who received GLP-1RA.

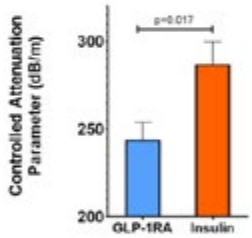
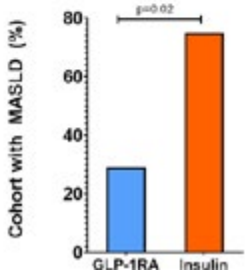


Figure 1C: Occurrence of metabolic dysfunction associated steatotic liver disease (MASLD) was significantly lower after 12 months of therapy in LT recipients who received GLP-1RA.



Disclosures: Joseph Spengler: Nothing to Disclose, Madison Nguyen: Nothing to Disclose, Rehan Rezzaq: Nothing to Disclose, Geneva Roche: Nothing to Disclose, Vaishali Patel: Nothing to Disclose, Mohammad Siddiqui: Grant/Research Support relationship with NovoNordisk; Has not ended; Advisor relationship with 89Bio; Has not ended; Advisor relationship with AMRA; Has not ended, Kavish Patidar: Nothing to Disclose

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1540 | DEEP LEARNING MODEL TO PREDICT STEATOTIC LIVER DISEASE DIAGNOSIS AND STAGING IN PREGNANT INDIVIDUALS

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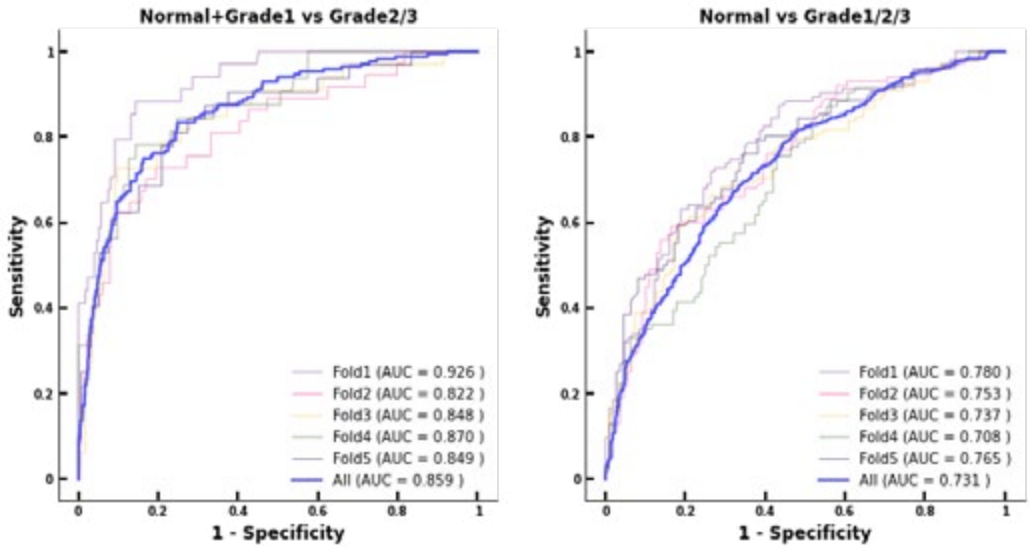
[1]Icahn School of Medicine at Mount Sinai, New York, USA, [2]BioMedical Engineering and Imaging Institute, Icahn School of Medicine at Mount Sinai, New York, USA, [3]Department of Radiology, Icahn School of Medicine at Mount Sinai, New York, USA, [4]Department of Obstetrics and Gynecology, Icahn School of Medicine at Mount Sinai, New York, USA, [5]University of Southern California, [6]Department of Internal Medicine, Icahn School of Medicine at Mount Sinai, New York, USA, [7]Division of Liver Diseases, Icahn School of Medicine at Mount Sinai, USA

Background: Steatotic Liver Disease (SLD) complicating pregnancy is increasing common and is independently associated with adverse pregnancy outcomes. Ultrasound is the most common imaging modality used to detect the presence and severity of steatosis, although it has previously shown suboptimal intra- and inter-rater reliability. We sought to create a deep learning (DL) model to improve assessment and staging of SLD in pregnant individuals. **Methods:** The FLIP study prospectively enrolled pregnant individuals seeking care in a large, urban health system and evaluated them for SLD with ultrasound performed between 18-22 weeks gestation and graded by a blinded radiologist with expertise in liver disease. For each participant, 4 to 11 images were captured that included right hemidiaphragm, hepatic vessels and right kidney. The de-identified dataset underwent a 5-fold cross-validation process organized by subject with 72% of the images for training, 8% for validation, and 20% for testing. The initial phase of training utilized a Swin-Transformer model, leveraging pre-trained weights from RadImageNet, which is a specialized dataset tailored for radiological images, enhancing the relevance and efficacy of pre-trained models in medical imaging tasks. We computed the average AUC across all 5 folds along with the 95% confidence interval. Initially, we contrasted normal liver images with Grades 1, 2, and 3 SLD combined. Afterward, we refined the model to contrast normal and Grade 1 SLD vs Grades 2 and 3 SLD. **Results:** We incorporated 1038 ultrasound images from 185 FLIP participants into the DL model. Of the selected participants, 78 (42.2%) had a diagnosis of SLD based on initial radiologist review, with 49 (62.8%) Grade 1, 23 (29.5%) Grade 2, and 6 (7.6%) Grade 3. Individuals from whom images were obtained were of mean age 29.3 years (SD 5.9); 102 (55.1%) self-identified as Hispanic and 52 (28.1%) as non-Hispanic Black. The Swin Transformer model achieved an average AUC of 0.71 (95%CI: 0.70, 0.76) on 5-fold cross validation of our initial model. The second model analyzing normal and Grade 1 vs Grade 2 and 3 SLD had an average AUC of 0.86 (95% CI: 0.83, 0.89), with a sensitivity of 0.38 (95%CI: 0.31, 0.45), specificity of 0.96 (95%CI: 0.95, 0.97) positive predictive value (PPV) of 0.67 (95%CI: 0.57, 0.76), and negative predictive value (NPV) of 0.89 (95%CI 0.87, 0.91). **Conclusion:** Our DL model successfully predicted presence and severity of steatosis on ultrasound images, particularly in distinguishing Grade 2 or above SLD from minimal or no SLD. Future directions include validating the model to eventually implement similar models into clinical practice, where pregnant individuals can obtain probabilities for SLD in real-time. Incorporation of DL model into SLD assessment in pregnancy can improve detection of liver disease, aid in potential early prognostication of SLD related pregnancy outcomes, and allow further assessment and linkage to MASLD care.



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1541 | SERUM NONINVASIVE TESTING SCORES AND MODELING TO PREDICT INTERMEDIATE OR HIGH RISK FOR ADVANCED FIBROSIS DUE TO METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD) IN A TYPE 2 DIABETES (T2D) POPULATION COHORT

Gretchen Arndt[1] Mark Lindsey[2] Sheila Swartwood[2] Susana Arrigain[2] Rocio Lopez Moscoso[2] Amanda Wieland[2] Thomas Jensen[1]

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Background: Guidelines published by the American Association for the Study of Liver Diseases (AASLD) recommend using FIB-4 serum screening score of ≥ 1.3 to evaluate patients who are at indeterminate or high risk for advanced fibrosis and should have secondary assessment by vibration-controlled elastography (VCTE) (such as Fibroscan™) or Enhanced Liver Fibrosis (ELF)[1]. Patients with T2D are especially at higher risk for advanced fibrosis and with recent advancements in clinical trials for medications approved for MASLD, it is critical to appropriately identify and manage these patients[2]. **Methods:** We retrospectively analyzed 98 subjects with a diagnosis of MASLD and T2D seen in our Endocrinology or Hepatology Clinics who had a Fibroscan™ within 6 months of calculated Noninvasive Tests (NIT), FIB-4, AST to Platelet Ratio Index (APRI), AST/ALT ratios, and NAFLD Fibrosis Score (NFS). We plotted receiver operating characteristic (ROC) curves and estimated the area under the curves (AUC) for each NIT with liver stiffness measurement (LSM) ≥ 8 kPa as the outcome and selected optimal cut-points for each of the scores to predict having LSM ≥ 8 kPa using the Youden index. Multivariable logistic regression was used to assess whether clinical characteristics or a combination of one score and other clinical characteristic improved prediction of LSM ≥ 8 kPa. **Results:** Neither FIB-4 (AUC; 95% CI: 0.59; 0.48, 0.71), AST/ALT ratio (0.53; 0.41, 0.65), nor NFS (0.61; 0.50, 0.73) where found to be significantly better than chance assignment (AUC of 0.5 is chance assignment) but APRI was better (0.70; 0.60, 0.81). Based on the Youden index, the optimal cut points for predicting LSM ≥ 8 kPa with FIB-4 or APRI are 1.26 and 0.22, respectively. APRI ≥ 0.22 has a sensitivity of 87% but a specificity of only 53%. The FIB-4 cut off 1.3 had a sensitivity of 55% and a specificity of 65%. Using an APRI cut point of 0.22 accurately identified the presence or absence of advanced fibrosis in 66% (n=65) of the 98 subjects, whereas FIB-4 could only accurately identify 61% (n=60). (n=60). There were 17 individuals who had LSM ≥ 8 kPA but had a FIB-4 score < 1.3 (false negative FIB-4), 13 (76%) of these had an APRI ≥ 0.22+ and would have correctly been sent for a confirmation Fibroscan if APRI were used for screening. There were 5 individuals who had liver stiffness ≥ 8 kPA but an APRI score < 0.22 (false negative APRI), only 1 (20%) of these had a FIB-4 ≥ 1.3 and would have correctly been sent for a confirmation Fibroscan if FIB-4 were used for screening. **Conclusion:** In our cohort of patients with T2D and MASLD, APRI score was found superior to other NITs including FIB-4 score for identifying patients with LSM ≥ 8 kPa. In addition, APRI score was superior to FIB-4 score to rule out patients with an intermediate or high risk for advanced fibrosis. Our data shows the importance of considering alternative tests to appropriately rule out advanced fibrosis in a population with T2D than what is proposed in current guidelines.

Disclosures: Gretchen Arndt: Nothing to Disclose, Mark Lindsey: Nothing to Disclose, Sheila Swartwood: Nothing to Disclose, Susana Arrigain: Nothing to Disclose, Rocio Lopez Moscoso: Nothing to Disclose, Amanda Wieland: Nothing to Disclose, Thomas Jensen: Nothing to Disclose

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1542 | SAFETY AND EFFICACY OF ENDOSCOPIC SLEEVE GASTROPLASTY AFTER ORTHOTOPIC LIVER TRANSPLANTATION

Benjamin Richter[1] Yazan Abboud[1] Jay Phansalkar[2] Ahmed Al-Khazraji[1] Keri Lunsford[3] Arpit Amin[1] Flavio Paterno[3] James Guarrera[1] Dhvani Doshi[1] Kaveh Hajifathalian[1]

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Background: Metabolic dysfunction-associated liver disease (MASLD) is one of the leading causes of chronic liver disease and Orthotopic Liver Transplantation (OLT) in the U.S. Patients after OLT are at elevated risk for weight regain and MASLD. Bariatric procedures may be helpful for long-term weight management; however, safety concerns, including increased risk of infection and dehydration for immunosuppressed patients have limited its use. Endoscopic Sleeve Gastroplasty (ESG) is effective for weight loss, with a superior safety profile to bariatric surgery. Here, we report preliminary data on safety and efficacy of ESG after OLT. **Methods:** This is a retrospective case-series of 5 patients who underwent ESG from 2021-2023 for treatment of weight regain after OLT. **Results:** All 5 patients successfully underwent ESG a median of 47.3 (16.1 - 150.0) months post-OLT. Patients were predominantly male (4/5, 80%), with a median age of 41 (41-61) years and body mass index of 38.8 (31.9 - 44.8) kg/m2 at the time of procedure. Median follow-up after ESG was 16.2 (3.4 – 22.5) months. The median total body weight loss percent (TBWL%) was 30% (10.3 - 43.9%) at end of follow-up. 5 post-op complications occurred in 4 (80%) patients, including transient acute kidney injury (n = 2), vomiting (n = 1), epigastric pain (n.= 1), and esophageal candidiasis (n = 1). Complications were all mild, and none exceeded grade I on the Clavien-Dindo Classification. No patient missed any doses of immunosuppressive medications, and liver graft function remained stable during follow-up. **Conclusion:** ESG was both safe and effective for treatment of weight regain in patients after OLT in our case series. All patients achieved at least 10% TBWL needed for improvement in liver inflammation and fibrosis. Median weight loss was comparable to bariatric surgery without any significant or lasting adverse events.

Patient Characteristics	
Variables*	
Age	41 (41-61)
Sex (Male)	4 (80%)
DM	4 (80%)
HTN	3 (60%)
Underlying Liver disease	
NASH	1 (20%)
ETOH	2 (40%)
HCV	1 (20%)
Cryptogenic	1 (20%)
Time between OLT and ESG (Months)	47.3 (16.1 - 150.0)
Pre-OLT Weight (Lbs)	222 (203-256)
Pre-ESG Weight (Lbs)	240 (204-280)
Pre-ESG BMI	38.8 (31.9-44.8)
Pre-ESG Liver Bx Macrosteatosis (%)	5% (0%-25%)
Pre-ESG Fib4 Score	1.4 (1.12-1.93)
Pre-ESG Elastography (kPa)	3.6 (2.7-3.8)
Outcomes	
Follow-up (Months)	16.2 (3.4 – 22.5)
Total body weight loss (Lbs)	72 (21-123)
Total body weight loss (%)	30% (10.3%-43.9%)
Post-ESG Admission (number of days)	0 (0-1)
Complications	
Mild	5
Moderate	0
Severe	0
Death	0
Vomiting (number of days)	1 (0-3)
Missed ISP (number of days)	0 (0-0)

* Median and range were reported for continuous variables; frequencies and percentages were reported for categorical variables.

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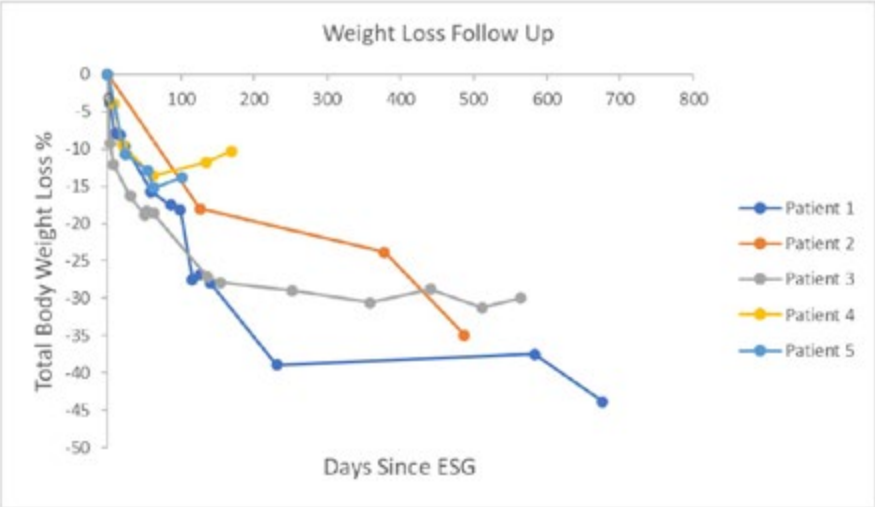

Disclosures: Benjamin Richter: Nothing to Disclose, Yazan Abboud: Nothing to Disclose, Jay Phansalkar: Nothing to Disclose, Ahmed Al-Khazraji: Nothing to Disclose, Keri Lunsford: GATT Technologies: Consultant, ROM Tech: Stock – privately held company, Johnson and Johnson: Stock - publicly traded company, Adaptive Biotechnology: Stock - publicly traded company, Tandem Diabetes: Stock - publicly traded company, Incyte: Stock - publicly traded company, Arpit Amin: Nothing to Disclose, Flavio Paterno: Nothing to Disclose, James Guarrera: Nothing to Disclose, Dhvani Doshi: Nothing to Disclose, Kaveh Hajifathalian: Nothing to Disclose

1543 | HEPATOCELLULAR CARCINOMA AND LIFESTYLE: HOW DO DIETARY PATTERNS DIFFER IN THOSE WITH METABOLIC AND NON-METABOLIC DYSFUNCTION ASSOCIATED STEATOTIC LIVER DISEASE?

Nikil Vootukuru[1] Elena George[2] Surbhi Sood[2] Nicholas Batt[1] Rohit Sawhney[1] Stephen Bloom[1] Alexander Hodge[1] Beverly Rodrigues[1] Carol McCrae[1] Stuart Roberts[3] Anouk Dev[4] Sally Bell[4] Siddharth Sood[5] Alexander Thompson[6] Marno Ryan[7] William Kemp[3] Paul Gow[8] Amanda Nicoll[1]

[1]Eastern Health, [2]Deakin University, [3]Alfred Health, [4]Monash Health, [5]Northern Health, [6]St Vincents Hospital, [7]St. Vincent's Hospital, [8]Austin Health

Background: Metabolic-Associated Steatotic Liver Disease (MASLD) is now a major cause of liver morbidity and mortality, including hepatocellular carcinoma (HCC). Unhealthy dietary patterns are more likely to predispose to HCC development. The aim of this study was to explore dietary patterns among patients with established HCC comparing those with and without MASLD. **Methods:** A multicentre, prospective cohort analysis of newly diagnosed HCC patients at six hepatology centres in metropolitan Melbourne (Victoria, Australia) was conducted from October 2020 to July 2022. A subset of seventy participants out of 313 recruited (22.4%) completed a three-day food diary. Food diaries were self-reported written records documenting the type, brand, and quantities of food and beverages consumed by participants, and recipes were provided where appropriate; they were entered and analysed the food diaries using the software FoodWorks 9™. Food diaries were used to measure adherence to MedDiet Score (0–45 points); higher scores indicating higher adherence. Demographic and clinical data was prospectively collected from hospital electronic medical records. All statistical analysis for this subgroup analysis was performed using the R programming environment. **Results:** : Seventy patients with HCC were included in the study of which: 35 (50%) had no features of MASLD (non-MASLD) and 35 (50%) had features of MASLD. There were no significant differences in baseline demographics between the groups except for age (Table 1). Cirrhosis was present in 77% of MASLD HCC, compared to 83% in non-MASLD group, and the majority were Child-Pugh A (55.7%) in both groups. An exploratory univariable analysis identified significant differences in daily energy intake (kJ) (p=0.03), processed meat serves (p=0.04), legumes serve (p=0.02), and yoghurt serves (p=0.03) but interestingly the daily energy intake (kJ) and processed meat serves were higher among the non-MASLD group. A multivariable analysis adjusting for energy, gender, BMI and age showed that processed meat serves (p = 0.04) were higher among non-MASLD than MASLD groups. There were no other dietary differences identified both on univariable and multivariable analysis between the non-MASLD and MASLD groups. The MedDiet Score

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which evaluates adherence to mediterranean dietary patterns was not significantly different between both groups. **Conclusion:** Differences in dietary patterns in patients with liver injury may contribute to the occurrence of HCC in patients with MASLD, and possibly in non-MASLD. However, further studies are required to explore habitual dietary intake and patterns that predispose to development of HCC.

MASLD	No, N = 35[1]	Yes, N = 35[1]	p-value[2]
Age	64 (60, 73)	70 (67, 77)	**0.003**
Gender			0.15
Female	5 (14%)	10 (29%)	
Male	30 (86%)	25 (71%)	
Child Pugh Class			0.46
CPA	22 (76%)	17 (63%)	
CPB	6 (21%)	7 (26%)	
CPC	1 (3.4%)	3 (11%)	
Cirrhosis	29 (83%)	27 (77%)	0.55
Energy Intake (kJ)	7,261 (6,557, 9,587)	6,002 (4,855, 7,815)	**0.030**
Protein (%) kJ	18.6 (16.9, 23.7)	20.5 (17.6, 25.3)	0.18
Fat (%) kJ	34 (27, 38)	31 (26, 36)	0.34
Saturated Fat (%) kJ	12.3 (9.4, 14.9)	13.1 (10.0, 15.3)	0.73
Polyunsaturated Fat (%) kJ	4.26 (3.52, 5.65)	4.10 (3.02, 4.98)	0.28
Added Sugars (g)	22 (11, 44)	20 (11, 39)	0.62
Carbohydrate (%) kJ	43 (38, 50)	42 (36, 40)	0.35
Dietary Fibre (g)	21 (16, 30)	17 (14, 22)	0.12
Sodium (mg)	2,202 (1,456, 2,880)	1,583 (1,135, 2,365)	0.16
Grains (Serve)	5.25 (3.98, 7.29)	4.16 (3.25, 5.86)	0.067
Fruit (Serve)	1.43 (0.68, 1.93)	1.13 (0.29, 2.27)	0.36
Vegetables (Serve)	2.58 (1.92, 3.58)	2.59 (1.41, 3.57)	0.67
Red Meats (Serve)	0.43 (0.11, 0.94)	0.63 (0.14, 1.14)	0.38
Poultry (Serve)	0.43 (0.05, 0.70)	0.33 (0.07, 0.68)	0.79
Processed Meats (Serve)	0.24 (0.00, 0.58)	0.03 (0.00, 0.15)	**0.034**
Seafood High LC and N3 (Serve)	0.00 (0.00, 0.08)	0.00 (0.00, 0.14)	0.25
Seafood Low LC and N3 (Serve)	0.00 (0.00, 0.10)	0.00 (0.00, 0.20)	0.38
Nuts and Seeds (Serve)	0.01 (0.00, 0.51)	0.02 (0.00, 0.09)	0.48
Legumes (Serve)	0.00 (0.00, 0.00)	0.00 (0.00, 0.02)	**0.024**
Dairy (Serve)	1.30 (0.84, 2.11)	1.25 (0.94, 2.26)	0.97
Alcohol (g)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.23
Caffeine (mg)	85 (26, 224)	89 (44, 190)	0.85
MedDiet Score	23.0 (21.0, 27.0)	22.0 (20.0, 27.5)	0.33

[1]Median (IQR), n (%), [2]Wilcoxon rank sum exact test, Pearson's Chi-squared test, Fisher's exact test, Wilcoxon rank sum test

Note: Serves are defined as per Australian guide to healthy eating

Disclosures: Nikil Vootukuru: Nothing to Disclose, Elena George: Nothing to Disclose, Surbhi Sood: Nothing to Disclose, Nicholas Batt: Nothing to Disclose, Rohit Sawhney: Nothing to Disclose, Stephen Bloom: Nothing to Disclose, Alexander Hodge: Nothing to Disclose, Beverly Rodrigues: Nothing to Disclose, Carol McCrae: Nothing to Disclose, Stuart Roberts: Nothing to Disclose, Anouk Dev: Nothing to Disclose, Sally Bell: Nothing to Disclose,

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Siddharth Sood: CSL Ltd: advice on albumin, Grifols: speaking fees, Alexander Thompson: Gilead Sciences: Consultant, Gilead Sciences: Speaking and Teaching, Abbvie: Consultant, Abbvie: Speaking and Teaching, Immunocore: Advisor, Marno Ryan: Nothing to Disclose, William Kemp: Nothing to Disclose, Paul Gow: Nothing to Disclose, Amanda Nicoll: Nothing to Disclose

1544 | DEGREE OF METABOLIC DYSFUNCTION IS LINKED TO STEATOHEPATITIS (MASH), FIBROSIS, AND HIGHER CARDIOVASCULAR RISK IN PATIENTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD)

David Kim[1] Yazan Abboud[1] Mohamed Ismail[1] Ritik Mahaveer Goyal[1] Nikolaos Pyrsopoulos[1] Hyunseok Kim[2] Kaveh Hajifathalian[1] Ahmed Al-Khazraji[1]

[1]Rutgers New Jersey Medical School, [2]Baylor College of Medicine

Background: The diagnosis of metabolic dysfunction-associated steatotic liver disease (MASLD) necessitates the presence of at least one metabolic risk factor. However, the impact of multiple metabolic dysfunction risk factors remains unclear. Our study investigates the relationship between the extent of metabolic dysfunction and its effects on hepatic fibrosis and metabolic dysfunction-associated steatohepatitis (MASH). **Methods:** The National Health and Nutrition Examination Survey from 2017 to 2020 was utilized. MASLD was defined using controlled attenuation parameter (CAP) scores ≥258 dB/m with cardiometabolic risk factors as previously defined. Advanced fibrosis and cirrhosis was defined as liver stiffness measurement (LSM) ≥9.0 kPa and ≥12 kPa, respectively. MASH was defined using the fibroscan-aspartate aminotransferase (FAST) score ≥0.35. 10-year atherosclerotic cardiovascular disease (ASCVD) risk was calculated using the American College of Cardiology risk score. Odds ratios were calculated with survey-weighted logistic regression. **Results:** In our cohort of 4,339 individuals, 9.7% had 1 metabolic risk factor, 22.1% had 2, and 68.1% had 3 or more. Among the cohort, 12.7% had advanced fibrosis, 5.2% had cirrhosis, and 10.0% had MASH. MASLD patients with 3 or more metabolic risk factors were significantly more likely to have advanced fibrosis (OR=12.997; 95% CI, 1.825–92.580; *P*=0.013), cirrhosis (OR=7.111; 95% CI, 1.068–47.344; *P*=0.043), MASH (OR=15.676; 95% CI, 2.676–91.814; *P*=0.004), and higher 10-year ASCVD risk (OR=1.347; 95% CI, 1.079–1.682; *P*=0.011) compared to those with MASLD and only 1 metabolic risk factor when adjusted for age, gender, and race. Advanced fibrosis and MASH were most associated with patients with elevated BMI or waist circumference and diabetes mellitus, respectively (Figure 1). **Conclusion:** We observed the increased risk of MASH, significant fibrosis, cirrhosis, and ASCVD risk in patients with multiple metabolic risk factors. Stratifying patients by the number of metabolic risk factors may more reliably identify those with MASH, aiding in recognizing patients at risk for liver-related events and identifying candidates for treatment.

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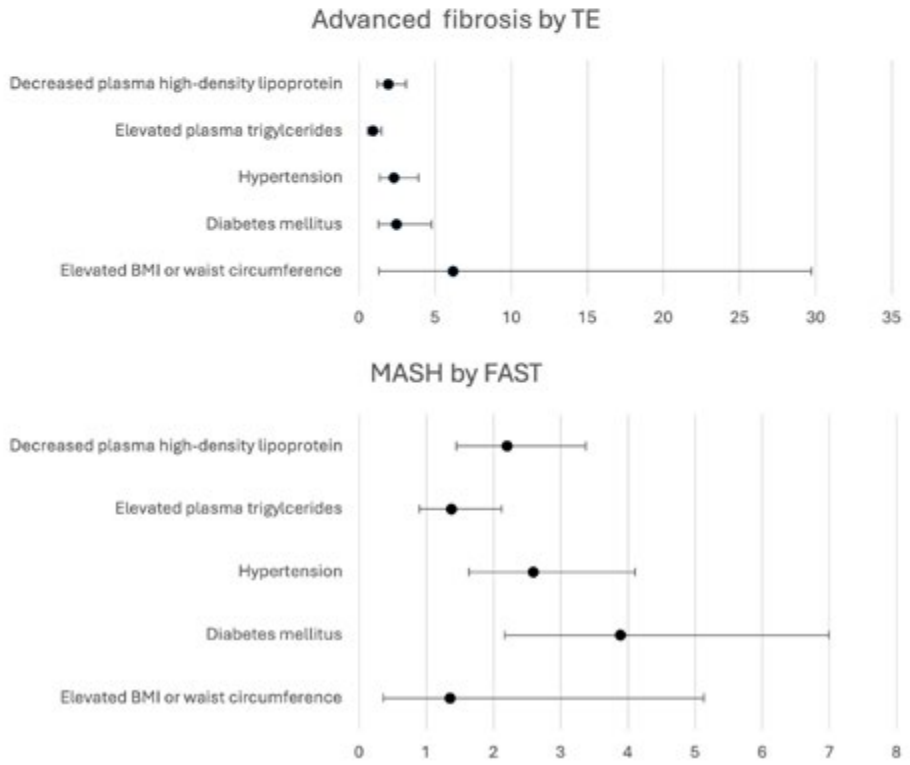
Table 1. Unadjusted and adjusted odds ratio of degree of metabolic dysfunction for fibrosis, MASH, and ASCVD

	Unadjusted		Model 1	
	Odd ratio (95% CI)	*P* value	Odd ratio (95% CI)	*P* value
Outcome: advanced fibrosis by TE				
1 metabolic risk factor	Reference		Reference	
2 metabolic risk factors	5.551 (0.729 - 42.354)	0.094	5.538 (0.748 - 40.984)	0.09
≥ 3 metabolic risk factors	**13.258 (1.745 - 100.717)**	**0.015**	**12.997 (1.825 - 92.580)**	**0.013**
Outcome: cirrhosis by TE				
1 metabolic risk factor	Reference		Reference	
2 metabolic risk factors	2.229 (0.219 - 22.707)	0.482	2.222 (0.224 - 22.001)	0.476
≥ 3 metabolic risk factors	**7.350 (1.009 - 53.541)**	**0.049**	**7.111 (1.068 - 47.344)**	**0.043**
Outcome: MASH by FAST				
1 metabolic risk factor	Reference		Reference	
2 metabolic risk factors	4.755 (0.587 - 38.506)	0.137	5.222 (0.649 - 42.002)	0.114
≥ 3 metabolic risk factors	**12.661 (2.150 - 74.544)**	**0.007**	**15.676 (2.676 - 91.814)**	**0.004**
Outcome: ASCVD risk				
1 metabolic risk factor	Reference		Reference	
2 metabolic risk factors	1.109 (0.652 - 1.887)	0.691	0.930 (0.655 - 1.321)	0.671
≥ 3 metabolic risk factors	**2.375 (2.056 - 2.744)**	**<0.001**	**1.347 (1.079 - 1.682)**	**0.011**

Model 1 adjusted for age, gender, and race.

MASH, metabolic dysfunction-associated steatohepatitis; ASCVD, atherosclerotic cardiovascular disease; TE, transient elastography; FAST, FibroScan-AST; CI, confidence interval.



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1545 | USING PANEL MANAGEMENT TO IDENTIFY ADULT PATIENTS WITH HIGH RISK MASLD/MASH FIBROSIS IN A PRIMARY CARE CLINIC: A PILOT STUDY

Sarah Householder[1] *Andrew Loza*[1] *Vikas Gupta*[2] *Benjamin Doolittle*[2]

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Background: As rates of metabolic dysfunction-associated steatotic liver disease (MASLD) and its more severe counterpart metabolic dysfunction-associated steatohepatitis (MASH) have increased, national organizations have released new guidance for primary care-driven detection of those patients with advanced fibrosis who are most at risk for significant morbidity. Yet time constraints, workflow, and provider awareness limit integration of risk identification into clinical care. **Methods:** At our primary care clinic we implemented a panel management strategy that utilized the electronic health record to identify patients older than 35 years of age at risk for MASLD with abnormal Fibrosis-4 (Fib-4) scores. Using a proactive model, these patients were contacted and offered sheer wave elastography (SWE) screening and follow-up appointments focused on metabolic health, with referrals to subspecialty care when indicated. **Results:** Of 855 patients older than 35 years of age, 384 were identified as having risk factors for MASLD/MASH. Of these, 53 had abnormal Fib-4 scores with no prior evaluation. 29 patients consented for SWE referral; 16 underwent the study; and 6 had moderate or high results concerning for at-risk fibrosis. 20 patients attended MASLD-focused appointments where they received personal risk assessment, lifestyle counseling, and management of associated metabolic conditions. Patients who underwent SWE had more recent appointments than those who did not (median 3.3 vs 4.9 months, p=0.019). Patients who underwent SWE and had subsequent normal studies were significantly older than those with abnormal results (median 70 vs 55 years, p=0.035). Follow through for interested patients was likely impacted by issues of access to care including transportation, language barriers, and work obligations as the clinic patients in our study experience multiple social determinants of health with a median state area deprivation index of 74% (IQR 56, 83). Highest reluctance to pursue further testing by patients was driven by skepticism surrounding preventative medicine, perceived cost, and desire to focus on other medical problems, some of which were life limiting. **Conclusion:** Panel management represents a scalable, time-sensitive strategy to quickly identify patients in a primary care practice most at risk for complications from MASLD/MASH and affords targeted interventions to mitigate risk and direct further management. Limitations include access to care, medical complexity, and patient acceptance. A gap in current guidance for the primary care provider is when risk identification is no longer in the patient's best interest, such as advanced age or other life-threatening illness.

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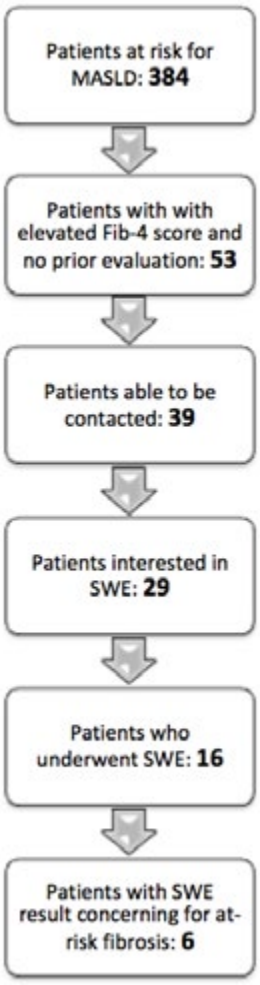

Disclosures: Sarah Householder: Nothing to Disclose, Andrew Loza: Nothing to Disclose, Vikas Gupta: Nothing to Disclose, Benjamin Doolittle: Nothing to Disclose

1547 | MASLD IS A NIGHT-TIME DISEASE DRIVEN BY NOCTURNAL HEPATIC, ADIPOSE, AND SKELETAL MUSCLE INSULIN RESISTANCE

Thomas Marjot[1] Sarah White[1] Elspeth Johnson[1] Felix Westcott[1] Kate Gralton[1] Riccardo Pofi[1] Hamish Miller[1] David Ray[1] Leanne Hodson[1] Jeremy Tomlinson[1]

[1]University of Oxford

Background: Rodent models show that hepatic lipid and glucose metabolism are under tight circadian control, yet there are no clinical studies exploring diurnal patterns in functional processes governing intrahepatic lipid accumulation. **Methods:** 12 MASLD patients and 12 controls underwent detailed metabolic phenotyping including a 2-step hyperinsulinaemic euglycaemic clamp with stable isotope assessments of glucose utilization during the day (07:00–13:00) and at night (19:00–01:00) under standardised fasting conditions. Identical day and night investigations were performed in MASLD patients after a 12-week weight loss programme. **Results:** In MASLD patients, glucose utilization (M/I value) was lower at night compared to day during low- (1.12 ± 0.36 vs. 2.39 ± 0.54 mg/kg/min per mU/L; p=0.016) and high-dose insulin infusions (1.40 ± 0.25 vs. 1.95 ± 0.32 mg/kg/min per mU/L; p=0.019) indicative of night-time hepatic and skeletal muscle insulin resistance respectively. In contrast, controls had no diurnal differences in glucose utilization. Endogenous glucose production (EGP) was also higher (p=0.0395) and glucose disposal (Gd) lower (p=0.0006) in MASLD patients at night compared to day. MASLD patients had elevated plasma non-esterified fatty acids (NEFA) at night compared to day during basal (p=0.001) and low-dose insulin phases of the clamp (p=0.006) reflecting nocturnal adipose tissue dysfunction. Although MASLD patients had hyperinsulinaemia relative to controls, they also had reduced plasma insulin

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concentrations at night compared to day despite identical rates of infused insulin. This was explained by striking diurnal differences in the metabolic clearance rate (MCR) of insulin with significantly higher values observed at night compared to day during both low (p=0.0005) and high dose insulin (p=0.0188). Plasma proteomics identified a number of metabolic and immune regulators which are differentially expressed at night compared to day (e.g. GDF15, CXCL5). After 6% weight loss, MASLD patients exhibited global improvements in insulin sensitivity and adipose function however diurnal differences in M/I values (p=0.02), NEFA (p=0.008), and MCR insulin (<0.001) persisted. This suggests that night-time metabolic dysfunction may be a primary driver of hepatic steatosis. Across all groups, there were no significant differences in calory intake, physical activity, and sleep quality in the week preceding day and night investigations indicating that observed metabolic differences were related to time-of-day rather than external lifestyle factors. **Conclusion:** Night-time metabolic dysfunction may represent a unique risk factor for MASLD with greater IR across multiple tissues observed at night compared to day. This IR is compounded by inappropriate upregulation of insulin clearance at night. These findings will help establish the optimal window for energy intake, exercise, and medication delivery in MASLD patients.

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1548 | LEAN NON-ALCOHOLIC FATTY LIVER DISEASE IS NOT A DISTINCT PATHOPHYSIOLOGICAL ENTITY

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Background: There are very few comparative studies worldwide between ‘lean’ and ‘non-lean/obese non-alcoholic fatty liver disease (NAFLD)’ patients analyzing the differences in gut microbiome, genotype and serum bile acids. We aimed to compare the genotype, gut microbiome, bile acid profile and metabolic patterns of lean NAFLD and obese NAFLD patients with special reference to hepatic fibrosis. **Methods:** Both lean and obese NAFLD patients diagnosed by ultrasonography along with matched controls were included. Genotyping, fecal microbiome analysis and estimation of serum total bile acid levels were done for patients as well as controls. **Results:** 157 NAFLD patients were evaluated out of which 71 patients were enrolled in the study. Out of 71 NAFLD patients, 38 patients were obese and 33 were lean. Stool samples of 52 subjects: 16 from Lean NAFLD, 16 from obese NAFLD, 10 from each control group were analysed. Biochemical and metabolic patterns of lean and obese NAFLD patients were comparable. Lean NAFLD patients had lower FPG(94.52±12.75 vs 105.32 ± 29.23, p<0.05) and HOMA-IR(2.39 ± 2.10 vs 4.09 ± 4.34, p<0.05), although the proportions of patients having elevated HOMA-IR and MS were comparable. Non-invasive scores of liver fibrosis were also comparable(APRI - 0.458 ± 0.25 vs 0.497 ± 0.30, p >0.05; FIB-4 - 1.11 ± 0.61 vs 1.21 ± 0.89, p >0.05; TE - 6.64 ± 2.15 kPa vs 7.42 ± 3.81 kPa, p >0.05). A greater proportion of lean NAFLD patients had PNPLA3 rs738409 (G/G) genotype (12 out of 33 vs 5 out of 38, p< 0.05). However, there was no association of genetic polymorphisms with steatosis or fibrosis. Non-lean and lean NAFLD patients had comparable serum total bile acid levels (mean rank, 8.20 vs 12.80, U = 27.0, p >0.05). On microbiome analysis, beta diversity was found to be significantly different across all groups. Regression analysis revealed strong positive and negative association of microbes with various clinical parameters. **Conclusion:** Differential expression of gut microbiota could underlie the pathogenesis of lean NAFLD, although it is difficult to label it as an entirely distinct pathophysiological entity. A long-term follow up focussing on the alterations in gut microbiota and metabolic fluctuations could help us understand the pathogenesis better.

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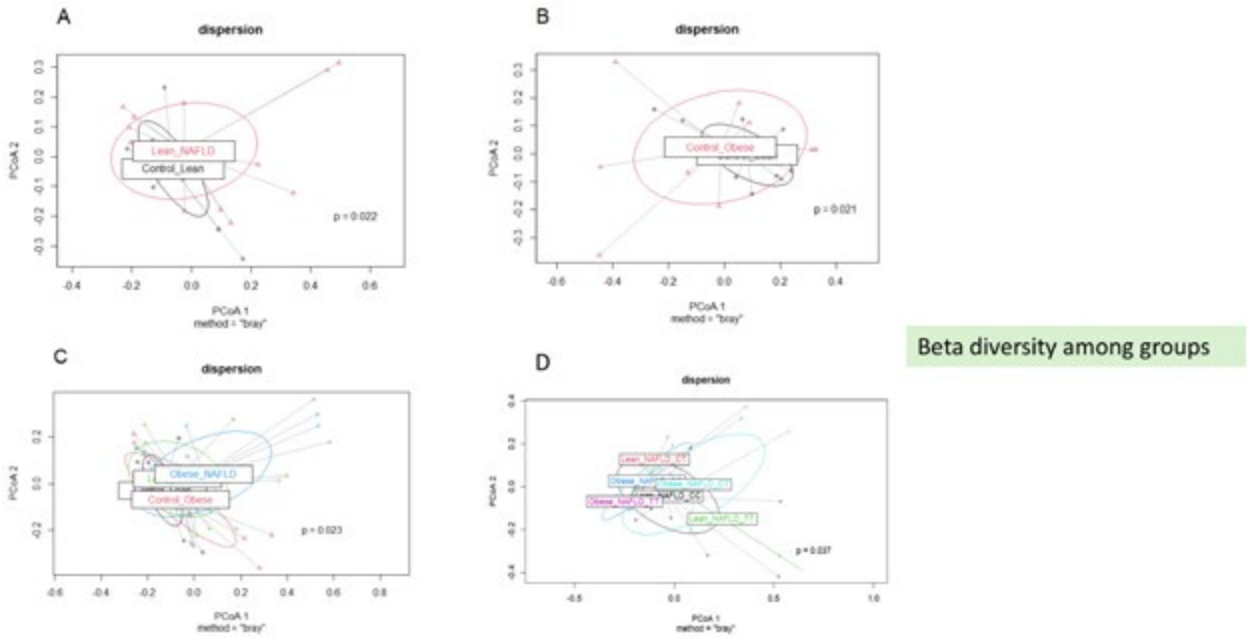

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1549 | BIOMARKER RESPONSE IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS (MASH) PATIENTS WITH HIGH-RISK BASELINE FAST SCORES: OBSERVATIONS FROM THE ENLIVEN PHASE2B TRIAL WITH PEGOZAFERMIN

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Background: ENLIVEN was a 48-week study of the FGF21 analog, pegozafermin (PGZ), in subjects with biopsy-proven F2/F3 MASH. We conducted this post hoc analysis to evaluate categorical shifts in risk and changes in non-invasive tests (NITs) based on baseline FibroScan-AST (FAST) scores at 24- and 48-weeks. **Methods:** The FAST score was calculated at baseline based on Fibroscan (VCTE and CAP scores) and AST. These scores were then used to categorize subjects into prespecified low risk (< 0.35), indeterminate (0.35-0.67), or high risk (>0.67) groups. NIT responses at 24- and 48-weeks were compared to baseline FAST to assess predictive potential. This analysis focused on treatment responses in subjects in the high-risk (most vulnerable) group. **Results:** The overall ENLIVEN population had a mean baseline FAST Score of 0.556 (n=192) with 33% of randomized subjects categorized as high-risk; mean baseline 0.81 for placebo [n=22] and 0.77 for pooled PGZ [30 mg QW and 44 mg Q2W; n=35]. As expected, baseline characteristics for the high-risk group reflected more advanced disease with higher liver stiffness, liver steatosis, ALT, AST, and a higher proportion of baseline F3 patients compared to the full study population. Interestingly, this group was also more likely to have hypertension, higher BMI, and higher ELF score at baseline and less likely to have Type 2 diabetes mellitus. At 24 weeks, high-risk subjects treated with PGZ had highly significant absolute reduction in FAST score compared to placebo (-0.47 vs -0.17 respectively p=0.0006) with 63% shifting from high to low-risk category compared to only a 15% shift for placebo. Importantly, significant reductions were observed across all three major FAST components: VCTE, CAP and

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AST. Placebo-corrected reductions in NITs at week 24 included 27% for MRI-PDFF (p=0.0005), 30% for ALT (p=0.0007), 27% for PRO-C3 (p<0.0001), and 0.7 for ELF score (p<0.0001). Responder rates to PGZ treatment were high for MRI-PDFF (82%), ALT (80%), PRO-C3 (56%) and ELF score (59%) with responders defined as reductions of: ≥30% in MRI-PDFF, 17 U/L in ALT, 20% in PRO-C3, and 0.5 in ELF score. These NIT responses endured in PGZ treated subjects out to 48-weeks. **Conclusion:** PGZ treatment in patients with a high FAST score at baseline shifted the majority to low-risk and was associated with benefit across various NITs over 48 weeks. These data suggest PGZ can be highly efficacious in non-cirrhotic patients with the greatest need for treatment.

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Worldwide Clinical Trials: Advisor, Inipharm: Stock – privately held company, Velacur: Received equipment, materials, drugs, medical writing, gifts, Maya Margalit: Nothing to Disclose, Mildred Gottwald: Nothing to Disclose,

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Germaine Agollah: Nothing to Disclose, Shibao Feng: Nothing to Disclose, Hank Mansbach: 89bio: Employee, Arun Sanyal: Genfit, Akarna, Tiziana, Durect, Inversago, Hemoshear, North: Stock - publicly traded company, Astra Zeneca (60K), Boston Pharmaceutical

1550 | THE INTERPLAY BETWEEN COAGULATION IMBALANCE AND PNPLA3 MUTATION IN MASLD DIABETIC PATIENTS: IMPACT ON HEPATIC AND VASCULAR COMPLICATIONS

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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) promotes fibrosis and vascular complications, mainly if associated with type 2 diabetes (T2DM). MASLD and T2DM exert a procoagulant imbalance. Aim: to evaluate the association between hypercoagulability, hepatic and vascular damage. **Methods:** 185 T2DM patients with MASLD (mean age 62 ± 11 ys, 59% males) and 192 healthy controls were evaluated for coagulation parameters (fibrinogen, FII, FVIII, protein C-PC and antithrombin, with the ratio FVIII/PC considered a hypercoagulability index). In the cohort of patients, thrombin generation assay, which directly measures thrombin production over time, was also performed and peak-thrombin (the greatest amount of generated thrombin) and endogenous thrombin potential (ETP) (total amount of generated thrombin) determined and expressed as ratio in the presence to absence of exogenous trombomodulin (as index of procoagulant imbalance). Patients underwent also a FibroScan® (LSM>8 kPa), genotyping for PNPLA3 and assessment of macro/microvascular complications. **Results:** MASLD diabetic patients presented a hypercoagulable state compared to controls (higher FVIII (149.5±55.1 vs 118.9±33.4, p<0.001), fibrinogen (361.9±79.9 vs 299.9±57.5, p<0.001) FVIII/PC ratio (1.36±0.58 vs 1.08±0.31, p<0.001) and ETP-TM ratio (0.68±0.22 vs 0.60±0.17, p=0.003) and lower antithrombin (105±14.3 vs 108±13.6, p=0.043). By dividing the whole cohort in four groups according to LSM quartiles (group 1: LSM<4.5 kPa; group 2: 4.6LSM<9.2 kPa; group 4: LSM>9.3KPa), the ETP-TM ratio and FVIII/proteinC increased across them (from 1 to 4: 0.63±0.12 to 4:0.89±0.42, pANOVA=0.012; 1.18±0.35 to 1.57±0.68, pANOVA=0.003) and independently associated with increasing LSM values (b-coefficient, 0.46; CI 95% 3.59-8.64; b-coefficient, 0.28; CI 95% 2.28-7.32) adjusted for age, sex, overweight, HbA1c, centre, antiplatelets therapy. Antithrombin and protein C were lower in patients with LSM>vs<8kpa (100.6±15.9 vs 107.3±13.2, p=0.008; 106.9±24.2 vs 115.5±19.6, p=0.022) and independently inversely correlated to LSM> 8kpa (OR 0.92, CI 95% 0.88-0.97; OR 0.97, CI 95% 0.94-0.99) in multivariate analysis adjusted for the same factors. Added to the model, PNPLA3 hampered these associations and remained independently associated with increased peak thrombin ratio (b-coefficient 0.266; CI 95% 0.016; 0.110) and decreased antithrombin (b-coefficient -0.213; CI 95% -11.824; -0.464). Increased fibrinogen levels were associated with microvascular complications. **Conclusion:** MASLD diabetic patients display a procoagulant profile which is independently related to the severity of hepatic fibrosis defined by LSM and microvascular complications. PNPLA3 is associated with a procoagulant profile in those with advanced fibrosis, but further studies are warranted to elucidate this mechanism.

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1551 | ANALYSIS OF CARDIOVASCULAR RISK FACTORS DURING THE TREATMENT OF METABOLIC DYSFUNCTION ASSOCIATED FATTY LIVER DISEASE WITH A LOW CARBOHYDRATE DIET

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Background: This study aimed to analyze cardiovascular risk factors during the treatment of metabolic dysfunction-associated fatty liver disease (MAFLD) with a low-carbohydrate diet. **Methods:** Patients diagnosed with MAFLD at Dongzhimen Hospital of Beijing University of Chinese Medicine between September 2021 and May 2024 were included in the study. Clinical indicators were compared before and after 2 to 6 weeks of low-carbohydrate treatment. Data collected included general information (gender, age, current residence), blood lipid indicators (total cholesterol (TC), triglycerides (TG), high-density lipoprotein (HDL-C), low-density lipoprotein (LDL-C), cardiovascular disease risk assessment indicators (waist circumference, blood pressure, antihypertensive drug use, history of diabetes and smoking, family history of cardiovascular disease, cardiovascular disease risk grade, 10-year risk assessment index, and lifelong risk assessment index), and metabolic indicators (body weight, body fat percentage (BMI), controlled attenuation parameter of transient elastography (CAP), fasting serum C-peptide (C-P), fasting serum insulin (FINS). Statistical analysis was performed using SPSS 27.0 software. results were expressed as mean ± standard deviation for normally distributed data, and comparisons were made using T-tests. Non-normally distributed data were analyzed using rank-sum tests, while count data were presented as frequencies (percentages). **Results:** Among 62 patients, MAFLD was more common in males, mostly under 44 and located in northern cities. Before treatment, average TC was 5.03 ± 1.10 mmol/L, and TG 2.34 ± 1.99 mmol/L; after, TC was 4.96 ± 1.16 mmol/L, TG 1.61 ± 0.92 mmol/L, with HDL-C stable and slight LDL-C increase post-treatment. Significant TG level changes were noted ($P < 0.05$). Cardiovascular disease risk using China-PAR model showed 52 low-risk, 9 intermediate, and 1 high-risk cases before treatment. Post-treatment, 54 were low, 7 intermediate, and 1 remained high-risk. Mean 10-year and lifetime cardiovascular risk estimates were 2.40±3.08% and 19.25±4.42% before, reducing to 2.03±2.57% and 17.78±3.86% after treatment, all showing statistical significance (P. **Conclusion:** Treatment of MAFLD with a low-carbohydrate diet led to reductions in triglycerides and total cholesterol levels, indicating improved lipid metabolism and insulin resistance. The low-carbohydrate diet was effective in treating MAFLD without increasing the risk of cardiovascular disease development.

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	Mean ± standard deviation	t	P
Before treatment-TC (Hmmol/L)(	5.03±1.10	0.83	0.407
After treatment-TC (Hmmol/L)	4.96±1.16		
Before treatment-TG (mmol/L)	2.34±1.99	3.58	0.001
After treatment-TG (mmol/L)	1.61±0.92		
Before treatment-HDL-C (Hmmol/L)	1.18±0.25	0.07	0.994
After treatment-HDL-C (Hmmol/L)	1.18±0.25		
Before treatment-LDL-C (Hmmol/L)	3.17±0.94	0.74	0.463
After treatment-LDL-C (Hmmol/L)	3.22±0.97		
Before treatment-weight (kg)	86.65±15.80 kg	15.51	<0.01
After treatment-weight (kg)	82.74±15.45 kg		
Before treatment-BMI (kg/m²)	29.65±4.00 kg/m²	14.33	<0.01
After treatment-BMI (kg/m²)	28.33±3.94 kg/m²		
Before treatment－CAP (dB/m)	315.35±36.78 dB/m	8.285	0.001
After treatment－CAP (dB/m)	278.92±46.12 dB/m		
Before treatment-waist circumference （cm）	97.83±6.86	19.040	0.000
After treatment-waist circumference （cm）	86.47±4.78		
Before treatment-FINS (μIU/mL)	21.62±2.12	3.489	0.001
After treatment-FINS (μIU/mL)	15.00±1.30		
Before treatment-C-P (ng/mL)	3.67±0.22	3.264	0.002
After treatment-C-P (ng/mL)	3.09±0.18		
Before-10-year risk assessment index （%）	2.40±3.08	3.847	0.000
After-10-year risk assessment index （%）	2.03±2.57		
Before-lifelong risk assessment index （%）	19.25±4.42	4.007	0.000
After-lifelong risk assessment index （%）	17.78±3.86		

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1552 | PLASMA IMMUNE PROFILE ASSOCIATED WITH MASLD IN PERSONS WITH HIV

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Background: The pathophysiology of metabolic dysfunction-associated steatotic liver disease (MASLD) in persons with HIV (PWH) is multifactorial, involving dysbiosis, altered glucose and lipid metabolism, and immune dysregulation. The aim of this study was to explore mechanisms of MASLD by describing differences in the plasma immune profile between PWH with and without MASLD. **Methods:** We examined 624 participants from two NIDDK-funded, prospective, cross-sectional cohorts of PWH. Participants had suppressed HIV-1 RNA and underwent vibration controlled transient elastography. MASLD was defined as controlled attenuation parameter

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(CAP)≥263 dB/m with at least one cardiometabolic risk factor, without heavy alcohol use (AUDIT≤8). We used the Invitrogen ProcartaPlex™ Human Immune Response 80-Plex Panel, comprising cytokines, chemokines, growth factors, soluble receptors, serine proteases and lectin pentraxins. Analyte levels were log transformed and zero values imputed by 0.1*lower limit of detection. Logistic regression models evaluated associations between analytes and MASLD. Statistical significance on univariate models was defined as p-value<0.05 and false discovery rate (FDR)<0.10. **Results:** MASLD was present in 327 PWH (52%). PWH with and without MASLD differed by mean age (53 vs 51 years), race (41% vs 60% Black), body mass index (BMI) (33.5 vs 26.5 kg/m^2), waist circumference (110 vs 92 cm), diabetes (30% vs 15%), hyperlipidemia (58% vs 38%) and hypertension (61% vs 53%) (p-value<0.05 for all). PWH with MASLD had higher CD4 count (709 vs 626 cells/mm^3) and more prior AIDS-defining illnesses (21% vs 14%), but similar time since HIV diagnosis. On univariate models, 16 analytes were associated with MASLD (p-value<0.05, FDR<0.10). After adjustment for age, sex at birth, race/ethnicity, BMI, and diabetes, increased levels of 2 chemokines (interferon-inducible T-cell alpha chemoattractant [I-TAC] and monocyte chemoattractant protein-4 [MCP-4]), and decreased levels of 6 analytes (chemokines: epithelial-neutrophil activating peptide [ENA-78], macrophage inflammatory protein 2 alpha [MIP-2/CXCL2]; functional molecule: galectin-3; other analytes: CD27, programmed cell death ligand 2 [PD-L2], nectin-2) were associated with MASLD (Table 1). **Conclusion:** Chemokines and analytes mediating cell-cell adhesion and cell death were associated with MASLD in PWH after adjustment for metabolic comorbidities. The immune response to HIV with persistent chemokine production may contribute to the development of MASLD in PWH.

Table 1: Logistic regression models for log-transformed levels of analytes and MASLD

Category	Analyte	Univariate		Multivariable		
		OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value	Direction^
Growth factors	TNF-related weak inducer of apoptosis	0.79 (0.68-0.93)	0.006*	-	-	-
	IL 7	1.29 (0.99-1.68)	0.061*	-	-	-
Chemokines	Chemokine (C-C motif) ligand 17	0.86 (0.70-1.06)	0.173	-	-	-
	Epithelial-derived neutrophil-activating peptide 78	0.85 (0.75-0.97)	0.015*	0.81 (0.68-0.95)	0.011	↓
	Monocyte chemoattractant protein-3	1.17 (0.99-1.38)	0.067*	-	-	-
	Interferon-inducible T-cell alpha chemoattractant	1.21 (1.07-1.39)	0.004*	1.42 (1.19-1.68)	<0.0001	↑
	Macrophage inflammatory protein 2 alpha	0.79 (0.63-1.00)	0.050*	0.74 (0.56-0.99)	0.045	↓
	Monocyte Chemoattractant Protein-4	1.26 (1.04-1.53)	0.019*	1.59 (1.24-2.04)	<0.0001	↑
Pro-inflammatory cytokines	IL 16	0.79 (0.61-1.03)	0.082	-	-	-
Anti-inflammatory cytokines	IL 4	1.23 (1.04-1.46)	0.018*	-	-	-
	IL 34	1.33 (1.08-1.65)	0.008*	-	-	-
	IL 37	1.20 (0.95-1.52)	0.123	-	-	-
Soluble receptors	CD30	0.88 (0.75-1.03)	0.110	-	-	-
Functional molecules	Galectin 3	0.70 (0.59-0.83)	<0.001*	0.70 (0.58-0.84)	<0.0001	↓
	Granzyme A	1.18 (0.94-1.49)	0.154	-	-	-
	Matrix metalloproteinase 1	0.79 (0.66-0.96)	0.017*	-	-	-
	Long pentraxin e	0.82 (0.70-0.98)	0.028*	-	-	-
Other	CD 27	0.80 (0.70-0.91)	0.001*	0.84 (0.72-0.98)	0.025	↓
	CD 28	0.85 (0.74-0.98)	0.026*	-	-	-
	Glucocorticoid-induced TNFR-related protein	0.92 (0.82-1.04)	0.184	-	-	-
	Programmed Cell Death Ligand 2	0.81 (0.66-0.99)	0.042*	0.74 (0.58-0.95)	0.020	↓
	CD 96	1.08 (0.97-1.21)	0.163	-	-	
	Nectin 2	0.85 (0.72-1.01)	0.069	0.79 (0.64-0.98)	0.029	↓
	Fibroproliferative growth factors	1.06 (0.98-1.16)	0.146	-	-	-
	UL16 binding protein 4	0.90 (0.78-1.05)	0.174	-	-	-
	CD 47	1.11 (1.004-1.22)	0.039*	-	-	-

*=FDR<0.10

^=indicates whether increasing or decreasing analyte level is associated with higher odds of having MASLD

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1553 | MUSCLE FUNCTION CORRELATES WITH QUALITY OF LIFE AND DISEASE SEVERITY IN PATIENTS WITH MASLD

Mohammed Abdurrahman[1] Giordano Sigon[2] Prerana Sruthi Vatsavayi[2] Jawad Aziz[2] Roberta Forlano[2] Benjamin Mullish[2] Michael Yee[3] Pinelopi Manousou[4]

[1]Imperial College, [2]Imperial College London, [3]Imperial College NHS Trust, [4]Imperial College Healthcare NHS Trust

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is an increasing global public health challenge that affects more than 30% of adults globally. The mainstay of treatment are lifestyle interventions, including exercise and healthy diet. Evidence on the direct impact of MASLD on quality of life (QoL) is limited. Also, emerging research highlights the role of muscle function in disease severity. This study aims to explore the association between Quality of Life, exercise, diet, muscle function, and MASLD severity defined by liver stiffness. **Methods:** Consecutive patients were prospectively enrolled from MASLD clinics at St. Mary's Hospital, London. Patients underwent anthropometric evaluation, and blood tests. Liver severity was assessed using transient elastography (TE). Muscle function was assessed via handgrip strength (HST) and the five-time sit-to-stand test (FTSST). Questionnaires evaluated adherence to the Mediterranean diet (MD), physical activity (PA), and QoL. **Results:** 120 patients were included. Univariate analysis revealed a significant association between increased liver severity and worse QoL outcomes in physical and social functioning ($p<0.001$, $p=0.042$). Increased adherence to MD and PA was associated with significantly improved QoL domain scores in physical functioning and general health for MD ($p=0.040$, $p=0.022$) and emotional well-being and general health for PA ($p=0.010$, $p=0.037$). Multivariate analysis showed significant associations between body mass index (BMI) and seven QoL domains ($p<0.05$ in all). Independent T-testing revealed significant associations between fibrosis and weaker handgrip strength ($p=0.023$). **Conclusion:** There was significant association between MASLD severity and reduced physical and social functioning. We also demonstrate that adherence to Mediterranean Diet and Physical Activity, significantly improved physical functioning and emotional well-being. Clinical practice requires comprehensive management strategies, and evaluation of muscle function which is easily reproducible in practice for MASLD patients.

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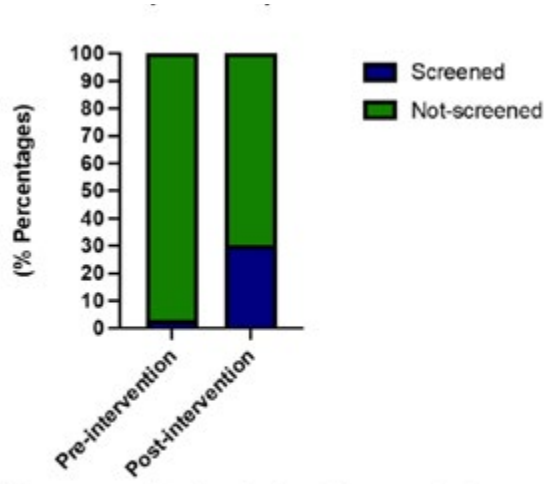
Disclosures: Mohammed Abdurrahman: Nothing to Disclose, Giordano Sigon: Nothing to Disclose, Prerana Sruthi Vatsavayi: Nothing to Disclose, Jawad Aziz: Nothing to Disclose, Roberta Forlano: Nothing to Disclose, Benjamin Mullish: Nothing to Disclose, Michael Yee: Nothing to Disclose, Pinelopi Manousou: Nothing to Disclose

1554 | IMPROVING SCREENING OF METABOLIC-DYSFUNCTION ASSOCIATED LIVER DISEASE (MASLD) IN PATIENTS WITH TYPE 2 DIABETES MELLITUS: A QUALITY IMPROVEMENT INITIATIVE

Maram Alenzi[1] *Iyiad Alabdul Razzak*[1] *Alya Usman*[1] *Jad Mitri*[1] *Monica Chavez*[1]

[1]*Boston University*

Background: The global burden of Metabolic Dysfunction-Associated Liver Disease (MASLD) has increased substantially in the past decade. In patients with type 2 diabetes mellitus (T2DM), liver steatosis, advanced fibrosis, and cirrhosis were observed in 73.8%, 15.4%, and 7.7% of cases, respectively. Recent guidelines recommend primary care (PC)-based screening for MASLD fibrosis in all T2DM patients by utilizing a non-invasive screening tool, Fibrosis-4 (FIB-4) index. Per these guidelines, we recognized inadequate screening for MASLD fibrosis. This quality improvement project aimed to enhance MASLD screening among T2DM patients in an academic PC setting. **Methods:** We evaluated PCP use of FIB-4 score before and after implementation of FIB-4 risk stratification algorithm. A retrospective chart review was conducted on 110 patients with T2DM seen in our PC clinic to assess baseline screening rates. A smartphrase was created through Athena electronic health record (EHR), integrating pertinent information to aid in screening for T2DM complications, including MASLD. This smartphrase was shared with all PCPs through several educational sessions. **Results:** Baseline assessment of 110 patients with T2DM showed that only 3.6% of patients had screening with FIB-4 score. Among those not screened, 31% had an indeterminate or high risk for advanced fibrosis. During cycle 1, there was a tenfold increase in the screening rate for MASLD, with a FIB-4 score recorded in 30.3% of patients ($p<0.001$) (Figure.1). Among these, 10 patients (50%) had a FIB-4 score ≤1.3, indicating low risk for advanced fibrosis and providers were recommended to continue regular follow-up over 1-2 years to monitor changes in liver health. An additional 8 patients (40%) fell into the indeterminate range (1.3-2.67), warranting risk stratification with elastography to guide appropriate management strategies. Lastly, 2 patients (10%) had FIB-4 score ≥2.67, necessitating referral to hepatologist for further management. **Conclusion:** An educational and EHR-based intervention significantly improved the utilization of FIB-4 to appropriately screen for MASLD fibrosis in T2DM patients. This results in an appropriate and timely referral of patients at high risk for advanced fibrosis to hepatologists, while continuing PCP management of low-risk patients. Further enhancement could be achieved by automatically calculating FIB-4 score and notifying providers if it has not been documented in the past 2 years.



nificance was detemined using Chi-square test

e 2: Difference in PCP use of FIB-4 based risk stratification before and after implementati

Disclosures: MARAM ALENZI: Nothing to Disclose, Iyiad Alabdul Razzak: Nothing to Disclose, Alya Usman: Nothing to Disclose, Jad Mitri: Nothing to Disclose, Monica Chavez: Nothing to Disclose

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1555 | COMPARISON OF STEATOSIS ASSESSMENT BETWEEN VCTE-CAP SCORE AND ULTRASOUND IN METABOLIC DYSFUNCTION ASSOCIATED STEATOTIC LIVER DISEASE (MASLD) IN A CANADIAN COHORT

Chinmay Bera[1] Nashla Hamdan[2] Heather Kosick[2] Nader Allam[2] Mina Fakhriyehasl[2] Kartik Jhaveri[2] Keyur Patel[2]

[1]Toronto General Hospital, [2]University of Toronto

Background: Vibration-controlled transient elastography (VCTE)-based controlled attenuation parameter (CAP) is a non-invasive method for assessing steatosis, but is not routinely accessible in non-tertiary clinical practice in Canada. Ultrasound (US) is readily available and often serves as the first line of investigation for the diagnosis of steatosis, but has not been directly compared with VCTE-CAP in the MASLD population. Our aim was to study the correlation between CAP score and US-based steatosis grade in patients with MASLD. **Methods:** This was a retrospective analysis of 382 MASLD patients from a tertiary center. CAP steatosis was graded as CAP (S0 <248; S1≥248; S2 ≥268; S3 >280 dB/m) and US abdomen (Grade 1 (mild), Grade 2 (moderate), and Grade 3 (severe)). All patients had valid VCTE examinations with either an M or XL probe within 6 months of US. Baseline demographic characteristics and laboratory parameters were assessed for independent associations with steatosis grade. All measurements are reported as mean (± standard deviation). **Results:** Our single-center MASLD study cohort included 382 patients, of whom 193 (50%) were male, with a mean age of 53 (±15) years, and a mean BMI of 31.2 (± 6.8) kg/m^2. Diabetes Mellitus was present in 44 (12%), hypertension in 128 (33.5%), and hyperlipidemia in 95 (25%). Cirrhosis features were reported in the US in 9.4% (36/382). The overall mean liver stiffness measurement (LSM) was 10.13 (±11.24) kPa, and FIB-4 1.51 (±1.4). CAP score grading of steatosis includes- S0, 69/382 (18%), CAP 254 (± 58) dB/m), S1, 113/382 (29.6%), CAP 295 (±54) dB/m), S2, 144/382 (37.7%), CAP 334 (±49) dB/m and S3, 56/382 (14.6%) CAP 365 (±29) dB/m.. US-based steatosis grade was associated with CAP-based measurement (p<0.0001) in the overall cohort, but was attenuated in the presence of cirrhosis (p=NS) (Figure). **Conclusion:** In patients with MASLD, there is good association between increasing CAP score and US-based steatosis grade in the absence of cirrhosis. If CAP is not routinely available, US can be used for assessing severity of steatosis, although absence of CAP thresholds for US steatosis severity, and interobserver variability are limitations of conventional US.

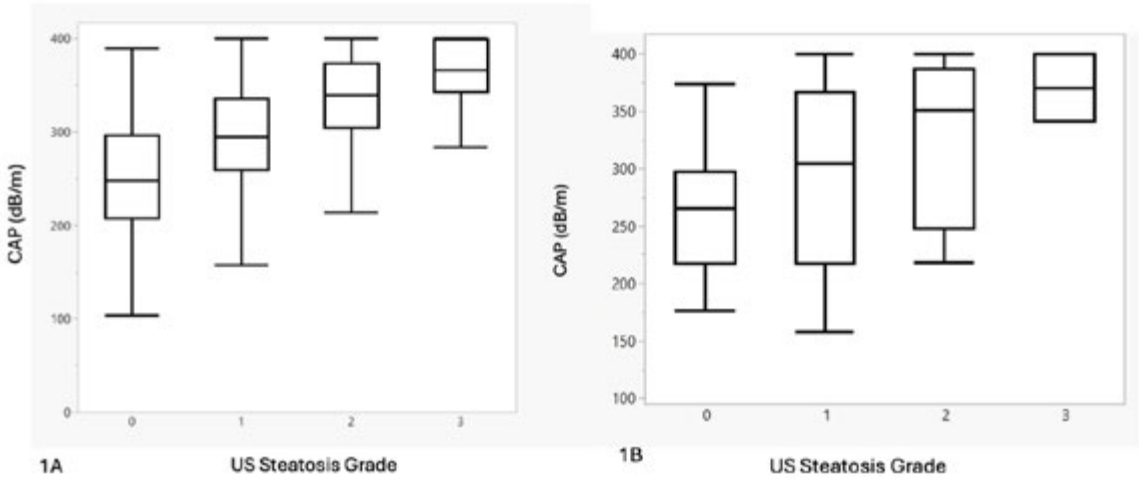

Figure: Boxplot for the distribution of CAP score by US-based steatosis severity grade for all patients (1A) and cirrhosis (1B)

Disclosures: Chinmay Bera: Nothing to Disclose, Nashla Hamdan: Nothing to Disclose, Heather Kosick: Nothing to Disclose, Nader Allam: Nothing to Disclose, Mina Fakhriyehasl: Nothing to Disclose, Kartik Jhaveri: Nothing to Disclose, Keyur Patel: Novo-Nordisk: Consultant, Gilead Sciences: Consultant, Merck: Consultant, Resalis: Advisor

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1556 | ASSOCIATION BETWEEN US ABDOMEN, FIB-4, AND VCTE DETERMINED STEATOSIS AND DISEASE SEVERITY IN A CANADIAN METABOLIC DYSFUNCTION ASSOCIATED STEATOTIC LIVER DISEASE (MASLD) COHORT

Chinmay Bera[1] Nashla Hamdan[2] Heather Kosick[2] Nader Allam[2] Mina Fakhriyehasl[2] Kartik Jhaveri[2] Keyur Patel[2]

[1]Toronto General Hospital, [2]University of Toronto

Background: Several non-invasive serum tests are available for the detection of advanced fibrosis in metabolic dysfunction associated steatotic liver disease (MASLD). FIB-4 has demonstrated excellent negative predictive value for advanced fibrosis. Vibration-controlled transient elastography (VCTE)-based controlled attenuation parameter (CAP) and liver stiffness measurement (LSM) is a non-invasive method for assessing steatosis and cirrhosis but is not easily accessible for non-tertiary clinical practice in Canada. Ultrasound (US) is readily available and often serves as the first line of investigation for the diagnosis of steatosis and features of cirrhosis, but has not been directly compared with VCTE- CAP or LSM in the MASLD population. Our aim was to study the correlation between CAP score and US-based steatosis measurement according to fibrosis severity in patients with MASLD. **Methods:** This was a retrospective analysis of 382 patients from a tertiary center. The US abdomen measurement of steatosis was graded as Grade 1 (mild), Grade 2 (moderate), and Grade 3 (severe), and features of cirrhosis were documented in the form of nodular contour (NC), hepatic vein nodularity (HVN), and lobar redistribution (LR). CAP steatosis was graded as CAP (S0: <248; S1≥248; S2 ≥268; S3 >280 dB/m). US was obtained within 6 months of VCTE. All patient's baseline demographic characteristics and laboratory parameters were recorded. **Results:** Our MASLD study cohort included 382 patients (Male 193 (50%), mean age (±SD) 53 (±15) years, and BMI 31.2 (± 6.8) kg/m^2. Diabetes Mellitus was present in 44 (12%), HTN in 128 (33.5%), and hyperlipidemia in 95 (25%). Cirrhosis features were reported in the US in 9.4% (36/382). The mean LSM was 10.13 (±11.24) kPa and FIB-4 was 1.51 (±1.4). CAP score steatosis graded as, S0: 69/382 (18%), FIB-4 1.97 (± 0.17); S1: 113/382 (29.6%), FIB-4 1.58 (±0.13); S2: 144/382 (37.7%), FIB-4 1.31±0.11; and S3: 56/382 (14.6%), FIB-4 1.32 (±0.18). US-based steatosis severity grade was associated with FIB-4 (p=0.0077). There were significant differences in FIB-4 forUS-based steatosis grade 0 vs 2 (1.98 vs 1.31; p=0.001), and grade 0 vs 3 (1.98 vs 1.32; p=0.009). However, there was no association between LSM and US-steatosis (p=NS). Both FIB-4 and LSM were significantly associated with US findings of NC, HVN, LR and cirrhosis (Table). **Conclusion:** In patients with MASLD, there is a significant association between the steatosis grades and the FIB-4 score but not with VCTE. However, both LSM and FIB-4 have a significant agreement with the findings of US-based cirrhotic features. US-based assessment may be useful for assessment of MASLD severity if VCTE is not readily available.

Table: Association of FIB-4 and LSM with US findings of cirrhotic features

US Cirrhosis Features	FIB-4 Mean (95% CI)	VCTE-LSM (95% CI) kPa	P value*
Nodular Contour			
Yes (n=54)	3.1 (2.7-3.4)	25.6 (23-28)	P<0.0001
No (n=328)	1.3 (1.1-1.4)	7.6 (6.6-8.6)	
Hepatic Vein Nodularity			
Yes (n=30)	3.6 (3.1-4.0)	27.2 (23.5-30.8)	P<0.0001
No (n=352)	1.3 (1.2-1.5)	8.7 (7.6-9.7)	
Lobar Redistribution			
Yes (n=36)	3.9 (3.5-4.3)	27.6 (24.4-30.7)	P<0.0001
No (n=346)	1.3 (1.1-1.4)	8.3 (7.3-9.4)	
Cirrhosis			
Yes (n=36)	3.5 (3.1-3.9)	28.7 (25.6-31.8)	P<0.0001
No (n=346)	1.3 (1.2-1.4)	8.2 (7.2-9.2)	

(*for both FIB-4 and LSM)

Disclosures: Chinmay Bera: Nothing to Disclose, Nashla Hamdan: Nothing to Disclose, Heather Kosick: Nothing to Disclose, Nader Allam: Nothing to Disclose, Mina Fakhriyehasl: Nothing to Disclose, Kartik Jhaveri: Nothing to Disclose, Keyur Patel: Novo-Nordisk: Consultant, Gilead Sciences: Consultant, Merck: Consultant, Resalis: Advisor

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1557 | DIABETES IS A RISK FACTOR FOR SARCOPENIA OF PATIENTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS-DRIVEN CIRRHOSIS

Shinya Sato[1] Hiroaki Takaya[1] NORIHISA NISHIMURA[1] KOSUKE KAJI[1] Tadashi Namisaki[1] Takemi Akahane[1] Hitoshi Yoshiji[1]

[1]Nara Medical University

Background: The relevance of metabolic disorders in causing liver diseases led the recent proposal by the international expert panel to rename the fatty liver as Metabolic dysfunction-Associated Steatotic Liver Disease (MASLD). It remains unclear whether different subtypes of cirrhosis caused by Metabolic dysfunction-Associated SteatoHepatitis (MASH) have differences in prognosis. We aimed to compare mortality, liver-related events (LREs), and other factors between MASH associated liver cirrhotic patients with and without diabetes mellitus (DM). **Methods:** MASH was diagnosed based on the presence of metabolic dysfunction and steatohepatitis. Patients with MASH-driven cirrhosis were initially classified into three subtypes: MASH with diabetes mellitus (DM-MASH), MASH with overweight or obesity (obese-MASH), or MASH with lean/normal weight and at least two metabolic abnormalities (metabolic dysfunction-MASH). To assess the DM's importance in the prognosis, MASH-driven cirrhotic patients were regrouped into MASH with DM (DM-MASH) and without DM (obese-MASH and metabolic dysfunction-MASH). We compared these two groups on mortality, liver-related events (LREs), and other factors such as sarcopenia. LREs include hepatic decompensation (ascites, hemorrhagic varices and encephalopathy) and hepatocellular carcinoma. Kaplan-Meier survival analyses and log-rank tests were used to compare the mortality and the incident rate of LREs between the groups. **Results:** The median survival time of DM-MASH patients was longer than that of MASH without DM patients (2618 days vs 1523 days, $p<0.05$). The incidence rate of LREs in MASH with DM cases was higher than in MASH without DM cases during the follow-up period. The prevalence of sarcopenia was higher in MASH with DM than MASH without DM using Fisher's exact test (36.1% vs 19.7%, $p<0.05$). We further explored risk factors for sarcopenia among cirrhotic patients and found that several factors including DM were identified with the univariate analysis. The multiple logistic regression analysis showed that DM was an independent risk factor for sarcopenia in patients with MASH-driven cirrhosis. **Conclusion:** In individuals with MASH associated liver cirrhosis, the presence of DM increased the risk of mortality caused by sarcopenia. DM can be thus used as a new additional diagnostic criterion to identify patients with poor prognosis in MASH associated cirrhotic patients.

Disclosures: Shinya Sato: Nothing to Disclose, Hiroaki Takaya: Nothing to Disclose, NORIHISA NISHIMURA: Nothing to Disclose, KOSUKE KAJI: Nothing to Disclose, Tadashi Namisaki: Nothing to Disclose, Takemi Akahane: Nothing to Disclose, Hitoshi Yoshiji: Nothing to Disclose

1558 | NOVEL INSIGHTS INTO THE ACCURACY OF FIB-4 AND FIBROSCAN SCORES COMPARED TO LIVER BIOPSY IN THE ASSESSMENT OF LIVER FIBROSIS IN PATIENTS WITH MASLD

Haya Omeish[1] Austin Mueller[1] Syed-Mohammed Jafri[2] Dilip Moonka[1]

[1]Henry Ford health, [2]Henry Ford Health System

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is prevalent, with fibrosis stage being a critical predicting prognosis. Liver biopsy is the gold standard for staging but is invasive and costly. Non-invasive tests like FibroScan and FIB4 aid in pre-selecting patients for biopsy. This study compares FibroScan and FIB4 accuracy in predicting fibrosis staging in patients with MASLD. **Methods:** A cross-sectional study on 116 MASLD patients undergoing both FibroScan and liver biopsy within one year was conducted. Demographic, biochemical data, and FIB4 levels were collected. Patients were categorized by fibrosis levels: minimal/no (F0-F1), moderate (F2-F3), and severe (F4), using FibroScan kPa scores, FIB4 levels, and biopsy results. **Results:** Of 116 patients (55 males, 61 females; 82 <65 years, 34 older; 89 white, 25 non-white; 26 BMI <30, 89 BMI >30), 37.07% were F0-1 by FIB4, with 64.71% agreement by FibroScan. For F2-3, 58.62% were identified by FIB4, with 60% agreement by FibroScan. In F4, 4.31% were classified by FIB4, with 60% agreement by FibroScan. Kappa statistic (0.1253) indicates slight agreement beyond chance, emphasizing caution when using these **Methods:** interchangeably. Table-1 compares FIB4 values and biopsy stages, showing moderate agreement, particularly for F4. Among 43 F0-1 cases by FIB4, 52.17% matched F0-1 biopsy, 38.24% were F2-3, and 11.63% were F4. For

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68 F2-3 cases by FIB4, 16.18% were F0-1, 58.82% were F2-3, and 25.00% were F4. Among 5 F4 cases by FIB4, none were F0-1, 40.00% were F2-3, and 60.00% confirmed F4 by biopsy. Table-1 also correlates FibroScan and biopsy stages. Of 17 F0-1 cases by FibroScan, 64.71% matched biopsy, 35.29% were F2-3, none F4. Among 55 F2-3 cases by FibroScan, 16.36% were F0-1, 74.55% F2-3, 9.09% F4. Of 44 F4 cases by FibroScan, 6.82% were F0-1, 47.73% F2-3, and 45.45% confirmed F4 by biopsy. Significant F2-3 agreement, some F0-1 and F4 discrepancies were observed. **Conclusion:** Both FIB-4 and FibroScan showed a correlation with liver fibrosis, particularly in moderate fibrosis. However, discrepancies exist across different stages, with better performance in moderate fibrosis. Caution is advised when using non-invasive tests interchangeably with biopsy for fibrosis assessment in MASLD patients.

Table 2: Comparison of FIB4 and FibroScan Values with Liver Biopsy Stages

FIB4 Category	Biopsy Stage: F0-1	Biopsy Stage: F2-3	Biopsy Stage: F4	Total Cases
F0-1	52.17% (22)	38.24% (16)	11.63% (5)	43
F2-3	16.18% (11)	58.82% (40)	25.00% (17)	68
F4	0.00% (0)	40.00% (2)	60.00% (3)	5
Total Cases	33	58	25	116
FibroScan Category	**Biopsy Stage: F0-1**	**Biopsy Stage: F2-3**	**Biopsy Stage: F4**	**Total Cases**
F0-1	64.71% (11)	35.29% (6)	0.00% (0)	17
F2-3	16.36% (9)	74.55% (41)	9.09% (5)	55
F4	6.82% (3)	47.73% (21)	45.45% (20)	44
Total Cases	23	68	25	116

Disclosures: Haya Omeish: Nothing to Disclose, Austin Mueller: Nothing to Disclose, Syed-Mohammed Jafri: Takeda: Speaking and Teaching, Gilead: Speaking and Teaching, Abbvie: Speaking and Teaching, Ironwood: Advisor, Intercept: Speaking and Teaching, Dilip Moonka: Nothing to Disclose

1559 | A PHASE 1/2A SINGLE-CENTER RANDOMIZED PLACEBO-CONTROLLED STUDY OF ORAL IDEBENONE TO TREAT METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS ◆

Toby Bradford[1] *Natalie Torok*[1]

[1]*Stanford University*

Background: Metabolic dysfunction-associated steatohepatitis (MASH) is one of the leading indications for liver transplantation. Idebenone has been shown to inhibit the Src homology and collagen (Shc) adaptor proteins, thereby reducing mitochondrial oxidative stress, inflammation, and subsequent hepatic fibrosis in preclinical studies. The aims of this clinical trial were to evaluate the safety and tolerability as well as efficacy of oral Idebenone in patients with MASH. **Methods:** A randomized, single-center, placebo-controlled phase 1/2a study was performed in patients 18 years of age or older with MASH and stage 1-3 fibrosis. Participants received either placebo or Idebenone 200 mg capsules initially at a frequency of once a day for 2 weeks, then 200 mg twice a day for two weeks, then three times a day for the remainder of the study. Patients were randomized in a 1:2 fashion. A total of 45 patients were recruited. Participants were assessed at weeks 2, 4, 12, 24, 36 and 48. **Results:** There were no treatment-related serious adverse events (SAEs) in patients receiving Idebenone. The most common adverse event (AE) was diarrhea which occurred in 15% and 17% of the Idebenone and placebo group, respectively. After 48 weeks, patients receiving Idebenone had a significantly greater mean reduction in liver stiffness compared to those receiving placebo, assessed by magnetic resonance elastography (a two-sample equal variance t-test demonstrated the mean difference of 0.642 was statistically significant, one-sided p = 0.0236). This mean reduction in fibrosis was more common in females compared to male patients. Patients receiving Idebenone also had a greater mean reduction in fibrosis 4 (FIB-4) scores after 48 weeks (a Wilcoxon

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rank-sum test demonstrated that the mean difference was statistically significant, p = 0.0473). Insulin resistance assessed by Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) was also significantly reduced by week 48 in the Idebenone group but not in the placebo (a paired t-test showed a statistically significant decrease in mean HOMA-IR of 8.52, one-sided p = 0.0160)**. Conclusion:** In conclusion, in this phase 1/2a single-center randomized placebo-controlled study, patients with MASH and stage 1-3 fibrosis who received oral Idebenone for 48 weeks tolerated the treatment well without any SAEs and had significant reduction in liver stiffness, FIB-4 scores, and insulin resistance compared to placebo.

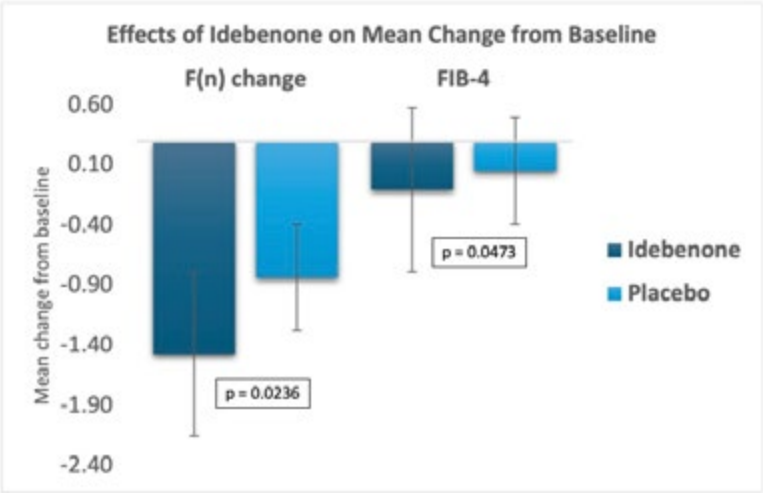

Figure 1. Efficacy of oral Idebenone versus placebo on fibrosis and FIB-4 reduction after 48 weeks. Values for F(n) changes calculated using a two-sample equal variance t-test. Values for FIB-4 were calculated using Wilcoxon rank-sum test. Values for F(n) change = baseline decrease in fibrosis stage. FIB-4 = Fibrosis-4 Index.

Disclosures: Toby Bradford: Nothing to Disclose, Natalie Torok: Nothing to Disclose

1560 | SPATIAL TRANSCRIPTOMICS MAPS THE METABOLIC ZONATION OF HEPATOCYTES IN MASLD I148M-PNPLA3 CARRIERS

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Background: The I148M polymorphism in the *PNPLA3* gene is the main genetic predictor of Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD). Few evidence showed that I148M overexpression in hepatoma cells correlated with metabolic switching and mitochondrial (mt) dysfunction. Thus, this study aims to: 1) deepen the impact of PNPLA3 variation on mitochondrial function by overexpressing the I148M protein in HepG2 and Hep3B cells, to force the effect or introduce the mutation, respectively; 2) translate our *in vitro* findings into clinics, by dissecting hepatocytes metabolic zonation in needle liver biopsy of MASLD I148M carriers. **Methods:** PNPLA3-I148M protein was upregulated in hepatoma cells by lentiviral transfection. Spatial transcriptomics was performed by Visium CytAssist in frozen liver biopsy. Data were analyzed by Loupe Browser. **Results:** The I148M protein upregulation in hepatoma cells fostered lipid accumulation, resulting in increased PGC1a activity as responsive strategy to clear fat overload. Both I148M overexpressed models showed lower OXPHOS capacity and ATP production. Moreover, the high ROS content and release of mtDNA fragments in cells supernatant corroborated the I148M-mediated mt dysfunction (adjusted ***p<0.001, **p<0.01 and *p<0.05). To translate our *in vitro* findings, we spatially mapped pericentral (PC) and periportal (PP) hepatocytes in hepatic biopsy of I148M carrier by *CYP3A4* and *HAL* genes, respectively. Physiologically, PC-PP axis outlined an oxygen metabolic gradient flowing toward the central vein opposed to lipogenesis. In keeping with this data, PP spots promoted *PGC1a* expression (p=0.002) trying to drain fat accumulation *via* boosted mitobiogenesis (*SREPF1*:p=0.1; *DGAT2*:p=1.04e^{-25}, *HSD17B*:p=0.03, *ACACA*:p=0.01; *CD36*:p=1.62e^{-9}; *FABP1*:p=0.083). Nevertheless, PP areas significantly reduced mt-genes related to fusion-mitophagy process (*RMDN3*:p=0.86, *MFn2*:p=0.081, *BNIP3*:p=0.076), respiration (*SDHA*:p=4.94e^{-9},

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ATP5MF:p=6.29e^{-5}, *UQCRC1*:p=0.005, *MT-ND2*:p=0.04) and fatty acids metabolism (*PPARA*:p=0.06, *Ehhadh*:p=2.48e^{-4}, *Gpam*:p=3.40e^{-7}, *Nadk2*:p=1.06e^{-5}), thus delineating the mechanism through which I148M variant impacts on mt dynamics thus possibly leading to hepatic injury in PP hepatocytes. **Conclusion:** The I148M overexpression in *in vitro* hepatocytes unveiled its involvement in mt maladaptation. Mismatched signature of mt genes in I48M PP-PC dichotomy provided new insights into genetic-based MASLD biology.

Disclosures: Erika Paolini: Nothing to Disclose, Miriam Longo: Nothing to Disclose, Marica Meroni: Nothing to Disclose, Anna Ludovica Fracanzani: Nothing to Disclose, Paola Dongiovanni: Nothing to Disclose

1561 | APPLICATION OF ARTIFICIAL INTELLIGENCE ALGORITHM AS A VASCULAR EVALUATION TOOL FOR INTRA-STAGE ASSESSMENT IN THE CIRRHOTIC PATIENTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE

Zhengxin Li[1] Meng Li[2] Qiang Yang[3] Yayun Ren[4] Xiao Teng[4] Dean Tai[4] Ian Wanless[5] Jörn Schattenberg[6] Chenghai Liu[7]

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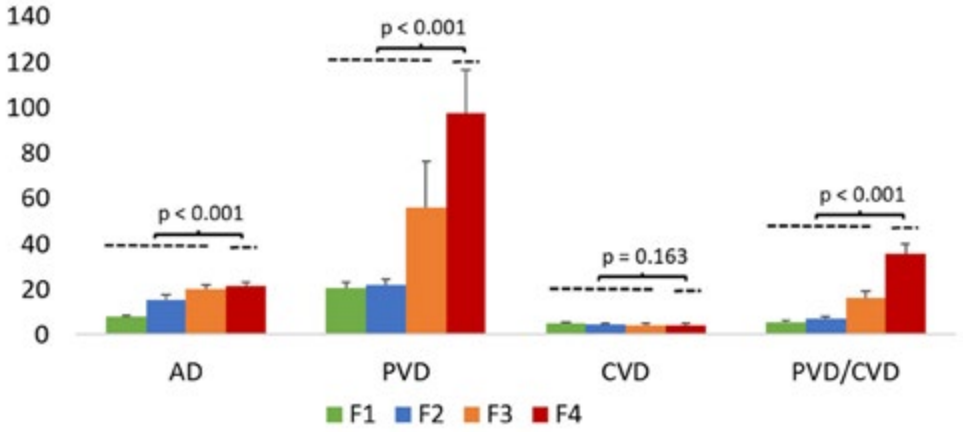
Background: Vascular changes are a critical factor that has garnered considerable attention in the context of liver fibrosis because of its ability to monitor fibrosis changes within cirrhotic stage. Previous studies have stated that angiogenesis intensifies during the liver fibrosis progressing, while it decreases when liver fibrosis regressing. This study was to explore a vascular evaluation for patients with metabolic dysfunction-associated steatotic liver disease (MASLD), which using second harmonic generation (SHG)/two-photon excited fluorescence (TPEF) microscopy imaging and artificial intelligence (AI)-based algorithm. **Methods:** 160 needle biopsy samples with MASLD were collected, including 41 from Shuguang Hospital and 119 from Medical Center of the Johannes Gutenberg-University. Fibrosis stages were assessed by the NASHCRN staging system. The AI-based algorithm was developed based on the samples from Shuguang Hospital. The artery density(AD), portal vein density(PVD) and central vein density(CVD) were quantified by the AI-based algorithm. The correlations between vessels' density and fibrosis stages were analyzed using Spearman's correlation. **Results:** The histological fibrosis stages were distributed as follows F1(26.25%), F2 (31.25%), F3 (24.38%) and F4 (18.12%). The AD showed the highest correlation with fibrosis stages than PVD and CVD, with r value of 0.54 (P<0.001). The PVD showed a mild correlation with fibrosis stages with r value of 0.41(P<0.001). These was a less correlation between CVD and fibrosis stages with r value of -0.19(P=0.548). PVD/CVD showed a similar rate to AD, with r value of 0.52(P<0.001). **Conclusion:** The changing of AD is the most significant vascular lesions in the liver fibrosis progressing of MASLD. AI-based algorithm can serve as a method for evaluating vascular changes in MASLD, especially to track intra-stage change for cirrhotic patients.



Disclosures: Zhengxin Li: Nothing to Disclose, Meng Li: Nothing to Disclose, Qiang Yang: Nothing to Disclose, Yayun Ren: HistoIndex Pte Ltd: Employee, Xiao Teng: Nothing to Disclose, Dean Tai: Histoindex.com: Employee, Ian Wanless: Nothing to Disclose, Jörn Schattenberg: Consultant relationship with Intercept Pharmaceuticals; Has ended; Speaking and Teaching relationship with MedicalTribune, MedPublico GmbH, MedScape,; Has

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1562 | LOWER PREVALENCE OF MASLD IN NON-HISPANIC BLACK PATIENTS IS NOT EXPLAINED BY HIGHER HEPATIC FAT OXIDATION

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Background: The prevalence of MASLD among non-Hispanic Black (nH-B) patients is lower compared to White (nH-W) patients, even if both groups are well-matched for adiposity and insulin resistance. The reasons for that difference are not well understood. The aim of this study was to compare hepatic fat oxidation in nH-B vs. nH-W in the fasting and postprandial periods. **Methods:** Patients underwent an oral glucose tolerance test (OGTT) with measurements every 30 minutes of glucose, insulin, C-peptide, free fatty acids (FFA), ketones. Patients also had liver fat measured by proton magnetic resonance spectroscopy, and a subgroup of patients had a liver biopsy. A ketone/FFA ratio was used as a surrogate marker of fat oxidation. **Results:** A total of 77 patients were recruited (53 nH-W and 24 nH-B). Clinical characteristics were similar between racial groups: Age: 53 ± 2 vs. 57 ± 2, p=0.18; Male: 66% vs. 75%, p=0.43; BMI: 35.0 ± 0.9 vs. 35.0 ± 0.9 kg/m^2, p=0.99; prediabetes or T2D: 83% vs. 83%, p=0.97. Fasting hepatic (HOMA-IR) and adipose tissue (ADIPO-IR) insulin resistance were also similar in both groups (HOMA-IR: 4.2 ± 0.7 vs. 4.4 ± 0.7, p=0.84; ADIPO-IR: 4.3 ± 0.6 vs. 4.0 ± 0.4, p=0.74). Postprandial adipose tissue insulin resistance measured as suppression of FFA by insulin was also similar in both racial groups (85% vs. 84%, p=0.90). Despite these similarities, liver fat was markedly higher in nH-W: 12.4 ± 2.0% vs. 3.3 ± 0.8%, p=0.003. Fasting glucose, insulin, and C-peptide were similar in both groups. However, fasting hepatic fat oxidation (ketone/FFA levels) was significantly higher in nH-W compared to nH-B: 475 ± 39 vs. 326 ± 19, p=0.017. This trend persisted during all timepoints of the OGTT, although of borderline significance (p=0.07, 0.09, 0.07, and 0.24 for times 30, 60, 90, and 120, respectively). Of note, this lower ketone levels in nH-B occurred despite lower postprandial insulin levels during the OGTT. Even when limiting the analysis to patients without MASLD, fasting hepatic fat oxidation (i.e., ketone/FFA levels) were also significantly higher in nH-W compared to nH-B (p=0.037). **Conclusion:** In non-Hispanic Black patients there is a dissociation between insulin resistance and the degree of liver fat accumulation. Based on our results, this lower liver fat content is not explained by increased hepatic fat oxidation as estimated by ketone to FFA ratio. Future studies focusing on other metabolic pathways, such as de novo lipogenesis, are needed to understand why nH-B patients accumulate less liver fat. Answering this question may hold the key to identify metabolic pathways that could be targeted to treat MASLD.

Disclosures: Fernando Bril: NovoNordisk: Consultant, NovoNordisk: Speaking and Teaching, Boehringer Ingelheim: Speaking and Teaching, Boehringer Ingelheim: Advisor, Srilaxmi Kalavalapalli: Nothing to Disclose, Kenneth Cusi: Nothing to Disclose

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1563 | PEGOZAFERMIN REDUCED PROGRESSION TO CIRRHOSIS: A POST-HOC ANALYSIS FROM THE PHASE 2B ENLIVEN STUDY ◆

Cynthia Hartsfield[1] Jörn Schattenberg[2] Arun Sanyal[3] Manal Abdelmalek[4] Maya Margalit[1] Mildred Gottwald[1] Shibao Feng[1] Germaine Agollah[1] Leo Tseng[1] Hank Mansbach[1] Rohit Loomba[5]

[1]89bio, [2]UKS, [3]Virginia Commonwealth University, [4]Mayo Clinic Rochester, [5]University of California, San Diego

Background: FGF21 analogs such as pegozafermin (PGZ) have direct effects on liver fibrosis and other hepatic and extrahepatic benefits in patients with MASH. The Phase 2b ENLIVEN trial demonstrated statistically significant improvements in fibrosis regression and MASH resolution at week 24 (W24) with PGZ versus placebo (PBO) in MASH patients with F2/F3 fibrosis. The primary treatment goal in noncirrhotic patients is to prevent progression to cirrhosis. This post-hoc analysis evaluated the effect of PGZ on histological progression to cirrhosis at W24. **Methods:** Subjects were randomized to PGZ 15mg QW, 30mg QW, or 44mg Q2W or PBO (n=222). Biopsies, performed at Baseline (BL) and at W24, were evaluated for NAS components and fibrosis stage using the NASH CRN system. The proportion of PGZ and PBO-treated subjects who progressed to cirrhosis at W24, additional histological parameters, non-invasive tests and adiponectin were evaluated. **Results:** Of the 106 total patients with BL F3, 13 (12.3%) progressed to cirrhosis at W24; no F2 subject (N=58) progressed to F4. At BL, F3 progressors had a higher mean VCTE score (21.1 vs. 13.0 kPa) and rates of hypertension and ELF score >9.8, and lower liver fat compared to all randomized subjects. Pooled PGZ-treated F3 progressors (n=6; 4 on PGZ 30 mg QW and 2 on 44 mg Q2W) were older and with a higher mean VCTE score (27.0 vs. 16.0 kPa) compared to PBO (n=7) (Table 1). Progression to cirrhosis occurred in 7/37 (18.9%) of PBO vs. 6/69 (8.7%) of PGZ subjects. Improvement in NAS score ≥ 1 point occurred in 5/6 (83%) of PGZ vs. 1/7 (14%) of PBO subjects. Marked, consistent improvements in liver-related non-invasive tests (ALT, AST, MRI-PDFF, VCTE, ELF score, ProC3, cT1, FAST score, FIB-4 score) and an increase in adiponectin (+60% vs. -1%) were noted in PGZ-treated vs. PBO progressors (Table 1). PGZ was well tolerated in F3 progressors. **Conclusion:** Treatment with PGZ led to a reduction in the proportion of subjects with BL fibrosis stage F3 who progressed to cirrhosis. Relative to PBO F3 progressors, PGZ-treated progressors demonstrated improvement in histological disease activity and multiple liver-related NITs, indicating that PGZ may have clinical benefits even in patients with histological fibrosis progression. PGZ is currently being studied in Phase 3 studies in non-cirrhotic and cirrhotic MASH. The reduction in progression to cirrhosis observed in ENLIVEN adds to the promise of PGZ to address one of the key treatment goals in MASH.

Table 1: Comparison between PGZ-treated and PBO F4 progressors at baseline and W24

	Placebo (n=7)[$]	Pooled PGZ (n=6)[$]
Baseline		
Age (years)	58.7	63.7
Female (%)	71.4	66.7
Type 2 diabetes (%)	42.9%	66.7%
Hypertension (%)	100.0%	83.3%
Liver fat content MRI-PDFF (%)	13.8%	11.1%
VCTE (kPa)	16.0	27.0
ELF score >9.8 (%)	85.7	83.3%
ALT (U/L)	53.8	47.4
AST (U/L)	49.2	40.0
Triglycerides (mg/dL)	149	125
Change at Week 24		
ALT (Relative change, %)*	-3	-53
AST (Relative change, %)*	0	-42
MRI-PDFF (Relative change, %)***	+2	-54
VCTE (kPa)	+2.5	-1.9
ELF score	-0.07	-0.18
Pro-C3 (Relative change, %)	+8	-12
cT1 (ms)*	+4.8	-75.0
FAST Score*	-0.05	-0.4
FIB-4 Score	-0.13	-0.31
Adiponectin (Relative change, %)**	-1	+60
Safety at Week 24		
Any TEAE (%)	100.0	66.7
Treatment-related AEs (%)	57.1	16.7

* p<0.05; **p<0.01; ***p<0.001 vs. placebo

[$] 7/37 (18.9%) of PBO and 6/69 (8.7%) of PGZ-treated subjects with BL F3 fibrosis progressed to F4

Disclosures: Cynthia Hartsfield: 89bio: Employee, Jörn Schattenberg: Consultant relationship with Intercept Pharmaceuticals; Has ended; Speaking and Teaching relationship with MedicalTribune, MedPublico GmbH,

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1564 | SEMAGLUTIDE IMPROVES LIVER ENZYMES AND FATTY LIVER INDEX IN PATIENTS WITH OBESITY AND CARDIOVASCULAR DISEASE – RESULTS FROM THE SELECT TRIAL ◆

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Background: Metabolic dysfunction-associated steatotic liver disease is a potential driver of cardiovascular (CV) risk in people with obesity. The SELECT CV outcomes trial showed that treatment with the glucagon-like peptide-1 analog semaglutide resulted in a 20% reduction in the risk of major CV events in patients with overweight or obesity and established atherosclerotic CV disease (ASCVD) but without diabetes. In this analysis, we assessed the effects of semaglutide on liver enzymes and predicted hepatic steatosis in SELECT participants. **Methods:** SELECT was a multicenter, randomized, double-blind, placebo-controlled, event-driven trial that enrolled 17,604 patients aged ≥45 years. Patients were randomized (1:1) to receive once-weekly subcutaneous semaglutide 2.4 mg or placebo in addition to standard of care for CV disease prevention. For this analysis, liver enzymes alanine aminotransferase (ALT), aspartate aminotransferase (AST) and gamma-glutamyl transferase (GGT), as well as the fatty liver index (FLI), an algorithm based on body mass index, waist circumference, triglycerides and GGT predictive of hepatic steatosis, were assessed over 104 weeks. **Results:** ALT, AST and GGT declined rapidly after initiation of semaglutide treatment, reaching a nadir at 20 weeks, after which ALT and AST increased over time while GGT remained stable. The estimated treatment difference vs placebo at week 104 was −1.9 U/L (95% confidence interval [CI] −2.6, −1.2; p<0.0001), −0.9 U/L (95% CI −1.3, −0.5; p<0.0001) and −8.2 U/L (95% CI −9.5, −6.8; p<0.0001), respectively (Figs. 1a–c). A 6% (95% CI 0.93, 0.95; p<0.0001) greater decrease from baseline with semaglutide vs placebo was observed for ALT, 3% (95% CI 0.96, 0.98; p<0.0001) for AST and 17% (95% CI 0.82, 0.84; p<0.0001) for GGT. In line, FLI decreased by 16.1 (95% CI −16.7, −15.6; p<0.0001) upon semaglutide treatment vs placebo (Fig. 1d), corresponding to a 28% greater decrease in FLI (95% CI 0.71, 0.73; p<0.0001). Semaglutide treatment also resulted in a −9.39% mean change in body weight over 104 weeks vs −0.88% with placebo. **Conclusion:** Semaglutide treatment resulted in a significant and rapid improvement in liver enzymes and FLI, suggesting a beneficial effect on liver health in patients with established ASCVD but without

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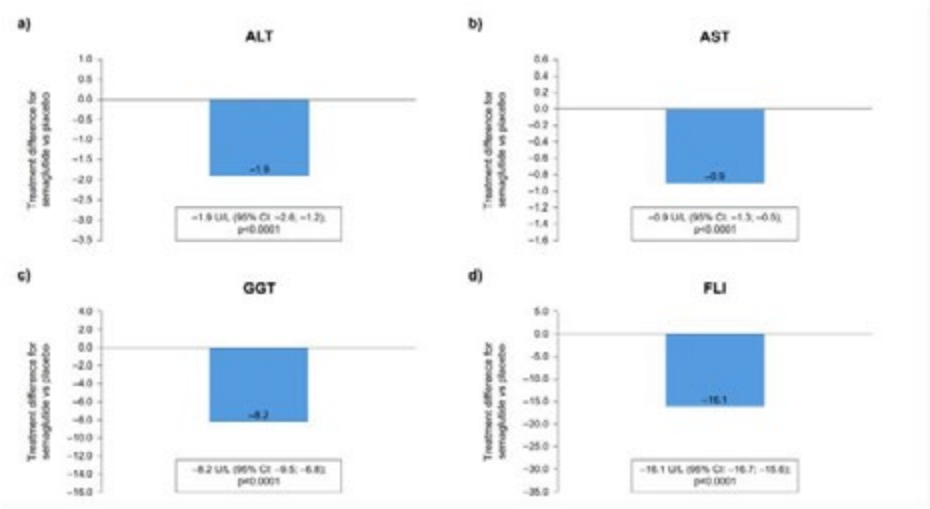
diabetes. These results are consistent with the weight loss induced by semaglutide, as excess body fat is a major risk factor for liver steatosis and inflammation.

FIGURE

Fig. 1 Treatment difference between semaglutide and placebo for change from baseline in (a) ALT, (b) AST, (c) GGT and (d) FLI at week 104 (analysis of covariance, full analysis set)



ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; ETD, estimated treatment difference; FLI, fatty liver index; GGT, gamma-glutamyl transferase.

Observed in-trial data. The responses were analyzed using an ANCOVA with treatment as a fixed factor and baseline value as a covariate.

Disclosures: Sebastian Meyhöfer: Amgen: Consultant, Astra Zeneca: Consultant, Bayer: Consultant, Boehringer Ingelheim: Consultant, Daichii-Sankyo: Consultant, esanum: Consultant, Gilead: Consultant, Ipsen: Consultant, Lilly: Consultant, Novartis: Consultant, Novo Nordisk: Consultant, Sandoz: Consultant, Sanofi: Consultant, Bertrand Cariou: Nothing to Disclose, Cintia Cercato: Nothing to Disclose, Helen Colhoun: IQVIA: Grant/Research Support, Chief Scientist Office: Grant/Research Support, DiabetesUK: Grant/Research Support, Juvenile Diabetes Research Foundation (JDRF): Grant/Research Support, Medical Research Council (MRC): Grant/Research Support, EU Commission: Grant/Research Support, Roche Pharmaceuticals: Stock – privately held company, Bayer AG: Stock – privately held company, Bayer AG: Advisor, Novo Nordisk: Advisor, Novo Nordisk: Speaking and Teaching, John Deanfield: Amgen: Speaking and Teaching, Boehringer Ingelheim: Speaking and Teaching, Merck: Speaking and Teaching, Pfizer: Speaking and Teaching, Novartis: Speaking and Teaching, Aegerion: Speaking and Teaching, Sanofi: Speaking and Teaching, Takeda: Speaking and Teaching, Novo Nordisk: Consultant, Bayer: Speaking and Teaching, Novo Nordisk: Member of Study Steering Committee, Alzheimer's Research UK: Grant/Research Support, British Heart Foundation: Grant/Research Support, Mette Skalshøi Kjær: Novo Nordisk A/S: Employee and stock owner, Ole Jeppesen: Nothing to Disclose, A. Michael Lincoff: Novo Nordisk: Consultant, Eli Lilly: Consultant, Akebia: Advisor, Alnylam: Advisor, Ardelyx: Advisor, Becton Dickson: Advisor, Brainstorm Cell: Advisor, Amgen: Consultant, Cadrenal: Consultant, Endologix: Advisor, Fibrongen: Advisor, Glaxo: Advisor, Intarcia: Advisor, Medtronic: Advisor, Neovasc: Advisor, Provention Bio: Advisor, ReCor: Advisor, AbbVie: Grant/Research Support, AstraZeneca: Grant/Research Support, CSL Behring: Grant/Research Support, Eli Lilly: Grant/Research Support, Esperion: Grant/Research Support, Novartis: Grant/Research Support, Ildiko Lingvay: Nothing to Disclose, Philip Newsome: Novo Nordisk: Consultant, B Ingelheim: Consultant, Madrigal: Consultant, 89 Bio: Consultant, Sagimet: Consultant, Echosens: Speaking and Teaching, Eli Lilly: Speaking and Teaching, Zydus Therapeutics: Consultant, Abbott: Speaking and Teaching, Stephen Nicholls: Nothing to Disclose, Maria De Los Angeles Quiroga Pelaez: Novo Nordisk A/S: Employee, Ferruccio Santini: Nothing to Disclose, Arun Sanyal: Genfit, Akarna, Tiziana, Durect, Inversago, Hemoshear, North: Stock - publicly traded company, Astra Zeneca (60K), Boston Pharmaceutical

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1565 | METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE IS ASSOCIATED WITH IMPAIRED HEALTH-RELATED QUALITY OF LIFE IN PEOPLE WITH HIV

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Background: Patients with metabolic dysfunction-associated steatotic liver disease (MASLD) often experience a range of mental, emotional and social problems, resulting in impaired health-related quality of life (HRQoL). People with HIV (PWH) are at high risk for both MASLD and impaired HRQoL. We investigated the association of MASLD with the HRQoL in PWH. **Methods:** We included PWH from the prospective multicenter LIVEr disease in HIV (LIVEHIV) Cohort in Canada, excluding those with hepatitis coinfection or significant alcohol intake. MASLD was defined as the presence of hepatic steatosis, diagnosed as controlled attenuation parameter >248 dB/m, plus any among overweight (BMI >25 Kg/m^2), type 2 diabetes, hypertension, or dyslipidemia. Liver fibrosis was defined as liver stiffness >7.1 kPa. HRQoL was measured by: (i) Short Form-36 (SF-36) questionnaire, consisting of 36 items divided into 8 domains, scored from 0 to 100, with higher scores indicating a better HRQoL; (ii) Chronic Liver Disease Questionnaire (CLDQ) specifically developed for people with liver diseases, consisting of 29 items divided into 6 domains, scored from 1 to 7, with higher scores indicating better HRQoL and 5. Cofactors associated with the SF-36 and CLDQ scores were investigated by multivariable linear regression analysis. **Results:** Among the 200 PWH included (mean age 41 years, 84% male, 87% with suppressed viral load, 10% with liver fibrosis), the prevalence of MASLD was 46%. PWH with MASLD were significantly older (48±5.6 vs 37±2.5 years, p=0.002) and had higher liver stiffness (5.2±0.5 vs 4.3±0.4 kPa, p=0.01) compared to PWH without MASLD. Mean (standard deviations) SF-36 domain scores and CLDQ domain scores are reported in the Table. Fatigue scored the lowest among the domains by both SF-36 questionnaire and CLDQ. When comparing PWH with and without MASLD, the activity domain of the CLDQ was more impaired in PWH with MASLD compared to those without (6.2±1.2 vs. 5.8±1.5, p=0.05). No differences were found between the two groups in other domains of the SF-36 or CLDQ. At multivariable analysis, after adjusting for age, biological sex and undetectable viral load, MASLD remained significantly and negatively associated with the CLDQ activity domain (correlation coefficient -2.31, 95% CI -1.1 − -0.9, p=0.023). **Conclusion:** Fatigue is the most impaired HRQoL domain in PWH. MASLD appears to worsen HRQoL in PWH, as it is independently associated with impairment of the activity domain.

Table 1: Mean (standard deviation) scores of the SF-36 questionnaire and CLDQ in the whole patient population and by MASLD category.

Domains	Whole study population (n=200)	PWH without MASLD (n=106)	PWH with MASLD (n=92)
Short Form-36 (SF-36)			
Physical functioning	83.2 (25.5)	84.6 (24.5)	81.3 (25.8)
Role limitations due to physical health	83.8 (32.5)	83.3 (33.9)	84.0 (31.3)
Role limitations due to emotional problems	82.8 (41.1)	80.7 (39.3)	84.1 (45.2)
Fatigue	63.7 (22.8)	65.6 (22.1)	60.8 (23.0)
Emotional well-being	73.2 (19.5)	73.5 (19.6)	72.3 (19.3)
Social functioning	81.3 (24.0)	79.5 (26.2)	83.7 (21.1)
Pain	79.7 (26.0)	79.5 (27.8)	79.4 (24.0)
General health	72.8 (21.4)	75.2 (21.0)	69.9 (21.7)
Health change	67.8 (25.8)	69.8 (26.0)	65.5 (25.6)
Chronic Liver Disease Questionnaire (CLDQ)			
Abdominal symptoms	6.1 (1.4)	6.2 (1.2)	5.9 (1.5)
Fatigue	5.4 (1.5)	5.6 (1.4)	5.2 (1.5)
Systemic symptoms	5.8 (1.2)	5.9 (1.1)	5.6 (1.4)
Activity	6.0 (1.3)	6.2 (1.2)*	5.8 (1.5)*
Emotional function	5.5 (1.3)	5.5 (1.4)	5.4 (1.3)
Worry	6 (1.3)	6.1 (1.2)	5.8 (1.4)

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Disclosures: Michael Nudo: Nothing to Disclose, Felice Cinque: Nothing to Disclose, Sahar Saeed: Novo Nordisk: Consultant, Amanda Lupu: Nothing to Disclose, James Gazetas: Nothing to Disclose, Luz Ramos Ballesteros: Nothing to Disclose, Wesal Elgretli: Nothing to Disclose, Erica Moodie: Nothing to Disclose, Colleen Price: Nothing to Disclose, Ken Monteith: Nothing to Disclose, Curtis Cooper: Nothing to Disclose, Sharon Walmsley: Nothing to Disclose, Neora Pick: Nothing to Disclose, Melanie Murray: Nothing to Disclose, Nadine Kronfli: Nothing to Disclose, Joseph Cox: Nothing to Disclose, Cecilia Costiniuk: Nothing to Disclose, Alexandra De Pokomandy: Nothing to Disclose, Jean-Pierre Routy: Nothing to Disclose, Marina Klein: Nothing to Disclose, Bertrand Lebouché: Merck Canada: Speaking and Teaching, Gilead: Speaking and Teaching, ViiV healthcare: Consultant, Gilead: ASAP study managed by RI-MUHC, Merck: I score study and core set study managed by RI-MUHC, ViiV: PIVHOT progra mfro patients managed by RI-MUHC, Giada Sebastiani: Novo Nordisk: Consultant, Abbvie: Speaking and Teaching, Merck: Consultant, Gilead: Speaking and Teaching, Theratechnologies Inc.: Grant/Research Support

1566 | FREE FATTY ACID INDUCES APOPTOSIS VIA LNCRNA NEAT1/MIR-26A/PTEN AXIS IN HEPATIC CELLS

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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is one of the leading causes of end stage chronic liver disease and HCC. Non coding RNA species like Long Non-Coding RNAs (lncRNAs) and MicroRNAs (miRNAs) are shown to be involved in various pathologies including MASLD. LncRNA NEAT1 was shown to be involved in hepatic lipid accumulation. Also, miR-26a is reported to be major regulator in fatty acid and sterol metabolism. In MASLD, apoptosis is a key mechanism for disease progression. Increased levels of Phosphatase and tensin homolog (PTEN) was shown to be involved in triggering apoptosis in MASLD. NEAT1 is reported to sponge miR-26a to facilitate endometrial cancers. Also, mir-26a is shown to be promoting hepatocellular carcinoma invasion and metastasis by targeting PTEN. There are no studies reporting the role of miR-26a-5p in NEAT1-induced MASLD in hepatic cells. **Methods:** Palmitic acid (300 mM) was incubated with HepG2 cells. siNEAT1 and miR-26a-5p mimics were transfected into HepG2 cells using SiPORT transfection reagent. After 48 hours and 72 hours of transfection, cells were collected for RNA and protein isolation, respectively. NEAT1 and miR-26a-5p expression were analysed by real-time PCR. Expression of PTEN, apoptosis markers, such as bax and Bcl-XL, were analysed by Western blots. **Results:** In palmitic acid treated HepG2 cells, RT PCR analysis showed lncRNA NEAT1 was upregulated while miR-26a-5p expression was downregulated ($p \leq 0.05$). Also, Western blot analysis showed an upregulation of PTEN and Bax, while the expression of Bcl-XL was inhibited. Similar expression of NEAT1 and miR-26a-5p was validated in NAFLD human samples. Upon transfection with siRNAs against NEAT1(siNEAT1), there was an upregulation of miR-26a-5p and downregulation of PTEN which further triggered the upregulation of Bcl-xL and downregulation of Bax. Similar pattern of regulation was observed in miR-26a-5p mimic transfection cells($p \leq 0.05$). Further upon treatment of palmitic acid in presence of siNEAT1, downregulation of PTEN and BAX and upregulation of Bcl-XL was observed. Similar pattern of regulation was observed in palmitic acid treated miR-26a-5p mimic transfected cells ($p \leq 0.05$). **Conclusion:** These findings confirmed that free fatty acids induced apoptosis via NEAT1/miR-26a-5p/PTEN axis. This suggests that targeting NEAT1 could be a novel approach to regulate MASLD progression.

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1567 | THE COMBINATION OF FATTY ACIDS DESATURASE 2 RS174583 AND PNPLA3 RS738409 POLYMORPHISMS IS A RISK FACTOR IN ADVANCED FIBROSIS IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE

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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most prevalent chronic liver disease worldwide. Genetic predisposition has a significant influence on the onset and progression of MASLD; however, many aspects remain unknown how the combination of genetic factors are involved in the complex pathophysiology of MASLD. Fatty acid desaturase 2 (FADS2) gene encodes a rate limiting enzyme in the synthesis of long chain poly unsaturated fatty acids from essential fatty acids, and FADS2 gene rs174583 single nucleotide polymorphism (SNP) has been reported to be a risk factor in cardiovascular events by affecting hyperglyceridemia, hyperglycemia and hyperinsulinemia. Our aim in this study was to investigate the impact of FADS2 polymorphism on progression of MASLD. **Methods:** A total of 40 patients with biopsy-proven MASLD were evaluated. A control group consisted of 10 healthy volunteers. Genotypes were established using TaqMan assays targeting PNPLA3 rs738409, FADS1 rs174556, and FADS2 rs174583. Allele frequencies in each group were evaluated by Chi-square test. MASLD patients were stratified to non-advanced fibrosis (fibrosis stage 0-2) and advanced fibrosis (stage 3-4). **Results:** The frequency of GG allele carriers of PNPLA3, TT allele carriers of FADS1, and TT allele carriers of FADS2 tended to be higher in the MASLD group, the levels reaching 55%, 23%, and 45%, compared with 30%, 20%, and 30% in the control group, respectively. The frequencies of the PNPLA3 GG allele and the FADS2 TT allele in the advanced fibrosis group were higher (64% and 57%, respectively) than in the non-advanced fibrosis group (50% and 38%), whereas the frequencies of the FADS1 TT allele were almost similar in both groups (21% and 23%). Interestingly, 45% of MASLD patients with PNPLA3 GG allele were also FADS2 TT allele-positive, and MASLD patients with the combination had a higher ratio of advanced fibrosis than PNPLA3 GG allele alone-positive patients (70% and 17%, p=0.027). Similarly, in patients with both PNPLA3 and FADS2 SNPs, the serum levels of type IV collagen were significantly higher than in the PNPLA3 GG allele alone-positive patients. In PNPLA3 GG allele-positive MASLD patients, FADS2 TT allele did not affect blood sugar or serum lipid levels. **Conclusion:** The findings indicated that the combination of PNPLA3 GG allele and FADS2 TT allele is involved in the progression of MASLD.

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1568 | FIBROBLAST GROWTH FACTOR 15/19 (FGF15/19) REGULATES CIRCADIAN ENERGY METABOLISM IN SHIFT WORKERS

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Background: Chronic disruption of circadian rhythm by shift work is an important risk factor for metabolic diseases. The NAD^+-dependent SIRT1 signaling is critical in maintaining hepatic homeostasis by linking hepatic metabolism to circadian rhythm. Fibroblast growth factor 15/19 (FGF15/19), a postprandial hormone secreted from intestines, potently suppresses bile acid (BA) synthesis and improves insulin sensitivity. FGF15/19 emerges as a novel pharmaceutical target for the prevention and treatment of metabolic diseases. Our preliminary clinical studies in shift workers showed a disruption of the circadian rhythmicity of plasma FGF19 levels with a significant decrease during daytime in night shift (NS) compared to day shift (DS) nurses, suggesting that FGF19 supplement during daytime may reset the metabolic rhythm in NS workers. **Methods:** In the human study, we collected blood samples from DS and NS nurses every 4 hrs over a 24-hr period. Circadian levels and rhythmicity of important components of NAD^+-dependent SIRT1 signaling, including NAD^+/NADH, SIRT1 activity, and *NAMPT* and *SIRT1* mRNA expression in peripheral blood mononuclear cells (PBMCs), were determined in DS and NS nurses. In the animal study, livers were collected from wild-type (WT), *Fgf15* transgenic (TG), and *Fgf15* knockout

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(KO) mice every 4 hrs over a 24-hr period. Circadian levels and rhythmicity of mRNA expression of core clock genes (CGs) and some clock-controlled genes (CCGs, *Sirt1*, *Nampt*, *Nmnat1*), NAD^+ level, NAD^+/NADH, and SIRT1 activity were determined in these liver tissues. **Results:** The circadian rhythmicity of NAD^+/NADH and SIRT1 activity and the circadian mRNA levels of *NAMPT* and *SIRT1* in PBMCs were affected by shift work. In mice, systemic deficiency of FGF15 did not perturb feedback loops of core components within the transcription/translation molecular circadian clock, nor disrupted the circadian rhythmicity of hepatic CGs. However, the circadian rhythms and levels of CCGs were disrupted in *Fgf15* KO mice compared to WT mice. Moreover, systemic FGF15 deficiency led to the circadian disturbance of NAD^+-dependent SIRT1 signaling and significant reduction of NAD^+ and SIRT1 activity during nighttime (active phase) in mice, indicating the important implications of FGF15/19 for the circadian regulation of energy homeostasis in response to the feeding/fasting signal. *Fgf15* TG mice presented similar circadian rhythms and levels of these indicators compared to WT mice. **Conclusion:** FGF15/19 may restore circadian expressions of genes involved in circadian rhythm and BA and lipid metabolism through the regulation of NAD^+-dependent SIRT1 signaling, leading to prevention against metabolic diseases associated with circadian disruption of energy metabolism in shift workers.

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1569 | EFFECT OF PEMVIDUTIDE, A GLP-1/GLUCAGON DUAL RECEPTOR AGONIST, ON PLASMA LIPIDOMIC PROFILES IN SUBJECTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD)

John Suschak[1] Maynara Lucca Andrade[1] Bertrand Georges[1] Sarah Browne[1] Christina Alonso[2] Scott Harris[1] Scot Roberts[1]

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Background: Subjects with metabolic dysfunction-associated steatohepatitis (MASH) can have dysregulated serum lipid profiles that result in hepatic inflammation and increased cardiovascular risk. Pemvidutide is a long-acting, balanced glucagon-like peptide 1 (GLP-1)/glucagon dual receptor agonist in development for the treatment of MASH and obesity. The balanced 1:1 potency ratio combines the reduced caloric intake effects of GLP-1 receptor agonism with the increased energy expenditure and lipometabolic effects of glucagon receptor agonism. In a 12-week double-blind clinical trial in subjects with metabolic dysfunction-associated steatotic liver disease (MASLD), pemvidutide reduced liver fat content by up to 68.5% and decreased total cholesterol and triglycerides by up to 12.2% and 44.6%, respectively. In this study, we employed lipidomics to investigate further the effects of pemvidutide on toxic lipid mediators associated with MASH pathogenesis. **Methods:** 94 subjects with overweight/obesity and MASLD (BMI ≥28.0 kg/m2, MRI-PDFF ≥10%) were randomized 1:1:1:1 to pemvidutide (1.2 mg, 1.8 mg, 2.4 mg) or placebo administered subcutaneously weekly for 12 weeks. Lipidomic profiling across multiple classes of phospholipids, glycerophospholipids, and sphingolipids was performed using ultra-high performance liquid chromatography–mass spectrometry on plasma samples at baseline and Week 12. **Results:** Pemvidutide treatment significantly reduced multiple glycerophospholipid biomarkers of MASH, including lysophosphatidylinositols (Lyso-PI) and lysophosphatidylethanolamines (Lyso-PE, Figure 1). Pemvidutide also resulted in significant reductions in atherosclerotic sphingolipids such as ceramides and sphingomyelins. **Conclusion:** Pemvidutide administered weekly for 12 weeks induced significant decreases in MASH associated lipid species. These findings support pemvidutide's potential benefit on MASH and MASH-associated co-morbidities, including atherosclerosis and metabolic syndrome.

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Figure 1: Pemvidutide treatment improved MASH-associated lipids in subjects with MASLD at Week 12.
The color code represents the log_2(robust fold-change from baseline). Wilcoxon signed rank test *p*-values: **p*<0.05, ***p*<0.01, ****p*<0.001, vs. baseline.



Lipid Class	Common name	Individual notation	PBO (n=13)	Pemvidutide 1.2mg (n=15)	Pemvidutide 1.8mg (n=15)	Pemvidutide 2.4mg (n=7)
Glycerophospholipids	Lyso-PI	LPI(16:0)		*		
		LPI(18:1)		*		
		LPI(18:1)		*		
		LPI(18:2)		***	***	
		LPI(18:2)		*	***	
		LPI(20:3)		*	**	
	Lyso-PC	PC(18:3/0:0)		*	*	
		PC(0:0/14:0)				*
		PC(14:0/0:0)		*		*
	Lyso-PE	PE(20:3/0:0)			**	*
		PE(0:0/16:1)			*	
		PE(0:0/18:2)			**	*
		PE(0:0/20:3)			**	*
Sphingolipids	Ceramides	Cer(d18:1/21:0)				
		Cer(d18:1/22:0)				
		Cer(d18:1/24:0)			*	*
		Cer(d18:1/23:0)			*	
	CMH	CMH(d18:1/23:0)				
		CMH(d18:1/24:0)			**	
	Sphingomyelin	SM(d18:0/22:0)		*	*	*
		SM(38:0)		*	*	
		SM(d18:0/14:0)		**	*	
		SM(d18:0/15:0)				

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1570 | STEATOTIC LIVER DISEASE IN PEOPLE LIVING WITH HEPATITIS C VIRUS FOLLOWING VIRAL ERADICATION WITH DIRECT-ACTING ANTIVIRAL THERAPY

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Background: Chronic hepatitis C is a known cause of hepatic steatosis (HS). Direct-acting antivirals (DAA) have revolutionized HCV treatment, achieving high rates of sustained virologic response (SVR). However, the impact of DAA on metabolic disturbances, particularly HS, remains unclear. With the updated nomenclature for steatotic liver disease (SLD), it is common for HCV to coexist with metabolic dysfunction-associated steatotic liver disease (MASLD). Thus, we aimed to explore early changes in SLD, namely MASLD and HCV-associated HS, and liver fibrosis, post-SVR. **Methods:** This was a retrospective study of patients with hepatitis C evaluated between 2016 and 2019 at two clinical centers. Adult patients who had achieved SVR following DAA therapy were eligible. Transient elastography was employed to evaluate HS and liver fibrosis through controlled attenuation parameter (CAP) and liver stiffness measurement (LSM), respectively, before initiating DAA and 6 months after SVR (end of follow-up). To identify HS and significant liver fibrosis, CAP of ≥248 dB/m and LSM of ≥8 kPa were utilized. Severe HS was defined as CAP >300 dB/m. MASLD was denoted as HS plus at least one of the following cardiometabolic risk factors: high body mass index or waist circumference, prediabetes or diabetes, hypertension, hypertriglyceridemia, and low HDL cholesterol. We employed a multivariate logistic regression analysis to identify

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factors associated with changes in SLD at 6 months post-SVR while accounting for potential confounders. **Results:** Among the included 108 patients, 47% and 49% had HS and liver fibrosis at baseline, respectively. The prevalence of HS increased from baseline to end of follow-up (47% vs 60%, p=0.05). At both baseline and end of follow-up, MASLD was the predominant etiology of HS, representing over 96% of cases. Notably, 32% of those who did not have HS initially developed it at the 6-month mark, and all new cases of HS post-SVR were classified as severe. Conversely, prevalence of liver fibrosis declined dramatically from 49% to 17% (p<0.001), accompanied by a marked reduction in the proportion of patients with elevated alanine aminotransferase (ALT) and aspertate aminotransferase (AST), which dropped from 70% to 5% and from 66% to 5%, respectively. After adjusting for age, sex, DAA regimen and liver transaminases, the multivariate model showed that having HS at baseline was associated with higher likelihood of HS persisting or developing into MASLD at the 6-month mark (see Table). **Conclusion:** Despite the anticipated improvement in liver stiffness and transaminases, MASLD tends to worsen following SVR with DAA. This highlights the importance of understanding the effect of treatment on liver health beyond viral clearance to optimize patient outcomes and provide comprehensive care. Thus, ongoing monitoring of MASLD and its complications following viral clearance is needed.

Table. Multivariate logistic regression analysis.

Variables	Adjusted odds ratio (aOR)	95%Cofidence interval (CI)	p-value
Steatosis at baseline	22.73	(5.66 – 91.13)	0.000
Age	1.03	(0.96 – 1.11)	0.353
Sex	0.43	(0.09 – 1.98)	0.281
DAA regimen	0.68	(0.37 – 1.24)	0.216
ALT	1.00	(0.97 – 1.03)	0.618
AST	0.98	(0.95 – 1.02)	0.582

Disclosures: Mohamed Shengir: Nothing to Disclose, Wesal Elgretli: Nothing to Disclose, Felice Cinque: Nothing to Disclose, Agnihotram Ramanakumar: Nothing to Disclose, Rosa Lombardi: Nothing to Disclose, Annalisa Cespiati: Nothing to Disclose, Anna Ludovica Fracanzani: Nothing to Disclose, Luz Esther Ramos Ballesteros: Nothing to Disclose, Marc Deschenes: Nothing to Disclose, Philip Wong: Nothing to Disclose, Tianyan Chen: Nothing to Disclose, Giada Sebastiani: Novo Nordisk: Consultant, Abbvie: Speaking and Teaching, Merck: Consultant, Gilead: Speaking and Teaching, Theratechnologies Inc.: Grant/Research Support

1571 | LIPIDOMIC AND EICOSANOID PROFILES IN INDIVIDUALS WITH STEATOTIC LIVER DISEASE IN PREGNANCY, GESTATIONAL HYPERTENSION, AND PREECLAMPSIA

Jeanette Rios[1] Tatyana Kushner[1] Yunping Qiu[2] Rachel Meislin[1] Scott Friedman[1] Rhoda Sperling[1] Michal Elovitz[3] Irwin Kurland[2]

[1]Icahn School of Medicine at Mount Sinai (ISMMS), [2]Albert Einstein College of Medicine, [3]Women's Biomedical Research Institute,Icahn School of Medicine at Mount Sinai, New York, USA

Background: Recent studies suggest an association of Steatotic Liver Disease (SLD) in pregnancy with gestational hypertension (gHTN) and preeclampsia (PE). Because SLD influences the peripheral lipidome and unique lipid profiles have been identified as potential biomarkers in PE/gHTN, we evaluated the peripheral lipidomic profiles in individuals with SLD, gHTN, and PE in pregnancy. **Methods:** We conducted a nested case-control study using serum samples collected at 24-32 weeks gestation from individuals from the Fatty Liver in Pregnancy (FLIP) study, which prospectively evaluates for SLD prenatally. We compared lipidomic profiles between pregnant individuals with vs without SLD, PE or gHTN. Triple quadrapole based targeted MS (sciex 6500+ QTRAP) equipped with ultra-high performance liquid chromatography based platforms measured key lipids in serum extracts, including: 1) quantification of non-esterified fatty acids including n-6 polyunsaturated fatty acids (PUFAs), monounsaturated fatty acids, oxidized fatty acids/ eicosanoids and 2) lipidomic profiling of ~1500 lipid species in up to 26 lipid classes in one run. Comparison of lipid profiles was performed with Orthogonal Partial Least Squares Discriminant Analysis. **Results:** Samples from 11 individuals with SLD, 8 with PE, 11 with gHTN and 30 controls were evaluated (see Figure). For lipidomic analysis, lipid mediators with the highest

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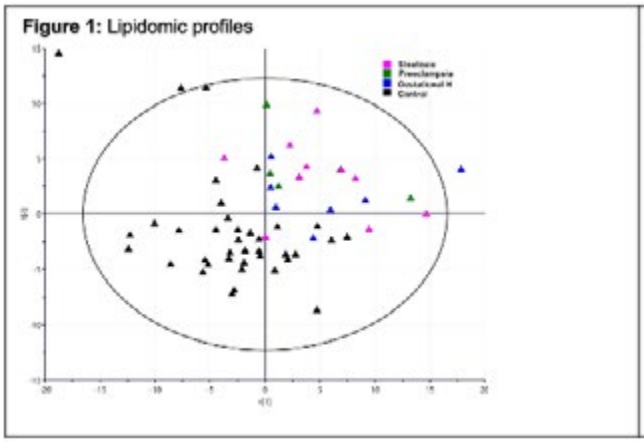
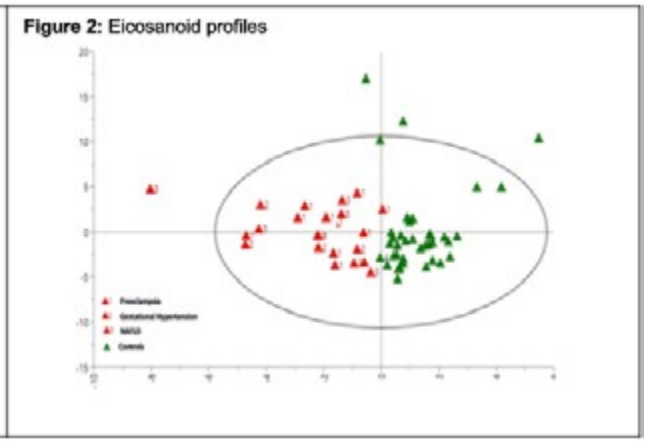
variable importance in projection (VIPs) were Lyso-platelet-activating factor C-16 (Lyso-PAF C-16) and PAF C-18. For eicosanoid analysis, significant group separation was found between PE, gHTN, and SLD vs controls for driven by decreased 12,13-dihydroxy-9Z-octadecenoic acid (12(13)-Di-HOME), 9- Hydroxyoctadecadienoic acid (9-HODE), and 13- Hydroxyoctadecadienoic acid (13-HODE), and increased 16,17-epoxy docosapentaenoic acid (16(17)-EpDPA) and 7- hydroxy-4Z,8E,10Z,13Z,16Z,19Z-docosahexaenoic acid (7-HDHA). There was a poor correlation between upstream plasma lipid species and eicosanoid levels, suggesting alternate source(s) of serum eicosanoids, possibly from circulating inflammatory cells. There was a high correlation between the 13-HODE, 12 (13)-Di-HOME and 9- HODE, eicosanoids all derived from linoleic acid, suggesting importance of this pathway in these conditions. **Conclusion:** Lipidomic analysis showed group separation driven mostly by PAFs, which play roles in inflammatory pathways. Eicosanoids that drove group separation were derived from linoleic acid and decosahexaenoic acid precursors, both PUFAs, the former predominant in Western diet. A decrease in 12 (13)-Di-HOME, a new therapeutic target in metabolic diseases, supports its potential as a biomarker linking SLD and hypertensive disorders of pregnancy. This early work shows shared lipidomic pathways between SLD, gHTN, and PE, needing further confirmation with larger cohort samples to determine biological mechanisms linking SLD and PE.





Disclosures: Jeanette Rios: Nothing to Disclose, Tatyana Kushner: Advisor relationship with Gilead; Has ended; Advisor relationship with GSK; Has ended; Advisor relationship with Eiger; Has ended; Grant/Research Support relationship with Gilead; Has not ended, Yunping Qiu: Nothing to Disclose, Rachel Meislin: Nothing to Disclose, Scott Friedman: 89 Bio: Consultant, Boehringer Ingelheim: Consultant, Boston Pharmaceutical: Consultant, Bristol Myers Squibb: Consultant, Merck: Consultant, Glycotest: Consultant, Morphic Therapeutics: Consultant, HepGene: Consultant, North Sea Therapeutics: Consultant, Pfizer Pharmaceuticals: Consultant, Sagimet: Consultant, Scholar Rock: Consultant, Prosciento: Consultant, Seal Rock: Consultant, Surrozen: Consultant, Takeda Pharmaceuticals: Consultant, Junevity: Consultant, Therasid Bio: Consultant, Merck: Consultant, Ochre Bio: Consultant, Gordian Biotechnology: Consultant, Abalone Bio: Grant/Research Support, Prosciento: Consultant, Rhoda Sperling: Nothing to Disclose, Michal Elovitz: Nothing to Disclose, Irwin Kurland: Nothing to Disclose

1572 | EXPLORING AN UNLIKELY ASSOCIATION: OUTCOMES OF MASLD PATIENTS HOSPITALIZED WITH UPPER GASTROINTESTINAL BLEEDING

Binyamin Abramowitz[1] Alexander Kaye[1] Selome Yewedalsew[1] Sonny Caceres[1] Daniel DiLeo[2]

[1]SUNY Downstate Health Sciences University, [2]VA NY Harbor Healthcare System

Background: The prevalence of metabolic dysfunction-associated steatotic liver disease (MASLD) is rising. MASLD is associated with worse outcomes in patients with congestive heart failure, chronic obstructive pulmonary disease, and pneumonia. However, in patients with upper gastrointestinal bleeding (UGIB), minimal existing data has shown MASLD to be associated with increased mortality, as well as development of respiratory failure and liver failure. Paradoxically, patients hospitalized with MASLD have lower rates of myocardial infarction (MI) and shorter hospitalizations. As an association between MASLD and outcomes in patients with UGIB is not well established, our study sought to determine whether MASLD is associated with poor outcomes in patients

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hospitalized for UGIB. **Methods:** A retrospective study was conducted utilizing the 2020 National Inpatient Sample database. Patients aged 18 and above hospitalized with UGIB were identified. Demographic and hospitalization data was collected and compared across patients with MASLD and patients without MASLD. Data on the rates of complications were also compared and analyzed. **Results:** 129,122 patients hospitalized with UGIB were identified. 6,782 patients had a diagnosis of MASLD while the other 122,340 patients did not. MASLD patients had lower mortality rates (3.1% vs 5.3%, p<0.001) and were more likely to have shorter hospitalizations (5.52 vs. 6.49 days, p<0.001) and decreased hospitalization costs ($75,665 vs $87,908, p<0.001). MASLD patients were also less likely to develop sepsis, respiratory failure, renal failure, MI, or pulmonary embolism during their hospitalizations. **Conclusion:** Our data unexpectedly supports an association between MASLD and better outcomes in patients hospitalized with UGIB. Although the mechanisms behind this association are largely unknown, it is likely multifactorial. Firstly, hepatic steatosis is associated with a hypercoagulable state. When MASLD patients are experiencing UGIB, their relative hypercoagulability may help to protect against further exacerbation of mucosal bleeding and subsequent decompensation. Additionally, gut dysbiosis may also play a role in this association. Species of Lachnospiraceae and Ruminococcaceae have been found to be decreased in MASLD patients while those same species have been found in greater abundance in patients with GI bleeding. As our study is retrospective, further larger prospective studies are warranted to further evaluate the association between MASLD and outcomes in UGIB.

Table 1. Clinical outcomes among UGIB patients with and without MASLD

	Patients with MASLD	Patients without MASLD	p-value
Mortality, *n* (%)	211 (3.1)	6,464 (5.3)	<0.001
Sepsis, *n* (%)	548 (8.1)	13,443 (11.0)	<0.001
Hypovolemic shock, *n* (%)	191 (2.8)	3,234 (2.6)	0.389
Respiratory failure, *n* (%)	798 (11.8)	19,839 (16.2)	<0.001
Myocardial infarction, *n* (%)	186 (2.7)	6,315 (5.2)	<0.001
Acute Renal Failure, *n* (%)	1,602 (23.6)	34,001 (27.8)	<0.001
Pulmonary Embolism	63 (0.9)	1,845 (1.5)	<0.001
Length of stay, mean (SD)	5.52 (6.27)	6.49 (8.52)	<0.001
Total hospitalization cost	$75,665.00 (106930.55)	$87,907.62 (164684.45)	<0.001

Disclosures: Binyamin Abramowitz: Nothing to Disclose, Alexander Kaye: Nothing to Disclose, Selome Yewedalsew: Nothing to Disclose, Sonny Caceres: Nothing to Disclose, Daniel DiLeo: Nothing to Disclose

1573 | VLDL LIPIDOMICS CAPTURE SIGNATURES OF MASLD-ASSOCIATED GENETICS AND DISEASE PROGRESSION THROUGH A NOVEL ACYL CHAIN DISTRIBUTION ANALYSIS ◆

David GUARDAMINO OJEDA[1] Yusuf Yalcin[2] Susmita Bhattarai[1] Aaron Hakim[1] Margery Connelly[3] Z. Gordon Jiang[1]

[1]Beth Israel Deaconess Medical Center, [2]Steward Carney Hospital, [3]Labcorp, Morrisville, NC

Background: Very low-density lipoprotein (VLDL) is produced specifically by liver cells in humans. VLDL carries lipids from the lipid droplet and endoplasmic reticulum, hepatocellular compartments relevant to MASLD pathogenesis. This study aims to assess VLDL lipidomic changes associated with MASLD-related genetics and disease stages. **Methods:** A total of 162 serum samples from biopsy-proven MASLD patients were used to prepare VLDL by ultracentrifugation and lipidomic profiling was obtained through high-performance liquid chromatography-mass spectrometry (HPLC-MS). Lipidome per VLDL particle was calculated from HPLC-MS data after adjustment by VLDL concentration and further analyzed with LipidR. Lipid class-specific acyl chain

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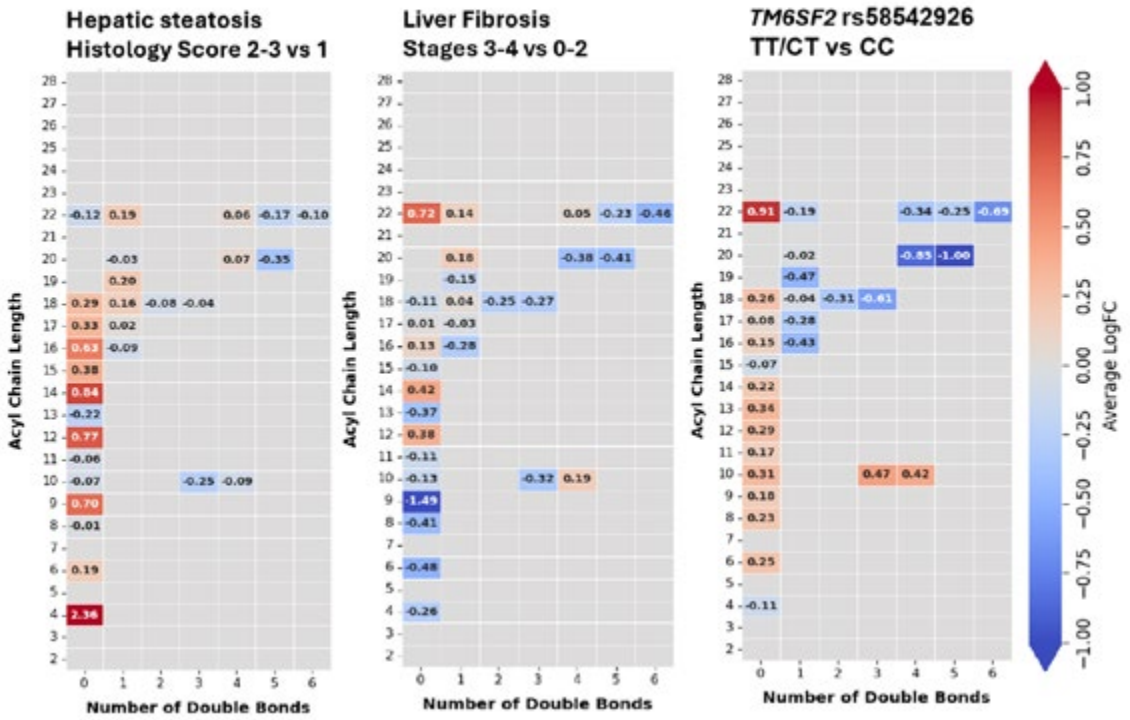
signatures were captured using a novel unified acyl chain distribution analysis. **Results:** We identified 1514 lipid species, with the top three most diverse and abundant lipid classes being triacylglycerol (TG), phosphatidylcholine (PC), and ceramide (Cer). Moderate-to-severe hepatic steatosis (histology scores 2-3 vs. 1) was associated with enrichment in TG, phosphatidylinositol (PI), and reductions of monoether phosphatidylcholine (MePC). Meanwhile, advanced liver fibrosis (stages 3-4 vs. 0-2) was associated with enrichment in Cer and reductions in diacylglycerols (DAG). Through unified acyl chain distribution analysis, we found distinct disease-related acyl chain signatures in various lipid classes. In VLDL-TG, moderate-to-severe hepatic steatosis exhibited increases of saturated acyl chains and decreases of polyunsaturated acyl chains (Figure 1). Conversely, in advanced liver fibrosis, there was a decreased abundance of both saturated and polyunsaturated acyl chains in VLDL-TGs. MASLD-related genetic variants demonstrated differential impact on VLDL-lipidome. For instance, *TM6SF2* rs58542926 C>T variant was associated with a significant increase in saturated acyl chains and marked reduction in all unsaturated acyl chains in VLDL-TG compared to non-carriers. Distinctive signatures were also found in *PNPLA3* rs738409, *GPAM* rs2792751, *HSD17B13* rs4607179, and *MTARC1* rs2642438. **Conclusion:** The use of VLDL-lipidomics provides a novel tool to study hepatocellular lipid homeostasis in MASLD. A unified acyl chain distribution analysis reveals disease-specific and genetic-specific lipidomic signatures at the acyl chain level of each lipid class.

Figure 1.



Disclosures: David GUARDAMINO OJEDA: Nothing to Disclose, Yusuf Yalcin: Nothing to Disclose, Susmita Bhattarai: Nothing to Disclose, Aaron Hakim: Olix Pharmaceuticals: Advisor, Deep Track Capital, LP: Consultant, Margery Connelly: Labcorp: Employee, Z. Gordon Jiang: Nothing to Disclose

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1574 | DEVELOPMENT AND VALIDATION OF A NATURAL LANGUAGE PROCESSING TOOL TO EXTRACT STEATOHEPATITIS DIAGNOSES FROM LIVER BIOPSY PATHOLOGY REPORTS

Julie Lynch[1] *Samiran Mukherjee*[2] *Kyong-Mi Chang*[2] *Kathryn Pridgen*[1] *Patrick Alba*[1]

[1]*Salt Lake City VA Medical Center,* [2]*University of Pennsylvania*

Background: Liver biopsy results are contained within unstructured pathology reports, making it difficult to create biopsy-confirmed patient cohorts for metabolic-associated steatohepatitis disease (MASLD). Our objective is to develop and validate a natural language processing (NLP) tool to identify patients with biopsy-confirmed hepatic steatosis. **Methods:** Using procedure codes, we identified 189,159 Veterans within the Million Veteran Program who received liver biopsies. After selecting for key terms within the report (biopsy, bx, liver, hepat) and excluding liver transplant recipients, there were 13,145 participants with liver biopsy pathology notes.
We randomly selected 1000 pathology reports for annotation. Multiple clinical annotators used a guideline to capture various histological scoring systems used by pathologists for steatosis, inflammation, ballooning, and fibrosis. The first 200 reports were double annotated and adjudicated by a clinical expert. Discrepancies were discussed before the next round of annotations. Inter-annotator agreement, assessed using Cohen's kappa, was >90% for steatosis and >80% for fibrosis and inflammation. The remaining 800 reports were annotated—with subsets double annotated and adjudicated for quality assurance—and split into a training and held-out testing set. Using LEO framework, we developed a rule-based NLP tool to extract key terms (anchor concepts) related to each liver biopsy concept with rules to extract relevant percentage, qualitative description, or severity. We evaluated its performance among 400 held-out reports. The tool was then deployed to the Liver Biopsy Cohort based on note selection criteria (n=13,145). **Results:** Precision was high (steatosis: 0.97, fibrosis: 0.92, inflammation: 0.90, ballooning: 0.97), as was recall (steatosis: 0.88, fibrosis: 0.93, inflammation: 0.95, ballooning: 0.89). F1 scores (harmonic mean of precision and recall) were >90% for all factors. Of 13,145 participants, we identified 4009 (30.5%) with histological steatosis. Of these, 1850 (46%) were defined as our histological MASLD cohort. Within this group, 1272 (69%) had hepatic inflammation, 514 (28%) had advanced fibrosis, and 635 (34%) had non-advanced fibrosis. Collectively, the tool identified 1532 (82%) MASH cases among the MASLD cohort. **Conclusion:** This NLP tool uses biopsy reports to define an MASLD cohorts with high precision and recall, making it a useful tool for researchers hoping to study MASLD in large patient populations.

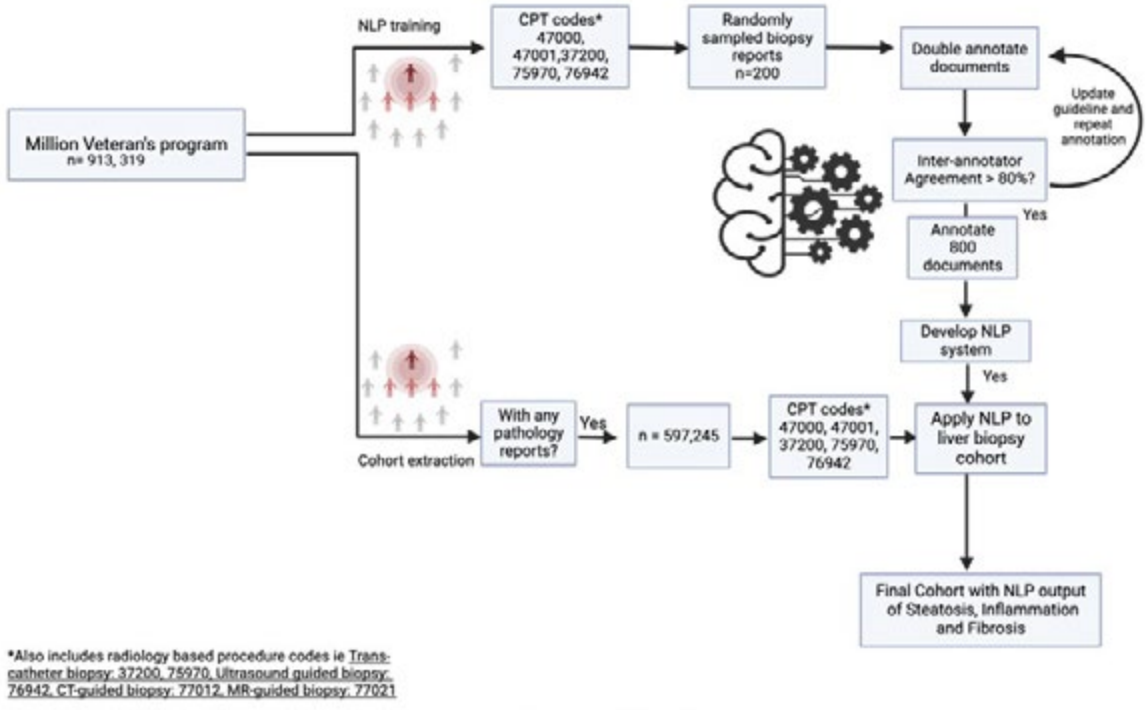

Figure 1: NLP development

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Disclosures: Julie Lynch: Nothing to Disclose, Samiran Mukherjee: Nothing to Disclose, Kyong-Mi Chang: Data Monitoring Committee member relationship with Virion Therapeutics; Has not ended; Advisor relationship with GSK; Has ended, Kathryn Pridgen: Nothing to Disclose, Patrick Alba: Nothing to Disclose

1575 | THE PROGNOSTIC IMPLICATIONS OF DIETARY VITAMIN D INTAKE AMONG PATIENTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE: AN ANALYSIS OF THE NHANES DATABASE ◆

David Lee[1] Mohammed Shaik[1] Sharmitha Yerneni[2] Ki Jung Lee[2] Youngjae Cha[1] Nathalie Urrunaga[1]

[1]University of Maryland School of Medicine, [2]Tufts School of Medicine

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) has emerged as the most prevalent chronic liver disease globally, driven by the rising epidemics of obesity and unhealthy lifestyle patterns. Dietary factors, such as vitamin D, have been implicated in MASLD pathogenesis, and modifying these factors remains a cornerstone of MASLD treatment. This study investigates the prognostic role of dietary vitamin D intake in MASLD. **Methods:** Patients with MASLD were selected from the 2009-2018 National Health and Nutrition Examination Survey (NHANES). Average daily vitamin D intake was calculated over a two-day period and categorized into low (<2.3 mcg/day), intermediate (2.3-4.8 mcg/day), and high (>4.8 mcg/day) terciles. The low intake group served as the reference, while the intermediate and high intake groups together formed the comparison group. The primary analysis compared patients in the low and high intake groups in the composite group. Subgroup analyses were performed based on initial serum vitamin D levels comparing those with normal vitamin D levels (30-125 ng/mL) vs. vitamin D deficiency (<30 ng/mL), and based on liver fibrosis severity comparing those with low vs. advanced fibrosis, as determined by FIB4 and APRI scores. Cox regression was used to compare all-cause mortality, as well as secondary outcomes including mortality from cardiovascular disease, stroke, and diabetes. **Results:** 4,202 patients with MASLD were included, stratified into low (n=1,405) and high (n=2,797) vitamin D intake groups. Those belonging to the low intake group were younger (47.03 vs. 49.38 years, p<0.001), higher proportion male (54.34% vs. 43.17%, p<0.001), had higher BMI (35.30 vs. 34.67, p=0.008), and more likely to be Black (p=0.04). No correlation was observed between vitamin D intake and all-cause mortality, with incidence rates of 5.23 per 1000 person-years in the low intake group, compared to 4.66 in the high intake group (aHR 0.98, 95%CI 0.68-1.42, p=0.91). Even when stratified into subgroups by initial serum vitamin D levels or liver fibrosis severity, no significant correlation was seen. Additionally, there was no association between vitamin D intake and specific causes of death. **Conclusion:** Our findings indicate that vitamin D intake patterns do not impact mortality in patients with MASLD. This suggests that either a higher dose of vitamin D is required to improve prognosis or that sequelae of vitamin D deficiency cannot be overcome by increasing intake.

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Figure 1: Comparison of Patient Survival using Different Terciles of Vitamin D Intake among Patients with MASLD

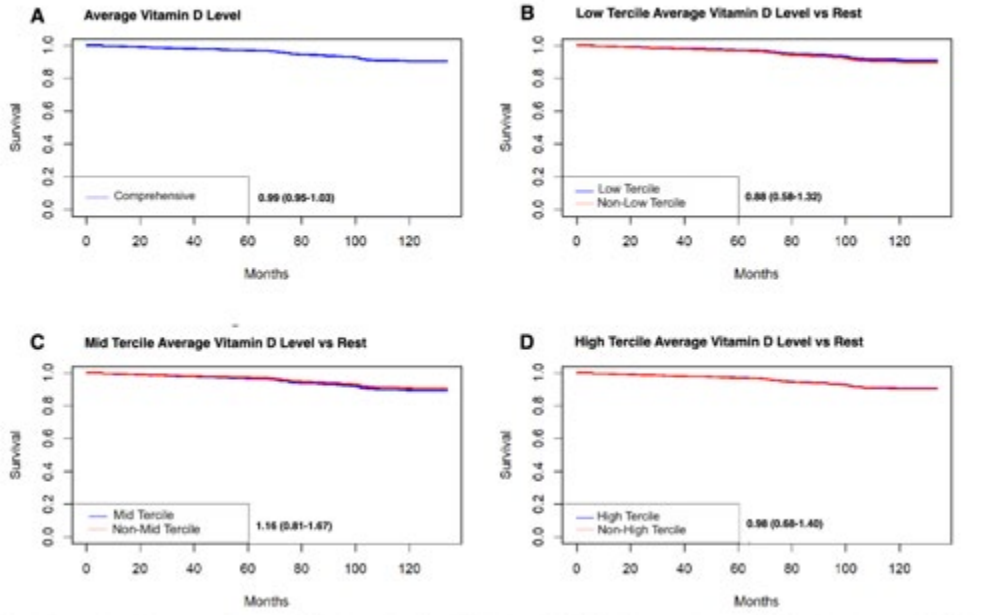

Figure 1 illustrates the survival curves among different vitamin D tercile groups (low, mid, and high) in patients with MASLD. Graph A represents the survival of MASLD patients with average vitamin D levels. Graphs B, C, and D illustrate the survival of MASLD patients with low, mid, and high tercile average vitamin D levels, respectively.

Disclosures: David Lee: Nothing to Disclose, Mohammed Shaik: Nothing to Disclose, Sharmitha Yerneni: Nothing to Disclose, Ki Jung Lee: Nothing to Disclose, Youngjae Cha: Nothing to Disclose, Nathalie Urrunaga: Nothing to Disclose

1576 | THE LONG-TERM PROGNOSTIC EFFECTS OF CAFFEINE INTAKE IN PATIENTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE: AN ANALYSIS OF THE NHANES DATABASE

David Lee[1] *Youngjae Cha*[1] *Mohammed Shaik*[1] *Nishat Anjum Shaik*[1] *Sharmitha Yerneni*[2] *Ki Jung Lee*[2] *Nathalie Urrunaga*[1]

[1]*University of Maryland School of Medicine,* [2]*Tufts School of Medicine*

Background: Lifestyle and dietary factors are closely linked to the development and progression of metabolic dysfunction-associated steatotic liver disease (MASLD). Among these factors, caffeine consumption has garnered attention as a potential prognostic indicator of MASLD outcomes. This study aims to investigate how different levels of caffeine intake affect the prognosis and complications experienced by patients with MASLD. **Methods:** Utilizing data from the National Health and Nutrition Examination Survey (NHANES) spanning from 2009 to 2018, patients diagnosed with MASLD were examined across various levels of caffeine intake. Participants were grouped into quartiles based on their average caffeine intake over a two-day period, with Quartile 1 serving as the reference group. Quartile divisions were as follows: Quartile 1 (≤25.5 mg/day), Quartile 2 (25.5 to ≤91 mg/day), Quartile 3 (>91 to ≤191.38 mg/day), and Quartile 4 (>191.38 mg/day). Univariate Cox regression analysis was utilized to assess all-cause mortality as the primary outcome across these quartiles. Secondary outcomes including mortality from cardiometabolic causes, including cardiovascular, neurovascular, and diabetes-related events, were similarly analyzed. **Results:** A total of 4,202 individuals with MASLD were stratified into quartiles based on their caffeine intake (Q1: 986, Q2: 1,007; Q3: 1,064; Q4: 1,145). Patients with the highest caffeine intake in Q3 and Q4 were older (48.10 vs. 47.90 vs. 50.20 vs. 53.30 years, p<0.001) and a higher proportion male (44.42% vs. 46.08% vs. 51.22% vs. 60.61%, p<0.001). No significant correlation was observed between daily caffeine consumption and all-cause mortality across all quartiles, with incidence rates of 0.88 per 1000 person-years in Q1, 0.82 in Q2 (cHR 1.33, 95%CI 0.79-2.25, p=0.29), 0.76 in Q3 (cHR 0.91, 95%CI 0.51-1.62, p=0.74), and 0.88 in Q4 (cHR 0.86, 95%CI 0.49-1.50, p=0.59. Furthermore, there was no significant correlation between caffeine intake and specific causes of mortality. **Conclusion:** Contrary to previous studies suggesting a protective

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role of caffeine in MASLD progression and fibrosis regression, this analysis found no significant association between caffeine consumption patterns and mortality outcomes in MASLD patients. The reported benefits of caffeine on fibrosis regression in earlier studies may be attributed to non-caffeine components. Further research is warranted to elucidate the intricate relationship between caffeine intake and MASLD prognosis.

Figure 1: Comparison of patient survival using different caffeine intake among patients with and without MASLD: 120-month analysis

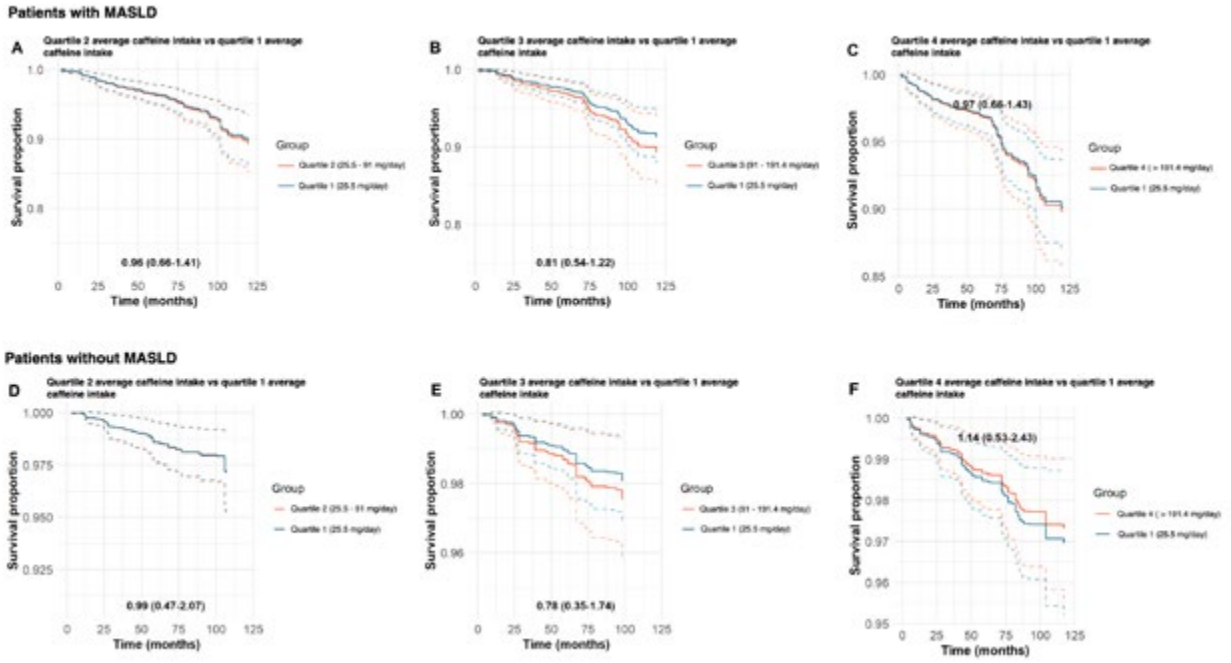

Figure 1 illustrates the patient survival curves over 120 months, stratified by quartiles of average caffeine intake levels. Graphs (A), (B), and (C) show the survival proportions of MASLD patients by each quartile of average caffeine intake over a 120-month period. Graphs (D), (E), and (F) display the survival proportions of patients without MASLD, also stratified by quartiles of average caffeine intake over 120 months.

Disclosures: David Lee: Nothing to Disclose, Youngjae Cha: Nothing to Disclose, Mohammed Shaik: Nothing to Disclose, Nishat Anjum Shaik: Nothing to Disclose, Sharmitha Yerneni: Nothing to Disclose, Ki Jung Lee: Nothing to Disclose, Nathalie Urrunaga: Nothing to Disclose

1577 | NATIONAL TRENDS IN THE COSTS ASSOCIATED WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE-RELATED ADMISSIONS STRATIFIED BY PATIENT DEMOGRAPHICS: AN ANALYSIS OF US HOSPITALS

David Lee[1] Sharmitha Yerneni[2] Mohammed Shaik[1] Youngjae Cha[1] Ki Jung Lee[2] Gregory Fan[2] Hannah Chou[2] Harrison Chou[2] Nathalie Urrunaga[3]

[1]University of Maryland School of Medicine, [2]Tufts School of Medicine, [3]University of Maryland, Baltimore

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is the fastest-growing cause of liver cancer and a leading indication for transplantation, often requiring inpatient care. We stratify MASLD admissions by demographics and graph trends using a hospital-weighted analysis to monitor the cost burden. **Methods:** The 2016-2019 National Inpatient Sample was used to select MASLD admissions. Patients were categorized into demographic strata of age, sex, and race. Inflation-adjusted charge-to-cost ratios were derived and converted to annual total and mean admission costs, then graphed across the years for each strata. R^2 and p-values were extracted for each trend. **Results:** All cost calculations have R^2 and p-values noted in parentheses as (R^2, p). Combining all strata, annual total costs (in million dollars) from 2016 to 2019 were: 5302.47, 5875.49, 6623.19, 7739.50 (0.98, 0.01). By age; 18-34y: 482.10, 532.78, 607.36, 710.57 (0.98, 0.01). 35-49y: 1115.52, 1205.95, 1347.47, 1557.81 (0.97, 0.02). 50-64y: 2035.52, 2209.02, 2473.97, 2823.60 (0.98, 0.01). >65y: 1669.32, 1927.75, 2194.40, 2647.51 (0.98, 0.01). By sex; Male: 2481.40, 2748.83, 3192.44, 3716.42 (0.98, 0.01). Female: 2821.00, 3126.66, 3430.76, 4023.08 (0.97, 0.02). By race; White: 3612.94, 3966.17, 4410.17, 5134.35 (0.97, 0.01). Black: 486.05, 534.28, 601.56, 706.51 (0.97, 0.02). Hispanic: 828.32, 925.76, 1109.98, 1322.31 (0.98,

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0.01). Asian or Pacific Islander (API): 146.74, 180.57, 202.81, 240.37 (0.99, 0.004). Other: 228.42, 268.71, 298.67, 335.97 (1.00, 0.001). The following were the mean annual costs (in dollars). By age; 18-34y: 12525.41, 12541.99, 12488.10, 12805.45 (0.49, 0.30). 35-49y: 13087.64, 12878.53, 12943.40, 13508.03 (0.37, 0.39). 50-64y: 15030.63, 14844.56, 14714.16, 15320.28 (0.12, 0.64). >65y: 14910.64, 14959.44, 14613.72, 15447.74 (0.22, 0.53). By sex; Male: 14886.50, 14812.91, 14930.14, 15477.67 (0.64, 0.20). Female: 13800.60, 13699.92, 13338.34, 14047.57 (0.03, 0.83). By race; White: 13795.12, 13785.80, 13655.24, 14298.43 (0.39, 0.37). Black: 13948.99, 13782.58, 13593.15, 14244.06 (0.11, 0.67). Hispanic: 15843.90, 15056.67, 15039.36, 15764.34 (0.01, 0.92). API: 18598.50, 18947.71, 19159.98, 19629.96 (0.98, 0.01). Other: 16097.01, 16469.97, 15375.77, 15485.81 (0.53, 0.27). **Conclusion:** The financial burden of MASLD-related hospitalizations has increased universally, regardless of age, sex, or race. This underscores the need for more cost-effective modes of care.

Figure 1a. Inflation-adjusted Total Costs Stratified by Age, Sex and Race in Patients With MASLD

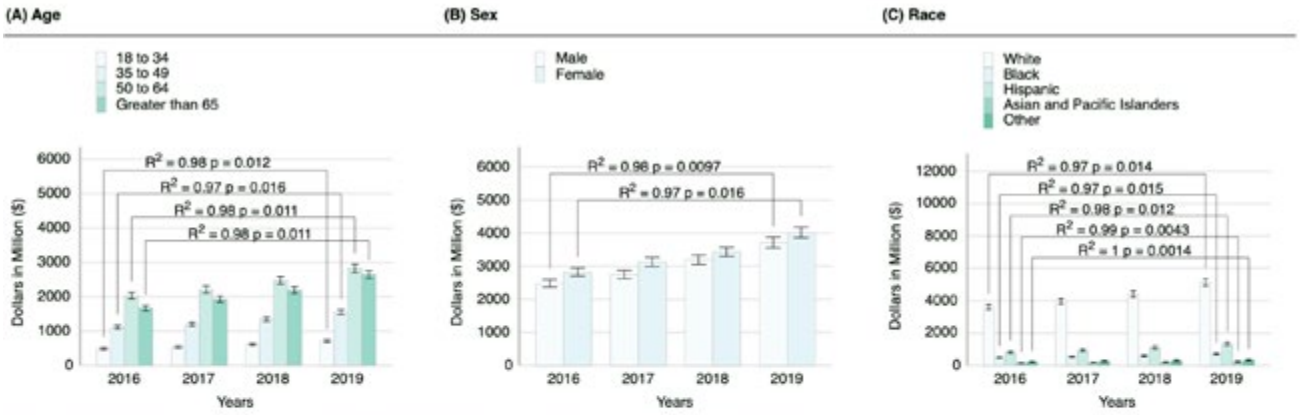
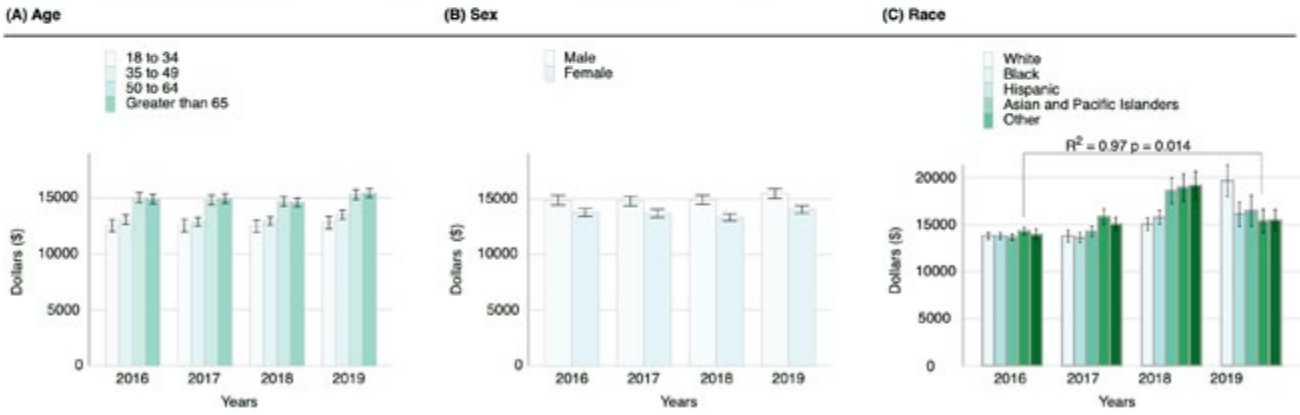


Figure 1b. Inflation-adjusted Mean Costs Stratified by Age, Sex and Race in Patients With MAFLD



The figures above show the total and mean costs of MASLD between 2016 and 2019. Each row stratifies the total and mean costs by age, sex, and race.

* p < 0.05, ** p < 0.01, *** p < 0.001 compared to the reference (REF) curve

Disclosures: David Lee: Nothing to Disclose, Sharmitha Yerneni: Nothing to Disclose, Mohammed Shaik: Nothing to Disclose, Youngjae Cha: Nothing to Disclose, Ki Jung Lee: Nothing to Disclose, Gregory Fan: Nothing to Disclose, Hannah Chou: Nothing to Disclose, Harrison Chou: Nothing to Disclose, Nathalie Urrunaga: Nothing to Disclose

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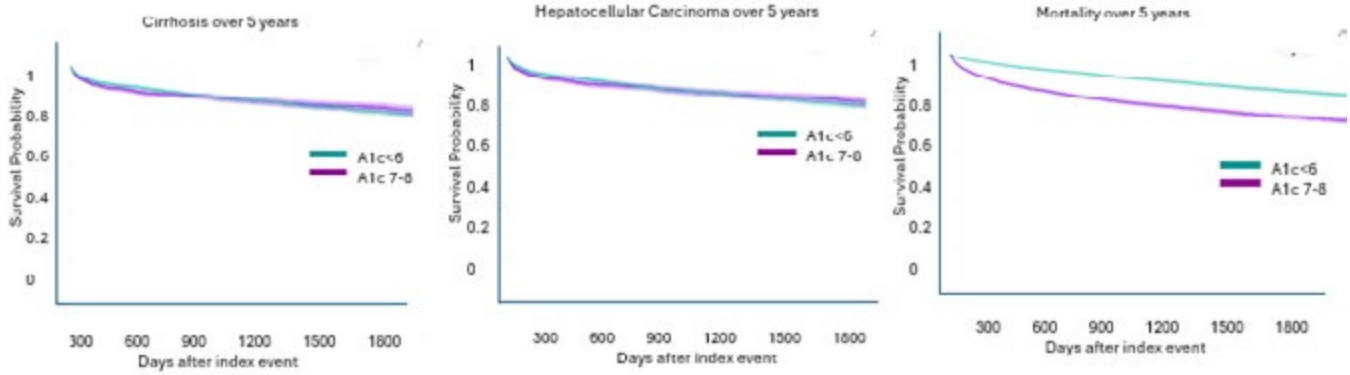
1578 | A1C GOALS RECONSIDERED: LOWER A1C TARGETS CAN IMPROVE PROGRESSION TO CIRRHOSIS DESPITE WORSENING MORTALITY FOR PATIENTS WITH TYPE 2 DIABETES AND MASLD

Saad Ahmed[1] *Aditya Sood*[1] *Maham Ghani*[1] *Sanjaya Satapathy*[1]

[1]*Northwell Health-NSLIJ*

Background: Metabolic associated steatotic liver disease (MASLD) is a common liver disease that has been on the rise. One of the diagnostic criteria of MASLD includes either a diagnosis of diabetes, treatment of diabetes, or an a1c at least 5.7%. Despite the role of a1c in diagnosing MASLD, there is limited literature to suggest effects of a1c targets for these patients. Therefore, the objective of this study is to explore different a1c targets in patients with a diagnosis of type 2 diabetes mellitus (T2DM) and MASLD over five years for progression to cirrhosis, hepatocellular carcinoma (HCC), and overall mortality. **Methods:** This was a retrospective cohort study conducted using the TriNetX database and the US Collaborative Network, which includes healthcare information records from 60 healthcare organizations. Two cohorts were generated for patients with both MASLD and T2DM: group 1 (G1) consisted of patients that had a1c only less than 6 in the five year period, and group 2 (G2), which included patients with a1c levels only between 7-8 in the five year period. These cohorts were propensity matched to age of diagnosis, sex, race, BMI, and comorbidities. This yielded two cohorts with each consisting of 6,603 patients who were followed for five years and analyzed to determine the risk of developing cirrhosis, HCC, and overall mortality. **Results:** At the end of the five year period, 331 patients in G1 developed cirrhosis compared to 587 in G2. The risk difference was 2.1% (p = 0.119) and the risk ratio was 0.85(95% CI: 0.751, 0.966). Additionally, 178 G1 patients were diagnosed with HCC versus 202 in G2 yielding a risk difference of –0.274% (p = 0.33) and a risk ratio of 0.908(95% CI: 0.744, 1.107). In examining mortality, 1,605 G1 patients experienced death compared to 1,058 in the G2. The risk difference was 7.8% (p<0.0001) and the risk ratio was 1.526 (95% CI: 1.422,1.637). **Conclusion:** Our findings reveal a significant improvement in cirrhosis for the group with an a1c goal less than 6, which intuitively is due to reduced insulin resistance and oxidative stress on the liver. At the same time, the data suggests improved mortality for the group with a1c goal of 7-8. This aligns with previous literature, such as the ACCORD trial, which showed tight glycemic control could increase mortality. This may be due to a reduction in hypoglycemic events and polypharmacy. Lastly, there was no significant difference for progression to HCC between the two groups. Overall, the data does not identify consistent a1c targets and interpretations should be cautious. Further investigation is warranted to reveal the mechanism of these results. Future directions can also examine specific agents used in glycemic control to mitigate the progression of MASLD.



Disclosures: Saad Ahmed: Nothing to Disclose, Aditya Sood: Nothing to Disclose, Maham Ghani: Nothing to Disclose, Sanjaya Satapathy: Gilead Sciences: Grant/Research Support, Durect Pharma: Grant/Research Support, Fibronostics: Grant/Research Support, Novartis: Grant/Research Support, Zydus Pharma: Grant/Research Support, Boehringer Ingelheim: Grant/Research Support, Intercept Pharma: Grant/Research Support

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1579 | UNLOCKING THE HEART-LIVER CONNECTION: EXPLORING DIASTOLIC HEART FAILURE RISK IN MASLD PATIENTS DEVOID OF CARDIOVASCULAR HISTORY ◆

Haya Omeish[1] Farah Haddadin[2] Rana Omeish[2] Suhail Haddadin[3]

[1]Henry Ford health, [2]Faculty of Medicine at the University of Jordan, [3]University of Minnesota

Background: MASLD, ranging from nonalcoholic fatty liver to MASH, shares metabolic risk factors with CVD, which is the leading cause of death in MASLD patients. While the association between MAFLD and heart failure with reduced ejection fraction (HFrEF) is established, the link with HFpEF is emerging, yet evidence remains scarce. This study aims to explore the risk and predictors of new-onset heart failure with preserved ejection fraction (HFpEF) in patients with a history of MASH but without prior CVD. **Methods:** This study analyzed data from 81,309 MASH patients from the 2016 National Inpatient Sample (NIS) to examine adult patients (>18 years) diagnosed with MASH. Patients with prior coronary artery disease and heart failure were excluded. Using ICD-10 codes, new-onset heart failure with preserved ejection fraction (HFpEF) was identified as the primary disease leading to hospitalization in MASLD patients without prior CVD. Demographics, baseline characteristics, and comorbidities were compared between MASH patients with and without new-onset HFpEF. The study also investigated predictors of new-onset HFpEF in MASH patients without prior CVD, utilizing multivariate analysis to adjust for various factors including age, gender, race, comorbidities, and hospital characteristics. STATA software was employed for statistical analyses. **Results:** In this retrospective study, 71.1% of patients lacked prior CVD and were analyzed. New-onset HFpEF occurred in 1.1% (n=645) of these patients (OR 1.2 [1.01 to 1.44], P=0.042). Comparatively, those with new-onset HFpEF were older (65.7 ±0.9 vs 58 ±0.2, P<0.001), predominantly female (75.9% vs 64.2%, P=0.008), and had a higher percentage of white race (P=0.016). They were also more likely to have dyslipidemia (39.5% vs 28.6%, P=0.005), CKD (38.7% vs 18.5%, P<0.001), OSA (34.9% vs 15.5%, P=0.001), and AF (20.7% vs 4.6%, P<0.001) as seen in Table-1. Multivariate analysis revealed older age (Coef. 1.03 per year [1.01 to 1.05], P<0.001), female gender (OR 2.1 [1.34 to 3.24], P=0.001), Native American race (OR 3.0 [1.22 to 7.48], P=0.017), OSA (OR 3.1 [2.01 to 4.63], P<0.001), AF (OR 3.7 [2.31 to 5.94], P<0.001), and CKD (OR 1.9 [1.16 to 3.21], P<0.001) as predictors of new-onset HFpEF in MASH patients without prior CVD as seen in Table-2. **Conclusion:** The current study demonstrated an association between MASH and new-onset HFpEF in patients without a prior history of CVD. Predictors of developing HFpEF in patients with MASH include older age, female gender, Native American race, history of AF, OSA, and CKD. Such findings highlight the importance of risk factor recognition and identification of susceptible groups in patients with MASH who are at risk of developing HFpEF. The growing body of evidence demonstrating the association between both diseases calls for further investigations to well establish the mechanism, risk factors, and morbidity of HFpEF in patients with MASH.

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	onset HFpEF (N=57,140)	onset HFpEF (N=645)	
Mean age	58 ±0.2	65.7 ±0.9	<0.001
Female	36.694 (64.2%)	490 (75.9%)	0.008
Race/ethnicity • White • Black • Hispanic • Asian or pacific islander • Native American • Other	 41,604 (72.8%) 2,430 (4.3%) 7,489 (13.1%) 870 (1.5%) 735 (1.3%) 4,012 (7%)	 525 (81.4%) 15 (2.3%) 45 (6.9%) - 25 (3.9%) 35 (5.5%)	0.016
Hospital location/teaching status: • Rural • Urban nonteaching • Urban teaching	 4,510 (7.9%) 11,954 (20.9%) 40,675 (71.2%)	 75 (11.6%) 125 (19.4%) 445 (69%)	0.309
Hospital bed-size • Small • Medium • Large	 8,799 (15.4%) 14,625 (25.6%) 33,716 (59%)	 146 (22.6%) 144 (22.3%) 355 (55.1%)	0.077
Dyslipidemia	16,350 (28.6%)	255 (39.5%)	0.005
Diabetes mellitus	17,164 (30%)	195 (30.2%)	0.963
Hypertension	24,644 (43.1%)	219 (33.9%)	0.044
Chronic kidney disease	10,594 (18.5%)	250 (38.7%)	<0.001
Tobacco use	6,149 (10.8%)	44 (6.8%)	0.166
Obesity	9.139 (15.9%)	69 (10.7%)	0.112
Obstructive sleep apnea	8,869 (15.5%)	225 (34.9%)	0.001
Atrial fibrillation	2,630 (4.6%)	134 (20.7%)	<0.001

Table 2: Multivariate analysis for the predictors of new onset HFpEF in patients with NASH without prior history of CVD.

Predictors of new HFpEF in NASH	Adjusted OR	P value
Age (OR per year of age)	1.03 [1.01 to 1.05]	<0.001
Female	2.1 [1.34 to 3.24]	0.001
Native American race	3.0 [1.22 to 7.48]	0.017
Obstructive sleep apnea	2.1 [1.01 to 4.63]	<0.001

Disclosures: Haya Omeish: Nothing to Disclose, Farah Haddadin: Nothing to Disclose, Rana Omeish: Nothing to Disclose, Suhail Haddadin: Nothing to Disclose

1580 | UNVEILING THE HIDDEN CONNECTION: EXPLORING THE INTERPLAY BETWEEN PERICARDITIS AND METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS (MASH)

Lisnaldy Ramirez[1] Wendy Garzon-Siatoya[2] Khalid Home[1] Arnold Nongmoh Forlemu[3] Praneeth Bandaru[4] Camelia Ciobanu[4] Ali Wakil[4] Raissa Nana Sede Mbakop Forlemu[5] Vura Naga Venkata Rama Krishna[6] Neha Sharma[6]

[1]St.Barnabas, [2]St. Barnabas, [3]Broonkly Hospital, [4]Brooklyn Hospital, [5]Piedmont Athens Regional, [6]UTHealth Houston

Background: Metabolic dysfunction-associated steatohepatitis (MASH), previously known as nonalcoholic steatohepatitis (NASH), is a severe form of metabolic dysfunction-associated steatotic liver disease (MASLD) that can lead to liver cirrhosis. Its incidence has risen significantly in the US over the past decade, and it is affecting over 115 million adults worldwide. Although MASH is the fastest-growing cause of hepatocellular carcinoma and a leading reason for liver transplantation in the US, cardiovascular diseases remain the most common cause of death in MASH and MASLD patients. Similar to NASH, pericarditis, characterized by inflammation of the pericardium, is also prevalent. Despite potential overlapping pathophysiological mechanisms, the relationship between MASH and pericarditis is underexplored. We aim to explore the association between MASH and pericarditis in a nationwide cohort. **Methods:** Data collected from the Nationwide Inpatient Sample (NIS) from

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2017 to 2020 was analyzed. All cases of NASH and pericarditis were identified using the appropriate International Classification of Diseases (ICD) codes. Chi-square test was used to compare characteristics of the two cohorts. Multivariable logistic regression analyses adjusted for age, sex, race, insurance status, median household income, hospital location, teaching status, and the Charlson Comorbidity index were employed to predict in-hospital mortality. Unweighted data from NIS were multiplied with appropriate discharge and hospital-level weights to represent the population across the US. **Results:** Data collected from the Nationwide Inpatient Sample (NIS) from 2017 to 2020 was analyzed. All cases of NASH and pericarditis were identified using the appropriate International Classification of Diseases (ICD) codes. Chi-square test was used to compare characteristics of the two cohorts. Multivariable logistic regression analyses adjusted for age, sex, race, insurance status, median household income, hospital location, teaching status, and the Charlson Comorbidity index were employed to predict in-hospital mortality. Unweighted data from NIS were multiplied with appropriate discharge and hospital-level weights to represent the population across the US. **Conclusion:** Among all adult patients admitted to US hospitals between 2017 and 2020 with a primary diagnosis of pericarditis with and without NASH, the Mortality rate is slightly higher in patients with NASH. The difference could be even higher if the providers added NASH to the list of diagnoses when a patient gets admitted to the hospital.

Disclosures: Lisnaldy Ramirez: Nothing to Disclose, Wendy Garzon-Siatoya: Nothing to Disclose, Khalid Home: Nothing to Disclose, Arnold Nongmoh Forlemu: Nothing to Disclose, Praneeth Bandaru: Nothing to Disclose, Camelia Ciobanu: Nothing to Disclose, Ali Wakil: Nothing to Disclose, Raissa Nana Sede Mbakop Forlemu: Nothing to Disclose, Vura Naga Venkata Rama Krishna: Nothing to Disclose, Neha Sharma: Nothing to Disclose

1581 | NEUTROPHIL EXTRACELLULAR TRAP SCORES PREDICT 90-DAY MORTALITY IN HEPATITIS B-RELATED ACUTE-ON-CHRONIC LIVER FAILURE

Yi Zhang[1] *Ke Shi*[1] *Xianbo Wang*[1]

[1]*Beijing Ditan Hospital*

Background: Hepatitis B virus-related acute-on-chronic liver failure (HBV-ACLF) is associated with a pronounced systemic inflammatory response. A key component of this response, Neutrophil Extracellular Traps (NETs), which are formed by neutrophils, have a potent pro-inflammatory capability. The primary objective of this study is to establish NETs-related scoring system in patients with HBV-ACLF. **Methods:** A prospective training cohort of 81 patients was included at the Beijing Ditan Hospital. The concentrations of NETs markers (cell-free DNA[cf-DNA], myeloperoxidase DNA[MPO-DNA], and citrullinated histone H3[CitH3]) in peripheral blood were quantified. Random survival forest, LASSO regression, multivariate Cox regression were used to identify prognostic factors associated with 90-day mortality in ACLF patients, and to develop a nomogram for visualization. These results were evaluated in the validation cohort (n=40). **Results:** NETs related markers were significantly increased in death group compared with survival ($p < 0.05$). The NETs-score was constructed by combining MPO-DNA, neutrophil to lymphocyte ratio, and age. This score's diagnostic efficacy was assessed using the Area Under the Receiver Operating Characteristic Curve, yielding values of 0.83 in the training set and 0.77 in the validation set, markedly surpassing those of other established models ($p < 0.05$). Within both the training and validation groups, the observed 90-day mortality rates were 88.8% and 75.0%, respectively, for patients categorized as high-risk, and 18.0% and 12.5% for those classified as low-risk. Conclusions: A NETs-score was developed to predict the 90-day mortality rate of HBV- ACLF patients. The scoring system helps in more accurate stratification of HBV-ACLF patients, and high-risk patients require close monitoring. **Conclusion:** NETs are emerging as potentially predictive biomarkers of 90-day mortality in patients with HBV-ACLF. Models that include NETs, which reflect neutrophil activation and extensive inflammatory responses in the body, are better predictors of short-term mortality than other models. According to this NET-related scoring system, the 90-day mortality rate of high-risk patients can reach 88%. This will assist clinicians in early patient stratification and management, thereby allowing the formulation of therapeutic strategies to improve patient outcomes.

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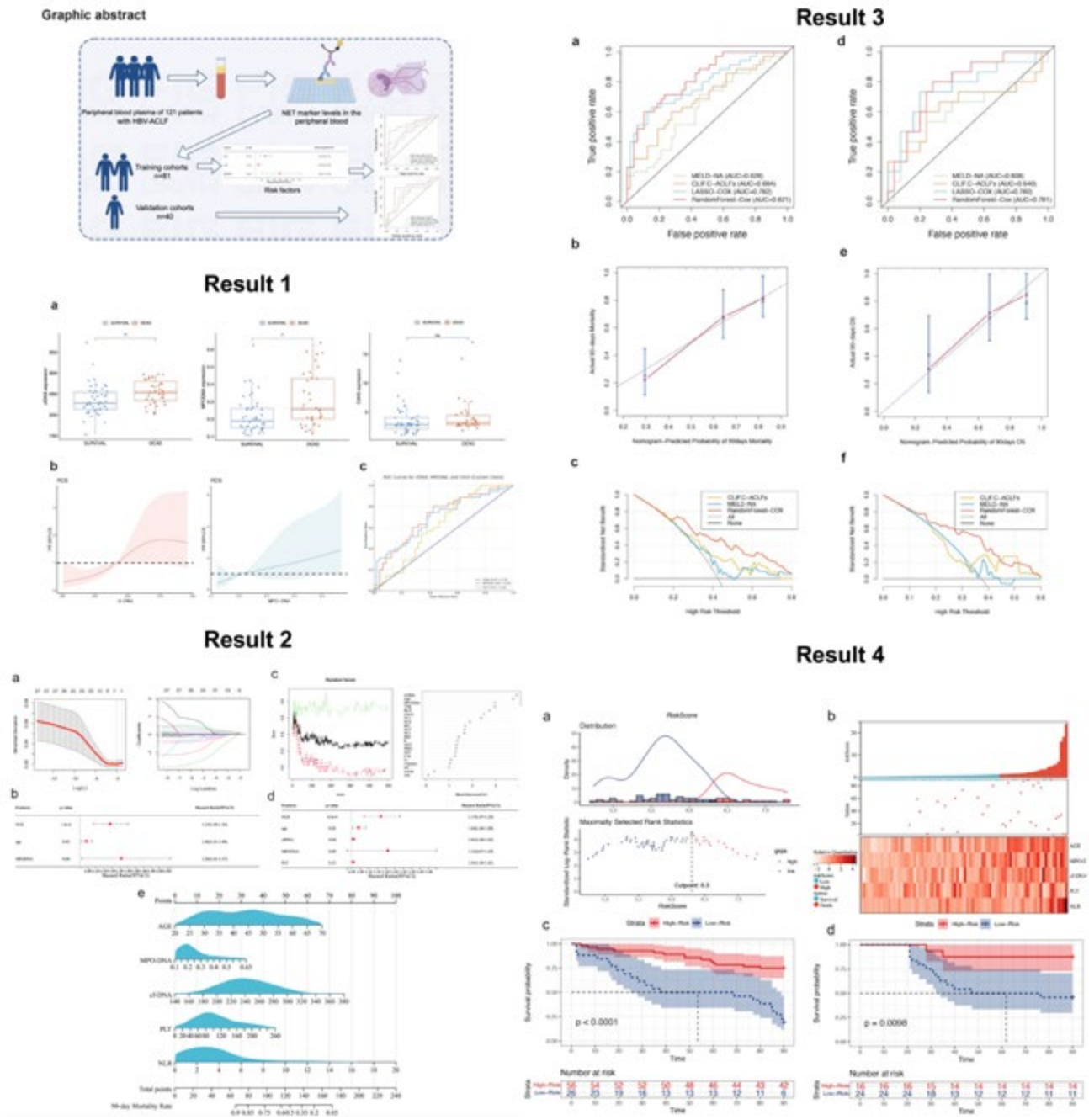

Disclosures: Yi Zhang: Nothing to Disclose, Ke Shi: Nothing to Disclose, Xianbo Wang: Nothing to Disclose

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1582 | ACTEIN INHIBITS NETOSIS IN ACUTE-ON-CHRONIC LIVER FAILURE BY TARGETING THE MAC-1/RHOA GTPASE/PAD4 AXIS ◆

Yi Zhang[1] *Xianbo Wang*[2] *Fangyuan Gao*[2] *Ke Shi*[2]

[1]*Beijing Ditan Hosptial,* [2]*Beijing Ditan Hospital*

Background: Acute-on-chronic liver failure (ACLF) is associated with a grim prognosis due to its complex pathogenesis, which remains inadequately understood, and the absence of efficacious therapeutic options. This study sheds light on the mechanism by which the release of neutrophil extracellular traps (NETosis) plays a role in the progression of ACLF and evaluates the therapeutic efficacy of Actein, a compound sourced from the Chinese herb cohosh, in reducing liver injury by hindering NETosis. **Methods:** This study assessed the production of neutrophil extracellular traps (NETs) in the peripheral blood and liver tissues of ACLF patients and in mouse models, illustrating Actein's capacity to suppress NETosis in mouse models and in isolated primary neutrophils. Employing a thorough analysis combining single-cell RNA sequencing (scRNA-seq) and RNA sequencing (RNA-seq), we delved into the NETs formation pathways and uncovered Actein's mechanism of action. The study further substantiated these mechanisms and Actein's liver-protective effects through a series of in vivo and in vitro experiments. **Results:** In this study, NETs were observed to be significantly elevated in both the peripheral blood and liver tissues of patients with ACLF and in model mice, a condition that correlated with the severity of the liver failure. Interventions aimed at depleting neutrophils or degrading NETs were found to mitigate liver injury, indicating a critical role of NETs in the exacerbation of liver damage. Further investigations revealed that activation of the neutrophil surface beta2 integrin (Mac1) and its enhanced interaction with the ligand ICAM1 occurred during liver failure, facilitating the process of NETosis. RNA sequencing (RNA-seq) analysis highlighted a significant enrichment of neutrophil differential genes in the GTPase Rho pathway, with RhoA GTPase identified as playing a central role in the reorganization of the neutrophil cytoskeleton, enhancing peptidylarginine deiminase 4 (PAD4)-mediated NETs release. Actein was found to attenuate the process of NETosis by specifically targeting the Mac1/RhoA-GTPase/PAD4 axis within neutrophils, offering a protective effect against liver failure. This discovery underlines the potential of Actein as a therapeutic agent in the management of ACLF by inhibiting a critical pathway involved in NETs formation and release, thereby reducing liver injury. **Conclusion:** Our study underscores the pivotal function of NETosis in the etiology of acute-on-chronic liver failure (ACLF) and unveils Actein as an innovative therapeutic compound with the capacity to mitigate liver injury by curtailing NETosis. Actein emerges as a promising drug for inclusion in therapeutic regimens targeting ACLF in the future.

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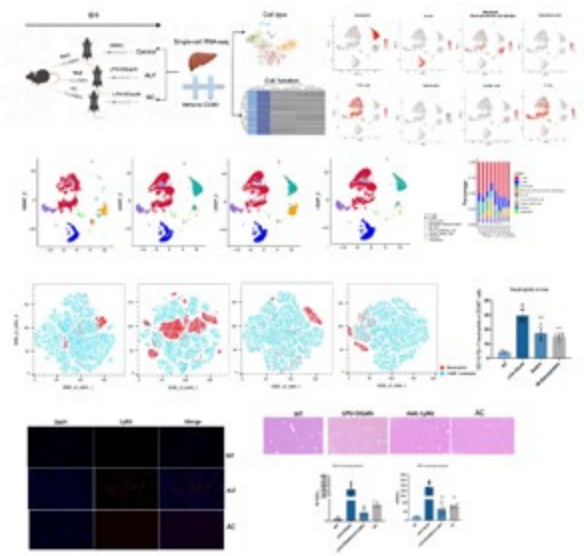
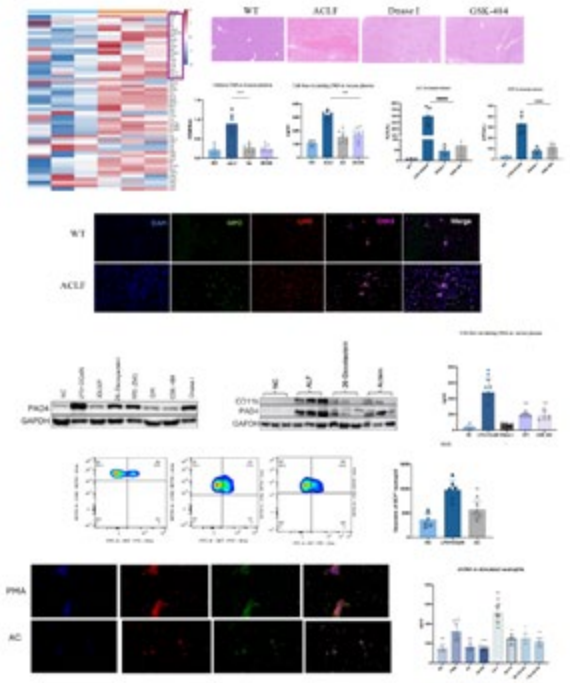
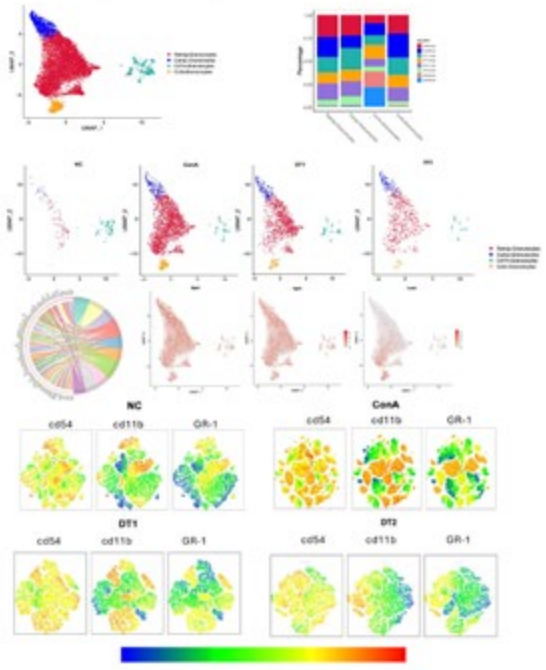
Results 1 Actein mitigates hepatic damage through the attenuation of neutrophil-mediated inflammation.



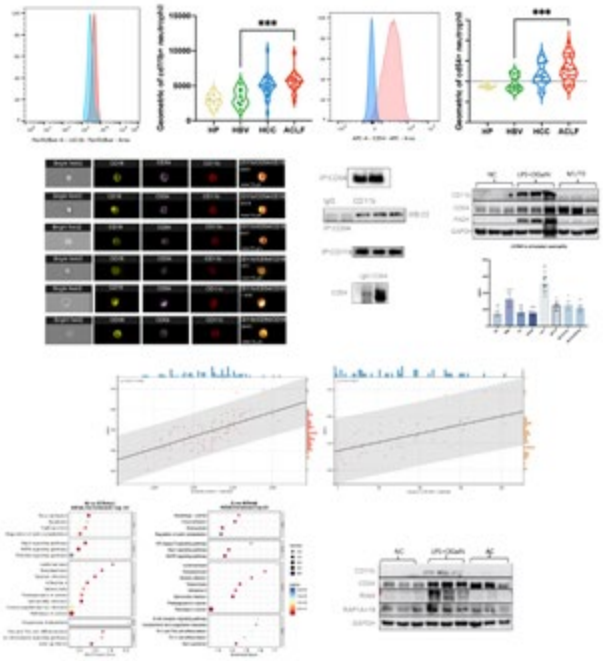
Results 2 Actein mitigates hepatic injury by targeting and suppressing the formation of neutrophil extracellular traps.



Results 3:The release of Neutrophil Extracellular Traps (NETs) correlates with the interaction of neutrophil Mac-1 integrin and ICAM-1 ligand.



Results 4:Actein disrupts the interaction between Mac-1 and ICAM-1, and inhibits the activation of RhoA-GTPase.



Disclosures: Yi Zhang: Nothing to Disclose, Xianbo Wang: Nothing to Disclose, Fangyuan Gao: Nothing to Disclose, Ke Shi: Nothing to Disclose

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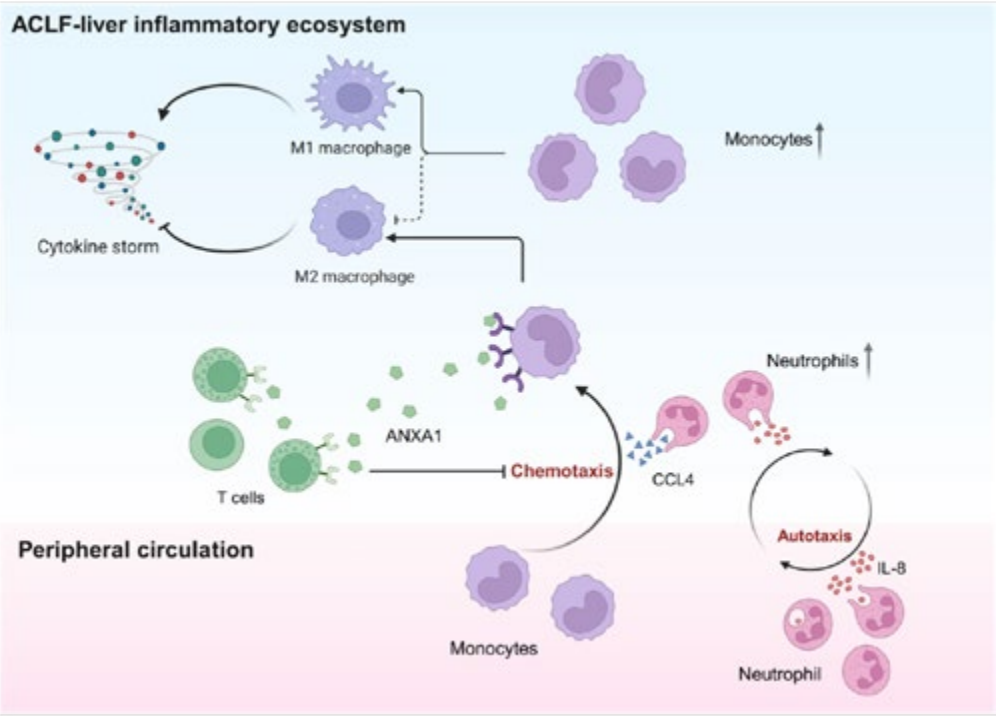
1583 | DISSECTING LIVER INFLAMMATION ECOSYSTEM IDENTIFIES ANNEXIN A1 AS A PRO-RESOLVING TARGET FOR LIVER FAILURE ◆

Xia Yu[1] Weihong Tian[2] Xuanwen Bao[3] Xianbin Xu[3] Huilan Tu[3] Jiyang Chen[3] Yida Yang[3] Jifang Sheng[3] Yu Shi[3]

[1]The First Affiliated Hospital, Zhejiang University, [2]Jiangsu University, [3]Zhejiang University

Background: Patients who do not recover from liver failure have non-resolving liver inflammation. This study utilized multi-omics technologies to characterize the liver inflammation ecosystem and identify potential therapeutic targets for resolving hepatic inflammation in liver failure. **Methods:** Single-cell sequencing, spatial gene expression and multiple immunohistochemistry (mIHC) were performed on liver explants from patients with acute-on-chronic liver failure (ACLF), acute liver failure (ALF), decompensated cirrhosis (DC), and disease controls to disssect cellular heterogeneity, differentiaion and distribution. Candidate targets were inferred by a analysis of ligand-receptor interaction between cells. The efficacy of therapeutic targets was tested both in vitro and in vivo experiments. **Results:** A subset of neutrophils expressing CCL4 that recruit blood monocytes was enriched in ACLF and ALF-liver. And there was a significant accumulation of inflammatory S100A9+ monocytes and TREM2+ scar-phenotypic macrophages, contrasted by a depletion of LYVE1+ Kupffer-like macrophages within ACLF and ALF-liver. A differentiation path from S100A9+ monocytes to TREM2+ macrophages, and ultimately to LYVE1+ macrophages, was marked by a spatial transition from peri-lobular to lobular regions within the liver. There is a spatial proximity between S100A9+ monocytes and T cells located at peri-lobule area. And ANXA1-FPR1 was predicted to be a significant interactive module between monocytes/macrophages and T cells, particularly in ACLF patients. Plasma and hepatic ANXA1 levels were both significantly higher in patients with ACLF compared to DC and controls and correlated with disease severity. In vitro, the ANXA1 peptide, Ac2-26, inhibited CCL4-mediated chemotaxis of peripheral monocytes and prevented M0 to M1 polarization in THP-1 and Raw264.7 cell lines. It also reduced the expression of pro-inflammatory cytokines such as IL-8, IL-6, and TNF-α. The in vitro effect of Ac2-26 was partially blocked by Randialic acid B, a FPR1 receptor inhibitor. Intraperitoneal injection of Ac2-26 (i.v. 4mg/kg) improved survival and liver function in ALF mice models induced by LPS (i.p. 5ug/kg) + D-GaIN (i.p. 400mg/kg) or Con A (i.v. 12mg/kg), as well as a ACLF mice model induced by CCL4 (10%-15% CCL4 0.6ml/kg biw by gavage for 8 weeks) and LPS (i.p. 5ug/kg) + D-GaIN (i.p. 400mg/kg). A significant reduction in monocyte-macrophage infiltration and a reversal of M1 to M2 macrophage phenotype were observed in these models. **Conclusion:** Our findings showed the complex interplay among neutrophils, monocytes/macrophages, and T cells that either sustain or resolve hepatic inflammation in liver failure. Importantly, ANXA1 emerges as a therapeutic target with potential to modulate monocyte/macrophage infiltration and polarization.



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Disclosures: Xia Yu: Nothing to Disclose, Weihong Tian: Nothing to Disclose, Xuanwen Bao: Nothing to Disclose, Xianbin Xu: Nothing to Disclose, Huilan Tu: Nothing to Disclose, Jiyang Chen: Nothing to Disclose, Yida Yang: Nothing to Disclose, Jifang Sheng: Nothing to Disclose, Yu Shi: Nothing to Disclose

1584 | THE USE OF SODIUM-GLUCOSE COTRANSPORTER-2 INHIBITORS (SGLT2-I) IN ADDITION TO FUROSEMIDE AND SPIRONOLACTONE IN PATIENTS WITH DECOMPENSATED CIRRHOSIS: AN INTERNATIONAL ANALYSIS ◆

Mark Ayoub[1] Carol Faris[2] Medha Rajamanuri[3] Harleen Chela[4] Nadeem Anwar[4] Ebubekir Daglilar[4] Julton Tomanguillo Chumbe[4]

[1]West Virginia University - Charleston Area Medical Center, [2]Bayonne Medical Center, [3]Southern Illinois University, [4]WVU-CAMC

Background: Patients with cirrhosis often have portal hypertension which can lead to ascites and volume overload. Patients with cirrhosis are often prescribed a diuretic regimen consisting of furosemide and spironolactone. Starting with both drugs appears to be the preferred approach in achieving natriuresis and maintaining normokalemia according to the American Association of the Study of Liver Disease (AASLD) practice guidelines. The use of SGLT2-I in patients with heart failure or kidney dysfunction has promising results and improving outcomes and mortality. This makes their use in addition to the standard diuretic regimen in patients with cirrhosis, an unexplored avenue. **Methods:** We queried the Global Collaborative Network from TriNetX deidentified research database. Patients with decompensated cirrhosis receiving standard diuretic therapy of furosemide and spironolactone into two cohorts; first cohort included patients on SGLT2-i (dapagliflozin or empagliflozin), second cohort included patients not on any SGLT2-i. Patients with alcoholic cirrhosis were excluded. Cohorts were matched using a 1:1 propensity-scored matching (PSM) based on patients' characteristics and comorbidities. We compared the rate of new decompensation (ascites requiring paracentesis, upper gastrointestinal bleed, jaundice, hepatic encephalopathy, or hepatorenal syndrome), mortality rate, need for paracentesis and hospital admission at 1, 3, and 6 months. **Results:** A total of 62,491 patients with decompensated cirrhosis on furosemide and spironolactone from April 2004 to April 2024 were identified. Of those, 6.4% (n=4,023) received SGLT2-I (dapagliflozin or empagliflozin) and 93.6% (n=58,459) did not. There was a lower rate of new decompensation at 1 month (28% vs 39.2%, p<0.001), 3 months (38% vs 49.6%, p<0.001), and 6 months (43.6% vs 55.2%, p<0.001) in the group receiving SGLT2-i. Furthermore, patients on SGLT2-I required significantly less paracentesis at 1 month (9.9% vs 14.2%, p<0.001), 3 months (13.1% vs 18.4%, p<0.001), and 6 months (14.9% vs 20.5%, p<0.001) with risk reduction between 4.3% to 5.5%. They also had a significantly lower hospital admission rate at 1 month (36.4% vs 43.8%, p<0.001), 3 months (41,2% vs 48.9%, p<0.001), and 6 months (45% vs 52.4%, p<0.001) with RR of 7.3% to 7.7%. Patients on SGLT2-I also had a lower mortality rate at 1 month (5.5% vs 9.9%, p<0.001), 3 months (11.1% vs 19.2%, p<0.001), and 6 months (15.3% vs 26%, p<0.001). **Conclusion:** The use of SGLT2-I in addition to standard diuretic therapy of spironolactone and furosemide appears to have mortality benefit in patients with decompensated cirrhosis. It also lowered hospital admission over the course of 6 months with less need for paracentesis. They also had lower decompensation events during that timeframe.

	1 month			3 months			6 months		
	SGLT2-I N=4,019	No SGLT2-I N=4,019	p-value	SGLT2-I N=4,019	No SGLT2-I N=4,019	p-value	SGLT2-I N=4,019	No SGLT2-I N=4,019	p-value
Decompensation	28%	39.2%	<0.001 RR 11.1%	38%	49.6%	<0.001 RR 11.7%	43.6%	55.2%	<0.001 RR 11.6%
Admission	36.4%	43.8%	<0.001 RR 7.3%	41.2%	48.9%	<0.001 RR 7.7%	45%	52.4%	<0.001 RR 7.5%
Mortality	5.5%	9.9%	<0.001	11.1%	19.2%	<0.001	15.3%	26%	<0.001
Paracentesis	9.9%	14.2%	<0.001 RR 4.3%	13.1%	18.4%	<0.001 RR 5.2%	14.9%	20.5%	<0.001 RR 5.5%

Disclosures: Mark Ayoub: Nothing to Disclose, Carol Faris: Nothing to Disclose, Medha Rajamanuri: Nothing to Disclose, Harleen Chela: Nothing to Disclose, Nadeem Anwar: Nothing to Disclose, Ebubekir Daglilar: Nothing to Disclose, Julton Tomanguillo Chumbe: Nothing to Disclose

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1585 | SHIFTING OF PBMC TRANSCRIPTOMIC LANDSCAPE FROM ACUTE DECOMPENSATION TO ACUTE-ON-CHRONIC LIVER FAILURE

Jiyang Chen[1] Sisi Yang[2] Zelu Meng[2] Xiaoli Zhang[2] jiangshan Lian[2] Shaorui Hao[2] Hongyu Jia[2] Yinfeng Lu[2] Xiaopeng Yu[2] Yu Shi[2] Lin Zheng[2] Yida Yang[2]

[1]The First Affiliated Hospital, Zhejiang University, [2]Zhejiang University

Background: Acute-on-chronic liver failure (ACLF) is a severe clinical syndrome characterized by multiple organ failures and high short-term mortality, emerging distinctly within the spectrum of cirrhosis, yet separate from acute decompensation (AD). Central to ACLF's pathology is an escalation of systemic inflammation (SI), a process already precedent in patients with decompensated cirrhosis. Despite its clinical significance, the specific inflammatory endotype characterizing SI in ACLF, and how it differs from that in AD, remains poorly understood. This study aimed to elucidate the distinct transcriptomic profiles of peripheral blood mononuclear cells (PBMCs) in AD versus ACLF, providing insights into the underlying molecular mechanisms driving these differential inflammatory responses. **Methods:** PBMCs were isolated from a cohort of 221 patients with AD and cirrhosis, admitted to The First Affiliated Hospital of Zhejiang University during 2022 to 2023. Total RNA was meticulously extracted from these cells and subsequently sequenced on the Illumina HiSeqTM 2500 platform. Comprehensive bioinformatic analyses were employed to delineate cell composition and differential gene expression profiles. These analyses incorporated advanced cell-type deconvolution using CIBERSORT, enabling the identification of enriched pathways and pivotal candidate genes crucial to understanding the pathophysiological underpinnings of cirrhosis in this patient population. **Results:** Transcriptomic analysis differentiated these groups by identifying 552 upregulated and 1155 downregulated genes in ACLF compared to AD. Notable genes such as MPO, CCL24, LYVE1, CD24, VSIG4, AZU1, ANXA3, and CYP4F2 were upregulated, while TPM2, BTLA, MCOLN2, PLD4, LILRA4, PLCE1, and MS4A1 were downregulated, reflecting significant shifts in immune regulation and inflammation. Gene Ontology and pathway enrichment analyses highlighted enhanced systemic responses in ACLF, particularly in immune processes and metabolic pathways. KEGG and Reactome pathways showed activation of complement cascades and neutrophil degranulation, signaling severe disease progression and a robust immune response. These findings suggest distinct molecular signatures in ACLF and AD, offering potential therapeutic targets for improving outcomes in these critically ill populations. **Conclusion:** Our findings elucidate the complex interplay of immune and metabolic pathways in the pathophysiology of cirrhosis complications, with distinct molecular profiles in AD versus ACLF. The distinct pathway activations underscore the potential for developing tailored therapeutic interventions that target these specific molecular processes to improve outcomes in these severely ill patient populations.

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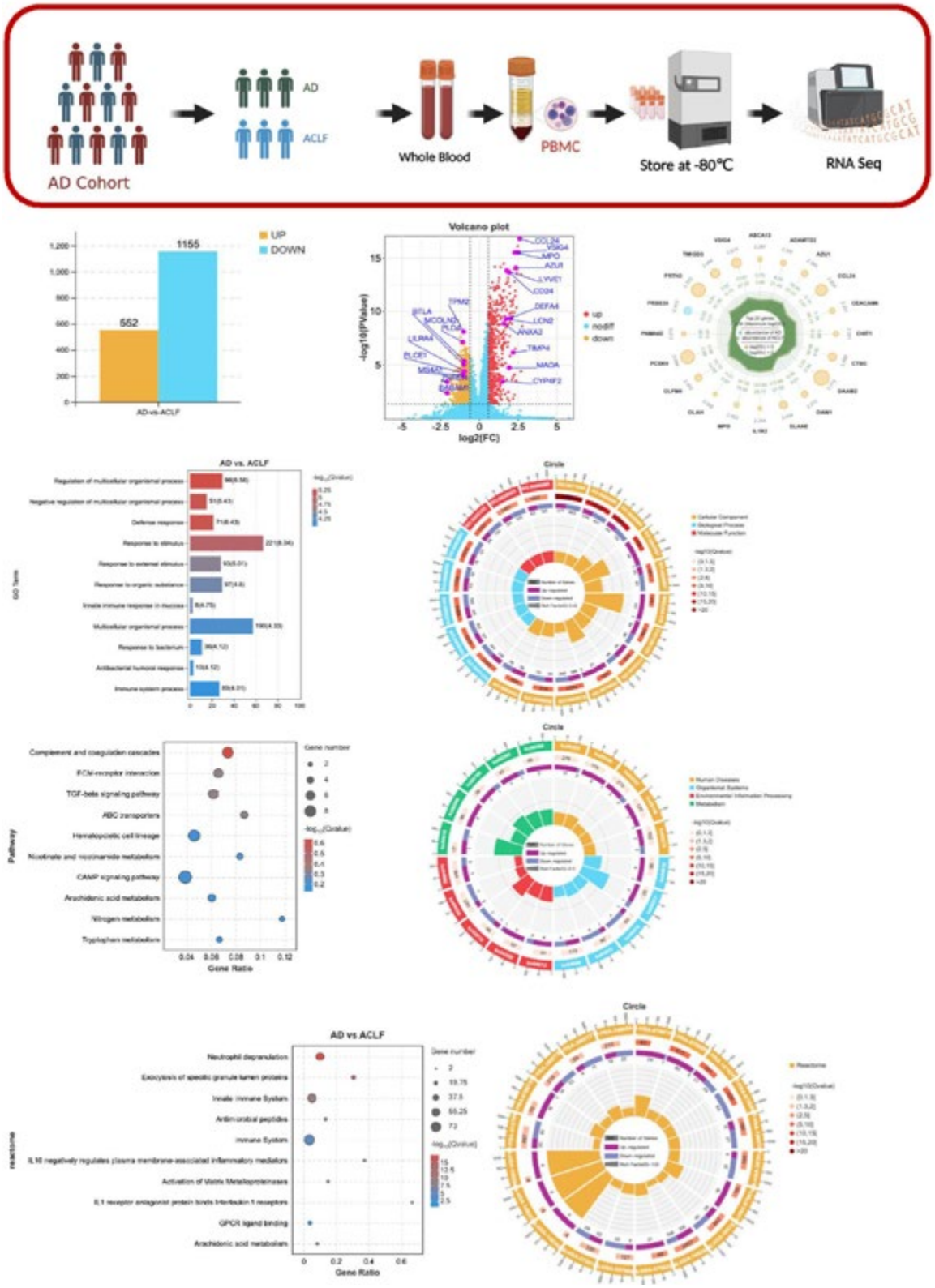

Disclosures: Jiyang Chen: Nothing to Disclose, Sisi Yang: Nothing to Disclose, Zelu Meng: Nothing to Disclose, Xiaoli Zhang: Nothing to Disclose, jiangshan Lian: Nothing to Disclose, Shaorui Hao: Nothing to Disclose, Hongyu Jia: Nothing to Disclose, Yinfeng Lu: Nothing to Disclose, Xiaopeng Yu: Nothing to Disclose, Yu Shi: Nothing to Disclose, Lin Zheng: Nothing to Disclose, Yida Yang: Nothing to Disclose

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1586 | MONOCYTE/MACROPHAGES-DERIVED RESISTIN IS A POTENTIAL THERAPEUTIC TARGET FOR ACUTE-ON-CHRONIC LIVER FAILURE

Xianbin Xu[1] Liang Hong[1] Xia Yu[1] Jiyang Chen[1] Huilan Tu[1] Xiaopeng Wu[1] Yida Yang[1] Yu Shi[1] Jifang Sheng[1]

[1]Zhejiang University School of Medicine

Background: Specified therapy for acute-on-chronic liver failure (ACLF) is still lacking. RESISTIN (*RETN*) has been reported to accumulate in the circulation of patients with end-stage liver diseases. The study aimed to investigate the exact role of resistin in the pathogenesis of ACLF. **Methods:** Single-cell RNA-sequencing (scRNA-seq) was performed on peripheral blood mononuclear cells (PBMCs) [ACLF=9; decompensated cirrhosis (DC)=5; healthy controls=4] and nonparenchymal cells isolated from explanted livers of healthy or diseased controls, DC and ACLF patients (ACLF=6; DC=3; controls=3). The transcripts and protein of RESISTIN in plasma and liver tissues were determined by Bulk-RNA sequencing, spectral flow cytometry, ELISA, and immunohistochemistry. The effect of RESISTIN on ACLF was assessed through resistin-neutralizing antibody blockade and recombinant resistin protein administration in ACLF models induced by CCl4+ ConA/D-GalN and LPS. **Results:** Compared with controls and DC patients, a subset of $RETN^{+}$ monocyte/macrophage was significantly enriched in both ACLF-PBMCs and hepatic immune cells. PBMC transcriptome confirmed upregulation of *RETN* in ACLF patients and the expression of *RETN* was inversely correlated with levels of pro-inflammatory cytokines (IL-1β, IL-6, CXCL8, TNF, and IFN-γ; $p<0.05$). Elevated RESISTIN was also found in the plasma and liver from ACLF patients compared to controls and DC patients. Moreover, significant negative correlation between plasma RESISTIN and inflammatory markers (white blood cell count, $p=0.026$; C-reactive protein, $p=0.0044$) were existed. Therapeutic administration of recombinant RESISTN protein ameliorated liver injury and systemic inflammation in ACLF mouse models. Conversely, administration of neutralizing anti-resistin antibody aggravated the ConA-induced ACLF model, as evidenced by increased serum liver injury markers (ALT and AST), as well as higher proportion of apoptotic cells. **Conclusion:** Therapeutic modulation of RESISTIN shows potential in ameliorating liver injury and systemic inflammation in ACLF, suggesting it as a possible target for ACLF treatment.

Disclosures: Xianbin Xu: Nothing to Disclose, Liang Hong: Nothing to Disclose, Xia Yu: Nothing to Disclose, Jiyang Chen: Nothing to Disclose, Huilan Tu: Nothing to Disclose, Xiaopeng Wu: Nothing to Disclose, Yida Yang: Nothing to Disclose, Yu Shi: Nothing to Disclose, Jifang Sheng: Nothing to Disclose

1587 | A NEW PROGNOSTIC METHOD FOR ACUTE-ON-CHRONIC LIVER FAILURE: A MACHINE LEARNING PROGNOSTIC MODEL BASED ON ELASTOGRAPHY

Jieyang Jin[1]

[1]the Third Affiliated Hospital of Sun Yat-Sen University

Background: Patients with chronic liver disease gradually progress from liver fibrosis to cirrhosis. If they suffer an acute insult during this process, acute-on-chronic liver failure (ACLF) may occur. Ultrasound elastography plays an essential role throughout course of monitoring the disease. However, clinical utility of ultrasound elastography in ACLF is still unclear. Our previous studies have preliminarily confirmed that shear wave elastography (SWE) combined with Model for End-stage Liver Disease (MELD) score has certain value in assessing the outcomes of ACLF. If ACLF patient is too sick from the beginning and not possible for spontaneous recovery, liver transplantation should be decided soon enough since the golden window for treatment is very short, only 7 days. By accurately predicting short-term (30-day), mid-term (90-day), and long-term (1-year) prognosis of ACLF, clinicians can take effective treatment measures and actively carry out clinical intervention for them. **Methods:** This is a retrospective dual-center study. Patients were screened at Department of Infectious Diseases of the hospital from November 2013 to August 2018, and divided into training, testing and validation cohorts. Clinical outcomes, which is recovering/steady or worsening/deterioration, of each patient in 30 days, 90 days and 1 year were recorded. Two-dimensional shear wave elastography (2D-SWE), serological data and prognostic scores of each patient were collected at baseline. Machine learning were used to screen indicators and establish novel prognostic model. **Results:** A total of 544 ACLF patients were enrolled. 2D-SWE, TB, PT, PTA and INR were correlated to all 30-day, 90-day and 1-year outcomes. Na was relevant to 30-day outcome and PLT was relevant to 1-year outcome. Based on these meaningful indicators, we have established a new prognostic model, SWE-SRM, through machine learning with fisher discriminant analysis. Performance of SWE-SRM in predicting 30-day,

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90-day and 1-year clinical outcome in both training and testing cohorts were higher than other prognostic scores. Predicted and observed probabilities of deterioration were similar across quartiles of SWE-SRM at main study time points in training, testing and validation cohorts. Cut-off values of SWE-SRM for 30-day, 90-day and 1-year of ACLF are 22.7%, 44.2% and 45.6%, respectively. There is a significant association between SWE-SRM and transplantation-free survival of ACLF patients between low-risk and high-risk group. In order to avoid complex calculations, we have designed a mobile application which doctors, patients and their families only need to input simple indicators to obtain 30-day, 90-day and 1-year outcomes. **Conclusion:** By using our novel prognostic model and mobile app to evaluate prognosis of ACLF patients at multiple time points, clinicians can take better care of patients and make reasonable decisions about liver transplantation.

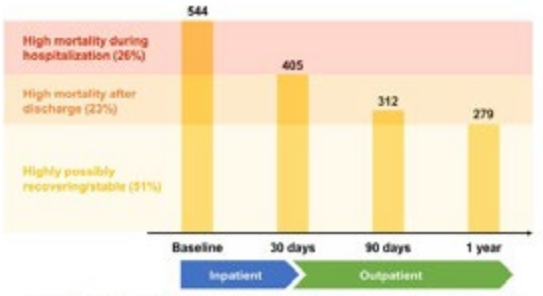

Figure 1 Non-transplant survival patients in this study at baseline, 30 days, 90 days and 1 year after enrollment. Among all 544 ACLF patients, the 30-day, 90-day, and 1-year transplant-free survival patients were 405, 312, and 279, respectively. In addition to paying attention to patients with high mortality during hospitalization, clinicians should also pay attention to patients with high mortality of medium/long prognosis to reduce liver transplantation rates and mortality after discharge.

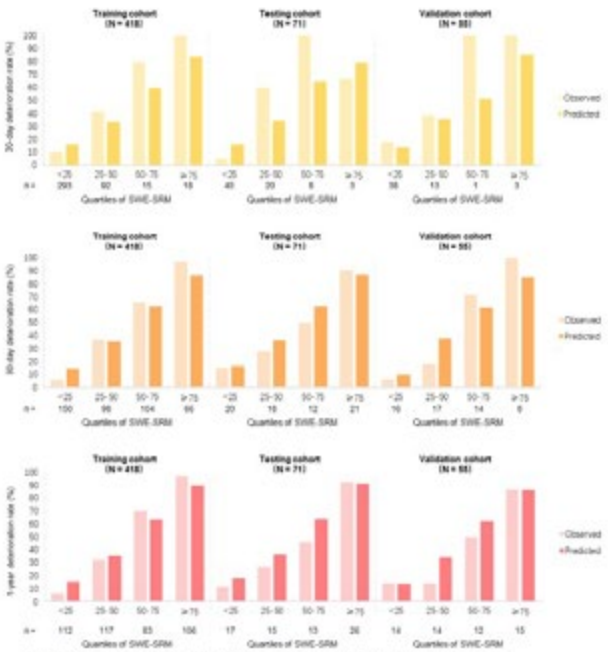

Figure 2 Observed vs. predicted 30-day, 90-day and 1-year deterioration rates: according to the approximate quartiles of SWE-SRM model in HBV-ACLF patients included in the training, testing and validation cohorts. The deterioration probabilities predicted using SWE-SRM model were similar to those observed in all three cohorts of HBV-ACLF patients.

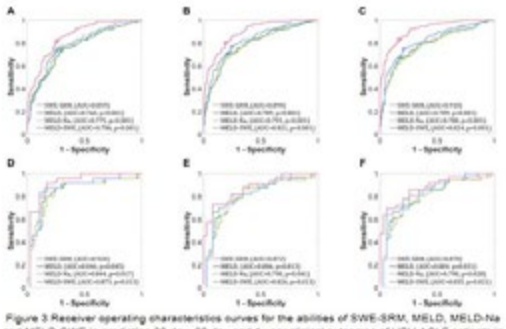

Figure 3 Receiver operating characteristics curves for the abilities of SWE-SRM, MELD, MELD-Na and MELD-SWE in predicting 30-day, 90-day and 1-year clinical outcomes of HBV-ACLF patients in training and testing cohort. SWE-SRM showed a significantly higher predictive ability in comparison with all the other prognostic scores.

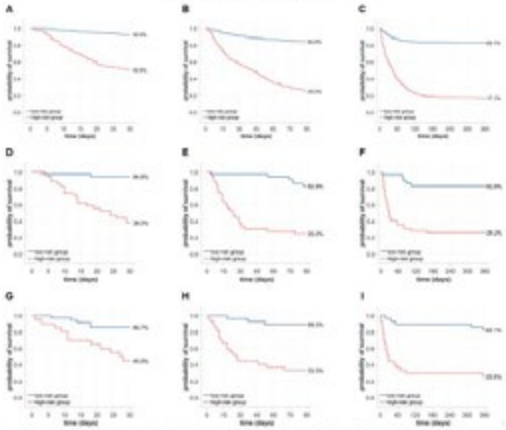

Figure 4 Kaplan-Meier survival analyses based on SWE-SRM for HBV-ACLF patients. 30-day transplantation-free survival curve of HBV-ACLF patients in training (A), testing (D) and validation (G) cohort. 90-day transplantation-free survival curve of HBV-ACLF patients in training (B), testing (E) and validation (H) cohort. 1-year transplantation-free survival curve of HBV-ACLF patients in training (C), testing (F) and validation (I) cohort.



Figure 5 The mobile application

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1588 | MALNUTRITION IMPACT ON PATIENTS WITH CIRRHOSIS; A NATIONWIDE ANALYSIS

Adham Obeidat[1] Ahmad Abou Yassine[2] Mohammad Aldiabat[3] Ratib Mahfouz[4] Michael Gavin[2]

[1]Presbyterian Health System, [2]University of New Mexico, [3]Washington University in St. Louis, [4]Henry Ford Hospital

Background: Malnutrition, sarcopenia and cachexia are common conditions in patients with cirrhosis. Malnutrition has been reported in 20% of patients with compensated cirrhosis and in more than 50% of patients with decompensated cirrhosis. The pathophysiology of malnutrition in cirrhotic patients is complex and multifactorial. In this study we examine the potential impact of malnutrition on the in-hospital mortality as well as other secondary outcomes in cirrhotic patients admitted to the hospital in the period between 2019-2021. **Methods:** The United States Nationwide Inpatient Sample (NIS) database was used to extract hospitalization data of patients admitted between 2019 to 2021. Using ICD10 revision codes, we identified adults with the diagnosis of cirrhosis with concomitant malnutrition, including sarcopenia and cachexia. The control group included cirrhotic patients without malnutrition. The primary outcome was the in-hospital mortality. Secondary outcomes included encephalopathy, ascites, variceal bleed, sepsis, respiratory failure (RF), acute kidney injury (AKI), hepatorenal syndrome (HRS) and length of stay (LOS). Multivariate logistic regression was used to adjust for relevant variables. **Results:** An estimated 212,067 patients were admitted with cirrhosis during the study period. Of these, 25,331 patients had the diagnosis of malnutrition. In malnourished cirrhotic patients, the mean age was 56.44 years vs 55.7 patients without malnutrition. 35.8% were females and 68.8% were Caucasians. 12.08% of malnourished cirrhotic patients died during hospitalization compared to 6.35% of cirrhotics without malnutrition. Further, total hospital charges were more in the malnourished group compared to the non-malnourished group (133,054 $ vs 75,661$). When adjusted to other relevant variables, malnutrition was associated with increased in-hospital mortality in cirrhotic patients (OR 1.93; P-value 0.00). Age and Caucasian race were also associated with increased in-hospital mortality. On multi-variate analysis, malnutrition was associated with an increased chance of developing sepsis, AKI, RF, HE, ascites, HRS and prolonged LOS. Interestingly, malnourished cirrhotic patients had a lower chance for variceal bleeding (see Table 1). **Conclusion:** Malnutrition is a common complication in patients with cirrhosis. In this study, cirrhotic patients with malnutrition had an increased chance of in-hospital mortality. Moreover, they had higher chances for decompensation including HE and ascites, and other in-hospital complications such as AKI, HRS and RF, which can lead to increased LOS and increased financial burden. Therefore, we recommend clinicians to pay close attention to cirrhotic patients with malnutrition and to have a multi-disciplinary approach which involve other team members in treating them.

Complication	Univariate	P-Value	Multivariate	P-Value
Sepsis	1.94	0.00	1.91	0.00
AKI	1.79	0.00	1.79	0.00
C diff	0.70	0.63	-	-
Respiratory Failure	1.75	0.00	1.77	0.00
Hepatic Encephalopathy	1.96	0.00	1.93	0.00
Ascites	2.07	0.00	2.02	0.00
Variceal Bleed	0.74	0.00	0.76	0.00
Hepatorenal Syndrome	2.13	0.00	2.07	0.00
LOS	2.45	0.00	2.44	0.00

Table 1. Univariate and Multivariate analysis of Malnutrition as a potential predictor of in-hospital complications in cirrhotic patients

Disclosures: Adham Obeidat: Nothing to Disclose, Ahmad Abou Yassine: Nothing to Disclose, Mohammad Aldiabat: Nothing to Disclose, Ratib Mahfouz: Nothing to Disclose, Michael Gavin: Nothing to Disclose

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1589 | ARGONAUTE-2 AUTOANTIBODIES REVEAL PROGNOSIS IN HBV-RELATED ACUTE-ON-CHRONIC LIVER FAILURE PATIENTS WITH CIRRHOSIS

Yixuan Wang[1] Yixuan Yang[2] Xiaofeng Shi[2]

[1]the second affiliated hospital, Chongqing medical University, [2]Chongqing medical university

Background: HBV infection initiates autoimmune responses, leading to the production of autoantibodies. These autoantibodies may be closely associated with the progression of HBV-related liver disease and exhibit specificity. This study investigates the role of autoantibodies in HBV-related Acute-on-Chronic Liver Failure (ACLF), providing new perspectives for clinical management. **Methods:** Serum IgG antibodies were purified from healthy controls and patients with HBV-related cirrhosis. These IgGs were incubated with HepG2 cell lysates to capture differential autoantigen/antibody complexes through immunoprecipitation. The captured complexes were identified using iTRAQ and screened for autoantibodies with potential as biomarkers. The potential biomarkers were subjected to large-scale detection using Conformation-stabilizing ELISA. The predictive value of these potential biomarkers was tested in a prospective cohort of 238 HBV-infected individuals and 49 healthy controls. The results were validated in a retrospective cohort comprising 106 ACLF patients. **Results:** Using iTRAQ technology, we identified and screened Argonaute1-3 autoantibodies (AGO-Abs), and verified the authenticity and specificity of these antibodies through a cell-based assay (Figure 1). In a prospective cohort, AGO2-Abs notably increased in cirrhosis, decompensation, and further in ACLF, unlike AGO1-Abs and AGO3-Abs (Figure 2), suggesting that AGO-Abs are closely related to disease severity. Logistic regression and COX models confirmed AGO2-Abs as independent prognostic indicators for decompensated liver cirrhosis (DLC) and ACLF. In ROC analysis, AGO2-Abs showed significant diagnostic value for predicting short-term mortality at 28 and 90 days (AUROC = 0.853 and 0.854, respectively), comparable to the predictive accuracy of Child-Pugh, MELD, and AARC scores (Figure 3). Additionally, combining AGO2-Abs improved the predictive accuracy of Child-Pugh, MELD, and AARC scores (Table 1). Kaplan-Meier analysis showed poorer survival for AGO2-Abs levels above 99.14μg/ml (Figure 4). These findings were supported by a retrospective validation cohort (Figure 4, Table 1). **Conclusion:** AGO2-Abs was identified as a significant prognostic marker in patients with HBV-ACLF, providing a novel approach for assessing the severity and prognosis of patients with HBV-related decompensated liver cirrhosis and ACLF. Integrating AGO2-Abs into existing prognostic models may enhances the accuracy of short-term mortality predictions, offering a valuable tool for clinical decision-making and patient management.The study identified AGO2-Abs as a significant prognostic marker for HBV-related ACLF.

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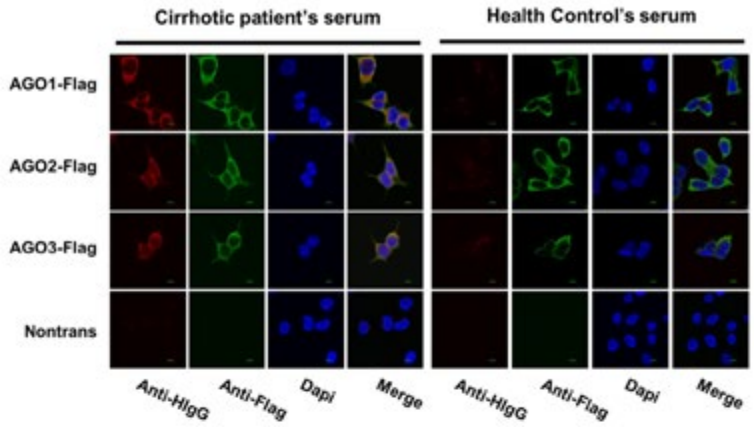

Fig 1. Validation of AGO-Abs in serum by cell-based assay.

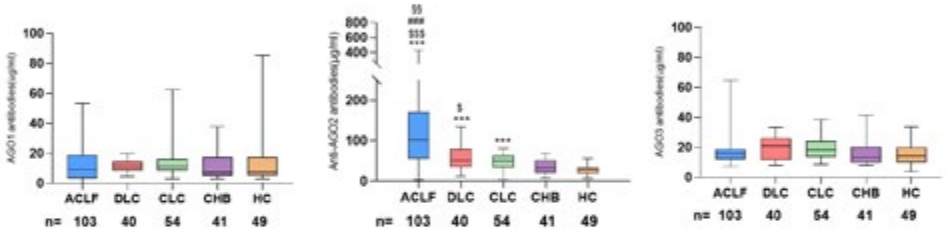

Fig 2. Distribution of AGO1-Abs, AGO2-Abs and AGO3-Abs levels across different severities of liver disease. ACLF: Acute-on-chronic liver failure, DLC: Decompensated liver cirrhosis without liver failure, CLC: Compensated liver cirrhosis, CHB: Chronic Hepatitis B, HC: Health controls. *p <0.05, **p <0.01, ***p <0.001 vs HC; $ vs CHB; # vs CLC; § vs DLC.

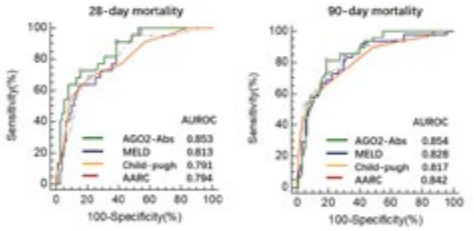

Fig3. ROC analysis comparing the predictive performance of AGO2-Abs and traditional liver disease scoring models (MELD, Child-Pugh, and AARC) for 28-day and 90-day mortality in patients with DLC/ACLF

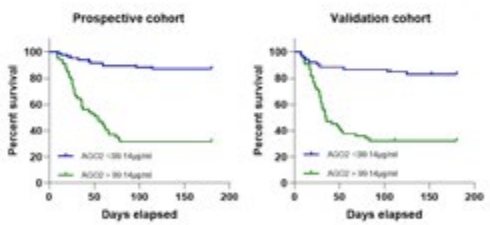

Fig4. Kaplan-Meier survival analysis in patients from prospective and validation cohorts. Survival rates are significantly lower in both cohorts when AGO2-Abs levels are >99.14 μg/ml.

Table 1. AUROC for Predicting Mortality in Patients with DLC/ACLF

	DLC/ACLF in prospective cohort (n=143)					
	28-day mortality			90-day mortality		
	Univariate	Combined with AGO2-Abs	P value	Univariate	Combined with AGO2-Abs	P value
AGO2-Abs	0.853(0.785-0.907)	-	-	0.854(0.786-0.908)	-	-
MELD	0.813(0.739-0.873)	0.876(0.811-0.925)	0.0505	0.828(0.756-0.886)	0.878(0.813-0.927)	0.0148
Child-pugh	0.791(0.715-0.854)	0.874(0.808-0.924)	0.0106	0.817(0.743-0.876)	0.875(0.809-0.924)	0.0062
AARC	0.794(0.719-0.857)	0.874(0.808-0.923)	0.0238	0.842(0.772-0.898)	0.883(0.819-0.931)	0.0412
	Validation cohort (n=105)					
AGO2-Abs	0.782(0.691-0.856)	-	-	0.829(0.744-0.896)	-	-
MELD	0.820(0.734-0.888)	0.858(0.776-0.918)	0.1902	0.804(0.716-0.875)	0.867(0.787-0.925)	0.0327
Child-pugh	0.799(0.710-0.870)	0.852(0.769-0.913)	0.0984	0.816(0.729-0.885)	0.866(0.786-0.924)	0.0656
AARC	0.840(0.756-0.904)	0.876(0.797-0.932)	0.0352	0.872(0.794-0.929)	0.905(0.832-0.953)	0.1073

Disclosures: Yixuan Wang: Nothing to Disclose, Yixuan Yang: Nothing to Disclose, Xiaofeng Shi: Nothing to Disclose

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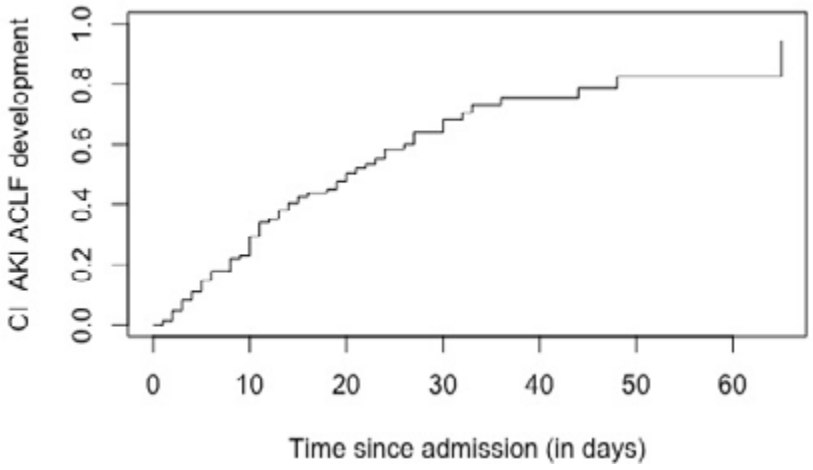
1590 | DEVELOPMENT AND PATTERNS OF ACUTE-ON-CHRONIC LIVER FAILURE IN CIRRHOTIC PATIENTS WITH ACUTE KIDNEY INJURY: IMPLICATIONS FOR PROGNOSIS AND THERAPEUTIC APPROACHES

Susan Fischer[1] Marta Fiocco[2] Jeetindra Balak[1] Jeroen Nieuwenhuizen[1] Minneke Coenraad[1]

[1]Leiden University Medical Center, [2]Leiden University

Background: Acute Kidney Injury (AKI), is frequently encountered among cirrhotic patients and is associated with a poor prognosis. The presence and development of acute-on-chronic liver failure (ACLF), especially of extrarenal organ failures is unknown in cirrhotic patients with AKI. This study investigates ACLF patterns in cirrhotic patients with AKI, aiming to provide insights into this complex clinical course and to identify leads for modifying the disease trajectory. **Methods:** A retrospective cohort study was performed in consecutive hospitalized cirrhotic patients with AKI at a tertiary center. Data on disease trajectory, renal outcomes, ACLF development/progression (EASL-CLIF-C criteria) and survival data were collected. Logistic regression analysis was used to investigate the association between AKI and ACLF on transplant-free survival and to identify risk factors for specific types of organ failure in ACLF. The findings of this study are currently being validated in a German tertiary center. **Results:** Between 2011-2023, 248 unique cirrhotic patients with AKI (77% male) were included. Mean age was 61 years [IQR◦ 54-67] with a median MELD score of 21 [17-28]. 189 patients (76%) were diagnosed with AKI upon admission. Etiology of AKI was 36% pre-renal, 44% Hepatorenal Syndrome-AKI and 20% other/mixed etiology. 212 patients (85%) received albumin and 151 (61%) received terlipressin, with a 30% response rate upon discharge. Progression of AKI or no response to therapy was reported in 51% during hospitalization.
ACLF was present at admission in 97 patients (39%), characterized by predominantly renal (69%) and liver (46%) failure. Among these patients, 59 (61%) showed progression of ACLF during hospitalization, with predominantly renal and liver failure (83% and 70% respectively). 76 out of 151 patients without ACLF at admission (50%) developed ACLF within 90 days. Remarkably, respiratory failure was second most frequent type of organ failure (62%), after renal failure (64%). Altogether, ACLF was diagnosed in 173 patients (70%) within 90 days of follow-up. Patients with ACLF development were at increased risk of developing circulatory failure if no response of AKI was observed (OR 3.57, CI 1.14-11.14). Patients with progression of ACLF who showed no response/ progression of AKI were more likely to develop respiratory failure (OR 4.12, CI 1.17-14.50).142 (57%) patients died within 90 days after AKI development. One-year transplant-free survival was 22%. **Conclusion:** Cirrhotic patients with AKI are at very high risk of short-term ACLF development and mortality. Respiratory failure is, after renal failure, the second most common organ failure in patients who develop ACLF after AKI diagnosis. Lack of response to treatment for AKI is a risk factor for the development of new respiratory and circulatory failure in patients who show progression of ACLF.



Disclosures: Susan Fischer: Nothing to Disclose, Marta Fiocco: Nothing to Disclose, Jeetindra Balak: Nothing to Disclose, Jeroen Nieuwenhuizen: Nothing to Disclose, Minneke Coenraad: Nothing to Disclose

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1591 | SINGLE-CELL MULTIMODAL ANALYSIS REVEALS THE DYNAMIC IMMUNOPATHOGENESIS OF HBV-ACLF PROGRESSION

Jun Li[1] Xi Liang[2] Jinjin Luo[1] Qian Zhou[1] Jiaojiao Xin[1] Jiaqi Li[3] Jing Jiang[1] meiqian hu[1] Peng Li[1] Pengcheng Chen[4] Heng Yao[1] Huafen Zhang[1] Xingping Zhou[1] Jiaxian Chen[1] Wen Hu[1] Bingqi Li[1] Shiwen Ma[1] Xiao Wu[1] Taoying Wei[1] Jing Zhang[1] Xin Chen[1] Dongyan Shi[1]

[1]Zhejiang University, [2]Taizhou Central Hospital, [3]Zhejiang Provincial People's Hospital, [4]Taizhou University

Background: Acute-on-chronic liver failure (ACLF) is a life-threatening syndrome involving dysfunction of multiple immune cell types. This study aimed to comprehensively depict the dynamic trajectory of immune responses throughout the disease course of hepatitis B virus-related ACLF (HBV-ACLF). **Methods:** Single-cell RNA sequencing (scRNA-seq) and single-cell proteomics were performed on the peripheral blood mononuclear cells of 45 samples from 17 hospitalized patients (progressive/stable/recovering course of HBV-ACLF, 6/5/6) and 15 control subjects (liver cirrhosis, chronic hepatitis B and healthy controls, 5/5/5). Bulk RNA-seq and flow cytometry were performed for external validation. **Results:** Single-cell transcriptomics revealed specific alterations in the peripheral immune response in ACLF. $VCAN^{+}CD14^{+}$-monocytes with activated interferon-stimulated genes and increased inflammatory functions expanded in ACLF-1. Low-density hyperinflammatory $CXCR2^{+}$-neutrophils and M2 macrophage-like $CD163^{+}$-monocytes predominated in progressive ACLF patients. Cell–cell interaction analysis revealed enhanced CD39 signalling and upregulated anti-inflammatory factors such as IL1R2 in the end stage of ACLF. Natural killer cells gradually decreased during ACLF progression, exhibiting impaired cytotoxic and metabolic functions. Highly activated cytotoxic T cells, including $GZMK^{+}CD4^{+}$- and $GZMK^{+}COTL1^{+}CD8^{+}$-T cells, were hallmarks of recovering patients. Six cellular modules were identified, highlighting a specific immune pattern (CM3) that could be focused as an optimal therapeutic window. The proteomic profiling **Results:** of immune cell compositions showed a high concordance with those of the transcriptomics. External validation with bulk RNA-seq and flow cytometry confirmed the specific immune cell clusters involved in ACLF progression. **Conclusion:** Our longitudinal multiomics study revealed the dynamic evolution of the immune response in HBV-ACLF and characterized diverse immune patterns for the precise management and therapeutic intervention.

Disclosures: Jun Li: Nothing to Disclose, Xi Liang: Nothing to Disclose, Jinjin Luo: Nothing to Disclose, Qian Zhou: Nothing to Disclose, Jiaojiao Xin: Nothing to Disclose, Jiaqi Li: Nothing to Disclose, Jing Jiang: Nothing to Disclose, meiqian hu: Nothing to Disclose, Peng Li: Nothing to Disclose, Pengcheng Chen: Nothing to Disclose, Heng Yao: Nothing to Disclose, Huafen Zhang: Nothing to Disclose, Xingping Zhou: Nothing to Disclose, Jiaxian Chen: Nothing to Disclose, Wen Hu: Nothing to Disclose, Bingqi Li: Nothing to Disclose, Shiwen Ma: Nothing to Disclose, Xiao Wu: Nothing to Disclose, Taoying Wei: Nothing to Disclose, Jing Zhang: Nothing to Disclose, Xin Chen: Nothing to Disclose, Dongyan Shi: Nothing to Disclose

1592 | SEMA6B ACCELERATES ACUTE-ON-CHRONIC LIVER FAILURE BY TRIGGERING SYSTEMIC INFLAMMATION AND HEPATOCYTE APOPTOSIS ◆

Jun Li[1] Hui Yang[1] Qun Cai[2] Jiaojiao Xin[1] Xi Liang[3] Jing Jiang[1] Dongyan Shi[1]

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Background: Patients with hepatitis B virus-related acute-on-chronic liver failure (HBV-ACLF) have high short-term mortality rates. Semaphorin-6B (SEMA6B) plays essential roles in the pathogenesis of HBV-ACLF, but its molecular basis is unclear. This study aimed to clarify the mechanisms of SEMA6B in HBV-ACLF progression. **Methods:** 321 subjects with HBV-ACLF, liver cirrhosis (LC) or chronic hepatitis B (CHB) and normal controls (NC) from a prospective multicenter cohort were studied. 84 subjects (HBV-ACLF, n = 50; LC, n = 10; CHB, n = 10; NC, n = 14) among them underwent mRNA sequencing using peripheral blood mononuclear cells (PBMCs) to clarify the mechanisms of SEMA6B in HBV-ACLF, and validated in vitro with hepatocytes and macrophages and in vivo with SEMA6B knockout mice. **Results:** Transcriptome analysis of PBMCs showed that SEMA6B was among the most frequently differentially expressed genes in comparisons between HBV-ACLF patients and those with liver cirrhosis, chronic hepatitis, or normal control. ROC analysis showed the most reliable diagnostic value of SEMA6B for HBV-ACLF in both the sequencing and external validation cohorts (AUROC = 0.9788 and 0.9026, respectively). SEMA6B was significantly highly expressed in HBV-ACLF patients, particularly in ACLF non survivors. This expression was mainly observed in macrophages and hepatocytes within liver tissues. Genes

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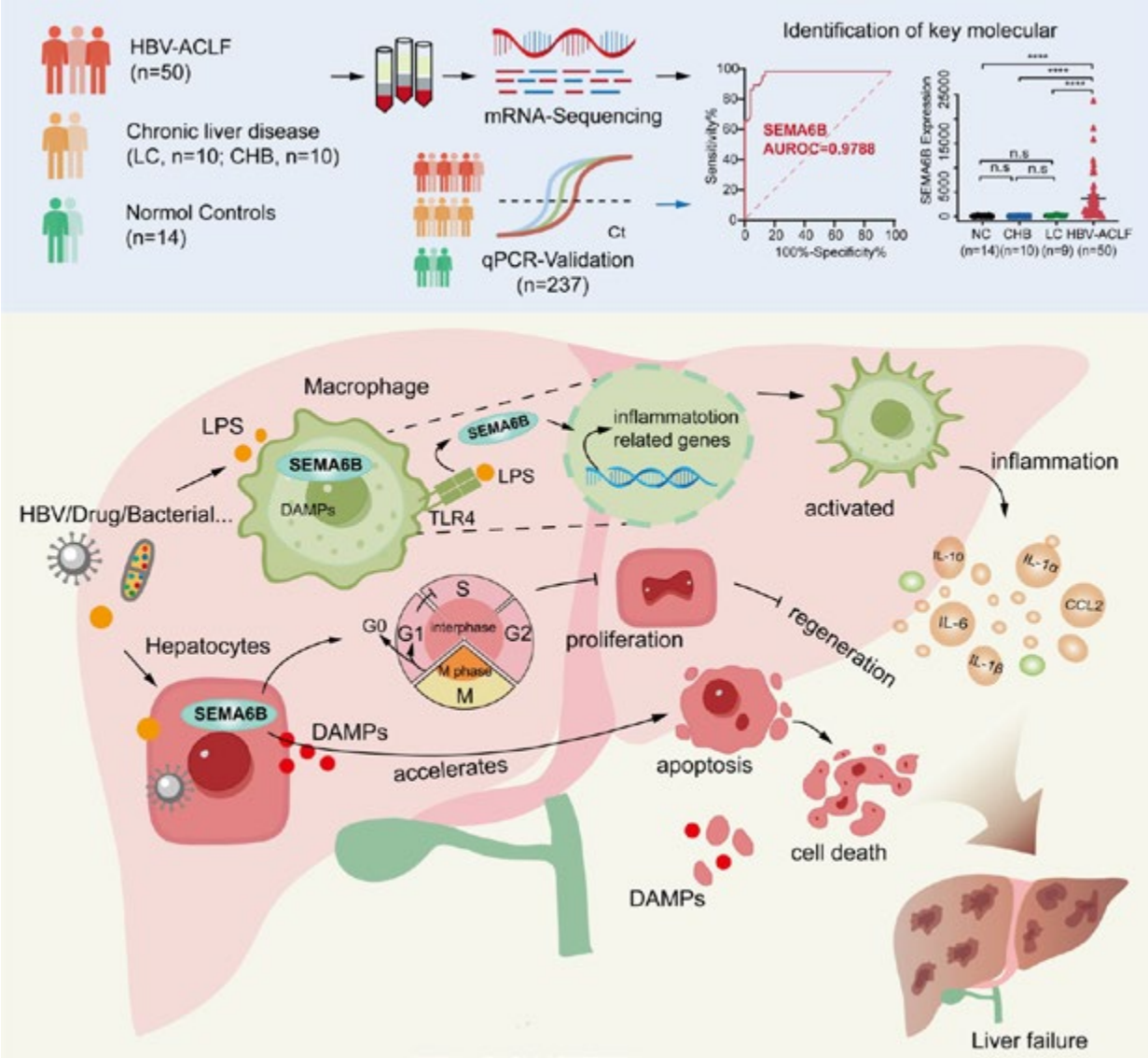
significantly associated with highly expressed SEMA6B were enriched in pathways involved in the inflammation and apoptosis pathways in ACLF non survivors. Overexpression of SEMA6B in macrophages activated systemic inflammation responses, while its overexpression in hepatocytes inhibited proliferation through G0/G1 cell-cycle phase arrest and triggered apoptosis. Conversely, knockout of SEMA6B rescued mice with liver failure by improving liver functions, attenuating inflammation, and reducing hepatocyte apoptosis. Transcriptome analysis of liver tissues showed that SEMA6B knockout significantly improved the signature of liver failure mice, and a significant downregulation of inflammation-related pathways was also observed in SEMA6B knockout mice with liver failure. **Conclusion:** SEMA6B, a potential diagnostic biomarker of HBV-ACLF progression, exacerbates liver failure through macrophage-mediated systemic inflammation and hepatocyte apoptosis. These findings underscore SEMA6B may as a potential early treatment target for HBV-ACLF patients.



Disclosures: Jun Li: Nothing to Disclose, Hui Yang: Nothing to Disclose, Qun Cai: Nothing to Disclose, Jiaojiao Xin: Nothing to Disclose, Xi Liang: Nothing to Disclose, Jing Jiang: Nothing to Disclose, Dongyan Shi: Nothing to Disclose

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1593 | COMPARATIVE ANALYSIS OF LIVER CIRRHOSIS AND ACUTE CORONARY SYNDROME (STEMI AND NSTEMI) AND THEIR OUTCOMES: CASE CONTROL STUDY OF AN IN-PATIENT ANALYSIS

Anwar Uddin Nazeera Ghanie[1] Ammar Abdulfattah[1] Ugochukwu Ebubechukwu[2] Nazima Khatun[3] Prashil Dave[2] Madia Ahad[3] Afgal Ahad[3] Rafat Uddin[3] Rahat Uddin[3] Sahil Chaddha[3]

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Background: Liver cirrhosis (LC) is associated with significant increase in cardiovascular morbidity and mortality. There are limited data on the outcomes of acute coronary syndrome (ACS) in patients with liver cirrhosis. The aim of present study is to examine the prevalence and outcomes of ACS in patients admitted with LC using the nationwide database. **Methods:** We used the Healthcare Cost and Utilization Project (HCUP) Nationwide Inpatient Sample (NIS) to identify adult patients admitted with LC during 2016 – 2020 using ICD-10-CM codes. We used ICD-10-CM codes to categorize patients into two groups: with and without ACS. We defined ACS as having concomitant ICD-10-CM diagnosis codes of ST-elevation myocardial infarction (STEMI) and non-STEMI (NSTEMI). Main outcomes were in-hospital mortality, length of stay (LOS), and hospital costs. We evaluate the association between ACS and outcomes using survey based multivariate logistic regression models for in-hospital mortality, Poisson regression for LOS, and generalized linear model with gamma distribution and log link for hospitalization cost. We used the Poisson regression to examine the annual trend of ACS hospitalizations among LC patients. Models were adjusted for age, sex, race and ethnicity, primary payer, Charlson comorbidity index, hospital bed size, hospital region and hospital teaching status. **Results:** We identified a total of 3,648,794 LC hospitalizations between 2016 and 2020 in the United States and 56,325 (1.54%) of them were associated with ACS. There were 10% annual decline in proportion of ACS hospitalizations among LC patients from 2016 to 2020 (11,715, 1.78% in 2016 to 10,600, 1.37% in 2020, adjusted rate ratio 0.90, 95% CI 0.89 – 0.92, p < <0.001). In-patient mortality was significantly higher in ACS patients with LC (17.0% vs 5.7%, adjusted OR: 2.89, 95%CI: 2.74 - 3.04, P < 0.001, Table 2). ACS patients with LC had an increased length of stay (7.5 ± 0.09 vs 6.1 ± 0.02 days, P < 0.001) an increased cost of hospitalization ($29,342 ± 434 vs $17,866 ± 115, P < 0.001, Table 1). **Conclusion:** ACS co-exists in about 1.5% of patients with LC with declining trend in recent years and is associated with higher in-hospital mortality, increased length of stay and increased cost of hospitalization.

Table 1: Comparison of primary outcomes: liver cirrhosis with versus without acute coronary syndrome

	Acute Coronary Syndrome		Adjusted OR / RR		
Characteristic	**No, N = 3,592,469**	**Yes, N = 56,325**	**OR/RR**	**95% CI**	**p-value**
In-hospital mortality - N (%)	205,115 (5.7%)	9,425 (17%)	2.89	2.74, 3.04	<0.001
LOS (days) - mean (SE)	6.1 (0.02)	7.5 (0.09)	1.2	1.17, 1.22	<0.001
Hospital Cost ($, 2020) - mean (SE)	17,865.9 (114.68)	29,342.0 (433.81)	1.59	1.55, 1.63	<0.001

Relative ratio is reported using Poisson regression model for LOS
Relative ratio is reported using generalized linear model with gamma distribution and log link for Hospital Cost; adjusted for inflation using Consumer Price Index (CPI) for Medical care services in U.S. city average, all urban consumers, chained, with 2020 as the reference point
Variables used for multivariate logistic regression: age, sex, race, insurance status, Charlson comorbidity index, hospital bed size, and hospital region

Disclosures: Anwar Uddin: Nothing to Disclose, Nazeera Ghanie: Nothing to Disclose, Ammar Abdulfattah: Nothing to Disclose, Ugochukwu Ebubechukwu: Nothing to Disclose, Nazima Khatun: Nothing to Disclose, Prashil Dave: Nothing to Disclose, Madia Ahad: Nothing to Disclose, Afgal Ahad: Nothing to Disclose, Rafat Uddin: Nothing to Disclose, Rahat Uddin: Nothing to Disclose, Sahil Chaddha: Nothing to Disclose

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1594 | HIV PATIENTS WITH LOW CD4 COUNTS AND THE DEVELOPMENT OF ACUTE LIVER INJURY AND CIRRHOSIS: AN IN PATIENT ANALYSIS STUDY FROM 2016-2020

Anwar Uddin Madia Ahad[1] Rafat Uddin[1] Nazeera Ghanie[1] Afgal Ahad[2] Rahat Uddin[3] Peter Lymberopoulos[2] Prashil Dave[2] Sahil Chaddha[2]

[1]State University of New York Downstate, [2]SUNY Downstate Medical Center, [3]SUNY Downstate Health Science University

Background: HIV infected patients are prone to develop liver diseases including acute liver injury (ALI) and cirrhosis and lower CD4 count was associated with more severe form of liver diseases. The aim of present study is to examine factors associated with development of ALI and cirrhosis among HIV patients using national database. **Methods:** We used the Healthcare Cost and Utilization Project (HCUP) Nationwide Inpatient Sample (NIS) to identify adult patients admitted having HIV status during 2016 – 2020 using ICD-10-CM codes. We used ICD-10-CM codes for lower WBC and lymphocytes as proxy for low CD4 counts as main exposure variable. Main outcome was ALI and cirrhosis which was identified as concomitant diagnosis. We evaluate the association between exposure and outcome using the survey based multivariate logistic regression model adjusted for age, sex, race and ethnicity, primary payer, Charlson comorbidity index, hospital bed size, hospital region and hospital teaching status. **Results:** We identified a total of 1,030,485 hospitalizations with HIV status between 2016 and 2020 in the United States and 20,595 (2.0%) of them were associated with low CD4 count. 1,430 (6.9%) of patients with low CD4 counts had ALI / cirrhosis while 56,280 (5.6%) of patients without low CD4 count had ALI / cirrhosis. Low CD4 count was significantly associated with development of ALI / cirrhosis among HIV patients (adjusted OR: 1.26, 95%CI: 1.12 – 1.43, P < 0.001, Table 1). Increasing age, male gender, Hispanic and Native American race, having Medicaid insurance, higher Charlson comorbidity index, and admission into large hospital bed size had significantly higher odds of having ALI / cirrhosis while Black and Asian or Pacific Islander race, admission into rural hospitals had lower odds of having ALI / cirrhosis (Table 1). **Conclusion:** HIV patients with Low CD4 count have higher risk of development of ALI / cirrhosis.

Table 1. Results of multivariate analysis on factors associated with development of ALI / cirrhosis in HIV patients

	Adjusted OR		
Variable	**OR**	**95% CI**	**p-value**
Low CD4 Counts	1.25	1.10, 1.41	<0.001
AGE	1.02	1.02, 1.03	<0.001
Gender			
Male	1	1	1
Female	0.85	0.81, 0.89	<0.001
Race			
White	1	1	1
Black	0.53	0.51, 0.56	<0.001
Hispanic	1.22	1.14, 1.30	<0.001
Asian or Pacific Islander	0.75	0.58, 0.96	0.023
Native American	1.6	1.24, 2.07	<0.001
Other	0.89	0.80, 0.99	0.037
Insurance			
Medicare	1	1	1
Medicaid	1.29	1.22, 1.36	<0.001
Private	0.95	0.88, 1.01	0.11
Other	1.05	0.97, 1.14	0.3
Charlson comorbidity index			
0-1	1	1	1
2	2.32	2.07, 2.60	<0.001
>=3	4.61	4.28, 4.97	<0.001
Hospital bedsize			
Small	1	1	1
Medium	1.05	0.98, 1.12	0.2
Large	1.11	1.04, 1.18	0.002
Hospital region			
Northeast	1	1	1
Midwest	0.91	0.84, 0.99	0.026
South	0.96	0.91, 1.02	0.2
West	0.83	0.77, 0.90	<0.001
Hospital teaching status			
Urban teaching	1	1	1
Rural	0.76	0.66, 0.87	<0.001

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1595 | PANOSE, AN INTESTINAL MICROBIAL DERIVED PREBIOTIC REDUCES THE RISK OF BACTERIAL INFECTION DURING ACUTE-ON-CHRONIC LIVER FAILURE BY REPAIRING THE OXIDATIVE STRESS-INDUCED INTESTINAL BARRIER DISRUPTION

Peng Chen[1] JIaxin Li[2] Jinjun Chen[1]

[1]Southern Medical University, [2]Soutrhern Medical University

Background: Acute-on-chronic liver failure (ACLF) is a leading cause of liver-related death worldwide, with a high short-term mortality rate (50-90%). Bacterial infection (BI) is a common trigger for ACLF progression in patients with decompensated cirrhosis, underscoring an urgent need for innovative approaches in BI prevention and management. **Methods:** We established the murine acute-on-chronic liver failure model and evaluated the potential effect of panose on ACLF development. **Results:** Here, we first demonstrated the potential of prebiotic panose in improving ACLF outcomes, including reduced liver injury and increased survival time in ACLF mice by diminishing bacterial infections. We observed that infected decompensated cirrhosis patients exhibited lower intestinal panose levels. Megamonas is a new contributor to generate panose in the gut, with 4α-glucanosyltransferase (4αGT) identified as a key enzyme for panose production. Animal studies revealed that panose resistance to bacterial infections was achieved by inhibiting oxidative stress-induced gut barrier disruption, which prevented dissemination and reduced the bacterial load. Mechanistically, panose interacted with the solute carrier family 7 member 11 (SLC7A11, also known as xCT) protein to boost antioxidant glutathione (GSH) levels in intestinal epithelial cells. **Conclusion:** This study revealed the efficacy of panose in preventing bacterial infections, highlighting its promise as an alternative agent in the clinical prevention and management of ACLF.

Disclosures: Peng Chen: Nothing to Disclose, JIaxin Li: Nothing to Disclose, Jinjun Chen: Nothing to Disclose

1596 | INTEGRATING PRIOR DECOMPENSATION IN ACLF DEFINITIONS FOR SIMPLIFIED CLINICAL MANAGEMENT

Jun Li[1] meiqian hu[1] Yu Wu[2] Jinjin Luo[1] Jing Zhang[1] Jiaojiao Xin[1] Jing Jiang[1] Dongyan Shi[1] Yu Chen[2]

[1]Zhejiang University, [2]Capital Medical University

Background: Acute-on-chronic liver failure (ACLF) is a complicated syndrome associated with a high short-term mortality and reversibility. There is controversy over the inclusion of patients with prior decompensation in the definition of ACLF and the clinical management is different. **Methods:** A total of 532 patients with chronic liver disease and acute decompensation (TB ≥ 85.5μmol/L plus INR ≥ 1.5, complicated within 4 weeks by clinical ascites and/or encephalopathy) were retrospectively enrolled and analyzed from two Chinese tertiary hospital from January 2018 to June 2023. Clinical data were used to compare the characteristics of prior decompensated patients and first decompensated patients. **Results:** Of the 532 patients, 433 patients met the APASL-ACLF criteria and 99 patients didn't meet APASL-ACLF criteria due to prior decompensation. Clinical characteristics didn't differ between prior decompensated patients and first decompensated patients, including organ failure, prognosis scores, distribution of ACLF-1/2/3 and the 28-/90-day mortality rates (30.5%/43.2% vs. 36.3%/43.1%, p=0.267/0.978). Further analysis showed that among the 99 patients with prior decompensation, there was a significant difference in 28-day mortality between patients with prior decompensation 1-2 times (n=84) and ≥ 3 times (n=15) (25.7 % vs. 58.3 %, p=0.023). Under COSSH-ACLF and EASL-ACLF criteria, there was also no significant difference in mortality rate and distribution of ACLF-1/2/3 between prior decompensated patients and first decompensated patients. ROC curve analysis showed that three prognostic scores had high diagnostic efficiency for 28-day mortality in prior decompensated patients. Under APASL-ACLF criteria, the auROC of AARC-ACLFs in patients with first decompensation, prior decompensation and the sum of the two groups were 0.768, 0.793 and 0.774, under COSSH-ACLF criteria, the auROC of COSSH-ACLF IIs were 0.821, 0.716 and 0.797, and under EASL-ACLF criteria, the auROC of CLIF-C-ACLFs were 0.735, 0.766 and 0.722. **Conclusion:** Prior

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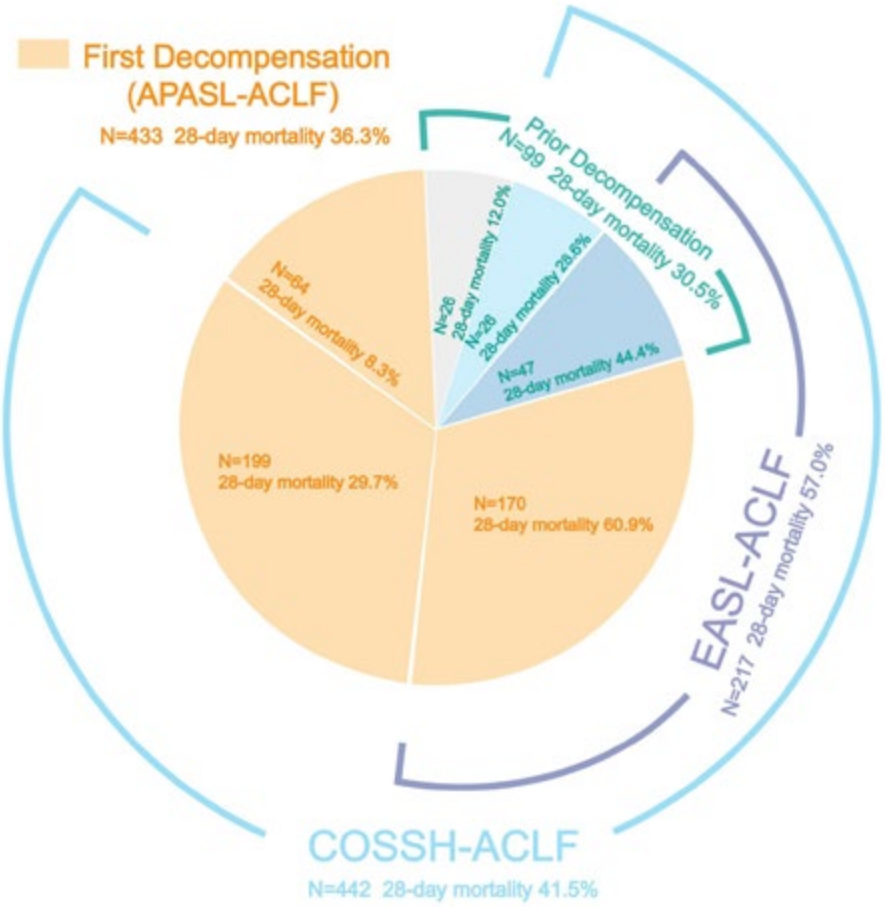
decompensated patients exhibited high mortality and had similar population distribution characteristics to first decompensated patients. Prior decompensated patients and first decompensated patients are homogeneous, and the inclusion of patients with prior decompensation into the definition of ACLF can simplify clinical management.



Disclosures: Jun Li: Nothing to Disclose, meiqian hu: Nothing to Disclose, Yu Wu: Nothing to Disclose, Jinjin Luo: Nothing to Disclose, Jing Zhang: Nothing to Disclose, Jiaojiao Xin: Nothing to Disclose, Jing Jiang: Nothing to Disclose, Dongyan Shi: Nothing to Disclose, Yu Chen: Nothing to Disclose

1597 | INTRAVENOUS ADMINISTRATION WITH THE ASK1 INHIBITOR SRT-015 ALLEVIATES LIVER INJURY AND SYSTEMIC INFLAMMATION IN DISEASE MODELS OF LIVER FAILURE

Vanessa Legry[1] Maryse Malysiak[1] Philippe POULAIN[1] Valérie Daix[1] Remy Hanf[2] Dean Hum[1] Bart Staels[3] Joan Claria[4] Sakina Sayah Jeanne[1]

[1]Genfit S.A., Loos, France, [2]Pradial-consulting, Lille, France, [3]INSERM U1011, Univ. Lille, Institut Pasteur de Lille, Lille, France, [4]Hospital Clínic-IDIBAPS-Barcelona University, European Foundation Study of Chronic Liver Failure

Background: Acute-on-chronic liver failure (ACLF) is characterized by multiple organ failures in patients with acutely decompensated cirrhosis and is associated with high short-term mortality. The development of ACLF occurs in the setting of systemic inflammation, which correlates with the number of organ failures and mortality. Systemic inflammation may cause ACLF through complex mechanisms including an exaggerated inflammatory response and systemic oxidative stress to pathogen-associated molecular patterns (PAMPs) translocated from the gut and damage-associated molecular patterns (DAMPs) released by dying cells. SRT-015 is a novel, small molecule inhibitor of the apoptosis signal-regulating kinase 1 (ASK1). ASK1 is a ubiquitous redox-sensitive kinase that is activated by pathological stimuli including oxidative stress, PAMPs and pro-inflammatory cytokines.

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Previous studies have demonstrated direct concentration-dependent anti-inflammatory and anti-apoptotic effects of SRT-015 *in vitro*, while oral SRT-015 administration reduced liver injury in rodent models of alcohol-related liver disease and acetaminophen (APAP) overdose (Plonowski et al, Hepatology 2020;72, 1031A; Elias et al, Hepatology 2022;76, S635; Elias et al, J Hepatol 2023;78, S139). The aim of this study was to evaluate the efficacy of intravenous (i.v.) SRT-015 administration in 2 models of acute liver failure. **Methods:** Acute liver failure was induced in C57Bl6 mice either by APAP (300 mg/kg, intraperitoneally (i.p.)) alone, or by i.p. co-injection of galactosamine (GalN, 700 mg/kg) and lipopolysaccharide (LPS, 25 µg/kg). SRT-015 was administered i.v. after APAP or GalN/LPS injection (0.5-1 hour). Mice were terminated 6 hours after pathological induction. **Results:** In APAP mice, i.v. SRT-015 administration (1 mg/kg) reduced ALT (825 vs 3046 U/L, p=0.01) and total bilirubin (0.03 vs 0.12 mg/dl, p=0.003) compared to the vehicle-treated control group. In GalN/LPS mice, i.v. SRT-015 administration (0.75 mg/kg) reduced liver injury as shown with ALT (1959 vs. 4618 U/L, p= 0.03) as well as serum pro-inflammatory cytokines TNFalpha (7.0 vs.15.8 pg/ml, p=0.02) and IL-6 (264 vs. 812 pg/ml, p=0.006) levels compared to the vehicle-treated control group. **Conclusion:** These results demonstrate that i.v. SRT-015 administration alleviates liver injury and counteracts systemic inflammation in curative settings in acute liver failure models, which support its development for the treatment of patients with ACLF.

Disclosures: Vanessa Legry: GENFIT SA: stock - privately held company, Maryse Malysiak: Nothing to Disclose, Philippe POULAIN: Nothing to Disclose, Valérie Daix: Nothing to Disclose, Remy Hanf: Nothing to Disclose, Dean Hum: Genfit: Executive role, Bart Staels: Genfit SA: Consultant, Joan Claria: Nothing to Disclose, Sakina Sayah Jeanne: Nothing to Disclose

1598 | MSC-DERIVED EXTRACELLULAR VESICLES ALLEVIATE ISCHEMIA LIVER INJURY VIA INHIBITING NETS FORMATION

Xiaoze Wang[1] *Xuefeng Luo*[1] *Li Yang*[1] *Guofeng Liu*[1]

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Background: Transjugular intrahepatic portosystemic shunt (TIPS) is a highly efficacious approach for managing portal hypertension complications. However, portal venous shunt-related ischemia often results in liver dysfunction or failure following TIPS. This study aims to investigate the therapeutic potential of mesenchymal stromal cells (MSCs) in mitigating ischemic liver injury and elucidating the underlying mechanism. **Methods:** We employed portal venous branch ligation to partially obstruct the blood supply to liver to establish a model of ischemic liver injury and performed transcriptome sequencing on liver tissue. Additionally, we utilized MSCs derived from human umbilical cord to treat the mouse model of ischemic liver injury, elucidating the mechanism through both in vitro and in vivo experiments. **Results:** The transcriptome sequencing and differential gene enrichment analysis revealed significant enrichment of cytokine pathways and glucose metabolism pathways. Additionally, the plasma levels of IL-6, IL-17A, MMP-9, and MPO, which serve as indicators of neutrophil activation, were found to be elevated in patients after TIPS and in mouse model. The average serum levels of AST, ALT, and bilirubin in the mice model treated with MSC were significantly reduced. MSC treatment inhibited the formation of neutrophil extracellular traps (NETs). We further confirmed that both MSC medium and MSC-derived extracellular vesicles (MSC-EVs) were able to inhibit the release of NETs from neutrophils by interfering with GSDMD shearing. **Conclusion:** Both MSC and MSC-EV possess the potential to mitigate ischemic liver injury through hindering the NETs formation. They may be considered for the prevention of liver dysfunction after TIPS procedure.

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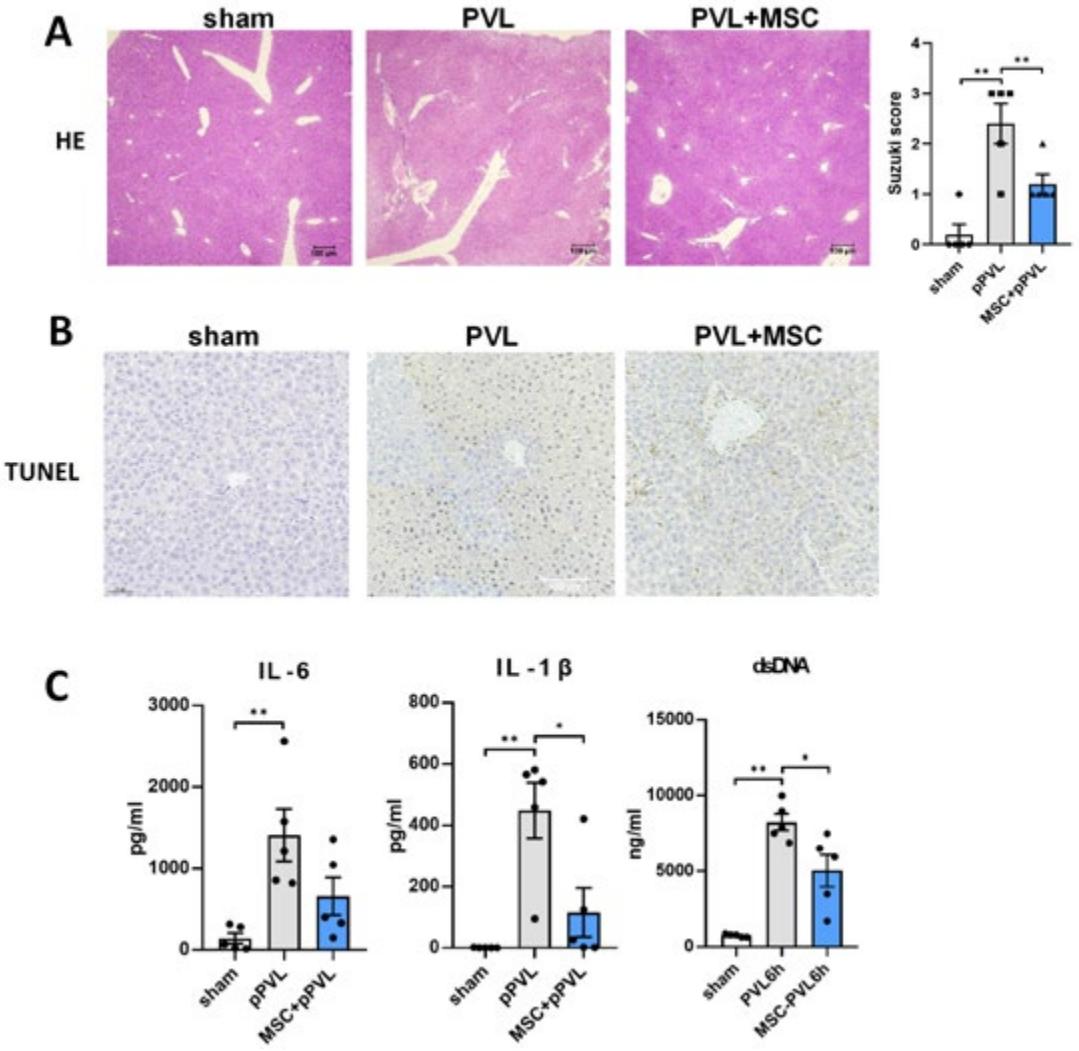

Disclosures: Xiaoze Wang: Nothing to Disclose, Xuefeng Luo: Nothing to Disclose, Li Yang: Nothing to Disclose, Guofeng Liu: Nothing to Disclose

1599 | NATURAL KILLER CELL-DERIVED EXTRACELLULAR VESICLES ALLEVIATE CD8+ T CELL EXHAUSTION IN ACUTE-ON-CHRONIC LIVER FAILURE VIA TGF-β/SMAD PATHWAY

Zhouhan Wang[1] Zhihui Li[2] Junyi Wang[2] Jing Zhang[2] Junfeng Chen[2] Bingliang Lin[2]

[1]The Third Affiliated Hospital of Sun Yat-Sen University, [2]Third Hospital of Sun Yat-sen University

Background: Acute-on-chronic liver failure (ACLF) is a severe syndrome with high short-term mortality due to lack of effective internal medical treatment. Immune injury is a key pathogenic mechanism of ACLF. Previous researched have demonstrated T cell exhaustion in various liver diseases including ACLF. However, the underlying mechanism of T cell exhaustion in ACLF remained unclear. In this study, we presented single-cell immune features of ACLF and demonstrated an underlying mechanism of $CD8^+$T cell exhaustion involving TGF-β/Smad pathway. We also demonstrated a possible immunotherapy approach of ACLF using natural killer cell-derived extracellular vesicles (NK-EVs). **Methods:** PBMCs of ACLF patients and Healthy controls (HC) were collected and isolated. Library were prepared and single-cell RNA sequencing were performed using the Illumina Hiseq 4000 sequencer. Cell Ranger toolkit and reference genome GRCh38 were used for alignment and quantification. Seurat and ggplot2 were mainly used R packages for downstream analysis and visualization. $CD8^+$ T cells derived from PBMCs were treated with ACLF or HC plasma and/or NK-EVs. TβRI/II inhibitor LY2109761

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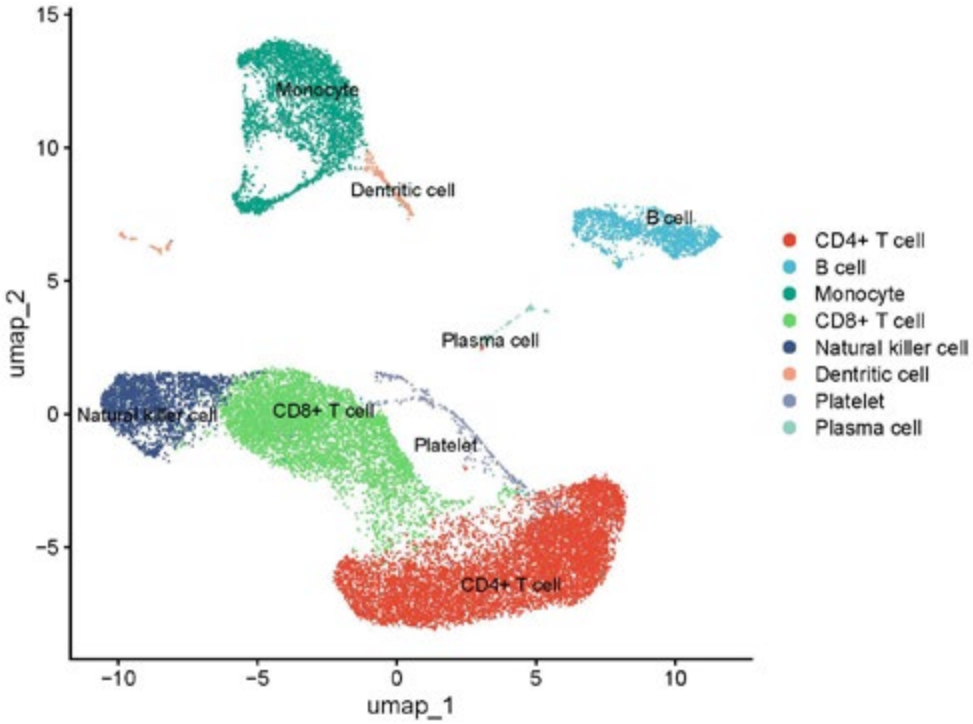
or recombinant TGF-β were cultured with cells to regulate TGF-β/Smad pathway. Flow cytometry were performed to validated the expression of perforin, granzyme B and inhibitory immune receptors such as TIGIT, LAG-3, PD-1 and CTLA-4. Protein and mRNA expression level of TGF-β1/2/3, TβRI/II, total and phosphorylated Smad2/3/4 were determined by western blot and qPCR. **Results:** ScRNA-seq of PMBCs presented higher expression level of PD-1, CTLA-4, LAG-3, TIGIT and 2B4 on $CD8^+$ T cell in ACLF patient, compared to HC. Flow cytometry validated the upregulated of TIGIT, LAG-3, PD-1 and CTLA-4 in $CD8^+$ T cell of ACLF patient. KEGG enrichment analysis revealed a significant enrichment of the TGF-β signaling pathway in the $CD8^+$ T cell subset. Cellchat analysis showed enhanced communication between NK and $CD8^+$ T cell, with high probability of involving TGF-β signaling pathway network. Compared to HC plasma treatment, $CD8^+$ T cells treated with ACLF plasma exhibit characteristics of exhaustion, which can be alleviated by NK-EVs or TβRI/II inhibitor. However, this therapeutic effect was diminished when TGF-β is added, and $CD8^+$ T cells presented a reappearance of exhaustion features. **Conclusion:** The circulating $CD8^+$ T cells in ACLF patients exhibit characteristics of exhaustion. NK-EVs alleviate $CD8^+$ T cell exhaustion in ACLF via TGF-β/Smad pathway.



Disclosures: Zhouhan Wang: Nothing to Disclose, Zhihui Li: Nothing to Disclose, Junyi Wang: Nothing to Disclose, Jing Zhang: Nothing to Disclose, Junfeng Chen: Nothing to Disclose, Bingliang Lin: Nothing to Disclose

1600 | A NATION-WIDE RETROSPECTIVE COHORT STUDY OF THE OUTCOMES, PREVALENCE AND COMPARATIVE ANALYSIS OF LIVER CIRRHOSIS AND PULMONARY HYPERTENSION

Anwar Uddin Prashil Dave[1] Madia Ahad[2] Rafat Uddin[2] Dipsa Shastri[3] Afgal Ahad[2] Rahat Uddin[2] Peter Lymberopoulos[2] Sahil Chaddha[1]

[1]SUNY Downstate Medical Center, [2]State University of New York Downstate, [3]East Tennessee State University

Background: Pulmonary vascular complications, including pulmonary hypertension (PH), are not uncommon in patients with liver cirrhosis (LC) and is now recognized as one of significant comorbidities among LC patients. There are limited data available comparing the outcomes of PH versus non-PH in patients with LC. The aim of present study is to examine the prevalence and outcomes of PH in patients admitted with LC using the nationwide database. **Methods:** We used the Healthcare Cost and Utilization Project (HCUP) Nationwide Inpatient Sample (NIS) to identify adult patients admitted with LC during 2016 – 2020 using ICD-10-CM codes.

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We used ICD-10-CM codes to identify patients with PH (I27.0 and I27.2X). Main outcomes were in-hospital mortality, length of stay (LOS), and hospital costs. We evaluate the association between PH and outcomes using survey based multivariate logistic regression models for in-hospital mortality, Poisson regression for LOS, and generalized linear model with gamma distribution and log link for hospitalization cost. We used the Poisson regression to examine the annual trend of ACS hospitalizations among LC patients. Models were adjusted for age, sex, race and ethnicity, primary payer, Charlson comorbidity index, hospital bed size, hospital region and hospital teaching status. **Results:** We identified a total of 3,648,794 LC hospitalizations between 2016 and 2020 in the United States and 206,050 (5.65%) of them were associated with PH. There were 2% annual increase in proportion of PH hospitalizations among LC patients from 2016 to 2020 (34,425, 5.22% in 2016 to 45,645, 5.92% in 2020, adjusted rate ratio 1.02, 95% CI 1.01 – 1.03, p < <0.001). In-patient mortality was significantly higher in PH patients with LC (7.2% vs 5.8%, adjusted OR: 1.12, 95%CI: 1.07 – 1.16, P < 0.001, Table 2). PH patients with LC had an increased length of stay (7.6 ± 0.05 vs 6.0 ± 0.02 days, P < 0.001) an increased cost of hospitalization ($23,363 ± 247 vs $17,725 ± 112, P < 0.001, Table 1). **Conclusion:** PH is common among patients with LC with increasing trend in recent years. PH in LC is associated with higher in-hospital mortality, increased length of stay and increased cost of hospitalization.

Table 1: Comparison of primary outcomes: liver cirrhosis with versus without pulmonary hypertension

	Pulmonary Hypertension		Adjusted OR / RR		
Characteristic	**No, N = 3,442,744**	**Yes, N = 206,050**	**OR/RR**	**95% CI**	**p-value**
In-hospital mortality - N (%)	199,745 (5.8%)	14,795 (7.2%)	1.12	1.07, 1.16	<0.001
LOS (days) - mean (SE)	6.0 (0.02)	7.6 (0.05)	1.23	1.21, 1.24	<0.001
Hospital Cost ($, 2020) - mean (SE)	17,724.8 (111.84)	23,362.8 (247.05)	1.26	1.25, 1.28	<0.001

Relative ratio is reported using Poisson regression model for LOS
Relative ratio is reported using generalized linear model with gamma distribution and log link for Hospital Cost; adjusted for inflation using Consumer Price Index (CPI) for Medical care services in U.S. city average, all urban consumers, chained, with 2020 as the reference point
Variables used for multivariate logistic regression: age, sex, race, insurance status, Charlson comorbidity index, hospital bed size, and hospital region

Disclosures: Anwar Uddin: Nothing to Disclose, Prashil Dave: Nothing to Disclose, Madia Ahad: Nothing to Disclose, Rafat Uddin: Nothing to Disclose, Dipsa Shastri: Nothing to Disclose, Afgal Ahad: Nothing to Disclose, Rahat Uddin: Nothing to Disclose, Peter Lymberopoulos: Nothing to Disclose, Sahil Chaddha: Nothing to Disclose

1601 | PREDICTING MORTALITY AND CIRRHOSIS-RELATED COMPLICATIONS WITH MELD3.0: AN ANALYSIS OF A MULTICENTER COHORT

JIHYE LIM[1] Jihoon Kim[2] Ahlim Lee[2] Ji Won Han[2] Soon Kyu Lee[2] Hyun Yang[3] Heechul Nam[2] Haelim Lee[2] Do Seon Song[2] Sung Won Lee[2] Hee Kim[2] Jung Hyun Kwon[2] Chang Wook Kim[4] U Im Chang[2] Soon Woo Nam[2] Seok-Hwan Kim[2] Pil Soo Sung[2] Jeong Won Jang[2] SI HYUN BAE[2] Jong choi[2] Seung Kew Yoon[2] Myeong Jun Song[2]

[1]Yeouido St. Mary's Hospital, [2]The Catholic University of Korea, [3]Seoul St. Mary's Hospital, [4]Uijeongbu St. Mary's Hospital

Background: The Model for End-Stage Liver Disease (MELD) 3.0 was recently proposed as a predicting model for liver transplantation-free survival in patients with end-stage liver disease. This study aimed to evaluate the performance of MELD3.0 for predicting mortality in comparison to Child-Pugh class, albumin-bilirubin (ALBI) grade, MELD, and MELD sodium (MELDNa) and liver related complications. **Methods:** We evaluated multicenter

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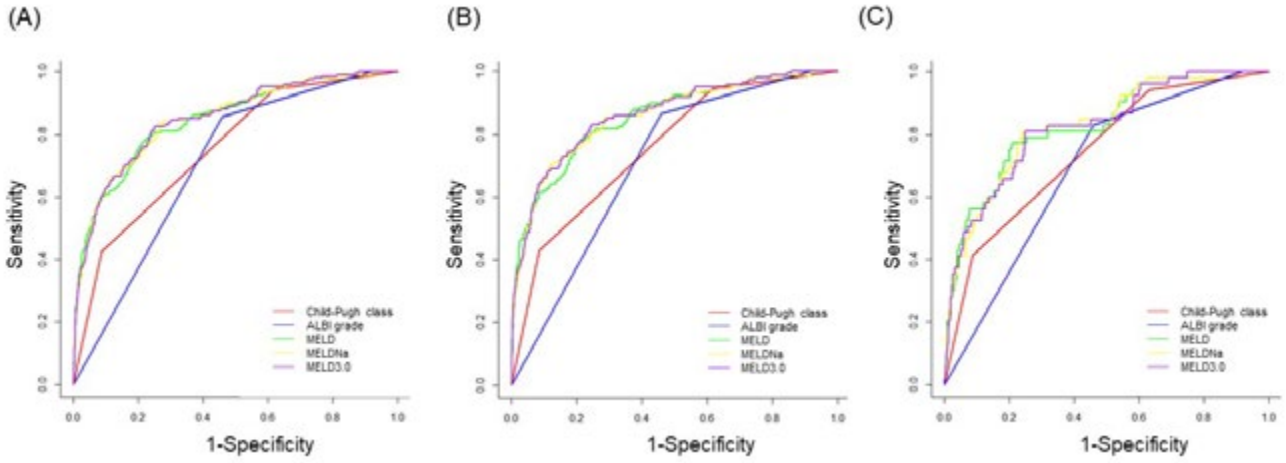
retrospective cohort incorporated patients with cirrhosis between 2013 and 2019. We conducted comparisons of the area under the receiver operating characteristic curve (AUROC) between MELD3.0 and other models for predicting 3-month mortality Additionally, we assessed the risk of cirrhosis-related complications according to the score of MELD3.0. **Results:** A total of 3,314 patients were comprised, with an average age of 55.9 ± 11.3 years, among whom 70.2% were male. The average scores for Child-Pugh, ALBI, MELD, MELDNa, and MELD3.0 upon admission were 7.4 ± 1.6, -1.5 ± 0.7, 14.7 ± 6.3, 15.7 ± 7.1, and 16.8 ± 7.1, respectively. Within the initial three months, 220 patients (6.6%) died, and MELD3.0 showed best predictive performance compared to other models with AUROC of 0.851 outperforming Child-Pugh class (0.754), ALBI grade (0.704), MELD (0.846) and MELDNa (0.849; Figure). MELD3.0 was associated with the increased risk of cirrhosis-related complications by 1.033-fold. The risk of hepatorenal syndrome showed the highest elevation with adjusted hazard ratio (HR) of 1.149 (95% confidence interval [CI]: 1.111-1.188), followed by hepatic encephalopathy (adjusted HR: 1.077, 95% CI: 1.063-1.090), and ascites (adjusted HR: 1.040, 95% CI: 1.028-1.053). **Conclusion:** MELD3.0 demonstrated robust prognostic performance in predicting both mortality in patients with cirrhosis. Moreover, it was linked to cirrhosis-related complications, particularly those involving kidney function, such as hepatorenal syndrome and ascites.



Disclosures: JIHYE LIM: Nothing to Disclose, Jihoon Kim: Nothing to Disclose, Ahlim Lee: Nothing to Disclose, Ji Won Han: Nothing to Disclose, Soon Kyu Lee: Nothing to Disclose, Hyun Yang: Nothing to Disclose, Heechul Nam: Nothing to Disclose, Haelim Lee: Nothing to Disclose, Do Seon Song: Nothing to Disclose, Sung Won Lee: Nothing to Disclose, Hee Kim: Nothing to Disclose, Jung Hyun Kwon: Nothing to Disclose, Chang Wook Kim: Nothing to Disclose, U Im Chang: Nothing to Disclose, Soon Woo Nam: Nothing to Disclose, Seok-Hwan Kim: Nothing to Disclose, Pil Soo Sung: Nothing to Disclose, Jeong Won Jang: Nothing to Disclose, SI HYUN BAE: Nothing to Disclose, Jong choi: Nothing to Disclose, Seung Kew Yoon: Nothing to Disclose, Myeong Jun Song: Nothing to Disclose

1602 | THE ETIOLOGY OF CHRONIC LIVER DISEASE IS AN INDEPENDENT PROGNOSTIC FACTOR IN PATIENTS WITH ACUTELY DECOMPENSATED CHRONIC LIVER DISEASE

Do Seon Song[1] Hee Yeon Kim[1] Young Kul Jung[2] Hyung Joon Yim[2] Eileen Yoon[3] Ki Tae Suk[4] Sang Gyune Kim[5] Moon Young Kim[6] Young Chang[7] Soung Won Jeong[7] JAE YOUNG JANG[8] Sung Eun Kim[9] Jung Gil Park[10] Won Kim[11]

[1]The Catholic University of Korea, [2]Korea University Ansan Hospital, [3]Hanyang University, [4]Hallym University, [5]Mayo Clinic Rochester, [6]Yonsei University Wonju College of Medic, [7]SoonChunhyang University Seoul Hospital, [8]Soonchunhyang University Seoul Hospital, [9]Hallym University college of Medicine, [10]Yeungnam University College of Medicine, [11]Seoul National University

Background: The prognosis for patients with acutely decompensated chronic liver disease (CLD) is very poor. There is a lack of research on the prognostic impact of underlying CLD in patients with acutely decompensated CLD. **Methods:** We enrolled a total of 1,352 patients, categorized into three groups: those with viral hepatitis (VH)

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(n=206), alcoholic liver disease (ALD) (n=1,017), and a combination of alcohol and viral hepatitis (Combination) (n=129) based on etiology of underlying CLD. Primary outcome was 28-day liver transplantation free survival (TFS). **Results:** The VH group had lower Child-Pugh, MELD, MELD-Na, CLIF-SOFA, and CLIF-C OF scores compared to the ALD and Combination groups, while the ALD and Combination groups had similar scores. The 28-day TFS was similar between the VH and ALD groups (*P*=0.661), but significantly lower in the Combination group compared to other groups (*P*<0.05). In the subgroup analysis comparing the VH and ALD groups (Subgroup 1), multivariate analysis was conducted using the prognostic factors identified in the univariate analysis for 28-day TFS, revealing independent factors such as hepatic encephalopathy (HE), systemic inflammatory response syndrome, albumin, bilirubin, AST, and International normalized ratio (INR). After adjusting for independent factors, the prognosis of the VH group was significantly poorer than that of the ALD group (Hazard ratio (HR) 1.781, 95% confidence interval (CI) 1.276-2.486, *P*=0.001). In the subgroup analysis comparing the ALD and Combination groups (Subgroup 2), multivariate revealed independent factors such as HE, albumin, bilirubin, AST, and INR. After adjusting for independent factors in multivariate analysis, the combination group also exhibited a significantly poorer prognosis (HR, 2.07, 95% CI 1.156-3.077, *P*=0.014). The underlying CLD categories were adjusted by the prognostic scores. In subgroup 1, the VH group exhibited a poorer prognosis than the ALD group, following adjustment for Child-Pugh, CLIF-SOFA, and CLIF-C OF scores (all *P*<0.05). In Subgroup 2, the Combination group demonstrated a poorer prognosis than the ALD group, following adjustment for Child-Pugh, MELD, MELD-Na, CLIF-SOFA, and CLIF-C OF scores (all *P*s<0.05). **Conclusion:** Patients with VH as the etiology of underlying CLD exhibit a poorer prognosis compared to those with ALD. Furthermore, the combined ALD and VH group also demonstrates a worse prognosis than the ALD-only group. Thus, different etiologies would require different risk prediction methods.

Disclosures: Do Seon Song: Nothing to Disclose, Hee Yeon Kim: Nothing to Disclose, Young Kul Jung: Nothing to Disclose, Hyung Joon Yim: Nothing to Disclose, Eileen Yoon: Nothing to Disclose, Ki Tae Suk: Nothing to Disclose, Sang Gyune Kim: Nothing to Disclose, Moon Young Kim: Nothing to Disclose, Young Chang: Nothing to Disclose, Soung Won Jeong: Nothing to Disclose, JAE YOUNG JANG: Nothing to Disclose, Sung Eun Kim: Nothing to Disclose, Jung Gil Park: Nothing to Disclose, Won Kim: Nothing to Disclose

1603 | EFFECT OF VS-01 ON ACUTE-ON-CHRONIC LIVER FAILURE-RELATED TOXINS SUCH AS LIPOPOLYSACCHARIDE AND HYDROPHOBIC BILE ACIDS IN VITRO

Marie Bobowski-Gerard[1] Désirée Füglistaller[2] Simon Debaecker[1] Bérénice Alard[1] Jérémy Magnanensi[1] Dean Hum[1] Bart Staels[3] Katharina Staufer[2] Meriam Kabbaj[2] Jonel Trebicka[4] Vanessa Legry[1] Sakina Sayah Jeanne[1]

[1]Genfit S.A., Loos, France, [2]Versantis AG (Genfit group), Zurich, Switzerland, [3]INSERM U1011, Univ. Lille, Institut Pasteur de Lille, Lille, France, [4]Hospital of the Goethe University Frankfurt,. University Hospital Münster, Germany

Background: Acute-on-chronic liver failure (ACLF) is a severe syndrome affecting patients with cirrhosis and is associated with high short-term mortality. Systemic inflammation, triggered by bacteria or pathogen-associated molecular patterns (PAMPs) such as lipopolysaccharides (LPS), is a key driver of ACLF. In addition, an altered bile acid profile has been described in ACLF. Glycochenodeoxycholic acid (GCDA), glycocholic acid (GCA) and cholic acid (CA) have for instance been associated with acute decompensation and ACLF (Horvatits et al., Liver Int., 2016). VS-01 is an intraperitoneal pH-gradient investigational liposomal drug to treat ACLF by enhancing the clearance of ammonia and other toxins. Using in vitro systems, we assessed the direct capacity of VS-01 to remove ACLF-related toxins, in particular LPS and hydrophobic bile acids. **Methods:** To assess the ability of VS-01 to counteract LPS-induced cytokine secretion, THP1 human macrophages were treated with 1 µg/mL LPS (Klebsiella) for 4h before measurement of cytokines in the supernatant. Increasing doses of VS-01 (up to 4 mM) were added concomitantly to LPS. To assess the ability of VS-01 to remove GCDA, GCA and CA, we used an in vitro dialysis system, composed of two chambers separated by a 12 kDa membrane. Both chambers were filled with a buffer containing the respective bile acid while VS-01 remained on one side. After 4h of incubation, samples were collected for measurement of bile acid concentration. **Results:** While LPS treatment of human macrophages led to a strong increase of TNFα and IL-6, the addition of VS-01 to the cell media reduced the LPS-induced cytokine secretion in a dose-dependent manner, with a maximum efficacy observed at 4 mM VS-01: 37% reduction of TNFα (p=0.02) and 67% reduction of IL-6 (p<0.001). In addition, we showed that VS-01 removed GCDA, GCA and CA in a dose-dependent manner; the most hydrophobic bile acid (GCDA) displaying the highest binding rate (19, 30 and 36% of bound GCDA at 2, 5 and 8 mM VS-01, respectively). **Conclusion:** This study shows mechanistic evidence that VS-01 inhibits LPS-induced cytokine release from macrophages and removes

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hydrophobic bile acids, on top of its ability to clear ammonia. This is in line with findings from the First-in-Human VS-01 study suggesting GCA to be captured by VS-01 (Tyc et al., J. Hepatol, THU-088, 2024).
Altogether, these studies support further development of VS-01 in ACLF (Phase 2a study UNVEIL-ITTM NCT05900050, status: recruiting).

Disclosures: Marie Bobowski-Gerard: Nothing to Disclose, Désirée Füglistaller: Versantis AG: Employee, Buss ChemTech AG: Employee, Simon Debaecker: Nothing to Disclose, Bérénice Alard: Nothing to Disclose, Jérémy Magnanensi: Genfit SA: Employee, Dean Hum: Genfit: Executive role, Bart Staels: Genfit SA: Consultant, Katharina Staufer: GENFIT: Employee, Meriam Kabbaj: Versantis AG: Employee, Jonel Trebicka: Nothing to Disclose, Vanessa Legry: GENFIT SA: stock - privately held company, Sakina Sayah Jeanne: Nothing to Disclose

1604 | MESENCHYMAL STEM CELL PROMOTE MACROPHAGE EFFEROCYTOSIS IN THE CONTEXT OF ACLF VIA ARID3A/MERTK AXIS

Junyi Wang[1] *Bingliang Lin*[1] *Zhouhan Wang*[1] *Zhihui Li*[1] *Jing Zhang*[1]

[1]*The Third Affiliated Hospital of SYSU*

Background: Acute-on-chronic liver failure is a disease with a high mortality rate and poor traditional treatment effect. Our group previously found through in vivo and in vitro experiments that BM-MSC can regulate the immune microenvironment in the liver under the background of ACLF, promoting the transformation of macrophages from M1 to M2.This mechanism is achieved by upregulating the expression of Mertk in macrophages.Efferocytosis refers to a multi-step process in which macrophages clear apoptotic cells, with the significance of quickly clearing apoptotic cells to prevent their accumulation and avoid releasing toxic substances that may induce inflammation and causing secondary necrosis. Mertk is the core of macrophage efferocytosis which can promote macrophage M2 polarization, while M2 macrophages have stronger phagocytosis ability than M1 macrophages. Arid3a has been shown to be an upstream negative regulatory transcription factor of the Mertk protein. MSC exosomes have emerged as the most promising cell-free alternative to MSC due to their nanoscale size,and abundant protein and nucleic acid composition. This study aims to demonstrate the hypothesis that MSC exosomes can enhance macrophage efferocytosis in the context of ACLF via the Arid3a/Mertk axis. **Methods:** The ACLF mouse model was treated with BM-MSC exosomes/PBS.Firstly, HE staining was performed on liver tissue. Secondly, immunofluorescence was performed on liver paraffin sections to detect macrophage efferocytosis. Then the mRNA expression of Arid3a and Mertk were detected by qPCR, as well as the various efferocytosis molecules and the inflammatory factors.Western blotting was performed on the extracted proteins from mouse liver tissue to detect the expression of Mertk,and the expression of M1 markers (iNOS) and M2 markers (Arg-1) in macrophages. **Results:** 1.HE staining showed that the degree of inflammation and necrosis in the liver of mice in exosome group was lower than the control group. 2.The qPCR results indicate that the expression of Mertk in the exosome group is higher, while the expression of Arid3a is lower than the control group. At the same time, the expression of various efferocytosis molecules in the exosome group is up-regulated.3.The WB results indicate that the expression level of Arid3a in the exosome group is lower and the expression of Mertk is higher than the control group. Meanwhile, The expression of Arg-1 was higher,while the expression of iNOS was lower than the control group; 4.The immunofluorescence results of liver tissue slices indicate that the extracellular vesicle group has stronger efferocytosis effect than the control group. **Conclusion:** MSC exosomes can enhance macrophage efferocytosis in the context of ACLF via the Arid3a/Mertk axis.

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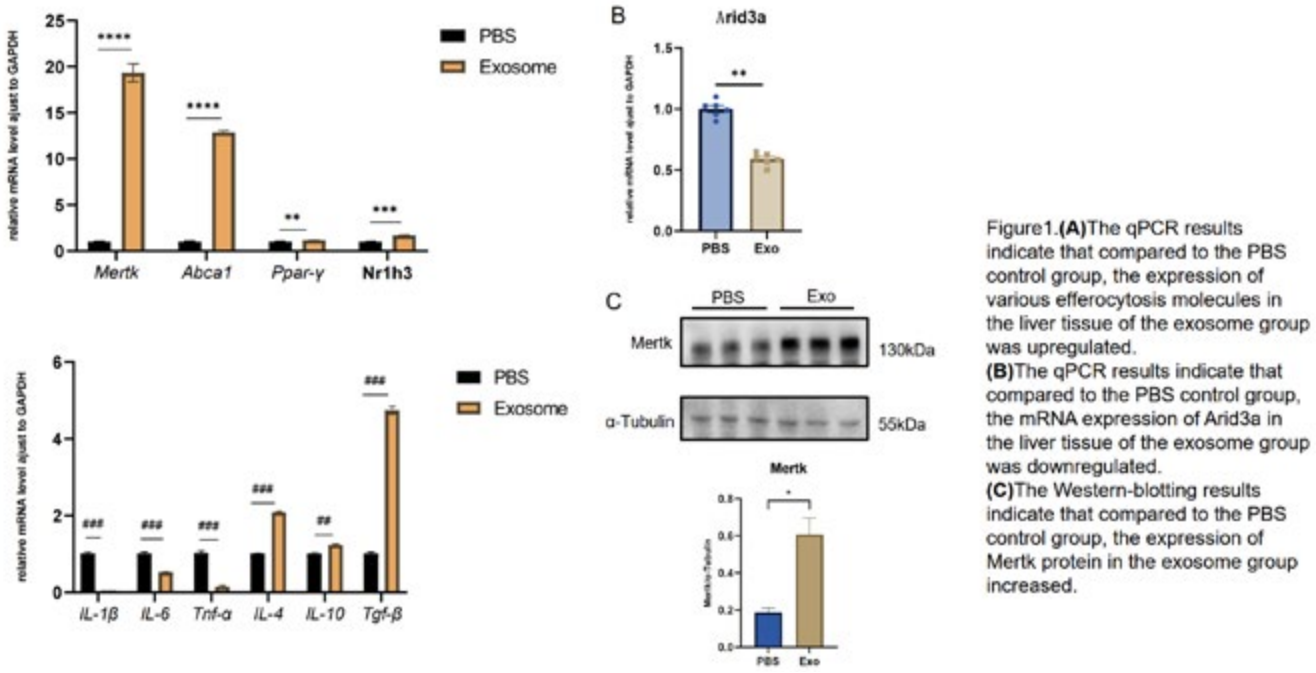

Figure1.**(A)**The qPCR results indicate that compared to the PBS control group, the expression of various efferocytosis molecules in the liver tissue of the exosome group was upregulated.
(B) The qPCR results indicate that compared to the PBS control group, the mRNA expression of Arid3a in the liver tissue of the exosome group was downregulated.
(C) The Western-blotting results indicate that compared to the PBS control group, the expression of Mertk protein in the exosome group increased.

Disclosures: Junyi Wang: Nothing to Disclose, Bingliang Lin: Nothing to Disclose, Zhouhan Wang: Nothing to Disclose, Zhihui Li: Nothing to Disclose, Jing Zhang: Nothing to Disclose

1605 | COMPARATIVE EFFICACY OF MYCOPHENOLATE MOFETIL VS. AZATHIOPRINE IN AUTOIMMUNE HEPATITIS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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[1]TriHealth Good Samaritan Hospital, [2]University of Toledo, [3]Alexandria University, [4]Aswan University, [5]Medical Director TriHealth

Background: Azathioprine (AZA) is the standard treatment for both induction and maintenance of response in autoimmune hepatitis (AIH). However, lifelong administration is typically required, and the combination therapy of prednisolone and azathioprine raises significant concerns regarding efficacy and tolerability, especially given the high relapse rates following AZA cessation. Consequently, there is a need to explore alternative treatment options. This systematic review and meta-analysis compared the efficacy and safety of mycophenolate mofetil (MMF) versus AZA, both in combination with prednisolone, for the treatment of AIH. **Methods:** PubMed, Cochrane, Scopus, and Web of Science were searched to identify randomized clinical trials and cohort studies comparing AZA and MMF for the treatment of AIH. Steroid withdrawal and complete biochemical response (CBR) were compared between the MMF and AZA groups in four studies. Subgroup analyses were performed based on age (above and below 50 years) and IgG levels (above and below 2400 mg/dL). RevMan (version 5.4) software was used for the meta-analysis. **Results:** Five studies comprising 505 patients were included in the final analysis. The pooled analysis showed a statistically significant association between the MMF group and increased CBR compared with the AZA group (RR= 0.69, 95% CI: 0.50 to 0.97), with no significant difference between the two groups regarding steroid withdrawal. Subgroup analysis by age revealed a significant association between the MMF group and increased CBR in patients over 50 years (RR= 0.61, 95% CI: 0.47 to 0.80), and a significant association between the MMF group and increased biochemical remission compared with the AZA group in patients under 50 years (RR=0.82, 95% CI: 0.71 to 0.94). IgG subgroup analysis indicated a significant association between the MMF group and increased biochemical remission compared with the AZA group in patients with IgG levels less than 2400 mg/dL (RR=0.61, 95% CI: 0.47 to 0.80). **Conclusion:** The use of MMF was significantly associated with increased CBR compared to AZA in patients with AIH. Additionally, there was no significant association between the two groups regarding steroid withdrawal. Further research is needed to fully elucidate the optimal treatment strategy for AIH patients across different subpopulations.

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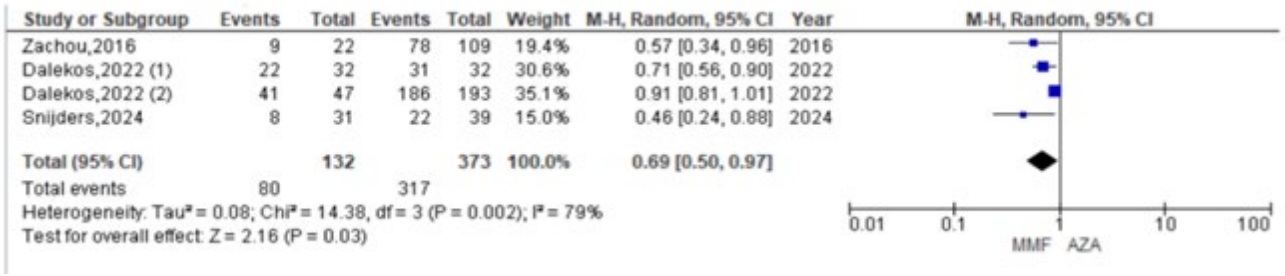

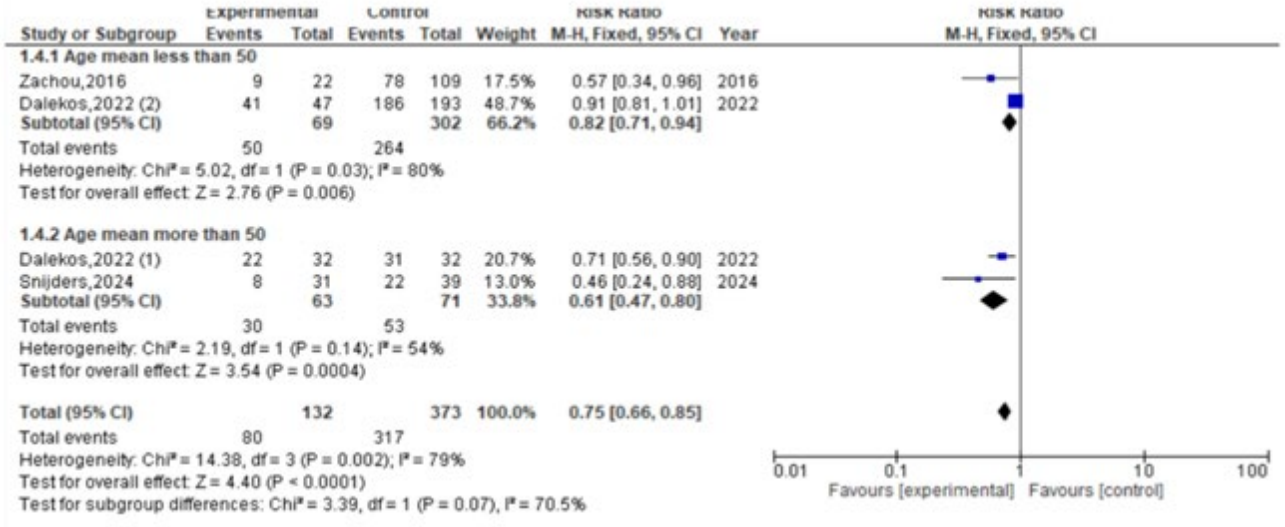

Disclosures: Mhd kutaiba Albuni: Nothing to Disclose, Bisher Sawaf: Nothing to Disclose, Karam R. Motawea: Nothing to Disclose, Momen Mohamed Ibrahim: Nothing to Disclose, Noheir Ashraf Ibrahem Fathy Hassan: Nothing to Disclose, Momen Moussa: Nothing to Disclose, Mayar Ibrahim: Nothing to Disclose, Maram Albandak: Nothing to Disclose, Venkata Muddana: Nothing to Disclose

1606 | EARLY INPATIENT PARACENTESIS ASSOCIATED WITH LOWER INPATIENT MORTALITY COMPARED TO THE LATE PARACENTESIS

Waqas Rasheed[1] Hassam Ali[2] Vinay Jahagirdar[3] Syed Adeel Hassan[1] Umar Hayat[4] Amna Iqbal[5] Gnanashree Dharmarpandi[6]

[1]University of Kentucky, [2]ECU Health Medical Center, Greenville,NC, [3]University of Missouri–Kansas City, MO, [4]Geisinger Medical Center, [5]University of Toledo, [6]Texas Tech University in Amarillo, TX

Background: Liver cirrhosis patients with ascites often require paracentesis, but the optimal timing for this procedure is often overlooked. This study aims to compare early versus late paracentesis outcomes in these patients. **Methods:** This retrospective cohort study utilized data from the TriNetX database. Liver cirrhosis patients with ascites who underwent inpatient paracentesis were identified and divided into early (<24 hours from admission) and late paracentesis groups (>24 hours from admission) based on when the first paracentesis was performed after hospitalization. Propensity score matching was used to balance baseline characteristics. Key outcomes included 30-day inpatient acute kidney injury (AKI), readmission, ICU transfer, and mortality rates, as well as 90-day mortality and liver transplant rates. **Results:** There were a total of 63,323 before matching, After matching, 21,351 patients were analyzed in each group. The early paracentesis group demonstrated a significantly lower 30-day mortality rate (15.63% vs. 17.14%, P < 0.0001; OR 0.90, 95% CI 0.85-0.94). Similarly, the 90-day mortality rate was also low compared to the late paracentesis group (23.17% vs. 25.22%, P < 0.0001; OR 0.89, 95% CI 0.86-0.94). Early paracentesis was also associated with higher liver transplant rates at 30 days (1.68% vs. 1.28%, P = 0.0006; OR 1.32, 95% CI 1.13-1.54) and 90 days (2.88% vs. 2.07%, P < 0.0001; OR 1.40, 95% CI 1.24-1.59). However, the early paracentesis group had higher 30-day inpatient AKI rates (34.84% vs. 24.76%, P < 0.0001; OR 1.63, 95% CI 1.56-1.70) and ICU transfer rates (17.10% vs. 11.11%, P < 0.0001; OR 1.65, 95% CI 1.56-1.75). **Conclusion:** Early paracentesis in liver cirrhosis patients with ascites is associated with

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lower 90-day and 30-day mortality rates and higher liver transplant rates, highlighting its potential benefits. These findings underscore the need for careful consideration of the timing of paracentesis in this patient population.

	Before matching			After Matching			
Outcome	Early paracentesis	Late paracentesis	P Value	Early paracentesis	Late paracentesis	P Value	OR (95% CI)
30-day mortality	3331 (15.80%)	7633 (17.14%)	<0.0001	3358 (15.63%)	3684 (17.14%)	<0.0001	0.90 (0.85-0.94)
90-day mortality	4961 (23.17%)	11078 (24.88%)	<0.0001	4961 (23.17%)	5400 (25.22%)	<0.0001	0.89 (0.86-0.94)
30-day AKI	7464 (34.73%)	11007 (24.56%)	<0.0001	7461 (34.84%)	5303 (24.76%)	<0.0001	1.63 (1.56-1.70)
30-day readmission	15390 (71.61%)	31107 (69.40%)	<0.0001	15390 (71.61%)	14949 (69.56%)	<0.0001	1.10 (1.06-1.15)
30-day ICU transfer	3417 (17.10%)	4007 (10.98%)	<0.0001	3417 (17.10%)	1944 (11.11%)	<0.0001	1.65 (1.56-1.75)
30-day liver transplant	362 (1.68%)	545 (1.22%)	<0.0001	361 (1.68%)	275 (1.28%)	0.0006	1.32 (1.13-1.54)
90-day liver transplant	617 (2.88%)	891 (2.00%)	<0.0001	617 (2.88%)	443 (2.07%)	<0.0001	1.40 (1.24-1.59)
30-day SBP infection	2289 (10.65%)	2861 (6.38%)	<0.0001	2289 (10.65%)	1470 (6.84%)	<0.0001	1.70 (1.58-1.73)

OR; Odds Ratio, AKI; Acute Kidney Injury, ICU; Intensive Care Unit, SBP; Spontaneous Bacterial Peritonitis

Disclosures: Waqas Rasheed: Nothing to Disclose, Hassam Ali: Nothing to Disclose, Vinay Jahagirdar: Nothing to Disclose, Syed Adeel Hassan: Nothing to Disclose, Umar Hayat: Nothing to Disclose, Amna Iqbal: Nothing to Disclose, Gnanashree Dharmarpandi: Nothing to Disclose

1607 | AARC LIVER FAILURE SCORE BASED ON REGISTRY OF 10,994 PATIENTS IS A BETTER PROGNOSTIC MODEL FOR ACLF PATIENTS JUSTIFYING GLOBAL APPLICATION AND EXPANSION OF AARC DATABASE

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Background: ACLF syndrome is associated with high short-term mortality. A universally acceptable prognostic model is an unmet need for guiding the therapy. APASL ACLF Research Consortium (AARC) score is the only liver specific model for cirrhosis patients. Influence of new onset complications and therapeutic responses are integral to an ideal dynamic model. We studied the impact of comorbidities, complications, therapy and organ failures over and above the AARC score in predicting the 90 days survival among the hospitalized ACLF patients. **Methods:** We analysed the prospectively collected data of ACLF patients (APASL criteria) from AARC registry. Predictors of 90 days mortality was analysed by considering the aetiology, complications, Organ failures, infection, laboratory parameters, treatment received, and a comparison of various disease severity models was done by AUROC. **Results:** Altogether 10,994 ACLF patients [mean age 44.1±10.2 years, 87.5% male], predominant acute insult being severe alcohol associated hepatitis (58%) and HBV reactivation (12.7%). At presentation the mean AARC score 9.4±1.9, MELD Na of 28.5±5.8 with Organ failure (none-5.5%, 1-2 in 62.1%, >2 in 32.4%). Renal failure at presentation was seen in 29.6% and RRT was needed in 16.3% (n=1795) in first week. Sepsis at presentation was present in 25.3%; new-onset sepsis developed in 6.5% in first week. Ventilatory support was needed in 2.2% (247), variceal bleed occurred in 2.8% (313) in-hospital with need of ICU care in 21.8% cases. Therapy received included plasma exchange (382,3.9%), GCSF (261,2.4%), steroid (866, 7.9%) and liver transplant in 349 cases (3.2%) with 90 days survival of 64%. The independent predictors of 90 day mortality were; age [HR-1.008(95 CI 1.005-1.011), P<0.001], baseline platelet [HR-0.856(95 CI 0.814-0.900), P<0.001] and WBC count [HR-1.258(95 CI 1.198-1.320), P<0.001] and at day 7, the number of organ failures [HR-1.119(95 CI 1.087-1.152), P<0.001] as well as need of RRT [HR-1.345(95 CI 1.243-1.4566), P<0.001] or ventilatory support [HR-2.788(95 CI 2.402-3.236), P<0.001] anytime in first week. We developed a prediction model with combination of these with AARC score as AARC Plus model. The highest AUROC [0.738. 95CI 0.728-0.748] by the AARC plus model was better than MELD Na, CTP and APACHE II and CLIF SOFA, but comparable to AARC score [AUROC= 0.726(95 CI 0.716-0.736, p<0.001]. **Conclusion:** ACLF is often a progressive and serious ailment. Variceal bleed, need of RRT or ventilator support, comorbid metabolic risk factors, and development of organ failure in first week dynamically influence the outcome. AARC score is the best prognostic model for ACLF cohort and merits global application as a reliable and universally applicable bedside tool in cirrhosis patients with liver failure.

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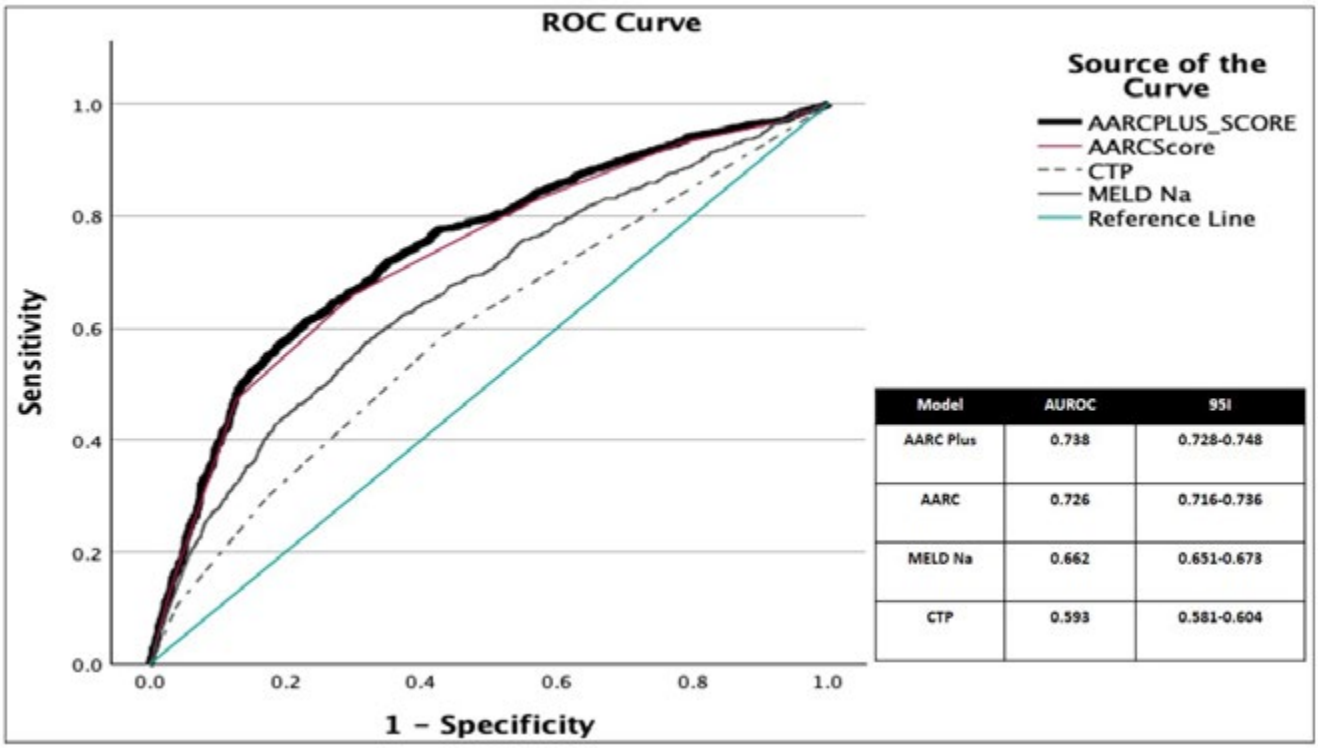

Model	AUROC	95I
AARC Plus	0.738	0.728-0.748
AARC	0.726	0.716-0.736
MELD Na	0.662	0.651-0.673
CTP	0.593	0.581-0.604

Disclosures: Ashok Kumar Choudhury: Nothing to Disclose, Mohd. Rela: Nothing to Disclose, Dinesh Jothimani: Nothing to Disclose, Mamun Al Mahtab: Nothing to Disclose, Harshad Devarbhavi: Nothing to Disclose, C E Eapen: Nothing to Disclose, Ashish Goel: Nothing to Disclose, Javed P: Nothing to Disclose, Q NING: Nothing to Disclose, Tao Chen: Nothing to Disclose, Jidong Jia: Nothing to Disclose, Duan Zhongping: Nothing to Disclose, S S Hamid: Nothing to Disclose, Amna Subhan Butt: Nothing to Disclose, WASIM JAFRI: Nothing to Disclose, Akash Shukla: Nothing to Disclose, Soek Siam Tan: Nothing to Disclose, Dong Joon Kim: Nothing to Disclose, Arun Koottumakkal Valsan: Nothing to Disclose, Jinhua Hu: Nothing to Disclose, Ajit Sood: Nothing to Disclose, Omesh Goel: Nothing to Disclose, Vandana Midha: Nothing to Disclose, Manoj Sahu: Nothing to Disclose, Guan Huei Lee: Nothing to Disclose, Sombat Treeprasertsuk: Nothing to Disclose, Kessarin Thanapirom: Nothing to Disclose, Ameet Mandot: Nothing to Disclose, Ravikiran Maghade: Nothing to Disclose, Laurentius A Lesmana: Nothing to Disclose, Hasmik GHAZINYAN: Nothing to Disclose, VG Prasad: Nothing to Disclose, A Kadir Dokmeci: Nothing to Disclose, Jose Sollano: Nothing to Disclose, Dr. Zaigham Abbas: Nothing to Disclose, Ananta Shrestha: Nothing to Disclose, George Lau: Nothing to Disclose, Diana A Payawal: Nothing to Disclose, Gamal Shiha: Nothing to Disclose, Ajay Duseja: Nothing to Disclose, SUNIL TANEJA: Nothing to Disclose, Nipun Verma: Nothing to Disclose, P N Rao: Nothing to Disclose, Anand Kulkarni: Nothing to Disclose, Md. Fazal Karim: Nothing to Disclose, Dr. Vivek A Saraswat: Nothing to Disclose, Dr Shahinul Alam: Nothing to Disclose, Dr.Osamu Yokosuka: Nothing to Disclose, Dr. Debashis Chowdhury: Nothing to Disclose, Chandan kumar Kedarisetty: Nothing to Disclose, Dr Sanjiv Saigal: Nothing to Disclose, anil Arora: Nothing to Disclose, Ashish Kumar: Roche: Consultant, Viatris: Consultant, Gupse Adali: Nothing to Disclose, Abraham Koshy: Nothing to Disclose, Ajay Kumar Patwa: Nothing to Disclose, Mohamed Elbasiony: Nothing to Disclose, Pravin Rathi: Nothing to Disclose, Sudhir Maharshi: Nothing to Disclose, V.M. Dayal: Nothing to Disclose, Ashish Kumar Jha: Nothing to Disclose, Kemal Fariz Kalista: Nothing to Disclose, Rino Gani: Nothing to Disclose, Prof MF Yuen: Nothing to Disclose, Virendra Singh: Nothing to Disclose, Ayaskanta Singh: Nothing to Disclose, Sargsyan Violeta: Nothing to Disclose, Akash Roy: Nothing to Disclose, Saurabh Mukewar: Nothing to Disclose, Xin Shaojie: Nothing to Disclose, Ruveena Bhavani: Nothing to Disclose, Charles Panackel: Nothing to Disclose, Sunil Dadhich: Nothing to Disclose, Sanjeev Sachdeva: Nothing to Disclose, Sanatan Behera: Nothing to Disclose, Lubna Kamani: Nothing to Disclose, Joy Varghese: Nothing to Disclose, Neeraj Saraf: Nothing to Disclose, GURESH KUMAR: Nothing to Disclose, Narendra Singh Choudhary: Nothing to Disclose, AARUSHI BHASIN: Nothing to Disclose, Pathik Parikh: Nothing to Disclose, Vinod Arora: Nothing to Disclose, Shiv Kumar Sarin: Nothing to Disclose

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1608 | DRIVERS OF ORGAN FAILURES AND PATIENT TRAJECTORIES FAVORING THE DEVELOPMENT OF ACUTE-ON-CHRONIC LIVER FAILURE AMONG HOSPITALIZED PATIENTS WITH ACUTE DECOMPENSATION OF CIRRHOSIS: A MULTI-CENTRIC COHORT STUDY

Nipun Verma[1] Akash Roy[2] Arun Koottumakkal Valsan[3] Pratibha Garg[4] Samonee Ralmilay[1] Venkitesh Girish[3] Parminder Kaur[5] Sahaj Rathi[5] Arka De[5] Madhumita Premkumar[4] SUNIL TANEJA[5] Mahesh Goenka[2] Ajay Duseja[4]

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Background: Identifying hospitalized patients with acute decompensation (AD) of cirrhosis at high risk of progression to acute-on-chronic liver failure (ACLF) is important for monitoring and developing personalized treatment plans, which can avert undue mortality. We investigated key determinants of progression to ACLF and patient trajectories predisposing to such progression among patients with AD. **Methods:** In a multi-center, prospective study conducted over two years (2021-2023), data was collected for clinical, biochemical, and 90-day outcomes from 625 AD patients across North, South, and East India (Derivation-cohort, DC: 318; Validation-cohort, VC: 307). Trajectories favoring progression to ACLF (pre-ACLF) were investigated through a mixed-effects regression model adjusting for individual patient inception points and rate-of-change of covariates. Predictive models for pre-ACLF were derived (DC), validated (VC), and compared with MELD3.0 and CLIF-C AD scores through receiver operating curves. **Results:** Among the participants (mean age 49 years, 83% males, 77.5% with alcohol-related liver disease), 32.2% progressed to ACLF (in DC: 27% and in VC: 37.4%). Patients progressing to ACLF in the DC showed significantly higher bilirubin (10.9 vs. 8.1mg/dl), leukocyte counts (9400 vs. 8000 per mm^3), INR (1.9 vs.1.8), and MELD 3.0 (28 vs. 25), but lower sodium (131 vs. 134 mEq/L) and 90-day survival (62% vs.86%) [Fig.1i] compared to those without such progression ($p<0.05$). Similar observations were noted in the VC, although, patients with alcohol-associated hepatitis, infections, and hepatic encephalopathy were more common in the pre-ACLF group ($p<0.05$). Liver failure at presentation predicted progression to ACLF (Odds Ratio: 2.4, 6.9, and 3.7 in the DC, VC, and overall cohort respectively; $p\leq0.001$). Levels of bilirubin, sodium, leucocyte, and MELD 3.0 at baseline were predictive of the development of pre-ACLF [Fig.1ii]. A PRE-ACLF Model including bilirubin, leucocyte, and sodium levels predicted the development of ACLF with AUC of 0.71; 0.65-0.78 in the DC, and 0.82; 0.77-0.87 in the VC ($p<0.001$), which was better than MELD3.0 (0.67 and 0.75) and CLIF-C AD (0.62 and 0.71) in DC and VC, respectively ($p<0.05$) [Fig.1iii]. The seven-day trajectories of bilirubin, INR, and MELD 3.0 were highly predictive of progression to ACLF in AD ($p<0.001$) [Fig.1iv]. **Conclusion:** In a large, diverse, contemporary, multi-centric Indian cohort, one-third of hospitalized patients with AD rapidly progressed to ACLF, conferring a high mortality. Liver dysfunction, systemic inflammation, and derived scores MELD 3.0 were the key drivers of progression. Early identification of pre-ACLF patients, can facilitate intense monitoring and prognosis. A combination of liver-directed and immunomodulatory interventions may halt the progression of AD to ACLF.

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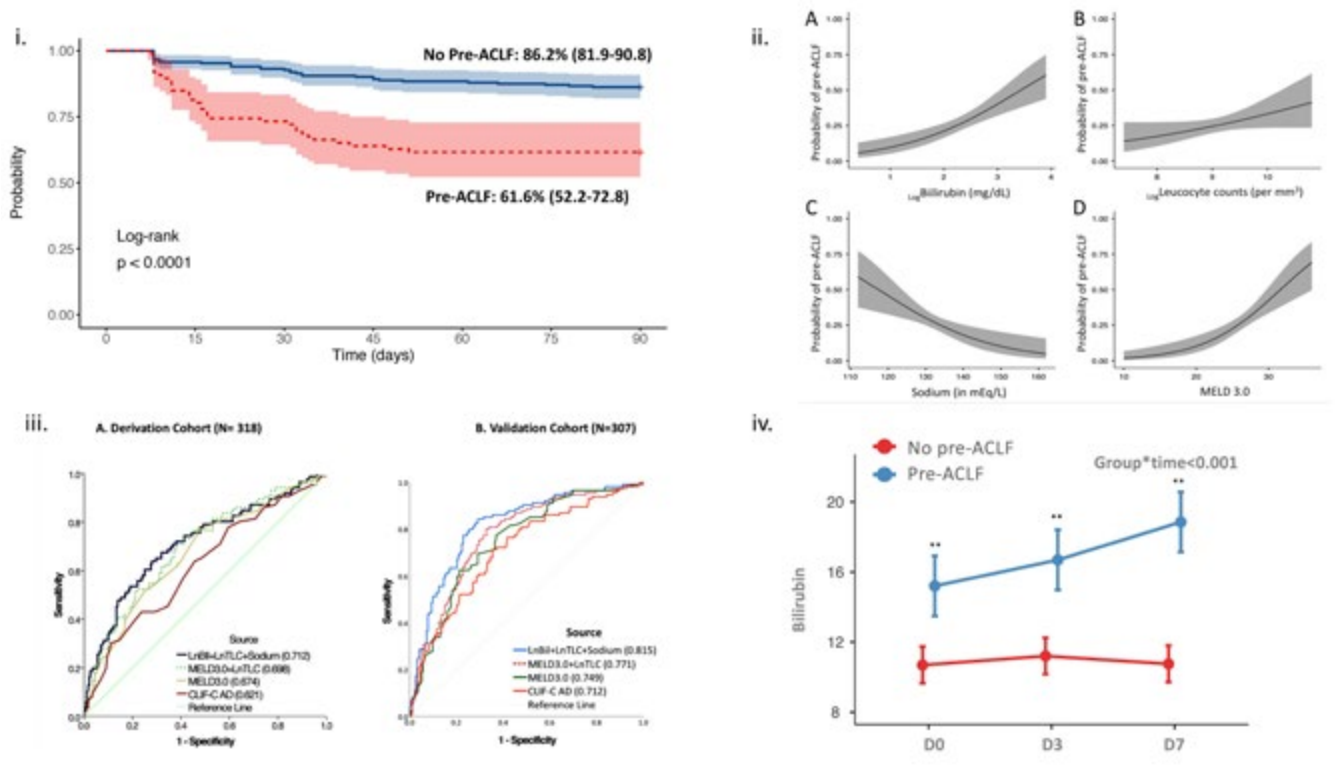

Disclosures: Nipun Verma: Nothing to Disclose, Akash Roy: Nothing to Disclose, Arun Koottumakkal Valsan: Nothing to Disclose, Pratibha Garg: Nothing to Disclose, Samonee Ralmilay: Nothing to Disclose, Venkitesh Girish: Nothing to Disclose, Parminder Kaur: Nothing to Disclose, Sahaj Rathi: Nothing to Disclose, Arka De: Nothing to Disclose, Madhumita Premkumar: Nothing to Disclose, SUNIL TANEJA: Nothing to Disclose, Mahesh Goenka: Nothing to Disclose, Ajay Duseja: Nothing to Disclose

1609 | RESOURCE UTILIZATION FOLLOWING LIVER TRANSPLANTATION FOR ACUTE ON CHRONIC LIVER FAILURE IN ALCOHOL ASSOCIATED LIVER DISEASE

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Background: Liver transplantation (LT) is the only treatment that offers survival benefit in acute on chronic liver failure (ACLF). Those with underlying alcohol associated liver disease (ALD) undergoing early liver transplantation (ELT) with limited sobriety present unique challenges in terms of selection for LT. Recent studies have demonstrated increased resource utilization in those undergoing LT for ACLF. However, these studies are not specific for those with underlying ALD. We conducted a retrospective cohort study to compare post-LT resource utilization in ALD patients with and without ACLF. **Methods:** Patients who underwent liver transplant at the University of Maryland Medical Center for ALD between January 1st 2014 and December 31st 2019 were included. ALD was defined as alcohol associated cirrhosis or alcohol associated hepatitis as primary indication for LT. Exclusion criteria included previous liver or multi-organ transplant, HIV and those with unknown date of last drink. Data on demographics, co-morbidities and severity of liver disease were collected. ACLF status was the exposure. Post-LT hospital length of stay (less than or more than 14 days) and 30-day readmission were used as surrogate markers for post-LT resource utilization. SAS software was used for data analysis. **Results:** The cohort included 239 transplant recipients, of which 63 met criteria for ACLF. The mean age was 47 years (SD 11.25) in the ACLF group compared to 51 years (SD 11.25) in the non-ACLF group (p 0.02). Race and gender

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distribution was comparable among the groups. The majority of those undergoing LT were White (83% in ACLF group vs 89% in the non-ACLF group). The MELD- Na score was significantly higher in the ACLF group, 36 (SD 7) compared to 31 (SD 9) in the non-ACLF group (Table 1). We selected diabetes mellitus and BMI as the most relevant comorbidities for further analysis. The non-ACLF group had more overweight subjects while the ACLF group was observed to have more obese patients (Table 1). The odds of prolonged hospital length of stay were 4.32 times higher in those with ACLF and underlying ALD (OR 4.32, 95% CI 2.1-8.8). When adjusted for age, BMI, and MELD-Na, the odds of prolonged hospital stay remained higher in those with ACLF (OR 3.2, 95% CI 1.5-6.8). The odds of 30-day readmission were not different between those with and without ACLF and underlying ALD (OR 0.56 95% CI 0.26-1.2), even after adjustment for age, BMI, and MELD-Na (OR 0.45 95% CI 0.19-1.03). **Conclusion:** Patients with ACLF undergoing LT for ALD are at increased odds of prolonged post-LT hospital length of stay, a surrogate marker for resource utilization. Our data did not suggest increased odds of 30-day readmission in those with ACLF. Future studies will focus on the utilization of organ support systems such as mechanical ventilation and hemodialysis in patients with ACLF. Insights into the utilization of limited resources will be vital in selecting candidates for LT in this challenging population.

Table 1: Baseline characteristics of the study cohort.

Characteristic	All subjects	ACLF (n=63) Col %	Non-ACLF (n=176) Col %	p- value
Age	49.9 +/-11.4	47 +/- 11.25	51 +/- 11.25	0.02*
Male	149 (62%)	36 (57%)	113 (64%)	0.32
Race				
White	208 (87%)	52 (83%)	156 (89%)	ref
Black	19 (8%)	6 (9%)	13 (7%)	0.53
Asian	2 (1%)	0	2 (1%)	0.83
Hispanic	7 (3%)	2 (3%)	5 (3%)	0.99
Other	3 (1%)	3 (5%)	0	0.99
BMI				
Underweight 12-18.4	10 (4%)	4 (7%)	6 (3%)	0.53
Normal 18.5-24.9	78 (33%)	15 (26%)	63 (36%)	ref
Overweight 25-29.99	76 (32%)	14 (23%)	62 (36%)	0.04*
Obese >30	71 (30%)	28 (46%)	43 (25%)	0.06*
Diabetes mellitus	37 (16%)	9 (14%)	28 (16%)	0.74
MELD-Na	32 +/-9	36+/-7	31 +/-9	<0.0001*

Disclosures: Nehna Abdul Majeed: Nothing to Disclose, Pei Xue: Nothing to Disclose, Kaitlyn Legg: Nothing to Disclose, Kirti Shetty: Nothing to Disclose

1610 | EVOLVING ROLE AND OUTCOME OF LIVER TRANSPLANTATION FOR ACUTE-ON-CHRONIC LIVER FAILURE: A 20-YEAR SINGLE-CENTER EXPERIENCE ◆

William Bernal[1] *Therese Bittermann*[2] *Mark McPhail*[3] *Pervez Khan*[4] *Stacey Calvert*[4] *Tasneem Pirani*[4] *Robert Loveridge*[5] *Christopher Willars*[4] *Georg Auzinger*[4] *Julia Wendon*[4]

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Background: Despite advances in the management of acute-on-chronic liver failure (ACLF), mortality remains high. The role of liver transplantation (LT) as definitive treatment for ACLF is evolving, though utilization remains low. We evaluated changes over 20 years in use and outcome of LT at a large center with a specialist liver intensive therapy unit (LITU), to inform the role and optimal timing of LT during and after an admission with ACLF. **Methods:** A retrospective cohort study of consecutive patients with cirrhosis and unplanned emergent first

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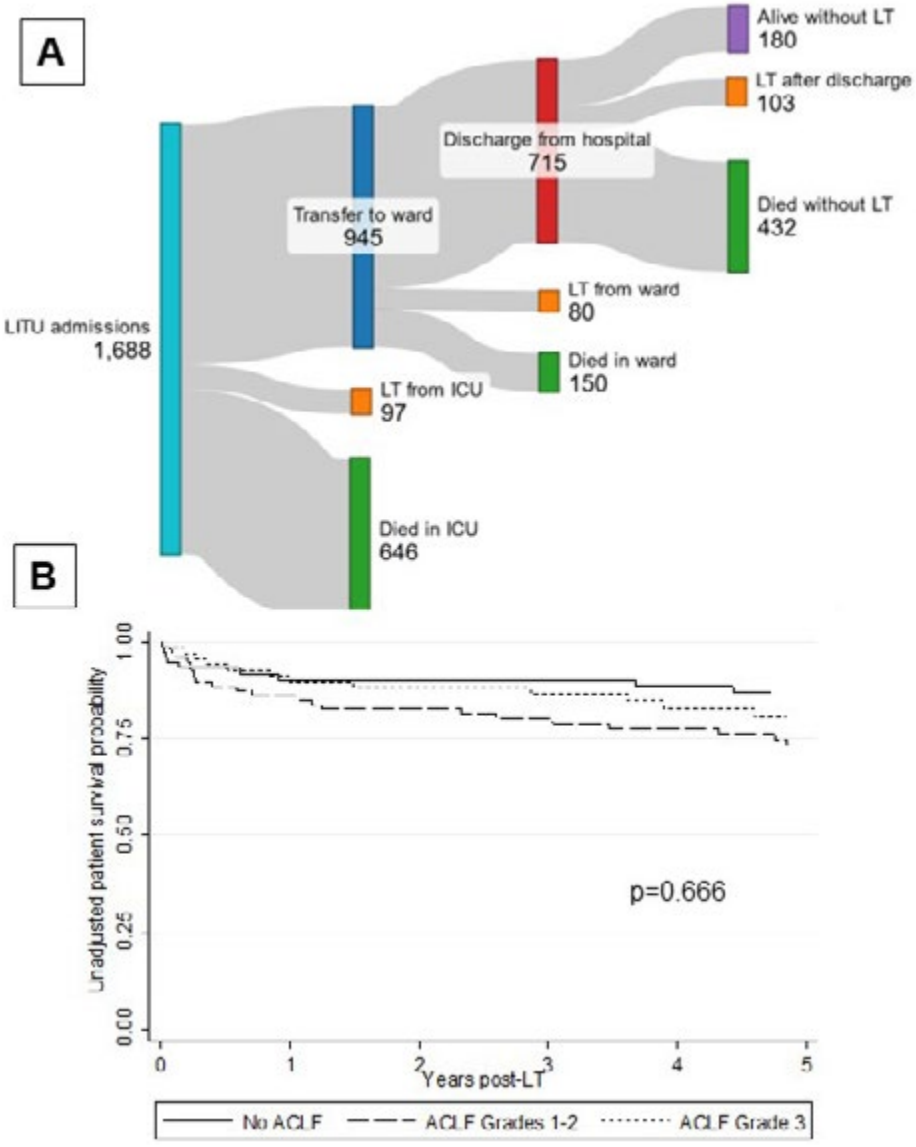
LITU admission 01/2000-03/2020. Demographic and clinical variables were obtained at admission. ACLF grade was categorized as 0 (no ACLF), 1-2 or 3. Transplant-free survival (TFS) and LT practices were characterized. Post-LT survival by ACLF grade was compared using time-to-event analysis. **Results:** The cohort comprised 1,688 patients and was 62% male, 78% White, of median age 52 (IQR 43-60) years. Cirrhosis etiology was 55% alcohol. Admission Model for End-stage Liver Disease (MELD) score was 28 (IQR: 18-37); 37% had no ACLF, 39% ACLF 1-2 and 37% ACLF 3. A total of 280 (17%) underwent LT (Figure 1A). This increased from 14% in 2000-2009 to 22% in 2010-2020 for ACLF 1-2 (p=0.014) and from 6% to 18%, respectively, for ACLF 3 (p<0.001). TFS in the LITU was 62% overall but only 39% for ACLF 3, though improved from 51% and 30% in 2000-2009 to 60% and 45% in 2010-2020 (p<0.001 each). From 2000-2020 the proportion undergoing LT from LITU (median 9 days after admission) was 6% and 8%, respectively. Of 945 LITU survivors, 80 (9%) had later LT from the ward (at median 18 days from LITU admission), including 22/199 (11%) with ACLF 3. Overall, in-hospital TFS was 53% and 29% for ACLF 3. After hospital discharge, 103/715 (14%) of survivors had LT (at median 160 days from LITU admission) including 10/118 (8%) with ACLF 3. At 1-year from LITU admission, only 20% overall and 8% of ACLF 3 had TFS. Post-LT survival was overall excellent and not different by ACLF grade (p=0.666; Figure 1B), which was 90% at 1-year and 81% at 5 years for ACLF 3. **Conclusion:** Despite improvements in TFS over 20 years, LITU and hospital mortality in patients with cirrhosis admitted to the intensive care unit (ICU) remains very high. Rapid LT from ICU in selected critically ill patients with ACLF is feasible and does not threaten post-LT outcomes. As post-ICU mortality remains high after ICU transfer, all surviving patients should be considered for LT.



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Disclosures: William Bernal: Nothing to Disclose, Therese Bittermann: Nothing to Disclose, Mark McPhail: Nothing to Disclose, Pervez Khan: Nothing to Disclose, Stacey Calvert: Nothing to Disclose, Tasneem Pirani: Nothing to Disclose, Robert Loveridge: Nothing to Disclose, Christopher Willars: Nothing to Disclose, Georg Auzinger: Nothing to Disclose, Julia Wendon: Nothing to Disclose

1611 | NUTRITION CARE IN ACUTE ON CHRONIC LIVER FAILURE IN THE INTENSIVE CARE UNIT

Vivian Nguyen[1] Constantine Karvellas[1] Puneeta Tandon[1] Carla Woelinga[2]

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Background: Malnutrition is a clinical syndrome that results from imbalances in nutrient intake and use, leading to adverse functional and/or clinical outcomes. Interconnected with sarcopenia and frailty, malnutrition is a prominent issue in critically ill patients with cirrhosis, thereby emphasizing the importance of attention to nutrition care in this population. However, there is limited data addressing nutritional factors for this population as most evidence has focused on outpatients and non-critically ill hospitalized patients. The objective of this study was to review current nutritional practices in the intensive care unit (ICU), assessing both adequacy and association with clinical outcomes. **Methods:** A retrospective review of 277 cirrhosis patients admitted to a quaternary care centre ICU was conducted. Nutrition data was gathered for the first 7 days of ICU admission and preliminary analyses were completed using descriptive statistics. **Results:** Dietitians were involved in the care of 179 (64.6%) patients, with official consultation order placed an average of 41(1.4) hours after time of ICU admission. 202 (74.0%) patients received either oral nutrition (PO), enteral nutrition (EN), parenteral nutrition (PN), or a combination. Supplemental nutrition was started an average of 43 (1.9) hours and 57 (1.6) hours after ICU admission for EN and PN, respectively. Of patients who were started on supplemental nutrition, 36 (26.2%) and 83 (60.6%) patients were initiated at a rate meeting recommendations of at least 25kcal/kg/day and 1.2g/kg/day of protein, respectively. At day seven, 31 (48.4%) and 53 (82.8%) of patients met their caloric and protein recommendations, respectively. **Conclusion:** Our data shows that current nutritional practices in the critical care setting do not meet nutrition guidelines for the care of cirrhosis patients. Further analyses are required to assess nutrition adequacy in this vulnerable population, and to assess the impact of nutritional factors on morbidity and mortality in the ICU and hospital setting.

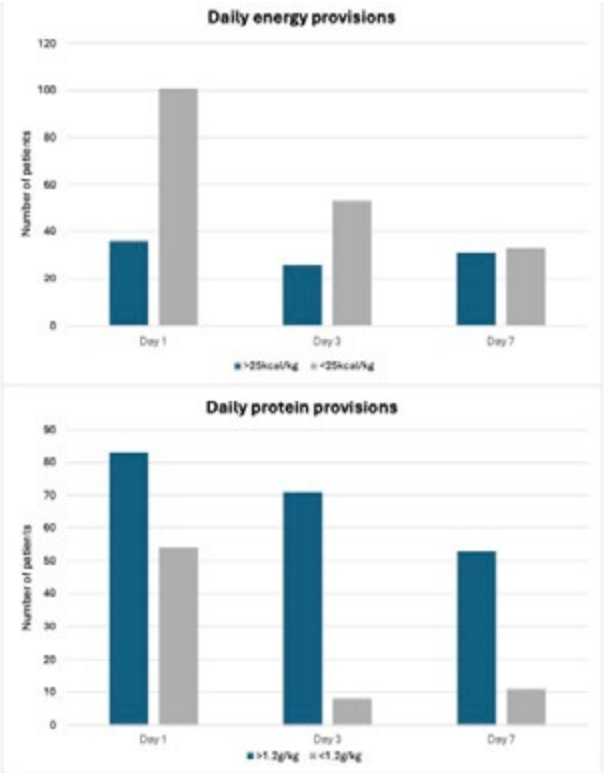

Figure 1. Daily energy and protein provisions.

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1612 | DESIGNATION OF ACUTE-ON-CHRONIC LIVER FAILURE IN PATIENTS WITH SEVERE ALCOHOLIC HEPATITIS

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Background: Acute on chronic liver failure (ACLF) incorporates hepatic and extrahepatic organ failure in cirrhosis and portends to identify patients (pts) that have a poor prognosis. Those with alcohol-related liver disease (ALD) and severe alcoholic hepatitis (AH) are increasingly undergoing liver transplantation (LT). However, AH is not often considered ACLF. Our study reviewed LT pts with and without ACLF prior to LT by primary liver disease etiology to determine the prevalence of ACLF in AH compared to other liver disease etiologies undergoing LT. **Methods:** A retrospective analysis of deceased donor LT 2018-2022 was performed. Demographic, clinical, and lab data were collected. Our study utilized the ACLF definition by the North American Consortium for the Study of End-Stage Liver Disease (NACSELD); >2 severe extrahepatic organ failures including: shock requiring vasopressors, grade III/IV hepatic encephalopathy (HE), renal replacement therapy (RRT), or mechanical ventilation (MV). For acute AH, the criteria by the National Institute on Alcohol Abuse and Alcoholism criteria were used. **Results:** Our study group consisted of 484 pts; mean (SD) Age 53 (12.6), 59% male, 78% White, 15%, Black, 93% non-Hispanic, MASH 24%, ALD with <6m sobriety, 28% (9% with AH), ALD > 6 m sobriety 25%, and other 23%, RRT 21%, HE 15%, MV 20%, and vasopressor 8%. Overall 114 (24%) fit the ACLF designation: 82% needing RRT; 60% with grade III or IV HE; 20% needing MV; and 33% needed vasopressors. Those with ACLF were younger (50 vs 54 yrs; p=.0028), less likely male (47 vs 63%; p=.0038), had a higher MELD at listing (35 vs 29; p=.001), and spent less time on the LT list (26 vs 130 d; p<.001) compared to non-ACLF (Table). In comparing liver disease groups, the highest proportion of ACLF was in those with ALD with less than 6m sobriety (57%) with 21% in those with AH compared to 15% in those with ALD and > 6m sobriety and 17% of MASH. All pts with AH had cirrhosis (98%) or bridging fibrosis (2%) on explant. Despite a longer post-LT hospital stay (45 vs. 27 days; p<.001), the overall 1-year pt survival was similar in those with and without ACLF (93%). **Conclusion:** ACLF is common, but not universal in those undergoing LT for ALD and AH. Despite higher MELD and comorbidities associated with ACLF, their 1-year survival was similar regardless of liver disease etiology. Because all AH pts had advanced fibrosis/cirrhosis, severe AH requiring LT should be considered to have ACLF if meeting NACSELD criteria. This will be important as more centers consider LT for AH and if higher priority beyond MELD is given to those with ACLF.

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	ACLF	Non-ACLF	P value
N= (total n=484)	114 (24%)	370 (76%)	
Age (years)^	**49.8 ± 12.5**	**53.8 ± 12.6**	**.0028**
Gender male	**47%**	**63%**	**.0038**
Race White	84%	77%	NS
Race Black	11%	16%	NS
MELD at transplant	**35 ± 8.8**	**29 ± 9.8**	**.001**
Alcohol-related liver disease (ALD) < 6 months abstinent	**57%**	**19%**	**<.0001**
Alcohol-related liver disease (ALD) > 6 months abstinent	**15%**	**27%**	
Non-alcohol liver disease	**28%**	**54%**	
Alcoholic hepatitis (AH)	**21%**	**6%**	**<.0001**
MELD at listing	**35 ± 9**	**21 ± 10**	**<.0001**
Time listed for LT (days)	**26 ± 63**	**130 ± 266**	**<.0001**
Needing RRT	**82%**	**2%**	**<.0001**
Grade III or IV HE	**60%**	**1%**	**<.0001**
Needing mechanical ventilator	**20%**	**1%**	**<.0001**
Needing IV vasopressor	**33%**	**1%**	**<.0001**
Length of hospital stay (days)	**45 ± 43**	**27 ± 38**	**<.0001**
1-year survival	93%	93%	NS

Disclosures: Kevin Houston: Nothing to Disclose, Hiba Khan: Nothing to Disclose, Hasan Alroobi: Nothing to Disclose, Niki Wadhwa: Nothing to Disclose, Nikita Chadha: Nothing to Disclose, Chad Spencer: Nothing to Disclose, Richard Sterling: Grant/Research Support relationship with HCV Vax; Has not ended; Grant/Research Support relationship with GSK; Has not ended; Grant/Research Support relationship with Gilead; Has not ended; Grant/Research Support relationship with Roche; Has not ended; Grant/Research Support relationship with AbbVie; Has not ended; Grant/Research Support relationship with Abott; Has not ended; GI Specialty Board relationship with ABIM; Has not ended, Amon Asgharpour: Galectin: Clinical Endpoint Committee, NovoNordisk: Advisor, Madrigal: Advisor, Nicole Keller: Nothing to Disclose, Scott Matherly: Nothing to Disclose, Joel Wedd: Nothing to Disclose, Hannah Lee: Nothing to Disclose, Mohammad Siddiqui: NovoNordisk: Grant/Research Support, 89Bio: Consultant, Vaishali Patel: Nothing to Disclose, Sayed Obaidullah Aseem: Galmed Pharmaceuticals: Grant/Research Support, Vinay Kumaran: Nothing to Disclose, Seung Duk Lee: Nothing to Disclose, Amit Sharma: Nothing to Disclose, Aamir Khan: Nothing to Disclose, Daisuke Imai: Nothing to Disclose, Marlon Levy: Nothing to Disclose, David Bruno: Nothing to Disclose

1613 | HEPATIC IRRADIATED PIGS DEVELOP RADIATION INDUCED VENO-OCCLUSIVE LIVER DISEASE WITH FERROPTOSIS ◆

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Background: While hepatic irradiation (HIR) is used for the treatment of liver cancer or as a regimen in preconditioning for hepatocyte transplantation, radiation-induced liver disease (RILD) is a major concern for the application of HIR. However, the lack of a reliable animal model for studying RILD has hindered the understanding of RILD pathogenesis as well as prevention and treatment of the disease. Given the convenient accessibility, we applied miniature pigs here to study RILD and test the safe therapeutic dose of HIR. **Methods:** We performed a dose-escalation study in miniature pigs, using hypofractionated stereotactic body radiotherapy in 9 animals. **Results:** Pigs exposed to 20Gy/30Gy doses of HIR showed symptoms resembling human RILD, including fatigue, weight gain, hepatomegaly, anicteric ascites, reduced albumin, and elevated alkaline phosphatase levels, with normal bilirubin. Histological analysis revealed liver damage to central veins, progressing to mild hepatic venous occlusion and moderate septal fibrosis. Occasional cell necrosis and senescence were observed, along with increased hepatocyte proliferation, indicating efficient liver regeneration. In contrast, pigs exposed to 40Gy

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experienced severe RILD, with significantly elevated alkaline phosphatase and transaminase levels, reduced albumin, fatigue, anorexia, jaundice ascites, and histologically evident VOD with severe fibrosis. Extensive hepatocellular necrosis and senescence, along with DNA damage impairing proliferation, were observed. Biopsy analysis identified a critical deterioration window 2-3 weeks post-irradiation. Ferroptosis, particularly pronounced at 40Gy, could be rescued by ferroptosis inhibitors like liproxstatin-1 (Lip-1). **Conclusion:** The miniature pig, one of the few large animal models to investigate RILD, provides a resource for characterizing the early changes and pathogenesis of VOD, liver fibrosis, liver regeneration and cell death, for establishing nonlethal therapeutic dosages, and for examining experimental therapies to minimize radiation injury.

Disclosures: Zhen Sun: Nothing to Disclose, Lijian Hui: Nothing to Disclose

1614 | USE OF CONTINUOUS RENAL REPLACEMENT THERAPY IN CRITICALLY ILL PATIENTS WITH CIRRHOSIS/ACUTE-ON-CHRONIC LIVER FAILURE: THE MULTICENTRE CRRTNET SUBSTUDY ◆

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Background: Continuous renal replacement therapy (CRRT) is the predominant form of acute RRT used for critically ill adult cirrhosis/acute on chronic liver failure (ACLF) patients with acute kidney injury (AKI). Given the variability in CRRT practice, specific data on cirrhosis/ACLF patients undergoing CRRT is lacking. **Methods:** We conducted a cohort analysis of the CRRTnet multicenter, prospective registry from 12/2013-02/2021 across 5 academic centers and 6 intensive care units (ICUs) of critically ill adult patients who received CRRT for at least 24 hours. Of 1541 critically-ill/ICU patients included in the overall cohort, Analysis One compared n=250 patients with cirrhosis/ACLF with n=1291 critically ill controls. Analysis Two stratified cirrhosis/ACLF patients who survived to hospital discharge (n=89) and those who did not (n=161). **Results:** ACLF patients were younger (57 vs 61 years; p<0.001) and had higher SOFA scores (16 vs. 14; p<0.001) at CRRT initiation. Receipt of mechanical ventilation (73% vs. 74%) and vasopressor support (79% vs. 74%) were similar. CRRT was initiated more rapidly in ACLF patients (21.6 vs. 29.2 hours, p<0.001) and ACLF patients were less likely to receive citrate regional anticoagulation (42% vs 54% p<0.001). CRRT prescription (32.3 vs. 30.6 ml/kg/hour, p=0.2) and duration (median 3 vs. 4 days, p=0.24) were comparable. Survival to hospital discharge was significantly lower in ACLF patients (38% vs. 49%, p=0.009 compared with critically ill controls while ICU lengths of stay were shorter (8 vs. 10 days, p<0.001). In comparison with ACLF patients who survived to hospital discharge (n=89), ACLF non-survivors (n=161) had higher SOFA scores (17 vs. 14, p=0.003) on ICU admission. Receipt of mechanical ventilation (72% vs 80%) and vasopressor support (81% vs. 75%) were similar. While CRRT dose was similar (34.5 vs. 36.7 ml/kg/hr, p=0.3), ACLF non-survivors had a shorter duration of CRRT (3 vs. 5 days, p<0.001) and were less likely to be eventually transitioned to intermittent hemodialysis (IHD) (24 vs. 67%, p<0.001). While more ACLF non-survivors received citrate regional anticoagulation (44% vs. 19%) it did not reach statistical significance (p=0.09). **Conclusion:** Among critically ill adult patients requiring CRRT, those patients with cirrhosis/ACLF were more likely to receive CRRT earlier and receive circuit anticoagulation with alternatives to citrate (most commonly no anticoagulation). Despite concerns for citrate toxicity in cirrhosis/ACLF, citrate regional anticoagulation appeared to be used safely in this cohort. Patients with ACLF/cirrhosis had higher in-hospital mortality than other critically ill patients requiring CRRT, and ACLF/cirrhosis non-survivors on CRRT had higher SOFA scores on admission and shorter duration of CRRT than survivors.

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Table 1.

Analysis 1	All Cohort n = 1541	Liver n=250	Non-liver n=1291	p-value
Age (years, mean ± SD)	60 [50 - 69]	57 [49 - 63]	61 [51 - 70]	<0.001
Charlson Score, median [IQR]	3 [1 - 4]	5 [3 - 6]	2 [1 - 4]	<0.001
SOFA score, median [IQR]	15 [12 - 17]	16 [13 - 18]	14 [12 - 16]	<0.001
ICU Length of Stay, days, median [IQR]	10 [4 - 20]	8 [3 - 14]	10 [4 - 21]	<0.001
Time (hours): ICU admission to CRRT initiation, median [IQR]	27.2 [10.5 -73.8]	21.6[8.2 -48.9]	29.2 [11.0 - 77.4]	<0.001
Prescription dose (mL/kg/h), median [IQR]	30.9 [25.3 - 38.9]	32.3 [25.5 - 41.0]	30.6 [25.3 - 38.7]	0.20
Anticoagulation type, n (%)	(1262)	(187)	(1075)	<0.001
Citrate	710 (52.0)	87 (41.8)	623 (53.9)	
Heparin	95 (7.0)	7(3.3)	88 (7.6)	
No anticoagulation	442 (47.7)	93 (44.7)	349 (30.2)	
CRRT modality				0.34
Continuous venovenous hemofiltration	15.0%	16.9%	14.6%	
Continuous venovenous hemodiafiltration	84.6%	82.6%	85.0%	
Other	0.4%	0.5%	0.4%	
Survival at hospital discharge	46.9%	37.7%	48.7%	0.009
Analysis 2	**Liver Cohort n = 250**	**Alive n=89**	**Deceased n=161**	**p-value**
SOFA score, median [IQR]	16 [13 - 18]	14 [13 - 16]	17 [14 - 19]	0.003
ICU Length of Stay, days, median [IQR]	8 [3 - 14]	11 [8 - 20]	5 [2 - 10.5]	<0.001
CRRT duration, days, median [IQR]	3 [1 - 8]	5 [3 - 9]	3 [1 - 7]	<0.001
Received any intermittent hemodialysis (%)	55.9%	67.0%	24.1%	<0.001

Abbreviations: CRRT (continuous renal replacement therapy IQR (interquartile range), ICU (intensive care unit), IHD (hemodialysis), IQR (interquartile range)

Disclosures: Constantine Karvellas: Consultant relationship with Mallinckrodt; Has not ended; Advisor relationship with Baxter; Has not ended; Advisor relationship with Grifols; Has not ended; Data safety monitoring board for clinical trial relationship with Miromatrix; Has not ended, Joshua Lambert: Nothing to Disclose, Oleksa Rewa: Nothing to Disclose, Michael Heung: Astute Medical Inc.: Grant/Research Support, CardioSounds LLC: Consultant, Andrew House: Baxter: Speaking and Teaching, Paladin: Advisor, Bayer: Advisor, Divya Monga: Nothing to Disclose, Luis Juncos: Fresenius Medical Care: Advisor, Baxter Medical: Advisor, Robin Piazza: Nothing to Disclose, Stuart Goldstein: Nothing to Disclose, Sean Bagshaw: Nothing to Disclose, Javier Neyra: Nothing to Disclose

1615 | CIRRHOTIC CARDIOMYOPATHY INDEPENDENTLY INCREASES POST-TRANSPLANT MORTALITY IN PATIENTS TRANSPLANTED FOR ACUTE ON CHRONIC LIVER FAILURE: THE MODEL CONSORTIUM EXPERIENCE

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Background: Cirrhotic Cardiomyopathy (CCM) is common among patients with advanced cirrhosis. CCM was re-defined in 2020 by the Cirrhotic Cardiomyopathy Consortium and the use of contemporary echocardiographic markers was incorporated in the new definition. However, the impact of the newly defined CCM on outcomes in patients with acute on chronic liver failure (ACLF) is unclear. **Methods:** This is a retrospective multicenter cohort study (MODEL Consortium of 15 North American Tertiary Centers) which included a total of 734 liver transplant (LT) recipients, between 2014-2019, who suffered ACLF pre-LT. Patients with prior myocardial infarction or significant valvular disease were excluded. The 2020 criteria were used to classify patients as CCM (having ≥ 2 abnormal diastolic function criteria) or non-CCM (having ≥ 3 normal diastolic function criteria). The criteria were: left atrial volume (LAVI)>34ml/m^2, medial or lateral e′<7 and 10 cm/seconds, respectively, tricuspid regurgitation peak velocity >2.8m/second, E/e′ ratio≥ 15. Echocardiographic data were sufficient to categorize 173 patients

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CCM status. Imputation was carried out to account for the missing values. Outcomes of interest were pre-LT circulatory failure, defined as needing pressors, and one-year post-LT mortality. **Results:** A total of 323 patients (44%) had circulatory failure and 136 (18.5%) died within one-year post-LT. Patients with CCM were more likely to be older, female, have higher BMI, have MASH as the etiology of liver disease, and have history of diabetes (all p value < 0.05[BF1]). There was no significant difference in the incidence of circulatory failure between patients with CCM and those without CCM (p=0.117). However, mortality at one-year post-LT was significantly higher among patients with CCM (28.1%) compared to those without CCM (17.5%) (p<0.001). Table 1 demonstrates that CCM had a significantly higher likelihood for post-LT mortality at one-year, after controlling for all available clinically relevant covariates. When the analysis was performed based on ACLF categories (as defined by the EASL-CLIF criteria), patients with ACLF 1 and 3 and concurrent CCM had higher mortality rates (p<0.001) compared to patients with ACLF 1 and 3 without CCM. **Conclusion:** CCM, per the revised 2020 criteria, confers an independently increased risk for one-year mortality post-LT. Assessment of CCM should be incorporated in the risk stratification for patients with ACLF undergoing LT.

Table 1. Association of CCM with post transplant mortality

Variable		Model 1			Model 2			Model 3		
		OR	95%CI	P-value	OR	95%CI	P-value	OR	95%CI	P-value
CCM	No	Ref	Ref	**<0.001**	Ref	Ref	**<0.001**	Ref	Ref	**0.003**
	Yes	1.84	1.49-2.29		1.77	1.39-2.26		1.59	1.17-2.15	

Model 1: Unadjusted Model.
Model 2: adjusted for Diabetes Mellitus, age, sex, etiology of liver disease, chronic kidney disease, acute on chronic liver failure category, race, multidrug resistant organisms and obesity.
Model 3: adjusted for diabetes mellitus, age, etiology of liver disease, multidrug resistant organisms, obesity, and MELD 3.0.

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relationship with Novonordisk; Has not ended; Grant/Research Support relationship with Viking; Has ended; Grant/Research Support relationship with Galectin; Has not ended, Manhal Izzy: Nothing to Disclose

1616 | THE ECHOCARDIOGRAPHIC MARKERS OF CIRRHOTIC CARDIOMYOPATHY CAN INDEPENDENTLY PREDICT CIRCULATORY FAILURE AND POSTTRANSPLANT DEATH IN PATIENTS WITH ACUTE ON CHRONIC LIVER FAILURE: 15 CENTERS EXPERIENCE

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Background: Cirrhotic cardiomyopathy (CCM) affects more than 30% of liver transplant (LT) candidates. The criteria for CCM were revised in 2020 by the Cirrhotic Cardiomyopathy Consortium. However, the data remain limited about the utility of the new echocardiographic markers of CCM in predicting clinical outcomes in acute on chronic liver failure (ACLF). **Methods:** A retrospective records review was performed for 734 patients transplanted with ACLF over 5 years at 15 Tertiary North American Centers (MODEL Consortium). Patients with prior myocardial infarction or significant valvular disease were excluded. Echocardiographic markers of the newly defined CCM (ejection fraction (EF), diastolic function markers (E/e′ ratio, lateral e′, medial e′, left atrial volume index (LAVI))) and right ventricular systolic pressure (RVSP) were assessed. Outcomes of interest were pre-LT circulatory failure (defined as needing vasopressors) and one-year post-LT mortality. Binary logistic regression was used to assess the associations of interest. **Results:** A total of 323 patients had circulatory failure and 136 died within one-year post-LT. The median time between echocardiography and vasopressors administration was 4 days prior to vasopressors. Older age, female sex, alcohol-related liver disease, chronic kidney disease, higher ACLF grade (as defined by the EASL-CLIF criteria), and infection by multidrug resistant organisms increased the risk for circulatory dysfunction and mortality (all p values < 0.011). Univariate analysis demonstrated that markers of CCM (EF, medial e′, lateral e′, tricuspid velocity, and LAVI) were associated with circulatory failure (p < 0.001). Multivariate regression models for the association of CCM echocardiographic markers with circulatory failure and mortality are described in Table 1. Significant predictors of post-LT circulatory failure were EF<65.5, medial e′<9.09, lateral e′ <11.70, tricuspid velocity<262.79, and LAVI<35.39. Additionally, EF, medial e′, lateral e′, E/ e′, and RVSP were associated with post-LT mortality (p<0.001). Significant predictors of post-LT mortality were EF<65.5, medial e′<9.07, lateral e′<11.57, E/e′>10.20, and RVSP>34.2. All echocardiographic markers demonstrated comparable prediction for circulatory dysfunction and mortality. **Conclusion:** The diastolic markers of CCM, and not only EF, are independently predictive of circulatory failure in patients with ACLF. Lower EF, higher E/ e′ (increased left sided filling pressure, reflecting diastolic dysfunction-CCM) and higher RVSP are independently associated with post-LT mortality. Prospective evaluation of the role of CCM markers in the prognostication of ACLF is warranted.

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Table 1. Association of the echocardiographic markers of CCM with Circulatory Failure and posttransplant mortality in patients with ACLF

Variable	Circulatory Failure									Variable	Mortality								
	Model 1			Model 2			Model 3				Model 1			Model 2			Model 3		
	OR	CI	P	OR	CI	P	OR	CI	P		OR	CI	P	OR	CI	P	OR	CI	P
medial e'	0.950	0.929-0.972	**<0.001**	0.952	0.929-0.977	**<0.001**	0.944	0.917-0.972	**<0.001**	medial e'	0.951	0.924-0.979	**0.001**	0.976	0.945-1.008	0.142	0.967	0.928-1.007	0.104
lateral e'	0.974	0.957-0.990	**0.002**	0.978	0.960-0.997	**0.021**	0.977	0.956-0.999	**0.038**	lateral e'	0.954	0.934-0.976	**<0.001**	0.968	0.945-0.993	**0.011**	0.972	0.943-1.002	0.069
LAVI	0.995	0.990-0.999	**0.028**	0.993	0.988-0.998	**0.006**	0.993	0.988-0.998	**0.012**	E/ e'	1.046	1.027-1.066	**<0.001**	1.036	1.014-1.058	**0.008**	1.026	0.999-1.054	0.061
EF	0.985	0.976-0.993	**<0.001**	0.986	0.977-0.995	**0.003**	0.984	0.974-0.995	**<0.001**	EF	0.982	0.972-0.993	**<0.001**	0.980	0.968-0.992	**0.002**	0.975	0.962-0.988	**<0.001**
TR velocity	0.998	0.997-0.999	**0.001**	0.997	0.995-0.998	**<0.001**	0.998	0.997-1.000	**0.034**	RVSP	1.015	1.008-1.023	**<0.001**	1.007	0.999-1.015	0.087	1.019	1.009-1.029	**<0.001**

E/ e'=ratio of early diastolic transmitral flow to early diastolic mitral annular tissue velocity; EF=ejection fraction; lateral e'=lateral early diastolic mitral annular velocity; LAVI= left atrial volume index; medial e'= medial early diastolic mitral annular velocity; RVSP= right ventricular systolic pressure; TR velocity= tricuspid valve velocity.

Model 1: Unadjusted Model.
Model 2: adjusted for diabetes mellitus, age, race, multidrug resistant organisms and sex.
Model 3: adjusted for diabetes mellitus, age, and MELD 3.0.

Model 1: Unadjusted Model.
Model 2: adjusted for diabetes mellitus, age, sex, etiology, chronic kidney disease, acute on chronic liver failure category, race, multidrug resistant organisms and obesity.
Model 3: adjusted for diabetes mellitus, age, etiology, and obesity, and MELD3.0.

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1617 | ALBUMIN REPROGRAMS THE B CELL TRANSCRIPTIONAL LANDSCAPE AND RESCUES NEUTROPHIL DYSFUNCTION IN IMMUNOCOMPROMISED PATIENTS WITH ADVANCED CIRRHOSIS

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Background: Patients with acutely decompensated (AD) cirrhosis are immunocompromised and have higher predisposition to infections. This study investigated the mechanisms by which patients with AD cirrhosis receiving albumin infusions have lower incidence of infections than patients receiving standard medical therapy. **Methods:** Immunophenotyping was performed by flow cytometry in patients with AD cirrhosis and healthy subjects. Bulk and single-cell RNA sequencing (scRNA-seq) and flow cytometry analysis were performed in peripheral blood mononuclear cells (PBMCs) exposed in vitro to albumin. The in vitro effects of albumin on neutrophil degranulation, phagocytosis, chemotaxis, and swarming were assessed by analysis of myeloperoxidase enzymatic activity, engulfment of fluorescently labeled-*E. coli* and zymosan and measurements at single-cell resolution of the neutrophil interactions with *C.albicans* in microfluidic chambers, respectively. In vivo whole blood RNA-seq analyses were performed in forty-nine patients admitted for severe AD cirrhosis of whom thirty received albumin during hospitalization. **Results:** As compared to healthy donors, patients with AD cirrhosis showed severe lymphopenia and defective neutrophil anti-microbial function. Bulk and scRNA-seq analyses revealed increased signatures related to B cells, myeloid cells and CD4+ T cells in PBMCs incubated with albumin. Changes in the B cell population were confirmed by flow cytometry. Neutrophils exposed to albumin also exhibited augmented chemotactic and degranulation responses, enhanced phagocytosis, and increased pathogen-restrictive swarming. Analysis of whole blood RNA-seq data in patients who had received albumin revealed specific upregulation of signatures related to B cells and neutrophils together with transcriptional changes in CD4+ T cells. **Conclusion:** These findings highlight the ability of albumin to promote the transcriptional reprogramming of the B cell compartment and rescue the impaired neutrophil antimicrobial functions, thus providing a mechanism for the lower incidence of infections in patients with severe AD cirrhosis receiving albumin therapy.

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1618 | DEEP LEARNING MODEL FOR PREDICTION OF PROGNOSIS IN PATIENTS WITH ACUTE-ON-CHRONIC LIVER FAILURE

Young Kul Jung[1] Hyung Joon Yim[2] Taehyung Kim[3] Do Seon Song[4] Eileen Yoon[5] Sung Won Lee[4] Ki Tae Suk[3] JAE YOUNG JANG[6] Moon Young Kim[7] Sang Gyune Kim[6] Soung Won Jeong[6] Jung Gil Park[8] Won Kim[9] Sung Eun Kim[3] Ji Won Park[3] Dong Joon Kim[10]

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Background: Acute on Chronic Liver Failure (ACLF) is associated with high mortality due to multisystem organ failure. However, the accurate prediction of mortality is to help guide better dialysis therapies and wait longer for liver transplantation. We hypothesized that artificial intelligence models are more precise than standard models for predicting outcomes in ACLF. **Methods:** A novel deep-learning-based model was developed from data collected from patients with MELD ≥21 prospectively from July 2015 to August 2018 and retrospectively from January 2013 to December 2013 from the Korean Acute-on-Chronic Liver Failure (KACLiF) cohort. The prospective data was split into training and validation sets in a 7:3 ratio and used as a derivation cohort (n=294), while the retrospective data was used as a validation cohort (n=177). We used a Decision Tree, Minimum Redundancy Maximum Relevance (MRMR), Elastic Net, and least absolute shrinkage and selection operator to refine the selection of important features. The selected features were evaluated using Random Forest to assess their ability to predict survival. **Results:** The mean MELD scores of the derivation cohort and the validation cohort were 29.6 (interquartile range [IQR] 25.5-33.4) and 28.2 (IQR, 24.7-33.6), respectively. The 30-day mortality rates of patients in the derivation and validation cohorts were 25.9% and 25.4%, respectively, and the 90-day mortality rates were 33.7% and 36.7%, respectively. For predicting 90-day mortality, the MRMR demonstrated the highest AUC in both derivation (0.745) and validation (0.617) cohorts. Baseline prothrombin time, previous acute deterioration events, circulatory failure, ascites, hepatic encephalopathy, GI bleeding, body temperature, respiratory rate, cause of liver disease, and albumin were the top features determining the 90-day outcomes. Although it demonstrated low predictive power, this model had the highest AUC among the previously reported models: MELD (0.522), MELD-Na (0.623), MELD 3.0 (0.543), CLIF-ACLF score (0.650), CLIF-C OFs (0.676), and CLIF-SOFA score (0.640). **Conclusion:** The deep-learning-based model performed better than the previous models for predicting mortality in patients with ACLF.

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1619 | CLINICAL CHARACTERISTICS OF RECURRENT BACTEREMIA IN END-STAGE LIVER DISEASE: 10-YEAR EXPERIENCE IN A SINGLE CENTER IN SOUTHWEST CHINA

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Background: Several factors contribute to the susceptibility to bacterial infections in patients with end-stage liver disease (ESLD), such as immune dysfunction, alterations and excessive growth of gut microbiome and bacterial translocation. Bloodstream infections (BSI, i.e., bacteremia) are a common type of infection in patients with ESLD, which are associated with high mortality, longer length of hospital stay and faster escalation of the liver disease. In previous study, about 10% patients with ESLD develop multiple episodes of bacteremia. The purpose of this study is to analyze the species of pathogen and resistance to antibiotics in those ESLD with multiple episodes of bacteremia. **Methods:** Consecutive, non-electively hospitalized patients with ESLD who had BSI were enrolled in this study between March 2012 and December 2022. The etiologies of cirrhosis, source of infection, species

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of pathogen, drug resistance to antibiotics, and presence of complications were assessed. And the statistical analysis of the clinical data was performed. **Results:** In total, 762 patients(874 episodes) with ESLD who had BSI were included. Of those, recurrent bacteremia occurred in 77 patients(10.1%)who presented with a total of 189 episodes of infection, 55 patients (71.4%) were male and 22 patients (28.6%) were female. The most common etiology of ESLD with recurrent bacteremia was chronic hepatitis B virus infection, accounting for 61.0% (47/77), followed by alcohol-related and autoimmune hepatitis in almost equal proportions(13.0%). Escherichia coli (46.1%), Klebsiella pneumonia(18.3%) and Streptococcus(13.6%) were the most frequently isolated microorganisms. The rate of multidrug-resistant (MDR) in ESLD cases with recurrent bacteremia is 24.7%, which is much higher than patients with one episode of infection(13.3%). The predominant MDR pathogens were Escherichia coli (72.2%) and Staphylococcus (16.7%). **Conclusion:** This study demonstrates that bacterial infections are common in hospitalized patients with ESLD. MDR infections are highly prevalent in ESLD cases with recurrent bacteremia. Escherichia coli is the most frequently isolated multi-resistant microorganism. Our data highlight the importance to follow local epidemiology for implementing appropriate preventative measures and for choosing appropriate empiric antibiotic therapy.

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1620 | PLATELET COUNT, LIVER AND SPLEEN STIFFNESS-BASED MODEL IDENTIFIES HIGH RISK ESOPHAGEAL VARICES IN ACUTE-ON-CHRONIC LIVER FAILURE

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Background: Transient elastography of liver and spleen and platelet count identify patients with risk of esophageal varices needing treatment (VNT) in compensated cirrhosis. In acute on chronic liver failure (ACLF) patients, apart from fibrosis, inflammation can also drive development and progression of varices. Inflammation also affects liver stiffness (LSM). Spleen stiffness (SSM) changes are more dynamic and reflective of hyperkinetic circulation typically seen in ACLF. Upper gastrointestinal endoscopy for variceal screening is invasive and may be poorly tolerated, more so in ACLF. Utility of noninvasive tests (NITs) in ACLF for VNT has not been assessed. The primary aim of study was to develop a model incorporating LSM and SSM in predicting VNT in ACLF. **Methods:** This was a cross-sectional study including ACLF (APASL criteria) patients with successful liver (75 Hz) and spleen stiffness (100Hz) measured by transient elastography (Fibroscan 630 xpert). Endoscopy done within one week of elastography was the standard for detecting VNT. Patients with moderate to severe ascites were excluded. The analysis also included developing a model, comparing it with other scores (LSPS, APRI, Fib-4, AST/ ALT ratio, PSR) by area under receiver operating characteristic curve (AUROC) with Hanley MacNeil method used to test for statistical difference between AUROCs. Performance of the model was also validated in a different set of patients. **Results:** In the training set (151 patients, age 43.01±9.42yrs, 94% males, 69.5% alcohol, mean s.bilirubin 15.67±9.49mg/dl, ALT 49.51±29.21 IU/ml, AST 121.39±43.22IU/ml, INR 2.02±0.52, MELD 24.91±4.64),112 (74.2%) patients had VNT. In the multivariate logistic regression, patients with VNT had higher SSM (kPa) (73.47±16.20 vs 48.71±19.28), OR (95% CI)1.080(1.043-1.118), p<0.001, LSM (kPa) (67.21±12.73 vs 52.66±21.06, OR (95%CI) 1.035 (1.006-1.066), p=0.02 and lower platelet count(10^9/L) (145.36±84.70 vs 206.28±116.48, OR (95%CI) 0.994 (0.989-0.999), p=0.013. A model was developed incorporating the three parameters. The equation of the model created utilising these 3 independent predictors was: ACLF VNT risk score = -4.734+(-0.006xPLT) + (0.034xLSM) + (0.077xSSM). The AUROC for the model was 0.868. At cutoff of 0.768, the model had sensitivity 86.61%, specificity 79.5 %, positive predictive value 92.38%, negative predictive value 67.39% and accuracy 84.77%. Model was superior to other noninvasive tests (p<0.01 for all). In the validation set, 65 patients (47 [72.3%] with VNT), the model had AUROC 0.859 with sensitivity 87.2 and specificity 66.6%. Stratifying the patients into alcohol and nonalcohol related etiologies of ACLF showed good performance with the AUROC of 0.836, sensitivity 85.6% and specificity 71.4% and AUROC 0.937, sensitivity 85% and specificity 86.7%, respectively. **Conclusion:** The model comprising SSM, LSM and platelet count can be used to identify VNT in patients of ACLF.

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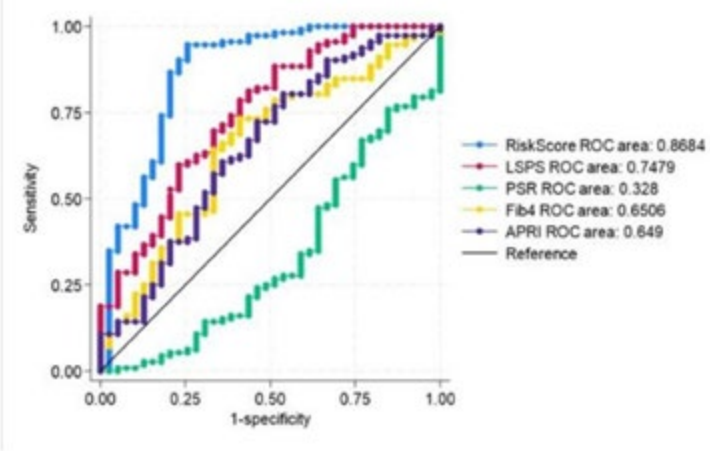

Fig 1 Comparison of ROC for predicting VNT by the model with other composite scores.

Disclosures: CHITRANSHU VASHISHTHA: Nothing to Disclose, Ankit Bhardwaj: Nothing to Disclose, Rajan Vijayaraghavan: Nothing to Disclose, Ankur Jindal: Nothing to Disclose, Shiv Kumar Sarin: Nothing to Disclose

1621 | PHARMACOKINETICS AND SAFETY OF TENOFOVIR ALAFENAMIDE IN CHINESE PATIENTS WITH ACUTE-ON-CHRONIC LIVER FAILURE

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Background: Tenofovir alafenamide (TAF) is recommended as a first-line oral nucleos(t)ide analogue in patients with chronic hepatitis B. Tenofovir (TFV), the major metabolite of TAF, is phosphorylated to TFV diphosphate, the active form that inhibits viral replication in hepatocytes. TFV is primarily eliminated by kidney. Patients with hepatitis B virus-related acute-on-chronic liver failure (HBV-ACLF) are at high risk of developing acute kidney injury. Data on the pharmacokinetics (PK) of TAF in Chinese patients with HBV-ACLF is lacking. We aimed to investigate the characteristics of TFV exposure and the renal safety of TAF in Chinese patients with HBV-ACLF patients. **Methods:** Patients with HBV-ACLF and normal renal function received TAF (Gilead Sciences, Inc., Foster City, CA, USA) with food at a dose of 25 mg per day. Intensive blood samples were collected immediately prior to dosing and at 15, 30, 45 minutes and 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, and 24 hours post-dosing on day 1 and day 14 for the assessment of plasma TFV concentration. PK parameters were estimated using non-compartmental analysis. Estimated glomerular filtration rate (eGFR) was monitored during the treatment. **Results:** We enrolled 12 HBV-ACLF patients with a mean age of 45.2 years for the PK analysis of TFV and renal safety evaluation. Majority of the patients were male (83.3%) and had cirrhosis (75%). Mean values of total bilirubin, album and international normalized ratio pre-treatment were 417μmol/L, 32g/L and 2.22. Child-Turcotte-Pugh and model for end-stage liver disease score of the patients at baseline were 10.5±1.7 and 26.6±3.8. All patients tolerated the treatment well, and none discontinued the therapy. Ten patients were followed up for more than 3 months, 2 patients underwent liver transplantation after 31 and 35 days of treatment, and 1 patient died on day 16. Single-dose (on day 1) and multiple-dose (on day 14) PK parameters of TFV are presented in Table. TFV exposure increased by approximately 100% after 14 days of TAF treatment compared to that after the first dose of TAF. Mean values of $AUC_{0\text{-}24h}$ on day 14 and day 1 were 224.5 and 123.8 ng·h/mL, and the median $t_{½}$ of TFV on day 14 and day 1 were 17 hours and 10.8 hours. Overall, there was no significant decline in eGFR during the treatment, eGFR pre-treatment, at week 1, 2 and 4 of treatment were 114.8±10.7, 115.8±17.6, 112.3±20.5 and 111.1±30.4 mL/min/1.73m^2, all P>0.05 in the comparison of eGFR between pre-treatment and week 1, 2 or 4 of the treatment. Only one patient, aged 60 years, was observed obvious eGFR decline from 104.6mL/min/1.73m^2 at baseline to 56.3mL/min/1.73m^2 at week 4 of treatment, while the eGFR returned to 99.3mL/min/1.73m^2 at week 7 of TAF treatment. **Conclusion:** TAF exhibited good tolerability and short-term renal safety in Chinese patients with HBV-ACLF, although TFV exposure increased by 100% after 14 days of TAF treatment compared to single dose of TAF.

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Table. Tenofovir pharmacokinetics on day 1 and 14 of tenofovir alafenamide treatment in Chinese patient with HBV-ACLF.

Parameter	Tenofovir pharmacokinetic on day 1	Tenofovir pharmacokinetic on day 14
C_{max} (ng/mL)	16.11±18.48	22.81±13.89
t_{max} (h)*	1.75 (0.94-3.50)	2.0 (0.75, 2.88)
$AUC_{0\text{-}24h}$ (ng·h/mL)	123.78±125.79	224.50±80.90
AUC_{inf} (ng·h/mL)	220.19±250.63	444.81±210.52
$t_{½}$ (h)*	10.8 (8.0-23.4)	17.0 (14.0-24.4)

HBV-ACLF, hepatitis B virus-related acute-on-chronic liver failure; C_{max}, maximum observed concentration; t_{max}, time to C_{max}; $AUC_{0\text{-}24h}$, area under the concentration-time curve from 0 to 24 hours; AUC_{inf}, area under the concentration-time curve extrapolated to infinity; $t_{½}$, apparent terminal half-life; *, reported as median and IQR.

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1622 | HEMOADSORPTION WITH CONTINUOUS RENAL REPLACEMENT THERAPY REDUCES CATECHOLAMINE REQUIREMENTS AND HYPERCYTOKINEMIA IN ACLF PATIENTS WITH SEPTIC SHOCK AND STAGE 3 AKI- A PROSPECTIVE COHORT STUDY

Rakhi Maiwall[1] Fagun Sharma[2] Harsh Vardhan Tevethia[2] Shiv Kumar Sarin[2]

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Background: The intensity of systemic inflammation drives organ failures in patients with acute on chronic liver failure (ACLF). Management of septic shock with severe AKI is a clinical challenge in ACLF patients and is associated with very high mortality. To reduce severe cytokinemia, extracorporeal cytokine hemoadsorption (HA-330) therapy as an add-on to continuous renal replacement therapy (CRRT) could be more effective compared to CRRT alone. **Methods:** In a prospective cohort, ACLF patients with septic shock and stage 3 AKI were treated with CRRT+HA-330(Group-1, n=31) or CRRT alone (Group 2, n=33). The primary outcome was a reversal of shock at 48 hours. Secondary outcomes included change in arterial lactate, SOFA score, PaO2/FiO2 ratio, and 14 and 28-day mortality. **Results:** Patients in both groups were comparable and the majority were males [27(87%) vs. 30(91%)] with alcohol-associated hepatitis [15(50%) vs. 21(62%)] and pneumonia [29(97%) vs. 28(82%)]. All patients had stage-3 AKI with a mean urine output (mL/hr) (of 19.79±11.96 vs. 34.2±10.4) in group 1 vs. 2 respectively. Patients in group 1 were younger with mean age [(39±8vs.44±9 p=0.05)], and similar SOFA score (11.51±3.88 vs. 11.03±3.00), MELD (32.01 ± 8.75 vs. 34.87 ± 9.77), norepinephrine (ug/kg/min) [(4.48 ±3.35vs.4.28±3.03)], arterial lactate [(1.99 ± 0.83vs.2.13±1.48] but significantly lower PaO2/FiO2 ratio [(171.58 ±81.28 vs. 334.43±63.89) and serum creatinine 3.03 ±1.60 vs. 3.64±1.1)**.** At 48 hours, more patients improved in shock in group 1 (87%vs.63.6% p=0.3), with a reduced incidence of early deaths at day 14 (22.6% 48.5% p =0.03). However, at 28 days, the mortality was similar in both groups, [41.9% vs. 51.5% HR= 0.74 (0.36-1.52)] and (26.6% vs.13%) underwent a liver transplant. At day 3 in group 1, there was a significant reduction in arterial lactate (umol/L) [(2.02 ± 0.86) to (1.56± 0.78); p= 0.01], SOFA score [(13.45±3.8) to (11.51±3.88); p=0.03] and improvement in Pao2/FiO2 ratio [(1164.97 ± 78.73) to (58.09 ± 110.64); p=0.001]. In group 2, the reduction in these parameters was not significant. Pro-inflammatory cytokines, C-reactive protein [(102.33±66.48 to 55.79±47.51;p=0.003)], interleukin-6[(51.11±62.23 vs.(22.85±14.12); p=0.05] and ferritin (522.51±407.17 vs. 449.72±333.10; p=0.45) showed reduction post-therapy in group 1. **Conclusion:** Cytokine hemadsorption with CRRT effectively ameliorates the cytokine storm. It improves hemodynamics, and arterial lactate but not the survival compared to CRRT alone in patients with ACLF with septic shock and stage 3 AKI.

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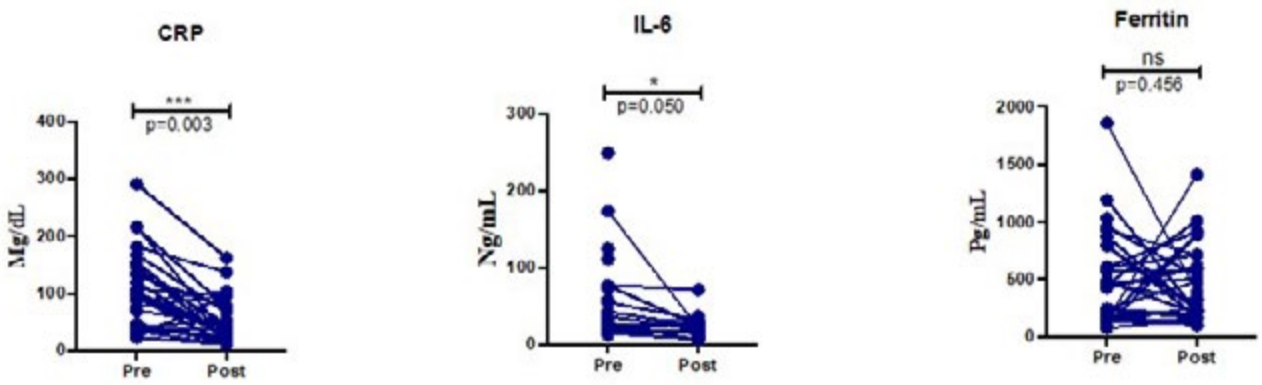

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1623 | ROLE OF NOTCH MEDIATED HEPATOCYTE REPROGRAMMING IN SEPSIS INDUCED LIVER FAILURE

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Background: Sepsis is defined as a life-threatening multiple organ dysfunction caused by the uncontrolled host response to an infection and is the leading cause of death in intensive care units globally. The liver plays a pivotal role in maintaining systemic metabolic and immune homeostasis. While hepatocyte reprogramming significantly contributes to liver dysfunction in chronic liver diseases like NASH and cirrhosis, its role in sepsis remains unexplored. Our preliminary data indicate that sepsis induces aberrant Notch signaling activation and reprograms hepatocytes into an immature progenitor-like state, which strongly correlates with sepsis mortality. This study aims to elucidate the role of Notch signaling activation in sepsis-induced hepatocyte reprogramming and its impact on liver failure and mortality. **Methods:** Polymicrobial sepsis was induced in Control (vehicle) mice and mice treated with DAPT, a γ-secretase inhibitor that blocks Notch signaling activation. Hepatocyte phenotypic changes, mortality, and the expression of genes associated with hepatocyte reprogramming were assessed. We also analyzed Notch signaling and related gene expression in normal and NASH human liver tissues. **Results:** Sepsis significantly decreases the expression of mature hepatocyte marker genes such as Nr0b2 and Foxa2, which are crucial for maintaining hepatocyte function. In contrast, genes associated with hepatocyte reprogramming, including Sox9, Tead1, and other liver progenitor cell markers, show remarkable increases. Treatment with the Notch inhibitor DAPT significantly attenuates this phenotypic reprogramming and notably improves survival in septic mice. Patients with NASH/cirrhosis exhibit a high incidence of bacterial infections and are prone to develop severe sepsis. Additionally, we observed that Notch transcriptional activity and hepatocyte reprogramming genes are markedly increased in both NASH and cirrhotic human liver tissues. **Conclusion:** Our findings suggest that Notch-mediated hepatocyte reprogramming is a major driver of sepsis-associated liver failure and mortality. This novel discovery underscores the critical role of Notch signaling in regulating hepatic function during sepsis and identifies potential therapeutic targets for preventing or treating sepsis-related liver dysfunction, particularly in patients with pre-existing NASH or cirrhosis.

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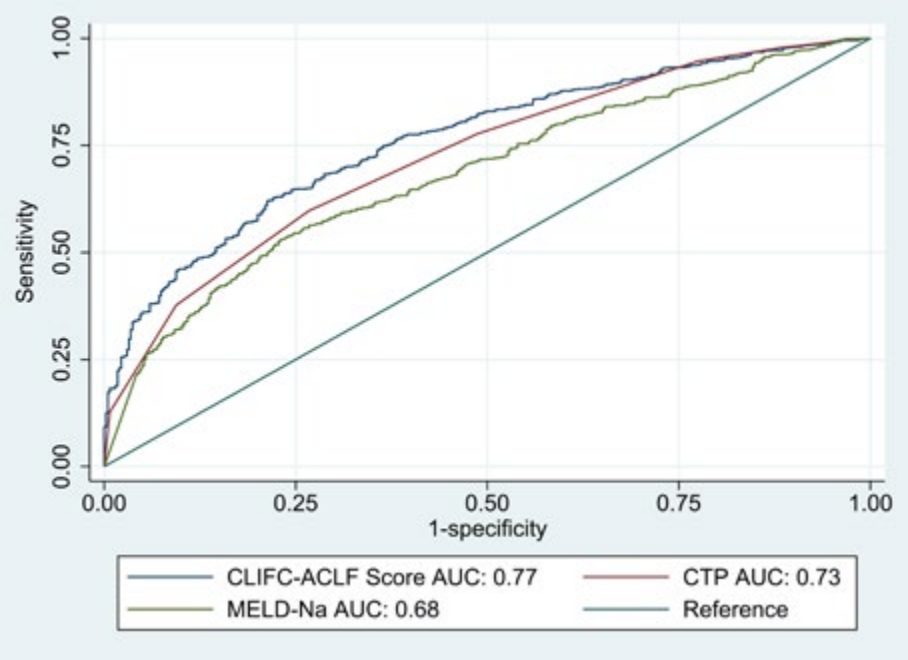

Disclosures: TINGTING LI: Nothing to Disclose, Xuechen Ren: Nothing to Disclose, Adams Joseph: Nothing to Disclose, Amy Gravitte: Nothing to Disclose, Fei Tu: Nothing to Disclose, David L Williams: Nothing to Disclose, Chuanfu Li: Nothing to Disclose, Xiaohui WANG: Nothing to Disclose

1624 | PREDICTORS OF ONE-YEAR TRANSPLANT-FREE SURVIVAL OF PATIENTS WITH ACUTE-ON-CHRONIC LIVER FAILURE AFTER HOSPITAL DISCHARGE ◆

Shubham Mehta[1] Dwarakanathan Vignesh[2] Sagnik Biswas[1] Shekhar Swaroop[1] Bodhisattya Roy Chaudhuri[1] Umang Arora[1] Arnav Aggarwal[1] Ayush Agarwal[1] Dr Shalimar[1]

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Background: Acute-on-chronic liver failure (ACLF) is characterized by an abrupt hepatic dysfunction in patients with chronic liver disease or cirrhosis and is associated with high short-term mortality. There is limited data on predictors of long term outcomes of ACLF patients after discharge from hospital.. Our aim was to evaluate 1-year transplant-free survival (TFS) among patients admitted with a diagnosis of ACLF at a tertiary care center in India. **Methods:** Clinical records of all patients admitted with a diagnosis of ACLF based on the European Association for the Study of the Liver-Chronic Liver Failure (EASL-CLIF) Consortium criteria at the All India Institute of Medical Sciences, New Delhi, India between January 2011 and April 2023 were reviewed. Patients who recovered from the initial episode of ACLF and survived for at least 1 year without receiving a liver transplant were included in the analysis. We assessed the correlation between baseline clinical data at the index hospital admission and 1-year (TFS) using the adjusted Cox proportional hazards model. **Results:** Out of 1526 admitted with a diagnosis of ACLF, 606 patients (39.7%) were discharged, of whom 297 patients (19.5%) survived for at least 1 year. The patients who survived for at least 1 year had lower mean age (p-value: <0.001), mean Chronic Liver Failure Consortium acute-on-chronic liver failure (CLIF-C ACLF) score (p-value: <0.001), mean Model for End-stage Liver disease – sodium score (MELD-Na) (p-value: <0.001) and Child-Turcotte-Pugh score (CTP) (p-value: <0.001) as compared to patients who died within 1 year. The overall probability of 1-year TFS at hospital admission was 0.19 (95% CI: 0.17-0.21) and at hospital discharge was 0.49 (95% CI:0.45-0.53). This rate varied with ACLF grade at admission, being highest in ACLF grade 1 at admission (0.25 [95% CI: 0.14-0.36]) and lowest in ACLF-3 patients (0.06 [95% CI: 0.04 – 0.09]) (p-value for trend: <0.001). After adjusting for age, sex, and etiology, a higher ACLF grade at admission and CLIF-C ACLF score were associated with increased risk of death within 1 year of hospital discharge (p-value: <0.001). CLIF-C ACLF score on the day of admission was the best predictor of 1-year TFS with area under the curve (AUROC) of 0.77 (95% CI: 0.74-0.80) and score of >50 having a sensitivity of 50% and specificity of 86% for mortality within 1 year (Figure 1a). **Conclusion:** In this retrospective analysis from an Asian

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cohort, ACLF grade and CLIF-C ACLF score at admission were shown to predict 1-year transplant free survival after hospital discharge. Age, sex, etiology of acute decompensation and etiology of underlying chronic liver disease did not affect 1-year transplant free survival after hospital discharge.

Disclosures: Shubham Mehta: Nothing to Disclose, Dwarakanathan Vignesh: Nothing to Disclose, Sagnik Biswas: Nothing to Disclose, Shekhar Swaroop: Nothing to Disclose, Bodhisattya Roy Chaudhuri: Nothing to Disclose, Umang Arora: Nothing to Disclose, Arnav Aggarwal: Nothing to Disclose, Ayush Agarwal: Nothing to Disclose, Dr Shalimar: Nothing to Disclose

1625 | EVALUATING THE IMPACT OF PRE-LIVER TRANSPLANT ACUTE-ON-CHRONIC LIVER FAILURE ON POST-LIVER TRANSPLANT PROGNOSIS IN PATIENTS WITH ALCOHOL-ASSOCIATED LIVER DISEASE

David Lee[1] Ki Jung Lee[2] Sharmitha Yerneni[2] Kuntal Bhowmick[3] Youngjae Cha[1] Andrew Yi[1] KeeSeok Lee[2] Gregory Fan[2] Nathalie Urrunaga[1]

[1]University of Maryland School of Medicine, [2]Tufts School of Medicine, [3]Warren Alpert Medical School of Brown University

Background: Alcohol-associated liver disease (ALD), the leading cause of chronic liver disease in the developed world, has created a growing need for liver transplantation (LT). With the recognition of acute-on-chronic liver failure (ACLF) and its impact on post-LT prognosis, it is crucial to assess its clinical significance in ALD patients undergoing LT. This study aims to investigate the prognostic impact of pre-LT ACLF on post-LT outcomes in ALD. **Methods:** We conducted a retrospective analysis on patients with ALD who underwent LT for ACLF between 2005 to 2019 using the UNOS-STAR registry. ACLF severities were based on the modified European Association for the Study of the Liver-Chronic Liver Failure Consortium (EASL-CLIF) criteria, with grade 0 (G0) indicating no ACLF. The primary outcomes, all-cause mortality (ACM) and graft failure (GF), and organ-specific causes of death were analyzed using Cox regression analyses. Cumulative hazard curves and the log-rank p-values were also derived for these outcomes. **Results:** 9,261 patients with ALD and ACLF who underwent LT were stratified by ACLF grade (G0: 4,149; G1: 1,656; G2: 1,745; G3: 1,711). With increasing ACLF severity, patients tended to be younger with a higher proportion of females and lower proportion of Whites. Patients with ACLF exhibited significantly higher ACM with incidence rates at 51.28 per 1000 person-years in grade 1 (aHR 1.26, 95% CI 1.11-1.43, p<0.001), 45.57 in grade 2 (aHR 1.19, 95% CI 1.03-1.37, p=0.02), and 63.21 in grade 3 (aHR 1.70, 95% CI 1.47-1.96, p<0.001), compared to 44.51 in grade 0. In terms of GF, only those with ACLF grade 3 had increased incidence rate of 13.30 (aHR 1.72, 95% CI 1.23-2.41, p=0.002), compared to 7.50 in grade 0. Increased rates of cardiac (G1: aHR 1.59, 95% CI 1.16-2.18, p=0.004; G3: aHR 1.87, 95% CI 1.30-2.71, p<0.001), infectious (G2: aHR 1.60, 95% CI 1.18-2.18, p=0.003; G3: aHR 2.54, 95% CI 1.88-3.44, p<0.001), renal (G1: aHR 2.26, 95% CI 1.40-4.24, p=0.003; G2: aHR 2.65, 95% CI 1.40-5.02, p=0.003; G3: aHR 2.70, 95% CI 1.31-5.57, p=0.007), respiratory (G3: aHR 2.10, 95% CI 1.21-3.64, p=0.009), and septic (G3: aHR 2.06, 95% CI 1.42-3.01, p<0.001) mortality were observed across different ACLF grades. **Conclusion:** Patients with ALD and advanced ACLF face increased risks of all-cause mortality and graft failure. Clinical recognition of advanced ACLF and appropriate pre-LT stratification are crucial for providing risk-appropriate transplant measures.

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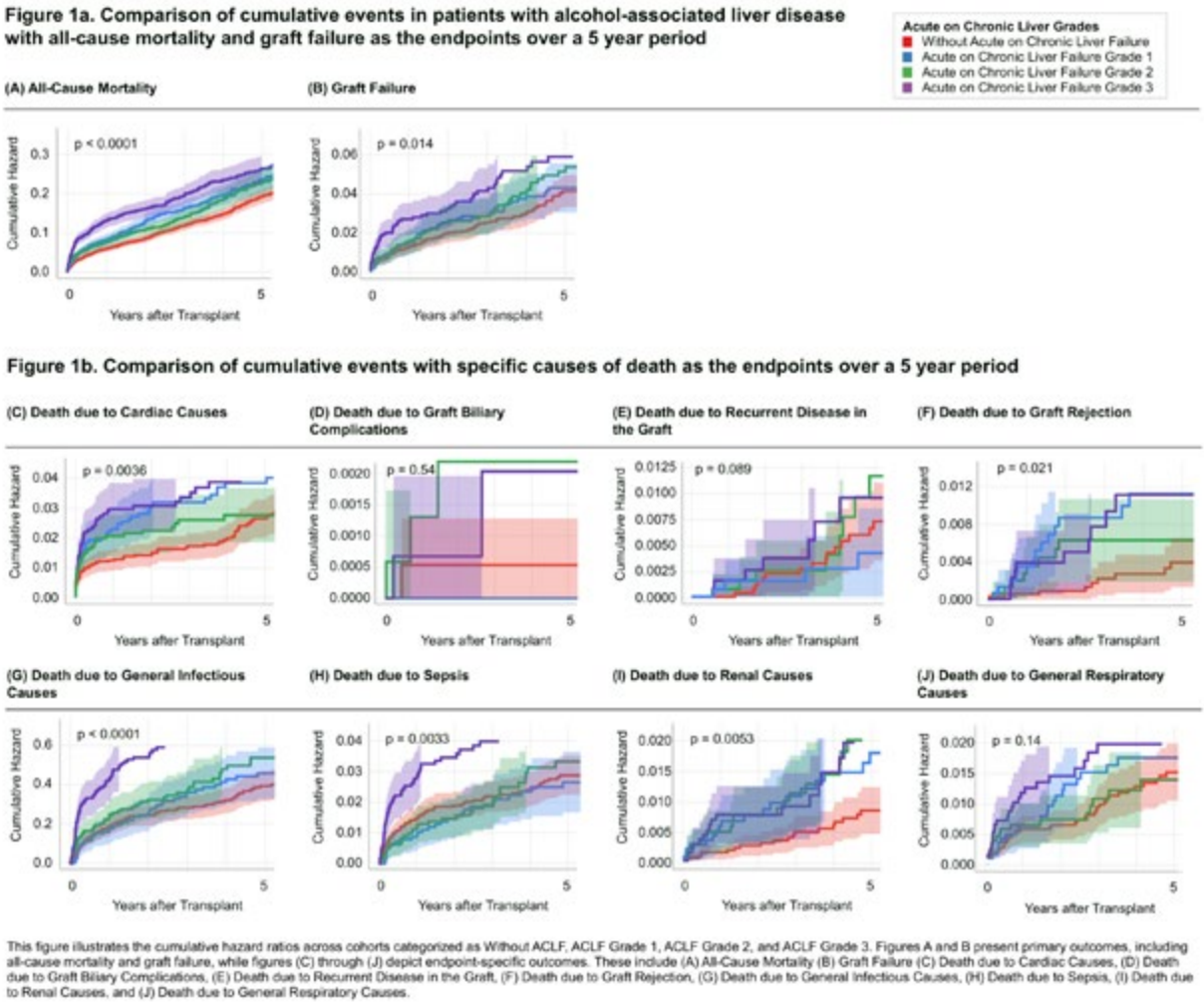

Disclosures: David Lee: Nothing to Disclose, Ki Jung Lee: Nothing to Disclose, Sharmitha Yerneni: Nothing to Disclose, Kuntal Bhowmick: Nothing to Disclose, Youngjae Cha: Nothing to Disclose, Andrew Yi: Nothing to Disclose, KeeSeok Lee: Nothing to Disclose, Gregory Fan: Nothing to Disclose, Nathalie Urrunaga: Nothing to Disclose

1626 | HOW DOES THE PRESENCE OF PRE-TRANSPLANT ACUTE-ON-CHRONIC LIVER FAILURE AFFECT POST-LIVER TRANSPLANT OUTCOMES AMONG PATIENTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE

David Lee[1] Kuntal Bhowmick[2] Sharmitha Yerneni[3] Kijung Lee[3] Youngjae Cha[1] Andrew Yi[1] Gregory Fan[3] Nathalie Urrunaga[1]

[1]University of Maryland School of Medicine, [2]Warren Alpert Medical School of Brown University, [3]Tufts School of Medicine

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is a growing public health concern, with MASLD-related cirrhosis emerging as a prominent indicator for liver transplantation (LT). Patients with MASLD who experience a precipitating event, such as infection, may develop acute-on-chronic liver failure (ACLF) for which LT remains the cornerstone of treatment. This underscore the necessity of understanding how ACLF severity influences post-LT outcomes in MASLD. **Methods:** Patients with MASLD undergoing LT from 2005-2019 were selected from the UNOS-STAR database. Severity of ACLF was determined by the modified European Association for the Study of the Liver-Chronic Liver Failure Consortium criteria, with Grade 0 (G0) representing no ACLF as the control group. Primary outcomes including all-cause mortality and graft failure were measured using multivariate Cox regression and cumulative hazard analysis, while secondary outcomes

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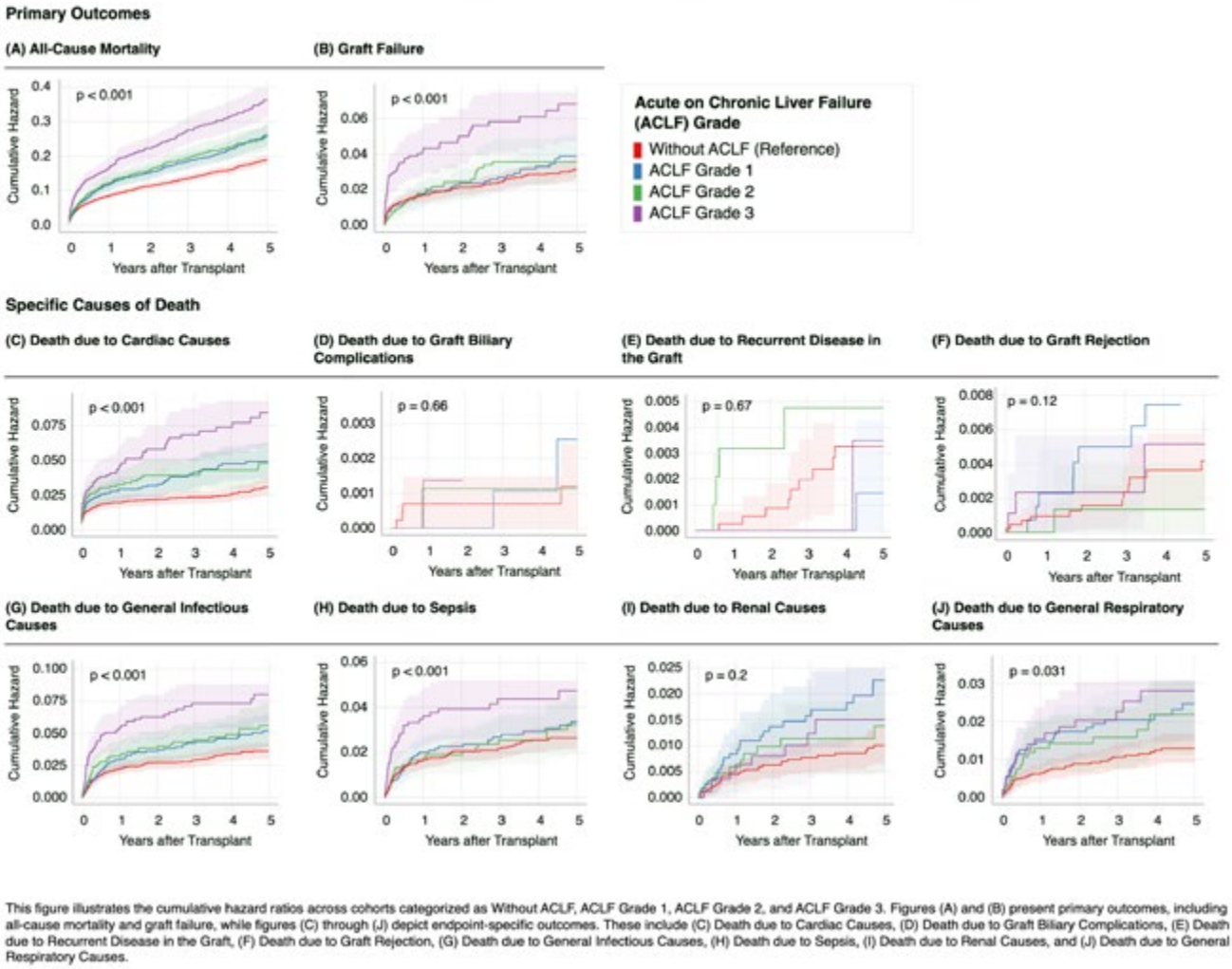
encompassed organ-specific mortality etiologies. **Results:** 8,580 patients with MASLD who underwent LT were included and stratified by ACLF grade (G0: 4,810; G1: 1,637; G2: 1,149; G3: 984). Higher incidence rates of all-cause mortality were seen across all ACLF grades (G1-G3) with 56.56, 55.50, and 79.98 per 1000 person-years, respectively, compared to 45.37 in G0 (G1: aHR 1.29, 95%CI 1.14-1-1.45, p<0.001; G2: aHR 1.34, 95%CI 1.16-1.55, p<0.001; G3: aHR 1.99, 95%CI 1.70-2.32, p<0.001). Graft failure was higher only in G3 with incidence rate of 16.06 (aHR 2.37, 95%CI 1.64-3.41, p<0.001), compared to 6.46 in G0. All ACLF grades experienced increased rates of cardiac (G1: aHR 1.48, 95%CI 1.12-1-1.95, p=0.005; G2: aHR 1.50, 95%CI 1.07-2.11, p=0.02; G3: aHR 2.32, 95%CI 1.65-3.27, p<0.001), infectious (G1: aHR 1.49, 95%CI 1.12-1.97, p=0.006; G2: aHR 1.47, 95%CI 1.05-2.05, p=0.02; G3: aHR 2.70, 95%CI 1.94-3.75, p<0.001), and neurologic (G1: aHR 2.33, 95% CI 1.33-4.09, p=0.003; G2: aHR 2.62, 95% CI 1.35-5.08, p=0.004; G3: aHR 4.70, 95% CI 2.41-9.14, p<0.001) mortality. Renal mortality was higher in G1 (aHR 1.68, 95%CI 1.05-2.71, p=0.03), respiratory in G2 (aHR 1.99, 95%CI 1.22-3.26, p=0.006) and G3 (aHR 0.01, 95%CI 1.15-3.66, p=0.01), and sepsis in G3 (aHR 2.39, 95%CI 1.59-3.60, p<0.001). **Conclusion:** Pre-transplant ACLF significantly impacts post-LT outcomes in patients with MASLD, with higher grades associated with increased mortality risk across multiple organ systems.

Comparison of Cumulative Events in Patients with MASLD or Cryptogenic Cirrhosis and Progressive Grades of Acute-on-Chronic Liver Failure (ACLF) over a 5-Year Post-Transplant Period



This figure illustrates the cumulative hazard ratios across cohorts categorized as Without ACLF, ACLF Grade 1, ACLF Grade 2, and ACLF Grade 3. Figures (A) and (B) present primary outcomes, including all-cause mortality and graft failure, while figures (C) through (J) depict endpoint-specific outcomes. These include (C) Death due to Cardiac Causes, (D) Death due to Graft Biliary Complications, (E) Death due to Recurrent Disease in the Graft, (F) Death due to Graft Rejection, (G) Death due to General Infectious Causes, (H) Death due to Sepsis, (I) Death due to Renal Causes, and (J) Death due to General Respiratory Causes.

Disclosures: David Lee: Nothing to Disclose, Kuntal Bhowmick: Nothing to Disclose, Sharmitha Yerneni: Nothing to Disclose, Kijung Lee: Nothing to Disclose, Youngjae Cha: Nothing to Disclose, Andrew Yi: Nothing to Disclose, Gregory Fan: Nothing to Disclose, Nathalie Urrunaga: Nothing to Disclose

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1627 | SERUM GALECTIN-3 AS A PREDICTOR OF INFECTIONS AND MORTALITY IN ACUTE-ON-CHRONIC LIVER FAILURE

Nalu NAVARRO-ALVAREZ[1] Osvely Mendez-Guerrero[2] Anaisa Carranza Carrasco[2] Alma Estanes[2] Eduardo Cervantes-Alvarez[2] Nathaly Limon-De La Rosa[2] Mario Enrique Rendon Macias[3] Alfonso Rodriguez Espada[3] Aldo Torre[2]

[1]University of Colorado and Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, [2]Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, [3]Universidad Panamericana

Background: Acute-on-Chronic Liver Failure (ACLF) is a severe condition in patients with cirrhosis, characterized by high mortality rates. This syndrome often **Results:** from excessive inflammatory responses and is frequently complicated by infections, which significantly contribute to the high mortality. Galectin-3 is a lectin that regulates inflammation and fibrosis and is linked to increased infection complications in cirrhosis following transplantation. Given the critical impact of infections on mortality in ACLF and the role of Galectin-3, this study aims to evaluate the association between serum Galectin-3 levels and the development of infections and mortality in ACLF patients. **Methods:** We conducted a prospective cohort study including cirrhotic patients hospitalized for a decompensation event and diagnosed with ACLF within 7 days of admission. We evaluated precipitants of ACLF, organ failures, and measured Galectin-3 levels in serum collected at diagnosis using ELISA. We assessed short-term mortality and infection development during a follow-up period of 28 and 90 days. **Results:** A total of 105 patients who developed ACLF upon admission were recruited, with the most frequent etiology of cirrhosis being autoimmune (30.5%). Overall survival rates at 28 and 90 days were 50% and 34%, respectively. At 28 days, 4 patients (3.8%) received a liver transplant, 53 (50%) died, and the remainder survived. The Galectin-3 levels in the group that died were significantly higher [32 (22-54), p = 0.01]. The Galectin-3 cutoff point for 28-day mortality, calculated using ROC curve analysis, was 19.75 ng/dL. Comparing mortality at 28 and 90 days, patients with higher Galectin-3 levels had lower survival, log-rank ($p < 0.001$, p = 0.004) (Figures 1A-1B). The development of infection was also evaluated in patients with follow-up beyond 7 days. The Galectin-3 cutoff point for infection was 16.14 ng/dL, and patients with levels above this had a higher incidence of infection at 28 and 90 days, log-rank (p = 0.04, p = 0.05) (Figures 1C-1D). In univariable Cox regression, Gal-3 levels (>16.14) were associated with infection at 28 days (HR: 2.39, 95% CI: 0.98-5.8, p = 0.05), and in multivariable analysis, the HR was 2.10 (95% CI: 0.83-5.3, p = 0.117), adjusted for age, ACLF score, and ACLF grade. **Conclusion:** Higher serum Galectin-3 levels are significantly associated with increased mortality and infection rates in patients with ACLF. Specifically, Galectin-3 levels above 19.75 ng/dL are predictive of lower survival at 28 and 90 days, while levels above 16.14 ng/dL are linked to a higher incidence of infections. These findings suggest that Galectin-3 could serve as a valuable prognostic biomarker for mortality and infection risk in ACLF patients.

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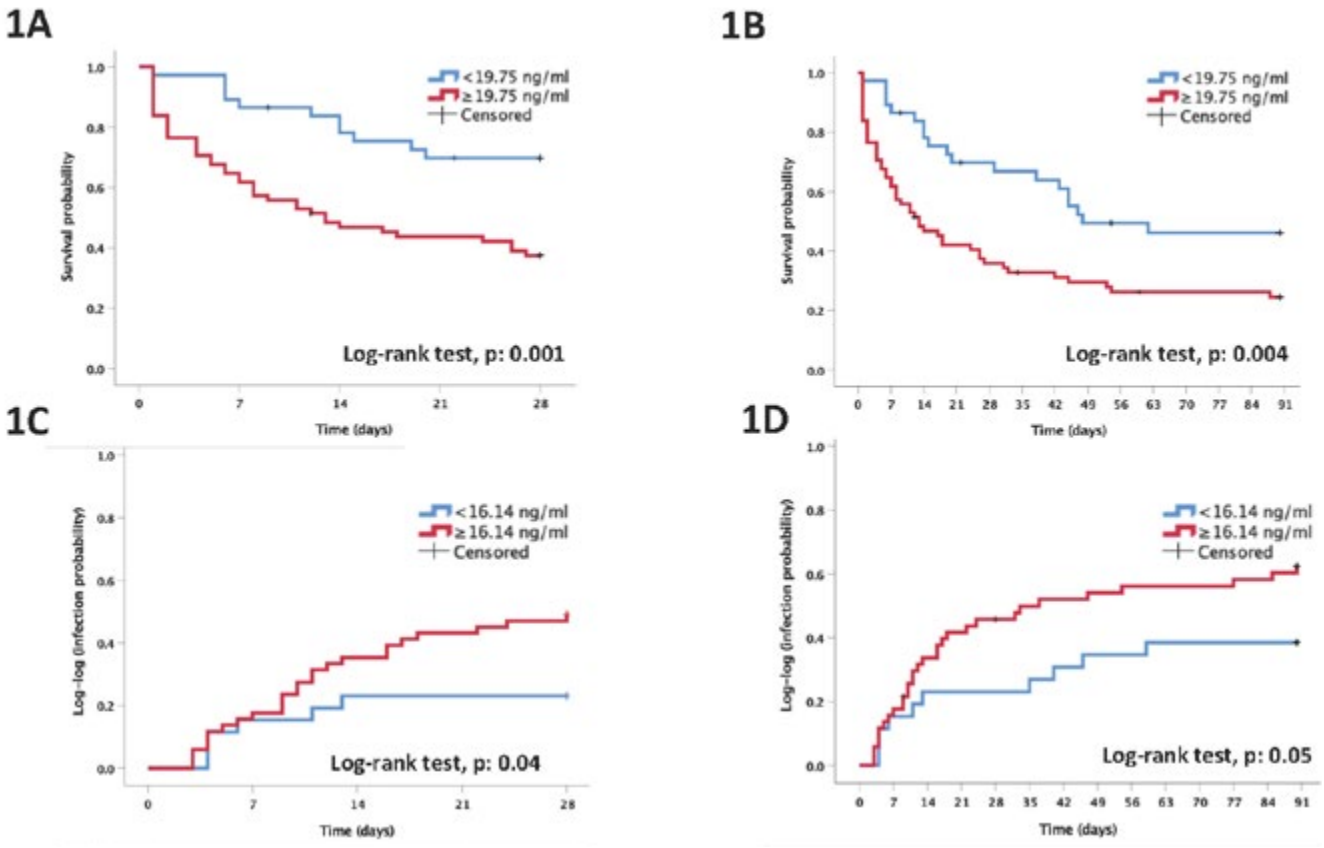

Disclosures: Nalu NAVARRO-ALVAREZ: Nothing to Disclose, Osvely Mendez-Guerrero: Nothing to Disclose, Anaisa Carranza Carrasco: Nothing to Disclose, Alma Estanes: Nothing to Disclose, Eduardo Cervantes-Alvarez: Nothing to Disclose, Nathaly Limon-De La Rosa: Nothing to Disclose, Mario Enrique Rendon Macias: Nothing to Disclose, Alfonso Rodriguez Espada: Nothing to Disclose, Aldo Torre: Nothing to Disclose

1628 | THE INFLUENCE OF GEOGRAPHICAL DIFFERENCES AND COVID-19 ON HEPATIC-FAILURE RELATED MORTALITY RATES

Qasim Chohdry[1] Sophia Hussain[1] Sophia Hussain[1] Muhammad Chohdry[2] Islam Mohamed[1] Kiel Corkran[1]

[1]University of Missouri- Kansas City School of Medicine, [2]University of Kansas School of Medicine

Background: Several studies have looked at the relationship between geographic location and prevalence of diseases. Other studies have focused on how the COVID-19 pandemic has influenced many walks of life, including its impact on people with pre-existing conditions. However, the correlation between geographic differences, COVID-19, and hepatic-failure related mortality from 2018-2022, is yet to be seen. **Methods:** De-identified publicly available population data from the Centers for Disease Control and Prevention Wide-ranging Online Data for Epidemiologic Research database was evaluated. Informed consent and institutional review board approval were not required per the Common Rule. Underlying deaths due to hepatic failure were included by International Classification of Diseases, Tenth Revision (ICD-10) code K72.0. Crude rates per 100,000 in the United States between 1999-2020 were included in the study. Correlation analysis was completed against June 2020 statewide COVID-19 statistics. **Results:** Preliminary findings show the mean crude death rate increased from 1.61 in 2018 to 1.82 in 2021. For states specifically, Alabama had the highest crude death rate at 3.3, followed by New Mexico (3.0) and West Virginia (2.9). Vermont, Maine, and Wyoming had the lowest crude death rates at 0.6, 0.7, and 0.8, respectively. When focusing on the relationship between COVID-19 and hepatic failure deaths, a moderate positive correlation (r = 0.62) was found between estimated new COVID-19 infections per day and hepatic failure deaths. A weak positive correlation (r = 0.24) was observed between the percentage of the

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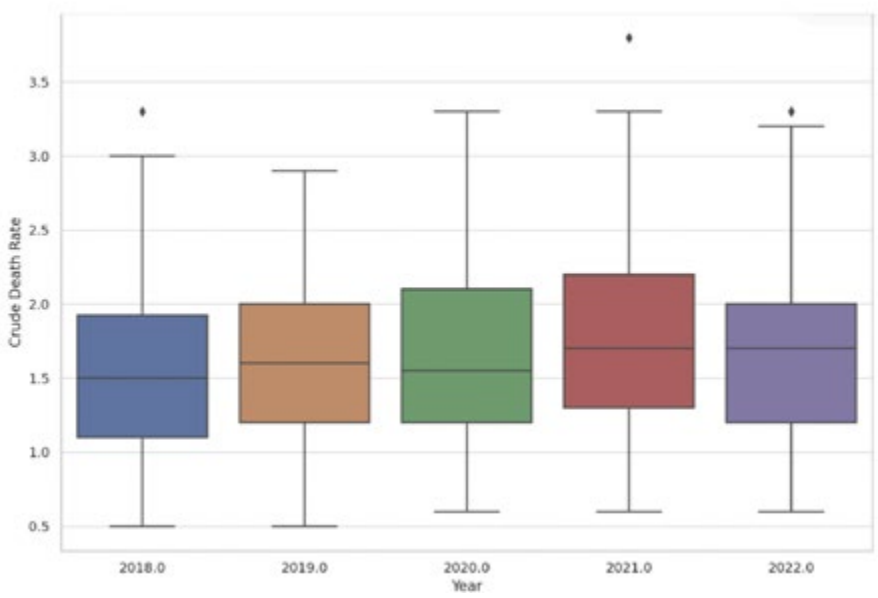
total population infected and hepatic failure deaths. A weak negative correlation (r = -0.26) was found between the infection ascertainment ratio and hepatic failure deaths. As shown in figure 1, over the course of the pandemic, from 2018-2022, the distribution of crude death rates for hepatic failure showed an increase in median rates. The variability in death rates increased during the COVID-19 pandemic, indicating a wider spread of mortality rates across states. **Conclusion:** This study focuses on the relationship between geographical disparities, COVID-19, and trends in hepatic failure-related mortality rates within the United States from 2018 to 2022. The findings suggest the need for targeted public health interventions at the local and state levels to mitigate illnesses such as COVID-19 and hepatic failure. Differences between states' hepatic failure deaths also indicate further investigation into the variability of hepatic failure care in the states with the highest and lowest hepatic failure deaths. Additionally, the emergence of the COVID-19 pandemic appears to have impacted hepatic mortality rates, prompting a need for investigation into the compounding effects of COVID-19 and other viruses on hepatic health outcomes.

Distribution of Crude Death Rates for Hepatic Failure by Year (Figure 1)



Disclosures: Qasim Chohdry: Nothing to Disclose, Sophia Hussain: Nothing to Disclose, Sophia Hussain: Nothing to Disclose, Muhammad Chohdry: Nothing to Disclose, Islam Mohamed: Nothing to Disclose, Kiel Corkran: Nothing to Disclose

1629 | HOW IMPORTANT IS ACUTE-ON-CHRONIC LIVER FAILURE GRADE FOR POST-LIVER TRANSPLANT OUTCOMES? A SINGLE-CENTER ANALYSIS

Constance Mobley[1] Andrea Meinders[1] Elizabeth Brombosz[1] Enshuo Hsu[2] Mozhgon Moaddab[1] Ashish Saharia[1] Ashton Connor[1] Mark Hobeika[1] Caroline Simon[1] Yee Lee Cheah[1] Linda Moore[1] Victor Ankoma-Sey[3] Chukwuma Egwim[3] Tamneet Basra[1] Sudha Kodali[1] David Victor[1] R. Mark Ghobrial[4]

[1]Houston Methodist Hospital, [2]University of Texas MD Anderson Cancer Center, [3]Liver Associates of Texas, [4]Houston Methodist JC Walter Transplant Center

Background: Short-term mortality for patients with acute-on-chronic liver failure (ACLF) is high, around 90% at 3 months. The prevailing paradigm in the transplant community is that patients with ACLF 3 (3 or more failing organ systems) are generally too sick to undergo LT. However, recent studies have shown that patients with ACLF 3 can receive LT with comparable post-transplant survival to patients with ACLF 1 or 2. The aim of this analysis was to determine what factors impacted post-LT survival for ACLF patients at a single high-acuity center serving a racially ethnically diverse region of the US. To our knowledge, this is the largest cohort of ACLF patients presented to date. **Methods:** Electronic medical records of patients admitted to the ICU undergoing LT (multi-organ recipients excluded) at Houston Methodist between 6/1/2016 and 11/30/2022 were retrospectively reviewed. Three time points were analyzed: the time of hospital admission, maximum ACLF grade, and transplant. Variables most

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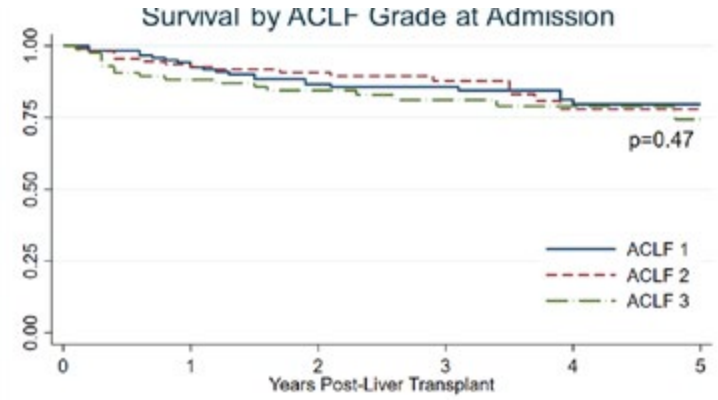
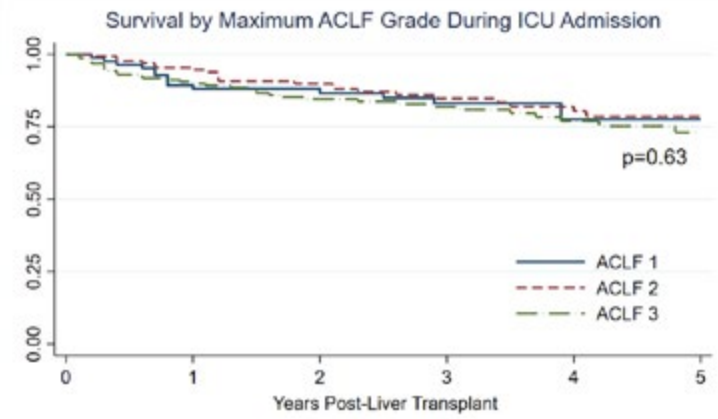
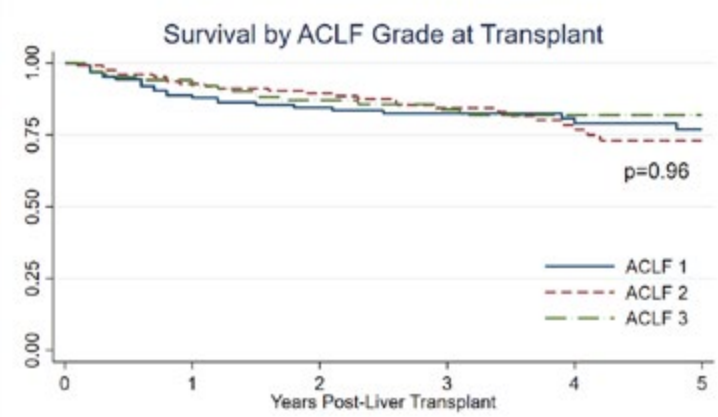
closely associated with survival were determined using multivariable Cox proportional hazards analysis with variables selected using the Lasso algorithm. **Results:** During the study period, 427 patients were in the ICU immediately pre-LT and were included in the analysis. ACLF grade at admission (p=0.47), maximum ACLF grade (p=0.63), and ACLF grade at transplant (p=0.63) were not associated with post-LT survival (Kaplan-Meier analysis with log-rank test). In univariable analysis, ACLF grade at all 3 time points was not associated with survival (all p>0.05). Interestingly, West-Haven hepatic encephalopathy grade at transplant was associated with greater risk of post-LT death (Grade 2: HR, 2.15; 95% CI, 1.07-4.30; p=0.03; Grade 3: HR, 3.29; 95% CI, 1.78-6.08; p<0.001; Grade 4: HR, 3.13; 95% CI, 1.22-8.03; p=0.02). Higher West-Haven grade at the time of maximum ACLF was also associated with increased mortality risk (Grade 2: HR, 2.32; 95% CI, 1.23-4.38; p=0.009; Grade 3: HR, 2.64, 95% CI, 1.39-5.10; p=0.004; Grade 4: HR, 3.62; 95% CI, 1.56-8.43; p=0.003). However, only recipient age was significant in multivariable analysis (aHR, 1.03; 95% CI, 1.01-1.05; p=0.01). **Conclusion:** These data support continuing to offer LT to patients with ACLF 3 at specialized centers with expertise in treating high-acuity patients. Older patients with ACLF should be evaluated with additional scrutiny. With proper medical management during the hospitalization before LT, these patients can have 5-year post-LT survival rates of >70%.







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1630 | NOVEL ROLE OF LSECS IN HEPATIC IMMUNE FUNCTION DURING SEPSIS

TINGTING LI[1] Xuechen Ren[1] Joseph Adams[1] Amy Gravitte[1] Fei Tu[1] David L Williams[1] Chuanfu Li[1] Xiaohui WANG[1]

[1]EAST TENNESSEE STATE UNIVERSITY

Background: Sepsis is caused by an uncontrolled host response to infection and is a leading cause of death in intensive care units. Liver dysfunction contributes significantly to the morbidity and mortality associated with sepsis. Liver sinusoidal endothelial cells (LSECs) play a critical role in hepatic immune and metabolic functions, but their role in bacterial infection and sepsis remains poorly understood. HSPA12B, a member of the HSP70 family, shows distinct expression in LSECs, being prominent in periportal LSECs and reduced in midzonal LSECs. **Methods:** To investigate the role of endothelial cell HSPA12B (eHSPA12B) in sepsis or bacterial infection, we induced polymicrobial sepsis or bacterial infection (E.coli-GFP, 5x10 / mice) in wild-type and eHSPA12B$^{-/-}$ mice. We evaluated the phenotypic changes and endocytic capacity of LSECs, and the bacterial capture ability of Kupffer cells. Additionally, we measured mortality, circulating levels of endotoxins and bacteria. **Results:** We found that mice lacking endothelial cell HSPA12B (eHSPA12B$^{-/-}$) exhibit disrupted hepatic Kupffer zonation and function. Furthermore, we induced sepsis in these mice and observed severe LSEC capillarization, along with increased bacterial load compared to WT septic mice. Further investigations revealed that eHSPA12B is necessary for GATA4 nuclear translocation in LSECs. Endothelial cell-specific GATA4 deficiency resulted in an abnormal LSEC phenotype, disrupted Kupffer cell zonation, and impaired bacterial clearance. These data suggest a cooperative role of eGATA4 and HSPA12B in maintaining the phenotype and function of LSECs. Additionally, patients with NASH/cirrhosis are more susceptible to bacterial infections and sepsis. Our study found decreased HSPA12B expression and impaired GATA4 transcriptional activity in LSECs of NASH/cirrhosis patients, suggesting their contribution to NASH/cirrhosis associated hepatic immune dysfunction and increased susceptibility to bacterial infections. **Conclusion:** Our findings suggest that LSEC HSPA12B is required for maintaining the unique phenotype and function of LSECs, which are essential for hepatic Kupffer cell periportal zonation and bacterial clearance during sepsis. This novel discovery highlights the critical role of LSECs in regulating hepatic immune function during sepsis and provides potential therapeutic targets for preventing or treating sepsis-related liver dysfunction.

Disclosures: TINGTING LI: Nothing to Disclose, Xuechen Ren: Nothing to Disclose, Joseph Adams: Nothing to Disclose, Amy Gravitte: Nothing to Disclose, Fei Tu: Nothing to Disclose, David L Williams: Nothing to Disclose, Chuanfu Li: Nothing to Disclose, Xiaohui WANG: Nothing to Disclose

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1631 | PREDICTORS OF REVERSAL OF ACUTE ON CHRONIC LIVER FAILURE AND NEED FOR THERAPEUTIC GOALS TO EXTEND TIMELINES BEYOND 90 DAYS

Shreyas sarvesh[1] Rajan Vijayaraghavan[1] Ashok Kumar Choudhury[1] Vinod Arora[1] Rakhi Maiwall[1] CHITRANSHU VASHISHTHA[2] Ankur Jindal[3] Shasthry Sm[2] Harsh Tevethia[4] Satender Pal Singh[1] Babu Lal Meena[1] Vikram Bhatia[1] Manoj Sharma[1] Guresh Kumar[1] Shiv Kumar Sarin[1]

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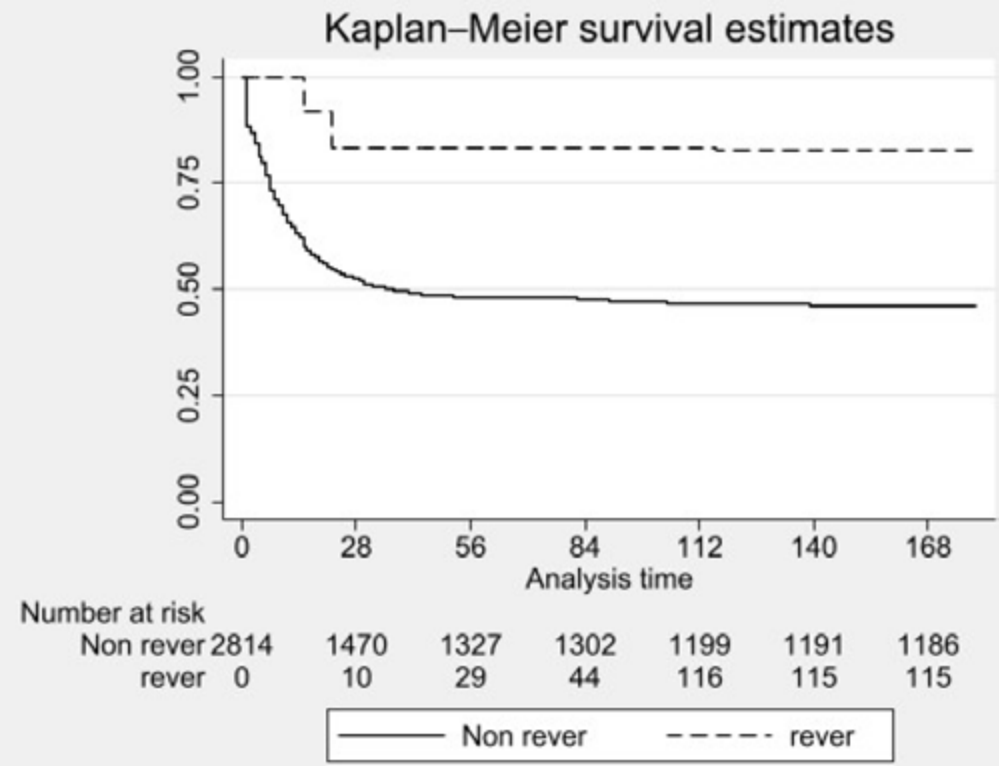
Background: Acute on chronic liver failure (ACLF) syndrome is severe and carries a high short-term mortality. Generally, data is available on survival at 90 days, and none on reversibility of the syndrome. While it is likely that patients who achieve reversal of ACLF have a more favourable outcome, but the exact timeline to define reversal is not known. We analysed the baseline factors predicting reversibility of ACLF syndrome at 90-days. **Methods:** Consecutive ACLF patients, fulfilling the APASL definition and prospectively enrolled at the ILBS were included and followed till 90-days. Reversal of ACLF was defined as per AARC ACLF Consensus 2019; decrease of bilirubin below 5 mg/dL and reversal of coagulopathy to INR below 1.5 and no hepatic encephalopathy, with or without resolution of ascites. **Results:** Electronic records of prospectively studied 2813 patients was analysed. Reversibility was achieved in 187 (6.64%) patients at 90-days. Among those who achieved reversal compared to who did not, a higher proportion had acute insult related to ethanol (35.4%) followed by HBV (33.1%). Patients who achieved reversal, at baseline, had low total leukocyte count (TLC, 11.8±11.11 vs. 17.12±17.93, p<0.001), lower lactate levels (2.04±2.00 vs. 2.81±2.91, p=0.006) and had less severe disease scores [AARC score- 8.27±1.57 vs. 9.65±1.99, CTP score- 10.1±1.13 vs. 11.6±1.41, MELD Na- 27.09±4.23 vs. 31.70±6.73, p<0.001]. On multivariate logistic regression analysis, a lower BMI (0.91, 0.86-0.97, p=0.002), lower TLC count (0.95, 0.91-0.99, p=0.014), higher albumin (2.55, 1.67-3.89, p<0.001), higher platelet (1.005, 1.002-1.007, p<0.001), and lower AARC score (0.69, 0.59-0.81, p=0.003) at baseline was associated with achieving reversibility of ACLF syndrome at day 90. AARC score of 11 or more, predicts non-reversibility of ACLF at 90days with a sensitivity of 94% and specificity of 69%, and an AUROC of 0.70 (p< 0.001(figure-1). When reversibility is considered as a time covariate (immortal time bias), there was a decrease of 3.4% in death rate. **Conclusion:** A small proportion of patients achieve reversal of ACLF syndrome and considerable patient proportion have ongoing liver injury due to the acute insult beyond 90-days. AARC score at baseline reliably predicts early reversal of ACLF syndrome.



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1632 | LONGITUDINAL TRAJECTORIES AND OUTCOMES IN ACUTE DECOMPENSATION AND ACUTE-ON-CHRONIC LIVER FAILURE

Pratibha Garg[1] Nipun Verma[2] Parminder Kaur[2] Samonee Ralmilay[2] Arun Koottumakkal Valsan[3] Akash Roy[4] Sahaj Rathi[2] Arka De[5] Madhumita Premkumar[1] SUNIL TANEJA[2] Ajay Duseja[2]

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Background: Understanding the long-term clinical trajectories of patients with Acute Decompensation (AD) and Acute-on-Chronic Liver Failure (ACLF) is essential for optimizing patient care and outcomes. This study aimed to comprehensively characterize these trajectories, focusing on complications and outcomes. **Methods:** Patients meeting EASL criteria for AD or ACLF were included. Baseline demographics and 30-day outcomes were recorded, alongside clinical variables until death, discharge, or day 30 of hospitalization. Complications and outcomes were assessed at 3, 6, 9, and 12 months. Generalized Mixed Models (GMM) were employed to analyze complication trajectories, while cox regression evaluated predictors of outcomes. **Results:** We enrolled 535 patients with AD/ACLF (29% AD, 71% ACLF), mostly males (91%) median age 42 years. Alcoholic hepatitis and infections were the primary acute precipitants of AD, with alcohol-associated cirrhosis (79%) as predominant etiology. ACLF patients had significantly higher levels of WBC, serum bilirubin, INR, and disease severity scores compared to AD patients ($p<0.001$, each). Mortality rates at 30 days, 90 days, and 1 year were markedly higher in ACLF compared to AD (65% vs. 24%, 74% vs. 33%, 76% vs. 36%, respectively). At 3 months, 49% of AD patients progressed to pre-ACLF (with 63% of them progressing to ACLF within 3-7 days of presentation), 6% became UDC, and 45% remained SDC. Pre-ACLF patients had the poorest outcomes, with a 1-year survival rate of 22%, similar to those presenting with ACLF. Between 0-6 months, 75% of patients with AD/ACLF expired, while 3% experienced a new episode of AD and survived, and 22% transitioned to Non-AD (NAD). GMM analysis demonstrated the probability of ascites, HE, and bleeding during the 0–3-month timeframe significantly correlated with outcomes ($p<0.001$, each). Additionally, Cox regression identified the presence (HR: 16.67, $p<0.001$) and number of AD/ACLF episodes (HR: 19.14, $p<0.001$) during follow-up as predictors of mortality, highlighting the importance of early and continuous complication monitoring. Finally, INR emerged as a key predictor of AD/ACLF or death at follow-up (HR: 1.59, 95%CI: 1.17-2.15, $p=0.003$). **Conclusion:** The study highlights the dynamic nature of AD and ACLF trajectories and emphasizes the importance of early complication monitoring and continuous disease severity assessment. These insights inform strategies for optimizing care and outcomes in AD and ACLF.

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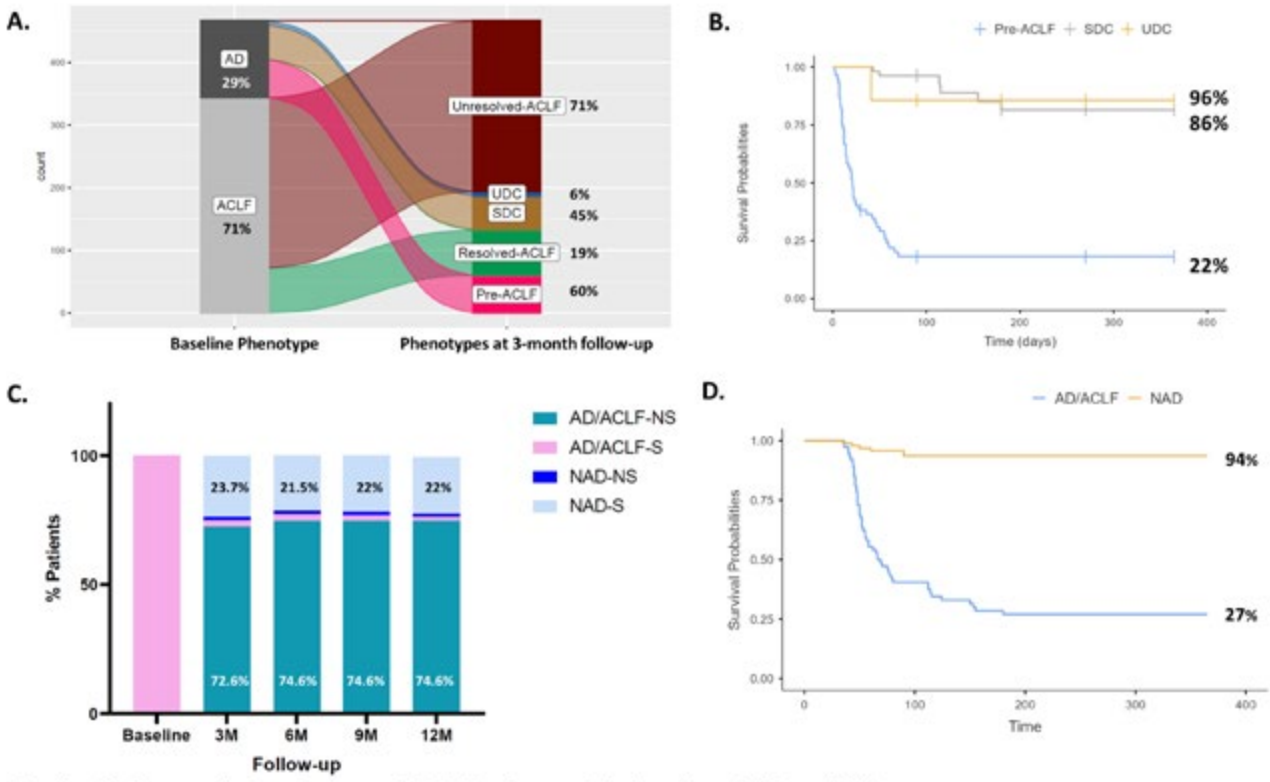

A: Sankey plot demonstrating the phenotypes of AD/ACLF patients transitioning at the end of 3-month follow-up
B: Kaplan Meier demonstrating the survival probabilities of Pre-ACLF, SDC and UDC phenotypes of AD non-ACLF patients at the end of 1-year follow-up. Interestingly, the cumulative 1-year mortality of pre-ACLF group was similar to the overall mortality observed in patients presenting with ACLF at baseline.
C: Bar plot showing the proportions of phenotypes and death during each follow-up timeframe during 1 year follow up in AD/ACLF patients
D. Kaplan Meier demonstrating the survival probabilities at end of 1-year, in patients who developed any episode of AD/ACLF compared to those who had no episode of AD [non- AD patients (NAD)] during the follow-up

Disclosures: Pratibha Garg: Nothing to Disclose, Nipun Verma: Nothing to Disclose, Parminder Kaur: Nothing to Disclose, Samonee Ralmilay: Nothing to Disclose, Arun Koottumakkal Valsan: Nothing to Disclose, Akash Roy: Nothing to Disclose, Sahaj Rathi: Nothing to Disclose, Arka De: Nothing to Disclose, Madhumita Premkumar: Nothing to Disclose, SUNIL TANEJA: Nothing to Disclose, Ajay Duseja: Nothing to Disclose

2001 | RISK FACTORS ASSOCIATED WITH DECREASED BONE MINERAL DENSITY IN PATIENTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE: A CROSS-SECTIONAL STUDY AT A HEALTH EXAMINATION CENTER

Shinya Yokoyama[1] Takashi Honda[2] Kenta Yamamoto[2] Takanori Ito[2] Norihiro Imai[2] yoji ishizu[2] Kazuyuki Mizuno[2] Tetsuhito Kojima[3] Naoyoshi Kariya[3] Hiroki Kawashima[2]

[1]Nagoya University Graduate School of Medicine, [2]Nagoya University, [3]Aichi Health Promotion Foundation

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is a condition often detected at health examinations, characterized by hepatic steatosis and metabolic dysfunctions. Despite increasing recognition, specific risk factors contributing to decreased bone mineral density (BMD) in patients with MASLD remain unclear. This study aims to elucidate these risk factors, which are crucial for early detection and management of potential bone-related complications in MASLD. **Methods:** This retrospective cross-sectional study included individuals aged 18 years or older who underwent abdominal ultrasonography and BMD measurements at a health examination center between April 2018 and March 2023. BMD was assessed using an AOS-10SA bone densitometer for the calcaneus, and decreased BMD was defined as a T-score below -1.0 standard deviation (SD) or the presence of treatment for osteoporosis. SLD was diagnosed based on specific ultrasonographic criteria including hepato-renal contrast, bright liver, and attenuation in the deep liver parenchyma. **Results:** Among 1,410 patients with MASLD, 347 were included in the decreased BMD group. In univariate analysis, two cardiometabolic criteria were associated with decreased BMD: a lower percentage

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of individuals met the criteria for high body mass index (BMI) or large waist circumference (80.7% vs. 90.4%), and there was a higher prevalence of hypertriglyceridemia (51.6% vs. 43.7%). Additionally, the decreased BMD group was significantly older (54 vs. 51 years), had a higher FIB-4 index (0.98 vs. 0.93), and had lower grip strength (36.4 vs. 38.1 kg) compared to the normal BMD group. Multivariate logistic regression analysis revealed that low BMI or small waist circumference (odds ratio [OR]: 0.48, 95% confidence interval [CI]: 0.34-0.67), hypertriglyceridemia (OR: 1.30, 95% CI: 1.01-1.66), and weak grip strength (OR: 0.98, 95% CI: 0.97-1.00) were independent predictors of decreased BMD. Subgroup analyses for individuals aged 50 or older, men, and those with a FIB-4 index of 1.3 or higher consistently showed that the absence of high BMI or large waist circumference and weaker grip strength were associated with decreased BMD. Interestingly, for women, age was the sole significant factor contributing to the risk of decreased BMD. **Conclusion:** This study highlights several potential risk factors for decreased BMD in individuals with MASLD, including low BMI or small waist circumference, hypertriglyceridemia, and weak grip strength. These findings underscore the importance of early BMD measurement and monitoring in patients with MASLD, especially those with identified risk factors, to prevent osteoporosis and related complications. Further research is necessary to explore the underlying mechanisms and develop targeted interventions for bone health in this population.

Table. Factors associated with decreased bone mineral density among examinees with metabolic dysfunction-associated steatotic liver disease

		Univariate analysis			Multivariate analysis	
	Overall MASLD, N=1,410	Normal BMD, N=1,063	Decreased BMD, N=347	P-value	Odds ratio (95% confidence intervals)	P-value
Cardiometabolic criteria BMI or waist circumference, present (%)	**1,241 (88.0)**	**961 (90.4)**	**280 (80.7)**	**<0.001**	**0.48 (0.34-0.67)**	**<0.001**
Cardiometabolic criteria DM, present (%)	1,109 (78.7)	823 (77.4)	286 (82.4)	0.05		
Cardiometabolic criteria HDL cholesterol, present (%)	450 (31.9)	332 (31.2)	118 (34.0)	0.353		
Cardiometabolic criteria HT, present (%)	641 (45.5)	480 (45.2)	161 (46.4)	0.71		
Cardiometabolic criteria triglyceride, present (%)	**643 (45.6)**	**464 (43.7)**	**179 (51.6)**	**0.011**	**1.30 (1.01-1.66)**	**0.039**
Current smoker (%)	315 (22.3)	235 (22.1)	80 (23.1)	0.711		
Exercise habit, present (%)	489 (34.7)	373 (35.1)	116 (33.4)	0.604		
Male sex (%)	1116 (79.1)	851 (80.1)	265 (76.4)	0.148		
Age (years)	52 [46, 60]	51 [45, 60]	54 [49, 61]	<0.001	1.01 (1.00-1.03)	0.13
Albumin (g/dL)	4.4 [4.2, 4.5]	4.4 [4.2, 4.5]	4.4 [4.2, 4.5]	0.341		
ALT (U/L)	30 [20, 44]	30 [21, 44]	28 [20, 44]	0.241		
AST (U/L)	23 [19, 29]	23 [19, 30]	22 [19, 29]	0.226		
Cholinesterase (U/L)	380 [340, 426]	380 [339, 426]	381 [341, 426]	0.526		
FIB-4 index	0.94 [0.72-1.25]	0.93 [0.70, 1.22]	0.98 [0.77, 1.34]	0.003	1.03 (0.73-1.46)	0.86
Grip strength (kg)	**37.6 [31.0, 43.1]**	**38.1 [31.6, 43.3]**	**36.4 [28.9, 41.1]**	**<0.001**	**0.98 (0.97-1.00)**	**0.0086**
Uric acid (mg/dL)	6.1 [5.3, 6.9]	6.2 [5.3, 6.9]	6.1 [5.2, 6.8]	0.251		

Continuous variables are reported as medians with interquartile ranges.
Non-parametric univariate analysis was conducted using the Mann-Whitney U test for continuous variables and Fisher's exact test for categorical variables. Multivariate analysis by logistic regression analysis was performed for binary variables.
ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMD = bone mineral density; DM = diabetes mellitus; HDL = high density lipoprotein; HT = hypertension

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2002 | ENHANCING PREDICTION OF MODERATE FIBROSIS OR HIGHER IN MASLD PATIENTS FOR RESMETIROM TREATMENT VIA MACHINE LEARNING ◆

Winston Dunn[1] Naim Alkhouri[2] Terry Cheuk-Fung Yip[3] Laurent Castera[4] Marina Takawy[5] Leon Adams[6] Nipun Verma[7] Juan Pablo Arab[8] Syed-Mohammed Jafri[9] Bihui Zhong[10] Julie DUBOURG[11] Vincent Chen[12] Ashwani Singal[13] Luis Antonio Díaz[14] Nicholas Dunn[1] Rida Nadeem[15] Vincent Wong[3] Manal Abdelmalek[16] Zhengyi Wang[6]

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Ajay Duseja[17] Yousef Almahanna[18] Haya Omeish[19] Junzhao Ye[20] Stephen Harrison[21] Marco Arrese[14] Sage Robert[1] Grace Wong[3] Bajunayd Bajunayd[22] Congxiang Shao[20]

[1]University of Kansas Medical Center, [2]Arizona Liver Health, [3]The Chinese University of Hong Kong, [4]Hopital Beaujon, [5]Mayo Clinic, Rochester, [6]University of Western Australia, [7]Postgraduate Institute of Medical Educat, [8]University of Western Ontario, [9]Henry Ford Health System, [10]First Affiliated Hospital, [11]Summit Clinical Research, [12]University of Michigan Medical Center, [13]University of Louisville, [14]Pontificia Universidad Católica de Chile, [15]Arizona Liver Health (ALH), [16]Mayo Clinic Rochester, [17]Postgraduate Institute of Medical Education & Research, [18]Western University, [19]Henry Ford Health, [20]First Affiliated Hospital, Sun Yat-sen U, [21]University of Oxford, [22]Western University & London Health Scien

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Background: The recent FDA approval of Resmetirom for treating Metabolic Dysfunction-Associated Steatohepatitis (MASLD) in patients with moderate to advanced fibrosis necessitates precise patient selection for liver biopsy. Currently, a Vibration-controlled Transient Elastography (VCTE) based algorithm FAST is utilized to diagnose at-risk MASH (≥F2 + NAS 4). However, no existing VCTE-based algorithm effectively targets moderate fibrosis or higher (≥F2) alone. The mAchine Learning ADvanceD fibrosis and at-risk mash Novel predictor (ALADDIN) study addresses this gap by introducing a novel machine learning-based web calculator that estimates the likelihood of moderate fibrosis using routine laboratory parameters with and without VCTE measurements. **Methods:** A total of 3708 patients with biopsy-confirmed MASLD from six centers worldwide were divided into Training and Test Set on a 1:1 basis, supplemented by 1289 patients from nine centers for External Validation. ALADDIN models, employing Random Forest, Gradient Boosting Machines, and XGBoost enhanced by Bayesian updates, were developed to evaluate moderate fibrosis (stage ≥F2). **Results:** In the Test Set, the ALADDIN-F2-VCTE model demonstrated an Area Under the Curve (AUC) of 0.789 (95% CI 0.767-0.810), significantly outperforming the FAST model (AUC: 0.663, 95% CI 0.637-0.689, p<0.0001). In the External Validation Set, this model maintained an AUC of 0.796 (95% CI 0.769-0.823), again outperforming FAST (AUC: 0.705, 95% CI 0.673-0.737, p<0.0001). The ALADDIN-F2-Lab model, which employs routine laboratory parameters without VCTE, achieved an AUC of 0.762 (95% CI 0.741-0.784) in the Test Set and 0.735 (95% CI 0.708-0.762) in the External Validation Set. The 95% CI for the difference in AUCs was 0.075 to 0.129 in the Test Set and -0.014 to 0.061 in the External Validation Set. It did not exceed the preset noninferiority margin Δ of -0.1. Furthermore, the ALADDIN-F2-VCTE model demonstrated superior calibration, decision curve analysis, and classification accuracy using a dual cut-off approach compared to the FAST model. **Conclusion:** The VCTE-based ALADDIN-F2-VCTE model, accessible through ALADDIN1, has demonstrated superior performance compared to established VCTE-based indices, FAST, for diagnosing moderate fibrosis or higher. As the only model specifically developed to target moderate fibrosis or higher using VCTE, ALADDIN-F2-VCTE uniquely supports the refined selection of patients, potentially reducing the necessity for liver biopsies and allowing more patients to receive appropriate treatment with Resmetirom. Additionally, the ALADDIN-F2-Lab model, employing routine laboratory parameters without VCTE, accessible through https://aihepatology.shinyapps.io/ALADDIN2/, offers an effective alternative when VCTE is unavailable, facilitating broader application in clinical practice.

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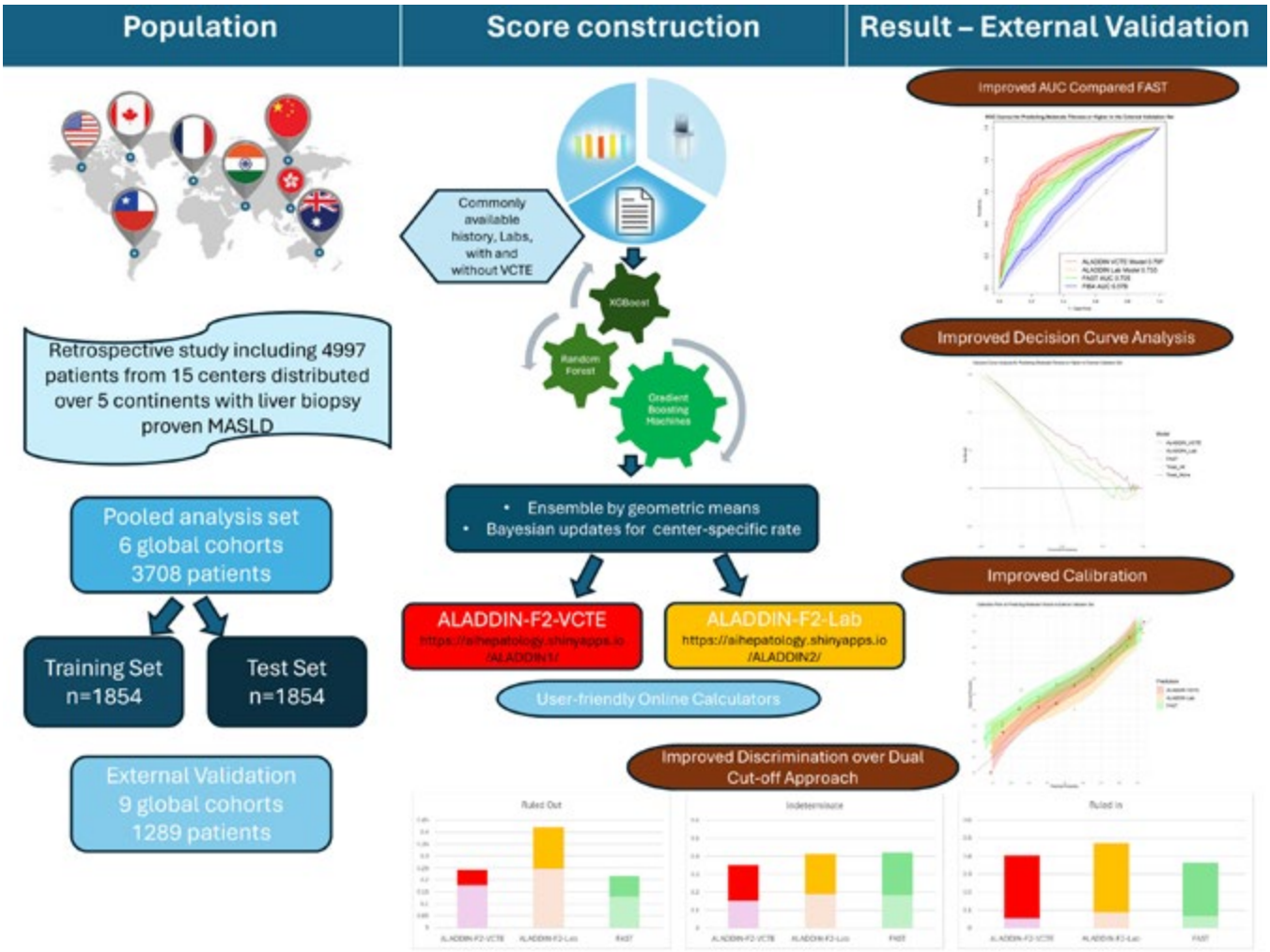

Disclosures: Winston Dunn: Nothing to Disclose, Naim Alkhouri: Madrigal: Grant/Research Support, Madrigal: Speaking and Teaching, Novo Nordisk: Consulting, Novo Nordisk: Grant/Research Support, Gilead: Grant/Research Support, Corcept: Grant/Research Support, Boehringer Ingelheim: Grant/Research Support, Echosens: Speaking and Teaching, Perspectum: Consultant, Cima: Consultant, Fibronostics: Consultant, 89Bio: Grant/Research Support, Inventiva: Grant/Research Support, Merck: Grant/Research Support, Pfizer: Grant/Research Support, Ipsen: Speaking and Teaching, Intercept: Speaking and Teaching, Madrigal: Consulting, Research Funding, Novo Nordisk: Consulting, Research Funding, Inventiva: Research Funding, Boehringer Ingelheim: Consulting, Research Funding, Corcept: Research Funding, Ipsen: Consulting, Research Funding, Gliead: Consulting, Research Funding, Speaking, Perspectum: Consulting, Research Funding, Cima: Advisor, 89Bio: Consulting, Research Funding, Akero: Grant/Research Support, Arbutus: Grant/Research Support, GSK: Grant/Research Support, Regeneron: Grant/Research Support, AstraZeneka: Grant/Research Support, Terry Cheuk-Fung Yip: Gilead Sciences: Consultant, Gilead Sciences: Advisor, Gilead Sciences: Speaking and Teaching, Laurent Castera: Nothing to Disclose, Marina Takawy: Nothing to Disclose, Leon Adams: Novo Nordisk: Advisor, SCL Behring: Advisor, Pfizer: Advisor, Nipun Verma: Nothing to Disclose, Juan Pablo Arab: Nothing to Disclose, Syed-Mohammed Jafri: Takeda: Speaking and Teaching, Gilead: Speaking and Teaching, Abbvie: Speaking and Teaching, Ironwood: Advisor, Intercept: Speaking and Teaching, Bihui Zhong: Nothing to Disclose, Julie DUBOURG: Poxel SA: Stock - publicly traded company, Vincent Chen: Site PI on industry-sponsored trial relationship with AstraZeneca; Has ended; site co-I on industry-sponsored trial relationship with Ipsen; Has not ended; site co-I on industry-sponsored trial relationship with Kowa; Has not ended, Ashwani Singal: Advisor relationship with CLD Foundation; Has not ended; Speaking and Teaching relationship with Medical Speaker's Network; Has not ended; Speaking and Teaching relationship with Madrigal; Has not ended; Stock â€“ privately held company relationship with Pleiogenix; Has not ended; Consultant relationship with Pleiogenix; Has not ended; Advisor relationship with Durect; Has ended; Royalties or patent beneficiary relationship with Up-to-Date; Has not ended; Executive role relationship with Gastro Endo News; Has not ended; Grant/Research Support

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2003 | DEEP LEARNING PREDICTS HEPATOCELLULAR CARCINOMA DEVELOPMENT IN STEATOTIC LIVER DISEASE USING DIGITAL PATHOLOGY ◆

Takuma Nakatsuka[1] Ryosuke Tateishi[1] Masaya Sato[1] Rie Irie[2] Hanako Tsujikawa[2] Yoshio Sumida[3] Masashi Yoneda[3] Norio Akuta[4] Takumi Kawaguchi[5] Hirokazu Takahashi[6] Yuichiro Eguchi[6] Yuya Seko[7] Yoshito Itoh[7] Eisuke Murakami[8] Kazuaki Chayama[8] Makiko Taniai[9] Katsutoshi Tokushige[9] Takeshi Okanoue[10] Michiie Sakamoto[2] Mitsuhiro Fujishiro[1] Kazuhiko Koike[1]

[1]The University of Tokyo, [2]Keio University, [3]Aichi Medical University, [4]Toranomon Hospital, [5]Kurume University School of Medicine, [6]Saga University Hospital, [7]Kyoto Prefectural University of Medicine, [8]Hiroshima University, [9]Tokyo Women's Medical University, [10]Osaka Saiseikai Suita Hospital

Background: Steatotic liver disease (SLD) is a growing global health concern, and identifying patients at high risk of developing hepatocellular carcinoma (HCC) remains challenging. While liver fibrosis is a well-established risk factor for HCC, other histopathological features may also contribute to hepatocarcinogenesis. Deep learning (DL) and digital pathology have shown promise in analyzing complex patterns and identifying novel features associated with disease progression. This study aimed to develop and validate a DL model for predicting HCC development in SLD patients using hematoxylin and eosin (H&E)-stained whole-slide images (WSI) of liver biopsy specimens. **Methods:** The study included 639 SLD patients who did not develop HCC for ≥7 years post-biopsy (non-HCC group) and 46 patients who developed HCC <7 years post-biopsy (HCC group). Paired cases from the non-HCC and HCC groups, matched by biopsy date and institution, were used for training the DL model, while the remaining non-paired cases were used for validation. The DL model, based on convolutional neural networks (CNN), was trained using 28,000 image tiles cropped from WSI of the paired cases. Five-fold cross-validation was performed on the paired cases, and the model's performance was further evaluated using the non-paired cases. The model's predictive ability was compared to that of a logistic regression model using fibrosis stage as a variable. **Results:** In the cross-validation with paired cases, the DL model achieved an accuracy of 81.0% and an area under the receiver operating characteristic curve (AUC) of 0.80 for predicting HCC development. Validation using the non-paired cases also demonstrated good performance, with an accuracy of 82.3% and an AUC of 0.84. These results were comparable to the predictive ability of the logistic regression model using fibrosis stage. Notably, the DL model also detected cases of HCC development in patients with mild fibrosis. Saliency maps generated by the DL model highlighted various pathological features associated with HCC development, including nuclear atypia, hepatocytes with a high nuclear-cytoplasmic ratio, immune cell infiltration, fibrosis, and a lack of

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large fat droplets. **Conclusion:** This study demonstrates the potential of DL-based analysis of histopathological images for predicting HCC development in SLD patients. The DL model's ability to capture subtle pathological features beyond fibrosis suggests its potential for identifying early signs of hepatocarcinogenesis, even in patients with mild fibrosis. Further validation in larger, diverse cohorts is necessary to confirm these findings and explore the clinical implementation of DL-based models in the management of SLD patients.

Disclosures: Takuma Nakatsuka: Nothing to Disclose, Ryosuke Tateishi: EA Pharma: Speaking and Teaching, MSD: Speaking and Teaching, Aska Pharma: Speaking and Teaching, AstraZeneca: Speaking and Teaching, Abbvie: Speaking and Teaching, Eisai: Speaking and Teaching, Gilead Sciences: Speaking and Teaching, Covidien: Speaking and Teaching, Bayer: Speaking and Teaching, Century Medical: Speaking and Teaching, Canon Medical: Speaking and Teaching, Asahikasei Pharma: Speaking and Teaching, Terumo: Speaking and Teaching, TechsoMed: Speaking and Teaching, Sumitomo Pharma: Speaking and Teaching, Taisho Pharmaceutical: Speaking and Teaching, Daiichi-Sankyo: Speaking and Teaching, Chugai: Speaking and Teaching, Fujifilm: Speaking and Teaching, Masaya Sato: Nothing to Disclose, Rie Irie: Nothing to Disclose, Hanako Tsujikawa: Nothing to Disclose, Yoshio Sumida: Nothing to Disclose, Masashi Yoneda: Nothing to Disclose, Norio Akuta: Nothing to Disclose, Takumi Kawaguchi: ASKA Pharmaceutical Co., Ltd.: Speaking and Teaching, Taisho Pharmaceutical Co., Ltd.: Speaking and Teaching, Kowa Company, Ltd.: Speaking and Teaching, AbbVie GK.: Speaking and Teaching, Eisai Co., Ltd.: Speaking and Teaching, Novo Nordisk Pharma Ltd.: Speaking and Teaching, Janssen Pharmaceutical K.K.: Speaking and Teaching, Janssen Pharmaceutical K.K.: Speaking and Teaching, Otsuka Pharmaceutical Co., Ltd.: Speaking and Teaching, EA Pharma Co.,Ltd.: Speaking and Teaching, Hirokazu Takahashi: Sysmex: Grant/Research Support, Novo Nordisk: Speaking and Teaching, Kowa: Speaking and Teaching, Taisho: Speaking and Teaching, Takeda: Grant/Research Support, Yuichiro Eguchi: Nothing to Disclose, Yuya Seko: AbbVie GK: Speaking and Teaching, Novo Nordisk Pharma Ltd: Speaking and Teaching, Merck & Co., Inc.: Speaking and Teaching, Gilead Sciences, Inc.: Speaking and Teaching, Mitsubishi Tanabe Pharma Corporation: Speaking and Teaching, Yoshito Itoh: Novo Nordisk Pharma LTD: Speaking and Teaching, ZERIA PHARMACEUTICAL CO., LTD.: Speaking and Teaching, Otsuka Pharmaceutical Co., Ltd.: Speaking and Teaching, Viatris Inc.: Speaking and Teaching, ASKA Pharmaceutical Co., Ltd.: Speaking and Teaching, Astelas Pharma Inc.: Speaking and Teaching, AstraZeneca K.K.: Speaking and Teaching, Gilead Sciences Inc.: Speaking and Teaching, Mitsubishi Tanabe Pharma Corporation: Speaking and Teaching, EA Pharma Co. Ltd.: Speaking and Teaching, Kowa Company Ltd.: Speaking and Teaching, CHUGAI PHARMACEUTICAL CO., LTD.: Speaking and Teaching, Takeda Pharmaceutical Company Limited.: Speaking and Teaching, ONO PHARMACEUTICAL CO., LTD.: Speaking and Teaching, AbbVie Inc.: Speaking and Teaching, Novartis Pharma Inc.: Speaking and Teaching, MYYARISAN Phramaceutocal Co.: Speaking and Teaching, Eli Lilly and Co.: Speaking and Teaching, Olympus Co.: Speaking and Teaching, AbbVie Inc.: Grant/Research Support, Otsuka Pharmaceutical Co., Ltd.: Grant/Research Support, CHUGAI PHARMACEUTICAL CO., LTD.: Grant/Research Support, SHIONOGI & CO., LTD.: Grant/Research Support, Eisai Co., Ltd.: Grant/Research Support, Mitsubishi Tanabe Pharma Corporation: Grant/Research Support, EA Pharma Co. Ltd.: Grant/Research Support, Sumitomo Pharma Co. Ltd.: Grant/Research Support, ASKA Pharmaceutical Co. Ltd.: Grant/Research Support, Eli Lilly and Co.: Grant/Research Support, Astra Zeneca plc.: Grant/Research Support, Pfizer Inc.: Grant/Research Support, Merk Sharp and Dohme: Grant/Research Support, Bristol-Myers Squibb Co.: Grant/Research Support, GSK plc.: Grant/Research Support, AbbVie Inc: Grant/Research Support, Eisuke Murakami: Nothing to Disclose, Kazuaki Chayama: Nothing to Disclose, Makiko Taniai: Nothing to Disclose, Katsutoshi Tokushige: Nothing to Disclose, Takeshi Okanoue: Nothing to Disclose, Michiie Sakamoto: Nothing to Disclose, Mitsuhiro Fujishiro: Nothing to Disclose, Kazuhiko Koike: Nothing to Disclose

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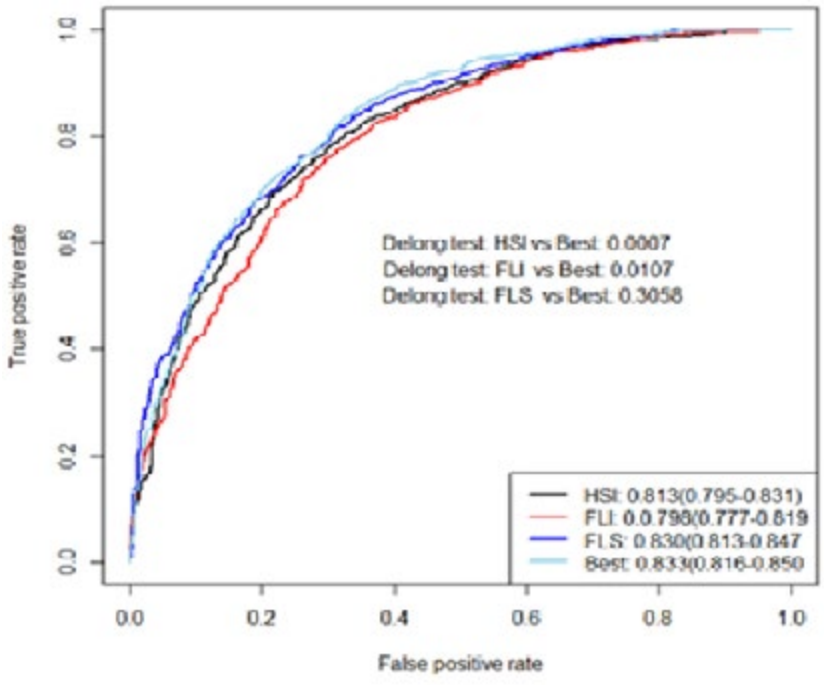
2004 | A NOVEL STEATOSIS LIVER DISEASE (SLD) INDEX WITH EASY-TO-USE CLINICAL PARAMETERS IN PRIMARY CARE SETTINGS FOR STEATOTIC LIVER DISEASE ◆

Dae Won Jun[1] Eileen Yoon[1] Ji Hyun An[1] HA IL KIM[1] Joo Hyun Sohn[1] Bo-Kyeong Kang Bo-Kyeong Kang[1] Chul-Min Lee[1] Hyunwoo Oh[2] Hyo Young Lee[3] Hye-Lin Kim[4] Sang Bong Ahn[5] Joo Hyun Oh[5]

[1]Hanyang University, [2]Kangbuk Samsung, Sungkyunkwan Univ., [3]Sanggye Paik Hospital, Inje University, [4]College of Pharmacy, Sahmyook University, [5]Eulji University

Background: The magnetic resonance imaging-proton density fat fraction (MRI-PDFF) method is a novel imaging technique that quantitatively measures the hepatic fat content. High MRI-PDFF values are closely correlated with biopsy-proven hepatic steatosis. We tried to suggest a new model for predicting hepatic steatosis using MRI-PDFF, leveraging commonly used clinical parameters in primary care clinics. The novel SLD index is designed to simplify the identification of SLD in primary care settings with restricted medical resources in SLD era, effectively. **Methods:** We retrospectively collected data from 35829 participants from the UK biobank who underwent magnetic resonance imaging-proton density fat fraction (MRI-PDFF). The development cohort (UK biobank data) was randomly assigned to the training and test cohort at a ratio of 7:3. The variables were selected via multivariate logistic regression analysis, and linearity was confirmed using the smoothing spine method. Additionally, the novel 'SLD index' underwent external validation in a multicenter Asian PDFF cohort comprising 2111 participants from tertiary medical hospitals and health check-up centers. **Results:** Diabetes mellitus, alanine aminotransferase, triglyceride levels, and body mass index were selected as the model's parameters to predict SLD. The novel 'SLD index' had an excellent diagnostic performance for predicting SLD, with an area under the curve of 0.796 (95% CI, 0.790–0.802) and 0.793 (95%CI 0.783–0.803) in the training and test cohorts, respectively. With an optimal cut-off of 2.6, the sensitivity was 70.0% (95% CI, 69.1–70.9%), and specificity was 74.5% (95% CI, 73.7–75.3). The new SLD index demonstrated an AUC of 0.832 (95% CI, 0.814–0.849) in the validation cohort, which was significantly superior to those of the FLI and HSI (P-values, 0.015 and 0.002, respectively). **Conclusion:** The new simplified prediction model, the SLD index, which employs common clinical parameters as variables and utilizes a single cut-off, demonstrated good diagnostic performance in predicting SLD.



Disclosures: Dae Won Jun: Nothing to Disclose, Eileen Yoon: Nothing to Disclose, Ji Hyun An: Nothing to Disclose, HA IL KIM: Nothing to Disclose, Joo Hyun Sohn: Nothing to Disclose, Bo-Kyeong Kang Bo-Kyeong Kang: Nothing to Disclose, Chul-Min Lee: Nothing to Disclose, Hyunwoo Oh: Nothing to Disclose, Hyo Young

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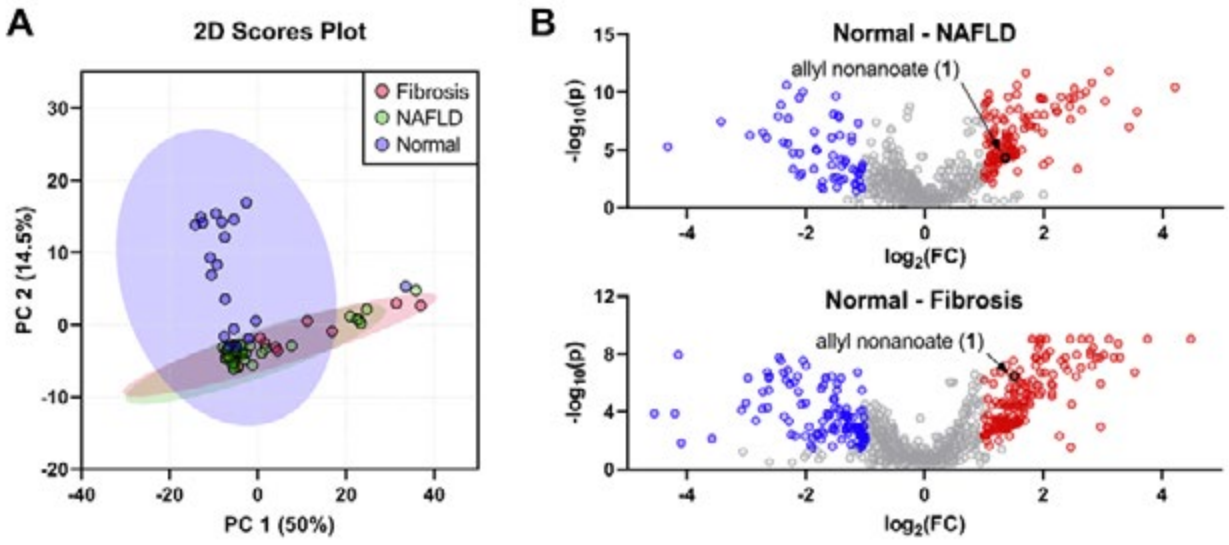
Lee: Nothing to Disclose, Hye-Lin Kim: Nothing to Disclose, Sang Bong Ahn: Nothing to Disclose, Joo Hyun Oh: Nothing to Disclose

2005 | ALLYL NONANOATE, A BILE METABOLITE, ACTIVATED HEPATIC STELLATE CELLS THROUGH GPR 119 SIGNALING IN METABOLIC DYSFUNCTION ASSOCIATED STEATOSIS DISEASE (MASLD)

Dae Won Jun Eileen Yoon[1] Ji Hyun An[1] HA IL KIM[1] Joo Hyun Sohn[1] Bo-Kyeong Kang[1] Chul-Min Lee[1] Hyo Young Lee[2] Hyun Woo Oh[3] Hye-Lin Kim[4] Sang Bong Ahn[5] Joo Hyun Oh[5]

[1]Hanyang University, [2]Sanggye Paik Hospital, Inje Univ., [3]Kangbuk Samsung, Sungkyunkwan Univ., [4]College of Pharmacy, Sahmyook University, [5]Nowon Eulji Medical Center, Eulji Univ.

Background: We hypothesized that specific metabolites from bile acids would significantly increase or decrease in MASLD patients, in relation to the degree of the hepatic fibrosis. The aim of this study was to compare the metabolite profiles between patients with biopsy-confirmed hepatic fibrosis and healthy subjects using metabolomics on primary bile acids. **Methods:** The study sample was derived from a prospectively assembled cohort of patients from two distinct hospitals in Korea. The cohort was subdivided into three groups based on the histological severity of metabolic dysfunction associated fatty liver disease (MASLD): Healthy control (n=19), fibrosis stage 0-1 (n=35), and fibrosis stage 2-3 (n=14). The targeted MS/MS analysis was performed on an Agilent 1290 Infinity II UPLC system coupled to a G6545B Q-TOF MS system equipped with a dual ESI source. Chemometric analysis, including Principal Component Analysis (PCA), and univariate analysis were performed using the MetaboAnalyst 5.0 to identify significant differences between groups. **Results:** Compared to healthy controls, the mild MASLD group demonstrated significant increases (> 2-fold, $p < 0.1$) in 139 metabolites, whereas the significant MASLD group showed increases in 173 metabolites. Subsequently, we obtained standards for the putative metabolite based on the database and conducted validation analysis using LC-HR-QTOF-MS. Finally, we confirmed that the substance with m/z 199.1693 was further verified by MS/MS analysis, and the metabolite was identified as allyl nonanoate. Bulk RNA sequencing was conducted on the HT-29 cell line following exposure to allyl nonanoate for 24 hours. Gene ontology analysis revealed an upregulation of the lipid catabolic pathway and sphingomyelin metabolic pathway, along with a downregulation of calcium ion signaling, in the allyl nonanoate treatment group compared to controls. When the human hepatic stellate cell line (LX-2 cells) was treated with allyl nonanoate, the expression of activation markers (type I collagen, and αSMA) of LX-2 cells increased. The moderate agonist interactions were identified: activation of GPR119 by allyl nonanoate (half maximum effective concentration (EC50)=9 μM). **Conclusion:** The bile acid concentration of allyl nonanoate increased with MASLD severity. And increasing allyl nonanoate an upregulation of the lipid catabolic pathway and sphingomyelin metabolic pathway, along with a downregulation of calcium ion signaling.



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2006 | IMPACT OF STEATOSIS AND CARDIOMETABOLIC ABNORMALITIES ON PLASMA FREE AMINO ACID LEVELS AND POTENTIAL ROLE OF AMINO ACID MODULATION IN MASLD

Eiji Kakazu[1] Masaaki Mino[2] Akitoshi Sano[3] Taiji Yamazoe[2] Michitaka Matsuda[2] Taizo Mori[2] Sachiyo Yoshio[1] Jun Inoue[4] Tatsuya Kanto[1]

[1]National Center for Global Health and Medicine, [2]National Center for Global Health and Me, [3]Mayo Clinic, Rochester, [4]Tohoku University Graduate School of Med

Background: Little is known about changes in peripheral blood free amino acids (FAAs) in metabolic dysfunction-associated steatotic liver disease (MASLD). This study aims to clarify the influence of steatosis and cardiometabolic abnormalities on FAAs in the MASLD and to evaluate the potential benefits of correcting amino acid imbalances. **Methods:** We analyzed plasma FAAs data from 23,036 individuals with information on steatosis, sourced from a biobank in Japan, and enrolled 310 patients clinically diagnosed with MASLD. The subjects were divided into five groups based on diagnostic criteria for SLD and cardiometabolic criteria (CC): MASLD (n = 712), ALD (n = 440, including MetALD), CC negative without SLD (CC-SLD-; n = 2,136), CC positive without SLD (CC+SLD-; n = 9,968), and CC negative with SLD (CC-SLD+; n = 68). We compared the levels of 20 kinds of FAAs among these groups. In a mouse experiment, we fed ob/ob mice with either amino acid-defined AIN-93G or AIN-93G modified to reduce excess amino acids in the blood for MASLD and then compared the phenotypes and biochemical tests. **Results:** Among the 20 FAAs, the levels of 16 FAAs; Threonine (Thr), glutamic acid (Glu), proline (Pro), alanine (Ala), valine (Val), leucine (Leu), isoleucine (Ile), cystine (Cys), methionine (Met), tyrosine (Tyr), phenylalanine (Phe), ornithine (Orn), histidine (His), Lysine (Lys), tryptophan (Trp), and arginine (Arg) increased according to the number of matches with CC. Among the five CC, the levels of these FAAs were more changed in subjects with impaired glucose tolerance and hypertriglyceridemia compared to subjects with obesity, low HDL, and hypertension. A weight gain of 3% over a year significantly increased 11 of these 16 FAAs in CC+SLD- subjects, while a weight loss of 3% did not significantly affect FAA levels. Eleven FAAs; Glu, Pro, Ala, Val, Leu, Ile, Cys, Tyr, Phe, Orn and Trp showed a significant increase in MASLD compared to CC+SLD-. These FAAs, except Phe and Orn, were significantly higher in ALD compared to MASLD. In CC-SLD+, Val, Leu, Ile, Ala and Glu were significantly increased compared to CC-SLD-. Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) suggest that these changes of FAAs were occurred by insulin resistance in patients with MASLD. Pathological assessments revealed that Tyr and Met significantly increased according to ballooning grade, and serine, asparagine, Met, Tyr, and Phe were significantly increased in fibrosis stage F4 in MASLD patients. Branched-chain amino acids (BCAAs) tended to increase at F2 and then decreased after F2. In MASLD model mice fed the amino acid-modified diet, significant improvements in liver function and steatosis were observed without body weight change. **Conclusion:** In MASLD, most FAAs were increased in association with insulin resistance and hypertriglyceridemia. Steatosis further aggravates hyperaminoacidemia. Correcting amino acid imbalances could potentially improve MASLD.

Disclosures: Eiji Kakazu: Nothing to Disclose, Masaaki Mino: Nothing to Disclose, Akitoshi Sano: Nothing to Disclose, Taiji Yamazoe: Nothing to Disclose, Michitaka Matsuda: Nothing to Disclose, Taizo Mori: Nothing to Disclose, Sachiyo Yoshio: Gilead Sciences: Speaking and Teaching, Jun Inoue: Nothing to Disclose, Tatsuya Kanto: Nothing to Disclose

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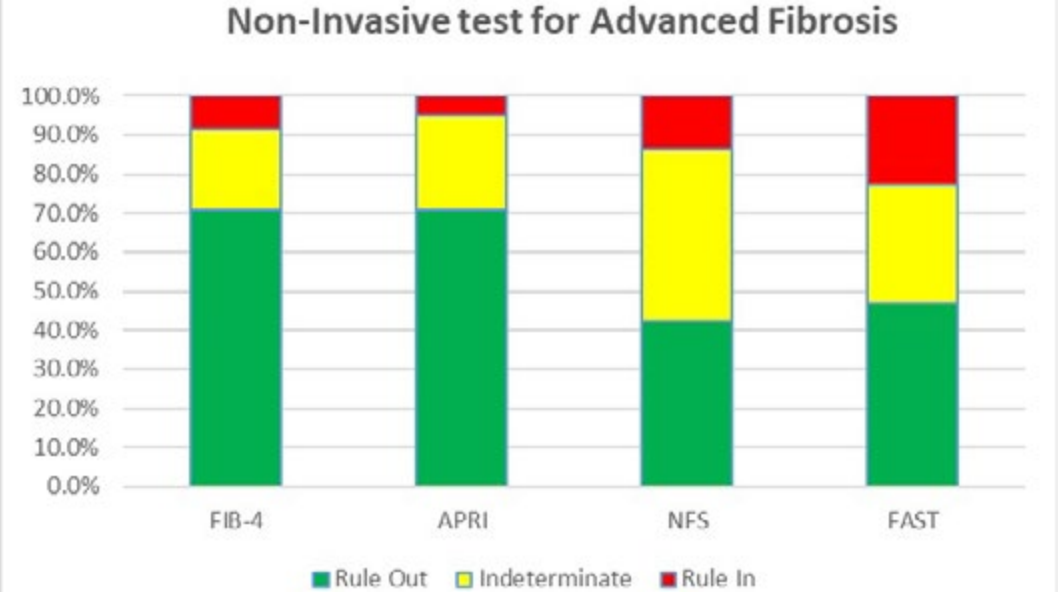
2007 | SCREENING FOR ADVANCED FIBROSIS AMONG ALASKA NATIVE PEOPLES WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE

Janet Johnston[1] Youssef Barbour[2] Lisa Townshend-Bulson[3] Kena Desai[2] Chriss Homan[2] Wileina Rhodes[2] Brian McMahon[4]

[1]Alaska Native Tribal Health Consortiu, [2]Alaska Native Tribal Health Consortium, [3]Alaska Native Tribal Consortium, [4]Alaska Native Medical Center

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD), caused by the build-up of fat in the liver, is a growing cause of cirrhosis, liver failure, liver transplant and hepatocellular carcinoma (HCC). However, little is known about MASLD among Alaska Native (AN) and American Indian peoples. The Liver Disease and Hepatitis Program (LDHP) at the Alaska Native Tribal Health Consortium provides specialty care and consultation to the Tribal Health System across the state. Primary care providers refer patients suspected of having MASLD to LDHP when clinical evaluation suggests these patients may be at risk for developing clinically significant liver fibrosis and progressing to cirrhosis or HCC. In 2023, 36.3% of LDHP clinic visits were for MASLD. **Methods:** Under a waiver of authorization from the Alaska Area IRB, we created a MASLD registry to learn more about MASLD among AN peoples served by LDHP. Most registry participants have one or more vibration-controlled transient elastography (FibroScan®) measurements as well as multiple lab tests. To determine which AN peoples with MASLD are most likely to progress to serious adverse outcomes we used FibroScan and lab results closest to the time of diagnosis to calculate four non-invasive tests (NITs) for advanced fibrosis: Fibrosis-4 (FIB-4), FibroScan-AST (FAST), AST to Platelet Ratio Index (APRI), and Non-Alcoholic Fatty Liver Disease (NAFLD) Fibrosis Score (NFS). **Results:** The registry includes 918 AN adults diagnosed with MASLD between 1997 and 2023, 62.5% female with mean age at time of diagnosis of 50.9+13.1 years. Of these, 97.9% have BMI >25, 45.3% have a record of hyperlipidemia, 43.8% have a record of hypertension, and 35.9% have been diagnosed with diabetes. Among the 902 with at least one valid FibroScan, 29.4% had liver stiffness score > 9.7 indicating possible advanced fibrosis or cirrhosis. NITs ruled out between 42.4% and 70.9% for advanced fibrosis and ruled in between 5.0% and 22.5%. (See figure) Likelihood of ruling in advanced fibrosis varied with BMI for FIB-4 and FAST, with FIB-4 less likely to rule-in advanced fibrosis in AN peoples with BMI > 30 (BMI < 30: 13.7%; BMI > 30: 7.6%; p=0.02) and FAST more likely to do so (BMI < 30: 15.2%; BMI > 30: 23.9%; p=0.02). **Conclusion:** Between 5.0% and 22.5% of AN peoples seen at LDHP with MASLD are at risk for clinically significant fibrosis. Surveillance for advanced fibrosis and HCC should be tailored to each individual's risk level.



Disclosures: Janet Johnston: Nothing to Disclose, Youssef Barbour: Nothing to Disclose, Lisa Townshend-Bulson: Gilead Sciences: Grant/Research Support, Kena Desai: Nothing to Disclose, Chriss Homan: Nothing to Disclose, Wileina Rhodes: Nothing to Disclose, Brian McMahon: Nothing to Disclose

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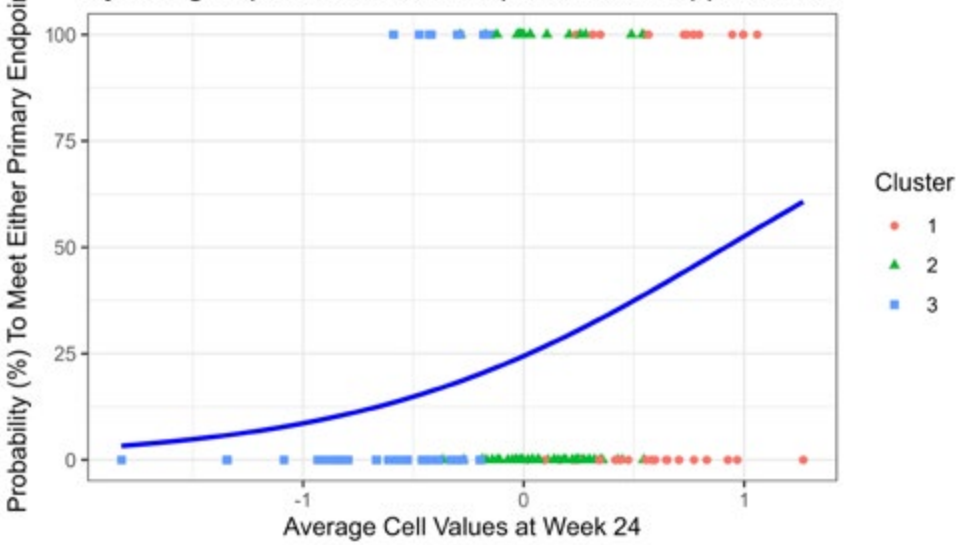
2008 | QUANTITATIVE ANALYSIS AND INTEGRATION OF MACHINE LEARNING FOR BIOMARKER ASSESSMENTS AND THEIR ASSOCIATION WITH TREATMENT RESPONSE: INSIGHTS FROM THE ENLIVEN PHASE 2B TRIAL OF PEGOZAFERMIN ◆

Oliver Mansbach[1] Arun Sanyal[2] Rada Savic[3] Leo Tseng[1] Kemal Balic[1] Shibao Feng[1] Lillian Tsai[1] Mildred Gottwald[1] Maya Margalit[1] Germaine Agollah[1] Hank Mansbach[1] Quentin Anstee[4]

[1]89bio, [2]Virginia Commonwealth University, [3]UCSF School of Pharmacy, [4]Newcastle University, UK

Background: Pegozafermin (PGZ) is a long-acting glycoPEGylated analog of fibroblast growth factor 21 (FGF21). The ENLIVEN Phase 2b trial previously demonstrated significant histologic improvements in subjects treated with PGZ at Week 24. This post-hoc analysis explores the relationship between biomarker improvement at Week 24 and histological endpoints (NASH resolution and/or fibrosis improvement) assessed at Week 24 by using unsupervised and supervised machine learning (ML) techniques. **Methods:** In ENLIVEN, subjects were randomized to PGZ 15 mg QW, 30 mg QW or 44 mg Q2W or placebo. The subset of subjects that had all identified biomarkers and Week 24 histology were included in this post-hoc analysis (n=149). Utilizing an unsupervised ML approach by k-means clustering on biomarkers, without histological endpoints or treatment, subjects were categorized into 3 distinct groups: high (Group 1), moderate (Group 2) and low (Group 3) responders. Heatmap analysis generated cell values for each biomarker after normalization (for each subject, biomarker values were normalized by subtracting the mean from each datapoint, followed by division by the standard deviation), and the average cell values from each subject were regressed against histological endpoints using logistic regression, notably a supervised ML approach. **Results:** At Week 24, subjects in Group 1 had 27% NASH resolution, 27% fibrosis improvement with 41% meeting either endpoint. For Group 2, endpoints were respectively met by 13%, 17% and 25% of subjects, while Group 3 accounted for 9%, 17% and 17% of responders, respectively. These findings align with treatment effects, as Group 1 had the highest proportion of pegozafermin patients (97%). 90% of pegozafermin treated patients were in Group 1 or 2. Logistic regression demonstrated a greater concordance of biomarker improvement (higher cell values) correlating with greater probability of meeting histological endpoints (Figure 1). **Conclusion:** Pegozafermin treatment led to improvements in multiple biomarkers which correlated to histological endpoints. The cluster analysis identified three distinct groups which remained consistent across both unsupervised and supervised ML approaches. Longer treatment duration (>24 weeks) can have different or better histological treatment effect; the relationship associated with the identified biomarkers shall be further explored.

Figure 1: The Relationship Between Biomarkers and Histological Treatment Response Was Established by Using Supervised and Unsupervised ML Approaches



Note: Biomarkers/parameters included in the analysis: HDL-c, LDL-c, triglycerides, PRO-C3, MRI-PDFF, liver stiffness (VCTE), FIB-4 score, ELF score, ALT, adiponectin, HbA1c, C-peptide and simulated cumulative AUC. Logistic regression (supervised ML) reached statistical significance (*p*-value=0.003). Cluster classification (unsupervised ML) was from Week-24 cluster analysis.

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Disclosures: Oliver Mansbach: Nothing to Disclose, Arun Sanyal: Genfit, Akarna, Tiziana, Durect, Inversago, Hemoshear, North: Stock - publicly traded company, Astra Zeneca (60K), Boston Pharmaceutical

2009 | COMPARISON OF SIMULATED VIBRATION CONTROLLED ELASTOGRAPHY SAMPLE VOLUMES AND GLOBAL MEASUREMENTS ON MRE AND MR-PDFF IN PATIENTS WITH SUSPECTED MASLD

Tania Siu Xiao[1] Cristina Kuon Yeng Escalante[1] Aylin Tahmasebi[1] Flavius Guglielmo[1] John Eisenbrey[1] Jesse Civan[2]

[1]Thomas Jefferson University, [2]Thomas Jefferson University Hospital

Background: Staging hepatic fibrosis is key to determining prognosis and making management decisions in various forms of chronic liver disease. Although liver biopsy remains the gold standard, this method is costly, susceptible to error, and has procedure-related complications. Therefore, vibration controlled transient elastography (VCTE; FibroScan) has emerged as a workhorse in clinical practice for non-invasive fibrosis staging. In contrast to the global ROI of the liver volume assessed by MR elastography (MRE), it is unknown whether a limited region of interest (ROI) sampled by FibroScan (a 4x1cm region accessible to the probe) may impact the accuracy of staging, potentially mediated by any heterogeneity of fibrosis deposition throughout the liver tissue. We aimed to address this question by analyzing MRE data from a cohort of patients with metabolic dysfunction associated steatotic liver disease (MASLD), comparing stiffness measured in a small region of interest "simulating" FibroScan to a global liver stiffness measurement. **Methods:** This retrospective study included participants with known risks for MASLD that had MRE. The magnitude series was used to identify liver segment VIII by anatomical landmarks, such as middle and right hepatic vein and the main portal vein bifurcation. Then, greyscale elastogram series was used to manually outline the ROI measurements of 4x1cm to obtain simulated liver stiffness scores. MRE was used as the reference standard for fibrosis and cirrhosis. The agreement of the simulated stiffness with MRE score reported was performed using Cohen's kappa (k) test. **Results:** Of 118 patients, our study showed a strong correlation between the simulated FibroScan's ROI and global MRE measurements (r= 0.72; p<0.0001). The agreement for overall liver stiffness was substantial (k=0.776). In cases where the stiffness was categorized as normal and normal/inflammation (mild), the agreement remained as substantial (k=0.688), for stage 1-2 and stage 2-3 (moderate), the agreement decreased to moderate (k=0.498), and for stage 3-4 and stage 4-cirrhosis (severe), the agreement increased to substantial (k=0.749). **Conclusion:** Our study showed that simulated FibroScan's ROI and global MRE measurements in patient population with suspected MASLD had substantial overall agreement. However, agreement decreased to moderate for stage 1-2 and stage 2-3 raising question whether additional testing for accurate staging may be warranted for these patients.

Disclosures: Tania Siu Xiao: Nothing to Disclose, Cristina Kuon Yeng Escalante: Nothing to Disclose, Aylin Tahmasebi: Nothing to Disclose, Flavius Guglielmo: Nothing to Disclose, John Eisenbrey: Nothing to Disclose, Jesse Civan: Nothing to Disclose

2011 | MULTIPLE DP/AI QUANTIFICATION APPROACHES ARE COMPLIMENTARY IN IDENTIFYING HISTOLOGY FEATURES: CROSS SECTIONAL STUDY IN A JAPANESE COHORT

Vandana Gupta[1], Ruixue Hou[1], Hiroaki Yashiro[1], Shuling Zhang[1], David Cordover[1], Simon Kim[1], Mark Chen[1], Erin Smith[1], Maria Paraskevopoulou[1], Yoshihito Kubotu[2], Zoltan Derdak[1], Paresh Thakker[1], Shinichi Aishima[3], Hirokazu Takahashi[2].

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Background: Liver biopsy is the reference standard for screening and efficacy in MASH drug development. However, pathologist lead scoring systems provide categorical scores with many limitations such as inter and intra-reader variability. This has led to many digital pathology (DP) and AI approaches being established.

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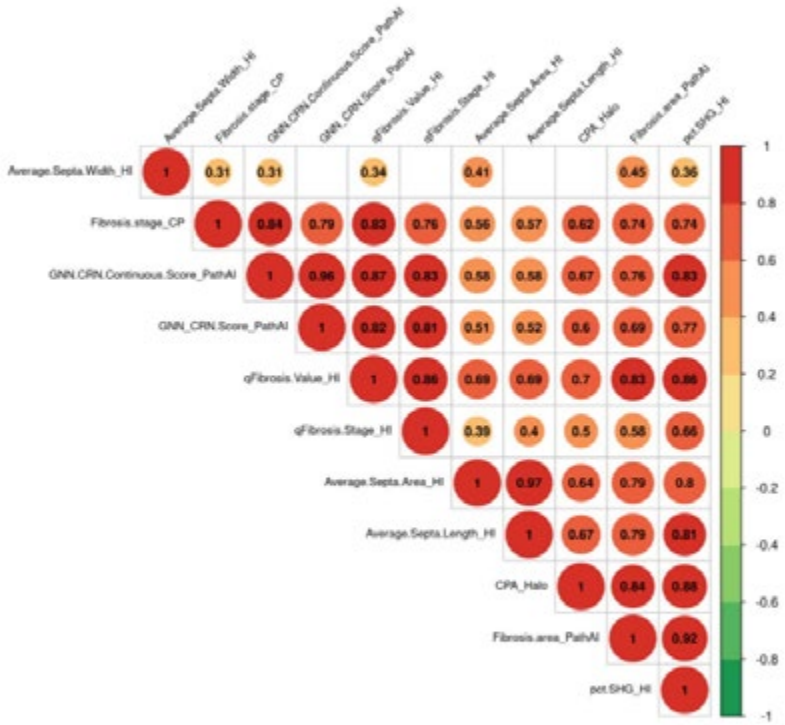
Goal of this study is to understand how multiple quantification methods (PathAI, HistoIndex and HALO) complement and differentiate from each other in a Japanese cohort. Comparisons are done with clinical metadata and non-invasive tests. **Methods:** Archived biopsy samples from 82 subjects with clinically and pathologically diagnosed MASLD/MASH enrolled from Saga University Hospital utilized. Fibrosis stage and NAS features were evaluated by a central pathologist (CP), PathAI's AIM-NASH, HistoIndex's stain free SHG/TPE imaging and HALO-AI. Fibrosis readouts or NAS features and their corresponding correlations with clinical data were evaluated by Pearson correlation analysis with p-value adjustments by Holm's method. **Results:** Fibrosis stage read by the central pathologist has strong correlation with fibrosis readouts measured by PathAI, HistoIndex and collagen proportionate area (CPA). Correlations were stronger for GNN continuous score (r=0.84, p<0.001) and qFibrosis (r=0.83, p<0.001) as compared to the categorical scores. CPA has the strongest correlation with %SHG and % fibrosis area. CPA and CP staging show a positive correlation with Zone 1 but a negative correlation with some Zone 2 qFibrosis based parameters. Strong correlations are observed in the two AI approaches evaluated here. Ballooning scored by CP is strongly correlated with GNN ballooning scores and HistoIndex's qBallooning, a new model recently established with input from 9 expert pathologists. Continuous ballooning values by two AI models are positively correlated (p<0.001). Non-invasive measurements, FIB-4, TypeIV collagen 7S and Hyaluronic acid show statistically significant moderate association with fibrosis measured by DP methods. **Conclusion:** PathAI's AIM-NASH and HistoIndex's SHG/TPE outputs for the quantification of liver fibrosis, steatosis and ballooning correlate are complimentary with some differentiating features. Fibrosis scored by multiple DP methods show positive correlation with central pathologist and NITs (FIB-4, TypeIV collagen 7S and Hyaluronic acid) in this Japanese cohort with potential utilization of DP in clinical trials.

Figure: Correlation plot of fibrosis evaluated by multiple digital pathology methods and central pathologist (CP)



Spearman correlation coefficients range from -1 (strong negative correlation) to +1 (strong positive correlation).

Abbreviations: CP, central pathologist; HI, HistoIndex; CPA, collagen proportionate area; pct, percentage; SHG, Second Harmonic Generation; GNN, graph neural network

Disclosures: VG, RH, HY, SZ, DC, SK, MC, ES, MP, ZD, PT are employees of Takeda Pharmaceuticals and own stocks/stock options in Takeda. HT is a collaborator of Takeda Pharmaceuticals. Vandana Gupta: Takeda Pharmaceuticals: Employee

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2012 | COMPARATIVE EVALUATION OF ZONAL FIBROSIS PATTERNS IN PEDIATRIC AND ADULT METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS BIOPSIES USING SECOND HARMONIC GENERATION/TWO PHOTON EXCITATION-BASED QFIBROSIS ANALYSIS

Naim Alkhouri[1] Kutbuddin Akbary[2] Yayun Ren[3] Nikolai Naoumov[4] Elaine Chng[2] Dean Tai[5] Dominique Brees[6]

[1]Arizona Liver Health, [2]HistoIndex Pte Ltd, [3]Choututech Pte Ltd, [4]Royal College of Physicians, London, [5]HistoIndex, [6]Novartis Pharma AG

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is prevalent among children, constituting the most common chronic liver ailment. Prior studies of liver biopsies from pre-adolescent children with metabolic dysfunction-associated steatohepatitis (MASH) identified an alternate pattern characterized by zone 1 centered steatosis, inflammation, and fibrosis, usually without ballooning, which may progress to advanced fibrosis. The aim of this study was to evaluate pediatric MASH biopsies using Second Harmonic Generation (SHG)/Two-Photon Excitation (TPE) microscopy and Artificial Intelligence (AI) analysis and compare the fibrosis patterns and distribution with biopsies from adults with MASH. **Methods:** Nine unstained biopsies from children (aged 8 to 16 years) with MASH underwent SHG/TPE and AI analysis, yielding qFibrosis continuous values categorized into qFibrosis stages, based on pre-defined cut-offs. Biopsies were segregated into early (qF0/qF1/qF2; n=3) and advanced (qF3/qF4; n=6) fibrosis groups. Comparative analysis involved an adult cohort from a MASH clinical trial (NCT02855164), similarly categorized into early (n=96) and advanced (n=60) fibrosis stages. Fibrosis distribution in both cohorts was plotted on radar maps illustrating portal; periportal; perisinusoidal (zone 2), pericentral and central vein fibrosis, with zonal differences statistically significant at p≤0.05 by Spearman test. **Results:** In the early fibrosis groups, pediatric biopsies exhibited significantly greater perisinusoidal (PS) (p=0.03) and more portal fibrosis compared to adults. In advanced fibrosis groups, pediatric biopsies demonstrated significantly less portal fibrosis (p=0.02) along with markedly increased PS fibrosis (p=0.01) compared to adult biopsies. Additionally, pediatric biopsies in advanced fibrosis group had more fibrosis in periportal (PP) and pericentral (PC) regions compared to adult biopsies. **Conclusion:** This quantitative digital evaluation of MASH fibrosis highlights significant differences in zonal fibrosis distribution in pediatric MASH biopsies compared to adults. During the early fibrosis stage, pediatric biopsies show increased perisinusoidal and portal fibrosis in contrast to their adult counterparts. At advanced stages, there is significantly less portal fibrosis in pediatric biopsies compared to adults, although perisinusoidal fibrosis remains significantly greater in the pediatric group. The observed differences in fibrosis patterns hold potential implications for accurate assessment of fibrosis regression in pediatric MASH clinical trials.

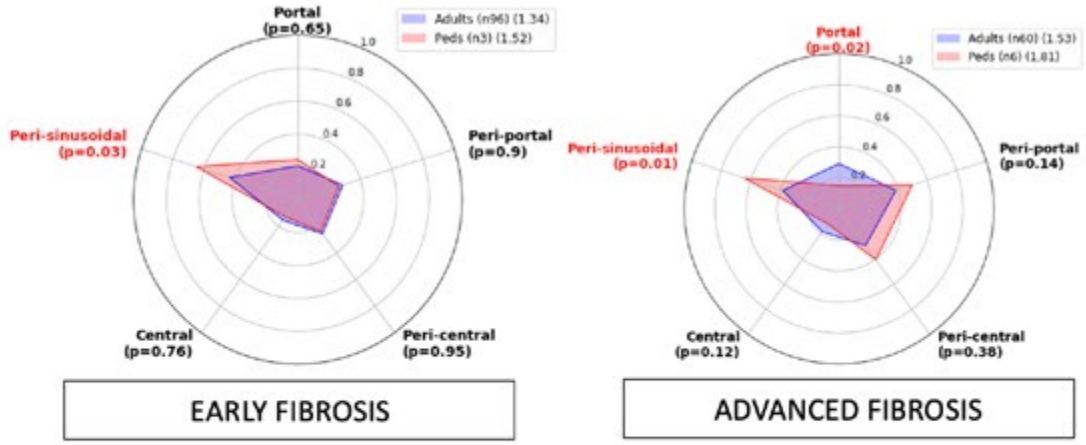

Figure 1: Radar plot illustrating the zonal distribution of fibrosis (according to the NASH-CRN system) in pediatric biopsies categorized as early and advanced fibrosis based on their qFibrosis staging, compared with adult biopsies of corresponding qFibrosis stages. Zonal measurements marked in red denote statistically significant differences between adult and pediatric qFibrosis values.

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2013 | FIBRO-SCOPE: AN ARTIFICIAL INTELLIGENCE/NEURAL NETWORK SYSTEM IS USEFUL IN PREDICTING LIVER RELATED EVENTS, CARDIOVASCULAR EVENTS, AND PROGNOSIS IN JAPANESE PATIENTS WITH METABOLIC-DYSFUNCTION ASSOCIATED STEATOTIC LIVER DISEASE

Yuya Seko[1] Kanji Yamaguchi[1] Toshihide Shima[2] Saiyu Tanaka[3] Yasuhide Mitsumoto[2] Yoshito Itoh[1] Takeshi Okanoue[4] Seita Kataoka[1]

[1]Kyoto Prefectural University of Medicine, [2]Saiseikai Suita Hospital, [3]Nara City Hospital, [4]Osaka Saiseikai Suita Hospital

Background: Fibro-Scope (Fscope)[1,2] is an artificial intelligence/neural network system to determine the stage of liver fibrosis in metabolic dysfunction-associated steatotic liver disease (MASLD) using 12 parameters. In this study, we compared the diagnostic performance of the Fscope for advanced fibrosis with the FIB-4 index and further examined its ability to predict events and mortality. **Methods:** The longitudinal multicenter cohort study enrolled 796 patients with biopsy-proven MASLD. We constructed area under the receiver operator characteristic curves (AUROC) to determine the diagnostic accuracies of the FIB-4 index and Fscope. **Results:** The AUROC of the Fib-4 index and Fscope for patients with F0–2 versus F3-4 was 0.883/0.907, respectively. The AUROC of the Fscope was greater than those of the FIB-4 index (p=0.040). The prevalence of intermediate score in Fscope was 5.2%, significantly smaller than FIB-4 index (38.7%). At low cut-off level, the specificity and negative predictive value were 86.3% and 94.3%. During follow-up (median [range], 6.4 [1.0–18.3] years), 37 patients developed HCC, 52 developed liver-related events, 22 developed cardio-vascular disease and 35 died of any cause. The patients with Fscope-positive had a significantly higher cumulative incidence of liver disease-related events (LRE) (p<0.01) and cumulative incidence of CVD (p=0.002), and a significantly lower survival rate (p<0.01) than the patients with Fscope-negative. Multivariate analysis revealed that Fscope-positive was significantly associated with poor mortality with the hazard ratio of 7.62 (95% CI 2.46–23.63). **Conclusion: Conclusions**: The Fibro scope demonstrated adequate ability to diagnose advanced fibrosis. It was also useful in identifying high-risk groups for LRE and CVD in Japanese MASLD patients, as well as poor prognosis.
Ref. 1) Okanoue T, et al. Hepatol Res 51:1044, 2021, 2) Yamaguchi K, et al. Hepatol Int 17:573, 2023

Disclosures: Yuya Seko: AbbVie GK: Speaking and Teaching, Novo Nordisk Pharma Ltd: Speaking and Teaching, Merck & Co., Inc.: Speaking and Teaching, Gilead Sciences, Inc.: Speaking and Teaching, Mitsubishi Tanabe Pharma Corporation: Speaking and Teaching, Kanji Yamaguchi: Nothing to Disclose, Toshihide Shima: Nothing to Disclose, Saiyu Tanaka: Nothing to Disclose, Yasuhide Mitsumoto: Nothing to Disclose, Yoshito Itoh: Novo Nordisk Pharma LTD: Speaking and Teaching, ZERIA PHARMACEUTICAL CO., LTD.: Speaking and Teaching, Otsuka Pharmaceutical Co., Ltd.: Speaking and Teaching, Viatris Inc.: Speaking and Teaching, ASKA Pharmaceutical Co., Ltd.: Speaking and Teaching, Astelas Pharma Inc.: Speaking and Teaching, AstraZeneca K.K.: Speaking and Teaching, Gilead Sciences Inc.: Speaking and Teaching, Mitsubishi Tanabe Pharma Corporation: Speaking and Teaching, EA Pharma Co. Ltd.: Speaking and Teaching, Kowa Company Ltd.: Speaking and Teaching, CHUGAI PHARMACEUTICAL CO., LTD.: Speaking and Teaching, Takeda Pharmaceutical Company Limited.: Speaking and Teaching, ONO PHARMACEUTICAL CO., LTD.: Speaking and Teaching, AbbVie Inc.: Speaking and Teaching, Novartis Pharma Inc.: Speaking and Teaching, MYYARISAN

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2014 | DIAGNOSTIC POTENTIAL OF FAST AND AGILE3+ SCORES FOR F2/F3 FIBROSIS: AN ANALYSIS OF THE PHASE 2 ENLIVEN STUDY

Naim Alkhouri[1] Arun Sanyal[2] Hank Mansbach[3] Germaine Agollah[3] Shibao Feng[3] Lillian Tsai[3] Mildred Gottwald[3] Maya Margalit[3] Rohit Loomba[4]

[1]Arizona Liver Health, [2]Virginia Commonwealth University, [3]89bio, [4]University of California, San Diego

Background: Background and Aims: Non-invasive tests (NITs) are commonly used to identify at-risk patients with metabolic dysfunction-associated steatohepatitis (MASH). In clinical trials, NITs can reduce screen-fail rates while in clinical practice, NITs can be used for patient stratification for therapy decisions. Two FibroScan-based NITs, the FAST (FibroScan-AST) score which identifies patients with ≥F2 fibrosis, and the AGILE3+ score which identifies patients with advanced fibrosis (≥F3), could be useful. The objective of this analysis was to characterize the diagnostic potential of FAST and AGILE3+ in the ENLIVEN population. **Methods:** ENLIVEN was a Phase 2, double-blind, placebo-controlled, 48-week study of pegozafermin (FGF-21 analog) in patients with biopsy-proven MASH with fibrosis (F2/F3). All patients had FibroScan conducted at baseline which allowed for calculation of FAST and AGILE3+ scores. Based on established cut-off scores for FAST (low-risk <0.35, indeterminate-risk ≥0.35 to <0.67, at-risk NASH ≥0.67) and AGILE3+ (low-risk <0.451, indeterminate-risk ≥0.451 to <0.679, at-risk NASH ≥0.679), patient's baseline score was compared to their biopsy staging to assess the accuracy of FAST and AGILE3+ scores. **Results:** ENLIVEN enrolled 192 patients with F2 (n=65) and F3 (n=127) fibrosis. Both scoring systems performed comparably at identifying their respective populations, with 21% of F2/F3 patients misclassified as "rule-out" by FAST and 22% of F3 patients for AGILE3+. The AGILE3+ score accurately identified as "rule-in" 55% of the patients staged as F3 by histology, whereas the FAST score identified as "rule-in" only 33% of F2/F3 patients. While categorizing more patients as indeterminate (46%), the FAST score was less likely to rule out patients who had F2 (29%) or F3 (17%) by histology compared to AGILE3+ (F2: 46%; F3 22%). AGILE3+ misclassified 34% of F2 patients as having at-risk NASH (F3+). **Conclusion:** Conclusion: FAST and AGILE3+ performed reasonably well in identifying their target populations in ENLIVEN. Because AGILE3+ was designed to identify F3+ patients, it was less accurate in identifying the overall F2/F3 population. These data suggest the FAST score would likely be a viable tool to reduce screen failures in clinical trials targeting F2/F3 fibrosis and/or to aid in treatment-making decisions, in the real-world setting.

Table 1: Summary of Baseline FAST and AGILE3+ Scores by Risk Categories Compared to 3-panel Consensus Biopsy Reading

		Rule out at-risk NASH		Indeterminate Risk		Rule in at-risk NASH	
	n	FAST <0.35	AGILE3+ <0.451	FAST ≥0.35 to <0.67	AGILE3+ ≥0.451 to <0.679	FAST ≥0.67	AGILE3+ ≥0.679
Overall population	192	21%	30%	46%	22%	33%	48%
Stage 3 Fibrosis	127	17%	22%	46%	23%	37%	55%
Stage 2 Fibrosis	65	29%	46%	46%	20%	25%	34%

Disclosures: Naim Alkhouri: Madrigal: Grant/Research Support, Madrigal: Speaking and Teaching, Novo Nordisk: Consulting, Novo Nordisk: Grant/Research Support, Gilead: Grant/Research Support, Corcept: Grant/Research Support, Boehringer Ingelheim: Grant/Research Support, Echosens: Speaking and Teaching, Perspectum: Consultant, Cima: Consultant, Fibronostics: Consultant, 89Bio: Grant/Research Support, Inventiva: Grant/Research Support, Merck: Grant/Research Support, Pfizer: Grant/Research Support, Ipsen: Speaking and Teaching, Intercept: Speaking and Teaching, Madrigal: Consulting, Research Funding, Novo Nordisk: Consulting,

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2015 | CLINICAL MANAGEMENT OF DISCREPANCIES BETWEEN FIB-4 AND LIVER STIFFNESS MEASUREMENT IN PATIENTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD)

Joseph Rabbat[1] Hye Won Lee[2] Terry Cheuk-Fung Yip[1] Huapeng Lin[3] Emmanuel Tsochatzis[4] Salvatore Petta[5] Elisabetta Bugianesi[6] Masato Yoneda[7] Ming-Hua Zheng[8] Hannes Hagström[9] Jérôme Boursier[10] Jose Luis Calleja[11] George Boon-Bee Goh[12] Wah Kheong Chan[13] Rocio Gallego-Durán[14] Arun Sanyal[15] Victor de Ledinghen[16] Philip Newsome[17] Jian-Gao Fan[3] Laurent Castera[18] Michelle Lai[19] Celine Fournier[16] Grace Wong[1] Grazia Pennisi[5] Angelo Armandi[6] Atsushi Nakajima[20] Wen-Yue Liu[8] Ying Shang[21] Marc De Saint Loup[10] Elba Llop[11] Kevin Teh[12] Carmen Lara Romero[14] Amon Asgharpour[22] Sara Mahgoub[23] Mandy Chan[16] Clemence Canivet[10] Manuel Romero-Gómez[14] Seung Up Kim[2]

[1]The Chinese University of Hong Kong, [2]Yonsei University College of Medicine, [3]Shanghai Jiaotong University, [4]University College London, [5]University of Palermo, [6]University of Turin, [7]Yokohama City University, [8]Wenzhou Medical University, [9]Karolinska University Hospital, [10]Angers University Hospital, [11]Hospital Universitario Puerta de Hierro, [12]Singapore General Hospital, [13]University of Malaya, [14]Virgen Del Rocío University Hospital, [15]Virginia Commonwealth University, [16]Echosens, [17]King's College London, [18]Université Paris Cité, [19]Beth Israel Deaconess Medical Center, [20]National Hospital Organization Yokohama Medical Center, [21]Karolinska Institutet, [22]VCU School of Medicine, [23]University of Birmingham

Background: Current AASLD guidance recommends a 2-step approach of FIB-4 followed by liver stiffness measurement (LSM) by vibration-controlled transient elastography to identify advanced liver fibrosis in patients with MASLD. Some studies have evaluated the effectiveness of this approach and determined the accuracy of FIB-4 by using LSM as a reference standard. This is potentially misleading as LSM is imperfect. In this study, we evaluated the histologic severity and outcomes of patients with discordant FIB-4 and LSM. **Methods:** A secondary analysis was performed on patients from the VCTE-prognosis database, which includes data from a multicenter longitudinal study of patients with MASLD. Patients were classified into 4 groups: low FIB-4 (<1.3) and LSM (<8 kPa), low FIB-4 and high LSM (≥8 kPa), high FIB-4 (≥1.3) and low LSM, and high FIB-4 and high LSM. The primary endpoint was a composite of liver-related events including hepatocellular carcinoma, hepatic decompensation, liver transplant and liver-related death. The secondary endpoint was histologic F3-F4 fibrosis. **Results:** 17,949 patients underwent at least 1 VCTE examination, and 12,950 patients were included in the final analysis after excluding pediatric patients, patients who had liver-related events before baseline and those with missing FIB-4. At a median follow-up of 48 months, the proportion of patients developing liver-related events was the lowest in the low-FIB-4-low-LSM group (0.3%) and the highest in the high-FIB-4-high-LSM group (9.1%) (Table). Only 0.5% of patients in the high-FIB-4-low-LSM group developed liver-related events, compared with 1.2% in the low-FIB-4-high-LSM group. Similarly, F3-F4 fibrosis was least prevalent in the low-FIB-4-low-LSM group (6.7%) and most prevalent in the high-FIB-4-high-LSM group (66.1%). Among patients with discrepant FIB-4 and LSM, a high LSM was associated with a higher risk of F3-F4 fibrosis (31.8% in the low-FIB-4-high-LSM group and 15.0% in the high-FIB-4-low-LSM group). **Conclusion:** The AASLD 2-step approach is effective in identifying a majority of advanced liver fibrosis cases and predicting the occurrence of a majority of liver-related events in patients with MASLD. In patients with discrepant FIB-4 and LSM, patients with high LSM appear more likely to suffer from pathological liver conditions, though the incidence of liver-related events remains low. (This study is supported in part by the General Research Fund of the Hong Kong SAR Government [project reference 14106923]).

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	All	FIB-4 <1.3 LSM <8 kPa	FIB-4 <1.3 LSM ≥8 kPa	FIB-4 ≥1.3 LSM <8 kPa	FIB-4 ≥1.3 LSM ≥8 kPa
Liver-related events					
N	12950	6403	1363	3017	2167
All liver-related events, n (%)	248/12950 (1.9)	19/6403 (0.3)	16/1363 (1.2)	16/3017 (0.5)	197/2167 (9.1)
Hepatocellular carcinoma, n (%)	109/12950 (0.8)	13/6403 (0.2)	6/1363 (0.4)	10/3017 (0.3)	80/2167 (3.7)
Hepatic decompensation, n (%)	174/12950 (1.3)	6/6403 (0.1)	9/1363 (0.7)	8/3017 (0.3)	151/2167 (7.0)
Liver transplantation, n (%)	15/12950 (0.1)	1/6403 (<0.1)	2/1363 (0.1)	1 /3017(<0.1)	11/2167 (0.5)
Liver-related death, n (%)	41/12950 (0.3)	0	0	2/3017 (0.1)	39/2167 (1.8)
Liver histology					
N	3065	934	648	440	1043
F2-F4 fibrosis, n (%)	1529/3065 (49.5)	201/934 (21.6)	349/648 (53.9)	149/440 (33.9)	830/1043 (79.6)
F3-F4 fibrosis, n (%)	1023/3065 (33.4)	62/934 (6.7)	206/648 (31.8)	66/440 (15)	689/1043 (66.1)
Cirrhosis, n (%)	365/3065 (11.9)	9/934 (1.0)	42/648 (6.5)	11/440 (2.5)	303/1043 (29.1)
MASH, n (%)	1831/2919 (62.7)	505/926 (54.5)	441/633 (69.8)	225/430 (52.4)	660/930 (70.9)
At-risk MASH*, n (%)	948/2919 (32.5)	124/926 (13.4)	231/633 (36.5)	92/430 (21.4)	501/930 (53.9)

Abbreviations: MASH, metabolic dysfunction-associated steatohepatitis

*At-risk MASH is defined as NAFLD activity score ≥4 with at least 1 point each in steatosis, lobular inflammation and hepatocyte ballooning together with F2-F4 fibrosis.

Disclosures: Joseph Rabbat: Nothing to Disclose, Hye Won Lee: Nothing to Disclose, Terry Cheuk-Fung Yip: Gilead Sciences: Consultant, Gilead Sciences: Advisor, Gilead Sciences: Speaking and Teaching, Huapeng Lin: Nothing to Disclose, Emmanuel Tsochatzis: NovoNordisk: Advisor, Siemens: Advisor, MSD: Advisor, Orphalan: Advisor, Univar: Advisor, Boehringer: Advisor, Echosens: Speaking and Teaching, Orphalan: Speaking and Teaching, Abbvie: Speaking and Teaching, NovoNordisk: Speaking and Teaching, Salvatore Petta: Nothing to Disclose, Elisabetta Bugianesi: Nothing to Disclose, Masato Yoneda: Gilead Sciences: Grant/Research Support, Gilead Siences inc.: Grant/Research Support, Ming-Hua Zheng: Nothing to Disclose, Hannes Hagström: Nothing to Disclose, Jérôme Boursier: Nothing to Disclose, Jose Luis Calleja: Nothing to Disclose, George Boon-Bee Goh: Nothing to Disclose, Wah Kheong Chan: Nothing to Disclose, Rocio Gallego-Durán: Nothing to Disclose, Arun Sanyal: Genfit, Akarna, Tiziana, Durect, Inversago, Hemoshear, North: Stock - publicly traded company, Astra Zeneca (60K), Boston Pharmaceutical

2016 | THE DIABETES RISK INDEX (DRI) PREDICTS FUTURE DEVELOPMENT OF TYPE 2 DIABETES MELLITUS IN EUGLYCEMIC AND PREDIABETIC PATIENTS WITH METABOLIC DYSFUNCTION ASSOCIATED STEATOTIC LIVER DISEASE

Arun Sanyal[1] Ekaterina Smirnova[1] Laura Wilson[2] Jeanne Clark[3] Kris Kowdley[4] Anna Mae Diehl[5] Raj Vuppalanchi[6] Nicole Welch[7] Liyun Yuan[8]

[1]Virginia Commonwealth University, [2]Johns Hopkins University, [3]Johns Hopkins University School of Medicine, [4]Liver Institute Northwest, [5]Duke University, [6]Indiana University, [7]Cleveland Clinic, [8]University of Southern California

Background: MASLD increases the risk of incident type 2 diabetes mellitus (T2DM). The Diabetes Risk Index (DRI, score range 0-100, Labcorp), based on lipoprotein-derived insulin resistance index and branch chain amino acids (BCAA), was developed to predict future T2DM. **Methods:** A retrospective analysis of non-diabetic participants in a prospective non-interventional cohort study of biopsy-proven MASLD of the NASH CRN was performed. T2DM was diagnosed by fasting plasma glucose (FPG)> 126 mg/dl. DRI scores were generated by Labcorp masked to clinical-laboratory data and analyzed independently. Time-to-event analyses were performed by DRI tertiles and in FPG-defined strata (< 100, 100-110, and 111-126 mg/dl). Ability to predict outcomes was assessed with C-statistic and Cox proportional hazard models. Specificity of DRI for T2DM was assessed by its relationship to liver outcomes. **Results:** 804 non-diabetic individuals with MASLD (females 57%, mean age: 49 yrs, BMI 33.3 kg/m^2, A1c 5.6, and definite/borderline steatohepatitis n= 346/189, stage ≥ 3 n=143) were studied. None were on metformin. Over a median follow up of 3.23 patient years, 218 (27.1%) developed T2DM. Within each DRI tertile, there was a progressive increase in T2DM with increasing FPG with 70% 5 yr-incidence in those with FPG 111-126 mg/dl within highest DRI tertile. In the full cohort, those who developed T2DM had higher BMI (34 vs 32 kg/m2, p< 0.008), FPG (96 vs 90 mg/dl, p< 0.001), DRI (mean 47± 17 vs 44 ± 17, p< 0.01), A1c

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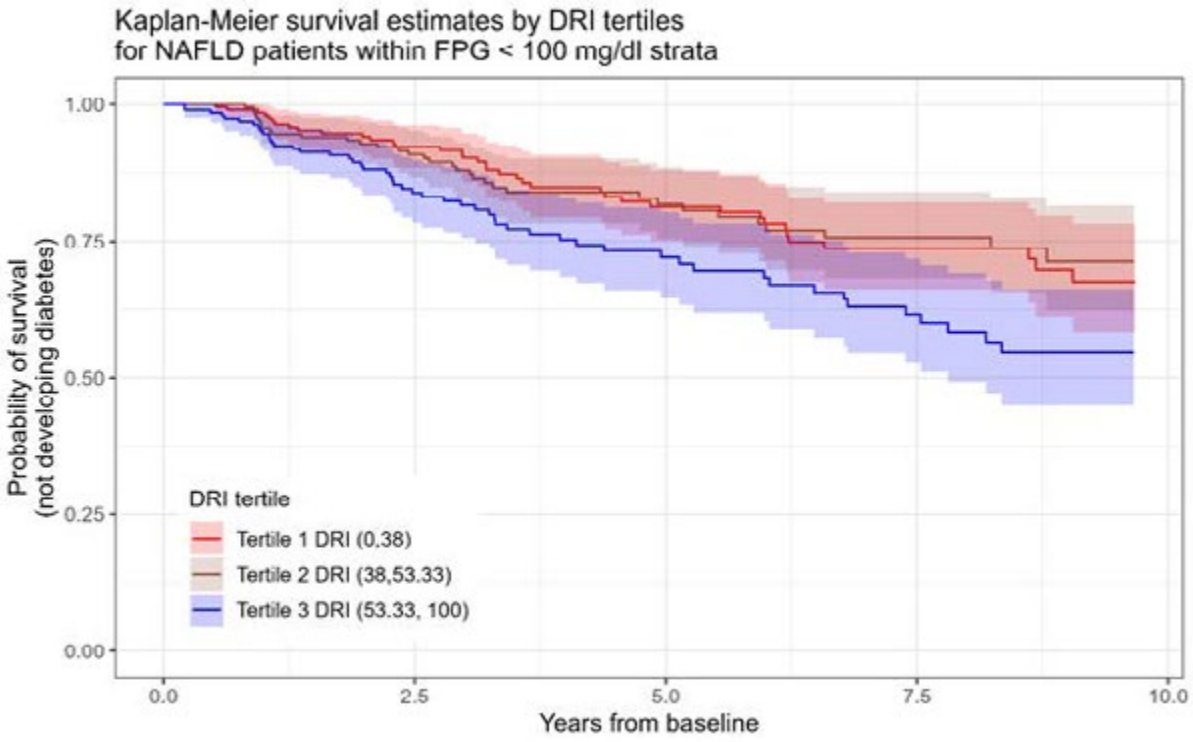
(5.8 vs 5.6, p< 0.001), longer follow up (6 vs 4 yrs, p< 0.001) and had higher proportion of steatohepatitis (57 vs 22, p< 0.001) and fibrosis stages ≥ 3 (21 vs 16.4, p< 0.01) vis-à-vis those who did not. DRI independently predicted development of T2DM (HR 1.016 (95% CI 1.005-1.021) for 1-point increase in DRI, p< 0.002) adjusting for FPG, BMI, steatohepatitis and fibrosis stage. Within FPG strata, DRI independently predicted T2DM (HR 1.7, p< 0.01) only in those with FPG < 100 mg/dl. Steatohepatitis predicted development of T2DM in all FPG strata and FPG was predictive only in those with FPG 110-126 mg/dl. DRI did not predict liver events (HR 0.95, p=ns). **Conclusion:** DRI predicts T2DM development in euglycemic patients with MASLD. Steatohepatitis also independently predicts risk of T2DM in non-diabetic patients with MASLD.



Disclosures: Arun Sanyal: Genfit, Akarna, Tiziana, Durect, Inversago, Hemoshear, North: Stock - publicly traded company, Astra Zeneca (60K), Boston Pharmaceutical

2017 | VALIDATION OF MICROBIAL SIGNATURE FOR ADVANCED FIBROSIS IN A GLOBAL MULTI-ETHNIC COHORT OF MASLD

Ekaterina Smirnova[1] Yusuf Yilmaz[2] Fatih Eren[3] Mark Muthiah[4] Claudia Oliveira[5] Mohammad Siddiqui[1] Faridoddin Mirshahi[1] Phillip Hylemon[1] Jonathan Lee[4] Arun Sanyal[1]

[1]Virginia Commonwealth University, [2]University of Rize, Turkey, [3]Marmara University, Istanbul, Türkiye, [4]National University of Singapore, [5]University of Sao Paulo, Brazil

Background: MASH is associated with altered intestinal microbiome. The microbiome is however diverse across different regions and it is not known if a consistent set of changes are seen with increasing MASH fibrosis stages across the world. **Aims**: (1) To characterize microbiome profile in MASLD patients from Middle East (Turkey), Latin America (Brazil), and Asia (Singapore) and relate them to those reported for US cohorts (2) To identify common and population-specific microbiome signatures of fibrosis**. Methods:** The study cohort consisted of 300 Biopsy-proven MASLD patients from Turkey (n=166), Brazil (n=52), Singapore (n=82), stratified by fibrosis stage: 0-1 (n=119); stage 2 (n = 57); stage 3 (n=78); stage 4(n=46). Stool samples were collected at each site and shipped to a central lab for 16S analysis. All samples were processed simultaneously to minimize technical differences. Differentially abundant taxa in advanced (stages <3 vs ≥3) fibrosis groups was identified using Linear Discriminant Analysis Effect Size (LEfSe) on the combined and site-stratified cohort. LDA score ≥2 was set for significance. **Results:** Combined cohorts analysis identified an increase in the following species

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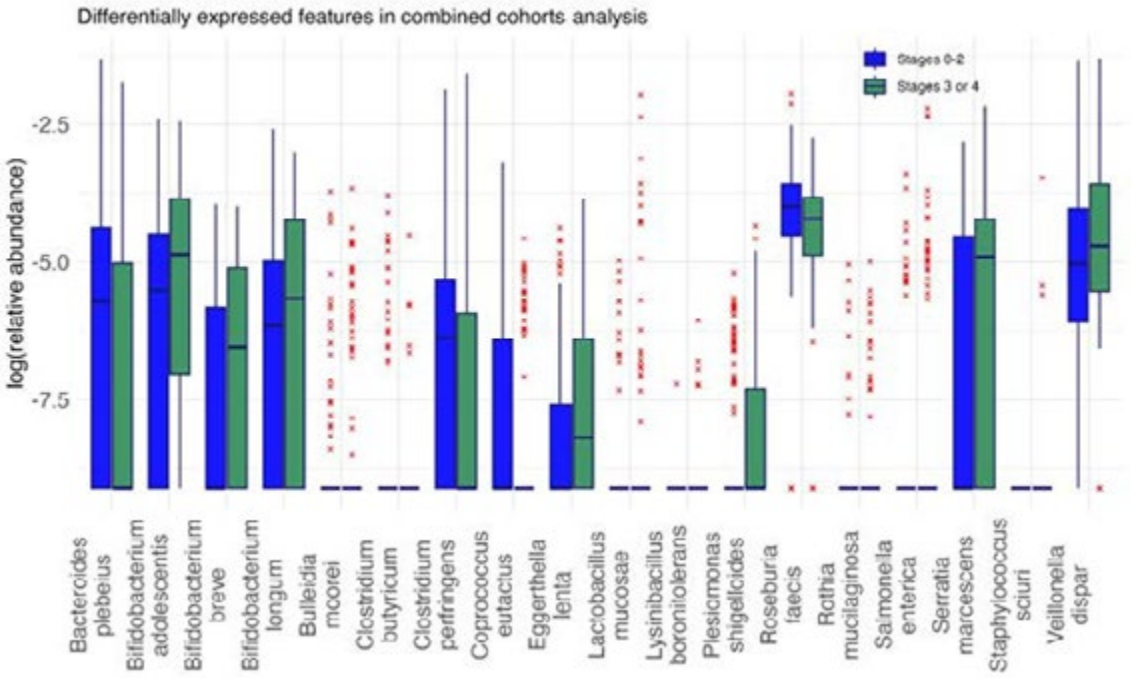
with increasing fibrosis; *Bifidobacterium adolescentis, B. breve, B. longum; Eggerthella lenta, Lactobacillus mucosae, Lysinibacillus boronitolerans, Plesiomonas shigelloides, Rothia mucilaginosa, Salmonella enterica, Serratia marcescens, Staphylococcus sciuri, Veillonella dispar. Bacteroides plebeius, Clostridium butyricum and C. perfringens. Coprococcus eutactus, Roseburia faecis* were decreased in patients with Fibrosis stages ≥3. An increase in *Parabacteroides distasonis* and decrease in *Roseburia faecis* were specific to the Turkey cohort. An increase in *Prevotella copri* was specific to the Singapore cohort, while the Brazil cohort had an increase in *Bifidobacterium adolescent*, which was not observed in the combined cohorts analysis. Several genera were differentially altered in advanced fibrosis vs early stage fibrosis across cohorts (Figure 1) inclusive of *Bifidobacterium*, *Eggerthella*, *Veillonella*, *Serratia*, *Coprococcus* and *Roseburia*: of these, *Coprococcus* and *Roseburia* were decreased. **Conclusion:** A common set of changes in microbial taxa with advanced fibrosis (stage 3-4) in MASH patients from different continents was identified. These support the development of a gut microbiome-based biomarker profile for advanced fibrosis and provide a rationale for targeted mechanistic studies.



Disclosures: Ekaterina Smirnova: Pfizer, Inc: Grant/Research Support, Yusuf Yilmaz: Nothing to Disclose, Fatih Eren: Nothing to Disclose, Mark Muthiah: Lerna Bio: Stock – privately held company, Olympus: Speaking and Teaching, Boston Scientific: Speaking and Teaching, Novo Nordisk: Grant/Research Support, Echosens: Grant/Research Support, Gilead: Advisor, Claudia Oliveira: Nothing to Disclose, Mohammad Siddiqui: Grant/Research Support relationship with NovoNordisk; Has not ended; Advisor relationship with 89Bio; Has not ended; Advisor relationship with AMRA; Has not ended, Faridoddin Mirshahi: Nothing to Disclose, Phillip Hylemon: Nothing to Disclose, Jonathan Lee: Nothing to Disclose, Arun Sanyal: Genfit, Akarna, Tiziana, Durect, Inversago, Hemoshear, North: Stock - publicly traded company, Astra Zeneca (60K), Boston Pharmaceutical

2018 | THROMBOSPONDIN 2: A KEY PLAYER IN FIBROGENESIS OF METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE UNCOVERED BY MULTI-OMICS ANALYSIS

Takefumi Kimura[1] *Shun-Ichi Wakabayashi*[1] *Naoki Tanaka*[1] *Takeji Umemura*[2]

[1]*Shinshu University School of Medicine,* [2]*Shinshu University of Medicine*

Background: Thrombospondins, a diverse group of extracellular matrix glycoproteins, are known to play crucial roles in numerous biological processes, including cell adhesion, migration, angiogenesis, and tissue repair. This study aims to elucidate the role of thrombospondin 2 (THBS2) in fibrogenesis of Metabolic dysfunction-associated

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steatotic liver disease (MASLD). **Methods:** Liver tissue and serum samples from 257 MASLD patients were utilized, alongside a comprehensive MASLD liver gene dataset obtained from RNA-seq analysis, spatial transcriptome analysis, and single-cell RNA sequencing analysis (scRNA-seq), to examine the expression of THBS2. Mechanistic studies of THBS2 expression were conducted with LX-2 cells derived from human hepatic stellate cells (HSCs). **Results:** RNA-seq analysis identified 1433 variable genes in patients with advanced fibrotic MASLD, ranking THBS2 among the top 2 genes. Hepatic mRNA THBS2 expression and serum THBS2 protein levels exhibited significant correlations with fibrosis stage in MASLD patients ($r = 0.35$ and $r = 0.53$, both $P < 0.001$). Additionally, serum THBS2 protein levels were significantly associated with the occurrence of liver-related events (P=0.005). Further analyses, including scRNA-seq, spatial transcriptome, and in situ hybridization, confirmed heightened THBS2 expression in HSCs within regions experiencing fibrosis progression. Pathway analysis unveiled a linkage between THBS2 expression and the activation of the transforming growth factor-beta (TGFβ) pathway and collagen-related gene expression. In LX-2 cells, THBS2 exhibited substantial upregulation concurrent with collagen gene induction by TGFβ, independently of the SMAD3 pathway. Remarkably, gene knockdown of THBS2 in LX-2 cells significantly suppressed collagen mRNA/protein expression ($P<0.001$). **Conclusion:** This study underscores the pivotal role of THBS2 in fibrogenesis and suggests its potential as a therapeutic target for fibrosis in MASLD. The findings provide valuable clues for the development of antifibrotic strategies in the management of MASLD.

Disclosures: Takefumi Kimura: Nothing to Disclose, Shun-Ichi Wakabayashi: Nothing to Disclose, Naoki Tanaka: Nothing to Disclose, Takeji Umemura: Nothing to Disclose

2019 | MACHINE LEARNING-FACILITATED PREDICTIVE MODEL FOR LIVER-RELATED EVENTS IN TYPE 2 DIABETES MELLITUS

Sherlot Juan Song[1] Vincent Wong[1] Grace Wong[1] Terry Cheuk-Fung Yip[1]

[1]The Chinese University of Hong Kong

Background: We aimed to develop a prediction model for liver-related events (LREs) in patients with type 2 diabetes mellitus (T2DM), considering the well-established association of T2DM with cirrhosis and hepatocellular carcinoma (HCC). **Methods:** This territory-wide retrospective study included adult patients with the diagnosis of T2DM in Hong Kong between 2007 and 2021. Excluded patients were pre-existing liver diseases, except for those with metabolic dysfunction-associated steatotic liver disease, or those who developed LREs before their T2DM diagnosis. The primary endpoint was incident LREs in 5 years, defined as hepatic decompensation or HCC. A conventional statistical risk model was developed using Cox regression with either stepwise or LASSO variable selection. Four machine learning algorithms were tested using the same covariates selected by the stepwise-Cox model. The final model was selected based on the time-dependent area under the receiver-operating characteristics curves (tAUCs). The designated model was then applied to stratify the validation cohort into three risk groups for LRE development using cutoffs at 90% sensitivity and specificity. **Results:** 460,000 patients with T2DM were included in the training cohort (mean age 61.9 years; 52.3% males); the incidence rate of LRE was 1.285 per 1,000 person-years (95% confidence interval [CI] 1.245-1.326) at a median follow-up duration of 6.25 years. The conventional model developed by stepwise-Cox regression on the training cohort included 9 covariates of age, sex, compensated cirrhosis, alanine aminotransferase, platelet, hemoglobin A1c, albumin, total bilirubin and creatinine. Among the machine learning approaches evaluated, XGBoost demonstrated the highest discrimination in the validation cohort and was selected as the final model. The tAUCs for XGBoost in the validation cohort at 1, 3, and 5 years were 0.805, 0.782 and 0.759 respectively, which were superior to the performance of Fibrosis-4 index and Aspartate aminotransferase-to-Platelet Ratio Index (Figure). In the validation cohort (n=115000), 36.8%, 53.5%, and 9.7% of patients were stratified into low-, mediate- and high-risk categories, respectively. The corresponding 5-year incidence rates per 1000 person-yearswere 0.285, 1.114, and 4.658, respectively. The age- and sex-adjusted hazard ratio for LRE was significantly elevated in the intermediate- (3.25; 95% CI 2.47-4.29) and high-risk (13.78; 95% CI 10.35-18.35) versus low-risk categories. **Conclusion:** This novel risk model may identify individuals at risk of adverse liver outcomes among patients with T2DM and facilitate early referral to specialty care. Figure**.** Discrimination of multiple risk models in predicting 5-year outcomes in the training and validation cohorts.FIB-4, Fibrosis-4 index. APRI, AST-to-Platelet Ratio Index. The legend included the Integrated time-dependent AUCs of models.

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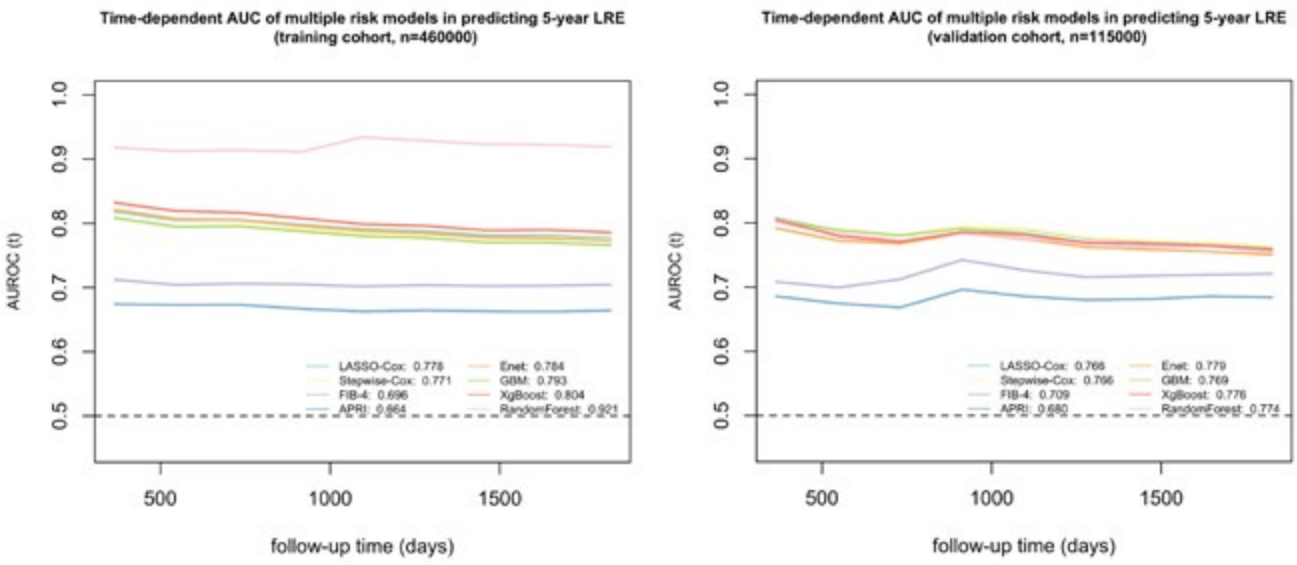

Disclosures: Sherlot Juan Song: Nothing to Disclose, Vincent Wong: Abbott: Speaking and Teaching, AbbVie: Advisor, AbbVie: Speaking and Teaching, Boehringer Ingelheim: Advisor, Echosens: Advisor, Echosens: Speaking and Teaching, Gilead Sciences: Advisor, Gilead Sciences: Speaking and Teaching, Gilead Sciences: Grant/Research Support, Intercept: Advisor, Inventiva: Advisor, Novo Nordisk: Advisor, Novo Nordisk: Speaking and Teaching, Pfizer: Advisor, Sagimet: Advisor, TARGET PharmaSolutions: Advisor, Unilab: Speaking and Teaching, Visirna: Consultant, Illuminatio Medical Technology: Stock – privately held company, Grace Wong: AstraZeneca: Advisor, Gilead Sciences: Advisor, Gilead Sciences: Speaking and Teaching, Janssen: Advisor, GSK: Advisor, GSK: Speaking and Teaching, Abbott: Speaking and Teaching, AbbVie: Speaking and Teaching, AstraZeneca, Gilead Sciences, GlaxoSmithKline and Janssen,: Advisor, Abbott, AbbVie, Ascletis, Bristol-Myers Squibb, Echosens, Gi: Speaking and Teaching, Gilead Sciences: Grant/Research Support, AstraZeneca, Gilead Sciences, GlaxoSmithKline and Janssen: Consultant, Abbott, AbbVie, Ascletis, Bristol-Myers Squibb, Echosens, Gi: Speaking and Teaching, AstraZeneca, Gilead Sciences, GlaxoSmithKline Pharmaceutical: Consultant, Gilead Sciences: Independent Contractor, AstraZeneca, Gilead Sciences, GSK and Janssen,: Advisor, Abbott, AbbVie, BMS, Gilead Sciences, GSK, Janssen, Roche: Speaking and Teaching, Gilead Sciences: Grant/Research Support, Terry Cheuk-Fung Yip: Gilead Sciences: Consultant, Gilead Sciences: Advisor, Gilead Sciences: Speaking and Teaching

2020 | DIGITAL PATHOLOGY AND AI SINGLE-NUCLEI LIVER ISSUE PANELS REVEAL THE QUANTITATIVE PARENCHYMAL INVOLVEMENT OF INFLAMMATION AND STEATOSIS IN RODENT MODELS OF MASH TREATED WITH MANNOSE

Mathieu Petitjean[1] Nathan Aist[2] Yvette Carbajal[3] Charles DeRossi[4] Aras Mattis[5] Dmitry Fedorov[6] Li Chen[1]

[1]PHARMANEST, [2]PHARMANEST INC, [3]Icahn School of Medicine at Mount Sinai, [4]Icahn School of Medicine at Mount Sinai (ISMMS), [5]University of California, San Francisco, [6]VIQI Inc

Background: While tissue injury and inflammation are hallmarks of disease activity in Metabolic dysfunction-associated steatohepatitis (MASH), current histological staging methods are semi-quantitative and subject to poor intra and inter observer variability. We report on the development, validation of a single-nuclei digital pathology and AI method that yields accurate and precise cell count tissue panels and its application to detect the effect of mannose supplementation in a rodent model of MASH. **Methods:** 43 mouse liver samples were histologically

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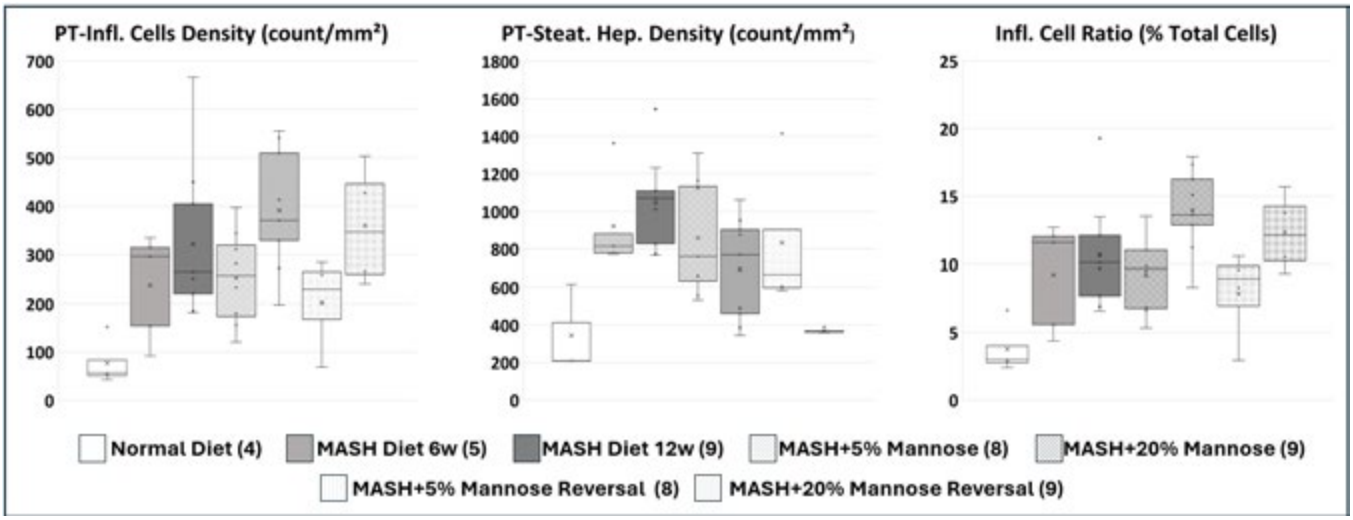
prepared for H&E and scanned at 40X. Study groups included normal diet (ND, n=4), MASH diet for 6 weeks (MASH-6w, n=5) or 12 weeks (MASH-12w, n=9), MASH diet for 12 weeks with mannose supplement at 5% (MP5, n=8) or 20% (MP20, n=9) at week 0 (prevention) or at 5% (MR5, n=4) or 20% (MR20, n=4) at week 6 (reversal). Three images per treatment group (21 total) were used to train a machine learning model with 7.5K total manual annotations (2209, 1802, 1449, 1449, 643) for liver specialized cells, inflammatory cells, debris, steatotic and normal hepatocytes, respectively. Cell densities (count/mm2) and relative cell count percents were calculated for each cell class except debris. Inflammatory cell clusters were grouped via “closest neighbor” method and classified into small and large inflammatory foci. Macro steatosis area was calculated elsewhere (doi:10.3390/ijms24108494) and used to normalize cell densities to the parenchymal tissue (PT-) area. **Results:** Classification accuracy was 70.8% (12.4%), 95.4% (10.6%), 85.2% (7.9%), and 88.4% (13.7%) for non-steatotic hepatocytes, steatotic hepatocytes, inflammatory cells, and liver specialized cells, respectively. Mean inflammatory cells density (count/mm2) were 43.31 (ND), 238.2 (MASH-6w), 321.3 (MASH-12w), 253.1 (MP5), 391.0 (MP20), 203.3 (MR5), and 359.6 (MR20). Mean steatotic hepatocyte cells densities (count/mm2) were 390.1 (ND), 921.7 (MASH-6w), 1046.0 (MASH- 12w), 858.8 (MP5), 693.7 (MP20), 833.8 (MR5), and 368.2 (MR20). Inflammation composite scores for large foci were 0.5 (ND), 1.3 (MASH-6w), 3.1 (MASH-12w), 2.1 (MP5), 3.9 (MP20), 1.4 (MR5), and 2.0 (MR20). **Conclusion:** Digital pathology and AI tissue panels from conventional H&E images to quantify inflammatory and steatotic involvement and their response to treatment, thus enriching adjacent methods used for fibrosis. These applications can assist the discovery and development of drug candidates for MASH.



Disclosures: Mathieu Petitjean: Nothing to Disclose, Nathan Aist: Nothing to Disclose, Yvette Carbajal: Nothing to Disclose, Charles DeRossi: Nothing to Disclose, Aras Mattis: BioMarin Pharmaceuticals: Consultant, Pliant Therapeutics: Consultant, Regeneron Phamaceuticals: Consultant, HepaTx: Consultant, Pharmanest: Consultant, Dmitry Fedorov: Nothing to Disclose, Li Chen: Nothing to Disclose

2021 | THE ASSOCIATIONS BETWEEN CIRCULATING METABOLIC BIOMARKERS ON THE RISK OF HEPATOCELLULAR CARCINOMA DEVELOPMENT IN THE USA

Rikita Hatia[1] Peng Wei[2] Donghui Li[2] Ping Chang[2] Reham Abdel-Wahab[2] Omnia Farahat[2] Prasun Jalal[3] Yun Shin Chun[2] Asif Rashid[2] Ahmed Kaseb[1] Manal Hassan[1]

[1]The University of Texas MD Anderson Cancer Center, [2]UT MD Anderson Cancer Center, [3]Baylor College of Medicine

Background: Metabolic disorders have been implicated in hepatocellular carcinoma (HCC) carcinogenesis; however, there is a paucity in data examining the role of metabolic-related biomarkers on the risk of HCC. We aimed to assess the associations of blood-based biomarkers involved in the metabolic pathway and HCC diagnosis. **Methods:**Between 2001 and 2014, all newly diagnosed HCC patients were ascertained as part of an ongoing IRB-approved study at The University of Texas MD Anderson Cancer Center. Control participants were selected from healthy spouses of patients who were diagnosed with cancers other than liver and gastrointestinal cancers. Blood samples were collected at time of diagnosis or enrollment and sent to Myriad RBM, Inc. to test for

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a panel of 10 metabolic-related biomarkers. Using the tertiles of the biomarkers among the controls as a cutoff point, all participants were categorized into subjects with low, moderate, and high levels of the biomarkers. Odds ratio (OR) and 95% confidence interval (CI) values were estimated using multivariable unconditional logistic regression analysis with adjustment for relevant confounders. The *P* value is adjusted for multiple testing using the Benjamini-Hochberg with the false discovery rate at 0.25. **Results:** A total of 378 nonviral HCC case patients and 200 healthy controls were analyzed. The mean age (± standard deviation) for cases was 64.96 (± 12.78) years, and for controls, it was 60.17 (± 9.53) years. Most of the study population was white (76.8%). Table 1 presents the estimated OR and corresponding 95% CIs of each metabolic-related biomarker with the risk of HCC among subjects with moderate and high levels of biomarkers (second and third tertiles, respectively) as compared to those with low levels of biomarkers (first tertile) after adjusting for risk factors. The table highlights the significant associations between 10 metabolic-related biomarkers and HCC diagnosis. Two biomarkers, prolactin and resistin, were observed to significantly increase the risk of HCC. For example, patients with a high level of prolactin had a 5.93-fold (95% CI: 2.74-12.80) increased risk for HCC compared to subjects with low levels of prolactin. Furthermore, we observed a synergistic effect between prolactin and resistin on the multiplicative scale in the presence and absence of diabetes mellitus. **Conclusion:** Two metabolic-related markers, prolactin and resistin, showed significant and independent associations with increased risk of HCC. These observations suggest a potential value of these plasma biomarkers in predicting the risk of HCC in the absence of viral hepatitis infection and expanding our current understanding of the role of inflammation in HCC development associated with the metabolic pathway. Future validation of the results in independent population will need to be assessed for independent samples of HCC cases and controls.

Table 1. ORs and 95% CIs for the association of each metabolic-related biomarker with the risk of hepatocellular carcinoma in 378 cases and 200 controls

	Tertile 1: Low	**Tertile 2: Moderate**	**Tertile 3: High**	
Metabolic biomarker	OR (95% CI)	OR (95% CI)	OR (95% CI)	P_{trend} [a]
Adiponectin	1.00 (Ref)	1.56 (0.85-2.85)	1.76 (0.92-3.34)	0.13
Angiotensin Converting Enzyme ACE	1.00 (Ref)	0.94 (0.53-1.67)	1.16 (0.65-2.05)	0.20
Follicle Stimulating Hormone	1.00 (Ref)	1.46 (0.79-2.72)	2.29 (0.76-6.96)	0.15
Glucagon-like Peptide-1 Total	1.00 (Ref)	1.24 (0.62-2.46)	1.03 (0.40-2.66)	0.25
Insulin	1.00 (Ref)	**0.47 (0.26-0.86)**	**0.33 (0.17-0.61)**	0.08
Leptin	1.00 (Ref)	**0.25 (0.13-0.48)**	**0.32 (0.16-0.65)**	0.10
Luteinizing Hormone	1.00 (Ref)	0.84 (0.44-1.58)	0.65 (0.24-1.74)	0.18
Pancreatic Polypeptide	1.00 (Ref)	0.81 (0.45-1.46)	0.91 (0.48-1.75)	0.23
Prolactin	1.00 (Ref)	**1.96 (1.19-3.21)**	**5.93 (2.74-12.80)**	**0.05**
Resistin	1.00 (Ref)	**2.31 (1.38-3.87)**	**4.51 (2.24-9.08)**	**0.03**

[a] Model adjusted for age, sex, race, smoking, alcohol consumption, history of diabetes, obesity family history of cancer. *P* is adjusted for multiple testing using the Benjamini-Hochberg with the false discovery rate set at 0.25.

Disclosures: Rikita Hatia: Nothing to Disclose, Peng Wei: Nothing to Disclose, Donghui Li: Nothing to Disclose, Ping Chang: Nothing to Disclose, Reham Abdel-Wahab: Nothing to Disclose, Omnia Farahat: Nothing to Disclose, Prasun Jalal: Nothing to Disclose, Yun Shin Chun: Nothing to Disclose, Asif Rashid: Nothing to Disclose, Ahmed Kaseb: Nothing to Disclose, Manal Hassan: Nothing to Disclose

2022 | FACTORS ASSOCIATED WITH OBTAINING LOWER IQR-CAP VALUES IN THE DETECTION OF HEPATIC STEATOSIS BY TRANSIENT ELASTOGRAPHY

Iván López-Méndez[1] Eva Juárez-Hernández[1] Juan Romero-Flores[1] Graciela Castro-Narro[1] Misael Uribe[1]

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Background: Controlled attenuation parameter (CAP) has been developed as an attainable and accurate noninvasive method for detecting hepatic steatosis. The aim of the study was to determine factors associated with non-obtaining lower IQR-CAP values in liver steatosis detection by transient elastography (TE). **Methods:** Retrospective revision of medical records of successful TE studies performed from January 2015 to December 2019 for liver steatosis screening. Demographic and anthropometrical data and quality variables of the studies

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were collected. A logistic regression analysis was performed to determine independent associations with non-obtaining IQR-CAP <30, <20, and <10 in all patients and then adjusted for obese patients and severity of liver steatosis. **Results:** A total of 5061 studies were analyzed; the prevalence of overweight was 43.3% (n=2193), and obesity 16.8% (n=848). The median CAP was 251 [IQR 213–294] dB, with a median IQR-CAP 26 [IQR 20–33] dB. Liver steatosis prevalence was 39.4% (n =1996). In all studies, obesity was an independent factor for non-obtaining IQR-CAP <30 and <20. In the adjusted analysis for overweight and obesity, the presence of S3 (≥313 dB/m) was an independent factor for non-obtaining IQR-CAP <30 and <10; meanwhile, in steatosis severity analysis, obesity was associated with non-obtaining IQR-CAP <30 and <20, only in patients with S2 (≥288 dB/m) obesity was independently associated with non-obtaining IQR-CAP <30. (Table) **Conclusion:** In liver steatosis detection by TE, steatosis severity and obesity are factors associated with non-obtaining lower values of IQR-CAP than established as basic reliability criteria (<40), and it seems to be that steatosis and obesity influence each other.

Factors associated with non-obtain IQR <30, IQR<20 and IQR<10

Factor	Univariate		Multivariate	
	OR (CI 95%)	p	OR (CI 95%)	p
All patients (n=5061)				
Correct probe + IQR<30				
Obesity	1.34 (1.22-1.47)	**≤0.001**	1.59 (1.31-1.93)	**≤0.001**
S1	1.13 (0.99-1.29)	0.064	1.58 (1.19-2.10)	**0.001**
Correct probe + IQR<20				
Obesity	1.14 (1.10-1.18)	**≤0.001**	1.82 (1.47-2.27)	**≤0.001**
Overweight (n=2193)				
Correct probe + IQR<30				
Male	1.18 (1.02-1.36)	**0.017**	1.24 (1.01-1.52)	**0.032**
S3	1.27 (1.10-1.47)	**0.001**	1.36 (1.06-1.74)	**0.015**
Obesity (n=848)				
Correct probe + IQR<10				
skPa >8	1.10 (1.04-1.28)	**0.027**	3.86 (1.05-14.08)	**0.041**
S3	1.02 (1.00-1.05)	**0.018**	3.77 (1.09-12.98)	**0.035**
S2 (n=548)				
Correct probe + IQR<30				
Obesity	1.26 (1.00-1.57)	0.060	1.50 (1.04-2.17)	**0.028**

S1 ≥268 dB/m; S2≥288 dB/m; S3≥313 dB/m.

Disclosures: Iván López-Méndez: Nothing to Disclose, Eva Juárez-Hernández: Nothing to Disclose, Juan Romero-Flores: Nothing to Disclose, Graciela Castro-Narro: Nothing to Disclose, Misael Uribe: Nothing to Disclose

2023 | FRAMINGHAM FIBROSIS INDEX FOR METABOLIC DYSFUNCTION ASSOCIATED STEATOTIC LIVER DISEASE: VALIDATION IN LARGE NATIONWIDE COHORT

Krisyah Clemons[1] Madeleine Haff[2] Ligong Chen[3] Paul Muntner[3] Michelle Long[4]

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Background: Metabolic dysfunction associated steatotic liver disease (MASLD) is a contributor to liver disease, and non-invasive predictors of liver fibrosis such as the Fibrosis 4 (FIB-4) require blood tests. In this study, we report the validation of a screening tool, the Framingham Fibrosis Index (FFI) to identify clinically meaningful liver fibrosis on vibration controlled transient elastography (VCTE). **Methods:** We used data from 6,384 NHANES 2017 to 2020 participants who consumed fewer than 14 (women) or 21 (men) alcoholic drinks per week with

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VCTE readings and data needed to estimate the FFI including age, gender, body mass index (BMI), diabetes, and systolic blood pressure (SBP). Discrimination metrics were used to calculate the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and C statistic of the FFI for identifying a liver stiffness measurement (LSM) >8.0 kilopascals (kPa) on VCTE. The test characteristics of FIB-4 >1.3 or >2.67 were also assessed. **Results:** NHANES participants had a mean age of 47.3 years and 51.7% were women. Mean BMI was 29.5 (standard error 0.2), 12.1% had diabetes, and the prevalence of LSM > 8.0 kPa was 8.9%. Using a probability level of 0.06 which was selected for high sensitivity, the FFI had a sensitivity of 91.6%, a specificity of 38.4%, PPV of 12.7% and NPV of 97.9%. At a probability level of 0.06, FIB-4 >1.3 had a sensitivity of 89.5%, specificity 22.5%, PPV of 14.4% and NPV of 93.6%, and FIB-4>2.67 had a sensitivity of 89.5%, specificity of 22.4%, PPV of 37.7% and NPV of 78.1% (Table 1). The C statistic was higher for the FFI (0.78) compared with FIB-4 >1.3 (0.69) and FIB-4 >2.67 (0.57). **Conclusion:** The FFI identified clinically meaningful fibrosis on VCTE with higher sensitivity and specificity than FIB-4, providing a practical approach to identify individuals at risk for clinically meaningful liver fibrosis from MASLD.

Table 1 – Test characteristics of Framingham Fibrosis Index and Fibrosis-4 in identifying vibration controlled transient elastography > 8.0 kilopascals

Screening index	Sensitivity*	Specificity*	PPV*	NPV*	C statistic
FFI	91.6%	38.4%	12.7	97.9	0.78
FIB-4 >1.3	89.5%	22.4%	14.4	93.6	0.69
FIB-4 > 2.67	86.6%	25%	37.7	78.1	0.57

FFI: Framingham fibrosis index; FIB-4: fibrosis 4 test; PPV: positive predictive value; NPV: negative predictive value

* Sensitivity, specificity, PPV, and NPV at a probability level of 0.06.

Disclosures: Krisyah Clemons: Nothing to Disclose, Madeleine Haff: Nothing to Disclose, Ligong Chen: Nothing to Disclose, Paul Muntner: Nothing to Disclose, Michelle Long: Novo Nordisk A/S: stock

2024 | AUTOMATED DIGITAL ANALYSIS OF SHH-INJURED AREA CORRELATES WITH CONVENTIONAL AND DIGITAL PATHOLOGIES IN MASLD AND MASH PATIENTS

Amon Asgharpour[1] Cindy Serdjebi[2] Bastien Lepoivre[2] Carolin Lackner[3] Florine Chandes[2] Arun Sanyal[1]

[1]Virginia Commonwealth University, [2]Biocellvia, [3]HistologiX

Background: Sonic hedgehog (Shh) pathway is involved in the progression of metabolic-dysfunction associated steatotic liver disease (MASLD) and its expression was shown to increase with disease severity. A previous computer-assisted morphometry study on 50 liver biopsies demonstrated that Shh expression was associated with ballooning and fibrosis. However, the analysis only considered limited typical hepatic parenchyma. In this study, 258 whole slide images of Shh-labeled liver biopsies were analyzed. **Methods:** Liver biopsies from patients with an MRI-proton density fat fraction ≥ 8% were collected. The biopsies were scored by a blinded expert pathologist according to the NASH CRN, and considered as MASH if the NAFLD activity score was ≥4, with at least 1 point for steatosis, ballooning and inflammation. Sections stained with picrosirius red, H&E and anti-Shh antibody were digitized at X20. MorphoQuant™, a fully automated and deterministic AI, was applied on the liver biopsies for detection and quantification of Shh-injured area and other MASH features from whole slide images. A 120-µm safety margin was automatically removed from all biopsies before analysis to avoid Shh edge effect. The quantitative data of Shh expression and Shh-injured area were thus compared to the pathologist's reading and MorphoQuant™ features using the Spearman's correlation test. **Results:** 258 biopsies were processed, including 145 MASH. Shh and Shh-injured area ranged from 0.168 to 82.95 and from 0 to 155.98 ‰ of the total liver section, respectively. Interestingly, MASH patients had both higher Shh and larger injured area than MASLD patients (6.80 vs 14.89 ‰; 4.71 vs 17.75 ‰, respectively; p-values < 0.0001 for both). Both readouts were significantly associated with fibrosis, ballooning, lobular inflammation, (*rho* = 0.489, 0.51, and 0.394 respectively, p < 0.0001) but not steatosis (Figure 1). They also correlated with total collagen, perivascular and septal collagens, as well as hepatic crown-like structures (*rho* = 0.53, 0.46, 0.48 and 0.49, respectively, p < 0.0001) as provided

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by digital pathology. **Conclusion:** The current study confirmed the correlation of Shh expression with fibrosis, ballooning and inflammation using an unbiased technique where the whole liver tissue was submitted for analysis. Longitudinal studies are required to investigate the potential prognostic and predictive values of Shh-injured area in MASH patients.

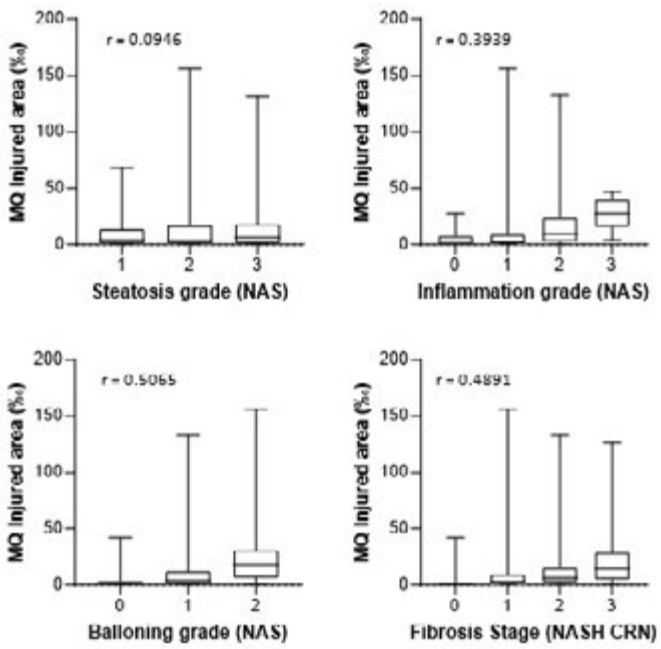

Figure 1. Spearman's correlations of NASH CRN components and fibrosis with Shh-injured area.

Disclosures: Amon Asgharpour: Galectin: Clinical Endpoint Committee, NovoNordisk: Advisor, Madrigal: Advisor, Cindy Serdjebi: Biocellvia: Employee, Bastien Lepoivre: Biocellvia: Employee, Carolin Lackner: Nothing to Disclose, Florine Chandes: Nothing to Disclose, Arun Sanyal: Genfit, Akarna, Tiziana, Durect, Inversago, Hemoshear, North: Stock - publicly traded company, Astra Zeneca (60K), Boston Pharmaceutical

2025 | VALIDATION OF THE DIAGNOSTIC ENRICHMENT UTILITY OF NIS2+® FOR VARYING PHENOTYPES OF METABOLIC DYSFUNCTION ASSOCIATED STEATOTIC LIVER DISEASE

Amon Asgharpour[1] Rohit Loomba[2] james bolognese[3] Katherine Yates[4] Roberto Calle[5] Alexander Pasek[6] Tania Kamphaus[6] Claude Sirlin[2] Anthony Samir[7] Theodore Pierce[7] Michael Middleton[2] Kathryn Fowler[2] Sarah Sherlock[8] Brent Neuschwander-Tetri[9] Bryce Hatfield[1] Kris Kowdley[10] James Tonascia[4] Sudha Shankar[11] Arun Sanyal[1]

[1]Virginia Commonwealth University, [2]University of California, San Diego, [3]Cytel, [4]Johns Hopkins University, [5]Regeneron, [6]FNIH, [7]Massachusetts General Hospital, [8]Pfizer, [9]Saint Louis University, [10]Liver Institute Northwest, [11]Astra Zeneca

Background: NIS2+® is based on two components (mir34a, YKL40) of the 4-component NIS4® (mir34a, Hgb A1c, α2-macroglobulin, YKL40) that was developed to identify those with MASH with NAFLD activity score (NAS) ≥ 4 and fibrosis stages ≥ 2 (at-risk MASH). Its diagnostic utility for at-risk MASH and its sub-phenotypes has not been independently evaluated. **Aims:** The diagnostic performance of NIS2+® for at-risk MASH and its histological components was evaluated. Three hypotheses were tested: (1) NIS2+ diagnoses at-risk MASH and its components with AUROC > 0.7 with C.I. that do not intersect 0.5, (2) NIS2+ performance is superior to ALT for MASH and NAS ≥ 4, and to FIB-4 for fibrosis stage ≥ 2, ≥ 3 and 4, (3) NIS2+ performance is non-inferior to NIS4. **Methods:** A retrospective analysis of samples from the NASH CRN curated to have balanced distribution of fibrosis stage was performed. Histology was read per the CRN protocol by its pathology committee masked to clinical data. Contemporaneous FIB-4 and ALT were measured in same serum sample as NIS2+® and NIS4®. Sensitivity/Specificity for various phenotypes were computed along with AUROCs. PPV/NPV were computed in current study population and modeled for various disease prevalence. AUROCs were compared using Delong

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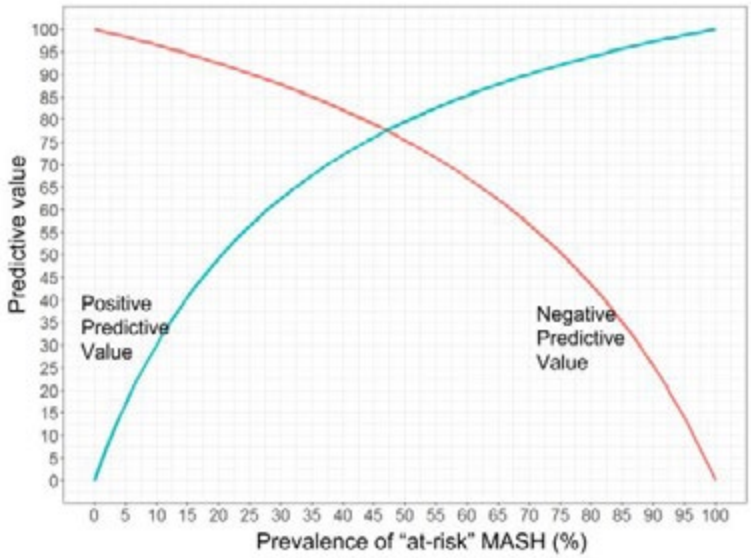
test. **Results:** A total of 810 individuals (MASH n=630, at-risk MASH n= 431, NAS ≥ 4 n= 431, ≥ stage 2 fibrosis n=562) were studied. The sensitivity and specificity for at-risk MASH for NIS2+® was 73.5% and 81% (AUROC 0.825 (95% CI 0.79-0.85) p< 0.001 for AUROC > 0.5), optimal cut-point=0.7, PPV/NPV= 81.5/72.9%. With specificity constrained at 90% sensitivity was 52.7%; conversely, with sensitivity constrained at 90%, specificity was 57.8%. Its performance (sensitivity/specificity) for the subcomponents were: MASH (67.6/87.8%), NAS ≥ 4 (73.5/81%), ≥ stage 2 fibrosis (79.5/84.3), ≥ stage 3 (81/64.8%), cirrhosis (87.1/47.5%). The AUROC for NIS2+® was superior to ALT for (MASH: 0.83 vs 0.68, p< 0.001, NAS ≥ 4 (0.82 vs 0.72, p< 0.001) and FIB-4 for fibrosis stage ≥ 2 (0.86 vs 0.8, p< 0.001) but not for ≥ stage 3 or cirrhosis. NIS2+® was non-inferior to NIS4® except for NAS ≥ 4 sub-phenotype where it was better (0.82 vs 0.80, p< 0.01). **Conclusion:** NIS2+® significantly enriches the likelihood of identifying those with at risk MASH in a population with MASLD. Its performance is weighted towards identification of those with stage 2 fibrosis and is as good as its predecessor NIS4® for its intended use.



Diagnostic utility of NIS2+

Disclosures: Amon Asgharpour: Galectin: Clinical Endpoint Committee, NovoNordisk: Advisor, Madrigal: Advisor, Rohit Loomba: Eli Lilly and Company: Consultant, 89bio: Consultant, Aardvark Therapeutics: Consultant, Altimmune: Consultant, Alnylam/Regeneron: Consultant, Amgen: Consultant, Arrowhead Pharmaceuticals: Consultant, AstraZeneca: Consultant, Bristol Myers Squibb: Consultant, CohBar: Consultant, Eli Lilly: Consultant, Galmed Pharmaceuticals: Consultant, Gilead: Consultant, Glympse Bio: Consultant, Hightide: Consultant, Inipharma: Consultant, Intercept: Consultant, Inventiva: Consultant, Ionis: Consultant, Janssen, Inc.: Consultant, Madrigal Pharmaceuticals: Consultant, Merck, Metacrine, Inc.: Consultant, NGM Biopharmaceuticals: Consultant, Novartis: Consultant, Novo Nordisk: Consultant, Pfizer: Consultant, Sagimet Biosciences: Consultant, Terns Pharmaceuticals: Consultant, Theratechnologies and Viking Therapeutics: Consultant, 89bio: Stock options, Sagimet Biosciences: Stock options, Arrowhead Pharmaceuticals: Research grant, AstraZeneca: Research grant, Boehringer Ingelheim: Research grant, Bristol Myers Squibb: Research grant, Eli Lilly: Research grant, Galectin Therapeutics: Research grant, Galmed Pharmaceuticals: Research grant, Gilead: Research grant, Hanmi: Research grant, Intercept: Research grant, Inventiva: Research grant, Ionis: Research grant, Janssen, Inc.: Research grant, Madrigal Pharmaceuticals: Research grant, Merck: Research grant, NGM Biopharmaceuticals: Research grant, Novo Nordisk: Research grant, Pfizer: Research grant, Sonic Incytes: Research grant, Terns Pharmaceuticals: Research grant, LipoNexus, Inc.: Co-founder, james bolognese: Napo Therapeutics: Consultant, Vascular Therapies: Consultant, Paradigm: Consultant, Katherine Yates: Nothing to Disclose, Roberto Calle: Regeneron Pharmaceuticals: Employee, Regeneron Pharmaceuticals: Stock - publicly traded company, Pfizer, Inc: Stock - publicly traded company, Alexander Pasek: Nothing to Disclose, Tania Kamphaus: Nothing to Disclose, Claude Sirlin: ACR Bayer GE Pfizer: Grant/Research Support, Gilead Philips Siemens: Grant/Research Support, OrsoBio: Independent Contractor, Enanta Gilead ICON Intercept Nusirt Shire Synageva Takeda: Independent Contractor, AMRA: Consultant, Exact Sciences Pfizer: Consultant, Ascelia Pharma AB Blade Boehringer Epigenomics Guerbet: Consultant, Livivos: Consultant, Livivos: Executive role, Livivos: Stock – privately held company, Medscape Wolters Kluwer: Royalties or patent beneficiary, Educational

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symposia: Speaking and Teaching, GE Siemens Bayer: Provision of equipment or contrast agent for research, HealthProMatch: Speaking and Teaching, Butterfly Network: Provision of equipment for research, Anthony Samir: Nothing to Disclose, Theodore Pierce: Wolters Kluwer: reviewed article on contrast reaction management, General Electric: Grant support for unrelated ultrasound research, AutonomUS Medical Technologies: Equity and Consultant, Michael Middleton: Nothing to Disclose, Kathryn Fowler: Bayer: Consultant, Ascelia Pharmaceutical: Consultant, guerbet: Consultant, Sarah Sherlock: Nothing to Disclose, Brent Neuschwander-Tetri: Akero: Consultant, Aligos: Consultant, Arrowhead: Consultant, Corcept: Consultant, GSK: Consultant, Hepion: Consultant, HIstoIndex: Consultant, Madrigal: Consultant, Madrigal: Grant/Research Support, Merck: Consultant, Mirum: Consultant, Sagimet: Consultant, Senseion: Consultant, HepGene: Stock – privately held company, HeptaBio: Stock – privately held company, Bryce Hatfield: Nothing to Disclose, Kris Kowdley: Boston Scientific: Grant/Research Support, Corcept: Grant/Research Support, CymaBay: Grant/Research Support, Genfit: Grant/Research Support, Gilead: Grant/Research Support, GSK: Grant/Research Support, Hanmi: Grant/Research Support, Intercept: Grant/Research Support, Ipsen: Grant/Research Support, Janssen: Grant/Research Support, Madrigal: Grant/Research Support, Mirum: Grant/Research Support, Novo Nordisk: Grant/Research Support, NGM: Grant/Research Support, Pfizer: Grant/Research Support, Pliant Therapeutics: Grant/Research Support, Terns: Grant/Research Support, Viking: Grant/Research Support, Zydus: Grant/Research Support, 89bio Inc: Grant/Research Support, UpToDate: Royalties or patent beneficiary, CymaBay: Consultant, Enanta: Consultant, Genfit: Consultant, Gilead: Consultant, HighTide: Consultant, Inipharm: Consultant, Intercept: Consultant, Ipsen: Consultant, Madrigal: Consultant, Mirum: Consultant, NGM: Consultant, Pliant Therapeutics: Consultant, Pfizer: Consultant, Protagonist: Consultant, Zydus: Consultant, 89bio Inc: Consultant, AbbVie: Payment or honoraria, Gilead: Payment or honoraria, Intercept: Payment or honoraria, US Department of Justice: Payment for expert testimony, CTI: Advisor, Medpace: Advisor, Labcorp: Advisor, Worldwide Clinical Trials: Advisor, Inipharm: Stock – privately held company, Velacur: Received equipment, materials, drugs, medical writing, gifts, James Tonascia: Nothing to Disclose, Sudha Shankar: Nothing to Disclose, Arun Sanyal: Genfit, Akarna, Tiziana, Durect, Inversago, Hemoshear, North: Stock - publicly traded company, Astra Zeneca (60K), Boston Pharmaceutical

2026 | PERFORMANCE METRICS OF SPLEEN STIFFNESS MEASUREMENT (SSM) OBTAINED BY TRANSIENT ELASTOGRAPHY IN PATIENTS WITH METABOLIC DYSFUNCTION ASSOCIATED STEATOTIC LIVER DISEASE (MASLD)

Amon Asgharpour[1] Laura Wilson[2] Raj Vuppalanchi[3] Katherine Yates[2] Srinivasan Dasarathy[4] Kris Kowdley[5] Anna Mae Diehl[6] Rohit Loomba[7] Brent Neuschwander-Tetri[8] Norah Terrault[9] Bilal Hameed[10] Emily Mitchell[2] Oscar Cummings[3] Cindy Behling[7] James Tonascia[2] Arun Sanyal[1]

[1]Virginia Commonwealth University, [2]Johns Hopkins University, [3]Indiana University, [4]Cleveland Clinic, [5]Liver Institute Northwest, [6]Duke University, [7]University of California, San Diego, [8]Saint Louis University, [9]University of Southern California, [10]University of California, San Francisco

Background: Spleen stiffness measurement (SSM) using vibration-controlled transient elastography (VCTE) is a relatively recent innovation used as a surrogate measure of the severity of fibrosis and portal venous pressure in patients with chronic liver disease such as MASLD. The technical performance of SSM has not been fully established in patients with MASLD, where obesity and lack of splenomegaly could be potential confounding factors. Aims: To perform a multi-center prospective study to define (1) the reproducibility and repeatability of SSM in MASLD, and the reasons for failed examinations, and (2) the relationship of SSM to liver stiffness measurements (LSM) by VCTE, FIB-4, and histologic fibrosis stage. Our aims were to perform a multi-center prospective study to define (1) the reproducibility and repeatability of SSM in MASLD, and the reasons for failed examinations, and (2) the relationship of SSM to liver stiffness measurements (LSM) by VCTE, FIB-4, and histologic fibrosis stage. **Methods:** Adult patients with histologically-confirmed MASLD were enrolled in a substudy of the NIDDK NASH CRN Database 3 study; operators were trained and certified by EchosensÒ. Individuals were tested twice on the same day by the same operator and in a subset by a different operator. Factors related to the technical success of SSM were evaluated. Intra- and inter-operator variances were evaluated by Bland-Altman plots. SSM scores were related to LSM, FIB-4, and histologic fibrosis stages **Results:** A total of 561 participants were studied in whom SSM exam was successful in 398 (71%). Failure was associated with higher BMI, waist circumference, and platelet counts and with lower AST, ALT, and FIB-4. Reasons for failure included skin to capsule distance >25mm (n=51), inability to visualize spleen (n=49) and inability to obtain valid measurements (n=105). The mean (SD) SSM in successful exams was 29.9 (17.6) during

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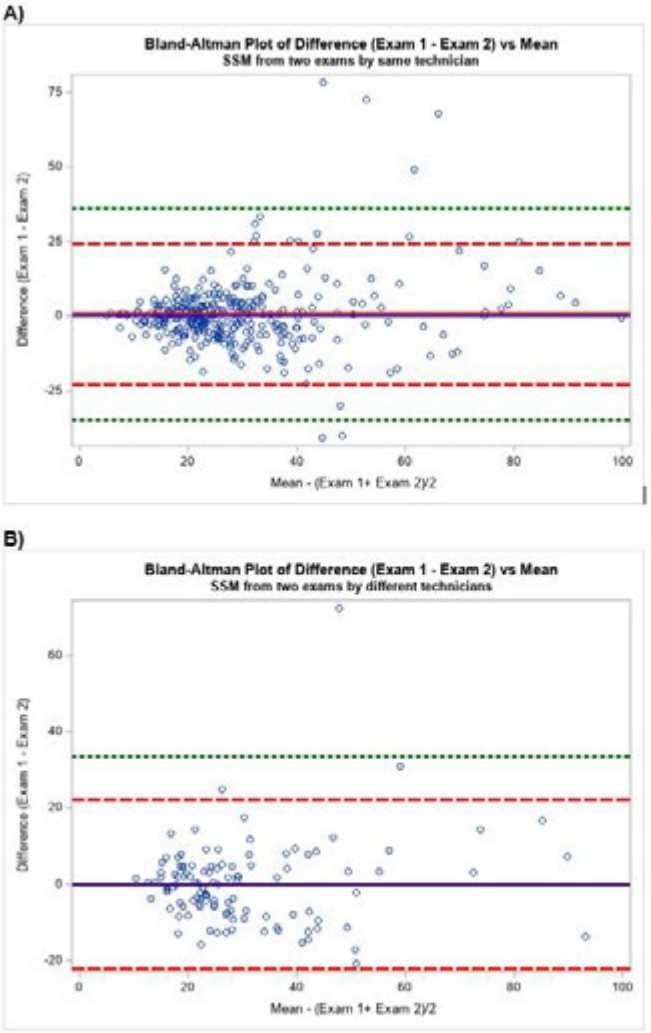
the first exam and 29.2 (15.8) at second exam by the same operator (median (SD) difference=0 (6.7); *rho*: 0.75) (n=325). The inter-rater concordance was similar (30.2 (17.3) vs 30.2 (16.1), median (SD) difference=0, *rho*: 0.7) (n=111). Bland-Altman plots (Fig 1.) showed good agreement between exams. SSM was higher in those with LSM≥8kPa vs. <8Kpa (mean 37 vs 25 kPa, p<0.001), and in those with FIB-4 >3.25 vs ≤3.25 (mean 50 vs 28 kPa, p< 0.001). SSM increased with each fibrosis stage (0-4), and was higher in those with clinically significant fibrosis (≥stage 2, p<0.001) and advanced fibrosis (stage 3 or 4, p<0.001) **Conclusion:** The technical success of SSM measurements are affected by obesity and ability to visualize the spleen. SSMs show good inter- and intra-operator agreement, and a higher SSM is associated with LSM ≥8 kPa, FIB-4 >3.2, and in those with clinically significant fibrosis.



Bland-Altman plots of the difference between first and second readings of SSM values against the mean of the two values; 95% of the difference between 1st and 2nd exams shown in A) occurred within ±13.2kPa (same technician) and within ±16.9 kPa (different technicians) shown in B), with no bias over the range of values (5-100kPa).

Disclosures: Amon Asgharpour: Galectin: Clinical Endpoint Committee, NovoNordisk: Advisor, Madrigal: Advisor, Laura Wilson: Nothing to Disclose, Raj Vuppalanchi: Eli LIlly: Advisor, GSK: Advisor, Madrigal: Advisor, Zydus Therapeutics: Grant/Research Support, Galectin Therapeutics: Grant/Research Support, Kowa: Grant/Research Support, Takeda: Grant/Research Support, GSK: Consultant, UBC: Consultant, Katherine Yates: Nothing to Disclose, Srinivasan Dasarathy: Nothing to Disclose, Kris Kowdley: Boston Scientific: Grant/Research Support, Corcept: Grant/Research Support, CymaBay: Grant/Research Support, Genfit: Grant/Research Support, Gilead: Grant/Research Support, GSK: Grant/Research Support, Hanmi: Grant/Research Support, Intercept: Grant/Research Support, Ipsen: Grant/Research Support, Janssen: Grant/Research Support, Madrigal: Grant/Research Support, Mirum: Grant/Research Support, Novo Nordisk: Grant/Research Support, NGM: Grant/Research Support, Pfizer: Grant/Research Support, Pliant Therapeutics: Grant/Research Support, Terns:

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Has not ended; >$10,000 relationship with HeptaBio; Has not ended, Rohit Loomba: Eli Lilly and Company: Consultant, 89bio: Consultant, Aardvark Therapeutics: Consultant, Altimmune: Consultant, Alnylam/Regeneron: Consultant, Amgen: Consultant, Arrowhead Pharmaceuticals: Consultant, AstraZeneca: Consultant, Bristol Myers Squibb: Consultant, CohBar: Consultant, Eli Lilly: Consultant, Galmed Pharmaceuticals: Consultant, Gilead: Consultant, Glympse Bio: Consultant, Hightide: Consultant, Inipharma: Consultant, Intercept: Consultant, Inventiva: Consultant, Ionis: Consultant, Janssen, Inc.: Consultant, Madrigal Pharmaceuticals: Consultant, Merck, Metacrine, Inc.: Consultant, NGM Biopharmaceuticals: Consultant, Novartis: Consultant, Novo Nordisk: Consultant, Pfizer: Consultant, Sagimet Biosciences: Consultant, Terns Pharmaceuticals: Consultant, Theratechnologies and Viking Therapeutics: Consultant, 89bio: Stock options, Sagimet Biosciences: Stock options, Arrowhead Pharmaceuticals: Research grant, AstraZeneca: Research grant, Boehringer Ingelheim: Research grant, Bristol Myers Squibb: Research grant, Eli Lilly: Research grant, Galectin Therapeutics: Research grant, Galmed Pharmaceuticals: Research grant, Gilead: Research grant, Hanmi: Research grant, Intercept: Research grant, Inventiva: Research grant, Ionis: Research grant, Janssen, Inc.: Research grant, Madrigal Pharmaceuticals: Research grant, Merck: Research grant, NGM Biopharmaceuticals: Research grant, Novo Nordisk: Research grant, Pfizer: Research grant, Sonic Incytes: Research grant, Terns Pharmaceuticals: Research grant, LipoNexus, Inc.: Co-founder, Brent Neuschwander-Tetri: Akero: Consultant, Aligos: Consultant, Arrowhead: Consultant, Corcept: Consultant, GSK: Consultant, Hepion: Consultant, HIstoIndex: Consultant, Madrigal: Consultant, Madrigal: Grant/Research Support, Merck: Consultant, Mirum: Consultant, Sagimet: Consultant, Senseion: Consultant, HepGene: Stock – privately held company, HeptaBio: Stock – privately held company, Norah Terrault: Grant/Research Support relationship with Eiger Pharmaceuticals; 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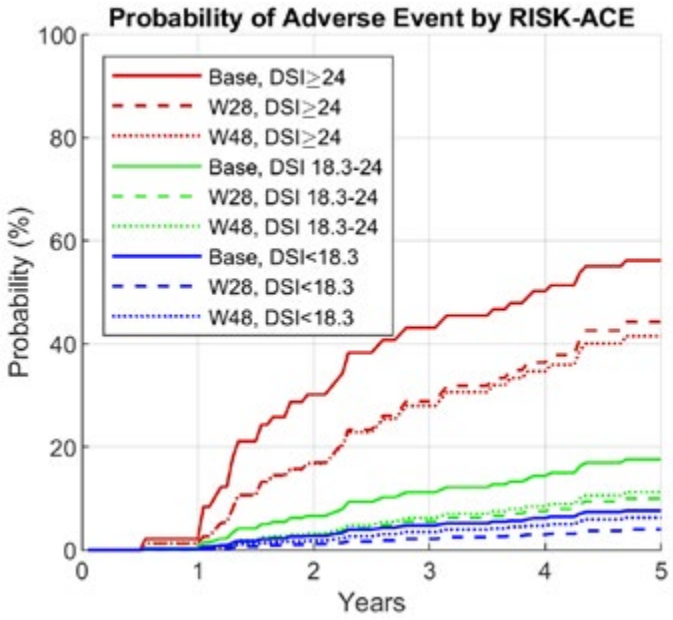
2027 | RESMETIROM THERAPY OF MASH-ASSOCIATED CHILD PUGH A CIRRHOSIS REDUCES ESTIMATED RISK FOR CLINICAL OUTCOME BASED ON HEPQUANT RISK ACE MODEL ◆

Gregory Everson[1] Michael McRae[2] Rebecca Taub[3]

[1]HepQuant, [2]Custom DX Solutions, [3]Madrigal Pharmaceuticals

Background: Resmetirom has been FDA-approved for use in F2/F3 MASH and is under study for use in cirrhosis. The HepQuant DuO test quantifies liver function and physiology from the clearance of orally administered isotopes of cholate. In this study, MAESTRO-NAFLD-1 (NCT04197479), an open label, single arm study of resmetirom in Child Pugh A cirrhosis, we used serial monitoring with DuO to quantify changes in liver function and portal-systemic shunting. **Methods:** The Disease Severity Index (DSI) from DuO was measured in 23 subjects with compensated MASH cirrhosis (eligibility required at least 3 metabolic risk factors, and MASH cirrhosis diagnosed on liver biopsy or according to accepted criteria) at baseline and at 28 (W28) or 48 weeks (W48). For each test, oral deuterium-labelled cholic acid (d4-CA) was administered, blood was sampled at 20 and 60 minutes, serum d4-CA concentrations were measured by LC-MS/MS, and test parameters including DSI were calculated. A Cox proportional hazards regression model (manuscript in progress) linking DSI to clinical outcome, Risk for Adverse Clinical Event (RISK ACE), was developed from 220 HCV subjects with 52 clinical decompensating events in the HALT-C trial. RISK ACE was evaluated for each of these 23 subjects in MAESTRO-NAFLD-1. **Results:** At W48 of resmetirom, 39% of subjects showed improvement from baseline (DSI reduction >2; Chi-square, p=0.046), 44% had stable hepatic function (ΔDSI within ±2), and 17% showed worsening (DSI increase >2). The 2-year risk of adverse clinical events decreased at W48 with resmetirom treatment in 20 of 23 subjects, with a significant reduction in average risk from baseline (−7.9%, p<0.001). Subjects with greater hepatic impairment by DSI at baseline showed greater reduction in RISK ACE at W28 and W48 (Figure). At W48, the stabilization or change in DSI from baseline to W48 lowered the estimation of an adverse clinical event within 2 years by 1.4% for low risk (baseline DSI <18.3, p=0.057), 3.3% for moderate risk (baseline DSI 18.3–24, p<0.001), and 15.3% for high risk (baseline DSI ≥24, p<0.001). **Conclusion:** This study demonstrated that 48 weeks of resmetirom in MASH-associated Child Pugh A cirrhosis is associated with estimated reduction in adverse clinical events as assessed by HepQuant's RISK ACE Model. These results show potential for DuO and RISK ACE to provide a sensitive and interpretable metric of risk in monitoring patients during treatment trials.



Disclosures: Gregory Everson: HepQuant LLC: Executive role, Michael McRae: HepQuant, LLC: Consultant, Rebecca Taub: Madrigal Pharmaceuticals: Employee, Madrigal Pharmaceuticals: Stock - publicly traded company, Madrigal Pharmaceuticals: Executive role

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2028 | THE ORAL CHOLATE CHALLENGE TEST IDENTIFIES THE MASH PATIENTS WITH ≥F3 FIBROSIS WITH GREATEST HEPATIC IMPAIRMENT WHO SHOW THE MOST BENEFIT FROM SHORT-TERM RENCOFILSTAT THERAPY

Gregory Everson[1] Stephen Harrison[2] Patrick Mayo[3] Todd Hobbs[3] Robert Foster[3] Michael McRae[4] Daren Ure[3]

[1]HepQuant, [2]University of Oxford, [3]Hepion Pharmaceuticals, Inc, [4]Custom DX Solutions

Background: Rencofilstat (RCF) is an antifibrotic cyclophilin inhibitor targeting MASH-related fibrosis. In MASH, liver dysfunction and altered portal physiology precede clinical complications. HepQuant DuO is a non-invasive, blood-based test of liver function, portal circulation, and portal-systemic shunting. In this study DuO quantified effects of RCF on liver function and physiology. **Methods:** 70 subjects with MASH and AGILE 3+ >0.53 (≥F3 fibrosis) were randomized 1:1:1 into 3 RCF treatment arms (75, 150, 225 mg/d) and underwent HepQuant SHUNT tests at baseline and days 60 and 120. Subjects were administered 40 mg of labeled cholate (CA) orally, and blood CA concentrations analyzed at 20 and 60 min for these DuO parameters: systemic and portal hepatic filtration rates (HFRs), disease severity index (DSI), hepatic reserve (HR), and portal systemic shunt (SHUNT%). Changes from baseline to 60 and 120 days were analyzed, and numerous other MASH non-invasive assessments were also collected. **Results:** Baseline characteristics revealed an advanced MASH population (Agile 3+ 0.73±0.15). Among subjects, 30.4% had significant hepatic functional impairment (DSI >18.3), 37.7% had increased portal-systemic shunting (SHUNT% >27%), and 23.2% had both. DuO results with 225 mg RCF revealed significant reductions after 60 and 120 days in DSI (−1.34, p=0.022; −1.61, p=0.019) and SHUNT% (–2.24%, p=0.043; –2.28%, p=0.094) in paired analysis (Table 1). Improved liver function (reduction of ≥2 DSI units) occurred in 10/18 subjects (55.6%) in the 225 mg group after 120 days (p=0.055). DuO test parameters showed the greatest improvement in subjects with the greatest baseline dysfunction (DSI >18.3) after 120 days with 225 mg RCF, with significant reductions in both DSI (–2.59, p=0.005) and SHUNT% (–4.75%, p<0.001). Additionally, there was a clear dose response in many of the other non-invasive assessments. **Conclusion:** RCF (225 mg) was associated with reduction in DSI and SHUNT% after 120 days, suggesting improvement in effective hepatic perfusion possibly due to fibrosis remodeling given RCF's anti-inflammatory and antifibrotic properties. These changes may be most effective in patients with more severe liver impairment. These results demonstrate the successful use of HepQuant DuO to assess hepatic function and the promise of RCF as a potential MASH treatment in patients with advanced fibrosis.

Dose Response and Time-Action of Rencofilstat Measured by HepQuant DuO in All Subjects and Subjects with Greatest Baseline Dysfunction (DSI >18.3)

Test Parameter	Day 60			Day 120		
	75 mg	150 mg	225 mg	75 mg	150 mg	225 mg
Change from Baseline, All Subjects						
n subjects	24	20	21	23	20	18
DSI	0.00	−0.49	**−1.34****	−0.47	0.24	**−1.61****
SHUNT% (%)	−1.64	−1.11	**−2.24****	−1.76	−0.65	−2.28*
Hepatic Reserve (%)	1.15	0.31	**2.87****	1.31	−1.10	**3.81****
Portal HFR (mL/min/kg)	−0.15	1.66	3.68*	1.05	0.66	2.41*
Systemic HFR (mL/min/kg)	−0.14*	0.00	**0.17****	−0.02	−0.09	**0.22****
Change from Baseline, Subjects with greatest baseline dysfunction						
n subjects	9	9	10	9	9	8
DSI	−0.74	0.15	−1.12	−0.44	0.48	**−2.59*****
SHUNT% (%)	−3.22	−0.61	−2.04	−2.96	−1.03	**−4.75******
Hepatic Reserve (%)	2.46	−0.32	2.71	1.83	−1.03	**6.78*****
Portal HFR (mL/min/kg)	1.10	−0.25	1.98	1.04	0.15	**3.96*****
Systemic HFR (mL/min/kg)	−0.09	−0.07	0.11	−0.15	−0.17	0.25

*p<0.10; **p<0.05; ***p<0.01; ****p<0.001

Abbreviations: DSI, Disease Severity Index; HFR, hepatic filtration rate; SHUNT%, portal-systemic shunting

Disclosures: Gregory Everson: HepQuant LLC: Executive role, Stephen Harrison: Nothing to Disclose, Patrick Mayo: Nothing to Disclose, Todd Hobbs: Hepion Pharmaceuticals: Employee, Diasome Pharmaceuticals: Executive role, Robert Foster: Hepion Pharmaceuticals, Inc.: Former CEO, Michael McRae: HepQuant, LLC: Consultant, Daren Ure: Nothing to Disclose

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2030 | AN AUTOMATIC TISSUE FOLDING DETECTION ALGORITHM TO AID AI SEGMENTATION MODELS

Kezia Hobson[1] Dylan Windell[1] Paul Aljabar[1] Rob Goldin[2] Kenneth Fleming[3] Caitlin Langford[1]

[1]Perspectum, [2]Imperial College London, [3]University of Oxford

Background: Folded tissue is present on many core biopsy slides, typically being introduced during sectioning. There are 2 main types of folding; 'large' characterised by a large region of 2 layers of overlapping tissue and 'concertina' characterised by many small dense regions. While folding has little impact on traditional pathology reporting, AI algorithms are prone to error within affected regions. Quality control of Whole Slide Images (WSIs) is an important but time-consuming step prior to running AI algorithms. To address this need, we have developed an automated fold detection algorithm for liver biopsies. **Methods:** Tiles containing known folded tissue were randomly selected from a large dataset (3 liver clinical trials) and extracted from WSIs. Tiles varied in fold type and stain (Haematoxylin and Eosin (H&E), Masson's Trichrome (TRC) and Picrosirius Red (PSR)). Each tile was converted to the HSV (Hue, Saturation and Value) colour space and colour-based thresholding was applied. A range of thresholds were used to determine the optimum one for each stain before calculating the fold as a percentage of the tissue. Validation was performed on 45 WSIs (9 PSR, 11 TRC and 25 H&E), 40 with known folds and the remaining 5 with no observed folding. Manual annotations of folds were curated using QuPath and converted into a percentage of the total tissue. The automated method was run on the same WSIs, and fold percentage was recorded. Bland-Altman analysis was used to assess agreement between manual annotations and the algorithm. **Results:** As can be seen in the Bland-Altman plot (Figure 1A), there is minimal bias (0.28) between the manually calculated tissue folding and the automated folding detection. Of the 40 WSIs with known folding, 37 WSIs had ≤2.5% difference between the automated and annotated measurements. Of the 3 WSIs with higher differences, 2 WSIs (1H&E and 1PSR) contained multiple large folds which are typically less dense than concertina folds and as a result, have gaps within the colour-based thresholding of the fold. The third WSI had overstained TRC. Of the 5 WSIs with no folding, 4 WSIs had 0% algorithm detected folds while 1 had 1.38% detected folding on a fibrotic capsule region. **Conclusion:** We can accurately determine the percentage of folded tissue present on a WSI across a range of commonly used stains from several laboratories (Figure 1B). Due to the accuracy, this can be utilised as an automated QC step in AI based pipelines in liver studies.

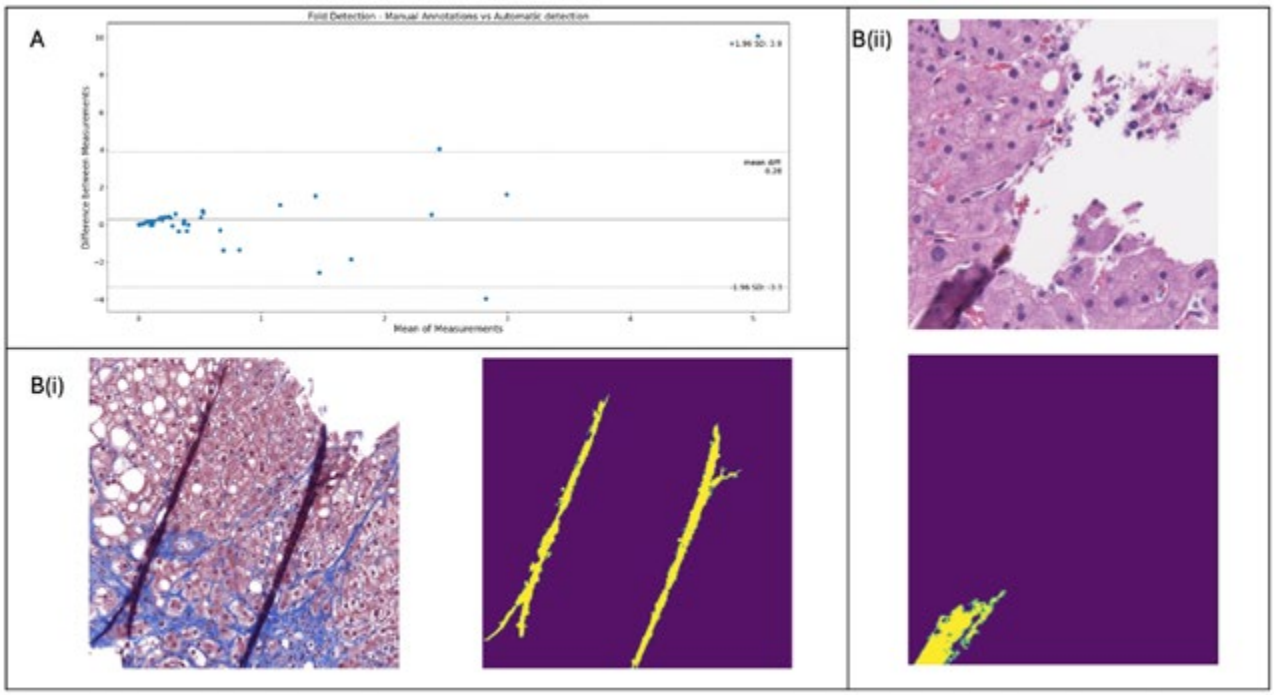

***Figure 1**: A - Bland-Altman plot showing agreement between Automatic and Manual detection methods. B(i) - Fold detection applied to TRC tile. B(ii) - Fold detection applied to H&E Tile.*

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Disclosures: Kezia Hobson: Perspectum Ltd: Employee, Dylan Windell: Perspectum: Employee, asd: Employee, Paul Aljabar: Nothing to Disclose, Rob Goldin: Nothing to Disclose, Kenneth Fleming: Nothing to Disclose, Caitlin Langford: Nothing to Disclose

2031 | AN AUTOMATIC OUT OF FOCUS DETECTION MODEL FOR ENABLING THE ASSESSMENT OF LIVER BIOPSIES

Kezia Hobson[1] Dylan Windell[1] Paul Aljabar[1] George Ralli[1] Rob Goldin[2] Kenneth Fleming[3] Caitlin Langford[1]

[1]Perspectum, [2]Imperial College London, [3]University Of Oxford

Background: As digitised workflows become predominant in clinical trials, new artefacts are introduced not observed in traditional glass workflows. Focus artefacts occur when glass slides are scanned to produce Whole Slide Images (WSIs). Quality Control (QC) of WSIs is required to enable robust reporting by pathologist. Manually checking WSIs for artefacts is time consuming and subject to error, thus automated QC is preferable. To address this, we developed an automated out of focus (OoF) detection algorithm for liver biopsies. **Methods:** A dataset of 100 in-focus tiles from 51 liver core WSIs were extracted randomly. Each tile was subsequently converted to greyscale and 3 levels of blurring were simulated using a gaussian filter, resulting in a final training (70%) and testing (30%) set of 400 tiles (288 Masson's Trichrome, 112 H&E). The entropy, skew and kurtosis of the tile was calculated before and after applying a further gaussian blur, as well as the change in entropy. These metrics were used to train a binary random forest classifier, which assigns each tile as OoF or not.
A validation study was run on 50 WSIs from 3 liver clinical trials (2 x MASLD/MASH and 1 mixed liver injury) and an additional 4 wedge biopsies. Ground truth labels were assigned to WSIs manually. Tiles including foreground tissue were classified as in focus or OoF and the resulting percentage was assigned a WSI level label. WSIs with >50% OoF tiles were flagged as inadequate quality for reporting. **Results:** The algorithm had a high prediction accuracy (98%) on the test set and validation study (98.1% with 0% false negative rate). Two incorrectly predicted tiles in the test data were highly fibrotic (liver capsule) where low levels of gaussian blur was applied and incorrectly classified as in focus. Five WSIs in the validation study were >50% OoF with 49 WSIs containing varying amounts of OoF but all below the threshold. **Conclusion:** Our Machine Learning (ML) model can correctly detect tiles that contain OoF regions on liver biopsies with high accuracy across differently stained WSIs from various laboratories. Due to the accuracy, this can be utilised as an automated QC step on WSIs for the diagnosis and monitoring of MASLD and MASH in clinical trials. While we trained on MASLD/MASH data, this ML algorithm could be applied to a wide range of clinical trials.

Disclosures: Kezia Hobson: Perspectum Ltd: Employee, Dylan Windell: Perspectum: Employee, asd: Employee, Paul Aljabar: Nothing to Disclose, George Ralli: Nothing to Disclose, Rob Goldin: Nothing to Disclose, Kenneth Fleming: Nothing to Disclose, Caitlin Langford: Nothing to Disclose

2032 | HISTOLOGICAL DIAGNOSTIC TOOL FOR DETECTING AND CHARACTERISING PORTAL TRACTS IN LIVER DISEASE USING ARTIFICIAL INTELLIGENCE

Dylan Windell[1] Alastair Magness[1] Abhishek Roy[1] Paul Aljabar[1] Timothy Kendall[2] Eve Fryer[3] Kenneth Fleming[4] Rob Goldin[5] Caitlin Langford[1]

[1]Perspectum, [2]University of Edinburgh, [3]Oxford University Hospitals NHS, [4]University of Oxford, [5]Imperial College London

Background: AI-driven digital workflows for liver biopsy grading and staging have the potential to produce more accurate and reproducible results than traditional assessments. In particular, the identification of Portal Tracts (PTs) in liver Whole Slide Images (WSIs) is important for the assessment of fibrosis, inflammation, and sample adequacy. However, this can be challenging due to variations in size, structure, and overall appearance which are further impacted by changes linked to disease severity. To address this, we developed an AI algorithm capable of determining the location, boundary, and other metrics of portal tracts. **Methods:** A training dataset of 43 H&E WSIs from three clinical cohorts were annotated for PTs using QuPath by three expert pathologists. All annotated PTs included two of the three key features of PTs (hepatic artery, portal vein, bile duct), while discrepancies between experts were resolved through the generation of a consensus geometry. Tiles were extracted from each

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WSI and given a binary classification depending on the presence of a PT within each tile according to pathologist consensus. A ResNet50 classification model was then trained to predict the presence of PTs in each tile. We applied the classifier via a sliding window to WSIs to produce multiple estimates of the presence of a PT at each pixel, which were averaged to generate a probability heatmap for the presence of PTs across tissue regions (Figure 1). We applied hysteresis thresholding to heatmaps to create semantic segmentation masks of PT content for the assessment of model accuracy. **Results:** Heatmaps provided a useful visual aid to the identification of PTs in unseen images. A ROC curve was generated for a validation set of six WSIs by applying a series of thresholds between 0-1, resulting in an AUC value of 0.92 and a balanced accuracy value of 0.87 at the optimised threshold. Quantitative performance of the model was assessed on a held-out test dataset of 12 WSIs with median precision, recall and F1 score of 70.3%, 63.1% and 61.3% respectively. **Conclusion:** Portal tract characterisation is key to establishing liver biopsy adequacy and accurately scoring liver fibrosis and inflammation. Our AI model for PT identification has the potential to assist in pathological review and clinical diagnosis.

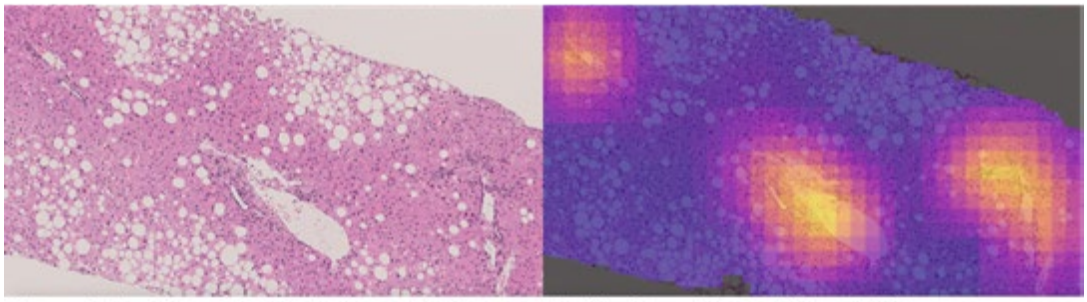

Figure 1: Heatmaps indicate tiles with the probability of containing PTs on WSIs.

Disclosures: Dylan Windell: Perspectum: Employee, asd: Employee, Alastair Magness: Nothing to Disclose, Abhishek Roy: Nothing to Disclose, Paul Aljabar: Nothing to Disclose, Timothy Kendall: Nothing to Disclose, Eve Fryer: Nothing to Disclose, Kenneth Fleming: Nothing to Disclose, Rob Goldin: Nothing to Disclose, Caitlin Langford: Nothing to Disclose

2033 | THE USE OF AI-ASSISTED DIGITAL PATHOLOGY IN DETERMINING THE INFLAMMATORY BURDEN IN LIVER DISEASE

Dylan Windell[1] Cayden Beyer[1] Sarah Larkin[1] Elizabeth Shumbayawonda[1] Paul Aljabar[1] Caitlin Langford[1] Andrea Dennis[1] Rob Goldin[2]

[1]Perspectum, [2]Imperial College London

Background: Liver pathology assessment remains the reference standard for assessing disease activity despite well reported limitations, notably the high variability between readers especially in the assessment of inflammation. Integrating AI algorithms into histopathology will assist pathologists in quantifying activity more objectively from Whole Slide Images (WSIs). In this study we utilised an AI trained algorithm to calculate the Inflammatory Burden (IB; percentage of inflammatory cells as a proportion of the entire tissue biopsy) across WSIs in Metabolic Dysfunction Associated Steatotic Liver Disease (MASLD) and Autoimmune Hepatitis (AIH). **Methods:** Inflammatory burden was quantified from Haematoxylin and Eosin (H&E) stained WSIs from patients with MASLD [N=204] and AIH [N=39]. Slides were also assessed by a pathologist for fibrosis (Ishak, 0-6) and inflammation (Batts and Ludwig score for AIH and modified HAI for MASLD Portal/Lobular, 0-4). Correlation between histological read and IB was assessed using Pearson correlation. Association of IB with traditional scoring for inflammation and fibrosis were assessed using Mann–Whitney U tests (Figure 1). **Results:** Overall grading on lobular inflammation correlated with IB (r = 0.60). There was a significant difference in the IB between MASLD and AIH. The IB, when comparing across lobular inflammation scores, was significantly higher in AIH patients than patients with MASLD (Figure 1B). When matching by fibrosis and portal and lobular inflammation scores, patients with AIH had higher IB than MASLD cases (4.95% and 1.74% respectively, p<0.001). Elevated IB is apparent in AIH across all combinations of fibrosis or inflammation scores, for example, it is 6.39% in AIH and 1.93% (p<0.001) in MASLD/MASH when matching for lobular inflammation (1≤3) and fibrosis (2≤5) (Figure 1C). **Conclusion:** Our findings show that, as expected, the total level of inflammation is elevated in AIH compared to MASLD. Importantly, this is also the case when matching cases for the same grade from histology reads; a lobular

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inflammatory score of 3 for a patient with AIH may have considerably higher IB than an individual with MASLD with the same inflammatory grade. Our IB metric shows that regardless of site and independent of pathologists, it correlates with the histology and inflammation score. The use of non-invasive approaches to quantify inflammation are becoming more prevalent, however, the low levels of IB that are present in MASLD need to be considered and thus will require a high degree of sensitivity to measure an anticipated effect size or impact of anti-inflammatory treatments.

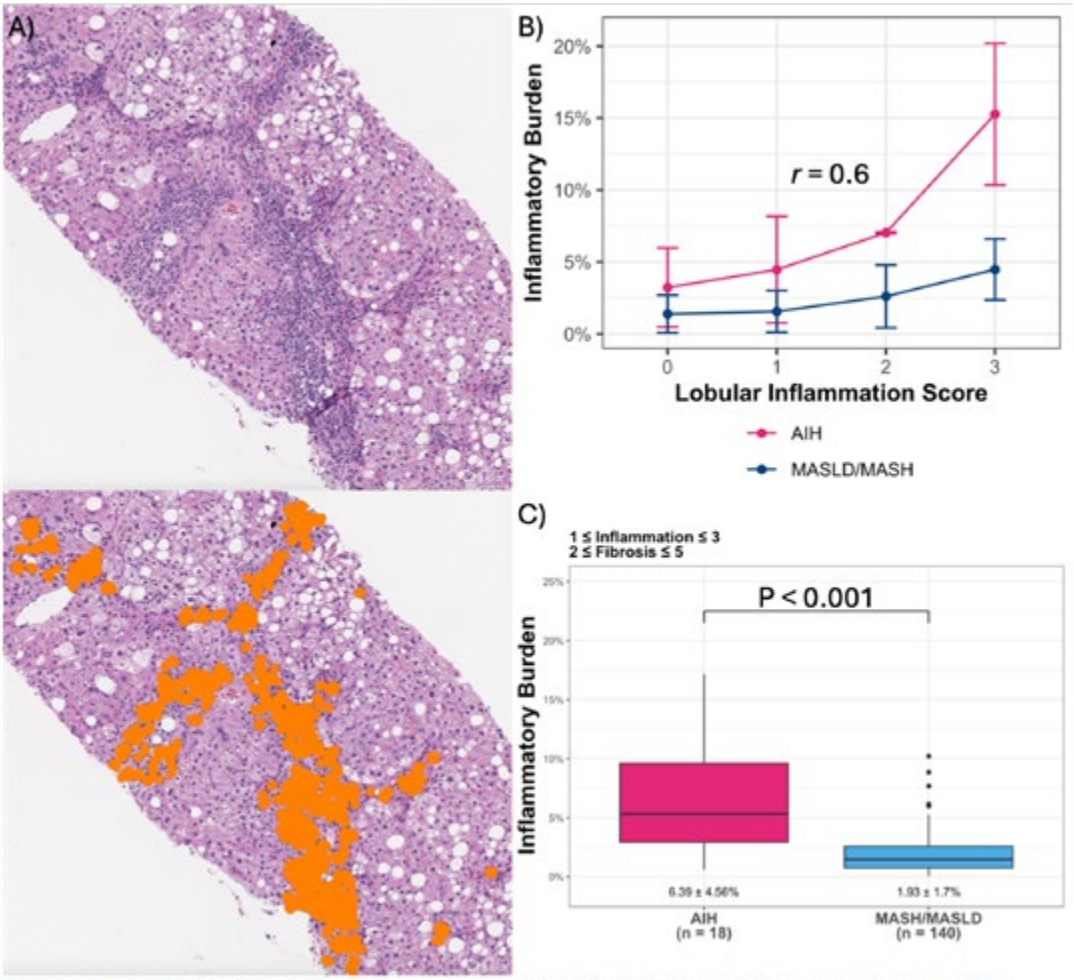

Figure 1: *(A) The inflammatory burden calculated from AI algorithms across WSIs. (B) Correlation of IB when matched for lobular inflammation and (C) comparison of IB when matched for lobular inflammation and fibrosis in MASLD/MASH and AIH cases.*

Disclosures: Dylan Windell: Perspectum: Employee, asd: Employee, Cayden Beyer: Nothing to Disclose, Sarah Larkin: Perspectum Ltd: Employee, Elizabeth Shumbayawonda: Perspectum Ltd.: Employee, Paul Aljabar: Nothing to Disclose, Caitlin Langford: Nothing to Disclose, Andrea Dennis: Perspectum: Employee, Rob Goldin: Nothing to Disclose

2034 | IDENTIFYING HEALTH-TO-DISEASE TRANSITIONAL CELL STATES IN A 3D HUMAN ORGANOTYPIC MODEL OF MASLD-MASH ◆

Anabel Martinez Lyons[1] *Debbie Neill*[1] *Callum Rafferty*[1] *Jonathan Fallowfield*[1] *Tim Kendall*[1] *Justyna Cholewa-Waclaw*[1] *Leonard Nelson*[1]

[1]*University of Edinburgh*

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) affects more than a third of the world's adult population (Miao *et al.*, 2024), and precedes the inflammatory condition metabolic

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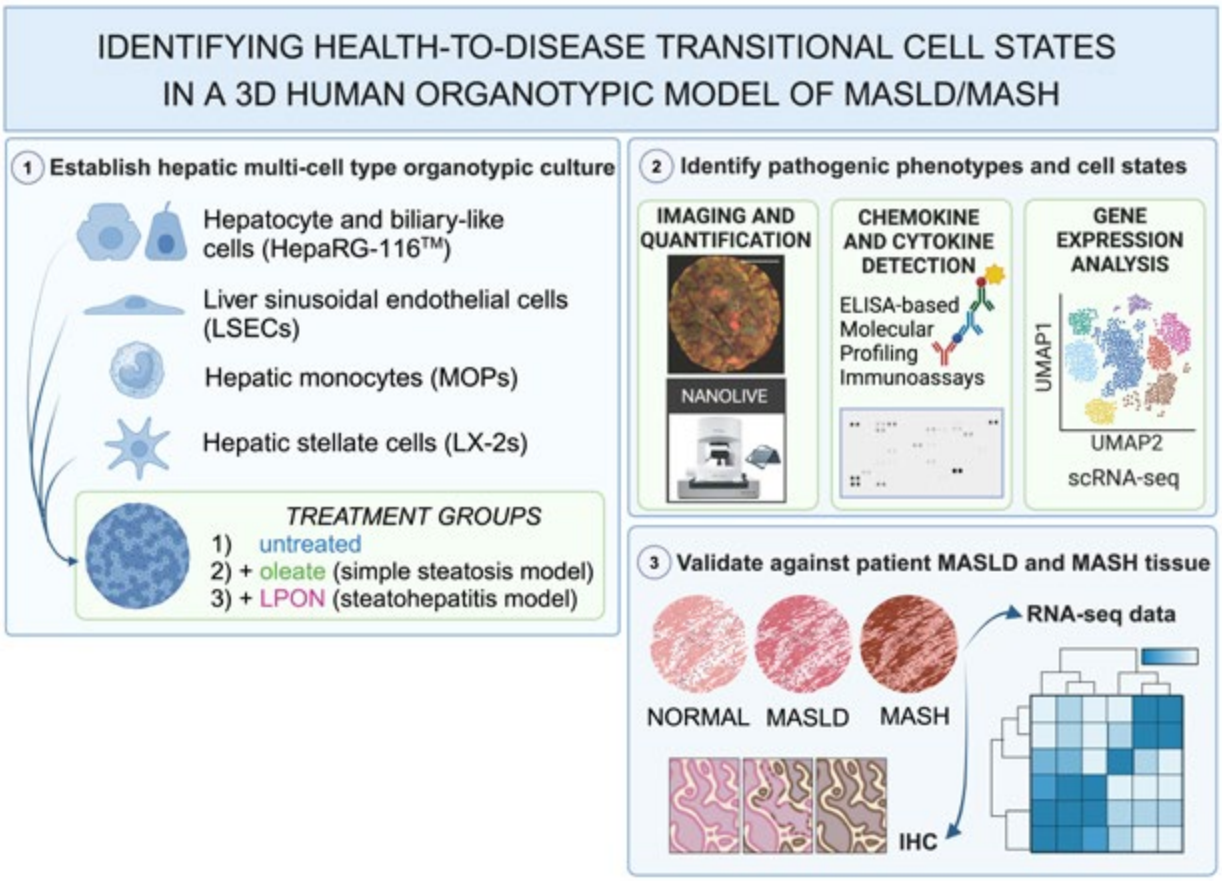
dysfunction-associated steatohepatitis (MASH). Diagnostic and therapeutic strategies are currently limited by a lack of cell-type specific biomarkers that can identify and target distinct stages of the health-MASLD-MASH pathogenic transition. In addition, existing *in vitro* and *in vivo* models fail to recapitulate the cellular complexity and plasticity present in patient livers. The aim of this study was to identify and interrogate cell type-specific biomarkers that delineate transitional states between health, MASLD and MASH. **Methods:** We generated human hepatic 3D spheroids of health-MASLD-MASH transition using co-cultured, differentiated biliary epithelial cells (BECs) and hepatocytes (HepaRG116™), stellate (LX-2), monocyte (MOP), and endothelial (HUVEC) cells treated with oleate (simple steatosis) or a lipogenic and pro-inflammatory cocktail of lactate, pyruvate, octanoate and nitrogen (LPON) for 72h. We assessed pathogenic cell states within these models by immunofluorescence (IF), Parse Evercode™ single cell RNA-sequencing (scRNA-seq) and validated these signatures with histological analyses of MASLD and MASH patient samples and matched patient RNA-sequencing data obtained from the curators of the SteatoSITE database. Lipid accumulation in live cells was assessed by Nanolive holographic tomography (HT) over 72h and quantified using CellPose/CellProfiler analytical software. Molecular profiling of secreted inflammatory proteins was performed using the Proteome Profiler Human XL 105 Cytokine Array (R&D Systems). **Results:** Human hepatic spheroids treated with LPON for 72h displayed fat-loading and immune activation mimicking *in vivo* MASLD-MASH pathogenesis. Nanolive HT revealed lipid accumulation within both the cytoplasm and nucleus of LPON-treated HepaRG116™ hepatocyte, as well as BECs. Cytokine molecular profiling of LPON-treated HepaRG cells revealed a unique cytokine/chemokine signature including elevated expression of osteopontin, RBP-4, angiogenin, cystatin C and CD-26 versus controls. IF analysis of patient tissue and matched RNA-seq data verified cell state signatures found via scRNA-seq in our MASLD and MASH spheroid models. **Conclusion:** This study sought to tackle the unmet need for reliable and specific molecular profiling for assessing patients with MASLD or MASH. The results of this study will enable the determination of cell-type specific roles in MASLD pathogenesis. Furthermore, we suggest several molecular biomarkers for 1) staging and 2) therapeutic targeting of MASLD/MASH.



Disclosures: Anabel Martinez Lyons: Nothing to Disclose, Debbie Neill: Nothing to Disclose, Callum Rafferty: Nothing to Disclose, Jonathan Fallowfield: Nothing to Disclose, Tim Kendall: Resolution Therapeutics: Consultant,

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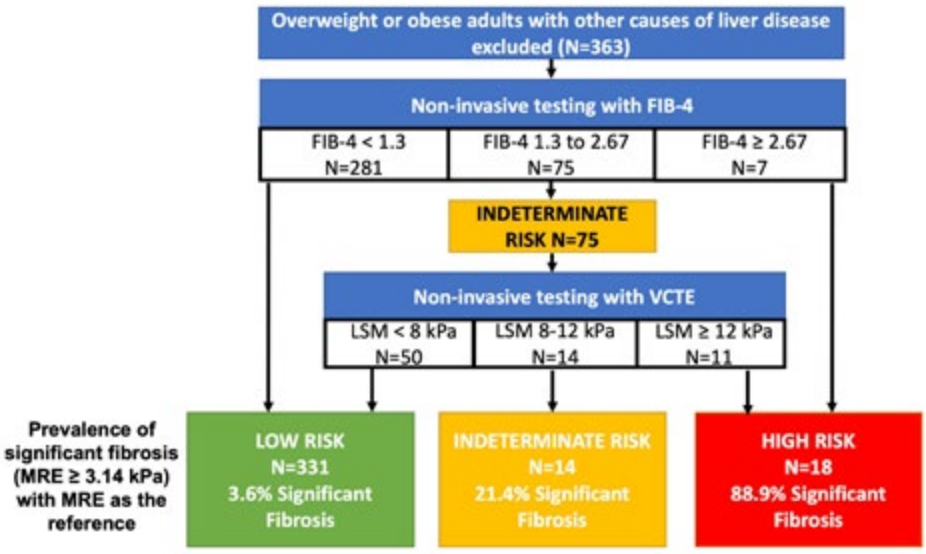
2035 | VALIDATION OF THE AGA AND AASLD CARE PATHWAYS FOR METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD) IN A PROSPECTIVE COHORT OF OVERWEIGHT AND OBESE INDIVIDUALS ◆

Veeral Ajmera[1] Monica Tincopa[1] Federica Tavaglione[2] Ricki Bettencourt[2] Lisa Richards[1] Rohit Loomba[1]

[1]University of California, San Diego, [2]UCSD MASLD Research Center

Background: The American Gastroenterological Association (AGA) and American Association for the Study of Liver Diseases (AASLD) both recently developed a care pathway that recommend sequential testing with FIB-4 and vibration-controlled transient elastography (VCTE) for populations at-risk for MASLD, including those with cardiometabolic comorbidities. We aimed to validate the pathway in a prospectively recruited cohort of overweight or obese patients at risk for MASLD using magnetic resonance elastography (MRE), the most accurate non-invasive biomarker of fibrosis. **Methods:** This prospective study enrolled overweight or obese adults aged 40-75 years recruited from the greater San Diego area from primary care clinics and community outreach. Participants underwent a standardized clinical research visit with MRI-PDFF, MRE and VCTE. Participants with alcohol intake consistent exceeding AASLD guidance for MASLD were excluded. The outcomes were the diagnostic performance of the clinical pathway for significant (stage ≥ F2) fibrosis using MRE ≥ 3.14 kPa based on a recently published cut-point from an individual patient data meta-analysis. **Results:** 363 patients (42.8% men) who were overweight or obese with FIB-4 and MRE data were included. The mean (±SD) age and BMI were 51.6 (±13.4) years and 32.0 (±6.0) kg/m2, respectively. The prevalence of MASLD was 71.9% and 8.5% had significant fibrosis (MRE ≥ 3.14 kPa). FIB-4 values of < 1.3, 1.3-2.67 and ≥ 2.67 were present in 281 (77.4%), 75 (20.7%), and 7 (1.9%) of patients respectively. VCTE values < 8 kPa, 8-12 kPa and ≥ 12 kPa were present in 288 (79.3%), 53 (14.6%), and 22 (6.1%) of patients respectively. Applying the care pathway (N=363), 281 patients were low risk by FIB-4 and 50 additional patients had VCTE < 8 kPa and were classified as low risk. The false negative rate for detecting *significant fibrosis* in patients classified as low risk was 3.6% and 8.8% of the cohort would qualify for specialty referral (Figure). Modifying the FIB-4 cut point for low risk to 1.0 did not significantly change false negative rate for detecting significant fibrosis, 3.4%, and increased the number of patients requiring VCTE from 75 to 145. **Conclusion:** Validation of the AGA and AASLD guidance in a well-phenotyped, prospectively recruited cohort of overweight and obese adults revealed excellent performance to detect patients with significant fibrosis who may be eligible for treatment and require specialty care. Decreasing the FIB-4 cut-off to 1 did not significantly improve performance in this cohort of overweight and obese patients.



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Disclosures: Veeral Ajmera: Nothing to Disclose, Monica Tincopa: Nothing to Disclose, Federica Tavaglione: Nothing to Disclose, Ricki Bettencourt: Nothing to Disclose, Lisa Richards: Nothing to Disclose, Rohit Loomba: Eli Lilly and Company: Consultant, 89bio: Consultant, Aardvark Therapeutics: Consultant, Altimmune: Consultant, Alnylam/Regeneron: Consultant, Amgen: Consultant, Arrowhead Pharmaceuticals: Consultant, AstraZeneca: Consultant, Bristol Myers Squibb: Consultant, CohBar: Consultant, Eli Lilly: Consultant, Galmed Pharmaceuticals: Consultant, Gilead: Consultant, Glympse Bio: Consultant, Hightide: Consultant, Inipharma: Consultant, Intercept: Consultant, Inventiva: Consultant, Ionis: Consultant, Janssen, Inc.: Consultant, Madrigal Pharmaceuticals: Consultant, Merck, Metacrine, Inc.: Consultant, NGM Biopharmaceuticals: Consultant, Novartis: Consultant, Novo Nordisk: Consultant, Pfizer: Consultant, Sagimet Biosciences: Consultant, Terns Pharmaceuticals: Consultant, Theratechnologies and Viking Therapeutics: Consultant, 89bio: Stock options, Sagimet Biosciences: Stock options, Arrowhead Pharmaceuticals: Research grant, AstraZeneca: Research grant, Boehringer Ingelheim: Research grant, Bristol Myers Squibb: Research grant, Eli Lilly: Research grant, Galectin Therapeutics: Research grant, Galmed Pharmaceuticals: Research grant, Gilead: Research grant, Hanmi: Research grant, Intercept: Research grant, Inventiva: Research grant, Ionis: Research grant, Janssen, Inc.: Research grant, Madrigal Pharmaceuticals: Research grant, Merck: Research grant, NGM Biopharmaceuticals: Research grant, Novo Nordisk: Research grant, Pfizer: Research grant, Sonic Incytes: Research grant, Terns Pharmaceuticals: Research grant, LipoNexus, Inc.: Co-founder

2036 | THE ORAL CHOLATE CHALLENGE TEST DEFINES LIKELIHOOD OF LARGE ESOPHAGEAL VARICES IN AN OVERWEIGHT AND OBESE US POPULATION ◆

Michael McRae[1] *Shailesh Chavan*[2] *Gregory Everson*[2]

[1]*Custom DX Solutions LLC,* [2]*HepQuant, LLC*

Background: Although well-validated in chronic viral hepatitis, the accuracy of transient elastography (TE) may be compromised in populations with high prevalence of obesity and MASLD/MASH. In the US-based SHUNT-V study prevalences of overweight, obesity, and MAFLD/MASH were 85%, 65%, and 50%, respectively. In this study, we evaluated the Disease Severity Index (DSI) from the oral-only HepQuant DuO test in the diagnostic performance for LEVs. **Methods:** Subjects were enrolled in two prospective studies linking HepQuant test results to endoscopic (EGD) findings. DuO test parameters were quantified from 20- and 60-min concentrations of orally administered d4-cholate (40 mg) (McRae et al., 2024). The SHUNT-V study enrolled 238 subjects with CP A cirrhosis (Hassanein et al., 2024). We added 217 subjects with prospective HepQuant and EGD data (HALT-C cohort) to expand the sample size and improve estimates of diagnostic performance. We evaluated DSI cutoffs for ruling out LEVs using a minimum acceptable sensitivity of ≥95% (miss rate <5%). The diagnostic performance was evaluated in terms of AUROC, sensitivity, and specificity. We determined the percentage of subjects who would have avoided EGD and miss rates for LEVs among those who avoided EGD. We normalized DSI according to subject body weight and by estimated blood volume. **Results:** DSI score from DuO was an accurate predictor of LEVs across all body sizes (Table 1). Overall, DSI at the cutoff of 18.3 to rule out LEVs had sensitivity 98% (95% CI, 89–100%), would have missed one LEV case (2.0%), and would have prevented 188 unnecessary EGDs (41.3%). AUROCs (95% CI) were comparable across body size groups. For the whole group, DSI normalized by estimated blood volume had the same sensitivity, greater specificity (48% vs. 46%), and would have prevented 7 (1.6%) more EGDs than DSI normalized by body weight. In obese individuals, specificity improved from 31% to 40% when normalizing DSI by blood volume. **Conclusion:** HepQuant DuO predicts the likelihood of finding LEVs on endoscopy in a population characterized by overweight, obesity, and enriched in MASLD/MASH. Normalizing DSI by estimated blood volume may improve the specificity of the test in obese individuals. The simplicity of DuO test administration will likely enhance its implementation by healthcare providers and acceptance by patients. HepQuant DuO may be a useful aid in the decision to avoid or proceed with endoscopic screening or surveillance of LEVs.

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Diagnostic performance of DSI for detection of large esophageal varices in normal (BMI<25), overweight (BMI 25-29.9), and obese (BMI >30) subjects in the HALT-C and SHUNT-V studies				
	Normal (n=64)	Overweight (n=145)	Obese (n=246)	All subjects (n=455)
DSI ≤18.3, normalized by body weight				
AUROC	0.84 (0.71-0.95)	0.90 (0.82-0.96)	0.77 (0.69-0.84)	0.82 (0.76-0.86)
Sensitivity	1.00 (0.63-1.00)	1.00 (0.69-1.00)	0.97 (0.83-1.00)	0.98 (0.89-1.00)
Specificity	0.64 (0.50-0.77)	0.62 (0.53-0.70)	0.31 (0.25-0.38)	0.46 (0.41-0.51)
Miss Rate	0 (0.0%)	0 (0.0%)	1 (3.2%)	1 (2.0%)
EGDs Prevented	36 (56.2%)	84 (57.9%)	68 (27.6%)	188 (41.3%)
DSI ≤17, normalized by estimated blood volume				
AUROC	0.85 (0.73-0.95)	0.90 (0.82-0.95)	0.79 (0.70-0.86)	0.83 (0.77-0.88)
Sensitivity	1.00 (0.63-1.00)	1.00 (0.69-1.00)	0.97 (0.83-1.00)	0.98 (0.89-1.00)
Specificity	0.54 (0.40-0.67)	0.59 (0.50-0.67)	0.40 (0.33-0.46)	0.48 (0.43-0.53)
Miss Rate	0 (0.0%)	0 (0.0%)	1 (3.2%)	1 (2.0%)
EGDs Prevented	30 (46.9%)	79 (54.5%)	86 (35.0%)	195 (42.9%)
Values are diagnostic performance (95% CI) or number (%) of subjects				

Disclosures: Michael McRae: HepQuant, LLC: Consultant, Shailesh Chavan: Nothing to Disclose, Gregory Everson: HepQuant LLC: Executive role

2037 | MAINTENANCE THERAPY WITH GLP-1 RECEPTOR AGONISTS DOES NOT IMPACT THE CLEARANCE OF ORALLY ADMINISTERED ISOTOPES OF UNCONJUGATED CHOLATE

Michael McRae[1] *Shailesh Chavan*[2] *Gregory Everson*[2]

[1]*Custom DX Solutions LLC,* [2]*HepQuant, LLC*

Background: Glucagon-like-peptide-1 receptor agonists (GLP-1 RAs) are prescribed for obese and diabetic patients with MASLD/MASH and may slow gastric emptying. A liquid solution of d4-cholate (d4-CA) is administered in the HepQuant SHUNT and DuO tests to measure liver function and portal-systemic shunting. If GLP-1 RAs slow gastric emptying of the d4-CA solution, the clearance curve would shift, potentially compromising accuracy of the HepQuant SHUNT and DuO test. For these reasons, we compared the characteristics of clearance of orally administered d4-CA between patients on maintenance GLP-1 RAs versus patients not taking these medications. **Methods:** The patients were enrolled in the SHUNT-V study. Forty mg of d4-CA was administered as an oral solution, 20 mg 13C-CA was injected intravenously, and blood was sampled at baseline and at 5, 20, 45, 60, and 90 min post-dose. Serum d4- and 13C-CA concentrations were measured by LC-MS/MS, and AUCs calculated. The test results were compared between subjects on maintenance GLP-1 RA treatment (n=32) and subjects not taking them (n=243). **Results:** The GLP-1 RAs (*n* subjects) were liraglutide (12), dulaglutide (12), semaglutide (6), exenatide (3), and dulaglutide plus exenatide (1). One subject on semaglutide had an invalid test due to low d4-CA concentrations. The figure demonstrates similar appearance of the clearance curves of d4-CA between subjects on GLP-1 RAs and subjects not taking them. The time-dependent pattern of absorption, peak concentration, and elimination, as reflected in the serum concentrations of d4-CA was similar. H The AUC of d4-CA -was significantly lower in subjects taking GLP-1 RAs (p=0.03) suggesting a potential impact on gastric emptying of the d4-CA solution. But, the AUC of 13C-CA was similarly decreased (p=0.02), and the prevalence of large varices was lower. In total, the results do not support an effect of GLP-1 RAs on gastric emptying d4-CA but rather suggest that patients on GLP-1 RAs had less severe hepatic disease. **Conclusion:** This analysis demonstrates that there is little to no impact of maintenance GLP-1 RAs on the clearance of an orally-administered d4-CA liquid solution. However, because the effect of GLP-1 RAs on gastric emptying may vary with type of GLP-1 RA and duration of GLP-1 RA treatment, and some may have dual (GIP) or triple (GIP, amylin) effects, we advise holding GLP-1 RAs (and other drugs that slow gastric emptying) for 7 days prior to administering the HepQuant tests.

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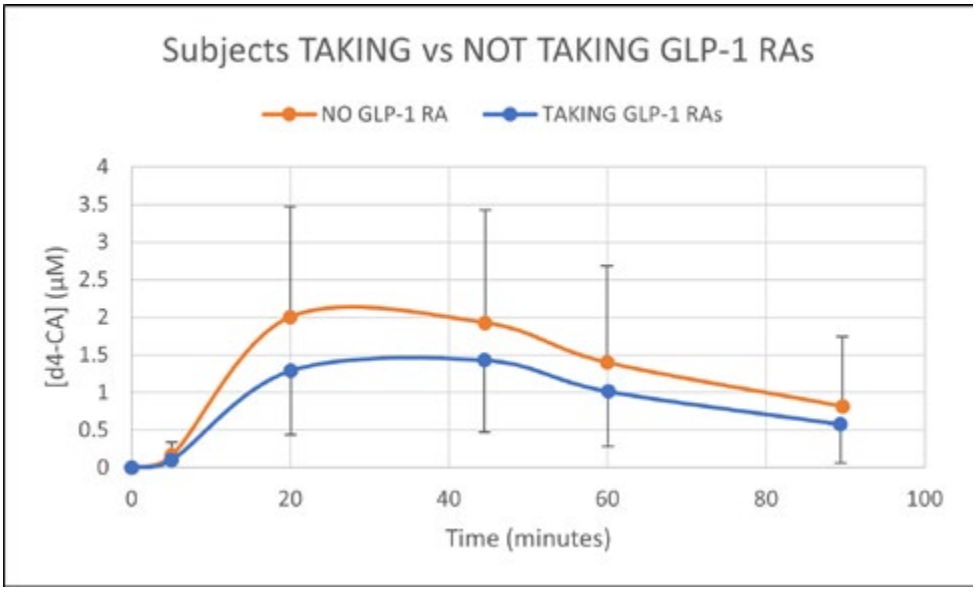

Disclosures: Michael McRae: HepQuant, LLC: Consultant, Shailesh Chavan: Nothing to Disclose, Gregory Everson: HepQuant LLC: Executive role

2038 | MULTIPLE GENETIC POLYMORPHISMS ARE ASSOCIATED WITH THE RISK OF METABOLIC SYNDROME, FATTY LIVER, AND AIRFLOW LIMITATION: A TAIWAN BIOBANK STUDY

Ying-Ying Yang[1] Hsiao-Chin Shen[2] Hwai-I Yang[3] Hsiao-Yun Yeh[2] Chia-Chang Huang[2]

[1]Taipei Veteran General Hospital, [2]Taipei Veterans General Hospital, [3]Academia Sinica, Taipei

Background: Links have been reported between the airflow limitation and both metabolic syndrome (MetS) and fatty liver (FL). Additionally, associations between genetic factors and risks of MetS, FL, and airflow limitation have been identified separately in different studies. Our study aims to simultaneously explore the association between specific single nucleotide polymorphisms (SNPs) of certain genes and the risk of the three associated diseases. **Methods:** Links have been reported between the airflow limitation and both metabolic syndrome (MetS) and fatty liver (FL). Additionally, associations between genetic factors and risks of MetS, FL, and airflow limitation have been identified separately in different studies. Our study aims to simultaneously explore the association between specific single nucleotide polymorphisms (SNPs) of certain genes and the risk of the three associated diseases. In this retrospective cross-sectional nationwide study, 150,709 participants from the Taiwan Biobank (TWB) were enrolled. We conducted a genotype–phenotype association analysis of nine SNPs on seven genes (ApoE-rs429358, MBOAT7-rs641738, LEPR-rs1805096, APOC3-rs2854116, APOC3-rs2854117, PPP1R3B-rs4240624, PPP1R3B-rs4841132, TM6SF2-rs58542926, and IFNL4-rs368234815) using data from the TWB1.0 and TWB2.0 genotype dataset. Participants underwent a series of assessments including questionnaires, blood examinations, abdominal ultrasounds, and spirometry examinations. **Results:** MetS was associated with FL and airflow limitation. ApoE-rs429358, LEPR-rs1805096, APOC3-rs2854116, APOC3-rs2854117, PPP1R3B-rs4240624, PPP1R3B-rs4841132, and TM6SF2-rs58542926 were significantly associated with the risk of MetS. The cumulative impact of T alleles of ApoE-rs429358 and TM6SF2-rs58542926 on the risk of FL was observed (*p* for trend <0.001). Individuals without MetS and airflow limitation carrying LEPR-rs1805096 G_G genotype exhibited a reduction in the forced expiratory volume in 1 second percentage prediction (Coefficient -35, 95% confidence interval (CI) -69.7- -0.4), low forced vital capacity percentage prediction (Coefficient -41.6, 95% CI -82.6- -0.6), and low vital capacity percentage prediction (Coefficient -42.2, 95% CI -84.2- -0.1). **Conclusion:** MetS significantly correlated with FL and airflow limitation. Multiple SNPs were notably associated with MetS. Specifically, T alleles of ApoE-rs429358 and TM6SF2-rs58542926 cumulatively increased the risk of FL. LEPR-rs1805096 shows a trend-wise association with pulmonary function, which is significant in patients without MetS or airflow limitation.

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Table 1. Characteristics of the participants

Characteristics	Total (n=53116)	non-MetS group (n=26558)	MetS group (n=26558)	*p*-value
Demographics				
Alcohol history (n, %)	5535(10.4)	2384(9.0)	3151(11.9)	<0.001
Body mass index (kg/m²)	25.0(22.6-27.7)	23.2(21.3-25.3)	26.8(24.7-29.3)	<0.001
Body waistline (cm)	86.5(80.0-93.0)	81.5(75.5-87.5)	91.0(85.5-97.0)	<0.001
Spirometry data				
FEV1 (L)	2.12(1.61-2.72)	2.11(1.57-2.72)	2.12(1.64-2.73)	<0.001
FEV1 % prediction	88.7(71.1-100.8)	88.7(68.8-101.5)	88.8(73.2-100.2)	0.042
FVC (L)	2.64(2.15-3.30)	2.68(2.19-3.35)	2.60(2.12-3.26	<0.001
FVC % prediction	90.0(80.0-100.2)	91.4(81.3-101.8)	88.7(78.8-98.4)	<0.001
VC	2.75(2.26-3.43)	2.79(2.29-3.45)	2.72(2.24-3.40)	<0.001
VC % prediction	93.7(83.8-103.8)	94.6(84.6-105.0)	92.7(83.0-102.5)	0.799
Airflow limitation	7396(13.9)	3347(12.6)	4049(15.2)	<0.001
Abdominal ultrasound (n= 10184)				
Fatty liver (n, %)	4929(48.4)	2021(34.3)	2908(67.7)	<0.001

Continuous data are expressed as median with interquartile range [IQR], and categorical data are expressed as number of patients (%). p value is analyzed by Chi-square test or Mann–Whitney U test. Airflow limitation is defined as FEV1/FVC<70%. MetS: Metabolic syndrome. SBP: systolic blood pressure. DBP: diastolic blood pressure. WBC: white blood cells. HbA1C: glycated hemoglobin. TG: triglyceride. HDL: high-density-lipoprotein. LDL: low-density-lipoprotein. SGPT: serum glutamic pyruvic transferase. EFV1: forced expiratory volume in one second. FVC: forced vital capacity. VC: vital capacity.

Table 2: Association between LEPR-rs1805096 and pulmonary function in patients with and without MetS and airflow limitation.

LEPR-rs1805096 (A_A as referent, n=39475)	A_G=2 (n=11471)			G_G=3 (n=848)		
	Coefficient	95% CI	*p*	Coefficient	95% CI	*p*
MetS(-) & airflow limitation(-) (n=23211)						
FEV1 % prediction	-9.1	-19.6-1.5	0.092	-35.0	-69.7- -0.4	0.047
FVC % prediction	-11.0	-23.5-1.5	0.084	-41.6	-82.6- -0.6	0.047
VC % prediction	-11.1	-24.0-1.7	0.088	-42.2	-84.2- -0.1	0.050
MetS(-) & airflow limitation (+) (n=3347)						
FEV1 % prediction	-0.6	-1.5-0.3	0.187	-1.0	-4.5-2.5	0.578
FVC % prediction	-0.3	-1.5-1.0	0.653	-1.1	-5.8-3.7	0.644
VC % prediction	0.2	-1.2-1.5	0.786	-2.1	-7.3-3.0	0.420
MetS(+) & airflow limitation (-) (n=22509)						
FEV1 % prediction	-3.5	-12.9-6.0	0.472	-6.0	-36.4-24.5	0.701
FVC % prediction	-4.2	-15.3-7.0	0.465	-5.6	-41.6-30.4	0.760
VC % prediction	-0.5	-1.6-0.7	0.417	-2/3	-5.8-1.2	0.204
MetS(+) & airflow limitation (+) (n=4049)						
FEV1 % prediction	-0.3	-1.0-0.5	0.520	0.9	-1.5-3.3	0.445
FVC % prediction	-0.4	-1.4-0.7	0.512	0.3	-2.9-3.4	0.862
VC % prediction	-0.5	-1.6-0.7	0.417	-2.3	-5.8-1.2	0.204

Coefficient and 95% confidence interval are calculated by linear regression. Airflow limitation is diagnosed in case with FEV1/FVC <0.7. LEPR: leptin receptor. MetS: Metabolic syndrome. EFV1: forced expiratory volume in one second. FVC: forced vital capacity. VC: vital capacity.

Disclosures: Ying-Ying Yang: Nothing to Disclose, Hsiao-Chin Shen: Nothing to Disclose, Hwai-I Yang: Nothing to Disclose, Hsiao-Yun Yeh: Nothing to Disclose, Chia-Chang Huang: Nothing to Disclose

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2039 | ENHANCING TRADITIONAL FIBROSIS PREDICTION MODELS WITH MACHINE LEARNING IN PATIENTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD)

David Kim[1] Imran Qureshi[1] Mohamed Ismail[1] Yazan Abboud[1] Nikolaos Pyrsopoulos[1] Hyunseok Kim[2] Kaveh Hajifathalian[1] Ahmed Al-Khazraji[1]

[1]Rutgers New Jersey Medical School, [2]Baylor College of Medicine

Background: Identification of high-risk metabolic-associated steatohepatitis (MASH) is crucial, as it is a precursor to liver-related events and is now used to identify candidates for therapy in patients with metabolic dysfunction-associated steatotic liver disease (MASLD). The FibroScan-AST (FAST) score has been well validated and demonstrates excellent ability to identify patients with MASH. Therefore, using easily accessible variables, we propose two different machine learning models to predict high-risk MASH in patients with MASLD. **Methods:** Data was derived from the 2017– 2020 pre-pandemic United States National Health and Nutrition Examination Surveys. MASLD was defined as controlled attenuation parameter ≥285 with metabolic risk factors as defined in previous studies. High-risk MASH was defined as FAST score ≥0.35. Participants with a history of alcohol use ≥2 or 1 drinks/day for males and females, respectively, were excluded. Two machine learning models, Least Absolute Shrinkage and Selection Operator (LASSO) and random forest (RF) were used to predict for MASH. All variables in FIB-4 and NFS models were included. The cohort was divided into 66.6% and 33.3% for the training and validation cohort, respectively. Delong test was used to compare the area under the receiver operating characteristics of the models. **Results:** Among 2,515 patients with MASLD, 15.3% were found to have MASH. The median age of the entire cohort was 52 years (IQR 37-63), with 55.5% male. MASH was found in 17.1% of patients in the training cohort and 11.8% in the validation cohort. In the training cohort, the LASSO model (AUC 0.950) was comparable to the RF model (AUC 0.945, P=0.595) and superior to FIB-4 (AUC 0.667, P<0.001) and NFS (AUC 0.609, P<0.001). In the validation cohort, the LASSO model (AUC 0.931) was again comparable to the RF model (AUC 0.932, P=0.937) and superior to FIB-4 (AUC 0.638, P<0.001) and NFS (AUC 0.596, P<0.001) (Figure 1). The top five predictors of high-risk MASH were AST, ALT, BMI, platelet count, and age. **Conclusion:** Using machine learning, we developed clinically relevant models based on easily accessible values, which improve upon traditional models for identifying MASH in patients with MASLD. These models have the potential to be implemented in resource-limited settings that struggle to access transient elastrography (FibroScan) or magnetic resonance elastography (MRE).

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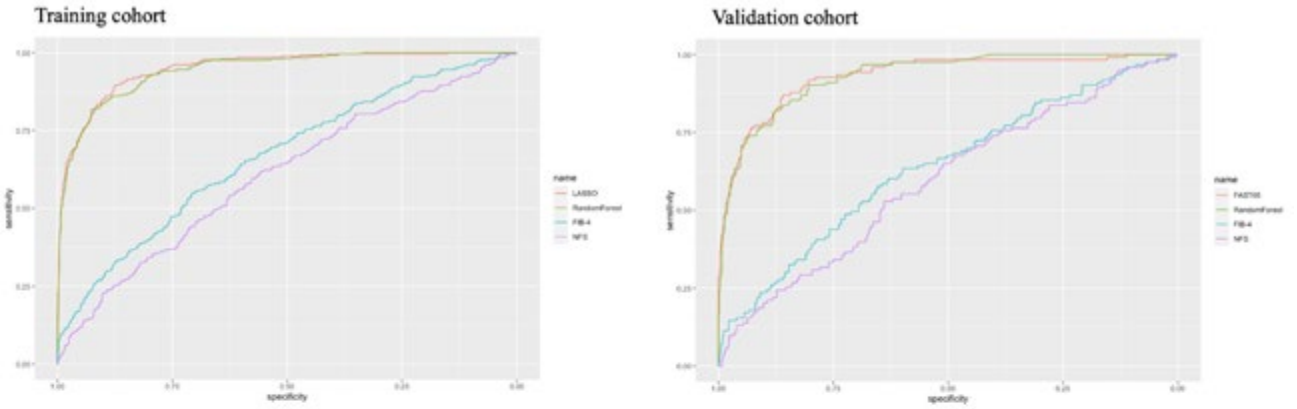

Table 1. Baseline characteristics of entire cohort

Variables	Total n = 2,515	Patients with MASH n = 383 (15.3%)	Patients without MASH n = 2,132 (84.7)	*P* value
Age, years	52 (37 - 63)	47 (37 - 60)	53 (36 - 64)	0.375
Male	55.5	70.8	52.7	0.001
Race				0.685
Non-Hispanic White	63.6	64.0	63.6	
Non-Hispanic Black	8.7	7.2	8.9	
Hispanic	19.2	20.9	18.9	
Other	8.5	7.9	8.6	
Body mass index, kg/m2	32.7 (29.0 - 38.0)	35.4 (31.7 - 42.9)	32.3 (29.7 - 37.3)	0.001
Glycohemoglobin, %	5.7 (5.3 - 6.1)	5.7 (5.4 - 6.6)	5.6 (5.3 - 6.1)	0.005
Serum glucose	109 (100 - 121)	117 (105 - 134)	107 (99 - 119)	0.004
Total cholesterol, mg/dL	185 (158 - 213)	182 (162 - 216)	188 (157 - 212)	0.884
Aspartate aminotransferase, IU/L	20 (16 - 25)	37 (27 - 46)	19 (16 - 23)	<0.001
Alanine aminotransferase, IU/L	21 (16 - 32)	47 (31 - 61)	20 (15 - 28)	<0.001
Serum albumin, g/dL	4.0 (3.8 - 4.2)	4.0 (3.8 - 4.2)	4.0 (3.8 - 4.2)	0.673
Total bilirubin, mg/dL	0.4 (0.3 - 0.6)	0.4 (0.3 - 0.6)	0.4 (0.3 - 0.6)	0.150
Platelet count, 10^9/L	237 (203 - 277)	217 (192 - 257)	242 (207 - 280)	<0.001
Fibrosis, FIB-4	0.9 (0.6 - 1.3)	1.2 (0.8 - 1.7)	0.9 (0.5 - 1.2)	<0.001
Fibrosis, NFS	-1.2 (-2.2 - -0.1)	-0.5 (-1.5 - 0.3)	-1.3 (-2.3 - -0.2)	<0.001
Liver stiffness, kPa	5.6 (4.5 - 7.1)	8.8 (6.3 - 15.1)	5.4 (4.4 - 6.5)	<0.001
Controlled attenuation parameter	325 (302 - 356)	365 (334 - 398)	319 (300 - 346)	<0.001

Variables are expressed as median (IQR) or %.
MASH, metabolic-associated steatohepatitis; FIB-4, fibrosis-4; NFS, non-alcoholic fatty liver disease fibrosis score; kPa, kilopascals.

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2040 | PREVALENCE AND CHARACTERISTICS OF HIGH-RISK FIB-4 AMONG PRIMARY CARE PATIENTS WITH PRE-DIABETES (PREDM): POTENTIAL TO IMPROVE THE CURRENT STATE OF DISEASE UNDER-RECOGNITION

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Background: AASLD guidelines recommend that primary care (PC) patients with any risk factor for MASLD be regularly assessed with FIB-4, with further evaluation recommended for those with indeterminate- or high-risk scores. PreDM is one such risk factor for MASLD, yet no studies have evaluated the impact of applying FIB-4 in the PreDM population. We aimed to determine the prevalence and clinical characteristics of indeterminate- and high-risk FIB-4 scores in patients with PreDM using preexisting lab data in the PC setting. **Methods:** We assembled a retrospective cohort of adults with PreDM in a large, urban PC practice. PreDM was defined as at least one hemoglobin A1c (A1c) of 5.7-6.4% within the 2018-2022 study period, yet without any prior A1c ≥6.5% or anti-hyperglycemic medication use. We excluded patients with DM, alcohol use, or hepatitis B/C. FIB-4 scores were calculated annually for each patient, and the highest score determined each patient's categorization into low-, indeterminate-, or high-risk groups based on established age-specific cutoffs. Descriptive statistics and

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group comparisons were performed using Chi-squared tests and one-way ANOVA. **Results:** A total of 4,192 PC patients with PreDM met inclusion criteria. The cohort was diverse: 37% White, 35% Asian, 11% Black, and 10% Latinx; and 84.3% were either overweight or obese (Table 1). The majority (69%) already had at least one computable FIB-4, and these patients were categorized as low- (63%), indeterminate- (27%), or high-risk (10%) for advanced fibrosis. Preexisting MASLD/MASH ICD codes were very uncommon across the cohort (9.3%), yet relative to those with low-risk, patients with high-risk FIB-4 were even less likely to have a MASLD diagnosis (9% vs 12%), less likely to be Black or Latinx, and were less obese (43% vs. 46%) despite similar mean A1c (5.8%). Only 25% of high-risk patients had a prior abdominal ultrasound, and only 8% had been seen by hepatology, indicating a low rate of evaluation for potential steatosis or advanced disease. **Conclusion:** In this real-world study of PC patients with PreDM, over two-thirds already had existing data to calculate FIB-4 prior to 2023 AASLD guidance, suggesting that FIB-4 assessment is both feasible and low-burden for patients and PC providers alike. Although 37% had either indeterminate- or high-risk scores, necessitating further workup, only 16% had a prior ultrasound and only 8-9% had a MASLD diagnosis or hepatology evaluation, indicating significant under-recognition in PC. For these reasons, increasing PC provider awareness of FIB-4 could improve the detection of advanced fibrosis in PreDM patients. In this study, PreDM patients with high-risk FIB-4 differed from low-risk patients in terms of race/ethnicity and BMI despite similar A1c, suggesting the need for further research to evaluate real-world outcomes of applying the FIB-4 algorithm across this population in PC.

Table 1. Characteristics of Primary Care Patients with Pre-Diabetes, Categorized by FIB-4 Risk Category

Variable	Total cohort	FIB-4 data available	Low-risk FIB-4	Indeterminate-risk FIB-4	High-risk FIB-4	p-value*
	n=4,192	n=2,904	n=1,822	n=796	n=286	
Age [mean (SD)]	66 (14)	67 (14)	64 (14)	70 (11)	81 (9.1)	<0.001
Sex						<0.001
Female	56.0%	57.0%	62.0%	48.5%	48.6%	
Male	44.0%	43.0%	38.0%	51.5%	51.4%	
Race/ethnicity						<0.001
White	37.2%	38.3%	37.1%	40.4%	39.9%	
Black or African American	10.5%	10.8%	12.2%	9.4%	5.7%	
Latinx	10.2%	10.3%	11.5%	9.0%	6.7%	
Asian	35.1%	33.8%	31.9%	34.6%	44.2%	
Other (AIAN, NHPI, Other)	6.9%	6.8%	7.4%	6.6%	3.5%	
BMI categories (highest BMI)‡						<0.001
Underweight	0.5%	0.5%	0.4%	0.5%	1.4%	
Normal	15.2%	14.4%	12.3%	17.3%	18.9%	
Overweight	34.2%	33.4%	30.8%	37.9%	37.1%	
Obese	50.1%	51.7%	56.4%	44.2%	42.7%	
MASH/MAFLD ICD 9/10	9.3%	11.9%	12.0%	12.7%	9.1%	0.27
Average A1C [mean (SD)]	5.8 (0.21)	5.8 (0.21)	5.8 (0.21)	5.7 (0.21)	5.8 (0.24)	0.005
Median FIB-4 [median (IQR)]¶	1.42 (1.01-1.95)	1.42 (1.01-1.95)	1.1 (0.93-1.44)	2.0 (1.55-2.25)	3.24 (2.91-3.75)	<0.001
Hepatology visit (ever)	3.7%	5.1%	4.4%	5.9%	7.7%	0.032
Prior abdominal ultrasound (ever)	15.9%	20.8%	19.9%	21.5%	24.5%	0.17
Liver biopsy (ever)	0.3%	0.4%	0.3%	0.3%	1.0%	0.14

*p-value statistically compares FIB-4 groups

‡BMI categories using different cutoffs for Asians and non-Asians: Underweight=BMI <18.5 for both Asians and non-Asians; Normal=BMI 18.5 to 24.9 for non-Asians and BMI 18.5 to 22.9 for Asians; Overweight=BMI 25 to 29.9 for non-Asians and 23 to 26.9 for Asians; Obese=BMI ≥30 for non-Asians and BMI ≥27 for Asians.

¶Calculated by taking the median of the highest FIB-4 for each patient

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2041 | PERFORMANCE OF NONINVASIVE TESTS IN IDENTIFYING APPROPRIATE PATIENTS FOR RESMETIROM TREATMENT: REAL WORLD DATA FROM FOUR TERTIARY CARE CENTERS ◆

Eda Kaya[1] Rida Nadeem[2] Ayana Jain[2] Reyana Shah[2] Sahasraara Hemant[2] Sohil Kahlon[2] Chloe Nguyen[2] Manal Chughtai[2] Jan-Peter Sowa[1] Ali Canbay[1] Raj Vuppalanchi[3] Yusuf Yilmaz[4] Naim Alkhouri[2]

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Background: Resmetirom was recently approved as the first medication for patients with metabolic dysfunction-associated steatohepatitis (MASH) and fibrosis stages F2-F3. There is an urgent need for noninvasive tests (NITs) to identify eligible patients accurately without the need for invasive liver biopsies. Recently, the following combination of NITs was proposed for the identification of eligible patients: controlled attenuation parameter (CAP)≥280 dB/m, liver stiffness measurement (LSM) 10-20 kPa, and platelet count≥150x10^3/ µL. We aimed to test this strategy for the correct classification of patients using liver biopsy data derived from two tertiary care centers as the gold standard. **Methods:** Data of consecutive patients with biopsy-proven MASLD derived from two tertiary care centers were collected between 2017 and 2023. Histological classification of biopsies was performed according to the Steatosis, Activity, Fibrosis/Fatty Liver Inhibition of Progression (SAF/FLIP) algorithm and the NASH-Clinical Research Network (NASH-CRN) scoring system. Eligible patients based on histological criteria were those with MASH (NAS≥4) and F2-F3. Cohen's Kappa statistic was used as a measure of agreement between the diagnostic tests and the liver biopsy. **Results:** Prospectively collected data from 1053 biopsy-proven MASLD patients were included in the analysis and retrospectively analyzed (Age: 55 [19-84] years, 394 males (37.6%)). A total of 366 patients (34.8%) met the histological criteria for resmetirom use and non-identical 366 patients (34.8%) the NIT criteria. The combination of the NIT criteria was able to identify the patients with accurate histological features with a sensitivity of 39.6% and specificity of 67.8% (positive predictive value: 39.6%, negative predictive value: 67.8%). Cohen´s Kappa indicated a poor agreement between the reference standard and non-invasive diagnostic algorithm (Kappa: 0.074, P=0.016). In patients that met the NIT criteria, the following reasons were exclusionary from treatment with resmetirom based on the histological findings: 34 (9.3%) had cirrhosis on biopsy (F4), 117 (32.0%) had F0-F1, and 70 (19.1%) had F2-F3 but NAS < 4. Similarly, the NIT criteria had poor performance in predicting the presence of F2-F3 on biopsy regardless of the presence of MASH or the NAS (Kappa: 0.077, P=0.007, Sensitivity 38.5%, specificity 69.4%, PPV 58.7%, and NPV 49.9%). **Conclusion:** The proposed non-invasive diagnostic criteria for selecting patients eligible for resmetirom use showed a poor performance in comparison to the histological criteria. Further studies and modification of the cut-offs are needed.

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Table 1. Clinical and histological characteristics of the patients (N=1053)

Parameter	
Age, years	55 [19-84]
Sex (male), (N, %)	394 (37.6%)
Diabetes mellitus (N, %)	509 (50.2%)
Hypertension (N, %)	515 (50.8%)
Dyslipidemia (N, %)	378 (39.3%)
Body mass index, kg/m^2	34.6 [17.9-83.0]
Alkaline phosphatase, U/L	82 [5-591]
Alanine transaminase, U/L	48 [9-1672]
Aspartate transaminase, U/L	38 [11-592]
Bilirubin (mg/dL)	0.6 [0.1-7.6]
Creatinine, mg/dL	0.8 [0.3-5.6]
Albumin, g/dL	4.4 [1.3-5.9]
Total protein, g/dL	7.3 [4.4-9.1]
Gammaglutamyl transferase, U/L	49 [5.6-1029]
Total cholesterol, mg/dL	183 [74-419]
Low density lipoprotein, mg/dL	111 [15-400]
High density lipoprotein, mg/dL	43 [4-140]
Triglycerides, mg/dL	152 [31-1314]
Platelet, x10^3/µL	232 [10-560]
Controlled attenuation parameter, dB/m	321 [100-400]
Liver stiffness measurement, kPa	11.1 [1.6-128]
Steatosis, S1/S2/S3 (N, %)	480 (47.7%)/259 (25.7%)/267 (26.5%)
Fibrosis stage, F0/F1/F2/F3/F4 (N, %)	76 (7.2%)/279 (26.5%)/314 (29.8%)/245 (23.3%)/139 (13.2%)
NAS≥4, (N, %)	620 (58.9%)
F2-F3, (N, %)	559 (53.1%)
NAS≥4+F2-F3 (N,%)	366 (34.8%)

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2042 | THE DIAGNOSTIC ABILITY FOR HEPATIC STEATOSIS USING ATTENUATION IMAGING AND CONTROLLED ATTENUATION PARAMETER; A PROSPECTIVE MULTICENTER STUDY IN JAPAN

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Background: Steatotic liver disease (SLD) have been increased worldwide, therefore, the diagnose of hepatic steatosis is very important. Attenuation Imaging (ATI) and controlled attenuation parameter '(CAP) are non-invasive method for diagnosing hepatic steatosis using ultrasound.The aim of this study is to compare the diagnostic ability for the degree of hepatic steatosis using ATI and CAP with MRI-PDFF as reference standard. **Methods:** The 562 chronic hepatitis patients performed ATI, CAP and MRI-PDFF from March 2021 to January 2022 were included in this study. The median MRI-PDFF value of three measurements was used. Steatosis grade was defined as grade 0 (S0) with MRI-PDFF < 5.2%, grade 1 (S1) with 5.2% ≤ MRI-PDFF < 11.3%, grade 2 (S2) with 11.3% ≤ MRI-PDFF < 17.1%, or grade 3 (S3) with MRI-PDFF ≥ 17.1%. ATI values were measured five times and defined as the median of five measurement values with IQR/Median≤0.3 and R^2 value ≥0.7. In patients with 10 valid CAP measurements, IQR/median >30% was defined as unreliable. Patients with SCD ≤ 25 mm were evaluated using the M probe and patients with SCD > 25 mm were evaluated using the XL probe. **Results:** Median age was 59 years old and there were 32 (5.7) patients with HBV, 33 (5.9%) with HCV, 5 (0.9%) with HBV and HCV, and 492 (87.5%) with nonBnonC including 344 (61.2%) with MASLD. The correlation coefficient (CC) for ATI and log MRI-PDFF was significantly higher than that for CAP and log MRI-PDFF (r=0.799, r=0.694, P<0.001). CC for CAP and log MRI-PDFF in the BMI ≥30 kg/m^2 groups were significantly lower than those in the BMI<30kg/m^2 groups, respectively, but CC for ATI and log MRI-PDFF were not. ATI and CAP according to hepatic steatosis grade increased significantly with increasing hepatic steatosis grade. The AUROCs for ATI in detecting ≥S1 steatosis was significantly higher than that for CAP (0.895 vs 0.845, P=0.004). The AUROCs for ATI in detecting ≥S2 steatosis was significantly higher than that for CAP (0.944 vs 0.881, P<0.001). The AUROCs for ATI in detecting S3 steatosis was significantly higher than that for CAP (0.928 vs 0.860, P<0.001). For detecting ≥S2 and S3 hepatic steatosis, ATI had significantly higher specificity, accuracy and PPV than CAP (all P<0.001). In all results, the almost same results were performed in patients with MASLD. **Conclusion:** ATI is a better non-invasive method for diagnosing hepatic steatosis than CAP.

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2043 | A SINGLE-CENTER, OBSERVATIONAL STUDY TO EVALUATE THE UTILITY OF FERRITIN AS A NONINVASIVE BIOMARKER IN PATIENTS WITH MASLD

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Background: Metabolic associated steatotic liver disease (MASLD) is one of the leading etiologies of chronic liver disease (CLD). Noninvasive tests (NITs) and lab markers are needed to monitor disease progression. Elevated serum ferritin is common in MASLD but its role in disease activity remains unclear. The aim of this study was to investigate the utility of ferritin in assessing MASLD severity. **Methods:** Patient charts between March 2022 and December 2023 were retrospectively reviewed. Those containing a diagnosis of MASLD and serum ferritin levels drawn within 6 weeks of steatosis assessment were included. MASLD diagnosis was based on hepatic steatosis on imaging or histology and exclusion of other causes of CLD. Serum biomarkers, imaging-based elastography, or liver biopsy were used for MASLD/MASH and fibrosis staging. Pearson correlation was used to determine association of ferritin with measures of MASLD/MASH. **Results:** 229 patients (59% female) were included in the dataset with 56% Caucasian and 41% Hispanic/Latino. Selected pertinent medians and interquartile ranges were age=55 [45,63] years, BMI=33 [29,38] kg/m^2, ferritin=141 [78,268] ng/mL, AST=38 [27,60] IU/L, and ALT=54 [33,81] IU/L. Metabolic risk factors included obesity (76%), type 2 diabetes (45%), dyslipidemia (66%) and hypertension (59%). In those with recorded FibroScan results (n=50), severe steatosis (median CAP 330 dB/m) and minimal fibrosis (median kPa 7.3) was identified in this patient cohort. In patients with FibroSure results (n=36), moderate/severe steatosis (median 0.71), mild to moderate NAS (median 0.5), and minimal fibrosis (0.33) were reported. Liver biopsy (n=77) demonstrated severe steatosis in 50% of patients and the median NAS score was 5. ALT was significantly correlated with ferritin level; however, there was no association between ferritin level and measures of steatosis or fibrosis (Table 1). **Conclusion:** This group previously reported a significant association between ferritin and ALT; however, ferritin was not associated with other routine laboratory markers measured in MASLD. In this cohort of 229 patients with MASLD, ferritin was not predictive of steatosis, NAS, or fibrosis stage. The association between ferritin and ALT again supports ferritin as only a marker of cellular damage.

Table 1 Ferritin level correlation with measures of MASLD/MASH and fibrosis.

Ferritin (ng/mL)		Correlation [95% CI]	P value
ALT	N=223	0.21 [0.08, 0.34]	**0.001**
Steatosis			
FibroScan CAP	N=50	0.18 [-0.11, 0.43]	0.218
FibroSure LabCorp steatosis score	N=36	-0.01 [-0.34, 0.32]	0.964
Steatosis (liver biopsy NAS component)	N=75	0.03 [-0.2, 0.26]	0.799
NAS score (liver biopsy)	N=77	0.04 [-0.19, 0.26]	0.730
Fibrosis			
FIB-4	N=225	0.06 [-0.07, 0.19]	0.381
FibroScan kPa	N=47	-0.06 [-0.34, 0.23]	0.699

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Nothing to Disclose, Andres Gomez-Aldana: Nothing to Disclose, Eric Lawitz: Nothing to Disclose, Fred Poordad: Nothing to Disclose, Lisa Pedicone: Nothing to Disclose, Eugenia Tsai: Nothing to Disclose

2044 | MISCLASSIFICATION AND DISCORDANCE WITH MAGNETIC RESONANCE ELASTOGRAPHY USING FIB-4-BASED STRATIFICATION FOR AT-RISK MASLD ◆

Akash Roy[1] Subarna Bhattacharya[2] Nipun Verma[3] Arka De[3] Shruti Keyal[2] Surabhi Jajodia[2] Usha Goenka[2] Mahesh Goenka[1]

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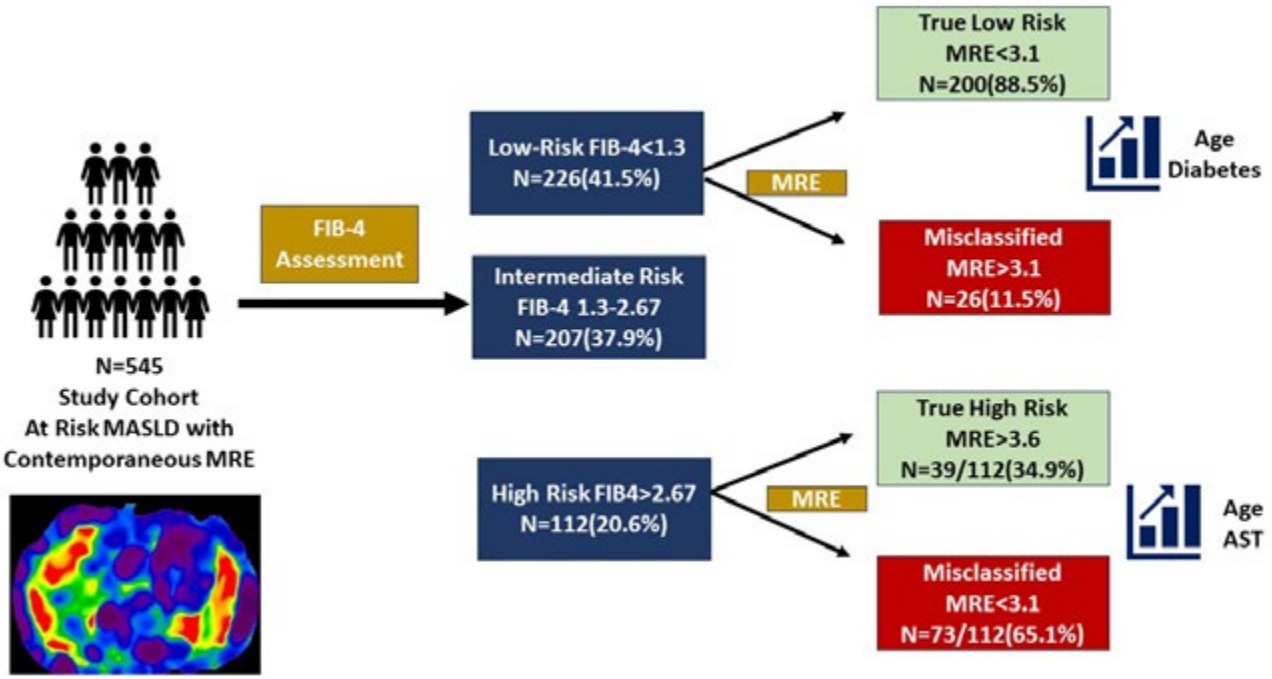
Background: Current guidelines recommend Fibrosis-4 (FIB-4) based stratification into low, intermediate, and high-risk for decision-making and further testing in metabolic dysfunction associated steatotic liver disease (MASLD). High misclassification has been reported compared to transient elastography (TE). TE has inherent limitations, especially in obese MASLD, and magnetic resonance elastography (MRE) is deemed to perform better **Methods:** In a prospective observational study, we identified individuals at risk for MASLD-associated fibrosis and categorized them as per current FIB-4-based stratification [low risk (LR): FIB-4<1.3, intermediate risk (IR) 1.3-2.67, high risk (HR) >2.67]. Misclassification and discordance were assessed with contemporaneous MRE as the outcome measure.Characteristics were identified for discordance at both low and high-risk ends. Predictors of misclassification were assessed using univariable and multivariable logistic regression **Results:** Among, 545 subjects at-risk individuals, [age44(36-53) years,35.7%females,77.9%obese, 34.6% diabetes,34.4% hypertensive, 36.1%dyslipedemic], 226(41.5%), 207(37.9%), and 112 (20.6%) were LR, IR, and HR by FIB-4 classification. Among those classified as LR, 26(11.5%) and 18 (7.9%) were at risk for significant and advanced fibrosis respectively by MRE. Individuals misclassified as having LR by FIB-4, were older[51.5(37-57) vs 36(31-45)]., had more diabetes (50% vs 22.5%) and dyslipidemia (50% vs 30.5%)(p=<0.05 for all), and lower albumin levels [4.3(4.1-4.4)vs. 4.4(4.1-4.7),p=0.03]. Among those identified FIB4-HR, 73 (65.1%) had no significant fibrosis on MRE (LSM<3.1 kPa) and 45(40%) had MRE-LSM <2.5 kPa. Individuals misclassified were younger [49(43-57) vs.53.5-50-64) and had higher AST [78(58-110)IU/ml)(p<0.01 for both). Age predicted misclassification with both LR-FIB-4(OR, 1.07(1.02-1.13, p=0.003) and HR-FIB-4[0.94(0.90-0.99)p=0.01] **Conclusion:** Using contemporaneous MRE, we identify that one in ten low-risk FIB-4 are at significant risk, while almost two-thirds of those identified as high risk by FIB-4 are not at risk. Caution is mandated in using FIB-4 based pathways, especially in older individuals and diabetics.



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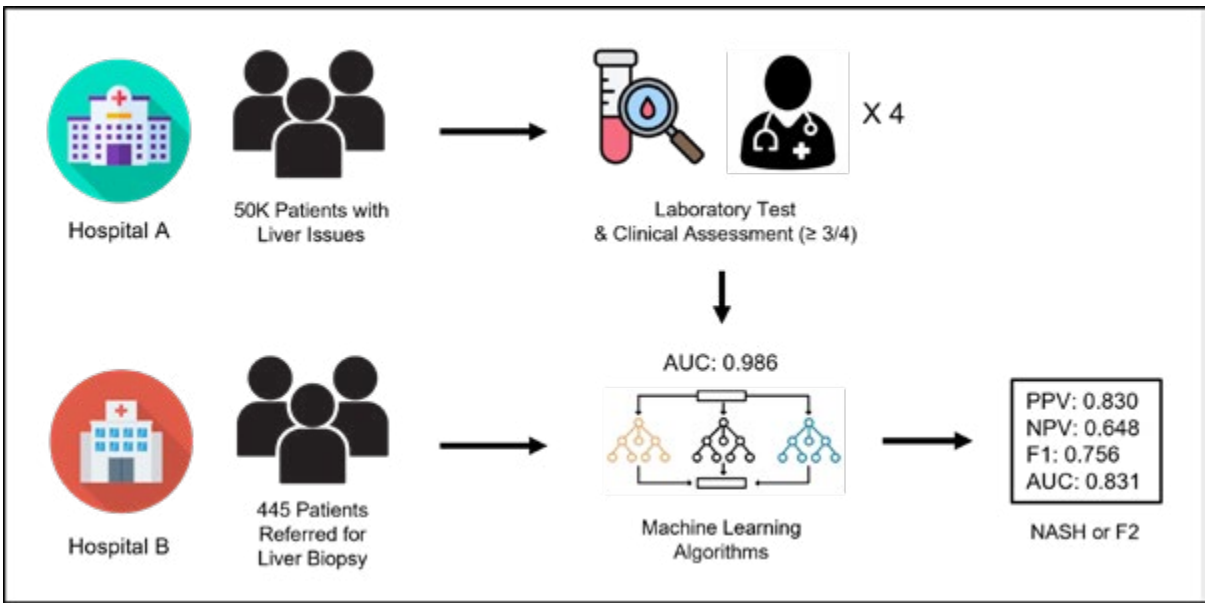
Disclosures: Akash Roy: Nothing to Disclose, Subarna Bhattacharya: Nothing to Disclose, Nipun Verma: Nothing to Disclose, Arka De: Nothing to Disclose, Shruti Keyal: Nothing to Disclose, Surabhi Jajodia: Nothing to Disclose, Usha Goenka: Nothing to Disclose, Mahesh Goenka: Nothing to Disclose

2045 | IDENTIFYING CANDIDATES FOR LIVER BIOPSY IN METABOLIC-ASSOCIATED STEATOTIC LIVER DISEASE: MACHINE LEARNING-BASED PREDICTIVE MODELS ◆ ★

Dong Yun Kim[1] Hye Won Lee[1] Ho Soo Chun[2] Jae Seung Lee[1] MiNa Kim[1] Hae Ryong Yun[1] Jun Yong Park[1]

[1]Yonsei University College of Medicine, [2]Ewha Womans University College of Medici

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD), an increasingly common cause of chronic liver disease. Although liver biopsy remains the gold standard for diagnosing liver fibrosis, it is an invasive procedure with inherent risks. Non-invasive tests have shown promise in reducing reliance on biopsies; however, they often lack the precision required for definitive diagnosis and fibrosis staging. Here, we developed a machine learning (ML)-based predictive algorithm that integrates the expertise of multiple hepatologists to guide decisions regarding liver biopsy in MASLD patients. **Methods:** We analyzed data from 45,392 patients to develop an ML-based algorithm that can guide liver biopsy decisions. The dataset was divided into training (80%) and test (20%) sets. Four independent hepatologists reviewed clinical information to determine the need for biopsy; their decision-making processes were modeled using XGBoost. These models were integrated into a unified algorithm. Subsequently, this algorithm was validated on a cohort of 445 patients with biopsy-proven diagnoses, assessing its ability to predict significant fibrosis or metabolic dysfunction-associated steatohepatitis (MASH). **Results:** Four independent hepatologists recommended liver biopsies in 1,639 (3.61%), 6,700 (14.8%), 4,511 (9.9%), and 8,732 (19.2%) patients, respectively. However, all four physicians agreed on the need for biopsy in 1,245 (2.74%) patients. Individualized predictive models achieved high area under the receiver operating characteristic curve values (0.979–0.995). These findings indicate that although biopsy decisions may differ among physicians, each follows a consistent pattern; this consistency allowed the development of individualized algorithms that effectively captured and replicated each physician's decision-making process. Furthermore, an integrated algorithm, combining the expertise of all four hepatologists, demonstrated over 98% concordance with the consensus of at least three physicians regarding biopsy necessity. In a cohort of 445 patients with prior liver biopsies, we assessed the ability of the integrated algorithm to predict MASH within patients recommended for biopsy. Of these patients, 261 (58.7%) had significant fibrosis (≥ 2) or MASH (≥ 5). The algorithm demonstrated good performance (area under the curve = 0.83) in identifying patients with MASH or significant fibrosis; its sensitivity, specificity, positive predictive value, and negative predictive value were 69%, 80%, 83%, and 64.8%, respectively. **Conclusion:** ML-based predictive models can effectively identify patients with MASLD who may benefit from liver biopsy, reducing the need for invasive procedures. This approach can significantly improve clinical decision-making and patient outcomes by integrating the expertise of multiple clinicians into a unified model.



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Disclosures: Dong Yun Kim: Nothing to Disclose, Hye Won Lee: Nothing to Disclose, Ho Soo Chun: Nothing to Disclose, Jae Seung Lee: Nothing to Disclose, MiNa Kim: Nothing to Disclose, Hae Ryong Yun: Nothing to Disclose, Jun Yong Park: Nothing to Disclose

2046 | CLINICAL UTILITY AND DIAGNOSTIC ACCURACY OF PHOSPHATIDYLETHANOL FOR DETECTING AND DIFFERENTIATING METALD FROM MASLD: A PROSPECTIVE STUDY

Federica Tavaglione[1] Maral Amangurbanova[1] Alexander Yang[1] Monica Tincopa[1] Veeral Ajmera[1] Lisa Richards[1] Christian Butcher[1] Christie Hernandez[1] Egbert Madamba[1] Seema Singh[1] Ricki Bettencourt[1] Claude Sirlin[1] Rohit Loomba[1]

[1]University of California, San Diego

Background: The new overarching nomenclature of steatotic liver disease (SLD) encompasses a dynamic spectrum of subcategories resulting in hepatic steatosis, namely metabolic dysfunction-associated steatotic liver disease (MASLD), MASLD with increased alcohol use (MetALD), and alcohol-related liver disease (ALD). The accurate quantification of alcohol use is crucial to identify SLD subcategories and remains challenging. Phosphatidylethanol (PEth) is a direct alcohol biomarker with high sensitivity and specificity, being an abnormal phospholipid formed only in the presence of ethanol. Herein, we aimed to assess the diagnostic accuracy of PEth for detecting and differentiating MetALD from MASLD in a large, population-based, multiethnic cohort of individuals with overweight/obesity. **Methods:** This is a cross-sectional analysis of a prospective cohort study including 374 well-characterized adults with overweight or obesity residing in Southern California who had SLD (defined as magnetic resonance imaging proton density fat fraction [MRI-PDFF] ≥5%). The clinical research visit included clinical history, biochemical and PEth testing, physical exam, and a detailed liver disease phenotyping using MRI-PDFF and MRE. Alcohol use was assessed by standardized validated questionnaires. PEth performance was estimated by the area under the receiver operating characteristic curve (AUROC). Cut-offs were derived based on the maximal sum of sensitivity and specificity (Youden index), on specificity ≥0.90, and maximizing sensitivity. AUROCs were compared using the DeLong test. **Results:** The mean (SD) age and BMI of the study population were 51.1 (12.6) years and 32.9 (6.1) kg/m^2, respectively. Among 374 adults with SLD, median PEth value increased in a step-wise manner from 9 ng/mL in MASLD versus 58 ng/mL in MetALD versus 83 ng/mL in alcohol-related liver disease (ALD) ($p<0.0001$). PEth had a robust diagnostic accuracy in the detection of MetALD (AUROC 0.81, 95%CI 0.73-0.89). Youden cut-off was 25 ng/mL; cut-offs based on specificity ≥0.90 and maximizing sensitivity were 35 ng/mL and 9.5 ng/mL, respectively. We then performed head-to-head comparison between PEth and indirect biomarkers of alcohol use, and demonstrated that PEth was both statistically and clinically superior as a diagnostic biomarker for MetALD compared to indirect alcohol biomarkers, including aspartate aminotransferase/alanine aminotransferase (AST/ALT) ratio, mean corpuscular volume (MCV), gamma-glutamyl transferase (GGT), and ALD/NAFLD index (ANI) (all $p<0.05$) (Figure 1). **Conclusion:** PEth is an accurate, quantitative, blood-based biomarker to detect MetALD and is better than previously available indirect alcohol biomarkers. Incorporation of PEth can facilitate effective and objective classification of MetALD.

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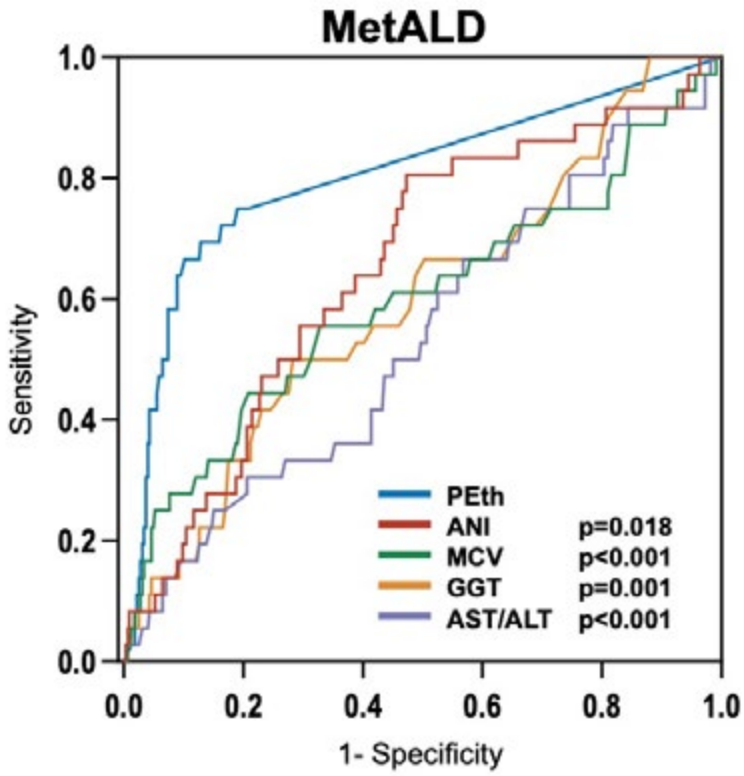
Figure 1: Diagnostic accuracy of PEth for detecting MetALD in individuals with complete data on alcohol biomarkers (N=362).



	AUROC (95% CI)	p-value
PEth	0.80 (0.72-0.89)	reference
ANI	0.66 (0.56-0.75)	**0.018**
MCV	0.60 (0.48-0.71)	**<0.001**
GGT	0.60 (0.50-0.70)	**0.001**
AST/ALT	0.54 (0.43-0.64)	**<0.001**

Disclosures: Federica Tavaglione: Nothing to Disclose, Maral Amangurbanova: Nothing to Disclose, Alexander Yang: Nothing to Disclose, Monica Tincopa: Nothing to Disclose, Veeral Ajmera: Nothing to Disclose, Lisa Richards: Nothing to Disclose, Christian Butcher: Nothing to Disclose, Christie Hernandez: Nothing to Disclose, Egbert Madamba: Nothing to Disclose, Seema Singh: Nothing to Disclose, Ricki Bettencourt: Nothing to Disclose, Claude Sirlin: Nothing to Disclose, Rohit Loomba: Eli Lilly and Company: Consultant, 89bio: Consultant, Aardvark Therapeutics: Consultant, Altimmune: Consultant, Alnylam/Regeneron: Consultant, Amgen: Consultant, Arrowhead Pharmaceuticals: Consultant, AstraZeneca: Consultant, Bristol Myers Squibb: Consultant, CohBar: Consultant, Eli Lilly: Consultant, Galmed Pharmaceuticals: Consultant, Gilead: Consultant, Glympse Bio: Consultant, Hightide: Consultant, Inipharma: Consultant, Intercept: Consultant, Inventiva: Consultant, Ionis: Consultant, Janssen, Inc.: Consultant, Madrigal Pharmaceuticals: Consultant, Merck, Metacrine, Inc.: Consultant, NGM Biopharmaceuticals: Consultant, Novartis: Consultant, Novo Nordisk: Consultant, Pfizer: Consultant, Sagimet Biosciences: Consultant, Terns Pharmaceuticals: Consultant, Theratechnologies and Viking Therapeutics: Consultant, 89bio: Stock options, Sagimet Biosciences: Stock options, Arrowhead Pharmaceuticals: Research grant, AstraZeneca: Research grant, Boehringer Ingelheim: Research grant, Bristol Myers Squibb: Research grant, Eli Lilly: Research grant, Galectin Therapeutics: Research grant, Galmed Pharmaceuticals: Research grant, Gilead: Research grant, Hanmi: Research grant, Intercept: Research grant, Inventiva: Research grant, Ionis: Research grant, Janssen, Inc.: Research grant, Madrigal Pharmaceuticals: Research grant, Merck: Research grant, NGM Biopharmaceuticals: Research grant, Novo Nordisk: Research grant, Pfizer: Research grant, Sonic Incytes: Research grant, Terns Pharmaceuticals: Research grant, LipoNexus, Inc.: Co-founder

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2047 | EVALUATION OF THE CONSISTENCY AND HETEROGENEITY OF FIBROSIS ASSESSMENT IN ADJACENT VIRTUAL LIVER NEEDLE BIOPSIES USING AI-BASED QFIBROSIS

Yayun Ren[1] Dean Tai[1] Elaine Chng[1] Kutbuddin Akbary[1] Nikolai Naoumov[2] Jonathan Fallowfield[3] Timothy Kendall[3] David Kleiner[4] Arun Sanyal[5]

[1]HistoIndex Pte Ltd, [2]Royal College of Physicians, [3]University of Edinburgh, [4]National Cancer Institute, [5]Virginia Commonwealth University

Background: Liver fibrosis serves as a key prognostic indicator in patients with metabolic dysfunction-associated steatohepatitis (MASH) and is a key surrogate endpoint in MASH clinical trials. Despite the increasing application of digital pathology in these trials, which offers quantitative and reproducible assessments of fibrosis dynamics, the impact of needle positioning and serial sectioning on fibrosis assessment remains inadequately addressed. This study evaluates the consistency and heterogeneity of fibrosis assessment in adjacent virtual liver needle biopsies using Second Harmonic Generation/Two Photon Excitation (SHG/TPE) microscopy with artificial intelligence (AI)-based qFibrosis (qF) assessment. **Methods:** SHG/TPE microscopy scanned 100 liver samples taken from liver resections or explants in the SteatoSITE cohort, spanning NASH-CRN stages F0 to F4. Two adjacent virtual needle biopsies (VNBs) were extracted from each image, each measuring 0.9 mm in width and 15 mm in length. qF assessment was performed independently for each VNB, focusing on fibrosis areas within 5 liver zones: portal tract (PT), periportal (PP), zone 2 perisinusoidal (PS), pericentral (PC) and central vein (CV). **Results:** The qF assessments of both VNBs correlated strongly with NASH-CRN stages, achieving Obuchowski indices of 0.90 and 0.94, respectively. There was substantial agreement between the two VNBs' qF stages (linear weighted kappa =0.71). 61 samples showed identical qF stages across the adjacent VNBs, with only 1 sample displaying a 2-point discrepancy. Statistical analysis (Wilcoxon signed rank test) confirmed no significant differences in the continuous qF values between the adjacent VNBs, with median difference of 3% (interquartile range: -12% to 13%). Zonal fibrosis differences were also non-significant ($p>0.05$). Among the zones, PP and PS fibrosis showed the smallest variations - median difference of 0% (-13%, 23%) and -4% (-16%, 14%), respectively. CV fibrosis showed the greatest variability, with a median difference of 5% (-60%, 99%). **Conclusion:** This systematic analysis confirms that adjacent VNBs are sufficiently reliable for fibrosis assessment using SHG/TPE microscopy. The high consistency observed in fibrosis evaluations across adjacent VNBs supports the reliability of qF as a method for quantitative fibrosis assessment in clinical trials.

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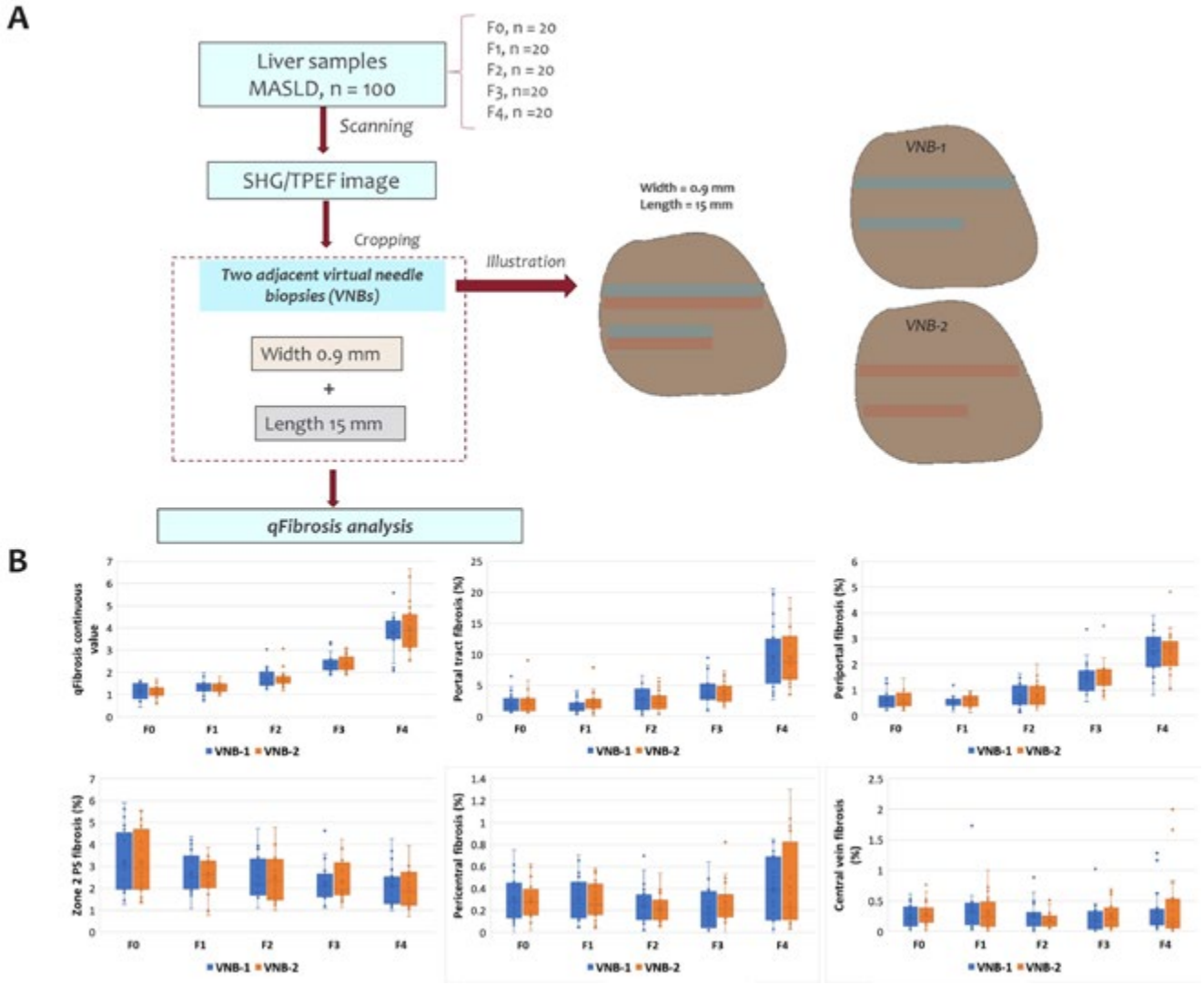

Disclosures: Yayun Ren: HistoIndex Pte Ltd: Employee, Dean Tai: Histoindex.com: Employee, Elaine Chng: Nothing to Disclose, Kutbuddin Akbary: HistoIndex Pte Ltd: Employee, Nikolai Naoumov: Nothing to Disclose, Jonathan Fallowfield: Stimuliver: Advisor, Ipsen: Advisor, Kynos Therapeutics: Advisor, Resolution Therapeutics: Consultant, River 2 Renal Corp.: Advisor, Global Clinical Trial Partners: Advisor, Guidepoint: Consultant, GlaxoSmithKline: Grant/Research Support, Genentech: Grant/Research Support, Intercept Pharmaceuticals: Grant/Research Support, Timothy Kendall: Nothing to Disclose, David Kleiner: Nothing to Disclose, Arun Sanyal: Genfit, Akarna, Tiziana, Durect, Inversago, Hemoshear, North: Stock - publicly traded company, Astra Zeneca (60K), Boston Pharmaceutical

2048 | SERUM IL-16 PREDICTS VISCERAL FAT INFLAMMATION ASSOCIATED WITH METABOLIC DYSFUNCTION IN PATIENTS WITH BARIATRIC SURGERY

Sachiyo Yoshio[1] Hiromasa Namba[2] Taiji Yamazoe[2] Susumu Inamine[3] Takumi Kawaguchi[4]

[1]National Center for Global Health and Medicine, [2]NCGM, [3]Ohama Daiichi Hospital, [4]Kurume University School of Medicine

Background: Obesity usually accompanies chronic adipose tissue inflammation, progressing to metabolic syndrome. Metabolic dysfunction associated steatotic liver disease (MASLD) is regarded as a phenotype in the liver of metabolic syndrome. Bariatric surgery dramatically improves glycolipid metabolism and MASLD. In this study, we aimed to identify the preoperative predictive biomarker for systemic inflammation associated with

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metabolic dysfunction in patients with obesity. **Methods:** This prospective study enrolled 69 patients with morbid obesity who underwent bariatric surgery (sleeve Gastrectomy) from July 2020 to July 2022. We examined 72 humoral factors in sera obtained from the patients before, 24w, and 48w after surgery, using multiplex assay and ELISA. We evaluated the volume of visceral and subcutaneous fat (CT), body composition, and liver stiffness (shear wave elastography), the expression levels of IL-16 in liver tissue, visceral and subcutaneous fat. We also examined peripheral blood mononuclear cells (PBMCs) by mass cytometory. As controls, we analyzed the sera and PBMCs from 8 healthy controls. **Results:** The median patient age was 43.8 years, and 62.3% of the patients were female. The median BMI was 45.3 kg/m^2. The numbers of patients diagnosed with Brunt criteria 0/1/2/3/4 were 14/11/33/9/2, respectively. The median AST/ALT levels were 43.0/57.8 U/L. At 24w after the operation, BMI, liver stiffness, AST, ALT, γGTP, M2BPGi, liver stiffness, CRP, ferritin, triglyceride, HbA1c were reduced. Twelve humoral factors (IL-16, TNF-α, CCL25, CX3CL1, CXCL12, CXCL13, CCL23, MIF, GM-CSF, CXCL1, IL-10, CXCL1, Leptin) increased in obese patients compared with healthy controls, and reduced at 24w after bariatric surgery. Among these 12 factors, directed acyclic graph selected IL-16 as an upstream factor among 12 factors, and IL-16 was positively correlated with the other 11 factors. IL-16 increased in obese patients with metabolic dysfunction, but not in metabolically healthy obese patients. IL-16 showed no correlation with BMI, but showed a positive correlation with the volume of visceral fat and insulin resistance. The expression levels of IL-16 mRNA was higher in visceral fat than in subcutaneous fat. Fluorescent immunostaining of stomach walls reveled that IL-16 was induced mainly by T cells. Intermediate monocytes (CD14^{++}CD16^{+}), which actively produce proinflammatory cytokines, were increased in obese patients compared with healthy controls, and reduced at 24w after bariatric surgery. Serum IL-16 showed a strong correlation with the cell counts of intermediate monocytes. These data suggest that IL-16 is produced mainly by T cells and is associated with systemic inflammation and metabolic dysfunction in obese patients. **Conclusion:** Serum IL-16 predicts visceral fat inflammation associated with metabolic dysfunction in patients with bariatric surgery

Disclosures: Sachiyo Yoshio: Gilead Sciences: Speaking and Teaching, Hiromasa Namba: Nothing to Disclose, Taiji Yamazoe: Nothing to Disclose, Susumu Inamine: Nothing to Disclose, Takumi Kawaguchi: ASKA Pharmaceutical Co., Ltd.: Speaking and Teaching, Taisho Pharmaceutical Co., Ltd.: Speaking and Teaching, Kowa Company, Ltd.: Speaking and Teaching, AbbVie GK.: Speaking and Teaching, Eisai Co., Ltd.: Speaking and Teaching, Novo Nordisk Pharma Ltd.: Speaking and Teaching, Janssen Pharmaceutical K.K.: Speaking and Teaching, Janssen Pharmaceutical K.K.: Speaking and Teaching, Otsuka Pharmaceutical Co., Ltd.: Speaking and Teaching, EA Pharma Co.,Ltd.: Speaking and Teaching

2049 | CHARACTERIZATION OF INTRACELLULAR ORGANELLE ABNORMALITIES IN MAFLD

Hidenori Kido[1] Masahiro Yanagi[1] Shihui Li[1] Takuya Seike[1] Hidetoshi Nakagawa[1] Toshikatsu Tamai[1] Tetsumori Yamashima[2] Eishiro Mizukoshi[1] Taro Yamashita[1]

[1]Department of Gastroenterology, Kanazawa University Hospital, [2]Department of Psychiatry and Behavioral Science, Kanazawa University Graduate School of Medical Scie

Background: Reported mechanisms of metabolic-associated fatty liver disease (MAFLD), include oxidative stress from mitochondria, ER stress from endoplasmic reticulum, and disruption of intracellular homeostasis due to autophagy abnormalities. However, the morphological changes of these intracellular organelles have not been thoroughly elucidated, and evaluation criteria are lacking. **Methods:** 1. Human Study: Liver biopsy samples from 25 patients at our hospital were assessed for patient background, light microscopy findings, and transmission electron microscopy (TEM) findings. 2. Animal Model Study: Liver tissues from mice fed a choline-deficient, methionine-reduced, amino acid-defined high-fat diet (CDAA diet), a model for MAFLD, were evaluated using light microscopy and TEM. 3. Correlation Analysis: The correlation between light microscopy and TEM findings was evaluated in the patient cohort using Spearman's rank correlation coefficient, with a p-value of <0.05 considered significant. **Results:** 1. Human Study: Seventeen patients met the diagnostic criteria for MAFLD, characterized by fatty liver and multiple metabolic disorders. The NAFLD activity score (NAS) breakdown was 0-2/3-4/5-8 in 14/10/1 cases, respectively. TEM revealed characteristic findings such as spherically deformed mitochondria with ruptured double membranes and cristae forming autophagosomes, reduced glycogen granules in the cytosol, dilated and degenerated rough endoplasmic reticulum, and increased autophagosomes with decreased lysosomes in MAFLD. 2. Animal Model: Light microscopy of liver tissues from CDAA-fed mice showed MAFLD-characteristic findings such as steatosis, lobular inflammation, and hepatocyte ballooning. Electron microscopy

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revealed similar mitochondrial, glycogen granule, rough endoplasmic reticulum, and autophagosome changes as observed in patient samples. 3. Correlation Analysis: TEM findings in mitochondria, glycogen granules, rough endoplasmic reticulum (graded on a 3-point scale, respectively), and autophagosomes (2-point scale) were evaluated for their correlation with NAS components using Spearman's rank correlation coefficient. Strong correlations were observed among multiple components, with abnormalities in mitochondria and glycogen granules showing a strong correlation with the total NAS score.We conducted Mann-Whitney U tests on the TEM findings between the non-MAFLD and MAFLD groups. Significant differences were observed between the non-MAFLD and MAFLD groups in the categories of Mitochondria, Glycogen granules, and rER (p-value=0.0208, 0.0019, 0.0446<0.05). **Conclusion:** TEM revealed characteristic intracellular organelle abnormalities in MAFLD, which were strongly correlated with histopathological scoring used for diagnosis. These findings provide mechanistic insights into the pathogenesis of MAFLD.

Disclosures: Hidenori Kido: Nothing to Disclose, Masahiro Yanagi: Nothing to Disclose, Shihui Li: Nothing to Disclose, Takuya Seike: Nothing to Disclose, Hidetoshi Nakagawa: Nothing to Disclose, Toshikatsu Tamai: Nothing to Disclose, Tetsumori Yamashima: Nothing to Disclose, Eishiro Mizukoshi: Nothing to Disclose, Taro Yamashita: Nothing to Disclose

2050 | DIAGNOSTIC PERFORMANCE OF FIBROSCAN'S CONTROLLED ATTENUATION PARAMETER (CAP) AND CONTINUOUS CAP IN MASLD WITH PDFF AS THE REFERENCE: A MULTICENTER STUDY

Asako Nogami[1] Michihiro Iwaki[1] Takashi Kobayshi[1] Sadanobu Ogawa[2] Tatsuya Gotoh[2] Hideki Hayashi[2] Kazuhito Kawata[3] Masashi Hirooka[4] Yohei Koizumi[4] Yoichi Hiasa[4] Masato Yoneda[1] Atsushi Nakajima[1] Takashi Kumada[5]

[1]Yokohama City University Graduate School of Medicine, [2]Ogaki Municipal Hospital, [3]Hamamatsu University, [4]Ehime University, [5]Gifu Kyoritsu University

Background: FibroScan's SmartExam feature, which includes the continuous controlled attenuation parameter (cCAP), is a new computation method that more accurately measures liver steatosis by continuously assessing the degree of fat attenuation. However, actual data on its clinical usefulness are scarce. This retrospective, multicenter study, conducted at five tertiary hospitals, compares the diagnostic accuracy of CAP measured by the original FibroScan and cCAP measured by the FibroScan with SmartExam, using magnetic resonance imaging-based proton density fat fraction (MRI-PDFF) as the reference, in patients with metabolic dysfunction-associated liver disease (MASLD). **Methods:** This retrospective study included 441 individuals with MASLD (male: 197 patients, 44.7%), with a mean BMI of 27.47±5.05 (range: 14.78-46.16), at five tertiary centers in Japan between 2021 and 2023. CAP measurements were performed using both FibroScan machines with M and XL probes for each individual. Each individual's CAP measurements were conducted with the same probe ("M probe only," "XL probe only," or "both M and XL probes") on both FibroScan machines. Of the 443 participants, 249 also had MRI-PDFF measurements within a month of the FibroScan measurements. Steatosis grade was defined as grade 0 with MRI-PDFF < 5.2%, grade 1 with 5.2% ≤ MRI-PDFF < 11.3%, grade 2 with 11.3% ≤ MRI-PDFF < 17.1%, and grade 3 with MRI-PDFF ≥ 17.1%. The reproducibility of CAP and cCAP was evaluated using Bland-Altman analysis and intraclass correlation coefficients, while the diagnostic performance for each steatosis grade of CAP and cCAP was assessed using receiver operating characteristic (ROC) analysis based on MRI-PDFF results. The Delong test was used to compare the ROCs. **Results:** The Bland-Altman analysis indicated moderate positive reproducibility with minimal fixed bias between CAP and cCAP. The ROC analysis for steatosis grade ≥1, ≥2 and 3 were 0.84, 0.81 and 0.81 for CAP and 0.83, 0.81 and 0.81 for cCAP, respectively, showing no significant difference. **Conclusion:** Continuous CAP of SmartExam is as effective a tool for noninvasively evaluating liver steatosis as the original CAP. Both Continuous CAP and CAP of FibroScan have excellent diagnostic accuracy for grading steatosis with reference to MRI-PDFF.

Disclosures: Asako Nogami: Nothing to Disclose, Michihiro Iwaki: Nothing to Disclose, Takashi Kobayshi: Nothing to Disclose, Sadanobu Ogawa: Nothing to Disclose, Tatsuya Gotoh: Nothing to Disclose, Hideki Hayashi: Nothing to Disclose, Kazuhito Kawata: Nothing to Disclose, Masashi Hirooka: Nothing to Disclose, Yohei Koizumi: Nothing to Disclose, Yoichi Hiasa: Nothing to Disclose, Masato Yoneda: Gilead Sciences: Grant/Research Support, Gilead Siences inc.: Grant/Research Support, Atsushi Nakajima: Nothing to Disclose, Takashi Kumada: Nothing to Disclose

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2051 | THE EFFICACY OF MEASURING NATURAL KILLER ACTIVATING RECEPTOR LIGANDS TO PREDICT THE PATHOGENESIS OF MASLD

Jun Arai[1] Akinori Okumura[2] Satoshi Kimoto[2] Kazumasa Sakamoto[2] Tomoya Kitada[2] Mayu Ibusuki[2] Rena Kitano[2] Tadahisa Inoue[2] Yukiko Muraki[2] Sayaka Nishimura[2] Noriko Inden[2] Naoya Kato[3] Kiyoaki Ito[4]

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Background: The proportion of non-B, non-C hepatocellular carcinoma (NBNC-HCC) is increasing, with metabolic dysfunction-associated steatotic liver disease (MASLD) being a principal factor. The degree of intrahepatic natural killer (NK) cell infiltration has been reported to correlate with the progression of MASLD. There are many clinical reports on MICA and MICB, which are the corresponding ligands to NK cell activating receptors, in chronic liver diseases and HCC. Recently, B7H6 has been identified as a ligand for another NK cell-activating receptor, NKp30. All of these ligands are expressed on the surface of hepatocytes due to various stresses including viral infection and transformation, but there are few reports on MASLD. Therefore, we investigated the relationship between NK cell-activating receptor ligands and the pathogenesis of MASLD. **Methods:** This study cohort comprised 69 biopsy-proven MASLD patients enrolled from 2012 to 2018 at our institute. Informed consent was obtained from all patients, and the study was approved by the ethics review board at Aichi Medical University Hospital. Blood samples and clinical data were obtained at the time of liver biopsy. (1) The concentrations of MICA, MICB, and B7H6 in the sera of patients were measured using ELISA Kits. The data were statistically compared between the MAFL group and the MASH group. (2) Clinical characteristics associated with higher concentrations of each NK cell-activating receptor ligands were also investigated. **Results:** Among MAFL (N=25) and MASH (N=44) patients, all three ligands were higher in the MASH group. B7H6 ($p<0.05$), FIB-4 index ($p<0.001$), and M2BPGi ($p<0.001$) were significantly higher in the MASH group. Compared patients with F0-2 to those with F3-4, the concentrations of MICB($P=0.07$) and B7H6 ($p<0.001$) were higher in the latter, while there was no significant difference in MICA. B7H6 tended to be higher as the NAS score increased ($P<0.05$). Logistic regression analysis adjusted for sex, age, and BMI, MICB ($p<0.05$) and M2BPGi ($p<0.01$) were significantly correlated with MASH. Importantly, MICA and MICB were positively related and all three ligands were strongly correlated with AFP, and PIVKA-2. While MICB levels were positively correlated with AST and ALT, the patients with higher B7H6 levels had higher M2BPGi and a lower number of platelets. **Conclusion:** The three NK cell-activating receptor ligands were higher in the sera of the MASH group and strongly correlated with tumor markers, indicating the potential of hepatocarcinogenesis. Whereas MICB was correlated with the severity of intrahepatic inflammation, B7H6 was correlated with the degree of intrahepatic fibrosis.

Disclosures: Jun Arai: Nothing to Disclose, Akinori Okumura: Nothing to Disclose, Satoshi Kimoto: Nothing to Disclose, Kazumasa Sakamoto: Nothing to Disclose, Tomoya Kitada: Nothing to Disclose, Mayu Ibusuki: Nothing to Disclose, Rena Kitano: Nothing to Disclose, Tadahisa Inoue: Nothing to Disclose, Yukiko Muraki: Nothing to Disclose, Sayaka Nishimura: Nothing to Disclose, Noriko Inden: Nothing to Disclose, Naoya Kato: Nothing to Disclose, Kiyoaki Ito: Nothing to Disclose

2052 | VALIDATION OF FIBROTEST-T2D AS A SERUM BIOMARKER OF EARLY BRIDGING FIBROSIS ACCORDING TO BIOPSY LENGTH, AND SEX-SPECIFIC DIFFERENCES IN LARGE POPULATIONS AT RISK OF MASLD

Thierry Poynard[1] olivier Deckmyn[2] Raluca Pais[3] Gilles Leanour[3] Jean-Michel Oppert[4] Jean Michel Siksik[4] Dominique Thabut[4] Karine Clement[4] Valerie Paradis[4] Dominique Valla[4] Vlad Ratziu[3]

[1]Sorbonne University, [2]BioPredictive, [3]INSERM, [4]APHP

Background: Bariatric surgery (BS) and new obesity drugs reduce mortality and announce the widespread use of biomarkers in patients at risk of MASLD. Few biomarkers have applied three essential STARD methods (Tri-methods) to assess their uncertainty, including weighted-area under the curve (wAUROC), biopsy length, and score more sensitive (7-tier) than the CRN score (5-tier). Furthermore, the risk of false positive/negative of tests components associated with major confounding factors (CFs) age, sex, type-2-diabetes (T2D) and body-mass-index (BMI) in large populations at risk are often unknown.

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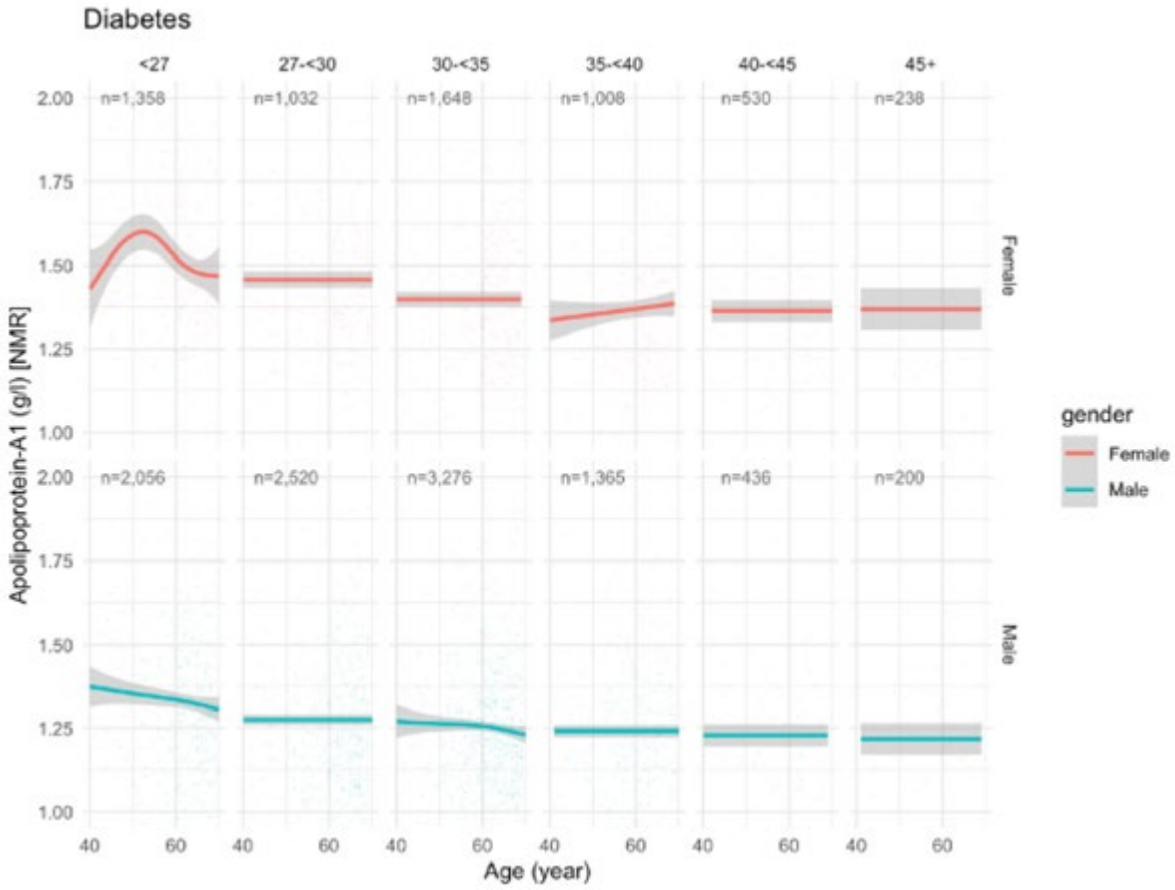
The aims were to apply the Tri-methods to the new optimized FibroTest for T2D (FibroTest-T2D) and to assess the risk of false positive/negative associated with CFs. **Methods:** Seven population subsets were analyzed cumulating 320,684 FibroTest-T2D and 1,903 biopsies (total/ patients/ controls): FibroTAGS 1289/1293/604, QuidNash (402/402/0), BARICAN (55/110/0), UK-Biobank (160380/0/0), USA-FibroTest (159,747/0/0), France-FibroTest (67,228/0/0) and LIDO (51,102/0). The accuracy of FibroTest-T2D was compared using Tri-methods or not, in T2D and BS. In 318,781 subjects at risk of MASLD, the trajectories of FibroTest-T2D components were analyzed against sex, T2D and BMI using spline curves, including UK-Biobank participants with (N=50,060) or without (N=12,898) menopause. **Results:** When biopsy length was above median, FibroTest-T2D wAUROC was 0.90 (SD=.01) vs 0.88 (SD=0.1) when lower (P<.001). After BS, histological F2-stage regression was observed in 16/29 (84%) by 7-tier vs. 3/20 (47%) by CRN (P=.005). In the three large populations (UK, USA and France), three major variabilities due to CFs were observed between sex (P<.0001). In women with T2D who are not overweight, there was an increase in apoA1 at perimenopausal age (Figure 1) confirmed using nuclear magnetic resonance in UK-Biobank, as well as 2) an increase in haptoglobin, both not seen in women without T2D nor in men and 3) in men alpha-2-macroglobulin in overweight men increased 10 years earlier than in women. These trajectories are in line with recent possible sex-dependent pathways such as formyl peptide receptor 2 for apoA1 or omega-3 fatty acids responsive proteins for A2M and haptoglobin. **Conclusion:** MASLD biomarkers validations need wAUROC, biopsy length stratification and a more sensitive scoring system than CRN. FibroTest-T2D predicts regression after BS. Confusion Factors adjustments on sex, age and T2D are needed to avoid misinterpretations in new obesity therapies.



Disclosures: Thierry Poynard: BioPredictive: Inovation Director, BioPredictive: FibroTest patents belong to Sorbonne University and APHP, olivier Deckmyn: Nothing to Disclose, Raluca Pais: Nothing to Disclose, Gilles Leanour: Nothing to Disclose, Jean-Michel Oppert: Nothing to Disclose, Jean Michel Siksik: Nothing to Disclose, Dominique Thabut: abbvie: Speaking and Teaching, gore: Speaking and Teaching, gilead: Speaking and Teaching, alfasigma: Consultant, satellite bio: Consultant, Karine Clement: Nothing to Disclose, Valerie Paradis: inventiva: Consultant, Dominique Valla: Nothing to Disclose, Vlad Ratziu: Nothing to Disclose

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2053 | THE DIABETESLIVER SCORE: A NON-INVASIVE ALGORITHM FOR ADVANCED LIVER FIBROSIS AND LONG-TERM LIVER-RELATED OUTCOMES IN TYPE 2 DIABETES MELLITUS POPULATION ◆

Chuan Liu[1] Xiaolong Qi[1] Jie Shen[2] Jie Li[3] Zhihui Li[4] Ming-Hua Zheng[5] Hua Bian[6] Xiqiao Zhou[7] Wenjing Ni[3] Xuan Liang[8] Min Li[9] Taolong Zhou[10] Heng Wan[2] Yuping Chen[1] Yan Wang[8] Wen-Yue Liu[5] Mingxing Huang[10] Shanghao Liu[1] Xiaomei Wang[8] Mingfeng Xia[6] Xuefeng Li[9] Yuehua Wang[11] Xinjie Li[12] Xiaoxiong Hu[13] Yan Wu[14] Huimin Ying[15] Jing He[16] Fengmei Wang[17] Wei Yan[18] Huili Wu[19] Qingge Zhang[20] Yuxia Qi[21] Weimin Jiang[22] Yan Huang[23] Yijun Tang[9] Yuwei Zhang[24] Ling Li[1] Terry Cheuk-Fung Yip[25] Gao-Jun Teng[1]

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Background: Type 2 diabetes mellitus (T2DM) has been recognized as a confirmed risk factor for the development of advanced liver fibrosis and hepatocellular carcinoma. Thus, this study aims to develop and validate a new model for screening advanced liver fibrosis. **Methods:** This study included 28,390 T2DM patients from five cohorts, including the derivation cohort (n=1,129), the internal validation cohort (n=1,000), the National Health and Nutrition Examination Survey (NHANES) cross-sectional cohort (n=1,433), the biopsy cohort (n=191) and UK biobank follow-up cohort (n=24,637). Advanced liver fibrosis defined as liver stiffness measurement ≥ 12kPa measured by transient elastography (FibroScan®, Echosens, Paris, France). **Results:** In derivation cohort, waist circumstances, alanine aminotransferase, aspartate aminotransferase, platelet count, and albumin were identified as independent risk factors of advanced fibrosis, and were fitted to develop the "DiabetesLiver score", which is available as a free calculator at https://chess.nuist.edu.cn/consult/gzconsult/DiabetesLiver_score. It boosted a receiver operating characteristic curve (AUC) of 0.835 (95% CI: 0.781-0.890), significantly higher than the AUCs of non-invasive tests (NITs) (all P < 0.01, Figure 1A-D). It maintained high AUCs of 0.870, 0.823 and 0.727 in internal validation (n=1,000), NHANES cross-sectional (n=1,432) and liver biopsy cohorts (n=191), respectively. A dual cutoff of 2.39 and 3.99 was applied to classify patients into three risk groups. In UK Biobank follow-up cohorts (n=24,636), the high-risk group had elevated risk for hepatocellular carcinoma and liver-related mortality. (all P<0.05, Figure 1E-F) **Conclusion:** The DiabetesLiver score showed a superior performance in identifying advanced liver fibrosis, and forecasting hepatocellular carcinoma incidence and liver-related mortality in T2DM population.

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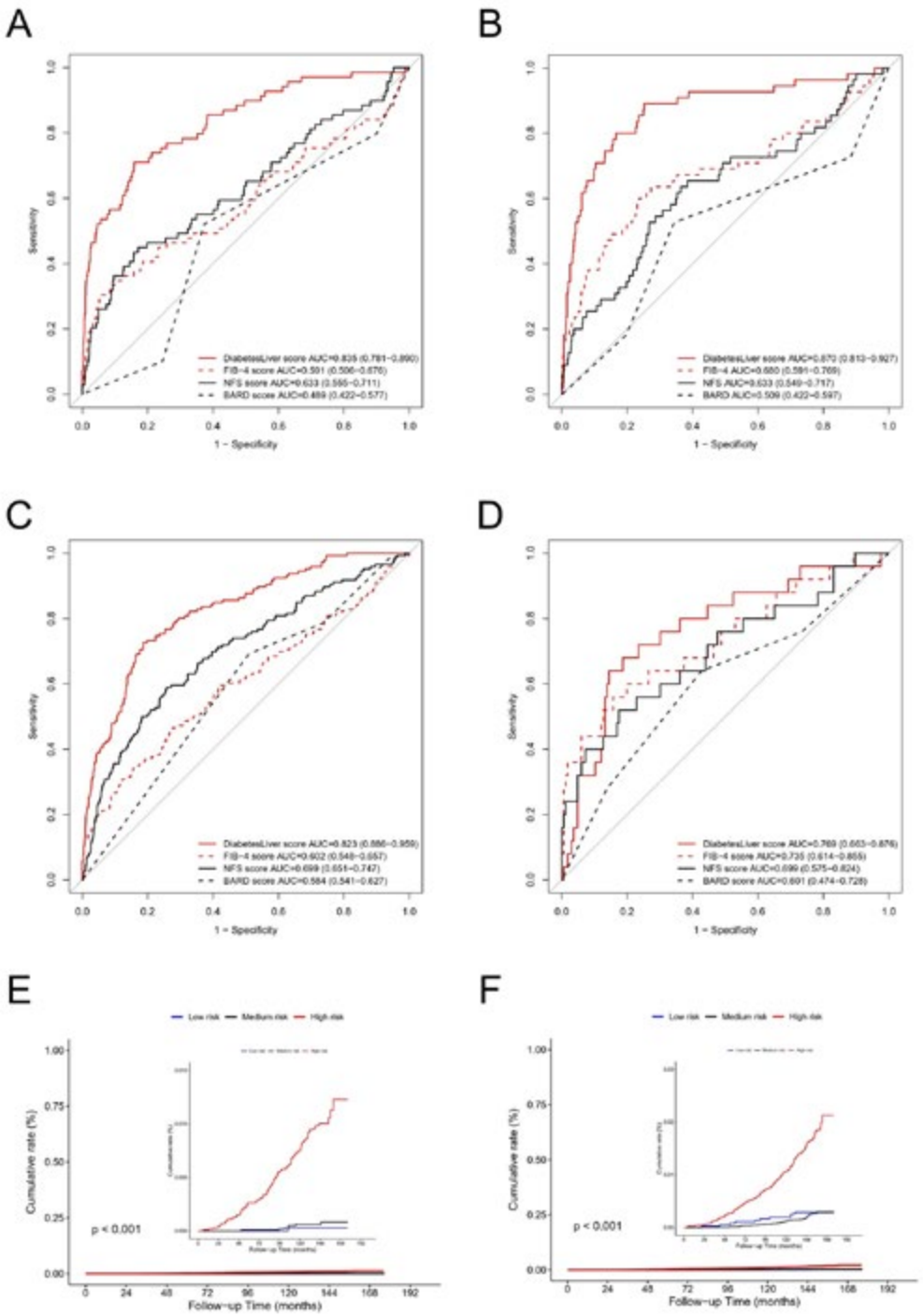

Disclosures: Chuan Liu: Nothing to Disclose, Xiaolong Qi: Nothing to Disclose, Jie Shen: Nothing to Disclose, Jie Li: Nothing to Disclose, Zhihui Li: Nothing to Disclose, Ming-Hua Zheng: Nothing to Disclose, Hua Bian: Nothing to Disclose, Xiqiao Zhou: Nothing to Disclose, Wenjing Ni: Nothing to Disclose, Xuan Liang: Nothing to Disclose, Min Li: Nothing to Disclose, Taolong Zhou: Nothing to Disclose, Heng Wan: Nothing to Disclose, Yuping Chen: Nothing to Disclose, Yan Wang: Nothing to Disclose, Wen-Yue Liu: Nothing to Disclose, Mingxing Huang: Nothing to Disclose, Shanghao Liu: Nothing to Disclose, Xiaomei Wang: Nothing to Disclose, Mingfeng Xia: Nothing to Disclose, Xuefeng Li: Nothing to Disclose, Yuehua Wang: Nothing to Disclose, Xinjie Li: Nothing to Disclose, Xiaoxiong Hu: Nothing to Disclose, Yan Wu: Nothing to Disclose, Huimin Ying: Nothing to Disclose, Jing He: Nothing to Disclose, Fengmei Wang: Nothing to Disclose, Wei Yan: Nothing to Disclose, Huili Wu: Nothing to Disclose, Qingge Zhang: Nothing to Disclose, Yuxia Qi: Nothing to Disclose, Weimin Jiang: Nothing to Disclose, Yan Huang: Nothing to Disclose, Yijun Tang: Nothing to Disclose, Yuwei Zhang: Nothing to Disclose, Ling Li:

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Nothing to Disclose, Terry Cheuk-Fung Yip: Gilead Sciences: Consultant, Gilead Sciences: Advisor, Gilead Sciences: Speaking and Teaching, Gao-Jun Teng: Nothing to Disclose

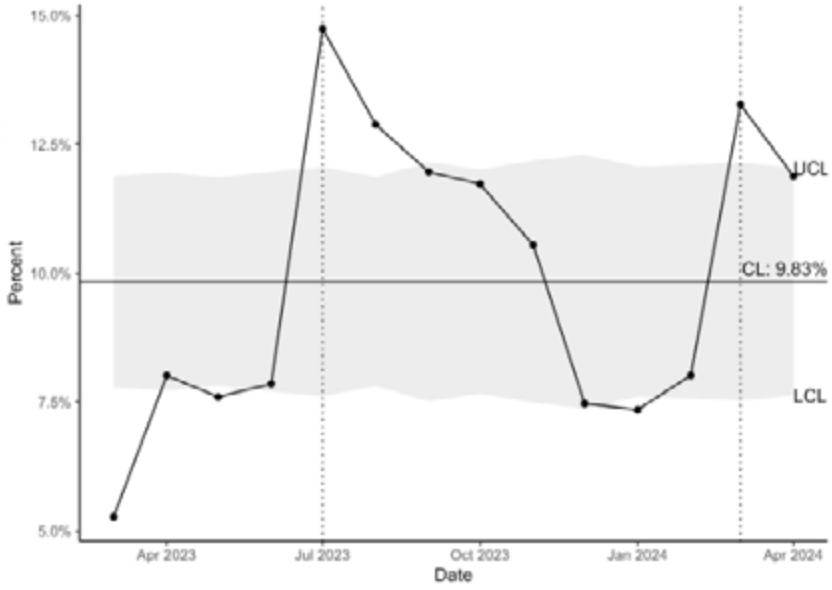
2054 | A REAL WORLD, LARGE SCALE APPLICATION OF THE AGA MASLD PATHWAY. PITFALLS, CHALLENGES AND SUCCESS STORY

Pratishtha Singh[1] Makda Bsrat[2] Gres Karim[2] Sarah Huang[2] Anas Zaher[2] Zhongqian Lin[2] Michelle Chanin[2] Wenna Xi[3] Robert Kim[3] Ilan Weisberg[3]

[1]New York Presbyterian Brooklyn Methodist Hospital, [2]NewYork-Presbyterian Brooklyn Methodist Hospital, [3]Weill Cornell Medicine

Background: Metabolic associated-steatotic liver dysfunction (MASLD) has rapidly evolved to become a leading indication for liver transplantation. The American Gastroenterological Association (AGA) proposes a clinical care pathway to guide the screening, diagnosis, and treatment of MASLD. Despite guidance statements, MASLD remains an underrecognized condition, increasing the likelihood of poor outcomes in affected patients. Our ongoing quality improvement project aims to screen and identify high-risk patients with clinically significant fibrosis (CSF, Fibrosis Stage > 2) in efforts to improve clinical outcomes and prevent cirrhosis by performing early intervention. **Methods:** We implemented a clinical care pathway based on AGA MASLD guidelines at four clinic practices within our institution (Internal Medicine, Endocrinology, Weight Management, and Gastroenterology). We created an electronic medical record screening smart tool to identify at-risk patients using FIB-4. Provider education sessions (PES) were regularly implemented between April 1, 2023 and April 30, 2024 at three-month intervals to improve uptake and adherence of our pathway (Figure 1). At-risk patients were directly referred to Fibroscan testing and MASLD clinic. **Results:** A total of 16,183 patients without a prior diagnosis of MASLD were seen in the four outpatient practices. Within our population, 9,480 (58.6%) patients met criteria for being at an increased risk for CSF. The average age was 60.7 years, while a large proportion was female (65%). Blacks constituted 49.5% of the population, and 14% were Hispanic. Cardiometabolic risk factors were highly prevalent with 58% of patients with type II diabetes, 39% with obesity, and 80% with hypertension (HTN). Although only 2,025 (21.4%) of at-risk patients were screened, 99 in individuals were identified with CSF. **Conclusion:** Our pilot MASLD screening pathway allowed for the detection and appropriate referral of 1 in 10 patients with CSF who would have otherwise been missed in one of the most diverse communities within New York City. Furthermore, our pathway allows providers and patients to overcome healthcare disparities known to exist in the spectrum of MASLD. This highlights the importance of integrating the pathway into routine clinical practice, as early intervention is associated with reduced health costs to the patient and healthcare system.

Figure: Shewhart Control Chart (P Chart) (Dotted line marking physician education sessions)



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Disclosures: Pratishtha Singh: Nothing to Disclose, Makda Bsrat: Nothing to Disclose, Gres Karim: Nothing to Disclose, Sarah Huang: Nothing to Disclose, Anas Zaher: Nothing to Disclose, Zhongqian Lin: Nothing to Disclose, Michelle Chanin: Nothing to Disclose, Wenna Xi: Nothing to Disclose, Robert Kim: Cleerly Health Inc.: Stock – privately held company, Ilan Weisberg: Nothing to Disclose

2055 | LIVER VIRTUAL BIOPSY USING CSE-MRI IN PATIENTS WITH CHRONIC LIVER DISEASE: A COMPARATIVE WORK WITH ELASTOGRAPHY AND BLOOD TEST

Juliette FOUCHER[1] Panteleimon PAPADOPOULOS[2] Paul Hermabessiere[3] Adèle DELAMARRE[2] benoit chardonnet[4] Renaud WINZENRIETH[4] Benjamin LEPORQ[5] Simon LAMBERT[4] Nora FRULIO[2]

[1]Hôpital Haut Lévêque, Bordeaux University Hospital, Bordeaux, France., [2]Hôpital Haut Lévêque, Bordeaux University Hospital, Bordeaux, France, [3]Hôpital Haut Lévêque Bordeaux University Hospital, Bordeaux, France, [4]SoQut-Imaging, [5]SoQut-Imaging / INSA–LYON, Université Claude Bernard1, CNRS, Inserm, CREATIS UMR 5220, U1294, France

Background: Liver chemical shift-encoded MRI (CSE-MRI) is used for simultaneous fat and iron liver content estimation through PDFF and R_2* measurement. However, monitoring chronic liver diseases (CLD) also requires evaluation of fibrosis severity. Although derived from a standard MRI sequence, CSE-MRI is underexploited. The use of phase information extracted from CSE-MRI allows the estimation of the magnetic susceptibility, a surrogate marker of the liver bulk macromolecule content. Previous work has demonstrated its interest in the diagnostic of MASH among MALFD patients (1). The aim of this study was to evaluate the feasibility of CSE-MRI for fibrosis assessment in a cohort of patients with CLDs. **Methods:** Between February and April 2024, among 50 patients with CLD who underwent a 1.5T MRI with CSE acquisition, 16 patient also had blood tests, liver stiffness measurement (FibroScan) and shear wave elastography (SWE) before MRI and were evaluated. PDFF, R_2* and magnetic susceptibility maps were automatically computed using a proprietary method developed by Soqut-Imaging and initially described in (1). From each map, whole liver was segmented to extract mean and standard deviation of each MRI metric. Correlations with blood tests, FibroScan LSM and SWE measurements were evaluated by computing the Spearman's coefficient. Based on a cut-off at 8.0 KPa on LSM, we also investigate the capacity of c to classify patients with non-significant and significant fibrosis. **Results:** Magnetic susceptibility was found strongly correlated to LSM (ρ=-0.70, $p<0.01$), SWE stiffness (ρ=-0.91, $p<0.001$) and viscosity (ρ=-0.96, $p<0.001$). Significant correlations were also found with blood tests: Fibrotest (ρ=-0.57, $p<0.05$), Hepascore (ρ=-0.77, $p<0.001$), Agile 3+ (ρ=-0.79, $p<0.001$), Agile 4 (ρ=-0.78, $p<0.001$), and Forns (ρ=-0.62, $p<0.01$). PDFF was correlated with the controlled attenuation parameters (ρ=-0.51, $p<0.05$). Magnetic susceptibility significantly decreased in significant fibrosis (-0.03 ± 0.017 ppm, n=9) in comparison to the other group (0.0009 ± 0.019 ppm, n=7, $p<0.01$). **Conclusion:** Due to sensitivity to bulk macromolecules, magnetic susceptibility has a great potential in fibrosis assessment. CSE-MRI could be a relevant alternative to provide a comprehensive liver analysis including fat and iron content quantification but also fibrosis assessment with only one apnea of 20 seconds. Leporq B, et *al*. NMR Biomed. 2017 Oct; 30(10).

Disclosures: Juliette FOUCHER: Viie: Speaking and Teaching, Gilead: Speaking and Teaching, Abbvie: Speaking and Teaching, Panteleimon PAPADOPOULOS: Nothing to Disclose, Paul Hermabessiere: Nothing to Disclose, Adèle DELAMARRE: Nothing to Disclose, benoit chardonnet: Nothing to Disclose, Renaud WINZENRIETH: SoQut-Imaging: Employee, Hekat Fluidics: Employee, Molzym GmbH: Employee, 3D-SHAPER MEDICAL SL: Employee, Benjamin LEPORQ: Nothing to Disclose, Simon LAMBERT: Nothing to Disclose, Nora FRULIO: Nothing to Disclose

2056 | FIB-4 SCORE IS AN UNRELIABLE NON-INVASIVE MARKER TO IDENTIFY PATIENTS WITH CIRRHOSIS DUE TO MASLD

Kristin Lescalleet[1] Talan Zhang[1] Nicol Tugarinov[1] Alok Shetty[1] Paul Thuluvath[2]

[1]Mercy Medical Center, [2]Mercy Medical Center and University of Maryland School of Medicine

Background: It has been suggested that FIB-4 score could be a reliable non-invasive test that could be used by practitioners to decide whether or when to refer patients with MASLD to a liver specialist (AASLD Practice

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Guidance 2023). Those with a score < 1.3 (<2.0 in age >65) have a lower likelihood of advanced fibrosis and can be monitored by a primary care provider. Patients with a score >2.67 are considered to have a higher likelihood of advanced fibrosis and should be referred to a specialist. Those with scores 1.3 to 2.67 (2.0 – 2.67 in age >65) need further non-invasive testing to assess for advanced fibrosis. Based on our anecdotal experience, we felt that FIB-4 is inadequate to identify those with cirrhosis. In this retrospective study, we determined the sensitivity and specificity of FIB-4 to identify those with cirrhosis secondary to MASLD. **Methods:** 443 patients with a known diagnosis MASLD were identified. Patients that were < 35 and > 90 years old, previous HCC diagnosis and previous liver transplant were excluded. Demographics, laboratory tests and the diagnosis during the initial outpatient visit were collected. The diagnosis of cirrhosis was based on clinical/imaging characteristics (portal hypertension on imaging, thrombocytopenia, ascites on exam), transient elastography (Kpa > 14), or liver histology. The agreement between FIB-4 and the diagnosis of cirrhosis was assessed by Kappa statistics. Logistic regression was performed to assess factors that had an impact on classification failure based on FIB-4. **Results:** The mean age was 55 ± 13 years and there were 42% men. Mean BMI was 34.5 ± 6.9 and 64% had hypertension, 55% had hyperlipidemia (55%), and 49% had type 2 diabetes. 150 (34%) patients had cirrhosis. secondary to NAFLD/MASLD and 293 were non-cirrhotic. Of the 150 cirrhotic patients, only 53% (p <0.001) were diagnosed with cirrhosis based on their FIB-4 score. Sensitivity, specificity, PPV and NPV were 53%, 89%, 71% and 79% respectively. Kappa score was only 0.45 (fair to moderate). Of the 150 patients with cirrhosis, 40% had FIB-4 scores between 1.3-2.67 and 7% had scores less than 1.3. On univariate analysis, only age (65 years or more) and the presence of DM2 had a significant impact on misclassification. **Conclusion:** Our study showed that 47% with cirrhosis would not have been referred to a specialist if FIB-4 scores alone were used to make that referral decision as suggested by AASLD Guidance paper. Although readily available, FIB-4 is an unreliable marker of cirrhosis in those with MASLD.

Disclosures: Kristin Lescalleet: Nothing to Disclose, Talan Zhang: Nothing to Disclose, Nicol Tugarinov: Nothing to Disclose, Alok Shetty: Nothing to Disclose, Paul Thuluvath: Abbvie, Bayer, Bristol Myers Squibb, Cirius Therapeutics, Co: Grant/Research Support, Gilead, AbbVie, Mallinckrodt, Madrigal: Speaking and Teaching, UpToDate, JHU Press: Royalties or patent beneficiary

2057 | A MACHINE LEARNING APPROACH IDENTIFIES PATIENTS AT RISK OF METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE-RELATED COMPLICATIONS AT THE POPULATION-LEVEL

Jaideep Behari[1] Rayid Ghani[2] Kasun Amarasinghe[2] Allison Bradley[1] Mohammad Ateya[3] Autumn Boyer[1] Kevin Townsend[3] Hansol Olivia Lee[1] Pamela Young[3] Laura Manzey[3] Feng Dai[3] Nickie Cappella[1] Julie Simonson[3] Julie Gouveia-Pisano[3] Jannette Escobar[3] Kathleen McTigue[1]

[1]University of Pittsburgh, [2]Carnegie Mellon University, [3]Pfizer Inc.

Background: Noninvasive testing for liver fibrosis is recommended for subgroups at risk of metabolic dysfunction-associated steatotic liver disease (MASLD), yet the optimal strategy for population-level screening is unclear. We aimed to develop a machine learning (ML) model to identify patients at risk of MASLD-related liver complications over a 3-year period. **Methods:** The study used 2240 derived features (predictors) from EHR data (demographics, encounters, diagnoses, prescriptions, procedures, labs, and vitals) from 1/1/11-5/1/23 from a US health system, including all eligible patients ≥18 years with ≥1 clinical encounter. Patients with baseline ICD-9/10 codes for non-MASLD liver diseases or liver-related complications were excluded. Liver-related complications were identified via ICD codes as the primary outcome. Over 80 ML models were developed on yearly cohorts between 5/1/15 and 5/1/23 to estimate the risk of liver-related complications within 3 years of prediction time and validated on repeated temporal cohorts from held out future data, using a tiered health system screening capacity approach based on risk. **Results:** Data were extracted from 2.86M patients. After applying exclusions, each yearly cohort consisted of ~1.7M patients (58% women, 85% white), with ~5500 patients reporting outcome events (0.3%) within 3 years. The top performing model (a balanced random forest), when evaluating at the top 1 percentile of estimated risk, had a Positive Predictive Value of 5.34% in the last validation cohort (as of 5/1/2020), a sensitivity of 16%, (~15x better than random and ~3x better than the best subgroup identification strategy), and AUROC of 0.82. This sensitivity increased to 52% for the highest 10 percentile of individuals based on their estimated risk. The Negative Predictive Values for liver-related complications for the top 3 performing models exceeded 99.7% for the top 1%, 5%, and 10% of individuals with the highest estimated risk. Model fairness analyses were

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conducted for race and gender by computing Sensitivity Disparity Ratio (SDR); sensitivity for Black patients was 1.1x higher than White patients and 1.25x higher for male patients than female patients. **Conclusion:** Machine learning models with EHR data could identify patients in the general population at high risk of MASLD-related complications. This approach may facilitate fair and cost-effective screening strategies for MASLD while adjusting for varying health system capacities.

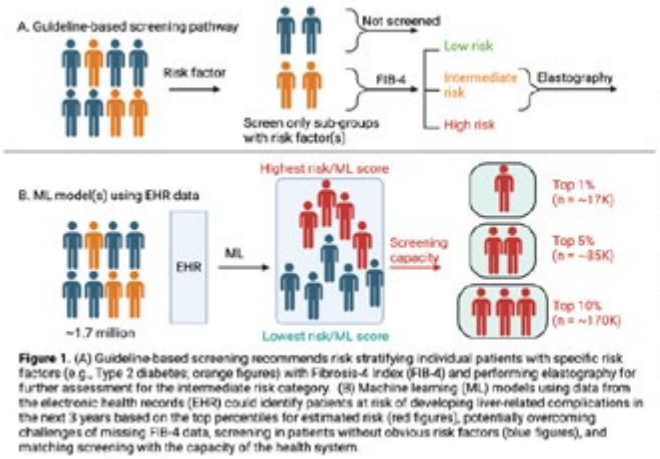

Figure 1. (A) Guideline-based screening recommends risk stratifying individual patients with specific risk factors (e.g., Type 2 diabetes; orange figures) with Fibrosis-4 Index (FIB-4) and performing elastography for further assessment for the intermediate risk category. (B) Machine learning (ML) models using data from the electronic health records (EHR) could identify patients at risk of developing liver-related complications in the next 3 years based on the top percentiles for estimated risk (red figures), potentially overcoming challenges of missing FIB-4 data, screening in patients without obvious risk factors (blue figures), and matching screening with the capacity of the health system.

Focusing on the top k% highest risk	Precision or PPV (% of patients identified who get diagnosed in the next 3 years)	Recall or Sensitivity (Of all the patients who get diagnosed in the next 3 years, % that we identified)
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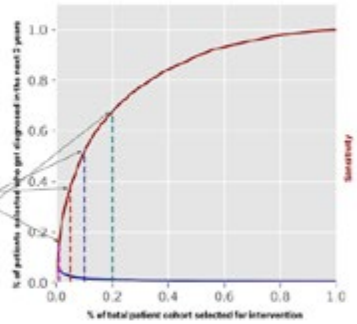
k=5%	2.6%	38%
k=10%	1.7%	52%
k=20%	1.1%	68%



Disclosures: Jaideep Behari: Pfizer: Grant/Research Support, Endra Life Sciences: Grant/Research Support, AstraZeneca: Grant/Research Support, Gilead: Grant/Research Support, Pfizer: Institutional research contract, Intercept: Institutional research contract, Madrigal: Institutional research contract, Inventiva: Institutional research contract, Rhythm: Institutional research contract, Galectin: Institutional research contract, Rayid Ghani: Nothing to Disclose, Kasun Amarasinghe: Nothing to Disclose, Allison Bradley: Nothing to Disclose, Mohammad Ateya: Pfizer Inc.: Employee, Pfizer Inc.: Stock - publicly traded company, Autumn Boyer: Nothing to Disclose, Kevin Townsend: Nothing to Disclose, Hansol Olivia Lee: Nothing to Disclose, Pamela Young: Pfizer Inc: Employee, Laura Manzey: Pfizer Inc.: Employee, Feng Dai: Pfizer Inc.: Employee, Nickie Cappella: Nothing to Disclose, Julie Simonson: Pfizer Inc: Employee, Julie Gouveia-Pisano: Pfizer Inc.: Employee, Jannette Escobar: Pfizer: Consultant, Parexel: Employee, Kathleen McTigue: Pfizer: Grant/Research Support, Eli Lilly: Grant/Research Support, Janssen Pharmaceutical: Grant/Research Support

2058 | DEVELOPING A BRIEF EVALUATION INDEX TO DIAGNOSIS METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE

Xinyuan He[1] Zhiluo Yang[1] Takanori Ito[2] Hideyuki Hyogo[3] Masafumi Ono[4] Kentaro Oniki[5] Tetsuhito Kojima[6] Zhanpeng Yang[1] Sally Tran[7] Zixuan Xing[1] Yi Liu[1] Naoyoshi Kariya[6] Shinya Yokoyama[2] Ming-Hua Zheng[8] Junji Saruwatari[5] Hirokazu Takahashi[9] Takashi Honda[2] Mindie Nguyen[7] Fanpu JI[10]

[1]Xi'an Jiaotong University, [2]Nagoya University, [3]Hyogo Life Care Clinic Hiroshima, [4]Kagawa University, [5]Kumamoto University, [6]Aichi Health Promotion Foundation, [7]Stanford University Medical Center, [8]Wenzhou Medical University, [9]Saga University Hospital, [10]Xi'an Jiaotong University

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is a newly adopted term to replace NAFLD as a more inclusive and positive term that also better reflects the underlying mechanism of the disease. We aimed to develop a novel noninvasive assessment index to characterize MASLD with its new diagnostic criteria. **Methods:** Using data from National Health and Nutrition Examination Surveys 2017-2020 (NHANES), we included participants aged 20-74 years old who met the diagnostic criteria of MASLD. Participants were randomly grouped into a training cohort and an internal validation cohort, with an over-sampling technique to balance the training cohort. We performed a forward stepwise logistic regression to create a MASLD index in the training cohort. Area under the curves (AUC), sensitivity analysis, and Brier Score were performed and compared with previous diagnostic indices including the Hepatic Steatosis Index (HSI), Fatty Liver Index (FLI), and the US FLI in the internal validation cohort as well as an external validation cohort from 6 centers from Japan. **Results:** The study included 1,853 eligible participants from NHANES (MASLD prevalence 40.9%) and an external validation cohort of 33,466 patients from 6 Japan centers (MASLD prevalence 28.2%). Using data derived

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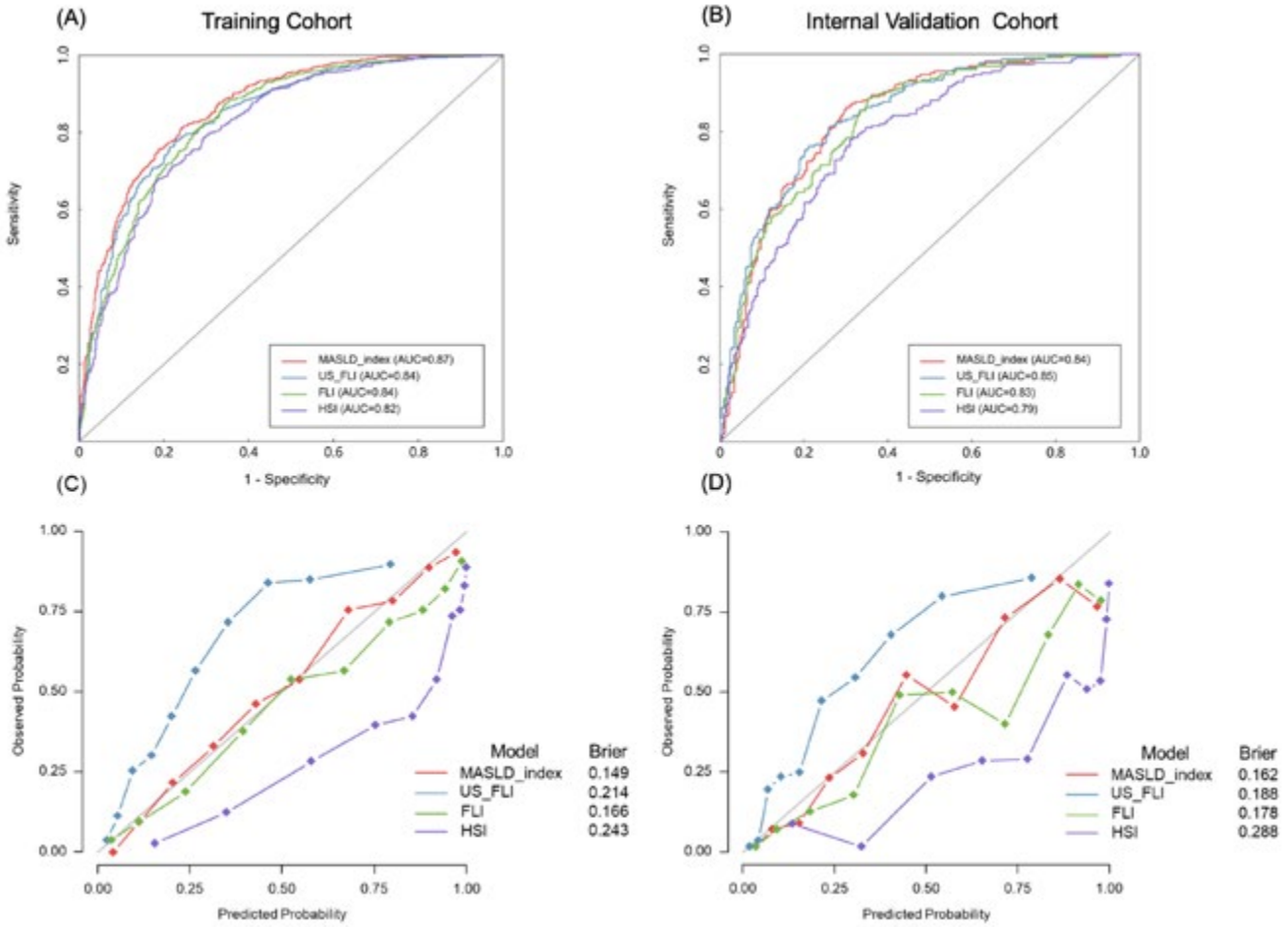
from the NHANES cohort, we developed a forecast formula named MASLD index with four variables (waist circumference [WC], triglyceride [TG]s, fasting glucose [FG], and race and ethnicity), which performed well in both the training (n=1,062) and internal validation cohort (n=556), with AUCs of 0.87 (95%CI 0.84-0.89) and 0.84, respectively. The AUCs in the training and internal validation cohorts for the US FLI for MASLD were (0.84, 0.85), followed by the FLI (0.84, 0.83) and HSI (0.82, 0.79), respectively. In both the training and internal validation cohorts, the curve of MASLD index was closest to the reference line, with the lowest Brier Score, indicating best agreement between the predicted and observed probabilities (Figure 1) and with superior performance over other indices across subgroups by sex, age, race and ethnicity, and abdominal obesity subgroups. The MASLD index also achieved an AUC of 0.88 and a Brier score of 0.13 in the external validation cohort. **Conclusion:** Using data derived from a large population-based U.S. cohort and a large multicenter external validation Japan cohort, we proposed a simple yet accurate novel diagnostic index for MASLD outperforming traditional indices.



Note: MASLD index, metabolic dysfunction-associated steatotic liver disease index; US FLI, U.S. population fatty liver index; FLI, fatty liver index; HSI, hepatic steatosis index.

Disclosures: Xinyuan He: Nothing to Disclose, Zhiluo Yang: Nothing to Disclose, Takanori Ito: Chugai Pharmaceutical Co., Ltd.: Grant/Research Support, Chugai Pharmaceutical Co., Ltd. and AstraZeneca: Speaking and Teaching, Hideyuki Hyogo: Nothing to Disclose, Masafumi Ono: Nothing to Disclose, Kentaro Oniki: Nothing to Disclose, Tetsuhito Kojima: Nothing to Disclose, Zhanpeng Yang: Nothing to Disclose, Sally Tran: Nothing to Disclose, Zixuan Xing: Nothing to Disclose, Yi Liu: Nothing to Disclose, Naoyoshi Kariya: Nothing to Disclose, Shinya Yokoyama: Nothing to Disclose, Ming-Hua Zheng: Nothing to Disclose, Junji Saruwatari: Nothing to Disclose, Hirokazu Takahashi: Sysmex: Grant/Research Support, Novo Nordisk: Speaking and Teaching, Kowa: Speaking and Teaching, Taisho: Speaking and Teaching, Takeda: Grant/Research Support, Takashi Honda: Nothing to Disclose, Mindie Nguyen: Nothing to Disclose, Fanpu JI: Gilead Sciences: consultant, Gilead Sciences: Speaking and Teaching, Gilead Sciences: Consultant, MSD: Consultant, MSD: Speaking and Teaching

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2059 | THE CORRELATION BETWEEN MEASUREMENTS OBTAINED BY THE ILIVTOUCH AND FIBROSCAN A MULTICENTER RANDOMIZED STUDY IN THE US

Calvin Pan Kumar Jalal[1] Hector Ye[2] Caroline A Ankoma-Sey[1] Fion Chen[2] Bai L Pan[3]

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Background: Non-invasive assessment of steatosis and fibrosis is essential for diagnosing and risk-stratifying liver disease. Both the FibroScan and the iLivTouch devices use shear wave-based transient elastography to assess steatosis and fibrosis and are FDA-approved. However, data on their correlation in the US is limited. This study aimed to evaluate the correlation between these devices in US patients through a multicenter, randomized, and back-to-back study. **Methods:** This multicenter, prospective, unblinded, and randomized study enrolled patients requiring liver scan assessments from September 2023 to May 2024. Exclusion criteria included excessive alcohol use, alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels >2.5× ULN, and decompensated cirrhosis. After determining the optimal test spot using iLivTouch, patients were randomly assigned to be assessed first with either the iLivTouch-FT9000 or FibroScan 530 (1:1 ratio, stratified by center) and completed both assessments. Primary evaluations included Pearson correlation coefficients and Bland-Altman plots for liver stiffness measurement (LSM) and ultrasound/controlled attenuation parameters (UAP/CAP) between the devices. Secondary evaluations included comparing FibroScan-AST (FAST) scores in patients with metabolic dysfunction-associated steatotic liver disease (MASLD) and safety during the study. **Results:** Among 205 enrollees with 418 examinations, the mean (SD) age was 56 (14) years, 54% were male, the mean (SD) BMI was 24.6 (4.2), 12% had mild alanine aminotransferase elevation, and 70% had MASLD. Patient characteristics are presented in Table 1. When comparing measurements from the two devices, there was a strong correlation between iLivTouch and FibroScan for both attenuation parameters (Pearson's rho 0.71, p<0.001) and LSM (Pearson's rho 0.61, p<0.001). There was also high agreement between the two devices in generating the FAST score in combination with aspartate aminotransferase values from individual patients (Pearson's rho 0.94, p<0.001) in MASLD patients (n=135). No adverse events were reported by the investigators during the study. **Conclusion:** In US patients, LSM and UAP/CAP measurements obtained with iLivTouch and FibroScan were strongly correlated. The iLivTouch's 2D image-guided function facilitated the identification of the optimal test spot. Both devices are effective for diagnosing and grading liver fibrosis and steatosis, and for composing FAST scores, without safety concerns.

Table 1. Assessments of baseline variable

Demographic and Clinical Variables	*Mean (SD), Median [IQR], or n/N (%)*
Age (year)	56 (14)
Male	109/205 (53 %)
Height (cm)	164.5 (8.1)
Weight (kg)	65.0 [57.0, 74.0]
BMI (kg/m^2)	24.6 (4.2)
Waist circumference (cm)	86.1 (13.3)
Clinical signs of cirrhosis	1/205 (0.5%)
Surgical history	2/205 (0.98%)
On treatment for liver disease	158/205 (77%)
History of excessive drinking	1/205 (0.5%)
History of Creational Drug Use	1/205 (0.5%)
History of smoking	20/205 (10%)
History of hyperlipidemia	1/205 (0.5%)
History of hypertension	27/205 (13%)
AST levels, U/L	21.0 [17.0, 26.0]
ALT levels, U/L	20.0 [15.0, 28.0]
Percentage with ALT elevation	25/205 (12%)
HBATC levels	5.7 [5.3, 6.0]
Albumin level, g/dL	4.5 [4.4, 4.7]
Total bilirubin level, mg/dL	0.5 [0.4, 0.7]
Platelet count, 10^3/uL	223.0 [193.0, 62.0]

ALT, alanine aminotransferase; AST, aspartate aminotransferase;

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Disclosures: Calvin Pan: Nothing to Disclose, Kumar Jalal: Nothing to Disclose, Hector Ye: Nothing to Disclose, Caroline A Ankoma-Sey: Nothing to Disclose, Fion Chen: Nothing to Disclose, Bai L Pan: Nothing to Disclose

2060 | DEEP-LEARNING-AIDED QUANTIFICATION OF STEATOHEPATITIS-ASSOCIATED PATHOLOGICAL FINDINGS IN LIVER SPECIMENS

Reiichiro Kondo[1] Shinji Mizuochi[1] Takashi Nishimura[2] Hiroko Iijima[2] Masayoshi Kage[3] Hironori Kusano[4] Yutaro Mihara[1] Yoshiki Naito[5] Masamichi Nakayama[1] Jun Akiba[5] Hirohisa Yano[6]

[1]Kurume University School of Medicine, [2]Hyogo Medical University, [3]Junshin Gakuen University, [4]Kokura Medical Center, [5]Kurume University Hospital, [6]Saiseikai Futsukaichi Hospital

Background: Hepatic steatosis, ballooning hepatocyte, and liver fibrosis are important pathological findings in steatohepatitis. Although semi-quantitative scoring is a common method for quantifying histopathological findings, semi-quantitative evaluation may lead to errors in objectivity and reproducibility depending on the histological findings. We established a deep learning model to quantify steatohepatitis-associated pathological findings from liver specimens. **Methods:** Eighteen liver specimens of non-alcohol-related steatohepatitis, and eight liver specimens of chronic hepatitis were used to train AI (convolutional neural network). Whole slide images (WSI) of all liver specimens were prepared, and annotation was performed by importing the WSIs into the HALO software (Indica Lab, CA, USA). The AI model measured percentages of the steatosis area (%Steatosis), area of hepatocytes with ballooning degeneration (%Ballooning), and fibrosis area (%Fibrosis) in the liver biopsy specimens. Subsequently, liver biopsy specimens were obtained for validation from 233 patient who underwent ultrasonography, with which controlled attenuation parameter (CAP), point-shear wave elastography (Virtual Touch Quantification, VTQ), and two-dimensional Shear Wave Elastography (SWE) were measured. Histological findings of these liver specimens were evaluated by three evaluators with expertise in liver pathology and compared with AI model evaluation. **Results:** %Steatosis, %Ballooning, and %Fibrosis could be measured for all liver specimens. In all patients for the validation study, %Steatosis was strongly correlated with the histological steatosis grade evaluated by pathologists ($R = 0.8$, $P<0.001$). **Conclusion:** Evaluation of steatohepatitis-associated pathological findings by our AI model was consistent with that by pathologists and correlated well with ultrasound findings.

Disclosures: Reiichiro Kondo: Nothing to Disclose, Shinji Mizuochi: Nothing to Disclose, Takashi Nishimura: Canon Medical Systems: Grant/Research Support, Canon Medical Systems: Grant/Research Support, GE HealthCare: Grant/Research Support, Philips Japan: Grant/Research Support, Hiroko Iijima: Nothing to Disclose, Masayoshi Kage: Nothing to Disclose, Hironori Kusano: Nothing to Disclose, Yutaro Mihara: Nothing to Disclose, Yoshiki Naito: Nothing to Disclose, Masamichi Nakayama: Nothing to Disclose, Jun Akiba: Nothing to Disclose, Hirohisa Yano: Nothing to Disclose

2061 | COMPARISON OF LIVER FIBROSIS BETWEEN MASLD IN PLHIV AND NON-PLHIV

Krishnadas Devadas[1] Ann Mary George[2] Antony George[2]

[1]Government Medical College, Thiruvananthapuram, [2]Government Medical College, Trivandrum

Background: Metabolic dysfunction associated steatotic liver disease(MASLD) has emerged as a major cause of liver-related morbidity and mortality in people living with Human Immunodeficiency Virus(PLHIV) with a prevalence of nearly 34%. However, little is known about the clinical profile and extent of fibrosis in HIV-associated MASLD and how it differs from non-PLHIV. We conducted an age and sex-matched study comparing MASLD in PLHIV and non-PLHIV populations. **Methods:** Cross-sectional observational study of 120 consecutive PLHIV with MASLD and 120 age and sex-matched non-PLHIV MASLD. All patients underwent standard blood investigations, APRI, FIB-4, and NFS scoring, anthropometry, ultrasonography with 2D-shear wave elastography(SWE), vibration-controlled transient elastography(VCTE), and visceral fat assessment by bio-impedance analyser. Significant and advanced fibrosis was defined by current AASLD guidelines. The study was commenced after obtaining clearance from National AIDS Control Organisation (1822/M&E/2020/KSACS) and Institutional Ethics Committee(04/29/2022/MCT). **Results:** Distribution of Diabetes Mellitus, Systemic Hypertension, Dyslipidemia and Metabolic syndrome were comparable between the 2 groups. Lean MASLD was present in 22.5% in the PLHIV and 6.6% of the non-PLHIV group(p=<0.001). Mean AST, total cholesterol, and

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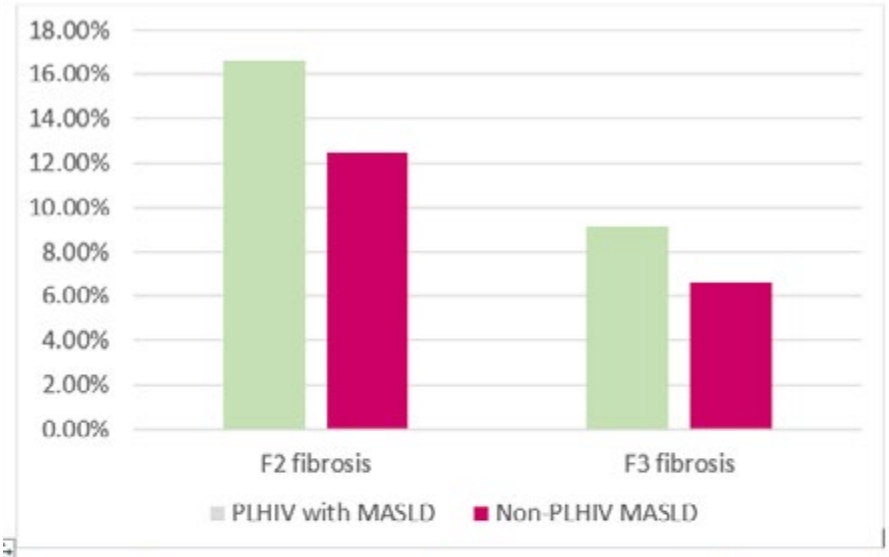
triglycerides were 46U/L, 210mg/dL and 121mg/dL in PLHIV and 37U/L, 219mg/dL and139mg/dL in non-PLHIV group(p<0.01). Mean visceral fat, Body Mass Index(BMI), waist circumference, hip circumference and waist-hip ratio were 12.4 ± 4.96%, 24kg/m^2, 89cm, 93cm, and 0.96 in PLHIV and 9.77 ± 2.52%, 28kg/m^2, 97.2cm, 100cm, and 0.97 in the non-PLHIV group(p<0.005). Mean VCTE, SWE, APRI, FIB-4 ad NFS scores were 7.85±1.57, 7.54±1.42, 0.47±0.56, 1.15±0.76 and -2.85±1.2 in PLHIV and 7.39±1.61, 6.79±1.4, 0.36±0.19, 0.97±0.39 and -2.29±1.2 in the non-PLHIV group(p<0.001). F2 and F3 fibrosis were 16.66% and 9.16% in PLHIV and 12.5% and 6.66% in the non-PLHIV group(p=0.026). **Conclusion:** PLHIV with MASLD tend to have more lean body habitus and higher fibrosis when compared to non-PLHIV, despite having a comparable metabolic profile. Higher prevalence of significant and advanced fibrosis in PLHIV group may have contributed to the higher SGOT, lower cholesterol and lower triglyceride levels in the PLHIV group. Lower BMI in PLHIV group may have resulted in the lower NFS score. NFS may underestimate the degree of fibrosis in PLHIV. Active screening and aggressive treatment of PLHIV with MASLD, especially lean MASLD, is crucial.



	PLHIV with MASLD	Non-PLHIV with MASLD	p value
TE	7.85±1.57 kPa	7.39±1.6kPa	0.029
SWE	7.54±1.42 kPa	6.79±1.4kPa	0.001
APRI	0.47±0.56	0.36±0.19	0.035
FIB-4	1.15±0.76	0.97±0.39	0.015
NFS	-2.85±1.2	-2.29±1.2	0.000

Disclosures: Krishnadas Devadas: Nothing to Disclose, Ann Mary George: Nothing to Disclose, Antony George: Nothing to Disclose

2062 | NIS2+®, AN EFFECTIVE MONITORING TOOL FOR TRACKING DISEASE EVOLUTION IN PATIENTS WITH FIBROTIC MASH ◆

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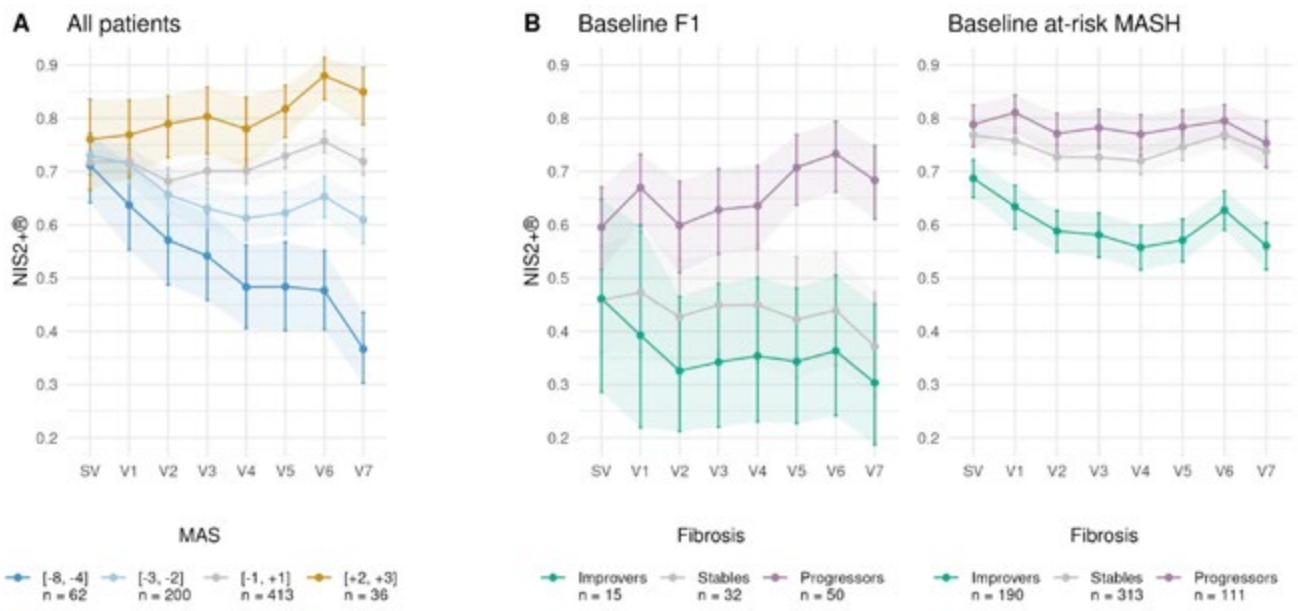
Arun Sanyal[1] Vlad Ratziu[2] Yacine Hajji[3] Jérémy Magnanensi[3] Zouher Majd[3] Dean Hum[4] Bart Staels[5] Margery Connelly[6] Sven Francque[7] Quentin Anstee[8] Stephen Harrison[9]

[1]Virginia Commonwealth University, [2]Service D' Hepatogastroenterologie (FR), [3]Genfit S.A., [4]GENFIT CORP, [5]University Lille 2, [6]Labcorp, [7]Antwerp university hospital, [8]Newcastle University, UK, [9]Summit Clinical Research, San Antonio

Background: The non-invasive monitoring of MASH represents an important unmet medical need. Fibrosis (F) evolution was shown to be correlated with the MASLD activity score (MAS). NIS2+® is an efficient blood-based technology, designed to robustly identify at-risk MASH (MAS ≥ 4; F ≥ 2). We aimed to assess: (1) the stability of NIS2+® over time in patients (pts) with stable histology and (2) the potential of NIS2+® for monitoring MAS and fibrosis changes. **Methods:** The study cohort contained pts from RESOLVE-IT Phase 3 trial (NCT02704403) with fibrotic MASH (F1-F3; MAS ≥ 4) at screening visit and NIS2+® available at every 8 visits (N = 711). MAS or fibrosis changes were defined as a 2- or 1-point change, respectively, between baseline and end of study (EOS). Histologically stable pts, defined as those with ≤ 1 point change in MAS and no change in fibrosis, were used to assess NIS2+® stability over time. We further assessed the association between changes in histology and NIS2+® score evolution using linear mixed-effect models. **Results:** Mean follow-up was 19 months. At baseline, 86% of pts (n = 614) had at-risk MASH. At EOS, 29% had stable histology; 37% improved MAS and 29% improved fibrosis; 5% had MAS progression and 23% fibrosis progression. Improvement in MAS was correlated with the direction of fibrosis evolution, with 57% of MAS improvers among pts with improved fibrosis vs 33% in those with stable fibrosis and 19% in those with fibrosis progression ($p < 0.0001$ for both). Among histologically stable pts, NIS2+® was highly stable (means: 0.70-0.78 across visits), with similar mean values at baseline and EOS (0.74 vs 0.74, $p = 0.82$). Compared with pts with stable MAS, NIS2+® decreased significantly when MAS improved ($p < 0.0001$) and increased when MAS progressed ($p < 0.01$). Importantly, the decrease in NIS2+® was larger in pts achieving a MAS reduction ≥ 4 points compared to those with a MAS reduction of 2-3 points ($p < 0.0001$). Within F1 pts at baseline, NIS2+® increased significantly in fibrosis progressors compared with pts with stable fibrosis ($p = 0.012$). Within pts with at-risk MASH (F2-F3) at baseline, NIS2+® decreased significantly in fibrosis improvers compared with pts with stable fibrosis ($p < 0.01$). **Conclusion:** NIS2+® was highly efficient in tracking MAS and fibrosis changes, and identified contrasting patterns of histological deterioration or improvement. Hence NIS2+® could be an effective non-invasive biomarker for monitoring pts with MASH.



Disclosures: Arun Sanyal: Genfit, Akarna, Tiziana, Durect, Inversago, Hemoshear, North: Stock - publicly traded company, Astra Zeneca (60K), Boston Pharmaceutical

2063 | NIS2+®, AN EFFECTIVE TOOL FOR MONITORING MASH RESOLUTION AND FIBROSIS IMPROVEMENT IN PATIENTS WITH AT-RISK MASH ◆

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Arun Sanyal[1] Vlad Ratziu[2] Yacine Hajji[3] Jérémy Magnanensi[3] Zouher Majd[3] Dean Hum[4] Bart Staels[5] Margery Connelly[6] Sven Francque[7] Quentin Anstee[8]

[1]Virginia Commonwealth University, [2]Service D' Hepatogastroenterologie (FR), [3]Genfit S.A., [4]GENFIT CORP, [5]University Lille 2, [6]Labcorp, [7]Antwerp University Hospital, [8]Newcastle University, UK

Background: With Rezdiffra™ now approved by FDA for the treatment of patients (pts) with MASH and fibrosis (F) stage 2-3, and an increasing number of clinical trials evaluating drug efficacy in this population, simple and reliable non-invasive monitoring tools are necessary. NIS2+® is an efficient blood-based biomarker panel designed to robustly diagnose at-risk MASH (MAS≥4; F≥2). We aimed to assess the potential of NIS2+® for monitoring pre-defined MASH histological endpoints (EPs). **Methods:** Pts with at-risk MASH (MAS≥4; F2-F3) included in the RESOLVE-IT phase 3 trial (NCT02704403), with ≤180 days between blood collection and liver biopsy at both screening (SV) and end of study (EOS) visits, and with NIS2+® available at all 8 trial visits were selected (N=614). EPs (MASH resolution, F improvement) were defined as in MAESTRO-NASH phase 3 trial (NCT03900429). A composite EP (MASH resolution & F improvement) was analyzed. To assess the monitoring performance of NIS2+®, the association between these EPs and NIS2+® score evolution was evaluated using linear mixed-effect models. For each patient, differences in NIS2+® score between SV and other visits were computed and compared across groups. The classification of pts using NIS2+® diagnostic cutoffs (rule-out: 0.46, rule-in: 0.68) was analyzed at SV and EOS. **Results:** Mean follow-up was 19 months. At EOS, 17% of pts had MASH resolution, 24% F improvement and 10% achieved the composite EP. For each EP, NIS2+® decreased significantly in pts who reached the EP compared with pts who did not ($p<0.0001$ each). For all 3 EPs, NIS2+® differences between SV and visit 1 (2 months) were already significantly different in pts achieving the EP at EOS compared with pts who did not ($p<0.05$), reaching high significance ($p<0.001$) after 8 months (visit 3). After 19 months (EOS), mean NIS2+® difference vs SV ranged -0.23 to -0.14 in pts who reached the EPs vs -0.04 to -0.03 in pts who did not ($p<0.0001$ each). At SV, 62% of at-risk MASH pts had a NIS2+® score ≥0.68, while only 15% were <0.46. Among pts who reached the composite EP (n=61), 66% had a NIS2+® score <0.46 at EOS, half of them achieving a 2-class decrease of NIS2+® (from ≥0.68 to <0.46). Importantly, none of these pts experienced a 2-class increase of NIS2+®. **Conclusion:** NIS2+® showed high performance for longitudinal monitoring of pts with at-risk MASH who would benefit from emerging treatments and may have potential for detecting MASH histological EPs.

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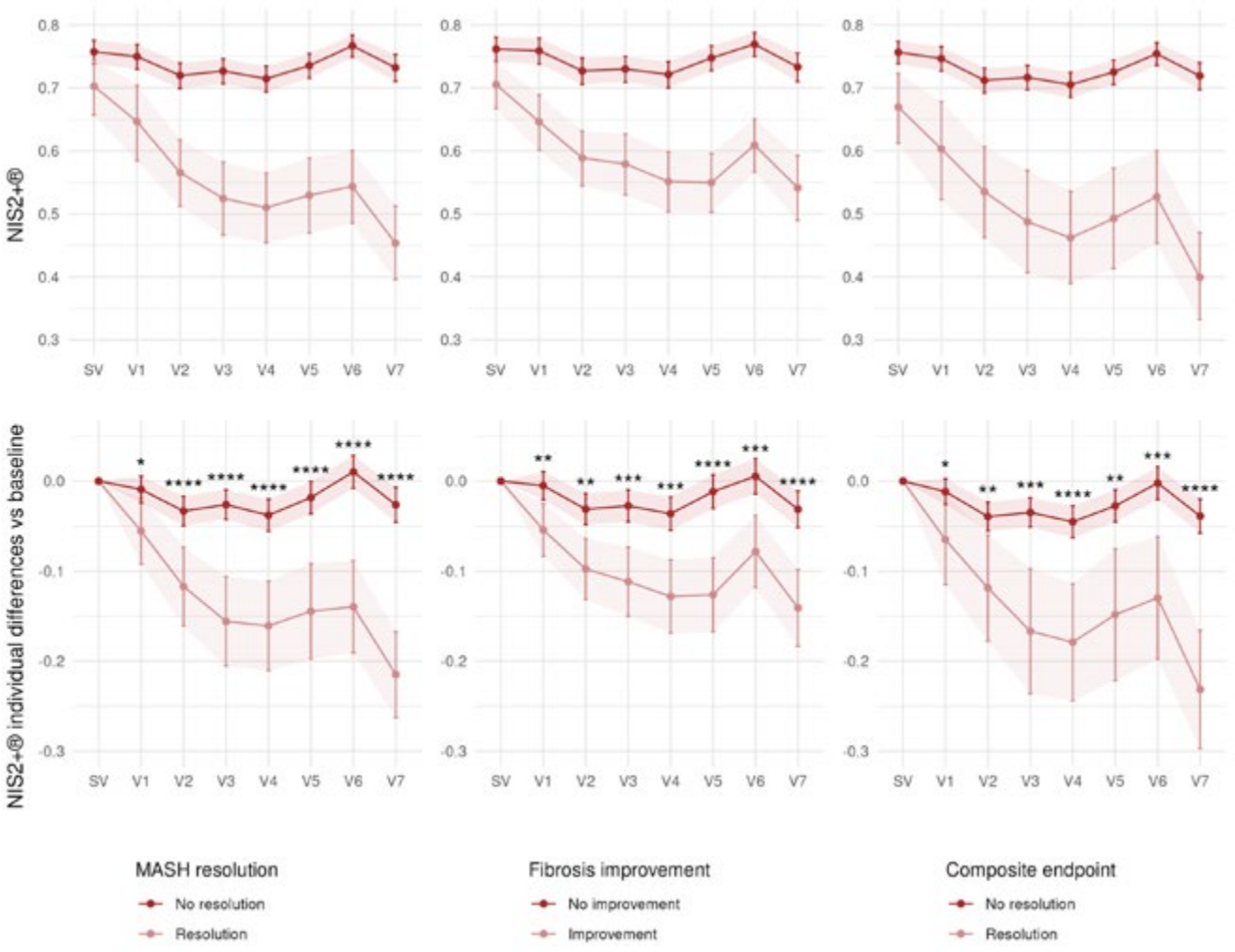

Disclosures: Arun Sanyal: Genfit, Akarna, Tiziana, Durect, Inversago, Hemoshear, North: Stock - publicly traded company, Astra Zeneca (60K), Boston Pharmaceutical

2064 | EVALUATION OF TWO NON-INVASIVE APPROACHES TO ASSESSING AT-RISK MASH IN CLINICAL PRACTICE: MASEF AND FAST SCORES

Naim Alkhouri[1] Ibon Martinez-Arranz[2] Rida Nadeem[1] Himanshi Kapoor[1] Mazen Noureddin[3]

[1]Arizona Liver Health, Chandler, AZ, USA, [2]OWL Metabolomics, Derio, Spain, [3]Houston Methodist Hospital

Background: Early identification of patients with at-risk metabolic dysfunction associated steatohepatitis (MASH), (NAS ≥ 4 and fibrosis stage ≥ 2) is an urgent matter, as these patients are at greater risk of liver complications and may benefit from novel therapeutic options. The FibroScan-AST (FAST) score demonstrated good accuracy in identifying at-risk MASH but has limited availability. Therefore, the MASEF score was developed using lipidomics as a simple, blood-based biomarker for at-risk MASH. The aim of this study is to evaluate the comparative effectiveness of the MASEF score against the FAST score in identifying patients at-risk for liver disease. **Methods:** Consecutive patients with suspected MASH that were seen in a tertiary hepatology clinic were included. On the same day, FibroScan was done, and a blood sample was obtained to calculate the FAST and MASEF scores. FAST and MASEF cutoffs were set at 0.67 and 0.33, respectively, with values below these thresholds indicating not at-risk MASH and values above indicating at-risk MASH. **Results:** Our cohort included 106 patients, 63.8% females with an average age of 52 years, CAP 313 dB/m, VCTE 8.7 kPa, AST 32.9 U/L, ALT 47.8 U/L, FAST 0.31 and MASEF 0.26. The FAST score identified 11 patients as at-risk MASH (FAST > 0.67), with the MASEF score confirming 8 of these diagnoses, resulting in a concordance rate of 72.7%. The figure

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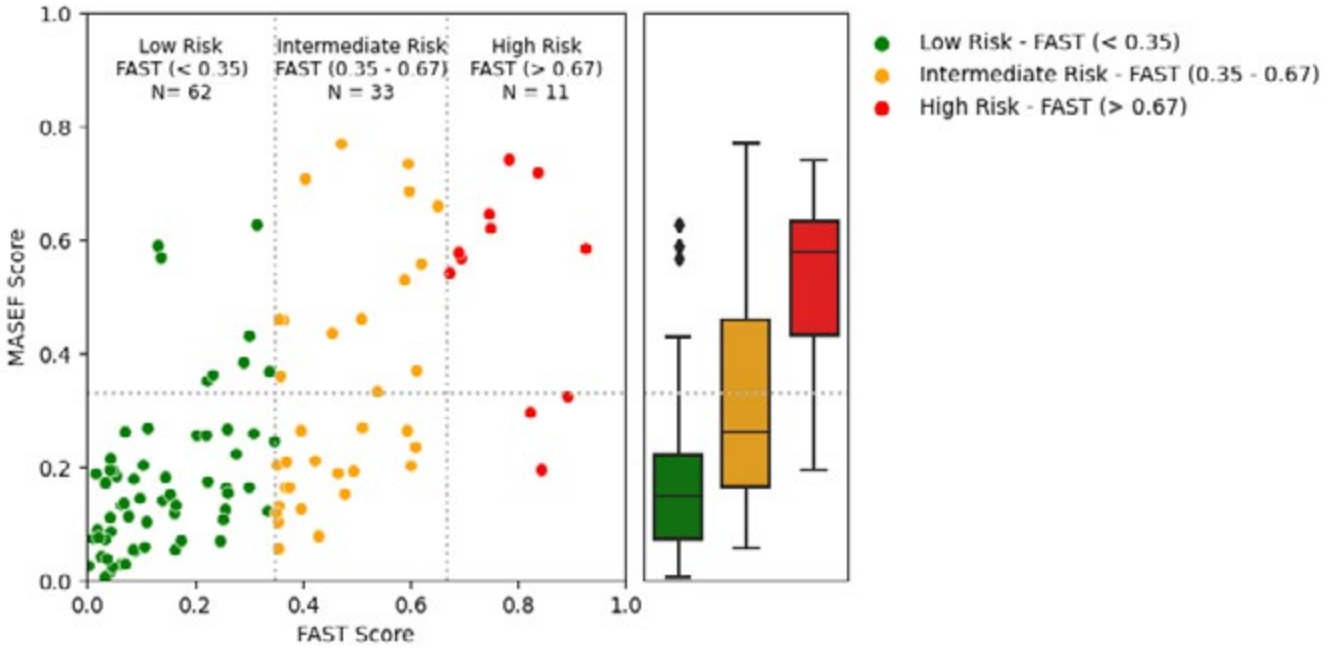
demonstrates the correlation between the FAST score category and the MASEF score. Among the 95 patients identified by FAST as not at-risk MASH (FAST ≤ 0.67), MASEF classified 22 (23.2%) as at-risk MASH. Notably, these patients showed significantly higher median ALT (30.0 U/L vs. 41.0 U/L, p=0.003) and AST (23.0 U/L vs. 37.0 U/L, p<0.001) levels. They also demonstrated higher median elastography readings (6.6 kPa vs. 8.1 kPa, p=0.026) and FAST scores (0.2 vs. 0.4, p<0.001), indicating a potential underestimation of risk by the FAST score. **Conclusion:** The MASEF Score demonstrated good correlation with the FAST score in predicting at-risk MASH. This suggests that MASEF may be an effective tool for early disease detection and intervention, particularly in patients who might be overlooked by FAST.



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2065 | INDEPENDENT VALIDATION OF SECOND HARMONIC GENERATION/TWO PHOTON EXCITATION IMAGING AND ARTIFICIAL INTELLIGENCE-BASED SNOF INDEX FOR METABOLIC DYSFUNCTION ASSOCIATED STEATOHEPATITIS CIRRHOSIS ASSESSMENT

Kutbuddin Akbary[1] Zachary Goodman[2] Galvin Gan[1] Yayun Ren[1] Dean Tai[3] Pol Boudes[4] Mazen Noureddin[5] Anne Minnich[6] Naga Chalasani[7]

[1]HistoIndex Pte Ltd, [2]INOVA Fairfax Hospital, [3]HistoIndex, [4]Galectin Therapeutics, [5]Houston Methodist Hospital, [6]Bristol Myers Squibb, [7]Indiana University Medical Center

Background: The Septa-Nodule-Fibrosis index (SNOF) was developed from a cohort of Metabolic dysfunction-Associated Steatohepatitis (MASH) cirrhosis with portal hypertension (PH) using machine learning (Noureddin et al. Aliment Pharmacol Ther 2023; 57: 409-2017). This novel index quantifies cirrhosis characteristics by features like septa width, length, cellularity; cirrhotic nodule diameter, area, number; and fibrosis parameters like number, length, perimeter, width of fibres. Initially, SNOF index demonstrated predictive value for clinical outcomes relevant to MASH cirrhosis, like hepatic venous pressure gradient (HVPG), clinically significant PH (CSPH), and varices. This study aims to validate SNOF on an independent cirrhotic cohort with pathologist-based staging to establish its use across different MASH cirrhosis populations and its relationship with histopathological staging. **Methods:** We analyzed 598 unstained liver biopsies from BMS Falcon 1 & 2 trials (NCT03486899, NCT03486912) having patients with early & advanced cirrhosis (NASH-CRN F3 & F4, respectively). Spearman correlation (r-values) was used for correlations between SNOF and NASH-CRN staging & Ishak staging. We also compared changes in SNOF (ΔSNOF value; change in SNOF from Baseline to End-of-treatment) for pathologist-based progression (≥1-stage fibrosis increase), no-change (unchanged fibrosis stage), and regression (≥1-stage fibrosis decrease) biopsies of patients by Ishak & NASH-CRN systems. **Results:** Study population had mean age of 58.06 years (median age 60 years); 40.3% were male, 59.7% female. Of the biopsies, 55.9% were F3, and 39.3% were F4 (NASH-CRN fibrosis staging). Median NAS scores were 1 for steatosis, 2 for ballooning, and 3 for lobular inflammation. Box-whisker plots show stage-wise correlation cut-offs, indicating strong correlation values for SNOF with both NASH-CRN (r = 0.604) and Ishak staging (r = 0.65) for fibrosis (Figure 1A). SNOF increased in progression patients for both Ishak and NASH-CRN and decreased in both no-change and regression patients, with greater decrease in regression cohort; for both NASH-CRN and Ishak staging (Figure 1B). **Conclusion:** SNOF has significant correlation with both NASH-CRN and Ishak fibrosis staging and their longitudinal changes, useful as a comprehensive tool to quantify cirrhosis features in patients with MASH cirrhosis in clinical trials and clinical practice. SNOF, as a quantifiable measure of cirrhosis severity, can help predict treatment outcomes in drug trials. Future research should validate it in larger, diverse cohorts, explore its predictive capabilities in longitudinal studies and integrate it into clinical practice to enhance patient management. Additionally, linking SNOF to clinical outcomes, predicting treatment response from initial biopsies, and identifying cirrhosis from other causes like congestive hepatopathy can be crucial areas of focus.

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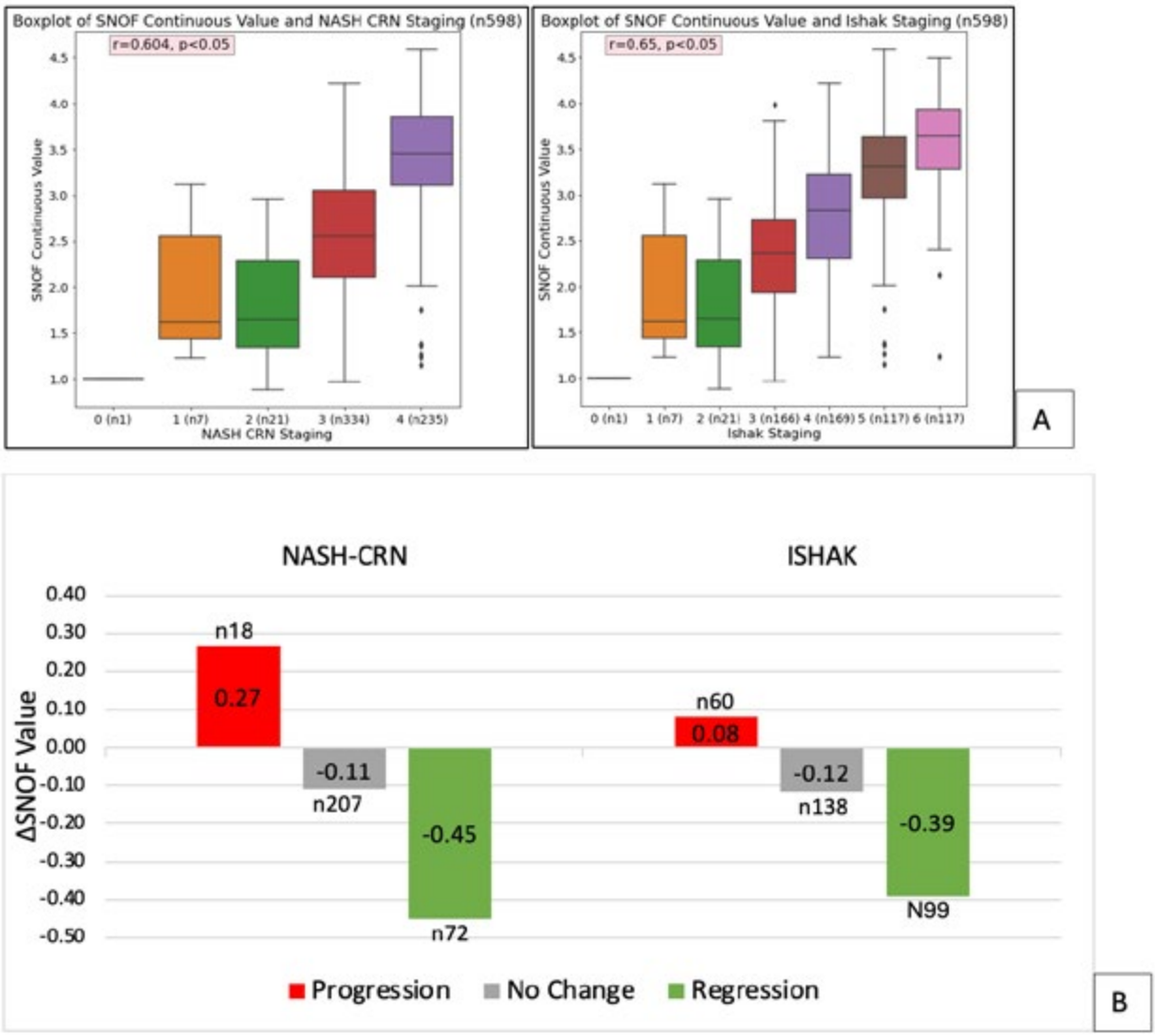

Figure 1 [A]: Box and Whisker plot demonstrating correlation of SNOF Index with pathologist-based NASH-CRN staging and Ishak staging in BMS Falcon 1&2 cohorts (includes Baseline and End-of-treatment samples). **[B]** Change in SNOF (ΔSNOF value) for progression, no-change, and regression cohorts as per NASH-CRN and Ishak fibrosis staging.

Disclosures: Kutbuddin Akbary: HistoIndex Pte Ltd: Employee, Zachary Goodman: Nothing to Disclose, Galvin Gan: HistoIndex Pte Ltd: Employee, Yayun Ren: HistoIndex Pte Ltd: Employee, Dean Tai: Histoindex.com: Employee, Pol Boudes: Galectin Therapeutics, Inc.: Employee, Mazen Noureddin: Principal Investigator for a Drug Study relationship with Viking; Has not ended; Consultant relationship with Eli Lilly; Has not ended; Consultant relationship with AstraZeneca; Has not ended; Consultant relationship with Boston Pharmaceuticals; Has not ended; Principal Investigator for a Drug Study relationship with Genfit; Has not ended; Principal Investigator for a Drug Study relationship with Galectin; Has not ended; Principal Investigator for a Drug Study relationship with Gilead; Has not ended; Principal Investigator for a Drug Study relationship with BMS; Has not ended; Principal Investigator for a Drug Study relationship with BI; Has not ended; Principal Investigator for a Drug Study relationship with Akero; Has not ended; Consultant relationship with Cytodyn; Has not ended; Consultant relationship with GSK; Has not ended; Consultant relationship with BI; Has not ended; Consultant relationship with Madrigal; Has not ended; Terns,Takeda, Zydus. relationship with Itimmune, BI, Cytodyn, 89BIO, GSK, Madrigal, Merck, Novo Nor; Has not ended; Principal Investigator for a Drug Study relationship with Allergan; Has not ended; Consultant relationship with Takeda; Has not ended; Consultant relationship with Terns; Has not ended; Terns, Corcept, Takeda, Madrigal, Novartis, Novo Nordisk, relationship with Allergan, Akero, BI, BMS, Gilead, Galectin, Zydus GSK; Has not ended; Consultant relationship with Novo Nordisk; Has not ended;

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2066 | IDENTIFICATION OF NEW EXOSOMAL MICRORNA MARKERS FOR METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE USING ARTIFICIAL INTELLIGENCE APPROACH

Michinori Kohara[1] Bouchra Kitab[2] Atsumasa Komori[3] Kyoko Tsukiyama-Kohara[2] Takahiro Ochiya[4] Masamichi Kimura[5] Kiminori Kimura[5] Hiroshi Yatsuhashi[3]

[1]Tokyo Metropolitan Institute of Medical Science, [2]Kagoshima University, [3]National Hospital Organization (NHO) Nagasaki Medical Center, [4]Tokyo Medical University, [5]Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital

Background: MASLD (metabolic dysfunction-associated steatotic liver disease) is a progressive liver disease in nature, which is marked by liver inflammation and may advance to cirrhosis and liver failure of MASH (steatohepatitis). Monitoring the pathological progression of MASLD into MASH is important. However, there is still no surrogate marker that can replace liver biopsy with effectively and accurately. We aimed to identify differentially expressed (extracellular vesicles) EVs miRNAs in MASH patients and validate their utility as novel biomarkers for diagnosing hepatic fibrosis using an artificial intelligence approach (AI). **Methods:** Serum-derived EVs were isolated from biopsy-confirmed 40 MASH patients and 20 healthy controls, and EV miRNAs were analyzed using 3D-Gene human miRNA oligo chips and *Next-generation sequencing*. The concordance rate between the fibrosis stage (New Inuyama or Brunt) and the miRNAs expression profile was analyzed using multiple LASSO- and ordinal logistic regression models. **Results:** Fourteen EV miRNAs were selected from an analysis of MASH patients, providing high accuracy in determining the fibrosis and Brunt stage. Six differentially expressed EV miRNAs were also identified by Brunt score analysis. Ordinal union analysis showed a high concordance rate between the fibrosis and Brunt stage and miRNA-based determination (kappa statistic for New Inuyama and Brunt =0.87 and 0.99, respectively). *Pathway Analysis* predicted that these miRNAs are mostly involved in inflammatory pathways modulating *myofibroblasts* and cytokines production, including *IFN-γ*, hepatocyte growth factor (*HGF*), *TGF-β, IL*-1β*, IL-6, and IL-8*. **Conclusion:** This study provides evidence of selected EV miRNAs identified by appropriate analysis models with high accuracy to determine the liver disorder stage in MASLD to MASH. We suggest that measuring their expression levels will lead to the development of novel non-invasive biomarkers that can predict liver pathological conditions and advanced fibrosis.

Disclosures: Michinori Kohara: Nothing to Disclose, Bouchra Kitab: Nothing to Disclose, Atsumasa Komori: Nothing to Disclose, Kyoko Tsukiyama-Kohara: Nothing to Disclose, Takahiro Ochiya: Nothing to Disclose, Masamichi Kimura: Nothing to Disclose, Kiminori Kimura: Nothing to Disclose, Hiroshi Yatsuhashi: Nothing to Disclose

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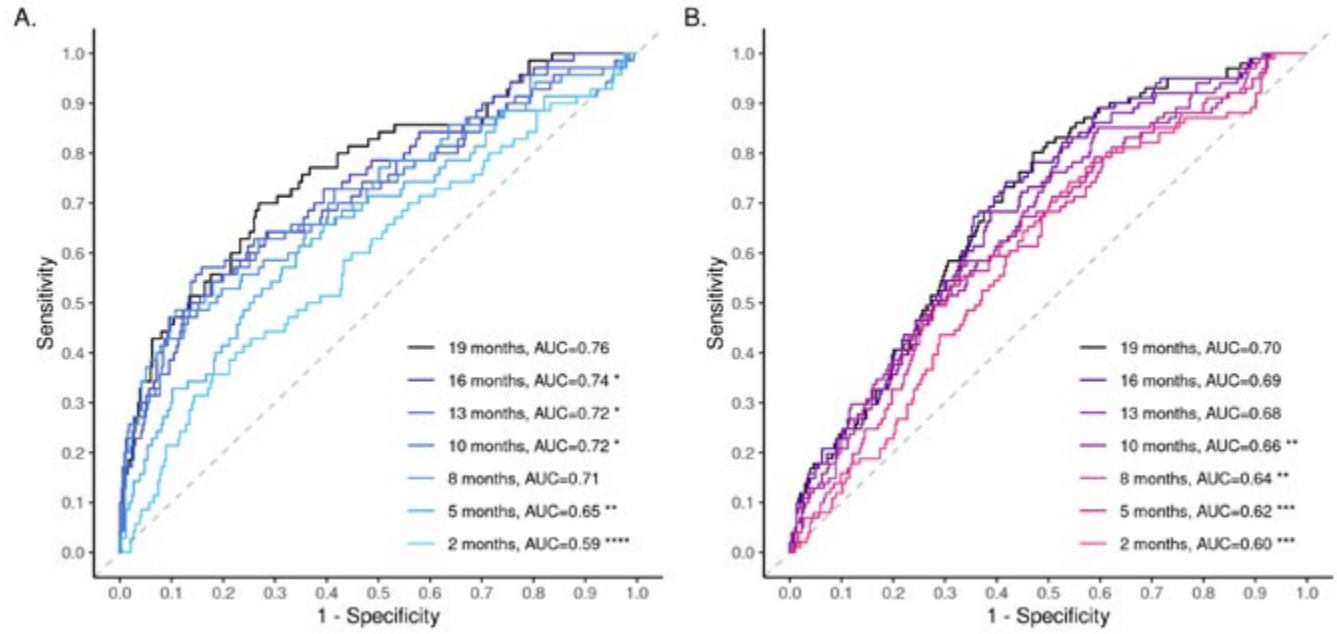
2067 | DETECTING MASH RESOLUTION AND FIBROSIS IMPROVEMENT WITH NIS2+® IN PATIENTS WITH AT-RISK MASH

Vlad Ratziu[1] Sven Francque[2] Yacine Hajji[3] Jérémy Magnanensi[3] Zouher Majd[3] Dean Hum[4] Bart Staels[5] Margery Connelly[6] Quentin Anstee[7] Arun Sanyal[8]

[1]Service D' Hepatogastroenterologie (FR), [2]Antwerp University Hospital, [3]Genfit S.A., [4]GENFIT CORP, [5]University Lille 2, [6]Labcorp, [7]Newcastle University, UK, [8]Virginia Commonwealth University

Background: The approval of Rezdiffra™ for the treatment of patients (pts) with MASH and fibrosis (F) 2-3 and the numerous drug trials in this population highlight the need for a simple and reliable non-invasive monitoring tool. NIS2+® is a validated blood-based biomarker panel to identify at-risk MASH (MAS≥4; F≥2). We aimed to provide classification rules for detecting pts with histological improvement using NIS2+® baseline and follow-up values. **Methods:** Pts from the RESOLVE-IT phase 3 trial (NCT02704403) with at-risk MASH (MAS≥4; F2-F3) at screening visit (SV) and NIS2+® available at all 8 trial visits, including end of study (EOS), were selected (N=614). Two histological endpoints (EP), defined as in the MAESTRO-NASH phase 3 trial (NCT03900429), were analyzed: MASH resolution (EP1) and F improvement (EP2). For each patient, baseline and delta (EOS – SV) of NIS2+®, as well as linear regression slope and mean of NIS2+® values from all visits were computed. For each EP, a selection of these features minimizing Akaike information criterion (AIC) was made to build a logistic model in a training dataset (n=209). Performance was assessed in a validation dataset (n=405) at different numbers of visits and durations of follow-up. **Results:** Mean follow-up was 19 months. In the validation dataset, 17% of pts achieved EP1 and 25% EP2. Among single features, mean NIS2+® had the largest AUCs: 0.73 for EP1 and 0.68 for EP2. For the detection of EP1, mean NIS2+® and slope were selected to build a model (M1), with an AUC of 0.77 in training and 0.76 in validation. For EP2, mean NIS2+® and baseline were retained in a model (M2), with an AUC of 0.75 in training and 0.70 in validation. At a cutoff of 0.23, M1 had a specificity (spe) of 0.81 and sensitivity (sen) of 0.56. At a cutoff of 0.27, M2 had a spe of 0.70 and sen of 0.56. Interestingly, 34% of false positives with M2 (no F improvement) still experienced a MAS decrease ≥2 points and 20% achieved EP1. Performance was stable vs number of visits (2-8) between SV and EOS (AUC=0.76-0.77 for M1, 0.66-0.70 for M2). High classification concordance was observed when using ≥4 visits (kappa≥0.8). AUCs of M1 and M2 increased with duration of follow-up; M1 reached an AUC of 0.72 at 10 months, allowing for early detection of EP1. **Conclusion:** Models built on NIS2+® baseline and follow-up values were effective for monitoring and detecting MASH resolution and F improvement, allowing a potential use for monitoring treatment response.



Disclosures: Vlad Ratziu: Nothing to Disclose, Sven Francque: Nothing to Disclose, Yacine Hajji: GENFIT S.A.: Employee, Jérémy Magnanensi: Genfit SA: Employee, Zouher Majd: Nothing to Disclose, Dean Hum: Genfit: Executive role, Bart Staels: Genfit SA: Consultant, Margery Connelly: Labcorp: Employee, Quentin Anstee:

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2068 | PLASMA PROTEOME SIGNATURES ASSOCIATED WITH STEATOHEPATITIS IN MORBIDLY OBESE PATIENTS

MELISSA MARIA MILITO[1] Cristina Banfi[2] Stefania Ghirlandi[2] Natalia Rosso[1] Milos Mihailovic[1] Claudio Tiribelli[1] Pablo Josè Giraudi[1] Silvia Palmisano[3] Deborah Bonazza[4]

[1]Fondazione Italiana Fegato - ONLUS, [2]Centro Cardiologico Monzino, [3]Cattinara Hospital, ASUITs, Trieste, [4]Cattinara Hospital, ASUGI, Trieste

Background: Obesity, Metabolic-Associated Steatotic Liver Disease (MASLD), and inflammation are intricately connected. MASLD embraces a spectrum of liver conditions ranging from simple steatosis (MASL) to more severe steatohepatitis (MASH), which can progress to fibrosis, cirrhosis, and even hepatocellular carcinoma. Obesity and Type 2 diabetes are major risk factors for the development of MASLD. The accumulation of fat and the associated oxidative stress trigger an inflammatory response, exacerbating liver injury. In this study, we explored the plasma proteome to identify inflammatory proteins as potential biomarkers for MASH. **Methods:** Ninety plasma samples of morbidly obese with MASLD biopsy proven (stratified as NO MASL n=10, MASL n=40, MASH n=40) were analyzed by targeted proteomics with the Proximity Extension Assay technology. Ninety-two proteins involved in the inflammation process were analyzed, and correlation analysis of clinical and biochemical parameters among the individuated markers were performed. Receiver operating characteristic (ROC) curves were used to determine MASH diagnostic performance of the identified candidates and their combination in a logistic regression model. **Results:** Significant differences were observed between subjects with and without MASH in several clinical and biochemical parameters. Plasma protein changes were independent of gender. Nine circulating proteins, including FGF21 (*Fibroblast growth factor 21*; p<0.0001), ADA, *adenine deaminase*(p=0.0097), CD6 (*T-cell differentiation antigen CD6;* p=0.0166), HGF (*Hepatocyte growth factor*; p=0.0039), CD5 (*T-cell surface glycoprotein CD5;* p=0.0054), GDNF (*glial cell line-derived neurotrophic factor*; p<0.0001), MCP-3 (*Methyl-accepting chemotaxis protein III*; p=0.016), IL-18R1 (*Interleukin-18 receptor 1*;p=0.0127) and CES-1 (*Carboxylesterase 1D;* p=0.0246) showed significant changes when comparing MASH vs. MASL/NO MASL. GGT, ALT, AST, White blood cells, platelets, and alkaline phosphatase significantly correlated with MASH diagnosis. FGF-21, APRI, and alkaline phosphatase combined in a logit model achieved a diagnostic performance for MASH with an AUC of 0.86 and SE(AUC) of 0.044. **Conclusion:** FGF-21, HGF, and GDNF, combined with other clinical parameters, are valuable tools for accurately diagnosing steatohepatitis. This emphasizes the importance of integrating novel markers into diagnostic algorithms for MASLD, as demonstrated by our logit model based on FGF21.

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2069 | PATHOLOGICAL SIGNIFICANCE OF INTRANUCLEAR LIPID DROPLETS AND GLYCOGENATED NUCLEI IN LIVER BIOPSY

Norihiro Imai[1] Yuki Ohsaki[2] Jinglei Cheng[3] Shinya Yokoyama[4] Kenta Yamamoto[4] Takanori Ito[4] yoji ishizu[4] Takashi Honda[4] Hiroaki Wake[4] Hiroki Kawashima[4] Jingjing ZHANG[4]

[1]Nagoya University Graduate School of Medicine, [2]Sapporo Medical University, [3]Nagoya University Graduate School of Med, [4]Nagoya University

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Background: Lipid droplets are organelles found not only in adipocytes but also in cells throughout the body. Recently, hepatocytes were discovered to contain lipid droplets within their nuclei, drawing attention to their formation mechanisms and functions. Glycogenated nucleus is glycogen deposited within the nucleus and is a frequent pathological finding in metabolic dysfunction-associated steatotic liver disease (MASLD). This study explored the pathological significance of intranuclear lipid droplets and glycogenated nuclei in liver biopsies. **Methods:** This study included 135 liver biopsies performed between 2020 and 2024. A portion of each liver biopsy specimen was examined using transmission electron microscopy (TEM) to investigate intranuclear lipid droplets in hepatocytes. Nuclear inclusion bodies with clear boundaries and unstained areas on HE staining were identified as glycogenated nuclei and examined under a light microscope. The frequencies of intranuclear lipid droplets and glycogenated nuclei were evaluated along with clinical characteristics. **Results:** The study included 72 men and 63 women, with a median age of 63 years. TEM revealed intranuclear lipid droplets in 64% of the liver biopsy specimens and 4.0% of the cell nuclei. Most of the intranuclear lipid droplets were smaller than 200 nm, which cannot be observed with visible light. In contrast, light microscopy showed glycogenated nuclei in 82% of the liver biopsy specimens and 1.4% of the cell nuclei. The frequencies of intranuclear lipid droplets and glycogenated nuclei were not significantly correlated. The frequency of intranuclear lipid droplets was not correlated with the degree of hepatic steatosis, suggesting that intranuclear lipid droplets do not directly reflect cytoplasmic lipid accumulation. However, the frequency of intranuclear lipid droplets was significantly and positively correlated with serum aspartate aminotransferase and alanine aminotransferase levels, implying that these droplets were formed as a stress response to liver injury. Glycogenated nuclei were frequently observed in liver biopsy specimens from patients with MASLD, and their frequency was significantly correlate with serum glycated hemoglobin level, but not with the degree of hepatic steatosis. **Conclusion:** The lack of significant correlation between the frequencies of intranuclear lipid droplets and glycogenated nuclei in liver biopsy specimens suggests that they have distinct pathological significance.

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2070 | T1-MAPPING IN THE LIVER: THE NEED FOR STANDARDIZATION

Irdina Nadziruddin[1] Darryl McClymont[1] Michele Pansini[1] Rajarshi Banerjee[1] Andrea Dennis[1]

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Background: Quantitative MRI is used to assess liver disease burden, fibrosis, and inflammation. The standardized, MRI T1 mapping metric, corrected T1 (cT1), is recommended in guidelines to stratify metabolic dysfunction-associated steatotic liver disease (MASLD) and it predicts cardiovascular and liver outcomes. cT1 correlates well with histologic features of the NAFLD activity score (NAS) and fibrosis grading. cT1 is measured using the MRI Modified Look-Locker inversion recovery (MOLLI) method and is adjusted with an algorithm which aligns T1 across scanner manufacturers and magnetic field strengths, while correcting for elevated iron levels which reduces T1 values and masks disease. Here we assess the impact of the standardization to MOLLI T1 provided by cT1. **Methods:** Participants with MASLD who underwent biopsies and MRI scans were grouped into 1 of 5 groups by MRI scanner and field strength. To ensure comparable disease states, we excluded patients with purely steatotic livers (both inflammation and ballooning of 0) and included those with fibrosis scores between 1–3. Liver iron concentration (from MRI T2*) and cT1 were calculated using LiverMultiScan. Median and interquartile range (IQR) of T1 and cT1 scores across all scanners were compared. The previously defined threshold of 875ms for cT1 has been suggested as the optimal cut-off for identifying at-risk MASH patients (NAS ≥4 and fibrosis ≥2 on biopsy). We compared the accuracy of this threshold applied to cT1 and T1 for identifying at-risk MASH patients. **Results:** 373 individuals scanned on 5 MRI scanners (GE 1.5T [n=70], GE 3T [n=79], Philips 3T [n=9], Siemens 1.5T [n=134], and Siemens 3T [n=81) were included. 33% of patients had elevated iron levels indicating the need for correction. The median and IQR of T1 across the scanners was 774ms (716–842, GE 1.5T), 882ms (802–932, GE 3T), 974ms (884–1011, Phillips 3T), 645ms (606–696, Siemens 1.5T) and 931ms (882–994, Siemens 3T). The spread of cT1 was significantly smaller across the respective scanners with median and IQR of 960ms (891–1045), 888ms (830–941), 955ms (905–990), 829ms (780–892), and 919ms (852–984),

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allowing for comparison of values across scanners. 65% had biopsy confirmed at-risk MASH. cT1 ≥ 875ms identified 60% of patients with at-risk MASH, versus 35% for T1 ≥ 875ms. **Conclusion:** Standardizing the MOLLI T1 signal with cT1 provides a reference that is independent of MRI hardware resulting in better classification of disease and a more versatile biomarker to assess MASH.

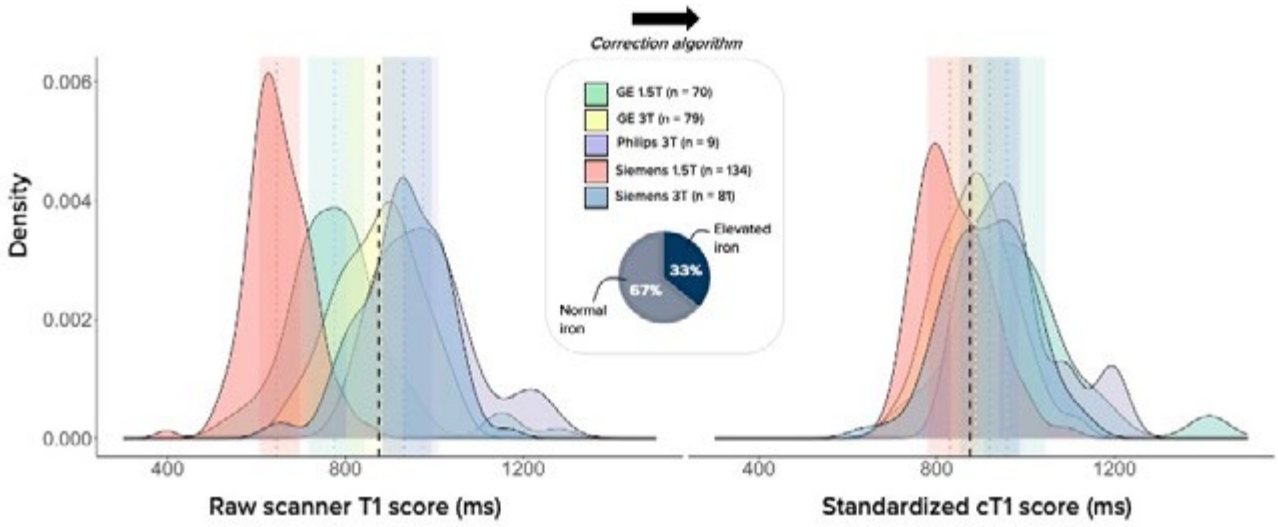

Figure 1. Standardized cT1 provides a signal reference that is applicable across scanners while correcting for increased levels of iron. The colored dotted lines represent the medians, and the shaded regions represent the interquartile range of T1 and cT1 across each scanner. The black dotted line represents the optimal threshold (875ms) at identifying patients with at-risk MASH.

Disclosures: Irdina Nadziruddin: Perspectum: Employee, Darryl McClymont: Nothing to Disclose, Michele Pansini: Nothing to Disclose, Rajarshi Banerjee: Perspectum: Employee, Perspectum: Executive role, Andrea Dennis: Perspectum: Employee

2071 | A COMBINED IMAGING AND PROTEOMIC APPROACH IDENTIFIES INFLAMMATORY RESPONSE PROTEINS UPREGULATED IN MASH: RESULTS FROM THE UK BIOBANK

Alessandro Fichera[1] Charlie Diamond[1] Sarah Larkin[1] Rajarshi Banerjee[1] Andrea Dennis[1] Helena Thomaides-Brears[1]

[1]Perspectum

Background: MASH (Metabolic dysfunction-associated steatohepatitis) is a severe form of liver disease characterized by presence of cardiometabolic risk factors, liver inflammation and damage due to fat accumulation. Multiparametric MRI (mpMRI) is recommended in MASH guidelines as imaging biomarkers cT1 and liver fat content (LFC) can quantify disease activity and steatosis in the liver, respectively. A multi-modality approach that combines imaging with proteomic analysis could significantly enhance our understanding of metabolic alterations in MASH. The UK Biobank, with its newly released extensive proteomic data linked to imaging data, provides an ideal resource for employing this approach. We aimed to identify the proteomic signature of MASH, shedding light on the proteins involved in fibro-inflammation and fat infiltration. **Methods:** We analysed a total of 1,464 proteins in plasma samples from 1,172 individuals from the UK Biobank, who had paired mpMRI data (46% male, median age 58 years, BMI 26 kg/m^2, 4% diabetes). Protein expression was measured using Olink® Explore platform. MASH was defined as LFC >5% and cT1 >800ms. Statistical analyses included t-test to assess significant protein dysregulation in the MASH group compared to controls, and hazard ratios (HR) for risk of clinical events or diagnoses from hospitalisation and death records. **Results:** 377 proteins were differentially expressed in participants with MASH from controls without steatotic liver disease; 86 of these (23%) have known roles in inflammatory pathways. Amongst those significantly upregulated in MASH ($p < 0.001$) were targets of drugs that are FDA-approved for other diseases: IL6 (interleukin-6, for rheumatologic disorders), VEGFA (Vascular endothelial growth factor A, for retinal disorders), CD4 (T-cell surface glycoprotein CD4, for breast cancer), CD79B (B-cell antigen receptor complex-associated protein beta chain, for lymphomas), PGF (Placenta growth factor, for macular degeneration) and CD22 (cluster of differentiation-22, for leukaemia). These 6 proteins had associations with chronic liver disease and cirrhosis and with all-cause mortality ($p < 0.001$), (for example, CD4 HR

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= 2.9 for chronic liver disease and cirrhosis, and PGF HR = 2.7 for all-cause mortality). **Conclusion:** This study presents a proteomic signature for MASH associated with inflammation and poor outcomes in the UK Biobank. An approach combining imaging and proteomics offers new insights into the pathophysiological mechanisms underlying MASH and provides potential targets for therapeutic intervention.

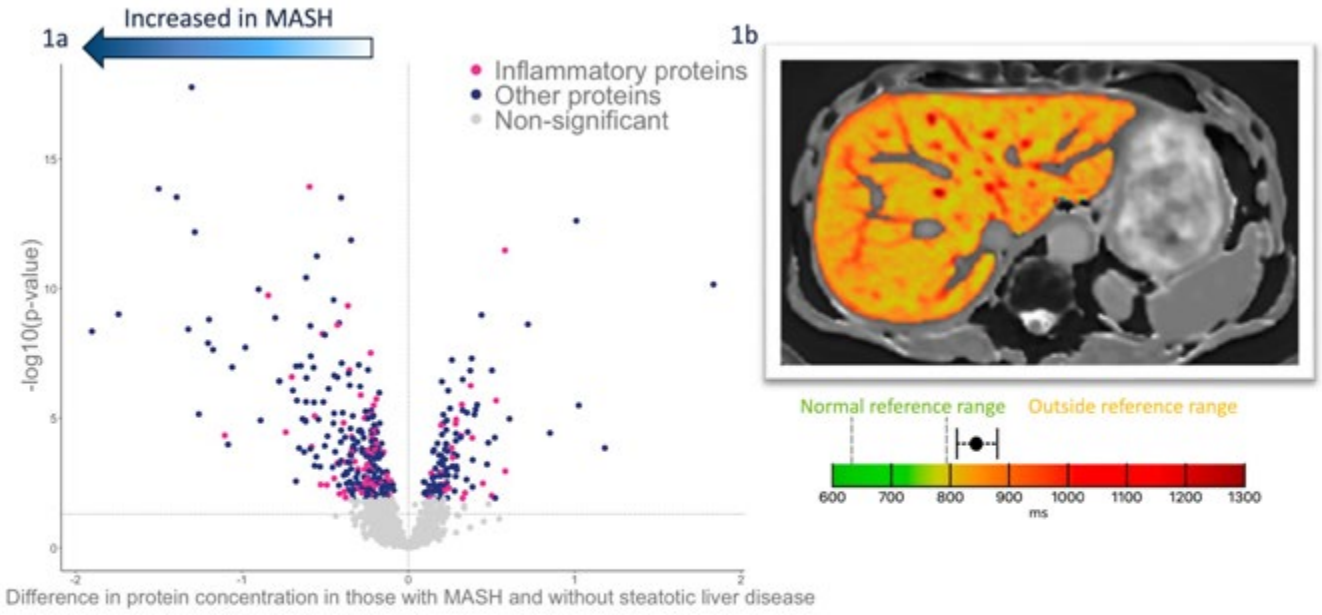

Figure 1a. Volcano plot showing difference in protein concentration for 1,464 proteins in participants with MASH compared to controls without steatotic liver disease. Blue and pink dots represents proteins and inflammatory markers significantly dysregulated in MASH ($p < 0.05$); 1b. cT1 map of a participants with MASH showing a notable liver disease activity (cT1 = 834 ms).

Disclosures: Alessandro Fichera: Perspectum: Employee, Charlie Diamond: Perspectum Ltd: Employee, Sarah Larkin: Perspectum Ltd: Employee, Rajarshi Banerjee: Perspectum: Employee, Perspectum: Executive role, Andrea Dennis: Perspectum: Employee, Helena Thomaides-Brears: Nothing to Disclose

2072 | ANTHROPOMETRIC FACTORS AND THEIR ASSOCIATION WITH FIBROSIS AND MASH IN PATIENTS WITH MASLD IN JAPAN AND THE UNITED STATES

Ryuki Hashida Lynn Gerber[1] James Paik[1] Takumi Kawaguchi[2] Dan Nakano[3] Tsubasa Tsutsumi[3] Tomoya Sano[3] Keisuke Amano[3] Machiko Kawaguchi[3] Machiko Kawaguchi[3] Hiroo Matsuse[3] Koji Hiraoka[3] Zobair Younossi[4]

[1]INOVA health system, [2]Kurume University School of Medicine, [3]Kurume University, [4]The Global NASH Council

Background: Obesity has been linked to the severity of MASLD. Anthropometric measurements are a simple and inexpensive indicator for assessing obesity at any medical facility. We aim to evaluate the associations of various anthropometric factors with significant fibrosis (SF) and MASH in MASLD patients in Japan and the US. **Methods:** This cross-sectional study utilized data from specialized hospitals in Japan (Kurume University) and the US (Inova Health System). BMI was defined as an assessment of obesity according to the WHO classification. Waist circumference (WC) and waist-to-height ratio (WHR) were indicators of central obesity. WC was classified according to the WHO classification, and the WHR cutoff was ≥ 0.6. SF was defined as liver stiffness of ≥ 8.0 kPa. MASLD with FibroScan-AST (FAST) score of ≥0.67 is defined as MASH. **Results:** Of a total of 368 MASLD patients (US: n=255; median [Interquartile] age, 61.5 [52.0-68.7] years, 51.4% male; and Japan: n=113; age, 57.0 [41.5-67.0] years, 62.8% male). Compared to MASLD patients in Japan, those in US had significantly higher rates of metabolic abnormalities including BMI-obesity (66.3 vs. 35.4%), WC-obesity (82.4 vs. 72.6%), WHR-obesity (82.4 vs. 72.6%), diabetes (94.9 vs. 85.0%), hypertension (74.1 vs. 62.8%), and elevated triglycerides (70.6 vs. 52.2%), but lower rates of SF (25.1 vs. 37.2%) and MASH (8.6 vs. 20.4%) (all p values < 0.03).

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After adjusting for age, sex, diabetes, hypertension, and triglycerides, we conducted a linear regression model for the prevalence of SF and MASLD divided by obesity and non-obesity in each anthropometric factor. For BMI, SF was 62.5 (obesity) vs. 23.3% (non-obesity) (adjusted difference 35.0% [95% confidence interval 15.4-54.7]), and MASH was 37.5 vs. 11.0% (23.9% [6.6-41.2]). For WC, SF was 48.8 vs. 6.45% (39.2% [24.2-45.2]), and MASH was 28.1 vs. 0.0% (28.2% [18.0-38.4]). For WHR, SF was 56.7 vs. 30.1% (24.8% [5.08-44.5]), and MASH was 33.3 vs. 15.7% (19.2% [0.9-37.4]) (all p values < 0.05). In the US, WC was significantly associated with SF (28.6 vs. 8.9%, 21.7% [10.8-32.5, p<0.001]) and MASH (28.6 vs. 8.9%, 16.2% [3.9-28.4, p=0.0109]). **Conclusion:** Central obesity (WC) is the best predictor of high levels of liver stiffness and MASH in the US. All three anthropometric measures likely predict liver stiffness and MASH among the Japanese. Anthropometric measurements may be useful for identifying high-risk patients from MAFLD at any medical institution, reducing economic burdens.

Disclosures: Ryuki Hashida: Nothing to Disclose, Lynn Gerber: Nothing to Disclose, James Paik: Nothing to Disclose, Takumi Kawaguchi: ASKA Pharmaceutical Co., Ltd.: Speaking and Teaching, Taisho Pharmaceutical Co., Ltd.: Speaking and Teaching, Kowa Company, Ltd.: Speaking and Teaching, AbbVie GK.: Speaking and Teaching, Eisai Co., Ltd.: Speaking and Teaching, Novo Nordisk Pharma Ltd.: Speaking and Teaching, Janssen Pharmaceutical K.K.: Speaking and Teaching, Janssen Pharmaceutical K.K.: Speaking and Teaching, Otsuka Pharmaceutical Co., Ltd.: Speaking and Teaching, EA Pharma Co.,Ltd.: Speaking and Teaching, Dan Nakano: Nothing to Disclose, Tsubasa Tsutsumi: Nothing to Disclose, Tomoya Sano: Nothing to Disclose, Keisuke Amano: Nothing to Disclose, Machiko Kawaguchi: Nothing to Disclose, Machiko Kawaguchi: Nothing to Disclose, Hiroo Matsuse: Nothing to Disclose, Koji Hiraoka: Nothing to Disclose, Zobair Younossi: Nothing to Disclose

2073 | A PROSPECTIVE STUDY OF THE CIRCULATING LIPIDOME IN MASLD REVEALS DISTINCT PROFILES ASSOCIATED WITH FIBROSIS PROGRESSION AND REGRESSION ◆

Ekaterina Smirnova[1] Katherine Yates[2] Edward Dennis[3] Oswald Quehenberger[3] Aaron Armando[3] Rohit Loomba[3] Bryce Hatfield[1] Cindy Behling[4] Oscar Cummings[5] Amon Asgharpour[1] Faridoddin Mirshahi[1] Anna Mae Diehl[6] Naga Chalasani[5] James Tonascia[2] Arun Sanyal[1]

[1]Virginia Commonwealth University, [2]Johns Hopkins University, [3]University of California at San Diego, [4]Pacific Rim Pathology, [5]Indiana University Health Medical Center, [6]Duke University

Background: There are no data on changes in the circulating lipidome with fibrosis progression or regression in MASLD. **Aims:** To quantify changes in the circulating lipidome associated with fibrosis progression or regression by ≥1 stage in MASLD. **Methods:** Plasma samples collected at the time of liver biopsies in a prospective non-interventional study of MASLD patients in the NIDDK NASH CRN with 2 biopsies separated by at least 1 year were evaluated. Lipid species within the following classes were measured by LCMS: diglycerides (DG), triglycerides (TG), Lyso-Phosphatidylethanolamines (LPE), Phosphatidylcholines (PC), Phosphatidylethanolamines (PE), Phosphatidylinositols (PI) and Sphingomyelins (SM), eicosanoids (EIC). Liver histology was read independently using the NASH CRN system. Differential changes in those with or without ≥ 1 fibrosis stage change were analyzed. Kruskal-Wallis (KW) test was performed on changes between visit 1 and baseline data for each lipid. For those lipids that passed FDR = 0.2 on KW test, pairwise differences between three fibrosis change groups were detected by Dunn-test with Holm adjustment for multiple comparisons. **Results:** A total of 301 patients (MASH: n= 274, fibrosis stages 0 (n=45), 1 (n=78), 2 (n=76), 3 (n=84) and 4 (n=18) were studied. Fibrosis changes (biopsy 2- biopsy 1) included: ≥ 1 stage progression (n=88), no change (n= 140), regression (n=73). Compared to regression, progression was associated with increased inflammatory lipids (15-HETE, LPE 22:5, LPE 16:0) and PC 32:0|16:0/16:0. Compared to those who had no change in fibrosis stage, those who progressed had decreased DG 36:4|18:2_18:2, multiple phospholipids (PC 32:0|16:0/16:0, PE 40:4|18:0_22:4, PE 38:5|18:1_20:4, PI 36:3|18:1/18:2,), triglycerides (TG 48:4|12:0_18:2_18:2, TG 46:3|12:0_16:1_18:2) and SM d35:2|d18:2/n17:0. Fibrosis regression (vs no change) was associated with decreased inflammatory lipids (EIC 9-HOTrE, EIC 12,13-EpOME, LPE 22:5), phospholipids (PC 34:3|16:1/18:2, PE 38:5|16:0/22:5, PE 38:5|18:1/20:4, PE 38:5|18:1/20:4, PE 38:3|18:0/20:3, PE 36:3|18:1/18:2, PE 34:2|16:0/18:2), and triglycerides (TG 56:4|18:0_18:1_20:3, TG 54:5|18:1_18:2_18:2, TG 54:4|18:1_18:1_18:2). **Conclusion:** Fibrosis progression and regression have distinct lipidomic profiles. Inflammatory lipids change coordinately with fibrosis stage.

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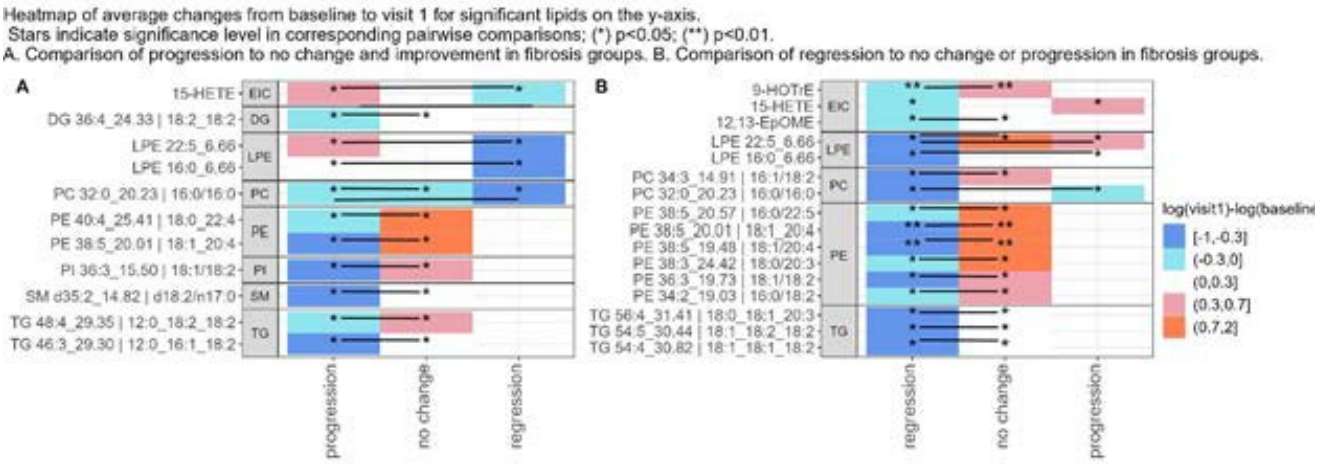

Disclosures: Ekaterina Smirnova: Pfizer, Inc: Grant/Research Support, Katherine Yates: Nothing to Disclose, Edward Dennis: Nothing to Disclose, Oswald Quehenberger: Nothing to Disclose, Aaron Armando: Nothing to Disclose, Rohit Loomba: Eli Lilly and Company: Consultant, 89bio: Consultant, Aardvark Therapeutics: Consultant, Altimmune: Consultant, Alnylam/Regeneron: Consultant, Amgen: Consultant, Arrowhead Pharmaceuticals: Consultant, AstraZeneca: Consultant, Bristol Myers Squibb: Consultant, CohBar: Consultant, Eli Lilly: Consultant, Galmed Pharmaceuticals: Consultant, Gilead: Consultant, Glympse Bio: Consultant, Hightide: Consultant, Inipharma: Consultant, Intercept: Consultant, Inventiva: Consultant, Ionis: Consultant, Janssen, Inc.: Consultant, Madrigal Pharmaceuticals: Consultant, Merck, Metacrine, Inc.: Consultant, NGM Biopharmaceuticals: Consultant, Novartis: Consultant, Novo Nordisk: Consultant, Pfizer: Consultant, Sagimet Biosciences: Consultant, Terns Pharmaceuticals: Consultant, Theratechnologies and Viking Therapeutics: Consultant, 89bio: Stock options, Sagimet Biosciences: Stock options, Arrowhead Pharmaceuticals: Research grant, AstraZeneca: Research grant, Boehringer Ingelheim: Research grant, Bristol Myers Squibb: Research grant, Eli Lilly: Research grant, Galectin Therapeutics: Research grant, Galmed Pharmaceuticals: Research grant, Gilead: Research grant, Hanmi: Research grant, Intercept: Research grant, Inventiva: Research grant, Ionis: Research grant, Janssen, Inc.: Research grant, Madrigal Pharmaceuticals: Research grant, Merck: Research grant, NGM Biopharmaceuticals: Research grant, Novo Nordisk: Research grant, Pfizer: Research grant, Sonic Incytes: Research grant, Terns Pharmaceuticals: Research grant, LipoNexus, Inc.: Co-founder, Bryce Hatfield: Nothing to Disclose, Cindy Behling: Pacific Rim Pathology Lab: Employee, Novo Nordisk: Consultant, Pathology Institute: Consultant, boehringer ingleheim: Consultant, akero: Independent Contractor, Oscar Cummings: Nothing to Disclose, Amon Asgharpour: Madrigal: Advisor, Galectin: Clinical Endpoint Committee, Faridoddin Mirshahi: Nothing to Disclose, Anna Mae Diehl: >$10,000 relationship with Tune Therapeutics; Has not ended; <$10,000 relationship with Boehringer Ingelheim; Has not ended; Associate Editor, < $10,000 relationship with EASL - Journal of Hepatology; Has not ended; >$10,000 relationship with HeptaBio; Has not ended, Naga Chalasani: Nothing to Disclose, James Tonascia: Nothing to Disclose, Arun Sanyal: Genfit, Akarna, Tiziana, Durect, Inversago, Hemoshear, North: Stock - publicly traded company, Astra Zeneca (60K), Boston Pharmaceutical

2074 | EVALUATION OF THE PERFORMANCE OF MASEF SCORE IN PATIENTS WITH METABOLIC DYSFUNCTION ASSOCIATED STEATOHEPATITIS (MASH) UNDER A LIPID-LOWERING MEDICATION ◆

Ibon Martinez-Arranz[1] Jesus Banales[2] Cristina Alonso[1] REBECA MAYO[1] Marco Arrese[3] Javier Crespo[4] Mazen Noureddin[5]

[1]OWL Metabolomics, Derio, Spain, [2]Biodonostia Research Institute, Donostia University Hospital, University of Basque Country, Spain, [3]Pontificia Universidad Católica de Chile, Santiago, Chile, [4]Marqués de Valdecilla University Hospital, Cantabria University, IDIVAL, Santander, Spain, [5]Houston Methodist Hospital

Background: Lipid-lowering medications are widely prescribed for managing dyslipidemia, common in patients with metabolic dysfunction associated steatohepatitis (MASH). MASEF score is a blood test based on lipidomics, developed for the identification of patients with at-risk MASH, defined as MASH with NAFLD activity score (NAS) ≥ 4 and fibrosis stage ≥ 2. Due to the characteristics of the analytes included in the MASEF score, lipid-lowering

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medications may influence its performance in the assessment of at-risk MASH. This study aims to evaluate whether lipid-lowering medications affect the performance of the MASEF score. **Methods:** A cohort of 562 patients with biopsy-proven MASH was divided into two groups based on their use of lipid-lowering treatment (60 using statins, fibrates or other lipid-lowering drugs, and 502 not using). The key clinical parameters for the overall cohort included: gender distribution with 351 females (62.5%) and 211 males (37.5%); average age of 49.9 years; Body Mass Index (BMI) 36.0 kg/m^2; HbA1c 6.4%; triglycerides 163.0 mg/dL; Alanine Aminotransferase (ALT) 54.0 U/L; and Aspartate Aminotransferase (AST) 37.9 U/L. MASEF score was calculated to assess the risk status, and its performance was evaluated in terms of area under the receiver-operating characteristic (AUC) vs. biopsy. Liver histology was assessed by NASH CRN criteria. Key clinical parameters such as age, BMI, HbA1c, and triglycerides were compared between both groups. **Results:** Patients using lipid-lowering medications were older (55.2 vs. 49.3 years, p<0.001) and had higher HbA1c (7.0% vs. 6.3%, p=0.011) and triglyceride levels (189.5 mg/dL vs. 159.9 mg/dL, p=0.020) compared to those not using these drugs. The performance of the MASEF score was consistent across both cohorts and no significant differences were found between the medicated and the not medicated groups, in both at-risk MASH and not at-risk MASH patients, with AUC of 0.77 for the entire cohort, 0.77 for those using lipid-lowering medication, and 0.76 for those not using it. **Conclusion:** The performance of the MASEF Score remains robust across different patient groups, independently if the patients are under a lipid-lowering therapy.

Disclosures: Ibon Martinez-Arranz: Nothing to Disclose, Jesus Banales: Nothing to Disclose, Cristina Alonso: Rubió Metabolomics, S.L.U.: Employee, REBECA MAYO: OWL Metabolomics: Employee, Marco Arrese: Nothing to Disclose, Javier Crespo: Nothing to Disclose, Mazen Noureddin: Principal Investigator for a Drug Study relationship with Viking; Has not ended; Consultant relationship with Eli Lilly; Has not ended; Consultant relationship with AstraZeneca; Has not ended; Consultant relationship with Boston Pharmaceuticals; Has not ended; Principal Investigator for a Drug Study relationship with Genfit; Has not ended; Principal Investigator for a Drug Study relationship with Galectin; Has not ended; Principal Investigator for a Drug Study relationship with Gilead; Has not ended; Principal Investigator for a Drug Study relationship with BMS; Has not ended; Principal Investigator for a Drug Study relationship with BI; Has not ended; Principal Investigator for a Drug Study relationship with Akero; Has not ended; Consultant relationship with Cytodyn; Has not ended; Consultant relationship with GSK; Has not ended; Consultant relationship with BI; Has not ended; Consultant relationship with Madrigal; Has not ended; Terns,Takeda, Zydus. relationship with Itimmune, BI, Cytodyn, 89BIO, GSK, Madrigal, Merck, Novo Nor; Has not ended; Principal Investigator for a Drug Study relationship with Allergan; Has not ended; Consultant relationship with Takeda; Has not ended; Consultant relationship with Terns; Has not ended; Terns, Corcept, Takeda, Madrigal, Novartis, Novo Nordisk, relationship with Allergan, Akero, BI, BMS, Gilead, Galectin, Zydus GSK; Has not ended; Consultant relationship with Novo Nordisk; Has not ended; Stock â€“ privately held company relationship with Rivus Pharma, Cytodyn, and ChronWell; Has not ended; Consultant relationship with Merck; Has not ended; Principal Investigator for a Drug Study relationship with Madrigal; Has not ended; Consultant relationship with Altimmune; Has not ended; Principal Investigator for a Drug Study relationship with Terns; Has not ended; Principal Investigator for a Drug Study relationship with Zydus; Has not ended; Stock â€“ privately held company relationship with Rivus Pharmaceuticals; Has not ended; Consultant relationship with Alligos; Has not ended; Stock - publicly traded company relationship with Cytodyn; Has not ended; Stock â€“ privately held company relationship with ChronWell; Has not ended; Speaking and Teaching relationship with Madrigal; Has not ended; Principal Investigator for a Drug Study relationship with Takeda; Has not ended; Principal Investigator for a Drug Study relationship with Shire; Has not ended; Principal Investigator for a Drug Study relationship with Novo Nordisk; Has not ended; Principal Investigator for a Drug Study relationship with Novartis; Has not ended; Principal Investigator for a Drug Study relationship with Enanta; Has not ended; Principal Investigator for a Drug Study relationship with Corcept; Has not ended; Principal Investigator for a Drug Study relationship with GSK; Has not ended; Principal Investigator for a Drug Study relationship with Conatus; Has not ended

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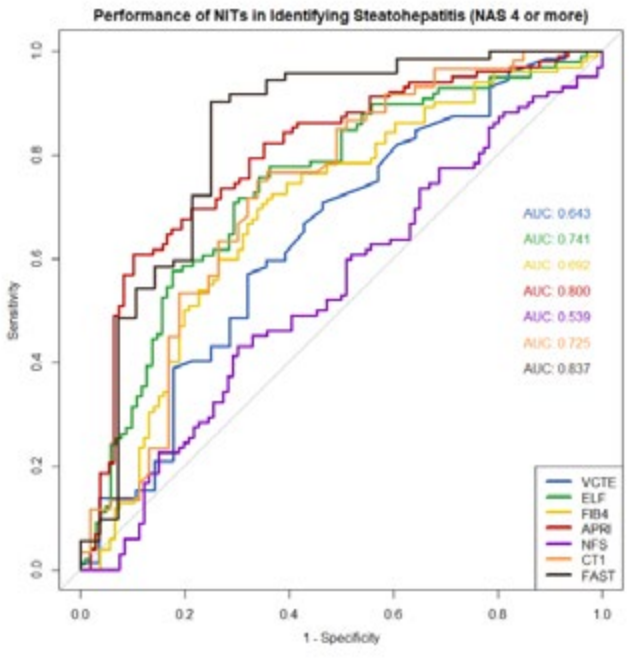
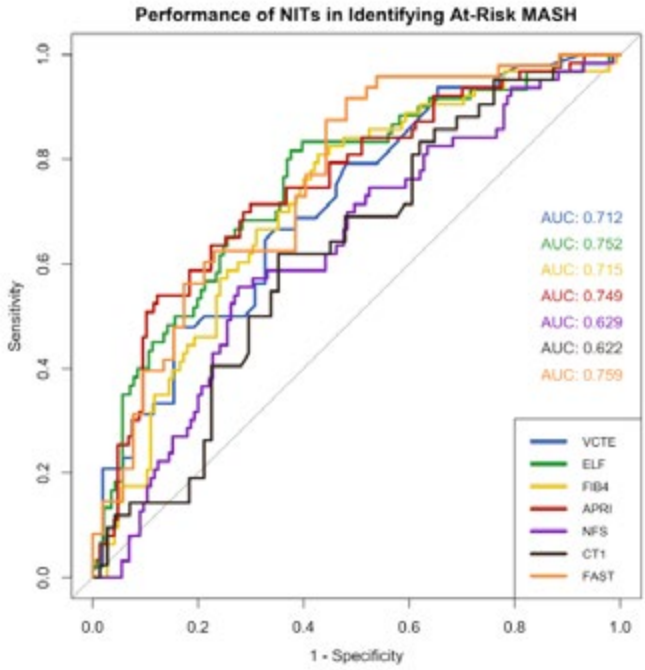
2075 | IMPROVED DIAGNOSTIC ACCURACY OF VIBRATION-CONTROLLED TRANSIENT ELASTOGRAPHY BASED TESTS IN IDENTIFYING METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS (MASH) AND AT-RISK MASH IN OBESE AND LEAN INDIVIDUALS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD)

Joo Wei Ethan Quek[1] EN YING TAN[2] Shi Yan Lee[2] Daniel Huang[2] Jonathan Lee[2] Margaret Teng[2] Cheng Han Ng[2] Nicholas Syn[2] Aileen Wee[2] Shook Ting Gwyneth Soon[2] Nur Halisah Jumat[2] Yock Young Dan[2] Mark Muthiah[2]

[1]National University of Singapore, [2]National University Hospital, Singapore

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is a leading cause of morbidity and mortality globally. Metabolic dysfunction-associated steatohepatitis (MASH) represents a severe form of MASLD, while at-risk MASH is associated with an increased risk of disease progression and complications and is a prerequisite for recruitment into most clinical trials for MASH. Despite advances in MASLD, liver biopsy remains the gold standard for identifying, monitoring and prognosticating MASH and at-risk MASH. We aim to compare the performance of various NITs in identifying MASH and at-risk MASH in a multi-ethnic Asian cohort of biopsy-proven MASLD patients. **Methods:** Patients from the National University Health System, Singapore with biopsy-proven MASLD across the entire spectrum of disease from normal to liver cirrhosis were enrolled to undergo non-invasive testing. The study compared the performance of Vibration-Controlled Transient Elastography (VCTE), Enhanced Liver Fibrosis (ELF) test, Fibrosis-4 index (FIB-4) AST to Platelet Ratio Index (APRI), NAFLD Fibrosis Score (NFS), iron-corrected T1 mapping (cT1) and FibroScan-AST score (FAST) in detecting MASH and at-risk MASH. We then evaluated their performance in obese and non-obese subgroups. We also combined blood-based and imaging-based NITs via logistic regression modeling to evaluate whether this improved diagnostic performance. **Results:** 210 multi-ethnic Asian patients with biopsy-proven MASLD were recruited to undergo non-invasive tests. Area under receiver-operator-characteristics values (AUCs) for identifying MASH for VCTE, ELF, FIB-4, APRI, NFS, cT1 and FAST were 0.643, 0.741, 0.692, 0.800, 0.539, 0.725, 0.837 respectively. AUC values for identifying at-risk MASH were 0.712, 0.752, 0.715, 0.749, 0.629, 0.622, 0.759 respectively. FAST performed better in identifying MASH in the non-obese cohort, while cT1 performed better in identifying at-risk MASH in the non-obese cohort. AUCs for combinations of blood-based and imaging-based NITs (FIB4 + VCTE, FIB4 + cT1, ELF + VCTE and ELF + cT1) for identifying at-risk MASH were 0.765, 0.714, 0.704 and 0.702 respectively. **Conclusion:** FAST score is the best performing NIT for MASH and at-risk MASH, and also performs well in non-obese MASH. Combining FIB4 and VCTE into a logistic regression model enhances diagnostic performance in identifying at-risk MASH.





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Disclosures: Joo Wei Ethan Quek: Nothing to Disclose, EN YING TAN: Nothing to Disclose, Shi Yan Lee: Nothing to Disclose, Daniel Huang: Nothing to Disclose, Jonathan Lee: Nothing to Disclose, Margaret Teng: Nothing to Disclose, Cheng Han Ng: Nothing to Disclose, Nicholas Syn: Nothing to Disclose, Aileen Wee: Nothing to Disclose, Shook Ting Gwyneth Soon: Nothing to Disclose, Nur Halisah Jumat: Nothing to Disclose, Yock Young Dan: Nothing to Disclose, Mark Muthiah: Lerna Bio: Stock – privately held company, Olympus: Speaking and Teaching, Boston Scientific: Speaking and Teaching, Novo Nordisk: Grant/Research Support, Echosens: Grant/Research Support, Gilead: Advisor

2076 | CORRECTED T1 MAPPING (CT1) OUTPERFORMS IN EVALUATING CLINICALLY SIGNIFICANT AND ADVANCED FIBROSIS IN NON-OBESE INDIVIDUALS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD): FINDINGS FROM A MULTI-ETHNIC ASIAN COHORT WITH HISTOLOGICALLY CONFIRMED MASLD ◆

Joo Wei Ethan Quek[1] EN YING TAN[2] Shi Yan Lee[2] Daniel Huang[2] Jonathan Lee[2] Margaret Teng[2] Cheng Han Ng[2] Nicholas Syn[2] Aileen Wee[2] Shook Ting Gwyneth Soon[2] Nur Halisah Jumat[2] Yock Young Dan[2] Mark Muthiah[2]

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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is a growing global health concern, with an estimated global prevalence of 30%. Fibrosis is the strongest independent predictor of long-term prognosis in MASLD and is associated with a higher risk of developing liver-related events. Evaluating fibrosis in MASLD is also crucial in monitoring, determining, and evaluating treatment plans. Non-invasive tests (NITs) present an attractive alternative to liver biopsy which, while gold standard, is limited by procedural risks, costs and sampling errors. We aim to evaluate the performance of various NITs in evaluating fibrosis in a multi-ethnic Asian cohort of biopsy-proven MASLD patients. **Methods:** Patients with biopsy-proven MASLD from the National University Health System, Singapore were enrolled to evaluate the performance of 7 NITs (Vibration-Controlled Transient Elastography (VCTE), Enhanced Liver Fibrosis (ELF) test, Fibrosis-4 index (FIB-4) AST to Platelet Ratio Index (APRI), NAFLD Fibrosis Score (NFS), iron-corrected T1 mapping (cT1) and AGILE 3+) in the assessment of clinically-significant fibrosis (CSF) and advanced fibrosis (AF). Subgroup analysis was then performed amongst obese and lean cohorts. **Results:** 210 multi-ethnic Asian patients with biopsy-proven MASLD were recruited to undergo non-invasive tests. In non-obese cohorts, Area under receiver-operator characteristics (AUC) values for identifying CSF for VCTE, ELF, FIB-4, APRI, NFS, cT1 and AGILE 3+ were 0.835, 0.822, 0.868, 0.850, 0.893, 0.825, 0.870 respectively. AUC values for identifying advanced fibrosis were 0.839, 0.856, 0.841, 0.859, 0.873, 0.917, 0.885. In obese cohorts, AUCs for CSF and AF of the respective NITs were 0.784, 0.753, 0.725, 0.740, 0.656, 0.575, 0.766 and 0.809, 0.847, 0.805, 0.807, 0.728, 0.556, 0.840. cT1 performed significantly better in the non-obese compared to obese group in identifying AF. However, there was no significant difference in NIT performance for other biomarkers and for CSF. **Conclusion:** VCTE and AGILE3 performed best for identifying CSF and AF in the combined analysis. In the obese cohort, VCTE and ELF were best for detecting CSF and AF respectively. In the non-obese cohort, NFS and cT1 performed better in predicting CSF and AF. Patients with obese and lean MASLD may be best served by different NITs for fibrosis assessment.

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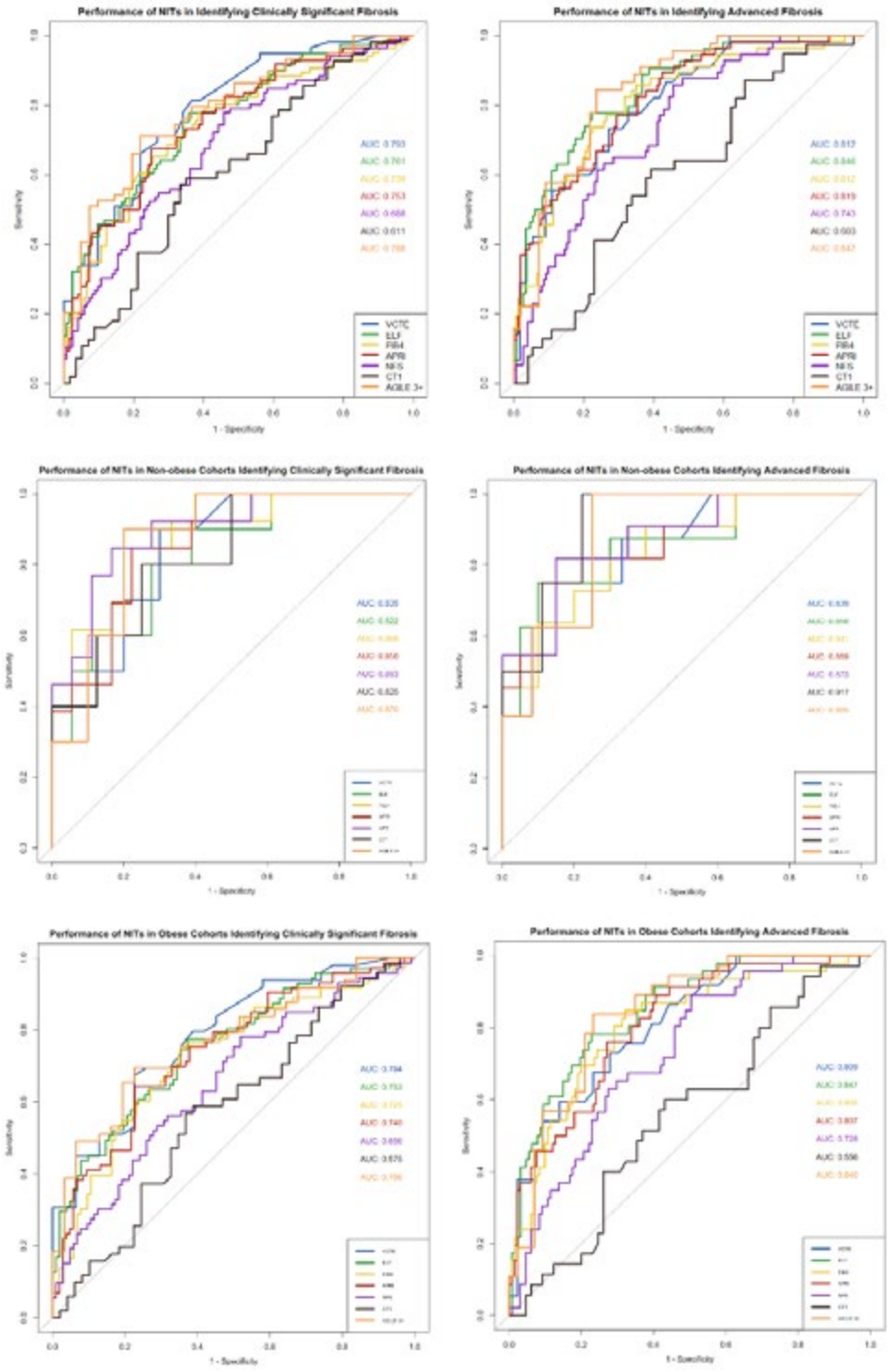

Disclosures: Joo Wei Ethan Quek: Nothing to Disclose, EN YING TAN: Nothing to Disclose, Shi Yan Lee: Nothing to Disclose, Daniel Huang: Nothing to Disclose, Jonathan Lee: Nothing to Disclose, Margaret Teng: Nothing to Disclose, Cheng Han Ng: Nothing to Disclose, Nicholas Syn: Nothing to Disclose, Aileen Wee: Nothing to Disclose, Shook Ting Gwyneth Soon: Nothing to Disclose, Nur Halisah Jumat: Nothing to Disclose, Yock Young Dan: Nothing to Disclose, Mark Muthiah: Lerna Bio: Stock – privately held company, Olympus: Speaking and Teaching, Boston Scientific: Speaking and Teaching, Novo Nordisk: Grant/Research Support, Echosens: Grant/Research Support, Gilead: Advisor

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2077 | CHITINASE-3-LIKE PROTEIN 1 BASED BIOMARKER PANEL FOR EARLY LIVER FIBROSIS ASSESSMENT IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

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Background: The efficiency of currently available non-invasive tests for detecting significant liver fibrosis in patients with type 2 diabetes mellitus (T2DM) remains limited. Previous studies had demonstrated that chitinase-3-like protein 1 (CHI3L1) was an independent risk factor for liver fibrosis. Therefore, we aimed to establish a non-invasive test based on CHI3L1 for diagnosing significant liver fibrosis in patients with T2DM, using transient elastography (TE) as the reference standard. **Methods:** This prospective study recruited patients with T2DM from endocrinology outpatient clinics between September 2023 and March 2024. All patients underwent TE and were tested for CHI3L1. Significant liver fibrosis in patients with T2DM was defined as TE-derived liver stiffness ≥ 8.2 kPa. Patients with missing data for age, sex, body mass index, platelet (PLT), alanine aminotransferase, aspartate aminotransferase (AST), hemoglobin (Hb), and albumin (ALB) were excluded. The least absolute shrinkage and selection operator method was used to identify independent risk factors associated with significant liver fibrosis. Diagnostic accuracy was evaluated using the area under the receiver operating characteristic curve (AUC). **Results:** A total of 65 patients with T2DM from two centers were enrolled in this study (Figure 1A). Among these patients, 43.1% (28/65) of patients presented with significant liver fibrosis. Risk factors including CHI3L1, PLT, AST, ALB, and Hb were identified and fitted into a novel score, termed "DiabetesFibroCHI", for evaluating significant liver fibrosis (Figure 1B). The diagnostic accuracy of the DiabetesFibroCHI score for diagnosing significant liver fibrosis in patients with T2DM was superior to that of fibrosis-4 index (a non-invasive test which is highly recommended for liver fibrosis assessment), with an AUC of 0.855 (95% confidence interval [CI] 0.755-0.956) compared to 0.757 (95% CI 0.626-0.889) (Figure 1C). Using 0.36 as a cut-off value, the sensitivity, specificity, and accuracy of the DiabetesFibroCHI score were 0.929, 0.757, and 0.815, respectively. Notably, the DiabetesFibroCHI score displayed a high negative predictive value of 0.903 for ruling out significant liver fibrosis in patients with T2DM. **Conclusion:** The DiabetesFibroCHI score exhibited a satisfactory diagnostic efficiency for significant liver fibrosis in patients with T2DM.

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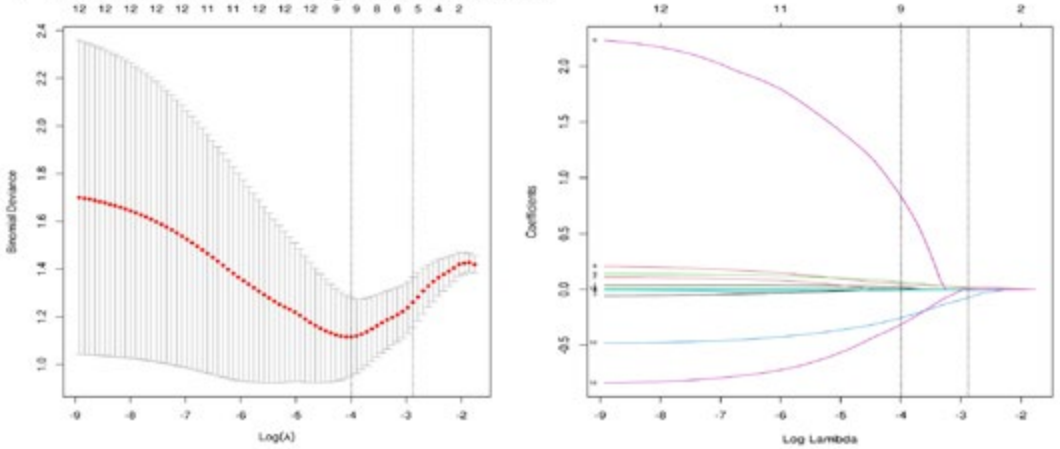
A Baseline characteristics.

Variables	*n* = 65
Age (years), mean (SD)	56.0 (12.2)
Male, *n* (%)	44 (67.7%)
BMI (kg/m^2), mean (SD)	26.0 (3.7)
CHI3L1 (ng/mL), median (Q1, Q3)	76.6 (55.8, 145.9)
FIB-4, median (Q1, Q3)	1.232 (0.838,1.918)
PLT (×10^9/L), median (Q1, Q3)	207.0 (173.0, 269.0)
HbA1c (%), mean (SD), *n* = 62	8.4 (1.8)
ALT (IU/L), median (Q1, Q3)	26.7 (16.7, 39.0)
AST (IU/L), median (Q1, Q3)	23.2 (19.0, 35.3)
Hb (g/L), mean (SD)	144.3 (18.7)
ALB (g/L), median (Q1, Q3)	47.0 (42.5, 48.6)

B Risk factors selection using the LASSO model.



C Receiver operating characteristic curves.

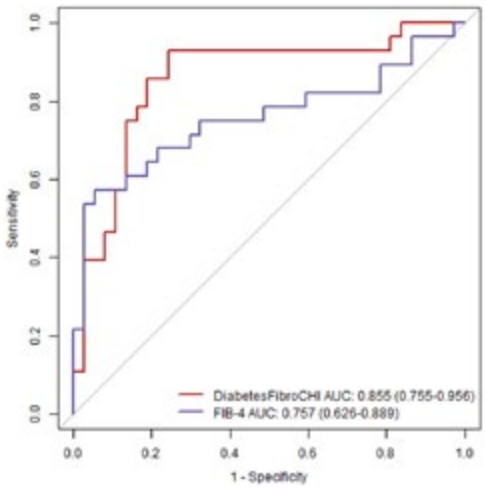


Figure 1. Chitinase-3-like protein 1 based biomarker panel for early liver fibrosis assessment in type 2 diabetes mellitus. A. Baseline characteristics; B. Risk factors selection using the LASSO model; C. Receiver operating characteristic curves.

Note: Five significant predictors of significant liver fibrosis, including CHI3L1, PLT, AST, Hb, and ALB, were selected. ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUC, area under the curve; BMI, body mass index; CHI3L1, chitinase-3-like protein 1; FIB-4, fibrosis-4 index; Hb, hemoglobin; HbA1c, hemoglobin A1c; LASSO, least absolute shrinkage and selection operator; PLT, platelet; Q1, lower quartile; Q3, upper quartile; SD, standard deviation.

Disclosures: Yuping Chen: Nothing to Disclose, Xuan Liang: Nothing to Disclose, Yan Wang: Nothing to Disclose, Xiaoxiong Hu: Nothing to Disclose, Jiaojian Lv: Nothing to Disclose, Xiaomei Wang: Nothing to Disclose, Jitao Wang: Nothing to Disclose, Lingyun Pan: Nothing to Disclose, Baiyun Li: Nothing to Disclose, Yuting Zhang: Nothing to Disclose, Shirui Hao: Nothing to Disclose, Xiaojuan Wang: Nothing to Disclose, Xiaolong Qi: Nothing to Disclose

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2078 | ADJUSTING FOR STEATOSIS CONTENT IN BASELINE AND FOLLOWUP MASH BIOPSIES CAN OVERESTIMATE CHANGES IN FIBROSIS

Deeksha Kartik[1] Lara Murray[1] Jacqueline Brosnan-Cashman[1] Neel Patel[1] Ylaine Gerardin[1] Robert Egger[1] Adam Stanford-Moore[1]

[1]PathAI

Background: In MASH clinical trials, the accurate and sensitive measurement of the change in fibrosis from baseline remains a challenge, exacerbated by concurrent changes in liver volume and steatotic content. As these parameters decrease, quantitative metrics of fibrosis (e.g., collagen proportionate area, CPA) can falsely appear to increase. Here, we leverage AI simulations to analyze assumptions of adjusting for steatosis content and demonstrate an AI measure of fibrosis change that shows little dependency on steatosis. **Methods:** CPA in Masson's Trichrome (MT)-stained slides was measured using AIM-MASH+[1], an AI tool for ordinal and continuous CRN scoring. Liver Explore[2], a suite of algorithms that extract granular features of liver microarchitecture, was used to measure steatosis area on hematoxylin and eosin (H&E)- and MT-stained slides and CPA on H&E-stained slides. Using one baseline H&E biopsy, followups were simulated assuming that 1) all steatosis tissue area disappears or 2) all steatosis is replaced by normal tissue (Fig 1A). The change in CPA was computed between baseline and simulated followups, with and without steatosis adjustment (Fig 1A). This simulation was expanded to baseline MT slides from EMMINENCE (NCT02784444; N=328). **Results:** From baseline to simulated followup, steatosis-adjusted CPA overestimates the change in fibrosis when any steatosis area is assumed to be replaced by healthy tissue; when steatosis regions are assumed to disappear, CPA underestimates the fibrosis change (Fig 1A). On an expanded cohort, when all steatosis disappears, uncorrected CPA was observed to increase >2-fold when the steatosis area proportion exceeds 50% (Fig 1B). In contrast, changes in AIM-MASH+ continuous score showed no systematic correlation with proportion of steatosis (Fig 1C). **Conclusion:** While steatosis adjustment has been proposed to measure fibrosis change independent of changes in steatosis, it poses a risk of overestimating fibrosis reduction if any amount of steatosis region reverts to normal tissue–potentially leading to falsely identifying a response in some patients. Conversely, unadjusted CPA will potentially underestimate fibrosis reduction. We demonstrate that AIM-MASH+, an area-independent tool, does not scale with steatosis change and therefore may be a more robust method of measuring fibrosis change. [1]AIM-MASH+ is for research use only. Not for use in diagnostic procedures. [2]Liver Explore is for research use only. Not for use in diagnostic procedures.

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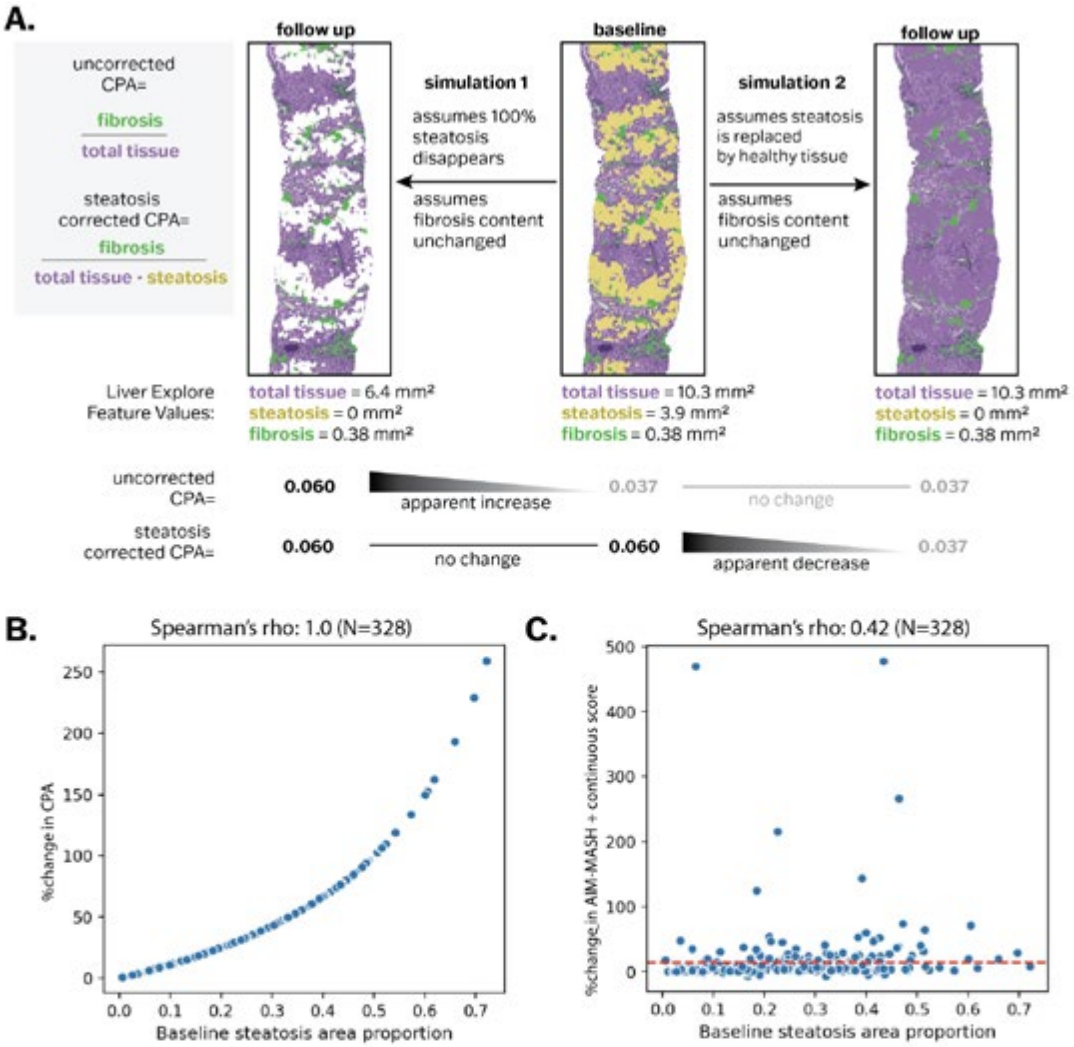

Figure 1. (A) Simulated followup scenarios for a single biopsy demonstrate CPA underestimates fibrosis reduction (simulation 1) and steatosis corrected CPA overestimates fibrosis reduction (simulation 2). Note that in simulation 1, the empty space in the image reflects steatosis that has completely disappeared from the baseline biopsy. In an actual liver, we do not expect empty space, but rather that the remaining tissue moves closer together, consistent with liver volume reduction. (B) Percent increase in CPA increases with baseline steatosis area proportion in a clinical cohort (N=328) (C) Percent change in AIM-MASH+ continuous score is typically much closer to zero in a clinical cohort (mean change = 0.17 (0.15, 0.20) or 14% (10%, 19%)).

Disclosures: Deeksha Kartik: Nothing to Disclose, Lara Murray: Nothing to Disclose, Jacqueline Brosnan-Cashman: PathAI: Employee, PathAI: Stock – privately held company, Neel Patel: PathAI: Employee, Ylaine Gerardin: PathAI: Employee, Robert Egger: Nothing to Disclose, Adam Stanford-Moore: Nothing to Disclose

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2079 | SIMPLE NONINVASIVE TESTS HAVE POOR DIAGNOSTIC ACCURACY FOR MASLD F2-3 IN A REAL WORLD CANADIAN COHORT

Nashla Hamdan[1] Chinmay Bera[2] Heather Kosick[1] Keyur Patel[1]

[1]University of Toronto, [2]Toronto General Hospital

Background: Several Non-invasive test (NIT) that have been proposed to identify patients with advanced fibrosis (F3-4) in patients with metabolic dysfunction-associated steatotic liver disease (MASLD). Following the recent approval of therapy for MASLD F2-3, our aims were to assess the diagnostic utility of simple NITs (NFS, FIB-4, APRI and VCTE) for F2-3 in a real world MASLD tertiary center cohort. **Methods:** We included adult patients at a single tertiary center with biopsy-proven MASLD from 2010 – 2021. Alternate causes of liver disease were excluded based on clinical review, laboratory parameters, and histopathology. **Results:** Our cohort included 404 MASLD patients, age median (range) 48 (19 – 75) years, 55% men, with diabetes n= 131 (32%), and dyslipidemia n=141 (35%). Prevalence of biopsy F2-3 was 29%, F0-1 35% and F4 35%. The Youden Index for NFS was 0.20, FIB-4 0.19, APRI 0.07, and VCTE 0.28, with all NITs showing a poor diagnostic performance to identify MASLD F2-3 with AUROC 0.52-0.58. Differences in AUROC were only significant for FIB-4 compared to APRI ($p<0.0176$). **Conclusion:** Simple NITs have poor diagnostic performance for MASLD F2-3 in a real world cohort. Improved NITs and diagnostic algorithms are required for clinical practice to improve accuracy for diagnosis of F2-3, and assess eligibility for MASLD therapy. Further validation in lower prevalence cohorts will be important.

Diagnostic performance of NITs for F2/3 vs non-F2/3

NITs	Sensitivity	Specificity	+LR	-LR	AUROC
NFS (n=208)	47.50	72.63	1.74	0.72	0.58
FIB-4 (n=359)	97.50	22.46	1.26	0.11	0.57
APRI (n=361)	90.83	16.49	1.09	0.56	0.52
VCTE (n=96)	96.97	31.75	1.42	0.1	0.56

LR: likelihood ratio

Disclosures: Nashla Hamdan: Nothing to Disclose, Chinmay Bera: Nothing to Disclose, Heather Kosick: Nothing to Disclose, Keyur Patel: Novo-Nordisk: Consultant, Gilead Sciences: Consultant, Merck: Consultant, Resalis: Advisor

2080 | STAIN-FREE DIGITAL PATHOLOGY IMAGING PROVIDES MICROARCHITECTURALLY-RESOLVED INSIGHTS INTO SCAR EVOLUTION AND HISTOLOGICAL INJURY ALLOWING DIRECT CLINICAL OUTCOME PREDICTION IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE

Timothy Kendall[1] Dean Tai[2] Elaine Chng[2] Yayun Ren[2] Jonathan Fallowfield[1]

[1]University of Edinburgh, [2]HistoIndex Pte Ltd

Background: Cardinal histological features reflecting activity are central to the diagnosis of metabolic dysfunction-associated steatotic liver disease (MASLD) and fibrosis stage is associated with increased mortality and liver-related events. Liver biopsies of the SteatoSITE cohort allowed stain-free quantification of histological features that are predictive of clinical outcomes but unapparent to human observers. **Methods:** Sections from n=452 biopsies were randomized into training (300) or test (152) sets and imaged for fibrosis, steatosis, and ballooning parameters using second harmonic generation/two-photon excitation fluorescence (SHG/2PE) microscopy. 5 of 184 fibrosis parameters have previously been used to derive separate fibrosis-based indices for risk of all-cause mortality

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(fMI) and hepatic decompensation (fDI). By feature traversing, the effect of adding 65 steatosis and 21 ballooning parameters to fMI and fDI was tested, and improved composite outcome indices (sf and bf) generated. In the testing set, the predictive power of the new composite indices was compared with assigned NASH-CRN fibrosis stage (F0/1/2 v F3/4), stain-free imaging derived qFibrosis stage (qF0/1/2 v qF3/4), and previously derived fibrosis-only indices using Kaplan–Meier analysis and Cox proportional hazards modelling. **Results:** The composite indices for all-cause mortality (bfMI) and hepatic decompensation (bfDI) generated by including ballooning parameters had greater predictive power than the fMI and fDI, respectively, as well as qFibrosis-derived stage and NASH-CRN fibrosis score (Table 1). The composite indices for all-cause mortality (sfMI) and hepatic decompensation (sfDI) generated by including steatosis parameters also had greater predictive power than the fMI, as well as qFibrosis-derived stage and NASH-CRN fibrosis score (Table 1). **Conclusion:** We show that microarchitectural features of injury and fibrosis quantified by stain-free SHG/2PE imaging can generate indices with greater predictive value for all-cause mortality and liver-related events than indices leveraging fibrosis parameters alone or ordinal fibrosis scores. These new indices may improve participant stratification and endpoint analysis in clinical trials. To establish a definitive link between microarchitectural features at baseline, their modification following drug treatment, and associated clinical outcomes, it is essential to incorporate validation within a prospective study.

	All-cause mortality (MI)			Hepatic decompensation (DI)		
	Hazard ratio (HR)	***p*-value**	**95% HR confidence intervals**	**Hazard ratio**	***p*-value**	**95% HR confidence intervals**
NASH-CRN fibrosis (F0/1/2 v F3/4)	3.41	0.003	1.428-8.15	3.65	<0.001	1.814-7.353
qFibrosis (qF0/1/2 v qF3/4)	3.07	0.007	1.295-7.257	3.59	<0.001	1.295-7.257
Fibrosis parameter-only indices fMI & fDI (low v high risk)	4.49	0.003	1.5-13.38	5.96	<0.001	2.924-12.14
Composite ballooning and fibrosis parameter indices bfMI & bfDI (low v high risk)	**7.84**	**<0.001**	**1.824-33.72**	**5.98**	**<0.001**	**2.944-12.14**
Composite steatosis and fibrosis parameter indices sfMI & sfDI (low v high risk)	**5.00**	**<0.001**	**1.681-14.88**	**5.87**	**<0.001**	**2.895-11.92**

Table 1. Hazard ratios and p-values for prediction of all-cause mortality and hepatic compensation using composite stain-free fibrosis, ballooning and steatosis parameter-derived indices compared with NASH-CRN fibrosis scores, qFibrosis scores, and stain-free fibrosis parameter-only indices.

Disclosures: Timothy Kendall: Nothing to Disclose, Dean Tai: Histoindex.com: Employee, Elaine Chng: Nothing to Disclose, Yayun Ren: HistoIndex Pte Ltd: Employee, Jonathan Fallowfield: Stimuliver: Advisor, Ipsen: Advisor, Kynos Therapeutics: Advisor, Resolution Therapeutics: Consultant, River 2 Renal Corp.: Advisor, Global Clinical Trial Partners: Advisor, Guidepoint: Consultant, GlaxoSmithKline: Grant/Research Support, Genentech: Grant/Research Support, Intercept Pharmaceuticals: Grant/Research Support

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2081 | USEFULNESS OF SERUM MICRORNAS AS BIOMARKERS FOR PEDIATRIC METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD)

Caroline Blakley[1] Benjamin Nelson[2] Shatha Qarooni[3] Wai Han Lee[3] Jeanie Tryggestad[3] Kevin Short[3] Sirish Kumar Palle[3]

[1]University of Oklahoma Health and Science Center, [2]Harold Hamm Diabetes Center (HHDC), [3]Department of Pediatrics, University of Oklahoma Health Sciences Center (OUHSC)

Background: Circulating microRNAs (miRNAs) may serve as biomarkers and provide insights about pathways that are affected by metabolic dysfunction-associated steatotic liver disease (MASLD). Our preliminary data demonstrated that serum miR-122 is increased in pediatric patients with MASLD. The goal of the current analysis was to perform comprehensive profiling of serum miRNAs in adolescents with MASLD compared to normal weight and obese peers. **Methods:** We compared three groups, ages 12-20 years: 1) obese with biopsy-confirmed MASLD (MASLD), 2) obese without MASLD (Ob), and 3) normal weight without MASLD (NW). Each group was comprised of 7 males and 5 females. All MASLD patients exhibited moderate to severe liver steatosis, with 80% displaying stage 1 or higher liver fibrosis. The NanoString nCounter Human v3 Panel was used to measure the abundance of ~800 miRNAs in each sample. Data were normalized for the number of reads across all samples. The data were fit to a linear model, and a moderated t-statistic was used to determine differences between groups. **Results:** We confirmed that miR-122-5p was higher in the MASLD group compared to the NW and Ob groups. No other miRNAs were significantly elevated in the MASLD group. Five miRNAs (miR-128-1-5p, miR-548j-5p, miR-548n, miR-1279, miR-340-5p) were lower in the MASLD group compared to NW. Additionally, miR-122-5p was positively correlated with body fat (r=0.42) and ALT (r=0.41), while the other miRNAs were negatively correlated with body fat (r=-0.34 to -0.49), ALT (r=-0.33 to -0.66), and NEFA (r=-0.36 to -0.47). **Conclusion:** These differential miRNA expressions suggest potential biomarker candidates for distinguishing MASLD from both normal weight and obese phenotypes, underscoring the significance of further research into their diagnostic and therapeutic implications. Our findings on miR-122, which is predominately produced in the liver, agree with studies of animal models and adults with MASLD. Larger, more diverse studies encompassing heterogeneous MASLD phenotypes are warranted to assess miRNAs as potential biomarkers of pediatric MASLD.

Disclosures: Caroline Blakley: Nothing to Disclose, Benjamin Nelson: Nothing to Disclose, Shatha Qarooni: Nothing to Disclose, Wai Han Lee: Nothing to Disclose, Jeanie Tryggestad: Abbot: Received sensor for investigator initiated study, Ascendis: PI for growth hormone study, no personal financial, Kevin Short: Nothing to Disclose, Sirish Kumar Palle: Nothing to Disclose

2082 | MACHINE LEARNING BASED PREDICTIVE MODELING USING PROTEOMIC SIGNATURES IN EXTRACELLULAR VESICLES AS DIAGNOSTIC INDICATORS OF METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS

Aleksandra Leszczynska[1] Benedikt Kaufmann[2] Christian Stoess[2] Hana Sung[2] Yeon-Kyung Choi[2] Andrea Kim[2] Agustina Reca[2] Trevor Crafts[3] Bruce Wolfe[3] Akiko Eguchi[4] Ariel Feldstein[2]

[1]University of California San Diego, [2]University of California, San Diego, [3]Oregon Health and Science University, Portland, [4]Mie University

Background: Blood based proteomics provides an unbiased approach for discovering novel biomarkers to monitor liver disease in Metabolic Dysfunction-Associated Steatohepatitis (MASH). Using an aptamer-based technology, we profiled the proteome from circulating extracellular vesicles (EVs) in serum from MASH patients, examining proteome features comprising all annotated proteins. By employing deep learning tools, we trained a neural network model on the selected markers to predict disease presence. **Methods:** EVs from the serum of healthy (n = 4) and MASH (n =33; fibrosis stage: F0=7, F1=7, F2=6, F3=12) subjects, EVs supernatants from normal primary human hepatocytes (PHH), and human liver organoids (HLO) cultured in normal, or MASH media underwent proteomic analysis by SOMAscan. From differentially expressed groups we uncovered EV protein - based signatures that served as an input disease biomarker for machine learning model. We designed the neural network architecture where we leveraged KERAS integrated with TensorFlow libraries to facilitate model development. Additional characterization of EVs for CXCL7 and HP was performed via nanoFCM and ONI (high resolution microscopy). **Results:** We identified proteins that were significantly altered in response to the distinct cellular environments of MASH. Hepatocytes - specific markers ASGPR, haptoglobin (HP), and C-X-C motif ligand 7 (CXCL7) expressing EVs were significantly increased in MASH groups compared to their respective healthy

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controls as assessed by nanoFCM. High resolution microscopy showed colocalization of ASGPR1 and CXCL7 in EVs from PHH, HLO and circulating EVs. We uncovered EV protein-based signatures that could represent diagnostic indicators of MASH. We based this on the distinctive protein MASH signatures from PHH, HLO, and circulating EVs. We implemented a neural network model for binary classification to predict whether new samples belong to the Healthy Class or MASH category. Further assessment of the model's performance involved evaluating its predictions against known outcomes in the Bariatric Surgery (BS) MASH cohort. The overall accuracy of this model was 97% in predicting test cases as revealed by confusion matrix. **Conclusion:** This comprehensive analysis provides evidence for utilizing distinctive protein based EVs signatures and underscores the potential clinical utility of leveraging EV-associated protein profiles in the accurate identification and diagnosis of MASH patients.

Disclosures: Aleksandra Leszczynska: Nothing to Disclose, Benedikt Kaufmann: Nothing to Disclose, Christian Stoess: Nothing to Disclose, Hana Sung: Nothing to Disclose, Yeon-Kyung Choi: Nothing to Disclose, Andrea Kim: Nothing to Disclose, Agustina Reca: Nothing to Disclose, Trevor Crafts: Nothing to Disclose, Bruce Wolfe: Nothing to Disclose, Akiko Eguchi: Nothing to Disclose, Ariel Feldstein: Nothing to Disclose

2083 | DEVELOPMENT OF A MACHINE LEARNING MODEL TO PREDICT PROGRESSION OF FIBROSIS IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE

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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) affects about 30% of the global population, with its prevalence rising. A small yet significant portion of these patients experience fibrosis progression, which is linked to liver decompensation and higher mortality. Recent studies have utilized advances in machine learning in predicting and managing various diseases. This study aims to identify factors associated with fibrosis progression in MASLD patients and develop a predictive machine learning model to predict who will have worsening fibrosis. **Methods:** This study was conducted at a large academic health center with a robust liver transplant program. We identified 500 adult patients who underwent at least two fibrosis evaluations (via fibroscan, magnetic resonance liver elastography, or liver biopsy) at least 1 year apart from January 2015 to October 2023. Among these, 108 patients had MASLD. We collected demographic data, fibrosis stage, MELD-Na scores, and lab **Results:** (complete blood count, basic metabolic panel, liver function panel, hemoglobin A1c, cholesterol panel, and coagulation panel) at both evaluation points. Logistic regression was done to identify variables of importance that predicted worsening fibrosis over time. Then, a random forest algorithm was used based on these variables to develop a machine learning model that would identify fibrosis progression. **Results:** The study included 108 MASLD patients (41% Non-Hispanic White, 38% male, mean age 56.3 ± 13.3 years). The average baseline MELD-Na score was 7.39, mean BMI was 30.3, and the average interval between evaluations was 749 days. Diabetes was present in 23.1% of patients, and 18.5% had advanced fibrosis at baseline. 26.9% of patients experienced fibrosis progression. Factors positively associated with fibrosis progression included a diagnosis of diabetes and increasing levels of AST, hemoglobin A1c, and triglycerides. Conversely, higher sodium and HDL levels were negatively associated with progression. The random forest classifier demonstrated a sensitivity of 93.8%, specificity of 100%, and an accuracy of 99.1% in identifying fibrosis progression compared to manual chart review (Table 1). **Conclusion:** Using longitudinal patient data, we developed a highly sensitive and specific random forest classifier to identify MASLD patients at risk for fibrosis progression. The predictive variables align with known risk factors, suggesting the classifier's potential utility in clinical practice to target high-risk patients for closer monitoring and aggressive intervention.

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Table 1: Confusion Matrix Comparing Random Forest Classifier of MASLD patients with Fibrosis Progression versus Manual Chart Review

		Manual Chart Review	
Random Forest Classifier		Patients with Fibrosis Progression	No Fibrosis Progression
	Patients with Fibrosis Progression	15	0
	No Fibrosis Progression	1	92

Test Parameters MASLD Progression	
Sensitivity	93.8%
Specificity	100%
Positive Predictive Value	100%
Negative Predictive Value	98.9%
Accuracy	99.1%

Disclosures: Jamie Yang: Nothing to Disclose, Mitchell Kamrava: Nothing to Disclose, Kirstin Peters: Nothing to Disclose, Nicholas Valle: Nothing to Disclose, Tien Dong: Mallinckrodt: Speaking and Teaching, PurposeBio: Consultant

2084 | DISPARITIES IN NON-INVASIVE TESTING-BASED RISK STRATIFICATION AMONG HISPANIC COMPARED TO NON-HISPANIC INDIVIDUALS AT-RISK FOR METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE: ANALYSIS OF A PROSPECTIVE COHORT OF 358 OVERWEIGHT AND OBESE INDIVIDUALS

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Background: Cut-points of non-invasive tests (NITs) for risk stratification in metabolic dysfunction-associated steatotic liver disease (MASLD) were derived from predominantly non-Hispanic populations. It is unknown if these cut-points perform well in Hispanic patients given differences in disease prevalence and severity. We assessed the performance of current risk stratification algorithms to identify significant fibrosis (F≥2) in Hispanic compared to non-Hispanic adults in a prospective cohort of adults with overweight and obesity. **Methods:** This prospective study enrolled overweight or obese adults aged 40-75 years recruited from the greater San Diego area from primary care clinics and community outreach. Participants underwent a standardized clinical research visit with magnetic resonance imaging proton-density-fat-fraction (MRI-PDFF), magnetic resonance elastography (MRE) and vibration controlled transient elastography (VCTE). Participants with alcohol intake exceeding American Association for the Study of Liver Diseases guidance for MASLD were excluded. Fibrosis was assessed via MRE, the most accurate non-invasive biomarker of fibrosis. Outcomes were the performance of current MASLD clinical pathways to detect significant fibrosis using MRE ≥ 3.14 kPa based on recently published cut-points from individual patient data meta-analysis. **Results:** 358 patients (43% male, 40% Hispanic) were included. The mean (±SD) age was 51.6 (13.4) years, and 28% had diabetes. Hispanic patients had higher body mass index (33.4 vs 31.1 kg/m2, p=0.001), and were more often female (63.6% vs 51.9%, p=0.03). The prevalence of MASLD was 73% and 71%, and significant fibrosis was 9.1% vs 7.4% among Hispanic vs non-Hispanic patients respectively. Current care pathways yielded high false negative rates among Hispanic patients (4% with low-risk FIB-4 and 10.5% with low-risk VCTE had significant fibrosis via MRE) compared to non-Hispanic patients (3% with low-risk FIB-4 and 0% with low-risk VCTE had significant fibrosis via MRE) (Figure). The area under the receiver operating curve of VCTE to detect significant fibrosis at a cut-point of ≥8 was 0.76 in Hispanic vs 0.83 in non-Hispanic patients with sensitivity of 69% vs 81%, respectively. In Hispanic individuals, the VCTE cut-point to detect significant fibrosis with 90% sensitivity was 5.3-5.5 kPa. **Conclusion:** In a well-phenotyped, prospective cohort of adults with overweight and obesity, current risk stratification algorithms had inferior performance among Hispanic compared to non-Hispanic individuals to identify significant fibrosis. To reduce false-negatives, lower cut-points for VCTE may be needed for Hispanic individuals with MASLD.

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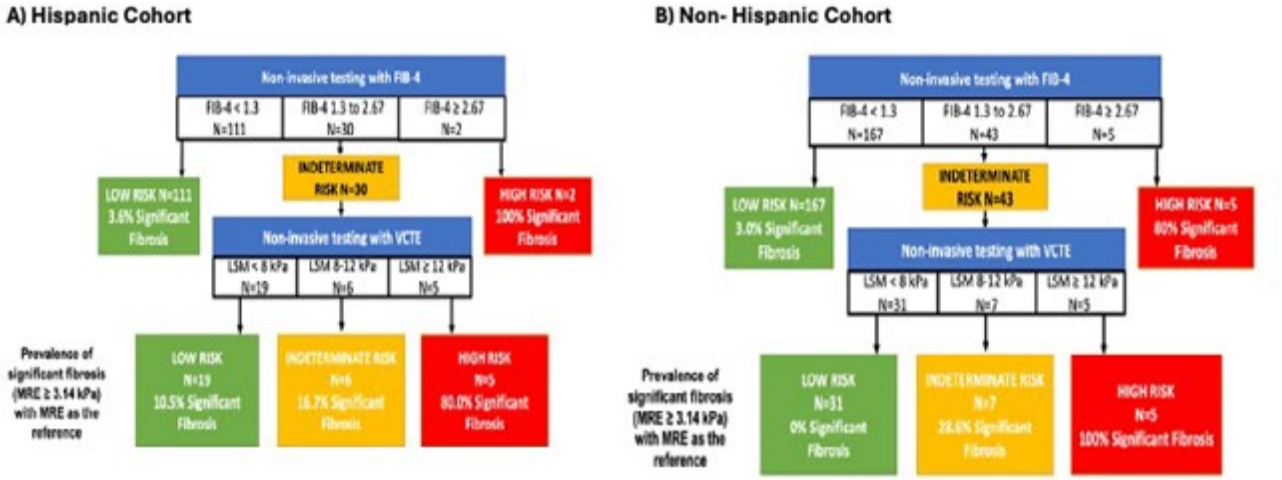

Disclosures: Monica Tincopa: Nothing to Disclose, Veeral Ajmera: Nothing to Disclose, Federica Tavaglione: Nothing to Disclose, Ricki Bettencourt: Nothing to Disclose, Lisa Richards: Nothing to Disclose, Rohit Loomba: Eli Lilly and Company: Consultant, 89bio: Consultant, Aardvark Therapeutics: Consultant, Altimmune: Consultant, Alnylam/Regeneron: Consultant, Amgen: Consultant, Arrowhead Pharmaceuticals: Consultant, AstraZeneca: Consultant, Bristol Myers Squibb: Consultant, CohBar: Consultant, Eli Lilly: Consultant, Galmed Pharmaceuticals: Consultant, Gilead: Consultant, Glympse Bio: Consultant, Hightide: Consultant, Inipharma: Consultant, Intercept: Consultant, Inventiva: Consultant, Ionis: Consultant, Janssen, Inc.: Consultant, Madrigal Pharmaceuticals: Consultant, Merck, Metacrine, Inc.: Consultant, NGM Biopharmaceuticals: Consultant, Novartis: Consultant, Novo Nordisk: Consultant, Pfizer: Consultant, Sagimet Biosciences: Consultant, Terns Pharmaceuticals: Consultant, Theratechnologies and Viking Therapeutics: Consultant, 89bio: Stock options, Sagimet Biosciences: Stock options, Arrowhead Pharmaceuticals: Research grant, AstraZeneca: Research grant, Boehringer Ingelheim: Research grant, Bristol Myers Squibb: Research grant, Eli Lilly: Research grant, Galectin Therapeutics: Research grant, Galmed Pharmaceuticals: Research grant, Gilead: Research grant, Hanmi: Research grant, Intercept: Research grant, Inventiva: Research grant, Ionis: Research grant, Janssen, Inc.: Research grant, Madrigal Pharmaceuticals: Research grant, Merck: Research grant, NGM Biopharmaceuticals: Research grant, Novo Nordisk: Research grant, Pfizer: Research grant, Sonic Incytes: Research grant, Terns Pharmaceuticals: Research grant, LipoNexus, Inc.: Co-founder

2085 | EXPLAINABLE ARTIFICIAL INTELLIGENCE ON PROTEOMICS FOR THE DIAGNOSIS OF ADVANCED LIVER FIBROSIS ON MASLD PATIENTS USING OPEN DATA

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Background: Steatotic liver disease, affecting 20-30% of the global population, is considered an epidemic. Recently, the FDA approved the first drug for advanced liver fibrosis (ALF) stages (F2, F3, F4), highlighting the need for non-invasive diagnostic alternatives to biopsy due to its variability and technical challenges. This study focuses on utilizing proteomics and artificial intelligence to impact ALF diagnosis in MASLD patients efficiently. We aimed to develop a machine learning (ML) model to predict advanced fibrosis stages (F2, F3, F4) versus early stages (F0, F1) using a minimal set of proteins, including uncommon ones, to advance research in this area.
Methods: In our study we included biopsy validated MASLD patients derived from the European NAFLD registry, as open data, comprised 191 plasma samples from 191 individuals. Samples were processed for proteomics using the SomaScan v.4.0 platform, measuring 4,730 unique proteins. The dataset has been split randomly in 90/10% on training-validation and test datasets. We tuned CatBoost ML models during a state of the art (SOTA) non-linear feature selection methodology (FS) that has been successfully applied in the biomedical field. For the

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training/validation we used 10-fold cross validation (10CV) in order to understand our models and to make them as robust as possible. In addition, feature engineering techniques (FE) has been applied. For the performance of our models we used the specificity (Spec), sensitivity (Sens), receiver operating characteristic of the area under the curve (ROC-AUC) and F1-score (F1). **Results:** The FS resulted in the following five proteins: ADAMTSL2, FCAR, MMP16, MFAP4, and GDF2. The ADAMTSL2 is strongly associated with ALF via interacting with ECM proteins, while FCAR constitutes a receptor for IgA, which promotes fibrosis. Additionally, MMP16 has a major role in tissue remodeling and wound healing under inflammation or/and fibrosis in liver parenchyma, while MFAP4 is also associated with fibrogenesis. Meanwhile, GDF2 transcription factor is highly expressed in hepatic tissue and closely implicated in hepatic lipid homeostasis through regulating PPARα and angiogenesis. Using these proteins and FE the final CatBoost model achieved on the 10CV and on the test set the following scores: (Spec, Sens, ROC-AUC, F1), 10CV(0.8408, 0.8420, 0.841, 0.8125), Test(1.000, 1.000, 1.000, 1.000). **Conclusion:** Using data science, SOTA FS non-linear methodology, CatBoost, FE and open data we identified five proteins that their role on MASLD ALF patients should be further examined. In addition, using these proteins we created a ML model and a potential diagnostic test that exceeds the threshold ROC-AUC: 0.80 of LITMUS project, for the identification of diagnostic tests for ALF. Our results should be further validated on different datasets though.

Disclosures: Eleni Myrto Trifylli: Nothing to Disclose, Anastasios Kriebardis: Nothing to Disclose, Nikolaos Papadopoulos: Nothing to Disclose, Melanie Deutsch: Gilead: Speaking and Teaching, Roche: Speaking and Teaching, Athanasios Angelakis: Nothing to Disclose

2086 | AN EFFECTIVE, INEXPENSIVE, AND SIMPLE ALTERNATIVE TO CURRENT AGA GUIDELINES FOR RISK-STRATIFYING LIVER FIBROSIS: MASHFIB-10 MACHINE LEARNING MODEL

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Background: AGA guidelines recommend using FIB-4 followed by transient elastography (FibroScan®) to assess patients suspected of MASLD. We evaluate a new machine learning (ML) model, MASHFIB-10, in risk-stratifying liver fibrosis in MASLD patients. **Methods:** MASHFIB-10, a new random forests model, uses only 10 routine demographic/clinical features. Meanwhile, MASML (random forests) (Chang et al. Hepatology 2022), logistic regression, and artificial neural network use 17 variables. Risk of significant/advanced fibrosis (≥F2/≥F3) was predicted in 953 patients from several US centers with ≥1 risk factors (≥2 metabolic risk factors, diabetes, steatosis, high aminotransferases) with liver biopsy, FibroScan®, and lab testing within a 6-month period. Mean age was 56.55 years, mean BMI was 34.73 kg/m^2, median FIB-4 was 1.32, median kPA was 9.1 kPA, 58.55% of the patients were female, 54.77% had diabetes, and 58.66% had hypertension. 25.39% of patients had F0, 26.02% had F1, 15.53% had F2, 17.42% had F3, and 15.63% had F4. We split the cohort into 80% to train and 20% to test the ML models. We assessed the correctly classified (CC) measurement (true negative for rule-out cutoff + true positive for rule-in cutoff / total), percent of indeterminate-risk patients (Ind), sensitivity (Sn), specificity (Sp), accuracy (Ac), positive predictive value (PPV), and negative predictive value (NPV) to compare MASHFIB-10 to FIB-4 only, FibroScan only, and sequential testing with FIB-4 followed by FibroScan (FIB-Fibro). **Results:** For most metrics, MASHFIB-10 performed statistically significantly better/similar vs other ML models. For ≥F2, MASHFIB-10 and FIB-4 performed similarly in Sn and PPV. MASHFIB-10 had higher Sp, Ac, AUC, and NPV vs FIB-4. MASHFIB-10 and FibroScan performed similarly in PPV. MASHFIB-10 had higher Sp, Ac, AUC, and NPV vs FibroScan. For ≥F3, MASHFIB-10 and FIB-4 performed similarly in PPV. MASHFIB-10 had higher Sn, Ac, AUC, and NPV compared to FIB-4. MASHFIB-10 and FibroScan performed similarly in Sn, Sp, Ac, PPV, and NPV. MASHFIB-10 had higher AUC than FibroScan. There was no statistically significant difference in CC or Ind between MASHFIB-10 and FIB-Fibro. Other ML models are shown in the figure. **Conclusion:** MASHFIB-10 may serve as an inexpensive, simple, but effective alternative to sequential FIB-Fibro, which is complex and requires costly imaging technology. MASHFIB-10 is more accessible and can be used in primary care settings, unlike FIB-Fibro.

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F2	Sn	Sp	Ac	AUC	PPV	NPV
MASHFIB-10	0.7 [0.66, 0.74]	0.86 [0.84, 0.88]	0.81 [0.79, 0.82]	0.86 [0.84, 0.88]	0.7 [0.66, 0.74]	0.86 [0.83, 0.88]
MASML	0.75 [0.73, 0.77]	0.77 [0.75, 0.79]	0.76 [0.74, 0.78]	0.84 [0.83, 0.86]	0.76 [0.73, 0.78]	0.77 [0.75, 0.79]
LR	0.74 [0.71, 0.77]	0.73 [0.71, 0.75]	0.74 [0.72, 0.75]	0.8 [0.78, 0.81]	0.72 [0.7, 0.74]	0.75 [0.73, 0.77]
ANN	0.73 [0.69, 0.76]	0.75 [0.71, 0.79]	0.74 [0.73, 0.75]	0.81 [0.79, 0.82]	0.73 [0.7, 0.76]	0.75 [0.73, 0.77]
FIB-4	0.73 [0.7, 0.76]	0.68 [0.64, 0.72]	0.7 [0.68, 0.73]	0.79 [0.77, 0.81]	0.68 [0.65, 0.71]	0.73 [0.71, 0.75]
FibroScan	0.81 [0.79, 0.83]	0.62 [0.6, 0.64]	0.71 [0.69, 0.72]	0.79 [0.78, 0.8]	0.66 [0.64, 0.68]	0.77 [0.75, 0.8]
F3	**Sn**	**Sp**	**Ac**	**AUC**	**PPV**	**NPV**
MASHFIB-10	0.73 [0.68, 0.78]	0.85 [0.83, 0.86]	0.81 [0.78, 0.83]	0.87 [0.85, 0.89]	0.7 [0.67, 0.74]	0.86 [0.84, 0.88]
MASML	0.7 [0.65, 0.75]	0.85 [0.83, 0.86]	0.8 [0.78, 0.82]	0.86 [0.85, 0.88]	0.69 [0.66, 0.71]	0.85 [0.83, 0.88]
LR	0.75 [0.73, 0.78]	0.75 [0.73, 0.78]	0.75 [0.74, 0.77]	0.82 [0.8, 0.84]	0.6 [0.57, 0.63]	0.86 [0.85, 0.87]
ANN	0.62 [0.54, 0.7]	0.8 [0.78, 0.83]	0.75 [0.71, 0.78]	0.81 [0.77, 0.84]	0.61 [0.57, 0.64]	0.82 [0.77, 0.86]
FIB-4	0.3 [0.27, 0.32]	0.94 [0.93, 0.96]	0.73 [0.71, 0.75]	0.81 [0.79, 0.84]	0.72 [0.68, 0.76]	0.73 [0.71, 0.76]
FibroScan	0.68 [0.63, 0.73]	0.84 [0.83, 0.85]	0.79 [0.77, 0.8]	0.81 [0.79, 0.83]	0.67 [0.64, 0.7]	0.84 [0.82, 0.87]

	Correctly Classified (CC) Measurement (%)	Percentage of Indeterminate-Risk Patients (%)
MASHFIB-10	63.87 [62.39, 65.36]	15.18 [13.3, 17.07]
MASML	64.19 [61.59, 66.79]	9.63 [7.88, 11.39]
LR	63.14 [60.67, 65.61]	14.24 [12, 16.48]
ANN	57.38 [54.82, 59.94]	16.54 [12.09, 21]
FIB-Fibro	66.86 [64.26, 69.45]	11.73 [9.92, 13.54]

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2087 | AGILE 3+ AND AGILE 4 SCORES PREDICT CARDIOVASCULAR EVENTS IN A LARGE GENERAL POPULATION COHORT

Madeleine Chang[1] *Mazen Noureddin*[2]

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Background: A recent study in JAMA (PMID: 38512249) found that AGILE 3+ and AGILE 4 demonstrated high accuracy in predicting liver-related events in MASLD patients (AGILE3+ was the best predictor). Since cardiovascular disease is the leading cause of mortality in patients with MASLD, we aimed to assess the performance of AGILE 3+, AGILE 4, and FibroScan® LSM in identifying cardiovascular events (CVE). **Methods:** Using the 2017-2020 NHANES dataset, we followed the AASLD MASLD Decision Tree to select subjects ≥18 years who drank <210 (men)/140 (women) grams of alcohol per week, had hepatic steatosis defined as FibroScan® CAP score ≥274 dB/m, and met 1 of 5 cardiometabolic criteria. The final cohort consisted of 2863 subjects, who were stratified as high risk and not-at-risk for advanced liver fibrosis/cirrhosis based on AGILE 3+, AGILE 4, and FibroScan® LSM using the cutoffs of ≥0.679, ≥0.565, and >12, respectively. CVE were defined as congestive heart failure, coronary heart disease, angina, myocardial infarction, and/or stroke. **Results:** Out of 2863 subjects (53.4% males and 46.6% females with a mean age of 52.52), 434 were deemed high risk for advanced fibrosis by AGILE 3+ while 2429 were not-at-risk. Among those at high risk for advanced fibrosis, 27.19% (n=118) had CVE, compared to only 10.00% (n=243) of those not-at-risk (p<0.05). Based on AGILE 4, 44 subjects were deemed at high risk of cirrhosis and 2819 were not-at-risk. 25% (n=11) of the high risk subjects had CVE, compared to 12.41% (n=350) of those not-at-risk (p<0.05).Using FibroScan® LSM, 202 subjects were classified as high risk for advanced fibrosis and 2661 were not-at-risk. 21.78% (n=44) of the high risk subjects had CVE, while 11.91% (n=317) of the not-at-risk subjects had CVE (p<0.05). CVE in patients deemed high risk by AGILE 3+, AGILE 4, and LSM showed OR of 3.357 (2.591-4.338)), 2.350 (1.062-4.821), and 2.059 (1.410-2.957), respectively, compared to patients not-at-risk. AGILE 3+ identified significantly more CVE in MASLD subjects compared to FibroScan® LSM (p<0.05). **Conclusion:** MASLD subjects deemed high risk for advanced fibrosis/cirrhosis by AGILE 3+, AGILE 4, and FibroScan® LSM had 2-3 times increased odds of developing CVE than subjects deemed not-at-risk. AGILE 3+ outperformed AGILE 4 and FibroScan® LSM in identifying cardiovascular risks in MASLD subjects.

Prevalence of Cardiovascular Events in High Risk MASLD Patients

	AGILE 3+ ≥0.679	**AGILE 3+ <0.679**	**P-Value**	**Odds Ratio**
Patients with CVE	118/434: 27.19%	243/2429: 10.00%	<0.00001	3.357 (2.591-4.338)
	AGILE 4 ≥0.565	**AGILE 4 <0.565**	**P-Value**	**Odds Ratio**
Patients with CVE	11/44: 25%	350/2819: 12.41%	.01242	2.350 (1.062-4.821)
	LSM >12	**LSM ≤12**	**P-Value**	**Odds Ratio**
Patients with CVE	44/202: 21.78%	317/2661: 11.91%	<0.00001	2.059 (1.410-2.957)

Disclosures: Madeleine Chang: Nothing to Disclose, Mazen Noureddin: Principal Investigator for a Drug Study relationship with Viking; Has not ended; Consultant relationship with Eli Lilly; Has not ended; Consultant relationship with AstraZeneca; Has not ended; Consultant relationship with Boston Pharmaceuticals; Has not ended; Principal Investigator for a Drug Study relationship with Genfit; Has not ended; Principal Investigator

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for a Drug Study relationship with Galectin; Has not ended; Principal Investigator for a Drug Study relationship with Gilead; Has not ended; Principal Investigator for a Drug Study relationship with BMS; Has not ended; Principal Investigator for a Drug Study relationship with BI; Has not ended; Principal Investigator for a Drug Study relationship with Akero; Has not ended; Consultant relationship with Cytodyn; Has not ended; Consultant relationship with GSK; Has not ended; Consultant relationship with BI; Has not ended; Consultant relationship with Madrigal; Has not ended; Terns,Takeda, Zydus. relationship with Itimmune, BI, Cytodyn, 89BIO, GSK, Madrigal, Merck, Novo Nor; Has not ended; Principal Investigator for a Drug Study relationship with Allergan; Has not ended; Consultant relationship with Takeda; Has not ended; Consultant relationship with Terns; Has not ended; Terns, Corcept, Takeda, Madrigal, Novartis, Novo Nordisk, relationship with Allergan, Akero, BI, BMS, Gilead, Galectin, Zydus GSK; Has not ended; Consultant relationship with Novo Nordisk; Has not ended; Stock â€“ privately held company relationship with Rivus Pharma, Cytodyn, and ChronWell; Has not ended; Consultant relationship with Merck; Has not ended; Principal Investigator for a Drug Study relationship with Madrigal; Has not ended; Consultant relationship with Altimmune; Has not ended; Principal Investigator for a Drug Study relationship with Terns; Has not ended; Principal Investigator for a Drug Study relationship with Zydus; Has not ended; Stock â€“ privately held company relationship with Rivus Pharmaceuticals; Has not ended; Consultant relationship with Alligos; Has not ended; Stock - publicly traded company relationship with Cytodyn; Has not ended; Stock â€“ privately held company relationship with ChronWell; Has not ended; Speaking and Teaching relationship with Madrigal; Has not ended; Principal Investigator for a Drug Study relationship with Takeda; Has not ended; Principal Investigator for a Drug Study relationship with Shire; Has not ended; Principal Investigator for a Drug Study relationship with Novo Nordisk; Has not ended; Principal Investigator for a Drug Study relationship with Novartis; Has not ended; Principal Investigator for a Drug Study relationship with Enanta; Has not ended; Principal Investigator for a Drug Study relationship with Corcept; Has not ended; Principal Investigator for a Drug Study relationship with GSK; Has not ended; Principal Investigator for a Drug Study relationship with Conatus; Has not ended,

2088 | PREVALENCE OF CARDIOVASCULAR EVENTS IN MASLD, METALD, AND ALD PATIENTS IN A LARGE GENERAL POPULATION COHORT

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Background: In 2023, NAFLD was replaced with the term MASLD. Along with this change in nomenclature, the term MetALD was coined to describe those who consume greater amounts of alcohol than MASLD patients but less than ALD patients. This has created 3 major SLD classifications: MASLD, MetALD, and ALD. Since SLD is associated with increased risks for cardiovascular events (CVE), we aimed to determine the prevalence of CVE in each population under the new nomenclature. **Methods:** Using the 2017-2020 NHANES dataset, we followed the AASLD MASLD Decision Tree to select subjects ≥18 years who had hepatic steatosis defined as FibroScan® CAP score ≥274 dB/m and met 1 of 5 cardiometabolic criterias. The final cohort consisted of 3276 subjects, who were stratified into MASLD, MetALD, and ALD based on <210 (men)/140 (women) grams of alcohol per week, between 210-420 (men)/140-350 (women) grams per week, and >420 (men)/>350 (women) grams per week, respectively. CVE were defined as congestive heart failure, coronary heart disease, angina, myocardial infarction, and/or stroke. Type 2 diabetes (T2D) was defined as subjects who answered yes to the questionnaire or had HbA1c≥5.7%. **Results:** Out of 3056 subjects with MASLD, 12.76% (n=390) had CVE. Subjects with MASLD developed more CVE compared to those with MetALD (10.13%, 16/158), ALD (8.06%, 5/62), and those without hepatic steatosis (8.64%, 371/4293). However, only the difference between subjects with MASLD and those without hepatic steatosis was statistically significant ($p<0.05$). The odds of CVE is 1.546 times higher in subjects with MASLD compared to those without hepatic steatosis (OR: 1.546 (1.327-1.803)). Among non-T2D subjects, 6.52% (81/1242) of the MASLD patients had CVE, compared to 2.97% (3/101) in MetALD, 4.88% (2/41) in ALD, and 5.42% (161/2970) in subjects without hepatic steatosis. Among T2D subjects, 22.81% (13/57) of MetALD subjects had CVE, compared to 17.03% (309/1814) in MASLD subjects, 14.29% (3/21) of ALD patients, and 15.87% (210/1323) of subjects without hepatic steatosis had CVE. However, these differences were not statistically significant ($p>0.05$). **Conclusion:** Trends suggest that MASLD patients are at the highest risk for CVE. Among non-T2D subjects, MASLD subjects were also at the highest risk for CVE. Interestingly, among T2D subjects, MetALD subjects had the highest prevalence of CVE, suggesting that the interplay between T2D and increased alcohol intake could increase the risk of CVE.

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Prevalence of Cardiovascular Events in MASLD, MetALD, and ALD Patients

	Non-Hepatic Steatosis	MASLD	P-Value	OR	MetALD	P-Value	OR	ALD	P-Value	OR
Patients with CVE	371/4293: 8.64%	390/3056: 12.76%	< .0001	1.546 (1.327-1.803)	16/158: 10.13%	.5157	1.191 (0.656-2.029)	5/62: 8.06%	.87288	0.927 (0.288-2.314)
Non T2D Patients with CVE	161/2970: 5.42%	81/1242: 6.52%	.16152	1.217 (0.912-1.614)	3/101: 2.97%	.28014	0.534 (0.107-1.637)	2/41: 4.88%	.88076	0.895 (0.103-3.51)
T2D Patients with CVE	210/1323: 15.87%	309/1814: 17.03%	.38978	1.09 (0.895-1.325)	13/57: 22.81%	.16452	1.565 (0.759-3.022)	3/21: 14.29%	.84148	0.883 (0.165-3.065)

Disclosures: Madeleine Chang: Nothing to Disclose, Mazen Noureddin: Principal Investigator for a Drug Study relationship with Viking; Has not ended; Consultant relationship with Eli Lilly; Has not ended; Consultant relationship with AstraZeneca; Has not ended; Consultant relationship with Boston Pharmaceuticals; Has not ended; Principal Investigator for a Drug Study relationship with Genfit; Has not ended; Principal Investigator for a Drug Study relationship with Galectin; Has not ended; Principal Investigator for a Drug Study relationship with Gilead; Has not ended; Principal Investigator for a Drug Study relationship with BMS; Has not ended; Principal Investigator for a Drug Study relationship with BI; Has not ended; Principal Investigator for a Drug Study relationship with Akero; Has not ended; Consultant relationship with Cytodyn; Has not ended; Consultant relationship with GSK; Has not ended; Consultant relationship with BI; Has not ended; Consultant relationship with Madrigal; Has not ended; Terns,Takeda, Zydus. relationship with Itimmune, BI, Cytodyn, 89BIO, GSK, Madrigal, Merck, Novo Nor; Has not ended; Principal Investigator for a Drug Study relationship with Allergan; Has not ended; Consultant relationship with Takeda; Has not ended; Consultant relationship with Terns; Has not ended; Terns, Corcept, Takeda, Madrigal, Novartis, Novo Nordisk, relationship with Allergan, Akero, BI, BMS, Gilead, Galectin, Zydus GSK; Has not ended; Consultant relationship with Novo Nordisk; Has not ended; Stock â€“ privately held company relationship with Rivus Pharma, Cytodyn, and ChronWell; Has not ended; Consultant relationship with Merck; Has not ended; Principal Investigator for a Drug Study relationship with Madrigal; Has not ended; Consultant relationship with Altimmune; Has not ended; Principal Investigator for a Drug Study relationship with Terns; Has not ended; Principal Investigator for a Drug Study relationship with Zydus; Has not ended; Stock â€“ privately held company relationship with Rivus Pharmaceuticals; Has not ended; Consultant relationship with Alligos; Has not ended; Stock - publicly traded company relationship with Cytodyn; Has not ended; Stock â€“ privately held company relationship with ChronWell; Has not ended; Speaking and Teaching relationship with Madrigal; Has not ended; Principal Investigator for a Drug Study relationship with Takeda; Has not ended; Principal Investigator for a Drug Study relationship with Shire; Has not ended; Principal Investigator for a Drug Study relationship with Novo Nordisk; Has not ended; Principal Investigator for a Drug Study relationship with Novartis; Has not ended; Principal Investigator for a Drug Study relationship with Enanta; Has not ended; Principal Investigator for a Drug Study relationship with Corcept; Has not ended; Principal Investigator for a Drug Study relationship with GSK; Has not ended; Principal Investigator for a Drug Study relationship with Conatus; Has not ended,

2089 | NONINVASIVE ASSESSMENT OF STEATOTIC LIVER DISEASE IN INDIVIDUALS WITH CLASS 2 AND CLASS 3 OBESITY

Michael Thornton[1] Jang Hwan Cho[1] Idan Steinberg[1] Jing Gao[2] Colby Adamson[2]

[1]ENDRA Life Sciences Inc, [2]Rocky Vista University

Background: The current standard of practice in the noninvasive assessment of steatotic liver disease at the point-of-care, is by quantitative Ultrasound (QUS). These QUS approaches have limited depth of penetration and often yield inaccurate results, or are unable to obtain measurements in severely obese individuals. In some extreme cases, Magnetic Resonance Imaging - Proton Density Fat Fraction (MRI-PDFF) may not be possible for the largest individuals due to the patient size limitation of MRI systems. The prevalence of class 2 obesity (BMI of

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35 - 39.9) and class 3 obesity (BMI equal to or greater than 40) is growing worldwide. In the United States, 15% of the population is currently classified as severely obese (class 2 or class 3 obesity). Severely obese individuals are at high risk for steatotic liver disease, and thus, there is a clear need to assess and monitor liver fat fraction in this at-risk population. Thermoacoustic (TA) approaches for quantifying liver fat fraction are well suited to large patients due to the intrinsic high tissue penetration of TA signals that are composed of low acoustic frequencies (up to 1 MHz). This work describes clinical results obtained from a sub-population of class 2 and class 3 obesity subjects as part of a larger study comparing thermoacoustic-derived liver fat fraction (TAdFF) assessment with MRI-PDFF. **Methods:** A triple modality study included ultrasound, TA measurements, and MRI-PDFF to measure the subjects' ground truth liver fat. Trained sonographers imaged 55 subjects with suspected steatotic liver disease (SLD). The cohort of individuals with severe obesity consisted of 7 individuals with class 2 obesity and 7 individuals with class 3 obesity, with a maximum BMI of 47 This study focuses on these difficult-to-image patients. B-mode ultrasound was used to determine the locations of the liver capsule and overlying tissue (muscle, fat, and skin), followed by a TA procedure consisting of 10 to 30 measurements consisting of 80 pulses of 1-microsecond Radio Frequency (RF) pulses, each containing 5.7 milliJoules of energy. The liver conductivity was estimated based on TA signals induced in the fat, muscle, and liver. Signals were normalized for energy distribution using a computer model based on the anatomical B-mode measurements. The median value of all valid TAEUS FLIP measurements was used for each study participant to avoid outlier values. Nonlinear regression compared TAdFF with MRI-PDFF. **Results:** Assessment of liver fat fraction by noninvasive thermoacoustics correlated strongly with MRI-PDFF measurements in this cohort of severely obese individuals, yielding an r-squared value of 0.79 (Pearson correlation coefficient > 0.89). For more than 78% of the patients, the TAdFF was within +-2.5% of the MRI-PDFF. **Conclusion:** TA technology can assess liver fat similarly to MRI-PDFF for obese individuals where QUS often fails.

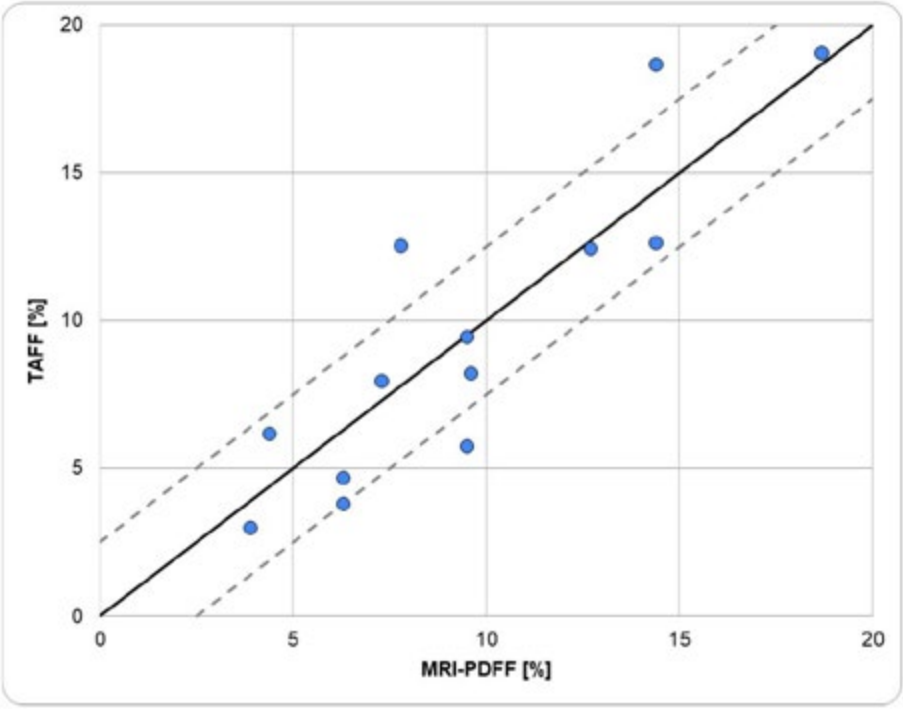

Figure 1: Thermoacoustic derived Fat Fraction (TAFF) vs MRI-PDFF for class 2 and class 3 obese patients

Disclosures: Michael Thornton: ENDRA Life Sciences Inc: Employee, Jang Hwan Cho: Endra Life Sciences, Inc.: Employee, Idan Steinberg: Nothing to Disclose, Jing Gao: Nothing to Disclose, Colby Adamson: Nothing to Disclose

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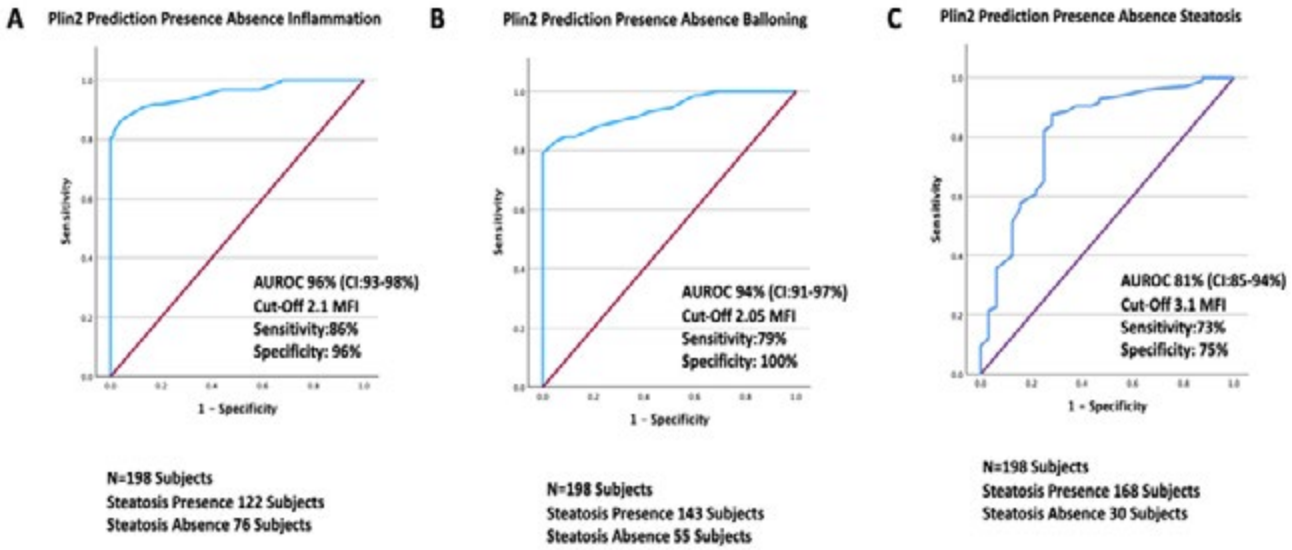
2090 | PLIN2 EXPRESSION IS A RELIABLE BIOMARKER OF MASH THAT IS SPECIFICALLY ASSOCIATED WITH INFLAMMATION AND BALLOONING RATHER THAN STEATOSIS

Giulia Angelini[1] Sara Russo[1] Erminia Lembo[1] Ornella Verrastro[1] Caterina Guidone[1] Aldo TRYLESINSKI[2] Antonio Liguori[1] Sven Francque[3] Arun Sanyal[4] William Alazawi[5] Luca Miele[1] Geltrude Mingrone[1]

[1]Università cattolica del sacro cuore, [2]Metadeq Diagnostic, [3]Antwerp University Hospital & University of Antwerp, [4]Virginia Commonwealth University, [5]Queen Mary University of London

Background: Metabolic dysfunction-associated steatohepatitis (MASH) is the most common liver disease worldwide. The large number of subjects with potential for progressive disease creates screening challenges because the precise diagnosis of MASH currently relies on a liver biopsy. Progress has been made in non-invasive diagnosis of steatosis and fibrosis, but remains challenging for the activity-component of the disease. Activity (reflected by ballooning and lobular inflammation on the liver biopsy) drives disease progression and hence its diagnosis and monitoring is key for patient management, including pharmacotherapy. Perilipin 2 (PLIN2) is a ubiquitously expressed protein that plays an important role in the pathophysiology of MASH and contributes to disease progression. The aim of this study was to evaluate the diagnostic performance of PLIN2 expression in circulating monocytes to detect the 3 individual cardinal components of MASH in a cohort of subjects with and without histologically-proven MASH using HeparDx™, a novel diagnostic test. **Methods:** Patients enrolled in this study (198 subjects) were participants from the BRAVES cohort (n=119 subjects with MASH) and LIBRA cohort (n=79 subjects without MASH). Area under the Receiver Operating Characteristic curve (AUROC) was used to assess the diagnostic performance of PLIN2 expression in circulating monocytes in predicting the presence of steatosis, inflammation or ballooning. Sensitivity and specificity were calculated using the Youden threshold. **Results:** For the prediction of presence/absence of lobular inflammation, PLIN2 produced an AUROC of 96% (CI: 93-98%) with a sensitivity and specificity of 86% and 96% respectively using a cut-off of 2.1 MFI (Figure1A). For ballooning the AUROC was 94% (CI: 91-97%) with a sensitivity and specificity of 79% and 100% respectively using a cut-off of 2.05 MFI (Figure1B). Conversely, for the prediction of presence/absence of steatosis PLIN2 analysis produced a sub-optimal AUROC of 81% (CI: 85-94%) with a sensitivity and specificity of 73% and 75% respectively using a cut-off of 3.1 MFI (Figure1C). **Conclusion:** PLIN2 expression in monocytes, detected by HeparDx™, can accurately detect inflammation and balloning with high sensitivity and specificity using a cut-off of 2.1 MFI. PLIN2 has hence the unique potential to non-invasively detect the steatohepatitis activity component of the disease help which could significantly improve the identification of patients eligible for MASH pharmacotherapy and/or surgical intervention.



Disclosures: Giulia Angelini: Nothing to Disclose, Sara Russo: Nothing to Disclose, Erminia Lembo: Nothing to Disclose, Ornella Verrastro: Nothing to Disclose, Caterina Guidone: Nothing to Disclose, Aldo TRYLESINSKI: Nothing to Disclose, Antonio Liguori: Nothing to Disclose, Sven Francque: Nothing to Disclose, Arun Sanyal:

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2091 | ARTIFICIAL INTELLIGENCE (AI) IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD): A DUAL APPROACH FOR INNOVATING GENOMIC ANALYSIS AND DEVELOPMENT OF RISK PREDICTION MODELS

Miriam Longo[1] Erika Paolini[2] Marica Meroni[2] Anna Alisi[3] Giorgio Soardo[4] Anna Ludovica Fracanzani[5] Paola Dongiovanni[6]

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Background: Artificial intelligence (AI) is transforming medicine, enabling big data mining even without high-tech resources. We explored generative AI tools (GPT-4) for MASLD, the commonest liver disorder worldwide, to assist in: 1) analyzing -omics data from a small dataset of human liver biopsies, who underwent mtDNA whole-genome sequencing (WGS cohort, n=39) to identify novel MASLD-related mutations; and 2) developing risk scores for disease monitoring using anthropometric (Age, BMI), genetic (*PNPLA3*, *TM6SF2*, *MBOAT7*) data and two new circulating mitochondrial biomarkers (*D-loop* and ccf-COXIII) in a larger dataset of biopsied MASLD patients (Hepatology service cohort, n=824). **Methods:** Customized GPT-4 models with coding capabilities were used for genomic data analysis (mGPT-4) and creating MASLD risk scores (rsGPT-4), furtherly validated using JMP Pro 17 (SAS, Cary, NC). **Results:** 1) In the WGS cohort, 520 mtDNA nonsynonymous variants were recorded. The H haplotype was the most common (36%), followed by T (23%), K, and J (7.6%). Patients belonging to phylocluster T exhibited a higher rate of steatosis, NAS≥5 (OR: 4.35, 95% CI: 2.11-9.5) and moderate/severe fibrosis (OR: 7.02, 95% CI: 2.11-9.5) compared to non-T subjects. mGPT-4 identified eight mtDNA variants shared across T haplotypes, five of which correlated with steatosis percentage. Of these, the m.4216A>G (*MT-ND1*) and m.10463T>C (*MT-TR*) showed the strongest association with MASLD severity, furtherly confirmed through unbiased analysis. 2) In the Hepatology service cohort, the rsGPT-4 optimized the combination of non-invasive variables to get robust prediction models named Mitochondrial, Anthropometric, and Genetic Integration with Computational intelligence ("MAGIC-") for assessing MASH, fibrosis, and HCC, respectively. The "MAGIC-"scores were built through the random forest analyses proposed by rsGPT-4, which captured non-linear relationships among variables. The MAGIC-MASH and MAGIC-Fib models showed AUCs of 73% and 76% in detecting MASH and fibrosis >1. Of note, MAGIC-HCC achieved an AUC of 86% (95% CI: 0.823-0.885), with 78.6% sensitivity and 81.5% specificity at a cut-off score around 30 (95% CI: 27.91-31.59) thus resulting the best model designed for the desired outcome. **Conclusion:** AI support allowed to facilitate the manipulation of -omics data and pioneered the proposal of risk scores offering high accuracy in HCC detection, with balanced sensitivity and specificity.

Disclosures: Miriam Longo: Nothing to Disclose, Erika Paolini: Nothing to Disclose, Marica Meroni: Nothing to Disclose, Anna Alisi: Nothing to Disclose, Giorgio Soardo: Nothing to Disclose, Anna Ludovica Fracanzani: Nothing to Disclose, Paola Dongiovanni: Nothing to Disclose

2092 | PLIN2 IS A SPECIFIC MARKER FOR MASH AND IS NOT A MARKER FOR CARDIOVASCULAR DISEASE OR DIABETES

Giulia Angelini Sara Russo[1] Aldo TRYLESINSKI[2] Federico Biscetti[1] Andrea Flex[1] Vlad Ratziu[3] Mazen Noureddin[4] Jörn Schattenberg[5] Amalia Gastaldelli[6] Luca Miele[1] Geltrude Mingrone[1]

[1]Università cattolica del sacro cuore, [2]Metadeq Diagnostic, [3]Service D' Hepatogastroenterologie (FR), [4]Houston Methodist Hospital, [5]Department of Medicine II, [6]CNR

Background: Metabolic dysfunction-associated steatohepatitis (MASH) represents the leading cause of liver disease worldwide. Patients with type 2 diabetes mellitus (T2DM) have a higher risk of developing MASH and represent >50% of the MASH patient population. Among those with MASH, coronary artery disease (CAD) is the

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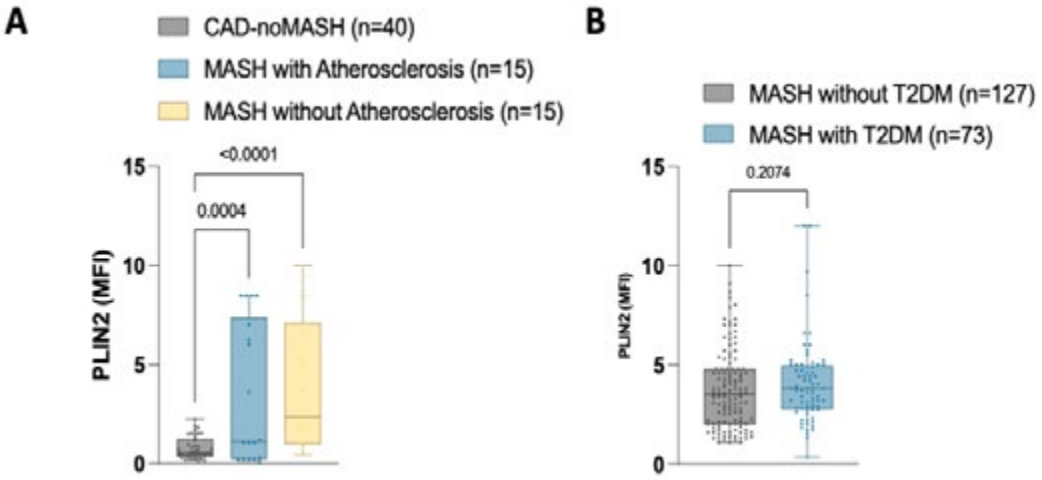
most common cause of mortality, and MASH can also be associated with the development of atherosclerosis and CAD. Circulating monocytes are involved in the pathophysiology of MASH, T2DM and atherosclerosis. Monocytes can accumulate large amounts of lipids, transform into foam cells and drive atherogenesis; accumulation of lipid-loaded monocytes is observed in MASH and T2DM. Perilipin 2 (PLIN2) is linked to lipid deposition in non-adipose tissues, and its increased expression is associated with various metabolic diseases (MASH, T2DM, and CAD). Several studies report high levels of PLIN2 in MASH and atherosclerosis. Here we compared the levels of PLIN2 in subjects with MASH with/without T2DM or atherosclerosis as well as in subjects with CAD-noMASH to assess whether PLIN2 is a specific biomarker for liver related disease. **Methods:** We measured circulating PLIN2 in 30 subjects with histologically proven MASH with measurement of carotid intima-media thickness (CIMT), a marker of subclinical atherosclerosis, along with 50 subjects with CAD-noMASH assessed by coronary angiography. Patients with documented CAD had normal liver AST and ALT. We also analyzed PLIN2 data from 200 subjects with histologically proven MASH with or without T2DM enrolled in the BRAVES RCT (NCT03524365).
Data were analyzed by Mann-Whitney U test and expressed as mean±SEM. **Results:** PLIN2 expression was significantly increased in MASH patients compared to those with CAD-noMASH (0.77±0.08 vs. 3.66±0.56 MFI; p<0.0001) (Figure 1A). Within the MASH group, there was no significant difference in PLIN2 expression between those with and without atherosclerosis confirmed by linear regression analysis that showed no correlation between PLIN2 and CIMT (Left CIMT R=0.04; P=0.14; CIMTsx R=0.0001; P=0.95). Moreover, there was no significant difference in PLIN2 expression between patients with MASH with or without T2DM (4.04±0.24 vs. 3.73±0.18 MFI; P=0.21) (Figure 1B). **Conclusion:** PLIN2 protein expression was significantly higher in subjects with MASH compared to those with CAD without MASH, but PLIN2 was not associated with early atherosclerosis or T2DM. In conclusion, PLIN2 is specific for liver disease, such as MASH, and not overexpressed in monocytes as a response to CAD or T2D.



Disclosures: Giulia Angelini: Nothing to Disclose, Sara Russo: Nothing to Disclose, Aldo TRYLESINSKI: Nothing to Disclose, Federico Biscetti: Nothing to Disclose, Andrea Flex: Nothing to Disclose, Vlad Ratziu: Nothing to Disclose, Mazen Noureddin: Principal Investigator for a Drug Study relationship with Viking; Has not ended; Consultant relationship with Eli Lilly; Has not ended; Consultant relationship with AstraZeneca; Has not ended; Consultant relationship with Boston Pharmaceuticals; Has not ended; Principal Investigator for a Drug Study relationship with Genfit; Has not ended; Principal Investigator for a Drug Study relationship with Galectin; Has not ended; Principal Investigator for a Drug Study relationship with Gilead; Has not ended; Principal Investigator for a Drug Study relationship with BMS; Has not ended; Principal Investigator for a Drug Study relationship with BI; Has not ended; Principal Investigator for a Drug Study relationship with Akero; Has not ended; Consultant relationship with Cytodyn; Has not ended; Consultant relationship with GSK; Has not ended; Consultant relationship with BI; Has not ended; Consultant relationship with Madrigal; Has not ended; Terns,Takeda, Zydus. relationship with Itimmune, BI, Cytodyn, 89BIO, GSK, Madrigal, Merck, Novo Nor; Has not ended; Principal Investigator for a Drug Study relationship with Allergan; Has not ended; Consultant relationship with Takeda; Has not ended; Consultant relationship with Terns; Has not ended; Terns, Corcept, Takeda, Madrigal, Novartis, Novo Nordisk, relationship with Allergan, Akero, BI, BMS, Gilead, Galectin, Zydus GSK; Has not ended; Consultant relationship with Novo Nordisk; Has not ended; Stock â€“ privately held company relationship with Rivus Pharma, Cytodyn, and ChronWell; Has not ended; Consultant relationship with Merck; Has not ended; Principal Investigator

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2093 | CLINICAL COMPARISON OF THE HEPARDX™ DIAGNOSTIC BLOOD TEST WITH MYLAB™ ELASTOGRAPHY OF SIGNIFICANT FIBROSIS IN PATIENTS WITH NON-CIRRHOTIC MASH

Giulia Angelini[1] Sara Russo[1] Aldo TRYLESINSKI[2] Jerome Boursier[3] Manuel Romero-Gómez[4] Quentin Anstee[5] Geltrude Mingrone[1]

[1]Università cattolica del sacro cuore, [2]Metadeq Diagnostic, [3]Angers University, [4]Virgen del Rocío University Hospital, [5]Newcastle University, UK

Background: Clinical trial enrollment for MASH drug trials usually requires participants with a NAS score ³4 and significant fibrosis (F2-F3). Patients with F2/3 MASH are at higher risk for disease progression and therefore candidates for pharmacological intervention. In 2024 resmetirom became the first drug approved by the U.S. FDA for treating patients with MASH and significant fibrosis. The FDA label does not require liver biopsy prior to treatment initiation; therefore, there is a need for non-invasive blood test that can identify at-risk MASH before treatment initiation and tests that may assist the monitoring of treatment response. Perilipin 2 (PLIN2) is associated with key features of MASH, specifically, liver inflammation and ballooning. Recently, a strong correlation was found between liver and monocyte expression of PLIN2 in subjects with MASH.
In this study, the aim was to compare the diagnostic performance of HeparDx™, a test based on the expression of PLIN2 in circulating monocytes, with liver elastography for detecting significant fibrosis in MASH patients.
Methods: The cohort consisted of 250 subjects enrolled in two clinical trials (BRAVES cohort, n=100; LIBRA cohort, n=150) with histologically proven non-cirrhotic MASH with or without significant fibrosis that also underwent two-dimensional shear wave elastography, performed with Esaote MyLab V.9 platform ultrasound system (Esaote, Genova, Italy). The Area Under the Receiver Operating Characteristic curve (AUROC) was used to assess the diagnostic performance of HeparDx™ and elastography in predicting significant fibrosis. Sensitivity and specificity were calculated using the Youden threshold. **Results:** Fibrosis stage 0 and 1 was present in 148 patients (59.2%), while 102 patients (40.8%) had significant fibrosis (stage 2 and 3). HeparDx™ analysis for the prediction of significant fibrosis produced an AUROC of 74% (CI: 68-80) with a sensitivity and specificity of 81%

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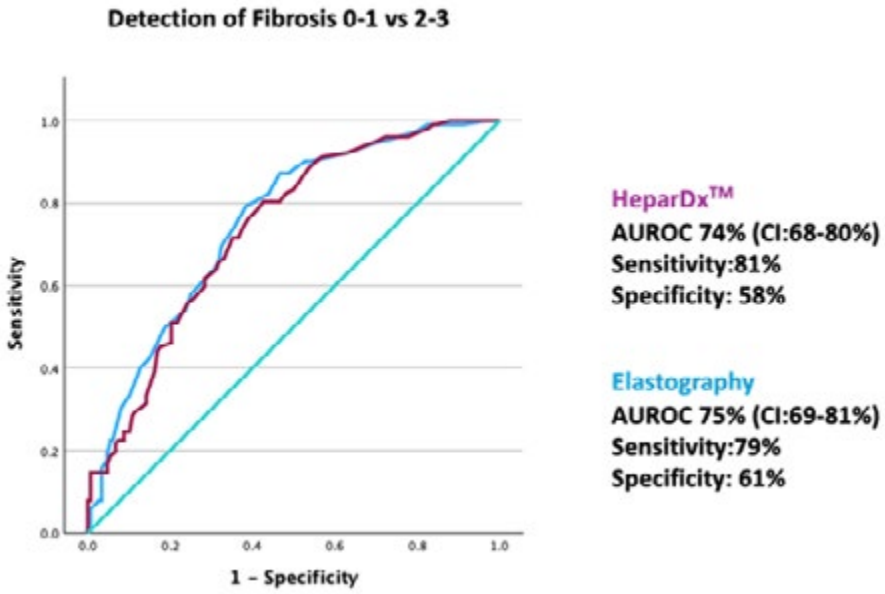
and 58%, respectively (Youden threshold:0.38) (Figure1). For elastography the AUROC was 75% (CI: 69-81%) with a sensitivity and specificity of 79% and 61%, respectively (Youden threshold:0.41). No significant difference was found in the performance of HeparDx™ vs. liver elastography. **Conclusion:** Non-invasive tests based on PLIN2, such as HeparDx™ can detect significant fibrosis (i.e. F2/3 vs F0/1) with the same accuracy as Esaote MyLab elastography. As a blood test, HeparDx™ might assist healthcare professionals in the identification of those individuals who may benefit from pharmacological intervention.



Disclosures: Giulia Angelini: Nothing to Disclose, Sara Russo: Nothing to Disclose, Aldo TRYLESINSKI: Nothing to Disclose, Jerome Boursier: echosens: Consultant, Inventiva: Consultant, Siemens: Consultant, Pfizer: Advisor, Novonordisk: Consultant, Gilead: Royalties or patent beneficiary, Siemens: Independent Contractor, Manuel Romero-Gómez: Nothing to Disclose, Quentin Anstee: AstraZeneca, Boehringer Ingelheim, Intercept.: Grant/Research Support, Alimentiv, Akero, AstraZeneca, Axcella, 89Bio: Consultant, Boehringer Ingelheim, Bristol Myers Squibb, Corcept: Consultant, Enyo Pharma, Galmed, Genfit, Genentech, Gilead, GlaxoSmithKl: Consultant, Hanmi, HistoIndex, Intercept, Inventiva, Ionis, IQVIA, Janss: Consultant, Madrigal, Medpace, Merck, Metadeq, NGMBio, North Sea T: Consultant, Novartis, Novo Nordisk, PathAI, Pfizer, Pharmanest: Consultant, Poxel, Prosciento, Resolution Therapeutics, Roche,: Consultant, Ridgeline Therapeutics, RTI, Shionogi, Terns: Consultant, Fishawack, Integritas Communications, Kenes,: Speaking and Teaching, Novo Nordisk, Madrigal, Medscape, Springer Healthcare: Speaking and Teaching, Elsevier Ltd: Royalties or patent beneficiary, Geltrude Mingrone: Nothing to Disclose

2094 | EXPLORING THE IMPACT OF MITOCHONDRIAL BIOMARKERS ON HCC RISK ACCORDING TO ETIOLOGIC DRIVERS: A MULTICENTER STUDY

Miriam Longo[1] Annalisa Cespiati[2] Erika Paolini[3] Marica Meroni[3] Anna Alisi[4] Andrea Dalbeni[5] Rosa Lombardi[6] Giorgio Soardo[7] Anna Ludovica Fracanzani[8] Paola Dongiovanni[2]

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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) overcame both viral (V) and alcohol (ALD) hepatitis, becoming the main cause of hepatocellular carcinoma (HCC). We recently showed that two new circulating mitochondrial (mt-) biomarkers (*D-loop*, ccf-COXIII) increases in MASLD patients. *D-loop* progressively raised with histological damage, resulting highly informative as early MASLD prognostic indicator. Instead, ccf-COXIII was closely related to advanced MASLD forms (cirrhosis, HCC). Still, combination of both

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biomarkers accurately predicted HCC risk (86%). However, whether these biomarkers are MASLD-specific remains to be further elucidated. We aimed to assess *D-loop* and ccf-COXIII levels across different etiologies (V, ALD and MASLD) in a multicenter cohort of 260 HCC patients from Milan, Rome, Verona and Udine. **Methods:** *D-loop* and ccf-mtDNA were measured in PBMCs and serum samples, respectively. **Results:** MASLD-HCC subjects had higher BMI, presence of diabetes mellitus (T2DM) and serum lipids compared to ALD-HCCs and V-HCCs ($p<0.05$). The highest levels of transaminases and alpha-fetoprotein were found in V-HCC patients. The mean size of HCC nodules was larger in both MASLD-HCCs and V-HCCs rather than ALD-HCCs. ccf-COXIII levels were higher in V-HCC patients compared to non-viral HCCs ($p<0.001$) at bivariate analysis and the association with viral etiology was statistically significant at generalized linear model adjusted for sex, age at diagnosis, BMI, T2DM and ALD/MASLD etiologies. At nominal logistic analysis adjusted as above, the ccf-COXIII correlated with increased risk of developing HCC from viral infections (OR:1.27 95% CI:1.08-1.5, $p=0.0009$). However, this association was lost after the correction for cirrhosis. Unlike, the highest levels of circulating *D-loop* were observed in MASLD-HCC patients and correlated with tumor size. Moreover, at multivariate analysis, the association between circulating *D-loop* and MASLD etiology was confirmed. Alongside, elevated *D-loop* levels correlated with enhanced cancer risk of metabolic origin (OR:1.62 95% CI:1.0-2.5, $p=0.02$), even after adjustment for the presence of cirrhosis. **Conclusion:** Mt-biomarkers changes in HCC patients according to etiology. ccf-COXIII rises most with virus infections in a condition of advanced liver disease, while *D-loop* seems to be MASLD-specific, possibly identifying HCC cases also in the absence of cirrhosis.

Disclosures: Miriam Longo: Nothing to Disclose, Annalisa Cespiati: Nothing to Disclose, Erika Paolini: Nothing to Disclose, Marica Meroni: Nothing to Disclose, Anna Alisi: Nothing to Disclose, Andrea Dalbeni: Nothing to Disclose, Rosa Lombardi: Nothing to Disclose, Giorgio Soardo: Nothing to Disclose, Anna Ludovica Fracanzani: Nothing to Disclose, Paola Dongiovanni: Nothing to Disclose

2095 | SINGLE-CELL RNA SEQUENCING REVEALS THE HETEROGENEITY OF MONOCYTE-DERIVED MACROPHAGES IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE ◆

Haozhe Xu[1] *Lu Yang*[1] *Jie Sun*[1] *Peiyang Fang*[1] *Xinjie Zhong*[1] *Dong Zhang*[2] *Guangyong Sun*[2]

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Background: The inflammatory response is crucial in the pathogenesis of metabolic dysfunction-associated steatotic liver disease (MASLD). Monocyte-derived macrophages (MoMFs) play a key role in liver inflammation and fibrogenesis, with their heterogeneity affecting MASLD progression. **Methods:** We developed various MASLD models and conducted single-cell RNA sequencing on liver-infiltrating $7AAD^{-}CD45^{+}LY6G^{-}CD11b^{int}F4/80^{low}$ MoMFs from MASLD (n=2) and control mice (n=2). **Results:** MoMFs were clustered into seven clusters (C0–C6). C0, marked by *Cd14* and recognized as CCR2+ MoMFs, increased the most in MASLD mice and was associated with fibrosis, pro-inflammatory responses and phagocytosis. C1, a basal state cluster, decreased significantly in MASLD mice liver. C2, highly expressed *Mrc1*, also decreased and was linked to anti-inflammation. Further analysis revealed that lipid droplet accumulation causing mitochondrial damage reduced the survival of C2. C3, marked by *Ccr3*, increased in MASLD. Deeper analysis showed that the MASLD group exhibited increased oxidative and endoplasmic reticulum stress in C3, leading to enhanced pro-inflammatory functions. C4, highly expressed *Ccr7*, increased in MASLD and was linked to antigen presentation. C5 and C6, marked by *Mki67* and *Cd3*, were associated with cell proliferation and TCR function, respectively. Additionally, the subsets discovered in the MASLD mice model were also confirmed in the MASLD human model. Notably, besides CCR2+ MoMFs, we found that CCR3+ and CCR7+ MoMFs also significantly increased in MASLD. CellChat analysis revealed CCR3+ and CCR7+ MoMFs may interact with endothelial cells or hepatic stellate cells via CCR3/CCL5, CCR7/CCL19 and CCR7/CCL21, inducing their chemotactic migration into the liver. For the C0 (CCR2+ MoMFs) subset, pseudotime analysis showed that C1 can differentiate into both C0 and C4. This indicates that CCR2+ MoMFs in MASLD livers may originate not only from the bone marrow but also from C1, a resident basal subset, suggesting a novel source of CCR2+ MoMFs. **Conclusion:** This study used single-cell RNA sequencing to reveal MoMFs heterogeneity in MASLD. We identified two new subsets, CCR3+ and CCR7+ MoMFs, which significantly increased in MASLD. Additionally, we discovered a novel source of CCR2+ MoMFs in MASLD livers. These findings enhance our understanding of MASLD pathogenesis and highlight potential therapeutic targets to modulate MoMFs functions in liver disease.

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Disclosures: Haozhe Xu: Nothing to Disclose, Lu Yang: Nothing to Disclose, Jie Sun: Nothing to Disclose, Peiyang Fang: Nothing to Disclose, Xinjie Zhong: Nothing to Disclose, Dong Zhang: Nothing to Disclose, Guangyong Sun: Nothing to Disclose

2096 | CLINICALLY SIGNIFICANT PORTAL HYPERTENSION BY NON-INVASIVE TESTS IN COMPENSATED ADVANCED CHRONIC LIVER DISEASE DUE TO METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS (MASH) WITH OBESITY AND OVERWEIGHT

Denise Vezozzo[1] Gleicy Reinoso[1] Betania Rocha[1] Patricia Ziteli[1] Sofia Rocha[1] JOSE TADEU STEFANO[1] Joao Italo Dias França[2] Flair Jose Carrilho[1] Claudia Oliveira[3]

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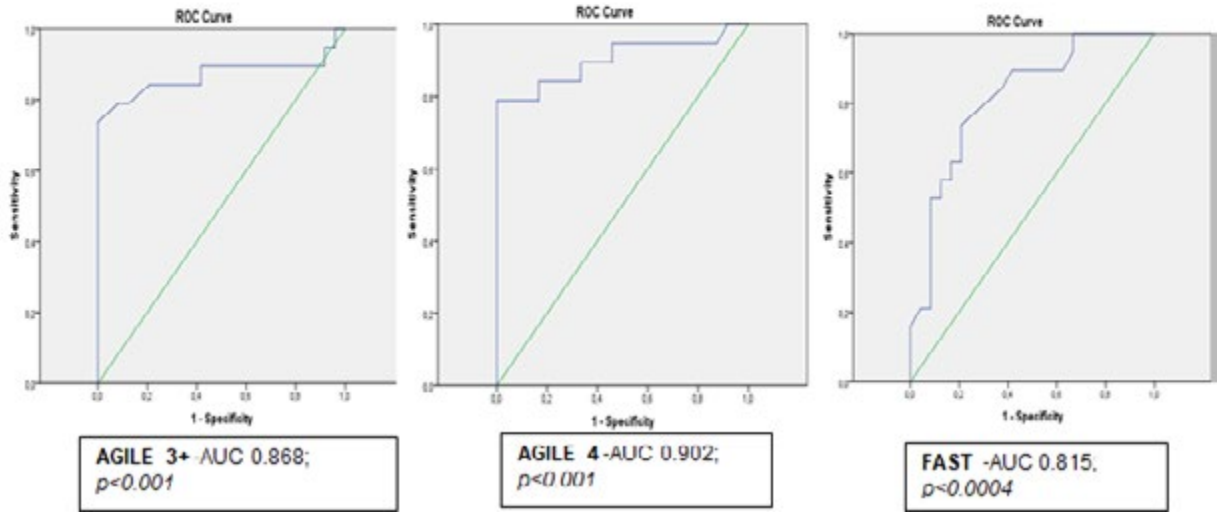
Background: This study aims to evaluate whether noninvasive tests (NITs) based on transient elastography and serum liver tests can predict Clinically Significant Portal Hypertension (CSPH) in patients with compensated advanced chronic liver disease (cACLD) due to Metabolic dysfunction-Associated SteatoHepatitis (MASH) in obesity and overweight patients methods. **Methods:** A cross sectional study evaluated patients with cirrhosis due to MASH with a previous liver biopsy. The selected patients underwent simultaneous Liver Stiffness Measurement (LSM) and Spleen Stiffness Measurement (SSM) using FibroScan™ Expert 630 (at 50 and 100 Hz), along with abdominal ultrasound and laboratory tests. The groups were classified based on the presence or absence of esophageal varices (EV) detected by upper endoscopy and/or collateral venous findings from imaging tests. NITs for fibrosis scores using LSM (FAST™, Agile™3+, and Agile™4) were also analyzed. **Results:** Forty-three patients with cACLD due to MASH were evaluated; 72% were female, with a mean BMI of 30.6 kg/m² and 19 (44%) presented EV. The median values were 42.1 kPa vs. 27.3 kPa ($p < 0.077$) for SSM and 31.4 kPa vs. 10.4 kPa ($p < 0.0001$) for LSM, respectively, with and without CSPH. The FAST score was 0.68 ($p < 0.0001$), Agile™ 3+ was 0.99 ($p < 0.0001$), and Agile™ 4 was 0.86 ($p < 0.0001$) for the CSPH group. AUROC curves from AGILE™ 4 and AGILE™ 3+ were respectively 0.902 and 0.868 ($p<0.001$). **Conclusion:** In our cohort, NITs for fibrosis scores using LSM, SSM, FAST™, Agile™3+, and Agile™4 were significantly associated with advanced liver fibrosis and CSPH.

Figure 1. *ROC curves for **AGILE 3+**, **AGILE 4**, and **FAST score** values comparing two groups with and without **Clinically Significant Portal Hypertension (CSPH).***



Disclosures: Denise Vezozzo: Nothing to Disclose, Gleicy Reinoso: Nothing to Disclose, Betania Rocha: Nothing to Disclose, Patricia Ziteli: Nothing to Disclose, Sofia Rocha: Nothing to Disclose, JOSE TADEU STEFANO: Nothing to Disclose, Joao Italo Dias França: Nothing to Disclose, Flair Jose Carrilho: Nothing to Disclose, Claudia Oliveira: Nothing to Disclose

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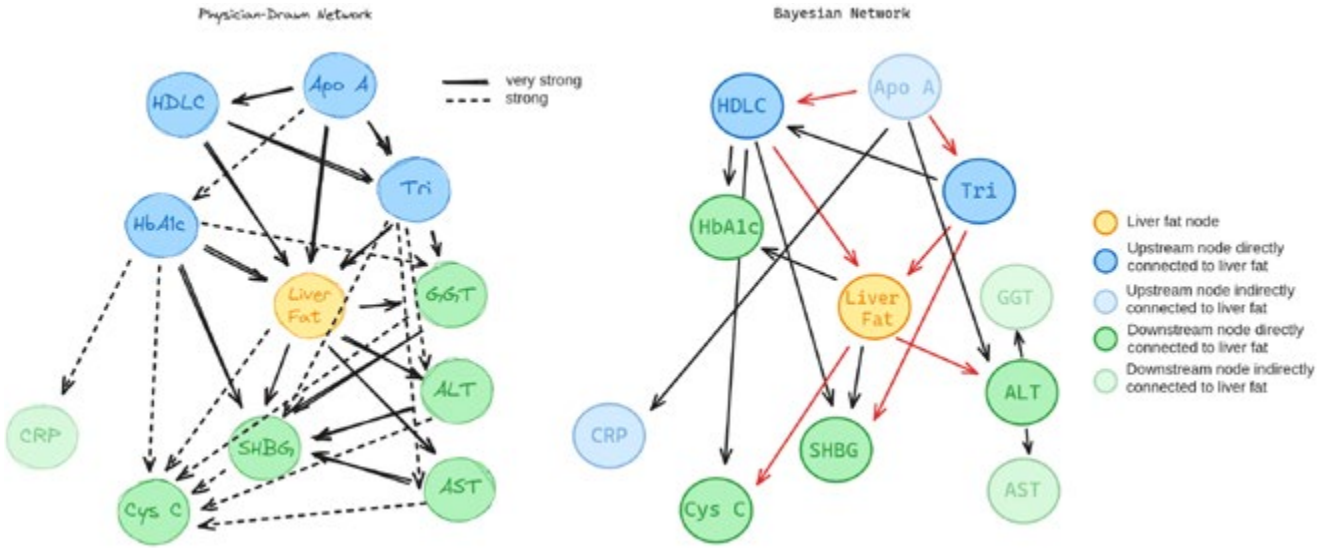
2097 | A BAYESIAN NETWORK IDENTIFIES CAUSAL RELATIONSHIPS OF SERUM BIOMARKERS WITH MASLD

Benjamin Laevens[1] *Yazhou Chen*[1] *Jan Clusmann*[1] *Niharika Jakhar*[1] *Thriveni Raju*[1] *Tobias Seibel*[1] *Kai Markus Schneider*[1] *Carolin Victoria Schneider*[1]

[1]*University Hospital Aachen*

Background: The Bayesian interpretation of statistics offers numerous advantages over frequentist approaches in clinical settings. Bayesian networks, in particular, are explainable and interpretable tools, which can increase physicians' understanding of disease development as well as assist them in their decision-making. By characterizing disease structures, a Bayesian network may be queried to obtain the most likely outcome of a particular disease given the information available. Besides the incorporation of prior knowledge, Bayesian networks may be continually updated in light of new evidence (e.g. more serum markers) and be successfully deployed on relatively small data sets. In this research, we compare a physician-drawn network with one Bayesian network for Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD). Using blood biomarkers and liver steatosis variables extracted from liver MRI of 35,000 participants in the UK Biobank, we obtain Bayesian networks which describe (causal) relationships between these variables. **Methods:** We classify the serum parameters by their ability to differentiate between two different groups: healthy (<5% proton density fat fraction; PDFF) or steatotic liver (>=5%), represented through a binary target variable. We obtain the top 10 most important biomarkers with a random forest classifier (RFC), enhanced by grid search hyperparameter tuning. We perform structure learning with a Hill Climb optimization algorithm, thus obtaining the best fitting Bayesian networks for the 11 variables (10 biomarkers and target PDFF). The best fitting networks are scored according to the Akaike Information Criterion. These networks show the favored dependencies within the data. **Results:** The optimal RFC reveals SHBG, triglycerides, ALT, HDL cholesterol, C-reactive protein, GGT, apolipoprotein A, cystatin C, HbA1c and AST as having the highest predictive value for MASLD (with an AUROC of 81% in the training set). The best network structure is characterized by 17 (causal) dependencies. Triglycerides and HDL cholesterol point towards liver fat, whereas ALT, cystatin C, SHBG and HbA1c point away from liver fat (i.e. a result of). The other markers are connected more distantly to liver fat. The network displays less dependencies than physician drawn networks of MASLD, which identifies 15 very strong dependencies and an additional 12 strong dependencies. Fig. 1: Comparison of a physician-drawn network (left) with a Bayesian network (right). The red arrows show the overlap between the two networks. **Conclusion:** Bayesian Networks are powerful decision tools due to their explainable and intuitive nature. By determining dependencies between serum parameters and disease, insights are obtained that can be contrasted with established physician-based views regarding MASLD. Future work will focus on using the Bayesian Network as a means of predicting MASLD based on serum markers.



Disclosures: Benjamin Laevens: Nothing to Disclose, Yazhou Chen: Nothing to Disclose, Jan Clusmann: Nothing to Disclose, Niharika Jakhar: Nothing to Disclose, Thriveni Raju: Nothing to Disclose, Tobias Seibel: Nothing to Disclose, Kai Markus Schneider: Nothing to Disclose, Carolin Victoria Schneider: Nothing to Disclose

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2098 | DEEP LEARNING CAN PREDICT MASLD-RELATED GENETIC RISK VARIANTS FROM LIVER MAGNETIC RESONANCE IMAGING

Yazhou Chen[1] Benjamin Laevens[1] Teresa Lemainque[1] Gustav Müller-Franzes[1] Tobias Seibel[1] Carola Dlugosch[1] Jan Clusmann[1] Paul-Henry Koop[1] Thriveni Raju[1] Niharika Jakhar[1] Rongpeng Gong[1] Simon Schophaus[1] Kai Markus Schneider[1] Daniel Truhn[1] Carolin Victoria Schneider[1]

[1]University Hospital Aachen

Background: Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) has become the most common chronic liver disease and a major threat to global health. A key clinical challenge is to identify individuals with high risk of disease progression towards cirrhosis. Single nucleotide polymorphisms (SNPs) in the HSD17B13 (rs72613567_TA) and MTARC1 (rs2642438_A) genes have been associated with protection against MASLD, whereas SNPs in GCKR (rs1260326_T), TM6SF2 (rs58542926_T) and most commonly PNPLA3 (rs738409_G) gene are considered harmful. However, clinical testing for risk variants in clinical routine is time consuming and costly, hampering personalized risk stratification and treatment. Here, we investigate deep learning-based approaches to predict the presence of SNP directly from routinely available MRI imaging data, aiming to identify homozygous carriers and non-carriers. **Methods:** We utilized MRI images and genetic variant labels from a cohort of 45,605 patients provided by the UK Biobank. Fat fraction maps were reconstructed from multi-echo magnitude and phase MRI images using a water-fat separation toolbox. The Live region was segmented by using a UNet model trained on 600 manually segmented ground truth images. The resulting liver masks and fat fraction maps were used to calculate the proton density fat fraction (PDFF) of the liver, 13559 fatty liver patients (PDFF ≥5%) were selected as our study cohort. Finally, the segmented liver regions, along with the genetic variant labels were used as input for the Vision Transformer classification model. The dataset was randomly split into an 8:2 ratio for training and validation purposes, AUC scores were calculated as our evaluation metric. **Results:** We achieved AUCs 0.561, 0.576, 0.573, 0.556, and 0.655 for the validation set for genes HSD17B13, MTARC1, GCKR, TM6SF2, and PNPLA3, respectively. Our findings indicate that the SNP rs738409_G in the PNPLA3 gene can be predicted with higher accuracy in the fatty liver cohort compared to other SNPs, for which accurate prediction has not yet been achieved. **Conclusion:** In this study, we implemented a novel deep learning-based method to identify genetic carriers using MRI image data from a well-characterized large cohort. Our approach offers an innovative and efficient technique for detecting genetic variants, especially rs738409_G which may make diagnostics of patients at risk of progression easier and advance the field of personalized healthcare. Future work could focus on visualizing the specific liver regions that contribute most to the predictions. Figure**:** Here illustrates the detailed process of our study. Example MRI images provided by the UK Biobank (can be downloaded here: https://biobank.ndph.ox.ac.uk/showcase/ukb/examples/eg_abdo_idealp.zip) were used to illustrate our study, and further reconstructed images were processed using the water-fat-separation toolbox.

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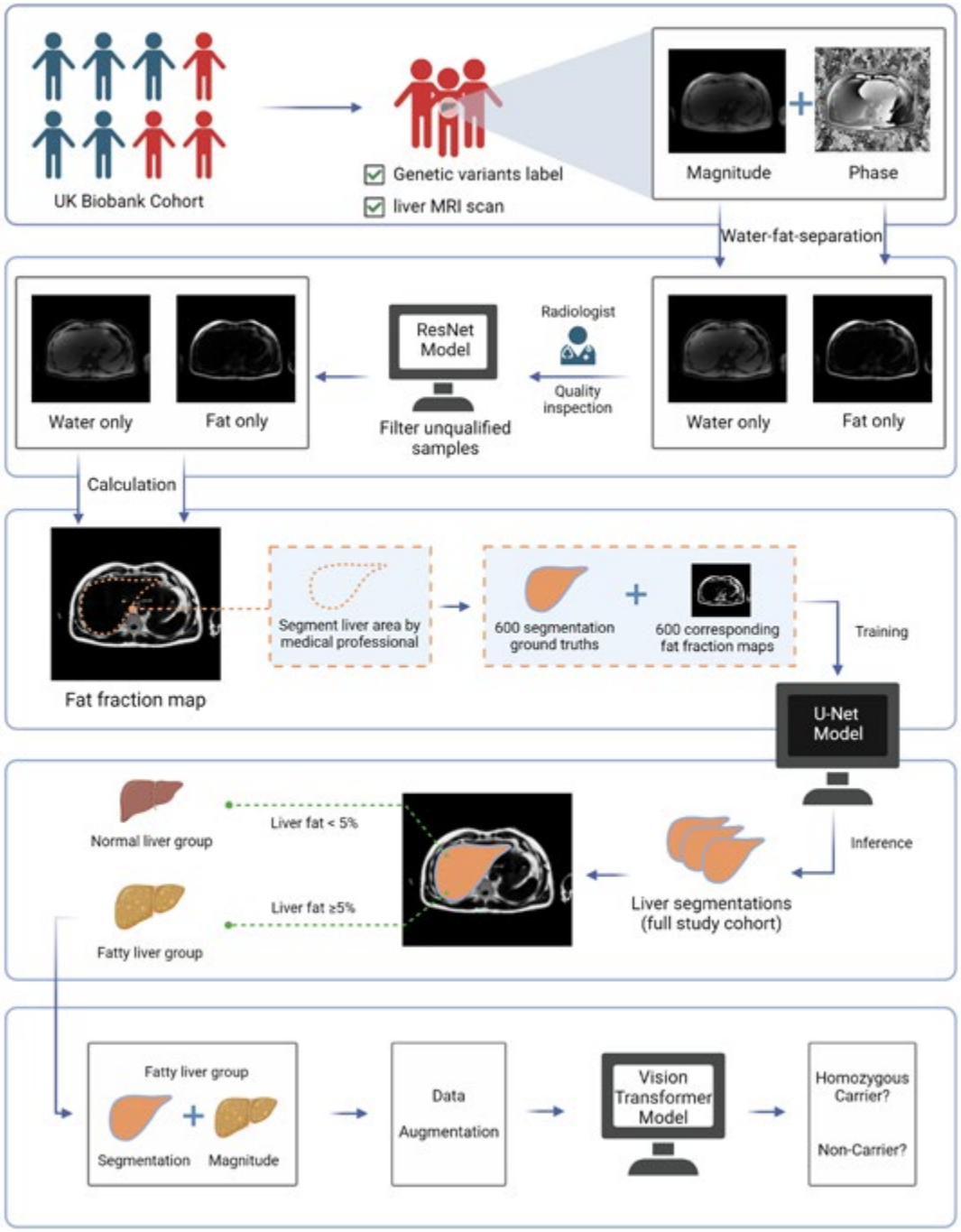

Disclosures: Yazhou Chen: Nothing to Disclose, Benjamin Laevens: Nothing to Disclose, Teresa Lemainque: Nothing to Disclose, Gustav Müller-Franzes: Nothing to Disclose, Tobias Seibel: Nothing to Disclose, Carola Dlugosch: Nothing to Disclose, Jan Clusmann: Nothing to Disclose, Paul-Henry Koop: Nothing to Disclose, Thriveni Raju: Nothing to Disclose, Niharika Jakhar: Nothing to Disclose, Rongpeng Gong: Nothing to Disclose, Simon Schophaus: Nothing to Disclose, Kai Markus Schneider: Nothing to Disclose, Daniel Truhn: Nothing to Disclose, Carolin Victoria Schneider: Nothing to Disclose

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2099 | METASIGHT'S METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS (MASH)-FIBROSIS SCORE: A BLOOD TEST ENABLING PATIENT MONITORING OF LIVER FIBROSIS

Shira Shaham-Niv[1] Eldad Kepten[1] Boris Sarvin[1] Mark Vernik[1] Ilya Podolsky[1] Carmel Shor[1] Claudia Filozof[2] Tomer Shlomi[1] Jerry Colca[3] Arun Sanyal[4]

[1]MetaSight Diagnostics, [2]Fortrea, [3]Western Michigan University, [4]Virginia Commonwealth University

Background: Non-invasive diagnosis of MASH-fibrosis and monitoring of disease progression are of major clinical need, emphasized by the recent approval of a first MASH drug. MetaSight's MASH-Fibrosis score was recently shown to accurately diagnose patients with significant fibrosis based on mass-spectrometry serum-proteomics. The objective of this study was to evaluate the performance of the MetaSight test in monitoring the progression of liver fibrosis. **Methods:** Serum samples were obtained from a completed randomized, double-blind, placebo-controlled phase 2b (EMMINENCE) trial (NCT02784444). Patients with biopsy-confirmed MASH, fibrosis stage 1–3, and a Non-alcoholic fatty liver disease Activity Score (NAS) ≥4 were enrolled and randomly assigned for oral daily doses with MSDC-0602K, or placebo, for 12 months. We performed a post-hoc analysis of serum samples collected at baseline and end-of-trial (EOT) for 220 patients, having consistent biopsy reads by two pathologies at baseline and a 2nd biopsy at EOT. The MASH-fibrosis score was calculated via LC-MS measurement of the concentration of 3 protein markers; associated with liver fibrotic processes and inflammation, as previously described. Biopsy data shows fibrosis stage progression in a total of 42 patients, either treated or in the placebo arm, no change in 120, and regression in 58. **Results:** MetaSight's MASH-Fibrosis Score shows high diagnostic performance for identifying significant fibrosis (stage ≥ F2) with an AUC of 0.79 and sensitivity of 57% at a specificity of 90%. FIB-4, FibroTest, and ELF AUCs in the same cohort were significantly lower: 0.6, 0.62, and 0.64, respectively; with sensitivities of 28%, 25%, and 20%, respectively (at a specificity of 90%). Patients with biopsy-confirmed regression in fibrosis stage (between baseline and EOT) had a statistically significant drop in MASH-fibrosis score (average drop of 8%; $p < 0.012$), while patients with fibrosis progression had a significant increase in score (average increase of 7%; $p < 0.05$). In contrast, no statistically significant drop in FIB-4, FibroTest, or ELF scores were detected in patients with a regressed fibrosis stage. **Conclusion:** The MetaSight test is a promising accurate approach for diagnosing MASH-fibrosis. Unlike currently utilized NITs, the MetaSight test enables monitoring fibrosis in patients under treatment, making it an option to be considered in clinical practice.

Disclosures: Shira Shaham-Niv: Nothing to Disclose, Eldad Kepten: Nothing to Disclose, Boris Sarvin: Nothing to Disclose, Mark Vernik: Nothing to Disclose, Ilya Podolsky: Nothing to Disclose, Carmel Shor: Nothing to Disclose, Claudia Filozof: Nothing to Disclose, Tomer Shlomi: Nothing to Disclose, Jerry Colca: Cirius Therapeutics: Stock – privately held company, Arun Sanyal: Genfit, Akarna, Tiziana, Durect, Inversago, Hemoshear, North: Stock - publicly traded company, Astra Zeneca (60K), Boston Pharmaceutical

2100 | COMPARISONS OF DIAGNOSTIC PERFORMANCE ACCORDING TO THE SCORING SYSTEMS USING MAGNETIC RESONANCE ELASTOGRAPHY AND TRANSIENT ELASTOGRAPHY FOR DISCRIMINATING PATIENTS WITH METABOLIC-ASSOCIATED STEATOHEPATITIS AND SIGNIFICANT FIBROSIS

Min Joo Yoon[1] Han Ah Lee[2] Jae Seung Lee[1] Seung-seob Kim[1] Yeon Seok Seo[3] Jeong-Ju Yoo[4] Hwi Young Kim[2] Seung Up Kim[1] Sang Gyune Kim[4]

[1]Yonsei University College of Medicine, [2]Ewha Womans University Mokdong Hospital, [3]Korea University Anam Hospital, [4]Soonchunhyang University Seoul Hospital

Background: Patients with metabolic-associated steatohepatitis (MASH) with significant fibrosis (fibro-MASH) are at a higher risk of disease progression. We validated the predictive value of the MRI-aspartate aminotransferase (AST) score (MAST) and other noninvasive surrogates in predicting fibro-MASH. **Methods:** The retrospective analysis included 247 patients who underwent liver biopsy, MRI-based elastography (MRE) and proton density fat fraction (MRI-PDFF), transient elastography (TE), and laboratory testing for metabolic-associated steatotic liver disease (MASLD). MAST score was calculated and compared to MRE combined with fibrosis index based on four (FIB-4) index (MEFIB), MRE-based NASH score (MRE-NASH), FibroScan-AST score (FAST), non-alcoholic

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fatty liver disease-fibrosis score (NFS), FIB-4, and aspartate aminotransferase to platelet ratio index (APRI). **Results:** Fibro-MASH was pathologically diagnosed in 64 (25.9%) patients, who showed significantly higher liver stiffness (LS) value by MRE (median: 4.04 vs. 2.58 kPa) and TE (median: 14.7 vs. 7.7 kPa). LS-MRE and LS-TE excellently predicted the histologic ≥F2, ≥F3, and F4 (all AUCs >0.8). MRI-PDFF showed higher AUCs (0.832–0.853) for the steatosis grade than CAP (0.673–0.704). MAST, MEFIB, and MRE-NASH showed higher AUCs (0.785, 0.794, and 0.796, respectively) than did those of FAST, NFS, APRI, and FIB-4 (0.743, 0.751, 0.675, and 0.780, respectively) for predicting Fibro-MASH, although there was no definite statistical significance. LS-MRE and LS-TE had higher AUCs for predicting Fibro-MASH (0.834 and 0.808, respectively) than the other surrogates. **Conclusion:** The MR-based surrogates performed acceptably in identifying fibro-MASH. However, the LS value alone, measured by MRE and TE, also showed comparable predictive ability to the MR-based surrogates.

Table. Diagnostic accuracy of noninvasive surrogates in predicting Fibro-MASH

Scoring system	AUC (95% CI) (vs. MAST)	*P* value vs. MAST	Cut-offs		Se	Sp	PPV	NPV	Accuracy
MAST	0.785 (0.722, 0.847)	-	90% Se	0.066	90.6	46.4	37.2	93.4	57.9
			Youden	0.157	76.6	71.6	48.5	89.7	72.9
			90% Sp	0.350	34.4	89.6	53.7	79.6	75.3
MEFIB	0.794 (0.734, 0.855) (-0.061, 0.041)	0.703	MRE >3.3kPa + FIB-4 <1.6		85.9	62.3	44.4	92.7	68.4
			MRE ≥3.3kPa + FIB-4 ≥1.6		59.4	86.3	60.3	85.9	79.4
MRE based NASH	0.796 (0.732, 0.859) (-0.076, 0.053)	0.736	90% Se	0.180	90.6	47.0	37.4	93.5	58.3
			Youden	0.283	82.8	66.1	46.1	91.7	70.4
			90% Sp	0.850	42.2	89.6	58.7	81.6	77.3
FAST	0.743 (0.675, 0.811) (-0.013, 0.096)	0.134	90% Se	0.37	90.6	38.3	33.9	92.1	51.8
			Youden	0.69	62.5	75.4	47.1	85.2	72.1
			90% Sp	0.78	34.4	89.1	52.4	79.5	74.9
NFS	0.751 (0.681, 0.820) (-0.044, 0.112)	0.395	90% Se	-2.319	90.6	48.1	37.9	93.6	59.1
			Youden	-1.648	84.4	62.3	43.9	91.9	68.0
			90% Sp	0.550	31.3	90.2	52.6	78.9	74.9
APRI	0.675 (0.602, 0.748) (0.053, 0.166)	<0.001	90% Se	0.43	92.2	30.6	31.7	91.8	46.6
			Youden	1.19	87.5	58.5	42.4	93.0	66.0
			90% Sp	1.63	26.6	90.2	48.6	77.8	73.7
FIB-4	0.780 (0.721, 0.839) (-0.061, 0.069)	0.902	90% Se	1.043	89.1	51.9	39.3	93.1	61.5
			Youden	1.190	87.5	58.5	42.4	93.0	66.0
			90% Sp	3.665	31.3	90.2	52.6	78.9	74.9
LS value by MRE (kPa)	0.834 (0.777, 0.890) (-0.096, -0.002)	0.041	90% Se	2.58	90.6	49.2	38.4	93.8	59.9
			Youden	3.10	85.9	74.3	53.9	93.8	77.3
			90% Sp	4.12	48.4	90.2	63.3	83.3	79.4
LS value by TE (kPa)	0.808 (0.747, 0.869) (-0.087, 0.039)	0.457	90% Se	7.3	90.6	42.6	35.6	92.9	55.1
			Youden	12.2	70.3	82.0	57.7	88.8	78.9
			90% Sp	14.4	51.6	90.2	64.7	84.2	80.2

Abbreviations: MASH, metabolic-associated steatohepatitis; AUC, area under the curve; CI, confidence interval; Se, sensitivity; Sp, specificity; PPV, positive predictive value; NPV, negative predictive value; LS, liver stiffness; MRE, magnetic resonance elastography; NASH, nonalcoholic steatohepatitis; TE, transient elastography.

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2101 | SCREENING FOR ADVANCED LIVER FIBROSIS DUE TO MASLD WITH VCTE ALONGSIDE RETINA SCANNING IN PATIENTS WITH TYPE 2 DIABETES: A CROSS-SECTIONAL STUDY OF 1005 PATIENTS

Andrea Lindfors[1] *Hannes Hagström*[1] *Rickard Strandberg*[1]

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Background: International guidelines suggest screening for advanced fibrosis due to metabolic dysfunction-associated steatotic liver disease (MASLD) in patients with type 2 diabetes (T2D), but how the implementation of these guidelines can be introduced in clinical care remains unclear. Here, we assessed the strategy of offering vibration-controlled transient elastography (VCTE) alongside retina scanning in patients with T2D. **Methods:** This prospective cross-sectional study included patients with T2D during routine retina scanning in Stockholm, Sweden. A total of 1301

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patients were eligible to undergo assessment using VCTE. Increased liver stiffness was defined as ≥8 kPa, and possible advanced fibrosis as >12 kPa. Hepatic steatosis was defined as a CAP value of 280 dB/m or above. Patients with a liver stiffness measurement of ≥8 kPa or those with unreliable measurements were subsequently referred for a secondary evaluation at a liver specialist. **Results:** Examination with VCTE was accepted by 1005 patients (77%). Of these, 504 (51.8%) had CAP values of ≥280 dB/m, indicating steatotic liver disease. Further, 15.8% exhibited values of ≥8 kPa, suggestive of liver fibrosis and 5.0% had values >12 kPa, indicating possible advanced fibrosis. However, upon reassessment with a second VCTE after referral, 45.2% of these individuals had values <8kPa. The final prevalence of liver stiffness ≥8kPa was 7.4%, and 2.9% had values >12kPa. The distribution of liver stiffness from those with reliable VCTE measurement at the first visit is depicted in Figure 1. **Conclusion:** Simultaneous examination with VCTE alongside retina scanning demonstrates high acceptance rates among patients with T2D and may be a strategy for case-finding of patients with fibrosis due to MASLD. However, false-positive findings are common.

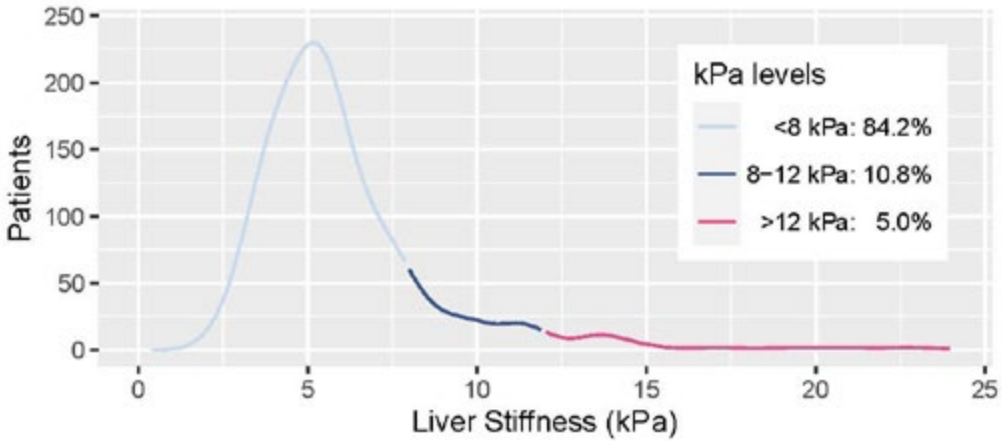

Figure 1. Distribution of liver stiffness from reliable measurements in patients with type 2 diabetes (n=977).

Disclosures: Andrea Lindfors: Gilead Sciences: The study was partly financed by Gilead Sciences, Hannes Hagström: Nothing to Disclose, Rickard Strandberg: Nothing to Disclose

2102 | AGILE3+ ENCOMPASSES THE TWO-STEP APPROACH NEEDED TO ENHANCE DIAGNOSTIC ACCURACY OF ADVANCED FIBROSIS IN PATIENTS WITH SUSPECTED MASLD

Savvoula Savvidou[1] Polyxeni Agorastou[2] Effrosyni Tsirogianni[2] Stefania Kiapidou[2] Ioanna Papagiouvani[2] Theodora Oikonomou[2] Lazaros Sideras[2] Prodromos Hytiroglou[3] Ioannis Goulis[2]

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Background: According to national Greek guidelines (2021) regarding diagnostic approach of suspected Metabolic dysfunction Associated Steatotic Liver Disease (MASLD), liver stiffness measurement (LSM) is suggested only to patients (pts) with ultrasonographic evidence of fatty liver, presence of at least one cardiometabolic factor in the absence of other aetiology for secondary hepatic steatosis (alcohol, drugs, viral hepatitis, etc), and intermediate risk for advanced fibrosis assessed by FIB-4 score. On the other hand, the new AGILE3+ score seems a promising alternative approach, as it combines age, presence of diabetes mellitus (DM), laboratory assessment of aminotransferases and platelets, and hepatic elastography performed with FibroScan® equipment. Aim of this study was to show the diagnostic superiority of AGILE3+ in detecting advanced fibrosis in pts with suspected MASLD. **Methods:** Consecutive pts with steatotic liver disease were assessed with FibroScan® mini 430+ (M, XL probes) by the same operator, and values of LSM and Controlled Attenuation Parameter (CAP) were recorded. FIB-4 and AGILE3+ scores were further calculated in all pts with suspected MASLD. Advanced fibrosis was defined as presence of histologic fibrosis stage ≥ F3. Diagnostic accuracy (sensitivity, specificity and AUROC) of current algorithm (FIB-4 followed by LSM in pts with intermediate risk)

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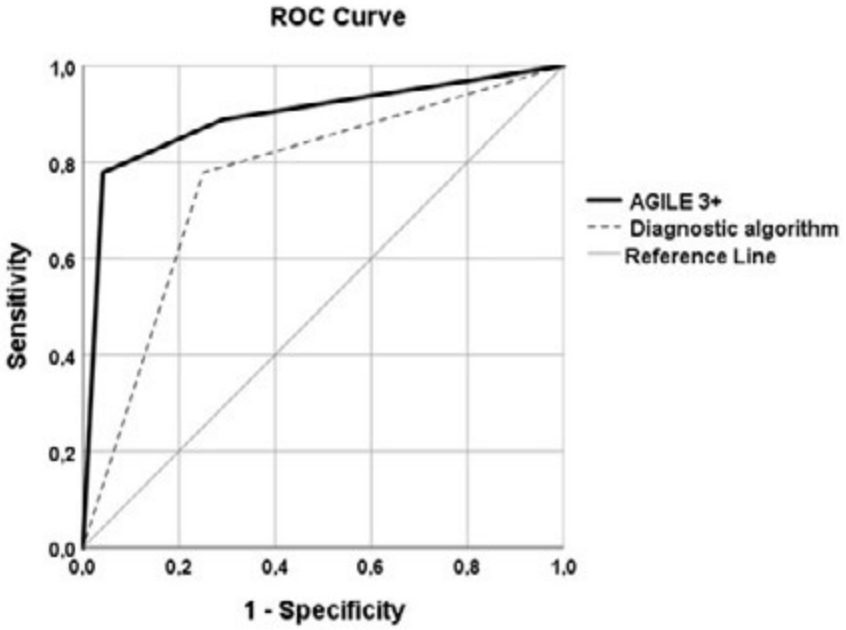
was compared to that of AGILE3+ alone. **Results:** A total of 96 patients with suspected MASLD were analyzed: 46 (47.9%) males, mean age 51.9±13.7 years-old, 33 pts (34.4%) with DM, 47 pts (49.5%) with dyslipidemia or under statins, BMI 30.7±5.8 kg/m^2. According to FIB-4, 55 pts (57.3%) were low-risk (FIB-4< 1.30), 37 pts (38.5%) intermediate-risk (1.3 ≥ FIB-4 ≤ 3.25), and 4 pts (4.2%) high-risk (FIB-4> 3.25) for advanced fibrosis. LSM≥ 8kPa were seen in 46 low-risk pts (83.6%), 24 intermediate-risk pts (64.9%), and all 4 high-risk pts (100%), while CAP≥ 250 dB/m was detected in all pts with suspected MASLD. Distribution of pts in different histological fibrosis stages F0 to F4 were 20.8%, 20.8%, 15.6%, 18.8% and 23.9%, respectively. Application of AGILE3+ score enhanced sensitivity from 77.8% to 87.5%, specificity from 75% to 94.4%, and AUROC from 0.764 (95% CI 0.613-0.915) to 0.894 (95% CI 0.783-1).[GRAPH 1] **Conclusion:** AGILE3+ score is superior in detecting advanced fibrosis, highlightening the screening benefits of FibroScan® (with CAP) in pts with suspected MASLD.



Disclosures: Savvoula Savvidou: Nothing to Disclose, Polyxeni Agorastou: Nothing to Disclose, Effrosyni Tsirogianni: Nothing to Disclose, Stefania Kiapidou: Nothing to Disclose, Ioanna Papagiouvani: Nothing to Disclose, Theodora Oikonomou: Nothing to Disclose, Lazaros Sideras: Nothing to Disclose, Prodromos Hytiroglou: Nothing to Disclose, Ioannis Goulis: Nothing to Disclose

2103 | DIFFERENTIATION OF STEATOTIC LIVER DISEASE FROM ADVANCED LIVER FIBROSIS/CIRRHOSIS BY BREATH VOLATILE ORGANIC COMPOUND ANALYSIS

Vaclav Smid[1] Ksenyia Dryahina[2] Barbora Nováková[1] Stefan Swift[3] Simon Dostal[1] Sarka Svobodova[1] Martin Lenicek[1] Patrik Spanel[2] Radan Bruha[1]

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Background: Analysis of volatile organic compounds (VOC) in breath is a promising innovative non-invasive diagnostic tool. VOC, which are metabolic by-products detectable in exhaled breath, can increase in breath due to their impaired metabolism in the liver. Thus, VOC have been proposed as biomarkers potentially useful for screening liver diseases, including MASLD. In particular, previous studies have shown elevated levels of D-limonene (LMN), trimethylamine (TMA), and pentane in MASLD. The aim of our study was to test the potential of breath analysis in differentiating steatosis from advanced liver fibrosis/cirrhosis. **Methods:** The VOC content in exhaled breath of 13 healthy controls (CTRL) and patients with MASLD (steatosis (SLD), n = 27; liver fibrosis, n = 6; and cirrhosis, n = 8) was analyzed using real-time monitoring by Selected ion flow tube mass spectrometry - both natively and during the “stress test” after ingestion of capsules with 250 mg of LMN and TMA-containing

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Fish oil capsules. Breath analyses were performed natively after an overnight fast and then at 15-min intervals for up to three hours after the ingestion of capsules. The grade of fibrosis and steatosis was assessed by transient elastography and Controlled Attenuation Parameter (CAP). Routine blood sampling was performed on the day of analysis and patients completed a dietary questionnaire. The VOC concentrations were compared between groups using Kruskal-Wallis with appropriate post-hoc tests. Correlations were examined using Spearman's correlation coefficient and Bonferroni correction. **Results:** The native LMN breath concentrations over 1.50 ppbv significantly discriminated patients with SLD compared to CTRL (p =0.003, AUROC 0.87, Se 75%, Sp 84%, PPV 0.96, NPV 0.71). Furthermore, the native LMN breath concentrations over 3.38 ppbv significantly distinguished patients with advanced fibrosis/cirrhosis (F3-F4) compared to those with SLD and F0-F2 (p = 0.002, AUROC 0.86, Se 74%, Sp 86%, NPV 0.93, PPV 0.70). The native LMN significantly correlated with CAP values (Spearman's R = 0.58, p = 0.001). Consequently, the LMN "stress test" confirmed significantly increased LMN concentrations 150 min after LMN ingestion in patients with advanced liver fibrosis/cirrhosis (F3-F4) compared to SLD and CTRL (p = 0.04, AUROC 0.79, Se 66%, Sp 91%, NPV 0.93, PPV 0.67). In addition, native pentane was significantly increased in cirrhosis compared to SLD (p = 0.006) and CTRL (p = 0.003). In contrast to LMN, native TMA was significantly increased only in cirrhosis compared to CTRL (p = 0.019). The administration of fish oil capsules did not affect TMA breath concentration. We found no correlations between VOC levels and other clinical parameters. **Conclusion:** Breath analysis of VOC appears to have the potential to stratify patients with MASLD. Supported by: MHCZ–DRO–VFN0064165; AZV MHCZ NU23-01-00288; AMULET project by the MEYS CZ - No. CZ020101/00/22_008/0004558, co-funded by the EU.

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2104 | BASELINE CHARACTERISTICS IN WELL-COMPENSATED NASH CIRRHOSIS PATIENTS DIAGNOSED WITH OR WITHOUT A LIVER BIOPSY IN MAESTRO-NASH-OUTCOMES, A CLINICAL OUTCOME PHASE 3 STUDY ASSESSING THE EFFECT OF RESMETIROM IN WELL COMPENSATED NASH CIRRHOSIS

Meena Bansal[1] Jörn Schattenberg[2] Kris Kowdley[3] Mazen Noureddin[4] Rohit Loomba[5] Rebecca Taub[6] Dominic Labriola[6] David Schneider[6]

[1]Icahn School of Medicine at Mount Sinai (ISMMS), [2]Saarland University Medical Center, Homburg and Saarland University, [3]Liver Institute Northwest, [4]Houston Methodist Hospital, [5]University of California, San Diego, [6]Madrigal Pharmaceuticals

Background: MAESTRO-NASH Outcomes (NCT05500222) is a multi-national, multicenter, double-blind, randomized, placebo-controlled study in well-compensated NASH cirrhosis. Patients were randomized 3:1 in a blinded manner to receive resmetirom 80 mg or matching placebo given orally once daily in the morning for the duration of the study (until the required number of Composite Clinical Outcome events are achieved). Composite Clinical Outcome events are defined as any of the following: mortality, liver transplant, and significant hepatic events, including potential hepatic decompensation events (ascites, hepatic encephalopathy, or gastroesophageal variceal hemorrhage), and confirmed increase of Model for End-stage Liver Disease (MELD) score from <12 to ≥15. The study comprises an up to 60-day screening period and an approximately 3-year treatment period. Baseline factors in patients who were diagnosed with NASH cirrhosis on liver biopsy were compared with those diagnosed with NASH cirrhosis who did not receive a liver biopsy. **Methods:** The study enrolls NASH cirrhosis patients with confirmed F4 fibrosis on biopsy with 3 metabolic risk factors, meeting other non-invasive testing and eligibility requirements, or NASH cirrhosis diagnosed non-invasively requiring at least 2 non-invasive testing requirements for screening: FibroScan VCTE ≥15 kPa and/or if FibroScan VCTE <15 kPa; at least two other non-invasive tests (MRE ≥4.2, platelets <140K, ELF ≥10.25, FIB-4 ≥3). Other screening tests include blood tests,

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MRE, MRI-PDFF and assessments for HCC and ascites, with MELD <12 (except for Gilbert). **Results:** Based on a current enrollment of 566 patients, baseline factors were generally similar between patients diagnosed as NASH cirrhosis on liver biopsy or diagnosed as NASH cirrhosis without a liver biopsy: mean age 63 years; 34-38% males; mean BMI of 35 kg/m^2, 82% with hypertension, 73-78% with T2DM. Approximately one third of patients had more advanced disease based on MRE ≥6, ELF ≥11.3, MRI-PDFF <5%. A slightly higher percentage of NASH cirrhosis patients diagnosed without a liver biopsy had baseline characteristics suggestive of more advanced portal hypertension (Platelets <140K, higher MRE, ELF and FibroScan VCTE). **Conclusion:** These data support the accuracy of using non-invasive testing to accurately diagnose well-compensated NASH cirrhosis.

	Patients with Biopsy		Patients without Biopsy	
Patient Baseline Characteristics	297		269	
Mean age, years (SD)	63.0	(8.3)	63.3	(9.1)
Male, n (%)	100	(34%)	103	(38%)
Female, n (%)	197	(66%)	166	(62%)
Hispanic/Latino, n (%)	58	(20%)	73	(27%)
Mean Body weight (SD) (kg)	93.9	(21.5)	96.7	(21.7)
BMI mean (SD) (kg/m2)	34.5	(17.0)	35.0	(7.4)
Hypertension, n (%)	244	(82%)	218	(81%)
Hypothyroid, n (%)	77	(26%)	71	(26%)
T2D, n (%)	231	(78%)	196	(73%)
Documented ASCVD[#], n	18	(6.1%)	14	(5.2%)
ELF Test	292		264	
ELF Test >= 11.3 (n, %)	78	(26.7%)	88	(33.3%)
ELF Test < 11.3 (n, %)	214	(73.3%)	176	(66.7%)
MELD	283		262	
MELD >=12 (n, %)	10	(3.5%)	20	(7.6%)
MELD 9-11 (n, %)	57	(20.1%)	93	(35.5%)
MELD <9 (n, %)	216	(76.3%)	149	(56.9%)
MRI-PDFF	254		237	
MRI-PDFF < 5 (n, %)	73	(28.7%)	83	(35.0%)
MRI-PDFF >= 5 (n, %)	181	(71.3%)	154	(65.0%)
MRI-PDFF mean (SD) (%FF)	8.5	(5.1)	8.0	(5.4)
MRE KPA	239		230	
MRE KPA >= 6 (n, %)	76	(31.8%)	87	(37.8%)
MRE KPA < 6 (n, %)	163	(68.2%)	143	(62.2%)
MRE mean (SD) (kPa)	5.6	(1.6)	5.9	(1.7)
Fibroscan TE mean (SD) (kPa)	23.7	(12.0)	26.8	(13.5)
Fibroscan CAP mean (SD)	301.9	(59.0)	301.2	(57.3)
Statin use (n, %)	168	(56.6%)	151	(56.1%)
Thyroxine Any (n, %)	79	(26.6%)	75	(27.9%)
GLP-1s (n, %)	108	(36.4%)	85	(31.6%)
SGLT2s (n, %)	66	(22.2%)	51	(19.0%)
Other lab parameters, mean (SD)				
Fib-4	2.9	(1.5)	3.4	(1.6)
Total bilirubin mean (SD) (mg/dL)	0.8	(0.4)	0.9	(0.4)
Direct bilirubin mean (SD) (mg/dL)	0.2	(0.1)	0.2	(0.1)
Platelet count mean (SD)	161.6	(59.9)	141.9	(59.5)
Albumin mean (SD) (g/dL)	4.3	(0.3)	4.2	(0.3)
INR mean (SD)	1.1	(0.2)	1.2	(0.1)
ELF Test mean (SD) (mg/dL)	10.7	(0.9)	11.0	(0.9)
ALT (IU/L)	41.6	(24.4)	39.9	(24.4)
AST (IU/L)	40.8	(18.8)	40.7	(20.8)
GGT (IU/L)	105.0	(125.6)	106.4	(102.8)

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Has not ended; Speaking and Teaching relationship with Madrigal; Has not ended; Principal Investigator for a Drug Study relationship with Takeda; Has not ended; Principal Investigator for a Drug Study relationship with Shire; Has not ended; Principal Investigator for a Drug Study relationship with Novo Nordisk; Has not ended; Principal Investigator for a Drug Study relationship with Novartis; Has not ended; Principal Investigator for a Drug Study relationship with Enanta; Has not ended; Principal Investigator for a Drug Study relationship with Corcept; Has not ended; Principal Investigator for a Drug Study relationship with GSK; Has not ended; Principal Investigator for a Drug Study relationship with Conatus; Has not ended, Rohit Loomba: Eli Lilly and Company: Consultant, 89bio: Consultant, Aardvark Therapeutics: Consultant, Altimmune: Consultant, Alnylam/Regeneron: Consultant, Amgen: Consultant, Arrowhead Pharmaceuticals: Consultant, AstraZeneca: Consultant, Bristol Myers Squibb: Consultant, CohBar: Consultant, Eli Lilly: Consultant, Galmed Pharmaceuticals: Consultant, Gilead: Consultant, Glympse Bio: Consultant, Hightide: Consultant, Inipharma: Consultant, Intercept: Consultant, Inventiva: Consultant, Ionis: Consultant, Janssen, Inc.: Consultant, Madrigal Pharmaceuticals: Consultant, Merck, Metacrine, Inc.: Consultant, NGM Biopharmaceuticals: Consultant, Novartis: Consultant, Novo Nordisk: Consultant, Pfizer: Consultant, Sagimet Biosciences: Consultant, Terns Pharmaceuticals: Consultant, Theratechnologies and Viking Therapeutics: Consultant, 89bio: Stock options,

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2105 | THE DIAGNOSTIC PERFORMANCE OF AGILE 3+ SCORE FOR DETECTING ADVANCED FIBROSIS IN INDIVIDUALS WITH CHRONIC HEPATITIS B AND CONCURRENT MASLD: A MULTICENTER STUDY ◆

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Background: Agile3+ was developed to detect advanced fibrosis in individuals with metabolic dysfunction associated steatotic liver disease (MASLD). However, chronic hepatitis B (CHB), a disease with about 300 million global burden, was excluded in the original study. Given the escalating prevalence of MASLD among CHB, this study aims to evaluate the diagnostic performance of Agile3+ and other non-invasive tests (NITs) in individuals with CHB and MASLD. **Methods:** Clinical data, including laboratory testing and biopsy data, of CHB patients with concurrent MASLD from 7 medical centers (NCT05766449) were included. Six NITs, including Agile3+, liver stiffness measurement (LSM), FibroScan-AST score (FAST), FIB-4, APRI, and nonalcoholic fatty liver disease fibrosis score (NFS), were assessed to predict advanced fibrosis (≥S3). The diagnostic performance was assessed using the area under the receiver operating characteristic curve and calibration plots with Brier scores. DeLong test was done to compare the AUROCs across the NITs. **Results:** Of 3157 individuals with concurrent CHB and MASLD who underwent biopsy, 794 complete cases had VCTE and laboratory testing within two weeks of the biopsy. The median age was 38.0 years, with 73.2% (581/794) being male. The median values for the 6 NITs were significantly higher in individuals with advanced fibrosis than those without. While the diagnostic accuracy of Agile3+ (AUROC 0.83 95%CI 0.80-0.87) was significantly higher than FAST, FIB-4, APRI, and NFS (all *PP*=0.090). Calibration curve analysis indicated that Agile 3+ provided the lowest Brier scores (10.8). This was followed by LSM, FAST, NFS, FIB-4, with APRI having the highest Brier score. In different age groups (*P* **Conclusion:** This multicenter cohort study validates the superior diagnostic accuracy of Agile3+ in detecting advanced fibrosis in individuals with concurrent CHB and MASLD. The findings support the broader applicability of the Agile3+ score.

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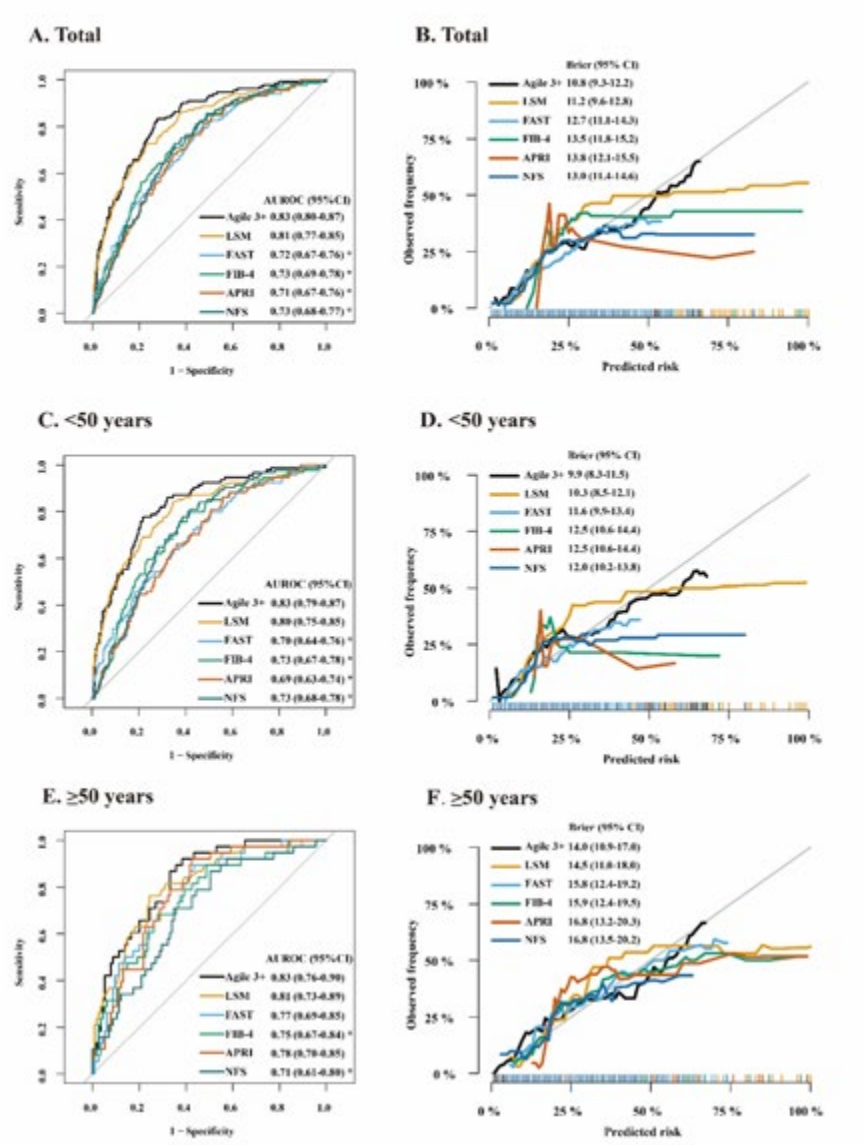
Figure. The diagnostic performance of non-invasive scoring for advanced fibrosis.
***: Indicates a significant difference in AUROC between this score and Agile 3+ as determined by the DeLong test.**



Disclosures: Fajuan Rui: Nothing to Disclose, Yee Hui Yeo: Nothing to Disclose, Wenjing Ni: Nothing to Disclose, Liang Xu: Nothing to Disclose, Qing Xie: Nothing to Disclose, Youwen Tan: Nothing to Disclose, Chao Wu: Nothing to Disclose, Junping Shi: Nothing to Disclose, Jie Li: Nothing to Disclose

2106 | PLIN2 AND RAB14 ARE POTENTIALLY USEFUL BIOMARKERS FOR MONITORING TREATMENT RESPONSE POST BARIATRIC SURGERY

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Background: Non-invasive tests to monitor metabolic dysfunction-associated steatohepatitis (MASH) progression and response to interventions are needed due to scalability issues and the risks associated with

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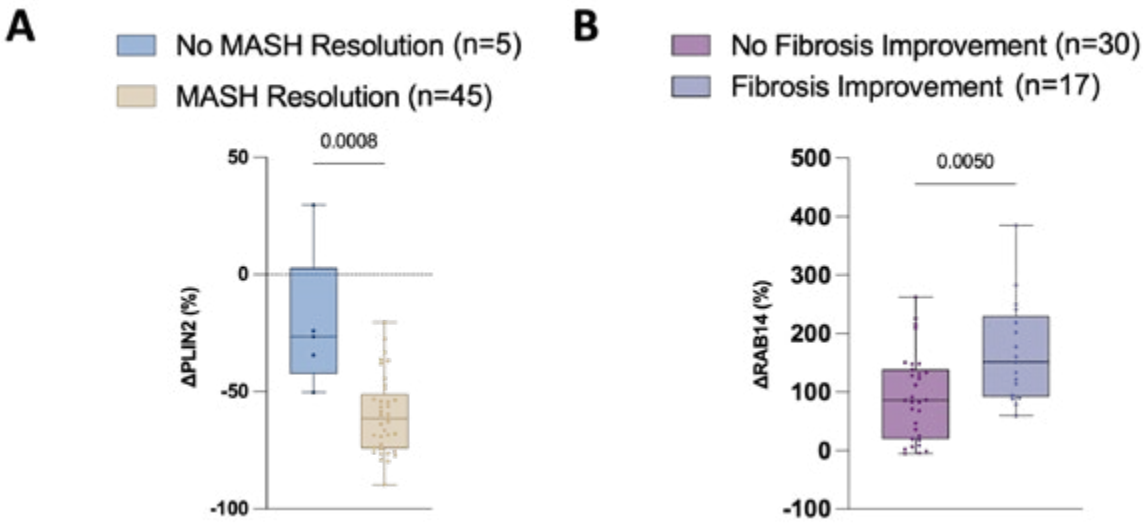
liver biopsy. Recently, HeparDx™, a monocyte-based diagnostic test PLIN2 and RAB14, was designed to identify and diagnose at-risk-MASH and liver fibrosis. The performance of PLIN2 and RAB14 was compared with cytokeratin-18 as assessed by Ella™ or M65 ELISA, to detect MASH resolution and fibrosis improvement following bariatric surgery. **Methods:** Patients enrolled in this study (n=50) were participants from the BRAVES RCT who underwent ultrasound-guided needle liver biopsy at baseline and at 1 year after surgery. MASH resolution was defined as a NAS<3 without worsening of fibrosis. Fibrosis improvement was defined as F values at 1-year follow-up smaller than the values preceding surgery. The performance of PLIN2 and RAB14 vs. liver biopsy was evaluated using AUROC and accuracy, sensitivity, and specificity were calculated based on the Youden threshold. **Results:** Before surgery 35 patients had NAS>=4 while 15 had NAS <4. After surgery, improvement of MASH was observed in 45 patients while no changes in MASH severity occurred in 5. MASH resolution without worsening of fibrosis, was observed in 37 patients. At baseline, stage 1 fibrosis was present in 23 patients, while 23 patients had significant fibrosis and 4 patients had advanced fibrosis. The resolution of significant fibrosis, defined as a postoperative fibrosis stage equal to 0 or 1, was observed in 17 patients while no improvement in fibrosis severity occurred in 30 patients. Worsening of fibrosis occurred only in 3 patients. Patients who experienced MASH resolution showed a significant decrease in PLIN2 expression, while patients with fibrosis improvement displayed an increase in RAB14 expression (Figure 1AB). The model using PLIN2 as a marker of MASH resolution following bariatric surgery resulted in an accuracy of 84% with an AUROC of 83(CI: 67-96), a sensitivity of 91% and a specificity of 76% (Figure 1A). The model including RAB14 for the detection of fibrosis improvement produced an accuracy of 85% with an AUROC of 87(CI: 74-97), a sensitivity of 88% and a specificity of 83%. The diagnostic accuracy of PLIN2 and RAB14, using HeparDx™was superior to CK18. **Conclusion:** With further validation, PLIN2 and RAB14 could serve as non-invasive markers for monitoring the liver's response to bariatric surgery and, possibly, medical interventions, reducing or even eliminating the need for frequent liver biopsies.



Disclosures: Giulia Angelini: Nothing to Disclose, Sara Russo: Nothing to Disclose, Simona Panunzi: Nothing to Disclose, Royce Vincent: Nothing to Disclose, Aldo TRYLESINSKI: Nothing to Disclose, Vlad Ratziu: Nothing to Disclose, Arun Sanyal: Genfit, Akarna, Tiziana, Durect, Inversago, Hemoshear, North: Stock - publicly traded company, Astra Zeneca (60K), Boston Pharmaceutical

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2107 | GLYCEMIC CONTROL PREDICTS ADVANCED FIBROSIS IN PATIENTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD): COMBINED DATA FROM MULTIPLE THERAPEUTIC TRIALS INCLUDING MORE THAN 4,000 LIVER BIOPSY DATA

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Background: While type 2 diabetes mellitus (T2D) is a well-known risk factor for more advanced fibrosis stage (FS) in metabolic dysfunction-associated steatotic liver disease (MASLD) / metabolic dysfunction-associated steatohepatitis (MASH), the predicitivity of degrees of glycemic control for adavanced FS has not been shown. We aimed to assess if glycated hemoglobin (HbA1c) levels, a measure of glycemic control, predict histological severity of MASH. **Methods:** We combined screening data from 10 MASLD/MASH phase 2 trials. We described patients' characteristics (lab values, imaging, histology) according to 4 groups of patients, based on their HbA1c level (1) <5.7 %, 2) 5.7-6.5 %, and, 3) ≥6.5 %). **Results:** 4,046 patients with liver histology and HbA1c data were included. The liver histology results and patients' characteristics in each group are shown in the Table. The proportion of at risk-NASH was significantly higher in patients with higher HbA1c: 46%, 50% and 56% in groups 1, 2 and 3, respectively (p<0.001). Lipid parameters (LDL and triglycerides) were associated with HbA1c level while liver enzymes level were not associated with HbA1c level. In a multivariate analysis, including age, gender, liver enzymes, glycemic control, and lipids, HbA1c was significantly and indepdendently associated with advanced liver fibrosis (p<0.0001). **Conclusion:** HbA1c level as a surrogate of glycemic control appears to be an independent risk factor of MASH and at-risk MASH. Additional studies are needed to further study the independent association of HbA1c with MASH severity.

	HbA1c < 5.7% N=1,081	HbA1c 5.7-6.5% N=1,450	HbA1c ≥ 6.5% N=1,515	p-value
No MASH	54%	45%	27%	<0.001
MASH				0.099
NAS 3	15%	13%	12%	
NAS 4-5	55%	58%	56%	
NAS 6-8	30%	29%	33%	
Fibrosis Stage				<0.001
0	27%	20%	10%	
1	27%	29%	24%	
2	19%	19%	19%	
3-4	27%	32%	47%	
Gender				0.002
Female	55%	59%	62%	
Male	45%	41%	38%	
Ethnicity				0.199
Hispanic/Latino	36%	36%	39%	
Not Hispanic/Latino	64%	64%	61%	
Age	51 (13)	56 (11)	57 (10)	<0.001
LSM	13.9 (7.7)	14.2 (9.2)	15.3 (9.3)	0.002
AST	39 (24)	39 (24)	41 (25)	0.061
ALT	53 (36)	52 (33)	51 (32)	0.091
GGT	59 (66)	59 (63)	71 (77)	<0.001
ALP	82 (28)	83 (29)	85 (29)	0.007
LDL	113 (36)	106 (36)	94 (35)	<0.001
TG	148 (70)	154 (73)	174 (94)	<0.001
Platelets	242 (66)	252 (68)	248 (72)	0.114
FIB-4	1.27 (0.83)	1.30 (0.70)	1.45 (0.77)	<0.001
MRI-PDFF	17 (8)	18 (8)	17 (7)	0.968

Disclosures: Mary Rinella: Consultant relationship with Sagimet; Has not ended; Consultant relationship with Takeda; Has not ended; Consultant relationship with Eli Lilly; Has not ended; Consultant relationship with Novo Nordisk; Has not ended; Consultant relationship with GSK; Has not ended; Consultant relationship with Madrigal; Has not ended; Consultant relationship with Intercept; Has not ended; Consultant relationship with Boehringer Ingelheim; Has not ended; Consultant relationship with 89Bio; Has not ended; Consultant relationship with akero;

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Has not ended; Consultant relationship with Histoindex; Has not ended; Consultant relationship with Cytodyn; Has not ended; Consultant relationship with Echosens; Has not ended, Julie DUBOURG: Poxel SA: Stock - publicly traded company, Vlad Ratziu: Nothing to Disclose, Naim Alkhouri: Madrigal: Grant/Research Support, Madrigal: Speaking and Teaching, Novo Nordisk: Consulting, Novo Nordisk: Grant/Research Support, Gilead: Grant/Research Support, Corcept: Grant/Research Support, Boehringer Ingelheim: Grant/Research Support, Echosens: Speaking and Teaching, Perspectum: Consultant, Cima: Consultant, Fibronostics: Consultant, 89Bio: Grant/Research Support, Inventiva: Grant/Research Support, Merck: Grant/Research Support, Pfizer: Grant/Research Support, Ipsen: Speaking and Teaching, Intercept: Speaking and Teaching, Madrigal: Consulting, Research Funding, Novo Nordisk: Consulting, Research Funding, Inventiva: Research Funding, Boehringer Ingelheim: Consulting, Research Funding, Corcept: Research Funding, Ipsen: Consulting, Research Funding, Gliead: Consulting, Research Funding, Speaking, Perspectum: Consulting, Research Funding, Cima: Advisor, 89Bio: Consulting, Research Funding, Akero: Grant/Research Support, Arbutus: Grant/Research Support, GSK: Grant/Research Support, Regeneron: Grant/Research Support, AstraZeneka: Grant/Research Support, Sophie Jeannin: Nothing to Disclose, Jörn Schattenberg: Consultant relationship with Intercept Pharmaceuticals; 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Has not ended; Consultant relationship with MSD, Northsea Therapeutics, Novartis, Novo Nordisk; Has not ended; Consultant relationship with Pfizer, Roche, Sanofi, and Siemens Healthineers; Has not ended; Grant/Research Support relationship with Boehringer Ingelheim, Siemens Healthcare GmbH; Has ended; Speaking and Teaching relationship with Novo Nordisk, Madrigal Pharmaceuticals,; Has not ended Mazen Noureddin: Principal Investigator for a Drug Study relationship with Viking; Has not ended; Consultant relationship with Eli Lilly; Has not ended; Consultant relationship with AstraZeneca; Has not ended; Consultant relationship with Boston Pharmaceuticals; Has not ended; Principal Investigator for a Drug Study relationship with Genfit; Has not ended; Principal Investigator for a Drug Study relationship with Galectin; Has not ended; Principal Investigator for a Drug Study relationship with Gilead; Has not ended; Principal Investigator for a Drug Study relationship with BMS; Has not ended; Principal Investigator for a Drug Study relationship with BI; 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Principal Investigator for a Drug Study relationship with Corcept; Has not ended; Principal Investigator for a Drug Study relationship with GSK; Has not ended; Principal Investigator for a Drug Study relationship with Conatus; Has not ended, Michael Charlton: Nothing to Disclose, Stephen Harrison: Nothing to Disclose

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2108 | NF-TE SCORE: A NOVEL PREDICTOR FOR LIVER FIBROSIS IN METABOLIC DYSFUNCTION ASSOCIATED STEATOTIC LIVER DISEASE

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Background: Accurate evaluation of liver fibrosis serves as a surrogate to predict liver-related outcomes in patients with Metabolic dysfunction Associated Steatotic Liver Disease(MASLD). We evaluated the diagnostic performance of non-invasive tests(NITs) individually and in combination, to rule-in advanced fibrosis(AF), thereby alleviating the need for liver biopsies. **Methods:** Single center observational study with prospective recruitment of biopsy-proven MASLD patients from 2022-2023. AF was defined as F3-F4 fibrosis. The diagnostic performance of NITs to rule in AF was compared with histological grade of fibrosis(NASH-CRN) individually and in paired combinations. Multiple regression analysis was done to develop a new score to rule in AF. **Results:** 92 patients (53 males) were included in the final analysis. The median age was 41 years. 64(69%) had biopsy-proven AF. Patients with AF were older, male, had T2DM and lower ALT, platelet count, triglyceride and cholesterol than those with mild or no fibrosis($p<0.05$). While using established cut-offs, the non-invasive tests had only moderate diagnostic accuracy - APRI (AUC 0.65), FIB-4 (AUC 0.73), and NFS (AUC 0.75). Using Youden's Index, newer cut-offs were derived to rule in AF - APRI-1.3, NFS-0.39 and FIB4-1.90, which performed better with AUC of 0.90, 0.92 and 0.90 respectively. VCTE had an AUC of 0.91. All the NITs were having a significant negative predictive value and a modest positive predictive value. Among individual NITs, NFS performed better than FIB4 in our cohort. We derived a new score by combining NFS and VCTE, namely the NF-TE, which at a cut-off of 9.7 demonstrated significant diagnostic accuracy (AUC 0.98) and discriminative power ($p<0.05$) to rule in AF. NF-TE had significant superior diagnostic performance when compared to all other individual NITs (De-long test). Bootstrap analysis revealed stable regression coefficients across re-sampled datasets, adjusted $??^2=0.74$ with 95% confidence intervals (0.15 - 0.3) for each coefficient confirming internal validity. **Conclusion:** NITs are point-of-care, reliable strategies to assess hepatic fibrosis in MASLD. This study has identified novel cut-off points for FIB-4, NFS, and APRI with excellent sensitivity and specificity for ruling in advanced fibrosis, which if applied may reduce the "indeterminate" zone of diagnosing fibrosis. The robustness and stability of regression coefficients observed for the new NF-TE score indicate potential clinical utility for predicting AF, thereby avoiding unnecessary liver biopsies and initiating pharmacotherapy and surveillance strategies.

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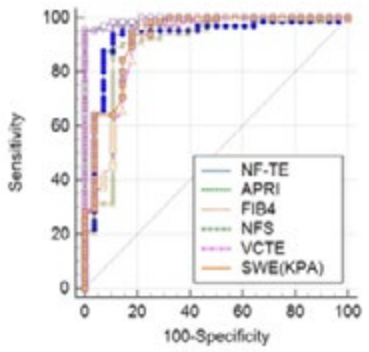
Test	AUROC (95% CI)	Cut Off	YI	Sensitivity	Specificity	PPV	NPV	LR +ve	LR -VE
						Prevalance Rate of 30 %			
APRI	0.90	0.50		96%	46%	43.2%	96.4%	1.8	0.1
		1.30	**0.84**	**93%**	**91%**	**81.6%**	**96.8%**	**10.3**	**0.1**
		1.50		85%	35%	35.9%	84.5%	1.3	0.4
FIB4	0.90	1.10	0.78	90%	88%	76.3%	95.4%	7.5	0.1
		1.90	**0.76**	**85%**	**91%**	**80.2%**	**93.4%**	**9.4**	**0.2**
		2.60		28%	93%	80.0%	75.9%	9.3	0.7
NFS	0.92	**0.39**	**0.87**	**90%**	**94%**	**86.5%**	**95.6%**	**15.0**	**0.1**
		0.70		95%	84%	77.8%	97.5%	5.9	0.1
VCTE	0.91	9.70		90%	84%	70.7%	95.1%	5.6	0.1
		9.30	**0.79**	**95%**	**84%**	**71.8%**	**97.5%**	**5.9**	**0.1**
SWE	0.90	9.80		93%	84%	71.4%	96.6%	5.8	0.1
		10.10	**0.74**	**90%**	**84%**	**70.7%**	**95.1%**	**5.6**	**0.1**

Description	Z Statistics	P value
NF_TE - APRI	1.938	0.042
NF_TE - NFS	1.988	0.035
NF_TE - FIB4	2.201	0.027
NF_TE - VCTE	2.204	0.0275
NF_TE - SWE	2.055	0.0399



Disclosures: Krishnadas Devadas: Nothing to Disclose, Gayathri Shivakumar: Nothing to Disclose

2109 | DIABETES RISK INDEX IN INDIVIDUALS WITH PCOS IS ASSOCIATED METABOLIC DYSFUNCTION ASSOCIATED STEATOTIC LIVER DISEASE (MASLD), CLINICALLY SIGNIFICANT FIBROSIS AND ADVANCED FIBROSIS

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[1]Indiana University, [2]Richard L. Roudebush VA Medical Center

Background: Polycystic Ovary Syndrome (PCOS) is one of the most common endocrine disorders in biologically female reproductive age individuals. We conducted a prospective study to investigate the metabolic indices associated with Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD), clinically significant fibrosis (CSF) and advanced fibrosis (AF) in individuals with PCOS. **Methods:** All eligible, consecutive individuals with PCOS were enrolled in this prospective cross-sectional study. PCOS was diagnosed using the Rotterdam Criteria after excluding competing etiologies. Liver Stiffness Measurement (LSM) via vibration controlled transient elastography were used to determine CSF (LSM ≥ 8 kPa) and AF (≥ 12 kPa). Nuclear Magnetic Resonance (NMR) lipoprofile of serum was performed using LabCorp NMR profile platform and the derived lipoprotein and amino acid values were used to calculate multi-marker indices- metabolic vulnerability index, Lipoprotein insulin resistance (LPIR) index, inflammation vulnerability index and diabetes risk index was performed. Univariate and multivariable logistic regression analyses (all adjusted for age, race and ethnicity) was used to identify factors independently associated with MASLD and CSF. **Results:** There were 258 individuals with PCOS, (71% White; 15% Black, 10% Hispanic, mean age =31 ± 6.3 years; mean BMI =27 ± 5 kg/m^2) of whom 32% had MASLD. LPIR Index was associated with MASLD (OR (95% CI) = 1.03(1.02-1.05)), CSF (OR (95% CI) = 1.04(1.02-1.06)), and AF (OR (95% CI) = 1.03(1.01-1.06)), p for all < 0.005). Diabetes Risk Index was associated with MASLD (OR

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(95% CI) = 1.04(1.03-1.06)), CSF (1.05(1.01-1.08), and AF (OR (95% CI) = 1.04(1.01-1.07), p for all < 0.001). Inflammation vulnerability indexwas associated with MASLD (OR (95% CI) = 1.02(1.00-1.05)), CSF (1.05(1.02-1.09), and AF (OR (95% CI) = 1.05(1.01-1.10), (p for all <0.05). Metabolic vulnerability index was associated with CSF (OR (95% CI) = 1.06(1.01-1.10), p = 0.007), and AF (OR (95% CI) = 1.06(1.00-1.12), p for all = 0.02), but not MASLD (OR (95% CI) = 1.00(0.97-1.03), p = 0.82). However, when adjusted for all indices, diabetes risk index alone was associated with both MASLD (1.04(1.01-1.07), p=0.007), CSF (1.05(1.01-1.08), p=0.004) and AF (1.04(1.00-1.08), p=0.02), independent of other indices. **Conclusion:** In a well characterized PCOS cohort, Diabetes risk index was associated with MASLD, CSF and AF, independent of other metabolic indices.

Table 1: Multivariable Logistic Regression Analysis of the Association of Metabolic Risk Indices with Metabolic Dysfunction Associated Steatotic Liver Disease (MASLD), Clinically Significant Fibrosis and Advanced Fibrosis in Individuals with PCOS

NMR Variables	MASLD	CSF	Advanced Fibrosis
Lipoprotein Insulin Resistance Index	1.00(0.97-1.03)	1.00(0.97-1.03)	1.00(0.96-1.04)
Diabetes risk Index	1.04(1.01-1.07)*	1.05(1.01-1.08)*	1.04(1.00-1.08)*
Inflammation vulnerability Index	1.04(0.96-1.12)	0.96(0.88-1.05)	0.95(0.85-1.06)
Metabolic vulnerability Index	0.96(0.87-1.06)	1.11(0.99-1.25)	1.13(0.98-1.13)

*p<0.05

Disclosures: Niharika Samala: Novo Nordisk: Consultant, Sreemala Murthy: Nothing to Disclose, Suneetha Naidu: Nothing to Disclose, Eduardo Vilar-Gomez: Nothing to Disclose, Naga Chalasani: Nothing to Disclose

2110 | CORRELATION OF HEPATOCYTE BALLOONING WITH FIBROSIS AND REPAIR IN MAFLD - A NOVEL EXPANDED HISTOLOGICAL SCORE AND SONIC HEDGEHOG IHC BASED STUDY

Abhilasha Yadav[1] Khushboo Agrawal[1] Ashily Koshy[1] Neha Agrawal[1] Chhagan Bihari[1] Gayatri Ramakrishna[1] Rakhi Maiwall[1] GURESH KUMAR[1] Archana Rastogi[1]

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Background: Ballooned hepatocytes in MAFLD have strong correlation with fibrosis, due to ER stress mediated production of SHh that activates fibrosis and HPC response. Due to variable definitions and scoring systems, improved methods needed to assess its relation with fibrosis and repair. We aimed to assess ballooning by novel expanded histological grade scale, CK8/18 and SHh and their correlation with fibrosis, hepatic repair. **Methods:** Retrospective study of 80 histologically confirmed MAFLD cases. HE,MT,PS stains, IHC markers (α-SMA-HSC, CK7-HPC, SHh, CK8/18-balooning) assessed. Semi-quantitative ballooning score of 1-5 calculated using 10x as % of the total surface area. It was based on the size and extent, included both classical (large, ≥2 times the size of normal hepatocyte) and non-classical ballooning. Small vs large ballooned and few vs many ballooned hepatocytes were compared with the fibrosis, activity, repair parameters. Pearson chi square test performed, p value <0.05 considered significant. **Results:** Demographic and laboratory parameters included: mean age (49 yrs), M:F 5:3, S. ALT (74 IU/L), BMI (27.5kg/m^2), FBS (114mg/dL), HbA1c (6.5), TGs (180.4mg/dL).
Large ballooned hepatocytes and 5-point scores of ballooning showed significant correlation with advanced fibrosis (p=0.04; p=0.008), higher HSCs activation (p=0.23; p=0.03), higher expression of CK8/18 (p<0.001; p=0.04), higher HPCs activation (p=0.008; p=0.02),portal inflammation (p=0.04; p=0.5), and higher NAS-CRN scores (p=0.04; p=0.03) respectively.Extent correlated with CK8/18 (p=0.006), high NAS-CRN (p=0.05) but not with the advanced fibrosis (p=0.38), repair markers (p=0.5). CK8/18 expression found superior to routine HE for detection of non-classical ballooned hepatocytes. Significant association of CK8/18 with advanced fibrosis(p=0.04), high NAS-CRN (p=0.008), HPCs(p=0.001), and HSCs activation(p=0.04). SHh expression showed significant association with advanced fibrosis (p=0.016), HSCs activation(p=0.03), portal inflammation (p=0.09). **Conclusion:** Ballooning and SHh pathway play an important role in fibrosis, HPC, disease activity. Size, not the proportion, appears the main driver. Novel expanded “ballooning”criteria provides better picture of hepatocyte degeneration,confirms the importance of hepatocyte size in pathogenesis of MAFLD.

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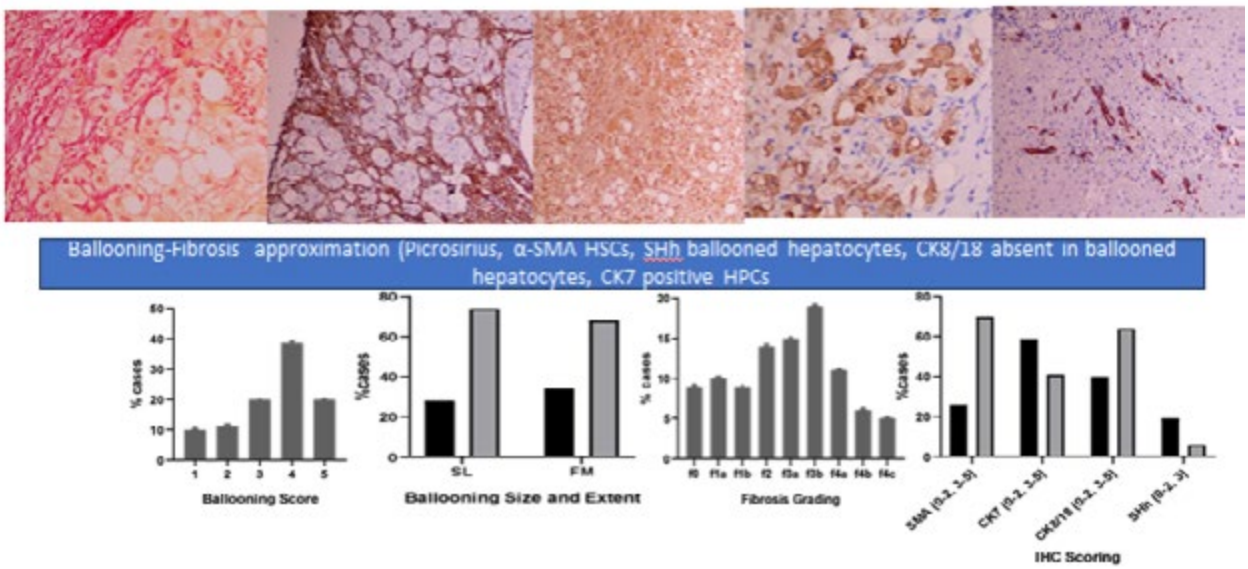

Disclosures: Abhilasha Yadav: Nothing to Disclose, Khushboo Agrawal: Nothing to Disclose, Ashily Koshy: Nothing to Disclose, Neha Agrawal: Nothing to Disclose, Chhagan Bihari: Nothing to Disclose, Gayatri Ramakrishna: Nothing to Disclose, Rakhi Maiwall: Nothing to Disclose, GURESH KUMAR: Nothing to Disclose, Archana Rastogi: Nothing to Disclose

2111 | IDENTIFICATION OF NOVEL CIRCULATING EXOSOMAL MIRNAS AND MRNA NETWORKS CONTRIBUTING TO THE PROGRESSION FROM MASH TO HCC

Jing Zeng[1] Derrick Zhao[1] Grayson Way[1] Hongkun Lu[1] Yun-Ling Tai[1] Sayed Obaidullah Aseem[1] Nan Wu[1] Xuan Wang[1] Emily Gurley[1] Arun Sanyal[1] Phillip Hylemon[1] Jiangao Fan[2] Huiping Zhou[1]

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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is the fastest-rising cause of end-stage liver disease requiring liver transplantation. Exosomes carry a variety of bioactive molecules, including miRNAs (miRs), lipids, and proteins. Dysregulation of miRs is closely related to MASLD progression from Metabolic dysfunction-associated steatohepatitis (MASH) to hepatocellular carcinoma (HCC). This study aimed to identify the potential circulating exosomal miRs (CE-miRs) contributing to the progression of MASH to HCC. **Methods:** Total RNA was isolated from the liver tissues of gender and age-matched MASH patients and healthy controls (HCs). Heptic miRs (H-miRs) were profiled using NanoString nCounter. GSE33857 and GSE82303 datasets were downloaded from the GEO database and analyzed using R to identify the differentially expressed CE-miRs (DE-CE-miRs) in MASH patients. In a separate study, the DIAMOND mouse model was used. Male mice (21-24 weeks old) were fed a Western diet and Surgar water (WDSW) or chow diet ad libitum for 1 year. H-miRs were profiled using Nanotring nCounter. TargetScan and mirnet2.0 were used to identify the potential target genes. Protein-protein interaction (PPI) was constructed based on the STRING database. Hub genes were visualized using Cytoscape software. Human HCC patient data were downloaded from the Cancer Genome Atlas (TCGA). **Results:** Bioinformatic analysis of the GSE33857 dataset (n=7-12) identified 85 DE-CE-miRs in MASH patients. Our NanoString hepatic miR profiling of human MASH patients identified 130 differentially expressed H-miRs (DE-H-miRs) compared to HCs. Interestingly, among the upregulated DE-H-miRs, 30 DE-CE-miRs were also upregulated in MASH patients. In the mouse MASH-HCC model, we identified 123 DE-H-miRs in HCC compared to corresponding controls. Among the DE-H-miRs, the miRs, including miR-140-5p, let-7i, and miR-221-3p, were also upregulated in the serum exosomes of HCC patients in the GSE82303 dataset compared to HC. PPI network analysis identified the top 50 hug genes. Among these, ten genes were downregulated in TCGA HCC data. Moreover, these DE-miRs are associated with multiple signaling pathways related to cancer, including apoptosis, stress response, and angiogenesis. **Conclusion:** This study identified potential DE-miRs in the liver and serum exosomes, which may contribute to MASH-HCC disease progression. These CE-miRs can be used as diagnostic and prognostic markers for MASH-HCC.

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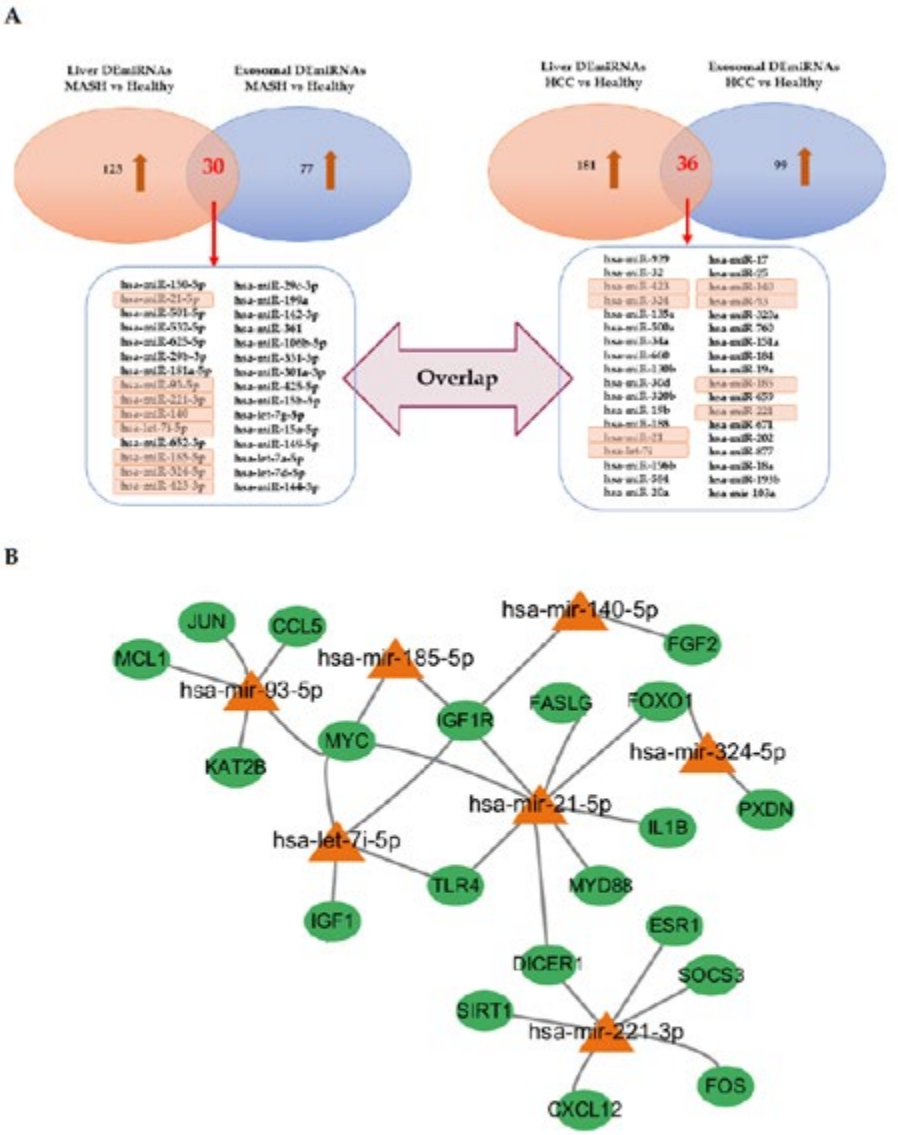

Fig: Novel Circulating Exosomal miRNAs and mRNA Networks Contributing to the Progression from MASH to HCC. (A) Intersection of DE-miRNAs in Liver and Circulating Exosome: This segment depicts the overlap of differentially expressed (DE) miRNAs identified in both liver tissue and circulating exosomes. The intersection highlights miRNAs dysregulated in both compartments during the transition from MASH to HCC. (B) Formation of a Network Contributing to the Progression from MASH to HCC Based on Overlapping miRNAs and Top 50 Hub Genes: This section indicates the construction of a network based on the shared miRNAs and the top 50 hub genes. These hub genes likely play pivotal roles in the progression from MASH to HCC. Abbreviations: MASH - Metabolic dysfunction-associated steatohepatitis; HCC - Hepatocellular carcinoma.

Disclosures: Jing Zeng: Nothing to Disclose, Derrick Zhao: Nothing to Disclose, Grayson Way: Nothing to Disclose, Hongkun Lu: Nothing to Disclose, Yun-Ling Tai: Nothing to Disclose, Sayed Obaidullah Aseem: Galmed Pharmaceuticals: Grant/Research Support, Nan Wu: Nothing to Disclose, Xuan Wang: Nothing to Disclose, Emily Gurley: Nothing to Disclose, Arun Sanyal: Genfit, Akarna, Tiziana, Durect, Inversago, Hemoshear, North: Stock - publicly traded company, Astra Zeneca (60K), Boston Pharmaceutical (<5K), Myovent (<5K),: Consultant, Variant (<5K), Cascade (<5K), Northsea (<5K): Consultant, Gilead, Salix, Tobira, Bristol Myers, Shire,. Intercept,: Institution has received grants from above companies, Merck, Astra Zenca, Mallinckrodt, Novartis: Institution has received grants from above companies, UpToDate, Elseiver: Royalties or patent beneficiary, Sanyal Bio: Employee, Phillip Hylemon: Nothing to Disclose, Jiangao Fan: Nothing to Disclose, Huiping Zhou: Nothing to Disclose

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2112 | THE DEGREE OF ADIPOSITY ENHANCES THE EFFECT OF THE *PNPLA3* RS738409 ON HEPATIC STEATOSIS IN PREPUBERTAL LATINX CHILDREN

Cristian Sanchez Torres[1] Ana Ramirez[1] Scott Gillespie[1] Helaina Huneault[1] Jack Knight-Scott[2] Adina Alazraki[3] Geetika Khanna[3] Claudia Yaranga[1] Nicola Santoro[4] Liliana Aguayo[1] Shasha Bai[1] Jean Welsh[1] Miriam Vos[3]

[1]Emory University, [2]Children's Healthcare of Atlanta, [3]Emory University, Children's Healthcare of Atlanta, [4]Yale University

Background: *PNPLA3* rs738409 is associated with hepatic steatosis (HS) and worst liver-related outcomes. In adults adiposity significantly amplifies the effect of *PNPLA3* variants on HS; however, the synergism between *PNPLA3* polymorphism and adiposity on HS in younger population needs to be tested. *PNPLA3* rs738409 GG allele is associated with HS in Latinx children. **Methods:** Here we present a preliminary, secondary analysis of data from an ongoing clinical trial (NCT05292352) enrolling Latinx children aged 6-9 years. At baseline, liver fat quantification was completed using MRI-PDFF, and DNA was genotyped for rs738409. All body measurements were performed twice by trained staff, and body mass index (BMI), BMI percentile (BMIp), and z-scores were calculated using pediatric CDC criteria. Univariable and multivariable logistic regression analyses were conducted to assess the association between *PNPLA3* G-allele (CC vs. CG vs. GG) and BMI z-score on HS (defined as hepatic fat ≥5%) after controlling for covariates. Interaction between adiposity and genotype on HS was also tested. **Results:** At baseline, 98 out of 122 (80 %) enrolled children had *PNPLA3* rs738409 genotype with the following proportions: 20% CC, 50% CG and 30% GG. Six-two % of subjects were Mexican origin and had approximately equal genotyped groups (60%, 62.5% and 63.3%). Groups did not differ significantly by age or gender. The association of the GG polymorphism with HS increased with BMIp Among children with BMIp less than 85th, the median of HS between the three groups was less than 5% with higher values among carriers of the GG genotype as compared with CC genotype (2.80% vs. 1.50%). This difference was enhanced among children with a BMIp >95 where the median of HS of the GG carriers was more than double the percentage of the CC carriers, (8.10% vs. 3.40%). After controlling for sex, age, and BMI z-score, *PNPLA3* GG carriers were nearly 20 times more likely to have HS than CC (Odds Ratio [OR] 19.93, p=0.003) and CG carriers nearly 6 times more likely than CC carriers (OR 5.61, p=0.069). A multivariable model that included *PNPLA3* polymorphism, BMI z-score, and ALT levels demonstrated an Area Underthe Curve (AUC) of 0.91. The interaction between *PNPLA3* and BMI z-score did not reach statistical significance (p=0.13) **Conclusion:** The association of the *PNPLA3* rs738409 variants with risk of HS were stronger among children with obesity. Our findings suggest a potential need for patient oriented, precision intervention in genetically predisposed children. Further analysis to test the interaction between *PNPLA3*, BMI and other variables in the final sample will be performed. Analysis in larger and more racially and ethnically diverse population will be needed to confirm and understand the generalizability of these findings.

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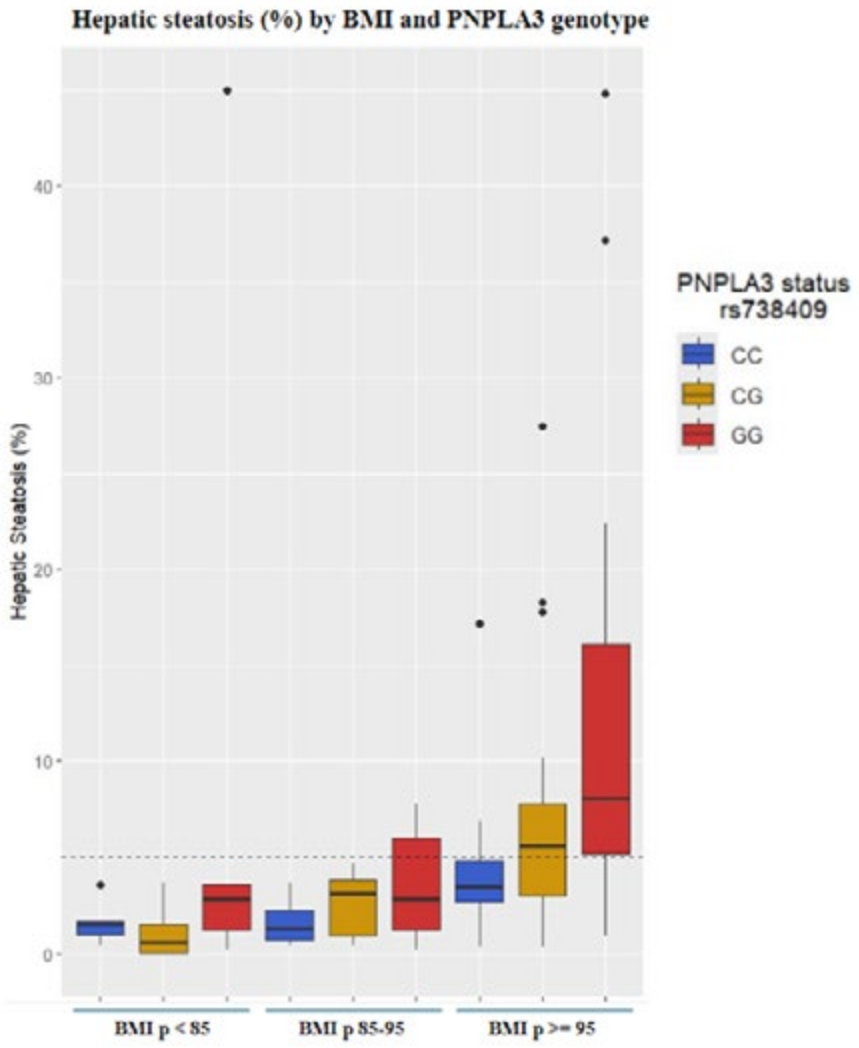

Disclosures: Cristian Sanchez Torres: Nothing to Disclose, Ana Ramirez: Nothing to Disclose, Scott Gillespie: Nothing to Disclose, Helaina Huneault: Nothing to Disclose, Jack Knight-Scott: Nothing to Disclose, Adina Alazraki: Nothing to Disclose, Geetika Khanna: Nothing to Disclose, Claudia Yaranga: Nothing to Disclose, Nicola Santoro: Nothing to Disclose, Liliana Aguayo: Nothing to Disclose, Shasha Bai: Nothing to Disclose, Jean Welsh: Nothing to Disclose, Miriam Vos: Nothing to Disclose

2113 | EFFICACY OF NON INVASIVE TESTS (NITS) IN DIFFERENTIATING METABOLIC DYSFUNCTION-ASSOCIATED FATTY LIVER DISEASE (MAFLD) AND METABOLIC-ALCOHOL ASSOCIATED LIVER DISEASE(METALD)-META-ALD STUDY

Harsh Tevethia[1] *Guresh Kumar*[2] *Shiv Kumar Sarin*[2]

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Background: MAFLD represents a global pandemic for liver diseases with a prevalence of 22% to 51% worldwide. MetALD is a term given to explain a combination of MAFLD and Alcohol Associated Liver Disease (ALD). It is however,difficult to distinguish MAFLD and ALD from MetALD. Due to recent changes in nomenclature and definition, comparative data is not available. The aim of the study was to evaluate the efficacy of NITs in differentiating MAFLD from MetALD population. **Methods:** Patients meeting criteria for MetALD (Group 1), MAFLD(Group 2) as well as Non-MAFLD NAFLD (Group 3) were prospectively enrolled between April 2019 to April 2024 at ILBS New Delhi. Baseline data including liver Stiffness (LS), spleen stiffness (SS), liver biopsy findings as well as demographic data were included. Associations were determined using logistic regression

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analysis. The primary objective of the study was to assess the role of NITs in discriminating MetALD from other study population. **Results:** Altogether 1646 patients were analysed with mean age 46.2±9.2 years, LS 19.71 ± 15.21kPa SS 50.02±11.23kPa with male predominance (53%); 373(22.6%) patients were in Group 1,762(46.2%) in group 2 and 511(31.2%) in group 3 respectively. Lasso regression analysis showed LS, SS,Gamma-glutamyl transferase (GGT), total cholesterol, high density lipoprotein (HDL) cholesterol levels were significant (p<0.001). On comparing MetALD with other groups,using multinomial logistic regression significant variables included LS(OR-1.07 95%C.I-1.06-1.81), SS(OR-1.13 95%C.I-1.11-1.16), GGT (OR-1.00 95%C.I-1.004-1.006),total cholesterol(OR-0.97 95%C.I-0.96-0.97), HDL cholesterol(O.R-0.91 95% C.I-0.89-0.92),FIB-4 score(O.R-1.31 95%C.I-1.25-1.38). The AUROC for SS was 86.8(95%C.I-83.3-89.9) as compared to FIB-4 which was 82.8 (95%C.I-79.9-85.6) and for LS 77.1(95%C.I-73.5-80.8). MetALD was predicted using LS >18 kPa (sensitivity -78% specificity -81), SS >48kPa (sensitivity-89%,specificity -94%), GGT levels>50 IU/L(sensitivity-76%,specificity-74%),HDL <33 IU/L(sensitivity-75 %,specificity-76%), total cholesterol levels <144IU/L(sensitivity-79%,specificity-78%). **Conclusion:** NITs are useful in the classification of identifying MetALD cases from MAFLD. Measurement of splenic stiffness represents a novel approach in distinguishing various disease subsets as well as in MetALD.

Disclosures: Harsh Tevethia: Nothing to Disclose, Guresh Kumar: Nothing to Disclose, Shiv Kumar Sarin: Nothing to Disclose

2114 | EVALUATING IMPACT OF WEIGHT CHANGES ON HISTOLOGICAL PATTERNS OF LIVER FIBROSIS IN MASH: IMPLICATIONS FOR SPATIAL INTERROGATION

Nicholas Syn[1] EN YING TAN[2] Joo Wei Ethan Quek[3] Daniel Huang[4] Kutbuddin Akbary[5] Yayun Ren[5] Jonathan Lee[6] Cheng Han Ng[6] Aileen Wee[7] Shook Ting Gwyneth Soon[6] Asim Shabbir[8] Nur Halisah Jumat[6] Yock Young Dan[9] Mark Muthiah[9]

[1]Yong Loo Lin School of Medicine, National University of Singapore, Singapore, [2]Department of Medicine, National University Hospital, Singapore, [3]National University of Singapore, Singapore, [4]National University Hospital, Singapore, [5]HistoIndex Pte. Ltd, Singapore, Singapore, [6]National University of Singapore, [7]National University Hospital, [8]Department of Surgery, National University of Singapore, Singapore, [9]Department of Medicine, National University Hospital (NUH), Singapore

Background: The mechanisms by which weight loss influences hepatic fibrosis and the role of pre-surgery weight dynamics in predicting fibrosis outcomes are not well understood. This study aims to evaluate the correlation between pre-surgery weight changes and patterns of fibrosis changes using Second Harmonic Generation/Two Photon Excitation (SHG/TPE) imaging with AI analysis-based collagen parameters (qF) in liver biopsies of bariatric surgery patients with MASH. **Methods:** Sixty-nine patients scheduled for bariatric surgery were evaluated for weight changes over six months preceding surgery when they were placed on a Very Low Caloric Diet (VLCD), and were categorized as either weight loss (n=60) or weight gain (n=8). Relative weight changes were assessed as percentage changes from baseline. Unstained core liver biopsies, obtained at time of surgery, were analysed, and quantified using qF. Spearman correlation analyses were conducted between relative weight changes and qF-derived collagen morphological parameters, with results presented as r-values. **Results:** Weight loss correlated with significant alterations in overall qF parameters, particularly in regions exhibiting “chicken wire” fibrosis (r = -0.4), pericentral region (r = -0.42), and overall hepatic region (r = -0.49). Weaker correlations were observed in zone 2 parameters (r = -0.32). Conversely, weight gain demonstrated positive correlations with qF parameters in the same regions. These NASH-CRN zonal parameters were selected due to their high r-values, highlighting a strong correlation between weight change and the extent of overall and chicken wire fibrosis. **Conclusion:** This study reveals that relative weight loss prior to bariatric surgery is strongly associated with reductions in overall hepatic fibrosis, especially chicken wire fibrosis. These highlight the spatial importance of zones of “chicken wire” fibrosis in disease regression with weight loss targeted therapies. This would further enhance our understanding of responders and non-responders and open up avenues for precision medicine in MASH.

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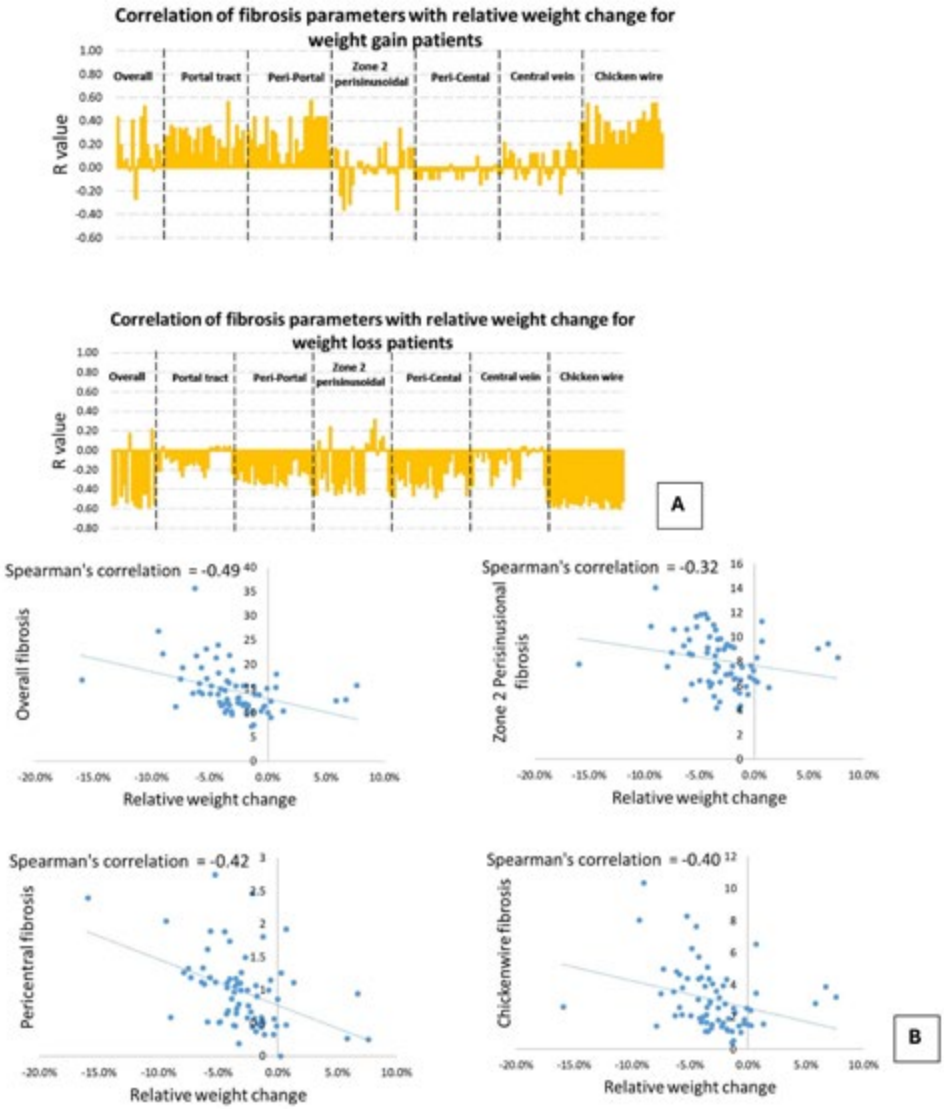

Figure 1: Demonstrates the correlations between qF parameters, based on zonal classification as per the NASH-CRN system, with pre-surgery weight loss and weight gain. **[A]** Shows the correlation of qF-based parameters with weight loss and weight gain, categorized according to the NASH-CRN zonal system. **[B]** Presents scatter plots and correlations of relative weight change with individual zonal qF parameters, highlighting those with high r-values.

Disclosures: Nicholas Syn: Nothing to Disclose, EN YING TAN: Nothing to Disclose, Joo Wei Ethan Quek: Nothing to Disclose, Daniel Huang: Nothing to Disclose, Kutbuddin Akbary: HistoIndex Pte Ltd: Employee, Yayun Ren: HistoIndex Pte Ltd: Employee, Jonathan Lee: Nothing to Disclose, Cheng Han Ng: Nothing to Disclose, Aileen Wee: Nothing to Disclose, Shook Ting Gwyneth Soon: Nothing to Disclose, Asim Shabbir: Nothing to Disclose, Nur Halisah Jumat: Nothing to Disclose, Yock Young Dan: Nothing to Disclose, Mark Muthiah: Lerna Bio: Stock – privately held company, Olympus: Speaking and Teaching, Boston Scientific: Speaking and Teaching, Novo Nordisk: Grant/Research Support, Echosens: Grant/Research Support, Gilead: Advisor

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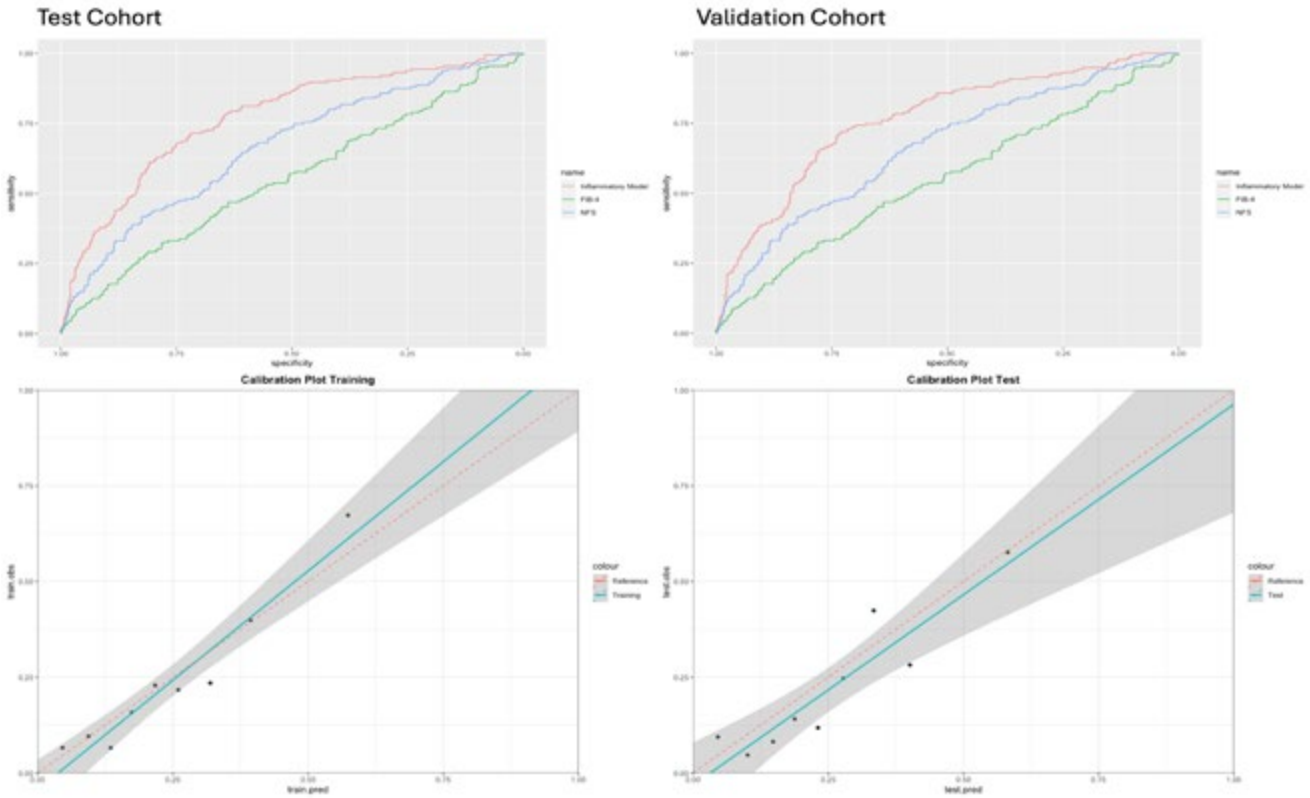
2115 | MODEL FOR ADVANCED FIBROSIS IN MASLD-INFORMED BY INFLAMMATION (MAM-I): A NOVEL MODEL TO PREDICT ADAVANCED FIBROSIS IN PATIENTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD)

David Kim[1] *Don Rockey*[2] *Paul Gaglio*[1] *Ahmed Al-Khazraji*[1] *Kaveh Hajifathalian*[1]

[1]*Rutgers New Jersey Medical School,* [2]*Montefiore Medical Center*

Background: Ferritin and C-reactive protein (CRP) are acute phase reactants that can serve as markers of overall inflammation. In this study, we investigated the association between serum ferritin and CRP levels and liver fibrosis in patients with metabolic dysfunction-associated steatotic liver disease (MASLD) and developed a prediction model to enhance the detection of advanced fibrosis. **Methods:** Ferritin and C-reactive protein (CRP) are acute phase reactants that can serve as markers of overall inflammation. In this study, we investigated the association between serum ferritin and CRP levels and liver fibrosis in patients with metabolic dysfunction-associated steatotic liver disease (MASLD) and developed a prediction model to enhance the detection of advanced fibrosis. **Results:** Among the 2,508 participants with MASLD, 18.0% had advanced fibrosis. In the training cohort, our model (AUC 0.771; 95% CI, 0.743–0.799) was superior in predicting advanced fibrosis compared to FIB-4 (AUC 0.589; 95% CI, 0.555–0.623; *P*<0.001) and NFS (AUC 0.706; 95% CI, 0.675–0.737; *P*<0.001). Similarly, in the validation cohort, our model demonstrated superior ability in predicting advanced fibrosis compared to FIB-4 (AUC 0.552; 95% CI, 0.503–0.602; *P*<0.001) and NFS (AUC 0.665; 95% CI, 0.620–0.711; *P*<0.001). **Conclusion:** We proposed a Model for Advanced fibrosis in MASLD-Informed by Inflammation (MAM-I) based on inflammatory markers, which showed significantly superior performance when compared to currently used models.



Disclosures: David Kim: Nothing to Disclose, Don Rockey: Grant/Research Support relationship with Versantis; Has not ended; Grant/Research Support relationship with AstraZeneca; Has not ended; Grant/Research Support relationship with Ipsen; Has not ended; Grant/Research Support relationship with Boehringer Ingelheim; Has not ended; Consultant relationship with WL Gore and Associates; Has not ended; Grant/Research Support relationship with Gilead; Has not ended; Grant/Research Support relationship with Durect; Has not ended; Consultant relationship with BD Medical; Has not ended; Consultant relationship with Cook Medical; Has not ended; Grant/Research Support relationship with Intercept; Has not ended; Grant/Research Support relationship

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2116 | DIFFERENTIAL PATTERNS OF LIVER AND SPLEEN STIFFNESS IN CHRONIC VIRAL HEPATITIS AND METABOLIC ASSOCIATED STEATOTIC LIVER DISEASE

Giovanni Petralli[1] Antonio Salvati[2] Simone Cappelli[3] Ranka Vukotic[2] Andrea Pinna[2] Francesco Damone[2] Veronica Romagnoli[2] Piero Colombatto[2] Ferruccio Bonino[4] Maurizia Brunetto[3]

[1]Dept of Surgical Medical, Molecular and Critical Area Pathology, University of Pisa; Hepatology Unit, [2]Hepatology Unit, University Hospital of Pisa, [3]Department of Clinical and Experimental Medicine, University of Pisa; Hepatology Unit, [4]Institute of Biostructure and Bioimaging, National Research Council

Background: Routine liver stiffness measure (LSM) is a reliable tool in discriminating the stage of liver fibrosis in chronic viral liver diseases (CVLD) and in metabolic dysfunction-associated steatotic liver disease (MASLD). In addition, LSM and spleen stiffness measures (SSM) can be used to predict clinically significant portal hypertension (CSPH). We analyzed a single center cohort of CVLD and MASLD cirrhotics in order to investigate their differential added values in clinical practice. **Methods:** We studied 120 patients (pts) with histologic and/or ultrasound scan (US) signs of liver cirrhosis, 81 (67.5%) due to CVLD of different etiology [30 (25.0%) NUC-treated HBV infections, 27 (22.5%) HDV infections (15 Bulevirtide-treated), 24 (20.0%) previous HCV infections treated with DAAs)] and 39 (32.5%) with MASLD followed up at the Hepatology Unit of the Pisa University Hospital. Physical examination, US, liver (LSM) and spleen (SSM) stiffness measures (FibroScan®, Echosens, France) and blood tests were performed on the same day. **Results:** In Table 1 are reported the main demographic, clinical, biochemical characteristics and the results of US, LSM and SSM measures in the pts enrolled compared by etiology. HBV pts showed significantly lower LSM than MASLD pts [9.7 (5.6-15.8) vs 18.1 (13.2-33.2) kPa, p=0.0003), whereas SSM was not significantly different [34.0 (25.4-52.7) vs 38.4 (25.1-49.3) kPa, p=0.8282]. The SSM/LSM ratio decreased significantly and progressively from HBV to MASLD pts (Table 1). The LSM was significantly lower in the whole group of 81 CVLD pts, as compared with 39 MASLD pts [11.7 (7.6-20.8) vs 18.1 (13.2-33.2) kPa, p=0.0004]. Analyzing only CSPH (Baveno 7 or varices) pts, LSM was lower in the 33 CVLD pts without metabolic co-factors, as compared to 27 MASLD pts [18.0 (10.0-25.2) vs 21.5 (12.8-41.3) kPa, p=0.0454]. SSM never showed significant differences in the above comparisons. LSM was higher but not significantly in the 38 pts treated with betablockers [16.8 (11.8-24.5) vs 12.8 (8.3-20.5) kPa, p=0.1157], nor was SSM [39.8 (24.9-57.2) vs 32.3 (24.3-46.4) kPa, p=0.2702]. In CVLD, but not in MASLD pts, SSM correlated with CSPH (r=0.273, p=0.006) with AUROC 0.694, 53% sensitivity and 84% specificity (cut-off SSM=38.4 kPa). **Conclusion:** The control of liver disease activity influences the lower LSM of CVLD patients with cirrhosis, also in patients with CSPH. SSM was comparable in CVLD and MASLD, but predicts CSPH with 84% specificity in CVLD only (cut-off 38.4 kPa).

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Demographic, clinical, biochemical and instrumental characteristics and whole cohort

		HBV (n=30)	HDV (n=27)	HCV (n=24)	MASLD (n=39)	P
Age	years	65.4 (54.3-75.0) **b**	48.1 (41.7-61.6) **a, c, d**	65.5 (57.4-78.3) **b**	66.0 (58.6-71.09 **b**	**<0.0001**
Gender	F	1 (3)	12 (44)	10 (42)	14 (36)	**0.0020**
BMI	Kg/m^2	25.3 (23.9-28.0) **d**	25.8 (22.7-28.1) **d**	27.3 (24.9-30.9) **d**	27.8 (26.8-32.2) **a, b, c**	**0.0003**
Child-Pugh		5 (max 10)	5 (max 8)	5 (max 7)	5 (max 8)	**ns**
LSM	dB/m	9.7 (5.6-15.8) **d**	13.3 (8.1-25.2)	14.1 (8.9-24.7)	18.1 (13.2-33.2) **a**	**0.0003**
CAP	dB/m	225 (196-270) **d**	206 (191-221) **d**	228 (198-263) **d**	296 (252-329) **a, b, c**	**<0.0001**
SSM	kPa	34.0 (25.1-52.7)	33.3 (23.1-64.4)	31.9 (23.7-38.8)	38.4 (25.1-49.3)	ns
SSM/LSM ratio		3.55 (2.64-5.88) **b, c, d**	2.55 (1.93-3.54) **a**	1.91 (1.30-2.99) **a**	1.55 (1.11-2.53) **a, b**	**<0.0001**
Spleen LA	cm	12.2 (10.9-14.0)	13.1 (11.0-15.7)	11.6 (9.5-13.0) **d**	13.3 (11.7-15.6) **c**	**0.0184**
Portal Caliper	mm	12 (11-13)	12 (10-13)	12 (11-13)	12 (10-14)	ns
Varices	No F1 F2 F3 EBL	6 3 \ 1 1	7 7 3 \ \	2 5 \ \ \	14 2 2 1 \	ns
AST	*(U/L)*	25 (20-34)	33 (23-43)	27 (19-34)	31 (24-46)	**0.0151**
ALT	*(U/L)*	18 (14-23) **b, d**	28 (21-44) **a**	18 (15-34)	31 (18-45) **a**	**0.0019**
gGT	*(U/L)*	24 (15-30) **d**	29 (20-79)	37 (17-50)	72 (31-188) **a**	**0.0005**
ALP	*(U/L)*	76 (65-93)	89 (70-106)	84 (66-108)	79 (67-105)	ns
Albumin	*(g/dl)*	4.7 (4.1-5.0) **b, d**	4.1 (4.0-4.4) **a**	4.4 (4.2-4.6)	4.2 (3.7-4.6) **a**	**0.0053**
Bilirubin	*(mg/dl)*	0.72 (0.52-1.12)	0.73 (0.60-1.17)	0.56 (0.45-0.93)	0.72 (0.46-0.99)	ns
PT	*(%)*	88 (81-97)	85 (74-94)	86 (80-100)	87 (75-93)	ns
PLTs	*x 10^3 /cc*	142 (96-181)	106 (79-188)	154 (116-197)	149 (126-200)	ns
PCHE	*(U/L)*	7205 (6093-8518)	6565 (4440-7388)	6745 (5236-7977)	6841 (5642-8309)	ns
AFP	*(ng/ml)*	2 (1-4) **d**	4 (3-9)	3 (2-4)	4 (2-5) **a**	**0.0066**
CSPH	*n. (%)*	17 (57)	19 (70)	12 (50)	27 (69)	ns
Betablockers	*Yes* *No*	9 (30) 21 (70	9 (33) 18 (67)	6 (25) 18 (75)	14 (36) 25 (64)	ns
Rifaximin	*Yes* *No*	1 (3) 29 (97)	2 (7) 25 (93)	3 (13) 21 (87)	2 (5) 36 (95)	ns

a ≠ HBV, b≠ HDV, c ≠ HCV, d ≠ MASLD

BMI=Body Mass Index, LSM=Liver Stiffness Measurement, CAP=Controlled Attenuation Parameter, SSM=Spleen Stiffness Measurement, Spleen LA=Spleen Long Axis, ALP=Alkaline Phosphatase, PT=Prothrombin Time, PLTs=Platelets, PCHE=Cholinesterase, AFP=Alpha Fetoprotein, CSPH=Clinically Significant Portal Hypertension

Disclosures: Giovanni Petralli: Nothing to Disclose, Antonio Salvati: Nothing to Disclose, Simone Cappelli: Nothing to Disclose, Ranka Vukotic: Nothing to Disclose, Andrea Pinna: Nothing to Disclose, Francesco Damone: Nothing to Disclose, Veronica Romagnoli: Nothing to Disclose, Piero Colombatto: Nothing to Disclose, Ferruccio Bonino: Nothing to Disclose, Maurizia Brunetto: Nothing to Disclose

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2117 | THE ELF™ TEST IMPROVES RISK STRATIFICATION VERSUS HISTOLOGICAL STAGING FOR PREDICTION OF CLINICAL AND HISTOLOGICAL OUTCOMES IN MASH AND ADVANCED FIBROSIS ◆

Arun Sanyal[1] *Rachel Fonstad*[2] *Chadwick Brown*[2] *Matthew Gee*[2]

[1]*Virginia Commonwealth University,* [2]*Siemens Healthineers*

Background: There is a need to validate biomarkers that can predict near-term clinical and histological outcomes in those with MASH and advanced fibrosis (AF) (CRN stages 3-4), as most patients do not experience an outcome within 1- to 2-years. While most prognostic biomarker studies have focused on 5–10-year timeframes, the Enhanced Liver Fibrosis (ELF™) Test was granted FDA marketing authorization based on prognostic datasets with less follow-up. We evaluated the prognostic performance of the ELF Test along its full range and conventional staging for clinical and histological outcomes. **Methods:** Data from six large placebo-controlled trials in patients with MASLD and AF (STELLAR 3 & 4, GS-US-321-0105, GS-US-321-0106, NASH CX and ATLAS) were pooled. Modified Ishak staging (stage 3-6) was done by a single pathologist. Liver outcomes (overt ascites, encephalopathy, portal hypertensive GI bleeding, liver transplant or rise in MELD score ≥ 15) were centrally adjudicated. Four analyses using ELF and Ishak stage to predict the following outcomes were done: (1) relationship to incidence of liver events, (2) prediction of progression from bridging (Ishak 3 and 4) to cirrhosis, (3) Regression from bridging fibrosis to < stage 3 Ishak, (4) regression from cirrhosis (Ishak 5 or 6) to < Ishak 5. Likelihood ratio (LR) and 95% CI are reported. Significance for trends were assessed using the Jonckheere-Terpstra test ($p< 0.05$). **Results:** A total of 2304 participants with MASH and AF were studied for mean follow up of 17.8 months. There was a progressive increase in outcome risk with increasing ELF scores ($p< 0.0001$) with risk approximately doubling with 0.75 ELF score increments after ≥9.8. This resulted in 5 strata for ELF with LR and 95% CI as follows: <9.0 (0), ≥9.0-<9.8 (0.3, 0.0-0.6), ≥9.8-<11.3 (0.7, 0.5-0.9), ≥11.3-<12.8 (2.8, 2.3-3.4), ≥12.80 (12.5, 6.1-25). Ishak stage 6 had modest prognostication (2.1, 1.8-2.4) with an event rate of 10% vs 40% for ELF ≥12.8. The LR for progression from bridging fibrosis to cirrhosis were: ELF ≥11.3 (4.2, 2.9-6.0), Ishak 4 (1.4, 1.2-1.6). The LR for regression from bridging fibrosis were: ELF <9.8 (1.8, 1.6-2), Ishak 3 (1.6, 1.4-1.7). The LR for regression from cirrhosis were: ELF <9.8 (2.4, 2.0-3.0), Ishak 5 (1.7, 1.5-1.9). **Conclusion:** The ELF Test adds risk strata that are significantly different from histological fibrosis staging for prediction of clinical events and histological changes, thereby improving risk stratification.

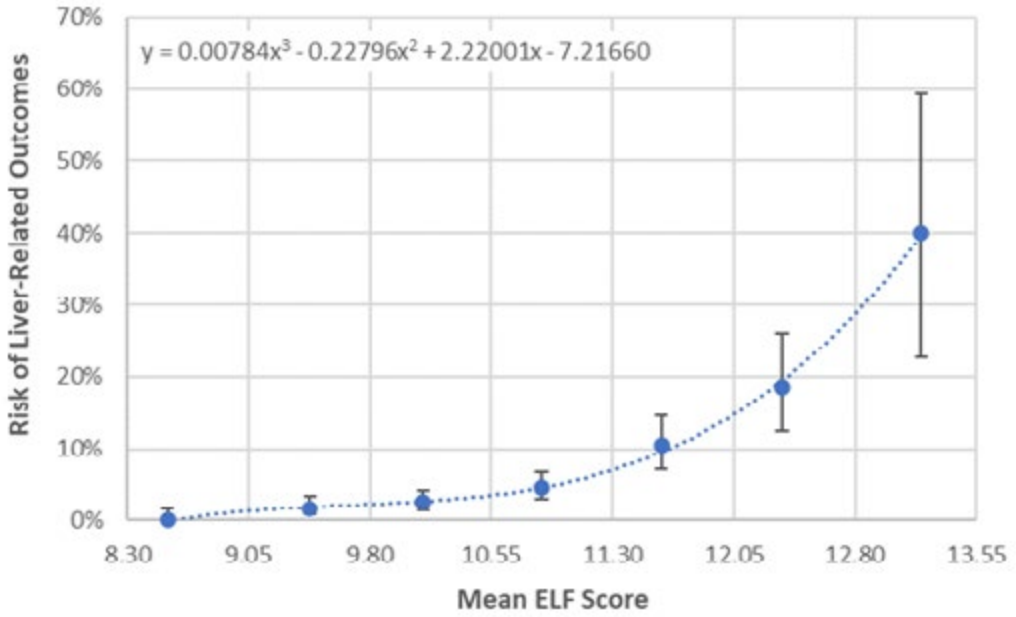

Figure 1: Risk of liver related outcomes as a multinomial function of baseline ELF scores

Disclosures: Arun Sanyal: Genfit, Akarna, Tiziana, Durect, Inversago, Hemoshear, North: Stock - publicly traded company, Astra Zeneca (60K), Boston Pharmaceutical (<5K), Myovent (<5K),: Consultant, Variant (<5K), Cascade

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(<5K), Northsea (<5K): Consultant, Gilead, Salix, Tobira, Bristol Myers, Shire,. Intercept,: Institution has received grants from above companies, Merck, Astra Zenca, Mallinckrodt, Novartis: Institution has received grants from above companies, UpToDate, Elseiver: Royalties or patent beneficiary, Sanyal Bio: Employee, Phillip Hylemon: Nothing to Disclose, Jiangao Fan: Nothing to Disclose, Huiping Zhou: Nothing to Disclose

2118 | INTERLEUKIN-9 LEVELS CORRELATES WITH LEAN-MASLD IN AN ANCESTRY-RELATED FASHION ACROSS A LATIN AMERICAN COHORT OF INDIVIDUALS WITH CIRRHOSIS

Amir Sultan Seid[1] Domingo Balderramo[2] Jhon Prieto Ortiz[3] Marco Arrese[4] ENRIQUE CARRERA ESTUPIÑAN[5] JAVIER DIAZ FERRER[6] Angelo Alves de Mattos[7] Andre Boonstra[8] Jose Debes[1]

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Background: Latin America has one of the highest prevalence rates of lean MASLD worldwide. In this study, we aimed to characterize differences in lean MASLD prevalence and immune profiling among individuals in a multi-national Latin American cohort of patients with varying degrees of liver disease, including cirrhosis and hepatocellular carcinoma (HCC). **Methods:** We retrospectively evaluated a total of 451 patients from the ESCALON network, which includes 6 countries across Latin America. Among these, 73 patients with MASLD (53 non-lean, 20 lean) had available cytokine profiles and were included in this analysis. Ancestry was self-reported as Latin American, European, or other. Lean MASLD was defined as MASLD in individuals with a BMI ≤ 25 kg/m². Blood samples were analyzed for 37 unique interleukins, chemokines, and growth factors using the multiplex Bio-Rad platform. Differences between groups were assessed by the chi-square test. **Results:** The cohort had a median age of 66.5 (SD 7.7) years, with 58.9% being female, and included patients from Argentina (8.2%), Brazil (24.7%), Chile (11.0%), Colombia (24.7%), Ecuador (17.8%), and Peru (13.7%). Cirrhosis was present in 90.0% of lean and 90.6% of non-lean patients (p=0.94). Baseline HCC prevalence was similar between lean (75.0%) and non-lean (54.7%) groups (p=0.114). Self-reported ancestry in the cohort was 25.4% Latin American descent, 26.8% European descent, and 47.9% other ancestry. Lean MASLD was more common in individuals of Latin American than European descent 38.9% vs 5.3%p=0.013). Among 37 immune markers evaluated, we found IL-9 to be the only one significantly elevated in lean compared to non-lean patients (94.7% vs 61.7%, p=0.007). Furthermore, among non-lean patients, elevated IL-9 was observed in 100% of Latin American descent individuals vs 31.3% of European descent (p=0.003) **Conclusion:** In this exploratory analysis of a cohort of patients with MASLD across Latin America, lean MASLD was significantly more common in Latin American descent individuals. Lean MASLD and Latin American ancestry were also associated with elevated IL-9 levels. Although IL-9 has previously been shown to be associated with some liver fibrosis, the significance of this finding among this group of population might warrant further exploration.

Disclosures: Amir Sultan Seid: Nothing to Disclose, Domingo Balderramo: Nothing to Disclose, Jhon Prieto Ortiz: Nothing to Disclose, Marco Arrese: Aztra Seneca: Steering Commitee, Inventiva: Consultant, ENRIQUE CARRERA ESTUPIÑAN: Nothing to Disclose, JAVIER DIAZ FERRER: Nothing to Disclose, Angelo Alves de Mattos: Nothing to Disclose, Andre Boonstra: Gilead: Grant/Research Support, Janssen Pharma: Grant/Research Support, GSK: Grant/Research Support, Fujirebio: Grant/Research Support, Jose Debes: Nothing to Disclose

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2119 | RETROSPECTIVE CROSS SECTIONAL EVALUATION OF THE LIVERFAST TEST FOR STAGING LIVER FIBROSIS IN MASLD PATIENTS IN NIDDK STUDIES' POPULATIONS USING LIVER BIOPSY

Mona Munteanu[1] Imtiaz Alam[2] Parvez Mantry[3] John Lee[1] Juan Manuel Muñoz Pérez[1] Mehdi Sakka[4] Rana Alkouri[4] Maxime Deregnaucourt[4] Dominique BONNEFONT-ROUSSELOT[5] Ronald Quiambao[1]

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Background: MASLD affects 25% of subjects of the general population and can progress to advanced fibrosis (AF) and cirrhosis, especially in patients with type 2 diabetes (T2D). Given the limitations of the liver biopsy there is a growing need for non-invasive cost-effective blood-based tests (NITs) for liver fibrosis assessment. Clinical care pathways are already integrating AI-based blood tests like Liverfast (LF) to identifying AF in patients with T2D. This retrospective research is intended to expand the validation of LIVERFASt against the liver biopsy in adults with MASLD. For that purpose we aimed to assess retrospectively the diagnostic performance of LIVERFASt against historically collected histopathology features in adults. **Methods:** The National Institute of Diabetes and Digestive and Kidney Disease has supported collection of data. Patients with biosample availability and histological results have been selected from several trials [e.g. Nonalcoholic Steatohepatitis Clinical Research Network]. Liverfast is an AI-based algorithm that uses 14 biomarkers (biochemistry and anthropometrics) that is providing three different assessments - fibrosis, steatosis and inflammatory activity-. Statistics uses AUC (95%CI), sensitivity (Se), Specificity (Sp), Positive and negative predictives values (PPV, NPV)., positive likelihood ratio (LR+) and diagnostics odds ratio (DOR) for clinically significant fibrosis (CSF, F234), advanced fibrosis (AF, F34) and cirrhosis (F4). **Results:** A total of 104 patients with MetS and MASLD have been included retrospectively with the following characteristics: males 41%, age 49yrs(range 18-75) T2DM41%, median BMI 33.7 (range 24-55), ALT 47, AST 38, HBA1c 5.9, LF Fibrosis/Steatosis/Activity 0.29 /0.63/0.53, platelets 239*10^3, 57% HTN, 41%T2DM, more than 3 metabolic factors in 74%, 53% CSF and 12% F4. In the overall population, Liverfast Fibrosis test AUC [(95%CI); LR+/DOR] and Se/Sp/PPV/NPV were; for cirrhosis (F4) 0.81 [(0.56-0.92); 5.9/11.9] and 0.55/0.92/0.52/0.93, for advanced fibrosis (AF) 0.86 [(0.75-0.93); 5.1/9.9] and 0.61/0.88/0.44/0.93 and for clinically significant fibrosis (CSF) 0.77 [(0.66-0.85); 2.3/6.2] and 0.75/0.68/0.28/0.95, respectively. In patients with T2DM, Liverfast Fibrosis test AUC [(95%CI); LR+/DOR] and Se/Sp/PPV/NPV were: for cirrhosis (F4) 0.85 [(0.66-0.94); 4.7/7.5] and 0.43/0.91/0.43/0.91, for advanced fibrosis (AF) 0.85 [(0.63-0.95); 3.3/5.5] and 0.50/0.85/0.35/0.91 and for clinically significant fibrosis (CSF) 0.77 [(0.56-0.88); 1.7/4.1] and 0.78/0.53/0.21/0.93, respectively. Patients with 3 or more metS facteurs had more preseumed steatosis with Liverfast compared to those with 2, 1 or zero metabolic factors, $p<0.05$. **Conclusion:** Liverfast has high performances in MASLD patients and can be used to identify patients with cirrhosis or those with MASH-related fibrosis in at-risk MASH patients

Disclosures: Mona Munteanu: Fibronostics: Employee, Imtiaz Alam: Fibronostics, Inc: Advisor, Gilead Sciences: Speaking and Teaching, Parvez Mantry: Nothing to Disclose, John Lee: Nothing to Disclose, Juan Manuel Muñoz Pérez: Nothing to Disclose, Mehdi Sakka: Nothing to Disclose, Rana Alkouri: Nothing to Disclose, Maxime Deregnaucourt: Nothing to Disclose, Dominique BONNEFONT-ROUSSELOT: Nothing to Disclose, Ronald Quiambao: Nothing to Disclose

2120 | COMPARISON OF TRANSIENT ELASTOGRAPHY AND MAGNETIC RESONANCE ELASTOGRAPHY FOR ASSESSMENT OF MASLD/MASH: A RETROSPECTIVE REVIEW

Anandita Mathur[1] Alejandra Paredes-Marin[1] Efe Ozkaya[1] Sonam Rosberger[1] Keith Sigel[1] Bachir Taouli[1] Meena Bansal[2]

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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is a highly prevalent chronic liver disease. Metabolic dysfunction-associated steatohepatitis (MASH) represents its advanced stage and patients with stages F2-F3 (moderate to advanced fibrosis) may be eligible for treatment with the new FDA-approved drug resmetirom. Our objective was to evaluate the concordance between vibration-controlled transient elastography

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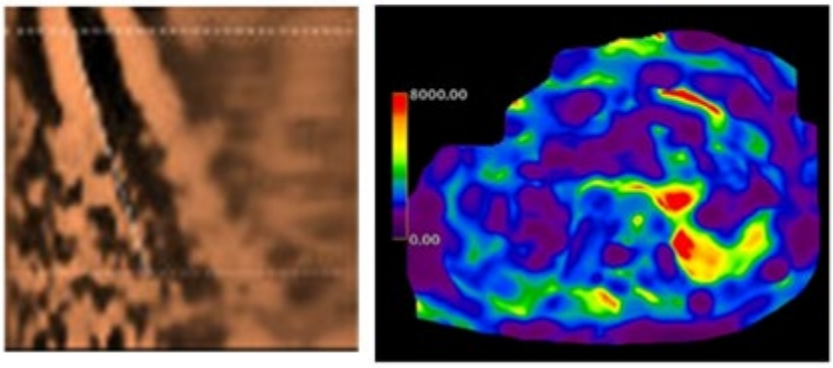
(VCTE) and magnetic resonance elastography (MRE) for staging liver fibrosis and diagnosing steatosis in MASH patients, and to assess for eligibility for treatment with resmetirom. **Methods:** This retrospective IRB approved study included 105 patients (M/F 62/43, mean age 55y) with suspected MASLD/MASH who underwent VCTE (Fibroscan) and MRE within 3 months. Liver stiffness measurements (LSM, in kPa) were obtained. Fibrosis stages were determined by the following thresholds for VCTE (kPa): F0-F1: <8, F2: 8-10, F3: 10-14, and F4: > 14 and for MRE: F0-1: <3.5, F2: 3.5-4, F3: 4-5, and F4: >5. Fisher exact test was used to assess the difference in stage distribution between VCTE and MRE. The presence of steatosis was defined as CAP ≥ 288 and MRI-PDFF≥ 5%. Fisher exact test was used to assess classification of steatosis between VCTE and MRE. The diagnostic performance of CAP against MRI-PDFF was determined by ROC analysis. **Results:** After excluding 2 cases with unreliable VCTE measurements, VCTE and MRE identified the following stage distributions: F0-F1 (n=32 vs 69), F2 (n=20 vs 9), F3 (n=15 vs 14), and F4 (n=36 vs 11) with statistically significant differences in distribution for F0-1 (p value <0.001) and F4 (p value: <0.001). Our results suggest that 35 vs 23 patients would qualify for treatment with resmetirom with VCTE vs MRE respectively. VCTE and MRI-PDFF diagnosed 61 (59%) and 81 (79%) patients with steatosis, respectively. There was a significant correlation between VCTE-CAP and MRI-PDFF (r=0.65 and p<0.001). CAP had AUC of 0.838 in diagnosing steatosis. **Conclusion:** VCTE appears to overestimate the degree of fibrosis compared to MRE, with a greater number of patients qualifying for resmetirom based on VCTE results, resulting in potential cost savings with MRE. VCTE-CAP is reliable for diagnosing steatosis. The observed discrepancies between VCTE and MRE for noninvasive fibrosis staging in MASH may have implications for stratifying patients for treatment with resmetirom.

Figure 1: 54-year-old male with MASH and discordant VCTE and MRE. Liver stiffness was 14.4 kPa with VCTE (reported as stage F4, left) and 2.1 kPa with MRE (reported as stage F0-F1, right).



Disclosures: Anandita Mathur: Nothing to Disclose, Alejandra Paredes-Marin: Nothing to Disclose, Efe Ozkaya: Nothing to Disclose, Sonam Rosberger: Nothing to Disclose, Keith Sigel: Nothing to Disclose, Bachir Taouli: Guerbet: Consultant, Bayer: Grant/Research Support, Heliogenomics: Grant/Research Support, Regenron: Grant/Research Support, Meena Bansal: Advisor relationship with Madrigal; Has not ended; Advisor relationship with Fibronostics; Has not ended; Advisor relationship with NOVO Nordisk; Has not ended; Advisor relationship with GSK; Has not ended; Advisor relationship with Merck; Has not ended; Advisor relationship with Boeheringer-Ingelheim; Has not ended; Advisor relationship with Boston Pharma; Has not ended; Advisor relationship with The Kinetix Group; Has not ended

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2121 | PROGNOSTIC SIGNIFICANCE OF ELF TEST COMPARED TO LIVER BIOPSY IN PATIENTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD) ◆

Antonio Liguori[1] Francesca D'Ambrosio[1] Nicholas Viceconti[1] Fabrizio Termite[1] Lucrezia Petrucci[1] Simone Galletti[1] Sara Cardinali[1] Laura Riccardi[1] Fabrizio Pizzolante[1] Nicoletta De Matthaeis[1] Maria Assunta Zocco[1] Maria Cristina Giustiniani[1] Giuseppe Marrone[1] Marco Biolato[1] Gian Ludovico Rapaccini[1] Maurizio Pompili[1] Antonio Grieco[1] Andrea Urbani[1] Maurizio Sanguinetti[1] Antonio Gasbarrini[1] Luca Miele[1]

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Background: *Liver fibrosis stands out as the main prognostic risk factor in MASLD. The enhanced liver fibrosis (ELF) test is a composite of direct fibrosis biomarkers (tissue inhibitor of metalloproteinases 1, amino-terminal peptide of type 3 procollagen and hyaluronic acid) that reflect extracellular matrix turnover. While the ELF test exhibits high diagnostic accuracy for advanced liver fibrosis in MASLD patients, its role as a prognostic biomarker remains uncertain. Our aim is to compare the prognostic effectiveness of ELF, FIB4, Liver Stiffness Measurement (LSM) and liver histology in patients with MASLD.* **Methods:** We retrospectively enrolled 289 patients with MASLD who underwent liver biopsy between 2013 and 2023. The ELF score was automatically calculated in accordance with the manufacturer's instruction (Siemens Healthineers) using a serum sample collected at baseline. FIB4 computation, LSM with Fibroscan and liver biopsy were performed at baseline. Liver fibrosis stage was assessed according to the METAVIR classification. The primary outcome was a composite endpoint including all-cause mortality, hepatocellular carcinoma, liver transplantation or complications related to cirrhosis (ascites, variceal bleeding, hepatic encephalopathy, MELD≥15). Subjects were stratified based on existing literature cut-offs for ELF (<9.8, 9.8-11.2, >11.2), LSM (<10, 10-15, >15 kPa), FIB-4 (<1.3, 1.3-2.67, >2.67), and histology (F≤2, F3, F4) to assess the risk of occurrence of the primary outcome. **Results:** *We included data of 289 patients (30.4% female, median age 50y [IQR 39-58]). Over a median follow-up time of 41 months (IQR 21-68), the composite endpoint occurred in 34 (11.8%) patients. The frequency of the primary outcome exhibited a stepwise increase with ELF scores <9.8 (0.5%), 9.8 to 11.2 (14.5%) and >11.2 (69.7%). Survival curves for comparisons between groups revealed significant differences for all index tests based on pre-defined histological and non-invasive test stratification (Log Rank test p <0.05). At multivariate Cox regression analysis, ELF and liver histology were significant predictors of the primary outcome after adjusting for gender, diabetes, age and BMI. (ELF > 11.2 vs < 9.8 HR 132.7 [95%CI 15.6-1127.4 p<0.01], 9.8-11.2 vs <9.8 HR 22.5 [95%CI 2.8-184.3 p=0.04]) (F4 vs F≤2 HR 92.0 [95%CI 20.1-421.9 p<0.01], F3 vs F≤2 HR 10.2 [95%CI 2.3-45.5 p=0.05]).* **Conclusion:** *The ELF test demonstrated comparable performance to histologically evaluated fibrosis in forecasting clinical outcomes. It should be regarded as a viable alternative to liver biopsy for conducting prognostic assessments in patients with MASLD.*

Disclosures: Antonio Liguori: Nothing to Disclose, Francesca D'Ambrosio: Nothing to Disclose, Nicholas Viceconti: Nothing to Disclose, Fabrizio Termite: Nothing to Disclose, Lucrezia Petrucci: Nothing to Disclose, Simone Galletti: Nothing to Disclose, Sara Cardinali: Nothing to Disclose, Laura Riccardi: Nothing to Disclose, Fabrizio Pizzolante: Nothing to Disclose, Nicoletta De Matthaeis: Nothing to Disclose, Maria Assunta Zocco: Nothing to Disclose, Maria Cristina Giustiniani: Nothing to Disclose, Giuseppe Marrone: IPSEN: Advisor, Marco Biolato: Nothing to Disclose, Gian Ludovico Rapaccini: Nothing to Disclose, Maurizio Pompili: Nothing to Disclose, Antonio Grieco: Nothing to Disclose, Andrea Urbani: Nothing to Disclose, Maurizio Sanguinetti: Nothing to Disclose, Antonio Gasbarrini: Nothing to Disclose, Luca Miele: Nothing to Disclose

2122 | FEASIBILITY OF FAT FREE LIVER VOLUME AS A BIOMARKER IN STEATOTIC LIVER DISEASE

Emil Brännström[1] Fredrik Rorsman[2] Johan Vessby[2] Paul Hockings[1] Lars Johansson[1]

[1]Antaros Medical, [2]Uppsala University

Background: Measurements of liver and spleen volumes are increasingly being used in clinical MASLD trials. A decrease in liver volume is usually interpreted as an improvement due to regression of steatosis, especially when accompanied with a reduction in hepatic proton density fat fraction. However, due to the tendency of both steatosis and liver volume to fall with increased levels of fibrosis, the liver volume often exhibits a pre-cirrhotic

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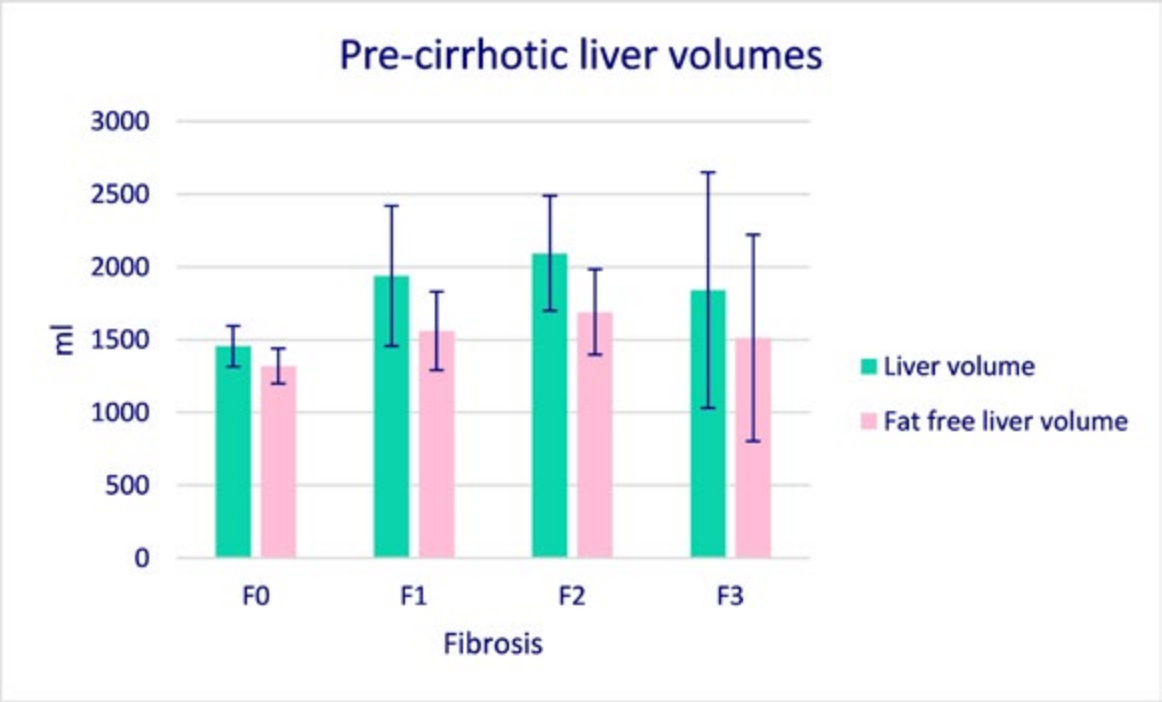
biphasic growth curve meaning this interpretation is not always accurate. A more valuable measurement, therefore, might be to use the fat free liver volume since this reduces the volumetric increase caused by steatosis and, hence, might better represent the underlying functioning parenchyma. In this study we therefore decided to investigate the feasibility of using fat free liver volume as a biomarker in the pre-cirrhotic stages of steatotic liver disease. **Methods:** A retroactive analysis was conducted on 68 MASLD patients whose livers had previously been analysed regarding proton density fat fraction and total liver volume for a different study. All patients had undergone liver biopsy confirming hepatic steatosis and fibrosis stage (F0-F4). Three patients were excluded due to having fibrosis grade 4 and therefore classified as cirrhosis. The fat free liver volume was calculated by subtracting the fat fraction from the total liver volume. This was then compared to the total liver volume. 28 patients had follow-up scans averaging ca 3 weeks apart. The volumes for these patients were added to Bland Altman plots to look for systematic biases. **Results:** The total liver volume exhibited a bi-phasic growth curve, increasing from 1455 ± 140 ml (mean ± SD) in F0 to a maximal volume of 2093 ± 395 ml in F2 before decreasing to 1841 ± 809 ml in F3. A markedly less pronounced curve was witnessed for fat free liver volume starting at 1319 ± 120 ml in F0, peaking at 1670 ± 293 ml in F2, before shrinking to 1512 ± 709 ml in F3. The Bland Altman plots did not show any systematic measurement biases. **Conclusion:** The total liver volume exhibited a bi-phasic growth curve, increasing from 1455 ± 140 ml (mean ± SD) in F0 to a maximal volume of 2093 ± 395 ml in F2 before decreasing to 1841 ± 809 ml in F3. A markedly less pronounced curve was witnessed for fat free liver volume starting at 1319 ± 120 ml in F0, peaking at 1670 ± 293 ml in F2, before shrinking to 1512 ± 709 ml in F3. The Bland Altman plots did not show any systematic measurement biases.



Disclosures: Emil Brännström: Nothing to Disclose, Fredrik Rorsman: Nothing to Disclose, Johan Vessby: Norgine: Speaking and Teaching, Gore: Speaking and Teaching, NovoNordisk: Advisor, Paul Hockings: Antaros Medical: Employee, Lars Johansson: Antaros Medical: Stock – privately held company, Antaros Medical: Employee

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2123 | FIB-4 BASED REFERRAL PATHWAYS TO IDENTIFY LIVER FIBROSIS AND INCIDENT ADVANCED LIVER DISEASE HAVE POOR CLINICAL UTILITY IN TWO INDEPENDENT GENERAL POPULATION COHORTS

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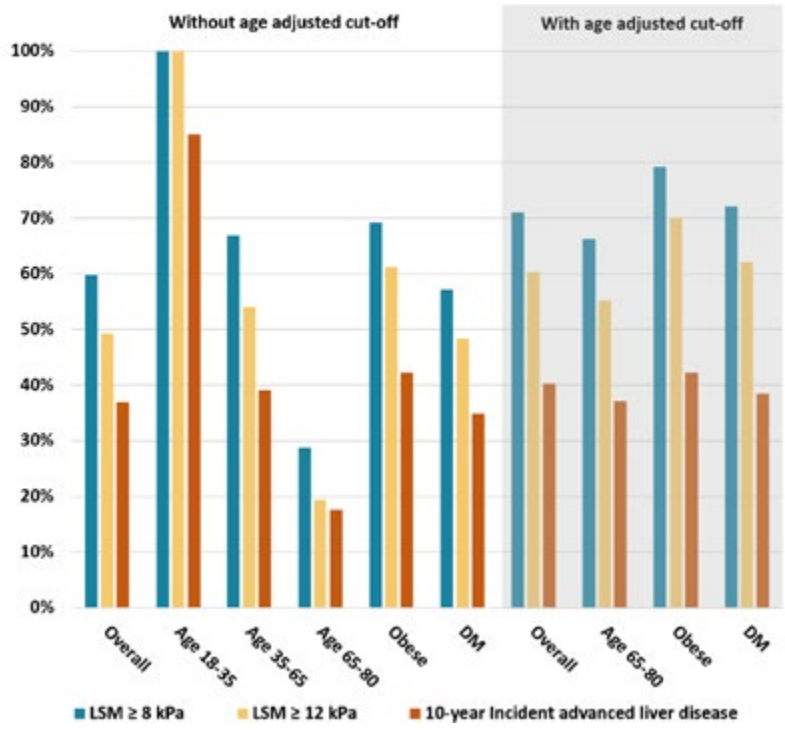
Background: The FIB-4 is the cornerstone of referral pathways aiming at identifying clinically relevant liver disease among low-prevalence populations at an early stage. Its diagnostic accuracy, however, is debated in population-based settings. **Methods:** Participants with metabolic dysfunction from the NHANES 2017-2020 (United States) were used for cross-sectional analysis and participants with metabolic dysfunction from the AMORIS cohort (Sweden) for longitudinal analysis. The ability of the FIB-4 based referral pathways (threshold 1.3, following the referral strategies) to detect increased liver stiffness (LSM) and ICD-based 10-year incident advanced liver disease was investigated in the target populations. Additional analysis included clinically relevant subgroups and the application of an age-adjusted cut-off (FIB-4 2.0 in participants aged > 65). **Results:** Cross-sectional analysis comprised 6,375 participants (aged 52 [36-64], 49% male), of them 10.3% had LSM≥8 and 3.4% LSM≥12. Among those considered to have no clinically relevant liver disease (72.3%), LSM≥8 was still present in 8.5% and LSM≥12 in 2.3%. Consequently, 59.8% and 49.3% of cases were missed. Particularly worrisome is the failure to detect any case of increased liver stiffness among participants aged <35 (sensitivity 0.0%) and either the high referral rate (70.8%) or low sensitivity (33.8%) among participants aged 65-80 depending on the application of age-adjusted cut-off. Finally, in the longitudinal analysis (n=56,241, age 52[45, 61], male 68.2%, events=361), the FIB-4 failed to detect 37% of incident cases of advanced liver disease (decompensated cirrhosis or HCC), whilst 16.6% had high FIB-4. **Conclusion:** FIB-4-based referral pathways to identify advanced liver disease among the general population have poor diagnostic accuracy, especially in younger and older populations. Replacing the FIB-4 with other tests, such as the MAF-5 or LiverRisk score, in referral pathways needs to be considered.

Figure: Increased transient elastography and 10-year incident advanced liver disease that remain undetected (1 - sensitivity) with FIB-4-based referral pathways in the overall population and subgroups



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2124 | GLYCATED HEMOGLOBIN AND AST AS PREDICTORS OF AT-RISK MASH ACROSS FIBROSIS STAGES: COMBINED DATA FROM MULTIPLE THERAPEUTIC TRIALS INCLUDING MORE THAN 4,000 LIVER BIOPSIES

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Background: The identification of at-risk metabolic dysfunction-associated steatohepatitis (MASH) patients remains a main challenge in both clinical practice and clinical trial settings. Several non-invasive biomarkers have been developed to MASH patients and fibrosis stage F2 or F3, who would benefit from pharmacological therapy. We aimed to describe the main predictors of MASH and fibrosis across multiple therapeutic clinical trials. **Methods:** We combined screening data from 10 MASH phase 2 trials. Using histology data, we defined 5 populations (see table). The proportion of each of these populations were calculated using different FIB-4, AST and HgbA1c thresholds. We also calculated their respective negative predictive values (NPV) to exclude at-risk MASH and cirrhosis. **Results:** 4,022 patients with centrally assessed liver biopsy, HgbA1c, AST, and FIB-4 data were included. Among them, 1,608 (40%) meet the histopathological criteria for at-risk MASH with moderate to advanced fibrosis (F2-4). The proportion of MASH and fibrosis stages, according to several non-invasive biomarkers thresholds are shown in the table. The proportion of at risk-MASH patients with F2-4 was 13%, 24%, 42% and 60% in patients with AST <20, AST 20-30, AST 30-40, and AST ≥ 40, respectively. In those with AST ≥ 30, 53% of patients had at risk MASH with F2-4 compared to only 22% in those with with AST <30. In patients with AST ≥ 30, those with HbA1c ≥ 6.5%, 67% of patients had "at-risk MASH" compared to 45% in those with HbA1c <6.5%. The prevalence of 'at-risk MASH' increased further in patients with AST ≥ 40, where 72% vs 52% in those with HbA1c ≥ 6.5% and HbA1c <6.5%, respectively, "at-risk MASH". HbA1c ≥ 6.5% was an independent and significant predictor of advanced fibrosis. A FIB-4 <1.3 excluded cirrhosis with a NPV of 96%. AST < 20 excluded at-risk MASH with a NPV of 87%. A stepwise approach, using FIB-4 then AST excluded at-risk NASH with a NPV of 90%. **Conclusion:** Simple, readily available labs can help identify those more likely to have MASH with moderate to advanced fibrosis who may benefit from treatment. Glycemic control, as a part surrogate for the presence of type 2 diabetes, significantly impacts the likelihood of having advanced fibrosis. A combination of FIB-4 and AST can effectively rule out at-risk MASH.

Non-Invasive Biomarkers	F0/F1 N=1,788	F2/F3 & no MASH N=308	MASH & F2 N=587	MASH & F3 N=901	F4 N=438	NPV (at-risk MASH (F2-4))	NPV (F4)
AST							
< 20	299 (17%)	37 (12%)	29 (5%)	27 (3%)	47 (11%)	86.7%	89.4%
20 – 30	729 (41%)	98 (32%)	163 (28%)	159 (18%)	107 (24%)		
≥ 30	760 (42%)	173 (56%)	395 (67%)	715 (79%)	284 (65%)		
HbA1c							
< 6.5	1,282 (72%)	224 (73%)	346 (59%)	449 (50%)	212 (48%)	67.4%	91.6%
≥ 6.5	506 (28%)	84 (27%)	241 (41%)	452 (50%)	226 (52%)		
AST & HbA1c							
AST < 20 & HbA1c < 6.5	199 (11%)	26 (8%)	14 (2%)	9 (1%)	28 (6%)	90.2%	89.9%
AST < 20 & HbA1c ≥ 6.5	100 (6%)	11 (4%)	15 (2%)	18 (2%)	19 (4%)	80.4%	88.3%
AST 20-30 & HbA1c < 6.5	528 (30%)	68 (22%)	100 (17%)	72 (8%)	50 (12%)		
AST 20-30 & HbA1c ≥ 6.5	201 (11%)	30 (10%)	63 (11%)	87 (10%)	57 (13%)		
AST ≥ 30 & HbA1c < 6.5	555 (31%)	130 (42%)	232 (40%)	368 (41%)	134 (31%)		
AST ≥ 30 & HbA1c ≥ 6.5	205 (11%)	43 (14%)	163 (28%)	347 (38%)	150 (34%)		

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Principal Investigator for a Drug Study relationship with Corcept; Has not ended; Principal Investigator for a Drug Study relationship with GSK; Has not ended; Principal Investigator for a Drug Study relationship with Conatus; Has not ended, Sophie Jeannin: Nothing to Disclose, Mary Rinella: Consultant relationship with Sagimet; Has not ended; Consultant relationship with Takeda; Has not ended; Consultant relationship with Eli Lilly; Has not ended; Consultant relationship with Novo Nordisk; Has not ended; Consultant relationship with GSK; Has not ended; Consultant relationship with Madrigal; Has not ended;

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Consultant relationship with Intercept; Has not ended; Consultant relationship with Boehringer Ingelheim; Has not ended; Consultant relationship with 89Bio; Has not ended; Consultant relationship with akero; Has not ended; Consultant relationship with Histoindex; Has not ended; Consultant relationship with Cytodyn; Has not ended; Consultant relationship with Echosens; Has not ended, Stephen Harrison: Nothing to Disclose

2125 | COMPARATIVE DIAGNOSTIC ACCURACY OF AGILE SCORES AND COMMON NON-INVASIVE TESTS IN DETECTING ADVANCED LIVER FIBROSIS IN PATIENTS WITH METABOLIC DYSFUNCTION ASSOCIATED STEATOTIC LIVER DISEASE

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Background: Metabolic dysfunction associated steatotic liver disease (MASLD) is a prevalent condition that can progress to advanced fibrosis and cirrhosis and significantly increase the risk of liver-related morbidity and mortality. The early identification of patients with advanced fibrosis and cirrhosis is crucial for effective management and predicting clinical outcomes. Currently, the non-invasive tests (NITs) of liver fibrosis are widely used in routine clinical practice and are recommended by most practice guidelines. However, the performance of NITs, such as Agile 3+ and Agile 4 scores, varies significantly across different patient groups, such as those with obesity or diabetes. Utilizing Agile scores can enhance the recognition of advanced liver fibrosis and facilitate patient referral to specialists. We aimed to evaluate the diagnostic accuracy of the Agile 3+ and Agile 4 scores in identifying advanced fibrosis in patients with MASLD compared with common non-invasive tests. **Methods:** The study included patients with MASLD attending hepatology clinics at a tertiary university hospital, who had liver stiffness measurement and blood tests within six months. Patients with secondary causes of hepatic steatosis were excluded The Agile 3+ and Agile 4, and common NITs were calculated for each patient. **Results:** A total of 612 patients were included, with advanced fibrosis or cirrhosis identified in 97 (15.8%) patients. The mean age was 49.3 ± 13.6 years; the majority were females (52.8%) and Saudi nationals (87.1%). Agile 3+ and Agile 4 were associated with the best-balanced sensitivity and specificity. The sensitivity, specificity, positive and negative predictive values for detecting liver fibrosis in Agile 3+ were 85.6%, 85.0%, 51.9%, and 96.9%, respectively. For Agile 4, the values were 90.7%, 89.9%, 62.9%, and 98.1%, respectively. The discriminative ability (area under the curve) of Agile 4 was better than that of Agile 3+ (0.940 vs. 0.927), although the difference was not statistically significant. The Agile scores demonstrated significantly better discriminative ability than the FIB-4 (0.740), APRI (0.760), and BARD (0.623) scores. **Conclusion:** The Agile scores have excellent diagnostic accuracy for identifying advanced liver fibrosis in patients with MASLD. Their performances were superior to common NITs. These findings suggest that the Agile scores can be valuable tools to enhance the recognition of advanced fibrosis in MASLD patients, allowing for timely referral to hepatology specialists and optimizing clinical management.

Disclosures: Mona Ismail: Nothing to Disclose, Hadi Kuriry: Nothing to Disclose, Marwa Ismail: Nothing to Disclose

2127 | THE DIAGNOSTIC UTILITY OF THE UNITED STATES FATTY LIVER INDEX FOR METABOLIC DYSFUNCTION ASSOCIATED LIVER DISEASE

Toby Bradford[1] Brian Nguyen[2] Vy Nguyen[3] Michael Le[4] Richie Manikat[5] Ramsey Cheung[6] Mindie Nguyen[1]

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Background: Serum based non-invasive tests (NITs) have been widely validated for the assessment of clinically significant fibrosis due to non-alcoholic fatty liver disease (NAFLD). Among these NITs, the United States Fatty Liver Index (US FLI) has demonstrated efficacy in predicting hepatic steatosis in the multiethnic US population. However, the diagnostic utility of the US FLI has not been assessed using the recently updated steatotic liver

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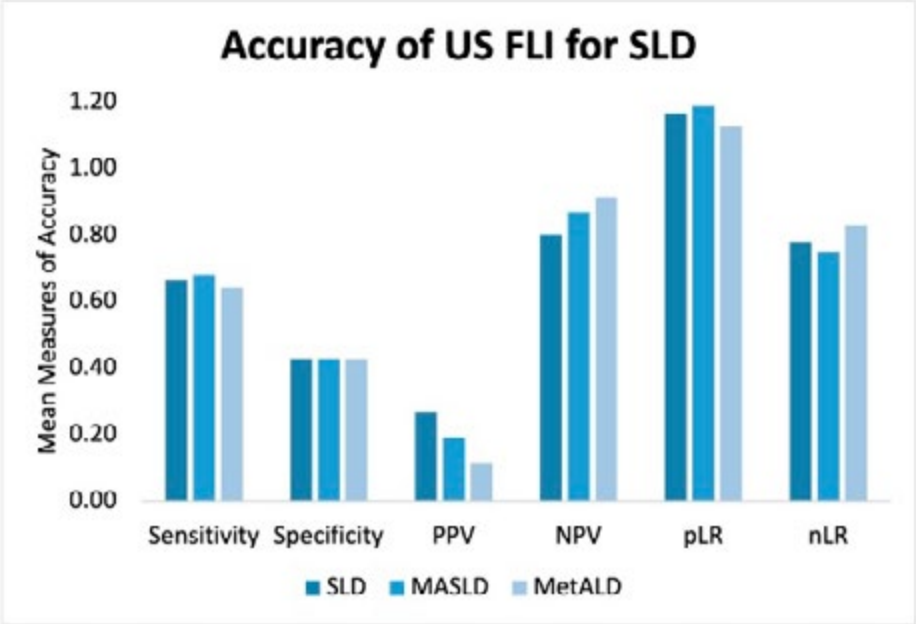
disease (SLD) diagnostic criteria. The aims of this study were to evaluate the diagnostic accuracy of the US FLI for SLD. **Methods:** We examined adults with SLD, MASLD, or MetALD identified in the 2017-2020 NHANES US population database. SLD was defined as hepatic steatosis from MASLD or MetALD with or without viral hepatitis B or C. MASLD was defined as SLD and ≥ 1 cardiometabolic risk factor and minimal alcohol intake. MetALD was defined as SLD and ≥ 1 cardiometabolic risk factor and moderate alcohol intake. US FLI ≥ 60 was used to rule in the presence of SLD. The presence of SLD was confirmed by a vibration controlled transient elastography (VCTE) detected hepatic steatosis calculated as controlled attenuation parameter (CAP) 285 decibels per milliwatt (dB/M). Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) was calculated to assess accuracy. **Results:** We analyzed 1660 eligible patients. The majority of patients with SLD were male (57%), Caucasian (83%), and diabetic (78%), with a mean age of 50. The prevalence was found to be 24%, 15%, and 9% for SLD, MASLD, and MetALD respectively. The sensitivity and specificity of the US FLI for SLD was 0.666 and 0.429 respectively with a NPV of 80.3%. The sensitivity and specificity of the US FLI for MASLD was 0.679 and 0.429 respectively with a NPV of 86.9%. The sensitivity and specificity of the US FLI for MetALD was 0.643 and 0.429 respectively with a NPV of 91.3%. **Conclusion:** The accuracy of the US FLI to predict MASLD using the recently updated diagnostic criteria was poor compared to previous studies evaluating its accuracy for NAFLD. The development of newer indices is warranted for accurate staging and risk stratification of patients with MASLD and MetALD.



	Sensitivity	Specificity	PPV	NPV	pLR	nLR
SLD	0.67	0.43	0.27	0.80	1.17	0.78
MASLD	0.68	0.43	0.19	0.87	1.19	0.75
MetALD	0.64	0.43	0.11	0.91	1.13	0.83

Disclosures: Toby Bradford: Nothing to Disclose, Brian Nguyen: Nothing to Disclose, Vy Nguyen: Nothing to Disclose, Michael Le: Nothing to Disclose, Richie Manikat: Nothing to Disclose, Ramsey Cheung: Nothing to Disclose, Mindie Nguyen: Nothing to Disclose

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2128 | EVALUATING THE IMPACT OF ENHANCED LIVER FIBROSIS (ELF) TESTING ON IDENTIFYING F2 AND/OR ADVANCED FIBROSIS AT A U.S. VETERANS AFFAIRS (VA) HEALTHCARE SYSTEM

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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) impacts at least 3.65 Million U.S. Veterans. 41% of Veterans (1.5 million) with a FIB-4≥1.3 require additional fibrosis work-up currently done by a specialty care workforce of ~70 hepatologists. Eligibility for liver-directed MASLD drug therapy is restricted to those with F2/F3 fibrosis based on liver histology. We evaluated the impact of a multi-tiered diagnostic strategy for primary care referral decisions to better identify those U.S. Veterans likely having F2/3 fibrosis in need of further specialty care evaluation and management. **Methods:** A prospective cohort study was conducted at a large VA Medical Center to evaluate the utility of ELF in the primary care setting to identify patients with ≥F2 fibrosis. The study population included patients ≥40 years with clinical diagnosis or suspicion of MASLD based upon lab tests and medical history or presence of ≥1 MASLD risk factor. Eligible Veterans were consented, enrolled, and asked to provide blood samples for standard of care labs and ELF. ELF results were withheld due to the observational nature of the study. Staging was determined in 128 patients by vibration controlled transient elastography (VCTE). VCTE staging cut offs were: F0-1 <7.5kPa, 7.5≤ F2≤10kPa, 10kPa14kPa. Unnecessary referrals were defined as referrals of patients found to have F0-F1. **Results:** Of the 150 patients enrolled, the mean age was 62.1±10.6 years and 83.3% were male (n=125). 52.7% (n=79) identified as White/Caucasian, 40.7% (n=61) as Black/African American, and 6.6% as Other. HbA1C>6.5 was noted in 38% (n=57) and the mean BMI was 33.7±4.5. 103 patients had a FIB-4<1.3 (5 were referred & 4 had ≥F2 fibrosis), 44 had a FIB-4 between 1.3-2.67 (26 were referred & 8 had ≥F2 fibrosis), and 3 had a FIB-4≥2.67 (3 were referred & 0 had ≥F2 fibrosis). Of the 150 patients, 117 had F0-F1 fibrosis (18.8% were referred), 24 had F2 fibrosis (33.3% were referred), 5 had F3 fibrosis (60% were referred), 1 had F4 fibrosis (100% referred), and 3 were missing staging data (0% referred). Table 1 illustrates the performance of 6 diagnostic scenarios. **Conclusion:** Compared to using FIB-4≥1.3 alone, a work-up utilizing FIB-4 followed by ELF≥9.8 (diagnostic scenario 5) prevented the greatest number of unnecessary primary care referrals. If applied to the entire U.S. VA Healthcare System, this strategy would increase the accuracy of appropriate referrals to Hepatology care and potentially avoid ~200,000 unnecessary referrals to specialized care. As a result, this would avoid substantial costs for unnecessary diagnostic work-up and reduce unnecessary liver biopsies given the current need to demonstrate F2/F3 fibrosis on liver biopsy to qualify for liver-directed MASLD drug therapy.

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Diagnostic Scenarios		Total Number Referred		Referred & Found to Have F0-F1 Fibrosis		Referred & Found to Have F2 Fibrosis		Referred & Found to Have ≥F3 Fibrosis		Unnecessary Referrals Added/Avoided (compared to actual)*	
		N	% of total population	N	% of total referred	N	% of total referred	N	% of total referred	N	% of total population
1	FIB-4 ≥ 1.3	47	31.33%	34	72.34%	9	19.15%	4	8.51%	12 added	8.00%
2	ELF ≥ 9.0	102	68.00%	77	75.49%	16	15.69%	6	5.88%	55 added	36.67%
3	ELF ≥ 9.8	43	28.67%	30	69.77%	9	20.93%	3	6.98%	8 added	5.33%
4	FIB-4 (≥ 1.3) -> ELF (≥9.0)	38	25.33%	29	76.32%	6	15.79%	3	7.89%	8 added	5.33%
5	FIB-4 (≥ 1.3) -> ELF (≥9.8)	18	12.00%	14	77.78%	2	11.11%	2	11.11%	8 avoided	5.33%
6	FIB-4 (≥ 1.3) -> ELF (≥7.7)	42	28.00%	29	69.05%	9	21.43%	4	9.52%	10 added	6.67%

Scenario 1: If FIB-4 <1.3 = low risk & manage in primary care; if FIB-4 ≥ 1.3 = refer to hepatology for further workup.

Scenario 2: If ELF <9.0 = low risk & manage in primary care; if ELF ≥ 9.0 = refer to hepatology for further workup.

Scenario 3: If ELF <9.8 = low risk & manage in primary care; if ELF ≥ 9.8 = refer to hepatology for further workup.

Scenario 4: If FIB-4 <1.3 = low risk & manage in primary care; if FIB-4 ≥ 2.67 = refer to hepatology; if FIB-4 ≥ 1.3 AND FIB-4 < 2.67 = order ELF; if ELF ≥ 9.0, refer to hepatology; if ELF <9.0 = low risk & manage in primary care.

Scenario 5: If FIB-4 <1.3 = low risk & manage in primary care; if FIB-4 ≥ 2.67 = refer to hepatology; if FIB-4 ≥ 1.3 AND FIB-4 < 2.67 = order ELF; if ELF ≥ 9.8, refer to hepatology; if ELF <9.8 = low risk & manage in primary care.

Scenario 6: If FIB-4 <1.3 = low risk & manage in primary care; if FIB-4 ≥ 2.67 = refer to hepatology; if FIB-4 ≥ 1.3 AND FIB-4 < 2.67 = order ELF; if ELF ≥ 7.7, refer to hepatology; if ELF <7.7 = low risk & manage in primary care.

*Unnecessary referrals defined as individuals with F0-1 fibrosis referred to hepatology; calculated as |(number of actual F0-F1 referrals) - (number of scenario F0-F1 referrals)|

Disclosures: Puneet Puri: Nothing to Disclose, HoChong Gilles: Madrigal: Speaking and Teaching, Maribeth Capuno: Nothing to Disclose, Joelle Lemmons: Nothing to Disclose, Mazen Noureddin: Principal Investigator for a Drug Study relationship with Viking; Has not ended; Consultant relationship with Eli Lilly; Has not ended; Consultant relationship with AstraZeneca; Has not ended; Consultant relationship with Boston Pharmaceuticals; Has not ended; Principal Investigator for a Drug Study relationship with Genfit; Has not ended; Principal Investigator for a Drug Study relationship with Galectin; Has not ended; Principal Investigator for a Drug Study relationship with Gilead; Has not ended; Principal Investigator for a Drug Study relationship with BMS; Has not ended; Principal Investigator for a Drug Study relationship with BI; Has not ended; Principal Investigator for a Drug Study relationship with Akero; Has not ended; Consultant relationship with Cytodyn; Has not ended; Consultant relationship with GSK; Has not ended; Consultant relationship with BI; Has not ended; Consultant relationship with Madrigal; Has not ended; Terns,Takeda, Zydus. relationship with Itimmune, BI, Cytodyn, 89BIO, GSK, Madrigal, Merck, Novo Nor; Has not ended; Principal Investigator for a Drug Study relationship with Allergan; Has not ended; Consultant relationship with Takeda; Has not ended; Consultant relationship with Terns; Has not ended; Terns, Corcept, Takeda, Madrigal, Novartis, Novo Nordisk, relationship with Allergan, Akero, BI, BMS, Gilead, Galectin, Zydus GSK; Has not ended; Consultant relationship with Novo Nordisk; Has not ended; Stock â€“ privately held company relationship with Rivus Pharma, Cytodyn, and ChronWell; Has not ended; Consultant relationship with Merck; Has not ended; Principal Investigator for a Drug Study relationship with Madrigal; Has not ended; Consultant relationship with Altimmune; Has not ended; Principal Investigator for a Drug Study relationship with Terns; Has not ended; Principal Investigator for a Drug Study relationship with Zydus; Has not ended; Stock â€“ privately held company relationship with Rivus Pharmaceuticals; Has not ended; Consultant relationship with Alligos; Has not ended; Stock - publicly traded company relationship with Cytodyn; Has not ended; Stock â€“ privately held company relationship with ChronWell; Has not ended; Speaking and Teaching relationship with Madrigal; Has not ended; Principal Investigator for a Drug Study relationship with Takeda; Has not ended; Principal Investigator for a Drug Study relationship with Shire; Has not ended; Principal Investigator for a Drug Study relationship with Novo Nordisk; Has not ended; Principal Investigator for a Drug Study relationship with Novartis; Has not ended; Principal Investigator for a Drug Study relationship with Enanta; Has not ended; Principal Investigator for a Drug Study relationship with Corcept; Has not ended; Principal Investigator for a Drug Study relationship with GSK; Has not ended; Principal Investigator for a Drug Study relationship with Conatus; Has not ended, Donald Chalfin: Siemens Healthiness: Employee, Kristi Cohn: Nothing to Disclose, Mohanish Savanth: The Kinetix Group: Employee, Michael Fuchs: Amgen: Grant/Research Support, Bio89: Grant/Research Support, ExactSciences: Grant/Research Support, Helio Health: Grant/Research Support, Intercept: Grant/Research Support, Galectin: Grant/Research Support, Viking: Grant/Research Support, GlaxoSmithKline: Grant/Research Support, NGM: Grant/Research Support, Kinetix: Grant/Research Support, Encaustics: Grant/Research Support, Altimmune: Grant/Research Support, AstraZeneca: Grant/Research Support, Akero: Grant/Research Support, HelioHealth: Grant/Research Support, Inventiva: Grant/Research Support, Madrigal: Grant/Research

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2129 | ASSESSMENT OF THE SENSITIVITY AND SPECIFICITY OF NON-INVASIVE SCORES FOR IDENTIFYING AT-RISK-MASH PATIENTS

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[1]*Tel Aviv medical center*

Background: MASH is a histology based diagnosis . Identify at-risk MASH patients non-invasively is crucial in the era of therapeutic agents recently approved. The aim of this study was to assess the sensitivity and specificity of four non-invasive strategies to identify at-risk-MASH patients. **Methods:** Consecutive patients with advanced liver fibrosis that were referred to a tertiary hepatology clinic and had liver biopsies performed. These patients have laboratory tests and imaging to calculate the following scores : 1) FIB-4 + VCTE; 2) FAST score; 3)AGILE3; 4) VCTE + CAP + ALT; 5)VCTE+CAP+PLT. Sensitivity and specificity were calculated. **Results:** 1163 patients were included with a mean age of 56.7 ±11 years, 62.7% were female, with a mean BMI 37.75 ± 8. 49.79% had type 2 diabetes. Of the subjects, 129/745 (17%) had FIB4>1.3 and VCTE >= 8. This score demonstrated a specificity of 0.58 and sensitivity of 0.65. the NPV and PPV are 0.82 and 0.35 subsequently. For 829 patients, the FAST score was available. using a cut-off of 0.67, a specificity of 0.68 and sensitivity of 0.57 were calculated with NPV of 0.82 and PPV of 0.57. among the 745 patients with data for AGILE3, a score of AGILE3 > 0.68 was defined. specificity of 0.6 and sensitivity of 0.63 were calculated, with NPV of 0.82 and PPV of 0.63.
In patients with CAP > 280 + VCTE > 8 kPa + ALT > 20, a specificity of 0.37 and sensitivity of 0.76 were calculated with NPV of 0.82 and PPV of 0.29. Finally, in patients with CAP > 280 + VCTE between 10-20 kPa + platelets > 140k, a specificity of 0.6 and sensitivity of 0.52 were calculated, with NPV of 0.77 and PPV of 0.32. **Conclusion:** Using non-invasive tests in patients with at-risk-MASH proven biopsies, some scores show promising sensitivity level, while others exhibit higher specificity. These findings suggest that a combination of different scoring systems may be beneficial in accurately identifying at-risk patients. Furthermore, approximately 30% of these patients could be over-diagnosed using these tests, indicating the need for caution making treatment decisions.

Disclosures: Siham Abdelgani: Nothing to Disclose

2130 | GUT MYCOBIOME IN THE SPECTRUM OF METABOLIC-DYSFUNCTION ASSOCIATED STEATOTIC LIVER DISEASE (MASLD): FROM MASH TO HEPATOCELLULAR CARCINOMA

Mario Alvares-da-Silva[1] *Cassio Perlin*[1] *Melina Keingeski*[1] *Bruno Basso*[1] *Juliane Medeiros*[2] *Francis Borges*[2] *Carolina Uribe-Cruz*[3]

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Background: Gut microbiome (GM) dysbiosis is associated with the development and progression of metabolic-dysfunction associated steatotic liver disease (MASLD) and steatohepatitis (MASH). Human GM contains bacteria, fungi, archaea, and viruses. Compared to the bacteriome, there is still very limited data on the gut mycobiome (GMyco). Therefore, this study aims to evaluate the composition of the GMyco at different stages of MASLD in humans. **Methods:** A total of 28 patients were eligible and recruited: controls, n=6; MASH, n=6; cirrhosis, n=7; and hepatocellular carcinoma (HCC), n=5. Stool samples were collected and stored in a -80°C freezer for subsequent DNA extraction (Nova Biotecnologia®) and sequencing with amplification of the 18S region - PCR (Illumina® MiSeq®) with the primers: CCCTGCCHTTTGTACAC/CCTTCYGCAGGTTCACCTAC. The single sequence variants (ASVs) obtained were compared to the SILVA database. **Results:** The sample included 77.93% women, with an average BMI of 31.4 kg/m2, daily alcohol consumption <30g in men or <20g in women (17.4%), active smoking (8.7%), use of antibiotics in the last 6 months (30.4%), and concurrent lipid-lowering drugs (26.1%). Individuals with MASH showed greater alpha diversity than the others, with a statistically significant difference between MASH and controls (p<0,05). With regard to fungal taxonomy, the control group

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had a higher abundance of the phylum Ascomycota, and the MASH patients showed a higher abundance of Basidiomycota. In terms of family taxonomy, the control group had a higher abundance of *Aspergillaceae*, while there was a higher abundance of *Malasseziaceae* and *Sporidiobolaceae* in cirrhotic and *Saccharomycetacea* in HCC patients. In the analysis of relative abundance among the groups, only one ASV (genus *Naganishia*, previously reported as *Cryptococcus*) was homogeneously distributed in MASH individuals and absent in healthy controls. **Conclusion:** This study shows in an unprecedented way GMyco profile in the different strata of MASLD. Basidiomycetes, that were higher in MASH, were previously described in obese patients. For the first time, the genus *Naganishia* was described in this population.. It is still too early to infer a mycobiomic signature of MASLD, but our findings suggest that fungi could be a potential biological marker in the MASLD spectrum in the future.

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2131 | RETROSPECTIVE ANALYSIS OF A COHORT OF PATIENTS WITH VARIOUS LIVER DISEASES FOLLOWED AT AN URBAN CLINIC WHO UNDERWENT A LIVER BIOPSY OVER THE PAST 25 YEARS. PATTERN OF LIVER BIOPSY UTILIZATION AND PITFALLS

Magdy Elkhashab[1] Jia Xu[1] Daniel Botros[1] Gabriel Tarzi[1] Kimia Behzad Moghadam[1] Mehrdad Modarresi[1] Elizaveta Shpilevaia[1] Anish Jammu[1] Aleena Ghafoor[1] Farah Imdad Ali[1] Eva Pavic[1] Eva Fragoso[1] Mohsina Chaklader[1] Claire Lee[1] Marzena Magnes[1]

[1]*Toronto Liver Centre*

Background: Over the past 25 years, liver biopsy has been traditionally used at our centre as 'gold standard' in evaluation of liver histology, particularly in steatotic liver disease and suspected MASH. We sought to explore the pattern of liver biopsy utilization in a cohort of patients attending Toronto Liver Centre with various liver diseases including Hepatitis B, Hepatitis C and MASH/MASLD. **Methods:** This is a single site retrospective cohort study involving 405 patients who have been followed at an urban liver centre in Toronto, Canada between 1998 to 2023. The selected cohort included 405 patients over the age of 18 who underwent a liver biopsy for histological evaluation. The histological reports and diagnoses were analyzed. **Results:** The cohort's female-to-male ratio was almost equal, with females accounting for approximately 52%. The median age of this cohort was 61 years old, ranging from the age of 24 to 88. Median BMI value was 29 kg/m2 and ranged from 16.4 kg/m2 to 65.3 kg/m2. Out of 405, 215 patients had MASLD and probable MASH attributing to 53.1% of the entire cohort. 30.6% of the entire cohort had elevated liver enzymes and 62.1% of cases were of MASLD patients alone. Chronic HBV and HCV was present in 15.1% and 11.8% of cohort respectively. A total of 390 patients had a diagnosis and histological report with 53.33% of them being MASLD patients and only 13.1% were diagnosed with MASH based on the histological NAS criteria. Eight percent (8%) were chronic HCV and 7.7% were chronic HBV patients. **Conclusion:** Utilization of liver biopsy has significantly decreased for HBV and HCV patients and increased for assessment of steatotic liver disease patients. Having said that, the results revealed a pitfall in MASH diagnosis since a significant number of patients with suspected MASH were not diagnosed as such by liver biopsy. Possible explanation include a requirement of all NAS components to be present in order to diagnose MASH. We are currently evaluating this finding in a large cohort of MASLD/MASH patients to explore the underlying reason for liver biopsy limitations. This emphasizes a desperate need for development of reliable non-invasive markers for MASH diagnosis and/or utilization of AI technology for reliable MASH diagnosis.

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2132 | FURTHER EXPLORATION OF DIFFERENCES BETWEEN LEAN AND NON-LEAN METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD) IN LATINO SUBJECTS: PNPLA3 FREQUENCY AND LIPIDOMIC PROFILES

Marco Arrese[1] María Ayala Valverde[2] Jorge Arnold Alvarez[2] Francisco Barrera[2] Daniel Cabrera[3] Luis Antonio Díaz[2] Juan Pablo Arab[4] Ibon Martinez-Arranz[5] Cristina Alonso[6] Jesus Bañales[7]

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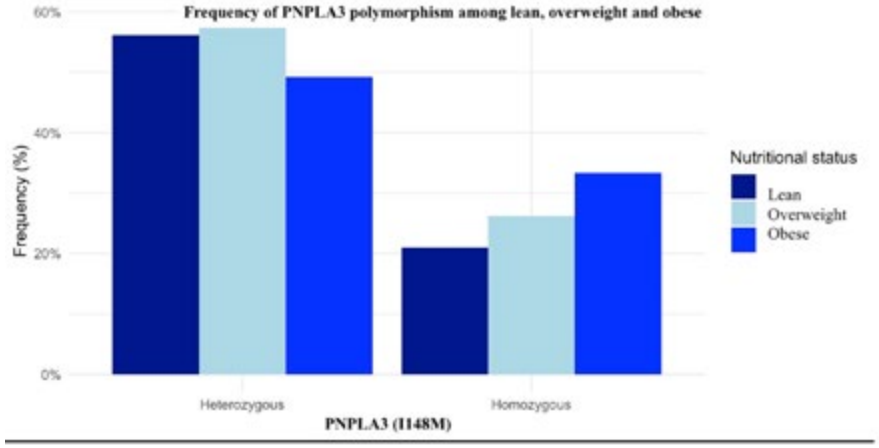
Background: A substantial number of MASLD patients have a normal body mass index (BMI). There is limited information on features of lean MASLD patients in Latino subjects. This study aimed to analyze the features of MASLD in Chilean patients with normal BMI and explore differences with those non-lean MASLD subjects. We also assessed the frequency of the rs738409 risk polymorphism (PNPLA3 I148M variant) and metabolomic profiles across the study groups. **Methods:** A cross-sectional study was conducted involving 181 randomly selected participants diagnosed with MASLD from the prospective Maule Cohort (MAUCO, BMC Public Health. 2016 Feb 4:16:122). Participants were categorized into lean, overweight, and obese groups based on their BMI. The presence of the rs738409 polymorphism was examined using Sanger sequencing. Metabolomics was assessed using UHPLC-MS in a separate group of biopsy-proven MASLD patients (15 lean and 112 non-lean). Statistical analyses of clinical data, genotypes and metabolomic profiles encompassed Fisher's exact test, Chi-square test, Kruskal-Wallis test. **Results:** 31.49% (57) were classified as thin, 36.3% (61) as overweight and 39.8% (67) as obese. Apart from higher ALT levels (p=0.004) and body fat percentage in obese subjects, no significant differences were found between the groups in terms of clinical characteristics or comorbidities. The allelic frequency of rs738409 was 77.1%, 83.6% and 82.5% in lean, overweight, and obese subjects, respectively, with no significant differences across the groups (Figure). Among the differential patterns of the circulating metabolome associated with MASH depending on the BMI, levels of ceramides were increased in overweight and obese patients compared to lean subjects (p<0.001 for five different species). The increment is higher if all the MASLD patients were considered (Figure). It is also remarkable the increment in bile acids, particularly chenodeoxycholic acid (p<0.001) and glycochenodeoxycholic acid (p=0.024). Lipidomic analysis also showed an increase of polyunsaturated diglyceride and triglyceride species in overweight and obese compared to lean subjects. Among them, most of the species included linoleic acid or alpha-linoleic acid in their esterified chains. **Conclusion:** PNPLA3 risk allele was equally frequent in lean and non-lean Chilean MASLD patients. Relevant metabolomic differences were found across the two groups with non-lean subjects exhibiting higher levels of ceramides and bile acid species compared with lean patients. (Supported by Fondecyt # 1241450)



Frequency: percentage of individuals per category.
Heterozygous: CG mutation for PNPLA3 (rs738409).
Homozygous: CC or GG mutation PNPLA3 (rs738409).

Figure 1: Changes in ceramide levels in overweight and obese compared to lean subjects.

Ceramide	MASLD	MASH
Cer(d18:1/16:0)	*	
Cer(d18:1/18:0)	*	
Cer(d18:1/20:0)	*	
Cer(d18:1/21:0)	***	**
Cer(d18:1/22:0)	***	**
Cer(40:2)	**	**
Cer(d18:1/23:0)	***	**
Cer(d18:1/24:0)	**	**
Cer(42:2)	**	
Cer(42:3)	*	
Cer(43:1)	*	
Cer(d18:1/25:0)	*	

Wilcoxon test p-value: *p<0.05; **p<0.01, ***, p<0.001)



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Disclosures: Marco Arrese: Aztra Seneca: Steering Commitee, Inventiva: Consultant, María Ayala Valverde: Nothing to Disclose, Jorge Arnold Alvarez: Nothing to Disclose, Francisco Barrera: Nothing to Disclose, Daniel Cabrera: Nothing to Disclose, Luis Antonio Díaz: Nothing to Disclose, Juan Pablo Arab: Nothing to Disclose, Ibon Martinez-Arranz: Nothing to Disclose, Cristina Alonso: Rubió Metabolomics, S.L.U.: Employee, Jesus Bañales: Nothing to Disclose

2133 | AN AI APPROACH FOR AUTOMATED AND NONINVASIVE IN VIVO LIVER SIZING IN MOUSE MODELS

Tomek Czernuszewicz[1] Alvin Chan[2] Kelsey Jarrett[2] Rochelle Lai[2] Christopher Hamad[2] Zara Mamouei[1] Juan Rojas[1] Thomas Kierski[1] Adam Aji[1] Brian Velasco[3] Phillip Durham[3] Kevin Francis[2] Nicholas Bernthal[2] Paul Dayton[3] Thomas Vallim[2] Ryan Gessner[1]

[1]Revvity, Inc., [2]University of California, Los Angeles, [3]University of North Carolina and North Carolina State University

Background: High throughput imaging with the automated Vega™ ultrasound platform has the potential to revolutionize noninvasive staging of liver diseases in rodent models by offering longitudinal, clinically translatable readouts such as liver stiffness, liver echogenicity, and liver volume. However, this increased throughput of imaging also increases the burden for analysis. Liver volume (i.e. hepatomegaly), in particular, can be challenging and time consuming to quantify as images must be annotated with a 3D segmentation demarcating the boundaries of the liver. Classical automated edge detection methods fail when applied to ultrasound data, so annotations must be drawn by hand. The goal for this work was to evaluate the effectiveness of an artificial intelligence (AI)-driven automated method for quantifying liver volume from 3D images in an effort to increase efficiency and replicability of in vivo imaging study analysis. **Methods:** A supervised machine learning model was trained to produce segmentations of mouse livers given 3D Vega ultrasound images. Longitudinal image data from numerous murine studies utilizing high fat diets and their corresponding manual segmentations were incorporated into the training algorithm. This model was then evaluated on longitudinal and cross-sectional image data from a separate held-out study consisting of two cohorts (N = 21, N = 70) of C57BL/6 mice on a modified Amylin diet (D09100310, Research Diets). Comparisons between the model volume estimation and the true ex vivo weight measurements were made (r, Pearson correlation). **Results:** The in vivo liver volume as computed by the AI model showed strong agreement (r = 0.89) with the ex vivo weight measurement across N=91 animals. Additionally, the automated volume estimation demonstrated the ability to track the manual volume estimation over longitudinally acquired images, showcasing a distinction between diseased and non-diseased animals. Discrepancies between the automated segmentation and the manual segmentation were most prominent in healthy livers, which were also more difficult to segment for human readers. Time-to-segment for one 3D image was reduced to a few seconds with the automated method using a modern GPU (NVIDIA GeForce RTX 3090) compared to several minutes of segmentation by hand. **Conclusion:** This work shows the potential of using AI-assisted automated segmentation to improve the analysis time and replicability of a longitudinal in-vivo imaging study, allowing for more images and measurements to be taken with less burden of analysis. Future studies will evaluate additional mouse models of varying liver pathologies.

Disclosures: Tomek Czernuszewicz: Revvity, Inc.: Employee, Alvin Chan: Nothing to Disclose, Kelsey Jarrett: Nothing to Disclose, Rochelle Lai: Nothing to Disclose, Christopher Hamad: Nothing to Disclose, Zara Mamouei: Revvity: Employee, Juan Rojas: Nothing to Disclose, Thomas Kierski: Nothing to Disclose, Adam Aji: Nothing to Disclose, Brian Velasco: Nothing to Disclose, Phillip Durham: Nothing to Disclose, Kevin Francis: Nothing to Disclose, Nicholas Bernthal: Nothing to Disclose, Paul Dayton: Nothing to Disclose, Thomas Vallim: Nothing to Disclose, Ryan Gessner: Nothing to Disclose

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2134 | NORMAL FIB-4 VALUES DO NOT EXCLUDE ADVANCED FIBROSIS IN 15% OF PATIENTS WITH MASLD

Jawad Aziz[1] Prerana Sruthi Vatsavayi[1] Mohammed Abdurrahman[1] Roberta Forlano[1] Benjamin Mullish[1] Michael Yee[1] Pinelopi Manousou[2]

[1]imperial college london, [2]imperial college

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) represents the leading cause of chronic liver disease globally. Identifying patients with MASLD who are at risk of advanced liver disease and require further evaluation in a specialist setting is paramount. Guidelines recommend screening for MASLD in high risk-groups following a 2-tier system: FIB-4 and/or NAFLD fibrosis score in primary care, followed by ELF and/or transient elastography in a specialist setting. However, both FIB-4 and ELF were historically derived by tertiary care cohorts and may underestimate the disease burden in a low-prevalence disease setting, such as primary care. In this study, we aimed to examine the performance of low FIB-4 in patients with MASLD when compared to transient elastography, histology at baseline and document the clinical outcomes of these patients. **Methods:** Consecutive patients diagnosed with MASLD from 2012 to 2015 (before the implementation of the two-tier system), were included. Patients' clinical and anthropometric characteristics as well as clinical outcomes at the end of follow upwere collected retrospectively. Clinical outcomes were defined as death, cardiovascular events, extrahepatic cancers and liver-related outcomes (new diagnosis of cirrhosis, HCC and decompensation (hepatic encephalopathy, variceal bleeding or ascites)). Baseline FIB-4 values were compared against liver stiffness measurements (LSM) (FibroScan®), fibrosis stage in liver biopsies and clinical outcomes. SPSS was used for data analysis. **Results:** 563 patients were included in the study: 66% male, median age 51 yo and BMI 29.6. 36% were Caucasian, 36% Arabs, 27% Asians. 302 (54%) patients had a low FIB-4 score (<1.3) and normal LSM (<8 kPa) (true negatives), and 52 patients (9%) had normal fib-4 (FIB-4 <1.3) but increased liver LSM (>8kPa). 77 patients with Fib-4<1.3 were biopsied. Interestingly, 15% had fibrosis stage 3. From those included in the false negative group (52 patients), 4 (7.7%) developed cirrhosis (median 8 years), 4(7.7%) had cardiovascular events (median time 6.5 years) and 1 patient developed extrahepatic cancer. Hypertension was significantly associated with false negative results in the multivariate analysis, with either LSM or fibrosis stage as the reference standard. **Conclusion:** The high prevalence of false negatives in this study highlights a vulnerable cohort of patients that would be missed following the current guidelines. Better referral pathways are required with the results validated in prospective studies.

Disclosures: Jawad Aziz: Nothing to Disclose, Prerana Sruthi Vatsavayi: Nothing to Disclose, Mohammed Abdurrahman: Nothing to Disclose, Roberta Forlano: Nothing to Disclose, Benjamin Mullish: Nothing to Disclose, Michael Yee: Nothing to Disclose, Pinelopi Manousou: Nothing to Disclose

2135 | VALIDATION OF THE 2023 DIAGNOSTIC CRITERIA FOR METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE AND THE ROLE OF *PNPLA3* I148M VARIANT IN LATIN AMERICA

Luis Antonio Diaz[1] Carolina Aguilera[2] Gustavo Ayares[3] Francisco Idalsoaga[3] Mauricio Pizarro[3] Fernando Barreyro[4] Sebastián Marciano[5] Jorge Martínez[5] Cristiane Villela-Nogueira[6] Nathalie Leite[6] Claudia Couto[7] Rafael Theodoro[7] Mísia Joyner de Sousa Dias Monteiro[7] Mario Pessoa[8] Mario Alvares-da-Silva[9] Fatima Higuera-de-la-Tijera[10] Adelina Lozano[11] Pedro Montes[12] Graciela Castro Narro[13] Constanza Sabate[14] Manuel Mendizabal[14] Francisco Barrera[3] Daniel Cabrera[15] Mazen Noureddin[16] Naim Alkhouri[17] Winston Dunn[18] Zobair Younossi[19] Jeffrey Lazarus[20] Rohit Loomba[1] Claudia Oliveira[21] Adrian Gadano[5] Marco Arrese[3] Juan Pablo Arab[22]

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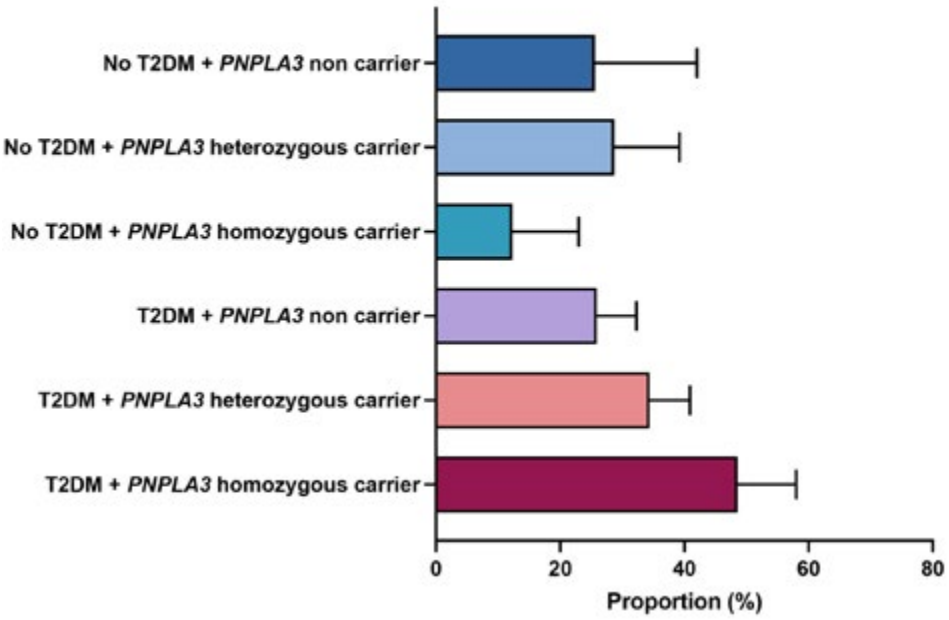
Background: Steatotic liver disease affects around one-third of the adult population in Latin America. Although Latinos living in the United States are at higher risk of metabolic dysfunction-associated steatotic liver disease (MASLD) development and progression, information from Latin American countries is extremely scarce. We aimed to validate the 2023 criteria for MASLD in Latin America and explore the role of the common genetic variant *PNPLA3* I148M in this region. **Methods:** Cross-sectional multicenter study including individuals with steatotic liver disease who undergo liver biopsy or transient elastography (TE) between 2003–2024. Liver biopsies and TE were performed in each center according to local regulations, and thresholds for TE were established as follows: significant fibrosis (F2) ≥8.2 kPa, advanced fibrosis (F3) ≥9.7 kPa, and cirrhosis (F4) ≥13.6 kPa. Analyses included logistic binary regression. **Results:** We included 2,124 patients from 13 centers in 5 countries (Argentina, Brazil, Chile, Mexico, and Peru). The mean age was 54.3±14.3 years old, 58.8% were female, and 60.2% had a liver biopsy. Around 18% had significant fibrosis, 18.7% advanced fibrosis, and 16.2% had cirrhosis. Additionally, 21.8% were homozygous carriers of the rs738409 risk polymorphism (*PNPLA3* I148M variant), 42.5% were heterozygotes, and 35.7% were non-carriers. Among the most frequent metabolic factors, 92.5% were overweight or obese, 60.9% had dyslipidemia, 58.4% had prediabetes or diabetes, and 54.4% had hypertension. In a multivariable model adjusted by baseline characteristics, metabolic dysfunction, and carrier of *PNPLA3* variants, only age (odds ratio [OR] 1.03; 95%CI: 1.01–1.04; p=0.001), prediabetes/diabetes (OR 1.75; 95%CI: 1.13–2.69; p=0.011), and *PNPLA3* risk allele carriers (heterozygotes: OR 1.48, 95%CI 1.01–2.18; p=0.046, and homozygous: OR 1.93, 95%CI 1.23–3.03; p=0.004) were associated with a higher risk of advanced fibrosis. Similar results were observed in multivariable models to assess the risk of cirrhosis. The prevalence of advanced fibrosis or cirrhosis was higher in those with prediabetes/diabetes and homozygous carriers of the *PNPLA3* I148M variant than those without both risk factors (48.6% versus 27.9%, p<0.0001)(Figure). **Conclusion:** Age, prediabetes, diabetes, and the *PNPLA3* risk allele carriers were the leading risk factors for fibrosis progression in MASLD. The MASLD diagnostic criteria should be refined, highlighting the potential role of diabetes as a major driver of liver fibrosis. *PNPLA3* I148M variant carriers are frequent in MASLD patients in Latin America, and genotyping could be established to stratify the risk of liver fibrosis routinely in clinical practice. (Supported by FONDECYT #1241450)

Prevalence of advanced fibrosis or cirrhosis according to the presence of prediabetes/diabetes (T2DM) and the *PNPLA3* I148M variant carriers



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Has not ended; Consultant relationship with Takeda; Has not ended; Consultant relationship with Terns; Has not ended; Terns, Corcept, Takeda, Madrigal, Novartis, Novo Nordisk, relationship with Allergan, Akero, BI, BMS, Gilead, Galectin, Zydus GSK; Has not ended; Consultant relationship with Novo Nordisk; Has not ended; Stock â€“ privately held company relationship with Rivus Pharma, Cytodyn, and ChronWell; Has not ended; Consultant relationship with Merck; Has not ended; Principal Investigator for a Drug Study relationship with Madrigal; Has not ended; Consultant relationship with Altimmune; Has not ended; Principal Investigator for a Drug Study relationship with Terns; Has not ended; Principal Investigator for a Drug Study relationship with Zydus; Has not ended; Stock â€“ privately held company relationship with Rivus Pharmaceuticals; Has not ended; Consultant relationship with Alligos; Has not ended; Stock - publicly traded company relationship with Cytodyn; Has not ended; Stock â€“ privately held company relationship with ChronWell; 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2136 | RAPID IDENTIFICATION OF RESMETIROM-ELIGIBLE PATIENTS IN A LARGE HEALTHCARE SYSTEM USING DATABASE PROGRAMMING AND NATURAL LANGUAGE PROCESSING

Marc Sherman[1] *Jessica Shay*[1] *Wolfram Goessling*[1]

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Background: Recent FDA-approval of resmetirom for patients with metabolic dysfunction-associated steatohepatitis (MASH) with fibrosis stages 2 or 3 offers an opportunity to stabilize or reverse fibrosis progression in this at-risk population. Rapid identification of resmetirom-eligible patients at scale, however, is complicated by assessment of patient fibrosis status, which is often communicated via narrative pathology or imaging reports. In addition, resmetirom interacts with several drugs commonly co-prescribed in patients with metabolic syndrome. CYP2C8 inhibitors like gemfibrozil and clopidogrel are contraindicated, while statins require dose reduction. Here, we evaluated a natural-language processing (NLP) algorithm rigorously validated on liver histopathology reports to rapidly identify candidates for resmetirom therapy. **Methods:** Pathology reports from patients who underwent liver biopsy in the Mass General Brigham healthcare system from 1987 to 2024 were analyzed using a previously validated NLP algorithm to ascertain fibrosis status. Patients' most recent biopsies were selected, and non-MASH liver diseases were excluded. Patients with ICD-coded cirrhosis at study end were excluded. The remaining patients were stratified by their probability of being a candidate for resmetirom. **Results:** 7,115 unique individuals were identified with NLP-detected MASH, of which 6,458 (90.7%) were pre-cirrhotic on biopsy. Another 662 individuals had ICD-coded cirrhosis as of study date end. Of non-cirrhotic MASH patients, 9.2% had F3 fibrosis and 5.4% had F2 fibrosis. Based on prior models of progression, patients with liver biopsies demonstrating F1 status >14.5 years ago (<2010) were at risk for having F2-F3 MASH. This yielded another 819 patients. In this combined cohort of established and at-risk candidates (n=1,667), only 2.7% (n=46) were prescribed a strong CYP2C8 inhibitor in the 5 years prior to study end, while 16.6% were prescribed a statin. These results were tabulated and prioritized by degree of fibrosis, flagged for dose changes, and merged with a database of last known hepatologist in our system for distribution. **Conclusion:** Database programming coupled with NLP-based ascertainment of fibrosis status enables rapid identification and stratification of patients most likely benefit from resmetirom therapy. This workflow is easily adapted to narrative imaging studies and has the potential to accelerate identification of eligible patients for future therapies or relevant clinical trials.

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2137 | GGT AS A BIOMARKER FOR THE DIAGNOSIS OF MASLD IN YOUNGER THAN 12 YEARS OLD

Ana Ramirez Tovar[1] Kelsey Chatman[1] Cristian Sanchez-Torres[1] Helaina Huneault[1] Shasha Bai[1] Katie Liu[1] Adina Alazraki[2] Geetika Khanna[2] Jack Knight-Scott[3] Miriam Vos[4]

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Background: The incidence of Metabolically Associated Steatotic Liver Disease (MASLD) in the pediatric population has risen dramatically in recent years. Detection has become fundamental for prompt treatment at an early age. Though non-invasive biomarkers, like Alanine aminotransferase (ALT) and Aspartate aminotransferase (AST), have been studied for diagnosis and monitoring of MASLD, little is known about the role of other hepatic biomarkers like gamma-glutamyl transferase (GGT) in the pediatric population This study describes the relationship between GGT levels and MASLD diagnosed via magnetic resonance imaging derived proton density fat fraction (MRI-PDFF) in a pediatric cohort. **Methods:** We conducted a retrospective chart review of all patients who had an MRI-PDFF at Children's Healthcare of Atlanta from 2017 to 2024. MRI-PDFF results were collected from the electronic medical record along with BMI, GGT, ALT, glucose, hemoglobin A1c, and other biomarkers, if available. Statistical analysis was performed using GraphPad Prism 10.2.2 and R; Continuous variables were summarized with median (IQR) and categorical variable were summarized with count (percentage); spearman correlation coefficients were calculated due to the sample's non-normality and area under the curve (AUC) was performed to determine a cutoff value for GGT in predicting Hepatic Steatosis ≥ 5% **Results:** 221 patients were identified. 37% of the patients were Female, 63% were Male, and 81.4% identified themselves as Hispanic. The median (IQR) age was 9 (8, 14). BMI and BMIp medians were 26.90 (22, 33.6) and 97.1 (94, 99), respectively. 63.8% of subjects had hepatic steatosis of ≥5% compared to 36.1% with a steatosis measurement of ≤5%. The median GGT was 23 IU/L (16, 39), median ALT was 39 (18, 89) and median MRI-PDFF was 7.6% (3.4, 17.4). Sub-analysis of the data was performed by age <12 vs ≥12 patients who had laboratory results within 90 days of the MRI-PDDF were included, leaving N=189 GGT data and N=185 ALT data. In patients < 12 years (N=121), there was a significant strong positive correlation between GGT and MRI-PDFF results (rho = 0.67, p<0.001). AUC for GGT vs Hepatic Steatosis >5% was 0.55 (p 0.56) for ≥12 years old (N=68) compared to 0.80 (p <0.001) in <12 years old (N=121) with the best cutoff at 20 UI/dL with a sensitivity of 83.6% and specificity of 69.7%. No statistically significant findings within the sexes. **Conclusion:** GGT is associated with hepatic steatosis greater than 5% for patients younger than 12 and could be used alone or with ALT and medical history to assess the diagnosis of MASLD. Prospective validation of the results is needed.

Disclosures: Ana Ramirez Tovar: Nothing to Disclose, Kelsey Chatman: Nothing to Disclose, Cristian Sanchez-Torres: Nothing to Disclose, Helaina Huneault: Nothing to Disclose, Shasha Bai: Nothing to Disclose, Katie Liu: Nothing to Disclose, Adina Alazraki: Nothing to Disclose, Geetika Khanna: Nothing to Disclose, Jack Knight-Scott: Nothing to Disclose, Miriam Vos: Nothing to Disclose

2138 | ETHNIC DIFFERENCES IN ELF SCORES IN A SUBURBAN MASH POPULATION

Kinnari Modi[1] Blake Thompson[1] Parvez Mantry[2]

[1]Methodist Dallas Medical Center, [2]The Liver Institute At Methodist Dallas

Background: Assessment of Liver Fibrosis is critical for the diagnosis, prognostication and more recently the ongoing monitoring of patients with MASH. At present, the primary noninvasive fibrosis assessment modalities are FIB-4 (screening and diagnosis), VCTE, MRE and the Enhanced Liver Fibrosis (ELF) score. Methodist Health consists of nine hospitals and over one hundred clinics that serve 7 to 10% of patients in the Dallas metroplex. In November 2021, we adopted the use of ELF in patients who had risk factors for metabolic dysfunction-associated steatotic liver disease and steatohepatitis (MASLD/MASH). We aim to explore the ELF score as an accurate marker of fibrosis in our uniquely primarily Hispanic population with MASLD/MASH. **Methods:** This is an investigator initiated retrospective study including 205 patients with MASLD/MASH with an ELF score seen at Methodist Health from November 2021 to March 2024. We collected data on other modalities of fibrosis staging including fibroscan, VCTE, MRE, and liver biopsy that were performed within a year of their ELF score. Our primary aim was to compare the accuracy of ELF score to FIB-4 in our population, assess the racial distribution

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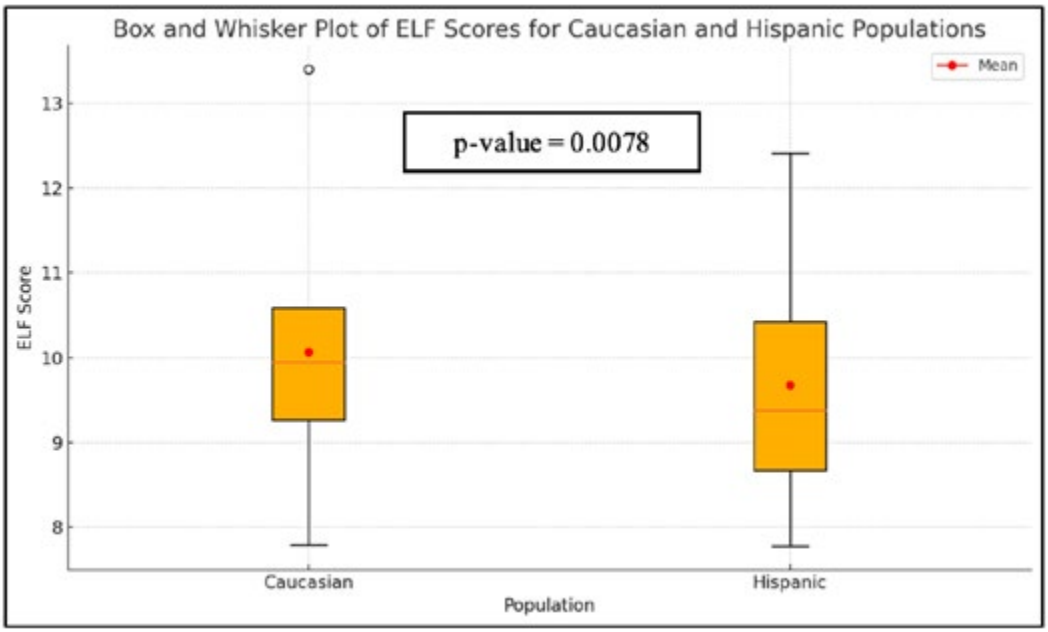
of ELF scores, and investigate potential predictors of ELF including gender, age, BMI and other metabolic risk factors. **Results:** Those with fibrosis stage 3 and 4 as determined by fibroscan, VCTE, MRE, and liver biopsy had higher ELF scores than those with Fibrosis stage 2 or less on the aforementioned modalities (Dunn's Pairwise Comparison 0.045). The Caucasian group had significantly higher ELF score than Hispanic group (Dunn's Pairwise Comparison 0.0078). Patients with higher age and BMI also have higher ELF (respectively, Coef .035, p<0.000, 95% CI[.023-.046]; Coef .028, p<0.008, 95% CI[.01-.049]). Patients with diabetes have higher ELF score than patients with no diabetes (respectively, mean ELF 10.38 vs 9.46, SD 1.09 vs 1.23). **Conclusion:** This study shows that ELF score is appropriately higher in those with fibrosis stage 3 or greater in our population. Greater age and BMI as well as the presence of diabetes are also predictors of higher ELF scores. Interestingly, the Caucasian group has significantly higher ELF scores than the Hispanic group, even though fibrosis stage as determined by fibroscan, VCTE, MRE, and liver biopsy are not significantly different between the groups. Further prospective studies are warranted to determine if ELF is underestimating the severity of fibrosis in this specific population.



Disclosures: Kinnari Modi: Nothing to Disclose, Blake Thompson: Nothing to Disclose, Parvez Mantry: Nothing to Disclose

2139 | PHASE 1 OF IMPACT OF NUTRITIONAL INTERVENTION ON THE PREVENTION OF METABOLIC ASSOCIATED STEATOTIC LIVER DISEASE IN CENTRAL VALLEY COLLEGE STUDENTS

Bilal Fazal Mehmood[1] Katherine Jones[1] Ernesto Rodriguez[1] Shabnam Pooya[2] Serhat Asci[2] Srinivasa Konduru[2] Lisa Herzig[2] Marina Roytman[1]

[1]UCSF Fresno, [2]CSU Fresno

Background: The Central Valley is considered an agricultural haven, yet its residents are disproportionately affected by metabolic disorders. Despite being a major supplier of fresh produce to the nation, its communities are marginalized by high concentrations of food deserts. In the Central Valley an estimated 45% of children and 38% of adults are classified as obese. This study aims to assess the efficacy of a prescriptive nutritional intervention program to reduce obesity and prevent metabolic associated steatotic liver disease (MASLD) in students at the California State University, Fresno (CSUF). **Methods:** Participants included freshman to junior level college students from CSUF. Inclusion criteria consisted of eligibility for Supplemental Nutrition Assistance Program (SNAP), body mass index (>25 kg/m2), and waist circumference (>35 inches in males, >40 inches in females). Baseline vibration controlled transient elastography (VCTE) established pre-intervention liver fibrosis and

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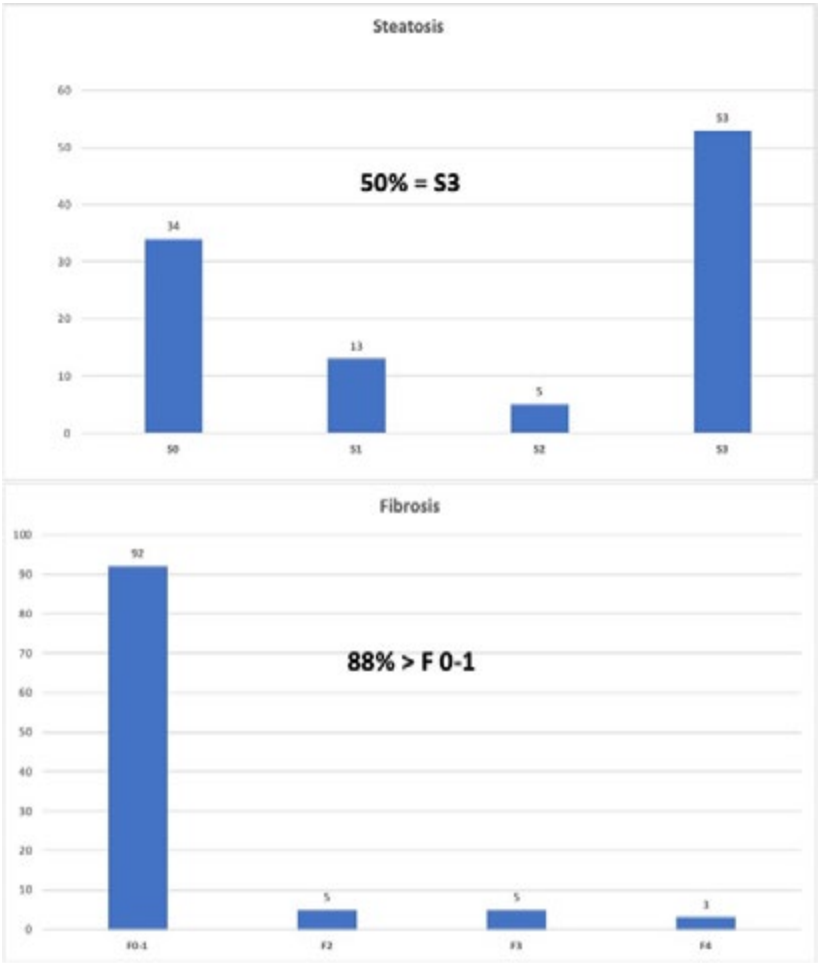
steatosis. Phase 2 will utilize nutritional interventions, with VCTE as a primary endpoint for fibrosis and steatosis post-intervention. **Results:** Our study identified 274 subjects, of which 105 were included due to incomplete data or withdrawal. Participants consisted of 78 (75%) females, 26 males, and 1 subject did not identify as either male or female. The average age was 25 years. Half of participants (53) had severe steatosis (S3) and 12% had a fibrosis score above the minimal value (F0-1). Subgroup analysis revealed that Hispanic ethnicity among men was a significant predictor of higher fibrosis grade ($p = 0.025$) and steatosis score ($p = 0.027$). Among women, Black ethnicity was found to be a significant predictor of higher fibrosis grade ($p = 0.034$). **Conclusion:** Food insecurity among college students results in obesity and metabolic disorders driven by high energy intake and unhealthy food choices. Our study revealed that half of the college students at CSUF had severe steatosis with a concerning proportion of them already developing fibrosis at a young age. Men of hispanic ethnicity and women of black ethnicity were at high risk for advanced steatosis and fibrosis. Students of ethnic minorities were found to be at a higher risk for advanced steatosis and fibrosis. These findings present an opportunity for non-invasive intervention to prevent fibrosis, which will be the second phase of our study.



Disclosures: Bilal Fazal Mehmood: Nothing to Disclose, Katherine Jones: Nothing to Disclose, Ernesto Rodriguez: Nothing to Disclose, Shabnam Pooya: Nothing to Disclose, Serhat Asci: Nothing to Disclose, Srinivasa Konduru: Nothing to Disclose, Lisa Herzig: Nothing to Disclose, Marina Roytman: Nothing to Disclose

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2140 | HIGH MORTALITY AT SAFETY-NET HOSPITALS FOR PATIENTS WITH CIRRHOSIS

Sachin Shah[1] Mignote Yilma[1] Sabrina Omer[2] Amy Shui[1] Nicole Kim[2] Kali Zhou[3] Michele Tana[1] Neil Mehta[1]

[1]University of California, San Francisco, [2]University of Washington Medical Center, [3]University of Southern California

Background: End-stage liver disease secondary to cirrhosis is a significant contributor to mortality in the US. Safety-Net Hospitals (SNHs) provide healthcare to a vulnerable patient population who often present with decompensated cirrhosis and experience worse outcomes, yet the circumstances of mortality are inadequately characterized in this population. This multicenter SNH-based study aims to evaluate the association between mortality and various clinical factors and social determinants of health (SDOH) among individuals with cirrhosis. **Methods:** This retrospective cohort study included patients with cirrhosis with a MELD-Na score ≥15 and at least 1 outpatient hepatology clinic visit at one of three SNHs between 01/01/2016-12/31/17. Manual chart review was performed with follow up until 12/31/23. Patient characteristics were described using frequencies and summary statistics, and Kaplan-Meier (KM) survival rates were estimated. A multivariable (MV) Cox proportional hazard regression model was developed to examine demographic, socioeconomic, and disease related factors associated with mortality. **Results:** The majority of the 498 patients were male (70%) and Hispanic (60%), with a median age of 54.9 years (Q1-Q3 47-61) and median MELD-Na score of 19 (Q1-Q3 16-22). The most common liver disease etiology was alcohol associated liver disease (51%). About half were primarily English-speaking (51%) and single (47%), and most had Medicaid insurance (64%) and stable housing (66%). A significant portion had missing data on education level (94%) and documentation status (40%). In a median follow-up time of 6.2 years, 45% of patients (n=222) died with a KM mortality probability of 21% within one year of initial hepatology clinic visit and 77% of deaths (n=172) occurred without a liver transplant referral. In the MV model, patients with unknown documentation status, hepatocellular carcinoma (HCC), older age, and higher MELD-Na score were associated with increased risk of death (Table 1). The KM survival probability for patients at one and five years for age≥60 and MELD-Na≥20 was 62% and 36%, respectively (Figure 1, p<0.001). The KM survival probability at one and five years for patients with unknown documentation status was 75% and 50%, respectively (p=0.005). **Conclusion:** In this multicenter study of patients with cirrhosis seen in SNH hepatology clinics, mortality rates were high with 21% of patients dying within the first year and nearly half (45%) of patients dying during follow-up. While MELD-Na, age, and HCC were associated with higher mortality, it is imperative providers pay close attention to SDOH including documentation status as a potential risk factor for patients. Early referral for liver transplant evaluation should be considered and may improve outcomes for this vulnerable population.

Table 1. Risk of death in patients with cirrhosis at three safety net hospitals using a multivariable model controlling for demographic, socioeconomic, and disease related factors.

Variable	Hazard Ratio	95% CI	p-value
Age	1.03	1.01-1.04	<0.001
MELD-Na	1.06	1.03-1.09	<0.001
HCC	2.47	1.69-3.61	<0.001
Unknown Documentation Status	1.63	1.24-2.16	<0.001

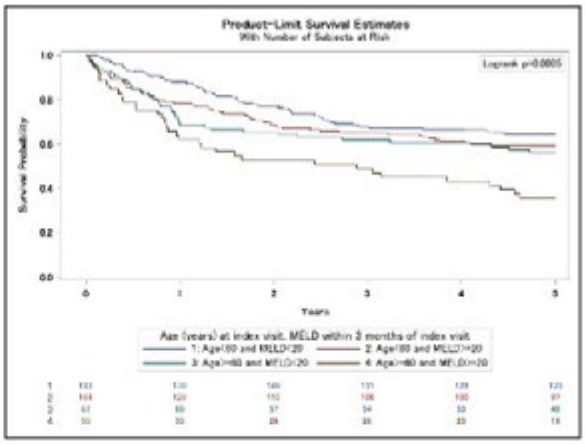

Figure 1. Kaplan Meier Survival Curves Following Initial Outpatient Hepatology Visit in Patients with Cirrhosis at Three Safety Net Hospitals Stratified by Age and MELD-Na: (1) Age<60 and MELD-Na<20, (2) Age<60 and MELD-Na≥20, (3) Age≥60 and MELD-Na<20, (4) Age≥60 and MELD-Na≥20

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2141 | SHIFTING BURDENS: GENDER DISPARITIES AND EVOLVING TRENDS IN LIVER CIRRHOSIS ACROSS LOW SDI COUNTRIES

Gautam Maddineni[1] Fnu Vikash[2] Yashwitha Sai Pulakurthi[3] Silpa Choday[4] Vikash Kumar[5] Navi Randhawa[6] Vaishnavi Boppana[7] Augustine Salami[1] Aamer Abbass[1] bhaumik brahambhatt[8]

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Background: Liver cirrhosis is a major global health issue, leading to significant illness and death. It is mainly caused by chronic hepatitis B (HBV) and C (HCV) infections, alcohol consumption, and metabolic-associated fatty liver disease (MAFLD). Understanding the trends and impact of liver cirrhosis is important to develop targeted public health interventions, especially in countries with low socio-demographic indexes (SDI) where healthcare resources are limited. **Methods:** The data was obtained from the Global Burden of Disease Study 2021, which assesses the disease burden and risk factors in 204 countries and territories. We gathered information on the occurrence of liver cirrhosis, deaths, and disability-adjusted life years (DALYs) from low SDI countries between 2012 and 2021. We used various statistical methods to handle data variability and employed Bayesian geospatial regression analysis to estimate mortality related to liver cancer. The study involved a detailed breakdown by country, gender, and year, and proportional models were used to determine the contribution of different causes to liver cancer cases. All values were measured to a p-value <0.01. **Results:** Between 2012 and 2021, cirrhosis cases from HCV increased to 1,043,136, with a decreasing Age standardized incidence rate (ASIR) for both genders (Annual percentage change(APC) -0.66). Males had a higher ASIR. Alcohol related cirrhosis cases rose from 35,917 to 43,407, with decreasing ASIR (APC -0.91), and males had a 250% higher ASIR. MASLD related cirrhosis cases surged from 251,660,517 to 345,059,834, with stable ASIR (APC 0.55), and males had a higher ASIR. Deaths from cirrhosis due to HBV and HCV rose to 60,784 and 46,862, with a declining Age standardized incidence rate (ASDR) (APC -1.5). Alcohol related cirrhosis deaths increased to 32,311, with males having a 237% higher ASDR (APC -2.07). MASLD related deaths rose to 5,192, with stable ASDR (APC -0.74), and females had a 35% higher ASDR. Cirrhosis from other causes had declining ASDR. Age-standardized disability adjusted life years (ASDALYs) for both HBV and HCV cirrhosis both have decreased (APC -2.05 and -1.78), as did alcohol related ASDALYs (APC -2.43), with males having higher burden. MASLD related ASDALYs remained stable (APC -0.6), with females having a higher burden. ASDALYs for other causes decreased (APC -2.9), with both genders carrying a similar burden. **Conclusion:** Our study shows gender differences in liver cirrhosis burden in low SDI countries. Females have a higher death rate due to metabolic-associated fatty liver disease (MAFLD) and other causes, while males have a higher death rate due to alcohol consumption. Despite rising cirrhosis cases from hepatitis C and MAFLD, improved treatment has led to a decline in related deaths from hepatitis B and C. This highlights the need for gender-specific public health strategies and better access to treatments to reduce the global burden of liver cirrhosis.

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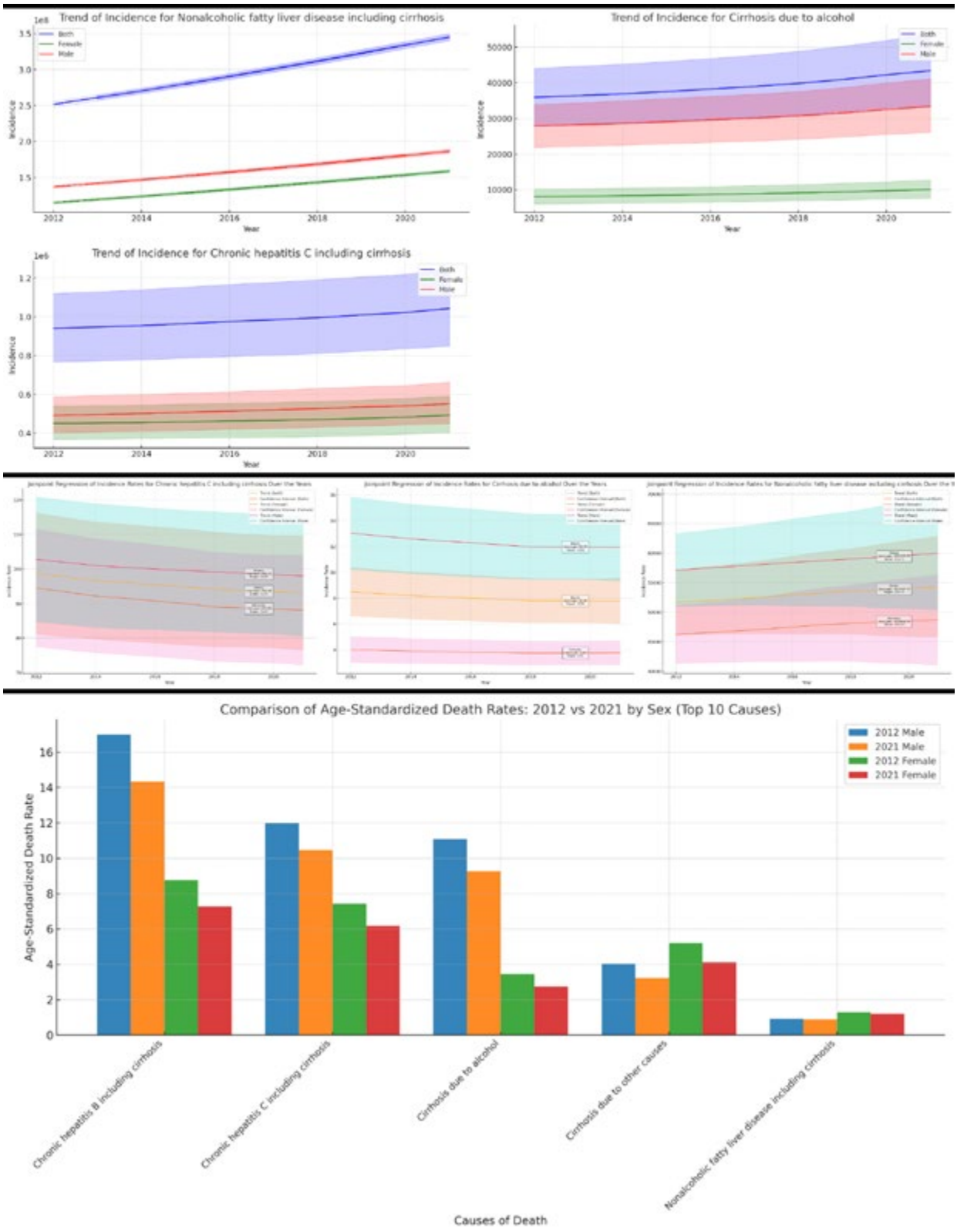

Disclosures: Gautam Maddineni: Nothing to Disclose, Fnu Vikash: Nothing to Disclose, Yashwitha Sai Pulakurthi: Nothing to Disclose, Silpa Choday: Nothing to Disclose, Vikash Kumar: Nothing to Disclose, Navi Randhawa:

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Nothing to Disclose, Vaishnavi Boppana: Nothing to Disclose, Augustine Salami: Nothing to Disclose, Aamer Abbass: Nothing to Disclose, bhaumik brahambhatt: Nothing to Disclose

2142 | RACIAL DISPARITIES IMPACT ACCESS TO AND OUTCOMES OF LIVER TRANSPLANTATION IN BLACK PATIENTS WITH HEPATOCELLULAR CARCINOMA: A SYSTEMATIC REVIEW

Isabelle Nguyen[1] *Nabil El Hage Chehade*[1] *Nour El Hage Chehade*[2] *Joy-Marie Hermes*[1] *Paul Pockros*[1] *Jennifer Au*[1] *Adam Deising*[1] *Julio Gutierrez*[1]

[1]*Scripps Clinic,* [2]*Cleveland Clinic Foundation*

Background: Liver transplantation (LT) continues to be a definitive treatment for those with hepatocellular carcinoma (HCC), which is becoming one of the fastest-rising cancers in the United States. Previous research has demonstrated Black patients with HCC tend to have higher mortality rates as compared with White patients with HCC, despite accounting for differences in tumor burden and etiology of liver disease. Policies, such as 2002 MELD allocation, 2015 revised Organ Procurement and Transplantation Network (OPTN) and Share 35, have been introduced in attempts to achieve equity in access to LT or improve post-LT outcomes, but the success of these policies in improving health disparities remains undefined in different racial groups. This systematic review sought to evaluate the potential racial disparities within LT for adult patients with HCC. **Methods:** In October 2023, the literature was reviewed across different databases, including PubMed/MEDLINE, Embase, and Google Scholar. Eligible studies included reported post-LT survival or odds of LT, stratified by race/ethnicity among eligible patients with HCC in the United States. The studies included were published between 2010 and 2023. The primary outcome was to assess LT rates and post-LT survival in Black patients with HCC compared to White patients with HCC in the United States. **Results:** Based on 13 retrospective studies including adult patients with HCC, 10 were considered large cohort databases. Our pooled results showed that Black patients were significantly less likely to receive LT than White patients with HCC, with OR ranging from 0.03 to 0.60 ($p<0.05$). Compared to Whites, Black patients had a stronger likelihood of increased post-LT mortality, with HR ranging from 1.17 to 1.53 ($p<0.05$). **Conclusion:** Our study demonstrates that Black patients with HCC are less likely to receive LT compared to Whites. Among those who end up receiving LT, Blacks have significantly lower survival rates despite adjusting for various socioeconomic, disease- and healthcare-related factors. These disparities have also persisted despite various policies implemented to achieve health equity within LT. Future research should emphasize specific initiatives to reduce racial barriers and to ensure equity in LT policies within the United States.

Disclosures: Isabelle Nguyen: Nothing to Disclose, Nabil El Hage Chehade: Nothing to Disclose, Nour El Hage Chehade: Nothing to Disclose, Joy-Marie Hermes: Nothing to Disclose, Paul Pockros: Gilead: Consultant, Intercept: Speaking and Teaching, Madrigal: Speaking and Teaching, ChemoMab: Grant/Research Support, Intercept: Grant/Research Support, Up To Date: Royalties or patent beneficiary, Orphalan: Advisor, Akero: Independent Contractor, Altimmune: Independent Contractor, Boston Pharmaceuticals: Independent Contractor, Jennifer Au: Nothing to Disclose, Adam Deising: Salix: Speaking and Teaching, Mallinckrodt: Speaking and Teaching, Julio Gutierrez: Nothing to Disclose

2143 | ANALYSIS OF THE DISTRIBUTION AND SEVERITY OF LIVER FIBROSIS STAGES AMONG THE LOCAL POPULATION WITHIN THE RIO GRANDE VALLEY: IDENTIFICATION OF RISK FACTORS AND ACCURACY OF NON-INVASIVE DIAGNOSTIC TOOLS

Dimple Desai[1] *Rashmee Patil*[1]

[1]*South Texas Research Institute*

Background: In the Rio Grande Valley of South Texas, a region with a high prevalence of metabolic disorders such as diabetes, obesity, and hypertension, liver fibrosis presents as a significant health challenge in the Hispanic population. This study examines the distribution and severity of liver fibrosis stages among the Hispanic population and assesses the accuracy of various non-invasive diagnostic tools. The aim is to evaluate the utility of non-invasive biomarkers—FIB-4, ELF, FAST, and VCTE (Fibroscan)—in predicting liver fibrosis stages and their potential association with common comorbid conditions. **Methods:** Data were collected from 283

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participants who underwent liver disease severity screening for potential inclusion into a clinical trial, focusing on demographics, liver biopsy results, and various fibrosis markers. Statistical analyses were conducted to explore correlations between fibrosis stages and metabolic conditions and to assess the predictive value of non-invasive biomarkers, with special attention paid to the cohort of moderate to advanced fibrosis patients (F2-F3). **Results:** The prevalence of diabetes (50.9%), obesity (89.7%), and hypertension (56.5%) was notably high in this enriched population. Liver fibrosis stages showed a significant correlation with metabolic syndrome components, and moderate to advanced fibrosis stages compared to no or mild fibrosis were correlated with higher rates of diabetes and hypertension. Non-invasive biomarkers varied in effectiveness; the FAST score and FIB-4 index demonstrated significant predictive value for differentiating fibrosis stages however several patients with F2-F3 disease presented with FIB-4 < 1.3. Similarly, the majority of patients with F2-F3 disease had FAST >0.5 but < 0.67. ELF and Fibroscan showed less discriminative power between fibrosis stages suggesting that subjects with ELF > 9.8 and elasticity > 12 kPa may not be the cut-off that is needed to identify patients with at-risk MASH in our specific demographic. **Conclusion:** The high prevalence of obesity and metabolic comorbidities in the Hispanic population of the Rio Grande Valley significantly contributes to liver disease severity – the more metabolic syndrome criteria a patient has, the more likely they are to have moderate-to-advanced fibrosis, with diabetes and hypertension being most associated. Non-invasive biomarkers, particularly FAST and FIB-4, are more effective than ELF and Fibroscan in staging liver fibrosis in our Hispanic patient cohort. More data needs to be collected around performance of biomarkers in diagnosing at-risk MASH in specific patient populations, as the disease is heterogeneous and biomarkers behave differently in different cohorts. These biomarkers provide critical insights for tailored interventions for developing culturally appropriate health initiatives and improving the liver health of Hispanics in this region.

Disclosures: Dimple Desai: Nothing to Disclose, Rashmee Patil: Akero Therapeutics: Grant/Research Support, Altimmune: Grant/Research Support, 89Bio: Grant/Research Support, Boehringer Ingelheim: Grant/Research Support, Boston Pharmaceuticals: Grant/Research Support, Eli Lilly: Grant/Research Support, Helio Health: Grant/Research Support, Inventiva: Grant/Research Support, Madrigal Pharmaceuticals: Grant/Research Support, Madrigal Pharmaceuticals: Speaking and Teaching, Merck: Grant/Research Support, Novo Nordisk: Grant/Research Support, Novo Nordisk: Consultant, Galectin Therapeutics: Grant/Research Support, Hepion Pharmaceuticals: Grant/Research Support, GlaxoSmithKline: Grant/Research Support, Corcept Therapeutics: Grant/Research Support

2144 | REAL-WORLD EXPERIENCE WITH FIBROSCAN® IN A TRIBAL SPECIALTY LIVER CLINIC

Janet Johnston[1] Youssef Barbour[2] Lisa Townshend-Bulson[3] Chriss Homan[2] Kena Desai[2] Wileina Rhodes[2] Julia Plotnik[2] Jennifer Gantz[2] Brian McMahon[4]

[1]Alaska Native Tribal Health Consortiu, [2]Alaska Native Tribal Health Consortium, [3]Alaska Native Tribal Consortium, [4]Alaska Native Medical Center

Background: The Liver Disease and Hepatitis Program (LDHP) at the Alaska Native Tribal Health Consortium provides specialty liver care to Alaska Native and American Indian (AN/AI) peoples. LDHP started using FibroScan® (FS) for liver stiffness measurement (LSM) in 2015, and added the controlled attenuation parameter (CAP) to evaluate steatosis in 2017. With both clinic-based and portable equipment, LDHP is able to make FS broadly available across the Alaska tribal health system. **Methods:** Using real-world data from AN/AI peoples consented to participate in our autoimmune liver disease (AILD), hepatitis B virus (HBV), and hepatitis C virus (HCV) studies, we examined LSM and CAP across diagnoses and over time. **Results:** Between 2015 and 2023, LDHP completed 3,454 FS tests on 1,536 AN/AI peoples (52.4% female, mean age 50.8+13.4 years at first FS). The most frequent diagnoses were HCV (n=981, 63.9%) followed by HBV (n=410, 26.7%) and AILD (n= 213, 13.9%). Some patients (n=330, 21.5%) had more than one liver disease diagnosis, including 55 (3.6%) with HCC. Mean LSM at first FS was 8.6+10.0 kPa, with a median of 5.5 kPA (Interquartile Range (IQR): 4.4-8.1). LSM varied by diagnosis (p<0.001; see figure). Approximately one-fifth (19.5%) of participants had advanced fibrosis or cirrhosis (F3/F4), based on an LSM > 9.5 kPa. F3/F4 prevalence varied by diagnosis (AILD: 24.4%; HBV: 6.4%; HCV: 15.6%; Multiple: 37.9%. p<0.001). Approximately half (n=884, 57.6%) had two or more valid FSs at least six months apart (mean time between scans 3.4+2.1 years), including 506 (57.2%) who were treated for and recovered from HCV. Change in LSM varied by diagnosis. Participants with HCV or multiple etiologies tended to show small improvement in fibrosis while those with AILD or HBV tended to progress (p<0.001). The median for

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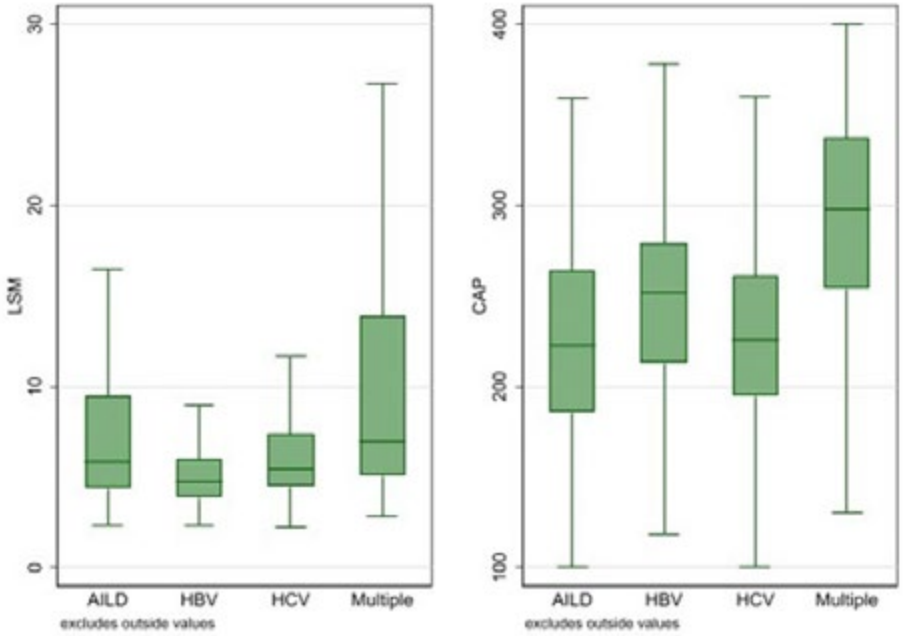
the first CAP was 244 dB/m, IQR: 206 to 286. The CAP varied with diagnosis (see figure; p = <0.001). CAP scores tended to decrease a small amount over time, with similar changes across diagnoses (p=0.23). Approximately one-third of participants (31.8%) had steatosis (CAP>274 dB/m) at baseline. The proportion of persons with their first CAP score above 274 varied by diagnosis (AILD: 20.0%, HBV: 28.3%, HCV: 17.7%; Multiple: 67.4%. p<0.001). **Conclusion:** FS is an important, non-invasive tool to measure liver stiffness and steatosis and monitor changes over time, FS can also identify persons with AILD, HCV and HBV in whom steatosis contributes to their liver disease.

Figure: (a) first LSM (kPa) and (b) first CAP, stratified by diagnosis



Disclosures: Janet Johnston: Nothing to Disclose, Youssef Barbour: Nothing to Disclose, Lisa Townshend-Bulson: Gilead Sciences: Grant/Research Support, Chriss Homan: Nothing to Disclose, Kena Desai: Nothing to Disclose, Wileina Rhodes: Nothing to Disclose, Julia Plotnik: Nothing to Disclose, Jennifer Gantz: Nothing to Disclose, Brian McMahon: Nothing to Disclose

2145 | SIGNIFICANT RACIAL/ETHNIC DISPARITIES IN LIVER TRANSPLANT WAITLIST OUTCOMES AMONG U.S. ADULTS WITH END-STAGE LIVER DISEASE DUE TO STEATOTIC LIVER DISEASE

Shyam Patel[1] Wei Zhang[2] Ashwani Singal[3] Ramsey Cheung[4] Robert Wong[5]

[1]California Pacific Medical Center, [2]Massachusetts General Hospital, [3]University of Louisville, [4]Stanford University Medical Center, [5]VA Palo Alto Healthcare System

Background: Steatotic liver disease (SLD), including alcohol-associated liver disease (ALD) and metabolic dysfunction-associated steatohepatitis (MASH), contributes to the majority of end-stage liver disease (ESLD) in the U.S. We assessed racial/ethnic disparities in patient outcomes among adults with ESLD due to SLD who are awaiting liver transplantation (LT) in the U.S. **Methods:** Adults (≥18 years old) with non-HCC ESLD due to SLD who were listed for LT were evaluated using 2010-2023 United Network for Organ Sharing (UNOS) registry data. Adjusted probabilities of LT waitlist removal (death or too sick) and receipt of LT within three years of listing were evaluated using competing-risks Cox proportional hazards models and Kaplan Meier methods. **Results:** Among 54,355 adults with non-HCC ESLD from SLD awaiting LT [median age [IQR] 56 years [48-62], 63.0% men, 77.0% non-Hispanic White (NHW), 3.0% African American (AA), 16.4% Hispanic, 1.9% Asian/Pacific Islander (API), 1.1% American Indian/Alaska Native (AI/AN)], 60.8% had ALD and 39.2% had MASH. Overall, median time to waitlist

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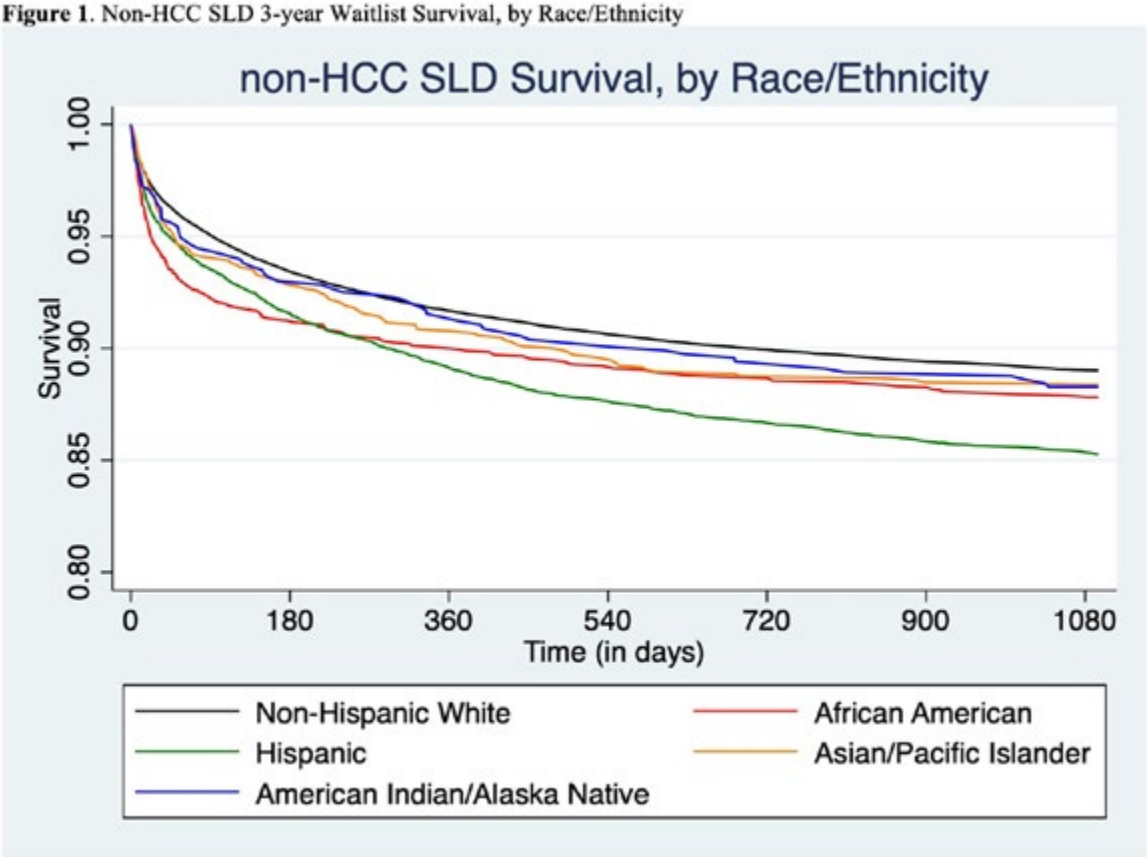
removal or receipt of LT was 152 days (IQR 28-513) and 30 days (IQR 7-136), respectively. Significantly greater risk of LT waitlist removal was observed among Hispanics (vs. NHW) (14.7% vs. 11.0%, aHR, 1.35; 95% CI, 1.27-1.44, *P*<0.05) (Figure 1). When analyzing patients with MASH or ALD separately, similar trends were observed, with significantly greater risk of waitlist removal among Hispanics (MASH: aHR, 1.24; 95% CI, 1.13-1.37; ALD: aHR, 1.40; 95% CI, 1.27-1.53; both *P*<0.05). When evaluating probability of LT, compared to NHW, significantly lower probability of LT was observed among AA (aHR, 0.86; 95% CI, 0.79-0.93), API (aHR,0.88; 95% CI, 0.80-0.97), AI/AN (aHR, 0.82; 95% CI, 0.72-0.93), and Hispanics (aHR, 0.83; 95% CI, 0.80-0.86) (all *P*<0.05). When analyzing patients with MASH, probability of LT was significantly lower among Hispanics (aHR, 0.82; 95% CI, 0.78-0.87; *P*<0.05). Among patients with ALD, probability of LT was significantly lower among AA (aHR, 0.87; 95% CI, 0.80-0.98), API (aHR, 0.86; 95% CI, 0.76-0.98), AI/AN (aHR, 0.80; 95% CI, 0.68-0.93), and Hispanics (aHR, 0.83; 95% CI, 0.79-0.87) (all *P*<0.05). **Conclusion:** Significant racial/ethnic disparities in LT waitlist outcomes were observed among adults with ESLD due to SLD, particularly among Hispanics and AA. Better understanding and addressing modifiable barriers to equitable LT care is needed to address existing disparities.

Figure 1. Non-HCC SLD 3-year Waitlist Survival, by Race/Ethnicity



*Censoring event is waitlist removal (due to death or illness)

Disclosures: Shyam Patel: Nothing to Disclose, Wei Zhang: Nothing to Disclose, Ashwani Singal: Advisor relationship with CLD Foundation; Has not ended; Speaking and Teaching relationship with Medical Speaker's Network; Has not ended; Speaking and Teaching relationship with Madrigal; Has not ended; Stock â€“ privately held company relationship with Pleiogenix; Has not ended; Consultant relationship with Pleiogenix; Has not ended; Advisor relationship with Durect; Has ended; Royalties or patent beneficiary relationship with Up-to-Date; Has not ended; Executive role relationship with Gastro Endo News; Has not ended; Grant/Research Support relationship with NIAAA; Has not ended; Employee relationship with Avera Medical Group; Has ended; Grant/Research Support relationship with GSK; Has not ended; Employee relationship with University of Louisville School of Medicine; Has not ended; Speaking and Teaching relationship with Medscape; Has not ended, Ramsey Cheung: Nothing to Disclose, Robert Wong: Theratechnologies: Grant/Research Support, Durect: Grant/Research Support, Gilead Sciences: Grant/Research Support, Exact Sciences: Grant/Research Support, Theratechnologies: Grant/Research Support, Durect Corporation: Grant/Research Support

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2146 | A NATIONWIDE RETROSPECTIVE STUDY: THE ASSOCIATION OF RACE WITH CLINICAL OUTCOMES IN HOSPITALIZED PATIENTS WITH HEPATORENAL SYNDROME

Mark Vander Weg[1] Tomohiro Tanaka[2]

[1]University of Iowa, [2]University of Iowa School of Medicine

Background: Hepatorenal syndrome-acute kidney injury (HRS-AKI) afflicts 10% of patients hospitalized with cirrhosis. Racial and ethnic disparities in outcomes have been previously reported with respect to both renal disease and hepatic diseases; however, HRS-AKI has not been specifically studied. We aimed to examine racial and ethnic differences in clinical outcomes among patients hospitalized with HRS-AKI. **Methods:** We utilized the United States (US) National Inpatient Sample from 2016-2020 to examine patients hospitalized with HRS-AKI (N = 16,377). To identify unique associations of clinical and sociodemographic factors with mortality and length of stay (LOS), hierarchical regression analysis was conducted. A mediation analysis was conducted to further estimate the extent to which associations between race and in-hospital mortality were related to payer type, area household income, and clinical severity. **Results:** Black patients demonstrated a significantly higher odds of in-hospital mortality [OR 1.16-1.20, 95% confidence interval (CI) >1], compared to their white counterparts, even after adjusting for (1) sex and age, (2) sex, age, and sociodemographic variables, and (3) sex, age, and APR-DRG severity (however, no effect was seen in the model when all variables were included). Higher mortality rates experienced by Black patients were partially mediated by greater clinical severity and lower median household income for patients' ZIP Codes [proportion mediated (PM): 0.19 (95% CI 1.189-1.192) and 0.17 (95% CI 0.16-0.18), respectively]. Hispanic patients tended to have lower odds of inpatient death [OR: 0.86 (95% CI: 0.77-0.97)] despite their lower income, increased proportion on Medicaid, and more severe illness. Black patients with HRS-AKI had longer LOS than White patients, even after adjusting for confounding factors. **Conclusion:** Our nationwide US study demonstrated that, partly due to increased clinical severity and lower median household income, Black patients with HRS-AKI experience higher inpatient mortality, compared to White patients. On the other hand, Hispanics with HRS-AKI have a survival advantage despite their lower income and greater tendency to use Medicaid insurance. The differences in outcomes among various races with HRS-AKI demands not only further study, but also increased awareness; this will ensure that attention is focused on patients with HRS-AKI who are most vulnerable.

Disclosures: Mark Vander Weg: Nothing to Disclose, Tomohiro Tanaka: Nothing to Disclose

2147 | RACIAL/ETHNIC DISPARITIES IN LIVER TRANSPLANT OUTCOME

Tomoki Sempokuya[1] Lung-Yi (Felix) Lee[1] Chuong Tran[1] Linda Wong[1]

[1]University of Hawaii

Background: Because liver transplantation (LT) is a resource-intensive procedure with a limited supply of donor organs, patients need to be carefully selected. Limited access promotes selection biases, and inevitably, disparities exist. Previous studies have focused on racial disparities in Black individuals, but this study explores LT outcomes in all races and ethnicities. **Methods:** Utilizing the UNOS database, we identified patients Age≥18 who received LT from 2014- 3/2024. We then divided into six race/ethnic groups: White, Black, Hispanic, Asian, American Indian/Alaskan Native (AIAN), and Native Hawaiian/Other Pacific Islanders (NHOPI). We excluded multiracial and unknown ethnicities. Continuous variables were analyzed with non-parametric tests. Survival analysis was done with the Kaplan-Meier survival curve. For multivariate analysis, the Cox proportional Hazard model was used. **Results:** A total of 81,955 patients were included in this study. AIANs (13.7%, 3.8%, respectively) and Hispanics (11.2%, 3.2%) had lower rates of college and graduate degrees, followed by Blacks (16.5%, 7.3%) and NHOPI (17.7%, 7.8%). The leading primary diagnosis for AIAN, Hispanic, and White was alcohol-associated cirrhosis, and Asian, Black, and NHOPI were HCC. AIAN had the highest median MELD score at the listing of 25 and a transplant of 28. Black, Hispanic, and NHOPI had the second-highest median MELD score at transplant at 25. For survival, AIAN and Blacks had worse graft survival compared to Whites and Hispanics, and Asians and NHOPI had better graft survival. A similar trend was also noted for patient survival, with the worst survival among Black and AIAN. The multivariate Cox Proportional Hazard analysis on graft survival showed a significant Hazard Ratio for Black (1.23, 95%CI: 1.16-1.30), Hispanic (0.95, 0.90-0.99), Asian (0.87, 0.79-0.95), compared to White. Other significant variables were male, age, rejection, education, diagnosis,

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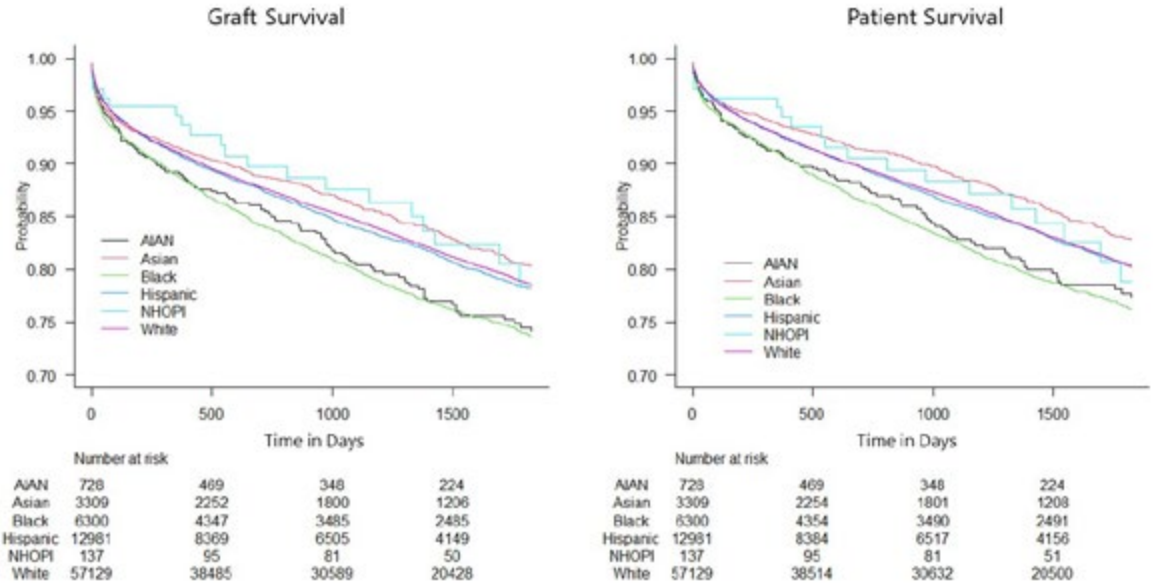
insurance, and MELD scores. For patient survival, the Hazard ratio for race/ethnicity was Black (1.21, 1.14-1.28), Hispanic (0.91, 0.86-0.95), Asian (0.81, 0.73-0.89), and AIAN (1.28, 1.09-1.52). **Conclusion:** This study showed Black and AIAN had the worst graft and patient survival, compared to other races/ethnicities, even after multivariate analysis. Particularly, AIAN had higher MELD at listing and at transplant, which may suggest delayed access to the care. Further studies are needed to facilitate prompt referral and optimize graft function in these vulnerable populations.



Disclosures: Tomoki Sempokuya: Nothing to Disclose, Lung-Yi (Felix) Lee: Nothing to Disclose, Chuong Tran: Nothing to Disclose, Linda Wong: Astra Zeneca: Speaking and Teaching

2148 | RACIAL/ETHNIC DISPARITIES IN LIVER TRANSPLANTATION: THE UNINTENDED CONSEQUENCE OF DISPARATE ALCOHOL-ASSOCIATED LIVER DISEASE

Tomoki Sempokuya[1] *Lung-Yi (Felix) Lee*[1] *Chuong Tran*[1] *Linda Wong*[1]

[1]*University of Hawaii*

Background: Previous studies have demonstrated racial disparities in liver transplant (LT) access, with Blacks being disadvantaged. However, data on other minorities are excluded in many analyses likely related to the much smaller number of overall transplants. We aimed to evaluate LTs over time trends by race/ethnicity. **Methods:** Utilizing the OPTN database, we identified adult patients who received LT from 2014 through 2023. We then separated the population into subgroups based on recipients' race/ethnic category: White, Black, Hispanic, Asian, American Indian/Alaskan Native (AIAN), Native Hawaiian/Other Pacific Islanders (NHOPI). Multiracial and unknown ethnicity were excluded. LT numbers by race/ethnicity were graphed with the Scatter Plot, and a trend line was added. For each ethnicity, LT numbers by primary diagnosis were trended over time to evaluate the change in primary diagnosis over time for each ethnicity. Subgroup analysis of alcohol-associated liver disease (both acute alcohol-associated hepatitis and alcohol-associated cirrhosis) was done using time trend analysis with a Scatter Plot with a trend line. **Results:** All ethnic groups showed increased numbers of transplants over time. However, the actual number of increases in LT was different. From 2014 to 2023, Whites had an increase of 2,651 transplants out of 3,856 overall among this study population. The slope of this linear trend line was 260.3, with an R^2 of 0.96. Hispanics showed the second fastest increase in LT numbers, with a slope value of 101.6 and an R^2 of 0.98. Asian and AIAN had an increasing trend, but it was to a much lesser degree. Black and NHOPI did not have a linear trend of increasing LT. For the time trend of LT related to alcohol, this also showed Whites had the greatest increase in LT related to alcohol with a slope of 231.9, with an R^2 of 0.99 on the linear trend

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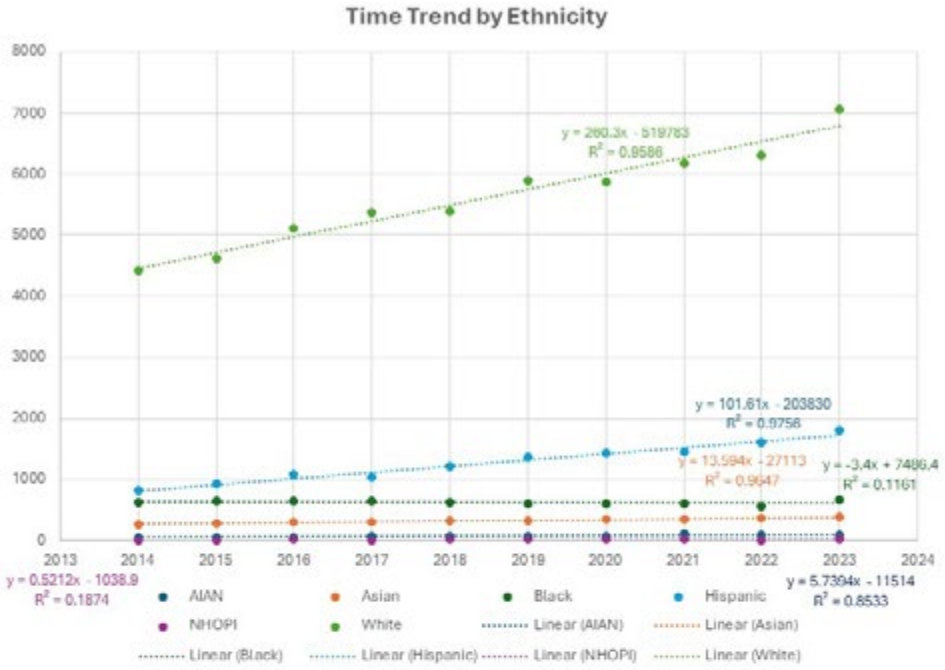
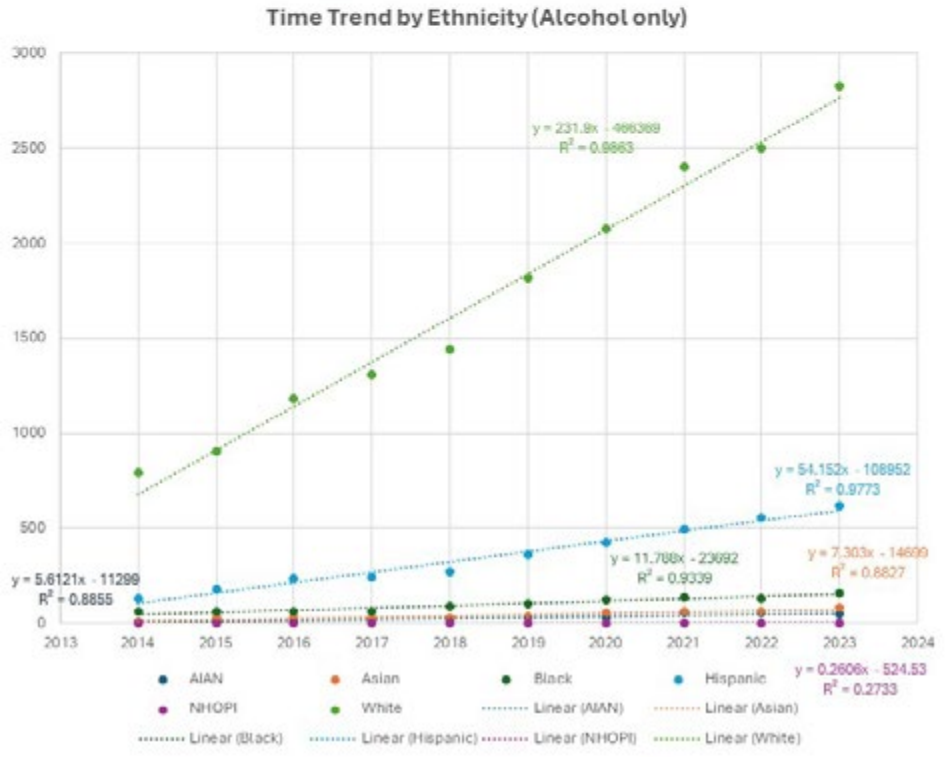
line. Hispanics had the second fastest increase, with a slope of 54.15 and an R^2 of 0.98. This trend was followed by Black (Slope: 11.79, R^2: 0.93), Asian (Slope: 7.30, R^2: 0.88), AIAN (Slope: 5.61, R^2: 0.89), but NHOPI did not have a linear trend change. **Conclusion:** This study showed an unequal increase in LT, which varied by race/ethnicity, with the recent increase in transplant volume mainly attributed to White patients with underlying alcohol-associated liver disease. A public health approach targeting responsible alcohol consumption should be a priority to increase LT availability for those with non-alcohol related diseases.





Disclosures: Tomoki Sempokuya: Nothing to Disclose, Lung-Yi (Felix) Lee: Nothing to Disclose, Chuong Tran: Nothing to Disclose, Linda Wong: Astra Zeneca: Speaking and Teaching

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2149 | HEALTH LITERACY AND EDUCATION LEVEL ARE DETERMINANTS OF DISEASE SEVERITY IN METABOLIC DYSFUNCTION ASSOCIATED STEATOTIC LIVER DISEASE ★

Alana Saddic[1] Jessica Mittler[1] Hannah Lee[1] Deborah DiazGranados[1] Arun Sanyal[1]

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Background: Health literacy is a multi-dimensional construct that captures a person's ability to access, understand, appraise and apply health information to manage their health. It is an important determinant of health outcomes. There are no data on the spectrum of health literacy in MASLD patients and its relationship to disease severity. Aim: To evaluate health literacy in patients with MASLD and its relationship to disease severity accounting for educational status. **Methods:** A prospective study using the health literacy questionnaire (HLQ) in MASLD patients was performed. Clinical, demographic and laboratory data were obtained from medical records and participants. Scores for the nine scales of the HLQ (five in "part 1" and four in "part 2") were computed. The continuous attenuation parameter (CAP) and liver stiffness measurement (LSM), assessed by vibration-controlled transient elastography (VCTE), were used as surrogates for steatosis and fibrosis respectively. HLQ scores or education were correlated with clinical and VCTE parameters. Significance was set at p<0.05. **Results:** 101 participants with MASLD (mean age: 57 yrs, females 61%, White 77%, African American 11%, Asian 8%, Latino 3%, mean CAP: 298, mean LSM: 11 Kpa) were studied. For HLQ part 1 (response scale 1-4), scores for questions related to "feeling understood and well supported by healthcare providers" (mean ± S.D.) (3.43 ± 0.6) were the highest and "actively managing my health" (2.98 ± 0.6) were the lowest. For part 2 of the HLQ (response scale 1-5), scores for questions related to "understanding health information well enough to know what to do" (4.12 ± 0.57) were the highest and "navigating the health system" (3.83 ± 0.71) were the lowest. Lower scores for "actively managing my health" and "social support for health" were both respectively associated with higher CAP scores (r=-0.29, p=0.012) (r=-0.30, p=0.008) and BMI (r=-0.38, p=< 0.001) (r=-0.2, p= 0.045). Higher education was positively correlated with finding (r=0.252, p=0.012), appraising (r= 0.242, p=0.015), and understanding (r=0.336, p=<0.001) health information. Higher LSM was correlated with lower education level (r=-0.26, p=0.022) and lower scores for understanding health information (r=-0.237, p=0.037). **Conclusion:** Lower health literacy is associated with more advanced MASLD. Lower education further affects multiple aspects of health literacy and is also inversely related to LSM (fibrosis) severity.

Disclosures: Alana Saddic: McKesson: Stock - publicly traded company, Eli Lilly: Stock - publicly traded company, Jessica Mittler: Nothing to Disclose, Hannah Lee: Nothing to Disclose, Deborah DiazGranados: Nothing to Disclose, Arun Sanyal: Genfit, Akarna, Tiziana, Durect, Inversago, Hemoshear, North: Stock - publicly traded company, Astra Zeneca (60K), Boston Pharmaceutical (<5K), Myovent (<5K),: Consultant, Variant (<5K), Cascade (<5K), Northsea (<5K): Consultant, Gilead, Salix, Tobira, Bristol Myers, Shire,. Intercept,: Institution has received grants from above companies, Merck, Astra Zenca, Mallinckrodt, Novartis: Institution has received grants from above companies, UpToDate, Elseiver: Royalties or patent beneficiary, Sanyal Bio: Employee, Phillip Hylemon: Nothing to Disclose, Jiangao Fan: Nothing to Disclose, Huiping Zhou: Nothing to Disclose

2150 | EVALUATING GAPS AND DISPARITIES IN HEPATITIS B TREATMENT AMONG US ADULTS: A REAL-WORLD ANALYSIS USING A NATIONWIDE ELECTRONIC HEALTH RECORDS DATABASE ◆

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[1]VA Palo Alto Healthcare System, [2]Gilead Sciences, [3]Gilead Sciences, Inc.

Background: Treatment of chronic HBV (CHB) infection is aimed at the prevention of disease progression and hepatocellular carcinoma (HCC) with the goal of improving survival and quality of life. Current AASLD HBV guidelines recommend antiviral therapy in patients with elevated HBV DNA and ALT, especially those with significant or advanced fibrosis. We aim to evaluate antiviral treatment patterns among U.S. adults with chronic HBV utilizing a nationwide Electronic Health Records (EHR) database. **Methods:** We identified CHB patients >=18 years of age using available laboratory data in a nationwide EHR database (TriNetX, LLC) from January 1, 2010 – December 31, 2022. Those included had at least one positive HBV DNA result and one ALT result. Index date was defined as the date of first non-zero HBV DNA, and the closest ALT value was used (time period: -2 to

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+ 1 months around index date). Patients with baseline evidence of coinfection with HIV, HCV, HDV or advanced liver disease (compensated or decompensated cirrhosis, HCC, or liver transplant), <180 days of activity in the dataset prior to index, or missing ALT values at index, were excluded. The proportion of patients on HBV antiviral therapy at index date were compared by sex, race/ethnicity, and FIB-4 score using chi-square methods. **Results:** Among 6,395 HBV patients identified, only 15.4% (n=983) had evidence of receiving antiviral treatment at index. Compared to the untreated cohort, treated individuals were older (51 vs 46 years; p <0.01). Among men, a greater proportion were treated (18.3%) than among women (12.6%; p<0.01) (Table 1). Significant differences by race were observed, with the highest proportion treated among whites (18.3%) and the lowest proportion treated among African American/blacks (13.6%), p<0.01. Among 421 patients with FIB-4 >3.25, 266 (63.2%) had no evidence of treatment. **Conclusion:** Among HBV patients in a large EHR database, less than one in six patients received HBV antiviral therapy, with differences observed by race and sex. Even more concerning, among HBV patients with FIB-4 >3.25, over 63% were not on any HBV antiviral therapy. Future studies using more comprehensive, longitudinal data are needed to better understand the drivers of these gaps and disparities in HBV treatment, which will guide interventions to improve timely access to antiviral therapy to improve patient outcomes.

Table 1. Distribution of HBV patients with available laboratory data and no evidence of treatment at time of index by race (A.) sex (B.) and fibrosis as assessed by FIB-4 (C.) in the TriNetX Database between January 1, 2010 and December 31, 2022.

A.	White	Black	Asian	Other[1]	Total
Treated	214 (18.3%)	240 (13.6%)	396 (16.2%)	133 (13.2%)	983 (15.4%)
Not treated	957 (81.7%)	1526 (86.4%)	2053 (83.8%)	876 (86.8%)	5412 (84.6%)
Total:	1171	1766	2449	1009	6395

Chi-sq=16.8; p< 0.01

B.	Male	Female	Total
Treated	568 (18.3%)	415 (12.6%)	983 (15.4%)
Not treated	2530 (81.7%)	2882 (87.4%)	5412 (84.6%)
Total:	3098	3297	6395

Chi-sq=40.6; p< 0.01

C.	FIB-4: <1.45	FIB-4: 1.45-3.45	FIB-4: >3.25	Total
Treated	397 (12.4%)	226 (21.1%)	155 (36.8%)	778
Not treated	2793 (87.6%)	846 (78.9%)	266 (63.2%)	3905
Total:	3190	1072	421	4683

Chi-sq; p < 0.01

[1]Other: includes American Indian or Alaskan Native, Native Hawaiian or Other Pacific Islander, and Unknown.

Disclosures: Robert Wong: Theratechnologies: Grant/Research Support, Durect: Grant/Research Support, Gilead Sciences: Grant/Research Support, Exact Sciences: Grant/Research Support, Theratechnologies: Grant/Research Support, Durect Corporation: Grant/Research Support, Leland Yee: Gilead Sciences: Employee, Yunhao Liu: Gilead Sciences: Employee, Laura Telep: Gilead Sciences, LLC: Employee, Gilead Sciences, LLC: Stock - publicly traded company, Shahed Iqbal: Gilead Sciences, Inc.: Stockholder, Gilead Sciences, Inc.: Stock - publicly traded company, Gilead Sciences, Inc.: Employee, Sarjita Naik: Gilead Sciences: Employee, Gilead Sciences: Stock – privately held company, Betty Chiang: Nothing to Disclose, Amanda Singer: Gilead Sciences: Employee, Gilead Sciences: Stock - publicly traded company, Anand Chokkalingam: Nothing to Disclose, Catherine Frenette: Nothing to Disclose

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2151 | DISPARITIES IN PRIMARY BILIARY CHOLANGITIS: A RETROSPECTIVE STUDY USING REAL-WORLD DATA FROM A SINGLE HEPATOLOGY CLINIC IN THE GREATER LOS ANGELES AREA

Sabrina Alff[1] Orlinda Ventura[1] Trinity Love Foster-Malave[1] Michel Mendler[1] Edward Mena[2]

[1]California Liver Research Institute, [2]California Liver Reasearch Instituite

Background: Primary Biliary Cholangitis (PBC) is an autoimmune disease that leads to cirrhosis. MASLD can lead to progressive liver disease and has a high prevalence among Hispanic/Latinos (HL). We aimed to describe disparities in a diverse population of patients followed for PBC in a real-world, non-academic hepatology clinic in Los Angeles County (LAC). **Methods:** Retrospective cohort study of patients with PBC diagnosed by accepted criteria (AMA positivity/IgM elevation/biopsy findings). Demographics, socioeconomic factors, metabolic data, associated liver disease, degree of severity of liver disease (Liver biopsy findings, FibroScan®, CAP and stiffness) were compared between races and ethnicities through univariate and multivariate analysis. **Results:** 207 patients seen between 2009 and 2023 met the inclusion criteria. 49.5% ethnically identified as HL and 50.5% as non-Hispanic/Latino (NHL). Of HLs, all racially identified as White, significantly different ($p<0.001$) from NHL who were 4.4% Black, 39.1% Asians, and 56.5% Caucasians. Median age was 61 y(20-90), and 83% were female. 63% of the patients were married. Employment was Blue-collar (15.3%), white-collar (32.3%), and retired (52.4%). The Area Deprivation Index (ADI, 1-10, least to most disadvantaged) was significantly higher ($p<0.0016$) in HLs vs NHLs (score 1-3: 16.5% vs. 34.4%; 4-6: 52.8% vs. 52.7%; 7-10: 30.7% vs. 12.9%). 26.4% of patients drank alcohol without excess. Response to UDCA was 85.0%. When compared to NHL, HLs exhibited significantly higher BMI [median: 26.7(15.6-48.5) vs 24.4(15.8-32.4), $p>0.0025$], more associated MASLD/MASH (45.6% vs 19.35%, $p<0.0001$) and F2-4 stages (80.4% vs 52.7%, $p=0.0059$). Patients with F2-4 staging (63%) had a lower rate of marriage (76.2% vs. 53.5%; $p>0.0147$), higher prevalence of MASLD/MASH (49.3% vs 31.0%; $p=0.0429$), and higher rate of autoimmune hepatitis (AIH) (33.3% vs. 14.3%; $p=0.0289$). By multivariate analysis, AIH [OR 3.91(1.33-11.5), $p=0.0131$], MASLD/MASH [OR 2.49(1.04-5.97), $p=0.0411$], and male gender [OR: 4.44(1.24-15.8), $p=0.0217$] were independently associated with stage F2-4. **Conclusion:** This “real-world” data in a diverse population with PBC from LAC suggests that HLs are more socially disadvantaged, have higher BMI, rates of associated MASLD/MASH and fibrosis. Overall, PBC patients with fibrosis have a higher prevalence of MASLD/MASH, AIH, and lower marriage rate. Associated AIH, MASLD and male gender were independently associated with F2-24.

Disclosures: Sabrina Alff: Nothing to Disclose, Orlinda Ventura: Nothing to Disclose, Trinity Love Foster-Malave: Nothing to Disclose, Michel Mendler: Nothing to Disclose, Edward Mena: Nothing to Disclose

2152 | TEMPORAL TRENDS IN DEATHS FROM ALCOHOL USE DISORDER, ALCOHOLIC LIVER DISEASE, AND HEPATOCELLULAR CARCINOMA IN THE UNITED STATES FROM 1999-2020

Yash Hegde[1] Adnan Said[2]

[1]University of Wisconsin, [2]University of Wisconsin School of Medicine and Public Health

Background: The incidence of alcohol use disorder (AUD) and alcoholic liver disease (ALD) has increased in the US over the last two decades. The aim of this study was to evaluate recent trends in mortality from AUD, ALD, and liver cancer (HCC) in the US from 1999-2020 and the population subgroups that are at increased risk for these prevalent diseases. **Methods:** We acquired deidentified data from the Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiological Research (CDC WONDER) underlying cause of death database from years 1999-2020 in the US. Deaths from AUD, ALD, and HCC were identified by International Classification of Diseases, Tenth Revision (ICD-10) codes. Age adjusted mortality rates (AAMRs) per 100,000 population were stratified by sex and race. Crude mortality rates per 100,000 population were used for comparisons between age groups. We used linear regression models to identify temporal trends in mortality rates for AUD, ALD, and HCC. **Results:** AUD, ALD, and HCC related mortality rates increased from 1999-2020. Men had higher AAMRs (6.3, 10.9, 4.5) than women (1.9, 5.0, 1.2) for AUD, ALD, and HCC in 2020. The 55-64 age group had the highest crude mortality rate for AUD and ALD (12.5, 24.0) while the 75-84 age group had the

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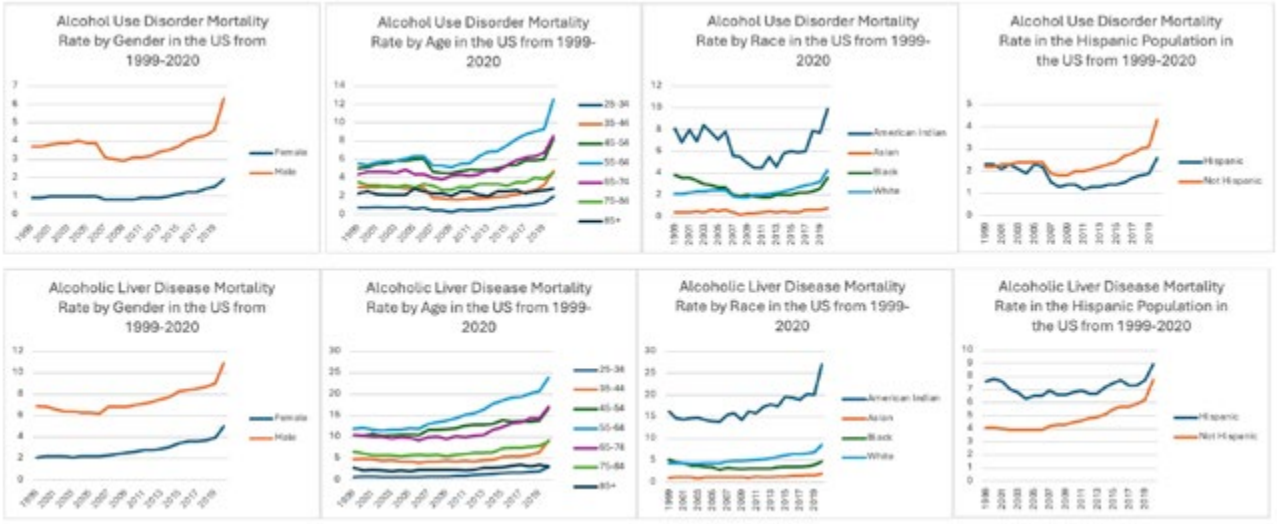
highest crude mortality rate for HCC (15). American Indian or Alaskan Native patients had the highest AAMRs for AUD and ALD (9.9, 27), followed by White (4.3, 8.6), Black or African American (3.6, 4.7), and Asian or Pacific Islander (0.8, 2). Non-Hispanic patients had a higher AAMR (4.3) than Hispanic patients (2.6) for AUD. Hispanic patients had a higher AAMR (8.9) than non-Hispanic patients (7.7) for ALD. **Conclusion:** There has been an overall increase in AAMRs for AUD, ALD, and HCC from 1999-2020 in the US with disparities in race, sex, and age. Temporal trends demonstrate a higher AAMR in Hispanic patients when compared to non-Hispanic patients for ALD. Non-Hispanic patients had a higher AAMR for AUD when compared to Hispanic patients. This finding may be related to Hispanic patients having a higher genetic frequency of PNPLA3 leading to increased risk for steatohepatitis. Addressing these differences can aid in surveillance and strategies to reduce the burden of these diseases. Further studies investigating societal factors that may contribute to these differences can help impact public policy decision making to reduce the incidence of harmful drinking and its adverse consequences.



Disclosures: Yash Hegde: Nothing to Disclose, Adnan Said: Mallinckrodt: Speaking and Teaching

2153 | SOCIAL ISOLATION IS HIGHER AMONG PEOPLE WITH CHRONIC LIVER DISEASE AND ASSOCIATED WITH INCREASED PYSCHOLOGICAL DISTRESS AND ALL-CAUSE MORTALITY

Tiana Walker[1] Alysa Alejandro-Soto[1] Lauren Nephew[2] Patricia Jones[3] Nneka Ufere[1] Carlos Lago Hernandez[4]

[1]Massachusetts General Hospital, [2]Indiana University, [3]University of North Carolina at Chapel Hill, [4]University California San Diego

Background: Social isolation has been identified as an important national public health concern; however, the effects of social isolation on health outcomes of adults with chronic liver disease (CLD) are unknown. **Methods:** Using the U.S. National Health Interview Survey from 2014 to 2018, we identified adults with self-reported CLD. We used complex weighted survey analysis to obtain national estimates of social isolation (defined as living alone) in this population. We used multivariable regression analyses to examine the association of social isolation with psychological distress (defined as a score >12 on the Kessler 6 distress scale). Kaplan-Meier methods were used to compare all-cause mortality by social isolation status. **Results:** Of the 3676 (representing 5.3 million) US adults with CLD, 22% (95% CI: 21–24%) reported experiencing social isolation and 9% (95% CI: 8-10%) reported experiencing psychological distress. A diagnosis of CLD was independently associated with social isolation [aOR 1.2 (1.1-1.4); p<0.001] and psychological distress [aOR 2.7 (2.3-3.2); p<0.001] after adjusting for age, income, insurance, race, alcohol use, and comorbidity burden. Social isolation was independently associated with psychological distress [aOR 1.4 (95% CI 1.3-1.6); p<0.001] on adjusted analyses. Socially-isolated adults with CLD were 1.8 (95% CI 1.3-2.6) times more likely to experience psychological distress than non-isolated adults with CLD, with a prevalence of 14% (12-17%) and 8% (6-9%), respectively **(**Figure**).** Social isolation was an independent predictor of mortality after adjusting for age, income level, insurance status, comorbidity burden, presence of transportation insecurity, and presence of psychological distress [aHR 1.4 (1.3-1.5); p <0.001].

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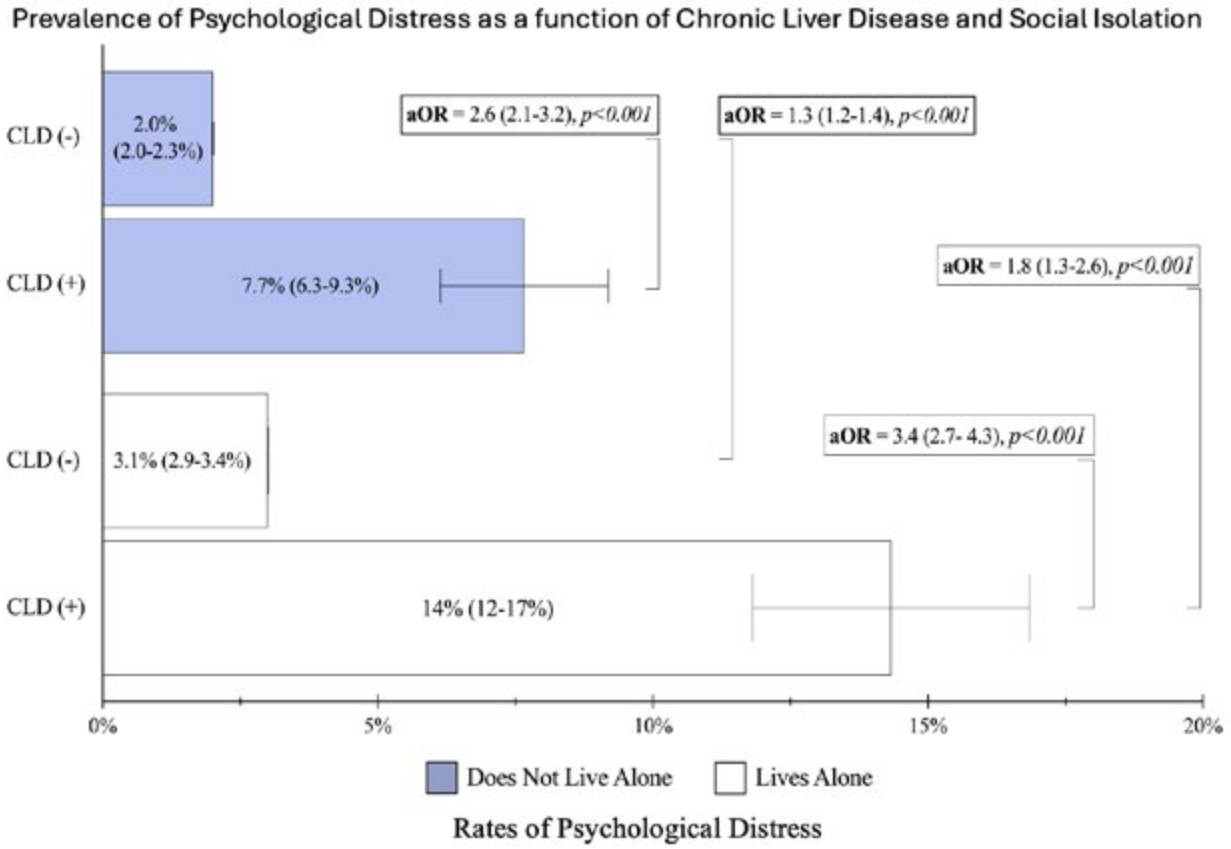
Conclusion: Adults with CLD were more likely to be socially isolated and experience psychological distress than adults who do not carry a CLD diagnosis. Among adults with CLD, both social isolation and psychological distress were associated with increased mortality risk. Further work should be done to develop more equitable considerations of the social support component in the care of patients with CLD undergoing liver transplant evaluation process. Additional investigation should aim to identify social services that modify the risk of social isolation and psychological distress among CLD patients.



Disclosures: Tiana Walker: Nothing to Disclose, Alysa Alejandro-Soto: Nothing to Disclose, Lauren Nephew: Nothing to Disclose, Patricia Jones: Gilead: Grant/Research Support, Nneka Ufere: Nothing to Disclose, Carlos Lago Hernandez: Nothing to Disclose

2154 | DISPARITIES IN THE AANHPI POPULATION WITH INTRAHEPATIC CHOLANGIOCARCINOMA: A DISAGGREGATED SURVIVAL STUDY OF THE SEER DATABASE

Christopher Huy Doan[1] *Ryan Nguyen-Flores*[1] *Vincent Yang*[1]

[1]*The University of Texas Medical Branch*

Background: Incidence and mortality rates of intrahepatic cholangiocarcinoma (CCA) have risen in the U.S. since 2000. The Asian American, Native Hawaiian, and Pacific Islander (AANHPI) population has disproportionately higher rates of CCA incidence compared to non-Hispanic Whites (NHW). They are particularly susceptible due to the prevalence of risk factors in the AANHPI population, such as Hepatitis B, Hepatitis C, and hepatobiliary flukes. The AANHPI population has long been studied as a “monolith”. Unfortunately, by grouping people from more than 30 different countries, each with their own geographic and socioeconomic distinctions, disparities could potentially be concealed. We aimed to investigate the need to disaggregate the AANHPI population due to the variability among the multiple racial groups it encompasses. **Methods:** The Surveillance, Epidemiology, and End results (SEER) National Database was queried for intrahepatic cholangiocarcinoma cases from 2000-2020. Cohorts

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were developed to disaggregate the AANHPI population. Due to the small sample size in some groups, some cohorts were grouped by geographical similarity (e.g. Native Hawaiian and Pacific Islander). Southeast Asians, outside of Vietnam, also had a small case count and were grouped by geographical similarity. The final cohorts were Non-Hispanic White (NHW), Black, Native American, Chinese, Japanese, Filipino, Korean, Vietnamese, Other Southeast Asians (Cambodia, Laos, Hmong, Kampuchean, Thai), South Asian, and Native Hawaiian/ Pacific Islander. Kaplan-Meier Survival and Cox Regression analyses were performed to compare overall survival outcomes between the disaggregated AANHPI populations with the NHW cohort serving as the control. **Results:** A total of 14,830 patients were included in the study. Cox Regression analysis revealed a statistically significant decrease in overall survival for intrahepatic cholangiocarcinoma in the Chinese and Black subpopulations as compared to Non-Hispanic White patients. These values were 23.3% and 14.8% respectively. Japanese patients saw a statistically significant increase in overall survival of 48.9%. Other subpopulations were similar or nonsignificant. Kaplan-Meier analysis revealed an average overall survival time of 80.17 months. The Chinese cohort experienced a shorter average survival time of 70.01 months. Japanese and NHPI patients had the longest overall survival time of 109.92 and 102.18 months, respectively. **Conclusion:** Disaggregating the AANHPI population reveals significant disparities in intrahepatic cholangiocarcinoma outcomes. Chinese and Black patients exhibit decreased survival compared to NHWs, while Japanese and NHPI patients show better survival. Other populations were quite small, which could indicate a need to improve AANHPI recruitment in research data collection. Targeted interventions are needed to address these disparities appropriately.

Ethnicity	Coefficient (SE)	Hazard Ratio	P-value
Black	0.075	1.148	0.065
Native American	0.259	0.877	0.614
Chinese	0.105	1.233	0.045
Japanese	0.22	0.511	0.002
Filipino	0.123	1.121	0.354
Korean	0.164	1.285	0.127
Vietnamese	0.171	1.066	0.708
Other SEA	0.26	1.083	0.758
South Asian	0.237	1.093	0.708
NHPI	0.202	1.135	0.529

Disclosures: Christopher Huy Doan: Nothing to Disclose, Ryan Nguyen-Flores: Nothing to Disclose, Vincent Yang: Nothing to Disclose

2155 | HOSPITALIZED PATIENTS WITH CIRRHOSIS, ESPECIALLY THOSE NOT IN HIGH INCOME COUNTRIES CONTINUE TO HAVE WORSE OUTCOMES REGARDLESS OF WHETHER OUTCOMES WERE STUDIED DURING AND AFTER THE COVID PANDEMIC

Jasmohan Bajaj[1] Qing Xie[2] Patrick S Kamath[3] Mark Topazian[4] Peter C Hayes[5] Aldo Torre Torre[6] Hailemichael Desalegn Mekonnen[4] Ramazan Idilman[7] Mario Alvares-da-Silva[8] Jacob George[9] Florence Wong[10] Zhujun Cao[2] Shiv K Sarin[11] Neil Rajoriya[12] Rosemary Faulkes[12] Aloysious Aravinthan[13] Suresh Vasan Venkatachalapathy[13] Dominik Bettinger[14] Michael Schultheiß[14] Chenghai Liu[15] Yanyun Zhang[15] Qunfang Rao[16] Xiaoping Wu[16] Jacqueline Cordova-Gallardo[17] Zhen Xu[18] Zhiliang Gao[18] Bin Xu[19] Linlin Wei[19] Jing Liu[20] Xin Zheng[20] Ningping Zhang[21] Wanqin Zhang[21] Feng Guo[22] Xiaozhong Wang[22] Mingqin Lu[23] Yijing Cai[23] Dedong Yin[24] Lei Wang[24] Caiyan Zhao[25] Wei Wang[25] Feng Peng[26] Yongfang Jiang[26] Adebayo Danielle[27] James Kennedy[27] Lilian Torres Made[28] Rene Male-Velazquez[28] Liana Mondlane[29] Mussagy Tarmamade[29] Xinrui Wang[30] Yanhang Gao[30] Man Su[31] Minghua Su[31] Chuanwu Zhu[32] Yingling Wang[32] Anil Anand[33] Dibyalochan Praharaj[33] Nabiha Faisal[34] Akash Roy[35]

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Radha Dhiman[35] Dinç Dinçer[36] Haydar Adanır[36] Francisco Felix-Tellez[37] José Antonio Velarde-Ruiz Velasco[37] Qing Xie[2] Zhujun Cao[2] Marie Jeanne Lohoues[38] Ponan Claude Regis Lah[38] Alper Uysal[39] Zeki Karasu[39] Adrian Gadano[40] Sebastián Marciano[40] Fiona Tudehope[41] Abdullah Emre Yildirim[42] Sezgin Barutcu[42] Dinesh Jothimani[43] Mohammad Rela[43] Anoop Saraya[44] Jatin Yegurla[44] K Rajender Reddy[45] Suditi Rahematpura[45] Busra Haktaniyan[46] Carlos Benítez[47] Marco Arrese[47] Kessarin Thanapirom[48] Tongluk Teerasarntipan[48] Hiang Keat Tan[49] Wei Lun Liou[49] Ajay Duseja[50] Akash Gandotra[50] Ashish Goel[51] C Eapen[51] Anand Kulkarni[52] Mithun Sharma[52] Jose Luis Perez Hernandez[53] Oscar Morales Gutierrez[53] Araceli Bravo Cabrera[54] Maria Sarai Gonzalez-Huezo[54] Paul Thuluvath[55] Somya Sheshadri[55] Shiva Kumar[56] Aabha Nagral[57] Ajay Jhaveri[57] Abha Nagral[58] Amey Sonavane[58] Chinmay Bera[59] Helena Katchman[60] Liane Rabinowich[60] Nik Arsyad Nik Muhamad Afendi[61] Ruveena Rajaram[62] David Bayne[63] Hugo Vargas[63] James Fung[64] HIBAT Allah BELIMI[65] Nabil Debzi[65] Mohammad Amin Fallahadeh[66] Sumeet Asrani[66] Henok Fisseha[67] Somaya Albhaisi[68] Jawaid Shaw[69] Brian Bush[68] Leroy R Thacker[68] Ashok Kumar Choudhury[70]

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Background: During the height of the pandemic, hospitals services were affected especially for COVID-negative patients. In hospitalized cirrhosis patients, changes in outcomes during and after the pandemic first waves are unclear globally. Aim: Determine outcomes in hospitalized cirrhosis patients admitted during and after the first wave of COVID-19. **Methods:** The CLEARED consortium prospectively enrolls inpatients with cirrhosis worldwide with demographics, cirrhosis details, hospital course and outcomes. Cirrhosis patients without COVID-19 admitted non-electively globally were enrolled in 2 waves; Wave 1: Dec 2020-21) & Wave 2 (2023-24). To ensure good representation, only 50 patients/per site were allowed. Sites that enrolled subjects in both Waves were included. World bank classifications of countries (low, middle, high-income) was used. We compared patients enrolled in both waves and performed logistic regression for inpatient and 30-day post-discharge outcomes. **Results:** 4953 patients (3177 Wave 1 & 1776 Wave 2) were enrolled from 69 centers across all continents. Both groups had similar demographics. Alcoholic liver disease was more common (49 vs 40%, p<0.001), and MASH and HBV flare were less common (18 vs 21%, p=0.005 and 21 vs 12%, p<0.001) in Wave 2 vs 1. Wave 2 pts had more advanced cirrhosis(greater complications and severity) but had similar comorbidities. Wave 1 participants were more likely from an upper- or middle-income country (UMIC). Both groups had similar PPI, statin & SBP prophylaxis use (Fig A). Wave 2 patients were less likely admitted for liver-related reasons, and more likely to have infection. Anasarca was a less common indication for admission in Wave 2, but HBV flare and HE were more common in Wave 2. Inpatient outcomes: Individual organ failures, transplant, & death/ mortality were similar, but ICU transfer was higher in Wave 2 (Fig B). There was a trend towards fewer infections

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in Wave 1 but incidence of second infections was similar. 30-day outcomes: Wave 2 patients were more likely to be readmitted, die, or receive LT vs Wave 1 (Fig B). Multivariable analysis: As seen in Fig C, patients with higher age, worse liver disease, and those from LMIC or UMIC versus HIC were more likely to die and less likely to get transplanted. **Conclusion:** Conclusions: Despite the subsidence of COVID-19 related strains on hospital infrastructure, a global consortium showed that inpatients with cirrhosis continue to have poor outcomes worldwide. Outcomes disparities between high-income and other countries continue and have worsened over time.

Fig A: Characteristics	LLMIC (n = 334)	UMIC (n = 1416)	HINC (n = 753)	p-value
Age (yrs) (mean (SD))	47.34 (12.96)	55.99 (12.67)	57.92 (12.86)	<0.0001
Male sex, n (%)	244 (73.1)	912 (64.4)	456 (60.6)	0.0004
Etiology of cirrhosis, n (%)				
Alcohol use	139 (41.6)	350 (24.7)	437 (58.0)	<0.0001
Nonalcoholic fatty liver disease	57 (17.1)	87 (6.1)	198 (26.3)	<0.0001
Hepatitis B	68 (20.4)	586 (41.4)	23 (3.1)	<0.0001
Hepatitis C	17 (5.1)	134 (9.5)	87 (11.6)	0.0036
Auto-immune hepatitis or cholestasis	27 (8.1)	190 (13.4)	70 (9.3)	0.0019
Cryptogenic	27 (8.1)	122 (8.6)	32 (4.2)	0.0008
Other*	37 (11.1)	85 (6.0)	53 (7.0)	0.0047
Comorbidities, n (%)				
Diabetes	82 (24.6)	352 (24.9)	270 (35.9)	<0.0001
Hypertension	54 (16.2)	265 (18.7)	217 (28.8)	<0.0001
Hyperlipidemia	25 (7.5)	87 (6.1)	194 (25.8)	<0.0001
Cirrhosis related history, n (%)				
Ascites	211 (63.2)	803 (56.7)	496 (65.9)	<0.0001
Variceal bleed	105 (31.4)	404 (28.5)	184 (24.4)	0.0329
Overt hepatic encephalopathy	80 (24.0)	228 (16.1)	238 (31.6)	<0.0001
Hyponatremia	58 (17.4)	133 (9.4)	175 (23.2)	<0.0001
Acute kidney injury	47 (14.1)	91 (6.4)	214 (28.4)	<0.0001
Hydrothorax	27 (8.1)	126 (8.9)	75 (10.0)	0.5602
Hospitalized in past 6 months	128 (38.3)	664 (46.9)	430 (57.1)	<0.0001
Infections in past 6 months	43 (12.9)	240 (16.9)	203 (27.0)	<0.0001
Listed for liver transplant	22 (6.6)	89 (6.3)	76 (10.1)	0.0046
Medications on admission, n (%)				
β-Blockers	135 (40.4)	298 (21.0)	260 (34.5)	<0.0001
Diuretics	138 (41.3)	689 (48.7)	450 (59.8)	<0.0001
Lactulose	147 (44.0)	352 (24.9)	369 (49.0)	<0.0001
Rifaximin	83 (24.9)	154 (10.9)	227 (30.1)	<0.0001
SBP prophylaxis	109 (32.6)	104 (7.3)	107 (14.2)	<0.0001

Fig A: Characteristics (continued)	LLMIC (n = 334)	UMIC (n = 1416)	HINC (n = 753)	p-value
Liver-related admission*, n (%)	329 (98.5)	1342 (94.8)	623 (82.7)	<0.0001
Anasarca, n/N (%)	79/329 (24.0)	573/1342 (42.7)	167/623 (26.8)	<0.0001
Hepatic encephalopathy, n/N (%)	100/329 (30.4)	249/1342 (18.6)	180/623 (28.9)	<0.0001
Gastrointestinal bleeding, n/N (%)	103/329 (31.3)	248/1342 (18.5)	155/623 (24.9)	<0.0001
Acute kidney injury, n/N (%)	83/329 (25.2)	146/1342 (10.9)	141/623 (22.6)	<0.0001
Electrolyte abnormalities, n/N (%)	93/329 (28.3)	190/1342 (14.2)	136/623 (21.8)	<0.0001
Hepatitis B flare, n/N (%)	22/329 (6.7)	200/1342 (14.9)	2/623 (0.3)	<0.0001
Liver and infection unrelated admission*, n (%)	3 (0.9)	40/1342 (2.8)	102 (13.5)	<0.0001
Lab data at admission*, median (IQR)				
Hemoglobin, g/dL	97.00 [80.00, 112.00]	105.00 [86.00, 124.00]	104.00 [85.00, 121.00]	<0.0001
White cell count, 10⁹ cells/mL	8.60 [5.20, 12.70]	4.90 [3.38, 7.24]	6.70 [4.40, 9.72]	<0.0001
International normalised ratio	1.95 [1.52, 2.60]	1.42 [1.22, 1.70]	1.50 [1.20, 1.80]	<0.0001
Sodium, mmol/L	134.00 [129.78, 139.00]	137.00 [133.00, 140.00]	135.00 [131.00, 138.00]	<0.0001
Creatinine, mg/dL	0.84 [0.60, 1.29]	0.81 [0.65, 1.12]	0.88 [0.56, 1.40]	0.0013
Fig B: Outcomes	LLMIC (n = 334)	UMIC (n = 1416)	HINC (n = 753)	p-value
Admission Outcomes, n (%)				
30-Day Outcomes, n (%)				
30-Day Lost to FU	24 (7.2)	126 (8.9)	68 (9.1)	0.2225
30-Day Readmission	76 (26.5)	272 (21.2)	247 (36.6)	<0.0001
30-Day Mortality	24 (7.7)	67 (5.2)	33 (4.6)	0.0001
30-Day Transplant	12 (3.8)	30 (2.3)	59 (8.7)	<0.0001
90-Day Outcomes, n (%)				
90-Day Lost to FU	69 (20.7)	203 (14.3)	118 (15.7)	0.0164
90-Day Readmission	80 (30.3)	334 (27.7)	305 (49.5)	<0.0001
90-Day Mortality	44 (16.2)	125 (10.3)	65 (10.2)	0.0138
90-Day Transplant	12 (4.5)	53 (4.4)	76 (12.2)	<0.0001

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2156 | RACIAL/ETHNIC DISPARITIES IN RISKS OF CIRRHOSIS AMONG VETERANS WITH METABOLIC DYSFUNCTION ASSOCIATED STEATOTIC LIVER DISEASE IN THE UNITED STATES

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Background: Metabolic dysfunction associated steatotic liver disease (MASLD) is the leading cause of chronic liver disease in the U.S. Cardiometabolic risk factors (CMRF) are the major drivers of MASLD risk. Racial/ethnic differences in underlying prevalence of CMRF contributes to differences in MASLD risk; however, it is unclear whether this translates into disparities in long-term outcomes among both MASLD and MetALD. We aim to evaluate racial/ethnic disparities in risk of cirrhosis among U.S. Veterans with MASLD or MetALD. **Methods:** U.S. Veterans with MASLD or MetALD from 1/1/2010 to 12/31/2018 (with follow-up through 12/31/2023) were identified using updated nomenclature (MASLD=hepatic steatosis (HS) + ≥1 CMRF and no alcohol use [AUDIT-C=0]; MetALD=HS + ≥1 CMRF and low-level alcohol use [AUDIT-C 1-2 for women, 1-3 for men]). Patients with baseline cirrhosis or hepatocellular carcinoma were excluded. Incidence of cirrhosis (per 1000-person-years (py)) was stratified by race/ethnicity and evaluated with competing risks methods and adjusted multivariable Cox proportional hazards models (adjusted for age, sex, race/ethnicity, metabolic co-morbidities, tobacco use, baseline FIB-4 score). **Results:** Among a total of 682,274 patients with MASLD (70.3% non-Hispanic white (NHW), 18.8% Black/African American (AA), 8.3% Hispanic, and 1.7% Asian-Pacific Islander (API)) and 517,464 patients with MetALD (71.5% NHW, 18.2% AA, 7.9% Hispanic, 1.8% API), overall incidence of cirrhosis was 4.3 per 1000-py (95% CI 4.2-4.3) and 3.9 per 1000-py (95% CI 3.9-4.0), respectively. Compared to NHW with MASLD, the risk of

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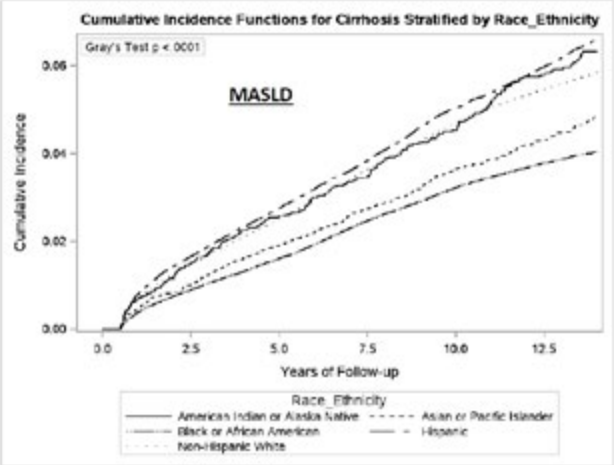
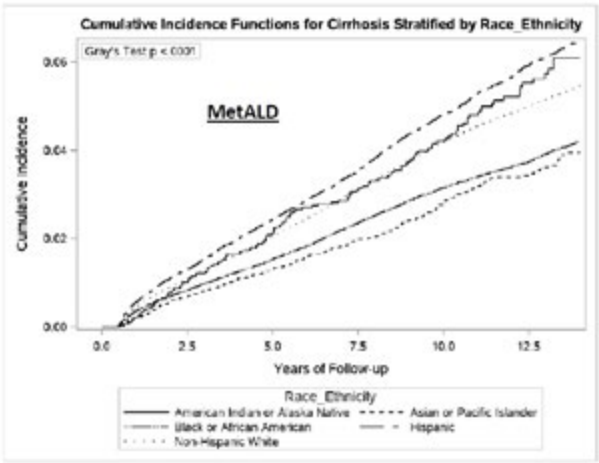
cirrhosis was significantly higher among Hispanics (5.0 vs. 4.6 per 1000-py; HR 1.19, 95% CI 1.12-1.27, p<0.01), whereas the risk was lower among AA (3.1 vs. 4.6 per 1000-py; HR 0.81, 95% CI 0.77-0.86, p<0.01) (Figure). Similarly, compared to NHW MetALD patients, the risk of cirrhosis was higher among Hispanics with MetALD (4.9 vs. 4.1 per 1000-py; HR 1.05, 95% CI 1.01-1.11, p<0.05) and lower among AA with MetALD (3.1 vs. 4.1 per 1000-py; HR 0.71, 95% CI 0.67-0.74, p<0.01) (Figure). **Conclusion:** Among a national cohort of nearly 1.2 million U.S. Veterans with MASLD or MetALD, significant race/ethnicity-specific disparities in long-term risks of cirrhosis were observed. Compared to NHW, the risk of cirrhosis was 5-19% higher among Hispanics and 19-29% lower among AA, even after adjusting for baseline demographics and clinical characteristics.





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2157 | GAPS AND DISPARITIES IN HEPATOCELLULAR CARCINOMA SURVEILLANCE AMONG A MULTI-CENTER SAFETY-NET COHORT OF ADULTS WITH CIRRHOSIS

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Background: Underuse of surveillance for hepatocellular carcinoma (HCC) in patients with cirrhosis contributes to advanced tumor stage at diagnosis, limited curative options, and worse patient outcomes. Understanding gaps and disparities in effective utilization of HCC surveillance in real-world settings can guide targeted interventions to improve HCC outcomes. We aim to evaluate gaps and disparities in HCC surveillance among adults with cirrhosis across four safety-net health systems in the U.S. **Methods:** Adults with cirrhosis from March 1, 2017 to February 28, 2022 were identified across four safety-net health systems in California, Florida, Ohio, and Texas, using established definitions based on ICD-9/10 codes. Patients with baseline HCC diagnosis were excluded. Receipt of HCC surveillance imaging (ultrasound, CT, or MRI) within first 6 months (HCC6mo) of cirrhosis diagnosis during the study period was evaluated using CPT codes and imaging indications were determined using associated ICD-9/10 codes. Multivariable logistic regression models were used to identify predictors of successful HCC6mo. **Results:** Among 14,556 patients with cirrhosis (61.8% men, mean age 56.8y ± 12.0, 40.9% Hispanic, 27.0% non-Hispanic white (NHW), 23.6% Black/African American, 3.6% Asian-Pacific Islander (API), 37.4% non-English speaking, 28.2% uninsured/indigent care, 26.2% Medicare insured, 26.2% Medicaid, 9.3% commercial), 70.9% (95% CI 70.1 – 71.7) received any abdominal imaging (ultrasound, CT, or MRI) within 6 months regardless of indication. When evaluating patients who received imaging specifically for an indication of HCC surveillance, only 29.1% (95% CI 28.3 – 29.9) received HCC6mo. Among those receiving imaging for HCC surveillance indication, the lowest proportion of HCC6mo was observed in Hispanics (28.8%), non-English speakers (27.3%), and commercially insured patients (23.3%) (Figure). On multivariable regression, lower odds of HCC6mo were observed in NHW vs. API (aOR 0.70, 95% CI 0.55 – 0.90) and higher odds in Medicaid vs. Medicare (aOR 1.19, 95% CI 1.05 – 1.35). No other significant differences were observed. **Conclusion:** Among a multi-center safety-net cohort of cirrhosis patients, over 70% received some form of abdominal imaging within 6 months, but less than 30% received imaging specifically for an indication of HCC surveillance. Significant disparities in HCC surveillance were observed across sociodemographic factors.

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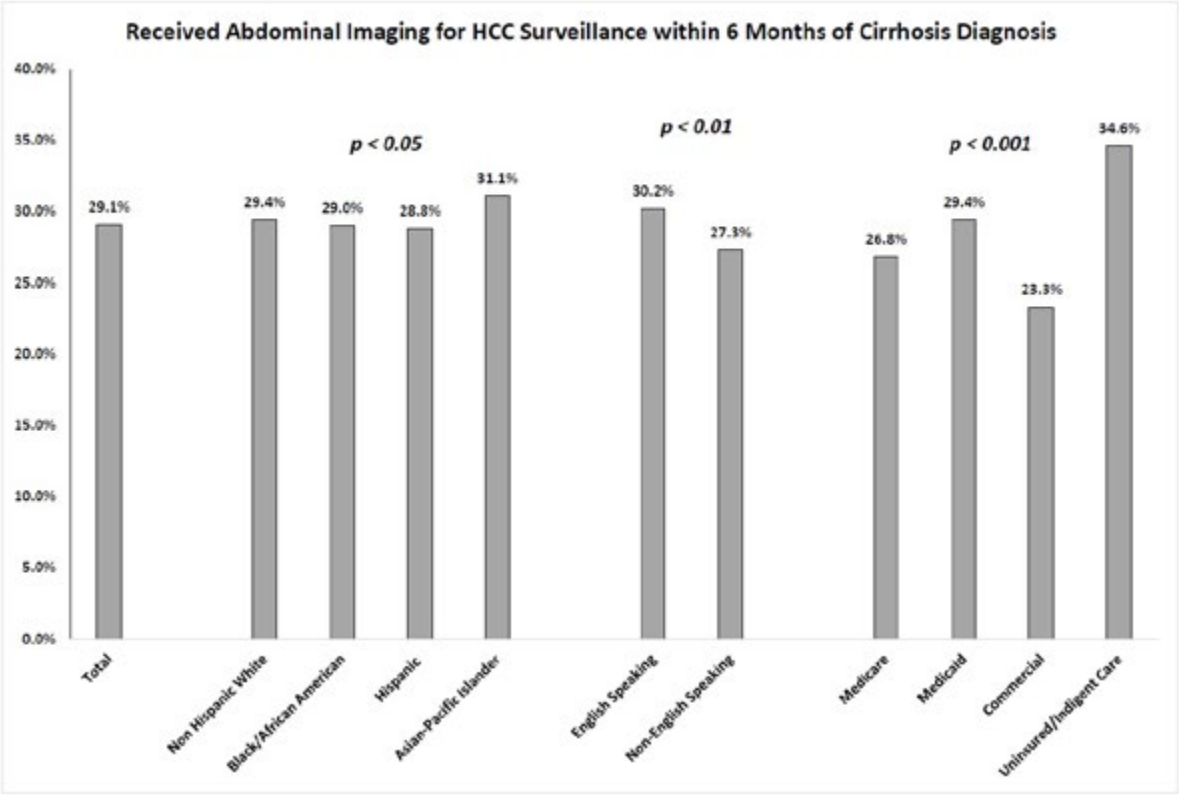

Disclosures: Robert Wong: Theratechnologies: Grant/Research Support, Durect: Grant/Research Support, Gilead Sciences: Grant/Research Support, Exact Sciences: Grant/Research Support, Theratechnologies: Grant/Research Support, Durect Corporation: Grant/Research Support, Patricia Jones: Gilead: Grant/Research Support, Bolin Niu: Nothing to Disclose, Paulo Pinheiro: Nothing to Disclose, Mae Thamer: Gilead Sciences: Grant/Research Support, Onkar Kshirsagar: Nothing to Disclose, Yi Zhang: Nothing to Disclose, fass ronnie: Nothing to Disclose, George Therapondos: Nothing to Disclose, Amit Singal: Consultant relationship with AstraZeneca; Has not ended; Consultant relationship with Sirtex; Has not ended; Consultant relationship with Boston Scientific; Has not ended; Consultant relationship with Bayer; Has not ended; Consultant relationship with Eisai; Has not ended; Consultant relationship with FujiFilm Medical Sciences; Has not ended; Consultant relationship with Elevar; Has not ended; Consultant relationship with Exact Sciences; Has not ended; Consultant relationship with Glycotest; Has not ended; Consultant relationship with Exelixis; Has not ended; Consultant relationship with Merck; Has not ended; Consultant relationship with Genentech; Has not ended; Consultant relationship with HistoSonics; Has not ended, Mandana Khalili: gilead sciences: Grant/Research Support, GSK pharmaceuticals: Consultant, Intercept pharmaceuticals: Grant/Research Support, Gilead Sciences Inc: Consultant

2158 | DISPARITIES AND BARRIERS IN IMPROVING ORAL HEALTH IN CIRRHOSIS: THE ORACLE (ORAL HEALTH IN CIRRHOSIS OF THE LIVER) STUDY

Mette Munk Lauridsen[1] Sara Khraibut[1] Andrew Fagan[2] Jennifer Montano[1] Amy Bartels[1] Janina Deeb[1] Jasmohan Bajaj[1]

[1]Virginia Commonwealth University, [2]Richmond VA Medical Center

Background: Poor orodental health, which is linked to socioeconomic challenges & disparities, is a risk factor for infections and poor nutrition in cirrhosis, which impacts outcomes. This is due to an altered oral-gut-liver axis & immune dysfunction that is exacerbated by lack of access to dental care. Current practice only evaluates oral health at the time of transplant evaluation, which excludes the majority of patients. **Aim:** Determine specific barriers to dental care in cirrhosis & provide complimentary dental care to alleviate access problems. **Methods:** We included adult cirrhosis outpatients after consent (non-edentulous, able to consent). The study offers a complimentary dental examination and cleaning, and determines barriers and reasons for seeking dental care

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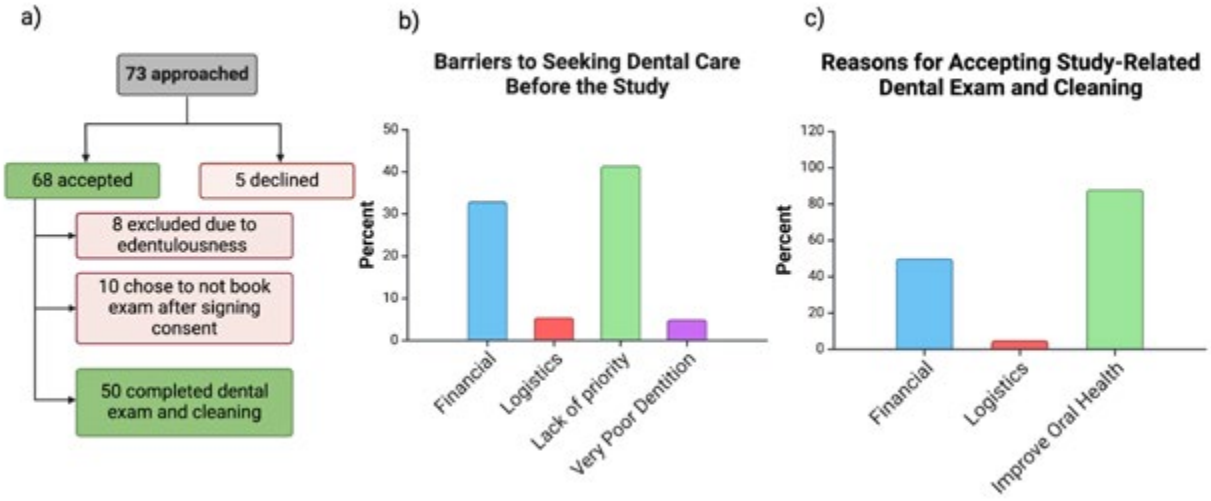
using semi-quantitative questionnaires. During the dental examination, orodental health is assessed using the (Decayed, Missing or Filled) DMFT Index (range 0–28, where 0 is best) by qualified dental professionals. Analysis of barriers to dental care were analyzed. **Results:** Study population: 73 patients were approached, of which 68 agreed (Figure 1a). After excluding 8 patients with <4 natural teeth, 60 patients remained (average age 62, 75% male, 35% African American, 75% Child-Pugh A, 40% HCV, 30% alcohol & 30% MASLD). 10% were Veterans, 80% unemployed, & 40% did not have dental insurance.Those who declined dental exam were less likely to have dental insurance (20%) vs those who agreed 75%,p<0.001); remaining demographics were similar. *Barriers and opportunities (Figures 1B-C): Barriers to not seeking dental care prior to study (all consented patients):* Financial concerns (high copayments) deterred 30% from seeking care, while logistical issues like missing work and no transportation affected 8%. Forty percent cited a lack of priority, e.g., perceived unimportance, no need, or prioritization of other health issues, including cirrhosis. Several commented that they felt too overwhelmed by the burden of liver disease to prioritize dental health. 5% felt that their dental condition was beyond help. *Reasons for accepting dental exam (n=50):* Financial incentives (50%) and the opportunity to improve oral health (88%) were major motivators. *Reasons for declining dental exam (n=10):* 70% had transportation issues. However, the majority of these stated that they will approach a local dentist. Oro-dental exam results: Dental health was poor, with a mean DMFT Index of 18 (SD 8.7, range 2–28), indicating that, on average, 18/32 teeth were decayed, missing, or filled. **Conclusion:** Financial constraints and the burden of cirrhosis prevent patients with cirrhosis from prioritizing dental care despite recognizing the need to improve oral health. Majority had poor dental health on specialized examination. This underscores the need for more accessible dental care with lower copays before the burden of cirrhosis worsens to improve dental health, nutrition, and immune status.



Disclosures: Mette Munk Lauridsen: Nothing to Disclose, Sara Khraibut: Nothing to Disclose, Andrew Fagan: Nothing to Disclose, Jennifer Montano: Nothing to Disclose, Amy Bartels: Nothing to Disclose, Janina Deeb: Nothing to Disclose, Jasmohan Bajaj: Bausch: Grant/Research Support, Sequana: Grant/Research Support, Cosmo: Grant/Research Support, Grifols: Grant/Research Support

2159 | A CROSS-SECTIONAL ANALYSIS OF DISPARITIES FOR ACUTE LIVER FAILURE-RELATED MORTALITY IN THE UNITED STATES

Nazli Begum Ozturk[1] Hoang Nhat Pham[2] Rama Mouhaffel[2] Leandro Sierra[3] Marwan Alsaqa[3] Ramzi Ibrahim[2] Ahmet Gurakar[4]

[1]Beaumont Hospital, Royal Oak, [2]University of Arizona-Tucson, [3]Beth Israel Deaconess Medical Center, [4]Johns Hopkins University

Background: Health disparities are well described in patients with chronic liver diseases and seen in populations who are socially disadvantaged. However, there is a lack of data for the presence of disparities in acute liver failure (ALF)-related mortality in the United States (US). We aimed the analyze the longitudinal trends and

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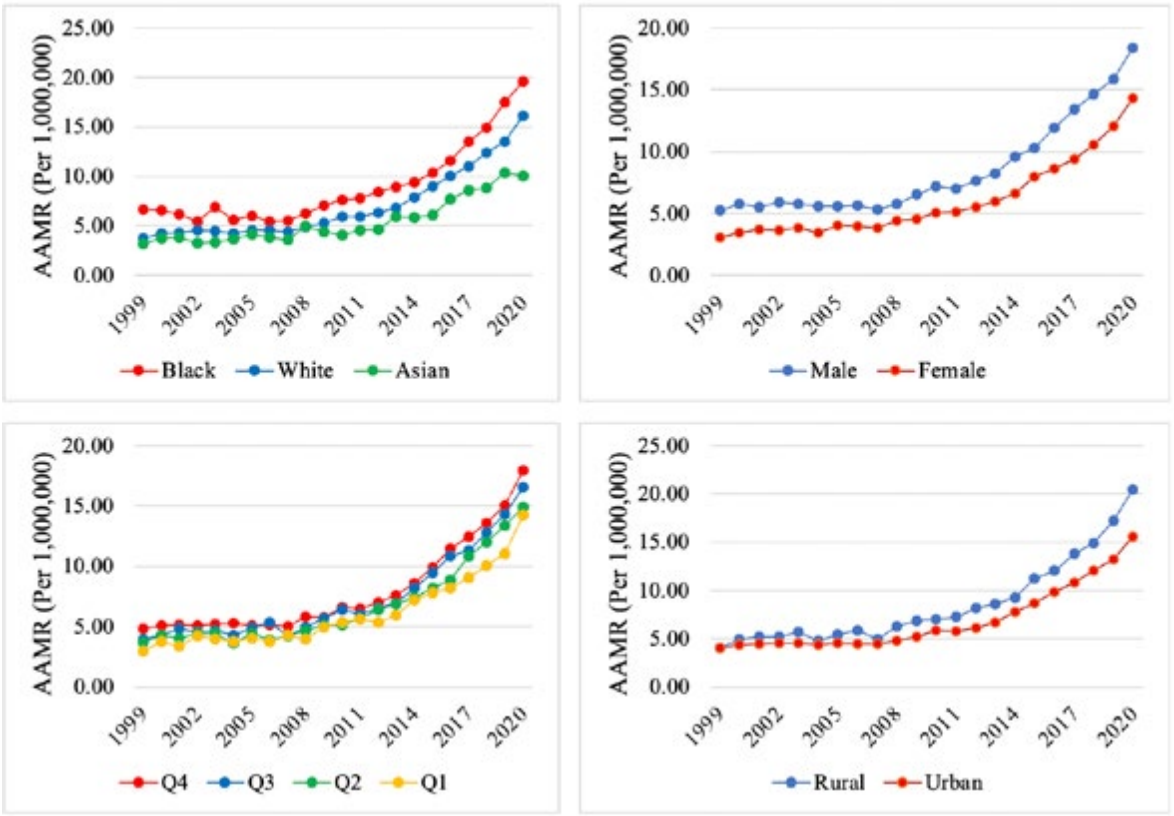
disparities in ALF-related mortality in the US. **Methods:** We queried the mortality and demographic data related to ALF-related mortality in adults (age≥15 years old) in the US between 1999-2020 through the Centers for Disease Control (CDC) and Prevention's Wide-ranging Online Data for Epidemiologic Research database. Age-adjusted mortality rates (AAMR) were calculated by using direct method of standardization. The 2020 social vulnerability index (SVI) was obtained from the CDC Agency for Toxic Substances and Disease Registry database. SVI was categorized into four quartiles, ranging from the lowest Q1 (least socially vulnerable) to the highest Q4 (most socially vulnerable). Average annual percentage change (AAPC) was estimated by taking the average of the annual percentage changes (APC), determined through Monte-Carlo permutation tests. Two-sided p-value <0.05 was considered as statistically significant. **Results:** A total of 55068 ALF-related mortality were identified between 1999-2020 with the mortality rate increasing from AAMR 4.04 [95% CI, 3.80-4.28] in 1999 to 16.24 [95% CI, 15.83-16.65] in 2020. The cumulative AAMR during our 22-year study period was 7.50 [95% CI, 7.44-7.57] with AAPC of +6.38% [95% CI, 5.60-7.16], p<0.001. Males (AAMR 8.90 [95% CI, 8.80-9.00]) were impacted by higher mortality rate compared to females (AAMR 6.31 [95% CI, 6.23-6.39]). Mortality was higher among Hispanic populations (AAMR 8.35 [95% CI, 8.12-8.57]) compared to non-Hispanic (NH) populations (AAMR 7.42 [95% CI, 7.35-7.48], and mortality was highest among American Indian/Alaska Native (AAMR 11.83 [95% CI, 10.98-12.69]), followed by Black (AAMR 9.56 [95% CI, 9.35-9.78]), White (AAMR 7.26 [95% CI, 7.19-7.32]), and lowest in Asian (AAMR 5.99 [95% CI, 5.72-6.26]) populations. Rural regions had higher mortality (AAMR 8.76 [95% CI, 8.59-8.93]) compared to urban regions (AAMR 7.26 [95% CI, 7.19-7.33]), and AAMRs were higher in US counties categorized as SVI-Q4 (AAMR 8.25 [95% CI, 8.13-8.36]), followed by regions with SVI Q3 (AAMR 7.61 [95% CI, 7.50-7.73]), SVI Q2 (AAMR 7.00 [95% CI, 6.88-7.12]), SVI Q1 (AAMR 6.31 [95% CI, 6.15-6.47]). Higher SVI accounted for 1.94 excess deaths in per 1,000,000 person-years. **Conclusion:** Our study highlights the presence of disparities for ALF-related mortality in the US, in particular in Hispanic individuals, and American Indian/Alaska Native, and Black populations. Males, patients in rural residences and higher SVI have the highest AAMR. Efforts should be made to improve disparities in the care of high-risk populations to promote equity in the care of liver diseases.



Disclosures: Nazli Begum Ozturk: Nothing to Disclose, Hoang Nhat Pham: Nothing to Disclose, Rama Mouhaffel: Nothing to Disclose, Leandro Sierra: Nothing to Disclose, Marwan Alsaqa: Nothing to Disclose, Ramzi Ibrahim: Nothing to Disclose, Ahmet Gurakar: Grant/Research Support relationship with DURECT; Has ended; Advisor relationship with Orphalan; Has ended

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2160 | SOCIAL VULNERABILITY (SV) IS ASSOCIATED WITH HIGHER PREMATURE MORTALITY FROM METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD) IN THE UNITED STATES (US)

James Paik[1] Linda Henry[2] Annette Paik[1] Shira Zelber-Sagi[2] Carina Kugelmas[3] Jeffrey Lazarus[4] Leyla de Avila[1] Lynn Gerber[5] Zobair Younossi[2]

[1]Beatty Liver/Obesity Research Program, [2]The Global NASH Council, [3]Denver Health Medical Center, [4]University of Barcelona, [5]Inova Health System

Background: SV represents the ability of communities to withstand outside stressors from disease influencing health outcomes. Using the SV Index (SVI), we aimed to assess disparities in Premature MASLD Related Mortality (PMRM) across the US. **Methods:** We used PMRM (deaths ≤75 years) data from the National Vital Statistics System (NVSS), MASLD risk factors from American Community Survey (ACS) 2017-2021, and SVI from the CDC/ASTSDR. Mixed-effects linear regression models, weighted by county population size and accounting for county level random effects, were used to assess disparities in MASLD risk factors and PMRM across quartiles of SV burden. **Results:** Of 2,313 US Counties, those with highest PMRM (quartile 4) were located in the South and rural areas of US with an older population, more Hispanics, no health insurance, higher rates of MASLD risk factors (T2D, obesity), inadequate leisure-time physical activity, insufficient sleeping time, food insecurity, and higher SVI as compared to lowest PMRM counties (Quartile 1). After adjusting for socio-demographics, most vulnerable counties (quartile 4) had higher PMRM rates (per 100,000) (23.39 vs. 13.44 [adjusted difference=8.68, 95% confidence interval, 7.22-10.15]). This was true for males (23.85 vs. 13.38 [8.59, 6.84-10.34]), females (15.90 vs. 10.10 [6.01, 4.59-7.43]}, non-Hispanic whites (23.26 vs. 13.96, [10.64, 9.26-12.02]), non-Hispanic blacks (15.83 vs. 12.57 [9.23, 5.58-12.88]), and Hispanics (25.89 vs. 13.71 [6.44, 0.03-12.84]. Similar patterns were observed across county locations with large metro (15.69 vs. 12.45 [10.76, 8.69-12.83]), medium/small metro (22.00 vs. 13.12 [8.88, 6.46-11.30]), and rural (29.38 vs. 15.63 [6.43, 3.47-9.40]). Adjusted differences in MASLD risk factor prevalence were significantly pronounced among most vulnerable vs least vulnerable counties for HTN (36.88% vs. 29.49% [= 4.22%, 3.81-4.63]), T2D (13.10% vs. 8.69% [2.24%, 2.08-2.40]), high cholesterol (29.35% vs. 28.14% [1.73%, 1.52-1.93]), obesity (34.39% vs. 30.83% [4.29%, 3.83-4.74]), food insecurity (13.83% vs. 8.74% [5.82%, 5.47-6.17]), food desert (6.36% vs. 4.89% [1.58, 0.87-2.29]), inadequate leisure-time physical activity (26.93% vs. 19.71%[6.58%, 6.11-7.05]), and insufficient sleeping time (35.86% vs. 31.92% [3.9%, 3.51-4.28]). **Conclusion:** The most socially vulnerable US populations (Hispanic, living in rural areas) have the highest rates of PMRM. US public health interventional policies should address these groups.

Disclosures: James Paik: Nothing to Disclose, Linda Henry: Nothing to Disclose, Annette Paik: Nothing to Disclose, Shira Zelber-Sagi: abbvie: one time consultant, simens: Consultant, Carina Kugelmas: Novo Nordisk: Consultant, Albireo: Consultant, Jeffrey Lazarus: Grant/Research Support relationship with Madrigal; Has not ended; Grant/Research Support relationship with Boehringer Ingelheim; Has not ended; Grant/Research Support relationship with Abbvie; Has ended; Grant/Research Support relationship with Echosens; Has not ended; Grant/Research Support relationship with Gilead Sciences; Has not ended; Grant/Research Support relationship with MSD; Has not ended; Grant/Research Support relationship with Pfizer; Has not ended; Speaking and Teaching relationship with Pfizer; Has not ended; Speaking and Teaching relationship with Novo Nordisk; Has not ended; Speaking and Teaching relationship with MSD; Has not ended; Speaking and Teaching relationship with Moderna; Has not ended; Speaking and Teaching relationship with Janssen; Has not ended; Speaking and Teaching relationship with Gilead Sciences; Has not ended; Speaking and Teaching relationship with Echosens; Has not ended; Speaking and Teaching relationship with Abbvie; Has not ended; Consultant relationship with Pfizer; Has not ended; Consultant relationship with GSK; Has not ended; Grant/Research Support relationship with Novo Nordisk; Has not ended; Grant/Research Support relationship with Roche Diagnostics; Has ended; Consultant relationship with Echosens; Has not ended; Consultant relationship with NovoVax; Has not ended; Consultant relationship with Novo Nordisk; Has not ended, Leyla de Avila: Nothing to Disclose, Lynn Gerber: Nothing to Disclose, Zobair Younossi: Nothing to Disclose

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2161 | THE ASSOCIATION BETWEEN FOOD ENVIRONMENT AND METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD) IN SOCIOECONOMICALLY DEVELOPED (SED) COUNTRIES: A GLOBAL STUDY OF THE UNITED NATIONS AND THE GLOBAL BURDEN OF DISEASE (GBD) DATA

Zobair Younossi Shira Zelber-Sagi[1] Carina Kugelmas[2] Jeffrey Lazarus[3] Annette Paik[4] Leyla deAvila[4] Lynn Gerber[5] Linda Henry[1] James Paik[4]

[1]The Global NASH Council, [2]Denver Health Medical Center, [3]University of Barcelona, [4]Beatty Liver/Obesity Research Program, [5]Inova Health System

Background: Food environment refers to factors influencing the availability, accessibility, affordability, and desirability of food which could potentially shape dietary behaviors and health outcomes. We aimed to assess the association between food environment burden (food insecurity [FI], cost of a healthy diet [HCOST], undernourishment, and unaffordability of a healthy diet [Unaffordability]) and MASLD (prevalence and mortality) among SED countries. **Methods:** This study integrated country-level food security data from the United Nations (2016-2019) with MASLD prevalence, liver-related mortality (LRM), the Socio-Demographic Index (SDI), and Healthcare Access and Quality (HAQ) data obtained from Global Burden of Disease Study (GBD) 2019. A total of 128 SED countries (SDI of ≥0.60) were included. Mixed-effects linear regression models, accounting for country-level random effects, were used to assess disparities across tertiles of food environment burden. **Results:** After adjusting for median age and %male, highest food environment burden countries (Tertile 3) had higher prevalence of MASLD as compared to the lowest burden countries (Tertile 1). This disparity was accompanied by increased food insecurity (mean MASLD prevalence [SD], 27.52% [8.54] vs. 18.83% [7.35]; adjusted difference, 95% CI: 8.17%, 4.28-12.06), higher HCOST (26.39% [7.83] vs. 21.87% [9.71]; 4.81%, 1.31-8.31), greater undernourishment (28.38% [8.30] vs. 21.82% [8.50]; 4.92%, 1.63-8.22), and increased unaffordability (27.63% [7.85] vs. 17.95% [6.69]; 9.37%, 5.64-13.10). Additionally, the highest food insecure countries had higher rates of obesity (28.86% [10.16] vs. 18.41% [8.11]; 8.35%, 2.29-14.42) and type 2 diabetes (T2D) (11.11% [3.59] vs. 9.95% [2.72]; 3.19%, 0.79-5.58) compared to the lowest food insecure countries. Furthermore, the lowest HAQ countries (tertile 1) also had higher prevalence of obesity (33.08% [17.98] vs. 22.24% [9.28]; 7.45%, 0.69-14.21), T2D (13.19% [6.64] vs. 10.74% [2.83]; 2.84%, 0.38-5.30), MASLD (27.59% [6.25] vs. 19.19% [7.83]; 7.75%, 4.12-11.38), and MASLD-LRM (4.44 [2.61] vs. 2.84 [1.06] per 100,000; 1.82, 0.85-2.79). **Conclusion:** Among SED countries, higher food environment burden and low healthcare access were associated with increased prevalence of MASLD and MASLD-LRM. This profile is different from those in less developed countries. These data suggest that future interventions should be tailored according to country's socio-economic realities.

Disclosures: Zobair Younossi: Nothing to Disclose, Shira Zelber-Sagi: abbvie: one time consultant, simens: Consultant, Carina Kugelmas: Novo Nordisk: Consultant, Albireo: Consultant, Jeffrey Lazarus: Grant/Research Support relationship with Madrigal; Has not ended; Grant/Research Support relationship with Boehringer Ingelheim; Has not ended; Grant/Research Support relationship with Abbvie; Has ended; Grant/Research Support relationship with Echosens; Has not ended; Grant/Research Support relationship with Gilead Sciences; Has not ended; Grant/Research Support relationship with MSD; Has not ended; Grant/Research Support relationship with Pfizer; Has not ended; Speaking and Teaching relationship with Pfizer; Has not ended; Speaking and Teaching relationship with Novo Nordisk; Has not ended; Speaking and Teaching relationship with MSD; Has not ended; Speaking and Teaching relationship with Moderna; Has not ended; Speaking and Teaching relationship with Janssen; Has not ended; Speaking and Teaching relationship with Gilead Sciences; Has not ended; Speaking and Teaching relationship with Echosens; Has not ended; Speaking and Teaching relationship with Abbvie; Has not ended; Consultant relationship with Pfizer; Has not ended; Consultant relationship with GSK; Has not ended; Grant/Research Support relationship with Novo Nordisk; Has not ended; Grant/Research Support relationship with Roche Diagnostics; Has ended; Consultant relationship with Echosens; Has not ended; Consultant relationship with NovoVax; Has not ended; Consultant relationship with Novo Nordisk; Has not ended, Annette Paik: Nothing to Disclose, Leyla deAvila: Nothing to Disclose, Lynn Gerber: Nothing to Disclose, Linda Henry: Nothing to Disclose, James Paik: Nothing to Disclose

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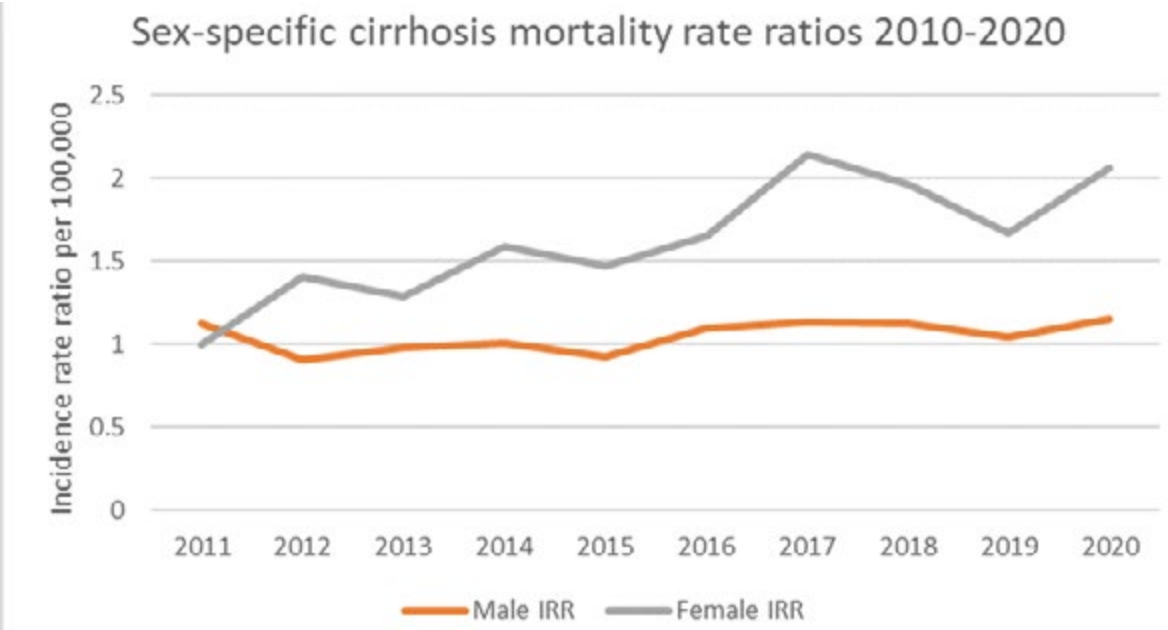
2162 | TRENDS IN ALCOHOL-ASSOCIATED CIRRHOSIS: INCIDENCE AND MORTALITY DISPARITIES BETWEEN MEN AND WOMEN, AND YOUNG AND OLDER INDIVIDUALS IN A CENTRAL CANADIAN PROVINCE (2010-2020)

Nabiha Faisal[1] *Harminder Singh*[1] *Eberhard Renner*[1] *Randy Walld*[1]

[1]*University of Manitoba*

Background: Alcohol-associated cirrhosis is a global public health concern Understanding its evolving trends and patterns is crucial for effective prevention and management strategies. This study aimed to analyze the incidence, prevalence, and mortality rates of alcohol-associated cirrhosis over a decade in Manitoba, Canada. **Methods:** This is a historical population-based cohort study utilizing linked administrative healthcare data housed at the Manitoba Centre of Health Policy. Patients aged 18 years or older with incident cirrhosis between 2010 and 2020 were identified using validated case finding algorithms. Annual incidence, prevalence, and mortality rates per 100,000 population were calculated using generalized linear models, adjusting for age and sex. Linear regression models tested linear trends by calendar year overall, as well as by age and sex. **Results:** The prevalence of alcohol-associated cirrhosis surged by 200%, from 967 cases in 2010 to 3012 cases in 2020. Mean age at diagnosis was 48.8 years (SD 14.38), with 62% men, and 30% belonging to the lowest income quintile (poorest 20% of the population). Incidence rose by an estimated 5.8% annually (95% CI 2.4-9.1), escalating from 32.6 (95% CI 27.9-38.2) per 100,000 in 2010 to 97.4 (95% CI 86.3-109.9) per 100,000 in 2020. Women exhibited a more pronounced increase in incidence compared to men (1.9, 95% CI 1.8- 5.9 vs. 1.4, 95% CI: 1.4, 3.6). The age groups 18-44 and 45-64 experienced a 60% and 56% increase in incidence, respectively, compared to 29% rise in the older age group (65+) during the study period. Mortality rates increased by 38%, climbing from 10.4 (95% CI 8.8-12.6) per 100,000 in 2010 to 14.5 95% CI 12.7-16.7) per 100,000 (in 2020. Men experienced a 15% increase in mortality, while women faced a staggering 106% rise. Young adults (age <55) exhibited a 54% increase in mortality rate, outpacing the 30% rise observed in older individuals (age ≥55). **Conclusion:** This population-based study shows an alarming increase in the incidence, prevalence, and mortality rates of alcohol-associated cirrhosis and highlights widening disparities across gender and age groups. Further studies are needed to explore potential underlying causes for these disparities.



Disclosures: Nabiha Faisal: Advanz Pharma: Consultant, Advanz Pharma: Consultant, Ipsen: Advisor, Harminder Singh: Nothing to Disclose, Eberhard Renner: Nothing to Disclose, Randy Walld: Nothing to Disclose

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2163 | SOCIAL DRIVERS OF HEALTH PREVALENCE AND SCREENING ACCEPTABILITY AMONG PATIENTS WITH CHRONIC LIVER DISEASE

Rebecca Kim[1] April Ballantyne[1] Rachel Codden[1] Morgan Millar[1] John Inadomi[1] Molly Conroy[1] Jennifer Price[2]

[1]University of Utah, [2]University of California San Francisco

Background: Vulnerable populations are disproportionately impacted by chronic liver disease (CLD), and are more likely to experience poor CLD outcomes, resulting in health disparities. Social drivers of health (SDoH), the conditions where people are born and live, are the primary causes of health disparities. Some SDoH, like health-related social needs (HRSN), are modifiable. Systematic SDoH screening allows for HRSN to be addressed to mitigate their impact on CLD outcomes. As there is currently no standardized screening method, ongoing research is critical. We aimed to incorporate HRSN screening into liver clinics to determine prevalence, particularly food insecurity (FI), and assess patients' screening experience. **Methods:** Patients ≥18yrs with a diagnosis of any etiology of CLD were included. 250 patients (87% participation rate) were recruited at University of Utah Health from 9/2023-2/2024. A validated SDoH screening tool focused on HRSN was administered via tablet to patients in English or Spanish during liver clinic visits. Upon completion of the ~12min survey, patients were given information on community resources and $10. Descriptive and comparative statistics were completed to test for associations between demographic variables and HRSN. A score of survey acceptability was calculated and summarized by demographic characteristics with medians and IQRs. Kruskal-Wallis tests were used to determine statistically significant differences between medians. **Results:** Of the 250 participants, 56% were women, mean age 56yrs, 67% White, 22% Hispanic, 29% reported an income of <$35,000. When asked about the past year, 34% indicated insufficient money for clothing or furniture and 21% reported difficulty paying utility bills. 30% of participants reported FI. When they were compared to those without FI, FI was significantly associated with race and ethnicity, gender identity, level of education, income, and difficulty paying rent/mortgage (see Tables). Regarding acceptability of SDoH screening, most respondents (69%) were comfortable or very comfortable completing the survey, and felt it took "no effort at all" (52%). However, there was a trend of lower acceptability with fewer years of education. **Conclusion:** In-clinic SDoH screening, which demonstrated the pervasiveness of social needs, was widely acceptable among CLD patients. Systematic SDoH screening should be optimized and prioritized to effectively implement community resource referrals and SDoH interventions.

Tables. A) Baseline Characteristics and 2) Factors Associated with Food Insecurity.

A) Baseline Characteristics	
	n (%)
Age, Mean (standard deviation)	55.7 (14.3)
Race or Ethnicity	
American Indian or Alaska Native	18 (7.3%)
Asian	8 (3.2%)
Black or African American	8 (3.2%)
Hispanic or Latino/a	54 (21.8%)
Native Hawaiian or Pacific Islander	3 (1.2%)
White	167 (67.3%)
Other	17 (34.0%)
Gender Identity	
Man	109 (44.1%)
Woman	137 (55.5%)
Non-binary	1 (0.4%)
Highest level of school completed	
Less than high school graduate/ GED	72 (29.2%)
2 year college degree or some college, no degree	100 (40.5%)
4 year college degree or more	75 (30.4%)
Current occupational status	
Employed	101 (40.2%)
Unemployed	30 (12.3%)
Homemaker/ Student	20 (8.1%)
Disabled/ Retired	93 (37.1%)
Other	6 (2.5%)
Combined annual income	
$0 - $34,999	63 (25.6%)
$35,000 - $99,999	83 (33.7%)
>$100,000	71 (28.9%)
Don't know/prefer not to answer	29 (11.8%)
Birthplace	
In the United States	195 (84.1%)
Outside the United States	37 (15.9%)
Health Related Social Needs	
Food insecurity	72 (30%)
Transportation needs	19 (8%)
Financial strain	106 (43%)

1. Fisher Exact Test
2. Monte Carlo approximation of Exact Test

B) Factors Associated with Food Insecurity (Patients with food insecurity vs those without)		
	With Food Insecurity, N (%)	**p-value**
Totals	72 (30.3%)	--
Race or ethnicity*		
American Indian or Alaska Native	9 (60.0%)	**0.017**[1]
Asian	2 (25.0%)	
Black or African American	1 (14.3%)	
Hispanic or Latino/a	22 (45.8%)	**0.013**[1]
Native Hawaiian or Pacific Islander	1 (33.3%)	
White	39 (24.1%)	**0.004**[1]
Gender Identity		**0.032**[1]
Man	24 (22.9%)	
Woman	47 (36.4%)	
Highest level of school completed		**0.004**[1]
Less than 12th grade	9 (52.9%)	
High school graduate/GED	20 (40.0%)	
Some college, no degree	20 (31.3%)	
2 year college degree/associate degree	11 (36.7%)	
4 year college degree/bachelor's degree	8 (18.6%)	
Graduate or professional degree	3 (9.4%)	
Combined annual income		**<0.001**[2]
$0 - $9,999	15 (83.3%)	
$10,000 - $14,999	4 (44.4%)	
$15,000 - $19,999	3 (33.3%)	
$20,000 - $34,999	15 (65.2%)	
$35,000 - $49,999	6 (40.0%)	
$50,000 - $74,999	11 (32.4%)	
$75,000 - $99,999	4 (13.3%)	
$100,000 - $199,999	1 (2.0%)	
Frequency of worry about rent/mortgage		**<0.001**[1]
Always	6 (85.7%)	
Usually	11 (73.3%)	
Sometimes	23 (54.8%)	
Rarely	8 (33.3%)	
Never	9 (7.7%)	

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Disclosures: Rebecca Kim: Nothing to Disclose, April Ballantyne: Nothing to Disclose, Rachel Codden: Nothing to Disclose, Morgan Millar: Nothing to Disclose, John Inadomi: Nothing to Disclose, Molly Conroy: Nothing to Disclose, Jennifer Price: Nothing to Disclose

2164 | DISPARITIES AND OUTCOMES OF PHYSICAL RESTRAINT USE IN HEPATIC ENCEPHALOPATHY: A NATIONAL INPATIENT ASSESSMENT

Yasmin Ali[1] Spencer Goble[1] Thomas Leventhal[2]

[1]Hennepin Healthcare, [2]University of Minnesota

Background: Physical restraints may be utilized in patients with cirrhosis and hepatic encephalopathy with the intention to ensure patient safety. However, data evaluating the clinical impact of restraints and social disparities in restraint use in patients with hepatic encephalopathy is lacking. **Methods:** We performed a cross-sectional retrospective study using the National Inpatient Sample from 2016- 2019 to assess hospitalized adults with hepatic encephalopathy as the primary diagnosis using ICD-10 codes. Characteristics of patients and outcomes were compared based on restraint use using multivariable regression analysis. Separate analyses were performed for hospitalizations with and without invasive cares defined as the presence of ICD-10 codes for mechanical ventilation, gastric tube placement and/or central venous catheter placement. **Results:** In 2.3% of 161,135 hospitalizations for hepatic encephalopathy, physical restraint use was documented. The mean age of the combined cohort was 61.6 years and 55.7% of patients were male with the majority of patients (64.8%) being white. Black patients had a higher rate of restraint use compared to white patients (3.4% vs 2.2%, p<0.001). In hospitalizations that did not involve invasive cares (no documentation of mechanical ventilation, gastric tube placement and/or central venous catheter placement), physical restraints use was associated with higher mortality (aOR = 1.72, 95% CI: 1.11-2.66, p<0.015), whereas in hospitalizations where invasive cares were employed, physical restraint use was associated with reduced mortality (aOR = 0.51, 95% CI: 0.34-0.76, p=0.001). **Conclusion:** Careful consideration of the necessity of restraints in hepatic encephalopathy hospitalizations without other invasive cares appears warranted as social disparities in restraint use and increased mortality were both found in this group.

Disclosures: Yasmin Ali: Nothing to Disclose, Spencer Goble: Nothing to Disclose, Thomas Leventhal: Nothing to Disclose

2165 | SEX DIFFERENCES IN DISEASE SEVERITY AT DIAGNOSIS OF CIRRHOSIS IN A NATIONAL COHORT

Mary White[1] Catherine Mezzacappa[2] Anahita Rabiee[2] Marina Serper[3] Nadim Mahmud[4] David Kaplan[5] Binu John[6] Ayse Aytaman[7] Tamar Taddei[2]

[1]Yale-New Haven Hospital, [2]Yale University, [3]University of Pennsylvania Health System, [4]Hospital of the University of Pennsylvania, [5]University of Pennsylvania, [6]University of Miami, [7]VA NY Harbor Healthcare System Brooklyn Campus

Background: There are known sex differences in cirrhosis and its disease progression. Metabolic dysfunction-associated steatotic liver disease (MASLD) is the leading cause of liver transplantation in women, but the incidence of alcohol-associated liver disease (ALD) in women is steadily increasing. Although women are less likely than men to develop hepatic decompensation, there is a paucity of data for disease severity at diagnosis and by etiology of cirrhosis. **Methods:** We performed a retrospective study of prospectively identified patients with cirrhosis in the Veterans Health Administration between 2008 and 2023. MELD-Na scores and Child-Turcotte-Pugh (CTP) class were used to measure cirrhosis disease severity and sexes were compared using t-tests and chi-squared tests. **Results:** The total sample included 3,746 women and 126,235 men with cirrhosis. Men were older than women (63.4 vs 57.7, P<.0001) and had higher MELD-Na (12.7 vs 11.9, P<.0001) scores at cirrhosis diagnosis. CTP classes were overall similar, though women had a higher percentage of CTP class A (62.6% vs 60.0%, P<.0001) and class C (8.6% vs 7.6%, P<.0001) when compared to men. Across both sexes, the most common etiologies of cirrhosis were MASLD (21.8% men, 30.4% women) and ALD (24.4% men, 22.6% women) followed by hepatitis C virus (HCV) (19.7% men, 18.8% women). Stratified by etiology, women with ALD and

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MetALD cirrhosis were significantly younger (ALD: 53.5 vs 62.0, P<.0001; MetALD: 56.6 vs 63.3, P<.0001) and significantly more likely to have CTP class C cirrhosis (ALD: 20.3% vs 13.6%, P<.0001; MetALD: 15.5% vs 8.1%, P<.0001) at diagnosis than men. For women with ALD and MetALD, MELD-Na scores did not differ significantly from men (ALD: 15.1 vs 14.7, P=0.2; MetALD: 14.0 vs 13.2, P=0.1). In MASLD, women had less severe disease compared to men by MELD-Na (10.1 vs 12.4, P<.0001) and CTP class (A: 74.3% vs 63.1%; B: 23.2% vs 32.8%; C: 2.5% vs 4.1%, P<.0001). For HCV, there were no significant differences in disease severity between sexes. **Conclusion:** In a national cohort of Veterans with cirrhosis, women generally presented with less severe disease than men at the time of cirrhosis diagnosis; however, the opposite was true in ALD and MetALD in which women were younger and almost twice as likely to have CTP class C disease at diagnosis. These findings call attention to a potential disparity in recognition, treatment, and prevention of ALD in women. Future research for early identification and intervention for ALD in women is necessary.

Characteristics at diagnosis of cirrhosis by sex and etiology

	Age Mean (SD)	MELD-Na Mean (SD)	CTP A % (N)	CTP B % (N)	CTP C % (N)
Total sample					
Men (N=126,235)	63.4 (9.2)	12.7 (9.3)	59.8% (75,505)	32.6% (41,149)	7.6% (9,581)
Women (N=3,746)	57.7 (9.6)	11.9 (9.6)	62.6% (2,344)	28.8% (1,080)	8.6% (322)
P value	P <.0001	P <.0001	P <.0001	P <.0001	P <.0001
ALD					
Men (N=30,801)	62.0 (10.1)	14.7 (10.2)	44.5% (13,725)	41.9% (12,902)	13.6% (4,174)
Women (N=848)	53.5 (10.2)	15.1 (10.6)	39.1% (332)	40.6% (344)	20.3% (172)
P value	P <.0001	P = 0.2	P <.0001	P <.0001	P <.0001
MetALD					
Men (N=11,597)	63.3 (9.2)	13.2 (10.1)	59.0% (6,841)	32.9% (3,816)	8.1% (940)
Women (N=330)	56.6 (8.5)	14.0 (12)	50.3% (166)	34.2% (113)	15.5% (51)
P value	P <.0001	P =0.1	P <.0001	P <.0001	P <.0001
MASLD					
Men (N=27,523)	68.2 (9.8)	12.4 (8.6)	63.1% (17,375)	32.8% (9,027)	4.1% (1,121)
Women (N=1,140)	61.2 (10.1)	10.1 (8.1)	74.3% (847)	23.2% (264)	2.5% (29)
P value	P<.0001	P<.0001	P < .0001	P < .0001	P <.0001
HCV					
Men (N=24,853)	62.7 (6.7)	11.0 (8.2)	75.1% (18,674)	21.1% (5,238)	3.8% (941)
Women (N=705)	59.0 (6.4)	10.3 (9.5)	78.4% (553)	19.9% (140)	1.7% (12)
P value	P <.0001	P = .06	P = 0.01	P = 0.01	P = 0.01
ALD+HCV					
Men (N=25,850)	60.3 (6.4)	12.4 (8.8)	59.2% (15,297)	32.7% (8,460)	8.1% (2,093)
Women (N=452)	56.2 (6.8)	11.9 (9.4)	61.1% (276)	30.8% (139)	8.2% (37)
P value	P <.0001	P = .03	P = 0.7	P = 0.7	P = 0.7

Disclosures: Mary White: Nothing to Disclose, Catherine Mezzacappa: Nothing to Disclose, Anahita Rabiee: Nothing to Disclose, Marina Serper: Grant/Research Support relationship with Grifols; Has not ended; Grant/Research Support relationship with Eurofins; Has not ended; Grant/Research Support relationship with Transplant Genomics; Has not ended, Nadim Mahmud: Nothing to Disclose, David Kaplan: Independent Contractor relationship with Roche Genentech; Has not ended; Grant/Research Support relationship with AstraZeneca Inc; Has not ended; Advisor relationship with AstraZeneca; Has ended; Advisor relationship with Exelixis; Has ended; Grant/Research Support relationship with Gilead; Has not ended; Advisor relationship with Sirtex; Has ended; Grant/Research Support relationship with Exact Sciences; Has not ended; Grant/Research Support relationship with Glycotest; Has ended, Binu John: Exact Sciences: Grant/Research Support, Genentech: Grant/Research Support, Glycotest, Inc: Grant/Research Support, Gilead: Grant/Research Support, Exelixis: Consultant, Takeda: Grant/Research Support, GlaxoSmithKline: Consultant, Astra Zeneca: Consultant, Ayse Aytaman: Nothing to Disclose, Tamar Taddei: Nothing to Disclose

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2166 | OUTCOMES IN A MULTIDISCIPLINARY MASLD CLINIC ARE AFFECTED BY RACE

Malcolm Chapman[1] *Joshua Fricker*[1] *Dalton Caviness*[1] *Meagan Gray*[1] *Fernando Bril*[1]

[1]*University of Alabama at Birmingham*

Background: Race and ethnicity affect metabolic dysfunction-associated steatotic liver disease (MASLD) prevalence, with the highest prevalence in Hispanic individuals, intermediate prevalence in non-Hispanic Whites (NHW), and the lowest prevalence in non-Hispanic Blacks (NHB). This lower rate of MASLD among NHB occurs despite higher rates of obesity, type 2 diabetes (T2D), and hypertension. Racial disparities in the management of patients with MASLD may explain why, despite the lower prevalence in NHB, a significant number still reach advanced stages of the disease. This study aimed to assess the outcomes of NHB versus NHW patients in a multidisciplinary MASLD clinic. **Methods:** Patients who established care at the University of Alabama at Birmingham's multidisciplinary MASLD clinic from February 2022 to January 2024 with at least one follow-up visit were included in the study. Presence of MASLD was defined based on the available evidence at the time of chart review. Race was self-reported and patients of mixed race or with missing data were excluded. Due to low numbers of other racial categories, only NHW and NHB patients were included. Participants with either excessive alcohol consumption, alternative etiologies of liver disease, or steatogenic medications were excluded. **Results:** A total of 167 patients were included (n=140 NHW and n=27 NHB) with a mean follow-up of 17 ± 12 months. Both groups had similar age and BMI (Table 1). The NHB group had significantly more women (78% vs. 54%, p=0.024), higher prevalence of T2D (63% vs. 33%, p=0.003), higher A1C (6.6 ± 1.1% vs. 5.9 ± 1.1%, p=0.006), and, despite lower ALT levels (34 ± 25 vs. 52 ± 42 U/L, p=0.037), they had similar FIB-4 index (1.14 ± 0.60 vs. 1.36 ± 1.14, p=0.35) (Table 1). Use of GLP1-RAs was similar in both groups (NHW 40% vs. NHB 44%, p=0.67). However, body weight loss among NHB patients was less than half that of weight loss achieved by their NHW counterparts although this did not reach statistical significance (-1.4 ± 7.8% vs. -3.1 ± 8.6%, p=0.36). Similarly, the rate of patients achieving ≥10% weight loss was more than double in NHW vs. NHB, but not statistically significant (18% vs. 8%, p=0.25), likely due to small sample size. **Conclusion:** In a multidisciplinary MASLD clinic, despite similar use of GLP-1RAs across groups, NHB patients lost numerically less weight than NHW patients and were numerically less likely to reach the ≥10% body weight loss goal. The higher prevalence of T2D in this racial group may explain the differences observed in our study.

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	Non-Hispanic White n = 140	Non-Hispanic Black n = 27	p value
Follow-up time (months)	17 ± 11	20 ± 14	0.196
Age (years)	52 ± 15	55 ± 11	0.34
Female n (%)	76 (54%)	21 (78%)	0.024
Body mass index (kg/m^2)	34.5 ± 6.6	36.7 ± 7.6	0.123
ALT (U/L)	52 ± 42	34 ± 25	0.037
AST (U/L)	30 ± 28	30 ± 22	0.174
FIB-4 index	1.36 ± 1.14	1.14 ± 0.60	0.35
Presence of T2D n (%)	46 (33%)	17 (63%)	0.003
A1c (%)	5.9 ± 1.1	6.6 ± 1.1	0.006
Use of GLP1-RA n (%)	56 (40%)	12 (44%)	0.67
Mean weight loss (%)	-3.1 ± 8.6	-1.4 ± 7.8	0.36
≥10% weight loss n (%)	25 (18%)	2 (8%)	0.25
Change in ALT (U/L)	-13 ± 46	-5 ± 14	0.44
Change in AST (U/L)	-7 ± 30	-6 ± 14	0.83
Change in A1C (%)	-0.1 ± 1.1	-0.2 ± 0.7	0.73

Data is presented as mean ± SD, unless otherwise specified.
Abbreviations: T2D (Type-2 diabetes mellitus), GLP-1RA (Glucagon-like peptide-1 receptor agonist)

Disclosures: Malcolm Chapman: Nothing to Disclose, Joshua Fricker: Nothing to Disclose, Dalton Caviness: Nothing to Disclose, Meagan Gray: NovoNordiesk: Consultant, Fernando Bril: NovoNordisk: Consultant, NovoNordisk: Speaking and Teaching, Boehringer Ingelheim: Speaking and Teaching, Boehringer Ingelheim: Advisor

2167 | NEIGHBORHOOD SOCIAL SUPPORT ASSOCIATED WITH INCREASED MORTALITY AMONG ADULTS WITH LIVER DISEASE

Tiange Zhang[1] Jennifer Dodge[1] Divya Ayyala[2] Norah Terrault[3]

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Background: Neighborhood environment is increasingly recognized as important to the prevalence and outcome of chronic liver disease (CLD). Neighborhood social support (NSS), or the degree of connectedness and solidarity within a community, may influence CLD by reinforcing healthy norms, increasing perceived safety, and reducing stress. Using a nationally representative sample, we examined the association of this novel social determinant on CLD prevalence and all-cause mortality. **Methods:** Adults with and without CLD were identified from the National Health Interview Survey 2013-2018 and linked to mortality data from the National Death Index. CLD was defined by ever had chronic liver condition, hepatitis, or liver cancer, or told of a liver condition in past 12 months. NSS was measured by a 4-point Likert scale using four questions related to 1) help availability, 2) accountability, 3) trustworthiness, and 4) connectedness among neighbors. The composite score (range 4-16) was categorized as minimal (4-7), low (8-10), moderate (11-13), and high (14-16). The association between NSS and (1) CLD and (2)

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all-cause mortality was estimated via logistic (odds ratio, OR) and Cox (hazard ratio, HR) regression, respectively, adjusted for sociodemographics and comorbidities. Differences in the effect of NSS on mortality by CLD status were tested with an interaction term. Analyses were weighted for the survey's sampling design. **Results:** Among 172,047 adults, the proportion with minimal, low, moderate, and high NSS were 8.6%, 14.1%, 34.2%, and 43.1%, respectively. 8,519 (4.1%) had CLD. 8,792 deaths occurred with mean follow-up of 3.8 years. In adjusted multivariable analysis, decreasing NSS was associated with increased odds of CLD in a dose-response manner: moderate NSS aOR 1.10, CI 1.03-1.18; low NSS aOR 1.23, CI 1.12-1.35, and minimal NSS aOR 1.36, CI 1.22-1.52 vs high NSS (trend p<0.001). Further adjustment for insurance and employment did not meaningfully change the association. Minimal NSS was associated with a 38% higher mortality risk among those with CLD (aHR 1.87, CI 1.40-2.51) vs non-CLD (aHR 1.36, CI 1.21-1.53) (interaction effect aHR 1.38, CI 1.00-1.89, interaction p=0.046). After adjusting for insurance and employment, the interaction effect was attenuated where minimal NSS was associated with a 28% higher mortality risk among those with CLD (aHR 1.59, CI 1.18-2.13) vs non-CLD (aHR 1.24, CI 1.10-1.39) (interaction effect aHR 1.28, CI 0.94-1.76, interaction p=0.12). **Conclusion:** Neighborhood environment is an important determinant of liver health. Lower NSS is associated with prevalent CLD with those with minimal NSS having a 36% higher odds of CLD. Importantly, among those with CLD, lower NSS also contributed to significantly increased mortality. Neighborhood social support and other modifiable features of the neighborhood social environment may serve as effective intervention targets to reduce liver-related diseases.

Table. Risk of all-cause mortality by chronic liver disease status and neighborhood social support.

	Mortality by neighborhood social support categories, HR (95% CI)			
	High	**Moderate**	**Low**	**Minimal**
Model 1: unadjusted				
CLD	[Ref]	1.20 (0.94-1.53)	1.42 (1.02-1.97)[a]	**2.00 (1.50-2.68)[a]**
Non-CLD	[Ref]	1.06 (0.99-1.13)	1.22 (1.12-1.34)[a]	**1.41 (1.26-1.58)[a]**
P for interaction[b]	[Ref]	0.33	0.40	**0.03**
Model 2: adjusted for sociodemograhics[c], CCI, CLD				
CLD	[Ref]	1.16 (0.91-1.49)	1.35 (0.96-1.88)	**1.87 (1.40-2.51)[a]**
Non-CLD	[Ref]	1.04 (0.97-1.12)	1.19 (1.08-1.30)[a]	**1.36 (1.21-1.53)[a]**
P for interaction[b]	[Ref]	0.40	0.48	**0.046**
Model 3: further adjusted for insurance, employment				
CLD	[Ref]	1.13 (0.89-1.43)	1.20 (0.86-1.67)	1.59 (1.18-2.13)[a]
Non-CLD	[Ref]	1.03 (0.96-1.10)	1.14 (1.04-1.25)[a]	1.24 (1.10-1.39)[a]
P for interaction[b]	[Ref]	0.474	0.77	0.12

[a]$p<0.05$
[b]P-values for interaction effect come from a model that included an interaction term between neighborhood social support and chronic liver disease status.
[c]Sociodemographic variables included sex, race and ethnicity, and age.
CCI, Charlson Comorbidity Index.

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2168 | UNEQUAL BURDEN: UNVEILING RACIAL AND REGIONAL DISPARITIES IN HEPATOCELLULAR CARCINOMA MORTALITY IN THE UNITED STATES (2018 TO 2022)

Saleha Aziz[1] Anjiya Shaikh[2] Hamid Ullah[1] Jan Petrasek[1]

[1]University of Mississippi Medical Center, [2]University of Connecticut Health Center

Background: The etiology of hepatocellular carcinoma (HCC) has shifted from viral to metabolic causes, potentially influencing epidemiological trends. This study examines recent mortality trends and demographic variations in HCC across the United States, focusing on racial, ethnic, and geographic disparities. Understanding

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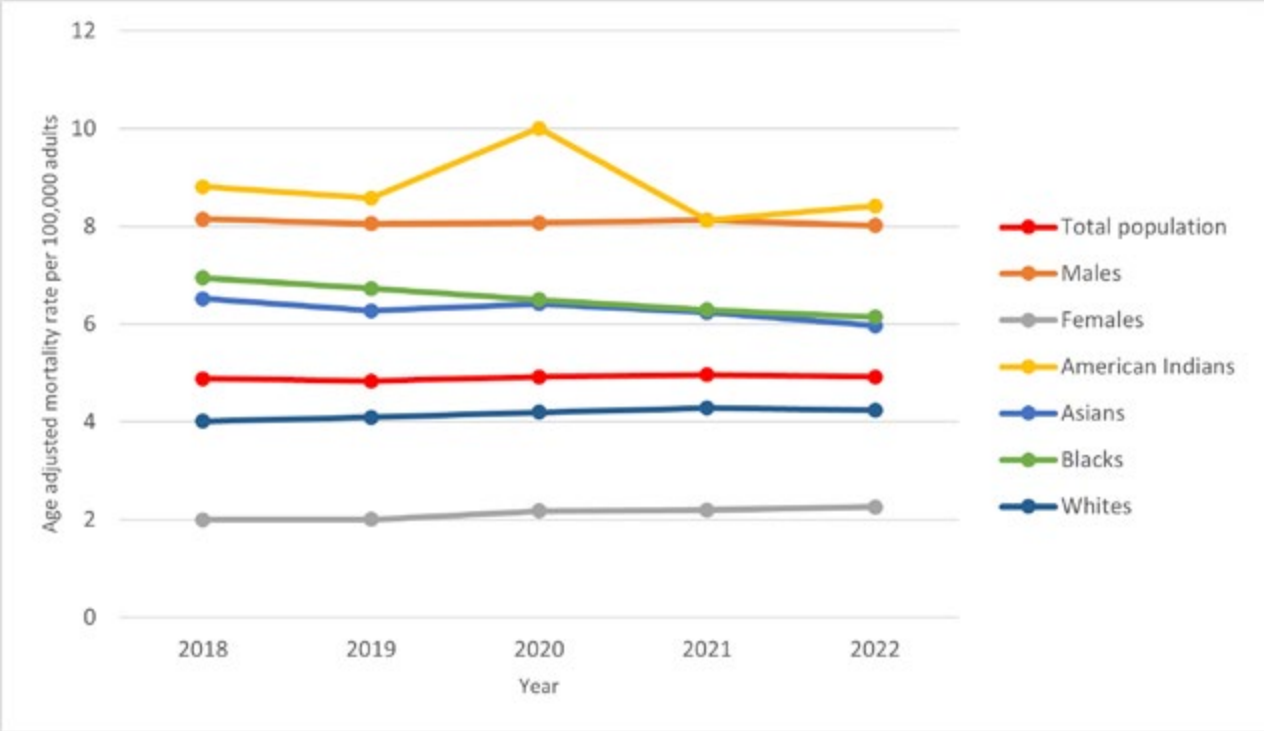
these disparities is crucial for developing targeted interventions and improving outcomes for vulnerable populations. **Methods:** Centers for Disease Control and Prevention Wide-Ranging OnLine Data for Epidemiologic Research was used to access National Vital Statistics System data from 2018 to 2022. Adults aged ≥25 years diagnosed with HCC (ICD-10 code C22.0) were included. Age-adjusted mortality rates (AAMR) per 100,000 adults were calculated. Joinpoint regression was used to assess trends through average annual percentage change (AAPC). Mortality was stratified by age, sex, race/ethnicity (White, Hispanic, Black, Asian, American Indian/ Alaska Native), and census region (South, West, Midwest, Northeast). The location of death (home, inpatient facility, hospice, nursing home, outpatient) was also examined. **Results:** Total HCC deaths from 2018 to 2022 were 69,192. Overall AAMR was 4.92, with a stable trend (AAPC 0.45, 95% confidence interval -0.14 to 1.04). AAMR was higher in males (8.09) than females (2.15) and increased with age. While total deaths were highest among white adults (43,060), AAMR was notably highest among American Indians/Alaska Natives (8.80), followed by Hispanics (7.32). Significant regional disparities were observed, with the South (AAMR 5.11) and West (5.59) experiencing higher rates than the Midwest (4.41) and Northeast (4.25). Most deaths occurred at home (30,216), followed by inpatient facilities (20,683). **Conclusion:** While overall mortality trends in HCC remained stable from 2018 to 2022, significant disparities persist across racial/ethnic groups and geographic regions. This study highlights the disproportionately high AAMR among American Indians/Alaska Natives and the pronounced regional variations in mortality, particularly in the South and West. These findings underscore the need for targeted interventions, such as culturally sensitive outreach programs and improved access to care, to address these disparities and reduce the burden of HCC in vulnerable populations.



Disclosures: Saleha Aziz: Nothing to Disclose, Anjiya Shaikh: Nothing to Disclose, Hamid Ullah: Nothing to Disclose, Jan Petrasek: Nothing to Disclose

2169 | MENTAL HEALTH DIAGNOSES ARE ASSOCIATED WITH DISPARITIES IN HEPATOCELLULAR CARCINOMA AMONG VETERANS

Nguyen Pham[1] Mei Leng[2] Steven-Huy Han[2] Folasade May[2] Jihane Benhammou[2]

[1]UCLA Ronald Reagan Medical Center, [2]University of California, Los Angeles

Background: Vietnam Veterans, whose self-reported race is Hispanic and non-Hispanic Black, were shown to be disproportionately affected by hepatocellular carcinoma (HCC), compared to their non-Hispanic White (NHW) counterparts. While mental illnesses are associated with poorer outcomes in HCC and all-cause mortality

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is higher among Veterans with mental illnesses, the relationship between mental health disorders (MHD) and incident HCC among Veterans is unknown. Understanding this relationship may provide new avenues to improve HCC detection and management. **Methods:** In a retrospective cohort study, we identified adult (≥18 years) Vietnam Veterans (1966-1975) who established care with the Veterans Health Administration (VHA) between 2000-2019. We extracted relevant clinical and socioeconomic data, including self-reported race/ethnicity. MHD were defined by ICD codes, VA MH surveys and categorized into three groups: alcohol use disorder/substance use disorder (AUD/SUD), non-AUD/SUD (anxiety, depression, post-traumatic stress disorder, schizophrenia and bipolar), and any MHD, based on their clinical relevance and correlations (>0.7). Cirrhosis was defined by 2 consecutives FIB-4 scores >3.25 or ICD codes. The association between incident HCC and race/ethnicity was analyzed by multivariable Cox regression in Veterans with cirrhosis adjusting for age and MHD/count of MHD. The numbers of MHD patients had in lieu of MH groups were also analyzed. To compare the numbers of MHD among the groups, we conducted an ANOVA. **Results:** Of the 296,505 eligible Veterans, 35,877 (12%) Veterans had cirrhosis and 2,654 (0.9%) had HCC. Of those with cirrhosis, 2,325 (6.6%) were Hispanic, 7,031 (19.9%) were non-Hispanic Black, and 23,807 (67.3%) were NHW. The mean number of MHD was higher in non-Hispanic Black (3.60 ± 1.71), compared to Hispanic (3.49 ± 1.66) and NHW Veterans (3.29 ± 1.72; p<0.001). After adjusting for age, Hispanic individuals were more likely to develop HCC (adj.HR=2.03, 95% CI 1.26-3.27) in the AUD/SUD group compared to NHW Veterans. Similarly, in the any MHD group, Hispanic (adj.HR=1.95, 95% 1.67-2.27) and Non-Hispanic Black (adj.HR=1.46, 95% CI 1.30-1.64) individuals were more likely to develop HCC, compared to NHW individuals. Veterans without any MHD did not have a higher incidence of HCC, independently of race/ethnicity. In a multivariable model adjusting for age, the mean counts of MHD and interactions between race/ethnicity and MHD counts, Hispanic were still more likely to develop HCC, compared to NHW Veterans. **Conclusion:** In this large retrospective cohort of Vietnam Veterans, Hispanic and non-Hispanic Black Veterans with cirrhosis had a higher incidence of HCC than NHW Veterans. Hispanic and non-Hispanic Black Veterans had disproportionately higher rates of any MHD, compared to NHW individuals. The number of MHD was significantly associated with incident HCC among Hispanic and non-Hispanic Black Veterans.

Disclosures: Nguyen Pham: Nothing to Disclose, Mei Leng: Nothing to Disclose, Steven-Huy Han: Nothing to Disclose, Folasade May: Nothing to Disclose, Jihane Benhammou: Nothing to Disclose

2170 | PALLIATIVE CARE CONSULTATION CAN IMPROVE END OF LIFE CARE FOR PATIENTS WITH CIRRHOSIS REMOVED FROM THE LIVER TRANSPLANT LIST COMPARED TO PATIENTS WITH PANCREATIC ADENOCARCINOMA ◆

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Background: End stage liver disease (ESLD) and pancreatic ductal adenocarcinoma (PDAC) are associated with high symptom burden and mortality risk with similar 5-year survival rates. Despite this, end-of-life (EOL) care often differs. **Methods:** We completed a single center retrospective analysis of patients removed from the LT waitlist (group 1: ESLD) or treated for pancreatic malignancy (group 2: PDAC) who died between 2018 and 2022. Invasive interventions were assessed in the last 30 and 90 days of life. The impact of a PC consult on invasive interventions was assessed within groups using Chi-squared and between groups using logistic regression with interaction testing. The impact of a PC consult on survival when no further disease-directed therapy options were offered, defined as delisting (ESLD) or when no cancer-direct treatment was offered (PDAC), was assessed using Kaplan Meyer analyses. **Results:** A total of 270 patients were included (170 ESLD and 100 PDAC). Patients with ESLD were younger (61 years vs. 68 years, p<0.01), more likely to be male (69% vs. 48%, p<0.01), and more likely to be Hispanic (18% vs. 4%, p<0.01). In ESLD patients, the most common liver disease etiology was alcohol (47%), and 19% had hepatocellular carcinoma. Most PDAC patients (82%) received > 1 prior treatment including chemotherapy (79%), radiation (14%), and/or surgery (11%). Patients with ESLD were less likely to receive a PC consult (24% vs. 71%, p<0.01) and more likely to undergo invasive interventions in the final 90 (85% vs. 51%, p<0.01) and 30 (82% vs. 32%, p<0.01) days of life as compared to PDAC. A PC consult was associated with fewer interventions in the final 90 days of life in ESLD patients (73% vs. 89%, p=0.01) but not in PDAC patients (51% vs. 52%, p=0.93). In the final 30 days of life, a PC consult was protective against intensive care admission (p=0.03) and intubation (p=<0.01) in ESLD patients while a PC consult was not associated with fewer

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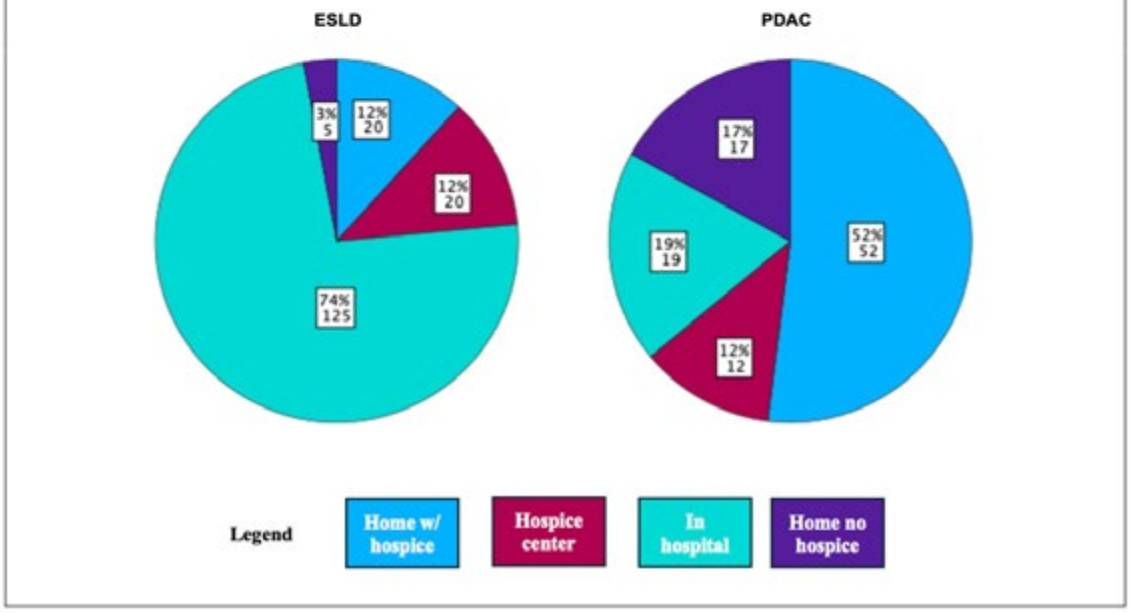
30-day interventions in PDAC patients (Table 1a). On interaction testing, the effect of a PC consult on 30-day interventions differed significantly in ESLD and PDAC patients (p=0.02). The median time to death when no disease-directed therapies were offered was shorter in ESLD patients (0 days ESLD vs. 49 days PDAC, p<0.01). A PC consult was associated with a survival benefit once no disease-directed therapies were offered in ESLD (p=0.02), but not PDAC (p=0.88). Further, a PC consult was associated with a lower risk of death in the hospital in ESLD patients (p<0.01) but not PDAC (p=0.43) (Table 1b). **Conclusion:** Patients with ESLD removed from the LT waitlist undergo significantly more interventions at the EOL compared to patients with PDAC. We observed that a PC consult is associated with reduced aggressive EOL interventions, overall survival benefit, and lower risk of death in the hospital in patients with ESLD but not PDAC. This research informs how collaboration with PC for patients with ESLD delisted for LT may help guide EOL care.

Table 1: End of Life Outcomes in patients with End Stage Liver Disease (ESLD) removed from the transplant waitlist compared to patients with Pancreatic ductal adenocarcinoma (PDAC)

Table 1a: Medical care in the final 30 days of life

	ESLD (n=170)			PDAC (n=100)			Impact of PC Consult	
	(-) PC consult	(+) PC consult	p	(-) PC consult	(+) PC consult	p	ESLD	PDAC
Any Intervention	86.2%	70.0%	**0.019**	24.1%	35.2%	0.281	-16.2%	11.1%
Intensive care admission	79.2%	62.5%	**0.032**	6.9%	8.5%	0.795	-16.7%	1.6%
Cardio-pulmonary resuscitation	6.9%	0.0%	0.087	6.9%	4.2%	0.578	-6.9%	-2.7%
Intubation	66.9%	40.0%	**0.002**	3.4%	4.2%	0.857	-26.9%	0.8%
Dialysis	48.5%	32.5%	**0.796**	0.0%	0.0%	-	+2.8%	-
Feeding Tube	49.4%	35.0%	**0.037**	3.4%	0.0%	0.116	-14.4%	-3.4%
Endoscopy	23.1%	12.5%	**0.148**	10.3%	9.9%	0.941	-10.6%	-0.4%
Transfusion	61.2%	53.5%	**0.198**	20.7%	15.5%	0.530	-11.3%	-5.2%
Any Hospice	17.7%	57.5%	**<0.001**	62.1%	71.8%	0.338	39.8%	9.8%

Table 1b: Location of death, by patient group



Disclosures: Katherine Cooper: Nothing to Disclose, Mary Bassaly: Nothing to Disclose, Kai-Lou Yue: Nothing to Disclose, Dhruval Amin: Nothing to Disclose, Daniel Belza: Nothing to Disclose, Nouran Nagy: Nothing to Disclose, Neil Marya: Boston Scientific: Consultant, Navine Nasser-Ghodsi: Boston Scientific: Consultant

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2171 | EXPLORING THE ROLE OF SOCIAL DETERMINANTS IN EARLY LIVER TRANSPLANTATION RELAPSE RATES AND OUTCOMES: A MULTICENTER ANALYSIS

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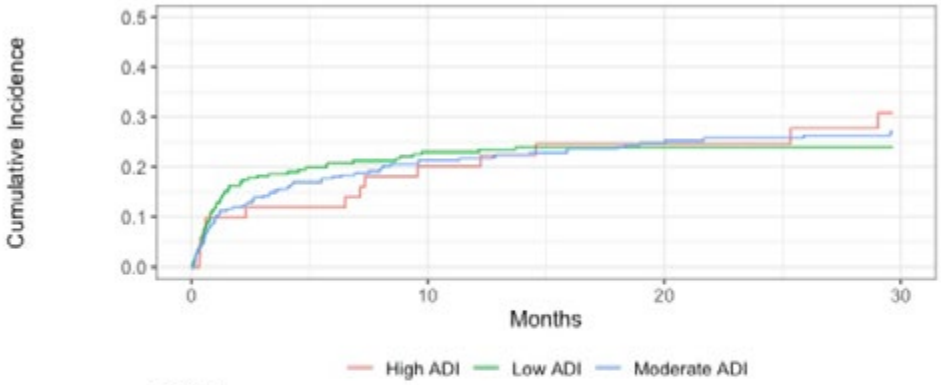
Background: Recent evidence on LT prior to a 6 month sobriety period (early LT) have shown a significant survival benefit while maintaining acceptable relapse rates. However, patients with social needs or historically disadvantaged backgrounds may not have the same access to early LT due to concerns for relapse and poor outcomes. Thus, we investigated the predictors of relapse across various social determinants of health (SDOH) domains and their post-LT outcomes. **Methods:** This was a multicenter, retrospective study involving the RESOLVE consortium which includes adult patients with ALD referred for early LT across 6 centers in the United States from 2018-2021. These data were merged with the Area Deprivation (ADI), a validated, publicly available, 17-item aggregate score that ranks community, zip code-level socioeconomic status. ADI was stratified into tertiles: Low ADI, Moderate ADI, High ADI. Competing risk analysis was used to estimate survival with LT as a competing event. Multivariable logistic regression was used to evaluate risk factors for relapse and adjusted for clinicodemographic covariates. **Results:** There were 621 patients with ALD who were evaluated for early LT. Of these, a minority of patients resided in High ADI (N=51, 8.2%) areas, while the majority resided in Low ADI (N=265, 42.7%) and Moderate ADI (N=305, 49.1%) areas. Patients residing in High ADI areas had lower rates of private insurance and colleg/post-graduate education (p<0.001). Similar proportion of patients in Low (42.6%, N=113), Moderate (39.0%, N=119), and High ADI (49.0%, N=25) cohorts were transplanted (P=0.07). Competing risk analysis showed that there were no differences in rates of survival or LT among ADI cohorts (Figure 1, P>0.05). There were also similar rates of post-LT infection, rejection, and re-transplant rates (P>0.05). SDOH covariates (e.g., ADI, insurance, education, marital status, employment) were not predictors of relapse on multivariable logistic regression analysis (P>0.05). Age (OR 0.97, 95%CI 0.95-0.99), male sex (OR 0.50, 95%CI 0.30-0.84), and MELD score at referral (OR 0.95, 95%CI 0.92-0.97) were protective factors of relapse. **Conclusion:** Patients residing in more deprived areas or those with previously known SDOH risk factors do not have higher rates of relapse and had similar post-LT outcomes. These data show evidence that select patients with SDOH risk factors who are referred to a transplant center for early LT can achieve satisfactory outcomes.

Figure 1. Cumulative incidence curves estimating death, with LT as a competing event, stratified by ADI groups.



	At Risk			
High ADI	51	20	14	7
Low ADI	265	86	56	33
Moderate ADI	305	118	81	46
	Events			
High ADI	0	10	12	14
Low ADI	0	59	61	61
Moderate ADI	0	63	72	76

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Disclosures: Bima Hasjim: Nothing to Disclose, Anjana Rajan: Nothing to Disclose, Nivetha Saravanan: Nothing to Disclose, Katherine Cooper: Nothing to Disclose, Deepika Devuni: Avania Medical: Grant/Research Support, Intercept: Grant/Research Support, Kawthar Mohamed: Nothing to Disclose, Nicholas Lim: Nothing to Disclose, Allison Kwong: Nothing to Disclose, Weiyu Wu: Nothing to Disclose, Kaleb Tesfai: Nothing to Disclose, Veeral Ajmera: Nothing to Disclose, Kevin Wang: Nothing to Disclose, Hersh Shroff: Nothing to Disclose, Amanda Cheung: Nothing to Disclose

2172 | ELEVATED RATES OF LIVER AND INTRAHEPATIC DUCT CANCER IN NATIVE AMERICAN AND ALASKAN NATIVE FEMALES VERSUS MALES WHEN COMPARED TO THEIR WHITE COUNTERPARTS: A 5-YEAR REGIONAL ANALYSIS

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Background: Liver and intrahepatic duct cancers are a leading cause of cancer deaths worldwide with over 700,000 deaths yearly. The rate of new cases has tripled, and the death rate has more than doubled since 1975 in the United States. The Native American and Alaskan Native (NA/AN) populations are known to have higher rates of chronic liver disease and cancer when compared to whites. In this study we examined the regional and gender related rates in recent new cases of liver and intrahepatic duct cancers. **Methods:** A retrospective cohort study was performed on 28,609 patients from 2016 to 2020 using the CDC and NCI 2022 submission data from years 1999-2020. Analysis of NA/AN patients was restricted to areas where healthcare services were provided by the Indian Health Service (IHS). Analysis of white patients was restricted to those who lived in IHS Purchased/ Referred Care Delivery Areas, which consisted of counties containing NA/AN reservations. Rates were age-adjusted to the US standard population in 2000. **Results:** The overall rate of liver and intrahepatic bile duct cancer in the United States was 7.2 per 100,000 in whites and 18.6 per 100,000 in NA/AN, a 2.58 times higher rate in NA/AN (Figure 1). The rate in white males was 10.8 per 100,000 and 26.5 per 100,000 in NA/AN males, a 2.45 times higher rate in NA/AN males. The rate in white females was 4.0 per 100,000 and 12.0 per 100,000 in NA/AN females, a 3.0 times higher rate in NA/AN females. The highest rate in NA/AN versus whites was in the Northern Plains region, where NA/AN females had a 3.85 times higher rate than white females. The lowest rate in NA/AN versus whites was in the Eastern region, where NA/AN females had only a 1.79 times higher rate than white females. **Conclusion:** Our study has demonstrated that even though NA/AN males have a higher overall rate, NA/AN females have a higher proportional rate of liver and intrahepatic duct cancer when compared to their white counterparts. This rate is much higher in the Northern Plains and much lower in the East, where the nongender related rates demonstrate the same overall trend. Due to the stark contrast between regions, more studies need to be done to demonstrate the risk factors that are present in these regions including access to care and gender related biases. We advocate physicians be aware of the higher rates of liver and intrahepatic duct bile cancer in NA/AN females in these regions and have a heightened suspicion when treating this population.

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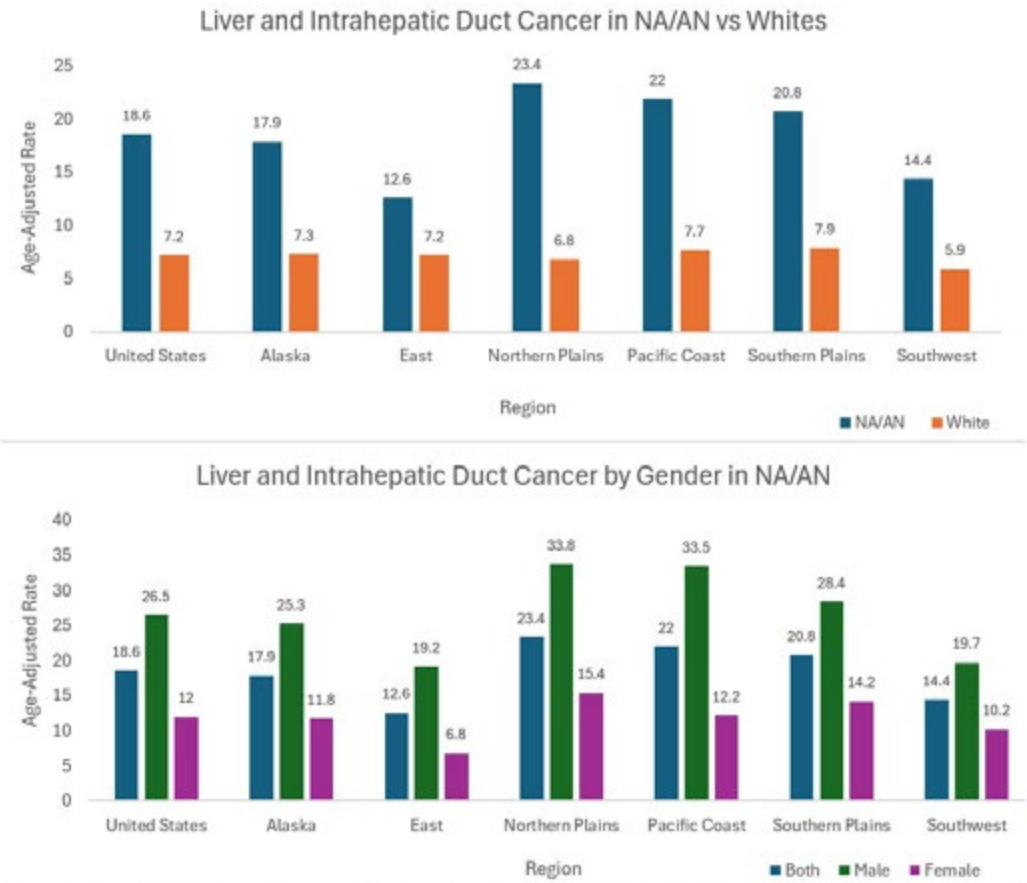

Figure 1: Age-adjusted rates of liver and intrahepatic duct cancer in Native American and Alaskan Natives compared to whites and by gender

Disclosures: Tulika Saggar: Nothing to Disclose, Atul Sinha: Nothing to Disclose, James Pellegrini: Nothing to Disclose, Ana Rivera: Nothing to Disclose, Paul Mustacchia: Nothing to Disclose

2173 | THE WALL WITHIN: UNDERSTANDING RACIAL DISPARITIES IN LIVER TRANSPLANT OUTCOMES IN THE US SOUTHWESTERN REGION CENTRE

Anandalakshmi Ponnaluri[1] Michael Fallon[1] Moises Nevah Rubin[1] Pooja Rangan[2] Claire Faulkner[1] Karn Wijarnpreecha[3]

[1]University of Arizona, [2]Banner Health, [3]University of Arizona College of Medicine-Phoenix

Background: Liver transplantation (LT) is a crucial treatment for individuals facing end-stage liver disease, but disparities persist, especially among racial and ethnic minorities. Despite important regulations like the National Transplant Act of 1980 and subsequent measures such as the Final Rule (2000), MELD (Model for End-stage Liver Disease) score adoption (2002), Share 35 policy (2013), Acuity circles (2020), Medicare expansion (2020), and Medi-Cal's removal of the six-month rule for ALD (since Feb 2022), these inequalities remain. Recent data from the OPTN (Organ Procurement Transplant Network) report of 2022 reveal changes in the types of people receiving LT, with more younger individuals, females, those with high BMI, and people from Hispanic and Native American backgrounds. Alcohol Liver disease and metabolic-associated steatohepatitis are increasingly common reasons for transplantation. This study aims to investigate barriers LT candidates encounter at different stages and assess racial disparities in referral, evaluation, listing, and post-transplant outcomes. **Methods:** A retrospective cohort study was conducted from January 1, 2012, to December 31, 2022, at Banner University Medical Centre-Phoenix. Statistical analyses included Pair-wise comparative tests, competing risk and multivariable Cox proportional hazards analysis. Continuous variables were summarised with medians and interquartile range, and frequencies and percentages were used for categorical variables. **Results:** Among the 2,877 referrals, Native Americans represented 8.8%, while Hispanics comprised 26% and non-Hispanic whites

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accounted for 61%. Demographic characteristics indicated a predominance of young, female individuals with high Body Mass Index (BMI-30) and median MELD scores of 30 and 35 at waitlisting and transplant, respectively, compared to non-Hispanic whites (NHW) with scores of 19 and 20. There was a notable prevalence of Alcohol Liver Disease and Metabolic metabolic-associated steatohepatitis. Disparities were evident in evaluation (39%) and listing (53%) compared to non-Hispanic whites (51% and 64%, respectively). Financial obstacles were significant barriers for Native Americans (15.5%) and Hispanics (19.81%). Waitlist mortality was substantially higher for Native Americans (Subdistribution Hazard Ratio, SHR: 5.26, p=0.005) and Hispanics (SHR: 2.92, p=0.017) compared to non-Hispanic whites. However, graft survival did not exhibit significant differences by race. **Conclusion:** Significant racial and ethnic disparities exist for liver transplantation Evaluation, listing, and post-transplant outcomes for Native Americans and Hispanics in the southwestern region. Efforts are needed to identify determinants for Liver transplantation in race and ethnicity disparities that can inform intervention strategies.

Baseline Demographic characteristics, waitlist, and post-transplant outcomes comparative analysis of LT referred patients in the United States southwestern region 2012–2022, stratified by race and ethnicity.

Total Referred (2877)		**Non-Hispanic Whites** (1760)	**Native Americans** (253)	**Hispanics** (744)	**Black** (77)	**Asian and Pacific Islander** (43)
Significant Demographic characteristics	Age (Y)	58(51-64)	53(44-60) *	58(51-63)	57(41-62)	60(54-64)
	BMI	28(24-31)	30(26-35) *	30(25-33) *	28(24-31)	27(23-30)
	Gender (female)	42%	55% *	41%	41%	37%
Insurance	Commercial	52%	62%*	54%	35%*	35%*
	Self-Pay	17%	17%	12%*	20%	20%
	Medicaid	16%	8% *	15%	25%	12%
	Medicare	10%	8%	14% *	8%	23%
Primary Disease	ALD	38%	48%*	30%	15%*	11%*
	Cirrhosis MASH	13%	20%*	21%*	6%	8%
MELD Scores	Waitlisting	19(12-32)	30(19-40) *	18(12-30)	32(14-40) *	13(7-35)
	Transplantation	20(11-34)	35(17-41) *	22(14-34)	31(16-43)	19(7-34)
Transplant outcomes						
Waitlist Mortality [a]	SHR (95% CI)	Cumulative Incidence When Compared to NHW	5.2(1.9-14.2)*	2.9(1.2-7.0) *	0.8 (0.1- 6.6)	1.3 (0.1 - 11.6)
Graft Survival [b]	SHR (95% CI)	Cumulative Incidence When Compared to NHW	2.2 (0.6-7.6)	1.1(0.4 - 3.2)	1.6(0.3 - 7.2)	1.1 (0.1 - 9.9)

Values(N) are in percentages or Median (interquartile range). * P ≤ 0.05 (all other P values > 0.05). LT-referred patients of non-Hispanic whites are compared with all other groups through pairwise comparisons of P value from a chi-squared test for categorical variables or Fisher Exact test as appropriate. For continuous variables a two-sample Wilcoxon rank test (all continuous variables failed the Shapiro–Wilks normality test) or 2 sample t-test.

a Waitlist mortality- analyses were adjusted for patient Race, Age, MELD Score at waitlisting, BMI at Listing, Gender, Insurance, and DM.

b Graft Survival-Analyses were adjusted for recipient Race, Age, Gender, MELD Score at Transplant, BMI at Listing, Length of Hospital stay, Insurance, DM and Donor characteristics DCD, and Cold Ischemic Time Hours.

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Disclosures: Anandalakshmi Ponnaluri: Nothing to Disclose, Michael Fallon: Nothing to Disclose, Moises Nevah Rubin: Nothing to Disclose, Pooja Rangan: Nothing to Disclose, Claire Faulkner: Nothing to Disclose, Karn Wijarnpreecha: Nothing to Disclose

2174 | REPRESENTATION OF WOMEN IN LIVER DISEASE CLINICAL TRIALS

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[1]Hospital of the University of Pennsylvania, [2]Perelman School of Medicine at the University of Pennsylvania, [3]University of Pennsylvania

Background: Studies have shown that underrepresentation of women in clinical trials can lead to systemic health inequities. Gender representation in liver disease clinical trials has previously not been studied. This study aims to identify trends in representation of women in clinical trials across multiple liver disease domains. **Methods:** To identify relevant articles, a Medical Subject Headings (MeSH) search string was developed and applied to the PubMed database. This included English language randomized controlled trials (RCTs) of adult subjects published between 2019 and 2023, and focused on domains of chronic liver disease (CLD), metabolic dysfunction-associated liver disease (MASLD), or a composite of cirrhosis, liver cancer, and/or liver transplantation. Articles were manually screened for appropriateness of inclusion, and data regarding study location, sample size, and proportion of women enrolled were extracted. To visualize proportions of women included in studies over time, scatterplots over time were plotted weighted by study sample size. Linear regression models were fit to evaluate trends in the proportion of women enrolled across domains over time, on a per-study basis. Benchmarks for proportions of women with CLD, MASLD, and cirrhosis/liver cancer/liver transplantation were obtained from NHANES and UNOS data, respectively. Differences between fitted regression lines and expected benchmarks were plotted to assess degrees of under- or over-representation of women in RCTs. **Results:** After the exclusion of 222 studies for missing gender data or non-RCT design, a total 557 studies including 227,376 randomized patients comprised the analytic cohort; 17.6% of these studies were performed in the US. The proportion of women enrolled in clinical trials increased significantly over time in CLD trials (beta 0.02, p=0.048; Panel A) and cirrhosis/liver cancer/liver transplantation trials (beta 0.02, p=0.041; Panel C). With respect to sex-based differences in liver disease prevalence, women are fairly represented in CLD and MASLD trials however they remain approximately 20% underrepresented in cirrhosis/liver cancer/liver transplantation trials. **Conclusion:** Women are significantly underrepresented in cirrhosis, liver cancer, and liver transplant related RCTs globally. Addressing this gender bias in clinical trial enrollment is a necessary step in promoting equitable representation and thus improving health outcomes.

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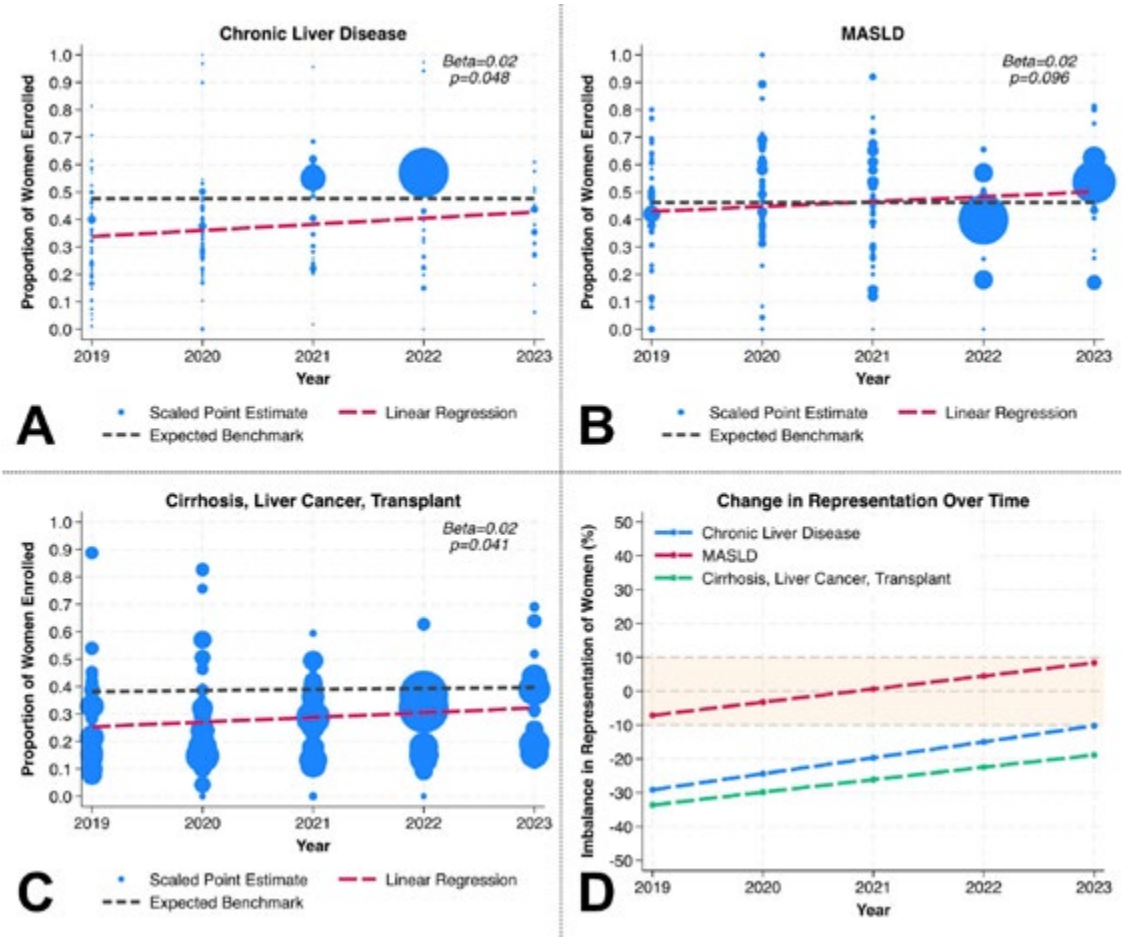

Disclosures: Anna Goebel: Nothing to Disclose, Emily Sheng: Nothing to Disclose, Pedro Ochoa-Allemant: Nothing to Disclose, Nadim Mahmud: Nothing to Disclose

2175 | RACIAL AND ETHNIC DISPARITIES IN LIVER CANCER RISK BY BIRTH COHORT: AN ELECTRONIC HEALTH RECORD (EHR)-BASED EPIDEMIOLOGIC COHORT STUDY

Chanda Ho[1] Janet Chu[2] Aly Cortella[2] Alison Canchola[2] Pushkar Inamdar[2] Pragati Kenkare[3] Jane Vu[3] Sixiang Nie[4] Ma Somsouk[5] Michele Tana[5] Caroline Thompson[6] Scarlett Gomez[2] Hashem El-Serag[7] Miok Kim[2] Mark Segal[2] Yihe Daida[4] Su-Ying Liang[3] Mindy Hebert-Derouen[2] Salma Shariff-Marco[2]

[1]Singapore General Hospital, [2]University of California San Francisco, [3]Sutter Health, [4]Kaiser Permanente Hawaii, [5]San Francisco General Hospital, [6]University of North Carolina, [7]Baylor College of Medicine

Background: Hepatocellular carcinoma (HCC) is the sixth leading cause of cancer-related death in the United States. Reports show that HCC incidence is decreasing; however, racial and ethnic disparities in HCC risk persist. Few studies have explored whether these disparities differ by birth cohort. **Methods:** Adults with at least one in-person visit between 2000-2017 across three distinct hospital systems in California and Hawaii were linked to state cancer registry data on incident HCC. The birth cohorts were defined as 1)1895-1944 (pre-baby boomer); 2)1945-1965 (baby boomer); 3)1966-1999 (post-baby boomer). We used Cox proportional hazards regression with age as the timescale to examine racial and ethnic disparities in HCC risk stratified by sex and birth cohort; we adjusted models for site, year of first visit to the system, number of encounters, and duration of active follow-up. **Results:** Of a pooled cohort of 4,248,553 individuals, 2,916 had an incident HCC. In the overall cohort, 15% were pre-baby boomers, 32% baby boomers, and 53% post-baby boomers. Overall, 55% patients were female, 38.7% were non-Hispanic (NH) White; 14.3% Asian American; 10.5% Hispanic; 4.6% NH Black, 2.7% Native Hawaiian or Pacific Islander (NHPI), 1.2% multiracial; 0.8% American Indian or Alaska Native (AIAN). In Cox regression models, among pre-baby boomers, HCC risk was highest among NHPI for both males (HR 4.15,

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95% CI 2.91-5.91) and females (HR=3.88, 95% CI 2.24-6.73). HCC risk was also higher among Black, Asian American, and Hispanic males and females in the pre-baby boomers compared to NH White males and females, respectively. Among baby boomers, multiracial males (HR 2.04, 95% CI 1.29-3.22) and females (HR 2.69, 95% CI 1.34-5.4) had the highest HCC risk. In the same cohort, AIAN, Black, Hispanic, and Asian American males had higher HCC risk, while multiracial, NHPI, and Black females had higher HCC risk. In post-baby boomers, risk of HCC was highest among Asian Americans for both males (HR 3.62, 95% CI 1.85-7.02) and females (HR 3.12, 95% CI 1.03-9.45) without significant risk in the other racial and ethnic groups for both males and females. **Conclusion:** In this large, racially and ethnically diverse EHR-based cohort, the highest HCC risk was seen among NHPI males and females among pre-baby boomers, multiracial males and females in the baby boomers, and Asian American males and females in the post-baby boomers. Etiology of liver cancer is likely contributing to these results. Understanding disparities in HCC risk can inform targeted preventive strategies and improve HCC outcomes for high-risk populations.

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2176 | SAFETY AND EFFICACY OF CONTRACEPTIVE AGENTS AFTER LIVER TRANSPLANTATION

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Background: The number of reproductive-aged liver transplant (LT) recipients is rising, and fertility is rapidly restored in the post-operative setting. Pregnancies within the first-year post-LT confer the greatest risks to the mother, graft, and infant, thus pregnancy prevention for those who wish to avoid pregnancy is key. Incident hypertension in the first-year post LT is also ~ 40%, raising concerns about combined hormonal contraception (CHC) in this period. However, data on contraceptive use and safety in LT recipients are limited. **Methods:** This was a retrospective study of reproductive-aged women with prior LT (including dual liver-kidney transplant) with follow-up at our center between 1/2013 to 2/2024. Contraceptive exposure (CTE) was identified by self-report and medication lists, defined as 90-day duration. CTEs included CHCs (pills, skin patch, vaginal ring), progestin-only agents (pills, subcutaneous implant, injection), intrauterine devices (IUDs; copper, progestin) and emergency contraception. Outcomes were evaluated from CTE start to 3 months since last use, including hypertension (HTN), VTEs, myocardial infarction (MI), stroke, pregnancy, and pelvic inflammatory disease (PID), identified by ICD codes and chart validation. **Results:** Among 74 LT recipients with 99 CTEs, median age was 31 yrs (IQR 23, 39), with time from LT to first CTE of 4 yrs (IQR 0, 16), and CTE duration of 22 months (IQR 9, 49). Thirty-four (46%) were White, 24 (32%) Latinx, 8 (11%) Asian, and 2 (3%) Black and 13 (18%) had liver-kidney transplants. CTEs included 35 (35%) CHCs, 32 hormonal (32%) and 2 copper IUDs (2%), 13 injections (13%), 9 subcutaneous implants (9%), 7 progestin-only pills (7%), and 1 progestin-only emergency contraceptive pill use (1%). Two out of 26 CHC users (8%) developed HTN; among the 5 with CHC use in the first-year post-LT, none developed incident hypertension during that time. There were no reports of unintended pregnancy, PID, stroke, MI, or VTE in the study cohort. **Conclusion:** In the largest study of hormonal contraception after LT, we identified no serious adverse events including VTE, MI, stroke, PID, or contraceptive failure. Incident hypertension was low with CHC use and none occurred in the first-year post-LT. These data support the safety and efficacy of a spectrum of contraceptive agents in LT recipients, in whom family planning counseling and contraceptive access can help to decrease rates of early and undesired pregnancies.

Disclosures: Grace Zhang: Nothing to Disclose, Cynthia Fenton: Nothing to Disclose, Dominika Seidman: Nothing to Disclose, Elle Oberweis-Manion: Nothing to Disclose, Monika Sarkar: GSK: Grant/Research Support, Zydus Pharmaceuticals: Grant/Research Support, Gilead Sciences: Grant/Research Support

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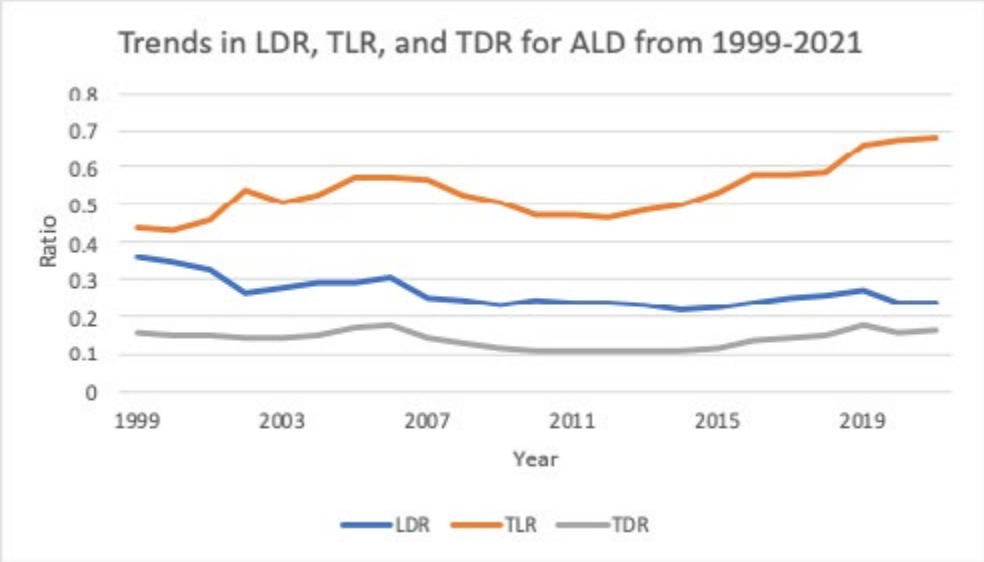
2177 | DISPARITIES IN ALCOHOL-ASSOCIATED LIVER DISEASE: TRENDS IN LIVER TRANSPLANTATION AND LISTING TO DEATH RATIO

Alexander Zhao[1] Nicole Ng[1] Xiaohan Ying[2] Arun Jesudian[1] Catherine Lucero[1] Russell Rosenblatt[1]

[1]Weill Cornell Medicine, [2]New York-Presbyterian Hospital/Weill Cornell Medical Center

Background: Alcohol-associated liver disease (ALD) is the most common indication for liver transplantation (LT) and a major cause of morbidity and mortality. Our previous study demonstrated disparities in ALD patients – with Black and female patients being listed less often for LT relative to their risk of dying. We now aim to describe the trends in ALD including LT listings, associated deaths, and the impacts of race/ethnicity and gender. **Methods:** We used the CDC WONDER database to analyze deaths from ALD cirrhosis (including alcohol associated hepatitis) and the UNOS STAR file to identify all patients listed and transplanted for ALD from 1999-2021. Patients aged 25-64 and patients living in the 50 states and Washington, D.C. were included. Our primary outcome, listing to death ratio (LDR), was calculated by the number of patients listed for LT over the number of patients who died. Our secondary outcomes were transplant to listing ratio (TLR), defined as number of patients who underwent LT over the number of patients listed for LT, and transplant to death ratio (TDR), the number of patients who underwent LT over the number of patients who died. Genders were analyzed separately, and minority race/ethnicities were compared to White patients. We compared outcomes using chi-square test and analyzed trends using annual percentage change (APC). **Results:** 244,773 patients died from ALD between 1999-2021, APC 5.3%, p<0.001. Female (APC 6.7%), Hispanic (APC 6.7%), and Asian (APC 7.1%) patients had the highest increases in annual deaths, p<0.001. 63,134 total patients were listed for LT for ALD, increasing from 2,411 in 1999 to 4,833 in 2021 (APC 3.8%, p<0.001). The largest annual increases were in women (APC 6.4%), Asian (APC 10.0%), and Hispanic (APC 4.4%) patients, p<0.001. LDR decreased from 0.36 in 1999 to 0.26 in 2021 (APC -1.6%, p<0.001). The largest decreases in LDR were noted in men (APC -1.7%) and in White (APC -2.1%) and Hispanic (APC -2.0%) patients, p<0.001.34,837 total patients received LT, (APC 6.0%, p<0.001). All races, ethnicities, and genders had higher rates of LTs, with the largest increases in women (APC 9.9%), Asian (13.8%), Hispanic (7.1%) patients, p<0.001. The TLR was 0.55, increasing from 0.44 in 1999 to 0.68 in 2021 (APC 1.4%, p<0.001). TDR for the overall cohort did not change, but TDR did increase in women (APC 1.4%) and Asian patients (4.1%), p<0.001. **Conclusion:** Annual deaths due to ALD have increased drastically. However, there has also been a concurrent and proportionate increase in LT listings and transplantation along with associated significant increases in TLR and decreases in LDR. Notably, LT and LT listing rates in women have improved and we anticipate that the gender disparity will narrow further with MELD 3.0, which was not yet in place during our study period. The TDR did not improve in Black and Hispanic patients. Major interventions are necessary to increase access to LT and save lives in these populations.



Disclosures: Alexander Zhao: Nothing to Disclose, Nicole Ng: Nothing to Disclose, Xiaohan Ying: Nothing to Disclose, Arun Jesudian: Salix Pharmaceuticals: Consultant, Salix Pharmaceuticals: Speaking and Teaching,

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Madrigal Pharmaceuticals: Speaking and Teaching, Novo Nordisk: Consultant, Orphalan: Consultant, Catherine Lucero: Nothing to Disclose, Russell Rosenblatt: Nothing to Disclose

2178 | THE IMPACT OF HOUSING INSECURITY ON HOSPITALIZED PATIENTS WITH DIAGNOSIS OF CIRRHOSIS: A COMPARATIVE ANALYSIS USING DATA FROM THE NATIONAL INPATIENT SAMPLE (2016-2019)

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[1]*Hennepin Healthcare,* [2]*University of Minnesota*

Background: Housing insecurity, including homelessness, is an understudied significant social determinant of health, that can impact hospitalization-related outcomes. Patients with cirrhosis may be particularly vulnerable to the effects of unstable housing due to the plethora of associated complications **Methods:** We conducted a retrospective cohort study using data from the National Inpatient Sample (NIS) for the years 2016 to 2019. Patients with diagnosis of cirrhosis were identified using ICD-10 codes. The cohort was divided into two groups: those with stable housing and homeless patients, as indicated by relevant ICD-10 codes for homelessness. Outcomes measured included length of hospital stay, healthcare costs, and in-hospital mortality. Multivariable regression was used to compare the two groups, adjusting for demographic variables and comorbid conditions. **Results:** A total of 2,951,519 hospitalizations for patients with cirrhosis were identified, of which 68,275 (2.3%) involved homeless individuals. Those experiencing homelessness were younger (mean age 53.5 vs 60.5 years, $p < 0.001$) and more likely to be male (80.8% vs 59.1%, $p < 0.001$). There was an increased proportion of Hispanic patients and a decreased proportion of white patients in the cohort experiencing homelessness (20.9% vs 16.6%, $p < 0.001$ and 61.0% vs 66.5%, $p < 0.001$, respectively), and no statistically significant difference in the proportion of Black patients (10.2% vs 10.4%, $p = 0.576$). Alcohol use (71.3% vs 39.4%, $p < 0.001$) and opioid use disorder (11.9% vs 3.7%, $p<0.001$) were both increased in the homeless cohort as was the presence of a psychiatric comorbidity (40.9% vs 27.1%, $p < 0.001$). Homeless patients with cirrhosis experienced a significantly longer mean hospital stay compared to those with stable housing (7.35 days vs. 6.08 days, $p < 0.001$). The average cost of hospitalization was lower for homeless patients ($15,948 vs. $16,564, $p = 0.031$). Likewise, the in-hospital mortality rate was decreased in those experiencing homelessness (2.6% vs. 5.8%, aOR = 0.52, 95% CI: 0.47-0.58, $p < 0.001$). **Conclusion:** Our results suggest that social situations contribute to a significant barrier to safe discharge in cirrhosis. In addition, in-hospital mortality and hospitalization costs were different among homeless patients, potentially reflecting different health care utilization patterns.

Disclosures: Joseph Akambase: Nothing to Disclose, Yasmin Ali: Nothing to Disclose, Spencer Goble: Nothing to Disclose, Jose Debes: Nothing to Disclose

2179 | THE EFFECT OF SOCIOECONOMIC FACTORS ON OUTCOMES OF VARICEAL HEMORRHAGE

Cerise Kleb[1] *Nehna Abdul Majeed*[1] *Kabir Chhabra*[1] *Abdel-Latif Ismail*[1] *Sindhura Kolachana*[1] *Patrick McCarthy*[1] *Hyun Kim*[2] *Kirti Shetty*[2]

[1]*University of Maryland,* [2]*University of Maryland, Baltimore*

Background: Patients with cirrhosis and acute variceal bleeding (AVB) typically undergo endoscopic band ligation (EBL) followed by long-term EBL, with transjugular intrahepatic portosystemic shunt (TIPS) as an option if EBL fails. Evidence shows that pre-emptive TIPS (pTIPS), placed immediately after an initial bleed, may reduce rebleeding and mortality in high-risk patients. We hypothesized that individuals with socioeconomic barriers to care would be less likely to undergo follow-up EGD, hence experiencing higher rates of rebleeding, and may benefit from pTIPS. **Methods:** A retrospective cohort study included patients (age ≥ 18) with cirrhosis and their first episode of AVB at two safety net hospitals serving a vulnerable urban population over five years (2018-2023). Exclusion criteria included liver transplant or death before discharge. The Social Vulnerability Index (SVI) was used as a marker for socioeconomic risk, with higher scores indicating greater risk. Data included demographics, MELD 3.0 scores, EGD findings, compliance with first follow-up EGD, SVI scores, and rebleeding rates at 90 days. Statistical analysis used the log-rank test or Cox proportional hazards regression to compare SVI categories

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to rebleeding outcomes and follow-up EGD compliance. **Results:** Sixty-six patients met the inclusion criteria, and the two groups were similar in demographics and liver disease severity according to the MELD 3.0 score (22 in the low SVI group and 20 in the high SVI group.) Compared to patients with low SVI (n=25), patients with high SVI (n=41) had an odds ratio (OR) of 3.98 for rebleeding within 90 days, though the difference was not statistically significant (confidence interval 0.8 -19.4). There was no significant difference in compliance rates with the first follow-up EGD between the two groups. **Conclusion:** Outcomes after AVB in cirrhosis are dependent on whether serial EBL results in variceal obliteration. However, compliance with follow up EGD/EBL may be influenced by socioeconomic barriers. In this limited study of a safety net population, we demonstrated higher (though not statistically significantly) rates of rebleeding in the group with a high SVI, a validated measure of socioeconomic and demographic factors that has been found to correlate with barriers to care. We plan to expand data collection over a broader period to achieve a larger sample size and adjust for confounding factors. Our findings will further define the role of pTIPS in patients with AVB who have socioeconomic barriers to serial EBL.

Table 1. Demographics

	Low SVI (n=25)	High SVI (n=41)
Age (years)	51.1 +/- 13.8	56.55 +/- 12
Race		
White	22 (88%)	21 (51%)
Black	2 (8%)	18 (44%)
Hispanic	1 (4%)	2 (5%)
Male	19 (76%)	32 (78%)
Female	6 (24%)	9 (22%)
MELD-3.0	22+/- 9	20+/- 8

Table 2. Outcomes

Rebleeding Within 90 Days			
	Yes, *n* (%)	No, *n* (%)	OR (95% CI)
High SVI (n=41)	10 (24.4%)	31 (75.6%)	3.98 (0.8-19.4)
Low SVI (n=25)	1 (4.0%)	24 (96.0%)	Reference 1.00
Follow Up EGD Post-Discharge			
Low SVI (n=25)	7	18	1.2 (0.39-3.7)
High SVI (n=41)	10	31	Reference 1.00

Disclosures: Cerise Kleb: Nothing to Disclose, Nehna Abdul Majeed: Nothing to Disclose, Kabir Chhabra: Nothing to Disclose, Abdel-Latif Ismail: Nothing to Disclose, Sindhura Kolachana: Nothing to Disclose, Patrick McCarthy: Nothing to Disclose, Hyun Kim: Nothing to Disclose, Kirti Shetty: Nothing to Disclose

2180 | SOCIAL DETERMINANTS OF HEALTH AND METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE IN CHILDREN WITH OVERWEIGHT OR OBESITY

Ananya Venkatesh[1] Nhat Thai[1] Patricia Ugalde Nicalo[1] Kimberly Newton[1] Cindy Behling[2] Romeo Ignacio[1] Laura Bauman[1] Martha Smith[1] Jeffrey Schwimmer[1]

[1]University of California, San Diego, [2]Pacific Rim Pathology

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most common pediatric liver disease. Known risk factors for MASLD do not fully account for the variability in disease development. For instance, while obesity is a major risk factor, most children with obesity do not develop MASLD. Therefore, it is crucial to consider other factors, such as social determinants of health (SDH), including income, education, housing, and environment. Data on the relationship between SDH and MASLD are limited. This study aimed to

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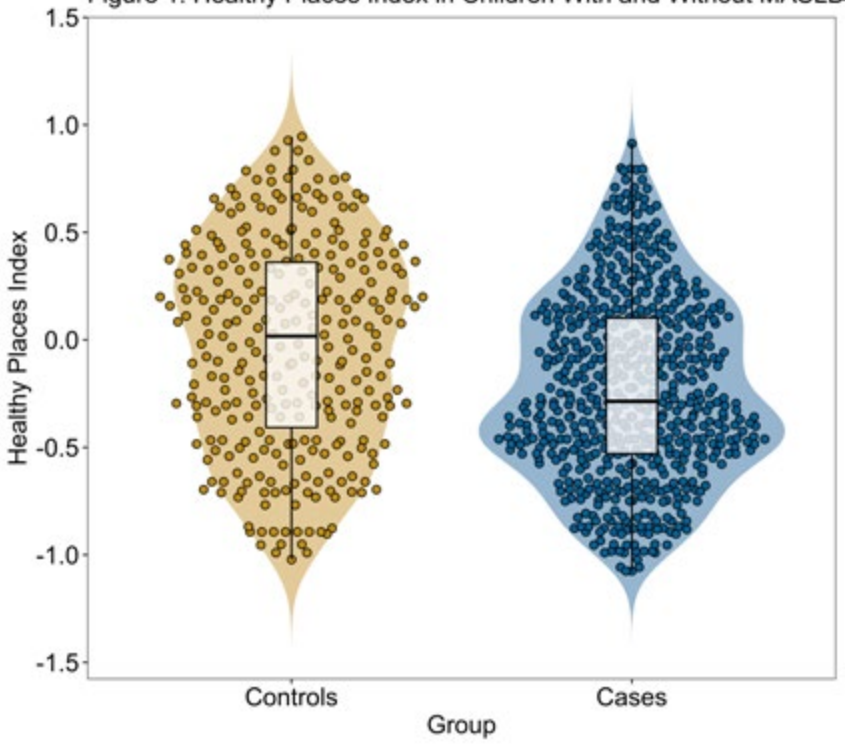
evaluate the association of SDH parameters with MASLD in children with overweight or obesity. **Methods:** This cross-sectional study included children with overweight or obesity evaluated in pediatric gastroenterology clinics at a free-standing children's hospital, stratified by the presence of MASLD. MASLD diagnosis was confirmed via liver histology, while children without MASLD had liver imaging negative for steatosis. Census tracts from participants' addresses were linked to the California Healthy Places Index, a validated composite index of 23 individual SDH variables, with higher values indicating greater socioeconomic advantage. Generalized linear regression was performed, controlling for age, sex, race, ethnicity, and body mass index (BMI). **Results:** The study included 888 children with overweight or obesity, with a mean age of 12.8 ± 2.9 years and a mean BMI of 30.6 ± 6.4 kg/m^2. Children with MASLD (n=593) had higher BMI z-scores than those without MASLD (n=295) (1.89 vs. 2.19, P<0.001). The Healthy Places Index was significantly lower for children with MASLD compared to those without MASLD (-0.222 vs. -0.027, P=0.007; Figure 1). Specifically, children with MASLD lived in areas with significantly lower access to parks, beaches, or open spaces (83.3% vs. 87.9%, P=0.003), lower land tree canopy cover (3.4% vs. 3.9%, P=0.022), higher air ozone levels (0.046 parts per million (ppm) vs. 0.045 ppm, P=0.012), and less uncrowded housing (87.5% vs. 90.4%, P=0.040) compared to children without MASLD. **Conclusion:** Among children with overweight or obesity, those with MASLD resided in areas with fewer social advantages compared to those without MASLD. These findings may identify specific SDH targets for individual and population level interventions to improve the health of children at risk for MASLD.

Figure 1. Healthy Places Index in Children With and Without MASLD



Disclosures: Ananya Venkatesh: Nothing to Disclose, Nhat Thai: Nothing to Disclose, Patricia Ugalde Nicalo: Nothing to Disclose, Kimberly Newton: Nothing to Disclose, Cindy Behling: Pacific Rim Pathology Lab: Employee, Novo Nordisk: Consultant, Pathology Institute: Consultant, boehringer ingleheim: Consultant, akero: Independent Contractor, Romeo Ignacio: Nothing to Disclose, Laura Bauman: Pfizer: Consultant, Gilead: Independent Contractor, Syneos: Independent Contractor, Martha Smith: Nothing to Disclose, Jeffrey Schwimmer: Intercept: Grant to institution, Seraphina: Grant/Research Support, Intercept: Grant/Research Support, Merck: Consultant

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2181 | NAVIGATING BEHAVIORAL CHANGE: THE LIVED EXPERIENCE OF MEXICAN AND CENTRAL AMERICAN PATIENTS WITH MASLD

Maya Balakrishnan[1] Fasiha Kanwal[2] Myriam Ibarra[2] Yarian Garcia[2] Crystal Arguelles[2] Alexis Moreleon[2] Jennifer Arney Cuevas[3]

[1]Ben Taub General Hospital, [2]Baylor College of Medicine, [3]University of Houston-Clear Lake

Background: Weight loss is an essential part of treating metabolic dysfunction associated steatotic liver disease (MASLD). Yet, the data show that most patients with MASLD do not lose sufficient weight for treatment of their liver disease. This is often because of struggles with making sustained behavioral changes. To understand patients' lived experiences with behavioral change, we undertook this qualitative study among Mexican and Central American (M/CA) patients with MASLD. We focused on M/CAs because this subgroup has the highest MASLD prevalence across the United States. **Methods:** We conducted in-depth interviews with nine adult M/CA patients with MASLD engaged in at least six months of Hepatology care and who had not lost significant weight since establishing specialty care. We used interpretive phenomenological analysis to understand their experience of the behavioral change process. **Results:** Patients felt defeat, dismissive, and fear in reaction to hearing medical advice to lose weight. Patients' behavioral change experiences entailed three main dimensions: loneliness, struggling with motivation, and resignation. Patients wanted more help in the form of personalized support and motivational measures but had mixed feelings about the use of weight loss medications and surgery. **Conclusion:** Patients feel alone and unsupported through their journey of weight management. This leaves them feeling resigned. Surprisingly, despite these disappointments, some patients continued to prefer behavioral change to weight loss medications. They had a strong desire to achieve healthy eating and exercise habits but wanted help to do so. These findings demonstrate that effective, personalized behavioral interventions are urgently needed to address both the public health impact of MASLD as well as to address patient treatment preferences.

Disclosures: Maya Balakrishnan: Madrigal Therapeutics: Independent Contractor, Intercept Pharmaceuticals: Independent Contractor, Viking Therapeutics: Stock – privately held company, Novo Nordisk: Grant/Research Support, Fasiha Kanwal: Nothing to Disclose, Myriam Ibarra: Nothing to Disclose, Yarian Garcia: Nothing to Disclose, Crystal Arguelles: Nothing to Disclose, Alexis Moreleon: Nothing to Disclose, Jennifer Arney Cuevas: Nothing to Disclose

2182 | HIGH PREVALENCE AND LOW AWARENESS OF MARKERS OF CHRONIC LIVER DISEASE AMONG MEN WHO HAVE SEX WITH MEN IN LOS ANGELES

Grace Yi[1] Marjan Javanbakht[2] Pamina Gorbach[2] Phillip Chen[3] Steven Shoptaw[4] Arpan Patel[5]

[1]David Geffen School of Medicine, [2]Fielding School of Public Health, Department of Epidemiology, UCLA, [3]Department of Medicine, UCLA, [4]Department of Family Medicine, UCLA, [5]University of California, Los Angeles

Background: Men who have sex with men (MSM) are disproportionately affected by viral hepatitis, alcohol use disorder, and metabolic syndrome, compared to their heterosexual peers. Such factors increase risk for chronic liver disease (CLD); however, prevalence of CLD and risk factors, along with knowledge of having liver disease, have not been well-described in this population. **Methods:** Self-reported survey data on substance use and medical history, as well as objective clinical measures, were collected every 6 months from MSM enrolled in a cohort study based in Los Angeles, CA between August 2014 to November 2023. Participants with AST ≥ 35 or ALT ≥ 45 across ≥ 2 study visits were defined as having "markers of CLD." Alcohol use disorder was assessed using the AUDIT-C screen. Metabolic syndrome was defined by presence of at least 2 of the 4 conditions: hypertension, hyperlipidemia, diabetes, and obesity. Qualitative comments on self-reported prior or current history of liver disease were reviewed and analyzed by a board-certified hepatologist. **Results:** We identified 542 MSM who attended at least two study visits. Most identified as Black (*n*=341/542, 63.0%) and Hispanic (*n*=271/542, 50%). Mean age reported was 31.7 (SD: 6.9) years. Over half (*n*=285/542, 52.6%) of the sample lived with HIV and reported substance (*n*=461/542, 85%) use in the 6 months prior to their study visit. Very few reported prior (*n*=21/542, 3.9%) or current (n=22/542, 4.1%) liver disease, of which HCV and HBV were most commonly reported. Nearly two-thirds of the sample (*n*=353/542, 65.1%) had markers of CLD. Of these, 9.5**%** had AUDIT-C scores consistent with alcohol use disorder, 13.9% had metabolic syndrome, and 4.8% reported active

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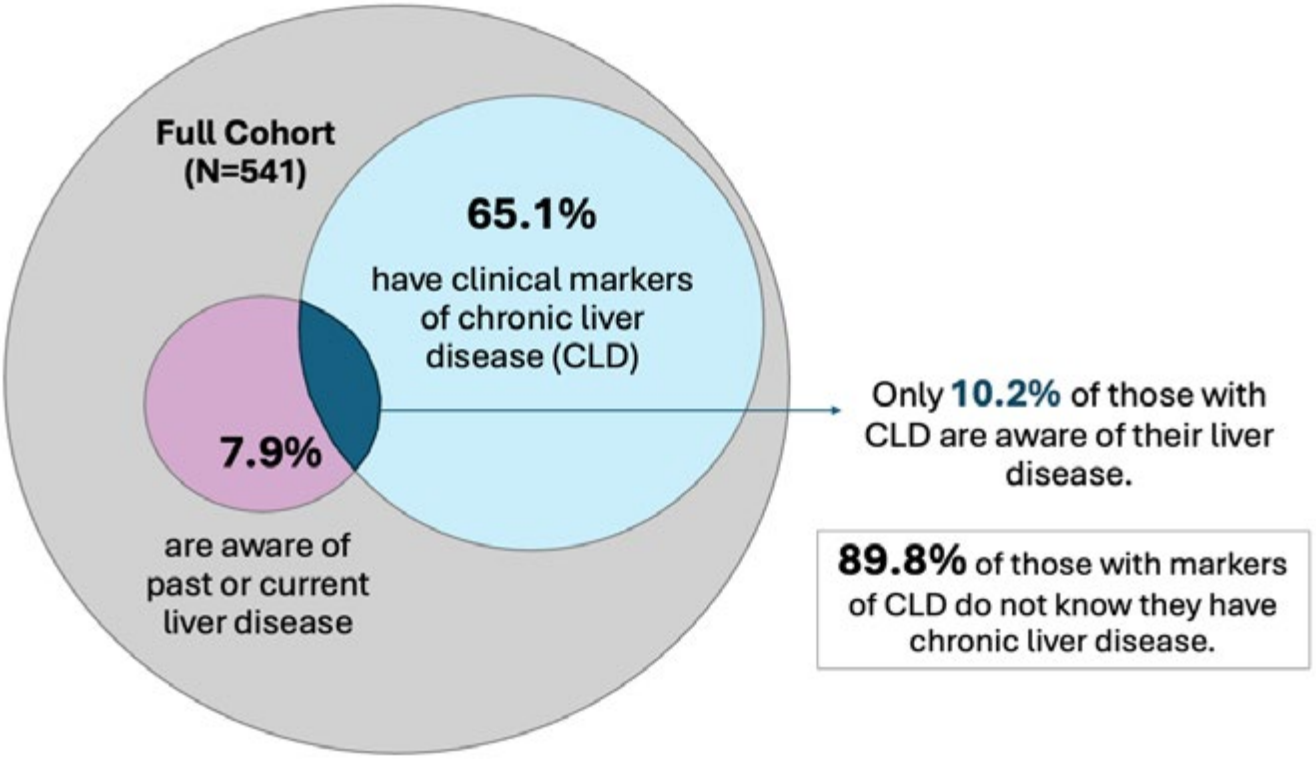
viral hepatitis (but not all were tested). Most individuals with markers of CLD had no definitive etiology identified (*n*=186/353, 65.1%) and reported no history of liver disease (n=317/353, 89.8%) (Figure 1)**. Conclusion:** Nearly two-thirds of our multi-ethnic cohort of MSM had markers of CLD; however, nearly nine in ten of those affected reported no personal history of liver disease. Metabolic syndrome and alcohol use disorder risk were the most common factors identified among those with markers of CLD. The majority had no definitive etiology identified, though most were not screened for viral hepatitis. Efforts to screen this population for liver disease and offer linkage to care and education for those affected are critically needed.



Disclosures: Grace Yi: Nothing to Disclose, Marjan Javanbakht: Nothing to Disclose, Pamina Gorbach: Nothing to Disclose, Phillip Chen: Nothing to Disclose, Steven Shoptaw: Nothing to Disclose, Arpan Patel: Nothing to Disclose

2183 | COMMUNITY RESILIENCE ESTIMATES (CRE) CAN PREDICT PATIENT OUTCOMES RELATED TO END-STAGE LIVER DISEASE AND LIVER TRANSPLANTATION IN THE UNITED STATE

Kenji Okumura[1] *Abhay Dhand*[1] *Ryosuke Misawa*[1] *Hiroshi Sogawa*[1] *Costica Aloman*[1] *Gregory Veillette*[1] *David Wolf*[1] *Seigo Nishida*[1]

[1]*Westchester Medical Center*

Background: Various disparities may influence outcomes related to end-stage liver disease (ESLD) and liver transplantation (LT). Community Resilience Estimates (CRE) includes various components of individual and household characteristics of social vulnerability and is a predictive tool assessing the ability of a community to withstand a disaster like pandemic or hurricane. The aim of this study was to assess the association of CRE with liver transplant related waitlist mortality, transplant probability, and post-transplant patient and graft survival. **Methods:** The 2022 state-wide CRE with % population with ≥ 3 risk factors were divided into tertiles of low, medium and high. Using the United Network for Organ Sharing database, outcomes of 182,371 adult LT candidates between Jan 2004 and Dec 2022 were analyzed. Multivariable cause-specific hazard ratios (HR)s with additional risk factors like model for end-stage liver disease (MELD), race, medical comorbidities were used to assess the association between CRE and LT outcomes. **Results:** State-level CRE distributions are shown in

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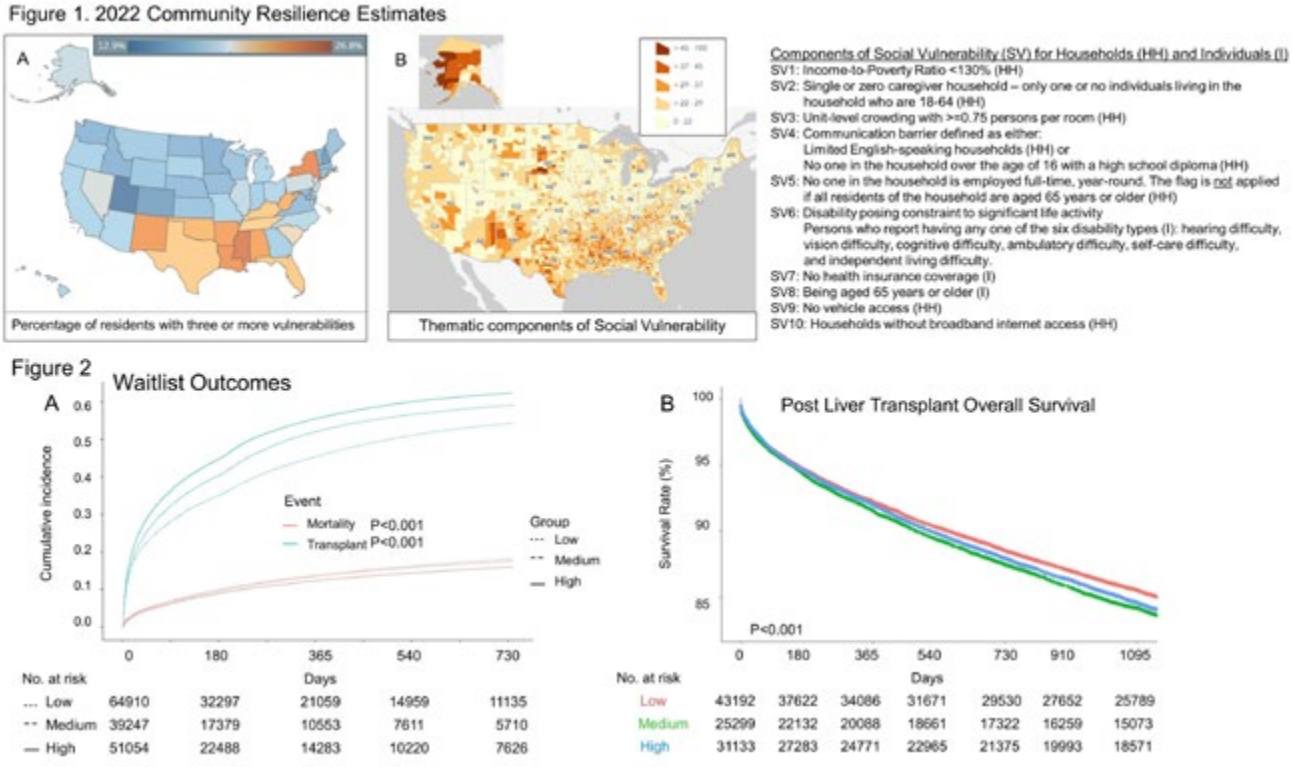
Figure 1. Among waitlist outcomes, transplant candidates among populations in medium/high CRE tertiles were associated with higher waitlist mortality (Medium HR 1.07, 95% CI 1.04-1.10, P<0.001; High HR 1.06, 95% CI 1.03-1.08, P<0.001) and increased transplant probability (Medium HR 1.20, 95% CI 1.18-1.22, P<0.001; High HR 1.21, 95% CI 1.19-1.23, P<0.001) (Figure 2A), when compared to the low tertile. Among 100,854 LT recipients, median MELD score at time of transplant was Low:22, Medium/High:21 (P<0.001). The percentage of MELD exception was Low:28%, Medium:27%, High:26% (P <0.001). Median waitlist time for LT recipients was Low:80 days, Medium:63 days, High:57 days (P <0.001). Dialysis at time of transplant in LT recipients as Low:13%, Medium:8.4%, High:9% (P <0.001). On multivariable survival analysis, patient and graft survivals were inferior in medium tertile (patient survival HR 1.09, 95% CI-1.06-1.12; graft survival HR 1.08, 95% CI 1.05-1.11) and high tertile (patient survival HR 1.08, 95% CI-1.05-1.11; graft survival HR 1.07, 95% CI 1.04-1.10) (Figure 2B). **Conclusion:** High CRE among populations with ≥ 3 risk factors were associated with higher waitlist mortality, increased transplant probability and lower post-transplant patient/liver graft survival. Patients with ESLD and LT remain vulnerable to adverse outcomes. CRE can be used to identify areas for resource allocation and targeted interventions to mitigate such risk.



Disclosures: Kenji Okumura: Nothing to Disclose, Abhay Dhand: Merck: Consultant, Ryosuke Misawa: Nothing to Disclose, Hiroshi Sogawa: Nothing to Disclose, Costica Aloman: Nothing to Disclose, Gregory Veillette: Nothing to Disclose, David Wolf: Abbvie: Speaking and Teaching, Gilead: Speaking and Teaching, Intercept: Speaking and Teaching, Madrigal: Speaking and Teaching, Mallinckrodt: Speaking and Teaching, Seigo Nishida: Nothing to Disclose

2184 | AN EXPLORATION OF SOCIO-ECONOMIC AND MEDICAL FACTORS INFLUENCING THE LOW CERVICAL CANCER SCREENING UPTAKE AMONG LIVER TRANSPLANT RECIPIENTS - A HIGH VOLUME SINGLE-CENTER RETROSPECTIVE COHORT STUDY

Jacquelin Blomker[1] Pavithra Ramakrishnan[1] Katherine Cooke[1] Virginia Hsiao[2] Jessica Makori[2] Claire Collins[2] Mary McConville[2] Jena Benson[2] Katie McLaughlin[2] Rachel Vogel[1] Taylor Bowler[1] Deanna Teoh[1] Elizabeth Aby[1]

[1]University of Minnesota, [2]University of Minnesota Medical School

Background: Liver transplant (LT) recipients are at 2 times higher risk of de novo cancer compared to the general population, necessitating appropriate pre-LT and post-LT screening. Currently, the guidelines for optimal pre-LT cervical cancer screening are inconsistent. Additionally, racial, ethnic, and neighborhood socioeconomic status

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(nSES) disparities are known to impact both access to LT and cervical cancer screening, but little is known about factors contributing to adherence to pre-LT screening recommendations. Our goal was to identify socioeconomic, racial and health care-associated risk factors associated with adherence to pre-LT cervical cancer screening. **Methods:** Female patients aged 18-75 with intact cervix who underwent LT between 2015-2021 at the University of Minnesota were included. Demographic, socioeconomic, clinical and pre transplant cervical cancer screening information was collected. The median area of deprivation index (ADI) was used to stratify individuals into low nSES (ADI < 50th percentile) and high nSES (ADI > 50th percentile). Descriptive statistics, Wilcox rank-sum test and Fisher's exact test were performed for analysis. **Results:** A total of 136 LT recipients were identified. The majority were White (75%) followed by Black (10%). 99 participants (73%) completed pre-LT cervical cancer screening within 5 years prior to LT with a median age of 57 (IQR 19). The most common etiologies of liver disease were alcohol (42.2%) and metabolic associated steatotic liver disease (23.2%). There was no significant difference in clinical characteristics including race, ethnicity, smoking or alcohol status, between those who did and did not receive pre-LT cervical cancer screening. When stratifying by ADI, we did not find significant differences in screening between low and high nSES. **Conclusion:** Despite the recommendations for pre-LT cervical cancer screening, 27% of patients did not complete screening. When using the ADI, no sociodemographic factors were found to be associated with the lack of pre-LT cervical cancer screening. Further research is needed to identify systemic and healthcare-related barriers to obtaining equitable access to preventive health services in the pre-LT phase.

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	Screened	Unscreened		Unscreened nSES: Low nSES (ADI < 50th percentile)	Unscreened nSES: High nSES (ADI > 50th precentile)	
	N=99	N=37		N=19	N=18	
	Median (IQR)	Median (IQR)	p-Value	Median (IQR)	Median (IQR)	p-Value
Age at transplant, years	57 (19)	54 (30.9)				
MELD score at LT evaulation	23 (12)	24 (17.5)	0.32	19.5 (14)	27 (14)	0.18
ADI	40 (30)	48 (32)				
	N (%)	N (%)		N (%)	N (%)	
Race			0.60			0.15
American Indian/Alaska Native	2 (2.0)	3 (8.1)		0 (0)	3 (16.7)	
Asian	5 (5.1)	2 (5.4)		1 (5.3)	1 (5.6)	
Black/ African/ African American	10 (10.1)	4 (10.8)		1 (5.3)	3 (16.7)	
Native Hawaiian/Pacific Islander	2 (2.0)	0 (0)		0 (0)	0 (0)	
White	76 (76.7)	26 (70.3)		16 (84.2)	10 (55.6)	
Other/Missing	4 (1.0)	2 (5.4)		1 (5.3)	1 (5.6)	
Ethnicity			0.52			0.71
Hispanic/Latina/o	2 (2.0)	0 (0)		0 (0)	0 (0)	
Non-Hispanic/Latina/o	78 (78.8)	27 (73.0)		13 (68.4)	14 (77.8)	
Missing/Unknown	19 (19.2)	10 (27.0)		6 (31.6)	4 (22.2)	
Insurance status						
Private Insurance	14 (37.8)	49 (49.5)	0.049			
Public Insurance	15 (40.5)	35 (35.4)				
Private & Public Insurance	5 (13.5)	15 (15.2)				
Missing	3 (8.1)	0 (0)				
Smoking status			0.23			
Current smoker	13 (13.1)	5 (13.5)				
Former smoker	42 (42.2)	10 (27.0)				
Never smoker	44 (44.4)	22 (59.5)				
Alcohol status			0.35			
No	51 (51.5)	24 (64.9)				
Yes	45 (45.5)	13 (35.1)				
Unknown	3 (3.0)	0 (0.0)				
Etiology of liver disease*						
MASLD	23 (23.2)	1 (2.7)		1 (5.3)	0 (0.0)	
Alcohol	42 (42.4)	11 (29.7)		6 (31.6)	5 (27.8)	
Hepatitis B	6 (6.1)	2 (5.4)		1 (5.3)	1 (5.6)	
Hepatitis C	10 (10.1)	5 (13.5		1 (5.3)	4 (22.2)	
Autoimmune hepatitis	6 (6.1)	3 (8.1)		1 (5.3)	2 (11.1)	
PSC	8 (8.1)	2 (5.4)		2 (10.5)	0 (0.0)	
PBC	5 (5.1)	4 (10.8)		2 (10.5)	2 (11.1)	
Other	14 (14.1)	12 (32.4)		8 (42.1)	4 (22.2)	

Table 1. Demographics and clinical characteristic stratified by cervical cancer screening and neighborhood socioeconomic status

* Not mutually exclusive

Abbrevations: Area of deprevation index (ADI), neighborhood socio-economic status (nSES), liver transplant (LT); metabolic associated steatotic liver disease (MASLD); primary sclerosing cholangitis (PSC); primary biliary cholangitis (PBC)

Disclosures: Jacquelin Blomker: Nothing to Disclose, Pavithra Ramakrishnan: Nothing to Disclose, Katherine Cooke: Nothing to Disclose, Virginia Hsiao: Nothing to Disclose, Jessica Makori: Nothing to Disclose, Claire Collins: Nothing to Disclose, Mary McConville: Nothing to Disclose, Jena Benson: Nothing to Disclose, Katie McLaughlin: Nothing to Disclose, Rachel Vogel: Nothing to Disclose, Taylor Bowler: Nothing to Disclose, Deanna Teoh: Tesaro/GSK: Grant/Research Support, Moderna: Grant/Research Support, Jounce Therapeutics: Grant/Research Support, Asieris: Advisor, Elizabeth Aby: United Health Care Group: Stock - publicly traded company, Medtronic: Stock - publicly traded company

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2185 | THE BURDEN OF STEATOTIC LIVER DISEASE IN CROATIAN VETERANS THREE DECADES AFTER THE WAR

Tatjana Reic[1] Ana Visic[1] Magda Pletikosa Pavic[2] Diana Nonkovic[3] Ivona Reic[1] Anna Mrzljak[4]

[1]Croatian Society for Liver Diseases Hepatos, [2]Teaching Institute for the Public Health Split - Dalmatia County, [3]Teaching Institute for Public Health Split - Dalmatia County, [4]University Hospital Center Zagreb

Background: Croatia is currently the only EU country with a large war veteran population (11%), making it the precursor to future EU challenges. Unhealthy diet, tobacco, alcohol and low physical activity endanger the health of veterans, making their problems even greater than in the general population. National screening programs show that 20.4% of Croatian veterans have excessive body weight, while 10.2% have abnormal liver tests. Considering obesity along with other behavioural factors as risks for the development of advanced liver disease, there is a need to improve early detection and diagnosis of liver disease in the veteran population. We aimed to evaluate the burden of steatotic liver disease (SLD) among Croatian veterans. **Methods:** As the only organization in the Western Balkans with a FibroScan® device as part of their Mobile InfoHep Clinic (MIHC), the NGO Hepatos partnered with the Croatian Gastroenterology Society and Public Health Institute Split-Dalmatia County to provide linkage-to-care services to veteran organizations nationwide. FibroScan® assessed veterans with liver stiffness measurement (LMS) cut-offs: mild up to 7kPa (F0-1), significant >7-9.5 kPa (F2), severe >9.5-12.5 kPa (3), cirrhosis > 12.5 kPa (4), and steatosis grade by controlled attenuation parameter (CAP) score: (S1) 238-260 dB/m, (S2) 261-290 dB/m, (S3) >290 dB/m. **Results:** In the period 2016-2023, 2,650 services were provided to 552 veterans (average age 59±7 yrs; 75% male) at 13 sites in 5 different counties (3 costal (72.6% of veterans) and 2 continental (27.4%)). On-spot FibroScan® exam represented 21% of services. 31.1% of veterans self-reported liver disease, mainly SLD 71.7%, followed by alcohol-related 15.7%, cholestatic 6%, HBV 3%, HCV 3% and liver transplant 0.6%. The median LMS was 5.8 kPa (range 2.5-75). The distribution of fibrosis stages (F1-F4) was 72.5%, 14.9%, 7.8% and 4.9%, respectively. The median CAP was 289 dB/m (range 110-400), and only 18% of veterans had no evidence of steatosis, whereas the majority (68%) had advanced steatosis (F3 49.5% and F2 18.5%). The fibrosis and steatosis grades did not differ between coastal and continental veterans, p = 0.94. **Conclusion:** Every second veteran in the country has advanced liver steatosis, and almost 13% have advanced fibrosis. Their liver-related events (cirrhosis, decompensation and hepatocellular carcinoma) are expected to rise shortly, and public health interventions are needed for better prevention and management of SLD. As Europe faces an increased number of war veterans, better patient health literacy, specific education of healthcare professionals, and awareness campaigns are necessary to mitigate the disease burden in the veteran population in order to ensure a healthier and more resilient society.

Disclosures: Tatjana Reic: Nothing to Disclose, Ana Visic: Nothing to Disclose, Magda Pletikosa Pavic: Nothing to Disclose, Diana Nonkovic: Nothing to Disclose, Ivona Reic: Nothing to Disclose, Anna Mrzljak: Nothing to Disclose

2186 | CHARACTERISTICS OF PATIENTS WITH PRIMARY BILIARY CHOLANGITIS THAT RECEIVED TRANSIENT ELASTOGRAPHY AT A TERTIARY LIVER TRANSPLANT CENTER IN NORTHERN CALIFORNIA ◆

Vishwajit Kode[1] Sylvia Sudat[2] Yinwen Wang[3] Kidist Yimam[4]

[1]California Pacific Medical Center Department of Internal Medicine, [2]California Pacific Medical Center, Center for Health Systems Research, [3]California Pacific Medical Center Research Institute, [4]California Pacific Medical Center Department of Hepatology and Liver Transplant

Background: Primary Biliary Cholangitis (PBC) is a rare, chronic cholestatic disease of the small intrahepatic bile ducts of autoimmune etiology. It leads to inflammation resulting in fibrosis and cirrhosis overtime leading to liver failure with increased risk of mortality. This disease is predominantly found in women in a 9:1 ratio compared to men. In addition, previous demographic studies found PBC to be more prevalent in Caucasian women, however these studies did not include a diverse patient population. Here we present the demographics of PBC patients seen at our liver transplant center in Northern California with access to transient elastography (TE) to assess liver stiffness as a prognostic tool at the time of their diagnosis or during follow up in our clinic. **Methods:** A retrospective analysis was done of a total of 450 patients that were seen at our tertiary care transplant center with

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PBC from January 1st 2004 to December 31st 2023 at different stages of their disease. Post-transplant patients, patients that did not have any TE and patients who had PBC with auto immune hepatitis (AIH) overlap were excluded from our study. A statistical analysis was then done to compare various demographic data, average TE values, fibrosis stage at diagnosis and hepatic clinical outcomes. **Results:** Of our 450-patient cohort with PBC at varying disease, 230 had one or more TE completed. Of these 230 patients, 54 had overlap with AIH and were excluded. Another 15 patients were excluded due to no kPa reported from their TE resulting in a final sample size of 161 patients. Patients had a mean age of 62 years, 93.8% were female and 6.2% were male. 16.9 % were Hispanic or Latino. 74 % White and 15.5 % Asian. We had only 1 Black patient with a TE, excluded due to AIH overlap. Mean baseline liver stiffness was 7.4 kPa in patients with F1-3 disease and 31.6 kPa for patients with F4 disease. Over the follow up period of 9 years (2015-2024), 25 patients had hepatic complications. In Hispanic or Latino patients compared to Non-Hispanic or Latino patients did have more events of hepatic encephalopathy (p-value of 0.02), more esophageal varices (p-value of 0.05) and more events of liver transplant listing (p-value of 0.05). (Table 1) In examining racial differences between White and Asian patients, we found no composite or subgroup differences that were statistically significant. **Conclusion:** The demographics of our PBC patients are diverse. In our analysis we find that Hispanic or Latino patients did have a statistically significant increase in events of esophageal varices, hepatic encephalopathy and liver transplantation listing compared to Non-Hispanic or Latino patients but did not have a statistically significant difference in total events of hepatic complications. We also find no difference in White and Asian populations for events of hepatic complications. We will perform future studies to understand the impact of race and ethnicity on PBC outcomes and access to specialized PBC care.

Variable Name	Hispanic or Latino	Not Hispanic or Latino	p-value[1]
Patient Count[2]	27	128	--
Outcomes – ever occurred, N (%)			
EV	5 (18.5)	8 (6.3)	0.05
EV Bleeding	2 (7.4)	1 (0.8)	0.08
Ascites	5 (18.5)	17 (13.3)	0.54
HE	4 (14.8)	3 (2.3)	0.02
LT Listing	4 (14.8)	5 (3.9)	0.05
Death	1 (3.7)	3 (2.3)	0.54
Any decompensation event, N (%)			
EV, EV Bleeding, Ascites, HE, LT, LT Listing, Death	6 (22.2)	27 (21.1)	>0.99

[1]From Fisher's exact test; [2]6 patients with unknown ethnicity excluded. N=155.

Table 1: Hepatic Complications in Hispanic and Non-Hispanic Patients.

Disclosures: Vishwajit Kode: Nothing to Disclose, Sylvia Sudat: Science Corporation: Spouse is employed by this company and has stock options, Yinwen Wang: Nothing to Disclose, Kidist Yimam: Nothing to Disclose

2187 | BRIDGING GAPS IN VIBRATION CONTROLLED TRANSIENT ELASTOGRAPHY (VCTE) USAGE FOR METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE/STEATOHEPATITIS (MASLD/MASH) PATIENTS: INSIGHTS ON SOCIODEMOGRAPHIC INFLUENCES AND CARE CONNECTIONS

Taranika Sarkar Das[1] Jahnavi Udaikumar[1] Kimberly Ho[1] Carolyn Wilson[1] Inna De Leon[1] Kripali Gautam[1] Xucong Meng[1] Jennifer Stromberg[1] Raiya Sarwar[1] Saikiran Kilaru[1] Bilal Hameed[2] Aasma Shaukat[1]

[1]NYU Langone Health, [2]UCSF

Background: We have limited data on VCTE usage and its sociodemographic correlates. Our retrospective cohort study examined MASLD and MASH screening disparities at NYU Langone Health and a Brooklyn Federally Qualified Health Center (FQHC), focusing on sociodemographic influences on VCTE completion, liver health outcomes, and hepatology referrals. **Methods:** Referrals for VCTE placed since 2020 were collected from Epic via Data Core. Socioeconomic Deprivation Index (SDI) was calculated using data derived from the Robert Graham Center. Chart reviews assessed VCTE and referrals to bariatric, gastroenterology (GI), and hepatology services. Chi-square and t-tests were used to analyze variables, and unadjusted logistic regression for significant findings. **Results:** We identified 685,453 patients with risk factors for MASLD and MASH, such as diabetes and

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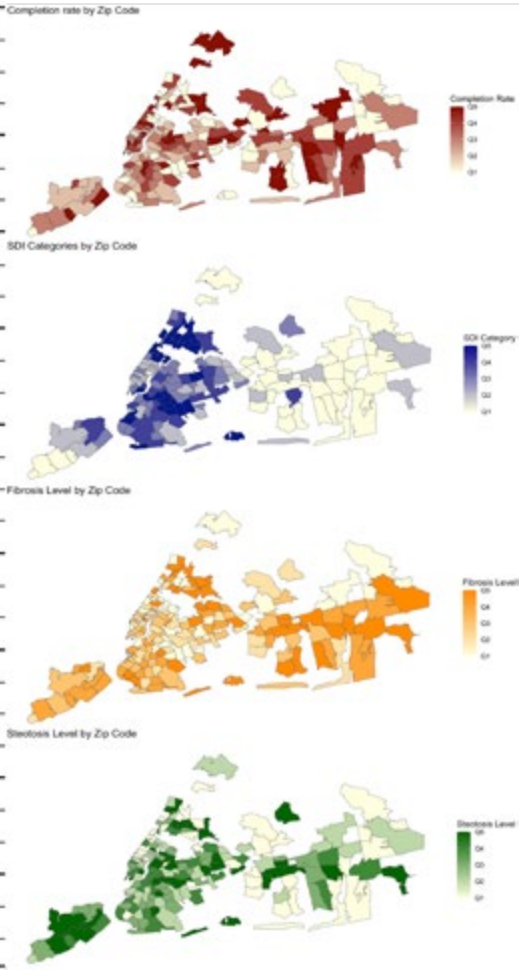
metabolic syndrome, excluding alcohol use, viral hepatitis, and other chronic liver diseases. 32% had FIB-4 scores ≥1.3 (219,223), and 4.9% (33,944) had a score >2.67. Only 2% (6,000) with FIB-4 ≥1.3 were referred for VCTE. 22% (7,629) with FIB-4 scores >2.67 were referred to GI or hepatology. Of those referred for VCTE, 75% from FQHC and 85% from non-FQHC completed the exam. Correct coding rates post VCTE for MASLD and MASH criteria were 83% and 19%, respectively. Table 1 shows lower VCTE completion odds for patients who are Black or Hispanic, diabetics, part-time workers, interpreter service users, Medicaid recipients, high SDI area residents, and FQHC patients. Hispanic ethnicity had the greatest impact on compliance differences between FQHC and non-FQHC. Among patients, 900 (15%) had significant fibrosis (≥F2) and 1,801 (30%) had severe steatosis (S3) on VCTE. Unemployment, retirement, and Medicare coverage increased ≥F2 risk. Higher SDIs were linked to increased severe steatosis (S3) odds, with patients who are non-Hispanic and Black having lower risk. ≥F2 was linked to three individual socioeconomic indicators but not area-level SDI. Figure 1 depicts correlations among S3, SDI, and low VCTE compliance. 45% (405 patients) with ≥F2 were referred to hepatology with 96% compliance. SDI didn't affect referral patterns; Hispanics had higher referral odds. **Conclusion:** Low referral rates for advanced diagnostics in high FIB-4 score patients reveal a significant gap in MASLD and MASH management. Despite high-risk scores, many patients lack appropriate follow-up care, highlighting the need for improved referral practices and coding accuracy to enhance outcomes. We observe a clear discordance between disease burden and patient compliance among socioeconomically disadvantaged groups. Improving point-of-care access, streamlining appointments, expanding Medicaid, offering affordable alternatives, enhancing patient navigation, and increasing community outreach could help alleviate these disparities.

Table 1. Association of VCTE Completion Rate And Patients' Demographics Or Socioeconomic Factors, Using Unadjusted Logistic Regression Analysis

	Complete	Not Complete	P-value	OR (95% CI)
Race				
White	2579 (85.14)	450 (14.86)		
Black or African American	380 (80.51)	92 (19.49)	**0.0099**	0.72 (0.56 - 0.93)
Ethnicity				
Hispanic	643 (80.38)	157 (19.62)		
Non-Hispanic	3368 (84.45)	620 (15.55)	**0.0040**	1.33 (1.09 - 1.61)
Diabetes				
Had diabetes	982 (79.64)	251 (20.36)		
No diabetes	4050 (84.96)	717 (15.04)	**< 0.0001**	1.44 (1.23 - 1.69)
Employment				
Full Time	1870 (84.54)	342 (15.46)		
Part Time	201 (78.52)	55 (21.48)	**0.0135**	0.67 (0.49 - 0.93)
Insurance				
Commercial	3889 (83.65)	760 (16.35)		
Medicaid	80 (70.18)	34 (29.82)	**0.0020**	0.46 (0.31 - 0.70)
Medicare	894 (86.13)	144 (13.87)	**0.0489**	1.21 (1.00 - 1.48)
Interpreter				
No Interpreter	4767 (84.24)	892 (15.76)		
Used interpreter service	265 (77.71)	76 (22.29)	**0.0016**	0.652 (0.503 - 0.855)
Provider specialty				
GI	2150 (83.40)	428 (16.60)		
Hepatology	701 (79.84)	177 (20.16)	**0.0168**	0.79 (0.65 - 0.96)
Medicine	594 (69.96)	255 (30.04)	**< 0.0001**	0.46 (0.39 - 0.56)
SDI				
Low SDI	2544 (85.03)	448 (14.97)		
High SDI	2488 (82.71)	520 (17.29)	**0.0149**	0.84 (0.73 - 0.97)
FHC				
No	4657 (84.61)	847 (15.39)		
Yes	375 (75.6)	121 (24.4)	**<0.0001**	0.56 (0.46 - 0.70)

Figure 1. VCTE Completion Rate, Socioeconomic Deprivation Level, Fibrosis And Steatosis Severity in NY States Areas



Disclosures: Taranika Sarkar Das: Nothing to Disclose, Jahnavi Udaikumar: Nothing to Disclose, Kimberly Ho: Nothing to Disclose, Carolyn Wilson: Nothing to Disclose, Inna De Leon: Nothing to Disclose, Kripali Gautam: Nothing to Disclose, Xucong Meng: Nothing to Disclose, Jennifer Stromberg: Nothing to Disclose, Raiya Sarwar:

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Nothing to Disclose, Saikiran Kilaru: Nothing to Disclose, Bilal Hameed: Consultant relationship with Gilead; Has not ended; Grant/Research Support relationship with Novo Nordisk; Has not ended; Stock â€“ privately held company relationship with Pleiogenix; Has not ended; Consultant relationship with Surrozen; Has not ended; Consultant relationship with Pioneering Medicine VII Inc; Has not ended; Grant/Research Support relationship with Gilead; Has not ended; Grant/Research Support relationship with Intercept; Has not ended; Grant/Research Support relationship with Pliant; Has not ended; Advisor relationship with Madrigal; Has not ended; Speaking and Teaching relationship with Scholars In Medicine; Has not ended; Advisor relationship with CLDF; Has not ended; Advisor relationship with Pleiogenix; Has not ended; Grant/Research Support relationship with Madrigal; Has not ended; Grant/Research Support relationship with Salix; Has not ended; Advisor relationship with Mallinckrodt; Has not ended, Aasma Shaukat: Nothing to Disclose

2188 | PSYCHOLOGICAL BURDENS, SYSTEM DISTRUST, AND FINANCIAL CONSTRAINTS AMONG THE BARRIERS FACING MARGINALIZED GROUPS REFERRED FOR LIVER TRANSPLANTATION FOR HEPATOCELLULAR CARCINOMA: A QUALITATIVE STUDY

Lauren Nephew[1] Courtney Moore[2] Nicole Garcia[1] Lisa Parks[2] Allison McKay[2] Alexandra Strauss[3] Sarah Wiehe[2] John Holden[1] Monica Kasting[4] Katie Ross-Driscoll[1] Marwan Ghabril[1] Eric Orman[1] Archita Desai[1] Naga Chalasani[5] Susan Rawl[1]

[1]Indiana University, [2]Indiana University Clinical and Translational Science Institute, [3]Johns Hopkins University, [4]Purdue University, [5]Indiana University Medical Center

Background: Black patients and those experiencing adverse social determinants of health (SDOH) face significant disparities in accessing curative therapies for hepatocellular carcinoma (HCC), impacting their survival. While provider-perceived barriers to liver transplantation (LT) have been explored, this study engages Black patients and those experiencing adverse SDOH to understand the informational, health system, and social barriers they encounter in the HCC-LT care cascade. **Methods:** Two focus groups were conducted: one with Black participants and one with participants experiencing adverse SDOH at one LT center. Black participants could have adverse SDOH, but non-Black participants were excluded from the Black focus group. Two individual interviews supplemented the focus groups. Adverse SDOH were defined as being insured by Medicaid or Medicare and being unmarried as these adverse SDOH were associated with worse survival in our published state-wide cohort study. Participants not referred for LT were excluded. Human-centered design methods, including journey mapping and group ideation were used to uncover unmet needs. Affinity diagramming and concept mapping were used to identify themes and differences between groups. **Results:** There were 17 participants (7 Black and 10 with adverse SDOH); 5 had undergone LT and 12 were or had been in evaluation for LT. Figure 1 illustrates major challenges identified by each group which included struggles with comprehending medical information and difficulty with decision making. Psychological and emotional burdens were more prevalent among Black patients, while both groups faced difficulties in securing adequate support systems. Only Black patients expressed distrust in the healthcare system including distrust in the information provided and the belief that treatments were motivated solely by profit rather than patient well-being. The adverse SDOH group voiced more concerns related to fragmented care coordination, difficulties in navigating complex healthcare systems, and financial constraints. **Conclusion:** Black patients and those with adverse SDOH face unique challenges in accessing LT for HCC. Tailored interventions addressing information challenges, distrust, emotional burdens, and financial constraints are essential to improve access for these populations. Eliciting barriers separately may ensure that specific issues, such as distrust and the need for emotional support among Black patients, are adequately addressed, allowing for the development of inclusive healthcare solutions.

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Disclosures: Lauren Nephew: Nothing to Disclose, Courtney Moore: Nothing to Disclose, Nicole Garcia: Nothing to Disclose, Lisa Parks: Nothing to Disclose, Allison McKay: Nothing to Disclose, Alexandra Strauss: Nothing to Disclose, Sarah Wiehe: Nothing to Disclose, John Holden: Nothing to Disclose, Monica Kasting: Merck and Company: Grant/Research Support, Merck and Company: Advisor, Katie Ross-Driscoll: Nothing to Disclose, Marwan Ghabril: Nothing to Disclose, Eric Orman: Sitero: Consultant, Biovie: Advisor, Archita Desai: Nothing to Disclose, Naga Chalasani: Madrigal: Consultant, Zydus, Ipsen, Pfizer, Merck, Altimmune, GSK: Consultant, Exact Sciences: Grant/Research Support, NIH: Grant/Research Support, Susan Rawl: Nothing to Disclose

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2189 | GLOBAL DISPARITIES IN LIVER DISEASES RESEARCH FUNDING: A ROOT CAUSE OF HEALTH DISPARITIES

Daniel Huynh[1] Matthew Obusan[2] Omar Albhaisi[3] Somaya Albhaisi[4]

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Background: Despite the increase in funding opportunities for liver disease research worldwide, disparities in funding persist globally, reflecting a scientific divide between the global North and global South. Therefore, we aimed to evaluate the global funding opportunities for liver disease research to address the critical unmet need for equity in research. **Methods:** We performed an extensive internet search for funding agencies in each country from all continents worldwide. We collected detailed information about publicly available funding opportunities for liver disease research from 2013 to 2023. These data included funder, region eligibility to apply, duration, and funding amount, among others. We compared the funding state between countries and regions to identify any disparities. **Results:** We identified 279 research grants targeting liver disease. The US led with 125 grants, followed by Geneva of Europe (47), Canada (42), Australia (17), Japan (15), the Philippines (7), Pakistan (3), and Chile (2). No African countries funded any liver disease-specific grants. We also identified 172 non-liver disease-specific grants that funded liver disease research. India funded 54, Australia 47, Canada 18, Malaysia 13, the US 11, Singapore 9. African countries such as Nigeria funded 8 and Tunisia 4. Figure 1 shows the distribution of countries listed as eligible to apply from the collected awards and funder distribution by region. Eligible countries for liver disease-specific awards included Canada (40.6%), the US (32.97%), and Mexico (25.36%). Additionally, 16.45% listed any European country, 3.58% any African country, 0.72% North American countries, and 0.72% any South American countries. Among the 279 awards targeting liver research, 70.6% did not specify a liver disease. 9.82% targeted viral hepatitis,1.82% metabolic dysfunction-associated steatotic liver disease, and 1.02% autoimmune liver disease research. As for research expenditures from 2013 to 2023, the NIH spent approximately $22.2 billion on liver disease research, the Japan Society for Promotion of Science spent $72 million, and Australia's National Health and Medical Research Council program spent $14.9 billion. Regarding liver foundations, the American Association for the Study of Liver Diseases funded $27.8 million, the European Association for the Study of the Liver funded at least $7.6 million, and the Canadian Liver Foundation funded $4 million. **Conclusion:** There is a paucity of studies that investigate global research funding opportunities for liver disease. We found that higher-income countries (HIC) such as US, Europe, and Canada comprised a larger proportion of funders for liver disease research. Additionally, of the awards found, HICs were listed as eligible to apply more frequently than low and middle-income countries (LMIC). This disparity underscores the current socioeconomic milieu and an unmet need to strive for global liver research equity.

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Figure 1a. Countries Eligible for Liver Research Grants.

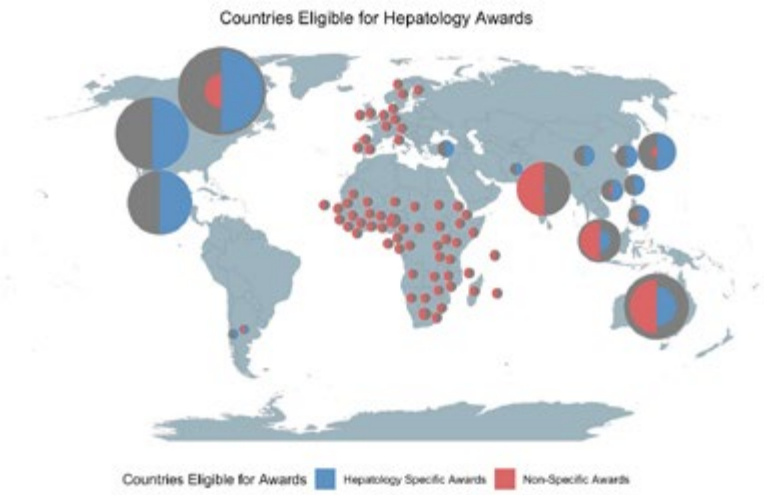
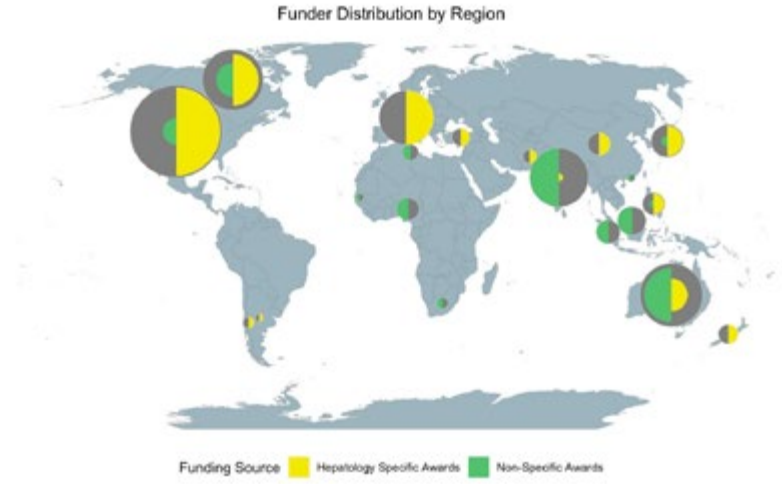


Figure 1b. Distribution of Liver Research Grant Funders by Country.



Disclosures: Daniel Huynh: Nothing to Disclose, Matthew Obusan: Nothing to Disclose, Omar Albhaisi: Nothing to Disclose, Somaya Albhaisi: Nothing to Disclose

2190 | DISPARITIES IN WAITLIST OUTCOMES FOR HEPATOCELLULAR CARCINOMA: INSURANCE STATUS AND ACCESS TO LOCOREGIONAL THERAPIES

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[1]*University of Miami Miller School of Medicine*

Background: Liver transplantation can be curative for patients with hepatocellular carcinoma (HCC), yet the shortage of donor livers means not all waitlisted patients will survive to transplant. Patients waitlisted for HCC with public insurance have been shown to face a higher risk of waitlist dropout compared to those with private insurance, although the root cause of this disparity is unknown. Locoregional therapies (LRTs) serve as the bridge to liver transplantation for patients with HCC and can prevent disease progression and waitlist dropout. We sought to determine whether insurance type is associated with differences in receipt of LRT among patients with HCC waitlisted for transplant, thereby exploring whether this explains the disparities in waitlist outcomes. **Methods:** We conducted a retrospective cohort study using OPTN/UNOS data on patients, aged 18 years and older, waitlisted

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with standardized HCC MELD exceptions from 1/1/2015-12/31/2022. To evaluate the association between insurance type and receipt of LRT, we fit mixed effects multiple variable logistic regression models (outcome: receipt of LRT; random effect: transplant center). We accounted for key clinical demographics and HCC-related variables, and defined LRT as: ablative therapies (e.g., radiofrequency ablation), as well as non-ablative therapies (e.g., TACE, Y-90, external beam radiation). **Results:** Our analysis included 141,469 adults waitlisted with HCC MELD exceptions. The percentage of patients receiving LRTs was 83.8% for those with Medicaid and 83.4% for those with private insurance, yet the percentage of patients who dropped off the waitlist due to being too sick or dying was 18.6% for Medicaid beneficiaries and 14.3% for those with private insurance. In multivariable models adjusting for gender, ethnicity, age at listing, ascites, bilirubin, and listing area, patients with Medicaid had significantly higher odds (OR: 1.10, 95% CI: 1.03, 1.18) of receiving LRT compared to patients with private insurance. **Conclusion:** Despite having significantly higher risk of waitlist dropout, patients with Medicaid were more likely to receive LRT compared to patients with private insurance. Although our data confirm other studies' findings that patients with Medicaid have a higher risk of waitlist dropout, lack of receipt of LRT does not appear to explain this survival disparity. Our findings underscore the need for further investigation of this disparity and identification of additional contributing factors.

Disclosures: Soobin Lee: Nothing to Disclose, Patricia Jones: Gilead: Grant/Research Support, Lindsay Thornton: Nothing to Disclose, David Goldberg: Nothing to Disclose

2191 | EQUITY IN LIVER TRANSPLANT ACCESS FOR CRITICALLY ILL PATIENTS

Alaina Miller[1] Aanchal Kapoor[1] Gianina Flocco[2] Christina Lindenmeyer[2]

[1]Cleveland Clinic Foundation, [2]Cleveland Clinic

Background: The Medical Intensive Liver Unit (MILU) was established in August 2018 as a specialized Intensive Care Unit dedicated to the care of critically ill patients with liver disease, primarily serving those with end-stage liver disease, acute-on-chronic liver failure (ACLF) and low transplant-free survival (TFS). A primary aim of the MILU's multi-disciplinary approach to patient care has been to increase access to the center's large liver transplant (LT) program. This study aims to assess the impact of the MILU's expedited LT evaluation and transplantation process on equity and representation in liver transplant recipients. **Methods:** Patients admitted to the MILU at a large tertiary care and LT center between 08/2018 and 08/2023 were included. Data was collected retrospectively with patients identified from a prospectively maintained MILU patient registry. Direct transplant (DT) patients were defined as those transplanted directly from the MILU to the operating room. 126 DT patients were compared to 662 non-DT patients transplanted at our center during the same time period. The severity of illness at the time of LT was assessed via the EASL-CLIF score for ACLF patients and the MELD-Na score for all patients. Socioeconomic status was indicated by Medicaid enrollment at the time of LT. To determine the statistical significance of data related to minority race and female patients, two-proportion z-tests were conducted. **Results:** Of the 126 DTs from 08/2018 to 08/2023, the average age was 51 (21-71), with alcohol-associated cirrhosis being the primary etiology in 50% (63/126) of cases. 38.89% of DTs had Medicaid coverage. The average MELD-Na score for DT patients was 35.61, and the average EASL-CLIF score for ACLF patients was 56.35. Minority race patients accounted for 23.02% (29/126) of DTs, compared to 12.39% (82/662) of non-DT LTs at the center during the same period ($p = 0.0017$). Additionally, 54.76% of DTs were female (69/126), compared to 37.00% of non-DT LTs ($p = 0.00019$). **Conclusion:** The MILU's multi-disciplinary team offers expedited transplant evaluations and specializes in the optimization of critically ill patients for LT. The increased access to DT for critically ill patients has contributed to addressing disparities and equity in LT at our center, facilitating early transplant for both racial and ethnic minority patients, and female patients. These findings emphasize the contributions of a liver disease-specific intensive care unit towards the goal of increasing equity and diversity for LT candidates, particularly for those who may be underserved by transplant services.

Disclosures: Alaina Miller: Nothing to Disclose, Aanchal Kapoor: Nothing to Disclose, Gianina Flocco: Nothing to Disclose, Christina Lindenmeyer: Nothing to Disclose

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2192 | ADVERSE SOCIAL DETERMINANTS OF HEALTH CONTRIBUTE TO WORSE CLINICAL OUTCOMES IN SARCOPENIC PATIENTS WITH CIRRHOSIS

Pratham Ved Bhashyakarla[1] Amy Attaway[2] Arnav Rao[1] Annette Bellar[2] Joe Zein[3] jaividhya dasarathy[4] Nicole Welch[2] Srinivasan Dasarathy[2]

[1]Case Western Reserve University, [2]Cleveland Clinic, [3]Professor of Medicine, [4]Metro Health

Background:
Sarcopenia and physical frailty are contributors to adverse clinical outcomes in patients with cirrhosis. Nutritional intake and physical activity influence a muscle loss phenotype (MLP). There is increasing recognition that social determinants of health (SDOH) that affect food security and access to safe physical activity play critical roles in nutritional status and disease management. We evaluated the impact of SDOH and sarcopenia defined by a MLP on clinical outcomes in hospitalized patients with cirrhosis. **Methods:** The Nationwide Inpatient Sample (NIS) database (years 2017-2020) was analyzed to study adult hospitalized patients with cirrhosis, MLP, and SDOH. SDOH was defined by ICD-10 Z-codes as a composite sum of multiple domains related to housing and economic status, unemployment, occupational, psychosocial, family, and healthcare access. Additional codes defined cirrhosis and MLP (see Table 1). Multivariate regressions between SDOH and MLP as the independent variables, both adjusted and not adjusted for age, race, sex, and comorbidities were analyzed in relation to outcomes. **Results:** Outcomes of cirrhotic patients from the 2018-2020 NIS datasets were analyzed (n=453,341). In the model adjusted for age, race, sex, and comorbidities, patients with MLP had higher healthcare costs (adj OR 1.49; 95% CI: 1.48-1.51), longer length of stay (adj OR 1.60, 95% CI: 1.58-1.61), a greater number of diagnoses on discharge (NDX) (adj OR 1.22, 95% CI: 1.21-1.22), higher in-hospital mortality (adj OR 1.91, 95% CI: 1.85-1.97), and were less likely to be discharged home (adj OR 0.47, 95% CI: 0.46-0.48). SDOH was also independently associated with longer length of stay (adj OR 1.16, 95% CI: 1.14-1.17) and a greater number of diagnoses on discharge (NDX) (adj OR 1.09, 95% CI: 1.08-1.09). Interestingly, SDOH was also associated with a small decrease in healthcare costs (adj OR 0.95, 95% CI: 0.93-0.96), a greater likelihood of being discharged to home (adj OR 1.11, 95% CI: 1.10-1.15), and a lower likelihood of in-hospital mortality (adj OR 0.49, 95% CI: 0.45-0.53). This may have represented confounding by indication, as patients with SDOH were more likely to be admitted for alcohol withdrawal compared to those without SDOH (Table 1). **Conclusion:** MLP and SDOH were both independently associated with adverse outcomes in cirrhotic patients, in regards to length of stay in the hospital, and number of concurrent diagnoses at discharge. Patients with MLP also had higher healthcare costs, higher in-hospital mortality, and were less likely to be discharged to home.

Table 1. Regression analysis to determine the impact of muscle loss phenotype and social determinants of health in patients with cirrhosis

	Unadjusted OR[A] (95% CI)		Adjusted OR*[A] (95% CI)		Adjusted OR**[A] (95% CI)	
	MLP	SDOH	MLP	SDOH	MLP	SDOH
Healthcare cost	1.52 (1.51-1.53)	0.94 (0.93-0.95)	1.53 (1.52-1.54)	0.93 (0.92-0.95)	1.49 (1.48-1.51)	0.95 (0.93-0.96)
Length of stay	1.63 (1.62-1.64)	1.14 (1.13-1.16)	1.62 (1.61-1.63)	1.15 (1.14-1.17)	1.60 (1.58-1.61)	1.16 (1.14-1.17)
No of diagnoses on discharge (NDX)	1.24 (1.24-1.24)	1.04 (1.04-1.05)	1.23 (1.23-1.24)	1.09 (1.08-1.09)	1.22 (1.21-1.22)	1.09 (1.08-1.09)
Discharge to home	0.47 (0.47-0.48)	1.46 (1.41-1.50)	0.46 (0.46-0.47)	1.11 (1.08-1.14)	0.47 (0.46-0.48)	1.11 (1.10-1.15)
In-hospital mortality	2.02 (1.97-2.07)	0.45 (0.41-0.48)	2.00 (1.95-2.05)	0.47 (0.43-0.51)	1.91 (1.85-1.97)	0.49 (0.45-0.53)

*Model adjusted for age, race, sex
**Model adjusted for age, race, sex, and comorbidities (Chronic kidney disease, Chronic anemia, Coagulopathy, AIDS/HIV, Depression, Diabetes, Congestive Heart Failure)
[A]All associations were statistically significant (p<0.001).
Social determinants of health are defined as the presence of a Z code related to different domains of education, employment, occupational exposures, the physical environment, housing, economic circumstances, and/or the social environment.
Top 3 diagnoses for cirrhosis without SDOH: K7031 - Alcoholic cirrhosis with ascites, A419 - Sepsis, K7290 - Hepatic failure
Top 3 diagnoses for cirrhosis with SDOH: K7031 - Alcoholic cirrhosis with ascites, A419 - Sepsis, F10239 - Alcohol withdrawal
Cirrhosis ICD-10 Codes: K717, K743, K744, K745, K7030, K7031, K7460, K7469
SDOH ICD-10 Z-codes: Z55.x-Z57.x, Z59.x, Z60.x, Z62.x-Z65.x, Z75.x
MLP ICD-10 Codes: R634, R636, E43, E440, E46, E638, E639, R64, M625, M6284, R627

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Disclosures: Pratham Ved Bhashyakarla: Nothing to Disclose, Amy Attaway: Nothing to Disclose, Arnav Rao: Nothing to Disclose, Annette Bellar: Nothing to Disclose, Joe Zein: Nothing to Disclose, jaividhya dasarathy: Nothing to Disclose, Nicole Welch: Nothing to Disclose, Srinivasan Dasarathy: Nothing to Disclose

2193 | LIVER TRANSPLANTATION DISPARITIES IN LISTING TO DEATH RATIO AND MORTALITY FROM 1999-2021

Alexander Zhao[1] Nicole Ng[1] Xiaohan Ying[2] Arun Jesudian[1] Catherine Lucero[1] Russell Rosenblatt[1]

[1]Weill Cornell Medicine, [2]New York-Presbyterian Hospital/Weill Cornell Medical College

Background: Racial, ethnic, and gender disparities have persisted in the field of liver transplantation (LT). The listing to death ratio (LDR) was developed as a novel metric to further evaluate disparities in LT. Our prior study found Black patients were less likely to be listed for LT when compared to dying from liver disease. However, little is known if these disparities have improved over time. In this study, we aimed to explore recent race, ethnicity, and gender trends in LDR and LT. **Methods:** We used the CDC WONDER database to analyze deaths from cirrhosis or hepatocellular carcinoma and the UNOS STAR file to identify all patients listed and transplanted from 1999-2021. Patients aged 25-64 were included while patients living outside the 50 states and Washington DC were excluded. Our primary outcome, LDR, was calculated by the number of patients listed for LT over the number of patients who died. Our secondary outcomes were transplant to listing ratio (TLR), defined as number of patients who underwent LT over the number of patients listed for LT, and transplant to death ratio (TDR), the number of patients who underwent LT over the number of patients who died. Genders were analyzed separately, and White patients were the reference race/ethnicity. We compared outcomes using chi-square and analyzed trends using annual percentage change (APC). **Results:** 532,702 patients died during the study. Deaths per year increased from 15,868 in 1999 to 34,727 in 2021 (APC 3.3%, $p<0.001$). Female (APC 4.5%) and Hispanic (APC 5.0%) had the highest rates of annual deaths, all $p<0.001$. 208,343 patients were listed for LT, increasing only slightly from 8,567 to 10,027 (APC 0.6%, $p<0.001$). Annual listing increases were greater in female (APC 0.8%) and in Hispanic (2.1%) patients, all $p<0.001$. LDR decreased from 0.54 in 1999 to 0.29 in 2021 (APC -2.5%, $p < 0.001$). A more drastic annual decrease was noted in women (APC -3.4% vs. -2.2% in men), all $p<0.001$. 119,453 total LTs were performed, increasing from 3,815 to 6,797 (APC 2.0%, $p < 0.001$). LTs in all races, ethnicities, and genders increased annually over time, with a higher APC in women (APC 2.6%), $p<0.001$. The annual TLR was 0.57, increasing from 0.45 to 0.68 (APC 1.3%, $p<0.001$). The overall TDR was 0.22, decreasing slightly from 0.24 in 1999 to 0.20 in 2021 (APC -3.1%, $p<0.001$). The largest decrease was noted in men (APC -6.6%, $p<0.001$). Hispanic populations had the largest decrease (APC -2.6%, $p<0.001$), while Black and Asian patients did not experience significant change. **Conclusion:** Annual deaths from liver disease have increased dramatically each year. Despite improvements in number of LT listings and LTs performed, these increases have not sufficiently offset the rising mortality rates, as demonstrated by decreased LDR and TDR despite increased TLR. Even though women's LDR decreased less than that of men, gaps still remain. Major interventions are required to improve access to LT and stem the rise of deaths from liver disease.

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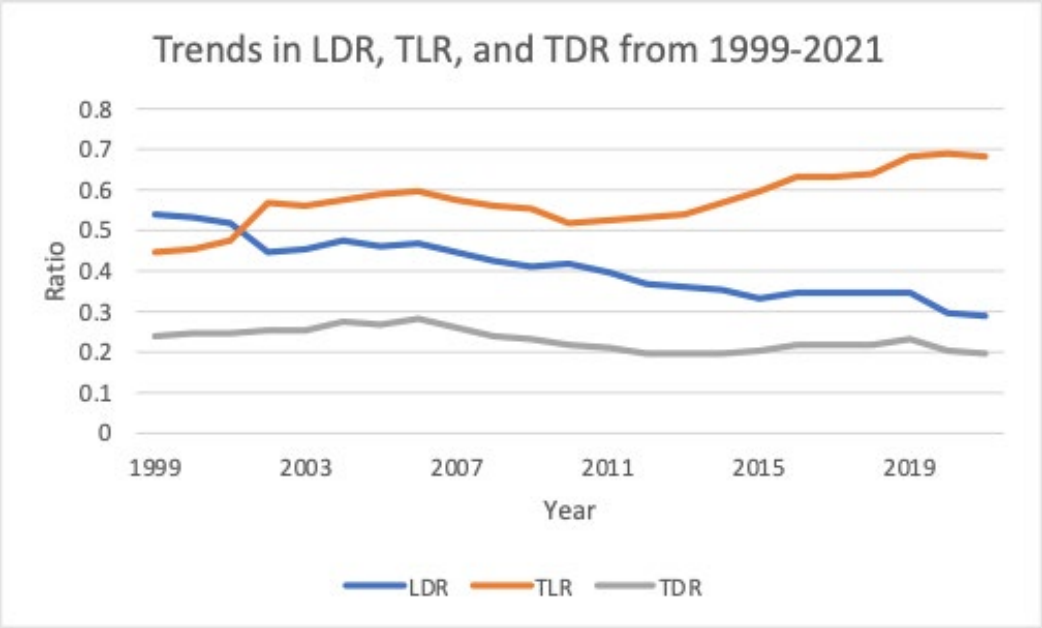

Disclosures: Alexander Zhao: Nothing to Disclose, Nicole Ng: Nothing to Disclose, Xiaohan Ying: Nothing to Disclose, Arun Jesudian: Salix Pharmaceuticals: Consultant, Salix Pharmaceuticals: Speaking and Teaching, Madrigal Pharmaceuticals: Speaking and Teaching, Novo Nordisk: Consultant, Orphalan: Consultant, Catherine Lucero: Nothing to Disclose, Russell Rosenblatt: Nothing to Disclose

2194 | SUBGROUP DISPARITIES IN PATIENTS WITH CIRRHOSIS THAT RECEIVED PALLIATIVE/HOSPICE CARE AND DISCUSSION: FINDINGS FROM A LARGE, SINGLE-CENTER STUDY

Annie Fung[1] Ashley Fong[1] Surya Gudapati[1] Vy Nguyen[1] Jung Eun Park[1] Isaac Le[1] KeeSeok Lee[1] Angela Chau[1] Sally Tran[1] Xinrong Zhang[1] Mayumi Maeda[1] Ramsey Cheung[1] Changqing Zhao[2] Minjuan Jin[3] Mindie Nguyen[4]

[1]Division of Gastroenterology and Hepatology, Stanford University Medical Center, Stanford, CA, USA, [2]Department of Cirrhosis, Institute of Liver Disease, Shuguang Hospital, Shanghai University of T.C., [3]Department of Epidemiology and Biostatistics, Zhejiang University School of Public Health, Hang Zho, [4]Stanford University Medical Center

Background: Despite cirrhosis being a common end stage liver disease, palliative and hospice care have been shown to be underutilized. However, it is unclear if there are significant differences between hospice/palliative care (PAL) utilization by demographic or clinical subgroups. We aimed to examine the disparities between different subgroups of cirrhosis patients in regards to PAL utilization. **Methods:** The study included consecutive adults with cirrhosis who were all seen by both a primary care physician and a liver specialist at a U.S. university hospital between 2000-2023. Patient records were reviewed to determine if either PAL care or discussion was mentioned in clinical notes. **Results:** We analyzed 15,882 patients with cirrhosis, of which only 5,895 (37.1%) received PAL while 9,987 (62.9%) did not. The average age of patients was 58.5 (PAL: 59.6, no PAL: 57.8, *P*<0.001) and 59% were male. There were significant differences in the proportions of patients receiving PAL among several demographic and clinical subgroups (Figure 1). By age, patients older than 60 were more likely to receive PAL compared to the younger group (40.5% vs. 33.9%,P<0.001). By sex, males were more likely to receive PAL compared to females (38.0% vs. 35.8%, *P*=0.005). Among the races/ethnicities, Asian patients had the highest proportion receiving PAL (45.9%), followed by Black (43.3%), then Hispanic (36.7%), and White patients (35.6%) (*P*<0.001). Patients with HCC were more likely to receive PAL (61.7%) than patients without HCC (*P*<0.001). In subgroups by liver disease etiology, patients with HCV/HBV coinfection were most likely to receive PAL (45.8%), followed by patients with HBV (43%), HCV (37.9%), NASH (30.6%), and alcohol-associated liver disease (30.3%, *P*<0.001).On multivariable logistic regression analysis adjusted for sex, age >60, ethnicity, HCC, hepatic decompensation, liver disease etiologies, and Charlson Comorbidity Index (CCI) >4, and death, age >60 (adjusted odds ratio [aOR]: 1.2, 95%CI: 1.1-1.3), Black patients (aOR: 1.5, 95%CI: 1.2-1.8), Asian patients

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(aOR: 1.4, 95%CI: 1.3-1.6), HCC (aOR: 2.9, 95%CI: 2.6-3.2), decompensation (aOR: 1.6, 95%CI: 1.5-1.8), CCI >4 (aOR: 2.6, 95%CI: 2.4-2.9), and death (aOR: 2.1, 95%CI: 1.9-2.3) were significant predictors of receiving PAL. **Conclusion:** Significant disparities in receipt of PAL exist among subgroups of patients with cirrhosis, with younger, White, and those with NASH or alcohol-associated cirrhosis less likely to receive PAL. Approaches to PAL care should be age and gender as well as cultural and language sensitive and appropriate.

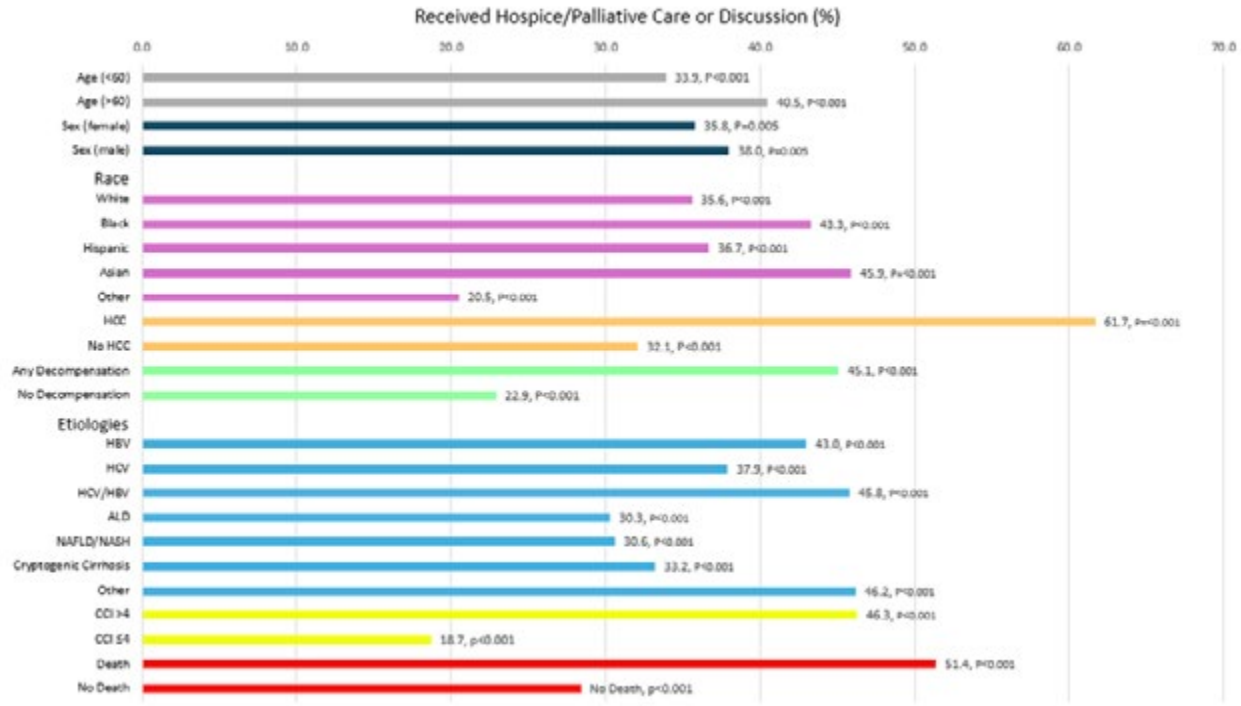

Figure 1. Percentage of patients in specific subgroups that received Hospice/Palliative care or discussion.

Disclosures: Annie Fung: Nothing to Disclose, Ashley Fong: Nothing to Disclose, Surya Gudapati: Nothing to Disclose, Vy Nguyen: Nothing to Disclose, Jung Eun Park: Nothing to Disclose, Isaac Le: Nothing to Disclose, KeeSeok Lee: Nothing to Disclose, Angela Chau: Nothing to Disclose, Sally Tran: Nothing to Disclose, Xinrong Zhang: Nothing to Disclose, Mayumi Maeda: Nothing to Disclose, Ramsey Cheung: Nothing to Disclose, Changqing Zhao: Nothing to Disclose, Minjuan Jin: Nothing to Disclose, Mindie Nguyen: Nothing to Disclose

2195 | ANTIVIRAL USE AMONG IMMIGRANTS WITH CHRONIC HEPATITIS B (HBV) IN METROPOLITAN-DC

Christine Lin[1] HUONG DANG[2] Lydia Tang[1]

[1]University of Maryland, Baltimore, [2]Dang Huong MD

Background: Globally, 296 million people are infected with chronic hepatitis B (HBV) and at risk for cirrhosis and hepatocellular carcinoma. In the Metropolitan-DC area, chronic hepatitis B infection (HBV) is 10 times more common in Asian, African, and Latin American communities than non-immigrants communities. Therefore, HBV-related liver disease, including cancer, is a major health disparity for immigrants. Antivirals reduce cancer risk but require long-term adherence. Immigrants face barriers to HBV antiviral adherence, including language, high cost of antivirals, and establishing care for HBV management. We examine antiviral use in a cohort of people with HBV. HOPE is a natural history study at the University of Maryland, Baltimore, enrolling adults with HBV. TEMUL, a sub-study of HOPE, provided free tenofovir alafenamide (TAF) for 2 years. After completing 2 years of TEMUL, participants transitioned to receiving antivirals through their non-study healthcare providers. We describe antiviral use behaviors during TEMUL and at follow-up within 2 years of TEMUL end. **Methods:** HOPE is a natural history study at the University of Maryland, Baltimore, enrolling adults with HBV. TEMUL, a sub-study of HOPE, provided free tenofovir alafenamide (TAF) for 2 years. After completing 2 years of TEMUL, participants transitioned to

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receiving antivirals through their non-study healthcare providers. We describe antiviral use behaviors during TEMUL and at follow-up within 2 years of TEMUL end. **Results:** From May 2017 to August 2022, 92 people enrolled in TEMUL. Most were foreign-born (78 born in Asia, 6 born in Africa) with mild (F1) liver fibrosis at enrollment. Seventy-nine completed TEMUL, all with sustained adherence to TAF during the 2 years. Fifty-nine completed a post-study follow-up. At follow-up, 44 of 59 (75%) were adherent (remained on antivirals without disruption). Eight of the 44 switched to another antiviral due to insurance coverage. Fifteen (25%) experienced antiviral disruptions: 5 had lapses (ranging from 1 month to 2 years) when switching antivirals, and 10 stopped antivirals due to loss of health insurance, high copay, and inability to follow-up with a healthcare provider. All 10 were foreign-born, Asian, and non-English speaking. Of these 10, 9 were viremic (mean: 2.2E6 IU/mL, range: 130-1.8E7 IU/mL) at follow-up. Resumption of antivirals was needed in all. Lack of health insurance, greater duration between end of TEMUL and post-study follow-up, and being a non-English speaker were associated with antiviral disruption. **Conclusion:** Language and poor health insurance coverage hinder antiviral adherence in immigrants with HBV. Foreign-born, non-English speaking patients may be especially vulnerable to lapses in antiviral use. Interventions to improve access to antivirals tailored to this patient group are needed.

Disclosures: Christine Lin: Nothing to Disclose, HUONG DANG: Nothing to Disclose, Lydia Tang: Arbutus: Grant/Research Support, Gilead Sciences: Grant/Research Support

2196 | A PREGNANT PAUSE – ROOM FOR IMPROVEMENT IN FERTILITY DISCUSSIONS WITH END STAGE LIVER DISEASE PATIENTS

Vandana Khungar[1] Mary White[2] Uyen To[1] Ariel Jaffe[1] Cole Cassady[1] Meagan Alvarado[3]

[1]Yale University, [2]Yale-New Haven Hospital, [3]Yale New-Haven Hospital

Background: Nationally, approximately 20% of liver transplants are performed in women of reproductive age. The incidence of end stage liver disease (ESLD) and transplantation in patients of reproductive age is increasing. Although fertility is impaired in the pre-transplant population, it rapidly returns to normal post-transplant. Medications in this population have teratogenic potential and there are possible maternal and fetal complications in both ESLD and transplant. Currently inadequate attention is paid to reproductive counseling in the hepatology and liver transplant space. **Methods:** A single center retrospective analysis was performed of female liver transplant patients between the ages of 18 and 50 from 2012 to 2022 to evaluate rates of reproductive counseling and trends that predict counseling. Descriptive statistics were performed with proportions, medians, and interquartile ranges (IQRs) reported. Proportions compared by chi-square tests with p value <0.05 were considered statistically significant. Exclusion criteria included hysterectomy or tubal ligation. **Results:** 48 patients were included with a median age at transplant of 29.8 years. 45.8% of patients received fertility counseling that was documented. There was a rate of counseling of 30.4% in 2012-2017 and 60.0% in 2017-2022, a 97.1% increase in fertility counseling between 2012-2017 and 2017-2022 cohorts. In the latter time cohort, there was a 100% increase in female physicians. There were statistically significant differences in rates of counseling for patients < 35 years (54.1% counseled) and > 35 years (33.3% counseled). There were statistically significant differences in rates of counseling by race (white 45%, Black 40%, Asian 100%, other/unknown 25%) and ethnicity (Hispanic 46.1% and non-Hispanic 42.4%) of patients. **Conclusion:** A minority of physicians provided fertility counseling to patients during encounters for end stage liver disease and transplantation. Female physicians were more likely to perform such counseling. Careful attention needs to be paid to patient age, race and ethnicity to ensure equitable care. As pregnancy becomes more common and safer in the ESLD and transplant population, reproductive counseling is paramount. Further efforts underway include multicenter assessments and interventions to easily increase counseling and patient satisfaction.

Disclosures: Vandana Khungar: Nothing to Disclose, Mary White: Nothing to Disclose, Uyen To: Nothing to Disclose, Ariel Jaffe: Nothing to Disclose, Cole Cassady: Nothing to Disclose, Meagan Alvarado: Nothing to Disclose

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2197 | REVEALING DISPARITIES: NATIVE AMERICANS ARE DEFERRED AND DENIED FOR LIVER TRANSPLANT AT A HIGHER RATE DUE TO PSYCHOSOCIAL REASONS ◆

Sandra Elmasry David Chascsa[1] Blanca Lizaola-Mayo[1] Rolland Dickson[1] Nathan Delafield[1] Adam Milam[1]

[1]Mayo Clinic Arizona

Background: American Indians (AI) face barriers to liver transplantation (LT) compared to non-Hispanic Whites (NHW). In 2020,30% of listed AI patients received LT, versus 49% of NHW Mayo Clinic Arizona (MCA) is in proximity of 12.9% of Arizona's AI population. Our aim was to assess the impact of medical and psychosocial barriers on LT disparities, reasons for deferral or denial, and the specific stages where AIs encounter the most obstacles. **Methods:** We performed a retrospective cohort study at MCA of all patients referred for LT between 2017– 2022. Demographic data, transplant indication, psychosocial parameters such as education level, SIPAT score, and insurance status were collected **Results:** Between 2017-2022 there were 2405 LT referrals to MCA, 83(3.5%) were AI patients and 1396 (58%) were NHW. The most common indications for LT among AI patients were ALD and MASLD. The median MELD score in AI population was 22 and median SIPAT score was 23 with no statistical significance compared to NWH (P=0.27, 0.372 respectively). AI compared to NHW had a higher proportion of government payers at 52.5% versus 33.7%, and statistically lower education level and English language proficiency There was a trend toward a lower rate of evaluation, presentation and listing for AI patients which led to a statistically lower rate of LT compared to NHW (P=0.0497, 0.0148, 0.0001 respectively).The most common cause for deferral or denial of AI patients were psychosocial or multifactorial reasons which was higher than other ethnicities (Figure 2) **Conclusion:** AI patients face significant healthcare disadvantages that reduce their likelihood of receiving a LT. Similar MELD scores and indications for LT with other groups argue against medical reasons being the reason for disparity. Notably, while SIPAT scores were not statistically different, the interpretation was stark: the median score for NHW patients was in the "good candidate" range (17), whereas AI patients were deemed "minimally acceptable" (23). Our data supports a significant role of social determinants of health accounting for this discrepancy given decreased percentage of AI completing LT eval, being presented to selection committee as well as a higher rate of psychological issues as part of the reason for deferral or denial reasons. At the same time, post-transplant outcomes, including graft failure and overall mortality, showed no difference between ethnicities. This suggests a need for a culture centric approach to assessment and listing in the AI population. Therefore, it is imperative to implement innovative pretransplant interventions to eliminate these disparities and ensure equitable access to LT for AI patients.

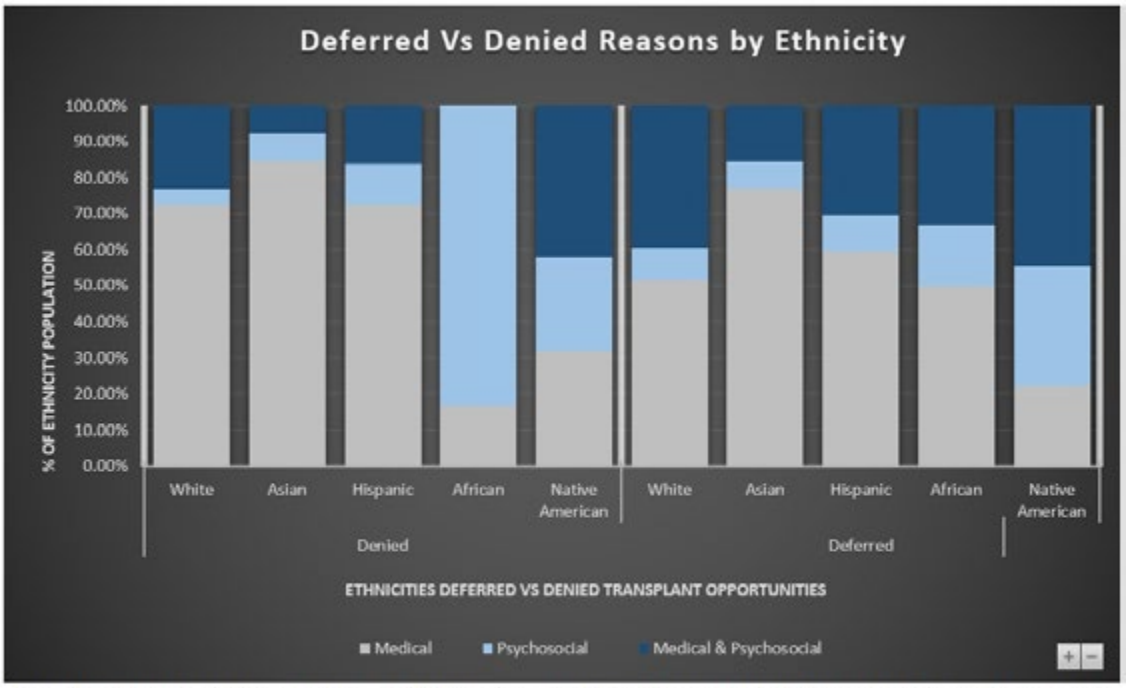

Figure 1: Deferred vs denial reason for each ethnicity shows that Native American have the highest psychosocial reasons with and without medical reasons for deferral and denial.

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Disclosures: Sandra Elmasry: Nothing to Disclose, David Chascsa: Nothing to Disclose, Blanca Lizaola-Mayo: Nothing to Disclose, Rolland Dickson: Nothing to Disclose, Nathan Delafield: Nothing to Disclose, Adam Milam: Nothing to Disclose

2198 | RACIAL DIFFERENCES IN PROGRESSION THROUGH LIVING DONOR LIVER TRANSPLANT DONOR CANDIDACY EVALUATION ◆

Melanie Zheng[1] Jessica Lin[2] Alexandra Strauss[2] Elizabeth King[2] shane ottmann[3] Benjamin Philosophe[1] Ahmet Gurakar[2]

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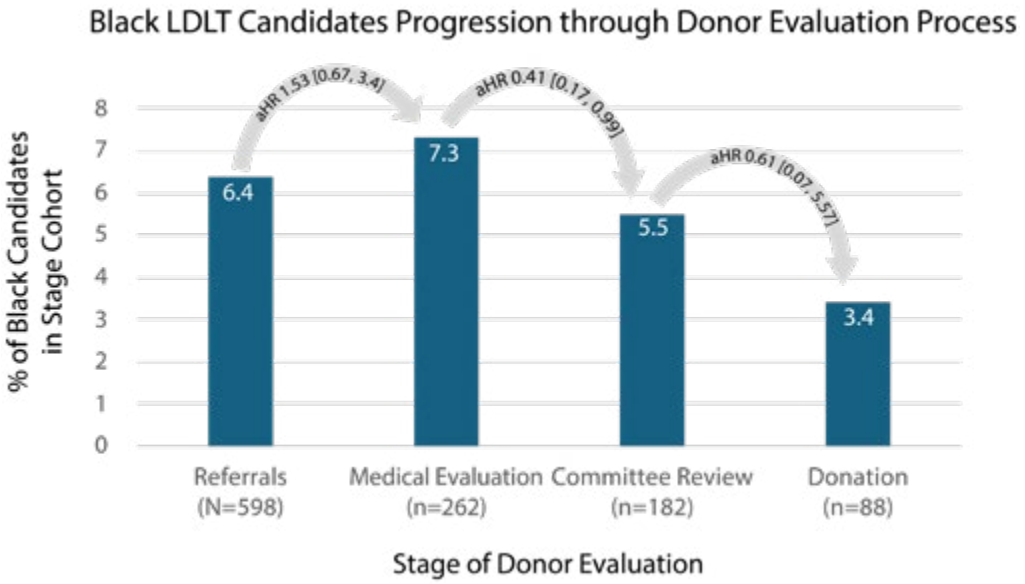
Background: Preliminary studies have shown racial/ethnic minority groups receive a disproportionately low percentage of LDLTs, with Black recipients comprising only 3.5% of LDLT nationally from 2002 to 2014. It has been proposed that racial differences in utilization of LDLT may be due to fewer initial inquiries by potential donors. Our study aimed to describe differences in LDLT candidate demographics through the evaluation process and their effects on evaluation progression to donation at our transplant center. **Methods:** We analyzed progression through evaluation process for 598 LDLT candidates at our center between Jan 2019 – Nov 2023. LDLT candidate characteristics including age, sex, race, ethnicity, BMI, and proximity to transplant center (Zip code <50 miles from transplant center) were collected through electronic medical chart review from earliest encounter post-referral. Characteristics were compared for LDLT candidates progressing through sequential steps of the LDLT evaluation process: (1) all-comer referrals, (2) in-person medical evaluation, (3) committee review, and (4) donation. Cox regression analysis was performed for days taken between each step of the evaluation process. **Results:** From the initial 598 LDLT referrals, 262 progressed to medical evaluation; 182 to committee review; and 88 to LDLT donation. Median age (41, 42, 42, 38), % female sex (56, 52, 51, 51), and % proximate to transplant center (26, 27, 26, 26) remained stable across the cohorts at each stage. % White race remained high across each stage and increased from medical evaluation to donation (85, 82, 85, 89). In comparison, % Black race decreased from medical evaluation to donation (6.4, 7.3, 5.5, 3.4) (Figure 1), despite an increase from referral to medical evaluation. In sub-stage analysis, Black race was associated with decreased rate of and time delay in progression from medical evaluation to committee review (aHR: 0.409 [0.168, 0.994]). **Conclusion:** Black LDLT candidates comprised 6.4% of our institution's initial referrals, and only smaller 3.4% of LDLT final donors. In regression analysis, Black race was associated with the candidacy process stalling after medical evaluation, prior to committee review.



Disclosures: Melanie Zheng: Nothing to Disclose, Jessica Lin: Nothing to Disclose, Alexandra Strauss: Nothing to Disclose, Elizabeth King: Nothing to Disclose, shane ottmann: Nothing to Disclose, Benjamin Philosophe:

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Nothing to Disclose, Ahmet Gurakar: Grant/Research Support relationship with DURECT; Has ended; Advisor relationship with Orphalan; Has ended

2199 | HEALTH DISPARITIES IN AUTOIMMUNE HEPATITIS

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Background: Autoimmune hepatitis (AIH) is an uncommon, chronic inflammatory condition of the liver. Racial and ethnic disparities have been uncovered within patients with AIH, including higher prevalence and worse outcomes in Black and Latinx patients. However, the pathogenesis of AIH remains unknown, and it is important to identify risk factors for both disease onset and progression. Social determinants of health (SDOH) contribute to many health inequities, but they have not been studied in patients with AIH. Thus, this cross-sectional study seeks to analyze the associations between SDOH and AIH to identify risk factors and further health equity in patients with AIH. **Methods:** Participants with AIH and without AIH (healthy controls and patients with non-AIH liver disease) completed an SDOH questionnaire comprised of validated instruments from the PhenX tool kit and other studies. SDOH variables included education, financial security, built environment, healthcare access, and social/community support. Participants were recruited from 1) the POSULD cohort, which comprised of participants from a local county hospital and tertiary care center, and 2) online via the Autoimmune Hepatitis Association (AIHA) and a research website. A diagnosis of AIH was analyzed in a multivariable model including SDOH (modeled with a composite score and individual domains). AIH disease severity, which was measured as cirrhosis at time of survey, was analyzed in a multivariable model including SDOH domains. **Results:** 136 AIH participants and 34 non-AIH participants were included in the study. In both multivariate models, there was no significant association between AIH diagnosis and SDOH. However, being male (OR 0.108, 95% CI: 0.024 – 0.427), non-Hispanic Asian (OR 0.073, 95% CI: 0.007 – 0.615), or in the POSULD cohort (OR: 0.118, 95% CI: 0.037 – 0.357) was significantly associated with lower odds of AIH diagnosis. Those with higher number of major experiences of discrimination (OR 2.19, 95% CI: 1.185 – 3.211) and lower levels of education: high school (OR 10.049, 95% CI: 10.049, 1.633 – 90.691) and associate/technical/trade school (OR: 9.33, 95% CI: 1.203 – 99.156), had significantly higher odds of having a diagnosis of cirrhosis. **Conclusion:** SDOH was not found to be a significant risk factor in having an AIH diagnosis. However, patients with AIH experiencing major discrimination and lower education levels had significantly higher odds of cirrhosis. We hypothesize that lower education levels may be related to lower health literacy or limited economic opportunity. Overall, given the limited sample size, further investigation is needed on the association between SDOH and a diagnosis of AIH. Education level and discrimination should also be further studied as possible risk factors for worse disease severity and potentially as targets for future interventions to reduce severity and disparity in patients with AIH.

SDOH variables in AIH patients with and without cirrhosis

SDOH Variable	Cirrhosis (n = 35)	No cirrhosis (n = 88)
Highest Education Level		
- Less than High School	*4 (12%)*	*4 (5%)*
- High School	*8 (23%)*	*11 (13%)*
- Associate Degree/ Technical/Trade School	*6 (17%)*	*8 (9%)*
- College	*12 (34%)*	*39 (44%)*
- Graduate School or above	*5 (14%)*	*26 (30%)*
# of participants with unmet health needs	7 (20%)	8 (9%)
Average number of Household Exposures	0.25	0.22
Average number of major discrimination experienced	1.34	0.63
# of participants with low job security	3 (9%)	8 (9%)

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Disclosures: Irina Dan Adao: Nothing to Disclose, Gerardo Rubio Monroy: Nothing to Disclose, Melawit Tekeste: Nothing to Disclose, Isaac Avila-Vargas: Nothing to Disclose, Franziska Bertram: Nothing to Disclose, Jennifer Price: Nothing to Disclose, Emily Perito: Mirum: Consultant, Ultragenyx: Consultant, BridgeBio: Consultant, Amagma: Consultant, Mirum: Grant/Research Support, Albireo: Grant/Research Support, Gilead: Grant/Research Support, Dicerna: Grant/Research Support, John Sauceda: Nothing to Disclose, Marcial Sebode: Nothing to Disclose, Craig Lammert: Nothing to Disclose, Michele Tana: Nothing to Disclose

2200 | SEVEN-YEAR FOLLOW-UP OF A PREDOMINANTLY HISPANIC PATIENTS WITH SIGNIFICANT STEATOSIS AT A PRIMARY CARE CLINIC: UPDATE ON THE SOUTH BAY COHORT

Nabil Baig[1] Anna Hefner[2] Julian Diaz-Moreno[2] Fatma Barakat[3] Jose Santos[1] Cristobal Soto[1] Deanna Oliver[1] Tarek Hassanein[2]

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Background: The prevalence of obesity and the metabolic syndrome continues to be on the rise in the US, especially in Hispanic patients. These are risk factors associated with increased risk for developing MASLD and progression to MASH. We previously reported on a fatty liver screening program we initiated in a primary care practice (PCP) in Southern California, amongst predominately Hispanic patients (South Bay Fatty Liver cohort). This is a 7-year report on the disposition of the patients who were at risk for developing MASLD. **Methods:** Between March, 2017 and June, 2017 958 adults (18 years and older) who had no known history of liver disease agreed to be screened for fatty liver. Screening included having an evaluable Fibroscan®, labs done, and medical history taken. Subsequent follow-up was done per standard of care in the PCP clinic independent of the screening program. **Results:** Of the 958 pts screening, only 80 (8.4%) patients continued to be seen by the PCP. This is a 47% drop compared to the number of patients seen, by the PCP, for the 5-year follow-up. The primary reason for lack of follow-up is changing health insurance carrier. The subjects of this analysis are 80 pts who returned for a 7-year follow-up. 68.8% were females; mean age was 54.0 ±11.8 years and 87.5% Hispanic. Refer to table for the 7-year change in BMI, and metabolic syndrome presentation. Liver-injury related lab results including ALT, AST, GGT, albumin as well as creatinine, and platelets remained stable and within normal range over the 7 years of follow-up. Similarly, the HgbA1c did not change in the 7 years (6.2% at baseline vs. 6.1% at year 7). However, there was significant increase (16.3% vs. 30%) in the patients classified as pre-diabetic (HgbA1c >6.4) from baseline to year 7, respectively ($p<0.05$). **Conclusion:** In a 7-year follow-up span in a pre-dominantly Hispanic community PCP patient population, with no known history of fatty liver disease, 1) Only 9% of patients continued to be followed up regularly, 2) there was significant new onset in the metabolic dysfunction-associated risk factors, particularly Diabetes Mellitus and Hypertension, and 3) almost 50% were newly diagnosed with MASLD. Significant progression in the presentation of the metabolic dysfunction-associated risk factors including diagnosis of MASLD, was despite weight loss and improvement in BMI as well as stability in liver injury-related lab results over the 7 years. These findings continue to underscore the urgent need for exploring innovative measures to incentivize PCPs to routinely assess patients for metabolic dysfunction-associated risk factors. They also highlight the importance of community educational programs on early identification, management, and referral of patients at risk for developing MASLD.

Table		Baseline	7-year follow-up
# of patients		80	80
BMI	Normal (18.5 to <25)	7.4%	16.3%
	Overweight (25 to <30)	36.3%	32.5%
	Obese (>=30)	56.3%	51.2%
Metabolic dysfunction-associated diagnosis	Diabetes Mellitus Type 2	25%	50%
	Hypertension	41.3%	67.6%
	Hyperlipidemia	12.5%	30%
	MASLD	2.5%	51.5%

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Disclosures: Nabil Baig: Nothing to Disclose, Anna Hefner: Nothing to Disclose, Julian Diaz-Moreno: Nothing to Disclose, Fatma Barakat: Nothing to Disclose, Jose Santos: Nothing to Disclose, Cristobal Soto: Nothing to Disclose, Deanna Oliver: Nothing to Disclose, Tarek Hassanein: Nothing to Disclose

2201 | FOOD INSECURITY AND NEIGHBORHOOD DISPARITIES: CORRELATION WITH MASLD AND ALCOHOL-ASSOCIATED LIVER DISEASE RATES IN CHICAGO'S LIVER TRANSPLANT PATIENTS

Kashif Osmani[1] *Anna Li*[2] *Jennifer Wang*[1]

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Background: Chronic liver diseases like metabolic-associated steatotic liver disease (MASLD) and alcohol-associated liver disease (ALD) are increasingly a public health concern, particularly in minority populations. Food insecurity has been identified as a contributor to higher mortality rates and outpatient healthcare utilization among patients with MASLD. Additionally, a neighborhood's socioeconomic status plays a critical role in the health outcomes of residents. Individuals in deprived areas are less likely to be listed for liver transplantation (LT) and face higher risks of hepatic decompensation and mortality. However, data on these patients' outcome post-transplantation are sparse. Using real-world data from an urban academic center in Chicago, we investigated the impact of geographic disparities and food insecurity on the prevalence of MASLD and ALD among patients who underwent LT at our center. **Methods:** A retrospective cohort study was conducted on adult LT patients between August 2008 and August 2023. Patient data were collected through chart review. This study focused on a subset of 199 patients residing within the City of Chicago, as identified by ZIP codes. Food insecurity data was obtained from the Chicago Health Atlas, which included metrics on food access categorized by ZIP codes. Using QGIS, the distribution of MASLD and ALD cases by ZIP codes was mapped to visualize the geographic spread of liver disease cases throughout the city. By overlaying liver disease cases with food insecurity data in QGIS, areas with both high prevalence of liver diseases and food insecurity were identified. **Results:** The ZIP codes with the highest number of MASLD cases included 60623, 60632, and 60616, and with the highest number of ALD cases were 60623, 60609, 60629, 60651, and 60652. A geographic overlap of MASLD and ALD cases was observed and was concentrated in the South and West neighborhoods of Chicago. Food insecurity data indicated an average rate of food insecurity across Chicago of 16.4%, but in the aforementioned ZIP codes, the average rate was 22.5%, and as high as 39.3% in some neighborhoods. In contrast, many ZIP codes on the North and Northwest ZIP codes exhibited lower food insecurity rates of 10% to 14%, corresponding to fewer MASLD and ALD cases. **Conclusion:** These findings highlight a significant geographic correlation between high rates of liver disease and food insecurity, that persists even among patients receiving LT. Next steps will include investigating differences in post-LT outcomes based on food insecurity distribution to further understand the impact of socioeconomic factors on long-term health after LT.

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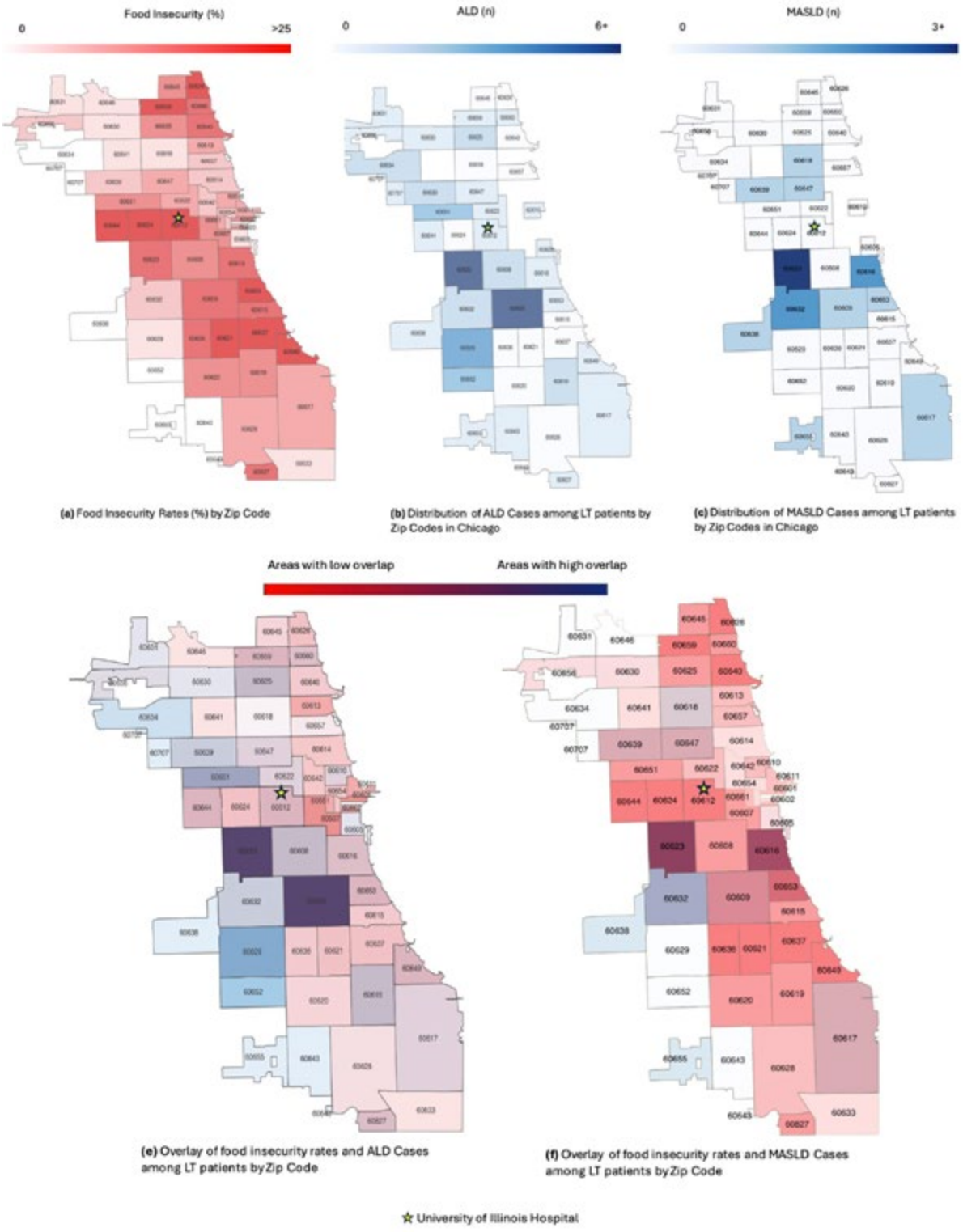

Disclosures: Kashif Osmani: Nothing to Disclose, Anna Li: Nothing to Disclose, Jennifer Wang: Nothing to Disclose

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2202 | EXPLORING MULTILEVEL RISK FACTORS FOR METABOLIC-DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD) IN A RACIALLY, ETHNICALLY, AND SOCIOECONOMICALLY DIVERSE COHORT

Janet Chu[1] Mindy Derouen[1] Alison Canchola[1] Aly Cortella[1] Pushkar Inamdar[1] Yihe Daida[2] Scarlett Gomez[1] Hashem El-Serag[3] Salma Shariff-Marco[1]

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Background: MASLD is the leading cause of chronic liver disease and a growing risk factor for liver cancer. Few studies have examined MASLD risk factors in racially, ethnically, and socioeconomically diverse populations, even though racial and ethnic minoritized groups and those with low socioeconomic status (SES) bear a disproportionate burden of diabetes and obesity, which are highly associated with MASLD. Elucidating multilevel risk factors can help identify targets for intervention for groups for which they are most relevant. **Methods:** We included adults 18+ years old with at least one in-person visit between 1/1/2000-12/31/2017 to Kaiser Permanente Hawai'i. From the electronic medical record we extracted sociodemographic characteristics; vital signs; diagnostic codes; medication prescriptions; and lab results. Census tract level neighborhood SES (nSES) was derived from census data. Incident MASLD was defined using ICD-codes (ICD-9: 571.8, 571.8; ICD-10: K75.81, K76.0, K75.8). We excluded those with MASLD at baseline (the first year after the first in-person visit). Patients were censored at diagnosis of MASLD, death, or end of the study (12/31/2017). We used sequential multivariable Cox proportional hazards regression with age as the timescale to explore factors associated with incident MASLD (outcome); models were adjusted for baseline year and number of encounters. Model 1 included sociodemographic variables; in Model 2 we added clinical characteristics to statistically significant variables in Model 1; in Model 3 we added nSES to statistically significant variables in Model 2. **Results:** Of 439,709 patients, 8,339 had incident MASLD during 18,350 person-years of follow up. In Model 1, males had higher risk of MASLD than females. Compared to non-Hispanic White individuals, those who identified as Chinese, Japanese, Korean, multiracial, and Hispanic had higher risk, and Native Hawaiian, Pacific Islander, and Black individuals had lower risk. BMI in the overweight and obese range, limited English proficiency, and being an ever smoker were associated with increased MASLD risk. In Model 2, elevated triglycerides, low HDL, and diabetes was associated with higher MASLD risk. In Model 3, nSES was not statistically significantly associated with MASLD risk when added to sociodemographic and clinical factors. **Conclusion:** Among this diverse cohort, in addition to known MASLD risk factors, including overweight and obese BMI, high triglycerides, low HDL, and diabetes, limited English proficiency was also associated with higher MASLD risk. Our study provided critical disaggregated data for ethnic groups that are typically understudied, and disparities in MASLD incidence persist despite adjusting for sociodemographic, clinical, and neighborhood factors. Other social and built neighborhood attributes such as food environment and access to parks will be included in future analyses.

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Table 1. Sequential multivariable Cox proportional hazard regression for incident MASLD* diagnosis using an electronic medical record-based cohort at a large, integrated healthcare system in Hawaii from 2000-2017

	Model 1: Sociodemographic + behavioral		Model 2: Clinical		Model 3: Neighborhood	
	HR	95% CI	HR	95% CI	HR	95% CI
Male (ref. Female)	**1.22**	**1.15-1.29**	1.06	1.00-1.12	**1.08**	**1.01-1.15**
Race/ethnicity detailed (ref. NH White)						
American Indian/Alaska Native	1.13	0.93-1.38	1.04	0.85-1.26	1.03	0.83-1.28
Native Hawaiian	**0.78**	**0.70-0.86**	**0.71**	**0.63-0.78**	**0.70**	**0.61-0.80**
Pacific Islander	**0.74**	**0.66-0.85**	**0.67**	**0.59-0.76**	**0.67**	**0.58-0.78**
Black	**0.54**	**0.40-0.75**	**0.51**	**0.37-0.71**	**0.51**	**0.36-0.72**
Asian Indian	1.32	0.68-2.55	1.13	0.59-2.19	1.22	0.63-2.38
Chinese	**1.42**	**1.21-1.66**	**1.24**	**1.06-1.45**	**1.27**	**1.08-1.49**
Japanese	**1.36**	**1.23-1.51**	**1.25**	**1.13-1.39**	**1.29**	**1.16-1.44**
Filipino	1.01	0.91-1.11	**0.87**	**0.79-0.96**	**0.87**	**0.78-0.97**
Korean	**1.83**	**1.49-2.26**	**1.65**	**1.34-2.04**	**1.72**	**1.40-2.12**
Vietnamese	1.26	0.84-1.88	1.04	0.69-1.55	1.12	0.75-1.66
Other Asian ethnicity	1.11	0.91-1.37	1.04	0.84-1.28	1.02	0.81-1.28
Multiple Asian ethnicities	1.01	0.85-1.18	0.92	0.79-1.09	0.96	0.81-1.15
Multiple races/ethnicities	**1.20**	**1.08-1.33**	1.10	0.99-1.22	1.10	0.99-1.23
NH Other	1.04	0.83-1.29	1.00	0.80-1.24	1.01	0.79-1.28
Hispanic	**1.46**	**1.27-1.68**	**1.32**	**1.15-1.52**	**1.32**	**1.14-1.58**
Unknown	0.99	0.85-1.15	0.97	0.84-1.13	0.96	0.83-1.11
BMI category (ref. Normal)†						
Overweight	**2.08**	**1.90-2.28**	**1.82**	**1.67-1.99**	**1.82**	**1.64-2.01**
Obese	**2.63**	**2.34-2.96**	**1.99**	**1.77-2.24**	**2.06**	**1.81-2.36**
Limited English proficiency‡	**1.52**	**1.30-1.78**	**1.43**	**1.22-1.67**	**1.46**	**1.24-1.73**
Smoking status (ref. Never)						
Ever (Current or Former)	**1.13**	**1.07-1.19**	**1.08**	**1.02-1.14**	1.06	0.99-1.12
Hypertension§			0.89	0.78-1.01	--	--
Elevated triglycerides¶			**2.15**	**1.99-2.31**	**2.11**	**1.93-2.30**
Low HDL#			**1.57**	**1.47-1.68**	**1.58**	**1.47-1.70**
Diabetes mellitus**			**1.59**	**1.50-1.69**	**1.56**	**1.46-1.67**
nSES (ref. Q5 - High)††						
Q1 - Low					1.06	0.94-1.19
Q2					1.06	0.95-1.18
Q3					1.03	0.94-1.14
Q4					1.05	0.96-1.16

Bolded values denote statistical significance at p-value<0.05
Abbreviations: BMI=body mass index; CI=confidence interval; HDL=high-density lipoprotein; HR=Hazard Ratio; nSES=neighborhood socioeconomic status; Q=quintile; ref=referent group;
*MASLD diagnosis includes ICD codes: ICD-9: 571.8, 571.8; ICD-10: K75.81, K76.0, K75.8
†BMI categories: Underweight = BMI <18.5 for both Asians and non-Asians; Normal = BMI 18.5-24.9 for non-Asians and BMI 18.5-22.9 for Asians; Overweight = BMI 25-29.9 for non-Asians and 23-26.9 for Asians; Obese = BMI ≥30 for non-Asians and BMI ≥27 for Asian
‡Limited English Proficiency is defined as: 1) denoting a language preference other than English; or 2) needing an interpreter
§Hypertension is defined as 1) Systolic blood pressure ≥130 or diastolic blood pressure ≥85 on two separate occasions; or 2) 1 inpatient or 2 outpatient ICD code for hypertension (ICD-9 codes: 401, 402, 403, 404, 405, 796.2, 437.2, 362.11; ICD-10 codes: I10, I11, I12, I15, R03.3, I67.4, H35.03x)
¶Elevated triglycerides defined as 1) triglycerides ≥150; or 2) ICD code for elevated triglycerides (ICD-9 codes: 272.1, 272.2, 272.3, 272.4; ICD-10 codes: E78.1, E78.2, E78.3, E78.4x)
#Low HDL defined as: 1) HDL <50 for women or HDL <40 for men; 2) ICD code for reduced HDL (ICD- 9 code 272.5; ICD-10 code E78.6)
**Diabetes is defined as: 1) Fasting glucose ≥126; ICD code for diabetes (ICD-9 codes: 250.xx, 249.xx, V58.67, 357.2, 362.0x, 366.41; ICD-10 codes: E10.xxxx, E11.xxxx, E13.xxxx, E08.xxxx, E09.xxxx, Z79.4); or 3) had a prescription order for diabetic medication.
††Neighborhood socioeconomic status (nSES) was derived using principal components analysis with census-tract level data. Categorized based on state-wide quintiles. Q1= low nSES, Q5=high nSES.

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2203 | ALCOHOL RELAPSE AFTER LIVER TRANSPLANTATION AMONG PATIENTS WITH ALCOHOL-ASSOCIATED LIVER DISEASE IN THE MOUNTAIN WEST

Rebecca Kim[1] April Ballantyne[1] Charles McDaniel[1] Blessing Ofori-Atta[1] Michael Zimmerman[1] Talia Baker[1] Juan Gallegos-Orozco[1]

[1]University of Utah

Background: Alcohol-associated liver disease (ALD), with and without severe acute alcohol-associated hepatitis (sAH), is one of the most common indications for liver transplant (LT). To decrease the risk of relapse post-LT, effective alcohol use disorder (AUD) treatment is critical. University of Utah (UofU) performs LTs for patients with ALD throughout the Mountain West, a region where access to healthcare varies widely. We hypothesize that access to care influences post-LT relapse and aimed to identify the association between location and relapse. **Methods:** A retrospective cohort study was conducted of 144 patients who received a LT for sAH or ALD at UofU from 01/2016-08/2023. The primary predictor was location (patient's home zip code), and the primary outcome was relapse (within 3yrs post-LT). Additional variables were demographics, clinical history, MELD, SIPAT, pre-LT sobriety. Location was calculated by the straight-line distance between the centroid of each patient's zip code and the UofU zip code. Logistic regression models were fit to assess the association of location, sAH and other pre-LT factors with relapse. **Results:** Of the 144 patients, 37% were women, mean age 49yrs, 81% White, 10% Hispanic, 7% American Indian/Alaska Native, 10% had sAH. Length of abstinence pre-LT was: 27% <6mo, 24% >6mo-1yr, 49% >1yr. Mean distance to the UofU was 176 miles and 57% traveled from out-of-state. 20% had relapse post-LT. On univariable analysis, age and psychiatric diagnoses were associated with odds of relapse, 0.66 (p=0.04) and 2.95 (p=0.023), respectively. This remained true on multivariable analyses (see Table). There was no significant association between sAH, distance to LT center or in-state vs out-of-state with relapse. Secondary analyses were conducted to further compare in-state and out-of-state patients. In-state patients had lower MELD at LT (23 vs 31). While there were no differences in sAH or SIPAT score, there was a lower incidence of relapse within 1 year post-LT among in-state patients (7% vs 18%). This remained true after adjusting for age and psychiatric diagnoses; in-state residence was associated with 78% lower odds (aOR 0.22, 95% CI 0.05-0.77, p=0.03) of relapse within 1 year post-LT. **Conclusion:** In this cohort, younger age and psychiatric diagnoses were associated with increased risk for alcohol relapse within 3yrs post-LT. State residence was associated with relapse within 1yr post-LT, with 18% relapse among out-of-state LT recipients. Access to LT for people located far from transplant centers is critical. Therefore, further studies evaluating inequitable access to care post-LT, specifically psychiatric and AUD treatment, are necessary to improve outcomes.

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Tables. A) Univariable and Multivariable Analysis for Alcohol Relapse within 3 years Post-Liver Transplant

Characteristic	Unadjusted OR (95% CI)	*p*-value	Adjusted OR (95% CI)	*p*-value	Adjusted OR (95% CI)	*p*-value
sAH vs Cirrhosis						
sAH	1.13(0.24, 3.96)	0.85	0.83(0.17, 3.17)	0.80	-	-
EtOH cirrhosis	-Reference-	-	-Reference-		-	-
In-State vs Out-State						
In-State	0.70(0.29, 1.62)	0.41	-	-	0.60(0.24, 1.45)	0.27
Out-State	-Reference-	-	-	-	-Reference-	-
Distance to UofU†	1.00(1.00, 1.01)	0.72	-	-	-	-
Age at transplant*	0.66(0.43, 0.98)	0.040	0.69(0.45, 1.05)	0.09	0.70(0.45, 1.06)	0.09
Sex						
Male	-Reference-	-	-	-	-	-
Female	0.93(0.38, 2.17)	0.87	-	-	-	-
BMI at transplant	1.04(0.94, 1.14)	0.46	-	-	-	-
Distance to PCP†	1.00(0.99, 1.00)	0.88	-	-	-	-
HCC						
No	-Reference-	-	-	-	-	-
Yes	0.48(0.07, 1.82)	0.34	-	-	-	-
Psychiatry diagnosis						
No	-Reference-	-	-Reference-		-Reference-	
Yes	2.95(1.21, 7.98)	0.023	2.63(1.06, 7.19)	0.045	2.80(1.12, 7.76)	0.035

B) Univariable and Multivariable Analyses for Relapse 1 year Post-Liver Transplant

Characteristic	Unadjusted OR (95% CI)	*p*-value	Adjusted OR (95% CI)	*p*-value	Adjusted OR (95% CI)	*p*-value
sAH vs Cirrhosis						
sAH	2.08(0.43, 7.76)	0.31	-	-	-	-
EtOH cirrhosis	-Reference-	-	-	-	-	-
In-State vs Out-State						
In-State	0.35(0.09, 1.06)	0.08	0.22(0.05, 0.77)	0.027	-	-
Out-State	-Reference-	-	-Reference-	-	-	-
Distance to UofU†	1.01(1.00, 1.02)	0.011	-	-	1.01(1.00, 1.02)	0.016
Age at transplant*	0.42(0.23, 0.71)	0.002	0.37(0.18, 0.68)	0.003	0.41(0.21, 0.75)	0.006
Sex						
Male	-Reference-	-	-	-	-	-
Female	1.05(0.34, 3.05)	0.93	-	-	-	-
BMI at transplant	1.04(0.91, 1.18)	0.59	-	-	-	-
Distance to PCP†	1.00(0.99, 1.01)	0.39	-	-	-	-
Psychiatry diagnosis						
No	-Reference-	-	-Reference-		-Reference-	
Yes	2.69(0.88, 10.09)	0.10	2.29(0.68, 9.12)	0.20	2.12(0.63, 8.43)	0.24

†2-mile increment.
*10-year increment

Disclosures: Rebecca Kim: Nothing to Disclose, April Ballantyne: Nothing to Disclose, Charles McDaniel: Nothing to Disclose, Blessing Ofori-Atta: Nothing to Disclose, Michael Zimmerman: Nothing to Disclose, Talia Baker: Nothing to Disclose, Juan Gallegos-Orozco: Gilead: Independent Contractor, Hanmi: Independent Contractor, Intercept: Independent Contractor, Durect: Independent Contractor, Mallinckrodt: Independent Contractor, UltraGenyx: Independent Contractor, Inventiva: Independent Contractor, Mirum: Independent Contractor

2204 | TEMPORAL TRENDS IN LIVER DISEASES IN PREGNANCY: DATA FROM A TERTIARY CARE CENTER

Monika Sarkar[1] *Seth Bokser*[1] *Roxanna Irani*[1] *Jasmine Gamez*[1] *Cynthia Fenton*[1]

[1]*University of California, San Francisco*

Background: The prevalence of chronic liver disease in reproductive-aged patients is rising, largely due to the rise of alcohol-related liver disease (ARLD) and metabolic dysfunction-associated steatotic liver disease (MASLD). However, prevalence data for acute and chronic liver diseases in pregnancy, and pregnancy-specific liver diseases are lacking. **Methods:** In this retrospective study we leveraged our center's electronic medical record to identify pregnancies with concurrent liver conditions from 1/1/2014 to 12/31/2023. Diagnoses were

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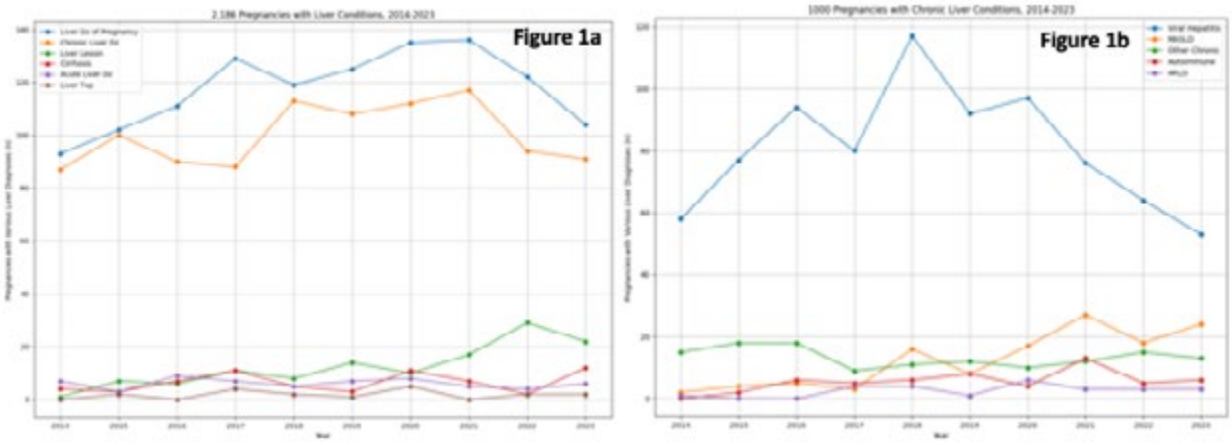
defined by ICD codes and diagnosis dates associated with hospitalizations, emergency department and ambulatory visits, medical history, and problem lists. Acute liver conditions included entities such as drug toxicity and acute viral hepatitides; chronic conditions included MASLD, ARLD, hepatitis B (HBV), hepatitis C (HCV), autoimmune (autoimmune hepatitis, primary sclerosing cholangitis, and primary biliary cholangitis); and pregnancy-specific liver diseases included HELLP syndrome, intrahepatic cholestasis of pregnancy, and acute fatty liver of pregnancy. We also report prior liver transplant and liver lesions in pregnancy. Liver conditions were not mutually exclusive. **Results:** From 2014-2023 we identified 2,186 pregnancies affected by liver disease, representing 2.8% of all pregnancies at our center. The racial/ethnic distribution was 34.8% White, 27.1% Asian, 4.7% Black, and 26.8% Hispanic; median age was 34 yrs (IQR 30-37). Liver conditions included 61 acute liver diseases (2.8%), 1000 chronic liver diseases (45.7%) of which 65 (6.5%) had cirrhosis, and 1176 (53.8%) were pregnancy-specific liver diseases. Chronic and pregnancy-specific liver diseases increased from 2014-2021, with subsequent decline in 2022-2023 (Figure). Among chronic liver diseases, MASLD increased over time, while viral hepatitis declined. Pregnancies with cirrhosis increased three-fold from 2014 to 2023; 70% were coded as cryptogenic/unspecified cirrhosis, 16.2% as ARLD, 6.3% HBV, and 5% HCV. **Conclusion:** In this large cohort of liver disease in pregnancy, we demonstrate rising rates of MASLD and cirrhosis, and decline in viral hepatitis. Over half of cases were pregnancy-specific liver diseases. These data highlight the epidemiologic and clinical relevance of liver disease in pregnancy and the importance of pregnancy counseling in the rising number of reproductive-aged patients with chronic liver disease.



Disclosures: Monika Sarkar: GSK: Grant/Research Support, Zydus Pharmaceuticals: Grant/Research Support, Gilead Sciences: Grant/Research Support, Seth Bokser: Nothing to Disclose, Roxanna Irani: Nothing to Disclose, Jasmine Gamez: Nothing to Disclose, Cynthia Fenton: Nothing to Disclose

2205 | RACIAL AND ETHNIC DIFFERENCES IN SELF-REPORTED DIETARY AND HEALTH BEHAVIORS IN A LARGE COHORT OF PATIENTS WITH CIRRHOSIS

Nicole Rich[1] Jennifer Kramer[2] Howard (Tzu-Hao) Lee[2] Donna Smith[2] Lisa Quirk[1] Juana Campos[3] yan Liu[2] Jahna Anyanwu[2] Donna White[2] yumei Cao[4] Aaron Loewy[2] Hadley McGhee[1] Noa Kopplin[1] Darine Daher[1] Karim Seif El Dahan[1] Julia Terrell[1] Erik Juarez Farfan[1] Meena Tadros[1] Riya Malhotra[1] David Ramsey[4] Fasiha Kanwal[4] Amit Singal[1]

[1]UT Southwestern Medical Center, [2]Baylor College of Medicine, [3]Michael E. DeBakey VA Medical Center, Houston, TX, [4]Michael E. DeBakey VA Medical Center

Background: Dietary behaviors are essential components of health interventions; however, 1 in 4 U.S. patients with cirrhosis experience food insecurity, with highest rates among Black, Hispanic, and low-income individuals. We aimed to describe dietary patterns in a large, racially and ethnically diverse cohort of patients with cirrhosis. **Methods:** Adult patients with confirmed cirrhosis at four large U.S. health systems were approached to complete a telephone survey that included the Latino Dietary Behaviors Questionnaire (LDBQ), a validated, 13-item measure that provides a general index of healthy eating and assesses eating behaviors across several domains. We used ANOVA to compare continuous LDBQ scores and the Chi-square test to compare categorical responses by race and ethnicity. **Results:** Among 5,853 eligible patients, 1037 (17.7%) completed the survey (41.6% White,

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21.4% Black, 28.9% Hispanic; 74.0% men). Nearly half of the cohort reported being low-income (49.3% with household income <$50K/year), with low educational attainment (43.5% high school or less). Overall, LDBQ scores were higher (i.e., healthier eating behavior) among Hispanic (mean, 24.5, SD 6.4) compared to Black (mean 22.7, SD 6.4) and White (mean 23.4, SD 6.7) patients (p=0.003). Fried food consumption was highest among Hispanic patients (p=0.04), whereas consumption of regular soft drinks and juice (p<0.001), diet soft drinks (p=0.002), sweets with artificial sweeteners (p=0.02), and white rice or white bread (p=0.02) were highest among White patients. A higher proportion of White patients reported eating at restaurants (including fast food) more than twice monthly compared to Black and Hispanic patients (57.8% vs. 46.1% and 51.2%, respectively; p=0.03). Fewer Black patients reported changing foods to make them healthier (54.3% vs. 59.5% White and 59.8% Hispanic; p=0.009) or controlling portions most of the time (50.9% vs. 61.8% for White, 61.7% for Hispanic patients; p<0.001). While alcohol use was prevalent in over three-fourths of the cohort, fewer Hispanic patients reported current or former alcohol use versus White and Black patients (65.8% vs. 79.8% and 80.2%, respectively; p<0.001). **Conclusion:** There are racial and ethnic differences in self-reported dietary and health behaviors among patients with cirrhosis. Identifying specific dietary behaviors can help modify contributors to cirrhosis outcomes by guiding targeted, culturally conscious interventions.

Disclosures: Nicole Rich: Advisor relationship with Exelixis; Has not ended; Advisor relationship with AstraZeneca; Has not ended; Consulting relationship with Genentech; Has not ended; Advisor relationship with Eisai; Has not ended, Jennifer Kramer: Nothing to Disclose, Howard (Tzu-Hao) Lee: Nothing to Disclose, Donna Smith: Nothing to Disclose, Lisa Quirk: Nothing to Disclose, Juana Campos: Nothing to Disclose, yan Liu: Nothing to Disclose, Jahna Anyanwu: Nothing to Disclose, Donna White: Nothing to Disclose, yumei Cao: Nothing to Disclose, Aaron Loewy: Nothing to Disclose, Hadley McGhee: Nothing to Disclose, Noa Kopplin: Nothing to Disclose, Darine Daher: Nothing to Disclose, Karim Seif El Dahan: Nothing to Disclose, Julia Terrell: Nothing to Disclose, Erik Juarez Farfan: Nothing to Disclose, Meena Tadros: Nothing to Disclose, Riya Malhotra: Nothing to Disclose, David Ramsey: Nothing to Disclose, Fasiha Kanwal: Nothing to Disclose, Amit Singal: Consultant relationship with AstraZeneca; Has not ended; Consultant relationship with Sirtex; Has not ended; Consultant relationship with Boston Scientific; Has not ended; Consultant relationship with Bayer; Has not ended; Consultant relationship with Eisai; Has not ended; Consultant relationship with FujiFilm Medical Sciences; Has not ended; Consultant relationship with Elevar; Has not ended; Consultant relationship with Exact Sciences; Has not ended; Consultant relationship with Glycotest; Has not ended; Consultant relationship with Exelixis; Has not ended; Consultant relationship with Merck; Has not ended; Consultant relationship with Genentech; Has not ended; Consultant relationship with HistoSonics; Has not ended

2206 | CHARACTERIZING NON-MEDICAL REFERRAL AND EVALUATION DROP-OFFS IN ADULT LIVER TRANSPLANTATION: A CALIFORNIA LIVER NETWORK STUDY

Shayana Seneviratne[1] Mark Wang[1] Mignote Yilma[2] Ashley Jowell[3] Allison Kwong[4] Jasleen Singh[5] Steven Wisel[6] Hirsh Trivedi[6] Justin Steggerda[6] Alexander Kuo[6] Aarshi Vipani[6] Tiffany Lim[6] Michie Adjei[6] Lana Bridi[7] Veeral Ajmera[7] Monica Tincopa[7] Irine Vodkin[7] Chris Freise[2] Ryutaro Hirose[2] Neil Mehta[2] Kali Zhou[1]

[1]University of Southern California, [2]University of California, San Francisco, [3]Duke University Medical Center, [4]Stanford University Medical Center, [5]UCLA, [6]Cedars-Sinai Medical Center, [7]University of California, San Diego

Background: Sociodemographic disparities in adult liver transplantation (LT) waitlist drop-offs are well-documented, but drop-offs between referral and waitlisting are less understood. This study examines the frequency and predictors of patient drop-offs–with a focus on non-medical reasons–at two key time points: 1) at referral before evaluation and 2) during the evaluation process. **Methods:** The California Liver Network (CLN) is a retrospective cohort of adults referred to six transplant centers for LT between 2018-2020. Age, sex, and insurance were available for most referred patients; additional demographic, psychosocial, and clinical factors were obtained for evaluated patients. Drop-off reasons were categorized into four groups: non-medical, medical, too early, and too sick/died. Multivariable logistic regression models compared each referral and evaluation drop-off category to patients that were evaluated and listed, respectively. **Results:** Among 6856 patients referred for LT in the CLN, 28.2% were not evaluated (ranging 11.8-47.5% by center) and 47.3% of evaluated were declined for listing. Non-medical reasons accounted for the highest frequency of drop-offs at both referral (non-medical: 45.6%; medical: 13.7%; too early: 15.6%; death: 10.8%) and evaluation (33.4%; 19.8%; 22.3%; 18.4%) – see Figure for detailed reasons. There was significant center-level variation in drop-off frequencies for all models. Insurance was the only other significant predictor of referral drop-offs (non-medical higher for Medicaid and

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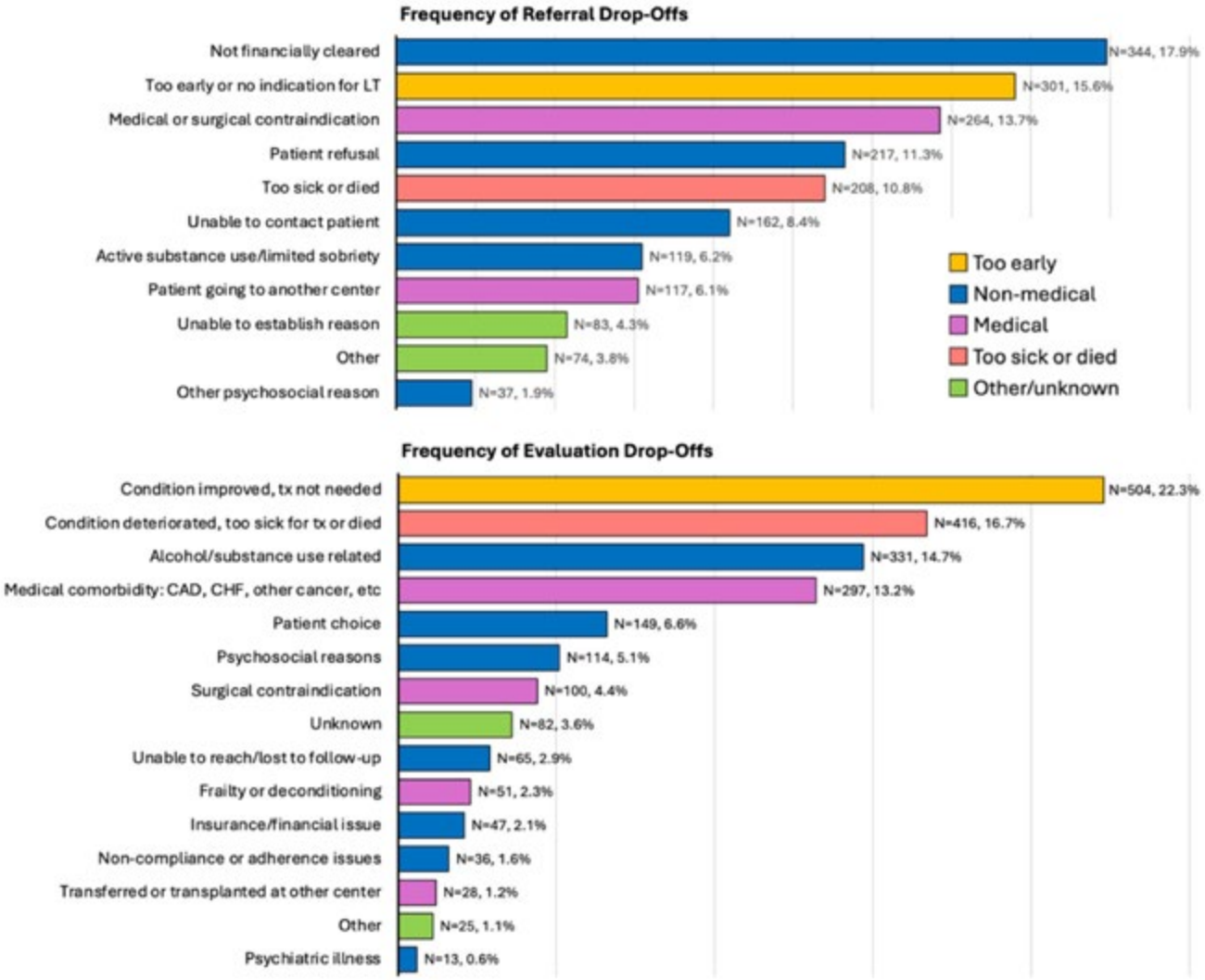
Medicare vs private). Among evaluated, Medicaid (vs private) insured had higher odds of non-medical (OR=2.31, p<0.001) and medical drop-offs (OR=2.16, p<0.001). Sex and racial/ethnic differences in evaluation drop-offs were largely absent. Unmarried patients had higher odds of non-medical drop-offs (OR=1.67, p<0.001) and death (OR=1.54, p=0.002). Those without social support had more (OR=4.55, p<0.001) while foreign-born had fewer non-medical drop-offs (OR=0.63, p=0.002). Alcohol etiology (vs viral) had higher odds of non-medical drop-offs (OR=1.50, p=0.02) while MASH had lower odds (OR=0.29, p<0.001). **Conclusion:** In this well-characterized multi-center referral cohort, nearly half of non-evaluated and one-third of listing declines were for non-medical reasons, highlighting the substantial impact of social vulnerability on early LT care cascade drop-offs. Financial navigation and social support resources may improve LT access and equity.



Disclosures: Shayana Seneviratne: Nothing to Disclose, Mark Wang: Nothing to Disclose, Mignote Yilma: Nothing to Disclose, Ashley Jowell: Nothing to Disclose, Allison Kwong: Nothing to Disclose, Jasleen Singh: Nothing to Disclose, Steven Wisel: Nothing to Disclose, Hirsh Trivedi: Nothing to Disclose, Justin Steggerda: Nothing to Disclose, Alexander Kuo: Nothing to Disclose, Aarshi Vipani: Nothing to Disclose, Tiffany Lim: Nothing to Disclose, Michie Adjei: Nothing to Disclose, Lana Bridi: Nothing to Disclose, Veeral Ajmera: Nothing to Disclose, Monica Tincopa: Nothing to Disclose, Irine Vodkin: Nothing to Disclose, Chris Freise: Nothing to Disclose, Ryutaro Hirose: Nothing to Disclose, Neil Mehta: Merck: Consultant, FujiFilm WAKO: Consultant, Kali Zhou: Nothing to Disclose

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2207 | RACIAL AND ETHNIC DISPARITIES IN BARRIERS TO CARE, SOCIAL SUPPORT AND HOUSING STABILITY IN A PROSPECTIVE COHORT OF PATIENTS WITH CIRRHOSIS

Nicole Rich[1] Jennifer Kramer[2] Howard (Tzu-Hao) Lee[3] Juana Campos[3] Lisa Quirk[1] Donna Smith[3] Yan Liu[3] Jahna Anyanwu[3] Donna White[3] yumei Cao[2] Aaron Loewy[3] Hadley McGhee[1] Noa Kopplin[1] Darine Daher[1] Karim Seif El Dahan[1] Julia Terrell[1] Riya Malhotra[1] Meena Tadros[1] Erik Juarez Farfan[1] David Ramsey[2] Amit Singal[1] Fasiha Kanwal[2]

[1]UT Southwestern Medical Center, [2]Michael E. DeBakey VA Medical Center, [3]Baylor College of Medicine

Background: Inequities in access to care and outcomes are well-documented among patients with cirrhosis, yet little is known about individual-level factors that may drive disparities. We aimed to assess racial and ethnic differences in patient-reported barriers to care, social support and housing stability among patients with cirrhosis. **Methods:** We enrolled adult patients diagnosed with cirrhosis at four large U.S. health systems to complete a telephone survey. Cirrhosis diagnosis was confirmed using manual review of the electronic medical records. Survey measures were selected using a health disparities conceptual model and included a 20-item questionnaire on barriers to care, as well as instruments assessing housing instability and social support. Chi-square tests were used to compare categorical data across racial and ethnic groups. **Results:** Among 5853 eligible patients, 1037 (17.7%) completed the survey (41.6% White, 21.4% Black, 28.9% Hispanic; 74.0% men). In total, 632 (60.9%) of 1037 patients reported at least one barrier to care. The most reported barriers were logistical issues: long driving time to clinic (36.0%), long wait time for appointments (32.4%), difficulty scheduling (28.3%), and difficulty reaching doctors between visits (27.0%). Specific barriers differed by race and ethnicity (Figure); Black and Hispanic patients more often reported difficulty with transportation (21.6% and 19.2% vs. 14.0% White; p=0.02), whereas White patients more commonly cited time driving to clinic (46.0% vs. 26% Black and 28.8% Hispanic; p=0.01) and lack of coordination between doctors (31.8% vs. 21.5% Black and 19.2% Hispanic, p=0.01). Disparities in social support and access to stable housing were also observed. Compared to White patients, fewer Black and Hispanic patients reported having someone to take them to the doctor (72.6% White vs 55.2% Black and 64.2% Hispanic; p=0.02), prepare meals (67.4% White vs 54.8% Black and 58.2% Hispanic; p=0.01) or help with daily chores (64.0% White, 52.6% Black and 56.3% Hispanic; p=0.01). Nearly 1 in 5 patients reported housing instability, with 34.5% of Black and 20.1% of Hispanic patients needing housing assistance compared to 9.1% of White patients (p<0.001). **Conclusion:** Significant disparities exist in barriers to care, social support and stable housing among patients with cirrhosis, which likely contribute to worse health outcomes among racial and ethnic minority groups. These barriers are tangible targets for intervention, and future studies are needed to determine their impact on cirrhosis outcomes.

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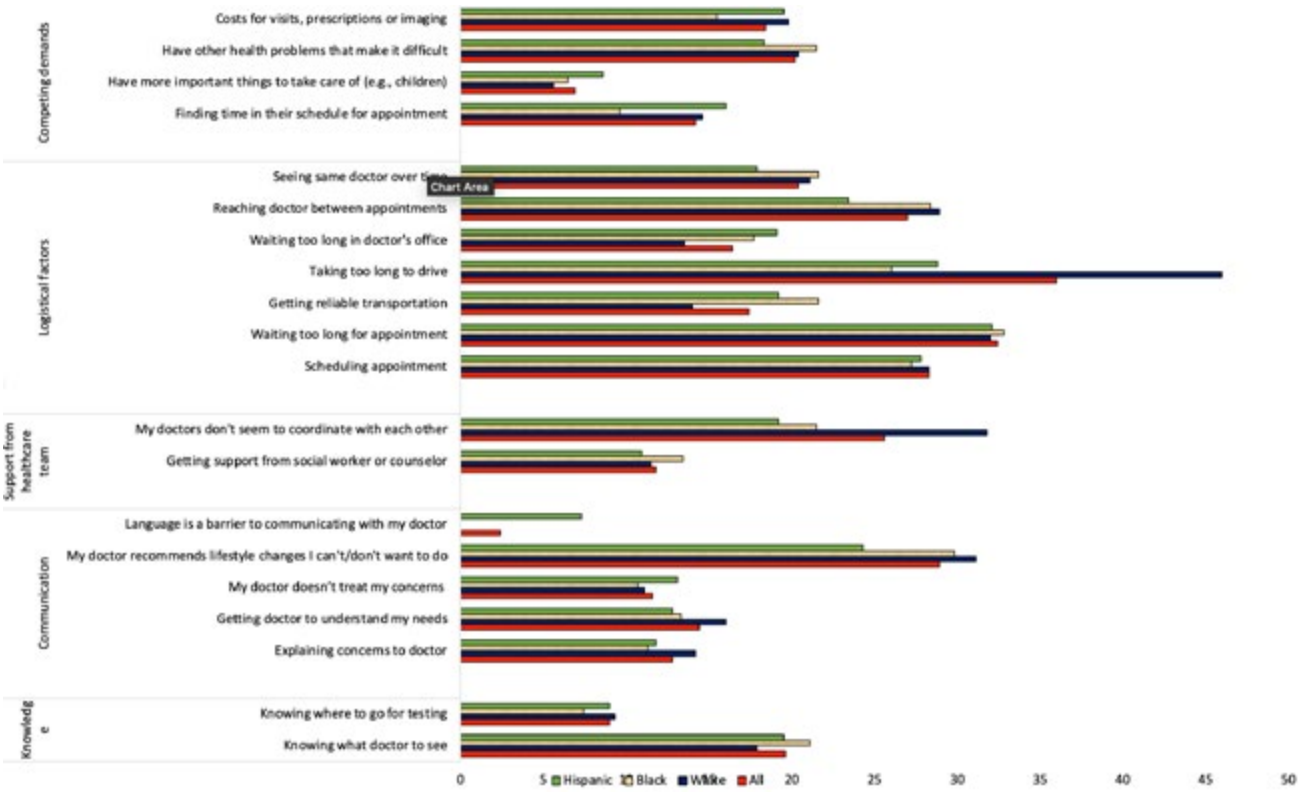

Disclosures: Nicole Rich: Advisor relationship with Exelixis; Has not ended; Advisor relationship with AstraZeneca; Has not ended; Consulting relationship with Genentech; Has not ended; Advisor relationship with Eisai; Has not ended, Jennifer Kramer: Nothing to Disclose, Howard (Tzu-Hao) Lee: Nothing to Disclose, Juana Campos: Nothing to Disclose, Lisa Quirk: Nothing to Disclose, Donna Smith: Nothing to Disclose, Yan Liu: Nothing to Disclose, Jahna Anyanwu: Nothing to Disclose, Donna White: Nothing to Disclose, yumei Cao: Nothing to Disclose, Aaron Loewy: Nothing to Disclose, Hadley McGhee: Nothing to Disclose, Noa Kopplin: Nothing to Disclose, Darine Daher: Nothing to Disclose, Karim Seif El Dahan: Nothing to Disclose, Julia Terrell: Nothing to Disclose, Riya Malhotra: Nothing to Disclose, Meena Tadros: Nothing to Disclose, Erik Juarez Farfan: Nothing to Disclose, David Ramsey: Nothing to Disclose, Amit Singal: Consultant relationship with AstraZeneca; Has not ended; Consultant relationship with Sirtex; Has not ended; Consultant relationship with Boston Scientific; Has not ended; Consultant relationship with Bayer; Has not ended; Consultant relationship with Eisai; Has not ended; Consultant relationship with FujiFilm Medical Sciences; Has not ended; Consultant relationship with Elevar; Has not ended; Consultant relationship with Exact Sciences; Has not ended; Consultant relationship with Glycotest; Has not ended; Consultant relationship with Exelixis; Has not ended; Consultant relationship with Merck; Has not ended; Consultant relationship with Genentech; Has not ended; Consultant relationship with HistoSonics; Has not ended, Fasiha Kanwal: Nothing to Disclose

2208 | HEPATIC OSTEODYSTROPHY IN CIRRHOSIS, ETIOLOGICAL SPECTRUM, AND OUTCOME

Babu Lal Meena[1] *Shiv Kumar Sarin*[1]

[1]*Institute of Liver and Biliary Sciences*

Background: Hepatic osteodystrophy is a frequent occurrence of cirrhosis. Its development depends on the nature and severity of the underlying liver disease. Whether decreased bone mineral density (BMD) is associated with clinical outcomes is not clear. **Methods:** This study aimed to investigate whether there is an association between the severity of reduced BMD and clinical outcomes in patients with different etiologies and gender. We analysed our electronic data and exhaustively evaluated clinical, biochemical, and bone density parameters in patients with cirrhosis. BMD was done using dual-energy X-ray Absorptiometry (DEXA) at the hip and spine. **Results:** We evaluated 415 cirrhosis patients who required hospitalization and had low bone mineral density,

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osteopenia(n=291, 70.2%), or osteoporosis(n=124, 29.8%), respectively. Alcoholic and non-alcoholic fatty liver disease(n=32, 25.8% each) related cirrhosis was the most common cause of osteoporosis, followed by autoimmune hepatitis (n=10, 8.06%), hepatitis B(n=12, 9.6%), PBC(N=6, 4.8%), and PSC(3.2%) respectively. Osteoporosis was significantly higher in the advanced CTP class: CTP-A(n=13, 8%), CTP-B(n=21, 12.9%), and CTP-C(n=90, 55.5%), respectively, p-0.003. Similarly, osteoporosis was higher in males(n=76) than in females(n=48). The mean t score in the osteoporosis group was -3.3(+/- 0.8), and the z score was -2.9(+/-0.4). The mean vitamin D level in the osteoporosis was 13ng/ml, ALP was 256IU/L, and GGT-267U/L, respectively. Osteoporosis was associated with higher mortality(4%) as compared to osteopenia (1.3%), p-0.05. However, there was no difference in the number and duration of hospitalizations. Univariate analysis showed that the occurrence of GI bleed, HE, ascites, ALBI score(Grade 2 or more), and presence of osteoporosis was predictive of poor survival. The multivariate model showed that the ALBI score(Grade 2 or more), presence of HE, and osteoporosis are independent predictors of mortality. ALBI score of more than -2.2 predicts mortality with 100% sensitivity and 90% specificity. **Conclusion:** Osteoporosis was predictive of poor survival in patients with cirrhosis. The multivariate model includes ALBI score, HE, and the presence of osteoporosis, which is associated with poor survival. Furthermore, prospective trials are to verify the study's findings.

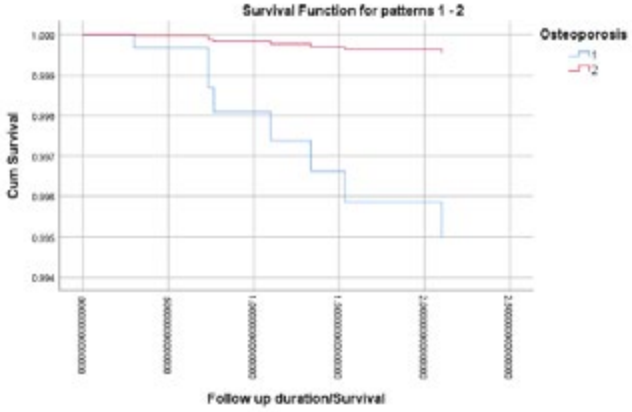

Figure 1a shows survival function in patients with osteoporosis with cirrhosis

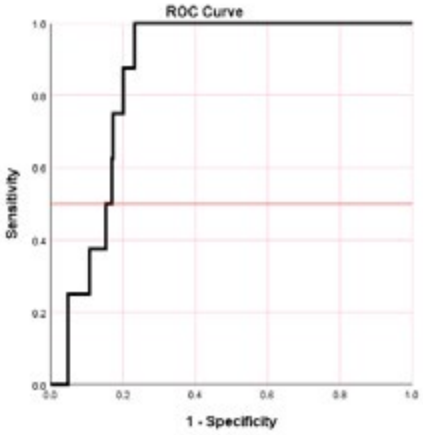

Figure 1b shows a prediction of survival function with ALBI score in patients with osteoporosis with cirrhosis

Area Under the Curve

Test Result Variable(s): ALBI

Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
.859	.027	.001	.805	.913

a. Under the nonparametric assumption

b. Null hypothesis: true area = 0.5

Disclosures: Babu Lal Meena: Nothing to Disclose, Shiv Kumar Sarin: Nothing to Disclose

2209 | ENROLLMENT OF MINORITY GROUPS IN CLINICAL TRIALS OF LIVER DISEASES IN THE US

Marcel Yibirin Wakim[1] Kadon Caskey[2] Gabriela Lombardo Pascarelli[3] George Cholankeril[4] Howard (Tzu-Hao) Lee[5]

[1]Boston Medical Center, [2]Department of Medicine. Baylor College of Medicine, Houston Tx., [3]Department of Medicine. Central University of Venezuela. Caracas, Venezuela., [4]Section of Gastroenterology and Hepatology, Department of Medicine, Baylor College of Medicine., [5]Baylor College of Medicine. Section of Gastroenterology and Hepatology, Department of Medicine, Bayl

Background: Liver diseases affect people from diverse backgrounds, with many disproportionally affecting minority populations. It is critical to document participants' demographic in clinical trials to ensure equitable enrollment. Our study aims to determine the documentation of racial, ethnic, sexual, and gender minorities (SGM) in clinical trials for liver diseases in the US. **Methods:** We systematically searched ClinicalTrials.gov using the predefined variable "digestive system disease" and included clinical trials conducted in the United States that enrolled adult patients, with start dates after 1/1/2013 and completion by 12/31/2022. We manually review the

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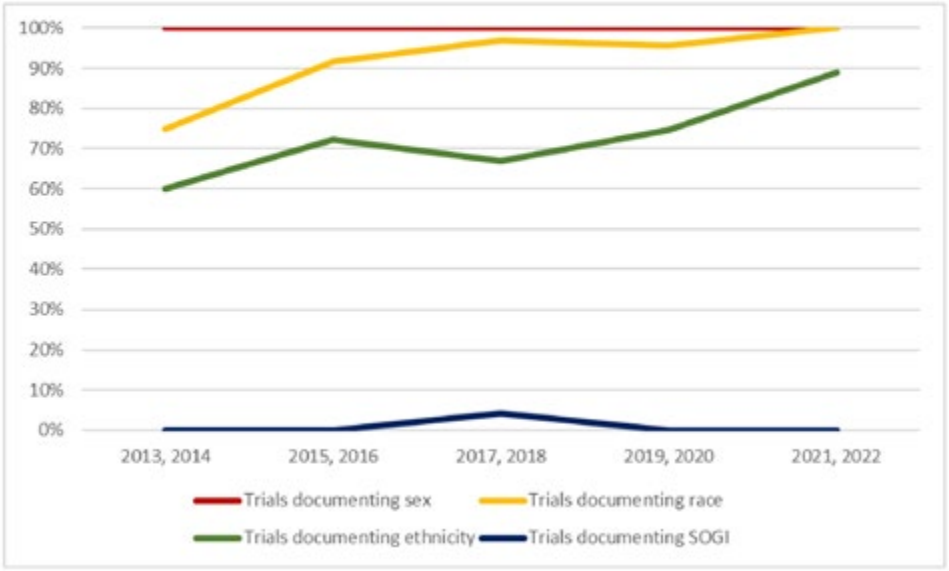
topics of these trials and include those related to liver diseases, including metabolic dysfunction-associated steatotic liver disease (MASLD), Alcoholic Liver Disease (ALD), Hepatitis C Virus (HCV), Hepatitis B Virus (HBV), and Hepatocellular Carcinoma (HCC). We examined each trial to see if participant demographic data, including race, ethnicity (reported as Hispanic or Latino), and sexual orientation and gender identity (SOGI, reported as lesbian, gay, bisexual, transgender, gender diverse, or non-binary) were collected. **Results:** We found 779 clinical trials related to gastrointestinal disorders, of which 265 were related to liver disorders (MASLD: 63; ALD: 8; HCV: 69; HBV: 23; HCC: 31 and Others: 71). All trials collected information about sex, and most (244 trials, 92%) collected racial data. However, only 184 trials (69%) collected ethnicity, and 4 trials (1.5%) collected SOGI. The documentation of race and ethnicity increased in more recent trials (Figure 1). SOGI data was only documented in four trials performed between 2017 and 2018. Three of the trials were associated with HCV treatment and one related to ALD. **Conclusion:** There have been improvements in documenting the race and ethnicity of the participants in clinical trials of liver diseases in the past decade. However, SOGI data collection is notably deficient, even in recent trials. Without collecting SOGI data, it is impossible to understand the enrollment status of SGM in clinical trials. This is critical given the growing number of SGM population in the US. Furthermore, some liver diseases, such as HBV and HCV, disproportionally affected the SGM population. Culturally sensitive strategies are urgently needed to improve the collection of SOGI data and to ensure equitable enrollment of SGM in clinical trials of liver diseases.

Figure 1: Documentation of Sex, Race, Ethnicity, and Sexual and Gender minorities (SGM) in clinical trials for liver disorders in the US from 2013-2022



Disclosures: Marcel Yibirin Wakim: Nothing to Disclose, Kadon Caskey: Nothing to Disclose, Gabriela Lombardo Pascarelli: Nothing to Disclose, George Cholankeril: Nothing to Disclose, Howard (Tzu-Hao) Lee: Nothing to Disclose

2210 | RACIAL DISPARITIES IN HEPATITIS C PREVALENCE, TREATMENT AND LONG-TERM OUTCOMES AMONG PATIENTS WITH CONCURRENT SUBSTANCE USE DISORDER ◆

Himsikhar Khataniar[1] *Muhammad Ali Butt*[1] *Balaji Jagdish*[1] *Michael Babich*[1]

[1]*Allegheny General Hospital*

Background: Hepatitis C (HCV) remains a critical public health issue in the USA, particularly among individuals with substance use disorder (SUD). The prevalence of HCV is notably high in this population due to practices such as needle sharing. Exploring HCV prevalence across various racial groups among SUD patients is crucial, as disparities in healthcare access and outcomes persist. **Methods:** We conducted a retrospective cohort study

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utilizing the TriNetX database to evaluate the prevalence of concurrent chronic Hepatitis C and substance use disorder among the three major racial groups in the USA—White, Black, and Asian—between 2010 and 2020. Patients in other racial groups were not accounted for. Racial disparities were evaluated in terms of those who qualified for Hepatitis C treatment and those who received treatment during the given period. Patients were identified as qualifying for treatment if they had Hepatitis C RNA and Hepatitis C antibody. Treatment was defined as receiving antiviral therapy or liver transplantation. Long-term outcomes of each cohort were compared, and 1:1 propensity score matching was performed for age, gender, race, comorbidities, liver-related characteristics, BMI, malignancies, and commonly used medications. The risk was expressed as adjusted odds ratios (aOR) with 95% confidence intervals (CI). **Results:** The study evaluated 175,246 individuals with chronic Hepatitis C and substance use disorder, categorized by race: Whites (111,374), Blacks (38,384), and Asians (1,496). Asians had the highest treatment eligibility (41.4%) but the lowest treatment receipt (19.3%) compared to Whites (20.5%) and Blacks (23.8%). Five-year outcomes varied significantly. Asians had the highest incidence of Hepatocellular Carcinoma (14.5%), significantly higher than Whites ($p=0.0009$) and Blacks ($p=0.01$). Cirrhosis was more common in Asians (36.9%) compared to Whites ($p=0.0015$) and Blacks ($p=0.002$). Whites had higher hepatic encephalopathy (1.9%) than Blacks ($p<0.0001$) and Asians ($p=0.002$). Variceal bleed rates were higher in Whites (0.92%) than Blacks ($p<0.0001$), with Asians having the lowest rates ($p=0.03$). Ascites prevalence was similar among Whites (9.73%) and Blacks ($p=0.01$), but higher in Asians (15.4%). Mortality was higher in Whites (13.4%) compared to Blacks ($p<0.0001$) and Asians ($p<0.0001$). Blacks had a higher incidence of lymphoma (2.83%) than Whites ($p=0.007$) and Asians (1.41%). End-Stage Renal Disease was most prevalent in Blacks (6.24%) compared to Whites ($p<0.0001$) and Asians (5.1%). **Conclusion:** To develop appropriate population-level interventions and address community needs, further investigation is needed. This includes examining the low treatment rate among the Asian American population, the higher mortality in the White population, and the higher rates of Hepatitis C-related lymphoma and ESRD in the Black population.

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Total population of Hepatits C + Substance use disorder	175,246					
*reference population from 2010-2020						
Racial Groups	**Qualified for treatment**	**Received treatment**				
Whites (111374)	33.023% (36753)	20.491% (22556)				
Blacks (38384)	33.963% (13015)	23.762% (9021)				
Asians (1496)	41.377% (619)	19.257% (285)				
5 year outcomes		**N**	**%**	**aOR**	**CI**	**P-Value**
HCC	Whites	1928	5.58	0.96	0.9-1.03	0.3
	Blacks	1989	5.75			
	Whites	157	10.5	0.69	0.5-0.86	**0.0009**
	Asian	217	14.5			
	Blacks	171	11.5	0.77	0.62-0.95	**0.01**
	Asians	214	14.4			
Cirrhosis	Whites	8984	26	1.04	1.01-1.08	**0.01**
	Blacks	8689	25.14			
	Whites	469	31.4	0.78	0.67-0.91	**0.0015**
	Asian	551	36.9			
	Blacks	470	31.6	0.79	0.68-0.92	**0.002**
	Asians	547	36.8			
Hepatic Encephalopathy	Whites	670	1.9	1.87	1.65-2.13	**<0.0001**
	Blacks	360	1.04			
	Whites	43	2.8	0.7	0.47-1.05	**0.08**
	Asian	60	4.02			
	Blacks	29	1.9	0.49	0.31-0.78	**0.002**
	Asians	57	3.8			
Variceal Bleed	Whites	318	0.92	1.53	1.28-1.82	**<0.0001**
	Blacks	208	0.6			
	Whites	26	1.7	0.96	0.55-1.65	0.88
	Asian	27	1.8			
	Blacks	13	0.8	0.49	0.25-0.96	**0.03**
	Asians	26	1.7			
Ascites	Whites	3362	9.73	1.06	1.01-1.11	**0.01**
	Blacks	3180	9.2			
	Whites	217	14.5	0.93	0.76-1.14	0.5
	Asian	230	15.4			
	Blacks	197	13.4	0.85	0.69-1.04	0.1
	Asians	226	10.9			
Mortality	Whites	4648	13.4	1.26	1.2-1.3	**<0.0001**
	Blacks	3795	10.9			
	Whites	237	15.9	1.74	1.39-2.17	**<0.0001**
	Asian	146	9.7			
	Blacks	214	14.4	1.56	1.2-1.9	**<0.0001**
	Asians	144	9.7			
Lymphoma	Whites	604	1.74	0.94	0.84-1.05	0.2
	Blacks	642	1.85			
	Whites	32	2.14	1.53	0.88-2.67	0.12
	Asian	21	1.4			
	Blacks	42	2.83	2.02	1.19-3.44	**0.007**
	Asians	21	1.41			
ESRD	Whites	1212	3.5	0.54	0.5-0.58	**<0.0001**
	Blacks	2156	6.24			
	Whites	54	3.62	0.69	0.48-0.98	**0.03**
	Asian	77	5.16			
	Blacks	97	6.5	1.27	0.93-1.73	0.11
	Asians	77	5.1			

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2211 | GLOBAL DISPARITIES IN LIVER TRANSPLANTATION OUTCOMES: EXTENSIVE STUDY UTILISING GLOBAL REGISTRY DATA

Srishti Kohli[1] Ira Gupta[2] Vikash Jaiswal[3] Arshiya Gupta[2] Prabhsimranjeet Singh Randhawa[4] Maskeen Kaur Kullar[4]

[1]Student, [2]Intern, [3]MD, [4]MBBS

Background: Liver transplantation is a vital intervention for terminal liver disease, yet the results differ greatly across various regions. This study aims to compare liver transplantation outcomes using data from various international registries to identify global disparities. **Methods:** A retrospective cohort study was done by utilising data from different global registries (like United Network for Organ Sharing (UNOS) in the United States, Eurotransplant in Europe, the UK Transplant Registry (NHS Blood and Transplant), the Australian and New Zealand Liver Transplant Registry (ANZLTR), the Chinese Liver Transplant Registry (CLTR), and the India Liver Transplant Registry, etc). All the adults who were liver transplant recipients from January 1,2010 to December 31,2020 were included. We calculated outcomes for 1 year, 5 year graft and patient survival rates, post-transplant complications and. waitlist mortality rates. Kaplan-Meier survival analysis, Cox proportional hazards models, chi-square tests, and multivariate regression analysis were done for statistical analysis. **Results:** Patient characteristics were varied with a significant difference in age, sex, primary liver disease and donor sources.. The 1 year and the 5 year graft survival rate were the highest in the USA and ANZLTR followed by UK and Europe with China and India showing lower rates($p<0.001$). China and India also showed inferior patient survival rates as compared to all the other regions . Greater post-transplant complications were seen in China(28%) and India(30%) in comparison to USA(20%) and Europe(22%)[$p<0.05$]. Waitlist mortality was highest in India(15%) and China(14%) followed by Europe(11%),USA(10%) UK(9%) and ANZTLR(8%). The adjusted cox proportional hazards models revealed that China and India had higher risks of graft failure and patient mortality. **Conclusion:** Conclusion- Significant global disparities were seen in transplantation results in different demographic regions. Therefore, there is a need to focus on targeted interventions and enhance the healthcare system in the developing countries to enhance liver transplantation outcomes worldwide.

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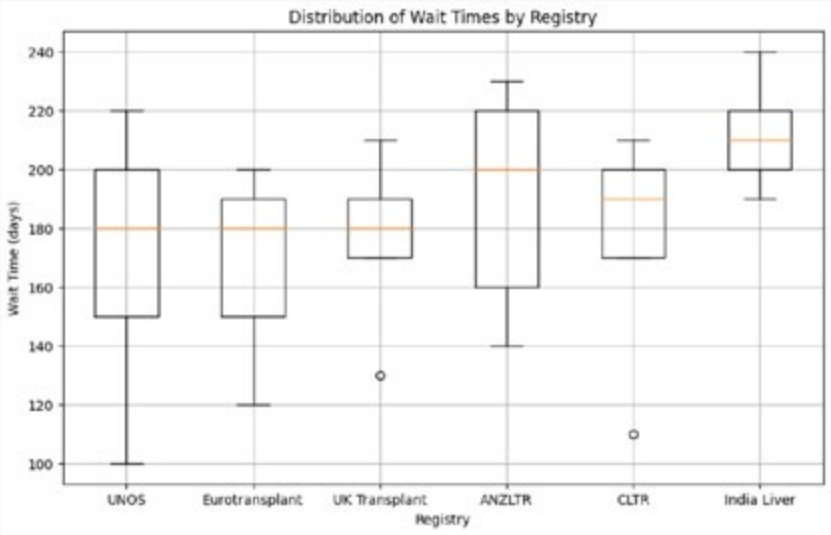

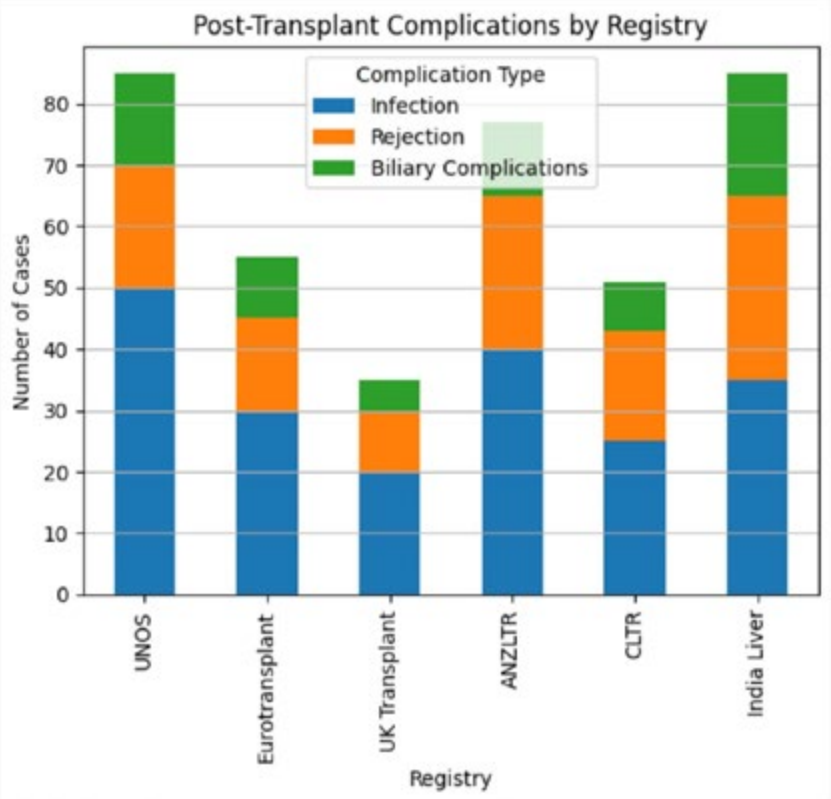

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2212 | DISSECTING RACIAL DISPARITIES IN HCC: MORTALITY RATES AND ACCESS TO TREATMENT: A MULTICENTER RETROSPECTIVE ANALYSIS

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Background: Hepatocellular carcinoma (HCC) represents a significant global health challenge, with marked disparities in incidence and outcomes along racial lines. Previous studies have consistently reported poorer survival among Black patients compared to their White counterparts, often associated with delayed diagnoses and reduced access to curative treatments. The goal of this study is to further investigate these disparities by examining mortality rates, transplantation access, and use of Sorafenib in matched cohorts of Black and White patients with HCC. **Methods:** In this retrospective analysis, data were drawn from the TriNetX and US Collaborative Network databases to form two cohorts: one of White patients (pre-match n=67,695) and one of Black patients (pre-match n=13,858) with HCC. Propensity score matching based on age, sex, liver function tests (INR, platelets), and BMI resulted in balanced cohorts of 13,513 patients per group. The primary outcomes analyzed included mortality, liver transplantation rates, and use of the therapeutic agent Sorafenib. **Results:** Contrary to much of the existing literature, our analysis found that the odds of mortality were higher in White patients compared to Black patients (OR: 1.185, 95% CI: 1.141-1.231, p<0.0001), suggesting a higher immediate mortality risk in this group. In alignment with previous findings, Black patients were less likely to undergo liver transplantation (OR: 1.774, 95% CI: 1.609-1.955, p<0.0001), reflecting significant barriers in accessing potentially curative procedures. Interestingly, Black patients were more likely to be treated with Sorafenib (OR: 0.695, 95% CI: 0.644-0.751, p<0.0001), indicating a possible reliance on medical management over surgical interventions. **Conclusion:** The unexpected finding of higher mortality rates among White patients may reflect underlying differences in disease aggressiveness or variations in end-of-life care practices. This contrasts with the broader literature and highlights the complexity of racial disparities in HCC outcomes. The disparities in transplantation access and the increased reliance on Sorafenib among Black patients underscore the persistent barriers to equitable care. Addressing these issues requires a nuanced understanding of the biological and systemic factors at play, as well as targeted interventions to ensure equitable healthcare access and treatment opportunities for all racial groups

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2213 | SOCIOECONOMIC DEPRIVATION IS AN INDEPENDENT RISK FACTOR FOR LIVER FIBROSIS IN FATTY LIVER DISEASE: A COMMUNITY-BASED PROPENSITY-SCORE MATCHED CASE-CONTROL STUDY

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Background: While numerous studies have identified various risk factors for liver fibrosis, the role of socioeconomic status (SES) remains less understood. This study aimed to investigate the association between SES and liver fibrosis, independent of other known risk factors, in a community-based propensity-score matched case-control study. **Methods:** We carried out a community-based study between 2021 and 2023 in New Delhi, India. Liver steatosis and fibrosis was diagnosed using transient elastography. Data was collected on socio-demographic and clinical variables, and blood investigations were carried out. Socioeconomic status was assessed using BG Prasad scale. Propensity score matching (PSM) was performed, matching patients with liver fibrosis (active group) to those without (control group) in a 1:3 ratio based on age and sex. The association between liver fibrosis and socioeconomic status was assessed by calculating odds ratios (ORs) using conditional logistic regression models, while controlling for other risk factors such as diabetes and BMI. **Results:** Out of a total of 2425 individuals screened, 33.2% (n=805) individuals belonged to middle socioeconomic class, followed

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by upper middle (23.2%, n=562) and lower middle (22.3%, n-540). Overall, liver fibrosis was diagnosed in 605 (24.9%), and steatosis in 1018 (42%). Individuals in lower and lower middle SES group constituted a greater proportion in lean fatty liver group as compared to obese or overweight group (31.9% vs 25.1%, p=0.059). The differences in proportions with significant liver fibrosis (LSM ≥7.9kPa) across SES categories did not achieve statistical significance (p=0.228). Conditional logistic regression analysis revealed that low SES was an independent risk factor for liver fibrosis in the population, which remained significantly associated after adjusting for history of hypertension, diabetes, BMI, physical activity, alcohol consumption, and hepatic steatosis (adjusted OR = 1.146, 95% CI: 1.011-2.317, p = 0.033). Other factors associated with liver fibrosis were duration of diabetes, obesity and hepatic steatosis (table). **Conclusion:** This study provides evidence that low socioeconomic status is an independent risk factor for liver fibrosis, even after accounting for other known risk factors. Factors that may mediate this association, such as disparities in health access, health behaviours, including unhealthy diet, fetal programming and chronic stress, need to be explored further.

Variable		p- value	OR(95%CI)
History of Hypertension (No^{R})	No	0.281	0.69(0.35,1.34)
	Yes	0.458	0.73(0.38,1.39)
Duration of Diabetes in years (Non-diabetes^{R})	≤ 5 years	0.117	2.06(1.47,2.90)
	6 – 10 years	0.036	2.41(1.49,3.90)
	> 10 years	0.921	1.75(0.98,3.12)
BMI Category (Normal^{R} (18.5–22.9))	Underweight (<18.5)	0.948	1.44(0.65,3.18)
	Overweight (23.0–24.9)	0.375	1.24(0.80,1.91)
	Obese I (25.0 – 29.9)	0.960	1.42(0.98,2.05)
	Obese II (>30)	0.001	2.21(1.49,3.29)
Glycaemic control status (Uncontrolled^{R})	Controlled	0.819	0.96(0.66,1.39)
Socio-economic status	Upper or upper middle class		Ref
	Middle	0.265	1.325 (0.926-1.897)
	Lower middle or lower class	0.033	1.146 (1.011-2.317)
Physical Activity (Moderate/ vigorous^{R})	Low	0.555	2.33(0.67,8.12)
Hepatic Steatosis (S0^{R}: CAP<248 dB/m)	S1: 248-267 dB/m	0.017	1.46(0.96,2.22)
	S2: 268-279 dB/m	0.090	2.72(1.71,4.32)
	S3: ≥280 dB/m	<.0001	4.61(3.45,6.17)

Disclosures: Manya Prasad: Nothing to Disclose, Shiv Kumar Sarin: Nothing to Disclose, Bharat Bhushan Rewari: Nothing to Disclose

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2214 | EVALUATION OF PHARMACEUTICAL CARE SERVICE (PCS) FOR LIVER CIRRHOSIS PATIENTS IN ACUTE TERTIARY HOSPITAL IN SINGAPORE ◆

Mei-Ling Yee[1] Samuel Rocky Candra[1] Jia Jie Wong[1] Jason Chang[1]

[1]Singapore General Hospital

Background: The drug pharmacokinetic changes in advanced cirrhosis predispose medication safety issues that requiring adjustment of pharmacotherapy and regular monitoring. The drug-related-problems (DRP) become more challenging when complicated with multiple comorbidities. Liver pharmacists collaborate with hepatologists to provide pharmaceutical care servive (PCS) to cirrhotic patients since 2018 in Singapore General Hospital (SGH). Aims (1) To describe and analyse the outcomes of the DRP managed (2) To identify pharmaceutical care practice gaps for the cirrhosis patients admitted to SGH. **Methods:** DRP, documented by Liver pharmacists from 1 Jan – 31 Dec 2023, was retrospectively extracted from electronic medical records and analysed. **Results:** A total 316 DRP were identified and prevented in 493 cirrhotic patients reviewed by liver pharmacists in 2023. Majority (93.7%) of liver pharmacists' recommendations were accepted. Recommendations were made when performing medication review (40.5%), medication reconciliation (MR) (23.1%) and care plan discussion at ward round (33.2%). The most common DRP was drug dose adjustment (37.7%), followed by avoidance of ADR (27.2%) where dose reduction made in 81.4% (70 of 86), discontinued in 15.1% and therapy substitution in 5.8%. Omission of therapy (19.3%) was mostly identified through MR with patient interview. There was 9.5% of cases where drugs were deprescribed for lack of indications, with proton-pump inhibitors the most common drug (36.7%). There was 12.9% of DRP on managing diabetic drug, antiplatelet, anticoagulant, antihypertensive and statin, often involving in acute decompensation and pre- & post large-volume paracentesis. Other DRP include changing diluent of intravenous medications to reduce sodium load for ascitic patients. Up to 31.1% of 28 patients surveyed had either inadequate knowledge of indications, dose regimen or not regularly taking non-selective beta-blockers (NSBB), diuretics or lactulose. Most of the patients were aware of indication of diuretics (80.4%) and lactulose (74.1%) but not so for NSBB (9.1%). Misunderstanding of the intended outcomes led to non-adherence to lactulose (29.6%) and NSBB (18.2%). Vaccination initiative for cirrhosis was initiated in late 2022. However, total number of patients received influenza and pneumococcal vaccines prior to discharge remained low (n=8) in 2023, mainly due to infections, recovery from acute illness and preference to defer vaccinations to outpatient visits. **Conclusion:** Medication safety for our cirrhosis patients improved when DRP resolved through the PCS. To close clinical gaps, patient counselling handouts and lactulose action plan were developed to improve the patients' knowledge about the drugs and their adherence to therapy, and implemented from Jan 2024. More collaborative effort is warranted to promote preventive care and extending PCS to outpatient setting for cirrhosis patients.

Disclosures: Mei-Ling Yee: Nothing to Disclose, Samuel Rocky Candra: Nothing to Disclose, Jia Jie Wong: Nothing to Disclose, Jason Chang: Boehdringer-Ingelheim: Advisor

2215 | TRANSPLANTING HEPATITIS C NAT POSITIVE SOLID ORGANS INTO HCV NEGATIVE RECIPIENTS; AN ADVANCED PRACTICE PROVIDER (APP) LED CLINIC, 4-YEAR REAL WORLD OUTCOMES ◆

Ariana Peguero[1] Mei Yi Worton[1] Ariana Peguero[1] Miguel Malespin[1] Christopher Albers[2] Nyingi Kemmer[1]

[1]Tampa General Medical Group, [2]James A Haley Veterans' Hospital

Background: Transplanting hepatitis C viremic organs (NAT positive) into hepatitis C negative (NAT negative) recipients is now an accepted practice. We report treatment outcomes from an APP led clinic of all hepatitis C negative solid organ transplant patients who received HCV viremic organs in our institution from 2019 to 2023. **Methods:** All patients who received NAT positive to negative solid organ transplants (SOT) at our center were tracked from April 2019-December 2023. The Hepatology inpatient team was consulted on post op Day 3-7 when patient became viremic. Medication (GP or SOF/VEL) was ordered through the recipients' insurance once a genotype resulted and an appointment was made in our outpatient APP led hepatitis C clinic before being discharged. Patients were started on treatment inpatient if deemed necessary then followed in hepatitis C clinic. Education was provided to patients by the APPs. Demographic data was collected from the electronic medical record (EMR) for legal sex and race. Genotype, treatment data and patient deaths were also collected. **Results:**

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223 NAT negative patients received NAT positive SOT at our center between April 2019 and December 2023; 102 kidneys, 60 livers, 7 simultaneous liver/kidneys (SLK), 29 lungs, 25 hearts. Demographics shown in table 1. Of the 223 patients, 3 kidney recipients never became viremic and 4 others died prior to treatment start, not attributed to hepatitis C. 216 patients were treated; 116 with G/P and 100 with SOF/VEL. Medication was chosen primarily based on drug interactions. The median time from transplant to treatment start was 35 days. Of the 216 patients treated, 213 had SVR data available. There were 2 patients who were treated but died before SVR labs could be obtained, and 1 patient failed to obtain labs for SVR. Of the 213 patients, 211 (99%) achieved SVR12. There were 2 relapses. One was a lung recipient, GT 1a, found to have a P32deld mutation. Patient was re-treated with SOF/VEL/VOX/RBV for 16w and achieved SVR12. The second was a kidney recipient, GT 1a with no resistant variants detected. Patient was re-treated with SOF/VEL/VOX for 24 weeks, still pending SVR12 to this date. There was 1 kidney recipient with fibrosing cholestatic hepatitis (FCH). Patient achieved SVR12 with treatment but later died for reasons unrelated to FCH. Only 1 patient stopped treatment early due to N/V, unclear if related to DAA therapy but still achieved SVR with only 8 weeks of G/P therapy. At the time of data collection, 202 patients were still alive (91%). No deaths were attributed to hepatitis C. **Conclusion:** This real-world cohort demonstrates a successful long-term APP-led Hepatitis C clinic focused on treating patients who received NAT positive organs with a high treatment success rate. Relapses when they occurred were successfully retreated. Treatment was well tolerated, and drug to drug interactions were manageable.

Demographics

	N (%)
Male	137 (61)
Female	86 (39)
White/Caucasian	158 (71)
Black/African American	32 (14)
Asian	4 (2)
Other	28 (13)
Unable to be obtained	1

Disclosures: Ariana Peguero: Nothing to Disclose, Mei Yi Worton: Nothing to Disclose, Ariana Peguero: Nothing to Disclose, Miguel Malespin: Nothing to Disclose, Christopher Albers: Nothing to Disclose, Nyingi Kemmer: Nothing to Disclose

2216 | IMPACT OF HEALTH COACHING FOR PATIENTS WITH MASLD IN A COMMUNITY-BASED LIVER CENTER ◆

Lita Petcharaporn[1] *Fatma Barakat*[2] *Tarek Hassanein*[1]

[1]*Southern California Liver Centers,* [2]*SCTI Research Foundation*

Background: Health coaching is an intervention with goal of helping individuals adopt and maintain health-supportive behaviors to improve both the health outcomes and quality of life. Health Coaches act as a partner in an individual's behavior change process. This process involves supporting the patient as they set goals, identify values & strengths, and access intrinsic motivations to encourage the development of sustainable healthy behaviors and attitudes. We piloted a health-coaching program in a community-based Hepatology specialty center to evaluate the impact of Health Coaching on patients diagnosed with MASLD. **Methods:** Between May and December 2023, we implemented the Health Coaching program. Patients diagnosed with MASLD, BMI >30 and CAP >250 were offered 6 months of complimentary support from a Health Coach free of charge. The first 2 sessions were conducted in person and were 1 hour long. Subsequent sessions were by telephone or in person, 30-60 minutes, and tailored to each patient's needs and preferences. Heath Coaching goals set by Hepatologist included weight loss, adherence to nutrition plan, and lifestyle change from sedentary to light activity or from light

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activity to moderate activity. **Results:** This analysis is on the first 13 consecutive adults aged 30-69 with MASLD. 7 agreed to work with a Health Coach and 6 declined due to time concerns or disinterest. Median number of sessions was 4 (1-11). The Transtheoretical Model (stage of change) was utilized to assess patients' readiness for change at the start of the Health Coaching sessions, 2 patients were in the Contemplation (understand they have a problem, but they're waiting for a magical moment to change), 3 patients were in the Preparation stage (preparing for change where they agreed to do something, but haven't started new habit or behavior yet), and 2 patients were in the Action stage (where they actually do something). At the end of the 6 months follow-up period, all 7 patients were unable to adhere to continuation of sessions. **Conclusion:** In patients with MASLD, Health Coaching can be a supportive tool to help ameliorate progression of disease. However to maximize benefits, other factors should be considered when determining whether a client is an appropriate candidate for coaching. Use of the Transtheoretical Model (stages of change) to assess the stage of change is important because where the clients are within the stages of change plays a part in getting to the "Action" stage. Health coaching has been shown to improve the health outcomes in patients with chronic health conditions, but patients with MASLD are still in the Precontemplation-Preparation stages. The goal of the Health Coach in MASLD pts will be to spend the time working with them in these stages until they transition them to the Action stage when the optimal time for the best benefit is achieved.

Disclosures: Lita Petcharaporn: Nothing to Disclose, Fatma Barakat: Nothing to Disclose, Tarek Hassanein: Nothing to Disclose

2217 | THE *PNPLA3* I148M VARIANT AGGRAVATES INFLAMMATION IN MACROPHAGES THROUGH IMPAIRED NUCLEAR RECEPTORS (LXR ALPHA, PPAR GAMMA, AND GR ALPHA) SIGNALLING

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Background: Most functional studies linking the single nucleotide polymorphism (rs738409; C>G) in patatin-like phospholipase domain-containing protein 3 (PNPLA3) to metabolic dysfunction-associated steatotic liver disease were conducted in hepatocytes and hepatic stellate cells, although macrophages play a crucial role in the disease progression. Here, we explored the impact of the PNPLA3 I148M variant on macrophage immunometabolism. **Methods:** We established a THP-1 stable cell line overexpressing the PNPLA3 wildtype, I148M variant, and THP-1 cells lacking the PNPLA3 gene. We conducted gel-shift, gene expression analysis, cytokine array analysis, immunofluorescence, and cholesterol efflux assay. **Results:** The transfected THP-1 WT^{oe} (+387%) and $I148M^{oe}$ (+428%) had increased levels of the *PNPLA3* compared to the untransfected cells. Consistent with increased staining for the surface expression of CD80, $I148M^{oe}$ M1 macrophages showed significant upregulation of *TLR4* (+24.5%), *IL-1β* (+446%), and *IL-6* (+24%) compared to WT^{oe}. Conversely, in M2 macrophages, the anti-inflammatory cytokine *IL-10* (-83.7%) was reduced markedly in $I148M^{oe}$ compared to the WT^{oe} and further reflected in reduced staining for CD163. Combined oleic and palmitic acid (OP21) treatment exacerbated inflammation in $I148M^{oe}$ while WT^{oe} macrophages remained unaffected. Mechanistically, we attributed the observed phenotype to impaired LXR alpha, PPAR gamma, and glucocorticoid receptor (GR) signalling. Gel-shift analysis revealed reduced LXR binding activity in the $I148M^{oe}$ M1 macrophage, leading to the downregulation of *ABCA1* (-36.7%) and *ABCG1* (-32%). Furthermore, T0901317, an LXR agonist, restored LXR signalling, cholesterol efflux, and improved inflammation as reflected by reduced levels of *IL-6* (-25%), *TNFA* (-75%), and *NFkB1* (-50%). Similarly, the macrophage carrying the PNPLA3 $I148M^{oe}$ had reduced PPAR gamma and GR alpha binding activity and induced their phosphorylation through CDK5. **Conclusion:** Our results suggest that the PNPLA3 I148M variant aggravates inflammation in macrophages because of, at least in part, impaired LXR alpha, PPAR gamma, and GR alpha signalling. These findings could enhance our understanding and therapeutic targeting of the metabolic role of the PNPLA3 in immunometabolism.

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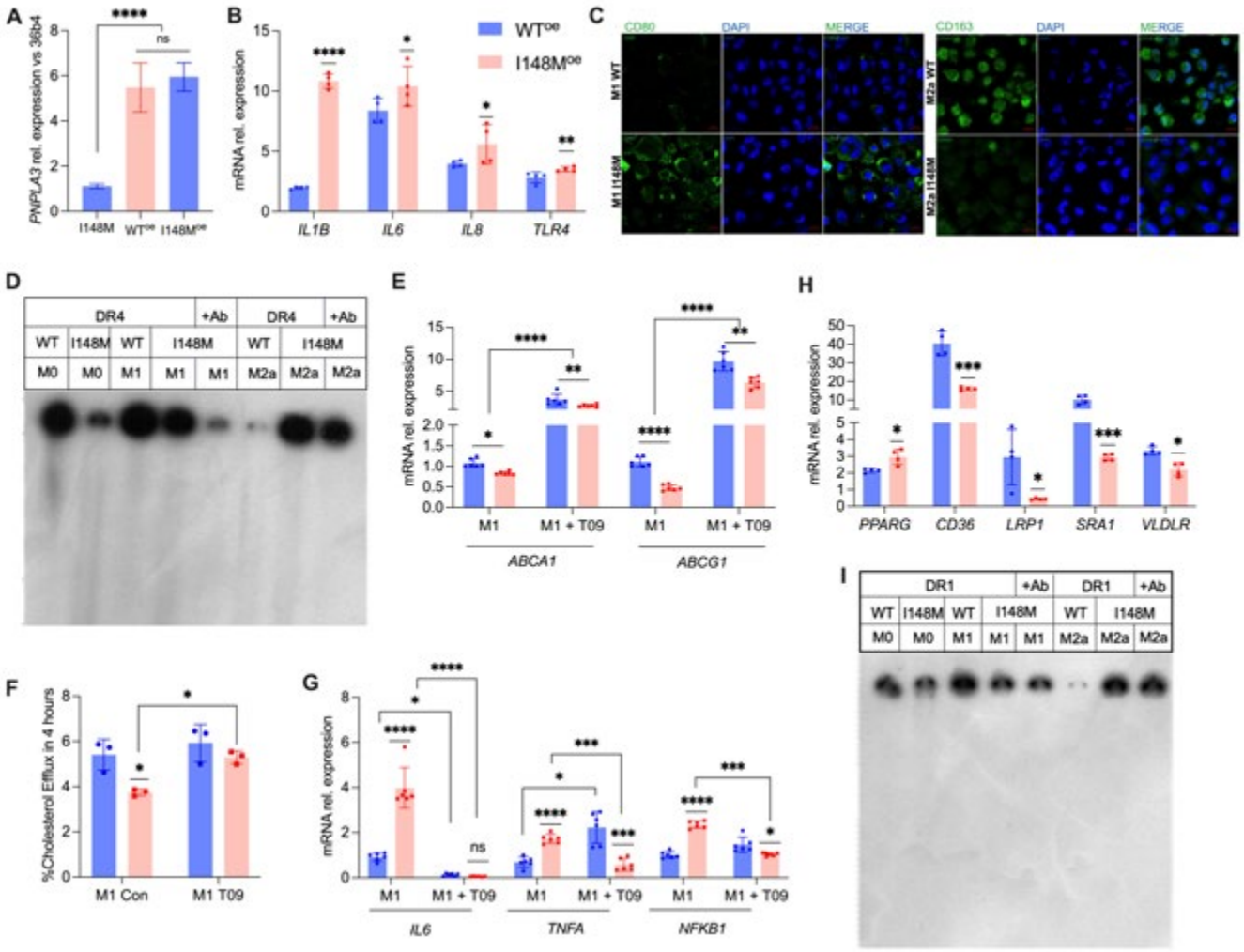

Disclosures: Emmanuel Dixon: Nothing to Disclose, thierry claudel: Nothing to Disclose, Jakob-Wendelin Genger: Nothing to Disclose, Ci Zhu: Nothing to Disclose, Alexander Nardo: Nothing to Disclose, Veronika Mlitz: Nothing to Disclose, Claudia Fuchs: Nothing to Disclose, Andreas Bergthaler: Nothing to Disclose, Paola Dongiovanni: Nothing to Disclose, Wilfried Ellmeier: Nothing to Disclose, Michael Trauner: Albireo: Grant/Research Support, Alnylam: Grant/Research Support, Cymabay: Grant/Research Support, Falk: Grant/Research Support, Gilead: Grant/Research Support, Intercept: Grant/Research Support, MSD: Grant/Research Support, Takeda: Grant/Research Support, Ultragenyx: Grant/Research Support, Abbvie: Travel Grants, Falk: Travel Grants, Gilead: Travel Grants, Intercept: Travel Grants, Janssen: Travel Grants, Abbvie: Advisor, Albireo: Advisor, BiomX: Advisor, Boehringer Ingelheim: Advisor, Falk Pharma GmbH: Advisor, Genfit: Advisor, Gilead: Advisor, Hightide: Advisor, Intercept: Advisor, Ipsen: Advisor, Janssen: Advisor, MSD: Advisor, Novartis: Advisor, Phenex: Advisor, Pliant: Advisor, Regulus: Advisor, Siemens: Advisor, Shire: Advisor, BMS: Speaking and Teaching, Falk: Speaking and Teaching, Gilead: Speaking and Teaching, Intercept: Speaking and Teaching, Ipsen: Speaking and Teaching, Madrigal: Speaking and Teaching, MSD: Speaking and Teaching, Medical Universities of Graz and Vienna: Co.Inventor of patents for medical use of norUDCA filed by, Genentech: Grant/Research Support

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2218 | METABOLIC DYSFUNCTION DRIVES CD8 T CELL HYPERFUNCTION AND IMPAIRED TUMOR RESPONSES IN MOUSE MODELS OF ADVANCED LIVER DISEASE

Jeff Li[1] Katrina Jorritsma[1] Natasha Campeau[1] Agatha Vranjkovic[2] Jood Madani[1] Torki Alothaimeen[2] Angela Cheung[3] Michele Ardolino[2] Angela Crawley[2]

[1]University of Ottawa, [2]Ottawa Hospital Research Institute, [3]The Ottawa Hospital

Background: Prolonged liver insults in chronic HCV (cHCV) infection and metabolic dysfunction-associated liver disease (MASLD) lead to progressive liver damage and increased risk for hepatocellular carcinoma. Our previous reports showed long-lasting systemic CD8 T cell hyperfunction and altered gene expression profiles heavily involving cellular metabolism, in cHCV associating with fibrosis severity. Metabolic activity, namely glycolysis and oxidative phosphorylation, are drivers of immune cell function. This study investigates underlying mechanisms of systemic CD8 T cell hyperfunction in mouse models of advanced liver diseases. **Methods:** Mouse models of advanced liver diseases were established by exposure to carbon tetrachloride (CCl_4) for 12 weeks, or high-fat, methionine-choline deficient diet (HFMCDD) for 16-20 weeks, mirroring human cHCV or MASLD pathology, respectively. Liver injury was assessed by Masson's trichrome and hematoxylin & eosin staining by a pathologist. CD8 T cell function and metabolic activity were assessed by flow cytometry and Seahorse XF Mito Stress test. **Results:** CCl_4-treated mice developed severe diffuse fibrosis (Metavir scores F3 to F4) with focal necrosis and surrounding mixed inflammation, reflecting human cHCV pathology. Circulating CD8 T cells in these mice exhibited IFN-γ, granzyme B, and CD107a hyperfunction compared to controls, associated with increased mitochondrial polarization. CCl_4-treated mice also show impaired control of ectopic tumor growth and delayed responses to anti-PD-1/CTLA-4 immunotherapy. Hyperfunction and impaired tumor responses persisted after 3 weeks of fibrosis regression. In parallel, HFMCDD-fed mice developed moderate to advanced peri-sinusoidal/pericellular fibrosis (F2-3 to F4) with moderate to severe steatosis (grade 2-3) and hepatocyte ballooning (grade 1-2), reflecting human MASLD pathology. CD8 T cell hyperfunction was also observed in these mice, associating with increased mitochondrial respiration and glycolytic activity, and impaired responses to ectopic tumor growth and anti-PD-1 immunotherapy. **Conclusion:** In advanced liver diseases, systemic CD8 T cell hyperfunction is coupled to overall disruptions in cellular metabolic activity, recapitulated in mouse models of advanced fibrosis and MASLD. Metabolic dysfunction may underlie impaired and delayed responses to tumor growth and immunotherapy. These models will enable mechanistic investigations which may translate to therapeutic strategies to improve clinical outcomes.

Disclosures: Jeff Li: Nothing to Disclose, Katrina Jorritsma: Nothing to Disclose, Natasha Campeau: Nothing to Disclose, Agatha Vranjkovic: Nothing to Disclose, Jood Madani: Nothing to Disclose, Torki Alothaimeen: Nothing to Disclose, Angela Cheung: Nothing to Disclose, Michele Ardolino: Nothing to Disclose, Angela Crawley: Nothing to Disclose

2219 | MONOCYTE TRANSCRIPTOMIC LANDSCAPE AND INTER-ORGAN CROSSTALK BETWEEN THE LIVER, BRAIN AND BONE MARROW IN A MODEL OF ALCOHOL MISUSE IN AGING

Marti Ortega-Ribera[1] Radhika Joshi[1] Sergi Guixé-Muntet[2] Veronika Brezani[1] Prashanth Thevkar Nagesh[3] Viliam Brezani[1] Arman Patel[1] Mrigya Babuta[1] Yuan Zhuang[1] Jordi Gracia-Sancho[4] Gyongyi Szabo[5]

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Background: The globally increasing aging population exhibits high vulnerability to infections due to inflammaging (basal pro-inflammatory state) and decreased efficiency to fight pathogens. Alcohol misuse is also an increasing trend among older adults, potentially compromising innate immunity at a multi-organ level. Monocytes (MO) and macrophages (MØ) are critical in both inflammation and host defense. Thus, we aimed to understand how MO and MØ populations respond to alcohol misuse across different alcohol-modulated niches by studying Kupffer cells (KC) and infiltrating liver MØ, brain microglia & bone marrow (BM) MO in aging. **Methods:** Young (3 months) or aged (20-24 months) C57BL/6N female mice were randomized to receive 10 alcohol (3.5 g/kg) or water binges via oral gavage every alternate day. Tissue collection and analysis was performed 18 hours after the last alcohol binge. Four cell populations were isolated/sorted and profiled by Smart RNAseq: 1-microglia,

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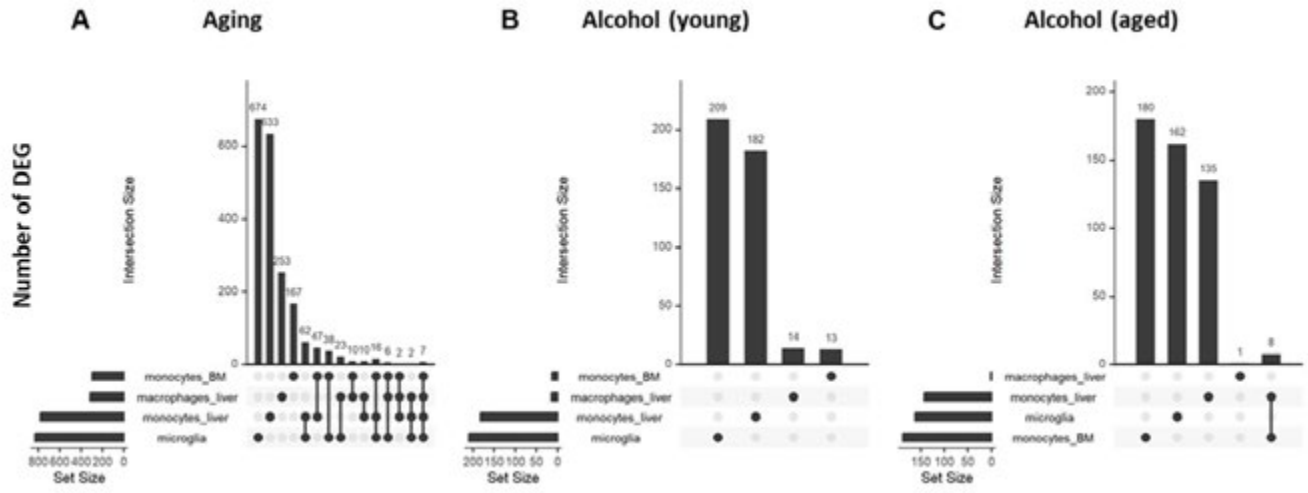
2-liver MO, 3-liver MØ (including both KC and infiltrating MØ) and 4-BM MO (n=4-6 animals/group). CellChat package for R was used to infer cell-cell communications. **Results:** Transcriptomic analysis of KC and infiltrating liver MØ, brain microglia & BM MO revealed common as well as uniquely differentially expressed genes (DEG) in response to age (Fig A) and/or alcohol (Fig B & C). Microglia and liver MO showed the highest and BM MO the lowest number of DEGs with aging. We identified a MO/MØ aging signature defined by seven common DEGs across all cell populations. Pathway analysis uncovered four commonly deregulated pathways with age in all MO/MØ: viral response, TNF-NFkB, JAK-STAT signaling and NOD-like receptor signaling. MO/MØ had unique responses to alcohol; however, inhibition of IFN signaling was commonly deregulated across all MO/MØ groups in aged mice receiving alcohol vs water. Lastly, we observed that liver MØ exhibit the highest number of ligand-receptor interactions being further increased in response to alcohol while BM MO were the least communicative. Regarding microglia, interactions with other MO/MØ populations were increased with age and alcohol. Further analysis revealed 3 main pathways, APOE, SELECTIN-P and CCL signaling guiding MO/MØ crosstalk between liver-brain and BM. Unique ligand-receptor partners were identified in age (ADIPONECTIN, MK, CNTN), alcohol (ADGRB, NT, EPHA), or in the aged alcohol group (SPP1, MSTN, NRXN). **Conclusion:** Our data describe that MO/MØ populations from alcohol-relevant niches show unique phenotypes in response to age and/or alcohol. We identified IFN suppression in the aged-alcohol group that may relate to susceptibility to infections with alcohol misuse. Finally, we discovered landmark and exclusive pathways characterizing inter-organ MO/MØ crosstalk in the context of age and/or alcohol misuse.



Disclosures: Marti Ortega-Ribera: Nothing to Disclose, Radhika Joshi: Nothing to Disclose, Sergi Guixé-Muntet: Nothing to Disclose, Veronika Brezani: Nothing to Disclose, Prashanth Thevkar Nagesh: Nothing to Disclose, Viliam Brezani: Nothing to Disclose, Arman Patel: Nothing to Disclose, Mrigya Babuta: Nothing to Disclose, Yuan Zhuang: Nothing to Disclose, Jordi Gracia-Sancho: Independent Contractor relationship with Oncomatryx; Has not ended; Independent Contractor relationship with Quinton; Has not ended; Independent Contractor relationship with Inventiva; Has ended; Independent Contractor relationship with Novo Nordisk; Has not ended; Independent Contractor relationship with Gilead Sciences; Has ended; Stock â€“ privately held company relationship with Barcelona Liver Bioservices; Has not ended, Gyongyi Szabo: Advisor relationship with Glympse Bio, Inc (acquired by Sunbird Bio); Has not ended; Consultant relationship with Terra Firma; Has not ended; Consultant relationship with Pfizer; Has not ended; Consultant relationship with Pandion Therapeutics; Has ended; Consultant relationship with Merck; Has ended; Consultant relationship with Durect Corporation; Has ended; Advisor relationship with Satellite Biosciences; Has not ended; Consultant relationship with Zomagen Bioscience/ Ventyx Biosciences; Has ended; Consultant relationship with CYTA Therapeutics; Has ended; Royalties or patent beneficiary relationship with Springer Nature Group; Has not ended; Royalties or patent beneficiary relationship with UpToDate Inc; Has not ended; Consultant relationship with LabCorp; Has not ended; Advisor relationship with Evive; Has not ended; Advisor relationship with Surrozen; Has not ended; Consultant relationship with Takeda; Has ended

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2220 | CD73 ENHANCES THE IMMUNOREGULATORY FUNCTIONS OF HEPATIC TREGS THROUGH ENZYMATIC AND NONENZYMATIC PATHWAYS IN MAFLD DEVELOPMENT ◆

Xinjie Zhong[1] Hua Jin[2] Chunpan Zhang[2] Yongle Wu[3] Dong Zhang[3] Guangyong Sun[3]

[1]Beijing Friendship Hospital, Capital Mdeical University, [2]Beijing Friendship Hospital, [3]Beijing chaoyang Hospital

Background: Regulatory T cells (Tregs) play a critical role in immunosuppression to delay the metabolic associated fatty liver disease (MAFLD). We found the expression of CD73, a functional molecule highly expressed on Tregs, was increased both in peripheral blood of MAFLD patients and liver tissue of MAFLD mouse model. However, the role of CD73 and the mechanism by which CD73 modulates Tregs in the pathogenesis of MAFLD are still unknown. **Methods:** Wild-type (WT) and CD73 knockout (KO) mice, or specifically transferring WT or CD73 KO Tregs into $Rag^{-/-}$ mice were fed either a choline-deficient high-fat diet (CD-HFD) for 16 weeks or choline deficient diet (MCD) for 4 weeks to establish MAFLD model. Liver injury and fat accumulation were evaluated via liver histopathology and serum biochemical parameters. The activation, differentiation, and cytokine secretion of liver infiltrated immune cells were determined. Transcriptome sequencing of hepatic Tregs from WT or CD73 KO MAFLD mice were analyzed. The mechanisms of CD73 regulating Tregs survival and immunoregulatory functions were explored *in vitro.* **Results:** CD73 expression was significantly increased in nonparenchymal cells, especially Tregs, in the livers of mice with MAFLD. The soluble CD73 concentrations and in MAFLD mice were significantly upregulated. MAFLD patients exhibited elevated levels of CD73 expression on Tregs as well as increased soluble CD73 in plasma. Compared with WT mice, CD73 KO mice fed a CDHFD or MCD displayed a more severe liver inflammation, fibrosis, and lipid accumulation. As well as dramatically impaired Tregs survival and immunosuppressive function. Adoptively transferred WT Tregs into $Rag1^{-/-}$ mice protected against MAFLD development, while CD73 KO Tregs failed to reduce liver injury, as shown by higher levels of plasma ALT, AST, TBIL and fasting glucose, more infiltrated proinflammatory monocytes and cytokine secretion. Transcriptome sequencing analysis showed FFAs in the liver of individuals with MAFLD promoted the transcription factor GATA2 through the p38 signaling pathway, leading to CD73 upregulation on Tregs. Mechanistically, CD73 via enzymatic pathways protect Tregs from adenosine monophosphate (AMP)AMP which cause apoptosis and exhaustion, and generated adenosine (ADO) that enhance the cell survival. In addition, CD73 could interact with DR5 to prevent Tregs from Trail induced apoptosis and maintained Tregs immunoregulatory function through nonenzymatic pathways in MAFLD. **Conclusion:** CD73 could downregulate inflammation in the liver and pathogenesis of MAFLD through regulating Tregs. Our study reveals a novel intrinsic mechanism that CD73 is crucial for Tregs homeostasis and immunosuppressive function in MAFLD development. These findings provide a promising immunotherapy strategy for MAFLD treatment and its feasibility for clinical application.

Disclosures: Xinjie Zhong: Nothing to Disclose, Hua Jin: Nothing to Disclose, Chunpan Zhang: Nothing to Disclose, Yongle Wu: Nothing to Disclose, Dong Zhang: Nothing to Disclose, Guangyong Sun: Nothing to Disclose

2221 | A PILOT STUDY OF THE COMBINATION OF SORAFENIB PLUS NIVOLUMAB IN UNRESECTABLE HEPATOCELLULAR CARCINOMA (HCC): SAFETY, EFFICACY, AND IMMUNE CELL PROFILING IN CHILD PUGH A AND B COHORTS

Bridget Keenan[1] Bryan Khuong Le[1] Quincy Harris[1] Jocelin Chen[1] Alexander Cheung[1] Zenghua Fan[1] Frances Lara[2] John Gordan[1] Paige Bracci[1] Spencer Behr[1] Lawrence Fong[1] Alan Venook[1] Edward Kim[2] Robin Kelley[1]

[1]University of California San Francisco, [2]UC Davis Comprehensive Cancer Center

Background: The anti-PD-1 mAb nivolumab (NIVO) achieves prolonged responses in ~15% of patients with advanced HCC. Inhibition of myelosuppressive immune cells and angiogenesis in the tumor microenvironment may reduce primary resistance and augment response. To test this, we conducted a clinical trial to assess the safety and efficacy of the multikinase inhibitor sorafenib (SOR) combined with NIVO in patients with HCC and Child Pugh A and B liver function. **Methods:** Multicenter, open-label pilot study with two consecutive patient cohorts: Part 1, Dose Escalation; Part 2, Child Pugh B Expansion (NCT0343891). Key eligibility: Histologic or radiographic diagnosis of unresectable HCC; measurable disease by RECIST 1.1; Child Pugh A/B7 (Part 1) or B (Part 2); no prior systemic therapy; no uncontrolled ascites or encephalopathy within 6 mo. or upper GI bleeding within 12 mo. Treatment: SOR dose levels (DL) 400 mg PO QD (DL0) and BID (DL1) (Part 1),

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maximum-tolerated dose (MTD) (Part 2); NIVO DL 240 mg IV Q2 weeks in all. Primary endpoint (EP): MTD (Part 1); rate of grade >/=3 treatment-related adverse events (TRAE) (Part 2). Objective response rate (ORR) was a secondary EP. Exploratory EP included immunologic and genomic biomarkers including peripheral blood mononuclear cell (PBMC) immune cell frequencies. **Results:** 16/25 consented patients were eligible and enrolled from 3/2018-5/2022 at UCSF and UCD. Median age 66 yrs (range: 50-82 yrs); 81% male; 50% White, 44% Asian, 7% Black; 19% Hispanic; 38% HBV, 38% HCV, 25% nonviral; Child Pugh A 63%, B7 25%, B9 13%; BCLC B 25%, BCLC C 75%. Part 1: DLT rate 1/6 for DL0, 2/5 for DL1; DL0 was determined to be the MTD. Part 2: 60% Grade >/=3 TRAE. Partial responses occurred in 6%, stable disease in 50%, and progression in 44%; ORR was 6%. Preliminary PBMC analyses revealed myeloid cell alterations based on etiology and treatment effect. **Conclusion:** The MTD for SOR+NIVO was SOR 400 mg QD plus NIVO 240 mg IV Q2 weeks and showed acceptable safety in a Child Pugh B expansion cohort. However, the cohort was closed early due to slow accrual and changing treatment landscape. The ORR of 6% for Parts 1 and 2 combined was below the pre-specified threshold for efficacy (15%). Ongoing PBMC analyses may identify differences in systemic immunity related to clinical characteristics.

Disclosures: Bridget Keenan: Genentech: Travel, Genentech: Grant/Research Support, Apexigen (now Pyxis Oncology): Grant/Research Support, Regeneron: Consultant, Regeneron: Grant/Research Support, Innovative Cellular Therapeutics: Grant/Research Support, Antengene: Grant/Research Support, AstraZeneca: Grant/Research Support, Partner Therapeutics: Grant/Research Support, Takeda: Grant/Research Support, Bryan Khuong Le: Nothing to Disclose, Quincy Harris: Nothing to Disclose, Jocelin Chen: Nothing to Disclose, Alexander Cheung: Nothing to Disclose, Zenghua Fan: Nothing to Disclose, Frances Lara: Nothing to Disclose, John Gordan: Nothing to Disclose, Paige Bracci: Nothing to Disclose, Spencer Behr: Nothing to Disclose, Lawrence Fong: Nothing to Disclose, Alan Venook: Nothing to Disclose, Edward Kim: Nothing to Disclose, Robin Kelley: Astra Zeneca: Grant/Research Support, Bayer: Grant/Research Support, Bristol Meyer Squibb: Grant/Research Support, Exelixis: Grant/Research Support, Eli Lilly: Grant/Research Support, Genentech/Roche: Grant/Research Support, Genentech/Roche: Grant/Research Support, GSK: Consultant, Kinnate: Consultant, J Pharma Inc.: Consultant, Loxo Oncology: Grant/Research Support, Merck: Grant/Research Support, Merck: Advisor, Moderna: Consultant, Partner Therapeutics: Grant/Research Support, Relay Therapeutics: Grant/Research Support, Surface Oncology: Grant/Research Support, Tyra Biosciences: Grant/Research Support, Regeneron: Consultant, Tyra Biosciences: Consultant, Compass Therapeutics: Grant/Research Support, Compass Therapeutics: Consultant, Servier: Grant/Research Support

2222 | EFFICACY OF NITAZOXANIDE (NTZ) IN PATHOGEN-ASSOCIATED MOLECULAR PATTERNS (PAMPS)-INDUCED DISEASE MODELS

Marie Bobowski-Gerard[1] Debaecker Simon[1] Philippe Delataille[1] Philippe POULAIN[1] Yacine Hajji[1] Sakina Sayah Jeanne[1] Dean Hum[1] David Dombrowicz[2] Vanessa Legry[1] Bart Staels[2]

[1]Genfit S.A., Loos, France, [2]INSERM U1011, Univ. Lille, Institut Pasteur de Lille, Lille, France

Background: Systemic inflammation, triggered by bacteria or Pathogen-Associated Molecular Patterns (PAMPs), is a primary driver of acute-on-chronic liver failure (ACLF), a severe syndrome affecting patients with acutely decompensated cirrhosis (Hernaez *et al., Gut*, 2016). We previously showed that the anti-parasitic drug nitazoxanide (NTZ) alleviates organ damage in disease models of ACLF (*J Hepatol*. 2022, 2023 and 2024). The aim of this study was to investigate NTZ efficacy in rodent models of polymicrobial sepsis or endotoxemia and to explore its ability to counteract cytokine release induced by a wide range of PAMPs. **Methods:** Endotoxemia was induced in healthy rats by intraperitoneal injection of 1 mg/kg LPS. A single oral dose of NTZ (30, 100 or 300 mg/kg) was administered concomitantly to LPS. Serum was collected 3h and 5h after LPS. Sepsis was induced through Cecal Ligation and Puncture (CLP) surgery in mice. NTZ (100 mg/kg/day) or vehicle was orally administered 3.5h post-CLP, then BID for 6 days. In vitro, the effect of tizoxanide (TZ), the active metabolite of NTZ, was assessed in murine Raw 264.7 macrophages, treated with agonists of Toll-Like Receptors (TLRs), key receptors in the recognition of PAMPs. **Results:** In rats with endotoxemia, NTZ dose-dependently alleviates LPS-induced plasma cytokine concentrations and hepatic marker levels, with the maximal effect observed at 300 mg/kg: -51% IL6 ($p<0.001$) and -69% TNFa ($p=0.0008$) at 3h post-LPS; and -69% AST ($p=0.007$), -110% total bilirubin ($p=0.007$) and -101% bile acids ($p<0.001$) at 5h post-LPS. In mice with sepsis, treatment with 100 mg/kg/day NTZ significantly improves the survival rate ($p=0.0015$, Figure). To further characterize the mechanism of action of NTZ, we assessed the effect of TZ on TLR agonist-induced cytokine release. While TAK-242 (a TLR4 antagonist)

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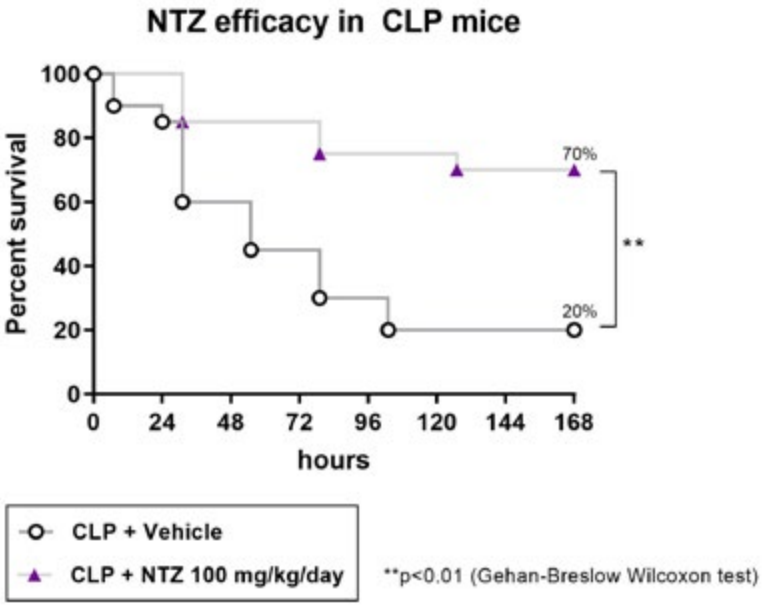
specifically blunts LPS-induced IL-6, TNFa and IFNb secretion by macrophages, TZ showed a broader effect on the inhibition of cytokine secretion induced by TLR1, TLR2, TLR4, TLR5, TLR6, and TLR9 activators. **Conclusion:** Oral NTZ treatment alleviates systemic inflammation and improves survival in endotoxemia and sepsis models, respectively. Combined with its antimicrobial and hepatoprotective properties, the ability of TZ to counteract the inflammatory response induced by a large range of PAMPs further supports the development of NTZ to counteract cytokine storm and prevent organ damage in ACLF.



Disclosures: Marie Bobowski-Gerard: Nothing to Disclose, Debaecker Simon: Nothing to Disclose, Philippe Delataille: Nothing to Disclose, Philippe POULAIN: Nothing to Disclose, Yacine Hajji: GENFIT S.A.: Employee, Sakina Sayah Jeanne: Nothing to Disclose, Dean Hum: Genfit: Executive role, David Dombrowicz: Nothing to Disclose, Vanessa Legry: GENFIT SA: stock - privately held company, Bart Staels: Genfit SA: Consultant

2223 | GLUCOCORTICOID RECEPTOR EXPRESSION IN HEPATOCYTES CONTROLS ENCLYSIS, RESPONDS DIFFERENTLY TO PREDNISOLONE AND FENOFIBRATE, 1212AND VARIES IN EXPLANTS FROM PATIENTS WITH AUTOIMMUNE BUT NOT METABOLIC LIVER INJURY

Yiyu Fan[1] Madeleine Hill[2] Robert Bryce[2] Fei Wang[3] Hanan Almakhayitah[2] Yuxin Li[2] Kulvinder Gill[4] Daniel Kearns[4] Gary Reynolds[5] Nicholas Barnes[6] Omar Qureshi[7] Aekkachai Tuekprakhon[2] Zania Stamataki[2]

[1]Centre for Liver and Gastrointestinal Research, [2]Institute of Immunology and Immunotherapy, University of Birmingham, UK, [3]Department of General Surgery, The Affiliated Hospital of Inner Mongolia Medical University, China, [4]Centre for Liver and Gastrointestinal Research, University of Birmingham, UK, [5]NIHR Birmingham Liver Biomedical Research Unit, University of Birmingham, [6]Institute of Clinical Sciences, College of Medical and Dental Sciences, University of Birmingham, UK, [7]Celentyx Ltd, UK

Background: The glucocorticoid prednisolone alone or in combination with azathioprine is the standard treatment for autoimmune hepatitis (AIH). However, up to 20% of patients fail to respond and need a transplant due to unregulated, immune-mediated hepatocyte damage. It is critical to identify early predictors of non-response to list patients for transplantation. Regulatory T cells can temper liver inflammation, but hepatocytes engulf and eliminate them by enclysis. We previously showed that AIH explants had increased enclysis compared to explants with metabolic dysfunction-associated steatohepatitis (MASH)(PMID:31693899). Further, Peroxisome proliferator-activated receptor alpha (PPAR-α) toggled enclysis at the hepatocyte level (PMID:37820069). Given than PPAR-α is regulated by glucocorticoids, we set out to determine their effect on enclysis. **Methods:** The glucocorticoid receptor (GCR) was assessed in non-cirrhotic livers, AIH and MASH (n=25) by immunohistochemistry (IHC)

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using QuPath software. Putative modulators of enclysis were tested by a fluorescence-based high-content assay using enclysis-competent Huh-7 cells. Cell-in-cell structures were quantified using custom algorithms by Celentyx Ltd. Hits were validated in dose-response assays by confocal microscopy. Agonist and antagonist effects on the hepatocyte GCR were tested ex vivo using non-cirrhotic liver tissue. **Results:** GCR agonists and antagonists inhibited or enhanced enclysis respectively in vitro, with nuclear translocation of the GCR confirmed after treatment. Ex vivo perfusion of liver tissue with prednisolone increased nuclear GCR expression in zone 2 hepatocytes in all non-cirrhotic livers tested (n=10), however hepatocytes at zones 1 and 3 varied, with some livers increasing and some reducing nuclear GCR expression upon treatment. In hepatocytes resistant to prednisolone, PPAR-α agonist fenofibrate increased nuclear GCR (Figure 1). Liver explants from AIH patients had a broad range of GCR-expressing periportal hepatocytes compared to donor livers (p= 0.028) but MASH explants did not. **Conclusion:** Glucocorticoid treatment inhibited enclysis in vitro via PPAR-α and resulted in GCR translocation to the nucleus in vitro and ex vivo. Zone 1 and 3 hepatocytes in some patients were resistant to prednisolone, but not to fenofibrate. Further research is needed to determine if GCR heterogeneity in hepatocytes may be useful to predict glucocorticoid response.

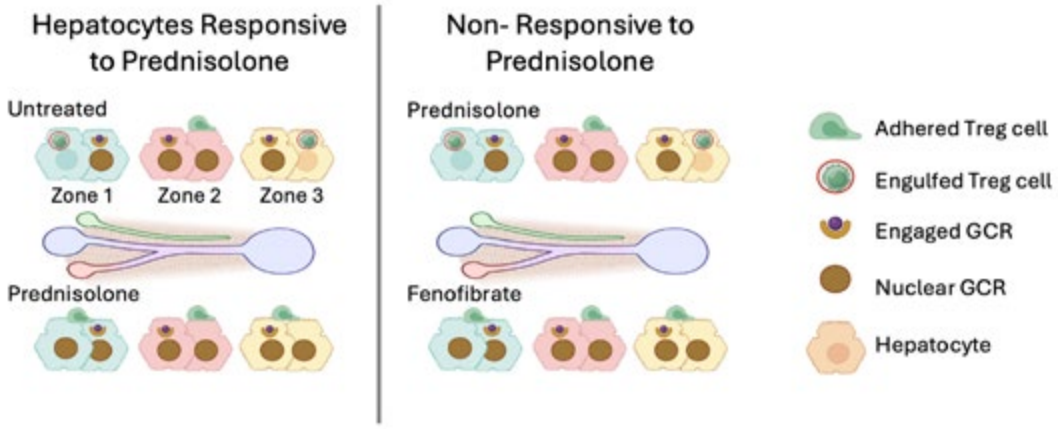

Figure 1. Fenofibrate may rescue prednisolone-resistant hepatocytes. Prednisolone treatment of non-cirrhotic donor human liver tissue ex vivo caused glucocorticoid receptor (GCR) translocation to the nucleus in some donors but not others, particularly in zone 1 and 3. Hepatocytes resistant to prednisolone treatment showed GCR translocation to the nucleus after fenofibrate treatment. Prednisolone and fenofibrate inhibit the engulfment of regulatory T cells (Treg) by enclysis, which may add to their anti-inflammatory activities.

Disclosures: Yiyu Fan: Nothing to Disclose, Madeleine Hill: Nothing to Disclose, Robert Bryce: Nothing to Disclose, Fei Wang: Nothing to Disclose, Hanan Almakhayitah: Nothing to Disclose, Yuxin Li: Nothing to Disclose, Kulvinder Gill: Nothing to Disclose, Daniel Kearns: Nothing to Disclose, Gary Reynolds: Nothing to Disclose, Nicholas Barnes: Nothing to Disclose, Omar Qureshi: Nothing to Disclose, Aekkachai Tuekprakhon: Nothing to Disclose, Zania Stamataki: Nothing to Disclose

2224 | INTERPLAY BETWEEN CD40 AND INTEGRIN α5β1 ENHANCES TUMOR CELL SURVIVAL IN POORLY DIFFERENTIATED HEPATOCELLULAR CARCINOMA

Le Thuy[1] *Hanh Ngo*[1] *Hoang Hai*[1] *Sawako Uchida-Kobayashi*[1] *Masaru Enomoto*[1] *Norifumi Kawada*[1]

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Background: Hepatocellular carcinoma (HCC), the most common primary liver cancers which is a leading cause of cancer-related death worldwide, is associated with elevated immunoe checkpoint proteins (ICPs) including

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CD27, CD28, and CD40. This sutyd investigated the role of CD40 in liver tumor progression. **Methods:** 168 HCV-infected patients including 47 HCC and 121 non-HCC were enrolled in this study. The level of soluble (s) and membrane-bound (m) CD40 were examined in plasma and human liver tissues, respectively. Immunoblot and quantitative RT-PCR were performed to assess the expression of CD40 in five human HCC cell lines. The methylation index of the CD40 promoter region was examined. $CD4^+$T cells isolated from the peripheral blood of healthy donors were stimulated to express CD40 ligand (CD40L). Human recombinant IFN-gamma was used to induce CD40 expression in HCC cells. RNA sequencing analysis was performed to explore the mechanisms of CD40 induction. **Results:** Patients with baseline levels of sCD40 ≥ 688 pg/mL predicted a significantly greater HCC cumulative rate. Poorly differentiated HCC tumour tissues exhibited high membrane-bound CD40 (mCD40) expression, in contrast to non-tumour areas. Poorly differentiated HCC cell lines showed high expression of mCD40 with low CD40 promoter methylation which were opposite of well-differentiated ones. Solely modulating CD40 expression by deletion or overexpression in HCC cells exerted no direct consequences on cell growth or appearance. Interestingly, HLFs co-cultured with activated (CD40L+) CD4+ T cells elevated CD40 levels and showed a modest 3.2% of dead cells, then increased to 10.9% underwent pre-neutralizing CD40 condition, while pre-blocking both CD40 and Integrin α5β1 concomitantly caused only 1.9% of cell death. RNA sequencing of co-cultured HLFs with activated CD4+ T cells revealed the upregulation of interferon (IFN) and immune response pathways. Elevated IFN-γ levels in the activated T cell media stimulated the JAK1/STAT3 pathway, resulting in increased CD40 expression in HLF. Jak1 inhibitor, CYT387 (2-16 μM), and ERK1/2 inhibitor, U0126 (5-80 μM), reduced CD40 expression in HLF cells under IFN-gamma stimulation. **Conclusion:** Collectively, we establish that CD40 on HCC cells interacts with CD40L on activated CD4+ T cells, thus, avoiding apoptosis caused by the Integrin α5β1–CD40L linkage, and contributing to cancer cell survival. These findings underscore the importance of the CD40–CD40L interaction in HCC progression and suggest that targeting this pathway may hold promise for therapeutic intervention in poorly differentiated HCC.

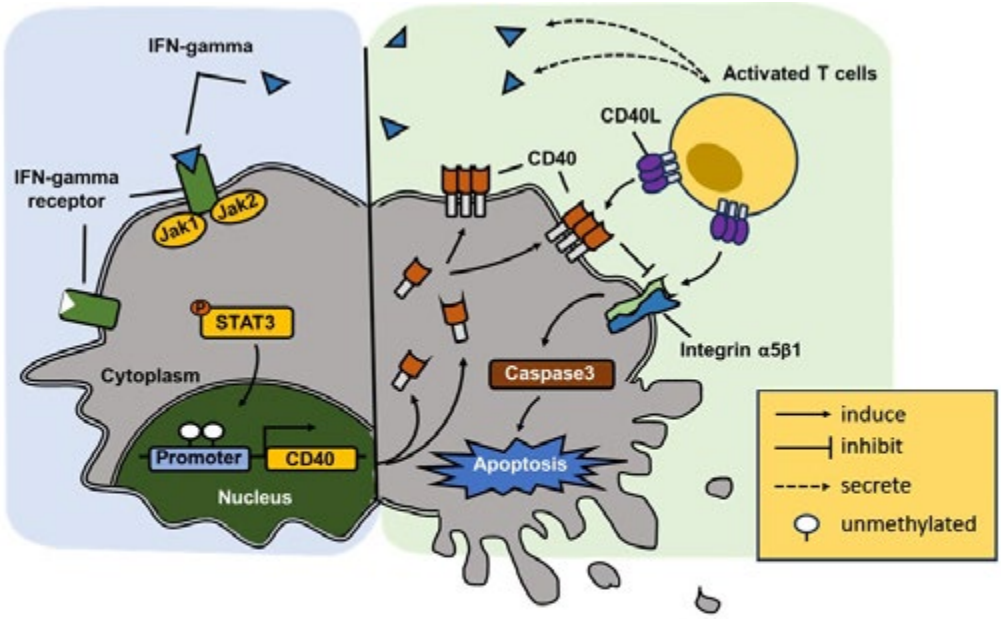

Figure 1. IFN-γ secreted from activated T cells induces CD40 expression through the JAK1/STAT3 pathway. CD40 on HCC cells interacts with CD40L on activated $CD4^+$ T cells, thus, avoiding apoptosis caused by the Integrin α5β1–CD40L linkage, and contributing to cancer cell survival.

Disclosures: Le Thuy: Nothing to Disclose, Hanh Ngo: Nothing to Disclose, Hoang Hai: Nothing to Disclose, Sawako Uchida-Kobayashi: Nothing to Disclose, Masaru Enomoto: Nothing to Disclose, Norifumi Kawada: Nothing to Disclose

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2225 | OXIDATIVE STRESS CONTRIBUTES TO PRO-INFLAMMATORY MONOCYTES AND AN INFLAMMATORY PROFILE OF INFILTRATING MACROPHAGES IN ADVANCED LIVER FIBROSIS

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Background: Monocyte-derived macrophages (MoMϕs) infiltrate the liver in large numbers to complement tissue resident Kupffer cells (KC) in maintaining homeostasis and mediating fibrosis and tissue repair. Macrophages' functional diversity and plasticity facilitate their response to a changeable microenvironment. Cellular oxidative stress has been associated with progressive diseases such as chronic hepatitis, diabetes and cancer and is linked to influence the polarization and function of myeloid cells. Previous work identified exaggerated inflammatory features of M1 macrophages derived from blood monocytes in chronic HCV infection with advanced liver fibrosis. However, it remains unclear if this is rooted in monocyte dysfunction and it extends to the liver environment. **Methods:** 10-week-old C57BL/6 mice were administered oil (control) or carbon tetrachloride (CCl_4, 1.0 mg/kg) in oil 2x per week (i.p.) for 14 weeks. Fibrosis scoring and inflammation were determined via hematoxylin & eosin and Masson's trichrome (MT) staining. Blood was collected for *ex vivo* analysis of mitochondrial and reactive oxygen stress in parallel with monocyte function studies by flow cytometry. At peak liver fibrosis, mice were euthanized, and livers were perfused, then digested and homogenized. Bone marrow-derived macrophages (BMDMs) were generated from the tibia and femur and cultured with MCSF for 6 days before polarization with IFN-γ and stimulation with LPS. **Results:** After 8 weeks, CCl_4 treatment increased oxidative stress and mitochondrial potential in circulating monocytes, mainly in the $Ly6C^{high}$ subset. Subsequent weeks revealed reduced frequencies of these oxidatively stressed $Ly6C^{high}$ monocyte populations within peripheral circulation in conjunction with muted TNF-α and IFN-γ expression in response to LPS. At endpoint, we confirmed mice administered CCl_4 developed extensive liver fibrosis. Moreover, fibrotic mice had increased proportions of intrahepatic $F4/80^{+}CD11b^{high}$ infiltrating MoMϕs in fibrotic mice compared to controls. Oxidative stress and M1 inflammatory polarization ($CD80^{+}CD206^{-}$) were more pronounced in the $CD11b^{high}$ infiltrating MoMϕs population compared to liver resident KC in liver disease mice. In addition, BMDMs from fibrotic mice tended to inherently express an M1 phenotype following differentiation, suggesting BMDM progenitors become predisposed to an inflammatory state in advanced liver disease. **Conclusion:** Cellular myeloid oxidative stress is pronounced in the periphery with progressive liver fibrosis. This may contribute to chronic liver injury with increasing monocyte infiltration and macrophage differentiation. Infiltrating MoMϕs favour an inflammatory M1 phenotype in advanced liver fibrosis, in contrast to tolerogenic KCs. Further studies are needed to identify how these cells influence immune cell interactions and contribute to adverse clinical outcomes in liver disease.

Disclosures: David Lawton: Nothing to Disclose, Angela Crawley: Nothing to Disclose

2226 | DIET-DERIVED FATTY ACID INDUCES DYSFUNCTIONAL INTESTINAL TFH CELLS VIA ELEVATED KLF2 THAT IMPAIRS INTESTINAL HOMEOSTASIS AND EXACERBATES MASH

Haiguang Wang[1] *Xavier Revelo*[1]

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Background: Metabolic dysfunction-associated steatohepatitis (MASH), characterized by hepatic inflammation and cellular damage, is the most severe form of fatty liver disease and the fastest-growing indication for liver transplantation. The intestinal immune system is a central modulator of local and systemic inflammation. In particular, T follicular helper (Tfh) cells in Peyer's patches (PPs) support germinal center (GC) responses are required for the generation of high-affinity intestinal IgA and the maintenance of intestinal homeostasis. However, the mechanisms regulating mucosal immunity during the pathogenesis of MASH remain incomplete. **Methods:** We used a preclinical mouse model that resembles the key features of human MASH. Mice were fed a high-fat high-carbohydrate (HFHC) diet to induce MASH. We performed histological analysis, flow cytometry, mass spectrometry, and single-cell RNA sequencing to examine the intestinal microenvironment, Tfh cell expansion, and functionality. Additionally, we analyzed the effects of palmitic acid on T-cell receptor signaling in Tfh cells

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and the role of KLF2 in Tfh cell dysfunction. **Results:** Mice fed an HFHC diet developed an inflamed intestinal microenvironment with enlarged PPs and expanded Tfh cells as early as 5 weeks after HFHC diet exposure. Tfh cells in MASH mice showed evidence of dysfunction, with defective GC responses and reduced IgA+ B cells. These dysfunctional Tfh-like cells were characterized by elevated KLF2, a transcription factor known to inhibit the differentiation of functional Tfh cells. Mechanistically, the HFHC diet increased palmitic acid levels in PP tissue, impairing TCR signal strength in T cells, leading to insufficient downregulation of KLF2 during Tfh differentiation. Tfh-deficient mice fed the HFHC diet showed compromised intestinal permeability, increased hepatic inflammation, and aggravated MASH. Transgenic mice with reduced KLF2 expression in CD4 T cells displayed improved Tfh cell function and ameliorated MASH, including hepatic steatosis, inflammation, and fibrosis after HFHC feeding. **Conclusion:** These findings highlight Tfh cells as key intestinal immune cells involved in the regulation of inflammation in the gut-liver axis during MASH. Elevated KLF2 in Tfh cells caused by diet-derived palmitic acid impairs their function, exacerbating disease progression. Targeting KLF2 in Tfh cells or diet-derived fatty acids may offer a novel therapeutic strategy for treating MASH.

Disclosures: Haiguang Wang: Nothing to Disclose, Xavier Revelo: Nothing to Disclose

2227 | DENDRITIC CELL MHC CLASS I EXPRESSION REGULATES DIET-INDUCED OBESITY AND METABOLIC DYSFUNCTION-ASSOCIATED FATTY LIVER DISEASE

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[1]North Carolina State University, Department of Molecular and Structural Biochemistry, [2]Mayo Clinic, Department of Immunology,

Background: Metabolic dysfunction-associated fatty liver disease (MASLD) is a rapidly increasing global epidemic. CD8+ T cells accumulate in the liver, driving hepatic inflammation and fibrosis known as metabolic dysfunction-associated steatohepatitis (MASH). However, factors responsible for activating CD8+ T cells remain unknown. CD8+ T cells are activated through T cell receptor signaling, which recognizes antigens presented on the major histocompatibility complex class I (MHC I) receptor. We discovered that myeloid cell expression of MHC I is necessary for diet-induced CD8+ T cell activation and liver fibrosis under high fat and carbohydrate diet conditions. Therefore, antigen-specific therapies may be beneficial for preventing MASH. Antigens can be presented by several cells, including dendritic cells. During MASH, XCR1+ dendritic cells are elevated and regulate hepatic inflammation and fibrosis. However, it is unknown if dendritic cell antigen presentation regulates MASH development. **Methods:** To address the role of antigen presentation and dendritic cells in MASH, we used a Cre-Lox mouse model targeting the knockdown of the MHC I gene H2Kb on CD11c+ cells (CD11c Kb KO). Wild-type (WT), MHC I KO, and CD11c Kb KO male mice were fed a chow or amylin diet for 28 weeks. At 28 weeks, liver tissues were collected and analyzed for activated CD8+ T cells and H2Kb+ myeloid cells by flow cytometry. Liver gene expression and histology were conducted to examine hepatic inflammation and fibrosis. Lipids were extracted by methyl-tert-butyl ether extraction and analyzed by a Vanquish UHPLC coupled with an Orbitrap Exploris 480 mass spectrometer. **Results:** MHC I KO and CD11c Kb KO mice fed the amylin diet demonstrated significant decreases in hepatic CD8+ T cells and collagen deposition compared to WT-fed mice. However, the CD11c Kb KO mice had significantly lower body, liver, and adipose tissue weights compared to WT and MHC I KO mice on the amylin diet. Lipidomics analysis revealed a significant reduction in total diglycerides in the CD11c Kb KO mice compared to WT and MHC I KO mice on the amylin diet. Additionally, the study examined hepatic lipid metabolism genes involved in diglyceride synthesis and fatty acid elongation. In WT mice on the amylin diet, the hepatic gene expression of elongation of very long chain fatty acids 3 (Elovl3) was reduced compared to mice fed a chow diet. Interestingly, the hepatic Elovl3 gene expression was significantly increased in CD11c Kb KO mice compared to WT mice on the amylin diet. **Conclusion:** Our research findings highlight the critical role of MHC I expression on dendritic cells in driving hepatic CD8+ T cell activation, inflammation, and fibrosis. Furthermore, the expression of MHC I on dendritic cells may be essential for regulating hepatic fatty acid elongation and diglyceride synthesis in MASH. This new insight into the pathogenesis of MASH identifies potential molecular targets for therapeutic interventions.

Disclosures: Victoria Adams: Nothing to Disclose, Kritika Shrestha: Nothing to Disclose, Xiaojing Liu: Nothing to Disclose, Aaron Johnson: Nothing to Disclose, Arion Kennedy: Nothing to Disclose

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2228 | SIRPA EXPRESSED IN T LYMPHOCYTES TRIGGERS ACTIVATION-INDUCED CELL DEATH IN HEPATOCELLULAR CARCINOMA

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[1]Peking University People's Hospital, Peking University Hepatology Institute

Background: Activation-induced cell death (AICD) is crucial for maintaining T lymphocytes homeostasis and peripheral immune tolerance. However, tumor-induced AICD of T lymphocytes is implicated in tumor immune evasion. This study focuses on unraveling the molecular mechanism of tumor-mediated AICD in hepatocellular carcinoma (HCC). **Methods:** Firstly, a genome-wide CRISPR/Cas9 knockout (GeCKO) library screening was conducted to identify key genes in Jurkat E6-1 cells. These cells were stimulated with ConA, PMA+PHA, or PMA+Ionomycin to induce activation-induced cell death (AICD). Subsequently, PCR and high-throughput sequencing were utilized to confirm the potential key genes, which was identified by enriched sgRNAs controlling AICD. The candidate genes were validated in Jurkat E6-1 cells, TCR-T cells (KRAS G12D), and T cells isolated from the blood of HCC patients using corresponding sgRNAs. Apoptosis assays were performed using flow cytometry. Immunohistochemistry (IHC) was employed to analyze the protein expression of these genes in T cells from human HCC tissues. Finally, knockout mice were used to identify the function of the candidate genes. **Results:** In the GeCKO library screening, 121 sgRNAs were identified to be enriched in the ConA group, PMA + PHA group, and PMA + Ionomycin group. Furthermore, transcriptome sequencing revealed distinct gene expression profiles of T lymphocytes in HCC tissues compared to adjacent tissues. Integrated analysis of the two datasets indicated that SIRPa may trigger AICD in T lymphocytes. In vitro experiments demonstrated that overexpression of SIRPa in Jurkat E6-1 cells, TCR-T cells, or T lymphocytes from HCC patient blood enhanced apoptosis, while depletion of SIRPa significantly inhibited apoptosis. Notably, the presence of $CD3^{+}SIRPa^{+}$ T cells in HCC tissues surpassed those in adjacent normal tissues. Analysis of RNA-seq data from the TCGA LIHC dataset showed that SIRPa levels were significantly higher in patients with advanced HCC compared to those with early HCC, and positively correlated with the frequency of tumor-infiltrating T cells. Importantly, T cells from SIRPa (-/-) mice could inhibit apoptosis following the stimulation with ConA. **Conclusion:** SIRPa expressed in tumor-infiltrating T cells may facilitate immune evasion in HCC by inducing AICD.

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

2229 | TARGETING INFLAMMATION AND IMMUNE DYSREGULATION IN ALCOHOLIC LIVER DISEASE WITH GRAPHENE OXIDE NANOPARTICLES

Hiral Aghara[1] Prashsti Chadha[2] Manali Patel[2] Palash Mandal[2]

[1]P D Patel Institute of Applied Science, [2]P D Patel Institute of Applied Sciences

Background: Excessive alcohol consumption is a primary cause of alcoholic liver disease (ALD), accounting for a 4% morbidity and mortality rate. ALD with several disease stages, involves sustained hepatic inflammation, oxidative and ER stress, which downregulate antioxidant and anti-inflammatory pathways. Gut dysbiosis exacerbates liver malfunction by translocating toxins from gut via portal vein, caused by disruption of barrier integrity and loss of antimicrobial agents like lectin. Several therapeutics are available, but none are FDA approved. Recently, nanoformulated materials have shown better results compared to individual forms. This study evaluates graphene oxide (GO) nanoparticles as mitigative and carrier agents. **Methods:** 8- 12 old male Wistar rats were fed Lieber-DeCarli diet with increasing concentrations of ethanol up to 5%, with 32% ethanol administered at 12-day intervals. The treatment group received 10 mg/kg GO suspension orally every 7th day. Blood parameters were evaluated, and tissue samples were collected for histological analysis. Lipid accumulation was assessed. Inflammatory markers (CCL2, IL1B, TNF-α, NFkB) and necroptosis-related genes were analysed, while anti-inflammatory and antioxidant activities were assessed through IL10 and Nrf2 expression, autophagy regulation markers were analysed using RT-qPCR. Gut barrier integrity and lectin activity analysed. **Results:** Chronic ethanol exposure severs the liver inflammation by upregulating inflammatory markers (IL1β, TNFα, NFκB) and necroptosis (RIPK1, RIPK3, MLKL) markers which was observed in histology staining. Further ethanol group showed higher liver/body weight ratio and blood parameter whereas, ethanol+GO (treatment) group had nearly identical results as control group. It was confirmed with downregulation of inflammatory genes, and

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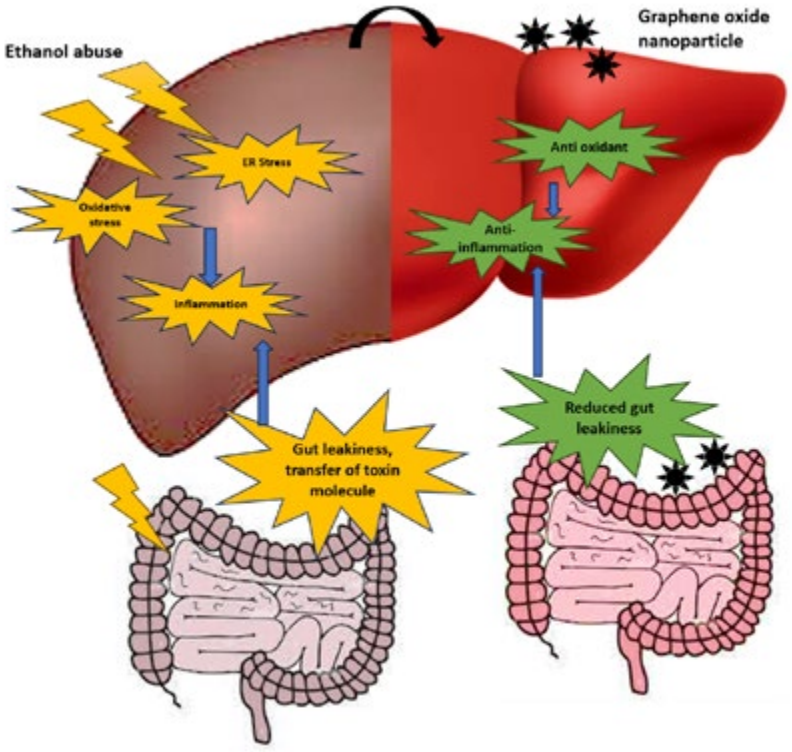
upregulation of antioxidant genes Nrf2 and IL10. GO downregulated CYP2E1 expression which was analysed with immunohistology study and targets autophagy-related genes (mTOR, beclin1, and protein kinase B) that regulate cell metabolism. GO also improved gut barrier function and lectin activity, mitigating gut dysbiosis. It further act as an anti-inflammatory molecule and help to protect liver from disrupted barrier integrity. **Conclusion:** GO nanoparticles show potential as therapeutic agents and drug delivery systems for ameliorating alcoholic liver disease, highlighting their role in disease prevention and treatment.



Disclosures: Hiral Aghara: Nothing to Disclose, Prashsti Chadha: Nothing to Disclose, Manali Patel: Nothing to Disclose, Palash Mandal: Nothing to Disclose

2230 | THE EFFECT OF HIGH-SALT DIET IN THE IMMUNOLOGY AND DEVELOPMENT OF HEPATOCELLULAR CARCINOMA

Amalia Tzoumpa[1] *Beatriz Lozano-Ruiz*[1] *Yin Huang*[1] *Joanna Pico*[1] *Melisa Gomez*[1] *Pedro Zapater*[1] *Jose Manuel Gonzalez-Navajas*[1]

[1]*ISABIAL*

Background: Tissue sodium storage has a significant impact on immune responses, and hepatocellular carcinoma (HCC) often arises in the context of chronic liver inflammation. We hypothesized that excessive salt intake, which may lead to sodium accumulation in the hepatic tumor microenvironment (TME), could modulate immune cell activation and response, thereby influencing the development of metabolic dysfunction-associated steatohepatitis (MASH)-associated HCC. **Methods:** C57BL6 male mice were fed with normal diet, Western Diet (WD) (high in fat, cholesterol, and sucrose), or a custom-made WD/high-salt-diet (WD/HS) that retains all the characteristics of WD except for a higher sodium content (4% NaCl). Mice received 16 weekly injections of carbon tetrachloride, and after 20 weeks, liver, spleen and blood samples were analyzed by flow cytometry, western blot and histology. In addition, $CD4^+$ T cells from the spleen and liver were isolated for *ex vivo* experiments. **Results:** All mice developed tumor after 20 weeks on either WD or WD/HS. Notably, significant differences were observed in HCC development between mice receiving WD or WD/HS as evidenced by tumor growth, histological analysis and Ki67 staining. In the TME, the WD/HS group exhibited changes in pathogenic macrophage-mediated inflammation, along with alterations in the mRNA levels of mrc1, cd274, and vegf. Immunophenotyping of the liver by flow cytometry showed a salt-dependent increase in Th1 and Th17/Th1 cells. Consistently, there was an

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upregulation in the protein level of Tbet and RORg; key transcription factors for Th1 and Th17 cells respectively. In addition, we detected altered levels of infiltrating $CD8^+$ $IFN\gamma^+$ cells in the WD/HS group, which were associated with tumor development. CD4+ T cells from the spleen and steatotic liver of the WD/CCL4 group were cultured *ex vivo* in the presence of sodium, either with TCR stimulation alone or with TCR stimulation combined with a Th1 cocktail. In both conditions, sodium strongly induced a Th1-like phenotype with increased IFN-γ production. *In vitro* experiments on HCC cell lines showed that salt does not have a direct effect on tumor growth suggesting that the observed phenotype *in vivo* may be attributed to the effect of salt on immune cells. **Conclusion:** High salt diet can alter tumor development on a MASH-HCC model by modulating immune response in the hepatic TME. Further experiments, including scRNA-seq on hepatic CD45 leukocytes, and impact on the efficacy of immune-checkpoint inhibitors therapy are ongoing to investigate specific mechanisms.

Disclosures: Amalia Tzoumpa: Nothing to Disclose, Beatriz Lozano-Ruiz: Nothing to Disclose, Yin Huang: Nothing to Disclose, Joanna Pico: Nothing to Disclose, Melisa Gomez: Nothing to Disclose, Pedro Zapater: Nothing to Disclose, Jose Manuel Gonzalez-Navajas: Nothing to Disclose

2231 | THE IMPACT OF PD-1$^+$INNATE-LIKE CD8+ T CELLS ON THE HBSAG REDUCTION IN ACTIVE CHRONIC HEPATITIS B PATIENTS RECEIVING NUCLEOS(T)IDE ANALOGUE THERAPY

Rachel Wen-Juei Jeng[1] Hsiang-Wei Huang[1] Chia-Wei Lin[1] Jian He Fan[1] Yen-Chun Liu[1] Wei-Ting Ku[1] Cheng-Heng Wu[1] Chien-Hao Huang[2] Yung-Chang Lin[1] CHUN YEN LIN[1]

[1]Chang Gung Memorial Hospital, Linkou Medical Center, Taiwan, [2]Chang Gung University

Background: HBsAg kinetics during Nuc treatment in CHB patients is essential for achieving a functional cure. This study investigates factors affecting on-treatment HBsAg reduction and the role of PD-1 positive and negative innate-like CD8+ T cells in active CHB patients undergoing Nuc treatment. **Methods:** CHB patients with active hepatitis [ALT >=2 times (x) ULN) were analyzed. Flow cytometry assessed innate-like T cells ($CD38^+HLADR^+CD8^+$ T cells, Huang CH, Hepatology, 2022), PD-1^+CD8+ T cells, PD-1^+ innate-like T cells, PD-1^- innate-like T cells, activated regulatory T cells ($CD45RA^-Foxp\text{-}3^{high}CD4^+$T cells). Spearman correlation explored relationships between pretherapy factors, innate-like CD8+ T cells, and on-treatment HBsAg kinetics. Logistic regression identified predictors for rapid HBsAg decline (>0.5 $\log_{10}$IU/mL/year), while linear regression analyzed factors associated with HBsAg reduction ($\log_{10}$IU/mL/year) during treatment. **Results:** Out of 43 CHB patients, with median age 54, 79% male, and 74% genotype B, 26% genotype C. Median HBV DNA, HBsAg, and ALT levels were 6.67 $\log_{10}$IU/mL, 3.35$\log_{10}$IU/mL, and 146 U/L, respectively. Hepatitis flare (ALT >= 5 x ULN) and rapid HBsAg decline occurred in 16 and 23 patients, respectively. Multivariate analysis identified pretherapy ALT levels as independent factors for rapid HBsAg decline or reduction magnitude (aOR: 1.015, P=00108; Estimate: 0.018, P=0.0005). Pretherapy HBsAg levels were associated with HBsAg reduction, with AUROC of 0.909 (P<0.0001). An HBsAg level >= 3.6 $\log_{10}$IU/mL indicated higher rapid decline in both ALT >=5X (100% vs. 40%, P=0.0179) and 2-5X ULN (66.7% vs. 12.5%, P=0.0786). As for the immunological aspect of these patients, PD-1^+innate-like T cells proportion was positively correlated with pretherapy ALT levels (r=0.324, P=0.034), but not with HBsAg (P=0.901) or HBV DNA (P=0.561) levels. Among patients with pretherapy HBsAg < 3.6 $\log_{10}$IU/mL, PD-1^+ innate-like T cells showed significant association with HBsAg decline (estimate: 0.0198, P=0.0230). **Conclusion:** In Nuc-treated active CHB patients, pretherapy ALT level is the main independent factor for HBsAg reduction. As for immunologic aspect, PD-1^+innate-like T cells showed positive correlation with pretherapy ALT levels. Its significant association with HBsAg decline only show in patients with pretherapy HBsAg < 3.6 $\log_{10}$ IU/mL.

Disclosures: Rachel Wen-Juei Jeng: Nothing to Disclose, Hsiang-Wei Huang: Nothing to Disclose, Chia-Wei Lin: Nothing to Disclose, Jian He Fan: Nothing to Disclose, Yen-Chun Liu: Nothing to Disclose, Wei-Ting Ku: Nothing to Disclose, Cheng-Heng Wu: Nothing to Disclose, Chien-Hao Huang: Nothing to Disclose, Yung-Chang Lin: Nothing to Disclose, CHUN YEN LIN: Nothing to Disclose

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2232 | CLM-022, A POTENT INHIBITOR OF NLRP3 INFLAMMASOME-MEDIATED PYROPTOSIS, AS A POTENTIAL TREATMENT FOR ACUTE AND CHRONIC INFLAMMATORY LIVER DISEASES

Guillaume Vidal[1] Hana El Khatib[1] Alexandra Caron[1] Elodie Delecroix[1] Maryse Malysiak[1] Nicolas Stankovic Valentin[1] Hum Dean[1] Bart Staels[2] Sakina Sayah Jeanne[1]

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Background: Inflammation is a common element in the pathogenesis of most chronic liver diseases leading to fibrosis, cirrhosis and liver failure. Inflammation is characterized by activation of innate immune cells, production of pro-inflammatory cytokines and pyroptosis. which is a lytic form of inflammatory regulated cell death, initially observed in bacteria-infected macrophages (Knorr et al 2021). Pyroptosis is regulated by inflammasomes which are intracellular multiprotein complexes also expressed in both parenchymal and non-parenchymal cells of the liver. In response to cellular danger signals, inflammasomes activate caspase-1, release IL-1β and IL-18. The aim of this work was to investigate the effect of CLM-022, a NLRP3 inhibitor, on inflammasome-driven inflammation and pyroptosis. **Methods:** To assess the in vitro activity of CLM-022 on inflammasome activation, LPS-primed THP1 macrophages were stimulated with nigericin. NLRP3 complex assembly, cleaved-gasdermin D production, IL1-β release and pyroptotic cell death were assessed by western blot, ELISA and ATP measurement, respectively. For in vivo studies, acute liver failure and inflammation were triggered through galactosamine (GalN) and lipopolysaccharide (LPS) injection in mice. A single dose of CLM-022 (10 mg/kg) or vehicle was orally administered 1h prior to GalN/LPS LPS injection. **Results:** CLM022 treatment blocks NLRP3 complex assembly, reflected by loss of ASC oligomers, and inhibits induction of cleaved-GSDMD (marker of pyroptosis). CLM022 is active when added both before or after nigericin stimulation, and strongly inhibits IL-1β production (IC_{50} ~200nM) and pyroptotic cell death (from 0.1µM to 1µM). In vivo CLM022 inhibits circulating IL-1β in the GalN/LPS model and decreases inflammasome pathway activation in the liver. **Conclusion:** There are currently no approved treatments that act directly on the underlying key pathophysiologic mechanisms that lead to liver failure, such as the systemic inflammatory response. Understanding the underlying molecular and regulatory mechanisms in inflammation and inflammatory cell death that might be involved in the progression of diseases will help to develop novel highly demanded therapies. CLM022, by inhibiting IL1-β production and pyroptosis through its activity on NLRP3, has potential for the treatment of acute and chronic inflammatory liver diseases, including ACLF.

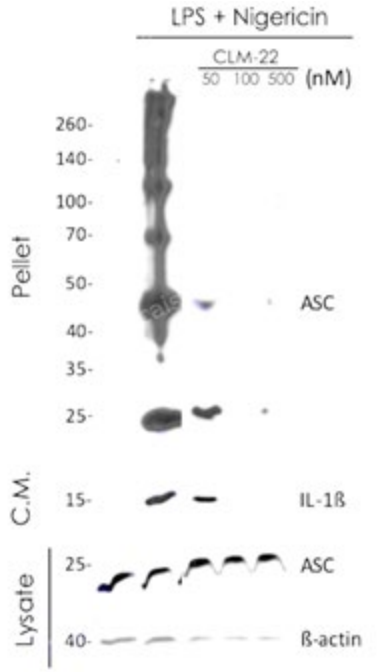

FIGURE depicts western blot images showing the antiinflammasome activity of CLM-022 by detecting the level of cellular ASC complex and the mature form of IL-1β

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Disclosures: Guillaume Vidal: Genfit SA: Employee, Hana El Khatib: Genfit SA: Employee, Alexandra Caron: Genfit SA: Employee, Elodie Delecroix: Genfit sa: Employee, Maryse Malysiak: Nothing to Disclose, Nicolas Stankovic Valentin: Nothing to Disclose, Hum Dean: Nothing to Disclose, Bart Staels: Genfit SA: Consultant, Sakina Sayah Jeanne: Nothing to Disclose

2233 | HIGH-THROUGHPUT IN VIVO POOLED SCREENING OF INFLAMMATION-RELATED TARGETS IN HEPATOCYTES PREDICTS CLINICAL OUTCOMES

Joanne Hsieh[1] Caroline Duwaerts[1] Hikaru Miyazaki[1] Chris Carrico[1] Vinay Kartha[1] Linda Chio[1] Daniel Fuentes[1] Jingshu Chen[1] Smitha Shambhu[1] Dimitry Popov[1] Ian Driver[1] Chris Towne[1] Francisco LePort[1] Martin Borch Jensen[1]

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Background: Inflammation is a key feature of MASH, yet there remains an incomplete understanding of the role of the immune system in its pathogenesis. *In vivo* models remain the best systems to study the intricacies of inflammation in MASH, as *in vitro* systems poorly recapitulate the myriad immune cells and the different microenvironments that promote their pathogenic or restorative roles. **Methods:** To screen in a context that accurately reflects the diseased liver milieu, we simultaneously targeted hundreds of barcoded gene therapies to hepatocytes in a diet-induced obese mouse model of MASH. In a single animal, we examined over 100 overexpression targets encompassing multiple aspects of inflammation. Since many of the interventions were chemokines and cytokines that affect neighboring cells, hepatocyte transduction rate was titrated so that the majority of hepatocytes (about 93%) were not affected, thereby minimizing cross-interactions of individual interventions. Each intervention's transcriptomic effect was then examined by single nucleus RNA-Seq to determine the expression of curated gene sets which we've deemed "disease features." **Results:** Multiple inflammatory interventions showed generally undesirable directionalities in many disease features. Hepatocytes with *Il6* overexpression had the greatest induction in the IL-6 signaling feature, as expected. *Il6* overexpression also promoted expression of pro-fibrotic and pro-tumorigenic features. There was reduced expression of genes associated with *de novo* lipogenesis and low density lipoprotein production, which would have suggested a beneficial metabolic effect. However, based on decreased transcriptional activity of liver functionality, this was likely due to an overall decline in hepatocyte identity. Multiple features of liver regeneration were upregulated, consistent with the essential role of IL-6 in recovery from partial hepatectomy. Overexpression of *Ccl3* (also known as MIP-1alpha) in hepatocytes increased expression of multiple fibrosis features and decreased indications of hepatocyte function. The transcriptome of *Ccl3* overexpression also suggested a tumorigenic effect of this chemokine. Overexpression of dominant negative *TLR4* was used to model the TLR4 antagonist that was outperformed by placebo in a clinical trial. This intervention showed increased gene expression of the transforming growth factor beta signaling and apoptosis features. **Conclusion:** The single nucleus-level transcriptome of a gene therapy intervention reveals information about the physiological and pathological functions of its target, and could predict clinical outcomes. As evidenced by the *Ccl3* overexpression results, the hepatocyte transcriptomic response could reveal implications of specific immune cell recruitment and activation. This enables us to use hepatocytes to query the effects of non-parenchymal cell-directed factors.

Disclosures: Joanne Hsieh: Gordian Biotechnology: Employee, Caroline Duwaerts: Gordian Biotechnology: Employee, Hikaru Miyazaki: Nothing to Disclose, Chris Carrico: Gordian Biotechnology: Employee, Vinay Kartha: Nothing to Disclose, Linda Chio: Gordian Biotechnology: Employee, Gordian Biotechnology: Stock – privately held company, Daniel Fuentes: Nothing to Disclose, Jingshu Chen: Nothing to Disclose, Smitha Shambhu: Nothing to Disclose, Dimitry Popov: Nothing to Disclose, Ian Driver: Nothing to Disclose, Chris Towne: Nothing to Disclose, Francisco LePort: Nothing to Disclose, Martin Borch Jensen: Nothing to Disclose

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2234 | NLRP3 ACTIVATION IN MONOCYTES DRIVES MURINE LIVER INFLAMMATION AND FIBROGENESIS

Christian Stoess[1] Janset Onyuru[1] ZheHao Tan[1] Yeon-Kyung Choi[1] Aleksandra Leszczynska[1] Lori Broderick[1] Ben Croker[1] Hal Hoffman[1] Ariel Feldstein[2]

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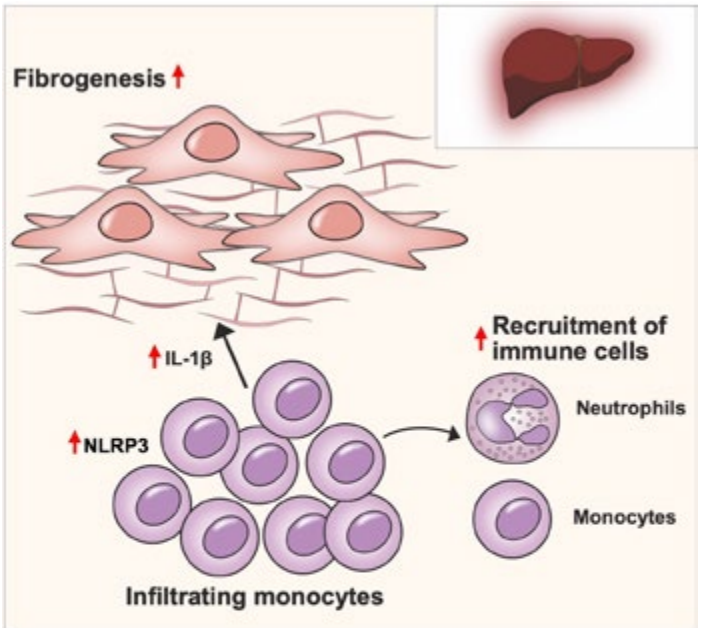
Background: Infiltrating monocytes play a role in various liver pathologies, including MASLD/MASH. Previous data have shown that NLRP3 activation contributes to liver inflammation and fibrosis. However, the role of the NLRP3 inflammasome in monocytes remains unknown. The chemokine receptor CX3CR1 is widely expressed in the mononuclear phagocyte system, whereas Kupffer cells do not express this receptor. Therefore, targeting inflammasome activation in infiltrating monocytes in the liver using CX3CR1-Cre models may help understand their specific roles in acute and chronic liver diseases. **Methods:** To study inflammasome activation in the mononuclear phagocyte system, we used an *Nlrp3*$^{D301N/+}$ CX3CR1-Cre knock-in mouse that constitutively expresses a mutant active Nlrp3 limited to monocytes. To complement this mutant active Nlrp3 line, we also utilized a monocyte-specific *Nlrp3*$^{fl/fl}$ CX3CR1-Cre knock-out mouse line. Mice were challenged with LPS + ATP i.p. to activate canonical inflammasome activation and pyroptosis. ELISA, PCR, immunostaining, TUNEL assay, flow cytometry and Western Blotting were used to investigate liver fibrosis, inflammation and cell death. **Results:** *Nlrp3*$^{D301N/+}$ CX3CR1-Cre knock-in mice displayed splenomegaly and elevated serum IL-1β. The liver fibrosis markers *Col1a*, *Col3a* and *Timp1* were increased, and sirius red staining confirmed increased collagen deposition in the liver. Flow cytometry analysis of the blood revealed neutrophilia but normal numbers of monocytes. In the liver, infiltration of monocytes and neutrophils was elevated. TUNEL assay showed a significant increase in cell death. Nlrp3 deficiency in monocytes abrogated monocyte infiltration to the liver after canonical inflammasome activation with LPS+ATP, consistent with reductions in IL-1β in the peritoneal lavage and the serum. **Conclusion:** Monocyte NLRP3 activation contributes to liver inflammation and fibrosis independently of Kupffer cells. Defining the host factors in the liver triggering pyroptosis of infiltrating monocytes may help delineate the pathobiology of other inflammatory liver diseases such as MASH with implications for targeted therapy.



Graphical abstract: NLRP3 activation in monocytes increases the infiltration of monocytes and neutrophils to the liver. Collagen deposition is increased in the inflamed liver. Nlrp3 deficiency in monocytes abrogated monocyte infiltration to the liver after LPS+ATP challenge, consistent with reductions in IL-1β.

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Disclosures: Christian Stoess: Nothing to Disclose, Janset Onyuru: Nothing to Disclose, ZheHao Tan: Nothing to Disclose, Yeon-Kyung Choi: Nothing to Disclose, Aleksandra Leszczynska: Nothing to Disclose, Lori Broderick: Novartis, Inc.: Independent Contractor, Ben Croker: Nothing to Disclose, Hal Hoffman: Nothing to Disclose, Ariel Feldstein: Nothing to Disclose

2235 | PYRUVATE-DRIVEN B CELL EFFECTOR RESPONSES AND IGG-MEDIATED HEPATIC STELLATE CELL ACTIVATION EXACERBATE MASH PROGRESSION

Fanta Barrow[1] Xavier Revelo[1] Enis Kostallari[2] Shalil Khanal[3] Haiguang Wang[1] Gavin Fredrickson[1] Erin Ciske[1] Kira Florczak[1] Preethy Parthiban[1]

[1]University of Minnesota, [2]Mayo Clinic Rochester, [3]Mayo Clinic

Background: Metabolic dysfunction-associated steatohepatitis (MASH) is an increasingly prevalent and severe form of steatotic liver disease. Characterized by inflammation, hepatocyte injury and fibrosis, MASH is driven by the global rise in obesity and metabolic syndrome. The immune system plays a crucial role in the pathogenesis and progression of MASH. Our previous studies have shown that pathogenic B cells accumulate in the livers of MASH patients and mouse models, where they contribute to the inflammatory milieu and influence hepatic injury and fibrosis. However, the precise mechanisms by which B cells drive fibrosis and the metabolic adaptations responsible for their pathogenic responses remain poorly understood. **Methods:** We established a mouse model of MASH by feeding mice a high-fat, high-carbohydrate diet to mimic human MASH. We functionally phenotyped B cells using mass cytometry and single-cell RNA and secretome sequencing. B cell receptor (BCR) repertoire sequencing was utilized to determine clonality in MASH livers. To investigate metabolic adaptations favoring B cell pathogenicity, we performed seahorse assays and metabolomics analyses. Furthermore, we explored the interactions between B cells and hepatic stellate cells (HSCs) using immunohistochemistry and co-cultures. To elucidate antigen-specific B cell responses, we employed a BCR restriction mouse model where the BCR repertoire is limited to an irrelevant antigen. **Results:** Mature B cells with heightened cytokine responses accumulated in the liver during MASH, along with increased IgG antibody deposition, both correlated with MASH severity in humans. BCR sequencing revealed a higher frequency of unique B cell clones in MASH livers, indicating an elevated response to multiple antigens. Furthermore, MASH intrahepatic B cells increased ATP production via oxidative phosphorylation selectively fueled by pyruvate oxidation to meet effector demands. Remarkably, blocking pyruvate oxidation completely abrogated the inflammatory capacity of MASH B cells in a BCR-specific manner. Accordingly, in a mouse model with of BCR restriction, MASH was attenuated, with reduced steatosis, hepatic inflammation, and fibrosis. BCR restriction decreased B cell maturation, activation and effector responses in the liver, accompanied by decreased T cell- and macrophage-mediated inflammation. Moreover, BCR-restricted mice had lower IgG production and decreased expression of Fc-gamma receptors on hepatic stellate cells, leading to substantial reduction in liver fibrosis. Notably, we discovered that IgG antibodies promote the activation of HSCs. **Conclusion:** Our findings reveal that intrahepatic B cells drive hepatic inflammation and fibrosis in MASH via metabolic shifts, pro-inflammatory cytokines, and pro-fibrogenic IgG. With few FDA-approved MASH therapies, targeting pyruvate and IgG shows promise for mitigating MASH progression and improving outcomes

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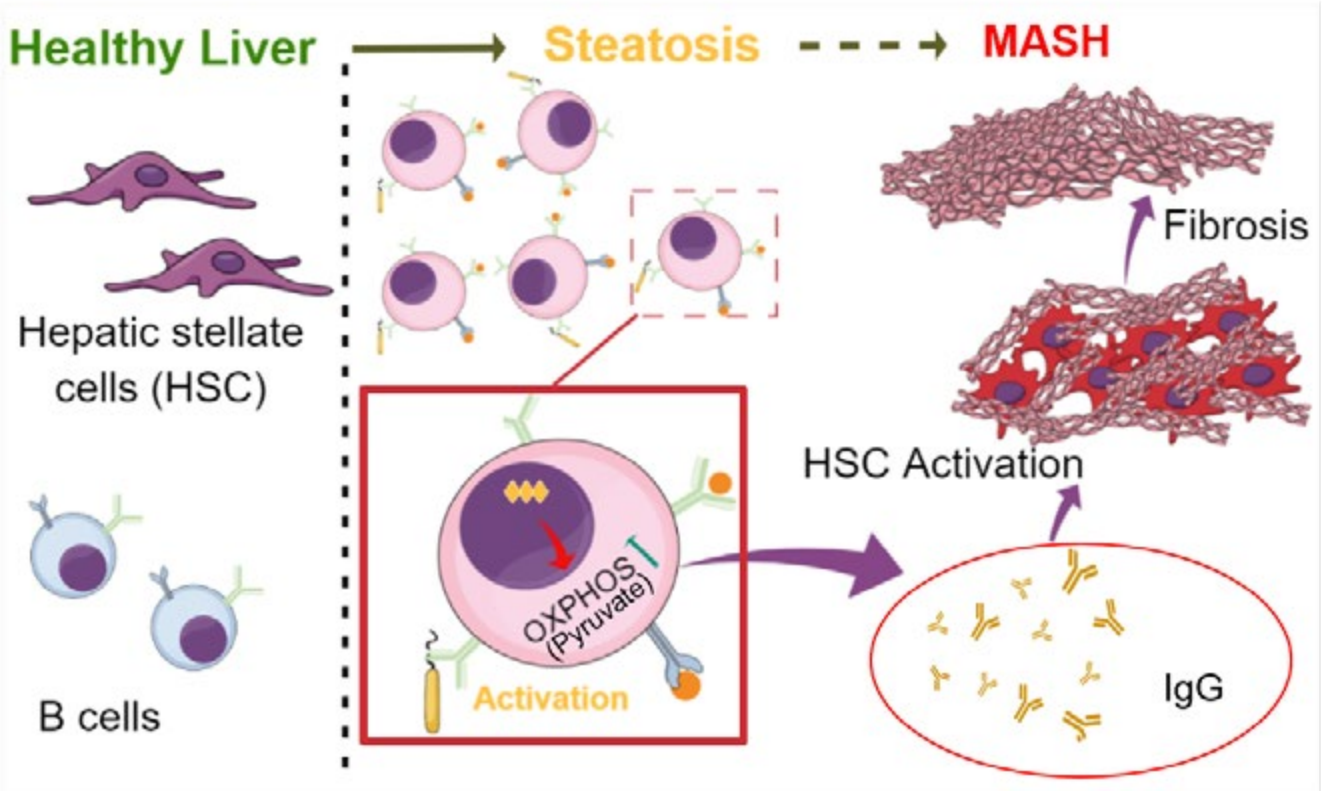

Disclosures: Fanta Barrow: Nothing to Disclose, Xavier Revelo: Nothing to Disclose, Enis Kostallari: Nothing to Disclose, Shalil Khanal: Nothing to Disclose, Haiguang Wang: Nothing to Disclose, Gavin Fredrickson: Nothing to Disclose, Erin Ciske: Nothing to Disclose, Kira Florczak: Nothing to Disclose, Preethy Parthiban: Nothing to Disclose

2236 | EXOGENOUS ARGININE DIFFERENTIALLY REGULATES INFLAMMATORY CYTOKINE AND INDUCIBLE NITRIC OXIDE SYNTHASE EXPRESSION IN MACROPHAGES

Kelsey Stayer[1] Saliha Pathan[1] Aalekhya Biswas[1] Huiqiao Li[1] Yi Zhu[1] Fong Lam[1] Juan Marini[1] Sundararajah Thevananther[1]

[1]Baylor College of Medicine

Background: Immune dysfunction and late mortality from multiorgan failure are hallmarks of severe sepsis. Cytokine storm and liver injury lead to the depletion of systemic Arginine (ARG). However, arginine supplementation in sepsis remains controversial due to the potential to upregulate inducible nitric oxide synthase (iNOS)-mediated excessive nitric oxide (NO) generation in macrophages, leading to vasodilation and hemodynamic catastrophe. Citrulline (CIT) supplementation has been considered as an alternative means of replenishing ARG via de novo synthesis which is orchestrated by argininosuccinate synthase 1 (ASS1) and argininosuccinate lyase (ASL). However, the functional relevance of the ASS1-ASL pathway in macrophages after endotoxin stimulation is unclear but is crucial to consider amino acid restoration as a tool for treating sepsis. We aimed to determine if CIT is a functional substitute for ARG for macrophage activation and NO generation. **Methods:** Murine bone-marrow derived (BMDM) and peritoneal (PM) macrophages or Raw264.7 cells were cultured in ARG-free media (DMEM for SILAC, 10% dialyzed FBS) or media supplemented with 125 μM ARG or CIT and activated with lipopolysaccharide (LPS, 1 μg/mL) for 30 mins to 24 hr. Total protein extracts were analyzed by Western blotting with densitometric analysis of band intensity and total RNA was analyzed by qRT-PCR. To determine NO production, media was supplemented with 0-1000 μM of ARG or CIT and activated with LPS (1 μg/mL) for 24 hr. Culture supernatants were analyzed for NO (Greiss assay) and proinflammatory cytokines and chemokines (Luminex xMAP bead-based assay). Data were analyzed using ANOVA with Tukey's post-hoc test or a 4PL regression model. **Results:** LPS-mediated iNOS, ASS1, ASL protein expression (BMDM, PM, Raw264.7), and NO generation (Raw264.7) depended on exogenous ARG in macrophages. Exogenous

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CIT was not sufficient to restore NO generation in ARG-free conditions. Despite the induction of iNOS and ASS1 mRNA in ARG-free conditions, exogenous ARG was necessary to overcome eIF2a (elongation initiation factor 2a)-mediated transcriptional repression of iNOS and ASS1 protein expression. Moreover, exogenous ARG, but not CIT, selectively modified the inflammatory cytokine and chemokine expression profile of LPS-activated macrophage. **Conclusion:** CIT is insufficient for LPS-mediated iNOS protein induction and NO production in macrophages, suggesting dependency on exogenous ARG. CIT supplementation may be a safe alternative to ensure ARG availability to deficient tissues while evading detrimental hyperproduction of NO. Our study highlights the complex, differential regulation of proinflammatory cytokine expression, and NO generation by exogenous arginine in macrophages. These findings have important implications for using amino acid supplementation as a potential therapy for sepsis.

Disclosures: Kelsey Stayer: Nothing to Disclose, Saliha Pathan: Nothing to Disclose, Aalekhya Biswas: Nothing to Disclose, Huiqiao Li: Nothing to Disclose, Yi Zhu: Nothing to Disclose, Fong Lam: Nothing to Disclose, Juan Marini: Nothing to Disclose, Sundararajah Thevananther: Nothing to Disclose

2237 | LIVER DISEASE IN PATIENTS WITH CTLA 4 HAPLOINSUFFICIENCY: AN IN VIVO SCENARIO TO UNDERSTAND CPI RELATED LIVER INJURY

Gracia Viana Rodriguez[1] Disha Sharma[1] Katherine Howe[2] Christopher Koh[1] Steven Holland[2] Gulbu Uzel[2] Theo Heller[1]

[1]National Institute of Diabetes and Digestive and Kidney Diseases, [2]National Institute of Allergy and Infectious Diseases

Background: Immune-mediated activation of the T lymphocyte antigen 4 (CTLA-4) pathway is well described, and the monoclonal antibody blockade with checkpoint inhibitors (CPI) has revolutionized cancer therapy. Acute hepatocellular and cholestatic liver injury secondary to T cell overactivation during CPI therapy is being increasingly understood. Heterozygous germline mutations in CTLA4 cause a rare autosomal dominant inborn error of immunity called CTLA 4 haploinsufficiency, which is mimicked by CPI-related immune adverse effects. This disease usually presents in childhood with recurrent infections, cytopenia, lymphoproliferative disorders & autoimmune infiltration of non-lymphoid organs. We aimed to characterize the patterns of liver disease involvement in patients with CTLA4 haploinsufficiency. **Methods:** Retrospective, single-center study. Patients with CTLA4 haploinsufficiency were selected from NIH protocol 93-I-0119. Demographic, laboratory, radiological, and histologic data were collected for all patients evaluated at the NIH clinical center. Ishak score was used to evaluate degree of fibrosis on liver biopsy and R factor was calculated to assess the pattern of liver injury. **Results:** Of 68 patients with CTLA4 haploinsufficiency, 52% were male, with a median age of 33 years & median onset of disease at 12 years (IQR 6-22). Only one patient (1.5%) was symptomatic with pruritus. 50% had at least one liver enzyme elevation above the upper limit of normal (ULN), with the cholestatic pattern being most common (74%), mixed (20%) & hepatocellular (6%). Liver enzyme elevation was usually mild, with a median of 1.5 x ULN (IQR 1.1-1.9). 32% (19/58) of patients who underwent cross-sectional abdominal imaging were noted to have hepatomegaly, and 37 % had splenomegaly. 9 patients with elevated liver enzymes and abnormal imaging findings underwent liver biopsy. All biopsies showed either hepatocyte or bile duct inflammation, with variable degrees of fibrosis (IF 0-6), including 1 patient with cirrhosis. 4 patients had histopathology consistent with Porto-sinusoidal vascular disease (PSVD), and 3/4 had evidence of collaterals on cross-sectional images. There was no reported decompensated liver disease in the cohort. **Conclusion:** CTLA-4 haploinsufficiency is a systemic immune dysregulation disorder with multi-organ involvement, including the liver. Liver disease pattern is primarily cholestatic with evidence of NRH and fibrosis in some patients. Most patients are asymptomatic which makes screening and early laboratory, radiological, and histological evaluation paramount for diagnosis and management in this high-risk patient population.

Disclosures: Gracia Viana Rodriguez: Nothing to Disclose, Disha Sharma: Nothing to Disclose, Katherine Howe: Nothing to Disclose, Christopher Koh: Nothing to Disclose, Steven Holland: Nothing to Disclose, Gulbu Uzel: Nothing to Disclose, Theo Heller: Nothing to Disclose

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2238 | THE ROLE OF HEME IN SEPSIS-INDUCED KUPFFER CELL LOSS AND SENESCENCE

Joseph Adams[1] *TINGTING LI*[1] *Xiaohui Wang*[2]

[1]*East Tennessee State University,* [2]*Harvard University Medical School*

Background: Sepsis, a leading cause of death in intensive care units (ICUs), lacks FDA-approved treatments. Hepatic dysfunction is a significant predictor of sepsis mortality and severity. Kupffer cells (KCs), the liver-resident macrophages, serve as a first line of defense in bacterial clearance. Our preliminary study observed that sepsis or bacterial infection leads to severe Kupffer cell loss; however, the underlying mechanisms remain unclear. Additionally, circulating heme levels significantly increase during the early stages of sepsis. This study aims to explore the mechanisms by which sepsis leads to Kupffer cell loss, with a specific focus on heme. **Methods:** C57BL/6 mice were treated with heme before inducing sepsis through the Cecal Ligation and Puncture (CLP) method. Liver tissues and blood samples were collected at 6 and 24 hours post-CLP. Circulating heme levels and bacterial load in the blood were measured using a heme assay kit and CFU assay, respectively. KC loss and senescence were analyzed by immunostaining. Survival rates were monitored for one week following CLP-induced sepsis. Additionally, Bone Marrow-Derived Macrophages (BMDMs) and THP-1 cells (a human macrophage cell line) were treated with heme (100 μM) and BAA 197, a multidrug-resistant E. coli strain. Post-treatment, cell death was examined by PI staining. The activation of the cGAS-STING pathway and cellular senescence were evaluated by western blot. THP-1 cells were pretreated with the STING inhibitor C-176 before being exposed to heme and bacteria, followed by analysis of cell death. **Results:** Sepsis leads to a marked reduction in KC populations and elevated serum heme levels. Increased heme contributes to KC loss and senescence in liver tissue and cultured cells. Furthermore, increased heme significantly impaired bacterial clearance and increased mortality. Additionally, increased heme exacerbates BAA-induced cGAS-STING signaling activation, which contributes to cellular senescence and death. STING inhibitor C-176 treatment attenuated heme and BAA-induced BMDM and THP-1 cell death and senescence. **Conclusion:** Sepsis-induced hemolysis leads to elevated free heme levels, which are major contributors to sepsis-associated Kupffer cell loss, senescence, and mortality. Mechanistically, increased heme enhances bacterial-induced cGAS-STING signaling activation, which contribute to heme and BAA-induced cell death and senescence.

Disclosures: Joseph Adams: Nothing to Disclose, TINGTING LI: Nothing to Disclose, Xiaohui Wang: Nothing to Disclose

2239 | A LARGE-SCALE METABOLOMICS SCREEN TO DEFINE PATHWAYS FOR MICROBIOME-DERIVED SMALL MOLECULES

Kazuma Sekiba[1] *Bi-Huei Hou*[1] *Haoqing Chen*[1] *Yuanyuan Liu*[1] *Zhiwei Zhou*[1] *Ayana Crawl-Bey*[2] *Dylan Dodd*[1]

[1]*Stanford University School of Medicine,* [2]*Howard University College of Medicine*

Background: The gut microbiome makes dozens of chemically diverse small molecules that are absorbed directly into the portal venous system, destined for the liver where they mediate critical functions related to liver health. However, the microbial genes that encode these metabolic pathways are largely unknown, and defining them is typically a slow serial process of gene prediction, targeted mutation, and phenotype testing. Here, we aimed to develop a tool to interrogate hundreds of microbial genes at scale. **Methods:** A mariner transposon mutagenesis system was used to induce mutations in one of the most metabolically versatile gut commensal bacteria, *Clostridium sporogenes*. Ten thousand individual transposon mutants were isolated using a colony-picking robot under anaerobic conditions and cultured in a defined medium. Culture supernatants were then subjected to a newly developed high-throughput liquid chromatography-mass spectrometry (LC-MS) assay to quantify >30 metabolites in less than 5 minutes per sample. Mutants with significant metabolic phenotypes were genotyped using arbitrarily primed PCR. CRISPR gene editing, isotope tracing, and gnotobiotic mouse colonization were used to mechanistically interrogate the identified genes. The distribution of identified genes in the human gut was assessed using human gut microbiome data. **Results:** By sequencing ~200 randomly selected mutants, we found that transposon insertion is evenly distributed across the bacterial chromosome. We applied this LC-MS platform to ~10,000 mutants and sequenced over 300 mutants with significant phenotypes. The identified genes were categorized into three groups: 1) genes likely involved in housekeeping functions

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manifesting pleiotropic effects on multiple metabolites, 2) genes previously known to be involved in pathways for metabolites, and 3) novel genes which we have now genetically linked to specific metabolic pathways for metabolites. The identified genes were not limited to those encoding metabolic enzymes, also genes encoding transporters and genes involved in cofactor synthesis were discovered. The novel genes were distributed in other human gut bacteria, demonstrating that our platform provides insight into the microbial processes in the gut that generate metabolites that influence liver health. **Conclusion:** We determined microbial genes responsible for microbial metabolites at a genome-wide scale. This comprehensive study provides valuable insights into the mechanisms underlying the microbiome's influence on the gut-liver axis.

Disclosures: Kazuma Sekiba: Nothing to Disclose, Bi-Huei Hou: Nothing to Disclose, Haoqing Chen: Nothing to Disclose, Yuanyuan Liu: Nothing to Disclose, Zhiwei Zhou: Nothing to Disclose, Ayana Crawl-Bey: Nothing to Disclose, Dylan Dodd: Nothing to Disclose

2240 | CHRONIC STRESS PROMOTES INTRAHEPATIC CHOLANGIOCARCINOMA PROGRESSION VIA T-CELL EXHAUSTION INDUCED BY LACTOBACILLUS_SP. AND TRYPTOPHAN METABOLISM

Xiaozai Xie[1] Zhiyuan Bo[2] Yi Wang[1]

[1]Wenzhou Medical University, [2]The First Affiliated Hospital of Wenzhou

Background: Intrahepatic cholangiocarcinoma (ICC) is one of the most aggressive malignant tumors with limited treatment options and poor prognosis. Chronic stress has been gradually recognized to play a role in regulating tumor immunity, particularly in reshaping the tumor microenvironment. We found chronic stress can induce disturbances in tryptophan metabolism through alterations in specific gut microbiota, leading to T-cell exhaustion in the tumor microenvironment and accelerating the progression of intrahepatic cholangiocarcinoma. **Methods:** We established intrahepatic-cholangiocarcinoma model through using high-pressure hydrodynamic injection of oncogene plasmids $KRAS^{G12D}$, CRISPR/Cas9 sgRNA-p19 and transposon plasmids pCMV-SB1 into the tail vein of mice, followed by chronic social defeat stress (CSDS). We analyzed the changes in gut microbiota and their metabolites in cholangiocarcinoma mice through metagenomic and metabolomic high-throughput sequencing. We confirmed the effects of differential microbiota and metabolite changes on tumor progression through gavage experiments. Changes in the tumor immune microenvironment were detected using multiple immunohistochemistry techniques and flow cytometry. Lastly, we explored the key role of gut microbiota and their metabolite changes in cholangiocarcinoma progression and tumor immune microenvironment through fecal microbiota transplantation (FMT) and pseudo germ-free mouse models which combined with differential gut microbiota and metabolite gavage treatments **Results:** We found that ICC mice under CSDS (ICC&CSDS mice) exhibited significant depressive-like behaviors. Furthermore, ICC&CSDS mice showed more rapid tumor progression. Additionally, metagenomic sequencing of gut microbiota in ICC&CSDS mice revealed a significant decrease in the abundance of Lactobacillus_sp. and downregulation of tryptophan metabolism compared to normal ICC mice. Subsequent observations of tumor progression after FMT and gavage with Lactobacillus_sp. and tryptophan confirmed that alterations in Lactobacillus_sp. and tryptophan induced by chronic stress significantly promoted cholangiocarcinoma progression. Furthermore, using multiplex immunohistochemistry and flow cytometry techniques, we found that gavage with Lactobacillus_sp. and tryptophan significantly alleviated T-cell functional impairment in the immune microenvironment and enhanced the therapeutic efficacy of immune checkpoint inhibitors. **Conclusion:** In summary, chronic stress significantly promotes the progression of cholangiocarcinoma, and the underlying mechanism may involve alterations in the gut microbiota Lactobacillus_sp. and tryptophan metabolism pathway, leading to T-cell exhaustion in the immune microenvironment and ultimately accelerating cholangiocarcinoma progression.

Disclosures: Xiaozai Xie: Nothing to Disclose, Zhiyuan Bo: Nothing to Disclose, Yi Wang: Nothing to Disclose

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2241 | CHRONIC STRESS-MEDIATED TAURINE ENTEROHEPATIC CIRCULATION IMBALANCE SHAPES THE IMMUNOSUPPRESSIVE MICROENVIRONMENT OF HEPATOCELLULAR CARCINOMA

Gang Chen[1] *Weiqi Guan*[1]

[1]*Wenzhou Medical University*

Background: Hepatocellular carcinoma (HCC) is one of the most common malignant tumors, ranking sixth in tumor incidence and third in mortality[1]. Recent studies have enriched our understanding of the role of chronic stress in the development of various diseases, especially on the development of cancer[2-3]. Here we focus on long-term chronic stress from social stress and the psychological stress of cancer alter the gut microbiota, promote the progression of HCC and disrupt treatment-induced anti-cancer immune surveillance. **Methods:** We used high-pressure hydrodynamic injection of c-myc-PT3EF1a, pT/Caggs-NRASV12 and pCMV-SB1 into the tail vein of mice to construct HCC model. On the basis of HCC model, chronic social defeat stress (CSDS) model was constructed. Feces were collected for 16S rRNA gene sequencing, serum samples were collected for metabolomics sequencing, and HCC tissues were collected for pathological section staining. The number of macrophages and T cells in the microenvironment was detected by flow cytometry. Taurine therapy intervention was used to verify whether chronic stress affects HCC progression by affecting the enterohepatic circulation of taurine. **Results:** The volume of HCC in the chronic stress group were significantly lager than those in the non-stress group. Chronic stress interferes with the balance of intestinal microecology. The results of metabolic sequencing showed that the serum taurine content in chronic stress group decreased significantly. Flow cytometry results showed that M2-type macrophages increased and CD8+ T cells decreased in the chronic stress group. Taurine intervention in HCC mice undergoing chronic stress proved that taurine therapy can partially reverse the promoting effect of chronic stress on HCC. **Conclusion:** In conclusion, we confirmed that chronic stress affects the intestinal microflora structure of HCC mice through brain-gut axis, reducing the intestinal metabolite taurine, thereby reducing the level of taurine translocation to the tumor microenvironment, and affecting the transport of taurine inside and outside macrophages. Inhibition of macrophages in the tumor microenvironment to M1 macrophages polarization, create HCC tumor immunosuppressive microenvironment, and ultimately promote the development of HCC by inhibiting the function of cytotoxic T cells.

Disclosures: Gang Chen: Nothing to Disclose, Weiqi Guan: Nothing to Disclose

2242 | EVOLUTION OF *RUMINOCOCCUS GNAVUS* IN CIRRHOSIS FACILITATES ITS PATHO-ADAPTATION TO MUCOUS

Jie Gao[1] *Xiaolong He*[2]

[1]*Guangzhou Medical University,* [2]*Zhujiang hosital, Guangzhou*

Background: *Ruminococcus gnavus (Rg)*, a bacterium enriched in the gut of liver cirrhosis patients, has been shown to be causally linked to cirrhotic complications, such as hepatic encephalopathy, as evidenced by previous research conducted by our team and others (1-2). In this study, we aim to identify the genetic factors of *Rg* that facilitate its colonization in the cirrhotic niche. **Methods:** We utilized a combination of culture-based bacterial genomics and population-based metagenomics to investigate the genomic variations between *Rg* strains from healthy individuals and cirrhosis patients. Their differed phenotypes were investigated through in vivo and in vitro experiment. **Results:** We generated complete genomes for 31 *Rg* strains: 11 strains from individuals with cirrhosis, 1 strain from inflammatory bowel disease patient, and 22 strains from healthy human guts. Phylogenetic analysis of the genomic composition and single nucleotide polymorphisms (SNPs) of marker genes revealed that *Rg* strains segregate into two distinct clusters: one predominantly consisting of strains isolated from healthy individuals (*Rg C1*) and the other primarily comprising strains isolated from diseased individuals (*Rg C2*). Pangenomic analyses identified 121 genetic factors enriched in *Rg C2*, many of which are linked to energy harvesting, host adhesion, and antioxidant activities, including carbohydrate ABC transporter permease, alpha-galactosidase, extracellular solute-binding protein, and NAD(P)/FAD-dependent oxidoreductase. Metagenomic analysis of stool samples from four liver disease cohorts, consisting of 246 patients and 225 healthy individuals, confirmed that only *Rg C2* is enriched in the cirrhotic niche. Furthermore, SNP analysis of metagenomically assembled *Rg* genes revealed increased strain variation within cirrhosis, with high nucleotide mutations occurring

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in genes involved in energy metabolism and host adhesion. Supporting this, *Rg C2* demonstrated superior colonization in the mucous of cirrhotic mice compared to *Rg C1*, leading to more severe gut inflammation and neurotoxic symptoms. Finally, using a combination of in vivo experimental evolution and comparative genomics, we discovered that *Rg C1* could evolve characteristics of *Rg C2* in cirrhotic, but not healthy mice, indicating a niche-driven evolution and pathoadaptation of *Rg*. **Conclusion:** Collectively, our findings identify the bifurcation of the *Rg* clade, highlight that *Rg C2* specifically drives the enrichment of *Rg* in cirrhosis, and uncover the genetic mechanisms underlying the pathoadaptation of *Rg* C2 to the cirrhotic niche.

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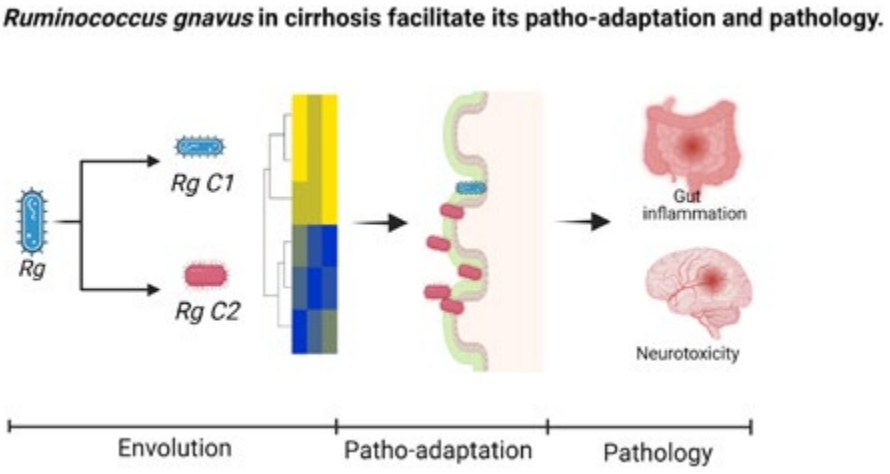

Disclosures: Jie Gao: Nothing to Disclose, Xiaolong He: Nothing to Disclose

2243 | INTESTINAL COLONIZATION BY A GUT PATHOBIONT ACCELERATES METABOLIC DYSFUNCTION ASSOCIATED STEATOTIC LIVER DISEASE: IMPLICATIONS OF THE GUT IMMUNE RESPONSE IN SHAPING THE LIVER CELLULAR LANDSCAPE

Erika Prando Munhoz[1] Mohamed Abdelnabi[1] Henry Nguyen[2]

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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) encompasses a range of liver pathology including simple fat accumulation in the liver (steatosis) to progressive liver inflammation and scarring (MASH). Treatment options for MASLD are currently limited. Understanding the drivers that promote the progression of liver injury will be important for the diagnosis and treatment of MASLD. We have consistently observed that a specific gut pathobiont can accelerate histological liver steatosis in a high-fat diet (HFD) animal model of MASLD. Interestingly, under specficic pathogen free conditions and in wild type animals, this pathobiont does not cause any intestinal or liver inflammation. Using this pathobiont, we aim to better understand its impact on the host immune responses within both the intestinal and liver environment in the setting of accelerated steatosis. **Methods:** 6-week-old C57BL/6 mice were gavage with the pathobiont and fed a high-fat diet (HFD) for a total of 8 weeks, an early time point that does not typically lead MASLD development in wild type mice not colonized with this pathobiont. The livers were subsequently collected and processed for immune cell profiling using spectral flow cytometry and histology. Oil Red O staining was utilized to quantify liver fat content and positive staining was scored in a blinded fashion. Quantification of stool microbial content was done using real time PCR. **Results:** At 8 weeks, mice colonized with the pathobiont had a significantly higher degree of liver steatosis noted on H&E histology. Blinded quantification of steatosis with Oil Red staining confirmed this. Pathobiont was detected in the stool throughout the 8 weeks of HFD with no significant changes in levels as measured by PCR. The pathobiont was absent in liver tissue (PCR and culture). Within the liver of pathobiont colonized mice vs pathobiont free mice fed HFD, there was a ~40% decrease in regulatory T cells (Tregs) (

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1.50% vs 2.47%). Interestingly, the total Tregs in the matching intestinal environment was noted to be significantly increased (~+70%) in HFD fed pathobiont colonized animals vs those not colonized (~4.1x10^4 vs ~1.3x10^4 cells). Other liver immune cells evaluated did not show significant differences between pathobiont colonized and free mice, including CD8 T cells, B cells, NK cells and Mo/MF cells. Although segmented filamentous bacteria (SFB) has been implicated in metabolic disease, pathobiont colonization had no impact on SFB levels in the stool at the end of the 8-week mark. **Conclusion:** Colonization with a pathobiont impacts the hosts gut immune response, which in turn can potentially shape the liver immune landscape in the setting of accelerated MASLD. Future investigation utilzing transgenic mice engineered to have pathogen specfic T cells are underway and will provide more granularity on the role microbe specific host regulatory and inflammatory T cells in MASLD.

Disclosures: Erika Prando Munhoz: Nothing to Disclose, Mohamed Abdelnabi: Nothing to Disclose, Henry Nguyen: Nothing to Disclose

2245 | MICROBIOTA DRIVEN INFLAMMATION CONTAINED TO THE INTESTINES IS AVERTED BY IL10 PRODUCING KRUPPEL-LIKE FACTOR 2 CD4+ T CELLS

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Background: The gut-liver axis is densely colonized with harmless microbes that reside in close proximity to host cells, highlighting the need for active immune tolerance to commensal microbes. Reciprocally, fractured tolerance to commensal microbiota is increasingly recognized as a key cornerstone in the pathogenesis of gut-liver overlap syndromes, including primary sclerosing cholangitis, autoimmune hepatitis, and inflammatory bowel disease (IBD). Fundamental knowledge gaps remain as to how commensal tolerance is achieved. **Methods:** To fill these knowledge gaps, an instructive preclinical model to precisely identify CD4+ T cells with surrogate commensal specificity was developed by establishing intestinal colonization with recombinant *Candida albicans.* **Results:** Tracking endogenous CD4+ T cells with defined commensal specificity using MHC class II tetramers (Fig. 1A, B) and RNA profiling (Fig. 1C) shows nearly half of the cells that expand in response to microbiota stimulation are unified by expression of the zinc finger transcription factor Kruppel-like factor-2 (KLF2). Mice with conditional deletion of KLF2 in CD4+ T cells develop isolated spontaneous colitis and rectal prolapse without hepatobiliary inflammation (Fig. 1D-G). These phenotypes reflect microbiota driven inflammation since each is overturned after eradication of commensal microbes (Fig. 1D, E). Production of the pleotropic immune suppressive cytokine IL10 by KLF2+ T cells is essential for their suppressive function (Fig. 1H-I). These preclinical observations dovetail nicely with selectively reduced accumulation of KLF2+ CD4+ T cells in intestinal biopsies of Crohn's disease patients (Fig. 1J). **Conclusion:** KLF2 identifies a new suppressive lineage of IL10 producing CD4 T cells that sustain intestinal commensal tolerance and are naturally reduced in human Crohn's disease. These findings significantly expand our knowledge of how commensal tolerance works by identifying a previously undefined subset of suppressive CD4 T cells that produce IL10 in response to commensal microbiota stimulation. Interestingly, loss of KLF2-dependent commensal tolerance does not result in hepatobiliary inflammation, suggesting independent tolerogenic mechanisms within the gut-liver axis. The immediate next priority is to interrogate the distinct immune mechanisms responsible for commensal tolerance in the gut-liver axis. This will shed important new light on the immune-pathogenesis of overlap syndromes and innovative targeted therapeutic approaches for suppressing aberrant inflammation.

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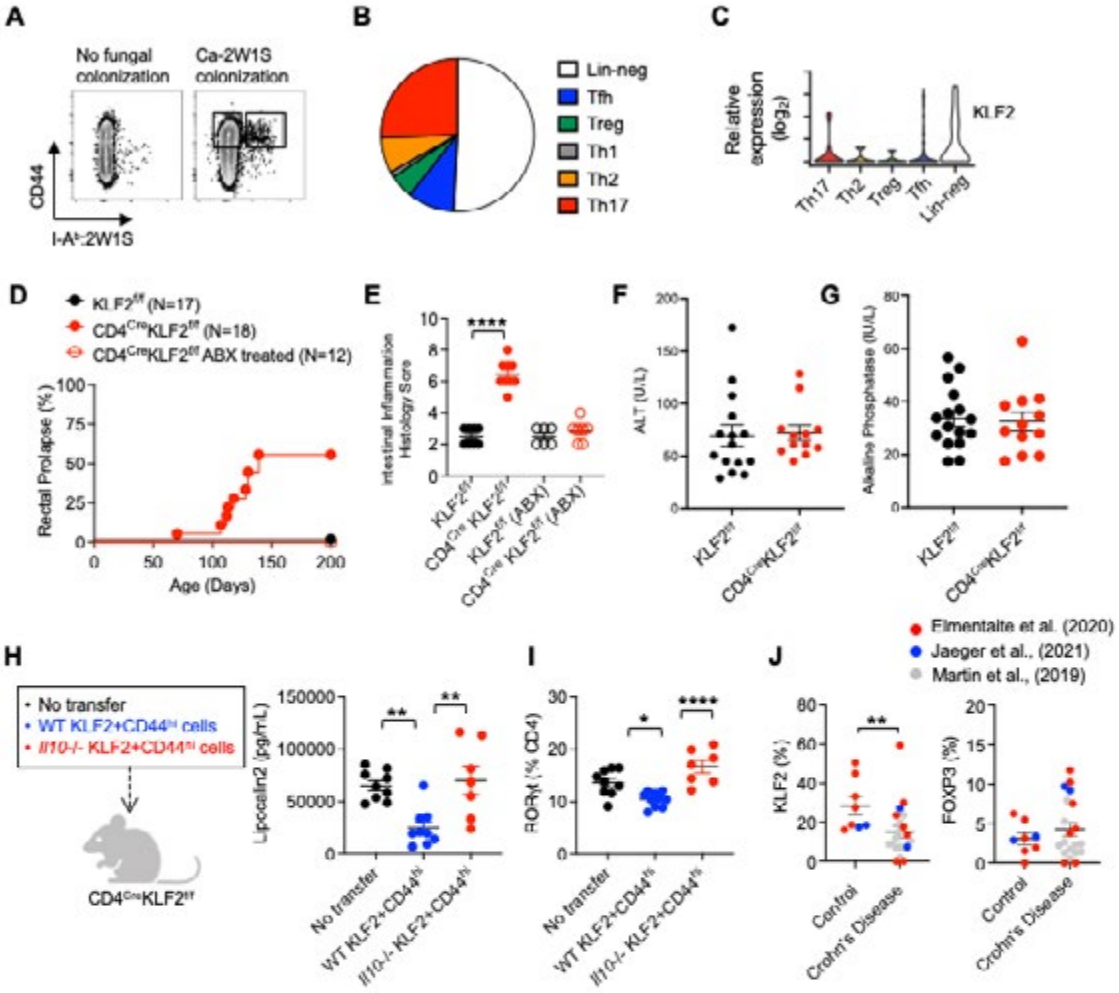

Figure 1. Microbiota driven inflammation contained to the intestines is averted by IL10-producing KLF2+ CD4+ T cells.
(A, B) Expansion of CD44^{hi} CD4 cells in the spleen and peripheral lymph nodes with I-A^{b}:2W1S$_{55-68}$ commensal Ca-2W1S specificity after intestinal colonization, and their expression of lineage defining markers including FOXP3 (Tregs), RORγt (Th17), TBET (Th1), IRF4 (Th2), and PD-1/CXCR5/BCL6 (Tfh).
(C) Single cell gene expression profiling of commensal Ca-2W1S I-A^{b}:2W1S$_{55-68}$ CD44^{hi} CD4 cells in the spleen and peripheral lymph nodes based on expression of lineage-defining markers (TBX21 for Th1, IRF4 for Th2, CXCR5 for Tfh, and FOXP3 for Treg), with the remaining unaccounted lineage-negative cells unified by KLF2 expression.
(D) Rectal prolapse incidence in CD4^{Cre} KLF2$^{f/f}$ (filled red) compared with co-housed KLF2$^{f/f}$ littermate controls (black), or for CD4^{Cre} KLF2$^{f/f}$ mice administered antibiotics (ampicillin, gentamicin, metronidazole, neomycin, vancomycin) in the drinking water beginning 40 days of age (open red).
(E) Colonic histology and inflammation scoring for CD4^{Cre} KLF2$^{f/f}$ mice that did not develop rectal prolapse through 150 days of age (red) compared with co-housed KLF2$^{f/f}$ littermate control mice (black), with some mice in each group administered antibiotics as described in panel A (open circles).
(F,G) Serum alanine transaminase (ALT) and alkaline phosphatase levels in age-matched CD4^{Cre} KLF2$^{f/f}$ and Cre-negative littermate controls.
(H) Fecal Lipocalin-2 levels in CD4^{Cre} KLF2$^{f/f}$ recipient mice day 20 after transfer of KLF2+ CD44^{hi} (FOXP3-negative) cells from WT (10^6 cells; blue) or *Il10-/-* donors (10^6 cells; red) compared with no transfer controls (black).
(I) Percent RORγt+ CD4 Th17 cells in the mesenteric lymph nodes for each group of mice described in panel H.
(J) Percent KLF2+ or FOXP3+ among CD4 cells in inflamed intestinal biopsy specimens from individuals with Crohn's disease compared with healthy controls pooled from three separate datasets.

Disclosures: Abigail Russi: Nothing to Disclose, Amelia Nguyen: Nothing to Disclose, Arianna Buehler: Nothing to Disclose, Jenny Shao: Nothing to Disclose, Sing Sing Way: Nothing to Disclose

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2246 | SULFASALAZINE AMELIORATES HEPATIC FIBROSIS BY REGULATING THE BSH BACTERIA-CDCA-FXR AXIS IN RATS

Zilin Sun[1] Hongyan Xiang[1] Jing Xu[1] Jing Xiao[1] Shuang Xiao[1] Ning Ling[1] Yinghua Lan[1] Hong Ren[1] Peng Hu[1] Mingli Peng[1]

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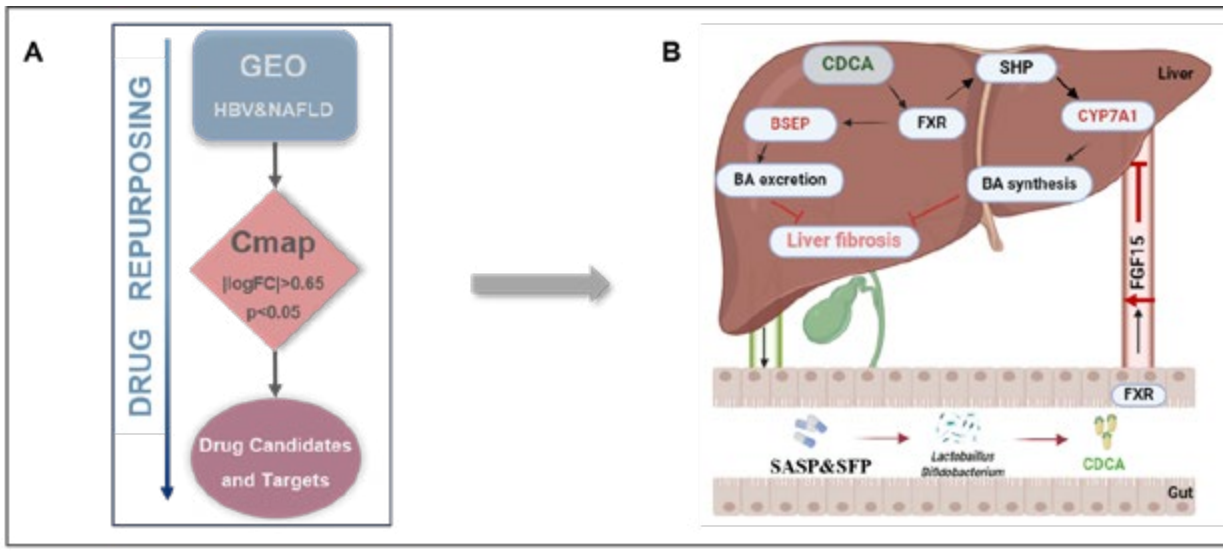
Background: There are no approved therapies for liver fibrosis. Drug repurposing based on the Connectivity Map (Cmap) database computational algorithm provides an effective means to discover new uses for already-available drugs. This study aimed to discover drugs for the treatment of liver fibrosis through drug repurposing. **Methods:** Cmap based on the transcriptome of hepatitis B virus- and nonalcoholic fatty liver disease-related liver fibrosis predicted the potential antifibrotic agents. The carbon tetrachloride (CCl_4)-induced liver fibrosis model was used to validate the safety and efficacy of the drug candidates; RNA-seq technology was applied to detect differential gene expression in the liver; UPLC-MS/MS technology was adopted in devoting bile acid (BA) profiles in the enterohepatic system; 16s rDNA was utilized to explore the effects of drugs towards gut microbiota. **Results:** Cmap prediction and the CCl_4-induced hepatic fibrosis model confirmed that sulfasalazine (SASP), a drug used to treat ulcerative colitis, had a good antifibrotic effect and safety profile. Liver RNA-seq analysis revealed that SASP could improve the bile salt secretion pathway. Bile acid (BA) and bile profile analysis demonstrated that SASP significantly reduced hepatic BA levels, influenced the distribution and composition of BAs in the enterohepatic system, and especially increased the levels of chenodeoxycholic acid (CDCA) in the liver and ileum. The 16S rDNA sequencing indicated that SASP modulated the composition of gut microbiota in different parts of the intestine and restored the abundance of bile salt hydrolase (BSH) bacteria. Mechanistically, CDCA increased by SASP, as the strongest endogenous agonist of farnesoid X receptor (FXR), activated the intestinal FXR-FGF15 and hepatic FXR-SHP to suppress BAs synthesis and promote BAs secretion, thereby reducing the accumulation of BAs in the liver and alleviating the reduction of intestinal BAs in the cirrhotic state. Further, we confirmed that the antifibrotic active ingredient of SASP is sulfapyridine (SFP), not mesalazine (MES), another drug for ulcerative colitis. **Conclusion:** We demonstrate that SASP ameliorates liver fibrosis by improving the bile salt secretion pathway through regulation of the BSH bacteria–CDCA–FXR axis. SASP repurposing provides a new attempt at clinical treatment of liver fibrosis.



(A). Schematic of Cmap drug prediction. **(B)** Schematic of the mechanism of the antifibrotic effect of SASP.

Disclosures: Zilin Sun: Nothing to Disclose, Hongyan Xiang: Nothing to Disclose, Jing Xu: Nothing to Disclose, Jing Xiao: Nothing to Disclose, Shuang Xiao: Nothing to Disclose, Ning Ling: Nothing to Disclose, Yinghua Lan: Nothing to Disclose, Hong Ren: Nothing to Disclose, Peng Hu: Nothing to Disclose, Mingli Peng: Nothing to Disclose

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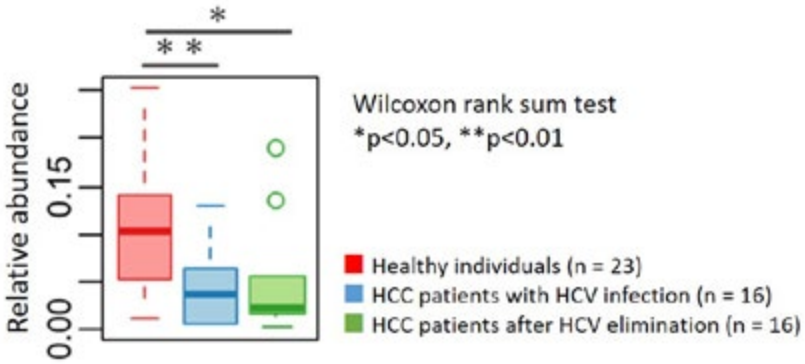
2247 | ASSESSMENT OF BACTERIAL INVOLVEMENT IN THE STAGNATION OF SECONDARY BILE ACID PRODUCTION AND DEACIDIFICATION IN THE GUT ENVIRONMENT AFTER HCV ELIMINATION ◆

Takako Inoue Hisayoshi Watanabe[1] Etsuko Iio[2] Masaya Ohnishi[3] Kei Moriya[4] Hideto Kawaratani[4] kentaro matsuura[5] Hitoshi Yoshiji[4] Yasuhito Tanaka[6]

[1]Yamagata University, [2]Kumamoto University, [3]The University of Tokyo, [4]Nara Medical University, [5]Nagoya City University, [6]Nagoya City University Graduate School of Medical Sciences

Background: A high concentration of primary bile acids (BAs) and conjugated BAs is found in the gut environment of liver cirrhosis (LC) and hepatocellular carcinoma (HCC) patients after HCV elimination. Our studies have shown a decrease in the numbers of bacteria which can process bile acid molecular species. Here, we aimed to identify the bacteria which are involved in the stagnation of secondary BA production and BA deconjugation reactions in decompensated LC (DLC) and HCC patients after they achieved a sustained virological response (SVR). **Methods:** The gut microbiome and fecal BAs were analyzed in 24 DLC and 16 HCC patients after they had achieved SVR. The findings were compared to those from 56 chronic hepatitis C patients with HCV infection (40 LC and 16 HCC patients) and 23 healthy individuals. The correlation between gut microbiome and fecal BAs was analyzed using Spearman's rank correlation. Fecal BA data were compared between groups using the Wilcoxon rank sum test, and the false discovery rate was corrected using the Bonferroni method. This study was approved by the ethics review committees of the relevant institutions. **Results:** Compared to healthy individuals, *Ruminococcaceae*, *Porphyromonadaceae*, and *Rikenellaceae* were reduced in the gut microbiomes of DLC patients with HCV infection. In DLC patients who had achieved SVR, they had decreased significantly (p <0.05, <0.01, and <0.05). Furthermore, comparing the gut microbiomes of healthy individuals and HCC patients, only *Ruminococcaceae* decreased significantly in HCC patients who had achieved SVR (p <0.05). Furthermore, analysis of the relationship between conjugated BA and intestinal bacteria at the operational taxonomic unit level showed that, in the DLC patients after achieving SVR, the decreases in *Bacteroides dorei*, *Bacteroides uniformis*, and *Parabacteroides distasonis* strongly affected the stagnation of BA deconjugation. Similarly, the decrease in *Bacteroides* species, particularly *Bacteroides uniformis* in HCC patients after achieving SVR strongly influences the stagnation of BA deconjugation. **Conclusion:** *Ruminococcaeae* are involved in secondary BA production and *Bacteroides* are involved in BA deconjugation. In DLC and HCC patients who have achieved SVR, the decrease in *Ruminococcaceae* may be involved in the reduction of conversion to secondary BAs, and the decrease in *Bacteroides* may be involved in the stagnation of BA deconjugation.

Figure. Relative abundance of Ruminococcaceae in healthy individuals and hepatocellular carcinoma (HCC) patients



Disclosures: Takako Inoue: Fujirebio, Inc.: Grant/Research Support, Sysmex Corporation: Grant/Research Support, Hisayoshi Watanabe: Nothing to Disclose, Etsuko Iio: Nothing to Disclose, Masaya Ohnishi: Nothing to Disclose, Kei Moriya: Nothing to Disclose, Hideto Kawaratani: Nothing to Disclose, kentaro matsuura: Nothing to Disclose, Hitoshi Yoshiji: Nothing to Disclose, Yasuhito Tanaka: Nothing to Disclose

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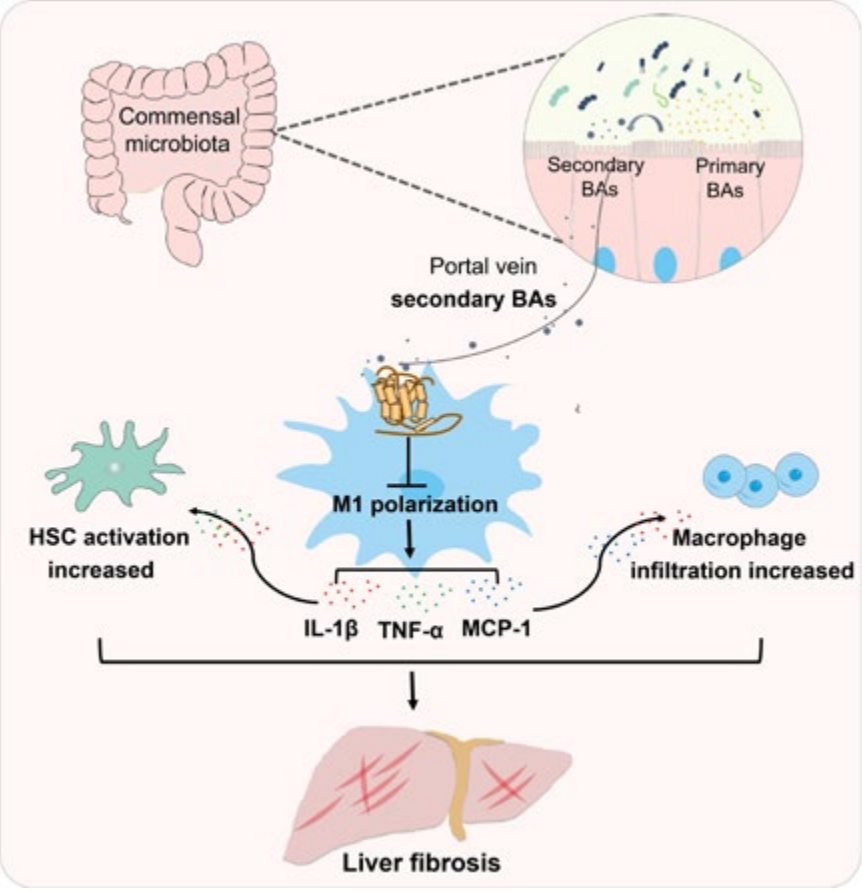
2248 | GUT COMMENSAL BACTERIA EXERT ANTI-INFLAMMATORY AND ANTI-FIBROTIC EFFECTS BY REGULATING MACROPHAGE POLARIZATION THROUGH SECONDARY BILE ACIDS

Hongyan Xiang[1] *Huanyu Xiang*[1] *Shuyun Wang*[1] *Peiyu Wu*[1] *Jie Zhang*[1]

[1]*Chongqing General Hospital*

Background: The correlation between gut microbiota and the progression of liver fibrosis is well-established, however, the specifical mechanism of this association remains unclear. The current study aims to elucidate the intrinsic mechanism through which the gut microbiota participates in liver fibrosis. **Methods:** The gut microbiota was depleted using an antibiotic cocktail (ABX). Liver fibrosis was induced in both conventional and antibiotic-treated pseudo-sterile mice via intraperitoneal injection of carbon tetrachloride. The relative abundance of ileal microbiota was determined using 16S ribosomal DNA sequencing. Bile acid (BA) profiles were detected using ultra-performance liquid chromatography-tandem mass. Subsequently, mouse bone marrow-derived macrophages and the macrophage cell line RAW264.7 were used to verify the effect of secondary bile acids (SBAs) on macrophage polarization in vitro. **Results:** The ABX treatment effectively eliminated a substantial portion of the gut microbiota in mice, leading to a decreased concentration of SBAs. Compared to the conventional mice, the ABX-treated mice showed increased levels of transaminase and collagen deposition. Meanwhile, gut microbiota elimination increased macrophage infiltration and expression of inflammation factors such as TNF-α, IL-β, and MCP-1. Mechanistically, gut microbiota-mediated SBAs like DCA could inhibit macrophage polarization toward the M1 phenotype. These results indicate that gut microbiota-mediated SBAs can protect the liver from inflammation and fibrosis. **Conclusion:** Our research indicates that gut commensal bacteria play a crucial role in liver fibrosis by modulating macrophage polarization through SBAs. The regulatory mechanisms of SBAs in modulating macrophage polarization and their potential therapeutic effects in combating hepatic fibrosis are under investigation.



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Disclosures: Hongyan Xiang: Nothing to Disclose, Huanyu Xiang: Nothing to Disclose, Shuyun Wang: Nothing to Disclose, Peiyu Wu: Nothing to Disclose, Jie Zhang: Nothing to Disclose

2250 | GUT MICROBE-PRODUCED INDOLE-3-PROPIONIC ACID ALLEVIATES HEPATITIS B-RELATED FIBROSIS BY REGULATING TH17 CELL DIFFERENTIATION THROUGH GLUCOSE METABOLISM REPROGRAMMING

Fangyuan Chen[1] Siqi Wang[1] Linlin Zheng[1] Shuyu Li[1] Jian Wu[2] Wei Jiang[3]

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Background: T helper (Th) 17 play a crucial role in promoting HSC activation in fibrotic progression by producing interleukin-17 (IL-17). Emerging evidence indicates that microbial metabolites are of pivotal importance in liver fibrosis. Our previous studies found that indole-3-propionic acid (IPA) as a microbially produced tryptophan-derived metabolite was significantly decreased in patients with chronic hepatitis B/cirrhosis compared to healthy controls. This study aimed to investigate its regulation of hepatitis B-related fibrosis through immune modulation. **Methods:** HBV transgenic (HBV-Tg) mice were intraperitoneally injected with CCl4 to construct a murine model of hepatitis B-related liver fibrosis. Human peripheral blood mononuclear cells (PBMCs) were isolated from patients with chronic hepatitis B/cirrhosis. Naive CD4+ T cells sorted from mouse spleen were cytokine-induced to differentiate towards Th17 cells. **Results:** IPA alleviated hepatic fibrosis and inflammation of HBV-Tg mice treated with CCl4, as demonstrated by fibrotic and inflammatory indicators. In differentiation of PBMCs from patients it was found that the proportion of Th17 cells were decreased significantly after the treatment of IPA, indicating that IPA may inhibit Th17 differentiation. Single cell RNA sequencing revealed that IPA treatment led to downregulation of Th17 differentiation-related genes, such as IL-17 and IL-2, with enrichment of the KEGG pathway suggesting a close association with the HIF1 pathway and glycolysis. Moreover, treatment with IPA inhibited Th17 differentiation and glucose uptake in both in vivo and in vitro settings, and protein and gene expression of glycolytic markers, such as HK2, LHDA, and HIF1α, was also down-regulated. Furthermore, the efficiency of Th17 glycolysis was reduced by IPA in a seahouse experiment. Indirect co-culture of Th17 with mouse HSCs demonstrated that IPA treatment attenuated the pro-activating effects on HSCs; whereas HIF1α agonists abrogated the IPA effects. Given that lactate is the glycolytic end product, IPA was found to reduce lactate production and lactylation levels in Th17. Using ChIP sequence, genes bound with lactylated proteins were enriched, in which Th17 differentiation-related genes such as IL-17, IL-2, and RORc were found to bind to lactylated proteins in promoter regions, while IPA effectively inhibited this binding. Taken together, IPA inhibited transcription of genes modulating Th17 cell differentiation by inhibiting lactylation. **Conclusion:** Gut microbe-generated IPA ameliorated hepatitis B-associated liver fibrosis by inhibiting Th17 differentiation through reducing glycolysis and consequent lactylation, thereby suppressing the transcription of genes involved in their differentiation. The delineation of vital role of Th17 cells in HBV-associated liver fibrosis and cirrhosis confers the molecular basis for immune modulation as an intervention option.

Disclosures: Fangyuan Chen: Nothing to Disclose, Siqi Wang: Nothing to Disclose, Linlin Zheng: Nothing to Disclose, Shuyu Li: Nothing to Disclose, Jian Wu: Nothing to Disclose, Wei Jiang: Nothing to Disclose

2251 | ANALYSIS FOR GUT MICROBIAL PROFILE CHANGES BY JAPANESE DIET IDENTIFIED SPECIFIC SPECIES THAT REFLECT MASLD PROGRESSION

Yoshimi Yukawa-Muto[1] Hideki Fujii[2] Yoshinari Matsumoto[2] Tomonori Kamiya[2] Norifumi Kawada[2] Naoko Ohtani[2]

[1]Osaka Metropolitan University Graduate School of Medicine, [2]Osaka Metropolitan University Graduate S

Background: Dietary habits significantly influence the composition of the gut microbiota. We reported that severity of liver fibrosis in MASLD patients is associated with Japanese Diet Pattern (*Nutrients* 2023). Therefore, we conducted a gut microbiota analysis on the same cohort of patients. This study aimed to elucidate the relationship between the Japanese-style diet, gut microbiota profile changes, and the pathophysiology of MASLD. **Methods:** We performed a cross-sectional analysis on patients with MASLD diagnosed by ultrasonography from September 2021 to November 2022. Dietary status was assessed using the 12-component modified Japanese diet pattern index (mJDI12). The mJDI12 was calculated based on the intake per 1000 kcal of soybeans and

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soybean foods, green and yellow vegetables, fruits, fish and shellfish, pickles, mushrooms, seaweeds, green tea, rice, miso soup, beef and pork, and coffee. Daily alcohol consumption was calculated in grams, using our modified template. We compared the gut microbiota profile using a sequence analysis of the 16S rRNA gene. 1) Patients were stratified into quartiles based on JDI scores and the intake of 12 dietary items. We identified a candidate gut bacteria of the highest and lowest quartiles detected by Lefse analysis. 2) We validated the relationship between the candidate gut bacteria and metabolic parameters. **Results:** We analyzed data from 140 eligible participants (50% women; median age 59 (22-86) years). 1) *Veillonellaceae Dialister* was identified as a characteristic species in the high-score group of JDI (above the 75th percentile, stratified by sex), showing significantly higher abundance in this group. In a study of 12-components, *Veillonellaceae Dialister* was identified as a characteristic gut microbial species associated with a high intake of green and yellow vegetables. Additionally, *Ruminococcus gnavus* was identified as a characteristic species in the low-score group of JDI (below the 25th percentile, stratified by sex), displaying significantly higher abundance in this group. 2) The relative abundance of *Veillonellaceae Dialister* exhibited a positive correlation with insulin (r=0.380, p=0.003) and blood sugar levels (r=0.266, p=0.042). In addition, the relative abundance of *Ruminococcus gnavus* showed a positive correlation with alanine aminotransferase (ALT, r= 0.260, p=0.047) and type 4 collagen 7S levels (r=0.319, p=0.037) in patients. Furthermore, both showed a significant positive correlation with patients' total bile acids (*Veillonellaceae Dialiste*r; r=0.509, p<0.001, *Ruminococcus gnavus*; r=0.318, p=0.014). **Conclusion:** These findings suggest a potential correlation between *Veillonellaceae Dialister* and glucose metabolism, which might reflect Japanese food intake, as well as *Ruminococcus gnavus* and liver dysfunction associated with liver inflammation and fibrosis in patients with MASLD.

Disclosures: Yoshimi Yukawa-Muto: Nothing to Disclose, Hideki Fujii: Nothing to Disclose, Yoshinari Matsumoto: Nothing to Disclose, Tomonori Kamiya: Nothing to Disclose, Norifumi Kawada: Nothing to Disclose, Naoko Ohtani: Nothing to Disclose

2252 | PREVALENCE, RISK FACTORS, AND OUTCOMES OF CLOSTRIDIOIDES DIFFICILE INFECTION IN LIVER TRANSPLANT RECIPIENTS ◆

Kelly Thomas[1] *Irena Helenowski*[1] *Filippa Trikantzopoulou*[1] *Hanna Larson*[1] *Ayokunle Abegunde*[1] *Steven Scaglione*[1]

[1]*Loyola University Health System*

Background: Clostridioides difficile infection (CDI) is associated with morbidity and mortality, but little is known about CDI after liver transplant (LT) as rates vary from 2.7-16%. Gut dysbiosis is a CDI risk factor. LT patients are at risk of dysbiosis from antibiotic use, hospitalizations, bile acid dysfunction, diet, and immunosuppression (IS). This study aimed to assess the prevalence, risk factors, and outcomes of CDI among LT recipients. **Methods:** A single-centered retrospective study was conducted of LT recipients between 2012-2021using a transplant database. Those included were separated into two groups: those with CDI and those without CDI post LT. CDI was defined as a positive stool sample for C diff with cell cytotoxic assay for C diff toxin A/B and/or PCR targeting toxigenic C diff toxin genes. Severe CDI was defined as CDI with fever, ICU admission, shock requiring pressors, and/or ileus. Clinical and demographic covariates were obtained via chart review. Multivariable (MV) logistic regression models were fit to assess effects of covariates, CDI and severe CDI. MV Cox regression models were fit to assess the effects of covariates and CDI on the outcome of mortality. **Results:** Of 436 LT recipients, 128 (29%) had CDI. Factors associated with CDI were female sex, alcohol use at LT, MASLD, simultaneous liver kidney transplant (SLK), number of hospitalizations within 1 year post LT, and BANFF score (Table 1). Among those with CDI, 11.9% had severe CDI with fever (6.3%), ICU admission (5.5%), shock requiring pressors (3.9%), ileus (3.1%). Factors associated with severe CDI include PBC/PSC, SLK, and BANFF Score. IV steroids to treat acute cellular rejection (ACR) was not associated with CDI or severe CDI. SLK was independently associated with CDI (OR 5, 95% CI, 1.5-18.2, p=0.01) and severe CDI (OR 5.4, 95% CI 1.6-18.6, p<0.01). CDI was not associated with worse survival. MV logistic regression identified current smoking, secondary biliary cirrhosis, MAFLD, antibiotics after discharge and PPI use within one year post LT to be associated with mortality, however, CDI was not. **Conclusion:** Our study suggests the prevalence of CDI and severe CDI are higher than previous studies. Over 18% developed severe CDI. SLK was a major factor independently associated with CDI and severe CDI, possibly from higher chronic IS requirements. Yet the increase in IS acutely to treat ACR was not associated with CDI or severe CDI. Further studies are needed to examine the role of intensive chronic (vs acute) IS and CDI.

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Characteristic	Overall, N = 436[1]	No CDI, N = 308[1]	CDI, N = 128[1]	p-value[2]
Age (y)				0.173
Mean (SD)	57.2 (10.3)	56.9 (10.1)	57.7 (11.0)	
Median (Range)	58.7 (18.9, 75.5)	58.2 (23.4, 75.5)	60.0 (18.9, 72.4)	
Sex				0.007
Male	291 (66.7%)	218 (70.8%)	73 (57.0%)	
Female	145 (33.3%)	90 (29.2%)	55 (43.0%)	
Alcohol use at LT				0.006
Current	10 (2.3%)	5 (1.6%)	5 (3.9%)	
Former	317 (72.7%)	237 (76.9%)	80 (62.5%)	
Never	109 (25.0%)	66 (21.4%)	43 (33.6%)	
Alcoholic Cirrhosis	199 (45.6%)	142 (46.1%)	57 (44.5%)	0.833
Hepatitis C	106 (24.3%)	82 (26.6%)	24 (18.8%)	0.087
Hepatitis B	18 (4.1%)	13 (4.2%)	5 (3.9%)	>0.999
Autoimmune Hepatitis	13 (3.0%)	10 (3.2%)	3 (2.3%)	0.764
Cryptogenic Cirrhosis	6 (1.4%)	3 (1.0%)	3 (2.3%)	0.365
Hepatocellular Carcinoma	109 (25.0%)	84 (27.3%)	25 (19.5%)	0.114
NAFLD	104 (23.9%)	65 (21.1%)	39 (30.5%)	0.048
Wilson's Disease	0 (0.0%)	0 (0.0%)	0 (0.0%)	
PBC/PSC	23 (5.3%)	17 (5.5%)	6 (4.7%)	0.818
Secondary Biliary Cirrhosis	1 (0.2%)	1 (0.3%)	0 (0.0%)	>0.999
Other	24 (5.5%)	20 (6.5%)	4 (3.1%)	0.247
Solid Organ Transplant Type				0.05
Single	374 (85.8%)	271 (88.0%)	103 (80.5%)	
Simultaneous	62 (14.2%)	37 (12.0%)	25 (19.5%)	
Antibiotics within 1 year post LT	424 (97.2%)	297 (96.4%)	127 (99.2%)	0.194
ACR therapy				0.278
No therapy	368 (84.4%)	258 (83.8%)	110 (85.9%)	
IV therapy	5 (1.1%)	2 (0.6%)	3 (2.3%)	
PO therapy	24 (5.5%)	17 (5.5%)	7 (5.5%)	
IV & PO therapy	39 (8.9%)	31 (10.1%)	8 (6.3%)	
Number of hospitalizations within 1 year				<0.001
1 to 5	279 (64.3%)	185 (60.5%)	94 (73.4%)	
6 to 10	32 (7.4%)	15 (4.9%)	17 (13.3%)	
> 10	2 (0.5%)	0 (0.0%)	2 (1.6%)	
None	121 (27.9%)	106 (34.6%)	15 (11.7%)	
Unknown	2	2	0	
Degree of ACR Banff				0.005
1	40 (37.0%)	18 (25.7%)	22 (57.9%)	
2	9 (8.3%)	7 (10.0%)	2 (5.3%)	
3	37 (34.3%)	26 (37.1%)	11 (28.9%)	
4	22 (20.4%)	19 (27.1%)	3 (7.9%)	
N/A (no ACR)	328	238	90	

[1]n (%)

[2]Wilcoxon rank sum test; Fisher's exact test

Disclosures: Kelly Thomas: Nothing to Disclose, Irena Helenowski: Nothing to Disclose, Filippa Trikantzopoulou: Nothing to Disclose, Hanna Larson: Nothing to Disclose, Ayokunle Abegunde: Ferring Pharmaceuticals: Consultant, Ferring Pharmaceuticals: Consultant, Steven Scaglione: Nothing to Disclose

2253 | SMP30 DEFICIENCY ACCELERATES GUT-LIVER NANOPLASTIC ACCUMULATION VIA DISRUPTED INTESTINAL BARRIER MEDIATED BY ALCOHOL CONSUMPTION

Woo Jun Kim[1] Tae-Un Kim[1] Jae-Hyuk Yim[1] Su-Min Baek[1] Jin-Kyu Park[1]

[1]Kyungpook National University

Background: SMP30 is an important protein responsible for Vit C synthesis, Ca^{2+} regulation, antioxidant effect, and anti-apoptotic effect. SMP30 has been mainly explored in liver and kidney. However, no papers have been

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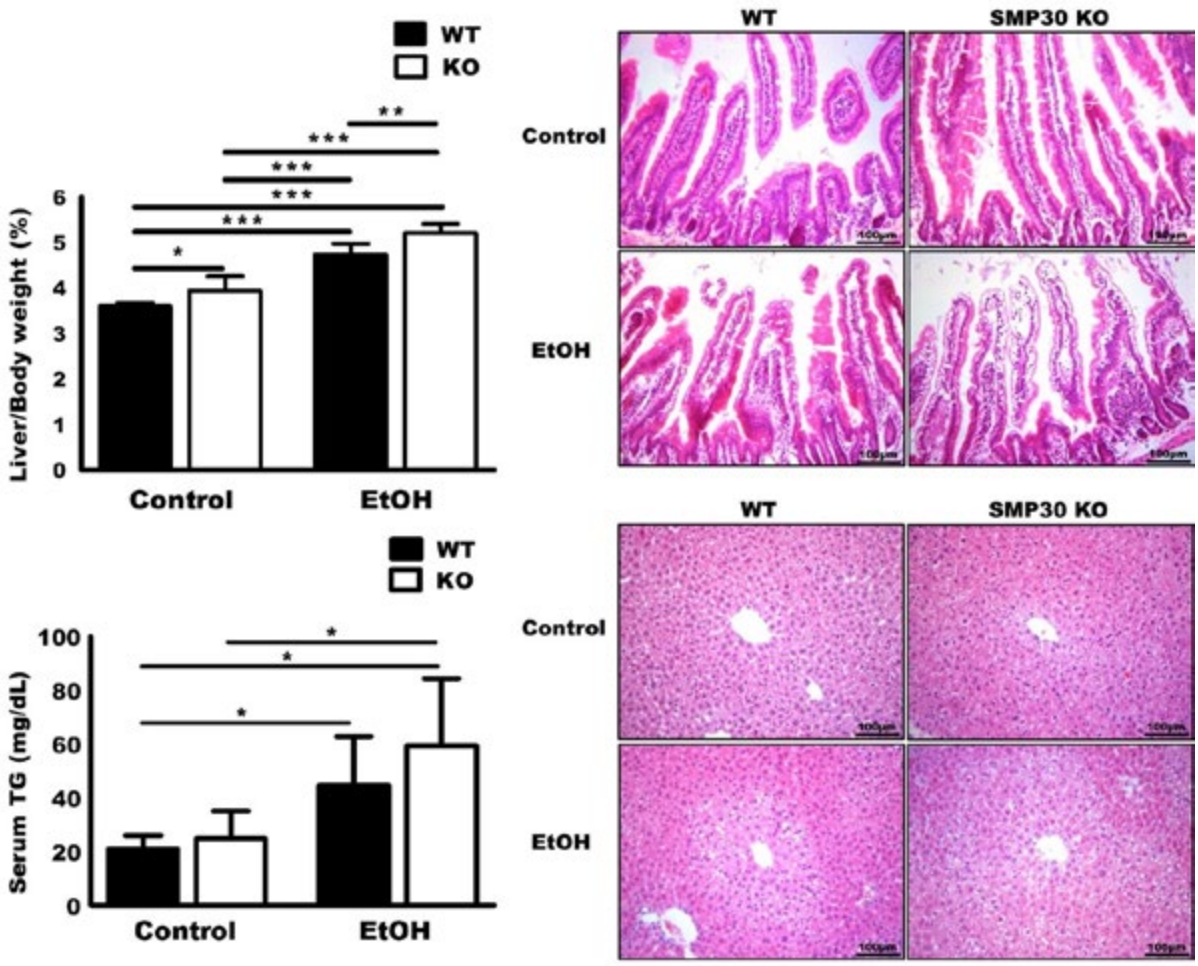
reported the protective mechanism of SMP30 in the intestine. Therefore, we investigated the role of SMP30 in gut permeability model. Meanwhile, nanoplastics (NPs) are emerging pollutants that can affect both human bodies and ecosystems. Since the accumulation of NPs is mainly achieved through oral ingestion, disruption of the intestinal epithelium accelerates the accumulation of NPs. For that reason, we used fluorescence-dyed NPs as an indicator to evaluate distribution and toxicity of NPs. **Methods:** Gut permeability model was induced by Lieber-deCarli diet, and polystyrene nanoplastics (PS-NP) was injected 5 times a week for 3 weeks. The SMP30 KO mice were fed a diet containing Vit C to rule out any effects caused by Vit C deficiency. Histopathological analysis, serum biochemistry, immunofluorescence (IF) and immunohistochemistry (IHC) were performed to assess intestinal and liver injury. Western blot and qRT-PCR were performed to reveal the related genes. **Results:** KO+EtOH (KE) group showed more severe vacuolization in the intestinal villi compared with WT+EtOH (WE) group. The expression of tight junction (TJ) proteins (ZO-1, claudin, occludin) decreased in KE group upon IHC, which was confirmed with western blot. F-actin expression was decreased, and more NPs were observed in the lamina propria in immunofluorescence staining. To evaluate gut permeability, hepatic E. coli mRNA levels and serum LPS levels were measured, which showed higher levels in KE group. Oxidative stress analysis indicated elevated levels of CYP2E1, iNOS, and MDA in the KE group. In the liver tissue, KE group showed higher steatosis grade compared with WE group. This pattern was confirmed in hepatic TG assay and ORO stain. NP accumulation was also elevated in the liver of KE group. **Conclusion:** This study demonstrates that SMP30 deficiency accelerates intestinal disruption and secondary injury to liver tissue. Intestinal damage attributes to higher oxidative stress by SMP30 deficiency. Consequently, the TJ protein expression was reduced, allowing increased translocation of bacteria-derived substances and NPs. Also, accumulated NPs induced severe hepatic steatosis. This study elucidates the novel function of SMP30 in intestinal epithelium, emphasizing its antioxidative effect.



Disclosures: Woo Jun Kim: Nothing to Disclose, Tae-Un Kim: Nothing to Disclose, Jae-Hyuk Yim: Nothing to Disclose, Su-Min Baek: Nothing to Disclose, Jin-Kyu Park: Nothing to Disclose

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2254 | DUODENAL MITOCHONDRIAL OXIDATIVE PHOSPHORYLATION WORSENS WITH DISEASE PROGRESSION AND IS AMELIORATED AFTER FMT IN PATIENTS WITH CIRRHOSIS

Jing Zeng[1] Derrick Zhao[1] Grayson Way[1] Andrew Fagan[1] Michael Fuchs[2] Puneet Puri[1] Brian Davis[3] Xuan Wang[1] Emily Gurley[1] Phillip Hylemon[1] Jian-Gao Fan[4] Huiping Zhou[1] Jasmohan Bajaj[1]

[1]Virginia Commonwealth University, [2]McGuire Veterans Affairs Medical Center, [3]Hunter Holmes McGuire VA Medical Center, [4]Xinhua Hospital, Shanghai, China

Background: Intestinal barrier dysfunction and the subsequent bacterial translocation accelerate the progression of cirrhosis, especially in the upper intestine. Intestinal oxidative phosphorylation (OXPHOS) activity consumes oxygen, leading to intestinal hypoxia, which can trigger inflammation and disrupt the intestinal barrier. Fecal microbiota transplant (FMT) can improve dysbiosis & intestinal barrier. However, the relationship between intestinal OXPHOS, gut microbiota change & impact of FMT in cirrhosis is unclear. **Methods:** Cross-sectional: Twelve age-matched males, including healthy controls (54±3 years), compensated cirrhosis (55±4 years, MELD 7), and decompensated cirrhosis (56±5 years, MELD 11, with prior hepatic encephalopathy (HE) on lactulose±rifaximin), underwent EGD & duodenal biopsy collection. FMT study: From a previous RCT where oral capsular FMT from a healthy donor enriched in beneficial short-chain fatty acid producers was administered to cirrhosis+HE patients, we analyzed the group randomized to FMT rather than placebo. EGDs for duodenal biopsy were performed at baseline & 15 days post-FMT. Gene profiling was analyzed using the NanoString nCounter® platform. 16S rRNA gene sequencing was conducted to characterize the intestinal mucosal microbiota. **Results:** Cross-sectional: Bioinformatics analysis revealed significant upregulation of nuclear-encoded OXPHOS genes in the duodenum of patients with cirrhosis compared to controls. In decompensated cirrhosis patients, some nuclear-encoded OXPHOS genes were further dysregulated, indicating a more pronounced mitochondrial dysfunction and increased oxygen consumption. Additionally, major differences in gut microbial relative abundance were noted between healthy controls and cirrhosis. A significant correlation between gut microbiota changes, MELD scores, and OXPHOS was identified in the cirrhosis group. FMT: Nine patients received FMT & did not have HE recurrence/hospitalizations or adverse outcomes before the repeat EGD. After FMT, patients showed significant downregulation of nuclear-encoded OXPHOS gene expression. Gene ontology (GO) function and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analyses emphasized these differences. **Conclusion:** Duodenal mucosal OXPHOS activity, which can worsen the intestinal barrier, exacerbates with disease progression in patients with cirrhosis. This is restored with successful FMT and is a potential target for newer therapies to slow the progression of liver disease.

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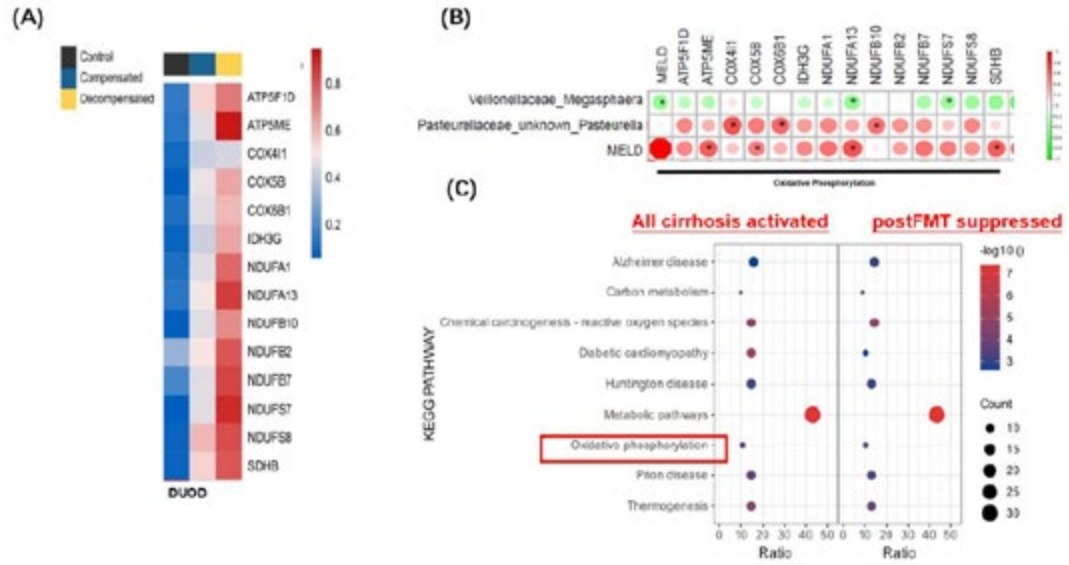

Fig: Oxidative Phosphorylation (OXPHOS) in Patients with Cirrhosis Compared to Healthy Controls and its Correlation with Gut Microbiota, MELD Scores, and Changes Before and After FMT.

(A) Heatmap illustrating differential OXPHOS gene expression profiles in duodenal tissues (DUOD) between cirrhosis subjects and healthy controls, with |Fold Change| > 1.3 and P < 0.05. (B) Relationship between gut microbiota composition, OXPHOS gene expression, and MELD scores. (C) KEGG pathway analysis comparing all cirrhosis patients to controls and patients before and after FMT. Abbreviations: OXPHOS - Oxidative Phosphorylation; DUOD - Duodenum; FC - Fold Change; MELD - Model for End-Stage Liver Disease; FMT - Fecal Microbiota Transplantation.

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2255 | LEVERAGING MACHINE LEARNING TO EXPLORE MICROBIOME VARIATIONS IN RESPONSE TO NUTRITION AND GENETIC VARIATION

Thriveni Raju[1] Alina Beckmann[1] Nicole Treichel[1] Madhuri Haque[1] Yazhou Chen[1] Benjamin Laevens[1] Kai Markus Schneider[1] Kirsten Schorning[2] Carolin Schneider[1]

[1]RWTH University Hospital, [2]Technische Universität Dortmund

Background: The gut-liver axis plays a major role in food intake and its subsequent processing, exposing the liver to both microbial metabolites and nutritional components. Studies have found specific associations between gut microbiota makeup and liver diseases; for instance, higher levels of Firmicutes and Proteobacteria are observed in mild to moderate fibrosis cases. Variations in the gut microbiota can be influenced by genetic

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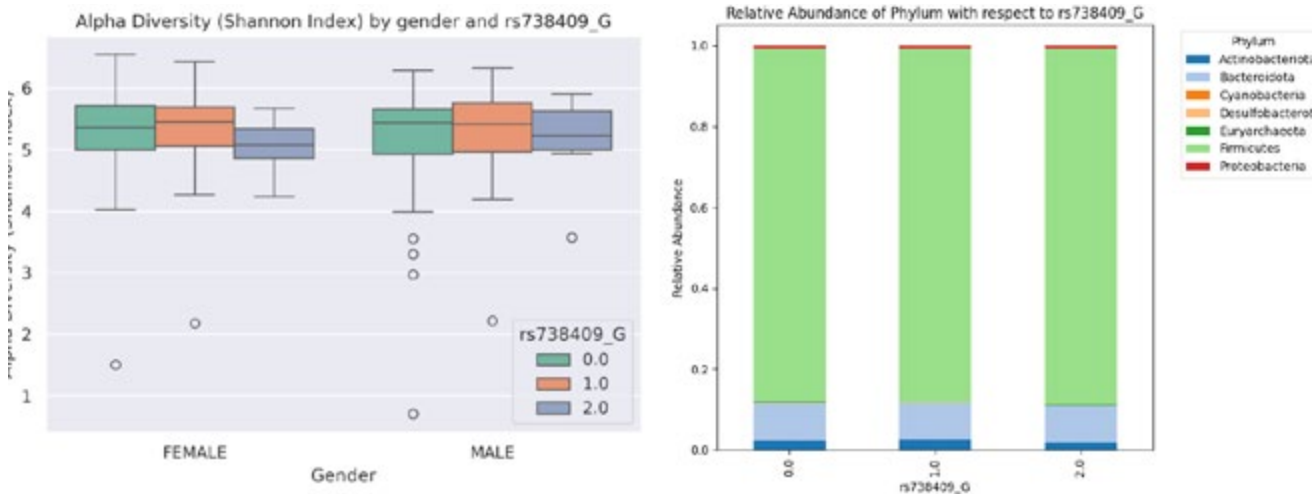
differences and dietary patterns, potentially affecting liver health. Genetic variants, such as the PNPLA3 rs738409 SNP, have been proven to have a significant effect on the development of liver diseases according to previous studies. Furthermore, nutritional interventions have been explored for liver disease treatment. Thus, our project seeks to examine the connections between genetic variability, gut microbiota composition, and nutrients using advanced statistical **Methods:** and machine learning models like random forests, aiming to better understand liver disease mechanisms and identify potential treatment approaches. **Methods:** The Lifelines Biobank data, which includes over 25,000 participants, was analyzed. A subset of 422 participants with health questionnaires, 16S rRNA gene sequencing, and PNPLA3 (I148M) variant info was drawn, comprising 235 females and 187 males, with PNPLA3 data showing 16 homozygotes, 160 heterozygotes, and 246 non-carriers. The amplicon sequencing variants (ASV) of the 16S rRNA gene were isolated to investigate the microbiomes. The analysis included computing the alpha diversity measure using the Shannon index and examining the relative abundances of isolated ASVs to understand microbiome composition across PNPLA3 variants. Using a random forest model, the impact of variables such as BMI, triglycerides, and the PNPLA3 variant (rs738409_G) on microbiome diversity was assessed. **Results:** Higher Shannon index values were noted across all three PNPLA3 variants, implying a subtle connection between genetic variants and microbiome composition. Females displayed a faint distinctions, with homozygotes showing lower Shannon index than heterozygotes and non-carriers. Males exhibited consistent microbial variability across all PNPLA3 genotypes. Abundance calculations revealed higher Firmicutes levels, while the other phyla were lower across all PNPLA3 groups, highlighting their relevance in liver health and potential implications in disease progression. In predictive modeling, BMI and triglyceride levels emerged as significant drivers compared to PNPLA3 variant. **Conclusion:** The study suggests a limited impact of genetic variability of PNPLA3 (I148M) variant on microbiome variations, as evidenced by the observed differences across genetic variants and gender groups. However, it highlights the complex relationship between gut microbiota composition and liver health indicators, pointing towards further investigation into disease mechanisms.



Disclosures: Thriveni Raju: Nothing to Disclose, Alina Beckmann: Nothing to Disclose, Nicole Treichel: Nothing to Disclose, Madhuri Haque: Nothing to Disclose, Yazhou Chen: Nothing to Disclose, Benjamin Laevens: Nothing to Disclose, Kai Markus Schneider: Nothing to Disclose, Kirsten Schorning: Nothing to Disclose, Carolin Schneider: Nothing to Disclose

2256 | ALCOHOL ADMINISTRATION DISRUPTS INTESTINAL AUTOPHAGY TO EXACERBATE LIVER INJURY

Murugadas Anbazhagan[1] Ahmed Bakheet[1] John Dickinson[2] Paul Thomes[1]

[1]College of veterinary medicine, Auburn University, AU, AL, [2]University of Nebraska Medical Center, Omaha, NE

Background: Autophagy is crucial for intestinal barrier integrity as it maintains key functions of intestinal epithelial cells, such as secreting antimicrobial peptides and mucins, and removing harmful microorganisms. This process helps maintain gut homeostasis and prevents harmful gut products from reaching the liver and causing injury. Our study examined whether alcohol disrupts intestinal autophagy to compromise the gut barrier and whether such

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autophagy dysfunction promotes alcohol-induced liver injury. **Methods:** Male wildtype and global autophagy-deficient ATG16L1 hypomorphic (ATG16L1 hm/hm) mice were subjected to chronic-binge ethanol administration (NIAAA feeding model) or to a control diet. We measured autophagy markers and intestinal permeability in the ilea of these animals, as well as serum endotoxin and markers of liver injury. Mouse and human ileal organoids were treated as indicated in the results. **Results:** Compared with controls, Ileal segments from wild-type mice fed chronic-binge ethanol (EtOH) showed lower mRNA levels for the autophagy-regulating transcription factor EB (TFEB) and its downstream targets, PGC1α and LAMP1, along with other autophagy and lysosomal markers including ATG4b, ATG14, and ATP6V0d2. The levels of the stem cell marker LGR5 and epithelial cell markers LYZ1 and IGFBP4 were also reduced in these animals. Human ileal organoids exposed to 0.5% EtOH for 24 hr exhibited lower levels of LC3B, LAMP1, LAMP2, Cathepsin B, PGC1α, and several other autophagy and lysosomal markers, including their regulator, TFEB. Compared with wild-type mice, ileal organoids from ATG16L1 hm/hm mice showed impaired autophagy flux. Compared with EtOH-fed wild type mice, EtOH-fed ATG16L1 hm/hm mice exhibited 1.6- and 2-fold increases in FITC-dextran leakage (ex vivo) and serum endotoxin, respectively, along with a 1.6-fold rise in serum ALT and liver triglycerides. Proinflammatory markers CXCL1 and CXCL2 were also elevated in the livers of EtOH-fed ATG16L1 hm/hm mice. **Conclusion:** we conclude that alcohol exposure disrupts autophagy in intestinal epithelial cells, thereby compromising their functions. Such disruption of autophagy leads to increased intestinal permeability and leakage of bacterial products into the circulation, causing liver injury and inflammation. Our findings also suggest that autophagy deficiency exacerbates alcohol-associated liver injury.

Disclosures: Murugadas Anbazhagan: Nothing to Disclose, Ahmed Bakheet: Nothing to Disclose, John Dickinson: Nothing to Disclose, Paul Thomes: Nothing to Disclose

2257 | ORAL CANNABIDIOL TREATMENT AMELIORATED ALCOHOL-ASSOCIATED LIVER DISEASE IN MICE BY REDUCING GUT PERMEABILITY

MD MANIRUJJAMAN[1] Lihua Zhang[1] Guihua Pan[1] Rahul Pushparaj[1] Jingdan Pei[1] Panpan Huang[1] Xing Gao[1] Craig McClain[2] Zhao-hui Song[2] Wenke Feng[1]

[1]Tulane University, [2]University of Louisville

Background: Cannabidiol (CBD) is one of the components of the cannabis plant and is approved for the treatment of epilepsy. CBD has been used for the treatment of experimental alcohol-associated liver disease (ALD), which is characterized by intestinal barrier dysfunction and bacterial translocation. This study aimed to determine whether the oral administration of CBD was effective in mitigating the restoration of gut barrier function. **Methods:** C57BL6 male mice were subjected to the NIAAA binge-on-chronic alcohol feeding model (10-day 5% Ethanol and one binge 5g/kg body weight). Mice were subjected to alcohol-feeding (AF) or isocaloric pair-feeding (PF). The treatment group received 2 mg/kg body weight CBD by oral gavage every other day for 10 days. **Results:** AF significantly elevated serum ALT and AST levels compared to PF. CBD treatment significantly reduced ALT and AST elevation, indicating the beneficial effect of oral CBD application on mediating liver injury. The liver section of Oil red O staining revealed an accumulation of lipids in AF mice, and it was reduced by CBD, suggesting that CBD reduced alcohol-induced hepatic steatosis. Further analysis showed that CBD oral administration reduced alcohol-induced hepatic inflammation evidenced by reduced macrophage activation the neutrophil infiltration determined by F4/80 and chloroacetate esterase (CAE) staining of hepatic sections. Reduced apoptosis by CBD in the liver was demonstrated by TUNEL assay and down-regulation of Bax and p53 protein. Importantly, serum LPS levels and hepatic bacteria were significantly upregulated by AF and decreased by CBD indicating CBD has protective effects on alcohol-induced gut bacterial translocation. Furthermore, we showed that alcohol-induced ileal apoptosis was suppressed by CBD oral administration. *In vitro* reporter assay showed that CBD activates Aryl hydrocarbon (AhR), which regulates intestinal IL22 and antimicrobial activity and gut microbiota homeostasis. 16s rRNA sequencing of fecal samples demonstrated a rebalanced gut microbiota. **Conclusion:** Our study suggested that oral CBD administration reduced alcohol-associated liver and gut injury and liver steatosis through the reduction of hepatic and gut apoptosis, restoring alcohol-challenged gut dysfunction, and inflammation pathways. The mechanisms underlying the action of oral CBD in ALD involving gut microbiome and intestinal immunoregulation warrant further investigation. (Supported by NIH-NIAAA).

Disclosures: MD MANIRUJJAMAN: Nothing to Disclose, Lihua Zhang: Nothing to Disclose, Guihua Pan: Nothing to Disclose, Rahul Pushparaj: Nothing to Disclose, Jingdan Pei: Nothing to Disclose, Panpan Huang: Nothing

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to Disclose, Xing Gao: Nothing to Disclose, Craig McClain: Novo Nordisk: Grant/Research Support, Intercept Pharmaceuticals: Grant/Research Support, Altimmune: Grant/Research Support, Target Pharma Solutions: Grant/Research Support, NIH: Grant/Research Support, VAMC: Grant/Research Support, Zhao-hui Song: Nothing to Disclose, Wenke Feng: Nothing to Disclose

2258 | *C. DIFFICILE* COLITIS DYSREGULATES HEPATIC LIPID METABOLISM, INDUCING A PRO-STEATOTIC AND PRO-INFLAMMATORY STATE

Farnaz Yousefi[1] *Shankumar Mooyottu*[1]

[1]*Auburn University*

Background: Recent studies suggest links between *Clostridioides difficile* infection (CDI) and liver disorders, with non-alcoholic fatty liver disease (NAFLD) significantly increasing CDI risk and severity. Moreover, gut dysbiosis, often leading to *C. difficile* overgrowth, is implicated in chronic liver conditions. We approach this association from the opposite angle, exploring CDI as a potential direct contributor to NAFLD. **Methods:** Fifty-four adult C57BL/6 mice were divided into Control, Antibiotic control (Abx), and *C. difficile* infection (C. diff) groups. The Abx and C. diff groups received an antibiotic mixture to induce gut dysbiosis and facilitate *C. difficile* colonization. The C. diff group was then inoculated orally with 1.4×10^4 *C. difficile* spores. Mice were euthanized 48 h post-inoculation to collect liver and cecum for metabolomic, transcriptomic, metagenomic, and multi-omics correlation analyses. **Results:** Gut dysbiosis and *C. difficile* colitis were confirmed in respective groups by histopathology and shotgun metagenomic analysis. The RNA sequencing analysis of liver tissue showed a marked increase in the expression of genes associated with insulin resistance, lipid accumulation, oxidative stress, endoplasmic reticulum stress response, and inflammation in C. diff group compared to control. Conversely, genes involved in antioxidant defense, triglyceride and cholesterol hydrolysis, lipogenesis regulation, xenobiotic detoxification, and anti-inflammatory pathways were significantly downregulated. Large-scale liver metabolomic and pathway analyses confirmed significant alteration in fatty acid metabolism, highlighted by increased levels of palmitic acid; amino acid metabolism, with elevated levels of free valine, glycine, tyrosine, and aspartate; and Coenzyme A synthesis, showing reduced dephospho-CoA and pantothenic acid levels. Increased levels of inflammatory mediators, such as prostaglandins and leukotrienes, along with reduced levels of free and oxidized glutathione, were observed in the C. diff group compared to controls. In addition, joint pathway analysis further validated a pro-inflammatory and pro-steatotic liver metabolic state in C.diff group compared to control. **Conclusion:** Our results indicate that CDI triggers gene expression and metabolic shifts that promote inflammation, lipid accumulation, oxidative damage, and insulin resistance, critical in NAFLD development and progression. These insights suggest that recurrent CDI may contribute to NAFLD onset and progression in infected individuals.

Disclosures: Farnaz Yousefi: Nothing to Disclose, Shankumar Mooyottu: Nothing to Disclose

2259 | COMPREHENSIVE PROFILES OF THE MICROBIOME AND METABOLOME WITHIN THE GUT-LIVER AXIS IN WESTERN DIET-FED MC4R KNOCKOUT MICE

Mitsuharu Matsumoto[1] *Osamu Miura*[2] *Takeo Moriya*[2] *Hitomi Ogino*[1] *Megumi Hirayama*[2] *Akira Mitsui*[2] *Takumi Sugawara*[2] *Yoshinori Satomi*[2] *Takaharu Hirayama*[2] *Yukihiko Ebisuno*[2] *Manami Kaneko*[2] *Yasunori Nio*[2]

[1]*Axcelead Drug Discovery Partners, Inc,* [2]*Axcelead Drug Discovery Partners, Inc.*

Background: Metabolic dysfunction-associated steatohepatitis (MASH) is highly associated with obesity and metabolic diseases. The gut-liver axis, an inter-organ network, is critical in the pathogenesis. However, the molecular perturbations within this axis and their relationships still need to be fully understood. To address these issues, we conducted microbiome and metabolome analysis (including lipidomics and sulfidomics) using plasma, liver and intestinal contents from MASH model mice that mimic the human MASH pathology with obesity and insulin resistance. The bioinformatics analysis were also conducted to select the disease-relating bacterial strains and metabolites. **Methods:** To create disease conditions with different severity, melanocortin 4 receptor knockout (MC4R KO) mice and wild type mice were fed with a Western diet (WD) or a normal diet for 12 weeks. We obtained plasma, liver, small and large intestinal contents from these groups for analysis. All these tissues were applied to LC/MS and GC/MS for metabolomics. Microbiome profiles of small and large intestinal contents

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were determined by 16S rDNA amplicon sequencing. We performed statistical analysis and WGCNA to examine molecular perturbations and their interrelationships. **Results:** We obtained microbiome and metabolome profiles of the small and large intestinal contents, liver and plasma parameters. In WD-fed MC4R KO mice, which showed the most severe pathology, there were large perturbations in the bacteria and the metabolite. In terms of changes in the metabolite, a large increase in phosphatidylcholine in the intestinal contents, liver and plasma. In the mild disease condition, these perturbations were less pronounced compared to WD-fed MC4R KO mice. In terms of changes in the microbiota, an increase in Desulfovibrionaceae and Clostridium celatum and a decrease in Allobaculum and S24-7 were observed in the diseased state. The relationship between them is currently being analyzed. **Conclusion:** This study provides the first comprehensive profiling of microbiome and metabolome in WD-fed MC4R KO mice. These profiles will contribute to future exploratory studies of clinical markers.

Disclosures: Mitsuharu Matsumoto: Nothing to Disclose, Osamu Miura: Nothing to Disclose, Takeo Moriya: Nothing to Disclose, Hitomi Ogino: Nothing to Disclose, Megumi Hirayama: Nothing to Disclose, Akira Mitsui: Nothing to Disclose, Takumi Sugawara: Nothing to Disclose, Yoshinori Satomi: Nothing to Disclose, Takaharu Hirayama: Nothing to Disclose, Yukihiko Ebisuno: Nothing to Disclose, Manami Kaneko: Nothing to Disclose, Yasunori Nio: Nothing to Disclose

2260 | IDENTIFICATION OF *RUMINOCOCCUS GNAVUS* AND ITS NEUROTOXIC ROLE IN HEPATIC ENCEPHALOPATHY THROUGH PHENYLALANINE/TRYPTOPHAN DECARBOXYLASE PATHWAY

Mengyao Hu[1] Mengyao Hu[1] Yi Xu[2] Xiaolong He[2] Xiaolong Qi[3] Jie Gao[2] Hongwei Zhou[2]

[1]Zhujiang Hospital of Southern Medical University, [2]Southern Medical University, [3]Southeast University

Background: Hepatic encephalopathy (HE) is the leading cause of re-hospitalization and mortality of cirrhotic patients. Strategies targeting gut microbiota, such as using non-absorbable antibiotics like rifaximin or fecal microbiota transplantation, may prevent or ameliorate HE symptoms, implicating a critical mechanistic role for the gut-liver-brain axis. Given the great diversity of the gut microbiota, we hypothesized that previously unrecognized bacteria might cause neurotoxicity in cirrhosis. **Methods:** We constructed the gut-brain modules, each corresponding to a specific neuroactive compound production or degradation process, to evaluate the neurotoxic potential of gut microbiota using four liver cirrhosis metagenomic datasets. The critical bacteria responsible for the generation of neuroactive compound was identified via analyzing metagenomic data from four cirrhosis cohorts. The neurotoxic effects of critical bacteria were assessed using a murine cirrhosis model. **Results:** We revealed that the monoamine synthesis module was significantly increased in cirrhosis patients across all four independent cohorts and identified phenylalanine/tryptophan decarboxylase (PDC) as the critical enzymes in this module. The PDC genes consistently expanded in cirrhotic patients across all four cohorts, and *Ruminococcus gnavus* (*R. gnavus*) showed the strongest correlation with PDC gene abundance. Additionally, we demonstrated that *R. gnavus* induced behavioral and neuropathological abnormalities in cirrhotic mice through PDC (Figure 1). **Conclusion:** Our study elucidates the critical neurotoxic effect of *R. gnavus* in the pathogenesis of HE through the enzyme PDC. These findings expand the understanding of the gut-liver-brain axis and identify a promising therapeutic and predictive target for HE.

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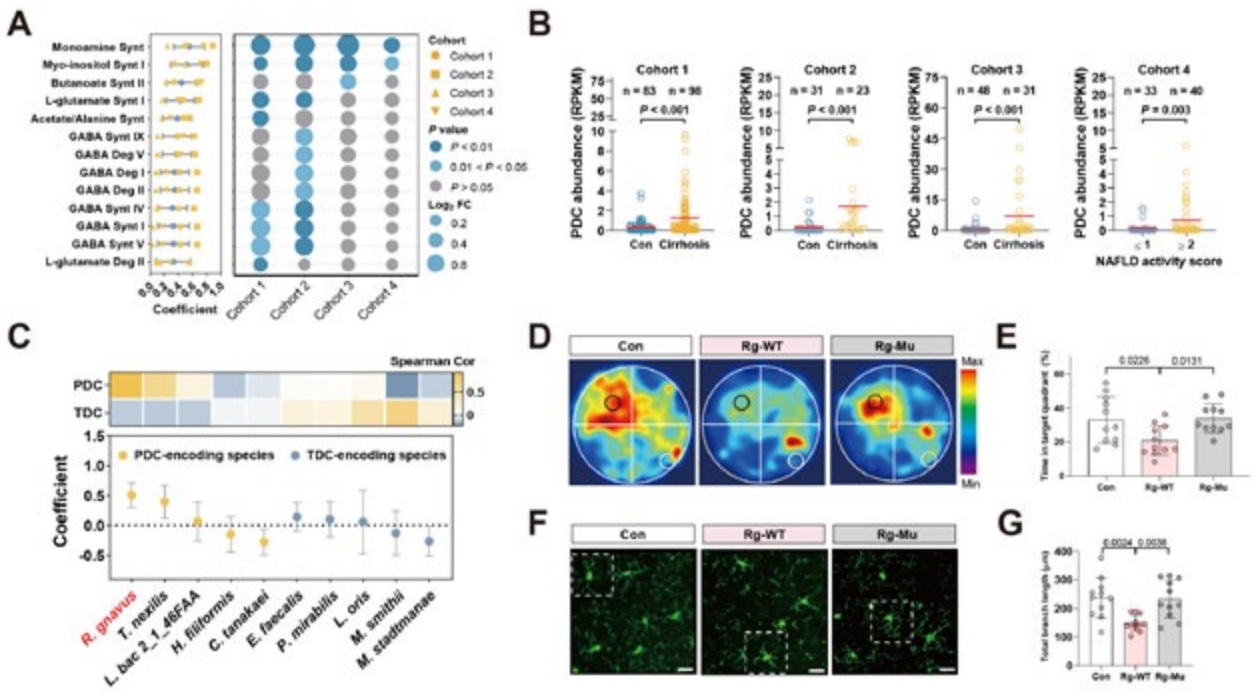

Figure 1. *R. gnavus*-derived PDC is increased in patients with cirrhosis across countries and PDC is required for the neurotoxic effects of *R. gnavus* in cirrhotic mice. (**A**) Pooled effect sizes for the significant GBMs, calculated using a meta-analysis of standardized mean differences and a random effects model (left panel), and their changes in each cohort calculated by linear regression analysis adjusting for age, sex and sequencing depth (right panel). (**B**) PDC abundance in four liver disease cohorts quantified by HUMANn2. Each dot represents a single individual. Data are presented as mean ± SD. Statistical analysis was performed using the linear regression analysis adjusting for age, sex and sequencing depth. (**C**) Spearman correlation (Cor) of AADC abundance and AADC-encoding species in four cohorts (upper panel), and changes of these species in liver diseases analyzed by meta-analysis of standardized mean differences and a random effects model (lower panel). (**D**) Heatmap of overall activity comparison between the three groups. (**E**) Time spent in the platform quadrant in the probe test (n = 11 mice per group). (**F**) Representative images of immunofluorescent labelling of Iba-1 (microglia, green) in the cerebral cortex of each treatment, scale bars, 20 μm. (**G**) Microglia morphological parameter of total branch length (n = 11 mice per group). Each dot represents a single individual, data are presented as mean ± SD.

Disclosures: Mengyao Hu: Nothing to Disclose, Mengyao Hu: Nothing to Disclose, Yi Xu: Nothing to Disclose, Xiaolong He: Nothing to Disclose, Xiaolong Qi: Nothing to Disclose, Jie Gao: Nothing to Disclose, Hongwei Zhou: Nothing to Disclose

2261 | BACTERIAL GENETIC DETERMINANTS OF SPECIES ADAPTION IN CIRRHOSIS ◆

Yi Xu[1] *Xiaolong He*[2] *Mengyao Hu*[2] *Hongwei Zhou*[2] *Jie Gao*[2]

[1]*Zhujiang Hospital, Southern Medical University,* [2]*Southern Medical University*

Background: The gut microbiota of cirrhosis patients exhibits consistent and reproducible changes in species composition and function across cohorts, suggesting that the dysbiosis in cirrhosis is not a random occurrence but is driven by specific factors. Understanding the specific factors may reveal the genetic factors essential for microbial species adaptations, potentially guiding targeted microbiome interventions. **Methods:** Characteristic bacteria of cirrhosis were identified using multi-cohort metagenomic data analysis. The distribution of metabolic genes in gut bacteria was systematically described by utilizing gut-metabolic-modules (GMMs). The correlation between GMM metabolic gene copies and species abundance change scores was analyzed using Spearman's

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method. A lasso regression model was constructed using genes related to bacterial energy harvest as variables to predict species outcomes in cirrhosis. **Results:** Analysis of metabolic genes in gut bacteria revealed significant differences in metabolic genes among different species. Comparative genomics showed that one of the key characteristics of bacteria enriched in cirrhosis, compared to those decreased, is the presence of high-copy lactate utilization genes. Genes involved in lactate metabolism are closely associated with species enrichment in disease states. Based on bacterial metabolic gene modules, changes in bacteria in cirrhosis can be accurately predicted, with lactate utilization gene modules being important variables for predicting bacterial increase in cirrhosis. Additionally, elevated lactate levels were detected in the pathology of cirrhosis, confirming the lactate-species correlation in cirrhosis cohorts. Experimental isolation of these disease-associated species and subsequent in vitro assessments revealed that lactate enhances the growth of species over-represented in diseases and suppresses that of species depleted in disease contexts. (Figure 1). **Conclusion:** This study systematically elucidates the genetic determinants that underlie bacterial proliferation in cirrhosis states and demonstrate the potential of cirrhosis-enriched lactate to drive gut microbiota towards dysbiosis, highlighting its implications for disease management and therapeutic strategies.

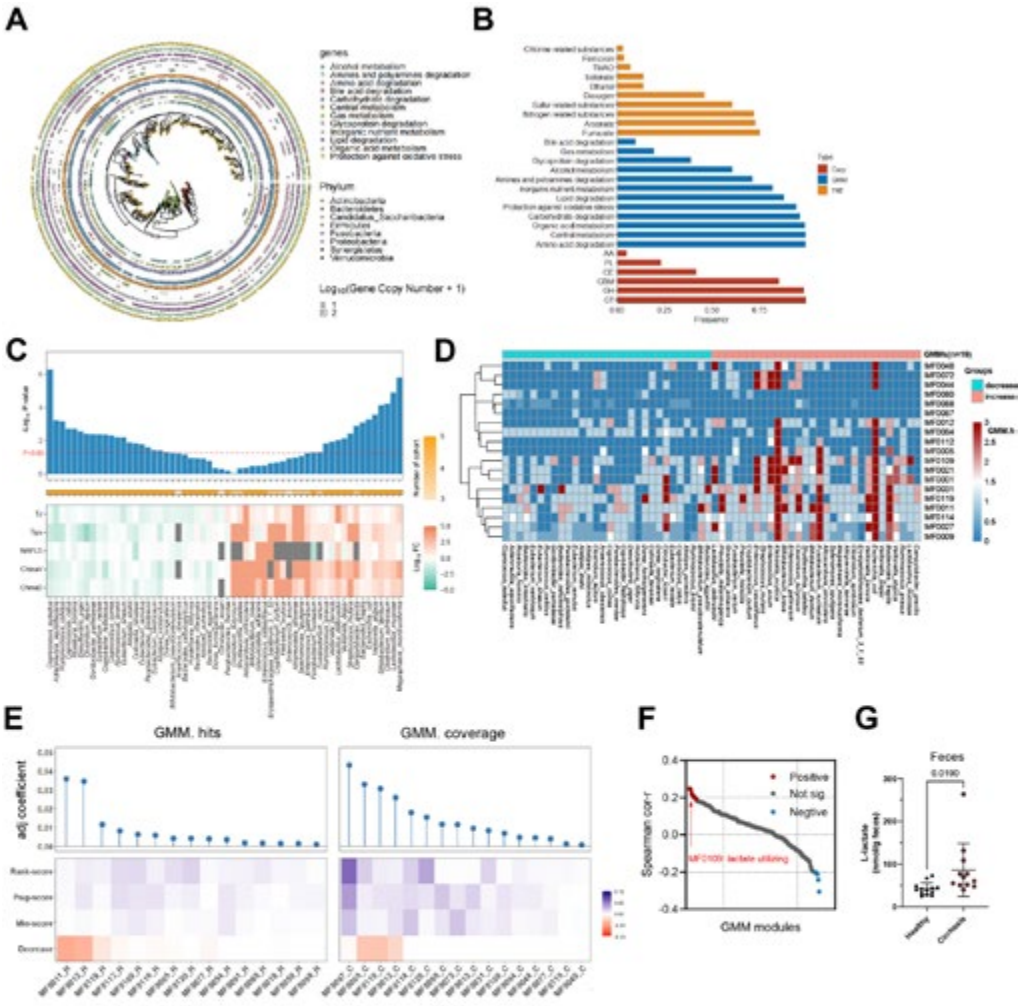

Fig. 1. Comparative genomics revealed the metabolic gene characteristics of bacteria enriched in cirrhosis. (A) The phylogenetic tree shows the distribution of different categories of gene modules within reference genomes of gut bacteria (branches in different colors represent different phyla of bacteria, with circles annotating the copy numbers of metabolic gene modules); (B) Statistics of the distribution of different metabolic gene modules. (C) In five cirrhosis cohorts, the meta-p values of the most significantly altered species (upper panel) and their fold changes in each cohort (lower panel). (D) The GMM hits in the most significantly altered species. (E) The coefficient of variables in the Lasso regression model. (F) The correlation between GMM metabolic gene copies and species abundance change scores. (G) The concentration of L-lactate in the feces of cirrhosis patients (n= 12) and healthy individuals (n = 13). Each dot represents a single individual, data are presented as mean ± SD.

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Disclosures: Yi Xu: Nothing to Disclose, Xiaolong He: Nothing to Disclose, Mengyao Hu: Nothing to Disclose, Hongwei Zhou: Nothing to Disclose, Jie Gao: Nothing to Disclose

2262 | THE ROLE OF GUT MICROBIOTA-DERIVED PHENYLETHYLAMINE IN HEPATIC ENCEPHALOPATHY PATHOGENESIS: BEYOND THE AMMONIA HYPOTHESIS

Xiaolong He Mengyao Hu[1] Yi Xu[1] Xiaolong Qi[2] Jie Gao[1] Hongwei Zhou[1]

[1]Southern Medical University, [2]Southeast University

Background: Up to 50-70% of liver cirrhosis patients develop hepatic encephalopathy (HE), which is closely related to gut microbiota dysbiosis, with unclear mechanism. Gut-derived ammonia has long been considered central in HE pathogenesis, however, hyperammonemia doesn't always correlate with the onset or severity of HE in the clinical setting. Furthermore, rifaximin's therapeutic effects appear to be ammonia-independent, suggesting that other microbiota-derived neurotoxins may play significant roles in HE pathogenesis. **Methods:** Neurotoxic potential of gut microbiota-derived metabolites was evaluated via analyzing metagenomic data from cirrhosis cohorts across countries. Mass spectrum was used to identify critical enzymes and bacteria responsible for generation of neurotoxin, with a significant emphasis on phenylalanine decarboxylase (PDC) derived from *Ruminococcus gnavus* (R. gnavus). In vivo and in vitro experiments were designed to assess the neuropsychiatric impact of R. gnavus, PDC and its metabolite phenylethylamine (PEA) on cirrhosis models. A longitudinal study on a cohort undergoing transjugular intrahepatic portosystemic shunts (TIPS) was incorporated to examine the association between baseline serum PEA levels and HE onset post-TIPS procedure. **Results:** We revealed a significant increase in the bacterial monoamine synthesis pathway in cirrhosis patients. The PDC enzyme from *R. gnavus* was identified as a key player in this pathway. We found that *R. gnavus*, through PDC and its metabolite PEA, induced neuropsychiatric symptoms akin to those seen in HE patients, but only under cirrhotic conditions. Serum PEA levels significantly elevated in HE patients, correlated with fecal PDC abundance and were identified as a warning marker for HE onset post-TIPS, linking high baseline PEA levels to a 7-fold increased risk of HE (Figure 1). **Conclusion:** This study demonstrated the critical role of gut microbiota-derived PEA, mainly produced by R. gnavus, in the pathogenesis of HE, expanding the understanding of the gut-liver-brain axis beyond the traditional ammonia-centric theory. The identification of serum PEA levels as a predictive marker for HE onset post-TIPS offers a novel approach for managing and preventing HE in cirrhosis patients, and targeting the microbial production of PEA could be a promising therapeutic strategy.

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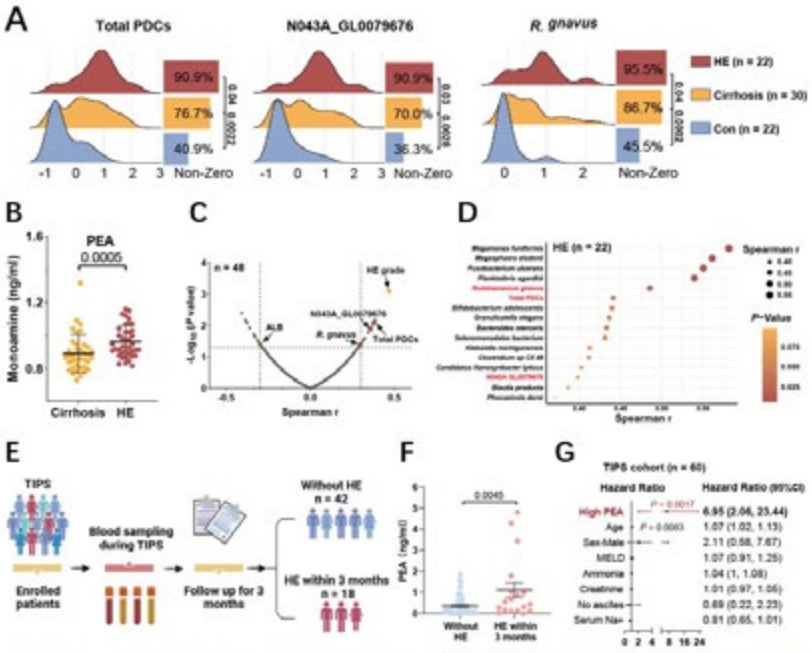

Figure. 1. Serum PEA level correlates with fecal PDC abundance and high baseline PEA level links to increased risk of HE after TIPS. (A) The abundance of total PDCs, N043A_GL0079676 or *R. gnavus* in control, cirrhosis or HE patients. Density plots show the $\log_{10}$ (abundance relative to control median). Bar plots show the presence rate in each group. **(B)** Quantification of PEA in the serum of cirrhosis (n = 37) or HE (n = 40) patients. **(C)** Clinical and microbiota factors that correlate with serum PEA levels. **(D)** Microbiota factors that correlate with serum PEA levels after adjusting for albumin levels in HE patients. **(E)** Schematic diagram of the longitudinal followed-up TIPS cohort, the serum was collected during TIPS surgery and used to predict the onset of HE over a period of 3 months. **(F)** Quantification of PEA in serum of patients with or without HE after TIPS surgery in 3 months. **(G)** Forest plot reporting hazard ratios (HR) of baseline clinical parameters on risk for HE onset within 3 months following TIPS procedures , high PEA refers to PEA upper the 50th percentile.

Disclosures: Xiaolong He: Nothing to Disclose, Mengyao Hu: Nothing to Disclose, Yi Xu: Nothing to Disclose, Xiaolong Qi: Nothing to Disclose, Jie Gao: Nothing to Disclose, Hongwei Zhou: Nothing to Disclose

2263 | ASSOCIATION BETWEEN THE GUT MICROBIOTA AND PRIMARY BILIARY CHOLANGITIS: A TWO-SAMPLE MENDELIAN RANDOMIZATION STUDY

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Background: Several recent observational studies have reported that the gut microbiota composition is associated with primary biliary cholangitis (PBC). However, the causal effect of changes in the gut microbiota on PBC is unknown. **Methods:** A two sample Mendelian randomization study was performed using data from the summary statistics of gut microbiota and PBC which were obtained from the European subjects in that cohort. Inverse variance weighted, maximum likelihood,MR-Egger,weighted median,weighted mode,and MR-PRESSO were used for the statistical analysis to examine the causal associations between the gut microbiota and PBC. Genetic variants for the gut microbiota were identified from the largest genome wide association studies published

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to date on gut microbiota composition conducted by the MiBioGen consortium(PMID: 33462485). GWAS summary statistics for PBC were obtained from multiple cohorts, which included PBC cases in Canadian-US, Italian, and UK discovery and validation cohorts that fulfilled the American Association for the Study of Liver Diseases criteria for PBC,comprising 2764 PBC cases and 10475 controls (PMID:26394269). **Results:** As shown in Table 1, class.Negativicutes, class.Bacteroidia, order.Selenomonadales, family.Ruminococcaceae, genus. Bilophila, genus.Lachnospira, genus. LachnospiraceaeUCG008, and genus.Prevotella9 were each found to be associated with PBC in at least one MR method before Bonferroni correction. The IVW estimates for class. Negativicutes (OR=1.86(1.08,3.18), P=0.024), order. Selenomonadales (OR=1.86(1.08,3.18), P = 0.024), and genus.Bilophila (OR=1.80(1.05,3.07), P=0.032) were causally associated with PBC. The IVW estimates for genus.Prevotella9 showed a protective effect against PBC(OR=0.64(0.43,0.93), P=0.021, q=0.13); however, these associations were no longer significant after false discovery rate (FDR) correction (q>0.1). Similarly, the weighted median estimates for class.Bacteroidia and genus.LachnospiraceaeUCG008 presented suggestive associations with PBC, while the Wald ratio estimate of genus.Lachnospira presented a suggestive association with PBC. Only family.Ruminococcaceae (ID:2050) had a protective effect against PBC after Bonferroni correction (OR=0.35(0.18,0.68), P=0.002, q=0.07). The results of Cochran's IVW Q test showed no significant heterogeneity for these IVs (Table 1). In addition, there was no significant directional horizontal pleiotropy observed according to the MR-Egger regression intercept analysis results. **Conclusion:** This two sample Mendelian randomization study found that a decrease in the abundance of family Ruminococcaceae causes PBC.

Table 1. MR estimates of the associations between the gut microbiota and PBC

Bacterial taxa (exposure)	MR method	No. of SNPs	beta	se	OR(95%CI)	*P*-value	*q*-value
class.Negativicutes (ID:2164)	MR Egger	6	0.452	3.069	1.57(0.00,643.18)	0.890	>0.1
	Weighted median	6	0.591	0.326	1.81(0.95,3.42)	0.069	>0.1
	Inverse variance weighted	6	0.619	0.275	1.86(1.08,3.18)	0.024	>0.1
	Simple mode	6	0.563	0.494	1.76(0.67,4.63)	0.306	>0.1
	Weighted mode	6	0.556	0.432	1.74(0.75,4.06)	0.254	>0.1
class.Bacteroidia (ID:912)	MR Egger	8	-0.101	1.058	0.90(0.11,7.19)	0.927	>0.1
	Weighted median	8	-0.609	0.306	0.54(0.30,0.99)	0.047	>0.1
	Inverse variance weighted	8	-0.389	0.243	0.68(0.42,1.09)	0.109	>0.1
	Simple mode	8	-0.685	0.488	0.50(0.19,1.31)	0.203	>0.1
	Weighted mode	8	-0.679	0.479	0.51(0.20,1.30)	0.199	>0.1
order.Selenomonadales (ID:2165)	MR Egger	6	0.452	3.069	1.57(0.00,43.18)	0.890	>0.1
	Weighted median	6	0.591	0.331	1.81(0.94,3.45)	0.074	>0.1
	Inverse variance weighted	6	0.619	0.275	1.86(1.08,3.18)	0.024	>0.1
	Simple mode	6	0.563	0.465	1.76(0.71,4.37)	0.280	>0.1
	Weighted mode	6	0.556	0.465	1.74(0.70,4.33)	0.285	>0.1
family.Ruminococcaceae (ID:2050)	MR Egger	4	-0.112	1.238	0.89(0.08,10.12)	0.936	>0.1
	Weighted median	4	-1.034	0.407	0.36(0.16,0.79)	0.011	>0.1
	Inverse variance weighted	4	-1.041	0.338	0.35(0.18,0.68)	0.002	0.07
	Simple mode	4	-1.273	0.517	0.28(0.10,0.77)	0.091	>0.1
	Weighted mode	4	-0.826	0.528	0.44(0.16,1.23)	0.216	>0.1
genus.Bilophila (ID:3170)	MR Egger	6	-1.978	3.426	0.14(0.00,114.05)	0.595	>0.1
	Weighted median	6	0.431	0.342	1.54(0.79,3.01)	0.208	>0.1
	Inverse variance weighted	6	0.586	0.273	1.80(1.05,3.07)	0.032	>0.1
	Simple mode	6	0.260	0.474	1.30(0.51,3.29)	0.607	>0.1
	Weighted mode	6	0.220	0.430	1.25(0.54,2.90)	0.631	>0.1
genus.Lachnospira (ID:2004)	Wald ratio	1	-1.310	0.664	0.27(0.07,0.99)	0.049	>0.1
genus.Lachnospiraceae UCG008 (ID:11328)	MR Egger	5	-1.201	1.400	0.30(0.02,4.67)	0.454	>0.1
	Weighted median	5	0.566	0.242	1.76(1.10,2.83)	0.019	>0.1
	Inverse variance weighted	5	0.343	0.211	1.41(0.93,2.13)	0.104	>0.1
	Simple mode	5	0.605	0.318	1.83(0.98,3.42)	0.130	>0.1
	Weighted mode	5	0.602	0.312	0.83(0.99,3.36)	0.126	>0.1
genus.Prevotella9 (ID:11183)	MR Egger	7	0.845	1.735	2.33(0.08,69.84)	0.647	>0.1
	Weighted median	7	-0.368	0.261	0.69(0.42,1.15)	0.159	>0.1
	Inverse variance weighted	7	-0.452	0.196	0.64(0.43,0.93)	0.021	>0.1
	Simple mode	7	-0.374	0.371	0.69(0.33,1.42)	0.353	>0.1
	Weighted mode	7	-0.374	0.371	0.69(0.33,1.42)	0.352	>0.1

Disclosures: Hongqin Xu: Nothing to Disclose, YANHANG GAO: Nothing to Disclose

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2264 | SALIVARY MICROBIOME IS INDEPENDENTLY ASSOCIATED WITH HOSPITALIZATIONS IN A MULTI-CENTER PROSPECTIVE COHORT OF OUTPATIENTS WITH CIRRHOSIS: NACSELD3 EXPERIENCE

Jasmohan Bajaj[1] Masoumeh Sikaroodi[2] Marcela Peña Rodríguez[3] Puneeta Tandon[4] Jennifer Lai[5] Jacqueline Oleary[6] Guadalupe Garcia-Tsao[7] Florence Wong[8] Hugo Vargas[9] Scott Biggins[10] Patrick Kamath[11] Brian Bush[12] K Rajender Reddy[13] Patrick Gillevet[2]

[1]Virginia Commonwealth University, [2]George Mason University, [3]Universidad de Guadalajara, [4]University of Alberta, [5]UCSF, [6]Dallas VAMC, [7]Yale University, [8]University of Toronto, [9]Mayo Clinic Arizona, [10]UPMC, [11]Mayo Clinic Rochester, [12]VCU, [13]University of Pennsylvania

Background: Inflammation is a main driver of poor outcomes in cirrhosis. Oral microbiome alterations link with systemic and local inflammation & worsen with cirrhosis progression. Caries, periodontitis and other tooth loss can further exacerbate systemic inflammation & lead to cirrhosis complications & resultant hospitalization. Saliva collection is also more acceptable to collect than stool for microbiome analysis. Aim: To determine whether salivary microbiome can predict hospitalizations over 6 months in a multi-center cirrhosis cohort. **Methods:** NACSELD3 is a prospective multicenter North American cohort of cirrhosis outpatients whose etiology is controlled (HCV eradication, alcohol abstinence, HBV suppression). Cirrhosis/comorbidity details, lab values, & saliva are collected at baseline. Patients are followed for 6 mths for non-elective hospitalizations. Baseline salivary microbiome was evaluated using 16SrRNA sequencing and comparisons between those who reached an outcome or not was performed. Finally, a multivariable regression model (MAASLin2 with RStudio) adding salivary microbiome to the clinical predictors of outcomes was performed. **Results:** 539 patients from 10 centers provided saliva, 115 (21%) of whom were hospitalized within 6 months. Most hospitalizations were liver-related (n=76) & 45% of patients had >1 hospitalizations. None of the hospitalizations were due to dental issues. Fig 1 shows that at baseline patients who were ultimately hospitalized had similar demographics but greater cirrhosis severity. Factors affecting oral health (alcohol use, tobacco use, no. of teeth) were similar. Salivary microbiome: Univariable analysis (FigB) shows that salivary *Streptococcus*, *Treponema, Enteroccaceae & Capnocytophagia* were higher and commensals such as *Veillonellaceae* & *Lachnospiraceae* spp were lower in those who were ultimately hospitalized. Multivariable analysis: We included demographic, etiology, prior hospitalizations, PPI, SBP prophylaxis, HE, ascites, Oral health (no. of teeth, alcohol & tobacco), hemoglobin & MELD3.0 in the clinical model and found that *Prevotellaceae_Paraprevotella (p=0.0003), Spirochetaceae_Treponema (p=0.0004), Porphyromonadaceae_Microbacter (p=0.007) & Prevotellaceae_Prevotella (p=0.0001)* were significantly additive to the clinical model for hospitalization prediction. *Treponema denticola, Porphyromonas & Prevotella spp are* associated with periodontitis and caries. **Conclusion:** In a prospective multi-center cohort of outpatients with cirrhosis, salivary microbiota enriched in organisms that cause caries and periodontitis are associated with hospitalizations at 6 months despite controlling for factors affecting oral health, cirrhosis severity, medications, comorbidities, and demographics. Modulating salivary microbiota by encouraging orodental interventions could reduce poor outcomes in cirrhosis over time.

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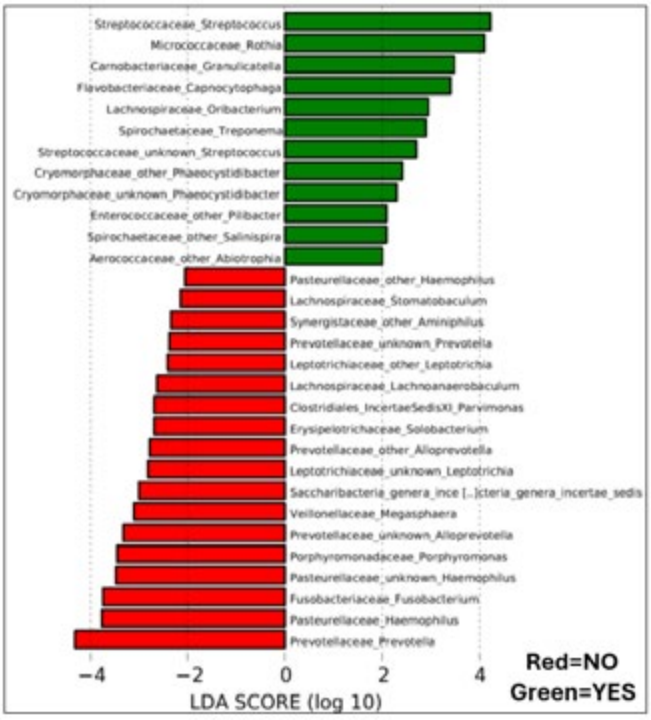
Hospitalized at 6M?	No (n=424)	Yes (n=115)	P value
Age	61.1±10.5	60.6±10.2	0.66
Male sex	293 (69%)	80 (70%)	0.92
Race (white/other)	346/78	91/24	0.54
Hispanic ethnicity	17 (2%)	3 (1%)	0.45
Oral health/ comorbidities			
AUDIT-10	1.95±3.63	1.56±2.97	0.23
No. of natural teeth	21.2±10.8	20.3±10.3	0.43
Tobacco use	90 (21%)	16 (14%)	0.06
Charlson comorbidity index	4.8±2.1	5.8±2.0	<0.0001
Cirrhosis details			
Alcohol etiology	263 (62%)	53 (46%)	0.11
Prior HE	88 (21%)	45 (39%)	<0.0001
Prior ascites	188 (44%)	83 (72%)	<0.0001
Prior hospitalizations	66 (16%)	43 (38%)	<0.0001
Labs & meds			
MELD3.0	11.5±4.9	14.3±5.7	<0.0001
WBC	5.5±2.1	5.6±2.9	0.67
Hemoglobin	13.2±2.1	11.7±2.4	<0.0001
Platelets	140.5±69.6	126.5±76.4	0.09
PPI	201 (47%)	75 (65%)	0.001
Beta-blockers	177 (42%)	59 (51%)	0.07
Statins	135 (32%)	44 (38%)	0.20
SBP prophylaxis	23 (5%)	11 (10%)	0.12



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2265 | DIETARY INTERVENTION IMPROVES INTESTINAL PERMEABILITY AND REDUCES COLON FIBRO-INFLAMMATION IN THE GAN DIET-INDUCED OBESE AND BIOPSY-CONFIRMED MOUSE MODEL OF MASH

Susanne Pors[1] Jacob Nøhr-Meldgaard[1] Kristoffer Voldum-Clausen[1] Anitta Kinga Sarvari[1] Sakthi Jagadeesan[2] Kasper Almholt[3] Natalia Petersen[3] Charlotta Dornonville de la Cour[3] Sebastian Beck Jørgensen[3] Henrik Hansen[1] Michael Feigh[1]

[1]Gubra, [2]Artus Therapeutics, [3]Novo Nordisk

Background: The gut-liver axis is considered playing an important role in metabolic dysfunction-associated steatohepatitis (MASH). Accordingly, MASH is associated with gut dysbiosis and impaired intestinal barrier function ('leaky gut') which may expose the liver to inflammatory microbial products and facilitate pro-fibrotic responses. The Gubra-Amylin NASH (GAN) diet-induced obese (DIO) mouse is an industry-standard translational model of biopsy-confirmed MASH and fibrosis. The present study aimed to assess the impact of dietary

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intervention (chow reversal) on markers of intestinal permeability, liver and colon inflammation, in addition to liver and colon fibrosis in the GAN DIO-MASH mouse. **Methods:** Male C57BL/6JRj mice were fed the GAN diet for 38 weeks. Only mice with liver biopsy-confirmed MASH (NAS≥5) and fibrosis (stage F2-F3) were included. GAN DIO-MASH mice received chow-reversal for 12 weeks (n=14). Vehicle-dosed GAN DIO-MASH mice remaining on the GAN diet served as controls (n=13). Age-matched chow-fed animals were included as healthy controls (n=8). Within-subject comparisons were performed for liver biopsy histopathological scores (NAS and fibrosis stage). Terminal quantitative endpoints included intestinal permeability (FITC-dextran), colon weight and length, quantitative histological markers of liver (CD45, Gal3) and colon inflammation (CD45, CD3) and fibrosis and fibrogenesis in liver (PSR, Col1a1, aSMA) and colon (PSR, Col1a1). **Results:** Chow-reversal markedly improved body weight, hepatomegaly, liver function (plasma ALT, AST, TC) and NAS (≥2-point), driven by reduced steatosis and liver inflammation (Gal3, CD45). Chow-reversal reduced α-SMA without improving fibrosis histology. GAN DIO-MASH mouse demonstrated diminished colon weight and length, increased intestinal permeability and elevated colon inflammation (CD45, CD3). The metabolic and liver histological benefits of chow-reversal were accompanied by restored intestinal barrier, reversal of loss in colon weight and length and reduced markers of colon fibrosis (PSR, Col1a1) and inflammation (CD45, CD3). **Conclusion:** The biopsy-confirmed GAN DIO-MASH mouse demonstrates increased intestinal permeability and colon hypotrophy and inflammation which is reversed by dietary intervention (chow reversal). Chow reversal also markedly improved metabolic and liver histological hallmarks of MASH, albeit not improving the liver fibrosis. Overall, the study outcomes emphasize the benefits of dietary intervention on liver and gut function in MASH and further highlights the clinical translatability and utility of the GAN DIO-MASH model in preclinical drug development.

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2266 | ACYL-COA THIOESTERASE 12-MEDIATED PPAR&GAMMA; ACTIVATION PRESERVES GUT BARRIER INTEGRITY BY SUPPRESSING INTESTINAL EPITHELIAL CELL NECROPTOSIS: PROTECTIVE ROLE IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS

Akiko Sugiyama[1] *Susan Hagen*[2] *David Cohen*[1]

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Background: Acyl-CoA thioesterase 12 (Acot12), a cytosolic enzyme that hydrolyzes acetyl-CoA into acetate, is expressed in small intestinal epithelial cells (IEC) and is markedly induced by high fat diet (HFD) feeding. Intestinal Acot12 deletion promotes metabolic dysfunction-associated steatohepatitis (MASH) due to increased intestinal permeability, which is attributable to IEC necroptosis and is associated with reduced PPARγ acetylation and anti-inflammatory gene expression. This study aimed to test the hypothesis that Acot12 in IECs protects against MASH by activating PPARγ and suppressing necroptosis. **Methods:** Intestinal-specific *Acot12*$^{-/-}$ (*I-Acot12*$^{-/-}$) and control mice were begun on a HFD at age 6 w. Mice fed the HFD for 4 w were either switched to a HFD containing the PPARγ agonist rosiglitazone or continued on the HFD alone for 8 w. Mice fed the HFD for 12 w were administrated the necroptosis inhibitor GSK872 targeting receptor-interacting protein kinase 3 (RIP3) or vehicle daily for 1 w. Intestinal permeability was evaluated using 70 kDa rhodamine B isothiocyanate dextran. Necroptosis was determined by immunolocalization of mixed lineage kinase domain-like (MLKL) and by immunoblotting for phosphorylated RIP3 (pRIP3) protein. Lipopolysaccharide (LPS) concentrations in portal blood were quantified enzymatically. Hepatic collagen deposition was assessed by Sirius red staining and hydroxyproline content. **Results:** *I-Acot12*$^{-/-}$ mice treated with rosiglitazone or GSK872 experienced significant reductions in intestinal permeability. Rosiglitazone reduced both translocation of MLKL to the IEC plasma membrane and jejunal pRIP3 levels, suggesting decreased necroptosis owing to PPARγ activation. In the jejunum, rosiglitazone upregulated the anti-inflammatory gene (*Il10*). In concert with decreased IEC necroptosis, we observed reductions of portal blood LPS levels and suppression of inflammatory genes (*Tnfa, Il6, Il1b*) and αSMA expression, as well as reduced collagen deposition in the liver. GSK872 treatment of *I-Acot12*$^{-/-}$ mice

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downregulated inflammatory genes expression in both jejunum and liver. **Conclusion:** By activating PPARγ to suppress IEC necroptosis and inflammation in response to overnutrition, intestinal Acot12 maintains gut barrier function, preventing bacterial translocation and thereby attenuating hepatic inflammation and fibrosis. We speculate that enhancing intestinal PPARγ activity through acetylation is a key mechanism by which Acot12 mitigates MASH.

Disclosures: Akiko Sugiyama: Nothing to Disclose, Susan Hagen: Nothing to Disclose, David Cohen: Nothing to Disclose

2267 | REDUCED BACTEROIDES THETAIOTAOMICRON CONTRIBUTES TO THE DISORDERED METABOLISM OF BILE ACIDS IN MASLD PATIENTS

Jian Wu[1] Chang Liu[1] Yu-Li Wang[1] Li Zhang[1] Li Xie[1] Yong-Yu Yang[1] Ning-Ping Zhang[2] Jia Ding[3] Yang Wu[1]

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Background: Bile acid metabolism is often disturbed in metabolic dysfunction-associated steatotic liver disease (MASLD) along with gut dysbiosis. How specific gut microbial species change affects bile acid metabolism is poorly understood. The present study aims to investigate the disruption of gut microbiota on metabolic disturbance of bile acids in MASLD patients. **Methods:** A total of 32 subjects were enrolled, including 8 with simple fatty liver (SFL), 8 with metabolic dysfunction-associated steatohepatitis (MASH), 8 with MASH-fibrosis, and 8 healthy controls (HC). Gut dysbiosis was determined with metagenomic sequencing. Serum and fecal levels of bile acids were quantitated by UPLC-MS analysis. The deletion and replenishment of 7-α-hydroxysteroid dehydrogenase (hdhA) gene was manipulated in anaerobic Bacteroides thetaiotaomicron to investigate its impact on conversion from primary to secondary bile acids. **Results:** Compared to HCs, serum levels of taurodeoxycholic acid (TDCA) and glycodeoxycholic acid (GDCA) were significantly reduced in MASLD patients; whereas levels of chenodeoxycholic acid (CDCA) and cholic acid (CA) were increased. Fecal levels of ursodeoxycholic acid (UDCA) and ursocholic acid (UCA) were significantly decreased in the MASH and MASH-fibrosis groups compared to the subjects with SFL. The abundance of Bacteroides thetaiotaomicron (BT), Phocaeicola vulgatus and Phocaeicola dorei was significantly dropped in the MASH and MASH-fibrosis groups compared to those with SFL. The reduction of BT species in MASH-fibrosis subjects was confirmed by absolute quantification. mRNA levels of hdhA enzyme that catalyzes the conversion from CA to UCA and CDCA to UDCA were significantly diminished in MASH-fibrotic patients. To verify the involvement of BT in the metabolism of bile acids, the hdhA deletion mutant (BT ΔhdhA) and replenishment strains were constructed, and the bacteria were cultured with CDCA under an anaerobic condition. Compared to controls, CDCA concentration in culture medium for BT wild type (WT) was significantly decreased at 24 hours (326.4±258.5 vs. 15379.3±1051.9 ng/mL, $p<0.001$). The deletion of hdhA (BT ΔhdhA) did not decrease CDCA concentration (12199.5±289.2 ng/mL); whereas, the replenishment of the hdhA gene restored the ability to metabolize CDCA (56.8±5.8 ng/mL). **Conclusion:** The abundance of Bacteroides thetaiotaomicron with hdhA enzyme was decreased in MASH liver fibrosis, leading to significant increase in serum primary bile acids, such as CA and CDCA, confers to overall disturbance in bile acid metabolism along with other metabolic disruption. The delineation of a metabolic link between the alteration of specific gut microbial species with bile acid conversion in gut would establish the molecular basis for microbial intervention in MASH progression.

Disclosures: Jian Wu: Nothing to Disclose, Chang Liu: Nothing to Disclose, Yu-Li Wang: Nothing to Disclose, Li Zhang: Nothing to Disclose, Li Xie: Nothing to Disclose, Yong-Yu Yang: Nothing to Disclose, Ning-Ping Zhang: Nothing to Disclose, Jia Ding: Nothing to Disclose, Yang Wu: Nothing to Disclose

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2268 | FECAL MICROBIOTA TRANSPLANT DONOR EXPOSED TO HIGH PROTEIN DIET IMPROVES THE REMISSION IN MURINE MODEL OF ALCOHOL-ASSOCIATED LIVER DISEASE

Ashi Mittal[1] *Nishu Choudhary*[1] *Anupama Kumari*[1] *Kavita Yadav*[1] *Jaswinder Maras*[1] *Shiv Kumar Sarin*[1] *shvetank sharma*[1]

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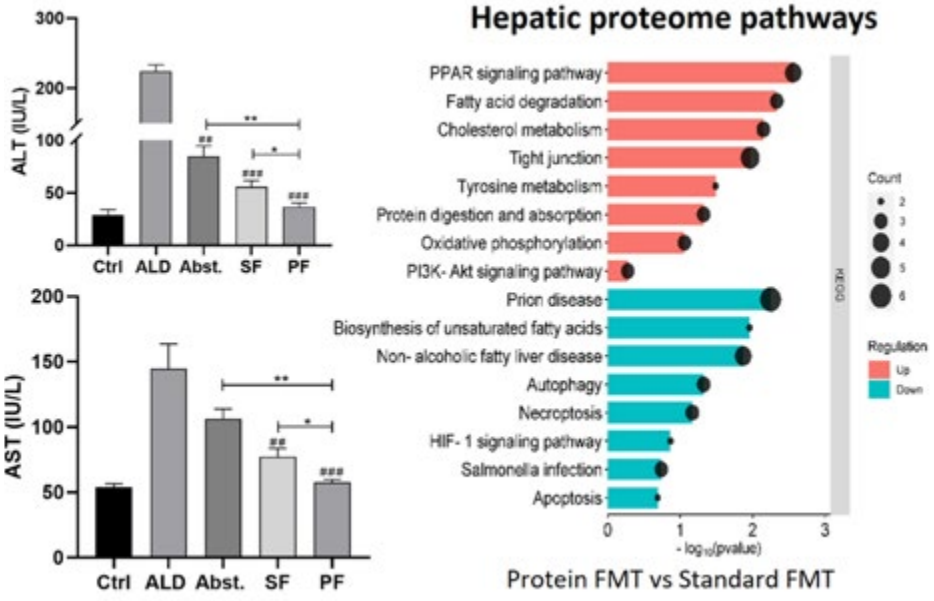
Background: Alcohol associated liver disease (ALD) patients are often recommended high protein diet. Fecal microbiota transfer (FMT) has now proven to be an effective alternative for ALD treatment. We investigated if pre-educating the donor microbiota with protein could improve remission of ALD in an animal model. **Methods:** Donor C57BL6N mice were pair-fed standard and protein (20% increased) diet for 2 weeks. FMT was performed in ALD mice (developed in 8 weeks using Lieber-DeCarli diet with incremental ethanol and twice weekly i.p. thioacetamide-150mg/kg bw). Serum biomarkers of liver injury, histopathology and gene expression of inflammation were assessed by RT-PCR. Gut microbiota and its effect on hepatic proteome were assessed by 16s-rRNA sequencing and LC-MS/MS respectively. **Results:** Protein FMT (PF) reduced the liver injury significantly compared to Standard FMT (SF) with a reduction in serum biomarkers- ALT (-1.5 fold change [FC], p=0.02), AST (-1.34 FC, p=0.04); steatosis (-1.8 FC, p=0.01) and fibrosis (-1.4 FC, p=0.04). PF also reduced the gene expression of hepatic pro-inflammatory markers- TNFα (1.5 FC, p=0.003) and IL6 (1.6 FC, p=0.02) whereas it increased the anti-inflammatory IL10 (2 FC, p=0.008). PF increased intestinal tight junction claudin-4 (2 FC, p=0.001) and occludin (1.6 FC, p=0.007) along with a reduction in plasma endotoxin levels as compared to SF (1.6 FC, p=0.03). SF and PF led to significant variation in gut microbiota composition (81%, p=0.001). PF increased Shannon diversity over SF (1.08 FC, p=0.06). PF also significantly increased the abundance of anti-inflammatory and SCFA producer- *Muribaculum* (2.4 FC, p=0.002). PF reduced the abundance of opportunistic pathogens- *Staphylcoccus* (-6.7 FC, p<0.001) and *Aerococcus* (-3.7 FC, p<0.001). In PF, hepatic proteome involved in PPAR signaling, fatty acid degradation, cholesterol metabolism, and oxidative phosphorylation were upregulated significantly (FC>2, p<0.05) whereas, necroptosis, HIF-1 signaling & biosynthesis of unsaturated fatty acids were downregulated. **Conclusion:** FMT from a high protein diet donor alleviated the ALD injury compared to that from a standard donor FMT. It increases the abundance of beneficial bacteria *Muribaculum* while decreasing the opportunistic pathogen *Staphylococcus*, concomitantly maintaining the intestinal integrity barrier. It further improves the liver injury by reducing the liver inflammation, steatosis and fibrosis along with an increase in proteins inlvoved in PPAR signalling, cholesterol metabolism, oxidative phosphorylation and decrease in necroptosis. Thus pre-educating the FMT donor microbiota with high protein diet holds a promising strategy in ALD.



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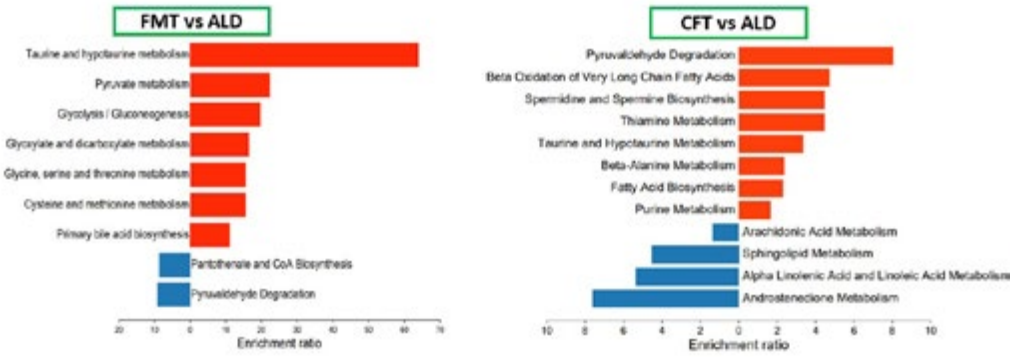
2269 | FECAL CELL FREE TRANSPLANTATION IS EFFECTIVE IN REMISSION OF ALCOHOL ASSOCIATED LIVER DISEASE IN MICE MODEL

Nishu Choudhary[1] *Ashi Mittal*[1] *shvetank sharma*[1] *Anupama Kumari*[1] *Kavita Yadav*[1] *Jaswinder Maras*[1] *Shiv Kumar Sarin*[1]

[1]*Institute of liver and biliary sciences*

Background: Fecal Microbiota Transplantation (FMT) is effective in treating alcohol-related liver disease(ALD). The microbiota of the donor, along with gut environment, contributes to disease remission. Thus, factors other than bacteria in the gut may also have a role in the remission of the disease. To confirm, we compared the efficacy of bacterial cell free transplantation(CFT) against FMT. **Methods:** Male C57BL/6N mice were pair-fed control or ethanol (22%) Lieber-DeCarli diet with thioacetamide(150mg/kg;ip) twice a week for 8 weeks to induce ALD. FMT and CFT(stool-slurry filtered from 0.22 micron filter) from healthy donors was performed in ALD animals. Samples were collected at baseline and post-FMT/CFT(day7). Liver injury was assessed by histopathology, biochemistry and RT-PCR. Fecal-microbiota was assessed by 16SrRNA sequencing. Hepatic metabolome was assessed by high-resolution LC-MS. **Results:** Liver histology in both the groups showed significant overall improvement from ALD: with reduction in steatosis (~9-fold, p=0.002), fibrosis(~5-fold, p=0.005),AST(~2-fold, p=0.002),ALT(~5-fold, p=0.0001), bilirubin(~4-fold,p=0.03). Hepatic pro-inflammatory markers IL6(~3-fold,p<0.05) and TNFa(~3.5-fold,p<0.05) reduced similarly in FMT and CFT. There was an associated decrease in opportunistic taxa *Staphylococcus*(2.8-fold,p=0.001) and *Sporosarcina*(2-fold,p=0.01) in FMT but *Desulfovibrio*(1.5-fold,p=0.0001), *Mucispirillum*(10-fold,p<0.0001) and *Escherichia-Shigella*(9-fold,p<0.0001) in CFT. FMT altered 56, while CFT altered 190 metabolites significantly(p<0.05). In FMT, metabolites were involved in upregulation of Taurine-hypotaurine metabolism(p=0.01) and Cysteine and methionine metabolism(p=0.05) and downregulation of Pyruvaldehyde Degradation(p=0.05) and pantothenate and CoA biosynthesis(p=0.02). Metabolic change in CFT resulted in an upregulation of beta oxidation of long chain fatty-acids (p=0.02), spermidine and spermine biosynthesis(p=0.04) and Taurine-hypotaurine metabolism (p=0.05) and downregulation of androstenedione metabolism(p=0.002) and alpha linolenicacid/linoleic-acid metabolism(p=0.05). **Conclusion:** In ALD, whereas both FMT and CFT reduce the opportunistic-taxa, the species targeted are different. The metabolic pathways modulated by the two strategies differ, but result in similar amount of remission from disease. Thus, CFT appears to be a promising alternative to FMT.



Disclosures: Nishu Choudhary: Nothing to Disclose, Ashi Mittal: Nothing to Disclose, shvetank sharma: Nothing to Disclose, Anupama Kumari: Nothing to Disclose, Kavita Yadav: Nothing to Disclose, Jaswinder Maras: Nothing to Disclose, Shiv Kumar Sarin: Nothing to Disclose

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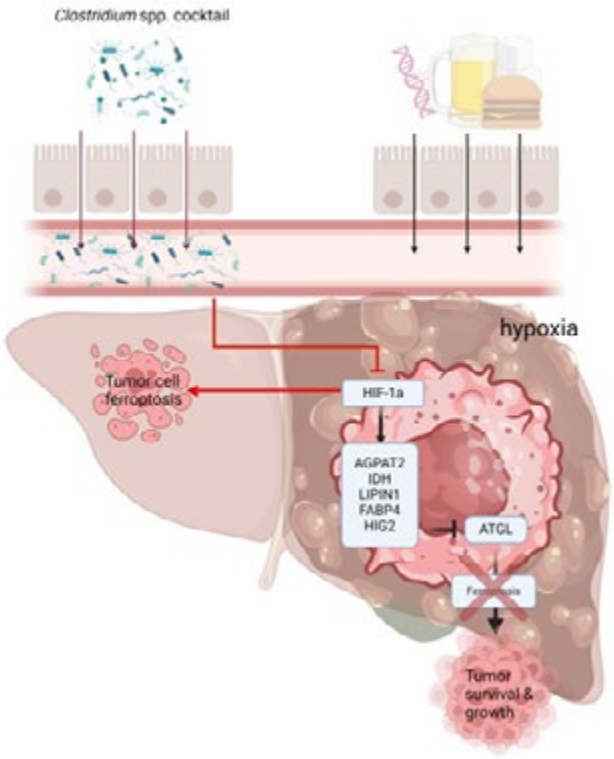
2270 | CLOSTRIDIUM SPP. COCKTAIL ALLEVIATES HEPATOCELLULAR CARCINOMA PROGRESSION BY MODULATING HIF1A-DERIVED LIPID PROFILING ◆

seol hee Song[1] Young Seok Kwon[2] Jeong Ha Park[2] JEONG SU KIM[2] Dong Joon Kim[3]

[1]hallym university/graduate student, [2]Hallym University College of Medicine, [3]Hallym University Medical Center

Background: Hypoxia factor-1alpha (HIF1a) is known to be a gene that promotes tumor growth and metastasis. Clostridium spp. has been associated with cell proliferation and hypoxia by inhibiting hif1a. We aimed to demonstrate the role of Clostridium spp. cocktail on hepatocellular carcinoma (HCC) progression. **Methods:** To identify distinctive factors in HCC progression, fecal microbiota and serum-metabolites analysis was conducted in healthy (n=64), MASLD (n=80), cirrhosis (n=37), and HCC (n=23) patients. C57BL/6J male mice received 20 mg/kg (i.p.) of diethylnitrosamine at 14 days of age. HCC was induced by a 60% high-fat diet with drinking water (300 mg/L of thioacetamide). Clostridium spp. cocktail was orally administered at a concentration of 109 CFU/day for 26 weeks. We compared liver and body weight, serum liver function, lipid profile, histology, liver molecular markers for inflammation, lipogenesis, and proliferation in the liver. **Results:** The Hif1a expression was significantly increased in HCC patients and Clostridium genus abundance was increased according to the liver disease progression. In the serum metabolite analysis, tumor-related lipids proportion was reduced in HCC patients. The supplementation of Clostridium spp. cocktail significantly decreased liver weight (2.2±1.0 vs 2.5±0.9), liver enzymes (AST 99.6±32.0 vs 156.3±47.4) and ALT (67.3±13.3 vs 173.3±62.1) and NAS score (2.6±0.5 vs 5.9±0.7) compared with non-supplementation group. Clostridium spp. cocktail significantly suppressed tumor progression by reducing HIF1a, GPC3, and G2/M phase transition. In the Clostridium spp. cocktail group, apoptosis, cell proliferation (Cyclin G2, CCNB2 and KI67), inflammation (TNF-α and TGF-B), fat metabolism (LIPIN, AGPAT2, and IDH1), and oxidation (CPT1A) were significantly regulated. In addition, lipolysis and lipid peroxidation were activated in the Clostridium spp. cocktail group, consequently causing cancer cells death. **Conclusion:** Clostridium spp. cocktail alleviates HCC progression by modulating HIF1a-derived lipid profiling. Clostridium spp. cocktail can be used as a next-generation probiotics for the prevention of HCC progression.



Disclosures: seol hee Song: Nothing to Disclose, Young Seok Kwon: Nothing to Disclose, Jeong Ha Park: Nothing to Disclose, JEONG SU KIM: Nothing to Disclose, Dong Joon Kim: Nothing to Disclose

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2271 | GUT MICROBIOME-NITROGEN METABOLIC IMBALANCE IN HEPATIC ENCEPHALOPATHY RESTORED BY DACUS CAROTA EXOSOMES

P. Debishree Subudhi[1] Jitendra Kumar[1] Anupama Parasar[1] Shivani Gautam[1] Shruthi Chalil Sureshan[1] Ananthu Narayan[1] Ashmit Mittal[1] Dinesh Mani Tripathi[1] Chhagan Bihari[1] Shiv Kumar Sarin[1]

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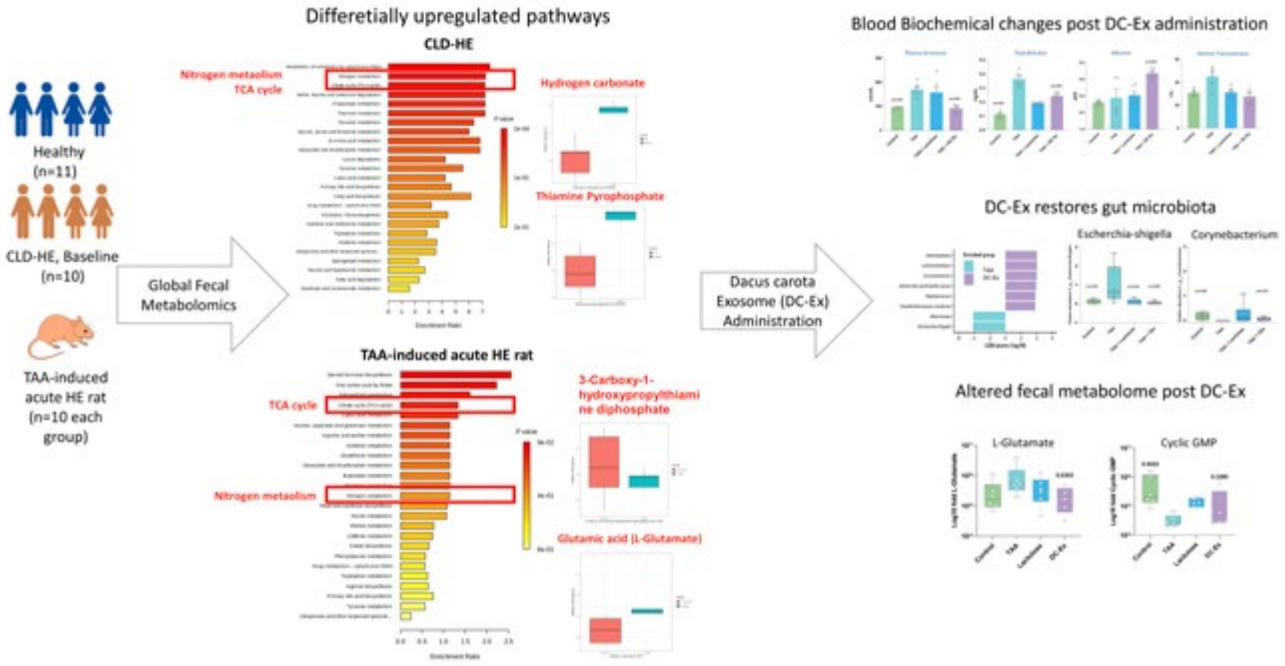
Background: Dysregulated nitrogen metabolism in chronic liver disease (CLD) causes hyperammonemia, impaired energy metabolism and contributes to hepatic encephalopathy (HE), worsened by Dysbiotic gut. We aimed to restore gut commensals and mucosal integrity by administering Dacus Carota L spp. (black carrot) Exosomes (DC-Ex) enriched with anthocyanins and multiple beneficial phytochemicals, to reduce blood ammonia levels and improve cognition. **Methods:** Fecal metabolomics was performed in baseline minimal HE patients with CLD, with no prior treatment for >6 months (n=10) using mass spectrometry (LC-MS) and compared to healthy control stools (n=11). Thioacetamide (TAA) acute HE rat model was developed and prophylactic oral administration of DC-Ex given. Fecal metagenomics and metabolomics were performed on rat stool samples post DC-Ex administration and compared with human fecal metabolic profiles. **Results:** 156 fecal metabolites (total 1263 annotated, 61-up, 95-downregulated, p<0.05) were differentially expressed in CLD-HE patients than healthy individuals. Fecal HE metabolome documented significant upregulation of nitrogen metabolism, TCA cycle and altered amino acid metabolism (p<0.001). Pentothenate-Co-A, folate biosynthesis, lysine degradation pathways and allysine, L-threonine were downregulated (p<0.05) while hydrogen carbonate, thiamine pyrophosphate were upregulated (1.5 fold, p<0.05). Fecal metabolomics of acute HE rats (plasma ammonia= 145.3±43.6umol/l; bilirubin=0.36±0.05; AST=83.05± 4.5 IU/ml,p<0.001) shared similarities with human HE altered pathways. 53 differentially discriminated rat fecal metabolites (up-15, dowregulated- 13, p<0.05) were common to pathways enriched in human HE feces, i.e. L-glutamate (2.5 fold, p<0.05) and cyclic GMP(-3 folds, p<0.001). However post DC-EX administration, achieved blood ammonia (92.2±23.6umol/l) reduction, and improved fecal metabolites L-Glutamate(-2.3 fold, p<0.05), cyclic GMP(1.3 fold, p<0.05). DC-Ex improved sensory-motor (p<0.0001), cognition(p=0.004), hepatic cholestasis, necrosis and inflammation. DC-Ex decreased growth of urease positive enterobactereacae taxa, Escherichia-Shigella(p<0.005) and increased Firmicutes[Lachnoclostridium,Corynebacterium,Bacteroides(p<0.01)]. Upon co-culture with LGG *in-vitro,* growth of LGG enhanced (p=0.004). DC-Ex cargo metabolic composition revealed presence of Quercetin Dopamine,3-O-glucoside, Xanthotoxin (anti-oxidant/inflammatory) and tangeretin which improves gut mucosal junctional communications. **Conclusion:** Fecal metabolome documents altered L-glutamate and cyclic GMP (nitrogen and energy/amino acid metabolism, shared in both human and acute HE animal model. The DC-Ex reduced ammonia, abundance of urease producing taxa, with improved cognition. DC-Ex is a potential therapy to mitigate HE in cirrhosis patients to improve gut-liver-brain axis.



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2272 | IMPACT OF FIBROSIS SEVERITY ON CLINICAL AND METAGENOMIC PROFILES IN MASH (METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS) PATIENTS

Hyunchae Joung[1] Jaeryang Joo[1] KyungHwan Kim[1] Chang Hun Shin[1] Hye Won Lee[2]

[1]CKDBiO Research Institute, [2]Yonsei Liver Center, Severance Hospital

Background: MASH is a severe form of MASLD (Metabolic dysfunction-associated steatotic liver disease) characterized by inflammation and fibrosis. The gut microbiota significantly influences the development and progression of MASH. Patients with MASH have distinct gut microbiota profiles compared to healthy individuals. Dysbiosis affects host metabolism and immune response through gut-derived metabolites like SCFAs, bile acids, and endotoxins, impacting liver function and contributing to inflammation and fibrosis. This study collected clinical data and fecal samples from healthy individuals and MASH patients to perform metagenomic analysis based on fibrosis severity and analyze correlations between clinical and metagenomic data. **Methods:** Healthy subjects and MASH patients were enrolled at Severance Hospital, Seoul, Republic of Korea (IRB No. 4-2020-0504 and 4-2023-0912). MASH patients were screened using Fibroscan®, and all participants provided informed consent and blood and fecal samples. Physical measurements, blood biochemical analysis, and metagenomic analysis were conducted. Statistical analysis was performed using GraphPad Prism Software (Version 10.2.3), with *p-value* < 0.05 considered statistically significant. **Results:** A total of 30 MASH patients recruited were divided into two groups based on LSM (Liver stiffness measurement) score: 14 patients in the F0-F1 group and 16 in the F2-F4 group. MASH patients had higher BMI, AST, ALT, TG, γGT, and fasting glucose levels compared to healthy subjects, with these levels increasing with fibrosis severity. Alpha diversity showed no difference, but beta diversity indicated distinct clustering among the groups. As fibrosis severity increased, levels of *Bacteroides uniformis*, *Anaerobutyricum hallii*, *Allistipes putredinis*, *Dorea longicatena*, and *Blautia obeum* decreased significantly, while *Roseburia inulinivorans*, *Lactobacillus rogosae*, and *Leyella stercorea* increased. *Anaerobutyricum hallii* was negatively correlated with BMI and ALT, while *Lachnospira eligens*, *Roseburia inulinivorans*, and *Lactobacillus rogosae* were positively correlated with TG. **Conclusion:** Higher fibrosis severity was associated with worsening BMI, liver function tests, and lipid profiles in MASH patients. Metagenomic analysis revealed distinct microbial clusters for each group and identified several species that varied with fibrosis severity, as well as their correlations with clinical data. Species significantly decreased in MASH patients may serve as potential live biotherapeutic products to restore gut microbiota and treat MASH.

Disclosures: Hyunchae Joung: Nothing to Disclose, Jaeryang Joo: Nothing to Disclose, KyungHwan Kim: Nothing to Disclose, Chang Hun Shin: Nothing to Disclose, Hye Won Lee: Nothing to Disclose

2273 | CRYPTOGENIC PYOGENIC LIVER ABSCESS: A SENTINEL MARKER FOR COLORECTAL CANCER?

Guneet Sidhu[1] Hussam Almasri[2] John Bassett[3]

[1]Mayo Clinic, [2]University of North Dakota, [3]Sanford Health

Background: Pyogenic liver abscess (PLA) and colorectal cancer (CRC) have been increasingly recognized for their potential interrelationship. Studies from Southeast Asia have indicated this association, suggesting that CRC may be an underlying cause of cryptogenic PLA. This association is hypothesized to stem from the translocation of intestinal bacteria through compromised mucosal barriers caused by colorectal neoplasms **Methods:** Cross-sectional study from January 2013 to January 2024 within Sanford Health System. A total of 1,083 patients were diagnosed with liver abscesses, out of which 83 patients developed CRC. Data were collected on patient demographics, timing of CRC and PLA diagnoses, and microbiological findings from abscess cultures. Patients with biliary, gallbladder and post-surgical causes leading to liver abscess were excluded. **Results:** The incidence rate of CRC in patients with PLA was significantly higher compared to the general population ($p < 0.001$). Timing

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of CRC diagnosis relative to PLA revealed that 15 patients (18.07%) were diagnosed with CRC within 6 months prior to PLA, 4 patients (4.82%) within 3 years of PLA diagnosis, 16 patients (19.28%) developed PLA after CRC diagnosis, and 8 patients (9.64%) developed PLA within 1 year post-CRC diagnosis. Using the Fine-Gray subdistribution hazard regression model, the hazard ratio (HR) for CRC incidence within the first year after PLA diagnosis was 2.95 (95% CI: 1.75-4.97, p < 0.001). For patients diagnosed with PLA within 6 months prior to CRC, the HR was 3.82 (95% CI: 2.18-6.68, p < 0.001). Microbiological analysis revealed that Bacteroides species and Streptococcus species were predominant in liver abscess cultures, each accounting for 10.34% of cases, followed by E. coli at 6.9%. The presence of Bacteroides species was particularly associated with a higher incidence of CRC (HR: 2.20, 95% CI: 1.35-3.60, p = 0.002). Using the Cox proportional hazards model, the HR for mortality in patients with both conditions was 1.75 (95% CI: 1.20-2.55, p = 0.004). **Conclusion:** Our cross-sectional study reveals a significant association between PLA and the incidence of CRC within our healthcare system over a 10-year period. Patients with PLA demonstrated a notably higher risk of developing CRC, particularly within the first 6 months to 3 years following PLA diagnosis, with hazard ratios indicating a nearly threefold increase in risk. The predominant microorganisms identified in abscess cultures, specifically Bacteroides and Streptococcus species, were significantly associated with CRC incidence, underscoring potential microbial pathways in CRC pathogenesis. Additionally, the overall mortality rate was elevated among patients with both PLA and CRC.This association calls for increased awareness and thorough screening protocols including colonoscopy for patients with unexplained liver abscesses. Future research should focus on validating these findings

Disclosures: Guneet Sidhu: Nothing to Disclose, Hussam Almasri: Nothing to Disclose, John Bassett: Nothing to Disclose

2274 | LACTULOSE IS ASSOCIATED WITH INCREASED RISK OF DISSEMINATED INFECTION FROM INTESTINAL PATHOGENS

Mark Goulian[1] Gary Wu[2] David Kaplan[2] Marina Serper[3] Nadim Mahmud[4]

[1]University of Pennyslvania, [2]University of Pennsylvania, [3]University of Pennsylvania Health System, [4]Hospital of the University of Pennsylvania

Background: Patients with cirrhosis are susceptible to disseminated infections including to the blood and peritoneal fluid. One major source is bacterial translocation of pathogens from the gut microbiota, including the *Escherichia coli*and *Klebsiella* species (spp). Lactulose, the first-line treatment for hepatic encephalopathy, is a drug that is known to be metabolized by intestinal bacterial commensals thereby increasing their growth. However, its effect on gut pathogens and resulting disseminated infection have not been well described. We therefore aimed to determine if lactulose treatment alters risk of blood and peritoneal infections in cirrhosis. **Methods:** This was a retrospective cohort study of incident patients with cirrhosis in the Veterans Health Administration from 1/2008-12/2023. New initiators of lactulose (+/- 60 days from cirrhosis diagnosis) were included; new initiation of rifaximin was identified in similar fashion. Detailed patient-level data were collected. The primary outcome was time of hospitalization with culture-positive infections from blood or peritoneal fluid sampling. A 1:1 propensity score matching (PSM) algorithm isolated similar patients with and without new lactulose initiation. Cox regression models additionally adjusted for rifaximin exposure were fit with a two-month lagged exposure (thus minimizing protopathic bias) to evaluate risk of infection hospitalization, separately for any organism and for individual common organisms (*E. coli*, *Enterococcus* spp., *Klebsiella* spp., *Staphylococcus aureus*). Data were resampled 500 times for PSM to ensure robustness of findings. **Results:** A total 109,307 patients with cirrhosis, 12,289 (11.2%) with lactulose new initiation and 97,018 (88.8%) without were evaluated for PSM inclusion. Excellent matching across key covariates was achieved (Panel A) and Cox regression demonstrated an increased risk of infection hospitalization with lactulose exposure (HR 1.13, 95% CI 1.04-1.24, p=0.006; Panel B). There was a significantly increased risk of *E. coli* infections (HR 1.28, 95% CI 1.05-1.57, p=0.015; Panel C). This finding was consistent across resampled PSM cohorts (HR range 1.07-1.48; Panel D); a potential signal towards increased infection risk was also observed with *Klebsiella* spp. (HR range 0.96-1.34). **Conclusion:** Our data suggest that lactulose initiation may be a risk factor for disseminated gram negative bacterial infections. The effect was limited to two intestinal pathogens, *E. coli* and *Klebsiella* spp., suggesting a direct effect of lactulose on these organisms in the gut microbiota. Future studies will be required to identify the mechanism(s) for this effect and remove residual confounders from this retrospective study.

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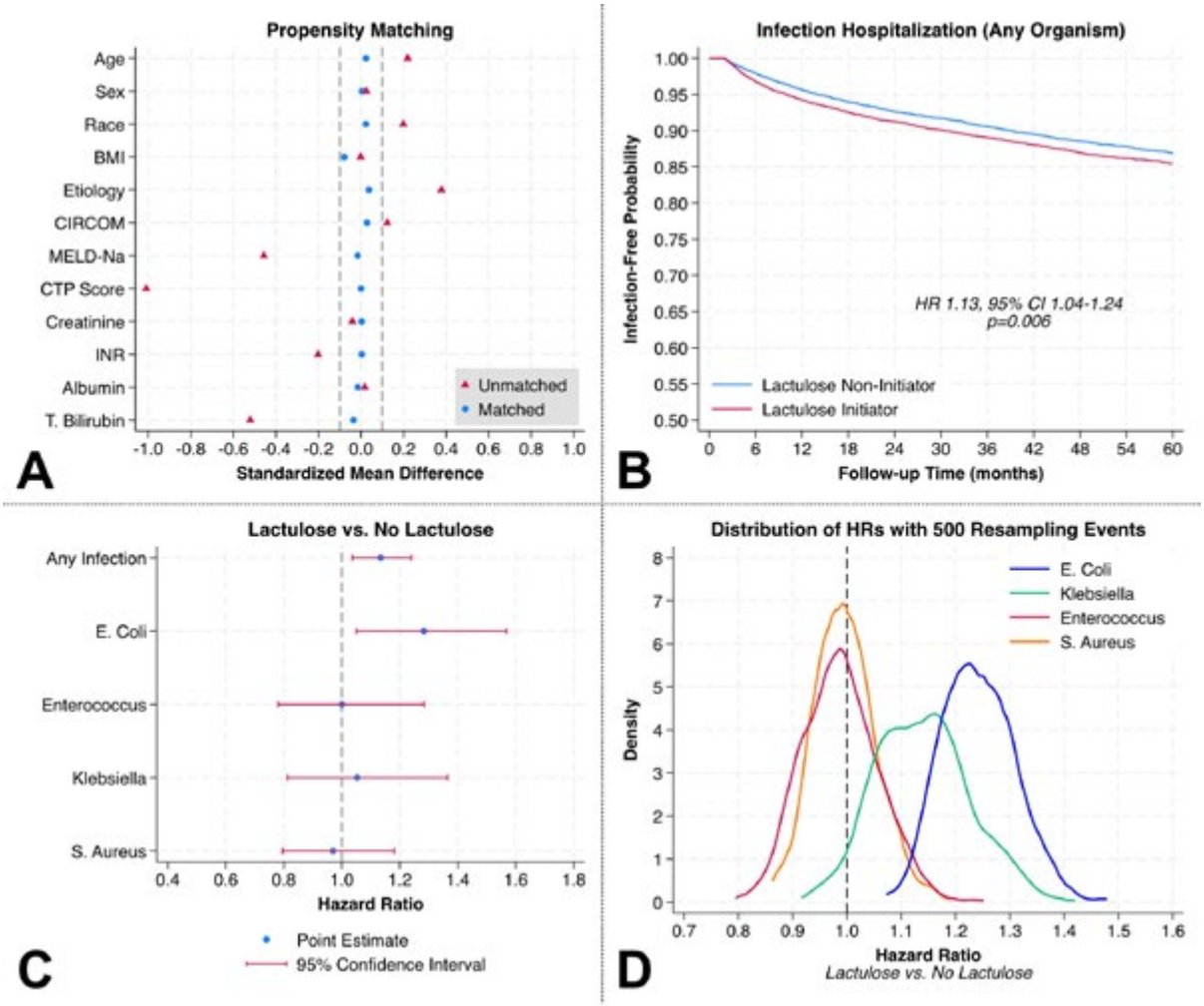

Disclosures: Mark Goulian: Nothing to Disclose, Gary Wu: Nothing to Disclose, David Kaplan: Independent Contractor relationship with Roche Genentech; Has not ended; Grant/Research Support relationship with AstraZeneca Inc; Has not ended; Advisor relationship with AstraZeneca; Has ended; Advisor relationship with Exelixis; Has ended; Grant/Research Support relationship with Gilead; Has not ended; Advisor relationship with Sirtex; Has ended; Grant/Research Support relationship with Exact Sciences; Has not ended; Grant/Research Support relationship with Glycotest; Has ended, Marina Serper: Grant/Research Support relationship with Grifols; Has not ended; Grant/Research Support relationship with Eurofins; Has not ended; Grant/Research Support relationship with Transplant Genomics; Has not ended, Nadim Mahmud: Nothing to Disclose

2275 | INTRA-TUMORAL MICROBIOME PROMOTE HEPATOCELLULAR CARCINOMA CELL PROLIFERATION AND IS ASSOCIATED WITH PROGNOSIS

Ming-Lun Yeh[1] Yishan Tsai[1] Chung-Feng Huang[1] Jee-Fu Huang[2] Chia-Yen Dai[2] Wan-Long Chuang[1] Ming-Lung Yu[2]

[1]Kaohsiung Medical University Hospital, [2]Kaohsiung Medical University

Background: Cancer specific intra-tumoral microbiome had been identified. We observed a more rapid cell growth in the cultured primary hepatoma cells with microbiome infiltration. We hypothesized that intra-tumoral microbiome promote hepatoma cell proliferation and we aim to explore the role of intra-tumoral microbiome in the pathogenesis of hepatocellular carcinoma (HCC). **Methods:** The method to harvest and culture primary hepatoma cells had been reported previously. Microbiome infiltration in more than 20% of areas under HPF was defined as abundant. Fluorescence in situ hybridization (FISH) was performed with bacterial 16s rRNA sequences in fresh HCC surgical tissues. Taxonomic compositions were analyzed by 16s rRNA sequencing. Hepatoma cell

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lines were cultured with microbiome medium, and WST-1 assay was performed for cell proliferation experiments. liquid chromatography-tandem mass spectrometry was done for metabolomics study. The clinical characteristics were compared between HCC patients with and without abundant intra-tumoral microbiome. **Results:** Abundant microbiome infiltration was found in 56 (30.9%) of the 181 HCC patients. HCC patients with abundant microbiome demonstrated a higher proportion of detectable HBV DNA, and larger tumor size. HCC patients with abundant microbiome also demonstrated a significantly decreased overall survival. FISH confirmed the presence of intra-tumoral microbiome in HCC. The most dominant microbe at the phylum level was Proteobacteria, and Xanthomonas, and Acetobacter were the most dominant microbes at the genus level. It showed no significant differences in the taxonomic compositions in different HCC stages and etiologies. We then conducted the *in vitro* cell proliferation experiments with WST-1 assay. The cell proliferation experiments showed hepatoma cells cultured with medium of microbiome showed a higher cell proliferation and the effect diminished after remove of microbiome. These cells exhibited higher expression levels of YAP1, and the YAP1 expression decreased after removal of microbiome. The untargeted metabolomic study demonstrated a significantly difference of metabolites before and after the removal of microbiome. **Conclusion:** Intra-tumoral microbiome were associated with poor HCC survival. *In vitro* study demonstrated the effect of intra-tumoral microbiome in hepatoma cell proliferation which was possibly through Hippo/YAP pathway. The results implicated a future therapeutic target of HCC.

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2276 | IRON REGULATORY PROTEIN 2 CONTRIBUTES TO ANTIMICROBIAL IMMUNITY BY PRESERVING LYSOSOMAL FUNCTION IN MACROPHAGES

Zhiwen Fan[1] *Jie Li*[2] *Mindie H. Nguyen*[3]

[1]*Department of Pathology, Nanjing Drum Tower Hospital,* [2]*Nanjing Drum Tower Hospital,* [3]*Division of Gastroenterology and Hepatology, Stanford University Medical Center, Palo Alto, CA, USA.*

Background: Colorectal cancer and Crohn's disease patients develop pyogenic liver abscesses (PLA) due to failures of immune cells fighting off bacterial infections. PLA was unexpectedly manifested in mice lacking iron regulatory protein 2 (*Irp2*) when the intestinal tissue was injured by dextran sodium sulfate (DSS) treatment. This study aimed to investigate the role of Irp2 in immunity to defend against bacterial invasion when the intestinal barrier was injured in miceWe show that Irp2 is crucial for bacterial clearance by maintaining lysosomal acidification and biogenesis. In *Irp2* deficient liver tissue or macrophages, the nuclear location of transcription factor EB (Tfeb) was remarkably reduced, leading to the downregulation of Tfeb target genes that encode critical components for lysosomal biogenesis. Tfeb mislocalization was reversed by Hif2 inhibitor PT2385 and, independently, through the inhibition of lactic acid production. These experimental findings were confirmed both clinically, in patients with Crohn's disease, and through bioinformatic searches in databases from colorectal cancer biopsies showing loss of IRP2 and Tfeb-dependent lysosomal gene expression. **Methods:** Mice lacking Irp2, globally (*Irp2*-/-) or specifically in macrophages and neutrophils (*Irp2***ΔLysM*), were treated with DSS in drinking water. *Irp2*-knockout RAW264.7 cells were treated with lipopolysaccharides to mimic the pro-inflammation condition. Drug intervention with inhibitors of lactate dehydrogenase A or hypoxia inducible factor 2 (Hif2) was carried out. Clinical database and samples were collected to verify the findings. **Results:** We show that Irp2 is crucial for bacterial clearance by maintaining lysosomal acidification and biogenesis. In *Irp2* deficient liver tissue or macrophages, the nuclear location of transcription factor EB (Tfeb) was remarkably reduced, leading to the downregulation of Tfeb target genes that encode critical components for lysosomal biogenesis. Tfeb mislocalization was reversed by Hif2 inhibitor PT2385 and, independently, through the inhibition of lactic acid production. These experimental findings were confirmed both clinically, in patients with Crohn's disease, and through bioinformatic searches in databases from colorectal cancer biopsies showing loss of IRP2 and Tfeb-dependent lysosomal gene expression. **Conclusion:** Our study highlights a mechanism whereby IRP2 preserves macrophage lysosomal function in antimicrobial activity to protect the liver against gut-originated bacterial invasion, shedding light on therapeutic intervention for patients with PLA.

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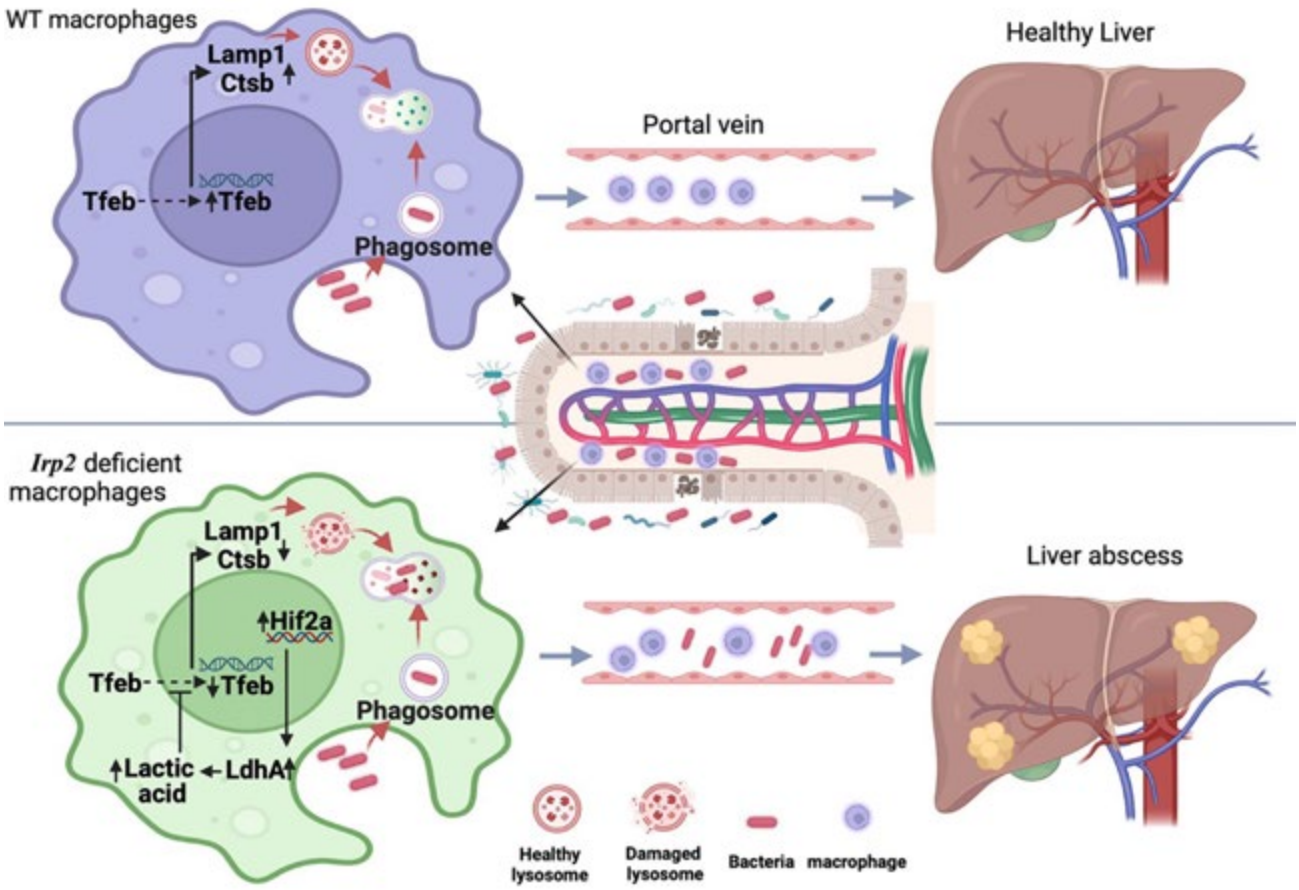

Disclosures: Zhiwen Fan: Nothing to Disclose, Jie Li: Nothing to Disclose, Mindie H. Nguyen: Nothing to Disclose

2277 | DISSECTING CAUSAL LINKS OF THE GUT MICROBIOME, GUT MICROBIOTA-ASSOCIATED METABOLITES ON PORTAL VEIN THROMBOSIS: A MENDELIAN RANDOMIZATION STUDY

Yangjie Li[1] *Lingna Lyu*[2] *Huiguo Ding*[2]

[1]*Beijing You'an Hospital,* [2]*Beijing You'an Hospital Affiliated to Capital Medical University*

Background: Increasing evidence has demonstrated the associations between gut microbiota, gut microbiota--associated metabolites, and thrombosis-related diseases. However, most of them mainly focused on the arterial or deep vein thrombosis, and the causal relationships between gut microbiota and portal vein thrombosis (PVT) is still unclear. **Methods:** Two-sample Mendelian randomization (MR) analysis and reverse MR were applied to infer the causal links among 412 gut microbiota traits, 288 gut microbiota--associated metabolites and portal vein thrombosis trait using inverse variance-weighted, MR-Egger, weighted median, weighted mode, and simple mode methods. Meanwhile, MR analysis were used to on analyze the causal links between positive gut microbiota/metabolite and several common thrombosis-related indicators to preliminarily explore how microbial communities and their metabolites affect the formation of PVT. **Results:** MR confirmed causal links between four gut microbiota species, nine gut microbiota metabolic pathways and PVT. Three gut species were protective factors (Bifidobacterium_bifidum, p=0.032; Bilophila_wadsworthia, p=0.042; and Pseudoflavonifractor_capillosus, p=0.0457), while Bacteroides_finegoldii (p=0.031) was a detrimental factor for PVT. Based on known causal gut microbiota--associated metabolites, we screened 13 shared causal metabolites closely related to PVT. Finally, MR analysis revealed 24 casual relationships between gut microbiota and associated metabolites and 15 common thrombosis-related indicators. Sensitivity analysis represented no heterogeneity or pleiotropy in this study. **Conclusion:** Our findings support a causal relationship among gut microbiota, gut microbiota-associated

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metabolites and portal vein thrombosis. These biomarkers provide new insights into the underlying mechanisms of PVT and contribute to its prevention, diagnosis, and treatment by targeting gut microbiota.

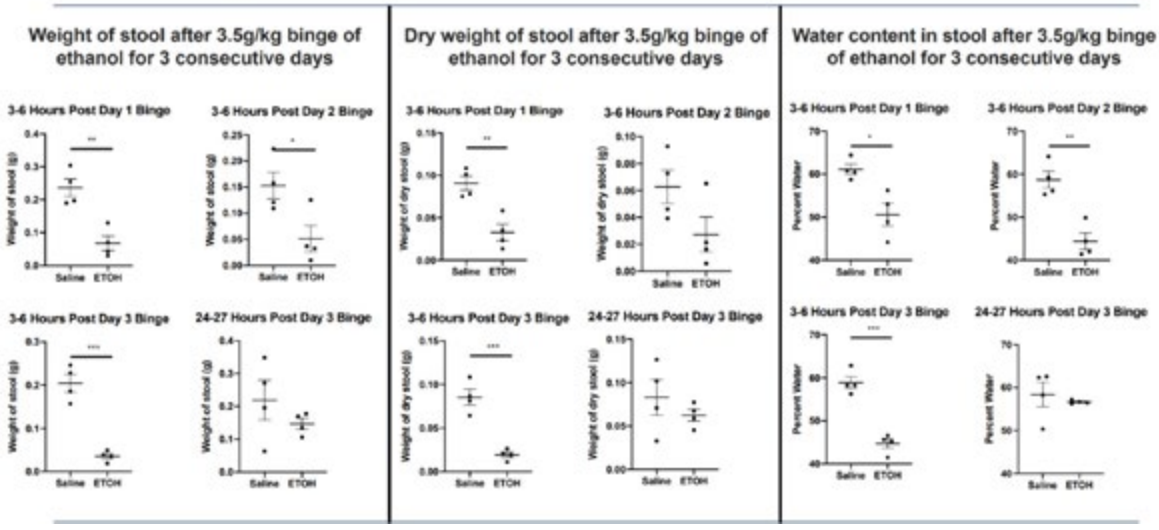
Disclosures: Yangjie Li: Nothing to Disclose, Lingna Lyu: Nothing to Disclose, Huiguo Ding: Nothing to Disclose

2278 | ACUTE ALCOHOL BINGES ALTER COLONIC MUCOSAL ARCHITECTURE TO CAUSE TRANSIENT CHANGES IN DEFECATION

Scott Minchenberg[1] Prashanth Thevkar Nagesh[1] Mrigya Babuta[1] Marti Ortega-Ribera[1] Veronika Brezani[1] Radhika Joshi[1] Viliam Brezani[1] Aditi Ashish Datta[1] Subhash Kulkarni[1] Gyongyi Szabo[1]

[1]Beth Israel Deaconess Medical Center

Background: While chronic alcohol use is associated with diarrhea and malabsorption, the effects of binge drinking on gut function are less understood. It has been reported that binge drinking may reduce motility throughout the GI tract. However, the nature of these changes and the underlying pathology driving these changes have not been ascertained and established in a pre-clinical model. This gap has not only resulted in a poor understanding of the associated pathobiology, but also prevented us from having a model to test disease modifying therapies. In this study, we aimed to assess the effects of acute alcohol binge and chronic alcohol on intestinal function using two established models of high alcohol consumption. **Methods:** To model acute alcohol exposure, adult female C57BL/6 mice were given a daily oral gavage of saline (n=4) or ethanol (n=4) at 3.5g/kg body weight (50% v/v in saline) for 3 consecutive days. 3 hours after each gavage, stool samples were collected over a course of 3 hours, and the total weight, dry weight, and percentage water content of stools were deduced. An additional analysis of stool content 24 hours after the last alcohol gavage was also performed. In the second model of chronic alcohol use, adult female C57BL/6 mice were fed a 5% (v/v) ethanol containing Lieber-DeCarli liquid diet (n=6) or a calorie-matched diet (n=6) for 9 weeks. Stool samples were collected and quantified for weight and water content every other week. The mice at the end of both treatments were euthanized, and the intestinal tissue was fixed for histology. **Results:** Alcohol binges caused an 82.5% reduction ($p<0.001$) in total stool weight and a 14.2% reduction in water content ($p<0.001$) 3-6 hours after the binge (Fig 1). 24 hours after the last binge this phenotype resolved (Fig 1). Histology from these mice show a reduction in villous to crypt ratio with increased goblet cells. In contrast, the proximal colon from these mice goblet cell numbers were reduced, but this was not significant. Chronic alcohol exposure resulted in no significant changes in total stool weight or water content at any point over 9 weeks. Histologic evaluation of the proximal small bowel did not demonstrate any changes in villous height to crypt depth. No changes in goblet cell numbers were observed in the proximal small bowel or proximal colon in mice fed with chronic alcohol. **Conclusion:** Our results suggest that acute alcohol binges but not chronic sustained alcohol exposure result in changes in stool quality and defecation pattern suggesting an effect of acute alcohol binge on gut motility. Changes in villous crypts and goblet cells after acute alcohol binges are likely due to alcohol-induced alterations in gut mucosa. Our study establishes the first pre-clinical model through which the mechanisms driving binge drinking-mediated gut dysmotility can be studied.



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Disclosures: Scott Minchenberg: Nothing to Disclose, Prashanth Thevkar Nagesh: Nothing to Disclose, Mrigya Babuta: Nothing to Disclose, Marti Ortega-Ribera: Nothing to Disclose, Veronika Brezani: Nothing to Disclose, Radhika Joshi: Nothing to Disclose, Viliam Brezani: Nothing to Disclose, Aditi Ashish Datta: Nothing to Disclose, Subhash Kulkarni: Nothing to Disclose, Gyongyi Szabo: Advisor relationship with Glympse Bio, Inc (acquired by Sunbird Bio); Has not ended; Consultant relationship with Terra Firma; Has not ended; Consultant relationship with Pfizer; Has not ended; Consultant relationship with Pandion Therapeutics; Has ended; Consultant relationship with Merck; Has ended; Consultant relationship with Durect Corporation; Has ended; Advisor relationship with Satellite Biosciences; Has not ended; Consultant relationship with Zomagen Bioscience/ Ventyx Biosciences; Has ended; Consultant relationship with CYTA Therapeutics; Has ended; Royalties or patent beneficiary relationship with Springer Nature Group; Has not ended; Royalties or patent beneficiary relationship with UpToDate Inc; Has not ended; Consultant relationship with LabCorp; Has not ended; Advisor relationship with Evive; Has not ended; Advisor relationship with Surrozen; Has not ended; Consultant relationship with Takeda; Has ended

2279 | GUT BACTERIA ASSOCIATED WITH MORTALITY AFTER FECAL MICROBIOTA TRANSPLANT IN SEVERE ALCOHOL ASSOCIATED HEPATITIS PATIENTS: AN APPROACH TO UNDERSTAND PATHWAYS FOR IMPROVED SURVIVAL ◆

Shvetank Sharma[1] Apurva Pande[2] Vikas Khillan[1] Archana Rastogi[1] Vinod Arora[1] Saggere Muralikrishna Shasthry[1] Rajan Vijayaraghavan[1] Rakesh Kumar Jagdish[1] Manoj Sharma[1] Guresh Kumar[1] Stanislas Mondot[3] Joel Dore[3] Shiv Kumar Sarin[1]

[1]Institute of Liver and Biliary Sciences, [2]ASTER DM HEALTHCARE, [3]Université Paris-Saclay, INRAE, Agro Paris Tech, Micalis Institute

Background: We have previously reported the clinical outcomes of a randomized trial of 120 SAH patients treated with prednisolone or FMT (Hepatology Intl, 2023). We report here the details of alterations of gut microbiota following FMT, more so, the species present in patients who died. **Methods:** The stool samples from baseline, days 14, 28, 60 and 90 were analyzed using 16rRNA sequencing. Correlation of microbiota at one time point earlier than mortality (day 28 or 90) was drawn to determine taxa associated with mortality. **Results:** In FMT, 11.6% (7/60) patients died by day28, whereas 45 of 60 (75%) patients survived till day90, compared to 6/60 (10%) and 34/60 (56%) in steroid arm. Recipients differed from donors in bacterial composition by 23% (p=0.01). At baseline 48 genera were significantly reduced (p<0.05) in patients compared to donors. Alpha diversity improved significantly at day28 (p=0.029) to day90 (p=0.19). Rare taxa (assessed by Chao1 index) demonstrated a shift towards healthy donor type from day28 (p=0.006) to day90 (p=0.41). 27 taxa from donors persisted for 90 days and were associated with survival benefit (p<0.05). Members of the phylum Bacteroidetes showed persistent increase post-FMT. Also, taxa with low relative abundances (<1 Log) were significantly associated with day-90 survival, corroborating with Chao1 index becoming similar to the donors by day90. In survivors, pathogenic taxa like *Campylobacter* reduced by 19-fold (p=0.035) by day90 (though it was non-significantly different at day28). Firmicutes, Lachnospiraceae, *Veillonella* and *Prevotella* favoured survival significantly (p=0.008, 0.051, 0.045, 0.033, respectively). 4 taxa- Fusobacteria [HR: 1.49 (95%CI:1.2-1.9, p<0.001)], Mycoplasma [HR: 5.92 (95%CI:0.87-40, p=0.006)], *Allisonella* [HR: 25.1 (95%CI:0.8-750, p=0.063)] and *Clostridium IV* [HR: 2.1 (95%CI:1.1-3.9, p=0.02)] were significantly associated with early mortality. Pathogenic genera like *Klebsiella, Salmonella,* and *Mycoplasma* remained significantly high (p=0.057, 0.011, 0.025 respectively) in the deceased. *Clostridium IV* (p=0.037), *Allisonella* (p=0.06) and phylum Tenericutes (p=0.025) were significantly associated with both day28 or day90 mortality. **Conclusion:** Taxa associated with mortality, like *Clostridium IV*, *Mycoplasma* and *Allinsonella*, along with *Veillonella* and *Prevotella* (which favour survival) should be rigorously screened for shifts in abundance in SAH patients before and after FMT. Attempts to reduce the pathogenic bacteria, could help improve survival post-FMT.

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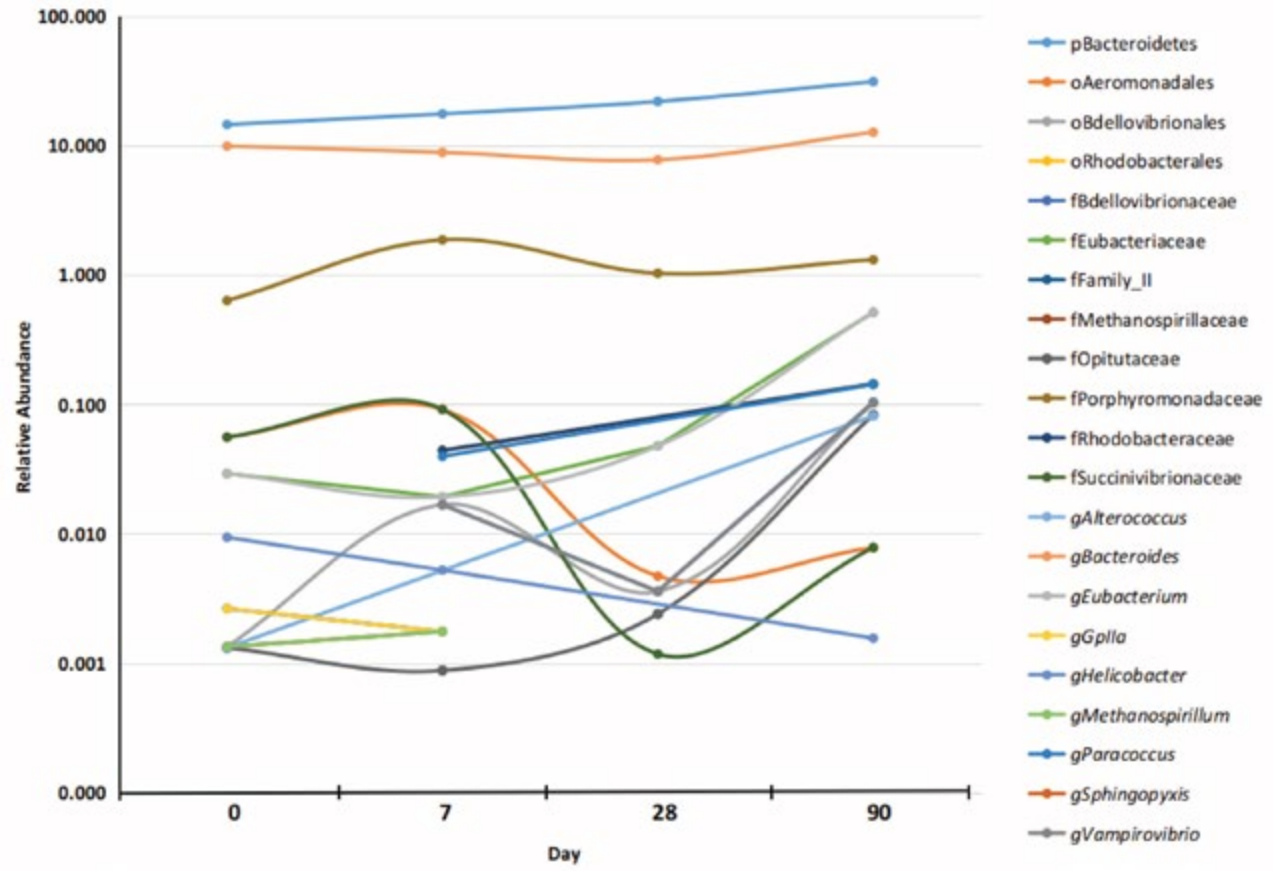

Disclosures: Shvetank Sharma: Nothing to Disclose, Apurva Pande: Nothing to Disclose, Vikas Khillan: Nothing to Disclose, Archana Rastogi: Nothing to Disclose, Vinod Arora: Nothing to Disclose, Saggere Muralikrishna Shasthry: Nothing to Disclose, Rajan Vijayaraghavan: Nothing to Disclose, Rakesh Kumar Jagdish: Nothing to Disclose, Manoj Sharma: Nothing to Disclose, Guresh Kumar: Nothing to Disclose, Stanislas Mondot: Nothing to Disclose, Joel Dore: Nothing to Disclose, Shiv Kumar Sarin: Nothing to Disclose

2280 | WESTERN DIET CONTRIBUTES TO MASH BY REMODELING GUT MICROBIOTA AND METABOLITE 2-OG

Ming Yang[1] *Eric Kimchi*[1] *Kevin Staveley-O'Carroll*[1] *Guangfu Li*[1]

[1]*University of Connecticut Health Center*

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most common cause of chronic liver disease. The interplay between western diet and gut microbiota drives the development of MASLD and its progression to metabolic dysfunction-associated steatohepatitis (MASH). However, the specific microbial and metabolic mediators contributing to MASH remain to be identified. **Methods:** We developed a choline-low high-fat and high-sugar diet, representing a typical western diet, named CL-HFS, which successfully induced male mouse MASH with some features of the human disease, such as hepatic inflammation, steatosis, and fibrosis. Multiomics analysis such as non-targeted gas chromatography-mass spectrometry (GC-MS), 16 S ribosomal RNA (rRNA) gene sequencing, real-time PCR, flow cytometry, hematoxylin and eosin (H&E) staining, immunohistochemical (IHC) staining, siRNA transfection, transmission electron microscopy (TME), Gut microbiota sterilization and targeted bacterial repopulation were used to characterize the impact of gut microbial metabolites derived from western diet on MASH imitation and progression. **Results:** Metataxonomic and metabolomic studies identified Blautia producta and 2-oleoylglycerol (2-OG) as clinically relevant bacterial and metabolic mediators contributed to CL-HFS-induced MASH. In vivo studies validated that both Blautia producta and 2-OG promoted liver inflammation and hepatic fibrosis in normal diet- or CL-HFS-fed mice. Cellular and molecular studies revealed that the GPR119/TAK1/NF-κB/TGF-β1 signaling pathway mediated 2-OG-induced macrophage priming

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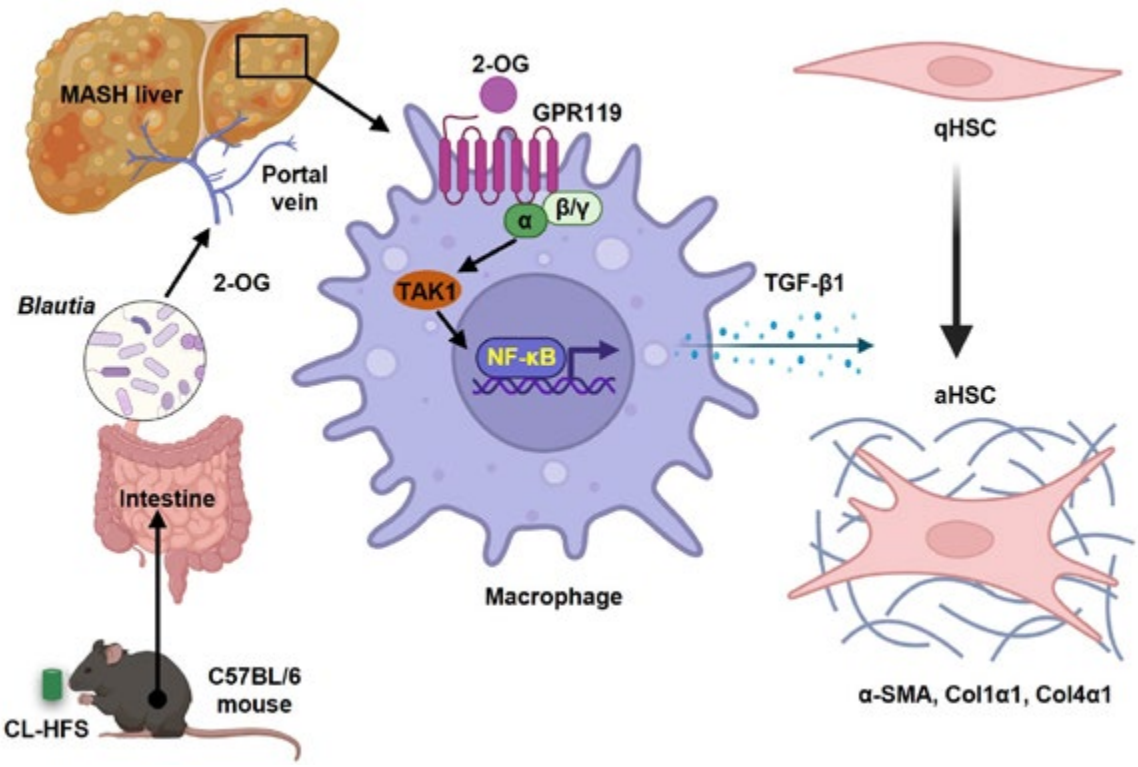
and subsequent hepatic stellate cell (HSC) activation. **Conclusion:** These findings advance our understanding of MASLD/MASH pathogenesis and provide targets for developing microbiome/metabolite-based therapeutic strategies against MASLD/MASH.



Disclosures: Ming Yang: Nothing to Disclose, Eric Kimchi: Nothing to Disclose, Kevin Staveley-O'Carroll: Nothing to Disclose, Guangfu Li: Nothing to Disclose

2281 | DIFFERENCES IN GUT MICROBIOME DIVERSITY IN PATIENTS WITH MASLD ASSOCIATE WITH RESPONSE TO FECAL MICROBIOTA TRANSPLANT (FMT) DEFINED BY PLASMA METABOLIC PROFILES

Nadeen Habboub[1] Despoina Chrysostomou[1] Benjamin Challis[2] Laura Martinez-Gili[1] Julian Marchesi[1] Marc Dumas[1] Mark Thursz[1] Benjamin Mullish[1] Pinelopi Manousou[1]

[1]Imperial College London, [2]AstraZeneca, Biopharmaceuticals Research and Early Development, Cambridge, UK

Background: The gut microbiome influences the pathogenesis and progression of metabolic dysfunction-associated steatotic liver disease (MASLD), at least partly via circulating gut microbial metabolites. Faecal microbiota transplant (FMT) from selected donors may restore pre-morbid microbiome-metabolome interactions in patients with MASLD. Our aim was to assess microbiome engraftment after FMT and its impact on MASLD patients' metabolism. **Methods:** 15 MASLD patients with liver stiffness of > 8 kPa were recruited from a specialist MASLD clinic (St Mary's Hospital, London, UK), and each received three healthy donor capsulised FMTs, each six weeks apart (ClinicalTrials.gov ID: NCT06024681). We designed a plasma poly-metabolic scoring model (PMRS) based on ^{1}H-NMR data that distinguished MASLD from healthy individuals, and stool donors (*n*=11). Plasma, stool samples and clinical parameters were collected fortnightly (week 0-24) during this longitudinal study. Fasted plasma samples were analysed by ^{1}H-NMR spectroscopy and scored based on their full metabolic profiles. A decrease in the poly-metabolic risk scores of MASLD FMT recipients by week 24, was used to determine their response status to FMT. 16S rRNA gene sequencing was performed on stool samples to profile changes in gut microbial composition, primarily assessed by alpha and beta diversity, comparing responders and non-responders. **Results:** 11/15 FMT recipients demonstrated metabolic profile shifts towards those of the healthy donors after receiving three FMTs and were deemed responders. Non-responders had higher baseline ALT levels (p=0.03) compared to responders and exhibited higher levels of triglycerides (p=0.001), HOMA-IR (p=0.026),

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and ALT (p=0.049) levels at the trial endpoint. Responders displayed greater gut microbial alpha diversity (Inverse Simpson, p=0.0007) at baseline, as well as increased beta diversity (p=0.028) after their first FMT. **Conclusion:** ^{1}H-NMR plasma PMRS could effectively differentiate MASLD FMT recipients to responders and non-responders, and this associated with gut microbiome diversity changes. These findings provide insight into the gut microbiome's contribution to metabolic perturbations in MASLD, highlighting the potential for personalised risk assessment and treatment options.

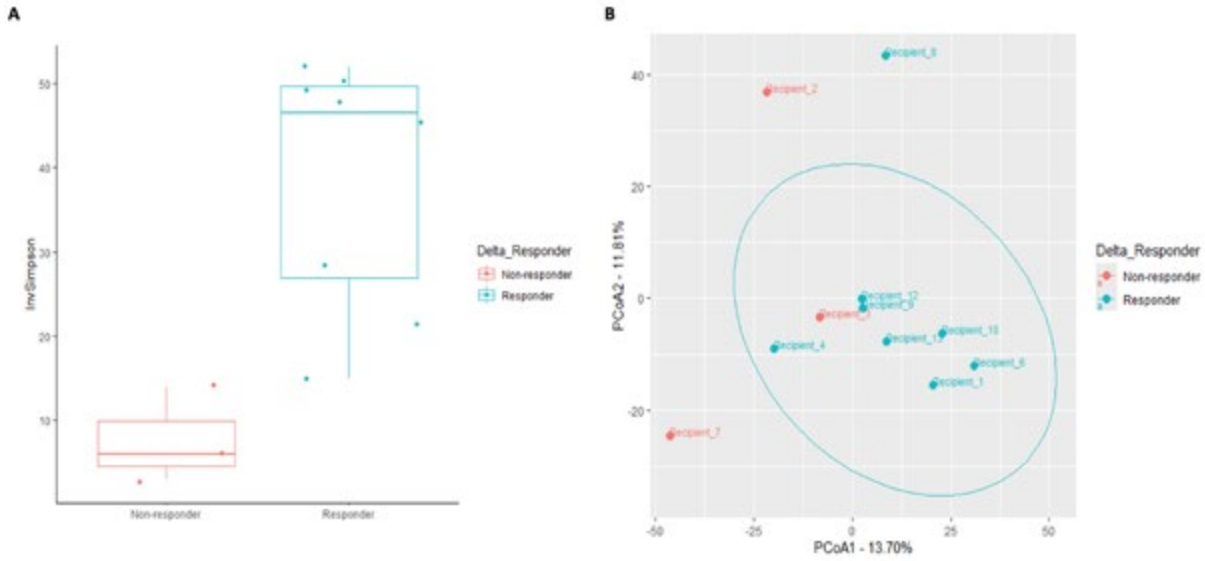

Figure 1: Gut microbial diversity in FMT-recipient metabolic responders and non-responders. (A) Alpha diversity measured by Inverse Simpson index, comparing baseline gut microbial diversity from FMT recipients who had a negative delta poly-metabolic risk score (PMRS) (Responders; blue) to those with a positive delta PMRS (Non-responders; red) at trial completion. (B) Beta-diversity assessed using Euclidean distance and illustrated via a Principal Coordinates Analysis (PCoA) plot, showing variation between FMT metabolic (PMRS) responders (blue) and non-responders (red) after their first capsulised FMT. The first principal coordinate explains 13.7% of the variance, while the second principal coordinate explains 11.8%.

Disclosures: Nadeen Habboub: Nothing to Disclose, Despoina Chrysostomou: Nothing to Disclose, Benjamin Challis: Nothing to Disclose, Laura Martinez-Gili: Nothing to Disclose, Julian Marchesi: Nothing to Disclose, Marc Dumas: Nothing to Disclose, Mark Thursz: Durect: Consultant, GSK: Consultant, Resolution Tx: Consultant, Intercept: Consultant, Galecto: Consultant, Durect: Consultant, Benjamin Mullish: Nothing to Disclose, Pinelopi Manousou: Nothing to Disclose

2282 | GROWTH HORMONE RESHAPES THE GUT MICROBIAL PROFILE IN INDIVIDUALS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE AFTER SIX MONTHS OF TREATMENT

Elizabeth Jensen[1] Jonathan Young[2] Mark Chicote[3] Edward List[2] Kathleen Corey[4] John Kopchick[2] Darlene Berryman[2] Laura Dichtel[4]

[1]Cleveland Clinic Foundation; Ohio University Heritage College of Osteopathic Medicine, [2]Ohio University Heritage College of Osteopathic Medicine; Edison Biotechnology Institute, [3]Massachusetts General Hospital/ Harvard Medical School, [4]Massachusetts General Hospital

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is a global concern due to its increasing frequency and risk for co-morbidities such as cirrhosis, hepatocellular carcinoma, and extrahepatic metabolic and endocrine complications. Interestingly, emerging evidence has shown that both the growth hormone (GH)/insulin-like growth factor-1 (IGF-1) axis and the gut microbiome play a role in the progression of MASLD, making both viable targets for therapies. Moreover, several animal studies highlight crosstalk between the gut microbiome and GH/IGF-1 axis and its impact on growth and metabolic disorders. However, limited research has examined its translatability and the role of acute GH administration on the human gut microbiome. Thus, this study aimed to characterize the changes in the gut microbial profile of individuals with MASLD following

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six months of GH therapy. **Methods:** Microbial composition was quantified from stool of male and female adults (aged 29 to 57 years with BMI ≥ 25 kg/m^2 and MASLD without diabetes [n = 7]) before and after 6 months of therapy (GH or placebo) through 16S rRNA gene sequencing and QIIME 2 bioinformatics. Additional statistical analyses assessed the unique microbial signature at the genus level and predictive metabolic function of the gut microbiome associated with GH (specifically comparing between pre-and post-GH stools). **Results:** Overall, six months of GH therapy showed an altered microbial abundance from the phylum to genus level. Post-GH was associated with a trending increase in both microbial richness (p = 0.26, Cohen's d = 0.87) and evenness (p = 0.10, Cohen's d = 1.47) with a large effect size. Unique bacterial genera including *Ruminococcaceae*, *Lachnospiraceae*, *Bifidobacterium*, and *Parasutterella* were identified in the post-GH group. Likewise, metabolic pathways involved in biosynthesis of heme b, vitamins B12, B6, K, thiamine, and folate along with short chain fatty acid production were associated with GH. **Conclusion:** Collectively, these results show that acute GH therapy alters the microbial profile in the setting of MASLD. Notably, several of the stated bacterial genera and metabolic pathways were associated with GH in prior mouse studies, suggesting translatability that GH may influence the longitudinal presence of certain gut microbes and metabolic functions. Additional studies need to be performed to further explore how the GH-associated gut microbiome impacts host health.

Disclosures: Elizabeth Jensen: Nothing to Disclose, Jonathan Young: Nothing to Disclose, Mark Chicote: Nothing to Disclose, Edward List: Nothing to Disclose, Kathleen Corey: Advisor relationship with Intercept; Has not ended; Advisor relationship with Sagimet; Has ended; Speaking and Teaching relationship with Medscape; Has not ended; Consultant relationship with Theratechnology; Has ended, John Kopchick: Nothing to Disclose, Darlene Berryman: Nothing to Disclose, Laura Dichtel: Nothing to Disclose

2283 | "FROM ABSCESS TO TUMOR: TRACKING THE PREVALENCE OF COLON CANCER AMONG PYOGENIC LIVER ABSCESS PATIENTS (2016-2020)"

Khalid Home[1] Amr Dokmak[2] Wendy Tatiana Garzon-Siatoya[1] Abdellatif Ismail[1] Camelia Ciobanu[2] Jeeva Jaganathan[3] Praneeth Bandaru[2] Ali Wakil[2] Arnold Nongmoh Forlemu[2] Vijay Bhaskar Reddy Gayam[4] Vikash Kumar[2] Raissa Nana Sede Mbakop[1] Lisnaldy Ramirez[1] Manasa Ginjupalli[2] Denzil Etienne[2] Nithan Narendra[5] Madhavi Reddy[2]

[1]St Barnabas Hospital, [2]The Brooklyn Hospital Center, [3]Saint Vincent Catholic Medical Centers, [4]State University of New York-Downstate, [5]St. Barnabas Hospital

Background: Colorectal cancer (CRC) is the third most common cause of cancer mortality in the US. Screening for CRC is recommended by numerous professional societies as it has shown to improve disease morbidity and mortality. Through infiltration of the colonic mucosa, CRC can potentially allow for bacterial entry into the systemic and portal circulation. Prior retrospective studies have demonstrated an association between pyogenic liver abscess (PLA) and increased CRC incidence. Despite the increased CRC incidence in PLA patients, there are currently no professional society recommendations pertaining to screening for CRC in such populations. **Methods:** Using the National Inpatient Sample (NIS) database, the study objective was to determine the incidence of CRC in those with PLA as compared to the general population. We conducted a matched retrospective cohort study of all patients with a diagnosis PLA from 2016 to 2020.Unweighted data from NIS were multiplied with appropriate discharge and hospital-level weights to represent the population across the US. **Results:** The total number of CRC cases in the whole population was 1014970 and a total of 3105 cases of CRC were found in 151105 cases of PLA. Prevalence of CRC with PLA was 2.05% vs 0.49% in CRC without PLA (p=0.00).The mean age of patients with CRC with history of PLA was 61 years vs 67 years in CRC without PLA (p=0.00) Significant difference in gender distribution was found as males in the CRC with PLA cohort were 60.4% compared to 50.9% males in CRC without PLA. (p=0.00) The CRC with PLA cohort had a higher Charlson Comorbidity Index (88% had CCI of 3 or above vs 78.42% in the CRC without PLA cohort, p=0.00). Mortality was found to be 5.16% in the CRC with PLA cohort vs 4.61% in CRC without PLA cohort but with no statistical significance (p=0.57). Chi-square test was used to compare the risk of comorbidities in the two cohorts, as listed in table1. Multivariable logistic regression showed an odds ratio of 2.33979 for developing CRC in PLA. (SE= 0.096, p=0.00, CI [2.159-2.536]) while adjusting for potential cofounders as age, gender, CCI, patient and hospital characteristics. **Conclusion:** Our results demonstrate an increased incidence of CRC in those with PLA when compared to the general population. Screening patients with PLA for CRC might therefore be warranted for early diagnosis and treatment, potentially reducing CRC associated morbidity and mortality. Limitations include lack of control of other variables that can contribute to CRC occurrence and accuracy of hospital diagnoses coding.

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	CRC with a history of PLA[%]	CRC without PLA[%]	P-value
Patient baseline characteristics			
Age	61 [60.44-63.05]	67 [67.12 67.34]	**0.00**
Race			0.09
White	64	70.31	
Black	15	14.04	
Hispanic	11	9.13	
Asian or Pacific Islander	4	3.24	
Native American	0.8	0.49	
Other	2.9	2.79	
Indicator of sex			**0.00**
Male	60.39	50.92	
Female	39.61	49.08	
Comorbidities			
CHF	9.5	13.75	**0.01**
Cardiac arrhythmic	20	22.16	0.54
Valvular disease	1.7	5.31	**0.00**
Pulmonary circulation	4.3	5.16	0.39
HTN complicated	14	18.86	**0.02**
Paralysis	0.16	1.01	**0.03**
Other neurological	8.5	8.08	0.73
Chronic pulmonary disease	12.4	17.17	**0.01**
Diabetes	10	14	0.06
Renal disease	10.47	14.9	**0.01**
Liver disease	11.27	6.97	**0.00**
Moderate/severe LD	4.99	1.99	**0.00**
HIV/AIDS	0	0.15	0.41
lymphoma	0.9	0.8	0.69
Metastatic cancer	71	44.8	**0.00**
coagulopathy	14.3	7.68	**0.00**
Obesity	10	13.49	0.09
Weight loss	40.58	19.92	**0.00**

	CRC with a history of PLA[%]	CRC without PLA[%]	P-value
Charlson Comorbidity Index			**0.00**
0	0	0	
1	0	0	
2	11	21.58	
3 or above	88	78.42	
Insurance			**0.00**
Medicare	48	60	
Medicaid	14.7	10	
Private Insurance	35	27.6	
Self-pay	2.3	2.4	
Hospital baseline characteristics			
Relative bed size			**0.01**
Small	16	20	
Medium	25	29	
Large	58	51	
Hospital location			0.78
Rural	4.0	9.1	
Urban	95	99	
Hospital teaching status			0.25
Non-teaching	16.3	29	
Teaching	83.7	71	
Outcomes			
Died during hospitalization	5.16	4.61	0.57
Length of stay	12.5 [11.45-13.60]	6.5 [6.54-6.63]	
Total cost of hospitalization	160716 $	82568 $	

Disclosures: Khalid Home: Nothing to Disclose, Amr Dokmak: Nothing to Disclose, Wendy Tatiana Garzon-Siatoya: Nothing to Disclose, Abdellatif Ismail: Nothing to Disclose, Camelia Ciobanu: Nothing to Disclose, Jeeva Jaganathan: Nothing to Disclose, Praneeth Bandaru: Nothing to Disclose, Ali Wakil: Nothing to Disclose, Arnold Nongmoh Forlemu: Nothing to Disclose, Vijay Bhaskar Reddy Gayam: Nothing to Disclose, Vikash Kumar: Nothing to Disclose, Raissa Nana Sede Mbakop: Nothing to Disclose, Lisnaldy Ramirez: Nothing to Disclose, Manasa Ginjupalli: Nothing to Disclose, Denzil Etienne: Nothing to Disclose, Nithan Narendra: Nothing to Disclose, Madhavi Reddy: Nothing to Disclose

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2284 | UTILIZING FIB-4 AND TRANSIENT ELASTOGRAPHY TO DIAGNOSE STEATOTIC LIVER DISEASE IN PATIENTS WITH TYPE 2 DIABETES: QUALITY IMPROVEMENT PROJECT AT A VETERANS AFFAIRS RESIDENT CLINIC

Nimmy Thomas[1] Christina Stull[1] Holli Sadler[2]

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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most common cause of chronic liver disease and is the leading cause of liver-related morbidity and mortality. Updated guidelines from the American Diabetes Association recommends all patients diagnosed with diabetes or prediabetes be screened with the FIB-4 score. The aim of this project was that from March 2023 – March 2024, veterans with a past medical history of diabetes seeking care at the resident primary care clinic at the Austin VA be screened for metabolic liver disease with advanced fibrosis through FIB-4 score with the aim of connecting at least 30% of these veterans to post-screening follow up care (including workup with transient elastography, weight loss intervention, and/or referral to hepatology). **Methods:** Initially, we calculated FIB-4 scores independently through MDCalc for all patients diagnosed with type 2 diabetes in the resident clinic. With the advent of the MASLD database at the VA, we were able to download a patient list from our panel of patients with diabetes with elevated FIB-4 scores. Patients were referred to transient elastography if they met the following criteria: between the ages of 36-64 with a FIB-4 score between 1.3 and 2.67, or between the ages of 65-75 with a score between 2 and 2.7. These patients were called to discuss their increased risk for chronic liver disease, schedule their FibroScan appointments, and discuss mitigating other risk factors by updating labs and hepatitis B/C serologies. **Results:** Through our project, all patients diagnosed with diabetes in the resident clinic had a FIB-4 score calculated. Of these patients, 34 were identified to have met the inclusion criteria for transient elastography. One patient was removed from the data analysis since they moved to a different VA facility for care. Of the remaining 33, 15 (45%) completed their FibroScan, 15 (45%) were lost to follow up after two outreach attempts with screening letters and phone calls, and 3 (9%) declined to be screened. Of the patients with completed scans, 5 (33%) were identified to have advanced fibrosis and were directed to appropriate management (medication-directed weight loss and/or GI referral). **Conclusion:** Through our QI project, we were able to screen all patients with diabetes for chronic liver disease and direct them to appropriate management to prevent progression of their illness. FibroScans for MASLD screen were previously only offered through the Central Texas VA main facility (70 miles away) through a GI consult or a community referral. Through this project, we have been able to expand access to veterans by offering it locally at the outpatient VA clinic through primary care. Additionally, our project has also offered the opportunity for all of our internal medicine residents to learn and practice transient elastography with direct attending supervision. We anticipate expanding access beyond the resident clinic in the next phase.

Disclosures: Nimmy Thomas: Nothing to Disclose, Christina Stull: Nothing to Disclose, Holli Sadler: Nothing to Disclose

2285 | RISK OF INCIDENT EXTRAHEPATIC CANCERS AMONG MEDICARE PATIENTS WITH NON-ALCOHOLIC STEATOHEPATITIS (NASH)

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Background: NASH, or metabolic dysfunction-associated steatohepatitis (MASH), is a severe form of non-alcoholic fatty liver disease (NAFLD), or metabolic dysfunction-associated liver disease (MASLD). NAFLD is associated with increased risk of extrahepatic malignancies; however, evidence is lacking for NASH specifically. This study aimed to characterize the risk of incident extrahepatic cancers among Medicare patients with NASH up to 5 years following diagnosis. **Methods:** Included patients were required to have a diagnosis of NASH [International Classification of Diseases 10th Revision (ICD-10): K75.81] in 100% Medicare fee-for-service claims (2015–2021); have been at least 66 years old at index (earliest diagnosis); have continuous enrollment in Parts A, B, and D for at least 12 months prior to and 6 months following index (unless death); and have no evidence of other causes of liver disease. Diagnosis codes defined liver severity states [NASH, compensated cirrhosis (CC), decompensated cirrhosis (DCC), hepatocellular carcinoma (HCC), and liver transplant] and cancer, by type. Kaplan-Meier survival analyses were conducted for time to cancer onset and pairwise Cox proportional hazards

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models estimated the hazard ratios (HRs) and 95% confidence intervals (CIs) of cancer onset associated with liver disease progression, controlling for baseline characteristics. **Results:** In 14,806 unique patients, mean age and follow-up were 72.2 and 2.8 years, respectively. For NASH, 5-year cumulative incidence was highest for breast cancer followed by lymphoma and leukemia, prostate, and lung cancers (Table 1). Progression to CC significantly increased the hazard of lung cancer (HR: 2.0; CI: 1.2 – 3.1), while progression to DCC increased the hazard of stomach (HR: 14.8; CI: 5.1 – 43.1), ovarian (HR: 11.6; CI: 4.5 – 30.0), esophageal (HR: 9.2; CI: 1.7 – 49.1), and lymphoma and leukemia (HR: 2.1; CI: 1.1 – 4.2) cancers (all $p<0.05$). Onset of HCC increased the hazard of pancreatic (HR: 12.3; CI: 4.4 – 34.7), stomach (HR: 10.5; CI: 1.3 – 82.9), lung (HR: 4.5; CI: 1.6 – 12.8), and colorectal (HR: 3.3; CI: 1.0 – 10.7) cancers (all $p<0.05$). Following liver transplant, patients had a higher hazard of lymphoma and leukemia (HR: 10.5; CI: 1.8 – 61.0; $p<0.05$). **Conclusion:** High incidence of gastrointestinal and blood cancers was found following NASH diagnosis. Progression to more advanced liver disease was associated with increased risk for several extrahepatic cancer types.

Table 1: Kaplan-Meier estimates of cumulative cancer incidence following NASH diagnosis

	Bladder	Breast	Colorectal	Esophageal	Gallbladder
NASH Cumulative Incidence, %[1]					
Year 1	0.1%	0.7%	0.4%	0.0%	0.0%
Year 2	0.3%	1.4%	0.8%	0.1%	0.0%
Year 3	0.4%	1.9%	1.2%	0.2%	0.1%
Year 4	0.6%	2.5%	1.5%	0.2%	0.1%
Year 5	1.0%	3.1%	1.8%	0.2%	0.1%
US Population Incidence, %[2]	0.1%	0.3%	0.2%	0.0%	0.0%

	Kidney	Liver	Lung	Lymphoma and Leukemia	Ovarian
NASH Cumulative Incidence, %[1]					
Year 1	0.3%	0.2%	0.4%	0.5%	0.2%
Year 2	0.4%	0.5%	0.7%	1.2%	0.3%
Year 3	0.6%	0.8%	1.1%	1.6%	0.4%
Year 4	0.7%	1.0%	1.6%	2.0%	0.5%
Year 5	1.0%	1.4%	2.3%	2.8%	0.5%
US Population Incidence, %[2]	0.1%	0.0%	0.3%	0.2%	0.0%

	Pancreatic	Prostate	Small Intestine	Stomach	Uterine
NASH Cumulative Incidence, %[1]					
Year 1	0.2%	0.6%	0.0%	0.1%	0.3%
Year 2	0.4%	1.0%	0.1%	0.2%	0.4%
Year 3	0.6%	1.6%	0.1%	0.3%	0.6%
Year 4	0.9%	2.2%	0.2%	0.4%	0.7%
Year 5	1.1%	2.6%	0.2%	0.5%	0.8%
US Population Incidence, %[2]	0.1%	0.3%	0.0%	0.0%	0.1%

[1]Calculated among enrollees aged 65 years or older in 100% Medicare fee-for-service claims with a NASH diagnosis from 2015–2021 (N=12,990).

[2]United States Cancer Statistics - Incidence: 1999 - 2020, WONDER Online Database. United States Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute; 2022 submission; 2023 release. Accessed at http://wonder.cdc.gov/cancer-v2020.html on Apr 3, 2024. Percentages calculated for each cancer among individuals aged 65 years or older from 2016-2020 (N=260,382,222).

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2286 | RISK OF ALL-CAUSE MORTALITY AND ADVERSE OUTCOMES FROM STEATOTIC LIVER DISEASE AND ITS SUBGROUPS IN THE GENERAL POPULATION ◆

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Background: With the implementation of the new nomenclature on steatotic liver disease (SLD), three main subgroups consisting of metabolic dysfunction-associated liver disease (MASLD), MASLD with increased alcohol intake (MetALD), and alcohol-related liver disease (ALD) have been defined. However, the risk of SLD for all-cause mortality and adverse outcomes as well as the different risks between MASLD, MetALD, and ALD needs further clarification. **Methods:** Data from 13,599 participants without cancer of the population-based Gutenberg Health Study (baseline enrollment between 2007 and 2012) were cross-sectionally and prospectively analysed. The fatty liver index (FLI) with a score of ≥60 was used to define SLD. The subgroups of SLD (MASLD, MetALD, and ALD) were defined according to the new nomenclature based on five cardiometabolic criteria and alcohol consumption. The fibrosis-4 score (FIB-4) was calculated to determine patients at risk of fibrosis (≥1.3). All-cause mortality (10-year follow-up) and several adverse outcomes (hepatic decompensation, major adverse cardiac events (MACE), extrahepatic cancer) were analysed and compared across the subgroups of SLD. Cox regression models were used to estimate adjusted hazard ratios (aHR) and their 95% confidence intervals (CIs). Adjustments were made for age, sex, socioeconomic status, education, and smoking. **Results:** The overall prevalence of SLD was 37.3% (n=5,074), whereas the prevalence of MASLD, MetALD, and ALD were 30.5% (n=4,154), 5.3% (n=717) and 1.5% (n=202), respectively. Almost half of the population were women (48.9%, n=6,644), and the mean age was 54.3 (±11.0) years. An elevated FIB-4 ≥1.3 was present in 20.2% (n=1,021) with SLD compared to 13.9% (n=1,184) without SLD (p<0.0001). The cumulative incidence of all-cause mortality was higher in SLD and all its subgroups MASLD, MetALD, and ALD compared to no SLD (p<0.0001). Stratification by FIB-4 ≥1.3 revealed a higher risk of all-cause mortality across all investigated SLD subgroups compared to FIB-4 <1.3 (p<0.0001). Each subgroup of SLD was associated with a higher risk of all-cause mortality: MASLD (aHR 1.6, 95% CI 1.4-1.9, p<0.0001), MetALD (aHR 1.6, 95% CI 1.3-2.1, p=0.00024) and ALD (aHR 1.6 95% CI 1.0-2.5, p=0.033). The risk of adverse outcomes was increased in MASLD (hepatic decompensation: aHR 1.2, 95% CI 1.0-1.5, p=0.0045; MACE: aHR 1.5, 95% CI 1.2-1.8, p<0.0001; extrahepatic cancer: aHR 1.2, 95% CI 1.1-1.4, p=0.0086), whereas no differences were seen for MetALD and ALD. **Conclusion:** The prevalence of SLD and especially MASLD is high in the general population. Patients with SLD and any of its three main subgroups show a higher risk of all-cause mortality, whereas the risk for adverse outcomes is particularly increased in those with MASLD. These results highlight the importance of screening for SLD and related risk factors to improve outcomes.

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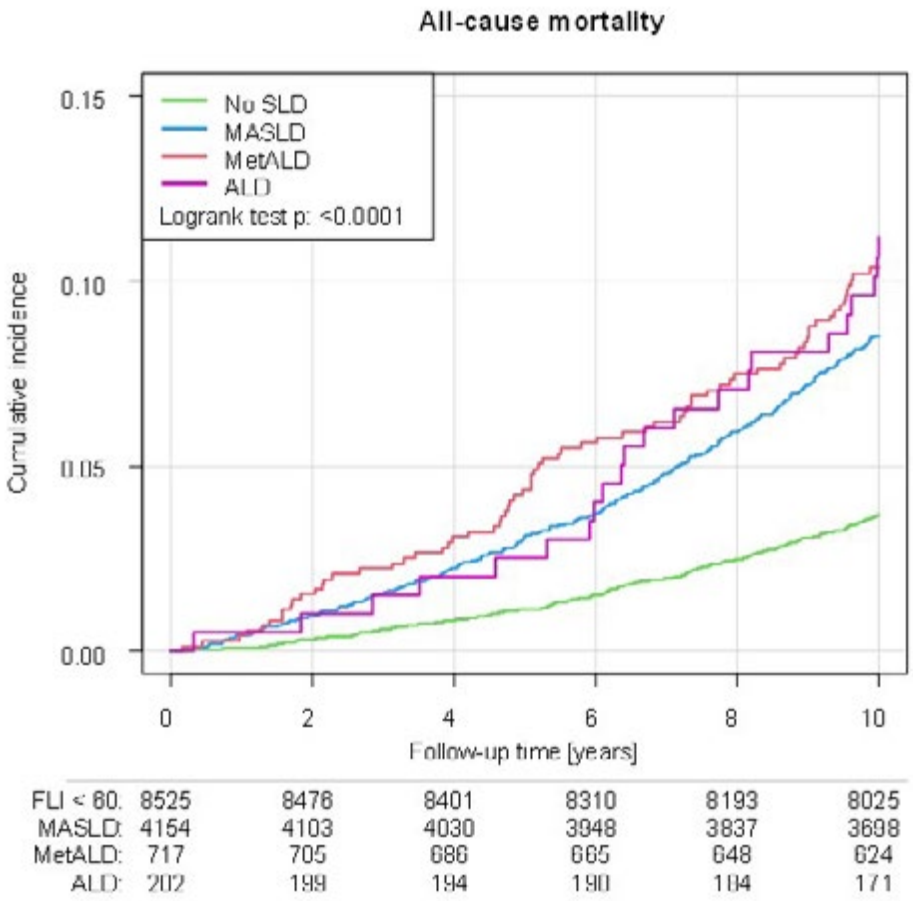

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2287 | RACIAL DIFFERENCES AND COMPARATIVE CLINICAL OUTCOMES AMONG PATIENTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE HOSPITALIZED FOR COVID-19: INSIGHTS FROM THE NATIONAL INPATIENT SAMPLE DATABASE

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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most common chronic liver disease in the United States. Literature has shown that patients with advanced chronic liver disease experience higher morbidity and mortality from COVID-19; however, the impact of COVID-19 on those hospitalized with MASLD remains unclear. This study compares the outcomes in MASLD patients with and without COVID-19 using a large nationwide inpatient database. **Methods:** National Inpatient Sample (NIS) datasets were used from 2020 to 2021 to identify patients with a diagnosis of MASLD (including MA steatohepatitis, MASH) using ICD-10 codes. Patients under 18 were excluded. Clinical outcomes were compared in hospitalized MASLD patients with or without COVID-19 using multivariable logistic regression, adjusting for confounders. **Results:** Of 1,434,504 patients with MASLD, 111,970 patients with MASLD were hospitalized with COVID-19. Outcomes were compared between those without COVID-19 and those with COVID-19. The adjusted odds of mortality were significantly higher in MASLD patients with COVID-19 [aOR: 6.9 (95% CI: 6.53–7.3, p<0.001)]. Additionally, linear regression analysis showed that the length of stay (LOS) was significantly longer in MASLD patients with COVID-19, with an estimated increase of 4.1 days (95% CI: 3.96–4.25, p<0.001). Total healthcare charges (THC) were also significantly higher, with an increase of $44,829 (95% CI: $41,571–$48,087, p<0.001). The odds of requiring endotracheal intubation (EI) were also significantly higher in MASLD patients with COVID-19 [aOR: 5.12 (95% CI: 4.83–5.43, p<0.001)]. Furthermore, these patients had increased odds of developing sepsis [aOR: 2.77 (95% CI: 2.59–2.96, p<0.001)], septic shock [aOR: 2.99 (95% CI: 2.81–3.19, p<0.001)], bacterial pneumonia [aOR: 1.63 (95% CI: 1.54–1.73, p<0.001), hepatic encephalopathy (HE) [aOR: 1.31 (95% CI: 1.19–1.44, p<0.001)], and acute kidney injury (AKI) [aOR: 1.24 (95% CI: 1.19–1.28, p<0.001)]. (Table 1 & 2) **Conclusion:** This study demonstrates that MASLD patients hospitalized with COVID-19 face significantly worse outcomes than those without COVID-19. These patients have higher odds of mortality, LOS, and THC. Additionally, they are at increased risk of requiring EI and developing severe complications such as sepsis, septic shock, bacterial pneumonia, HE, and AKI. Moreover, our study demonstrates significant racial differences, with higher representation of Hispanics, Asian/Pacific Islanders, and Native Americans in the COVID-19 cohort. Given that these findings are based on pre-vaccine data, it is crucial to consider how vaccination may alter these severe outcomes in the post-vaccine era.

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In-Hospital Outcomes of Patinets with MASLD With and Without COVID-19			
Table 1:	**MASLD Without COVID-19**	**MASLD With COVID-19**	**P-value**
Number of Patients	1,322,534	111,970	
Mean Age (Years)	56.4	54.9	
Baseline Characterstics			
Gender, n (%)			<0.001
Male	630,729 (47.7%)	60,024 (53.6%)	
Female	691,604 (52.3%)	51,934 (46.3%)	
Race, n (%)			<0.001
White	865,814 (66.91%)	597,780 (54.76%)	
Black	143,365 (11.08%)	12,220 (11.19%)	
Hispanic	203,875 (15.76%)	27,935 (25.59%)	
Asian/Pacific	30,665 (2.37%)	3,660 (3.35%)	
Native American	12,340 (0.95%)	1,340 (1.23%)	
Other	37,850 (2.93%)	4,235 (3.88%)	
Mortality (Died)	29,504 (2.2%)	12,030 (10.7%)	<0.001
Length of Stay (Days)	5.3	9.1	-
Total Healthcare Charges (USD)	75,277	119,345	-
Endotracheal Intubation	31,034 (2.3%)	10,680 (9.5%)	<0.001
Sepsis	31,025 (2.35%)	6,725 (6%)	<0.001
Septic Shock (SS)	37,815 (2.8%)	8,035 (7.18%)	<0.001
Bacterial Pneumonia	90,204 (6.8%)	11,180 (9.98%)	<0.001
Hepatic Encephalopathy (HE)	82,005 (6.2%)	4,975 (4.4%)	<0.001
Acute Kidney injury	260,984 (19.7%)	23,089 (20.6%)	0.002

Table 2:	**Ajusted-Odd's ratio (aOR)**	**95% CI**		**P-value**
Outcomes: Reference - MASLD Patinets Without COVID-19				
Mortality	6.9	6.53	7.3	<0.001
Length of Stay (LOS) Days	4.1	3.96	4.25	<0.001
Total Healthcare Charges (THC) ($)	44,829	41,571	48,087	<0.001
Endotracheal Intubation (EI)	5.12	4.83	5.43	<0.001
Sepsis	2.77	2.59	2.96	<0.001
Septic Shock (SS)	2.99	2.81	3.19	<0.001
Bacterial Pneumonia (BP)	1.63	1.54	1.73	<0.001
Hepatic Encephalopathy (HE)	1.31	1.19	1.44	<0.001
Acute Kidney injury (AKI)	1.24	1.19	1.28	<0.001

Disclosures: Fnu Vikash: Nothing to Disclose, Siddharth Pravin Agrawal: Nothing to Disclose, Vikash Kumar: Nothing to Disclose, Sindhu Vikash: Nothing to Disclose, Anuj Sharma: Nothing to Disclose, Don Rockey: Grant/Research Support relationship with Versantis; Has not ended; Grant/Research Support relationship with AstraZeneca; Has not ended; Grant/Research Support relationship with Ipsen; Has not ended; Grant/Research Support relationship with Boehringer Ingelheim; Has not ended; Consultant relationship with WL Gore and Associates; Has not ended; Grant/Research Support relationship with Gilead; Has not ended; Grant/Research Support relationship with Durect; Has not ended; Consultant relationship with BD Medical; Has not ended; Consultant relationship with Cook Medical; Has not ended; Grant/Research Support relationship with Intercept; Has not ended; Grant/Research Support relationship with Inventiva; Has not ended; Grant/Research Support relationship with Madrigal; Has not ended; Grant/Research Support relationship with Ocelot; Has ended; Grant/Research Support relationship with Bio89; Has not ended; Grant/Research Support relationship with Salix; Has not ended; Grant/Research Support relationship with Novonordisk; Has not ended; Grant/Research Support relationship with Viking; Has ended; Grant/Research Support relationship with Galectin; Has not ended

2288 | PROGNOSTIC VALUE OF THE FIB-4 INDEX FOR ALL-CAUSE MORTALITY IN HEART FAILURE WITH STEATOTIC LIVER DISEASE: RESULTS FROM THE MYOVASC STUDY

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Background: The stage of hepatic fibrosis potentially contributes to heart failure (HF) in metabolic dysfunction-associated steatotic liver disease (MASLD). We aimed to identify the prognostic value of the fibrosis-4 (FIB-4) index in HF with underlying MASLD. **Methods:** Patients with HF and controls were prospectively enrolled in the

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MyoVasc study (NCT04064450) and followed for nine years. The Fatty Liver Index (FLI) and FIB-4 index were used to classify steatotic liver disease (SLD) and hepatic fibrosis, respectively. The primary endpoint was all-cause mortality. **Results:** A total of 2726 participants with a mean age of 64.4 +/- 11.2 years and median FIB-4 index of 1.59 (IQR [1.17; 2.17]) were included in the analysis, in which 532 deaths occurred. The FIB-4 index was predictive for all-cause mortality in HF irrespective of SLD. When adjusted for age, sex, hypertension, type 2 diabetes, smoking, obesity, dyslipidemia and family history of myocardial infarction/stroke, the highest hazard ratios (HRs) were observed in patients without evidence of SLD (FIB-4 index with FLI < 30: HR 1.597 (95% CI [1.256;2.031], p = 0.00013), FIB-4 index with FLI 30 to 60: HR 1.802 (95% CI [1.519;2.138], p <0.0001), and FIB-4 index with FLI ≥ 60: HR 1.292 (95% CI [1.215;1.374], p <0.0001)) Multivariate linear regression analyses revealed potent and independent relationships between the FIB-4 index and N-terminal pro-B-type natriuretic peptide, systolic dysfunction (*i.e.* left ventricular ejection fraction), diastolic dysfunction (*i.e.* E/E' ratio) and left ventricular hypertrophy (*i.e.* left ventricular mass indexed to height$^{2.7}$) in patients without evidence of SLD. **Conclusion:** In HF, the FIB-4 index predicts all-cause mortality and relates to cardiac functional and structural changes, especially in patients without evidence of SLD.

Disclosures: Joost Boeckmans: Nothing to Disclose, Jürgen Prochaska: Nothing to Disclose, Alexander Gieswinkel: Nothing to Disclose, Philipp Wild: Nothing to Disclose, Jörn Schattenberg: Consultant relationship with Intercept Pharmaceuticals; Has ended; Speaking and Teaching relationship with MedicalTribune, MedPublico GmbH, MedScape,; Has not ended; Consultant relationship with Ipsen, Inventiva Pharma, Madrigal Pharmaceuticals; Has not ended; Consultant relationship with Apollo Endoscopy, Boehringer Ingelheim, Gilead Sciences; Has not ended; Speaking and Teaching relationship with Forum fÃ¼r Medizinische Fortbildung (FOMF), Gilead Sciences; Has not ended; Speaking and Teaching relationship with Boehringer Ingelheim, Echosens; Has not ended; Speaking and Teaching relationship with AbbVie, Academic Medical Education (AME),; Has not ended; Consultant relationship with Novo Nordisk, Pfizer, Roche, Sanofi, and Siemens Healthineer; Has not ended; Consultant relationship with Madrigal Pharmaceuticals, Lilly, MSD, Northsea Therapeutics,; Has not ended; Consultant relationship with Boehringer Ingelheim, Gilead Sciences, GSK, Ipsen, Inventiva; Has not ended; Consultant relationship with Alentis, Alexion, Altimmune, Astra Zeneca, 89Bio,Bionorica,; Has not ended; Consultant relationship with MSD, Northsea Therapeutics, Novartis, Novo Nordisk; Has not ended; Consultant relationship with Pfizer, Roche, Sanofi, and Siemens Healthineers; Has not ended; Grant/Research Support relationship with Boehringer Ingelheim, Siemens Healthcare GmbH; Has ended; Speaking and Teaching relationship with Novo Nordisk, Madrigal Pharmaceuticals,; Has not ended

2289 | PRURITUS IS COMMON AND PERSISTENT IN PATIENTS WITH MASLD

Nasir Hussain[1] Matthew Armstrong[1] Philip Newsome[1] Usha Gungabissoon[2] Linda Casillas[3] Sumanta Mukherjee[3] Andrea Ribeiro De Souza[4] Megan McLaughlin[3] Palak Trivedi[1]

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Background: Pruritus is a recognized symptom of cholestatic diseases. However, the prevalence and burden in metabolic dysfunction associated steatotic liver disease (MASLD) is not well understood. We conducted a prospective, observational study to determine the A) prevalence of pruritus in MASLD, B) factors associated with pruritus intensity, C) impact on quality of life (QoL), and D) persistence and variability of pruritus intensity over time. **Methods:** Health-related QoL data was collected from adults with MASLD (aged >16y, non-transplant), using the 5-D itch questionnaire, itch numerical rating scale (NRS), chronic liver disease questionnaire (CLDQ) and EuroQol-5 dimension tool (EQ5D). Assessments were conducted at baseline (week 0) and week 48. **Results:** Between Feb 2022 and Aug 2023, 200 pts with MASLD were recruited (median age: 60y, median MELD score: 7). Pts were distinguished by disease severity: no/early fibrosis (transient elastography <8.0kPa and/or liver biopsy stage F0-F2, n=66), advanced fibrosis (biopsy F3, n=47), cirrhosis (n=66) and fibrosis unclassified (n=21). At baseline, 51.5% of all MASLD pts (n=103) reported pruritus with 36.5% (n=73) having moderate-severe intensity (NRS ≥4, worst itch; 24 hr. recall). Median 5D-itch was greater in women (10 vs 7 in men, p=0.04), and with advanced liver disease (no/early fibrosis: 6, advanced fibrosis: 8, cirrhosis: 10, p=0.04). 5D itch scores correlated positively with body mass index (rho 0.30, p<0.01) and serum bile acid values (rho 0.17, p=0.02). There was no significant correlation with serum ALT, ALP, or bilirubin. Metformin use was associated with lower pruritus intensity (median 5D score: 5 vs 10 without metformin, p=0.03), however no association seen with diabetes status or HbA1c. Pruritus intensity negatively correlated with QoL scores (Fig 1a), with the greatest impact on fatigue (rho -0.51, p<0.01) and systemic symptom (rho -0.64, p<0.01) domains of the CLDQ.At follow up, 55% of pts with

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moderate-severe pruritus at baseline continued to experience persistent symptom intensity at week 48. Among pts who reported no or mild itch at baseline, 19% reported moderate-severe itch at 48 weeks. Development of de novo pruritus, of any severity was found in 27% of pts. (Fig 1b) **Conclusion:** Moderate to severe itch is experienced by 1 in 3 pts with MASLD and persists over time in over 50% of pts. Those with more advanced disease, higher BMI and females experience greater pruritus intensity. This data provides justification for clinical trials of antipruritic therapy in MASLD.

Figure 1a: Pruritus intensity negatively correlates with QoL

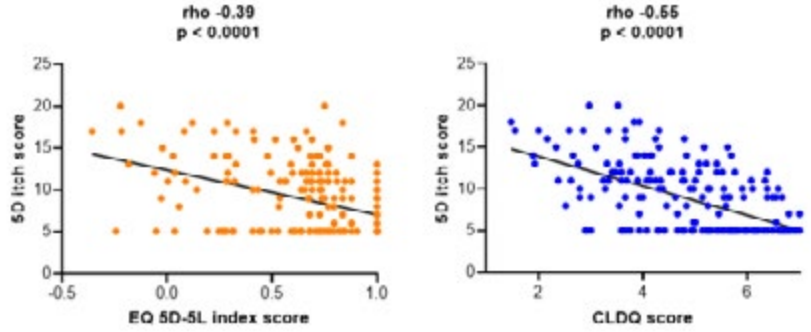
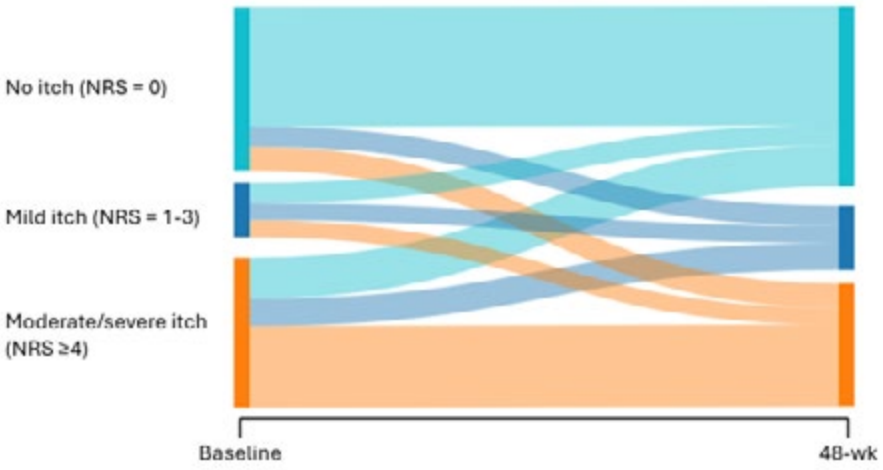


Figure 1b: Variability in pruritus over 48 weeks. (NRS worst itch; 24hr recall)



Disclosures: Nasir Hussain: Nothing to Disclose, Matthew Armstrong: Nothing to Disclose, Philip Newsome: Novo Nordisk: Consultant, B Ingelheim: Consultant, Madrigal: Consultant, 89 Bio: Consultant, Sagimet: Consultant, Echosens: Speaking and Teaching, Eli Lilly: Speaking and Teaching, Zydus Therapeutics: Consultant, Abbott: Speaking and Teaching, Usha Gungabissoon: GSK: Employee and stockholder, Linda Casillas: GSK: Employee, GSK: Stock - publicly traded company, Sumanta Mukherjee: GSK: Own GSK stocks, Andrea Ribeiro De Souza: Nothing to Disclose, Megan McLaughlin: Nothing to Disclose, Palak Trivedi: Nothing to Disclose

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2290 | STRUCTURAL EQUATION MODELLING IDENTIFIES SEX-SPECIFIC CLASSES TO CHARACTERIZE SUBTYPES OF METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE

Carlos Pirola[1] *Silvia Sookoian*[2]

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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is a heterogeneous disease. The disease biology is modified by the presence of comorbidities and sex-specific molecular signatures that affect complex regulatory pathways. To characterise the contribution of individual risks factors and sex to the heterogeneity of MASLD, we analyzed epidemiological, clinical, biochemical, and imaging data from two large population cohorts of different ages. **Methods:** We used generalized structural equation modelling (GSEM) including latent variables to derive sex-specific latent classes (LC). We analysed data from young adults of the Bogalusa Heart Study (BHS) (men=579; women n=843), a cohort designed to assess the natural history of CVD. To replicate the findings, we used data from participants of the National Health and Nutrition Examination Survey (2017-2018 cycle, NHANES) (men=2568; women n=2767). Variables included in the models were: type 2 diabetes, arterial hypertension, plasma levels of ALT, AST, HHT, triglycerides, HDL-C, HOMA-IR and alcohol consumption. Liver phenotype was defined using fatty liver index (FLI) and NAFLD fibrosis score (NFS) in the BHS, and controlled attenuation parameter (CAP) and liver stiffness measurement (LSM) in the NHANES population for steatosis and fibrosis, respectively. LC were adjusted for age and ethnicity. Regression analysis and margins were used for summary estimation. **Results:** Figure illustrates 8 classes identified by the best-fitted model. There were three dominant classes representing 87.2% and 87.8% of males (classes 1, 2, and 5) and females (classes 2, 3, and 4), respectively, in the BHS and four dominant classes representing 93.5% of females (classes 1, 2, 7, and 8) and 89.5% of males (classes 1, 5, 6, and 7) in the NHANES population. The characteristics of classes were not necessarily comparable between sexes or databases. In general, central obesity, diabetes, hypertension, and insulin resistance were associated with hepatic steatosis and fibrosis. In other classes, the interaction of comorbidities is more complex, and one may predominate over others, i.e., hypertriglyceridemia and/or low HDL-cholesterol. **Conclusion:** Our results demonstrate that there may be sex differences in patients with MASLD which can be analyzed by structural equation modelling. Knowledge of these associations between sex, risk factors, and associated comorbidity with MASLD may allow precision medicine to target specific groups to improve health, prevent disease, and reduce morbidity and mortality.

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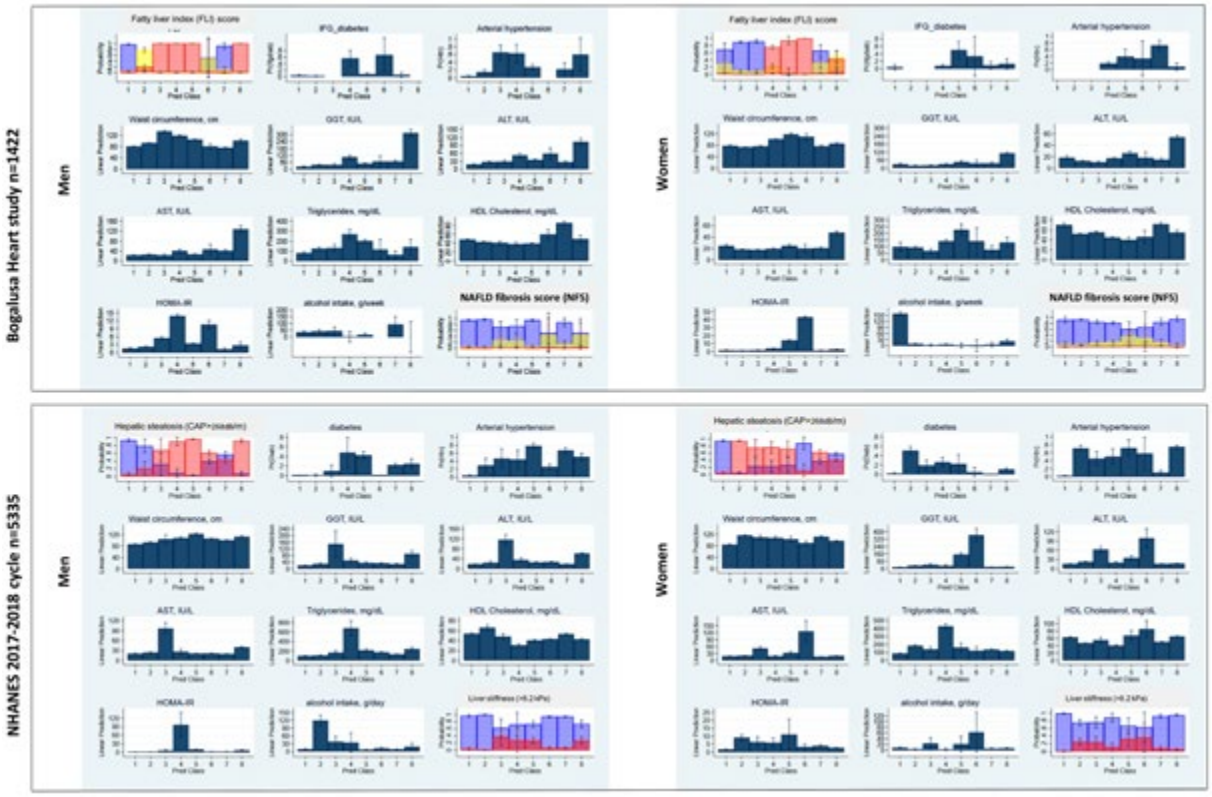

Disclosures: Carlos Pirola: Nothing to Disclose, Silvia Sookoian: Nothing to Disclose

2291 | CLINICAL OUTCOMES OF STEATOTIC LIVER DISEASE IN JAPAN

Tomomi Kogiso[1] *Yuri Ogasawara*[1] *Makiko Taniai*[1] *Yousuke Nakai*[2]

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Background: In recent years, fatty liver disease (SLD) has been categorized into groups based on heart disease risk factors and alcohol consumption. However, many uncertainties remain regarding the clinical course. This study aims to assess the clinical courses of SLD by dividing them into metabolic dysfunction-associated steatotic liver disease (MASLD), MASLD and increased alcohol intake (MetALD), and alcohol-associated liver disease (ALD) groups. **Methods:** We included 1,160 cases of SLD diagnosed clinically and pathologically at our hospital from 1989 to 2021 with a follow-up of more than half a year (803 cases of MASLD, 81 cases of MetALD, 266 cases of ALD). Using the Kaplan-Meier method, we compared survival rates, hepatocellular carcinoma (HCC) incidence, cardiovascular events (CVD), and extrahepatic malignant tumor incidence by fibrosis in a retrospective cohort. **Results:** The median age of diagnosis for MASLD/MetALD/ALD was 53/65/62 years, respectively. The proportion of males was 49.3%/83.7%/86.8%, with complications including type 2 diabetes (41.6%/49.4%/47.0%), hypertension (43.3%/58.0%/40.2%), dyslipidemia (57.0%/34.6%/21.8%), and advanced fibrosis of F3 or higher (31.7%/57.7%/82.5%). In mild fibrosis cases below F3 (532/30/44 cases), the 5-year survival rate was 100.0%/74.0%/79.9%, with a 5-year incidence rate of new HCC and malignant tumors other than liver cancer at 0.2%/0.0%/0.0%. CVD incidence was 3.3%/18.3%/11.0% (p=0.03), and CVD incidence was 1.8%/14.4%/5.3%. In severe fibrosis cases (247/41/208 cases), the survival rate was 100.0%/66.5%/67.8%, with new HCC incidence at 6.9%/15.7%/19.9%, malignant tumor incidence at 4.1%/23.0%/9.8%, and CVD incidence at 2.9%/0.0%/8.5% (Log-rank test, other p<0.01). When matched for age, there was no significant difference in CVD among patients younger than 60 years, but the incidence of other complications was significantly higher in patients with MetALD/ALD. **Conclusion:** The survival rate of MetALD was worse than that of MASLD. The incidence of complications was high in both mild and severe liver fibrosis, with a clinical picture similar to that of ALD.

Disclosures: Tomomi Kogiso: Nothing to Disclose, Yuri Ogasawara: Nothing to Disclose, Makiko Taniai: Nothing to Disclose, Yousuke Nakai: Nothing to Disclose

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2292 | GENDER DISPARITIES IN METABOLIC DYSFUNCTION ASSOCIATED STEATOTIC LIVER DISEASE: TRANSCRIPTOMIC RESULTS FROM THE BARIA LONGITUDINAL COHORT STUDY

Mijra Koning[1] Nordin Hanssen[1] Joanne Verheij[1] Michael Doukas[2] Arnold van de Laar[3] Sjoerd Bruin[3] Hilde Herrema[1] Victor Gerdes[1] Abraham Meijnikman[1] Max Nieuwdorp[1]

[1]Amsterdam University Medical Center, [2]Erasmus Medical Center, [3]Spaarne gasthuis

Background: Metabolic dysfunction associated steatotic liver disease (MASLD), is the leading cause of chronic liver disease worldwide. MASLD can lead to end-stage liver disease as well as to an increased risk of cardiovascular diseases. This underscores the high need to unravel its pathophysiology and the risks associated with this condition. Longitudinal studies indicate large sex disparities between women and men with MASLD. Women have a lower risk of developing MASLD but once the disease is established, women have a higher risk of disease progression and worse outcome. Also there are differences in adipose tissue and fat distribution between women and men. The aim of this study was to identify differences between women and men with MASLD in Functional pathways using RNA sequencing data of liver, visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) obtained during bariatric surgery. **Methods:** Participants of the BARIA study (n=318,76,4% women; median BMI 38kg/m2 and 25.8% diabetes) were analyzed for this study. Biopsies from liver, VAT and SAT were collected at the time of the bariatric surgery. Total RNA was isolated followed by RNA sequencing. Differential gene expression analysis was determined using Deseq in tissues from women and men with and without MASLD. **Results:** Of the 318 participants included, A total of 58.7% had MASLD (M/F=58/132). The median age was 49 (IQR,41-55) years for women and 51 (IQR,45-57.25) years for men. MASH was found in 24.2% of the women compared to 25.9% of men(p=0.956). Additionally, 25.8% of women with MASLD had T2DM compared to 43.1% of men (p=0.027). We found 670 differentially expressed genes (DEG's) with a p-adjusted value < 0.05 in the liver when comparing women with men with MASLD. For SAT and VAT, this was 2571 and 821, respectively. Comparing women and men with MASH, liver, VAT and SAT comprised 108, 204 and 146 DEGs, respectively. Functional analyses using KEGG pathway enrichment revealed that, when compared to men, in women the liver had amongst others an upregulation of the immune response and MAPK signaling, P13K-AKt signaling and TNF signaling pathway. In VAT there was an upregulation of fatty acid metabolism and in SAT we found an upregulation of the immune response-regulation signaling pathway. **Conclusion:** Women with MASLD tend to have upregulated pathways involved in immune signaling whereas men with MASLD had upregulated pathways involved in oxidative phosphorylation and ATP synthesis and processing. In line, we observed significantly elevated CRP levels in women compared to men with MASLD, while a higher diabetes prevalence was observed in men (43.1%). This suggests that disease pathways are different in men and women, calling for a sex specific approach in MASLD.
Disclosures: Mijra Koning: Nothing to Disclose, Nordin Hanssen: Nothing to Disclose, Joanne Verheij: Nothing to Disclose, Michael Doukas: Nothing to Disclose, Arnold van de Laar: Nothing to Disclose, Sjoerd Bruin: Nothing to Disclose, Hilde Herrema: Nothing to Disclose, Victor Gerdes: Nothing to Disclose, Abraham Meijnikman: Nothing to Disclose, Max Nieuwdorp: caelus health: Stock – privately held company, advanced microbiome interventions: Stock – privately held company

2293 | INCIDENCE OF MAJOR ADVERSE CARDIOVASCULAR EVENTS AND MAJOR ADVERSE LIVER OUTCOMES ACROSS THE SPECTRUM OF STEATOTIC LIVER DISEASE: A NATIONAL COHORT STUDY ◆

Pedro Ochoa-Allemant[1] Rebecca Hubbard[1] David Kaplan[1] Marina Serper[1]

[1]University of Pennsylvania

Background: Steatotic liver disease (SLD) encompasses a heterogeneous group of phenotypes, with metabolic dysfunction and harmful alcohol use increasing the risk of adverse long-term outcomes. However, incidence rates of major adverse cardiovascular events (MACE) and major adverse liver outcomes (MALO) in population-based cohorts are not well characterized. **Methods:** We conducted a retrospective cohort study of patients aged 18 years or older with hepatic steatosis identified using natural language processing receiving care from the Veterans Health Administration between fiscal years 2010 and 2021. The exposure was SLD subtype

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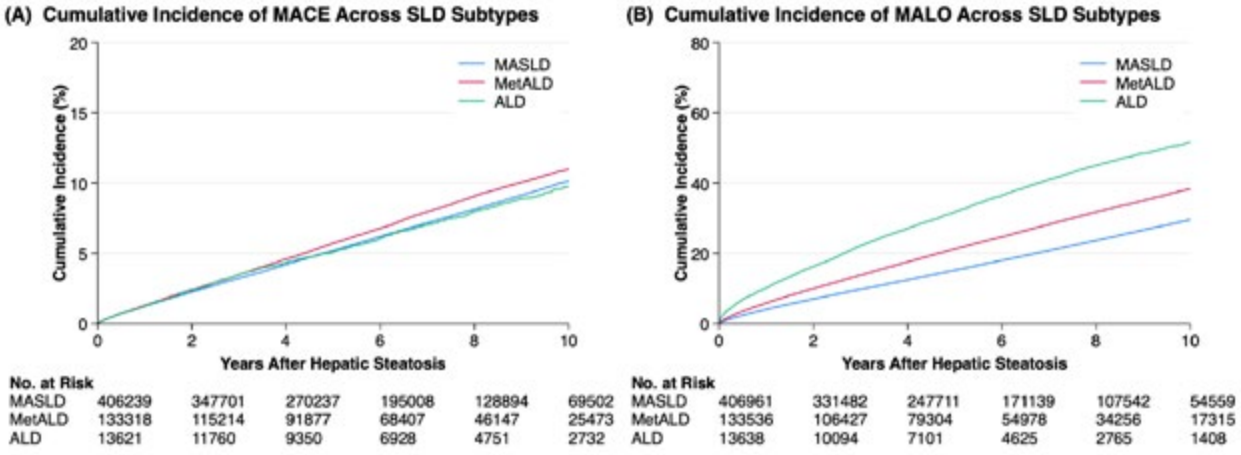
(metabolic dysfunction-associated steatotic liver disease [MASLD], metabolic and alcohol-associated liver disease [MetALD], alcohol-associated liver disease [ALD]) determined using a combination of cardiometabolic risk factors, alcohol use disorder diagnosis codes, and alcohol use disorders identification test-consumption (AUDIT-C) scores. The primary outcomes were the incidence of MACE (acute myocardial infarction, stroke, heart failure, or cardiovascular mortality) and MALO (cirrhosis, hepatic decompensation, hepatocellular carcinoma, liver transplantation, or all-cause mortality). We estimated cumulative incidence using Kaplan-Meier methods and hazard ratios (HR) using Cox regression models. Models were adjusted for age, sex, race/ethnicity, advanced fibrosis (FIB-4 score > 2.67), and index year. **Results:** Among 554,135 patients with SLD (MASLD 73.4%, MetALD 24.1%, ALD 2.5%), the median age was 60 years (interquartile range [IQR], 57-67 years), 7.9% were female, and 66.9% were non-Hispanic White. The overall median follow-up was 6.2 years (IQR, 3.5-9.3 years). The 10-year cumulative incidence of MACE was 10.3%, 11.2%, and 9.9% for MASLD, MetALD, and ALD, respectively. The 10-year cumulative incidence of MALO was 9.4%, 16.1%, and 23.1% for MASLD, MetALD, and ALD, respectively. Compared to those with MASLD, the risk of MACE was significantly higher among patients with MetALD (adjusted HR [aHR], 1.08; 95% confidence interval [CI], 1.06-1.11), but not among patients with ALD (aHR, 0.96; 95% CI, 0.90-1.03). The risk of MALO was significantly higher among patients with MetALD (aHR, 1.27; 95% CI, 1.25-1.28) and ALD (aHR, 1.66; 95% CI, 1.61-1.71) compared to those with MASLD. **Conclusion:** The incidence of MACE was higher among patients with MetALD compared to those with MASLD, whereas the incidence of MALO progressively increased from MASLD, through MetALD, to ALD.



Disclosures: Pedro Ochoa-Allemant: Nothing to Disclose, Rebecca Hubbard: Nothing to Disclose, David Kaplan: Independent Contractor relationship with Roche Genentech; Has not ended; Grant/Research Support relationship with AstraZeneca Inc; Has not ended; Advisor relationship with AstraZeneca; Has ended; Advisor relationship with Exelixis; Has ended; Grant/Research Support relationship with Gilead; Has not ended; Advisor relationship with Sirtex; Has ended; Grant/Research Support relationship with Exact Sciences; Has not ended; Grant/Research Support relationship with Glycotest; Has ended, Marina Serper: Grant/Research Support relationship with Grifols; Has not ended; Grant/Research Support relationship with Eurofins; Has not ended; Grant/Research Support relationship with Transplant Genomics; Has not ended

2294 | ANALYSIS OF THE DISTRIBUTION AND SEVERITY OF LIVER FIBROSIS STAGES AMONG THE LOCAL POPULATION WITHIN THE RIO GRANDE VALLEY: IDENTIFICATION OF RISK FACTORS AND ACCURACY OF NON-INVASIVE DIAGNOSTIC TOOLS

Dimple Desai *Rashmee Patil*[1]

[1]*South Texas Research Institute*

Background: In the Rio Grande Valley of South Texas, a region with a high prevalence of metabolic disorders such as diabetes, obesity, and hypertension, liver fibrosis presents as a significant health challenge in the Hispanic population. This study examines the distribution and severity of liver fibrosis stages among the Hispanic population and assesses the accuracy of various non-invasive diagnostic tools. The aim is to evaluate the

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utility of non-invasive biomarkers—FIB-4, ELF, FAST, and VCTE (Fibroscan)—in predicting liver fibrosis stages and their potential association with common comorbid conditions. **Methods:** Data were collected from 283 participants who underwent liver disease severity screening for potential inclusion into a clinical trial, focusing on demographics, liver biopsy results, and various fibrosis markers. Statistical analyses were conducted to explore correlations between fibrosis stages and metabolic conditions and to assess the predictive value of non-invasive biomarkers, with special attention paid to the cohort of moderate to advanced fibrosis patients (F2-F3). **Results:** The prevalence of diabetes (50.9%), obesity (89.7%), and hypertension (56.5%) was notably high in this enriched population. Liver fibrosis stages showed a significant correlation with metabolic syndrome components, and moderate to advanced fibrosis stages compared to no or mild fibrosis were correlated with higher rates of diabetes and hypertension. Non-invasive biomarkers varied in effectiveness; the FAST score and FIB-4 index demonstrated significant predictive value for differentiating fibrosis stages however several patients with F2-F3 disease presented with FIB-4 < 1.3. Similarly, the majority of patients with F2-F3 disease had FAST >0.5 but < 0.67. ELF and Fibroscan showed less discriminative power between fibrosis stages suggesting that subjects with ELF > 9.8 and elasticity > 12 kPa may not be the cut-off that is needed to identify patients with at-risk MASH in our specific demographic. **Conclusion:** The high prevalence of obesity and metabolic comorbidities in the Hispanic population of the Rio Grande Valley significantly contributes to liver disease severity – the more metabolic syndrome criteria a patient has, the more likely they are to have moderate-to-advanced fibrosis, with diabetes and hypertension being most associated. Non-invasive biomarkers, particularly FAST and FIB-4, are more effective than ELF and Fibroscan in staging liver fibrosis in our Hispanic patient cohort. More data needs to be collected around performance of biomarkers in diagnosing at-risk MASH in specific patient populations, as the disease is heterogeneous and biomarkers behave differently in different cohorts. These biomarkers provide critical insights for tailored interventions for developing culturally appropriate health initiatives and improving the liver health of Hispanics in this region.

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2295 | THE EFFECT OF DIET COMPOSITION EXPOSOME ON THE NATURAL HISTORY OF METABOLIC-ASSOCIATED STEATOTIC LIVER DISEASE IN THE MILLION VETERAN PROGRAM COHORT ◆

Lauren Callans[1] David Kaplan[2] Kerry Ivey[3] Kyong-Mi Chang[4]

[1]Perelman School of Medicine, University of Pennsylvania, [2]Perelman School of Medicine, [3]Harvard Medical School, [4]Corporal Michael J. Crescenz VA Medical

Background: Metabolic-associated steatotic liver disease (MASLD) is closely linked to risk factors including obesity, metabolic syndrome, and type 2 diabetes mellitus. Animal studies have associated a fructose-rich diet to development of fatty liver, but human data remain sparse. We aimed to identify specific dietary components that might be associated with fibrosis progression and liver outcomes in MASLD in a well-characterized human cohort. **Methods:** We used a cohort of patients with MASLD, identified by previously validated criteria, from the Veterans Affairs Million Veteran Program of whom a subset completed a detailed lifestyle including the Food Frequency Questionnaire (FFQ). The primary outcome of interest was fibrosis progression using the recently validated Fibrosis-4 (FIB4) slope (rate of change of FIB4/year); secondary outcome was time to cirrhosis by ICD code. Key baseline covariates included: race/ethnicity, body mass index (BMI) class, metabolic syndrome criteria, diabetes mellitus, AUDIT-C score, liver-related laboratory tests (total bilirubin, AST, alkaline phosphatase), and baseline FIB4 score. The dataset was split into 70% training and 30% validation sets. Using bootstrapped Ridge and Elastic Net regression in R, scaled nutrient variables of interest associated with the outcome were identified. Training-identified variables were then validated using multivariable GLM and Cox models including key clinical covariates with significance corrected by the Benjamini-Hochberg method. **Results:** 84,024 individuals with

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MASLD with nutritional data were available. 90% of participants were male, and 80% were white. Median age at MASLD diagnosis was 56 years (IQR 49-63). After selection by Elastic net models and validation, iron from non-heme sources (β = 0.00176/sd, SE = 0.00056), B vitamin (β = 0.0013/sd, SE = 0.00055), gluten (β = 0.0012/sd, SE = 0.00055), caffeine (β = 0.00166/sd, SE = 0.00055) and acrylamide (β = -0.0017/sd, SE = 0.00056) intake were all significantly associated with FIB4 slope (p <0.05) after adjustment for key covariates. Iron from non-heme sources (HR 1.1 [1.02-1.16]) and caffeine (HR 0.88 [0.81-0.96]) were also significantly associated with time to cirrhosis. **Conclusion:** These data suggests that dietary factors including iron intake from non-heme sources, vitamin B, and gluten might play a role in progression of MASLD, while caffeine, and acrylamide might play a protective role.

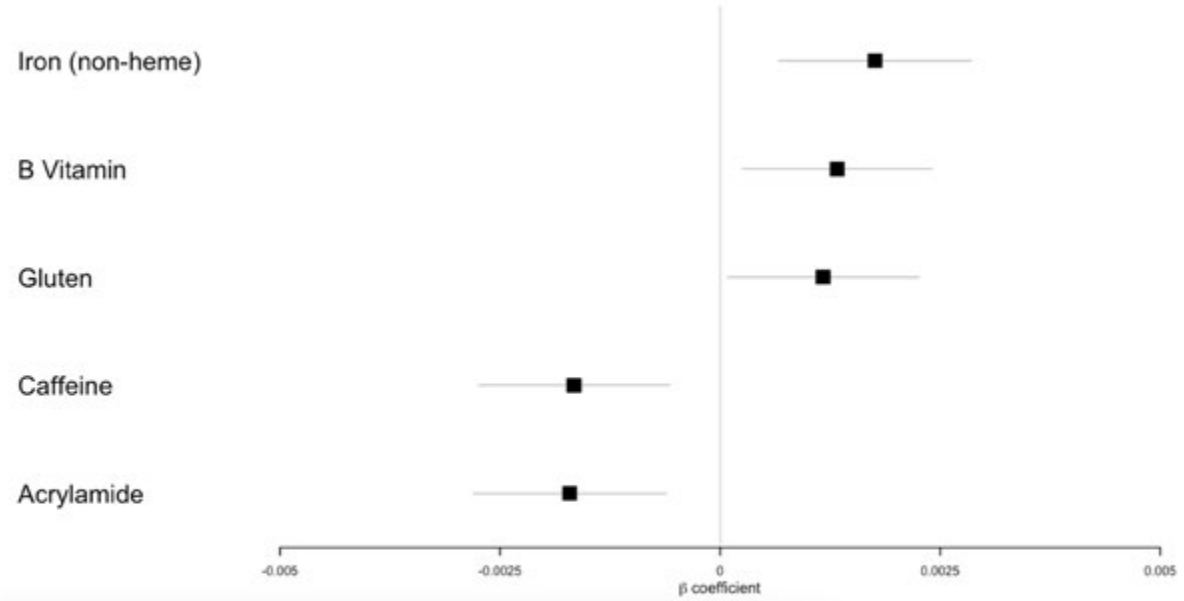

Figure 1. Forest plot of validated nutrients identified by elastic net regression at alpha = 0.05 associated with fibrosis progression

Disclosures: Lauren Callans: Nothing to Disclose, David Kaplan: Independent Contractor relationship with Roche Genentech; Has not ended; Grant/Research Support relationship with AstraZeneca Inc; Has not ended; Advisor relationship with AstraZeneca; Has ended; Advisor relationship with Exelixis; Has ended; Grant/Research Support relationship with Gilead; Has not ended; Advisor relationship with Sirtex; Has ended; Grant/Research Support relationship with Exact Sciences; Has not ended; Grant/Research Support relationship with Glycotest; Has ended, Kerry Ivey: Nothing to Disclose, Kyong-Mi Chang: Data Monitoring Committee member relationship with Virion Therapeutics; Has not ended; Advisor relationship with GSK; Has ended

2296 | METABOLIC-ASSOCIATED STEATOTIC LIVER DISEASE IN RELATION TO FOOD BEHAVIORS IN THE MILLION VETERAN PROGRAM COHORT: EAT YOUR BROCCOLI

Lauren Callans[1] David Kaplan[2] Kerry Ivey[3] Kyong-Mi Chang[4]

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Background: Metabolic-associated steatotic liver disease (MASLD) is associated with risk factors that are closely linked with lifestyle and food-related behaviors including obesity, metabolic syndrome, and type 2 diabetes mellitus. We aimed to identify specific lifestyle behaviors that might be associated with fibrosis progression in MASLD, specifically examining food behaviors related to MASLD risk factors such as frequency of sugar intake. **Methods:** We utilized a cohort of patients with MASLD, identified by validated criteria, with available Lifestyle Questionnaires from the Veterans Affairs Million Veteran Program (MVP). Follow-up time began at the identification of MASLD. The outcome of interest was fibrosis progression using Fibrosis-4 (FIB4) slope (rate of

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change of FIB4/year). Key baseline covariates collected included: race/ethnicity, body mass index (BMI) class, metabolic syndrome criteria, diabetes mellitus, AUDIT-C score, liver-related laboratory tests (total bilirubin, AST, alkaline phosphatase), and baseline FIB4 score. The dataset was split into 70% training and 30% validation sets. Using bootstrapped Ridge and Elastic Net regression in R, lifestyle variables of interest were identified in the training set using FIB4 slope as the dependent variable. Training-identified variables were then validated using multivariable GLM and Cox models adjusting for key clinical variables with Benjamini-Hochberg significance correction. **Results:** The cohort included 84,024 individuals with MASLD and available lifestyle questionnaires. 90% of participants were male, and 80% were white. Median age at time of entry into the cohort was 56 years (IQR 49-63). Specific food frequency behaviors including intake of cookies (4-5/day, β = 0.0642, SE = 0.0110), potatoes (2-3 cups/day, β = 0.0485, S = 0.0124), eggs (2-3/day, β = 0.0127, SE = 0.00361), hamburger (4-5 patties/day, β = 0.156, SE = 0.0381), and liver consumption (3-4 oz/day, β = 0.108, SE = 0.0322) were associated with greater fibrosis progression (all adjusted p<0.05). By contrast, modest butter use (pat/week, β = -0.00609, SE = 0.00186), and broccoli intake (light: 1-3 ½ cups/month, β = -0.00540, SE = 0.00149; moderate broccoli 2-4 ½ cups/week, β = -0.00752, SE = 0.00171) were associated with a protective effect on fibrosis progression (p<0.05). **Conclusion:** These data suggests that food behaviors such as daily cookie, potato, egg, hamburger, and liver intake may be associated with fibrosis progression in MASLD, while occasional butter and light to moderate broccoli intake might be protective.

Table 1. Validated food frequency and lifestyle behaviors identified by elastic net regression at alpha = 0 associated with fibrosis progression

Survey Question		β	SE	p (unadj.)	p (BH adj.)
Cookies (1)					
	Never or less than once a month	REF			
	4-5 per day	0.0642	0.01095	4.46E-09	3.01E-07
Potatoes, baked, boiled (1) or mashed (1 cup)					
	Never or less than once a month	REF			
	2-3 per day	0.0485	0.0124	0.0000918	0.00436
Eggs (1)					
	Never or less than once a month	REF			
	2-3 per day	0.0127	0.00361	0.000455	0.0172
Hamburger (1 patty)					
	Never or less than once a month	REF			
	4-5 per day	0.156	0.0381	0.0000442	0.00236
Liver (3-4 oz)					
	Never or less than once a month	REF			
	Once a day	0.108	0.0322	0.000788	0.0259
Butter (pat) added to food or bread					
	Never or less than once a month	REF			
	Once a week	-0.00609	0.00186	0.00107	0.0327
Broccoli (1/2 cup)					
	Never or less than once a month	REF			
	1-3 per month	-0.00540	0.00149	0.000298	0.0121
	2-3 per week	-0.00752	0.00171	0.0000105	0.000583

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Disclosures: Lauren Callans: Nothing to Disclose, David Kaplan: Independent Contractor relationship with Roche Genentech; Has not ended; Grant/Research Support relationship with AstraZeneca Inc; Has not ended; Advisor relationship with AstraZeneca; Has ended; Advisor relationship with Exelixis; Has ended; Grant/Research Support relationship with Gilead; Has not ended; Advisor relationship with Sirtex; Has ended; Grant/Research Support relationship with Exact Sciences; Has not ended; Grant/Research Support relationship with Glycotest; Has ended, Kerry Ivey: Nothing to Disclose, Kyong-Mi Chang: Data Monitoring Committee member relationship with Virion Therapeutics; Has not ended; Advisor relationship with GSK; Has ended

2297 | LIFESTYLE HABITS SIGNIFICANTLY MITIGATE MASLD RISK: RESULTS FROM A PROSPECTIVE MULTI-CENTER STUDY

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Background: The development of metabolic dysfunction-associated steatotic liver disease (MASLD) is closely linked to lifestyle. However, the combined role of lifestyle habits in predicting MASLD risk is not fully assessed. Therefore, we aimed to investigate the association of Mediterranean diet adherence score (MEDAS), physical activity level (PAL), alcohol consumption, smoking and a history of dietitian follow-up with the odds of MASLD in a cohort of adults with multiple metabolic disorders. **Methods:** We recruited 968 subjects in 2 sites presented at least with one component of the MASLD adult criteria. Anthropometrical assessment and blood tests were performed in a standardized research visit. Individuals with excess alcohol intake (>20 g/day, women and >30 g/day, men) were excluded. Controlled attenuation parameter (CAP), and liver stiffness measurements (LSM) were assessed by vibration controlled transient elastography (VCTE). MASLD was defined as CAP≥248 db/M. Fibrosis was defined as LSM ≥7.2 kPa in XL probe and ≥7.9 kPa in M probe. Multivariable logistic regression models were used to investigate the association of MASLD and fibrosis with MEDAS, PAL, dietitian consultation history, alcohol consumption, and smoking. Models were initially controlled for age, sex, education, marital status, and income level, and then for the presence of obesity, diabetes, hypertension, and dyslipidemia. **Results:** Mean MEDAS and PAL was 6.34 ± 2.08 and 903.83 ± 975.39, respectively. In a crude model, MEDAS (OR=0.87, 95% CI 0.81-0.93, P<.001), moderate PAL (OR=0.37, 95% CI 0.27–0.51, P<.001), high PAL (OR=0.11, 95% CI 0.06–0.22, P<.001), and a history of dietitian consultation (OR=0.67, 95% CI 0.49–0.91, P=0.011) were inversely associated with MASLD. After adjusting for age, sex, marital status, education, and income, MEDAS (OR=0.87, 95% CI 0.81–0.94, P<.001), moderate PAL (0.36, 95% CI 0.26–0.51, P<.001), high PAL (0.11, 95% CI 0.05–0.21, P<.001), history of dietitian consultation (OR=0.59, 95% CI 0.43–0.81, P=0.001) was still associated with lower odds of MASLD. After further adjustment for obesity, diabetes, hypertension, dyslipidemia, the inverse association has remained significant for all (MEDAS, OR=0.85, 95% CI 0.78–0.93, P<.001; moderate PAL, OR=0.48, 95% CI 0.33–0.70; P<.001, high PAL, OR=0.14, 95% CI 0.06–0.31; P<.001, history of dietitian consultation (OR=0.66, 95% CI 0.46–0.94, P=0.021). Only moderate PAL was associated with lower odds of fibrosis (OR=0.35, 95% CI 0.21–0.57, P<.001) in a crude model, which remained significant after initial (OR=0.35, 95% CI 0.28–0.82, P=0.007) and further adjustments (OR=0.48, 95% CI 0.28–0.82, P=0.007). **Conclusion:** Our findings suggest a strong protective role of maintaining adequate physical activity, dietitian follow-up, and adhering to a Mediterranean dietary pattern in MASLD. Further studies investigating the impact of lifestyle in liver-related outcomes are warranted.

Disclosures: Gediz Dogay Us: Nothing to Disclose, Ger Koek: Nothing to Disclose

2298 | RISK DIFFERENCE FOR LONG-TERM CLINICAL OUTCOMES IN STEATOTIC LIVER DISEASE (MASLD, METALD AND ALD)

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Background: The multi-society consensus group proposed a new nomenclature for steatotic liver disease (SLD) including metabolic-dysfunction associated steatotic liver disease (MASLD), MASLD and increased alcohol

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intake (MetALD), and alcohol-associated liver disease (ALD). However, the risk of liver-related, major adverse cardiovascular events (MACE) and all-cause mortality among various sub-groups in SLD is unknown. In this nationwide, population-based cohort study, we investigated the risk of liver-related events, MACE, and death among these patients. **Methods:** We conducted a nationwide, population-based study using a large claims database and enrolled 761,400 patients diagnosed with MASLD, MetALD, or ALD. The *primary endpoint* was the occurrence of liver-related events, MACE, and death in patients with MASLD, MetALD, and ALD, respectively. **Results:** This study included 620,832 patients with MASLD, 108,494 patients with MetALD, and 32,074 patients with ALD. The median follow-up periods (IQR) were 4.3 (2.8–4.9) years. During the follow-up period, a total of 419 patients (0.1%), 5791 patients (0.8%), and 1408 patients (0.2%) experienced liver-related events, MACE or died. The 5-year cumulative incidence of liver-related events in MASLD, MetALD, and ALD was 0.06%, 0.12%, and 0.27%, respectively. Similarly, the 5-year cumulative incidence of death in MASLD, MetALD, and ALD was 0.03%, 0.35%, and 0.52%, respectively. The cumulative incidence of liver-related events and death were highest in ALD, followed by MetALD, and MASLD ($p < 0.001$ for both liver-related events and death). Contrary, the 5-year cumulative incidence of MACE in MASLD, MetALD, and ALD was 1.1%, 0.9%, and 0.7%, respectively, and the incidence of MACE was highest in MASLD, followed by MetALD, and ALD ($p < 0.001$). Using MASLD as the reference and adjusting for age, gender, smoking, diabetes mellitus, dyslipidemia, and hypertension, the adjusted hazard ratio (95% confidence interval) for liver-related events, MACE, and prognosis in MetALD were 1.42 (1.1–1.8), 0.68 (0.63–0.73), and 1.13 (0.98–1.3), respectively. Similarly, the ratios in ALD for liver-related events, MACE, and prognosis were 3.42 (2.6–4.6), 0.58 (0.49–0.67), and 1.60 (1.3–2.0), respectively. **Conclusion:** The new consensus nomenclature can be used to stratify the risk of complications and prognosis. The nomenclature is beneficial for risk stratification and identifying new mechanisms for disease-specific therapeutic implications.

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2299 | EVOLUTION OF MASLD/MASH PATIENT EXPERIENCES: INSIGHTS FROM 'THE STATE OF STEATOTIC (FATTY) LIVER CARE IN AMERICA' SURVEYS 2022-2024

Neeraj Mistry[1] Tiffany Mensah[1] Surya Gollapudi[1] Tarek Hassanein[2] Henry Chang[1] Wayne Eskridge[1]

[1]Fatty Liver Foundation, [2]Southern California Liver Centers, Inc.

Background: This study examines the evolving experiences of patients with steatotic liver disease (SLD) using data from the 'State of Steatotic (Fatty) Liver Care in America' surveys (2022-2024). Understanding these experiences helps identify care needs and gaps to inform effective interventions and policies. **Methods:** Data from the 2022-2024 surveys were analyzed to identify trends. Surveys included adults diagnosed with SLD, available in English and Spanish, covering 49 items on diagnosis, staging, management, physical impact, psycho-social and environmental impact, and current health. Items were finalized with input from the patient community and the FLF Medical Advisory Group. Due to SLD's nomenclature change in 2023, a question on steatosis etiology was added in 2024. The survey was distributed via social media, web forums, email, and community organizations. **Results:** Primary care was the most common diagnosis entry point each year, with respondents often reporting insufficient information at diagnosis. There was a decrease in respondents not referred to specialists and an increase in those who felt they understood their condition better after specialist visits. More respondents in 2023 reported visiting a specialist within six months of diagnosis compared to 2022. Care teams mainly consisted of PCPs, hepatologists, and gastroenterologists. Less than 10% of respondents in 2023 and preliminary 2024 data were enrolled in clinical trials.Living arrangements shifted in 2023, with fewer respondents living alone and more with a spouse or partner, though this reversed in 2024. Most respondents managed their own needs, with spouses or partners increasingly seen as crucial support from 2022 to 2023. Anxiety, depression, and irritability were frequently reported across all years. Mental health professionals in care teams decreased from 2022 to 2023. Health insecurity was the most common social issue between 2023 and 2024, followed by financial concerns and loneliness. **Conclusion:** Enhancing CME for PCPs and maintaining it for hepatologists and gastroenterologists is crucial, especially with the approval of new therapies for MASH. Resources for home-based care and spousal caretakers are needed. Interventions to improve health service accessibility, mental health support, and reduce loneliness are essential.

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Disclosures: Neeraj Mistry: Nothing to Disclose, Tiffany Mensah: Madrigal Pharmaceuticals: Consultant, Surya Gollapudi: Nothing to Disclose, Tarek Hassanein: Nothing to Disclose, Henry Chang: Nothing to Disclose, Wayne Eskridge: Nothing to Disclose

2300 | ASSOCIATIONS BETWEEN METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE AND ABDOMINAL PAIN: A SINGLE-CENTER RETROSPECTIVE STUDY

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[1]*UT-Southwestern,* [2]*Massachusetts General Hospital*

Background: Background: Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) affects an estimated 1.7 billion persons globally. While most patients are asymptomatic at the time of diagnosis, prior data suggests that 10-35% of patients with MASLD present with abdominal pain. Despite this known association, factors associated with MASLD and abdominal pain have yet to be fully characterized. In our study, we aimed to more closely examine a variety of clinical elements to try to better understand the relationship between MASLD and abdominal pain. **Methods:** We conducted a single-center, retrospective study of 378 initial visits for patients diagnosed with MASLD from November 2022 to October 2023. Basic demographics data and relevant clinical information including metabolic syndrome-related risk factors, laboratory data, and patient reported symptoms were collected and analyzed according to presence or absence of abdominal pain. Factors identified with a p-value ≤ 0.10 on bivariate analysis were then included in logistic regression analysis to assess potential predictors of abdominal pain in patients with MASLD. **Results:** At the time of initial visit, 16% of patients endorsed abdominal pain; of these patients, 72% were female ($p = 0.03$). There were no other significant demographic differences. Only 2.4% of patients had a prior diagnosis of a Disorder of Gut-Brain Interaction (DGBI). Other statistically significant factors included a pre-existing diagnosis of a DGBI ($p < 0.01$), higher HDL ($p = 0.07$), prior cholecystectomy ($p < 0.01$), and statin use ($p = 0.03$). Only prior diagnosis of DGBI was found to be a significant predictor of symptoms (OR: 6.7; $p = 0.04$), with prior cholecystectomy trending toward significance (OR: 2.03; $p = 0.09$). **Conclusion:** Discussion: Our findings are consistent with the rates of abdominal pain in MASLD suggested in prior data. Prior studies estimate DGBI prevalence to be over 40% in the general population; the low prevalence of DGBI diagnoses in our cohort is suggestive of underdiagnosis of functional gastrointestinal disorders within the MASLD population. Abdominal pain in patients with chronic liver disease is often attributed to a variety of causes such as hepatomegaly or capsular stretch, though such associations have not been rigorously studied and may represent a mischaracterization of these symptoms. Our study highlights the need for further studies to better understand the features of abdominal pain in MASLD and explore associations with various risk factors and overlap with other conditions (e.g., DGBIs).

Disclosures: George Waldenmaier: Nothing to Disclose, Indira Bhavsar-Burke: Nothing to Disclose, Maddie Kubiliun: Nothing to Disclose

2301 | SYNERGISTIC IMPACT OF LOW BODY MASS INDEX AND METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE ON INCIDENT ALZHEIMER'S DISEASE RISK: A NATIONWIDE COHORT STUDY

Tae Seop Lim[1] *Seok Jong Chung*[1] *JA-KYUNG KIM*[1] *Jinkwon Kim*[1]

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Background: The relationship between metabolic dysfunction-associated steatotic liver disease (MASLD) and Alzheimer's disease (AD) risk is controversial, possibly due to varying effects of MASLD subtypes based on body mass index (BMI). We investigated how MASLD and BMI together influence the incidence of Alzheimer's disease in South Korea's general population. **Methods:** Utilizing data from the "National Screening Program for Transitional Ages" conducted for 66-year-old Koreans in 2010 and 2011, we constructed a cohort with dementia-free participants. MASLD was defined as a fatty liver index (FLI) ≥ 30 along with at least one metabolic abnormality, while overweight and lean were defined as BMI ≥ 23 kg/m² and BMI < 23 kg/m², respectively. Participants were categorized into overweight non-MASLD, overweight MASLD, lean non-MASLD, and lean MASLD. Primary outcome, the development of incident AD, was assessed through national health claims data.

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Results: This cohort included 376,902 dementia-free participants with 66-years-old at baseline. The number of overweight non-MASLD, overweight MASLD, lean non-MASLD, lean MASLD was 114,528 (30.4%), 139,551 (37.0%), 126,692 (29.9%), and 10,131 (2.7%), respectively. During an average follow-up period of 10.38 ± 1.90 years, 23,874 (6.3%) individuals were newly diagnosed with AD. Compared to the overweight non-MASLD (reference), the adjusted hazard ratios [95% confidence interval] for AD were as follows: lean MASLD, 1.42 [1.32–1.54]; lean non-MASLD, 1.18 [1.14–1.22]; obese MASLD, 1.08 [1.04–1.11]. **Conclusion:** The results of this study indicate that low BMI and MASLD synergistically increase the risk of AD. Further prospective studies are required to evaluate the complex interactions between body composition, metabolic health, and neurodegenerative disease risk, which might inform more effective interventions and preventive strategies in public health.

Disclosures: Tae Seop Lim: Nothing to Disclose, Seok Jong Chung: Nothing to Disclose, JA-KYUNG KIM: Nothing to Disclose, Jinkwon Kim: Nothing to Disclose

2302 | EXPLORING PREDICTORS OF RAPID PROGRESSION TO MAJOR ADVERSE LIVER OUTCOMES IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE

Ying Shang[1] Johan Vessby[2] Kamal Mangla[3] Riku Ota[4] Marc Pedersen[4] Mattias Ekstedt[5] Hannes Hagström[1]

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Background: Patients with metabolic dysfunction-associated steatotic liver disease (MASLD) may progress at different rates toward cirrhosis and major adverse liver outcomes (MALO). We aimed to identify factors associated with rapid progression to MALO. **Methods:** We used data from 959 patients in Sweden with biopsy-proven MASLD. Over a median follow-up of 17 years, 103 patients (10.7%) experienced MALO events and 52 (5.4%) had a repeat liver biopsy. Rapid progressors were defined as patients experiencing MALO events earlier than the median time to MALO, stratified by baseline fibrosis stage. MALO events were compensated cirrhosis, decompensated cirrhosis, liver failure, hepatocellular carcinoma, liver transplant, and death due to other liver diseases, identified from national registers and by chart review. Factors associated with rapid progressors were analyzed with Cox regression models. **Results:** For the 103 patients who experienced MALO events, the median times to event, stratified by fibrosis stage, were 20.0 years in F0, 15.1 years in F1, 8.8 years in F2, 5.5 years in F3, and 3.0 years in F4. Compared with non-rapid progressors (n=51), rapid progressors (n=52) were older at baseline (59 vs 55 years, p=0.050), had a higher prevalence of type 2 diabetes (T2D; 50% vs 29%, p=0.033), and had less severe hepatic steatosis (grade 3 steatosis, 15% vs 41%, p=0.034 for overall comparison); no other major differences in patient characteristics were observed. Baseline T2D (hazard ratio [HR]: 3.90, 95% CI 1.15–13.20; p=0.029) was associated with rapid progression, but not when considering the development of T2D over time (HR: 2.52, 95% CI 0.75–8.42; p=0.134) (**Table**). Similar findings were observed in patients with repeat liver biopsies, of whom 24 (46%) progressed by at least one fibrosis stage. **Conclusion:** No strong predictors were identified for rapid progression of fibrosis at the time of MASLD diagnosis, apart from the presence of T2D. Although T2D may affect incidence rates, the association was stronger at baseline, suggesting that duration of T2D may be a stronger predictor of MALO events than the diagnosis itself.

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Table. Factors associated with rapid progression to MALO in patients with MASLD

	Univariate HR (95% CI)	*p*	Adjusted HR[a] (95% CI)	*p*	Adjusted HR[b] (95% CI)	*p*
Histologic features						
Steatosis						
1	3.41 (1.47–7.95)	0.004	6.18 (2.17–17.50)	0.001	5.05 (1.87–13.70)	0.001
2	2.96 (1.25–7.01)	0.013	3.56 (1.26–10.10)	0.016	3.01 (1.12–8.57)	0.030
3	Ref	–	Ref	–	Ref	–
Lobular inflammation						
0	1.25 (0.33–4.63)	0.739	–	–	–	–
1	0.41 (0.18–0.95)	0.036	–	–	–	–
2	0.44 (0.19–1.01)	0.053	–	–	–	–
3	Ref	–	–	–	–	–
Ballooning						
0	1.00 (0.46–2.13)	0.996	–	–	–	–
1	0.57 (0.27–1.96)	0.137	–	–	–	–
2	Ref	–	–	–	–	–
Comorbidity, baseline						
T2D	2.15 (1.23–3.73)	0.007	3.90 (1.15–13.20)	0.029	–	–
Hyperlipidemia	1.61 (0.88–2.90)	0.116	1.20 (0.49–2.90)	0.689	–	–
Hypertension	0.94 (0.49–1.80)	0.863	–	–	–	–
Obesity	1.27 (0.70–2.32)	0.425	–	–	–	–
Comorbidity, as time-varying covariates						
T2D	1.97 (1.14–3.42)	0.016	–	–	2.52 (0.75–8.42)	0.134
Hyperlipidemia	1.80 (1.02–3.16)	0.042	–	–	1.43 (0.61–3.36)	0.412
Hypertension	1.07 (0.48–2.40)	0.857	–	–	–	–
Obesity	1.23 (0.71–2.15)	0.445	–	–	–	–

[a]HR adjusted for age, sex, calendar year of liver biopsy, steatosis grade, alanine aminotransferase level, total cholesterol level, baseline T2D, and baseline hyperlipidemia.
[b]HR adjusted for age, sex, calendar year of liver biopsy, steatosis grade, alanine aminotransferase level, total cholesterol level, time-varying T2D, and time-varying hyperlipidemia.
CI, confidence interval; HR, hazard ratio; MALO, major adverse liver outcomes; MASLD, metabolic dysfunction-associated steatotic liver disease; Ref, reference; T2D, type 2 diabetes.

Disclosures: Ying Shang: Nothing to Disclose, Johan Vessby: Norgine: Speaking and Teaching, Gore: Speaking and Teaching, NovoNordisk: Advisor, Kamal Mangla: Novo Nordisk A/S: has stocks distributed by the company itself to its employee, Novo Nordisk A/S: Employee, Novo Nordisk Service Center India Pvt. Ltd.: Employee, Riku Ota: Novo Nordisk A/S: Employee, Novo Nordisk A/S: Stock - publicly traded company, Marc Pedersen: Novo Nordisk A/S: Employee, Mattias Ekstedt: Nothing to Disclose, Hannes Hagström: Nothing to Disclose

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2303 | NEIGHBORHOOD-LEVEL SOCIAL DETERMINANTS OF HEALTH ARE ASSOCIATED WITH MASLD BURDEN, COMPLICATIONS, AND MORTALITY

Claire Faulkner[1] Majd Aboona[1] Likith Surendra[1] Pooja Rangan[1] Cheng Han Ng[2] Daniel Huang[2] Mark Muthiah[2] Donghee Kim[3] Michael Fallon[1] Mazen Noureddin[4] Vincent Chen[5] Ani Kardashian[6] Karn Wijarnpreecha[1]

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Background: Significant health disparities exist in metabolic dysfunction-associated steatotic liver disease (MASLD), driven by social determinants of health (SDOH). Few studies have explored neighborhood-level SDOH in MASLD. We sought to investigate how neighborhood-level SDOH influence MASLD burden, comorbidities, and mortality. **Methods:** This was a retrospective cohort study of patients with MASLD at a multi-state healthcare institution. Neighborhood SDOH were assessed using the Social Deprivation Index (SDI), a composite score based on American Community Survey data. Patients were split into quartiles based on SDI score, with quartile 4 comprising those living in the most disadvantaged neighborhoods. Primary outcomes were MASLD burden, mortality, and comorbidities, assessed through cross-sectional and longitudinal analyses. **Results:** A total of 43,241 MASLD patients with SDI scores were included and 28,904 patients had ≥365 days of follow-up. Patients living in the most disadvantaged neighborhoods, as compared to the least, were significantly younger, more likely to be female, more often had class 2-3 obesity, and more often spoke a non-English primary language, compared to those living in the least disadvantaged neighborhoods. They also had higher odds of cirrhosis, any cardiovascular disease, coronary artery disease, congestive heart failure, cerebrovascular accident, diabetes mellitus, and hypertension after adjusting for confounders. On longitudinal analysis, patients in quartile 4 neighborhoods had increased mortality, incidence of cirrhosis, liver-related events, diabetes mellitus, and major adverse cardiovascular events (Table 1). Patients in the most disadvantaged neighborhoods were disproportionately Hispanic, Black, or Native American/Alaska Native. While adjustment for neighborhood SDOH attenuated some racial and ethnic disparities in outcomes, Hispanic and Native American/Alaska Native patients had higher incidence of cirrhosis and liver-related events, and Native American/Alaska Native patients had higher mortality compared to non-Hispanic White patients even after adjusting for SDI. **Conclusion:** In this large, diverse cohort of patients with MASLD, neighborhood-level SDOH were associated with MASLD burden, comorbidities, and mortality. In addition to patient-specific interventions, efforts to address SDOH at the neighborhood level through community engagement and partnerships, advocacy, and health policy are needed to alleviate these disparities at multiple levels.

Table 1. Competing risk analysis for death and incidence of disease by SDI quartile.

SDOH Quartile		Quartile 1 SDI (Least Disadvantaged)	Quartile 2 SDI	Quartile 3 SDI	Quartile 4 SDI (Most Disadvantaged)
Mortality[a]	aHR (95% CI)[b]	Referent	1.41 (1.14-1.74)	1.45 (1.15-1.82)	1.66 (1.30-2.11)
	p value		0.002	0.002	<0.001
Cirrhosis	aHR (95% CI)[b]	Referent	1.34 (1.03-1.76)	1.67 (1.26-2.19)	1.64 (1.22-2.20)
	p value		0.031	<0.001	0.001
Liver-Related Events[c]	aHR (95% CI)[b]	Referent	1.08 (0.86-1.35)	1.26 (1.00-1.59)	1.34 (1.06-1.71)
	p value		0.519	0.049	0.016
Type 2 Diabetes Mellitus[d]	aHR (95% CI)[b]	Referent	1.16 (1.06-1.28)	1.31 (1.18-1.45)	1.66 (1.50-1.84)
	p value		0.002	<0.001	<0.001
Any Cancer	aHR (95% CI)[b]	Referent	0.97 (0.84-1.12)	0.91 (0.78-1.07)	0.90 (0.76-1.08)
	p value		0.671	0.258	0.253
MACE[e]	aHR (95% CI)[b]	Referent	1.18 (1.06-1.30)	1.19 (1.06-1.32)	1.28 (1.14-1.44)
	p value		0.002	0.002	<0.001

Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; MACE, major adverse cardiovascular event; SDI, Social Deprivation Index.
[a]Cox proportional hazards model was performed for mortality analysis.
[b]HR was adjusted for age, sex, race, smoking status, alcohol consumption, type 2 diabetes mellitus, hypertension, dyslipidemia, and use of aspirin and statin.
[c]Liver related events were defined as the incidence of hepatic encephalopathy, ascites, hepatocellular carcinoma, or variceal bleeding.
[d]For type 2 diabetes mellitus, HR was adjusted with the same confounders a excluding type 2 diabetes mellitus.
[e]MACE is defined as the incidence of coronary artery disease, all-cause mortality, congestive heart failure, or cerebrovascular accident.

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2304 | ECONOMIC COST OF INACTION FOR METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS (MASH) IN GERMANY, JAPAN, AND THE UNITED STATES

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Background: MASH is responsible for significant mortality and morbidity; however, the cost burden of inaction to the society is unknown **Aim:** To model 20-year economic burden of MASH in Germany, Japan, and the United States (US) encompassing both direct medical expenses and societal costs. **Methods:** Utilizing a Markov Model, disease states for prevalent (2020) and incidental MASH cases (2021-2040) were updated over 20 years to evaluate clinical and economic trends associated with MASH. Prevalent and incidental MASH cases as clinical input were estimated using a combination of back calculation method and population projections. Transition probabilities for disease progression/regression were derived from literature sources and adjusted for age and country-specific factors. Calibrations and validations against the incidence and mortality from hepatocellular carcinoma and liver transplant rates were performed using the Global burden of disease (GBD) and Global

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Observatory on Donation and Transplantation (GODT). Societal costs, including Work Productivity Impairment (WPI), were calculated based on historical data and national income per capita from World bank. **Results:** MASH cases in the Germany, Japan and US are projected to increase by +13.1% (3.01 million to 3.81 million), +19.1% (3.97 million to 5.01 million) and +26.87% (16.70 million to 24.01 million), respectively, from 2021 to 2040. By 2040, Hepatocellular carcinoma (HCC) cases and liver transplants due to MASH are expected to increase by +67.5% and +63.5% in Germany (1,475 to 2,470 and 115 to 188), +93.3% and +109.8% in Japan (4,920 to 9,509 and 61 to 128) and +71.4% and +81.1% in the US (4,951 to 8,484 and 2,866 to 5,190). Liver-related deaths due to MASH are forecasted to increase +22.0% in Germany (23,417 to 28,578), +53.3% in Japan (19,134 to 29,333) and +55.2% in the US (28,328 to 43,953). In 2040, annual direct healthcare costs associated with MASH are projected to reach $3.05 billion ($891 per patient) in Germany, $3.05 billion ($644 per patient) in Japan and $61.66 billion ($2,909 per patient) in the US with productivity loss reaching $38.82 billion ($11,329 per patient) in Germany, $32.94 billion ($6,961 per patient) in Japan and $258.73 billion ($12,203 per patient) in the US. (Table) **Conclusions:** Clinical and economic burdens of MASH are expected to increase significantly in Germany, Japan, and the US by 2040. These findings underscore the urgent need for effective strategies to mitigate the growing clinical and economic impact of MASH on healthcare systems and societies.

Projected Clinical and Economic Burden for MASH						
Year	MASH prevalence (%)	HCC-MASH Cases (Rate per 100,000)	Liver Transplant Cases (Liver Transplant Rate per 100,000)	MASH-Liver Mortality Cases (Rate per 100,000)	Direct healthcare costs associated with MASH ($ per patient)	Productivity loss associated with MASH ($ per patient)
Germany						
2021	3,029 K (4.36)	1,475 (2.12)	115 (0.17)	23,417 (33.74)	$1.38B (448)	$18.04B (5,842)
2025	3,101 K (4.39)	1,907 (2.70)	133 (0.19)	24,504 (34.70)	$1.62B (521)	$20.91B (6,737)
2030	3,309 K (4.58)	2,138 (2.99)	178 (0.25)	26,607 (37.24)	$2.03B (633)	$25.81B (8,038)
2035	3,425 K (4.69)	2,354 (3.26)	197 (0.27)	28,124 (38.96)	$2.51B (758)	$31.63B (9,554)
2040	3,809 K (5.12)	2,470 (3.38)	188 (0.26)	28,578 (39.13)	$3.05B (891)	$38.82B (11,329)
Japan						
2021	3,970 K (3.70)	4,920 (4.58)	61 (0.06)	19,134 (17.81)	$1.27B (312)	$14.57B (3,585)
2025	4,154 K (3.91)	6,079 (5.72)	72 (0.07)	21,182 (19.93)	$1.55B (374)	$17.17B (4,131)
2030	4,582 K (4.49)	7,394 (7.08)	102 (0.10)	23,820 (22.80)	$2.00B (456)	$21.56B (4,925)
2035	4,729 K (4.97)	8,443 (8.27)	125 (0.12)	26,234 (25.70)	$2.50B (545)	$26.87B (5,859)
2040	5,011 K (5.48)	9,509 (10.00)	128 (0.13)	29,333 (30.85)	$3.05B (644)	$32.94B (6,961)
US						
2021	16,701 K (6.40)	4,951 (1.90)	2,866 (1.10)	28,328 (10.86)	$22.51B (1,316)	$106.32B (6,216)
2025	17,650 K (6.55)	6,174 (2.29)	3,340 (1.24)	33,088 (12.28)	$27.63B (1,563)	$127.34B (7,209)
2030	19,986 K (6.94)	7,358 (2.63)	4,757 (1.70)	39,945 (14.30)	$38.82B (2,059)	$163.12B (8,658)
2035	21,188 K (7.15)	8,590 (2.98)	5,403 (1.88)	43,462 (15.09)	$50.48B (2,524)	$206.09B (10,305)
2040	24,013 K (7.74)	9,484 (3.20)	5,190 (1.75)	43,953 (14.84)	$61.66B (2,909)	$258.73B (12,203)

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2305 | UNDERSTANDING METABOLIC DYSFUNCTION–ASSOCIATED STEATOHEPATITIS: DIFFERENCES IN CLINICAL AND DEMOGRAPHIC CHARACTERISTICS ACROSS RACIAL AND ETHNIC GROUPS

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[1]Target RWE, [2]Novo Nordisk Inc.

Background: Metabolic dysfunction–associated steatohepatitis (MASH) is estimated to affect 1.5%-6.5% of US adults. In the US, studies have shown significant racial disparities in the prevalence and severity of MASH. This analysis assessed health disparities across racial and ethnic groups among patients with MASH and MASH cirrhosis enrolled in TARGET-NASH. **Methods:** Adults with MASH or MASH cirrhosis enrolled in TARGET-NASH, a longitudinal real-world US cohort with >6500 patients, were assessed for demographic/clinical characteristics, diagnostic testing, and all-cause mortality by racial and ethnic group (Hispanic/Latino, non-Hispanic White, non-Hispanic Black, and non-Hispanic Other) in patients with MASH aged ≥18 years. The index date was defined as the earliest date evidence of MASH was observed, and the study period was August 2016-November 2023. Outcomes were examined descriptively at index. Incidence rates (IRs) and proportions were determined for post-index all-cause mortality. **Results:** The cohort included 2738 adults with non-cirrhotic MASH or MASH cirrhosis and comprised 325 (11.9%) Hispanic/Latino, 1999 (73.0%) non-Hispanic White, 145 (5.3%) non-Hispanic Black, and 269 (9.8%) non-Hispanic other patients (Table 1). Insurance type was significantly different across racial and ethnic groups with highest Medicaid use among non-Hispanic Black patients (P<.01). Rates of overweight/obesity (BMI >25 kg/m^2/>30 kg/m^2), hypertension, type 2 diabetes, and hyperlipidemia were highest among non-Hispanic Black patients, while rates of cardiovascular (CV) disease/events were highest among non-Hispanic White patients. Levels of ALT were highest among Hispanic/Latino patients, while levels of AST and alkaline phosphatase were highest among non-Hispanic Black patients. Ultrasonography and vibration-controlled transient elastography were the most prevalent diagnostic testing methods used by >45% of all patients. Stage 4 fibrosis was highest in Hispanic/Latino (27.3%; n=35) and non-Hispanic White patients (28.1%; n=211). The likelihood of progressing to all-cause mortality was lowest in non-Hispanic Black patients (IR, 0.32) and highest among non-Hispanic White patients (IR, 1.72). **Conclusion:** Significant differences in demographic and clinical characteristics, laboratory assessments, insurance type, and diagnostic testing, were observed across racial and ethnic groups among patients with MASH or MASH cirrhosis with non-Hispanic White patients having the greatest incidence of all-cause mortality.

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Table 1. Demographics, clinical characteristics, and diagnostic testing at index and post-index progression to all-cause mortality stratified by racial and ethnic groups among patients with MASH or MASH cirrhosis enrolled in the real-world TARGET-NASH cohort

Variable	Hispanic/ Latino (n=325)	Non-Hispanic White (n=1999)	Non-Hispanic Black (n=145)	Non-Hispanic Other or not reported (n=269)	*P* value	All (N=2738)
Mean age (SD), y	53.5 (14.0)	57.5 (12.7)	54.3 (11.9)	55.5 (13.8)	<.01	56.7 (13.0)
Female, n (%)	203 (62.5)	1156 (57.8)	103 (71.0)	124 (46.1)	<.01	1586 (57.9)
BMI, n, kg/m²	322	1976	144	268	<.01	2710
≤25, n (%)	22 (6.8)	124 (6.3)	8 (5.6)	61 (22.8)		215 (7.9)
>25-30, n (%)	95 (29.5)	461 (23.3)	28 (19.4)	102 (38.1)		686 (25.3)
>30-35, n (%)	105 (32.6)	576 (29.1)	34 (23.6)	58 (21.6)		773 (28.5)
>35-40, n (%)	54 (16.8)	415 (21.0)	37 (25.7)	28 (10.4)		534 (19.7)
>40, n (%)	46 (14.3)	400 (20.2)	37 (25.7)	19 (7.1)		502 (18.5)
Comorbidities, n (%)						
CVD or CV event	54 (16.6)	542 (27.1)	36 (24.8)	38 (14.1)	<.01	670 (24.5)
Hypertension	187 (57.5)	1351 (67.6)	109 (75.2)	142 (52.8)	<.01	1789 (65.3)
Type 2 diabetes	179 (55.1)	1142 (57.1)	91 (62.8)	122 (45.4)	<.01	1534 (56.0)
Hyperlipidemia	160 (49.2)	1209 (60.5)	90 (62.1)	145 (53.9)	<.01	1604 (58.6)
Liver enzymes, mean (SD), IU/L						
ALT	68.0 (71.2)	60.0 (59.7)	66.7 (92.9)	67.2 (66.1)	.08	62.1 (64.1)
AST	52.8 (51.7)	50.7 (43.0)	64.8 (105.4)	49.6 (56.9)	.02	51.6 (51.1)
Alkaline phosphatase	103.8 (53.8)	99.9 (60.6)	111.4 (77.8)	88.2 (52.3)	<.01	99.9 (60.3)
Diagnostic test, n (%)						
Biopsy	129 (39.7)	757 (37.9)	64 (44.1)	67 (24.9)	<.01	1017 (37.1)
Ultrasonography	218 (67.1)	1125 (56.3)	89 (61.4)	211 (78.4)	<.01	1643 (60.0)
CT/MRI	69 (21.2)	417 (20.9)	22 (15.2)	38 (14.1)	<.01	546 (19.9)
VCTE	175 (53.8)	935 (46.8)	81 (55.9)	143 (53.2)	<.01	1334 (48.7)
All-cause mortality						
Incident new cases	29	206	3	11	-	-
Incidence proportion	8.9	10.3	2.1	4.1	-	-
Mean person-time (SD), mo	59.7 (20.6)	59.7 (22.2)	64.0 (21.1)	60.5 (20.8)	-	-
IR	1.50	1.72	0.32	0.68	-	-

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CT, computed tomography; CV, cardiovascular; CVD, cardiovascular disease, IR, incidence rate; MASH, metabolic dysfunction–associated steatohepatitis; MRI, magnetic resonance imaging; VCTE, vibration-controlled transient elastography.

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2306 | VALIDATION AND EPIDEMIOLOGIC DEFINITION OF THE NOVEL STEATOTIC LIVER DISEASE NOMENCLATURE IN A NATIONAL COHORT WITH CIRRHOSIS ◆

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Background: Novel steatotic liver disease (SLD) definitions were introduced in 2023 with a diagnostic algorithm based on the presence of cardiometabolic risk factors (CMRFs) and thresholds for alcohol exposure to define metabolic dysfunction-associated SLD (MASLD), alcohol-associated liver disease (ALD), and metabolic and alcohol-associated liver disease (MetALD). There remains uncertainty in classifying MetALD versus ALD depending on degree of alcohol use and CMRF burden. **Methods:** In a national cohort of Veterans with cirrhosis

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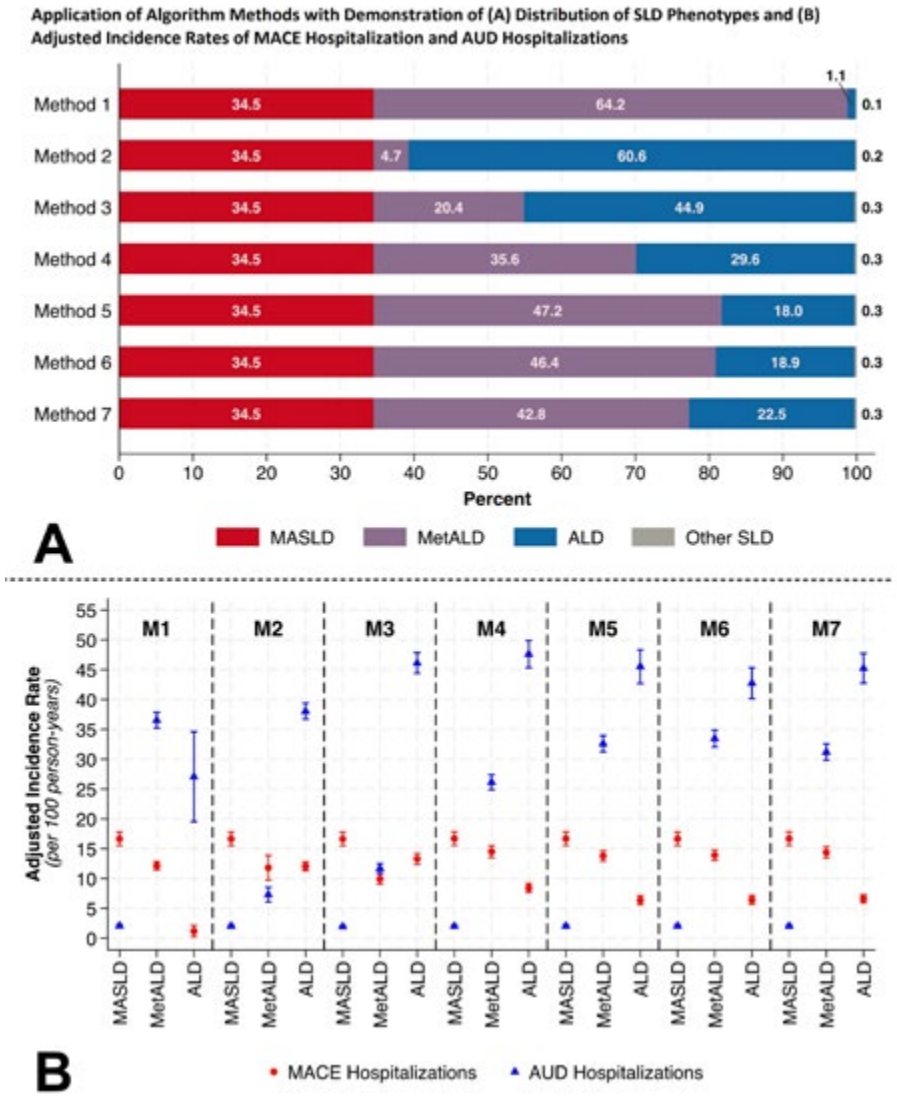
and imaging-confirmed steatosis, seven algorithms differentially emphasizing CMRF burden and degree of alcohol exposure were developed to classify MASLD, ALD, and MetALD and compare clinical outcomes for validation purposes. The primary outcomes were hospitalizations for major adverse cardiovascular events (MACE) and alcohol use disorder (AUD), modeled using each of the seven classification algorithms. Secondary outcomes included incident hepatocellular carcinoma and all-cause mortality, modeled on SLD subtypes as classified by the best performing algorithm. **Results:** A total of 31,514 patients with cirrhosis with a median age 64 years were included. CMRFs (98.8% of sample had ≥1) and hazardous alcohol use (65.3%) were highly prevalent. The distributions of MASLD, MetALD, and ALD varied substantially across classification **methods** depending on stringency of CMRF and alcohol use criteria. For example, classification of MetALD ranged from 4.7% to 47.2%. Using method 4, incidence rates of MACE hospitalizations for MASLD, MetALD, and ALD were 16.7, 14.5, and 8.4 per 100 person-years, respectively and incidence rates of AUD hospitalizations were 2.0, 26.1, and 47.6 per 100 person-years, respectively. Patients with ALD (HR 1.41, 95% CI 1.34-1.48) but not with MetALD (HR 1.03, 95% CI 0.98-1.07) had significantly higher hazards of mortality relative to those with MASLD. **Conclusion:** Classification of SLD in clinical cohorts following the novel nomenclature is highly sensitive to both data availability on alcohol consumption and investigator choices in weighting cardiometabolic disease against alcohol exposure, which varies over time. Clinical outcomes in cirrhosis with both excessive alcohol use and extreme cardiometabolic risk aligned more with a classification of MetALD than ALD. Future epidemiologic studies of SLD require careful attention to avoid misclassification of disease states.



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2307 | THYROID DISORDERS (HYPOTHYRODISM AND HYPERTHYRODISM) AND THEIR ASSOCIATIONS WITH NONALCOHOLIC FATTY LIVER DISEASE AND NONALCOHOLIC STEATOHEPATITIS: A STUDY ON INPATIENT OUTCOMES, INCIDENCE AND PREVALENCE

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Background: Thyroid disorders are one of most common comorbid conditions present in patients with nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH).
There is limited data available regarding the outcomes and prevalence of NAFLD/NASH among thyroid disorder patients. The aim of present study is to examine the outcomes and prevalence of NAFLD/NASH among patients admitted with thyroid disorders using national database. **Methods:** We used the Healthcare Cost and Utilization Project (HCUP) Nationwide Inpatient Sample (NIS) to identify adult patients admitted with thyroid disorders during 2016 – 2020 using ICD-10-CM codes. We divided the patients into two groups based on concomitant diagnosis / procedure of NAFLD/NASH based on ICD-10 codes, defined as having diagnosis codes of fatty liver not elsewhere classified (K76.0), NASH (K75.81), hepatic fibrosis (K74.0), or cryptogenic liver disease with or without cirrhosis (K76.9 and K74.6, respectively). Main outcomes were in-hospital mortality, length of stay (LOS), and hospital costs. We evaluate the association between NAFLD/NASH and outcomes using survey based multivariate logistic regression models for in-hospital mortality, Poisson regression for LOS, and generalized linear model with gamma distribution and log link for hospitalization cost. Models were adjusted for age, sex, race and ethnicity, primary payer, Charlson comorbidity index, hospital bed size, hospital region and hospital teaching status. We also evaluated national trend of NAFLD/NASH among thyroid disorders hospitalizations over time using Poisson regression. **Results:** We identified a total of 18,171,339 hospitalizations associated with thyroid disorders between 2016 and 2020 in the United States and 643,240 (3.5%) of them were associated with NAFLD/NASH. The prevalence of NAFLD/NASH among thyroid disorders increased from 3.1 % in 2016 to 4.2 % in 2020 (P-trend < 0.001, Table 1). In-patient mortality was significantly higher in NAFLD/NASH patients with thyroid disorders (3.4% vs 2.6%, adjusted OR: 1.20, 95%CI: 1.16 – 1.24, P < 0.001, Table 2). NAFLD/NASH patients with thyroid disorders had an increased length of stay (5.6 ± 0.02 vs 5.1 ± 0.01 days, P = 0. 035) and cost of hospitalization ($14,909 ± 56 vs $ 16,530 ± 107, P < 0.001, Table 2). **Conclusion:** NAFLD/NASH in patients with thyroid disorders has been increasing over time and is associated with higher in-hospital mortality with increased length of stay, and increased cost of hospitalization.

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Table 1: Trend analysis on NAFLD/NASH among thyroid disorder admissions, 2016-2020

	2016, N = 3,581,407	2017, N = 3,687,938	2018, N = 3,725,349	2019, N = 3,782,185	2020, N = 3,394,460	IRR	95% CI	p-value
NAFLD/NASH, n (%)	109,320 (3.1%)	118,695 (3.2%)	129,360 (3.5%)	142,525 (3.8%)	143,340 (4.2%)	1.06	1.06, 1.07	<0.001

IRR = Incidence Rate Ratio, CI = Confidence Interval
Variables used for multivariate Poisson regression: age, sex, race, insurance status, Charlson comorbidity index, hospital bed size, and hospital region
N represents weighted counts

Table 2: Comparison of primary outcomes: thyroid disorders with NAFLD/NASH versus thyroid disorders without NAFLD/NASH)

	NAFLD/NASH		Adjusted OR / RR		
Characteristic	No, N = 17,528,099	Yes, N = 643,240	OR/RR	95% CI	p-value
In-hospital mortality - N (%)	454,875 (2.6%)	21,670 (3.4%)	1.2	1.16, 1.24	<0.001
LOS (days) - mean (SE)	5.1 (0.01)	5.6 (0.02)	1.01	1.00, 1.01	0.035
Hospital Cost ($, 2020) - mean (SE)	14,909 (56)	16,530 (107)	1.02	1.01, 1.03	<0.001

Relative ratio is reported using Poisson regression model for LOS
Relative ratio is reported using generalized linear model with gamma distribution and log link for Hospital Cost; adjusted for inflation using Consumer Price Index (CPI) for Medical care services in U.S. city average, all urban consumers, chained, with 2018 as the reference point
Variables used for multivariate logistic regression: age, sex, race, insurance status, Charlson comorbidity index, hospital bed size, and hospital region

Disclosures: Anwar Uddin: Nothing to Disclose, Madia Ahad: Nothing to Disclose, Rafat Uddin: Nothing to Disclose, Selome Yewedalsew: Nothing to Disclose, Prashil Dave: Nothing to Disclose, Dipsa Shastri: Nothing to Disclose, Afgal Ahad: Nothing to Disclose, Rahat Uddin: Nothing to Disclose, Peter Lymberopoulos: Nothing to Disclose, Nazeera Ghanie: Nothing to Disclose, Sahil Chaddha: Nothing to Disclose

2308 | IMPACT OF METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE ON THE INCIDENCE OF OSTEOPOROSIS

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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is one of the most prevalent diseases worldwide and is a result of metabolic disease, which may also contribute to other disorders of metabolism, such as bone mineralization. This study seeks to investigate the relationship between MASLD and osteoporosis (OP). **Methods:** This is a cross-sectional study using subjects from the National Health and Nutrition Examination Survey (NHANES) 2017-2020. To investigate the relationship between MASLD and bone mineral density (BMD), multivariate linear regression models were performed. MASLD was defined as a controlled attenuation parameter >= 285 with metabolic dysfunction. BMD was measured using dual-energy X-ray absorptiometry and osteoporosis risk was calculated using the mean femoral BMD of non-hispanic white men and women aged 20-29 from NHANES III as reference. R studio was used for analysis. **Results:** Out of 2,135 patients assessed, 225 (10.7%) patients had OP, 797 patients had MASLD (42.8%). 34 men (1.4%) out of 1148, 188 women (20.0%) out of 987 had OP. Patients>= 60 yr old with MASLD had higher BMD [Odds ratio (OR): 1.053; 95% confidence interval (CI), 1.031 - 1.077; *P*<0.001] and lower risk of OP [OR: 0.877; 95% CI, 0.837 - 0.919; *P*<0.001] when compared to patients>=60 without MASLD. When stratified by gender, men with

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MASLD had a lower risk when adjusted for age, BMI, and non-white ethnicity [OR: 0.985; 95% CI, 0.973 - 0.998 ; *P*=0.023], compared to men without MASLD. Women with MASLD had a lower risk of OP when adjusted for age, BMI, and non-white ethnicity [OR: 0.874; 95% CI, 0.807 - 0.947 ; *P*=0.002], compared to women without MASLD. Higher BMI was significantly associated with lower risk of OP in women only [OR: 0.988; 95% CI, 0.982 - 0.995 ; *P*=0.001]. When adjusted for fibrosis (TE>=8), cirrhosis (TE>=12) or elevated liver enzymes (AST or ALT>=40), the results were non-significant (OR = 0.898 (0.768 - 1.051), P=0.168; OR = 0.922 (0.770 - 1.104), P=0.327; OR = 0.810 (0.611 - 1.073), P=0.128 respectively). **Conclusion:** This study suggests a potential protective effect of MASLD on bone mineral density (BMD) despite chronic inflammatory status. Women with MASLD and higher BMI appear to have a lower risk of osteoporosis. However, our study is limited in proving a causal relationship. These findings encourage further research into the biochemical effects of MASLD on BMD and osteoporosis.

Disclosures: Wajiha Khan: Nothing to Disclose, David Kim: Nothing to Disclose, Ariana Shari: Nothing to Disclose, Hamza Khan: Nothing to Disclose, Alexander Le: Nothing to Disclose, Christopher Hawryluk: Nothing to Disclose, Ivan Bobkov: Nothing to Disclose, Ahmed Al-Khazraji: Nothing to Disclose, Kaveh Hajifathalian: Nothing to Disclose

2309 | IMPROVED LIVER FIBROSIS REGRESSION AFTER DIRECT-ACTING ANTIVIRAL THERAPY IN HEPATITIS C PATIENTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE

Alexis McCary[1] *Yi-shin Sheu*[1] *Karen Chesbrough*[1] *Cabell Jonas*[1]

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Background: One third of the US population has some degree of liver steatosis, and many patients with Chronic Hepatitis C (CHC) meet criteria for metabolic dysfunction-associated steatotic liver disease (MASLD). An important benefit of CHC treatment is liver fibrosis regression. However, because MASLD can also cause liver fibrosis, it is unclear how concurrent MASLD affects liver fibrosis regression following CHC treatment. Before MASLD was defined, research into the effects of liver steatosis on fibrosis regression after CHC therapy reported both increased and decreased rates of fibrosis regression. Given that MASLD allows for coexisting liver disease, this study aimed to examine the impact of MASLD on the fibrosis regression effects following direct-acting antiviral (DAA) therapy for CHC. **Methods:** This observational retrospective data analysis of patients aged 18–65 who completed CHC treatment with a DAA agent between January 2016 and December 2022. FIB-4 scores were taken at three timepoints: just prior to DAA initiation, 6 months post-DAA completion, and 12 months post-DAA completion. These scores categorized liver fibrosis as likely advanced (>3.25), indeterminate (1.45–3.25), or unlikely advanced (<1.45). An ordinal logistic regression model assessed the degree of fibrosis regression across these timepoints in CHC patients with and without MASLD. **Results:** We identified 852 CHC patients, of whom 228 (26.76%) met MASLD criteria. CHC patients, regardless of MASLD presence, exhibited a significant decrease in FIB-4 category (coefficient = - 0.355, p<0.001) following DAA therapy, indicating a notable improvement in liver fibrosis risk from pre-treatment to post-treatment. Importantly, the reduction in FIB-4 category post-treatment was more pronounced in the MASLD group compared to the non-MASLD group, as evidenced by a significant interaction between group and timepoint (coefficient = - 0.430, p = 0.004). **Conclusion:** CHC patients with MASLD experienced greater liver fibrosis regression following DAA therapy compared to those without MASLD. These findings suggest that the MASLD group may derive more benefits from DAA therapy than the non-MASLD group. Further research is needed to determine the specific mechanisms behind DAA-associated fibrosis regression in patients with concurrent CHC and MASLD.

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2310 | CHARACTERISTICS AND CLINICAL OUTCOMES IN PATIENTS WITH CIRRHOSIS DUE TO METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD) IN SWEDEN

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Background: There are limited real-world data on the prognosis of patients with cirrhosis due to MASLD. The aim of this study is to describe the characteristics and clinical outcomes of these patients. **Methods:** We used data from 225 patients with compensated cirrhosis, and 68 patients with decompensated cirrhosis, due to MASLD between 1980 and 2019, identified at the Karolinska University Hospital, Huddinge and Uppsala University Hospital, and Linköping University Hospital in Sweden. The baseline characteristics of patients were described. Patients with compensated cirrhosis were followed from cirrhosis diagnosis to the occurrence of a decompensating event, liver transplant, or death. Patients with decompensated cirrhosis were followed until liver transplant or death. Event rates for each outcome and cumulative incidence of the composite outcome were estimated. Factors associated with progression were analyzed using multivariable Cox regression models. **Results:** In compensated cirrhosis (50% females, median age 67), 65% had type 2 diabetes (T2D); the median Model for End-stage Liver Disease (MELD) score and median Child-Pugh score were 8 (Interquartile range (IQR) 7-10) and 5 (IQR 5-6), respectively. In decompensated cirrhosis (32% females, median age 68), the most frequent prior decompensating event was ascites (77%), followed by esophageal variceal bleeding (28%) and hepatic encephalopathy (25%), with 26% having more than one prior decompensating event. 79% of patients with decompensated cirrhosis had T2D, and the median MELD score and median Child-Pugh score were 11 (IQR 9-15) and 8 (IQR 7-9), respectively. In compensated cirrhosis, 50.2% progressed to outcomes during a median follow-up of 3.8 years. The individual event rate was 34.6%, 5.8%, and 38.2% for decompensation, liver transplant, and death, respectively. In decompensated cirrhosis, 73.5% patients experienced outcomes with a median follow-up of 1.2 years. The individual event rate was 25% for liver transplant and 54% for deaths. Within five years of follow-up, 41% of patients with compensated cirrhosis developed the composite outcome, compared to 76% in decompensated cirrhosis (Figure 1). In the multivariable Cox regression analysis, T2D was associated with a higher risk of the composite outcome in compensated cirrhosis (hazard ratio=1.67, 95% confidence interval: 1.08-2.59); higher Child-Pugh and MELD scores were consistently associated with faster progression in both compensated and decompensated cirrhosis. **Conclusion:** This cohort study describes the natural history of patients with cirrhosis due to MASLD. In compensated cirrhosis, T2D was associated with a higher risk of outcomes. In both compensated and decompensated cirrhosis, Child-Pugh and MELD scores were associated with faster progression.

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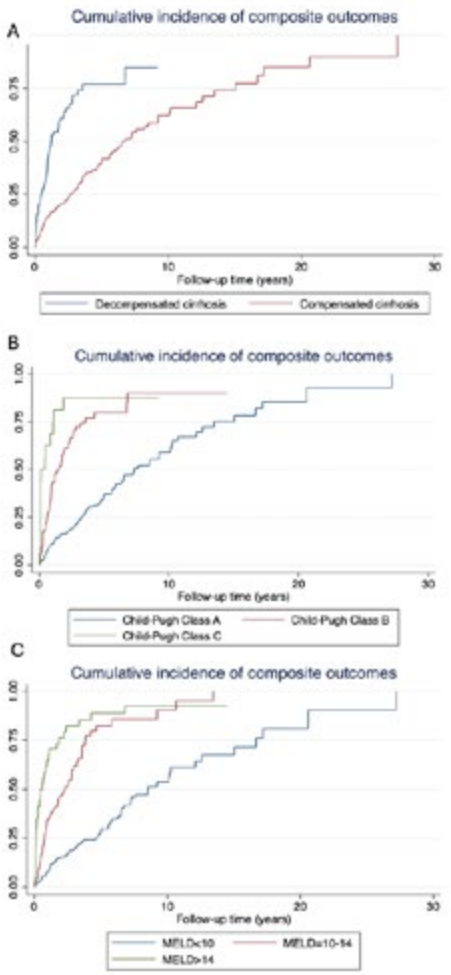
Figure 1. Cumulative incidence of composite outcomes



*Composite outcomes are defined as having decompensated events, liver transplant, and death.
**For figure A, composite outcomes for decompensated cirrhosis include liver transplant and death.

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2311 | CLINICAL FEATURES OF METALD: DATABASE ANALYSIS OF 108,446 SUBJECTS

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Background: The clinical features contributing to liver fibrosis development in different types of steatotic liver disease (SLD) are not well understood. We examined the clinical features of SLD subtypes using a large health checkup cohort . **Methods:** We conducted a cross-sectional analysis on a total of 108,446 subjects (MIRACLE-J). SLD was diagnosed by ultrasonography. Patients with SLD who did not meet one of the five cardiometabolic risk factors were excluded. The remaining patients were classified as metabolic dysfunction-associated SLD

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(MASLD), MASLD with increased alcohol intake (MetALD), or alcohol-related liver disease (ALD) with metabolic dysfunction (ALD&Met), according to the amount of daily alcohol intake (MASLD: men<30 g/d, women<20 g/d; MetALD: men=30–60 g/d, women=20–50 g/d; ALD&Met: men>60 g/d, women>50 g/d). An aminotransferase to platelet ratio index (APRI) >1.0 indicated advanced liver fibrosis. **Results:** Among the qualifying 30,857 patients with SLD, 21,049 (68%) had MASLD, and 7,884 (25%) had MetALD. Compared to patients with MASLD, patients with MetALD included significantly more males (62% vs. 89%), former and current smokers (45% vs. 74%), and hypertension (33% vs. 41%); significantly higher fatty liver index (44.7 vs. 55.0) and Fibrosis-4 index (1.14 vs. 1.27); and significantly lower rates of abnormal lipid metabolism (52% vs. 46%) (all P<0.001). After adjusting for clinical variables, in male patients (n=51,596) being over age 65 (odds ratio [OR]=1.30; 95% confidence interval [CI]:1.03–1.65, P=0.026), the presence of SLD (OR=2.66; 95% CI: 2.15–3.29, P<0.001), alcohol intake for MetALD (OR=1.75; 95% CI: 1.43–2.13, P<0.001) and ALD&Met (OR=5.54; 95% CI: 4.16–7.37, P<0.001), and blood pressure (OR=1.67; 95% CI: 1.21–1.73, P<0.001) and insulin resistance criteria (OR=1.51; 95% CI: 1.21–1.73, P<0.001) were independent contributors to advanced liver fibrosis diagnosis. Likewise, in females (n=56,850), being over age 65 (OR=2.27; 95% CI: 1.71–3.03, P<0.001), the presence of SLD (OR=2.66; 95% CI: 1.94–3.65, P<0.001), alcohol consumption for ALD&Met (OR=4.76; 95% CI: 2.44–9.29, P<0.001), and blood pressure criteria (OR=1.80; 95% CI: 1.36–2.39, P<0.001)were also determined as independent factors for advanced liver fibrosis diagnosis. **Conclusion:** Daily alcohol intake and higher blood pressure are independent contributors to APRI-assessed liver fibrosis progression in SLD.
Disclosures: Hideki Fujii: Nothing to Disclose, Yoshihiro Kamada: Nothing to Disclose, Yuichiro Suzuki: Nothing to Disclose, Koji Sawada: Nothing to Disclose, Hiroshi Tobita: Nothing to Disclose, Miwa Kawanaka: Nothing to Disclose, Hirokazu Takahashi: Sysmex: Grant/Research Support, Novo Nordisk: Speaking and Teaching, Kowa: Speaking and Teaching, Taisho: Speaking and Teaching, Takeda: Grant/Research Support, Yoshio Sumida: Nothing to Disclose

2312 | DIFFERENCES IN PREVALENCE OF MASLD WITH CLINICALLY SIGNIFICANT FIBROSIS BY SEX/MENOPAUSE STATUS IN A LARGE PROSPECTIVE US COHORT OF PERSONS WITH HIV

Kara Wegermann[1] Ayako Suzuki[1] Elisa Sarmiento[2] Yang Li[2] Laura Wilson[3] Audrey Lloyd[4] Paula Debroy Monzon[5] Jennifer Price[6] Tinsay Woreta[7] Holly Crandall[2] Richard Sterling[8] Rohit Loomba[9] Naga Chalasani[10] Jordan Lake[5]

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Background: Post-menopausal women and men are at higher risk for metabolic dysfunction-associated steatotic liver disease (MASLD) with clinically significant fibrosis (CSF) compared to pre-menopausal women, but data are lacking in persons with HIV (PWH). The aim of this study was to discover prevalence and severity of MASLD in PWH by sex assigned at birth and menopause status. **Methods:** We examined participants from a prospective, cross-sectional study of steatotic liver disease in PWH conducted by the NIDDK-funded HIV NASH CRN. Participants had suppressed HIV-1 RNA and underwent vibration controlled transient elastography. The primary outcome was MASLD+CSF, defined as controlled attenuation parameter (CAP) ≥ 263 dB/m and liver stiffness measurement (LSM) ≥ 8 kPa with at least one cardiometabolic risk factor, without heavy alcohol use or other causes of liver disease. Menopause status was self-reported for participants assigned female sex at birth; those who had not completed menopause were considered pre/peri-menopausal. Participants reporting pre-menopausal status at ≥ 62 years of age (N=15) were excluded. **Results:** 949 PWH were included: 709 men, 102 pre/peri-menopausal women, and 138 post-menopausal women. Median time from HIV diagnosis was 18.6 years and 52% were Black. Sex/menopause groups differed by median age (men: 55.1 years, pre/peri-menopausal women: 47 years, post-menopausal women: 60 years), median body mass index (BMI) (men: 28.5 kg/m^2, pre/peri-menopausal women: 34.2 kg/m^2, post-menopausal women: 30.7 kg/m^2), race, and waist circumference. MASLD prevalence was 45.7% (men: 46.0%, pre/peri-menopausal women: 45.1%, post-menopausal women: 44.9%, p-value=0.97). CSF was present in 14.1% of PWH (men: 15.9%, pre/peri-menopausal women: 7.8%, post-menopausal women: 9.4%, p-value=0.02). PNPLA3 genotype did not differ by sex/menopause group. Adjusted by covariates, pre/peri-menopausal women had a lower risk of MASLD+CSF compared to men (relative risk [RR]: 0.14, 95% confidence interval [CI]: 0.05-0.45, p-value=0.0009), but not compared to post-menopausal women (RR: 0.61, 95% CI: 0.16-2.33, p-value=0.47) (Table 1). Diabetes, hyperlipidemia, higher BMI, and White

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race were associated with MASLD+CSF. **Conclusion:** Pre/peri-menopausal status was associated with lower prevalence of MASLD+CSF compared to men but not post-menopausal women. Metabolic risk factors (diabetes, hyperlipidemia) were associated with MASLD+CSF, suggesting pathophysiologic similarities with MASLD in persons without HIV. Group sizes were unbalanced; further studies with more women are needed.

Table 1: Univariate and multivariable models for MASLD+CSF by sex/menopause status

	Univariate risk of MASLD + CSF (RR, 95% CI)	p-value	Multivariable risk of MASLD + CSF (RR, 95% CI)	p-value
Sex/menopause status (compared to pre/peri-menopausal women)				
Post-menopausal women	1.19 (0.38-3.76)	0.76	1.64 (0.43-6.23)	0.47
Men	2.30 (0.91-5.82)	0.08	6.93 (2.21-21.73)	0.0009
Age	1.02 (1.00-1.04)	0.06		
Time since HIV diagnosis	1.02 (1.00-1.04)	0.053		
On estrogen	<.001 (<0.001->999.999)	0.99		
Race (compared to White)				
Black	0.45 (0.27-0.73)	0.001	0.46 (0.27-0.80)	0.04
Asian	0.99 (0.21-4.57)	0.99	1.14 (0.19-6.71)	0.84
Other	0.74 (0.09-6.09)	0.78	1.69 (0.18-16.08)	0.57
Multiracial	0.78 (0.10-6.40)	0.82	2.33 (0.26-20.94)	0.36
Refused/Unknown	0.39 (0.16-0.94)	0.04	0.41 (0.16-1.07)	0.08
Diabetes	4.88 (3.07-7.74)	<.0001	3.48 (2.06-5.88)	<.0001
Hyperlipidemia	3.16 (2.00-5.00)	<.0001	2.21 (1.25-3.91)	0.007
Body mass index	1.16 (1.12-1.20)	<.0001	1.16 (1.11-1.20)	<.0001
Low HDL (< 50 for women, < 40 for men)	3.41 (1.68-6.91)	0.0007	1.12 (0.48-2.63)	0.79
PNPLA3 Genotype				
CG +GG (1) v CC (0)	1.77 (0.98-3.20)	0.06		

Disclosures: Kara Wegermann: Madrigal Pharmaceuticals: Research funds to institution, Mirum Pharmaceuticals: Study investigator (research funds to institution), Madrigal Pharmaceuticals: Study investigator (research funds to institution), Ayako Suzuki: Nothing to Disclose, Elisa Sarmiento: Nothing to Disclose, Yang Li: Nothing to Disclose, Laura Wilson: Nothing to Disclose, Audrey Lloyd: Nothing to Disclose, Paula Debroy Monzon: Nothing to Disclose, Jennifer Price: Nothing to Disclose, Tinsay Woreta: Nothing to Disclose, Holly Crandall: Nothing to Disclose, Richard Sterling: Grant/Research Support relationship with HCV Vax; Has not ended; Grant/Research Support relationship with GSK; Has not ended; Grant/Research Support relationship with Gilead; Has not ended; Grant/Research Support relationship with Roche; Has not ended; Grant/Research Support relationship with AbbVie; Has not ended; Grant/Research Support relationship with Abott; Has not ended; GI Specialty Board relationship with ABIM; Has not ended, Rohit Loomba: Eli Lilly and Company: Consultant, 89bio: Consultant, Aardvark Therapeutics: Consultant, Altimmune: Consultant, Alnylam/Regeneron: Consultant, Amgen: Consultant, Arrowhead Pharmaceuticals: Consultant, AstraZeneca: Consultant, Bristol Myers Squibb: Consultant, CohBar: Consultant, Eli Lilly: Consultant, Galmed Pharmaceuticals: Consultant, Gilead: Consultant, Glympse Bio: Consultant, Hightide: Consultant, Inipharma: Consultant, Intercept: Consultant, Inventiva: Consultant, Ionis: Consultant, Janssen, Inc.: Consultant, Madrigal Pharmaceuticals: Consultant, Merck, Metacrine, Inc.: Consultant, NGM Biopharmaceuticals: Consultant, Novartis: Consultant, Novo Nordisk: Consultant, Pfizer: Consultant, Sagimet Biosciences: Consultant, Terns Pharmaceuticals: Consultant, Theratechnologies and Viking Therapeutics: Consultant, 89bio: Stock options, Sagimet Biosciences: Stock options, Arrowhead Pharmaceuticals: Research grant, AstraZeneca: Research grant, Boehringer Ingelheim: Research grant, Bristol Myers Squibb: Research grant, Eli Lilly: Research grant, Galectin Therapeutics: Research grant, Galmed Pharmaceuticals: Research grant, Gilead: Research grant, Hanmi: Research grant, Intercept: Research grant, Inventiva: Research grant, Ionis: Research grant, Janssen, Inc.: Research grant, Madrigal Pharmaceuticals: Research grant, Merck: Research grant, NGM Biopharmaceuticals: Research grant, Novo Nordisk: Research grant, Pfizer: Research grant, Sonic Incytes: Research grant, Terns Pharmaceuticals: Research grant, LipoNexus, Inc.: Co-founder, Naga Chalasani: Madrigal: Consultant, Zydus, Ipsen, Pfizer, Merck, Altimmune, GSK: Consultant, Exact Sciences: Grant/Research Support, NIH: Grant/Research Support, Jordan Lake: Gilead Sciences: Consultant, CytoDyn: Consultant

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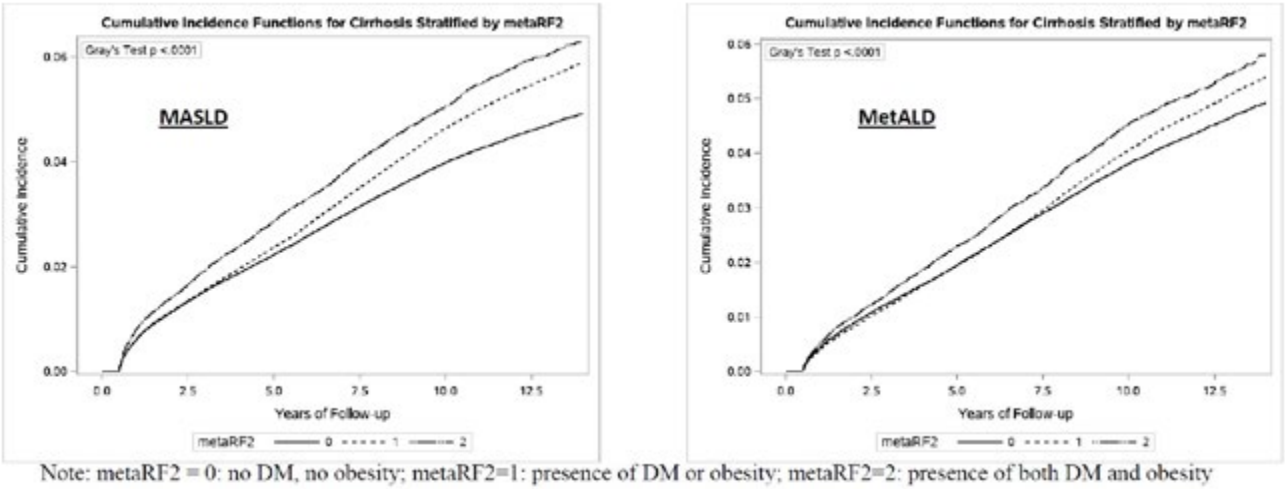
2313 | THE CUMULATIVE IMPACT OF CONCURRENT DIABETES MELLITUS AND OBESITY ON LONG-TERM RISKS OF CIRRHOSIS AMONG A NATIONAL COHORT OF U.S. VETERANS WITH MASLD OR METALD

Robert Wong[1] Zeyuan Yang[1] Ashwani Singal[2] Mario Pessoa[3] Aleksander Krag[4] Jörn Schattenberg[5] Linda Henry[6] Saleh Alqahtani[7] Jeffrey Lazarus[8] Zobair Younossi[6]

[1]VA Palo Alto Healthcare System, [2]University of Louisville, [3]University of São Paulo School of Med, [4]University of Southern Denmark, [5]Universitätsklinikum des Saarlandes, [6]Global NASH Council, [7]Johns Hopkins University, [8]University of Barcelona

Background: High prevalence of cardiometabolic risks (CMR) among U.S. Veterans predisposes to metabolic dysfunction associated steatotic liver disease (MASLD). Concurrent multiple CMR may have additive risks of liver disease progression. It is not clear if additive risks due to multiple CMR affect patients with MASLD and those with MASLD and concurrent low level alcohol use (MetALD) similarly. We aim to evaluate the cumulative impact of concurrent diabetes mellitus (DM) and obesity on long-term risks of cirrhosis among US Veterans with MASLD and MetALD. **Methods:** Using national Veterans Affairs (VA) data, Veterans with MASLD or MetALD from 1/1/2010 to 12/31/2018 (with follow-up through 12/31/2023) were identified using updated nomenclature (MASLD=hepatic steatosis (HS) + ≥1 CMR and no alcohol use [AUDIT-C=0]; MetALD=HS + ≥1 CMR and low-level alcohol use [AUDIT-C 1-2 for women, 1-3 for men]). Patients with other causes of chronic liver disease or baseline cirrhosis or hepatocellular carcinoma were excluded. Incidence of cirrhosis (per 1000-person-years (py)) was stratified by presence of DM and/or obesity (body mass index (BMI) ≥30kg/m^2) using competing risks **Methods:** and adjusted multivariable Cox proportional hazards models. **Results:** 682,274 patients with MASLD and 517,464 patients with MetALD were identified. The majority were men (93.3%, 94.0%) and non-Hispanic white (70.3%, 71.5%); mean age (63.3y, 60.0y) and mean BMI were similar (32.6 kg/m^2, 32.8 kg/m^2). Proportions of patients with CMR were also similar between MASLD and MetALD: DM (12.3%, 13.4%), hypertension (11.4%, 14.5%), dyslipidemia (76.4%, 72.5%). Overall incidence of cirrhosis was similar between MetALD vs. MASLD (3.9 vs. 4.3 per 1000-py; HR 0.99, 95% CI 0.96-1.01, p=0.36). Compared to MASLD without DM or obesity, there was an additive risk of cirrhosis among those with either DM or obesity (4.5 vs. 3.8 per 1000-py; HR 1.10, 95% CI 1.05-1.15, p<0.01), and even higher in those with both DM and obesity (5.1 vs. 3.8 per 1000-py; HR 1.21, 95% CI 1.12-1.30, p<0.01) (Figure). Similar trends were seen in MetALD; compared to patients without DM or obesity, higher risk of cirrhosis was observed among those with either DM or obesity (4.0 vs. 3.8 per 1000-py; HR 1.24, 95% CI 1.19-1.28, p<0.01), and even higher in those with both DM and obesity (4.5 vs. 3.8 per 1000-py; HR 1.33, 95% CI 1.25-1.42, p<0.01). **Conclusion:** Among US Veterans with MASLD or MetALD, the presence of obesity and/or DM leads to an additive cumulative impact on long-term risk of disease progression to cirrhosis.



Note: metaRF2 = 0: no DM, no obesity; metaRF2=1: presence of DM or obesity; metaRF2=2: presence of both DM and obesity

Disclosures: Robert Wong: Theratechnologies: Grant/Research Support, Durect: Grant/Research Support, Gilead Sciences: Grant/Research Support, Exact Sciences: Grant/Research Support, Theratechnologies: Grant/Research Support, Durect Corporation: Grant/Research Support, Zeyuan Yang: Nothing to Disclose, Ashwani Singal: Advisor relationship with CLD Foundation; Has not ended; Speaking and Teaching relationship

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2314 | LONGITUDINAL RISK OF CIRRHOSIS ACROSS THE SPECTRUM OF STEATOTIC LIVER DISEASE AMONG A NATIONAL COHORT OF VETERANS IN THE UNITED STATES

Robert Wong[1] Zeyuan Yang[1] Ashwani Singal[2] Mario Pessoa[3] Aleksander Krag[4] Jörn Schattenberg[5] Linda Henry[6] Saleh Alqahtani[7] Jeffrey Lazarus[8] Zobair Younossi[6]

[1]VA Palo Alto Healthcare System, [2]University of Louisville, [3]University of São Paulo, [4]University of Southern Denmark, [5]Universitätsklinikum des Saarlandes, [6]Global NASH Council, [7]Johns Hopkins University, [8]University of Barcelona

Background: Steatotic liver disease (SLD), which includes both metabolic-associated and alcohol-related liver disease (ALD), is the leading cause of chronic liver disease in the U.S. Veterans, in particular, are at high risk of SLD given the high prevalence of metabolic co-morbidities and unhealthy alcohol use. We aim to evaluate long-term risks of cirrhosis across the spectrum of SLD among U.S. Veterans to better understand differences in the influence of metabolic vs. alcohol factors. **Methods:** Veterans with SLD (presence of hepatic steatosis) from 1/1/2010 to 12/31/2018 (with follow-up through 12/31/2023) were identified from the national Veterans Affairs (VA) database using updated nomenclature. Patients with other causes of chronic liver disease or baseline cirrhosis or

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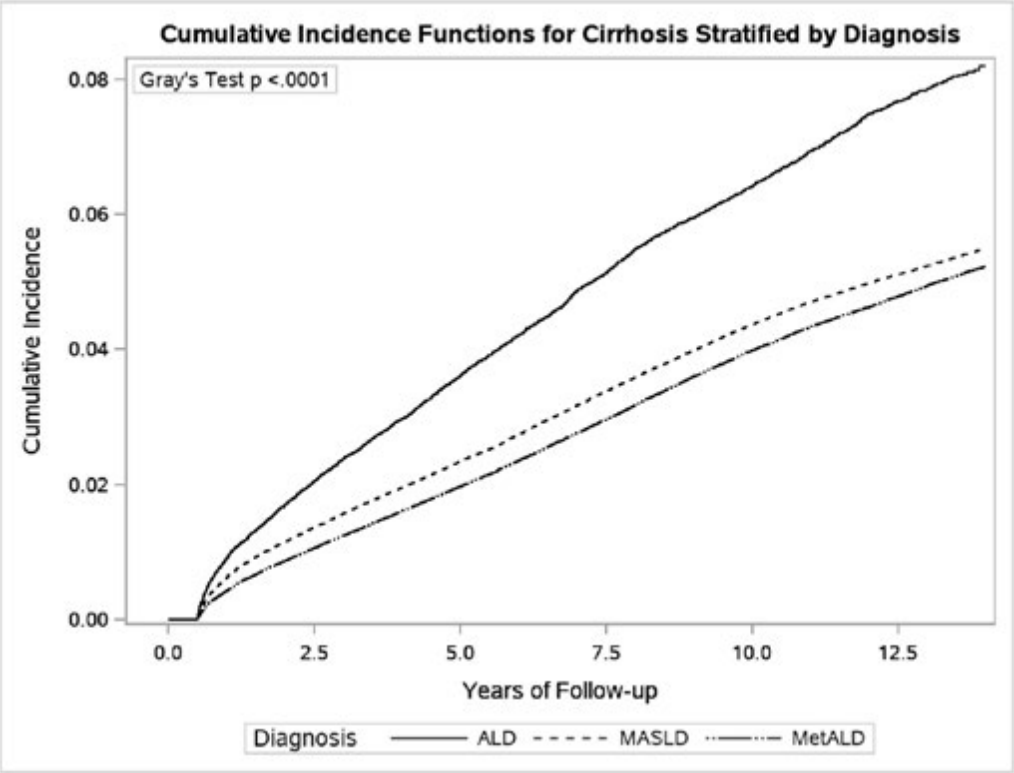
hepatocellular carcinoma were excluded. Alcohol use was assessed using AUDIT-C scores. SLD was categorized into MASLD (SLD with ≥1 cardiometabolic risk factor (CMRF) + no alcohol use [AUDIT-C=0]), MetALD (SLD with ≥1 CMRF + low level alcohol use [AUDIT-C 1-2 for women and 1-3 for men]), and ALD (SLD + high level alcohol use [AUDIT-C >2 for women and >3 for men] without CMRF). Differences in the incidence of cirrhosis (per 1000 person-years) were evaluated using competing risks **Methods:** (censored for death) and adjusted multivariable Cox proportional hazards models. **Results:** Among 1.26 million Veterans with SLD identified, 54.1% (n=682,274) had MASLD, 41.1% (n=517,464) had MetALD, and 4.8% (n=60,461) had ALD. The cohort was predominantly male (93%) and non-Hispanic white (68-71%). Compared to patients with MASLD or MetALD, patients with ALD were significantly younger (mean age 55.1y vs. 60.0y (MetALD), vs. 63.3y (MASLD), p<0.001 for both) and had significantly lower body mass index (22.4 kg/m^2 vs. 32.8 kg/m^2 (MetALD), vs. 32.6 kg/m^2 (MASLD), p<0.001 for both). The long-term incidence of cirrhosis was significantly higher in ALD compared to MetALD (6.6 vs. 3.9 per 1000 person-years, p<0.001) or MASLD (6.6 vs. 4.3 per 1000 person-years, p<0.001) (Figure). On multivariable analysis, compared to MASLD, the risk of cirrhosis was significantly higher in ALD (HR 1.76, 95% CI 1.62-1.91, p<0.001), but no difference was observed among MetALD (HR 0.99, 95% CI 0.96-1.01, p=0.36). **Conclusion:** Among a national cohort of 1.26 million Veterans with SLD, patients with a predominantly alcohol-driven cause of SLD had 53-69% higher risk of cirrhosis than those with a predominantly metabolic driver of SLD or those with a mixed contribution of metabolic and alcohol factors.



Disclosures: Robert Wong: Theratechnologies: Grant/Research Support, Durect: Grant/Research Support, Gilead Sciences: Grant/Research Support, Exact Sciences: Grant/Research Support, Theratechnologies: Grant/Research Support, Durect Corporation: Grant/Research Support, Zeyuan Yang: Nothing to Disclose, Ashwani Singal: Advisor relationship with CLD Foundation; Has not ended; Speaking and Teaching relationship with Medical Speaker's Network; Has not ended; Speaking and Teaching relationship with Madrigal; Has not ended; Stock â€“ privately held company relationship with Pleiogenix; Has not ended; Consultant relationship with Pleiogenix; Has not ended; Advisor relationship with Durect; Has ended; Royalties or patent beneficiary relationship with Up-to-Date; Has not ended; Executive role relationship with Gastro Endo News; Has not ended; Grant/Research Support relationship with NIAAA; Has not ended; Employee relationship with Avera Medical Group; Has ended; Grant/Research Support relationship with GSK; Has not ended; Employee relationship with University of Louisville School of Medicine; Has not ended; Speaking and Teaching relationship with Medscape; Has not ended, Mario Pessoa: Nothing to Disclose, Aleksander Krag: Independent Contractor relationship with Siemens; Has ended; Speaking and Teaching relationship with Norgine; Has not ended; Advisor relationship

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2315 | SEXUAL DIMORPHISM IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE AMONG 1,472 PEOPLE WITH HIV

Sahar Saeed[1] Dana Kablawi[2] Tyler Thomas[1] Jovana Milic[3] Thierry Fotsing Tadjo[4] Felice Cinque[4] Al Shaima Al Hinai[4] Wesal Elgretli[4] Claudia Gioe[5] Emmanuel Tsochatzis[6] Jemima Finkel[6] Luz Ballesteros[4] Sanjay Bhagani[6] Antonio Cascio[7] Giovanni Guaraldi[8] Giovanni Mazzola[9] Giada Sebastiani[4]

[1]Queen's University, [2]McGill University, [3]University of Modena and Reggio Emilia, [4]McGill University Health Centre, [5]AOU Policlinico "P. Giaccone", [6]Royal Free London NHS Foundation Trust, [7]AOU Policlinico "P. Giaccone", Palermo, [8]Modena HIV Metabolic Clinic, [9]Sant'Elia Hospital

Background: People with HIV (PWH) are at high risk for metabolic dysfunction-associated steatohepatitis (MASH), with prevalence over 20%. Sex differences of MASH have been reported in the general population, with higher prevalence in men compared to women. However, after menopause MASH occurs at a higher rate in women. We investigated sexual dimorphism in MASH as a function of age in the setting of HIV infection. **Methods:** FibroScan was performed in PWH without viral hepatitis coinfection from four prospective cohorts in Canada, UK, and Italy. We employed the FibroScan-AST (FAST) score as it was validated to identify MASH with significant liver fibrosis (stage F2-F4). Moreover, the FAST score incorporates AST, which may better reflect liver damage in PWH by providing a signal of mitochondrial toxicity occurring in both MASH and antiretroviral therapy-associated hepatotoxicity. A FAST score >0.35 was employed to identify MASH with significant liver fibrosis. We employed a segmented linear mixed-effects model to evaluate the differences of MASH by sex as a function of age. Random effects accounted for the four sites, adjusted models included ethnicity, diabetes, hypertension, detectable HIV viral load. **Results:** We included 1,472 PWH (mean age 52 years, 25% female, diabetes prevalence 42%). Prevalence of MASH with significant liver fibrosis by FAST score was lower in women than in men (4.8% vs. 9.2%, p=0.008). Based on the adjusted model, male sex (+0.034; p=0.04), age per year (+0.003; p=0.05), detectable HIV viral load (+0.034; p=0.01) and hypertension (+0.03; p=0.01) were positively associated

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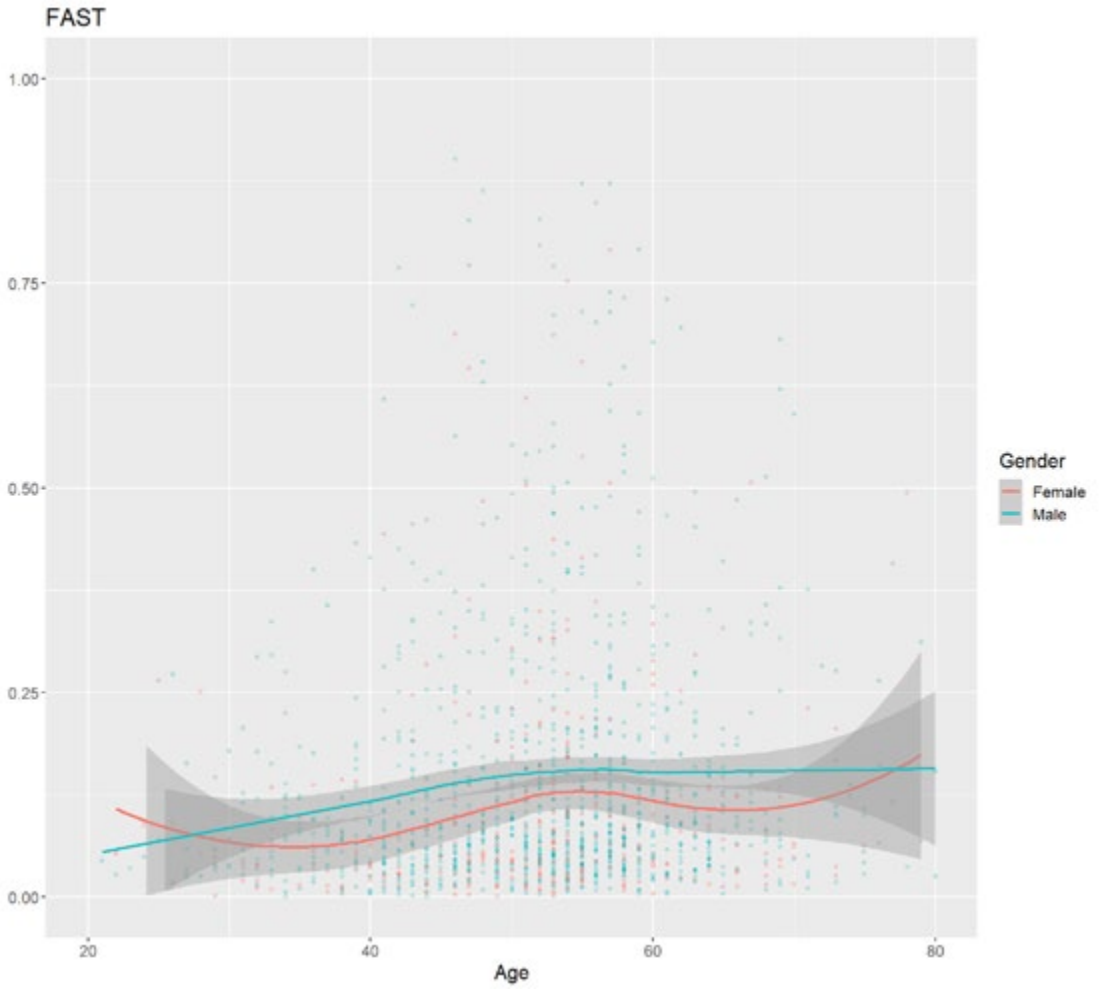
with MASH with fibrosis. While males had higher overall levels of FAST score, during the critical biological age of perimenopause to menopause (between 40- and 55-years) women had a more rapid increase in FAST score than men. By the age of 55 years men and women had similar levels of MASH with fibrosis (see Figure). Women who had MASH with fibrosis also presented with higher levels of total testosterone compared to women without MASH with fibrosis (4.54±0.99 nmol/l vs 3.19+1.70 nm/l, p=0.048). **Conclusion:** Our data support MASH as a sexual dimorphic disease in PWH. Despite women with HIV having lower prevalence of MASH with significant liver fibrosis compared to men, women exhibit an acceleration in FAST score increase around the perimenopausal age. Future studies should target adequate consideration of sex differences in clinical investigation of MASLD to fill current gaps and implement precision medicine for PWH.



Disclosures: Sahar Saeed: Novo Nordisk: Consultant, Dana Kablawi: Nothing to Disclose, Tyler Thomas: Nothing to Disclose, Jovana Milic: Nothing to Disclose, Thierry Fotsing Tadjo: Nothing to Disclose, Felice Cinque: Nothing to Disclose, Al Shaima Al Hinai: Nothing to Disclose, Wesal Elgretli: Nothing to Disclose, Claudia Gioe: Nothing to Disclose, Emmanuel Tsochatzis: NovoNordisk: Advisor, Siemens: Advisor, MSD: Advisor, Orphalan: Advisor, Univar: Advisor, Boehringer: Advisor, Echosens: Speaking and Teaching, Orphalan: Speaking and Teaching, Abbvie: Speaking and Teaching, NovoNordisk: Speaking and Teaching, Jemima Finkel: Nothing to Disclose, Luz Ballesteros: Nothing to Disclose, Sanjay Bhagani: Nothing to Disclose, Antonio Cascio: Nothing to Disclose, Giovanni Guaraldi: Nothing to Disclose, Giovanni Mazzola: Nothing to Disclose, Giada Sebastiani: Novo Nordisk: Consultant, Abbvie: Speaking and Teaching, Merck: Consultant, Gilead: Speaking and Teaching, Theratechnologies Inc.: Grant/Research Support

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2316 | PATIENTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD) AND SEVERE FIBROSIS HAVE WORSE EXECUTIVE FUNCTION PERFORMANCE

Ali Weinstein[1] Leyla de Avila[2] Brian Lam[2] Maria Stepanova[2] Jillian Price[2] Carey Escheik[3] Lynn Gerber[2] Zobair Younossi[4]

[1]George Mason University, [2]Beatty Liver/Obesity Research Program, [3]Beatty Liver/ Obesity Research Program, [4]The Global NASH Council

Background: Evidence suggests that Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) is associated with cognitive dysfunction. The impact of severity of fibrosis on cognitive performance needs additional investigation. In order to begin to understand the relationship, fibrosis can be used as a marker of liver disease severity. Our aim was to determine if there was a difference in cognitive performance comparing MASLD with severe fibrosis to those without. **Methods:** Patients with excess alcohol consumption or viral liver disease were excluded. Patients who did not have clinical evidence of cirrhosis were enrolled. After providing informed consent, clinical, demographic, transient elastography, and cognitive performance data were collected. The presence of severe fibrosis was defined using the following criteria: Fibroscan score>12 or ELF score>11.2 or FIB-4>2.67. Each participant completed subtests from the Delis-Kaplan Executive Function System (D-KEFS) and Wechsler Adult Intelligence Scale-Fourth Edition (WAIS-IV). Cognitive domains measured included perceptual reasoning, processing speed, and measures of executive function (working memory, cognitive flexibility and inhibition). **Results:** A total of 254 participants (6% severe fibrosis, 47% female, age: 52.3±14.3 years, body-mass index (BMI): 31.0±7.3 kg/m^2) completed the assessments. There was a statistically significant difference on BMI (p=0.039) between those with severe fibrosis (36.5±11.6 kg/m^2) and those without (30.7±6.9 kg/m^2). Cognitive flexibility showed a statistically significant difference between groups and inhibition showed a statistical trend for a difference between groups (see Table), with the severe fibrosis group performing worse. These differences remained significant after adjustment for BMI. There were no other statistically significant differences. **Conclusion:** Presence of severe fibrosis in MASLD is associated with lower executive functioning compared to those without severe fibrosis. This is consistent with a large body of literature linking hepatic fibrosis severity with health outcomes. Prospective studies are needed to evaluate the potential predictive value of severe fibrosis in the development of mild cognitive impairment.

		Severe Fibrosis n=15	No Severe Fibrosis n=239	p-value (between groups)
D-KEFS Color-Word Test	Inhibition Scaled Score (inhibition)	8.86 (3.74)	10.7 (2.9)	0.056
	Inhibition/Switching Scaled Score (cognitive flexibility)	8.43 (3.92)	10.5 (2.7)	0.037
WAIS-IV	Arithmetic Scaled Score (working memory)	9.86 (3.35)	10.4 (3.5)	0.68
	Coding Scaled Score (processing speed)	10.4 (3.4)	10.3 (3.0)	0.96
	Symbol Search Scaled Score (processing speed)	10.8 (2.6)	10.3 (2.8)	0.58
	Matrix Reasoning Scaled Score (perceptual reasoning)	10.6 (3.9)	10.9 (3.3)	0.50

Disclosures: Ali Weinstein: Nothing to Disclose, Leyla de Avila: Nothing to Disclose, Brian Lam: Madrigal: Speaking and Teaching, Maria Stepanova: Nothing to Disclose, Jillian Price: Nothing to Disclose, Carey Escheik: Nothing to Disclose, Lynn Gerber: Nothing to Disclose, Zobair Younossi: Nothing to Disclose

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2317 | SIGNIFICANT SEX/GENDER DISPARITIES IN THE PREVALENCE, CARDIOMETABOLIC RISK PROFILES AND MANAGEMENT OF MASLD: RESULTS FROM A COHORT OF 24,888 CANADIANS

Jessica Burnside[1] Giada Sebastiani[2] Felice Cinque[2] Keyur Patel[3] Alnoor Ramji[4] Mark Swain[5] Sahar Saeed[1]

[1]Queen's University, [2]McGill University Health Centre, [3]University of Toronto, [4]University of British Columbia, [5]University of Calgary

Background: Steatotic Liver Disease (SLD) is largely absent from public health agendas. We conducted Canada's first SLD prevalence study, focusing on sex/gender disparities. **Methods:** We used data from the Canadian Longitudinal Study on Aging (n=30,097), a cohort that prospectively follows adults between 45 and 85 years old from 11 sites across Canada between 2012-2018. Data on sociodemographic, lifestyle, clinical and treatment variables are collected on all participants every 3 years. Steatosis was identified using the serum biomarker NAFLD Ridge Score (NRS), based on ALT, HDL cholesterol, triglycerides, hemoglobin A1c, leukocyte count, and hypertension. An NRS cut-off >0.44 has a sensitivity of 92% and specificity of 90% to identify steatosis against proton magnetic resonance spectroscopy. Using AASLD's nomenclature of SLD, we estimated the prevalence of MASLD, MetALD and ALD. Poisson regression with robust standard errors and sampling weights were used to estimate adjusted prevalence ratios (aPR) with (95% CI). **Results:** Our observational cohort included 24,888 people (51.4% female, median age 58 years (IQR: 51-67)). The most common subtype of SLD was MASLD, 35% (34-36%), followed by MetALD 2.6% (2.3-2.9%), and ALD 0.8% (0.6-1.0%). The prevalence of MASLD and MetALD among males was significantly higher than in females (p<0.001). Prevalence of males with MASLD was 46% (45-48%) compared to females with MASLD 24% (23-26%) and males with MetALD 3.7% (3.2-4.2%) compared to females 1.6% (1.2-2.1%). After stratifying by sex and adjusting for age and lifestyle factors, differences by gender-associated variables were more pronounced in females than in males. Among females, lower household incomes (aPR: 2.9, 95%CI: 2.4-3.5), post-menopausal status (aPR: 1.4, 1.2-1.6) or had a hysterectomy (aPR: 1.9, 1.7-2.2) were associated with higher MASLD prevalence. Females with MASLD were more likely to have all 5 cardiometabolic conditions (35%, 32%-39%) compared to males (29%, 26%-31%) (p<0.001) (figure 1). We also found significant sex disparities in disease management: 38% (95%CI: 35-42%) of females had low HDL cholesterol but were not on lipid-lowering therapy, compared to 29% of males (95%CI: 26-32%) (p<0.001). **Conclusion:** In this large Canadian cohort, we found significant MASLD sex/gender disparities in SLD prevalence, cardiometabolic risk factors, and management. Epidemiological assessments are necessary to improve national preparedness for the significant projected increase in advanced liver disease by 2040.

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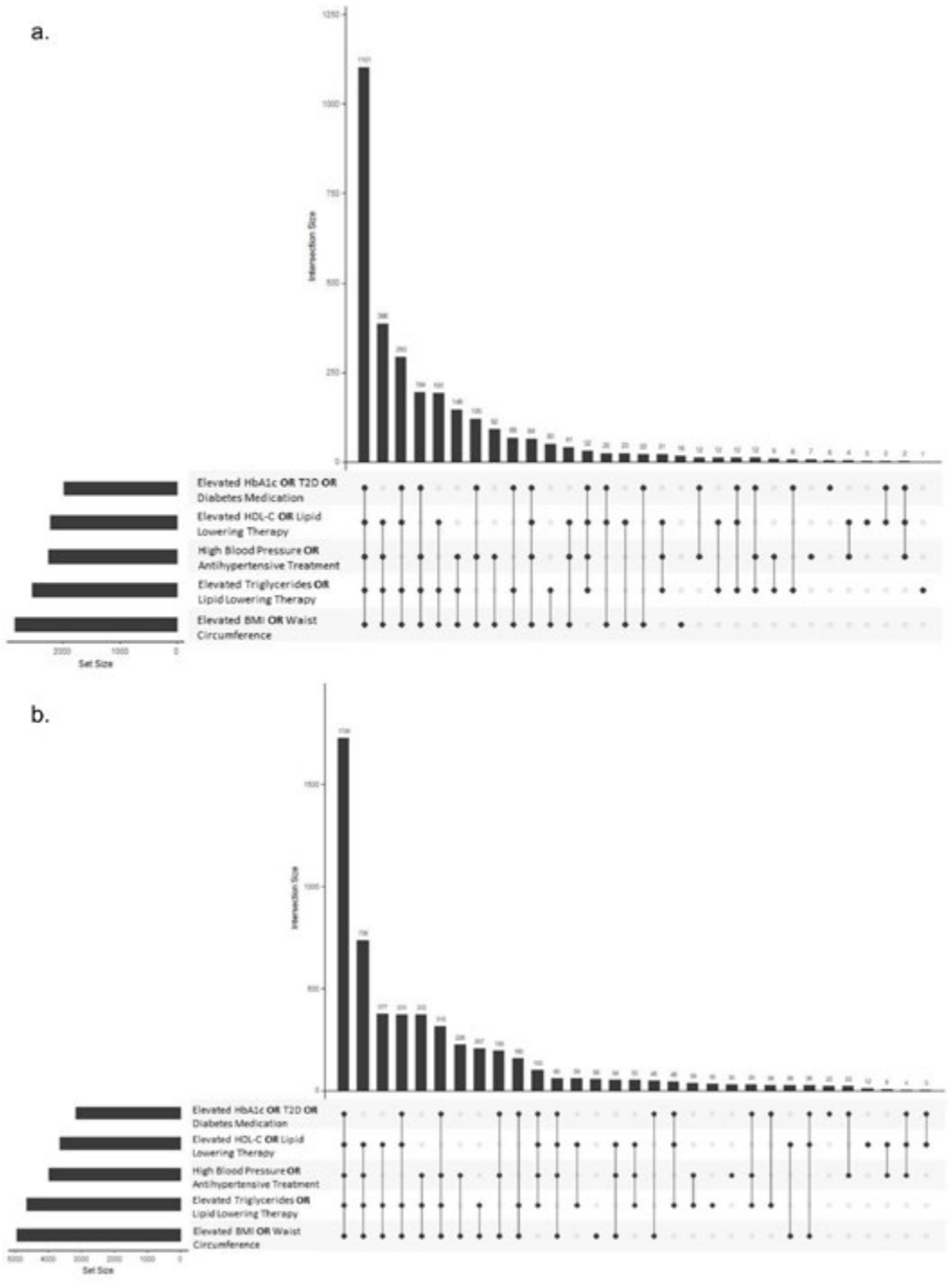

Figure: Upset plot depicting the phenotypes of MASLD (based on the frequency and combinations of the five cardiometabolic criteria) amongst females (a) and males (b)

Disclosures: Jessica Burnside: Nothing to Disclose, Giada Sebastiani: Novo Nordisk: Consultant, Abbvie: Speaking and Teaching, Merck: Consultant, Gilead: Speaking and Teaching, Theratechnologies Inc.: Grant/ Research Support, Felice Cinque: Nothing to Disclose, Keyur Patel: Novo-Nordisk: Consultant, Gilead Sciences: Consultant, Merck: Consultant, Resalis: Advisor, Alnoor Ramji: Nothing to Disclose, Mark Swain: Ipsen: Advisor, Abbott: Advisor, Advanz: Advisor, Novo Nordisk: Advisor, GSK: Advisor, Ipsen: clinical trial research grant support, Novo Nordisk: clinical trial research grant support, Madrigal: clinical trial research grant support, Kowa: clinical trial research grant support, Gilead: clinical trial research grant support, Abbvie: clinical trial research grant support, Merck: clinical trial research grant support, Galectin: clinical trial research grant support, Sahar Saeed: Novo Nordisk: Consultant

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2318 | INVESTIGATION OF FACTORS CONTRIBUTING TO LIVER FIBROSIS IN MASLD THROUGH SERIAL MR ELASTOGRAPHY AND MRI-PDFF

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Background: Liver fibrosis is an important prognostic factor in chronic liver disease, but the factors contributing to fibrosis progression in MASLD remain unclear. This study aimed to analyze the long-term course of hepatic fibrosis and steatosis using MR elastography (MRE) and MRI-PDFF, and to identify factors contributing to fibrosis progression. **Methods:** We retrospectively analyzed 503 MASLD patients who underwent MRE at least twice. Based on liver stiffness measurements (LSM) in the initial MRE, patients were categorized into non-cirrhotic (LSM < 4.67 kPa) and cirrhotic (LSM ≥ 4.67 kPa) groups. Additionally, patients were classified into progression (ΔLSM ≥ +19%) and non-progression (ΔLSM < +19%) groups based on the rate of change in LSM (ΔLSM). We analyzed the longitudinal changes in LSM and MRI-PDFF, and investigated their correlation. Furthermore, we conducted an analysis to identify factors contributing to the changes in LSM. **Results:** The study included 268 females (53.3%) with a mean age of 58.0±14.1 years and a BMI of 29.5±23.3. The average interval between MREs was 45.1±70.2 months. The non-cirrhotic/cirrhotic groups comprised 447 patients (88.9%)/56 patients (11.1%), and the non-progression/progression groups comprised 443 patients (88.1%)/60 patients (11.9%). A positive correlation was observed between the rate of PDFF change (ΔPDFF) and ΔLSM in the non-cirrhotic group (p=0.029), whereas a negative correlation was seen in the cirrhotic group (p=0.031). For all patients (n=503), multivariate analysis identified BMI > 25 (OR 2.37, p=0.023) as a factor contributing to fibrosis progression (ΔLSM ≥ +19%). In the non-cirrhotic group (n=447), factors contributing to fibrosis progression were BMI > 25 (OR 2.75, p=0.013) and platelets < 220 × 10^9 /L (OR 1.94, p=0.044). **Conclusion:** Changes in PDFF and LSM show a positive correlation in non-cirrhotic patients and a negative correlation in cirrhotic patients. The negative correlation between ΔPDFF and ΔLSM in cirrhotic patients may reflect “burnt-out MASH”. In MASLD, BMI and platelet count may be useful predictors of fibrosis progression in earlier stages.

Disclosures: Takashi Kobayashi: Nothing to Disclose, Naohiro Wada: Nothing to Disclose, Michihiro Iwaki: Nothing to Disclose, Asako Nogami: Nothing to Disclose, Masato Yoneda: Gilead Sciences Inc.: Grant/Research Support, Satoru Saito: Nothing to Disclose, Atsushi Nakajima: Nothing to Disclose

2319 | METABOLIC-ASSOCIATED STEATOTIC LIVER DISEASE AND INFECTIONS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: Previous literature suggests that patients with metabolic-associated steatotic liver disease (MASLD) might be at increased risk of infections. In this systematic review and meta-analysis, we aimed to investigate the association between MASLD and infections. **Methods:** We performed a systematic review of the literature using Medline, Embase and Cochrane databases from inception to May 2024 to identify studies evaluating the association of MASLD with any type or severity of infection. We performed a subgroup analysis based on the site of infection and the presence of cirrhosis. We excluded studies examining the association of MASLD and COVID-19 infection. Risk of bias assessment was performed with ROBINS-I tool. Random effects model was used and analysis was performed with STATA 17. **Results:** Nine observational studies assessing the association of MASLD with any type or severity of infection were included in the final analysis. Patients in the MASLD group were more likely to have diabetes or obesity at baseline. Overall, pooled analysis showed a higher risk of infection in MASLD group compared to no MASLD group (OR 1.84, 95% CI 1.54-2.20, Figure 1, I^2=97.9%). The presence of cirrhosis in patients with MASLD was associated with higher risk of infection (2 studies, OR 1.90, 95% CI 1.67-2.17, Figure 2) compared to patients with no cirrhosis (simple steatosis or fibrosis) at baseline . In the subgroup analysis based on the site of infection, the presence of MASLD increased the risk of respiratory infections (3 studies, OR 1.57, 95% CI: 1.31-1.89, Figure 3), gastrointestinal infections (3 studies, OR 2.01, 95% CI 1.70-2.39, Figure 4), urinary

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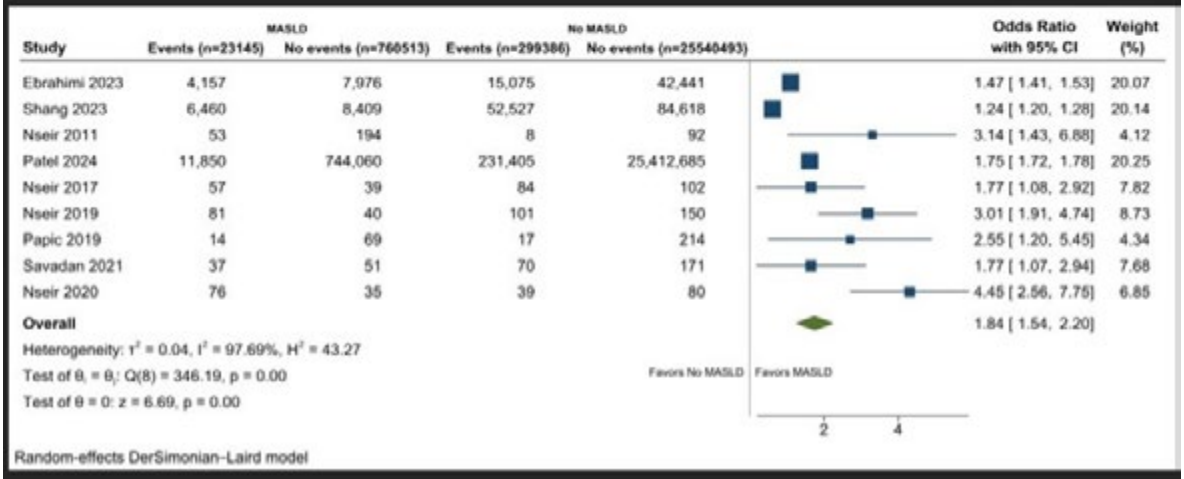
tract infections (3 studies, OR 1.83, 95% CI 1.37-2.44, Figure 5) and Clostridium difficile infection (4 studies, OR 2.28, 95% CI 1.44-3.60, Figure 6). No information was available regarding the causative agent and the type of infection. High heterogeneity was present in the analysis; however, each study was associated with significantly higher risk of infection and baseline differences between the groups may account for this finding. **Conclusion:** In this systematic review and meta-analysis, we demonstrated a significant association between the presence of MASLD and risk of infection, which was more evident in patients with MASLD-associated cirrhosis. Thus, clinicians should have an increased clinical vigilance for infections among patients with MASLD. Future studies are warranted to identify modifiable risk factors aimed at preventing infections in this vulnerable population and elucidating the predominant types of infections.

Table 1. Baseline demographic data of the included studies in the final analysis

Study	N of patients		Diabetes, n (%)		Obesity, n (%)		Cirrhosis, n (%)		Prior antibiotic use, n (%)		IBD, n (%)	
	MASLD	No MASLD	MASLD	No MASLD	MASLD	No MASLD	MASLD	No MASLD	MASLD	No MASLD	MASLD	No MASLD
Ebrahimi 2023	12133	57516	1524 (12.6)	1928 (3.4)	542 (4.5)	251 (0.4)	678	0	NA	NA	NA	NA
Shang 2023	14869	137145	2980 (20.0)	5584 (4.1)	2450 (16.5)	2860 (2.1)	687 (4.6)	5 (0.0)	NA	NA	565 (3.8)	1365 (1.0)
Nseir 2011	247	100	111 (45)	21 (21)	NA	NA	NA	NA	NA	NA	NA	NA
Patel 2024	755.910	25.644.090	348.225 (46.07)	7.186.560 (27.9)	249.200 (32.9)	4.685.809 (18.2)	NA	NA	NA	NA	12 950 (1.7)	278.615 (1.0)
Nseir 2017	96	186	151 (53.5)		NA	NA	NA	NA	NA	NA	NA	NA
Nseir 2019	121	251	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Papic 2019	83	231	31 (37.35)	58 (25.11)	15 (18.07)	19 (18.23)	NA	0	32 (35.5)	96 (41.56)	NA	NA
Savadan 2021	88	241	NA	NA	NA	NA	NA	NA	Total: 148 (45.0)		NA	NA
Nseir 2020	111	119	98 (42.6)		NA	NA	NA	NA	Total: 119 (51.7)		NA	NA

NA: not available; N, n: number; MASLD: metabolic associated steatotic liver disease; IBD: inflammatory bowel disease;

Figure 1. Forest plot depicting the association between MASLD and any type or severity of infection



MASLD: metabolic-associated steatotic liver disease; CI: confidence intervals; I^2: heterogeneity

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2320 | PROGNOSIS OF LEAN AND NON-LEAN MASLD IN A LARGE-SCALE ASIAN POPULATION STUDY

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Background: The prognosis of lean metabolic dysfunction-associated steatotic liver disease (MASLD) has remained uncertain due to inconsistent evidence. This study seeks to clarify the prognosis of lean MASLD by conducting an extensive analysis of a large Asian cohort. **Methods:** Using a nationwide, population-based database, this study analyzed data from 2.9 million patients. The primary outcomes measured were liver-related events (LREs) and cardiovascular events (CVEs) among patients with lean MASLD, non-lean MASLD, and a normal liver control group. **Results:** The median follow-up period was 4.2 years. The 5-year incidence rates of LREs in the lean MASLD, non-lean MASLD, and normal liver control groups were 0.065%, 0.039%, and 0.006%, respectively. The risk of LREs in lean MASLD was significantly higher compared to the normal liver control group (adjusted hazard ratio [aHR]: 5.94, 95% confidence interval [CI], 3.95–8.92), but similar to that in non-lean NAFLD (aHR: 1.35, 95% CI, 0.87–2.08). In contrast, for CVEs, the non-lean MASLD group exhibited a higher 5-year cumulative incidence rate (0.779%) than the lean MASLD (0.600%) and normal liver control (0.254%) groups. The lean MASLD group had a lower risk of CVEs compared to the non-lean MASLD group (aHR, 0.73; 95% CI, 0.64–0.84) and a comparable risk to the normal liver control group (aHR, 0.99; 95% CI, 0.88–1.12). The 5-year cumulative total mortality rate was higher in the lean MASLD group (0.202%) and non-lean MASLD group (0.170%) compared to the normal liver control group (0.104%). Notably, the 5-year cumulative liver-related mortality rates were the highest in the lean MASLD group (0.014%) followed by the non-lean MASLD group (0.005%), and the lowest in the normal liver control group (0.001%) On the other hand, the 5-year cumulative cardiovascular- related mortality rate was higher in the non-lean MASLD group (0.027%) compared to the normal liver control group (0.012%), but it did not show a statistically significant difference from the lean MASLD group. **Conclusion:** Lean MASLD presents a similar risk of LREs and a lower risk of CVEs when compared to non-lean MASLD. Therefore, monitoring and treatment strategies should be customized to the specific type of MASLD.

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2321 | LIVER-RELATED OUTCOMES OVER 15 YEARS FOLLOWING METABOLIC DYSFUNCTION–ASSOCIATED STEATOHEPATITIS DIAGNOSIS

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[1]Regeneron Genetics Center

Background: Metabolic dysfunction–associated steatohepatitis (MASH) is a severe inflammatory form of metabolic dysfunction–associated steatotic liver disease (MASLD). Large real-world datasets offer an opportunity to better understand MASH disease progression. **Methods:** Our analysis was conducted in patients with MASH sourced from two cohorts of real-world populations (Geisinger Health System [GHS] and United Kingdom Biobank [UKB]), identified using ICD-10 codes. Patients were included if they had no history of chronic viral hepatitis, alcohol dependency, or alcohol-related liver disorders. We assessed the prevalence and incidence of clinical hepatic endpoints following MASH diagnosis, including esophageal varices, liver transplant, ascites, liver failure, liver cancer, liver fibrosis, liver cirrhosis, and death. **Results:** A total of 3495 and 1756 patients with MASH were included from the GHS and UKB cohorts, respectively. Median age and body mass index were 57–59 years and 31–35 kg/m^2, respectively. Year 1 liver fibrosis rates were 6.5% in GHS and 0.8% in UKB. The incidence of all liver events was low at 3 months after MASH diagnosis, and increased over time: 3.2% and 0.2% at 3 months and 19.0% and 23.7% at 15 years in the GHS and UKB cohorts, respectively (**Table**). The incidence of all-cause mortality was also low at 3 months after MASH diagnosis and increased over time: 3.6% and 3.1% at 3 months

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and 29.5% and 21.3% at 15 years in the GHS and UKB cohorts, respectively. **Conclusion:** These real-world data from heterogeneous US and UK populations depict the progression of hepatic complications and death in people with MASH. Although real-world data may not reflect the true course of illness, these data represent large patient cohorts with MASH and are among the longest durations of follow-up studied. A greater understanding of disease progression in patients with MASH may help to inform clinical care and clinical trial design.

Table. Cumulative incidence of liver outcomes at varying timepoints after initial MASH diagnosis

Events, %	Analyzed (n)[a]	Month 3	Year 1	2	3	5	10	15
GHS cohort								
Liver fibrosis[b]	2650	3.7	6.5	8.4	9.9	11.8	15.2	19.4
Liver failure[c]	3226	1.7	3.9	5.2	6.0	7.9	10.9	10.9
Liver ascites[d]	3257	0.4	1.6	2.2	2.8	3.4	5.2	5.5
Esophageal varices[e]	3376	0.2	0.6	1.0	1.4	2.0	2.8	2.8
All liver events	2580	3.2	5.9	7.7	9.3	11.1	14.8	19.0
All-cause mortality	3442	3.6	7.3	10.6	13.6	17.6	24.7	29.5
All events	2580	3.8	7.2	9.8	11.9	14.9	21.3	29.5
UKB cohort								
Liver fibrosis[b]	1668	0.2	0.8	2.3	3.6	7.0	16.0	23.0
Liver failure[c]	1737	0	0	0.4	0.7	2.2	5.7	6.8
Liver ascites[d]	1724	0	0.2	0.9	1.4	2.9	7.3	9.3
Esophageal varices[e]	1745	0	0	0.1	0.2	0.4	1.2	1.6
All liver events	1662	0.2	0.9	2.4	3.7	7.5	17.0	23.7
All-cause mortality	1756	3.1	5.3	7.8	8.8	10.8	15.3	21.3
All events	1662	2.4	5.0	8.5	10.2	14.0	22.0	31.7

[a]Patients with respective events prior to index time were excluded from analysis.

The following ICD-10 codes were used: [b]K74.0, hepatic fibrosis; [c]K72, liver failure, K76.7, hepatorenal syndrome; [d]R18, ascites; [e]I85.01, esophageal varices with bleeding; I85.11, secondary esophageal varices with bleeding;

GHS, Geisinger Health System; MASH; metabolic dysfunction-associated steatohepatitis; UKB, United Kingdom Biobank.

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2322 | CHANGES IN HEMOGLOBIN A1C AND BODY WEIGHT ARE STRONGLY ASSOCIATED WITH CHANGES IN LIVER STIFFNESS IN ADULTS WITH BIOPSY-PROVEN MASLD

Matthew Dukewich[1] Liyun Yuan[2] Bilal Hameed[3] Laura Wilson[4] Katherine Yates[4] Rohit Loomba[5] Brent Neuschwander-Tetri[6] Norah Terrault[2]

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Background: Metabolic dysfunction associated steatotic liver disease (MASLD) shares an underlying pathophysiology with cardiometabolic disorders. While current MASLD treatment guidance emphasizes optimizing treatment of these metabolic comorbidities, the dynamic relationship between changes in cardiometabolic risk factors (CMRF) and MASLD severity is unclear. This study examined longitudinal changes in CMRF and

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noninvasive prognostic parameters of MASLD, particularly VCTE-derived liver stiffness (LSM). **Methods:** Adult participants from the NASH CRN prospective study with biopsy-proven MASLD and at least two sequential VCTE exams separated by at least one year were included in this analysis. Annual changes (relative to previous exam) in CMRF values of A1c, BMI, waist circumference, or body weight were compared against annual changes (relative to previous exam) in VCTE LSM using a mixed-effects multinomial logistic regression analysis with annual changes in CMRF as repeated measures, adjusted for baseline values, demographics, and diabetes medication category (if used). The primary outcome was LSM change categorized as (i) worsened if increase of >5kPa, (ii) no change if change ≤5kPa, or (iii) improved if decreased by >5kPa. **Results:** Among 1417 participants, the mean age was 52 years, with 38% male, and a baseline mean BMI of 34 kg/m^2. Comorbid diabetes was present in 52%, with a baseline mean A1c of 6.4%, and a baseline mean LSM of 11.2 kPa. Annual worsening of A1c by 1% was associated with a 23% greater risk for worsening of LSM (versus no change in LSM, $p < 0.001$), while an annual improvement of A1c by 1% was associated with a 45% greater probability for improved LSM (versus no change in LSM, $p < 0.001$). Similar findings were seen with BMI, with an annual worsening of BMI by 1 kg/m^2 associated with a 9% greater risk for worsening of LSM (versus no change, $p < 0.001$) while an annual improvement of BMI by 1 kg/m^2 was associated with a 10% greater probability for improved LSM (versus no change in LSM, $p < 0.001$) (Table 1). **Conclusion:** This study demonstrates the dynamic relationship between changes in metabolic comorbidities and clinically significant MASLD prognostic parameters, particularly LSM. The finding that annual improvements in A1c and BMI are associated with clinically meaningful improvements in LSM can be utilized to educate and motivate patients and providers in optimizing overall metabolic and liver health.

Table 1. Association between LSM change and change in HbA1c, BMI, weight, and waist circumference from longitudinal mixed-effects multinomial logistic regression analysis

	LSM worsened vs. no change		LSM improvement vs. no change	
	RRR (95% CI)*	P	RRR (95% CI)*	P
Change in HbA1c†	1.27 (1.15, 1.40)	<0.001	0.70 (0.63, 0.77)	<0.001
Change in HbA1c, adjusted‡	1.23 (1.12, 1.37)	<0.001	0.69 (0.62, 0.76)	<0.001
Change in BMI†	1.09 (1.05, 1.14)	<0.001	0.91 (0.88, 0.94)	<0.001
Change in BMI, adjusted§	1.09 (1.05, 1.14)	<0.001	0.91 (0.88, 0.94)	<0.001
Change in weight (kg) †	1.05 (1.03, 1.07)	<0.001	0.95 (0.94, 0.97)	<0.001
Change in weight (kg), adjusted§	1.05 (1.03, 1.07)	<0.001	0.96 (0.94, 0.97)	<0.001
Change in waist circumference (cm)†	1.03 (1.01, 1.04)	<0.001	0.99 (0.97, 1.00)	0.02
Change in waist circumference (cm), adjusted§	1.03 (1.01, 1.04)	<0.001	0.99 (0.97, 1.00)	0.02

*RRR=Relative Risk Ratio

† Models included terms for baseline value of the change measure and time.

‡ Adjusted for age, sex, race, ethnicity, BMI, diabetes medications, baseline HbA1c, and time.

§ Adjusted for age, sex, race, ethnicity, baseline value of the change measure (BMI, weight, waist), and time.

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2323 | IMPACT OF NEW NOMENCLATURE ON HOSPITALIZATION OUTCOMES: COMPARING MASLD, METALD, AND ALD

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Background: Recent nomenclature categorizes hepatic steatosis conditions into Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD), Alcohol-Related Liver Disease (ALD), and introduces metALD (MASLD and increased alcohol intake). While MASLD and Non-Alcoholic Fatty Liver Disease (NAFLD) have greater than 99% overlap, the clinical implications of this new nomenclature are underexplored. We aim to evaluate hospitalization outcomes for these steatotic subgroups. **Methods:** Data from the Healthcare Cost and Utilization Project, National Inpatient Sample (NIS) database (October 1, 2015 - March 1, 2020) were analyzed. Patients were categorized into MASLD, METALD, ALD, and ALD+ (ALD with cardiometabolic risk factors) using ICD-10-CM codes. All groups excluded patients with codes for other chronic liver diseases. MASLD was defined using “fatty liver” or NASH codes with at least one cardiometabolic risk factor code, excluding all ALD codes. METALD included “fatty liver” and at least one cardiometabolic risk factor with added chronic alcohol use or uncomplicated alcohol dependence codes. ALD included ALD codes or “fatty liver” with alcohol abuse and complicated alcohol dependence codes. Outcomes included length of hospitalization, in-hospital mortality, liver transplant rates, and liver-related hospitalizations. Statistical analyses included chi-square tests, t-tests, and multivariate logistic regression models. **Results:** The study included 625,437 patients: ALD (27.1%), ALD+ (30.1%), MASLD (41.7%), and METALD (1.1%). Most hospitalizations were short-term (1-14 days) across subgroups (90-94%), with ALD patients exhibiting the highest long-term stays (>2 weeks) (Table 1). Mortality rates during hospitalization were highest in ALD (6.5%), followed by ALD+ (4.4%), MASLD (1.6%), and METALD (1%) *. ALD and ALD+ had more liver-related hospitalizations (28% and 23.4%) compared to MASLD and METALD (12.8% and 4.7%) *. ALD and ALD+ had more hepatorenal syndrome, esophageal varices with bleeding, and spontaneous bacterial peritonitis than MASLD and METALD* (Table 1). Among Black patients, those with ALD and ALD+ had higher mortality compared to MASLD (OR = 3.23 and OR=2.25* respectively). ALD and ALD+ had higher mortality for both liver (OR=3.45 and OR=2.6* respectively) and non-liver-related hospitalizations (OR = 3.96 and OR = 2.71* respectively) when compared to MASLD.
*Note: * P<0.0001* **Conclusion:** ALD patients had the highest mortality and longest length of hospital stay, while METALD had the lowest. ALD and ALD+ patients had increased mortality for both liver and non-liver related hospitalizations compared to MASLD. Prospective studies are needed to further characterize these outcomes.

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Variable	Total Hospitalizations N = 625,437 (%)	Patients with Steatotic Liver Disease: Alcohol Liver Disease (ALD) n = 169,808 (%)	Alcohol Liver Disease Plus Metabolic Risk (ALD-Plus) n = 188,284 (%)	Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) n = 260,540 (%)	Metabolic Dysfunction and Alcohol-Related Steatotic Liver Disease (MetALD) n = 6,805 (%)	*P* value
Year of Admission						
2015	4.7	5.0	5.2	4.3	5.1	<0.0001
2016	20.2	20.7	21.2	19.1	21.4	<0.0001
2017	21.3	21.9	21.4	20.9	19.7	<0.0001
2018	23.0	23.1	22.6	23.3	21.2	<0.0001
2019	24.6	23.7	23.7	25.9	25.3	<0.0001
2020	6.1	5.7	5.9	6.6	7.2	<0.0001
Sex						
Male	57.9	66.5	73.3	40.8	70.9	<0.0001
Female	42.1	33.5	26.7	59.2	29.1	<0.0001
Age, *y*						
< 20	5.1	5.0	5.2	5.0	5.2	<0.0001
21-30	3.6	4.8	1.8	4.0	3.4	<0.0001
31-40	9.7	14.0	8.0	8.1	11.6	<0.0001
41-50	16.3	19.6	16.9	13.7	18.1	<0.0001
51-60	25.6	27.3	30.6	20.7	28.6	<0.0001
61-70	20.1	15.4	20.9	22.7	18.2	<0.0001
71-80	8.8	4.4	6.8	13.1	5.4	<0.0001
> 80	2.5	1.0	1.4	4.3	0.9	<0.0001
Missing	8.4	8.4	8.5	8.4	8.6	<0.0001
Race						
White	63.8	62.1	63.3	65.2	62.8	<0.0001
Black	8.8	8.1	9.8	8.2	14.2	<0.0001
Hispanic	14.4	15.5	13.8	14.2	10.9	<0.0001
Other	13.1	14.3	13.1	12.3	12.1	<0.0001
Hospital Length of Stay						
< 1 Day	1.5	1.8	1.3	1.4	1.3	<0.0001
1 - 14 Days	92.4	90.2	91.6	94.2	95.7	<0.0001
> 14 Days	6.2	8.1	7.0	4.4	3.0	<0.0001
Death in Hospital						
Alive at Discharge	96.3	93.5	95.6	98.4	99.0	<0.0001
Died	3.7	6.5	4.4	1.6	1.0	<0.0001
Liver Transplant						
Transplant	0.4	0.5	0.4	0.3	0.0	<0.0001
No Transplant	99.6	99.5	99.6	99.7	100.0	<0.0001
Liver Related Hospitalization						
Yes	20.1	28.0	23.4	12.8	4.7	<0.0001
No	79.9	72.0	76.6	87.2	95.3	<0.0001
Acute Liver Complications						
Hepatorenal Syndrome	3.1	5.9	3.7	1.0	0.1	<0.0001
Spontaneous Bacterial Peritonitis	2.0	3.7	2.6	0.6	0.1	<0.0001
Esophageal Varices with Bleeding	0.7	1.0	0.9	0.3	0.2	<0.0001

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2324 | THE GLOBAL PROFILE OF METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD): CLINICAL PRESENTATION, HISTOLOGIC STAGE, NON-INVASIVE TESTS AND MORTALITY FROM THE GLOBAL NAFLD/MASLD REGISTRY

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Background: MASLD is prevalent across the world. We aimed to evaluate clinical presentation and performance of common NITs for MASLD from different global regions. **Methods:** Enrollees of the Global Registry with liver biopsies and NITs [FIB-4, ELF, and liver stiffness measurement (LSM)] were included. **Results:** Of 15,991 NAFLD/NASH subjects from 39 countries [37% North America (NA), 28% Europe (EU), 21% Southeast Asia (SEA), 7% MENA, 5% South Asia (SA), 3% Latin America and the Caribbean (LA)], 97.2% met MASLD criteria: age 52±13 years, 47% male, BMI 34±9, 71% obese, 50% type 2 diabetes (T2D), 59% significant fibrosis (histologic stage≥F2), 40% advanced fibrosis (stage≥F3), 14% cirrhosis (stage F4). Also, 54% had FIB-4<1.30 and 13% FIB-4≥2.67; 26% had ELF<9.2 and 11% ELF≥11.3; 48% had LSM<10 kPa and 15% LSM≥20 kPa. Across the global regions, the prevalence of significant and advanced fibrosis was the highest in NA (72% and 51%), the lowest in SEA (43% and 28%). In all regions, advanced fibrosis subjects were older with more T2D (all adjusted p<0.05). Diagnostic performance of NITs showed some variability across regions: AUC of FIB-4 for advanced fibrosis was 0.79 (95% CI 0.78-0.80), lowest in EU [0.77 (0.76 - 0.78)], highest in SEA [0.81 (0.79 - 0.83)]. The AUC of ELF was 0.77 (95% CI 0.75-0.80), lowest in EU [0.72 (0.69 - 0.75)], highest in SEA [0.80 (0.74 - 0.85)]. The AUC for LSM was 0.82 (0.81-0.83) and was similar (up to 0.85) in all regions except NA [0.75 (0.73-0.77)]. There was minimal regional variability in NIT cutoffs needed to achieve high sensitivity but some variability in NIT cutoffs for specificity (Table). Of the entire group, 3191 had follow-up (mean 8.8 years) with 12% deaths. In age- and sex-adjusted Cox proportional hazards models, T2D and histologic fibrosis stage [adjusted hazard ratio (aHR) (95% CI) = 1.48 (1.20 - 1.84) for significant fibrosis, 2.02 (1.57 - 2.58) for advanced fibrosis, 2.57 (1.91 - 3.46) for cirrhosis] or higher NITs [aHR = 1.52 (1.13 - 2.03) for FIB-4 ≥2.67; 1.59 (1.13 - 2.23) for FIB-4 ≥ 3.25; aHR = 2.85 (1.65-4.93) for LSM ≥10 kPa; 3.35 (2.00-5.63) for LSM ≥15 kPa; 3.88 (2.28-6.59) for LSM ≥ 20 kPa] were independently associated with higher mortality (all p<0.01). **Conclusion:** Clinical presentation and NIT diagnostic performance of MASLD have some variability across regions of the world. Presence of T2D, stage of fibrosis and NITs similarly predict MASLD mortality from different regions of the world.

NIT score / cutoff criterion	Region *	Sensitivity 80%	Sensitivity 90%	Specificity 90%	Specificity 95%	Specificity 98%
FIB-4 predicting advanced fibrosis (F3-F4)	Europe	1.14	0.91	2.00	2.47	3.20
	MENA	1.06	0.85	1.70	2.05	2.63
	South Asia	1.53	1.06	2.44	3.50	6.70
	Southeast Asia	1.11	0.80	2.14	2.81	3.93
	North America	1.11	0.90	1.91	2.32	3.02
ELF predicting advanced fibrosis (F3-F4)	Europe	9.3	8.9	10.5	10.9	11.3
	Southeast Asia	9.6	9.2	10.6	11.2	11.6
	North America	9.3	8.9	10.4	10.7	11.3
LSM (kPa) predicting advanced fibrosis (F3-F4)	Europe	9.6 kPa	8.3 kPa	13.6 kPa	16.6 kPa	22.2 kPa
	MENA	9.6 kPa	8.6 kPa	12.6 kPa	14.5 kPa	18.0 kPa
	South Asia	10.2 kPa	8.4 kPa	13.2 kPa	19.1 kPa	33.0 kPa
	Southeast Asia	9.6 kPa	7.8 kPa	13.2 kPa	16.7 kPa	21.2 kPa
	North America	9.9 kPa	8.3 kPa	17.0 kPa	21.2 kPa	29.8 kPa

* The sample size was insufficient for Latin America, ELF in MENA, South Asia

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2325 | ASSOCIATION BETWEEN METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE AND DEMENTIA-RELATED BRAIN STRUCTURE IN ELDERLY PEOPLE LIVING IN JAPAN: THE ARAO COHORT STUDY

Katsuya Nagaoka[1] Maiko Nagaoka[2] Naoto Kajitani[3] Tomoyuki Imai[3] Seiji Yuki[3] Etsuko Iio[4] Yoko Yoshimaru[4] Takehisa Watanabe[4] Hiroko Setoyama[4] Shuken Boku[3] Noboru Fujise[2] Minoru Takebayashi[3] Yasuhito Tanaka[4]

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Background: The Arao Cohort Study is a population-based prospective study of dementia and depression in 1,577 residents aged 65 years and older in Arao City, Kumamoto Prefecture, Japan, who consented to participate in the study. In this study, we examined the association between cognitive impairment-related brain region measurements using brain MRI and metabolic dysfunction-associated steatotic liver disease (MASLD) among Arao cohort participants from 2016 to 2017. **Methods:** The subjects were 1,448 Arao Cohort participants with no missing data for this study. Those who rarely drank alcohol or had quit for more than 5 years were defined as “light drinkers.” “Fatty liver index (FLI)” (Bedogni *et al*. 2006) was used to assess steatotic liver disease (SLD), with FLI ≥30 considered to be SLD. Among these, those who met any of the following criteria were classified as having MASLD: (1) obesity (BMI ≥ 23 kg/m^2 or abdominal circumference ≥ 94 cm (male) and ≥ 80 cm (female)), (2) diagnosed/ treated diabetes, (3) hypertension/ treatment, (4) high serum triglycerides/ treatment, or (5) low serum HDL cholesterol/ treatment. Brain MRI images were segmented into regions based on the Desikan-Killiany atlas using FreeSurfer 5.3, and the volume of each region was measured. The Mini-Mental State Examination (MMSE) was used as a screening test for cognitive impairment. This study was approved by the Ethics Committee of Kumamoto University. **Results:** Of the 1,448 subjects, 885 were light drinkers, 377 had SLD, and 366 had MASLD. Among light drinkers, those with SLD had significantly decreased hippocampal volume involved in episodic memory (reduction rate: 1.78, P=0.037) and significantly increased cerebral white matter hypointensities compared to those without SLD (increase rate: 14.5%, P=0.045). In the analysis of MASLD, those with FIB-4 index ≥2.67 had significantly decreased hippocampal volume (decrease rate: 5.64%, P=0.010) and significantly increased cerebral white matter hypointensities (increase rate: 47.8%, P=0.015) compared to those with FIB-4 index <2.67. In addition, MASLD with FIB-4 index ≥2.67 showed a significant association with a cognitive impairment screening test (MMSE) score ≤23 points (suspected dementia) (P=0.020). **Conclusion:** In the general population aged 65 years and older, MASLD and high FIB-4 index showed significant associations with decreased hippocampal volume and increased cerebral white matter hypointensities. These findings suggest that SLD, especially MASLD with high Fib4 index, may be a risk for cognitive impairment via atrophy of brain volumes involved in event memory and via cerebrovascular events.

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2326 | REAL-WORLD EXPERIENCE OF A MULTIDISCIPLINARY MASLD CLINIC ◆

Joshua Fricker[1] *Dalton Caviness*[1] *Malcolm Chapman*[1] *Fernando Bril*[1] *Meagan Gray*[1]

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Background: Recent updates in MASLD definition emphasized that cardiometabolic risk factors are an intrinsic component of MASLD. This underscores the importance of a multidisciplinary clinic addressing all aspects of metabolic health. The aim of this study was to evaluate the outcomes of a real-world multidisciplinary MASLD clinic on weight and metabolic factors. **Methods:** Patients who established care at the University of Alabama at Birmingham's Multidisciplinary MASLD clinic from 2/2022 to 1/2024, with at least one follow-up visit, were included in the study. Presence of MASLD was defined based on available evidence at the time of chart review. Participants with excessive alcohol consumption, alternative etiologies of liver disease, and/or steatogenic medications were excluded. **Results:** A total of 191 adults were included (52 ± 14 years old; 42% male, 73% Non-Hispanic White, 14% Non-Hispanic Black; 39% with T2DM, 76% with obesity, 13% with compensated cirrhosis). Mean follow-up was 17 ± 12 months. Use of GLP1RA increased from 20.9% at initial visit to 38.0% at follow-up. From the initial visit to most recent follow-up, there were significant improvements in BMI (34.8 ± 6.8 kg/m2 to 33.6 ± 6.6 kg/m2, representing a -2.9% weight loss, p<0.001), A1c (6.0 ± 1.1% to 5.9 ± 1.0%, p=0.041), HDL-C (43 ± 14 to 51 ± 24 mg/dl, p<0.001), triglycerides (146 [103 – 205] to 130 [90-188] mg/dl, p=0.040), as well as ALT (50 ± 42 to 37 ± 29 U/L, p<0.001) and AST (37 ± 27 to 29 ± 21 U/L, p=0.001). Of note, ≥5% and ≥10% body weight loss was achieved by 32.4% and 17.0%, respectively, with higher percentages in patients on GLP1RA. When patients were divided into quartiles of liver fibrosis based on US or MR elastography we observed similar weight loss regardless of fibrosis stages. Even in those patients with a confirmed diagnosis of compensated cirrhosis (n=30) weight loss was of similar magnitude (-3.4%, p=0.07 for before vs. after). **Conclusion:** In a multidisciplinary MASLD clinic, patients achieved significant improvements in A1c, lipids, ALT, and AST despite a rather modest reduction in body weight (-2.9%), further emphasizing the importance of weight loss in the management of MASLD patients. While not directly compared to routine hepatology clinics, multidisciplinary clinics may offer patients the best chance at achieving comprehensive metabolic health.

Disclosures: Joshua Fricker: Nothing to Disclose, Dalton Caviness: Nothing to Disclose, Malcolm Chapman: Nothing to Disclose, Fernando Bril: NovoNordisk: Consultant, NovoNordisk: Speaking and Teaching, Boehringer Ingelheim: Speaking and Teaching, Boehringer Ingelheim: Advisor, Meagan Gray: NovoNordiesk: Consultant

2327 | ASSOCIATION OF STAPLE FOODS INTAKE WITH THE RISK OF METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE: A PROSPECTIVE COMMUNITY-BASED COHORT STUDY

Yurou Xu[1] *Xing Liu*[1]

[1]*Fudan University*

Background: Dietary habits and staple food structures vary significantly between Western and Asian populations. Limited evidence exists regarding the association between staple food sources and the risk of metabolic dysfunction-associated steatotic liver disease (MASLD), particularly in Chinese populations. **Methods:** We conducted a large-scale prospective cohort study among Chinese adults from Shanghai Suburban Adult Cohort and Biobank (SSACB) to investigate the association between different staple foods and MASLD risk. A validated food frequency questionnaire was used to assess dietary intake. MASLD was diagnosed by ultrasound and health examinations. Cox proportional hazard models were employed to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) after adjusting for potential confoundings. **Results:** A total of 12,134 participants were included in the analysis. Over the median follow-up period of 4.32 years, 4447 incident cases of MASLD were documented. We found an overall positive association between rice intake and MASLD incidence ($HR_{10+ \text{ vs } 0\sim<4 \text{ servings/day}}$: 1.43, 95%CI: 1.18-1.74; $HR_{\text{per serving/day increase}}$:1.04, 95%CI: 1.02-1.06). The highest intake levels of wheat (0.78, 0.70-0.86), coarse grains (0.86, 0.78-0.94) and yams (0.78, 0.67-0.90) were inversely associated with MASLD risk among total population, and the HRs (95%CIs) of per serving/day increase were 0.91 (0.87-0.96), 0.95 (0.92-0.98), and 0.93 (0.87-1.00), respectively. When stratified by sex, the above significant associations remained in females but not in males. Replacing one serving of rice per day with wheat or coarse grain was associated with a lower risk of MASLD in all participants (0.92, 0.88-0.97; 0.94, 0.91-0.97) and females (0.89,

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0.83-0.95; 0.91, 0.87-0.95), but not in males (0.96, 0.90-1.03; 1.00,0.95-1.06). The proportion of energy intake from total staple foods above 90% was positively associated with MASLD (1.22, 1.04-1.43). “Low Rice Pattern” score was negatively related with MASLD (0.91, 0.88-0.95), while “High Rice Pattern” indicated a positive association with MASLD among females (Q4 vs Q1: 1.19, 1.01-1.40). **Conclusion:** Our findings suggested that higher rice intake was positively related with MASLD, and increasing consumption of wheat, coarse grains and yams might mitigate the risk of MASLD in Chinese population. These findings suggest potential dietary interventions and alteration in staple food structure to mitigate MASLD risk in community settings.

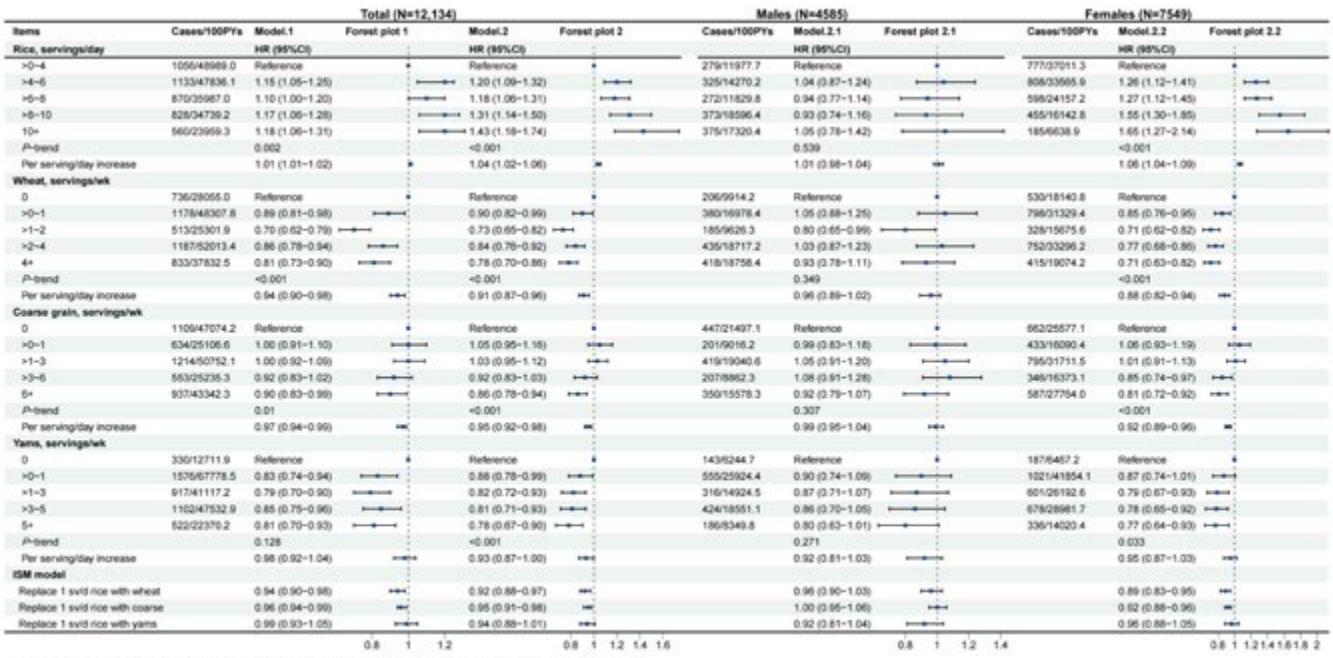

Figure 1. The associations between staple food intake with risk of MASLD from Songjiang Cohort.
Svid: servings/day; PY: Person-year; HR: Hazard ratio; CI: Confidence interval;
Model1 adjusted for Age, sex, BMI;
Model2 adjusted for Age, sex, BMI, Energy intake, aMED score, Education Group, Occupation group, Marriage Group, physical activity, packyear, alcohol, hypertension, diabetes;

Disclosures: Yurou Xu: Nothing to Disclose, Xing Liu: Nothing to Disclose

2328 | EPIGENETIC AGE ACCELERATION IS ASSOCIATED WITH STEATOTIC LIVER DISEASE IN ADOLESCENCE AND EARLY ADULTHOOD: A 10 YEAR COHORT STUDY

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Background and Aims: Biological age may be a better predictor of the development of disease and death than chronological age. Biological age is associated with epigenetic changes such as DNA methylation, and thus epigenetic biomarkers can determine differences between biological age and chronological age (called age acceleration). Epigenetic biomarkers of age and age acceleration are associated with obesity and type 2 diabetes. We aimed to determine the longitudinal association between epigenetic markers of age, age acceleration and steatotic liver disease (SLD). **Methods:** Participants in the Raine Study, a longitudinal cohort study in Australia, were assessed at age 17 years (n=1192) including epigenome-wide DNA methylation profiling using the Illumina Infinium HumanMethylation 450 BeadChip array. Hepatic steatosis was assessed at age 17 years by ultrasound (n=708) and at age 27 years by magnetic resonance imaging (n=542). Epigenetic biomarkers of age (Horvath, Hannum, Skin & Blood, GrimAge, PhenoAge) and age acceleration (DunedinPACE) at age 17, were examined for associations with SLD at 17- and 27-years. Liver fibrosis was assessed at age 27 years by FIB-4. **Results:** The prevalence of SLD was 17% (121/708) at age 17 and 19% (101/542) at age 27 years. SLD at both ages, was associated with greater waist circumference, higher blood pressure, higher serum triglycerides and greater insulin resistance.Epigenetic markers of age (PhenoAge, GrimAge) and age acceleration (Dunedin PACE) were

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associated with SLD at 17- and 27-years (all p<0.05). Other epigenetic models were not associated with SLD at either age.The association between age acceleration (Dunedin PACE) and SLD at age 17 years remained significant (p=0.038) after adjustment for sex, waist circumference, alcohol consumption and physical activity. Similarly, the association between epigenetic age (PhenoAge) and age acceleration (Dundedin PACE) at 17-years and future SLD at 27-years remained significant following adjustment for sex, waist circumference, alcohol consumption, smoking and physical activity (both p<0.05). GrimAge and GrimAge acceleration were significantly positively associated with FIB-4 at age 27 following adjustment (both p<0.05). **Conclusion: Conclusion**: Biological age and age acceleration determined by epigenetic markers are associated with SLD in adolescence and in young adulthood. Epigenetic determined age may aid with risk-predition of SLD and understanding of disease pathogenesis

Disclosures: Phillip Melton: Nothing to Disclose, Trevor Mori: Nothing to Disclose, Lawrence Beilin: CSL: Shares, Cochlear Ltd: Shares, Rae-Chi Huang: Nothing to Disclose, John Olynyk: Nothing to Disclose, Oyekoya Ayonrinde: Canon Medical Systems ANZ Pty Limited: Loan of a research liver ultrasound machine (in kind support, Norgine: Advanced liver disease lecture to Family Physicians, Luis Calzadilla Bertot: Nothing to Disclose, Brendan Adler: Nothing to Disclose, Leon Adams: Novo Nordisk: Advisor, SCL Behring: Advisor, Pfizer: Advisor

2329 | CURRENT MULTI-DIMENSIONAL VIEW OF NON-ALCOHOLIC STEATOHEPATITIS (NASH)/ METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS (MASH) GLOBAL EPIDEMIOLOGICAL RATES

Michael Charlton[1] *Jesse Fishman*[2] *Yestle Kim*[2] *Gauri Saal*[3]

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Background: Despite strong evidence of growing NASH/MASH burden, there is variability in estimates of epidemiology and disease progression, thus hindering disease awareness. Current published epidemiological data are discrepant, potentially reflecting barriers to diagnosis, unclear guideline-recommended non-invasive tests (NITs)/cut-offs, and low biopsy frequency. This targeted literature review aims to capture the current and multi-dimensional view of NASH/MASH epidemiology by characterizing prevalence, disease progression, and mortality, by both population and diagnostic approaches. **Methods:** Targeted epidemiology literature searches (2014–2024) covered US and global studies for population / intervention / outcomes, respectively: adults with/without obesity or T2D; NITs and biopsy; prevalence/incidence of NASH/MASH, fibrosis, cirrhosis, and liver-related mortality. **Results:** Included publications (4 systematic literature reviews; 11 primary studies) showed a range of NASH/MASH, fibrosis, and cirrhosis prevalence rates (**Table**). In US patients with steatosis, NASH prevalence varied per NIT used: 2–5% on FAST, 0.4-12% on FIB-4, 0.1–2% on APRI, 5% on FS-LSM. NASH with fibrosis was 11.6% for NAFLD activity score ≥4. NASH prevalence on FAST scores in a US lean population was 0.1-1%, and 4% in a US lean population with T2D. Biopsy-based prevalence estimates varied by population: 37–61% among patients with steatosis and a biopsy indication [66% in T2D] vs. 5% in a voluntarily biopsied general population. NIT-based estimates of abnormal fibrosis (F1-F4) prevalence in US lean adults was 0.4–4.4%, and 15.5% in T2D with obesity. Prevalence rates for fibrosis progression from baseline stage F0–F2 to F3–F4 over 12 years were 26% (T2D) and 14% (non-T2D); with 93% and 76% 12-year cumulative one-stage progression incidences in T2D and non-T2D biopsy-confirmed NAFLD, respectively. NASH cirrhosis prevalences in US patients aged ≥50 with T2D and T2D with obesity, respectively, were 7% and 9%; and 43% in those with NASH with fibrosis (per MEFIB, FAST, and MAST scores). Global mortality rate ratios attributable to fibrosis vs no fibrosis showed exponential increases for each increased fibrosis stage. **Conclusion:** NASH epidemiology estimates vary widely depending on diagnostic approaches, diagnostic parameters, and the populations studied. With the recent availability of a novel treatment for NASH with moderate to advanced fibrosis, capturing the epidemiological burden of NASH through a multidimensional approach may provide useful input for clinical decision-making.

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Table: Summary of Epidemiological Estimates for NASH, Advanced Fibrosis, Cirrhosis, and Liver-Related Mortality

Population	Diagnostic approach			Epidemiological estimate	Study type	
NASH prevalence						
NAFLD/steatosis[1]	NIT	FAST	≥0.35	4.8%	National Health and Nutrition Examination Survey (n=6969; 2017–2020)	
			≥0.48	3.0%		
			≥0.57	2.1%		
		FIB-4	≥0.67	1.3%		
			≥0.90	12.3%		
			≥1.30	5.7%		
			≥1.59	3.2%		
			≥2.67	0.4%		
		APRI	≥0.50	1.9%		
			≥0.70	0.7%		
			≥1.50	0.1%		
		LSM/FIB	≥8 kPa / ≥2.67	4.6%		
NAFLD (CAP ≥ 274 dB/m)[1]	NAFLD activity score ≥4 and fibrosis stage ≥2 (at-risk NASH)			11.6%	National Health and Nutrition Examination Survey (n=9254; 2017–2018)	
Lean general population[1]	FAST	≥0.35		1.3%	National Health and Nutrition Examination Survey (n=1628); 2017–2020	
		≥0.67		0.1%		
		≥0.35 and T2D		4.0%		
General population aged ≥50 w T2D[1]	MEFIB score (MRE >3.3 kPa + Fib4 > 1.6), FAST score ≥0.67 or a MRI-AST score ≥0.242			13.6%	Multicentre, prospective; 2016–2023	n=530
General population aged ≥50 w obesity/T2D[1]				15.9%		n=302
NAFLD/steatosis	Biopsy			60.6%[1]	Meta-analysis (n=209,303; 2006–2014)	
				59.1%[2]	Meta-analysis (n=8,515,431; 1989–2015)	
NAFLD/steatosis				37.0%[1]	Single center clinical cohort (n=664; 2015–2018)	
NAFLD/steatosis/T2D				66.4%[2]	Meta-analysis (n=2733; 1990–2023)	
Projected general population (from voluntarily biopsied patients)				5.0%[1]	Meta-analysis, 1990–2019	n=56,133
				5.3%[2]		n=9,361,716
Fibrosis prevalence						
Lean general population[1]	NIT	LSM ≥8 kPa		4.4%	National Health and Nutrition Examination Survey (n=1628; 2017–2020)	
		LSM ≥13.1 kPa		0.4%		
General population w T2D +obesity[2]	Biopsy and NIT	LSM ≥7.0–8.2		15.5%	Meta-analysis (n=2733; 1990–2023	
Biopsy-confirmed NASH[1]	Biopsy	F>2 prevalence		35.0%	Single center clinical cohort (n=664; 2021)	
Biopsy-confirmed NAFLD[1]	T2D	Prevalence of progression from baseline F0–2 to F3–4 over 12 years		26.0%	Multicentre, prospective; 2004–2022	n=208
	Non-T2D			14.0%		n=239
	T2D	4, 8, 12-years cumulative incidence of 1-stage increase:	Y4	24.0%		n=208
			Y8	60.0%		
			Y12	93.0%		
	Non-T2D		Y4	20.0%		n=239
			Y8	50.0%		
			Y12	76.0%		
Cirrhosis prevalence						
Patients aged ≥50 w at risk NASH: FAST ≥0.67/MAST ≥0.242, or MEFIB ≥1/FIB-4 ≥1.6 kPa plus MRE ≥3.3 kPa) w T2D[1]	NIT	MRE ≥4.67 kPa or VCTE ≥15 kPa		43.1%	Multicentre, prospective; 2016–2023)	n=72
Patients aged ≥50 w T2D[1]				6.8%		n=530
Patients aged ≥50 w obesity and T2D[1]				9.0%		n=302
NAFLD/steatosis[1]	Biopsy and NITs (AST/FIB/MRI)			Age 40–59:3.7% Age ≥60: 4.7%	Retrospective study in tertiary care center (2010–2021)	Age 40–59, n=15,035 Age ≥60, n=8218
Fibrosis/liver-related mortality						
Patients w fibrosis[2]	Biopsy (NASH Clinical Research Network histologic scoring system)			Morality rate ratio for fibrosis level (relative to F0 reference mortality rate)	Meta-analysis of 5 cohort studies (2011–2016), n=1495/17,452 patient years of follow-up	
			F1	1.41		
			F2	9.57		
			F3	16.69		
			F4	42.3		

[1]US/North America; [2]Global.
APRI, AST to platelet ratio index; **AST**, Aspartate aminotransferase; **FAST**, FibroScan AST; **FIB**, Liver fibrosis index; **HCP**, Healthcare practitioner; **LSM**, Liver stiffness measurement; **MEFIB**, Liver stiffness on MRE; **MRE**, Magnetic resonance elastography; **MRI**, Magnetic resonance imaging; **NAFLD**, Non-alcoholic fatty liver disease; **NIT**, Non-invasive test; **T2D**, Type 2 diabetes mellitus; **VCTE**, Vibration-controlled transient elastography.

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2330 | LIVER-RELATED EVENTS AND MORTALITY IN PATIENTS WITH METABOLIC DYSFUNCTION ASSOCIATED STEATOTIC LIVER DISEASE VARIES WITH THE TYPE OF CARDIOMETABOLIC RISK FACTOR

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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD), formerly known as non-alcoholic fatty liver disease, is the most common cause of liver disease globally. MASLD is defined by the presence of any cardiometabolic risk factor (CMRF). Liver-related events (LRE) are a significant cause of morbidity and mortality in MASLD. However, the risk of LRE based on the various CMRFs is not well characterised and may vary across populations. We aimed to assess the frequencies of various CMRFs, and their association with LRE and mortality in MASLD patients. **Methods:** In this retrospective analysis from a tertiary care center in Asia, all consecutive patients diagnosed with MASLD were included. CMRFs were defined as per established criteria, including body mass index (BMI) cut off 23 kg/m^2. LRE was defined as the presence of any of the following: ascites, hepatic encephalopathy, GI bleeding, hepatocellular carcinoma, and death due to liver-related causes. Liver stiffness measurements (LSM) were performed using vibration-controlled transient elastography (VCTE). **Results:** We included a total of 1047 patients, with mean age 41.4 ± 11.8 years, males (67.5%), mean LSM (n=861): 9.2 ± 9.7 kPa, and LSM (≥10 kPa): 166 (19.3%). The prevalence of CMRFs was: BMI (≥23 kg/m^2): 948 (90.5%), diabetes mellitus (DM) 290 (27.7%), hypertension 202 (19.3%), hypertriglyceridemia 484 (46.2%), low HDL 619 (59.1%). The number of CMRFs was 1, 2, 3, 4 and 5 in 19.3%, 37.1%, 29.2%, 10.7% and 3.6% cases, respectively. During a follow-up of 2225 ± 1218 days, 29 new liver events occurred. Among the 5 CMRFs, only diabetes was associated with higher LREs: 19 (7.0%) vs 12 (1.3%), P<0.001. LREs were significantly higher in patients with baseline LSM ≥10kPa compared to those with LSM <10 kPa: 23/166 (13.9%) vs 2/695 (0.3%), P<0.001. LREs among patients, vis-a-vis LSM and DM (LSM<10 No-DM, LSM<10 DM+, LSM≥10 No-DM and LSM≥10 DM+) were: 2/544 (0.4%), 0, 6/86 (7.0%) and 17/80 (21.3%), respectively (P<0.001). Mortality was higher among diabetics compared to non-diabetics: 21/290 (7.2%) vs 12/757 (1.6%), P<0.001. Patients with LSM ≥10kPa had higher mortality compared to LSM <10 kPa: 19/190 (10.0%) vs 11/699 (1.6%), P<0.001. Mortality among patients, vis-a-vis LSM and DM (LSM<10 No-DM, LSM<10 DM+, LSM≥10 No-DM and LSM≥10 DM+) was 5/547 (0.9%), 6/152 (3.9%), 6/96 (6.3%) and 13/94 (13.8%), respectively (P<0.001). The overall total number of CMRFs was not significantly associated with either LREs or death. **Conclusion:** Presence of diabetes and Liver Stiffness Measurements (LSM) ≥10 kPa are associated with Liver Related Events (LRE) and death in patients with Metabolic dysfunction associated steatotic liver disease (MASLD).

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2331 | COMPARING RATES OF DECOMPENSATION, HEPATOCELLULAR CARCINOMA, OVERALL AND LIVER-RELATED DEATH BETWEEN MASLD, METALD AND ALD IN A NATIONAL COHORT

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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD), and MASLD with increased alcohol intake (MetALD) have been identified as separate clinical entities based on expert consensus- however, large population-based studies are essential to compare the associations of these newly defined diseases with liver-related outcomes. This study's primary aim was to compare rates of decompensation, hepatocellular carcinoma (HCC), all-cause, and liver-related mortality (LRM) between patients with MASLD, MetALD and ALD in a large, national cohort. **Methods:** Participants determined to have steatosis were classified into the etiologies of MASLD, MetALD, and ALD. Classifications were determined based on having at least one cardiometabolic risk factor (CMRF) and/or increased alcohol use in the five years prior to steatosis classification. Elevated alcohol use was checked as the highest AUDIT-C each year for the 5 years leading up to classification.

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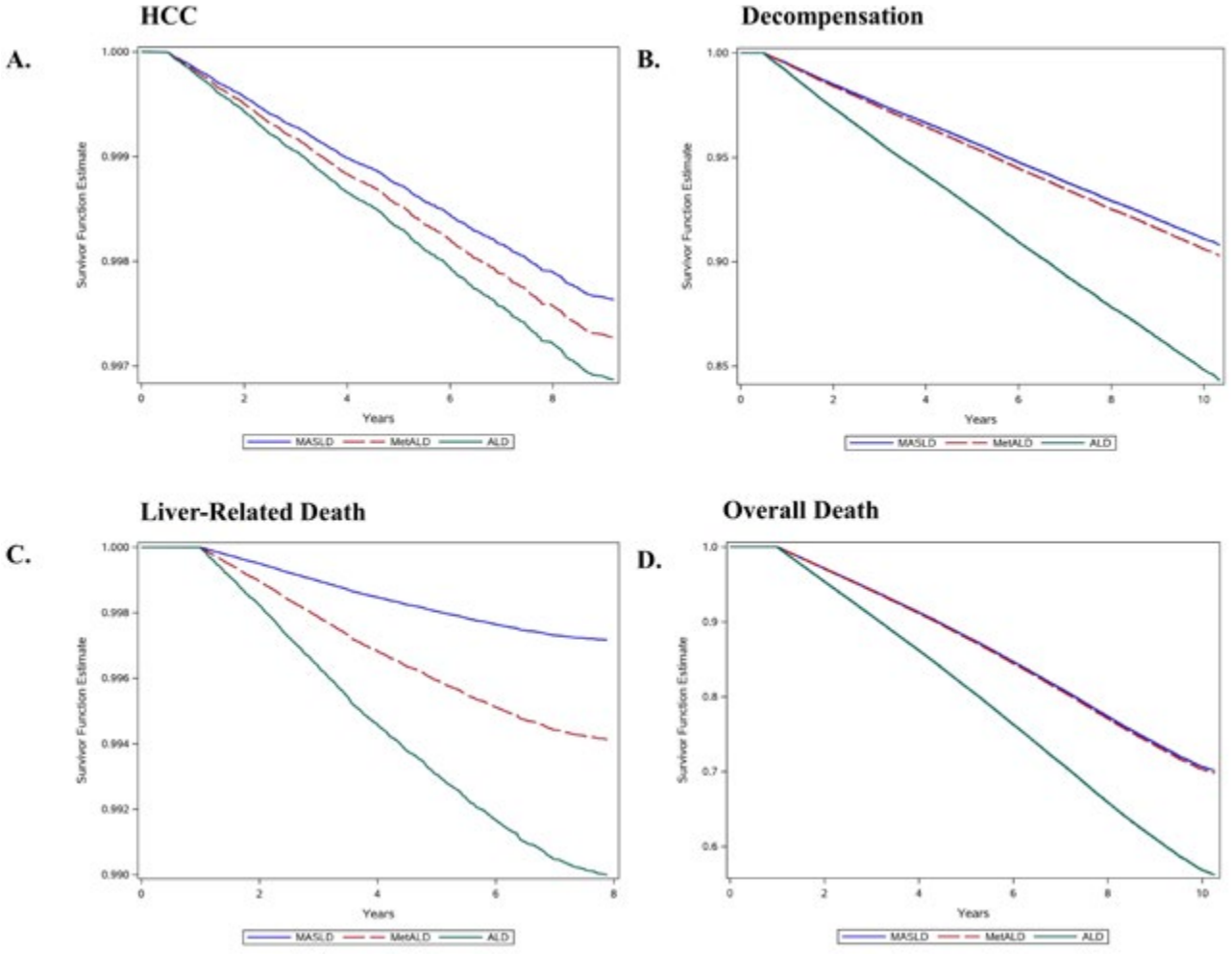
The rate of HCC, decompensation, overall and LRM were reported using events per 1000 person-years and adjusted rates examined using Poisson regression models. Differences in time to HCC, decompensation, all-cause mortality and LRM by etiology were examined in four Cox proportional hazard models, adjusted for age, sex, race, diabetes, BMI, ALT, AST, and platelet count. **Results:** Of 436,974 study participants, 299,259 had MASLD, 99,163 MetALD, and 38,552 had a diagnosis of ALD. The adjusted rates for HCC were were 0.3 (95% CI 0.2-0.4) per 1000 person-years (P-Y) for MASLD, 0.3 per 1000 P-Y (95% CI 0.3-0.5) for MetALD, and 0.4 per 1000 PY (95% CI 0.3-0.6) for ALD. Similarly, adjusted rates of hepatic decompensation were 9.1 (8.6-9.6), 9.6 (9.1-10.3), and 16.0 (15.0-17.0) per 1000 P-Y for MASLD, Met ALD and ALD respectively. Outcomes of liver-related and all-cause mortality death were 0.3 per 1000 PY (0.3-0.4) and 22.5 (21.7-23.3) per 1000 PY respectively for MASLD, 0.7 (0.6-0.9) and 23.0 (22.2-23.9) per 1000 PY respectively for MetALD, and 1.2 (1.0-1.5) and 36.1 (34.7-37.6) per 1000 PY respectively for ALD. On multivariable analysis, compared to MASLD as reference, participants with MetALD had an increased hazard of HCC (adjusted Hazard Ratio [aHR] 1.15, 95% CI 1.01-1.32, p=0.04), decompensation (aHR 1.06, 95% CI 1.02-1.09, p=0.001), and LRM (aHR 2.08, 95% CI 1.84-2.34, p<.0001), but not all-cause mortality (aHR 1.01, 95% CI 0.99-1.01, p=0.16). Rates of all liver related complications were highest with ALD, with an increased hazard of HCC (aHR 1.32, 955% CI 1.09-1.60, p=0.004), decompensation (aHR 1.77, 95% CI 1.70- 1.84, p<.0001), all-cause mortality (aHR 1.63, 95% CI 1.58-1.67, p<0.0001), and LRM (aHR 3.55, 95% CI 3.11-4.06, p<.0001). **Conclusion:** In a large national cohort of patients with SLD, rates of HCC, decompensation and LRM increases from MASLD, to MetALD to ALD. These findings justify the identification of MetALD as a unique entity.



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2332 | INDEPENDENT RISK FACTORS FOR CHRONIC KIDNEY DISEASE: THE IMPACT OF SLD AND OBESITY IN A LARGE-SCALE HEALTH CHECKUP COHORT

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Background: Metabolic syndrome and steatotic liver disease (SLD) are widely known to increase the risk of chronic kidney disease (CKD). However, it is not fully understood which specific metabolic factors contribute to CKD. We investigated the association between metabolic factor and CKD using a large-scale health checkup cohort (MIRACLE-J). **Methods:** We conducted a cross-sectional analysis of 106,830 participants, excluding those without eGFR, urinary protein, or cardiometabolic risk factors. The diagnosis of SLD was made by ultrasonography and divided into metabolic dysfunction-associated SLD (MASLD), MASLD with increased alcohol intake (MetALD) and ALD with metabolic dysfunction (ALD&Met). Univariate and multivariate analysis were performed to examine risk factors for estimated glomerular filtration rate (eGFR) <60 and proteinuria included in the definition of CKD. **Results:** Among the participants, 11,424 (10.7%) had eGFR <60, and 2,758 (2.6%) had proteinuria. In terms of SLD types, 2,651 (12.26%) of 21,623 MASLD patients and 815 (10.10%) of 8,068 MetALD patients had eGFR <60, significantly higher than the 5.64% of 957 ALD&Met patients. Conversely, 749 (3.46%) of MASLD patients and 313 (3.88%) of MetALD patients had proteinuria, significantly lower than 5.33% of 957 ALD&Met patients. Multivariate analysis identified the following risk factors for eGFR <60: advanced age, hyperuricemia, hyperglycemia, male gender, hypertension, low HDL cholesterol, and MASLD. Notably, advanced age (odds ratio [OR] 4.33; 95% confidence interval [CI] 4.15-4.53, P < 0.001), hyperuricemia (OR 2.62; 95% CI 2.49-2.77, P < 0.001), and MASLD (OR 2.30; 95% CI 1.98-2.73, P < 0.001) were strongly associated. Risk factors for proteinuria included obesity, advanced age, hyperuricemia, hypertension, smoking, low HDL cholesterol, hyperglycemia, and hypertriglyceridemia. Obesity showed a particularly strong association. Compared to a BMI <25, the risk of proteinuria increased with higher BMI levels: 35 ≤ BMI (OR 4.16; 95% CI 3.27-5.30, P < 0.001), 30 ≤ BMI < 35 (OR 2.31; 95% CI 1.99-2.69, P < 0.001), and 25 ≤ BMI < 30 (OR 1.40; 95% CI 1.28-1.53, P < 0.001). **Conclusion:** In addition to advanced age and hyperuricemia, MASLD and obesity are suggested to be independent risk factors for CKD. The causality of these associations should be verified in future prospective studies.

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2333 | DIFFERENTIAL EXERCISE REQUIREMENTS FOR NONALCOHOLIC FATTY LIVER DISEASE RESOLUTION ACROSS AGE GROUPS: A LONGITUDINAL STUDY OF KOREAN MILITARY OFFICERS

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Background: Nonalcoholic fatty liver disease (NAFLD) is a global health concern, and despite its high prevalence, lifestyle modifications such as exercise remain the only practical option for resolving this condition. This study aims to identify factors associated with NAFLD resolution, with a focus on the role of exercise, in different age groups. **Methods:** Longitudinal data from Korean military officers, during the period 2019–2021, were obtained from the National Health Information Database. NAFLD was defined as a hepatic steatosis index (HSI) ≥ 36, and NAFLD resolution was defined as individuals achieving HSI < 36 in the subsequent year of diagnosis. Information on alcohol consumption, exercise frequency, and family history of diabetes was collected

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through self-reported questionnaires. **Results:** The analysis included a total of 163,728 individuals, with a mean age of 36.87, predominantly male (91.62%). The prevalence of NAFLD was 27.04%, 28.11%, and 28.54% in 2019, 2020, and 2021, respectively. Favorable factors for NAFLD resolution encompassed moderate-intensity exercise for more than 180 minutes/week, vigorous-intensity exercise for more than 90 minutes/week, female sex, age, and resistance exercise for more than 3 d/week. Hypertension, family history of diabetes, and smoking were identified as factors against NAFLD resolution. The exercise requirements for NAFLD resolution varied among age groups, with those < 30 years old requiring more than 180 minutes/week of moderate or vigorous-intensity exercise and those > 50 needing only 90 minutes/week of such exercise. **Conclusion:** The exercise requirements for NAFLD resolution exhibit age-related differences. Individualized guidance for NAFLD management should consider these variations and be tailored to specific age groups.

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2334 | A PROSPECTIVE ASSESSMENT OF THE IMPACT OF DECOMPENSATION OF CIRRHOSIS ON PATIENT-REPORTED OUTCOMES IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE

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Background: Metabolic dysfunction-associated steatotic liver disease and steatohepatitis (MASLD and MASH) are major causes of liver-related morbidity and mortality. While clinical event rates and patient-reported outcomes (PRO) have been studied in cirrhosis with generic patient-reported outcome measures (PROMs), there is a paucity of data on the impact of decompensation of cirrhosis with a disease-specific PROM. This analysis is a prospective, cross-sectional analysis of MASLD-specific PRO in patients with compensated versus decompensated MASH cirrhosis in a real-world setting. **Methods:** A prospective analysis of the previously developed and validated NASH-CHECK (version 1.0) PROM in the real-world TARGET-NASH observational longitudinal cohort in patients enrolled in the US was performed from 2021-2023. MASLD was defined per previously described TARGET-NASH definitions using available biopsy, imaging, and/or clinical criteria. Two categories of patients were compared: compensated MASH cirrhosis and decompensated (ascites/complications from ascites, hepatic encephalopathy, variceal bleeding) MASH cirrhosis. NASH-CHECK has 6 symptom scores and 3 HRQOL scores; each has a score of 0-10 with higher scores indicating greater impairment. Scores across classes were compared using a linear regression model controlling for clinically relevant covariates; p-value <0.05 was considered significant. **Results:** 281 participants with a completed NASH-CHECK and MASH cirrhosis (186 compensated, 95 decompensated), representing ~45% of the TARGET-NASH cirrhotic cohort, were obtained. Median age was 64.0, 62.6% female, 85.1% Non-Hispanic White, 3.9% Non-Hispanic Black, 5.3% Hispanic/Latino, 77.2% BMI ≥25, 82.2% type 2 diabetes. Significant differences between compensated and decompensated MASH cirrhosis were noted for activity limitations (p=0.004) and social impact (p=0.005); however, there were no significant differences between compensated and decompensated MASH cirrhosis for abdominal bloating, abdominal pain, fatigue, itchy skin, sleep, cognitive symptoms, emotional impact. **Conclusion:** In a real-world clinical setting, the MASLD-specific PROM, NASH-CHECK, demonstrated a differential impact of decompensation on PRO: greater activity limitation and social impact but no worsening of any other domains of the PROM. Further research should focus on this differential, and approaches to ameliorate these impacts should be considered.

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Item	Comp cirrhosis	Decomp cirrhosis
symptom single-item		
Abdominal bloating	2.44 (3.084)	2.87 (3.067)
Abdominal pain	1.72 (2.599)	1.98 (2.768)
Fatigue	3.81 (2.973)	4.67 (3.344)
Itchy skin	2.49 (2.865)	3.12 (3.082)
Sleep	3.60 (3.067)	4.01 (3.450)
symptom scale		
Cognitive symptoms	2.11 (1.930)	3.04 (2.728)
HRQOL		
Activity limitation	***2.77 (2.587)**	***4.24 (2.776)**
Emotional impact	2.88 (2.555)	3.15 (2.463)
Social impact	***1.46 (2.242)**	***2.84 (2.849)**

*p<0.05 indicating significantly worse scores in the decompensated participants

Disclosures: Ian O'Connor: Nothing to Disclose, Andrea Mospan: Nothing to Disclose, Cheryl Schoen: Nothing to Disclose, Alfred Barritt IV: Merck (Any division): Advisor, Madrigal: Consultant, Life Edit: Consultant, Boehringer Ingelheim: Consultant, Target-RWE: Consultant, Arun Sanyal: Genfit, Akarna, Tiziana, Durect, Inversago, Hemoshear, North: Stock - publicly traded company, Astra Zeneca (60K), Boston Pharmaceutical

2335 | GLP-1'S ROLE IN LOWERING HCC RISK IN PATIENTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS AND TYPE 2 DIABETES – A MULTICENTER PROPENSITY-MATCHED STUDY

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Background: Metabolic dysfunction-associated steatohepatitis (MASH), previously known as nonalcoholic steatohepatitis, and Type 2 Diabetes Mellitus (T2DM) are significant risk factors for hepatocellular carcinoma (HCC). Preclinical studies indicate that GLP-1 receptor agonists may inhibit the development of HCC in the context of MASH. However, clinical evidence is limited. This study aims to assess the impact of GLP-1 receptor agonists on HCC incidence in patients with concurrent T2DM and chronic hepatitis C (CHC), utilizing data from a comprehensive research network. **Methods:** In this retrospective cohort study and time-to-event analysis, we utilized the TriNetX electronic health records network, encompassing data from over 120 million patients between January 1, 2005, and December 31, 2022. We included patients aged 18 years or older diagnosed with co-existing T2DM and MASH. Propensity score matching was applied to pair patients with and without GLP-1 use based on factors such as age, gender, race, comorbidities, liver-related characteristics, BMI, and background medications. Patients with a history of HCC, liver transplant, type 1 diabetes mellitus, and acute pancreatitis were excluded from the study. A Cox proportional hazards regression model was employed to evaluate the association between GLP-1 use and the incidence of HCC in both groups. **Results:** We identified 15,460 patients in the GLP-1 group and 73,465 in the non-GLP-1 group, with 15,448 patients included after propensity score matching. Baseline demographic characteristics, comorbid conditions, and medications before and after propensity score matching are detailed in Table 1. The incidence of HCC was 3.94% in the GLP-1 group compared to 4.77% in the non-GLP-1 group (RR = 0.82, 95% CI [0.74-0.91], P<0.01). This association remained significant across various subgroups, including age, gender, ethnicity, obesity, hypertension, cirrhosis, alcoholic liver disease, viral hepatitis, and background medications. **Conclusion:** Based on a large global retrospective study of patients with coexisting MASH and T2DM, GLP-1 use was associated with a significantly lower risk of HCC. The protective effect against

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HCC development may be attributed to improvements in steatohepatitis (including steatosis, inflammation, and hepatocyte ballooning), enhanced glycemic control, and weight loss, leading to a reduced systemic inflammatory state and lower oxidative stress. However, confirmation through future large-scale prospective studies is required.

Baseline Characteristics						
	Before propensity matching			After propensity matching		
	GLP-1 Group (N=15460)	non-GLP-1 Group (N=73465)	P value	GLP-1 Group (N=15448)	non-GLP-1 Group (N=15448)	P value
Characteristics:						
Age, y, mean ± SD	56.75 ± 12.25	59.48 ± 12.88	<0.01	56.74 ± 12.25	56.65± 12.74	0.72
Male, n(%)	5631 (36.4%)	29,429 (40.1%)	<0.01	5623 (36.4%)	5562 (36%)	0.46
Female, n (%)	9,219 (59.6%)	41,624 (56.7%)	<0.01	9215 (59.7%)	9366 (60.6%)	0.46
Race, n (%)						
Caucasian	11553 (74.73%)	53896 (73.36%)	<0.01	11544 (74.73%)	11648 (75.4%)	0.17
Black or African American	917 (5.93%)	3863 (5.26%)	<0.01	917 (5.94%)	826 (5.35%)	0.2
Hispanic or Latino	1938 (12.54%)	10103 (13.75%)	<0.01	1936 (12.53%)	2184 (14.14%)	0.19
Others	1918 (12.40%)	10040 (13.70%)	<0.01	1917 (12.40%)	1889 (12.20%)	0.62
Comorbid Conditions:						
Hypertensive diseases	12143 (78.55%)	45524 (61.97%)	<0.01	12134 (78.55%)	12096 (78.3%)	0.6
Disorders of lipoprotein metabolism	11878 (76.83%)	39362 (53.58%)	<0.01	11869 (76.83%)	11822 (76.53%)	0.53
Cirrhosis of liver	10880 (70.38%)	32707 (44.52%)	<0.01	5780 (37.42%)	5680 (36.77%)	0.48
Overweight and obesity	5784 (37.41%)	26114 (35.55%)	<0.01	10877 (70.41%)	10820 (70.04%)	0.24
Alcoholic liver disease	682 (4.41%)	3877 (5.28%)	<0.01	682 (4.42%)	747 (4.84%)	0.08
Chronic lower respiratory diseases	5130 (33.18%)	17125 (23.31%)	<0.01	5128 (33.2%)	5019 (32.49%)	0.19
Ischemic heart diseases	3900 (25.23%)	15572 (21.2%)	<0.01	3898 (25.23%)	3915 (25.34%)	0.82
Heart failure	1988 (12.86%)	8857 (12.06%)	<0.01	1987 (12.86%)	1916 (12.4%)	0.22
Medications:						
Insulins	9118 (58.98%)	26241 (35.72%)	<0.01	9110 (58.97%)	9070 (58.71%)	0.64
Biguanides	11500 (74.39%)	28780 (39.18%)	<0.01	11494 (74.4%)	11502 (74.46%)	0.92
Sulfonylureas	5471 (35.39%)	12715 (17.31%)	<0.01	5466 (35.38%)	5279 (34.17%)	0.03
Dipeptidyl peptidase 4 inhibitors	3782 (24.46%)	7595 (10.34%)	<0.01	3782 (24.48%)	3565 (23.08%)	0
Thiazolidinediones	1570 (10.16%)	2916 (3.97%)	<0.01	1570 (10.16%)	1464 (9.48%)	0.04

Disclosures: Abdullah Sohail: Nothing to Disclose, Aysha Aslam: Nothing to Disclose, Kyle Brown: Nothing to Disclose

2336 | IMPACT OF HEMOGLOBIN A_{1C} (HBA_{1C}) TRAJECTORY ON THE RISK OF LIVER-RELATED COMPLICATIONS IN PATIENTS WITH TYPE 2 DIABETES MELLITUS (T2DM): A TERRITORY-WIDE COHORT STUDY

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[1]*The Chinese University of Hong Kong*

Background: Elevated HbA_{1c} has been linked to a higher risk of liver disease progression. We examined the impact of the trajectory of HbA_{1c} on top of HbA_{1c} level on the risk of liver-related complications including hepatic decompensation, hepatocellular carcinoma, and liver-related death in patients with T2DM. **Methods:** A retrospective cohort of adult patients with T2DM based on fasting glucose ≥7 mmol/L, HbA_{1c} ≥6.5%, use of antidiabetic medications, or diagnosis codes from 2000-2016 was identified from an electronic health database in Hong Kong, which covers about 80% of the local population. Patients with type 1 diabetes, chronic viral hepatitis infection, HIV infection, excessive use of alcohol, or liver-related complications or follow-up <5 years were excluded. Unsupervised trajectory partitional clustering was performed to identify up to 4 distinct trajectories using different distance measures with prototyping functions including dynamic time warping (DTW) with DTW

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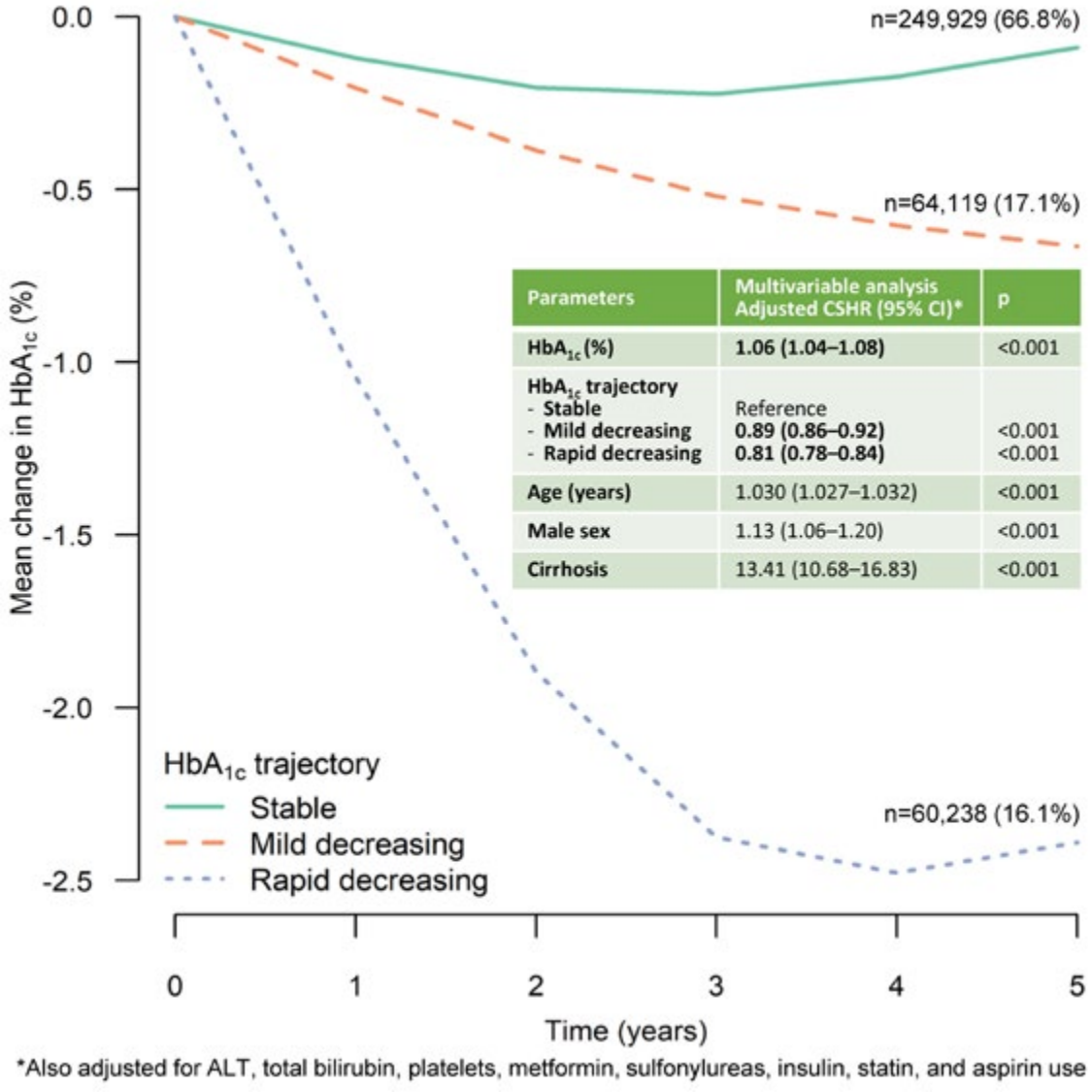
barycenter averaging (DBA), triangular global alignment kernel with DBA, and shape-based distance (SBD) with shape extraction. Patients were followed from T2DM diagnosis to liver-related complications, last follow-up, or 15 years, whichever earlier; non-liver-related death was considered a competing event. **Results:** Of 374,286 patients with T2DM included (mean age 61±12 years, 51.4% females, 1.0% cirrhosis, HbA_{1c} 7.8±2.0%), 4,295 (1.1%) developed liver-related complications at a median (25th-75th percentile) follow-up of 12.4 (8.9-15.0) years. Trajectory clustering based on SBD revealed 3 distinct trajectories of HbA_{1c} in the first 5 years after T2DM diagnosis: stable (n=249,929 [66.8%]), mild decreasing (n=64,119 [17.1%]), and rapid decreasing (n=60,238 [16.1%]) trends (Figure). Compared to the stable trend, patients with mildly decreasing (adjusted cause-specific hazard ratio [aCSHR] 0.89, 95% CI 0.86-0.92, p<0.001) and rapidly decreasing HbA_{1c} (0.81 [0.78-0.84], p<0.001) had a lower subsequent risk of developing liver-related complications. Higher HbA_{1c} level (aCSHR 1.06 [95% CI 1.04-1.08], p<0.001), older age (1.030 [1.027-1.032]), male sex (1.13 [1.06-1.20]), cirrhosis (13.41 [10.68-16.83]), and use of sulfonylureas (1.19 [1.11-1.28]) and insulin (1.34 [1.24-1.45]) were associated with an increased risk of developing liver-related complications, while the use of statin (aCSHR 0.34 [95% CI 0.13-0.88]) was associated with a reduced risk (Figure). **Conclusion:** Good glycemic control over time is associated with a lower risk of developing liver-related complications among patients with T2DM. Trajectories of HbA_{1c} are prognostic of liver-related complications on top of the HbA_{1c} level.



Parameters	Multivariable analysis Adjusted CSHR (95% CI)*	p
HbA_{1c} (%)	1.06 (1.04–1.08)	<0.001
HbA_{1c} trajectory - Stable - Mild decreasing - Rapid decreasing	 Reference 0.89 (0.86–0.92) 0.81 (0.78–0.84)	 <0.001 <0.001
Age (years)	1.030 (1.027–1.032)	<0.001
Male sex	1.13 (1.06–1.20)	<0.001
Cirrhosis	13.41 (10.68–16.83)	<0.001

*Also adjusted for ALT, total bilirubin, platelets, metformin, sulfonylureas, insulin, statin, and aspirin use

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Sciences: Speaking and Teaching, Janssen: Advisor, GSK: Advisor, GSK: Speaking and Teaching, Abbott: Speaking and Teaching, AbbVie: Speaking and Teaching, AstraZeneca, Gilead Sciences, GlaxoSmithKline and Janssen,: Advisor, Abbott, AbbVie, Ascletis, Bristol-Myers Squibb, Echosens, Gi: Speaking and Teaching, Gilead Sciences: Grant/Research Support, AstraZeneca, Gilead Sciences, GlaxoSmithKline and Janssen: Consultant, Abbott, AbbVie, Ascletis, Bristol-Myers Squibb, Echosens, Gi: Speaking and Teaching, AstraZeneca, Gilead Sciences, GlaxoSmithKline Pharmaceutical: Consultant, Gilead Sciences: Independent Contractor, AstraZeneca, Gilead Sciences, GSK and Janssen,: Advisor, Abbott, AbbVie, BMS, Gilead Sciences, GSK, Janssen, Roche: Speaking and Teaching, Gilead Sciences: Grant/Research Support, Jimmy Che-To Lai: Nothing to Disclose, Vincent Wong: Abbott: Speaking and Teaching, AbbVie: Advisor, AbbVie: Speaking and Teaching, Boehringer Ingelheim: Advisor, Echosens: Advisor, Echosens: Speaking and Teaching, Gilead Sciences: Advisor, Gilead Sciences: Speaking and Teaching, Gilead Sciences: Grant/Research Support, Intercept: Advisor, Inventiva: Advisor, Novo Nordisk: Advisor, Novo Nordisk: Speaking and Teaching, Pfizer: Advisor, Sagimet: Advisor, TARGET PharmaSolutions: Advisor, Unilab: Speaking and Teaching, Visirna: Consultant, Illuminatio Medical Technology: Stock – privately held company

2337 | PREDICTING HEPATIC DECOMPENSATION IN PATIENTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE-RELATED CIRRHOSIS: THE ABID-LSM MODEL

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Background: Predicting the risk of hepatic decompensation in cirrhosis patients due to metabolic dysfunction-associated steatotic liver disease (MASLD) is crucial for prognostication and identification of those who may benefit from therapy. We previously developed a predictive tool of hepatic decompensation consisting of AST/ALT ratio, bilirubin, international normalized ratio, Type 2 diabetes and esophageal varices (EV) determined by gastroscopy (ABIDE model). We aimed to validate a modified ABIDE model replacing EV with liver stiffness measurement (LSM) by transient elastography and compare it with other risk prediction models. **Methods:** We conducted a multicenter (8 tertiary centers, Spain) retrospective cohort study of 388 patients with compensated cirrhosis due to MASLD. Patients with previous HCC, hepatic decompensation or liver transplant were excluded. ABIDE, NFS, FIB-4, ALBI, ALBI-FIB-4 and NAFLD decompensation risk score were computed at baseline. Outcomes and accuracy were assessed based on competing risk regression, time dependent area under the curve (tAUC) and Brier score. Comparisons were made between ABIDE, modified ABID-LSM and LSM alone. **Results:** Hepatic decompensation occurred 105 (27%) patients during a median follow-up of 31 months (range 18-60), and in 20% in the subset of patients (n=273) with available LSM. The predictive accuracy at 5 years of ABID-LSM (tAUC 0.80) was better than ABIDE (tAUC 0.75, p=0.03) and LSM (tAUC 0.63, p<0.001). ABID-LSM showed better net reclassification compared to ABIDE and LSM. Discriminative measures were also better for ABID-LSM (k-statistic 0.73, D–statistic 1.91) than ABIDE (k-statistic 0.71, D–statistic 1.77) and LSM (k-statistic 0.68, D–statistic 1.65) The cumulative incidence of hepatic decompensation at 5 years was significantly higher using a model threshold of ≥7.1 (22% vs 5%, sHR=5.3, 95% CI 1.71-7.89; p<0.001)(Figure). ABID-LSM calibrated well (slope 0.99) with good overall performance (Integrated Brier score 0.15). The ABID-LSM model had better prediction values at 5 years (tAUC=0.80) than NFS and ALBI (tAUC= 0.72), FIB-4 (tAUC= 0.74), ALBI-FIB-4 (tAUC= 0.73) and NAFLD decompensation risk score (tAUC= 0.65)(all p<0.001). **Conclusion:** The ABID-LSM model has greater accuracy in predicting hepatic decompensation than existing models. Research is needed to determine if ABID-LSM identifies at-risk patients who may benefit from pharmacological interventions.

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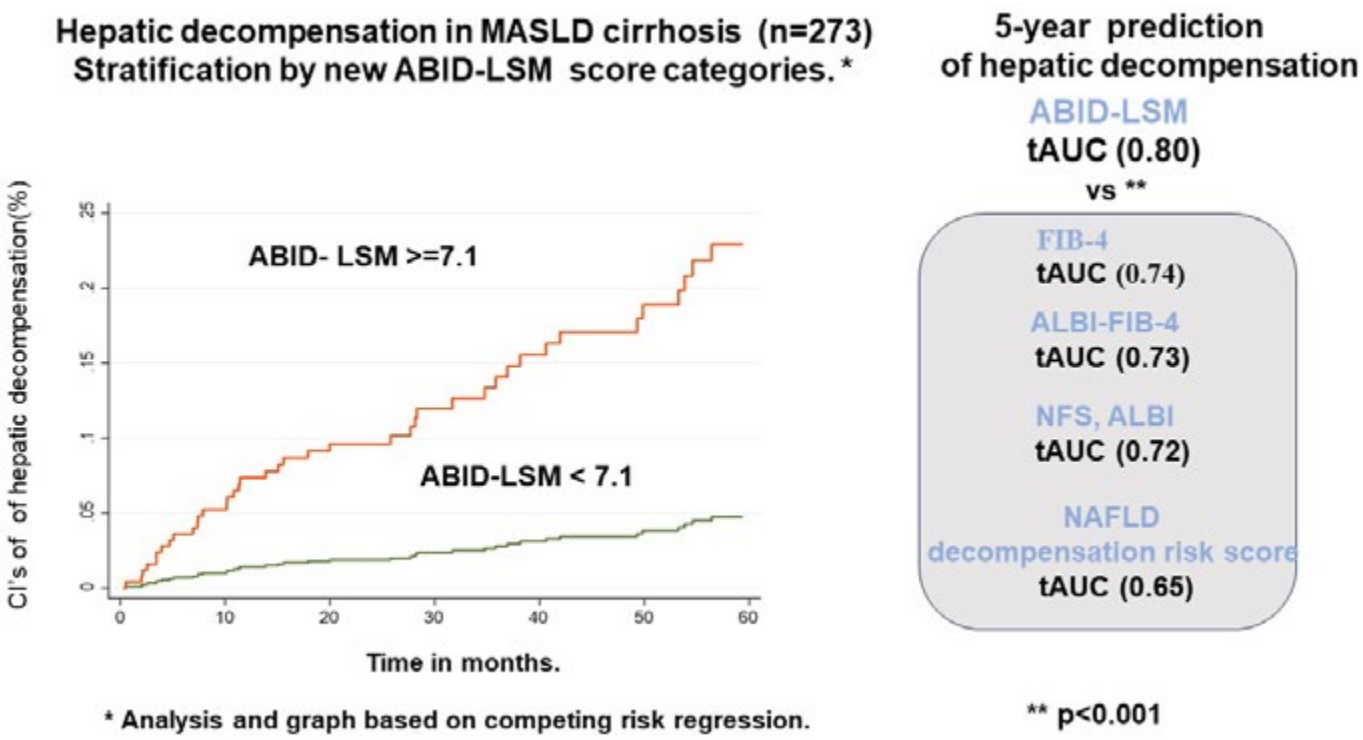

Disclosures: Luis Bertot: Nothing to Disclose, Anna Soria: Nothing to Disclose, Alba Jimenez-Massip: Nothing to Disclose, Isabel Serra: Nothing to Disclose, Teresa Broquetas: Nothing to Disclose, Mercedes Vergara: Nothing to Disclose, Adria Rodriguez: Nothing to Disclose, Carles Aracil: Nothing to Disclose, Octavi Bassegoda: Nothing to Disclose, Sergio Munoz-Martinez: Asofarma Pharma: Speaker in congress, Jose Carrion Rodriguez: Nothing to Disclose, Albert Pardo: Nothing to Disclose, Juan Pericas: Nothing to Disclose, Leon Adams: Novo Nordisk: Advisor, SCL Behring: Advisor, Pfizer: Advisor, Isabel Graupera: Nothing to Disclose

2338 | EXAMINING WAITLIST MORTALITY AND TRANSPLANTATION PROBABILITY IN MASH CIRRHOSIS UNDER THE MELD 3.0 SYSTEM. A SRTR/UNOS DATABASE ANALYSIS

Cheng Han Ng[1] Wen Hui Lim[2] Darren Jun Hao Tan[2] Karn Wijarnpreecha[3] Pojsakorn Danpanichkul[4] Daniel Huang[5] Mazen Noureddin[6] Mohammad Siddiqui[7] Mark Muthiah[8]

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Background: The recently introduced Model for End-Stage Liver Disease (MELD) 3.0 aims to refine the allocation of liver transplants (LT) by improving prognostic accuracy. This study investigates the impact of MELD 3.0 on waitlist outcomes for patients with metabolic dysfunction-associated steatohepatitis (MASH) cirrhosis using the SRTR/UNOS database. **Methods:** A retrospective analysis of the SRTR/UNOS database was conducted, focusing on LT waitlist registrants from January 1, 2016, to December 31, 2022. Exclusion criteria included patients under 18, those listed as Status 1, or those who underwent living donor LT. Demographic and clinical data were collected at listing and removal from the waitlist. MELD 3.0 scores were categorized into four groups (6-9, 10-19, 20-29, 30-40). Competing risk regression models were used to compare waitlist outcomes between MASH and non-MASH patients, adjusting for age, gender, ethnicity, and MELD 3.0 scores. **Results:** A total of 44,037 LT waitlist registrants were included in the primary analysis, with 12,790 MASH and 31,247 non-MASH patients. MASH patients were older and had a higher prevalence of metabolic comorbidities. Despite having lower MELD 3.0 scores, MASH patients exhibited higher portal hypertension complications. MASH patients had higher 90-day (HR: 1.15, 95% CI: 1.10-1.22) and 1-year waitlist mortality (HR: 1.24, 95% CI: 1.17-1.31) compared to non-MASH patients. Additionally, MASH patients had lower 90-day (HR: 0.840, 95% CI: 0.817-0.865) and 1-year transplantation probabilities (HR: 0.839, 95% CI: 0.815-0.863). Gender disparities were noted, with female MASH

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patients experiencing lower transplantation probabilities and higher 90-day mortality. Furthermore, MASH patients listed with native MELD 3.0 had significantly lower transplantation probabilities compared to those with HCC MELD exemption points. **Conclusion:** The current study evaluates the impact of MELD 3.0 in MASH patients awaiting for liver transplantation. Despite the change in scoring in MELD 3.0, MASH cirrhosis was still associated with higher waitlist mortality and lower transplantation probability compared to non-MASH cirrhosis, and highlights the importance for future developments of the MELD score that can potentially classify by etiology.

Disclosures: Cheng Han Ng: Nothing to Disclose, Wen Hui Lim: Nothing to Disclose, Darren Jun Hao Tan: Nothing to Disclose, Karn Wijarnpreecha: Nothing to Disclose, Pojsakorn Danpanichkul: Nothing to Disclose, Daniel Huang: Nothing to Disclose, Mazen Noureddin: Principal Investigator for a Drug Study relationship with Viking; Has not ended; Consultant relationship with Eli Lilly; Has not ended; Consultant relationship with AstraZeneca; Has not ended; Consultant relationship with Boston Pharmaceuticals; Has not ended; Principal Investigator for a Drug Study relationship with Genfit; Has not ended; Principal Investigator for a Drug Study relationship with Galectin; Has not ended; Principal Investigator for a Drug Study relationship with Gilead; Has not ended; Principal Investigator for a Drug Study relationship with BMS; Has not ended; Principal Investigator for a Drug Study relationship with BI; Has not ended; Principal Investigator for a Drug Study relationship with Akero; Has not ended; Consultant relationship with Cytodyn; Has not ended; Consultant relationship with GSK; Has not ended; Consultant relationship with BI; Has not ended; Consultant relationship with Madrigal; Has not ended; Terns,Takeda, Zydus. relationship with Itimmune, BI, Cytodyn, 89BIO, GSK, Madrigal, Merck, Novo Nor; Has not ended; Principal Investigator for a Drug Study relationship with Allergan; Has not ended; Consultant relationship with Takeda; Has not ended; Consultant relationship with Terns; Has not ended; Terns, Corcept, Takeda, Madrigal, Novartis, Novo Nordisk, relationship with Allergan, Akero, BI, BMS, Gilead, Galectin, Zydus GSK; Has not ended; Consultant relationship with Novo Nordisk; Has not ended; Stock â€“ privately held company relationship with Rivus Pharma, Cytodyn, and ChronWell; Has not ended; Consultant relationship with Merck; Has not ended; Principal Investigator for a Drug Study relationship with Madrigal; Has not ended; Consultant relationship with Altimmune; Has not ended; Principal Investigator for a Drug Study relationship with Terns; Has not ended; Principal Investigator for a Drug Study relationship with Zydus; Has not ended; Stock â€“ privately held company relationship with Rivus Pharmaceuticals; Has not ended; Consultant relationship with Alligos; Has not ended; Stock - publicly traded company relationship with Cytodyn; Has not ended; Stock â€“ privately held company relationship with ChronWell; Has not ended; Speaking and Teaching relationship with Madrigal; Has not ended; Principal Investigator for a Drug Study relationship with Takeda; Has not ended; Principal Investigator for a Drug Study relationship with Shire; Has not ended; Principal Investigator for a Drug Study relationship with Novo Nordisk; Has not ended; Principal Investigator for a Drug Study relationship with Novartis; Has not ended; Principal Investigator for a Drug Study relationship with Enanta; Has not ended; Principal Investigator for a Drug Study relationship with Corcept; Has not ended; Principal Investigator for a Drug Study relationship with GSK; Has not ended; Principal Investigator for a Drug Study relationship with Conatus; Has not ended, Mohammad Siddiqui: NovoNordisk: Grant/Research Support, 89Bio: Consultant, Mark Muthiah: Lerna Bio: Stock – privately held company, Olympus: Speaking and Teaching, Boston Scientific: Speaking and Teaching, Novo Nordisk: Grant/Research Support, Echosens: Grant/Research Support, Gilead: Advisor

2339 | CORONASH STUDY: PROSPECTIVE STUDY OF PREVALENCE AND SEVERITY OF METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD) IN PATIENTS UNDERGOING CORONARY ANGIOGRAPHY

Raluca Pais[1] Gerard helft[2] Emmanuel Berman[3] Maharajah Ponnaiah[4] Thomas Maurel[3] Vlad Ratziu[3]

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Background: Because of shared metabolic risk factors and the strong association between coronary artery disease (CAD) and metabolic dysfunction-associated steatotic liver disease (MASLD), international guidelines advise screening for CAD in patients with MASLD. Conversely, there are no recommendations to screen for MASLD in patients with CAD because the prevalence and severity of MASLD among these patients are not well characterized. **The aim** of our study is to determine the prevalence and impact of MASLD on the severity of CAD. **Methods:** This is a prospective cohort study of patients who underwent coronary angiography for known or suspected CAD and vibration controlled transient elastography (VCTE) by Fibroscan. Clinical, anthropometric

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and biological data were collected; the severity of CAD was determined according to the presence of significant stenosis (≥ 50%) and the number of coronary arteries involved. MASLD was defined as CAP ≥ 280 dB/m and significant fibrosis as liver stiffness measurement (LSM)≥ 8 kPa. **Results:** 229 pts were screened between 2019 and 2022. 70 patients were excluded because of missing data. 159 patients were included: mean age 63±11 years, 81% males, mean BMI 26±4 kg/m2, type two diabetes (T2D) 18%, high blood pressure (HBP) 47%, dyslipidemia 60%, 40% were active smokers (25±19 paq/year). 52% had elective coronarography (44% had ≥ 50% stenosis in ≥2 coronary arteries) and 48% had emergency coronarography. The mean CAP was 249±67 dB/m, mean LSM was 5.4 ±2.5 kPa; 33% of patients had steatosis and 11% had significant fibrosis. Patients with steatosis were more often males, had higher BMI (29 ±3.6 kg/m² vs 25±3.4 kg/m², P< 0.001) and waist circumference, higher HOMA-IR but similar prevalence of T2DM; higher triglycerides and lower HDL-C. The severity of CAD was similar between groups with and without steatosis. Patients having elective coronarography for stable CAD had more significant liver damage (higher LSM and FIB4) despite a younger age and similar prevalence of metabolic risk factors. Younger age, active tobacco use, dyslipidemia and LSM were independent predictors for stable CAD. **Conclusion:** MASLD was diagnosed in one third of patients who underwent coronary angiography for confirmed or suspected CAD. The amount of liver fibrosis measured by LSM but not the amount of steatosis was correlated with stable CAD. Screening for MASLD should be considered in symptomatic patients with known or suspected CAD.

Disclosures: Raluca Pais: Nothing to Disclose, Gerard helft: Nothing to Disclose, Emmanuel Berman: Nothing to Disclose, Maharajah Ponnaiah: Nothing to Disclose, Thomas Maurel: Nothing to Disclose, Vlad Ratziu: Nothing to Disclose

2340 | LOW ANTI-MULLERIAN HORMONE IN REPRODUCTIVE-AGED WOMEN IS ASSOCIATED WITH MASLD IN MIDLIFE: DATA FROM THE LONGITUDINAL CARDIA COHORT

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Background: Reproductive aging is a risk factor for metabolic disease in women. As a marker of ovarian aging, previous studies have shown lower anti-Mullerian hormone (AMH) levels to increase the risk for presence and severity of metabolic dysfunction associated steatohepatitis (MASH) in young women with metabolic dysfunction associated steatotic liver disease (MASLD). Whether AMH also increases the risk for MASLD itself is not known. **Methods:** Using the prospective population-based multicenter Coronary Artery Risk Development in Young Adults (CARDIA) study, we evaluated whether low AMH level measured during reproductive years was associated with prevalent MASLD in midlife, measured 10 years later. AMH was analyzed as a continuous variable and dichotomized as “low AMH” for levels indicative of menopausal transition using established thresholds of AMH level < 0.16 ng/ml for women ≤ age 40 and < 0.10 ng/ml for women > age 40. MASLD was defined by CT scan using liver attenuation of ≤40 Hounsfield units, after excluding non-metabolic causes of hepatic steatosis. Multivariable logistic regression considered a priori selected covariates of age, body mass index (BMI), cholesterol and insulin levels, polycystic ovary syndrome (PCOS), and hormonal replacement therapy (HRT). Stratified analyses were performed by receipt of HRT, and in women ≤ 40 years of age. **Results:** Data from 657 reproductive-aged women were analyzed, median age 42 years (IQR 39,51). Metabolic co-morbidities included obesity (n=254, 39%), hypertension (n=110, 17%), dyslipidemia (n=113, 17%), and type 2 diabetes mellitus (DM2) (n=54, 8%). Twenty-six (4%) reported ≥1 oophorectomy and 14 (2%) were prescribed HRT. Fifty-seven women (8.7%) had prevalent MASLD in midlife. The median (IQR) AMH levels were 0.69 (0.20-2.01) and 107 (16%) met criteria for low serum AMH. MASLD was more common in women with low AMH (14.0% vs. 7.6%, p=0.031). On multivariable analyses, continuous levels of AMH were not associated with MASLD (Adjusted OR 1.04, 95% CI 0.92-1.18, p=0.535). However, low AMH as a marker of menopausal transition was associated with a two-fold higher risk of MASLD (aOR 2.03, 95% 1.00-0-4.04, p=0.049). Low AMH was an even stronger predictor of subsequent MASLD in those without HRT (aOR 2.05, 95% CI 1.02-4.14, p=0.044). Among the 243 women under age 40 years, low AMH was also associated with 2-fold higher odds of MASLD (aOR 2.01, 95 CI 1.04-3.89, p=0.046). This finding was more even more pronounced in the smaller group (n=239) of young women

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without HRT (aOR 4.28, 95% CI 1.05-17.48, p=0.043). **Conclusion:** Low AMH at levels indicative of menopausal transition was associated with a two-fold higher risk of prevalent MASLD in midlife, which was attenuated by HRT. This was also apparent in women at risk of premature ovarian insufficiency, defined as menopausal transition at < 40 years of age, supporting the protective effects of estrogen against MASLD risk.

	All Women (n=657)			Women without HRT (n=643)		
	OR	95% CI	p	OR	95% CI	p
Low AMH	2.01	1.00, 4.04	0.049	2.05	1.02, 4.14	0.044
Age	1.00	0.92, 1.08	0.925	1.02	0.94, 1.11	0.626
PCOS	0.85	0.18, 4.09	0.842	0.97	0.20, 4.78	0.965
BMI	1.05	1.02, 1.09	0.005	1.06	1.02, 1.10	0.002
LDL	1.01	1.00, 1.02	0.020	1.01	1.00, 1.02	0.076
Insulin	1.03	1.00, 1.05	0.064	1.03	1.00, 1.06	0.034
HRT	1.64	0.32, 8.57	0.555	-	-	-

Disclosures: Katherine Cooper: Nothing to Disclose, Melissa Wellons: Nothing to Disclose, James Terry: Nothing to Disclose, Heather Huddleston: Nothing to Disclose, Marcelle Cedars: Nothing to Disclose, Stephanie Maldonado: Nothing to Disclose, Monika Sarkar: GSK: Grant/Research Support, Zydus Pharmaceuticals: Grant/Research Support, Gilead Sciences: Grant/Research Support

2341 | STABILITY OF THE NASH-CHECK PATIENT-REPORTED OUTCOME MEASURE OVER TIME IN PATIENTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE AND STABLE CLINICAL STATUS

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Background: A key aspect of a valid patient-reported outcome (PRO) measure (PROM) is the stability of the scores over time in those whose clinical status remains stable. While several PROMs have been used for patients with metabolic dysfunction-associated steatotic liver disease and steatohepatitis (MASLD and MASH), none has been fully validated to regulatory standards for use in drug development. The NASH-CHECK PROM was developed in accordance with regulatory standards, but its stability over time has not been established. We aimed to define the stability of NASH-CHECK scores over time in patients with varying severity of disease at baseline who have unchanged overall clinical status. **Methods:** The NASH-CHECK PROM was tested at two time points in a subset of patients with MASLD enrolled in TARGET-NASH, an ongoing prospective longitudinal non-interventional real-world cohort of >6500 patients with MASLD in the US with over 6 years of follow-up. The analysis population included patients without a change in MASLD disease severity between completion of the first and second NASH-CHECK. Previously developed TARGET-NASH definitions for disease severity were utilized, decompensation events included ascites/complications from ascites, hepatic encephalopathy, variceal bleeding. The individual component scores were derived and compared pairwise with the first and second set of scores. The distribution, mean, and variance of each score was evaluated. *The null hypothesis was that the second score was significantly different from the first score*. Significance was set at a $p < 0.05$. **Results:** A total of 272 patients with MASLD (MASL n=75, MASH n=92, MASH cirrhosis n=105) were studied. Patients with both compensated (n=64) and decompensated MASH cirrhosis (n=39) were included. The mean (±S.D.) duration between tests was 9.3 (5.4) months. The mean (±S.D.) scores for NASH-CHECK components are tabulated below. Scores were not statistically different between the first and second NASH-CHECK within the disease severity subgroups except for emotional impact among compensated cirrhosis patients where an improvement was observed at the second NASH-CHECK ($p < 0.001$). **Conclusion:** The NASH-CHECK PROM scores were stable over an extended period of time (mean [±S.D.] 9.3 [5.4] months) in patients with varying severity of MASLD whose clinical status remained unchanged during this time.

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Item	MASL		MASH		Comp cirrhosis		Decomp cirrhosis	
	1st vs 2nd NC		1st vs 2nd NC		1st vs 2nd NC		1st vs 2nd NC	
symptom single-item								
Abdominal bloating	2.32 (2.652)	2.53 (2.713)	2.15 (2.840)	1.82 (2.573)	2.58 (3.186)	2.21 (2.824)	2.67 (3.239)	2.55 (3.055)
Abdominal pain	1.72 (2.618)	1.68 (2.406)	1.46 (2.662)	1.43 (2.477)	1.81 (2.606)	1.63 (2.617)	1.85 (2.691)	1.63 (2.775)
Fatigue	3.64 (2.917)	3.71 (2.865)	3.12 (2.953)	3.36 (2.769)	3.91 (3.069)	3.67 (2.845)	3.87 (3.139)	4.00 (3.361)
Itchy skin	1.97 (2.564)	2.07 (2.965)	1.85 (2.676)	1.91 (2.763)	2.16 (2.749)	1.97 (2.890)	1.82 (2.535)	2.22 (2.554)
Sleep	3.21 (3.068)	3.46 (3.126)	3.10 (3.006)	3.08 (3.061)	3.97 (3.008)	3.50 (3.303)	2.95 (3.385)	2.61 (3.009)
symptom scale								
Cognitive symptoms	2.34 (2.436)	2.21 (2.220)	1.66 (2.426)	1.61 (2.056)	2.37 (2.521)	1.97 (2.291)	2.22 (2.585)	1.85 (1.985)
HRQOL								
Activity limitation	2.49 (2.726)	2.48 (2.512)	2.29 (2.722)	2.36 (2.682)	2.82 (2.823)	2.83 (2.798)	3.31 (2.728)	3.39 (2.764)
Emotional impact	2.13 (2.263)	1.99 (2.096)	1.84 (2.008)	1.68 (1.876)	***2.46** (2.405)	***1.81** (1.845)	2.35 (2.528)	2.01 (1.904)
Social impact	0.92 (1.765)	1.07 (2.043)	0.63 (1.547)	0.54 (1.317)	1.21 (2.294)	0.88 (1.694)	1.88 (2.635)	2.20 (2.648)

*p<0.05 indicating significant improvement of emotional impact scores in compensated cirrhosis participants over time

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2342 | STEATOTIC LIVER DISEASE WITH METABOLIC DYSFUNCTION AND MODEST ALCOHOL CONSUMPTION CUMULATIVELY IMPACT SURVIVAL IN THE YOUNGER POPULATIONS

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Background: With the adoption of the new steatotic liver disease (SLD) nomenclature, MetALD has been introduced to describe those with metabolic dysfunction-associated SLD (MASLD) and above-average alcohol consumption. It is currently unknown if modest alcohol consumption, in addition to SLD with metabolic dysfunction (MD), impacts survival. **Methods:** We studied the population-based cohort of National Health and Nutrition Survey III for the association between SLD with MD and modest alcohol consumption with all-cause mortality. Participants with excessive alcohol consumption (>50/60 grams daily for females/males [F/M]) or missing data on SLD, age, alcohol consumption, or follow-up were excluded. SLD was defined as hepatic steatosis on abdominal ultrasound, and modest alcohol consumption as >10/20 grams (F/M) daily. Multivariable Cox regression analyses were adjusted for age, sex, race, marital status, education, and smoking, with results stratified by age groups (20-40, 40-60, 60-80). Additional analyses were performed using the >20/30 grams daily threshold, in line with current SLD definitions. **Results:** Of the 12,940 included participants, 5,799 (44.8%) were male, SLD with MD was present in 4,104 (31.7%) and modest alcohol use in 2,187 (16.9%). During a median follow-up of 23 [20-25] years, 3,993 (31%) deaths occurred. Presence of SLD with MD showed an important significant detrimental effect on survival in all age categories: 20-40 years: aHR 1.25 (95% CI 1.01-1.56), 40-60 years: aHR 1.25 (95% CI 1.09-1.43), 60-80 years: aHR 1.13 (95% CI 1.03-1.23). Modest alcohol consumption had a significant association with all-cause mortality in the younger population of 20-40 years: aHR: 1.25 (95% CI 1.01-1.56). When analyses were performed with the 20/30 grams (F/M) daily cut-off, alcohol consumption was no longer significantly associated with survival in any age group. **Conclusion:** SLD with MD and modest alcohol consumption have a cumulative detrimental effect on survival in younger populations. These results further guide screening for at-risk liver disease in the general population and questions the validity of the 20/30 grams daily (M/F) threshold used in the current nomenclature.

Table 1. All-cause mortality risk for the presence of steatotic liver disease with metabolic dysfunction and alcohol consumption in adjusted models, stratified by age

		Alcohol >10/20 grams daily			Alcohol >20/30 grams daily		
	N	aHR	95% CI	P	aHR	95% CI	P
Entire population	12,940						
SLD + metabolic dysfunction		1.12	1.05 – 1.19	**<0.001**	1.12	1.05 – 1.19	**<0.001**
Alcohol consumption		1.01	0.92 – 1.10	0.84	1.05	0.94 – 1.18	0.38
20-40 years	5,958						
SLD + metabolic dysfunction		1.25	1.04 – 1.52	**0.021**	1.25	1.03 – 1.51	**0.021**
Alcohol consumption		1.29	1.05 – 1.57	**0.014**	1.18	0.92 – 1.51	0.19
40-60 years	3,922						
SLD + metabolic dysfunction		1.19	1.05 – 1.35	**0.005**	1.19	1.05 – 1.31	**0.007**
Alcohol consumption		1.02	0.87 – 1.19	0.82	1.17	0.97 – 1.41	0.111
60-80 years	3,060						
SLD + metabolic dysfunction		1.10	1.09 – 1.11	**0.026**	1.10	1.09 – 1.11	**0.024**
Alcohol consumption		0.90	0.79 – 1.03	0.12	0.90	0.74 – 1.08	0.25

Model adjusted for: Age, sex, smoking, education, race, marital status
Abbreviations: aHR, adjusted hazard ratio; CI confidence interval; MD, metabolic dysfunction

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2343 | INCREASING LIVER FIBROSIS IN MASLD IS ASSOCIATED WITH HIGHER RISK OF HIP FRACTURES IN MALES

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Background: Cirrhosis is associated with osteoporosis and increased risk of fractures. However, obesity is associated with higher bone mineral density (BMD). As patients with MASLD are oftentimes obese, we assessed whether increasing amounts of liver fibrosis in MASLD is associated with higher risk of fractures or lower BMD. **Methods:** Data were derived from the National Health and Nutrition Examination Surveys (NHANES) 2017-2020. Adults ≥ 50 years old with valid transient elastography (TE) measurements were included. This age was chosen as DXA and bone fracture survey in NHANES were only performed in this age range. MASLD was defined as a controlled attenuation parameter (CAP) ≥ 274 dB/s in the presence of ≥1 cardiometabolic risk factors. Participants with excessive alcohol consumption, alternative etiologies of liver disease, and/or medications that affect BMD or liver fat were excluded. Liver stiffness measurements ≥ 9.7 kPa were used to define the presence of advanced (F3-F4) fibrosis. **Results:** A total of 3,385 patients were included in the study (age: 65 ± 9 years; Male 48%; BMI: 29.9 ± 6.7 kg/m^2; MASLD: 49%; F3-F4: 7.6%). Spine, total hip, and femoral neck bone mineral density were higher in patients with F3-F4 vs. F0-2 (all $p<0.05$). Rates of hip, spine, and wrist fractures reported were no different between patients with vs. without F3-F4. To assess the impact of liver fibrosis by TE on BMD and risk of fracture, independently of other confounding factors, we performed a multiple regression analysis. After adjustment for age and BMI, transient elastography was independently associated with higher risk of hip fracture in men (OR: 1.05 [1.02-1.07], $p<0.001$), but not in women (OR: 0.89 [0.73-1.09], $p=0.25$), where age remained the strongest predictor of hip fracture. Of note, the effect on hip fracture with increasing fibrosis by TE occurred despite no association between TE fibrosis and BMD after adjustment for age, gender, and BMI. Increasing fibrosis by TE was not associated with increased risk of spine or wrist fractures. **Conclusion:** In a large national dataset, increasing fibrosis by TE was associated with increased risk of hip fracture in males independent of age, BMI, or race. Given the substantial risk of morbidity and mortality associated with hip fractures, these findings suggest that patients with advanced liver fibrosis related to MASLD, especially males, may benefit from osteoporosis screening as currently recommended in cirrhosis.

Disclosures: Elena Gibson: Nothing to Disclose, Meagan Gray: NovoNordiesk: Consultant, Fernando Bril: NovoNordisk: Consultant, NovoNordisk: Speaking and Teaching, Boehringer Ingelheim: Speaking and Teaching, Boehringer Ingelheim: Advisor

2344 | INCIDENCE OF CIRRHOSIS AND EXTRAHEPATIC MANIFESTATIONS AMONG LEAN AND NON-LEAN INDIVIDUALS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE

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Background: The prevalence of Metabolic dysfunction-associated steatotic liver disease (MASLD) has risen in recent years and projected to be 50% by 2040. With the new MASLD nomenclature, there is a lack of studies investigating the natural history using MASLD criteria among lean versus non-lean individuals and assessing the incidence of extrahepatic manifestations. The aim of this study is to assess the incidence of both hepatic and extrahepatic manifestations of lean vs non lean MASLD. **Methods:** MASLD patients were included from Banner

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Health System, representing hospitals across Arizona, California, and Colorado, and the University of Michigan Health System from 2012 to June 2023. Patients from Banner Health System were identified as MASLD using ICD code and patients from University of Michigan were identified as MASLD based on imaging evidence of hepatic steatosis. We excluded patients with other causes of liver disease, underweight, baseline decompensated cirrhosis, baseline cancer diagnosis, prior bariatric surgery, or missing data on body mass index (BMI), aspartate and alanine aminotransferase, and platelet. Patients who met 1/5 cardiometabolic criteria including BMI >25 (BMI >23 in Asians), hypertension, diabetes mellitus, dyslipidemia, or hypertriglyceridemia were included. Outcomes included mortality and the incidence of cirrhosis, cardiovascular disease (CVD), liver related events (LRE), cirrhosis, any cancer, obesity related cancer, and major adverse cardiac event (MACE). We performed a competing risk analysis to determine the risk of diseases incidence among lean vs non lean MASLD and adjusted for multiple confounders **(Table). Results:** We included 51,625 MASLD patients in the cohort, 4.92% were lean, 22.39% were overweight, 28.32% were obese class I, and 44.38% were obese class II-III. In the multivariate analysis, non-lean patients had a lower mortality, lower incidence of LRE, and lower incidence of CVD and MACE compared with lean patients. Moreover, incidence of cirrhosis was higher in the non-lean population. **Conclusion:** In this multicenter study, lean patients with MASLD had a higher mortality and higher incidence of CVD and MACE despite lower DM incidence compared to non-lean individuals with MASLD. Lean patients also had lower cirrhosis incidence but higher LRE suggesting they have worse outcomes when they develop cirrhosis, likely from sarcopenia effect. These findings also suggest that cardiac risk assessments are essential in MASLD, particularly in lean individuals.

Table: Competing risk analysis for death and incidence of diseases by BMI category[a]

BMI Category	Death[b]		Any cardiovascular disease		Cirrhosis		Liver-related events[c]		Type 2 Diabetes Mellitus[d]		Obesity-related cancer		Any Cancer		MACE[e]	
	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value
Lean	Referent		Referent		Referent		Referent		Referent		Referent		Referent		Referent	
Overweight	0.52 (0.42-0.65)	<0.01	0.85 (0.75-0.97)	0.01	1.15 (0.82-1.61)	0.43	0.74 (0.56-0.98)	0.04	1.08 (0.93-1.26)	0.31	0.93 (0.73-1.19)	0.58	0.97 (0.81-1.16)	0.76	0.83 (0.74-0.94)	<0.01
Obesity class 1	0.47 (0.38-0.58)	<0.01	0.82 (0.73-0.93)	<0.01	1.47 (1.05-2.04)	0.02	0.75 (0.57-0.99)	0.045	1.65 (1.42-1.91)	<0.01	0.89 (0.70-1.14)	0.36	0.83 (0.70-1.00)	0.05	0.82 (0.73-0.92)	<0.01
Obesity class 2-3	0.56 (0.46-0.69)	<0.01	0.94 (0.84-1.07)	0.36	1.69 (1.22-2.35)	<0.01	0.84 (0.64-1.11)	0.22	2.49 (2.15-2.87)	<0.01	1.08 (0.85-1.36)	0.52	0.92 (0.73-1.10)	0.35	0.93 (0.83-1.05)	0.24

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a]HR was adjusted for age, sex, race, smoking status, alcohol consumption, type 2 diabetes mellitus, hypertension, dyslipidemia, and use of aspirin and statin.

[b]Cox proportional hazards model was performed for death analysis.

[c]Liver related events were defined as the incidence of hepatic encephalopathy, ascites, hepatocellular carcinoma, or variceal bleeding

[d]For type 2 diabetes mellitus, HR was adjusted with the same confounders[a] excluding type 2 diabetes mellitus.

[e]MACE is defined as the incidence of coronary artery disease, all-cause mortality, congestive heart failure, or cerebrovascular accident

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2345 | RISK OF COMORBID MENTAL HEALTH CONDITIONS IN CHILDREN WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE

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Background: Steatotic liver disease (SLD) affects nearly 1 in 10 children in the United States. Specifically, metabolic dysfunction-associated steatotic liver disease (MASLD) is associated with several extrahepatic comorbidities. Therefore, it is important to consider its interaction with all dimensions of health – including mental health – especially given the increasing rate of mental health conditions in youth, a growing public health concern. This study aimed to: 1) determine the cumulative prevalence and incidence rate of various mental health conditions in children with MASLD and 2) assess the risk factors for developing mental health conditions in children with MASLD. **Methods:** This study included children diagnosed with MASLD prior to age 18 at Rady Children's Hospital San Diego between 2000-2017 and followed through 2021. The diagnosis of MASLD was based on liver histology demonstrating macrovesicular steatosis and the presence of 1 or more cardiometabolic

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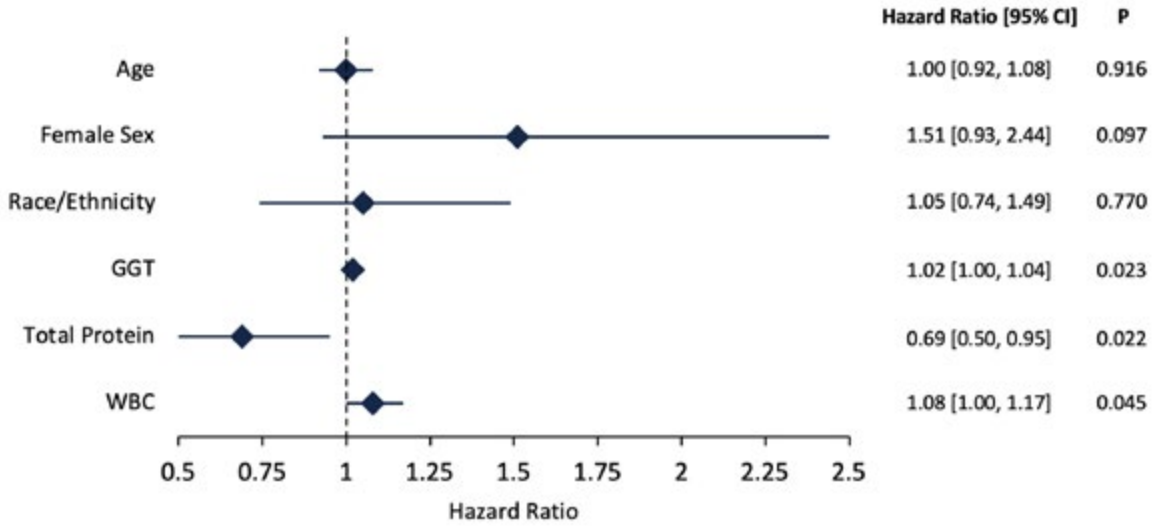
risk factors. Our study outcome was the diagnosis of a mental health condition (depression, anxiety, bipolar disorder, obsessive compulsive disorder, schizophrenia). The prevalence and incidence of mental health conditions were calculated. Cox proportional hazard regression was performed to identify risk factors for the development of mental health conditions in children with MASLD. **Results:** A total of 997 children with MASLD, with a mean age of 12.8±2.9 years, were followed for an average of 6.1±4.2 years, totaling 6,120 person-years. Cumulatively, 20.9% of children with MASLD were diagnosed with a mental health condition over the study period: depression 13.6%, anxiety 12.6%, bipolar disorder 2.0%, obsessive compulsive disorder 0.7%, and schizophrenia 0.6%. The incidence rates of mental health conditions (per 100,000 person-years) were as follows: depression (1,626), anxiety (1,500), and bipolar disorder (183). In the multivariate model, female sex, lower serum total protein, higher gamma-glutamyl transferase, and higher white blood cell count at baseline were significantly associated with increased risk for developing mental health conditions in children with MASLD (Figure 1). **Conclusion:** Children with MASLD are at high risk for developing mental health conditions. Several risk factors underscore a potential pathophysiological relationship between mental health conditions and MASLD. Increased awareness and prevention of mental health conditions in children with MASLD are crucial at both the patient and systems levels.

Figure 1. Forest Plot of Risk Factors for Developing Mental Health Conditions in Children with MASLD



Disclosures: Sheila Noon: Nothing to Disclose, Nhat Thai: Nothing to Disclose, Kimberly Newton: Nothing to Disclose, Nidhi Goyal: Nothing to Disclose, Benjamin Maxwell: Nothing to Disclose, Elizabeth Yu: Nothing to Disclose, Warren Shapiro: Nothing to Disclose, Jeffrey Schwimmer: Intercept: Grant/Research Support, Seraphina: Grant/Research Support, Merck: Consultant

2346 | METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD) AND ASSOCIATED RISK FACTORS IN A COMMUNITY-BASED SAMPLE OF AMERICAN INDIANS

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Background: American Indian (AI) communities experience higher rates of liver cancer incidence and mortality than the general United States population. Common risk factors for liver cancer include having hepatitis B or hepatitis C, cirrhosis, excessive alcohol consumption, lack of physical activity, non-alcoholic fatty liver disease (NAFLD), and obesity. Notably, a disproportionate prevalence of obesity-related diseases is experienced by AI people in the U.S. when compared to all other racial/ethnic groups, making their health status a key public health issue. Despite the clear need to develop effective liver cancer prevention strategies, a gap remains among AI communities and the scientific literature. To address these significant gaps, we assessed the prevalence of

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NAFLD in a community sample of AI adults residing in Navajo Nation and determined risk factors associated with NAFLD **Methods:** A total of 100 AI adults from Navajo Nation completed an in-person study visit, including a FibroScan® for the assessment of NAFLD status identified as having a continuous attenuation parameter (CAP) score ≥288 dB/m. Liver stiffness measurements (LSM) in kilopascals (kPa) indicated fibrosis values. Multivariable logistic regression was employed to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for NAFLD. **Results:** Of the 100 participants, 53 experienced NAFLD (53.0%). Participants who developed NAFLD were more likely to be older (52.6 versus 49.1 years), male (40.4% versus 20.8%), have a higher BMI (31.9 versus 29.9 kg/m^2), and HbA1c values (6.67 versus 6.36) compared to participants who did not develop NAFLD. The prevalence of S1, S2, and S3 steatosis stage by CAP were 31%, 24%, and 45%, respectively. Nearly 33% of participants were identified as having significant fibrosis. Among the three predictors in the model, one predictor (i.e., body mass index (BMI)) showed significance at the 0.05 significance level. There was some evidence for effect modification of BMI by sex ($P_{interaction}$ = 0.09). The estimated OR for an increase in BMI of 1 kg/m^2 was 1.25 (95% CI, 1.05, 1.57) for men and 1.05 (95% CI, 0.69, 1.59) for women. **Conclusion:** The prevalence of NAFLD is among the highest observed among all racial and ethnic groups. Lifestyle interventions to reduce body weight are needed to stem the higher rates of NAFLD observed for this high-risk and underserved population.

Disclosures: David Garcia: Nothing to Disclose, Edgar Villavicencio: Nothing to Disclose, Caitlin Baird: Nothing to Disclose, Xiaoxiao Sun: Nothing to Disclose, Timian Godfrey: Nothing to Disclose, Kimberly Shea: Nothing to Disclose, Adriana Maldonado: Nothing to Disclose, Denver Seaton: Nothing to Disclose, Priscilla Sanderson: Nothing to Disclose

2347 | IMPACT OF SURVEILLANCE ON OVERALL SURVIVAL IN PATIENTS WITH MASLD-ASSOCIATED HEPATOCELLULAR CARCINOMA: RESULTS FROM A MULTICENTER COHORT STUDY

Darren Tan[1] Karn Wijarnpreecha[2] Nobuharu Tamaki[3] Cheng Han Ng[1] Majd Aboona[4] Claire Faulkner[5] Wen Hui Lim[1] Charlotte Kench[6] Shirin Salimi[6] Abdul-Hamid Sabih[6] Benjamin Tay[1] Yi Qing Teh[1] John Mok[1] Mark Muthiah[1] Anand Kulkarni[7] Ken Liu[6] Sung Won Lee[8] Beom Kyung Kim[9] Daniel Huang[10]

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Background: The effectiveness of hepatocellular carcinoma (HCC) surveillance for patients with metabolic dysfunction-associated steatotic liver disease (MASLD) remains contentious due to the lack of data from randomized trials. Additionally, data from cohort studies have been limited by lead-time bias and the survival benefit of HCC surveillance remains unclear. Hence, we aimed to evaluate the benefit of HCC surveillance in a diverse cohort of patients with MASLD after adjusting for lead-time bias. **Methods:** We conducted a retrospective, multicenter cohort study of 285 adult patients diagnosed with MASLD-associated HCC from January 2003 to August 2023 at four academic centers in Australia, South Korea, Singapore and the United States. Screen-detected HCC was defined as abnormal surveillance-intent abdominal imaging or alpha-fetoprotein within 6 months before diagnosis. Lead-time bias was corrected for using the parametric method proposed by Duffy et al. We assumed a mean sojourn time (defined as the period where a tumor is asymptomatic but detectable by surveillance methods) of 4 months based on existing literature. Multivariate cox regression was used to analyze difference in overall survival (OS) between patients with screen detected versus non-screen detected HCC. **Results:** Of a total 285 patients, 143 (50.2%) patients had screen-detected HCC and 142 (49.8%) patients had non-screen detected HCC. Patients with screen-detected HCC were more likely to present with early-stage cancers (defined as Barcelona Clinic Liver Cancer (BCLC) stage 0/A) compared to patients with non-screen detected HCC (69.85% versus 44.93%, p<0.001). Median survival was longer in the screen detected group compared to the non-screen detected group (58.0 months versus 34.5 months, p<0.001). Multivariate cox regression accounting for patient age, sex, body mass index, diabetes, and cirrhosis found that patients with screen-detected HCC had significantly improved OS compared to non-screen detected HCC (Hazard Ratio [HR] 0.60; 95%CI 0.41 - 0.89; p=0.011). When accounting for lead-time bias with a mean sojourn time of 4 months, median survival time in the screen-detected group decreased to 54.0 months. After adjusting for lead-time bias, screen-detected HCC continued to be associated with improved survival compared to non-screen detected HCC (HR 0.67; 95%CI 0.45 - 0.99; p=0.042). **Conclusion:** HCC surveillance is associated with improved survival in

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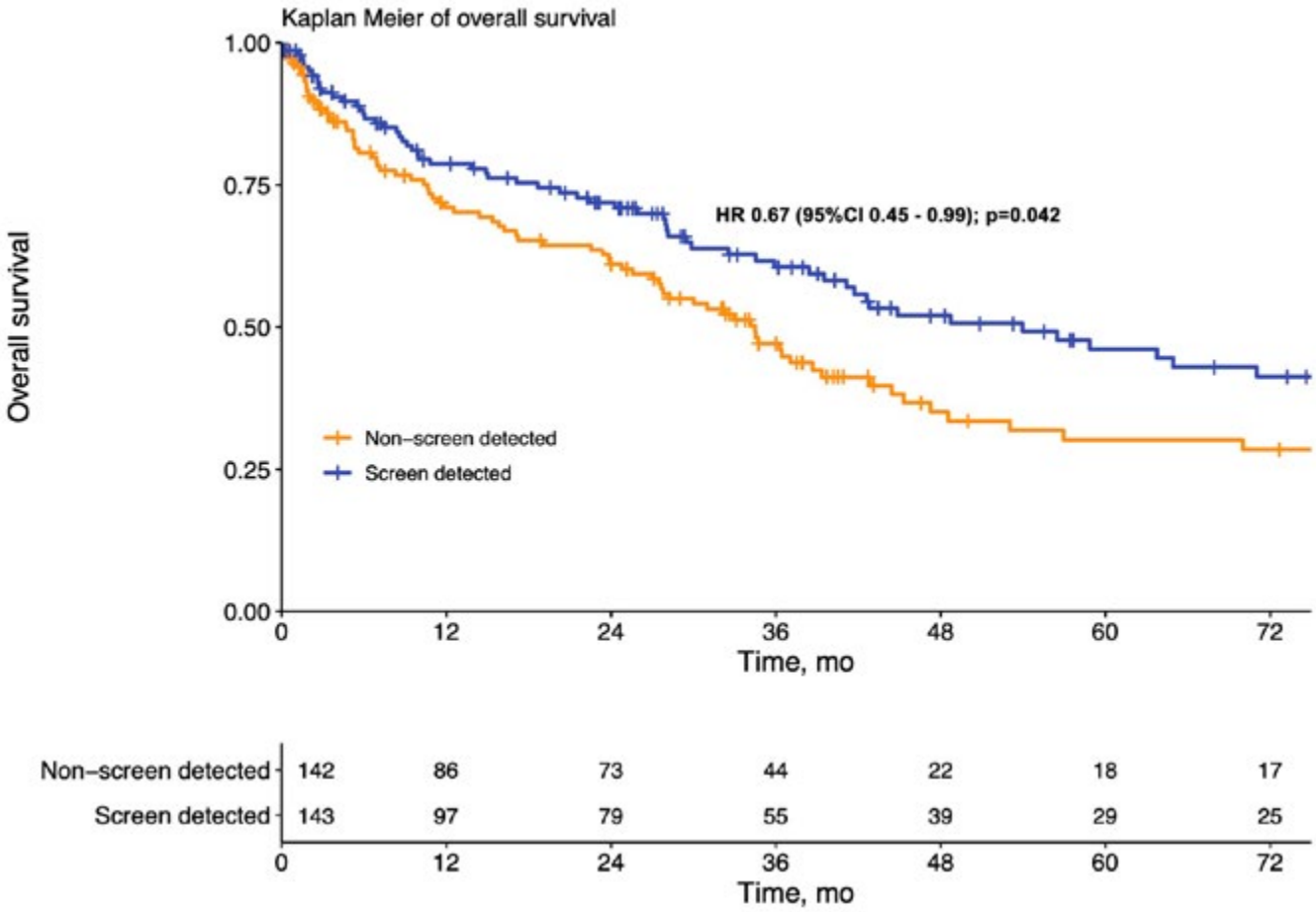
patients with MASLD even after accounting for lead-time bias. Further investigation is required regarding optimal pathways for cancer surveillance in patients with MASLD.



Disclosures: Darren Tan: Nothing to Disclose, Karn Wijarnpreecha: Nothing to Disclose, Nobuharu Tamaki: Nothing to Disclose, Cheng Han Ng: Nothing to Disclose, Majd Aboona: Nothing to Disclose, Claire Faulkner: Nothing to Disclose, Wen Hui Lim: Nothing to Disclose, Charlotte Kench: Nothing to Disclose, Shirin Salimi: Nothing to Disclose, Abdul-Hamid Sabih: Nothing to Disclose, Benjamin Tay: Nothing to Disclose, Yi Qing Teh: Nothing to Disclose, John Mok: Nothing to Disclose, Mark Muthiah: Lerna Bio: Stock – privately held company, Olympus: Speaking and Teaching, Boston Scientific: Speaking and Teaching, Novo Nordisk: Grant/Research Support, Echosens: Grant/Research Support, Gilead: Advisor, Anand Kulkarni: Nothing to Disclose, Ken Liu: Nothing to Disclose, Sung Won Lee: Nothing to Disclose, Beom Kyung Kim: Nothing to Disclose, Daniel Huang: Nothing to Disclose

2348 | OBESOGENIC MEDICATION USE IS ASSOCIATED WITH INCREASED RISK OF MASLD AND LIVER FIBROSIS

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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) and resulting metabolic dysfunction-associated steatohepatitis (MASH) is the leading cause of liver disease, with obesity as the main risk factor. Use of prescription medications known to increase weight is common (20% of the US population) and may contribute to obesity and thus MASLD. We quantified the association between obesogenic medication use and MASLD, liver fibrosis (LF), and fibrotic MASH (fMASH). **Methods:** National Health and Nutrition Examination

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Survey data (2017-2020) were used. Exclusion criteria included chronic hepatitis B/C and alcohol consumption >210/>140 g/week for men/women. MASLD was defined per the Nomenclature Consensus Group definition. LF was defined as MASLD plus mean liver stiffness ≥7.0 kPa. fMASH was defined as a FibroScan-AST score ≥ a high-specificity cutoff of 0.67. Use of medications known to be obesogenic was compared using multivariate logistic regression adjusting for age, sex, race, for overall medication use and specific medication sub-classes, and stratified by obesity class. **Results:** Of those selected for FibroScan (9,023), 8,524 were included: 41.0% had MASLD, 13.7% had LF, and 0.9% had fMASH. While 16.6% took any obesogenic medication, those with MASLD had a higher use rate (23.8% vs. 11.1%; p<0.001). In multivariate regressions (Table 1), use of any obesogenic medication was associated with increased odds of MASLD (adjusted odds ratio [aOR] 1.45, 95% confidence interval [CI]: 1.18-1.79) and LF (aOR 1.73, 95%CI: 1.20-2.49), but not fMASH. This association demonstrated a per-medication effect for MASLD (aOR 1.24, 95%CI: 1.04-1.46) and LF (aOR 1.42, 95%CI: 1.16-1.74). Use of obesogenic medications for diabetes was associated with increased odds of LF (aOR 3.10, 95%CI: 1.94-4.96) and fMASH (aOR 3.51, 95%CI: 1.11-11.02), but not MASLD. After stratification by obesity class, obesogenic medication use was no longer associated with MASLD or LF but was associated with increased odds of fMASH amongst those without obesity (aOR 5.36, 95%CI: 1.22-23.45). **Conclusion:** Obesogenic medication use is associated with MASLD and liver fibrosis, largely mediated by weight differences. As focus shifts towards state-of-the-art pharmacologic treatments (e.g., GLP-1s, resmetirom), attention to a straightforward, guideline-supported approach to avoid or minimize obesogenic medications when possible is warranted. This may have outsized benefits given the high prevalence of obesogenic medications in the MASLD/MASH populations identified in this study.

Table 1: Association between obesogenic medications and MASLD, liver fibrosis, and fibrotic MASH (N=8,524). NHANES sampling weights were accounted for to obtain nationally representative estimates. Odds Ratios and 95% confidence intervals were obtained by multivariate logistic regression, accounting for age, sex, and race.

	aOR (95% CI)		
	MASLD	Liver Fibrosis	Fibrotic MASH
Obesogenic medication use			
Per 1 medication	**1.24 (1.04, 1.46)**	**1.42 (1.16, 1.74)**	1.40 (0.84, 2.34)
Any medication	**1.45 (1.18, 1.79)**	**1.73 (1.20, 2.49)**	1.62 (0.65, 4.01)
Medication subclass			
Anti-inflammatories	0.98 (0.43, 2.23)	0.64 (0.35, 1.17)	1.70 (0.33, 8.67)
Anticonvulsants	1.46 (0.98, 2.16)	**1.86 (1.09, 3.17)**	0.90 (0.17, 4.68)
Antidepressants	0.81 (0.49, 1.37)	0.76 (0.45, 1.28)	0.82 (0.11, 6.24)
Medication for diabetes	1.45 (0.88, 2.42)	**3.10 (1.94, 4.96)**	**3.51 (1.11, 11.02)**
Antipsychotics	0.73 (0.40, 1.33)	**2.19 (1.28, 3.76)**	1.13 (0.13, 9.63)
Beta blockers	**1.64 (1.23, 2.20)**	1.27 (0.96, 1.67)	1.43 (0.41, 5.05)
Stratified by Obesity Class			
Any obesogenic medication			
Absence of obesity	1.23 (0.97, 1.56)	1.55 (0.94, 2.57)	**5.36 (1.22, 23.45)**
Class 1 obesity	0.90 (0.60, 1.36)	1.68 (0.89, 3.17)	2.72 (0.78, 9.51)
Class 2-3 obesity	1.05 (0.72, 1.52)	1.08 (0.66, 1.77)	0.47 (0.14, 1.56)
BMI subgroup			
Absence of obesity	1.12 (0.91, 1.38)	1.32 (0.99, 1.77)	**1.75 (1.10, 2.79)**
Class 1 obesity	0.91 (0.68, 1.22)	1.41 (0.95, 2.09)	**2.19 (1.13, 4.25)**
Class 2-3 obesity	0.92 (0.70, 1.22)	1.07 (0.86, 1.34)	0.59 (0.25, 1.41)

Disclosures: Ian Jaffe: Nothing to Disclose, Jingyao Hong: Nothing to Disclose, Yiting Li: Nothing to Disclose, AnnMarie Liapakis: Nothing to Disclose, Christine Ren-Fielding: Intuitive: Consultant, Reshape: Consultant, Holly Lofton: Nothing to Disclose, Akash Gujral: Nothing to Disclose, Dorry Segev: Nothing to Disclose, Mara McAdams-DeMarco: Nothing to Disclose, Babak Orandi: Nothing to Disclose

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2349 | PREDICTIVE MODELS FOR HEPATOCELLULAR CARCINOMA (HCC) DEVELOPMENT IN CIRRHOTIC AND NON-CIRRHOTIC METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE PATIENTS

Prerana Sruthi Vatsavayi[1] Jawad Aziz[1] Mohammed Abdurrahman[1] Michael Yee[2] Benjamin Mullish[1] Roberta Forlano[1] Shahid Khan[1] Pinelopi Manousou[1]

[1]Imperial College London, [2]Imperial College Healthcare NHS Trust

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is the fastest growing cause of hepatocellular carcinoma (HCC) worldwide. Although 20-50% of MASLD HCC cases occur in non-cirrhotic patients, surveillance in this group is not recommended. Risk stratification is needed for future HCC screening recommendations. We aimed to determine predictive factors for HCC development in a diverse MASLD population and to derive novel HCC risk prediction models in a cirrhotic and non-cirrhotic background. **Methods:** Clinical, anthropometric and demographic predictors of MASLD patients with/without HCC were evaluated. Baseline characteristics, independently predictive of HCC development on multivariate cox regression analysis, were incorporated into risk prediction models for MASLD and non-cirrhotic MASLD patients. The study population was also divided into derivation and validation groups in a 70:30 ratio and two further models (MASLD and non-cirrhotic MASLD) were developed for internal validation. Harrell's c-index values were used to assess model discrimination. **Results:** We followed 524 Non-HCC and 99 HCC patients for a median of 9.7 and 7.5 years respectively. There were no significant differences in gender or ethnicity. Patients with HCC had a significantly higher baseline median age ($p<0.001$). A significantly higher proportion ($p<0.001$) of HCC patients (65.7%) had cirrhosis compared to Non-HCC patients (8.6%). The Index of Multiple Deprivation (IMD) was significantly higher in HCC cases. Older age, presence of cirrhosis, moderate alcohol consumption (MAC), Fibrosis-4 (FIB-4) index, alkaline phosphatase (ALP) and glycated haemoglobin (HbA1c) were independent predictors of HCC in MASLD patients. In non-cirrhotic patients, older age, MAC, FIB-4, gamma-glutamyl transferase (GGT) and HbA1c independently predicted HCC. BMI and IMD were not significant predictors on multivariate analysis. The Harrell's c-index was 0.89 for the MASLD and 0.85 for the non-cirrhotic MASLD model. In MASLD and Non-Cirrhotic MASLD derivation cohorts, models displayed good discrimination with Harrell's c-index values of 0.90 and 0.87 respectively for predicting HCC. In validation cohorts, Harrell's c-index values were 0.86 for both models. **Conclusion:** We identified predictors of HCC development and derived HCC risk prediction scores in an ethnically diverse group of MASLD patients. These models have the potential to support risk stratification and guide patient selection for HCC surveillance. External validation and cost effectiveness studies are needed to assess generalisability to broader patient populations.

Disclosures: Prerana Sruthi Vatsavayi: Nothing to Disclose, Jawad Aziz: Nothing to Disclose, Mohammed Abdurrahman: Nothing to Disclose, Michael Yee: Nothing to Disclose, Benjamin Mullish: Nothing to Disclose, Roberta Forlano: Nothing to Disclose, Shahid Khan: Nothing to Disclose, Pinelopi Manousou: Nothing to Disclose

2350 | BALANCING THE BOOZE: HOW LIGHT TO MODERATE DRINKING AFFECTS LIVER AND CARDIOVASCULAR OUTCOMES IN STEATOTIC LIVER DISEASE ◆

Felice Cinque[1] Andrea Dalbeni[2] Annalisa Cespiati[1] Floriana Santomenna[1] Jaqueline Currà[1] Daniel Smith[1] Erika Fatta[3] Cristina Bertelli[3] Giovanna Oberti[3] Giuseppina Pisano[1] Gabriele Maffi[1] Edoardo Pulixi[3] Alessandro Mantovani[2] Mirko Zoncapé[2] David Sacerdoti[2] Anna Fracanzani[1] Rosa Lombardi[4]

[1]University of Milan, [2]University of Verona, [3]Ospedale Maggiore Policlinico di Milano, [4]University of the Study of Milan

Background: With the new definitions of metabolic dysfunction-associated steatotic liver disease (MASLD) and met-ALD, there is increasing interest in the impact of alcohol consumption on the natural history of steatotic liver disease associated with metabolic dysregulation. Aim: To evaluate the effect of light alcohol consumption versus total abstinence and met-ALD on liver and cardiovascular outcomes in a multicenter Italian cohort of steatotic patients with metabolic alterations. **Methods:** 729 patients (mean age 52 ±12 years, 77% male) with ultrasound (US)-proven steatosis plus at least one cardiometabolic risk factor in the absence of other liver disease were enrolled and classified by drinking habits: abstainers (0 g/day, A-MASLD), light consumers in MASLD (<30/20 g/day male/female, LAC-MASLD), or met-ALD (30-60/20-50 g/day male/female). Steatosis was

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graded by US, significant liver fibrosis defined by liver stiffness measurement (LSM) >8.0 kPa by Fibroscan, and cardiovascular disease assessed by carotid ultrasound (Carotid Intima-Media thickness (cIMT) >0.9 mm, plaques) and echocardiography (systolic and diastolic function, epicardial adipose tissue EAT >7.5/9.5 mm male/female). **Results:** 397 (54%) patients were A-MASLD, 290 (40%) LAC-MASLD and 42 (6%) met-ALD. Comparing LAC-MASLD to A-MASLD, liver disease severity was similar (severe US steatosis 22% vs 16% p=0.06, LSM>8kpa 9% vs 9%, p=0.89), but LAC-MASLD had significantly lower prevalence of cIMT>0.9mm (18% vs 28%, p=0.005), with no difference in other cardiovascular parameters. Light alcohol consumption was an independent protective factor against increased cIMT (adjusted for age, sex, active smoking, diabetes, hypertension, dyslipidemia, overweight; OR 0.58, CI 95% 0.36-0.93). Comparing LAC-MASLD to met-ALD, LAC-MASLD had significantly lower LSM values (5.4 ±2.2 vs 6.4 ±3.2, p=0.02), similar prevalence of LSM>8kPa (9% vs 19%, p=0.10) and severe US steatosis (16% vs 16%, p=1.000) and significantly lower prevalence of carotid plaques (33% vs 55%, p=0.003). Met-ALD resulted an independent risk factor for carotid plaques (adjusted for sex, active smoking, type 2 diabetes, hypertension, dyslipidemia, overweight, statins use; OR 2.01, CI 95% 1.00-4.12). **Conclusion:** Light drinking in middle-aged MASLD patients may protect against early atherosclerosis without worsening liver disease. However, higher alcohol consumption at met-ALD levels hampers cardiovascular protection and is associated with both liver and cardiovascular damage.

Table: Baseline characteristics of the cohort by alcohol consumption

Characteristics	**Abstainers (A-MASLD) n=397**	**Light alcohol consumers (LAC-MASLD) n=290**	**Met-ALD (n=42)**	**P (LAC-MASLD vs A-MASLD)**	**P (LAC-MASLD vs met-ALD)**
Age, ys	52 ±12	51 ±12	58 ±11	0.877	0.001
Sex, male, %	306(77)	171(59)	34(80)	<0.001	0.005
Overweight, n(%)	356(90)	249(86)	39(93)	0.291	0.326
Diabetes, n(%)	75(19)	26(9)	7(17)	<0.001	0.161
Hypertension, n(%)	115(29)	64(22)	17(41)	0.056	0.011
Hypertriglyceridemia, n(%)	167(42)	84(29)	21(51)	0.002	0.007
Hypercholesterolemia, n(%)	318(80)	220(76)	36(87)	0.340	0.253
Hepatic steatosis grade 3, n(%)	87(22)	46(16)	7(17)	0.051	1.000
LSM>8.0 kPa, n(%)	36(9)	26(9)	8(19)	0.893	0.103
LSM, kPa	5.8 ±3.0	5.4 ±2.2	6.4 ±3.2	0.422	0.020
cIMT>0.9mm, n(%)	112(28)	52(18)	11(26)	0.005	0.274
Carotid plaques, n(%)	135(34)	87(30)	23(55)	0.322	0.003
EAT>7.5/9.5mm (M/F), n(%)	124(31)	81(28)	9(21)	0.416	0.553
Systolic dysfunction (%)	24(6)	0(0)	0(0)	0.941	1.000
Diastolic dysfunction, n(%)	108(27)	72(25)	9(21)	0.705	0.800

Disclosures: Felice Cinque: Nothing to Disclose, Andrea Dalbeni: Nothing to Disclose, Annalisa Cespiati: Nothing to Disclose, Floriana Santomenna: Nothing to Disclose, Jaqueline Currà: Nothing to Disclose, Daniel Smith: Nothing to Disclose, Erika Fatta: Nothing to Disclose, Cristina Bertelli: Nothing to Disclose, Giovanna Oberti: Nothing to Disclose, Giuseppina Pisano: Nothing to Disclose, Gabriele Maffi: Nothing to Disclose, Edoardo Pulixi: Nothing to Disclose, Alessandro Mantovani: Nothing to Disclose, Mirko Zoncapé: Nothing to Disclose, David Sacerdoti: Nothing to Disclose, Anna Fracanzani: Nothing to Disclose, Rosa Lombardi: Nothing to Disclose

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2351 | ASSOCIATION OF BMI TRAJECTORY WITH MORTALITY AMONG NON-ALCOHOLIC FATTY LIVER DISEASE INDIVIDUALS: A PROSPECTIVE COHORT STUDY

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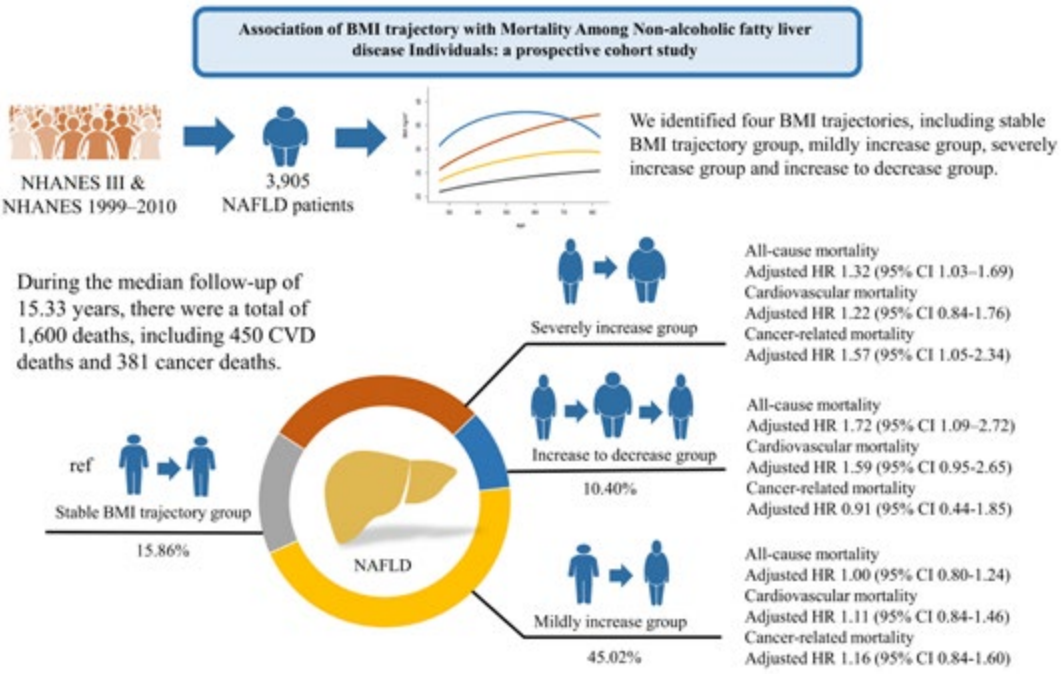
Background: Weight is a dynamically changing physiological indicator, the relationship between historical weight trends and mortality in patients with Non-alcoholic fatty liver disease (NAFLD) remains unclear. This study aimed to investigate the relationship between historical body mass index (BMI) trends and mortality outcomes in patients with NAFLD. **Methods:** In this study, participants with NAFLD aged 40 years or over from the Third National Health and Nutrition Examination Survey (NHANES III) and NHANES 1999–2010 were included. The latent class trajectory model (LCTM) was employed to identify BMI trajectories in NAFLD patients, utilizing data on BMI at baseline, 10 years prior to baseline, and at age 25. Mortality outcomes were determined by correlating participants' data with the National Death Index records through 31 December 2019. The Cox proportional hazards model was utilized to estimate the hazard ratios (HR) and 95% confidence intervals (CIs) for all-cause, cardiovascular disease (CVD), and cancer mortality among NAFLD patients with different BMI trajectories. **Results:** Among 3,905 NAFLD patients, we identified four BMI trajectories, including stable BMI trajectory group (n = 817, 15.86%), mildly increase group (n = 1788, 45.02%), severely increase group (n = 988, 28.72%), and increase to decrease group (n = 312, 10.40%). During a median follow-up of 15.33 years, we identified 1,600 deaths. The risk of all-cause mortality was higher in the severely increase and increase to decrease groups compared to NAFLD individuals in the stable group (HR=1.32, 95% CI 1.03-1.69; HR=1.72, 95% CI 1.09-2.72). This association was found to be more significant in males (p-value for interaction = 0.01). In addition, a U-shaped association between weight change in early adulthood and late adulthood with all-cause mortality among NAFLD patients. **Conclusion:** NAFLD patients have a higher risk of all-cause mortality with both severely increase and increase to decrease in BMI. Excessive weight gain and subsequent weight loss after excessive weight gain should be avoided in NAFLD, and more repeated-measurement BMI data are needed to confirm these findings in the future.



Disclosures: Junping Shi: Nothing to Disclose, Pengwei Zhang: Nothing to Disclose, Xianhui Dong: Nothing to Disclose, Yixuan Zhu: Nothing to Disclose, Run zhou: Nothing to Disclose, Fajuan Rui: Nothing to Disclose, Jie Li: Nothing to Disclose, Li Li: Nothing to Disclose

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2352 | ASSOCIATION BETWEEN USE OF ANTI-HYPERTENSIVE DRUGS AND RISK OF HEPATOCELLULAR CARCINOMA (HCC) IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD) PATIENTS WITH CIRRHOSIS

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Background: Approximately 40-50% of MASLD patients have hypertension. Calcium channel blockers (CCBs) and angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin receptor blockers (ARBs) are widely used anti-hypertensive drugs. However, the impact of using these medications among patients with MASLD has not been well-studied. Previous studies showed conflicting **Results:** regarding the role of CCBs and ACEIs/ARBs in cancer development, specifically an increased risk of breast and lung cancers. We aimed to study the prognostic effect of these medications and their risk of developing HCC in patients with MASLD-induced cirrhosis. **Methods:** We conducted a case-control study at Baylor College of Medicine (BCM). Cases were defined as MASLD-induced HCC diagnosed by histology or radiology using LIRADs system and controls were defined as MASLD patients without HCC. Between September 2020 and April 2024, we recruited 153 newly diagnosed HCC cases with different etiologies and 170 MASLD patients without HCC. Patients in both groups were recruited from BCM's outpatient clinics. In this study, we selected age and sex-matched 47 MASLD-induced HCC patients and 47 MASLD control patients. All cases and controls had radiological or pathological evidence of cirrhosis. Only patients with a history of hypertension were included in our study. Demographic characteristics and other risk factors of metabolic syndrome and HCC including diabetes were collected, and a detailed history of medication use including metformin and statins was retrieved from the physician and pharmacy notes. Descriptive statistics were performed for the comparison between cases and controls. Odds ratio (OR) and 95% confidence interval (CI) values were estimated using multivariable unconditional logistic regression analysis with adjustment for relevant confounders. **Results:** A total of 42 HCC cases and 39 MASLD controls had a history of hypertension and were treated with anti-hypertensive medications. The mean age-years (±SD) for cases and controls are 66.5±6.8 and 63.5±10.1, respectively, *P*=.1. Body mass index (BMI) is not significantly different between cases and controls. The mean BMI (±SD) is 31.1±6.4 and 31.7±6.8 for cases and controls, respectively. Table-1 describes the association between CCB, ACEIs/ARBs, and HCC risk after adjustment of the age, Hispanic ethnicity, sex, BMI, use of, and other risk factors and medications. There is a 2.7-fold increase in HCC risk among CCB users compared to non-users and a 2.5-fold increase in HCC among ACEI/ARB users compared to non-users. **Conclusion:** There is a positive association between the use of antihypertensive medications including ACEIs/ARBs and CCBs, and the risk for HCC development in MASLD patients with cirrhosis. Future studies are needed to confirm this association and highlight the underlying mechanism.

Table 1: The association between anti-hypertensive medications and risk of HCC development in MASLD patients with cirrhosis

Variable	Cases N= 42 (%)	Controls N= 39 (%)	OR (95% CI)	P value
Age	42 (100%)	39 (100%)	1.03 (0.97-1.10)	.32
BMI	42 (100%)	39 (100%)	0.99 (0.92-1.08)	.98
Gender				
Female	17 (40.5%)	23 (59.0%)	1 (reference)	
Male	25 (59.5%)	16 (41.0%)	1.84 (0.71-4.75)	.21
Ethnicity				
Non-Hispanics	26 (62.0%)	22 (56.4%)	1 (reference)	
Hispanics	16 (38.0%)	17 (43.6%)	0.92 (0.34-2.49)	.88
Beta-Blockers				
No	14 (33.3%)	12 (30.8%)	1 (reference)	
Yes	28 (66.7%)	27 (69.2%)	0.87 (.32-2.45)	.79
ACEIs/ARBs				
No	17 (40.5%)	25 (64.0%)	1 (reference)	
Yes	25 (59.5%)	14 (36.0%)	2.54 (.99-6.47)	.05
CCBs				
No	28 (66.7%)	33 (84.6%)	1 (reference)	
Yes	14 (33.3%)	6 (15.4%)	2.76 (0.88-8.72)	.08

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2353 | REAL-WORLD OUTCOMES OF PATIENTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS (MASH) COMPENSATED CIRRHOSIS AT A LARGE ACADEMIC REFERRAL CENTER

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Background: Epidemiologic data on MASH compensated cirrhosis patients and their disease progression are limited. A better understanding of these can inform future study designs and assist with clinical decision making – therefore, we sought to characterize and assess outcomes of patients with MASH compensated cirrhosis in a real-world setting. **Methods:** We retrospectively identified a cohort of patients with MASH compensated cirrhosis at the University of California, San Francisco (UCSF) from 1/1/2012 to 12/31/2022. Adults with MASH compensated cirrhosis without hepatocellular carcinoma (HCC) or prior liver transplantation at baseline were included. MASH diagnoses were ascertained using a validated natural language processing (NLP) algorithm. Clinical and demographic characteristics were extracted from the UCSF electronic health record (EHR). Annual incidences of cirrhosis decompensation events were assessed by ICD codes. **Results:** We identified 510 patients with MASH compensated cirrhosis (Table 1): median age at diagnosis was 58 (IQR 49-66) years and 61.8% were female. At baseline, 55% were obese based on BMI thresholds and the median Charlson Comorbidity Index was 5 (IQR 4-6) with hypertension (63.1%), hyperlipidemia (50.9%), and diabetes (43.7%) being the most common comorbid conditions. Based on their treatment history, 9.2% of patients taking vitamin E and 5.2% were on a GLP-1 receptor agonist. Median MELD-3.0 score was 7 (IQR 6-11) and median HbA1c was 6.1% (IQR 5.4-7.3). Annual incidence of any decompensation event was 5.4% including 3.7% for ascites, 2.7% encephalopathy, 1.1% HCC, and 1.0% varices. Annual incidences of all-cause mortality and liver transplantation were 1.7% and 0.8%, respectively. **Conclusion:** This study characterized a diverse cohort of patients with MASH compensated cirrhosis featuring a high proportion of women and ethnic minorities with high comorbidity burden – reflecting the referral base of UCSF. Of the decompensations evaluated, ascites was the most common complication of cirrhosis. This study provides insights on the clinical burden of compensated MASH cirrhosis in a real-world setting and highlights the need of effective treatments to improve patient outcomes.

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Table 1: Baseline characteristic of patients with compensated MASH cirrhosis

Characteristic	N = 510
Age at diagnosis, median years [IQR]	58 [49, 66]
Year of diagnosis, median [IQR]	2019 [2016, 2021]
Female, n (%)	315 (61.8)
Ethnicity / Race, n (%)	
White	195 (38.2)
Hispanic/Latino	174 (34.1)
Asian	68 (13.3)
African American	8 (1.6)
Unknown	65 (12.7)
Primary insurance, n (%)	
Commercial	208 (41.0)
Medicare	177 (34.9)
Medicaid	119 (23.4)
Self-pay/Other Government	3 (0.6)
BMI by category, n (%)*	
Underweight or Normal	36 (7.1)
Overweight	92 (18.0)
Obese	283 (55.5)
Missing	99 (19.4)
Comorbidities, n (%)	
Hypertension	322 (63.1)
Hyperlipidemia	259 (50.8)
Type 1 or 2 Diabetes Mellitus	223 (43.7)
Prediabetes	112 (22.0)
Obstructive sleep apnea	86 (16.9)
CAD/PVD	56 (11.0)
Chronic kidney disease	29 (5.7)
Polycystic ovarian syndrome	22 (4.3)
Charlson comorbidity index, median [IQR]	5 [4, 6]
Medication use, n (%)	
Anti-hyperglycemic medications	
Oral Diabetic Medication	162 (31.8)
Insulin	83 (16.3)
GLP-1 receptor agonists	27 (5.3)
Anti-hypertensive	203 (39.8)
Lipid lowering therapy	148 (29.9)
Antiplatelet	85 (16.7)
Vitamin E	47 (9.2)
Laboratory values, median [IQR]	
Liver function	
Alkaline phosphatase (U/L)	85 [64, 119]
Alanine aminotransferase (U/L)	48 [31,77]
Aspartate aminotransferase (U/L)	44 [32, 67]
Total bilirubin (mg/dL)	0.7 [0.5, 1.0]
Platelet count (10^9/L)	168 [113, 230]
Albumin g/dL	4.0 [3.7, 4.3]
HbA1c (%)	6.1 [5.4, 7.3]
MELD – 3.0	7.5 [6.2, 11.0]
Renal function	
Serum creatinine (mg/dL)	0.8 [0.7, 0.9]
eGFR (mL/min)	99 [80, 109]
Cardiovascular biomarkers	
Triglycerides (mg/dL)	156 [118, 221]
LDL-C (mg/ dL)	97 [79, 121]

*BMI thresholds were defined as Underweight and Normal (< 24.9) Overweight (25-29.9) Obese (≥ 30) for non-Asian and for Underweight and Normal (< 22.9) Overweight (23-27.4) and Obese (≥ 27.5) for Asian.

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2354 | PNPLA3 RS738409 IS SIGNIFICANTLY AND INDEPENDENTLY ASSOCIATED WITH HISTOLOGICAL PROGRESSION AND REGRESSION IN MASLD: A LARGE PAIRED AND PROSPECTIVE LIVER BIOPSY STUDY

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Background: The association between *PNPLA3* rs738409 and longitudinal changes in liver histology has not been well characterized. We examined relationships between *PNPLA3* rs738409 and longitudinal changes in selected liver histology outcomes. **Methods:** 976 participants prospectively enrolled in the NASH CRN observational studies and RCTs with biopsy-proven MASLD and at least two consecutive liver biopsies were evaluated. After excluding those assigned to experimental agents in RCTs, the analysis included 671 participants (adults, n=444; children, n=227) with a follow-up period limited to 10 years. Liver biopsies were assessed by experienced pathologists in a blinded fashion. Changes in liver histology outcomes were defined as PROGRESSION (from MASLD to MASH or at least a 1-point increase in the fibrosis score) and REGRESSION (from MASH to MASLD without fibrosis worsening or at least a 1-point decrease in the fibrosis score). Interval-censored Cox models were performed to examine associations between *PNPLA3* rs738409 and, histology outcomes, adjusting for race/ethnicity, sex, age, BMI, and T2DM. **Results:** *PNPLA3* CG (40%) was the most prevalent genotype, followed by GG (32%), and CC (27%). The mean size of all liver core biopsies was 1.9 ± 0.9 cm. The mean follow-up time between baseline histology assessment and outcomes development ranged from 3.4 to 3.6 years. Crude annual incident rates (AIR) were 8.7 for MASH progression, and 8.3 and 4.5 for fibrosis progression ≥1 point and ≥2 points per 100 person-years respectively. The AIR of MASH and fibrosis regression ≥1 or ≥2 points were 10.8, 11.8, and 3.1 per 100 person-years respectively. The figure shows adjusted cumulative probabilities of histology outcomes by *PNPLA3*. *PNPLA3* G-allele was associated with fibrosis (adj.HR for ≥1 point: 1.8, 95% CI: 1.2-2.7, and for ≥2 points: 1.6, 95% CI: 1.02-3.04) and MASH (adj.HR: 2.4, 95% CI: 1.5-3.9) progression, and a lower likelihood of MASH resolution (adj.HR: 0.61, 95% CI: 0.39-0.95) after adjusting for relevant confounders. There was no independent association between the *PNPLA3* G-allele and either regression of ≥1 (adj. P value =0.77) or ≥2 (adj. P value =0.71) points in the fibrosis score. **Conclusion:** *PNPLA3* rs738409 is significantly and independently associated with histological progression and regression in MASLD. Therefore, it should be considered in the design and interpretation of MASH clinical trials.

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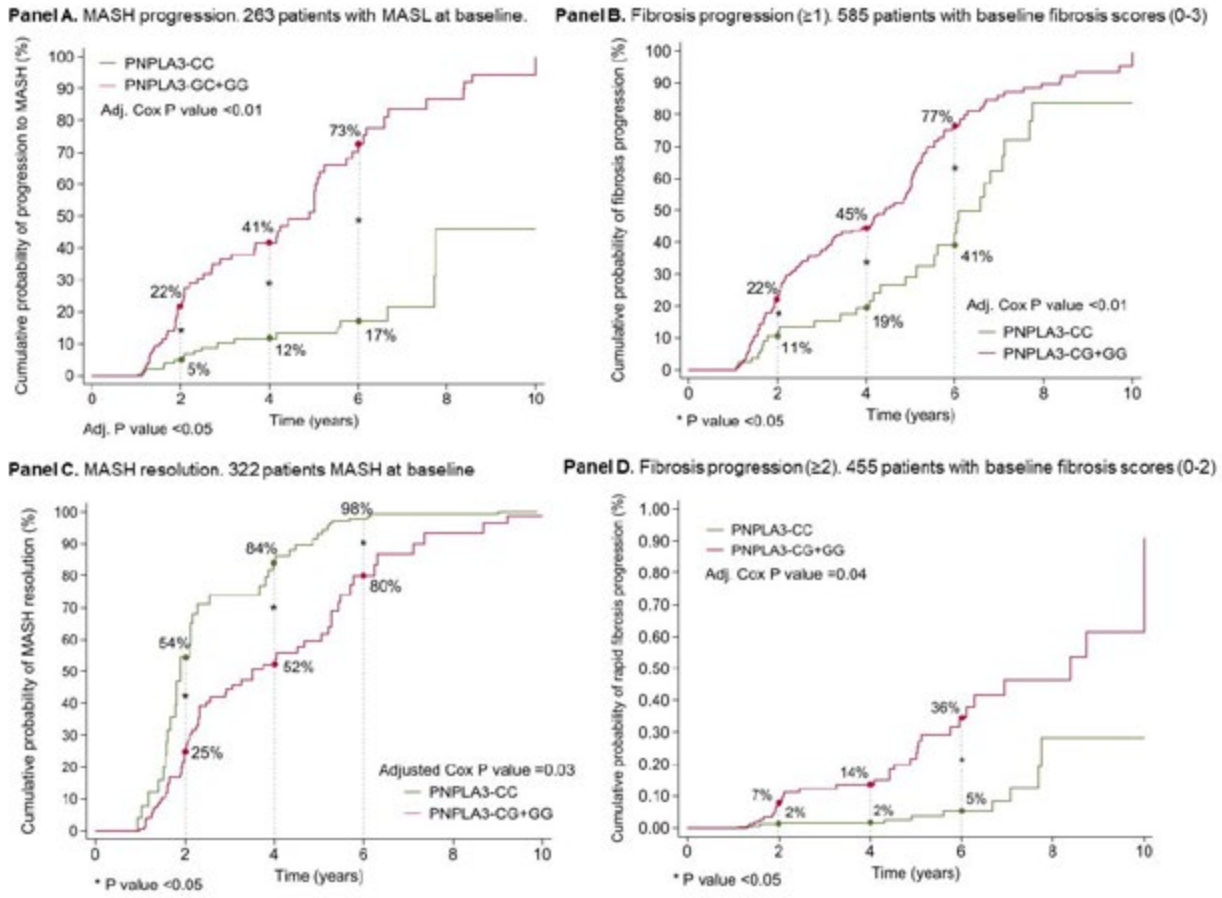

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2355 | EVALUATING ACUTE HEALTHCARE UTILIZATION POST IMPLEMENTATION OF A PRIMARY CARE METABOLIC-ASSOCIATED STEATOTIC LIVER DISEASE RISK STRATIFICATION PATHWAY: A LARGE CANADIAN COHORT STUDY

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Background: The impact of implementing risk stratification pathways for patients with metabolic-associated steatotic liver disease (MASLD) in primary care on acute care utilization, particularity emergency department (ED) visits, is unknown. We aimed to evaluate causes of ED visits in a large cohort of MASLD patients after implementing a MASLD risk stratification pathway, and to describe change of ED visits pre-post implementation of the pathway. **Methods:** Adult patients (≥18 years) enrolled in the Calgary MASLD risk stratification pathway between March 2017 and February 2020 were included (n=5,141). The Calgary MASLD pathway risk stratified MASLD patients using shearwave elastography (SWE). The National Ambulatory Care Reporting System database was linked to the Calgary MASLD pathway database and the cause of ED visit was defined by the primary diagnostic code. Exposure variables included patient age, sex, body mass index (BMI), type 2 diabetes mellitus (DM), Charlson comorbidity score (0-2 vs. ≥3), SWE score (<8kPa vs. ≥8kPa) and residence status (urban vs. rural). We compared ED use for each patient during the two years prior, and after, assessment by SWE. Four years of ED use data was collected per patient. **Results:** For the entire MASLD cohort, the mean age was 52.6±13.3 and 50.3% were female (Table 1). Only 18.6% of our cohort had at least one ED visit during the four years. Elevated SWE (≥8kPa) was not significantly associated with ED visits (p=0.091) (Table 1). Female sex, BMI ≥30kg/m^2, DM diagnosis, Charlson comorbidity index of ≥3, and a rural residence status were significantly associated with ED visits (p<0.001) (Table 1). ED use for liver- and diabetes-related complications were low in our cohort (0.3% and 1.1%, respectively). Abdominal pain and cardiovascular disease (CVD) related causes were more common (10.8% and 8.2%, respectively). There were no significant changes in liver- and abdominal pain-related ED visits post pathway implementation. However, among urban residents, ED visits for CVD- and DM-related causes were higher post implementation (total observations: CVD before = 128, CVD after = 145, p=0.047; DM before = 11, DM after = 25, p=0.032). **Conclusion:** The implementation of a primary care MASLD risk stratification pathway did not increase overall ED visits for patients. Liver-related ED visits were very low and remained unchanged post pathway implementation. CVD- and DM-related ED visits increased only among urban residents post pathway implementation.

Table 1. Baseline cohort characteristics and comparison between those admitted and not admitted to the emergency department.

Characteristic	Entire cohort n=5,141	No ED visits (n=4,185, 81.4%)	All-cause ED visits (n=956, 18.6%)	p-value[1]
Age (years) (mean, SD)	52.61 (13.25)	52.61 (13.12)	52.57 (13.82)	0.925
Age (years)	-	-	-	0.333
<50	2,037 (39.62)	1,645 (39.31)	392 (41.00)	-
≥50	3,104 (60.38)	2,540 (60.69)	564 (59.00)	-
Sex	-	-	-	<0.001
Female	2,583 (50.24)	2,035 (48.63)	548 (57.32)	-
Male	2,535 (49.31)	2,127 (50.82)	408 (42.68)	-
Missing	23 (0.45)	23 (0.55)	-	-
BMI	-	-	-	<0.001
<30	1,744 (33.92)	1,483 (35.44)	261 (27.30)	-
≥30	2,441 (47.48)	1,941 (46.38)	500 (52.30)	-
Missing	956 (18.60)	761 (18.18)	195 (20.40)	-
T2DM status	-	-	-	<0.001
No	3,661 (71.21)	3,025 (72.28)	636 (66.53)	-
Yes	1,480 (28.79)	1,160 (27.72)	320 (33.47)	-
Charlson comorbidities	-	-	-	<0.001
0-2	3,239 (63.00)	2,763 (66.02)	476 (49.79)	-
≥3	1,902 (37.00)	1,422 (33.98)	480 (50.21)	-
SWE	-	-	-	0.091
<8kPa	4,706 (91.54)	3,844 (91.85)	862 (90.17)	-
≥8kPa	435 (8.46)	341 (8.15)	94 (9.83)	-
Residence status	-	-	-	<0.001
Urban	4,785 (93.08)	3,949 (94.36)	836 (87.45)	-
Rural	356 (6.92)	236 (5.64)	120 (12.55)	-

1. Two sample t-test and chi-squared tests to compare characteristics between no ED visits and all-cause ED visits.

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Disclosures: Elizabeth Baguley: Nothing to Disclose, Seungwon Lee: Nothing to Disclose, Meng Wang: Nothing to Disclose, Abdel-Aziz Shaheen: Nothing to Disclose

2356 | CHARACTERISTICS OF ADULT MASH PATIENTS AND FACTORS ASSOCIATED WITH MASH-RELEVANT CLINICAL ENDPOINTS IN A REAL-WORLD US COHORT

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Background: Metabolic dysfunction associated steatohepatitis (MASH) affects 3-5% of adults in the US. The purpose of this analysis is to describe characteristics of patients with MASH by disease severity, and to investigate factors associated with MASH-relevant clinical endpoints in routine clinical practice. **Methods:** Adults (≥ 18) enrolled between 2016-2023 in the TARGET-NASH longitudinal cohort includes patients receiving routine clinical care in the US meeting criteria for non-cirrhotic MASH, MASH with compensated cirrhosis or MASH with decompensated cirrhosis, based on TARGET-NASH definitions, were included in this analysis. Fine-Gray multivariable hazard models (adjusted for competing risks) were used to assess the longitudinal risk of composite clinical endpoints by group: non-cirrhotic MASH (progression to cirrhosis, MELD score >15 from <12, FIB-4 change to ≥2.67 from <2.67, HCC, liver transplant, mortality); compensated MASH cirrhosis (ascites/ascites complications, variceal hemorrhage, hepatic encephalopathy, MELD score >15 from <12, HCC, liver transplant, mortality); decompensated MASH cirrhosis (HCC, liver transplant, mortality). **Results:** 1,949 adults met inclusion criteria for this analysis; 1084 with MASH, 495 with compensated cirrhosis and 370 with decompensated cirrhosis (Table 1). Among patients with non-cirrhotic MASH, multivariable modeling indicated that age (45-65 vs 18-44 and >65 vs 18-44 years; p=0.012) and site type (community-based clinical practice vs. academic sites, p=0.004) were significantly associated with the composite endpoint. Multivariable modeling for compensated MASH cirrhosis patients indicated that FIB-4 category (p=0.001) and site type (p=0.044) were significantly associated with the composite endpoint. Multivariable modeling for MASH with decompensated cirrhosis indicated that FIB-4 category (p=0.043), site type (p=0.031), site region (p=0.009), history of CKD (p=0.025), type 2 diabetes and cardiovascular events (p=0.004) were significantly associated with the composite endpoint. **Conclusion:** This analysis showed a high overall burden of disease among those with non-cirrhotic MASH, compensated MASH cirrhosis and decompensated MASH cirrhosis. Receipt of care at an academic site (vs. community) was significantly associated with higher risk of MASH-relevant clinical endpoints for all three cohorts. For patients with more advanced disease, FIB-4 was significantly associated with MASH-relevant clinical endpoints.

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Table 1. Baseline Demographic and characteristics by disease severity for patients aged 18 or older enrolled in TARGET-NASH

Summary	MASH (N = 1084)	Cirrhosis		Overall Cirrhosis (N= 865)	Total (N = 1949)
		Compensated (N= 495)	Decompensated (N = 370)		
Age at enrollment (years)					
Median (n)	55 (1084)	62 (495)	63 (370)	62 (865)	58 (1949)
Mean (SD)	53 (14)	60 (11)	62 (10)	61 (10)	57 (13)
Q1 - Q3 (IQR)	45 - 64 (19)	53 - 67 (14)	56 - 68 (12)	55 - 68 (13)	49 - 66 (17)
Sex, n (%)					
n	1084	495	370	865	1949
Female	689 (63.6%)	297 (60.0%)	205 (55.4%)	502 (58.0%)	1191 (61.1%)
Race-Ethnicity, n (%)					
n	1084	495	370	865	1949
Hispanic/Latino	154 (14.2%)	60 (12.1%)	39 (10.5%)	99 (11.4%)	253 (13.0%)
Non-Hispanic White	720 (66.4%)	387 (78.2%)	303 (81.9%)	690 (79.8%)	1410 (72.3%)
Non-Hispanic Black	78 (7.2%)	17 (3.4%)	5 (1.4%)	22 (2.5%)	100 (5.1%)
Non-Hispanic Asian	40 (3.7%)	7 (1.4%)	1 (0.3%)	8 (0.9%)	48 (2.5%)
Other/Not Reported	92 (8.5%)	24 (4.8%)	22 (5.9%)	46 (5.3%)	138 (7.1%)
Region, n (%)					
n	1084	495	370	865	1949
Midwest	141 (13.0%)	65 (13.1%)	37 (10.0%)	102 (11.8%)	243 (12.5%)
Northeast	228 (21.0%)	64 (12.9%)	46 (12.4%)	110 (12.7%)	338 (17.3%)
Southeast	495 (45.7%)	245 (49.5%)	205 (55.4%)	450 (52.0%)	945 (48.5%)
Southwest	138 (12.7%)	57 (11.5%)	38 (10.3%)	95 (11.0%)	233 (12.0%)
West	82 (7.6%)	64 (12.9%)	44 (11.9%)	108 (12.5%)	190 (9.7%)
Site type, n (%)					
n	1084	495	370	865	1949
Academic	688 (63.5%)	387 (78.2%)	304 (82.2%)	691 (79.9%)	1379 (70.8%)
Community	396 (36.5%)	108 (21.8%)	66 (17.8%)	174 (20.1%)	570 (29.2%)
Insurance Type, n (%)					
n	1084	495	370	865	1949
Private	717 (66.1%)	250 (50.5%)	145 (39.2%)	395 (45.7%)	1112 (57.1%)
Medicaid	94 (8.7%)	45 (9.1%)	40 (10.8%)	85 (9.8%)	179 (9.2%)
Medicare	222 (20.5%)	187 (37.8%)	172 (46.5%)	359 (41.5%)	581 (29.8%)
Uninsured	14 (1.3%)	3 (0.6%)	7 (1.9%)	10 (1.2%)	24 (1.2%)
Other/Unknown	37 (3.4%)	10 (2.0%)	6 (1.6%)	16 (1.8%)	53 (2.7%)
BMI (kg/m^2)					
Median (n)	33 (1074)	34 (491)	34 (365)	34 (856)	33 (1930)
Mean (SD)	34 (7)	35 (7)	35 (8)	35 (8)	34 (7)
Q1 - Q3 (IQR)	29 - 38 (9)	29 - 39 (10)	30 - 40 (10)	30 - 40 (10)	29 - 39 (10)
Follow-up time (months)					
Median (n)	55 (1084)	53 (495)	45 (370)	48 (865)	51 (1949)
Mean (SD)	51 (21)	51 (21)	44 (22)	48 (22)	50 (21)
Q1 - Q3 (IQR)	34 - 68 (34)	35 - 69 (34)	27 - 65 (38)	31 - 67 (36)	33 - 67 (34)
FIB-4 category*, n (%)					
n	898	441	364	805	1703
Low risk	588 (65.5%)	82 (18.6%)	14 (3.8%)	96 (11.9%)	684 (40.2%)
Indeterminate risk	254 (28.3%)	132 (29.9%)	60 (16.5%)	192 (23.9%)	446 (26.2%)
High Risk	56 (6.2%)	227 (51.5%)	290 (79.7%)	517 (64.2%)	573 (33.6%)

*FIB-4 categories are as follows: low risk (FIB-4 <1.3), indeterminate risk (FIB-4 ≥1.3 and <2.67), and high risk (FIB-4 ≥2.67).
Note: All measures were taken at or close to enrollment (index).

Disclosures: Philip Newsome: Novo Nordisk: Consultant, B Ingelheim: Consultant, Madrigal: Consultant, 89 Bio: Consultant, Sagimet: Consultant, Echosens: Speaking and Teaching, Eli Lilly: Speaking and Teaching, Zydus Therapeutics: Consultant, Abbott: Speaking and Teaching, Alfred Barritt IV: Merck (Any division): Advisor, Madrigal: Consultant, Life Edit: Consultant, Boehringer Ingelheim: Consultant, Target-RWE: Consultant, Heather Morris: Nothing to Disclose, Feng Yu: Nothing to Disclose, Andrea Mospan: Nothing to Disclose, Taruja Karmarkar: Nothing to Disclose, Matthew Melaragno: Merck & Co., Inc.: Stock ownership, Merck & Co., Inc.: Employee, Merck & Co., Inc.: Stock - publicly traded company, Xiao Zhang: Merck: Employee, Mickie Cheng: Nothing to Disclose, Gail Fernandes: Merck & Co., Inc: Hold Stocks, Merck & Co., Inc: Employee, Merck & Co., Inc: Stock - publicly traded company, Arun Sanyal: Genfit, Akarna, Tiziana, Durect, Inversago, Hemoshear, North: Stock - publicly traded company, Astra Zeneca (60K), Boston Pharmaceutical

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2357 | TIME TO DISEASE PROGRESSION AND ALL-CAUSE MORTALITY IN ADULT MASH PATIENTS IN A REAL- WORLD US COHORT

Alfred Barritt IV[1] Philip Newsome[2] Heather Morris[3] Feng Yu[3] Andrea Mospan[3] Taruja Karmarkar[4] Matthew Melaragno[4] Xiao Zhang[4] Mickie Cheng[4] Gail Fernandes[4] Arun Sanyal[5]

[1]University of Chapel Hill, [2]University of Birmingham, [3]Target RWE, [4]Merck & Co., Inc., [5]Virginia Commonwealth University

Background: Metabolic dysfunction associated steatohepatitis (MASH) is a progressive disease that affects 3-5% of adults in the US. Rate of disease progression outside of clinical trials and in real world clinical practice is unclear. This analysis assessed time to disease progression for patients with MASH without cirrhosis, compensated MASH cirrhosis, and decompensated MASH cirrhosis in a real-world setting. **Methods:** Adults (≥18 years) enrolled between 2016-2023 in the TARGET-NASH longitudinal cohort includes patientsreceiving routine clinical care in the US meeting criteria for non-cirrhotic MASH, MASH with compensated cirrhosis or MASH with decompensated cirrhosis, based on TARGET-NASH definitions, were included. Time to event analysis from enrollment was used to assess time from MASH without cirrhosis to compensated cirrhosis, time to the first decompensation event (ascites/complications from ascites, hepatic encephalopathy, variceal bleeding) in patients with MASH compensated cirrhosis, and time to all-cause mortality in each of the 3 sub-cohorts. **Results:** 1,949 participants met inclusion criteria for this analysis and were categorized at enrollment into 3 sub cohorts by disease severity: non-cirrhotic MASH (n=1084), compensated MASH cirrhosis (n=495), decompensated MASH cirrhosis (n=370). Incidence rates of MASH progression to compensated cirrhosis and compensated to decompensated cirrhosis were 1.39 and 3.53 per 100 person year, respectively. Among patients with non-cirrhotic MASH, 6% progressed to compensated cirrhosis within 72 months (Figure 1a). Among patients with compensated MASH cirrhosis, 14% had a decompensation event within 72 months (Figure 1b). Incidence rates for mortality were 0.14, 2.04, and 8.45 per 100 person year for MASH, compensated cirrhosis, and decompensated cirrhosis, respectively. MASH patients with compensated cirrhosis and with decompensated cirrhosis had an approximately 10% and 30% risk of death within 72 months. Patients with decompensated MASH cirrhosis were at an increased risk of all-cause mortality (HR: 52.24, 95% CI 24.28,112.40) followed by compensated MASH cirrhosis (HR: 13.62, 95% CI 6.13,30.29) compared to MASH without cirrhosis (Figure 1c). **Conclusion:** In a cohort of patients followed in routine clinical practice, those with MASH compensated cirrhosis had a 10% probability of mortality within 72 months. This represents an unmet need for MASH therapy.

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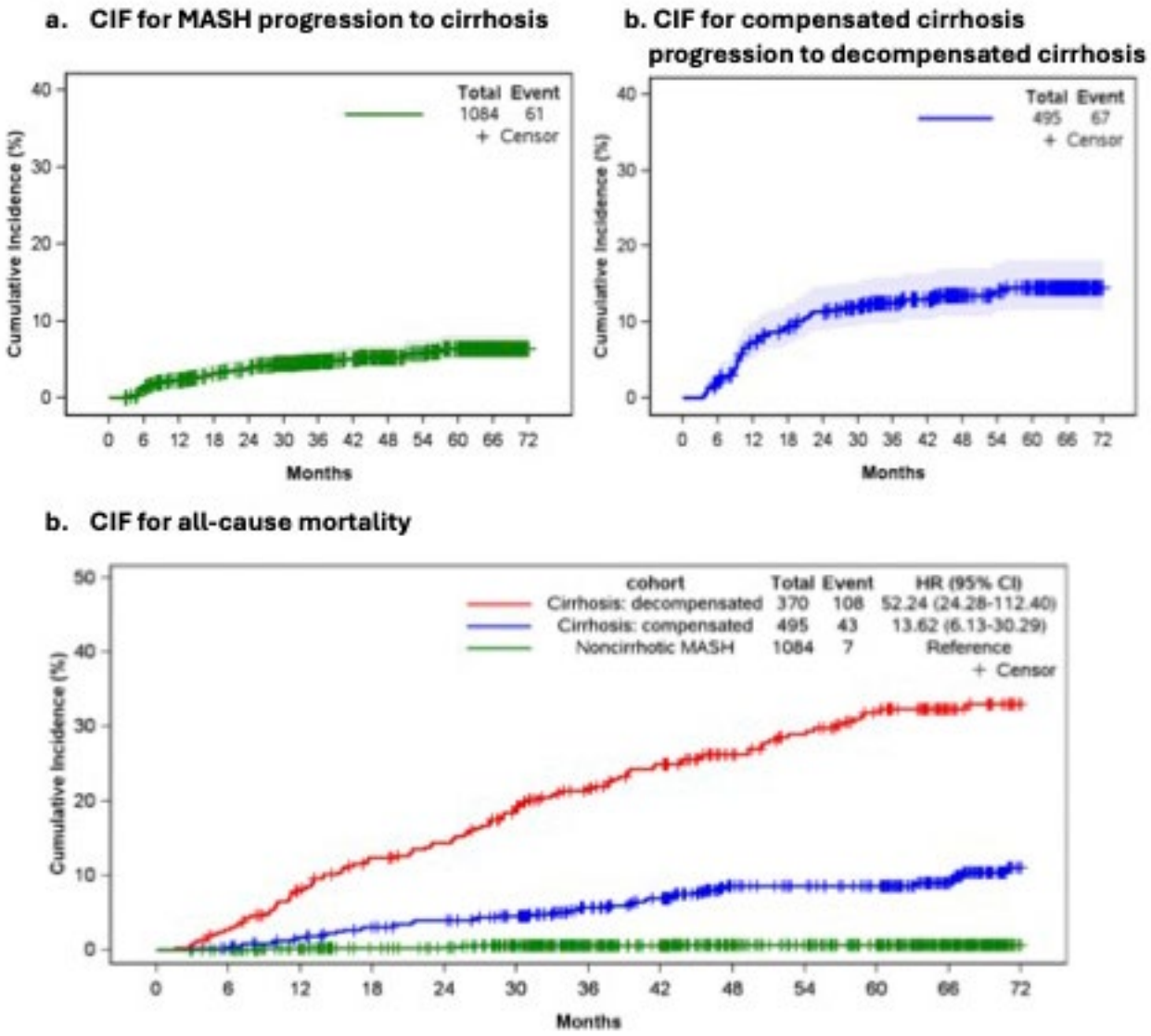
FIGURE 1: Cumulative Incidence of Disease Progression and All-Cause Mortality Among Patients in the Real-World TARGET-NASH Cohort*



CIF = Cumulative incidence function.

*Patients were censored at the time of follow-up if they did not have the event of interest.

Disclosures: Alfred Barritt IV: Merck (Any division): Advisor, Madrigal: Consultant, Life Edit: Consultant, Boehringer Ingelheim: Consultant, Target-RWE: Consultant, Philip Newsome: Novo Nordisk: Consultant, B Ingelheim: Consultant, Madrigal: Consultant, 89 Bio: Consultant, Sagimet: Consultant, Echosens: Speaking and Teaching, Eli Lilly: Speaking and Teaching, Zydus Therapeutics: Consultant, Abbott: Speaking and Teaching, Heather Morris: Nothing to Disclose, Feng Yu: Nothing to Disclose, Andrea Mospan: Nothing to Disclose, Taruja Karmarkar: Nothing to Disclose, Matthew Melaragno: Merck & Co., Inc.: Stock ownership, Merck & Co., Inc.: Employee, Merck & Co., Inc.: Stock - publicly traded company, Xiao Zhang: Merck: Employee, Mickie Cheng: Nothing to Disclose, Gail Fernandes: Merck & Co., Inc: Hold Stocks, Merck & Co., Inc: Employee, Merck & Co., Inc: Stock - publicly traded company, Arun Sanyal: Genfit, Akarna, Tiziana, Durect, Inversago, Hemoshear, North: Stock - publicly traded company, Astra Zeneca (60K), Boston Pharmaceutical

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2358 | QUANTITATION OF PLASMA CELLS, CYTOTOXIC T CELLS, AND KUPFFER CELLS/MACROPHAGES WITH HEPATIC FIBROSIS STAGE IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS (MASH)

Michael Estep[1] Annie Masters[1] Lakshmi Alaparthi[1] Gary Bratthauer[1] Aybike Birerdinc[2] Fanny Monge[1] Cassandra Sharp[1] Daisong Tan[1] Hala Abdelaal[1] Zachary Goodman[1] Zobair Younossi[3]

[1]Beatty Liver/ Obesity Research Program, [2]George Mason University, [3]The Global NASH Council

Background: Inflammation and the progression of hepatic fibrosis in the context of metabolic dysfunction-associated liver disease (MASLD) has not been formally characterized. This pilot study's aim is to quantify Plasma Cells, Cytotoxic T cells, and Kupffer cell/Macrophage populations in the liver biopsies of MASH patients over a range of fibrosis stages. **Methods:** Included subjects (N=110) were positive for steatosis, ballooning degeneration, and some degree of hepatic fibrosis in the absence of other hepatic disease. Hepatic fibrosis was staged as follows: Stage 1: mild pericellular and/or portal fibrosis (N=13), Stage 2: Moderate pericellular and/or portal fibrosis without bridging (N=18), Stage 3: Mild bridging fibrosis (N=20), Stage 4: Moderate/marked bridging fibrosis (N=20), Stage 5: incomplete cirrhosis (N=20), Stage 6: cirrhosis (N=19). Liver needle biopsies from participating subjects were immunohistochemically stained in multiplex (Discovery Ultra, Roche) for CD8 (Yellow; cytotoxic T-cells), CD68 (Green; Kupffer cells/macrophages), and CD38 (Purple; plasma cells) and counterstained with hematoxylin. Stained slides were digitized (Aperio AT2, Leica Microsystems) and analyzed for positive cell count (Multiplex IHC module, HALO). Frequency of cell types (positive cells per cells counted) by fibrosis stage was assessed by descriptive statistics and Mann-Whitney analysis. **Results:** The total number of both CD38+ and CD8+ cells generally increased with fibrosis stage (rho=0.437, P<0.0001 and rho=0.419, P<0.0001, respectively), due primarily to the differences between stages 1, 2, and 3 vs. stages 4, 5, and 6 (P<0.00001 for both); additionally differences between adjacent stages were only significant between stages 3 and 4 (CD38+ P=0.0083, CD8+ P=0.0003). **Conclusion:** This pilot study demonstrates a method for quantifying immune cells that may, in future studies, be used to assess zone specific immune cell infiltration with regard to MASH fibrogenesis. These data imply a sharp distinction in CD8+ and CD38+ immune cell involvement between early and later stages of hepatic fibrosis in MASH.

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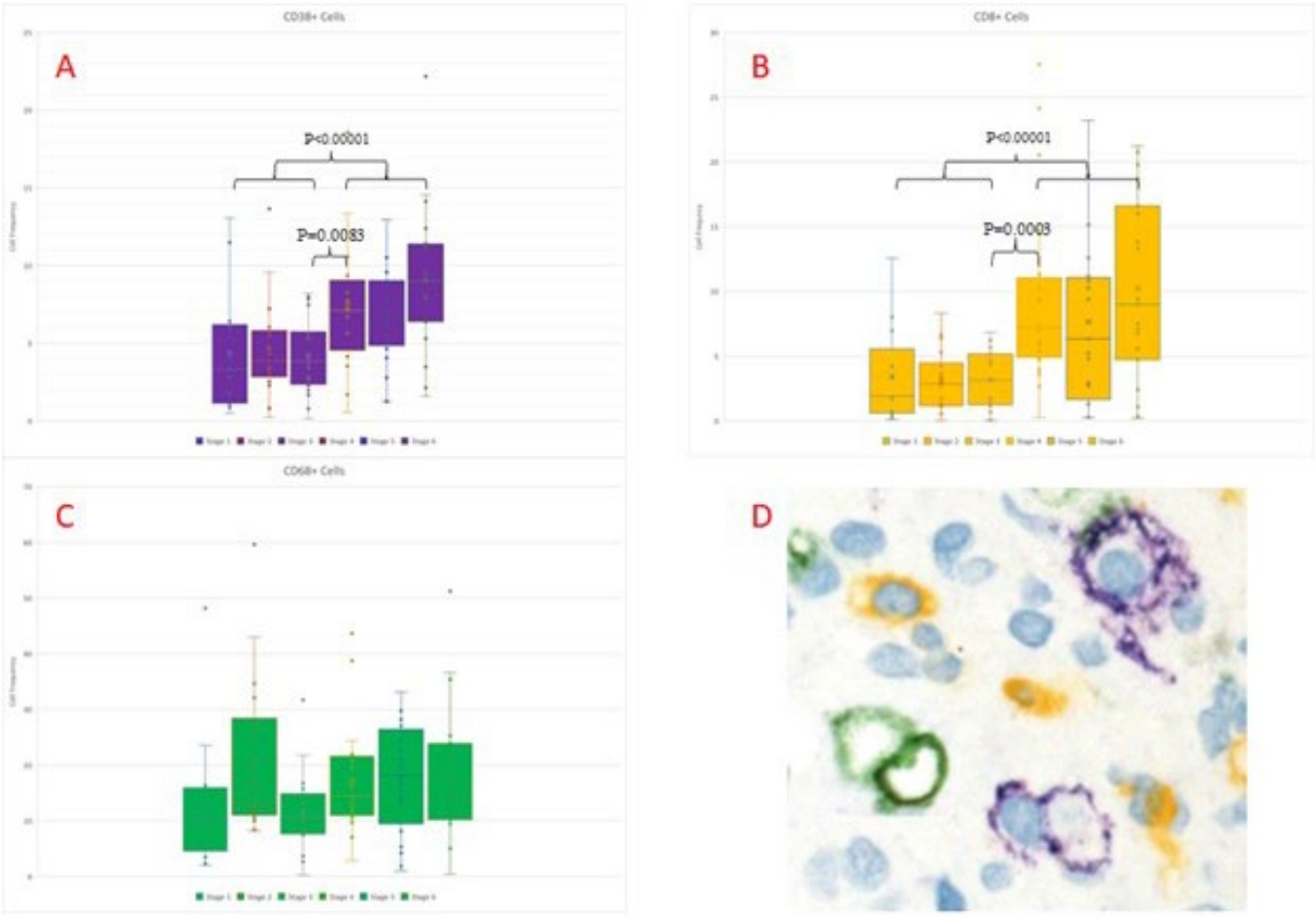

Figure: Hepatic Expression of CD8, CD38, and CD68: "A"-"C"; Box and whisker plots showing assessed expression of surface markers by fibrosis stage. "D"; Representative photograph of showing staining of CD8 (yellow), CD38 (purple), and CD68 (green).

Disclosures: Michael Estep: Nothing to Disclose, Annie Masters: Nothing to Disclose, Lakshmi Alaparthi: Nothing to Disclose, Gary Bratthauer: Nothing to Disclose, Aybike Birerdinc: Nothing to Disclose, Fanny Monge: Nothing to Disclose, Cassandra Sharp: Nothing to Disclose, Daisong Tan: Nothing to Disclose, Hala Abdelaal: Nothing to Disclose, Zachary Goodman: Nothing to Disclose, Zobair Younossi: Nothing to Disclose

2359 | ASSOCIATION OF STEATOTIC LIVER DISEASE (SLD) WITH ADVERSE PREGNANCY OUTCOMES: RESULTS FROM THE PROSPECTIVE FATTY LIVER IN PREGNANCY (FLIP) COHORT.

Tatyana Kushner[1] Jeanette Rios[1] Rachel Meislin[1] Sonam Rosberger[1] Lauren Alpert[1] Rhoda Sperling[1] Scott Friedman[2] Michal Elovitz[1] Norah Terrault[3] Keith Sigel[1]

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Background: Retrospective data has suggested an independent association of steatotic liver disease (SLD) with adverse pregnancy outcomes (APOs), including gestational hypertension (GHTN), preeclampsia (PE), and cholestasis of pregnancy (ICP), but has been limited by small sample size, misclassification/ under-detection of SLD, and lack of validated assessment of SLD in pregnancy. Given the rising burden of SLD in women of childbearing age, it is vital to determine the independent influence of SLD on maternal and fetal outcomes.

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Methods: The Fatty Liver in Pregnancy (FLIP) study prospectively evaluates pregnant individuals for SLD. Maternal liver ultrasound images were obtained during routine fetal anatomy ultrasound at 18 to 22 weeks gestation, were deidentified and scored (presence and grade of hepatic steatosis) by a radiologist blinded to clinical data. A sub-set obtained vibration controlled transient elastography/ continued attenuation parameter (VTCE/CAP) at 24-32 weeks gestation. Multivariate logistic regression was performed to determine independent association of SLD stratified by BMI and grade 2/3 (advanced) versus non-advanced SLD with pregnancy outcomes. **Results:** From 12/2019 to 3/2024, 1215 individuals were enrolled; mean age 29 (SD 6), 646 (55%) Hispanic ethnicity, 460 (38%) Black race, and median pre-pregnancy BMI 29 (IQR 25, 33). A total of 197 (18%) had SLD; 147 (75%) had grade 1, 32 (22%) had grade 2, and 6 (3%) had grade 3 steatosis; 172 (16%) met criteria for MASLD. Those with SLD were more likely to have pre-pregnancy BMI≥25 (87% vs 74%, p<0.001), pre-existing hypertension (13% vs 8%, p=0.03) and more likely to be on aspirin (ASA) for prevention of PE (39% vs 29%, p=0.012). Of 233 who underwent VTCE/CAP; nine (4%) had CAP≥300; 18 (8%) had kPa≥ 7. Among those with delivery data (n=930), 109 (12%) individuals had GDM, 116 (12%) had GHTN, 124 (13%) had PE, 30 (3%) had ICP, and 162 (13%) had preterm delivery. Table 1 shows adjusted analysis of association of SLD/MASLD with APOs, stratified by BMI and SLD grade. SLD was independently associated with GHTN (OR 1.69) and neonatal jaundice (OR 1.80), and advanced SLD was associated with GDM (OR 2.66) (p<0.001). There was an increased odds of developing ICP and large for gestational age (LGA) infants in individuals with CAP≥300 (OR 12.2 and OR 16.7, p<0.001) on VCTE. **Conclusion:** Individuals with advanced SLD in pregnancy are at increased risk of GDM and neonatal jaundice. Individuals with “lean” SLD are at higher risk of GHTN. Frequently prescribed ASA, particularly in the SLD group may have influenced any association with PE. Elevated VCTE/CAP scores may be predictive of LGA and ICP, and if validated, can potentially be integrated into clinical practice to predict these outcomes. Detection and risk stratification of SLD during pregnancy can identify individuals at highest risk for APOs who should be targeted with interventions to optimize pregnancy course.

Table 1: Adjusted logistic regression of association of SLD with adverse pregnancy outcomes.

	GHTN* (n=116)	GDM** (n=109)	PE* (n=124)	Preterm (n=162)	SGA*** (n=84)	LGA^ (n=30)	Neonatal**** Jaundice (n=238)	Neonatal Hypoglycemia^ (n=175)
SLD overall (n=197)	**1.69 (1.01-2.81)**	1.33 (0.76-2.32)	0.69 (0.39, 1.23)	0.78 (0.48-1.29)	0.67 (0.31-1.45)	0.86 (0.28-2.65)	**1.85 (1.18-2.87)**	1.23 (0.73-2.07)
BMI<25	**3.98 (1.08-14.6)**	NA	0.58 (0.07-4.82)	0.29 (0.04-2.31)	2.91 (0.81-10.58)	NA	1.47 (0.47-4.61)	0.59 (0.13-2.80)
BMI ≥25	1.47 (0.84, 2.56)	1.28 (0.72-2.27)	0.65 (0.36, 1.19)	0.91 (0.54-1.54)	0.41 (0.14-1.15)	0.99 (0.32-3.09)	**1.83 (1.12, 2.99)**	1.21 (0.74, 2.00)
Advanced SLD	1.91 (0.74, 4.90)	**2.65 (1.11-6.37)**	0.86 (0.21, 2.38)	1.13 (0.47-2.73)	0.43 (0.05-3.34)	2.04 (0.42-9.84)	**3.40 (1.28-9.03)**	1.64 (0.57-4.75)
MASLD	1.48 (0.85-2.60)	1.29 (0.73, 2.29	0.71 (0.40-1.28)	0.84 (0.51-1.41)	0.39 (0.13-1.10)	0.99 (033-3.09)	1.70 (1.06-2.73)	1.32 (0.76 - 2.30)

*adjusted for Aspirin use, advanced maternal age
**adjusted for advanced maternal age, gestational weight gain
***adjusted for chronic hypertension, smoking
****adjusted for preterm delivery, DM
^adjusted for maternal DM and GDM

Disclosures: Tatyana Kushner: Advisor relationship with Gilead; Has ended; Advisor relationship with GSK; Has ended; Advisor relationship with Eiger; Has ended; Grant/Research Support relationship with Gilead; Has not ended, Jeanette Rios: Nothing to Disclose, Rachel Meislin: Nothing to Disclose, Sonam Rosberger: Nothing to Disclose, Lauren Alpert: Nothing to Disclose, Rhoda Sperling: Nothing to Disclose, Scott Friedman: 89 Bio: Consultant, Boehringer Ingelheim: Consultant, Boston Pharmaceutical: Consultant, Bristol Myers Squibb: Consultant, Merck: Consultant, Glycotest: Consultant, Morphic Therapeutics: Consultant, HepGene: Consultant, North Sea Therapeutics: Consultant, Pfizer Pharmaceuticals: Consultant, Sagimet: Consultant, Scholar Rock: Consultant, Prosciento: Consultant, Seal Rock: Consultant, Surrozen: Consultant, Takeda Pharmaceuticals: Consultant, Junevity: Consultant, Therasid Bio: Consultant, Merck: Consultant, Ochre Bio: Consultant, Gordian

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Biotechnology: Consultant, Abalone Bio: Grant/Research Support, Prosciento: Consultant, Michal Elovitz: Nothing to Disclose, Norah Terrault: Grant/Research Support relationship with Eiger Pharmaceuticals; Has ended; Grant/Research Support relationship with GSK; Has not ended; Royalties or patent beneficiary relationship with Elseiver; Has not ended; Grant/Research Support relationship with Helio Health; Has ended; Grant/Research Support relationship with Durect Corp; Has ended; Executive role relationship with AASLD; Has not ended; Board member relationship with HBV Foundation; Has not ended; Grant/Research Support relationship with ImmunoCore; Has ended, Keith Sigel: Nothing to Disclose

2360 | ARTIFICIAL INTELLIGENCE FOR EARLY MASLD IDENTIFICATION IN THE ELECTRONIC MEDICAL RECORD

Ariana Stuart[1] Katya Swarts[1] Marion Granich[1] Jessica Yeung[1] Arthi Thirumalai[1] Manish Dhyani[1] James Perkins[1] Rotonya Carr[1]

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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) affects approximately 30% of the US adult population and its prevalence is increasing. Early-stage disease is often missed by clinicians, as it is largely asymptomatic until cirrhosis develops. Here, we describe the development of an electronic medical record (EMR) artificial intelligence (AI) algorithm for MASLD identification that has high diagnostic accuracy, improves our ability to identify individuals with MASLD prior to clinician recognition, and enables the design of interventions to increase MASLD awareness and influence management decisions during early-stage disease. **Methods:** Patients meeting the American Association for the Study of Liver Diseases' MASLD criteria were identified via an iterative natural language processing (NLP) pattern-recognition AI algorithm. Validation was carried out via manual review of monthly generated cohorts, performed independently by two physicians. The algorithm was then utilized to retrieve a MASLD cohort for initial analysis. Demographics were summarized and additional variables pertaining to early MASLD management were analyzed. Early diagnosis efficiency was estimated as the proportion of individuals identified by AI compared to those who carried an associated ICD-9/10 diagnosis. Data were adjusted to account for over-identification errors. **Results:** Our AI algorithm achieved ~88% accuracy compared with manual MASLD diagnosis. From a cohort spanning six months, 957 individuals were identified by the algorithm as meeting criteria for MASLD. Demographics were 56% female, 2% American Indian/Native Alaskan, 6% Black/African-American, 16% Asian, 68% White, and 12.2% Hispanic/Latino(a)/Latinx. 25.6% of patients had GI or hepatology referral. Only 140 had a MASLD-associated diagnostic code. Accounting for an over-inclusion error rate of 12.8%, 697 individuals were identified as meeting criteria for MASLD diagnosis who did not already carry a MASLD diagnosis. **Conclusion:** We developed a MASLD AI algorithm with 88% accuracy that can perform large-scale EMR review. Our initial analysis suggests that a substantial proportion of individuals meeting MASLD criteria do not yet carry this diagnosis. Our algorithm has potential to aid in the early identification of MASLD, allowing for targeted interventions to prevent disease progression and improve outcomes. Future studies will use integrated machine learning algorithms such as deep learning/large language models.

Disclosures: Ariana Stuart: Nothing to Disclose, Katya Swarts: Nothing to Disclose, Marion Granich: Nothing to Disclose, Jessica Yeung: Nothing to Disclose, Arthi Thirumalai: Fractyl Health: Grant/Research Support, Novo Nordisk Inc: Grant/Research Support, Manish Dhyani: Nothing to Disclose, James Perkins: Nothing to Disclose, Rotonya Carr: Grant/Research Support relationship with Merck; Has ended; Consultant relationship with Intercept; Has not ended; Consultant relationship with Astra Zeneca; Has ended

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2361 | CLINICAL CHARACTERISTICS AND FIB-4 RISK STRATIFICATION OF PRIMARY CARE PATIENTS WITH OBESITY, DIABETES, OR BOTH: REAL-WORLD IMPLICATIONS FOR ADOPTING A FIB-4 REFERRAL ALGORITHM TO DETECT METABOLIC DYSFUNCTION-ASSOCIATION STEATOTIC LIVER DISEASE (MASLD) WITH ADVANCED FIBROSIS

Janet Chu[1] Mandana Khalili[1] Max Goldman[2] Bilal Hameed[1] Nghiem Ha[1] Rena Fox[1]

[1]University of California, San Francisco, [2]Kaiser Permanente San Francisco Medical Center

Background: Despite recommendations for FIB-4 testing for primary care (PC) patients with MASLD risk factors, few studies have evaluated the potential impact of a FIB-4 algorithm in the PC setting among patients with different MASLD risk factors. We aimed to compare the clinical characteristics and distribution of FIB-4 scores among real-world PC patients with obesity, diabetes mellitus (DM), or both. **Methods:** From a large, diverse PC practice, we used the electronic medical record to create 3 cohorts of patients with 1) obesity without DM, 2) DM without obesity, or 3) both obesity and DM. We defined obesity as BMI>=30 for non-Asians and >=27 for Asians. We defined DM as A1c>=6.5% and/or a prescription for an anti-DM medication. We excluded patients with alcohol use disorder or chronic hepatitis B/C. From 2018-2023, we calculated an annual FIB-4 for each patient with available lab data; we used the most recent score to categorize each patient into low-, indeterminate-, or high-risk groups for advanced fibrosis, using established age-based cutoffs. We compared the groups using Chi-squared tests for categorical variables and one-way ANOVA for continuous variables. **Results:** Among 22,806 PC patients, 7,014 (31%) were included in the analysis: obesity (n=3,644), DM (n=1,896), or obesity + DM (n=1,474); 72% had data to compute at least one FIB-4. Compared to the obesity and obesity + DM group, the DM only group had more patients >65 years old (69% vs. 28% and 46%, respectively; p<0.001); more Asian American patients (40% vs. 27% and 29%, respectively; p<0.001); more patients at high-risk for advanced fibrosis (10% vs. 3% and 5%, respectively; p<0.001) and had higher rates of comorbidities (Table 1). Overall, 1% had ICD codes for cirrhosis, including 2% of the DM group (p<0.001). There was an average of 2.5 PC visits per year; 12% of patients also had at least one visit to Weight Management clinic. **Conclusion:** Among PC patients with obesity, DM, or both, more patients in the DM only cohort had diagnosed cirrhosis and a high-risk FIB-4 score. All 3 cohorts had frequent PC visits, available data to compute FIB-4, and prior abdominal ultrasound, suggesting that a FIB-4 based algorithm could be readily implemented in PC. The FIB-4 based algorithm may be most beneficial in detecting advanced fibrosis among patients with DM, with or without obesity, while patients with obesity alone may be at lower risk of advanced fibrosis and can be managed in the PC setting.

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Table 1. Characteristics of primary care patients with obesity, diabetes, or both at a large, diverse academic medical center (n=7,014)

	Total	Obese only	DM only	DM+Obese	p-value
	N=7,014	N=3,644	N=1,896	N=1,474	
Age (mean [SD])	60 (17)	54 (16)	71 (14)	62 (14)	<0.001
Age Categories					<0.001
18-64	4,012 (57.2%)	2,632 (72.2%)	581 (30.6%)	799 (54.2%)	
>=65	3,002 (42.8%)	1,012 (27.8%)	1,315 (69.4%)	675 (45.8%)	
Sex					<0.001
Female	3,827 (54.6%)	2,049 (56.2%)	953 (50.3%)	825 (56.0%)	
Male	3,185 (45.4%)	1,595 (43.8%)	943 (49.7%)	647 (44.0%)	
Race/Ethnicity					<0.001
White	2,282 (32.7%)	1,315 (36.3%)	548 (29.0%)	419 (28.6%)	
Black or African American	989 (14.2%)	505 (13.9%)	198 (10.5%)	286 (19.5%)	
Latinx	960 (13.8%)	543 (15.0%)	198 (10.5%)	219 (14.9%)	
Asian American	2,150 (30.8%)	976 (27.0%)	750 (39.7%)	424 (28.9%)	
Other (AIAN, NHPI, Other)	522 (7.5%)	244 (6.7%)	172 (9.1%)	106 (7.2%)	
Unknown/missing	71 (1.0%)	38 (1.0%)	21 (1.1%)	12 (0.8%)	
Preferred language					<0.001
English	6,130 (87.7%)	3,387 (93.2%)	1,441 (76.7%)	1,302 (88.3%)	
Spanish	163 (2.3%)	53 (1.5%)	68 (3.6%)	42 (2.8%)	
Chinese	341 (4.9%)	91 (2.5%)	199 (10.6%)	51 (3.5%)	
Other	354 (5.1%)	105 (2.9%)	170 (9.1%)	79 (5.4%)	
Insurance Type					<0.001
Medi-Cal	1,014 (14.5%)	631 (17.3%)	156 (8.2%)	227 (15.4%)	
Medicare or Medicare Advantage	2,841 (40.5%)	955 (26.2%)	1,213 (64.0%)	673 (45.7%)	
Private	3,150 (44.9%)	2,055 (56.4%)	524 (27.7%)	571 (38.8%)	
MASLD	954 (13.6%)	361 (9.9%)	254 (13.4%)	339 (23.0%)	<0.001
Cirrhosis	67 (1.0%)	10 (0.3%)	41 (2.2%)	16 (1.1%)	<0.001
Hypertension	4,209 (60.0%)	1,598 (43.9%)	1,452 (76.6%)	1,159 (78.6%)	<0.001
Hyperlipidemia	4,365 (62.2%)	1,760 (48.3%)	1,528 (80.6%)	1,077 (73.1%)	<0.001
Sleep Apnea	1,867 (26.6%)	901 (24.7%)	349 (18.4%)	617 (41.9%)	<0.001
PCOS	143 (2.0%)	93 (2.6%)	11 (0.6%)	39 (2.6%)	<0.001
Hypothyroidism	1,005 (14.3%)	410 (11.3%)	348 (18.4%)	247 (16.8%)	<0.001
HCC	9 (0.1%)	2 (0.1%)	5 (0.3%)	2 (0.1%)	0.12
Abdominal ultrasound (ever)	2,146 (30.6%)	915 (25.1%)	669 (35.3%)	562 (38.1%)	<0.001
Liver biopsy	25 (0.4%)	6 (0.2%)	15 (0.8%)	4 (0.3%)	<0.001
Hepatology visit (ever)	420 (6.0%)	139 (3.8%)	139 (7.3%)	142 (9.6%)	<0.001
Weight Management visit (ever)	823 (11.7%)	422 (11.6%)	76 (4.0%)	325 (22.0%)	<0.001
PC visit (mean [SD])	2.5 (2)	2 (1.8)	2.9 (2)	3.2 (2.3)	<0.001
EMR messages (mean [SD])	4.2 (7.5)	3.5 (6)	4.7 (8)	5.2 (9.8)	<0.001
FIB-4 Score (mean [SD])	1.3 (.85)	1.1 (.73)	1.6 (.95)	1.3 (.79)	<0.001
FIB-4 categories*					<0.001
FIB-4: Low	3,855 (76.4%)	1,969 (82.9%)	987 (65.4%)	899 (77.3%)	
FIB-4: Indeterminate	910 (18.0%)	342 (14.4%)	359 (23.8%)	209 (18.0%)	
FIB-4: High	282 (5.6%)	64 (2.7%)	163 (10.8%)	55 (4.7%)	

Abbreviations: DM=diabetes mellitus; SD=standard deviation; AIAN=American Indian Alaska Native; NHPI=Native Hawaiian Pacific Islander; MASLD=metabolic- dysfunction-associated steatotic liver disease; PCOS= polycystic ovary syndrome; HCC=hepatocellular carcinoma; PC=primary care; EMR=electronic medical record

*FIB-4 age-based cutoffs: 1) For age <65: a) Low risk is FIB-4 score <1.3; b) Indeterminate risk is FIB-4 score between 1.3-2.67; c) High risk is FIB-4 score>2.67; 2) For age>=65: a) Low risk is FIB-4 score <2; b) Indeterminate risk if FIB-4 score between 2-2.67; c) High risk is FIB-4 score>2.67

Disclosures: Janet Chu: Gilead Sciences, Inc.: Grant/Research Support, Mandana Khalili: gilead sciences: Grant/Research Support, GSK pharmaceuticals: Consultant, Intercept pharmaceuticals: Grant/Research Support, Gilead Sciences Inc: Consultant, Max Goldman: Eli Lilly: Stock - publicly traded company, Novo Nordisk: Stock - publicly traded company, Eli Lilly: Stock - publicly traded company, Madrigal: Stock - publicly traded company, Bilal Hameed: Consultant relationship with Gilead; Has not ended; Grant/Research Support relationship with Novo Nordisk; Has not ended; Stock â€“ privately held company relationship with Pleiogenix; Has not ended; Consultant relationship with Surrozen; Has not ended; Consultant relationship with Pioneering Medicine VII Inc; Has not ended; Grant/Research Support relationship with Gilead; Has not ended; Grant/Research Support relationship with Intercept; Has not ended; Grant/Research Support relationship with Pliant; Has not ended; Advisor relationship with Madrigal; Has not ended; Speaking and Teaching relationship with Scholars In Medicine; Has not ended; Advisor relationship with CLDF; Has not ended; Advisor relationship with Pleiogenix; Has not ended; Grant/Research Support relationship with Madrigal; Has not ended; Grant/Research Support relationship with Salix; Has not ended; Advisor relationship with Mallinckrodt; Has not ended, Nghiem Ha: Nothing to Disclose, Rena Fox: Nothing to Disclose

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2362 | THREE GRADIENT BOOSTING MACHINE-LEARNING MODELS IN INDETERMINATE FIB-4 SCORE ARE SUPERIOR TO NONINVASIVE TESTS IN PREDICTING CIRRHOSIS: A NATIONAL AND VA ANALYSIS

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[1]University of Pittsburgh, [2]Yale University, [3]VA Long Beach Healthcare System, [4]VA San Diego, [5]Virginia Commonwealth University, [6]University of Utah, [7]University of Michigan Medical Center

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most prevalent chronic liver disease in the United States and leading cause of liver-related morbidity and mortality. Despite advancements, risk stratification of MASLD progression to advanced fibrosis and cirrhosis through noninvasive testing (NITs) can yield indeterminate results. The AASLD, AGA, and AACE recommend first-pass screening with FIB-4. However, many patients have indeterminate results. Algorithms which discriminate risk for this large population are urgently needed to improve detection and reduce costs. **Aim:** To develop and cross-validate three machine-learning models to predict prevalence of advanced fibrosis and cirrhosis in patients with an indeterminate FIB-4 score (IFS). **Methods:** We implemented three gradient boosting machine-learning models including standard GBM, XGBoosting, and LightGBM using the National Health and Nutrition Examination Survey (NHANES) 2017-2018 cohort for advanced fibrosis based on vibration-controlled transient elastography (VCTE) (kPa > 12.5). Features included were variables utilized for MASLD diagnosis including demographics, metabolic comorbidities, laboratory data, and treatment, restricted to IFS (FIB-4: 1.3 – 2.67). We used 70% of the cohort to train and 30% to test the machine learning models. DeLong's test was used to compare the difference in performance among the three models. AUC and accuracy were compared to FIB-4, FIB-4+, and APRI. Cross-validation with the highest performing model was employed using the VA Corporate Data Warehouse (CDW) dataset from 2019-2022 for diagnosis and problem list codes for cirrhosis using multivariable logistic regression modelling. **Results:** 6,879 participants from NHANES 2017-2018 with complete VCTE and FIB-4 data were extracted for machine learning modelling. From the 1,304 participants with IFS, a statistically significant increase in prevalence of metabolic comorbidities and their respective treatments were evident compared to FIB-4 < 1.3. All three models found that BMI was the highest risk feature in this group, followed by waist circumference and ALT in both LightGBM and XGBoost. Following these variables, AST, fasting blood glucose, history of diabetes, and A1c were less informative. The highest performing model was the standard GBM model with AUC of 0.76, which was statistically significantly superior to FIB-4, FIB-4+ and APRI, and not significantly different in performance compared with other boosting models. Among 1,416,646 Veterans with complete data and IFS, this model was significantly associated with diagnosis of cirrhosis (AOR 1.6; 95% CI 1.5 – 1.7; p<0.001). **Conclusion:** Gradient boosting machine-learning models performed better overall than FIB-4, FIB-4+, and APRI in identifying cirrhosis in IFS. ML could be an effective adjunct to these scores in risk-stratifying patients with IFS.

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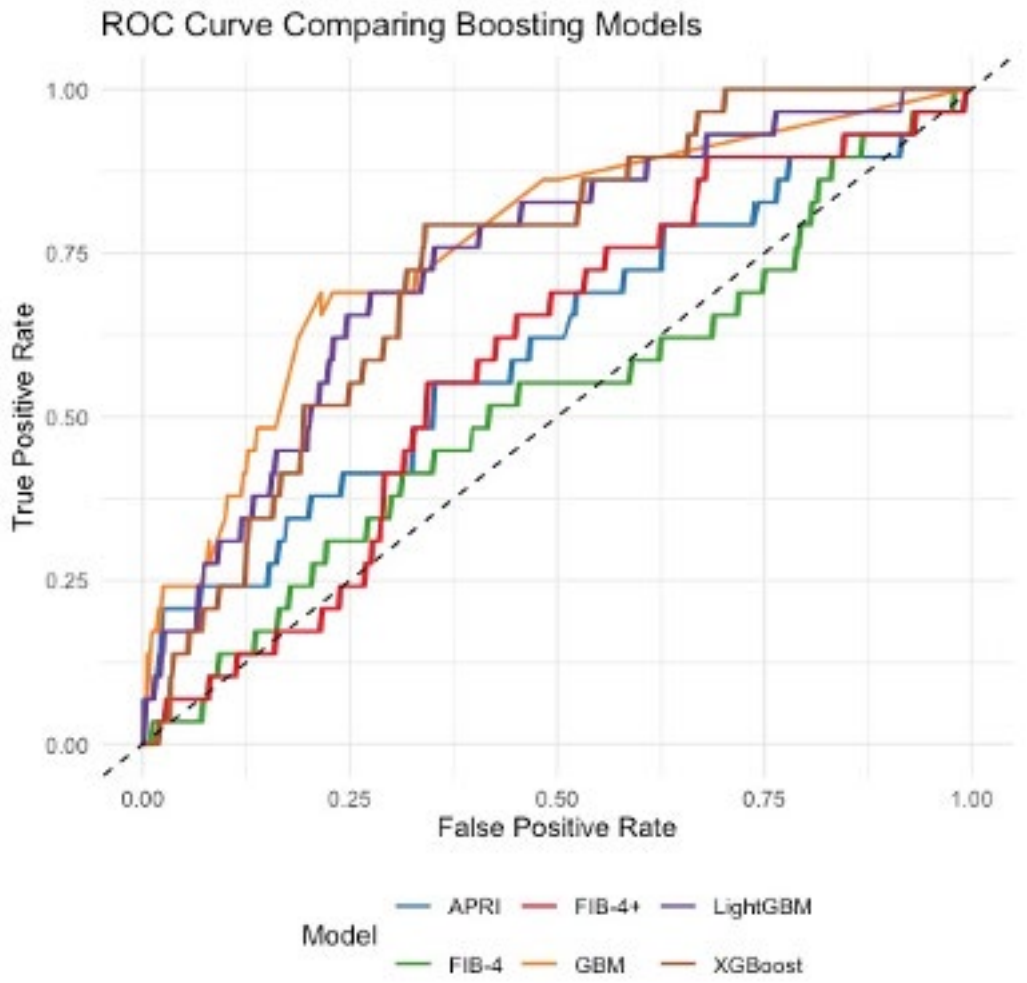

Disclosures: Sebastian Niezen: Nothing to Disclose, Daniela Goyes: Nothing to Disclose, Timothy Morgan: Nothing to Disclose, Heather Patton: Nothing to Disclose, Jasmohan Bajaj: Bausch: Grant/Research Support, Sequana: Grant/Research Support, Cosmo: Grant/Research Support, Grifols: Grant/Research Support, Yiwen Yao: Nothing to Disclose, Elliot Tapper: Nothing to Disclose, Shari Rogal: Nothing to Disclose

2363 | SMOKING AND PROGRESSION TO CIRRHOSIS

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Background: About 40% of patients with liver disease have a smoking history. In this study, we aim to determine the association of tobacco use with progression to advanced fibrosis in primary care patients. **Methods:** We performed a retrospective cohort study of primary care patients with chronic liver disease and inputs for at least two separate Fibrosis-4 Index (FIB-4) calculations. Patients with index FIB-4 values ≥ 3.25 or with diagnoses of cirrhosis, hepatocellular carcinoma, or liver transplant prior to their first FIB-4 score were excluded. Our primary outcome of interest was the time to a FIB-4 ≥ 3.25 (high-risk for advanced fibrosis). The primary exposure was tobacco use, categorized as ever or never smoked. Other cardiometabolic risk exposures (diagnoses of metabolic dysfunction, statin prescriptions) and demographic variables (age, sex, race) were collected. We performed univariate and bivariate analyses to describe the cohort overall and by tobacco use status. We developed unadjusted and adjusted Cox regression models to evaluate the association of tobacco use with time to high-risk for advanced fibrosis. We tested for interactions between tobacco use and other cardiometabolic risk exposures. SAS 9.4 (Cary, NC) was used for all statistical analyses. This study was approved by the IRB at MUSC. **Results:** The study cohort included 2,587 primary care patients with chronic liver disease and a mean age of 48 years.

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55% were female, 46% were identified as Black, and 59% (1,539) were former or current tobacco users. After a mean follow-up of 5.4 (± 2.6) years, 24% (657) of the cohort progressed to a FIB-4 ≥ 3.25. Of patients that smoked, 27% progressed to a high-risk FIB-4 compared to 20% of those that did not smoke ($p < 0.001$). In the unadjusted Cox regression model, tobacco use was associated with an increased risk of progressing to a FIB-4 ≥ 3.25 (HR 1.39; 95% CI 1.18-1.64, Table 1). After adjusting for other cardiometabolic risk exposures, statin prescriptions, and demographics, smoking was still associated with an increased hazard of progressing to a FIB-4 at high-risk for advanced fibrosis (HR 1.24; 95% CI 1.05-1.48). **Conclusion:** A history of smoking is associated with progression to a high-risk FIB-4 even when adjusted for metabolic and demographic factors.

Table 1. Estimated hazard ratios and 95% confidence intervals for the unadjusted and adjusted Cox regression models for the association of smoking with the outcome of time to a Fibrosis-4 Index score at high-risk for advanced fibrosis (FIB-4 ≥ 3.25).

	Model 1	Model 2	Model 3
	Unadjusted	Adjusted for cardiometabolic risk exposures	Adjusted for demographics
Variables	HR 95% CI	HR 95% CI	HR 95% CI
Smoking	1.39 1.18 – 1.64	1.19 1.00 – 1.40	1.24 1.05 – 1.48
BMI		0.95 0.94 – 0.97	0.96 0.95 – 0.98
Hypertension		1.75 1.38 – 2.21	2.02 1.59 – 2.56
Diabetes		1.20 1.01 – 1.42	1.34 1.13 – 1.60
CVD		1.64 1.39 – 1.94	1.85 1.57 – 2.19
Hypothyroidism		1.03 0.83 – 1.29	1.10 0.88 – 1.38
CKD		2.01 1.69 – 2.39	2.04 1.70 – 2.44
Statin prescription			0.40 0.33 – 0.49
Male			1.21 1.02 – 1.43
Black			1.11 0.92 – 1.33
Unmarried			1.01 0.84 – 1.21

BMI=body mass index. CKD=chronic kidney disease. CVD=cardiovascular disease. Model 1 is the unadjusted Cox regression model. Model 2 is Model 1 with adjustment for cardiometabolic risk factors. Model 3 is Model 2 with adjustment for demographic variables. Age was not included in the model given that FIB-4 is the outcome (threat of endogeneity). Interactions between Smoking and the other cardiometabolic risk factors were not significant.

Disclosures: Samantha Wray: Nothing to Disclose, Andrew Schreiner: Nothing to Disclose, David Koch: Nothing to Disclose

2364 | THE EFFECTS OF VISCERAL ADIPOSE TISSUE ON SURVIVAL IN MASLD

James Lee[1] Mohamed Elsaid[2] Yesung Kweon[3] Bhargav Vemulapalli[1] Rahul Kukreja[1] Nishali Shah[1] Vinod Rustgi[1]

[1]Rutgers Robert Wood Johnson Medical School, [2]The Ohio State University Wexner Medical Center, [3]Center for Biostatistics, The Ohio State University College of Medicine

Background: Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) prevalence is estimated at 38% globally and 27.8% in the US, with a predicted 23% increase in the US by 2050. MASLD is associated with comorbidities such as metabolic syndrome, obesity-related malignancies, cardiovascular disease, and diabetes. Body mass index (BMI), derived by height and weight, fails to accurately represent body fat content or account for muscle mass, bone density, or race/sex. Visceral Adipose Tissue (VAT) excess is a clinical predictor of metabolic

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syndrome, body composition, and mortality. Using nationally representative data, we examined the association between excess VAT and all-cause mortality risk in MASLD patients. **Methods:** The study included 14,167 adult participants aged 20 to 74 of the Third National Health and Nutrition Examination Survey (NHANES) and National Death Index. MASLD was defined as hepatic steatosis on ultrasound in the absence of hepatitis B, hepatitis C, iron overload, alcohol restriction, or excessive alcohol use. VAT was calculated by validated sex-specific equations that included age, BMI, and thigh/waist circumference, and was grouped into quintiles. Adjusted Cox proportional models tested association between increased VAT and all-cause mortality in MASLD. Complex survey methods with sampling weights, clusters, and strata yielded nationally representative estimates. **Results:** Prevalence of MASLD was 26.7% (95% CI: 24.3%-29.1%). MASLD patients had a mean age of 45.3 years, 57.7% were females, and 9.6% identified as non-Hispanic Black. MASLD patients had higher BMI (no MASLD vs. MASLD) [mean BMI (25.7 Kg/M^2 vs. 28.8 Kg/M^2)], [mean waist circumference (89.8 inches vs. 97.4 inches)], and [mean VAT (147.2 vs. 185.8)], p<0.001. Median follow-up was 19.2 years. Mortality incidence rate in MASLD was 1.3% (95% CI: 1.3 to 1.5) per 100-person years. In MASLD patients, an increase in VAT quintile was associated with higher cumulative mortality incidence (lowest vs. highest quintiles; 3.2% vs. 44.3%). Increased VAT was significantly associated with higher all-cause mortality risk. In MASLD patients, age-adjusted mortality risk was significantly higher per quintile increase in VAT hazard ratio (HR) 1.22 (95% CI: 1.08 to 1.38). Adjusted for sex, race-ethnicity, education, tobacco use, health eating index, and history of cancer/myocardial infarction/diabetes, VAT quintile increase remained a significant predictor of higher mortality risk in those with vs. without MASLD; HR 1.20 (95%; CI: 1.05 to 1.38). **Conclusion:** The obesity burden is higher in MASLD patients compared to those without MASLD. We propose using VAT over traditional obesity measures to predict all-cause mortality, as VAT is associated with a 20% increase in the adjusted risk of all-cause mortality for MASLD patients. Efforts are currently needed to promote weight management for MASLD patients.

Disclosures: James Lee: Nothing to Disclose, Mohamed Elsaid: Nothing to Disclose, Yesung Kweon: Nothing to Disclose, Bhargav Vemulapalli: Nothing to Disclose, Rahul Kukreja: Nothing to Disclose, Nishali Shah: Nothing to Disclose, Vinod Rustgi: Gilead: Speaking and Teaching, Abbvie: Speaking and Teaching, Madrigal: Speaking and Teaching

2365 | DISPARITIES IN THE ASSOCIATION BETWEEN METABOLIC ASSOCIATED STEATOTIC LIVER DISEASE AND VISCERAL ADIPOSE DYSFUNCTION ACROSS SEXES, RACES, AND DIABETES STATUS: A CROSS-SECTIONAL STUDY OF US ADULTS.

Bhargav Vemulapalli[1] Rahul Kukreja[1] Mohamed Elsaid[2] Yesung Kweon[3] James Lee[1] Nishali Shah[1] Vinod Rustgi[4]

[1]Rutgers Robert Wood Johnson Medical School, [2]The Ohio State University Wexner Medical Center, [3]Center for Biostatistics, The Ohio State University, [4]Rutgers Robert Wood Johnson School of Medicine

Background: Visceral Adiposity Index (VAI) is a validated sex-specific measure of visceral fat function and cardiometabolic risk that predicts progressive liver histology in Metabolic Associated Steatotic Liver Disease (MASLD). However, the link between visceral adipose dysfunction (VAD) and MASLD, and the effects of sex, race, and diabetes, remains unknown. We aim to (1) create a metric for VAD using VAI, (2) describe the relationship between VAD and MASLD prevalence, and (3) examine how sex, race, diabetes status, and their interactions affect this relationship. **Methods:** 11,760 US adults aged 20 to 74 from the Third National Health and Nutrition Examination Survey were included. MASLD was identified through sonographic evidence of hepatic steatosis (mild, moderate, or severe). Those with iron overload, alcohol intake restrictions, excessive alcohol consumption, hepatitis B, or hepatitis C were excluded. Sex-specific values for BMI, waist circumference, triglycerides, and high-density lipoprotein were used to calculate VAI. VAD status (no=no/mild vs. yes=moderate/severe) was then derived from age-specific VAI estimates. Adjusted multivariable logistic models assessed the association between VAD status and MASLD occurrence while incorporating race-by-VAD, race-by-sex-by-VAD, and race-by-VAD-by-diabetes status to test for effect modification. Complex survey methods with sampling weights, clusters, and strata were applied to yield nationally representative estimates. **Results:** Of 11,760 participants, 3,389 had MASLD. Moderate/severe VAD was present in 46.53% of participants with MASLD but 23.84% without MASLD (p<0.0001). Moderate/severe VAD was associated with MASLD (AOR=1.80; 95%CI=1.56-2.07) compared to no/mild VAD with racial and racial-sexual disparities present (Table). VAD predicted MASLD among White Non-Hispanics (WHNs; AOR=1.77; 95%CI=1.43-2.19) and Mexican-Americans (MAs; AOR=1.77; 95%CI=1.43-2.19), but not among Black Non-Hispanics (BNHs; AOR=1.28; 95%CI=0.99-1.86).

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Among non-diabetes, the effect of VAD was significant in MAs and WNHs, but not BNHs. However, among diabetics, the effect of VAD was only significant in BNHs (AOR=2.90; 95%CI=1.50-5.59). In participants with moderate/severe VAD, BNHs had a 0.57 (95%CI= 0.45-0.72) lower AOR of MASLD compared to WNHs. Among MAs with moderate/severe VAD, female sex was linked to a 1.51 (95% CI=1.09-2.09) higher AOR of MASLD compared to males. We observed a significant three-way interaction between race, VAD status, and diabetes ($p<0.0001$). **Conclusion:** Disparities based on race, sex, and diabetes status modified the relationship between VAD and MASLD. VAD status raised the odds of MASLD for WNHs and MAs, the latter of which may be explained by a MASLD-associated PNPLA3 polymorphism. MA females with moderate/severe VAD had higher odds of MASLD than males.

Disclosures: Bhargav Vemulapalli: Nothing to Disclose, Rahul Kukreja: Nothing to Disclose, Mohamed Elsaid: Nothing to Disclose, Yesung Kweon: Nothing to Disclose, James Lee: Nothing to Disclose, Nishali Shah: Nothing to Disclose, Vinod Rustgi: Gilead: Speaking and Teaching, Abbvie: Speaking and Teaching, Madrigal: Speaking and Teaching

2366 | PREVALENCE OF METABOLIC DYSFUNCTION-ASSOCIATED FATTY LIVER DISEASE (MAFLD) IN PATIENTS WITH DIABETES MELLITUS: A CLINICAL INVESTIGATION OF PATIENTS IN PUERTO RICO WEST AREA

Milaris Sanchez-Cordero[1] *Milton Carrero Quiñones*[1] *Karla Velez*[1]

[1]*Mayaguez Medical Center*

Background: MAFLD is the most common cause of abnormal liver test results. Most patients have insulin resistance, obesity, hypertriglyceridemia, and type 2 diabetes mellitus. Approximately 20% of patients with MAFLD have nonalcoholic steatohepatitis (MASH), characterized by hepatic steatosis, inflammation, and often fibrosis. A presumptive diagnosis of MAFLD can be made in a patient with mildly elevated aminotransferase levels, risk factors (diabetes, obesity, and hyperlipidemia), and hyperechoic pattern on ultrasonography or low-density parenchyma on CT. **Methods:** This prospective study enrolled adults aged ≥21 years old with Diabetes Mellitus type II who were hospitalized in Puerto Rico (West area) from 2023 to 2024. One hundred twenty-four patients were evaluated with a distribution greater in males than females. The trend found that older adults with an average of 65 years (SD 17.3) have hepatic steatosis with toxic habits of alcohol (39.5%) and smoking (16.9%) without patients with hepatitis B or hepatitis C. The average number of patients did not present with transaminitis (41.228), and the average did not present with thrombocytopenia (227.475). Average FIB-4 score of 2.321.89 (stage 2-3 fibrosis). 72% of the sample has a BMI 25 Kg/m2. **Results:** The prevalence of MALFD in overweight patients is 45.7% and 56.3% in non-overweight patients. The FIB-4 score did not have statistically significant **Results:** compared to overweight and non-overweight patients. In conclusion, the prevalence of MAFLD among the general population aged ≥21 years old was 45.7% in patients with BMI ≥ 25 Kg/m^2 and 56.3% in patients with BMI < 25 Kg/m^2 in Puerto Rico West area. Male gender, old age, and hypertriglyceridemia were risk factors for MAFLD, as hypercholesterolemia and elevated LDL were not. Although lean/regular weight MAFLD constituted a small proportion of MAFLD, they had a higher degree of hepatic steatosis. Liver function enzymology indexes, commonly related to the occurrence and development of metabolic syndrome and fatty liver, were not predictable in our studied population compared to the non-MAFLD subjects. **Conclusion:** People, even with normal BMI, should be aware of the risks of MAFLD. In summary, NAFLD's global burden is substantial and projected to increase. Maintaining and increasing data collection is essential to improve the understanding of the burden of disease associated with MAFLD and MASH worldwide. Improving our understanding of the burden of MAFLD can facilitate the development of healthcare policies and strategies to slow this epidemic. The prevalence of MASH amongst the US population is approximately 5% to 6% and is expected to increase to 30%-40% by 2030.

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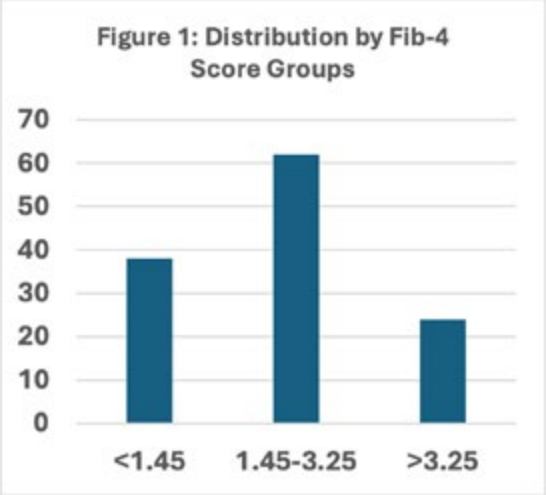

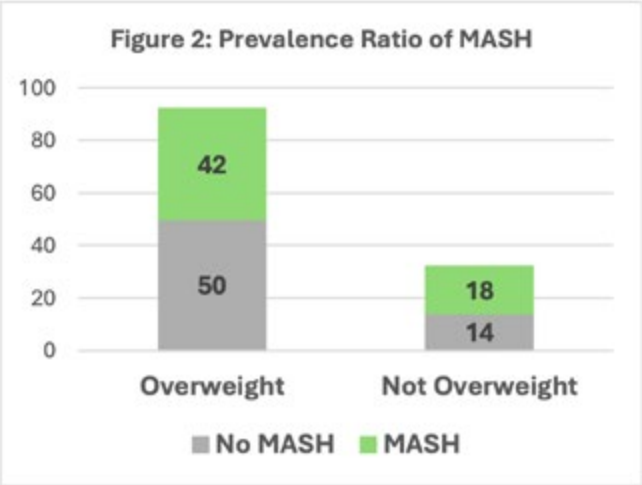

Disclosures: Milaris Sanchez-Cordero: Nothing to Disclose, Milton Carrero Quiñones: Nothing to Disclose, Karla Velez: Nothing to Disclose

2367 | SEX DIFFERENCES IN CLINICAL OUTCOMES OF PATIENTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE –RESULTS OF A NATIONWIDE REAL-WORLD U.S. COHORT

Taotao Yan[1] *Tyler Wong*[1] *Xinrong Zhang*[1] *Ramsey Cheung*[1]

[1]*Stanford University Medical Center*

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) has become the leading cause of chronic liver disease worldwide. Many chronic liver diseases such as viral hepatitis and autoimmune hepatitis exhibit significant sex-based differences, but data on sex differences in MASLD is limited. We aimed to investigate the relationship between sex and clinical outcomes of MASLD using a large U.S. nationwide database. **Methods:** We conducted a retrospective study of adult patients with MASLD using the Truven Health MarketScan Research Database between 2007 and 2023. The primary study outcomes included the incidence (per 1000 person-years [PU]) of liver-related events (cirrhosis, hepatic decompensation and hepatocellular carcinoma [HCC]) and non-liver events (cardiovascular disease [CVD], chronic kidney disease [CKD] and non-liver cancer). Kaplan-Meier curves were used to estimate the incidence per 1000 person-years (PY) of the events of interest. **Results:** We identified a total of 761,403 patients with MASLD: 355,220 males and 406,183 females. Compared to females, males were younger (52.6 vs. 53.4), less likely obese (16.4% vs. 22.7%) or diabetic (32.9% vs. 34.3%) with lower usage of metformin (10.1% vs. 11.7%) but more likely to have hypertension (63.4% vs. 61.6%) and hyperlipidemia (49.1% vs. 44.5%) and higher usage of statins (27.2% vs. 23.9%) use. Propensity-score matching (on age, geographic region, insurance type, provider specialty type, Charlson Comorbidity Index, metformin and statin use, baseline comorbidities including obesity, diabetes, hypertension, hyperlipidemia, CVD, CKD and non-liver cancer) yielded 344,436 pairs of male and female patients with similar characteristics for outcome analysis. Males with MASLD (vs. females) had lower incidence (per 1000 PY) of cirrhosis (11.4 vs. 12.5), but higher incidence rate of hepatic decompensation (10.3 vs. 9.3), HCC (1.9 vs. 0.7), CVD (17.6 vs. 12.6) and CKD (16.3 vs. 14.1), all $P<0.001$ (Table). On the multivariable Cox regression analysis, male sex was associated with increased risk hepatic decompensation (aHR 1.20, 95%CI 1.16-1.23), HCC (aHR 2.83, 95%CI 2.61-3.07), CVD (aHR 1.52, 95%CI 1.49-1.56), CKD (aHR 1.23, 95%CI 1.20-1.26), and non-liver cancer (aHR 1.07, 95%CI 1.04-1.10) (all $PP=0.63$). **Conclusion:** Male patients with MASLD have higher risk of hepatic decompensation, HCC, CVD, CKD and non-liver cancer but not cirrhosis as compared to their female counterparts. Sex disparities should be considered in the management of patients with MASLD.

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Table. Incidence rates (per 1000 person years) of liver-related and non-liver-related events by sex.

	No. of patients	Person-years	No. of events	Incidence of events per 1000 person-years (95%CI)	*P* value
Cirrhosis					
Female	265492	987177	12315	12.47 (12.26-12.70)	< 0.0001
Male	256720	944779	10764	11.39 (11.18-11.61)	
Decompensation					
Female	290663	1085347	10047	9.26 (9.07-9.44)	< 0.0001
Male	286799	1050649	10825	10.30 (10.11-10.50)	
HCC					
Female	303667	1138012	810	0.71 (0.66-0.76)	< 0.0001
Male	299809	1098329	2051	1.87 (1.79-1.95)	
CVD					
Female	272124	963729	12176	12.63 (12.41-12.86)	< 0.0001
Male	265196	910389	16031	17.61 (17.34-17.88)	
CKD					
Female	272314	955111	13486	14.12 (13.88-14.36)	< 0.0001
Male	266074	908301	14845	16.34 (16.08-16.61)	
Non-liver cancer					
Female	277066	1021598	8785	8.60 (8.42-8.78)	0.99
Male	275249	1001053	8608	8.60 (8.42-8.78)	

HCC, Hepatocarcinoma; CVD, Cardiovascular disease; CKD, Chronic kidney disease.

Disclosures: Taotao Yan: Nothing to Disclose, Tyler Wong: Nothing to Disclose, Xinrong Zhang: Nothing to Disclose, Ramsey Cheung: Nothing to Disclose

2368 | CAUSE-SPECIFIC MORTALITY AMONG AUSTRALIANS WITH CIRRHOSIS DIFFERS BY CIRRHOSIS ETIOLOGY AND DECOMPENSATION STATUS ◆

Vikas Bhasker[1] Paul Clark[2] Gunter Hartel[1] Richard Skoien[3] Elizabeth Powell[1] Patricia Valery[1]

[1]QIMR Berghofer Medical Research Institute, [2]Mater Hospital Brisbane, [3]Royal Brisbane and Women's Hospital

Background: Liver disease in Australia is among the top 10 leading causes of years of life lost, with a 10% increase in disease burden during 2003-2022. Over the last decade, there have been advances in treatment and a change in the prevalence of aetiological factors and comorbidities of liver disease. However, Australian data are limited about the principal causes of death among people living with cirrhosis. Using Queensland-wide data we determined cause-specific mortality in people with cirrhosis according to liver disease aetiology and severity. **Methods:** A retrospective analysis of adults hospitalized for cirrhosis during 2007-2022 was performed using state-wide hospital admissions and mortality data. ICD-10 codes identified admissions with cirrhosis, etiology, and underlying (UCOD) or contributing (CCOD) cause of death based on validated algorithms. Patients were considered to have cirrhosis decompensation (CD) if they had at least one admission with variceal bleeding, ascites or hepatic encephalopathy. **Results:** 22,525 individual patients had at least one admission with cirrhosis and/or died with cirrhosis as UCOD or CCOD, with a median follow-up of 6.9 years (interquartile range 3.5-11.1). At index admission mean age was 61.2 years (SD=13.0) with a male predominance (66.1%). The most common cirrhosis etiologies were alcohol (n=9,550, 42.4%), MASLD (n=5,108, 22.5%) and hepatitis C virus (HCV) (n=4,780, 21.2%). During follow-up, 12,387 (55%) patients died, with overall mortality 57.9%, 52.1% and 51.6% among alcohol, MASLD and HCV subgroups, respectively (p<0.001). The UCOD was liver disease in 50.3%

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and varied significantly by cirrhosis aetiology and CD status (p<0.001; **Figure**). Following inclusion of CCODs, liver-related deaths were reported in 79.1%, 54.9% and 86.9% in the alcohol, MASLD and HCV subgroups, respectively. Moreover, in patients with MASLD, other key UCOD/CCODs included major adverse cardiovascular events (42.4%), extrahepatic cancer (25.2%), respiratory disease (23.6%), and diabetes (23.8%). **Conclusion:** Our data highlight the high mortality of patients with cirrhosis. Liver-related mortality contributed most to patients with alcohol and HCV-related liver disease, while those with MASLD were less likely to have a liver-related death. With the declining prevalence of HCV-related liver disease and the increasing prevalence of MASLD cirrhosis, hepatologists need to address cardiovascular disease mortality risks, in addition to preventing hepatic decompensation.

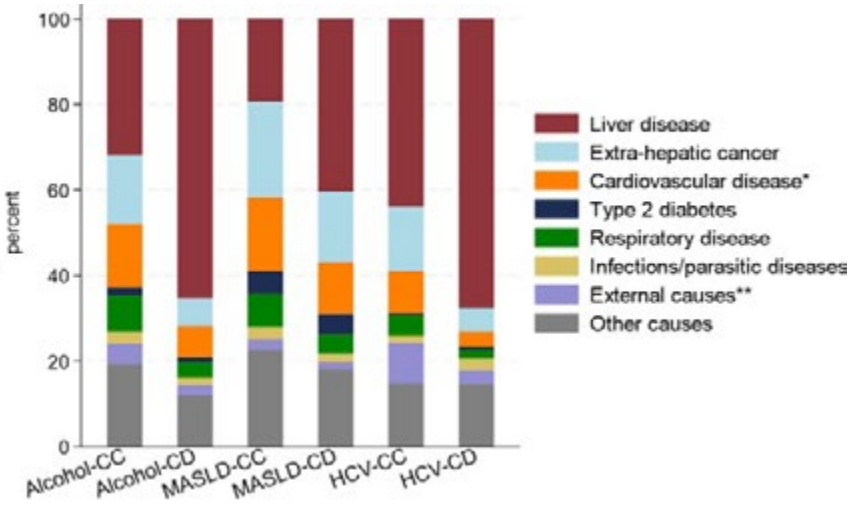

Figure. Underlying cause of death among patients with alcohol, MASLD/Cryptogenic and HCV cirrhosis (* Major cardiovascular adverse event; ** Accident, self-harm, suicide or homicide; Cirrhosis compensated (CC); Cirrhosis decompensation (CD))

Disclosures: Vikas Bhasker: Nothing to Disclose, Paul Clark: Nothing to Disclose, Gunter Hartel: Nothing to Disclose, Richard Skoien: Nothing to Disclose, Elizabeth Powell: Nothing to Disclose, Patricia Valery: Nothing to Disclose

2369 | PATTERNS OF DIETARY SUPPLEMENT USE AMONG PATIENTS WITH STEATOTIC LIVER DISEASE IN THE UNITED STATES: VITAMINS, MINERALS AND BOTANICALS

Gabrielle Jutras[1] Melinda Wang[2] Giuseppe Cullaro[3] Anand Dhruva[1] Jennifer Lai[1]

[1]University of California, San Francisco, [2]Yale University, [3]University of California - San Francisco

Background: Dietary supplements usage among adults in the U.S. has increased in parallel with evidence supporting their effectiveness for addressing some medical conditions. Patients with steatotic liver disease (SLD) may have unique motivations to take dietary supplements in light of their liver condition *and* co-morbidities. We aimed to characterize dietary supplement use in SLD patients and explore motivations for their use **Methods:** Adults≥18 years old with complete transient elastography and dietary data from the National Health and Nutrition Examination Survey (NHANES) between January 2017 and March 2020 were studied. SLD was defined using consensus criteria, combining clinical indicators with elastography thresholds. The Dietary Supplement Questionnaire (DSQ) was used to record participants' use of vitamins, minerals, botanicals, and other supplements within the past month. Sample weights were applied to estimate national prevalence. **Results:** Of 2413 participants with SLD, 1058 reported using dietary supplements, for an estimated prevalence of 44.8% (SE 2.4) with an average of 2.6 (SE 0.2) supplements per person. Among SLD patients taking supplements, 53.2% (SE 3.3) reported using non-vitamin/non-mineral ones, with an average of 1.8 (SE 0.1) such supplements per person. Supplement users tended to be older, female, with higher levels of education, and less food insecurity (p<0.02 for all). Top vitamins/mineral supplements included vitamin B complex (16.2%, SE 0.6), vitamin D (6.7%, SE 0.4) and vitamin C (4.2%, SE 0.3) (Table 1). Top non-vitamin/non-mineral supplements included fish oil (4.3%, SE 0.3), turmeric (0.5%, SE 0.1), and saw palmetto (0.3%, SE 0.1). Most common motivations for using supplements were to follow doctor's advice (36.7%, SE 1.8), improve overall health (22.1%, SE 2.0), and maintain health (19.2%, SE1.9). **Conclusion:** Nearly half of individuals with SLD report taking dietary supplements, of whom half use non-vitamin/non-mineral ones. Given this high dietary supplement usage rate and the increasing

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presence of patients with SLD in hepatology clinics, this study underscores the pressing need to deepen our understanding of the risks and benefits of dietary supplements, particularly botanical ones, in the setting of SLD and to develop tailored counseling strategies for our patients in clinics.

Table 1. Top 10 Dietary Supplements per Category among Patients with SLD

Dietary Supplement	% (SE)
Vitamins	
Vitamin B complex	16.2 (0.6)
Vitamin D	6.7 (0.4)
Vitamin C	4.2 (0.3)
Folate and derivates	2.9 (0.2)
Vitamin E and Derivates	2.8 (0.2)
Vitamin A	2.2 (0.1)
Vitamin K and Derivates	1.2 (0.2)
Choline	0.6 (0.1)
Minerals	
Calcium	4.1 (0.2)
Magnesium	3.0 (0.2)
Zinc	2.2 (0.2)
Copper	1.8 (0.1)
Selenium	1.6 (0.1)
Manganese	1.6 (0.2)
Chromium	1.6 (0.1)
Iron	1.5 (0.2)
Iodine	1.4 (0.1)
Molybdenum	1.2 (0.1)
Botanicals	
Turmeric	0.5 (0.1)
Palmetto	0.3 (0.1)
Cinnamon	0.3 (0.1)
Gingko Biloba	0.3 (0.1)
Olive	0.2 (0.04)
Cranberry	0.2 (0.1)
Grape	0.2 (0.1)
Green Tea	0.1 (0.1)
Garlic	0.1 (0.03)
Ginger	0.1 (0.04)
Other Supplements	
Omega 3 supplements	3.1 (0.2)
Fish Oil	1.2 (0.1)
Lutein	0.8 (0.1)
Inositol	0.7 (0.2)
Lycopene	0.7 (0.1)
Glucosamine	0.6 (0.1)
Coenzyme Q10	0.5 (0.1)
Fiber	0.5 (0.1)
Chloride	0.4 (0.1)
Melatonin	0.3 (0.1)

Disclosures: Gabrielle Jutras: Nothing to Disclose, Melinda Wang: Nothing to Disclose, Giuseppe Cullaro: Nothing to Disclose, Anand Dhruva: Nothing to Disclose, Jennifer Lai: Nestle Nutrition Institute: Grant/Research Support, Novo Nordisk: Consultant, Genfit: Consultant, Boehringer Ingelheim: Advisor

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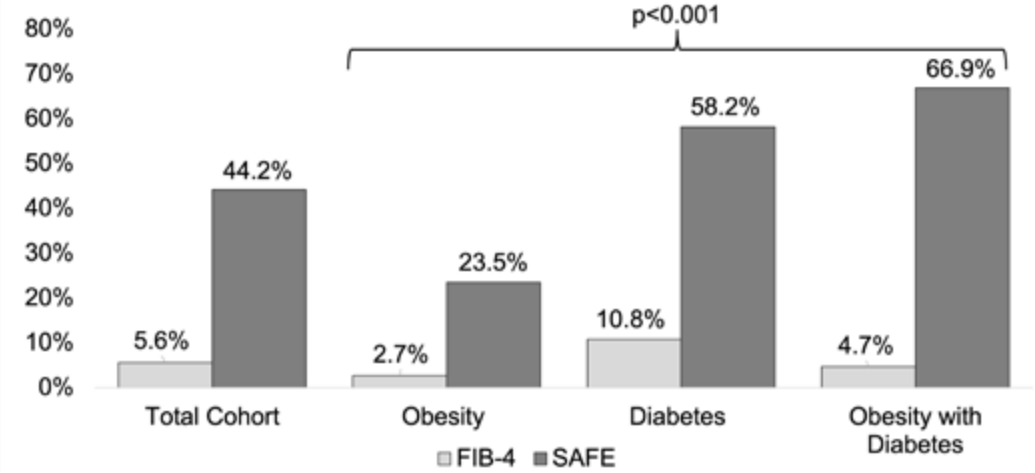
2370 | DISCORDANCE OF FIB-4 AND SAFE SCORES FOR THE PREDICTION OF ADVANCED FIBROSIS IN PRIMARY CARE PATIENTS WITH OBESITY, DIABETES, OR BOTH

Janet Chu[1] *Nghiem Ha*[1] *Mandana Khalili*[1] *Max Goldman*[2] *Bilal Hameed*[1] *Rena Fox*[1]

[1]*University of California, San Francisco,* [2]*Kaiser Permanente San Francisco Medical Center*

Background: The steatosis-associated fibrosis estimator (SAFE) score, like FIB-4, estimates risk of fibrosis among patients with metabolic dysfunction-associated steatotic liver disease (MASLD). SAFE has been shown to outperform FIB-4 in established cohorts but has not been studied in primary care (PC), where FIB-4 has a high negative predictive value. We evaluated SAFE and FIB-4 in PC patients with DM, obesity, or both to examine its distribution and utility. **Methods:** Retrospective cohort study using a large, diverse PC practice at an academic medical center. We derived three cohorts based on obesity (BMI>=30 for non-Asians and>=27 for Asians) and diabetes mellitus (DM) (HbA1c>=6.5% and/or an anti-DM prescription) status: 1) obesity without DM, 2) DM without obesity, and 3) obesity + DM. When BMI >40, the maximum value of 40 was used for SAFE calculation. We excluded patients with alcohol use disorder and/or chronic hepatitis B/C. For each patient, we calculated one FIB-4 and one SAFE score per year from 2018-2023. Using established age-based cutoffs, we categorized each as low-, indeterminate-, or high-risk for advanced fibrosis by most recent FIB-4 and SAFE, separately. We calculated a correlation coefficient between FIB-4 and SAFE scores. **Results:** Among 22,806 PC patients, 7,014 (31%) were included in the analysis: obesity (n=3,644), DM (n=1,896), or obesity + DM (n=1,474). During the 5-year study period, data for SAFE and FIB-4 scores were available for 63% and 72% of patients, respectively. Twenty-four percent of the obesity, 58% of DM, and 67% of obesity + DM group had a high-risk SAFE score; 3% of obesity, 11% of DM, and 5% of obese + DM had high-risk FIB-4 score (Figure 1). Among those categorized as high-risk by SAFE, only 16% were high-risk, 42% were indeterminate-, and 71% were low-risk by FIB-4. Conversely, 100% of patients classified as low or intermediate SAFE score (n=2,449) had low or indeterminate FIB-4 score. The correlation coefficient between FIB-4 and SAFE was 0.42. **Conclusion:** Discordance exists in classifying PC patients at risk for MASLD with advanced fibrosis using SAFE and FIB-4 scores. We found significant differences in high-risk SAFE and FIB-4 score among PC patients with obesity and/or DM. A potential SAFE-based algorithm for PC could substantially increase patients referred for transient elastography and hepatology evaluation. Prospective studies are essential to determine the effectiveness of implementing SAFE or FIB-4 score algorithms in PC settings.

Figure. Distribution of high-risk FIB-4 and SAFE scores among primary care patients with various risk factors for MASLD



Disclosures: Janet Chu: Gilead Sciences, Inc.: Grant/Research Support, Nghiem Ha: Nothing to Disclose, Mandana Khalili: gilead sciences: Grant/Research Support, GSK pharmaceuticals: Consultant, Intercept pharmaceuticals: Grant/Research Support, Gilead Sciences Inc: Consultant, Max Goldman: Eli Lilly: Stock - publicly traded company, Novo Nordisk: Stock - publicly traded company, Eli Lilly: Stock - publicly traded company, Madrigal: Stock - publicly traded company, Bilal Hameed: Consultant relationship with Gilead; Has not ended; Grant/Research Support relationship with Novo Nordisk; Has not ended; Stock â€“ privately held company

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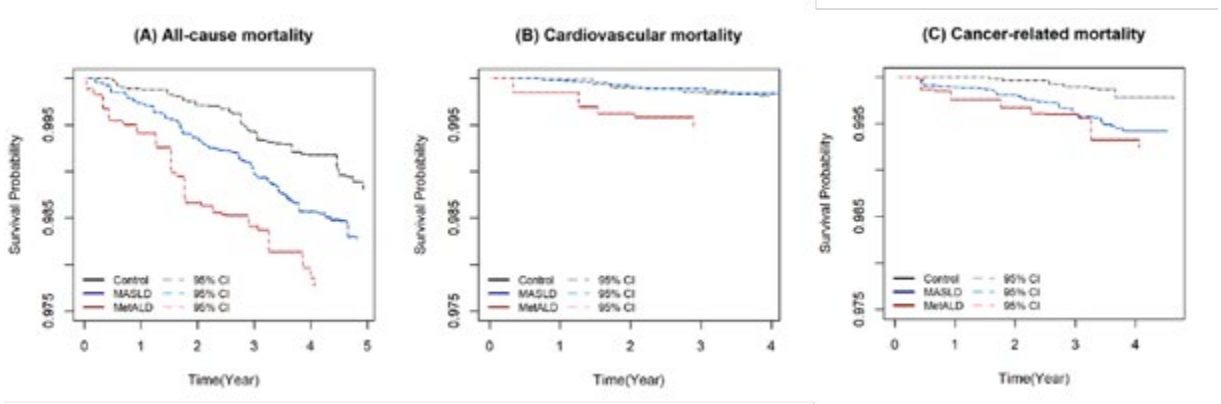
2371 | DIFFERENTIAL PROGNOSIS AND IMPACTS OF CARDIOMETABOLIC RISK FACTORS AND ALCOHOL INTAKE IN MASLD AND METALD PATIENTS

Young Chang *JAE YOUNG JANG*[1] *Soung Won Jeong*[1]

[1]*Soonchunhyang University*

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) and MASLD with increased alcohol intake (MetALD) are distinct yet overlapping conditions that significantly impact liver disease progression and mortality. This study aims to delineate the differential impacts of cardiometabolic risk factors (CMRFs) and alcohol consumption on liver fibrosis, cancer-related mortality, cardiovascular mortality, and all-cause mortality in patients with MASLD and MetALD. **Methods:** Individuals aged 20–79 years without any history of cancer, cardiovascular disease, or secondary causes of chronic liver disease were selected from the Korean National Health and Nutrition Examination Surveys from 2007 to 2015. Mortality data until November 2023 were retrieved from the National Death Registry. MASLD and MetALD were defined based on hepatic steatosis index >36, cardiometabolic risk factors, and alcohol consumption. Significant fibrosis was defined as a fibrosis-4 index ≥ 2.67. **Results:** Patients with MASLD and MetALD exhibited significantly higher risks of cancer-related mortality compared to controls, with hazard ratios (HR) of 2.610 (95% confidence interval [CI] 1.029–6.618, p=0.043) and 3.355 (95% CI 1.097–10.263, p=0.034), respectively. High alcohol intake (350-420g/week in males, 280-350g/week in females) was identified as a particularly detrimental factor for cancer mortality in MetALD patients, significantly increasing the risk (HR 7.632, 95% CI 1.772–32.869, p=0.006). Cardiovascular mortality did not significantly differ between MASLD or MetALD patients and controls, yet the number of CMRFs emerged as a significant independent risk factor influencing cardiovascular mortality (HR 1.838, 95% CI 1.320–2.558, p<0.001) in MASLD patients. All-cause mortality was notably higher in the MetALD group compared to controls (HR 2.085, 95% CI 1.127–3.860, p=0.019). The MASLD group also showed higher all-cause mortality than controls, though this was not statistically significant (HR 1.527, 95% CI 0.930–2.507, p=0.094). In MASLD patients, significant liver fibrosis was more prevalent in women (odds ratio [OR] 3.463, 95% CI 1.391–8.622, p=0.008) than in men, and the number of CMRFs was a significant risk factor for significant fibrosis (OR 1.792, 95% CI 1.196–2.683, p=0.005). **Conclusion:** Patients with MASLD and MetALD exhibited increased cancer-related and all-cause mortality rates compared to healthy controls, particularly in the MetALD group. In MASLD, the number of CMRFs is considered a major factor influencing prognosis, whereas in MetALD, the amount of alcohol intake is the primary determinant.



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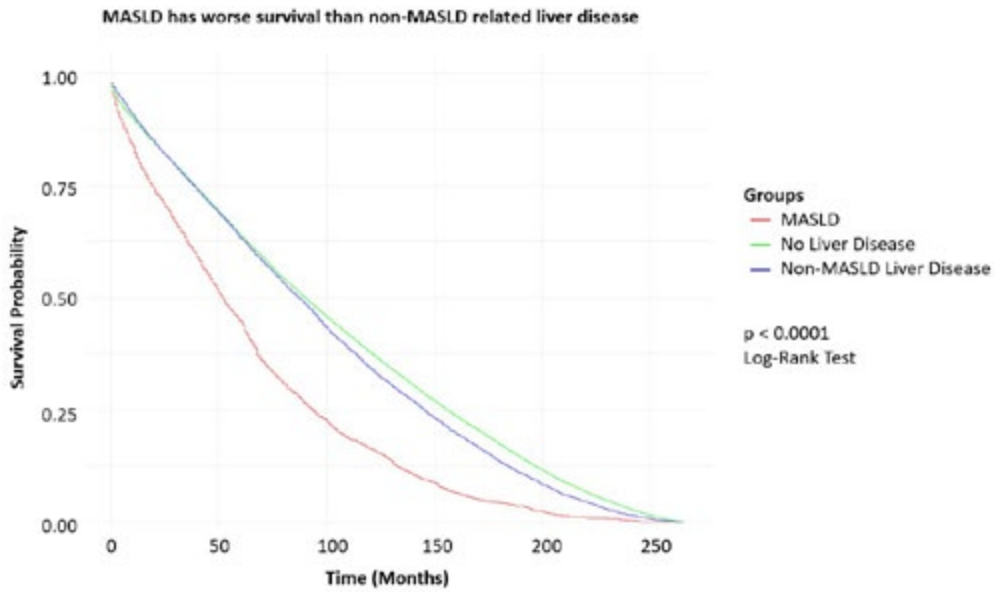
Disclosures: Young Chang: Nothing to Disclose, JAE YOUNG JANG: Nothing to Disclose, Soung Won Jeong: Nothing to Disclose

2372 | NONCIRRHOTIC METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE INCREASES RISK OF HEPATOCELLULAR CARCINOMA AND NEW CIRRHOSIS, AND OVERALL DEATH COMPARED TO OTHER LIVER DISEASES AMONG US VETERANS

Puneet Puri[1] Thuy-Duyen Vu[2] Vinod Aggarwal[3] HoChong Gilles[4] Michael Fuchs[4]

[1]Richmond VA Medical Center and Virginia Commonwealth University, [2]Richmond VA Medical Center, [3]MDClone Limited, Israel and VHA OHIL, VA Central Office, Washington, DC, [4]McGuire Veterans Affairs Medical Center

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) afflicts estimated 3.65 million US veterans and 30% of the general US population. Mortality risk in MASLD, and new cirrhosis (Cx) and hepatocellular carcinoma (HCC) in noncirrhotic MASLD are not well described. We aimed to study the impact of MASLD on mortality, Cx and HCC. **Methods:** Data from Veterans Affairs Corporate Data Warehouse via MDClone ADAMS platform identified patients seen at least once at our institution (1999-2016) with outcomes through 2021. Using ICD-9/10 codes we classified patients as MASLD (Grp 1), with non-MASLD liver disease (Grp 2) and those without known liver disease (Grp 3). Primary outcome of death and cumulative incidence for new Cx and HCC were examined in each group. Groups were compared using odds ratio and Kaplan-Meier survival curves. **Results:** We identified 119,341 unique patients (83% men), with 4,620 (3.9%) in Grp 1, 12,515 (10.5%) in Grp 2 and 102,206 (85.6%) in Grp 3. The mean age (±SD) for Grps 1-3 were 56±12, 53±10, 51±17, respectively. The presence of Cx and/or HCC was significantly higher in Grp 1 compared to Grps 2 & 3 (14% vs. 6.7% vs. 2.3%, p<0.0001 for trend) with ~7-fold higher odds of Cx and HCC (vs. Grp 3, OR 6.9, 95 % CI: 6.3-7.5, P < 0.0001). New diagnosis of cirrhosis was observed in 17.5% (697/3973) of Grp 1 patients vs. 0.5% (498/99842) of Grp 3 patients (OR 35.2, 95 % CI: 31.2-39.6, P < 0.0001). Similarly, new HCC in noncirrhotic patients was diagnosed in 2.7% (107/3973) of Grp 1 patients vs. 0.1% (94/99842) of Grp 3 patients (OR 28.6, 95 % CI: 21.6-37.8, P < 0.0001). On Kaplan-Meier survival analysis, Grp 1 had greater observed death than expected resulting in higher $(O-E)^2/V$ value (Gr 1=484 vs. Grp 2=215 vs. Grp 3=50, p<0.0001 log rank test). **Conclusion:** In this large healthcare system-wide analysis patients with MASLD related liver disease had worse survival compared to non-MASLD and without known liver disease. Patients with MASLD without cirrhosis were 35-times more likely to develop new cirrhosis and 28-fold of new HCC compared to those without known liver disease.These data demonstrate that MASLD increases mortality and burden of liver disease. results and additional analyses will inform policy makers of the greater magnitude for risks of cirrhosis and HCC than previously reported. Future efforts should focus on early recognition and intervention in patients with MASLD.



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Disclosures: Puneet Puri: Nothing to Disclose, Thuy-Duyen Vu: Nothing to Disclose, Vinod Aggarwal: Nothing to Disclose, HoChong Gilles: Madrigal: Speaking and Teaching, Michael Fuchs: Amgen: Grant/Research Support, Bio89: Grant/Research Support, ExactSciences: Grant/Research Support, Helio Health: Grant/Research Support, Intercept: Grant/Research Support, Galectin: Grant/Research Support, Viking: Grant/Research Support, GlaxoSmithKline: Grant/Research Support, NGM: Grant/Research Support, Kinetix: Grant/Research Support, Encaustics: Grant/Research Support, Altimmune: Grant/Research Support, AstraZeneca: Grant/Research Support, Akero: Grant/Research Support, HelioHealth: Grant/Research Support, Inventiva: Grant/Research Support, Madrigal: Grant/Research Support, NorthSea: Grant/Research Support, NovoNordisk: Grant/Research Support, Oncoustics: Grant/Research Support, Pfizer: Grant/Research Support

2373 | POPULATION-BASED STEATOTIC LIVER DISEASE SCREENING RECOMMENDATIONS COULD HELP ADDRESS WOMEN'S HEALTH INEQUITIES IN THE UNITED STATES: A NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEY ANALYSIS

Sheena Bhushan[1] *Monika Wahi*[2] *Jawad Ilyas*[3]

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Background: Post-menopausal women suffer from inequities in healthcare that could be improved by targeting secondary prevention in that age group. Many existing studies estimating cost-effectiveness of screening for steatotic liver disease (SLD) are simulations, that used non-optimal screening strategies, considered high-cost diagnostics and treatments without an evidence-base, and only focused on patients with a co-morbid condition. The aim of this analysis was to estimate the expanded capacity needed in primary care to accommodate potential guidelines recommending United States (US) women to undergo vibration-controlled transient elastography (VCTE) screening for SLD at age 55, with positive cases referred for diagnostic confirmation, management, and intensive lifestyle intervention (ILI). **Methods:** Data from the United States 2017-2020 National Health and Nutrition Examination Survey (NHANES) was used to create population-based estimates for US women aged 55 and older using two potential screening cut points for SLD: Median controlled attenuated parameter (CAP) ≥ 263 dB/m and CAP ≥ 285 dB/m. **Results:** Of the 15,560 records, 7,721 were for men and 5,695 were for women <55, and were removed, leaving 2,144, 78% of which included a complete VCTE and were included in this weighted analysis (n = 880). Using the lower CAP cut point, there was an estimated SLD prevalence of 52% (95% confidence interval [CI] 51-53%), translating to an additional 21.38 million (95% CI 4.99-37.77) who would be referred for follow-up. With the higher cutpoint, the prevalence was lowered to 38% (95% CI 36-39%) and translated to an additional 15.46 million (95% CI 3.47-27.46) referred to follow-up. Using the lower cut point, this estimate would include 13.27 million (95% CI 3.27-23.26) who were also obese, and 4.52 million (95% CI 0.85-8.19) who have also Type II diabetes mellitus (T2DM). **Conclusion:** If US policy recommended VCTE screening for SLD in women aged 55 and over, between 3 and 38 million additional patients would be referred to ILI in primary care, which could include as many as 23 million with concomitant obesity and 5 million with T2DM. This effort considers intersectionality and could address historical women's health inequities. To determine the most optimal cut point and the feasibility of treating these additional patients in primary care, future research into optimizing cost-effective ILI delivery in primary care is as necessary predicate.

Disclosures: Sheena Bhushan: Nothing to Disclose, Monika Wahi: Nothing to Disclose, Jawad Ilyas: Nothing to Disclose

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2374 | RACIAL DISPARITIES AND HIGHER SUBSTANCE AND OPIOID USE DISORDER IN LEAN PATIENTS WITH MASLD: RISK FACTORS AND MORTALITY

Pooja Rangan[1] Majd Aboona[2] Claire Faulkner[2] Pojsakorn Danpanichkul[3] Anandalakshmi Ponnaluri[2] Karn Wijarnpreecha[4]

[1]Banner University Medical Center, Phoenix, [2]University of Arizona College of Medicine - Phoenix, [3]Department of Internal Medicine, Texas Tech University Healt, [4]University of Arizona College of Medicine-Phoenix

Background: There is limited literature on prevalence of substance use disorder (SUD), especially opioid use disorders (OUD) in Metabolic Dysfunction-associated Steatotic Liver Disease (MASLD) patients. Thus, we aim to explore the current understanding of the prevalence and incidence of OUD/SUD within an ethnically diverse population and compare between lean vs non-lean patients with MASLD. **Methods:** This retrospective cohort study identified MASLD patients between January 2012 – June 2023 using ICD codes from a multi-center health network. All patients were included in the prevalence cohort, and patients with a follow up of 6 months or greater were included in the incidence cohort. The primary outcomes were prevalence and incidence of SUD/OUD and mortality. Multivariable logistic regression was conducted to determine the risk factors for SUD/OUD and competing risk analysis for incidence adjusting for confounders. **Results:** We included 59,180 MASLD patients in the prevalence cohort and 44,322 in the incidence cohort. The mean age (SD) was 50.9 (15.8) years, 60.1% were females and 5.1% were lean in the prevalence cohort. The overall prevalence of SUD was 31.9% and OUD was 6.3%. Both SUD (38.4% vs 31.6%, p=<0.001) and OUD (9.7% vs 6.1%, p=<0.001) prevalence was significantly higher in lean as compared to non-lean patients. On multivariable analysis, compared to Non-Hispanic Whites, Hispanics had a lower prevalence of SUD/OUD and lower incidence of OUD. Blacks and Native Americans had a higher incidence of SUD compared to Non-Hispanic Whites. Lean patients had a higher prevalence and incidence of SUD/OUD compared to non-lean patients with MASLD. The presence of SUD (aOR: 1.41, 95% CI: 1.24-1.60, p=<0.001) and OUD (aOR: 1.72, 95% CI: 1.45-2.04, p=<0.001) was an independent predictor of higher mortality. **Conclusion:** There is a concerningly high SUD/OUD among MASLD patients, with significantly higher rates observed in lean individuals and certain racial/ethnic groups. Further research is warranted to explore underlying reasons for racial disparities. Addressing racial and ethnic disparities in SUD/OUD prevalence in MASLD patients calls for culturally sensitive approaches and addressing underlying social inequities.

Prevalence Cohort Multivariable Logistic Regression

Outcomes	SUD		OUD	
Variables	aOR (95% CI)[a]	P-Value	aOR (95% CI)[a]	P-Value
Lean	Referent		Referent	
Non-Lean	0.68 (0.62-0.76)	<0.01	0.63 (0.55-0.73)	<0.01
Race				
Non-Hispanic White	Referent		Referent	
Asian / Pacific Islander	0.50 (0.40-0.62)	<0.01	0.13 (0.05-0.35)	<0.01
Black	0.94 (0.84-1.04)	0.22	1.03 (0.86-1.23)	0.75
Hispanic	0.83 (0.79-0.87)	<0.01	0.83 (0.76-0.91)	<0.01
Native American/Alaskan	1.04 (0.88-1.22)	0.66	1.10 (0.81-1.50)	0.52

Incidence Cohort Competing-Risk Regression[b]

Variables	aSHR (95% CI)[a]	P-Value	aSHR (95% CI)[a]	P-Value
Lean	Referent		Referent	
Non-Lean	0.62 (0.46-0.82)	<0.01	0.61 (0.49-0.76)	<0.01
Race				
Non-Hispanic White	Referent		Referent	
Asian / Pacific Islander	0.30 (0.09-0.93)	0.04	0.09 (0.01-0.66)	0.02
Black	1.34 (1.01-1.77)	0.04	0.97 (0.73-1.29)	0.86
Hispanic	0.88 (0.75-1.02)	0.10	0.85 (0.74-0.97)	0.02
Native American/Alaskan	1.74 (1.19-2.53)	<0.01	1.18 (0.76-1.85)	0.46

Abbreviations: CI- confidence interval; aOR- adjusted odds ratio; aSHR- adjusted sub-hazard ratio
a- adjusted for age, sex, race, smoking status, hypertension, dyslipidemia, Diabetes,Area Deprivation Index(ADI), and any mental disorder
b- mortality is the competing event

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Disclosures: Pooja Rangan: Nothing to Disclose, Majd Aboona: Nothing to Disclose, Claire Faulkner: Nothing to Disclose, Pojsakorn Danpanichkul: Nothing to Disclose, Anandalakshmi Ponnaluri: Nothing to Disclose, Karn Wijarnpreecha: Nothing to Disclose

2375 | ASSOCIATION BETWEEN METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE AND MORTALITY: A NATIONWIDE COHORT STUDY

Gi-Ae Kim[1] Yewan Park[2] Jooyi Jung[3]

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Background: The new nomenclature of metabolic dysfunction-associated steatotic liver disease (MASLD) that substitutes non-alcoholic fatty liver disease presents challenges in exploring its clinical outcomes. This study aimed to investigate the risk of all-cause and cause-specific mortality using the new nomenclature in the nationwide Korean population. **Methods:** This nationwide cohort study included 3,596,709 participants who underwent a health check-up in 2011 in South Korea. Steatotic liver disease (SLD) was defined as a fatty liver index ≥60. Participants were categorized into MASLD, MASLD with increased alcohol intake (MetALD), other combination etiology, and no SLD. The adjusted hazard ratios (aHR) for all-cause and cause-specific mortality were calculated using multivariable Cox proportional hazards regression models. **Results:** During the median follow-up of 10 years, 201,200 deaths (5.6%) occurred. In the age- and sex-adjusted analysis, MASLD (aHR 1.34; 95% CI, 1.32−1.37, p<0.001), MetALD (aHR 1.41; 95% CI, 1.37−1.45, p<0.001), and other combination etiology (aHR 1.84; 95% CI, 1.79−1.89, p<0.001) had an increased risk of all-cause mortality compared with no SLD. In multivariable analysis, MASLD had an increased risk of all-cause mortality (aHR 1.57; 95% CI, 1.52−1.62, p<0.001) and cause-specific mortality including cardiovascular (aHR 1.35; 95% CI, 1.25−1.45, p<0.001) and cancer-related mortality (aHR 1.27; 95% CI, 1.20−1.35, p<0.001) than no SLD. MetALD and other combination etiology had an increased risk of all-cause-, cardiovascular-, and cancer-related mortality. **Conclusion:** This study showed that MASLD and MetALD carry an increased risk of all-cause and cause-specific mortality compared to no SLD. The findings indicate that managing MASLD properly and decreasing alcohol intake can contribute to reducing unnecessary mortality.

Disclosures: Gi-Ae Kim: Nothing to Disclose, Yewan Park: Nothing to Disclose, Jooyi Jung: Nothing to Disclose

2376 | GREEN FOOD FOR LIVER PROTECTION? COMPARATIVE ANALYSIS OF FAT SOURCES AND RISK OF LIVER DISEASE AND MORTALITY ◆

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Background: Growing incidence of metabolic dysfunction-associated steatotic liver disease (MASLD) is a major concern for Western countries. Previous studies have shown the advantages of a pure vegan diet in managing MASLD but the specific effects of fats from animal and plant sources are not well understood. This study compares the impacts of these fat sources on MASLD development. **Methods:** Nutritional data was taken from 24h-food questionnaires at five time points in the UK Biobank. After exclusion (Fig. A), we analyzed the impact of higher proportions of plant-based versus animal fats in total fat intake on occurrence of hepatic ICD10-diagnoses for >200.000 people. For a subset of >25,000 participants, MASLD status (defined by the presence of PDFF≥5% and cardiometabolic risk factors) could be analyzed in line with novel nomenclature. Analyses were adjusted for age, sex, BMI, Townsend index, energy, alcohol, and carbohydrate intake. **Results:** For ICD-coded conditions as SLD (K76.0, OR = 0.643 (0.425-0.973), p = 0.037), liver diseases overall (K70-77, OR = 0.740 (0.597-0.917), p = 0.006) and liver failure (OR = 0.258 (0.093-0.713), p = 0.009) significantly lower odds could be observed in association with higher proportional vegetable fat intake. Consequently, higher animal fat intake was associated with higher odds for any of these conditions (e.g. liver failure: OR = 3.876, SLD: OR = 1.555). Same effects became evident for labelled MASLD status (OR = 0.719 vs. OR=1.391). Cox proportional hazard models revealed that higher consumption of plant-based fats was associated with reduced risk of overall mortality (OR = 0.786 (0.689-0.986)) and death from digestive diseases (OR = 0.295 (0.139-0.626)). In contrast, greater intake of animal fats was linked to increased risk of overall mortality (OR = 1.273 (1.117-1.450)) and death from

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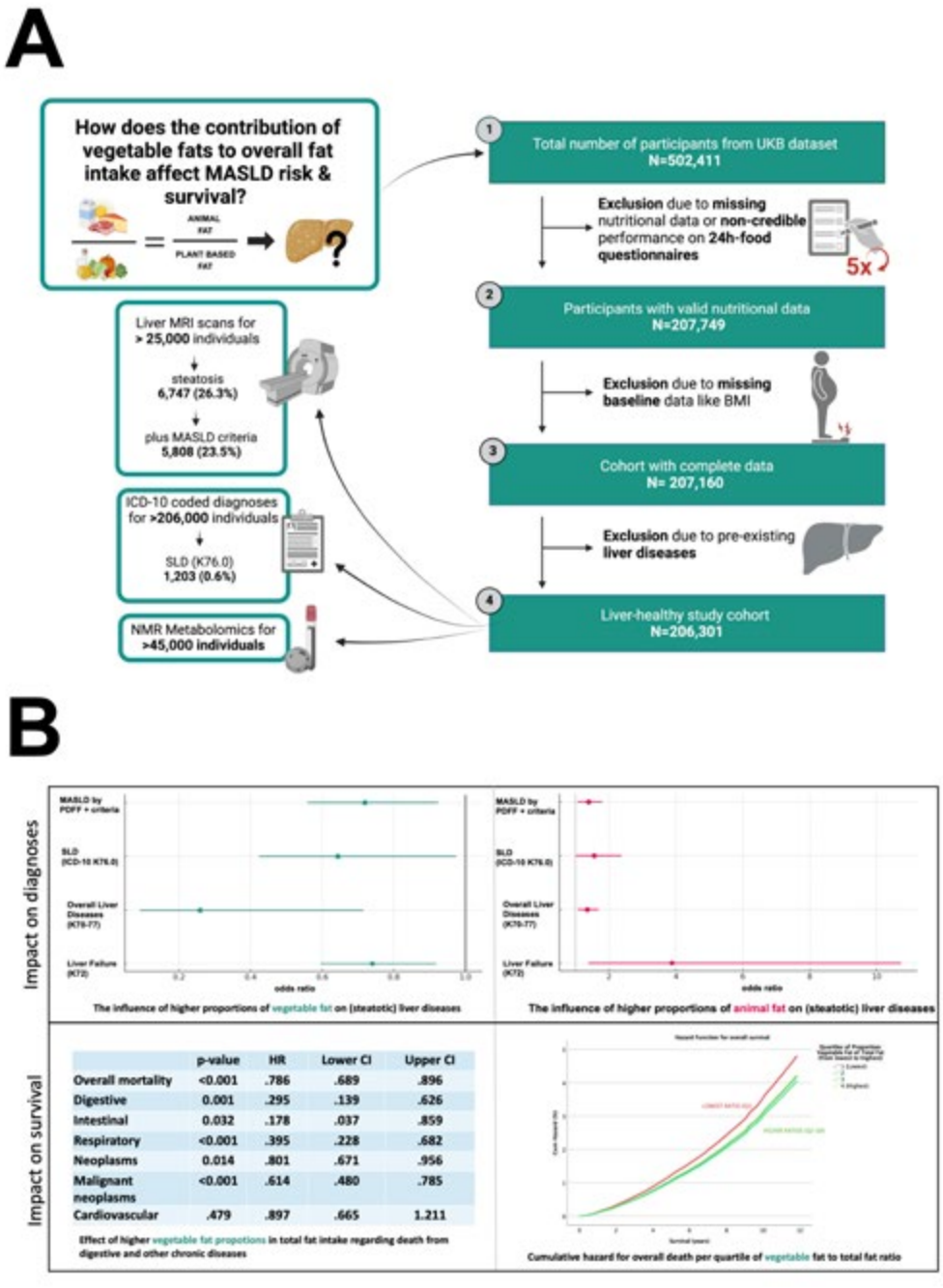
digestive diseases (OR = 3.393 (1.597-7.208)). Interestingly, this effect could not be seen for cardiovascular diagnoses suggesting that proportional elevation of vegetable fat intake might be particularly beneficial for the liver. Moreover, advantage in overall survival between the lowest vs. the remaining quartiles of vegetable to total fat ratio could be seen indicating that only a slight shift in this ratio towards vegetable fat comes with important benefit in the form of prevention from death (see also Figure B for key results). **Conclusion:** Our findings suggest that diets rich in plant-based fats may offer protective benefits against MASLD and other liver conditions, while higher consumption of animal fats appears to elevate the risk of MASLD. These insights show new opportunities for dietary interventions in the prevention of liver disease stressing the undeniable positive effects of plant-based dietary choices on liver health. Figure A: Design and subgrouping of the study cohort. Figure B: Brief overview of key findings.



Disclosures: Simon Schophaus: Nothing to Disclose, Paul-Henry Koop: Nothing to Disclose, Jan Clusmann: Nothing to Disclose, Kai Markus Schneider: Nothing to Disclose, Carolin Victoria Schneider: Nothing to Disclose

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2377 | MASLD AND METALD: THE AMOUNT OF LIVER FAT AND NUMBER OF CARDIOMETABOLIC RISK FACTORS IN RELATION TO THE RISK OF TYPE 2 DIABETES AND CARDIOVASCULAR DISEASE

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Background: Metabolic dysfunction associated steatotic liver disease (MASLD) and metabolic alcohol-associated liver disease (MetALD), defined as the presence of liver fat in combination with at least one of five cardiometabolic risk factors and alcohol consumption of maximum 50 gram/day for women and 60 gram/day for men, is associated with an increased risk of type 2 diabetes and cardiovascular diseases. It is unclear to what extent increasing amounts of liver fat or cardiometabolic risk factors may result in further risk increases. We aimed to examine the associations between increasing amounts of liver fat and the number of cardiometabolic risk factors with the occurrence of cardiometabolic disease (CMD). **Methods:** In the Netherlands Epidemiology of Obesity study, a population-based prospective cohort study, liver fat content was assessed at baseline using proton magnetic resonance spectroscopy in middle-aged population with overweight. During 10 years of follow-up, incident CMD (type 2 diabetes, myocardial infarction, stroke, TIA) were collected via medical records. Cox regression was used to examine associations, adjusted for age, sex, education, ethnicity, alcohol use, physical activity and total body fat **Results:** The overall population (50% women) had a mean age (95% CI) of 55 (55-56) years, BMI of 29.2 (29.0-29.4) kg/m^2, liver fat content of 8.1 (7.7-8.6)%. At baseline, 9% had obesity and 0.4% hypertension, lipid abnormalities and diabetes were not present as single criterion in the MASLD/metALD group. After exclusion of preexisting diabetes and cardiovascular disease, 139 new cases of CMD occurred, which resulted in an adjusted hazard ratio (HR, 95% CI) of 2.07 (1.5-3.3) for those with MASLD/metALD, compared with those without MASLD. Participants with liver fat content between 2.5-5% had an adjusted HR 1.02 (0.54-1.93), between 5-10% 1.86 (1.04-3.31), for 10-15% 1.89 (0.96-3.72), for 15-20% 1.98 (0.96-4.05), for 20-25% 2.27 (1.04-4.98), for 25-30% 2.44 (0.93-6.44)), and for those with liver fat content of 30% or more it was 3.23 (1.57-6.63) for the occurrence of CMD, compared to those with a liver fat content between 0 and 2.5%. Having MASLD/metALD with one cardiometabolic criterion resulted in an adjusted HR of 0.98 (0.42-2.24) for the occurrence of CMD, compared with those without MASLD. The adjusted HR with two criteria was 2.18 (1.32-3.58), three 2.58 (1.49-4.46) and four 2.98 (1.68-5.32). **Conclusion:** Participants with MASLD/metALD have a 2-fold increased risk of cardiometabolic disease compared with participants without MASLD. Liver fat content above 5% resulted in an increased HR of the occurrence of CMD up to 3 fold for >30% liver fat. Having four cardiometabolic criteria resulted in a 3 fold increased risk for the occurrence of CMD. Showing that the amount of liver fat and the number of cardiometabolic risk factors matter, therefore a multidisciplinary approach to treat the cardiometabolic risk factors is essential.

Disclosures: Gabrielle Alblas: Nothing to Disclose, Jeroen van der Velde: Nothing to Disclose, Maarten Tushuizen: Nothing to Disclose, Wouter Jukema: Nothing to Disclose, Hildo Lamb: Nothing to Disclose, Frits Rosendaal: Nothing to Disclose, Bart van Hoek: Nothing to Disclose, Renée de Mutsert: Nothing to Disclose, Minneke Coenraad: Nothing to Disclose

2378 | MINIMAL OR MODERATE ALCOHOL USE BEFORE LIVER TRANSPLANTATION FOR MASLD IS NOT ASSOCIATED WITH STEATOSIS RECURRENCE OR SURVIVAL

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Background: Patients with metabolic dysfunction-associated steatotic liver disease (MASLD) and alcohol-associated liver disease (ALD) have historically been placed into distinct cohorts. The introduction of metabolic and alcoholic-associated liver disease (MetALD) places a greater emphasis on minimum and maximum drinking levels to characterize different steatotic liver diseases. The aim of this study was to examine differences in patient characteristics and liver transplantation (LT) outcomes in MASLD based on pre-LT drinking levels. **Methods:** A retrospective cohort-comparison study was conducted in patients who underwent LT for MASLD at

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a high-volume transplant center in New York City from 2012 to 2023. Demographic, clinical, psychosocial, and social determinants of health data were collected. The patients were divided into minimal alcohol and moderate alcohol use groups. The minimal alcohol group included patients who never consumed alcohol and those who consumed it a few times per year. The moderate alcohol group included patients who consumed alcohol up to 140 g/week and 210 g/week for females and males respectively (below the MetALD threshold). Steatosis recurrence was defined by the presence of steatosis on post-LT imaging, including transient elastography. **Results:** Over the 11-year study period, a total of 129 patients underwent LT for MASLD. Median age was 61 [IQR 55-67], and sex proportions were 51% male and 49% female. Race breakdown was 47.5% White, 3.7% Black, 31.3% Hispanic, and 17.5% Other. The median MELD score at LT was 30 [IQR 22-35]. 78 (61%) and 51 (40%) patients were part of the minimal alcohol and moderate alcohol use groups respectively. Both groups had similar levels of social support, psychiatric disease, and stable employment ($p>0.05$). The moderate alcohol group had higher tobacco use (31%) compared to the minimal alcohol group (13%), $p<0.05$. Steatosis recurrence was similar in both groups: 23% in minimal alcohol group and 26% in moderate alcohol group ($p>0.05$). Survival during the study period was similar in both groups; 83.3% in minimal alcohol group and 82.4% in moderate alcohol group ($p>0.05$). After adjusting for covariates, the odds of steatosis post-LT were 13% lower in the minimal alcohol group compared to the moderate alcohol group, but did not reach statistical significance (OR 0.87, p 0.77). **Conclusion:** Minimal or moderate alcohol use before liver transplantation for MASLD is not associated with steatosis or survival. This supports the current MetALD minimal drinking threshold as a unique steatotic liver disease.

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2379 | LONG-TERM VASCULAR OUTCOMES AND MORTALITY AFTER BARIATRIC SURGERY AMONG PATIENTS WITH OBESITY, TYPE 2 DIABETES, AND METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE

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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) and type 2 diabetes (T2D) frequently coexist and synergistically increase the risk of adverse clinical outcomes. While bariatric surgery (BS) is increasingly performed in these patients, its effect on cardiovascular diseases (CVD) is not well established. Similarly, the long-term impact of BS on individuals with obesity, T2D, and MASLD is not Studied. The present study aimed to explore the long-term impact of BS on adverse macro and microvascular events, as well as mortality among individuals with obesity, T2D, and MASLD. **Methods:** This large population-based, retrospective cohort study was conducted using the data from the global federated health research network. We included adult patients (>18 years) diagnosed with MASLD, T2D, and obesity between 2010 and 2022 after excluding other chronic liver disease etiologies. We compared these patients to similar controls without a BS through 1:1 propensity score matching (PSM) for demographics, body mass index (BMI), comorbidities, and medication. BS procedures included Roux-en-Y gastric bypass and sleeve gastrectomy.The primary outcomes were the incidence of macrovascular diseases, defined as the composite indicator of the CVD, first occurrence of heart failure (HF), major adverse cardiovascular events (MACE), or cerebrovascular disease. Secondary outcomes were microvascular diseases and all-cause mortality. Microvascular diseases were the composite indicator of the first occurrence of retinopathy, neuropathy, or nephropathy. Sensitivity analyses were conducted to assess the robustness of the findings. We performed a secondary analysis to evaluate the consistency of our outcomes over 10 years by increasing the exposure lag. Cox proportional hazard models were used to estimate hazard ratios (HR). **Results:** A total of 82,877 patients were identified; 3890 patients had a history of BS, with a median follow-up of 4.2 years, up to 10 years. After PSM, BS and nonsurgical groups (3245 each) were well-matched. Among the BS cohort, most participants were female, and they were younger, White, and had a history of smoking. BS patients had a higher mean BMI. The risks of composite CVD (HR, 0.56), MACE (HR, 0.47), HF (HR, 0.56), and cerebrovascular diseases (HR, 0.33) were significantly lower for the BS group (Table 1). BS was also associated with a lower incidence of microvascular and all-cause mortality. These outcomes were consistent

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at a follow-up of 5, 7, and 10 years. The sensitivity analysis results were consistent, and all statistically significant associations remained unchanged. **Conclusion:** BS was associated with significantly reduced long-term occurrence of macro and microvascular outcomes as well as all-cause mortality in patients with MASLD, obesity, and T2D.

Table 1: Outcomes of bariatric surgery and nonsurgical patients with obesity, metabolic dysfunction-associated steatotic liver disease, and T2D.

Outcomes	BS (n=3245), N	Nonsurgical care (n=3245), N	Hazard Ratio (95% CI)
Primary outcome (Macrovascular)			
Composite CVD	129	79	0.56 (0.34-0.82)
MACE*	178	135	0.47 (0.32-0.65)
HF	134	189	0.56 (0.41-0.73)
Composite cerebrovascular disease*	78	121	0.33 (0.29-0.67)
Secondary outcome (Microvascular and All-Cause Mortality)			
Diabetic Neuropathy	289	456	0.56 (0.45-0.79)
Diabetic Nephropathy	301	389	0.65 (0.53-0.78)
Diabetic Retinopathy	189	164	0.92 (0.89-1.34)
All-Cause Mortality	89	65	0.87 (0.64-0.92)

Abbreviations: BS, bariatric surgery; CVD, cardiovascular disease; HF, heart failure; MACE, major adverse cardiovascular events.
*A composite endpoint of MACE was defined as the occurrence of myocardial infarction (ST-segment elevation myocardial infarction and non-ST-elevation myocardial infarction), unstable angina, and ischemic heart disease.
*A composite endpoint of cerebrovascular disease was defined as the occurrence of stroke, carotid stenosis, transient ischemic attack, and carotid interventions or surgeries)

Disclosures: Arunkumar Krishnan: Nothing to Disclose, Diptasree Mukherjee: Nothing to Disclose, Carolin Schneider: Nothing to Disclose, Tinsay Woreta: Nothing to Disclose, Saleh Alqahtani: Nothing to Disclose

2380 | ASSOCIATION OF GLUCAGON-LIKE PEPTIDASE 1 RECEPTOR AGONIST WITH LIVER AND NON-LIVER COMPLICATIONS IN PATIENTS WITH TYPE 2 DIABETES MELLITUS AND METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE ◆

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Background: Although individuals with type 2 diabetes mellitus and metabolic dysfunction-associated steatotic liver disease (diabetic MASLD) face a higher lifelong risk of developing liver and non-liver morbidities, there so far are limited effective pharmacological strategies to reduce the disease burden in this population. We aimed to examine the association of glucagon-like peptidase 1 receptor agonist (GLP-1a), when compared with other glucose-lowering drugs (oGLD), with liver and non-liver complications in patients with diabetic MASLD. **Methods:** In a population-based cohort study, we identified all adults with diabetic MASLD initially receiving GLP-1a or oGLD between 2010 and 2020 in Merative™ Marketscan® Research Databases. Primary outcomes included (1) hepatocellular carcinoma (HCC) and cirrhosis, and (2) cardiovascular disease (CVD), chronic kidney disease (CKD), and non-liver cancer. We used propensity score analysis to balance baseline characteristics for each study outcome respectively. Cox regression models were conducted to estimate hazard ratio (HR) and 95% confidence interval (CI). **Results:** The baseline characteristics before and after propensity score matching are shown in **Table**. All standardized mean differences are less than 0.1, indicating a balance after matching. Compared with oGLD, GLP-1a users were associated with a significantly lower incidence (per 1000 person-years) and risk of HCC (1.1 vs. 1.9; HR 0.59, 95%CI 0.47-0.73), cirrhosis (29.9 vs. 35.9; 0.76, 0.73-0.80), CVD (77.4 vs. 84.9; 0.86, 0.83-0.89), CKD (21.6 vs. 24.3; 0.87, 0.82-0.92), and non-liver cancer (21.0 vs. 22.7; 0.86, 0.81-0.91) (all $P < 0.001$). The effects of GLP-1a appeared to be duration-response (all $P_{trend} < 0.05$); compared with oGLD, a stepwise decreasing risk was found in GLP-1a use of 1-12, 13-24, and >24 months for HCC (HR 0.78, 0.34, 0.34), cirrhosis (0.81, 0.72, 0.65), CVD (0.96, 0.90, 0.84), CKD (0.96, 0.94, 0.89), and non-liver cancer (0.93, 0.87, 0.76). **Conclusion:** In a nationwide real-world U.S. cohort of patients with diabetic MASLD, GLP-1a use, when compared with oGLD, was associated with a duration-dependent lower risk of liver and non-liver complications.

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Table. Patient baseline characteristics, before and after PSM.

Characteristics	Before PSM			After PSM for HCC analysis*			After PSM for liver cirrhosis analysis*		
	GLP-1a (N=63434)	oGLD (N=396836)	SMD	GLP-1a (N=46629)	oGLD (N=46629)	SMD	GLP-1a (N=42045)	oGLD (N=42045)	SMD
Age, years	52.6 (9.7)	54.4 (11.6)	0.165	52.2 (9.8)	52.0 (11.9)	0.017	52.0 (9.8)	51.7 (11.7)	0.027
Female sex, %	38099 (60.1)	205391 (51.8)	0.168	27967 (60.0)	28232 (60.5)	0.012	25316 (60.2)	25416 (60.4)	0.005
Obesity, %	10577 (16.7)	31003 (7.8)	0.273	6610 (14.2)	6850 (14.7)	0.015	5445 (13.0)	5632 (13.4)	0.013
Smoking, %	6706 (10.6)	52172 (13.1)	0.080	5153 (11.1)	5268 (11.3)	0.008	4510 (10.7)	4534 (10.8)	0.002
Alcohol use disorder, %	1990 (3.1)	18366 (4.6)	0.077	1405 (3.0)	1343 (2.9)	0.008	992 (2.4)	949 (2.3)	0.007
Time since first glucose-lowering drug, years	2.6 (2.9)	0.4 (1.1)	1.024	1.5 (1.9)	1.4 (2.5)	0.051	1.5 (1.9)	1.4 (2.4)	0.051
Diabetes severity, %									
Diabetic nephropathy	8452 (13.3)	26721 (6.7)	0.221	5420 (11.6)	5745 (12.3)	0.021	4802 (11.4)	5074 (12.1)	0.020
Diabetic retinopathy	5295 (8.3)	16738 (4.2)	0.171	3388 (7.3)	3650 (7.8)	0.021	3072 (7.3)	3292 (7.8)	0.020
Diabetic neuropathy	14130 (22.3)	44342 (11.2)	0.301	9178 (19.7)	9887 (21.2)	0.038	8168 (19.4)	8644 (20.6)	0.028
Comorbidity, %									
Hyperlipidemia	48979 (77.2)	288774 (72.8)	0.103	34970 (75.0)	34927 (74.9)	0.002	31610 (75.2)	31701 (75.4)	0.005
Hypertension	49064 (77.3)	285758 (72.0)	0.123	35252 (75.6)	35696 (76.6)	0.022	31656 (75.3)	31968 (76.0)	0.017
Hepatitis B	329 (0.5)	2961 (0.7)	0.029	237 (0.5)	234 (0.5)	0.001	194 (0.5)	185 (0.4)	0.003
Hepatitis C	741 (1.2)	8587 (2.2)	0.078	563 (1.2)	519 (1.1)	0.009	414 (1.0)	409 (1.0)	0.001
Liver cirrhosis	6860 (10.8)	42989 (10.8)	0.001	4561 (9.8)	4592 (9.8)	0.002	0 (0.0)	0 (0.0)	<0.001
Hepatocellular carcinoma	97 (0.2)	1384 (0.3)	0.039	0 (0.0)	0 (0.0)	<0.001	0 (0.0)	0 (0.0)	<0.001
Cardiovascular disease	16925 (26.7)	99215 (25.0)	0.038	10863 (23.3)	11495 (24.7)	0.032	8987 (21.4)	9486 (22.6)	0.029
Chronic kidney disease	4110 (6.5)	16199 (4.1)	0.107	2542 (5.5)	1943 (4.2)	0.060	2070 (4.9)	1543 (3.7)	0.062
Non-liver cancer	6055 (9.5)	40149 (10.1)	0.019	3976 (8.5)	4503 (9.7)	0.039	3333 (7.9)	3683 (8.8)	0.030
Medication, %									
Metformin	46675 (73.6)	195370 (49.2)	0.517	31742 (68.1)	31837 (68.3)	0.004	28734 (68.3)	28770 (68.4)	0.002
SGLT-2i	23349 (36.8)	26177 (6.6)	0.788	12179 (26.1)	12693 (27.2)	0.025	11147 (26.5)	11544 (27.5)	0.021
DPP-4i	34635 (54.6)	231174 (58.3)	0.074	22634 (48.5)	21292 (45.7)	0.058	20340 (48.4)	19165 (45.6)	0.056
Sulfonylureas	21153 (33.3)	60834 (15.3)	0.429	12513 (26.8)	12885 (27.6)	0.018	11249 (26.8)	11658 (27.7)	0.022
Thiazolidinediones	8114 (12.8)	21720 (5.5)	0.256	4534 (9.7)	4670 (10.0)	0.010	4128 (9.8)	4169 (9.9)	0.003
Insulin	24329 (38.4)	62812 (15.8)	0.524	15001 (32.2)	15795 (33.9)	0.036	13414 (31.9)	14146 (33.6)	0.037
Other antidiabetic medications	1499 (2.4)	3211 (0.8)	0.125	789 (1.7)	799 (1.7)	0.002	719 (1.7)	755 (1.8)	0.007

Characteristics	After PSM for CVD analysis*			After PSM for CKD analysis*			After PSM for non-liver cancer analysis*		
	GLP-1a (N=35562)	oGLD (N=35562)	SMD	GLP-1a (N=44298)	oGLD (N=44298)	SMD	GLP-1a (N=42626)	oGLD (N=42626)	SMD
Age, years	50.8 (9.6)	50.5 (11.2)	0.031	51.9 (9.7)	51.6 (11.7)	0.024	51.8 (9.7)	51.6 (11.7)	0.018
Female sex, %	21820 (61.4)	22095 (62.1)	0.016	26901 (60.7)	26963 (60.9)	0.003	25344 (59.5)	25733 (60.4)	0.019
Obesity, %	4046 (11.4)	4333 (12.2)	0.025	6124 (13.8)	6347 (14.3)	0.014	5770 (13.5)	6115 (14.3)	0.023
Smoking, %	3585 (10.1)	3660 (10.3)	0.007	4891 (11.0)	4992 (11.3)	0.007	4665 (10.9)	4893 (11.5)	0.017
Alcohol use disorder, %	865 (2.4)	813 (2.3)	0.010	1290 (2.9)	1272 (2.9)	0.002	1284 (3.0)	1236 (2.9)	0.007
Time since first glucose-lowering drug, years	1.3 (1.8)	1.2 (2.2)	0.061	1.5 (1.9)	1.4 (2.4)	0.053	1.5 (1.9)	1.4 (2.4)	0.052
Diabetes severity, %									
Diabetic nephropathy	3822 (10.7)	4108 (11.6)	0.026	4247 (9.6)	4579 (10.3)	0.025	4874 (11.4)	5186 (12.2)	0.023
Diabetic retinopathy	2504 (7.0)	2707 (7.6)	0.022	3115 (7.0)	3370 (7.6)	0.022	3143 (7.4)	3267 (7.7)	0.011
Diabetic neuropathy	6421 (18.1)	7015 (19.7)	0.043	8511 (19.2)	9197 (20.8)	0.039	8372 (19.6)	8778 (20.6)	0.024
Comorbidity, %									
Hyperlipidemia	26244 (73.8)	26279 (73.9)	0.002	33031 (74.6)	33255 (75.1)	0.012	31960 (75.0)	31845 (74.7)	0.006
Hypertension	26110 (73.4)	26389 (74.2)	0.018	33256 (75.1)	33423 (75.5)	0.009	32119 (75.4)	32480 (76.2)	0.020
Hepatitis B	148 (0.4)	230 (0.6)	0.032	215 (0.5)	210 (0.5)	0.002	207 (0.5)	304 (0.7)	0.029
Hepatitis C	344 (1.0)	686 (1.9)	0.081	530 (1.2)	503 (1.1)	0.006	452 (1.1)	890 (2.1)	0.080
Liver cirrhosis	2578 (7.2)	3118 (8.8)	0.056	4130 (9.3)	4051 (9.1)	0.006	3738 (8.8)	4522 (10.6)	0.062
Hepatocellular carcinoma	32 (0.1)	88 (0.2)	0.038	57 (0.1)	95 (0.2)	0.021	41 (0.1)	71 (0.2)	0.019
Cardiovascular disease	0 (0.0)	0 (0.0)	<0.001	9785 (22.1)	10233 (23.1)	0.024	9328 (21.9)	9990 (23.4)	0.037
Chronic kidney disease	1291 (3.6)	1006 (2.8)	0.045	0 (0.0)	0 (0.0)	<0.001	2104 (4.9)	1652 (3.9)	0.052
Non-liver cancer	2485 (7.0)	2819 (7.9)	0.036	3609 (8.1)	4016 (9.1)	0.033	0 (0.0)	0 (0.0)	<0.001
Medication, %									
Metformin	24440 (68.7)	24804 (69.7)	0.022	30377 (68.6)	30546 (69.0)	0.008	29058 (68.2)	29108 (68.3)	0.003
SGLT-2i	9700 (27.3)	10057 (28.3)	0.022	11800 (26.6)	12347 (27.9)	0.028	11260 (26.4)	11682 (27.4)	0.022
DPP-4i	16543 (46.5)	15509 (43.6)	0.058	21300 (48.1)	19954 (45.0)	0.061	20507 (48.1)	19202 (45.0)	0.061
Sulfonylureas	9421 (26.5)	9648 (27.1)	0.014	11800 (26.6)	12142 (27.4)	0.017	11423 (26.8)	11815 (27.7)	0.021
Thiazolidinediones	3482 (9.8)	3552 (10.0)	0.007	4260 (9.6)	4396 (9.9)	0.010	4167 (9.8)	4294 (10.1)	0.010
Insulin	11363 (32.0)	12061 (33.9)	0.042	14090 (31.8)	14635 (33.0)	0.026	13790 (32.4)	14532 (34.1)	0.037
Other antidiabetic medications	574 (1.6)	624 (1.8)	0.011	734 (1.7)	821 (1.9)	0.015	698 (1.6)	746 (1.8)	0.009

CKD, chronic kidney disease; CVD, cardiovascular disease; DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1a, glucagon-like peptidase 1 receptor agonist; HCC, hepatocellular carcinoma; oGLD, other glucose-lowering drugs; PSM, propensity score matching; SGLT-2i, sodium-glucose cotransporter-2 inhibitor.

*For CVD, CKD, and non-liver cancer analyses, they are matched for age, sex, obesity, smoking, alcohol use disorder, time since first glucose-lowering drug, diabetic nephropathy, diabetic retinopathy, diabetic neuropathy, hyperlipidemia, hypertension, metformin, SGLT-2i, DPP-4i, sulfonylureas, thiazolidinediones, insulin, and other antidiabetic medications; for cirrhosis analysis, it was matched for the aforementioned variables and hepatitis B and C; for HCC analysis, it was further matched for cirrhosis.

Disclosures: Mindie Nguyen: Nothing to Disclose, Xianhua Mao: Nothing to Disclose, Xinrong Zhang: Nothing to Disclose, Rongtao Lai: Nothing to Disclose, Ka-Shing Cheung: Nothing to Disclose, Man-Fung Yuen: Speaking and Teaching relationship with Fujirebio Incorporation, Gilead Sciences, Roche, Sysmex Corp; Has not ended; Consultant relationship with Clear B Therapeutics, Dicerna Pharmaceuticals; Has not ended; Consultant relationship with AbbVie, Abbott Diagnotics, Aligos Therapeutics; Has not ended; Consultant relationship with Arbutus Biopharma, Arrowhead Pharmaceuticals, Assembly Biosc; Has not ended; Consultant relationship with Immunocore, Janssen, Precision BioSciences; Has not ended; Consultant relationship with Fujirebio Incorporation, GlaxoSmithKline, Gilead Sciences; Has not ended; Grant/Research Support relationship with

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2381 | CAUSE-SPECIFIC MORTALITY IN PATIENTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE: A NATIONWIDE POPULATION-BASED COHORT STUDY

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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is associated with a higher mortality rate than the general population, but data on cause-specific mortality are limited. We aimed to determine the rate and risk of death from different causes in patients with MASLD compared to the general population. **Methods:** In this population-based cohort study, we identified all patients with an ICD-10 code for MASLD in Swedish healthcare registers 2002-2020 (n=13,099) and matched them with ≤10 controls from the general population for age, sex, municipality, and calendar year (n=118,884). We used Cox regression to estimate adjusted HRs for cause-specific mortality in patients with MASLD compared to controls. The models were conditioned on the matching variables and adjusted for education, country of birth and the Charlson comorbidity index. Cumulative incidences of death were calculated while accounting for competing risks. We considered 11 primary causes of death: liver, hepatocellular carcinoma, extrahepatic cancer, cardiovascular, infections, gastrointestinal, respiratory, external causes, mental health disorder, endocrine disorders, and other. **Results:** In the patients with MASLD, the median age was 56 years, 50% were men, 12,483 (95.3%) had no cirrhosis, 435 (3.3%) had compensated cirrhosis, and 181 (1.4%) had decompensated cirrhosis at baseline. A total of 1,628 (12.4%) deaths occurred in patients with MASLD and 9,119 (7.7%) in controls during a median follow-up of 4.7 (IQR 2.0-9.2) and 5.8 (IQR 2.7-10.5) years, respectively. MASLD was associated with higher all-cause mortality (HR=1.9, 95%CI=1.7-2.0) and higher rates of all specific causes of death except mental health disorder. The strongest associations were for liver-related (HR=26.9, 95%CI=19.4-37.3) and hepatocellular carcinoma-related mortality (HR=35.0, 95%CI=17.0-72.1). However, the highest 15-year cumulative incidence of death in patients with MASLD was for extrahepatic cancer (7.9%) and cardiovascular disease (7.2%). Of the 1,628 deaths in patients with MASLD, 454 (27.9%) were from extrahepatic cancer, 421 (25.9%) from cardiovascular disease, 175 (10.8%) from liver disease, and 49 (3.0%) from hepatocellular carcinoma. However, of the patients with cirrhotic MASLD who died, most died from liver disease (33.6% for those with compensated cirrhosis and 45.5% for those with decompensated cirrhosis). **Conclusion:** MASLD was in relative terms strongly associated with liver- and hepatocellular carcinoma-related mortality, but the absolute risk of death was highest for extrahepatic cancers and cardiovascular disease. The results are important to inform clinicians, patients, and policymakers about the absolute risks of death in MASLD. In addition, as MASLD was associated with higher mortality from a wide range of causes, a holistic approach is likely required to effectively reduce the risk of excess mortality in patients with MASLD.

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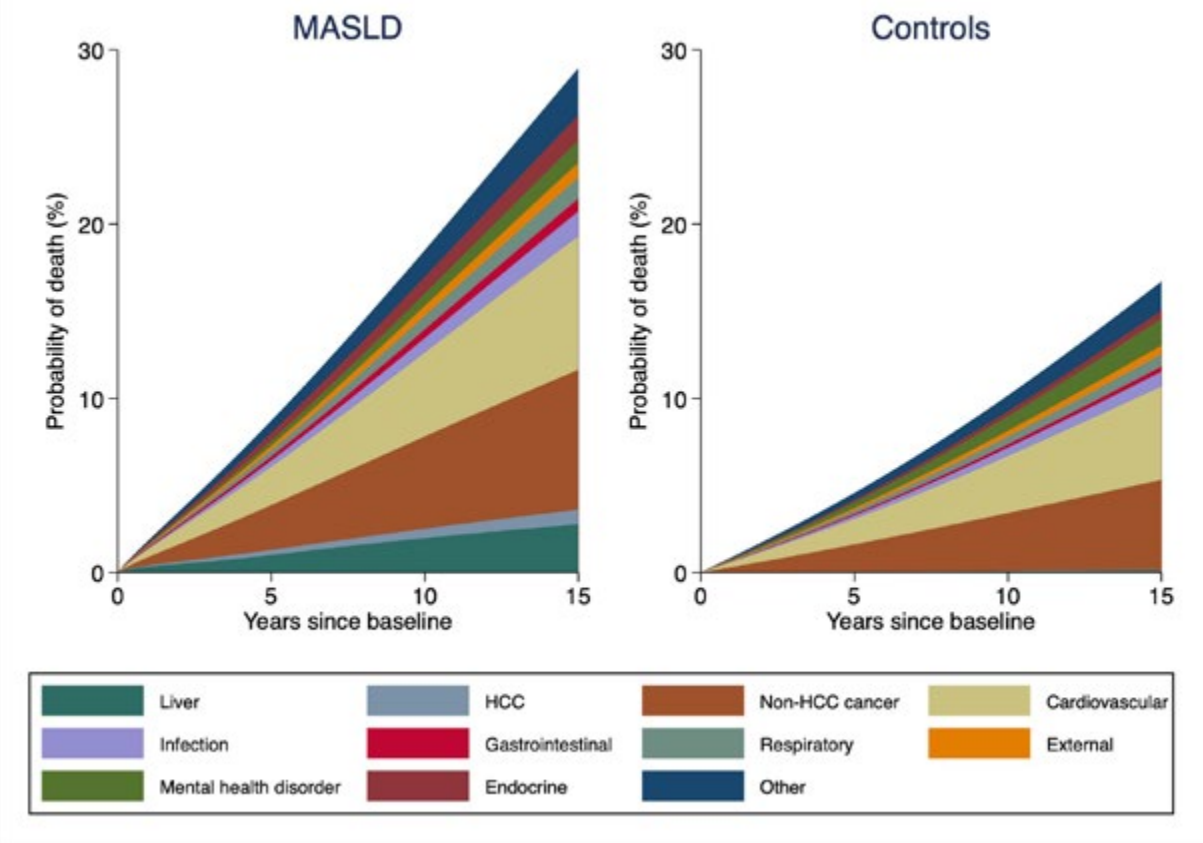

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2382 | EFFECT OF GLUCAGON-LIKE PEPTIDE 1 RECEPTOR AGONISTS ON METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE IN ADULTS WITH TYPE 2 DIABETES MELLITUS AND WITH OVERWEIGHT OR OBESITY: A TARGET TRIAL EMULATION STUDY

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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD), which frequently co-exists with type 2 diabetes mellitus (T2DM), overweight, or obesity, represents the most common chronic liver disease. We aimed to evaluate the association between glucagon-like peptidase 1 receptor agonist (GLP-1a) vs other glucose-lowering drugs (oGLD) and MASLD among patients with T2DM and with overweight or obesity. **Methods:** This was a target trial emulation study using observational data that retrieved U.S. adults with T2DM and with overweight or obesity aged 18 years or older receiving GLP-1a or oGLD between January 2015 and June 2021. The primary outcome was MASLD incidence, and the secondary outcome was advanced chronic liver disease (cirrhosis and hepatocellular carcinoma). Propensity score matching was applied to emulate the randomization between GLP-1a and oGLD users while Cox regression models were used to estimate hazard ratio (HR) and 95% confidence interval (CI). **Results:** After propensity score matching, all patient characteristics are well balanced, with all standardized mean differences less than 0.1 (**Table**). Among 59927 propensity score-matched patients (mean [SD] age: 40.4 +/- 12.6; 79.3% female), 20090 were GLP-1a users and 39837 were oGLD users. GLP-1a users, when compared with oGLD users, had a lower incidence (per 1000 person-years) and risk of MASLD in both intention-to-treat (21.0 vs 26.1; HR 0.79, 95%CI 0.72-0.87) and per-protocol analyses (26.7 vs 37.9; HR 0.73, 95%CI 0.63-0.84). The risk reduction was consistent when compared with metformin, SGLT-2i, DPP-4i,

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and sulfonylureas (intention-to-treat HR: 0.58-0.80; per-protocol HR: 0.43-0.75). Inverse association between GLP-1a and advanced chronic liver disease was also observed (intention-to-treat HR 0.70, 95%CI 0.53-0.92; per-protocol HR 0.48, 95%CI 0.30-0.76). **Conclusion:** In a target trial emulation study of patients with T2DM and with overweight or obesity, the use of GLP-1a decreased the risk of MASLD than the use of oGLD. This suggests the need for clinical trials to validate the benefits of GLP-1a in the primary prevention of MASLD.

Table. Baseline characteristics.

Characteristics[a]	Before propensity score matching			After propensity score matching		
	GLP-1a (n=20131)	oGLD (n=120278)	SMD	GLP-1a (n=20090)	oGLD (n=39837)	SMD
Age, year	40.8 (10.2)	40.3 (13.0)	0.044	40.8 (10.2)	41.1 (12.4)	0.028
Female, %	17743 (88.1)	93566 (77.8)	0.278	17702 (88.1)	35070 (88.0)	0.002
Lifestyle, %						
Alcohol use	377 (1.9)	1948 (1.6)	0.019	373 (1.9)	745 (1.9)	0.001
Smoking	240 (1.2)	1530 (1.3)	0.007	237 (1.2)	466 (1.2)	0.001
BMI, kg/m^2, %			0.233			0.010
25-29	1583 (7.9)	18137 (15.1)		1583 (7.9)	3238 (8.1)	
30-39	10121 (50.3)	58250 (48.4)		10109 (50.3)	20085 (50.4)	
≥40	8427 (41.9)	43891 (36.5)		8398 (41.8)	16514 (41.5)	
Diabetes duration, year	0.2 (0.9)	0.4 (1.3)	0.199	0.2 (0.9)	0.2 (0.8)	0.027
Diabetic severity, %			0.103			0.006
Mild	19693 (97.8)	115533 (96.1)		19652 (97.8)	38933 (97.7)	
Moderate	412 (2.0)	4458 (3.7)		412 (2.1)	852 (2.1)	
Severe	26 (0.1)	287 (0.2)		26 (0.1)	52 (0.1)	
Diabetes complications, %						
Heart failure	123 (0.6)	1210 (1.0)	0.044	123 (0.6)	259 (0.7)	0.005
Stroke	362 (1.8)	2656 (2.2)	0.029	360 (1.8)	719 (1.8)	0.001
Myocardial infarction	31 (0.2)	446 (0.4)	0.042	31 (0.2)	64 (0.2)	0.002
Chronic kidney disease	112 (0.6)	883 (0.7)	0.022	112 (0.6)	228 (0.6)	0.002
Chronic liver diseases, %						
Hepatitis B	31 (0.2)	237 (0.2)	0.010	31 (0.2)	59 (0.1)	0.002
Hepatitis C	42 (0.2)	319 (0.3)	0.012	42 (0.2)	89 (0.2)	0.003
Other chronic liver diseases[b]	101 (0.5)	415 (0.3)	0.024	100 (0.5)	192 (0.5)	0.002
Healthcare use (department visit), %						
Internal medicine	8130 (40.4)	35094 (29.2)	0.237	8089 (40.3)	16195 (40.7)	0.008
Cardiology	2604 (12.9)	11898 (9.9)	0.096	2566 (12.8)	5067 (12.7)	0.002
Endocrinology & metabolism	2420 (12.0)	9928 (8.3)	0.125	2391 (11.9)	4783 (12.0)	0.003
Pharmacy	394 (2.0)	1940 (1.6)	0.026	388 (1.9)	778 (2.0)	0.002
Dietitian	535 (2.7)	1831 (1.5)	0.079	518 (2.6)	1022 (2.6)	0.001
Diabetes medication, %			NA			NA
Metformin	0 (0.0)	94835 (78.8)		0 (0.0)	33551 (84.2)	
SGLT-2i	0 (0.0)	2654 (2.2)		0 (0.0)	824 (2.1)	
DPP-4i	0 (0.0)	17544 (14.6)		0 (0.0)	3994 (10.0)	
Sulfonylureas	0 (0.0)	4482 (3.7)		0 (0.0)	1237 (3.1)	
Thiazolidinediones	0 (0.0)	763 (0.6)		0 (0.0)	231 (0.6)	
Other medications, %						
Statins	320 (1.6)	10388 (8.6)	0.324	320 (1.6)	820 (2.1)	0.035
NSAIDs	844 (4.2)	3544 (2.9)	0.067	836 (4.2)	1703 (4.3)	0.006
Clopidogrel	24 (0.1)	657 (0.5)	0.074	24 (0.1)	72 (0.2)	0.016
Pentoxifylline	0 (0.0)	28 (0.0)	0.022	0 (0.0)	0 (0.0)	< 0.001
Laboratory test[c]						
HbA1c, %	7.4 (1.6)	7.6 (1.7)	0.117	7.4 (1.6)	7.4 (1.7)	0.013
ALT, IU/L	22.6 (16.8)	26.6 (23.5)	0.197	22.6 (16.8)	25.2 (23.3)	0.098
AST, IU/L	19.1 (12.1)	19.8 (14.9)	0.051	19.1 (12.2)	19.2 (13.6)	0.002
LDL-C, mg/dL	103.0 (28.5)	103.8 (32.6)	0.028	103.0 (28.5)	102.4 (29.6)	0.022
HDL-C, mg/dL	54.4 (14.6)	50.3 (16.2)	0.074	54.4 (14.6)	53.3 (12.4)	0.012
Total cholesterol, mg/dL	179.5 (32.6)	179.2 (39.0)	0.010	179.7 (32.4)	177.9 (36.0)	0.053
Albumin, g/L	43.0 (15.6)	43.1 (5.4)	0.002	43.0 (15.7)	42.8 (5.4)	0.021
Total bilirubin, mg/dL	0.4 (0.2)	0.5 (0.3)	0.074	0.4 (0.2)	0.4 (0.3)	0.006

ALT, alanine transaminase; AST, aspartate transaminase; DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1a, glucagon-like peptide 1 receptor agonist; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NSAIDs, non-steroidal anti-inflammatory drugs; oGLD, other glucose-lowering drugs; SGLT-2i, sodium-glucose transport protein 2 inhibitor; SMD, standardized mean difference.

[a]Data are presented as mean (SD) unless otherwise indicated.

[b]Other chronic liver disease included autoimmune liver disease, alpha-1 antitrypsin deficiency, hemochromatosis, Budd-Chiari syndrome, and Wilson's disease.

[c]Only available in a subset of the population and not included in the PS models.

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Disclosures: Mindie Nguyen: Nothing to Disclose, Xianhua Mao: Nothing to Disclose, Xinrong Zhang: Nothing to Disclose, Rongtao Lai: Nothing to Disclose, Man-Fung Yuen: Speaking and Teaching relationship with Fujirebio Incorporation, Gilead Sciences, Roche, Sysmex Corp; Has not ended; Consultant relationship with Clear B Therapeutics, Dicerna Pharmaceuticals; Has not ended; Consultant relationship with AbbVie, Abbott Diagnotics, Aligos Therapeutics; Has not ended; Consultant relationship with Arbutus Biopharma, Arrowhead Pharmaceuticals, Assembly Biosc; Has not ended; Consultant relationship with Immunocore, Janssen, Precision BioSciences; Has not ended; Consultant relationship with Fujirebio Incorporation, GlaxoSmithKline, Gilead Sciences; Has not ended; Grant/Research Support relationship with Fujirebio Incorporation, Gilead Sciences, Immunocore; Has not ended; Grant/Research Support relationship with AbbVie, Assembly Biosciences, Arrowhead Pharmaceuticals; Has not ended; Consultant relationship with Vir Biotechnology and Visirna Therapeutics; Has not ended; Consultant relationship with Roche, Sysmex Corporation, Tune Therapeutics; Has not ended; Grant/Research Support relationship with Sysmex Corporation and Roche; Has not ended, Ramsey Cheung: Nothing to Disclose, Ka-Shing Cheung: Nothing to Disclose, Wai-Kay Seto: Nothing to Disclose

2383 | CHANGE IN NOMENCLATURE AND DEFINITION FROM NAFLD TO MASLD MAINTAINS THE DISEASE SEVERITY DETERMINING ASSOCIATION BETWEEN TYPE 2 DM AND MASLD - THE RESULTS OF MULTI-CENTRE INDIAN CONSORTIUM ON MASLD (ICOM-D)

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Background: The association between diabetes mellitus and liver fibrosis is well studied in patients with nonalcoholic fatty liver disease (NAFLD). With recent change in nomenclature and definition, similar data is not available in patients with metabolic dysfunction-associated steatotic liver disease (MASLD). The aim of the present study was to analyse the association of type 2 diabetes mellitus (T2DM) and advanced fibrosis (stage 3 or 4) in patients with MASLD. **Methods:** In an on-going multicentre study of Indian Consortium on MASLD (ICOM-D) across 30 centres of the country, data of last 4 years was analysed for the factors responsible for the histological severity of liver disease in patients with MASLD. MASLD was defined as per the recent Delphi consensus

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paper. Presence of type 2 DM and metabolic syndrome was defined as per the Adult Treatment Panel III criteria. Histological severity was graded and staged as per NASH-CRN histological score. **Results:** Out of total of 8877 patients with steatotic liver disease in the ICOM-D data base, the study included 400 biopsy proven patients with MASLD [mean age 42±11 years, mean BMI 27±9 kg/m^2, 258 (64.5%) males]. Metabolic syndrome was present in 159 (39.7%) of patients, hypertension in 67 (16.8%), T2DM in 93 (23.3%) patients, central obesity (gender specific higher waist circumference) in 322 (80.5%), serum triglycerides > 150 mg/dl in 178 (44.5%) and a low HDL (as per gender cut off) was present in 271 (67.8%) patients. The fibrosis stages were stage 0 in 114 (28.5%), 1 in 130 (32.5%), 2 in 73 (18.3%), 3 in 35 (8.8%) and 4 in 48 (12%). In comparison to those with F0-F2 fibrosis, patients with advanced fibrosis (F3-4) had higher age (46.6±11.8 years versus 41.4±11.4 years, p=0.000), higher prevalence of T2DM (38.6% versus 19.2% p=0.000), more chances of being female gender (48.2% versus 32.2%, p=0.010), lower chances of having serum triglycerides >150 mg/dl (24.1% versus 49.8%, p=0.000) and higher chances of having low HDL (77.1% versus 65.3%, p=0.048). Serum triglycerides and HDL were not included in the multivariate analysis as these values are affected by cirrhosis. The multivariate analysis model including age, gender and T2DM showed that age [OR 1.025 (95% CI 1.001-1.049, p=0.042] and T2DM [OR 1.943 (95% CI 1.099-3.433, p=0.022] were significant predictors of advanced fibrosis. Higher number of patients with T2DM (35/93 - 38%) had advanced fibrosis in comparison to those without T2 DM (59/307 - 19.2%) (p=0.000). **Conclusion:** Both higher age and T2DM were associated with advanced fibrosis in patients with MASLD. In comparison to those without T2DM, the risk of advanced fibrosis is almost twice in patients with MASLD with type 2DM. Change in nomenclature and definition from NAFLD to MASLD maintains the disease severity determining association between type 2 DM and MASLD.

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2384 | CONTEMPORARY ETIOLOGIC DIFFERENCES FOR CAUSE OF DEATH IN PATIENTS WITH CIRRHOSIS ◆

George Cholankeril[1] Yan Liu[1] Kavish Patidar[1] Tzu-Hao Lee[1] Ruben Hernaez[1] Abbas Rana[1] Thom Taylor[1] Jennifer Kramer[1] Hashem El-Serag[1] Fasiha Kanwal[2]

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Background: Limited data exist on cause-specific mortality in cirrhosis, especially from non-liver related (NLR) causes. This gap is problematic with the rise of cirrhosis from steatotic liver disease (SLD), where the competing mortality from cardiovascular disease (CVD) and non-liver cancers may be high. We evaluated cause-specific mortality in a contemporary cirrhosis population, comparing liver-related (LR) *versus* NLR causes of death overall and by liver disease etiology. **Methods:** We identified all adult patients with cirrhosis who received care at 130 Veterans Affairs (VA) hospitals and associated ambulatory clinics from January 1, 2010, to December 31, 2018. We defined cured HCV based on evidence of sustained virologic response in HCV seropositive patients, alcohol-related liver disease (ALD) based on ICD-codes or positive AUDIT-C (≥4 in men and ≥3 in women), and MASLD based on type 2 diabetes or body mass index ≥ 25 and in the absence of other causes of liver disease. We used the National Death Index to ascertain cause of death, categorized as LR (with separate category for hepatobiliary cancer) or NLR (with separate categories for CVD and extra-hepatic malignancy). Cause-specific

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models, adjusted for age and sex, were used to compare differences in the cause of death between subgroups by cirrhosis stage. **Results:** Of the 107,939 patients with cirrhosis (1742 cured HCV, 23,292 ALD, 66,314 MASLD), 52.8% (n=56,940) died during a median follow up of 1.8 years. In total, 62.2% (n=35,414) of deaths were due to LR causes, of which 30.2% (n=10,705) were from hepatobiliary cancer. Of the 37.8% of deaths from NLR causes, 35.5% (n=7,650) were from CVD and 29.0% (n=6,237) were related to extra-hepatic cancer. The leading causes of extra-hepatic cancer was lung cancer (24.3%, n=1,513) and pancreatic cancer (22.5%, n=1,402). Table 1 shows five-year cumulative incidence rates and cause-specific mortality by cirrhosis stage and etiology. For compensated cirrhosis, cured HCV and ALD had similar LR and NLR mortality rates, while MASLD had higher NLR mortality. This incremental risk for NLR mortality in MASLD was attributable to a 66% higher risk for extra-hepatic cancer (HR 1.66 vs. cured HCV, 95% CI, 1.11-2.48). In patients with decompensated cirrhosis, LR mortality predominated across all etiologies. However, patients with MASLD had a lower risk of experiencing LR death and a higher risk of experiencing NLR death than other groups. For example, patients with decompensated cirrhosis due to MASLD had a 75% higher risk of dying from CVD and a 2-fold higher risk of dying from extra-hepatic cancers than patients with cured HCV (HR, 2.07, 95% CI, 1.39-3.07). **Conclusion:** Our study highlights significant differences in cause-specific mortality among cirrhosis patients, with varying risks based on etiology. The findings emphasize the need for tailored management strategies, particularly for those with MASLD, to address the distinct risks of LR and NLR deaths.

Table 1. Five-year cumulative incidence rates and cause-specific mortality in patients with cirrhosis by etiology and cirrhosis stage. Hazard ratios (HR) adjusted for age, gender, and race and ethnicity.

	Liver-related Death				Non-liver-related Death					
	All Liver-related		Hepatobiliary Cancer		All Non-liver-related		Cardiovascular Death		Extra-hepatic Cancer	
	5-year Cumulative incidence (95% CI)	Adjusted HR (95% CI)	5-year Cumulative incidence (95% CI)	Adjusted HR (95% CI)	5-year Cumulative incidence (95% CI)	Adjusted HR (95% CI)	5-year Cumulative incidence (95% CI)	Adjusted HR (95% CI)	5-year Cumulative incidence (95% CI)	Adjusted HR (95% CI)
Compensated Cirrhosis										
Cured HCV	0.17 (0.14-0.19)	Reference	0.04 (0.02-0.05)	Reference	0.11 (0.09-0.13)	Reference	0.05 (0.04-0.07)	Reference	0.03 (0.02-0.04)	Reference
Cured HCV+ALD	0.20 (0.18-0.22)	1.11 (0.95-1.31)	0.05 (0.04-0.06)	1.37 (0.89-2.12)	0.17 (0.15-0.19)	**1.62 (1.27-2.06)**	0.06 (0.04-0.07)	1.17 (0.78-1.75)	0.05 (0.04-0.07)	1.77 (1.09-2.88)
ALD	0.18 (0.17-0.19)	0.87 (0.74-1.02)	0.04 (0.04-0.05)	1.17 (0.81-1.67)	0.12 (0.11-0.12)	1.07 (0.87-1.32)	0.04 (0.04-0.05)	0.84 (0.61-1.16)	0.03 (0.03-0.04)	1.09 (0.72-1.65)
MASLD	0.14 (0.14-0.15)	1.02 (0.86-1.21)	0.02 (0.02-0.03)	0.72 (0.50-1.02)	0.13 (0.13-0.14)	**1.22 (1.00-1.49)**	0.05 (0.05-0.05)	1.00 (0.74-1.37)	0.05 (0.05-0.05)	1.66 (1.11-2.48)
Decompensated Cirrhosis										
Cured HCV	0.67 (0.64-0.70)	Reference	0.44 (0.41-0.48)	Reference	0.10 (0.08-0.12)	Reference	0.05 (0.04-0.07)	Reference	0.03 (0.02-0.05)	Reference
Cured HCV+ALD	0.68 (0.66-0.70)	0.67 (0.64-0.70)	0.44 (0.41-0.47)	1.00 (0.87-1.15)	0.11 (0.10-0.13)	1.23 (0.96-1.57)	0.04 (0.03-0.06)	0.81 (0.53-1.24)	0.04 (0.03-0.05)	1.24 (0.76-2.01)
ALD	0.58 (0.57-0.58)	0.68 (0.66-0.70)	0.32 (0.31-0.33)	**0.65 (0.58-0.72)**	0.12 (0.11-0.12)	1.06 (0.86-1.30)	0.05 (0.05-0.06)	0.87 (0.63-1.21)	0.03 (0.03-0.04)	0.93 (0.62-1.40)
MASLD	0.39 (0.39-0.40)	0.58 (0.57-0.58)	0.14 (0.13-0.14)	**0.27 (0.24-0.30)**	0.23 (0.23-0.24)	**1.95 (1.60-2.39)**	0.11 (0.11-0.11)	**1.75 (1.28-2.41)**	0.08 0.07-0.08)	**2.07 (1.39-3.07)**

Disclosures: George Cholankeril: Nothing to Disclose, Yan Liu: Nothing to Disclose, Kavish Patidar: Madrigal Pharmaceuticals: Medical Advisory Board, Tzu-Hao Lee: Nothing to Disclose, Ruben Hernaez: Nothing to Disclose, Abbas Rana: Nothing to Disclose, Thom Taylor: Nothing to Disclose, Jennifer Kramer: Nothing to Disclose, Hashem El-Serag: Nothing to Disclose, Fasiha Kanwal: Nothing to Disclose

2385 | CUMULATIVE DOSE AND DURATION OF STATIN USE ARE ASSOCIATED WITH A REDUCED RISK OF LIVER CANCER AFTER ADJUSTING FOR AGE, FIB-4 SCORE, AND PRIOR CIRRHOSIS DIAGNOSIS IN MASLD PATIENTS; A 10-YEAR COHORT STUDY

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Background: Statins are associated with reduced risks of cirrhosis and hepatocellular carcinoma in patients with NAFLD. Our recent analysis showed greater protection against cirrhosis by statins among older NAFLD patients. In this MASLD cohort study, we aimed to elucidate the association between statin use and the incidence of primary liver cancer (PLC), characterizing the effects of statins by age, sex, and their relation to hepatic fibrosis risk. **Methods:** We identified a MASLD cohort between 2007 and 2009 (baseline period), applying the validated algorithm (PMID: **30144434)** to the VA EHR and selecting patients with at least one metabolic feature at baseline. The cohort was followed for up to 10 years for incident PLC, defined by ICD codes. In addition to baseline demographics, the following were collected at baseline and during follow-up: BMI, comorbidities, relevant co-medications, FIB-4 scores, previous cirrhosis diagnosis (Dx), and statin dose and duration. Patients were censored at the diagnosis of other chronic liver diseases, excess alcohol use, death without prior PLC diagnosis, or loss of follow-up. Cox proportional hazards regression models, with and without time-dependent covariates, were used to associate incident PLC with statin use at baseline and during follow-up, respectively, in the total population and by age (65 years) and sex subgroups. **Results:** A total of 329,577 MASLD pts at baseline were included in the analysis (prevalent PLC cases, incident PLC within one-year follow-up, and those lacking follow-up data post-index date were excluded). Median age was 62 years, predominantly males (92%), and White (78%), median BMI of 31.6 kg/m2, 40% were diabetic, and 66% were on statins at baseline. Over a median follow-up of 118 [50, 121] months, the cumulative incidence of PLC was 8.6% vs. 0.8% for those with and without prior cirrhosis diagnosis, respectively. Variations by sex and age groups were summarized in the table. After adjusting for potential confounders, baseline statin use was associated with a 28% lower risk of PLC development (HR [95%CI]: 0.72 [0.64,0.81]). In the models with time-dependent covariates, higher cumulative dose/longer duration were associated with lower risk of PLC, with the highest dose/longest duration category vs. no statin use showing HR [95%CI] of 0.46 [0.40,0.54] and HR [95%CI] of 0.51 [0.45,0.58] ($p<0.05$), respectively. The addition of time-dependent cirrhosis Dx variable to the model did not significantly alter the protective effects of statins; HR [95%CI] of the highest dose/longest duration category vs. no statin use were 0.58 [0.50,0.68] and 0.61 [0.53, 0.69], respectively. **Conclusion:** Statin use showed protection against PLC after adjusting for age, sex, baseline cirrhosis Dx, and other clinical confounders. Interestingly, adjustment for FIB-4 score or new cirrhosis Dx during follow-up did not significantly reduce the protective effect of statins.

Table. Summary of the cumulative incidence of primary LC overall, by age of 65 years old and sex.

	History of Cirrhosis Dx (n=1,556) Cumulative incidence (%)	No history of Cirrhosis Dx (n=328,012) Cumulative incidence (%)
Overall	**8.6%**	**0.8%**
Women	**6.6%**	**0.3%**
Women ≤65 yo	4.5%	0.3%
Women >65yo	12.5%	**0.4%**
Men	**8.7%**	0.8%
Men ≤ 65 yo	8.9%	0.7%
Men > 65 yo	8.5%	1.1%

Disclosures: Georgia Sofia Karachaliou: Nothing to Disclose, Amy Perkins: Nothing to Disclose, Chad Dorn: Nothing to Disclose, Qingyi Wei: Nothing to Disclose, Xiaoming Xu: Nothing to Disclose, Sheng Luo: Nothing to Disclose, Glenn Gobbel: Nothing to Disclose, Ruth Reeves: Nothing to Disclose, Mustafa Bashir: Rectify Pharma: Consultant, Siemens Healthineers: Grant/Research Support, Bayer Healthcare: Grant/Research Support, Madrigal Pharmaceuticals: Grant/Research Support, Corcept Therapeutics: Grant/Research Support, Carmot Therapeutics: Grant/Research Support, Manal Abdelmalek: Madrigal: Advisor, Madrigal, Gilead, Inventiva, Hanmi, Oasis, 89BIo: Grant/Research Support, Madrigal, Inventiva, Novo Nordisk, 89Bio, Intercept: Advisor, Hanmi: Consultant, 89BIo: Advisor, Anna Mae Diehl: >$10,000 relationship with Tune Therapeutics; Has not ended; <$10,000 relationship with Boehringer Ingelheim; Has not ended; Associate Editor, < $10,000 relationship with EASL - Journal of Hepatology; Has not ended; >$10,000 relationship with HeptaBio; Has not ended, Ayako Suzuki: Nothing to Disclose

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2386 | HEALTH GOAL COACHING IS ASSOCIATED WITH HIGHER HEALTH GOAL MOTIVATION AND SATISFACTION IN PARTICIPANTS AT RISK FOR METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD)

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Background: MASLD is associated with type 2 diabetes mellitus (T2D) causing significant mortality and morbidity. Lifestyle intervention is effective but difficult to achieve. Our aim was to evaluate whether patient health goal coaching (HGC) compared with usual care resulted in goal attainment, motivation and satisfaction. **Methods:** Patients with steatotic liver disease (SLD) and insulin resistance (fasting fingerstick glucose ≥ 100, fingerstick hemoglobin A 1c (hbA1c) ≥ 5.8, or HOMA-IR) were recruited for pilot HGC program. Patients with excessive alcohol consumption and other liver diseases or overt T2D were excluded. Participants were randomized to 14 weeks of remote HGC or standard clinical care (control), and scheduled for remote coaching and 5 in-person visits (clinical exam, exercise testing, blood draw for glucose and hbA1c) through 6 months post intervention. Goal satisfaction and motivation were each rated on a Likert scale of 1-7 (1=low, 7=high). Pearson correlations, chi square contingency tables and independent t-tests were run. **Results:** Sixty-five participants [51.7±13.1 years, 60.7% female, BMI 32.0±3.80, 37.3±6.0% body fat, 104±9 fasting glucose, 5.6±0.4 HbA1c] not differing significantly by sociodemographic, metabolic, or cardiovascular measure were randomized. At the end of 14 weeks intervention, motivation was significantly higher in HGC group (5.0±1.8 vs 3.6±1.6, p=0.024). This improvement persisted at 3-month post-intervention follow-up (5.4±1.5 vs 3.5±1.3, p=0.004). Female subjects reported significantly higher satisfaction by week 14 (6.3±0.8 vs 5.3±1.4, p=0.011). At 6-month after intervention, HGC group reported significantly more health goal satisfaction (6.4±0.7 vs 5.5±0.9, p=0.041). Goal satisfaction significantly correlated with goal motivation (Pearson's r 0.434, p=0.009 (95% CI 0.670-0.118)). Serum glucose levels were associated with improved goal satisfaction (p<0.05). **Conclusion:** HGC for self-selected health goals can lead to higher and sustained motivation and satisfaction in patients with SLD. This approach may lead to more effective lifestyle intervention programs to manage patients with SLD.
Disclosures: Jillian Price: Nothing to Disclose, Sai Greeshma Gayam: Nothing to Disclose, Diborah Gutema: Nothing to Disclose, Carey Escheik: Nothing to Disclose, Ali Weinstein: Nothing to Disclose, Leyla de Avila: Nothing to Disclose, Lynn Gerber: Nothing to Disclose, Zobair Younossi: Nothing to Disclose

2387 | HEALTHCARE PROVIDERS' PERSPECTIVES ON NEW METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD) NOMENCLATURE

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Background: Despite the increasing global burden of nonalcoholic fatty liver disease (NAFLD) and important gains in the field including the change in nomenclature, providers' awareness of these changes may be limited. In this cross-sectional study, we aimed to understand perspectives on new MASLD nomenclature among healthcare providers. **Methods:** A REDCap survey containing 35 questions covering 2 domains (clinical practice and level of understanding of new NAFLD terminology) were completed electronically by hospitalists, hepatologists, gastroenterologists, endocrinologists, and primary care physicians at Virginia Commonwealth University. Between February and May 2024, 41 surveys were completed (Internal Medicine (26, 65.0%), Primary Care (3, 7.5%), Gastroenterology (1, 2.5%), Hepatology (5, 12.5%), Endocrinology (5, 12.5%)). **Results:** Most responders (34.1%) see 5-9 NAFLD patients monthly. Their primary source of NAFLD knowledge is practice guidelines (66.7%). A significant majority of providers (92.7%) are aware of the NAFLD nomenclature change. Nearly half (46.3%) understand the meaning of MASLD, while 17.1% need more information, and 14.6% are unfamiliar with the term (Table 1). When it comes to understanding the reasons behind the change, 46.3% have slight understanding, 17.1% moderate, 14.6% none, and only 9.8% understand extremely well. Most providers (45%) agree with the MASLD term. Over half (51.2%) find MASLD useful, but 36.6% are unsure, and 12.2% disagree. Currently, 51.2% of responders are using the term MASLD in practice. Most responders (61%) believe

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the terminology change will not impact their practice, while a minimal 2.4% foresee a positive impact. A majority (53.7%) anticipate a slightly positive effect on patient understanding and management. Levels of comfort in explaining MASLD to patients vary: 7.3% very uncomfortable, 19.5% somewhat uncomfortable, 29.3% neutral, 26.8% comfortable, and 17.1% very comfortable. Regarding patient perception, 60% predict no significant change, 25% a positive change, and 15% a negative change due to the new term. The main challenges for using the new term as identified by 68% of providers relate to patient education, health literacy, billing, documentation, and discomfort of change. Nonetheless, most providers (80.5%) plan on using the new term in the future.
Conclusion: The perception of NAFLD nomenclature change varies among providers, highlighting the need for educational interventions to improve acceptance and adoption of the new MASLD nomenclature.

Question	Internal Medicine, n (%)	Primary Care, n (%)	Gastroenterology, n (%)	Hepatology, n (%)	Endocrinology, n (%)	P values*
To what extent are you familiar with the term 'Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD)'?						
I am unfamiliar with this term	3 (7.3%)	1 (2.4%)	0	0	1 (2.4%)	0.008
I have heard of it but need more information	7 (17.1%)	0	0	0	0	0.008
I understand its meaning	14 (34.1%)	2 (4.9%)	1 (2.4%)	0	2 (4.9%)	0.008
I am well-versed in its implications	2 (4.9%)	0	0	5 (12.2%)	2 (4.9%)	0.008
How well do you understand the reasons behind the proposed change?						
Not at all	6 (14.6%)	0	0	0	0	0.002
Slightly	14 (34.1%)	2 (4.9%)	0	0	3 (7.3%)	0.002
Moderately	5 (12.2%)	1 (2.4%)	0	0	0	0.002
Very well	1 (2.4%)	0	1 (2.4%)	2 (4.9%)	1 (2.4%)	0.002
Extremely well	0	0	0	3 (7.3%)	1 (2.4%)	0.002
Do you agree with the new terminology "(MASLD)"?						
Strongly Disagree	0	1 (2.4%)	0	0	0	0.003
Disagree	4 (9.8%)	0	0	0	0	0.003
Neutral	19 (46.3%)	0	1 (2.4%)	1 (2.4%)	3 (7.3%)	0.003
Agree	3 (7.3%)	1 (2.4%)	0	3 (7.3%)	2 (4.9%)	0.003
Strongly Agree	3 (7.3%)	0	0	0	1 (2.4%)	0.003
How do you think the change will impact your practice?						
Negative impact	0	1 (2.4%)	0	0	0	0.020
Slightly negative	1 (2.4%)	0	0	1 (2.4%)	0	0.020
No impact	17 (41.5%)	0	0	3 (7.3%)	4 (9.8%)	0.020
Slightly positive	8 (19.5%)	2 (4.9%)	1 (2.4%)	1 (2.4%)	0	0.020
Positive impact	0	0	0	0	1 (2.4%)	0.020
How comfortable are you explaining the new terminology to patients?						
Very Uncomfortable	2 (4.9%)	0	0	0	1 (2.4%)	0.183
Somewhat Uncomfortable	6 (14.6%)	2 (4.9%)	0	0	0	0.183
Neutral	9 (21.9%)	0	0	0	2 (4.9%)	0.183
Comfortable	7 (17.1%)	0	1 (2.4%)	2 (4.9%)	1 (2.4%)	0.183
Very Comfortable	2 (4.9%)	1 (2.4%)	0	3 (7.3%)	1 (2.4%)	0.183
Do you believe the updated nomenclature will positively influence research and scientific publications related to NAFLD?						
Strongly Disagree	0	1 (2.4%)	0	0	0	0.222
Disagree	1 (2.4%)	0	0	0	0	0.222
Neutral	17 (41.5%)	1 (2.4%)	0	3 (7.3%)	3 (7.3%)	0.222
Agree	8 (19.5%)	1 (2.4%)	1 (2.4%)	2 (4.9%)	2 (4.9%)	0.222
Strongly Agree	0	0	0	0	0	0.222
Do you plan on using the new term "MASLD" in the future?						
Yes	22 (53.7%)	1 (2.4%)	1 (2.4%)	5 (12.2%)	3 (7.3%)	0.217
No	1 (2.4%)	1 (2.4%)	0	0	0	0.217
Not sure	3 (7.3%)	1 (2.4%)	0	0	2 (4.9%)	0.217

**p values returned by Pearson's chi-square test.*

Disclosures: Somaya Albhaisi: Nothing to Disclose, Omar Albhaisi: Nothing to Disclose

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2388 | SODIUM-GLUCOSE COTRANSPORTER-2 INHIBITORS AND THE RISK OF HEPATOCELLULAR CARCINOMA AMONG PATIENTS WITH TYPE 2 DIABETES, METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE, AND OBESITY: A LARGE POPULATIONBASED COHORT STUDY

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Background: Hepatocellular carcinoma (HCC) incidence rates have been rising and are predicted to rise due to the role metabolic dysfunction-associated steatotic liver disease (MASLD) plays in HCC development. This is further impacted by the increasing incidence of obesity and type 2 diabetes (T2DM) worldwide. There has been a growing interest in the effects of antidiabetic drugs, such as glucagon-like peptide-1 receptor agonists (GLP-1RAs) and sodium-glucose cotransporter-2 inhibitors (SGLT-2i), on reducing hepatic fat content beyond their glucose-lowering effects. The association between antidiabetic medications and HCC risk has not been explored at a population level. Thus, we aimed to investigate the association between GLP-1RAs, SGLT-2i, and HCC among patients with MASLD, T2DM, and obesity. **Methods:** This population-based, retrospective cohort study used the TriNetX database to identify consecutive adult patients diagnosed with MASLD, T2DM, and obesity from 2012 to 2022. Cohort entry was defined as the date of the first-ever prescription for one of the drugs of interest, GLP-1 RA or SGLT-2i, compared to other antidiabetic drugs during the study period. A lag of 6 months for all exposures to minimize protopathic bias as well as a 1:1 propensity score matching (PSM) for demographics, body mass index (BMI), comorbidities, laboratory parameters, and medication to reduce confounding effects. The primary outcome was the new incidence of HCC. A secondary and sensitivity analysis assessed the robustness of the findings. Cox proportional hazard models were used to estimate hazard ratios (HR). **Results:** In this cohort, 425,641 patients received GLP-1A treatment, 353,887 received SGLT-2i treatment, and 352,098 received DPP-4i and were included after PSM matching (341,015 patients). The new incidence of HCC was lower among new users of GLP1-RA (HR 0.41). SGLT2i (353,051 patients after PSM) was associated with lower HCC risk (HR: 0.33) than DPP-4i. (Table 1). However, there was no difference in the HCC incidence (HR 1.10) between the GLP-1RA and SGLT2i groups. The secondary analysis by increasing lag exposure of drugs and sensitivity analyses by excluding patients with outcomes 2 years after the index event remained consistent with the **Results:** generated in the primary analyses. **Conclusion:** The findings suggest that new users of GLP1-RA or SGLT2i were associated with lower risks of HCC, and both appeared safe and efficacious drugs. These initial results should be confirmed in a larger randomized clinical trial to optimize therapeutic strategies for this growing patient population.

Table 1: Incidences of Hepatocellular Carcinoma Between the New Users of GLP-1RA, SGLT-2i, and DPP-4i Among Patients with MASLD, Obesity, and Type 2 Diabetes

Event and Treatment Group	Patients with Event, N	Hazard Ratio (95% CI)
Cohort 1:		
GLP1-RA (n=341015)	1203	0.41 (0.29 – 0.60)
DPP-4i (n=341015)	1897	
Cohort 2:		
SGLT-2i (n= 353051)	2894	0.33 (0.24 – 0.49)
DPP-4i (n= 353051)	2079	
Cohort 3:		
SGLT-2i (n= 321455)	1220	1.10 (0.86 - 1.40)
GLP-1RA (n= 321455)	1194	

Abbreviations: MASLD, metabolic dysfunction-associated steatotic liver disease; GLP-1RA, glucagon-like peptide 1 receptor agonists; SGLT-2, sodium-glucose cotransporter-2 inhibitors; DPP-4i, dipeptidyl peptidase-4 inhibitors

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Disclosures: Arunkumar Krishnan: Nothing to Disclose, Diptasree Mukherjee: Nothing to Disclose, Faisal Abaalkhail: Nothing to Disclose, Aldanah Althwanay: Nothing to Disclose, Tinsay Woreta: Nothing to Disclose, Saleh Alqahtani: Nothing to Disclose

2389 | PRIMARY CARE BASED IMPLEMENTATION OF ELECTRONIC CLINICAL DECISION SUPPORT FOR METABOLIC DYSFUNCTION ASSOCIATED STEATOTIC LIVER DISEASE IMPROVES CARE DELIVERY INDEPENDENT OF PATIENT DEMOGRAPHICS AND CLINICAL FACTORS: A PROSPECTIVE IMPLEMENTATION STUDY

Ashley Spann[1] Kristy Bishop[2] Sarah Marbach[1] Asli Weitkamp[1] Shane Stenner[1] Scott Nelson[1] Xiangyu Ji[1] Christopher Slaughter[1] Christine Lopez[1] Cecelia Theobald[1] Manhal Izzy[1]

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Background: Clinical guidelines recommend screening & risk stratification for metabolic dysfunction associated steatotic liver disease (MASLD) in primary care settings to promote earlier detection & management of advanced liver disease. Given the complexities of clinical workflows within primary care, additional tools are needed to better support providers. We aimed to assess the implementation of an electronic health record (EHR) embedded electronic clinical decision support system (eCDSS) during primary care visits. **Methods:** We performed a prospective, before-after study of patients with an existing MASLD diagnosis (by code or problem list) seen at a single primary care clinic within an academic medical center over an 11-month period. Liver transplant recipients and patients seen by a hepatologist within prior 3 years were excluded. During implementation, patients were classified into one of four categories with an appropriate corresponding alert presented to providers to guide subsequent care. These alerts prompted providers to utilize a customized MASLD order set providing patient-specific recommendations for the following 4 categories: 1) missing screening labs within the past 1 year to calculate FIB4 (AST, ALT, platelets); 2) abnormal liver chemistry for those with abnormal transaminases; 3) normal labs with an abnormal calculated FIB4 > 1.3; and 4) normal labs with a normal calculated FIB4 < 1.3. Provider actions were assessed both prior to and after implementation, with appropriate actions (i.e., linkage to needed care) being considered as a new order for laboratory studies for FIB4 calculation (category #1), Hepatology referral (category #2), an imaging based elastography study (category #3), or weight loss counseling (category #4), in accordance with society guidelines. Odds ratios for adherence to recommendations were estimated using logistic regression fit by generalized estimating equations clustering on subject and controlling for age, race, gender, diabetes status and body mass index (BMI). **Results:** 503 patient encounters occurred during the study accounting for 347 unique patients, with 263 visits occurring pre-implementation and 240 visits after implementation. Implementation of eCDSS significantly increased the odds of adherence to guideline-based recommendations independent of age, race, gender, diabetes status and BMI (OR 2.06, CI 1.4-3.0, p < 0.001) (Table 1). Hepatology referrals increased significantly by 10% post-implementation for abnormal liver chemistry patients and less than 5% overall for all patients (p = 0.011). **Conclusion:** Implementation of MASLD-specific eCDSS significantly improves guideline-directed management of patients with MASLD within primary care settings independent of various risk factors. Utilization of EHR functionality provides a scalable opportunity for advancing care delivery for MASLD outside of hepatology-centric settings for patients with MASLD.

Table 1: Guideline Adherence per Visit Before and After Implementation of Steatotic Liver Disease Clinical Decision Support Tools

	Before Implementation N = 263 *n (%)*	After Implementation N = 240 *n (%)*	p-value
MASLD Diagnosis Added to Visit Encounter	23 (8.7%)	36 (15%)	**0.029**
Hepatology Referral Ordered (All Categories)	6 (2.3%)	17 (7.1%)	**0.011**
Provider Adherence to Guideline Recommendations	78 (29.7%)	110 (45.8%)	**<0.001**
Missing Labs	110 (41.8%)	86 (35.8%)	
Recommended Action: Order FIB4 Labs	51/110 (46.4%)	65/86 (75.6%)	
Abnormal Liver Chemistry	76 (28.9%)	86 (35.8%)	
Recommended Action: Hepatology Referral	3/76 (4.0%)	12/86 (14.0%)	
Normal Labs, Abnormal FIB4	25 (9.5%)	16 (6.7%)	
Recommended Action: Order Elastography	0/25 (0%)	4/16 (25%)	
Normal Labs, Normal FIB4	52 (19.8%)	52 (21.7%)	
Recommended Action: Weight Loss Recommendations, No Further Testing	24/52 (46.2%)	29/52 (55.8%)	

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2390 | ALL-CAUSE MORTALITY DIFFERS BETWEEN STEATOTIC LIVER DISEASE SUBTYPES: RESULTS FROM A PROSPECTIVE COHORT OF 16,560 ADULTS IN CANADA

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Background: Steatotic Liver Disease (SLD) has emerged as a significant public health concern due to its increasing prevalence and potential to contribute to severe health outcomes. This study investigates the relationship between three SLD subtypes: MASLD, MetALD and ALD and all-cause mortality. **Methods:** We used data from the Canadian Longitudinal Study on Aging (n=30,097), a cohort that prospectively follows adults between 45-85 years old from 11 sites across Canada. Steatosis was identified using the serum NAFLD Ridge Score (NRS), based on ALT, HDL cholesterol, triglycerides, hemoglobin A1c, leukocyte count, and hypertension. NRS was validated against proton magnetic resonance spectroscopy with a dual cut-off of <0.24 to rule out and >0.44 to rule in steatosis with a sensitivity of 92% and specificity of 90%. At baseline, we identified participants as MASLD, MetALD and ALD using AASLD's SLD definitions. A weighted Cox proportional hazard model was used to evaluate the association between the subtypes (compared to no steatosis) and all-cause mortality adjusted for sociodemographic factors (age, sex and income); sociodemographic+lifestyle factors (diet, exercise and smoking) and sociodemographic+lifestyle+cardiometabolic factors (T2DM, hypertension, obesity and dyslipidemia). **Results:** Between 2012 and 2021, after exclusions, 16,560 participants were included in the study (52.1% female, median age 58 years (IQR: 51-66)). MASLD was the most prevalent subtype (n=8430), followed by MetALD (n=666), and then ALD (n=144) (Figure). A total of 961 participants died during a median follow-up time of 5.8 years. After adjustment for sociodemographic factors, we found that adults with MASLD (adjusted hazard ratio (aHR) 1.5; 95% CI 1.2-1.9) and ALD (aHR 5.3; 1.9, 13.3) had a higher risk for all-cause mortality compared to patients without steatosis while adults with MetALD did not (aHR 1.3; 0.80, 2.11). After adjustment for sociodemographic and lifestyle factors, the elevated mortality risk remained significant for MASLD (aHR 1.4; 1.1-1.8) and ALD (aHR 3.9; 1.5-10.2). Additionally, controlling for cardiometabolic conditions attenuated the risk of all-cause mortality for MASLD (aHR 1.3; 0.9-1.8); however, having diabetes (aHR 2.1; 1.7-2.7), ALD (aHR 4.5; 1.7-11.8) were significant. **Conclusion:** MASLD contributed to a higher attributable fraction of deaths compared to other subtypes. However, the ALD group had a significantly worse prognosis, highlighting the dual role of metabolic steatosis and alcohol use disorder on mortality.

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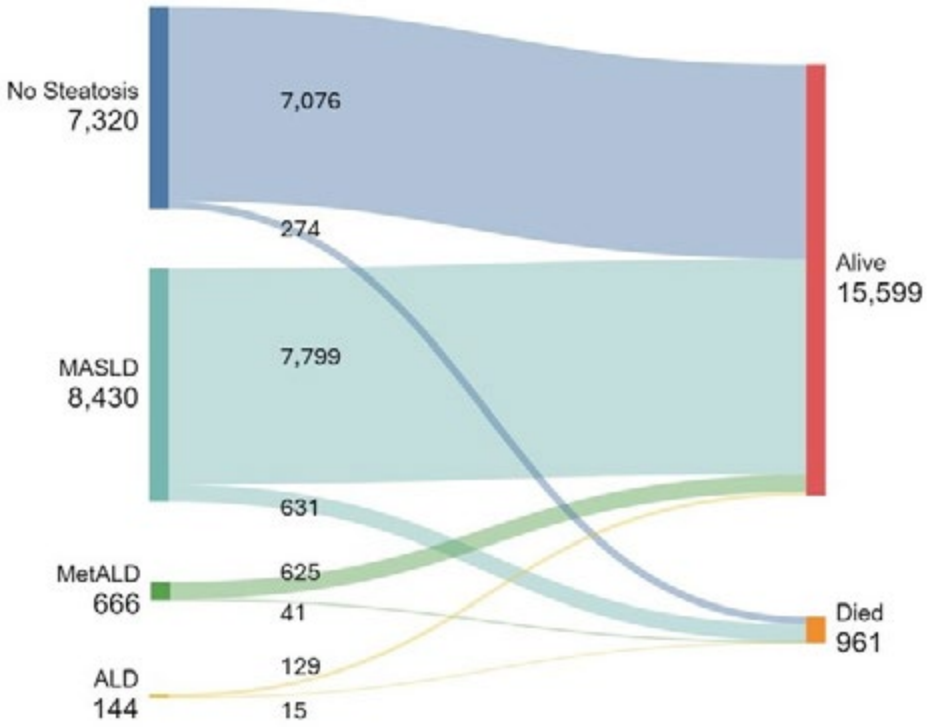

Disclosures: Jessica Burnside: Nothing to Disclose, Giada Sebastiani: Novo Nordisk: Consultant, Abbvie: Speaking and Teaching, Merck: Consultant, Gilead: Speaking and Teaching, Theratechnologies Inc.: Grant/Research Support, Keyur Patel: Novo-Nordisk: Consultant, Gilead Sciences: Consultant, Merck: Consultant, Resalis: Advisor, Alnoor Ramji: Nothing to Disclose, Mark Swain: Ipsen: Advisor, Abbott: Advisor, Advanz: Advisor, Novo Nordisk: Advisor, GSK: Advisor, Ipsen: clinical trial research grant support, Novo Nordisk: clinical trial research grant support, Madrigal: clinical trial research grant support, Kowa: clinical trial research grant support, Gilead: clinical trial research grant support, Abbvie: clinical trial research grant support, Merck: clinical trial research grant support, Galectin: clinical trial research grant support, Sahar Saeed: Novo Nordisk: Consultant

2391 | STATIN USE WITH CARDIOVASCULAR DISEASE AND ALL-CAUSE MORTALITY IN PATIENTS WITH HYPERTENSION, METABOLIC DYSFUNCTION-ASSOCIATED LIVER DISEASE, AND OBESITY: A POPULATION-BASED COHORT STUDY

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Background: Cardiovascular (CV) disease remains the leading global cause of disease burden and mortality among patients with metabolic dysfunction–associated liver disease (MASLD). Hypertension (HTN) and MASLD are common CV risk factors and are closely related to metabolic syndrome. MASLD and HTN have reached epidemic proportions in parallel to obesity. The effectiveness of statins in patients with HTN, MASLD, and obesity remains unclear. Similarly, the association between statins and the risks of CVD and mortality has not been explored in these patients. Thus, we aimed to examine the association between statins and major adverse CV events (MACE) and mortality among patients with HTN, MASLD, and obesity. **Methods:** This population-based cohort study used the global health research network to identify consecutive patients with HTN, MASLD, and obesity from 2012 to 2022. Cohort entry was defined as the date of the first-ever prescription for statins (statin users). A lag of 6 months for all exposures to minimize protopathic bias was applied. All patients (>18 years) diagnosed with MASLD were identified after excluding other chronic liver disease etiologies. A 1:1 propensity score matching (PSM) was performed to reduce confounding effects. The primary outcomes were defined as the first incidence of new-onset heart failure (HF), composite MACE, and a composite cerebrovascular disease, and

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the secondary outcome was all-cause mortality. Sensitivity analysis assessed the robustness of the findings. Cox proportional hazard models were used to estimate hazard ratios (HR). **Results:** We identified 176,983 patients with HTN, MASLD, and obesity. Among these, 51481 received statins, with a median follow-up time of 5.1 years. After PSM, stain users and non-users (42,227 each) were well-matched. Statin use was associated with lowering the risk of CV outcomes, such as MACE (HR, 0.29), HF (HR, 0.94), and cerebrovascular diseases (HR, 0.87) (Table 1). All-cause mortality (HR, 0.85) was significantly lower in statin users. However, there was a significant interaction with sex with decreased risk of MACE for women but not for men (HR 0.66 vs. HR 1.09). These outcomes were consistent with a sensitivity analysis by estimating risk after excluding patients with outcomes within 1 year or 2 years after the index event. **Conclusion:** Among patients with HTN, MASLD, and obesity, statin users were significantly associated with a lower incidence of CV disease and reduced risk of mortality, which further supports current guidelines recommending statin use in patients with liver disease and high-risk populations. Our results emphasize their role as a crucial component in managing high-risk populations.

Table 1: Cardiovascular outcomes and all-cause mortality between the statin users vs. non-users in patients with hypertension, MASLD, and obesity

Outcomes	Statin Users (n=42227)	Non-Statin Users (n=42227)	Hazard Ratio (95% CI)[¥]
	Patients with events, N	Patients with events, N	
Primary outcome (cardiovascular diseases)			
MACE[+]	2246	1679	0. 29 (0.17-0.34)
HF	1056	897	0.84 (0.56-0.91)
Composite cerebrovascular disease[*]	789	457	0.77 (0.41-0.84)
Secondary outcome			
All-Cause Mortality	457	347	0. 85 (0.67-0.93)

Abbreviations: MASLD, metabolic dysfunction–associated liver disease; MACE, major adverse cardiovascular events; HF, heart failure.
[+]A composite endpoint of MACE was defined as the occurrence of myocardial infarction (ST-segment elevation myocardial infarction and non-ST elevation myocardial infarction), unstable angina, and ischemic heart disease.
[*]A composite endpoint of cerebrovascular disease was defined as the occurrence of stroke, carotid stenosis, transient ischemic attack, and carotid interventions or surgeries)
[¥]Adjusted for confounders such as demographics, BMI, smoking status, comorbid conditions, baseline blood pressure, laboratory parameters, and medications.

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2392 | FIBROSIS RISK STRATIFICATION IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE PATIENTS WITH DIABETES IN TAIWAN- A MULTI-CENTER COHORT STUDY

Jee-Fu Huang[1] Ming-Lun Yeh[1] Mei-Hsuan Lee[2] Chia-Yen Dai[1] Chung-Feng Huang[1] Ming-Lung Yu[3] Wan-Long Chuang[1]

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Background: Type 2 diabetes mellitus (T2DM) is commonly associated with steatotic liver disease (SLD). Metabolic dysfunction-associated steatotic liver disease (MASLD), the severe form of SLD, carries a high risk for T2DM. The study aimed to assess the risk of advanced fibrosis in MASLD patients with T2DM compared to the non-T2DM MASLD counterparts. We also aimed to investigate the risk factors predictive of advanced fibrosis in MASLD patients. **Methods:** We conducted a multi-center cohort study by recruiting SLD patients from a registry database in Taiwan. Those eligible MASLD patients were analyzed based on the current definition and the metabolic manifestations. We used inverse probability of treatment weighting (IPTW) as the propensity score method aiming to decrease the confounding bias and to balance the baseline characteristics. **Results:** A total of 1,692 MASLD patients (948 males, age= 55.4 ± 13.8 years) were recruited. There're 528 (31.2%) patients (307 males, age= 59.8 ± 12.7 years) with T2DM. There were T2DM (1,704, 50.2%) and non-T2DM (n= 1,691) groups

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after IPTW matching. Those T2DM patients were significantly older, had higher body mass index (BMI), and had a higher chance of hypertension and dyslipidemia than their non-T2DM counterparts. They also had a worse renal function and a lower platelet count than non-T2DM patients. The mean FIB-4 of DM patients was 1.5 ± 0.9, which was significantly higher than non-DM group (1.3 ± 1.3) (P< 0.001). The DM patients had a significantly higher proportion of advanced fibrosis (FIB-4> 2.67) than non-DM group (9.5% vs 5.4%, P= 0.007). Multivariate logistic regression analysis demonstrated that the major risk for advanced fibrosis was age >50 years (adjusted OR= 12.0, 95% CI= 6.4-22.1, P<0.001), followed by elevated ALT level (adjusted OR= 7.1, 95% CI= 3.2-16.7, P<0.001) and eGFR< 60 ml/min/1.73m^2 (adjusted OR= 3.3, 95% CI= 2.0-5.5, P<0.001). **Conclusion:** The DM MASLD patients carried a higher risk of advanced fibrosis than non-DM counterparts. Disease severity surveillance should be actively performed for those aged, patients with abnormal ALT level and impaired renal function.

Disclosures: Jee-Fu Huang: Roche: Consultant, Gilead: Consultant, Sysmex: Consultant, Aligos: Consultant, Abbvie: Speaking and Teaching, Gilead: Speaking and Teaching, Merck: Speaking and Teaching, Sysmex: Speaking and Teaching, Novo Nordisk: Speaking and Teaching, Ming-Lun Yeh: Nothing to Disclose, Mei-Hsuan Lee: Nothing to Disclose, Chia-Yen Dai: Nothing to Disclose, Chung-Feng Huang: Gilead Sience: Grant/Research Support, Ming-Lung Yu: Abbvie, Gilead and Roche diagnostics.: Grant/Research Support, Abbott, Abbvie, Gilead, Roche and Roche diagnostics: Consultant, Abbvie, BMS, Gilead, Roche and Roche diagnostics: Speaking and Teaching, Wan-Long Chuang: Gilead: Speaking and Teaching, AbbVie: Speaking and Teaching, BMS: Speaking and Teaching, Vaccitech: Consultant, PharmaEssentia: Consultant

2393 | HEPATIC FIBROSIS BUT NOT STEATOSIS IS ASSOCIATED WITH EARLY-STAGE/SUB-CLINICAL MARKERS OF HEART FAILURE IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE

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Background: How changes in subclinical markers of heart failure (HF) vary with hepatic fibrosis in compensated metabolic dysfunction-associated steatotic liver disease (MASLD) is understudied. Left atrial volume index (LAVi) is a marker of long-term increased cardiac filling pressures, hence an early-stage marker of HF. We explored associations between markers of cardiac structure in echocardiography (TTE) and markers of hepatic steatosis and fibrosis on vibration-controlled transient elastography (VCTE). **Methods:** Ambulatory patients with MASLD diagnosis enrolled into a longitudinal registry as of May 2022 also referred for TTE between May 2021-2024 were identified. LAVi, interventricular septum thickness (IVSD), and left ventricular ejection fraction (LVEF) were obtained from TTE, and controlled attenuation parameter (CAP), and liver stiffness measurement (LSM) from VCTE. Patients with LVEF <40% were excluded. Correlations and sub-group comparisons were performed with Spearman R and Kruskal-Wallis, latter using steatosis (CAP <288 dB/m, n=55 vs. >288, n=73) and fibrosis (LSM <8 kPa, n=74 vs. 8-12, n=26 vs. >12, n=31; FIB4 <1.3, n=64 vs. 1.3-2.66, n=43 vs. >2.67, n=24). **Results:** 131 MASLD patients (63% female) had a TTE, FIB4, and VCTE. Median age, body mass index, LAVi, IVSD, LVEF, CAP, LSM, FIB4, ALT, AST, and platelets were 61 years, 32.3 kg/m^2, 23.3 ml/m^2, 1 cm, 63%, 308 dB/m, 6.9 kPa, 1.31, 31 IU/L, 26 IU/L, 224 x 10^9/L, respectively. Age showed weak correlation with LAVi, IVSD, and LVEF (R= 0.19, 0.18, 0.16, respectively, p<0.05). Platelets, FIB4, and LSM showed significant associations with LAVi (R= -0.31, 0.28, 0.26, respectively, p<0.05). Multi-variate linear regression analysis of LAVi with age, platelets, FIB4, and LSM showed no independent association but collectively the four variables remained significant (p-value=0.002). When stratified for fibrosis and steatosis, LAVi was elevated in advanced fibrosis (FIB4 p-value=0.002, LSM p-value=0.002) but not steatosis (CAP p-value=0.95). **Conclusion:** LAVi correlates with hepatic fibrosis based on VCTE stiffness and FIB4, the latter of which could serve as a risk-stratification tool for cardiac outcomes in MASLD. Association of LAVi with fibrosis and platelets but not steatosis suggests a relationship between hepatic fibrosis, portal hypertension, and early-stage or sub-clinical heart failure. Larger MASLD cohorts are needed to explore a predictive role of LAVi linking liver and cardiac outcomes, especially in cirrhosis given competing risks.

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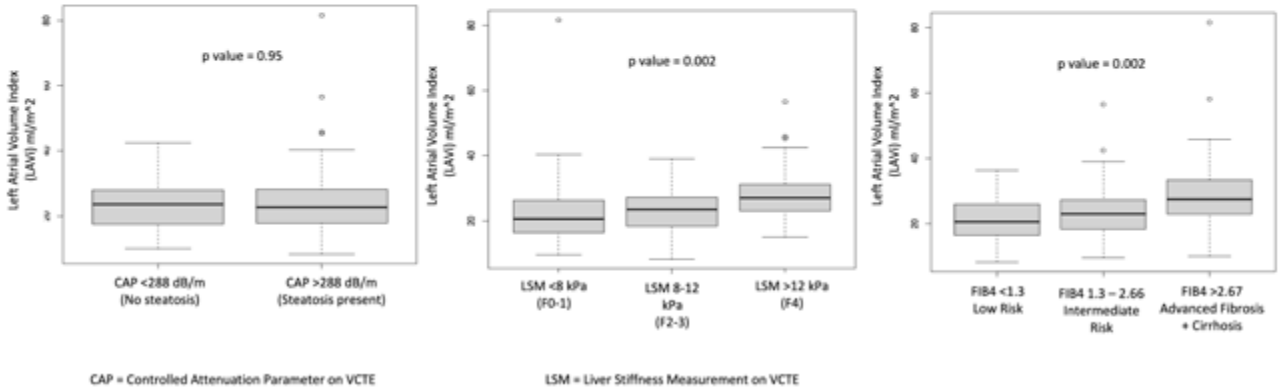
LAVi Is Elevated Based On Fibrosis, Not Steatosis (Kruskal-Wallis)



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2394 | ASSOCIATION OF SEVERITY OF METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE WITH GUT DYSBIOSIS AND SHIFT IN THE METABOLIC FUNCTION OF THE GUT MICROBIOTA IN PEOPLE WITH HIV

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Background: The progression of metabolic dysfunction-associated steatotic liver disease (MASLD) to its severe forms, including metabolic dysfunction-associated steatohepatitis (MASH) and liver fibrosis, is influenced by a combination of lifestyle and genetic factors. Recently, several studies have emphasized gut microbial dysbiosis as a key driver in this process.However, the role of gut dysbiosis in people with HIV (PWH), a population with a complex MASLD pathogenesis and at risk for severe liver disease, is not known. We aim to evaluate the association between gut dysbiosis and severe MASLD, that is, MASH and liver fibrosis, in PWH. **Methods:** PWH from a prospective Cohort, underwent liver stiffness measurement (LSM) with controlled attenuation parameter (CAP) by Fibroscan and the measurement of serum cytokeratin-18, a biomarker of hepatocyte apoptosis used to diagnose MASH. We included patients with a diagnosis ofMASLD, defined as CAP ≥238 dB/m without viral hepatitis coinfection or alcohol abuse. Severe MASLD was defined as presence of MASH (cytokeratin-18 ≥130.5 U/L) and/or significant liver fibrosis (LSM ≥7.1 kPa). Taxonomic composition of gut microbiota was determined using 16S ribosomal RNA gene sequencing of stool samples. PICRUSt-based functional prediction was employed. Bacterial and functional differences were assessed using a generalized linear model, with adjustment for age and sex as confounding factors, using a negative binomial distribution. **Results:** 34 patients with MASLD were enrolled (mean age 52 years, 15% females, mean LSM 6.7 kPa, mean cytokeratin-18 184 U/L). Among them, 32% had severe MASLD. After adjusting for age and sex, liver health status (severe MASLD yes vs. no) explained seven percentage of the overall variation (r2 = 0.07, p = 0.09) in bacterial composition. Several genera were found to be significantly different between PWH with severe MASLD. Participants with severe MASLD had increases of genera *Eubacterium*, *Bacteroides*, *Roseburia*, *Ruminococcus*, *Slackia*, *Holdemanella*, *Bilophila* and decreases of *Alloprevotella*, *Paraprevotella*, *Prevotella*, *Olsenella*, *Oribacterium*, *Romboutsia*, *Desulfovibrio*, *Dialister*. In severe MASLD, functional analysis revealed increases in fatty acid degradation and flavonoid biosynthesis, and decreases in pyrimidine metabolism, steroid biosynthesis, folate biosynthesis, and alanine, aspartate, glutamate metabolism. **Conclusion:** In PWH, MASLD severity is associated with gut dysbiosis and a shift in metabolic function of the gut microbiota. Some of these taxa are similar to those associated with MASLD in populations without HIV. Thus, gut microbiota analysis adds information to classical predictors of MASLD severity and suggests novel metabolic targets for pre-/probiotics therapies. Larger, longitudinal studies are needed to define the role of the gut microbiota in the pathogenesis of liver disease in this high risk population.

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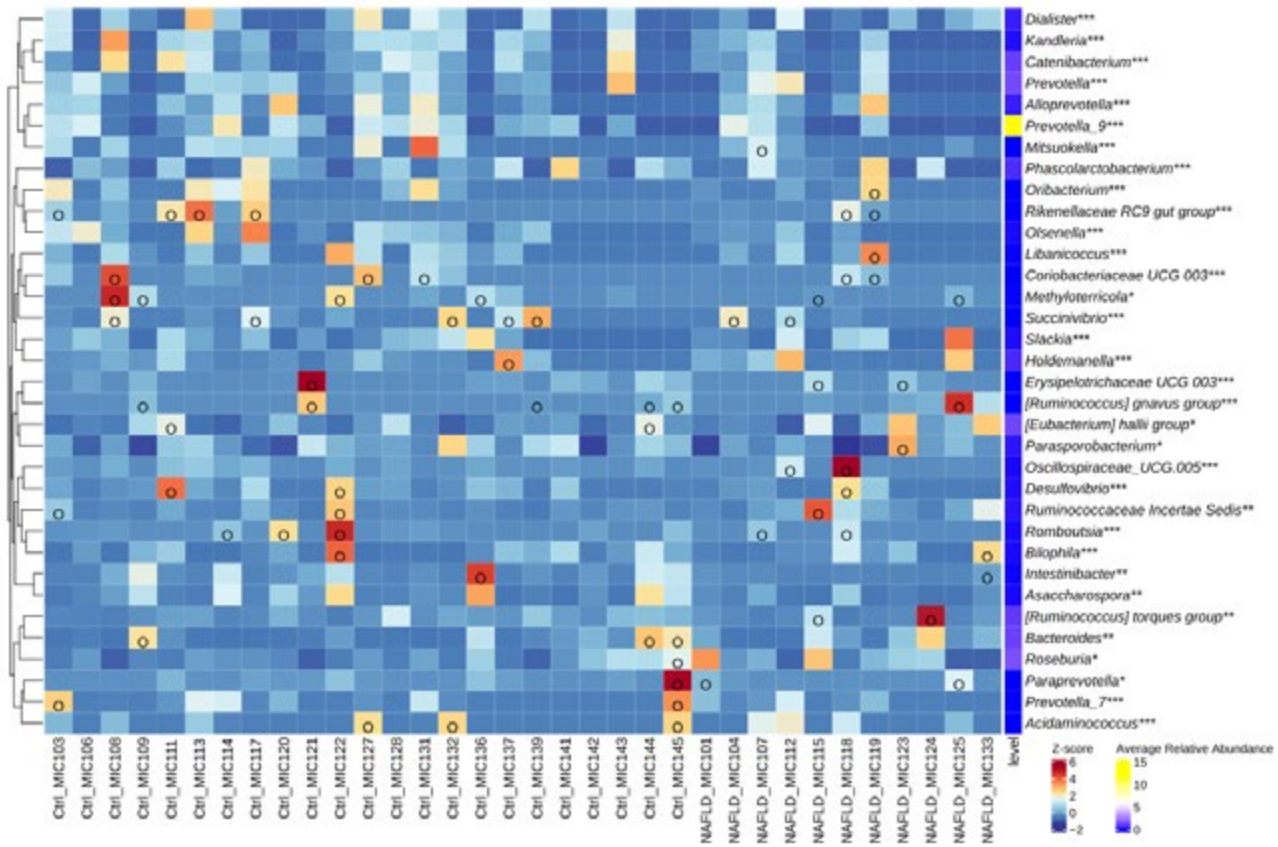

Disclosures: Luz Esther Ramos Ballesteros: Nothing to Disclose, Bertrand Lebouché: Merck Canada: Speaking and Teaching, Gilead: Speaking and Teaching, ViiV healthcare: Consultant, Gilead: ASAP study managed by RI-MUHC, Merck: I score study and core set study managed by RI-MUHC, ViiV: PIVHOT progra mfro patients managed by RI-MUHC, Jean-Pierre Routy: Nothing to Disclose, Marina Klein: Nothing to Disclose, Jason Szabo: Nothing to Disclose, Joseph Cox: Nothing to Disclose, Julian Falutz: EMD Sermon: Advisor, ViiV: Speaking and Teaching, Merck: Speaking and Teaching, Louis-Patrick Haraoui: Nothing to Disclose, Cecilia Costiniuk: Nothing to Disclose, Alexandra De Pokomandy: Nothing to Disclose, Felice Cinque: Nothing to Disclose, Tom Pembroke: Nothing to Disclose, Marco Constante: Nothing to Disclose, Manuela Santos: Nothing to Disclose, Giada Sebastiani: Novo Nordisk: Consultant, Abbvie: Speaking and Teaching, Merck: Consultant, Gilead: Speaking and Teaching, Theratechnologies Inc.: Grant/Research Support

2395 | NEW STEATOTIC LIVER DISEASE DIAGNOSTIC PERFORMANCE IN A CHILEAN AGRICULTURAL POPULATION COHORT ★

Maria Spencer Sandino[1] Laura Andrea Huidobro[2] Franco Godoy[1] Danilo Alvares[3] Juan Pablo Arab[4] Daniel Cabrera[5] Marco Arrese[1] Francisco Barrera[1] Catterina Ferreccio[1]

[1]Pontificia Universidad Católica de Chile, [2]Universidad Católica del Maule, [3]University of Cambridge, [4]Western University and London Health Sciences Centre, [5]Universidad de los Andes

Background: Non-alcoholic fatty liver disease (NAFLD) is the most prevalent liver disease globally, with rising rates, particularly in Latin America, due to the increasing tide of obesity and type 2 diabetes. Recognizing the limitations of NAFLD and the consequently suggested criteria for metabolic dysfunction-associated fatty liver disease (MAFLD), experts proposed a new nomenclature for conditions of excess liver fat in the liver. Steatotic Liver Disease (SLD) was chosen as an overarching term that encompasses all causes of liver steatosis within various health contexts. This study aims to assess the accuracy of SLD in identifying liver steatosis compared to NAFLD and MAFLD definitions. **Methods:** This is a cross-sectional study based on the Maule cohort (MAUCO). A prospective population-based cohort of adults ages 38 to 74 years, located in the Maule Region, Chile. Health conditions, socio-demographics, anthropometric measures, hepatic ultrasonography, blood pressure,

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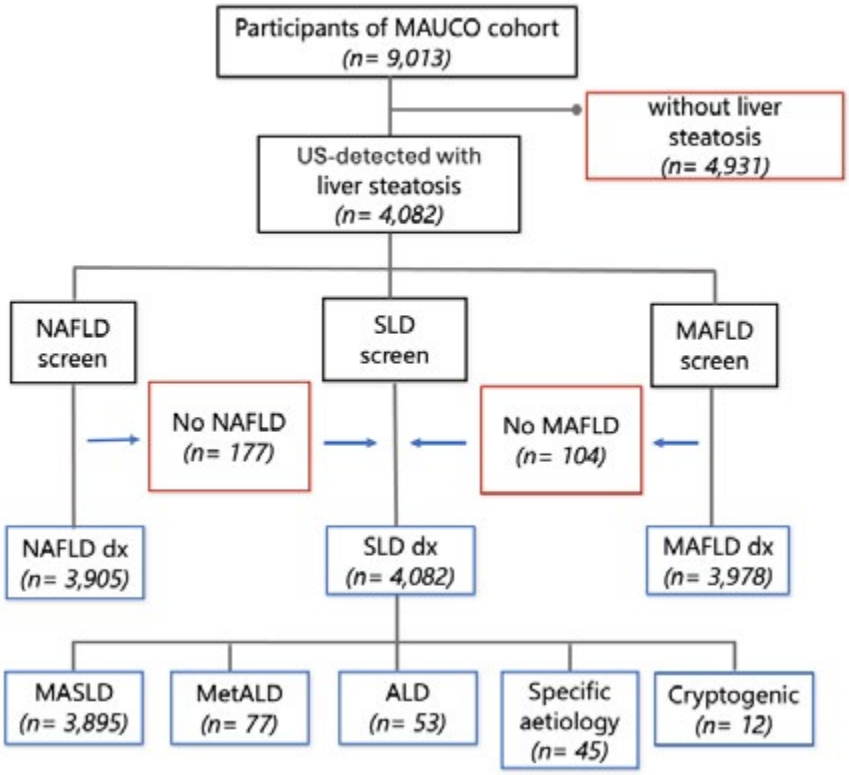
and biological samples were obtained. Participants were categorized based on the NAFLD and MAFLD criteria and SLD into five groups: 1) Metabolic dysfunction-associated steatosis liver disease (MASLD), 2) Metabolic Alcohol-Associated Liver Disease (MetALD), 3) Alcohol-Associated Liver Disease (ALD), 4) Specific etiologies, and 5) Cryptogenic. We obtained cardiovascular risk scores using the Framingham algorithm and liver fibrosis scores using the BARD. **Results:** Among 9,013 participants, 45% had confirmed liver steatosis. Transitioning to SLD criteria included 177 additional participants who were previously excluded under NAFLD, who had a poor metabolic profile, alcohol consumption, and risks of liver fibrosis and cardiovascular disease (Figure 1). In contrast, 104 individuals excluded under MAFLD were included in SLD, primarily women with healthier cardiometabolic profiles but still at risk for liver fibrosis and cardiovascular disease (Figure 1). SLD classification showed MASLD as the predominant group (95%), followed by MetALD (1.9%) and ALD (1.3%) (Figure 1). MetALD and ALD groups had worse liver steatosis and a higher risk of cardiovascular disease. Specific Etiology and Cryptogenic are composed of younger participants with better health profiles but a higher risk of developing liver fibrosis. **Conclusion:** The study reveals that SLD offers a more inclusive and accurate classification, identifying high-risk individuals in the Chilean population. Using this new diagnostic criterion allows us to manage patients with SLD more effectively, understand the context in which their disease develops, and design more effective interventions. (This study was funded by ANID FONDECYT Regular 1241450 (MA) and 1212066 (CF)).

Figure 1. **Patient classification flowchart**



Disclosures: Maria Spencer Sandino: Nothing to Disclose, Laura Andrea Huidobro: Nothing to Disclose, Franco Godoy: Nothing to Disclose, Danilo Alvares: Nothing to Disclose, Juan Pablo Arab: Nothing to Disclose, Daniel Cabrera: Nothing to Disclose, Marco Arrese: Nothing to Disclose, Francisco Barrera: Nothing to Disclose, Catterina Ferreccio: Nothing to Disclose

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2396 | FORECASTED CHANGES IN TUMOR CHARACTERISTICS AND SURVIVAL OF PATIENTS WITH NONVIRAL HEPATOCELLULAR CARCINOMA IN THE UNITED STATES: A MODELING STUDY BASED ON THE SEER-MEDICARE DATABASE

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[1]Division of Gastroenterology and Hepatology, Dept of Medicine, Stanford University Medical Center, [2]Division of Oncology, Department of Medicine, Stanford University Medical Center

Background: HCC incidence related to nonviral liver diseases is rising. Nonviral HCC may also have worse survival. However, population-based U.S. data are limited. Using a national U.S. database, we determined patient and tumor characteristics, HCC surveillance rates, and survival rates of nonviral HCC overall and in subgroups of patients with metabolic dysfunction-associated steatotic liver disease (MASLD) and alcohol-associated liver disease (ALD). We also determined trend and future forecast of nonviral HCC burden and characteristics through 2035. **Methods:** We included adult HCC patients with nonviral liver disease from the SEER Medicare database from 2000-2017 and excluded those with non-liver cancer or HIV infection. We used linear regression to model changes in patient survival and characteristics from 2000-2017 and applied this model to describe the future HCC population up to 2035. **Results:** We analyzed 23,926 patients with HCC (18,266 MASLD, 5,660 ALD). The percentage of male among nonviral HCC in 2030 was stable over time (69.1% in 2013-2017). The proportion of patients with a history of HCC surveillance remained low over the years (13% in 2000-2003 vs. 12% in 2013-2017, P= 0.15). Using linear modeling, we estimated an increase in 5-year survival rates from 4.79% in 2000 to 22.0% in 2027 (P<0.001) and in median survival from 0.28 years in 2000 to 1.31 years by 2035 (P<0.001, Figure). Additionally, while there was significant increase in the 5-year and median survival for the MASLD subgroup between 2000 and 2027 (5.68% to 23.2% and 0.33 to 1.4 years, both P<0.001, respectively), there was significant improvement only in the median survival (0.23 to 1.09 years, P<0.001) but not 5-year survival rates (7.32% to 11.2%, P=0.16) for ALD-related HCC. The proportion of patients diagnosed with HCC at TNM stage I however is predicted to increase to 49.9% in 2027, with stage IV decreasing to 8.56% in 2027 (both P<0.001). The percentage of Asian patients decreased while those of Hispanic patients increased reaching 11.5% and 28% by 2030 from 15.1% and 13.4% in 2000-2003, respectively. **Conclusion:** Though there have been improvements in early-stage detection of patients with nonviral HCC, the proportion of nonviral HCC diagnosed via surveillance remains dismally low (13%), 5-year survival rates remain <25% by 2027, and median survival remains <1.5 years by 2035. More effort is needed to improve HCC surveillance and therapeutic strategies.

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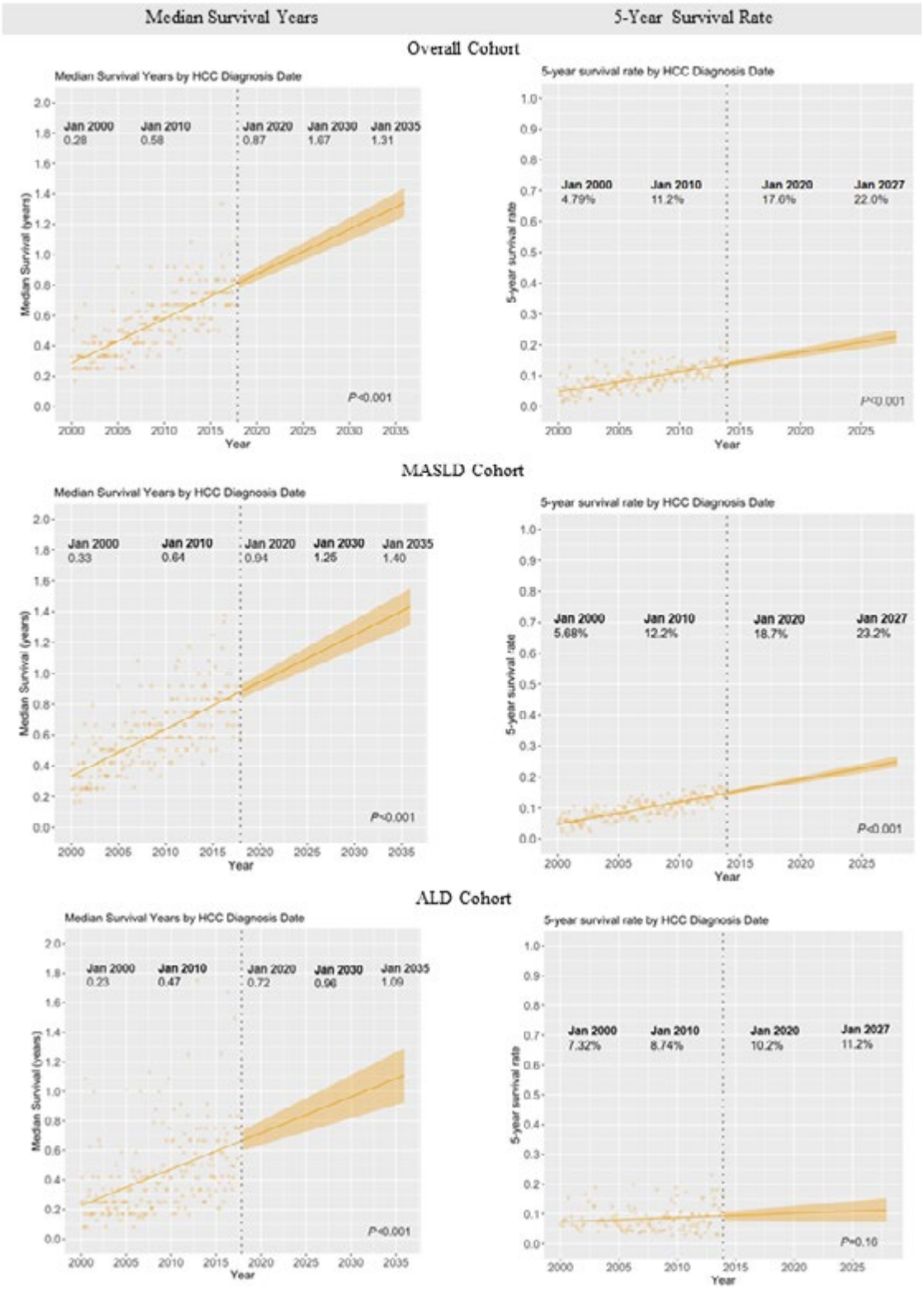

Disclosures: Joanne Liu: Nothing to Disclose, Nicholas Chien: Nothing to Disclose, Curtis Chong: Nothing to Disclose, Scott Barnett: Nothing to Disclose, Ramsey Cheung: Nothing to Disclose, Mindie Nguyen: Nothing to Disclose

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2397 | SEX DIFFERENCES IN LONG-TERM OVERALL, LIVER AND NONLIVER-RELATED MORTALITY OF PATIENTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE: A REAL-WORLD LONGITUDINAL COHORT STUDY

Taotao Yan[1] Nicholas Chien[1] Ashley Fong[1] Vy Nguyen[1] Isaac Le[1] Annie Fung[1] Surya Teja Gudapati[1] Sally Tran[1] Angela Chau[1] Xinrong Zhang[1] Jung Eun Park[1] Ramsey Cheung[1] Changqing Zhao[2] Mingjuan Jin[3]

[1]Stanford University Medical Center, [2]Shuguang Hospital, Shanghai University of T.C.M., [3]Zhejiang University School of Public Health

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is a major cause of both liver and nonliver-related complications. However, data on the impact of sex on long-term overall, liver and nonliver mortality of patients with MASLD are limited. We aimed to investigate the relationship between sex and mortality of real-world patients with MASLD. **Methods:** Consecutive patients with MASLD were identified from any clinics (primary care and subspecialty) at a U.S. university medical center (1995-2023). Primary study outcomes were incidence of mortality (overall, liver and nonliver-related) and liver complications (significant fibrosis, cirrhosis and hepatocellular carcinoma [HCC]). Analysis of liver complications were performed using a Fine and Gray model with death as a competing risk. **Results:** Our study included 8,593 adult patients (4,548 males and 4,045 females) with MASLD. Over a median follow-up of 3.0 years (IQR 1.2-6.1), 209 males and 259 females died, with most deaths from nonliver causes. The overall (12.1 vs. 13.6), liver (11.1 vs. 12.6) and nonliver-related (1.1 vs. 1.1) mortality per 1000 person-years (PY) were all comparable between male and female groups. Males with MASLD (vs. female) had comparable incidence of significant fibrosis (6.5 vs. 6.2) and cirrhosis (5.0 vs. 5.2) but a significantly higher incidence of HCC (2.3 vs. 0.8, *P*<0.001) per 1000 PY (Figure). In the multivariable Cox regression model adjusted for race and ethnicity, BMI, Charlton Comorbidity Index, FIB-4 index and viral hepatitis, male sex (vs. female) was significantly associated with an increased risk of HCC (subdistribution hazard ratio [SHR] 2.28, 95%CI 1.23-4.25, *P*<0.05), while there was no significant association between sex and the development of significant fibrosis (SHR 0.94, 95%CI 0.69-1.26), cirrhosis (SHR 0.89, 95%CI 0.65-1.21), overall (aHR 0.95, 95%CI 0.79-1.14), liver (aHR 0.89, 95%CI 0.65-1.21) or nonliver-related (aHR 0.89, 95%CI 0.65-1.21) mortality. In subgroup analysis, male sex was associated with a decreased risk of mortality (aHR 0.66, 95%CI 0.45-0.98, *P*<0.05) in MASLD patients aged ≤50 years and an increased risk of HCC (SHR 2.11, 95%CI 1.09-4.11, *P*<0.05) in MASLD patients aged >50 years. **Conclusion:** Among patients with MASLD, males with 50 years of age or younger had 34% lower risk of mortality, while males older than 50 had more than two times higher risk of development of HCC as compared to their female counterparts. Sex differences should be taken into account in the monitoring and management of patients with MASLD, especially in HCC surveillance.

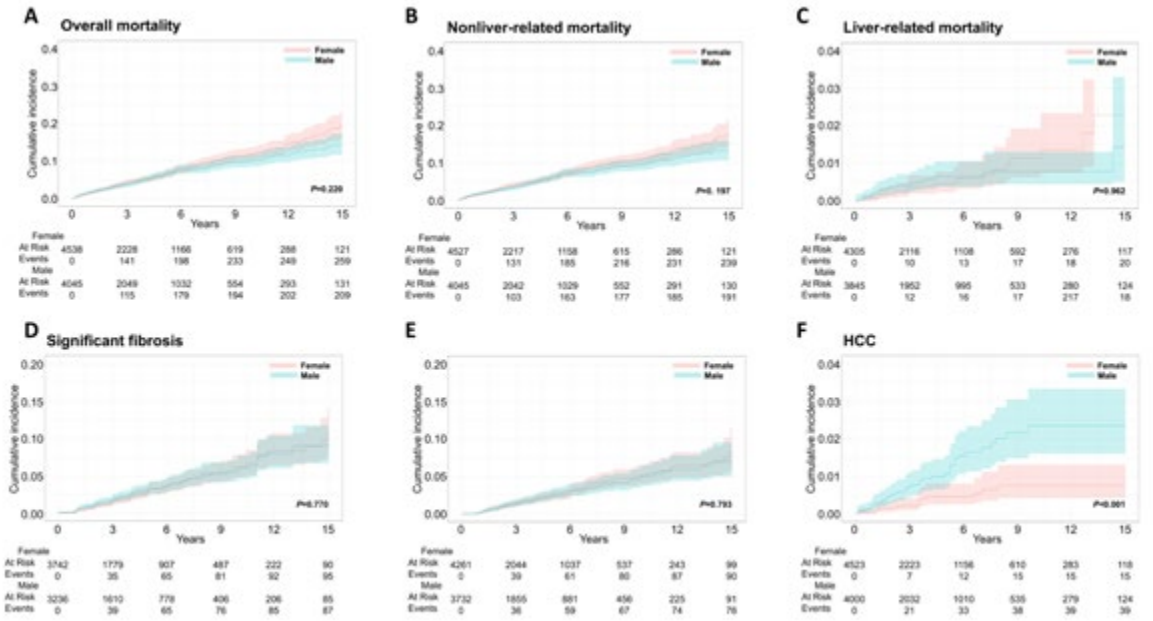

Figure. Cumulative incidence of overall, liver and nonliver-related mortality, and liver complicagions (significant fibrosis, cirrhosis and HCC) in MASLD by sex. HCC, Hepatocarcinoma; MASLD, Metabolic dysfunction-associated steatotic liver disease.

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Disclosures: Taotao Yan: Nothing to Disclose, Nicholas Chien: Nothing to Disclose, Ashley Fong: Nothing to Disclose, Vy Nguyen: Nothing to Disclose, Isaac Le: Nothing to Disclose, Annie Fung: Nothing to Disclose, Surya Teja Gudapati: Nothing to Disclose, Sally Tran: Nothing to Disclose, Angela Chau: Nothing to Disclose, Xinrong Zhang: Nothing to Disclose, Jung Eun Park: Nothing to Disclose, Ramsey Cheung: Nothing to Disclose, Changqing Zhao: Nothing to Disclose, Mingjuan Jin: Nothing to Disclose

2398 | SUBOPTIMAL DIAGNOSIS RATE AND PERI-COMPLICATION DIAGNOSIS OF METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD) IN THE U.S.: A POPULATION-BASED STUDY

Vy Nguyen[1] Scott Barnett[1] Xinrong Zhang[1] Ramsey Cheung[2] Mindie Nguyen[2]

[1]Division of Gastroenterology and Hepatology, Stanford University Medical Center, Palo Alto, CA, USA, [2]Stanford University Medical Center

Background: The incidence of MASLD is estimated to affect over half of the global adult population by 2040, yet disease awareness remains low in the U.S. We aimed to characterize the overall diagnosis rate and identify peri-complication diagnoses of MASLD at the time of MASLD-related complications. **Methods:** This retrospective cohort study used data from the Truven Health MarketScan Research Database®, 2007-2020, National Health and Nutrition Examination Survey 2017–2020 (NHANES), and the US Census Bureau American Community Survey. Peri-complication diagnosis of MASLD is defined as having a MASLD diagnosis within 12 months of having any MASLD-related complication, including cirrhosis, hepatocellular carcinoma, and receiving a liver transplant. We used multivariable logistic regression to identify factors associated with peri-complication diagnosis of MASLD. **Results:** We estimated there were 171,686,780 adult patients with private insurance using the US Census database. Based on the NHANES database, we calculated an MASLD prevalence of 32.6% among patients with private insurance, thus estimating that there should be 55,969,890 insured adults who should have MASLD (**Figure**). However, we found that only 1,745,221 patients were ever diagnosed with MASLD (3.12%). Notably, 73% of patients with MASLD had hypertension, 36.8% had diabetes, and 39.8% were overweight or obese. During follow-up, 97409 (5.58%) patients developed a MASLD-related complication, but 89945 (92.3%) of them received an MASLD diagnosis at or after the complication and a quarter of patients with complications had a peri-complication diagnosis of MASLD within 1 year of developing a complication. In multivariable logistic regression, male patients were more likely to have a peri-complication diagnosis for any complication, and nearly three times greater odds of being diagnosed with MASLD at within 1 year of their HCC diagnosis compared to females after adjusting for age, Charlson Comorbidity Index, and geographic care region (adjusted odds ratio 2.81, 95% CI: 2.62 – 3.01, p <0.0001). **Conclusion:** MASLD is severely underdiagnosed even in privately insured individuals in the U.S. Additionally, among those who were ever diagnosed with MASLD, the diagnosis is severely delayed, with 1 in 4 patients receiving an MASLD diagnosis within a year of their MASLD-related liver complication. Additional effort is needed to improve the current state of MASLD care cascade.

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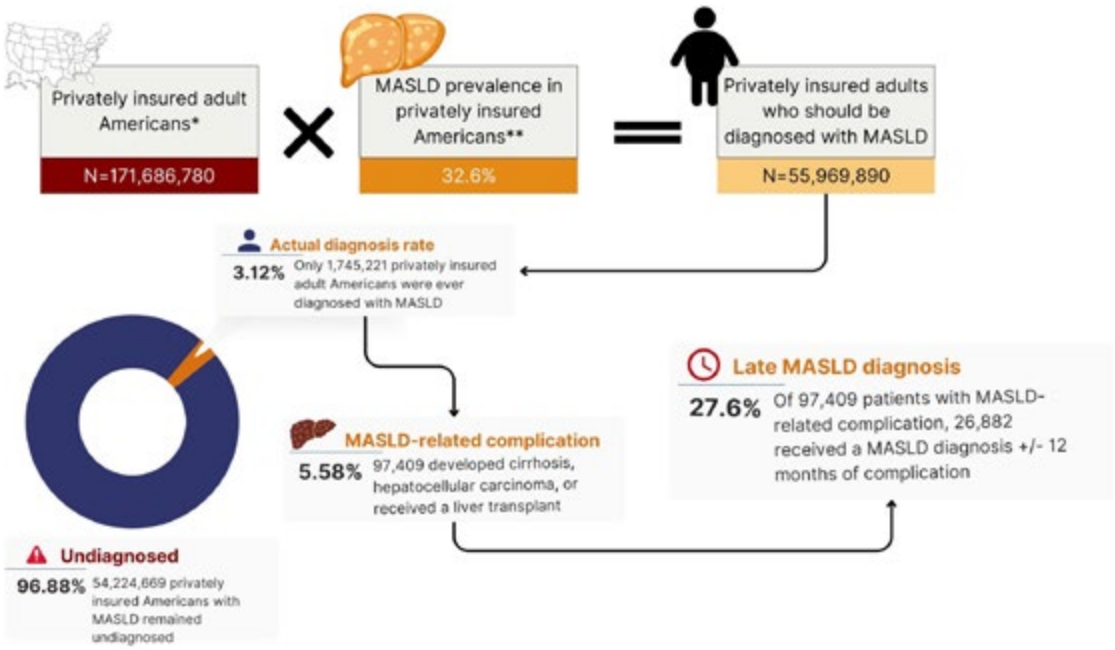
Figure 1. Graphical summary of study flow (*Based on US Census Bureau data. **Based on National Health and Nutrition Examination Survey data 2017-2020)



Disclosures: Vy Nguyen: Nothing to Disclose, Scott Barnett: Nothing to Disclose, Xinrong Zhang: Nothing to Disclose, Ramsey Cheung: Nothing to Disclose, Mindie Nguyen: Nothing to Disclose

2399 | COST UTILITY OF BARIATRIC SURGERY AMONG OBESE PATIENTS WITH CHRONIC LIVER DISEASE

Shalini Bansal[1] *Nadim Mahmud*[2] *Amanda Bader*[3] *David Kaplan*[3]

[1]*Thomas Jefferson University,* [2]*Hospital of the University of Pennsylvania,* [3]*University of Pennsylvania*

Background: Obesity and steatotic liver disease are associated with excess morbidity and mortality from cardiovascular, pulmonary, metabolic and hepatic causes. Bariatric surgery (BS) induces rapid weight loss and reduces mortality. However, high initial cost has led to insurance restrictions that limit BS access. We hypothesized that long-term cost savings might partially offset upfront costs and sought to quantify the cost utility of BS in an integrated national health system. **Methods:** This retrospective cohort included Veterans with abnormal ALT (>30 U/l) who attended MOVE!, the national VA behavioral weight loss program. Patients undergoing bariatric surgery (BS) from 9/30/2008 to 9/30/2020 (sleeve gastrectomy (LSG) or gastric bypass (RYGB)) were risk-set matched 4:1 to MOVE! participants who did not undergo BS on age, sex, BMI, tobacco use, AUDIT-C, diabetes mellitus, hypertension, hyperlipidemia, sleep apnea, cirrhosis, and MOVE! treatment duration. Inpatient, outpatient, pharmacy and external (fee-basis) Year 0 costs were obtained for 6 months before and after the surgery date (or index date for controls), as were baseline pre-surgical (year -1), and post-surgical costs up to Year +10 from Health Economic Resource Center (HERC) and Decision Support System (DSS) datasets. All costs were inflation-adjusted to 2024 dollars with post-surgical costs discounted at 3%/year. Generalized linear models with Gaussian distribution and log link, incorporating treatment assignment and key covariates, were used to predict 10-year total costs. The average marginal effect (incremental cost) of surgery was estimated, adjusting for survival likelihood and missingness. Additional life years gained by treatment were evaluated by comparing restricted mean survival times (RMST) of survival models (R surv2sampleComp package) and incremental costs per life-year gained were then calculated. **Results:** Of 11,649 patients, 714 underwent RYGB, 1413 LSG and 9522 were controls. Median age was 54 [IQR 45-62]; 73% were men; 62%/12%/16% were White/Black/Hispanic; median BMI at intervention was 33.3 [30.2-37.3]; and 53% were diabetic. 58% were nondrinkers; 37% AUDIT-C 1-3; and 5% with AUDIT-C ≥ 4. Median MOVE! participation was 24 weeks [IQR 12-42]. Median follow-up time was 7.9 years [5.6-10.3]. Median year 0 excess cost of surgery was $36,917. Total 10-year healthcare expenditures in LSG patients were $143M for 12,129 patient years,

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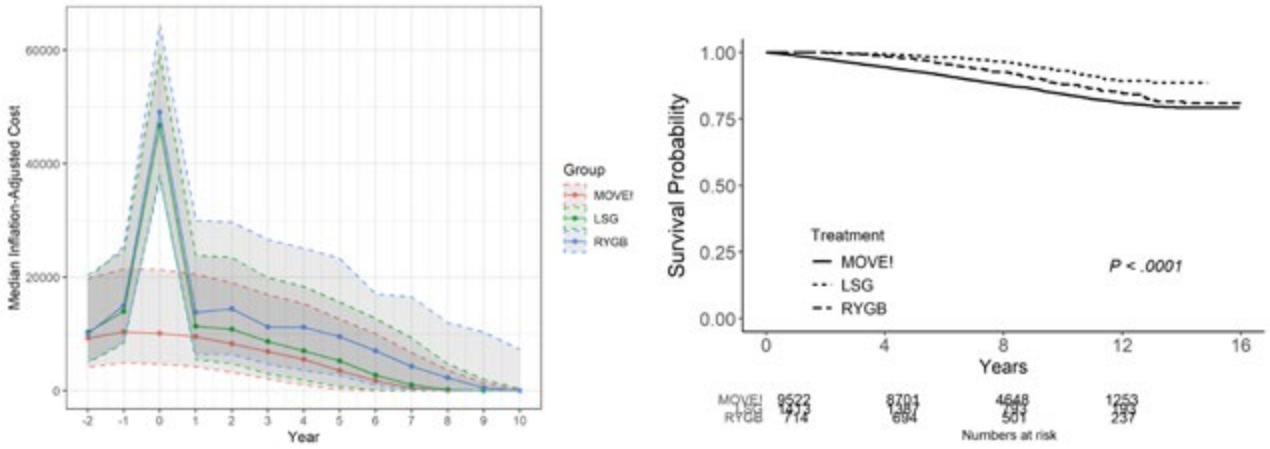
RYGB $86M for 7,191 patient years, and controls $623M for 77,005 patient years. The average marginal effect (incremental cost) over 10-years of LSG was $12,778 (95%CI 12,003-13,552) and RGB was $14,263 (13,237-15,288). Both LSG and RYGB significantly reduced mortality risk compared to MOVE! with HR 0.37 (95%CI 0.29-0.47) and 0.69 (0.55-0.85), respectively. RMST was 9.8 years (95% 9.8-9.9) for LSG, 9.6 (9.5-9.7) for RYGB and and 9.3 (9.2-9.3) for MOVE!, resulting in average marginal effect (life years gained) of 0.54 years for LSG and 0.35 years for RYGB. Thus, the incremental cost per life year gained was $23,662 for LSG and $40,751 for RYGB. **Conclusion:** Bariatric surgery for obesity among patients with abnormal ALT significantly improves overall survival and is highly cost effective with ICER < $50,000/year of life gained.



Disclosures: Shalini Bansal: Nothing to Disclose, Nadim Mahmud: Nothing to Disclose, Amanda Bader: Nothing to Disclose, David Kaplan: Independent Contractor relationship with Roche Genentech; Has not ended; Grant/Research Support relationship with AstraZeneca Inc; Has not ended; Advisor relationship with AstraZeneca; Has ended; Advisor relationship with Exelixis; Has ended; Grant/Research Support relationship with Gilead; Has not ended; Advisor relationship with Sirtex; Has ended; Grant/Research Support relationship with Exact Sciences; Has not ended; Grant/Research Support relationship with Glycotest; Has ended

2400 | USE OF A COMPUTERIZED CLINICAL DECISION SUPPORT (CCDS) TOOL IN PRIMARY CARE INCREASES RATES OF CONFIRMATORY TESTING IN PATIENTS WITH METABOLIC ASSOCIATED STEATOTIC LIVER DISEASE (MASLD) AT RISK FOR ADVANCED LIVER FIBROSIS: A PILOT STUDY

James Miller[1] Ted Xiao[1] Lauren Witek[1] Richa Bundy[1] Adam Moses[1] Corey Obermiller[1] Ajay Dharod[1] Mark Russo[2] Sean Rudnick[3]

[1]Wake Forest University School of Medicine, [2]Carolinas Medical Center, [3]Atrium Health Wake Forest Baptist

Background: The prevalence of MASLD in the general population is estimated to be 25-30%. Advanced fibrosis (AF) is associated with greater risk for liver-related morbidity and mortality than lower degrees of fibrosis. Identifying patients at highest risk for AF would allow appropriate subsequent testing and interventions to reduce liver-related complications. The aim of this pilot study was to determine if implementation of a cCDS tool designed to identify patients at risk for MASLD and AF in primary care settings would affect rates of subsequent testing. **Methods:** An electronic health record (EHR)-based cCDS tool identifying patients at-risk for MASLD and AF was implemented over 3 months in 3 primary care clinics. The tool risk-stratified patients into low, indeterminate, or high risk of AF by calculating FIB-4 score. An interruptive alert notified providers if patients were indeterminate or high risk for AF and provided recommendations for subsequent testing and referral to GI/Hepatology. Pre and post-intervention comparisons were made between the pilot-site clinics and control clinics in a prospective case-control study. **Results:** In 3 pilot-site clinics there were 18,510 total encounters, with 1,374 (7.4%) encounters in which the alert was triggered an average of 1.7 times. For patients with high or indeterminate FIB-4 scores, orders for elastography increased from 0 to 30 (2.1%) in the pilot-site clinics. In 5,023 control-clinic patient encounters, subsequent testing orders remained at 0.0%. The percentage of subspecialty referral for MASLD increased from

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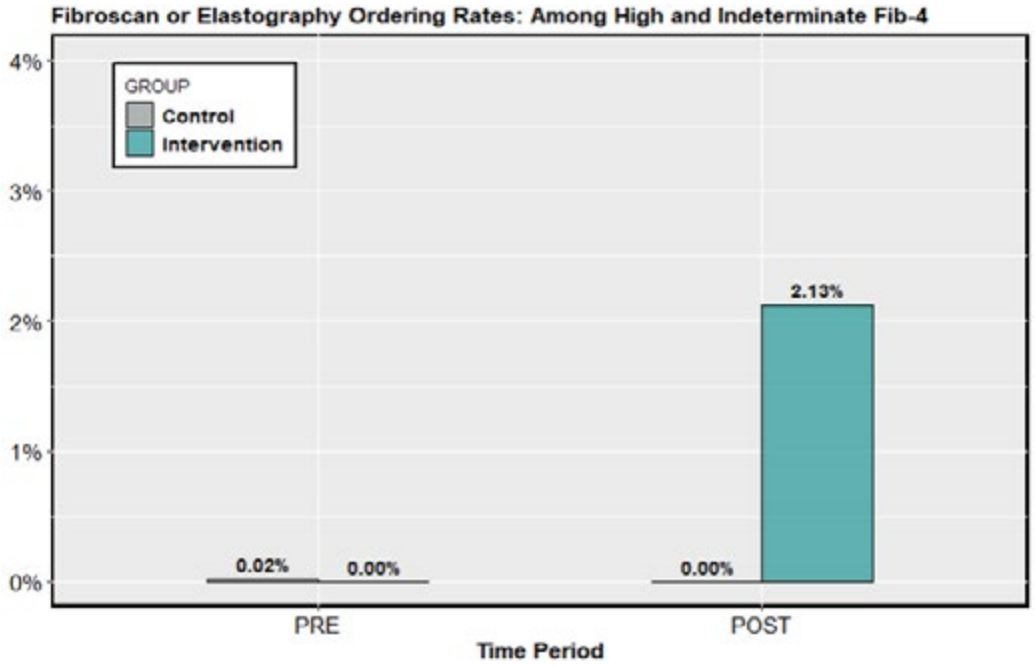
4% to 20.6% in the pilot-site clinics. A modest increase from 13.4% to 16.2% was observed in the control clinics. **Conclusion:** This pilot study suggests that a cCDS tool identifying patients at risk of MASLD with AF can increase subsequent testing in the primary care setting. The low alert trigger rate suggests appropriate specificity of the cCDS tool. Low observed rates of subsequent testing are consistent with prior studies. However, increases in subsequent testing were observed in pilot-site clinics. We hypothesize that increasing both the duration of the intervention and the number of clinics would result in more demonstrable increases in subsequent testing orders. This pilot study demonstrates the feasibility of prospective implementation of the cCDS tool.



Disclosures: James Miller: Nothing to Disclose, Ted Xiao: Nothing to Disclose, Lauren Witek: Nothing to Disclose, Richa Bundy: Nothing to Disclose, Adam Moses: Nothing to Disclose, Corey Obermiller: Nothing to Disclose, Ajay Dharod: American Association of Medical Colleges: Consultant, American Association of Medical Colleges CORE program: EHR Consultant, DHN dba mPATH: Executive & co-inventor of mPATH. Equity. Grants. Patent., IllumiCare Inc.: Royalties or patent beneficiary, Mark Russo: Nothing to Disclose, Sean Rudnick: Nothing to Disclose

2401 | INCREASING METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE-RELATED MORTALITY RATES IN THE UNITED STATES FROM 2006 TO 2023 AND FUTURE FORECAST TO 2040

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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is a major cause of morbidity and mortality globally, but population-based data for MASLD-related mortality trend and future forecast in the United States (U.S.) are limited. We evaluated temporal changes in MASLD-related mortality in the U.S. from 2006 to 2023 and estimated future MASLD-related mortality rates up to 2040 in overall and subgroups of age, sex, ethnicity/race and urbanization. **Methods:** We analyzed age-standardised mortality rates (ASMRs) for MASLD-related deaths using the U.S. National Vital Statistic System from the Center for Disease Control and Prevention Wide-Ranging Online Data for Epidemiologic Research (CDC WONDER) database among deceased adults aged ≥25 years during 2006-2023. We conducted joinpoint regression analysis to determine the annual percentage change (APC) for mortality trends from 2006-2023 and forecasted mortality rates to 2040 using Prophet prediction model. **Results:** Among 27,961 MASLD-related deaths between 2006 and 2023, ASMRs

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(per 100,000 persons) rose from 0.25 to 1.27, with APC increased from 9.27% in 2006-2018 to 22.66% in 2018-2021, but decreased at -1.23% from 2021 to 2023, leading to predicted ASMRs to 2.24 in 2040 **(Figure)**. There was significant heterogeneity in the distribution of MASLD-related mortality among the states after the COVID-19 pandemic, with the highest ASMRs experienced in Kentucky, Vermont, Oklahoma, West Virginia and Wyoming. There were significant differences in the rise of ASMRs by age with the ≥65 age group having the steepest rise (average APC [AAPC]: 15.34%, vs. 8.76% and 2.65% for the 45-64 and 25-44 age group, all *P* <0.05) and a predicted increase from 4.10 in 2023 to 7.12 in 2040. However, there was no significant difference in ASMRs between females and males (AAPC 11.24% for females and 11.04% for males). ASMRs rose for all major racial ethnic groups with the highest ASMRs increase observed for Non-Hispanic Whites (0.28 in 2006 to 1.43 in 2023; AAPC: 11.12%, *P*<0.001), followed by Hispanics (0.28 to 1.32; AAPC: 10.67%, *P*<0.001), Non-Hispanic Blacks (0.19 to 0.61; AAPC: 9.20%, *P*<0.001), and Non-Hispanic Asians (0.15 to 0.39; AAPC: 7.97%, *P*<0.001), while the predicted values of these four groups showed similar increasing trends to 2040. There were also significant differences in ASMRs by metropolitan categories overall, with the highest rise in non-metropolitan areas (AAPC: 13.50%, *P*<0.001). **Conclusion:** MASLD-related mortality increased rapidly during 2006-2023 and is predicted to rise over the next 20 years, with the largest disparities among those aged ≥65 years, the non-Hispanic Whites and Hispanics and non-metropolitan populations.

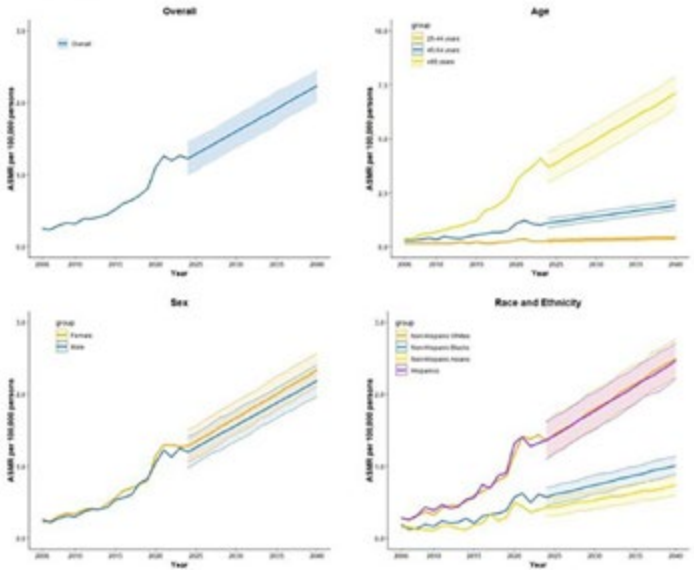
Figure. Age-standardized mortality rates (ASMR) and predicted value for MASLD in the United States in 2006-2040, overall, by age, sex, ethnicity/race and urbanization (A) Annual percentage change, (B) Forecast to 2040

(A) Annual percentage change

	Age Standardized Mortality Rate (Per 100,000 Persons)							Average APC (95% CI)	Trend Segment	
	2006	2010	2015	2020	2021	2022	2023	2006-2023	Year	APC (95% CI)
Overall	0.25	0.32	0.52	1.11	1.26	1.20	1.27	10.21 (8.65-12.13)**	2006-2018 2018-2021 2021-2023	9.27 (5.29 to 17.64)* 22.66 (3.97 to 27.92)* -1.23 (-13.69 to 15.21)
Age										
25-44 years	0.15	0.15	0.21	0.31	0.36	0.25	0.25	2.65 (0.49-4.86)*	2006-2017 2017-2021 2021-2023	0.95 (-4.90 to 5.99) 18.84 (-2.91 to 33.36) -16.03 (-31.39 to 8.46)
45-64 years	0.30	0.34	0.56	1.08	1.21	1.05	1.01	8.76 (7.29-10.22)**	2006-2023	8.76 (7.29-10.22)**
≥65 years	0.39	0.68	1.20	3.05	3.46	3.68	4.10	15.34 (14.40-16.32)**	2006-2023	15.34 (14.40-16.32)**
Sex										
Female	0.22	0.34	0.57	1.15	1.29	1.29	1.28	11.24 (10.09-12.40)**	2006-2023	11.24 (10.09-12.40)**
Male	0.26	0.30	0.54	1.05	1.22	1.13	1.25	11.04 (9.56-12.63)**	2006-2014 2014-2023	8.64 (-2.26 to 18.91) 13.77 (0.93 to 25.54)*
Race and ethnicity										
Non-Hispanic Whites	0.28	0.33	0.60	1.17	1.41	1.38	1.43	11.12 (9.48-12.83)**	2006-2014 2014-2023	8.85 (-2.15 to 22.85) 13.17 (-1.21 to 25.98)
Non-Hispanic Blacks	0.19	0.16	0.20	0.57	0.62	0.50	0.61	9.20 (7.32-11.11)**	2006-2023	9.20 (7.32-11.11)**
Non-Hispanic Asians	0.15	0.11	0.18	0.49	0.44	0.36	0.39	7.97 (4.66-11.75)**	2006-2014 2014-2023	1.46 (-26.38 to 9.31) 84.12 (6.18 to 47.34)*
Hispanics	0.28	0.39	0.56	1.32	1.40	1.28	1.32	10.67 (9.11-12.26)**	2006-2023	10.67 (9.11-12.26)**
Urbanization[a]										
Large and fringe Metro	0.23	0.25	0.41	0.89	N/A	N/A	N/A	10.96 (8.42-12.42)**	2006-2018 2018-2020	8.60 (-0.36 to 23.24) 26.21 (8.07-38.52)*
Small and Medium Metro	0.28	0.37	0.64	1.21	N/A	N/A	N/A	10.67 (9.51-11.84)**	2006-2020	10.67 (9.51-11.84)**
Non-Metro	0.24	0.32	0.69	1.60	N/A	N/A	N/A	13.50 (10.70-16.32)**	2006-2020	13.50 (10.70-16.32)**

**P<0.001 and *P<0.05; [a]Age-standardized mortality rate did not have data from 2021 to 2023 in urbanization categories. Metropolitan categories defined: large and fringe central metropolitan areas (>1 million people), small and medium metropolitan areas (between 50,000-249,999 to 250,000-999,999 people), and non-metropolitan areas (<50,000 people). APC, annual percentage change; CI, confidence interval

(B) Forecast to 2040



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2402 | GLOBAL EPIDEMIOLOGY AND CHARACTERISTICS OF MASLD IN TYPE 1 DIABETES: AN UPDATED SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is often overlooked in patients with type 1 diabetes (T1D). Our study aims to provide a comprehensive overview of the burden of MASLD in T1D by assessing the prevalence of MALSD and its advanced stages in individuals with T1D. **Methods:** We systematically searched PubMed and Embase databases (from inception to May 5, 2024) for original articles on the prevalence or characteristics of MASLD (as detected by blood scores, ICD codes, imaging techniques or liver biopsy) in adults (≥18 years) with T1D. Data were extracted, and we performed meta-analysis of proportions using generalized linear mixed model, and pairwise meta-analysis using the DerSimonian-Laird method. Heterogeneity was investigated with further subgroup and meta-regression analyses, and publication bias was assessed. **Results:** We identified 23 studies with a total of 13006 individuals. Of these, 22.24% (95%CI 15.62; 30.66, I^2=99.2%) of T1D patients had MASLD. The prevalence of MASLD varied significantly according to the diagnostic method (p<0.0001), with prevalence rates in liver biopsy, magnetic resonance imaging, ultrasound, vibration-controlled transient elastography, fatty liver index, and hepatic steatosis index estimated to be 19.30% (95%CI 11.02; 31. 58, I^2=NA), 9.79% (95%CI 6.52; 14.44, I^2=66.9%), 25.75% (95%CI 17.68; 35.91, I^2=96.9%), 25.86% (95%CI 15.83; 39.27, I^2=95.6%), 14.95% (95%CI 8.80; 24.26, I^2=93.3%) and 57.01% (95%CI 44.18; 68.96, I^2=99.3%), respectively. Based on non-invasive diagnostic methods, significant fibrosis (≥F2) and advanced fibrosis (≥F3) in T1D patients with MASLD were found in 13.70% (95%CI 11.49; 16.25 I^2=0%) and 5.31% (95%CI 3.89; 7.21, I^2=0%), respectively. They were more likely to be older, overweight, male, have a longer duration of diabetes, require higher daily doses of insulin, have metabolic dysfunction and were at a higher risk for chronic microvascular diabetic complications. **Conclusion:** MASLD is common in T1D patients, with a small proportion of MASLD-T1D patients affected by significant/advanced fibrosis. Screening for MASLD in metabolically unhealthy T1D patients is warranted, with further assessment of fibrosis in the presence of multiple metabolic risk factors for early intervention. More studies with reliable MASLD diagnosis are certainly needed to elucidate the epidemiology of MASLD in this population, especially in underrepresented regions.

Disclosures: Matheus Souza: Nothing to Disclose, Lubna Al-Sharif: Nothing to Disclose, Samira Khalil: Nothing to Disclose, Alessandro Mantovani: Nothing to Disclose, Cristiane Villela-Nogueira: Nothing to Disclose

2403 | IDENTIFYING SOCIAL DETERMINANTS OF HEALTH AND ENVIRONMENTAL FACTORS ASSOCIATED WITH SIGNIFICANT FIBROSIS IN MASH PATIENTS ENROLLED IN THE MOUNT SINAI MASH CENTER OF EXCELLENCE REGISTRY AND BIOBANK

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Background: Principal management of Metabolic-dysfunction associated steatotic liver disease/steatohepatitis (MASLD/MASH) emphasizes lifestyle changes which can be significantly impacted by environmental and socioeconomic factors. The association of these factors with significant liver fibrosis in the diverse multi-ethnic NYC population is underexplored and could inform both mechanistic translational studies and more targeted population screening strategies to link patients to appropriate care earlier in disease progression. **Methods:** In this cross-sectional analysis, the link between health disparities/environmental factors and significant fibrosis (kPa>8) in MASH

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was explored using the Mount Sinai MASH Center of Excellence Longitudinal Registry. Participants aged 5-90 were included. Fibrosis stage was determined via Vibration-controlled transient elastography (VCTE) (F0/1: <8kPa, F2: 8-10 kPa, F3: 10-14, F4: >14 kPa). Four hundred sixty-three NYC residents were evaluated for health disparities and environmental risk factors using NYC.gov data (income, air quality, high school graduation rate, and access to parks and education per community district tabulation area (CDTA)). Both univariate and multivariable logistic regression analyses between these factors with significant fibrosis were conducted. For multivariable regression models, we controlled for sex, ethnicity, obesity, diabetes, alcohol consumption and smoking. **Results:** Of the 422 adults and 41 pediatric eligible patients, 38% of patients have significant fibrosis (kPa >8), with the highest mean elasticity score found in Staten Island (15.8 kPa) and the lowest found in Manhattan (8.9 kPa). The intersection of air pollution and obesity was evident in patients with a BMI over 30 kg/m² living in high-air-pollution areas (>7 PM2.5), having nearly double the odds of significant fibrosis (OR=1.85, 95%CI (1.11, 3.09)). No association between lower income and increased fibrosis was seen; instead, higher CDTA income correlated with higher odds of significant fibrosis (OR=1.02, 95%CI (1.01, 1.02)). Among non-Hispanics, education access was linked to significantly lower odds of significant fibrosis (OR=0.96, 95%CI (0.927, 1.00)). In adults, alcohol (AUDIT-C score) was protective against significant fibrosis (OR=0.75, 95%CI (0.61, 0.92)). **Conclusion:** Patients with BMI>30 kg/m² in high-air-pollution areas have nearly double the odds of significant liver scarring. Higher CDTA income slightly correlates with increased odds of significant scarring while better education access in non-Hispanics is associated with lower odds of significant fibrosis. The interplay between adiposity and air pollution and its association with significant fibrosis requires further investigation and may inform screening strategies in particularly high-risk groups.

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Table 1. Social determinants in patients on the MASH/NASH registry and their association with significant fibrosis on sub-populations

	Fibrosis stage		
Frequency (proportion) or Mean (SD)	**F0-F1**	**F2 and above**	**Adjusted OR (95% CI)**
Total adult population	(n=261)	(n=161)	
Income	**44.7 (23.6)**	**51.4 (25.5)**	**1.02 (1.01,1.02)**
High School graduation rate	73.5 (8.57)	73.3 (8.26)	1.01 (0.98,1.04)
Education access	70.47 (10.7)	68.9 (9.5)	0.98 (0.96,1.01)
Park access	91.3 (12.06)	91.2 (12.37)	0.99 (0.97,1.01)
Air Pollution (PM25)	6.92 (0.59)	6.98 (0.63)	1.32 (0.92,1.90)
Hispanic background	0.66 (0.766)	0.76 (0.68)	1.20 (0.89, 1.64)
Smoking	0.34 (0.57)	0.48 (0.65)	1.20 (0.82,1.74)
Alcohol consumption	**1.21 (1.9)**	**0.68 (0.63)**	**0.75 (0.61,0.92)**
Non-Hispanic patient population	(n=104)	(n=47)	
Income	**41.36 (26.1)**	**56.7 (28.9)**	**1.02 (1.01, 1.04)**
High School graduation rate	75.65 (8.84)	75.35 (8.85)	0.998 (0.97, 1.04)
Education access	**75.26 (10.30)**	**71.28 (9.63)**	**0.96 (0.927, 1.00)**
Park access	90.47 (12.7)	87.32 (14.45)	0.98 (0.96, 1.01)
Alcohol consumption	**1.36 (1.94)**	**0.61 (1.25)**	**0.73 (0.54,0.98)**
Air Pollution	6.90 (0.55)	7.03 (0.55)	1.44 (0.77, 2.66)
Hispanic patient population	(n= 123)	(n= 95)	
Income	**46.11 (20.5)**	**49.91 (22.7)**	**1.014 (1.00, 1.03)**
High School graduation rate	70.91 (7.77)	71.66 (7.97)	1.015 (0.98, 1.05)
Education access	66.45 (9.69)	66.81 (8.76)	1.000 (0.97, 1.0)
Park access	93.26 (10.7)	94.38 (10.16)	1.004 (0.98, 1.03)
Alcohol consumption	0.98 (1.87)	0.44 (1.06)	0.776 (0.59, 1.02)
Air Pollution	6.93 (0.62)	7.00 (0.69)	1.43 (0.91, 2.24)
Diabetes patient population	(n=261)	(n=161)	
Income	**44.75 (23.6)**	**51.40 (25.58)**	**1.02 (1.01,1.03)**
High School graduation rate	73.46 (8.57)	73.33 (8.26)	1.01 (0.98, 1.04)
Education access	70.47 (10.79)	68.99 (9.54)	1.02 (0.99, 1.04)
Park access	91.28 (12.06)	91.28 (112.37	0.99 (0.97, 1.01)
Alcohol consumption	**1.21 (1.92)**	**0.68 (1.36)**	**0.76 (0.62, 0.93)**
Air Pollution	6.92 (0.59)	6.98 (0.63)	1.25 (0.87, 1.79)
Obese patient population	(n=143)	(n=104)	
Income	**45.44 (22.84)**	**51.79 (25.07)**	**1.02 (1.01, 1.04)**
High School graduation rate	73.37 (8.41)	72.5 (7.80)	0.99 (0.95, 1.02)
Education access	70.08 (10.54)	68.66 (9.072)	1.03 (1.00, 1.06)
Park access	90.71 (12.46)	92.59 (11.9)	1.01 (0.98, 1.03)
Alcohol consumption	1.30 (2.07)	0.76 (1.47)	0.85 (0.68, 1.07)
Air pollution	**6.85 (0.48)**	**7.018 (0.69)**	**1.85 (1.11, 3.09)**

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2404 | CLINICAL, PSYCHOSOCIAL AND SOCIAL DETERMINANTS OF HEALTH FACTORS ASSOCIATED WITH DEGREE OF HEPATIC STEATOSIS AND LIVER STIFFNESS AMONG OVERWEIGHT AND OBESE ADULTS AT RISK OF METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE

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Background: The severity of metabolic dysfunction-associated steatotic liver disease (MASLD) among patients with overweight and obesity is heterogeneous and may be moderated by behavioral, psychosocial and social determinant of health (SDOH) factors. We identified covariates independently associated with magnetic resonance imaging proton-density-fat-fraction (MRI-PDFF) and MR Elastography (MRE) liver stiffness measurement (LSM) in a well characterized prospective cohort of adults with overweight and obesity. **Methods:** This prospective study enrolled overweight or obese adults aged 40-75 years recruited from the greater San Diego area from primary care clinics and community outreach. Participants underwent a standardized clinical research visit with MRI-PDFF and MRE. Alcohol use and physical activity were assessed using validated questionnaires and biomarkers. SDOH included race/ethnicity, employment, marital status, income, education, country of birth, and zip code. Participants with alcohol use exceeding American Association for the Study of Liver Diseases guidance for MASLD were excluded. Correlates of MRI-PDFF and MRE LSM were assessed via linear regression. **Results:** 414 patients [44.5% male, 43% Hispanic, 31.4% with type II diabetes (DM2)] with overweight or obesity were included. The median age and body mass index (BMI) were 53 years and 31 kg/m2 respectively. 71.7% had MRI-PDFF ≥5% with a median MRI-PDFF and MRE kPa of 10.74 and 2.22 respectively. 8.2% and 34.8% were on a glucagon-like peptide (GLP) 1 receptor agonist and statin therapy respectively. GLP-1 and statin use were not correlated with MRI-PDFF nor MRE LSM. On univariate analysis, metabolic factors, family history, exercise, alcohol use, education and zip code were associated with outcomes of interest. On multivariate analysis, MRI-PDFF was independently positively associated with BMI, triglycerides, family history of cirrhosis, and alanine aminotransferase whereas MRE kPa was independently positively associated with DM2, aspartate aminotransferase and zip code (**Table**). **Conclusion:** In a well-phenotyped, prospective cohort of adults with overweight and obesity, metabolic factors and family history of cirrhosis were independently associated with higher MRI-PDFF whereas higher LSM were independently associated with DM2 and SDOH factors (zip code). These data highlight the key role family history and SDOH may play in moderating MASLD disease severity.

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Table. Multivariate analysis of correlates of MRI-PDFF and MRE kPa

Variable (median, IQR)	Coefficient (95% CI)	p-value	Coefficient (95% CI)	p-value
	MRI-PDFF		*MRE kPa*	
Age (yr)	-0.01 (-0.09-0.05)	0.64	0.01 (-0.00-0.01)	0.25
Male sex	1.86 (-0.28-4.0)	0.08	-0.05 (-0.28-0.17)	0.62
BMI	0.37 (0.14-0.60)	**0.002**	0.009 (-0.15-0.03)	0.45
Waist cir	-.01 (-0.12-0.10)	0.87	0.01 (-0.003-0.02)	0.14
Fasting glucose	0.01 (-0.01-0.04)	0.32	xxx	
DM2	xxx		0.45 (0.20-0.70)	**<0.001**
TG	0.01 (0.001-0.02)	**0.03**	xxx	
LDL	xxx		0.00 (-0.00-0.00)	0.99
HDL	-0.04 (-0.12-0.03)	0.28	xxx	
Fhx cirrhosis	5.07 (2.10-8.05)	**0.001**	xxx	
AST	-0.01 (-0.12-0.09)	0.80	0.02 (0.01-0.03)	**<0.001**
ALT	0.11 (0.06-0.17)	**<0.001**	-0.01 (-0.01-0.001)	0.12
AUDIT (none) Monthly Weekly	xxx		 -0.01 (-0.2-0.2) 0.07 (-0.32-0.47)	0.96 0,72
Physical activity (vigorous) Moderate Light	3.52 (-0.8-7.8) 2.71 (-1.5-6.9)	0.11 0.21	xxx	
Hr/day physical activity	xxx		-0.02 (-0.04-0.00)	0.05
< HS education	xxx		0.18 (-0.17-0.53)	0.31
Zipcode		NS	4.36 (2.43-6.29)	**<0.001**

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2405 | REPRESENTATION OF SEX, RACE AND ETHNICITY IN MASH TRIALS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: Despite efforts by National Institutes of Health and the US Food and Drug Administration to promote diverse participation in trials, randomized controlled trials (RCTs) in several areas have historically underrepresented female, racial and ethnic minorities. Our aim is to characterize the global distribution, reporting and participation of diverse groups by sex, race and ethnicity in metabolic dysfunction-associated steatohepatitis (MASH) trials. **Methods:** PubMed and Cochrane Library databases were systematically searched for MASH RCTs

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that were published as original articles and involved any pharmacotherapy as the intervention arm. RCTs were qualitatively reviewed to assess their global distribution and reporting of diverse groups by sex, race, and ethnicity. A meta-analysis of proportions was performed using a generalized linear mixed model with Clopper-Pearson intervals. Heterogeneity was further assessed by subgroup analysis based on trial characteristics, followed by meta-regression to examine the effect of the year of publication and sample size on representativeness. **Results:** 104 studies were identified, reporting data from 107 RCTs and 18680 MASH participants. Of the 50 countries that conducted trials, most of the RCTs (68.0%; 34/50) were from high-income countries. The USA was the country with the highest number of trials (70 RCTs). Sex, race, and ethnicity were reported in 106 (99.1%), 63 (58.9%), and 52 (48.6%) trials, respectively, with an increasing trend in reporting in recent years. The pooled proportions of female, White, Asian, Black and Hispanic or Latino groups were 54.73% (95%CI: 51.85 to 57.58, I^2=85.2%), 87.50% (95%CI: 84.93 to 89.68, I^2=93.0), 4.39% (95%CI: 2.98 to 6.43, I^2=95.3%), 2.27% (95%CI: 1.94 to 2.66, I^2=14.2%), and 31.28% (95%CI: 26.19 to 36.86, I^2=94.2%), respectively. Meta-regressions indicated a trend toward more female, White, and Hispanic or Latino participants in MASH RCTs over the years, and fewer Hispanic or Latino participants in larger sample size trials. **Conclusion:** This systematic review and meta-analysis shows unequal global distribution of MASH trials, good inclusion of females and limited reporting and inclusion of racial and ethnic minorities. Future research is needed to address social and economic barriers to enrollment, and collaborative efforts between developers, clinical trial organizations and pharmaceutical companies should be encouraged to ensure diverse representation.

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2406 | UNVEILING THE REACH: ESTIMATING RESMETIROM-ELIGIBLE POPULATION AMONG US ADULTS

Phuc Le[1] Anh Phan[2] Eda Kaya[3] Yusuf Yilmaz[4] Naim Alkhouri[5]

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Background: The U.S. Food and Drug Administration (FDA) approved resmetirom for adults with noncirrhotic metabolic dysfunction-associated steatohepatitis (MASH) and fibrosis stage F2 or F3. This study aimed to estimate the population size of U.S. adults who would be eligible for the drug. **Methods:** We conducted a cross-sectional analysis of the 2017-March 2020 National Health and Nutrition Examination Survey. We included adults aged ≥18 years and excluded those with liver cirrhosis, pregnancy, viral hepatitis, and excessive alcohol use (>1 drink/day for women and >2 drinks/day for men). We identified eligibility in two scenarios based on the pre-screening protocol and actual patient laboratory values from the MAESTRO-NASH trial. In the liberal scenario, eligible patients would have a controlled attenuation parameter (CAP) of >280 dB/m, liver stiffness measurement (LSM) of >8 kPa, and alanine transaminase (ALT) level of >17 U/L for women or >20 U/L for men. In the strict scenario, eligible patients would have a CAP of >280 dB/m, LSM >10 kPa, and ALT >30 U/L for both sexes. In a secondary analysis, we estimated the population size for two scenarios among patients with type 2 diabetes (T2D). The study sample was weighted to be representative of the U.S. civilian non-institutionalized population, and demographics were reported. **Results:** We included a final of 8,319 adults (mean age = 44.6 years, 49.9% male, mean BMI = 28.9 kg/m^2, mean CAP = 258 dB/m, mean LSM = 5.7 kPa, mean ALT = 21.6 U/L). Almost 3.7% (95% CI 3.0%-4.4%), or 8.4 (6.8-10.1) million, of US adults would meet the liberal eligibility criteria for resmetirom treatment. When applying the more stringent criteria, an estimate of 1.0% (0.6%-1.5%) or 2.4 (1.4-3.3) million US adults would be eligible for treatment. Compared to those in the liberal scenario, patients in the strict scenario were more likely to be male (76.8% vs. 60.1%) and younger (mean age, 45.9 years vs. 47.7 years) but had similar BMI (mean BMI, 38.6 kg/m^2 vs. 38.1 kg/m^2). In patients with T2D, 12% (8.4%-16.0%) or 3.5 (2.4-4.5) million people would meet the liberal criteria and 3% (1.8%-4.1%) or 0.85 (0.5-1.2) million people would meet the strict criteria. **Conclusion:** The study suggests that a significant portion of the adult population in the US could benefit from resmetirom.

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Disclosures: Phuc Le: Nothing to Disclose, Anh Phan: Nothing to Disclose, Eda Kaya: Nothing to Disclose, Yusuf Yilmaz: Nothing to Disclose, Naim Alkhouri: Madrigal: Grant/Research Support, Madrigal: Speaking and Teaching, Novo Nordisk: Consulting, Novo Nordisk: Grant/Research Support, Gilead: Grant/Research Support, Corcept: Grant/Research Support, Boehringer Ingelheim: Grant/Research Support, Echosens: Speaking and Teaching, Perspectum: Consultant, Cima: Consultant, Fibronostics: Consultant, 89Bio: Grant/Research Support, Inventiva: Grant/Research Support, Merck: Grant/Research Support, Pfizer: Grant/Research Support, Ipsen: Speaking and Teaching, Intercept: Speaking and Teaching, Madrigal: Consulting, Research Funding, Novo Nordisk: Consulting, Research Funding, Inventiva: Research Funding, Boehringer Ingelheim: Consulting, Research Funding, Corcept: Research Funding, Ipsen: Consulting, Research Funding, Gliead: Consulting, Research Funding, Speaking, Perspectum: Consulting, Research Funding, Cima: Advisor, 89Bio: Consulting, Research Funding, Akero: Grant/Research Support, Arbutus: Grant/Research Support, GSK: Grant/Research Support, Regeneron: Grant/Research Support, AstraZeneka: Grant/Research Support

2407 | PATIENTS WITH ADVANCED MASLD AND DECOMPENSATION HAVE DISTINCT DIETARY HABITS

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Background: Western diet has been associated with MASLD. In individuals with MASLD, we examined if dietary habits were different between individuals with and without clinically significant fibrosis (CSF), advanced fibrosis (AF) and cirrhosis. **Methods:** All eligible, and consenting individuals with MASLD were prospectively enrolled at an academic center in the US from July 2017-Jan 2024 (N = 991), who completed Rapid Eating Assessment for Participants (REAP) (N=815), and beverage questionnaire (N=801). REAP was designed to quickly assess diet and physical activity; beverage questionnaire (Bev Q). MASLD was defined as hepatic steatosis, in the absence of heavy alcohol consumption (AUDIT < 8) and competing etiologies. CSF and AF were defined using liver stiffness measurement (LSM) of ≥8.6kPa and ≥ 12.1kPa on Vibration Controlled Transient Elastography using FibroScan® and cirrhosis was based on histology, imaging, or clinical decompensation. T-test was used to compare continuous variables and chi-square was used to compare categorical variables. **Results:** Of 991 individuals with MASLD (64% female, 93% White, 2% Hispanic; 46% with type 2 diabetes) 25% had cirrhosis, 36% had AF and 51% had CSF. Individuals with MASLD and CSF were more likely to eat regular processed food (67% vs. 56%), use regular salad dressing & mayonnaise (77% vs. 68%), consume high-sodium processed foods (58% vs. 51%), have trouble shopping or cooking (26% vs. 17%) (P <0.05 for all). MASLD with CSF also drank more sweetened juice (11% vs. 6%), whole milk (9% vs. 5%), and drank regular soft-drinks most days of the week (24% vs. 18%) (P <0.05 for all). MASLD with AF also were more likely to use higher fat red meats (70% vs. 63%), regular processed meats (71% vs. 57%), and regular salad dressing (81% vs. 76%) (P <0.05 for all). Compared to patients with compensated cirrhosis, those with decompensation ate fewer servings of vegetables (85% vs. 73%), eat regular ice cream (74% vs. 52%), less likely to eat > 6oz animal protein (68% vs. 86%), and less likely add salt to their food (46% vs. 64%); and drank more juice (2.28 ± 1.72 vs. 1.74 ±1.25) (P <0.05 for all). **Conclusion:** Differences in the dietary habits of patients with MASLD are associated with severity of fibrosis and decompensation. While further studies are needed to understand the impact of targeting these dietary habits to alter disease severity, these **Results:** offer modifiable lifestyle targets for individuals with MASLD.

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2408 | CARDIOVASCULAR OUTCOMES AND MORTALITY IN PATIENTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE: A POPULATION-BASED ANALYSIS

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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is a significant health concern, affecting 25% of the world population. Whether MASLD is associated with cardiovascular disease (CVD) risk has been controversial. This study aimed to investigate the incidence of adverse CVD and all-cause mortality in patients with MASLD using real-world data from a large national database in the United States (US). **Methods:** This retrospective cohort study used the TriNetX research network database to identify patients ≥18 with MASLD. Patients in the MASLD cohort were matched with patients without a history of MASLD (non-MASLD group) according to age, demographics, comorbidities, and medication using 1:1 propensity matching in the same database. The primary outcome was an incident of CVD. The secondary outcome was all-cause mortality. COX proportional hazard models were used to assess the effect of MASLD on CVD outcomes. **Results:** 751,681 individuals with MASLD (age: 47.9 +/- 15.9 years; 51.5% female) were matched with 751,681 individuals (49.2 +/- 17] years; 50.6% female) without MASLD. The MASLD group had significantly higher risk of myocardial infarction (aHR, 2.48 95% CI, 2.37-2.6), strokes (aHR, 1.84; 95% CI, 1.76-1.91), TIA (aHR, 1.17; 95% CI, 1.1-1.25), heart failure (aHR, 1.82; 95% CI, 1.77-1.86) compared with the non-MASLD group. Similarly, all-cause mortality was substantially higher in the MASLD group (aHR, 2.39; 95% CI, 2.3-2.5). These outcomes were consistent at follow-up durations of 1, 3, 5, and 10 years. **Conclusion:** These findings provide real-world evidence that suggests a strong correlation between MASLD and increased adverse CVD events and all-cause mortality in this patient population. Management of patients with MASLD should focus on cardiovascular risk prevention to reduce morbidity and mortality in this patient population.

Table 1. Cardiovascular outcomes after propensity matching when comparing patients with and without MASLD at 1-year, 3-year, 5-year, and 10-year follow-up.

	PROPENSITY MATCHING ANALYSIS aHR* [95%CI]			
Cardiovascular outcomes	**One-year**	**Three-year**	**Five-year**	**Ten-year**
Myocardial infarction	2.481 [2.368, 2.600]	1.516 [1.468, 1.565]	1.443 [1.398, 1.489]	1.455 [1.410, 1.502]
Ischemic strokes	1.706 [1.630, 1.787]	1.255 [1.214, 1.297]	1.212 [1.173, 1.252]	1.219 [1.180, 1.260]
Hemorrhagic strokes	3.310 [2.960, 3.701]	1.942 [1.796, 2.100]	1.879 [1.740, 2.030]	1.887 [1.747, 2.038]
Transient ischemic attack	1.172 [1.101, 1.248]	1.008 [0.965, 1.052]	0.979 [0.939, 1.022]	0.980 [0.939, 1.022]
Heart failure	1.815 [1.772, 1.858]	1.365 [1.340, 1.391]	1.322 [1.298, 1.347]	1.316 [1.292, 1.340]
Unstable angina	1.948 [1.796, 2.114]	1.433 [1.356, 1.514]	1.382 [1.310, 1.460]	1.384 [1.310, 1.461]
Strokes (total)	1.838 [1.760, 1.919]	1.315 [1.274, 1.357]	1.270 [1.232, 1.310]	1.278 [1.239, 1.319]
All-cause mortality	2.394 [2.322, 2.468]	1.719 [1.683, 1.757]	1.696 [1.661, 1.733]	1.705 [1.669, 1.741]

**aHR: adjusted Hazard Ratio. Adjusted for age, race, ethnicity, comorbidities, and medications.*

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2409 | NON-INVASIVE ASSESSMENT COMPARISON FOR LIVER DISEASE SCREENING: UTILIZING HEPATOSCOPE® AND FIBROSCAN® FOR THE ASSESSMENT OF HEPATIC STEATOSIS AND FIBROSIS IN SOUTHERN ARIZONA

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Background: Rates of metabolic dysfunction-associated steatotic liver disease (MASLD) are steadily increasing in the United States (U.S). Yet, there is a lack of robust non-invasive liver disease screening efforts for adults. Transient elastography (TE) by FibroScan® (Echosens, France) has emerged as the non-invasive tool to identify hepatic steatosis and fibrosis within the context of the clinical care pathway model for the prevention and treatment of MASLD. However, as other noninvasive tests (NITs) for TE are introduced to the commercial market, it is important to assess the comparisons of such tests. Therefore, this study compares Hepatoscope®, a new commercially available TE, and FibroScan® for the non-invasive assessment of hepatic steatosis and fibrosis among adults from a community-based sample in Southern Arizona. **Methods:** Paired sample t-tests were conducted to analyze data from 329 Southern Arizona residents (women=181; men=143; mean age=52.8 ±13.9; Hispanic origin=296; non-Hispanic origin=28; mean BMI=30.7kg/m^2). Hepatic steatosis was assessed via FibroScan® and Hepatoscope® using continuous attenuation parameter (CAP) values measured in decibels per meter (dB/m). MASLD was identified as having a CAP score ≥288 dB/m. Liver stiffness measurements (LSM) in kilopascals (kPa) indicate fibrosis values. **Results:** The proportion of participants with MASLD differed by NIT used. Using FibroScan® 130 (39.5%) participants were identified with MASLD, including 45.2% men and 54.8% women (p >0.05). Whereas Hepatoscope® identified 83 participants with MASLD, including 56.8% men and 43.1% women (p <0.01). Overall, CAP scores were higher for FibroScan® (M=273.5, ± 53.2 dB/m) compared to Hepatoscope® (M=252.3, ± 47.2dB/m). More specifically, a 21.2-point difference (SD=48.9 dB/m) between FibroScan® and Hepatoscope® was observed (95%CI=15.8, 26.5, p<0.001) for CAP scores. Fibrosis levels were slightly higher for Hepatoscope® (M=5.8, ± 3.4kPa) than for FibroScan® (M=5.5, ± 3.1kPa). Particularly, a -0.3-point difference (SD=2.6) between FibroScan® and Hepatoscope® was observed (95%CI=-0.62, -0.05, p=0.02). **Conclusion:** Hepatic steatosis **Results:** via Hepatoscope® were underestimated when compared to FibroScan®. Conversely, both NITs demonstrated a relative agreement when comparing liver fibrosis scores. This study highlights the need for a more consistent and reliable availability of NITs for the assessment of liver disease prevention and treatment efforts in the U.S.

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2410 | THE BEST CUTOFF FOR TRANSIENT ELASTOGRAPHY AS A PREDICTOR OF LIVER OUTCOMES IN METABOLIC-ASSOCIATED STEATOTIC LIVER DYSFUNCTION (MASLD) PATIENTS ◆

Gil Salles[1] Cristiane Villela-Nogueira[2] Nathalie Leite[3] Ana Carolina Cardoso[3] Natalia Balassiano Wajsbrot[4] Claudia Equi[4] Ligia Rocha[4] Lais Arrivabene Barbieri[4] Henrique Sérgio Coelho[5] Claudia Cardoso[6]

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Background: Noninvasive **Methods:** are useful tools in stratifying liver fibrosis in patients with MASLD. However, their role in predicting liver outcomes is not yet clearly established, nor are their cutoff points. **Methods:** At the beginning of their follow-up in a tertiary care setting, a cohort of MASLD individuals who underwent transient elastography (TE) by Fibroscan® (Echosens, Fr) were included. Liver outcomes that occurred during the follow-up period were registered (hepatocellular carcinoma, upper gastrointestinal bleeding, ascites, encephalopathy, liver transplant) and liver-related death) with the first outcome considered for analysis. Cox regression analysis was used to evaluate variables independently associated with liver outcomes. **Results:** 612 patients with TE were included (65% women, 61 ± 12 years old, 53% obese, 81% DM, 78% hypertensive, 69% using Statins and 70% Aspirin). Liver outcomes were observed in 28 (5%) patients over a follow-up of 67±24 months. Regarding TE **Results:** for liver stiffness at baseline, 32% were ≥ 8kPa and 20% ≥ 10 kPa. In the survival analysis, a significant difference was observed when comparing the Kaplan-Meier curves between patients with TE <8.0 kPa vs ≥ 8kPa and also in those with TE <10 vs 10 kPa (both with log-rank- p= <0.001). However, based on the sensitivity (S) and specificity (E) values of each cutoff point defined by the AUROC curve (0.93 - 95% CI 0.87- 0.94; p<0.001), It was noted that for the cutoff point of 8 kPa, S is 96% and E is 72%, whereas when considering the cutoff point of 10 kPa, S is 89% and E is 84%. **Conclusion:** Transient elastography is an excellent predictor of liver outcomes in patients with MASLD, with cutoff points of 8 kPa and 10 kPa. However, due to the higher specificity, those with a 10 kPa cutoff should be followed up carefully, mainly in a tertiary care setting.

Disclosures: Gil Salles: Nothing to Disclose, Cristiane Villela-Nogueira: Nothing to Disclose, Nathalie Leite: Nothing to Disclose, Ana Carolina Cardoso: Nothing to Disclose, Natalia Balassiano Wajsbrot: Nothing to Disclose, Claudia Equi: Nothing to Disclose, Ligia Rocha: Nothing to Disclose, Lais Arrivabene Barbieri: Nothing to Disclose, Henrique Sérgio Coelho: Nothing to Disclose, Claudia Cardoso: Nothing to Disclose

2411 | ASSOCIATION OF NAFLD WITH AND WITHOUT ADVANCED FIBROSIS WITH FATAL, NON-FATAL, AND COMBINED CARDIOVASCULAR EVENTS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background:
Non-alcoholic fatty liver disease (NAFLD) is increasingly recognized as a risk factor for cardiovascular disease (CVD). However, the association between NAFLD with and without advanced fibrosis, and the risk of fatal and non-fatal CVD events remains unclear. We conducted a systematic review with meta-analysis to quantify these associations and investigate the impact of the fibrosis stage on CVD risk. **Methods:** Following PRISMA guidelines, a systematic search of PubMed, Scopus, Web of Science, and Cochrane Library was conducted up to 2024. We included studies conducted in adults > 18 years old, with a confirmed diagnosis of NAFLD either through imaging or histology. results were reported as pooled hazard ratios (HR) with 95% confidence intervals

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(CI) for the association of NAFLD, with and without advanced fibrosis, with fatal, non-fatal, or combined CVD events. Random effects meta-analysis was performed using standard methodology and heterogeneity was assessed using the I2% statistics. **Results:** Forty-nine studies, encompassing 1,553,770 individuals with NAFLD were included. Mean age was 67.73 years (SD 4.07); the median follow-up duration was 7.0 years (IQR 7.70). Patient populations were diverse, with varying prevalence of obesity, hypertension, and type 2 diabetes and mean BMI of 24.7. Several studies reported a high prevalence of overweight and obese patients (58%), arterial hypertension (58%), and type 2 diabetes mellitus (26%) in their NAFLD cohorts. NAFLD without advanced fibrosis was significantly associated with increased risks of fatal (HR 1.46, 95% CI 1.23-1.73, p<0.01), non-fatal (HR 1.54, 95% CI 1.29-1.84, p<0.01), and combined CVD events (HR 1.60, 95% CI 1.30-1.97, p<0.01). In the group with advanced fibrosis, a significant association was observed only for combined CVD events (HR 1.79, 95% CI 1.09-2.92, p<0.01), while the risks for fatal (HR 1.23, 95% CI 1.00-1.52) and non-fatal CVD events (HR 1.08, 95% CI 0.82-1.42) were not statistically significant. **Conclusion:** This meta-analysis of 49 studies, encompassing over 1.5 million individuals, confirms that NAFLD, even without advanced fibrosis, is an independent risk factor for CVD. The risk is further amplified with advanced fibrosis, particularly for combined CVD events. The lack of statistical significance for individual fatal and non-fatal events in advanced fibrosis may be due to limited data, emphasizing the need for further research in this subgroup. These results underscore the importance of early NAFLD detection and management to mitigate CVD risk, especially in populations with high cardiometabolic comorbidities. Given the high prevalence of overweight and obese patients, hypertension, and type 2 diabetes mellitus in NAFLD cohorts, integrated management strategies addressing these cardiometabolic risk factors are warranted.

	Pooled random-effect (95% confidence interval, I2% heterogeneity) no.of studies		
	Fatal CVD events	Non-fatal CVD events	Combined CVD events
NAFLD without advanced fibrosis with incident CVD events	1.46 (1.23-1.73; 84%), 12 (p< 0.01)	1.54 (1.29-1.84; 93%), 24 (p< 0.01)	1.60 (1.30-1.97; 97%), 17 (p< 0.01)
NAFLD with advanced fibrosis with incident CVD events	1.23 (1.00-1.52; 65%), 3	1.08 (0.82-1.42; 70%), 4	1.79 (1.09 - 2.92; 81%), 7 (p< 0.01)

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2412 | MAGNESIUM DEPLETION SCORE AND MORTALITY IN INDIVIDUALS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE OVER A MEDIAN FOLLOW-UP OF 14 YEARS

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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) was recently associated with increased risks of all-cause and cardiovascular disease (CVD) mortality. Identifying MASLD patients at higher risk of mortality will facilitate precision-based intervention strategies in this population. Magnesium (Mg) deficiency measured using either Mg intake or serum Mg has been associated with higher risk of nonalcoholic fatty liver disease (NAFLD) as well as mortality due to liver diseases. We developed and validated an instrument tool, the Mg depletion score (MDS), in predicting body Mg status. The MDS incorporates pathophysiological factors that influence the kidneys' reabsorption capability and outperforms both serum Mg and Mg intake. This study aims to examine whether MDS in combination with Mg intake are associated with mortality among individuals with MASLD. **Methods:** A total of 2,906 participants was identified as MASLD and followed up over 14.2 years in the National Health and Nutrition Examination Survey (NHANES) III cohort. The MDS was calculated by aggregating

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four factors influencing the kidneys' reabsorption capability. The associations between MDS and all-cause, CVD and cancer mortality were quantified using the Cox proportional hazards regression models. **Results:** In the MASLD cohort, higher MDS was significantly associated with increased risk of all-cause mortality in multivariable-adjusted model comparing participants with MDS>2 to MDS=0 (HR, 2.39; 95%CI, 1.31-4.35; $P_{\text{-trend}}$=0.007). The association was primarily present and became stronger among participants who did not meet the estimated average requirement (EAR) level of Mg intake for all-cause mortality (HR, 3.22; 95%CI, 1.46-7.08; $P_{\text{-trend}}$ =0.004) while null association was observed when Mg intake was above EAR ($P_{\text{-interaction}}$=0.07). A similar association pattern was observed for CVD mortality (HR, 2.60; 95%CI, 1.11-6.08; $P_{\text{-trend}}$=0.04), but not cancer mortality overall and in stratified analysis by Mg intake level. **Conclusion:** In individuals with MASLD, higher MDS (MDS>2), indicative of worse body Mg status, was associated with over two-fold increased risks of all-cause and CVD mortality compared to those with MDS=0. The associations were primarily present in participants who did not meet the EAR level of Mg intake. These findings can pave the path for interventions aiming to mitigate CVD risk and improve survival in patients with MASLD.

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2413 | EXAMINING THE PREVALENCE OF HEPATIC STEATOSIS AND ADVANCED FIBROSIS USING MULTIPLE NON-INVASIVE MEASURES IN CANADA: A NATIONAL ESTIMATE USING THE CANADIAN HEALTH MEASURES SURVEY (CHMS) FROM 2009-2019

Jacob Romano[1] Jessica Burnside[1] Giada Sebastiani[2] Keyur Patel[3] Alnoor Ramji[4] Mark Swain[5] Sahar Saeed[1]

[1]Queen's University, [2]McGill University Health Centre, [3]University of Toronto, [4]University of British Columbia, [5]University of Calgary

Background: Prevalence estimates are crucial for understanding and enhancing the preparedness to manage, treat, and prevent the burden of MASLD. This is the first study to estimate the prevalence of hepatic steatosis and advanced fibrosis in Canada, leveraging a nationally representative survey and multiple validated non-invasive tests (NITs). **Methods:** The Canadian Health Measures Survey (CHMS) is Canada's largest direct health measures survey, which collects data on sociodemographic, clinical factors, and blood chemistry in a representative population. We identified steatosis using two NITs: the Hepatic Steatosis Index (HSI) (including ALT /AST, BMI, type 2 diabetes (T2D), and sex) using the cut-off of >35 and the NAFLD Ridge Score (NRS) (ALT, HDL cholesterol, triglycerides, hemoglobin A1c, leukocytes, and hypertension) using the cut-off of >0.44. Advanced fibrosis was assessed amongst adults with steatosis using the FIB-4 Index (>2.67) and NAFLD fibrosis score (NFS) (>0.676). Agreement between the measurements was evaluated using Cohen's kappa statistics. Survey weights were incorporated to account for oversampling, survey nonresponse, and post-stratification. **Results:** Between 2009 and 2019, after excluding people with viral hepatitis and HIV, 1365 children (between 9-17 years) and 4664 adults (18-79 years) were included in this study. Among adults, 51% were male; 75% were White, 13% were Asian, 29% had a household income of $30-65,000/year, 5% had T2D, and 18% had hypertension. There was substantial agreement between the NITs (kappa statistics was 0.62 between HSI and NRS and 0.79 between NFS and FIB-4). Steatosis prevalence ranged from 36.2-49.6% and varied by sociodemographic and clinical factors (Fig 1A). HSI estimated higher prevalence compared to NRS, particularly for females, 45% (95%CI: 42,49%) vs. 22% (19,25%), respectively (Fig. 1A). Notably, 11% (8,15%) of children had evidence of steatosis. Overall, 2.4-3.5% of adults with steatosis had evidence of advanced liver fibrosis (no children), and people with T2D had double the prevalence (Fig. 1B). **Conclusion:** We estimate between 1 in 3 and 1 in 2 adults have steatosis based on two validated NITs, and 388,800-567,000 Canadians could have advanced liver fibrosis. Despite its prevalence, there are no routine screening guidelines in Canada, leaving most patients unaware of their condition. Studies like this are essential for raising awareness and advocating for the inclusion of MASLD on the national and global public health agendas.

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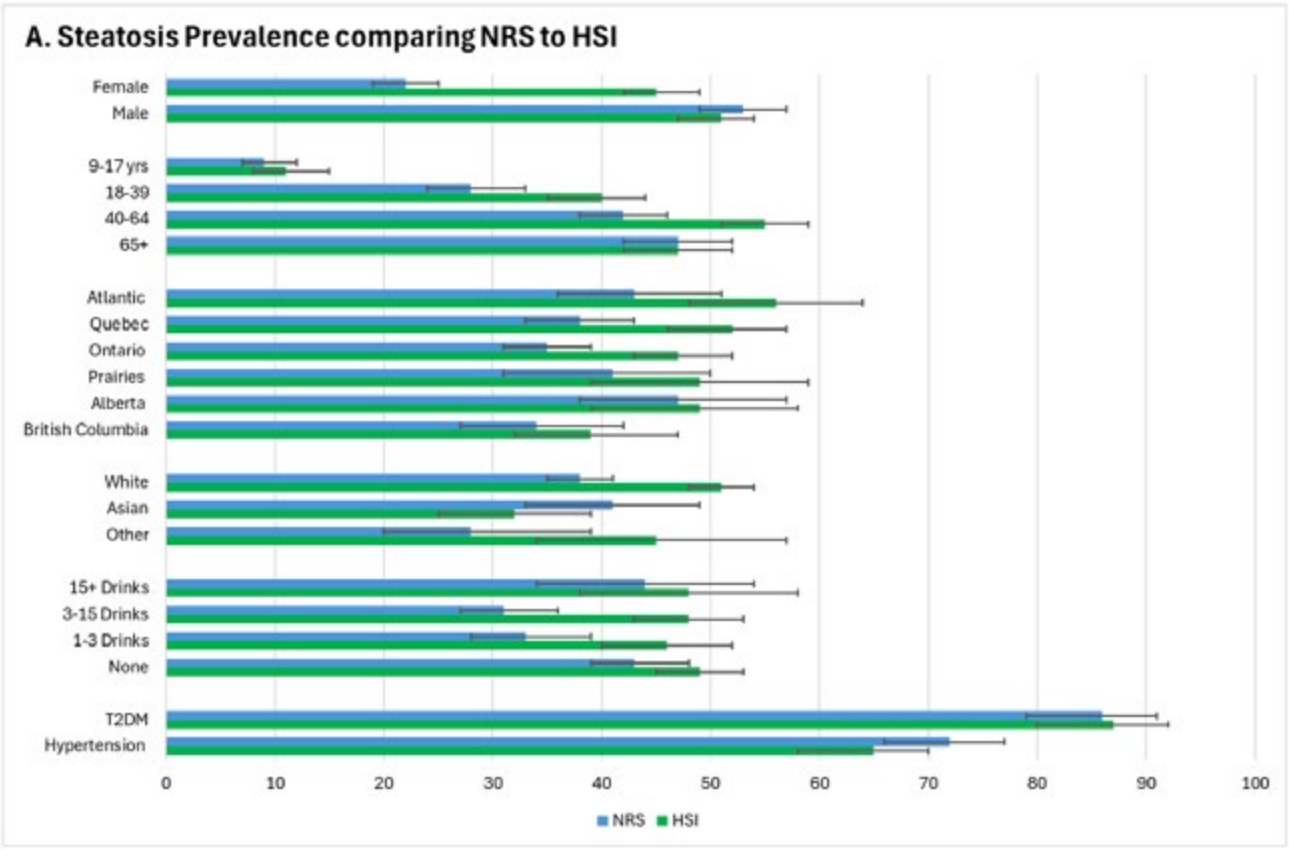

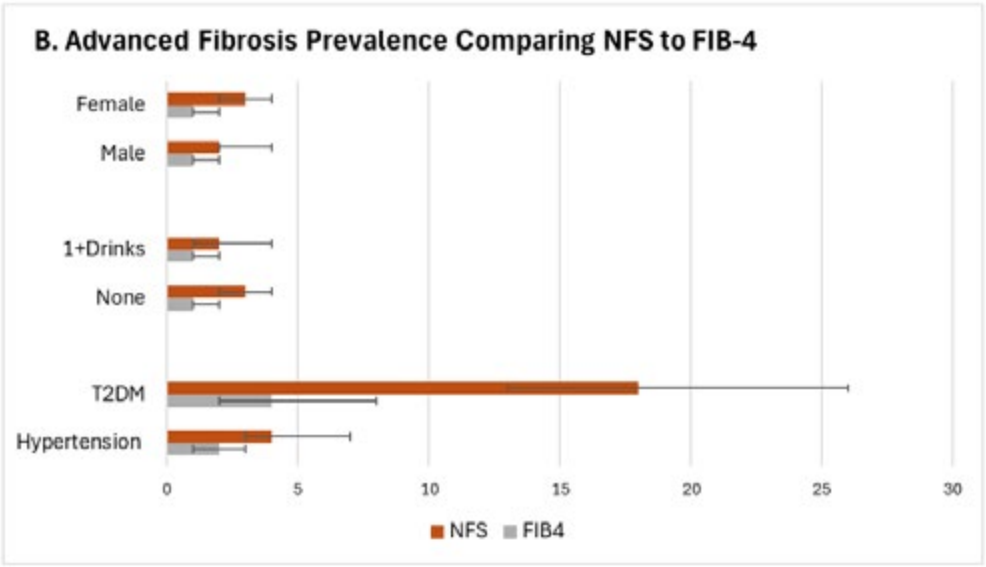

Disclosures: Jacob Romano: Nothing to Disclose, Jessica Burnside: Nothing to Disclose, Giada Sebastiani: Novo Nordisk: Consultant, Abbvie: Speaking and Teaching, Merck: Consultant, Gilead: Speaking and Teaching, Theratechnologies Inc.: Grant/Research Support, Keyur Patel: Novo-Nordisk: Consultant, Gilead Sciences: Consultant, Merck: Consultant, Resalis: Advisor, Alnoor Ramji: Nothing to Disclose, Mark Swain: Ipsen: Advisor, Abbott: Advisor, Advanz: Advisor, Novo Nordisk: Advisor, GSK: Advisor, Ipsen: clinical trial research grant support, Novo Nordisk: clinical trial research grant support, Madrigal: clinical trial research grant support, Kowa: clinical trial research grant support, Gilead: clinical trial research grant support, Abbvie: clinical trial research grant support, Merck: clinical trial research grant support, Galectin: clinical trial research grant support, Sahar Saeed: Novo Nordisk: Consultant

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2414 | HELICOBACTER PYLORI CAGA/VACAS1-M1 STRAIN IS ASSOCIATED WITH HIGH RISK OF FIBROSIS IN METABOLIC-DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE

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[1]National University of Misiones, [2]Barcelo University Institute of Health Sciences

Background: Background: Recent studies have suggested an association between *H. pylori* and metabolic dysfunction associated steatotic liver disease (MASLD). We aim to evaluate the association of *H. pylori* virulence genes with non-invasive markers of liver injury and fibrosis in MASLD subjects. **Methods:** A total of 362 dyspeptic patients who underwent gastroscopy were selected. Biochemical, clinical parameters, ultrasound, FIB-4 score, liver stiffness measurement (LSM) by vibration-controlled transient elastography (VCTE), gastric biopsies, and *H. pylori* virulence genes (cagA, vacA) were evaluated. **Results:** A cohort comprised of 61% women and 39% men with a median age of 52 (40-60) years. MASLD was observed in 42%, and *H. pylori*-positive in 45%. No differences were observed regarding *H. pylori*status at co-morbid metabolic conditions. In MASLD cohort, *H. pylori*-positive was associated with higher AST, ALT, FIB-4 and LSM. Indeed, carriers of *cagA/vacA-s1/m1*-positive allelic combination were associated with higher AST, ALT, FIB-4 and LSM but not *cagA/vacA-s1/m1*-negative. The OR for high-risk of significant/advanced- fibrosis by LSM-VCTE (≥8kPa) with *H. pylori*-positive was 2.56 (95% CI, 1.2-5.75) and for *cagA/vacA-s1/-m1*-positive allelic carriers was 4.01 (95% CI, 1.38-11.56), but non-significant association in *cagA/vacA-s1/-m1*-negative. After adjusting for age, gender, diabetes, BMI and hypertension the OR for LSM-VCTE ≥8kPa with *H. pylori*-positive was 2.43 (95% CI, 1.88–12.44), and *cagA/vacA-s1/m1*-positive allelic carriers was 4.06 (95% CI, 1.22-14.49). **Conclusion:** Conclusions: In our cohort of FD patients with MASLD, *H. pylori* was associated with non-invasive markers of liver injury and fibrosis. Carriers of *cagA/vacA-s1/m1*-positive allelic combination showed an independent risk of significant/advanced fibrosis by LSM-VCTE.

Disclosures: Fernando Barreyro: Nothing to Disclose, Facundo Maiorana: Nothing to Disclose, Magali Neschuk: Nothing to Disclose, Maria Viriginia Caronia: Nothing to Disclose, Karina Elizondo: Nothing to Disclose, Adolfo Schneider: Nothing to Disclose, Georgina Veron: Nothing to Disclose, Pedro Dario Zapata: Nothing to Disclose

2415 | ALCOHOL USE IS ASSOCIATED WITH INCREASED MORTALITY AMONG THOSE WITH STEATOTIC LIVER DISEASE: A POPULATION-BASED STUDY

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[1]Stanford University Medical Center, [2]Stanford University and Duke University, [3]University of Vermont, [4]Nagoya University Graduate School of Medicine

Background: In the last decade, cirrhosis-related mortality in the United States has been increasing mainly from steatotic liver disease (SLD) and alcohol-associated liver disease (ALD). This current study aimed to identify the impacts of alcohol use on mortality among those with SLD. **Methods:** This is a cross-sectional study of patients from the National Health and Nutrition Examination Survey (NHANES) from 1988-1992 with mortality follow-up to 2019. Adults aged ≥18 years with complete demographic, laboratory, and hepatic ultrasound data were included. SLD was defined as the presence of hepatic steatosis identified on ultrasound. Moderate alcohol use was defined as ≤1 drink/day for females and ≤2 drinks/day for males. ALD was defined by >1 drink/day for females and >2 drinks/day for males and evidence of hepatic steatosis on ultrasound or alanine transaminase or aspartate aminotransferase >1x upper limit of normal. Advanced fibrosis was assessed via FIB-4 score. Analyses were weighted to represent the civilian United States population. **Results:** We analyzed 9,781 adult persons, with weighted prevalence for SLD without alcohol use 6.2% (95% CI: 5.30-7.25), SLD with moderate alcohol use 10.3% (95% CI: 8.95-11.7), and ALD 4.8% (95% CI: 3.92-5.85). Compared to SLD without alcohol use and SLD with moderate alcohol use, those with ALD were older (41.4 vs. 43.6 vs 43.2), more likely with diabetes (19.9% vs. 41.7% vs. 42.2%), hypertension (35.0% vs. 63.2% vs. 58.8%), advanced fibrosis (2.24% vs. 3.03% vs. 10.5%), hepatitis B (1.13% vs. 3.00% vs. 8.80%) or C coinfection (5.62% vs. 6.07% vs. 11.1%) (all p<0.001 except for hepatitis B, p=0.045). A total of 815 persons died after a median follow-up time of 26.7 years. There were significant differences in the mortality rates (per 1000 person-years) among the different SLD categories (log-rank p<0.001) as follows: SLD without alcohol use (10.4, 95% CI: 8.87-12.1), SLD with moderate alcohol use (16.4,

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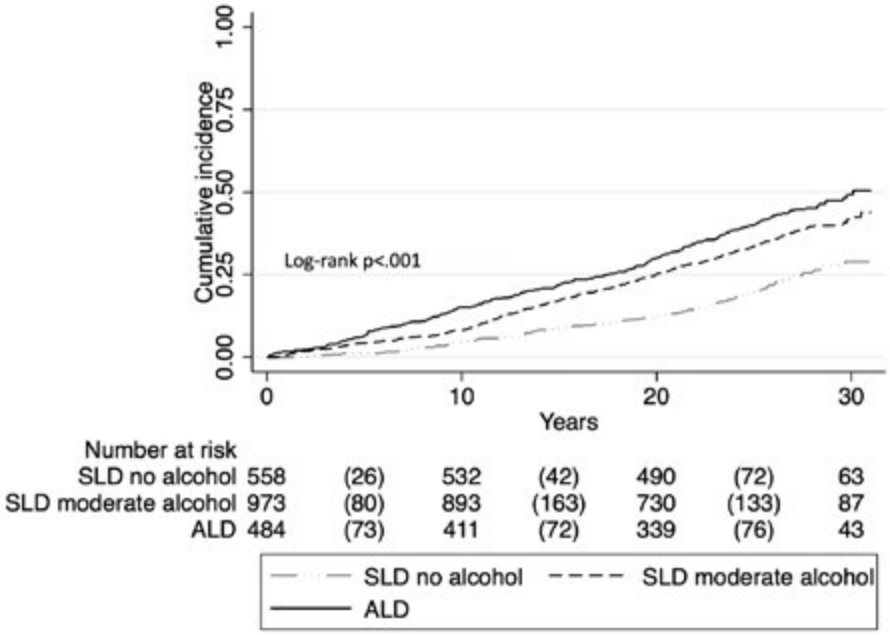
95% CI: 14.9-18.1), and ALD (20.3, 95% CI:17.9-23.0) (Figure 1). **Conclusion:** In this population-based cohort, persons with moderate or heavy alcohol use were older, had increased comorbidities and mortality compared to SLD without alcohol use. Prevention of adverse outcomes among those with SLD should include alcohol cessation (including moderate consumption) and treatment of underlying metabolic and liver-related diseases.



Disclosures: Ramsey Cheung: Nothing to Disclose, Sahith Kudaravalli: Nothing to Disclose, Michael Le: Nothing to Disclose, Takanori Ito: Chugai Pharmaceutical Co., Ltd.: Grant/Research Support, Chugai Pharmaceutical Co., Ltd. and AstraZeneca: Speaking and Teaching

2416 | THE INTERPLAY BETWEEN HELICOBACTER PYLORI INFECTION AND RS738409 PNPLA3 IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE

Fernando Barreyro[1] Facundo Maiorana[2] Magali Neschuk[1] Maria Virginia Caronia[1] Karina Elizondo[3] Adolfo Schneider[3] Gerogina Veron[3] Pedro Dario Zapata[2]

[1]National University of Misiones, [2]National Universisty of Misiones, [3]Barcelo University Institute of Health Sciences

Background: Background: Recent studies have suggested an association between *H. pylori* and MASLD. However, epidemiologic studies have yielded inconsistent results. We aim to evaluate the association of *H. pylori* and the rs738409 G-allele in the PNPLA3 in MASLD diagnosis and severity. **Methods:** A multi-center cross-sectional study was conducted. A total of 224 dyspeptic patients who underwent gastroscopy was selected. Biochemical, clinical parameters, ultrasound, FIB-4 score, LSM by VCTE, gastric biopsies, *H. pylori* status, and rs738409 PNPLA3 were evaluated. A second retrospective cohort of 86 patients with biopsy-proven MASLD who underwent gastroscopy with gastric biopsies was analyzed. **Results:** A cohort comprised of 65% women and 35% men with a median age of 52 (42-60) years. MASLD was observed in 52%, and *H. pylori*-positive in 51%. *H. pylori* infection was associated with MASLD, but in multivariate analyses adjusted for G-allele PNPLA3, it became not significant. Then in MASLD dyspeptic cohort, *H. pylori* infection was associated with higher AST, LSM by VCTE. The OR for FIB-4 ≥1.3 and LSM ≥8 kPa with *H. pylori* infection was 2.76 (95% CI, 1.19-6.89; p = 0.022) and 3.97 (95% CI, 1.63-10.8; p = 0.004), respectively. This association remained unchanged after adjusting for the most clinically relevant MASLD risk factors for fibrosis (obesity, type-II DBT, and G-allele PNPLA3). In patients with biopsy-proven MASLD, *H. pylori* infection was associated with higher markers of liver injury, lobular inflammation, ballooning, NAS score, and fibrosis stage (Table). Notably, the combination of *H. pylori* infection and G-allele PNPLA3 appeared to exacerbate MASLD severity. *H. pylori*-positive infection with G-allele PNPLA3 was significantly associated with higher proportion of patient with MASH (74%), versus *H. pylori*-negative status with G-allele PNPLA3 (37%), *H. pylori*-positive infection without G-allele PNPLA3 (33%), and *H. pylori*-negative status

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without G-allele PNPLA3 (5%) (p<0.001). **Conclusion:** Conclusions: our results suggest that *H. pylori* infection may play a role in the progression of liver injury and fibrosis in patients with MASLD, especially in those with specific genetic predispositions.

Variable		Total cohort	H. pylori (-)	H. pylori (+)	p
	n (%)	n: 86	n: 52 (59.5)	34 (49.5)	
Liver Histology					
Steatosis Grade	1, n (%)	41 (47.7)	26 (50.0)	15 (44.1)	ns
	2, n (%)	41 (47.7)	25 (48.1)	16 (47.1)	
	3, n (%)	4 (4.7)	1 (1.9)	3 (8.8)	
Lobular Inflammation Grade	0, n (%)	6 (7.0)	6 (11.5)	0 (0.0)	ns
	1, n (%)	68 (79.1)	41 (78.8)	27 (79.4)	
	2, n (%)	12 (14.0)	5 (9.6)	7 (20.6)	
Ballooning Grade	0, n (%)	28 (32.6)	25 (48.1)	3 (8.8)	<0.001
	1, n (%)	41 (47.7)	25 (48.1)	16 (47.1)	
	2, n (%)	17 (19.8)	2 (3.8)	15 (44.1)	
NAS Score	1, n (%)	2 (2.3)	2 (3.8)	0 (0.0)	0.001
	2, n (%)	13 (15.1)	12 (23.1)	1 (2.9)	
	3, n (%)	34 (39.5)	25 (48.1)	9 (26.5)	
	4, n (%)	21 (24.4)	9 (17.3)	12 (35.3)	
	5, n (%)	13 (15.1)	4 (7.7)	9 (26.5)	
	6, n (%)	3 (3.5)	0 (0.0)	3 (8.8)	
MASH (NAS ≥ 4)	0, n (%)	49 (57.0)	39 (75.0)	10 (29.4)	<0.001
	1, n (%)	37 (43.0)	13 (25.0)	24 (70.6)	
Fibrosis Stage	0, n (%)	18 (20.9)	13 (25.0)	5 (14.7)	0.001
	1, n (%)	37 (43.0)	27 (51.9)	10 (29.4)	
	2, n (%)	12 (14.0)	8 (15.4)	4 (11.8)	
	3, n (%)	4 (4.7)	2 (3.8)	2 (5.9)	
	4, n (%)	15 (17.4)	2 (3.8)	13 (38.2)	

Disclosures: Fernando Barreyro: Nothing to Disclose, Facundo Maiorana: Nothing to Disclose, Magali Neschuk: Nothing to Disclose, Maria Virginia Caronia: Nothing to Disclose, Karina Elizondo: Nothing to Disclose, Adolfo Schneider: Nothing to Disclose, Gerogina Veron: Nothing to Disclose, Pedro Dario Zapata: Nothing to Disclose

2417 | INVESTIGATING THE PREVALENCE OF METALD IN COMPARISON TO MASLD IN PATIENTS PREVIOUSLY DIAGNOSED WITH NAFLD

Yousef Almahanna[1] Ahmed Almohsen[2] Yi Nong Song[2] Amani Bajunayd[2] Rokhsana Mortuza[2] Jeemin Kim[2] Adrienne Abaya[2] Mohammad Qasim Khan[2] Juan Pablo Arab[2]

[1]The University of Western Ontario, [2]University of Western Ontario

Background: Steatotic liver disease (SLD) encompasses various liver conditions, including metabolic-dysfunction associated steatotic liver disease (MASLD), alcohol-associated liver disease (ALD), and the dual-etiology form known as MetALD. This study aimed to determine the prevalence of MASLD and MetALD in patients previously diagnosed with Non-Alcoholic Fatty liver Disease (NAFLD), by accurately assessing their alcohol intake patterns. **Methods:** A cross-sectional analysis was conducted on patients referred to the NAFLD clinic at an academic center in Ontario, Canada. Electronic medical records of 312 patients seen between October 1, 2021, and October 2022, were retrospectively reviewed. Patients were categorized based on their alcohol consumption patterns to determine the prevalence of MASLD, MetALD, and ALD. We used the limits of alcohol consumption that were suggested in the new SLD nomenclature. **Results:** In our sample of 312 patients (137 male and 175 females), the majority of patients met the criteria for MASLD with a percentage of 89.4% (n=279), compared to 8.0% of the patients (n=25) meeting the MetALD criteria. Despite the fact that females were more than males in all SLD-class groups, female gender was more prominent across the three groups with statistically significant difference (p=0.006), with more females meeting criteria for MetALD (84%), ALD (75%) and MASLD (53%). Age

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was almost similar across all groups with no significant difference between them, with a mean ages of 53.8, 53.7, 53.6 years for ALD, MASLD, and MetALD groups, respectively. Race also was not significantly different between groups with the Caucasian race being the most prevalent among all groups. **Conclusion:** Our findings suggest that the new SLD nomenclature captured a significant portion of alcohol intake in patients previously categorized as having NAFLD. It also highlights the importance of clarifying the accurate alcohol intake by primary care physicians at the time of referral to hepatology/GI specialists, taking into account gender-based-safe alcohol consumption thresholds. Although it was not statistically significant, older age and certain ethnicities can be additional helpful indicators in predicting the possibility of having SLD.

	ALD (N=8)	MASLD (N=279)	MetALD (N=25)	Total (N=312)	p value
Age At Initial Consultation					0.998[1]
Mean (Sd)	53.8 (15.8)	53.7 (15.7)	53.6 (14.5)	53.7 (15.5)	
Range	30.0 - 74.0	18.0 - 85.0	23.0 - 80.0	18.0 - 85.0	
Sex					0.006[2]
Female	6.0 (75.0%)	148.0 (53.0%)	21.0 (84.0%)	175.0 (56.1%)	
Male	2.0 (25.0%)	131.0 (47.0%)	4.0 (16.0%)	137.0 (43.9%)	
Race/Ethnicity					0.370[2]
Asian	0.0 (0.0%)	31.0 (11.1%)	3.0 (12.0%)	34.0 (10.9%)	
Hispanic	0.0 (0.0%)	13.0 (4.7%)	4.0 (16.0%)	17.0 (5.4%)	
African	0.0 (0.0%)	7.0 (2.5%)	0.0 (0.0%)	7.0 (2.2%)	
Caucasian	8.0 (100.0%)	224.0 (80.3%)	18.0 (72.0%)	250.0 (80.1%)	
Middle East	0.0 (0.0%)	4.0 (1.4%)	0.0 (0.0%)	4.0 (1.3%)	

Disclosures: Yousef Almahanna: Nothing to Disclose, Ahmed Almohsen: Nothing to Disclose, Yi Nong Song: Nothing to Disclose, Amani Bajunayd: Nothing to Disclose, Rokhsana Mortuza: Nothing to Disclose, Jeemin Kim: Nothing to Disclose, Adrienne Abaya: Nothing to Disclose, Mohammad Qasim Khan: Nothing to Disclose, Juan Pablo Arab: Nothing to Disclose

2418 | THE BURDEN OF MASLD IN SOUTH ASIA (2017-2021): A GLOBAL BURDEN OF DISEASE ANALYSIS

Sheena Bhushan[1] *Lisa Gambini*[1] *Idopise Umana*[1]

[1]*Northeast Georgia Medical Center*

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) affects more than 30% of the population worldwide and poses a significant global health challenge. Growing economies, particularly in South Asia have seen a recent uptick in the prevalence of lifestyle and chronic diseases. The aim of this study is to assess the burden of MAFLD in this region of the world. **Methods:** Using the Global Burden of Diseases, Injuries and Risk Factors Study from 2017-2021, we examined the trend of disability-adjusted life years (DALYs), death rates and prevalence rates in 5 countries in South Asia (India, Bangladesh, Pakistan, Nepal and Bhutan). **Results:** Overall, the prevalence rate of MASLD in the 5 countries from 2017-2021 was 23,1622.24 per 100,000 individuals. Women had significantly higher death rates than men (Mean 3.18, SD 4.57 vs Mean 2,06, SD 2.83, P <0.001). The highest death rate is observed in individuals aged 65 and older (mean 7.26 per 100,000, SD=4.84). The highest prevalence rate was seen in Bangladesh (mean 260,032.51 per 100,000; SD= 405,042.20), followed by India (Mean 211,351.54 per 100,000, SD=340,429.84) Nepal (Mean 45,472.17 per 100,000, SD=57,577.62), Pakistan (31,080.10 per 100,000, SD= 51,711.27) and Bhutan (Mean 9321 per 100,000, SD=12,211.02). The highest death rate was seen in India (mean 118.04 per 100,000, SD= 218.39), followed by Pakistan (mean 15.72

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per 100,000, SD 28.67), Bangladesh (mean 12.01 per 100,000, SD 23.96), Nepal (mean 3.64 per 100,000, SD= 5.06) and Bhutan (1.33 per 100,00, SD=3.24). The highest DALYs rate was observed in India (mean 3,868.98 per 100,000, SD=6,431.13), followed by Pakistan (mean 524.90 per 100,000, SD= 838.36), Bangladesh (mean 524.90 per 100,000, SD=836.36), Nepal (mean 109.05 per 100,000, SD=132.33) and Bhutan (mean 27.65 per 100,000, SD=44.60).A post hoc analysis using Tukey's HSD revealed that India consistently exhibited the highest prevalence rates (p <0.001), death rates (p <0.001) and highest DALYs rate (p <0.001) compared to other countries. A multiple regression analysis suggested that a higher age and gender were significant predictors of death rate (p<0.001), while the location was not a significant predictor (p=.134) **Conclusion:** The increasing burden of MASLD in South Asia accompanies the rapid economic growth, lifestyle changes, and an increasing aging population. These trends the need to pivot our global health focus from predominantly infectious diseases to also include chronic diseases.

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2419 | RELATIONSHIP BETWEEN ALCOHOL CONSUMPTION AND ALL-CAUSE MORTALITY IN PATIENTS WITH STEATOTIC LIVER DISEASE: FINDINGS FROM NHANES III

Jie Li[1] Fajuan Rui[2] Nan Geng[1] Amir Goujol[3] Yixuan Zhu[4] Rahma Issa[5] Wenjing Ni[2] Sisi Zhou[4] Leyao Jia[4] Zhiwen Fan[1] Chao Wu[1] Junping Shi[6] Yee Hui Yeo[7] Mindie Nguyen[3]

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Background: Steatotic liver disease (SLD) is an umbrella term proposed to encompass the entire spectrum of liver disease including individuals with history of alcohol use, but data on the impact of alcohol use on the natural history of SLD is limited We aimed to determine the association between different levels of alcohol consumption and all-cause mortality in a population-based cohort of U.S. people with SLD. **Methods:** This study included individuals aged 20-74 years who were diagnosed with hepatic steatosis via ultrasound in the Third National Health and Nutrition Examination Survey. Individuals with unavailable alcohol consumption data were excluded from the study. Alcohol consumption data were self-reported via a patient questionnaire. The primary study outcome was all-cause mortality. **Results:** The study cohort included 2420 eligible participants, with 51.7% males, median age 42.0 years, and median alcohol intake 3.7 (0.0-14) g/d. Participants were grouped into four categories based on their daily alcohol consumption (amount listed as for female/male): 0-10/15g (72.9%, n=333), 10/15-20/30g (13.8%, n=333), 20/30-50/60g (9.3%, n=226), and >50/60g (4.0%, n=98). During a median follow up of 316 (268-340) months, 826 patients died. The all-cause mortality were 33.3%, 39.0%, 46.9% and 54.1% for those consuming 0-10/15g, 10/15-20/30g, 20/30-50/60g, and more than 50/60g of alcohol per day, respectively. There were significant differences in the all-cause mortality rates among patients with different levels of alcohol consumption (*P*<0.001) (Figure 1A). After adjusting for covariates, daily alcohol consumption levels of 10/15-20/30g (adjusted hazard ratio [aHR]=1.38, 95% CI 1.13-1.69, *P*=0.002), 20/30-50/60g (aHR=1.61, 95% CI 1.28-2.01, *P*<0.001), and >50/60g (aHR=1.96, 95% CI 1.46 to 2.63, *P*<0.001) were independently associated with increased all-cause mortality. However, in subgroup analysis by diabetes status, there were significant differences in all-cause mortality across various levels of alcohol consumption among non-diabetic patients (Figure 1B) but not among diabetic patients (Figure 1C). **Conclusion:** Alcohol consumption has a harmful effect on SLD, and the relationship is dose-dependent, with an increase in consumption level leading to a greater mortality, especially in non-diabetic individuals. Our study emphasizes the importance of alcohol abstinence in patients with SLD, even low levels of alcohol consumption should be avoided.

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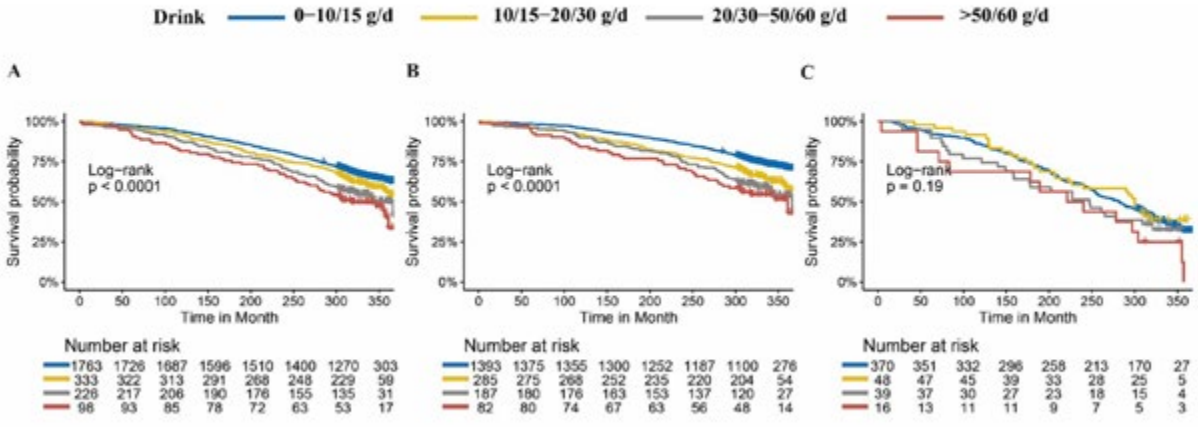
Figure 1. Kaplan-Meier Curves Demonstrating the Effect of Incremental Alcohol Consumption Traits on All-cause Mortality among Participants with steatotic liver disease. A. overall, B. non-diabetes, C. diabetes.



Disclosures: Jie Li: Nothing to Disclose, Fajuan Rui: Nothing to Disclose, Nan Geng: Nothing to Disclose, Amir Goujol: Nothing to Disclose, Yixuan Zhu: Nothing to Disclose, Rahma Issa: Nothing to Disclose, Wenjing Ni: Nothing to Disclose, Sisi Zhou: Nothing to Disclose, Leyao Jia: Nothing to Disclose, Zhiwen Fan: Nothing to Disclose, Chao Wu: Nothing to Disclose, Junping Shi: Nothing to Disclose, Yee Hui Yeo: Nothing to Disclose, Mindie Nguyen: Nothing to Disclose

2420 | ASSESSING THE PREVALENCE OF CARDIOMETABOLIC RISK FACTORS IN PATIENTS REFERRED TO A STEATOTIC LIVER DISEASE CLINIC

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[1]University of Western Ontario

Background: The metabolic syndrome is a known risk factor for development of hepatic steatosis. Under the umbrella of steatotic liver disease (SLD), a new set of cardiometabolic criteria have been suggested to identify patients at risk of developing MASLD. We aimed to assess these new cardiometabolic criteria and its ability to successfully identify patients in the community with MASLD, MetALD, and ALD. **Methods:** A cross-sectional analysis of patients referred to the Non-Alcoholic Fatty Liver Disease (NAFLD) clinic at an academic center in Ontario, Canada. Referrals were based on radiographic or biochemical findings suggestive of hepatic steatosis. Electronic medical charts of 312 patients between October 1, 2021, and October 2022 were reviewed. Cardiometabolic criteria, according to the most recent SLD nomenclature including BMI, diabetes, hypertension and dyslipidemia were reviewed for each patient. Comparisons of clinical and biochemical factors were also made between patients with MASLD, MetALD, and ALD to identify potential correlations. **Results:** Among the patients 312 patients assessed, 58% (n=183) exhibited elevated HbA1c levels suggestive of underlying diabetes. 49% (n=153) of the patients already had a prior diagnosis of hypertension at the initial NAFLD clinic visit. Dyslipidemia was also prevalent, with 46.1% (n=144) meeting triglyceride criteria and 37.5% (n=117) meeting HDL criteria. Obstructive sleep apnea was noted in 32 of 279 MASLD patients (11.8%) and 2 of 25 of the MetALD patients (8%). Interestingly, 9.8% of the patients referred to clinic were found not meeting BMI criteria (25 females and 5 males). However, none of those cardiometabolic risk factors were correlated with any of the studied groups with statistical significance. **Conclusion:** These findings, although were statistically not significant, underscore the relationship between cardiometabolic risk factors and associated conditions within our patient cohort. Identifying and addressing these factors is crucial in preventing the progression of hepatic steatosis to more severe liver diseases and cardiovascular outcomes.

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	ALD (N=8)	MASLD (N=279)	MetALD (N=25)	Total (N=312)	p value
HTN					0.067[1]
Normotensive	5.0 (62.5%)	136.0 (48.7%)	18.0 (72.0%)	159.0 (51.0%)	
Hypertensive	3.0 (37.5%)	143.0 (51.3%)	7.0 (28.0%)	153.0 (49.0%)	
A1C ≥ 5.7					0.512[1]
Elevated	6.0 (75.0%)	164.0 (58.8%)	13.0 (52.0%)	183.0 (58.7%)	
Not Elevated	2.0 (25.0%)	115.0 (41.2%)	12.0 (48.0%)	129.0 (41.3%)	
DM					0.255[1]
Not Diabetic	6.0 (75.0%)	191.0 (68.5%)	21.0 (84.0%)	218.0 (69.9%)	
Diabetic	2.0 (25.0%)	88.0 (31.5%)	4.0 (16.0%)	94.0 (30.1%)	
OSA					0.509[1]
N-Miss	0.0	1.0	0.0	1.0	
Not diseased	6.0 (75.0%)	246.0 (88.5%)	22.0 (88.0%)	274.0 (88.1%)	
Diseased	2.0 (25.0%)	32.0 (11.5%)	3.0 (12.0%)	37.0 (11.9%)	
Dyslipidemia					0.615[1]
Not diseased	5.0 (62.5%)	144.0 (51.6%)	15.0 (60.0%)	164.0 (52.6%)	
Diseased	3.0 (37.5%)	135.0 (48.4%)	10.0 (40.0%)	148.0 (47.4%)	
HDL					
Male HDL criteria (<=1)					0.157[1]
Not meet the criteria	7.0 (87.5%)	226.0 (81.0%)	24.0 (96.0%)	257.0 (82.4%)	
Meet the criteria	1.0 (12.5%)	53.0 (19.0%)	1.0 (4.0%)	55.0 (17.6%)	
Females HDL criteria (<=1.3)					0.075[1]
Not meet the criteria	3.0 (37.5%)	198.0 (71.0%)	15.0 (60.0%)	216.0 (69.2%)	
Meet the criteria	5.0 (62.5%)	81.0 (29.0%)	10.0 (40.0%)	96.0 (30.8%)	
TG					0.537[1]
Not elevated TG	3.0 (37.5%)	150.0 (53.8%)	15.0 (60.0%)	168.0 (53.8%)	
Elevated TG	5.0 (62.5%)	129.0 (46.2%)	10.0 (40.0%)	144.0 (46.2%)	
Elevated BMI					0.147[1]
N-Miss	0.0	5.0	1.0	6.0	
Healthy range	0.0 (0.0%)	25.0 (9.1%)	2.0 (8.3%)	27.0 (8.8%)	
Obesity	4.0 (50.0%)	133.0 (48.5%)	12.0 (50.0%)	149.0 (48.7%)	
Overweight	2.0 (25.0%)	73.0 (26.6%)	6.0 (25.0%)	81.0 (26.5%)	
Severe Obesity	1.0 (12.5%)	41.0 (15.0%)	4.0 (16.7%)	46.0 (15.0%)	
Underweight	1.0 (12.5%)	2.0 (0.7%)	0.0 (0.0%)	3.0 (1.0%)	

Disclosures: Yousef Almahanna: Nothing to Disclose, Ahmed Almohsen: Nothing to Disclose, Yi Nong Song: Nothing to Disclose, Amani Bajunayd: Nothing to Disclose, Jeemin Kim: Nothing to Disclose, Adrienne Abaya: Nothing to Disclose, Rokhsana Mortuza: Nothing to Disclose, Mohammad Qasim Khan: Nothing to Disclose, Juan Pablo Arab: Nothing to Disclose

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2421 | DIABETIC MICROVASCULAR COMPLICATIONS ARE ASSOCIATED WITH MORTALITY IN INDIVIDUALS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD) AND TYPE 2 DIABETES MELLITUS: A NATIONWIDE STUDY

Yee Hui Yeo[1] Jie Li[2] Qianqian Chen[2] Wenjing Ni[2] Yixuan Zhu[2] Nan Geng[2] Leyao Jia[2] Fajuan Rui[2] Chao Wu[2] Junping Shi[3] Xiaolong Qi[4] Susan Cheng[5] Amanda Velazquez[6] Alan Kwan[5] Hirsh Trivedi[1]

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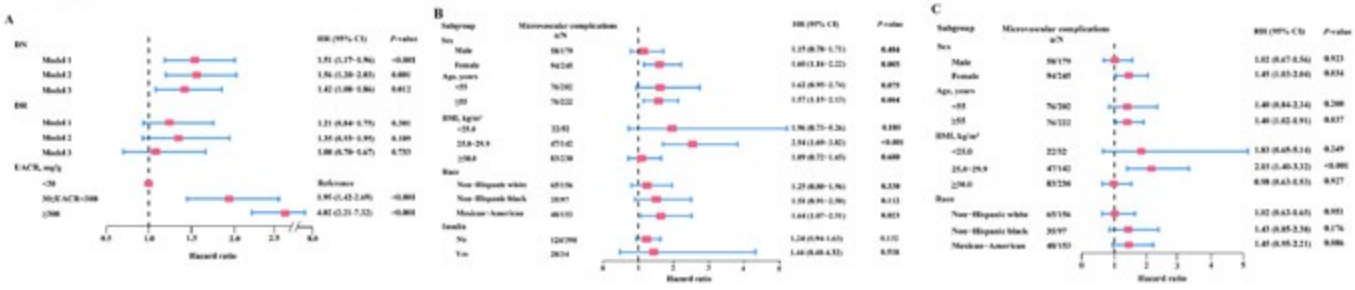
Background: Type 2 diabetes mellitus (T2DM) is a key cardiometabolic risk factor of metabolic dysfunction-associated steatotic liver disease (MASLD). Diabetic microvascular complications are negative health indicators in people with T2DM. Here, we aimed to examine the association between microvascular complications and all-cause mortality in MASLD patients with T2DM. **Methods:** Demographic, clinical, and longitudinal follow-up data were extracted from the NHANES III dataset. Hepatic steatosis was defined by ultrasound. Diabetic nephropathy (DN) was defined using the ratio of urine albumin to creatinine (UACR) and estimated glomerular filtration rate while diabetic retinopathy (DR) was diagnosed by using a fundus photograph. The Cox regression model with inverse probability of treatment weighting (IPTW) was applied for assessing all-cause mortality. E-value was estimated to evaluate the potential impact of unmeasured confounders on risk estimates. **Results:** A total of 424 eligible patients were included, with 31.1% of DN patients and 13.2% of DR patients. During a follow-up of 8657.6 person-years, 99 deaths were recorded. After IPTW, DN (aHR1.56, 95%CI 1.20-2.03), but not DR (aHR 1.35, 95%CI 0.93-1.95), were significantly associated with all-cause mortality when insulin usage was not adjusted. However, only DN markedly maintained the association after insulin usage was adjusted (aHR1.42, 95%CI 1.08-1.86) (Figure 1A). The high E-values indicated a very low residual confounding in these models. There was a dose-dependent relationship between UACR and mortality, with a significant incremental risk shown across the UACR subgroups (30≤UACR<300mg/g: aHR 1.95, 95%CI 1.42-2.69, UACR≥300mg/g: aHR 4.02, 95%CI 2.21-7.32, reference: UACR<30mg/g). In subgroup analysis without adjusting for insulin usage, females, older age, BMI between 25 to 29.9 kg/m2 and Mexican-Americans were associated with significantly higher all-cause mortality risks in the presence of microvascular complications, compared to their counterparts (Figure 1B), and such association consistently maintained after insulin usage was adjusted, except for Mexican-Americans (Figure 1C). **Conclusion:** T2DM microvascular complications, particularly DN, significantly increased the risk of all-cause mortality in MASLD patients with T2DM.

Figure 1 Cox regression models for the relationship between T2DM microvascular complications and all-cause mortality in MASLD patients with T2DM. (A) Overall cohort; (B) Subgroup analyses unadjusted for insulin usage; (C) Subgroup analyses adjusted for insulin usage.
Note: Model 1: unadjusted; Model 2: adjusted for sex, age, BMI, race, and PIR; Model 3: Model 2 + adjusted for insunlin. In figure 1B, the model in each subgroup was additionally adjusted for sex (not for the sex subgroup), age (not for the age subgroup), BMI (not for the BMI subgroup), race (not for the race subgroup), and PIR. Compared with Figure B, UACR in Figure A and subgruops in Figure C were adjusted by insulin additionally. T2DM microvascular complications: patients with DN and/or DR. N, total numbers of patients in each subgroup; n: numbers of patients with microvascular complications.
MASLD, metabolic dysfunction-associated steatotic liver disease; T2DM, type 2 diabetes mellitus; DN, diabetic nephropathy; DR, diabetic retinopathy; UACR, ratio of urine albumin to creatinine; BMI, body mass index; HR, hazard Ratio; 95% CI, 95% confidence interval.



Disclosures: Yee Hui Yeo: Nothing to Disclose, Jie Li: Nothing to Disclose, Qianqian Chen: Nothing to Disclose, Wenjing Ni: Nothing to Disclose, Yixuan Zhu: Nothing to Disclose, Nan Geng: Nothing to Disclose, Leyao Jia: Nothing to Disclose, Fajuan Rui: Nothing to Disclose, Chao Wu: Nothing to Disclose, Junping Shi: Nothing to Disclose, Xiaolong Qi: Nothing to Disclose, Susan Cheng: Nothing to Disclose, Amanda Velazquez: Novo Nordisk: Consultant, Lilly: Consultant, Weight Watchers: Advisor, Intellihealth: Advisor, Alan Kwan: Nothing to Disclose, Hirsh Trivedi: Nothing to Disclose

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2422 | FREQUENT MISCLASSIFICATION OF METALD RESULTS IN UNDERESTIMATION OF ITS PREVALENCE AND LONG-TERM PROGNOSIS

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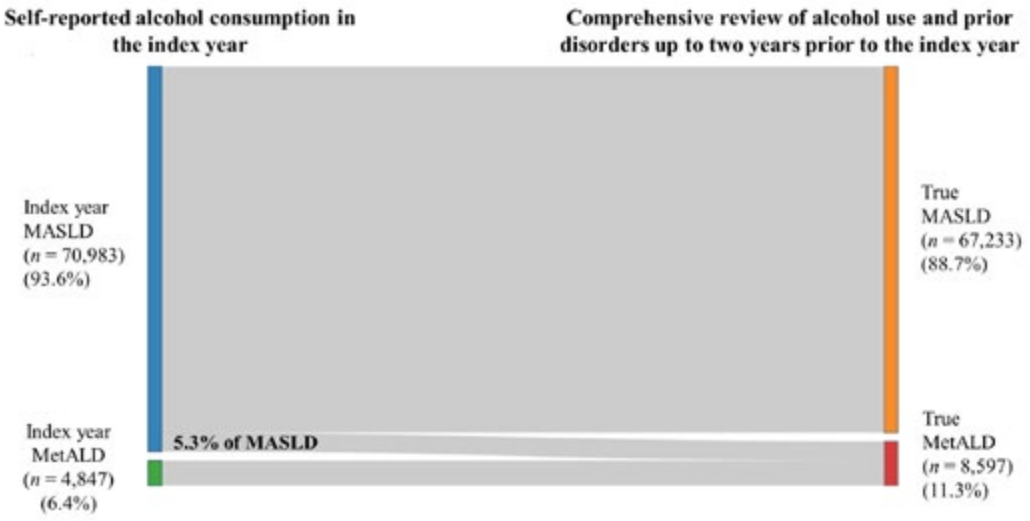
Background: The prevalence of metabolic and alcohol related/associated liver disease (MetALD) is reported to be low, and its long-term outcomes have not shown a clear difference from those of metabolic dysfunction-associated steatotic liver disease (MASLD). We investigated the prevalence and long-term outcomes of MetALD using alcohol consumption history up to 2 years prior, as well as medical history. **Methods:** The study enrolled 401,342 adults who underwent a national health checkup. Alcohol consumption data from the index year (2011–2012) and two years prior (2009–2010) were evaluated. Alcohol use disorder was defined using ICD-10 codes from the two time periods. Patients were initially classified as having MASLD or MetALD using index year data. For index-year MASLD, suspected MetALD was reassessed using self-reported alcohol consumption from two years prior and history of alcohol use disorder. True MetALD was defined as a combination of the index-year MetALD and suspected MetALD. **Results:** The prevalence of MetALD in the index year was 2.0%, but inclusion of suspected MetALD increased this to 3.5%. The misclassified MetALD group had a higher proportion of men, and higher body mass index, waist circumference, blood pressure, AST, ALT, γ-GTP, and type 2 diabetes than true MASLD. No difference was observed between index-year MASLD and MetALD in terms of overall and liver-related mortality. True MetALD had a higher risk of overall and liver-related mortality compared to true MASLD **Conclusion:** A considerable number of suspected MetALD cases were misclassified as MASLD in cross-sectional investigations of alcohol consumption. Consequently, the prevalence and long-term outcomes of MetALD are often underestimated.



Disclosures: Dae Won Jun: Nothing to Disclose, Jun-Hyuk Lee: Nothing to Disclose, Eileen Yoon: Nothing to Disclose, Sang Bong Ahn: Nothing to Disclose

2423 | HIGH ADHERENCE TO THE MEDITERRANEAN DIET IS ASSOCIATED WITH LOWER LIVER RISK SCORES – ANALYSIS OF THE NHANES 2017-2018 COHORT

Tsubasa Tsutsumi[1] Mary Rinella[2] Sarah Vilt[1] Matthew Odenwald[1] Dejan Micic[3] Michael Charlton[3]

[1]University of Chicago, [2]The University of Chicago, [3]University of Chicago Medical Center

Background: Diet and nutrition are perceived to be cornerstones of metabolic and liver health. Based on overwhelming scientific evidence, the Mediterranean diet is a common component of dietary recommendations. Although patients with higher Mediterranean Diet Scores (MDS) have been shown to exhibit lower hepatic

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fat and fibrosis, the impact of the Mediterranean diet on major adverse liver-related outcomes (MALO) is not well established. Recently, the Liver Risk score (LRS) demonstrated superior predictive accuracy compared to FIB-4 and APRI scores, for the early diagnosis of liver fibrosis and risk for MALO in the general population. Thus, we investigated how the MDS affects the LRS. **Methods:** An analysis of the NHANES 2017-2018 data was conducted. A total of 4,741 participants with complete dietary, physical, and laboratory data were initially included. Individuals under 40 years and those over 80 years were excluded, resulting in a final sample size of 3,004 participants. SLD was diagnosed using a FibroScan with a Controlled Attenuation Parameter of over 288 dB/m and IQR/Med ≤ 0.3. The MDS was calculated based on the sum of two-day interview. Results for nine food groups, assigning scores of -1, 0, or 1 based on relative intake within the cohort, and summing these for a total score ranging from -1 to 8. The MDS was further classified into tertiles based on its distribution. The LRS was calculated (Miquel et al.), derived from age, glucose, cholesterol, AST, ALT, GGT and platelets, with scores of 6 or higher defined as high risk. We performed a Cochran-Armitage trend test to compare factors in the three MDS groups. A logistic regression analysis was performed for factors associated with the high-risk group for LRS. **Results:** The study included 1,156 individuals with steatotic liver disease (mean 60 years, 49.7% female). MDS was classified as MED 1, 2, or 3 with thresholds of 1 and 3 points, with MED-3 being the most adherent. There were no significant differences in age, sex, fatty liver, hypo HDL-C, hypertension, hyper TG, prevalence of obesity, and FIB-4 index among the three MDS groups Logistic regression analysis showed that factors associated with the high-risk group for LRS were diabetes (OR: 4.03, 95% CI: 3.32 — 4.90), SLD (OR: 1.72, 95% CI: 1.42 — 2.09), hypertension (OR: 1.52, 95% CI: 1.18 — 1.96), and hypertriglyceridemia (OR: 1.41, 95% CI: 1.16 — 1.71). MED3, compared to MED1 (OR: 0.72, 95%CI: 0.57 — 0.92), and female gender were associated with a significantly lower risk group for LRS (OR: 0.27, 95%CI: 0.22 — 0.33). **Conclusion:** Strong adherence to a Mediterranean diet is associated with a lower risk of liver-related outcomes as measured by the LRS. Males and patients with diabetes and hypertension are particularly at risk for higher LRS and may be more appropriate targets. Diet may impact long-term risk for MALO.

Disclosures: Tsubasa Tsutsumi: Nothing to Disclose, Mary Rinella: Consultant relationship with Sagimet; Has not ended; Consultant relationship with Takeda; Has not ended; Consultant relationship with Eli Lilly; Has not ended; Consultant relationship with Novo Nordisk; Has not ended; Consultant relationship with GSK; Has not ended; Consultant relationship with Madrigal; Has not ended; Consultant relationship with Intercept; Has not ended; Consultant relationship with Boehringer Ingelheim; Has not ended; Consultant relationship with 89Bio; Has not ended; Consultant relationship with akero; Has not ended; Consultant relationship with Histoindex; Has not ended; Consultant relationship with Cytodyn; Has not ended; Consultant relationship with Echosens; Has not ended, Sarah Vilt: Nothing to Disclose, Matthew Odenwald: Nothing to Disclose, Dejan Micic: Takeda Pharmaceuticals: Speaking and Teaching, Vectiv Pharmaceuticals: Consultant, Michael Charlton: Nothing to Disclose

2424 | OLANZAPINE-INDUCED LIVER INJURY: A CASE REPORT

Karen Young[1] *Cynthia Guy*[2] *Amreen Dinani*[2]

[1]*Duke University Hospital,* [2]*Duke University*

Background: Olanzapine is a second-generation antipsychotic which has been shown to be an effective second-line treatment for non-combat related post-traumatic stress disorder (PTSD). Olanzapine has been reported as a culprit of severe drug induced liver injury (DILI). Here we discuss a case of olanzapine-induced DILI, with unusual histological findings that mimic other etiologies of liver disease. **Methods:** A 24-year-old woman with BMI 31.7kg/m^2, PTSD and anxiety was started on olanzapine in March 2023 after failing first-line therapy. In August 2023, she developed nausea, vomiting, abdominal swelling and elevated liver enzymes: total bilirubin 3.5, alkaline phosphatase 77, ALT 327, AST 501. She reported 2 alcoholic drinks daily. She underwent serologic work-up, liver imaging, and liver biopsy. **Results:** Serologic work-up revealed a low ceruloplasmin level of 9.8 but was otherwise negative. Abdominal ultrasound revealed hepatic steatosis. MRCP showed no biliary duct abnormalities. Histology showed >95% microvesicular steatosis, mild canalicular and hepatocellular cholestasis. There was no hepatocellular ballooning or lobular inflammation. (Figure 1). Portal vessels and interlobular bile ducts were unremarkable. Trichrome, iron and PASD stains were negative for evidence of fibrosis, hemochromatosis or alpha 1 antitrypsin deficiency respectively. Copper quantitative analysis showed <10 mcg Cu/gm of dry weight and quantification of 24-hour urine copper was normal. Her presentation was concluded to be secondary

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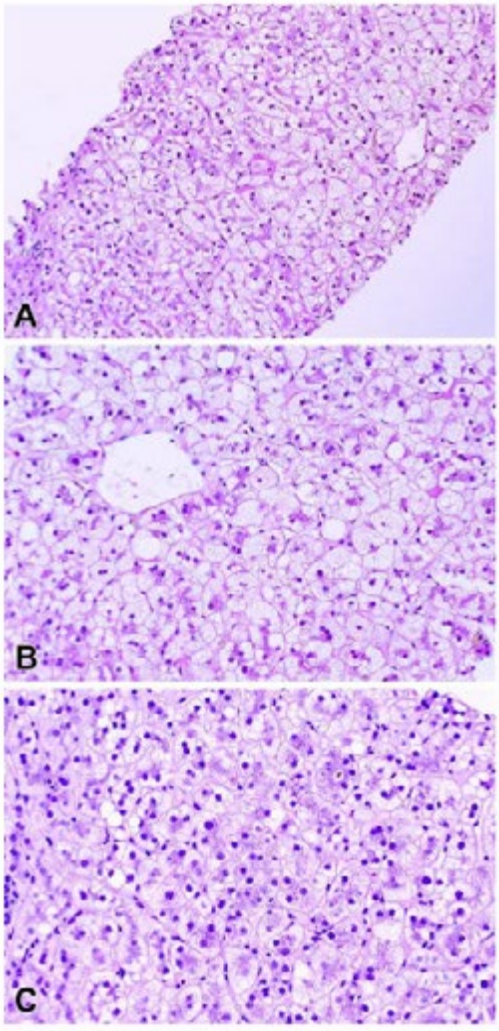
olanzapine-induced DILI, which was promptly discontinued, and her liver enzymes normalized within three months. **Conclusion:** Olanzapine-induced DILI can arise anytime between 1 and 12 months of initiating therapy with a typical hepatocellular pattern of liver injury. Here we report a unique pattern of severe microvesicular steatosis and cholestasis. Although metabolic dysfunction-associated steatotic liver disease (MASLD, defined as evidence of hepatic steatosis and ≥ 1 criteria of cardiometabolic syndrome) was initially considered, findings of diffuse *microvesicular steatosis* narrowed the differential diagnosis to Wilson disease or DILI. In the setting of daily alcohol consumption with a medication insult and diffuse microvesicular steatosis, alcohol-related foamy degeneration could also be considered. Expedient recognition of olanzapine-related DILI is important since medication cessation typically leads to rapid improvement of liver injury.

Figure 1. Representative images from the needle core biopsy showing diffuse, severe microvesicular steatosis and moderate cholestasis. (A) Low power view demonstrating panzonal microvesicular steatosis. (B) Medium power view highlights the small "foamy appearing" cytoplasmic fat droplets. (C) Canalicular bile is present and lack of ballooning and lobular inflammation.



Disclosures: Karen Young: Nothing to Disclose, Cynthia Guy: Nothing to Disclose, Amreen Dinani: Madrigal Pharmaceuticals: Consultant, Novo Nordisk: Consultant, Guidepoint: Consultant

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2425 | LIPOFUSCINOSIS AS A NOVEL DISCRIMINATING FEATURE FOR DRUG-INDUCED LIVER INJURY VS. AUTOIMMUNE HEPATITIS

Sabine Weber[1] Franziska Erhardt[1] Jens Neumann[1] Julian Allgeier[1] Didem Saka[1] Nirali Donga[1] Christian Lange[2] Alexander Gerbes[1]

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Background: Differentiating drug-induced liver injury (DILI) from autoimmune hepatitis (AIH) is a challenge in clinical practice[1, 2]. Liver biopsy is recommended in unclear cases[1], however data on typical features is scarce thus far[3, 4]. We therefore aimed to further identify typical histopathological features of DILI in comparison to AIH. **Methods:** Clinical and histopathological data of well-characterized 136 DILI and 43 AIH patients from our prospective cohort on patients with acute liver injury and potential drug-related cause were analyzed. Logistic regression was performed to identify models that could differentiate both entities and predict adverse outcome. **Results:** We identified high overlaps regarding histological patterns between DILI and AIH, leading to a low overall agreement between clinical and histopathological diagnosis of only 48.9%. Interface hepatitis, plasma cell infiltration and portal-intralobular infiltration was favoring AIH over DILI, however relevant proportions of DILI patients also presented with those features (44.1%, 46.3% and 29.2%, respectively). Interestingly, lipofuscinosis showed the strongest association with DILI diagnosis on univariate analysis (odds ratio [OR] 1.33, 95 % confidence interval [CI] 1.17-1.50). A model comprised of interface hepatitis, cholestasis, lipofuscinosis, portal-intralobular inflammation and steatosis could differentiate DILI from AIH with an accuracy of 77.7%. Multivariate analysis also identified lipofuscinosis as a highly discriminatory feature (OR 8.05, Table 1). Prediction of adverse outcome (death or liver transplantation [LT]) in DILI and AIH patients using only histopathological patterns was possible with an accuracy of 88.7%. Severe necrosis and ductular proliferation were associated with poor outcome (OR 5.48 and OR 5.00) while presence of eosinophilic cells and lipofuscinosis (OR 0.36 and OR 0.16) lowered the risk for death or LT significantly. **Conclusion:** To the best of our knowledge we here present the largest prospectively collected cohort of DILI and AIH patients for whom histopathological analysis was performed. Interestingly, DILI and AIH showed highly similar histological patterns, neither interface hepatitis nor plasma cell infiltration could specifically exclude DILI. However, lipofuscinosis was identified as a novel distinctive feature for DILI with a high discriminatory power. Moreover, a model combining histological features could differentiate both entities with high sensitivity. Histological analysis was especially helpful for predicting severe outcome in DILI and AIH patients showing higher specificity when compared to traditional risk scores predicting acute liver failure in DILI[5].

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Histopathological parameters discriminating DILI vs. AIH [1]			
	OR	**95% CI**	**p**
Interface hepatitis	0.453	0.209-0.982	**0.045***
Cholestasis	1.986	0.925-4.267	0.079
Lipofuscinosis	8.050	1.019-63.617	**0.048***
Portal-intralobular inflammation	0.471	0.222-1.000	**0.050***
Steatosis	2.784	0.881-8.801	0.081
Association of baseline parameters with adverse outcome in DILI and AIH [2]			
	OR	**95% CI**	**p**
Eosinophilic cells	0.356	0.133-0.956	**0.040***
Severe necrosis	5.479	2.000-15.008	**<0.001***
Lipofuscinosis	0.163	0.016-1.634	0.123
Ductular proliferation	4.979	1.849-13.406	**0.001***

[1] Stated are the baseline factors which show an association with DILI diagnosis using stepwise backward logistic regression analysis. Variables considered in the respective models were parameters with $p<0.200$ in univariate analysis. The binomial logistic regression model was statistically significant, $\chi^2(5)=26.563$, $p<0.001$, with an overall accuracy of 77.7 %. [2] Shown are the baseline factors which showed an association adverse outcome in DILI and AIH patients using stepwise backward logistic regression analysis. Adverse outcome is defined as death or liver transplantation as opposed to remission or chronic liver injury. Variables considered in the respective models were histological and / or clinical parameters with $p<0.200$ in univariate analysis. The binomial logistic regression model was statistically significant, $\chi^2(5)=38.604$, $p<0.001$.

Abbreviations: AIH: Autoimmune hepatitis; CI: Confidence interval; DILI: Drug-induced liver injury; OR: Odds ratio.

Disclosures: Sabine Weber: Falk Foundation: Speaking and Teaching, Orphalan: Travel grants, Franziska Erhardt: Nothing to Disclose, Jens Neumann: Nothing to Disclose, Julian Allgeier: Nothing to Disclose, Didem Saka: Nothing to Disclose, Nirali Donga: Nothing to Disclose, Christian Lange: Nothing to Disclose, Alexander Gerbes: Nothing to Disclose

2427 | UNVEILING PREVENTABLE LIVER DAMAGE: EXPLORING LAAT AND HALLAS TOOLS IN HOSPITALIZED PATIENTS ASSESSED WITH UPDATED RUCAM SCALE

Hussam Almasri[1] Guneet Sidhu[2] Ibtihal Abdallah[3] Fadi Khir[3] Hadeel Alfar[3] Naim Battikh[3] Rita Ahmad[3] Alia Albattah[3] Mohammed Ibn-Mas'ud Danjuma[3]

[1]University of North Dakota, [2]Mayo Clinic Rochester, [3]Hamad Medical Corporation

Background: Drug-induced liver injury (DILI) poses a significant concern, especially for hospitalized patients when the cause of liver injury is considered an adverse effect to medication use. The prevalence and burden of DILI in this setting remain under-presented, necessitating the exploration of the preventability of DILI to guide therapeutic decision-making and intervention strategies. We aimed to assess the preventability of DILI in a diverse age group using the modified Hallas tool and the Liverpool adverse drug reactions avoidability tool (LAAT). **Methods:** Retrospective analysis of electronic records of patients who were assessed for suspected DILI at Weill Cornell College of Medicine-affiliated Hamad General Hospital, Qatar, between February 2019 and January 2020. Patients aged 18 years and above were included. Clinical and demographic data were extracted, and DILI causality was assessed using the updated Roussel Uclaf Causality Assessment Method (RUCAM). Cases were evaluated for avoidability using modified Hallas and LAAT tools by six general physicians (i.e. 3 pairs). Inter-rater agreement and reliability were analyzed. **Results:** Out of 94 cases, 47 (50%) were attributed to antimicrobials, with hepatocellular injury being the most common pattern. 42 (44.5%) were classified as "probable" or "highly probable" while 22 (23.4%) were categorized as possible DILI by the updated RUCAM scale (fig 1). Inter-class correlation for avoidability assessment was 0.7 (CI 0.57-0.78) for the modified Hallas and 0.61 (CI 0.6-0.8) for LAAT. The average pairwise percent agreement was 75% for Hallas and 77% for LAAT. "Not avoidable" was the most common outcome for both tools. "Definitely avoidable" outcome ranged between 5.5-9.5% (fig 2). Further rearranging the cases to assess only those categorized as "probable" and "highly probable", the ICC was 0.52 (95% CI 0.27-0.71) for Hallas and 0.56 (95% CI 0.31-0.73) for LAAT. **Conclusion:** This study

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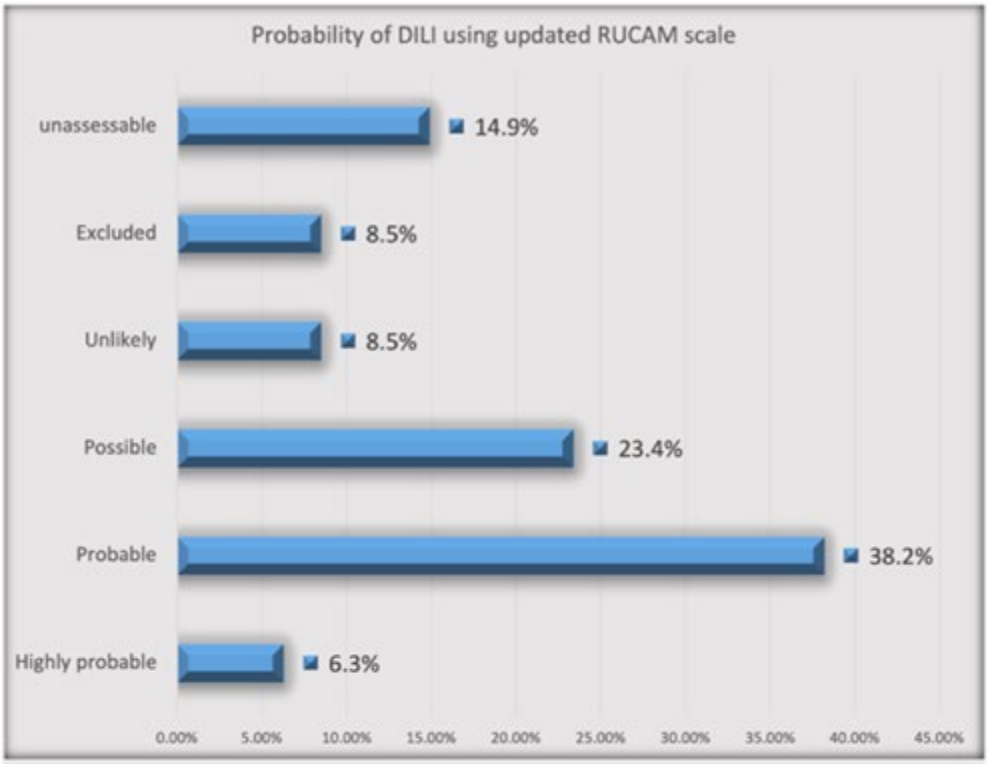
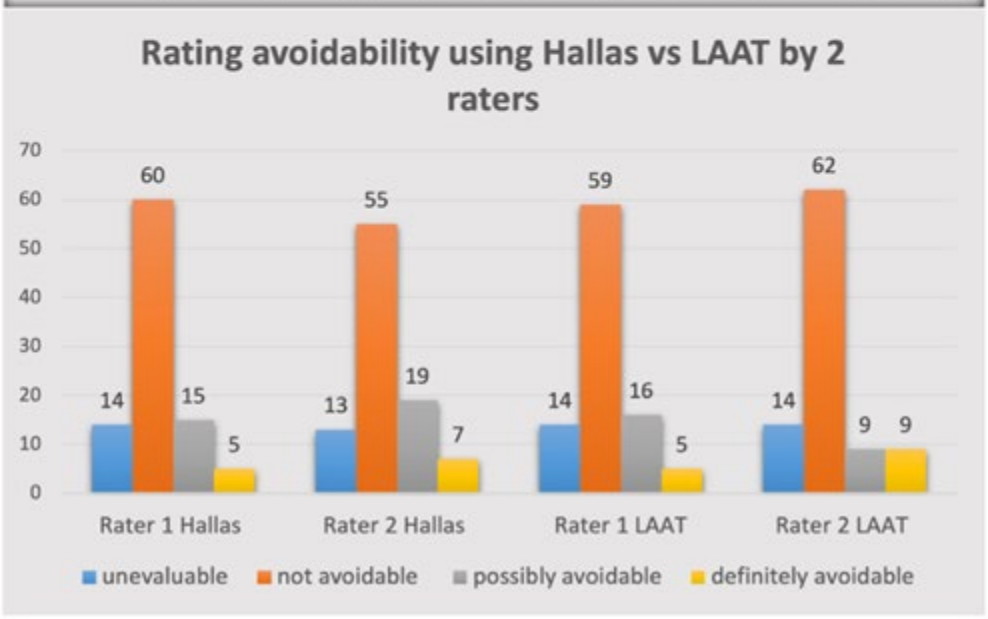
sheds light on the preventability of DILI in hospitalized patients, indicating that a considerable proportion of DILI cases may be avoidable. The findings underscore the importance of systematic preventability assessments in guiding medication use decisions and interventions to mitigate DILI burden, particularly in populations vulnerable to polypharmacy or severe illness. Despite limitations, such as the small sample size, this study contributes to the growing body of evidence supporting the utility of modified Hallas and LAAT tools in assessing DILI avoidability.





Disclosures: Hussam Almasri: Nothing to Disclose, Guneet Sidhu: Nothing to Disclose, Ibtihal Abdallah: Nothing to Disclose, Fadi Khir: Nothing to Disclose, Hadeel Alfar: Nothing to Disclose, Naim Battikh: Nothing to Disclose, Rita Ahmad: Nothing to Disclose, Alia Albattah: Nothing to Disclose, Mohammed Ibn-Mas'ud Danjuma: Nothing to Disclose

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2428 | SINGLE-CELL INVESTIGATION OF MERCAPTOPURINE-ASSOCIATED LIVER INJURY

Keito Hoshitsuki[1] Yu-Chih Hsiao[1] Maud Maillard[1] Xu Yang[1] Qingfei Pan[1] Sheetal Bhatara[1] Wenjian Yang[1] Zhenhua Li[1] Jiyang Yu[1] Jun Yang[1]

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Background: A dose-limiting toxicity of mercaptopurine (MP) is to drug-induced liver injury (DILI). However, the hepatic cell populations involved and underlying biology are unknown. MP undergoes extensive intracellular metabolism, including the production of methylated metabolites by thiopurine S-methyltransferase (TPMT), suspected to be involved in MP-DILI. This study aimed to identify the cell populations involved in MP-DILI and within those cell populations, the molecular mechanisms driving cellular damage. **Methods:** Wild-type (WT) and *Tpmt* knockout (KO) Balb/c mice were treated with MP or vehicle control for 5 days and livers were harvested for single nuclei RNA-sequencing (snRNAseq) using the 10X Genomics FLEX platform. Data pre-processing and quality control included ambient RNA removal (SoupX), doublet removal (scDblFinder), batch effect correction (Harmony), log(x+1) transformation, normalization, clustering (Leiden), and dimensionality reduction (UMAP). Cell populations were annotated using a machine learning classifier (Cell Typist). **Results:** A total of 94,449 nuclei passing data pre-processing and quality control were included in the analysis. Cell annotation and UMAP projection identified distinct clusters of hepatocytes, endothelial, cholangiocytes, stellate, mesothelial, myeloid, and lymphoid cell populations. The largest differences in gene expression signatures between treatment groups were found between the hepatocytes from MP-treated WT mice versus those from vehicle control mice. Subclustering of these hepatocytes revealed the emergence of a unique new population in the MP-treated group that was absent in controls. This subpopulation lost classical zonation features and had significantly higher expression of *Anxa2* (log2-fold change 3.38, q=3.14e-4), a hallmark of migratory, regenerative hepatocytes. In contrast, *Tpmt* KO mice were unable to generate methylated MP metabolites, thus were protected from MP-DILI. SnRNAseq unequivocally showed that hepatocytes from MP-treated Tpmt KO mice "phenocopied" cells from WT control mice. In fact, the Anxa2+ subpopulation was also absent in KO mice despite MP treatment. Pathway analysis in MP-treated WT vs KO hepatocytes were enriched for gene sets in oxidative phosphorylation and mitochondrial injury, suggesting a mechanism by which methyl-MP metabolites cause MP-DILI. **Conclusion:** SnRNAseq analysis revealed MP-DILI affects hepatocytes predominantly in a TPMT-dependent manner, including the emergence of an *Anxa2*+ migratory hepatocyte population implicated in liver injury repair. Together, we demonstrate a unique pathogenesis of MP-DILI mediated by TPMT and its methylated products and a potential liver repair mechanism.

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2429 | DEEP LEARNING-BASED DIAGNOSTIC MODEL OF PYRROLIZIDINE ALKALOID-RELATED HEPATIC SINUSOIDAL OBSTRUCTION SYNDROME BASED ON CT: DEVELOPMENT AND VALIDATION STUDY

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[1]Zhongshan Hospital, Fudan University

Background: Early diagnosis of pyrrolizidine alkaloid-induced hepatic sinusoidal obstruction syndrome (PA-HSOS), a type of severe vascular drug-induced liver injury is challenging due to generic manifestations and lacking specific diagnostic approaches. This study explores a non-invasive deep learning-based diagnostic model for PA-HSOS based on CT, which aims to improve the diagnosis validity and efficiency. **Methods:** CT images from patients with PA-HSOS, Budd-Chiari syndrome or hepatitis B cirrhosis admitted to Zhongshan hospital, Fudan University from Jun 2008 and Sep 2022 were retrospectively evaluated. Transfer learning-based method was first used to segment the liver on CT images automatically, to reduce the potential influence of extraneous organs. Then, a deep learning-based diagnostic model was constructed for PA-HSOS, using multi-scale convolutional modules. Liver region was cropped based on annotations. More than 2,800 regions of interest (ROI) are obtained

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and used as input for model training and testing. Models were trained in five-fold cross-validation on training cohort and test on the internal test cohort. The models were also compared with the diagnostic **Results:** of gastroenterologists, junior radiologists and junior internists, to verify its practical application value. Furthermore, the models were validated on the external test cohort from patients admitted to the First Affiliated Hospital of Zhengzhou University. **Results:** A total of 67 patients with PA-HSOS, 61 patients with Budd-Chiari syndrome, and 107 patients with hepatitis B cirrhosis were included, splitting into training cohort (N=150), internal test cohort (N=37) and external test cohort (N=48). Among constructed models, Model 96 (96-mm input size) achieved the best performance with the area under the curve (AUC) values of 0.944 in the internal test cohort, and 0.873 in the external test cohort. With the assistance of the deep learning-based diagnostic model, the diagnostic accuracy of gastroenterologists (p=0.031) and junior internists (p=0.21) were significantly improved. Moreover, introducing the model resulted in a substantial reduction in diagnostic time for physicians (p<0.05). **Conclusion:** A first clinical useful deep learning-based diagnostic model for PA-HSOS was successfully developed based on CT images. The model achieves promising performance on PA-HSOS classification which is comparable and even better to physicians. In experiments with practical clinical applications, the model improves the diagnosis validity and accelerates the diagnosis process.

Disclosures: Hong Gao: Nothing to Disclose

2430 | 'SHROOMS' AND SEVERE HEPATITIS – A UNIQUE ENTITY

Lakshmi Chirumamilla[1] Sneha Adidam[1] Srilekha Bathi[1] Angesom Kibreab[1]

[1]Howard University Hospital

Background: There are currently over 5,000 known species of mushrooms worldwide. Only 20-25% of mushrooms have been named, and 3% of these are poisonous [1]. Mushroom poisoning (MP) can lead to different clinical outcomes ranging from mild gastrointestinal issues to severe liver damage leading to acute hepatic necrosis and possibly necessitating a liver transplant [2]. Amanita and Psilocybe mushrooms are consumed for its psychoactive and hallucinogenic effects respectively. They act as a potent agonist for the GABA and serotonin receptor [3, 4]. The effects range from euphoria and a dream-like (lucid) state of mind to out-of-body experiences and synesthesia. We report a rare case of liver injury from ingesting mushrooms for their hallucinogenic effects. **Methods:** This is a case report **Results:** A 47-year-old male patient with a medical history of hypertension and alcohol use disorder was admitted to the emergency room (ER) with weakness, nausea, vomiting, and abdominal pain. Patient developed hematemesis after multiple attempts of retching and vomiting. After further history, he reported consuming large quantity of alcohol with mushrooms mixed in it about 12-24 hours before presentation to the ER. He was awake and fully oriented on admission. There are no signs of encephalopathy and vital signs were normal. His physical examination was unremarkable except for scleral icterus. Labs showed marked elevation in liver enzymes (Fig 1). Coagulation profile was normal (INR=1.4). R factor is 14.3 suggests hepatocellular pattern of injury. Per chart review, last normal liver enzymes were two years ago. The hepatitis panel workup and viral etiology was negative. Autoimmune workup including ANA, AMA, ASMA and ceruloplasmin levels were within normal limits/negative. CT of the abdomen with contrast was significant for fatty infiltration of the liver. Given his history, clinical presentation, and laboratory findings - a diagnosis of acute liver injury likely secondary to toxin ingestion was suspected. For management, intravenous fluids and Acetylcysteine was given. Upper endoscopy showed antral gastritis and superficial healing esophageal ulcer and H. pylori negative. With a MELD score of 16, this patient has a 6% expected mortality rate within three months, signaling a favorable prognosis. Following the supportive treatment regimen, the patient exhibited significant improvement and was discharged. **Conclusion:** MP can result in severe or fatal outcomes, often presenting with overt liver or kidney failure [5]. There is no standardized protocol for the treatment of mushroom-induced hepatotoxicity. A meta-analysis found that silibinin and acetylcysteine are particularly effective in treating human mushroom poisoning [6]. In patients with psychedelic mushroom use thorough history with close follow up of liver enzymes is beneficial and these patients should be closely monitored for signs of acute liver failure.

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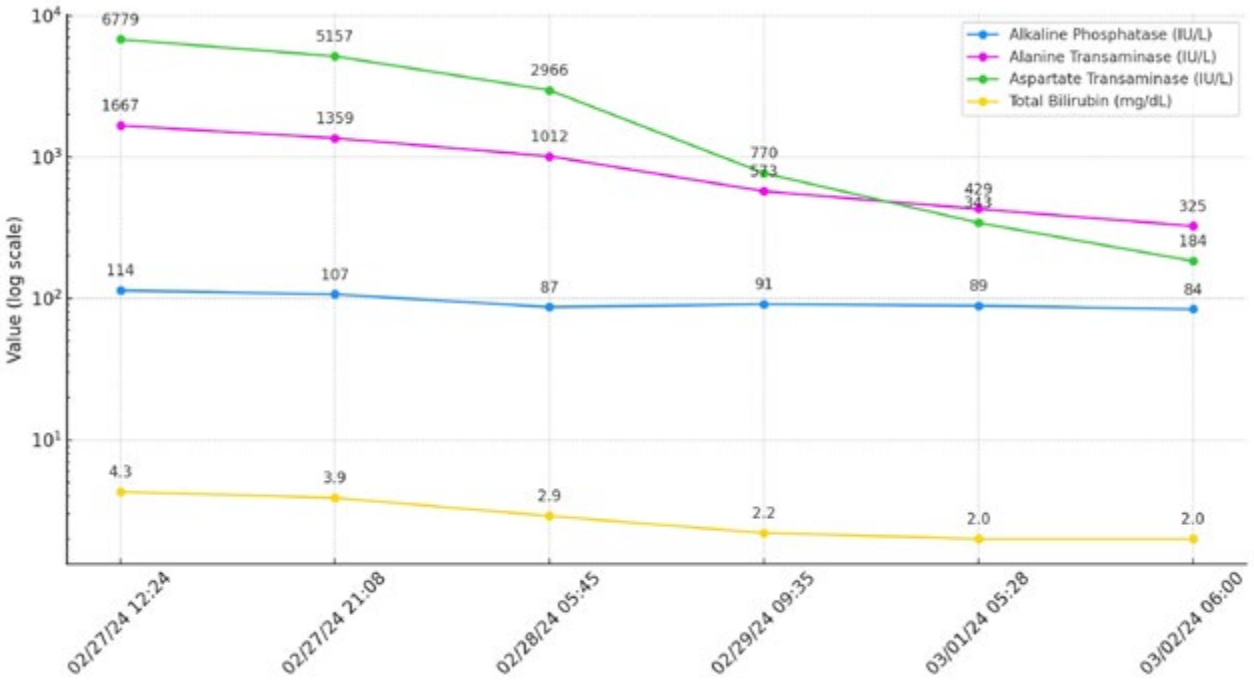

Disclosures: Lakshmi Chirumamilla: Nothing to Disclose, Sneha Adidam: Nothing to Disclose, Srilekha Bathi: Nothing to Disclose, Angesom Kibreab: Nothing to Disclose

2431 | INDUCTION OF CYP2E1 CONTRIBUTES TO ASPARAGINASE-INDUCED HEPATOCYTE SENSITIZATION TO LIPOTOXICITY

Yin Zhu[1] *Yuyin Wang*[1] *Keito Hoshitsuki*[1] *Da Yang*[1] *Lauren Kokai*[1] *Xiaochao Ma*[1] *Wen Xie*[1] *Christian Fernandez*[1]

[1]*University of Pittsburgh*

Background: One of the leading therapies for acute lymphoblastic leukemia (ALL) is PEGylated E. coli-derived L-asparaginase (PEG-ASNase). However, its use in adults is limited due to the high risk of dose-limiting liver injury. Our preclinical investigations suggest that PEG-ASNase-induced liver injury involves the release of free fatty acids (FFAs) from white adipose tissue (WAT), indicating potential lipotoxic effects. It remains uncertain whether PEG-ASNase directly induces hepatotoxicity or sensitizes hepatocytes to FFA-induced toxicity. Based on our previous studies showing increased adipose triglyceride lipase (ATGL) expression in adipocytes after PEG-ASNase treatment, we hypothesize that PEG-ASNase activates ATGL, leading to enhanced lipolysis and FFA accumulation in the liver. We further posit that PEG-ASNase sensitizes hepatocytes to lipid-induced toxicity or lipotoxicity. **Methods:** Eight-week-old male and female C57BL/6 mice received a single dose of 1,500 IU/kg PEG-ASNase or PBS vehicle control intraperitoneally. Blood, liver, and WAT were collected after three days. Liver triglycerides were quantified, and plasma ALT, AST, and FFAs were measured. Lipid peroxidation, apoptosis, and lipid accumulation were assessed using 4-HNE immunochemistry, TUNEL, and Oil-Red-O, respectively. Primary murine hepatocytes were treated with palmitic acid (PA) and PEG-ASNase. MTT and intracellular ROS assays determined if PEG-ASNase sensitizes hepatocytes to FFA-induced toxicity. Human and murine adipose tissues were used to assess the effect of PEG-ASNase on ATGL activation, FFA mobilization from TG stores, and the lipolytic signaling cascade. RNA-sequencing (RNA-seq) analysis was performed on primary mouse hepatocytes treated with PA alone and with PEG-ASNase to elucidate mechanisms of PEG-ASNase-induced sensitization to lipotoxicity. **Results:** Our results show that PEG-ASNase treatment results in hepatocyte apoptosis and lipid peroxidation. Mice showed elevated liver enzymes, plasma FFAs, and hepatic triglycerides. Ex vivo and in vitro studies in mouse and human WAT demonstrate that PEG-ASNase induces the expression of ATGL, activates the lipase, and stimulates WAT lipolysis, suggesting that the FFAs from WAT may contribute to the observed liver injury. Moreover, treatment with PEG-ASNase sensitizes hepatocytes to FFA-induced lipotoxicity. Mechanistically, our RNA-seq analyses reveal that the induction of Cyp2e1 accompanies the PEG-ASNase-induced sensitization

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to lipotoxicity, and pharmacological inhibition of Cyp2e1 attenuates the sensitization effect of PEG-ASNase. **Conclusion:** In summary, our findings indicate that PEG-ASNase activates adipocyte ATGL, induces adipose tissue lipolysis, and leads to hepatic lipotoxicity. We demonstrate that in the liver, PEG-ASNase induces the expression of Cyp2e1 and sensitizes hepatocytes to lipotoxicity.

Disclosures: Yin Zhu: Nothing to Disclose, Yuyin Wang: Nothing to Disclose, Keito Hoshitsuki: Nothing to Disclose, Da Yang: Nothing to Disclose, Lauren Kokai: Nothing to Disclose, Xiaochao Ma: Nothing to Disclose, Wen Xie: Nothing to Disclose, Christian Fernandez: Nothing to Disclose

2432 | THE IMPACT OF COVID-19 AND COVID-19 VACCINATION ON DETECTION, ASSESSMENT AND MANAGEMENT OF SUSPECTED ACUTE DRUG-INDUCED LIVER INJURY OCCURRING DURING CLINICAL TRIALS: CONSENSUS RECOMMENDATIONS FROM THE IQ DILI CONSORTIUM

Melissa Palmer[1] Daniel Seekins[2] Ajit Dash[3] John Marcinak[4] Arie Regev[5] James Lewis[6]

[1]CEO Liver Consulting LLC, [2]Bristol-Myers Squibb, [3]Genentech, [4]Abbvie, [5]Eli Lilly, [6]Georgetown university hospital

Background: COVID-19, the illness due to SARS-CoV-2, was declared a worldwide pandemic in March 2020. The challenges of execution and performance of clinical trials were promptly addressed, liver-related manifestations of acutely ill hospitalized patients were characterized, and the management of patients with chronic liver disease infected with COVID-19 were outlined. While the pandemic has waned, its implications for clinical trials are still pertinent. In particular, there remains a lack of guidance regarding evaluation of a new onset of elevated liver tests occurring during a clinical trial as they relate to COVID-19, its treatments, and COVID-19 vaccination. In an effort to provide meaningful guidance to sponsors and investigators, the IQ DILI Consortium, comprised of experts from academia, regulatory agencies and industry, are proposing recommendations to address this gap. **Methods:** Extensive literature review of PUBMED, Embase and MEDLINE utilizing key words DILI, hepatotoxicity, SARS-CoV-2, COVID-19, COVID-19 vaccination, liver, treatment, and clinical trial in various combinations was conducted. In addition, structured discussions between IQ DILI industry members, academic and regulatory experts in hepatology and DILI occurred. **Results:** Liver-related manifestations associated with non-hospitalized patients with COVID-19 varied in latency, pattern, severity, and time to resolution. Liver injury may occur after COVID-19 symptoms resolved and testing was negative. Treatments for COVID-19 may cause liver injury and/or interfere with study or concomitant drug pharmacokinetics (e.g. Paxlovid which contains ritonavir a potent CYP3A4), potentially increasing the likelihood of DILI. COVID-19 vaccination has been associated with rare hepatotoxicity which is typically autoimmune in nature, although various patterns, severity, latency and time to resolution have been reported. Liver injury occurred with both the mRNA and viral vector vaccines, and was more common and severe with the booster versus the prime dose. Hepatotoxicity was reported in individuals with and without underlying autoimmune disease. **Conclusion:** It is important for study sponsors, medical monitors and investigators to be aware of the potential hepatotoxicity related to COVID-19, its treatment, and COVID-19 vaccination, which may impact study eligibility, as well as causality assessment of a new onset of elevated liver tests occurring during a clinical trial. As such, COVID-19 testing should be considered to be performed as part of causality assessment, as a positive test may avoid premature study drug termination. As clinical trial participants may not consider vaccination a part of their medical history, specific inquiry as to vaccination history is important when liver biochemical tests are abnormal during screening and as part of DILI causality assessment. Further studies are needed to address gaps identified in the literature.

Disclosures: Melissa Palmer: Nothing to Disclose, Daniel Seekins: Bristol-Myers Squibb: Employee, Ajit Dash: Nothing to Disclose, John Marcinak: AbbVie: Employee, Arie Regev: Eli Lilly and Company: Employee, James Lewis: Nothing to Disclose

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2433 | NUCLEAR FACTOR ERYTHROID 2-RELATED FACTOR 2 (NRF2) ACTIVATION AGGRAVATES LIVER INJURY BY CAUSING MITOCHONDRIAL DYSFUNCTION

Alejandro H. Gutierrez[1] *Laura Morán*[1] *Javier Vaquero*[2] *Rafael Bañares*[2] *María José Frutos*[3] *Bruno Ramos-Molina*[4] *Yulia Nevzorova*[1] *Francisco Javier Cubero*[1]

[1]*Complutense University School of Medicin,* [2]*Hospital General Universitario Gregorio,* [3]*Virgen de la Arrixaca University Hospita,* [4]*IMIB-Arrixaca*

Background: The Kelch-like ECH-associated protein-1 (Keap1)/Erythroid 2-related factor 2 (NRF2) system is of particular importance in redox homeostasis. When disturbed by excessive oxidant stress, NRF2 is released from the sensor Keap1 and subsequently binds to antioxidant response elements (ARE) in the nucleus, triggering mitochondrial dysfunction. In the present work, we elucidated the role of hepatocyte-derived NRF2 activation specifically in acute and chronic liver injury. **Methods:** Two models of liver injury were performed in C57B/6J mice with hepatocyte-specific *Keap1* deletion (*Keap1*$^{\Delta hepa}$) and its respective controls (floxed mice, *Keap1*$^{f/f}$) which were challenged with a single injection of APAP [500mg/kg, i.p.] – a widely used model of DILI- and sacrificed between 0-24h later. As a model of liver fibrosis, mice were challenged with repeated doses of CCl_4 [0,6ml/kg, i.p., twice per week] at different time points (0-28 days). DMSO and corn oil were used as controls, respectively. Finally, primary hepatocytes from *Keap1*$^{fx/fx}$ and *Keap1*$^{\Delta hepa}$ mice were isolated and treated with APAP [10mM] for 24 h. Samples were processed for histopathological examination and protein (IF, IHC and WB) and mRNA expression were evaluated. **Results:** Keap1$^{\Delta hepa}$ mice showed significantly increased markers of liver injury (AST, ALT, LDH), liver inflammation (BW/LW ratio, CD45, F4/80, CD11b+ cells), cell death (% of necrotic foci, TUNEL), cell proliferation (PCNA, Ki-67) and overexpression of the antioxidant response elements (NQO1, GCLC, HO-1) compared with Keap1$^{f/f}$ animals, both after APAP (0-24h) and CCl_4 (0-28 days). Moreover, collagen deposition - evaluated as Sirius red (SR) staining – and markers of hepatic fibrosis and hepatic stellate cell (HSC) activation including αSMA and COLL IA1 were significantly elevated in Keap1$^{\Delta hepa}$ mice after 14 and 28 days of CCl_4. Functional experiments with primary isolated hepatocytes (PIH) treated with APAP or DMSO evidenced increased NRF2 transactivation, mitochondrial membrane depolarization and fission (DRP1) in *Keap1*-deficient hepatocytes. Finally, in human cohorts, NRF2 protein and mRNA expression correlated with the degree of inflammation and was associated to HO-1 and NQO1 overexpression. **Conclusion:** NRF2 activation in hepatocytes aggravated acute and chronic liver disease by promoting liver injury, cell death and proliferation, inflammation, and fibrosis. These results were associated to the induction of the ARE triggering changes in mitochondrial dynamics. Our results indicate that the KEAP1/NRF2 system could be a potential theragnostic target for the treatment of liver disease.

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2434 | KEAP1 DELETION RESCUES CELL DEATH ASSOCIATED WITH GPX4 KNOCKDOWN IN HEPATOCYTES IN ACUTE MODELS OF LIVER INJURYDELTA

Leticia Colyn[1] *Julia Grube*[1] *Chaochao Wang*[1] *Jana Dietrich*[1] *Mark Kuehnel*[1] *Christian Trautwein*[2]

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Background: Acute liver failure (ALF) is a clinical event that needs to be resolved. In cases not related to acetaminophen overdose, there is no curative option other than liver transplantation. The loss of liver function is a consequence of hepatocyte death, where high levels of reactive oxygen species (ROS) play a critical role. Nuclear factor erythroid-2 like 2 (Nrf2) is pivotal role for the defense against ROS as it regulates numerous genes, including glutathione peroxidase 4 (GPX4), which is essential for preventing lipid peroxidation (LPO) and subsequent cell death in high ROS situations. GPX4 has been found to be associated with multiple regulated cell mechanisms, including apoptosis, necroptosis, pyroptosis, and especially ferroptosis. **Methods:** GPX4 levels were quantified in liver samples from healthy individuals (n=5) and liver transplanted patients (ALF, n=16; ACLF, n=14). To functionally investigate GPX4 in ALF and the endogenous antioxidant defense system, mice with a deletion of *Gpx4* in hepatocytes (*Gpx4*^{hepa}) and mice with a deletion of the Nrf2 repressor, Kelch-like ECH-associated protein 1 (*Keap1*), plus Gpx4 deletion (*Gpx4*^{hepa} *Keap1*^{hepa}) were generated. ALF was induced

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through the intraperitoneal injection of carbon tetrachloride (CCl_4) for a period of 48 hours. **Results:** In patients with ALF, a reduction in GPX4 levels was observed in comparison to healthy individuals and ACLF patients. This same event was observed in wild-type (WT) mice with CCl_4-induced ALF. In *Gpx4*^{hepa} mice, CCl_4 resulted in increased cell death and severe loss of liver function. Despite the known protective role of GPX4 against LPO, its absence did not affect 4-hydroxynonenal levels. We observed increased apoptosis-mediated cell death as indicated by TUNEL and cleaved caspase-3 staining, and mRNA induction of pro-apoptotic mediators. Activation of *Nrf2* in *Gpx4*^{hepaKeap1hepa} mice resulted in the reversal of CCl_4-induced damage, with levels of necrosis and transaminases comparable to those observed in the WT group. Furthermore, apoptosis markers were reduced in the *Gpx4*^{hepaKeap1hepa} group, while there was a strong induction of anti-apoptotic BCL2 protein levels. **Conclusion:** In acute liver failure, *Gpx4* plays a critical role. Its absence results in hepatocyte apoptosis. Stimulation of the endogenous antioxidant defense system, mediated by *Nrf2*, showed a protective effect *in vivo*. Our findings provide evidence that *Nrf2* activation is a promising therapeutic intervention in situations of acute liver injury.

Disclosures: Leticia Colyn: Nothing to Disclose, Julia Grube: Nothing to Disclose, Chaochao Wang: Nothing to Disclose, Jana Dietrich: Nothing to Disclose, Mark Kuehnel: Nothing to Disclose, Christian Trautwein: Nothing to Disclose

2435 | HEPATIC SINUSOIDAL CONGESTION ASSOCIATED WITH INOTUZUMAB IN PATIENTS WITH B-CELL ACUTE LYMPHOBLASTIC LEUKEMIA: A CASE SERIES REPORT

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[1]*Loma Linda University,* [2]*UCSF Fresno,* [3]*University of Southern California,* [4]*Loma Linda University Cancer Center*

Background: Inotuzumab (InO) is an FDA approved anti-CD22 immunoconjugate for patients with relapsed or refractory CD22 positive B-cell Acute Lymphoblastic Leukemia (ALL). Liver toxicity is a recognized side effect of InO but its pathophysiology and full spectrum of clinical presentations are not well understood. This study describes a new aspect of InO-induced hepatotoxicity by outlining four patients who developed abnormal liver function tests (LFTs) and liver biopsies with evidence of sinusoidal congestion. **Methods:** Our case series identified four patients diagnosed with ALL who experienced hepatotoxicity while undergoing treatment with InO at an academic hematology outpatient cancer center. Hepatotoxicity was defined as elevated LFTs with and without clinical symptoms of RUQ pain. Liver biopsies were obtained from all four patients when InO-induced hepatotoxicity was clinically diagnosed, and LFTs were monitored before initiating InO treatment, during treatment, and after discontinuing treatment. Length of time from initiating InO to development of hepatotoxicity with subsequent recovery was noted as well. **Results:** At a median of 15 days after initiating InO, all patients experienced abnormal LFTs. At a median of 23 days after discontinuing InO, all four patients displayed improvement in their LFTs but did not return to baseline levels. Initial baseline AST, ALT, Alkaline Phosphatase, and Total Bilirubin values prior to InO therapy ranged from 10-45U/L, 10-45U/L, 60-175U/L, and 0.2-0.9mg/dL respectively and increased up to 2 to 4 times the upper limit of normal after completing varying cycles of InO. LFTs returned to 1 to 1.5 times the upper limit of normal after discontinuing InO. Finally, the patients' liver biopsies all demonstrated different levels of hepatic sinusoidal congestion (HSC), but not sinusoidal obstruction syndrome (SOS). **Conclusion:** This study provides new evidence describing a reversible InO-induced toxic effect and HSC which is different from SOS and its associated poor clinical outcomes. With early intervention, HSC can be reversed as seen through improved LFTs and clinical symptoms. Further research is warranted to explore InO-induced HSC, its pathophysiology, and if it is a precursor to SOS.

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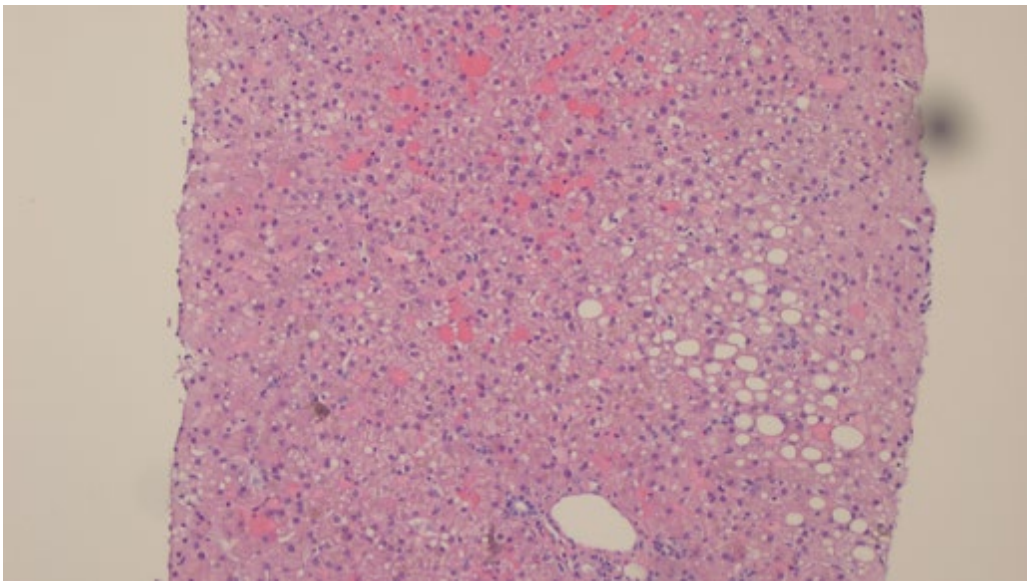

Disclosures: Derek Tai: Nothing to Disclose, Daniel Park: Nothing to Disclose, Kum-Ja Lee: Nothing to Disclose, Mojtaba Akhtari: Nothing to Disclose

2436 | VARIABILITY IN REFERENCE RANGES OF HEPATIC BIOCHEMICAL TESTS IN PEDIATRIC POPULATIONS: IMPLICATIONS FOR MONITORING AND ASSESSMENT OF DRUG INDUCED LIVER INJURY

Arie Regev[1] John Marcinak[2] Linyun Zhou[3] Funan Huang[4] Ruby Mehta[5] Benjamin Shneider[6] Jean Molleston[7] Kathy Kordy[8] Eric Maller[9] William Treem[10] Linda Wang[11] Deepa Chand[12] David Brott[3] James Lewis[13]

[1]Eli Lilly and Company, [2]AbbVie, [3]Takeda, [4]Bayer, [5]Food and Drug Administration, [6]Baylor College of Medicine, [7]Indiana University, [8]Johnson & Johnson, [9]MEMS Biopharma Consulting, [10]Uno Consulting Services, [11]Gilead, [12]Novartis, [13]Georgetown University Hospital

Background: Monitoring of routine liver biochemical tests is an important tool for detection, evaluation, and management of the risk of drug induced liver injury (DILI) during drug development in pediatric populations. The magnitude and severity of changes in liver tests are typically determined in comparison to what is considered to be the normal reference range (NRR) of the studied population. However, NRR values for routine liver tests vary significantly among different laboratories and geographical regions, which may lead to inconsistency and misinterpretation of abnormal values. **Methods:** We conducted a systematic review of published literature and databases of NRR for liver tests across ages 0-18 (neonates through adolescents) from multiple countries and regions. Databases that included individuals with suspected underlying liver disease were excluded. NRR values were reviewed and compared for alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin (TBL), and gamma-glutamyl transferase (GGT) for regions including Europe, United States, Eastern Africa, Australia, India, China, Central America, and Canada. **Results:** In most datasets, there was a pattern of a higher upper limit of normal (ULN) values for serum ALT, AST, ALP, and GGT in the first 2 years of life compared to older children and adolescents. NRR and ULN values for ALT, AST, ALP, TBL and GGT varied substantially among different labs and regions (Figure 1). For example, in 2-year-old boys, ALT ULN values ranged from 22 to 55 U/L, AST ULN ranged from 49 to 71 U/L, and GGT ULN ranged from 14 to 90 U/L. In 2-year-old boys, TBL ULN ranged from 0.5 to 1.4 mg/dL. In 15-year-old male adolescents, ALP ULN ranged from 381 to 810 U/L. Differences in mean values were also observed in boys and girls across geographic regions (ALT differences shown in Figure 1). **Conclusion:** Pediatric NRR values for routine liver tests exhibit high variability among labs and across various populations and regions. This can be related to variance in analytic **Methods:** and differences in the reference populations. This variability complicates the use of thresholds of ULN or universal NRRs (as recently suggested for adults) for detection of DILI and assessment of drug safety in medical care and in clinical trials which often use multiple laboratories in various geographies. Consequently, it is currently preferred to use the NRR of the testing laboratory rather than a universal NRR.

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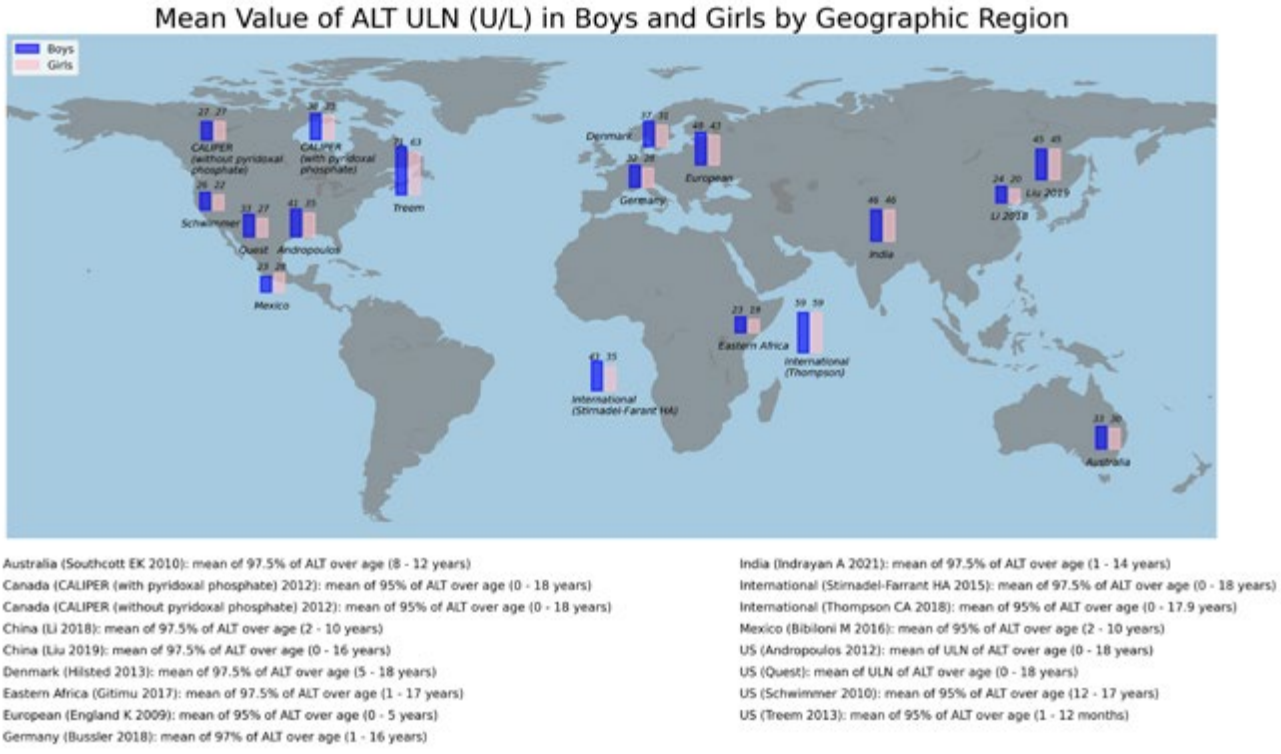

Disclosures: Arie Regev: Eli Lilly and Company: Employee, John Marcinak: AbbVie: Employee, Linyun Zhou: Nothing to Disclose, Funan Huang: Nothing to Disclose, Ruby Mehta: Nothing to Disclose, Benjamin Shneider: Nothing to Disclose, Jean Molleston: Mirium: Grant/Research Support, Albireo: Grant/Research Support, Abbvie: Grant/Research Support, Gillead: Grant/Research Support, CF Foundation: Grant/Research Support, Kathy Kordy: Nothing to Disclose, Eric Maller: Nothing to Disclose, William Treem: Nothing to Disclose, Linda Wang: Gilead Sciences: Employee, Deepa Chand: Novartis: Employee and Shareholder, David Brott: Nothing to Disclose, James Lewis: Nothing to Disclose

2437 | EARLY BILE DRAINAGE SAVES BEAGLES FROM AMANITA SUBJUNQUILLEA-INDUCED ACUTE LIVER FAILURE

Xiuying Ma[1] Wenxue Wang[1] Jiawei Geng[2] Huijie Zhong[3] Chibing Li[1]

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Background: Mistaken ingestion of poisonous mushroom containing amantoxin normally induces acute liver failure(ALF) presenting extremely high mortality rate. Most foodborne toxins show an enterohepatic circulation that can be interrupted by numerous clinical strategies, such as bile drainage. However, the safeness and effective of bile drainage for Amanita Subjunquillea-induced ALF need to be validated in animal model, the related mechanism also be uncovered at the single-cell level. **Methods:** Amanita Subjunquilleas were collected at Yeyahu Park in Kunming, Southwest China. Beagles were randomly divided into four groups, including *control*, *liver failure*, *liver failure plus bile drainage*, and *liver failure plus silibinin*. Beagles of ALF groups were fed with 60 mg/kg of dried Amanita Subjunquillea. Beagles of liver failure plus bile drainage group additionally underwent ultrasound-guided cholecystocentesis to extract bile at 24h, 48h, and 72h after Amanita ingestion. Meanwhile, beagles of liver failure plus silibinin group were additionally given intravenous injection of (50mg/kg). ALF were assessed using toxic reactions, biochemical and pathological experiments, single-cell sequencing was applied to analyze hepatic cellular damage and composition variation. **Results:** All beagles fed with Amanita Subjunquillea exhibited toxic reactions in 14-23 h after Amanita ingestion. When the beagles with ALF were comatose, they were sacrificed in 28h-71h after Amanita ingestion. The bile of ALF beagles were characterized with dark green, thick and pullable. Pathological lesions showed diffuse hemorrhage with sparing hepatocyte necrosis. Compared

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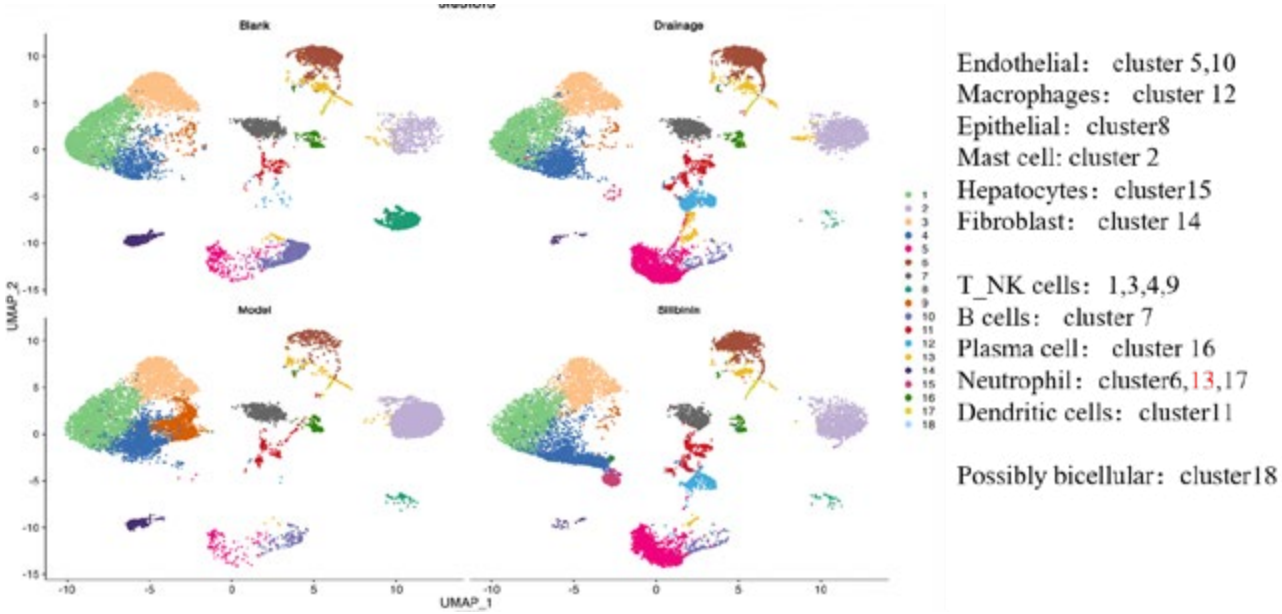
with control group, biochemical indexes of ALF beagles increased to peak at 24 hours after Amanita ingestion. this indexes included ALT(257.8±107.5)U/L□AST(8388±3384)U/L□TBIL(14.00±1.963)μmol/l, PT(15.91±6.14) s□APTT(42.63±18.58)s. The bile color of both bile drainage and silibinin-managed beagles was changed into normal (yellow), these beagle's survival condition had been significantly improved. Interestingly, pathological and partial biochemical indexes of bile drainage beagles were further improved than silibinin. Single-cell sequencing indicated that macrophages, endothelial cells, epithelial cells, and mast cells of liver tissue were severely damaged in beagles fed with Amanita Subjunquillea, both bile drainage and silibinin management elevated these cell's survival, but bile drainage gave better performance(See in Figure 1). **Conclusion:** Bile drainage for the treatment of Amanita Subjunquillea-induced ALF is safe and more effective, than the intravenous silibinin management. Single-cell sequencing suggests liver failure caused by Amanita Subjunquillea ingestion was a consequence of not only amanitin-induced direct cellular damage, but also hepatic immune cell excessive activities.



Disclosures: Xiuying Ma: Nothing to Disclose, Wenxue Wang: Nothing to Disclose, Jiawei Geng: Nothing to Disclose, Huijie Zhong: Nothing to Disclose, Chibing Li: Nothing to Disclose

2438 | DRUG-INDUCED LIVER INJURY DUE TO MEDICATIONS FOR ALCOHOL USE DISORDER: INSIGHTS FROM THE DILIN PROSPECTIVE STUDY

Harish Gopalakrishna[1] Marwan Ghabril[2] Jiezhun Gu[3] Yi-Ju Li[3] Robert Fontana[4] David Kleiner[5] Christopher Koh[1] Naga Chalasani[6]

[1]National Institutes of Health, [2]Indiana University, [3]Duke Clinical Research Institute, Duke U, [4]University of Michigan Hospitals and Health Centers, [5]National Cancer Institute, Bethesda, [6]Indiana University Medical Center

Background: Alcohol use disorder (AUD) and its complications are increasing globally. Medications for alcohol use disorder (MAUD) can improve survival, even in patients with advanced alcohol-related liver disease. However, concerns about drug-induced liver injury (DILI) often deter physicians from prescribing MAUD. We aim to explore DILI due to MAUD enrolled in the US Drug-Induced Liver Injury Network (DILIN). **Methods:** High confidence cases (scores of definite, highly likely, or probable) of DILI due to MAUD enrolled into the DILIN prospective study from 2004 to 2024 were reviewed. HLA allele frequency (AF) of disulfiram DILI cases (n=9) was compared to 456 matched non-disulfiram DILI controls from the DILIN (DILI controls). **Results:** Among 1975 high confidence cases, 13 were attributed to MAUD (11 disulfiram, 1 naltrexone, 1 baclofen, and none to acamprosate). Median age was 45 years, 77% were female and 85% White. In the disulfiram group, median time from drug initiation to DILI onset was 34 days. Most common symptoms at presentation were abdominal pain and jaundice, seen in 73% of patients. Median peak in ALT was 2516 U/L, AST was 2009 U/L, ALP was 244 U/L, total bilirubin was 16 mg/dL and INR was 1.6. Five (71%) patients with severe or fatal disulfiram DILI had underlying liver disease. Eight

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patients developed jaundice, with 3 fatal or near-fatal cases, including 2 requiring liver transplants and 1 liver-related death. The AF for HLA-C*01:02 in disulfiram cases was significantly higher than in DILI controls (AF: 0.167 vs 0.031, OR: 6.29, 95% CI: 1.10-24.1) and the AF for *DRB1*09:01* in disulfiram cases was significantly higher than in DILI controls (AF: 0.111 vs 0.012, OR: 10.16, 95% CI: 1/01, 52.7). DILI from naltrexone and baclofen occurred in white females, causing a mild to moderate hepatocellular pattern of liver injury. This resolved after stopping the drugs, with no chronic DILI development. **Conclusion:** Disulfiram is the leading cause of DILI among MAUD, is most frequently encountered in women, and is associated with significant fatality/transplant. Disulfiram DILI is associated with *HLA-C*01:02* and *DRB1*09:01*. Baclofen and naltrexone can cause mild to moderate self-limited DILI. However, there were no cases of acamprosate DILI. These findings demonstrate the generally favorable safety profile of pharmacotherapy, other than disulfiram, in treating alcohol use disorder.

Table: Characteristics of individuals with DILI due to medications for alcohol use disorder

Characteristic	Disulfiram N=11	Baclofen N=1	Naltrexone N=1
Age, (years)	43.8 (31.5, 61.3)	61	59.7
Sex, Female	8 (72.7%)	1 (100.0%)	1 (100.0%)
Drug start to DILI onset (days)	34 (21, 52)	112	8
R-value at onset	27.9 (7.6, 72.5)	19.3	13.3
Peak value of ALT (U/L)	2516 (1365, 4691)	1446	730
Peak value of AST (U/L)	2009 (919, 2675)	2078	216
Peak value of ALP (U/L)	244 (176, 357)	129	126
Peak value of total bilirubin (mg/dL)	16.0 (4.9, 28.4)	2.6	0.7
Peak INR	1.6 (1.2, 2.3)	1.1	0.9
Improvement in liver tests-median days			
Peak ALT to below ULN	31 (12, 103)	13	1
Peak total bilirubin to <2.5 mg/dL	51	1	-
Hospitalization or non-DILI hospitalization was prolonged	10 (90.9%)	1 (100.0%)	1 (100.0%)
DILI persistent at 6 months, n/N	0/9	0/1	0/1
Causality			
- Definite/highly likely/probable	4/6/3	0/0/1	0/0/1
Severity score			
- Mild	2 (18%)	-	1 (100%)
- Moderate-hospitalized	2 (18%)	1 (100%)	-
- Severe	4 (37%)	-	-
- Fatal	3 (27%)	-	-
Death	1 (9%)	-	-
Liver transplant	2 (18%)	-	-

Continuous variables are presented as median (range) and categorical variables are presented as n (%).
Abbreviations: AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; ULN: Upper limit of normal; DILI: Drug induced liver injury

Disclosures: Harish Gopalakrishna: Nothing to Disclose, Marwan Ghabril: Nothing to Disclose, Jiezhun Gu: Nothing to Disclose, Yi-Ju Li: Nothing to Disclose, Robert Fontana: Grant/Research Support relationship with kezar pharmaceuticals; Has not ended; Consultant relationship with moderna; Has ended; Grant/Research Support relationship with Takeda Pharmaceuticals; Has not ended, David Kleiner: Nothing to Disclose, Christopher Koh: Nothing to Disclose, Naga Chalasani: Madrigal: Consultant, Zydus, Ipsen, Pfizer, Merck, Altimmune, GSK: Consultant, Exact Sciences: Grant/Research Support, NIH: Grant/Research Support

2439 | LIVER INJURY IN CLINICAL TRIALS OF BIOLOGIC AGENTS HAS A LOWER RATE OF ATTRIBUTION TO DRUG-INDUCED LIVER INJURY (DILI) COMPARED TO NON-BIOLOGIC AGENTS

Jasmine Amirzadegan[1] *Edwige Chiogo Vouffo*[1] *Ling Lan*[1] *Eileen Navarro Almario*[1] *Mark Avigan*[2] *Paul Hayashi*[1]

[1]*Food and Drug Administration,* [2]*Food and Drug Adminstration*

Background: Background: The risk of drug-induced liver injury (DILI) from biologic agents (proteins >40 amino acids) may be different from non-biologic agents (smaller proteins, small molecule drugs) due to different mechanistic and catabolic pathways. Aim: To compare the rates of attribution of liver injury to DILI between biologic (BLA) and non-BLA (nBLA) agents in clinical trials. **Methods:** We retrospectively analyzed all pre-market liver injury cases assessed by the FDA DILI Team between Jul 1, 2020, to Apr 10, 2024. We categorized cases as at least probable (≥50% likelihood) and at least possible (≥25% likelihood) DILI due BLAs vs nBLAs. We

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describe DILI phenotypes for at least probable cases in each group. **Results:** We assessed 1314 patients for DILI across 73 applications (12 BLA, 61 nBLA). Ten of the 12 BLAs were monoclonal antibodies. Of these ten, eight were humanized and none were immune checkpoint inhibitors (ICI). Sixteen (5%) of 352 BLA cases were assessed as at least probable vs 278 (29%) of 962 non-BLA cases (p<0.0001). 54 (15%) of BLA cases were at least possible vs 528 (55%) of nBLA cases (p<0.0001). Amongst those assessed as at least probable DILI, BLA cases were more likely to be male (62% vs. 41%) and younger (median age 37 yr, range 29-61 vs. 52 yr, range 3-85). Median latency was longer for BLA cases but there was substantial overlap (56 days, range 8-434 vs 35 days, 1-406). Median R-values [(ALT/ULN)/(AP/ULN)] for BLA compared to nBLA cases were similar at onset (3.2 vs. 4.0) but lower at peak injury (4.4 vs. 7.6). At peak injury, a smaller proportion of BLA cases had hepatocellular DILI (R-value >5) compared to nBLA cases (40% vs. 70%). There were no DILI fatalities (death or transplant) in the BLA group but 4 fatalities amongst 278 probable DILIs (1.4%) in the nBLA group. Subjects with liver injury in BLA trials had lower rates of possible and probable DILI compared to subjects in nBLA trials, but the ratio of possible to probable cases was higher (3:1 vs. 2:1). BLA DILI cases were non-fatal, less hepatocellular, and had longer latencies compared to nBLA DILI. DILI fatality rate was low, and none were due to BLAs. In both groups, R-values tended to increase from onset to peak. **Conclusion:** Conclusions: In trials, DILI risk may be lower with non-immune checkpoint inhibitor BLAs compared to non-biologic agents, but attributing liver injury to study drug may also be more difficult in BLA trials. Conclusions are the author's & not an FDA official position.

Disclosures: Jasmine Amirzadegan: Nothing to Disclose, Edwige Chiogo Vouffo: Nothing to Disclose, Ling Lan: Nothing to Disclose, Eileen Navarro Almario: Nothing to Disclose, Mark Avigan: Nothing to Disclose, Paul Hayashi: Nothing to Disclose

2440 | IMPACT OF LIPOPHILICITY AND DAILY DOSE ON DRUG-INDUCED LIVER INJURY IN THE JAPANESE COHORT

Kota Tsuruya[1] Yusuke Mishima[1] Yoshitaka Arase[1] Hajime Takikawa[2] Tatehiro Kagawa[1]

[1]Tokai University, [2]Teikyo University

Background: Drug-induced liver injury (DILI) is a significant medical condition that, while often mild, can occasionally lead to serious complications such as acute liver failure. It is also one of the most common reasons for the withdrawal of drugs from the market. Reports suggest that drugs with high lipophilicity and high daily doses are more likely to cause DILI, but this observation has not been extensively verified. This study investigated the lipophilicity and daily dosage of drugs that caused DILI in the Japanese cohort. **Methods:** We enrolled a total of 397 DILI cases, including 307 cases collected from multiple centers between 2010 and 2018, and 90 cases from our hospital, excluding cases caused by herbal medicines and dietary supplements. We compiled a list of DILI-causing drugs, which included both the causative drugs identified in this DILI cohort and those implicated in over 100 cases of acute liver failure as reported by the Pharmaceuticals and Medical Devices Agency in Japan between 2007 and 2016. The lipophilicity and daily doses of these drugs were investigated and compared with control drugs that have few reports of hepatotoxicity in the literature. Lipophilicity was calculated using the octanol/water partition coefficient (logP) from the United States Environmental Protection Agency website, with logP > 3 defined as high lipophilicity (HL). Drug doses were obtained from package inserts, with doses > 100 mg/day defined as high daily dose (HDD). Statistical analysis was performed using the two-tailed chi-squared test, with $P < 0.05$ considered significant. Additionally, the odds ratio for the occurrence of DILI was calculated. **Results:** We identified 187 drugs as DILI-causing drugs, without duplicates. Among them, 84 drugs (44.9%) were in the HDD group, 76 drugs (40.6%) were in the HL group, and 32 drugs (17.1%) were in both HDD and HL groups. In contrast, 46 drugs were listed as control drugs, with 15 drugs (32.6%) in the HDD group, 16 drugs (34.8%) in the HL group, and 2 drugs (4.3%) in both HDD and HL groups. The proportion of both HDD and HL drugs was significantly higher for the DILI-causing drugs than the control drugs ($P = 0.034$). The odds ratios for DILI were 1.9 (95% CI: 0.85-3.33) for the HDD group, 1.2 (95% CI: 0.65-2.52) for the HL group, and 4.5 (95% CI: 1.05-19.7) for both HDD and HL groups. **Conclusion:** We confirmed that drugs with higher daily doses and higher lipophilicity had a higher risk of causing DILI in the Japanese cohort. Additional caution should be taken when prescribing these drugs.

Disclosures: Kota Tsuruya: Eisai Co., Ltd.: Speaking and Teaching, Eisai Co., Ltd.: Speaking and Teaching, Eisai Co., Ltd.: Speaking and Teaching, Takeda Pharmaceutical Co., Ltd.: Speaking and Teaching, Kowa Company, Ltd.: Speaking and Teaching, Chugai Pharmaceutical Co., Ltd.: Speaking and Teaching, ASKA Pharmaceutical

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Co., Ltd.: Speaking and Teaching, AbbVie GK: Speaking and Teaching, Yusuke Mishima: Nothing to Disclose, Yoshitaka Arase: Nothing to Disclose, Hajime Takikawa: DAIICHI SANKYO Co. Ltd.: Adviser, Sanofi in Japan: Adviser, Seagen Inc.: Adviser, Tatehiro Kagawa: Nothing to Disclose

2441 | THE LIVER-ENDOCRINE AXIS PLAYS A MECHANISTIC ROLE IN DRIVING CHEMICAL PLUS DIET-INDUCED STEATOTIC LIVER DISEASE IN FEMALES ★

Oluwanifemi Esther Bolatimi[1] Yuan Hua[1] Bana Luulay[1] Shikshita Singh[2] Hao Zheng[1] Tyler Gripshover[1] Walter Watson[1] Maiying Kong[1] Michael Merchant[1] Banrida Wahlang[3]

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Background: Persistent organic pollutants (POPs) including polychlorinated biphenyls (e.g. PCB126) and organochlorine pesticides (e.g. chlordane) are well-associated with steatotic liver disease (SLD). Historically, these associations were reported primarily in chemical/agricultural workers who were chiefly men and toxicity studies performed mostly in male models. Critical knowledge gaps exist in how these chemicals impact women's health, specifically in the context of hypercaloric and western diets. Thus, the study's objective is to determine the sex-specific impact of environmental chemicals with primary focus on female liver health and metabolic dysfunction. **Methods:** Male and female C57BL/6 mice were fed a high-fat (HFD) or low-fat diet (LFD) and administered either vehicle control or a mixture of chlordane(20 mg/kg)+PCB126(20µg/kg) via oral gavage over a 12-week period. Tissues and plasma were collected at euthanasia for downstream analyses. **Results:** Compared to their diet- and sex-matched controls, HFD-fed female mice exposed to the POP mixture exhibited steatosis, confirmed by H&E staining of liver sections and quantification of hepatic triglycerides/cholesterol, and decreased physical activity (assessed using metabolic cages). These observations were absent in males. Exposed females on both diets also displayed increased liver weight, indicating hepatomegaly with chemical exposure. While HFD caused greater liver inflammation in females *vs.* males as demonstrated by neutrophil infiltration (CAE staining) and cytokine gene expression, LFD-fed females also showed increased *Timp1* levels with exposure. Strikingly, hepatic albumin (*Alb*) expression was decreased in exposed females on both diets, suggesting sex-specific liver dysfunction. Mechanistically, although chemical exposure, irrespective of sex and diet, activated hepatic xenobiotic receptors, namely AHR (*Cyp1a2* induction) and CAR (*Cyp1b10* induction), more robust CAR activation was observed in LFD-fed females. Further, liver proteomic analysis revealed a sex-specific upregulation for fatty acid synthase (FAS) in HFD-fed exposed females. This group also showed decreased liver gene expression for estrogen sulfotransferase, a key enzyme in estrogen metabolism. Concordantly, exposed females had lower circulating estradiol levels *vs.* exposed males, implicating dampened estrogen signaling and altered liver-endocrine crosstalk. **Conclusion:** Female mice exposed to the POP mixture developed steatosis and metabolic dysfunction and were more susceptible to toxicant-associated SLD than males. Findings suggested xenobiotic receptor-sex hormone interactions resulted in loss of protective estrogenic effects against steatosis in females. Studies using ovariectomized models and estradiol supplementation will validate mechanisms and provide insights on potential sex-specific interventions/therapy in toxicant-associated SLD.

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2442 | INTRATHECAL METHOTREXATE IS ASSOCIATED WITH ACUTE TRANSIENT HEPATOCELLULAR LIVER INJURY

Harish Gopalakrishna[1] Nirali Shah[1] Mark Roschewski[1] Yaron Rotman[1]

[1]National Institutes of Health

Background: Methotrexate (MTX) is used to treat malignancies and immune conditions, through oral, intravenous (IV) or intrathecal (IT) routes. IT-MTX is used in management of hematological malignancies with potential central nervous system involvement. Hepatotoxicity is a known risk of oral and IV MTX, but whether IT-MTX is also hepatotoxic remains unknown. We aimed to systematically explore whether IT-MTX is associated

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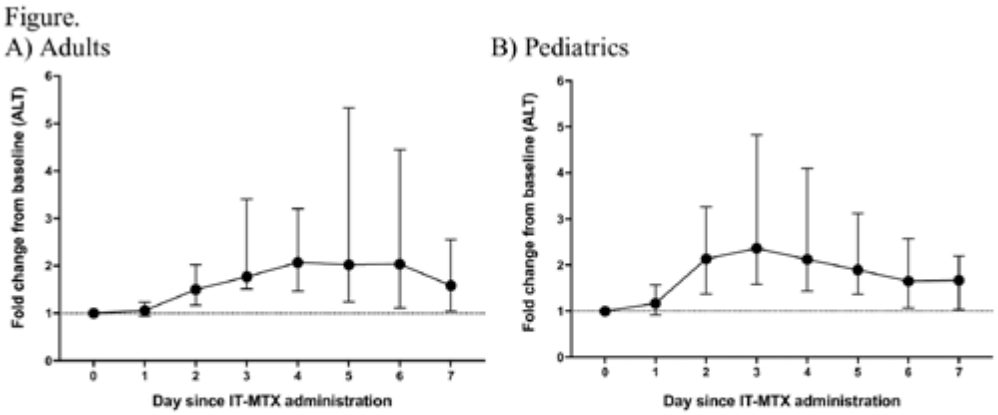
with acute liver injury. **Methods:** A single-center retrospective analysis of all adult and pediatric subjects treated with IT-MTX from 2000-2020. We compared liver associated enzymes (LAE) at baseline (within 7 days before IT-MTX) to post-treatment (within 7 days) levels. Liver injury was defined as ≥ 50% increase in LAE from baseline, along with post-MTX level > upper limit of normal (ULN). We assessed whether LAE elevation incidence was significantly different from chance unrelated fluctuations using a block bootstrapping analysis. **Results:** 270 subjects (184 adults and 86 pediatric) received at least one dose of IT-MTX and had available baseline and post-MTX data. Liver injury with transaminase elevation was seen post-MTX in 107 (40%) of treated subjects, of whom 96 (36%, p<0.01) had ALT elevation and 68 (25%, p<0.01) had elevated AST. The incidence of alkaline phosphatase or bilirubin elevation was not significantly different than chance. Greater than 3-fold and 5-fold rise in ALT was seen in 41 (15%) and 19 (7%) subjects, respectively. ALT and AST peaked a median of 4 (3-5) days after exposure to IT-MTX and subsequently returned near baseline by day 7 (Figure). Compared to adults, ALT and AST elevations were more frequent in pediatric subjects (28% vs 51% and 18% vs 41%, respectively; p<0.01 for both). No significant predictors of liver injury were identified, including age, gender, dose, other chemotherapeutic agents, baseline LAE, or underlying liver disease. No subject developed liver failure and only one (pediatric) met Hy's law criteria, with LAE returning to baseline values within 7 days. 132 (49%) of the subjects received a second dose of IT-MTX of whom 46 (35%) had ALT elevation and 33 (25%) had AST elevation post-MTX. Interestingly, ALT elevation after first dose did not predict ALT elevation with second dose. **Conclusion:** Acute transient hepatocellular liver injury is common after IT-MTX especially in pediatric subjects. However, injury is mild and self-limited with no sensitization or liver failure.

Figure.



Change in alanine aminotransferase (ALT) over time. ALT fold-change from baseline after the first dose of intrathecal methotrexate (IT-MTX) (limited to subjects with ALT elevation) in (a) adult (age ≥ 18 years) or (b) pediatric (age < 18 years) subjects.

Disclosures: Harish Gopalakrishna: Nothing to Disclose, Nirali Shah: Nothing to Disclose, Mark Roschewski: Nothing to Disclose, Yaron Rotman: Astra Zeneca: My spouse is an employee

2443 | ELEVATED BASELINE SERUM CD8 AND IL-2 LEVELS MAY PREDICT SYSTEMIC ANTICANCER THERAPY RELATED LIVER INJURY

Nathaniel Ash[1] Sonia Mehra[2] Mohammed Umair Masood[1] Matthew Galsky[1] William Oh[1] Lauren Grinspan[1] Priya Grewal[3] JAWAD AHMAD[1] Joseph Odin[3]

[1]Icahn School of Medicine at Mount Sinai, [2]Mount Sinai Hospital Morningside/West, [3]Icahn School of Medicine at Mount Sinai (ISMMS)

Background: Liver injury is a concern when initiating cancer-directed medications. Liver injury is difficult to predict pre-treatment and there is a need for reliable serum biomarkers to aid in safe initiation of these therapies. Proteins IL-2 and CD8 may play a role in inflammation and liver injury during systemic anticancer therapy. We hypothesized that levels of these proteins may predict liver injury in patients undergoing cancer treatment. This study aimed to identify serologic biomarkers by comparing pre-treatment levels of a large panel of serum proteins between patients with and without subsequent liver injury. **Methods:** 34 prospective patients were enrolled in

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this prospective study with 10 healthy controls. Serum was collected within two weeks prior to starting treatment. Patients had genitourinary cancers treated with chemotherapy and/or immunotherapy. Those with underlying liver disease were excluded. Liver enzymes were monitored at 2-week intervals after starting treatment by three hepatologists to determine the cause of the increase. Liver injury was defined as a 3x increase in AST/ALT or a 2x increase in ALP. A validated, commercially available immuno-oncology protein assay panel (Olink Bioscience, Uppsala, Sweden) was used to quantitatively compare IL-2 and CD8 as well as other immune protein concentrations. The non-parametric Mann-Whitney U test was used to compare pre-treatment serum protein levels in patients with and without subsequent liver injury. **Results:** The baseline levels of IL-2 and CD8 differed significantly between the non-liver injury (n=28) and liver injury groups (n=5). Liver injury attributed to DILI only occurred in 3 cases. Given that the elevation in IL-2 and CD8 were not limited to the cases of DILI, the cases were grouped together in the liver injury group for further analysis. The IL-2 and CD8 levels were independent of cancer type or known prior treatments and were significantly higher than in the controls. Median levels of IL-2 in the non-liver injury and liver injury groups were 9.31 and 10.76 U/mL respectively (Mann–Whitney U=111, n_1=28, n_2=5, p=0.039 2-tailed). Median levels of CD8 in the non-liver injury and liver injury groups were 785.00 and 1256.51 U/mL respectively (Mann–Whitney U=111, n_1=28, n_2=5, p=0.039 2-tailed). When a positive result was defined as IL-2>10 U/mL and CD8>1000 U/mL, PPV, NPV, sensitivity, and specificity were 60.0%, 92.9%, 60.0%, and 92.9% respectively for predicting liver injury. **Conclusion:** Serum IL-2 and CD8 levels may be useful pre-cancer treatment biomarkers to identify those at increased risk of treatment induced liver injury. Both serum IL-2 and CD8 levels may reflect T cell activation, which is believed to play an important role in liver injury. Our results show promise for using IL-2 and CD8 in combination as a pre-treatment predictor of liver injury. Further testing in a larger, independent replicate group is needed to confirm these associations.

Disclosures: Nathaniel Ash: Nothing to Disclose, Sonia Mehra: Nothing to Disclose, Mohammed Umair Masood: Nothing to Disclose, Matthew Galsky: Nothing to Disclose, William Oh: Nothing to Disclose, Lauren Grinspan: Nothing to Disclose, Priya Grewal: Nothing to Disclose, JAWAD AHMAD: Nothing to Disclose, Joseph Odin: Nothing to Disclose

2444 | DRUG INDUCED LIVER INJURY: A UNUSUAL CASE OF CHOLESTATIC HEPATITIS CAUSED BY HIGHLY ACTIVE ANTI-RETROVIRAL THERAPY (HAART)

haniya waseem[1] adnan muhammad[1] Georolyn Torkelson[1]

[1]Advent Health Tampa

Background: Drug-induced liver injury (DILI) is an uncommon adverse reaction to a drug. It accounts for less than 1% cases of acute liver injury. DILI can lead to fatal outcome if not recognized in a timely fashion. There are 3 types of DILI classified as direct, idiosyncratic, and indirect. Idiosyncratic DILI follows a more unpredictable course and is usually seen in a smaller subset of patients. We present a case of idiosyncratic DILI in a patient taking highly active antiretroviral therapy (HAART). **Methods:** Case: 46-year-old Hispanic female was diagnosed with HIV 6 months ago and subsequently started on HAART therapy that include bictegravir, emtricitabine & tenofovir alafenamide. She presented to the ER with complaints of fatigue, malaise, and jaundice. Initial metabolic profile showed AST and ALT elevated at 4824 and 1396, with bilirubin at 6.9. Her CD4 count at admission was 55. Viral hepatitis serologies and autoantibodies were nonreactive. Ultrasound, CT scan and MRCP showed normal liver and no evidence of biliary obstruction. Based on the RUCAM assessment patient had a high probability of having DILI with a score>8. HAART was stopped and the patient was subsequently started on Ursodiol for cholestasis and IV N-acetylcysteine for DILI which led to positive de-challenge. Patient subsequently underwent trans jugular liver biopsy by IR in the setting of coagulopathy and thrombocytopenia. Liver biopsy revealed acute/subacute cholestatic liver injury with extensive central to portal bridging necrosis, mixed, predominantly acute inflammation, and early portal/bridging. This histopathology favored drug-induced cholestatic/necro inflammatory liver injury. Patient had a prolonged course in the ICU because of complications related to acute liver failure. Patient was deemed not a candidate for liver transplantation in the setting of low CD4 count **Results:** n/a **Conclusion:** The incidence of DILI is not well known for most antiviral therapies. Multiple pathogenic mechanisms are reported including direct drug toxicity, immune reconstitution, hypersensitivity reaction and mitochondrial toxicity. Liver toxicity ranges from asymptomatic mild elevation of transaminases with spontaneous resolution to liver failure and death.Current best practice involves maintaining a high level of clinical suspicion and conducting thorough hepatological investigations, guided by the international RUCAM criteria, a diagnostic algorithm for DILI. Our patient presented with acute cholestatic hepatitis with biopsy-proven extensive necrosis of hepatocytes

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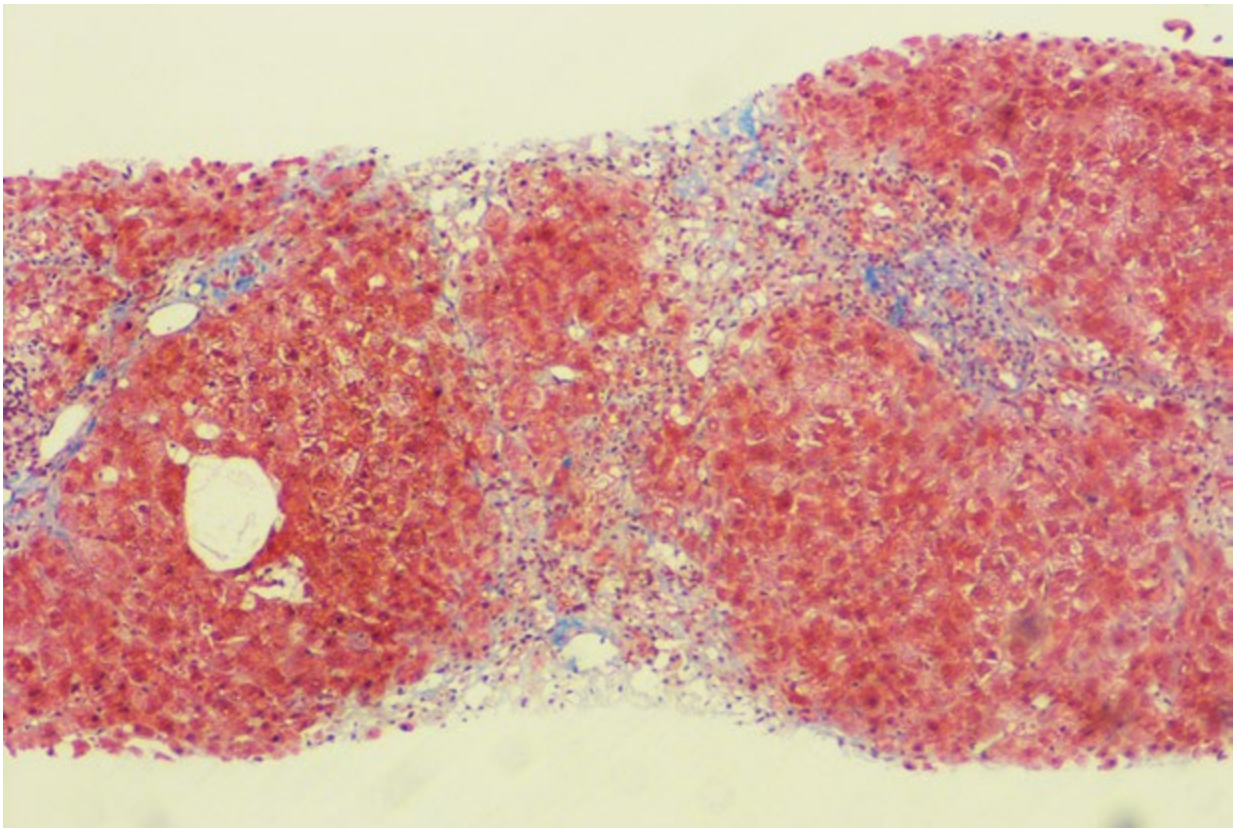
resulting in complications of acute liver failure. Clinical course did not reverse after removing the offending drug. Clinicians need to be aware of the incidence and clinical impact of HAART related liver toxicity.



Disclosures: haniya waseem: Nothing to Disclose, adnan muhammad: Nothing to Disclose, Georolyn Torkelson: Nothing to Disclose

2445 | EVOLVING PATTERNS OF POTENTIALLY HEPATOTOXIC BOTANICAL USE IN THE UNITED STATES: RESULTS FROM NHANES 2003 - 2018 SURVEYS

Alisa Likhitsup[1] Vincent Chen[2] Robert Fontana[3]

[1]University of Michigan, [2]University of Michigan Medical Center, [3]University of Michigan Hospitals and Health Centers

Background: Green tea extract (GTE) can cause clinically significant liver injury and turmeric hepatotoxicity is also increasing in the US (Am J Med 2023: 136: 200). Newer formulations of turmeric contain a black pepper additive to enhance absorption. The aim of this study is to estimate the prevalence of GTE and turmeric +/- black pepper usage in the general US population using NHANES. **Methods:** The 2003-2018 NHANES biannual data of adults (>/=18 years) were analyzed. Intake of GTE and turmeric +/- black pepper containing products within the past 30 days were identified using dietary supplement ingredients database. The characteristics and prevalence of GTE and turmeric +/- black pepper use and time-trend regression analysis are reported. **Results:** Amongst 80,312 NHANES adults surveyed from 2003 to 2018, there were 48,379 non-HDS users, 680 GTE users, and 390 turmeric users which included 48 combination turmeric/black pepper formulation users. There were 273 unique GTE and 189 unique turmeric products consumed. The prevalence of any HDS use increased from 53% in 2003-2004 to 57.6% in 2017-2018 ($p<0.0001$). Similarly, the prevalence of any turmeric and turmeric+blackpepper use significantly increased from 0.6% & 0% in 2003-2004 to 5.6%, and 0.6% in 2017-2018 ($p<0.0001$). However, the prevalence of GTE use decreased from 4.2% in 2003-2004 to 1.7% in 2017-2018 ($p<0.05$) (Figure 1). The median number of concomitant HDS products use for turmeric, turmeric+blackpepper, and GTE users, were 4.5, 6.5, and 2, respectively. Adults who took turmeric with black pepper were older than turmeric only consumers and less likely to consume alcohol ($p=0.04$). Multivariable analysis showed older age (aOR 1.91 for age 40-59, 5.42 for

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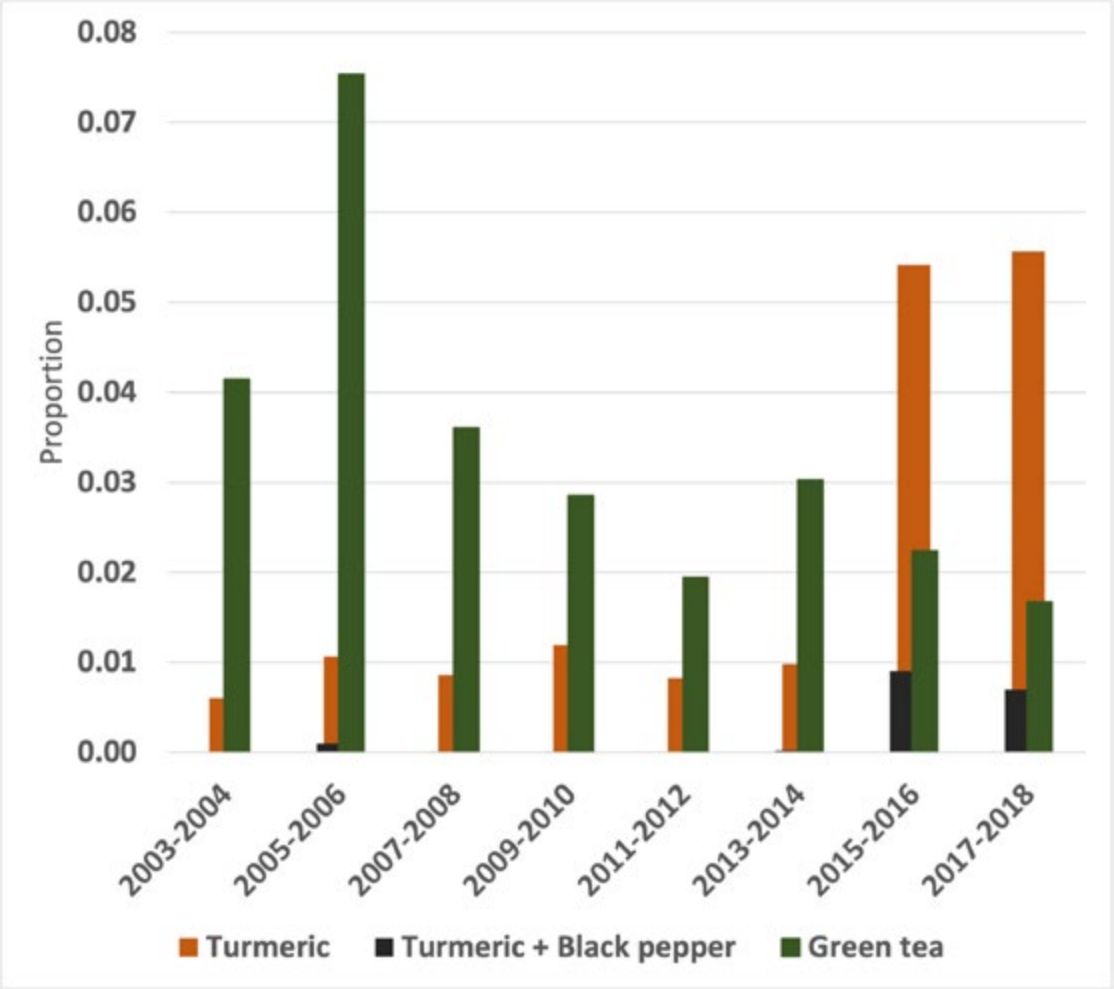
age >/=60), non-Hispanic white (aOR 1.73), higher income (aOR 1.87), higher education (aOR 3.45), presence of arthritis (aOR 1.71), thyroid disorder (aOR 1.81), and cancer (aOR 1.70) were independently associated with turmeric use (p<0.05). **Conclusion:** HDS associated liver injury is increasingly reported in the United States due to a variety of products including multi-ingredient botanicals .While GTE use has decreased, turmeric +/- black pepper use has increased significantly overtime amongst American adults. Clinicians should be aware that an increasing proportion of turmeric products contain black pepper which may lead to a higher incidence of inadveretent hepatototoxicity.



Disclosures: Alisa Likhitsup: Nothing to Disclose, Vincent Chen: Site PI on industry-sponsored trial relationship with AstraZeneca; Has ended; site co-I on industry-sponsored trial relationship with Ipsen; Has not ended; site co-I on industry-sponsored trial relationship with Kowa; Has not ended, Robert Fontana: Grant/Research Support relationship with kezar pharmaceuticals; Has not ended; Consultant relationship with moderna; Has ended; Grant/Research Support relationship with Takeda Pharmaceuticals; Has not ended

2446 | BIODISTRIBUTION OF THERAPEUTIC NANOPARTICLES DEPENDING ON GENDER AND PROGRESSION OF CHRONIC LIVER DISEASE

Tae-Un Kim[1] *Jae-Hyuk Yim*[1] *Woo Jun Kim*[1] *Su-Min Baek*[1] *Jin-Kyu Park*[1]

[1]*Kyungpook National University*

Background: Nanotechnology has long been studied as therapeutics for chronic liver disease, and various nanoparticles including PLGA, silica, gold nanoparticles and liposomes had been used in attempt to establish strategies for efficient drug delivery. However, there is a lack of studies on the differences in the delivery of nanoparticles depending on the stage of chronic liver disease. Therefore, we assessed the distributions of

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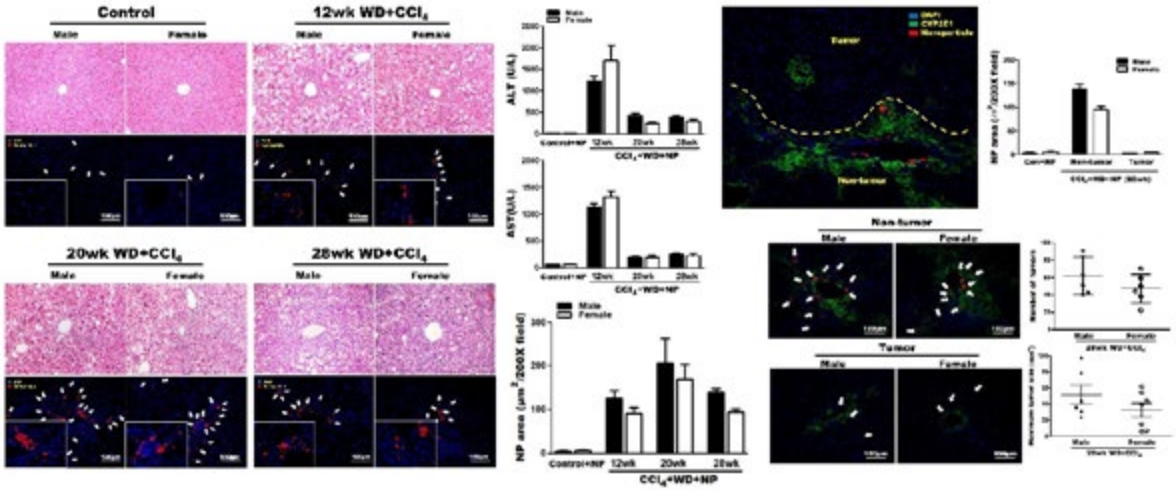
nanoparticles in various stages of chronic liver diseases, and the factors that facilitate or hinder the nanoparticle distribution. **Methods:** Chronic liver disease was induced with Western diet and high-sugar water in combination with CCl4 injection for 12 weeks (fibrosis), 20 weeks (cirrhosis), and 28 weeks (hepatocellular carcinoma). Nanoparticles were injected 24hrs before sacrifice. Gross examination and histopathological analysis, serum biochemistry, immunofluorescence (IF), and immunohistochemistry (IHC) had been performed to assess the stage of chronic liver disease and nanoparticle distribution. **Results:** Hepatic nanoparticle distribution was observed in mouse livers. Interestingly, nanoparticle distribution differed depending on gender and the stage of chronic liver disease. Overall nanoparticle distribution was higher in male mouse than female mouse in all stages of liver disease. Nanoparticle distribution was highly increased in fibrotic livers and reached its peak level in cirrhotic livers. However, as the liver exhibited tumor nodules in 28 week-experiment, distribution of nanoparticles decreased in the liver parenchyma. Upon immunofluorescence findings, nanoparticles were mainly distributed in zone 3, being co-localized with collagen matrix and Kupffer cells. In tumor-induced mouse livers, nanoparticles were mainly distributed in the borderline of tumor region, showing limited entrance into the tumor tissue. Nanoparticles showed tendency to exist in macrophages, which were highly distributed in damaged livers, but showed significant decrease in tumor tissues. **Conclusion:** This study shows the efficiency of therapeutic nanoparticle treatment depending on gender and the stage of chronic liver diseases. The factors that hinder the distribution of therapeutic nanoparticles in hepatic cancers owes to limited macrophage interventions in tumor tissue. Gender difference in nanoparticle distribution is due to the decreased liver damage and macrophage recruitment in female mice, of which the cause is still to be elucidated.



Disclosures: Tae-Un Kim: Nothing to Disclose, Jae-Hyuk Yim: Nothing to Disclose, Woo Jun Kim: Nothing to Disclose, Su-Min Baek: Nothing to Disclose, Jin-Kyu Park: Nothing to Disclose

2447 | IMPROVING THE DIAGNOSTIC ACCURACY OF THE RECAM IN NORTH AMERICAN PATIENTS WITH SUSPECTED IDIOSYNCRATIC DRUG-INDUCED LIVER INJURY

Jacob Ciricillo[1] Adam Myer[1] Amoah Yeboah-Korang[1] Askanda Osman[1] Farrah Rahim[1] Kenneth Sherman[2] Robert Fontana[3]

[1]University of Cincinnati, [2]Massachusetts General Hospital-Harvard, [3]University of Michigan Hospitals and Health Centers

Background: The Revised Electronic Causality Method (RECAM) is an updated version of the Roussel Uclaf Causality Assessment Method (RUCAM) to diagnose patients with idiosyncratic drug-induced liver injury (DILI). The primary aim of this study was to compare the diagnostic accuracy of RECAM versus RUCAM in a real-world cohort of suspected DILI cases seen at a single North American medical center. Given RECAM requires more extensive serologic evaluation with heavy penalties for missing data, the secondary aim was to determine if incremental improvements could be made in RECAM performance by adjusting weighting criteria for individual data fields. **Methods:** Patient encounters from 2015-2019 were searched for potential DILI cases using ICD-10 codes for toxic liver injury. Gold standard DILIN expert opinion causality scores were assigned to each case (1/2/3

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= probable-DILI, 4/5 = non-DILI). Agreement between RECAM and RUCAM scores with DILIN expert opinion scores were compared. **Results:** Among 766,930 encounters searched, 120 unique patients met inclusion criteria with 72 (60%) adjudicated as probable-DILI. The most frequent suspect drugs were antimicrobials (38.3%), antineoplastics (8.3%), and antirheumatic drugs (8.3%). Mean age was 49.2 ± 15.6 years and 50% were female with 45.8% having hepatocellular injury. RUCAM had better agreement with DILIN expert opinion for probable-DILI versus RECAM (66.7% vs. 44.4%, p=0.018). Both had 100% agreement with DILIN expert opinion for non-DILI. Frequently missing laboratory data included HCV RNA (68.3%) and anti-HEV IgM testing (77.5%), leading to loss of up to 6 points in RECAM scoring without impacting RUCAM scores. Given this discrepancy, a modified RECAM was developed, making HCV RNA and anti-HEV IgM optional. This model had better agreement with DILIN expert opinion compared to RUCAM (79.2% vs. 66.7%, p=0.09) and RECAM (79.2% vs 44.4%, p=0.0008) for probable-DILI. The new RECAM model offered improved sensitivity and NPV compared to RECAM and RUCAM, while maintaining high specificity and PPV. **Conclusion:** Among 120 suspected DILI cases, RUCAM had better agreement with DILIN expert opinion versus RECAM. Making HCV RNA and anti-HEV IgM testing optional significantly improved agreement between RECAM and DILIN expert opinion. Future modifications to RECAM are needed to improve causality assessment in North American patients with suspected DILI.

Disclosures: Jacob Ciricillo: Nothing to Disclose, Adam Myer: Nothing to Disclose, Amoah Yeboah-Korang: Nothing to Disclose, Askanda Osman: Nothing to Disclose, Farrah Rahim: Nothing to Disclose, Kenneth Sherman: AbbVie: Grant/Research Support, Gilead: Grant/Research Support, Helio: Grant/Research Support, Intercept: Grant/Research Support, Zydus: Grant/Research Support, NovoNordisk: Advisor, MedPace: Consultant, Pliant: Consultant, Horizon/Amgen: Consultant, Robert Fontana: Grant/Research Support relationship with kezar pharmaceuticals; Has not ended; Consultant relationship with moderna; Has ended; Grant/Research Support relationship with Takeda Pharmaceuticals; Has not ended

2448 | INTERLEUKIN-19 PROTECTS AGAINST ACETAMINOPHEN-INDUCED LIVER INJURY BY LIMITING MACROPHAGE INFILTRATION VIA ENHANCING C/EBPβ SUMOYLATION

Peng Xiao[1] *Yanhang Gao*[1]

[1]*First Hospital of Jilin University*

Background: Acetaminophen (APAP) overdose is a leading cause of acute liver failure worldwide. The interleukin (IL)-20 subfamily of cytokines, which belong to the IL-10 family, is comprised of IL-19, IL-20, IL-22, IL-24, and IL-26. IL-20 subfamily cytokines signal through heterodimeric receptors comprising various combinations of several shared receptor subunits, namely, IL-20R1, IL-20R2, IL-10R2, and IL-22R1. IL-22 is a well-studied cytokine that activates STAT3 in epithelial cells, reducing epithelial cell damage and bacterial infection. It has significant therapeutic potential for a variety of diseases. While IL-22 has a well-defined function, the function of other IL-20 family cytokines remains unclear. For example, although IL-19 was discovered over 20 years ago and the evidence from IL-19-associated research suggest IL-19 plays a role in regulating neutropenia and atherosclerosis by binding to the previously reported IL-20R complex, comprising of IL-20R1 and IL-20R2; however, the function of IL-19 remains largely unknown. **Methods:** *Il19* knockout (*Il19*KO) mice and wild-type (WT) littermates were generated and injected with APAP to induce acute liver injury. Clodronate was used to deplete macrophages. Multiplex immunofluorescence staining was performed to determine IL-20R2 expression in different cell types. The effect of IL-19 on APAP-induced liver injury was tested by administration of recombinant IL-19 protein and adenovirus-IL-19. **Results:** After injection of APAP in mice, serum levels of IL-19 were highly elevated. APAP injection upregulated IL-20R1 and IL-20R2 expression in liver monocyte-derived macrophages (MoMFs). Interestingly, compared with WT mice, *Il19*KO mice were more susceptible to APAP-induced hepatocyte damage and inflammation. Bulk RNA-seq analysis suggested that *Il19* deficient mice had a distinct transcriptional landscape characterized by an increased inflammatory status after APAP challenge. As expected, *Il19*KO mice had greater degree of MoMF infiltration and oxidative stress than WT mice post APAP injection. More importantly, macrophage depletion by Clodronate injection diminished the susceptibility of *Il19*KO to APAP-induced liver injury. Furthermore, administration of recombinant IL-19 protein or adenovirus-IL-19 significantly suppressed liver MoMF infiltration, thus ameliorating APAP-induced liver injury. Mechanistically, IL-19 could not lead to STAT3 activation in macrophages but increased the post-translational SUMOylation of CCAAT/enhancer-binding protein beta (C/EBPβ), which plays a central role in inducing the transcription of genes encoding several proinflammatory

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chemokines such as MIP-1β. **Conclusion:** IL-19 plays an immunosuppressive role in APAP-induced liver injury by limiting macrophage infiltration via enhancing C/EBPβ SUMOylation. Administration of IL-19 may be a novel strategy for the treatment of drug-induced liver injury.

Disclosures: Peng Xiao: Nothing to Disclose, Yanhang Gao: Nothing to Disclose

2449 | THE METAHEPS® TECHNOLOGY FOR DRUG CAUSALITY ASSESSMENT IN PATIENTS DIAGNOSED WITH IDIOSYNCRATIC DRUG-INDUCED LIVER INJURY (DILI)

Michele Visentin[1] Sophia Samodelov[2] Armin Wolf[2] Gerd Kullak-Ublick[3]

[1]University Hospital Zürich, [2]University of Zurich, [3]University Hospital Zurich

Background: DILI is the leading cause of acute liver failure in Western countries, and a major reason of drug attrition in development. Patient-specific hyper-reactive immune cells are accountable for the onset and progression of the injury. Causality assessment relies on expert opinion and adjudication, with the use of clinical scores such as CIOMS/RUCAM. However, causality assessment poses significant challenges in polymedicated patients with simultaneous intake of more than one potentially DILI causing drug. There is a need for biomarkers/assays that can identify the causative agent among a panel of co-medications. MetaHeps cells (MH) are differentiated from peripheral bone marrow cells (PBMCs) and hence carry the genetic makeup and immunogenicity of the donor. We have developed further the technique of in vitro drug re-challenge in MH derived from DILI patients, particularly in cases in which adjudication could not identify the causative drug. **Methods:** MH generated from PBMCs of healthy volunteers (HV) and DILI patients were exposed to each of the suspected perpetrator drugs. Lactate dehydrogenase (LDH) release into the medium was assessed as a measure of sensitivity to the drug. Drug-induced LDH release by DILI-derived MH was compared to the upper limit of the 95% CI calculated from HV-derived MH cells (n≥4) treated with the same drug. The 95% CI determined in HV-derived MH was set as the upper limit of normal value (ULN) for the specific drug. **Results:** MH were generated from eight DILI patients. A single causative drug (terbinafine, ibuprofen) was determined by adjudication in only two cases. LDH release from MH derived from these two patients was higher than the ULN in response to terbinafine or ibuprofen, indicating a 95% probability of the respective drug being the cause of DILI. In three patients in whom adjudication could not determine a single causative drug, the LDH values from DILI-derived MH were higher than ULN in response to nivolumab, amoxicillin or ipilimumab, respectively. In one case, both suspected drugs (nivolumab, ipilimumab) led to LDH values higher than ULN. In two cases, the DILI-derived MH LDH value was lower than ULN for all the suspected perpetrators. **Conclusion:** The MetaHeps® technology has the potential to serve as a sensitive and specific tool for clinicians and drug developers to confirm or refute the causal role of suspected drugs in the onset of drug-induced liver injury.

Disclosures: Michele Visentin: Nothing to Disclose, Sophia Samodelov: Nothing to Disclose, Armin Wolf: Nothing to Disclose, Gerd Kullak-Ublick: Novartis: Employee

2450 | SEQUENTIAL ANALYSIS OF SERUM LEVELS OF TEN INTESTINAL PERMEABILITY AND INFLAMMATION MARKERS IN PATIENTS WITH DRUG-INDUCED LIVER INJURY AND OTHER FORMS OF ACUTE LIVER INJURY

Daniel Di Zeo-Sánchez[1] Marina Villanueva[1] Irene Díaz-Alberola[2] José María Pinazo Bandera[3] MIREN GARCIA CORTES[3] Enrique del Campo Herrera[2] Mercedes Robles-Diaz[1] Ismael Alvarez-Alvarez[1] Hao Niu[1] M Lucena[1] Raul Andrade[1] Camilla Stephens[1]

[1]IBIMA-Plataforma Bionand, UMA, CIBEREHD, [2]IBIMA-Plataforma Bionand, UMA, [3]UGC aparato digestivo, HUVV

Background: Pathogen-associated molecular patterns entering the circulation as a result of alterations in intestinal permeability may underlie the development or worsening of liver diseases such as drug-induced liver injury (DILI) by exacerbating adverse immunological responses. Several proteins such as LBP, CD14, zonulin and I-FABP, among others, have been indirectly linked to intestinal permeability by playing key roles in the response to bacterial compounds or intestinal barrier integrity. Innate and adaptive immune responses, which are

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known to play pivotal roles in DILI, may precede or trigger increased intestinal permeability. This study aimed to assess intestinal permeability and immunoinflammatory status in patients with liver injury by quantifying serum proteins LBP, CD14, CD163, ICAM-1, MAdCAM-1, I-FABP, zonulin, MCSF-1R, S100A12 and S100A9. **Methods:** Peripheral blood serum was collected from 36 healthy controls (HC), 30 DILI patients (recruited from the Spanish DILI Registry), 13 autoimmune hepatitis (AIH) patients, and 13 viral hepatitis (VH) patients and stored at -80°C until analysis. All patients with acute liver injury fulfilling the biochemical DILI criteria were identified (visit 1) and followed up for > 30 days (visit 2). Serum protein levels were measured by ELISA or Luminex and results were statistically analyzed using Kruskal-Wallis, Mann-Whitney and Wilcoxon matched-pairs signed rank tests. **Results:** The concentration of CD163, ICAM-1 and MCSF-1R proteins was higher in DILI, VH and AIH patients compared to HC at visit 1 ($p<0.001$). LBP and CD14 levels were also higher in DILI and VH compared to HC ($p<0.05$). The levels of all these proteins decreased significantly at visit 2 and approached HC levels. Interestingly, the levels of MAdCAM-1 and zonulin were decreased in patients compared to HC ($p<0.05$), but increased at visit 2. Significant differences were observed between DILI, AIH and VH patients for MCSF-1R, with the highest levels in AIH and the lowest levels in DILI ($p<0.05$). **Conclusion:** Altered serum concentrations of LBP, CD14, CD16, ICAM-1, zonulin, MAdCAM-1 and MCSF-1R detected in DILI patients during the acute episode could indicate an immunoinflammatory state and may reflect increased translocation of bacterial products due to altered intestinal permeability. Funding: CIBERehd-ISCiii, FEDER, PI19/00883, PI21/01248, PEMP-0127-2020.

Disclosures: Daniel Di Zeo-Sánchez: Nothing to Disclose, Marina Villanueva: Nothing to Disclose, Irene Díaz-Alberola: Nothing to Disclose, José María Pinazo Bandera: Nothing to Disclose, MIREN GARCIA CORTES: Gilead: Speaking and Teaching, EISAI: Speaking and Teaching, ORPHALAN: Speaking and Teaching, ADVANZ: Speaking and Teaching, Enrique del Campo Herrera: Nothing to Disclose, Mercedes Robles-Diaz: Nothing to Disclose, Ismael Alvarez-Alvarez: Nothing to Disclose, Hao Niu: Nothing to Disclose, M Lucena: Nothing to Disclose, Raul Andrade: Bayer: Consultant, Boehringer Ingelhein: Consultant, Roche: Consultant, Novo-Nordisk: Consultant, Sanofi: Consultant, GSK: Consultant, Inventiva: Consultant, Silence Therapeutics: Consultant, Camilla Stephens: Nothing to Disclose

2451 | THE ONGOING PROBLEM OF MISLABELING OF HERBAL AND DIETARY SUPPLEMENTS IMPLICATED IN HEPATOTOXICITY

Victor Navarro[1] Bharathi Avula[2] Dina Halegoua-De Marzio[1] Ikhlas Khan[2] Huiman Barnhart[3]

[1]Jefferson Health System, [2]University of Mississippi, [3]Duke Clinical Research Institute

Background: The Drug-Induced Liver Injury Network (DILIN) demonstrated that over 50% of Herbal and Dietary Supplements (HDS) consumed by its enrollees had labels that did not reflect actual contents (PMID: 31168513, PMCID: PMC6545864). Since that 2019 report, the DILIN has continued to collect HDS from its enrollees. The aim of this study is to analyze contents of HDS and determine the prevalence of product mislabeling. **Methods:** Between 2003 and April 2024, DILIN collected 810 HDS from 2627 enrolled patients. To date, 633 products with available product labels have been analyzed at the National Center for Natural Products Research (NCNPR) at the University of Mississippi using high-performance liquid chromatography-mass spectroscopy with electrospray ionization. Chemically verified product ingredients were compared with the listed label ingredients. Mislabeling was defined as a mismatch between chemical analysis and the label ingredients. HDS were categorized according to their marketed purpose for use. **Results:** Amongst the 633 analyzed products, 134 were adjudicated as causing hepatotoxicity with a DILIN causality score of 1,2, or 3. 262 of 633 (41%) of HDS with available product labels consumed by enrollees were mislabeled with a decreasing trend in mislabeling rates over time ($p=0.0004$) (Table). The most commonly mislabeled HDS were marketed for weight loss (42 of 70, 60% rate) followed by products marketed for liver cleansing/toxin removal (10 of 17, 59%), bodybuilding (44 of 77, 57%), energy boosters (11 of 20, 55%), sexual enhancement/performance (4 of 8, 50%), immune support (19 of 44, 43%), sedative/hypnotics (7 of 19, 37%), and circulation/cardiovascular health (5 of 16, 31%). Among the 360 HDS judged to be responsible for liver injury, 134 were collected and analyzed, with a mislabeling rate of 46% (95% confidence interval, 38% - 54%). **Conclusion:** The problem of frequent mislabeling of HDS products continues and, although the overall temporal trend is favorable, products responsible for liver injury are more likely to be mislabeled. Mislabeling is particularly common in products used for weight loss; given the current focus on agents to achieve weight reduction, there may be considerable risk to consumers.

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DILIN Enrollment Period	Number of HDS Products	Rate of HDS Mislabeling
2004-2005	12	33%
2006-2007	36	56%
2008-2009	64	58%
2010-2011	54	50%
2012-2013	56	41%
2014-2015	116	41%
2016-2017	83	30%
2018-2019	97	42%
2020-2021	54	39%
2022-2023	61	26%
Total	633	41.4%

Disclosures: Victor Navarro: Nothing to Disclose, Bharathi Avula: Nothing to Disclose, Dina Halegoua-De Marzio: Novo Nordisk: Advisor, Galectin: Grant/Research Support, Madigral: Advisor, Novo Nordisk: Grant/Research Support, Madigral: Advisor, Viking: Grant/Research Support, Akero: Grant/Research Support, Intercept: Grant/Research Support, Ikhlas Khan: Nothing to Disclose, Huiman Barnhart: Nothing to Disclose

2452 | SAFETY OF FOMEPIZOLE WITH N-ACETYLCYSTEINE IN ACETAMINOPHEN OVERDOSE: A CASE SERIES

Nasima Mehraban[1] Bradley Gustafson[1] Deena Kapadia[2] Marlon Montoya[3] KV Narayanan Menon[4]

[1]Medical City Arlington, [2]Medical City Liver & Digestive Disease S, [3]Medical City Dallas, [4]Medical City Liver & Digestive Disease Specialists

Background: Acetaminophen (APAP) overdose is a leading cause of hepatotoxicity and acute liver failure. The current treatment for APAP overdose is n-acetylcysteine (NAC) which helps reduce hepatotoxicity. However, unknown time of ingestion, delayed presentation, or concomitant alcohol use can complicate the picture. APAP causes liver injury by accumulating the toxic metabolite N-acetyl-p-benzoquinone imine (NAPQI) which causes oxidative stress and mitochondrial dysfunction leading to hepatocellular necrosis. Fomepizole, an alcohol dehydrogenase and cytochrome 2E1 inhibitor reduces NAPQI, decreasing oxidative stress and allowing the liver to repair. Therefore, fomepizole could potentially be used as an adjunct with NAC for APAP overdose. **Methods:** This is a retrospective case series of eight patients that presented to the emergency department with APAP overdose. They had elevated APAP levels and were treated with NAC and fomepizole. APAP levels and liver enzymes were monitored during the hospitalization stay to ensure normalization. **Results:** Fourteen patients at one institution who received fomepizole as an adjunct to NAC from January 2022 to May 2024 were included in this study. Of these, 6 people were excluded for using fomepizole as a treatment for ingestion of other substances. There were 4 males and 4 females, with a mean age of 40 years (range: 21-64). The mean initial APAP level was 218.33 mg/L (range: 2-600), with the mean time from ingestion to treatment being 24.97 hours (two unknown ingestion times). The mean calculated fomepizole benefit was 730,208.49 (two unknown ingestion times excluded). At admission, 5 patients were encephalopathic. The mean peak total bilirubin level was 8.05 mg/dL (range: 0.7-30), AST 6757.25 units/L (range: 32-20,863), ALT 6178.00 units/L (range: 33-19,184), INR 4.06 (range: 1.4-10). During the hospitalization stay, two patients underwent dialysis. At discharge, 1 patient was transferred to inpatient hospice, 3 to inpatient psychiatric facility, 3 discharged home, and 1 left against medical advice. No patient died or needed a liver transplant. The excluded patients who received fomepizole as a treatment for ingestion of other substances were also discharged with no major adverse events. **Conclusion:** Using fomepizole in adjunct with NAC for the treatment of APAP overdose is a novel and effective strategy, especially in cases of delayed presentation or uncertainty regarding time of ingestion. Due to the paucity of research, large-scale randomized controlled trials are warranted to validate the efficacy, safety, and dosing of this therapy.

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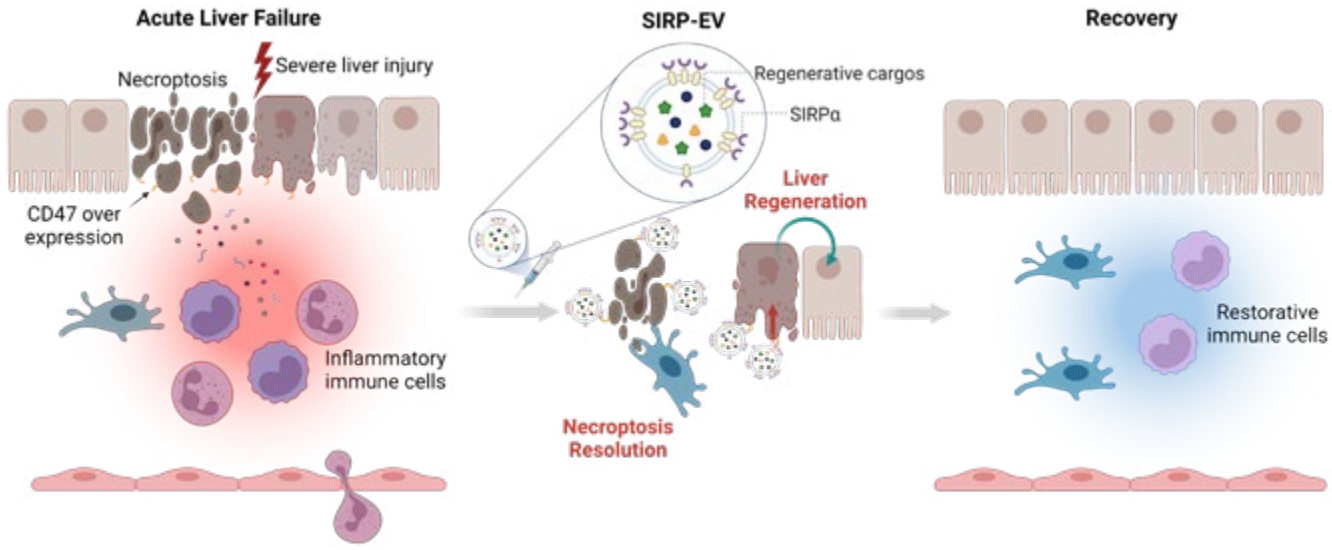
Disclosures: Nasima Mehraban: Nothing to Disclose, Bradley Gustafson: Nothing to Disclose, Deena Kapadia: Nothing to Disclose, Marlon Montoya: Nothing to Disclose, KV Narayanan Menon: Nothing to Disclose

2453 | DUAL-MODE ACTION OF SCALABLE, HIGH-QUALITY ENGINEERED STEM CELL-DERIVED SIRPα EXTRACELLULAR VESICLES FOR TREATING ACUTE LIVER FAILURE

Seohyun Kim[1] Yoon Kyoung Kim[1] Inkyu Lee[1] Gi Beom Kim[1] Gi-Hoon Nam[1] In-San Kim[2]

[1]SHIFTBIO INC., [2]KU-KIST Graduate School

Background: Acute liver failure (ALF) is a critical inflammatory condition characterized by rapid hepatocyte death, impaired liver regeneration due to the delayed removal of necroptotic cells, and high mortality rates. This study introduces a novel dual-mode action therapeutic approach using extracellular vesicles expressing Signal Regulatory Protein Alpha (SIRP-EVs) derived from genetically engineered mesenchymal stem cells (MSCs). These SIRP-EVs are designed to concurrently resolve necroptosis and promote liver regeneration. **Methods:** We evaluated CD47 expression across diverse ALF models using histological analysis, flow cytometry, western blot, confocal microscopy, and spatial transcriptomics. EVs were harvested through a 3D bioreactor-based process and subsequently purified. These purified EVs underwent various established characterization assays. After a single systemic injection, CD47-dependent accumulation of SIRP-EVs in liver tissues was evaluated using the *in vivo* imaging system. The therapeutic efficacy of SIRP-EVs was determined by measuring liver enzyme levels, examining histological changes, tracking survival rates, and analyzing inflammatory cytokine profiles. **Results:** Our studies identified CD47 and SIRPα as promising therapeutic targets for ALF. We developed a scalable 3D bioreactor-based process that produces high-purity SIRP-EVs, which preserve MSC properties and achieve significant production levels. SIRP-EVs effectively bind to and block CD47, a 'don't eat me' signal on necroptotic hepatocytes, while concurrently delivering MSC-derived regenerative proteins to the damaged tissue. Comprehensive *in vitro* and *in vivo* studies demonstrate that SIRP-EVs effectively target CD47-overexpressing hepatocytes, reduce liver damage markers, and enhance survival rates in ALF models. **Conclusion:** These findings highlight the potential of SIRP-EVs as a dual-mode action therapeutic for ALF, offering promising prospects for their application in other inflammatory diseases. Moreover, these results pave the way for advancing engineered EV-based therapies toward clinical implementation.



Disclosures: Seohyun Kim: Nothing to Disclose, Yoon Kyoung Kim: Nothing to Disclose, Inkyu Lee: Nothing to Disclose, Gi Beom Kim: Nothing to Disclose, Gi-Hoon Nam: Nothing to Disclose, In-San Kim: Nothing to Disclose

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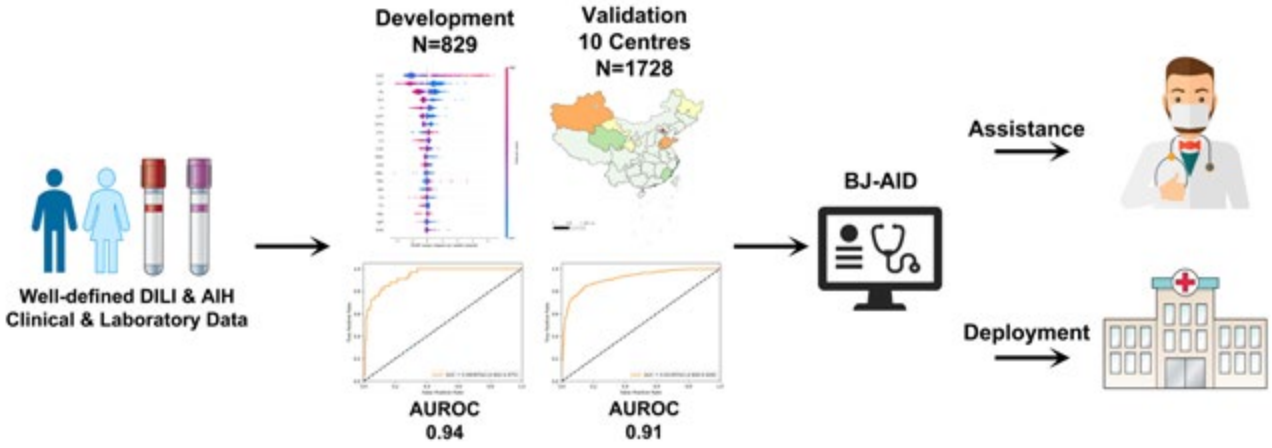
2454 | A NOVEL MACHINE LEARNING MODEL FOR DISTINGUISHING DRUG-INDUCED LIVER INJURY FROM AUTOIMMUNE HEPATITIS: DEVELOPMENT AND VALIDATION ◆

Yu Wang[1]

[1]*Beijing Friendship Hospital, Capital Medical University*

Background: Discriminating between drug-induced liver injury (DILI) and autoimmune hepatitis (AIH) is critical but challenging. We aimed to develop and validate a machine learning (ML)-based model to aid in this differentiation. **Methods:** This multi-center cohort study utilized a development set from Beijing Friendship Hospital, with retrospective and prospective validation sets from 10 tertiary hospitals across various regions of China, spanning from January 2009 to May 2023. Different ML algorithms were tested using 24 routine laboratory parameters. The Shapley Additive Explanations (SHAP) analysis was employed to evaluate the contribution of each parameter in the ML model. **Results:** A total of 2,557 patients (1,750 for DILI and 807 for AIH) were included. Using the Gradient Boost Decision Tree algorithm, five key parameters-aspartate transaminase, globulin, prealbumin, creatinine, and platelet count- were selected to construct the ML model. Consequently, a web-based tool named Beijing-AID (BJ-AID) was developed (http://43.143.153.225:5000/). The BJ-AID model demonstrated excellent discrimination performance, with an area under the receiver operating characteristic curve (AUROC) of 0.94 (95% CI, 0.902-0.975) in the development set, 0.91 (95%CI, 0.900-0.928) in all external validation sets, and 0.92 (95% CI, 0.882-0.968) in a prospective validation set. Furthermore, the BJ-AID performs similarly in different subtypes of DILI and AIH, like injury patterns, severity, RUCAM score, IAIHG score, etc. Notably, the BJ-AID model also effectively discriminated atypical cases (defined as drug-induced autoimmune-like hepatitis and AIH patients with drug consumption history), achieving an AUROC=0.84 (95%CI, 0.742-0.947). **Conclusion:** We successfully developed and validated a machine learning-based model, BJ-AID, which exhibits strong discrimination performance. BJ-AID can assist practitioners and hepatologists in diagnosing both typical and atypical cases of DILI and AIH.



Disclosures: Yu Wang: Nothing to Disclose

2455 | HIGHER PRE-TREATMENT ALT LEVEL AND PRE-EXISTING LIVER DISEASE ARE ASSOCIATED WITH INCREASED RISKS OF FLUCONAZOLE RELATED LIVER TOXICITY

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Background: Fluconazole is known to be associated with liver toxicity. However, the association between the pre-treatment alanine aminotransferase (ALT) level, the pre-existing liver disease, and the risk of fluconazole related liver toxicity has not been extensively studied. **Methods:** We conducted a retrospective cohort study using the TrinetX platform, a global research network based on real-world electronic heath records. Patients were included if they (1) received systemic fluconazole between 10/01/2015 and 12/31/2023 (the date of the first dose was

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the index date), (2) had a baseline ALT value 0-7 days prior to the index date, and (3) had a follow-up ALT value between 3-14 days after the index date. Patients with a diagnostic ICD-10 code of hepatic failure (K72) any time before the index date or ALT>5 times the upper limit of normal (ULN) between 0-7 days prior to the index date were excluded. Patients were divided into 12 groups according to the pre-treatment ALT level and the pre-existing liver conditions. The liver toxicity outcomes included significantly elevated ALT (>5xULN), hyperbilirubinemia (total bilirubin >2 mg/dL), and development of liver failure within 3-28 days after the index date. The group with normal pre-treatment ALT and no pre-existing liver disease was selected as the control group. After balancing the baseline demographics and the non-liver co-morbidities of the other 11 groups with the control group using propensity score matching, the odds ratio of the toxicity outcomes in each group were analyzed. **Results:** A total of 126,886 patients were included. Demographics were as follows: age (56.9 ± 18.6 years), gender (M/F: 54%/46%), and race (Caucasian/African American/Asian/Others: 65%/16%/3%/15%). Among them, 106,530 (84.0%) had no pre-existing liver diseases. 12,517 (9.9%) had non-viral chronic liver disease, 4,458 (3.5%) had viral hepatitis, and 3,110 (2.5%) had cirrhosis. Within 3-28 days after the first dose of fluconazole, 2,426 (1.91%) patients had elevated ALT >5xULN, 5,591 (4.4%) had serum bilirubin >2mg/dL, and 795 (0.62%) developed hepatic failure. The crude event rates and the odds ratio of liver toxicity outcomes among all propensity score-matched groups were shown in Table 1. Among patients with similar pre-treatment ALT levels, those with pre-existing liver diseases were more likely to develop liver toxicity, especially cirrhotic patients. Among patients with similar pre-existing liver diseases, higher pre-treatment ALT levels were associated with higher risk of liver toxicity. **Conclusion:** Higher pre-treatment ALT levels and pre-existing liver diseases are associated with significantly higher incidences of liver injuries after exposure to fluconazole. These findings underscore the importance of pre-treatment assessing and on-treatment monitoring of liver function when using fluconazole, especially in patients with underlying liver diseases.

TABLE 1. Association between Pre-treatment ALT, Baseline liver condition, and fluconazole related liver toxicity

BASELINE LIVER CONDITION	Pretreatment ALT <1 x ULN	Pretreatment ALT 1-2 x ULN	Pretreatment ALT 2-5 x ULN
No liver disease	75011	20302	11217
Viral hepatitis	2853	961	644
Non-viral chronic liver disease	7516	2744	2257
Cirrhosis	2017	676	417
Post treatment ALT > 5X ULN (crude rate %, OR, 95% CI)			
No liver disease	0.72%; 1.0	1.48%; 2.10 (1.72-2.57) ***	3.74%; 5.81 (4.52-7.48) ***
Viral hepatitis	1.21%; 1.36 (0.81, 2.29)	1.04%; 2.01 (0.60-6.69)	3.05%; 2.88 (1.13-7.36) *
Non-viral chronic liver disease	0.84%; 1.32 (0.90-1.92)	1.80%; 2.75 (1.60-4.74) ***	4.90%; 6.01 (3.63-9.95) ***
Cirrhosis	1.15%; 1.78 (0.90-3.52)	1.50%; 4.51 (1.70-11.99) **	4.25%; 4.39 (1.46-13.15) **
Post treatment Total bilirubin > 2 mg/dL (crude rate %, OR, 95% CI)			
No liver disease	2.20%; 1.0	4.00%; 1.76 (1.56-1.97) ***	5.68%; 2.30 (1.99-2.66) ***
Viral hepatitis	3.45%; 1.46 (1.07-2.01) *	4.91%; 1.66 (1.01-2.77) *	7.19%; 3.91 (1.99-7.68) ***
Non-viral chronic liver disease	3.94%; 1.72 (1.42-2.08) ***	5.92%; 2.06 (1.56-2.72) ***	7.15%; 3.06 (2.22-4.22) ***
Cirrhosis	6.33%; 2.59 (1.85-3.62) ***	9.99%; 4.85 (2.74-8.58) ***	7.92%; 4.11 (1.86-9.04) ***
Development of liver failure (crude rate %, OR, 95% CI)			
No liver disease	0.25%; 1.0	0.43%; 1.76 (1.25-2.50) ***	0.67%; 2.83 (1.82-4.39) ***
Viral hepatitis	1.02%; 4.22 (1.59-11.22) **	1.35%; 13.16 (1.72-100.84) *	2.64%; 17.43 (2.31-131.40) **
Non-viral chronic liver disease	1.09%; 3.94 (2.44-6.37) ***	1.23 %; 6.55 (2.28-18.80) ***	1.46%; 11.15 (3.41-36.40) ***
Cirrhosis	4.12%; 17.27 (6.99-42.68) ***	3.11%; 21.64 (2.90-161.35) **	2.88%; 12.33 (1.60-95.23) *

Odds ratio 1-2 | Odds ratio 2-4 | Odds ratio 4-8 | Odds ratio >8 | * p<0.05 | ** p< 0.01 | *** p< 0.001

Disclosures: Pinghsin Hsieh: Nothing to Disclose, Yao-Chun Hsu: Gilead Sciences: Grant/Research Support, Gilead Sciences: Advisor, Sysmex: Advisor, Abbvie: Speaking and Teaching, Bristol Myers Squibb: Speaking and Teaching, Gilead Sciences: Speaking and Teaching, Roch: Speaking and Teaching

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2456 | IMMUNE-MEDIATED LIVER INJURY CAUSED BY IMMUNE CHECKPOINT INHIBITORS EXHIBITS DISTINCT CLINICAL FEATURES THAT DIFFER FROM AUTOIMMUNE HEPATITIS

Yu Su[1] *Yan Wang*[2] *Mengyu Zhao*[2] *Liwei Liu*[3] *Wei Chen*[2] *Xinyan Zhao*[2]

[1]*Beijing Friendship Hospital, Capital Medical University,* [2]*Beijing Friendship Hospital,* [3]*Beijing You'an Hospital*

Background: Immune-mediated liver injury caused by immune checkpoint inhibitors (ILICI) and autoimmune hepatitis (AIH) are both related to the distorted immune system. However, ILICI differs from AIH in several distinct ways. We aimed to study the differences in clinical features between ILICI and AIH. **Methods:** This is a retrospective study at Beijing Friendship Hospital collecting clinical data of patients with ILICI (2016-2022) and AIH (2002-2022). Demographic, clinicopathological, radiological characteristics, treatment regimen, and outcomes were all collected and compared between the two groups. **Results:** A total of 69 cases with ILICI and 158 with AIH were included in the study. The ILICI group had significantly older patients (66.0 [56.5, 70.0] vs. 56.0 [47.0, 63.0], *P*<0.001) and a lower proportion of females (27.5% vs. 85.4%, *P*<0.001). Patients in the ILICI group had significantly lower levels of ALT, AST and TBil both at the time of onset and at peak time than the AIH group (all *P*<0.01). Moreover, patients in the ILICI group exhibited lower levels of immunoglobulin G (IgG) and a smaller percentage of higher titer of positive ANA (≥1:160) (all *P*<0.05). Some of the ILICI patients exhibited radiological features of bile duct edema and dilation, whereas AIH patients normally presented characteristics of liver fibrosis. The histological features of ILICI usually comprised bile duct injury with ductular reaction, lymphocyte and neutrophil infiltration with less plasma cell infiltration. While AIH generally presents with more severe portal inflammation, interface hepatitis, and fibrosis. Fewer patients in the ILICI patients needed glucocorticoid treatment compared with AIH patients (33 (47.8%) vs. 158 (100.0), *P*<0.001). In contrast, ILICI patients exhibited a more rapid recovery of ALT levels compared to those with AIH (42.5 [15.8, 138.3] vs. 414.0 [169.0, 933.0] days, *P*<0.001). **Conclusion:** In summary, ILICI is a heterogeneous disease distinct from AIH. It differs from AIH in the characteristic, biochemical, radiological, and histological features. Furthermore, fewer patients in the ILICI group need immunosuppressive therapy than the AIH group and experience a shorter recovery period.

Table. Comparison of demographic and clinical data between ILICI and AIH patients

Variants	ILICI (N=69)	AIH (N=158)	*P*
Age (Years)	66.0(56.5,70.0)	56.0(47.0,63.0)	<0.001
Gender (F%)	19(27.5)	135(85.4)	<0.001
ALT onset (U/L)	96.0(53.0,165.4)	259.0(110.0,578.0)	<0.001
AST onset (U/L)	91.6(50.2,165.5)	236.0(115.0,481.0)	<0.001
ALP onset (U/L)	134.0(98.0,309.0)	140.6(104.0,176.9)	0.429
GGT onset (U/L)	119.0(50.0,291.0)	130.5(77.3,249.2)	0.304
TBil onset (μmol/L)	17.6(11.5,24.6)	31.7(19.4,96.1)	<0.001
ALT max (U/L)	133.0(78.5,237.0)	475.0(217.8,778.8)	<0.001
AST max (U/L)	138.6(87.9,306.9)	437.0(218.0,704.5)	<0.001
ALP max (U/L)	208.8(102.0,427.0)	160.6(130.7,205.4)	0.098
GGT max (U/L)	189.0(51.3,637.8)	186.0(106.0,311.0)	0.932
TBil max (μmol/L)	24.6(17.4,64.4)	52.0(25.5,122.1)	0.001
IgG (mg/dL)	1230.0(1040.0,1450.0)	2160.0(1840.0,2565.0)	<0.001
ANA titer			0.041
ANA≤1:80 (%)	7.0(46.7)	29(18.4)	
ANA≥1:80 (%)	8(53.3)	113(80.1)	

Abbreviations: AIH, autoimmune hepatitis; ALT, alanine transaminase; ALP, alkaline phosphatase; ANA, anti-nuclear antibody; AST, aspartate aminotransferase; GGT, γ-glutamyltransferase, IgG, immunoglobulin G; ILICI, immune mediated liver injury from checkpoint inhibitors; TBil, total bilirubin.

Disclosures: Yu Su: Nothing to Disclose, Yan Wang: Nothing to Disclose, Mengyu Zhao: Nothing to Disclose, Liwei Liu: Nothing to Disclose, Wei Chen: Nothing to Disclose, Xinyan Zhao: Nothing to Disclose

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2457 | IDENTIFICATION OF RISK PROFILES FOR LIVER INJURY IN ADULTS WITH MULTIPLE SCLEROSIS USING ARTIFICIAL INTELLIGENCE METHOD

Dominique Larrey[1] Dominique Larrey[2] Claire Brulle-Wohlhueter[2] Myriam Benamor[2] Jeffrey Chavin[2] Neda Razaz[3] Raphael Bejuit[2] Julien Dauriat[4] Romane Péan[4] Théophile Reppelin[4] Sam Ekhtiari[4] Nicolas Wagner[4] Fred Lublin[5]

[1]CHU St Eloi Hospital, [2]Sanofi, [3]Aixial, [4]Quinten Health, [5]Icahn School of Medicine at Mount Sinai

Background: The evolution of multiple sclerosis (MS) treatment in the past two decades has raised concerns regarding potential liver injury (LI) associated with disease-modifying therapies (DMTs). Lifestyle and generic factors may also contribute to LI. Nevertheless, predicting and identifying risk factors for LI among MS patients remained challenging. This study aims to identify high-risk profiles for liver injury among MS patients by analysis of electronic health record (EHR) and the use of an artificial intelligence (AI) based subgroup discovery algorithm. **Methods:** This retrospective cohort study was conducted using Optum Market Clarity EHR data. Adult patients with first known diagnosis of MS between January 1st, 2015, and December 31st, 2019 (cohort entry date (CED) was the date of the initial MS diagnosis), and actively managed in EHR during the baseline period (730 days prior to CED) were included in the study. Patients were excluded if they had a LI event or ALT>2xULN or a diagnosis of liver disease in the baseline period. Patients were followed until first LI event or 3 years after the CED whichever occurred earlier. LI event was defined either as meeting the international lab criteria (ALT, ALP, total bilirubin) or the presence of an acute LI diagnosis [Fontana et al., Drug Safety 2009]. Q-Finder, a supervised non-parametric proprietary subgroup discovery algorithm, was used to identify subgroups associated with increased LI risk and defined by baseline demographic and clinical characteristics. **Results:** The analysis involved 5,986 MS patients, of whom 233 (4%) developed a LI event within 3 years following CED. The Q-Finder algorithm identified 6 risk factors associated with elevated levels of baseline liver enzymes (ALP, ALT, AST). Additionally, 11 clinically relevant risk factors were identified focusing on factors unrelated to liver enzymes, which were summarized into 6 clinical themes: substance abuse and mental health disorders, anemia, anemia and kidney, immune disorders, male patients and diabetes, and chronic obstructive pulmonary disease (COPD) (see Figure). **Conclusion:** This study demonstrated that elevated liver enzymes at baseline were a strong risk driver for liver injury among MS patients. The Q-Finder also allowed the discovery of new risk factors that may help predict MS patients who are at higher risk of LI and provides insights to improve patient screening criteria for clinical trials and clinical management of MS.

Figure. Clinical theme for profiles with higher risk of liver injury



[1]For these laboratory values, the normal range depends on the gender. The gender is therefore indicated in square brackets after the associated value ([m] for male; [f] for female).

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2458 | TRANSDILI: A DEEP TRANSFER LEARNING BASED PREDICTION FOR DRUG-INDUCED LIVER INJURY THROUGH LEVERAGING MOLECULAR STRUCTURE IMAGES

Yue Li[1] Bingyan Liu[2] Yuanchun Guo[2] Jinyan Deng[1] Yi Guo[1] Hongbo Du[1]

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Background: Drug-induced liver injury (DILI) poses a global threat to acute liver failure. Current preclinical models inadequately mimic human liver metabolism, necessitating more accurate assessment methods. Artificial Intelligence (AI) shows promise in DILI prediction using molecular representations and there is a growing interest in utilizing 2D molecular images for enhanced performance. Recent advancements demonstrate potential but are limited to binary classification, failing to explore the fine-grained correlation between drugs and liver injury occurrences. To address these gaps, we propose TransDILI, a deep transfer learning-based approach for multi-level DILI risk prediction. **Methods:** TransDILI includes two main phases: Dataset Construction Phase: We manually partition public datasets (Livertox, DILI Rank, and DILIst) to create a comprehensive fine-grained target dataset for evaluation. The DILI Rank serves as the standard, with other datasets merged accordingly. Drugs are classified based on hepatotoxicity levels, and the final dataset is divided into training and testing sets in an 8:2 ratio, maintaining the proportion of DILI samples.Transfer Learning Phase: Due to the limited scale of the target dataset, we use large-scale pre-trained datasets for better performance. Pre-training involves using focal loss and a warm-up mechanism to address class imbalance and improve generalization. Pre-trained models are fine-tuned with the target dataset to transfer knowledge effectively, enhancing performance and convergence speed. **Results:** The pre-training process achieved high levels of training accuracy across various AI architectures and large-scale public datasets, confirming the effectiveness of our approach. For instance, using our method, pre-training with the HIV dataset led to increases of 52.13% and 36.93% in training and testing accuracy, respectively. Besides, the effectiveness of pre-training varied across different model architectures, but all pre-training knowledge enhanced performance to varying degrees, emphasizing the value of transfer learning. Concerning model convergence, Mux and Tox21 datasets exhibited superior convergence during pre-training. Without pre-training, convergence was notably slow across all models. However, with pre-training and knowledge transfer, there was a clear improvement in convergence speed. **Conclusion:** We have designed TransDILI, an advanced deep transfer learning framework. Rooted in molecular image representation learning, TransDILI excels

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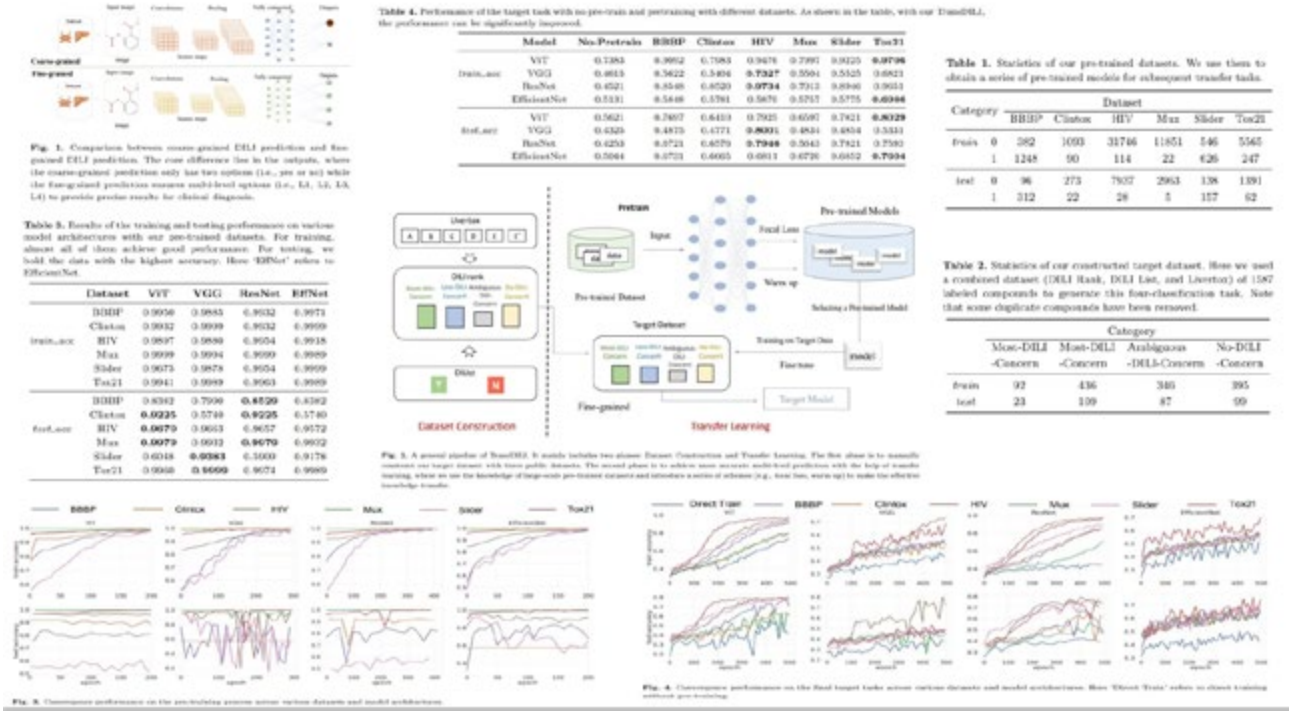
at multi-class outcome prediction. Through rigorous evaluation across direct and transfer learning scenarios using a purpose-built dataset, TransDILI's performance has been benchmarked against state-of-the-art visual neural learning networks.



Disclosures: Yue Li: Nothing to Disclose, Bingyan Liu: Nothing to Disclose, Yuanchun Guo: Nothing to Disclose, Jinyan Deng: Nothing to Disclose, Yi Guo: Nothing to Disclose, Hongbo Du: Nothing to Disclose

2459 | CLINICAL OUTCOMES OF IDIOSYNCRATIC DILI ARE IMPROVING IN THE UNITED STATES: RESULTS FROM THE DILIN PROSPECTIVE STUDY, 2004 TO 2024

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Background: The NIH Drug Induced Liver Injury Network (DILIN) has enrolled adult and pediatric patients with suspected idiosyncratic DILI since 2004. All cases undergo extensive phenotyping and are prospectively followed for 6 months. The aim of this study is to identify temporal trends in the etiology and outcomes of consecutive high causality DILI cases. **Methods:** 2627 patients were enrolled in DILIN between 4/04 and 4/24 including 1983 high causality cases scored as definite (20%), highly likely (52%) or probable (28%). The etiologies and features of cases from the first (2004-10), second (2011-17), and third (2018-24) eras were compared. **Results:** The proportion of female (59%), white (78%) and diabetic (23%) patients was unchanged (**Table**). In addition, the median BMI and onset and peak serum AST, ALT, and alk P levels remained stable. However, there was a significant increase in median age (50 vs 53 vs 56 years; p<0.001) while median peak total bilirubin decreased (9.6 vs 9.4 vs 5.3 mg/dL; p < 0.001) as well as DILIN severity scores (p < 0.001) with fewer patients requiring liver transplants or dying (p=0.059). There were fewer cases attributed to antimicrobials and anticonvulsants but greater numbers due to herbal and dietary supplements (HDS) and antineoplastic agents (p< 0.001), the latter driven by an increase in immune checkpoint inhibitor cases (none vs 2.3 vs 7.5 %, p < 0.001). Significant decreases in cases due to isoniazid (6 vs 3 vs 1%), nitrofurantoin (5 vs 3.6 vs 1.8%) and minocycline (4.1 vs2.3 vs1.4%) occurred along with decreases in aromatic anticonvulsant cases (3.5 vs 2.5 vs 1.6%, p=0.05). Amongst the HDS products, the proportion attributed to anabolic steroids decreased over time (26 vs 48 vs

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26 %, p < 0.001). Finally, mini “outbreaks” of DILI due to OxyElite Pro (2013-14, n=7), mRNA COVID vaccines (2021-23, n=18) and French Lentil and Leek Crumbles (2022, n= 17) were observed. **Conclusion:** The DILIN has documented important trends in the causes and outcomes of DILI in the US over the last 20 years. The increasing patient age may be due to increased polypharmacy and enrollment of checkpoint inhibitor cases. Although antimicrobials remain the leading cause of DILI, the proportion is decreasing, particularly for isoniazid, nitrofurantoin, and minocycline. The increase in HDS cases was likely due to their increased use in the general population and periodic outbreaks due to changes or newly introduced HDS formulations.

Table 1. Clinical features and outcomes of DILI in the US over the past 20 years

Time Intervals (n)	’04-10 (690)	’11-17 (854)	’18-23 (439)	P-value
Age (yrs)	49.7	52.8	56	< 0.001
% Female	59	57	61	0.28
% White	78	78	76	0.41
% Chronic liver disease	10	6	6	0.014
% Hepatocellular	53	53	57	0.50
Onset T bili (mg/dl)	5.0	4.7	2.9	< 0.001
Peak T bili (mg/dl)	9.6	9.4	5.3	< 0.001
% HDS	15	22	23	< 0.001
% Antineoplastic	4.6	7.6	17.5	< 0.001
% Mild-moderate	45	41	50	0.26
% Mod-hosp	26	37	34	0.0016
% Severe	21	16	11	< 0.001
% Fatal	8	6	5	0.059
% Death	6.7	6.3	5.3	0.53
% DILI related	60	53	39	0.17

Disclosures: Robert Fontana: Grant/Research Support relationship with kezar pharmaceuticals; Has not ended; Consultant relationship with moderna; Has ended; Grant/Research Support relationship with Takeda Pharmaceuticals; Has not ended, Paul Hayashi: Nothing to Disclose, Vincent Chen: Site PI on industry-sponsored trial relationship with AstraZeneca; Has ended; site co-I on industry-sponsored trial relationship with Ipsen; Has not ended; site co-I on industry-sponsored trial relationship with Kowa; Has not ended, Huiman Barnhart: Nothing to Disclose, Raj Vuppalanchi: Eli LIlly: Advisor, GSK: Advisor, Madrigal: Advisor, Zydus Therapeutics: Grant/Research Support, Galectin Therapeutics: Grant/Research Support, Kowa: Grant/Research Support, Takeda: Grant/Research Support, GSK: Consultant, UBC: Consultant, Dina Halegoua-DeMarzio: Grant/Research Support relationship with Viking; Has ended; Advisor relationship with Novo Nordisk; Has not ended; Advisor relationship with Madigral; Has not ended; Grant/Research Support relationship with Galectin; Has not ended; Grant/Research Support relationship with Akero; Has not ended; Advisor relationship with Madigral; Has not ended; Grant/Research Support relationship with Novo Nordisk; Has not ended; Grant/Research Support relationship with Intercept; Has ended, Victor Navarro: Nothing to Disclose, Andrew Stolz: Nothing to Disclose, Naga Chalasani: Madrigal: Consultant, Zydus, Ipsen, Pfizer, Merck, Altimmune, GSK: Consultant, Exact Sciences: Grant/Research Support, NIH: Grant/Research Support, Jiezhun Gu: Nothing to Disclose, A. Sidney Barritt: Nothing to Disclose, Jay Hoofnagle: Nothing to Disclose

2460 | MUSCLE STEATOSIS SIGNIFICANTLY INCREASES THE RISK OF DEATH IN PATIENTS WITH CIRRHOSIS - A RETROSPECTIVE COHORT STUDY

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Background: The aim of this study was to investigate the effect of muscle steatosis on mortality in patients with liver cirrhosis. **Methods:** Patients with liver cirrhosis in the Department of Hepatology, Hospital of Traditional Chinese Medicine of Xinjiang Autonomous Region from January 2020 to December 2022 were retrospectively enrolled, and calculated the third lumbar vertebra skeletal muscle index (L3-SMI) and subcutaneous adipose

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tissue index (SATI). Sarcopenia was diagnosed by L3-SMI **Results:** A total of 208 patients with liver cirrhosis were included in this study, with an average follow-up of 16.9months. The restrictive cubic spline Cox proportional hazards regression model showed that there was a clear U-shaped association between SATI and long-term mortality in patients with liver cirrhosis (nonlinear P=0.018). The SATI values corresponding to the risk ratio (HR)=1.2 (27.8cm2/m2 and 99.5 cm2/m2, respectively) were selected as cut-off values, and the patients with liver cirrhosis were divided into three groups: low SATI group (SATI99.5 cm2/m2).The cumulative risk curve showed that the mortality risk of patients in the low SATI group and the high SATI group was higher than that in the standard SATI group, and there was no significant difference in the cumulative mortality rate between the patients in the low SATI (P=0.292) and high SATI groups (P=0.198) compared with the standard SATI group. SATI99.5 cm2/m2 were defined as non-standard SATI groups; Survival analysis showed that the mortality risk of the non-standard SATI/sarcopenia group was significantly higher than that of the standard SATI/non-sarcopenia group (HR 7.34 (95%CI: 1.56~34.61), P=0.003). **Conclusion:** Muscle steatosis significantly increases the risk of death from cirrhosis.

Disclosures: Hong Yu: Nothing to Disclose, Yi Jiang: Nothing to Disclose

2461 | *HLA-B*35:01* ALLELE IS A RISK FACTOR FOR DRUG-INDUCED LIVER INJURY DUE TO ANTI-HYPERTENSIVES ◆

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Background: Anti-hypertensives (Anti-HTN) are used worldwide. The rate of hepatotoxicity, phenotype of injury, and genetic associations are not known for these drugs. **Methods:** We examined 2207 enrolled subjects in DILIN from 2003 to 2024 adjudicated as definite, highly likely, or probable DILI due to anti-HTN. Descriptive statistics were computed to characterize DILI. Patients with Anti-HTN DILI were age, sex, and ancestry matched to 1892 dbGAP population controls and 172 DILIN cases with DILI ascribed to other medications. HLA sequencing was performed for DILIN patients while HLA allele imputation from genotype data was carried out for matching population controls. Fisher Exact test was applied to evaluate the allele frequency difference between controls and the overall or drug/drug class-specific cases. **Results:** A total of 43 patients with high confidence DILI were identified. There were 14 patients with DILI from ACE/ARBs, 12 a-methyldopa, 11 hydralazine, 3 beta-blockers (BB), and 3 calcium channel blockers (CCB). Stratifying by genetic ancestry, the patients were 56% non-Hispanic White (NHW), 35% non-Hispanic Black (NHB), and 9% Hispanic. Patients with α-methyldopa DILI were exclusively young females with hepatocellular DILI. Among the rest, 60% had hepatocellular, 28% cholestatic, and 9% mixed injury. Nearly 50% developed severe DILI, 2 patients required liver transplantation, and 2 died (lisinopril, hydralazine). Notably, 50% of Anti-HTN DILI patients carry *HLA-B*35:01*, compared to 13% among the population controls, with an OR = 4.25 (CI 2.4-7.2, P = 6.6×10^{-7}). There were no race/enthnicity differences in risk allele carriage rate. The *B* 35:01* allele appears to be a risk factor for all Anti-HTN DILI, as it was found in 66% of cases due to methyldopa, BB, and CCB, 27% of hydralazine DILI, and 42% of DILI from ACE/ARBs. Clinically, *HLA-B*35:01* was associated with a statistically significant shorter latency for DILI (70 vs 206 days, P = 0.023), but did not affect severity (Table 1). **Conclusion:** A wide range of antihypertensives can cause liver injury which is predominantly hepatocellular in nature and can lead to liver transplantation or death. However, this is rare given their widespread use. There is a strong and significant risk association between *HLA-B*35:01* and DILI due to Anti-HTN, in particular a-methyldopa DILI. Patients positive for *HLA-B*35:01* display a shorter latency for DILI indicating an accelerated adaptive immune response which needs to be explored further.

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Clinical summary statistics for B*35:01 Carriage Analysis					
		Non-carrier (N=22)	B*35:01 carrier (N=21)	Total (N=43)	p value
AGE	Median	55	51.1	53	0.38
	Q1, Q3	46.6, 60.5	32.0, 64.6	39.4, 64.6	
GENDER	Female	12 (54.5%)	16 (76.2%)	28 (65.1%)	0.20
	Male	10 (45.5%)	5 (23.8%)	15 (34.9%)	
RACE ETHNICITY	Hispanic	2 (9.1%)	2 (9.5%)	4 (9.3%)	0.9785
	Non-Hispanic Black	8 (36.4%)	7 (33.3%)	15 (34.9%)	
	Non-Hispanic White	12 (54.5%)	12 (57.1%)	24 (55.8%)	
BMI	Median	29.4	28.7	29	0.84
	Q1, Q3	25.0, 37.2	25.8, 37.4	25.1, 37.2	
PMX DM	No	15 (68.2%)	10 (47.6%)	25 (58.1%)	0.22
	Yes	7 (31.8%)	11 (52.4%)	18 (41.9%)	
LATENCY	Median	109	48	85.5	0.02
	Q1, Q3	74.0, 238.0	31.0, 96.0	35.0, 167.0	
JAUNDICE	No	10 (45.5%)	4 (19.0%)	14 (32.6%)	0.104
	Yes	12 (54.5%)	17 (81.0%)	29 (67.4%)	
PHENOTYPE Presentation R	Cholestatic	7 (31.8%)	5 (23.8%)	12 (27.9%)	0.84
	Hepatocellular	13 (59.1%)	14 (66.7%)	27 (62.8%)	
	Mixed	2 (9.1%)	2 (9.5%)	4 (9.3%)	
PEAK ALT/AST	Median	732/508	1315/1320	787	0.29
	Q1, Q3	325.0, 1292.0	338.0, 1808.0	325.0, 1577.0	
PEAK ALP	Median	255	209	220	0.45
	Q1, Q3	165.0, 578.0	135.0, 346.0	141.0, 483.0	
PEAK TBILI	Median	6.4	16.8	11.1	0.19
	Q1, Q3	1.7, 20.7	10.9, 21.7	2.1, 21.7	
PEAK INR	Median	1.1	1.4	1.2	0.35
	Q1, Q3	1.1, 1.6	1.2, 1.6	1.1, 1.6	
ALL CAUSE MORTALITY	No	21 (95.5%)	19 (95.0%)	40 (95.2%)	>0.9999
	Yes	1 (4.5%)	1 (5.0%)	2 (4.8%)	
TRANSPLANT	No	21 (95.5%)	20 (95.2%)	41 (95.3%)	>0.9999
	Yes	1 (4.5%)	1 (4.8%)	2 (4.7%)	

Disclosures: Lily Dara: Consultant relationship with Intercept Pharmaceuticals; Has not ended; Grant/Research Support relationship with Intercept Pharmaceuticals; Has not ended, Paola Nicoletti: Nothing to Disclose, Chaudry Majeed: Nothing to Disclose, Andrew Dellinger: Nothing to Disclose, David Kleiner: Nothing to Disclose, Mahmoud Mohamed: Nothing to Disclose, Tatyana Kushner: Advisor relationship with Gilead; Has ended; Advisor relationship with GSK; Has ended; Advisor relationship with Eiger; Has ended; Grant/Research Support relationship with Gilead; Has not ended, Mohammed Umair Masood: Nothing to Disclose, Raj Vuppulanch: Eli Lilly: Grant/Research Support, Echosens: Consultant, Zydus THerapeutics: Grant/Research Support, GSK: Consultant, MERCK: Advisor, Takeda: Grant/Research Support, Huiman Barnhart: Nothing to Disclose, Jiezhun Gu: Nothing to Disclose, Herbert Bonkovsky: Nothing to Disclose

2462 | CO-ADMINISTRATION OF ALCOHOL, RITONAVIR AND LOPINAVIR AFFECTS EXPRESSION OF THE SET CHEPERONE PROTEIN IN HEPATOCYTES AND MONOCYTES AND HIV-1 INFECTIVITY *IN VITRO*

Liting Chen[1] *Marina Kaypaghian*[1] *Cheng Ji*[1]

[1]*University of Southern California*

Background: Combined use of alcohol and antiviral drugs is known to cause cellular stress and organ injury raising people's vulnerability to virus infection. The underlying mechanisms are multiple. The SET protein is

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a multitasking chaperone protein residing in endoplasmic reticulum (ER), which has recently been implicated in influencing HIV-1 DNA stability. Since alcohol and anti-HIV drugs are known to induce ER stress in various cell and animal models, we investigated *in vitro* the effects of alcohol and antiviral drugs on the SET protein expression and HIV-1 infection. **Methods:** Primary human hepatocytes (PHH) and primary human peripheral blood mononuclear cells (PBMC) were treated with alcohol and/or current anti-HIV/SARS-CoV-2 drugs including ritonavir (RTV), lopinavir (LPV), derunavir (DRV), and dolutegravir (DTG). Transcriptional and translational expressions of the *SET*, cellular loalization of the SET protein, and the ER stress response molecular marker X-box binding protein 1 (Xbp1) were assessed. HIV infectivity in PBMC treated with alcohol and the drugs was examined using a HIV-1 pseudovirus expressing the *pol* gene region and a luciferase reporter. **Results:** Ethanol at 50 mM and antiviral drugs at 25 μg/mL each induced expression of Xbp1 and SET proteins in whole cell protein extracts from either PHH or PBMC. *Xbp1* mRNA but not *SET* mRNA was increased in PHH and PBMC. Cytosolic SET protein and SET binding protein 1 (SETBP1) but not nuclear SET protein were increased in PBMC treated with alcohol and the drugs, which were correlated with increased expression of HIV-1 *pol* RNA or the luciferase reporter. Cytochrome P450 2E1 (CYP2E1) and aldehyde dehydrogenase 2 (ALDH2) were increased whereas cytochrome P450 3A4 was reduced in PBMC treated with alcohol and the drugs. Antagonistic inhibition of the SET protein complex with a polypeptide (COG) further increased the cytosolic SET, expression of Xbp1, and the HIV-1 reporter in the treated PBMC. The alcohol and drug-induced cytosolic SET protein and HIV-1 expression were decreased upon inhibition of CYP2E1 with diallyl sulfide (DAS) or oxidative stress with vitamin C/E, decreased more upon inhibition of ER stress with pharmaceutical molecular chaperone 4-phenylbutyrate (PBA), and decreased further upon inhibition of both ER stress and oxidative stress. **Conclusion:** The results suggest that alcohol-induced CYP2E1 and oxidative stress might potentiate anti-HIV drug-induced ER stress and cytosolic retention of the SET protein in hepatocytes and mononuclear cells, which might augment HIV-1 infectivity in the monocytes. (This work is supported by NIH/NIDA grant R01DA058458).

Disclosures: Liting Chen: Nothing to Disclose, Marina Kaypaghian: Nothing to Disclose, Cheng Ji: Nothing to Disclose

2463 | THE PIVOTAL ROLE OF ABCB11 ON GENETIC SUSCEPTIBILITY TO DRUG-INDUCED LIVER INJURY FROM ANABOLIC STEROIDS ◆

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Background: Anabolic steroids (AS) are commonly used by bodybuilders to enhance performance and muscle mass. Predisposed males can develop prolonged and severe bland cholestasis with significant pruritus and elevated bilirubin with minimal GTT elevation. We aimed to identify genetic variants associated with the risk of AS-induced bland cholestasis. **Methods:** Whole genome sequencing data from 93 males with AS-induced drug-induced liver injury cases (AS-DILI) [61 Non-Hispanic White (NHW); 12 Non-Hispanic Black (NHB); 16 Hispanics; 4 Asians] enrolled in DILIN prospective study and 912 ancestry-matched population controls from 1000 Genome Project (1KGP) were compared. Rare (ancestry-specific MAF < 0.01) damaging variants were analyzed using the SKAT-O test for each gene and the STAAR-O method for the non-coding regulatory regions. Gene pathway analysis was undertaken for damaging rare variant enrichment by RVTEST. **Results:** Comparison of 61 NHW AS-DILI cases to 422 1KGP controls revealed *ABCB11* as the only gene significantly enriched by rare damaging variants (predicted by *REVEL*, *LOFTEE*) or splice variants (predicted by *SpliceAI*) that remained significant after multiple testing corrections ($P = 7.7x10^{-6}$). 7% of the NHW cases carried a functionally damaging variant compared to 1.7% in controls. Independently from these *ABCB11* carriers, the non-coding-centric analysis identified an additional 2% of cases with 0.005% of controls carrying functional regulatory variants in CAGE-predicted *ABCB11* enhancers (P = 0.03). *ABCB11* role in AS-DILI from other ancestries was also confirmed by a similar enrichment of functional coding variants with 8% carriers in AS-DILI cases vs 2% controls among NHB, 12.5% vs 0.6% among Hispanic, and 25% carriers among Asian cases. The higher carriage frequency in Hispanic and NHB cases than in NHW could be due to higher prevalence in those populations (13% and 11% vs 8%). Genes modulating ABCB11's function reported in the GO-term *Bile Acid Signaling Pathway* showed a significant rare variant enrichment in cases (P = 0.008) with an additional 7% of carriers in cases and 5% in controls. **Conclusion:** While the study is limited by the rare phenotype and lack of AS-exposed controls, *ABCB11* is a universally shared risk gene for AS-DILI, as evident by enrichment in damaging coding variants across ancestries.

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Other genes interacting or regulating *ABCB11* function in the secretion or synthesis of bile acids could also be involved in genetic susceptibility.

Table 1: Demographics

	Acetaminophen + Alcohol Liver Failure (n = 3,365)	Alcohol Liver Failure Without Acetaminophen (n = 636,415)	P Value	Odds Ratio (95% Confidence Interval)
Mean Age, years	49.1	62.5	<0.001	
Gender, n				
Male	1045 (31.1%)	352070 (55.3%)	<0.001	2.750 (2.327-3.250)
Female	2320 (68.9%)	284240 (44.7%)		0.364 (0.308-0.430)
Race, n				
White	2265 (67.3%)	408955 (64.3%)	0.094	1.145 (0.977-1.343)
Black	545 (16.2%)	98855 (15.5%)	0.637	1.050 (0.855-1.292)
Hispanic	245 (7.3%)	58775 (9.2%)	0.081	0.772 (0.576-1.033)
Asian or Pacific Islander	54 (1.6%)	19450 (3.1%)	0.032	0.527 (0.290-0.957)
Native American	25 (0.7%)	5205 (0.8%)	0.829	0.908 (0.377-2.185)
Other	95 (2.8%)	19970 (3.1%)	0.635	0.897 (0.572-1.401)
Obesity, n	365 (10.8%)	92285 (14.5%)	0.006	0.717 (0.565-0.910)
Congestive Heart Failure, n	360 (10.7%)	291175 (45.8%)	<0.001	0.142 (0.111-0.182)
COPD, n	365 (10.8%)	110260 (17.3%)	<0.001	0.580 (0.455-0.741)
ESRD, n	75 (2.2%)	57285 (9.0%)	<0.001	0.230 (0.138-0.384)
Diabetes, n	475 (14.1%)	203575 (32.0%)	<0.001	0.349 (0.281-0.434)
Cerebrovascular Disease, n	60 (1.8%)	61215 (9.6%)	<0.001	0.171 (0.096-0.302)
Drug Use, n	755 (22.4%)	584500 (91.8%)	<0.001	2.858 (2.375-3.438)
Smoking History, n	1450 (43.1%)	185880 (29.2%)	<0.001	1.835 (1.582-2.129)
Cancer, n	70 (2.1%)	42095 (6.6%)	<0.001	0.300 (0.176-0.510)
Mean Length of Stay, days	6.8	11.4	<0.001	-
Charlson Comorbidity Index				
3 or less	2865 (85.1%)	379860 (59.7%)	<0.001	3.870 (3.111-4.814)
4	210 (6.2%)	75580 (11.9%)	<0.001	0.493 (0.362-0.674)
5	105 (3.1%)	58040 (9.1%)	<0.001	0.321 (0.208-0.495)
6	80 (2.4%)	55380 (8.7%)	<0.001	0.256 (0.156-0.418)
7 or more	105 (3.1%)	67555 (10.6%)	<0.001	0.271 (0.169-0.435)

Table 2: Hospitalization Co-illnesses

	Acetaminophen + Alcohol Liver Failure (n = 3,365)	Alcohol Liver Failure Without Acetaminophen (n = 636,415)	P Value	Odds Ratio (95% Confidence Interval)
Cardiac Arrest, n	45 (1.3%)	33995 (5.3%)	<0.001	0.240 (0.124-0.464)
Pulmonary Embolism, n	20 (0.6%)	26965 (4.2%)	<0.001	0.135 (0.051-0.360)
Hepatic Encephalopathy, n	185 (5.5%)	22340 (3.5%)	0.006	1.599 (1.142-2.238)
Ascites, n	145 (4.3%)	50310 (7.9%)	<0.001	0.525(0.362-0.761)
HRS, n	130 (3.9%)	12670 (2.0%)	<0.001	1.978 (1.320-2.964)
SBP, n	10 (0.3%)	4440 (0.7%)	0.212	0.424 (0.106-1.700)
Blood Transfusion, n	225 (6.7%)	86915 (13.7%)	<0.001	0.453 (0.336-0.610)
Mechanical Ventilation, n	930 (27.6%)	331300 (52.1%)	<0.001	0.352 (0.297-0.416)
Vasopressors, n	210 (6.2%)	88490 (13.9%)	<0.001	0.412 (0.301-0.564)
Shock, n	690 (20.5%)	226135 (35.5%)	<0.001	0.468 (0.389-0.563)
ICU, n	980 (29.1%)	351480 (55.2%)	<0.001	0.333 (0.282-0.393)
Mortality, n	11 (0.3%)	505 (0.1%)	<0.001	0.250 (0.203-0.308)

Disclosures: Paola Nicoletti: Nothing to Disclose, Samreen Zafer: Nothing to Disclose, Yi-Ju Li: Nothing to Disclose, Andrew Dellinger: Nothing to Disclose, Huiman Barnhart: Nothing to Disclose, Andrew Stolz: Nothing to Disclose

2464 | EXPLORING THE IMPACT OF ACETAMINOPHEN OVERDOSE ON PATIENTS WITH ACUTE ALCOHOLIC LIVER FAILURE

Nisha Sanghani[1] *Het Patel*[1] *Janak Bahirwani*[1] *Hammad Liaquat*[1]

[1]*St. Luke's University Health Network*

Background: Acetaminophen generally is very pharmacologically safe with minimal side effects and interactions. However, at high doses acetaminophen is known to be hepatotoxic and associated with significant mortality. The goal of this study is to identify the complications associated specifically with acetaminophen overdose when

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patients are already admitted for acute alcoholic liver failure. **Methods:** This is a retrospective cohort study using National Inpatient Sample data including patients hospitalized between 2016 and 2020 age 18 and greater who were admitted for acute alcoholic liver failure with or without concomitant acetaminophen overdose. The study compares risk factors including demographics and chronic medical conditions for the patients in our sample who did or did not also have acetaminophen overdose. Statistical analyses were all performed using STATA software. **Results:** Of the 639,780 patients age 18 or older with acute alcoholic liver failure, 3,365 patients (0.5%) presented with concomitant acetaminophen overdose. The average age of patients with acetaminophen overdose was less than that of patients without this factor (49.1 vs 62.5; p<0.001). Patients with acute alcoholic liver failure without acetaminophen overdose had significantly more frequent complications of cardiac arrest (OR= 0.240; 95% CI 0.124-0.464), pulmonary embolism (OR= 0.135; 95% CI 0.051-0.360), ascites (OR= 0.525; 95% CI 0.362-0.761), and ICU stay (OR= 0.333; 95% CI 0.282-0.393) in comparison to those with concomitant acetaminophen overdose. Patients with acetaminophen overdose with acute alcoholic liver failure developed HRS (OR= 1.978; 95% CI 1.320-2.964) and hepatic encephalopathy (OR= 1.599; 95% CI 1.142-2.238) more frequently than those without additional acetaminophen overdose. **Conclusion:** Our study showed that patients who presented with both acetaminophen overdose and acute alcoholic liver failure were younger in age, had fewer comorbidities, had higher rates of developing HRS and hepatic encephalopathy, and had higher overall mortality. Surprisingly, most complications including ICU stay, increased length of stay, cardiac arrest, and shock were higher in the group without concomitant acetaminophen overdose. These results demonstrate that acetaminophen at dangerous levels severely impacts the liver specifically, however, does not have as large of a systemic impact as acute alcoholic liver failure alone does.

Disclosures: Nisha Sanghani: Nothing to Disclose, Het Patel: Nothing to Disclose, Janak Bahirwani: Nothing to Disclose, Hammad Liaquat: Nothing to Disclose

2465 | CXXC-TYPE ZINC FINGER PROTEIN 5 DEFICIENCY IN MICE AMELIORATES ACETAMINOPHEN-INDUCED LIVER INJURY VIA THE STAT1 SIGNALING PATHWAY

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Background: Acetaminophen (paracetamol; APAP) overdose is a leading cause of acute liver failure, characterized by extensive hepatocellular necrosis primarily due to the formation of the toxic metabolite N-acetyl-p-benzoquinone imine. This metabolite depletes glutathione and induces oxidative stress, leading to liver cell damage and inflammation. CXXC-type zinc finger protein 5 (CXXC5) is a regulatory protein involved in DNA methylation and transcriptional control, influencing pathways like Wnt/β-catenin signaling which are crucial for liver function and repair. Its dysregulation has been associated with liver pathologies, including fibrosis and hepatocellular carcinoma, making it a potential factor in hepatotoxicity and liver disease progression. Therefore, this study was designed to evaluate the effects of CXXC5 deficiency in mice on the progression of acetaminophen-induced acute liver disease (ALD). **Methods:** To induce ALD in 6-week-old male CXXC5$^{+/+}$ or CXXC5$^{-/-}$ mice, a single dose of APAP (300 mg/kg) was intraperitoneally injected to the mice. Liver tissue and serum samples were collected at 12 hours post injection. Serum alanine aminotransferase (ALT) levels, gene expression associated with liver injury, and histopathological changes in the liver (evaluated through hematoxylin and eosin staining, TUNEL staining, and immunohistochemistry (IHC)) were examined. Additionally, the protein levels of iNOS, p-NF-kB, NF-kB, p-STAT1, STAT1, and β-actin were assessed using western blotting. **Results:** Compared to CXXC5$^{+/+}$-APAP mice, those with CXXC5$^{-/-}$-APAP mice group exhibited attenuated ALD, characterized by increased survival rates, decreased serum alanine aminotransferase levels, and diminished histopathological lesions. Correspondingly, CXXC5 deficiency was linked with reduced release of pro-inflammatory cytokines and decreased expression of oxidative stress factors in the liver of mice. The activation of the signal transducer and activator of transcription 1 (STAT1) signaling pathway was identified as the underlying molecular mechanism of CXXC5 action, with a significant decrease in phosphorylated STAT1 protein observed in CXXC5$^{-/-}$-APAP group compared to CXXC5$^{+/+}$-APAP group. Furthermore, we confirmed a markedly reduction in the expression of target genes and neutrophil infiltration in the APAP-induced liver of the CXXC5$^{-/-}$ mice group compared to the control group. **Conclusion:** Our findings indicate that CXXC5 plays a critical role in alleviating APAP-induced liver injury through involvement in the STAT1 pathway.

Disclosures: Hyuneui Jeong: Nothing to Disclose, Daram Yang: Nothing to Disclose, Bumseok Kim: Nothing to Disclose, Chae-Woong Lim: Nothing to Disclose

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2466 | EXPOSURE TO CIGARETTE SMOKE AGGRAVATES HEPATIC DAMAGE IN MICE INDUCED BY ETHANOL OR ACETAMINOPHEN

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Background: Cigarette smoke (CS) contains numerous toxic chemicals, including carcinogens and oxidants, leading to systemic inflammation and oxidative stress with widespread effects on the body. These harmful substances not only contribute to the development of chronic and acute liver diseases by adversely affecting cellular and molecular functions, but their mechanisms are also highly complex. The purpose of this study was to identify the role of CS in liver by analyzing its effects on chronic and acute liver disease models induced by ethanol or acetaminophen (APAP) in mice. **Methods:** A CS exposure model was established by exposing 6-week-old male C57BL/6 mice to CS generated from 3R4F reference cigarettes for a total duration of 1 to 4 weeks through inhalation. Mice were exposed to inhalation of total particulate matter concentrations ranging from 150 to 600 µg/L for 2 hours per day, 5 days per week. After exposure to CS, chronic and binge alcoholic liver disease was induced by feeding the Lieber-DeCarli diet containing 6.3% ethanol (EtOH) (v/v) for 10 days, while APAP-induced acute liver disease was induced by *i.p.* injection of APAP. **Results:** Exposure to CS exacerbated ethanol-induced liver disease (ELD), as confirmed by serum biochemical analysis. Additionally, in mice fed an EtOH diet and exposed to high doses of CS, there were increased expression levels of pro-inflammatory factors (interleukin-1 beta and tumor necrosis factor-alpha) and hepatic fibrosis factors. Interestingly, exposure to CS significantly increased the expression levels of cytochrome P450 (CYP) 1A2 and CYP2E1 in the livers of EtOH-fed mice. Similar to the ELD model, in the acetaminophen-induced acute liver disease (ALD) model, exposure to CS significantly increased hepatocyte necrosis and apoptosis. Additionally, APAP treatment notable increased the expression levels of CYP1A1 and CYP1A2, along with a significant upregulation of aryl hydrocarbon receptor (AhR), a transcription factor regulating these CYP enzymes. Hence, we examined whether inhibiting AhR upon exposure to CS mitigates liver damage in ALD. Treatment with an AhR inhibitor alleviated hepatic damage in the ALD model with CS exposure. Such results were demonstrated through hematoxylin and eosin staining, as well as by confirming the mRNA expression of pro-inflammatory factors and oxidative stress factors. **Conclusion:** Inhalation exposure to CS exacerbated both ELD and ALD in mice. These results indicate that smoking with alcohol consumption or with excessive intake of APAP can profoundly compromise liver health.

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2467 | LOW DOSE EXPOSURE TO DIOXINS ALTERS HEPATIC ENERGY METABOLISM AND STEATOTIC LIVER DISEASE DEVELOPMENT IN A SEX-SPECIFIC MANNER

Oluwanifemi Esther Bolatimi[1] *Yuan Hua*[1] *Frederick Ekuban*[1] *Tyler Gripshover*[1] *Abigail Ekuban*[1] *Bana Luulay*[1] *Josiah Hardesty*[1] *Banrida Wahlang*[1]

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Background: Epidemiological and toxicological reports have shown correlative effects between persistent organic pollutants (POPs) exposures and metabolic dysfunction-associated steatotic liver disease (MASLD). POPs like “dioxins” are released through anthropogenic, industrial, and natural combustion processes such as forest wildfires and remain present in the environment in appreciable levels. Nonetheless, the current understanding on how low levels of these pollutants, relevant to current real-life environmental exposures, impact MASLD development is still limited. Therefore, the objective of this study is to investigate the acute effects of a mixture of dioxins: 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD), 2,3,4,7,8-Pentachlorodibenzofuran (PeCDF) and Polychlorinated biphenyl 126 (PCB126), in the context of MASLD and underlying sex differences. **Methods:** Male and female C57BL/6 mice were fed a low-fat and administered either vehicle control or TCDD(10ng/kg)+PeCDF(80ng/kg)+PCB 126(140ng/kg) over a two-week period. At euthanasia, plasma and tissue were collected for phenotypical and biochemical characterization. **Results:** In general, female mice displayed greater fat content and steatosis vs males as reflected by H&E staining of liver sections. Mixture-exposed females also showed elevated hepatic triglyceride and cholesterol, in addition to upregulation of lipogenic genes (*Acaca, Fasn* and *Scd1*) compared to their sex-matched controls. In contrast, glucose clearance was decreased in

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mixture-exposed males versus exposed females. Furthermore, TCDD+PeCDF+PCB126 activated the AHR (*Cyp 1a1*, *Cyp 1a2* induction); although *Cyp 1a1* induction was observed only in exposed females. Interestingly, gene expression of hepatic estrogen receptor (*Esr1*), androgen receptor (*Ar*) and albumin were reduced only in exposed females. **Conclusion:** Overall, exposure altered male glucose metabolism while females were more susceptible to steatosis. Toxicant-sex interactions also resulted in decreased *Esr1* expression in females implicating altered protective-estrogenic effects. **Results:** indicate that activation of AHR is sex-dependent as the induction of target genes was more pronounced in mixture-exposed females vs. males. Additionally, the upregulation of lipogenic genes in mixture-exposed females suggest sex-specific transcriptional dysregulation due to AHR activation and/or reduced estrogen signaling due to mixture-mediated decrease in *Esr1*. Further assessment of extrahepatic effects and organ-organ crosstalk will help elucidate how dioxin mixtures drive progression of MASLD and unravel currently unknown mechanism on how real-life exposures to these pollutants impact liver health.

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2468 | CORRELATION BETWEEN DECREASED TYPE 3 INNATE LYMPHOCYTE AND DETERIORATION OF LIVER FUNCTION IN CHOLESTATIC DRUG INDUCED LIVER INJURY

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Background: Host immunity may play an essential role in the severity of idiosyncratic drug induced liver injury (DILI). Group innate lymphocytes (ILCs) are innate immune effectors that lack the rearranged antigen receptors but mimic the phenotypes and functions of adaptive T cells, contributing to injury repair and tissue remodeling. ILC3s have been identified as a primary source of interleukin-22. Our prior studies have shown that interleukin-22 has potential hepatoprotective effects in DILI. However, the role of ILC3 in patients with acute DILI patients remains unknown. We aim to determine the relationship between peripheral blood ILC3 expression and clinical phenotypes and severity of DILI in affected patients. **Methods:** DILI patients were enrolled within 7 days of injury onset and consecutively between May 2019 and November 2020, along with 100 healthy controls (HC). The diagnostic process was shown in Figure. Peripheral blood mononuclear cells were isolated using Ficoll density gradient centrifugation. Flow cytometry was used to quantify the frequency of lineage$^-$CD45$^+$CD127$^+$lymphocytes, defining ILCs. Also,lineage-CD45$^+$CD127$^+$CD117$^-$CD294$^-$ILCs were identified as ILC1, lineage$^-$CD45$^+$CD127$^+$CD117$^\pm$CD294$^+$ILCs as ILC2, and lineage$^-$CD45$^+$CD127$^+$CD117$^+$CD294$^-$ lymphocytes were utilized to identify ILC3s. Differences between two groups were determined by unpaired t test. Pearson or Spearman correlation was used for correlation analysis. p value <0.05 was considered statistically significant. **Results:** The frequencies of ILCs were significantly lower in patients with the onset of DILI than in HC (0.27% ± 0.16% *vs* 0. 51% ± 0.20%, p *vs* 0.30% ± 0.13%, p *vs* 0.16% ± 0.09%, p p=0.390). A significant negative correlation was observed between the frequency of ILCs and alkaline phosphatase (r = -0.252, p = 0.035). In clinical subgroup analysis, a significant decrease in the frequency of ILC3s was found in the cholestatic DILI group compared to the Hepatocyte-mixed DILI group (0.08% ± 0.07% vs 0.13% ± 0.09%, p = 0.038). Notably, in patients with cholestatic DILI, the frequency of ILC3s was significantly negatively correlated with TBil (r = -0.714, p = 0.004). **Conclusion:** This study found a decreased frequency of ILCs in patients with DILI. Further analysis revealed a strong association between the frequency of ILC3s and cholestatic DILI. In cholestatic patients, ILC3 frequency was significantly negatively correlated with liver severity, suggesting a greater suppression of host innate immunity in cholestatic DILI. This implies that altered immune function of ILC3s may be a mechanism contributing to the deterioration in cholestatic DILI, presenting a potential target for future therapy.

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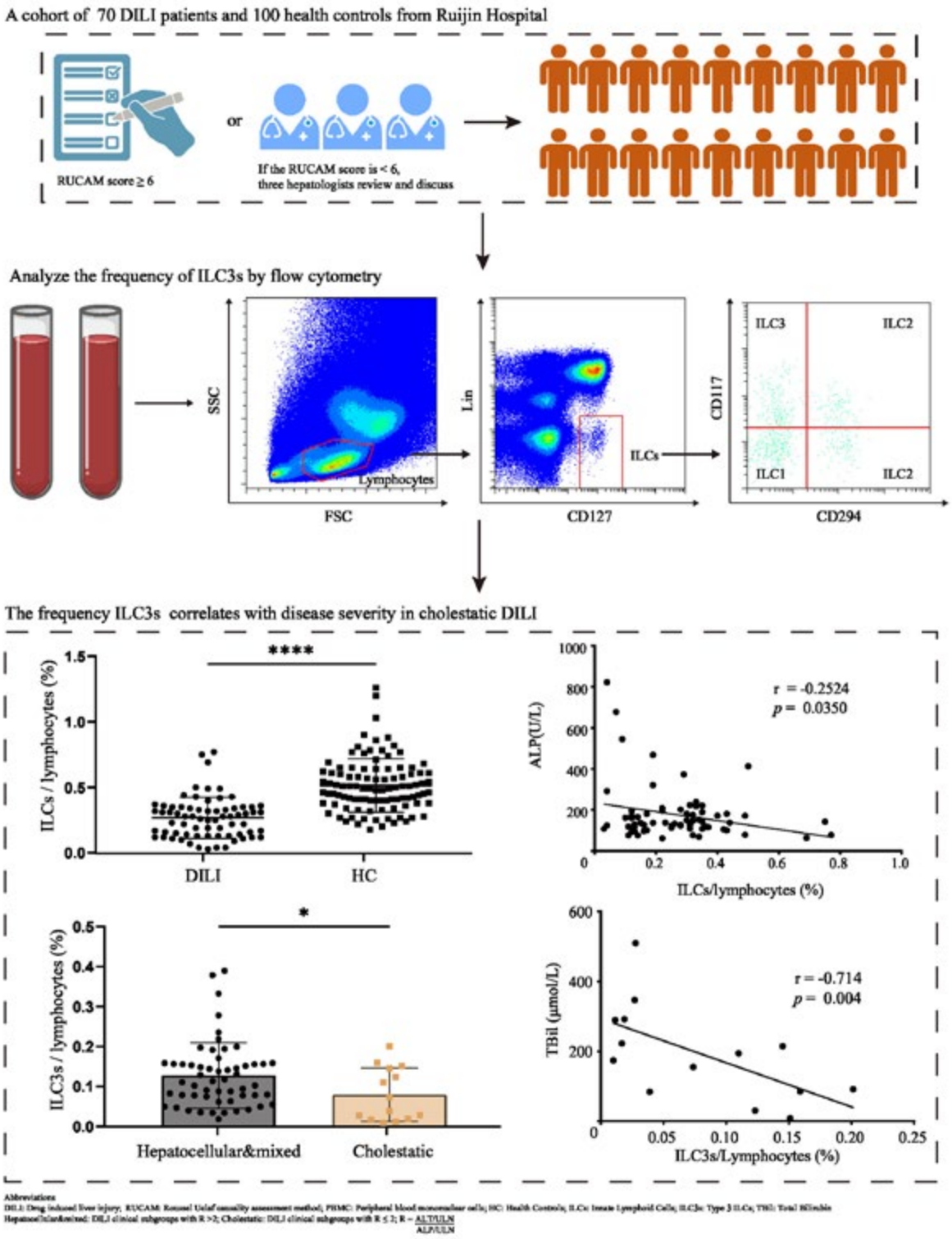

Disclosures: Rongtao Lai: Nothing to Disclose, Jingjing Jiang: Nothing to Disclose, Qing Li: Nothing to Disclose, Ruidong Mo: Nothing to Disclose, Tianhui Zhou: Nothing to Disclose, Yan Huang: Nothing to Disclose, Haoshuang Fu: Nothing to Disclose, Xiaogang Xiang: Nothing to Disclose, Qing Xie: Nothing to Disclose

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2469 | CHARACTERIZATION OF LIVER INJURY INDUCED BY CDK 4/6 INHIBITORS INDUCED LIVER INJURY

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Background: Cyclin-dependent kinase inhibitors (CDKIs) are essential in treating HR+ HER2-negative metastatic breast cancer (MBC). Grade 3 elevations of ALT and AST occur in up to 11% and 6% of patients on ribociclib or abemaciclib, respectively. The mechanism of liver toxicity is unclear. **Methods:** Patients assessed by the Réseau Francophone pour l'étude de l'Hépatotoxicité des Produits de Santé (REFHEPS) between January 2022 and April 2024 were evaluated. Those with CDKI-induced liver toxicity were included. Hepatotoxicity was defined as ALT or AST ≥ 5x ULN, ALP ≥ 2x ULN, or total bilirubin ≥ 2x ULN associated with ALT ≥ 3x ULN. Causality was assessed using the RUCAM method, and severity by DILIN score and CTCAE v5. Statistical analysis included medians (ranges) for quantitative variables and counts (percentages) for qualitative variables, using Wilcoxon rank sum and Chi-squared tests. A p-value < 0.05 was significant. Kaplan-Meier method estimated survival probabilities from the date of DILI onset to recovery. This study was approved by an ethics committee (IRB number: 198711). **Results:** Of 330 cases, 34 involved CDKIs; one was excluded due to another likely diagnosis. Included were 33 patients (ribociclib [n=29], abemaciclib [n=4]), all women, median age 63 years (39-83), treated for MBC. All had concomitant hormonal treatment. Median time to hepatitis onset was 69 days (16-500). Most hepatitis cases were hepatocellular (n=32), one mixed, with CTCAE grades 3 (n=22) or 4 (n=11). Median peak liver tests: AST 346.5 IU/L (100-1443), ALT 696 IU/L (200-2523), ALP 127 IU/L (67-423). Comprehensive work-up, including viral serologies and liver antibodies, was performed. Eleven patients had positive anti-nuclear antibodies or elevated IgG levels. Liver biopsy (13 patients) showed centrilobular hepatitis, no fibrosis. RUCAM scores were 3-9. Median improvement time post-CDKI withdrawal was 54.5 days (5-221). Fifteen (45.5%) patients received steroids (0.5-1 mg/kg) introduced due to a lack of spontaneous resolution followed by complete resolution. Eight patients (ribociclib n=2, palbociclib n=2, abemaciclib n=4) were rechallenged with CDKIs, three relapsed with non-severe hepatitis. **Conclusion:** CDKIs, especially ribociclib, are associated with hepatocellular hepatitis in MBC treatment. Corticosteroids appear beneficial when spontaneous improvement is absent, but further data are needed

Disclosures: LUCY MEUNIER: Nothing to Disclose, Benedicte Delire: Nothing to Disclose, Eleonora De Martin: Nothing to Disclose, Yves Horsmans: Nothing to Disclose, Dominique Larrey: Sanofi: Employee, Sanofi: Stock - publicly traded company, SANOFI: Consultant

2470 | THE BURDEN OF ANTI-CANCER DRUGS IN DRUG-INDUCED LIVER INJURY IN THE FRENCH-SPEAKING HEPATOTOXICITY NETWORK

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Background: Drug hepatotoxicity is a major cause of drug withdrawals from the market and the cessation of new drug development. Among these drugs, anti-cancer drugs are a class frequently implicated. This study aims to analyze the cases of hepatotoxicity reported to REFHEPS (Réseau Francophone pour l'étude de l'Hépatotoxicité des Produits de Santé) during its first two years, highlighting key findings and their implications for clinical practice. **Methods:** All cases submitted to REFHEPS from January 2022 to April 2024 were retrospectively analyzed by hepatotoxicity experts. Hepatitis pattern (hepatocellular, cholestatic, or mixed), severity, and drug imputability were assessed using international criteria (RUCAM and DILIN methods). We compared hepatitis induced by anti-cancer drugs to other drugs. **Results:** Since 2022, 330 cases were submitted to REFHEPS. Twenty-one cases were excluded due to differential diagnoses or insufficient data, and 79 are under review. Thus, 230 cases were analyzed. The mean age of patients was 52.4 years (±18.8), with a majority being female (n=148; 64.3%). The mean RUCAM score was 6.8 (±2). The pattern of DILI was mainly hepatocellular (n=153;

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66.5%), followed by cholestatic (n=55; 23.9%) and mixed (n=21; 9.1%). Severity distribution was: mild (n=87; 37.8%), moderate (n=67; 29.1%), moderate-severe (n=44; 19.1%), severe (n=20; 8.7%), and fatal or requiring transplantation (n=12; 5.2%). DILI was treated with UDCA or steroids in 59 cases (25.7%) and N-acetylcysteine in 32 cases (13.9%). A total of 179 patients improved (77.8%) with a median recovery time of 53 days (range: 5-567 days). Anticancer drugs were the most frequent causes of DILI (n=125; 54.3%). Comparison of patient characteristics between anticancer drugs and others revealed that anticancer DILI cases involved older patients, more frequent biopsies, and less severe hepatitis (table). **Conclusion:** In its first two years, REFHEPS collected over 200 cases of DILI, with anticancer drugs being the most common cause. Immune checkpoint inhibitors, in particular, were frequently implicated. Compared to other drugs, anticancer DILI cases involved older patients, more frequent biopsies, and generally less severe hepatitis. These findings underscore the importance of monitoring and managing DILI in patients undergoing cancer treatment.

Variable	Antic Anticancer drugs n=125	Others drugs n=105	p value
Sex, female (%)	82 (65.6)	66 (62.9)	0.768
Age (years), mean	60.3 (± 12.8)	43.0 (± 20.6)	<0.001
AST (IU/L), mean	338.1 (± 542.8)	1871.5 (± 3785.2)	<0.001
ALT (IU/L), mean	441.1 (± 572)	1473.5 (± 2205.4)	<0.001
GGT (IU/L) mean	345.2 (± 392.7)	284.4 (± 489.4)	0.038
ALP (IU/L), mean	334.7 (± 464.6)	218.4 (± 286.7)	0.004
Total bilirubin (µmol/l), mean	38.9 (± 87.5)	65.3 (± 103.7)	0.002
Liver biopsy (%)	60 (48)	33 (31.4)	0.016
Delay drugs – liver injury (days)	160.49 (± 409.57)	72.83 (± 229.43)	<0.001
RUCAM score	6.8 (± 1.9)	6.8 (± 2.1)	0.909
DILIN score severity			<0.001
Mild	57 (45.6)	30 (28.6)	
Moderate or moderate severe	61 (48.8)	50 (47.6)	
Severe, fatal or transplantation	7 (5.6)	25 (23.8)	
Hospitalisation (%)	27 (21.6)	55 (52.4)	<0.001

Disclosures: LUCY MEUNIER: Nothing to Disclose, Eleonora De Martin: Nothing to Disclose, Bénédicte Delire: Nothing to Disclose, Dominique Larrey: Sanofi: Employee, Sanofi: Stock - publicly traded company, SANOFI: Consultant, Yves Horsmans: Nothing to Disclose

2471 | SS-31 PROTECTS FROM VINYL CHLORIDE AND WESTERN DIET-INDUCED HEPATIC INJURY

Charis-Marie Vanderpuye[1] *Pooja Muddasani*[1] *Olivia Bannister*[1] *Dexi Chen*[1] *Jiang Li*[1] *Samuel Taborski*[1] *Gavin Arteel*[1] *Juliane Beier*[1]

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Background: Vinyl chloride (VC), a common industrial chemical and environmental pollutant, directly causes liver injury at high exposure levels. However, while lower concentrations (i.e., < 1 ppm) do not overtly damage the liver, they can exacerbate injury due to overnutrition. Impaired mitochondrial function, dysregulated mitochondrial membrane potential, and impaired respiration are key pathological features. Here, SS-31, a mitochondrial-targeted peptide, which has been shown to reduce mtROS production while also increasing respiratory function, and preventing mitochondrial permeability transition, was tested for therapeutic intervention. **Methods:** C57Bl/6J mice were exposed to VC (sub-OSHA standard: <1 ppm), or air for 6 hrs./d, 5 d/wk. for up to 12 wks. Mice were fed a Western diet (WD) or control diet (CD). A subset of mice was injected with SS-31 (3 mg/kg/d i.p.), three times a week for the last 9 weeks of exposure. Plasma and liver samples were collected for determination of injury

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and mitochondria were isolated for respirometry and analysis of mt-(dys)function. AML-12 cells were exposed to chloroacetaldehyde (CAA, 0-5 μM) ± SS-31 for a subsequent mitochondrial reconstruction analysis. **Results:** VC exposure enhanced liver injury caused by WD feeding, as previously observed. The primary effect appeared to impact hepatic metabolic function, coupled with oxidative damage and mitochondrial dysfunction. Respirometry indicated that mitochondria from VC-exposed mice exhibited impaired electron transport chain (ETC) function. Intervention with SS-31 significantly decreased indices of liver injury (ALT). Despite not protecting against lipid peroxidation (MDA), SS-31 decreased histologic assessment of lipid accumulation (ORO) and inflammation (F4/80). This correlated with a decrease in hepatic free fatty acids. Moreover, SS-31 protects mitochondria from chloroacetaldehyde (CAA)-induced swelling in AML-12 cells. **Conclusion:** Taken together, these data support our previous findings that mitochondria have a central role in VC+WD-induced liver injury. Moreover, SS-31, in part, protected against damage and mitochondrial swelling caused by VC and overnutrition. Additional experiments are needed to elucidate the underlying mechanisms. This research is supported by R01 DK133454-03 and R21 ES036032-01.

Disclosures: Charis-Marie Vanderpuye: Nothing to Disclose, Pooja Muddasani: Nothing to Disclose, Olivia Bannister: Nothing to Disclose, Dexi Chen: Nothing to Disclose, Jiang Li: Nothing to Disclose, Samuel Taborski: Nothing to Disclose, Gavin Arteel: Nothing to Disclose, Juliane Beier: Nothing to Disclose

2472 | TARGETED DELETION OF EPIDERMAL GROWTH FACTOR RECEPTOR IN HEPATOCYTES MITIGATES ACETAMINOPHEN-INDUCED LIVER DAMAGE AND ENHANCES COMPENSATORY REGENERATION IN MICE ◆ ★

Siddhi Jain[1] Ranjan Mukherjee[1] John Stoops[1] Anne Orr[1] Wendy Mars[1] Bharat Bhushan[1]

[1]University of Pittsburgh

Background: Epidermal growth factor receptor (EGFR) is a key driver of hepatocyte proliferation following partial hepatectomy (PH). However, its role in acetaminophen-induced liver injury (AILI), a clinically significant model of acute liver failure, remains largely unexplored. Unlike PH in a healthy liver, AILI entails substantial liver damage and inflammation, intricately influencing the regenerative process. Hence, the function of EGFR in AILI cannot be presumed to parallel its role in the regeneration of a healthy liver following PH. In our previous study, EGFR inhibition paradoxically prevented AILI in mice, indicating a role of EGFR activation in promoting AILI. Further investigation using a hepatocyte-specific EGFR KO model is warranted to validate this unexpected role of EGFR in promoting AILI. **Methods:** To explore EGFR's role in AILI and subsequent regeneration, we utilized a targeted method in $EGFR^{fl/fl}$ mice, employing AAV8-TBG-CRE to specifically delete EGFR in hepatocytes. The control group, comprising wild-type (WT) mice, received AAV8-TBG-GFP. Both WT and EGFR KO mice were given doses of 300 and 500 mg/kg of APAP to assess liver injury, regeneration markers, and associated signaling pathways at different time intervals. **Results:** The initial liver injury was similar in both WT and EGFR KO mice, with APAP metabolic activation and APAP-protein adduct formation remaining unchanged. However, in EGFR KO mice, the progression of subsequent injury was markedly subdued. This was attributed to the decreased activation of JNK, accompanied by rapid replenishment of glutathione in EGFR KO mice at the later time points. Further, the translocation of JNK to mitochondria was reduced in EGFR KO mice resulting in reduced mitochondrial damage and lower release of cell death mediator, AIF, into cytosol. After 24 hours, EGFR KO mice displayed a distinct pattern characterized by increased activation of crucial components of the cell cycle machinery, including increased phosphorylation of retinoblastoma protein, induction of cyclin D1, and elevated levels of PCNA. This molecular cascade ultimately resulted in a significant augmentation of the compensatory liver regeneration response. **Conclusion:** The targeted removal of EGFR specifically from hepatocytes halted the progression of liver damage and promoted liver regeneration after APAP overdose in mice. Our study uncovered an unexpected death-promoting function of EGFR, which has wide implications in liver biology.

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2473 | VERBASCOSIDE PROTECT AGAINST OXIDATIVE DAMAGE OF BENZO[α]PYRENE EXPOSURE ON HEPATOCELLULAR CELLS

Wen-ting Xiong[1]

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Background: Benzo[α]pyrene (B[α]P) is a highly toxic environmental pollutant among the polycyclic aromatic hydrocarbons (PAHs) class. A natural caffeoyl phenylethanoid glycosides from Cistanche tubulosa (Schenk) R. Wight named verbascoside has protective effect against hepatotoxicity of inhalation exposure to B[α]P, but the mechanism is unknown. **Methods:** Mouse hepatocellular cell line (AML12) was cultured in Dulbecco's Modified Eagle Medium (DMEM), with 10% fetal bovine serum (FBS) and 1% penicillin-streptomycin at 37 °C in a humidified incubator containing 5% CO2. We used 0, 4, 20 and 100 μM B[a]P (with 0.5% DMSO) to culture cells for 12 hours, then treated the cells with 0, 0.06. 0.12 μM verbascoside for 24 hours. The vehicle controls were incubated with 0.5% DMSO. All the groups had six biological replicates. Then we collected cells, analyzed the total glutathione peroxidase activity using a total Glutathione Peroxidase Assay Kit, assessed total ROS levels using a Reactive Oxygen Species Assay Kit, analyzed GSH levels by Agilent liquid chromatography-mass spectrometry, extracted total protein from AML12 cell lysate and detected superoxide dismutase 3 (SOD3) and glutathione peroxidase protein levels by Western Blotting, normalized data to β-actin. **Results:** After 12 hours' B[α]P exposure to AML 12 cells, all B[α]P groups' total intracellular ROS levels increased markedly, meanwhile the glutathione peroxidase activity, GSH levels and SOD3 protein levels significantly decreased, suggesting that B[α]P exposure could disrupt the antioxidant system of AML12. After a 12 hours treatment of 4 and 20 μM B[a]P on AML 12 cells, incubation with verbascoside at 0.12 μM for 24hours could partially recovered the glutathione peroxidase activity, GSH levels and SOD3 protein levels that were decreased by B[α]P exposure. **Conclusion:** Verbascoside exhibit protection effect against oxidative damage in mouse hepatocellular cells induced by exposing to benzo[α]pyrene, on glutathione peroxidase activity, GSH levels and SOD3 protein levels on AML 12 cells. This suggesting that verbascoside is a possible hepatoprotective agent to prevent benzo[α]pyrene induced oxidative damage.

Disclosures: Wen-ting Xiong: Nothing to Disclose

2474 | HEPATIC CELL MEMBRANE SYNTHESIS IS SUPPRESSED DURING LIVER REGENERATION AFTER ACETAMINOPHEN HEPATOTOXICITY

Ahsan Hameed[1] *Colin Kay*[1] *Mario Ferruzzi*[1] *Andrew Morris*[1] *Mitchell McGill*[1]

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Background: We previously demonstrated that the lipid phosphatidic acid (PA) increases in the liver during acetaminophen (APAP) hepatotoxicity and promotes liver repair by inhibiting glycogen synthase kinase 3β (GSK3β). Interestingly, the mechanism of PA elevation appears to be downregulation of the PA phosphatases lipin 1 and 2. Normally, these enzymes convert PA to diacylglycerols (DAGs), which are then used for de novo synthesis of new cell membrane glycerophospholipids (GPLs) as well as triacylglycerols (TAGs) for energy. Based on these observations, we hypothesized that GPL and TAG synthesis are counterintuitively shut down during liver regeneration. To test this, we used global lipidomics to map changes in the regenerating liver lipidome downstream of PA in a mouse model of APAP overdose. **Methods:** We treated 8 to 9-week old C57Bl/6J mice with 300 mg/kg APAP or an equal volume of 1x phosphate-buffered saline (PBS) vehicle and harvested liver tissue 6, 24, and 48h later. Lipids were extracted using acidified CHCl3/MeOH, with addition of class-specific internal standards. The lipids were then separated by reversed-phase UHPLC and analyzed by positive and negative mode electrospray ionization tandem mass spectrometry. Peak identification, alignment integration and lipid identification were performed using MS-Dial v5.1. Data visualization and statistical analysis were done using Metaboanalyst 5.1. Univariate analyses were carried out to test for differences between the APAP and PBS groups. Analysis of variance-simultaneous component analysis was also performed, and leverage and squared prediction error scores were used to identify significant varying metabolites and their dependency on time, treatment, and interaction effects. **Results:** Consistent with our hypothesis, total DAG and GPL content were reduced as early as 6 hours after APAP (33±14% and 22±6%, respectively). All individual, detectable GPL species from all major membrane GPL classes (PC, PE, PI, PS) were also decreased up to a maximum of 6.3x lower than

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PBS vehicle at multiple time points. Interestingly, total hepatic TAG content increased despite decreased DAGs. In addition, two species of sphingomyelin, also implicated in liver regeneration, were also elevated, and several oxidized phosphatidylcholine species were increased, reflecting oxidative stress. **Conclusion:** Overall, our data support the idea that synthesis of membrane GPLs is suppressed in the injured and regenerating liver after APAP overdose. Proliferating hepatocytes likely have an alternative source of GPLs and TAGs, such as scavenging them from neighboring necrotic cells. Finally, sphingomyelins may have a role in liver regeneration after APAP hepatotoxicity, though that requires further investigation.

Disclosures: Ahsan Hameed: Nothing to Disclose, Colin Kay: Nothing to Disclose, Mario Ferruzzi: Nothing to Disclose, Andrew Morris: Nothing to Disclose, Mitchell McGill: GlaxoSmithKline: Provided research funding, Haleon: Provided research funding, Acetaminophen Toxicity Diagnostics, LLC: Paid consultant, Butler Snow, LLP: Expert Witness, GlaxoSmithKline: Grant/Research Support, Haleon: Grant/Research Support, Acetaminophen Toxicity Diagnostics, LLC: Consultant, Butler Snow, LLP: Consultant, Thomas, Combs, and Spann, PLLC: Consultant

2475 | EFFICACY OF UDCA AS FIRST-LINE TREATMENT FOR CHOLESTATIC CHECKPOINT INHIBITOR-INDUCED LIVER INJURY

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[1]Hepatology and Liver transplantation unit, Saint Eloi Hospital, Montpellier University Hospital, Mon, [2]logy and Liver transplantation unit, Saint Eloi Hospital, Montpellier University Hospital, Montpelli, [3]Department of Medical Pharmacology and Toxicology, Lapeyronie Hospital, Montpellier University Hospi, [4]Internal Medicine & Immuno-Oncology (MedI2O), Institute for Regenerative Medicine and Biotherapy (IR

Background: Checkpoint Inhibitor-induced Liver Injury (CHILI) is a well-known immune-related adverse event of immune checkpoint inhibitors (ICI) due to the restoration of anti-tumor T lymphocyte responses. Corticosteroids are the cornerstone of CHILI treatment, but ESMO guidelines also recommend UDCA for immune-related cholangitis secondary to immunotherapy. UDCA is fundamental in treating autoimmune cholangiopathies and is empirically used in cholestatic DILI. Literature suggests an association between ICI-induced cholangiopathy and steroid resistance. We hypothesized the efficacy of UDCA as a first-line treatment for cholestatic CHILI. Our study aimed to analyze real-world data on the off-label use of first-line UDCA alone for CHILI. **Methods:** We conducted a multicenter retrospective study among patients presented at the “Toximmun” multidisciplinary meeting from December 2018 to December 2023 at Montpellier University Hospital. Inclusion criteria were: i) adults treated with ICI; ii) normal liver tests prior to ICI; iii) CHILI with abnormal liver tests after excluding other hepatitis causes; iv) first-line UDCA monotherapy. Patients treated with corticosteroids first-line or with cirrhosis were excluded. Hepatitis pattern was classified using the ratio (R) = (ALT/ULN)/(ALP/ULN) as cholestatic (R ≤ 2), hepatocellular (R ≥ 5), or mixed (2 < R < 5). Response to UDCA was a decrease in ALP and GGT ≥ 50%. Recurrent CHILI (rCHILI) was defined as ALP ≥ 2x ULN after initial improvement, and chronic CHILI as ALP > 2x ULN or ALT > 5x ULN after 12 months. **Results:** The analysis included 21 patients treated with first-line UDCA, with a mean follow-up of 10.3 months (± 8.4). The median age was 68.7 (46-87) years; sex ratio was 1.3 (12 males, 57.1%). Most patients received PD-1 inhibitors alone (n=13, 61.9%) or with CTLA-4 inhibitors (n=3, 14.3%). Median ICI infusions were 4.8 (1-19), and median CHILI onset was 19.5 days (3-52). Cholestatic hepatitis was in 20 patients (95.2%) and mixed in 1 (4.8%). Severity: 18 patients (85.7%) were CTCAE grade ≥3, 2 were grade 2 (14.3%). No liver dysfunction per DILI classifications. Patients with macroscopic biliary tract injury (all anti-PD1; n=7, 100%; p=0.02) had more recurrent CHILI (n=4, 57.1%; p=0.006) and higher eosinophil levels (p=0.04). 18 patients (85.7%) improved with UDCA only within a median of 36 days (5-168); 2 had chronic CHILI (9.5%). Recurrent CHILI was linked to eosinophil count at onset (p<0.001). ICI was rechallenged in 12 patients (57.1%); UDCA continued in 11 (91.7%). **Conclusion:** This observational study of 21 CHILI patients treated with first-line UDCA monotherapy indicates that cholestatic and mixed CHILI may benefit from UDCA alone rather than corticosteroids. Further prospective studies are needed.

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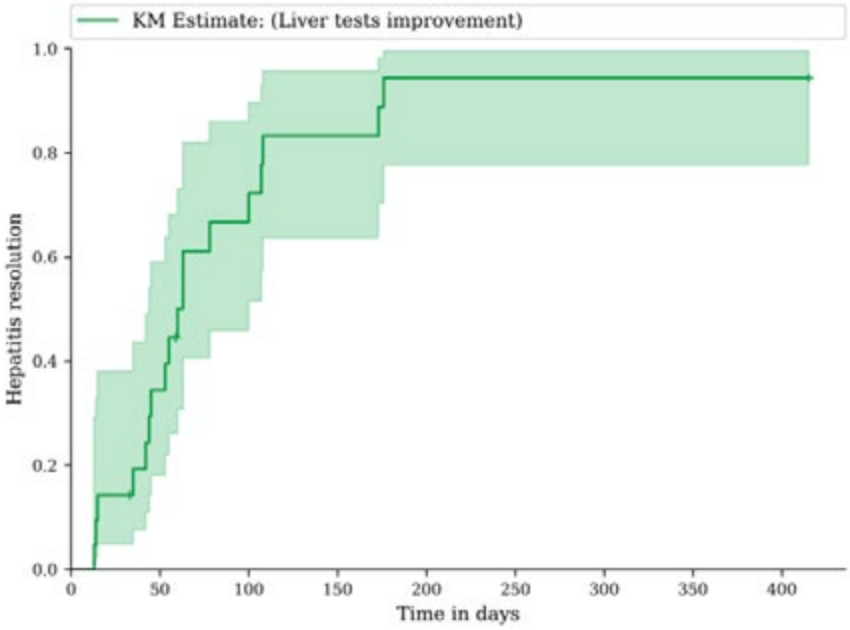

Disclosures: LUCY MEUNIER: Nothing to Disclose, Lina Hountondji: Nothing to Disclose, Stéphanie Faure: Nothing to Disclose, Pascale Palassin: Nothing to Disclose, Georges-Philippe Pageaux: Nothing to Disclose, Alexandre Maria: Nothing to Disclose

2476 | TRENDS AND OUTCOMES OF ACETAMINOPHEN-INDUCED HEPATOTOXICITY: A 2016 TO 2021 ANALYSIS USING THE NATIONAL INPATIENT SAMPLE DATASET

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Background: Acetaminophen (Tylenol) is a widely used over-the-counter analgesic and antipyretic. Despite its therapeutic benefits, acetaminophen overdose can result in severe hepatotoxicity, a critical and potentially fatal condition. This study aims to analyze the trends, demographic characteristics, and clinical outcomes of acetaminophen-induced hepatotoxicity. **Methods:** We conducted a retrospective analysis of the National Inpatient Sample (NIS) dataset from 2016 to 202. Hospital admissions with a diagnosis of intentional or accidental acetaminophen overdose, along with acute liver failure, were identified using ICD-10-CM codes. Patients under 18 years old and those without information on age, gender, and inpatient mortality were excluded. We evaluated baseline characteristics of patients along with hospital characteristics, and other comorbidities. We also analyzed pertinent outcomes, including acute liver toxicity, mortality, liver transplantation, length of stay, and hospital charges.. Using multivariate logistic regression, we adjusted for confounders. The Cochran-Armitage test was used to assess mean and proportional trends. P-values for significance were predetermined at 0.05 for all trend directions (two-sided). **Results:** There were 97,610 hospitalizations for acetaminophen-induced hepatotoxicity from 2016 to 2021. During the 6-year period, 28% were due to accidental ingestion and 72% to intentional ingestion. The mean age of patients was 38.2 years, with females representing 66% of cases. The racial distribution was predominantly White (65.2%), followed by Black (14.8%). Patients with intentional ingestion were younger (mean age 35.6 years) compared to those with accidental ingestion (mean age 45 years). Chronic conditions such as diabetes (13.7% vs. 7.8%), hypertension (28.7% vs. 18.0%), and nicotine dependence (35.5% vs. 32.2%) were more prevalent in accidental ingestions. Overall, acute liver toxicity occurred in 6.1% of cases (OR 0.39, CI: 0.35 to 0.45) and increased from 4.7% in 2016 to 7.8% in 2021 (p-value 0.000). In-hospital mortality was 1.7% with higher rates in intentional ingestion cases (3.4%) compared to accidental cases (1.1%); with an OR of 0.65 and a 95% CI of 0.51 to 0.82. Liver transplantation was rare (0.1%). The average hospital stay was 3.6 days, with mean hospital charges of $41,300. Toxicity-related complications as shown in figure 2 had an increasing trend ($p < 0.0001$). **Conclusion:** The study reveals a concerning upward trend in hospitalizations for

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acetaminophen-induced hepatotoxicity from 2016 to 2021. There was a predominance of intentional ingestions among younger patients and females. Chronic conditions such as diabetes, hypertension, and nicotine dependence were more common in accidental ingestions . During the study period, hospitalization and inpatient mortality and rates of acute liver toxicity increased.

Table 1: Patient and Hospital Characteristics

Characteristics	Accidental Acetaminophen Ingestion	Intentional Acetaminophen ingestion	p-value
Total Hospitalizations - 97,610	28.0% (27,335)	72.0% (70,275)	0.000
Age Mean: 38.2 years	45 years	35.6 years	0.000
Gender Male - 34.0% Female - 66%	35.8% 64.2%	33.4% 66.6%	0.002
Race White - 65.2% Black- 14.8% Hispanic- 12.2% Asian- 2.7% Native Americans- 1.5%	67.2% 15.6% 10.8% 2.1% 1.3%	64.5% 14.5% 12.7% 2.9% 1.6%	0.000
Insurance Type (%) Medicare Medicaid Private Insurance Uninsured	27.9% 33.5% 25.4% 13.2%	15.4% 34.8% 35.4% 14.4%	0.000
Hospital Location (%) Rural Urban	7.4% 92.7%	8.5% 91.5%	0.010
Type of Institution Non - Teaching Teaching	27.5% 72.5%	29.5% 70.5%	0.007
Hospital Bed Size (%) Small Medium	21.1% 28.6%	21.4% 29.7%	0.218

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Large	50.3%	48.9%	
Charlson Index (%)			
0	41.9%	70.4%	0.000
1	20.3%	16.8%	
2	8.9%	4.6%	
3 or more	28.2%	8.2%	
Obesity	11.1%	10.9%	0.694
Diabetes	13.7%	7.8%	0.000
Hypertension	28.7%	18.0%	0.000
Nicotine dependence	35.5%	32.2%	0.000
Hyperlipidemia	15.2%	8.7%	0.000

Table 2: Outcomes of Acetaminophen Overdose

Outcomes	Accidental Acetaminophen Ingestion	Intentional Acetaminophen Ingestion	Adjusted Odds ratio (95% CI)	p-value
Mortality - 1.7%	3.4%	1.1%	0.65 (0.51 - 0.82)	0.000
Acute Liver Failure - 6.1%	12.1%	3.8%	0.39 (0.35 0.45)	0.000
Liver Transplantation - 0.1%	0.2%	0.001%	1.01 (0.37 - 2.77)	0.989
Length of Stay - 3.6 days	3.9 days	3.5 days	NA	0.000
Hospital Charges - $41,300	$52,180	$37,088	NA	0.008

Figure 1: Trends in Acetaminophen Overdose from 2016 to 2021

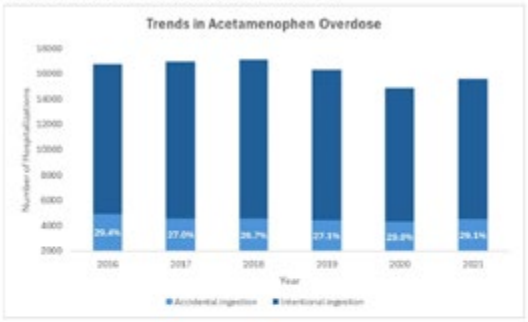
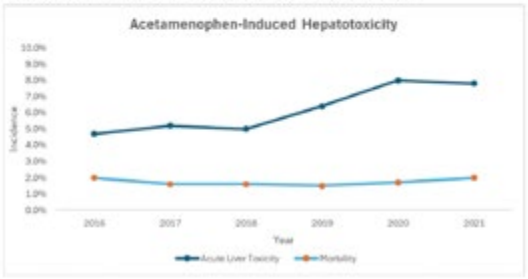


Figure 2: Trends in Acetaminophen-induced hepatotoxicity from 2016 to 2021



Disclosures: Chineye (Brenda) Amuchi: Nothing to Disclose, Chidiebele Omaliko: Nothing to Disclose, Elizabeth Soladoye: Nothing to Disclose

2477 | THE ROLE OF 2'-5'-OLIGOADENYLATE SYNTHASE-LIKE PROTEIN (OASL1) IN CHOLESTATIC- AND HEPATOTOXIN-MEDIATED LIVER FIBROSIS

Daram Yang[1] Leya Mwense[1] Tien Huyen Ton Nu Bao[1] Hyuneui Jeong[1] Sang-Ik Oh[1] Jong-Hoon Kim[1] Jong-Won Kim[1] Bumseok Kim[1]

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Background: Following an injury, the liver embarks on a process that drives the accumulation and reformation of the extracellular matrix, leading to hepatic fibrosis. Type 1 interferons (IFNs), including IFN-α and IFN-β, play a crucial role in averting chronic liver injury through the activation of IFN-stimulated genes (ISGs), which are instrumental in sculpting adaptive immunity. The role of 2'-5'-oligoadenylate synthase-like protein 1 (OASL1), an antiviral ISG, in the context of liver fibrosis remains to be elucidated. **Methods:** To elicit liver fibrosis, a diet containing 0.1 % diethoxycarbonyl-1,4-dihydrocollidine (DDC) and carbon tetrachloride (CCl_4) were employed to induce cholestatic- and hepatotoxin-mediated liver fibrosis, respectively for 4 weeks. In addition, primary hepatocytes were isolated using two-step collagenase perfusion and stimulated with 0.2% CCl_4 for 24 hours. **Results:** Histological analyses of both models revealed that OASL1$^{-/-}$ mice exhibited reduced liver damage and, consequently, expressed lower levels of fibrotic mediators, notably α-smooth muscle actin. OASL1$^{-/-}$ mice demonstrated significantly elevated IFN-α and IFN-β mRNA levels, which were regulated by the IFN regulatory factor 7 (IRF7). Additionally, OASL1$^{-/-}$ ameliorated chronic liver fibrosis through the modulation of nuclear factor-κB (NF-κB) signaling. *In vitro* stimulation of primary hepatocytes with 0.2 % CCl4 revealed that OASL1 markedly facilitated the upregulation of IFN-α and IFN-β mRNA levels, which was intriguingly modulated by IRF3. **Conclusion:** These results demonstrate that in instances of liver fibrosis, OASL1 inhibits the production of type 1 IFN by modulating the NF-κB signaling pathway, thereby worsening liver injury.

Disclosures: Daram Yang: Nothing to Disclose, Leya Mwense: Nothing to Disclose, Tien Huyen Ton Nu Bao: Nothing to Disclose, Hyuneui Jeong: Nothing to Disclose, Sang-Ik Oh: Nothing to Disclose, Jong-Hoon Kim: Nothing to Disclose, Jong-Won Kim: Nothing to Disclose, Bumseok Kim: Nothing to Disclose

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2478 | MATERNAL SMOKING EXACERBATES SUBSEQUENT LIVER DAMAGE IN OFFSPRING MICE

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Background: Cigarette smoke (CS) that is exhaled by smokers has been classified by IARC as a Group 1 carcinogen. CS exposure during pregnancy may even have adverse effects on the health of the fetus. Therefore, our aim was to evaluate effects of *in utero* CS exposure on acute and chronic liver disease/injury in offspring mice. **Methods:** Pregnant C57BL/6 mice were exposed to fresh air or mainstream CS (MSCS; 150, 300, or 600 μg/L) by nose-only exposure system for 2 hours/day, 5 days/week for 2 weeks from gestational day 6 to 17. Acute liver injury (ALI) on offspring was induced by a single intraperitoneal injection of acetaminophen (APAP; 300 mg/kg) in 4-week-old male mice. Liver tissues and serum were collected 24 hours later. To induce metabolic dysfunction-associated steatohepatitis (MASH) on offspring, 3-week-old male mice were fed a methionine and choline-supplemented (MCS) diet or a methionine and choline-deficient including high-fat (MCDHF) diet for 6 weeks. **Results:** In the ALI model, alanine transferase (ALT) levels increased by APAP administration were significantly increased by maternal MSCS exposure. Histopathological evaluation of the liver showed that perivascular inflammation, hepatocyte necrosis, and apoptosis induced by APAP treatment were exacerbated by maternal MSCS exposure. Immunohistochemical staining for 4-hydroxynonenal and myeloperoxidase, inflammatory mediators secreted by neutrophils, showed that maternal MSCS exposure exacerbated the inflammatory response in APAP-induced ALI. Interestingly, maternal smoking affected the protein expression of cytochrome P450 (CYP) enzymes in the liver of offspring, and the expressions of three CYP enzymes (CYP2E1, 3A11, and 1A2) were significantly increased by APAP treatment. In the MASH model, maternal MSCS exposure did not affect liver/body weight ratio in offspring. Levels of ALT, total cholesterol, and triglyceride, which increased due to MCDHF diet intake, were significantly increased by maternal smoking. These results were the same in hematoxylin & eosin staining and metabolic dysfunction-associated fatty liver disease (MAFLD) activity score results. Maternal smoking significantly elevated the expression of pro-inflammatory factors, fibrotic factors, and fatty acid biosynthetic factors, which were increased in MASH condition. **Conclusion:** *In utero* MSCS exposure worsened APAP-induced ALI and MCDHF diet-induced MASH in offspring. This indicates that smoking during pregnancy can have a significant impact not only on the maternal organs that are directly exposed, but also on the liver health of the fetus afterwards.

Disclosures: Daram Yang: Nothing to Disclose, Hyuneui Jeong: Nothing to Disclose, Jong-Hoon Kim: Nothing to Disclose, Bumseok Kim: Nothing to Disclose

2479 | DECODING ACETAMINOPHEN RISKS: A U.S. INPATIENT DATA COMPARISON OF ACETAMINOPHEN TOXICITY IN PATIENTS WITH ALCOHOLIC AND WITHOUT ALCOHOLIC LIVER DISEASE

Raj Patel[1] Charmy Parikh[2] Sneh Sonaiya[3]

[1]St Mary Medical Center, PA, USA, [2]Mercy Catholic Medical Center, PA, USA, [3]University of Nevada- Las Vegas, USA

Background: Acetaminophen (APAP) stands as a widely utilized analgesic and antipyretic agent globally. APAP toxicity accounts for over 30,000 hospitalizations per year in the United States. While generally deemed safe and efficacious within recommended dosage ranges, its narrow therapeutic window renders overdoses notably hepatotoxic. In this study, we aim to investigate healthcare outcomes associated with acetaminophen toxicity in patients with alcoholic liver disease compared to those without alcoholic liver disease. **Methods:** Our retrospective analysis, based on the National Inpatient Sample (NIS) database, aimed to compare the outcomes of acetaminophen toxicity in two groups: patients with alcoholic liver disease (ALD) and those without alcoholic liver disease, spanning from 2016 to 2020. We prioritized examining in-hospital mortality rates, length of hospital stays, and treatment costs as our primary outcomes. Furthermore, we investigated various secondary outcomes to provide a comprehensive understanding of the topic. **Results:** 4310 patients with APAP toxicity along with ALD and 4310 patients with APAP toxicity without ALD were analyzed following propensity score matching. APAP toxicity in patients with ALD was associated with higher all-cause mortality compared to patients without ALD

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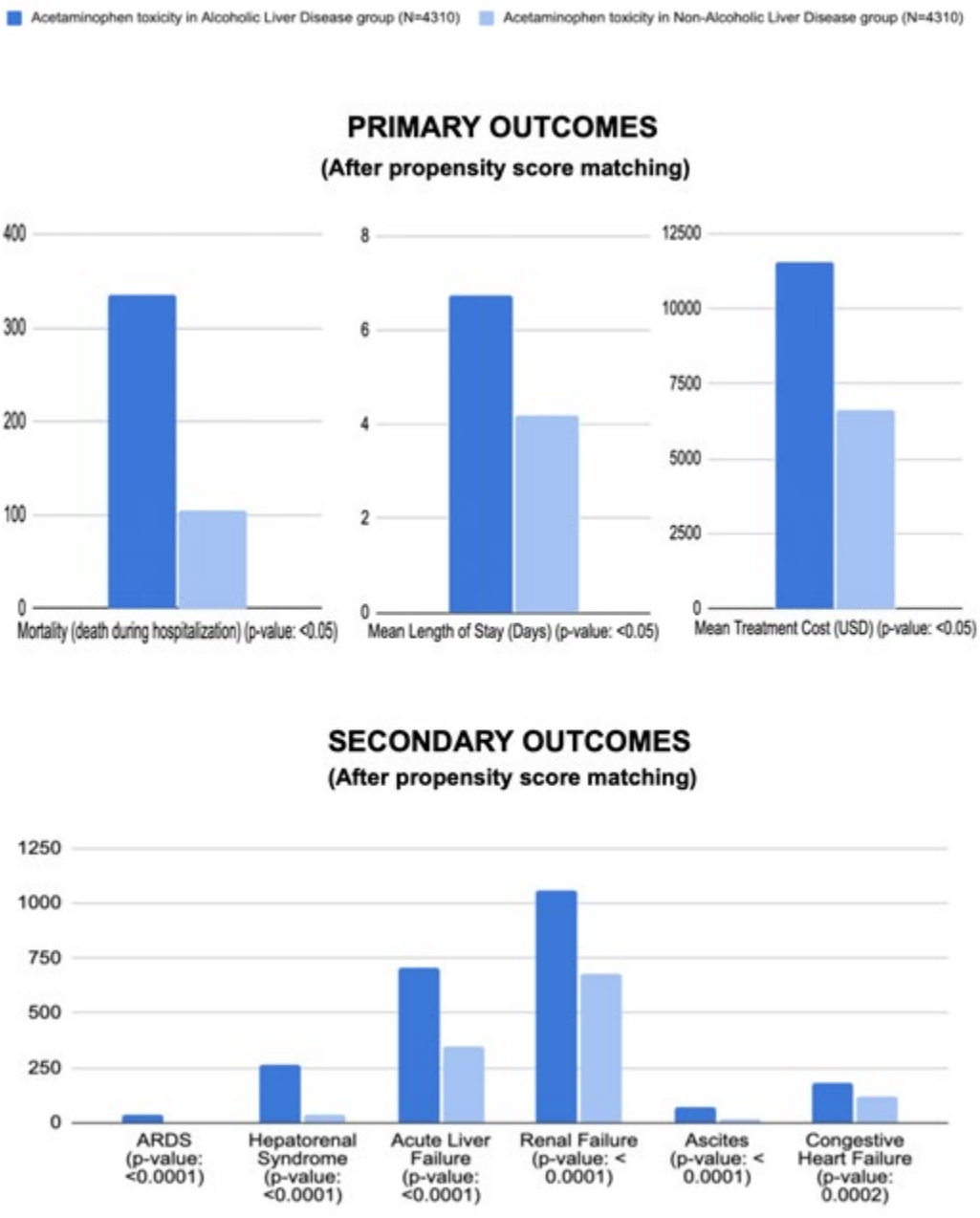
(OR: 3.37, 95% CI: 1.83-6.21, p<0.0001). APAP toxicity in the ALD group is also associated with a higher mean length of stay and overall treatment costs compared to those with APAP toxicity but without ALD (6.75 days vs 4.19 days, p<0.05; $11,553 vs $6,638, p<0.05) (Fig 1). In terms of secondary outcomes, APAP toxicity in the ALD group was associated with a higher incidence of hepatorenal syndrome (6.15% vs 0.81%, p<0.05), acute liver failure (16.4% vs 8%, p<0.05), and renal failure (24.6% vs 15.8%, p<0.05) in comparison to the population without ALD. **Conclusion:** The results indicate significantly high all-cause mortality, increased length of stay, and higher overall treatment costs in patients with APAP toxicity with ALD compared to patients without ALD. APAP toxicity in patients with ALD is also associated with a higher incidence of acute respiratory distress syndrome, hepatorenal syndrome, acute liver failure, heart failure, and renal failure. This finding underscores the intricate interplay between APAP, alcohol-related liver dysfunction, and clinical prognosis. To improve the prognosis and clinical outcomes for patients with APAP toxicity with ALD, interdisciplinary collaboration, targeted preventative measures, and evidence-based early intervention are essential.



Disclosures: Raj Patel: Nothing to Disclose, Charmy Parikh: Nothing to Disclose, Sneh Sonaiya: Nothing to Disclose

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2481 | AGING PROMOTES LIVER INJURY: STUDIES ON C57BL/6 MICE

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[1]University of Nebraska Medical Center, [2]Department of Veterans Affairs, Veterans Affairs Nebraska-Western Iowa Health Care System

Background: Many extrahepatic factors determine the liver disease phenotype and outcome. Among these, aging is a predominant risk factor for the development of advanced chronic liver diseases of various etiologies. Emerging evidence indicates that advanced age alters liver anatomy and physiology and also causes dysfunction in many other organs including the gut that can increase the pro-inflammatory environment of the liver. Since the global population is aging and is predicted to double by 2050, this study was undertaken to establish a baseline of liver injury parameters in the young and old mice. **Methods:** Young (8-10 weeks old) and aged (20-22 months old) C57Bl/6 mice, purchased from the Charles River Laboratories (Wilmington, MA, USA), were housed in an AAALAC-accredited Animal Research Facility at the Omaha VA Medical Center. Metabolic phenotyping was done using the Sable Systems Promethion system. The animals were euthanized, and the serum and liver collected for subsequent analyses. **Results:** Aged mice exhibited higher body weight compared to their younger counterparts despite aged mice exhibiting higher energy expenditure. Aged mice of both sexes showed higher hepatic triglycerides, lipid peroxidation and lower lysosomal acid lipase activities compared to their younger counterparts. However, only aged females exhibited lower hepatic S-adenosylmethionine levels, methylation potential, trypsin-like proteasome and lysosomal cathepsin B & cathepsin L activities compared to young female mice. Increased hepatic expression of chemokine (C-C motif) ligand 2 and chemokine (C-X-C motif) ligand 2 in aged female mice was associated with a lower liver methylation potential. Age did not affect serum AST or ALT levels nor had any effect on hepatic activities of alcohol metabolizing enzymes or the liver's ability to utilize betaine in aged mice of either sex compared with their younger counterparts. **Conclusion:** Chow-fed aged mice of both sexes exhibited some parameters of liver injury compared to their younger counterparts. However, more severe liver injury was seen in aged female mice. The data from this study will be used as a baseline to determine the effect of alcohol on gut-liver axis in aged versus younger mice.

Disclosures: Sathish kumar Perumal: Nothing to Disclose, Ramachandran Rajamanickam: Nothing to Disclose, Poonam Sagar: Nothing to Disclose, Natalia Osna: Nothing to Disclose, Karuna Rasineni: Nothing to Disclose, Kusum Kharbanda: Nothing to Disclose

2482 | NILOTINIB INDUCED HEPATOTOXICITY WITH DECADE LONG LATENCY AND NEWLY DISCOVERED PANCREATIC HEAD MASS

Jason John[1] Neethi Dasu[2] Lucy Joo[1] Brian Blair[1] C. Jonathan Foster[1] Matthew Everwine[1]

[1]Jefferson Health NJ, [2]Beth Israel Lahey Health,

Background: Nilotinib is a tyrosine kinase inhibitor used primarily in the treatment of chronic myeloid leukemia. While there are studies that associate Nilotinib with liver injury, the severity to which this can happen and the timeframe of onset are still largely uninvestigated. Here we present a case of a 76 year old female with Chronic Myeloid Leukemia on Nilotinib therapy for 10 years who presented with newly developed drug induced liver injury and pancreatic head mass. **Methods:** A 76 year old female with past medical history of Schatzki's ring and chronic myeloid leukemia on Nilotinib for 10 years presented with several months of postprandial abdominal pain and bloating. Initial laboratory exams were notable for Total Bilirubin of 11.4, Direct Bilirubin of 7.2, Alkaline Phosphatase of 1209, AST of 668 and ALT 561. Transaminases were noted to be within normal limits the previous year. Ultrasound abdomen was performed which was remarkable for cholelithiasis. MRCP subsequently performed which showed possible pancreatic head mass. She then underwent Endoscopic ultrasound-guided fine-needle aspiration of the pancreatic mass which was negative for malignancy. This was followed by a liver biopsy in which the pathology demonstrated hepatocellular cholestasis with accompanying feathery degeneration of hepatocytes, bile duct damage and inflammation consistent with drug induced liver injury. Hematology/Oncology was consulted who also concurred that Nilotinib was the culprit agent and thus was discontinued. She was started on IV Solumedrol 20mg q12hrs with marked improvement in her transaminases within one week. **Results:** Nilotonib does have an association with elevated transaminases, however only 4-9% of cases have a

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rise greater than 5x ULN. In our case, not only were transaminases markedly elevated but there was significant direct hyperbilirubinemia, which is also uncommon given most cases cause indirect hyperbilirubinemia due to underlying Gilbert's disease. The decade-long latency period is also extremely rare as most cases of DILI usually manifest within 6 months after initial drug exposure. Additionally, having a concurrent new pancreatic head mass is also unique as one would expect the obstructive nature of the pancreatic mass would be a more likely cause of elevated liver enzymes and than DILI from a decade long drug exposure. Further research is warranted to further investigate the hepatotoxic effects of Nilotinib and potential extra-hepatic complications including development of non malignant pancreatic tumors. **Conclusion:** In conclusion, further research is warranted to further investigate the hepatotoxic effects of Nilotinib and potential extra-hepatic complications including development of non malignant pancreatic tumors.

Disclosures: Jason John: Nothing to Disclose, Neethi Dasu: Nothing to Disclose, Lucy Joo: Nothing to Disclose, Brian Blair: Nothing to Disclose, C. Jonathan Foster: Nothing to Disclose, Matthew Everwine: Nothing to Disclose

2483 | FRONTAL EEG MONITORING REDUCES ANESTHESIA REQUIREMENT DURING LIVER TRANSPLANTATION

Gabriel Rice[1] *Nicholas Douville*[1] *Sathish Kumar*[1] *Patricia Bloom*[1]

[1]*University of Michigan*

Background: Minimizing anesthesia during liver transplant may improve postoperative outcomes like time to extubation, post-operative delirium, and hospital length of stay. Intraoperative frontal electroencephalogram (fEEG) is a novel tool for monitoring sedation depth and has the potential to reduce anesthetic requirements. **Methods:** We conducted a single-center retrospective cohort study to evaluate the association between fEEG and anesthetic requirement in liver transplant. Patients undergoing their first liver-alone transplant for chronic liver disease from 2021-2023 were included. Patients were categorized by utilization of fEEG: monitored and non-monitored. Use of Masimo SedLine®, a commercially available fEEG, was left to the discretion of the anesthesiologist. Minimal alveolar concentration (MAC), the partial pressure of exhaled anesthetic, is universally used by anesthesiologists to titrate anesthetic dosing. MAC is charted throughout the operation and mean MAC was used as a measure of anesthetic requirement. Patients either received isoflurane or sevoflurane inhaled anesthetics with occasional propofol or midazolam supplementation. A regression model was used to compare the mean MAC between the monitored and non-monitored patients while controlling for potentially confounding variables of operation duration, MELD, age, and sex. We serially added other possible confounders including propofol, midazolam, and donor type (brain death, cardiac death, or living donor) to the model. **Results:** Overall, 32 monitored and 141 non-monitored patients were evaluated. Monitored and non-monitored patients were similar in age (58 vs 55, P = 0.26), proportion male (59% vs 61%, P = 0.99), MELD at transplant (20 vs 18, P = 0.49), and proportion of each donor type (P = 0.21). Use of fEEG was associated with lower mean MAC while controlling for operation duration, MELD, age, and sex (Beta: -0.07, P = 0.002). MAC was 8% lower in monitored patients than non-monitored patients. In a sensitivity analysis, we added supplemental propofol and midazolam to the above model, and use of fEEG continued to be associated with lower mean MAC (Beta with propofol: -0.07, P = 0.002; Beta with midazolam: -0.06, P = 0.003). A lower mean MAC in monitored patients was also observed when controlling for donor type (Beta: -0.07, P = 0.002). This association was maintained when analyzing only patients receiving sevoflurane (Beta: -0.11, P = 0.02) and only patients receiving isoflurane (Beta: -0.17, P < 0.001). There were no reports of intraoperative awareness or waking in either group. **Conclusion:** Use of fEEG during liver transplant was associated with lower anesthetic requirement while maintaining adequate sedation. Previous research shows that anesthetic reduction is associated with improved time to extubation and post-operative delirium. fEEG is a novel tool to improve the clinical course and prognosis of liver transplant recipients.

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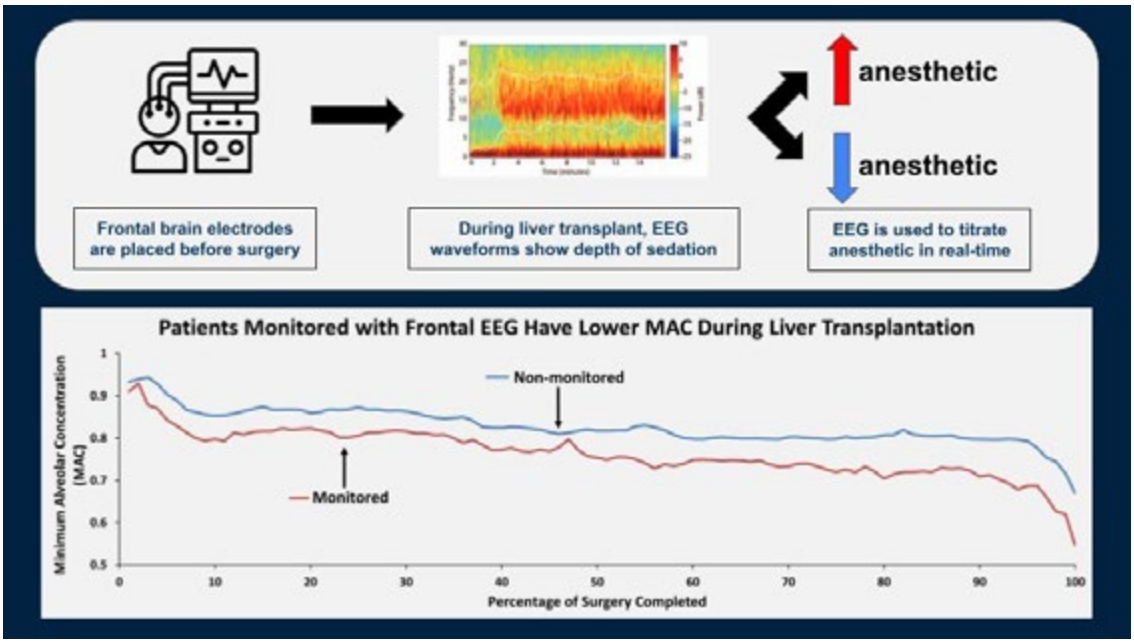

Disclosures: Gabriel Rice: Nothing to Disclose, Nicholas Douville: Nothing to Disclose, Sathish Kumar: Nothing to Disclose, Patricia Bloom: Vedanta Biosciences: Research grant, Nexilico: Consultant

2484 | COMPREHENSIVE DEEP LEARNING-BASED ASSESSMENT OF LIVING LIVER DONOR CT ANGIOGRAPHY: FROM VASCULAR SEGMENTATION TO VOLUMETRIC ANALYSIS

Jinsoo Rhu[1]

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Background: Precise preoperative assessment of liver vasculature and volume in living donor liver transplantation is essential for donor safety and recipient surgery. Traditional manual segmentation **Methods:** are being supplemented by deep learning (DL) models, which may offer more consistent and efficient volumetric evaluations. **Methods:** This study analyzed living liver donors from Samsung Medical Center using preoperative CT angiography data between April 2022 and February 2023. A DL-based 3D residual U-Net model was developed and trained on segmented CT images to calculate the liver volume and segment vasculature, with its performance compared to traditional manual segmentation by surgeons and actual graft weight. **Results:** The DL model achieved high concordance with manual methods, exhibiting Dice Similarity Coefficients of 0.94±0.01 for the right lobe and 0.91±0.02 for the left lobe. The liver volume estimates by DL model closely matched those of surgeons, with a mean discrepancy of 9.18 ml, and correlated more strongly with actual graft weights (R-squared value of 0.76 compared to 0.68 for surgeons). **Conclusion:** The DL model demonstrates potential as a reliable tool for enhancing preoperative planning in liver transplantation, offering consistency and efficiency in volumetric assessment. Further validation is required to establish its generalizability across various clinical settings and imaging protocols.

Disclosures: Jinsoo Rhu: Nothing to Disclose

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2485 | THE IMPACT OF ARRHYTHMIAS: OUTCOMES OF PATIENTS WITH LIVER TRANSPLANTATION AND ATRIAL FIBRILLATION

Jason John[1] Brian Blair[1] Lucy Joo[1] Neethi Dasu[2] Christopher Chhoun[1]

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Background: Atrial fibrillation (AF) is the most common arrhythmia in the population. However, there are limited studies that examine the outcomes of patients with AF and those who undergo liver transplants. Furthermore, no studies have shown the baseline characteristics for patients with AF and liver transplant versus those that have undergone a liver transplant without any episodes of AF. Our study aims to study this patient group. This study aimed to evaluate the economic burden and various hospital outcomes associated with patients with liver transplants with and without AF. **Methods:** Patients aged 18 years with liver transplant and AF versus liver transplant alone were identified from the US Nationwide Inpatient Sample (NIS), from the years 2015-2020, and various parameters were analyzed using propensity matching using the Kernel Method. ICD 9 and 10 codes were utilized and multivariate regression analysis was used to estimate the odds ratios of in-hospital mortality, the average length of hospital stay (LOS), and hospital charges (TOTHC), after adjusting for confounders. Weighted analysis utilizing Stata 17 MP was performed. Baseline characteristics are listed in Table 1. Those with liver transplant and AF had increased mortality (OR: 1.84, p<0.002, 1.25-2.72), LOS (+2.17 days, p< 0.0001, 1.74-2.60), and TOTHC ($13,212, p<0.005, CI: 3,972-22,452) compared to those with liver transplant without AF. Positive predictors of mortality were acute kidney injury (AKI), sepsis, and thrombocytopenia. Positive predictors of LOS and TOTHC were AKI and sepsis (Table 2). **Results:** Baseline characteristics are listed in Table 1. Those with liver transplant and AF had increased mortality (OR: 1.84, p<0.002, 1.25-2.72), LOS (+2.17 days, p< 0.0001, 1.74-2.60), and TOTHC ($13,212, p<0.005, CI: 3,972-22,452) compared to those with liver transplant without AF. Positive predictors of mortality were acute kidney injury (AKI), sepsis, and thrombocytopenia. AKI and sepsis were positive predictors of LOS and TOTHC (Table 2). **Conclusion:** Our study revealed that patients with a history of liver transplant and AF had increased mortality, LOS, and TOTHC were increased compared to patients with liver transplant only. Previous studies have demonstrated that cardiovascular insults are a leading cause of mortality for patients who have undergone liver transplantation. The results of this study show that close monitoring must be performed for the development of atrial fibrillation and perhaps more aggressive management to return patients to normal sinus rhythm. Randomized trials will be needed to develop a management strategy for this patient population.

Table 1: Baseline Characteristics

	Liver Transplant and Atrial Fibrillation (AF)	Liver Transplant Only
Number of Patients	1,466	9,501
Average Age	67.7	57.4
Females	33.2%	39.8%
White	79.5%	68.5%
Black	5.1%	8.5%
Hispanic	9.8%	14.5%

Table 2: Risk factors associated with Increased Mortality, Length of Stay (LOS), and Hospital Charges (TOTHC) in Liver Transplant Patients and AF

Increased Mortality	Increased LOS	Increased TOTHC
AKI (OR: 2.44, p=0.000, CI: 1.74- 3.42) Sepsis (OR: 4.88, p=0.000, CI: 3.43- 6.81) Thrombocytopenia (OR: 1.56, p=0.058, CI: .99- 2.47)	AKI (+2.44 p=0.000, CI: 2.20- 3.01) Sepsis (+3.52, p=0.000, CI: 2.70 - 4.35)	AKI ($30773.06,p=0.000, CI: $23462.24- $38083.88) Sepsis ($59481.24, p=0.000, CI: $42864.60 -$76097.88)

Disclosures: Jason John: Nothing to Disclose, Brian Blair: Nothing to Disclose, Lucy Joo: Nothing to Disclose, Neethi Dasu: Nothing to Disclose, Christopher Chhoun: Nothing to Disclose

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2486 | THE CLASSIFICATION OF PORTAL VEIN THROMBOSIS AND A TACTICAL ALGORITHM BASED ON IT ★

Boris Yaremin[1] Ekaterina Anosova[2] Bakhtiyar Kazymov[2] Kyamran Alekberov[2] Alexandra Kuznetsova[3] Murad Novruzbekov[2]

[1]Sklifosovsky Emergency Medicine Institut, [2]Sklifosovsky Emergency Medicine Institute, [3]Ryazan State Medical University

Background: Portal vein thromboses remain a significant problem in liver transplantation. The wide variation in the frequency and severity of thromboses in waiting lists across different institutions is partly due to some centers being hesitant to include such patients in their waiting lists. In our center, these patients make up 17.4%, with the frequency of portal vein thrombosis changing over time, from 4% in the first year to 38.7% in the tenth year after the manifestation of decompensated cirrhosis. Despite routine CT scans for patients on the waiting list, up to 38% of portal vein thromboses worldwide are discovered intraoperatively. **Methods:** The study include patients at the Sklifosovsky Emergency Medicine Institute's liver transplantation center that underwent transplantation between 2008 and 2024. The total observation included 1167 patients, with 980 patients without portal vein thrombosis and 187 patients with thrombosis. To more accurately determine the extent of portal vein thrombosis, our MLTR classification system shown at the figure used. To ensure objectivity, we used computational hemodynamics calculations to select the optimal reconstruction method. **Results:** Patients were divided into two groups: those before the implementation of the new approach and those after. Both groups included various methods of portal vein reconstruction: eversion thrombo-endovenectomy with standart reconstruction, gastric vein with portal anastomosis, pericholedocheal varix – portal anastomosis, upper mesenteric vein - portal jump graft, renoportal anastomosis, porto-caval and spleno-portal anastomosis. As a result, based on the developed classification and simulation data, it was possible to develop a portal vein reconstruction strategy, presented in the figure. For each variant of thrombosis, as shown at the figure, the corresponding tactical reconstruction option was chosen, presented on the right. The proposed strategy was implemented in 65 patients with thromboses, with a comparison group of 122 people. As a result, the rate of early postoperative deaths was reduced from 16.4% to 7.7%. The frequency of re-thromboses was reduced from 3.3% to 1.5%. The duration of the operation was reduced from 506.00 [420; 600]* minutes to 404.00 [360; 477]* minutes, and the volume of blood loss was reduced from 2121.31 [1800; 2300]* to 1336.29 [1100; 1500]*, cold sichemia time from 418,11 [380; 440]* to 370,89 [340; 390]* minutes. **Conclusion:** Optimization of portal reconstruction technique during liver transplantation allows for improved clinical outcomes and increased accessibility of transplantation services to patients.The developed MLTR classification and strategy enable improved survival after liver transplantation, reduced blood loss, shorter operative time, and reduced transplant ischemia.



Disclosures: Boris Yaremin: Nothing to Disclose, Ekaterina Anosova: Nothing to Disclose, Bakhtiyar Kazymov: Nothing to Disclose, Kyamran Alekberov: Nothing to Disclose, Alexandra Kuznetsova: Nothing to Disclose, Murad Novruzbekov: Nothing to Disclose

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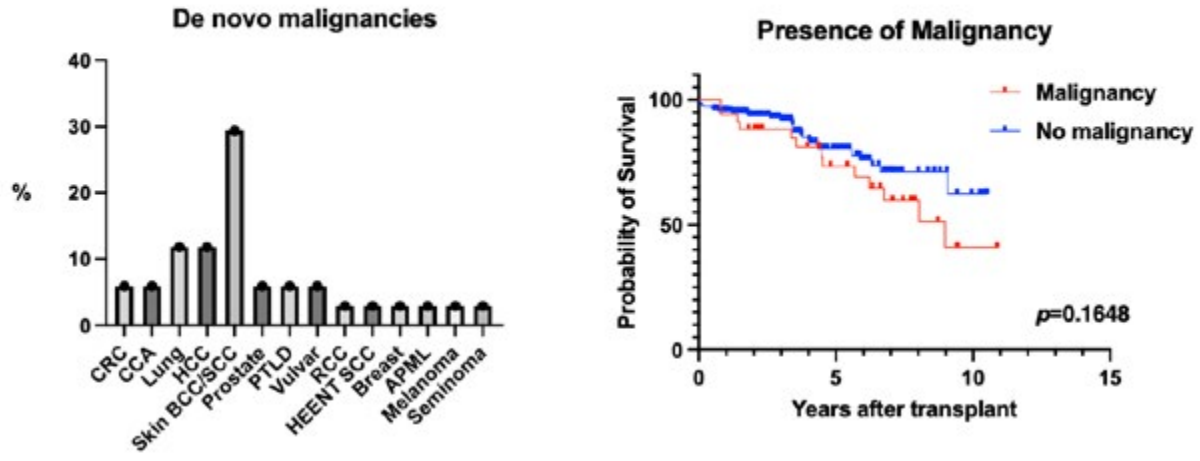
2487 | RISK FACTORS AND SURVIVAL IN PATIENTS WITH DE NOVO MALIGNANCIES FOLLOWING LIVER TRANSPLANTATION ALONE OR SIMULTANEOUS LIVER-KIDNEY TRANSPLANTATION

Nazli Begum Ozturk[1] Ahmed Aref[1] Usman Bin Hameed[1] Ewelina Niedzialkowska[1] Tatjana Blazin[1] Laith Jamil[1]

[1]Beaumont Hospital, Royal Oak

Background: Long-term immunosuppression increases the risk of de novo malignancies (DNM), and DNMs are one of the major causes of death in transplant recipients. We aimed to assess the patient characteristics and post-transplant mortality in patients undergoing liver transplantation alone (LTA) or simultaneous liver-kidney transplantation (SLK). **Methods:** An analysis was conducted on all adult patients who underwent to LTA or SLK at our center between 2013-2023. The primary outcomes were the development of a DNM and survival rates. Categorical variables are reported as numbers and %, and continuous variables are reported as means and ± or median with interquartile range. Kaplan-Meier curves for survival analysis. Statistical significance was defined as $p<0.05$. **Results:** Out of 239 transplant recipients, a total of 34 (14.2%) patients developed DNM. The most common malignancies were skin basal cell carcinoma and squamous cell carcinoma (29.4%), followed by hepatocellular carcinoma (11.8%), lung cancer (11.8%), cholangiocarcinoma (5.9%), colorectal cancer (5.9%), post-transplant lymphoproliferative disorder (PTLD) (5.9%), prostate cancer (5.9%), and vulvar carcinoma (5.9%) (Figure 1). In patients with DNM, the malignancy was diagnosed at a median of 1121 (425-1771) days after transplant. The majority of patient characteristics, post-op complications and length of stay were similar in both groups, except for inflammatory bowel disease (14.7% vs 4.9%, $p=0.02$) and post-LT portal vein thrombosis (14.7% vs 3.4%, $p=0.005$), which were significantly more common in patients with DNM compared to those without. Death rate was significantly higher in patients with DNM (38.2%) compared to those without (15.1%) during the follow-up period ($p=0.001$); however, there was no significant difference in post-transplant survival ($p=0.16$). Overall, the 1-year survival rate was 94.1% in DNM group vs 95.5% in no DNM, 3-year survival rate 84.7% in DNM group vs 92.0% in no DNM, and 5-year survival rate 73.4% in DNM group vs 80.6% in no DNM. There was no significant difference in the development of post-transplant de DNM in patients who underwent SLK (21.3%) vs LTA (11.8%), $p=0.06$, and no significant differences was present in the duration of DNM development after transplantation (1629 ±1353 vs 1287 ±986 days, $p=0.39$) in the SLK and LTA groups, respectively. **Conclusion:** DNMs are important causes of mortality in transplant recipients. Consistent with prior studies, non-melanoma skin cancer was the most common DNM, comprising approximately 30% of all malignancies in our cohort, and interestingly followed by HCC and lung cancer rather than PTLD. Although mortality rates were significantly higher in patients with DNM, the duration of time-to-death or censoring remained comparable in both groups. This finding may be attributed to the relatively high rate of skin cancers in our cohort, as these typically do not affect overall post-transplant survival.

Figure 1.



Disclosures: Nazli Begum Ozturk: Nothing to Disclose, Ahmed Aref: Nothing to Disclose, Usman Bin Hameed: Nothing to Disclose, Ewelina Niedzialkowska: Nothing to Disclose, Tatjana Blazin: Nothing to Disclose, Laith Jamil: Nothing to Disclose

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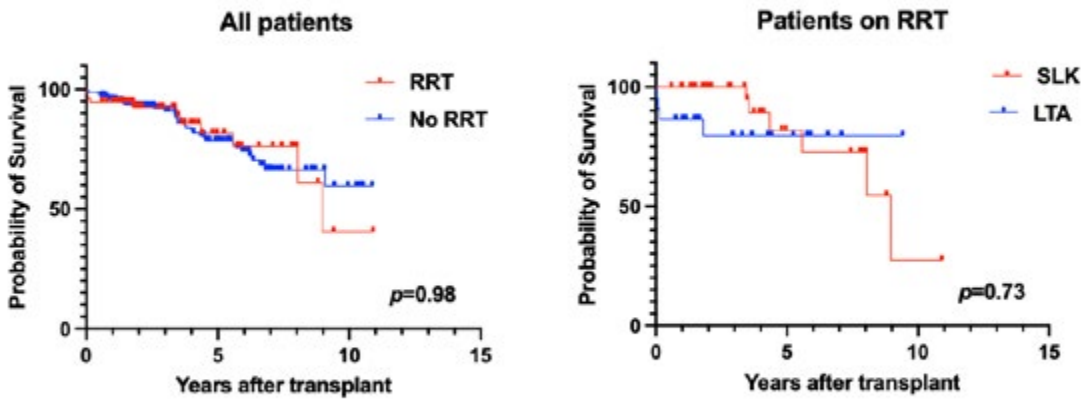
2488 | OUTCOMES OF SIMULTANEOUS LIVER-KIDNEY TRANSPLANTATION VS LIVER TRANSPLANTATION ALONE IN PATIENTS WITH CIRRHOSIS REQUIRING RENAL REPLACEMENT THERAPY

Nazli Begum Ozturk[1] *Usman Bin Hameed*[1] *Ahmed Aref*[1] *Ewelina Niedzialkowska*[1] *Tatjana Blazin*[1] *Laith Jamil*[1]

[1]*Beaumont Hospital, Royal Oak*

Background: Simultaneous liver-kidney transplantation (SLK) has shown to offer superior graft and patient survival in patients with longstanding chronic kidney disease or those on long-term renal replacement therapy (RRT). However, controversies remain for predicting renal recovery and outcomes following liver transplantation alone (LTA) in patients with with concomitant kidney dysfunction. We aimed to compare the characteristics and outcomes of patients on RRT who underwent SLK compared to LTA. **Methods:** A retrospective analysis was done for all adult patients who underwent LTA or SLK at our center between 2013-2023. Patients on RRT prior to transplantation were identified. The primary outcome was post-transplant mortality. Categorical variables are reported as numbers (%), continuous variables are reported as means ±standard deviation or median (interquartile range). Kaplan-Meier curves were used for survival analysis. Statistical significance was defined as $p<0.05$. **Results:** A total of 239 patients received LTA or SLK. Of those, 57 (23.8%) patients were on RRT while on the waitlist, and 61.4% underwent SLK and 38.6% LTA. Patients on RRT had shorter waitlist time [17 (4.0-110) vs 128 (14-266) days, $p=0.003$], higher MELD score [36 (30-40) vs 24 (17-30), $p=0.0001$], more commonly had ascites (96.5% vs 79.7%, $p=0.002$) and hepatic encephalopathy (82.5% vs 64.3%, $p=0.01$) compared to patients not on RRT, and had longer post-transplant ICU [13 (6.0-24) vs 5.0 (3.0-8.0) days, $p=0.0001$] and hospital [22 (12-41) vs 11 (8-17) days, $p=0.0001$] length of stay. There were no statistically significant differences for age, gender, MELD score, the presence of ascites, esophageal varices or hepatic encephalopathy in patients who underwent SLK vs LTA. Post-transplant ICU and hospital length of stay, post-transplant infections within the first 6 months, and rates of portal vein thrombosis were similar in both SLK and LTA groups. Post-transplant malignancy was more common in the SLK group compared to LTA (28.6% vs 4.5%, $p=0.02$). Death rates (17.1% vs 18.2%, $p=0.9$) and post-transplant survival were similar in both groups, but the duration to death was longer in patients with SLK compared to LTA (2066 ±861 vs 185 ±314 days, $p=0.003$). Overall, 1-year survival rate was 100% in SLK vs 86.3% in LTA, 3-year survival rate 100% in SLK vs 79.2% in LTA, and 5-year survival rate 81.7% in SLK vs 79.2% in LTA. **Conclusion:** The rising incidence of metabolic dysfunction is expected to increase the number patients on RRT in the US. In our cohort, among patients on RRT on the waitlist, there was no difference in post-transplant survival, ICU or hospital length of stay in patients who underwent SLK or LTA. Post-transplant malignancy was significantly more common in the SLK group compared to LTA, however no statistically significant survival difference was seen. Transplant centers should carefully weigh when to perform LTA when patients have concomitant kidney dysfunction.

Figure 1.



Abbreviations: LTA: liver transplantation alone; RRT, renal replacement therapy; SLK, simultaneous liver-kidney

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Disclosures: Nazli Begum Ozturk: Nothing to Disclose, Usman Bin Hameed: Nothing to Disclose, Ahmed Aref: Nothing to Disclose, Ewelina Niedzialkowska: Nothing to Disclose, Tatjana Blazin: Nothing to Disclose, Laith Jamil: Nothing to Disclose

2489 | CYSTATIN C VS. CREATININE: WHO WINS IN CIRRHOSIS?

Alexandra Fiedler[1] *Kaeli Samson*[1] *Brian Benes*[1] *Prasanth Ravipati*[1] *Faruq Pradhan*[1]

[1]*University of Nebraska Medical Center*

Background: Renal dysfunction and sarcopenia are common in cirrhosis. Currently, serum creatinine (SCr) is included in the Model for end-stage liver disease (MELD) 3.0 score used in liver transplant allocation and simultaneous liver-kidney transplant eligibility. However, cystatin C (CysC) may be a better marker of renal dysfunction in cirrhosis as it is unaffected by muscle mass, age, gender, or jaundice, but this remains largely understudied. Our objective is to evaluate the effectiveness of pre-transplant CysC compared to SCr at predicting renal outcomes post-liver transplantation. **Methods:** A single-center retrospective study of 59 patients who underwent isolated liver transplantation between 12/1/2022 and 11/1/2023 was performed. The primary endpoint was a composite outcome entitled 'adverse renal outcome,' defined by the need for dialysis or a doubling of baseline SCr within 6 months post-transplant. We also assessed the difference between SCr and CysC based on frailty. Differences in variables between the two time periods were assessed using Fisher's exact and Wilcoxon rank sum tests. **Results:** Most patients were middle-aged Caucasian men with alcohol-related cirrhosis, with an average MELD 3.0 score of 24.9. Table 1 shows no significant difference in rates of adverse renal outcomes based on pre-transplant estimated glomerular filtration rates (eGFR) determined from SCr (p = 0.89) or CysC eGFR (p = 0.73). The median SCr eGFR for those with an adverse renal outcome was 60.4 (IQR = 56.5, 80.7), while the median CysC eGFR was 43.5 (IQR = 34.6, 66.8). There was no difference in adverse renal outcomes based on the presence of hematuria, proteinuria, diabetes, or hypertension. Frailty was associated with lower median SCr eGFR (frail = 60.6, non-frail = 88.0; p = 0.06) and CysC eGFR (frail = 45.4, non-frail = 77.9; p = 0.02). **Conclusion:** We found no significant difference between SCr and CysC eGFR in predicting adverse renal outcomes post-transplant despite a large difference in median eGFR (16.9 mL/min). Factors known to contribute to kidney disease (i.e. diabetes or hypertension) were not associated with these outcomes. Despite theoretical advantages of CysC, it did not outperform SCr in this setting; however, only four patients had post-transplant renal complications in our sample. Further research with larger sample sizes is needed to determine if CysC should be used in clinical practice to assess renal function in liver transplant patients.

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Table 1. Renal Outcome Within 6 Months Following Liver Transplantation

	Adverse Renal Outcome* (n=4)	Positive Renal Outcome (n=55)	P-value
SCr eGFR at T0			0.89[1]
Median (IQR)	60.4 (56.5, 80.7)	69.5 (42.8, 99.7)	
CysC eGFR at T0			0.73[1]
Median (IQR)	43.5 (34.6, 66.8)	55.0 (35.2, 84.0)	
SCr eGFR – CysC eGFR at T0			0.29[1]
Median (IQR)	15.5 (9.9, 25.8)	11.5 (4.0, 18.8)	
MELD 3.0			0.64[1]
Median (IQR)	29.3 (21.5, 32.7)	27.3 (18.0, 31.2)	
Hematuria, n (%)			0.57[2]
No	4 (8.7%)	42 (91.3%)	
Yes	0 (0.0%)	13 (100.0%)	
Proteinuria†, n (%)			0.57[2]
No	4 (8.7%)	42 (91.3%)	
Yes	0 (0.0%)	13 (100.0%)	
HTN, n (%)			1.00[2]
No	2 (6.7%)	28 (93.3%)	
Yes	2 (6.9%)	27 (93.1%)	
DM, n (%)			0.57[2]
No	4 (8.5%)	43 (91.5%)	
Yes	0 (0.0%)	12 (100.0%)	
A1c			1.00[1]
Median (IQR)	5.3 (4.9, 5.9)	5.4 (4.8, 5.8)	
n	3	51	

[1]Wilcoxon rank sum p-value; [2]Fisher Exact p-value
*Adverse renal outcome is defined by doubling of pre-transplant SCr or need for dialysis
†Assessment was based on macroscopic urinalysis only
SCr=Serum Creatinine; CysC= Cystatin C; eGFR=Estimated glomerular filtration rate in mL/min based on CKD-EPI equations for both SCr and CysC; HTN=Hypertension, DM=Diabetes mellitus; MELD=Model for end-stage liver disease

Disclosures: Alexandra Fiedler: Nothing to Disclose, Kaeli Samson: Nothing to Disclose, Brian Benes: Nothing to Disclose, Prasanth Ravipati: Nothing to Disclose, Faruq Pradhan: Nothing to Disclose

2490 | STREAMLINING NUTRITIONAL SUPPORT FOR INPATIENT CIRRHOSIS MANAGEMENT

Alexandra Fiedler[1] *Kaeli Samson*[1] *Faruq Pradhan*[1]

[1]*University of Nebraska Medical Center*

Background: Frailty is an important prognostic factor affecting outcomes in patients with cirrhosis. Malnutrition, a contributor towards frailty, can lead to disease progression and complications such as ascites and hepatic encephalopathy. As a quality improvement initiative, we surveyed internal medicine (IM) trainees and faculty to assess their knowledge of nutrition management in patients with cirrhosis. We also examined changes in prescribed diets after introducing a dedicated cirrhosis diet in the electronic medical record (EMR). **Methods:** A specialized cirrhosis diet, restricting salt intake (<2 grams/day) and emphasizing high protein/calorie intake was added to our EMR in September 2023. A pre-intervention and two post-intervention surveys (3 and 6 months later) were sent to IM trainees and hospitalists to assess their background nutritional knowledge of managing patients with cirrhosis. Diets selected for patients hospitalized with an admitting diagnosis related to cirrhosis at 0-3 months post-intervention (T1) and 3-6 months post-intervention (T2) were obtained from the EMR, as well as the length of stay, patient disposition, and the frequency of physical therapy (PT), occupation therapy (OT), and nutrition consultation. Differences in variables of interest between the two time periods were assessed using Chi-square, independent samples, and Wilcoxon rank sum tests. **Results:** Survey results at all time points

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showed that >80% of physicians correctly identified the recommended salt intake and < 20% correctly identified the recommended protein intake. Demographics (age, gender, race, and ethnicity) were comparable between T1 and T2. As shown in Table 1, diet selection changed significantly (P < 0.001), with cirrhosis-specific diets increasing from 0.3% to 22.0% and general diets decreasing from 74.0% to 53.8%. The use of other specialized diets remained stable (T1 = 25.7%, T2 = 24.1%). There was no significant difference in length of hospital stay, discharge disposition, or consultation frequency (PT, OT, and nutrition) over the two periods, with nutrition consultation occurring < 10% of the time. **Conclusion:** Introducing a specialized cirrhosis diet showed promising changes in diet selection trends. Despite the increased use of the cirrhosis diet, there was no difference in ancillary service consultation or discharge disposition. Overall, this project highlights the need for heightened awareness of the importance of proper nutritional care in patients with cirrhosis.

Table 1. Diet Selections and Related Outcomes at 0-3 Months and 0-6 Months Post-Intervention

	0-3 Months Post-Intervention (n=292)	3-6 Months Post-Intervention (n=277)	P-value
INPATIENT DIET, n (%)			<0.001[1]
Cardiac	32 (11.0%)	27 (9.7%)	
Cirrhosis	1 (0.3%)	61 (22.0%)	
Diabetic/Renal/Other	8 (2.7%)	31 (11.2%)	
General	216 (74.0%)	149 (53.8%)	
Sodium or Protein Modified	35 (12.0%)	9 (3.2%)	
LENGTH OF STAY, days			0.42[3]
Median (IQR)	5.5 (3.0, 11.0)	5.0 (3.0, 10.0)	
LEVEL OF CARE AT DISCHARGE, n (%)			0.65[1]
Acute Care	10 (3.4%)	5 (1.8%)	
Community-based Care	3 (1.0%)	3 (1.1%)	
Deceased/Hospice	32 (11.0%)	22 (7.9%)	
Home	173 (59.2%)	171 (61.7%)	
Home with service	44 (15.1%)	42 (15.2%)	
Other	11 (3.8%)	9 (3.2%)	
Post-Acute Care	19 (6.5%)	25 (9.0%)	
NUTRITION CONSULTATION, n (%)			0.53[1]
No	265 (90.8%)	247 (89.2%)	
Yes	27 (9.2%)	30 (10.8%)	
OCCUPATIONAL THERAPY CONSULTATION, n (%)			0.63[1]
No	239 (81.8%)	231 (83.4%)	
Yes	53 (18.2%)	46 (16.6%)	
PHYSICAL THERAPY CONSULTATION, n (%)			0.60[1]
No	234 (80.1%)	217 (78.3%)	
Yes	58 (19.9%)	60 (21.7%)	

[1]Chi-Square p-value; [2]Equal variance two sample t-test; [3]Wilcoxon rank sum p-value

Disclosures: Alexandra Fiedler: Nothing to Disclose, Kaeli Samson: Nothing to Disclose, Faruq Pradhan: Nothing to Disclose

2491 | REPROGRAMMING OF BILE ACID METABOLISM ATTENUATES LIVER INFLAMMATION DURING ISCHEMIA/REPERFUSION INJURY

Kunpeng Huang[1] Jinxiang Zhang[2] Yunwei Zhang[2] Zhili Wen[1] Guoliang Wang[2] Jinglei Li[2] Wenming Pan[2]

[1]2nd Hospital of Nanchang University, [2]Wuhan union hospital

Background: Persistent cholestasis has been associated with poor prognosis after orthotopic liver transplantation (OLT). However, one study has shown that paradoxically, cholestasis can reduce tissue necrosis and inflammation severity in murine liver ischemia/reperfusion injury (IRI). In this study, we aimed to investigate how bile acid (BA) metabolism regulates hepatic inflammation in reperfusion injury. **Methods:** Ingenuity Pathway Analysis (IPA) was

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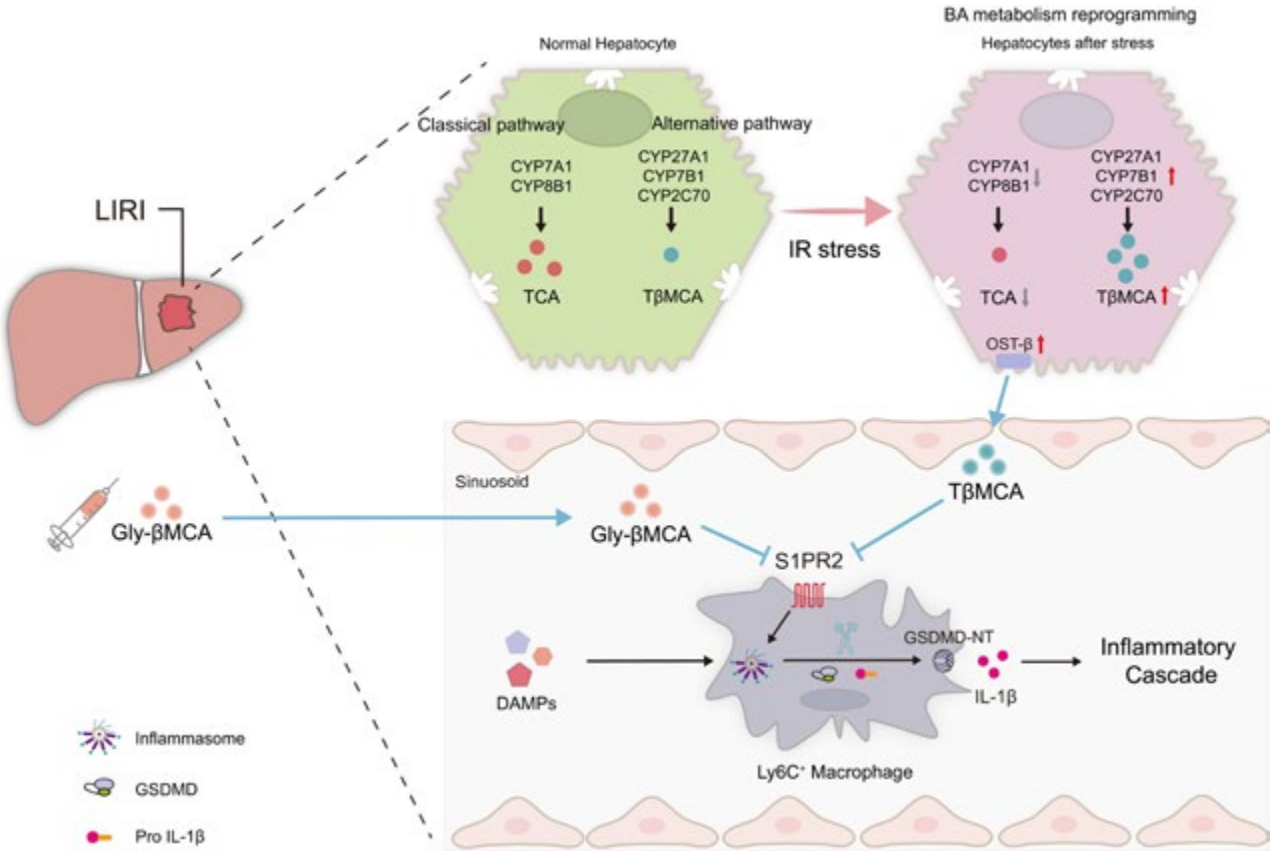
performed using transcriptome data from a murine hepatic IR model. Three different models of hepatic IR (liver warm IR, bile duct separation-IR, common bile duct ligation-IR) were employed. We generated AAV-transfected mice and CD11b-DTR mice to assess the role of BAs in regulating the myeloid S1PR2-GSDMD axis. Hepatic BA levels were analyzed using targeted metabolomics. Finally, the correlation between the reprogramming of BA metabolism and hepatic S1PR2 levels was validated through RNA-seq of human OLT biopsies. **Results:** We found that liver IR stress triggers reprogramming of BA metabolism, leading to increased synthesis of tauro-beta-muricholic acid (TβMCA), an alternative pathway product catalyzed by the enzyme CYP2C70. The levels of hepatic TβMCA were negatively correlated with the severity of hepatic inflammation, as indicated by the serum IL-1β levels. Inhibition of hepatic CYP2C70 resulted in reduced TβMCA production, which subsequently increased serum IL-1β levels and exacerbated IR injury. Moreover, our findings suggested that TβMCA could inhibit canonical inflammasome activation in macrophages and attenuate inflammatory responses in a myeloid-specific S1PR2-GSDMD-dependent manner. In contrast, taurocholic acid (TCA), a product of the classical BA synthesis pathway, activates the inflammasome at a concentration of 100 μM. We propose that conflicting **Results:** on BA-mediated inflammasome regulation in past studies stem from the lack of simultaneous assessment of cell death. Cell death-induced inhibition of inflammasomes might be misinterpreted as inhibition in living cells. Human OLT biopsies showed elevated hepatic *S1pr2* expression without systematic changes in BA synthase. This suggests a potential lack of regulatory mechanisms to repress S1PR2 during the human IR process. Additionally, Gly-βMCA, a derivative of TβMCA, could effectively attenuate inflammatory injury *in vivo* and inhibit human macrophage pyroptosis *in vitro*. **Conclusion:** IR stress orchestrates hepatic BA metabolism to generate TβMCA, which attenuates hepatic inflammatory injury by inhibiting the myeloid S1PR2-GSDMD axis. Our results highlight the crucial role of bile acids in regulating hepatocyte-immune cell crosstalk, which demonstrates an immunomodulatory function in liver reperfusion injury that may guide therapeutic strategies targeting bile acids and their receptors.



Disclosures: Kunpeng Huang: Nothing to Disclose, Jinxiang Zhang: Nothing to Disclose, Yunwei Zhang: Nothing to Disclose, Zhili Wen: Nothing to Disclose, Guoliang Wang: Nothing to Disclose, Jinglei Li: Nothing to Disclose, Wenming Pan: Nothing to Disclose

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2492 | FRAILTY IS ASSOCIATED WITH MULTIPLE NEGATIVE CLINICAL OUTCOMES IN PATIENTS REFERRED FOR LIVER TRANSPLANTATION

Heidi Johnston[1] Melita Andelkovic[2] Hannah Mayr[2] Tahnie Takefala[2] Yanyan Chen[3] Aaron Thrift[3] Ingrid Hickman[4] Graeme Macdonald[2]

[1]Princes Alexandra Hospital, [2]Princess Alexandra Hospital, [3]Baylor College of Medicine, [4]The University of Queensland

Background: Frailty is associated with mortality in patients referred for liver transplant (LT) but the impact on other clinical outcomes is less clear. We investigated the impact of frailty (liver frailty index, LFI) on likelihood of receiving a LT, unplanned hospitalizations and peri-LT ICU/hospital length of stay (LOS). **Methods:** Between May 2018-Sept. 2022, adults with cirrhosis referred for LT had their LFI determined at their initial dietitian appointment. Clinical outcomes included receiving a LT, waitlist mortality, pre-LT unplanned hospitalizations (excluding booked procedures like paracentesis), and peri-LT ICU/hospital LOS. Chi2/Mann-Whitney U tests, Kaplan-Meier, Cox proportional hazards model and competing risk analysis were performed to explore associations between LFI and clinical outcomes. **Results:** In 266 patients (75% male, median age 58 [IQR 50-63]; median MELD 16 [11-19]), the median LFI was 3.7 [3.3-4.1]. 19% of patients were robust, 68% pre-frail, and 14% frail. 144 (54%) patients received a LT. The LFI was significantly better in LT recipients (3.6 [3.3-4.0]) than in those not transplanted (3.8 [3.4-4.2], p=0.02, Table 1). Frail and pre-frail patients were less likely to receive a LT than robust patients (HR 0.63, 95% CI 0.5-0.9, p=0.04). After adjusting for confounders (age, sex, HCC presence, MELD), every 1-point increase in the LFI was associated with a 29% decrease in the likelihood of LT (HR 0.71, 95%CI 0.54-0.94, p=0.02). Competing risk analysis found that every 1-point increase in LFI was associated with a 90% increased risk of waitlist mortality (HR 1.90, 95% CI 1.3-2.7, p<0.001). This was not seen for other reasons for not progressing to LT. The risk of waitlist mortality was almost 5-fold higher for frail compared to robust patients (HR 4.92, 95% CI 1.8-13.5, p=0.002). LFI was significantly worse in patients with unplanned hospitalizations with every 1-point increase in the LFI associated with a 42% increased risk of unplanned hospitalization (HR 1.42, 95 % CI 1.1-1.9, p=0.02). At the time of LT, baseline LFI was associated with prolonged ICU LOS but not hospital LOS with a 1-point increase in the LFI associated with a 3.2-fold (95% CI 1.1-9.8, p=0.04) increased odds of having an ICU LOS >4days. **Conclusion:** In patients referred for LT, frailty increases the risk of not receiving a LT, waitlist mortality, pre-LT unplanned hospitalization and prolonged ICU LOS at the time of LT.

Table 1. Pre-transplant clinical outcomes by LFI and frailty categories

Total cohort n=266	Median LFI [IQR]	P value#	Robust n (%)	Pre-frail n (%)	Frail n (%)	P value#
Liver transplant (n=144)	3.6 [3.3-4.0]	0.02	33 (66)	97 (54)	14 (38)	0.03
Waitlist mortality (n=61)	3.9 [3.5-4.6]		6 (12)	39 (22)	16 (43)	
Left QLTS: Liver disease improved (n=29)	3.7 [3.3-4.2]		4 (14)	21 (12)	4 (8)	
Left QLTS: Other reasons* (n=32)	3.6 [3.3-3.9]		7 (8)	22 (12)	3 (11)	
Unplanned Admission (n=105)		<0.001				<0.001
Yes	3.9 [3.5-4.3]		9 (18)	75 (42)	21 (57)	
No	3.6 [3.2-3.9]		41(82)	104(58)	16 (43)	

LFI: Liver frailty index, QLTS: Queensland Liver Transplant Service, # Multivariable regression adjusting for age, sex, presence of HCC and MELD score, * other reasons: alcohol/drug recidivism; patient decision not to proceed; still undergoing evaluation at study end point.

Disclosures: Heidi Johnston: Nothing to Disclose, Melita Andelkovic: Nothing to Disclose, Hannah Mayr: Nothing to Disclose, Tahnie Takefala: Nothing to Disclose, Yanyan Chen: Nothing to Disclose, Aaron Thrift: Nothing to Disclose, Ingrid Hickman: Nothing to Disclose, Graeme Macdonald: Nothing to Disclose

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2493 | COMPARATIVE OUTCOMES OF TRANS-ARTERIAL CHEMOEMBOLIZATION AND RADIOEMBOLIZATION AS BRIDGING THERAPY FOR HEPATOCELLULAR CARCINOMA IN LIVER TRANSPLANT CANDIDATES

Butros Fakhoury[1] Leandro Sierra[2] Marwan Alsaqa[3] Alan Bonder[2] Behnam Saberi[2]

[1]St. Elizabeth's Medical Center, [2]Beth Israel Deaconess Medical Center, [3]BIDMC HMS

Background: Bridging locoregional therapy (LRT) for hepatocellular carcinoma (HCC) has become the standard of care for the majority of liver transplant (LT) candidates, offering a lower risk of waitlist dropout. However, uncertainties persist regarding their impact on the long-term post-transplant outcomes and the relative advantages of different bridging LRT methods. This study aimed to compare post-LRT outcomes, specifically overall survival (OS), between trans-arterial chemoembolization (TACE) and trans-arterial radioembolization (TARE) for HCC in LT candidates. **Methods:** This is a retrospective comparative cohort study included patients diagnosed with HCC and listed in the Organ Procurement and Transplantation Network (OPTN)/United Network for Organ Sharing (UNOS) between 2013 and 2022. Included in the study were patients who were granted a LT exception and received bridging LRT with either TACE or TARE, irrespective of their Milan criteria status or whether they underwent LT. Patients who received additional LRTs, such as thermal ablation or external beam radiation were excluded. Propensity score matching was employed to balance covariates. Five-year overall survival rates were assessed using Kaplan-Meier curves, and log-rank test was used to compare survival curves among different groups. Cox proportional hazards analysis was utilized to identify predictors of overall survival. Secondary endpoints include pre-LT AFP levels and complete tumor necrosis on explant histology among patients who received LT. **Results:** Among 21,061 patients listed for LT and granted HCC exception, 18,718 received bridging LRT. Of these, 3,241 received TARE, and 10,810 received TACE. After propensity score matching, both groups had a sample size of 2,330 patients. The 5-year overall survival (OS) rates were similar between TARE recipients (62%, 95% CI 59%-64%) and TACE recipients (63%, 95% CI 61%-65%). Kaplan-Meier curves stratified by liver transplant status demonstrated a significant difference in survival curves among patients who did not receive a transplant (p-value = 0.02), while there was no difference in survival among LT recipients. Cox proportional hazards model revealed no significant difference in OS between both groups (HR 0.99, 95% CI 0.9 - 1.11). In comparison to TACE, TARE was more likely to achieve normalization of pre-LT AFP (aOR 2.14, 95% CI 1.63-2.82) and achieve complete tumor necrosis on explant histology (aOR 1.68, 95% CI 1.38 – 2.05). **Conclusion:** In a large nationwide cohort of liver transplant candidates approved for HCC exception and treated with either TACE or TARE, no significant difference was observed in overall survival. However, TARE may offer a potential advantage over TACE for patients listed for LT who did not ultimately undergo transplantation.

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Figure1. Kaplan-Meier survival estimates of overall survival in patients with HCC who received either TACE or TARE, with and without liver transplant

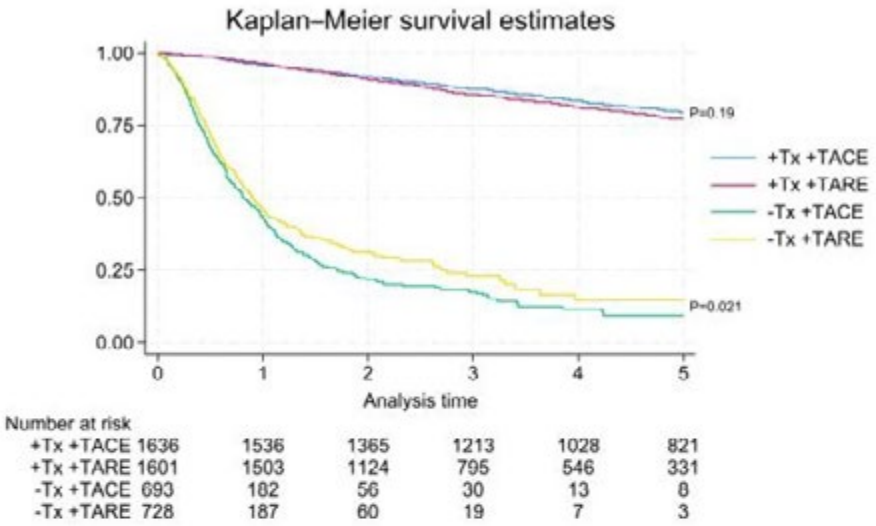

Table 1. Baseline Characteristics of Patients Undergoing TACE versus TARE as Bridging Locoregional Therapy, Matched Using Propensity Scores.

	TACE	TARE	Test	SMD
N	2,330 (50.0%)	2,330 (50.0%)		
Age, (IQR)	63 (59-66)	63 (59-67)	0.380	0.018
Gender, M, (%)	1,775 (76.2%)	1,792 (76.9%)	0.557	0.017
Etiology of Liver Disease, (%)			<0.001	0.023
Alcohol	385 (16.5%)	429 (18.4%)		
HBV	98 (4.2%)	139 (6.0%)		
HCV	1,052 (45.2%)	899 (38.6%)		
MAFLD	351 (15.1%)	426 (18.3%)		
Other	444 (19.1%)	437 (18.8%)		
Within Milan Criteria, (%)	1,891 (81.2%)	1,876 (80.5%)	0.577	0.016
Total days on waiting list, (IQR)	224 (124-359)	236 (166-356)	<0.001	0.004
Received Liver transplant, (%)	1,636 (70.2%)	1,601 (68.7%)	0.266	0.033
MELD score, (IQR)	10 (8-13)	10 (8-13)	0.511	0.008
AFP at listing, (IQR)	7 (4-21)	8 (5-20)	0.013	0.018
Tumor number, (%)			0.106	0.0346
1	1,546 (66.4%)	1,611 (69.1%)		
2	550 (23.6%)	496 (21.3%)		
≥3	234 (10%)	223 (9.6%)		

Disclosures: Butros Fakhoury: Nothing to Disclose, Leandro Sierra: Nothing to Disclose, Marwan Alsaqa: Nothing to Disclose, Alan Bonder: GSK: Grant/Research Support, Mirium: Grant/Research Support, Gilead: Grant/Research Support, Ipsen: Grant/Research Support, Cymabay: Grant/Research Support, Intercept: Grant/Research Support, Intercept: Consultant, GSK: Consultant, Ipsen: Consultant, Chemobab: Grant/Research Support, Alnylam: Consultant, Thirammune: Consultant, Behnam Saberi: Nothing to Disclose

2495 | CHARACTERIZATION AND POST-TRANSPLANT OUTCOMES OF MACHINE PERFUSION ORGANS FOR LIVER RE-TRANSPLANTATION

Roy Wang[1] *Peter Abt*[1] *Therese Bittermann*[1]

[1]*Hospital of the University of Pennsylvania*

Background: Liver re-transplantation (Re-LT) remains the only treatment for liver graft failure. However, Re-LT has been shown to have lower survival compared to initial liver transplantation (LT). Machine perfusion (MP)

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is a novel organ preservation technique that may increase the use of marginal donors, ultimately increasing opportunities for Re-LT. Utilization and outcomes of MP organs for Re-LT are currently unknown. We aimed to characterize usage of MP for Re-LT and explore outcomes using a national organ registry. **Methods:** We performed a retrospective cohort study, using data from UNOS, of patients who underwent first Re-LT between 2022-2023 and who were re-transplanted at centers that utilized MP preservation techniques. Donor and recipient characteristics of re-transplant allografts preserved by MP were compared to those of allografts preserved by cold storage (CS). Kaplan-Meier analyses were performed to plot patient and allograft survival. Cox regression analyses adjusted for a priori selected variables were performed to evaluate associations between organ preservation technique and patient and allograft survival. **Results:** There was a total of 228 patients who received Re-LT across 26 transplant centers during the study period of which 71 (31.1%) patients received organs preserved by MP. One center performed 16 (22.5%) MP Re-LTs. MP organs were more often from donors with higher BMI (median (IQR) 26.9 (23.6-31.0) vs 25.8 (22.9-29.0); p=0.04), donor after cardiac death (19.7% vs 1.9%; p<0.001), biopsied (46.5% vs 30.7%; p=0.02), and had longer preservation time (12.7 (9.4-15.4) hrs vs 6.4 (5.0-7.9) hrs; p<0.001) compared to organs preserved by CS (Figure A). Recipients of MP organs had longer waitlist time (24 (6-223) days vs 9 (3-73) days; p=0.008), longer time from initial transplant (757 (91-3463) days vs 194 (13-2836) days; p=0.01), and were less likely to have vascular complication of initial graft (7.0% vs 19.1%; p=0.02) compared to recipients of CS organs. There were no differences in characteristics of liver transplant recipients at time of initial liver transplant. At one-year post-transplant, there were no differences in patient (log-rank: p=0.75; hazard ratio [HR]: 1.06, 95% CI: 0.42-2.68, p=0.90) (Figure B) and graft survival (log-rank: p=0.80; HR: 0.94, 95% CI: 0.37-2.37, p=0.89) (Figure C) between recipients of MP and CS preserved organs. **Conclusion:** MP allows for Re-LT using grafts with characteristics associated with inferior survival outcomes compared to CS. Nonetheless, recipients of MP organs had similar one-year post-transplant patient and allograft survival. Use of MP may increase opportunities for Re-LT.

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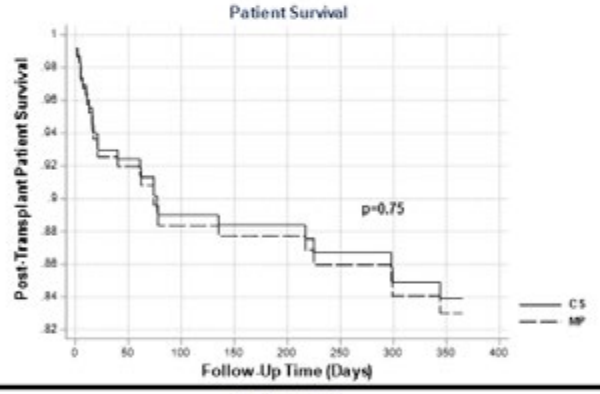
A

Donor Characteristics at Re-Transplant			
Factor, n (%)	Cold Storage Allograft Recipients (n=157)	Machine Perfusion Allograft Recipients (n=71)	p-value
Age (yrs), median (IQR)	36 (26, 47)	38 (27, 49)	0.38
Male Sex	85 (54.1%)	32 (45.1%)	0.20
White Race	93 (59.2%)	44 (62.0%)	0.05
Body Mass Index (BMI), median (IQR)	25.8 (22.9, 29.0)	26.9 (23.6, 31.0)	0.03
Donor after Cardiac Death	3 (1.9%)	14 (19.7%)	<0.001
Machine Perfusion Type			
Normothermic Perfusion		61 (92%)	
Hypothermic Perfusion		5 (8%)	
Donor Graft Liver Biopsy	47 (30.7%)	33 (46.5%)	0.02
Donor Use of Inotropes	55 (37.4%)	14 (19.7%)	0.008
Preservation Time (hrs), median (IQR)	6.4 (5.0, 7.9)	12.7 (9.4, 15.4)	<0.001
Recipient Characteristics at Re-Transplant			
Factor, n (%)	Cold Storage Allograft Recipients (n=157)	Machine Perfusion Allograft Recipients (n=71)	p-value
Recipient Age (yrs), median (IQR)	52 (39, 60)	55 (44, 62)	0.08
Male Sex	95 (60.5%)	46 (64.8%)	0.54
White Race	93 (59.2%)	52 (73.2%)	0.23
Body Mass Index, median (IQR)	26.4 (22.5, 30.7)	25.7 (22.1, 30.0)	0.18
Contributory Causes of Graft Failure			
Primary Graft Nonfunction	22 (20.0%)	6 (18.2%)	0.82
Graft Vascular Complication	30 (19.1%)	5 (7.0%)	0.02
Diffuse Cholangiopathy	17 (15.6%)	8 (25.0%)	0.22
Graft Rejection	17 (10.8%)	5 (7.0%)	0.37
Disease Recurrence	10 (9.2%)	4 (12.5%)	0.58
Infection	7 (6.4%)	1 (3.1%)	0.48
Viral Hepatitis	2 (1.3%)	2 (2.8%)	0.41
MELD Score at Transplant, median (IQR)	30 (20, 36)	29 (21, 36)	0.64
Waitlist Time (days), median (IQR)	9 (3, 73)	24 (6, 223)	0.009
Days from Previous Transplant, median (IQR)	194 (13, 2836)	757 (91, 3463)	0.01

B



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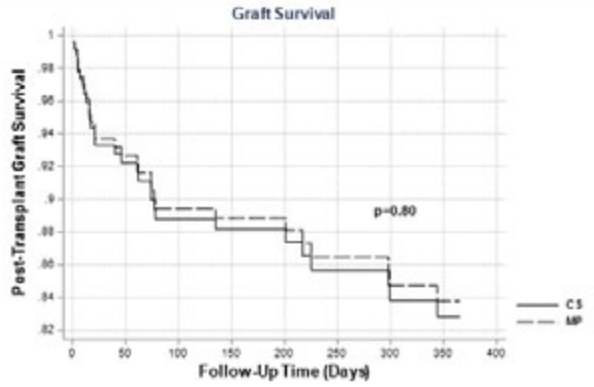

Disclosures: Roy Wang: Nothing to Disclose, Peter Abt: Nothing to Disclose, Therese Bittermann: Nothing to Disclose

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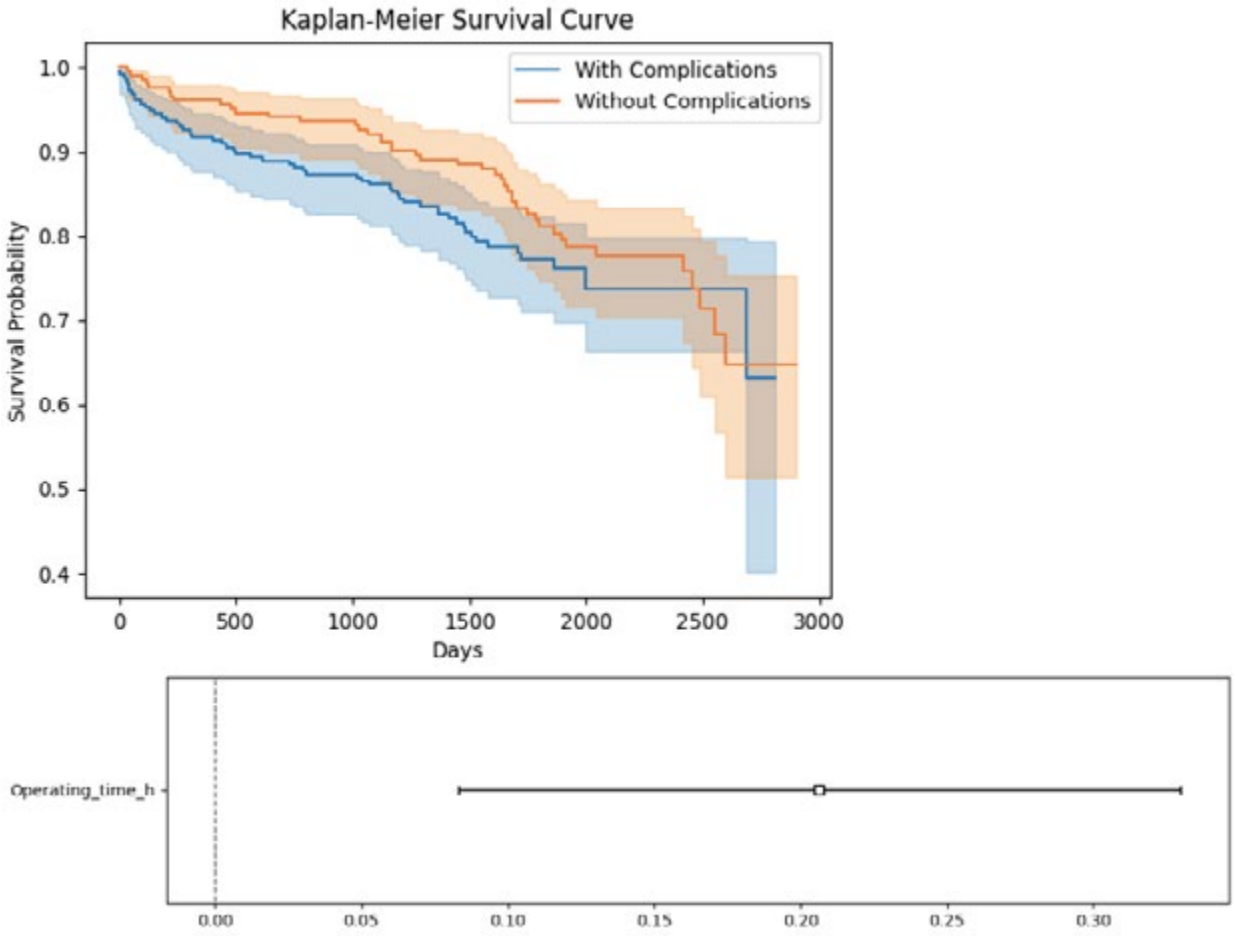
2496 | OPERATIONAL TIME AND SEVERE POSTOPERATIVE COMPLICATIONS: THEIR IMPACT ON LONG-TERM SURVIVAL IN LIVER TRANSPLANT PATIENTS

Ayato Obana[1] Khalid Mumtaz[2] Austin Schenk[3] Ashley Limkemann[3] Sai Rithin Punjala[3] Musab Alebrahim[3] Navdeep Singh[3] Sylvester Black[2] W. Kenneth Washburn[2]

[1]Ohio State University Wexner Medical Center, [2]Ohio State University, [3]Ohio State University Wexner Medical Cen

Background: Traditionally, severe postoperative complications have been recognized as a determinant of patient outcomes in various surgeries. However, the impact severity of surgical complications and operating time has not been studied comprehensively in liver transplant recipients (LTRs). **Methods:** This retrospective cohort study included patients who underwent liver transplantation. Patients were divided into two groups based on the presence of Grade 3, 4, or 5 Clavien-Dindo complications. Propensity score matching was performed using logistic regression on the covariates: age, sex, BMI, MELD score, and operating time, resulting in 100 matched pairs. Cox proportional hazards regression was used to assess the impact of operating time on survival. Kaplan-Meier survival curves were generated, and the log-rank test was used to compare survival between groups. **Results:** Median survival date is 1573 in complication group and 1840 in non-complication group. Cox proportional hazards regression analysis showed that operating time significantly affected survival, with a hazard ratio of 1.229 (p = 0.001), indicating a 22.9% increase in mortality risk per additional hour of operating time. Kaplan-Meier survival analysis demonstrated lower survival probabilities for patients with complications compared to those without. However, the log-rank test indicated no significant difference in survival between the complication and no complication groups (p = 0.239). **Conclusion:** While operating time significantly affects survival in liver transplant recipients, the presence of severe postoperative complications alone does not result in a statistically significant difference in survival between matched groups. These findings suggest that factors such as operating time play a critical role in determining patient outcomes following liver transplantation.



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Disclosures: Ayato Obana: Nothing to Disclose, Khalid Mumtaz: Nothing to Disclose, Austin Schenk: Nothing to Disclose, Ashley Limkemann: Nothing to Disclose, Sai Rithin Punjala: Nothing to Disclose, Musab Alebrahim: Nothing to Disclose, Navdeep Singh: Nothing to Disclose, Sylvester Black: Nothing to Disclose, W. Kenneth Washburn: Nothing to Disclose

2497 | ADVANCING LIVER TRANSPLANTATION INTO THE NEXT DECADE: LIVER TRANSPLANT OUTCOMES IN PATIENTS 70 YEARS OR OLDER

Avi Toiv[1] Abdulmalik Saleem[1] Mark Obri[1] Hope O'Brien[2] Syed-Mohammed Jafri[1]

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Background: Since the introduction of direct-acting antivirals for hepatitis C virus, liver transplantation (LT) has undergone a change in patient demographics, with patients receiving increasingly more LT for other chronic liver diseases and at older ages. Historically, younger patients have been prioritized for LT due to concerns about post-transplant outcomes in older patients; however, emerging evidence suggests that the impact of age on transplant eligibility criteria may need to be reevaluated. This study describes the clinical characteristics and postoperative LT outcomes of patients ≥70 years compared to patients < 70 years old. **Methods:** Single center retrospective chart review of all patients who underwent LT at a high-volume academic transplant center between January 1, 2014, and September 26, 2023. **Results:** Of 999 liver transplant recipients (36% women; 64% men), 43 were ≥70 years old (median 71 y; range 70-75) and 956 were <70 years old (median 58 y; range 16-69). The older group had more baseline comorbidities but a lower median MELD at LT (21 vs 25; p=.014). Indications for LT differed between groups; while the younger group had a higher rate of alcoholic cirrhosis (39% vs 14%; p=<.001), the older group had greater proportions of patients with metabolic dysfunction-associated steatohepatitis (51% vs 23%; p=<.001), primary biliary cholangitis (9.3% vs 2.8%; p=.040), and cryptogenic cirrhosis (14% vs 5%; p=.022). Older and younger patients had similar postoperative liver function laboratory values, biliary complication rates, need for further procedures, and hospital readmission. The older cohort had a significantly longer mean length of stay (25.5 vs 14.0 days; p=.002), an association that was confirmed on regression analysis (p<.001). Notably, no differences in mortality or graft failure at 1, 3, and 5 years were observed between older and younger LT recipients. **Conclusion:** LT recipients ≥70 years-old had positive post-transplant outcomes and similar patient and graft survival as patients <70 years old, although older age was associated with a longer hospital stay. Overall, LT evaluation and eligibility age criteria may need to be reevaluated to be more age inclusive.

Disclosures: Avi Toiv: Nothing to Disclose, Abdulmalik Saleem: Nothing to Disclose, Mark Obri: Nothing to Disclose, Hope O'Brien: Nothing to Disclose, Syed-Mohammed Jafri: Takeda: Speaking and Teaching, Gilead: Speaking and Teaching, Abbvie: Speaking and Teaching, Ironwood: Advisor, Intercept: Speaking and Teaching

2498 | CENTER-LEVEL VARIABILITY IN UTILIZING NORMOTHERMIC MACHINE PERFUSION AND THE ASSOCIATION WITH RECIPIENT INSURANCE ★

Chawin Lopimpisuth[1] David Goldberg[2]

[1]University of Miami/Jackson Health System, [2]University of Miami

Background: Recent advances in ex-situ normothermic machine perfusion (NMP) have transformed the field of transplantation. The Food and Drug Administration (FDA) approved two NMP devices in 2021, resulting in a paradigm shift in the ability to use marginal livers and increase storage time to allow for more daytime operations. However, center-level variability has never been explored. Despite the promise of NMP, a major rate-limiting factor is costs. This could lead to disparities among recipients, given different reimbursements based on insurance type. Therefore, we aim to evaluate center-level variability in use of NMP, and to determine whether recipient insurance type was associated with NMP. **Methods:** This cohort study used the United Network for Organ Sharing data. We evaluated adult deceased donor liver transplant (DDLT) recipients between 1/1/2022-12/31/2023. To focus on center-level variability we only included "high-volume NMP centers", defined as those that performed ≥15 DDLTs using NMP. The primary outcome was whether the DDLT was performed using NMP, compared to static cold storage. To explore center-level and factors associated with use of NMP, we evaluated variables related to donor quality and insurance. We defined a nighttime procurement as those occurring between 7PM - 7AM. We

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fit multivariable logistic regression models to evaluate factors associated with NMP. **Results:** Among the 142 liver transplant centers, 72 (50.7%) had ≥1 DDLT using NMP, and 28 (19.7%) were high-volume NMP centers. These centers performed 6,816 DDLTs, of which 1,814 (26.6%) involved NMP. Recipients of a liver using NMP were more likely to have private insurance (52.7% vs 47.2%, p<0.001). Although livers undergoing NMP were more likely to be from a DCD donor (52.4% vs 9.2%, p<0.001), there was marked center-level variability in the proportion of DCD vs DBD allografts that underwent NMP (Figure 1). In multivariable logistic regression, liver allografts procured using NMP were 26% more likely to occur during the nighttime (OR 1.26, CI 1.10 - 1.43, p<0.001), more than 13-times likely to be used for DCD allografts (OR 13.2, CI 11.3 - 15.3, p < 0.001), and less likely to occur in recipients insured by Medicaid or the Veterans Health Administration (VHA) (OR 0.62, CI 0.51 - 0.76, p<0.001 for Medicaid; OR 0.55, CI 0.31 - 0.98, p=0.04 for VHA). **Conclusion:** Our study highlights center-level variability in utilizing NMP, with respect to type of donor, timing of donor operations, and differential utilization based on the type of insurance. Because of the increased costs with NMP, without specific direct reimbursements, it is possible that centers select whether to use NMP based on the patient's insurance type. This is simply a hypothesis, but the disparity in utilization based on insurance type is concerning. While the change in practice may help to increase DCD utilization, and shift the timing of transplants, the disparity is alarming and requires further investigation.

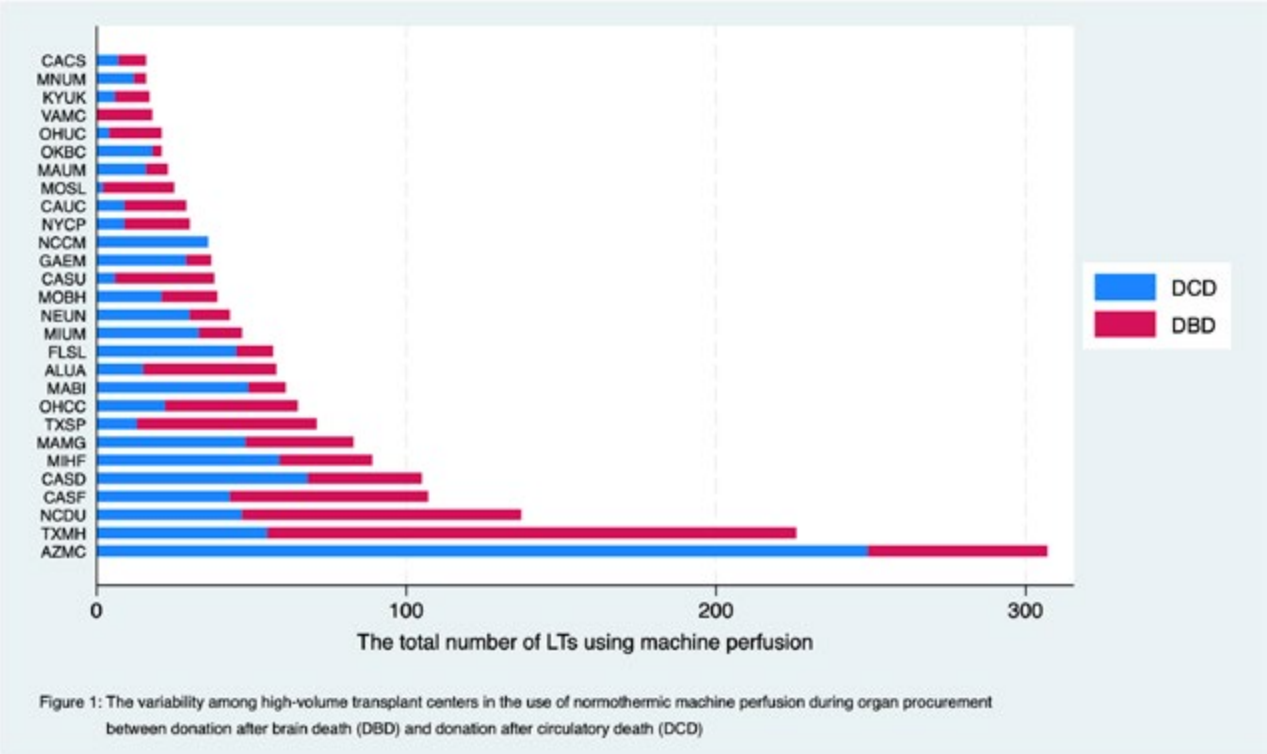

Figure 1: The variability among high-volume transplant centers in the use of normothermic machine perfusion during organ procurement between donation after brain death (DBD) and donation after circulatory death (DCD)

Disclosures: Chawin Lopimpisuth: Nothing to Disclose, David Goldberg: Nothing to Disclose

2499 | TRACKING LONG-TERM OUTCOMES IN ALPPS PROCEDURE: A FOLLOW-UP STUDY ANALYZING EXTENDED SURVIVAL

Mohammad AbuAssi[1] Saqr Alsakarneh[2] Yaseen Perbtani[1] Tony Brar[1] Raghav Bassi[1] Thomas Lorf[3] Aiman Obed[4]

[1]University of Central Florida, [2]University of Missouri-Kansas City, [3]University of Goettingen, [4]Ibn Sina University for Medical Sciences

Background: Associating Liver Partition and Portal vein Ligation for Staged hepatectomy (ALPPS) presents a novel approach to treating patients with unresectable liver tumors. This technique was first introduced by Professor Hans Schlitt from Regensburg, Germany, who performed the initial ALPPS procedure in 2007. The method gained recognition when it was formally described in 2012. Despite its promising resectability rates, the long-term survival outcomes and factors determining these outcomes require further exploration. This

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study provides an update on a cohort initially included in Hans Schlitt's pioneering 2012 ALPPS study, focusing on long-term survival. Remarkably, it features a patient who achieved an extraordinary survival milestone, becoming the longest documented survivor worldwide following the ALPPS procedure. **Methods:** We conducted a retrospective analysis of seven patients who underwent ALPPS at the University Hospital Göttingen, focusing on extended hemihepatectomy cases for various liver malignancies. Comprehensive data were collected, including demographics, preoperative liver function, tumor characteristics, surgical details, and follow-up. Survival analysis was performed using Kaplan-Meier methods, with log-rank tests for survival comparisons. **Results:** The study cohort exhibited a broad spectrum of survival outcomes. Notably, one patient with complete situs inversus achieved an unprecedented long-term survival of 156 months post-operatively without disease recurrence. Diagnosed with hepatocellular carcinoma, this patient had not undergone preoperative chemotherapy. The cohort's overall survival rates were 42.9% at one year and 14.3% at three years. The median disease-free survival (DFS) was 10 months, while the median overall survival (OS) was 28 months. **Conclusion:** The ALPPS procedure can yield substantial long-term survival benefits in select patients, as evidenced by a record-breaking survival case in this cohort. This follow-up study highlights the importance of detailed patient selection and perioperative management to optimize outcomes. Ongoing research is necessary to pinpoint the factors that contribute to successful long-term survival following ALPPS.

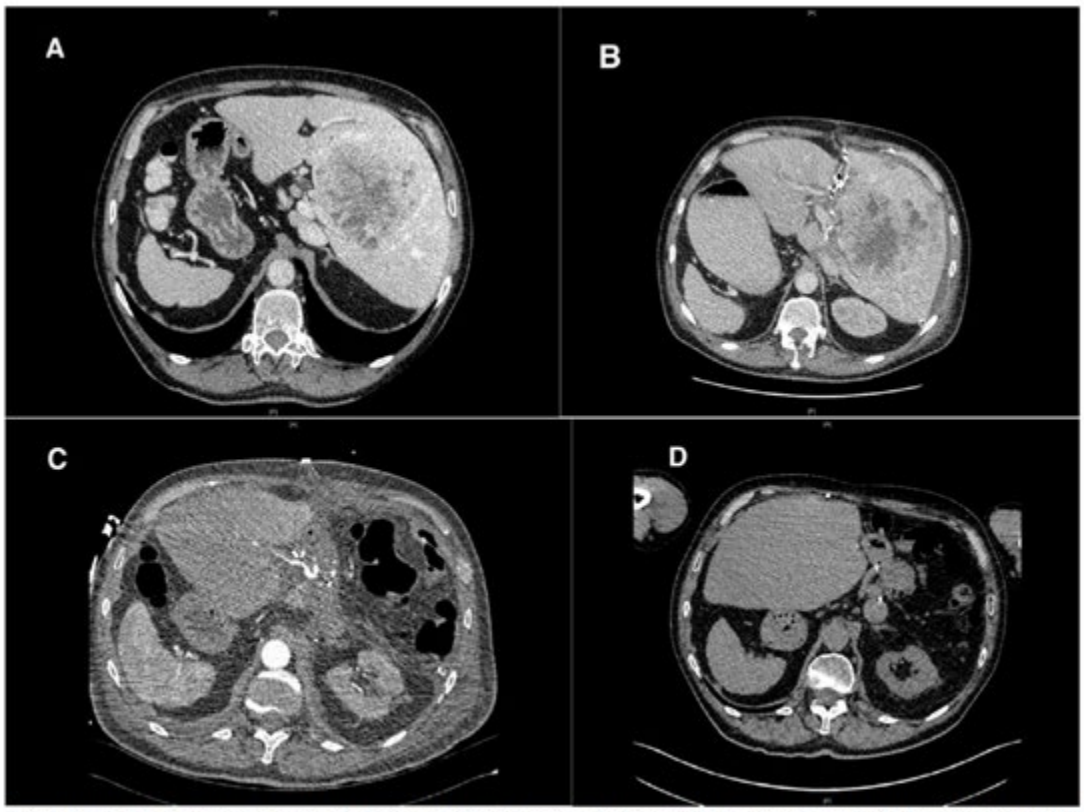

Figure 1: This figure presents a series of CT scans at different stages of the patient's treatment. Panel (A) displays the initial CT scan taken before the first operation. Panel (B) shows the CT scan taken post Stage 1, used to assess the Future Liver Remnant Volume (FLRV). Panel (C) illustrates the CT scan taken after Stage 2. Lastly, Panel (D) presents the CT scan from the patient's most recent follow-up in March 2023.

Disclosures: Mohammad AbuAssi: Nothing to Disclose, Saqr Alsakarneh: Nothing to Disclose, Yaseen Perbtani: Nothing to Disclose, Tony Brar: Nothing to Disclose, Raghav Bassi: Nothing to Disclose, Thomas Lorf: Nothing to Disclose, Aiman Obed: Nothing to Disclose

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2500 | CLINICAL OUTCOMES OF TACE IN PATIENTS LISTED FOR LIVER TRANSPLANTATION AT A SINGLE CENTER FROM 2018-2022

Elizaveta Makarova[1] *Xuanjia Fan*[1] *Iman Farooqi*[1] *Katrina Bakhl*[1] *Terrence Murphy*[2] *Alison Faust*[3]

[1]*Penn State College of Medicine,* [2]*Penn State University,* [3]*Penn State Milton S. Hershey Medical Center*

Background: Trans arterial chemoembolization (TACE) is the most frequently utilized locoregional therapy for patients with hepatocellular carcinoma. Data has been mixed with respect to outcomes in patients undergoing TACE with decompensated cirrhosis. The Barcelona Clinic Liver Cancer algorithm recommends transplant or palliative care for patients with any stage cancer and decompensated cirrhosis. In clinical practice, however, patients awaiting transplant require treatment to prevent progression of cancer. Therefore, many centers still perform TACE, even in patients with decompensated cirrhosis. We aimed to evaluate clinical outcomes of patients listed for liver transplant that underwent TACE. **Methods:** This was a retrospective cohort study of patients listed for transplant between February 2018 and April 2022. We analyzed 74 patients that had a total of 177 TACE procedures. We used a four-level categorical outcome within 90 days of TACE whose levels were defined as follows: clinical stability/improvement (1), worsening of liver functioning (2), hospitalization (3), and death or delisting (4). The primary statistical analysis was based on multinomial modeling of this categorical outcome with weighting based on each participant's propensity score for decompensation. Secondary analysis used multivariable multinomial modeling based on the three continuous variables that were chosen by backwards selection via minimization of the Bayesian Information Criterion. **Results:** Patients with decompensated cirrhosis at the time of TACE (N=65) had odds of being hospitalized within 90 days of the TACE procedure that were 8 times higher than persons who were not decompensated (p=0.007). There was no significant difference in death and delisting after TACE between compensated and decompensated patients, though numbers were low in this outcome level of highest severity. In secondary multivariable modeling, albumin less than or equal to 3.0 g/dL was strongly associated with worsening (p=<0.0001) and hospitalization (p=0.03). Bilirubin greater than 3.0 mg/dL was positively associated with clinical worsening and death (p=0.002 and p=0.005, respectively). **Conclusion:** TACE procedures completed in patients with decompensated liver cirrhosis were more likely to result in hospitalization but not in death/delisting. Patients with low albumin and high bilirubin were more likely to experience poor outcomes within 90 days following TACE.

Disclosures: Elizaveta Makarova: Nothing to Disclose, Xuanjia Fan: Nothing to Disclose, Iman Farooqi: Nothing to Disclose, Katrina Bakhl: Nothing to Disclose, Terrence Murphy: Nothing to Disclose, Alison Faust: Nothing to Disclose

2501 | TRENDS IN CANDIDATE HCV NAT+ LISTING AND ASSOCIATED IMPACTS ON LIVER TRANSPLANTATION WAITLIST OUTCOMES ◆

Natalia Salinas Parra[1] *Maarouf Hoteit*[2] *Puru Rattan*[2] *Peter Abt*[2] *Nadim Mahmud*[1]

[1]*Hospital of the University of Pennsylvania,* [2]*Hospital of the University of Penn*

Background: There remains a substantial supply-demand mismatch in liver transplantation. Since the development of direct-acting antiviral agents, utilization of hepatitis C-virus (HCV)+ organs has expanded for HCV nucleic acid amplification test (NAT)- recipients. Historically, consenting to receive an HCV NAT+ organ presumably conferred a substantial reduction in expected time to transplant, however it is unclear if such a benefit currently persists. We evaluated trends in HCV NAT+ consent over time and listing impact on transplant probability, waitlist mortality, and likelihood of receiving an HCV NAT+ donor organ. **Methods:** This retrospective cohort study used the United Network for Organ Sharing dataset of adult patients without hepatocellular carcinoma who were waitlisted for liver transplantation between 1/2016 and 12/2022. Trends in initial HCV NAT+ listing were evaluated across transplant eras (2016-2017, 2018-2020, 2021-2023), and multivariable regression models accounting for competing risks were fit to study the association between initial HCV NAT+ listing and waitlist outcomes. **Results:** A total of 21,776 patients were initially listed for HCV NAT+ organs while 45,378 were not. Males had 6% higher odds of HCV NAT+ listing relative to women (OR 1.06, 95% CI 1.02-1.10, p=0.002) and Hispanic and Asian patients had lower relative odds versus White patients (OR 0.78 and 0.73, respectively, each p<0.001). The proportion of waitlisted patients initially listed increased significantly from 2016 to 2023 (0.088 to 0.608, p<0.001), though with substantial U.S. regional differences (p<0.001; Figure panels A/B). Initial HCV NAT+

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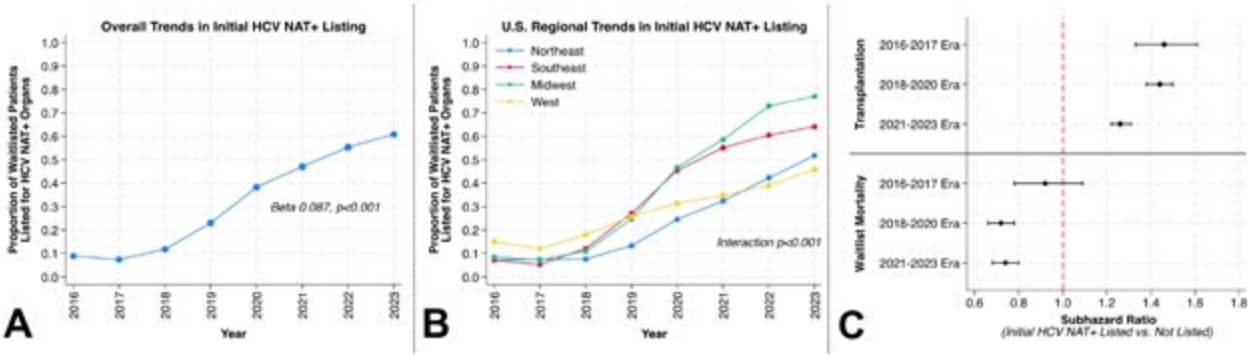
listing was associated with a waitlist mortality benefit in later eras (e.g., SHR 0.74 in 2021-2023, 95% CI 0.68-0.80, p<0.001). However, the increased subhazard of transplantation relative to non-listed patients declined over time (SHR 1.46, 95% CI 1.33-1.61, p<0.001 in 2016-2017 versus SHR 1.26, 95% CI 1.22-1.31, p<0.001; Figure panel C). **Conclusion:** Patients not listed for HCV NAT+ organs in the modern era are relatively disadvantaged in terms of waitlist outcomes. While listings have risen substantially over time, there remain center-level and geographic variation with marginalized groups less likely to be listed. Patient and provider factors that contribute to low rates of HCV NAT+ listing should be explored to inform targeted interventions and promote equity in transplant.



Disclosures: Natalia Salinas Parra: Nothing to Disclose, Maarouf Hoteit: HepQuant, LLC: Advisor, Puru Rattan: Nothing to Disclose, Peter Abt: Nothing to Disclose, Nadim Mahmud: Nothing to Disclose

2502 | ETIOLOGY-SPECIFIC TRENDS OF DELISTING FOR LIVER DISEASE IMPROVEMENT AND RE-COMPENSATION AMONG CANDIDATES ON LIVER TRANSPLANT LIST IN THE US ◆

Mohamed Elfeki[1] Chencheng Xie[2] Mohanad Awadalla[3] Abdellatif Ismail[4] Prabha Bhandari[5] shaikhoon mohammed[6] Juan Pablo Arab[7] Gene Im[8] Yong-Fang Kuo[9] Ashwani Singal[5]

[1]University of South Dakota Sanford School of Medicine, [2]Avera McKennan Hospital, [3]Beth Israel Deaconess Medical Center, [4]University of Maryland Medical Center, [5]University of Louisville, [6]Atrium Health Navicent-Baldwin, [7]University of Western Ontario, [8]Mount Sinai Ichan School of Medicine, [9]University of Texas Medical Branch

Background: Data are limited regarding etiology-specific trends for delisting due to liver disease improvement among candidates listed for liver transplant (LT) in the US. **Methods:** This retrospective cohort study evaluated the United Network for Organ Sharing database for etiology-specific trends for delisting and recompensation due to liver disease improvement among candidates listed for LT from 2002-2022. 1-year cumulative delisting rates for improvement competing for waitlist mortality and receipt of a liver transplant were evaluated. Fine and Gray regression model was used to derive baseline characteristics associated with delisting for improvement. Results expressed as as sub-hazard ratio, 95% CI. Among delisted candidates for improvement, logistic regression multivariable model identified variables associated with recompensation. Results expressed as odds ratio, 95% CI. **Results:** Of 248,469 listings for LT (2002-22), 120,451 listed for cirrhosis in adults (≥18 yrs.) after excluding those with hepatocellular cancer, status 1A listings were stratified based on listing year: 2002-2008 (n=34,444), 2009-2015 (n=38,296), and 2016-2022 (n=47,711). Of these, 7196 (6.2%) were delisted for liver disease improvement, with 5.6, 7.2, and 5.3% in three respective periods, Armitage trend p<0.001. Candidates delisted for improvement differed on baseline characteristics from other listings (Table). Delisting for improvement for etiology was 8.1, 5.8, 4.0, 3.9, and 3.1% among listings for alcohol-associated liver disease (ALD n=41,647), chronic viral hepatitis (CVH n=41,824), cholestatic liver disease (CCLD n=12,131), non-alcoholic steatohepatitis (NASH n=22,162), and metabolic liver disease (MLD n=2687) respectively.1-year cumulative delisting rates for improvement competing for waitlist mortality and receipt of LT were 1.2, 0.6, 0.4, 0.3, and 0.2% for ALD, CVH, NASH, MLD, and CCLD, respectively, P<0.001 for all. Compared to CCLD, SHR (95% CI) for delisting for improvement at 1-year were 3.0 (2.7-3.2), 1.8 (1.6-1.9), and 1.6 (1.4-1.8) for ALD, HCV, and NASH, respectively. Of candidates delisted for improvement, 567 of 5750 (9.8%) decompensated at listing developed recompensation, 17.5% MLD (n=63), 16.3% CCLD (n=227), 9.9% ALD (n=2990), 9.8% CVH (n=1770), and 6.9% NASH (n=700). In a multivariate logistic regression model, female sex was associated with 30% higher odds of re-compensation, 1.3

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(1.1-1.5). In contrast, listing variables associated with lower odds of re-compensation were candidate's age [0.98 (0.97-0.99)], MELD score [0.94 (0.92-0.96)], obesity [0.76 (0.62-0.93)], listings 2009-16 vs. 2002-08 [0.69 (0.57-0.83), and listings 2016-22 vs. 2002-20 [0.69 (0.57-0.83)]. **Conclusion:** In this UNOS database analysis, ALD is the most frequent etiology for delisting due to liver disease improvement. Models and biomarkers are needed to identify these candidates for optimal use of deceased donor livers.

Table 1 Baseline characteristics based on delisting for liver disease improvement and for re-compensation within 1 yr. of listing for liver transplant

Variables	Not improved (N=113,255)	Improved (N=7196)	P	No recompensation (N=5183)	Recompensation (N=567)	
Age in yrs.	54.2, 9.6	53.5, 9.8	<0.001	53.8, 9.6	51.8, 9.6	<0.001
Females N (%)	40,008 (35.3)	2897 (40.3)	<0.001	2069 (40)	274 (48)	<0.001
C, AA, H N (%)	69, 6, 21	77, 5, 13	<0.001	78, 4, 13	79, 5, 10	<0.001
Diabetes mellitus (%)	31,461 (28)	1476 (21)	<0.001	1081 (21)	87 (15.3)	<0.001
Obesity N (%)	45,289 (40)	2205 (31)	<0.001	1617 (31.2)	133 (23.5)	<0.001
CVH N (%)	39412 (35)	2412 (34)		1596 (31)	174 (31)	
ALD N (%)	38,296 (34)	3351 (46)		2693 (52)	297 (52)	
NASH N (%)	21,290 (19)	872 (12)	<0.001	652 (12)	48 (9)	<0.001
CCLD N (%)	11652 (10)	479 (7)		190 (4)	37 (6)	
Metabolic N (%)	2605 (2)	82 (1)		52 (1)	11 (2)	
Listing MELD	20.7, 9.3	13.6, 5.8	<0.001	14.2, 5.7	12.3, 6	<0.001

Disclosures: Mohamed Elfeki: Nothing to Disclose, Chencheng Xie: Nothing to Disclose, Mohanad Awadalla: Nothing to Disclose, Abdellatif Ismail: Nothing to Disclose, Prabha Bhandari: Nothing to Disclose, shaikhoon mohammed: Nothing to Disclose, Juan Pablo Arab: Nothing to Disclose, Gene Im: Consultant relationship with KorroBio; Has not ended; Device support for research relationship with Echosens; Has not ended; Advisor relationship with Novo Nordisk; Has not ended; Consultant relationship with Alimentiv; Has not ended, Yong-Fang Kuo: Nothing to Disclose, Ashwani Singal: Advisor relationship with CLD Foundation; Has not ended; Speaking and Teaching relationship with Medical Speaker's Network; Has not ended; Speaking and Teaching relationship with Madrigal; Has not ended; Stock â€“ privately held company relationship with Pleiogenix; Has not ended; Consultant relationship with Pleiogenix; Has not ended; Advisor relationship with Durect; Has ended; Royalties or patent beneficiary relationship with Up-to-Date; Has not ended; Executive role relationship with Gastro Endo News; Has not ended; Grant/Research Support relationship with NIAAA; Has not ended; Employee relationship with Avera Medical Group; Has ended; Grant/Research Support relationship with GSK; Has not ended; Employee relationship with University of Louisville School of Medicine; Has not ended; Speaking and Teaching relationship with Medscape; Has not ended

2503 | METABOLIC VULNERABILITY INDEX

Rehan Razzaq[1] Hiba Khan[2] Margery Connelly[3] Alok Baral[1] Shreya Garg[1] Madison Nguyen[4] Audrey Ang[1] Geneva Roache[2] Kavish Patidar[5] Anh Bui[1] Idris Yakubu[1] Susan Wolver[1] Irina Shalaurova[3] Stephan Bakker[6] Robin Dullaart[6] Danielle Kirkman[1] Vinay Kumaran[1] Vaishali Patel[1] Mohammad Siddiqui[1]

[1]VCU Health System, [2]VCU Healthy System, [3]Labcorp, [4]VCUHS, [5]Baylor College of Medicine, [6]University Medical Center Groningen

Background: Frailty and chronic inflammation are negative prognostic indicators in end-stage diseases, however, measuring them in clinical practice simultaneously is challenging. Metabolic Vulnerability Index (MVX) is a

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novel NMR-based composite biomarker quantifying nutritional risk (Metabolic Malnutrition Index or MMX), and inflammatory markers (Inflammatory Vulnerability Index or IVX). Recent studies highlight a strong relationship between MVX and cardiometabolic disease related and all cause mortality. Liver transplant (LT) recipients are at exceedingly high risk for cardiometabolic risk and mortality risk and the present study evaluated MVX and its components in a prospective cohort of LT recipients. **Methods:** The study analyzed plasma samples collected from a prospective cohort of adult participants (≥ 18 years of age) enrolled in natural history study of LT recipients at author's institution. To better quantify MVX after transplantation, LT recipients (n=181) were matched 1:1 with non-transplant controls from the PREVEND study of healthy individuals. All LT recipients were 1:1 propensity with the following two control groups: a) Lean: age and gender matched but BMI <25 kg/m^2 b) Weight controlled: age, gender and BMI matched MMX is comprised of citrate, leucine, isoleucine and valine. IVX is comprised of small HDL particles (S-HDL-P) and GlycA, a composite biomarker of systemic inflammation. Higher values of MVX, IVX and MMX signify higher risk. **Results:** Compared to lean- and BMI-matched controls, LT recipients had significantly higher IVX, MMX and MVX (Figure 1A). Compared to both control groups, the MMX components in LT recipients was similar to previously described high risk group. While no significant differences in the composite IVX, MMX or MVX scores was noted across various etiologies of cirrhosis requiring LT (Figure 1B), patients transplanted for MASH cirrhosis had worse MMX profile compared to non-MASH patients characterized by lower serum leucine and valine levels (Figure 1C). Choice of immunosuppression did not affect MVX, IVX or MMX. A trend towards higher MVX and MMX was noted in female LT recipients, however, this did not reach statistical significance. **Conclusion:** A novel NMR-based composite marker associated with higher risk of cardiovascular disease and mortality was considerably higher in LT recipients compared to controls with highest burden in patients transplanted for MASH cirrhosis. Future studies are necessary to calibrate MVX to clinical outcomes in LT recipients with the overarching goal of improving risk stratification after LT.

Figure 1A: Comparison of inflammation vulnerability index (IVX), metabolic malnutrition index (MMX) and metabolic vulnerability index (MVX) in liver transplant (LT) recipients compared to lean and body mass index (BMI) matched controls

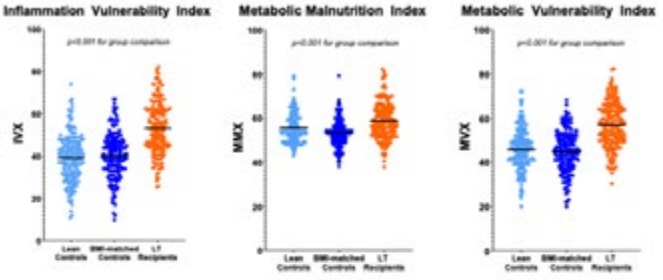


Figure 1B: No significant differences in MVX, IVX or MMX across etiologies of cirrhosis requiring LT

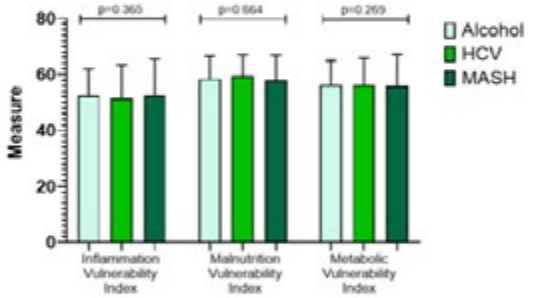
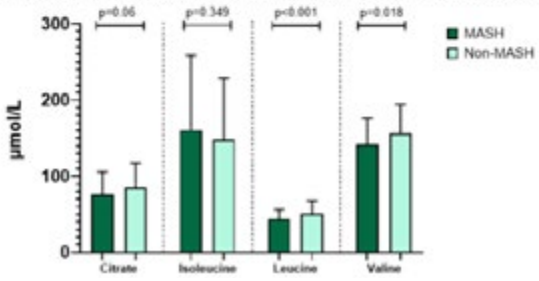


Figure 1C: LT recipients transplanted for metabolic dysfunction associated steatohepatitis (MASH) have worse metabolic profile as defined by components of MMX that include leucine and valine.



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Disclosures: Rehan Razzaq: Nothing to Disclose, Hiba Khan: Nothing to Disclose, Margery Connelly: Labcorp: Employee, Alok Baral: Nothing to Disclose, Shreya Garg: Nothing to Disclose, Madison Nguyen: Nothing to Disclose, Audrey Ang: Nothing to Disclose, Geneva Roache: Nothing to Disclose, Kavish Patidar: Madrigal Pharmaceuticals: Medical Advisory Board, Anh Bui: Zydus: Consultant, Idris Yakubu: Nothing to Disclose, Susan Wolver: Nothing to Disclose, Irina Shalaurova: Nothing to Disclose, Stephan Bakker: Nothing to Disclose, Robin Dullaart: Nothing to Disclose, Danielle Kirkman: Nothing to Disclose, Vinay Kumaran: Nothing to Disclose, Vaishali Patel: Nothing to Disclose, Mohammad Siddiqui: Grant/Research Support relationship with NovoNordisk; Has not ended; Advisor relationship with 89Bio; Has not ended; Advisor relationship with AMRA; Has not ended

2504 | INHIBITION OF FERROPTOSIS IN FATTY LIVER ISCHEMIA-REPERFUSION INJURY ATTENUATES SUBSEQUENT ACUTE KIDNEY INJURY

Wenjun Zhang[1] Zachary Rokop[1] Shunhua Guo[1] Shan Li[1] Alexander Scherer[1] indiana university[1] Richard Mangus[2] Weinian Shou[1] Chandrashekhar Kubal[1]

[1]Indiana University School of Medicine, [2]Indiana University Medical Center

Background: The association between ischemia reperfusion injury (IRI) of fatty livers and subsequent acute kidney injury (AKI) has been well established. We previously established that ferroptosis is an important injury mechanism in fatty liver damage upon IRI in a murine model [1]. Using the same model, we sought to investigate the role of ferroptosis in AKI after fatty liver IRI. **Methods:** 10-week-old C57BL6 mice were fed with either high fat, high sucrose (HFD) diet or maintained on normal chow (ND) for 12 weeks. Animals underwent hepatic IRI (hIRI) via 70% portal pedicle clamping for 1 hour, or sham operations. Animals were euthanized following 6 or 24 hours of reperfusion depending on the experiment and kidney tissue and serum were collected. Creatinine was measured in the sera. Ferroptosis and sensitivity for ferroptosis was measured by arachidoniccacid phosphatidylenol (AA-PE) by masspectrometry and long-chain acyl-CoA synthetase-4 (ACSL4) by ELISA respectively. To investigate non-ferroptotic mechanisms, apoptosis, necrosis and were measured along with RNA-seq and spatial transcriptomics analysis using VISIUM 10X platform. To inhibit ferroptosis, in separate experiments Liproxstatin-1 (Lip-1) or control vehicle was administered for 7 consecutive days prior to hIRI. **Results:** Significant AKI was observed in mice undergoing hIRI compared to sham evident by serum creatinine increase and pathologic changes. In HFD fed mice, AKI was more prominent compared to ND counterparts after hIRI (Fig. 1a). Histopathology and immunohistochemistry (Fig 1b) of kidneys demonstrated increased apoptosis and infiltration of neutrophils and macrophages in the kidneys from HFD+hIRI animals. Markers of ferroptosis were not prominent in kidneys from either groups (ND+hIRI and HFD+hIRI) (Fig 1c,d). Spatial transcriptomic analysis demonstrated increased gene expression for apoptosis (Fig.1e) and some other pathways. Gene expression for ACSL4 was increased in both ND+hIRI and HFD+hIRI (Fig.1f). RNA-seq on kidney tissue rcollected 6 hours after hIRI revealed pathway activities associated with leukocyte chemotaxis and migration, granulocyte chemotaxis and migration, cytokine production, and a decrease the expression of the gene set associated with cilium assembly and organization (Fig.1g). Inhibition of ferroptosis with Lip-1 showed preservation of kidney function evident by reduced serum creatinine and improved kidney histology in HFD fed animals but not in ND fed animals (Fig.1f). **Conclusion:** In colclusion, inflammation and apoptosis are the significant mechanisms associated with AKI in the setting of hIRI in fatty livers. Although end products of ferroptosis are not observed in kidneys in the setting of hIRI, gene expression for ferroptosis is present and inihibition of ferroptosis, perhaps in the liver prevents AKI. Further charachetrization of ferroptosis along the liver-kidney axis of injury is required.

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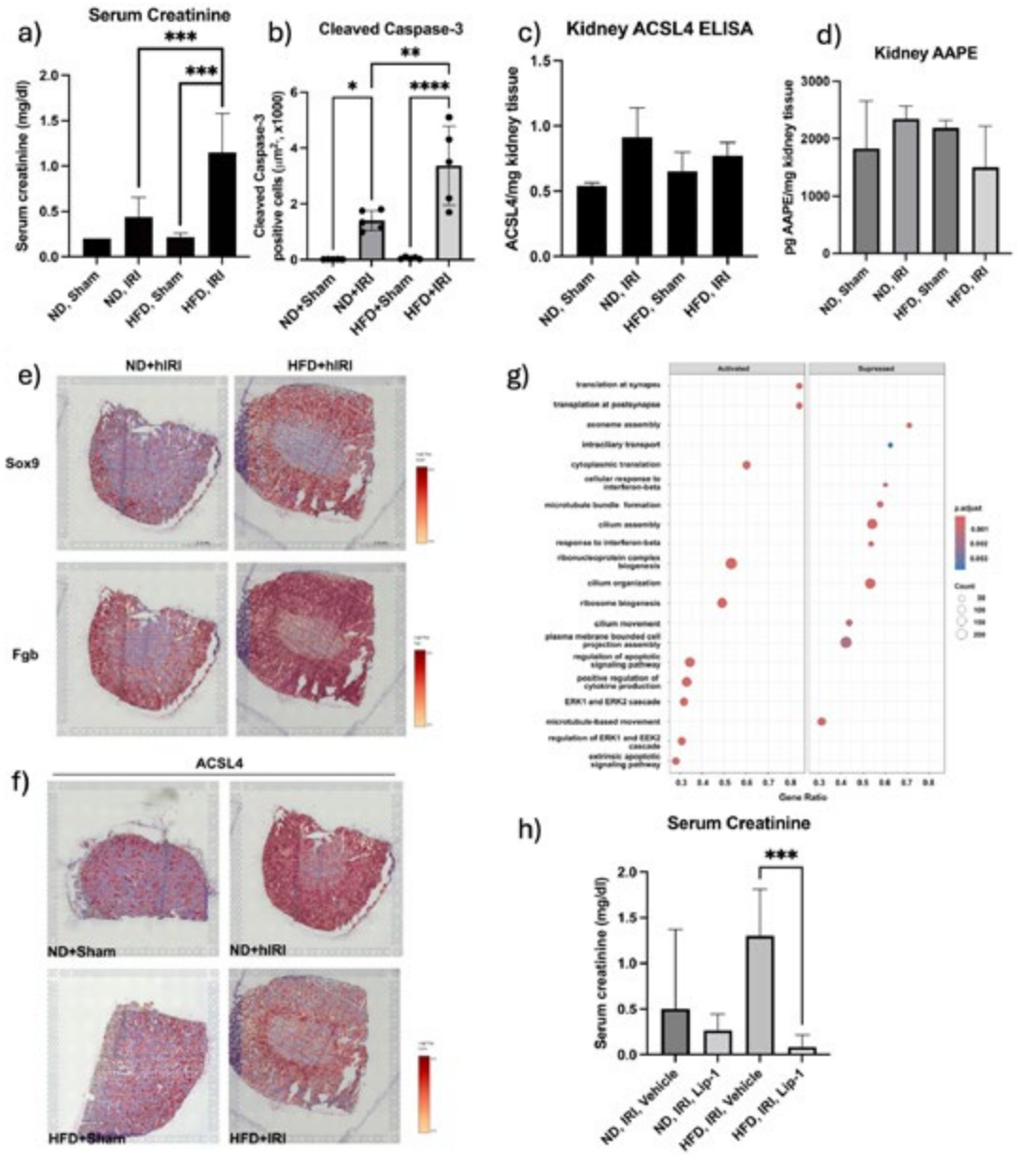

Figure 1: (a) AKI measured by serum creatinine in the setting of hIRI, AKI is noted to be prominent in HFD animals compared to ND; (b) significantly higher levels of cleaved caspase-3 in kidney tissues measured by IHC indicating apoptosis after hIRI, intensity of staining being significantly higher in kidneys from HFD animals; (c) markers of ferroptosis in the kidney tissues were not elevated upon hIRI, ACSL4 was measured by ELISA and AAPE was measured by mass spectrometry; (e-f): spatial transcriptomics revealed significantly increased gene expression for apoptosis (Sox9 and Fgb) in HFD kidneys, however gene expression for ACSL4 showed stronger expression in ND fed animal's kidneys; (g) RNA-seq analysis on the kidney tissue demonstrated pathway activities associated with leukocyte chemotaxis and migration, granulocyte chemotaxis and migration, cytokine production, and a decrease the expression of the gene set associated with cilium assembly and organization; (h) kidney function was preserved in animals receiving liproxstatin-1 (Lip-1), with significantly lower serum creatinine in HFD animals.

Disclosures: Wenjun Zhang: Nothing to Disclose, Zachary Rokop: Nothing to Disclose, Shunhua Guo: Nothing to Disclose, Shan Li: Nothing to Disclose, Alexander Scherer: Nothing to Disclose, indiana university: Nothing to Disclose, Richard Mangus: Nothing to Disclose, Weinian Shou: Nothing to Disclose, Chandrashekhar Kubal: Nothing to Disclose

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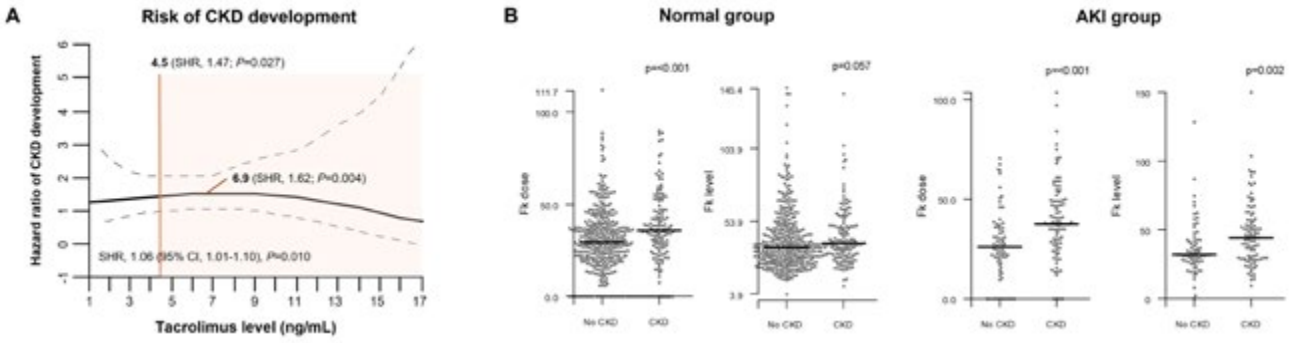
2505 | THE IMPACT OF TACROLIMUS LEVEL AND ITS INTRAPATIENT VARIABILITY ON THE DEVELOPMENT OF CHRONIC KIDNEY DISEASE FOLLOWING LIVER TRANSPLANTATION

Soon Kyu Lee[1] Ho Joong Choi[2] Young Kyoung You[2] Jung Hyun Kwon[3] Pil Soo Sung[2] Jeong Won Jang[2] Seung Kew Yoon[2] Jong Young Choi[2]

[1]College of Medicine, The Catholic University of Korea, [2]College of Medicine, The Catholic Univer, [3]The Catholic University of Korea

Background: Although potent immunosuppressants (ISs), such as tacrolimus, has significantly improved the long-term management of liver transplantation (LT) patients, prolonged use of these ISs post-LT has been linked to several complications, including chronic kidney disease (CKD), consequently affecting survival rates compared to healthy individuals. This study aimed to identify the risk factors for CKD and end-stage renal disease (ESRD) following LT, with a specific focus on tacrolimus levels and intrapatient variability (IPV). **Methods:** Among the 1,076 patients who underwent LT between 2000 and 2018, 952 were included in the analysis. The tacrolimus doses and levels were recorded every 3 months, and the IPV was calculated using the coefficient of variability. The cumulative incidence rates of CKD and ESRD were calculated based on baseline kidney function at the time of LT. The impact of tacrolimus levels and their IPV on the development of CKD and ESRD was evaluated, and the significant risk factors were identified. **Results:** Within a median follow-up of 97.3 months, the 5-year cumulative incidence rates of CKD (0.58 vs. 0.24) and ESRD (0.07 vs. 0.01) were significantly higher in the acute kidney injury (AKI) group than in the normal glomerular filtration rate (GFR) group. In the normal GFR group, the tacrolimus levels were identified as a risk factor for CKD, with a level of ≤4.5 ng/mL suggested as optimal for minimizing the risk of CKD (Figure A). Both in the normal and AKI groups, patients with CKD development demonstrated higher IPV in the drug dose and level compared to patients without CKD during follow-up (Figure B). Furthermore, the IPV of tacrolimus levels and doses emerged as a significant risk factor for CKD development in both groups (P<0.05), with tenofovir disoproxil fumarate also being a risk factor in HBV-infected patients. The IPV of tacrolimus levels was also a significant factor in ESRD development (P<0.05). **Conclusion:** This study elucidated the optimal tacrolimus through level and highlighted the impact of IPV on the CKD and ESRD development post-LT.



Disclosures: Soon Kyu Lee: Nothing to Disclose, Ho Joong Choi: Nothing to Disclose, Young Kyoung You: Nothing to Disclose, Jung Hyun Kwon: Nothing to Disclose, Pil Soo Sung: Nothing to Disclose, Jeong Won Jang: Nothing to Disclose, Seung Kew Yoon: Nothing to Disclose, Jong Young Choi: Nothing to Disclose

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2506 | ENHANCED RECOVERY OF WARM ISCHEMIC DAMAGED RAT LIVER GRAFT USING NORMOTHERMIC MACHINE PERFUSION (NMP) BY SUPPLEMENTING PERFUSATE WITH BONE MORPHOGENETIC PROTEIN-7 (BMP-7) MIMETIC TBD 184

Anil Kharga[1] Huyun Chen[1] Korkut Uygun[1] James Markmann[2] William Carlson[1]

[1]Massachusetts General Hospital, [2]University of Pennsylvania Health System

Background: Donation after cardiac death (DCD) is a major source for a donor pool; however, long warm ischemic time (WIT) in DCD livers can result in primary and delayed graft dysfunction and especially ischemic cholangiopathy, which can require multiple biliary interventions and even retransplantation due to the development of non-anastomotic biliary strictures as a long-term complication. Historically, these issues made DCD grafts inferior to brain death donation (DBD). Ex vivo models of perfusion offer an opportunity to investigate treatments that limit ischemic injury and promote recovery of livers for transplant. This may expand the number of livers available and provide a path for the development of new treatments for clinical disorders leading to liver failure. In this study, we investigated a new therapy for the treatment of warm ischemic liver injury in a DCD rat liver model with normothermic machine perfusion (NMP). The work focuses on a growth factor, Bone Morphogenetic Protein-7 (BMP-7) mimetics known to have anti-inflammatory, anti-apoptotic, anti-fibrotic, and regenerative properties but lacking bone-forming activity, distinguishing them from BMP-7 monomers. **Methods:** Rat livers were flushed with normal saline (NS) and stored in 50 ml of NS for 30 min @ 37^0C to simulate the DCD model for control (N=7) and experimental group, TBD 184 (N=5). The experimental group received 3 µg/ml BMP-7 mimetic (TBD 184) in 500 ml acellular William's E-based hepatocyte culture media for 6 hours during NMP. The control group and **fresh (N=3)**, healthy controls (without warm ischemia) received no drugs during NMP. ANOVA with Tukey's post-hoc test and simple linear regression were used for comparing NMP parameters among the groups. **Results:** Treatment with TBD 184 increased O2 uptake (Fig A), which remained unchanged with time compared to negative slopes of both healthy and ischemic controls (Fig B). Treatment improved pH, glucose metabolism (Fig C & D), and bile production (not statistically significant, p=0.07, Fig J). Although lactate (Fig E) and potassium (K) (not shown) were higher, lactate clearance (Fig F) improved and steepened over time, indicating hepatocellular function improvement. In addition, lower transaminase (ALT: alanine transaminase & AST: aspartate aminotransferase) in inflow perfusate (Fig G & H) and gamma-glutamyl transferase (GGT) in bile (Fig I) indicate lower hepatocyte and cholangiocyte damage, respectively. **Conclusion:** By improving hepatocellular function and reducing injury, BMP-7 mimetic (TBD 184) helps liver grafts recover from warm ischemic damage on ex-vivo NMP. Lactate (Fig E) may be higher because BMP-7 induces glycolysis via hypoxia-induced factors. Further experiments with the treatment of donor and recipient with BMP-7 mimetic for upstream and downstream management, respectively, for minimizing ischemic reperfusion injury, are to be explored in an in vivo model.

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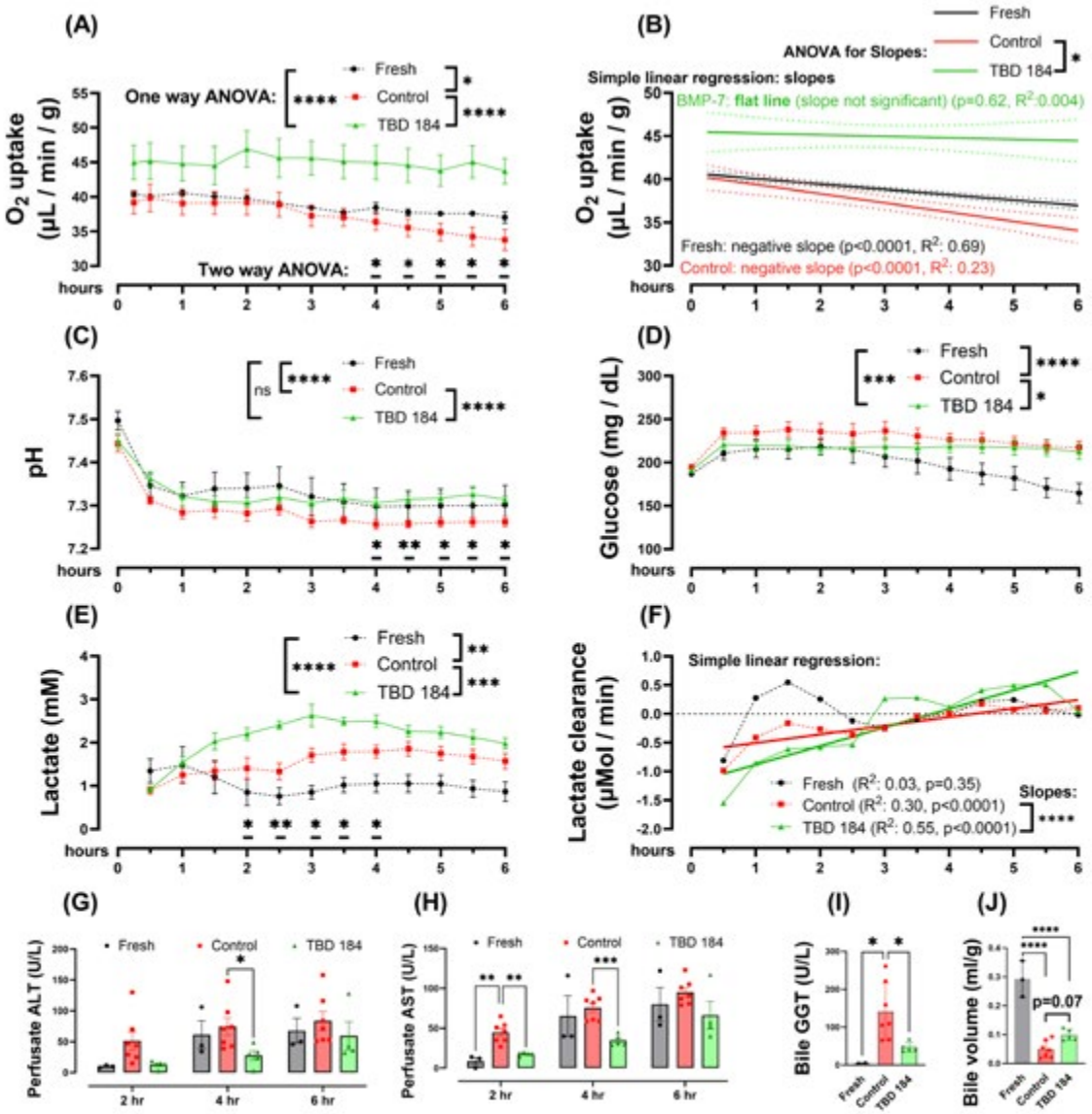

Fig: Assessment using normothermic machine perfusion (NMP) in donation after cardiac death (DCD) rat liver model with Bone Morphogenetic Protein -7 (BMP-7) mimetic (TBD 184) shows effective graft recovery on pump from warm ischemic damage. Fresh (N:3)- healthy control without warm ischemia time (WIT) and TBD 184, **Control (N:7)-** with 30 min WIT @ 37°C but without TBD 184, **BMP-7 (N:5)-** with 30 min WIT @ 37 °C and TBD184; ANOVA with Tukey's post-hoc test; results are expressed from inflow line as mean with SEM; ns: $p > 0.05$, * : $p \leq 0.05$, ** : $p \leq 0.01$, *** : $p \leq 0.001$, **** : $p \leq 0.0001$. ALT: alanine transaminase, AST: aspartate aminotransferase, GGT: gamma-glutamyl transferase.

Disclosures: Anil Kharga: Nothing to Disclose, Huyun Chen: Nothing to Disclose, Korkut Uygun: Nothing to Disclose, James Markmann: Transmedics: stock, Vertex: Advisor, Transmedics: Advisor, iTolerance: Advisor, eGenesis: Advisor, William Carlson: Nothing to Disclose

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2507 | APPLICATION OF HEMOPURE BASED OXYGENATED SOLUTION DURING PIG TO BABOON LIVER XENOTRANSPLANTATION TO MINIMIZE DURATION OF ISCHEMIA DURING BACK BENCHING: BIOENERGETIC METABOLITES ANALYSIS

Anil Kharga[1] Katsuhiro Tomofuji[1] Kohei Kinoshita[1] Olivia Bourgeois[1] Alban Longchamp[1] Heidi Yeh[1] Shoko Kimura[1] Korkut Uygun[1] James Markmann[2]

[1]Massachusetts General Hospital, [2]University of Pennsylvania Health System

Background: The three most important mechanisms from allotransplant that contribute to ischemic reperfusion injury (IRI) in xenotransplantation are complement pathway activation, sterile inflammation, and endothelial activation. Therefore, IRI minimization in xenotransplantation involves complement inhibition, limiting cross-species coagulation dysregulation, anti-inflammatory medications, and ischemia minimization. Thus, we evaluated here a continuous cold flush by an intravenous (IV) drip using the University of Wisconsin (UW) cold storage preservative solution oxygenated with Hemopure (HBOC-201), a hemoglobin-based oxygen carrier (HBOC) to reduce the otherwise unavoidable ischemic injury during procurement and back-table preparation of the genetically modified liver graft as illustrated in Fig 1. **Methods:** Three genetically modified pig liver grafts (GTKO: GGTA1 knockout = α1,3-galactosyltransferase gene inactivation/deletion) were flushed with an oxygenated solution: HBOC-201 + UW (25-75% V/V) (pO_2 ≈700mmHg and HBOC saturation ≈95%) during back-benching to minimize the cold ischemic time (CIT) in the experimental (OxyFlush, N=3) group. Eight livers in the **control** (N=8) group received regular UW flush. The oxygenation protocol is illustrated in Fig 2 and Fig 3. A. Liquid chromatography-mass spectrometry (LC-MS) was utilized for bioenergetic metabolic molecules analysis from the flash-frozen samples collected at the end of back-benching. Unpaired two-sided student's t-test with Welch's correction was used for comparison between the groups. **Results:** Bioenergetic metabolic molecules analysis showed that flushing with oxygenated solutions toward the end of back-benching improves ATP maintenance (Fig 3. J) and overall organ health indicated by adenylate energy charge (Fig 3. K). A continuous supply of O_2 keeps anaerobic respiration low marked by low NADH : NAD ratio (Fig 3. G). Surprisingly, reducing agent marker (NADPH : NADP ratio, Fig 3. D) is lower in the experimental group due to the slow production of reactive oxygen species with a supply of O_2 from hemopure during flushing, resulting in the conversion of NADPH to NADP (Fig 3. B & C). **Conclusion:** Slow and continuous hypothermic oxygenated flushing, similar to an IV drip, can reduce cold ischemic injury in xenotransplantation without requiring a costly perfusion device or surgical technique modifications. This offers a streamlined approach to minimizing cold ischemia in the operating room. Future plans are to use an IV cannula inserted as a side branch during portal vein anastomosis to reduce warm ischemia during graft implantation, which may help in achieving a relative ischemia-free state.

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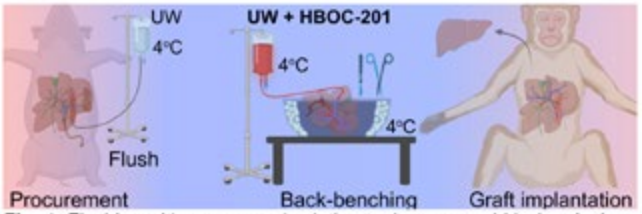

Fig: 1: Flushing with oxygenated solution to decrease cold ischemic time

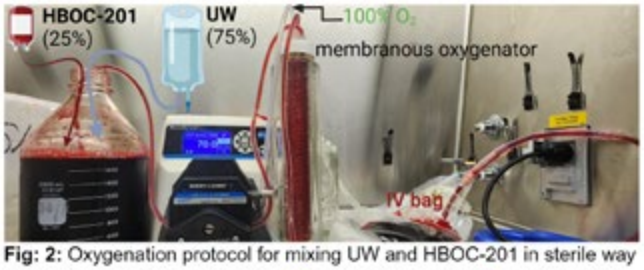

Fig: 2: Oxygenation protocol for mixing UW and HBOC-201 in sterile way

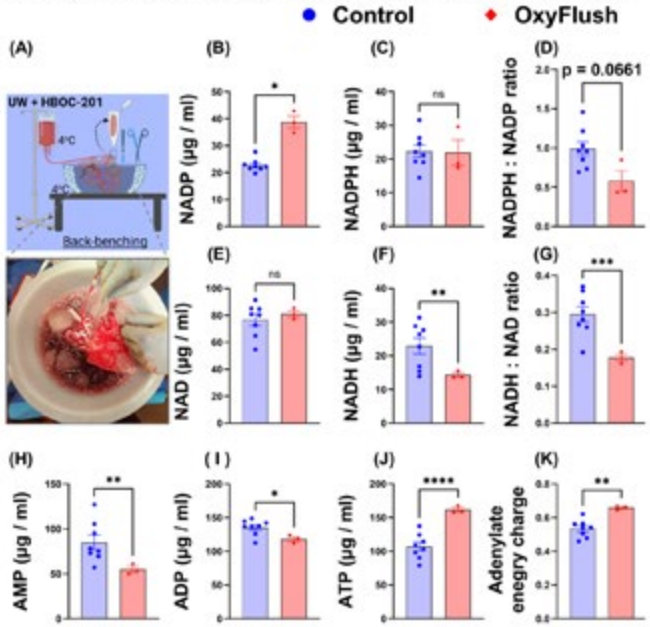

Fig: 3: Liquid chromatography–mass spectrometry (LC–MS) shows graft flushed with oxygenated HBOC-201 + UW towards end of back-benching performs better than regular UW flush; control (N=8), oxyFlush (N=3); unpaired two-sided t-test; mean with SEM; **Adenylate energy charge** = ([ATP] +0.5[ADP])/([ATP] + [ADP] + [AMP]).

UW: University of Wisconsin, **HBOC**: Hemoglobin Based Oxygen Carrier

Disclosures: Anil Kharga: Nothing to Disclose, Katsuhiro Tomofuji: Nothing to Disclose, Kohei Kinoshita: Nothing to Disclose, Olivia Bourgeois: Nothing to Disclose, Alban Longchamp: Nothing to Disclose, Heidi Yeh: Nothing to Disclose, Shoko Kimura: Nothing to Disclose, Korkut Uygun: Nothing to Disclose, James Markmann: Transmedics: stock, Vertex: Advisor, Transmedics: Advisor, iTolerance: Advisor, eGenesis: Advisor

2508 | BIOMARKER ASSESSMENT OF DONOR SYSTEMIC INFLAMMATION DURING THE WARM ISCHEMIC PERIOD

Daljeet Chahal[1] *Donald Griesdale*[1] *Laura Hornby*[2] *Jordan Bird*[1] *Mypinder Sekhon*[1]

[1]*Vancouver General Hospital,* [2]*Independent Consultant*

Background: Donation after circulatory death (DCD) liver transplantation is plagued by high rates of post-transplant complications. One proposed mechanism by which complications arise is inflammatory priming of the liver graft due to donor systemic inflammation. However, this hypothesis has not been confirmed in translational

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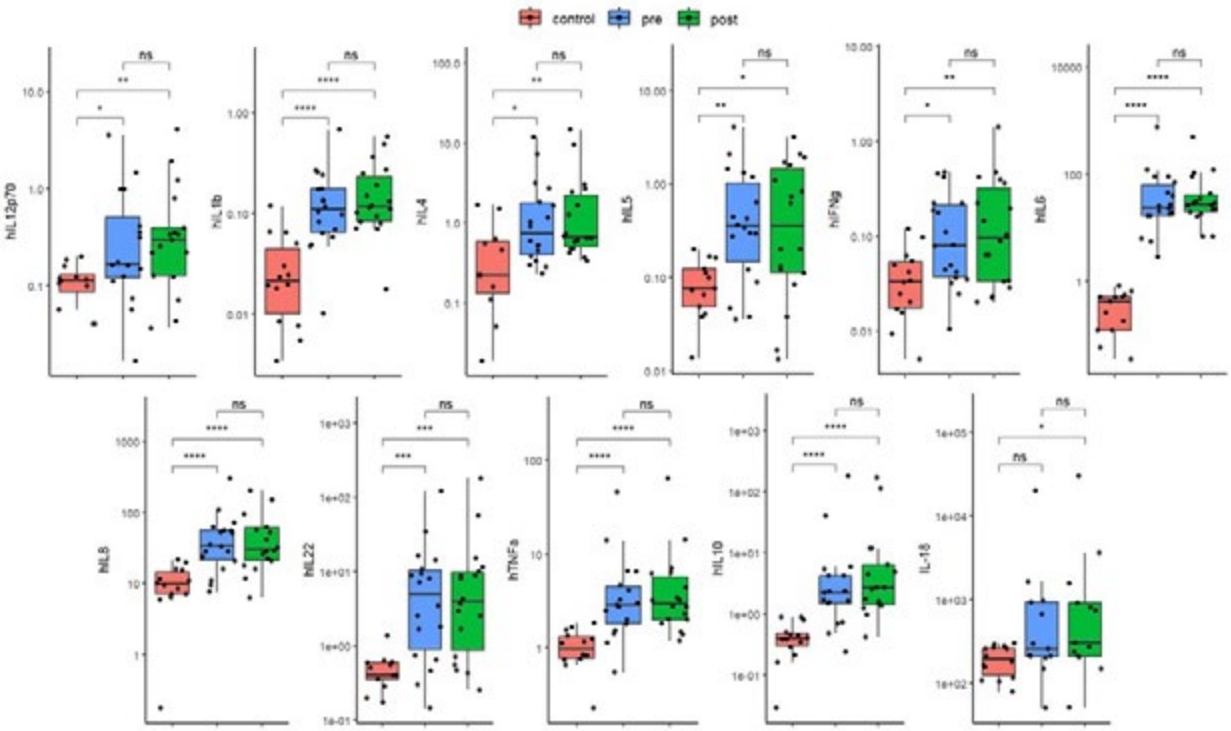
studies. It is unknown if donor warm ischemia time (dWIT) worsens donor systemic inflammation. The aim of this study was to characterize inflammatory burden in potential DCD donors undergoing withdrawal of care. **Methods:** Patients >18 years life-support withdrawal were eligible for enrolment. Blood presure was monitored continuously from withdrawal until asystole. We obtained arterial bio-specimens at two time points: 1) immediately before withdrawal of care, and 2) peri-mortem. We quantified levels of IL-12p70, IL-1b, IL-4, IL-5, IFNg, IL-6, IL-8, IL-22, TNFa, IL-10 and IL-18 using an ELISA platform at each time point. Biomarker levels at both time points were compared to a healthy volunteer control cohort. We also compared biomarker levels between patients with dWIT <30 minutes and dWIT >30 minutes. **Results:** 18 patients were recruited, and 15 volunteer patients were used as a control cohort. Of the 18, 6 were DCD donors. 12 were not eligible for DCD donation, due to non-registration or family wishes. All underwent standard withdrawal of care protocol for DCD donation. Eligible DCD patients had longer withdrawal to asystole times than non-eligible patients ($p<0.05$) but did not have longer SBP60 mmHg to asystole times ($p>0.05$). Biomarker values did not differ between eligible DCD donors and those not eligible ($p>0.05$). All biomarkers, both before life support withdrawal and peri-mortem, were elevated compared to controls ($p<0.05$). Pre-withdrawal biomarker levels did not differ from peri-mortem levels ($p>0.05$). There was no difference in biomarker values when patients were stratified by dWIT <30 vs >30 minutes ($p > 0.05$). **Conclusion:** Donor inflammatory burden was increased relative to non-critically ill patients, indicating that donor inflammation may play a role in long term DCD graft dysfunction. However, this burden did not change over dWIT; that is, peri-mortem inflammatory biomarker levels did not increase relative to pre-withdrawal levels. It can thus be inferred that donor inflammation does not represent a major mechanism of DCD related complications such as ischemic cholangiopathy.



Disclosures: Daljeet Chahal: Nothing to Disclose, Donald Griesdale: Nothing to Disclose, Laura Hornby: Nothing to Disclose, Jordan Bird: Kent Imaging Inc.: Consultant, Mypinder Sekhon: Nothing to Disclose

2509 | ANALYSIS OF THE IMPACT OF FEMALE SEX AND SARCOPENIA ON SERUM CREATININE AND WAITLIST PRIORITY FOR LIVER TRANSPLANTATION

Shivangi Gupta[1] Angus Jeffrey[2] Zhengyi Wang[3] Leon Adams[4] George Garas[4] Gerry MacQuillan[4] Michael Wallace[2] Briohny Smith[2] Wai Lim[4] Ros Francis[4] Christopher Welman[5] Gary Jeffrey[4]

[1]Sir Charles Gairdner Hospital, Nedlands, Western Australia, Australia, [2]Sir Charles Gairdner Hospital, [3]University of Western Australia, Perth, [4]Sir Charles Gairdner Hospital, WA, Aus, [5]Fiona Stanley Hospital, Perth, WA, Aus

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Background: Model for End-Stage Liver Disease (MELD) score incorporates sCr, which is a poor measure of renal function in cirrhotic patients. Females have a higher waitlist mortality rate which is proposed to be due to lower muscle mass and consequent lower sCr values in the MELD scores. This study evaluated the difference between sCr and calculated creatinine (cCr) derived from measured GFR (mGFR), in patients with cirrhosis. The effect of sex and sarcopenia on delta creatinine (ΔCr, difference of cCr and sCr) and on MELD values was studied for bias. **Methods:** Retrospective data was collected from a single-center Australian database of cirrhotic patients who had workup for Liver transplantation (LT) from 2019-2023. A control population was live renal donors with normal renal function (n=48). The CKD-EPI equation was rearranged to determine cCr as a function of mGFR. MELD, MELD-Na and MELD 3.0 scores were calculated using cCr and sCr; and the difference was ΔMELD. Skeletal muscle index (SMI, cm2/m2) was calculated from CT images at L3 vertebral level using automated software. Data analysis was performed using SPSS. **Results:** 119 patients included (32% females; mean age 53.8±11.4yrs; mean mGFR 80.5± 28.6 ml/min/1.73m2, mean MELD 15.4±6.2). 64.2% of males (SMI<50 cm^2/m^2) and 52.6% of females (SMI <39 cm^2/m^2) were sarcopenic, p=0.236. In the study group, the mean cCr (110.6±53.7μmol/L) was significantly higher than mean sCr (80.5±45.8μmol/L), p<.001. In the controls, mean cCr (78.7±24.6μmol/L) was not different to mean sCr (73.0±13.2μmol/L), p=.115. In the study group, there was no difference in the ΔCr between males (27.6±43.0μmol/L) and females (35.2±55.2μmol/L), p=.720. SMI was inversely associated with ΔCr, p=.023. Multivariate analysis using age, sex, SMI, INR, bilirubin, and sodium, found that SMI and bilirubin were independently associated with ΔCr (p=0.022, p=0.020 respectively). Mean cCr-MELD (17.0±6.8) was higher than sCr-MELD (15.4±6.3), p<.001. There was no significant difference between male and female ΔMELD (p=.801), ΔMELD-Na (p=0.819) or ΔMELD3.0 (p=.616). Multivariate analysis using sex and SMI, found SMI was independently associated with ΔMELD (p=0.016), ΔMELD-Na (p=.027) and ΔMELD 3.0 (p=.017). Subgroup analysis in patients with GFR ≤60ml/min/1.73m^2 (n=36) showed sarcopenic patients had a higher ΔCr (36.1±19.1μmol/L) and ΔMELD (2.5±1.4) compared with non-sarcopenic patients (ΔCr, 10.5±59.7μmol/L), p=0.060; ΔMELD, 1.1±2.1, p=0.020). There was no difference between the ΔCr or ΔMELD of males (26.3±51.8μmol/L, 2.3±2.2) and females (29.1±16.7 μmol/L, 1.8±1.2), p=0.834 and p=0.384 respectively. Multivariate analysis found that sarcopenia was independently associated with ΔCr (p=0.046) and ΔMELD (p=0.032). **Conclusion:** The higher waitlist mortality seen in females is unlikely due to lower serum creatinine, and other factors need to be further investigated

Disclosures: Shivangi Gupta: Nothing to Disclose, Angus Jeffrey: Nothing to Disclose, Zhengyi Wang: Nothing to Disclose, Leon Adams: Novo Nordisk: Advisor, SCL Behring: Advisor, Pfizer: Advisor, George Garas: Nothing to Disclose, Gerry MacQuillan: Nothing to Disclose, Michael Wallace: Nothing to Disclose, Briohny Smith: Nothing to Disclose, Wai Lim: Nothing to Disclose, Ros Francis: Nothing to Disclose, Christopher Welman: Nothing to Disclose, Gary Jeffrey: Nothing to Disclose

2510 | PREDICTIVE POWER OF BUBBLE ECHO FOR DIAGNOSIS OF HEPATOPULMONARY SYNDROME

Mary Sullivan Hannah Laird[1] Kavindya Wickramasinghe[1] Mira Sridharan[1] Curtis Argo[1]

[1]UVA

Background: Liver transplantation evaluation commonly requires agitated saline echocardiogram (bubble ECHO) to assess for intrapulmonary shunting (IPS). We aimed to evaluate the sensitivity/specificity and negative/positive predictive values (NPV and PPV) of the finding of IPS on bubble ECHO for an eventual diagnosis of hepatopulmonary syndrome (HPS) **Methods:** A retrospective chart review (February 2019 – December 2020) identified patients undergoing initial liver transplantation evaluation. Exclusions included lack of performance of bubble ECHO at time of transplant evaluation or bubble ECHO performed at an outside center. Patient demographics and clinical data were extracted. The primary study outcome was sensitivity/specificity and NPV/PPV of IPS on bubble ECHO for diagnosis of HPS. Univariate methods and multivariable logistic regression analysis were performed in attempts to identify prognostic factors for HPS diagnosis in IPS positive patients. **Results:** 330 patients underwent bubble ECHO at liver transplant evaluation during the study period and met inclusion criteria. Mean age was 54.9 years (SD, 11.1), male gender comprised 60%. The two most common etiologies of cirrhosis were cryptogenic/NASH (37%) and alcohol (34%). Mean BMI was 30.6 (SD, 8.6), mean MELD was 17.5 (SD, 7.7). 58.4% of these patients underwent liver transplant. 164 (49.4%) of patients had IPS on bubble ECHO. Of these, 9 (2.7%) had a diagnosis of HPS. HPS was significantly more frequent in IPS positive patients (p=0.02). 1 of 9 patients with HPS did not have IPS reported on ECHO. In patients with IPS on bubble

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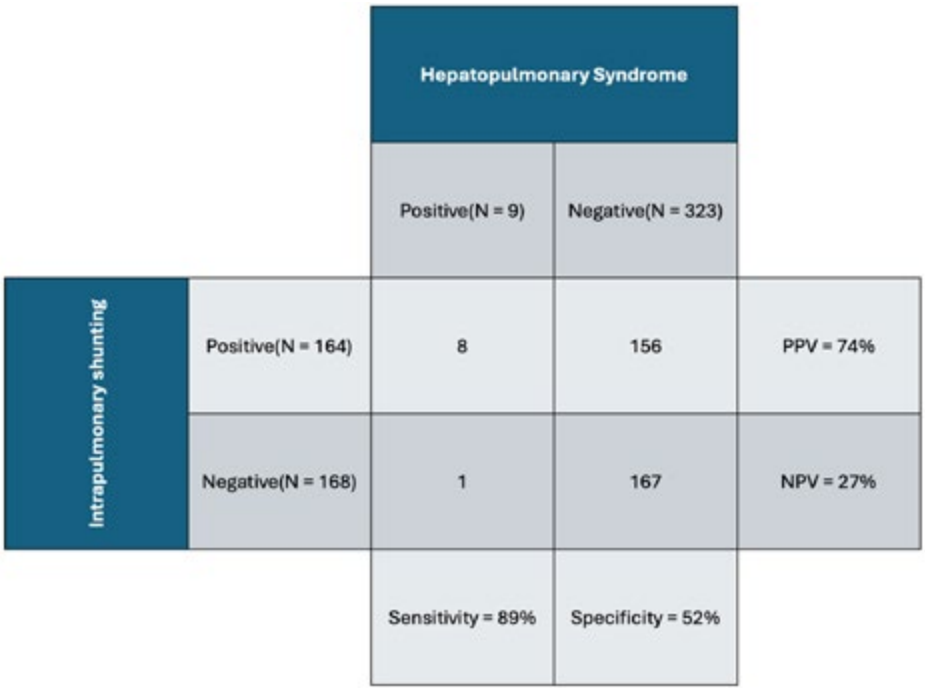
ECHO, there was a statistically significant association with ascites (p=0.0002), SBP (p=0.008), and TIPS (0.0004) on univariate analysis. Using HPS prevalence above of 2.7%, the sensitivity and specificity of IPS on ECHO for HPS was 89% and 52% respectively. The NPV and PPV were 27% and 74% respectively. Using a multivariate logistic regression model, age was the only statistically significant variable for a diagnosis of HPS. **Conclusion:** Bubble ECHO's diagnostic utility for predicting HPS in liver transplant evaluation is limited, demonstrating low specificity, NPV, and PPV. Intrapulmonary shunting was reported in about half of new liver transplant evaluation patients, yet only 2.7% were diagnosed with HPS. Routine bubble ECHO does not add significant diagnostic value unless supported by exam, imaging, or lab findings.



Disclosures: Mary Sullivan: Nothing to Disclose, Hannah Laird: Nothing to Disclose, Kavindya Wickramasinghe: Nothing to Disclose, Mira Sridharan: Nothing to Disclose, Curtis Argo: Nothing to Disclose

2511 | ONE YEAR POST TRANSPLANT OUTCOMES IN HCV POSITIVE DONOR TO HCV NEGATIVE RECIPIENT LIVER TRANSPLANTATION: A DESCRIPTIVE ANALYSIS OF A UNITED STATES TRANSPLANT CENTER'S EXPERIENCE

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[1]Banner University Medical Center, University of Arizona College of Medicine Phoenix, [2]Mount Sinai Morningside, [3]University of Arizona College of Medicine-Phoenix, [4]Emory University School of Medicine

Background: Each year the number of patients awaiting liver transplant (LT) vastly exceeds the number of available donor organs. The success of direct-acting antiviral agents (DAA) in curing hepatitis C virus (HCV) supports greater use of HCV positive (+) donors to increase the donor pool. We present one year post transplant outcomes following the use of HCV+ grafts in HCV negative (-) LT recipients at Emory University Hospital. **Methods:** This is a prospective cohort study of patients who underwent LT at Emory University Hospital between 2019 – 2021. Data and outcomes were collected and compared between (1) LT recipients who received an HCV – graft (n = 96) and (2) HCV – LT recipients who received an HCV + graft (n = 16). We performed descriptive analyses to compare baseline demographics of the recipient and donor, and immediate transplant related outcomes. We also assessed differences between groups with regards to admissions, infections, acute kidney injury (AKI), biliary complications, graft failure (GF), hepatocellular carcinoma (HCC) recurrence, and post transplant diabetes in the one year following liver transplant. **Results:** Patients who received a HCV+ graft had a statistically significant lower MELD at transplant compared to those who received an HCV – graft and a shorter hospital stay following transplant. There were no cases of primary non function or delayed graft function in the

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group that received HCV+ livers. Between HCV – and HCV + graft recipients, there was no statistical differences in the number of admissions or days of hospitalization within the first year post transplant. During the first post-transplant year, there was no difference in the incidence of GF, ACR, or death between groups. There was no statistical difference between the reasons for admission between the two groups with regards to admissions for infection, rejection, liver chemistry abnormalities, or biliary obstruction. Similarly, there was no statistical difference in post transplant complications such as AKI, infection, or biliary stricture between groups within the first year post transplant. Patients who received a HCV+ graft had a statistically significant lower incidence of post transplant diabetes in the one year post transplant. This may be attributed to greater physiologic reserve perhaps as a result of their lower MELD at transplant. There was no recurrence of HCC in the one year post transplant amongst patients who received an HCV+ graft. **Conclusion:** Our center's experience shows HCV+ donor livers without fibrosis should be routinely used for liver transplantation. Utilization of these grafts will expand the donor pool thereby improving waitlist and post transplant outcomes.

Table 1: Demographics & Transplant Outcomes

	HCV negative donor to recipient (n = 96)	HCV + donor to negative recipient (n = 16)	p value
Transplant Demographics and Outcomes			
MELD at Tx	31.86	27.63	0.04
Age at Tx (years)	55.01	61.00	0.06
Warm time (minutes)	36.30	33.38	0.36
Cold time (minutes)	425.58	376.7	0.09
Graft primary nonfunction	0	0	
Delayed graft function	4	0	
Days hospitalized after transplant	15.18	11.81	0.05
One Year Post Transplant Outcomes			
Admissions in transplant year	1.54	2.17	0.19
Total days hospitalized in 1 year post transplant	13.34	13	0.35
Death in 1 year	5.41%	0%	1
Reasons for Admission in 1 year post transplant			
Infection	27.03%	25%	1
ACR or liver chemistry abnormalities	18.92%	41.67%	0.13
AKI	16.22%	33.33%	0.22
Biliary obstruction	2.7%	8.33%	0.37
Complications in 1 year post transplant			
GF	2.7%	0%	1
ACR	12.16%	25%	0.36
AKI	37.84%	58.33%	0.22
Infection	32.43%	41.67%	0.53
Biliary stricture	14.86%	16.67%	1
Post transplant diabetes	18.67%	0%	0.02
HCC recurrence	1	0	

Disclosures: Raha Sadjadi: Nothing to Disclose, Anudeep Neelam: Nothing to Disclose, Pooja Rangan: Nothing to Disclose, Karn Wijarnpreecha: Nothing to Disclose, Giorgio Roccaro: Nothing to Disclose

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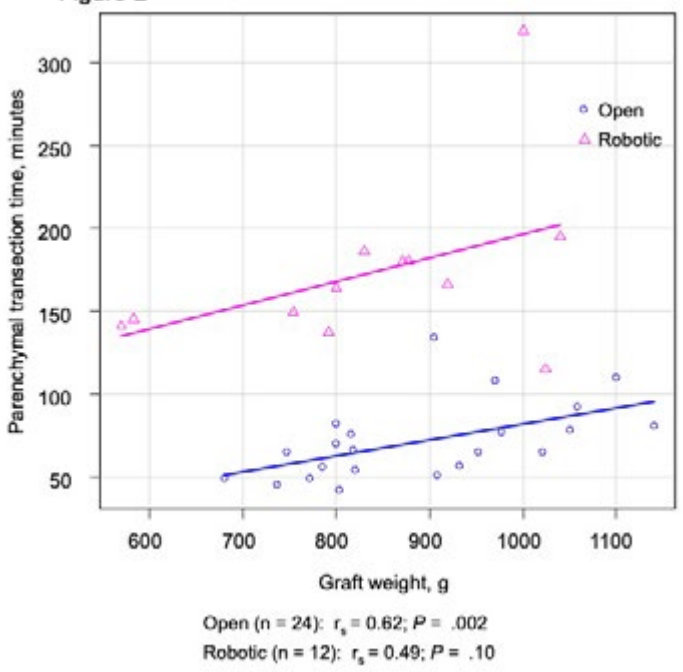
2512 | EARLY OUTCOMES OF ROBOTIC VS OPEN LIVING DONOR RIGHT HEPATECTOMY IN A US CENTER

Seung Duk Lee[1] *Yuzuru Sambommatsu*[2] *Vinay Kumaran*[2]

[1]*Virginia Commonwealth University,* [2]*VCU health system*

Background: Robotic living donor hepatectomy offers potential advantages but has been limited to high-volume centers, primarily in Asia and the Middle East. We report our experience establishing a robotic living donor right hepatectomy program in a U.S. center with low LDLT volume and no prior laparoscopic donor hepatectomy experience and analyze early outcomes. **Methods:** This retrospective cohort study included 36 living liver donors (12 robotic, 24 open) who underwent right hepatectomy between June 2022 and February 2024. **Results:** The robotic group had longer operative times (median [range], 461 [374–568] minutes vs 368 [276–421] minutes; P < .001) but less blood loss (median [range], 175 [50–700] mL vs 900 [300–2500] mL; P < .001). Two hematomas/bleeding (ClavienDindo grade □B) occurred in the robotic group, but no biliary complications. Comprehensive Complication Index, liver function tests, and hospital stays were similar between the two groups, with no 90-day graft failure/mortality. **Conclusion:** With meticulous preparation, U.S. centers with lower LDLT volume and no laparoscopic experience can safely implement robotic living donor right hepatectomy, achieving comparable shortterm outcomes to the open approach. Further research on long-term outcomes and donor quality of life is necessary

Figure 2



Disclosures: Seung Duk Lee: Nothing to Disclose, Yuzuru Sambommatsu: Nothing to Disclose, Vinay Kumaran: Nothing to Disclose

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2513 | SLEEP DISTURBANCE IS ASSOCIATED WITH FRAILTY, IMPAIRED PHYSICAL FUNCTION, FATIGUE, ANXIETY, AND DEPRESSION IN LIVER TRANSPLANT RECIPIENTS: RESULTS FROM THE LIVCOG COHORT STUDY

Minjee Kim[1] Douglas Schaubel[2] Anna Gurian[2] Alexander Burdzy[2] Nianfu Song[2] Lindsay Berg[2] Lauren Cogar[3] Hannah Berman[3] Allison Novorita[3] Justin Boike[4] Michael Wolf[3] Sumeet Asrani[5] Julia Benavente[3] Marina Serper[2]

[1]Northwestern University Feinberg School of Medicine, [2]University of Pennsylvania, [3]Northwestern University Feinberg School, [4]Northwestern Memorial Hospital/Northwestern University, [5]Baylor College of Medicine

Background: Subjective poor sleep is common after liver transplant (LT). Little is known about post-LT sleep quality and how different sleep measures correlate with frailty and quality of life. **Methods:** Data were derived from the NIDDK-funded, prospective LivCog cohort study conducted at four U.S. transplant centers. At 90±30 days after LT, patients wore a wrist actigraphy (ActiGraph GT3X-BT) for 8 consecutive days to measure time in bed, sleep duration, and sleep efficiency (percent time spent sleeping while in bed). Binary variables were created for short sleep duration (<6h) and poor sleep efficiency (<80%). Subjective sleep disturbance was defined as PROMIS Sleep Disturbance T-score >55. Frailty was defined as Liver Frailty Index ≥4.5. Quality of life measures included PROMIS Physical Function, Fatigue, Anxiety, and Depression subscales. Regression models examined associations of objective and subjective sleep measures with frailty, physical function, fatigue, anxiety, and depression, adjusting for age, sex, and liver disease etiology. **Results:** A total of 99 LT recipients (median (IQR) age 57 (51, 63); 39% female; 72% White, 12% Hispanic, 6% Black; etiology NASH (29%), alcohol (26%), HCC (11%)) provided valid actigraphy data at 80 (71, 92) days post-LT. By objective measures, patients spent 7.0 (5.7, 7.9) hours in bed, achieving 5.9 (4.4, 6.8) hours of sleep with 85 (80, 89)% efficiency. Short sleep duration and poor sleep efficiency were found in 57% and 26%, respectively. Subjective sleep disturbance was observed in 45%. Female sex (aOR 1.22 [95% CI 1.04-1.45]) and alcohol-associated liver disease (aOR 1.38 [1.13-1.68]) were positively associated with subjective sleep disturbance. No significant difference in objective sleep duration, efficiency, or midpoint was observed by subjective sleep disturbance. Post-LT physical frailty (17%), poor physical function (61%), fatigue (44%), anxiety (29%), and depression (24%) were common. Poor sleep efficiency was significantly associated with frailty (aOR 1.29 [1.05-1.57]), while subjective sleep disturbance was associated with poor physical function (aOR 1.22 [1.01-1.48]), fatigue (aOR 1.36 [1.13-1.63]), anxiety (aOR 1.28 [1.02-1.59]), and depression (aOR 1.29 [1.10-1.51]), after adjusting for covariates. (see Table) **Conclusion:** Subjective sleep disturbance is associated with poor mental and physical health, while objective poor sleep efficiency is associated with concurrent frailty. Future research may examine how distinct constructs of sleep change over time and relate to post-LT outcomes.

Table. Associations of sleep measures with frailty and quality of life

		Frailty[3], aOR[5] [95% CI], p-value	Quality of life measures[4], aOR[5] [95% CI], p-value			
			Poor Physical Function	Fatigue	Anxiety	Depression
Objective sleep measures[1]	Poor sleep efficiency (<80%)	**1.29 [1.05, 1.57]*, p=0.02**	1.01 [0.78, 1.30], p=0.97	0.80 [0.62, 1.04], p=0.10	0.87 [0.68, 1.10], p=0.25	0.83 [0.67, 1.02], p=0.08
	Short sleep duration (<6 hours)	1.00 [0.95, 1.05], p=0.94	0.99 [0.93, 1.06], p=0.83	1.00 [0.79, 1.26], p=0.99	1.07 [0.86, 1.32], p=0.54	1.20 [1.00, 1.44], p=0.05
Subjective sleep measure[2]	Sleep disturbance	1.13 [0.97, 1.33], p=0.13	**1.22 [1.01, 1.48]*, p=0.04**	**1.36 [1.13, 1.63]**, p=0.001**	**1.39 [1.17, 1.65]***, p<0.001**	**1.29 [1.10, 1.51]**, p=0.002**

aOR = adjusted odds ratio; CI = confidence interval
* denotes p-value < 0.05; ** denotes p-value <0.01; *** denotes p-value <0.001

[1] Objective sleep measures were calculated from an 8-day wrist actigraphy recording.
[2] Subjective sleep disturbance was defined by PROMIS Sleep Disturbance T-score >55
[3] Frailty was defined as Liver Frailty Index ≥4.5
[4] Poor quality of life was defined as PROMIS T-score >55 for Fatigue, Anxiety, and Depression and PROMIS T-score <45 for Physical Function.
[5] Multivariable models included covariates of age, sex, and liver disease etiology

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2514 | STRESS-INDUCED CARDIOMYOPATHY IN LIVER TRANSPLANT RECIPIENTS: A SYSTEMATIC REVIEW

Mohammad AbuAssi[1] Dara Suleiman[2] Saqr Alsakarneh[3] Farah Khraisat[2] Talib Al-Abcha[2] Harsimran Kalsi[1] Tony Brar[1] Yaseen Perbtani[1]

[1]University of Central Florida, [2]University of Jordan, [3]University of Missouri-Kansas City

Background: Takotsubo syndrome (TTS), also known as stress-induced cardiomyopathy, is characterized by transient left ventricular wall motion abnormalities and acute, reversible heart failure. Liver transplantation (OLT) represents a significant physical and emotional stressor, potentially increasing the risk of TTS. Previous research into TTS in the context of solid organ transplants (SOT) is limited, with inconclusive findings regarding its incidence and management. This systematic review aims to summarize the incidence, clinical presentations, and management strategies for TTS following liver transplantation, and to compare these findings with TTS cases in other SOTs. **Methods:** We conducted a systematic review of the literature using electronic databases, including PubMed, Scopus, and Web of Science, up to February 2024. Search terms included “Takotsubo syndrome,” “Takotsubo cardiomyopathy,” “stress-induced cardiomyopathy,” “solid organ transplant,” and “liver transplant.” After applying predetermined inclusion and exclusion criteria, we included 9 studies reporting TTS cases in liver transplant recipients. Data extraction focused on patient demographics, clinical presentations, TTS characteristics, diagnostic testing, management strategies, and clinical outcomes. Descriptive statistical analysis was performed to summarize the findings. **Results:** A total of 204 liver transplant recipients who developed TTS were included. The majority of TTS cases (approximately 75.8%) occurred intraoperatively or within the first 24 hours post-transplant, with an additional 9.8% occurring within the first week, and 6.4% reported beyond the first week. The average age of patients was 56.06 ± 6.65 years, with 50.5% being male. Common symptoms included chest discomfort (67%), dyspnea (58%), and dizziness (45%). Most patients (89.7%) were managed medically. Non-medical interventions included intra-aortic balloon pump (IABP) in 8.3% of cases and extracorporeal membrane oxygenation (ECMO) in 1.5%. The acute mortality rate across all studies was 9.3%. **Conclusion:** TTS following liver transplantation is a significant complication with a higher incidence compared to other solid organ transplants. The majority of cases occur within the first 24 hours post-transplant, highlighting the need for early recognition and intervention. Despite varied management strategies, the overall acute mortality rate is substantial. These findings highlights the importance of heightened vigilance and tailored management protocols in liver transplant recipients to improve outcomes. Further research is needed to better understand the pathophysiology and optimal management of TTS in this population.

Overview of Takotsubo Syndrome (TTS) Cases Across Different Solid Organ Transplant

Organ Type	Number of Cases	Average Age (years)	Gender (M/F)	Common Triggers	Timing of TTS Onset	Common Management
Liver (OLT)	204	56.06	50.5% M / 49.5% F	Surgery, stress	75.8% <24h, 9.8% <1 week, 6.4% >1 week	89.7% Medical, 8.3% IABP, 1.5% ECMO
Heart	11	46.4	45% M / 55% F	Emotional stress, medications	>1 year post-transplant	Predominantly medical
Kidney	5	54.0	40% M / 60% F	Tacrolimus toxicity, stress	Within 48h to several days	Predominantly medical
Lung	7	56.3	57% M / 43% F	Acute respiratory failure	Varied (intraoperative to years post-transplant)	Medical, Mechanical support

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Disclosures: Mohammad AbuAssi: Nothing to Disclose, Dara Suleiman: Nothing to Disclose, Saqr Alsakarneh: Nothing to Disclose, Farah Khraisat: Nothing to Disclose, Talib Al-Abcha: Nothing to Disclose, Harsimran Kalsi: Nothing to Disclose, Tony Brar: Nothing to Disclose, Yaseen Perbtani: Nothing to Disclose

2515 | HIGH-THROUGHPUT PROTEOMICS ANALYSIS IDENTIFIES CHANGES IN CIRCULATING PROTEOME SIGNATURES ACROSS DIFFERENT STAGES OF LIVER TRANSPLANTATION SURGERY

Xing Li[1] *Emily Bethea*[1] *Leigh Anne Dageforde*[1] *Katherine Specht*[1] *Russell Goodman*[1]

[1]*Massachusetts General Hospital*

Background: Circulating proteomics, the unbiased global analysis of quantitative protein expression, has been applied to identify the diagnostic and pathophysiologic signatures of various liver diseases such as ALD, MASLD and HCC. In this study, we aim to characterize changes in protein abundances occurring at different stages of liver transplantation surgery to uncover insights into underlying biological processes. **Methods:** We used the aptamer-based, high-throughput SomaScan platform to simultaneously measure the relative concentrations of over 7000 proteins in venous blood samples taken from three patients with cirrhosis and HCC undergoing OLT at three time points during the liver transplantation surgery: pre-hepatectomy stage, anhepatic stage, and post-reperfusion stage. **Results:** Out of 6622 unique protein targets measured, we found 330 unique proteins that were differentially expressed in the pre-hepatectomy stage compared to the anhepatic stage (Fig. 1a), 1327 unique proteins differentially expressed in the post-reperfusion stage compared to the anhepatic stage (Figure 1b), and 1886 unique proteins differentially expressed in the pre-hepatectomy stage compared to the post-reperfusion stage (Fig.1c). 73 unique proteins overlapped among the three pairwise comparisons, and over-representation analysis (ORA) clustered proteins correlating to pathways involving fibroblast growth factor receptor (FGFR) activation and regulation, which is known to play significant roles in liver fibrosis and regeneration. We then performed unsupervised hierarchical cluster analysis to characterize differential protein abundances at the three stages of the LT surgery (Fig. 1d). A specific cluster of proteins was found to have higher abundances in the pre-hepatectomy stage compared to the anhepatic and post-reperfusion stages, and ORA identified genes enriched in pathways involving the complement cascade and its regulation, highlighting the likely key role of complement activation in driving liver damage and fibrosis in cirrhosis. We then looked at the subset of proteins with the highest abundances in the anhepatic stage compared to the other two stages. ORA again identified a significant enrichment of genes in pathways associated with FGFR2 and FGFR3 activation. Additionally, we identified 8 Wnt ligand antagonists with peak expressions during the anhepatic stage, along with the Wnt signaling co-receptor LRP5, which showed the lowest expression during the anhepatic stage. This pattern suggests the presence of rapid extra-hepatic Wnt signaling. **Conclusion:** We identified significant and dynamic changes in circulating proteomics across the pre-hepatectomy, anhepatic and post-perfusion stages of LT surgery by utilizing the SomaScan platform. By identifying these changes we hope to better understand the biological mechanisms and disease progression and identify potential targets for further research.

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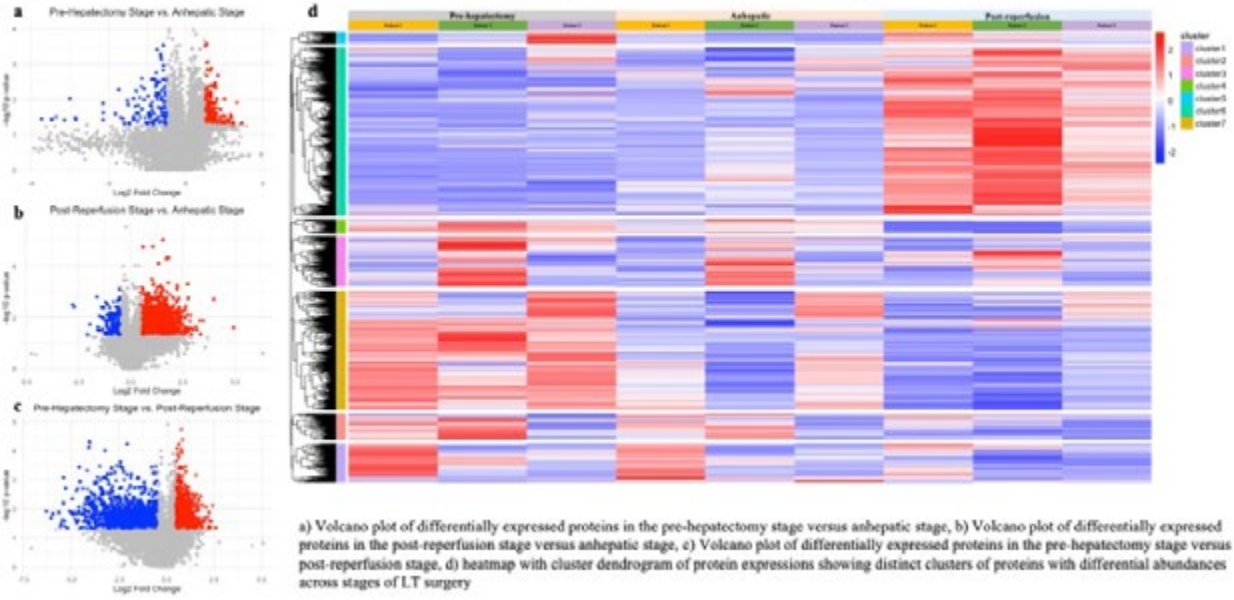
Figure 1. Broad Changes in Protein Abundances Across Different Stages of the Liver Transplantation Surgery Measured by the SomaScan Proteomics Platform



a) Volcano plot of differentially expressed proteins in the pre-hepatectomy stage versus anhepatic stage, b) Volcano plot of differentially expressed proteins in the post-reperfusion stage versus anhepatic stage, c) Volcano plot of differentially expressed proteins in the pre-hepatectomy stage versus post-reperfusion stage, d) heatmap with cluster dendrogram of protein expressions showing distinct clusters of proteins with differential abundances across stages of LT surgery

Disclosures: Xing Li: Nothing to Disclose, Emily Bethea: Nothing to Disclose, Leigh Anne Dageforde: Nothing to Disclose, Katherine Specht: Nothing to Disclose, Russell Goodman: Nothing to Disclose

2516 | EVALUATING EFFECTS OF TWO OXYGENATED SOLUTIONS FOR FLUSHING BY SIMULATING LIVER TRANSPLANTATION ON PUMP: HEMOPURE COMBINED WITH WILLIAM'S E CULTURE MEDIA OR UNIVERSITY OF WISCONSIN (UW) SOLUTION

Anil Kharga[1] Huyun Chen[1] McLean Taggart[1] Mohammadreza Mojoudi[1] Alban Longchamp[1] Heidi Yeh[1] Korkut Uygun[1] James Markmann[2]

[1]Massachusetts General Hospital, [2]Penn Medicine

Background: Because of the limited donor pool and ischemia arising during various transplantation stages causing graft dysfunction, optimizing these stages is crucial to prevent poor outcomes. A graft experiences cold ischemia during procurement, transportation, and back-benching until the start of graft implantation, during which the graft suffers from warm ischemia because of a slow rise in temperature. Cold and warm ischemia upon reperfusion has a synergistic effect in producing ischemic reperfusion injury (IRI). At physiological concentration ([Hb]: 12–14 mg/dL), hemopure, a hemoglobin-based oxygen carrier (HBOC-201), can deliver more oxygen than water (98% vs 2%). In order to prepare an oxygenated solution for flush to reduce cold and warm ischemia, we investigated two types of solutions: first, Hemopure with William's E (WE) hepatocyte culture media (OxyFlush 1) and second, Hemopure with the University of Wisconsin (UW) cold preservative solution (OxyFlush 2). **Methods:** *Control (n=[3])* livers were kept in 50 ml UW at 4°C for 2 hr to simulate cold ischemia of procurement and back-benching, followed by 1 hr of simulation of graft implantation, achieved by gradually increasing temperature from 4°C towards room temperature. Experimental group livers during the entire 3 hr of simulation phases received continuous cold (4°C) slow (0.05 ml/min/g of liver mass) flush with either Hemopure (25%) + WE (75%) in *OxyFlush [1] (n=[4])* or Hemopure (25%) + UW (75%) in *OxyFlush [2] (n=[5])* as illustrated in Fig 1. A. Normothermic Machine Perfusion (NMP) for 6 hr was used to compare graft functions. **Results:** At the end of the simulation phase, OxyFlush 2 had no edema, but both control and OxyFlush 1 had significant edema (Fig 1. B). During NMP, OxyFlush 1 & 2 showed improved hepatocellular functions, as demonstrated by higher O_2 uptake for both (Fig 2. A). Glucose metabolism and lactate levels were slightly better with OxyFlush 1 (Fig 2. B & D). Injury markers were higher in OxyFlush 1 than 2, as shown by higher portal vascular resistance, liver transaminase (AST & ALT), and edema at the end of NMP (Fig 2. C, F, G, H); however, potassium (K) was higher in OxyFlush 2 (Fig 2. E). **Conclusion:** OxyFlush 1 has partially improved hepatic function in terms of O_2 uptake, glucose, and lactate metabolism; however, edema is significant due to the lack of hydroxyethyl starch (oncotic agent: balances

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hydrostatic pressure in capillaries during flush) and lactobionic acid (impermeable anion: prevents hypothermia-induced cell swelling), both present in UW. Increased portal vascular resistance could be due to hypothermia-induced endothelial cell swelling in OxyFlush 1 and due to flushing out UW with NS in the control group during the simulated graft implantation phase. The elevated K level in OxyFlush 2 is due to the remnant of a high concentration of K [125 mM] in UW and, therefore, should be interpreted cautiously. Hence, Hemopure with UW is optimal for preparing an oxygenated solution for flush.

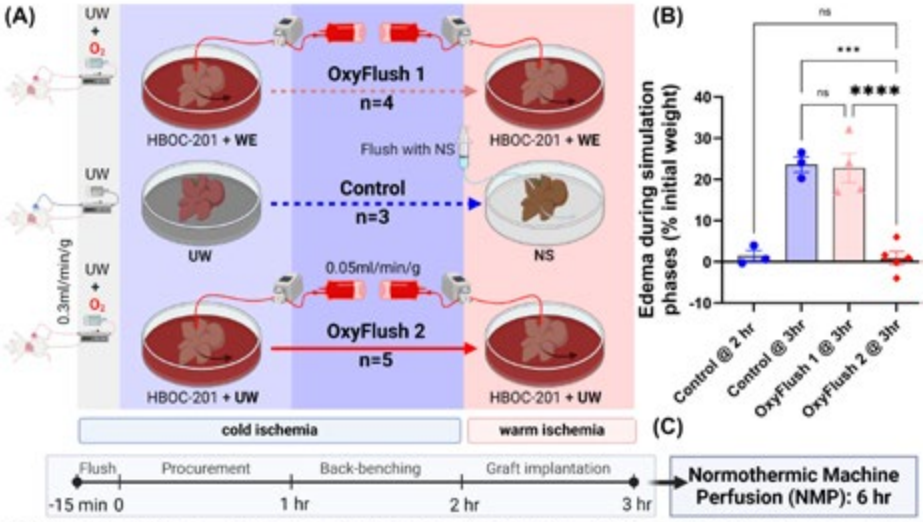

Fig 1: Simulation of cold and warm ischemia during transplantation with intervention for ischemia minimization: (A) Study design, (B) Edema developed at the end of ischemia simulation compared to initial weight at procurement, (C) 3 hr of simulation followed with 6 hr of NMP for assessment.

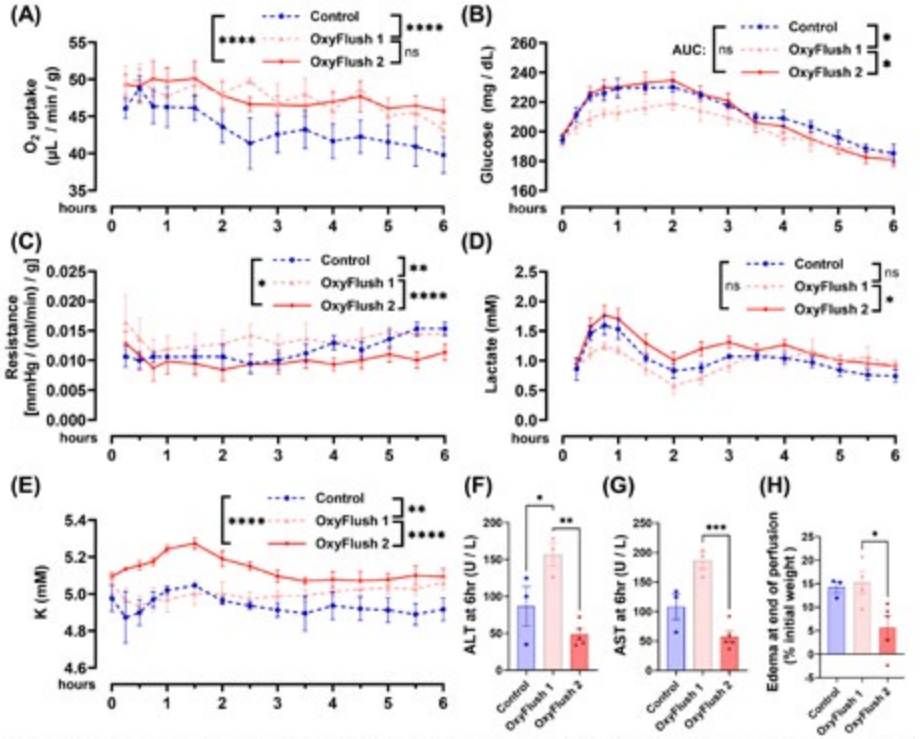

Fig 2: Normothermic machine perfusion (NMP) shows flushing with Hemopure + UW (OxyFlush 2: n=5) during 3hr of simulation performs better than Hemopure + WE (OxyFlush 1: n=4) solution; Control (n=3): without oxygenated flushing.

One-way ANOVA, followed by Tukey's post-hoc, results are from inflow line and expressed as mean with SEM; ns: $p > 0.05$, * : $p \le 0.05$, ** : $p \le 0.01$, *** : $p \le 0.001$, **** : $p \le 0.0001$; **Hemopure = HBOC-201**: hemoglobin-based oxygen carrier-201, K: potassium, AST: aspartate transaminase, ALT: alanine transaminase, **UW**: University of Wisconsin cold storage preservative solution, **WE**: William's E hepatocyte culture media, **NS**: normal saline, **AUC**: area under curve.

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Disclosures: Anil Kharga: Nothing to Disclose, Huyun Chen: Nothing to Disclose, McLean Taggart: Nothing to Disclose, Mohammadreza Mojoudi: Nothing to Disclose, Alban Longchamp: Nothing to Disclose, Heidi Yeh: Nothing to Disclose, Korkut Uygun: Nothing to Disclose, James Markmann: Transmedics: stock, Vertex: Advisor, Transmedics: Advisor, iTolerance: Advisor, eGenesis: Advisor

2517 | ESTABLISHMENT AND OBSERVATION OF A LONG-TERM VIABLE ALLOGENIC MURINE LIVER TRANSPLANTATION MODEL

Keiko Iwaisako[1] Momoko Fujita[1] Kaito Suzumura[2] Shuhei kanda[3] Daisuke Kyuno[4] Hiroto Nishino[3]

[1]Faculty of Life and Medical Sciences, Doshisha University, [2]Graduate School of Life and Medical Sciences, Doshisha University, [3]Graduate School of Medicine, Kyoto University, [4]Sapporo Medical University

Background: Immune rejection after liver transplantation remains largely unknown, and there are cases of chronic rejection that are difficult to treat, so there is a need to elucidate the mechanism and develop effective treatments. In rodent liver transplantation models used in basic research, most studies have not performed arterial reconstruction and long-term observation. We established a liver transplantation model with hepatic artery reconstruction between MHC-mismatched mice to observe the time course of rejection after liver transplantation. **Methods:** Male BALB/c mice (11-13 weeks) as donors and male C57BL/6 mice (11-13 weeks) as recipients were used for allogeneic liver transplantation. Transplanted recipient mice were sacrificed every few weeks until 64 weeks after liver transplantation, and organs and peripheral blood were collected. The liver was subjected to histopathological analysis. Plasma biochemical analysis and immunoglobulin quantification were performed. **Results:** Histopathological analysis revealed no rejection in the syngeneic group. In contrast, the allogeneic group showed marked immune cell infiltration from 1 week postoperatively and fibrosis from 4 weeks postoperatively. Although the rejection decreased and the mice gained weight by 8 weeks after transplantation, a mild immune cell infiltrate persisted and fibrosis was observed even 64 weeks after transplantation. Regarding antibody production after transplantation, all subclasses showed a sharp increase in peripheral blood in the acute phase up to about 4 weeks postoperatively, after which the concentration tended to decrease but remained higher than preoperative levels. Antibodies adsorbed in liver tissue were highest at 8 weeks postoperatively, according to histologic observations. **Conclusion:** Despite complete MHC mismatch, our murine liver transplantation model with arterial reconstruction demonstrated viability for 64 weeks. However, immune tolerance was not achieved. In some post-transplant patients, serum biochemistry tests may show minimal elevations in bilirubin or liver enzymes and no overt complications despite the presence of liver fibrosis. Such graft fibrosis is known as “silent fibrosis”. There are similarities between the pathology observed in our mouse model at 30 weeks post-operatively and human silent fibrosis. We hope that this model will prove to be a useful tool for studying acute rejection, antibody-associated rejection and silent fibrosis, and will contribute to the development of more effective immunosuppressive therapies.

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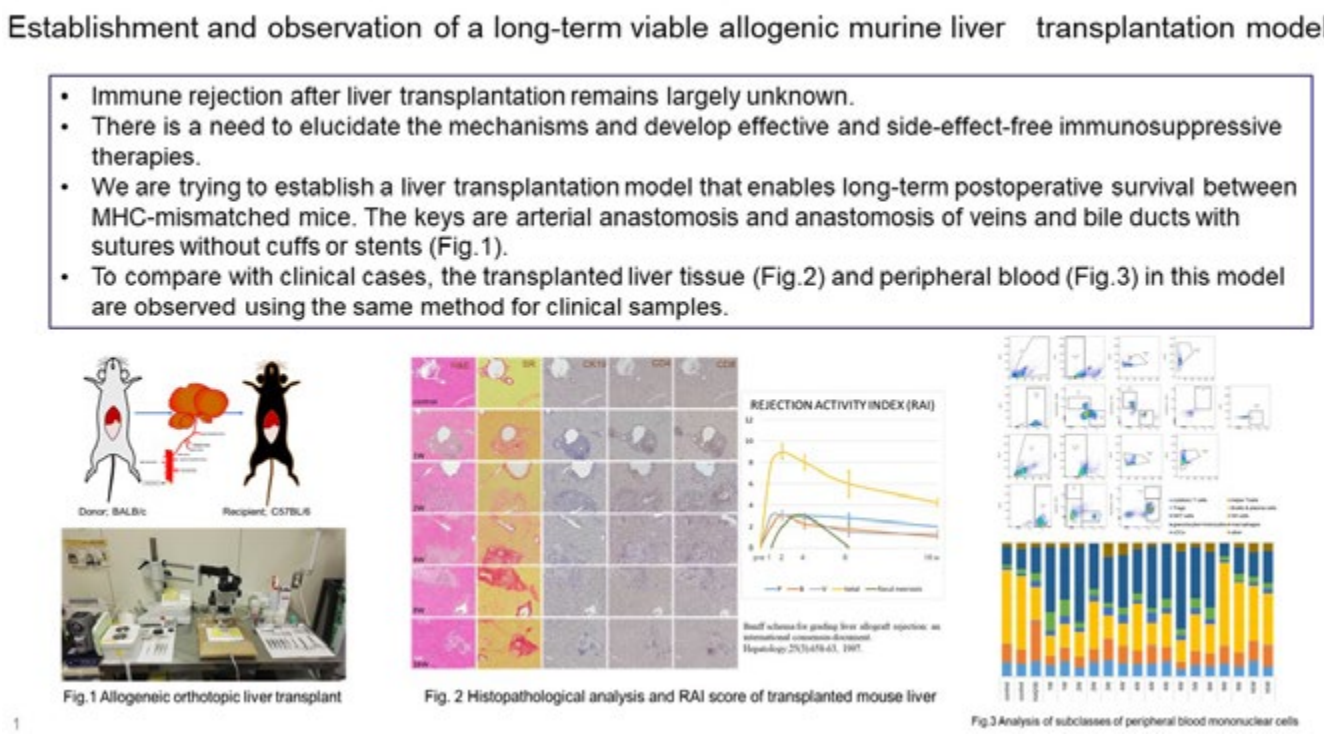

Disclosures: Keiko Iwaisako: Nothing to Disclose, Momoko Fujita: Nothing to Disclose, Kaito Suzumura: Nothing to Disclose, Shuhei kanda: Nothing to Disclose, Daisuke Kyuno: Nothing to Disclose, Hiroto Nishino: Nothing to Disclose

2518 | EFFECTIVENESS AND SAFETY OF TENOFOVIR ALAFENAMIDE FOR HBV PROPHYLAXIS IN HBV NEGATIVE RECIPIENTS OF ORTHOTOPIC LIVER TRANSPLANT WITH HBCAB+ DONORS:24 WEEKS INTERIM ANALYSIS

Aiwei Zhou[1] Zhifeng Xi[2] Kang He[2] Hualian Hang[2] Hanyong Sun[2] Yongbing Qian[2] Wei Geng[2] Jie Cao[2] Lei Xia[2] Jianjun Zhang[2] Qiang Xia[2]

[1]Shanghai Jiaotong University School of Medicine, [2]Renji hospital

Background: Liver transplantation (LT) is now the established standard of care for individuals suffering from end-stage liver disease. However, the demand for LT has outpaced organ availability. With a scarcity of suitable liver grafts, proper use of HBcAb+ grafts could potentially expand the donor pool and save more patients. Tenofovir alafenamide (TAF) has demonstrated non-inferior efficacy compared with tenofovir disoproxil fumarate (TDF), with improved bone and renal safety. The present study aims to evaluate the effectiveness and safety of TAF for HBV prophylaxis in HBV negative recipients of orthotopic liver transplant (OLT) with HBcAb+ donors in China. **Methods:** In this prospective single-arm study, eligible patients were over-12-year-old HBsAg-/HBV DNA- LT recipients who received grafts from HBsAg-/HBcAb+ deceased donors. Patients received TAF 25 mg/day immediately after OLT. Treatment continued until development of unacceptable adverse events (AEs) or withdrawal of consent. Laboratory tests were taken weekly (month 1), biweekly (month 2-3) and monthly (month 4-6). FibroScan were performed at week 12 and week 24. Key efficacy endpoint of this interim analysis was HBV DNA+ or HBsAg+ rate at week 24. Key safety endpoints included changes in hepatic and renal function, and incidence of treatment-emergent AEs. This trial is registered with ClinicalTrials.gov, number NCT04703465. **Results:** Between July 30, 2022 and May 18, 2024, 16 patients were enrolled and 12/16 completed 24 weeks of TAF treatment and follow-up. Baseline characters were as follows: mean age 52.1 years, 68.8% males, median serum creatinine 66 μmol/L, median eGFR 103 mL/min/1.73m^2. Median study follow-up was 48 (Q1 16, Q3 48) weeks. Throughout the follow-up period, no patient was detected HBV DNA+ or HBsAg+. There was no grade 3 or higher laboratory abnormalities in hepatic function. Mean alanine aminotransferase (ALT), aspartate aminotransferase (AST) and median total bilirubin (TBIL) at week 24 were 23.5 (95% CI 15.2, 31.8) U/L, 24.3

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(95% CI 19.9, 28.8) U/L and 13.6 (Q1 10.8, Q3 18.7) µmol/L respectively. Mean LSM at week 24 was 7.3 (95% CI 6.6, 7.8) kPa. Median LSM change compared to week 12 was +0.2 (Q1 -0.1, Q3 +0.3) kPa. For renal function assessment, median serum creatinine and eGFR change between week 24 and week 0 were +10.5 (Q1 -8.8, Q3 +19.3) µmol/L and -7.5 (Q1 -12.3, Q3 -1.3) mL/min/1.73m^2 respectively. Serious AEs occurred in 7 (43.8%) patients, but none were treatment related. **Conclusion:** Long-term outcomes among HBV negative LT recipients receiving TAF monotherapy showed sustained prevention of de novo HBV infection from HBcAb+ donors alongside continued improvements in essential hepatic and renal safety indicators.

Disclosures: Aiwei Zhou: Nothing to Disclose, Zhifeng Xi: Nothing to Disclose, Kang He: Nothing to Disclose, Hualian Hang: Nothing to Disclose, Hanyong Sun: Nothing to Disclose, Yongbing Qian: Nothing to Disclose, Wei Geng: Nothing to Disclose, Jie Cao: Nothing to Disclose, Lei Xia: Nothing to Disclose, Jianjun Zhang: Nothing to Disclose, Qiang Xia: Nothing to Disclose

2519 | THE UTILITY OF FOLLOW-UP TRANSTHORACIC ECHOCARDIOGRAM (TTE) TO SCREEN FOR SEVERE PORTOPULMONARY HYPERTENSION (POPH) IN PATIENTS GRANTED POPH MODEL FOR END-STAGE LIVER DISEASE (MELD) EXCEPTIONS

Kathryn del Valle[1] Dana Kay[2] Michael Krowka[3] James Runo[4] Corey Sadd[4] Julie Heimbach[3] Rodrigo Cartin-Ceba[5] Hector Cajigas[3] Charles Burger[6] John Moss[6] Hilary DuBrock[3]

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Background: Current Model for End Stage Liver Disease (MELD) exception policies for patients with portopulmonary hypertension (POPH) require serial right heart catheterizations (RHC) every 3 months in order to accrue and maintain exception points. RHC is necessary for the initial diagnosis of POPH, but the utility of serial catheterizations in these patients has not been studied. In patients with POPH MELD exceptions, we sought to compare non-invasive and invasive hemodynamic assessments and to determine the sensitivity of echocardiography for detection of hemodynamically severe POPH that would preclude liver transplantation (LT). **Methods:** We performed a single-center retrospective cohort study of patients with POPH MELD exceptions who underwent LT between December 2008 and January 2024. results were validated at an external academic medical center. Data are summarized using median (interquartile range) or number (%). We compared transthoracic echocardiograms (TTE) and RHCs performed within one month of each other. Pearson correlation coefficient and Bland-Altman plots were used to assess the association between TTE and RHC variables. We examined varied echocardiographic parameters and thresholds to optimize sensitivity for detection of hemodynamically severe POPH. **Results:** Twenty-two individuals underwent 60 follow-up RHCs with paired TTEs. The majority of patients were male (68%) and Caucasian (86%) with median age of 58 years and median laboratory MELD-Na score of 16. Overall, the cohort had severely elevated right ventricular systolic pressure (RVSP) (median 79 mmHg, IQR 67-86) on baseline TTE. Median baseline hemodynamics on initial (diagnostic) RHC were consistent with severe POPH: mPAP 52 mmHg (IQR 41-58), PVR 6.4 WU (IQR 4.4-9.9). See Table 1 for additional baseline characteristics. Follow-up TTEs were performed within median 2 days of RHC. Right ventricular systolic pressure (RVSP) and cardiac index (CI) estimated by TTE were not strongly correlated with the counterpart RHC measurements at follow-up (RVSP and RHC pulmonary artery systolic pressure: R=0.30, p=0.02; CI: R=0.17, p=0.21) . However, TTE with an RVSP ≥ 48 mmHg had 100% sensitivity for detecting hemodynamically severe POPH, with 100% negative predictive value (NPV) and specificity 28%. In an external validation of 13 paired TTEs and RHCs, our algorithm had 64% specificity and 100% NPV. **Conclusion:** Follow-up TTE was not a good surrogate for RHC in assessing exact hemodynamics but had excellent sensitivity and NPV in assessing high risk hemodynamics that would preclude accrual of MELD exception points and overall LT eligibility. These findings may have important implications for current exception policies which require serial follow-up RHC every 3 months for patients granted POPH MELD exceptions.

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Table 1: Baseline Characteristics. N=22	
Female Sex	7/22 (32%)
Age at time of LT	58 years (50-60)
Race (Self-identified)	
White	19/22 (86.4%)
American Indian	2/22 (9.1%)
Hispanic	1/22 (4.5%)
Etiology of liver disease	
Alcohol	6/22 (27.3%)
Non-alcoholic fatty liver disease	3/22 (13.6%)
Hepatitis C	6/22 (27.3%)
Cryptogenic cirrhosis	3/22 (13.6%)
Other	4/22 (18.2%)
Laboratory values (MELD) (n=20)	
Na	140 (137-141)
Creatinine	1.04 (0.9-1.5)
Total bilirubin	2.3 (1.5-3.4)
INR	1.4 (1.3-1.8)
Calculated MELD-Na (n=20)	16 (14-20)
Echocardiogram at Diagnosis (median)	
Estimated right atrial pressure, mmHg (n=18)	10 (5-14)
Estimated right ventricular systolic pressure, mmHg (n=19)	79 (67-86)
Estimated cardiac output (L/min) (n=16)	6.4 (5.9-7.6)
RV function: n=19	
Normal	5/19 (26.3%)
Mild dysfunction	7/19 (36.8%)
Moderate dysfunction	4/19 (21%)
Moderate-severe dysfunction	3/19 (15.8%)
Pulmonary Hemodynamics at Diagnosis	
Right atrial pressure, mmHg (n=21)	11 (7-18)
Pulmonary artery systolic pressure, mmHg (n=21)	87 (65-95)
Mean pulmonary artery pressure, mmHg (n=22)	52 (41-58)
Pulmonary artery wedge pressure, mmHg (n=22)	11 (9-15)
Cardiac output, L/min (n=22)	5.8 (4.7-6.8)
Cardiac index, L/min/m^2 (n=21)	2.8 (2.5-3.2)
Pulmonary vascular resistance, Wood units (n=19)	6.4 (4.4-9.9)

Disclosures: Kathryn del Valle: Nothing to Disclose, Dana Kay: Nothing to Disclose, Michael Krowka: Nothing to Disclose, James Runo: Nothing to Disclose, Corey Sadd: Nothing to Disclose, Julie Heimbach: Nothing to Disclose, Rodrigo Cartin-Ceba: Nothing to Disclose, Hector Cajigas: Nothing to Disclose, Charles Burger: INSMED: Consultant, GossamerBio: Consultant, Janssen: Consultant, John Moss: Nothing to Disclose, Hilary DuBrock: Nothing to Disclose

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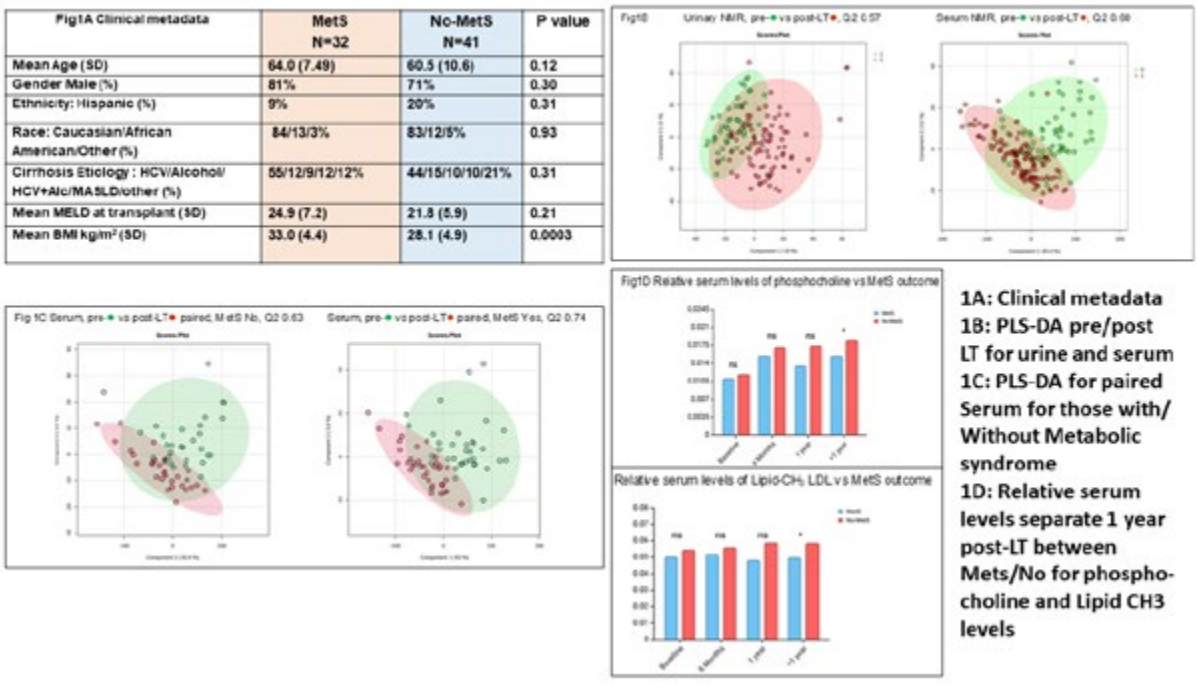
2520 | SERUM AND URINARY METABOLOMICS ARE ASSOCIATED WITH THE DEVELOPMENT OF DE NOVO METABOLIC SYNDROME AFTER LIVER TRANSPLANT: A MULTI-CENTER LONGITUDINAL STUDY ◆

Jasmohan Bajaj[1] Isobel Jane Cox[2] Mette Munk Lauridsen[1] Adrien Le Guennec[3] Andrew Fagan[4] Geena George[5] Amy Bartels[1] Thresiamma Lukose[5] Elizabeth Verna[5]

[1]Virginia Commonwealth University, [2]Roger Williams Institute for Hepatology, [3]Kings College London, [4]Richmond VA Medical Center, [5]Columbia University Medical Center

Background: Liver transplantation (LT) is associated with development of *de novo* metabolic syndrome (MetS) and adverse cardiovascular events over time. Gut microbiota-related products such as trimethylamine-*N*-oxide (TMAO) are linked with negative cardiovascular outcomes in the general population through atherogenesis promotion. The long-term impact of LT on microbial functionality, which could modulate the adverse pro-atherogenic profile, is unclear. Our aims were to determine the effect of LT on ongoing gut microbial functionality in long-term (up to 9 years) follow-up post-LT, as measured by serum & urinary metabolomics using nuclear magnetic resonance spectroscopy (NMR). **Methods:** We enrolled 73 patients from two USA LT centres at baseline (Fig1A), who received LT 6±3 months after enrolment. A subset was re-evaluated at 6 months (n=47), 1 year (n=26) and 2-9 years (n=33) after LT. The remaining either died post-LT, did not return for post-LT visits, or did not provide samples. All post-LT patients were on calcineurin inhibitors. We only included those post-LT pts who did not require re-LT, were stable clinically & did not have recent rejection episodes or infections. Serum NMR, and urinary NMR on a subset, at these timepoints were analysed and relative signal levels (to total signal intensity) of relevant metabolites was determined & compared between those with/without post-LT MetS. **Results:** MetS post-LT was definitively present in 32 (43%) patients (Fig1A). There were marked differences pre- and post-LT using partial least squares discriminant analysis (PLS-DA) (Q2>0.4) for both the urine and serum NMR profiles (Fig1B). Metabolites contributing to the differences included increased phosphocholines, increased urinary TMAO and phenylacetylglutamine (PAG), and decreased serum formate, acetate, tyrosine & phenylalanine. PLS-DA and metabolite differences post- vs pre-LT, of relevance to phosphatidylcholine turnover, were observed according to presence or absence of the MetS (Fig1C,D), which might indicate alterations in lipoprotein homeostasis. **Conclusion:** The increases in urinary TMAO and PAG, and reductions in serum formate and acetate, during the months post-LT indicate microbial restoration. Changes in gut microbiota related metabolites, and in phosphochlines and some lipids, differed in those who developed *de novo* MetS post-LT and may indicate an atherogenic milieu. These studies add weight to a role for microbial modulation as a target to modulate these outcomes.

Fig1A Clinical metadata	MetS N=32	No-MetS N=41	P value
Mean Age (SD)	64.0 (7.49)	60.5 (10.6)	0.12
Gender Male (%)	81%	71%	0.30
Ethnicity: Hispanic (%)	9%	20%	0.31
Race: Caucasian/African American/Other (%)	84/13/3%	83/12/5%	0.93
Cirrhosis Etiology : HCV/Alcohol/ HCV+Alc/MASLD/other (%)	55/12/9/12/12%	44/15/10/10/21%	0.31
Mean MELD at transplant (SD)	24.9 (7.2)	21.8 (5.9)	0.21
Mean BMI kg/m^2 (SD)	33.0 (4.4)	28.1 (4.9)	0.0003



1A: Clinical metadata
1B: PLS-DA pre/post LT for urine and serum
1C: PLS-DA for paired Serum for those with/ Without Metabolic syndrome
1D: Relative serum levels separate 1 year post-LT between Mets/No for phospho-choline and Lipid CH3 levels

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2521 | ASSESSING LIVER TRANSPLANT REJECTION USING PAIRED BLOOD AND BIOPSY SAMPLES

Katelynn Madill-Thomsen[1] Jeff Reeve[1] Sunil Kurian[2] Philip Halloran[1] Josh Levitsky[3]

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Background: Blood-based molecular assessments for liver transplant rejection are being evaluated for their predictive capability in guiding immunosuppression management. We recently developed the Molecular Microscope Diagnostic System (MMDx) for liver transplant rejection and injury using biopsies (Madill-Thomsen et al, AJT, 2020 & 2022). Here, we studied the relationship between histologic and molecular rejection, and compared the potential of using blood vs biopsy gene expression to detect histologic or molecular rejection in liver transplants. **Methods:** We used genome-wide expression in 72 paired biopsy and blood samples (using hgu219 and hgu133 arrays, respectively, transcripts common to both per gene symbol (N=14937) were used in these analyses). Diagnostic categories were assigned as acute rejection (AR), HCV recurrence with AR (HCVAR) or without (HCV), or acute dysfunction no rejection (ADNR). Class comparisons used either histologic (positive class = AR/HCVAR, negative class = ADNR/HCV) or molecular rejection categories (positive class=TCMR, negative class=no rejection 'NR'/recent injury 'RI'). Classifiers development used previously described ensemble **Methods:** (Reeve et al, AJT, 2019). Pathogenesis-based transcript sets (PBTs) were used to annotate disease processes. **Results:** Of 23 biopsies called TCMR by MMDx archetypes, 12 also had histologic TCMR (Fig1A). In a class comparison of histologic rejection vs. no rejection (Fig1B), top transcripts in biopsies included IL18BP, GBP5, and IFNG (P=2.0E-8 to 4.8E-6). In blood samples, transcripts were less significant though some were previously annotated as rejection-associated or interferon-gamma (IFNG)-inducible e.g. VAMP5, ATF3 (P=8.7E-5 to 8.4E-4). While scores for the T cell burden (TCB) and IFNG-inducible (GRIT1) transcript sets were correlated in blood and biopsy samples (Fig1C-D), scores for most rejection-associated transcript sets were not. A molecular classifier trained on histologic rejection vs no rejection in biopsies predicted molecular rejection with AUC=0.87 but histologic rejection less well (AUC=0.65, Fig1E). When the same labels were used to train a rejection classifier in blood-based expression, AUCs were 0.55 and 0.52, respectively. **Conclusion:** Gene expression in blood correlates weakly with histologic or molecular rejection in liver transplant biopsies; however, some gene sets in blood (GRITs, TCB) correlate with expression of those gene sets in the biopsy. In biopsies, histologic rejection correlated with molecular TCMR. A molecular classifier trained on histologic rejection predicted molecular rejection better than histologic rejection. In this dataset, biopsy-based expression had higher diagnostic accuracy than blood-based expression for detecting molecular and histologic rejection, and may be more clinically useful, but larger cohorts are needed for validation.

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A. Clinical calls vs MMDx liver rejection 4AA archetype groups in 72 biopsies

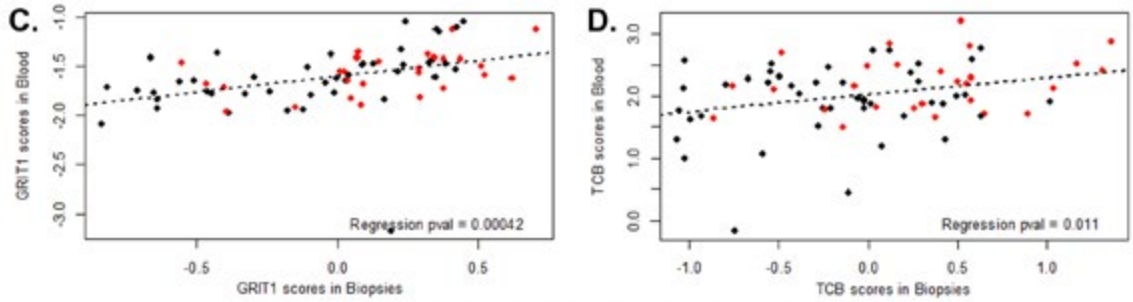
		Histology-based diagnoses				Row Sum
		ADNR[1]	HCV[1]	AR[2]	HCVAR[2]	
MMDx-Liver Rejection 4AA archetype groups	RI[1]	1	6	5	1	13
	NR[1]	13	9	3	1	26
	NKRL[3]	0	5	1	4	10
	TCMR[2]	1	10	7	5	23
Column Sum		15	30	16	11	72

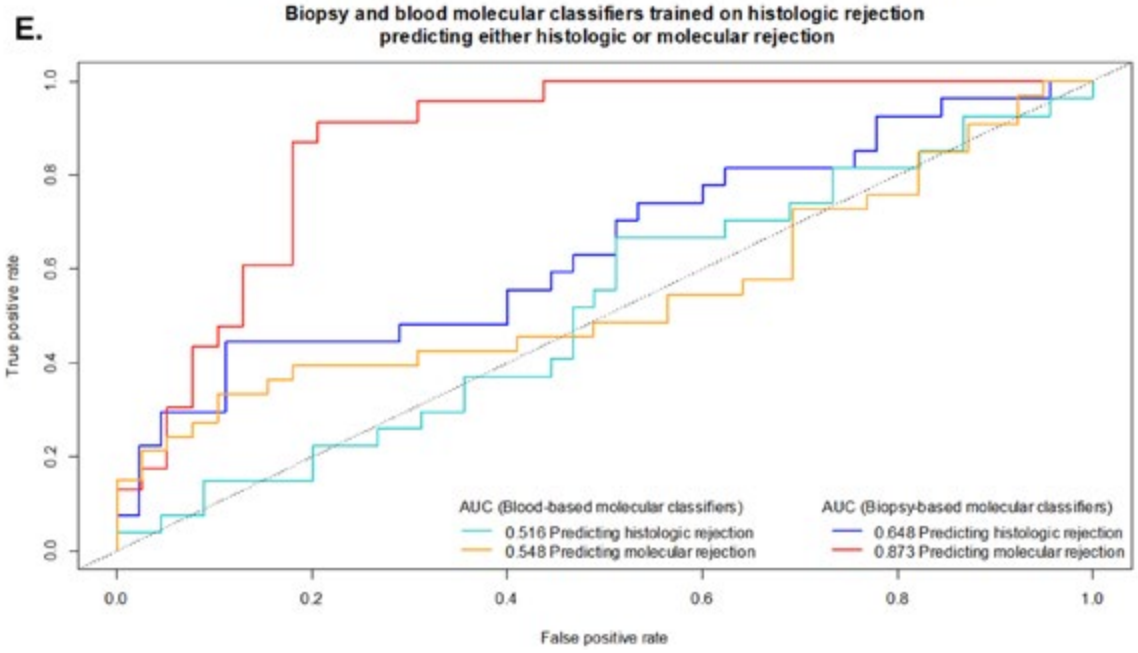
1. Treated as No rejection in class comparisons and in classifier training.
2. Treated as Rejection in class comparisons and in classifier training.
3. Left out of the molecular rejection versus no rejection class comparison.

B. Top 10 transcripts from the Bayesian t-test comparing biopsies (top) and blood (bottom): Histologic rejection (AR and HCVAR) versus everything else (ADNR and HCV)

Gene Symbol	Gene Name	PBT Annotation	P value	Adjusted P value
In biopsies				
IL18BP	interleukin 18 binding protein	GRIT,TCMR-RAT	0.00000002	0.00025
GBP5	guanylate binding protein 5	GRIT	0.00000092	0.0039
IFNG	interferon, gamma	QCAT,TCMR-RAT	0.00000093	0.0039
CCL4	chemokine (C-C motif) ligand 4	Rej-RAT	0.0000014	0.0044
GCNT1	glucosaminyl (N-acetyl) transferase 1	TCMR-RAT	0.0000018	0.0046
EGR2	early growth response 2	IRRAT	0.0000026	0.0055
FCGR1A	Fc fragment of IgG, high affinity Ia	GRIT,TCMR-RAT	0.0000034	0.0055
GBP2	guanylate binding protein 2, IFNG-inducible	GRIT,IRRAT	0.0000044	0.0055
LILRB2	leukocyte immunoglobulin-like receptor	QCMAT	0.0000044	0.0055
PRF1	perforin 1 (pore forming protein)	QCAT,Rej-RAT	0.0000048	0.0055
In blood				
C3orf14	chromosome 3 open reading frame 14		0.000067	0.84
PAPLN	papilin, proteoglycan-like sulfated glycoprotein		0.00016	0.84
CENPM	centromere protein M		0.00024	0.84
ZNF687	zinc finger protein 687		0.00042	0.84
KCNJ3	potassium channel		0.00052	0.84
CDCA7	cell division cycle associated 7		0.00058	0.84
VAMP5	vesicle associated membrane protein 5	GRIT	0.00074	0.84
ATF3	activating transcription factor 3	GRIT,IRRAT	0.0008	0.84
SYN2	synapsin II		0.00084	0.84
PUS3	pseudouridylate synthase 3		0.00084	0.84

Abbreviations: GRITs - IFNG-inducible transcripts, TCMR-RAT – TCMR associated transcripts, QCAT – quantitative cytotoxic T cell-associated transcripts, Rej-RAT – rejection associated transcripts, IRRAT – injury-repair response associated transcripts, QCMAT – quantitative constitutive macrophage-associated transcripts.





Disclosures: Katelynn Madill-Thomsen: Nothing to Disclose, Jeff Reeve: Nothing to Disclose, Sunil Kurian: Nothing to Disclose, Philip Halloran: Nothing to Disclose, Josh Levitsky: Nothing to Disclose

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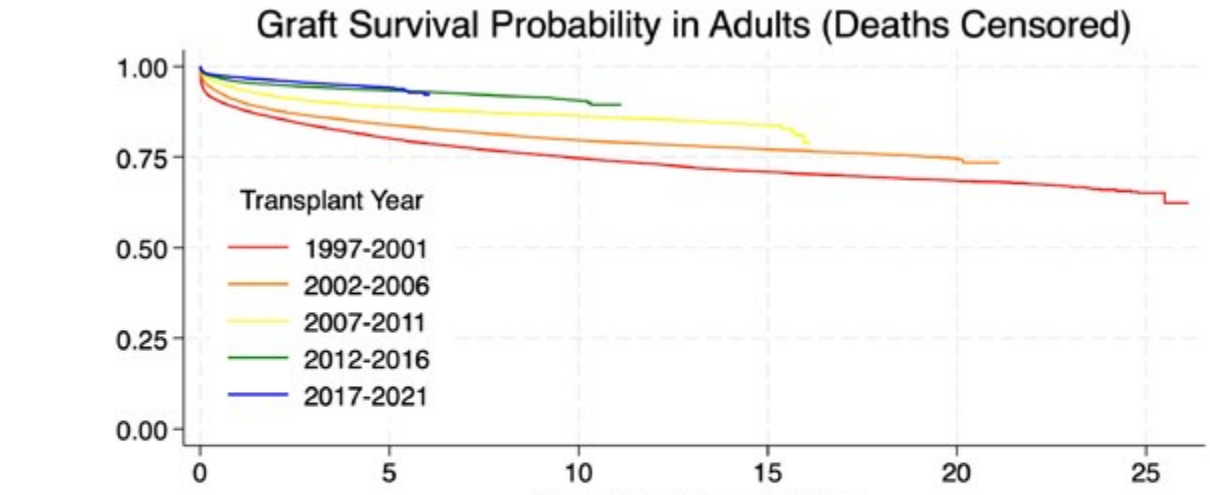
2522 | ADVANCEMENTS IN LIVER TRANSPLANT OUTOMES FROM 1997 TO 2023

Fawaz Al Ammary[1] Abhinav Humar[2] Simeon Adeyemo[1] Kate Kriby[1] Ahmet Gurakar[3]

[1]University of California Irvine, [2]University of Pittsburgh Medical Center, [3]Johns Hopkins University

Background: Improvment in liver transplant techniques and immunosuppression impact the lifespan of liver transplantation. Prior research often involved relatively small cohorts or had limited follow-up periods. Understanding long-term outcomes is crucial for shaping future strategies in the light of increasing burden of liver disease. We sought to investigate the impact of liver transplant practice on long-term graft and patient survival. **Methods:** Using data from the Scientific Registry of Transplant Recipients between January 1, 1997, and December 31, 2021, we studied 139, 343 adult liver transplant recipients (median age=55 years; 72.3% White, 13.7% Hispanic, 8.5% Black, 4.2% Asian). Patients were followed for up to 26 years, until graft failure, death, or the end of the study in December 2023. We used Kaplan-Meier survival and Multivariable Cox regressions to adjust for confounders. We stratified analyses by era (1997–2001, 2002–2006, 2007–2011, 2012–2016, and 2017–2021). **Results:** Overall survival after liver transplantation improved over time. In the eras 1997–2001, 2002–2006, 2007–2011, 2012–2016, and 2017–2021, the 5-year death-censored graft survival rate was 80.7%, 84.3%, 88.9%, 93.5%, and 94.3%, respectively [Figure]; the 5-year patient survival rate was 76.6%, 75.4%, 76.6%, 81.8%, and 82.5%, respectively. **Conclusion:** This study highlights significant improvements in long-term survival after liver transplantation over the past three decades. Continued efforts are needed to expand access to liver transplantation reducing the burden of end-stage liver disease.



Number at risk

1997-2001	18756	11348	7999	5530	3456	123
2002-2006	25034	15669	11585	7916	341	0
2007-2011	26727	18155	13441	663	0	0
2012-2016	29991	21952	963	0	0	0
2017-2021	38835	1879	0	0	0	0

Disclosures: Fawaz Al Ammary: Nothing to Disclose, Abhinav Humar: Oncocyte: Advisor, Simeon Adeyemo: Nothing to Disclose, Kate Kriby: Nothing to Disclose, Ahmet Gurakar: Grant/Research Support relationship with DURECT; Has ended; Advisor relationship with Orphalan; Has ended

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2523 | FEASIBILITY AND EARLY OUTCOMES OF A NOVEL MULTIDISCIPLINARY POST-LIVER TRANSPLANT ALCOHOL USE DISORDER CLINIC: THE LONG-TERM INDIVIDUALIZED FOLLOW-UP AFTER TRANSPLANT (LIFT) EXPERIENCE

Wei Zhang[1] Ana Ivkovic[1] Kimberly Schoener[1] Kelly Hsu[1] Sienna Li[1] Samantha Nunes[1] KIMBERLY SULLIVAN[1] Emily Bethea[1] Heidi Yeh[1]

[1]Massachusetts General Hospital

Background: As early liver transplantation for alcohol-associated liver disease becomes increasingly common, post-transplant alcohol relapse remains a significant concern. We established a novel multidisciplinary clinic aimed at enhancing the prevention and treatment of alcohol relapse and improving patient outcomes in high-risk liver transplant recipients. **Methods:** The co-located multidisciplinary clinic, named Long-term Individualized Follow-up to Transplant (LIFT), comprised a hepatologist, psychiatrist, social worker, and case manager. Patients who received liver transplants for alcohol-associated liver disease (ALD) and were considered high risk for relapse, as well as those who had already relapsed, were referred to the clinic. Pre-transplant psychosocial metrics, patient demographics, alcohol use disorder (AUD) management before and after transplant, and outcomes--including relapse rates--were collected. **Results:** Between December 2022 and April 2024, 73 post-liver transplant patients were referred to the LIFT clinic, with 37 patients seen during this period. The cohort consisted of 17 females (46%) and 33 Caucasians (89%), with an average age of 51.62 ± 10.04 years old. Eighteen patients (49%) had not consumed alcohol by the time of referral (prevention group), while 19 (51%) had experienced a relapse at the time of referral (treatment group). Thirty-three patients (89.2%) had a diagnosis of AUD prior to liver transplantation, with 15 (40.54%) achieving less than 6 months of abstinence before transplant and 11 (29.73%) maintaining abstinence for 6-12 months prior to transplantation. The average follow-up time with the clinic was 9.00 ± 5.11 months. Post-visit AUD treatment adjustments were made in 24 patients (64.87%). In the prevention group, no patients relapsed during the study period. In the treatment group, one patient died from recurrent alcohol-associated cirrhosis. Among the remaining 18 patients in the treatment group, 7 (38.89%) achieved abstinence, 6 (33.33%) exhibited decreased phosphatidylethanol (PETh) levels, and 4 (22.22%) had higher PETh levels compared to their pre-LIFT visit levels; one did not have PETh tests during follow-ups. **Conclusion:** Our dedicated co-located multidisciplinary post-liver transplant AUD clinic demonstrated feasibility and encouraging early outcomes in preventing and treating alcohol relapse among high-risk liver transplant recipients. Longer-term follow-up and a larger patient cohort are needed to assess the sustainability of these outcomes and the cost-effectiveness of this innovative care model to support its expansion and increased capacity. Dedicated resources and ongoing multidisciplinary support are crucial for successful post-transplant outcomes and effective AUD management in this high-risk population.

Disclosures: Wei Zhang: Nothing to Disclose, Ana Ivkovic: Nothing to Disclose, Kimberly Schoener: Nothing to Disclose, Kelly Hsu: Nothing to Disclose, Sienna Li: Nothing to Disclose, Samantha Nunes: Nothing to Disclose, KIMBERLY SULLIVAN: Nothing to Disclose, Emily Bethea: Nothing to Disclose, Heidi Yeh: Nothing to Disclose

2524 | INCIDENCE AND OUTCOME OF REJECTION IN HYPERIMMUNIZED LIVER TRANSPLANT RECIPIENTS RECEIVING AN INDUCTION THERAPY

Faouzi Saliba[1] Nada El-Domiaty[2] Iea Duhaut[1] Audrey Coilly[1] Eleonora De Martin[1] Sophie-Caroline Sacleux[1] Wafaa Ibrahim[3] Philippe Ichai[1] Gabriella Pittau[1] Oriana Ciacio[1] Chady Salloum[1] Daniel Azoulay[1] Eric Vibert[1] René Adam[1] Jean Luc Taupin[4] Mylene Sebagh[1] Daniel Cherqui[1] Didier Samuel[1]

[1]AP-HP Hôpital Paul Brousse, [2]Hôpital Paul Brousse& Helwan university, [3]Cairo University, [4]Groupe Hospitalier St-Louis Lariboisière

Background: Liver transplantation (LT) for hyperimmunized recipients with positive crossmatch or with preformed Donor specific antibodies (pDSA) present a unique challenge due to increased risk of antibody-mediated rejection (ABMR) and graft failure. Induction therapy aimed to reduce the incidence of both acute T-cellular rejection (ATCR) and ABMR.**Aim:** To study the outcome of high-risk hyperimmunized patients (D/R positive crossmatch or high MFI titers of pDSA at time of transplant) transplanted and receiving induction therapy using rATG and IVIG after LT. **Methods:** 92 LT recipients between 2016 and 2022 were retrospectively reviewed: 46 consecutive hyper-immunized recipients (high-risk group) were matched to 46 non-immunized LT recipients (D/R negative

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crossmatch and no pDSA, low-risk group). Patient and graft survival were compared using Kaplan-Meier survival analysis and log-rank test. The high-risk group received induction therapy with rATG (ATG-Grafalon®) (3mg/kg/day at day 0,1,2) associated to high dose human immunoglobulins (IVIG, 2g/Kg) to lower anti-HLA antibodies titers. **Results:** In the high-risk group, 13 patients (28.2%) developed biopsy proven ATCR, mild (n=7) and moderate (n=4) Banff; 8/46 (17.4%) required and resolved after a treatment with 1 bolus of steroids. Four patients (8.7%) developed biopsy proven (ABMR) associated with features of ATCR Banff 3 to 5 in 2 patients, all treated. In the low-risk group, 12 patients developed ATCR (26.1%), mild (n=10) and moderate (n=2) Banff, all treated. The 1- and 2-years overall survival for the high and low-risk groups were respectively comparable (83.6%, 95.6% and 78.0%, 91.2%, p= 0.051). Recipients in the high-risk group were more likely to develop bacterial infections. No serious adverse event was related to induction. Mean intensive care unit stay was significantly high among high-risk group compared to low-risk group (10.85±9.92 vs 7.22±5.77 days, respectively, p=0.035) days. **Conclusion:** Induction therapy using short-term rATG and IVIG for high-risk hyperimmunized LT recipients with either positive crossmatch or high MFI titers of pDSA minimized the incidence and impact of ATCR and ABMR on patient and graft survival. No severe ATCR and very few ABMR with no long-term impact were observed in the high-risk population.

Disclosures: Faouzi Saliba: Nothing to Disclose, Nada El-Domiaty: Nothing to Disclose, lea Duhaut: Nothing to Disclose, Audrey Coilly: Nothing to Disclose, Eleonora De Martin: Nothing to Disclose, Sophie-Caroline Sacleux: Nothing to Disclose, Wafaa Ibrahim: Nothing to Disclose, Philippe Ichai: Nothing to Disclose, Gabriella Pittau: Nothing to Disclose, Oriana Ciacio: Nothing to Disclose, Chady Salloum: Nothing to Disclose, Daniel Azoulay: Nothing to Disclose, Eric Vibert: Nothing to Disclose, René Adam: Nothing to Disclose, Jean Luc Taupin: Nothing to Disclose, Mylene Sebagh: Nothing to Disclose, Daniel Cherqui: Nothing to Disclose, Didier Samuel: Nothing to Disclose

2525 | VIBRATION-CONTROLLED TRANSIENT ELASTOGRAPHY AS A NON-INVASIVE TOOL TO EXCLUDE HEPATIC STEATOSIS IN LIVING LIVER DONOR EVALUATION

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Background: The number of living donor liver transplantations (LDLT) has been increasing because of the shortage of deceased donors. LDLT with hepatic steatosis > 20 – 30% is a risk factor for post-transplant liver graft dysfunction. Vibration-controlled transient elastography (VCTE) with a controlled attenuation parameter (CAP) is a non-invasive test used to assess hepatic steatosis. Using VCTE with CAP as an assessment of hepatic steatosis for living-donor evaluation might eliminate the need for invasive liver biopsies. This study aimed to evaluate the correlation between CAP and histologic amount and percentage of liver fat and between CAP and magnetic resonance imaging fat signal fraction (MRI-FSF). **Methods:** This was a retrospective study of living donors for LDLT between January 2019 and June 2023 in Ramathibodi Hospital, Bangkok, Thailand. Subjects with pre-existing liver disease, including hepatitis B virus infection, hepatitis C virus infection, or alcoholic liver disease, were excluded. Stepwise living donor evaluations included a medical history review, physical examination, laboratory, imaging studies, VCTE, MRI-FSF, and liver biopsy (only for indicated subjects). Histopathological reports were obtained during the pre-LDLT evaluation or surgery. We defined hepatic steatosis ≥5% as the cut-off level because it was intended to be a screening tool for liver donor evaluation. Receiver operating characteristic (ROC) curve analysis was used to predict hepatic steatosis with appropriate sensitivity, specificity, and Youden's index for liver donor screening. **Results:** Fifty-three subjects were living donors, including 15 (28.3%) men with a mean age of 31.9 ± 6.9 years. Body mass index, CAP, alanine transaminase, and fasting blood sugar levels were significantly higher in subjects with hepatic steatosis ≥5% than in those with hepatic steatosis <5%. The area under the curve (AUC) for CAP in predicting hepatic steatosis ≥5% by histology was 0.851 (95% CI 0.727–0.974, p < 0.001). The optimal cutoff value of CAP was ≥240 dB/m to detect histological steatosis ≥5%, with a sensitivity of 72.7% and a specificity of 83.3%. To predict hepatic steatosis >5% using MRI-FSF, the AUC for CAP was 0.771 (95% CI, 0.609–0.933; p = 0.004). The optimal cut-off value of CAP was ≥254 dB/m for the detection of MRI-FSF >5%, with a sensitivity of 61.5% and a specificity of 92.1%. **Conclusion:** VCTE is a noninvasive test that can be

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used for hepatic steatosis assessment in living donors for LDLT evaluation. Subjects evaluated for living donors with CAP <240 dB/m avoided liver biopsy. Further studies are needed to confirm the results of this study.

Table 1. Liver donor characteristics.

	Hepatic steatosis <5% (n = 42)	Hepatic steatosis ≥5% (n = 11)	*P*-value
Male, n (%)	10 (23.8%)	5 (45.5%)	0.26
Age, years, mean ± SD	32.1 ± 7.0	31.7 ± 6.8	0.86
BMI, kg/m², mean ± SD	22.2 ± 3.3	24.5 ± 3.5	**0.03**
Vibration-controlled transient elastography			
Liver stiffness, kPa, mean ± SD	4.1 ± 0.8	4.1 ± 1.1	0.47
IQR, kPa, mean ± SD	0.46 ± 0.19	0.58 ± 0.28	0.10
CAP, dB/m, mean ± SD	199.1 ± 39.6	253.66 ± 36.0	**<0.001**
IQR, dB/m, mean ± SD	20.5 ± 4.8	18.5 ± 7.1	0.20
Laboratory, mean ± SD			
ALP (U/L)	74.1 ± 20.0	82.6 ± 21.5	0.11
AST (U/L)	21.5 ± 6.5	23.7 ± 5.8	0.15
ALT (U/L)	21.1 ± 13.4	30.6 ± 15.8	**0.03**
Albumin (g/L)	42.2 ± 6.5	44.0 ± 1.8	0.19
Total bilirubin (mg/dL)	0.6 ± 0.2	0.6 ± 0.3	0.28
Fasting blood sugar (mg/dL)	87.5 ± 8.6	95.0 ± 7.1	**0.005**
Cholesterol (mg/dL)	198.1 ± 42.8	211.0 ± 52.0	0.40
LDL (mg/dL)	131.1 ± 41.9	149.6 ± 50.6	0.22
Triglyceride (mg/dL)	98.1 ± 60.2	127.6 ± 60.8	0.08
MRI fat signal fraction, n (%)			
Grade 0	35 (87.5%)	3 (27.3%)	**<0.001**
Grade 1	5 (12.5%)	8 (72.7%)	

Abbreviations: ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; CAP, controlled attenuation parameter; LDL, low-density lipoprotein; MRI, Magnetic Resonance Imaging.

Disclosures: Sarita Ratana-Amornpin: Nothing to Disclose, Pongphob Intaraprasong: Nothing to Disclose, nuttapon arpornsujaritkun: Nothing to Disclose, Goragoch Gespresert: Nothing to Disclose, Bundit Sakulchairungrueng: Nothing to Disclose, Sutipong Jongjirasiri: Nothing to Disclose, Pattana Sornmayura: Nothing to Disclose, Piyaporn Kaewduang: Nothing to Disclose, Sasiwimol Thurapokol: Nothing to Disclose, Abhasnee Sobhonslidsuk: Boerhinger Ingelheim: Advisor, Boeringer Ingelheim: Advisor

2526 | THE IMPACT OF RECIPIENT BODY MASS INDEX AND COLD ISCHEMIC TIME ON POST-LIVER TRANSPLANT BILIARY STRICTURES

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Background: The impact of prolonged cold ischemic time (CIT) on the occurrence of post-transplant biliary strictures (PTBS) is controversial and varies geographically. Also, the association between high recipient BMI and PTBS has not been studied. Our study evaluated whether recipient BMI and prolonged CIT are independent risk factors for PTBS. **Methods:** We conducted a retrospective cohort study using all eligible adult patients(pts) who underwent LT at the UMMC in 2016 (n=165) with BMI < 18.5 kg/m² and those without key post-transplant data. Data collection covered January 1, 2016, to January 31, 2024. Univariate analyses described study population characteristics using frequencies, proportions, means, and medians. Confounding was assessed using bivariate analyses (p-value ≤ 0.2) and stratified analyses (≥10% change in the stratum-specific estimates from the crude estimate). Recipient BMI and prolonged CIT as independent predictors of PTBS were assessed using a multivariable logistic regression model. Statistical significance was set at $p < 0.05$ (SAS version 9.4). **Results:** The study included 165 LT recipients aged ≥25, stratified by BMI into normal weight, overweight, and obese categories. No significant difference was found in gender distribution or race/ethnicity across BMI groups.

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Liver disease etiology showed no significant differences. Smoking status differed by BMI but was not significant (p=0.09). ICU stay and readmission rates were similar across BMI groups. CIT and postoperative bile duct leaks did not differ significantly. After adjusting for confounders, the multivariate analysis showed reduced odds of PTBS in individuals with higher BMI, particularly in overweight individuals (OR 0.28, 95% CI 0.10-0.84). Prolonged CIT was associated with a non-significant decrease in PTBS. **Conclusion:** Interestingly, being overweight or obese was associated with significantly lower odds of PTBS, while prolonged CIT did not have a significant impact on the occurrence of PTBS. The protective effect of high BMI against PTBS may involve complex factors, including higher caliber bile ducts in pts with high BMI compared to normal-weight pts. Further studies with larger sample sizes are necessary to corroborate our conclusions and clarify the underlying mechanisms of this finding.

Table 1: Characteristics of 2016 Liver Recipients (Aged ≥25) at the University of Maryland Medical Center Stratified by Recipient BMI

Sample Characteristic[1]	Normal n=36 N(row%)	Overweight n=54 N(row%)	Obese n=69 N(row%)	p-value*
Recipient's Characteristics				
Sex				0.50
Male	26(25.0)	36(34.6)	42(40.4)	
Female	10(18.2)	18(32.7)	27(49.1)	
Age at transplant, years (Mean ± SD)	55.7±10.8			
Age at transplant, years				0.36
25–44	8(30.8)	8(30.8)	10(38.4)	
45–64	22(22.2)	30(30.3)	47(47.5)	
65–77	6(17.6)	16(47.1)	12(35.3)	
Race/ethnicity				0.86
White	26(22.4)	39(33.6)	51(44.0)	
Black	8(25.8)	11(35.5)	12(38.7)	
Asian	2(33.4)	2(33.3)	2(33.3)	
Hispanic	0(0.0)	2(33.3)	4(66.7)	
Etiology				
Alcoholic liver disease	10(21.3)	17(36.2)	20(42.5)	0.92
Chronic Hepatitis C	10(22.2)	13(28.9)	22(48.9)	0.63
Metabolic associated steatosis hepatitis	3(13.0)	6(26.1)	14(60.9)	0.18
Mixed	5(33.34)	5(33.3)	5(33.3)	0.54
Other	3(23.0)	5(38.5)	5(38.5)	0.93
Primary sclerosing cholangitis	3(50.0)	2(33.3)	1(16.7)	0.20
Primary biliary cirrhosis	1(16.7)	4(66.6)	1(16.7)	0.27
Cryptogenic	1(25.0)	2(50.0)	1(25.0)	0.82
Smoking Status				0.09
Current	11(27.5)	12(30.0)	17(42.5)	
Former	6(10.3)	23(39.7)	29(50.0)	
Never	19(31.2)	19(31.2)	23(37.6)	
Follow-up, years (Median(Q1–Q3))	6.5(2.5–7.1)			
Total bilirubin levels, mg/dl (Median(Q1–Q3))				
Pre–transplant	4.0(1.3–11.6)	3.6(1.3–14.3)	5.9(2.1–18.1)	0.29
Day 7	2.7(1.1–6.7)	2.5 (1.3–5.2)	2.6(1.4–5.5)	0.96
1 year	0.8(0.4–1.8)	0.5(0.4–0.8)	0.5(0.3–0.8)	0.30
AST levels, IU/L (Median(Q1–Q3))				
Pre–transplant	71(43–99)	64(44–88)	66.(49–106)	0.69
At 1 year	30(17–51)	29.0(17–49)	19(16–28)	0.12
ALT levels, IU/L (Median(Q1–Q3))				
Pre–transplant	45(34–66)	29(37–58)	42(33–64)	0.46
At 1 year	30(14–56)	32.50(19–55)	18(12–31)	0.06
ALP levels, IU/L (Median(Q1–Q3))				
Pre–transplant	164(95–224)	157.(111–208)	124.0(100–186)	0.29
1 year	114(84–238)	117.0(83–212)	121.0(85–163)	0.95
ICU length of stay, days				0.79
1–6	22(22.4)	33(33.7)	43(43.9)	
7–13	7(23.3)	11(36.7)	12(40.0)	
≥14	7(22.5)	10(32.3)	14(45.2)	
All cause Readmission (Median(Q1–Q3))				
≤30 days	0(0–1)	0(0–1)	0(0–1)	0.86
31 –90 days	0(0–1)	0(0–1)	0(0–1)	0.10
>90 days –1 year	1(0–1)	0(0–3)	0(0–2)	0.10
Peri–Operative Parameters				
CIT, min (Median(Q1–Q3)).	248.5(200.5–317)			
CIT, min				0.13
<300 min	16(19.5)	35(42.7)	31(37.8)	
≥300 min	10(26.3)	9(23.7)	19(50.0)	
Post–Operative bile duct leak				0.06
Absent	33(22.0)	51(34.0)	66(54.0)	
Present	3(33.4)	3(33.3)	3(33.3)	
Biopsy–proven ACR				0.79
Absent	25(21.4)	41(35.0)	51(43.6)	
Present	11(26.2)	13(30.9)	18(42.9)	
Donor Characteristic				
Type of Graft				
DBD	21(18.9)	37(33.3)	53(47.8)	0.54
DCD	9(27.2)	12(36.4)	12(36.4)	
LD	6(40.0)	5(33.3)	4(26.7)	

[1]Reported as n(%) unless otherwise specified.
*Pearson's Chi-squared test, Wilcoxon –Mann-Whitney test, Fisher's exact test.
Abbreviations: BMI, Body Mass Index; mg/dl, milligram per deciliter; AST, Aspartate Aminotransferase; ALT, Alanine Aminotransferase; AP, Alkaline Phosphatase; IU/L, International Unit per Liter; ICU, Intensive Care Unit; CIT, Cold Ischemic Time; min, minute; ACR, Acute Cellular Rejection; DBD, Donation after Brain Death; DCD, Donation after Cardiac Death; LD, Living Donor

Table 2: Multivariable Adjusted Logistic Regression Analysis between Recipient BMI and CIT with Post-transplant Biliary Stricture

	Crude OR	95% CI
Recipient BMI*		
Normal Weight	1.00(Ref)	–
Overweight	0.28	0.10–0.84
Obese	0.35	0.12–0.99
CIT#		
<300 min	1.00(Ref)	–
≥ 300 min	0.89	0.35–2.29

* Adjusted for age, sex, race, CIT, and smoking
# Adjusted for age, sex, race, and donor-type graft
Odds ratio (OR), 95% confidence interval (CI)

Disclosures: Ebehiwele Ebhohon: Nothing to Disclose, Ashton Harmacinski: Nothing to Disclose, Patrick McCarthy: Nothing to Disclose, Sabtain Saroya: Nothing to Disclose, Nathalie Urrunaga: Nothing to Disclose

2527 | RISK FACTORS, PREGNANCY AND TRANSPLANT OUTCOMES ASSOCIATED WITH INTRAHEPATIC CHOLESTASIS OF PREGNANCY IN LIVER TRANSPLANT RECIPIENTS

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Background: Intrahepatic cholestasis of pregnancy (ICP) is a liver disorder characterized by pruritus and elevated serum bile acid levels and is associated with elevated risk of adverse obstetrical outcomes including preterm delivery, stillbirth, and miscarriage. Prior data from the Transplant Pregnancy Registry International (TPRI) showed a 17% incidence of ICP in women post liver transplant (LT), compared to a 1% in the general population. Predictors of ICP post LT and the effects of ICP on pregnancy and transplant outcomes in LT recipients have not been investigated. **Methods:** Utilizing the TPRI database, a self-reported registry of solid organ recipients who had post-transplant pregnancies, we conducted a retrospective cohort study between 1991 and 2024 of persons who underwent LT with subsequent pregnancy(ies). A total of 422 persons were identified with a collective of 901 pregnancies. Exclusion criteria include surrogate birth, twin pregnancies, and current pregnancy (in which the

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outcomes are not yet known), narrowing the number of cases from 901 to 837. Of the 837 pregnancies, a total of 450 pregnancies contained interview and/or medical record data to classify as having 'yes' or 'no' ICP. Univariate analyses followed by multivariate logistic regression analysis were conducted using STATA software to determine risk factors and pregnancy outcomes associated with ICP. **Results:** The study included post LT patients from 14 countries, with racial data available for 422 pregnancies: 75% Caucasian, 8% African American, 3% Asian, and 14% Other. The mean conception age was 30±5 years. Of the 450 pregnancies, 73 (16%) reported to have ICP. Factors significantly associated with ICP on multivariate analysis include gestational diabetes (OR 3.20, 95% CI 1.44–7.10) and viral hepatitis as cause of LT (OR 4.29, 95% CI 1.29–14.23). Patients who developed ICP post LT were at significantly increased risk of adverse pregnancy outcomes, including a composite of adverse fetal outcomes comprising neonatal death, birth defect, low birth weight, and preterm birth (OR 3.38, 95% CI 1.93–5.93). Patients with ICP had a significantly increased risk of loss of LT within 2 years postpartum (OR 22.43, 95% CI 2.46–204.39) (Table 1). **Conclusion:** Consistent with prior data, we observed a high prevalence of ICP in the post-LT population. ICP was associated with gestational diabetes and viral hepatitis as cause of LT. Given the high rates of ICP and its associated risk of adverse pregnancy outcomes, bile acid screening and potential treatment with ursodeoxycholic acid prior to symptom onset should be considered in this population. We also observed a high likelihood of graft loss within two years of pregnancy in LT recipients who developed ICP. Postpartum, there may be a role for closer monitoring of LFTS to detect early changes that may lead to graft loss.

Table 1. Risk factors and outcomes associated with ICP in post-liver-transplant pregnancies

	ICP (n=73)	No ICP (n=377)	Univariate[a]		Multivariate[b]	
			OR (95% CI)	p	OR (95% CI)	p
Conception Age (years) (mean, SD)	30.07 (5.44)	30.06 (5.50)	1.00 (0.96-1.05)	0.992[c]		
Race (n=422)[e]						
White	46 (67%)	271 (64%)	0.63 (0.36-1.12)	0.112		
Asian	3 (4%)	10 (2%)	1.62 (0.43-6.04)	0.443[d]		
Black/African American	5 (7%)	29 (7%)	0.91 (0.34-2.43)	0.846		
American Indian/Alaskan Native	2 (3%)	3 (1%)	3.61 (0.59-22.03)	0.160[d]		
Native Hawaiian/Pacific Islander	1 (1%)	1 (<1%)	5.34 (0.33-86.8)	0.293[d]		
Other	11 (16%)	41 (10%)	1.60 (0.733.10)	0.266		
Ethnicity (n=385)						
Hispanic	14 (22%)	46 (14%)	1.64 (0.84-3.19)	0.147		
Indication for Liver Transplant (LT)						
Viral Hepatitis (HCV/HBV)[f]	5 (7%)	8 (2%)	3.39 (1.00-10.68)	0.027	4.29 (1.29-14.23)	0.017
Autoimmune	8 (11%)	49 (13%)	0.82 (0.37-1.82)	0.632		
Cholestatic	27 (37%)	102 (27%)	1.58 (0.93-2.68)	0.086	1.26 (0.69-2.31)	0.449
Time from Transplant to Pregnancy (years) (mean, SD)	12.42 (9.77)	10.50 (8.88)	1.02 (0.99-1.05)	0.097[c]	1.03 (0.99-1.06)	0.089
Multiparous prior to LT	40 (55%)	245 (65%)	0.65 (0.39-1.08)	0.098	0.92 (0.44-1.89)	0.821
Pregnancy # post-LT (mean, SD)	1.64 (0.82)	1.94 (1.16)	0.76 (0.58-0.99)	0.093[c]	0.76 (0.52-1.11)	0.159
Gestational DM (n=448)	11 (15%)	24 (6%)	2.59 (1.21-5.57)	0.012	3.20 (1.44-7.10)	0.004
Gestational HTN (n=447)	2 (3%)	25 (7%)	0.40 (0.09-1.73)	0.283[d]		
Pre-eclampsia (n=434)	11 (16%)	69 (19%)	0.82 (0.41-1.63)	0.561		
Medication Used During Pregnancy						
MTOR[f] inhibitors (n=348)	3 (4%)	4 (1%)	4.22 (0.92-19.31)	0.079[d]	3.20 (0.69-15.96)	0.135
Purine analogs/anti-metabolites (n=448)	30 (41%)	154 (41%)	1.00 (0.60-1.67)	0.996		
CNIs[f]	71 (97%)	366 (97%)	1.07 (0.23-4.92)	1.000[d]		
Prednisone (n=448)	27 (36%)	106 (28%)	1.53 (0.90-2.59)	0.113		
Transplant Outcomes						
Rejection After Pregnancy (n=439)	6 (8%)	14 (4%)	2.33 (0.87-6.30)	0.086		
LT Loss <2 years post-partum (n=375)	4 (7%)	1 (<1%)	22.42 (2.46-204.39)	0.003[d]		
Pregnancy and Fetal Outcomes						
Miscarriage, Stillbirth, or Termination	0	18 (5%)	-	0.054[d]		
Pre-term	54 (74%)	149 (40%)	4.35 (2.48-7.63)	0.000		
Cesarean Section (n=432)	26 (36%)	171 (48%)	0.61 (0.36-1.02)	0.060		
Induced Labor (n=430)	50 (68%)	195 (55%)	1.81 (1.06-3.09)	0.029		
Composite Adverse Fetal Outcome (Death, Birth Defect, Low Birth Weight, Pre-Term) (n=443)	54 (74%)	169 (46%)	3.38 (1.93-5.93)	0.000		

[a]Chi-square test used for univariate analysis unless otherwise indicated.

[b]Multivariate logistic regression model used. Analysis only performed for potential risk factors of ICP.

[c]Student t-test was used.

[d]Fisher's exact test was used.

[e]If n=x not listed next to variable, then there were no missing values (n=450).

[f]Abbreviations: HCV/HBV=Hepatitis B Virus/Hepatitis C Virus; DM=Diabetes Mellitus; HTN=Hypertension; MTOR=mammalian target of rapamycin (i.e., sirolimus and everolimus); CNI=Calcineurin inhibitors (i.e., Tacrolimus, cyclosporine, and envarsus)

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2528 | CALIBRATING EXCEPTION POINTS FOR CONTINUOUS DISTRIBUTION: WHY MATCHING HCC TO NON-HCC WAITLIST DROPOUT FALLS SHORT

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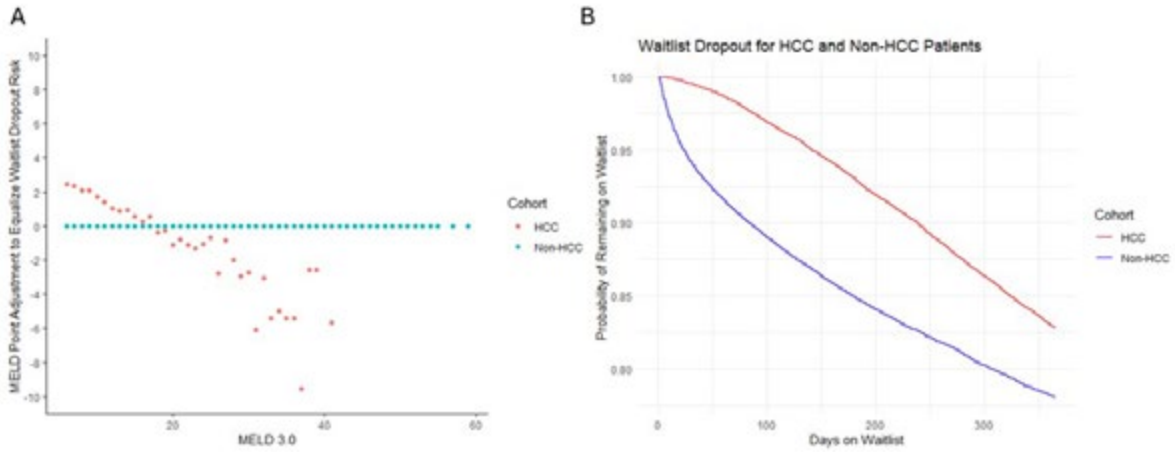
Background: In the United States, patients with hepatocellular carcinoma (HCC) listed for liver transplant (LT) receive MELD exception points on the waiting list (WL), as their laboratory MELD score does not reflect their medical urgency. UNOS is implementing a continuous distribution framework which provides an opportunity to improve allocation through separate urgency and access points. We aimed to test the feasibility of matching the WL dropout of patients with HCC to those without exception as estimated by MELD 3.0 (i.e. interdigitation). **Methods:** We identified patients listed for LT in the OPTN database with (1) HCC exception and (2) without exception from 10/8/2015 to 12/31/22 with a 70% training and 30% validation split. We fitted a Cox proportional hazards model for HCC using MELD 3.0, AFP, and tumor size and number and a non-HCC model with MELD 3.0 alone to predict 90-day WL dropout, a surrogate for mortality, with censoring at LT. The MELD score difference required to align the dropout risk of patients with and without HCC was estimated by linear regression. **Results:** During the study period 18,237 patients with HCC were listed for LT with a median MELD 3.0 of 11 (IQR 8-15), and AFP of 6 (IQR 4-17). Among those without HCC, 62,787 patients were listed for LT with a MELD 3.0 of 22 (IQR 17-30). At 90 days on the WL, patients with HCC had an overall WL dropout of 1.9% compared to 5.0% for those without HCC. We estimated the MELD 3.0 point adjustment to match the WL dropout of a patient with HCC to a patient without HCC (Figure 1A). For the HCC group our model predicted an increased dropout risk of patients with MELD 3.0 of 6-17 compared to patients without HCC that corresponded to an increase of only 1-2 MELD points. Above a MELD 3.0 of 18, patients with HCC had lower dropout risk than those without HCC relative to their MELD resulting in negative point corrections. Base rates of WL dropout in patients with and without HCC are shown in Figure 1B. **Conclusion:** The average number of MELD points that patients with HCC would gain to match an equivalent patient without HCC in terms of short-term mortality was modest. While WL dropout at 90 days is the typical surrogate of medical urgency for LT for patients without HCC, this end point may be less clinically meaningful for patients with HCC who have different base rates, trajectories, and reasons for WL dropout. Under this schematic, patients with HCC would gain relatively few urgency points, and additional access points would be needed to preserve their access to LT.



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2529 | ATRIAL FIBRILLATION PRE-LIVER TRANSPLANT ASSOCIATED WITH INCREASED ALL-CAUSE AND CARDIOVASCULAR MORTALITY POST-TRANSPLANT

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Background: Cardiovascular (CV) disease is a leading cause of morbidity and mortality following liver transplant (LT). The primary aim of this study was to examine the association between pre-LT patient characteristics and CV mortality in post-LT year 1. **Methods:** Retrospective chart review was performed on all LT recipients at an academic medical center from 2012 to 2018. Pre-LT patient characteristics, including pre-existing CV disease, were extracted. Each patient received a pre-LT CV risk classification using the Cardiovascular Risk in Orthotopic Liver Transplantation (CAR-OLT) score – low (CAR-OLT < 16), moderate (16–30), or high (> 30). CV death was defined as sudden cardiac death or death from acute myocardial infarction, heart failure, stroke, CV procedures, or other CV causes. Univariate associations between pre-LT variables and outcomes in post-LT year 1 were determined using Mann-Whitney U and Fisher's exact tests. **Results:** Among the 576 patients included in this study, mean age was 57.0 years, 37.5% were female, and 92% were white. Metabolic dysfunction-associated steatohepatitis was the primary indication for LT in 29.9%, and 36.6% had diabetes, 7.1% heart failure, 6.4% ischemic heart disease, and 5.0% atrial fibrillation. Using CAR-OLT scores, 45.7% of patients were deemed high CV risk pre-LT, 48.1% moderate risk, and 6.2% low risk. In post-LT year 1, 49 (8.5%) LT recipients died from all-causes. Compared to recipients alive after post-LT year 1, those who died were more likely to have atrial fibrillation pre-LT (16.3% vs. 4.0%, p=0.002). Ten of the 49 deaths (20.4%) were CV deaths. Compared to the non-CV death group, the CV death group included more females (60.0% vs 23.1%, p=0.049) and recipients with a prior diagnosis of atrial fibrillation pre-LT (40.0% vs 10.3%, p=0.044). There was a trend toward higher all-cause mortality (57.1% vs. 44.6%, p=0.10) in the high CAR-OLT CV risk group, as well as death from CV causes (80.0% vs 51.3%, p=0.16). **Conclusion:** It is vital to identify modifiable pre-LT factors that increase risk for post-LT mortality. The findings of this study suggest that pre-LT atrial fibrillation may increase the risk of all-cause mortality and CV mortality in post-LT year 1. Larger, multi-center studies are needed to better understand the association between pre-LT atrial fibrillation and post-LT mortality, as well as potential interventions for pre-LT atrial fibrillation that can be used to reduce post-LT deaths.

Disclosures: John Barnes: Nothing to Disclose, Jacob Ciricillo: Nothing to Disclose, Debra Yen: Nothing to Disclose, Askanda Osman: Nothing to Disclose, Yeshika Sharma: Intercept Pharmaceuticals: Speaking and Teaching, Inuk Zandvakili: Nothing to Disclose, Amoah Yeboah-Korang: Nothing to Disclose

2530 | LIVING DONOR LIVER TRANSPLANTATION: THE ROLE OF TRANSPLANT KINSHIP ON REJECTION RATES AND ALLOGRAFT SURVIVAL, USING GENETIC RELATED VS UNRELATED LIVE DONORS

Maisa Elbadawi[1] Ali Shaat[1] Taha Shakarchi[1] Ishan Antony[1] Neev Mehta[1] Raza Malik[1] Mary Ann Simpson[2] David Lee[3] Sarah Meade[1] Roger Jenkins[1] Amir Qamar[1] Mohamed Akoad[1]

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Background: Liver transplantation from living donors (LDLT) is a common practice, but comparative outcomes of transplants from related versus unrelated donors are poorly understood. This study aimed to investigate the role of Transplant Kinship on rejection rates and allograft survival, using genetic related vs unrelated live donors **Methods:** We conducted a retrospective cohort analysis, of368 living donors, liver donor transplant conducted in the Division between 1998 and 2023 The study cohort consisted of i) 195 males and ii) 173 females; a) 251 were genetically related and b) 117 were genetically unrelated, of which 55 were friends, 24 wives, 15 brothers-in-law, 6 sisters-in-law, 6 altruistic donors, 3 significant others, 4 husbands, 2 stepsons, and 2 stepdaughters. Additionally, the 251 genetically related donors, included 77 sons, 65 daughters, 46 brothers, 35 sisters, 9

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nephews, 7 nieces, 7 cousins, 4 fathers, and 1 grandson. The study evaluated rejection rates and graft survival outcomes at 1- and 5-years post-transplant through analysis of variance (ANOVA) to evaluate graft survival rates and rejection outcomes, odds ratios (OR) to compare the odds of rejection between related and unrelated recipients, and Wilcoxon rank sum tests to support the findings related to graft outcomes **Results:** indicated no significant difference in rejection rates between genetically related and unrelated recipients ($p = 0.5213$). Related recipients had lower odds of rejection, but not significantly different (OR = 0.87984) with a 95% confidence interval ranging from 0.28553 to 1.9124. While differences in rejection outcomes were observed between related and unrelated cases, rejection rates themselves did not significantly differ. However, genetically related donors exhibited a significant advantage in graft survival rates at 1 year ($p < 0.033$), suggesting a potential influence of genetic relatedness on short-term outcomes. The analysis highlighted Relational Status as a significant predictor, particularly impacting recipient status and graft function at 1 year. Rejection episodes were infrequent, with no significant difference between related and unrelated cases ($p = 0.9$). Graft function at 1 year showed a significant difference ($p = 0.005$) based on genetic relatedness, indicating a potential long-term impact on graft function. However, no significant difference was observed in graft function at 5 years ($p = 0.57$), suggesting a waning influence of genetic relatedness over time. Wilcoxon rank sum tests supported these findings, further emphasizing the importance of genetic relatedness on short-term graft outcomes. **Conclusion:** While genetic relatedness appears to influence certain aspects of liver transplant outcomes, such as graft survival rates and graft function at 1 year, the differences in rejection rates between related and unrelated cases were not significant, as was the graft survival rate at 5 years.

Disclosures: Maisa Elbadawi: Nothing to Disclose, Ali Shaat: Nothing to Disclose, Taha Shakarchi: Nothing to Disclose, Ishan Antony: Nothing to Disclose, Neev Mehta: Nothing to Disclose, Raza Malik: Nothing to Disclose, Mary Ann Simpson: Nothing to Disclose, David Lee: Nothing to Disclose, Sarah Meade: Nothing to Disclose, Roger Jenkins: Nothing to Disclose, Amir Qamar: Nothing to Disclose, Mohamed Akoad: Nothing to Disclose

2531 | A 13-YEAR NATIONWIDE ANALYSIS OF NOCARDIA AND ACTINOMYCES INFECTION OUTCOMES IN LIVER TRANSPLANT RECIPIENTS

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Background: Liver transplant (LT) recipients have a profound susceptibility to infections. Although Nocardia and Actinomyces (NA) are well-known bacteria that typically affect immunosuppressed patients, a scarcity of research exists on the effects of LT with NA infections. Our study aims to evaluate the outcomes associated with NA infections in LT patients. **Methods:** Patients were selected from the National Inpatient Sample (NIS) from 2008 through 2020—International Classification of Disease (ICD) 9 and 10 codes. Patients admitted with a history of LT were subdivided into those who were and were not diagnosed with an NA infection. Records were weighted using the NIS algorithm. Primary outcomes: all-cause hospital mortality, acute kidney injury (AKI), acute myocardial infarction (AMI), shock, and a composite of these. Secondary outcomes: length of stay, total charges, cytomegalovirus (CMV), and transplant rejection. Demographics and comorbidities were compared between groups with a weighted chi-square test. Outcomes were compared between the two groups, and adjusted odds ratios and regression coefficients were calculated using weighted logistic or linear regression as appropriate. Odds ratios (OR) were adjusted for age, gender, race, hospital characteristics, Charlson Comorbidity Index (CCI), median income based on zip code, weekend admission, and insurance. **Results:** 469,141 LT patients were included in this study, 310 had NA infection (0.07%). Patients in each group were of similar age, race, and overall medical complexity ($p>0.05$). Patients with NA infection were less likely to have a history of CAD (4.84% vs 16.20%, $p<0.05$), hypertension (14.53% vs 25.82%, $p<0.05$), and obesity (1.61% vs 9.0%, $p<0.05$) than controls. LT patients with NA infection were found to have higher odds of mortality (OR 5.50, $p<0.001$), AKI (OR 1.9, $p<0.05$), composite outcome (OR 2.19, $p<0.01$), and more likely to have CMV infection (OR 6.38, $p<0.01$). LT patients with NA infection stayed 13.11 days longer in the hospital ($p<0.01$) with charges $60,399 more ($p<0.01$) than controls. LT patients who acquired an NA infection were at nearly 6-fold higher odds of death and other negative outcomes. **Conclusion:** Based on previous research that has demonstrated organ transplant patients to be at high risk of infections. More vigilant care should be taken to protect LT patients from such opportunistic infections.

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Table 1: Outcomes of Nocardia and Actinomyces Infection in Liver Transplant Recipients

Outcome	Nocardia or Actinomyces	No Nocardia or Actinomyces	*Odds ratio/coefficient	95% CL	P-value
All-cause in-hospital mortality	9.54	1.88	5.50	2.20-13.78	0.0003
Shock	4.66	2.02	2.31	0.71-7.51	0.1626
Acute myocardial infarction	1.61	2.31	0.63	0.09-4.38	0.6396
Acute kidney injury	45.18	28.55	1.90	1.10-3.28	0.0209
Composite Outcome	31.22	51.60	2.19	1.27-3.78	0.0049
Length of stay (mean, days)	13.11	5.66	7.23	2.57-11.90	0.0024
Hospital charges (mean, (dollars)	124403	60902	60399	16398-104400	0.0071
CMV	6.38	1.35	4.108	1.46-11.56	0.0075
Transplant Rejection	4.82	1.32	3.165	0.73-13.71	0.1234
*Odds ratios were computed for binary response variables and coefficients of regression for continuous variables.					

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2532 | OUTCOMES OF CABG PATIENTS WITH AND WITHOUT A HISTORY OF LIVER TRANSPLANT

Andrej Sodoma[1] *James Pellegrini*[2] *Samuel Greenberg*[3] *Jaspreet Singh*[4]

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Background: Liver transplant (LT) patients face a wide variety of challenges, including an increased risk of coronary artery disease. Coronary artery bypass graft (CABG) remains one of the most commonly performed major surgical procedures in the U.S. Our study aimed to gauge the outcomes of CABG in patients with and without a history of LT. **Methods:** Patients who underwent CABG with or without a history of LT were selected from the National Inpatient Sample (NIS) from 2008 to 2020. International Classification of Disease (ICD) 9 and 10 codes were used to identify suitable records. Records were weighted using the algorithm provided by the NIS to create accurate population estimates. Primary outcomes of interest were all-cause hospital mortality, shock, acute myocardial infarction, acute kidney injury (AKI), and a composite of these. Secondary outcomes included length of stay and total charges. Patient demographics and incidence of comorbidities were compared with a chi-square test. Outcomes were compared between the groups, and odds ratios and coefficients of regression were calculated using weighted logistic regression and linear regression, respectively. Odds ratios (OR) and coefficients were adjusted for common co-founders such as age, gender, race, Charlson comorbidity index (CCI), hospital traits, and income quartile. **Results:** A weighted total of 2,407,349 CABG hospitalizations were included in this study. Of these, 1,833 had a history of LT (0.076%). Overall, patients with a history of LT were more likely to be younger (65.16 vs 66.16, p<0.001), male (81.6% vs. 73.66%, p<0.001), and more complex (CCI 5.89 vs. 4.16, p<0.001) than patients without a history of LT. Patients with a history of LT also had higher rates of diabetes mellitus type 2 (57.02% vs 43.39%, p<0.001), end-stage renal disease (11.21% vs 2.95%, p<0.001), and GERD (28.39% vs. 21.26%, p<0.001). CABG patients with a history of LT were less likely, however, to have hyperlipidemia (56.72% vs. 74.26%, p<0.001), hypertension (25.95% vs 58.45%, p<0.001), obesity (19.00% vs. 23.42%, p=0.046), history of smoking (12.06% vs 18.66%, p<0.01), or alcohol use disorder (9.04% vs. 13.44%,

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p=0.017). We found that patients admitted for CABG with a history of LT had significantly higher adjusted odds of mortality (OR 1.84, p<0.01), AKI (OR 2.65, p<0.001), and composite outcome (OR 2.04, p<0.001), They also experienced longer length of stay (1.7 days, p=0.02), and greater hospital charges ($26,761, p=0.029). **Conclusion:** We found that CABG patients with a history of LT had nearly 2-fold higher odds of mortality, nearly 3-fold higher odds of AKI, and 2-fold higher odds of composite outcome than CABG patients without liver transplants. This corresponded to longer lengths of stay and increased hospital charges. Patients should require lower thresholds for left heart catheterization and standardized coronary artery disease testing before a liver transplant.

Outcomes for CABG Patients with and without a history of liver transplant. Odds ratios were calculated using weighted logistic regression for binary outcomes, while regression coefficients were calculated using weighted linear regression for continuous outcomes.

Outcome	Liver Transplant	No Liver Transplant	Odds ratio/coefficient	95% CL	P-value
All-cause in-hospital mortality	5.62	2.50	1.84	1.17-2.90	0.0085
Shock	11.16	7.50	1.11	0.80-1.55	0.5348
Acute myocardial infarction	6.95	5.49	0.73	0.49-1.10	0.1284
Acute kidney injury	48.64	18.23	2.65	2.12-3.32	<.0001
Composite Outcome	55.03	26.48	2.04	1.63-2.55	<.0001
Length of stay (mean, days)	12.16	9.60	1.70	0.26-3.15	0.0211
Hospital charges (mean, (dollars)	230,309	187,516	26,761	2,734-50, 787	0.0290

Disclosures: Andrej Sodoma: Nothing to Disclose, James Pellegrini: Nothing to Disclose, Samuel Greenberg: Nothing to Disclose, Jaspreet Singh: Nothing to Disclose

2533 | LIVER TRANSPLANTATION FOR MASH CIRRHOSIS HAS BETTER POST-TRANSPLANT OUTCOMES THAN NON-MASH CIRRHOSIS

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Background: The number of liver transplants has increased by 18% and outcomes after transplant have improved over the last few years. Post-transplant outcomes may vary depending on the underlying cause of cirrhosis, but have been speculated to be impacted by metabolic syndrome before and after transplant. As metabolic dysfunction-associated steatohepatitis (MASH) is the fastest-growing indication for liver transplantation (LT), we aimed to compare the post-transplant outcomes for MASH cirrhosis versus non-MASH cirrhosis using real-world data from a multicenter US database. **Methods:** We included adult patients with a history of LT using the TrinetX database US Collaborative Network from January 1, 2000, and May 23, 2024. We stratified patients into MASH and non-MASH cohorts based on the etiology of chronic liver disease leading to LT. A 1:1 propensity score matching was performed based on age, gender, race, and comorbidities, including essential hypertension, diabetes mellitus, obesity, hyperlipidemia, chronic ischemic heart disease, chronic lower respiratory diseases, peripheral vascular disease, mood and behavioral disorders, nicotine, alcohol or drug abuse, and socioeconomic factors. The outcomes were measured at 6 months or later post-LT. **Results:** Out of 34,103 patients with a history

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of LT, we matched 2,863 MASH cirrhosis patients to the same number of non-MASH cirrhosis patients. Patients transplanted for MASH cirrhosis were found to have a 3-fold higher risk of recurrent MASH and a 22% higher risk of cirrhosis of the allograft. However, they had lower odds of liver transplant rejection, liver biopsy, chronic kidney disease, malignant neoplasm of any organ, heart failure, stroke, myocardial infarction, and all-cause mortality compared to their non-MASH counterparts. **Conclusion:** We found that a history of MASH increases the risk of recurrent allograft MASH by 3-fold, along with an increased risk of cirrhosis, without a higher risk of liver retransplantation. Patients transplanted for non-MASH indications had higher odds of rejection, chronic kidney disease, malignancies, cardiovascular complications, and higher all-cause mortality. The worse post-transplant outcomes in non-MASH patients are likely multifactorial which warrants further long-term studies.

Table 1. Primary and Secondary Post-Transplant Outcomes Analyzed on Propensity-Matched Cohorts

	Liver Transplant for MASH Cirrhosis, n (%)	Liver Transplant for non-MASH Cirrhosis, n (%)	P-value	OR (95% CI)
Number of patients	2,863	2,863		
Post-liver transplant MASH	351 (11.82%)	127 (4.28%)	**<0.0001**	**3.000 (2.432,3.700)**
Post-liver transplant Cirrhosis	349 (12.19%)	292 (10.20%)	0.0169	1.222 (1.037,1.441)
Liver transplant rejection	217 (7.31%)	438 (14.75%)	**<0.0001**	**0.456 (0.384,0.541)**
Liver biopsy	217 (7.31%)	268 (9.02%)	**0.0157**	**0.795 (0.659,0.958)**
Retransplantation of liver	99 (3.33%)	103 (3.47%)	0.7746	0.96 (0.725,1.271)
Chronic kidney disease	1,137 (38.28%)	1,322 (44.51%)	**<0.0001**	**0.773 (0.697,0.858)**
Malignant neoplasm	783 (26.36%)	1,074 (36.16%)	**<0.0001**	**0.632 (0.566,0.706)**
Severe sepsis	176 (5.93%)	199 (6.7%)	0.2198	0.877 (0.711,1.082)
Heart failure	403 (13.57%)	497 (16.73%)	**0.0007**	**0.781 (0.677,0.901)**
Stroke (infraction or hemorrhagic)	139 (4.68%)	191 (6.43%)	**0.0032**	**0.714 (0.571,0.894)**
Myocardial infarction	138 (4.64%)	190 (6.40%)	**0.0031**	**0.713 (0.569,0.839)**
All cause mortality	355 (11.95%)	538 (18.11%)	**<0.0001**	**0.614 (0.531,0.709)**

MASH; metabolic dysfunction-associated steatohepatitis, OR; odds ratio, CI; confidence interval. Statistically significant results highlighed as bold.

Disclosures: Waqas Rasheed: Nothing to Disclose, Anna Leyson: Nothing to Disclose

2534 | EXERCISE STRESS ECHOCARDIOGRAPHY IS A FEASIBLE ALTERNATIVE TO PHARMACOLOGIC STRESS ECHOCARDIOGRAPHY FOR CARDIAC RISK EVALUATION IN PATIENTS WITH CIRRHOSIS PRIOR TO LIVER TRANSPLANTATION

Madeleine Gill[1] Joanna Huang[1] Daniel Brieger[2] Jessica Handreck[1] Fiona Fraser[1] Andrew Brodzeli[1] Imre Hunyor[1] Michele McGrady[1] Rachael Jacob[1] Talal Valliani[1] Ken Liu[1] David Bowen[3] Simone Strasser[1] Anoop Koshy[4] GEOFF McCaughan[5] Avik Majumdar[4]

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Background: Dobutamine stress echocardiography (DSE) is often used in preference to exercise stress echocardiography (ESE) for cardiac risk evaluation prior to liver transplantation (LT) due to perceived challenges in attaining adequate workload with ESE. This study aimed to determine the tolerability and ability of ESE to attain target heart rate (THR) compared to DSE. **Methods:** A retrospective cohort study of consecutive patients with cirrhosis undergoing cardiac evaluation prior to LT at a state-wide transplant centre between 2010-2020 was performed. Choice of stress modality was at the clinician's discretion. Treadmill ESE utilized Bruce protocol to maximum capacity. DSE utilized incremental dosing from 10-50mcg/kg, with hand grip and atropine to augment heart rate (HR) if required, according to standardized protocol. THR was defined as 85% of the maximum predicted HR (220-age). Functional capacity on ESE was assessed by metabolic equivalents (METs). Beta-blockers were withheld 48 hours prior to both DSE and ESE; patients inadvertently continuing were excluded from analysis. **Results:** Overall, 452 patients were included. In our cohort, 169 (37%) underwent ESE. Model for end-stage liver disease (MELD) score was lower in ESE patients (ESE: 13; IQR, 9-17; vs DSE: 18; IQR, 15-22; *P*<0.001). Fewer patients undergoing ESE had ascites (24% vs 52%; *P*<0.001). More DSEs were prematurely ceased due to complications, mainly hypotension and arrhythmia, compared with ESE (8% vs 3%; *P*=0.04). THR was attained in 85 of 169 (50%) ESEs, compared with 91 of 283 (32%) DSEs (*P*<0.001). The median METs achieved on ESE were 7.0 (IQR, 5.4-9.8). Of the patients who did not attain THR on ESE, 43 (51%) achieved ≥7 METs and this was considered an adequate test at our institution. Similarly, on DSE, 121 (63%) achieved 80-84% of maximum predicted HR, also considered adequate. On multivariate logistic regression, DSE was

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an independent predictor of failure to attain THR, after adjusting for sex, age, hypertension, diabetes, ascites, hepatic encephalopathy and MELD (OR 1.82; 95% CI, 1.16-2.87, P=0.009). Additionally, moderate-to-severe ascites (OR 1.79; 95% CI, 1.04-3.10; P=0.037) and age (OR 1.04; 95% CI, 1.01-1.08; P=0.007; per unit increase in age) also predicted failure to attain THR in the overall cohort. For ESEs alone, the only independent predictor was MELD (OR 1.05; 95% CI, 1.00-1.11; *P*=0.048; per unit increase in MELD), and age for DSE (OR 0.95; 95% CI, 0.92 – 0.99; *P*=0.025; per year increase in age). **Conclusion:** ESE was feasible in over a third of patients undergoing cardiac evaluation prior to LT. When compared to DSE, patients undergoing ESE were almost twice as likely to attain THR, although these patients had less severe liver disease. Given the higher complication rate observed during DSE, ESE may be considered as an alternative modality in selected individuals undergoing LT assessment.

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2535 | NATIONAL TRENDS OF BRIDGING LOCOREGIONAL THERAPY IN LIVER TRANSPLANT CANDIDATES WITH HEPATOCELLULAR CARCINOMA

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Background: Bridging locoregional therapy (LRT) is frequently utilized in hepatocellular carcinoma (HCC) patients eligible for liver transplant (LT) and is linked to a lower risk of waitlist dropout. Various bridging LRT options are available, with selection influenced by tumor-related factors such as size, location, and number, as well as liver function, and center protocols. Our study aims to conduct a comprehensive analysis of the evolving trends in bridging LRT over time across OPTN regions. **Methods:** This study conducted a comprehensive analysis of the different bridging LRT subtypes among patients who received HCC exception for LT between 2003 and 2023. Data from the Organ Procurement and Transplantation Network (OPTN)/United Network for Organ Sharing (UNOS) were extracted. The study included patients who received an approved HCC exception, irrespective of their Milan criteria status or whether they underwent LT. We characterized trends in the types of locoregional therapy administered, categorized by era. To assess trends across eras, Statistical analysis included Cochran–Armitage tests for binary categorical variables, Jonckeereh-Terpstra tests for ordinal categorical variables, and Mann–Kendall tests for continuous variables. Pearson chi-squared was used to compare different types of bridging LRT among OPTN regions. **Results:** Among 45,782 patients listed for LT and approved for HCC exception, 36,335 received bridging LRT, with the percentage of bridging LRT recipients increasing over time from 3,594 (50.5%) in 2003-2008 to 12,300 (91.6%) in 2018-2023 ($p < 0.001$). There was a marked increase in trans-arterial radioembolization (TARE) starting in 2013, along with a moderate increase in the use of thermal ablation and external beam radiation. In contrast, trans-arterial chemoembolization (TACE) significantly decreased, and cryoablation remained low with no significant change over time. In 2023, TARE emerged as the most common bridging LRT with 749 cases (36%), followed by thermal with 607 cases (29%) and TACE with 477 cases (23%). A significant variation in the types of bridging LRTs used was observed across different OPTN regions ($p < 0.001$). **Conclusion:** In a large nationwide cohort of liver transplant candidates, TARE emerged as the predominant bridging LRT modality, exhibiting a significant increase over time, while TACE showed a marked decline. Significant regional differences in the utilization of bridging LRT types across various OPTN regions underscore the need for consolidated guidelines regarding their use in treating HCC patients awaiting LT.

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Figure 1. Proportion of LRT types by year of treatment

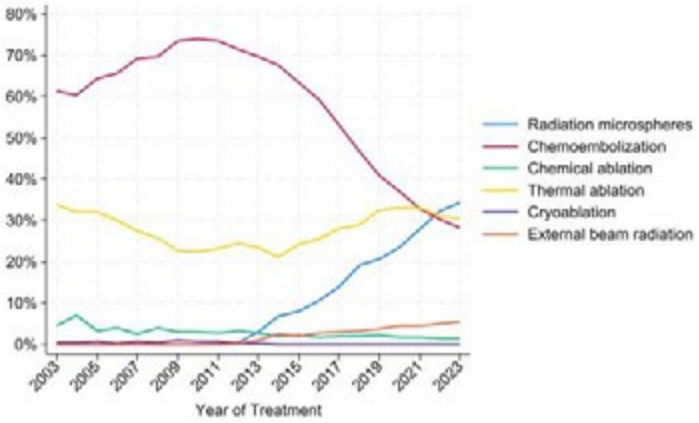
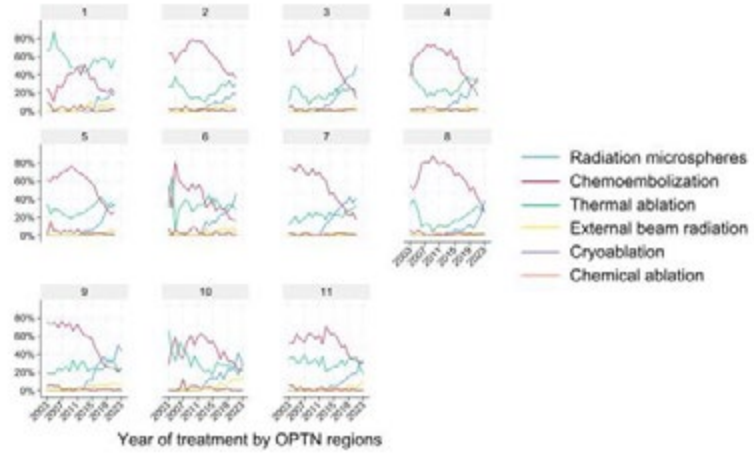


Figure2. Proportion of LRT types by year of treatment across OPTN regions.



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2536 | SEX AND RACE DISPARITIES IN LIVER LISTINGS AND TRANSPLANTS FOR NON-HEPATOCELLULAR CARCINOMA INDICATIONS IN THE UNITED STATES

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Background: Alcohol-associated liver disease (ALD) and metabolic dysfunction-associated steatohepatitis (MASH) are emerging as major indications for liver transplant (LT) in the US. The aim of this study is to examine etiology-based trends on listing for and receiving LT for non-HCC indication in the US. **Methods:** The United Network for Organ Sharing (UNOS) database was used to extract a retrospective cohort (2011-2023) of adults who were listed for or received first LT for non-HCC indication due to ALD, MASH, and HCV etiology. **Results:** Of a total of 51,167 non-HCC listings (Fig. 1, Upper Panel), ALD led since 2015 (60.5% listings in 2023), with an increase of 94% between 2011 and 2023. In males, ALD led in all races since 2019. In females, ALD led in Blacks (63.8% of listings in 2023), while MASH led in Caucasians (51.3% of listings in 2023). Of a total of 30,193

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LT for non-HCC indication (Fig. 1, Lower Panel), ALD led since 2015 (60.8% in 2023), with an increase of 71% (76% in males and 70% in females) between 2011 and 2023. In males, ALD led in all races, with 65.9%, 70.6%, and 67.2% in 2023 among Caucasians, Hispanics, and blacks respectively, with the highest increase of 465% in blacks. In females, ALD led in blacks since 2018 (63.4% in 2023) and MASH led in Hispanics since 2015 (49.2% in 2023). In Caucasian females, MASH led since 2014 but switched to ALD in 2021 (51% in 2023). The highest increase for ALD was in black females at 343%. **Conclusion:** Overall, ALD has emerged as the leading indication for non-HCC listings and LT, except in Hispanic females with MASH being the leading indication. These trends are relevant in developing strategies and policy implementation for the control of liver disease in the US.

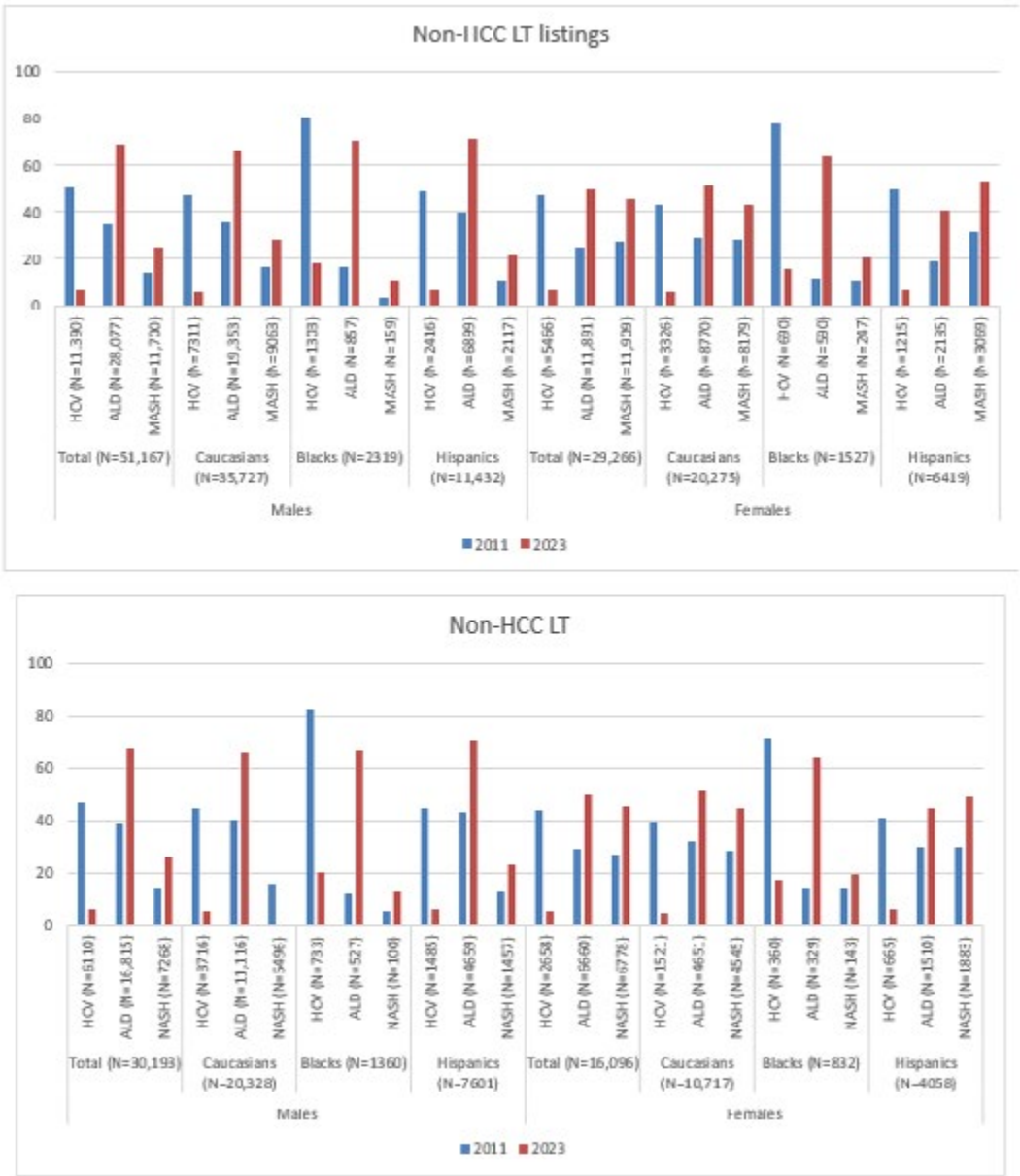

Figure 1 *Upper Panel: Trends in liver listings for non-HCC (2011-2023) for hepatitis C virus (HCV), alcohol-associated liver disease (ALD), and non-alcoholic steatohepatitis (MASH).*
Lower Panel: Trends in receiving LT for non-HCC (2011-2023) for HCV, ALD, and MASH.

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Grant/Research Support, Exact Sciences: Grant/Research Support, Theratechnologies: Grant/Research Support, Durect Corporation: Grant/Research Support, Zobair Younossi: Nothing to Disclose, Ashwani Singal: Advisor relationship with CLD Foundation; Has not ended; Speaking and Teaching relationship with Medical Speaker's Network; Has not ended; Speaking and Teaching relationship with Madrigal; Has not ended; Stock â€“ privately held company relationship with Pleiogenix; Has not ended; Consultant relationship with Pleiogenix; Has not ended; Advisor relationship with Durect; Has ended; Royalties or patent beneficiary relationship with Up-to-Date; Has not ended; Executive role relationship with Gastro Endo News; Has not ended; Grant/Research Support relationship with NIAAA; Has not ended; Employee relationship with Avera Medical Group; Has ended; Grant/Research Support relationship with GSK; Has not ended; Employee relationship with University of Louisville School of Medicine; Has not ended; Speaking and Teaching relationship with Medscape; Has not ended

2537 | IMPACT OF NOSOCOMIAL INFECTIONS IN POST-LIVER TRANSPLANTATION PATIENTS

Harshavardhan Sanekommu[1] *Vera Hapshy*[1] *Christopher Schreiber*[1] *Talal Bhatti*[2] *Lee Peng*[1]

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Background: Following liver transplantation, infections remain a primary cause of mortality and graft failure. The administration of powerful immunosuppressants increases patients' susceptibility to infections. However, this risk can be mitigated through preventive measures, early diagnosis, and effective treatment. This study aims to investigate nosocomial infections (NI) in post-liver transplantation patients. **Methods:** Retrospective analysis was performed using the National Inpatient Sample (NIS) database from the year 2016 to 2019. Patients were identified using the ICD-10 procedure codes for liver transplant and the study focused on patients with a length of stay (LOS) of >3 days. NI was defined as having any one of the following: catheter-associated urinary tract infections (CAUTI), catheter-associated bloodstream infections (CLABSI), ventilator-associated pneumonia (VAP), Clostridioides difficile infection (CDI), and surgical site infections (SSI). The primary outcome was the mortality of NI, and secondary outcomes included length of stay (LOS) and hospitalization charges. We evaluated the association between NI and outcomes using multivariate logistic regression models for in-hospital mortality, Poisson regression for LOS, and generalized linear model with gamma distribution and log link for hospitalization cost. Models were adjusted for age, gender, race, hospital characteristics, and Elixhauser comorbidities. **Results:** A total of 21,465 patients underwent liver transplantation, of which 440 (2.0%) developed NI. Patients with NI had higher rates of congestive heart failure, cardiac arrhythmias, uncomplicated hypertension, and fluid and electrolyte disorders. Patients with NIs had significantly higher in-hospital mortality (15% vs. 2.9%, Adjusted OR 3.28, CI: 1.39-7.74), longer LOS (43.6 days vs. 15.3 days), and increased hospital costs ($303,478.4 vs. $129,137.3) **(**Table 1**)**. Those with VAP had a mortality rate of 60% (30 of 50 patients, AOR 29.6, CI: 5.24-169). Those with CDI had a mortality rate of 8.6% (25 of 290 patients), but it was not significant (AOR 2.25, CI: 0.67-8.23). Similarly, those with SSI had a mortality rate of 25% (5 out of 20 patients), which was not significant (AOR 6.36, CI: 0.79-52.9). Factors associated with increased odds of developing NI included congestive heart failure (OR 2.08, CI: 1.03-4.23) and fluid and electrolyte disorders (OR 2.4, CI: 1.24-4.62). **Conclusion:** NI significantly increase the risk of in-hospital mortality, extend the length of hospital stay, and elevate hospitalization costs for post-liver transplantation patients. Specifically, infections such as VAP are associated with alarmingly high mortality rates. These findings underscore the critical need for effective prevention, early diagnosis, and targeted treatment strategies to mitigate the adverse outcomes associated with NI in this patient population.

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Table 1. Impact of NI on mortality, length of hospital stay, and hospital cost

Characteristic	Without infection (N)	With infection (N)	Adjusted OR/RR	95% CI	P-value
All infections					
In-hospital mortality	600 (2.9%)	65 (15%)	3.28	1.39, 7.74	0.007
LOS	15.3 (0.46)	43.6 (4.39)	2.1	1.74, 2.55	<0.001
Hospital Cost	129,137.3 (3,780.94)	303,478.4 (31,837.31)	1.92	1.60, 2.30	<0.001
CAUTI					
In-hospital mortality	665 (3.1%)	0 (0%)	0	0.00, 0.00	<0.001
LOS	15.9 (0.49)	31.4 (9.50)	1.41	1.14, 1.75	0.002
Hospital Cost	132,669.1 (4,012.84)	171,493.1 (39,731.11)	1	0.84, 1.18	>0.9
CLABSI					
In-hospital mortality	645 (3.0%)	20 (29%)	3.33	0.56, 19.7	0.2
LOS	15.7 (0.48)	69.7 (12.98)	2.53	1.69, 3.79	<0.001
Hospital Cost	131,677.6 (3,983.75)	449,289.6 (104,976.60)	2.49	1.51, 4.11	<0.001
VAP					
In-hospital mortality	635 (3.0%)	30 (60%)	29.8	5.24, 169	<0.001
LOS	15.8 (0.48)	71.3 (16.07)	2.73	1.81, 4.10	<0.001
Hospital Cost	131,505.8 (3,928.16)	649,834.3 (97,600.72)	3.51	2.69, 4.57	<0.001
CDI					
In-hospital mortality	640 (3.0%)	25 (8.6%)	2.35	0.67, 8.23	0.2
LOS	15.7 (0.47)	32.8 (4.09)	1.76	1.39, 2.23	<0.001
Hospital Cost	131,404.4 (3,883.49)	228,273.7 (24,339.70)	1.62	1.34, 1.96	<0.001
SSI					
In-hospital mortality	660 (3.1%)	5 (25%)	6.36	0.76, 52.9	0.087
LOS	15.9 (0.49)	62.0 (18.72)	2.26	1.35, 3.79	0.002
Hospital Cost	132,504.7 (4,006.01)	357,342.6 (101,100.44)	1.92	1.14, 3.23	0.014

Disclosures: Harshavardhan Sanekommu: Nothing to Disclose, Vera Hapshy: Nothing to Disclose, Christopher Schreiber: Nothing to Disclose, Talal Bhatti: Nothing to Disclose, Lee Peng: Nothing to Disclose

2538 | ANXIETY AND DEPRESSION ARE SIGNIFICANTLY ASSOCIATED WITH WORSE HEALTH-RELATED QUALITY OF LIFE IN LIVER TRANSPLANT SURVIVORS

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Background: The prevalence of mental health disorders (MHDs) in liver transplant (LT) survivors is significantly higher than in the general population. It is unknown if MHDs impact post-transplant health-related quality of life (HRQOL), a patient-centered outcome important to LT survivors. We aimed to measure the impact of MHDs on HRQOL in LT survivors. **Methods:** We performed a cross-sectional study of 221 patients presenting for routine post-transplant care at a single large-volume LT center from January 2020 – February 2023. Participants completed survey instruments to measure HRQOL (PROMIS Profile-29), the Hospital Anxiety and Depression Scale (HADS), the Brief Health Literacy Screen (BHLS), and active post-traumatic stress (PTSD) symptoms using the Impact of Event Scale-Revised (IES-R). Participants also self-reported sociodemographics and a history of MHD diagnoses and treatment. We completed a chart review of clinical data on patients' peri- and post-transplant course and prior MHD history and treatment. The primary outcomes were the Mental and Physical Health component scores of Profile-29 (MCS, PCS) with predictors including clinical data, demographic data, and MHD history. Predictors of the MCS and PCS scores were tested using univariate and multivariate regression models. Variables for multivariate analysis were chosen a priori or from univariate p<0.25. **Results:** Overall, 221 patients [59% male, 89% white, median age 63 years (IQR: 54-69)] consented to participate. Median time from LT was 4.6 years (IQR: 1.4-10.0). Median MELD-Na at LT was 21 (IQR: 16-25), median ICU days post-transplant were 3 days (IQR: 2-6), and 42% had post-LT complications. The prevalence of anxiety, depression, or both after LT was 29% and PTSD was 6.4%; prevalence on self-reported diagnoses were similar to rates of active symptoms of anxiety (18%), depression (17%), and PTSD (11.8%) on HADS and IES-R surveys. A new MHD after LT was noted in

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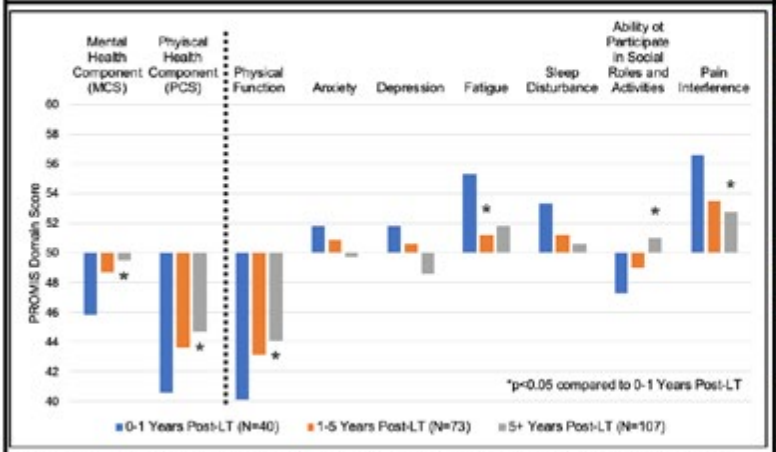
12%, and only 8% of LT survivors were seeing a therapist. There was significant improvement in HRQOL in those 5+ years vs. 0-1 years post-LT (MCS scores: 49.5±8.7 vs. 45.8±9.3, p=0.03 and PCS scores: 44.7±9.1 vs. 40.6±8.8, p=0.02). In multivariate logistic regression, the combination of anxiety and depression after LT, as well as inadequate health literacy on BHLS, were associated with lower MCS and PCS scores. **Conclusion:** Anxiety, depression, or both are prevalent in nearly 1 out of every 3 LT survivors, associated with poor HRQOL, and may represent modifiable factors to improve patient-reported outcomes for after transplant. Further study is necessary to determine the interactions between MHDs, social determinants of health, including health literacy, and HRQOL.

Figure 1. Summary of PROMIS Profile-29 Measures of HRQOL and Predictors of PROMIS MCS and PCS after Liver Transplant

A. PROMIS Profile-29 Domain and Component Scores by Time After Liver Transplant



T-score range 0-100, higher score indicates indicates more of the concept being measures (i.e., higher score in physical function indicates better physical function, higher score in anxiety indicates more anxiety); US population mean = 50.

B. Predictors of PROMIS Profile-29 MCS and PCS after Liver Transplant

Multivariable analysis	MCS		PCS	
Variable	Estimate	P value	Estimate	P value
Complications None	0.896	0.4879	0.997	0.4722
Liver disease (Hep B + Hep C)	---	---	**3.779**	**0.0268**
Liver disease (MASH)	0.114	0.9371	0.350	0.8333
Age	-0.063	0.2520	**-0.230**	**0.0001**
Male	0.782	0.5448	0.595	0.6710
New mental health diagnosis after transplant	0.372	0.8673	-1.890	0.4238
Marital status/living partner				
Married vs. live alone	1.111	0.5573	---	---
Not married, live w/ adult vs. live alone	0.195	0.9370	---	---
Highest education: High school diploma	4.078	0.1256	4.332	0.1277
BHLS inadequate health literacy	**-2.792**	**0.0330**	**-4.621**	**0.0014**
Time from transplant (years)	0.129	0.1841	0.071	0.4990
PTSD after transplant	-4.972	0.0669	-1.002	0.7303
Anxiety/Depression after transplant				
Anxiety alone vs. neither	-2.825	0.3294	-0.745	0.8115
Depression alone vs. neither	-2.536	0.3701	-4.882	0.1101
Anxiety AND depression vs. neither	**-10.055**	**<.0001**	**-7.880**	**0.0003**

N=147 for multivariable analysis based on missing data for some respondents

Disclosures: Alexander Scherer: Nothing to Disclose, Umer Bhatti: Nothing to Disclose, Qing Tang: Nothing to Disclose, Christine Abeysekera: Nothing to Disclose, Miranda Stovall: Nothing to Disclose, Rachel Holmes: Nothing to Disclose, Anahli Patel: Nothing to Disclose, Eric Orman: Sitero: Consultant, Biovie: Advisor, Lauren Nephew: Nothing to Disclose, Marwan Ghabril: Nothing to Disclose, Chandrashekhar Kubal: Nothing to Disclose, Naga Chalasani: Madrigal: Consultant, Zydus, Ipsen, Pfizer, Merck, Altimmune, GSK: Consultant, Exact Sciences: Grant/Research Support, NIH: Grant/Research Support, Archita Desai: Nothing to Disclose

2539 | EARLY EXTUBATION: A PROMISING STRATEGY TO MITIGATE POST-LIVER TRANSPLANT COMPLICATIONS AND ENHANCE RECOVERY

Justin Lin[1] Maham Ghani[1] Reanay Berezovskiy[1] Bryana Belin[1] Aditya Sood[1] Hatef Massoumi[2] Elliot Grodstein[1] Lawrence Lau[1] Nabil Dagher[1] Sanjaya Satapathy[1]

[1]Northwell Health, [2]Lenox Hill Hospital

Background: Liver transplantation is the definitive treatment for end-stage liver disease. While remarkable advancements in transplantation techniques have improved outcomes, the postoperative period remains challenging. Acute kidney injury (AKI) is a significant complication associated with increased morbidity, mortality, and prolonged hospitalization. Mechanical ventilation is a known risk factor for AKI, contributing to hemodynamic instability, systemic inflammation, and fluid overload. Early extubation after liver transplantation has been associated with decreased complications and improved outcomes, but the optimal timing remains unresolved. **Methods:** This retrospective observational cohort study enrolled 204 adult orthotopic liver transplantations performed between Dec 3rd, 2019 and Jan 19th, 2024. Patients were categorized into two groups: those extubated within 12 hours (EE, n=98) and those extubated after 12 hours (LE, n=106) post-transplant. Baseline characteristics, disease severity, ICU and hospital length of stay, reintubation rates, and AKI occurrence within 14 days were compared between groups. Subgroup analysis was conducted to evaluate the impact of an early extubation protocol implemented in 2022. **Results:** Patients in the EE group demonstrated better functional status, reflected in higher Karnofsky Performance Scale (KPS) scores (79.3 ± 9.6% vs 74.6 ± 15.6%, p = 0.010). EE was also associated with a shorter ICU length of stay (4.0 ± 4.5 days vs 5.9 ± 6.8 days, p = 0.042) and overall

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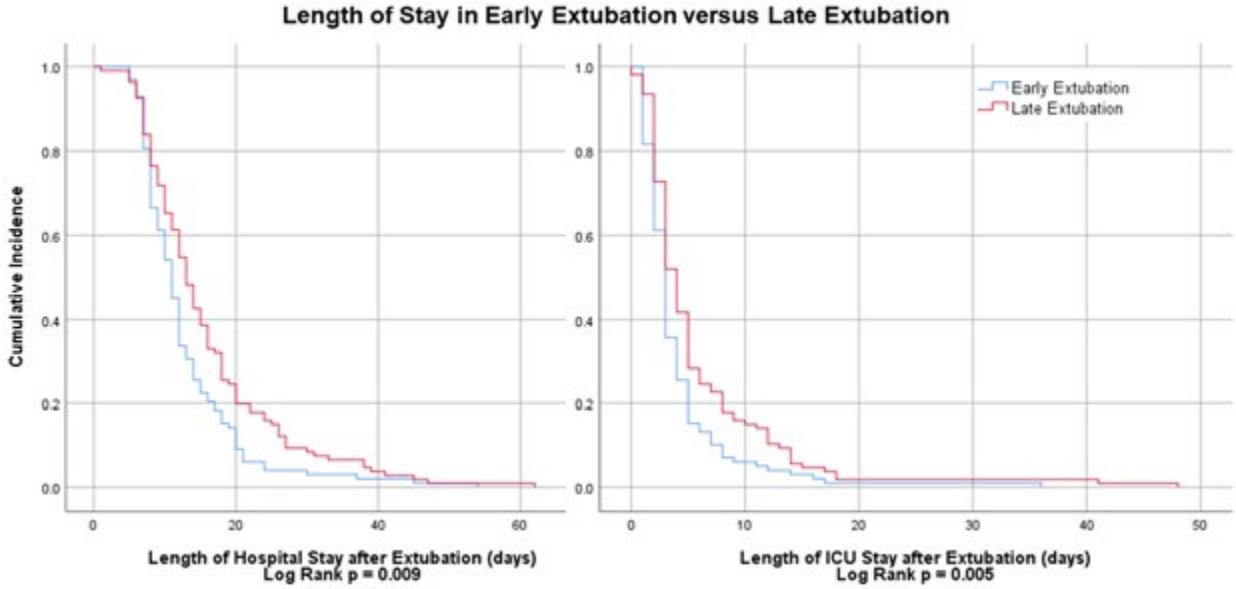
hospital length of stay (12.8 ± 7.7 days vs 15.9 ± 10.2 days, p = 0.037). These associations remained significant after adjusting for age, BMI, MELD 3.0 score, and KPS. There was no significant difference in reintubation rates between the groups. The rate of acute kidney injury (AKI) was lower in the EE group (59.2%) compared to LE (79.2%; OR = 0.375 [95% CI 0.193, 0.727], p = 0.004). This difference persisted after adjusting for age, BMI, MELD 3.0 score, and KPS. The implementation of the early extubation protocol resulted in a significant increase in the proportion of patients extubated within 12 hours from 9.7% pre-protocol to 54.9% post-protocol. This was associated with a decrease in ICU length of stay (8.8 ± 10.8 days vs 4.3 ± 4.1 days, p = 0.028), remaining significant after adjusting for age, BMI, MELD 3.0 score, and KPS. Comparing within the LE group, while higher rates of AKI were observed post-protocol, this difference was not statistically significant. **Conclusion:** This study demonstrated early extubation following liver transplantation to be associated shorter ICU and hospital stays and lower post-transplant AKI without increasing reintubation rates. Early extubation should be further explored as a potential cost-effective strategy to optimize postoperative outcomes in select liver transplant recipients.



Disclosures: Justin Lin: Nothing to Disclose, Maham Ghani: Nothing to Disclose, Reanay Berezovskiy: Nothing to Disclose, Bryana Belin: Nothing to Disclose, Aditya Sood: Nothing to Disclose, Hatef Massoumi: Nothing to Disclose, Elliot Grodstein: Nothing to Disclose, Lawrence Lau: Nothing to Disclose, Nabil Dagher: Nothing to Disclose, Sanjaya Satapathy: Gilead Sciences: Grant/Research Support, Durect Pharma: Grant/Research Support, Fibronostics: Grant/Research Support, Novartis: Grant/Research Support, Zydus Pharma: Grant/Research Support, Boehringer Ingelheim: Grant/Research Support, Intercept Pharma: Grant/Research Support

2540 | RECOGNIZING THE NEED FOR STATIN USE IN LIVER TRANSPLANT RECIPIENTS: HOW EFFECTIVE ARE PROVIDERS AT ADHERING TO PRIMARY AND SECONDARY PREVENTION GUIDELINES?

Jacob Ciricillo[1] *Debra Yen*[1] *John Barnes*[1] *Askanda Osman*[1] *Yeshika Sharma*[1] *Inuk Zandvakili*[1] *Amoah Yeboah-Korang*[1]

[1]*University of Cincinnati*

Background: Cardiovascular disease (CVD) remains a leading cause of morbidity and mortality post-liver transplantation (LT). In the general population, statin therapy is recommended for primary or secondary prevention of atherosclerotic cardiovascular disease (ASCVD). However, provider adherence to statin prescription in liver transplant recipients (LTRs) may be limited due to under-recognition of risk, as well as concern for hepatotoxicity and drug-interactions. This study explores the percentage of LTRs meeting indication for statin use for ASCVD prevention and provider adherence to statin guidelines published by the American College of Cardiology/American

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Heart Association. **Methods:** Retrospective chart review was performed on all LTRs transplanted 2012-2018 at a single center. Statin use for secondary prevention was indicated in patients with prior ASCVD such as ischemic heart disease, ischemic stroke/TIA, and peripheral vascular disease. Indication for primary prevention was determined using 2013 ACC/AHA guidelines including LDL ≥ 190 mg/dL, history of diabetes at age 40-75 and LDL 70-189 mg/dL, or no diabetes with LDL 70-189 mg/dL and 10-year ASCVD risk ≥7.5%. Statin indication criteria and adherence were compared at 1 and 5-years post-LT. Those with insufficient data to determine prevention criteria and statin use were excluded. **Results:** Baseline characteristics of the 576 LTRs: 62.5% male, 92.0% white, mean age 57.0 ± 10 years at LT, 29.9% MASLD cirrhosis, 24.0% alcohol. Prior to LT, 9.0% had a history of ASCVD while 36.7% had diabetes. At post-LT year 1, 52.7% met indication for primary or secondary prevention, but only 27.5% of those with an indication were on a statin. At post-LT year 5, 63.7% met indication primary or secondary prevention, but only 47.9% of those with an indication were on a statin. For primary prevention, only 18.3% that met indication were on a statin at year 1 and 40.4% at year 5. For secondary prevention, only 55.2% that met indication were on a statin at year 1 and 66.7% at year 5. About 39% of LTRs meeting secondary prevention at year 5 were on a high-intensity statin. **Conclusion:** Despite a large portion of this cohort meeting indication for statin use, provider adherence to statin guidelines was low. Although adherence improved at post-LT year 5 compared to year 1, these findings highlight that statin therapy is significantly underused among LTRs who need statins for ASCVD prevention. A limitation of this study is that lack of statin prescription was assumed to due to provider decision-making rather than patient factors such as reluctance or statin intolerance. We hypothesize that improved provider adherence and greater statin utilization will improve post-LT cardiovascular outcomes, which warrants further study.

Disclosures: Jacob Ciricillo: Nothing to Disclose, Debra Yen: Nothing to Disclose, John Barnes: Nothing to Disclose, Askanda Osman: Nothing to Disclose, Yeshika Sharma: Intercept Pharmaceuticals: Speaking and Teaching, Inuk Zandvakili: Nothing to Disclose, Amoah Yeboah-Korang: Nothing to Disclose

2541 | FAVORABLE OUTCOME IN PATIENTS OVER 65 YEARS WITH HEPATOCELLULAR CARCINOMA UNDERGOING LIVER TRANSPLANTATION

Saad Alghamdi[1] Dimitri Raptis[2] Lina Aljurf[2] Mona Jefri[2] Fuat Saner[2] Waleed Al Hamoudi[3] Saleh Alqahtani[4] Dieter Broering[2] Massimo Malago[2]

[1]King Faisal Specialist Hospital and Research Center, [2]KFSHRC, [3]King Saud University/KKUH, [4]Johns Hopkins University

Background: Hepatocellular carcinoma (HCC) is the fourth leading cause of cancer-related mortality worldwide. With the aging population, more people above the age of 65 may become liver transplant (LT) candidates. The aim of this study is to evaluate the outcomes of LT in patients over 65 years of age with HCC. **Methods:** Using our electronic medical record system, we collected data of patients who underwent LT from January 2001 - December 2021 at our hospital. We included patients who underwent LT and with HCC. **Results:** 244 patients with HCC were included in the study with a mean age of 59 (SD9) years, 74 (30%) were female. The maximum diameter of HCC was 28 mm (SD 15). The median time between HCC diagnosis and LT was 226 (IQR 79-435) days. 178 (73%) patients were 65 years or less, while 66 (27%) above 65 years. Incidental HCC was found in 19 (8%) patients. 58 (24%) were out of Milan Criteria. 129 (53%) received treatment for HCC prior to the transplant. The most common pre-transplant treatment was RFA in 59 patients (45%), followed by TACE in 37 (28%) patients. The in-hospital mortality rate was 5%. The Comprehensive Complication Index™ (CCI™) was 22.6 (IQR 8.7-39.7). The overall survival rates at 1, 2, 3, and 5 years were 92%, 88%, 86%, and 89%, respectively. **Conclusion:** Patients older than 65 years of age with HCC have excellent outcome post LT. Age alone should not discourage transplant centers from considering patients with HCC for transplantation.

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Parameters	Overall 244 (100%)	< 65 years 178 (73%)	≥ 65 years 66 (27%)	Odds Ratio	95% CI	p value
Age, median (IQR), years	60.7 (54.8 – 65.6)					
Female sex, n (%)	74 (30)	55 (31)	19 (29)	1.11	0.5 - 2	0.876
BMI, mean (SD) kg/m2	27.6 (8.71)	30 (5)	30 (5)	-	-	
Underlying liver disease						*0.111*
NASH, n (%)	43 (18)	30 (17)	13 (20)	-	-	-
AIH, n (%)	2 (0.80)	2 (1.1)	0 (0)	-	-	-
Alcohol, n (%)	5 (2)	3 (1.7)	2 (3)	-	-	-
Budd Chiari, n (%)	1 (0.4)	1 (0.6)	0 (0)	-	-	-
HBV, n (%)	80 (33)	68 (38.2)	12 (18.2)	-	-	-
HCV, n (%)	79 (32)	51 (29)	28 (42.4)	-	-	-
PSC, n (%)	1 (0.4)	0 (0)	1 (1.5)	-	-	-
PFIC, n (%)	1 (0.4)	1 (0.6)	0 (0)	-	-	-
Other, n (%)	31 (13)	21 (12)	10 (15.2)	-	-	-
None, n (%)	1 (0.4)	1 (0.6)	0 (0)	-	-	-
Treatment before LT, n (%)	129 (52.9)	97 (54.5)	32 (48.5)	0.79	0.43 – 1.44	0.471
Type of Treatment before LT						
Any type	129 (52.9)	97 (54.5)	34 (48.5)	0.79	0.43 – 1.44	0.471
Specific types*						0.158
PEI, n (%)	1 (0.76)	1 (0.1)	0 (0.0)	-	-	-
Resection, n (%)	6 (4.58)	2 (0.2)	4 (12.9)	-	-	-
RFA/MWA, n (%)	59 (45.04)	45 (45.0)	14 (45.2)	-	-	-
TACE, n (%)	37 (28.24)	31 (31.0)	6 (19.4)	-	-	-
TACE + RFA, n (%)	1 (0.76)	1 (0.1)	0 (0.0)	-	-	-
TARE, n (%)	27 (20.61)	20 (20.0)	7 (22.6)	-	-	-
Number of treatment sessions, median (IQR)	1 (0-1)	1 (0-1)	0 (0-2)	-	-	0.573
Time between diagnosis and LT, median (IQR), days	226 (79 – 453)			-	-	-
Time between beginning of treatment and LT, median (IQR), days	289 (178.5 – 570.5)			-	-	-
Time between end of treatment and LT, median (IQR), days	213 (127 – 335)			-	-	-
AFP at beginning of treatment, mean (SD)	188 (887)	200 (1000)	100 (500)	-	-	-
Last AFP Prior to LT, mean (SD)	115 (521)	100 (600)	30 (60)	-	-	-
Stage of response at time of LT						*0.308*
CR, n (%)	61 (47.3)	44 (45.4)	27 (53.1)	-	-	-
PD, n (%)	20 (15.5)	13 (13.4)	7 (21.9)	-	-	-
PR, n (%)	45 (34.9)	37 (38.1)	8 (25)	-	-	-
SD, n (%)	3 (2.3)	3 (3.1)	0 (0)	-	-	-

Disclosures: Saad Alghamdi: Nothing to Disclose, Dimitri Raptis: Nothing to Disclose, Lina Aljurf: Nothing to Disclose, Mona Jefri: Nothing to Disclose, Fuat Saner: Nothing to Disclose, Waleed Al Hamoudi: Nothing to Disclose, Saleh Alqahtani: Nothing to Disclose, Dieter Broering: Nothing to Disclose, Massimo Malago: Nothing to Disclose

2542 | METABOLIC REPROGRAMMING OF BILE ACIDS AMELIORATES ACUTE INFLAMMATORY INJURY OF LIVER TRANSPLANTATION BY REGULATING DIFFERENTIATION OF MACROPHAGES ◆

Xin Hu[1] *Yisu Song*[1] *Ronggao Chen*[2] *Xiao Xu*[1]

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Background: The blockage of enterohepatic circulation during liver transplantation (LT) and aseptic inflammation caused by ischemia-reperfusion injury lead to metabolic reprogramming of bile acids (BAs). In addition to the classical biological function of regulating cholesterol metabolism, the ability of bile acids to regulate the immune system has been increasingly valued. However, it is unknown how BAs regulate inflammation process during LT. In this study, we aimed to identify potential probiotic BA that can ameliorate the inflammation injury of LT. **Methods:** The pre-LT and post-LT liver tissue samples of human, rat and mouse were used to investigated changes in metabolism-related pathways during liver transplantation by transcriptome sequencing. Change of BAs profiling in human and rat LT was explored via targeted metabolomics sequencing. Two different models (mouse ischemia-reperfusion injury (IRI) and mouse LT) were performed to evaluate the protective effect of bile acids on LT inflammation injury. ScRNA-seq analysis was further employed to investigate the mechanism of BAs on LT. **Results:** Transcriptome analysis of LT tissue in three species showed that BAs-related pathways were significantly enriched, demonstrating a significant change in BA metabolism. Targeted metabolomics sequencing revealed that isolithocholic acid (isoLCA), a derivative of lithocholic acid, was one of the most significantly decreased bile acids. After intraperitoneal injection of isoLCA during transplantation, acute IRI could be alleviated significantly, with the decrease of ALT and AST. Through the analysis of scRNA-seq, The numbers of myeloid

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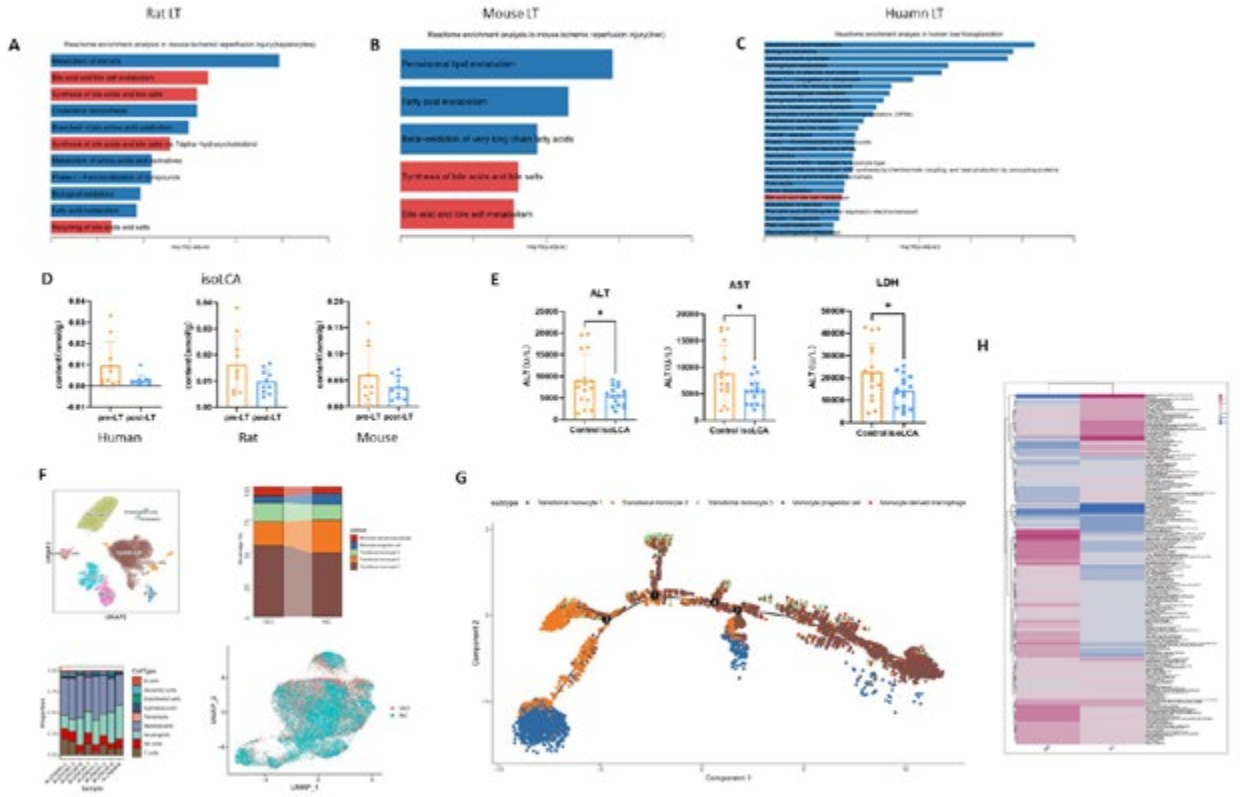
cells and neutrophils were the largest and changed most significantly in both groups. Furthermore, we found that liver myeloid cells can be mainly divided into three groups in the mouse LT model, namely monocyte precursor cells, transitional monocytes and monocyte-derived macrophages. Among them, transitional monocytes can be further subdivided into three subpopulations. Through the specific markers and functional enrichment of each cell population, we discovered the cell proliferation function and lipid metabolism of monocyte precursor cells and transitional type 2 monocytes are activate, while the other three types of cells are mainly responsible for immune and metabolic functions, and through pseudotime trajectory, it was found that there is a temporal relationship between these cell subtypes. We further analyzed the transitional monocytes 1, the largest number among myeloid subpopulations, and found that complement-related pathways and amino acid metabolism were significantly inhibited. **Conclusion:** IsoLCA attenuates liver inflammatory injury after liver transplantation by inhibiting complement response and amino acid metabolism of transitional monocytes.



Disclosures: Xin Hu: Nothing to Disclose, Yisu Song: Nothing to Disclose, Ronggao Chen: Nothing to Disclose, Xiao Xu: Nothing to Disclose

2543 | CHOLESTEROL CONTENT AND EXPRESSION OF SREBF-2 AND HMGCR PREDICT EARLY ALLOGRAFT DYSFUNCTION AND THE OUTCOME OF HUMAN LIVER TRANSPLANTATION

Sandra Torres[1] Anna Baulies[1] Raquel Fucho[1] Susana Nuñez[1] Antoni Rimola[2] Ferran Torres[3] Naira Rico[4] Joanna Ferrer-Fabrega[5] Josep Fuster[6] Jose Fernandez-Checa[7] Carmen Garcia-Ruiz[1]

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Background: Hepatic steatosis presents a raising challenge in liver transplantation (LT), but the underlying mechanisms are not fully understood. Given that metabolic-dysfunction associated fatty liver disease (MAFLD) has a worldwide prevalence of 25% in the normal population, escalating to 70-80% in obese subjects, the

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incidence of fatty liver among organ donors is expected to escalate progressively, leading to the urgent need to discriminate the viability of fatty liver grafts for transplantation. Previous results showed that liver samples from patients with MASH exhibited increased levels of free cholesterol (FC) and enhanced expression of SREBF-2 and HMGCR compared with subjects with simple steatosis. Recent findings have shown that cholesterol deposited in the liver acinus (microvesicular fat) predisposed the liver to ischemia/reperfusion (IR) damage through sensitization to inflammatory cytokines and oxidative stress, suggesting it may be a key factor in determining the outcome of LT. As steatosis reflects the accumulation of several types of lipids, including cholesterol, which has emerged as a key player in MAFLD, our aim was to characterize the profile of lipids and the expression of cholesterol metabolic genes in pre- and post-LT samples in order to optimize selection criteria of liver grafts and to predict the outcome of LT. **Methods:** We evaluated the lipid content, including free fatty acids (FFA), triglycerides (TG) and cholesterol, and the expression of cholesterol-related genes, ER stress marker CHOP and PDK-1 in liver biopsies of 174 patients obtained Pre-LT and Post-LT and correlated these values with early allograft dysfunction (EAD), clinical outcome and survival within the first year after LT. Viability of grafts for LT was evaluated by the Eurotransplant Donor Risk Index. **Results:** We evaluated 174 patients undergoing LT in the Liver Unit of the Hospital Clinic Barcelona. The primary cause for LT was hepatitis C (40.2%), followed by alcoholic cirrhosis (29.8%) and HCC (27%). 70% of recipients were either overweight (BMI 25-29) or obese (BMI>30). Unlike FFA and TG, cholesterol levels are maintained in pre- and post-LT samples. Expression of *CHOP* and *STARD1* increased in post-LT biopsies. However, expression of *PDK1,* a gene involved in glucose metabolism and I/R injury*,* remained unchanged in pre- and post-LT samples. Increased expression of *SREBF*2 in the pre-LT biopsies positively correlated with FC and FFA. Moreover, increased FC, and FFA levels in pre-LT samples were associated with EAD. The increase in the expression of cholesterol regulatory proteins *SREBF-2* and *HMGCR* are associated with potential risk of death within 1 year after LT, with *SREBF-2* emerging as a risk factor of EAD and graft loss. **Conclusion:** Collectively, these data suggest that cholesterol content the expression of SREBF-2 and HMGCR discriminate the viability of steatotic livers for LT and predict the final outcome of LT.

Disclosures: Sandra Torres: Nothing to Disclose, Anna Baulies: Nothing to Disclose, Raquel Fucho: Nothing to Disclose, Susana Nuñez: Nothing to Disclose, Antoni Rimola: Nothing to Disclose, Ferran Torres: Nothing to Disclose, Naira Rico: Nothing to Disclose, Joanna Ferrer-Fabrega: Nothing to Disclose, Josep Fuster: Nothing to Disclose, Jose Fernandez-Checa: Nothing to Disclose, Carmen Garcia-Ruiz: Nothing to Disclose

2544 | RISK FACTORS AND OUTCOMES OF REJECTION IN LIVER TRANSPLANT RECIPIENTS WITH AUTOIMMUNE LIVER DISEASES: A COMPREHENSIVE ANALYSIS

Ahmad Yanis[1] *Garren Montgomery*[2] *Megan Jones*[3] *Jinyuan Liu*[1] *Ashley Spann*[1] *Manhal Izzy*[1]

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Background: Autoimmune liver diseases (AILD) including autoimmune hepatitis (AIH), primary biliary cirrhosis (PBC), and primary sclerosing cholangitis (PSC) are common indications for liver transplant (LT). The data on AILD as a risk factor for T-cell mediated rejection (TCMR) and chronic rejection (CR) are inconsistent. To date, no study has adjusted for tacrolimus exposure when analyzing risk of TCMR among AILD liver transplant recipients (LTR). We aim to evaluate the risk factors and outcomes of TCMR and CR among LTR with AILD, while controlling for tacrolimus exposure for TCMR. **Methods:** This retrospective cohort study included adult patients who underwent liver transplantation at a tertiary North American center between 1/1/2009 and 10/31/2018, and who were maintained on tacrolimus-based immunosuppression. Univariate and multivariate Cox Proportional Hazard models were performed to detect potential risk factors of TCMR, adjusting for tacrolimus median levels and secondary immunosuppressant medications. Univariate logistic regression was used to identify the risk factors for CR. Graft and overall survival comparing TCMR vs. non-TCMR LTR and CR vs. non-CR LTR were analyzed using the log-rank test. **Results:** A total of 733 LTR were included. Of these, 44 had AIH, 25 had PBC, 32 had PSC, and 632 had non-AILD etiologies. TCMR (≥ 1 episode) occurred in 153 LTR (28 AILD, 125 non-AILD) in the study period. On multivariate analysis, the only risk factor associated with TCMR was sex mismatch (HR, 0.630; 95% CI 0.445-0.893, p=0.01) and there was no significant difference in risk of TCMR in AILD when compared to non-AILD LTR (Figure 1**)**, even after adjusting for age, gender, African American race, donor age, CMV mismatch, MELD, cold ischemia time, and median tacrolimus levels. There was no association between the presence of TCMR and graft or overall survival (p=0.74). Fourteen LTR had CR, of whom 2 had AILD and 12 had non-AILD etiologies. History of TCMR was the only variable associated with increased risk of CR (HR, 15.03; 95% CI 4.14-54.59; p<0.01). CR was associated with decreased graft survival (p=0.001). **Conclusion:** In this comprehensive

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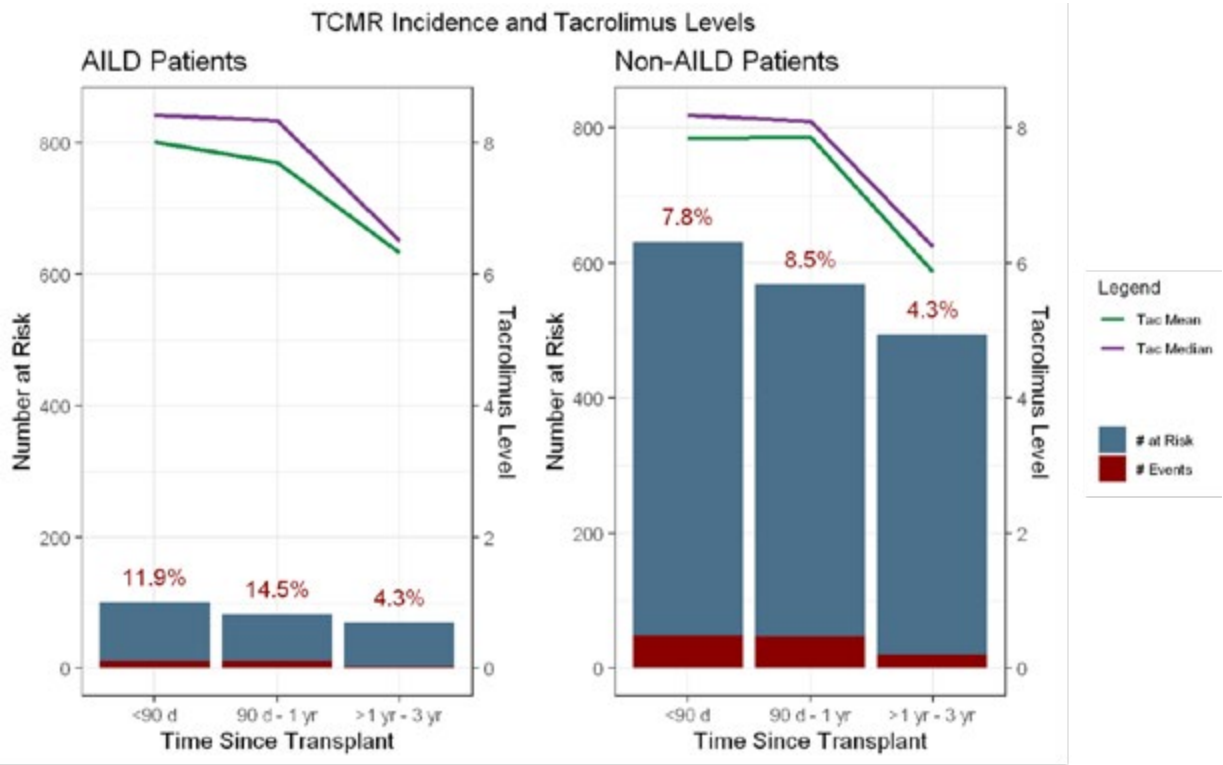
analysis, after accounting for multiple covariates including median tacrolimus levels, sex mismatch between donor and recipient was the only predictor associated with increased risk of TCMR. Importantly, unlike the prevailing paradigm, there was no difference in TCMR risk between AILD and non-AILD LTR. TCMR was associated with increased risk of CR, and graft survival was affected only by CR.



Disclosures: Ahmad Yanis: Nothing to Disclose, Garren Montgomery: Nothing to Disclose, Megan Jones: Nothing to Disclose, Jinyuan Liu: Nothing to Disclose, Ashley Spann: Bristol Myers Squibb Foundation: Grant/ Research Support, Manhal Izzy: Nothing to Disclose

2545 | EPSTEIN-BARR VIRUS NEGATIVE MONOTYPIC PLASMA CELL INFILTRATES IN LIVER ALLOGRAFTS: A CLINICOPATHOLOGIC REVIEW

Murli Krishna[1] Basma Elhaddad[2] Jason Lewis[2] Mohamed Elrefaei[2] Raouf Nakhleh[2] Andrew Keaveny[2] Liuyan Jiang[2] David Menke[2]

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Background: Plasma cell infiltrates in liver allografts (LA) are often due to hepatitis or cellular rejection. We reviewed clinicopathologic features of allografts with Epstein-Barr virus (EBV) negative monotypic plasma cell infiltrates (MPCI) distinct from classic post-transplant lymphoproliferative disorder. **Methods:** Pathology data search was performed (2000-2023) for LAs with MPCIs. Cases were included only if MPCI was present initially in the allograft. Histology and clinical data were reviewed. **Results:** Study cohort consisted 18 patients (11F, 7M; 24-7 years) from 4,100 liver transplants (LT). Indications were steatotic liver disease (8; 4 alcohol-associated, 4 metabolic dysfunction-associated), 4 primary sclerosing cholangitis, 3 autoimmune hepatitis, 2 hepatitis C, 1 cryptogenic). Two had simultaneous liver-kidney transplants (SLK), and 5 had multiple (2) LTs. There was no correlation between MPCI and donor antibodies (DSA) or crossmatch (CM). MPCI was diagnosed 2-157 months (mos) (median 33.5) after LT, including 3 after reLT. Histology showed periportal and centrilobular MPCIs with necrosis, with or without fibrosis. One patient with SLK had involvement of kidney allograft. Eight patients had multiple episodes of cellular rejection requiring treatment. EBV in-situ hybridization performed on 16 patients were negative. MPCIs were kappa-restricted in all cases; serum immunofixation revealed corresponding monoclonal protein in 11. Bone marrow biopsy was performed on 13 patients, and 2 showed slight (biopsy. After diagnosis a majority of patients' baseline immunosupression was decreased, and 9 received oncologic treatment. Follow-up

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(F/U) ranged from 7 to 198 mos (median 137). 16 patients had F/U liver biopsies; 10 showed persistent disease and 4 progressed to cirrhosis. One patient underwent reLT for graft failure related to MPCI. In 6 patients F/U biopsies became negative for MPCI. Three patients died of allograft failure (17-147 mos post LT), including one due to MPCI and cholangiopathy. **Conclusion:** 1) EBV-negative MPCI in liver allografts is rare (<0.5% of transplants) and not well defined. 2) All our cases were kappa-restricted. 3) MPCIs are largely confined to the LA, but may involve multiple transplant organs. 4) Presence of DSA or a positive CM may not be associated with MPCI. 5) MPCI may cause severe allograft dysfunction, but does not appear to be systemically aggressive.

Disclosures: Murli Krishna: Nothing to Disclose, Basma Elhaddad: Nothing to Disclose, Jason Lewis: Nothing to Disclose, Mohamed Elrefaei: Nothing to Disclose, Raouf Nakhleh: Nothing to Disclose, Andrew Keaveny: BioVie Inc: Grant/Research Support, River 2 Renal Corporation: Grant/Research Support, HepQuant LLC: Grant/Research Support, Liuyan Jiang: Nothing to Disclose, David Menke: Nothing to Disclose

2546 | WORSE TUMOR BIOLOGY, AND NOT TUMOR SIZE, IS ASSOCIATED WITH LOWER POST-LIVER TRANSPLANT SURVIVAL IN RECIPIENTS WITH HEPATOCELLULAR CARCINOMA ◆

Behnam Saberi[1] Marwan Alsaqa[1] Leandro Sierra[1] Ximena Parraga[1] Merve Gurakar[2] Butros Fakhoury[3] Nazli Begum Ozturk[4] Alan Bonder[1] Ahmet Gurakar[2]

[1]BIDMC, [2]JHMI, [3]St. Elizabeth Medical Center, [4]Beaumont Hospital, Royal Oak

Background: Liver transplant (LT) programs in the US continue to use Milan/UCSF criteria in candidate selection in patients with hepatocellular carcinoma (HCC). Although these criteria have helped to improve post-LT outcomes in HCC, they have limitations. We aimed to evaluate post-LT survival based on tumor size using a large national US database. **Methods:** LT recipients with one reported pre-LT HCC lesion between 2015-2022, who had complete clinical/explant data using the UNOS/OPTN database, were identified. Patients with T1 lesions (one lesion<2cm) were excluded. Kaplan-Meier curves were used for survival analysis. **Results:** 6015 HCC LT recipients with one lesion were identified. 332 (5.5%) patients had tumor size>5 cm in size. On the explant, 58.9% had one lesion, while 41.1% had more than one lesion. 71% had received pre-LT locoregional therapy. At the same time, approximately one-third of patients had complete necrosis on the explant. Only 24 (0.4%) had AFP≥1000 ng/mL, and 350 (5.8%) had AFP≥100ng/mL. 112 (1.8%) had macrovascular invasion, while 632 (10.5%) had microvascular invasion on explant. Among patients without complete necrosis, 8.5% had poor differentiation, while 27.6% and 63.8%, had well and moderate differentiation. Only 81 (1.3%) of patients had positive lymph nodes on pathology. 1, 3, and 5-year survival were comparable between tumor size≤5 and tumor size>5 cm groups (93.9%,85.8%,78.7%, and 93.2%,83.0%,77.2%, p=0.21). On multivariate analysis, poor differentiation (HR=1.991, 95% CI 1.633-2.427), macrovascular invasion(HR=2.558, 95% CI 1.875-3.489), lymph node involvement(HR=1.574, 95% CI 1.061-2.334) had a higher hazard of mortality. Tumor size (5 cm cut-off) was not associated with mortality. **Conclusion:** There is a significant discrepancy between explant and pre-LT imaging in HCC LT recipients. Poor tumor differentiation, vascular invasion, and lymph node involvement but not tumor size were associated with lower post-LT survival in HCC. These findings suggest that tumor biology is an essential factor in determining post-LT outcomes in HCC patients.

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2547 | RELAPSE OF ALCOHOL USE IN LIVER TRANSPLANT RECIPIENTS BEFORE AND DURING THE COVID-19 PANDEMIC

Abla Alj[1] Isaac Ruiz[2] Hélène Castel[1] Alexandre Bourgeois[3] Geneviève Huard[1] Julien Bissonnette[1] Catherine Vincent[1] Marc Bilodeau[1] Julian Hercun[4]

[1]CHUM, [2]Centre Hospitalier de l'Universite de Montreal, [3]CRCHUM, [4]National Institutes of Health

Background: During the COVID-19 lockdown, alcohol consumption patterns changed. Data from the Canadian Centre on Substance and Addiction showed that 1 in 5 Canadians increased their alcohol consumption during that period. The effect of this change in drinking habits has not been studied in recipients of liver transplantation (LTx). The aim of this study was to evaluate the rate and pattern of alcohol relapse in liver transplant recipients during the COVID-19 pandemic. **Methods:** This retrospective study included all consecutive patients who underwent LTx at the Centre hospitalier de l'Université de Montréal (CHUM). Two cohorts were created to compare the pattern of alcohol consumption: Cohort A (before COVID) included all patients undergoing LTx: between Mars 2017 and December 2018 ; Cohort B (COVID period) included all patients undergoing LTx between Mars 2020 (February 27, 2020 was the first confirmed COVID-19 patient in Québec) and December 2021. These cohorts were subdivided according to the cause of underlying liver disease into alcoholic liver disease (ALD) and non-ALD. The percentage of patients who relapsed and the type of relapse were defined according to the WHO risk drinking levels. Relapse was evaluated at 3, 6, 12, 18, and 24 months after LT. **Results:** Cohort A included 107 patients while Cohort B included 97 patients (Table 1). In the pre-COVID cohort, 4/107 (3.7%) patients relapsed alcohol consumption 2 years after LTx. All patients were men with a mean age of 47 years. The indication for LTx was fulminant hepatitis (acetaminophen) in 2 patients and decompensated cirrhosis in 2 patients. Among the subgroup of patients with ALD 2/107 (1.9%) relapsed. The other 2 relapses were in the non-ALD group. Relapsed occurred on average 5.3 months after LTx (range: 1-12).The type of alcohol relapse was classified as severe in 3 cases and mild in one. In the COVID cohort, 4/97 (4.1%) patients relapsed alcohol consumption at 2 years. Three out of these 4 patients were female (75%) with a mean age of 52 years. The indication for LTx was decompensated cirrhosis in 2 patients and hepatocellular carcinoma in the other 2 patients. Among the subgroup of patients with 4/97 (4.1%) relapsed which underlines that all relapses during the COVID period occurred in the ALD group. Relapses occurred on average 11.3 months after LTx (range: 3-22). The type of alcohol relapse was classified as mild to moderate. No patient experienced graft loss because of relapse of alcohol consumption. **Conclusion:** Overall, patients transplanted during the COVID-19 pandemic had a higher incidence of alcohol relapse at 2 years compared to a pre-pandemic control period (p=0.042).

Table 1: Relapses of alcohol use in liver transplant recipients before and during the COVID-19 pandemic

Liver transplantation	Pre-COVID 2017-2018		2 years relapse		COVID 2020-2021		2 years relapse		p
	n	%	n	%	n	%	n	%	
Total	107		4	3,7	97		4	4,1	
Alcohol	29	27,1	2	1,9	33	34,0	4	4,1	0.042
No-alcohol	78	72,9	2	1,9	64	66,0	0	0	0.003

Disclosures: Abla Alj: Nothing to Disclose, Isaac Ruiz: Nothing to Disclose, Hélène Castel: Nothing to Disclose, Alexandre Bourgeois: Nothing to Disclose, Geneviève Huard: Nothing to Disclose, Julien Bissonnette: Nothing to Disclose, Catherine Vincent: Nothing to Disclose, Marc Bilodeau: Mirum Pharmaceuticals: Speaking and Teaching, Julian Hercun: Nothing to Disclose

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2548 | THE DIFFERENCE IN LIVER TRANSPLANT OUTCOMES BETWEEN NORMOTHERMIC AND HYPOTHERMIC MACHINE PERFUSED LIVERS

Ahmad Anouti[1] Hamza Dahshi[2] Thomas Cotter[1] Christine Hwang[1] Timucin Taner[3] Julie Heimbach[3] Madhukar Patel[1] William Lee[1] Sara Hassan[3]

[1]UT Southwestern Medical Center, [2]Case Western School of Medicine, [3]Mayo Clinic Rochester

Background: The pilot study of machine perfusion on extended criteria liver donor grafts in the United States in 2010 marked the inaugural use of this technology. Machine perfusion use has surged, driven by the prospect of expanding the donor pool. Machine perfusion technology is primarily applied to enhance the quality of grafts and to decrease waitlist mortality. There are two main types of machine perfusion: normothermic, which is the more prevalent method, and hypothermic perfusion. The objective of our study is to evaluate the characteristics and outcomes of donated organs subjected to machine perfusion versus no perfusion, and to further stratify normothermic versus hypothermic perfusion. **Methods:** We queried the United Network of Organ Sharing UNOS database from January 2016 till April 2024 to assess US transplanted donor liver organs. We stratified patients into two groups based on machine perfusion status then further divided those that underwent machine perfusion into normothermic vs hypothermic grafts. Bivariate analysis of continuous and categorical variables was performed. Graft failure was assessed using Kaplan-Meier curves and a Cox proportional hazards model was used to detect variables associated with graft survival. **Results:** 69,282 donated grafts were included in the study period of which 66,200 did not undergo perfusion while 3,082 did. Of the 3,085 perfused grafts, 2,725 had normothermic perfusion while 179 had hypothermic perfusion. Hypothermic perfused grafts were more likely to come from donors with HCV (7.3% vs 2.9%, p=0.003). The one and five year graft survival rate among non-perfused grafts was 97.1% and 95.2% while perfused grafts had 97.6% and 96.3% survival, respectively (p=0.09 and 0.06, respectively). Furthermore, among normothermic and hypothermic perfused grafts one and five year survivals were 97.9% and 97.9% vs 97.6% and 96.5%, respectively (p=0.83 and 0.30, respectively) **(**Figure 1**)**. Machine perfusion was associated with significantly improved outcomes compared to non-perfused grafts (HR: 0.69, 95%CI:0.53-0.88). Moreover, hypothermic perfusion showed no significant difference (HR: 0.82, 95%CI: 0.25-2.70) compared to normothermic perfusion. However, donor race (Non-Hispanic Blacks HR: 1.27, 95%CI: 1.15-1.40 and Hispanics HR: 1.16, 95%CI: 1.04-1.30) and recipient ICU stay (HR: 1.32, 95%CI: 1.17-1.49) resulted in significantly inferior outcomes post-transplant **(**Table 1**)**. **Conclusion:** The differences between normothermic and hypothermic perfusion were not statistically significant. This suggests that while machine perfusion can be a beneficial tool in enhancing graft viability, the choice between normothermic and hypothermic methods may be less critical. Disparities in outcomes were observed based on donor race and recipient ICU stay, underscoring the need for further investigation into how clinicodemographic factors influence transplant success.

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Variables	Machine vs No Machine Perfusion			Normothermic vs Hypothermic		
	Adjusted HR	95%CI	P-value	Adjusted HR	95%CI	P-value
Donor Age	1.01	1.01-1.02	<0.001	1.03	1.01-1.05	0.01
Donor Race (Ref: White)						
• Non-Hispanic Black	1.27	1.15-1.40	<0.001	1.13	0.51-2.31	0.75
• Hispanic	1.16	1.04-1.30	0.01	1.23	0.57-2.63	0.60
Donor History of Diabetes	1.37	1.23-1.53	<0.001	1.16	0.60-2.22	0.66
Donor Heavy Alcohol Use	0.90	0.79-0.99	0.03	1.46	0.84-2.54	0.18
Donor Graft Machine Perfusion	0.69	0.53-0.88	0.003	N/A	N/A	N/A
Hypothermic Perfusion	N/A	N/A	N/A	0.82	0.25-2.70	0.75
Deceased Cardiac Donation	2.22	1.98-2.49	<0.001	1.40	0.77-2.5	0.26
Recipient Age	0.99	0.98-0.99	<0.001	1.00	0.97-1.02	0.95
Recipient Race (Ref: White)						
• Non-Hispanic Black	1.51	1.34-1.70	<0.001	1.04	0.31-3.49	0.95
• Hispanic	1.04	0.93-1.16	0.52	1.57	0.79-3.09	0.19
Recipient Diabetes	1.00	0.92-1.10	0.97	1.05	0.61-1.79	0.86
Recipient Life Support	1.22	1.05-1.41	0.01	1.60	0.49-5.24	0.43
Recipient Status 1A/B	1.08	0.91-1.29	0.36	1.35	0.15-12.18	0.79
Recipient ICU stay	1.32	1.17-1.49	<0.001	1.45	0.56-3.76	0.44
MELD Score	N/A	N/A	N/A	1.03	0.99-1.06	0.10
Center Volume (Ref: Low vol)						
• Middle Volume	1.00	0.99-1.10	0.98	1.20	0.62-2.31	0.59
• High volume	1.14	1.02-1.27	0.02	0.99	0.40-2.47	0.99
Transplant Era (Ref: 2016-08/2021)						
• 09/2021-2024	0.80	0.72-0.88	<0.001	0.86	0.41-1.81	0.26

Table 1: Model assessing variables associated with survival in patients that did and did not undergo machine perfusion and those with normothermic vs hypothermic perfusion.

*Model also adjusted for UNOS region and recipient insurance

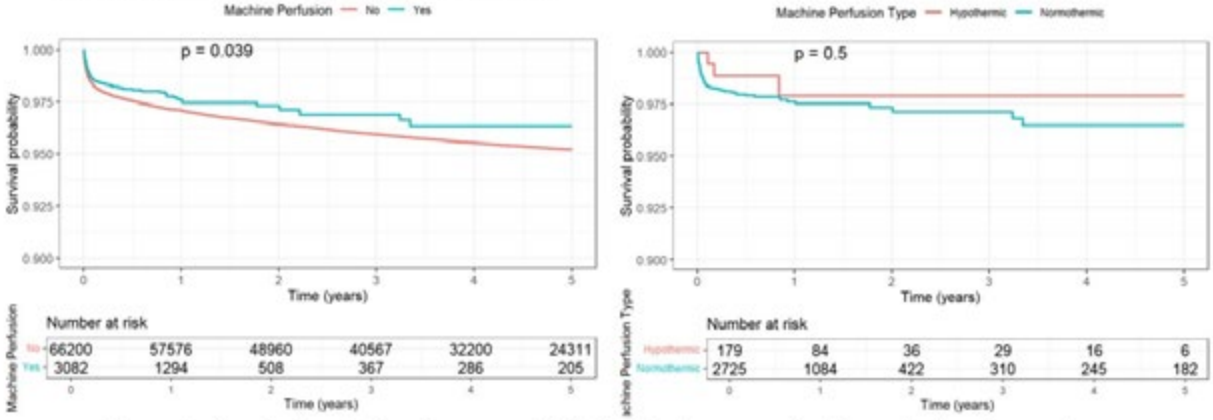

Figure 1: Survival analysis of curves of **A)** all patients comparing those that underwent machine perfusion compared to those that did not receive machine perfusion and **B)** patients that underwent normothermic vs hypothermic perfusion.

Disclosures: Ahmad Anouti: Nothing to Disclose, Hamza Dahshi: Nothing to Disclose, Thomas Cotter: Nothing to Disclose, Christine Hwang: Nothing to Disclose, Timucin Taner: Nothing to Disclose, Julie Heimbach: Nothing to Disclose, Madhukar Patel: Nothing to Disclose, William Lee: Nothing to Disclose, Sara Hassan: Nothing to Disclose

2549 | PREDICTING LIVER GRAFT DISCARD CRITERIA: A MACHINE LEARNING APPROACH TO KEY DONOR CHARACTERISTICS

Ahmad Anouti[1] Hamza Dahshi[2] Thomas Cotter[1] Samar Ibrahim[3] William Lee[1] Timucin Taner[3] Julie Heimbach[3] Madhukar Patel[1] Sara Hassan[3]

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Background: One of the primary challenges in liver transplantation is the shortage of available donor organs. Not all donated organs are suitable for transplantation; those deemed to be of lower quality are often discarded. To address this issue, our study aims to examine the trends in liver grafts discard rate over time and to explore how factors such as increased micro and macro steatosis affect liver discard. **Methods:** Unites States discarded donor liver grafts were assessed from January 2004 till April 2024 using the UNOS database. We stratified discard

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grafts into overall discard, macro and micro steatosis<30% grafts, and macro and micro steatosis≥ 30% grafts. Bivariate analysis of continuous and categorical variables was performed between macro and micro steatosis graft groups, respectively. A logistic regression model was performed to assess variables that increased the risk of discard among grafts. Following the logistic regression, we implemented a machine learning algorithm based on gradient boosting decision trees to assess the level of importance in discard for each variable selected in the model. Importance was determined relative to other variables in the logistic regression model. **Results:** A total of 15,266 donated liver grafts were discarded during the study period. Of these grafts 6,245 (40.9%) and 3,560 (23.3%) had macro-steatosis of< and ≥30%, respectively; and 6,841 (45%) and 2,162 (14%) had micro-steatosis< and ≥30%, respectively. Both discarded grafts with macro- and micro steatosis≥30% were more likely to come from donors that had significantly increased BMIs (both p<0.01). Discarded grafts with macro-steatosis ≥30% were significantly more likely to come from donors with heavy alcohol use (both p<0.01), compared to grafts with macro-steatosis<30%. Discarded grafts with macro-steatosis ≥ 30% (77 vs 41% p<0.01) and micro-steatosis≥30% (74 vs 47%, p<0.01) were more likely to be discarded due to biopsy findings. Macro-steatosis ≥ 30% (OR: 3.8, 95%CI: 3.6-4.0) and micro-steatosis≥30% discard (OR: 1.5, 95%CI: 1.4-1.6) were associated with increased risk of organ discard. Deceased cardiac donation (DCD) (OR: 4.5, 95%CI: 4.2-4.8) was associated with an increased risk of discard **(**Table 1**)**. Furthermore, the machine learning model showed that macro-steatosis≥30% was associated with 55% level of relative importance while micro-steatosis≥30% and DCD had 2% and 14% level of relative importance, respectively **(**Figure 1**)**. **Conclusion:** Discard remains closely associated with factors such as macro-steatosis and micro-steatosis at levels of ≥ 30%. Factors associated with increased risk for discarding organs including BMI, alcohol use and diabetes further highlight the devastating impact of alcohol use disorders and obesity. Adopting innovative approaches, to optimize the use of grafts with higher degrees of steatosis could transform the landscape of liver transplantation, making more grafts available.

Variables	Adjusted Odds Ratio	95%Confidence Interval	P-value
Donor Age	1.01	1.006-1.01	<0.001
Donor Race (Ref White)			
• **Non-Hispanic Black**	0.84	0.78-0.90	<0.001
• **Hispanics**	1.12	1.04-1.21	0.002
History of Diabetes	1.30	1.22-1.38	<0.001
History of Heavy Alcohol Use	0.95	0.89-1.01	0.08
History of Hypertension	1.10	1.04-1.16	<0.001
Macro-steatosis ≥ 30%	3.77	3.56-3.99	<0.001
Micro-steatosis ≥ 30%	1.54	1.44-1.64	<0.001
Deceased Cardiac Donor	4.47	4.15-4.82	<0.001
Transplant Era (ref: 2004-2009)			
• **2010-2015**	0.79	0.74-0.84	<0.001
• **2016-08/2-21**	0.52	0.49-0.56	<0.001
• **09/2021-2024**	0.44	0.41-0.48	<0.001

Table1: Variables associated with organ discard.

*Model adjusted for UNOS Regions

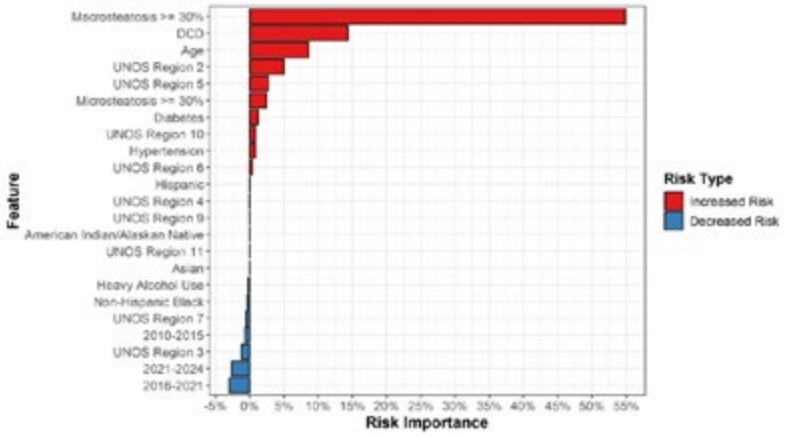

Figure 1: Feature importance for predicting liver discard outcomes using gradient boosting decision trees.

*Model adjusted for UNOS Regions

Disclosures: Ahmad Anouti: Nothing to Disclose, Hamza Dahshi: Nothing to Disclose, Thomas Cotter: Nothing to Disclose, Samar Ibrahim: Advisor relationship with Mirum pharmaceutical; Has not ended; Advisor relationship

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with Albeiro pharma; Has ended, William Lee: Nothing to Disclose, Timucin Taner: Nothing to Disclose, Julie Heimbach: Nothing to Disclose, Madhukar Patel: Nothing to Disclose, Sara Hassan: Nothing to Disclose

2550 | ALCOHOL USE DISORDER TREATMENT IN PATIENTS WITH ALCOHOL USE AFTER LIVER TRANSPLANT SEEN IN A MULTIDISCIPLINARY ALCOHOL-ASSOCIATED LIVER DISEASE CLINIC

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Background: Alcohol use disorder remains one of the most common indications for transplantation with recurrent use post transplant posing significant risk of morbidity and mortality to patients. We sought to characterize alcohol use disorder (AUD) treatment and demographics in patients who received liver transplant for alcohol associated liver disease (ALD) and returned to alcohol use after transplant who were evaluated in a single center multidisciplinary ALD program (MAP clinic). **Methods:** Retrospective chart review was performed of patients meeting above criteria who were referred to MAP clinic between 9/2022-11/2023. Findings are presented as mean with standard deviation or counts with percentages. Unpaired t-test was used to analyze continuous variables. **Results:** 41 post-transplant patients were referred and 26(63.4%) were evaluated in MAP clinic. 13(50.0%) patients were female; the mean age was 50.9(±10.6) years. 23(88.5%) patients were diagnosed with severe AUD at the initial MAP clinic visit. 10(38.5%) patients had co-existing tobacco use disorder, and 1(3.8%) patient had an opioid use disorder. The most common pre-transplant AUD treatment setting was an intensive outpatient program (IOP); 10(38.4%) patients completed in-person IOP and 4(15.4%) engaged in virtual IOP. 11(42.3%) patients did not participate in any pre-transplant AUD treatment. 25(96.1%) patients were not prescribed any medication-assisted treatment (MAT) prior to transplant; 1(3.9%) patient was prescribed naltrexone before transplant. After evaluation in MAP clinic, 3(11.5%) patients were recommended to complete residential treatment and 14(53.8%) were referred to IOP. 3(11.5%) patients expressed no interest in AUD treatment. For MAT, 14(53.8%) patients were prescribed naltrexone, 7(26.9%) were given gabapentin, and 6(23.1%) had no MAT prescribed due to renal or liver dysfunction or lack of willingness to participate in AUD treatment. All patients had Peth testing post-transplant; the mean initial Peth level was 289(±469). The mean time between transplant and the first positive Peth level after transplant was 589(±840) days. **Conclusion:** Nearly 90% of patients who use alcohol after liver transplant have severe AUD. Pre-transplant AUD treatment rates are <60%; IOP is the most common treatment setting pre-and-post liver transplant. MAT is rarely prescribed pre-transplant; after transplant, naltrexone and gabapentin are the most commonly prescribed medications. The mean time to alcohol use is 1.6 years post-transplant. Long-term follow-up in a multidisciplinary setting can be beneficial for detecting and treating post-transplant alcohol use and AUD.

Disclosures: Jeffrey Schwartz: Nothing to Disclose, Meghan Reagan: Nothing to Disclose, Akhil Anand: Nothing to Disclose, Shreya Sengupta: Nothing to Disclose

2551 | THE IMPACT OF MACHINE PERFUSION ON TRANSPLANTED LIVER GRAFTS WITH MACRO-STEATOSIS ◆

Ahmad Anouti[1] Hamza Dahshi[2] Thomas Cotter[1] Amal Aqul[1] William Lee[1] Christine Hwang[1] Timucin Taner[3] Julie Heimbach[3] Madhukar Patel[1] Sara Hassan[3]

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Background: Metabolic dysfunction associated steatohepatitis (MASH), a leading cause of liver transplant needs, is reducing the donor pool, as livers with over 30% steatosis are often rejected due to risks of post-transplant complications. Despite this, many livers with macro-steatosis ≥ 30% are still transplanted in the U.S. We aim to evaluate the effects of hepatic steatosis on transplant outcomes in both pediatric and adult recipients and investigate how machine perfusion might enhance the quality and success of these compromised grafts. **Methods:** We analyzed the UNOS database from January 2010 to April 2024 to study hepatic steatosis outcomes in grafts, categorizing patients into three groups: grafts with <30% macro-steatosis, ≥30% macro-steatosis, and ≥30% macro-steatosis with machine perfusion. We used bivariate analysis, propensity score matching to compare perfused vs. non-perfused

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livers, and assessed graft failure using Kaplan-Meier curves and a Cox proportional hazards model. **Results:** 48,863 transplanted grafts with reported macro-steatosis were included. 44,814 (92%) grafts had macro-steatosis<30% while only 4,049 (8%) had macro-steatosis≥30% of which 158 (4%) underwent machine perfusion. Grafts with≥30% macro-steatosis came from donors with significantly higher BMIs (32.1 vs 29.5 kg/m^2, p<0.01) and history of heavy alcohol (23.9% vs 20.5%, p<0.01) use compared to grafts with macro-steatosis<30%. Perfused grafts were significantly more likely to be transplanted in high volume centers (p<0.01). Grafts with macro-steatosis<30% had a one year graft survival of 95.6% and 92.4% compared to grafts with ≥ 30% that had a one-year graft survival of 94.4% and 91.6% (p<0.01 and 0.1, respectively), while grafts that underwent perfusion had a one and five year graft survival of 96.7% and 96.7% (vs 94.3% and 91.5% for those without perfusion) (p=0.2 and <0.01, respectively) **(**Figure 1**)**. The impact of graft macro-steatosis on graft survival post-transplant was further stratified and only grafts with >40% macro-steatosis were associated with inferior outcomes (HR: 1.5, 95%CI:1.2-1.7). Moreover, machine perfusion was not significantly associated with improved outcomes (HR: 0.7, 95%CI: 0.2-2.0) **(**Table 1**)**. **Conclusion:** Grafts with steatosis levels≥30% typically poorer outcomes early on than those with less steatosis. Although machine perfusion doesn't significantly improve overall survival, it seems to enhance five-year survival rates for high-steatosis grafts compared to non-perfused ones. This method, however, requires further study. Additionally, the success of these grafts depends on certain clinicodemographic factors. Managing these factors well could optimize outcomes for recipients, particularly for grafts with steatosis <40%. This highlights the need for strategies to improve the viability of compromised grafts, thereby boosting transplant success and expanding the donor pool.

Variables	Group 1 vs 2			Group 2 vs 3		
	Adjusted HR	95%CI	P-value	Adjusted HR	95%CI	P-value
Donor Age	1.01	1.01-1.02	<0.001	1.01	0.99-1.02	0.10
Donor Race (Ref: White)						
• Non-Hispanic Black	1.15	1.04-1.23	0.001	0.84	0.57-1.23	0.37
• Hispanic	1.08	0.97-1.19	0.18	1.28	0.93-1.76	0.12
Donor History of Diabetes	1.24	1.14-1.34	<0.001	1.24	0.93-1.65	0.14
Donor Heavy Alcohol Use	0.97	0.89-1.05	0.47	0.96	0.73-1.26	0.76
Graft Macro-steatosis (Ref: <30%)						
• 30-35%	1.10	0.94-1.27	0.23	N/A	N/A	N/A
• 35-40%	1.30	0.83-2.01	0.25	N/A	N/A	N/A
• >40%	1.45	1.24-1.69	<0.001	N/A	N/A	N/A
Donor Graft Machine Perfusion	N/A	N/A	N/A	0.68	0.23-2.00	0.49
Deceased Cardiac Death	2.01	1.76-2.29	<0.001	2.12	1.23-3.65	0.01
Recipient Age	0.98	0.97-0.98	<0.001	0.98	0.97-0.99	0.001
Recipient Race (Ref: White)						
• Non-Hispanic Black	1.48	1.34-1.63	<0.001	1.74	1.23-2.47	0.002
• Hispanic	1.02	0.92-1.13	0.75	1.08	0.75-1.57	0.67
Recipient Diabetes	0.97	0.90-1.05	0.42	0.87	0.67-1.14	0.32
Recipient Life Support	1.30	1.13-1.47	<0.001	1.49	0.84-2.64	0.18
Recipient Status 1A/B	0.72	0.60-0.8	0.001	0.43	0.14-1.34	0.14
Recipient ICU stay	1.29	1.13-1.47	<0.001	1.34	0.81-2.22	0.26
Recipient MELD	1.00	0.99-1.00	0.41	0.99	0.98-1.01	0.79
Center Volume (Ref: Low vol)						
• Middle Volume	0.99	0.91-1.07	0.76	0.91	0.68-1.22	0.53
• High volume	1.07	0.97-1.18	0.17	0.93	0.64-1.34	0.70
Transplant Era (Ref: 2004-2009)						
• 2010-2015	0.54	0.49-0.58	<0.001	0.44	0.33-0.60	<0.001
• 2016-08/2021	0.36	0.32-0.37	<0.001	0.42	0.32-0.56	<0.001
• 09/2021-2024	0.27	0.24-0.31	<0.001	0.30	0.19-0.50	0.006

Table 1: Model assessing variables associated with survival in patients with macro-steatosis <30% and ≥30% and macro-steatosis ≥30% without and with machine perfusion.

*Model also adjusted for UNOS region and recipient insurance. Group 1: macro-steatosis<30%, Group 2: macro-steatosis≥30%, and Group 3: macro-steatosis≥30% with machine perfusion

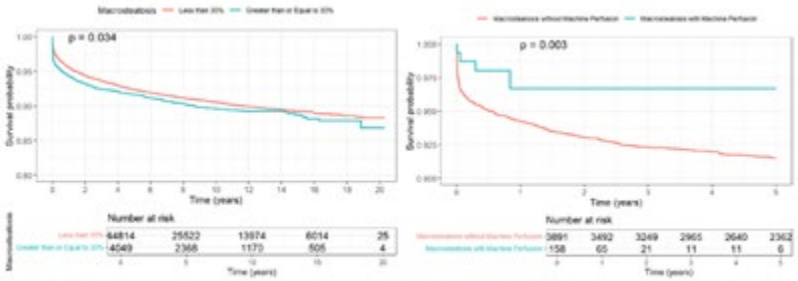

Figure 1: Survival analysis of **A)** all patients with macro-steatosis <30% and ≥30% and **B)** all patients with macro-steatosis ≥30% and macro-steatosis ≥30% with perfusion

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2552 | THE ROLE OF SMOKING IN POST-TRANSPLANT CANCER DEVELOPMENT: INSIGHTS FROM A TWO-DECADE COHORT STUDY

Carmen Alonso Martín[1] Natalia Marcos Carrasco[1] Carolina Almohalla Alvarez[1] FELIX GARCIA PAJARES[1] Elena Velasco Martínez[1] Samuel Juan Fernandez Prada[1] Miryam Moreta Rodriguez[1] Alicia Sanjose Crespo[1] Cristina Martinez Cuevas[1] Gloria Sanchez Antolín[1]

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Background: De novo neoplasms after liver transplantation are a common cause of morbidity in transplant recipients. Smoking is a well-known risk factor for the development of neoplasia in the general population. Liver transplant patients with a history of smoking are at an increased risk of developing post-transplant de novo cancer due to their immunosuppressed state. However, the extent of this increased risk compared to non-smokers is unclear. This study aimed to investigate the impact of pretransplant smoking on tumor development in a large cohort of liver transplant patients **Methods:** A retrospective analysis was performed on a prospective database that included 692 liver transplant patients at a Spanish tertiary hospital from January 2002 to December 2022, focusing on patients who had developed tumors and their tobacco use prior to transplantation. Non-smokers were defined as those who had never smoked, former smokers were patients with a smoking history of more than 20 pack-years who had quit less than 2 years before transplant, and smokers were those still smoking at the time of transplant. results showed that 108 out of 692 patients (15.6%) developed neoplasia post-transplant (86% males, age 60.06 – SD 6.60), with 80 of these being smokers or former smokers (74%). The most common cancers were oropharyngeal and laryngeal (n=26), followed by skin (n=22), and adenocarcinomas of the prostate (n=19) and lung (n=19). Digestive tract tumors affected 16 patients, lymphoma 7, and bladder cancer 5. The risk of cancer in smokers was 18.39% and in non-smokers 10.89% (p<0.0118). When considering the impact of tobacco, except for lymphoma and skin cancer where no significant differences were found, smoking was shown to have a negative effect on cancer development. 100% of lung and bladder tumors affected smokers, as did 92% of oropharyngeal and laryngeal tumors, and nearly 70% of digestive tract tumors (especially esophagus and stomach). In 7 patients, multiple tumors developed (6 of them were smokers). Although 62.86% of all patients were smokers, only 6.22% were female smokers and 56.65% were male. Women smokers were only 9.9% of smokers but 46.3% of non-smokers. The lower incidence of cancer in women may be associated with the lower rate of smokers **Conclusion:** In our series, 15.6% of the patients developed a neoplasm during follow-up. We found a significant risk of developing a solid organ tumor among pre-transplant patients with a smoking habit compared to non-smokers. Oropharyngeal and laryngeal, lung, and prostate were the most frequent tumors in smokers, while skin and lymphoma were more common in non-smokers. Women had a lower cancer rate, likely related to lower tobacco consumption. These findings emphasize the importance of smoking cessation interventions for liver transplant candidates and recipients to reduce cancer risk and improve long-term outcomes

Neoplasm de novo	Non-Smokers N (%)	Smokers or former smokers N (%)
Skin	11(50)	11(50%)
Lung	0	19 (100%)
Oropharyngeal and laryngeal	2	24 (92%)
Prostate	5 (32%)	13 (68%)
Digestive tract tumors	5 (31%)	11 (69%)
Lymphoma	3 (43%)	4 (57%)
Bladder cancer	0	5 (100%)
Cervix cancer	0	1 (100%)

Table 1: Rate of Smokers or Former Smokers Among Liver Transplant Patients with De Novo Neoplasms Post-Transplantation

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2553 | THE RISKS ASSOCIATED WITH THYMOGLOBULIN USE IN PATIENTS WITH LIVER TRANSPLANT REJECTION: A NATIONAL DATABASE ANALYSIS

Jordan Carty[1] Yurilu Gonzalez Moret[1] Audry Chacin-Suarez[1] Kevin Lo[2] John Knorr[1] Manish Thapar[1]

[1]Jefferson Einstein Hospital, [2]Brigham and Women's Hospital

Background: Thymoglobulin is used in patients with steroid refractory Acute T cell Rejection. Thymoglobulin use is associated with serious risk of infections and transfusion reactions. The survival benefit with thymoglobulin use in patients with steroid refectory liver rejection has not been studied well. **Methods:** The study used data from the Trinet X Database. We identified patients older than 18 years of age with a diagnosis of liver rejection and treated with thymoglobulin using the International Classification of Diseases 10th revision coding system during the period 2019 to 2024. A total of 10,639 patients were analyzed through propensity score matching, yielding 208 patients. Patients who received a liver transplant within one year were excluded. Categorical variables were analyzed using Chi-squared and 95% confidence Interval (CI) with a two-tailed p-value <0.05 set as the significance level. The hazard ratio was used to determine the significance of the various outcomes between the two groups at 1 and 5 years. **Results:** A total of 208 patients with liver rejection were included in the final analysis, 104 underwent treatment with thymoglobulin. The average age within both groups was 47 ± 16 years. Both the groups were well matched demographically. Likewise, conditions such as hypertension, chronic kidney disease, diabetes mellitus, hyperlipidemia, infections such as EBV and CMV, as well socioeconomic determinants of health, such as employment and family support, exhibited no significant differences between the two groups. Additionally, patients in both groups received similar immunosuppressive medications. Our analysis showed that patients receiving thymoglobulin had higher mortality at 1 year (HR=2.242, 95% CI (1.307-3.848); p<0.003) and 5 years (HR=2.471, 95% CI (1.580-3.864); p<0.0001). (See Figure 1). Additionally, these patients had a higher incidence of acute kidney injury (AKI) at both 1 year (HR=1.717, 95% CI (1.158-2.546); p<0.006) and 5 years (HR=1.654, 95% CI (1.144-2.391); p<0.007). (See table 1) **Conclusion:** The study shows that patients with liver rejection treated with thymoglobulin led to a higher incidence of AKI and mortality up to 5 years. Further studies are needed to evaluate the underlying causes of mortality and AKI and to examine survival benefits.

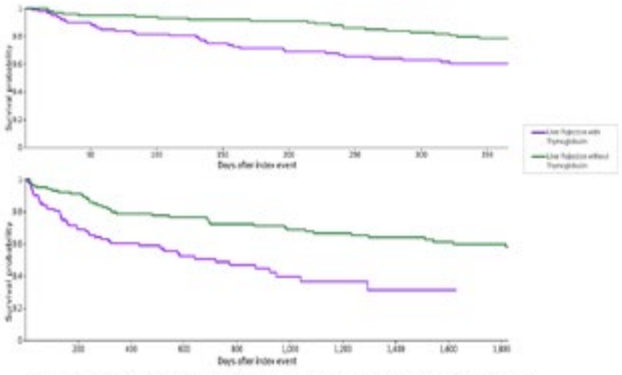

Figure-1. Kaplan-Meier Curve Showing Mortality Outcomes at 1 year (Top Graph) and 5 years (Bottom Graph) in Patients with Liver Rejection Treated with Thymoglobulin

Table 1. Outcomes of Patients with Liver Rejection Treated with Thymoglobulin

Outcomes	Liver Rejection with thymoglobulin			
	Hazard Ratio			
	1 year	P-Value	5 year	P-Value
Acute Kidney Injury	1.717(1.158-2.546)	0.006	1.654(1.144-2.391)	0.007
Sepsis	1.358(0.755-2.443)	0.306	1.142(0.684-1.908)	0.611
Infections	1.880(0.649-5.446)	0.237	1.513(0.603-3.795)	0.374
Coronary Artery Disease	0.953(0.426-2.132)	0.908	0.724(0.345-1.522)	0.393
Acute Coronary Syndrome	0.713(0.334-1.525)	0.381	0.578(0.282-1.187)	0.131
Heart Failure	1.858(0.868-3.978)	0.105	1.298(0.681-2.474)	0.427
Systemic Lupus Erythematosus	2.716(0.245-30.138)	0.397	1.589(0.219-11.551)	0.644
Gastronintestinal Bleeding	1.759(0.495- 6.254)	0.376	1.821(0.584-5.674)	0.295
Pulmonary Embolism	0.896(0.240-3.343)	0.87	1.379(0.434-4.384)	0.584
Hospitalizations	1.192(0.809-1.755)	0.384	1.142(0.780-1.671)	0.52
Mortality	2.242(1.307-3.848)	0.003	2.471(1.580-3.864)	0.0001

Disclosures: Jordan Carty: Nothing to Disclose, Yurilu Gonzalez Moret: Nothing to Disclose, Audry Chacin-Suarez: Nothing to Disclose, Kevin Lo: Nothing to Disclose, John Knorr: Nothing to Disclose, Manish Thapar: Alnylam Pharaceuticals: Consultant, Disc Medicine: Consultant, Recordarti Rare Diseases: Consultant

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2554 | A SYSTEMATIC REVIEW OF TREATMENT AND OUTCOMES FOR LATE CELLULAR REJECTION, CHRONIC DUCTOPENIC REJECTION, AND ANTIBODY MEDIATED REJECTION AFTER LIVER TRANSPLANTATION

Yianni Protopapadakis[1] *Mark Russo*[1]

[1]*Carolinas Medical Center*

Background: The treatment of acute cellular rejection has been better described than the treatment of late cellular rejection (LCR), chronic ductopenic rejection (CDR), antibody mediated rejection (AMR) and chronic antibody mediated rejection (CMR). Given the relative paucity of data on treatment approaches and efficacy of LCR, CDR, AMR and CMR, we conducted a systematic review to determine types of therapies and effectiveness for these 4 types of rejection. **Methods:** The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines were followed and a search of the PubMed, Embase, and Cochrane databases was conducted. Inclusion criteria included 1) adult patient population (>18 years), 2) diagnostic criteria for rejection, and 3) provided treatment regimen(s) and outcomes. Studies were excluded if the study type was case reports and if they did not provide diagnostic criteria for rejection diagnosis or report outcomes. Primary outcomes included efficacy of treatment and patient survival. **Results:** Our search yielded 1375 studies, of which 39 studies with a combined 2257 subjects were included in the analysis. Among these, 356 total episodes of rejection were described (TABLE). Six studies of LCR reported response rates from 33%-100% and the most common regimens included high dose steroids ± thymoglobulin followed by an increase in baseline immunosuppression (IS). Six studies of CDR reported response rates of 17%-100% and the most common regimens included increasing baseline IS, switching from cyclosporine to tacrolimus or adding an mTOR inhibitor. Twenty-five studies evaluated AMR with response rates from 0%-100% with the most common and effective regimens including high dose steroids, IVIG, plasmapheresis, and rituximab. Only two studies of CMR were identified meeting criteria with treatment success reported in 60%-75%. The studies were too heterogeneous to report pooled results. Patient survival data was only reported in 3, 5, 24, 2, studies for LCR, CDR, AMR, CMR, respectively. Patient survival ranged from was 72-100%, 17-92%, 0-100%, and 60-75% for LCR, CDR, AMR, CMR, respectively, with a median follow up of 1-182 months. **Conclusion:** Treatment regimens for late cellular rejection, chronic ductopenic rejection, and antibody mediated rejection are variable with a wide range of response rates. Data are sparse for CMR. Multicenter studies incorporating standardized diagnostic criteria and regimens for these types of rejection are needed to determine the most effective and safe therapies.

Rejection Type	# Studies	Total # Subjects	# Subjects With Rejection	Treatments	Response Rates
Late Cellular	6	246	81	Maintenance dose increase (Tacrolimus) Anti-thymocyte globulin Corticosteroids	33-100%
Chronic Ductopenic	6	720	143	Tacrolimus Sirolimus / Cyclosporine Mycophenolate Corticosteroids	17-100%
Acute Antibody Mediated	25	1234	123	Rituximab Corticosteroids Plasmapheresis + IVIG OKT3 Anti-thymocyte globulin [PGE1; candesartan]	0-100%
Chronic Antibody Mediated	2	57	9	Rituximab Plasmapheresis + IVIG Bortezomib	60-75%

Table 1: Composite data of included studies, stratified by rejection type.

Disclosures: Yianni Protopapadakis: Nothing to Disclose, Mark Russo: Nothing to Disclose

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2555 | DEFINING THE ROLE OF LIVING DONOR LIVER TRANSPLANT IN THE ERA OF MACHINE PERFUSION FOR DONATION AFTER CIRCULATORY DEATH

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Background: There has recently been renewed interest in expanding donation after circulatory death (DCD-LT) and living donor liver transplantation (LDLT) programs to expedite transplant at low Model for End-stage Liver Disease (MELD) scores. This study investigates center expansion (or lack thereof) in LDLT/DCD expansion and its effects on center-level metrics in the era of machine perfusion. **Methods:** This retrospective cohort study using United Network for Organ Sharing data included adult LT recipients between 2018-2023. The study period was divided into 3 eras: 2018-2019 (baseline), 2020-2021 (allocation policy change) and 2022-2023 (machine perfusion era). Demographics and clinical characteristics of recipients were compared using descriptive statistics. Center expansion/contraction of LDLT and DCD, defined as ≥ +/-10% change during the study period, was examined using a heatmap. **Results:** Of 127 active liver transplant centers in 2018-2023, 44 (35%) performed ≥10 LDLT and 72 (57%) performed ≥10 DCD-LT; 38 (49%) did both. These centers had lower overall median match MELD compared to centers doing neither (27 vs 30; p<0.001). Compared to DCD-LTs, LDLT recipients more often were female (49% vs 33%; p<0.001) and had autoimmune disease (26% vs 9%; p<0.001), lower median match MELD (15 vs 22; p<0.001), and longer median waitlist times (116 vs 84 days; p<0.001). Total center transplant volumes were directly proportional to LDLT (Spearman's ρ=0.30) and DCD volumes (ρ=0.61, p<0.001 for both), as well as % DCD performed (ρ=0.18, p=0.03), but not % LDLT performed (p=0.18). 24 centers expanded DCD-LT, but only 4 centers expanded LDLT (Figure 1). Of centers performing ≥10 LDLT and ≥10 DCD, 12 (32%) expanded DCD at the expense of LDLT. At all centers % LDLT and % DCD were inversely proportional (ρ=-0.28, p=0.001). Centers favoring DCD expansion instead of LDLT had no differences in median match MELD (p>0.05) before expansion, but longer waiting times (69 vs 48 days; p=0.02) and higher waitlist mortality (12 vs 7; p=0.007). These differences were no longer apparent after expansion (p>0.05 for both). **Conclusion:** In the era of machine perfusion, center expansion of DCD allograft use has led to improved transplant waitlist metrics and has often superseded LDLT expansion. Nevertheless, LDLT still offers a key pathway to transplant for certain populations, such as women and candidates with MELD <20, that DCD-LT may not consistently provide.

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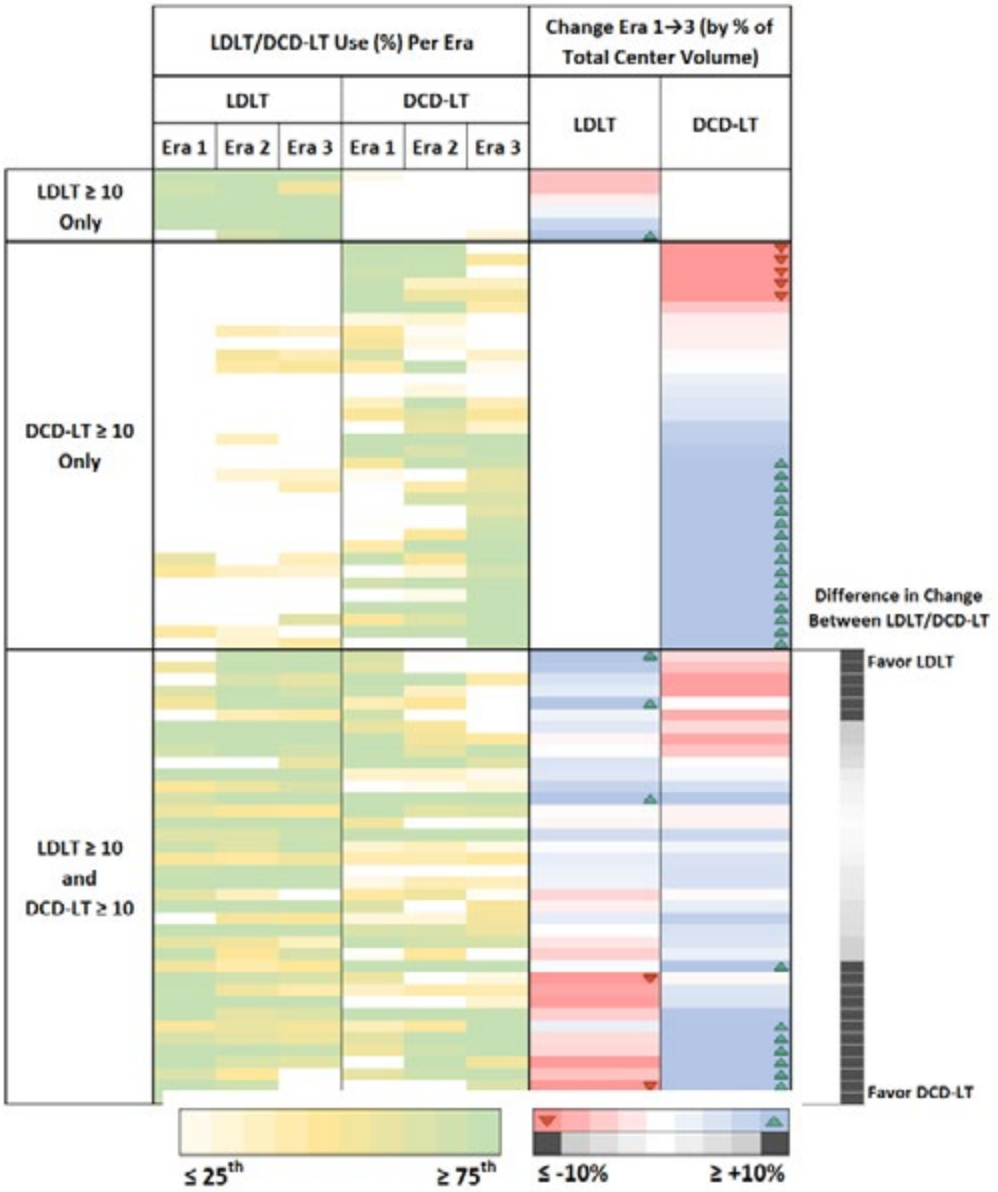

Figure 1: Heatmap of LDLT/DCD-LT % Use by Center from 2018-2023. Relative change in LDLT/DCD-LT use among centers, grouped in two-year eras (2018-2019, 2020-2021, 2022-2023) with yellow-green color scale reflecting 25th percentile, median, and 75th percentile of DCD/LDLT utilization within each era. Each row represents a unique transplant center; total, n=78 (LDLT ≥10, n=6; DCD-LT ≥10, n=34; both ≥10, n=38). % change between Era 1 and Era 3 in red-blue color scale, with positive/negative changes ≥10% denoted by green/red arrows, respectively. Range of change was -27% to +42% for DCD-LT and -13% to +20% for LDLT. For centers performing both types of transplants, an additional column with the difference in LDLT vs DCD-LT change is included to describe centers favoring one over the other, with differences ≥10% denoted by a darker shade of gray.

Disclosures: Daniel Lai: Nothing to Disclose, Therese Bittermann: Nothing to Disclose, Samir Abu-Gazala: Nothing to Disclose, Peter Abt: Nothing to Disclose

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2556 | RACIAL AND GENDER DISPARITIES IN ACCESS TO LIVING DONOR LIVER TRANSPLANTATION BETWEEN 1999-2021 ★

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[1]Weill Cornell Medicine, [2]Columbia University Medical Center

Background: Living donor liver transplants (LDLT) provide excellent outcomes at all MELD scores, but unfortunately, disparities in access still remain. By incorporating death data, we previously created novel metrics to compare listing and LT access among race/ethnicities. The purpose of this study was to evaluate disparities in access to LDLT using these ratios to compare LDLT with death and listing for LT in race/ethnicities and genders. **Methods:** This study utilized two databases. The UNOS STAR was queried for all patients listed for LT in the US from 1999-2021. The CDC WONDER database was queried for adults who died of cirrhosis or hepatocellular carcinoma. All patients aged 25-64 were included. The primary outcomes were the LDLT to listing ratio (LDLR), the rate of receiving an LDLT while on the list, and LDLT to death ratio (LDDR), the rate of receiving LDLT compared to dying of liver disease. Categorical outcomes and trends were analyzed using chi square and annual percentage change (APC), respectively, with breakpoints noted if present. **Results:** From 1999 to 2021, a total of 5087 patients received LDLT, of 80% were white patients, 4% Black, 3% Asian, and 44% female. From 1999-2021, annual LDLT increased from 124 to 361 ($p>0.05$). There were 2 breakpoints: APC +53% from 1999-2021, APC -11% from 2001-2009, and APC +8% from 2009-2021, all $p<0.001$. Female patients had different breakpoints – from 1999-2013, LDLTs decreased (APC -3.5%), but increased from 2013-2021 (APC 14%), all $p<0.001$, and surpassing men in 2021. No significant changes were observed in Black patients. Deaths increased annually from 15,868 to 34,727 (APC 3.3%, $p<0.001$). Women (APC 4.5%, $p<0.001$) had the highest increases in deaths. Listing for LT increased barely increased (APC 0.6%, $p<0.001$), but more gains were observed in Hispanic and Asian patients, $p<0.001$. There were no significant trends in LDLR overall or within race/ethnicities. Black patients had significantly lower LDLR when compared to all other race/ethnicities ($p<0.001$). The overall LDDR was 0.0095 and had similar breakpoints as LDLT rates with an APC +49% in 1999-2001, -13% in 2001-2009, and +4.6% in 2009-2021. Black patients had the lowest LDDR (0.0029, $p<0.001$) and no breakpoints were observed. Women had less of a decline in LDDR (APC 2.4 vs. -3.7%), $p<0.001$. **Conclusion:** Because of the decline in LDLT between 2001-2009, LDLT rates are only starting to return to earlier levels. Black patients remain no significant improvement in low LDLT rates. Women have made some progress with higher rates of LDLT but death rates counteract that gain. Overall, LDLT remains an underutilized tool to improve transplant access and save lives with unaddressed disparities.

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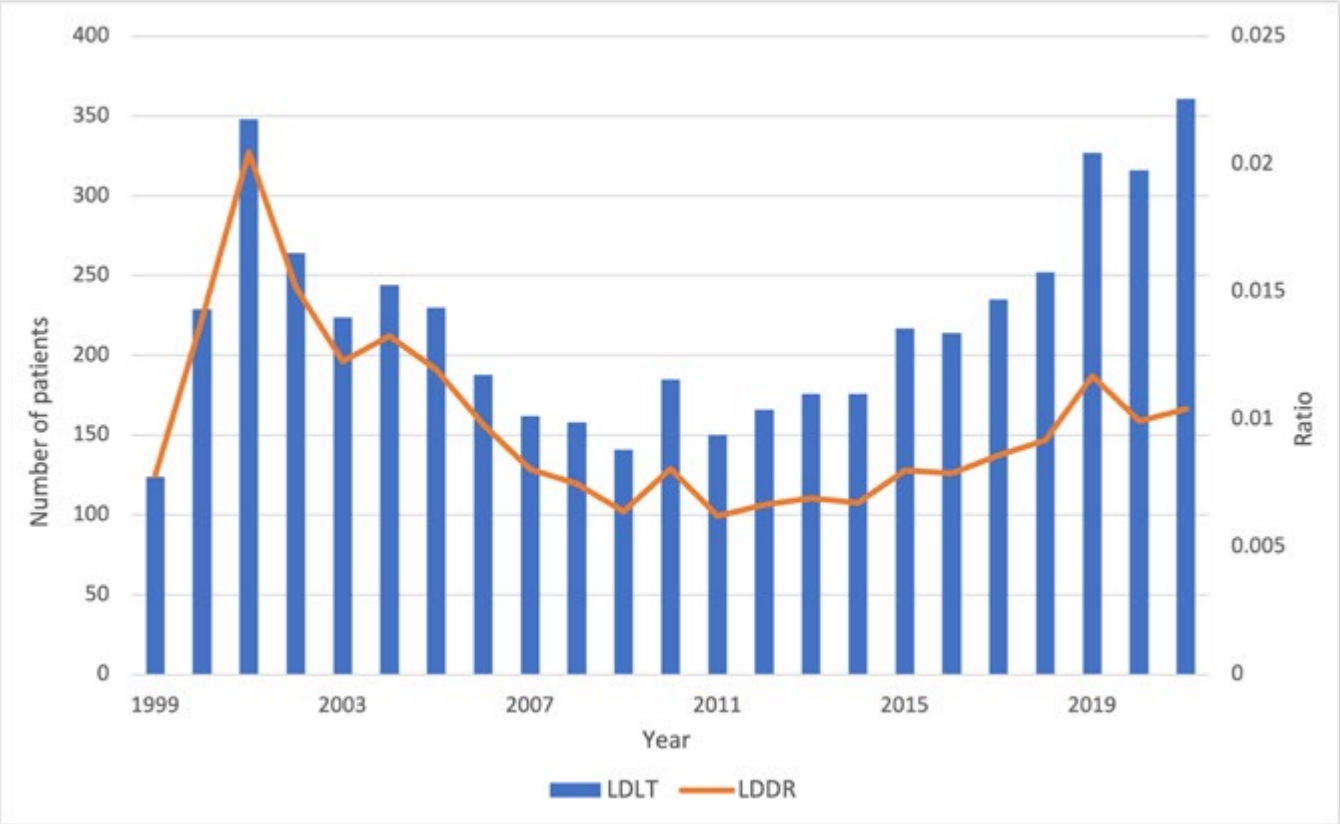

Disclosures: Nicole Ng: Nothing to Disclose, Alexander Zhao: Nothing to Disclose, Benjamin Samstein: Nothing to Disclose, Abhishek Mathur: Nothing to Disclose, Jason Hawksworth: Nothing to Disclose, Jennica Kim: Nothing to Disclose, Pamela Cobbs: Nothing to Disclose, Alyson Fox: Nothing to Disclose, Russell Rosenblatt: Nothing to Disclose

2557 | IMPACT OF POST-TRANSPLANT BODY MASS INDEX TRAJECTORY ON LIVER TRANSPLANT OUTCOMES

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Background: Prior studies have demonstrated increased risk of poor post-transplant outcomes at the extremes of pre-transplant body mass index (BMI). However, there are limited data investigating the impact of post-transplant BMI trajectory on liver transplant outcomes. To further characterize the effect of BMI on liver transplant outcomes, we examined the impact of post-transplant BMI trajectory on patient and graft survival in a large, diverse cohort of liver transplant recipients. **Methods:** We performed a retrospective cohort study of adult liver transplant recipients from 2002-2022 at the Hospital of the University of Pennsylvania who survived to at least one-year post-liver transplant. Detailed electronic medical record data were linked to center-specific transplant registry data. For each patient, BMI closest to one-year post-transplant within a 60-day window was determined. BMI difference was calculated relative to BMI at transplant and categorized as BMI neutral (+/- 3 units), BMI loss (<-3), and BMI gain (>3). Cox regression analyses adjusted for a priori selected variables (donor age and BMI; recipient age, sex, race, BMI at listing, diabetes, etiology of liver disease, MELD score at transplant, functional status, and time on waitlist) were performed to evaluate associations between BMI change at one-year post-transplant and patient and allograft survival. **Results:** There was a total of 924 patients with recorded BMI at one-year post-transplant with 141 patients (15.3%) having BMI gain and 254 patients (27.5%) having BMI loss. Patients who were BMI neutral were older and more often men (Figure A). BMI neutral patients had lower rates of pre-transplant hepatic encephalopathy (BMI neutral: 45.8%, BMI loss: 61.6%, BMI gain: 61.2%; p<0.001), pre-transplant ascites (BMI neutral: 65.4%, BMI loss: 74.8%, BMI gain: 74.8%; p=0.009), and lower MELD score at transplant (median (IQR) BMI neutral: 18 (12, 28), BMI loss: 24 (16, 32), BMI gain: 22 (14, 30); p<0.001). There

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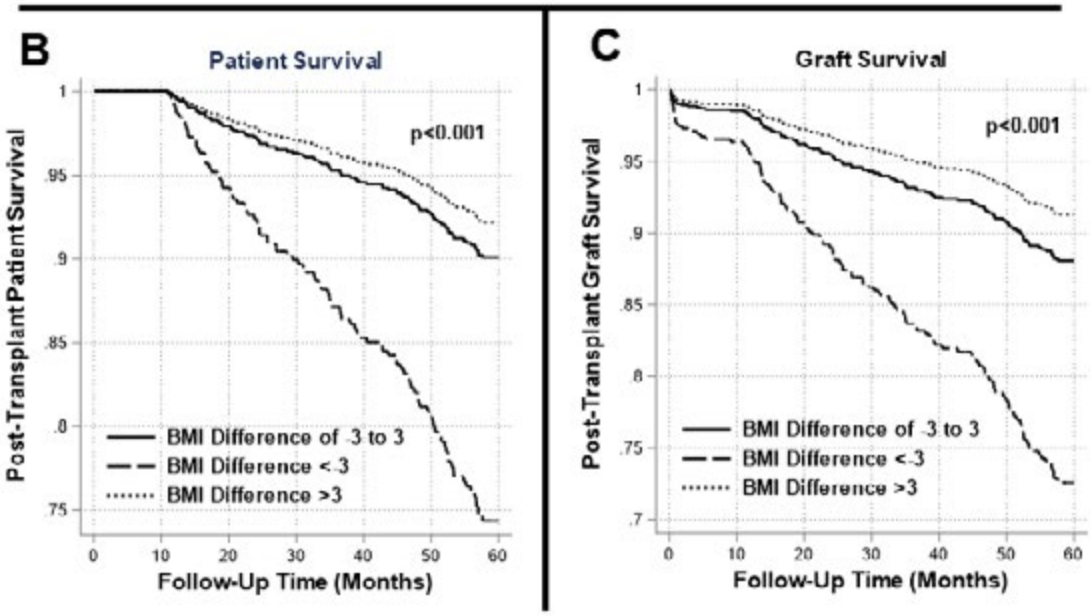
were no differences in donor characteristics between BMI groups. In adjusted Cox regression models, BMI loss at one-year post-transplant was associated with increased mortality (hazard ratio [HR]: 2.84, 95% CI: 1.74-4.64; p<0.001) (Figure B) and graft loss (HR: 2.52, 95% CI: 1.62-3.94; p<0.001) (Figure C) compared to BMI neutral patients. Patients with BMI gain did not have increased mortality (HR: 0.78, 95% CI: 0.41-1.49; p=0.45) or graft loss (HR: 0.72, 95% CI: 0.39-1.33; p=0.29) compared to BMI neutral patients. **Conclusion:** Post-transplant BMI loss was associated with worse patient and graft survival. While additional studies are needed to elucidate mechanisms that may underly this association, weight loss post-transplant should be closely monitored as it may be a risk indicator of poor outcomes.

A

Recipient Characteristics by BMI Trajectory at One-Year Post-Transplant				
Factor, n (%)	BMI Neutral (n=529)	BMI Loss (n=254)	BMI Gain (n=141)	p-value
Age, median (IQR)	59 (52, 64)	57 (51, 62)	56 (48, 62)	0.02
Male Sex	404 (76.4%)	157 (61.8%)	100 (70.9%)	<0.001
White Race	390 (73.7%)	190 (74.8%)	88 (62.4%)	0.004
History of Diabetes	134 (25.4%)	59 (23.2%)	45 (32.1%)	0.14
Hepatic Encephalopathy at Listing	241 (45.8%)	154 (61.6%)	85 (61.2%)	<0.001
Ascites at Listing	344 (65.4%)	187 (74.8%)	104 (74.8%)	0.009
Etiology of Liver Disease				0.01
HCV	210 (39.7%)	109 (42.9%)	43 (30.5%)	
Alcohol-Associated	124 (23.4%)	54 (21.3%)	54 (38.3%)	
HBV	17 (3.2%)	8 (3.1%)	0 (0.0%)	
MASLD	86 (16.3%)	42 (16.5%)	16 (11.3%)	
PSC/PBC/Autoimmune	48 (9.1%)	24 (9.4%)	15 (10.6%)	
Other	44 (8.3%)	17 (6.7%)	13 (9.2%)	
HCC Exception	145 (27.4%)	52 (20.5%)	21 (14.9%)	0.003
MELD Score at Transplant, median (IQR)	18 (12, 28)	24 (16, 32)	22 (14, 30)	<0.001
BMI at Transplant, median (IQR)	26.9 (24.1, 30.5)	31.9 (28.2, 36.3)	26.5 (23.6, 30.3)	<0.001
Serum Creatinine at Waitlisting, median (IQR)	1.0 (0.8, 1.3)	1.1 (0.8, 1.6)	1.1 (0.8, 1.5)	0.08
Serum Albumin at Waitlisting, median (IQR)	3.2 (2.7, 3.7)	3.0 (2.5, 3.6)	3.2 (2.7, 3.7)	0.003
No Functional Assistance Needed at Listing	230 (43.6%)	88 (35.2%)	42 (30.4%)	0.004
Time on Waitlist (Days), median (IQR)	141 (28, 325)	112 (13, 338)	94 (16, 353)	0.36



Disclosures: Roy Wang: Nothing to Disclose, Nadim Mahmud: Nothing to Disclose

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2558 | COMPARATIVE ANALYSIS OF LIVER BIOPSY COMPLICATIONS ACROSS THE UNITED STATES: A PROPENSITY MATCHED STUDY OF PATIENTS WITH NORMAL AND REDUCED PLATELET COUNTS USING INPATIENT DATA

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[1]St Mary Medical Center, PA, [2]Mercy Catholic Medical Center, PA, [3]University of Nevada- Las Vegas, [4]Carle Health, [5]Jamaica Hospital Medical Center, NY

Background: The evaluation of liver tissue in chronic liver disease typically involves biopsy, which is acknowledged as the gold standard. However, its invasive nature carries a risk of various complications. Major adverse events, such as death and significant bleeding, have been documented in the literature. Additionally, rare complications such as hemoperitoneum, hemobilia, hemothorax, pneumothorax, organ perforation, biliary issues, and sepsis have been reported. In this study, we aim to evaluate liver biopsy-related complications between two patient groups: those with normal platelet counts and those with thrombocytopenia using the United States Inpatient data. **Methods:** We conducted a retrospective analysis using the National Inpatient Sample (NIS) database. Our goal was to examine and compare complications related to liver biopsies in two patient groups: those with normal platelet counts and those with thrombocytopenia, spanning from 2016 to 2020. The primary outcome of our study was to analyze the in-hospital mortality rate, length of stay, and treatment cost. Other secondary outcomes were also studied. **Results:** 14385 patients with thrombocytopenia and 14385 without thrombocytopenia following liver biopsy were analyzed after propensity score matching. The development of thrombocytopenia following liver biopsy is associated with high all-cause mortality compared to the non-thrombocytopenia group (OR:1.847, 95% CI: 1.684 to 2.032, $p<0.0001$). Thrombocytopenia following liver biopsy is also associated with a higher length of stay and higher treatment cost compared to the non-thrombocytopenia group (12.5 days vs 8.3 days, $p<0.05$; $49625 vs $30404, $p<0.05$). The primary and secondary outcomes of the study are given in the figure. **Conclusion:** Our study highlights the significant association between thrombocytopenia following liver biopsy and adverse outcomes, including higher mortality rates, prolonged hospital stays, and increased treatment costs. These findings underscore the importance of careful consideration and risk assessment, particularly in patients with pre-existing thrombocytopenia, when contemplating liver biopsy as part of diagnostic or therapeutic interventions in liver disease. Alternative non-invasive diagnostic modalities or tailored approaches may warrant exploration to mitigate the risks associated with liver biopsy in this patient population. Further research and clinical strategies are needed to optimize patient outcomes and enhance the safety profile of liver biopsy procedures.

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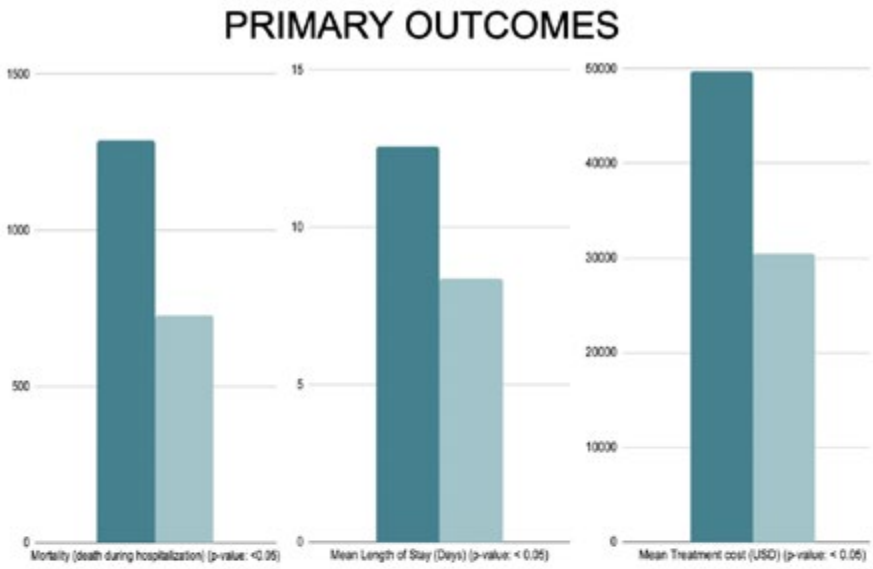

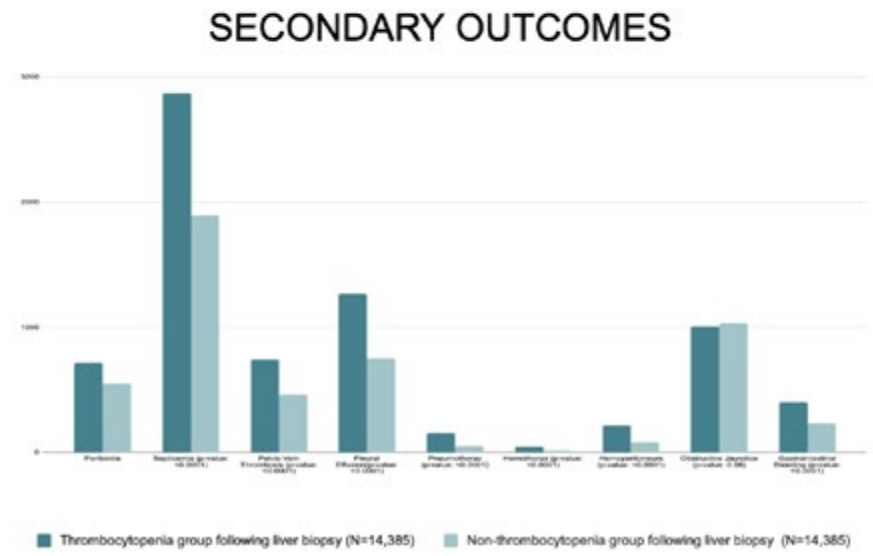

Disclosures: Raj Patel: Nothing to Disclose, Charmy Parikh: Nothing to Disclose, Sneh Sonaiya: Nothing to Disclose, Muhammad Raheel Awan: Nothing to Disclose, Pratiksha Moliya: Nothing to Disclose

2559 | HEPATOCELLULAR CARCINOMA RECURRENCE AFTER LIVER TRANSPLANT: AN AUSTRALIAN SINGLE-CENTRE STUDY

Matthew Garas[1] Luis Calzadilla Bertot[1] Briohny Smith[2] Luc Delriviere[2] Bryon Jaques[2] Lingjun Mou[2] Leon Adams[1] Gerry MacQuillan[2] George Garas[1] Gary Jeffrey[1] Michael Wallace[2]

[1]University of Western Australia, [2]Sir Charles Gairdner Hospital

Background: Hepatocellular carcinoma (HCC) is the 7th leading cause of cancer-related deaths in Australia and the 3rd worldwide. The 5-year survival is approximately 20%, however liver transplantation (LT) offers the most effective treatment. HCC recurrence is an important risk factor that decreases post-LT survival in patients transplanted for HCC, with a reported recurrence rate between 8-20%. Many variables have been established as well recognised predictors of HCC recurrence and are part of the selection criteria for LT. We aim to determine

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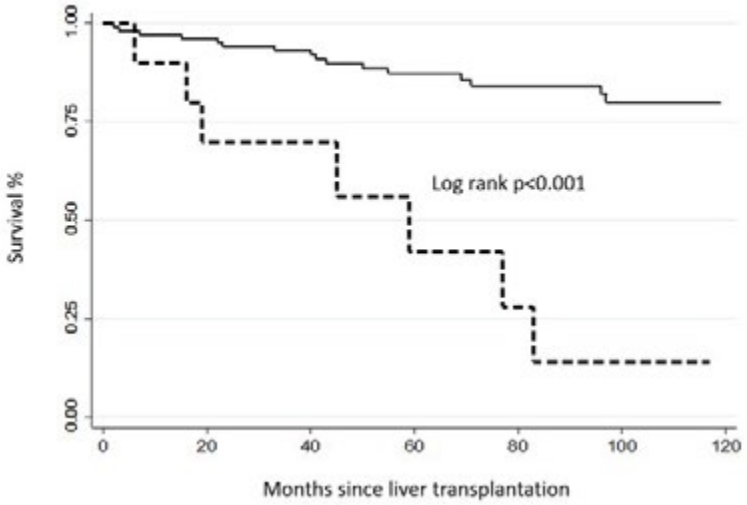
the rate and identify predictors of HCC recurrence in a contemporary Western Australian LT cohort. **Methods:** We performed a retrospective cohort study of all liver transplants in patients with HCC at Sir Charles Gairdner Hospital (SCGH), Western Australia (WA), between 2006 and 2021. Data was collected from various health record databases and included recipient demographics, serum biochemistry, radiology, operation notes, explant histopathology, treatment modalities, and details of recurrence. Overall survival of HCC patients post-LT, stratified for recurrence, was calculated by Kaplan Meier analysis. Univariate and multivariate Cox regression was used to determine predictors of HCC recurrence post-LT. **Results:** Of 119 subjects, recurrent HCC was documented in 10 (8.4%) patients. When comparing baseline characteristics to those without recurrence, a greater proportion of subjects with recurrence were female (P=0.05), had underlying HBV (P=0.001), had higher AFP levels (P=0.01), and had common characteristics on explant histopathology, including >3 viable nodules (P=0.001), vascular invasion (P=0.003) and poorly differentiated disease (P=0.03). Unadjusted survival curves showed lower 1-, 3-, 5- and 10-year survival rates in subjects with HCC recurrence compared to those without HCC recurrence (90% vs. 92%, 70% vs. 88%, 42% vs. 80%, 14% vs. 76%, respectively; log rank p<0.001) (Figure). The median time to recurrence was 2.9 years. Late recurrence (>2 years) was more common than early recurrence (60% vs. 40%) with the majority of recurrences (90%) being extrahepatic in location. **Conclusion:** The HCC recurrence rate is low at 8.4% in a contemporary Australian cohort however it significantly impacts upon post-transplant survival. An Australia-wide multicentre study is required to confirm these predictors of recurrence and to help improve recipient outcomes.

Figure: Survival of hepatocellular carcinoma patients stratified according to hepatocellular carcinoma recurrence.



Year	Without recurrence	With recurrence
1	92	90
3	88	70
5	80	42
10	76	14

Numbers represent percentages.

Disclosures: Matthew Garas: Nothing to Disclose, Luis Calzadilla Bertot: Nothing to Disclose, Briohny Smith: Nothing to Disclose, Luc Delriviere: Nothing to Disclose, Bryon Jaques: Nothing to Disclose, Lingjun Mou: Nothing to Disclose, Leon Adams: Novo Nordisk: Advisor, SCL Behring: Advisor, Pfizer: Advisor, Gerry MacQuillan: Nothing to Disclose, George Garas: Nothing to Disclose, Gary Jeffrey: Nothing to Disclose, Michael Wallace: Nothing to Disclose

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2560 | MRI-SERUM BASED SCORE ACCURATELY IDENTIFIES LIVER TRANSPLANT PATIENTS WITHOUT REJECTION AVOIDING NEED FOR LIVER BIOPSY: A MULTISITE EUROPEAN STUDY

Jelte Schaapman[1] Elizabeth Shumbayawonda[2] Miguel Castelo-Branco[3] Filipe Caseiro Alves[3] Tania Costa[3] Emer Fitzpatrick[4] Katie Tupper[4] Anil Dhawan[4] Maesha Deheragoda[5] Eva Sticova[4] Marika French[2] Cayden Beyer[6] Soubera Rymell[2] Dimitar Tonev[7] Hein Verspaget[1] Stefan Neubauer[8] Rajarshi Banerjee[2] Hildo Lamb[1] Minneke Coenraad[1]

[1]Leiden University Medical Center, [2]Perspectum Ltd., [3]Universidade de Coimbra, [4]King's College London, [5]King's College Hospital, [6]Perspectum Ltd, [7]HCV Research UK, [8]Oxford NIHR Biomedical Research Centre

Background: Liver function and histological assessment for fibrosis, inflammation and T-cell mediated rejection are essential elements of post-liver transplant monitoring. However, liver biopsy carries a risk of complications which are preferably avoided in low-risk patients. Multiparametric MRI (mpMRI) is a reliable non-invasive diagnostic method which quantifies liver disease activity (including fibroinflammation (cT1), liver fat content (PDFF) and liver iron) and has shown prognostic utility in chronic liver disease management. Our aim was to determine whether using mpMRI in combination with standard serum biochemistry (serum) tests could noninvasively identify low-risk post-liver transplant patients who are eligible to avoid invasive liver biopsies. **Methods:** RADIcAL2, a multicentre prospective study, included 131 adult and paediatric (children and adolescent) patients with previous liver transplant from the Netherlands, Portugal and UK. Biopsies were centrally read by two expert pathologists. T-cell mediated rejection (rejection) was assessed using BANFF global assessment (BANFF-GA). Diagnostic accuracy to discriminate no rejection vs. indeterminate or T-cell mediated liver transplant rejection was performed using area under the receiver operating characteristic curve (AUC). **Results:** In the RADIcAL2 cohort, 38% of patients had no rejection, while 62% had either indeterminate (21%) or T-cell mediated rejection (41%). There was a wide range of inter-observer variability (0 ≤ Cohen's Kappa < 0.85) across all histology scores with moderate agreement between pathologists (Kappa <0.58) for BANFF-GA. A combination of mpMRI cT1 and liver fat with standard serum tests had AUC 0.7 (NPV: 0.8) to identify those without rejection (either indeterminate or T-cell mediated rejection). In the 18% of RADIcAL2 participants where therapy changed, cT1 (841ms vs. 789ms; p=0.006), and GGT (284 vs. 125; p=0.013) were significantly higher compared to those who did not get a change in therapy. **Conclusion:** A combination of mpMRI cT1 and liver fat with standard serum tests accurately identified patients without indeterminate or T-cell mediated rejection who could avoid liver biopsy. mpMRI used alongside serum markers has utility to support noninvasive patient management in both adult and paediatric post-transplant populations.

Disclosures: Jelte Schaapman: Nothing to Disclose, Elizabeth Shumbayawonda: Perspectum Ltd.: Employee, Miguel Castelo-Branco: Nothing to Disclose, Filipe Caseiro Alves: Nothing to Disclose, Tania Costa: Nothing to Disclose, Emer Fitzpatrick: Nothing to Disclose, Katie Tupper: Nothing to Disclose, Anil Dhawan: Bit Bio: Consultant, Aspect Bio: Consultant, Astellas: Consultant, Univar: Advisor, Orphalan: Advisor, Maesha Deheragoda: Nothing to Disclose, Eva Sticova: Nothing to Disclose, Marika French: Perspectum: Employee, Cayden Beyer: Nothing to Disclose, Soubera Rymell: Perspectum: Employee and stock holder of private company, Dimitar Tonev: Nothing to Disclose, Hein Verspaget: Nothing to Disclose, Stefan Neubauer: Perspectum: Stock – privately held company, Caristo Diagnostics: Stock – privately held company, Caristo Diagnostics: Consultant, Rajarshi Banerjee: Perspectum: Employee, Perspectum: Executive role, Hildo Lamb: Nothing to Disclose, Minneke Coenraad: Nothing to Disclose

2561 | ACUPUNCTURE IN THE PRE AND POST LIVER TRANSPLANTATION SETTING IS SAFE, WELL ACCEPTED AND IMPROVES QUALITY OF LIFE

Giada Pietrosi[1] Salvatore Gruttadauria[1] Massimo Pinzani[1] Antonio Arcadipane[1] Loredana Testa[2] Angelo Luca[1]

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Background: Acupuncture is an established form of complementary medicine characterized by the insertion of needles in the skin at specific points along lines of energy (meridians), used in the treatment of various physical and mental conditions. Although recognized and recommended by World Health Organization (WHO), acupuncture treatment is not routinely prescribed in industrialized western countries. IRCCS-ISMETT, a

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multi organ transplant center in Palermo (Italy), has recently introduced the use of acupuncture, in patients with advanced chronic liver diseases for the treatment of acute or chronic symptoms and to avoid new drug prescription and related toxicity. **Methods:** Patients with chronic liver diseases and liver transplanted patients, with new onset symptoms or symptoms unresponsive to standard therapy, were evaluated for acupuncture treatment after signing the informed consent. Eligible patients were treated following classical and traditional Chinese medicine prescriptions and were periodically monitored through physical examination and routinary blood sample to evaluate treatment's safety and efficacy. Sterile needles and vaccaria seeds were used in each patient. Elettro-acupuncture was used when indicated. **Results:** From January 2023 to May 2024, 10 patients (2 with liver cirrhosis, 1 with polycystic liver disease, and 7 with LT), M: F=6:4, mean age 55.5 (33-81 years) underwent treatment with acupuncture and auricular reflexology to treat agitation, insomnia, fatigue, paresthesia, itching, post-herpetic neuralgia and menopausal syndrome. The treatments performed ranged between 1 and 20 (mean 8.1) sessions. Six patients fully recovered from their symptoms, three had an important improvement and 1 patient did not complete the treatment because of needle's fear. In all patients the prescription of new drugs became unnecessary and in 1 patient with post herpetic neuralgia pain-killers were withdrawn and pregabalin reduced. The beneficial effects of acupuncture persisted at six-months follow-up. No side effects were recorded during treatments and an elevated patient's satisfaction was recorded. **Conclusion:** In this small case series acupuncture proved to be a safe and well accepted treatment before and after LT. It could be considered an alternative therapy in specific clinical conditions to avoid new drug prescriptions and the related toxicity. These preliminary positive results will pave the way to perform larger prospective studies.

Disclosures: Giada Pietrosi: Nothing to Disclose, Salvatore Gruttadauria: Nothing to Disclose, Massimo Pinzani: Nothing to Disclose, Antonio Arcadipane: Nothing to Disclose, Loredana Testa: Nothing to Disclose, Angelo Luca: Nothing to Disclose

2562 | RESEARCH TRENDS IN LIVER TRANSPLANTATION FOR HEPATOCELLULAR CARCINOMA AND RELATED TUMORS: A COMPREHENSIVE BIBLIOMETRIC REVIEW (2000-2022)

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Background: Liver transplantation (LT) is a critical treatment for hepatocellular carcinoma (HCC), a leading cause of cancer-related mortality globally. Despite its importance, there is a lack of comprehensive data on research trends in this field. This bibliometric analysis aims to explore the trends, key contributors, and research focuses in LT for HCC from 2000 to 2022, providing insights into the evolution and current state of research on this topic. **Methods:** Data were retrieved from the Web of Science database using specific search terms related to LT and HCC. A total of 2,855 search results were analyzed, including 1,924 articles and 431 reviews. Key metrics included annual publication trends, citation counts, and contributions by countries, institutions, authors, and journals. Visualization tools such as VOSviewer and MS Excel were used for data analysis and presentation. **Results:** There was a significant upward trend in LT-related publications for HCC, particularly from 2015 onwards, with a peak in 2022. The United States led in research output, followed by Italy and China. Prominent institutions included the University of California, San Francisco, and the Mayo Clinic. Key journals were "Liver Transplantation," "Transplantation Proceedings," and the "American Journal of Transplantation." The most recurring keywords were "Hepatocellular Carcinoma," "Survival," and "Recurrence." **Conclusion:** This bibliometric analysis highlights a significant upward trend in liver transplantation (LT) research for hepatocellular carcinoma (HCC) from 2000 to 2022, driven by advancements in technology and increasing incidence of risk factors such as hepatitis B and C, metabolic-associated fatty liver disease (MAFLD), and non-alcoholic steatohepatitis (NASH). The collaborative efforts of leading institutions and countries, particularly the United States, Italy, and China, have been pivotal. Future research is expected to focus on personalized medicine and innovative immunosuppressive therapies, aiming to further improve patient outcomes and survival rates.

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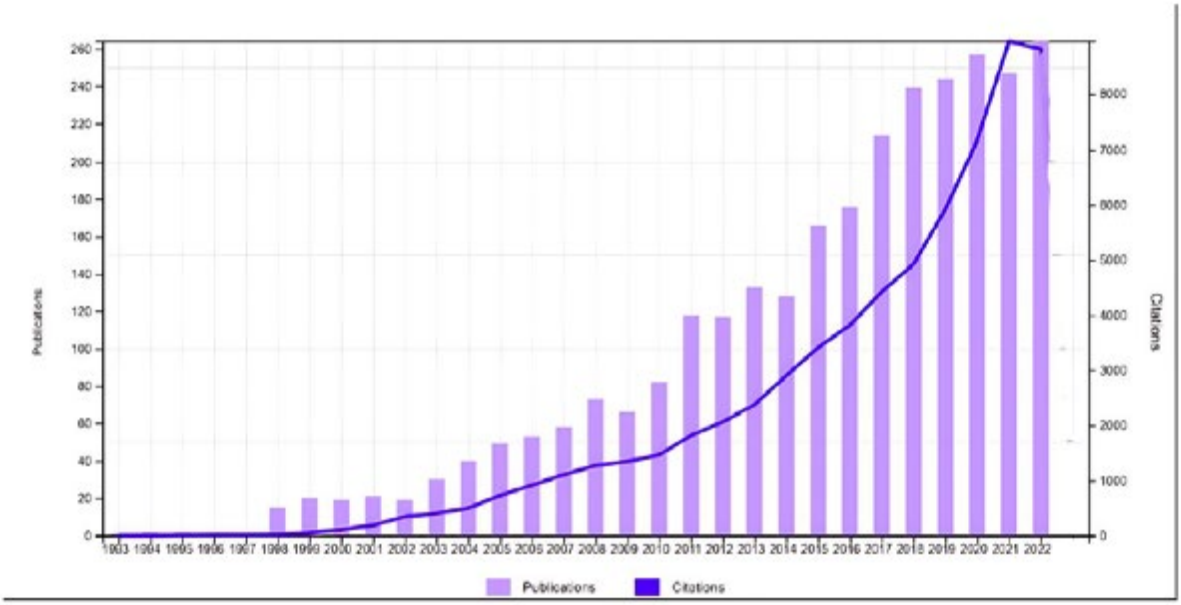
Top Contributors in Liver Transplantation Research for Hepatocellular Carcinoma (2000-2022)

Category	Top 1	Top 2	Top 3	Top 4	Top 5
Countries	United States (1386 documents)	Italy (270 documents)	China (220 documents)	Spain (187 documents)	England (147 documents)
Institutions	University of California, San Francisco (131 articles)	Mayo Clinic (94 articles)	University of California, Los Angeles (74 articles)	Stanford University (67 articles)	University of Pittsburgh (67 articles)
Authors	Mehta, Neil (48 documents)	Dodge, Jennifer L. (41 documents)	Yao, Francis Y. (41 documents)	Cillo, Umberto (40 documents)	Roberts, John P. (32 documents)
Journals	Liver Transplantation (175 articles)	Transplantation Proceedings (155 articles)	American Journal of Transplantation (149 articles)	Hepatology (142 articles)	Transplantation (133 articles)
Keywords	Hepatocellular Carcinoma (1251 occurrences)	Survival (464 occurrences)	Cirrhosis (400 occurrences)	Recurrence (307 occurrences)	Cancer (232 occurrences)



Annual Trends in Liver Transplantation Research publications and citations for Hepatocellular Carcinoma (1993-2022)

Disclosures: Mohammad AbuAssi: Nothing to Disclose, Ibrahim Shanti: Nothing to Disclose, Mohammad Alsarayreh: Nothing to Disclose, Carson Creamer: Nothing to Disclose, Tony Brar: Nothing to Disclose, Yaseen Perbtani: Nothing to Disclose

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2563 | TENOFOVIR ALAFENAMIDE MONOTHERAPY IS EFFECTIVE IN SUPPRESSING HEPATITIS B VIRUS AFTER LIVER TRANSPLANTATION

Ying-hong Shi[1] Wei-ren Liu[2] Zhen-bin Ding[2] Xiao-wu Huang[2] Jia Fan[2] Jian Zhou[2]

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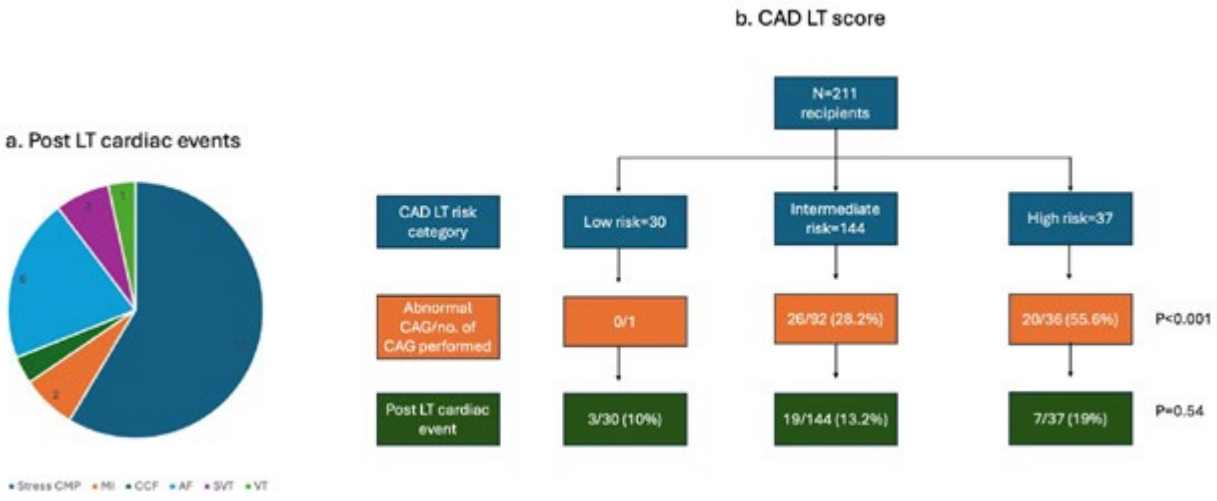
Background: The prodrug tenofovir alafenamide (TAF) was approved for HBV patients in 2017. Although TAF is established as a treatment for HBV patients, the availability of data regarding the efficacy and safety of administering TAF to liver transplant recipients is still limited. We report the efficacy of TAF monotherapy without HBIG as prophylaxis in patients who underwent a liver transplant for hepatitis B-related complications. **Methods:** This study prospectively analyzed data from patients who were treated with TAF as prophylaxis against HBV recurrence. All were positive for HBsAg for at least 6 months at the time of transplant. All patients received TAF as primary prophylaxis for the prevention of HBV recurrence. The standard dose of 25 mg daily was used. None of the patients received HBIG at the time of transplant. Patients were followed up routinely after transplantation at 3-month intervals once clinically stable. Viral and serological markers were determined including HBsAg, HBsAb, HBeAg, HBeAb,HBcAb and HBV DNA. The HBV DNA level was measured using the COBAS TaqMan assay with a lower limit of detection of 50 IU/mL. The primary endpoint of the interim analysis was HBV DNA undetectable rate at 24 weeks post liver transplant. The analysis was conducted in accordance with the Helsinki Declaration of 1975 and was approved by the ethics committee of the Zhongshan Hospital, Fudan University. **Results:** Between October 2022 and January 2024, 66 patients were enrolled in the study and treated with TAF. Before transplant, 4.5 %(3/66) were not on antiviral therapy. At the time of transplant, the median HBV DNA level was <50 IU/mL (range, <50-738), with 83.3%(55/66) patients having undetectable levels of HBV DNA. The virology status and liver biochemistry at the time of liver transplant are shown in Table 1. Up to date, 2 patients had died of HCC recurrence and pneumonia respectively, 3 patients had discontinued therapy because of unscheduled injection of hepatitis B immunoglobulin, 11 patients did not reach the 24-week follow-up, and the remaining 55 patients still taking TAF were involved in this 24 weeks interim analysis. The indications for 55 transplant recipients included HBV-HCC (n= 35, 63.6%), decompensation cirrhosis (n= 16,29.1%), cirrhosis (n= 3,5.5%),and acute-on-chronic hepatitis B (n= 1, 1.8%). At the time of the 24 weeks treatment of TAF, 92.7% patients (51/55) tested seronegative for HBsAg; 100% patients (55/55) having undetectable levels of HBV DNA. No patients had reactivation of HBV. No side effects attributable to TAF were noted during the 24 weeks follow-up period. **Conclusion:** 92.7% of patients underwent loss of HBsAg after 24 weeks of follow-up, with 100% achieving undetectable HBV DNA levels with TAF as the sole antiviral agent after liver transplant. An HBIG-free regimen using TAF monotherapy is effective after liver transplant for patients with hepatitis B.



Disclosures: Ying-hong Shi: Nothing to Disclose, Wei-ren Liu: Nothing to Disclose, Zhen-bin Ding: Nothing to Disclose, Xiao-wu Huang: Nothing to Disclose, Jia Fan: Nothing to Disclose, Jian Zhou: Nothing to Disclose

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2564 | CORONARY ARTERY DISEASE LIVER TRANSPLANTATION (CAD-LT) SCORE CAN ACCURATELY IDENTIFY PATIENTS REQUIRING INVASIVE CORONARY ANGIOGRAPHY

Nandhakumar Rajadurai[1] Abdul Haqq[2] Harika Chigatapu[2] Anuj Kapadia[2] Mithun Sharma[3] Rajesh Gupta[2] Padaki Nagaraja Rao[2] Nageshwar Reddy[2] Anand Kulkarni[2]

[1]Asian Institute of Gastroenterology, Hyderabad, [2]Asian Institute of Gastroenterology, [3]ASIAN INSTITUTE OF GASTROENTROLOGY PVT LTD

Background: Coronary Artery Disease Liver Transplantation (CAD-LT) score is a useful criterion for assessing the need for coronary angiography (CAG), but no studies have validated this in the Indian population. Cirrhotic cardiomyopathy (CCM) is common in advanced cirrhosis, and recently, the diagnostic criteria have been modified. We aimed to assess the prevalence of CCM and validate CAD LT score in patients undergoing living donor liver transplantation (LDLT). **Methods:** This retrospective study included patients undergoing LDLT and had complete data regarding the cardiac evaluation from June 2021 to December 2023. The primary objective was to describe the cardiac findings in these patients, the proportion of patients developing cardiac complications post-transplant, compare mortality with the presence or absence of CCM, and lastly, assess the accuracy of CAD-LT score. **Results:** 211 adult candidates (median age-48 years; women-7.6%; alcohol-43.6%; MELD Na-24;) were included after excluding 23 pediatric patients. Diabetes, hypertension and history of coronary artery disease were concomitantly reported in 37%, 21% and 3.3% of patients. Sixteen percent had a history of smoking. Echocardiography identified moderate mitral regurgitation in 2.8%, moderate-severe tricuspid regurgitation in 2.3%, and severe aortic regurgitation in 1% of patients. Pulmonary artery pressure was 25-34 mmHg in 5.2% and 35-44 mmHg in 0.9% of patients. Of the 146 patients who underwent CT coronary angiography, 16.4% had mild,14.4% had moderate, and 9% had extensive evidence of CAD based on calcium scoring. Of the 129 patients who underwent percutaneous coronary angiography (CAG) for various indications, 35.6% had abnormal findings, and one patient underwent PTCA. Only one patient developed angio site hematoma. Approximately 14% (29/211) had some form of cardiac event post-surgery. (Fig. a). Of the 43 patients who died within 1 year, 42% had cardiac event, while only 6.5% of those who were alive had cardiac event (P<0.001). Among 54 patients with CCM diagnosed based on current diagnostic criteria, 29.6% died compared to 17.2% in those without CCM (P=0.05). The median CAD-LT score was 6 (-2 to 21). Most patients were intermediate-risk (68.3%), followed by high-risk (17.5%) and low-risk (14.2%). The accuracy, sensitivity, specificity, positive predictive value, and negative predictive value of CAD-LT score to identify individuals requiring CAG was 74.4%, 69.6%, 75.7%, 44.5% and 90%, respectively. (Fig. b) **Conclusion:** CAD-LT score can accurately identify patients requiring CAG. Cirrhotic cardiomyopathy is common in pre-transplant candidates and is a risk factor for post-transplant mortality.

Disclosures: Nandhakumar Rajadurai: Nothing to Disclose, Abdul Haqq: Nothing to Disclose, Harika Chigatapu: Nothing to Disclose, Anuj Kapadia: Nothing to Disclose, Mithun Sharma: Nothing to Disclose, Rajesh Gupta: Nothing to Disclose, Padaki Nagaraja Rao: Nothing to Disclose, Nageshwar Reddy: Nothing to Disclose, Anand Kulkarni: Nothing to Disclose

2565 | YAP IN MACROPHAGES REDUCES STERILE INFLAMMATION AND HEPATIC INJURY DURING THE LIVER ISCHEMIA-REPERFUSION STRESS

Beng Yang[1]

[1]Zhejiang University

Background: Liver ischemia-reperfusion injury (IRI) is a local inflammatory response driven by innate immunity, which manifests in various clinical scenarios such as liver resection, transplantation, trauma, and shock. Our previous research has shown that the activation of YAP (Yes-associated protein) in the liver reduces hepatic damage during IRI. Nevertheless, the role of YAP in regulating the inflammatory response specifically in macrophages during hepatic ischemia-reperfusion remains unknown. **Methods:** Molecular and functional studies were performed to assess the involvement of myeloid YAP in autophagy induction and hepatic inflammation. Myeloid-specific YAP knockout or YAP/TAZ knockout mice were generated and subjected to liver warm ischemia-reperfusion injury. Western blot analysis was employed to determine the expression of YAP and TAZ in primary hepatocytes and macrophages. Hepatic architecture integrity and hepatocyte damage were evaluated using HE staining, TUNEL assay, and serum alanine aminotransferase (sALT) detection. QPCR assay was conducted to

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measure the expression of inflammation-related genes in LIRI-insulted liver. **Results:** Following liver ischemia-reperfusion injury, the expression of YAP and TAZ significantly increased. Myeloid YAP and TAZ deficient mice exhibited increased hepatocellular damage, as evidenced by elevated sALT levels and poor-preserved hepatic architecture. Myeloid YAP deficiency resulted in enhanced hepatic inflammation during LIRI, characterized by reduced neutrophil and macrophage infiltration in the liver of Myeloid YAP/TAZ knockout mice. Furthermore, compared to the negative control group, the expression of inflammatory cytokines (including TNF-α and IL-6) was elevated in the liver of Myeloid YAP/TAZ knockout mice. **Conclusion:** These findings highlight the crucial role of myeloid-specific YAP and TAZ in regulating inflammatory responses during hepatic ischemia-reperfusion injury. YAP and TAZ in macrophages represent potential therapeutic targets for minimizing organ injury in ischemia-reperfusion-stressed organs.

Disclosures: Beng Yang: Nothing to Disclose

2566 | SOCIAL DETERMINANTS OF HEALTH MEASURED BY SDI AND ADI DO NOT IMPACT LIVER TRANSPLANT OUTCOMES

Hiba Khan[1] Kevin Houston[1] Niki Wadhwa[1] Hasan Alroobi[1] Nikita Chadha[1] Chad Spencer[1] Amon Asgharpour[1] Sheila Bullock[1] Stephan Weinland[1] Nicole Keller[1] Ekaterina Smirnova[1] Scott Matherly[2] Joel Wedd[1] Hannah Lee[2] Mohammad Siddiqui[1] Vaishali Patel[1] Sayed Obaidullah Aseem[1] Albert Arias[2] Vinay Kumaran[1] Seung Lee[1] Amit Sharma[1] Aamir Khan[1] Daisuke Imai[1] Marlon Levy[1] David Bruno[1]

[1]Virginia Commonwealth University Health, [2]Virginia Commonwealth University

Background: Liver transplant (LT) is the established cure for end stage liver disease. The impact of social determinants of health (SDOH) on LT outcomes are poorly defined. The social deprivation index (SDI) and area deprivation index (ADI) can be utilized to assess SDOH with higher scores indicating worse SDOH. Both of these indices are crucial in charting neighborhood poverty and establishing post-LT outcomes. The aim of our study is to chart the impact of SDI and ADI in LT recipients on pre-LT demographics, psychiatric testing, MELD, and 1-year survival. **Methods:** A retrospective analysis of LT patients (pts) from 10/2018 to 12/2022 was performed. Demographic, clinical, and laboratory data were collected. Pre-LT psychiatric testing included the Stanford Integrated Psychosocial Assessment for Transplant (SIPAT), General Anxiety Disorder-7 (GAD-7), and Patient Health Questionnaire-9 (PHQ-9). SDI was collected off generalized United States Postal Service zip codes called Zip Code Tabulation Area (ZCTA) using the Robert Graham Center's SDI data (range 1-100). ADI was generated by inputting LT recipients' addresses into the Neighborhood Atlas at the University of Wisconsin's Center for Health Disparities Research map (range 1-10). Those with poor SDOH (SDI ≥ 50 and ADI ≥ 5) were compared across liver disease etiology (MASH, alcohol-related liver disease [ALD] with < 6 month (m) sobriety with or without acute alcoholic hepatitis [AH] and ALD > 6 m sobriety). **Results:** Our study group consisted of 492 pts; mean (SD) age 53 (12.6), 59% male, 78% White, 15% Black, 93% non-Hispanic, 24% MASH, 28% ALD with < 6m sobriety (9% with AH), 25% ALD > 6m sobriety, and 23% other. The mean (SD) SDI was 42 (25) with 37% with SDI ≥ 50 and mean (SD) ADI was 5.6 (2.3) with 50% ADI ≥ 5. The correlation between SDI and ADI was significant ($r = 0.446$, $p < .001$) with 71% of people ADI ≥5 also had SDI ≥50 and 62% of people ADI < 5 also had SDI < 50. Those with SDI ≥ 50 or ADI ≥ 5 were younger and Black. Those with SDI ≥ 50 were also less likely employed with higher GAD-7. Those with ADI ≥ 5 were more likely female (Table). We did not observe any differences in MELD, underlying liver disease, history of incarceration, anxiety, depression, PSQ-9, SIPAT, and 1-year survival. **Conclusion:** While both high SDI and ADI, indices of poor SDOH were prevalent in our cohort of LT recipients, they were not associated with disease etiology, MELD or 1-year post-LT survival.

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Table: Comparison of subjects by SDI and ADI. ns = not significant

	SDI < 50	SDI ≥ 50	p	ADI < 5	ADI ≥ 5	p
N	307	183		241	248	
Age (yrs)	54 ± 12	51 ± 12	.008	54 ± 12	51 ± 12	.017
Sex (% Male)	58	60	ns	65	53	.009
Race (% White/Black)	83/11	68/23	.0009	81/10	75/20	.0051
MELD	24 ± 11	24 ± 12	ns	24 ± 12	24 ± 11	ns
Alcohol Use Disorder (%)	65	35	ns	53	47	ns
Alcohol Liver Disease (%)	45	50	ns	51	49	ns
Alcoholic Hepatitis (%)	65	34	ns	57	42	ns
MASH (%)	65	36	ns	44	55	ns
History of incarceration	56	44	ns	50	50	ns
Employed (%)	59	41	.03	49	50	ns
Psych history of anxiety	67	33	ns	51	48	ns
Psych history of depression (%)	60	40	ns	52	48	ns
GAD-7	5.7 ± 5	7.2 ± 6	.03	5.9 ± 5.2	6.5 ± 5.7	ns
PSQ-9	8.1 ± 5.6	8.3 ± 6.2	ns	8.3 ± 5.5	8.0 ± 6.1	ns
SIPAT	19 ± 10	18 ± 10	ns	19 ± 10	19 ± 10	ns
ADI/SDI	4.9 ± 2.1	6.7 ± 2.2	<.0001	32 ± 23	52 ± 24	<.0001
Days listed for LT	102 ± 229	115 ± 251	ns	108 ± 226	107 ± 249	ns

Disclosures: Hiba Khan: Nothing to Disclose, Kevin Houston: Nothing to Disclose, Niki Wadhwa: Nothing to Disclose, Hasan Alroobi: Nothing to Disclose, Nikita Chadha: Nothing to Disclose, Chad Spencer: Nothing to Disclose, Amon Asgharpour: Madrigal: Advisor, Galectin: Clinical Endpoint Committee, Sheila Bullock: Nothing to Disclose, Stephan Weinland: Nothing to Disclose, Nicole Keller: Nothing to Disclose, Ekaterina Smirnova: Nothing to Disclose, Scott Matherly: Nothing to Disclose, Joel Wedd: Nothing to Disclose, Hannah Lee: Nothing to Disclose, Mohammad Siddiqui: Grant/Research Support relationship with NovoNordisk; Has not ended; Advisor relationship with 89Bio; Has not ended; Advisor relationship with AMRA; Has not ended, Vaishali Patel: Nothing to Disclose, Sayed Obaidullah Aseem: Galmed Pharmaceuticals: Grant/Research Support, Albert Arias: Nothing to Disclose, Vinay Kumaran: Nothing to Disclose, Seung Lee: Nothing to Disclose, Amit Sharma: Nothing to Disclose, Aamir Khan: Nothing to Disclose, Daisuke Imai: Nothing to Disclose, Marlon Levy: Nothing to Disclose, David Bruno: Nothing to Disclose

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2567 | HUMAN VERSUS ARTIFICIAL INTELLIGENCE: HEAD-TO-HEAD COMPARISON OF PREDICTIVE PERFORMANCE OF MELD 3.0 AND LATEST MACHINE LEARNING MODELS

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[1]*Stanford University School of Medicine,* [2]*Stanford University Medical Center*

Background: MELD 3.0 (and its predecessors) is derived from a Cox proportional hazards (PH) model. Recent technical developments in machine learning (ML) have enabled rapid advances in clinical risk prediction, raising the question of whether these more complex models are superior at prediction tasks. We perform a head-to-head comparison of latest ML methods for risk prediction with MELD 3.0. **Methods:** US waitlist registry data from the OPTN were used for training and testing of the models. For direct comparison between the models, the training data set was identical to that used to develop MELD 3.0, consisting of a 70% random sample of liver transplant candidates newly waitlisted between 01/15/2016 and 12/31/2018 (n=20587). The first testing set consisted of the 30% complement (n=8823); the second testing set of new registrants from 01/01/2019 to 12/31/2019 (n=10459). The primary outcome of interest was 90-day waitlist removal for death or being too sick. We considered four ML models for right-censored data: random survival forests (RSFs), gradient boosted machines (GBMs), and two deep learning models, DeepHit and DeepSurv. We considered two analyses. First, to evaluate whether the flexibility of the ML models might outperform MELD 3.0, we fit ML models using covariates included in MELD 3.0 (female sex, bilirubin, sodium, INR, creatinine, albumin). Second, we evaluated how the inclusion of additional clinical variables (age, race/ethnicity, ascites and encephalopathy) might improve prediction. Predictive performance of each model was evaluated by estimating the area under the receiving operating characteristic (AUROC) curve. **Results:** For models considering only the variables included in MELD 3.0, the ML models performed well overall (AUROCs 0.84-0.86), but consistently worse than MELD 3.0 at predicting 90-day waitlist dropout/mortality (MELD 3.0 AUROC 0.87, p<0.05; Figure 1). Only the DeepSurv model achieved comparable, but not superior, performance to MELD 3.0. With the inclusion of additional clinical variables, the conventional Cox PH model marginally improved on MELD 3.0 alone (AUROC 0.88 v. 0.87, p<0.05), while the ML models failed to outperform the Cox PH model and MELD 3.0 alone. **Conclusion:** Complex ML models do not improve the predictive capacity of MELD 3.0 when the identical variables are incorporated. Marginal improvement in prediction is possible with the inclusion of additional prognostic clinical variables, although these may not be suitable for allocation.

Models considering MELD3.0 variables only				
Model	*Test#1 AUROC*	*p-value**	*Test#2 AUROC*	*p-value**
MELD 3.0	**0.86927**	-	**0.86824**	-
RSF	0.85937	0.01622	0.84820	0.00000
GBM	0.86309	0.01141	0.85797	0.00000
DeepHit	0.83581	0.00000	0.84101	0.00000
DeepSurv	0.86449	0.14097	0.86272	0.04573
Models considering MELD 3.0 variables + age, race/ethnicity, ascites and encephalopathy				
Model	*Test#1 AUROC*	*p-value**	*Test#2 AUROC*	*p-value**
Cox PH	0.88120	0.00001	0.87605	0.00323
RSF	0.87426	0.19082	0.86499	0.39673
GBM	0.87286	0.27345	0.86759	0.84075
DeepHit	0.85539	0.01719	0.84882	0.00086
DeepSurv	0.86347	0.24867	0.85472	0.00813

*p-value refers to comparisons between each model and MELD3.0

Disclosures: Vivek Charu: Nothing to Disclose, Jane Liang: Nothing to Disclose, Ajitha Mannalithara: Nothing to Disclose, Allison Kwong: Nothing to Disclose, W. Ray Kim: Nothing to Disclose

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2568 | LONG-TERM OUTCOMES OF PATIENTS TRASPLANTED FOR ACUTE LIVER FAILURE IN THE UNITED STATES: AN ANALYSIS OF THE UNOS DATABASE

Ana Marenco-Flores[1] Romelia Barba[2] Daniela Goyes[3] John Esli Medina Morales[4] Leandro Sierra[1] Marwan Alsaqa[5] Denisse Rubio-Cruz[1] Vilas Patwardhan[1] Alan Bonder[1]

[1]Beth Israel Deaconess Medical Center, [2]Texas Tech University, [3]Yale School of Medicine, [4]Rutgers New Jersey Medical School, [5]BIDMC HMS

Background: The annual incidence of acute liver failure (ALF) in the US ranges from 2,000-4,000 cases. Liver transplantation (LT) serves as a life-saving treatment for ALF patients. Previously, the mortality rate for ALF was as high as 85%. This study aimed to analyze long-term patient and graft survival following LT for ALF, focusing on outcome variations by etiology. **Methods:** We conducted a retrospective analysis of the United Network for Organ Sharing (UNOS/OPTN) database including adult ALF patients who underwent LT from January 2002-December 2020, listed as status 1/1A. Outcomes were post-LT patient and graft survival. Clinical, laboratory, and demographic characteristics were compared between the ALF groups. We used Kaplan-Meier analysis for survival calculations. To identify survival predictors, we conducted forward stepwise multivariate Cox regression analyses adjusted for recipient and donor characteristics. **Results:** We identified 1,455 LT recipients with ALF. Drug-induced liver injury (DILI) is the main etiology of ALF (40%), followed by unknown causes (35%), and Wilson disease (WD) (12%). Most patients were white Caucasian, with a female predominance in most of the groups. Patients with WD exhibited the lowest age for LT, at 27. In the multivariate analysis, being African American (Hazard ratio, HR,1.53; 95% Confidence interval, CI, 1.21–1.93; p = 0.001), having diabetes mellitus (DM) (HR, 1.82; 95% CI, 1.31–2.52; p = 0.001), and having grade 3–4 hepatic encephalopathy (HR, 1.42; 95% CI, 1.14–1.77; p = 0.002) had a detrimental impact on post-LT patient survival. The same variables were associated with an increased risk of post-LT graft failure. Patients with DILI showed the lowest 5-year survival (77%, p = 0.001), autoimmune hepatitis (AIH) exhibited the lowest 10-year survival (63%, p = 0.001), and WD had the highest overall 5- and 10-year survival rates (89% and 85%, p = 0.001). Regarding graft survival, patients with DILI showed the lowest 5-year survival rate (73%, p = 0.002), while cholestatic etiology had the lowest 10-year survival (58%, p = 0.002). WD had the highest overall graft survival (93% at 5 years and 81% at 10 years, p = 0.002). **Conclusion:** Our study highlights the need to consider WD in adults with ALF and the benefits of urgent LT. Notably, DM and hepatic encephalopathy (grades 3–4) at LT have the strongest association with reduced post-LT survival. ALF cases from AIH, DILI, and cholestatic diseases show lower survival rates, urging better prognostic tools and etiology-specific post-LT care.

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Table 1. Cohort characteristics (n=1455)

Variable	*Viral Infection HAV, HBV (n=105)*	*DILI (n=575)*	*AIH (n=77)*	*Cholestatic Liver Disease (n=11)*	*Wilson Disease (n=178)*	*Unknown (n=509)*	P Value
			RECIPIENT				
Age, (IQR)	48 (39-61)	37 (27-48)	51 (35-59)	46 (25-60)	27 (21-37)	41 (29-53)	0.001
Female Gender, n (%)	36 (34)	444 (77)	64 (83)	7 (63)	106 (60)	332 (65)	<0.001
Race, n (%)							<0.001
White Caucasian	53 (50)	379 (66)	33 (43)	8 (73)	130 (73)	267 (52)	
Black	14 (13)	96 (17)	26 (34)	1 (9)	10 (6)	124 (24)	
Hispanic	11 (10)	60 (10)	12 (16)	0	26 (15)	67 (13)	
Asian	27 (26)	26 (5)	2 (3)	2 (18)	10 (6)	38 (7)	
Other	0	14 (2)	4 (5)	0	2 (1)	13 (3)	
Blood type, n (%)							0.260
O	46 (44)	267 (46)	41 (53)	7 (64)	87 (49)	239 (47)	
A	39 (37)	202 (35)	20 (26)	4 (36)	63 (35)	193 (38)	
B	13 (12)	79 (14)	12 (16)	0	16 (9)	65 (13)	
AB	7 (7)	27 (5)	4 (5)	0	12 (7)	12 (2)	
BMI, (IQR)	27 (24-31)	26 (23-30)	30 (25-36)	27 (23-29)	27 (24-33)	28 (25-33)	0.001
Diabetes, n(%)	17 (17)	27 (5)	9 (12)	0	3 (2)	39 (8)	<0.001
Sodium, (IQR)	138 (135-140)	138 (136-142)	138 (135-141)	138 (137-138)	137 (136-138)	138 (136-140)	<0.001
INR, (IQR)	4 (2.7-5.4)	4 (2.8-6.4)	3 (2.3-3.7)	2.9 (1.8-6.8)	3.1 (2.3-4.1)	3.5 (2.6-5.1)	<0.001
Total Bilirubin, (IQR)	22 (16-29)	8 (4-23)	24 (18-29)	11 (5-23)	23 (11-35)	21 (14-28)	<0.001
Creatinine, (IQR)	1.3 (0.8-2.4)	1.5 (0.8-2.6)	0.9 (0.7-1.4)	1 (0.8-1.4)	1.2 (0.8-2)	1.1 (0.8-2.1)	<0.001
Ascites, n (%)	59 (56)	214 (37)	43 (56)	5 (45)	130 (73)	242 (48)	<0.001
Grade ¾ Hepatic encephalopathy, n (%)	59 (56)	353 (61)	40 (52)	6 (55)	39 (22)	285 (56)	<0.001
Wait time (days), (IQR)	3 (2-4)	2 (1-3)	3 (2-7)	3 (3-8)	3 (2-6)	2 (2-4)	<0.001
			DONOR				
Age, (IQR)	41 (22-50)	36 (23-50)	34 (23-54)	45 (24-51)	35 (23-49)	36 (22-49)	0.754
Female Gender, n (%)	45 (43)	261 (45)	30 (39)	6 (55)	72 (40)	214 (42)	0.685
BMI, (IQR)	25 (22-28)	25 (22-29)	26 (23-28)	24 (23-29)	25 (22-29)	25 (22-28)	0.698
Cold ischemia time (hours), (IQR)	6 (5-8)	6 (5-8)	6 (5-7)	7 (5-9)	7 (5-8)	6 (5-8)	0.114

AIH: autoimmune hepatitis, BMI: body mass index, DILI: drug-induced liver injury, HAV: hepatitis A virus, Hepatitis B virus. Reference ranges: sodium: 135–145 mmol/L, creatinine: 0.50–1.10 mg/dL, bilirubin: 0.3–1.2 mg/dL, INR: 0.8–1.1. Kruskal–Wallis test for continuous variables and Pearson's chi-squared test ($\chi 2$) for categorical variables. Continuous variables were reported as median with interquartile range (IQR), and categorical variables were summarized using percentages.

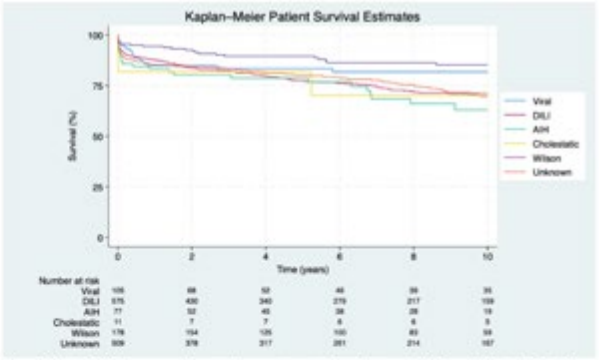

Figure 1. Kaplan-Meier curve demonstrating post-transplant patient survival by underlying ALF etiology (p=0.001). Viral: viral infection with Hepatitis A and Hepatitis B virus, DILI: drug induced liver injury, AIH: autoimmune hepatitis, Cholestatic: cholestatic liver disease.

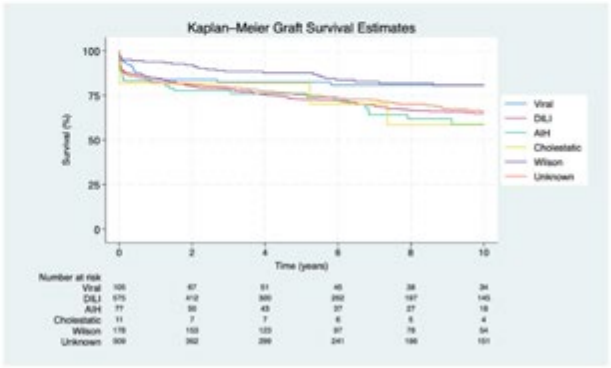

Figure 2. Kaplan-Meier curve demonstrating post-transplant graft survival by underlying ALF etiology (p=0.002). Viral: viral infection with Hepatitis A and Hepatitis B virus, DILI: drug induced liver injury, AIH: autoimmune hepatitis, Cholestatic: cholestatic liver disease.

Disclosures: Ana Marenco-Flores: Nothing to Disclose, Romelia Barba: Nothing to Disclose, Daniela Goyes: Nothing to Disclose, John Esli Medina Morales: Nothing to Disclose, Leandro Sierra: Nothing to Disclose, Marwan Alsaqa: Nothing to Disclose, Denisse Rubio-Cruz: Nothing to Disclose, Vilas Patwardhan: Nothing to Disclose, Alan Bonder: GSK: Grant/Research Support, Mirium: Grant/Research Support, Gilead: Grant/Research Support, Ipsen: Grant/Research Support, Cymabay: Grant/Research Support, Intercept: Grant/Research Support, Intercept: Consultant, GSK: Consultant, Ipsen: Consultant, Chemobab: Grant/Research Support, Alnylam: Consultant, Thirammune: Consultant

2569 | OUTCOME OF UTILIZING MELD 3.0 FROM A CANADIAN PERSPECTIVE: A RETROSPECTIVE STUDY IN A SINGLE TERTIARY-CARE TRANSPLANT CENTRE

Crystal Liu[1] *Carlos Moctezuma-Velazquez*[1] *Rahima Bhanji*[1] *Vincent Bain*[1] *Malcolm Wells*[1]

[1]*University of Alberta*

Background: The model for end-stage liver disease (MELD) 3.0 has recently been implemented by UNOS in the United States to determine organ allocation priorities. It optimizes the existing MELD with added variables for sex and serum albumin. We conducted this study to assess whether utilizing MELD 3.0 would change classification or mortality outcomes in the Canadian context. **Methods:** The study was conducted at the University of Alberta Hospital. All patients registered for liver transplants between January 2015 through December 2023 were examined. The main outcome is survival up to 90 days from the time of waitlist registration. Each subject's baseline demographic was extracted, and their respective MELD, MELD-Na, and MELD 3.0 scores were calculated. Subjects were stratified by whether they were up- or down-classified with the MELD 3.0 score, along with their respective mortality outcomes. **Results:** In total, 902 patients were listed for liver transplant between January 2015 through December 2023, and 512 subjects were enrolled in the study. The population studied had a median MELD 19.0 (15.0-26.0), MELD-Na of 21.0 (IQR 16.0-28.0), and a MELD 3.0 of 22.1 (IQR 16.9-28.6). The Harrell's C-statistics for MELD-Na and MELD 3.0 were 0.8739 and 0.8764, respectively. Overall, a net of 7.9% of subjects were correctly re-classified to a higher MELD 3.0 class, which would result in a meaningful increased

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likelihood of liver transplant for those subjects. This is similar to what was found based on the original MELD 3.0 model development by Kim et al with a net reclassification of 8.8%. We did not find a significant difference between male and female subjects who were re-classified, though the sample size was limited. **Conclusion:** The MELD 3.0 score offers a more accurate mortality prediction than the MELD-Na score and should be more widely adopted in Canadian transplant centres.

Table 1. Reclassification of liver transplant candidates between MELD-Na and MELD3.0 at the University of Alberta Hospital from 2015-2023. (A) the number of patients, (B) the number of deaths and (C) the proportion of death

N=512		MELD 3.0				
		6-9	10-19	20-29	30-39	>40
MELD-Na	6-9	16				
	10-19	4	166	25		
	20-29		8	171	14	
	30-39			5	72	8
	>40				2	21

N=89		MELD 3.0				
		6-9	10-19	20-29	30-39	>40
MELD-Na	6-9					
	10-19		13	4		
	20-29		2	35		
	30-39			1	18	6
	>40					10

89=100%		MELD 3.0				
		6-9	10-19	20-29	30-39	>40
MELD-Na	6-9					
	10-19		14.6%	4.5%		
	20-29		2.2%	39.3%		
	30-39			1.1%	20.2%	6.7%
	>40					11.2%

Disclosures: Crystal Liu: Nothing to Disclose, Carlos Moctezuma-Velazquez: Nothing to Disclose, Rahima Bhanji: Nothing to Disclose, Vincent Bain: Nothing to Disclose, Malcolm Wells: Nothing to Disclose

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2570 | LIVER TRANSPLANT IMMUNOSUPPRESSION EDUCATION IN THE US: A SURVEY OF TRANSPLANT HEPATOLOGY FELLOWSHIP PROGRAM DIRECTORS

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Background: Immunosuppression (IS) management is a core component of transplant hepatology (TH) fellowship. Due to limited consensus guidelines for IS after liver transplantation (LT), practices vary widely among centers. We surveyed program directors (PDs) regarding the practices and perspectives of adult and pediatric TH fellowship programs, aiming to provide insights into potential opportunities for establishing a more standardized framework for IS education. **Methods:** A 107-item survey using the RedCap platform was sent to the PDs for all 67 adult and 17 pediatric TH fellowship programs, identified through the AASLD TH program listing for 2023-2024 and public platforms. The survey was divided into two main sections: general center characteristics and IS practices, IS TH fellow training and perspectives in IS education. Descriptive statistics were used. **Results:** 45 (53.6%) of 84 invited PDs initiated the survey, with 43 (51.2%) completed it in its entirety. Regarding center characteristics, heterogeneity was observed in several areas, including the number of annual transplants, typical approaches to IS, and roles of clinicians involved in the decision-making of management in IS and rejection. 43 (95.6%) of the 45 centers reported having a formal protocol for IS management after LT. Most (76.7%) PDs answered *favorably* (agree or strongly agree) for routine use of the protocol at their center, as well as in TH fellow education (81.40%). Differences in the timing of TH fellow involvement and exposures to special populations, such as post-LT malignancies, were noted. Only 50.0% of programs reported having a formal IS curriculum. Figure 1A compares the exposure of IS between fellows in programs with or without a formal curriculum. 85.8% of PDs without a formal curriculum agreed their fellows would benefit from a dedicated IS curriculum. Finally, PDs were asked about IS education on a national level (Figure 1B) with one-third of PDs answering neutral for fellow preparedness in this area countrywide and 46.5% for IS management of special populations. 74.5% of PDs answered *favorably* that a national standard IS curriculum could be useful. 65.1% and 46.5% of PDs answered *favorably* that standardized guidance on IS teaching should be provided by AASLD and ACGME respectively. **Conclusion:** IS management education for TH fellows largely follows their transplant centers' practices, which are known to be heterogeneous across the U.S. A formal, standardized TH fellowship IS curriculum could help alleviate center variation in training. A substantial number of PDs were neutral on fellows being well-prepared in IS management, suggesting this critical aspect of TH fellowship education warrants improvement.

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Figure 1A

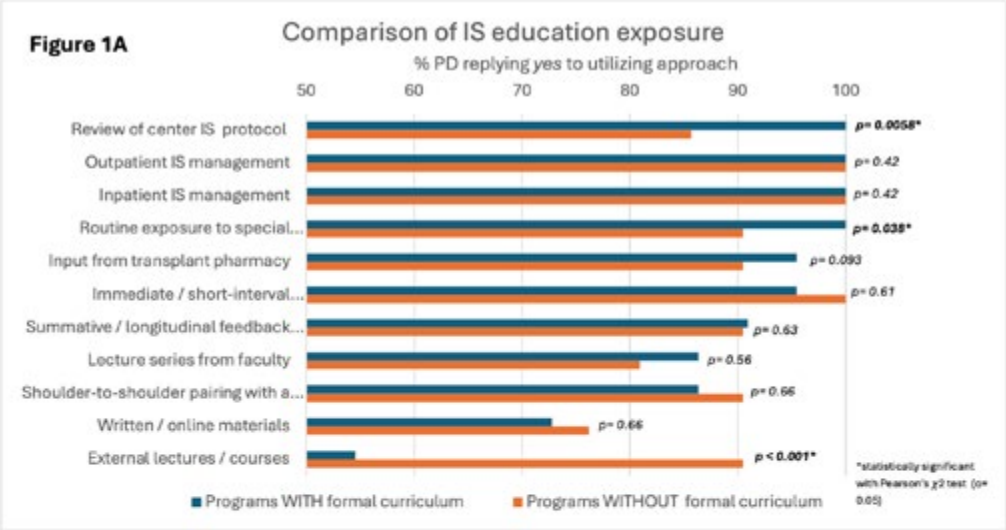

Figure 1B

Statements	Strongly disagree	Disagree	Neutral	Agree	Strongly agree	Unknown
A national standard IS curriculum for fellows could be useful	0.0%	2.3%	23.3%	41.9%	32.6%	0.0%
The AASLD should provide more standardized guidance on IS teaching	0.0%	4.7%	30.2%	37.2%	27.9%	0.0%
The ACGME should provide more standardized guidance on IS teaching	9.3%	16.3%	27.9%	30.2%	16.3%	0.0%
Most fellows nationally feel well prepared in routine IS management	0.0%	11.6%	32.6%	37.2%	4.7%	14.0%
Most fellows nationally feel well prepared in IS management for special populations	0.0%	14.0%	46.5%	20.9%	2.3%	16.3%

Disclosures: Jinxuan Hao: Nothing to Disclose, Therese Bittermann: Nothing to Disclose, Christine Chan: Nothing to Disclose

2571 | ALBUMIN INFUSIONS CAN LEAD TO CLINICALLY SIGNIFICANT CHANGES IN MELD 3.0 SCORES FOR PATIENTS WAITLISTED FOR LIVER TRANSPLANTATION

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Background: The Model for End-Stage Liver Disease (MELD) score has been the basis for liver transplant (LT) allocation for the last twenty years. Although albumin infusion is frequently used in the care of hospitalized LT patients, the effect of albumin infusion on MELD 3.0 scores among waitlisted patients has yet to be studied. Herein, we calculated the effect of a hypothetical albumin infusion on the MELD 3.0 scores of a real-world cohort of listed LT candidates. **Methods:** Adult cirrhotic patients listed for LT at the University of Michigan from Jan 2019 to Feb 2024 were reviewed. Baseline demographics and lab values from the UNOS database were used and excluding exception-related scores. MELD 3.0 was calculated at baseline and after modeling an increase of 0.7 mg/dL and 1.5 mg/dl of albumin (as estimated by albumin effect in the ANSWER, ATTIRE, and CONFIRM trials). Hypothesis testing was performed using Chi-square tests and analysis of variance (ANOVA) test for categorical and continuous variables. The change in transplant priority was simulated by comparing a given MELD 3.0 score's initial rank in the dataset to its rank after albumin infusion. **Results:** During the study period, 472 patients met the inclusion criteria, contributing 2,341 non-exception MELD scores for analysis. Mean MELD 3.0 score was 20.3. After a simulated albumin increase of 0.7g/dl and 1.5g/dl, MELD 3.0 score was unchanged in 64.9% and 63.8% of patients respectively. When stratified based on pre-infusion MELD 3.0 quartiles (<15, 15-18, 19-25, 26+), the middle quartiles (n=1094) of MELD 3.0 scores (15-25) were affected the most by an increase in serum albumin of 0.7mg/dL, with 415 (38%) of patients dropping by 1 point and 62 (6%) dropping by two points (Figure).

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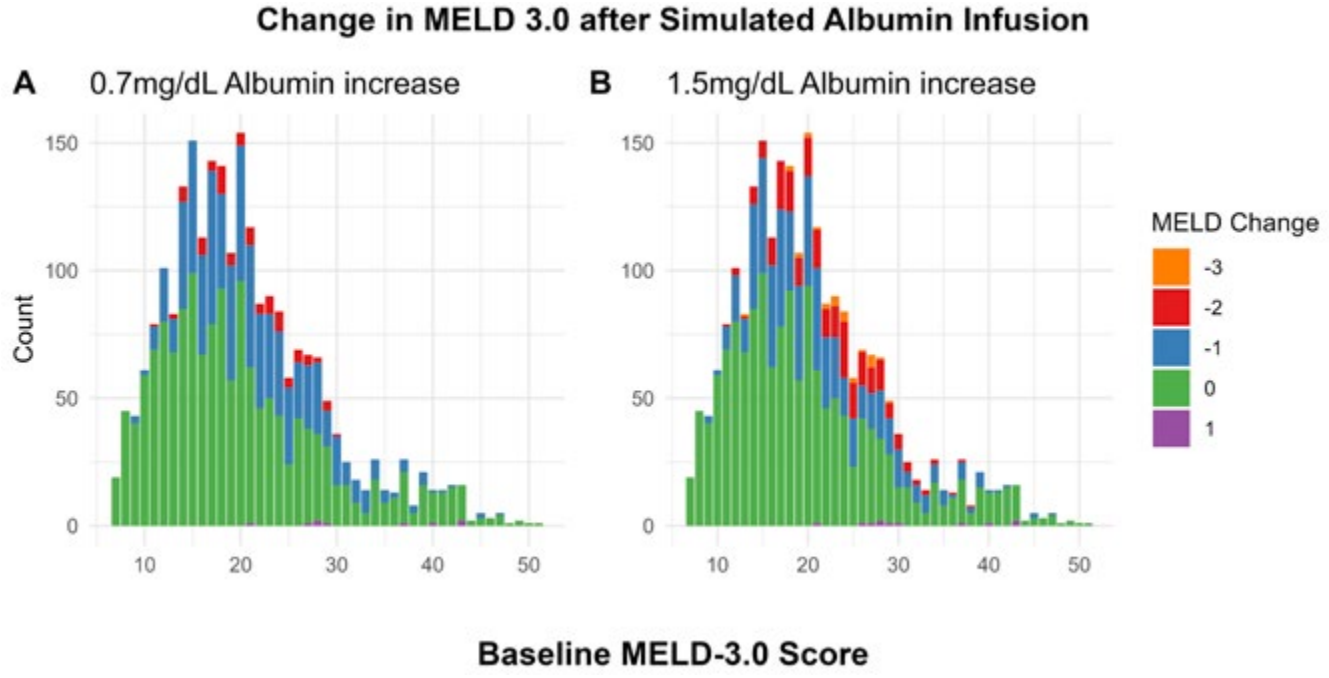
This effect was even more pronounced when albumin was increased by 1.5mg/dL with 323 (30%), 146 (13%), and 19 (2%) of patients dropping by 1, 2, or 3 MELD 3.0 points. Within the cohort, simulated albumin infusion resulted in a small drop in waitlist rank for both the 0.7 mg/dL (average rank drop 39, 1.7% change, p<0.001) and 1.5 mg/dL cases (rank drop by 47, 2.0% change, p<0.001) however this was again most pronounced in the middle MELD group (rank drop by 57, 3.0%) compared to the low MELD group (rank drop by 27, 1.1%) and high MELD group (rank drop by 17, 0.7%). A similar pattern was noted with the 1.5mg/dL simulation data. **Conclusion:** Albumin is an integral medication for LT candidates. Our data demonstrates that albumin infusion can lead to clinically significant changes in MELD 3.0 scores of ≥ 2 points in a small but important minority of patients. Additionally, the impact on listing priority is not uniform and is greatest in those with MELD 3.0 scores in the 15 to 25 range.



Disclosures: Priyata Dutta: Nothing to Disclose, Robert Fontana: Grant/Research Support relationship with kezar pharmaceuticals; Has not ended; Consultant relationship with moderna; Has ended; Grant/Research Support relationship with Takeda Pharmaceuticals; Has not ended, Nikhilesh Mazumder: Nothing to Disclose

2572 | THE PATIENT AND KIDNEY GRAFT OUTCOMES OF SAFETY NET KIDNEY TRANSPLANTS ARE SIMILAR TO KIDNEY TRANSPLANT RECIPIENTS WITHOUT A PREVIOUS LIVER TRANSPLANT: A RETROSPECTIVE UNOS DATABASE ANALYSIS ◆

Mohanad Awadalla[1] *Yong-Fang Kuo*[2] *Ashwani Singal*[3]

[1]*Beth Israel Deaconess Medical Center, Harvard Medical School, Boston,* [2]*UTMB Galveston,* [3]*University of Louisville*

Background: The Organ Procurement and Transplantation Network (OPTN) implemented the allocation policy in 2017 to standardize the approach to simultaneous liver-kidney (SLK) listing and optimize the use of deceased donor kidneys. Recent data show that the SLK allocation policy has led to more effective use of the deceased donor kidney pool without impacting the liver graft and patient survival. However, kidney graft and patient survival have not been studied well among recipients of LT alone, requiring a safety net kidney transplant. The aim of our study is to compare the outcomes of safety net kidney transplants among liver transplant recipients (KAL) with recipients of kidney transplants (KT) without a previous liver transplant. **Methods:** Using the UNOS database, a retrospective cohort was extracted of recipients of first liver transplant with renal dysfunction (estimated GFR<30 mL/min. or on dialysis) at transplant since the implementation of the medical eligibility criteria for simultaneous liver-kidney transplantation (08/10/17-06/30/21). Of these, those needing KAL were compared for graft and patient survival with a propensity-matched cohort of KT over the same period. **Results:** KAL recipients (n=94) were

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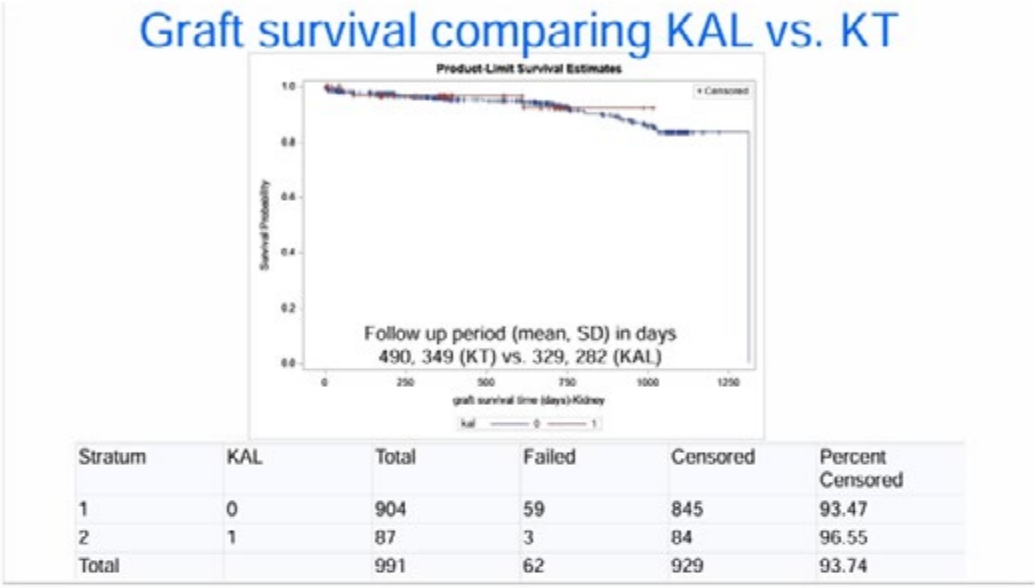
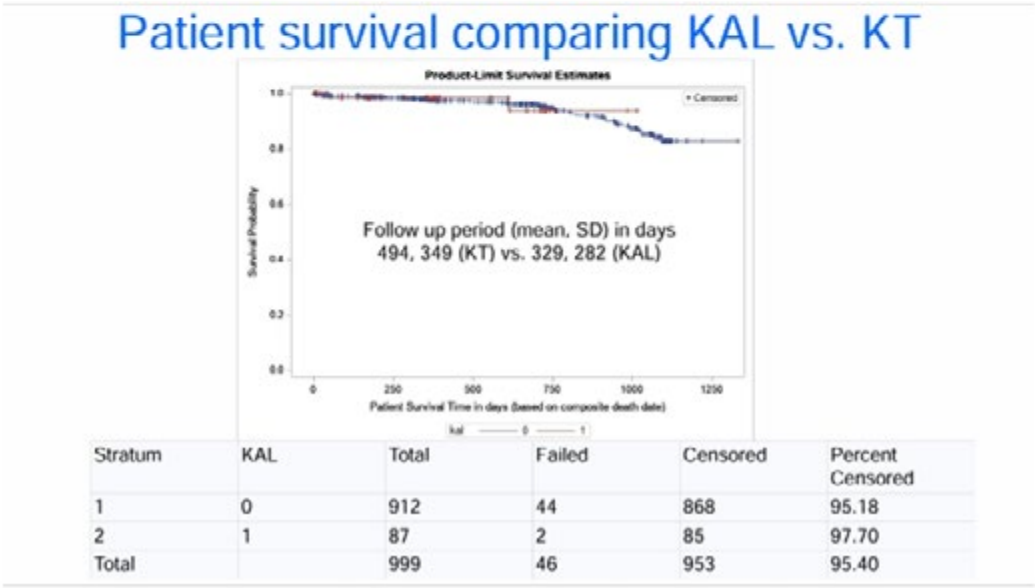
matched with 940 of 67,786 KT for age, gender, race, diabetes and BMI. The baseline characteristics were similar, except for higher serum creatinine and increased wait time among KTA recipients. Over a mean follow-up of 329 and 494 days in KAL and KT recipients, graft survival rates were 96.5 and 93.5% (Figure 1A), and patient survival rates were 97.7 and 95.2% (Figure 1B), respectively. Controlling for the calendar year, KDPI, GFR, and on dialysis, KAL vs. KT showed similar survival on graft [0.75 (0.23-2.45)] or patient [0.86 (0.20-3.71). **Conclusion:** Our retrospective study showing similar outcomes comparing KAL and KT is encouraging and supports medical eligibility criteria to list candidates for a simultaneous liver-kidney transplant.

Figure 1 A: Graft Survival Comparing KAL vs. KT



Stratum	KAL	Total	Failed	Censored	Percent Censored
1	0	904	59	845	93.47
2	1	87	3	84	96.55
Total		991	62	929	93.74

Figure 1 B: Patient Survival Comparing KAL vs. KT



Stratum	KAL	Total	Failed	Censored	Percent Censored
1	0	912	44	868	95.18
2	1	87	2	85	97.70
Total		999	46	953	95.40

Disclosures: Mohanad Awadalla: Nothing to Disclose, Yong-Fang Kuo: Nothing to Disclose, Ashwani Singal: Advisor relationship with CLD Foundation; Has not ended; Speaking and Teaching relationship with Medical Speaker's Network; Has not ended; Speaking and Teaching relationship with Madrigal; Has not ended; Stock â€“ privately held company relationship with Pleiogenix; Has not ended; Consultant relationship with Pleiogenix; Has not ended; Advisor relationship with Durect; Has ended; Royalties or patent beneficiary relationship with

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2573 | POST-LIVER TRANSPLANTATION RENAL DYSFUNCTION PRIMARILY DRIVEN BY OLDER AGE AND MELD AT LISTING RATHER THAN LIVER DISEASE ETIOLOGY TYPE

Niki Wadhwa[1] Kevin Houston[1] Hiba Khan[1] Hasan Alroobi[1] Nikita Chadha[1] Chad Spencer[1] Richard Sterling[2] Amon Asgharpour[1] Nicole Keller[1] Joel Wedd[1] Hannah Lee[2] Mohammad Siddiqui[1] Vaishali Patel[1] Sayed Obaidullah Aseem[1] Vinay Kumaran[1] Seung Lee[1] Amit Sharma[1] Aamir Khan[1] Daisuke Imai[1] Marlon Levy[1] David Bruno[1]

[1]Virginia Commonwealth University Health System, [2]Virginia Commonwealth University

Background: Those with metabolic dysfunction-associated steatohepatitis (MASH) are at risk for renal dysfunction post-liver transplantation (LT). Due to the multifactorial nature of post-LT renal dysfunction, the ability to accurately identify patients (pts) at risk for renal disease is paramount. Our study aim was to assess the 1-year post-LT prevalence of renal dysfunction by underlying liver disease etiology and then identify factors that may have influenced renal dysfunction across these groups. **Methods:** A retrospective analysis of deceased donor LT from 2018-2022 was performed. Baseline demographic, clinical, and lab data were collected. The primary outcome was renal dysfunction defined as glomerular filtration rate (GFR) <60 ml/min and serum creatinine (sCr) >2 mg/dL) and the impact of pre-LT MELD, pre-LT renal disease (acute kidney injury [AKI] or chronic kidney disease [CKD]), liver disease etiology (MASH vs alcohol-related liver disease [ALD] and other non-MASH), and 1-year trough tacrolimus (Tac) level on developing renal dysfunction following LT. **Results:** Our study group consisted of 479 pts; mean age 53 (SD 12.6), 59% male, 78% white, 15%, black, 93% non-Hispanic. Liver etiology: MASH 24%, ALD with <6 months of sobriety 28% (9% with alcoholic hepatitis), ALD >6 months of sobriety 25%, and other 23%. Mean MELD at listing 24 (11), median sCr 1.14 (IQR 0.8-2.05), 23% with diabetes, 24% with CKD and 43% with AKI (grade [G]1 9%, G2 8%, G3 26%). At 1-yr after LT, 44% had GFR < 60 ml/min and 11% had sCr > 2 mg/dL. Those with GFR < 60 ml/min post LT were older (55 vs 51; p=.0034), had higher MELD (27 vs 22; p<.0001), pre-LT AKI (55% vs 45%; p<.0001) or CKD (67% vs 33%; p<.0001), and were more likely to have MASH (50 vs 42%; p=.049) with no differences in sex, race, presence of diabetes, or post-LT Tac trough (Table). Independent predictors for GFR < 60 ml/min at 1-yr follow-up were: age (p=.0007), MELD (p=.00124), and CKD at listing (p<.0001) while AKI at listing and MASH were no longer significant following LT. Importantly, we did not observe any impact on post-LT renal dysfunction on 1-yr survival after LT. **Conclusion:** In our cohort undergoing LT, renal dysfunction was observed in 44% and was higher in those with higher MELD and CKD pre-LT, but not in those with pre-LT AKI or MASH. Not all with GFR < 60 ml/min had sCr > 2 mg/dL at 1-year, suggesting that sCr alone is not predictive of low GFR following LT. Longer follow up on the impact of post-LT renal dysfunction on patient and graft survival is needed.

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Table: comparing characteristics by GFR at 1 year after LT

	GFR < 60 ml/min	GFR > 60 ml/min	P value
N	211	268	
Age^	55 ± 11	51 ± 13	.0034
Gender (male)	53%	62%	NS
Race (White/Black)	74/19%	82/12%	NS
Diabetes mellitus	51%	49%	NS
AKI at listing	55%	45%	<.0001
AKI Grade 1/2/3	11/10/33%	8/7/20%	<.0001
CKD at listing	67%	33%	<.0001
MELD at transplant	26.9 ± 11.8	22.1 ± 10.9	<.0001
Pre-LT ascites	46%	54%	.04
MASH	50%	42%	.049
Alcoholic Hepatitis	47%	53%	NS
ALD < 6 mo sobriety	45%	55%	NS
ALD > 6 mo sobriety	44%	56%	NS
Time on list (days)	77 ± 200	130 ± 264	.017
Post LT length of stay (days)	33 ± 35	28 ± 38	NS
Trough Tacrolimus at 1-year (ng/mL)	5.6 ±-2.7	5.4 ±-3.6	NS
sCr > 2 mg/dL post-LT	27%	0%	<.0001
1-year survival	97%	91%	.06

Abbreviations: AKI, acute kidney injury; CKD, chronic kidney disease; GFR, glomerular filtration rate; LT, liver transplant; ALD, alcohol-associated liver disease; sCr, serum creatinine; MASH, metabolic dysfunction steatohepatitis; NS, non-significant. ^ mean ± standard deviation

Disclosures: Niki Wadhwa: Nothing to Disclose, Kevin Houston: Nothing to Disclose, Hiba Khan: Nothing to Disclose, Hasan Alroobi: Nothing to Disclose, Nikita Chadha: Nothing to Disclose, Chad Spencer: Nothing to Disclose, Richard Sterling: Grant/Research Support relationship with HCV Vax; Has not ended; Grant/Research Support relationship with GSK; Has not ended; Grant/Research Support relationship with Gilead; Has not ended; Grant/Research Support relationship with Roche; Has not ended; Grant/Research Support relationship with AbbVie; Has not ended; Grant/Research Support relationship with Abott; Has not ended; GI Specialty Board relationship with ABIM; Has not ended, Amon Asgharpour: Madrigal: Advisor, Galectin: Clinical Endpoint Committee, Nicole Keller: Nothing to Disclose, Joel Wedd: Nothing to Disclose, Hannah Lee: Nothing to Disclose, Mohammad Siddiqui: Grant/Research Support relationship with NovoNordisk; Has not ended; Advisor relationship with 89Bio; Has not ended; Advisor relationship with AMRA; Has not ended, Vaishali Patel: Nothing to Disclose, Sayed Obaidullah Aseem: Galmed Pharmaceuticals: Grant/Research Support, Vinay Kumaran: Nothing to Disclose, Seung Lee: Nothing to Disclose, Amit Sharma: Nothing to Disclose, Aamir Khan: Nothing to Disclose, Daisuke Imai: Nothing to Disclose, Marlon Levy: Nothing to Disclose, David Bruno: Nothing to Disclose

2574 | POST-TRANSPLANT PREDICTORS AND OUTCOMES OF PERSISTENT CHOLESTASIS AFTER LIVER TRANSPLANTATION

Aaroh Patel[1] Vaishali Patel[1] Alexis Kim[1] Rehan Razzaq[1] Madison Nguyen[2] Mohammad Siddiqui[1]

[1]Virginia Commonwealth University, [2]VCUHS

Background: Liver transplantation (LT) is the only curative treatment for end-stage liver disease (ESLD). The rising prevalence of ESLD and waitlist mortality has led to an expansion of the donor pool to include donors after circulatory death (DCD) and extended criteria (advanced age, obesity) to meet organ demand. However, enthusiasm towards such donors is tempered by high onset of biliary complications. Post-liver transplant cholestasis (PLTC) may result in re-transplantation and death; however, while the clinical drivers (ischemia

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time, DCD) inciting PLTC are well studied, little is known of population characteristics that may drive the progression of PLTC. Thus, the objective of the present study was to better characterize patients with ESLD who develop cholestasis following LT and to identify factors associated with worse clinical outcomes. **Methods:** In a retrospective study, 611 patients who underwent LT at author's institution between 2004-2022 were divided into three groups of cholestasis (normal [402], borderline [146], high [63]) based on alkaline phosphatase (ALP) values (ALP < 120, ALP 120-240, ALP ≥ 240 U/L) at 6 months post-LT. Univariate, bivariate and multivariate analyses were performed to characterize population characteristics of each group. **Results:** Pre-transplant characteristics such as age, body mass index, gender and smoking/alcohol use were not associated with degree of cholestasis in multivariate or bivariate analyses. ALP levels at 3 months were highly predictive of borderline and high cholestasis subsequently through 36 months ($p < .001$). Patients with primary sclerosing cholangitis as their underlying liver disease were more likely to be in the high group (OR = 3.494, $p = .048$, 95% CI = [1.011, 12.074]). Length of hospital/ICU stay was significantly longer in patients with high cholestasis in bivariate ($p<0.001$) but not multivariate analyses. A trend towards higher mortality was noted in patients with higher degree of cholestasis although not statistically significant. Cholestasis was not significantly associated with infection or rejection. **Conclusion:** LT patients with elevated ALP at 3 months post-LT and those with PSC as the underlying liver disease were likely to have persistent cholestasis. A higher mortality or disease burden in the form of longer hospital stay, infection or liver rejection was not clearly associated with high degree of cholestasis in this study.

Disclosures: Aaroh Patel: Nothing to Disclose, Vaishali Patel: Nothing to Disclose, Alexis Kim: Nothing to Disclose, Rehan Razzaq: Nothing to Disclose, Madison Nguyen: Nothing to Disclose, Mohammad Siddiqui: Grant/Research Support relationship with NovoNordisk; Has not ended; Advisor relationship with 89Bio; Has not ended; Advisor relationship with AMRA; Has not ended

2575 | LIVER TRANSPLANTATION FOR SHORT TELOMERE SYNDROME: OUTCOMES, AND DETAILED HISTOPATHOLOGIC EVALUATION OF EXPLANTS

Ashwin Akki[1] Joy Yates[1] Omar Sims[1] Koji Hashimoto[1] Jamak Modaresi Esfeh[1] Dane Olevian[2] Clifton Fulmer[1] Mohamed El Hag[1]

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Background: Short Telomere Syndrome (STS) is an extremely rare inherited disorder caused by abnormally short telomeres resulting in premature aging, in turn, leading to bone marrow failure and hepatopulmonary disease among others. The characteristic presentation in STS patients with liver involvement is portal hypertension, portosinusoidal vascular disease (PSVD) and advanced fibrosis. Nonetheless, histologic changes in STS livers have not been fully elucidated. STS patients with advanced liver disease frequently undergo liver transplantation. However, long term outcomes in these patients are not known. We aim to detail the histologic findings in liver explants and post-transplantation outcomes in this population. **Methods:** We searched our database for STS patients who underwent liver transplant from 1984 to 2024. **Results:** A total of seven cases were identified, (see table 1). Four patients received combined liver and lung allografts, one patient received a simultaneous liver kidney (SLK) after a lung transplant, and two patients received liver-only transplants. All patients showed evidence of portal hypertension prior to liver transplant. Grossly, all liver explants had a micronodular texture with a median weight of 909 grams (range: 566-2247 grams). Median follow-up after liver transplant is 12 months (range: 1.5 - 39 months). None of the patients showed recurrence of portal hypertension or PSVD post-transplantation. One case developed moderate TCMR within two months post-transplantation. There were no significant histologic differences in the liver explants from STS patients with combined lung-liver transplants (vs. those with only liver transplants) except that the latter patients were younger (Table 1). **Conclusion:** Portal venopathy and nodular regenerative hyperplasia (NRH) with incomplete septal cirrhosis constitute the most common hepatic phenotype in STS patients. This brief series highlights liver transplantation is a successful therapy for STS-associated portal hypertension and PSVD, showing no clinical recurrence.

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Table 1: Recipient demographics

Patient #	Age at TXP	Gender	Organs Transplanted	PreTransplant Biopsy	Liver Explant Pathologic Findings	Follow-up (months)
1	51	Male	Liver and Lung	Yes, Cirrhosis	Portal venopathy, NRH, Incomplete septal cirrhosis with foci of complete nodule formation, Moderate Steatohepatitis	1.5
2	31	Male	Liver	None	Portal venopathy, NRH, Strong Perisinusoidal fibrosis with Incomplete septal cirrhosis	2.5
3	58	Female	SLK after lung	Yes, Portal fibrosis and portal venopathy	Portal venopathy, NRH and Incomplete septal cirrhosis	9.5
4	47	Male	Liver and Lung	None	Portal venopathy, NRH and Incomplete septal cirrhosis	12
5	62	Female	Liver and Lung	None	Portal venopathy, NRH, Perisinusoidal fibrosis, Incomplete septal cirrhosis, Moderate Steatosis	13.5
6	19	Male	Liver	Yes, NRH	Portal venopathy, NRH, perisinusoidal fibrosis and Incomplete septal cirrhosis	35
7	57	Male	Liver and lung	Yes, NRH with portal fibrosis	Portal venopathy, NRH, Incomplete septal cirrhosis, mild steatosis	39

Disclosures: Ashwin Akki: Nothing to Disclose, Joy Yates: Nothing to Disclose, Omar Sims: Nothing to Disclose, Koji Hashimoto: Nothing to Disclose, Jamak Modaresi Esfeh: Nothing to Disclose, Dane Olevian: Nothing to Disclose, Clifton Fulmer: Nothing to Disclose, Mohamed El Hag: Nothing to Disclose

2576 | PLASMA CELL-RICH REJECTION: POTENTIAL ROLE OF NON-HLA ANTIBODIES

Joy Yates[1] Anthony Demetris[2] Alessandro Gambella[2] Qingyong Xu[3] Ashwin Akki[1] Heather Stevenson-Lerner[4] Adriana Zeevi[3] Mohamed El Hag[1]

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Background: Plasma cell-rich rejection (PCR) is recognized as an atypical manifestation of rejection, potentially indicating a combined etiology involving both T cell (TCMR) and antibody-mediated rejection (AMR). PCR, previously referred to as “plasma cell hepatitis” or “de novo autoimmune hepatitis,” is a poorly understood cause of late allograft dysfunction, typically manifesting more than a year after liver transplantation (LT). PCR is being linked to antibody mechanisms involving both HLA and non-HLA antibodies. This study aims to investigate the role of HLA and non-HLA antibodies in PCR and analyze its histology, phenotype and outcomes. **Methods:** PCR cases from 2014 to 2019 were identified using an electronic database. PCR is defined according to Banff as infiltration in the portal and perivenular regions with a plasma cell component exceeding 30%. Cases of LT for autoimmune hepatitis were excluded. A normalized mean fluorescence intensity (MFI) value greater than 1000 was considered positive. AT1R-AA testing was performed on patients with available serum. **Results:** Fifteen patients were identified, including 9 deceased and 6 living liver donors. Primary sclerosing cholangitis (PSC) was the most common etiology of LT (40%), followed by Viral Hepatitis C (HCV, 27%). The mean age at LT was 53.2 (± 11.8) years, with the index biopsy occurring an average of 64 (± 34.9) months post-transplant. 11 patients developed PCR more than a year after LT. Ten patients had prior biopsy-proven TCMR, and 3 patients had recurrent plasma cell-rich rejection on follow-up biopsies. There was 1 case of graft loss due to chronic AMR, 1 graft developed chronic rejection, and 1 had biopsy-proven TCMR.46% of patients had positive anti-HLA donor-specific antibodies (DSA): DQ8 was the most frequently detected (20%), with DQ2, DR51, and DR53 having the highest MFI values. Five patients had multiple specificities. AT1R-AA testing was performed in 6 patients with available serum: 2 showed at-risk levels (10-17 U/mL) and four were positive (>17 U/mL). Of the 3 anti-HLA negative patients tested for AT1R-AA, two were positive and one was at-risk. Most patients (66.7%) had elevated liver enzymes at the time of the index biopsy. Histologically, the mean rejection activity index (RAI) score was 6.1 (± 1.1), with focal and diffuse C4d deposition observed in 9 out of 15 index biopsies. **Conclusion:** PCR shares features of both AMR and TCMR and is associated with antibodies and C4d deposition. Both anti-HLA and non-HLA antibodies likely play a role in its pathogenesis.

Disclosures: Joy Yates: Nothing to Disclose, Anthony Demetris: Nothing to Disclose, Alessandro Gambella: Nothing to Disclose, Qingyong Xu: Nothing to Disclose, Ashwin Akki: Nothing to Disclose, Heather Stevenson-Lerner: Nothing to Disclose, Adriana Zeevi: Nothing to Disclose, Mohamed El Hag: Nothing to Disclose

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2577 | PSYCHOLOGICAL BURDEN OF THE LIVER TRANSPLANT PROCESS

Christina Tsai[1] Paola Mejia[1] Bishoy Gad[1] Hemali Rochlani[1] Danielle Garfunkel[1] Nicholas Samel[2] Sara Abdelhalim[1] Alvin Oommen[1] Don Rockey[1] Clara Tow[1] Lisa Teh[1]

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Background: Liver transplantation is an extensive process from initial evaluation through post-transplant immunosuppression. It is the only long-term treatment for end-stage liver disease; however patients often have a lengthy wait time for transplant, increasing risk of psychosocial distress. We aim to characterize the psychological burden over the course of transplant evaluation and listing. **Methods:** This prospective survey study assesses depression, anxiety, and quality of life among patients evaluated for liver transplant at a large urban center from January 2023 to May 2024. Patient Health Questionnaire-9 (PHQ-9), Generalized Anxiety Disorder-7 (GAD-7), and Centers for Disease Control and Prevention (CDC) Health-Related Quality of Life (HRQOL) surveys are administered upon study enrollment, then at 3 months if they remained a transplant candidate. Data for each survey were analyzed using a series of one-sample T-tests to compare means from baseline to 3 months. The baseline data was also compared across groups of patients with and without ascites, hepatocellular carcinoma, hepatic encephalopathy, esophageal variceal bleeds, and alcoholic liver disease using two-sample T-tests. **Results:** 40 participants completed initial surveys, with 22 of those surveys within 1 month of transplant listing. On initial survey, the average GAD-7 score was 5.30 (range 0-15) and average PHQ-9 score 5.75 (range 0-18). For the CDC HRQOL surveys, most reported their general health to be “fair” (n=11) or “good” (n=10) with activity limitations due to health impairments (n=26). Those with hepatocellular carcinoma reported less days of poor physical health compared to those without ($t(38)=-1.71$, $p<0.05$). 9 follow-up 3-month surveys were completed (8 received transplants prior to, 6 declined or could not be reached) where patients reported increased number of days with poor physical health ($t(38)=2.85$, $p=0.02$). All other scores were not significantly different. **Conclusion:** Patients undergoing the liver transplant process have mild anxiety and depression. While our sample size was small, the results show significant decline in subjective physical wellbeing over 3 months as a liver transplant candidate. Patients were at enhanced risk for psychosocial distress if they did not have hepatocellular carcinoma. Our findings suggest that patients may benefit from enhanced psychosocial support pre-transplant. More patients will need to be surveyed to assess further changes with time.

Table 1. Data Analysis and Results

	Questionnaire	T-test	*p*-value
3-month wait time	*GAD-7*	0.53	0.61
	PHQ-9	0.35	0.74
	CDC: days with subjective poor physical health	**2.85**	**0.02**
	CDC: days with subjective poor mental health	1.16	0.28
	CDC: days poor physical or mental health impacted ability to do usual activities	-0.36	0.73
Hepatic encephalopathy	*GAD-7*	-0.21	0.42
	PHQ-9	0.52	0.30
	CDC: subjective general perception of health	0.44	0.33
	CDC: days with subjective poor physical health	0.77	0.22
	CDC: days with subjective poor mental health	-0.17	0.43
	CDC: days poor physical or mental health impacted ability to do usual activities	0.20	0.42
Ascites	*GAD-7*	0.19	0.42
	PHQ-9	-0.15	0.44
	CDC: subjective general perception of health	-0.70	0.25
	CDC: days with subjective poor physical health	0.43	0.33
	CDC: days with subjective poor mental health	-0.72	0.24
	CDC: days poor physical or mental health impacted ability to do usual activities	0.10	0.46
Esophageal variceal bleed	*GAD-7*	0.31	0.38
	PHQ-9	0.25	0.40
	CDC: subjective general perception of health	0.33	0.37
	CDC: days with subjective poor physical health	1.50	0.07
	CDC: days with subjective poor mental health	-0.66	0.26
	CDC: days poor physical or mental health impacted ability to do usual activities	-0.54	0.30
Hepatocellular carcinoma	*GAD-7*	0.97	0.17
	PHQ-9	0.29	0.39
	CDC: subjective general perception of health	0.65	0.26
	CDC: days with subjective poor physical health	**-1.71**	**0.05 (0.04871)**
	CDC: days with subjective poor mental health	-1.36	0.09
	CDC: days poor physical or mental health impacted ability to do usual activities	0.20	0.42
Alcoholic liver disease	*GAD-7*	-0.20	0.42
	PHQ-9	0.01	0.50
	CDC: subjective general perception of health	-1.61	0.06
	CDC: days with subjective poor physical health	1.45	0.08
	CDC: days with subjective poor mental health	1.60	0.06
	CDC: days poor physical or mental health impacted ability to do usual activities	0.12	0.45

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Disclosures: Christina Tsai: Nothing to Disclose, Paola Mejia: Nothing to Disclose, Bishoy Gad: Nothing to Disclose, Hemali Rochlani: Nothing to Disclose, Danielle Garfunkel: Nothing to Disclose, Nicholas Samel: Nothing to Disclose, Sara Abdelhalim: Nothing to Disclose, Alvin Oommen: Nothing to Disclose, Don Rockey: Grant/Research Support relationship with Versantis; Has not ended; Grant/Research Support relationship with AstraZeneca; Has not ended; Grant/Research Support relationship with Ipsen; Has not ended; Grant/Research Support relationship with Boehringer Ingelheim; Has not ended; Consultant relationship with WL Gore and Associates; Has not ended; Grant/Research Support relationship with Gilead; Has not ended; Grant/Research Support relationship with Durect; Has not ended; Consultant relationship with BD Medical; Has not ended; Consultant relationship with Cook Medical; Has not ended; Grant/Research Support relationship with Intercept; Has not ended; Grant/Research Support relationship with Inventiva; Has not ended; Grant/Research Support relationship with Madrigal; Has not ended; Grant/Research Support relationship with Ocelot; Has ended; Grant/Research Support relationship with Bio89; Has not ended; Grant/Research Support relationship with Salix; Has not ended; Grant/Research Support relationship with Novonordisk; Has not ended; Grant/Research Support relationship with Viking; Has ended; Grant/Research Support relationship with Galectin; Has not ended, Clara Tow: Nothing to Disclose, Lisa Teh: Nothing to Disclose

2578 | HUMAN IMMUNE ORGANOIDS TO MODEL LIVER TRANSPLANT REJECTION

Elsa Solà[1] Pari Waghela[2] Chen Wang[1] Lilit Kamalyan[1] Lei Chen[1] Varavara Kirchner[2] Kasunari Sasaki[2] Marc Melcher[2] Carlos Esquivel[2] Mark Davis[1]

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Background: Liver transplantation (LT) is the only definitive therapy for patients with end-stage liver disease. Despite advances in the field, only modest progress has been made in immunosuppression strategies for preventing and managing acute rejection. Biomarkers to identify patients at high risk of rejection are lacking. Discovery and validation of new drugs is a long and laborious process, and results in animal models are frequently not translated into human benefits. Here we aimed at developing a fully human in vitro platform to investigate human liver rejection. For this, we used immune organoids that have previously been shown to recapitulate human immune responses in vitro. **Methods:** Immune organoids were developed from dissociated tonsil tissue from patients undergoing tonsillectomy for obstructive sleep apnea. Tonsil cells were stained with a cell tracer before culture. Hepatic artery and bile duct sections were obtained from explanted livers during LT. A wedge biopsy was obtained from donor liver. Artery, bile duct, and liver tissue were selected as the three key tissue targets in LT. The main readouts were immune cell infiltration into tissues and tissue injury. Tissue injury was evaluated by Immunohistochemistry. Immune cell infiltration and tissue cell death were also evaluated by flow cytometry in dissociated tissues. **Results:** The organoid models were successfully established by the co-culture of immune organoids with small sections of allogeneic artery, bile duct or liver tissue. Co-cultures were incubated for up to 7 days. On day 7 after co-culture, we observed that tonsil immune cells infiltrate into allogeneic artery, bile duct or liver tissue. Infiltrating immune cells were mainly CD3+ T cells (52+/-4%) followed by B cells (35+/-6%). Infiltrating CD3+ T cells showed markers of immune activation, with a higher frequency of T cells expressing CD38+ HLA-DR+ or PD1+ phenotype compared to tonsil CD3+ T cells not infiltrating the tissue. There was no difference in cell death as evaluated by flow cytometry. Immunohistochemistry showed that tissue injury was higher in liver and artery co-cultured with allogeneic immune organoids than in tissues incubated alone. **Conclusion:** Our study presents a novel organoid model that replicate acute rejection of the liver, demonstrating key features such as immune cell infiltration and tissue injury. This can be an excellent tool to expedite mechanistic studies for rejection in LT and the discovery of new therapeutic targets.

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2579 | PALLIATIVE MEDICINE UTILIZATION FOR OLDER ADULTS WITH END-STAGE LIVER DISEASE REFERRED FOR LIVER TRANSPLANTATION

Gavisha Waidyaratne[1] Jason Benedict[2] Leanna Perez Eiterman[2] Laura Rush[2] Sean Kelly[1] Ann McAlearney[3] Brittany Waterman[1]

[1]The Ohio State University Wexner Medical Center, [2]The Ohio State University, [3]The Ohio State University College of Medicine

Background: The prevalence, mortality, and number of older adults (≥ 65 years) diagnosed with end-stage liver disease (ESLD) have each risen over the past decade, leading to a steadily increasing proportion of older adults referred for liver transplantation (LT) evaluation over time. There is little evidence to guide palliative care (PC) practices for older adults with ESLD referred for LT. Our aim was to describe the PC utilization and health outcomes for older adult ESLD patients referred for LT evaluation and to id entify patient-level characteristics associated with PC consultation. **Methods:** We conducted a retrospective chart review examining older adults with ESLD referred for LT evaluation between 7/1/2015 and 6/30/2021. Outcomes were followed through 6/30/22. Data was collected on patient demographics, comorbidities, LT outcomes, PC consultation, code status, hospice referral, and mortality. **Results:** Amongst the cohort (n=421), median age was 68 [IQR: 66, 70] and etiology of cirrhosis was predominantly non-alcoholic (49%). Three-hundred nineteen patients had at least one ED visit or hospitalization during the study period. LT evaluation was initiated for 68% of patients (n=287). During the initial evaluation of those patients, 100 (35%) were deferred, and 187 were listed (65%). LT was completed for 130 patients (31%). Two-hundred one patients (48%) died during the study period. PC encounters occurred for 108 patients (25.7%). LT evaluation was initiated at the same rate for both groups (68%), with more deferrals in the PC group (n=41, 56% vs. n=59, 28%; p<0.001). Completion of HCPOA documentation was significantly higher in the PC group (n=55, 51% vs. n=86, 27%; p<0.001). The median number of ED visits (1 [IQR: 0, 3] vs. 1 [IQR: 0, 2]) and hospitalizations (2 [IQR: 1, 4] vs. 2 [IQR: 0, 4]) were similar between the PC group and no PC group. Similarly, both groups had similar rates of liver transplantation (n=22, 69% vs. n=108, 70%; p=0.88). A larger proportion of patients died within the group who received PC (n=88, 81% vs. n=113, 36%; p<0.001). **Conclusion:** More than two-thirds of referrals did not result in LT, and nearly half of all patients died within the study period. Receipt of PC was associated with a higher completion rate of HCPOA documentation, a higher rate of deferral from the LT evaluation process, and a higher mortality rate.

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2580 | IMPROVED SELF-EFFICACY IN POST-LIVER TRANSPLANT PATIENTS IN MANAGEMENT OF POST-TRANSPLANT METABOLIC SYNDROME THROUGH BEHAVIORAL RESOURCES AND INTERVENTION THROUGH DIGITAL GROUP EDUCATION (BRIDGE): A SHARE MEDICAL APPOINTMENT PROGRAM

Asal Bastani[1] Nghiem Ha[1] Eliana Agudelo[1] Sara Miller[1] Simone Madan[1] Riley Tan[1] Danielle Brandman[2] Jennifer Lai[1] Lisa Catalli[1]

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Background: Post-transplant metabolic syndrome (PTMS) affects nearly half of liver transplant (LT) recipients and is associated with poor graft and patient survival. Integrating education and behavioral health through shared medical appointments (SMA) encourages LT recipients to engage in the management of PTMS through peer-based learning and support. We implemented BRIDGE, a telehealth SMA program led by advanced practice providers (APPs) to improve patients' self-efficacy in managing PTMS. **Methods:** BRIDGE is a bi-weekly, 6-session (90 min each), small group psychoeducational program led by APPs. Each session incorporates motivational interviewing and cognitive behavioral strategies in didactics, peer discussions and individual consultations. Participants rated their knowledge, importance and confidence in making health changes on a 5-point scale. Self-efficacy in managing mental and social health domains was measured using 6 PROMIS short forms 2-weeks before and after the program. **Results:** Included were 25 adult LT recipients with MASLD who

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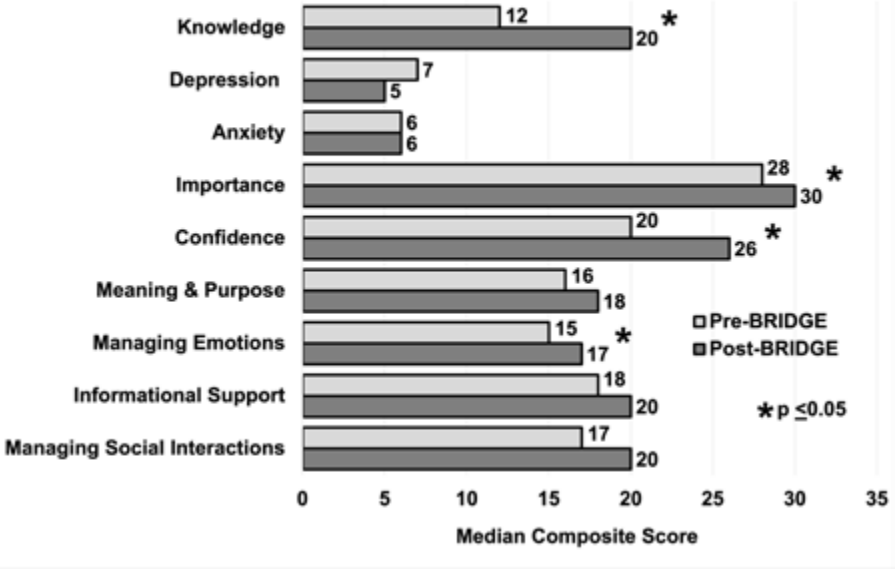
attended a median of 6 (IQR 5-6) BRIDGE sessions between 3/2022-3/2024 and completed pre-/post-surveys. Nearly half (48%) had MASH as their primary LT etiology, with a median post-LT duration of 4 (IQR 2-9) years. Over half were women (56%) with a median age of 60 years and BMI of 31.9 kg/m^2; 64% were obese, 52% had diabetes, 80% had hypertension, and 56% had hyperlipidemia. Race/ethnicity: 40% non-Hispanic white, 24% Hispanic, 12% Asian and 12% Black. Nearly two-thirds (69%) had severe steatosis with a median CAP of 307 (IQR 266-340) dB/m. Following completion of BRIDGE, patients reported improvements in various life domains, including meaning and purpose, mental health, and seeking support, with significant improvements in knowledge and confidence related to lifestyle modifications including managing emotions, and the importance of healthy habits in managing MASLD (Figure). Most (80%) achieved weight loss, averaging a 2.0 ± 5.7 lbs reduction. Qualitative feedback indicated high levels of satisfaction with the program. **Conclusion:** Our innovative group telehealth psychoeducational SMA program significantly improved knowledge, confidence, and self-efficacy around making changes in health-related behaviors among LT recipients with PTMS, leading to improved weight loss. Future research should explore the ideal program duration for sustainability of behavior change in LT recipients to manage PTMS and improve clinical outcomes.

Figure. Pre- and post-BRIDGE median composite score of patients' knowledge, importance and confidence in changing health habits, including change in mental and social domains of health



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2581 | POST LIVER TRANSPLANT RESOURCE UTILIZATION IN EARLY VERSUS STANDARD LIVER TRANSPLANT IN ALCOHOL ASSOCIATED LIVER DISEASE

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Background: Alcohol associated liver disease (ALD) which includes cirrhosis and alcohol associated hepatitis (AAH) is a leading indication for liver transplantation. Historically, a 6-month period of abstinence (standard liver transplant, SLT) was mandated by most transplant centers. Several studies have demonstrated similar post-liver transplant outcomes (patient and graft survival) in those undergoing LT without a mandated period of abstinence, leading to a shift in practice towards offering early liver transplant (ELT) in selected individuals. However, there is limited knowledge about post-liver transplant resource utilization in ELT. We conducted this study to compare post-LT resource utilization after ELT and SLT in ALD. **Aim:** A retrospective cohort study to assess post-LT

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resource utilization in ALD patients who underwent ELT compared to SLT. **Methods:** Patients who underwent deceased donor liver transplant at the University of Maryland Medical Center for ALD between January 1st 2014 and December 31st 2019 were included. ALD was defined as alcohol associated cirrhosis or alcohol associated hepatitis as primary indication for LT. Exclusion criteria included previous liver or multi-organ transplant, current multiorgan transplant, HIV and those with unknown date of last drink. Data on demographics, co-morbidities and severity of liver disease were collected. ELT was the exposure, defined as less than 180 days of alcohol abstinence. Post-LT hospital length of stay less than or more than 14 days and 30-day readmission were used as surrogate markers for post-LT resource utilization. SAS software was used for data analysis. **Results:** The total cohort included 176 subjects, 111 underwent ELT. The mean age was 47 years (SD 11.4) in the ELT group compared to 58 years (SD 6.9) in the SLT group (p <0.02). Race distribution was comparable among the groups with the majority being White. No significant differences between the two groups were seen in terms of gender, race, diabetes mellitus or BMI. We selected diabetes mellitus and BMI as the most relevant comorbidities for further analysis. The mean MELD-Na score was 33 (SD 8) in the ELT group compared to 26 (SD 9) in the SLT group (Table 1). The odds of prolonged hospital length of stay were comparable between the two groups (OR 1.6, 95% CI 0.88-3.02) even after adjustment for age and MELD-Na (OR 1.3, 95% CI 0.6-2.8). Similarly, the odds of 30-day readmission were not different between the two groups (OR 1.59 95% CI 0.76-3.3), even after adjustment for age and MELD-Na (OR 1.4 95% CI 0.59-3.34). **Conclusion:** In this population, our data did not suggest prolonged post-LT hospital stay or 30-day readmission in those undergoing ELT compared to SLT. This is an important consideration in the decision-making underlying selection for LT in patients with alcohol associated liver disease.

Table 1: Baseline characteristics of the study cohort.

Characteristic	All subjects	ELT (n=111)	SLT (n=65)	p- value
Age	51 +/-11.3	47 +/- 11.25	51 +/- 11.25	<0.02*
Male	113 (64%)	67 (60%)	46 (71%)	0.19
Race				
White	156 (89%)	100 (90%)	56 (86%)	ref
Black	13 (7%)	7 (6%)	6 (9%)	0.24
Asian	5 (3%)	3 (3%)	2 (3%)	0.49
Hispanic	2 (1%)	1 (1%)	1 (2%)	0.99
BMI	27+/-6.7	26.6 +/- 7.5	27.6 +/- 5.3	0.47
Diabetes mellitus	28 (16%)	10 (9%)	18 (28%)	0.74
MELD-Na	31 +/-9	33+/-8	26 +/-9	<0.0001*

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2582 | SURVIVAL OUTCOMES FOR LIVING VERSUS DECEASED DONOR LIVER TRANSPLANTATION FOR PSC: A 2 DECADE MULTICENTER EXPERIENCE

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Background: Expanding the donor pool through living donor liver transplantation (LDLT) is important given the traditional deceased donor liver transplantation (DDLT) pool is insufficient to meet the demand for LT. While data on long term outcomes after LDLT for PSC are limited, a recent large study suggested a higher mortality after LDLT for PSC over a 15 year follow up. We aimed to compare long term survival outcomes after LT for PSC in large transplant centers, and evaluate the causes of graft failure (GF) and death. **Methods:** 439 patients from 3 academic centers underwent LT for PSC between 1/1/02 and 12/31/22. Children (< 18 yr), patients with a diagnosis of cholangiocarcinoma or hepatocellular carcinoma, and those with prior LT were excluded. Kaplan-Meier (KM) survival analysis and log-rank comparisons were performed. **Results:** Eighty-three (19%) of recipients received LDLT. LDLT patients were younger (44.2±14.8 vs. 51.2±13.3 yr; p<0.0001), and had lower MELD/MELD-Na at transplant (18.1±5.4 vs. 22.7±7.1; p<0.0001). Recipient sex and BMI were not different (63.9% vs. 64.9% male, and 24.9±4.4 vs. 26.1±5.4). Overall survival at 1, 5, 10 and 15 years were 96.3%, 93.4%, 89.7% and 70.5% after LDLT, and 95.9%, 90%, 80% and 67% after DDLT. Graft survival at 1, 5, 10 and 15 years were 92.7%, 88.5%, 82.5% and

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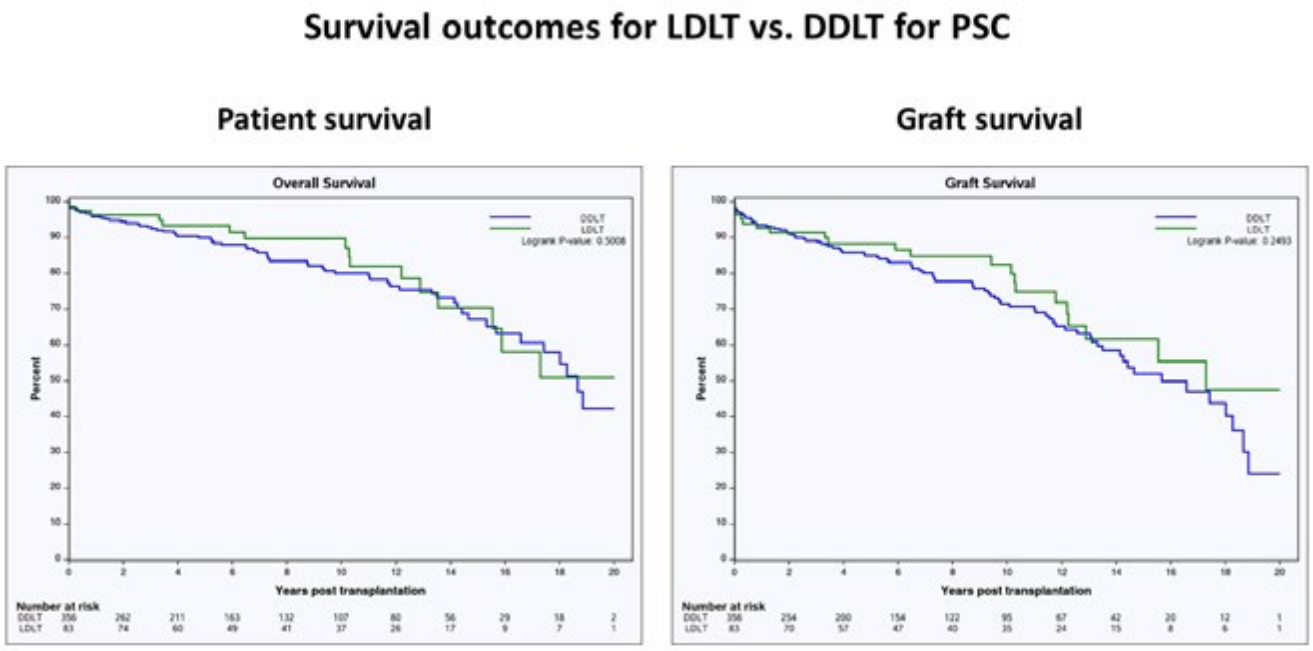
61.6% after LDLT, and 93.5%, 84.9%, 71.6% and 52.1% after DDLT. After 20 years, overall survival was 50.9% in the LDLT group vs 42.4% in the DDLT group, and graft survival was 47.5% vs. 24.1%. KM patient and graft survival distributions were not statistically different between the two groups (log-rank p=0.501 and p=0.251, respectively) (Figure). GF was due to higher rates of graft rejection (9.4% vs 6.6%), vascular (23.8% vs. 15.4%) and biliary complications (9.5% vs. 0%) following LDLT compared to DDLT, but due to lower rates of PSC recurrence (4.7% vs. 25.5%) post LDLT. Top causes of death related to malignancy included: PTLD (4/65 in DDLT vs. 0 in LDLT), pancreatic (3/65 in DDLT vs. 1/16 in LDLT), colon (3/65 in DDLT vs 0 in LDLT) and head and neck (3/65 in DDLT vs 1/16 in LDLT). **Conclusion:** Patients with PSC who underwent LDLT had excellent survival outcomes after 20 years, similar to patients who underwent DDLT, despite having higher rates of rejection, vascular and biliary complications. Patients who underwent LDLT for PSC experienced less GF due to PSC recurrence and less PTLD. LDLT for PSC is associated with excellent outcomes and should help expand the donor pool.



Disclosures: Omar Mousa: Nothing to Disclose, Kymberly Watt: Madrigal: Stock - publicly traded company, Viking: Stock - publicly traded company, Julie Heimbach: Nothing to Disclose, Andrew Keaveny: BioVie Inc: Grant/Research Support, River 2 Renal Corporation: Grant/Research Support, HepQuant LLC: Grant/Research Support, Denise Harnois: Nothing to Disclose, Burcin Taner: Nothing to Disclose, Michael Leise: Nothing to Disclose, Elizabeth Carey: Nothing to Disclose, Adyr Moss: Nothing to Disclose, Timucin Taner: Nothing to Disclose

2583 | LIVER TRANSPLANTATION FOR WILSON DISEASE: A SPECTRUM FROM ACUTE LIVER FAILURE TO NEURO-WILSON

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Background: Wilson disease (WD) is a rare autosomal recessive disorder of copper metabolism characterized by excess copper accumulation in various organs. Patients may present with abnormal liver function tests, symptoms related to chronic liver disease, acute liver failure (ALF), or neuropsychiatric symptoms. In this study, we aim to evaluate the outcomes of liver transplantation (LT) for patients with WD at a large liver transplant center. **Methods:** From our prospectively collected database, we obtained data on patients who underwent LT

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for WD from January 2001 to December 2022 at our hospital. We collected data on demographics, indications for LT, prior treatment, and survival outcomes. Additionally, we gathered data related to WD, such as genetic testing results, presence of Kayser-Fleischer rings, ceruloplasmin levels at presentation, 24-hour urine copper levels, and presence of hemolysis at the time of transplantation. Furthermore, we obtained information on various disease presentations, including decompensated liver disease, ALF, and the presence of CNS manifestations of Wilson disease (Neuro-Wilson). For the latter, we assessed changes in neurological manifestations post-liver transplantation. **Results:** Thirty-four patients underwent LT for WD with a median age of 22.2 years at the time of transplantation, and 17 (50%) were female. Half of patients had living donor LT. The median MELD score at LT was 23, with six patients (18%) presenting with ALF. Genetic testing was obtained in 8 (23.53%) patients, all of whom were homozygous for ATP7B. Seven patients had Neuro-Wilson, and 5 of them (71%) showed improvement in their CNS status post-transplantation based on the Unified Wilson's Disease Rating Scale score. The 1-, 5-, and 10-year survival rates were 94%, 94%, and 82%, respectively. No patients in the cohort required re-transplantation. Ten patients (31%) experienced at least one episode of acute cellular rejection. **Conclusion:** Liver transplantation for patients with Wilson disease demonstrated excellent long-term survival rates irrespective of disease presentation. Our study showed significant improvement in neurological symptoms for those with Neuro-Wilson.

Parameters	Overall
	34 (100%)
Age, median at diagnosis (IQR), years	18.5(54.8 – 65.6)
Age, median at transplantation (IQR), years	22.5
Female sex, n (%)	17 (50)
BMI, mean (SD) kg/m2	22.2 (4.39)
MELD at transplantation, median	23
Acute liver failure on presentation, n (%)	6 (17.6)
Hemolysis at presentation, n (%)	4 (11.76)
Genetic testing for ATP7B, n (%)	8 (23.53)
KF Ring, n (%)	7 (20.59)
Chronic liver disease related complications	
Ascites, n (%)	*22 (66.67)*
Encephalopathy, n (%)	*12 (37.5)*
HCC, n (%)	*1 (2.94)*
CKD, n (%)	*6 (17.65)*
PA pressure > 25 based on TTE, n (%)	*8 (24.24)*
Treatment prior to liver transplantation	
Penicillamine, n (%)	*13 (38.23)*
Trientine, n (%)	*10 (29.4)*
Zinc, n (%)	*16 (47.06)*
Autoimmune markers	
ANA, n (%)	*9 (26.47)*
ASMA, n (%)	*16 (47.06)*
AMA, n (%)	*0*

Disclosures: Saad Alghamdi: Nothing to Disclose, Ibrahim Alomar: Nothing to Disclose, Dimitri Raptis: Nothing to Disclose, Khalid Bzeizi: Nothing to Disclose, Ali Albenmousa: Nothing to Disclose, Bandar Aljudaibi: Nothing to Disclose, Abeer Alabdullah: Nothing to Disclose, Saleh Alqahtani: Nothing to Disclose, Wejdan AlOtaibi: Nothing to Disclose, Dieter Broering: Nothing to Disclose, Waleed Al Hamoudi: Nothing to Disclose

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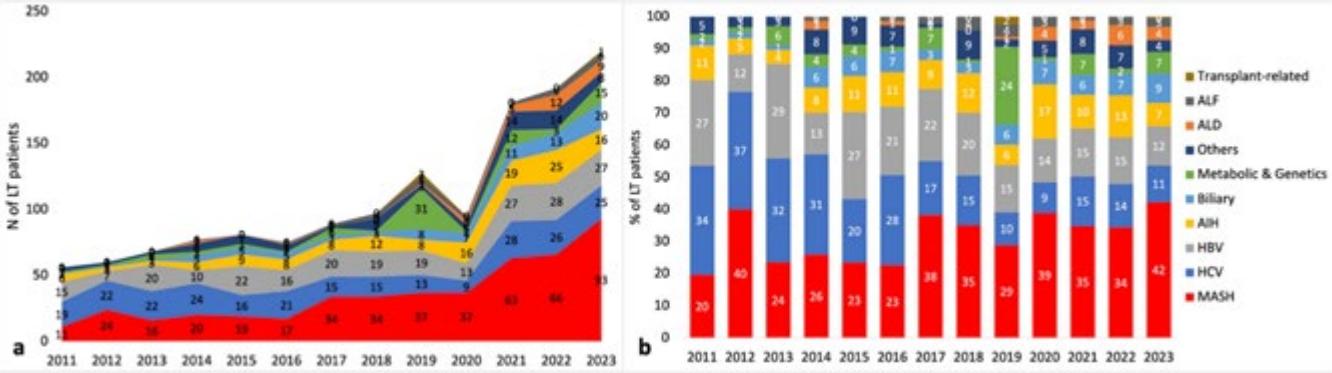
2584 | METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS EMERGES AS THE LEADING CAUSE FOR ADULT LIVER TRANSPLANTATION IN SAUDI ARABIA: A SINGLE-CENTER STUDY ◆

Saleh Alqahtani[1] *Shadan Almuhaidib*[1] *Dimitri Raptis*[1] *Waleed Al-Hamoudi*[1] *Dieter Broering*[1] *Saad Alghamdi*[1]

[1]*King Faisal Specialist Hospital and Research Center*

Background: Liver transplantation (LT) represents the ultimate cure for patients with advanced liver disease. In recent years, indications for LT have shifted from viral hepatitis to fatty liver disease, which is primarily driven by the availability of potent hepatitis C virus (HCV) treatment and the sharp rise in fatty liver diseases, such as metabolic dysfunction-associated steatohepatitis (MASH). **Methods:** We conducted a retrospective analysis of adult LT patients from 2011 to 2023 at a tertiary referral center in Saudi Arabia. We analyzed demographic details, LT indications, model for end-stage liver disease (MELD) scores, donor type, and survival outcomes. Survival rates were calculated using Kaplan-Meier, compared with log-rank tests, and hazard ratios (HR) were estimated using Cox regression models. **Results:** A total of 1419 patients underwent LT during the study period. The median age was 56.9 years (interquartile range [IQR]: 46.3–63.2), 20% were aged ≥65 years, and 37% were female. Living donor LT (LDLT) represented 80%, with hepatocellular carcinoma in 22%. MASH was the predominant LT indication (33%), showing a 10-fold increase from 2011 to 2023, followed by HCV (18%) and hepatitis B (HBV) cirrhosis (17%). Overall patient survival rates at 1, 2-, 3-, 5-, and 10-year post-transplantation were 88%, 85%, 82%, 78%, and 71%, respectively, and graft survival rates 88%, 85%, 82%, 77%, and 70%, respectively. The stratified analysis revealed significant differences across primary indications, with MASH showing lower rates. Patient survival rates at 1 and 10 years were as follows: HBV (93% and 86%), HCV (87% and 66%), and MASH (87% and 65%) ($p < 0.001$). Similarly, graft survival rates at 1 and 10 years, stratified by primary indications, were HBV (92% and 83%), HCV (87% and 66%), and MASH (79% and 65%) ($p = 0.009$). HR for mortality was lower in patients with HBV compared to MASH (HR: 0.44, 95% confidence interval [CI]: 0.28–0.69, $p < 0.001$), and higher in patients aged ≥65 years (HR: 1.37, 95% CI: 1.02–1.84, $p = 0.036$), diabetes (HR: 1.33, 95% CI: 1.03–1.73, $p = 0.029$), and increased MELD score (HR: 1.02, 95% CI: 1.00–1.04, $p = 0.022$). LDLT was associated with reduced mortality risk (HR: 0.68, 95% CI: 0.51–0.92, $p = 0.013$). **Conclusion:** MASH represents the leading indication for LT in this large cohort of patients. This necessitates that healthcare agencies provide more measures for the prevention and early detection of liver diseases.

Figure 1: a. Number of liver transplant patients by primary indication, 2011–2023. **b.** Percentage of liver transplant patients by primary indication, 2011–2023.



Abbreviations: AIH, autoimmune hepatitis; ALD, alcoholic liver diseases; ALF, acute liver failure; HBV, hepatitis B virus; HCV, hepatitis C virus; LT, liver transplant; MASH, metabolic dysfunction-associated steatohepatitis; N, Number; %, percentage.

Disclosures: Saleh Alqahtani: Nothing to Disclose, Shadan Almuhaidib: Nothing to Disclose, Dimitri Raptis: Nothing to Disclose, Waleed Al-Hamoudi: Nothing to Disclose, Dieter Broering: Nothing to Disclose, Saad Alghamdi: Nothing to Disclose

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2585 | FEATURES OF A VERY LONG-TERM SURVIVAL AFTER LIVER TRANSPLANTATION IN ITALY: A PRELIMINARY SINGLE CENTER EXPERIENCE

Maria Donato[1] Clara Dibenedetto[1] Enrico Sguazzini[1] Michele Sagasta[1] Barbara Antonelli[1] Elisa Farina[1] Federica Invernizzi[1] Lucio Caccamo[1] tullia maria de feo[1] Pietro Lampertico[1]

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Background: Liver transplant (LT) is recognized as a standard therapy for curing liver diseases since 1983, when many LT-programs started worldwide. Donor (D), recipient (R) and transplant factors (TFs) had shown a significant impact on LT-recipient's outcome overtime, together with technological and therapeutic evolution. Our aim was to evaluate post-transplant long-term survival **Methods:** All consecutive adult patients transplanted at Ospedale Maggiore Policlinico (Milan-Italy 1983-2004) were enrolled. Long-term survivors (LTSs), defined as transplant R living ≥20 yrs, were compared with patients unable to reach this F-up length (non-LTSs). Data collected included D/R/TFs. A multivariate logistic regression model was used to identify factors independently associated with survival **Results:** 436 patients were included in the study (males= 292), median age=47yrs. HBV±HDV/HCV etiology=63%, Autoimmune (AILD)=15%, ASH/cryptogenic/other=22%; 68% had decompensated cirrhosis, 20% had HCC, 8% FHF. CNI-based immunosuppression ± AZA/MMF was used. LTSs were 189 while 247 were classified as non-LTSs. By univariate analysis, LTSs were more often females, younger, received younger D-graft, more commonly transplanted for HBV±HDV and ALD. HCV and ASH/cryptogenic/other were more frequent in non-LTSs. Combined-immunosuppression was more commonly used in non-LTSs, more often developing kidney impairment and diabetes. Overall, a median F-up of 16 yrs was observed (LTSs=24 vs non-LTSs=3yrs, p<0.05). By Kaplan-Meier curves 79, 60, 43 and 26% of LT-R were alive at 1-10-20-30 yrs, notably 1-yr mortality was deeply affected by LT era (see Figure). According to etiology the estimated survival of AILD and HBV±HDV-R was significantly higher compared to HCV and ASH/cryptogenic/other. By Cox regression analysis, R-age (HR 1.05, 95% CI 1.02-1.07), D-age (HR 1.02, 95% CI 1.01-1.03), etiology (HR 1.38, 95% CI 1.13-1.70), CKD (HR 1.59, 95% CI 1.03-2.47) and diabetes (HR 1.87, 95% CI 1.18-2.95) were independently associated with survival. Transplant-related events and recurrent diseases were more frequently the cause of death in non-LTSs compared to LTSs group (61% vs 38%, p=0.01) while LTSs more often died for liver-unrelated complications (62% vs 39%, p=0.01) **Conclusion:** Our study showed a very long-term survival particularly in the setting of AILD and HBV±HDV LT-R. While HBV±HDV LT-R benefited from the early advent in the '90s of anti-HBV prophylaxis, HCV LT-R showed unfavorable outcome due to late availability of anti-HCV drugs.

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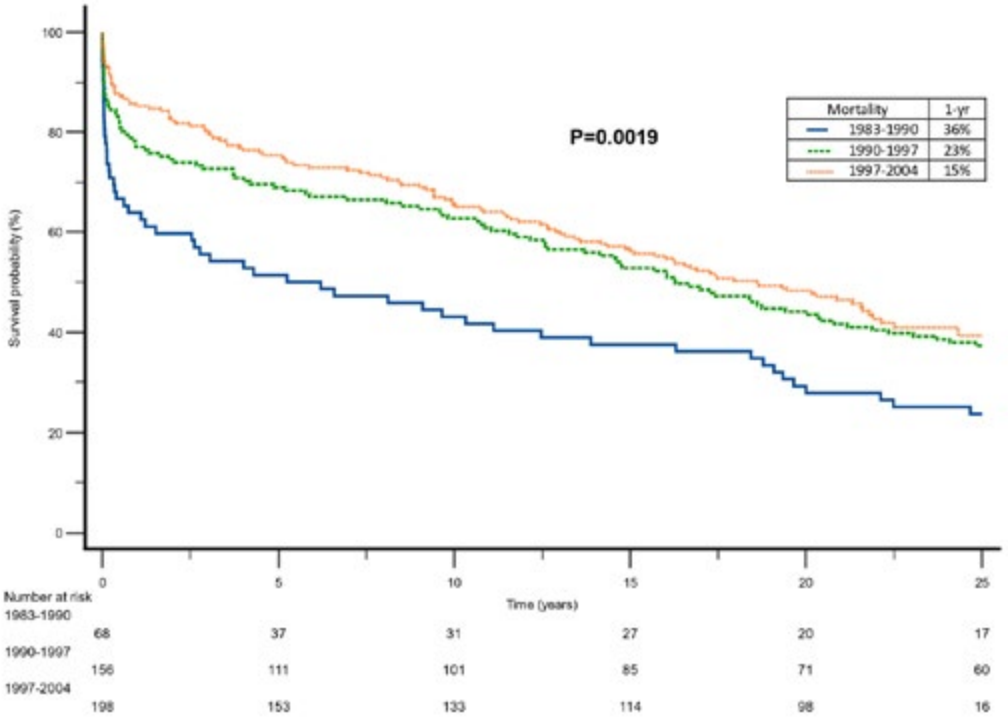
Figure. Overall survival curve according to different eras of transplant.



Disclosures: Maria Donato: Nothing to Disclose, Clara Dibenedetto: Nothing to Disclose, Enrico Sguazzini: Nothing to Disclose, Michele Sagasta: Nothing to Disclose, Barbara Antonelli: Nothing to Disclose, Elisa Farina: Nothing to Disclose, Federica Invernizzi: Nothing to Disclose, Lucio Caccamo: Nothing to Disclose, tullia maria de feo: Nothing to Disclose, Pietro Lampertico: ROCHE PHARMA/DIAGNOSTICS, GILEAD SCIENCES, GSK, ABBVIE, JANS: Advisor

2586 | NEUROCOGNITIVE IMPAIRMENT IN LIVER TRANSPLANT (LT) RECIPIENTS: COMPREHENSIVE COGNITIVE EVALUATION

Kacey Berry[1] Fawzy Barry[2] Elena Tsoy[2] Jonathan Tablante[2] Anne-Marie Rodriguez[2] Randi Wong[2] Srilakshmi Seetharaman[2] Sara Lahue[2] Julio Rojas[2] Lawren VandeVrede[2] Jennifer Lai[2]

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Background: Patients with cirrhosis manifest a broad spectrum of neurocognitive impairment that is typically attributed to hepatic encephalopathy (HE) and thought to be fully reversible with LT. Yet, a few studies using brief cognitive screening tools have found high rates of cognitive impairment *after* LT, suggesting long-term sequelae of pre-LT factors or previously-masked underlying cognitive disorder. We therefore comprehensively characterized cognitive profiles of LT recipients to identify factors contributing to cognitive impairment. **Methods:** Adults with a history of cirrhosis who received LT >6 months prior were screened for cognitive impairment via TabCAT Brain Health Assessment (BHA). 20 patients (10 BHA-positive/10 BHA-negative) were enrolled for comprehensive cognitive phenotyping via the National Alzheimer's Disease Research Center protocol: patient and caregiver interview, neuropsychological and neurologic examinations, and brain MRI. Presence of neurocognitive disorder (NCD) using DSM-5 criteria, potential etiologies, and salient risk factors were determined by consensus review (neurologist, neuropsychologist, and hepatologist blinded to BHA). Neuropsychological data were transformed into domain-specific composites (averaging age-, sex-, and education-adjusted Z-scores). MRIs were read by expert neuroradiologist. results were tabulated; descriptive statistics were used given exploratory design and small sample size. **Results:** Among all participants, mean age=61y±6 (mean±SD), 40% female, mean

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education=14±4 y, and mean BHA=-1.2±1.1 [≥ -1.5 = “unimpaired”]. MRI showed 75% had vascular disease; 35% had atrophy beyond expected for age. 60% (N=12) met criteria for NCD: N=10 for minor NCD and N=2 for major NCD. Those w/ vs w/o NCD were younger (59±4 vs. 64±8 y), more often men (67% vs 50%), and further from LT (39±21 vs. 29±12 mos). Those w/ vs w/o NCD had lower BHA scores (-1.6±1.0 vs. -0.5±0.9) and lower scores in all cognitive domains, especially executive functioning (-1.1± 0.4 vs. -0.2±0.7). Neither pre-LT factors (MELDNa, pre-LT HE) nor post-LT factors (MRI pathology) were found to be higher in those w/ vs. w/o neurocognitive disorder. Despite a high prevalence of multiple potential contributors to cognitive impairment in this population, no single etiology was fully explanatory for cognitive symptoms across the cohort. **Conclusion:** Comprehensive cognitive phenotyping of 20 LT recipients identified that 60% of LT recipients met formal criteria for neurocognitive impairment. Our findings highlight the need for detailed investigation of post-LT cognitive impairment and its etiologic factors, to develop clinical algorithms and interventions targeting cognitive impairment in this population.

Characteristics		All *n=20 (100%)*	By Cognitive Status: With Neurocognitive disorder *n=12 (60%)*	By Cognitive Status: Without Neurocognitive disorder *n=8 (40%)*
Age, years		61 (6)	59 (4)	64 (8)
Male Sex at birth		60%	33%	50%
Education, years		14 (4)	14 (4)	14 (2)
Race	Non-Hispanic White	50%	67%	25%
	Black	5%	0%	1%
	Asian	15%	8%	25%
	Hispanic	30%	25%	38%
MELDNa at transplant		22 (12)	22 (3)	22 (4)
Creatinine, mg/dL[†]		1.2 (0.6)	1.1 (0.7)	1.4 (0.5)
History of Hepatic Encephalopathy		56%	58%	50%
Hypertension		35%	33%	38%
Diabetes		15%	0%	38%
Coronary Artery Disease		5%	0%	13%
Etiology of liver disease	EtOH	15%	8%	25%
	Chronic hepatitis C	20%	25%	13%
	Chronic hepatitis B	10%	8%	0%
	Non-alcoholic fatty liver disease	25%	8%	50%
	Autoimmune/ cholestatic	20%	33%	33%
	Other	10%	17%	0%
Time since transplant, months		35 (18)	39 (21)	29 (12)
TabCAT-BHA Cognitive Score		-1.2 (1.1)	-1.6 (1.0)	-0.5 (0.9)
MMSE (≥26 = “unimpaired cognition”)		28 (2)	28 (2)	28 (2)
Participant concern for cognitive disorder in self		65%	58%	75%
Caregiver concern for cognitive disorder in patient		60%	66%	50%
Domain-specific composite Z score **	Memory	-0.2 (0.6)	-0.3 (0.7)	0.0 (0.3)
	Executive function	-0.7 (0.7)	-1.1 (0.4)	-0.2 (0.7)
	Attention	-0.7 (0.8)	-0.8 (0.9)	-0.4 (0.6)
	Speed	-0.6 (0.9)	-0.8 (1.0)	-0.3 (0.7)
	Visuospatial function	-0.7 (1.6)	-1.1 (2.1)	-0.1 (0.3)
	Language	-0.4 (1.0)	-0.7 (1.1)	0.1 (0.6)
Factors contributing to neuro-cognitive disorder	Vascular disease	80%	75%	88%
	Traumatic Brain Injury	35%	33%	38%
	Early learning difficulty	30%	42%	13%
	Psychiatric co-morbidity	70%	67%	75%
	Hx of substance use	30%	42%	13%
	Sleep disorder	60%	50%	75%
	Medication effect	25%	33%	13%
Brain MRI pathology	Microvascular disease (mild or moderate)	75%	58%	100%
	Atrophy (mild or moderate)	35%	25%	50%
	Structural (eg stroke)	10%	8%	13%

* Mean (standard deviation) or %; † Among those who were not on dialysis; ** Z score = SD from expected mean for age, sex and education.
Abbreviations: Model of End-Stage Liver Disease Sodium, MELDNa; Tablet-based Cognitive Assessment Tool-Brain Health Assessment, TabCAT-BHA (PMCID: PMC7306617, PMCID: PMC10942726); Mini-Mental State Examination, MMSE; Magnetic resonance imaging, MR

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2587 | IMPACT OF EARLY MTOR INHIBITOR IMMUNOSUPPRESSIVE THERAPY FOLLOWING LIVER TRANSPLANTATION: ENHANCEMENT OF GLOMERULAR FILTRATION RATE

Sidart Pradeep[1] Saleh Elwir[2] Cynthia Arriaga[1] Genita Adkins[1] cindy petty[1] Richard Ruiz[1] Gregory McKenna[1] Stevan Gonzalez[1]

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Background: In contrast with calcineurin inhibitors (CNI), mTOR inhibitors (mTORi) are not associated with nephrotoxicity. Although mTORi have been evaluated in combination with CNI in reducing the long-term risk of nephrotoxicity, studies on early transition to mTORi-based immunosuppressive regimens among liver transplant (LT) recipients are limited. **Methods:** An immunosuppression protocol of early conversion to mTORi with discontinuation of CNI at 12 weeks was initiated in all eligible LT recipients. A retrospective chart review was performed on consecutive LT recipients at Baylor Scott & White All Saints Medical Center Fort Worth from 2018-2022. Analysis was performed to identify barriers to mTORi conversion, assess tolerability, and evaluate the effects of mTORi-based therapy on post-LT estimated glomerular filtration rate (eGFR) defined by the GRAIL equation. **Results:** Of 177 LT recipients, 131 (74.0%) underwent conversion from CNI to mTORi therapy. Among the 131 who converted to mTORi (77% everolimus, 23% sirolimus), 100 (76.3%) converted within 6 months of LT (early conversion). Biliary complications (17.4%), proteinuria (15.2%), and leukopenia (15.2%) most frequently limited eligibility for conversion to mTORi among the 46 who maintained CNI therapy. The majority who converted to mTORi maintained therapy for ≥1 year (79/131, 60.3%). Two-year follow up data were available in 94.4% (median follow up 3.7 yrs, range 4 months to 6 yrs); 13 deaths, 7 received kidney after LT. Among patients with 2-year data who underwent early conversion to mTORi (n=93), those who maintained therapy for ≥1 year experienced improvement in eGFR with a reduction in chronic kidney disease (CKD) stage (29.8% vs 11.1%, p=0.04), particularly among those with 12-week eGFR <60 mL/min/1.73m^2 (57.1% vs 7.7%; p<0.001; Figure). An increase in eGFR from 12 weeks to 2 years post-LT was observed among patients who converted to mTORi and maintained therapy ≥1 year vs <1 year (median 6.8% increase vs 1.7%, p=0.03). Years duration of mTORi-based therapy predicted a reduction in CKD stage at 2 years post-LT among all who received mTORi (OR 1.26; 95% CI 1.01-1.57; p=0.05) and especially among those who underwent early conversion (OR 1.41; 95% CI 1.08-1.85; p=0.01). **Conclusion:** Overall, the majority of LT recipients underwent conversion to mTORi and most were able to convert at an early time point as well as maintain therapy ≥1 year. Early conversion to mTORi with discontinuation of CNI within 6 months post-LT and the subsequent duration of mTORi-based therapy were associated with improvement in eGFR at 2 years post-LT. In particular, mTORi-eligible LT recipients with eGFR <60 mL/min/1.73m^2 by 12 weeks post-LT may benefit most from early conversion. These data suggest a targeted approach to immunosuppression therapy with early use of an mTORi-based regimen could optimize the trajectory of post-LT GFR among at-risk individuals.

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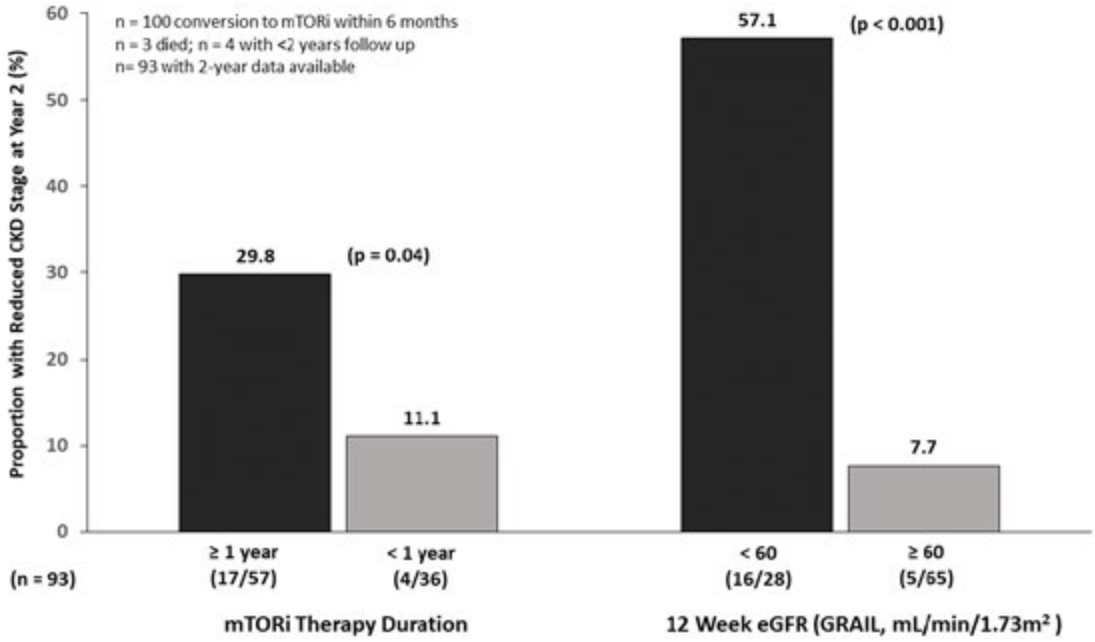

Disclosures: Sidart Pradeep: Nothing to Disclose, Saleh Elwir: Nothing to Disclose, Cynthia Arriaga: Nothing to Disclose, Genita Adkins: Nothing to Disclose, cindy petty: Nothing to Disclose, Richard Ruiz: Nothing to Disclose, Gregory McKenna: Nothing to Disclose, Stevan Gonzalez: Nothing to Disclose

2588 | UTILIZATION OF DONATION AFTER CIRCULATORY DEATH LIVER GRAFTS BY PROCUREMENT TYPE AND STORAGE MODALITY: A COMPARISON OF CARDIAC AND NON-CARDIAC DONORS IN THE US

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Background: Utilization of donation after circulatory death (DCD) liver grafts has evolved with in situ and ex sit machine perfusion technology. In the US, in situ perfusion, or normothermic regional perfusion (NRP) is mostly provided by cardiac recovery centers while ex-situ machine perfusion (es-MP) is available for any DCD graft. We evaluated how these technologies are used for liver grafts across the US in cardiac and non-cardiac DCD donors. **Methods:** All adult (≥ 18 years old) DCD donors in which the liver was used for transplantation in the US from October 1, 2020, to September 30, 2023, categorized by cardiac versus non-cardiac donor and then by procurement technique (NRP versus super rapid recovery [SRR]) and storage strategy (es-MP versus static cold storage [SCS]). **Results:** 84 centers transplanted at least one liver graft from a cardiac DCD donor. Of these, 40 used both NRP and SRR donors, 14 exclusively used NRP donors, and 30 exclusively used SRR donors. Of the 29 centers that did more than 5 DCD liver transplants during the study period, 28 (97%) transplanted livers from both NRP and SRR DCD donors. 27 (32%) centers used a combination of es-MP and SCS, 2 (2%) used es-MP only (one that did one transplant and one that did 2 transplants) and 55 used SCS only. 100 centers transplanted at least one liver graft from a non-cardiac DCD donor, 33 used both NRP and SRR donors, 1 used only NRP, and 66 used only SRR. 55 used es-MP for at least 1 graft while 45 used SCS only. **Conclusion:** Perfusion technologies are increasingly being used for DCD liver grafts. In the US, cardiac DCD donors use NRP with SCS more commonly while non-cardiac donor liver grafts use es-MP more commonly. This is likely due to the limited availability of NRP for noncardiac donors. There is an opportunity to further expand the utilization of liver grafts from non-cardiac donors by increasing the availability of NRP for DCD donation.

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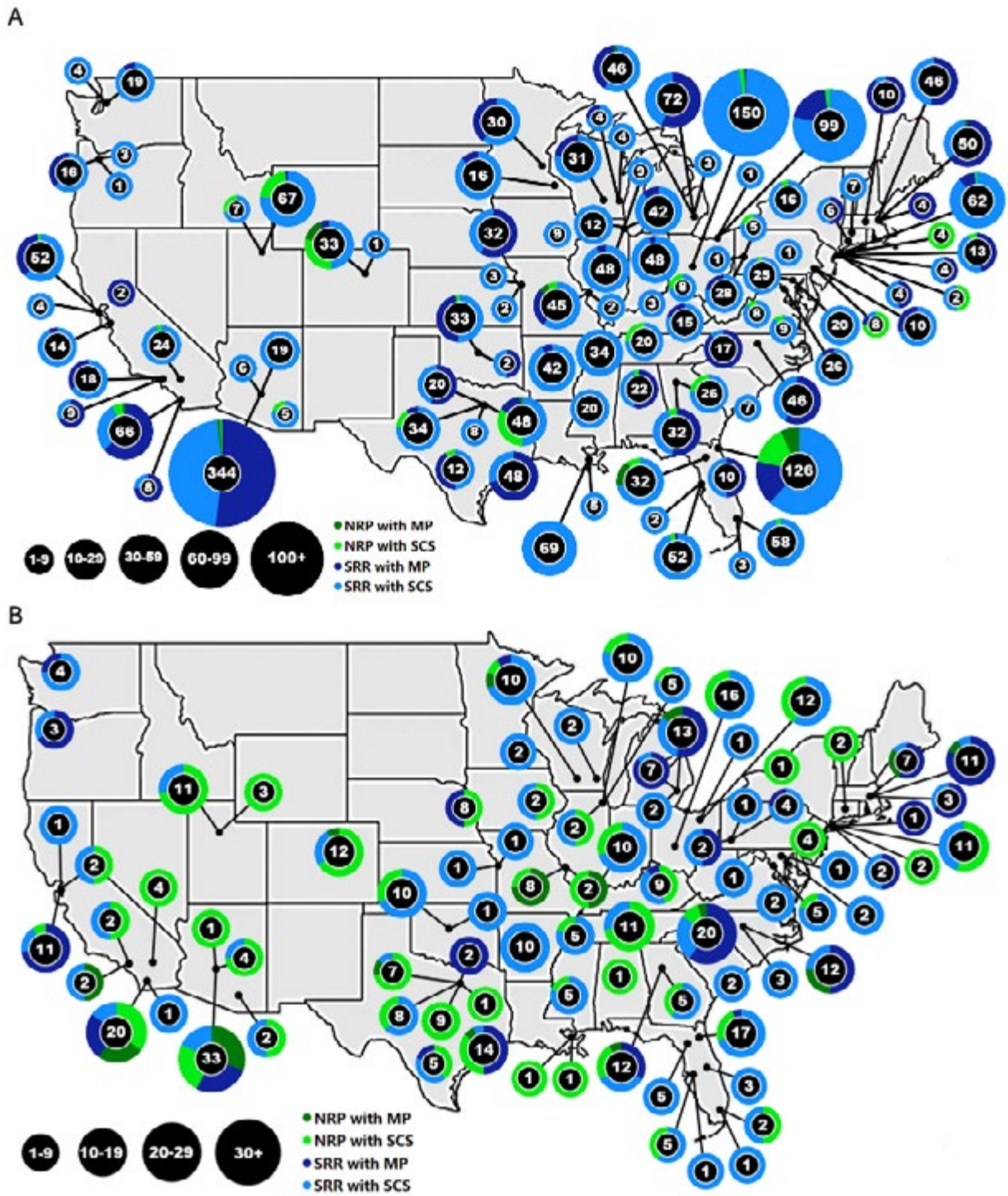

Disclosures: Anji Wall: Nothing to Disclose, Matthew Snoddy: Nothing to Disclose, Jinyu Du: Nothing to Disclose, Johanna Bayer: Nothing to Disclose, Sebastian Danobeitia: Nothing to Disclose, Amar Gupta: Nothing to Disclose, Seung-Hee Lee: Nothing to Disclose, Eric Martinez: Nothing to Disclose, Giuliano Testa: Nothing to Disclose

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2589 | EXTENDED CRITERIA DONORS IN DONATION AFTER CIRCULATORY DEATH: CAN ABDOMINAL NORMOTHERMIC REGIONAL PERFUSION SAFELY EXPAND THE DECEASED DONOR POOL?

Philippe Paci[1] Brian Cook[1] Randi Ryan[1] Ivan Zendejas[1] Richard Gilroy[1] James Trotter[1] Shane Froebe[1] Scott Froebe[1] Alan Contreras Saldivar[1] Gabriel Oniscu[2] Jean Botha[1]

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Background: This study describes the early outcomes of liver transplants at our center after implementation of abdominal normothermic regional perfusion (A-NRP) for controlled donation after circulatory death (cDCD) donors in extended criteria (EC) donors. Prior to implementation of A-NRP, our center did not accept cDCD donors >65 years old. **Methods:** After initiation of A-NRP at our center in August 2023, all liver allografts from cDCD donors were procured using A-NRP. Following IRB approval, donor and recipient data were retrospectively collected. We defined the following warm ischemic time variables as follows. Functional warm ischemic time (fWIT): interval between donor systolic blood pressure <50mmHg and initiation of pump.Total warm ischemic time (tWIT): interval between donor withdrawal and initiation of pump. Standard rapid recovery warm ischemic time (SRR-WIT): interval between donor oxygen saturation <80% or systolic blood pressure <80mmHg and initiation of pump. EC donors were defined as donors >50 years old, with a body mass index >35, or with SRR-WIT > 30min. Donor data included demographics, fWIT, tWIT, total time on A-NRP, and lactate and liver enzymes measured every 30 minutes while on pump. Recipient data included demographics, MELD score at transplant, etiology of liver disease, cold ischemic time, primary non-function, early allograft dysfunction (EAD), ICU and hospital length of stay (LOS) and biliary complications. **Results:** From August 2023 to May 2024, 40 livers were retrieved using A-NRP in cDCD donors from a total of 67 potential cases. 30 allografts were retrieved from EC donors, and 14 allografts (47%) were from donors > 65 years old. Median fWIT was 23 minutes [20-27], median tWIT was 38 minutes [31-50] and the mean time on pump was 128±15 min. Mean recipient age was 59±11 years and median MELD at transplant was 18[16-25]. EAD occurred in 8 patients (27%), there was no PNF, there were only 2 (7%) biliary strictures and no ischemic cholangiopathy has been identified. Median Model for Early Allograft Function (MEAF) score was 4.3[2.9-5.8]. To date no patient has required re-transplantation. Median ICU and hospital LOS were 2[2-3] and 7[6-9] days respectively. The median follow-up was 90 days [57-152]. The summary of results is presented in Table 1. **Conclusion:** This is the largest single-center U.S. case series of liver transplant outcomes from allografts retrieved from EC cDCD donors with A-NRP. The implementation of A-NRP at our center has demonstrated good early graft and patient outcomes similar to experiences described in the United Kingdom and Europe. Our experience suggests that the deceased donor pool could be further expanded using EC donors without increasing complications. Further studies from other U.S. centers are needed to support this in the North American setting.

Table 1. Summary of results

	EC-cDCD Allografts (n=30)
Donor data	
Donors >65 years	14 (47)
fWIT, median [IQR], min	23 [20-27]
tWIT, median [IQR], min	38 [31-50]
Pump time, mean±SD, min	128 ± 15
Recipient data	
Age, mean±SD, years	59 ± 11
MELD, median [IQR]	18 [16-25]
EAD	8 (27)
MEAF, median [IQR]	4.3 [2.9-5.8]
PNF	0
Ischemic cholangiopathy	0
Biliary strictures	2 (7)
ICU LOS, median [IQR], days	2 [2-3]
Hospital LOS, median [IQR], days	7 [6-9]
Follow-up, median [IQR], days	90 [57-152]

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Disclosures: Philippe Paci: Nothing to Disclose, Brian Cook: Nothing to Disclose, Randi Ryan: Nothing to Disclose, Ivan Zendejas: Nothing to Disclose, Richard Gilroy: Abbvie: Speaking and Teaching, Salix: Speaking and Teaching, James Trotter: Nothing to Disclose, Shane Froebe: Nothing to Disclose, Scott Froebe: Nothing to Disclose, Alan Contreras Saldivar: Nothing to Disclose, Gabriel Oniscu: Nothing to Disclose, Jean Botha: Nothing to Disclose

2590 | IMMUNE CHECKPOINT INHIBITORS AFTER LIVER TRANSPLANTATION: A MULTICENTER STUDY

Eleonora De Martin[1] Teresa-Maria ANTONINI[2] Massih Ningarhari[3] Marie-Noel Hilleret[4] Manon Allaire[5] Arnaud Del Bello[6] Giuliana Amaddeo[7] Camille Besch[8] Martine Neau[9] Anais Jaillais[10] Isabelle Ollivier Hourmand[11] Thomas Decaens[4] Filomena Conti[5] Sébastien Dharancy[3] Faouzi Saliba[1] Olivier Rosmorduc[1] Jérôme Dumortier[12] Audrey Coilly[1]

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Background: The use of immune checkpoint inhibitors (ICI) after liver transplantation (LT) is still a matter of debate, given the potential risk of rejection, which can be fatal, reported in about 40% of treated patients. However, the risk factors for rejection have not yet been clearly identified. The aim of the present study was to describe the characteristics of patients treated with immune checkpoint inhibitors after liver transplantation as well as to identify the risk factors for rejection. **Methods:** This is a retrospective, observational, multicenter study which has included adult patients who received an ICI (anti-PD1, anti-PDL1 or anti-CTLA4) after LT for hepatocellular carcinoma (HCC) recurrence or a *de novo* tumor. Tumor therapy and immunosuppression (IS) management was at physician discretion. **Results:** Thirty-five patients were included, 27 (77%) males, median age 60.4 [51.5; 64.3] years. Fourteen (40%) patients were transplanted for alcohol related cirrhosis and 8 (23%) for HCV related cirrhosis, 28 (80%) had an HCC before LT. HCC recurrence was diagnosed in 20 (57%) patients. The median interval time between LT and cancer diagnosis was 3.27 [1.28; 6.94] years: 2.29 [1.07; 3.86] years for HCC recurrence and 6.71 [1.56; 10.6] years for *de novo* cancer (p=0.03). ICI used were: anti-PD1 in 13 (37%) and anti-PDL1 in 22 (63%) patients. The median interval time between LT and ICI introduction was 4.67 (2.97; 9.66) years: 4.04 [2.71; 5.7] years for HCC and 9.42 [4.01; 12.15] for *de novo* cancer (p=0.05). IS was increased a priori in 20 (57%) patients before ICI. The median trough level of tacrolimus was 3.30 [2.90; 6.05] ng/mL with no significant difference in patients who undergone a change in their IS regimen prior ICI (p=0.87). Six (17%) patients developed acute rejection. These patients compared to the ones without rejection were less frequently on tacrolimus (33% vs 83%, p=0.027) and with a trend of being on a single IS drug (67% vs 14%, p=0.065). Moreover, ICI treatment duration was significantly shorter (p=0.026), and the number of injection lower (p=0.021) in patients with rejection (Table 1). Twenty-four (69%) patients died and among them 4 had a fatal rejection. Survival after initiation of ICI was significantly lower in patients who developed acute rejection (p=0.011). However, rejection was not the cause of death in all patients. **Conclusion:** In patients who were treated with ICI after LT, survival is poor due to the progression of the oncological disease. The rejection rate is lower than that reported in the literature (17%), but fatal in the majority of cases. Acute rejection seems to develop rapidly after ICI introduction, particularly in patients on immunosuppression monotherapy and in the absence of tacrolimus. The outcome of this study indicates a need for an increase in immunosuppression prior to the introduction of an ICI.

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Table 1. Characteristics of patients treated with immune checkpoint inhibitors after liver transplantation with and without rejection

	Overall 35	Without rejection 29 (83%)	With rejection 6 (17%)	p
Age, years	60.4 [51.5; 64.3]	61 [50.0; 66.2]	59 [54.3; 60.3]	0.43
Sex, male	27 (77%)	23 (79%)	4 (67%)	0.6
Indication of LT				0.81
Alcohol	14 (40%)	12 (41%)	2 (33%)	
HCV	8 (23%)	6 (21%)	2 (33%)	
Mix	4 (11%)	3 (10%)	1 (17%)	
Other	9 (26%)	8 (28%)	1 (17%)	
HCC	28 (80%)	23 (79%)	5 (83%)	
Interval time between LT and tumor, years	3.27 [1.28; 6.94]	3.74 [1.20; 9.38]	2.52 [1.51; 5.85]	0.75
Type of tumor				1
HCC recurrence	20 (57%)	17 (59%)	3 (50%)	
de novo tumor	15 (43%)	12 (41%)	3 (50%)	
Interval time between LT and ICI, years	4.67 [2.97; 9.66]	5.33 [2.74; 10.4]	3.80 [3.40; 6.70]	0.59
Type ICI				1
Anti-PD1	13 (37%)	11 (38%)	2 (33%)	
Anti-PDL1	22 (63%)	18 (62%)	4 (67%)	
Immunosuppression change before ICI	20 (57%)	18 (62%)	2 (33%)	0.37
Type of immunosuppression before ICI				
Corticosteroids	19 (54%)	17 (59%)	2 (33%)	0.38
Tacrolimus	26 (74%)	24 (83%)	2 (33%)	**0.027**
mTOR inhibitors	19 (54%)	15 (52%)	4 (67%)	0.67
MMF	13 (37%)	12 (41%)	1 (17%)	0.38
Number of immunosuppressors before ICI				0.065
1	8 (23%)	4 (14%)	4 (67%)	
2	15 (43%)	14 (48%)	1 (17%)	
3	9 (26%)	8 (28%)	1 (17%)	
4	3 (8.6%)	3 (10%)	0 (0%)	
T0 tacrolimus before ICI	3,30 [2,90 ; 6.05]	3,30 [2,90; 6.05]	3.45 [2.88; 5.17]	1
Duration of ICI therapy, months	5.50 [2.35; 8.31]	5.92 [3.50; 10.3]	1.58 [0.29; 3.63]	**0.026**
Number of ICI injections	4 [1.50; 7.00]	4.00 [2.25; 8.00]	1.00 [1.00; 2.00]	**0.021**
Death	24 (69%)	18 (62%)	6 (100%)	0.15
Survival after ICI initiation, months	3.72 [1.91; 11.9]	5.10 [2.14; 12.4]	2.81 [1.83; 3.35]	0.12

Disclosures: Eleonora De Martin: Nothing to Disclose, Teresa-Maria ANTONINI: Nothing to Disclose, Massih Ningarhari: Nothing to Disclose, Marie-Noel Hilleret: Nothing to Disclose, Manon Allaire: Nothing to Disclose, Arnaud Del Bello: Nothing to Disclose, Giuliana Amaddeo: Nothing to Disclose, Camille Besch: Nothing to Disclose, Martine Neau: Nothing to Disclose, Anais Jaillais: Nothing to Disclose, Isabelle Ollivier Hourmand: Nothing to Disclose, Thomas Decaens: Nothing to Disclose, Filomena Conti: Nothing to Disclose, Sébastien Dharancy: chiesi: Speaking and Teaching, Faouzi Saliba: Nothing to Disclose, Olivier Rosmorduc: Nothing to Disclose, Jérôme Dumortier: Nothing to Disclose, Audrey Coilly: Nothing to Disclose

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2591 | GEOGRAPHIC DISTRIBUTION OF US DONOR RECOVERY FACILITIES IN RELATIONSHIP TO LIVER TRANSPLANT CENTERS: SHOULD WE RETHINK THE ORIGIN OF DONOR ALLOCATION?

Anji Wall[1] Matthew Snoddy[1] Jinyu Du[1] Johanna Bayer[1] Sebastian Danobeitia[1] Amar Gupta[1] Seung-Hee Lee[1] Eric Martinez[1] Giuliano Testa[1]

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Background: Liver allocation is geographically determined by nautical mile (NM) radii around the 4,300 donor hospitals in the US but many donor recoveries take place in donor recovery facilities (DRFs). This means that the distance from the location where the organ recovery occurs can be different from where the organ allocation takes place, which may lead to longer distances between donors and recipients in some cases, leading to longer cold ischemia times. In this study, we assessed the location of donor recovery facilities in relationship to liver transplant centers in the US to determine how access to organs could change if allocation changed from DRFs rather than donor hospitals. **Methods:** Data for DRFs was obtained from the Organ Procurement & Transplantation Network (OPTN) website via the US Department of Health & Human Services, and the Health Resources & Services Administration (HRSA), and was cross-referenced using Google Maps and direct contact with organ procurement organization staff. Data for Transplant Centers was obtained from the Organ Procurement & Transplantation Network (OPTN) website via the US Department of Health & Human Services, and the Health Resources & Services Administration (HRSA), and was cross-referenced using the Scientific Registry of Transplant Recipients (SRTR). Data for Donor Hospitals, which included facilities with ICU beds and an operating room, was obtained from the United Network for Organ Sharing (UNOS). Connections from Donor Recovery Facilities to Transplant Centers were geocoded at varying radii distances: 150, 250, and 500 nautical miles. **Results:** 27 Donor Recovery Facilities, 121 Transplant Centers, and 4,353 Donor Hospitals were initially geocoded. Focusing on the contiguous United States, data from Alaska, Hawaii, and Puerto Rico was omitted, leaving 27 Donor Recovery Facilities, 119 Transplant Centers, and 4,267 Donor Hospitals to be analyzed. We found that all DRFs are collocated within driving distance (50 NM) of at least one liver transplant center. Only 8 transplant centers fall outside of 250 NM of a DRF. All liver transplant centers are within 500 NM of a donor recovery facility, while all DRFs have at least 9 liver transplant centers within 500 NM. **Conclusion:** If allocation were changed to originate donors at DRFs rather than hospitals where death was declared, there would likely be better geographic efficiency in allocation and given the wide distribution of DRFs, all transplant programs would have access to donors from at least one facility within a 500 NM range, while all DRFs would allocate to at least 9 liver transplant programs within a 500 NM range. However, there may be concerns if donors are moved over far distances but this should be balanced with the alternative of moving multiple procurement teams over large distances. Further research is needed to determine the current state of DRC utilization and how an allocation origination change would impact each transplant center.

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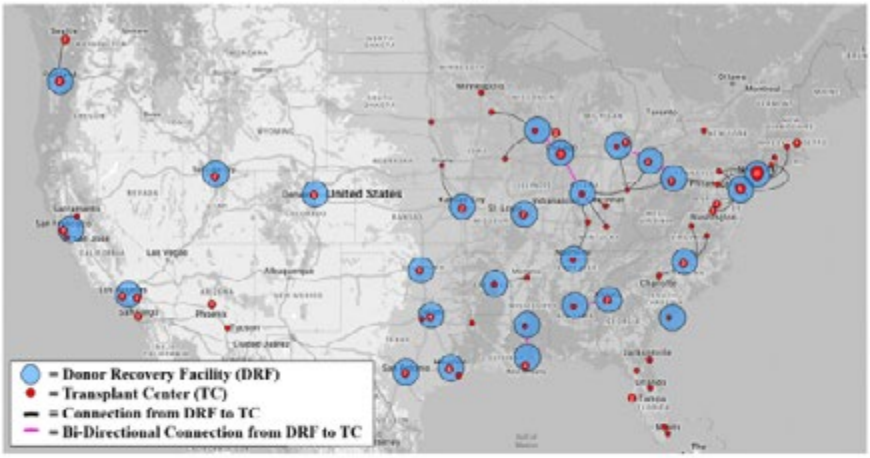
150 Nautical Miles



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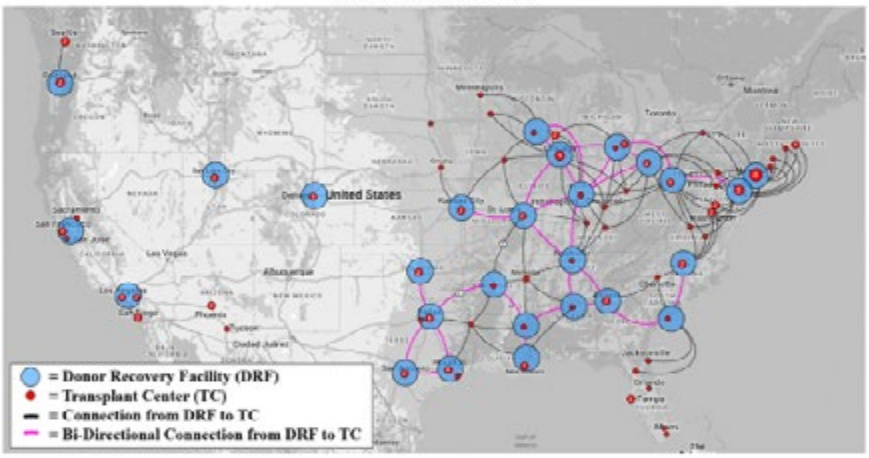

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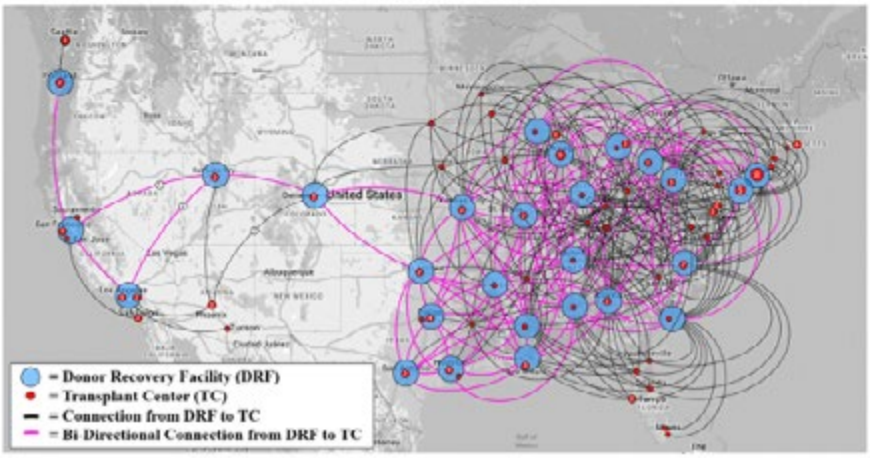

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2592 | ROLES OF MITONEET IN ISCHEMIA/REPERFUSION INJURY OF DIET-INDUCED MOUSE STEATOTIC LIVERS ◆

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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) prevails globally. It remains elusive how steatotic livers become hypersensitive to ischemia/reperfusion (I/R) injury during liver resection and transplantation. mitoNEET (mNT) is a unique homo-dimeric protein located in mitochondrial outer membranes. It is unknown how steatosis and I/R impact mNT. **Methods:** Age-matched male mNT wild type (WT) and knockout (KO) mice were fed either a chow diet (CD) or a high fat diet (HFD: 60 Kcal % fat) for 8 weeks. Isolated hepatocytes and livers were subjected to 2 h of in vitro and 30 min of in vivo ischemia, respectively, brief ischemia inducing minimal injury in lean counterparts. Changes in hepatic injury, mNT, autophagic flux, oxidative stress, and onset of mitochondrial permeability transition (MPT) were assessed after reperfusion. Additionally, whole tissue lysates were prepared from four discarded human steatotic livers deemed unsuitable for transplant. Biopsies from disease-free lean livers were collected from three patients who underwent liver resection. **Results:** Serum levels of alanine aminotransferase (ALT) at 6 and 24 h after reperfusion were greater in HFD livers than in CD livers. Like in vivo I/R, necrosis was significantly higher in HFD hepatocytes after I/R. Heightened I/R injury in HFD WT mice was, however, markedly suppressed in HFD mNT KO mice. Immunoblot analysis revealed that mNT monomer (mNTm), a dysfunctional form of mNT, significantly increased before and after I/R in HFD mouse hepatocytes and livers. Accumulation of mNTm was also evident in human steatotic livers. Confocal microscopy with tetramethylrhodamine methylester, calcein, propidium iodide, and dichlorodihydrofluorescein revealed a rapid burst of reactive oxygen species and onset of MPT in reperfused HFD hepatocytes, which was, however, blocked by mNT deletion. Immunoblot analysis of LC3-II with chloroquine indicated impaired autophagy by chronic overnutrition with HFD, which was reversed by mNT deletion. In some experiments, HFD cells were treated with Pioglitazone, an FDA-approved anti-diabetic drug known to stabilize mNT dimers. This agent significantly reduced the accumulation of mNTm, defective autophagy, and increased cell death in reperfused HFD hepatocytes. **Conclusion:** Accumulation of dysfunctional mNTm in steatotic livers may lead to enhanced oxidative stress, defective autophagy, mitochondrial dysfunction, and severe I/R injury.

Disclosures: Jae-Sung Kim: Nothing to Disclose, Jun-Kyu Shin: Nothing to Disclose, Sung-Kook Chun: Nothing to Disclose, William Chapman: Nothing to Disclose, Yiing Lin: Nothing to Disclose

2593 | AH AND METALD HAVE HIGHER OVERALL SURVIVAL AFTER LIVER TRANSPLANTATION FOR SLD COMPARED TO ALD AND MASLD

Smruti Rath[1] Ashish Bibireddy[1] Ishaan Dharia[2] Thomas Schiano[3] Sander Florman[3] Gene Im[4]

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Background: Steatotic liver disease (SLD) is a new nomenclature that includes alcohol-associated cirrhosis (AC), alcohol-associated hepatitis (AH), metabolic dysfunction-associated liver disease (MASLD), and the newly created metabolic and alcohol-associated liver disease (MetALD). Outcome studies of LT for SLD with biomarker monitoring for disease recurrence and long-term follow-up are lacking. The aim of this study is to examine the clinical characteristics and outcomes, including disease recurrence, in patients undergoing LT for SLD. **Methods:** We performed a retrospective cohort-comparison study of patients who underwent LT for SLD at Mount Sinai Hospital from 1/1/2012-1/1/2023. Demographic and clinical data were analyzed. The primary outcome of analysis was patient survival. Secondary outcomes included post-LT disease recurrence defined as alcohol relapse based on interview or alcohol biomarkers as per NIAAA definitions and/or steatosis on imaging, including transient elastography. Patients with HCC and other causes of liver disease were excluded. Statistical analyses were performed using SPSS. **Results:** Over the 11-year study period, 405 LT for SLD were performed at our center: 126 (31%) ALD, 114 (28%) AH, 137 (34%) MASLD, and 28 (7%) MetALD. The AH group was younger than the other 3 groups (median age 43 years [IQR 36-51] v 57 [IQR 49-62] (ALD), 61 [IQR 55-67] (MASLD), and 54 [IQR 50-63] (MetALD) (years, p<0.01). The ALD group had the highest proportion of males (79%), compared to MASLD

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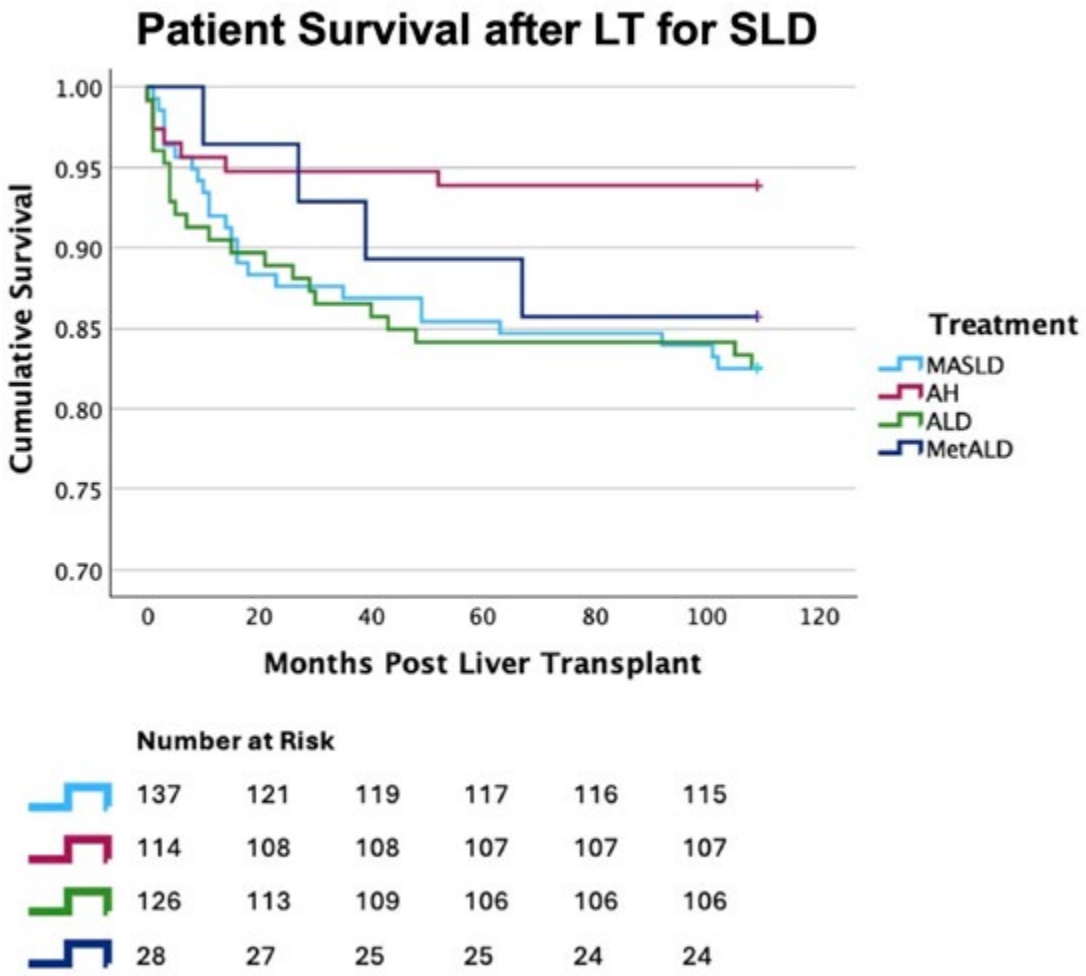
(51%), AH (63%), and MetALD (54%) (p<0.01). The MetALD group had the highest proportion of White race (82%) compared to MASLD (47%), AH (64%), and ALD (52%) (p<0.01). Alcohol biomarker monitoring rates after LT were 100% AH, 70% ALD, 64% MetALD, and 17% MASLD. Despite lower rates of monitoring, the MetALD group had higher numerical rates of alcohol relapse (n=7, 25% at median 1.8 years post-LT) compared to ALD (n=17, 13% at 2.1 years; p=0.13), and similar rates to AH (n=34, 30% at 0.9 years; p=0.61). Median PEth levels at relapse detection for MetALD and ALD were 97 ng/mL (IQR 60-206) and 106 ng/mL (IQR 74-147), respectively (available in 57% and 71%, respectively). The MetALD group had similar average BMI at LT as the MASLD group (28.4 v 33.3, p=0.17). BMI increases occurred in 64% of MetALD and 61% of MASLD groups post-LT, with average increases of 4.3 and 4.5, respectively (p=0.71) at 2.4 years post-LT. Steatosis recurrence occured in 21% of MetALD and 25% of MASLD groups at an average of 2 years post-LT (p=0.70). While 1-year survival rates were similar (all >90%, all p=NS), LT for AH had significantly higher overall survival compared to ALD, MASLD, but not MetALD (94% v 83% v 82%, p<0.01; v 86%) at median of 2 years follow-up. **Conclusion:** Despite higher rates of relapse, AH and MetALD have higher overall survival after LT for SLD compared to ALD and MASLD.



Disclosures: Smruti Rath: Nothing to Disclose, Ashish Bibireddy: Nothing to Disclose, Ishaan Dharia: Nothing to Disclose, Thomas Schiano: eurofins: ad board, Sander Florman: Nothing to Disclose, Gene Im: Consultant relationship with KorroBio; Has not ended; Device support for research relationship with Echosens; Has not ended; Advisor relationship with Novo Nordisk; Has not ended; Consultant relationship with Alimentiv; Has not ended

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2594 | PRE-TRANSPLANT ORAL MIDODRINE EXPOSURE DOES NOT AFFECT MORTALITY AMONG LIVER TRANSPLANT RECIPIENTS

Sudharshan Achalu[1] Richie Manikat[1] Seren Gedallovich[1] Mai Sedki[1] Nikki Duong[1] Amir Hossein Gougol[1] Sajid Jalil[1] Howard Masuoka[1] Roger Sands[1] Ashwani Singal[2] Paul Kwo[1]

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Background: Oral midodrine is an alpha-1 receptor agonist that has been employed to increase mean arterial pressure in the setting of end-stage liver disease with hypotension as well as acute or chronic kidney disease with hypotension including treatment of hepatorenal syndrome in combination of octreotide. The aim of this study was to investigate the impact of pre-transplant oral midodrine exposure on 1-year mortality in a cohort of liver only and simultaneous liver/kidney transplant recipients. **Methods:** We conducted a retrospective analysis of patients who underwent liver only or simultaneous liver/kidney (SLK) transplantation at a single center between 2015 to present. Transplant patients with oral midodrine exposure during index hospitalization were included in the cohort. Demographics, baseline comorbidities, clinical outcome data were collected. The midodrine cohort was compared to a cohort of transplant patients who did not have exposure to oral midodrine at time of transplant. Cohorts were compared in unmatched, matched on basic demographics, and matched on high dimensionality propensity scores for mortality. **Results:** We identified 285 individuals who received oral midodrine during index hospitalization with a group of 325 post-transplant individuals without midodrine exposure prior to liver or SLK transplant. The midodrine group had significantly higher rates of renal disease, baseline dialysis, and severe liver disease (Table). Regarding outcomes, the midodrine exposed groups were more likely to require hemodialysis within 1 year of transplant [Liver + SLK: OR 4.51 (2.46-8.26); SLK only: OR 1.71 (0.14, 23.4); Liver only: OR 5.13 (2.76-9.62)] and longer index hospitalization [Liver + SLK: OR 2.43 (1.88, 3.15); SLK only: OR 2.95 (1.16, 7.51); Liver only: OR 2.39 (1.82, 3.14)]. After propensity matching, there were no differences in 1-year graft rejection rates [Liver + SLK: OR 0.62 (0.31-1.23); SLK only: OR 2.26 (0.09, 1.65); Liver only: OR 0.78 (0.39, 1.56)] and 1-year mortality [Liver + SLK: OR 0.761 (0.27-2.13); Liver only: OR 1.00 (0.34, 2.97)]. **Conclusion:** Pre-transplant oral midodrine exposure in liver/SLK transplant recipients is associated with higher rates of pre- and post-transplant dialysis within 1 year of transplant. Despite this sicker population, 1-year mortality and rejection rates were similar irrespective of exposure to midodrine.

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Demographics and Baseline Clinical Characteristics of Propensity Matched Cohorts						
	Liver & SLK Transplant Mean (SD or %)		SLK Only Mean (SD or %)		Liver Transplant Only N or Mean (SD or %)	
	No Oral Midodrine N=325	+ Oral Midodrine N=285	No Oral Midodrine N=12	+ Oral Midodrine N=28	No Oral Midodrine N=313	+ Oral Midodrine N=259
Age	55.6 (12.2)	53.4 (11.8)	54.5 (10.7)	55.3 (13.5)	55.7 (12.3)	53.1 (11.7)
Female	103 (32%)	123 (43%)	4 (33%)	13 (43%)	99(43%)	111 (43%)
Follow-up Days	1605 (862)	1393 (825)	1724 (878)	1858 (863)	1601 (863)	1339 (805)
Baseline Dialysis Rates	45 (14%)	95 (33%)	7 (58%)	20 (71%)	38 (12%)	77 (30%)
Sodium (mmol/L)	136 (4.7)	132 (6.9)	138 (3.4)	133 (6.5)	136 (5)	133 (6)
Bilirubin (mg/dL)	4.3 (5.9)	8.4 (8.5)	4.1 (6.7)	5.1 (5.4)	4.4 (6)	9 (9)
INR	1.6 (0.7)	2 (0.7)	1.3 (0.2)	1.9 (0.8)	1.6 (0.7)	2 (0.7)
Serum Creatinine (mg/dL)	1.1 (0.7)	2 (0.7)	4 (2.3)	4.1 (1.9)	1 (0.5)	1.4 (0.7)
MELD- Na at Time of Transplant	14.8 (12)	28.4 (8.8)	23.5 (7.1)	31.8 (6.2)	14.5 (12.6)	28 (9)
Baseline Comorbidity Score	8.4 (3.7)	8.7 (3.3)	11.4 (2.4)	10.9 (3.2)	8.3 (3.6)	8.1 (3.2)
Severe Liver disease	295 (91%)	279 (98%)	12 (100%)	28 (100%)	283 (90%)	253 (98%)
Severe Renal Disease	97 (30%)	117 (62%)	12 (100%)	28 (100%)	85 (27%)	151 (58%)
Index Hospitalization Duration (Days)	14 (24)	29 (41)	11 (8)	21 (29)	14 (24)	29 (42)
1-year Rejection	56 (17%)	58 (20%)	2 (17%)	9 (32%)	54 (17%)	50 (19%)
Dialysis within 1 year of Transplant	74 (23%)	213 (75%)	5 (42%)	17 (61%)	69 (22%)	198 (76%)
Death	17 (5%)	22 (8%)	0 (0%)	0 (0%)	17 (5%)	22 (8%)

Disclosures: Sudharshan Achalu: Nothing to Disclose, Richie Manikat: Nothing to Disclose, Seren Gedallovich: Nothing to Disclose, Mai Sedki: Nothing to Disclose, Nikki Duong: Nothing to Disclose, Amir Hossein Gougol: Nothing to Disclose, Sajid Jalil: Nothing to Disclose, Howard Masuoka: Nothing to Disclose, Roger Sands: Nothing to Disclose, Ashwani Singal: Advisor relationship with CLD Foundation; Has not ended; Speaking and Teaching relationship with Medical Speaker's Network; Has not ended; Speaking and Teaching relationship with Madrigal; Has not ended; Stock â€“ privately held company relationship with Pleiogenix; Has not ended; Consultant relationship with Pleiogenix; Has not ended; Advisor relationship with Durect; Has ended; Royalties or patent beneficiary relationship with Up-to-Date; Has not ended; Executive role relationship with Gastro Endo News; Has not ended; Grant/Research Support relationship with NIAAA; Has not ended; Employee relationship with Avera Medical Group; Has ended; Grant/Research Support relationship with GSK; Has not ended; Employee relationship with University of Louisville School of Medicine; Has not ended; Speaking and Teaching relationship with Medscape; Has not ended, Paul Kwo: Nothing to Disclose

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2595 | CHALLENGES OF LONG-TERM CARE OF POST-LIVER TRANSPLANTATION PATIENTS

Deanna Oliver[1] Renee Pozza[1] Fatma Barakat[2] Julian Diaz-Moreno[1] Michael Tunkelrott[3] Victoria Aksakovska[3] Jutta Kurz[3] Mustafa Behan[3] Emmanuel Gorospe[4] Tarek Hassanein[1]

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Background: The post-transplant care for liver transplant patients have been improving over the past decades. The 1-year survival rate post liver transplant reached >=92% in 2015. However, the long-term outcomes following liver transplantation have not shown any improvements over the last decades. The long term outcomes for recipients of deceased donor liver transplants showed graft failure rates of 15.0% at 3 years for transplants done in 2018, 20.7% at 5 years for transplants done in 2016, and 38.5% at 10 years for transplants done in 2011. These findings suggest stable or similar outcomes over time across the specified transplant years. **Objective:** Understand the level of care, education, and complications of post-liver transplant patients and their long-term needs. **Methods:** The Amsety database comprises of over 600,000 participants with history of liver disease. The Amsety database, was originally created to communicate with individuals about liver health and nutrition. Between January and May 2024, 33 individuals who had history of liver transplantation responded to the post-transplant survey. **Results:** Average age: 55±14.3 years. 17% are below 40 years, 37% are between 41 and 60 years, 46% are above 60 years of age. On average, the last liver transplant occurred 7 years earlier – with only 4% of respondents had received more than 1 liver transplant and 8% had received both, a liver and a kidney transplant. 100% of respondents claim that they have experienced post-transplant complications. 62% experienced elevated liver enzymes, 37% experienced kidney dysfunction, and 8% experienced post-transplant new-onset diabetes mellitus. All respondents have discussed changes of their medications with their physician during the past 24 months; 96% of the respondents continue to take immunosuppressant drugs. 92% of the respondents take Tacrolimus, 40% Cellcept, and 21% still on Prednisone. 92% of respondents claim that they take their medicine regularly and 100% claim that they have discussed the level of immunosuppressants with their physician. The 4% that do not take immunosuppressant drugs had their transplants done over 8 years earlier. In respect to nutrition, 58% claim that they would like to know more about “How do my nutrition and diet choices help maintain liver grafts”. 33% would like to know more about proper nutrition post liver transplantation. Over 25% would like to know about available resources and specialists for long term post-transplant care. **Conclusion:** In patients who had liver transplants, our survey clearly underscored their needs for better education and guidance for long-term care of the transplanted patient. This could be achieved by (i) better understanding of the stack of frequently asked questions and (ii) offer digital tools to address these questions, ideally using a liver-specific generative AI to support physicians with a simple patient interface.

Disclosures: Deanna Oliver: Nothing to Disclose, Renee Pozza: Nothing to Disclose, Fatma Barakat: Nothing to Disclose, Julian Diaz-Moreno: Nothing to Disclose, Michael Tunkelrott: Nothing to Disclose, Victoria Aksakovska: Amsety: Employee, Jutta Kurz: Nothing to Disclose, Mustafa Behan: Amsety GmbH: Founder and Co-Owner, Emmanuel Gorospe: Nothing to Disclose, Tarek Hassanein: Nothing to Disclose

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2596 | NO INITIAL INCREASE IN CANCER RISK WITH GLUCAGON LIKE PEPTIDE-1 THERAPIES FOLLOWING LIVER TRANSPLANTATION

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Background: Patients who undergo liver transplantation are at higher risk of complications from diabetes and obesity. Recently, Glucagon-like peptide-1(GLP-1) analogues have revolutionized management of these conditions and are increasingly being used in post-transplant patients. However, the safety of these agents in this population, particularly their association with cancer risk, is controversial. We aimed to assess the association of semaglutide and tirzepatide with cancer in patients who undergo liver transplant. **Methods:** All patients who underwent liver transplant at our institution were included from 1/2018-12/2023. We did a retrospective cohort study to assess whether they received GLP-1 analogues, including semaglutide and tirzepatide, after the liver transplant. Data including patient demographics, comorbidities and exposure to semaglutide or tirzepatide were collected. Primary outcome was development of malignancy. Secondary outcomes were 1-and 3-year mortality. **Results:** 366 patients were included who underwent liver transplant from 01/2018-12/2023. Of these, 42(13%) were exposed to semaglutide or tirzepatide while 324(88%) had no such exposure. The mean age of the population was 58.12 +/- 7.6 in the exposed group and 58.44 +/- 11.5 in the control group. 14(33.6%) were female in the exposed group while (119) 36.7% were female in the control group. Comorbidities, including HTN, stroke and ESRD were comparable in both groups. 37(88.1%) in the exposed group had diabetes while 111(34.2%) in the control group had diabetes($p<0.001$). Similarly, 28(66.7%) patients in the exposed group had BMI>30 while 111(34.5%) patients in the control group had BMI>30($p<0.001$). The follow up period was 3.74 +/-1.3 years for the exposed group and 4.01 +/-1.5 years in the control group. For outcomes, 2(4.8%) patients in the exposed group were diagnosed with cancer in the follow up period versus 26(8.1%) in the control group ($p=0.76$). There was no cancer related mortality at one year while at 3 years, it was similar in both groups. For malignancies, 1(50%) patient in the exposed group had HCC, while 5(18%) patients in the control group had either HCC or cholangiocarcinoma. No patients in the exposed group were diagnosed with skin related malignancies including BCC, SCC and Malignant Melanoma, while 13(46%) patients in the control group were diagnosed with such malignancies. 1 patient in the exposed group was diagnosed with Post Transplant Lymphoproliferative Disorder. 11 patients in the control group were diagnosed with other malignancies including prostate cancer, lymphoma, follicular thyroid cancer, and leukemia. **Conclusion:** In our cohort, the use of semaglutide and tirzepatide was not associated with cancer in patients who undergo liver transplantation. We were limited by single center and smaller number of patients. Further large scale, multicenter studies are needed to confirm the safety of these medications.

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	Exposure to Semaglutide or Tirzepatide (n=42)	No exposure to Semaglutide or Tirzepatide (n=324)	P- value
Age, Years +/- SD	58.12+/- 7.6	58.44+/- 11.5	0.86
Sex, Female, n (%)	14 (33.3)	119 (36.7	0.67
Race, Caucasian, n (%)	38 (90.5)	274 (84.6)	0.67
Race, Black, n (%)	1 (2.4)	24 (7.4)	0.67
Race, Asian, n (%)	1 (2.4)	11 (3.4)	0.67
Race, Others, n (%)	2 (4.8)	15 (4.6)	0.67
Comorbidities:			
Diabetes Mellitus, n (%)	37(88.1)	111(34.3)	<0.001
Hypertension, n (%)	30(71.4)	205(63.3)	0.56
Coronary Artery Disease, n (%)	7(16.7)	40(12.3)	0.43
Stroke, n (%)	2(0.6)	0(0)	1
ESRD, n (%)	4(9.5)	36(11.1)	1
BMI>30, n (%)	28(66.7)	111(34.5)	<0.001
Donor Liver Status:			
Live Donor, n (%)	3(7.1)	19(5.9)	0.73
Deceased Donor, n (%)	39(92.9)	305(94.1)	0.73
Outcomes:			
Cancer, n (%)	2(4.8)	26(8.1)	0.76
Mortality 1 Year, n (%)	0(0)	0(0)	0
Mortality 3 years, n (%)	1(2.4)	8(2.5)	1

Disclosures: Muhammad Saad Faisal: Nothing to Disclose, Abdulmalik Saleem: Nothing to Disclose, Ammad Chaudhary: Nothing to Disclose, Minahil Fatima: Nothing to Disclose, Muhammad Shahzil: Nothing to Disclose, Mohammed Abusuliman: Nothing to Disclose, Muhammad Salman Faisal: Nothing to Disclose, Syed-Mohammed Jafri: Takeda: Speaking and Teaching, Gilead: Speaking and Teaching, Abbvie: Speaking and Teaching, Ironwood: Advisor, Intercept: Speaking and Teaching

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2597 | THE SAFETY AND TOLERABILITY OF QEL-001, AN AUTOLOGOUS CHIMERIC ANTIGEN RECEPTOR (CAR) T REGULATORY (TREG) CELL THERAPY, IN LIVER TRANSPLANTATION – A SAFETY COHORT IN THE LIBERATE STUDY

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Background: In contrast to short-term graft/patient survival, which are excellent, long-term outcomes after liver transplantation remain suboptimal. This is due to the adverse effects of chronic immunosuppression (IS). Operational tolerance could address this medical unmet need, but only occurs spontaneously in a minority of patients long term after transplantation. Previous studies in animal models and humans indicate that the administration of donor-reactive Tregs can induce tolerance early post-transplantation. LIBERATE (NCT05234190) is a phase I/IIa, single-arm, open-label study to investigate the potential of QEL-001 to induce allograft tolerance and allow the complete discontinuation of IS, post liver transplantation. QEL-001 is an autologous engineered Treg cell therapy, expressing an HLA-A2 specific CAR, a FOXP3 phenotype lock and an inducible safety switch. **Methods:** The safety cohort was conducted in 2 centres in the UK. Eligible subjects were aged 18-70 years and underwent liver transplantation 1-5 years previously. A Data Safety Monitoring Board (DSMB) performed an independent review of the data. The primary safety endpoint was the incidence of Dose-Limiting-Toxicities (DLTs) within 28 days post QEL-001 infusion. Assessment of safety and tolerability of QEL-001 was based on all available study data, including the incidence and severity of treatment emergent adverse events (TEAEs). Exploratory endpoints included the characterization of QEL-001 in peripheral blood and liver biopsy, and persistence and expansion of QEL-001 in vivo. **Results:** Three subjects, all males, aged 32-58 years, received a dose of QEL-001 in the protocol target range. Within 28 days post-infusion, there were no DLTs or serious adverse events (SAE), no infusion related adverse events (AE), and no TEAE considered to be related to QEL-001 by the principal investigator (PI). No infections and no evidence of viral re-activation were observed post dose. Clinical batches produced for all three subjects were within the pre-defined product specifications, and without CD8 impurities. QEL-001 CAR Treg maintained phenotypic stability, and consistently across batches in vivo, post-infusion. QEL-001 CAR Tregs were detected in liver biopsies performed 28 days after infusion, and in blood up to 6 months. **Conclusion:** QEL-001 was well-tolerated in the safety cohort. QEL-001 trafficked and engrafted in the transplanted livers. Current data supports further QEL-001 dosing with progression to the efficacy cohort in LIBERATE.

Disclosures: Alberto Sanchez-Fueyo,: Quell Therapeutics Ltd: Consultant, Alison Taylor: Nothing to Disclose, Kourosh Saeb-Parsy: Nothing to Disclose, Marc Martinez-Llordella: Nothing to Disclose, Nathalie Clerget: Quell therapeutics: Employee, Chris Sharpe: Quell Therapeutics Limited: Employee, Nathalie Belmonte: Nothing to Disclose, Aaron Vernon: Nothing to Disclose, Jie Wang-Jairaj: Quell Tx: Employee, Rupert Kenefeck: Nothing to Disclose, Peter Cooper: Nothing to Disclose, Gareth Wright: Nothing to Disclose, Luke Devey: Nothing to Disclose

2598 | PERI-OPERATIVE OUTCOMES AND SHORT-TERM POST-OPERATIVE OUTCOMES IN LIVER TRANSPLANT RECIPIENTS WITH PORTAL THROMBOSIS AFTER TIPS

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Background: Portal vein thrombosis (PVT) occurs in a subset of patients with cirrhosis and increases morbidity/mortality in the perioperative period. Despite improved surgical techniques, PVT continues to complicate liver transplant (LT). Resolving pre-LT PVT may improve peri- and post-operative outcomes. Pre-LT anticoagulation carries bleeding risk and has limited efficacy. Transjugular intrahepatic portosystemic shunt (TIPS) presents an alternative for PV recanalization. We aimed to determine whether pre-LT TIPS improves peri-operative and

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short-term post-operative outcomes in patients with PVT. **Methods:** This was a retrospective study of adult patients with PVT who underwent LT from 2016-2023 at a single institution. Patients were stratified by the presence of TIPS. Data collection included demographics and clinical information. Differences between the two groups were assessed with the chi square and T tests. **Results:** Among 79 total patients with PVT, 49% had undergone pre-LT TIPS placement. TIPS recipients tended to be younger (59 vs. 64 years, p=0.01) and had higher BMI (30 vs. 27, p=0.03). Main indications for TIPS included PVT (41%) and refractory ascites (36%). Patients with TIPS had lower MELD at time of LT (MELD 22 vs. 27, p=0.01). TIPS recipients were more likely to have clot extension into the SMV (44% vs. 20%, p=0.02) and were more likely to have been on anticoagulation (46% vs. 20%, p=0.01). Patients without TIPS were more likely to be an inpatient at time of LT (48% vs. 21%, p=0.01). At time of LT, patients with TIPS had a significantly lower LT operative time (6.3 hours vs. 7.1 hours, p=0.02). Estimated blood loss (EBL) was significantly lower in patients with TIPS (4.4 L vs. 7.7 L, p=0.013). Patients with TIPS were less likely to require surgical thrombectomy (21% vs. 40%, p=0.06) or a jump graft (3% vs. 18%, p=0.03). In patients who received TIPS, there was no significant difference in terms of length of stay, post-operative bleeding, pressor needs, return to operating room, use of renal replacement therapy, and 90-day post-LT readmission or mortality. **Conclusion:** Patients with PVT who had TIPS pre-LT had significantly improved peri-operative outcomes, including reduced operative time and EBL along with less need for surgical thrombectomy and use of venous jump grafts. Interestingly, TIPS recipients underwent LT at lower MELD which could reflect higher surgical risk tolerance. TIPS should be considered pre-operatively in patients in transplant evaluation with PVT.

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Table 1: Characteristics, Peri-Operative Outcomes, and Short-Term Post-Operative Outcomes

Variable	TIPS (n=39)	No TIPS (n=40)	p-value
Liver Disease Characteristics			
Etiologies of Cirrhosis			
Alcohol	40%	23%	0.05
NASH	12%	33%	
Viral	30%	18%	
History of HCC	28%	25%	0.75
History of VTE	5%	5%	0.98
PVT Characteristics			
Acute	33%	28%	0.57
Occlusive	26%	18%	0.38
SMV Extension	44%	2%	**0.02**
Pre-Operative Factors			
MELD 3.0 at Transplant	22	27	**0.01**
Inpatient at Transplant	21	48	**0.01**
RRT at Transplant	10%	23%	0.14
Anticoagulated Prior to Transplant	46%	20%	**0.01**
Anticoagulated During Transplant	13%	20%	0.39
SLK	10%	15%	0.53
Surgical Outcomes			
Operative Time (Hours)	6.3	7.1	**0.02**
Blood Loss (L)	4.4	7.7	**0.01**
Blood Products Given (units)			
RBC	7.7	9.8	0.42
Cryo	0.6	0.2	0.34
PLT	1.5	1.6	0.84
FFP	6.7	9.6	0.23
Thrombectomy Required	21%	40%	0.06
Jump Graft Required	3%	18%	**0.03**
Outcomes			
Total Length of Stay (Days)	21	16	0.25
Length of ICU Stay (Days)	6.7	5.2	0.42
Duration of Pressor Requirement Post-Operatively (Days)	1.2	1.6	0.51
Post-Operative Bleeding	31%	25%	0.57
Takeback to Operating Room Required	15%	23%	0.42
90-Day Procedure-Specific Readmission	44%	45%	0.90
90-Day Procedure-Specific Mortality	13%	10%	0.69
RRT Required Post-Operatively	28%	30%	0.86

Disclosures: Harjit Singh: Nothing to Disclose, Bryce Kunkle: Nothing to Disclose, Serena Korkmaz: Nothing to Disclose, Advait Suvarnakar: Nothing to Disclose, Angela Troia: Nothing to Disclose, Maryam Dadashzadeh: Nothing to Disclose, Arul Thomas: Nothing to Disclose, Pejman Radkani: Nothing to Disclose, Amol Rangnekar: Nothing to Disclose

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2599 | EFFECT OF PANCYTOPENIA AND LEUKOPENIA ON DISEASE PROGRESSION IN PATIENTS WITH ADVANCED LIVER DISEASE

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Background:
Pancytopenia, including leukopenia, is common among patients with hepatic cirrhosis, with its prevalence increasing as liver disease severity progresses. The effect of cytopenia on disease progression among patients with cirrhosis is unknown. We aim to investigate the relationship between pancytopenia (PC) and leukopenia (LP) on outcomes for patients on the liver transplant (LT) waitlist. **Methods:** We performed a retrospective cohort study among 488 adult patients (aged > 18) consecutively added to the LT waitlist at Baylor St. Luke's Medical Center from January 1, 2017, to November 30, 2019, with clinical follow up through December 2023. Demographics, etiology, factors for decompensation (FD) (ascites, HE, hepatic hydrothorax, TIPS, variceal bleed), and waitlist outcomes were recorded. LP was defined as leucocytes <4, and PC was defined as LP, platelets <150, and hemoglobin <13.5 in men and <12 in women. Competing risk analysis was performed to assess risk of waitlist dropout (death or clinical deterioration) accounting for competing risks of undergoing LT and delisting for clinical improvement. Competing risk Fine-Gray proportional hazard regression models were constructed to compare waitlist mortality (removal from waitlist due to death or clinical deterioration) between patients with and without PC or LP with LT and clinical improvement as competing risks. 95% confidence intervals (CIs) were estimated by modeling the cumulative incidence function. **Results:** Overall, there were 488 patients added to the LT waitlist, of which 20.5% (n=100) had PC at listing. Compared to non-PC patients, a larger proportion of PC patients had underlying MASH (29.0 v. 18.8%), and a smaller proportion had an etiology of alcohol use (27.0 v. 37.6%) (P<0.05). PC patients had a longer waitlist duration than those without (331.5 days v. 146 days, P<0.001). In our competing risks analysis, there was no significant difference between waitlist dropout (0.806, CI 0.510 – 1.272) in patients with and without PC. Regarding LP, the prevalence was 25.6% with no statistically significant difference between cirrhosis etiologies. Similarly, median waitlist time was longer in patients with LP compared to those without (355 v. 115 days) (P<0.001). MELD at listing was lower for LP compared to non-LP patients (15 v. 19, P<0.005). LP patients had a longer median time to drop out compared to the non-LP group (408 v. 151 days, P<0.05). No statistically significant difference in waitlist mortality hazard ratios was seen. [Table 1.] **Conclusion:** PC was associated with longer waitlist times, but not associated with increased mortality or rates of FD. PC was more often seen among patients with MASH and less among those with ALD. LP patients had longer waitlist time, lower MELD at listing, and no significant difference in waitlist mortality. Future directions include investigation of causal relationship of PC and LP related to longer average waitlist time.

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Table 1. Pancytopenia vs non-pancytopenia and leukopenia vs non-leukopenia waitlist characteristics and outcomes.

Waitlist characteristics	Pancytopenia (n = 100)	Non-pancytopenia (n = 388)	*P* value	Leukopenia (n = 125)	Non-leukopenia (n = 363)	*P* value
Median age, years [IQR]	58.6 [13.7]	58.0 [15.8]	0.706	58.7 [13.6]	57.8 [15.8]	0.669
Female, n (%)	46 (46.0)	145 (37.4)	0.115	55 (44.0)	136 (37.5)	0.197
Race/ethnicity, n (%)	-	-	-	-	-	-
White	46 (46.0)	227 (58.5)	0.025	59 (47.2)	214 (59.0)	0.022
Black	11 (11.0)	40 (10.3)	0.840	14 (11.2)	37 (10.2)	0.751
Hispanic	39 (39.0)	100 (25.8)	0.009	47 (37.6)	92 (25.3)	0.009
Other	4 (4.0)	21 (5.4)	0.568	5 (4.0)	20 (5.5)	0.509
Etiology, n (%)	-	-	-	-	-	-
ALD	27 (27.0)	146 (37.6)	0.048	36 (28.8)	137 (37.7)	0.072
HCV	22 (22.0)	84 (21.6)	0.940	29 (23.2)	77 (21.2)	0.642
MASH	29 (29.0)	73 (18.8)	0.026	32 (25.6)	70 (19.3)	0.134
Other	22 (22.0)	85 (21.9)	0.984	28 (22.4)	79 (21.8)	0.882
Median MELD [IQR]	17 [9]	17 [18]	0.150	15 [9]	19 [20]	0.003
Median albumin, g/dL [IQR]	3.0 [0.7]	3.2 [1.1]	0.216	3.2 [0.8]	3.2 [1.2]	0.957
Hepatic decompensation, n (%)	-	-	-	-	-	-
Hepatic encephalopathy	57 (57.0)	210 (54.1)	0.698	66 (52.8)	201 (55.4)	0.517
Ascites	72 (72.0)	262 (67.5)	0.489	83 (66.4)	251 (69.1)	0.439
TIPS	7 (7.0)	32 (8.2)	0.658	10 (8.0)	29 (8.0)	0.972
Hepatic hydrothorax	13 (13.0)	28 (7.2)	0.064	14 (11.2)	27 (7.4)	0.197
Dialysis	6 (6.0)	38 (9.8)	0.217	8 (6.4)	36 (9.9)	0.224
Variceal bleeding	22 (22.0)	99 (25.5)	0.421	28 (22.4)	93 (25.6)	0.418
Waitlist outcomes	-	-	-	-	-	-
Underwent LT, n (%)	46 (46.0)	175 (45.1)	0.872	53 (42.4)	168 (46.3)	0.452
Median time to LT, days [IQR]	331.5 [397]	146 [344]	< 0.001	355 [366]	115 [300]	< 0.001
Deteriorated, n (%)	23 (23.0)	93 (24.0)	0.839	30 (24.0)	86 (23.7)	0.944
Median time to dropout, days [IQR]	306 [991]	168.5 [365.5]	0.131	408 [921]	151 [297]	0.012
Deteriorated HR [95% CI][a]	0.806 [0.510 – 1.272]	Reference	0.354	0.802 [0.529 – 1.216]	Reference	0.299
Deteriorated sHR [95% CI][b]	0.964 [0.615 – 1.511]	Reference	0.873	1.016 [0.675 – 1.528]	Reference	0.941
Clinically improved, n (%)	3 (3.0)	20 (5.2)	0.365	5 (4.0)	18 (5.0)	0.663

[a]Multivariable Cox proportional hazards model was adjusted for candidate age, sex, race/ethnicity, MELD at listing.

[b]Competing risk Fine-Gray proportional hazards model was adjusted for candidate age, sex, race/ethnicity, MELD at listing. Competing risk events included waitlist removal due to LT and clinical improvement.

Disclosures: Patrick Boddie: Nothing to Disclose, Peter Lymberopoulos: Nothing to Disclose, Anwar Uddin: Nothing to Disclose, Vinh Tran: Nothing to Disclose, Madeleine Hines Salge: Nothing to Disclose, Michael Shi: Nothing to Disclose, Pooja Prasad: Nothing to Disclose, Karthik Goli: Nothing to Disclose, Anjiyah Shaikh: Nothing to Disclose, Ronald Samuel: Nothing to Disclose, Tzu-Hao Lee: Nothing to Disclose, Kavish Patidar: Nothing to Disclose, George Cholankeril: Nothing to Disclose

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2600 | MACHINE PERFUSION STRATEGIES IN LIVER TRANSPLANTATION: A SYSTEMATIC REVIEW AND NETWORK META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

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Background: Machine perfusion (MP), including hypothermic oxygenated machine perfusion (HOPE), dual HOPE, normothermic machine perfusion (NMP), NMP ischemia-free liver transplantation (NMP-ILT), and controlled oxygenated rewarming (COR) are increasingly being investigated to improve liver graft quality from extended criteria donors and donors after circulatory death to expand the donor pool. This network meta-analysis aims to investigate the comparative efficacy and safety of various liver MP strategies versus traditional static cold storage (SCS). **Methods:** We searched PubMed, Scopus, Web of Science, and Cochrane Controlled Register of Trials for randomized controlled trials (RCTs) comparing liver transplant (LT) outcomes between SCS and MP techniques. The primary outcome was the incidence of early allograft dysfunction (EAD). Secondary endpoints included 1-year graft survival, the incidence of post-reperfusion syndrome, biliary complications, the need for renal replacement therapy (RRT), graft-related patient mortality, final recipient survival, peak alanine transaminase (AST) and aspartate transaminase (AST), intraoperative packed RBC (PRBC) transfusion, intraoperative fresh frozen plasma (FFP) transfusion, the length of intensive care unit (ICU) stay and comprehensive complication index (CCI). R-software was used to conduct a network meta-analysis, using a frequentist framework. **Results:** We included 12 RCTs involving 1,682 patients undergoing LT (818 in the MP groups and 864 in the SCS group). Compared to SCS, HOPE/dHOPE and NMP were associated with a significantly lower risk of EAD (Relative risk [RR]: 0.53, 95% CI [0.37, 0.74], and (RR: 0.61, 95% CI [0.42, 0.90]) respectively (Figure 1-A). Also, HOPE/dHOPE was associated with improved 1-year graft survival rate (RR: 1.07, 95% CI [1.01, 1.14]), lower risk of graft failure/loss (RR: 0.38, 95% CI [0.16, 0.90], and a reduction in the risk of biliary complications (RR: 0.52, 95% CI [0.43, 0.75]) (Figure 1-B&C). Compared to SCS, NMP (RR: 0.49, 95% CI [0.24, 0.96] and NMP-ILT (RR: 0.15, 95% CI [0.04, 0.57], both significantly reduced the risk of post-perfusion syndrome (Figure 1-D). NMP-ILT was also associated with a significant reduction in ICU duration (MD: -16.30, 95% CI [-32.38, -0.22] and in peak ALT and AST within 7 days (MD: -319.30, 95% CI [-615, -23.60] and (MD: -706.30, 95% CI [-1356.10, -56.50] respectively. There were no differences between SCS and MP groups in the risk of RRT, graft-related patient mortality, final recipient survival, intraoperative PRBC transfusion, intraoperative FFP transfusion, and CCI. **Conclusion:** Our meta-analysis demonstrates that HOPE/dual-HOPE and NMP are promising alternatives to SCS for donor liver preservation. These new techniques can help expand the donor pool with similar or even better post-LT outcomes.

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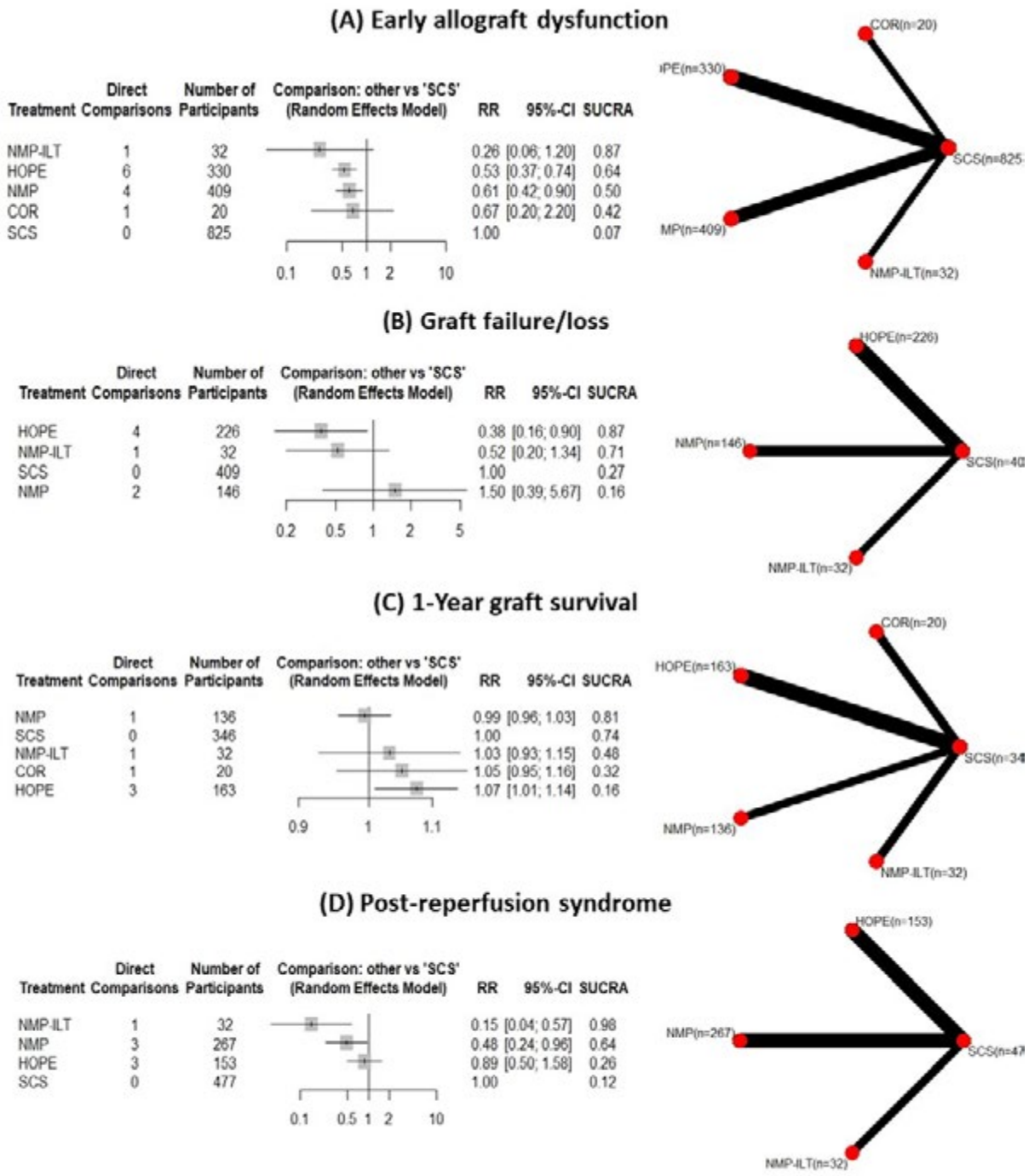

Figure 2: Forest plot and network meta-analysis for efficacy outcomes (A: Early Allograft dysfunction, B: Graft failure/loss, C: 1-year graft survival, D: Post-reperfusion syndrome)

Disclosures: Fouad Jaber: Nothing to Disclose, Mohamed Abuelazm: Nothing to Disclose, Youssef Soliman: Nothing to Disclose, Mahmoud Madi: Nothing to Disclose, Husam Abusuilik: Nothing to Disclose, Ahmed Mazen Amin: Nothing to Disclose, Abdallah Saeed: Nothing to Disclose, Ibrahim Gowaily: Nothing to Disclose, Basel Abdelazeem: Nothing to Disclose, Yazan Sallam: Nothing to Disclose, Abbas Rana: Nothing to Disclose, Kamran Qureshi: Phathom Pharmaceuticals: Speaking and Teaching, Intercept Pharmaceuticals: Speaking and Teaching, Gilead Sciences: Speaking and Teaching, Salix Pharmaceuticals: Speaking and Teaching, Madrigal Pharmaceuticals: Speaking and Teaching, Tzu-Hao Lee: Nothing to Disclose, George Cholankeril: Nothing to Disclose

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2601 | IS PRE-LIVER TRANSPLANT CANNABIS USE ACTUALLY RISKY? ASSOCIATION WITH SURVIVAL, REJECTION, AND FUNGAL INFECTIONS

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Background: Cannabis use was once a contraindication for liver transplantation (LT). Initial reports linked pre-transplant cannabis use to poor medication adherence (and thus higher rejection rates) and increased incidence of fungal infections. Despite recent evidence showing similar post-LT outcomes regardless of pre-transplant cannabis use, many centers still consider it a contraindication for LT. The purpose of this study was to determine whether pre-LT cannabis use affects outcomes in a large, diverse transplant center. **Methods:** Medical records of patients who underwent LT between 6/2016 and 12/2019 at a single center were retrospectively reviewed. Analysis was restricted to LT recipients with cannabinoid test results within 6 months prior to transplant evaluation. Logistic regression was used to analyze factors associated with graft rejection and post-LT fungal infection. Kaplan-Meier analysis and log-rank tests were used to compare differences in survival. P<0.05 was statistically significant. **Results:** Of the 269 LT recipients with pre-evaluation cannabinoid test results, 21 (7.8%) had a positive test. Patients testing positive for cannabinoids pre-LT were more likely to be active tobacco smokers (42.9% vs 10.1%; p<0.001). They were also more likely to be minimally acceptable (23.8% vs 19.0%) or poor (28.6% vs 8.1%; p=0.003) candidates psychosocially according to the Stanford Integrated Psychosocial Assessment for Transplant (SIPAT) score. Cannabinoid test status did not affect overall (p=0.41), graft (p=0.82), or rejection-free survival (p=0.94). Per multivariable logistic regression, only poor SIPAT gro1851uping was associated with increased odds of biopsy-proven rejection (aOR, 8.17; 95% CI, 1.01-65.97; p=0.049). The only variable associated with higher odds of post-LT fungal infection was viral etiology of liver disease (aOR, 4.22; 95% CI, 1.17-15.25; p=0.03). **Conclusion:** Testing positive for cannabinoids within the 6 months prior to LT did not affect survival outcomes, nor was it associated with rejection or fungal infection. The strongest predictors of rejection and fungal infection were SIPAT score and liver disease etiology, respectively. This analysis lends further support to offering LT to candidates testing positive for cannabis who are otherwise good medical and psychosocial candidates for transplant.

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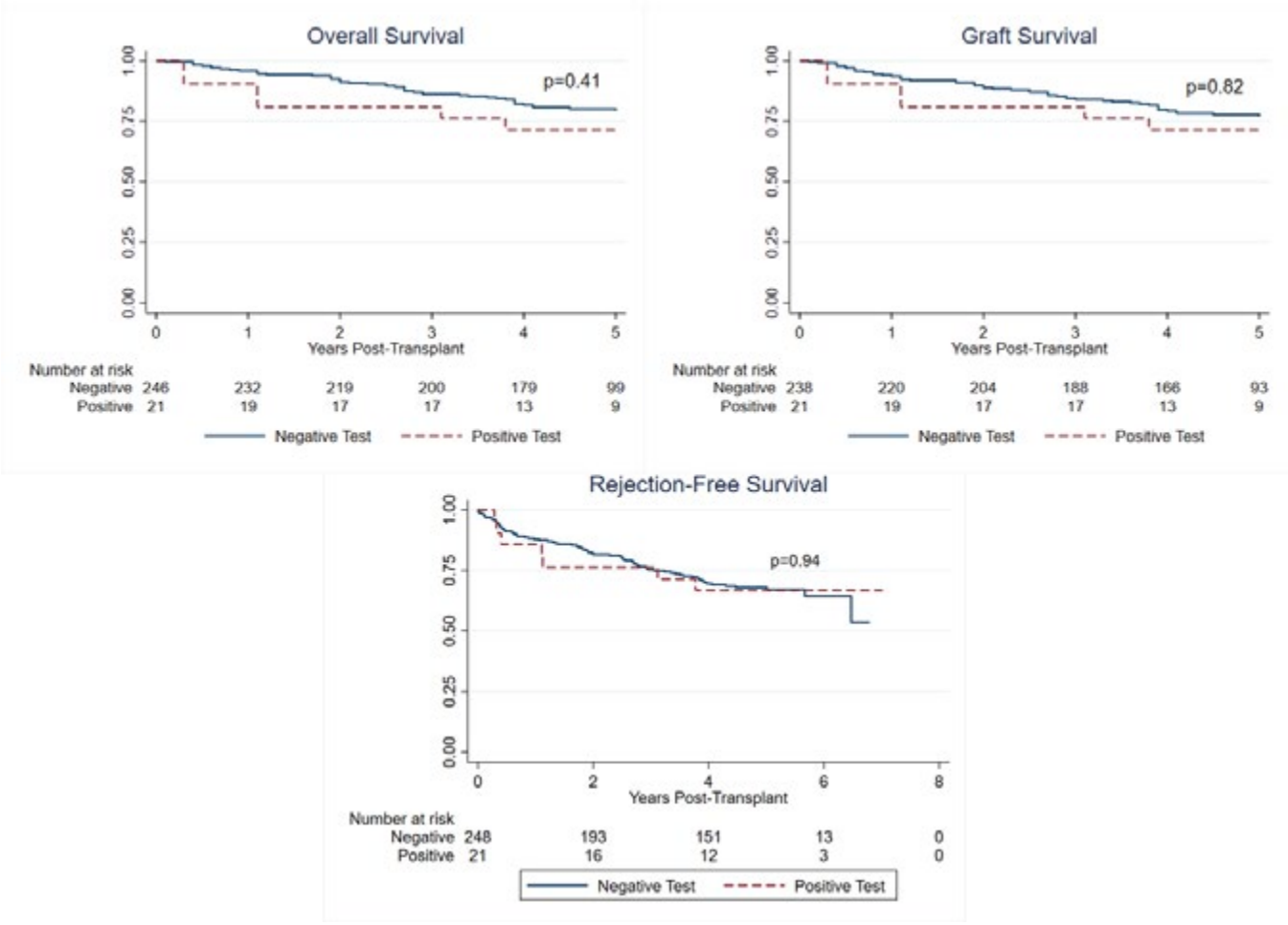

Disclosures: Sudha Kodali: Advisor relationship with Astrazeneca; Has not ended; Speaking and Teaching relationship with Gilead; Has not ended; Advisor relationship with SIRTEX; Has not ended; Speaking and Teaching relationship with Gilead; Has ended; Advisor relationship with SIRTEX; Has ended; Consultant relationship with Astrazeneca; Has ended, Elizabeth Brombosz: Nothing to Disclose, John Ontiveros: Nothing to Disclose, David Victor: Nothing to Disclose, Tamneet Basra: Nothing to Disclose, Mazen Noureddin: Principal Investigator for a Drug Study relationship with Viking; Has not ended; Consultant relationship with Eli Lilly; Has not ended; Consultant relationship with AstraZeneca; Has not ended; Consultant relationship with Boston Pharmaceuticals; Has not ended; Principal Investigator for a Drug Study relationship with Genfit; Has not ended; Principal Investigator for a Drug Study relationship with Galectin; Has not ended; Principal Investigator for a Drug Study relationship with Gilead; Has not ended; Principal Investigator for a Drug Study relationship with BMS; Has not ended; Principal Investigator for a Drug Study relationship with BI; Has not ended; Principal Investigator for a Drug Study relationship with Akero; Has not ended; Consultant relationship with Cytodyn; Has not ended; Consultant relationship with GSK; Has not ended; Consultant relationship with BI; Has not ended; Consultant relationship with Madrigal; Has not ended; Terns,Takeda, Zydus. relationship with Itimmune, BI, Cytodyn, 89BIO, GSK, Madrigal, Merck, Novo Nor; Has not ended; Principal Investigator for a Drug Study relationship with Allergan; Has not ended; Consultant relationship with Takeda; Has not ended; Consultant relationship with Terns; Has not ended; Terns, Corcept, Takeda, Madrigal, Novartis, Novo Nordisk, relationship with Allergan, Akero, BI, BMS, Gilead, Galectin, Zydus GSK; Has not ended; Consultant relationship with Novo Nordisk; Has not ended; Stock â€“ privately held company relationship with Rivus Pharma, Cytodyn, and ChronWell; Has not ended; Consultant relationship with Merck; Has not ended; Principal Investigator for a Drug Study relationship with Madrigal; Has not ended; Consultant relationship with Altimmune; Has not ended; Principal Investigator for a Drug Study relationship with Terns; Has not ended; Principal Investigator for a Drug Study relationship with Zydus; Has not ended; Stock â€“ privately held company relationship with Rivus Pharmaceuticals; Has not ended; Consultant relationship with Alligos; Has not ended; Stock - publicly traded company relationship with Cytodyn; Has not

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2602 | ONE-THIRD OF LIVER DONORS FOR RECIPIENTS OF SEVERE ALCOHOLIC HEPATITIS EXPERIENCE PSYCHOLOGICAL DISTRESS

Chinmay Hegde[1] Ramya shruthi[1] Mithun Sharma[2] Shantan Venishetty[1] Sowmya T R[1] Manasa Alla[1] Rajesh Gupta[1] Padaki Nagaraja Rao[1] kumaraswamy P[1] Sumana K Ramachandra[1] Balachandran Menon[1] Anand Kulkarni[1] Nageshwar Reddy[1]

[1]Asian Institute of gastroenterology, [2]ASIAN INSTITUTE OF GASTROENTROLOGY PVT LTD

Background: Living donor liver transplantation (LDLT) is common in Asia pacific region. The psychological impact of donation, particularly for recipients with severe alcoholic hepatitis (SAH) who undergo early LDLT is less known, which we aimed to assess. **Methods:** In this cross-sectional study, we contacted donors of the recipients who underwent early LDLT for SAH. The primary objective was to assess the psychological profile of these individuals using the General Health Questionnaire (GHQ)-28. A score of more than 23 is considered an indicator of psychological distress. Donors were contacted telephonically, and verbal consent was taken prior to administering the GHQ-28 questionnaire. **Results:** Of the 31 donors we contacted, 19 (61.2%) consented to respond to the questionnaire. Of the 12 donors who were unwilling, three attributed the disease to addiction, and other donors were unwilling due to time/work commitments, and the recipients were alive and healthy. Of the 19 responders, four recipients had died. The median age of the donors was 32 (20-50) years, and males were 10 (52.6%). Donors relation to the recipient was son(36.8%), spouse (36.8%), brother (15.8%), and daughter (10.5%). Forty-two percent had no symptoms and were doing well. While others had some form of symptoms such as incisional site discomfort, abdominal pain, reduced appetite and excessive worrying about donation in varying combinations. The median score of the GHQ-28 was 10 (3-55), with 32% scoring above 23, indicating significant psychological distress. These individuals were suggested seek psychiatric counselling; only three followed through and were initiated on anti-depressants. 75% of those whose recipients died had scores more than 23 compared to 20% of those whose recipients were alive (P=0.03). The median donor GHQ-28 score was 9 (3-55) for those with living recipients and 28.5 (23-34) for those whose recipients had died (P=0.04). The median scores in somatic, anxiety and insomnia, social dysfunction and severe depression domains were 2 (0-10), 3 (0-18), 3 (1-14) and 0 (0-15) respectively. **Conclusion:** One-third of liver donors of SAH experience psychological distress. The outcome of the recipient has a significant influence on the donor's psychological health.

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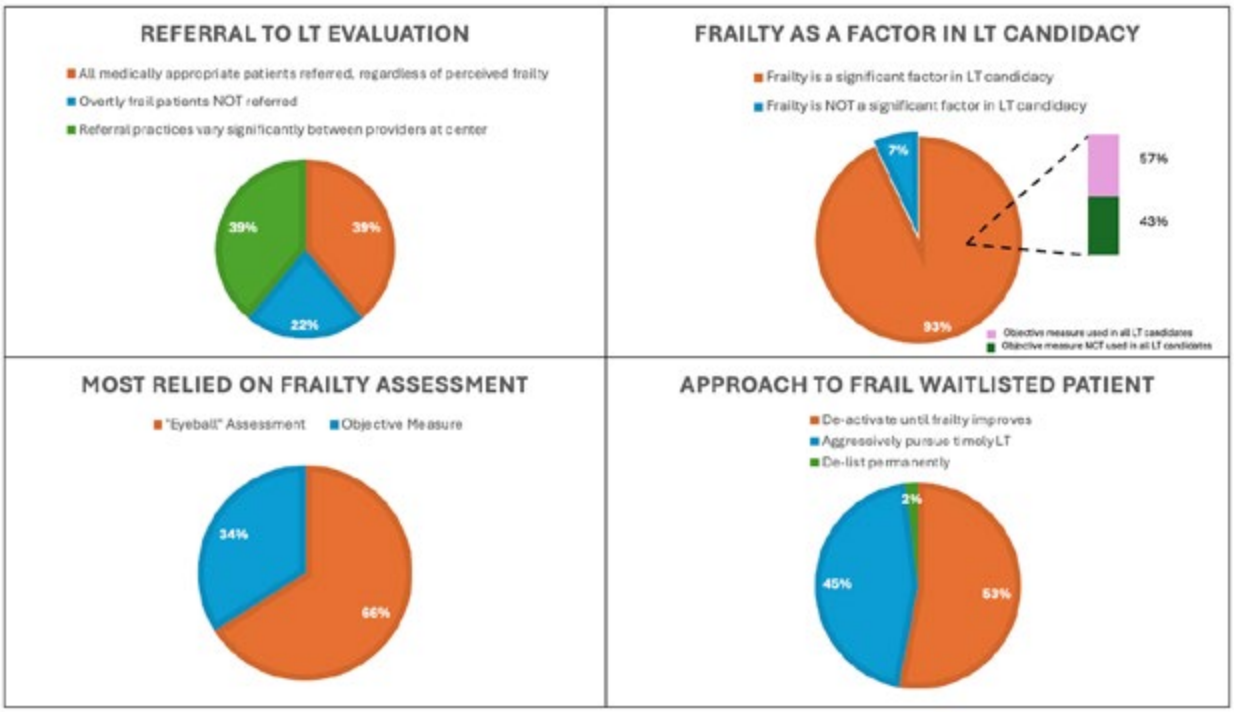
FIGURE 1



Disclosures: Chinmay Hegde: Nothing to Disclose, Ramya shruthi: Nothing to Disclose, Mithun Sharma: Nothing to Disclose, Shantan Venishetty: Nothing to Disclose, Sowmya T R: Nothing to Disclose, Manasa Alla: Nothing to Disclose, Rajesh Gupta: Nothing to Disclose, Padaki Nagaraja Rao: Nothing to Disclose, kumaraswamy P: Nothing to Disclose, Sumana K Ramachandra: Nothing to Disclose, Balachandran Menon: Nothing to Disclose, Anand Kulkarni: Nothing to Disclose, Nageshwar Reddy: Nothing to Disclose

2603 | A NATIONAL SURVEY ON THE PERCEPTION AND APPROACH TO FRAILTY IN LIVER TRANSPLANTATION

Avesh Thuluvath[1] Adam Buckholz[2] Arpan Patel[3] Elizabeth Verna[1] Andres Duarte-Rojo[4]

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Background: Frailty is a critical determinant of liver transplant (LT) outcomes, yet there is limited consensus in the transplant community on whether frailty should inform waitlisting or de-listing decisions. The purpose of this study was to understand how frailty is being used in listing decisions throughout the U.S. **Methods:** We performed a survey of clinicians at adult LT centers in the U.S. to capture center-specific approaches to frailty in LT candidates. The survey was distributed to all members of the AST Liver and Intestinal Community of Practice and directly emailed to medical and surgical directors of LT centers. **Results:** 97 clinicians (63 hepatologists [27 medical directors], 18 surgeons [all LT surgical directors]) responded to the survey, representing 37 centers and 23 of the top 50 highest volume LT centers in 2023. 93% reported that frailty was a significant factor in LT candidacy but only 57% reported using objective measures of frailty during every LT evaluation (Figure 1). The Liver Frailty Index was the most frequently used measure (75%). 16% said an exercise professional evaluated all LT candidates and 26% said some form of “prehabilitation” (home exercises or supervised rehabilitation) was recommended for all LT candidates. At centers without standardized prehabilitation, 40% relied on subjective assessments to determine which patients need prehabilitation. Hepatologists were more likely than surgeons to use objective measures of frailty to guide exercise recommendations (49% vs 15%, p=0.01). 66% of clinicians stated that they relied most heavily on an “eyeball” assessment when determining LT candidacy and only 51% said that objective measures were typically used during LT selection meetings. Referral practices varied

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significantly based on frailty; 39% endorsed referring all medically suitable patients to LT evaluation regardless of perceived frailty, whereas 22% did not refer overtly frail patients; 39% stated that referral practices varied significantly between providers at their center. Regarding approaches to patients on the LT waitlist, 45% favored de-activating frail patient until frailty improved, while 53% favored maintaining waitlist status and aggressively pursuing options for timely LT. **Conclusion:** Though frailty is nearly universally considered an important factor in LT candidacy, there is significant variability in applying objective measures and using frailty for decision-making regarding LT referral, prehabilitation, waitlisting and de-listing. Greater consensus can promote increased transparency, more equitable access and optimization of outcomes.

Disclosures: Avesh Thuluvath: Nothing to Disclose, Adam Buckholz: Nothing to Disclose, Arpan Patel: Nothing to Disclose, Elizabeth Verna: Nothing to Disclose, Andres Duarte-Rojo: Echosens: Grant/Research Support

2604 | COGNITIVE IMPAIRMENT, PHYSICAL FRAILTY, QUALITY, AND LIVER TRANSPLANT RECOVERY: AN INTERIM ANALYSIS FROM LIVCOG, A PROSPECTIVE MULTICENTER COHORT

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[1]UMass Chan Medical School, [2]University of Pennsylvania, Perelman School of Medicine, [3]Northwestern University, Feinberg School of Medicine, [4]Liver Consultants of Texas, [5]University of Pennsylvania Health System

Background: Few studies in liver transplantation (LT) have comprehensively evaluated cognitive and physical health and how it affects post-transplant quality of life, function, and longitudinal health outcomes. The NIH-funded LivCog cohort study is enrolling 450 LT recipients at 4 transplant centers in Pennsylvania, Illinois, and Texas and their caregivers to comprehensively examine cognitive function, physical function and how those factors affect post-LT quality of life and health outcomes. **Methods:** All enrolled patients have detailed clinical data on demographics, comorbidity, and pre-LT liver disease severity. Serial post-LT assessments include: global cognition assessed with Montreal Cognitive Assessment (MoCA), physical function assessed with the liver frailty index (LFI), health literacy assessed with the newest vital sign (NVS), health-related quality of life assessed with Patient-Reported Outcomes Measurement Information System, and liver transplant knowledge evaluated using a novel questionnaire (LTKQ). Correlations among cognitive, frailty, and health-related quality of life measures were assessed with logistic regression models evaluating factors associated with mild cognitive impairment (MCI). **Results:** We present baseline data on n=195 recent LT recipients (LTRs), predominantly within 1 month of LT. Median patient age is 56 (IQR: 50-63; 84% are White; 7% are Black; 3% are Asian; 13% are of Hispanic ethnicity. Prior to LT 51% had viral hepatitis, 28% had MASLD/MASH, 32% had alcohol-associated liver disease (ALD), and 25% had hepatocellular carcinoma (HCC); 42% had hepatic encephalopathy (HE) pre-LT. A total of 23% of patients were frail by LFI. A significant proportion of LTRs reported anxiety (21%), fatigue (33%), pain (47%), and sleep disturbance (34%). Based on MoCA (score <26), 53% exhibited MCI. MCI was significantly correlated with LTKQ (Rho=0.25, p=0.001). Independent predictors of post-LT MCI were age (OR 1.14, 95% CI 1.01-1.30) per 5 years, lower level of education (OR 0.40, 95% CI 0.21-0.73), and pre-LT HE (OR 2.1, 95% CI 1.15-33.92). Physical frailty (LFI) demonstrated significant positive correlations with self-reported health-care quality of life measures, with greater frailty correlated with worse anxiety, depression, pain, and instrumental support (perceived availability of assistance with material or cognitive performance). **Conclusion:** In early results, we document the high post-LT burden of cognitive impairment and impaired quality of life. Pre-transplant HE independently predicts post-transplant MCI and transplant knowledge. The LivCog cohort will examine longitudinal cognitive, physical, and health outcome trajectories to identify distinct phenotypes of post-LT health and their predictive factors.

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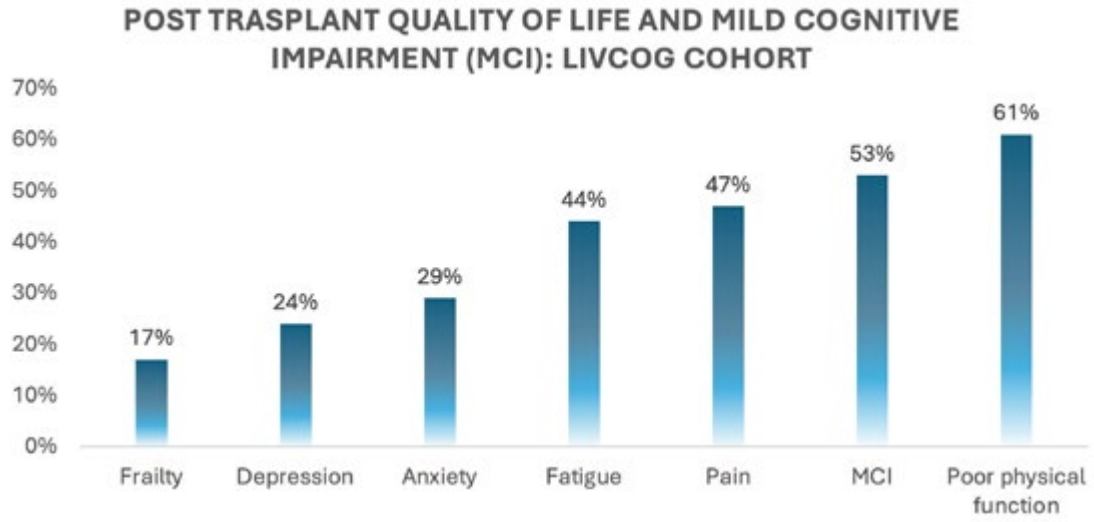

Disclosures: Joyce Tien: Nothing to Disclose, Douglas Schaubel: Nothing to Disclose, Anna Gurian: Nothing to Disclose, Lindsay Berg: Nothing to Disclose, Allison Novorita: Nothing to Disclose, Julia Benavente: Nothing to Disclose, Sumeet Asrani: Nothing to Disclose, Michael Wolf: Nothing to Disclose, Marina Serper: Grant/Research Support relationship with Grifols; Has not ended; Grant/Research Support relationship with Eurofins; Has not ended; Grant/Research Support relationship with Transplant Genomics; Has not ended

2605 | PRE-TRANSPLANT FRAILTY IS ASSOCIATED WITH COMPOSITE CARDIAC EVENTS WITHIN 1 YEAR OF LIVER TRANSPLANTATION

Avesh Thuluvath[1] Fawzy Barry[2] Brendan Blackburn[3] Sri Seetharaman[2] Anand Vissa[2] Asal Bastani[2] Dorothea Kent[2] Jacqueline Lam[2] Thresiamma Lukose[3] Geena George[3] Rebecca Yeh[3] Nayda Pichardo Fernandez[3] Jennifer Lai[2] Elizabeth Verna[3]

[1]Columbia University Irving Medical Center, [2]University of California San Francisco, [3]Columbia University Medical Center

Background: Cardiovascular disease (CVD) is a leading cause of morbidity and mortality after liver transplantation (LT). Frailty independently predicts post-LT mortality but it's specific impact on CVD after LT has not been well-described. However, numerous studies have shown that frailty is an independent predictor of CVD in the elderly population. The purpose of this study was to leverage the Multicenter Functional Assessment in Liver Transplantation (FrAILT) consortium to investigate the impact of frailty on the risk of post-LT cardiovascular events. **Methods:** We performed a retrospective chart review of adult patients who underwent LT between 1/1/2021-12/31/2023 at 2 large transplant centers in the prospective FrAILT consortium cohort study. The most recent Liver Frailty Index (LFI: grip, chair stands, balance testing) prior to LT was the primary predictor of interest. Cardiovascular outcomes were defined as major adverse cardiovascular events (MACE, a composite of acute coronary syndrome, coronary revascularization, congestive heart failure and cerebrovascular events) and composite cardiac events (CCE, including MACE, atrial fibrillation and cardiac arrest). A time-to-event analysis was performed, with MACE/CCE as the event of interest and death as a competing risk. **Results:** 105 patients were included in the study (Table 1). 59% were male and the mean age was 58.2 (± 10.5) years. Metabolic-dysfunction associated steatotic liver disease (21%) and hepatitis C (21%) were the most common etiologies of liver disease. The mean ambulatory LFI was 3.78 (± 0.77), with 66% classified as pre-frail, 11% as frail and 23% as robust using previously established cut-offs. 5 patients developed CCE events (4 with atrial fibrillation, 1 cardiac arrest), 0 patients developed MACE events and 2 patients died during the follow up period. Pre-LT LFI was significantly associated with the development of CCE (HR 2.09, 95% CI 1.07-4.09, p=0.03) on time-to-event competing risk analysis, after adjusting for age and history of hypertension, hyperlipidemia, diabetes mellitus and coronary artery disease prior to LT. **Conclusion:** In this retrospective multi-center study, only 5% of patients developed a MACE or CCE event in the 1 year following LT. However, despite a low incidence of cardiovascular

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events, pre-LT frailty measured by LFI was significantly associated with the development of CCE within 1 year of LT. Future studies, including larger cohorts, are likely necessary to detect the association between frailty and MACE.

TABLE 1

Baseline Clinical Characteristics

	Total	With CCE	Without CCE	p-value
N	105	5 (5%)	100 (95%)	
Sex, male (%)	62 (59%)	1 (20%)	58 (58%)	p=0.09
Age, mean (± SD)	58.2 (± 10.5)	67 (± 4.5)	57.7 (±10.6)	p=0.09
Etiology of ESLD (%)				
ALD	18 (17%)	2 (40%)	16 (16%)	p=0.16
MASLD	22 (21%)	2 (50%)	20 (20%)	p=0.28
HCV	22 (21%)	0 (0%)	22 (22%)	p<0.01
PSC/PBC	9 (8%)	0 (0%)	9 (9%)	p<0.01
AIH	7 (7%)	0 (0%)	7 (7%)	p<0.01
Other	27 (26%)	1 (20%)	26 (26%)	p=0.76
Comorbidities				
HTN	68 (64%)	5 (100%)	63 (63%)	p<0.01
HLD	35 (33%)	4 (80%)	31 (31%)	p=0.02
DMII	47 (44%)	4 (80%)	43 (43%)	p=0.10
CAD	12 (11%)	2 (40%)	10 (10%)	p=0.04
CHF	4 (4%)	1 (20%)	3 (3%)	p=0.05
Atrial Fibrillation/Flutter	7 (7%)	1 (20%)	6 (6%)	p=0.22
CKD	20 (29%)	3 (60%)	17 (17%)	p=0.02
Pre-LT LFI, mean (± SD)	3.78 (± 0.77)	4.29 (± 1.29)	3.76 (±0.74)	p=0.14

Disclosures: Avesh Thuluvath: Nothing to Disclose, Fawzy Barry: Nothing to Disclose, Brendan Blackburn: Nothing to Disclose, Sri Seetharaman: Nothing to Disclose, Anand Vissa: Nothing to Disclose, Asal Bastani: Nothing to Disclose, Dorothea Kent: Nothing to Disclose, Jacqueline Lam: Nothing to Disclose, Thresiamma Lukose: Nothing to Disclose, Geena George: Nothing to Disclose, Rebecca Yeh: Nothing to Disclose, Nayda Pichardo Fernandez: Nothing to Disclose, Jennifer Lai: Nestle Nutrition Institute: Grant/Research Support, Novo Nordisk: Consultant, Genfit: Consultant, Boehringer Ingelheim: Advisor, Elizabeth Verna: Nothing to Disclose

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2606 | PEDIATRIC LIVER TRANSPLANT TRENDS AND OUTCOMES IN 2011-2023: A SINGLE-CENTER STUDY

Saleh Alqahtani[1] Alexandra Aldana[1] Kishwer Kumar[1] Ali Syed Muhammad Akhtar[1] Dalal Albugami[1] Shadan Almuhaidib[1] Dimitri Raptis[1] Dieter Broering[1] Saad Alghamdi[1] Mohammad Shagrani[1]

[1]King Faisal Specialist Hospital & Research Center

Background: Pediatric liver transplantation (LT) poses unique challenges, with outcomes influenced by various factors, including etiology, transplant type, and hepatectomy approach. Understanding these factors is crucial for optimizing patient care and transplant outcomes. **Methods:** We analyzed the data of pediatric LT recipients in a tertiary referral center in Saudi Arabia between 2011 and 2023, assessing LT indications, patient and graft survival, and factors affecting survival post-LT using Kaplan-Meier and Cox regression analysis. **Results:** There were 761 pediatric LT recipients during the study period. Of which, 50% were female, with 91% receiving living donor LT (LDLT). Robotic donor hepatectomy was performed in 49%, followed by open (34%) and laparoscopic (17%) approaches. Hepatocellular carcinoma was present in 3%. Median age at transplant was 2.2 (interquartile range [IQR] 0.9–6.9) years, and median body weight was 10.8 kg (IQR: 7.2–19.1). The top three LT indications were Metabolic noncirrhotic liver diseases (urea cycle disorder, organic academia, hypercholesterolemia, hyperoxaluria) (41%), biliary atresia (25%), and progressive familial intrahepatic cholestasis (25%). Pediatric LT cases rose from 4.3% in 2011 to 11.3% in 2023. Patient survival rates at 1, 2, 3, 5, and 10 years were 96%, 94%, 92%, 92%, and 89%, respectively, with graft survival rates of 95%, 93%, 91%, 90%, and 87%, respectively. Stratified patient survival rates by hepatectomy approach at 1, 2, and 3 years were as follows: Robotic (97%, 95%, 94%), laparoscopic (95%, 93%, 92%), and open (96%, 92%, and 90%), although not statistically significant (p=0.426). Cox regression analysis revealed no significant difference in 1-year post-LT survival between metabolic and genetics and other indications (hazard ratio [HR]: 0.73, 95% confidence interval [CI]: 0.34–1.57, p=0.423). Factors associated with the mortality rate at 1 year were LDLT (HR: 0.35, 95% CI: 0.15–0.83, p=0.017) and recipient readmission within 3 months post-LT (HR: 0.24, 95% CI: 0.07–0.80, p=0.020). **Conclusion:** Our findings highlight the evolving field of pediatric LT in Saudi Arabia, with metabolic and genetic indication emerging as the leading cause, alongside increasing case volumes and favorable long-term survival rates. Additionally, the robotic hepatectomy approach showed potentially higher patient survival. Early post-transplant readmission appears to correlate with improved 1-year survival. These insights contribute to refining pediatric LT protocols and enhancing post-transplant care practices.

Disclosures: Saleh Alqahtani: Nothing to Disclose, Alexandra Aldana: Nothing to Disclose, Kishwer Kumar: Nothing to Disclose, Ali Syed Muhammad Akhtar: Nothing to Disclose, Dalal Albugami: Nothing to Disclose, Shadan Almuhaidib: Nothing to Disclose, Dimitri Raptis: Nothing to Disclose, Dieter Broering: Nothing to Disclose, Saad Alghamdi: Nothing to Disclose, Mohammad Shagrani: Nothing to Disclose

2607 | LONGER COLD ISCHEMIA TIME PREDICTS INCREASED TRANSFUSION REQUIREMENTS DURING LIVER TRANSPLANTATION

Maham Ghani[1]

[1]Northwell Health

Background: Increased transfusion requirements during orthotopic liver transplantation (OLT) are associated with increased infections, mortality, and resource utilization. Prolonged cold ischemia time (CIT) has also been shown to be related to worse graft outcomes. There are no guidelines on CIT, but CIT <10 hours are generally acceptable for OLT. This study investigates the relationship between CIT and transfusion needs during OLT. **Methods:** All patients who received OLT from 12/2019-1/2024 at NSUH were enrolled in this study. Patients with dual transplants and missing data were excluded. Long CIT was defined as >6 hours, and short CIT was defined as < 6 hours. Baseline characteristics including age, gender, BMI, pre-transplant MELD 3.0, coagulation and liver studies as well as post-operative acute kidney injuries (AKI), ICU length of stay (LOS), hospital LOS, as well as intraoperative transfusion needs such as packed red blood cells (PRBCs), cryoprecipitate, platelets, fresh frozen plasma (FFP), albumin were collected via chart review. Statistical analysis was performed to assess significance and correlation. **Results:** 204 patients were enrolled with 191 patients included in final analysis; 113 patients were stratified into the short CIT group and 78 into the long CIT group. There were no significant differences

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in MELD 3.0, AKI, albumin requirement, length of hospital or ICU stay between the long and short CIT groups. Longer CIT had significantly more intraoperative transfusions of pRBCs (12±9 vs 8±6 units; p=0.007), FFP (9±8 vs 6±6 units; p=0.013), and cryoprecipitate (4±4 vs 3±3 units; p=0.046). Transfusion requirements remained significantly increased after adjusting for age, gender, race/ethnicity, BMI, and MELD 3.0. **Conclusion:** Our study demonstrates that CIT >6 hours is significantly associated with increased transfusion requirements. Longer CIT may require increased transfusions secondary to reperfusion injury or increased inflammation in senescent RBCs. Our findings can serve as a valuable tool for predicting transfusion needs, optimizing resource allocation, and improving patient care. Given the limited availability of blood products and the correlation between increased requirements and adverse patient outcomes, larger retrospective and prospective studies are needed to explore post-transplant outcomes and establish causality.

Table 1. Baseline Characteristics and Selected Outcome Measures

		Cold Ischemia Time			
		≤6 Hours	>6 Hours	Total	
		N; Mean±SD	N; Mean±SD	N; Mean±SD	p
Cold Ischemia Time (hr)		113; 5.2±0.6	78; 7.2±1.5	191; 6±1.5	-
Age at Transplant (yr)		113; 54±11	78; 50±13	191; 53±12	**0.029**
BMI at Transplant		113; 26.9±5.3	78; 28.6±6.5	191; 27.6±5.8	**0.047**
Race/Ethnicity*	White	62/113 (54.9%)	40/78 (51.3%)	102/191 (53.4%)	0.841
	Black	13/113 (11.5%)	12/78 (15.4%)	25/191 (13.1%)	
	Asian	11/113 (9.7%)	10/78 (12.8%)	21/191 (11%)	
	Hispanic/Latino	26/113 (23%)	15/78 (19.2%)	41/191 (21.5%)	
	Unknown	1/113 (0.9%)	1/78 (1.3%)	2/191 (1%)	
Sex*	Female	39/113 (34.5%)	28/78 (35.9%)	67/191 (35.1%)	0.844
	Male	74/113 (65.5%)	50/78 (64.1%)	124/191 (64.9%)	
KPS^ at OLT		101; 0.8±0.1	62; 0.7±0.2	163; 0.8±0.1	0.084
MELD 3.0		113; 21.8±8.0	78; 23.7±6.9	191; 27±9	0.094
Diabetes*		20/105 (19%)	13/71 (18.3%)	33/176 (18.8%)	0.902
Length of Hospital Stay (days)		101; 15±9	64; 15±7	165; 15±9	0.934
Length of ICU Stay (days)		111; 6±5	76; 7±6	187; 6±6	0.884
pRBC Transfused (unit)		111; 8±7	76; 12±9	187; 10±8	**0.007**
Platelets Transfused (unit)		110; 3±3	76; 4±4	186; 3±3	0.066
FFP Transfused (unit)		111; 6±6	76; 9±8	187; 8±7	**0.013**
5% Albumin Infused (mL)		110; 1012±837	76; 1234±1038	186; 1103±928	0.124
Cryoprecipitate Transfused (unit)		111; 3±3	75; 4±4	186; 3±3	**0.046**
AKI Within 14 Days of OLT*^		54/113 (47.8%)	41/78 (52.6%)	95/191 (49.7%)	0.516
Hemoglobin day of OLT		98; 9.6±1.9	62; 9.2±1.5	9.5±1.8	0.110
INR day of OLT		112; 1.73±0.75	78; 1.9±0.76	203; 1.8±0.75	0.127

*Count and column percentages reported. p derived from chi-square test.
^ Karnofsky Performance Scale
*Defined as rise in serum creatinine by 0.3 within 48 hrs, 1.5 x baseline serum creatinine, or <0.5ml/hr urine output within 2 weeks of OLT

Disclosures: Maham Ghani: Nothing to Disclose

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2608 | WORSE METABOLIC OUTCOMES IN BLACK FEMALES WHO RECEIVE A LIVER TRANSPLANTATION

Hiba Khan[1] Rehan Razzaq[1] Shreya Shah[2] Ibrahim Siddiqui[3] Audrey Ang[1] Madison Nguyen[4] Alexis Kim[1] Sheila Bullock[1] Vaishali Patel[3]

[1]Virginia Commonwealth University Health, [2]Virginia Commonwealth University, [3]VCU Division of Gastroenterology & Hepatology, [4]VCUHS

Background: Prior research aimed at demonstrating gender disparities has focused on female vs. male comparison, however, such a comparison ignores key biological processes as male gender serves as the reference standard. Thus, in the present study we aimed to evaluate healthcare disparities in female liver transplant recipients using the female sex, itself as the reference standard. As the burden of metabolic disease is high following LT, we evaluated the interaction between ethnicity and socioeconomic status on future risk of cardiometabolic disease and survival. **Methods:** This is a retrospective study including 246 adult females who had received a LT between 2015-2023. Social vulnerability index (SVI) was used and is a composite of 4 factors (socioeconomic status, household characteristics, racial/ethnic minority status, and housing type & transportation), and established marker of external stressors to individual health by the Centers of Disease Control and Prevention (CDC). LT recipients were then divided into two groups: those above the median SVI of the cohort and those below the median SVI. Kaplan-Meier curves were constructed to determine the association between ethnicity, SVI and likelihood of developing metabolic complications including type 2 diabetes mellitus (T2DM), obesity, hypertension, and all-cause mortality following LT. **Results:** The cohort consisted of 246 females (73% white and 23% black patients) with the most common etiology of liver disease being alcohol cirrhosis (24%), followed by MASH (22%). Over a 36 month post-LT period, no significant differences in cardiometabolic outcomes and mortality were noted when patients were stratified based on SVI status (above vs. below SVI). Similarly, no significant differences in cardiometabolic burden was noted when women were stratified according to ethnicity (non-Hispanic white vs. black). However, in patients who were below the median SVI, black women had worse survival and a higher likelihood of developing new onset T2DM and obesity (Figure 1). These associations remained significant in Cox regression models when accounting for age and immunosuppressant use. **Conclusion:** In females, healthcare disparities are most prominent in the form of racial disparities, particularly in Black women [compared to Caucasian women] who have lower access to resources (i.e. higher SVI). These novel findings underscore the importance of better understanding the key driver of this disparity to improve outcomes in LT recipients.

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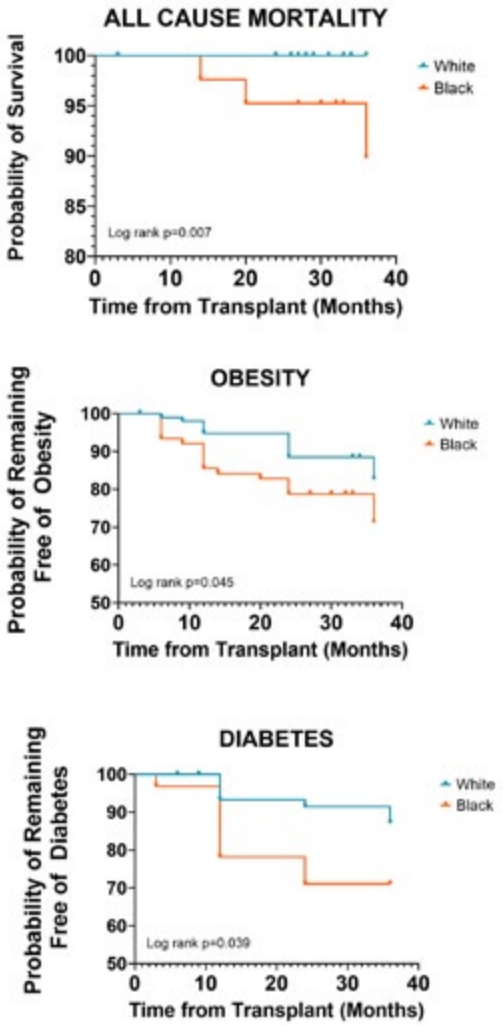
Figure 1: Higher Social Vulnerability Is Associated with Higher Metabolic Burden in Black Female Liver Transplant Recipients



Disclosures: Hiba Khan: Nothing to Disclose, Rehan Razzaq: Nothing to Disclose, Shreya Shah: Nothing to Disclose, Ibrahim Siddiqui: Nothing to Disclose, Audrey Ang: Nothing to Disclose, Madison Nguyen: Nothing to Disclose, Alexis Kim: Nothing to Disclose, Sheila Bullock: Nothing to Disclose, Vaishali Patel: Nothing to Disclose

2609 | IMPACT OF SARCOPENIA, FRAILTY, AND MUSCLE FAT INFILTRATION ON MORTALITY IN PATIENTS UNDERGOING LIVER TRANSPLANT EVALUATION

Maham Ghani[1] *Alexa Giammarino*[1]

[1]*Northwell Health*

Background: Frailty and sarcopenia predict increased mortality and poor outcomes. Sarcopenia is typically measured using the skeletal muscle index at the L3 level via CT scans. However, MRI can evaluate both muscle quantity and quality through the proton density fat fraction (PDFF). Few studies have used MRI to examine the association between frailty, sarcopenia, and intramuscular fat in patients undergoing liver transplant evaluation. This study assesses MRI fat fraction's utility and its relationship to mortality in this cohort. **Methods:** This retrospective study involved 180 liver transplant evaluation patients at a New York tertiary care center from

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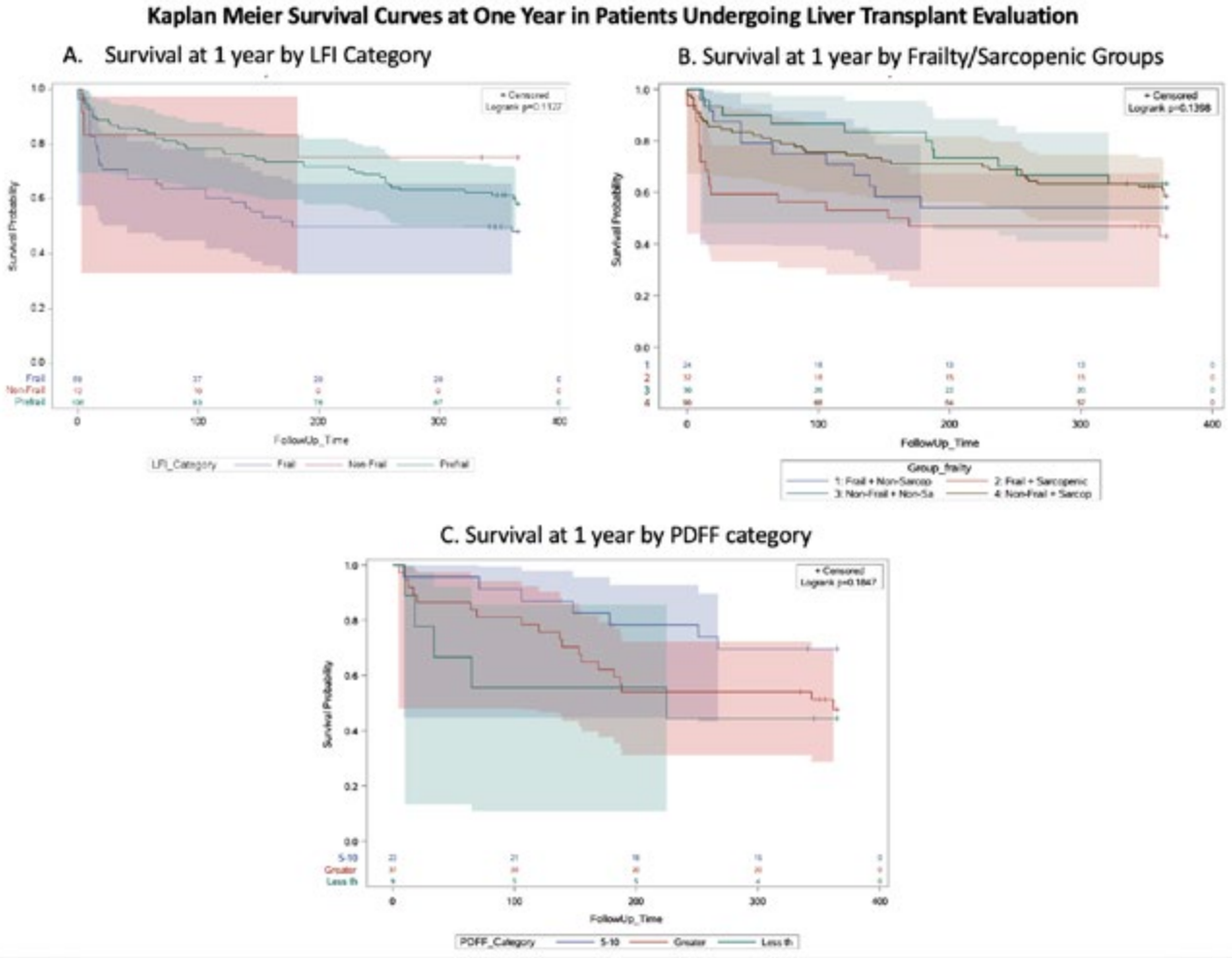
April 2021 to July 2023 (67 inpatients and 113 outpatients). Among them, 176 had Liver Frailty Index (LFI) assessments about one year from the initial evaluation and were categorized as non-frail, pre-frail, or frail, and as sarcopenic or non-sarcopenic based on MRI. MRI sequences at the L3 endplate included abdominal spin-echo (SE; n=155) or 2-point Dixon gradient recall echo (GRE; n=73). In addition to the standard psoas muscle measurement, the erector spinae and quadratus lumborum muscles were segmented bilaterally at the L3 endplate level using ITK-SNAP software. PDFF was calculated from GRE cohort images containing both water and fat fractions (n=69). Baseline clinical data, length of stay, and 1-year mortality were collected. Kaplan-Meier survival curves were created to evaluate LFI, combinations of sarcopenia and frailty levels, and PDFF in relation to mortality. **Results:** Of the 180 patients, 124 were sarcopenic, and 56 were non-sarcopenic. Among them, 176 had completed LFI scores (58 frail, 106 pre-frail, and 12 non-frail). Higher frailty levels were associated with lower survival probabilities (p=0.1127). Sarcopenia significantly impacted mortality when combined with frailty (p=0.1398). Robust patients (non-frail and non-sarcopenic) had the highest survival rates, followed by non-frail sarcopenic patients. The frail sarcopenic group had the lowest survival rates. Among the 176 patients, 69 GRE scans were available for intramuscular fat fraction analysis, divided into three PDFF levels: <5% (n=9), 5-10% (n=23), and >10% (n=37). Patients with 5-10% PDFF had the highest survival chances compared to those with PDFF <5% or >10% (p=0.1847). **Conclusion:** Sarcopenia and frailty significantly impact mortality in patients undergoing liver transplant evaluations, our study shows frailty plays a more prominent role. Additionally we found patients with intermediate PDFF (5-10%) have the best survival outcomes, suggesting PDFF as a valuable survival predictor. Larger studies are needed to further explore the correlation between PDFF and outcomes in this patient population, potentially enhancing pre-transplant evaluation and risk stratification.



Disclosures: Maham Ghani: Nothing to Disclose, Alexa Giammarino: Nothing to Disclose

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2610 | THE IMPACT OF ACUTE PANCREATITIS IN PATIENTS WITH LIVER FAILURE IN A SINGLE TERTIARY ICU

Julia Nowik[1] Julia Nowik[1] Kondragunta Prasad[1] Calvin Eriksen[2] Veronica Loy[3]

[1]Medical College of Wisconsin, [2]Medical College of Wisconsin Department of Surgery, [3]MCW

Background: Acute pancreatitis is linked to serious complications and poses a significant co-morbid risk, especially in post liver transplant (LT) patients. The high mortality rate associated with acute pancreatitis is due to infection, multiple organ system dysfunction (MODS), and systemic inflammatory response syndrome (SIRS). Post-LT patients have an increased risk of mortality due to acute pancreatitis within the first thirty days of LT and in patients with a history of pancreatitis prior to transplant. This observational study is to evaluate which effects of acute pancreatitis in patients with liver failure correlate with likelihood of progressing to LT by examining medical history, transplant listing status, and mortality. **Methods:** A retrospective analysis of a single center from Medical College of Wisconsin was conducted from 2017 to 2020. Inclusion criteria consisted of an evaluation by the LT team, age >18 years, documented liver disease, and documented acute pancreatitis meeting the Atlanta Classification criteria. Exclusion criteria included chronic pancreatitis, pancreatitis due to endoscopic retrograde cholangiopancreatography (ERCP), or history of pancreatitis without a documented episode. In total, 73 patients met our inclusion criteria. Unless specified otherwise, all statistical tests were two-sided using SAS software, with a p-value less than 0.05. **Results:** Patients with liver failure and pancreatitis who did not undergo LT were found to have a higher likelihood of having acute kidney injury (51.6% versus 100%, p=0.008), chronic kidney disease (20.6% versus 88.9%, $p < 0.001$), and diabetes mellitus (20.6% versus 55.6%, p=0.038) when compared with patients who had LT. Patients who underwent LT had higher MELD scores approaching statistical significance (p=0.087). There were no deaths in patients who underwent LT (p=0.051). Out of the patients who did not undergo LT, those who were listed had a mortality of 61.5% versus 15.8% in patients who were not. There is significant evidence that MELD score is related to mortality after controlling for all other variables. For every unit increase in MELD score, the odds of mortality increased by 14%. Patients with LT also had a lower likelihood of mortality compared to patients without LT. **Conclusion:** Overall, transplant recipients showed decreased mortality rates despite experiencing pancreatitis within thirty days before transplant. Of those that did not undergo LT but were listed had a higher mortality rate from decompensation.

Disclosures: Julia Nowik: Nothing to Disclose, Julia Nowik: Nothing to Disclose, Kondragunta Prasad: Nothing to Disclose, Calvin Eriksen: Nothing to Disclose, Veronica Loy: Nothing to Disclose

2611 | LIPOPROTEIN-INSULIN RESISTANCE (LP-IR) SCORE PREDICT FUTURE RISK OF ATHEROGENIC EVENTS IN LIVER TRANSPLANT RECIPIENTS: A PROSPECTIVE STUDY ◆

Madison Nguyen[1] Alexis Kim[2] Rehan Rezzaq[2] Ibrahim Siddiqui[2] Hiba Khan[2] Idris Yakubu[2] Geneva Roache[2] Vaishali Patel[2] Mohammad Siddiqui[2]

[1]VCUHS, [2]Virginia Commonwealth University

Background: Liver Transplant (LT) recipients are high risk for atherogenic events, however, risk stratification in these patients remains clinically challenging as routinely used parameters of cardiovascular risk (i.e lipid profile) has poor diagnostic performance. Prior studies have implicated perturbed atherogenesis in LT recipients and exposure to chronic immunosuppression increases insulin resistance in LT recipients. Lipoprotein insulin resistance (LP-IR) score is a composite score that measures insulin resistance derived from lipoprotein particles and has demonstrated future risk of cardiovascular disease in non-LT population. The goal of the current study was to evaluate the impact of LP-IR score on risk of atherogenic events in LT recipients. **Methods:** The study was performed in LT recipients (n= 83) who were prospectively recruited between 1/2013-1/2016 in a cohort study evaluating the impact of metabolic disease following LT. Patients had fasting blood samples analyzed for LP-IR at time of study enrollment. All patients were managed according to best practices at discretion of hepatologist. Atherogenic events were defined as myocardial infarction (MI), embolic stroke or sudden cardiac death. Time to clinical event or last clinical follow up was used to construct Kaplan Meier curves. Cox regression analysis was used to determine the significance and strength of association between LP-IR and atherogenic events. **Results:** A total of 16 atherogenic events were observed after median follow up of 107 months. No significant differences in LP-IR score was noted according to etiology of cirrhosis requiring LT. In Cox regression analysis, LP-IR score was a strong predictor of future risk of atherogenic events with HR 1.028 (95% CI 1.001, 1.046, p = 0.04). This association was independent of etiology of liver disease, immunosuppression,

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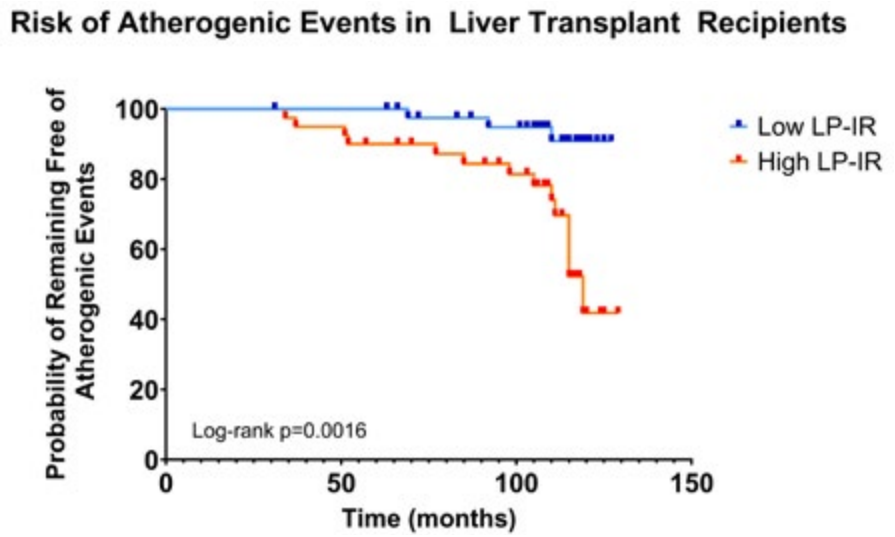
statin use, age and diabetes. In survival analysis, LT recipients with high LP-IR (above median LP-IR score) were significantly higher risk of having atherogenic events compared to those with low-IR score (above median LP-IR value) [Figure 1]. No relationship between individual lipoprotein composition of LP-IR score that includes VLDL, LDL and HDL and atherogenic events was noted. **Conclusion:** Present study provides data demonstrating a positive relationship between LP-IR score and future risk of atherogenic events, potentially providing a novel biomarker for atherogenic risk assessment in LT, however, study findings require validation in prospective studies



Disclosures: Madison Nguyen: Nothing to Disclose, Alexis Kim: Nothing to Disclose, Rehan Rezzaq: Nothing to Disclose, Ibrahim Siddiqui: Nothing to Disclose, Hiba Khan: Nothing to Disclose, Idris Yakubu: Takeda Pharmaceuticals: Speaking and Teaching, Veloxis Pharmaceuticals: Speaking and Teaching, Geneva Roache: Nothing to Disclose, Vaishali Patel: Nothing to Disclose, Mohammad Siddiqui: NovoNordisk: Grant/Research Support, 89Bio: Consultant

2612 | ASSESSING THE PROGNOSTIC IMPACT OF ACUTE-ON-CHRONIC LIVER FAILURE SEVERITY ON POST-LIVER TRANSPLANT OUTCOMES

David Lee[1] Ashton Harmacinski[1] Sharmitha Yerneni[2] Ki Jung Lee[2] Catherine Sun[1] Sarah Yang[1] Andrew Chan[1] Gregory Fan[2] Nathalie Urrunaga[3]

[1]University of Maryland School of Medicine, [2]Tufts School of Medicine, [3]University of Maryland, Baltimore

Background: While liver transplant (LT) offers the best chance of survival in patients with end-stage liver disease, there has been a recent emergence in our understanding of acute-on-chronic liver failure (ACLF) with respect to post-transplant prognosis. This study analyzes the mortality rates after LT stratified by ACLF severity, specifically evaluating rates of death, graft failure, and mortality due to various organ dysfunction. **Methods:** LT patients with ACLF were selected from the UNOS-STAR transplant registry 2005-2019 and stratified into severity of liver failure based on the modified European Association for the Study of the Liver-Chronic Liver Failure Consortium (EASL-CLIF) criteria. Those without ACLF served as the reference group (grade 0) while ACLF grades (ACLF grades 1-3) represented the exposures. Cox regression analysis was used to evaluate the risks associated with primary outcomes, which included all-cause mortality and graft failure. Risks associated with specific causes of death were also measured using a similar approach. Cumulative hazard curves and the log-rank p-values were also derived for the outcomes. **Results:** 47,447 patients who underwent LT were included, stratified by ACLF grade (ACLF 0: 25,400; ACLF 1: 7,704; ACLF 2: 7,049; ACLF 3: 7,294). ACLF patients, who were younger with more women and fewer white patients, had higher mortality rates. ACLF 1, ACLF 2, and ACLF 3 case incidence rates were 53.91 (aHR 1.18, 95% CI 1.12-1.24, p<0.001), 51.59 (aHR 1.17, 95% CI 1.10-1.24, p<0.001), and 66.98 (aHR 1.60, 95% CI 1.51-1.69, p<0.001) per 1000 person-years, respectively, compared to 46.69 for grade 0. There were no significant differences in graft failure for grades 1 or 2, but grade 3 showed an increased graft failure incidence rate of 15.78 (aHR 1.43, 95% CI 1.27-1.60, p<0.001) compared to 9.98 for grade 0. There was increased cardiac, infectious, neurologic, and renal mortality across all grades and respiratory mortality for grades 1 and 3. ACLF-3 patients had an increased risk of graft vascular complications and

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rejection mortality. **Conclusion:** Patients with ACLF had worse outcomes in terms of mortality than those without ACLF. Advanced ACLF (grade 3) carries the highest risk of both mortality and graft failure.

Figure 1: Comparison of Cumulative Events with All-Cause Mortality and Graft Failure as the Endpoint Over a 5 Year Period

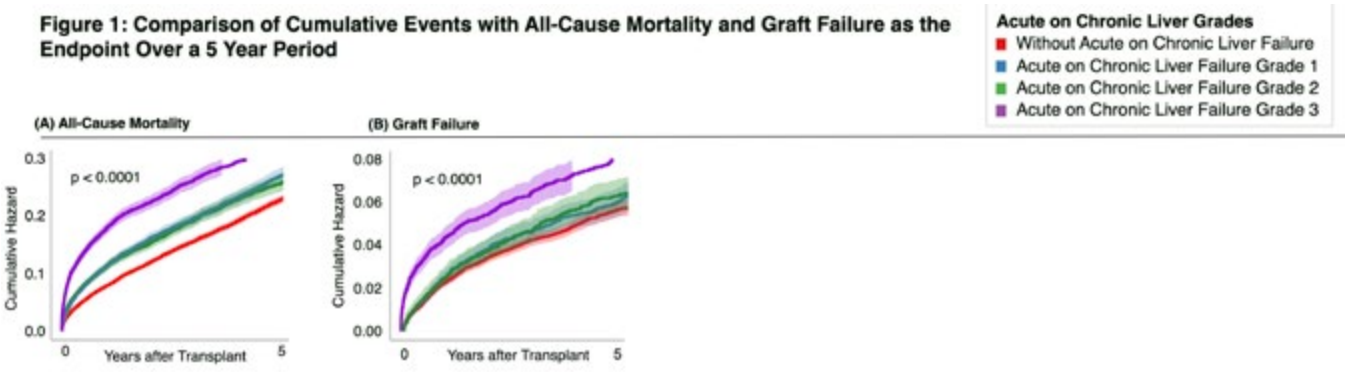
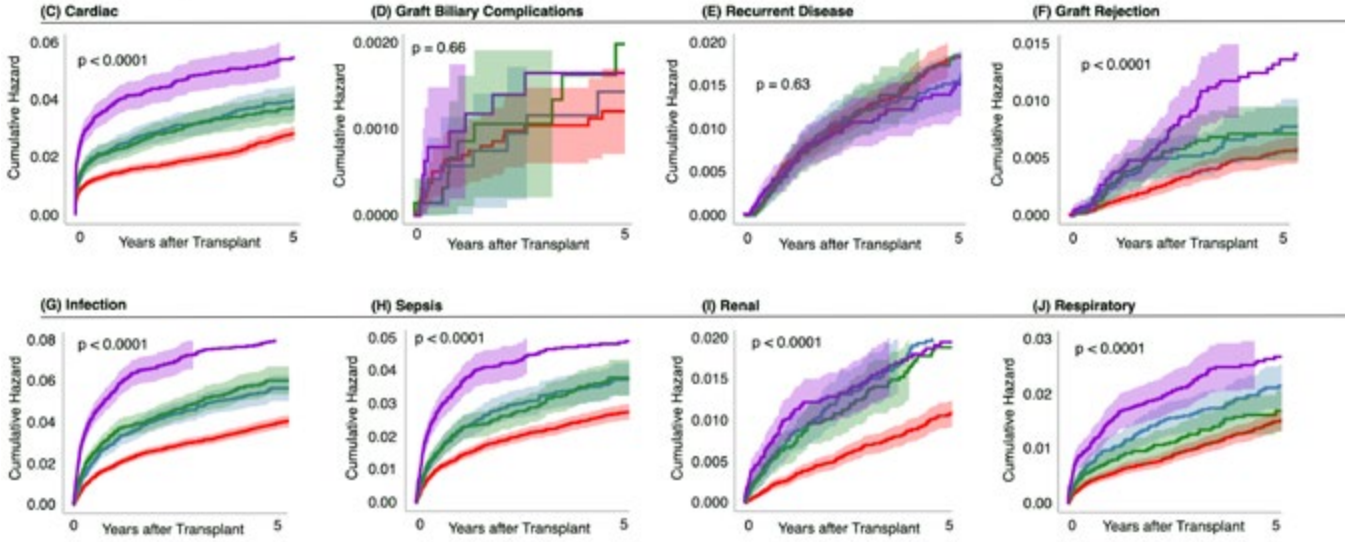


Figure 2: Comparison of Cumulative Events with Specific Causes of Death as Endpoints Over a 5 Year Period



(A) represents the cumulative hazard(s) for all-cause mortality in liver transplant recipients stratified by the grade of acute-on-chronic-liver-failure (ACLF) over a 5 year period. (B) represents the cumulative hazard(s) for graft failure in liver transplant recipients stratified by the grade of ACLF over a 5 year period. (C), (D), (E), (F), (G), (H), (I), and (J) represents the cumulative hazard(s) death due to cardiac causes, graft biliary complications, recurrent liver disease, graft rejection, infection, sepsis, renal, and respiratory causes respectively, in liver transplant recipients stratified by the grade of ACLF over a 5 year period.

Disclosures: David Lee: Nothing to Disclose, Ashton Harmacinski: Nothing to Disclose, Sharmitha Yerneni: Nothing to Disclose, Ki Jung Lee: Nothing to Disclose, Catherine Sun: Nothing to Disclose, Sarah Yang: Nothing to Disclose, Andrew Chan: Nothing to Disclose, Gregory Fan: Nothing to Disclose, Nathalie Urrunaga: Nothing to Disclose

2613 | THE PROGNOSTIC RELATIONSHIP BETWEEN VARYING DEGREES OF ACUTE-ON-CHRONIC LIVER FAILURE ON THE POST-TRANSPLANT PROGNOSIS OF PATIENTS WITH AUTOIMMUNE LIVER DISEASES UNDERGOING LIVER TRANSPLANTATION

David Lee[1] Sindhura Kolachana[1] Mohammed Shaik[1] Kimberly Schuster[2] Sharmitha Yerneni[2] Hannah Chou[2] Harrison Chou[2] Gregory Fan[2] Nathalie Urrunaga[3]

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Background: Patients with autoimmune liver diseases (AiLD), which include autoimmune hepatitis, primary biliary cholangitis and primary sclerosing cholangitis, are at higher risk for developing advanced liver disease and hepatic complications, which may require liver transplantation (LT). The concept of acute-on-chronic liver failure (ACLF) has emerged as a critical factor in prognostication, however its significance in AiLD patients is understudied. This study aims to investigate the impact of ACLF on the prognosis of AiLD patients undergoing LT.

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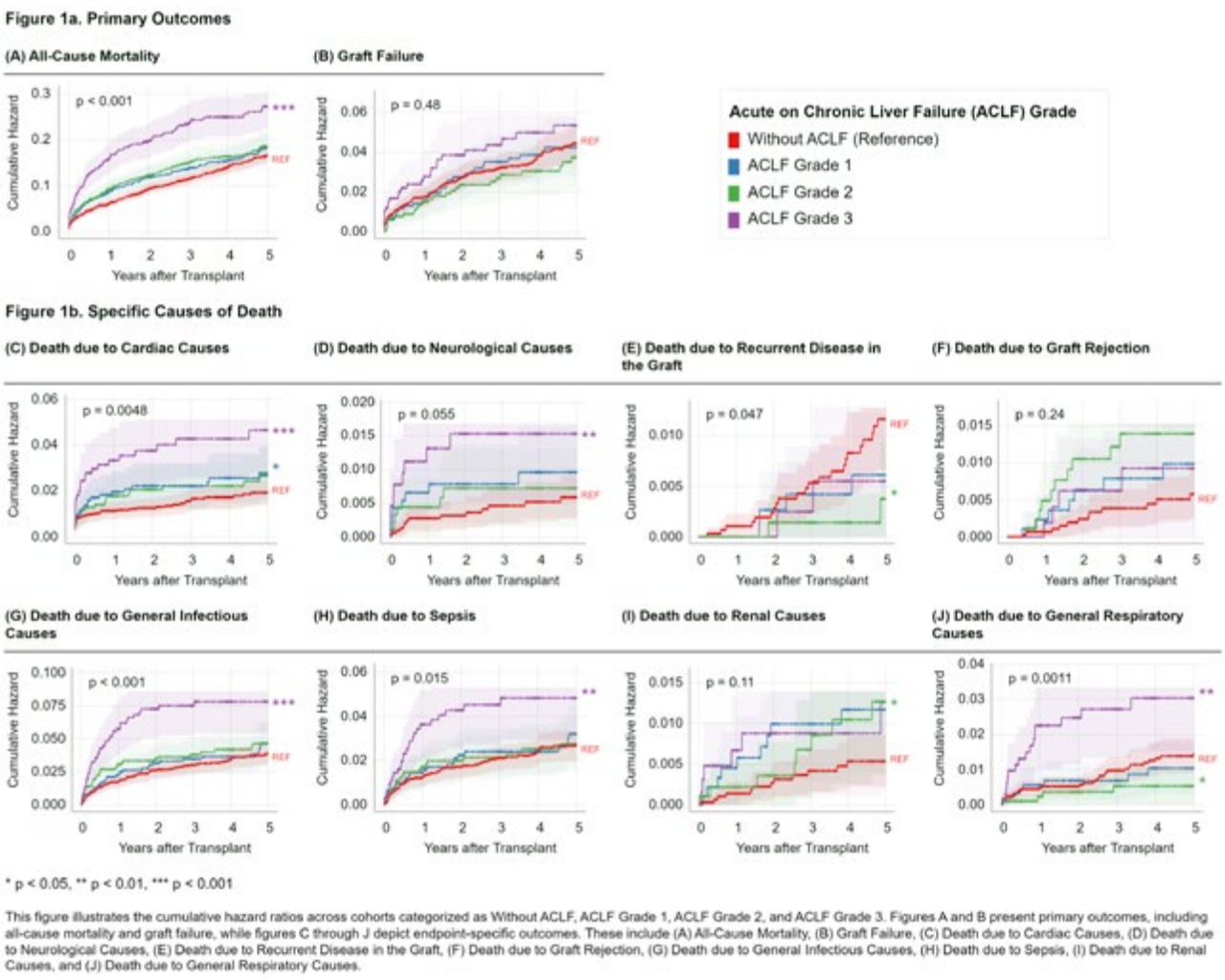
Methods: Patients with AiLD and ACLF who underwent LT from 2005-2019 were selected from the UNOS-STAR database and stratified based on the modified European Association for the Study of Liver-Chronic Liver Failure Consortium (EASL-CLIF), with Grade 0 representing no ACLF. Multivariate Cox regression analyses were used to compare the primary outcomes, all-cause mortality and graft failure, as well as other organ-specific mortality causes. Cumulative hazard curves and the log-rank p-value were derived for the study endpoints. **Results:** 5,679 patients with AiLD and pre-transplant ACLF who underwent LT were included and stratified by ACLF grade (ACLF-0: 3,088; ACLF-1: 963; ACLF-2: 956; ACLF-3: 672). With higher ACLF grades, the proportion of female patients increased (55.34% vs 58.26% vs 62.66% vs 70.24%, p<0.001) while the proportion of Whites decreased (74.22% vs 69.57% vs 63.18% vs 56.55%, p<0.001). There were no significant differences in all-cause mortality in the ACLF-1 and 2 cohorts, however ACLF-3 demonstrated greater all-cause mortality with incidence rate 54.97 per 1000 person years (aHR 1.53, 95%CI 1.25-1.86, p<0.001), compared to 34.68 for Grade 0. No significant differences were seen in graft failure across all ACLF grades. Higher mortality from respiratory causes was seen in ACLF-2 (aHR 0.30, 95%CI 0.10-0.85, p=0.02) and from cardiac (aHR 1.99, 95%CI 1.17-3.37, p=0.01), infectious (aHR 1.98, 95%CI 1.34-2.93, p<0.001), neurologic (aHR 2.77, 95%CI 1.15-6.67, p=0.02), respiratory causes (aHR 2.26, 95%CI 1.18-4.33, p=0.01) and sepsis (aHR 1.88, 95%CI 1.15-3.07, p=0.01) in ACLF-3. **Conclusion:** The severity of ACLF in LT recipients with AiLD significantly affects prognostic outcomes, with advanced ACLF-3 patients faring higher all-cause mortality. Further research on early complication detection and targeted interventions is essential for optimizing outcomes in this high-risk population.

Comparison of Cumulative Events in Patients with Autoimmune Liver Disease and Progressive Grades of Acute-on-Chronic Liver Failure (ACLF) over a 5-Year Post-Transplant Period



This figure illustrates the cumulative hazard ratios across cohorts categorized as Without ACLF, ACLF Grade 1, ACLF Grade 2, and ACLF Grade 3. Figures A and B present primary outcomes, including all-cause mortality and graft failure, while figures C through J depict endpoint-specific outcomes. These include (A) All-Cause Mortality, (B) Graft Failure, (C) Death due to Cardiac Causes, (D) Death due to Neurological Causes, (E) Death due to Recurrent Disease in the Graft, (F) Death due to Graft Rejection, (G) Death due to General Infectious Causes, (H) Death due to Sepsis, (I) Death due to Renal Causes, and (J) Death due to General Respiratory Causes.

Disclosures: David Lee: Nothing to Disclose, Sindhura Kolachana: Nothing to Disclose, Mohammed Shaik: Nothing to Disclose, Kimberly Schuster: Nothing to Disclose, Sharmitha Yerneni: Nothing to Disclose, Hannah

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Chou: Nothing to Disclose, Harrison Chou: Nothing to Disclose, Gregory Fan: Nothing to Disclose, Nathalie Urrunaga: Nothing to Disclose

2614 | MENTAL HEALTH NEEDS OF PATIENTS SEEKING SUPPORT THROUGH TRANSPLANT RECEIPIENTS' INTERNATIONAL ORGANIZATION (TRIO)

Lorrinda Gray-Davis[1] Alexis Bobu[2] Wendy Balliet[3] Faith Parsons[4] Solaf Al Awadhi[4] Amy Waterman[4]

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Background: Patient-led nonprofit organziations serve critical roles outside of the transplant centers supporting patients as they plan for and recover from transplants. We examined the mental health and social support needs, stressors, and interest in mentoring of individual members of Transplant Recipients' International Organization (TRIO) **Methods:** From July-Aug. 2023, we invited 90 members from 6 TRIO chapters to complete an online survey measuring their demographic characteristics and assessing their levels of depression (PHQ-8 score), mental and physical health (SF-12), social support (8-LAC Social Support Assessment Tool), and patient activation (PAM score). We assessed which transplant-related challenges they were facing and whether they were interested in participating in peer-to-peer mentoring programs. **Results:** Pre- and post-transplant TRIO members were predominantly female (54%) with a college level education or higher (61%). Most had received transplants (82%) of these types: liver (55%), kidney (23%), heart (16%), lung (3%), and multiple organs (3%) and were ≤5 years post-transplant (60%). Overall, the majority were managing some level of depression (57%), (Table). Pre-transplant patients were more likely to report having moderate to severe depression (50% vs. 11%, p<.002) and poorer physical health (mean score 32 vs. 43, p<.001) than transplanted patients. Members reported their greatest challenges were adjusting to organ failure, managing loneliness and stress, and medication and disease management. 89%were either interested in or already participating in peer-to-peer mentoring programs, with the majority reporting being more activated patients. **Conclusion:** TRIO members are commonly managing some level of depression and learning how to manage and cope with their disease and its treatments. Peer-to-peer support programs were seen as valuable by members, particularly for pre-transplant patients who were reporting greater depression and poorer physical health and support.

Variation in Mental Health and Stressors by TRIO Members

Measure	Overall (n=90,100%)	Pre-transplant (n=16,18%)	Post-transplant (n=74, 82%)	p=value
Depression (PHQ-8 Score category, n(%)				0.002*
<5(minimal depression)	39(43%)	5(31%)	34(46%)	
5-9 (mild depression)	35(39%)	3(19%)	32(43%)	
> 10 (moderate to severe depression	16(18%)	8(50%)	8(11%)	
Mental Health (SF12), mean (SD))	47.7 (9.8)	45.0 (9.6)	48.3 (9.8)	0.227
Physical Health (SF12), mean (SD)	40.6 (11.6)	31.6 (9.7)	42.6 (11.1)	.001*
Social Support Score (8-LAC), mean (SD)	36.0 (7.1)	35.8 (7.1)	36.0 (7.1)	0.0795
Patient activation (PAM level), n-%				0.0321
1(Disengaged & overwhelmed)	1 (1.1%)	0 (0%)	1 (1.4)	
2 (becoming aware but still struggling	14 (16%)	5(31%)	9 (12%)	
3(Taking action & gaining control)	32 (36%)	5 (31%)	27 (26%)	
4 (Maintaining behaviors & pushing further)	43 (48%)	6 (38%)	37 (50%)	

Disclosures: Lorrinda Gray-Davis: Nothing to Disclose, Alexis Bobu: Nothing to Disclose, Wendy Balliet: Nothing to Disclose, Faith Parsons: Nothing to Disclose, Solaf Al Awadhi: Nothing to Disclose, Amy Waterman: Nothing to Disclose

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2615 | THE PROGNOSTIC CORRELATION BETWEEN PRE-LIVER TRANSPLANT ACUTE-ON-CHRONIC LIVER FAILURE AND POST-TRANSPLANT OUTCOMES AMONG PATIENTS WITH HEPATITIS C ◆

David Lee[1] Ashton Harmacinski[1] Sharmitha Yerneni[2] Ki Jung Lee[2] Catherine Sun[1] Sarah Yang[1] Andrew Chan[1] Gregory Fan[2] Nathalie Urrunaga[1]

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Background: Direct-acting antiviral (DAA) therapy offers a highly effective, curative option for individuals with Hepatitis C virus (HCV). However, less than one-third receive timely DAA treatment. HCV therefore remains a common cause of chronic liver disease and liver failure in the United States. Acute-on-chronic liver failure (ACLF) is a recently recognized complication of chronic liver disease that can lead to multi-organ dysfunction and the need for liver transplantation (LT). However, the impact of pre-transplant ACLF on post-LT outcomes in HCV is not well understood. **Methods:** Patients with pre-transplant HCV who underwent LT from 2005 to 2019 were selected from the UNOS-STAR database, then stratified by ACLF grade using a modified European Association for the Study of the Liver-Chronic Liver Failure Consortium (EASL-CLIF) criteria with Grade 0 (G0) representing no ACLF. Multivariate Cox regression analyses, cumulative hazard curves, and log-rank p-values were determined for the primary outcomes (all-cause mortality, graft failure) and secondary outcomes (specific causes of death). **Results:** 10,765 patients with pre-transplant HCV who underwent LT were included and stratified by ACLF grade (G0: 6,804; G1: 1,554; G2: 1,239; G3: 1,168). Patients with more severe ACLF were more likely to be female and from non-White racial/ethnic backgrounds. There was significantly higher all-cause mortality across all ACLF grades with incidence rates of 64.80 (per 1000 person-years) in G1 (aHR 1.22, 95%CI 1.10-1.34, p<0.001), 66.29 in G2 (aHR 1.27, 95%CI 1.14-1.42, p<0.001), and 90.18 in G3 (aHR 1.78, 95%CI 1.59-1.99, p<0.001), compared to 52.83 in G0. Graft failure rates were significantly higher only in G3 with incidence rate of 24.29 per 1000 person-years (aHR 1.48, 95%CI 1.19-1.83, p<0.001), compared to 14.41 in G0. There was increased mortality from cardiac, infectious, renal, and septic causes across all ACLF grades, and from neurologic and respiratory causes in G3. Graft rejection and graft vascular complications were also significantly higher within G3. **Conclusion:** Our findings demonstrate that patients with pre-existing HCV who develop ACLF requiring LT have a higher risk of all-cause mortality across all grades, as well as higher risk of graft failure in those with the most severe form of ACLF. Early detection and treatment of HCV, combined with prompt identification of ACLF, is crucial to prevent disease progression and improve outcomes in this population.

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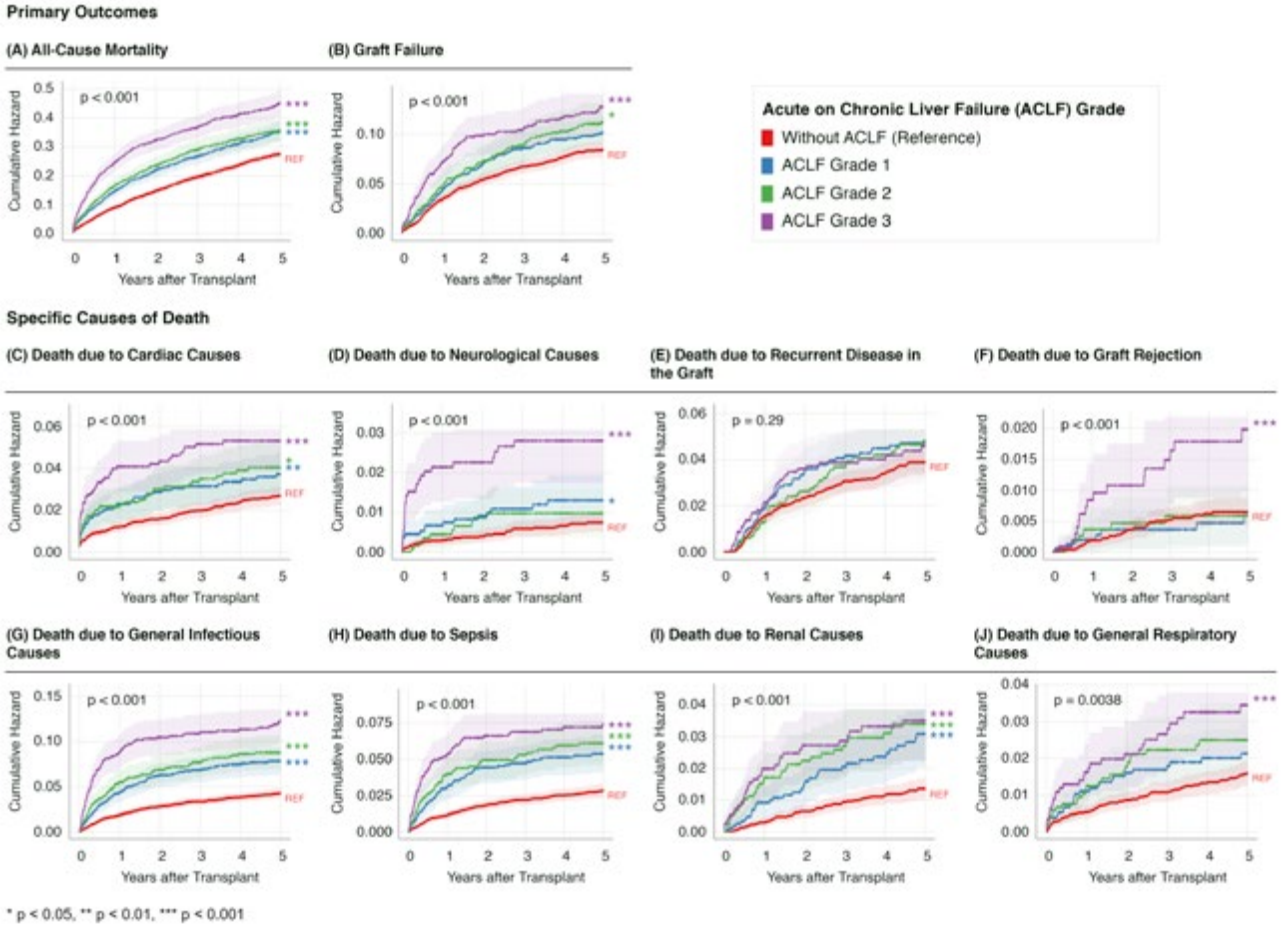
Comparison of Cumulative Events in Patients with Hepatitis C and Progressive Grades of Acute-on-Chronic Liver Failure (ACLF) over a 5-Year Post-Transplant Period



* p < 0.05, ** p < 0.01, *** p < 0.001

Cumulative risks of post-transplant outcomes in patients with hepatitis C and progressive grades of acute-on-chronic liver failure (ACLF) are shown over a 5-year post-transplant period. Compared to patients in the without ACLF cohort, figures (A), (C), (G), (H), and (I) show that patients in the ACLF Grade 1, ACLF Grade 2, and ACLF Grade 3 cohorts have significantly higher cumulative risks of all-cause mortality, death due to cardiac causes, death due to general infectious causes, death due to sepsis, and death due to renal causes, respectively, figure (B) shows that patients in the ACLF Grade 2 and ACLF Grade 3 cohorts have significantly higher cumulative risks of graft failure, figure (D) shows that patients in the ACLF Grade 1 and ACLF Grade 3 cohorts have significantly higher cumulative risks of death due to neurological causes, figure (E) shows that patients in the without ACLF, ACLF Grade 1, ACLF Grade 2, and ACLF Grade 3 cohorts have similar cumulative risks of death due to recurrent disease in the graft, and figures (F) and (J) shows that patients in the ACLF Grade 3 cohort have significantly higher cumulative risks of death due to graft rejection and death due to general respiratory causes, respectively.

Disclosures: David Lee: Nothing to Disclose, Ashton Harmacinski: Nothing to Disclose, Sharmitha Yerneni: Nothing to Disclose, Ki Jung Lee: Nothing to Disclose, Catherine Sun: Nothing to Disclose, Sarah Yang: Nothing to Disclose, Andrew Chan: Nothing to Disclose, Gregory Fan: Nothing to Disclose, Nathalie Urrunaga: Nothing to Disclose

2616 | SURVIVAL OUTCOMES OF PATIENTS WITH AUTOIMMUNE LIVER DISEASE AND ACUTE-ON-CHRONIC LIVER FAILURE AWAITING LIVER TRANSPLANT: A 20-YEAR PERSPECTIVE

Romelia Barba[1] Khawaja Hassam[2] John Esli Medina Morales[3] Ana Marenco-Flores[4] Leandro Sierra[4] Jerapas Thongpiya[1] Sebastian Sanchez[1] Daniela Goyes[5] Vilas Patwardhan[4] Alan Bonder[4]

[1]Texas Tech University, [2]Lahey Hospital & Medical Center, [3]Rutgers New Jersey Medical School, [4]Beth Israel Deaconess Medical Center, [5]Yale School of Medicine

Background: Acute-on-chronic liver failure (ACLF) affects 5% to 30% of hospitalized patients globally, with mortality rates ranging from 25% to 42%. Liver transplantation (LT) serves as a crucial, life-saving intervention

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for these patients. Autoimmune liver diseases (AILDs), including autoimmune hepatitis (AIH), primary biliary cholangitis (PBC), and primary sclerosing cholangitis (PSC), significantly contribute to liver failure cases. However, data on waitlist survival (WL) of ACLF patients with AILDs is limited. This study aims to analyze WL survival among ACLF-listed candidates with different AILDs, as well as patient and graft survival among those who undergo LT. **Methods:** Using the United Network for Organ Sharing (UNOS) database, we identified 13,702 patients with autoimmune liver etiologies listed for LT between 2002 and 2021. From this, we extracted a cohort with ACLF at listing. Organ failure and ACLF were defined using the EASL-Chronic Liver Failure (CLIF) criteria. Outcomes included WL survival, post-LT patient survival, and graft survival. WL survival was defined as death or removal due to clinical deterioration (UNOS codes 5, 8, and 13). Kaplan-Meier analysis was used for survival calculations. Multivariate Cox regression analyses identified survival predictors, adjusting for candidate age, gender, race, diabetes, MELD score at listing, and organ failure. **Results:** We identified 3,769 patients with AILD and ACLF. PSC was the most common etiology (37%) of ACLF. The majority were white Caucasians, with a female predominance in the PBC and AIH groups. PSC patients had the lowest mean age at listing (53 years). In multivariate analysis, PBC (HR, 1.57; 95% CI, 1.35-1.84; p=0.000), high MELD score at listing (HR, 1.12; 95% CI, 1.11-1.14; p=0.000), brain failure (HR, 1.39; 95% CI, 1.15-1.68; p=0.001), and respiratory failure (HR, 2.60; 95% CI, 1.99-3.40; p=0.000) increased the risk of WL removal due to death or clinical deterioration. Of this cohort, 2,815 (75%) received LT, with PSC (41%) being the most frequent indication. Patient survival at 1, 3, and 5 years was worst for AIH (89%, 84%, and 79%, respectively) and best for PSC (92%, 87%, and 81%, respectively); no significant difference among groups (p=0.267). Graft survival was lowest for PSC at five years (76%; p=0.0125). **Conclusion:** Our findings underscore the critical role of liver disease etiology in predicting survival outcomes for patients with ACLF, both on the transplant WL and post-LT. Respiratory and brain failure at the time of listing are strongly associated with reduced survival on the WL. ACLF resulting from PSC is associated with lower graft survival. Prospective validation of these **Results:** could support the integration of liver disease etiology into LT selection criteria for patients with AILD and ACLF.

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Table 1. Cohort characteristics (n=3769)

Variables	*AIH (n= 1331)*	*PBC (n=1045)*	*PSC (n=1393)*	*P-value*
Age, (IQR)	55 (42-56)	55 (51-58)	53 (38-57)	<0.001
Female gender, n (%)	980 (74)	910 (87)	429 (31)	<0.001
Race, n (%)				
White	703 (53)	643 (62)	973 (70)	<0.001
Black	314 (24)	115 (11)	277 (20)	<0.001
Hispanic	245 (18)	235 (22)	83 (6)	<0.001
Asian	44 (3)	30 (3)	38 (3)	<0.001
BMI, (IQR)	29 (25-34)	26 (23-31)	25 (22-28)	<0.001
Diabetes Mellitus, n (%)	293 (22)	185 (18)	181 (13)	<0.001
MELD at listing, (IQR)	30 (25-36)	26 (21-32)	25 (21-31)	<0.001
Liver failure, n (%)	931 (33)	734 (26)	1166 (41)	<0.001
Renal failure, n (%)	351 (26)	267 (26)	260 (19)	<0.001
Coagulation failure, n (%)	643 (48)	198 (19)	267 (19)	<0.001
Brain failure, n (%)	330 (25)	190 (29)	127 (20)	<0.001
Pulmonary failure, n (%)	125 (9)	50 (5)	36 (3)	<0.001
CV failure, n (%)	153 (12)	63 (6)	53 (4)	<0.001
Ascites, n (%)	1114 (84)	855 (82)	954 (68)	<0.001
Wait time (days), (IQR)	12 (4-49)	26 (9-90)	33 (9-114)	<0.001

AIH: autoimmune hepatitis, PBC: primary biliary cholangitis, PSC: primary sclerosing cholangitis, BMI: Body mass index, MELD: Model for end-stage liver disease, CV: Cardiovascular. Kruskal-Wallis test for continuous variables and Pearson's chi-squared test (x2) for categorical variables. Continuous variables were reported as median with Interquartile range (IQR), and categorical variables were summarized using percentages.

Table 2. Cox proportional-hazards regression model of predictors of waitlist mortality

	Univariate analysis			Stepwise multivariate analysis		
Variable	Hazard Ratio	95% CI	*p*-Value	Hazard Ratio	95% CI	*p*-Value
Disease						
AIH		[Reference]			[Reference]	
PBC	1.16	0.98–1.37	0.085	1.57	1.35-1.84	0.000
PSC	0.52	0.44-0.63	0.000	-	-	-
Age	1.04	1.04–1.05	0.000	1.04	1.03-1.05	0.000
Male gender	0.62	0.53–0.72	0.000	0.78	0.67-0.92	0.003
Race						
White		[Reference]			[Reference]	
Black/AA	0.95	0.77–1.16	0.612	0.84	0.74–0.96	0.016
Hispanic	1.37	1.15–1.64	0.001	-	-	-
Asian	0.96	0.63–1.44	0.831	-	-	-
Diabetes mellitus	1.33	1.12–1.58	0.001	1.31	1.19–1.45	0.000
BMI	1.00	0.99–1.00	0.670			
MELD at listing	1.12	1.11–1.13	<0.001	1.12	1.11–1.14	0.000
Liver failure	1.13	0.97–1.31	0.123			
Renal failure	2.24	1.92–2.6	0.000			
Coagulation failure	1.49	1.27- 1.75.	<0.001	0.77	0.64–0.92	0.004
Brain failure	1.87	1.57–2.22	0.000	1.39	1.15–1.68	0.001
Respiratory failure	6.02	3.97–6.16	0.001	2.60	1.99–3.40	0.000
CV failure	4.9	3.97–6.16	<0.001			

CI: confidence interval, AIH: Autoimmune hepatitis, PBC: primary biliary cholangitis, PSC: primary sclerosing cholangitis, BMI: body mass index, MELD: Model for end-stage liver disease, CV: cardiovascular.

Disclosures: Romelia Barba: Nothing to Disclose, Khawaja Hassam: Nothing to Disclose, John Esli Medina Morales: Nothing to Disclose, Ana Marenco-Flores: Nothing to Disclose, Leandro Sierra: Nothing to Disclose, Jerapas Thongpiya: Nothing to Disclose, Sebastian Sanchez: Nothing to Disclose, Daniela Goyes: Nothing to Disclose, Vilas Patwardhan: Nothing to Disclose, Alan Bonder: GSK: Grant/Research Support, Mirium: Grant/Research Support, Gilead: Grant/Research Support, Ipsen: Grant/Research Support, Cymabay: Grant/Research Support, Intercept: Grant/Research Support, Intercept: Consultant, GSK: Consultant, Ipsen: Consultant, Chemobab: Grant/Research Support, Alnylam: Consultant, Thirammune: Consultant

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2617 | RACIAL AND ETHNIC DISPARITIES IN POST-LIVER TRANSPLANT OUTCOMES FOR PATIENTS WITH ACUTE-ON-CHRONIC LIVER FAILURE: AN ANALYSIS OF THE UNOS DATABASE

David Lee[1] Sindhura Kolachana[1] Kimberly Schuster[2] Ki Jung Lee[2] Mohammed Shaik[1] Sharmitha Yerneni[2] Hannah Chou[2] Harrison Chou[2] Nathalie Urrunaga[1]

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Background: Liver transplantation (LT) offers definitive management for acute-on-chronic liver failure (ACLF). However, the influence of demographic factors on transplant outcomes is poorly understood. This study aims to evaluate the impact of race and ethnicity on outcomes following LT in ACLF. **Methods:** This was a retrospective analysis of the UNOS-STAR database, including LT patients from 2005-2019, with White race as the control group. Patients of Black, Hispanic, and Asian races were compared at each ACLF severity grade per the modified European Association for the Study of Liver-Chronic Liver Failure Consortium (EASL-CLIF) criteria, with Grade 0 (G0) representing no ACLF. Primary outcomes, including all-cause mortality (ACM) and graft failure (GF), and organ-specific mortality etiologies as secondary outcomes were compared using multivariate Cox regression analysis, cumulative hazard curves and log-rank p-values. **Results:** 46,792 patients were included, stratified by ACLF grade (G0: 25111; G1: 7586; G2: 6935; G3: 7160). Across all grades, Black patients exhibited higher ACM with incidence rate of 72.23 per 1000-person years in G1 (aHR 1.36, 95%CI 1.18-1.57, p<0.001), 60.50 in G2 (aHR 1.27, 95%CI 1.08-1.48, p=0.003), and 78.67 in G3 (aHR 1.19, 95%CI 1.04-1.37, p=0.01), compared to 54.10, 51.10, and 69.05 in Whites, respectively. Hispanic patients experienced lower ACM in G1 with incidence rate of 43.75 (aHR 0.83, 95%CI 0.72-0.96, p=0.01) and in G3 with rate of 58.95 (aHR 0.90, 95%CI 0.70-0.91, p<0.001) compared to 54.10 and 69.05 in Whites, respectively. Asians demonstrated decreased ACM only in G3 with incidence rate of 38.40 (aHR 0.55, 95%CI 0.41-0.73, p<0.001) compared to 69.05 in Whites. Graft failure was higher across all ACLF grades only in Black patients with incidence rate of 23.88 in G1 (aHR 2.05, 95%CI 1.58-2.67, p<0.001), 20.67 in G2 (aHR 1.91, 95%CI 1.43-2.54, p<0.001), 22.82 in G3 (aHR 1.50, 95%CI 1.15-1.96, p=0.002), compared to 9.52, 10.29, and 14.92 in Whites, respectively. Black patients had higher graft rejection and recurrent disease across all grades, mortality from GI hemorrhage and cardiac or infectious causes in G1, and sepsis in G2. **Conclusion:** Our findings highlight significant disparities, with Black patients experiencing the poorest outcomes across all ACLF grades. In contrast, Hispanic and Asian patients demonstrated more favorable mortality outcomes compared to White patients.

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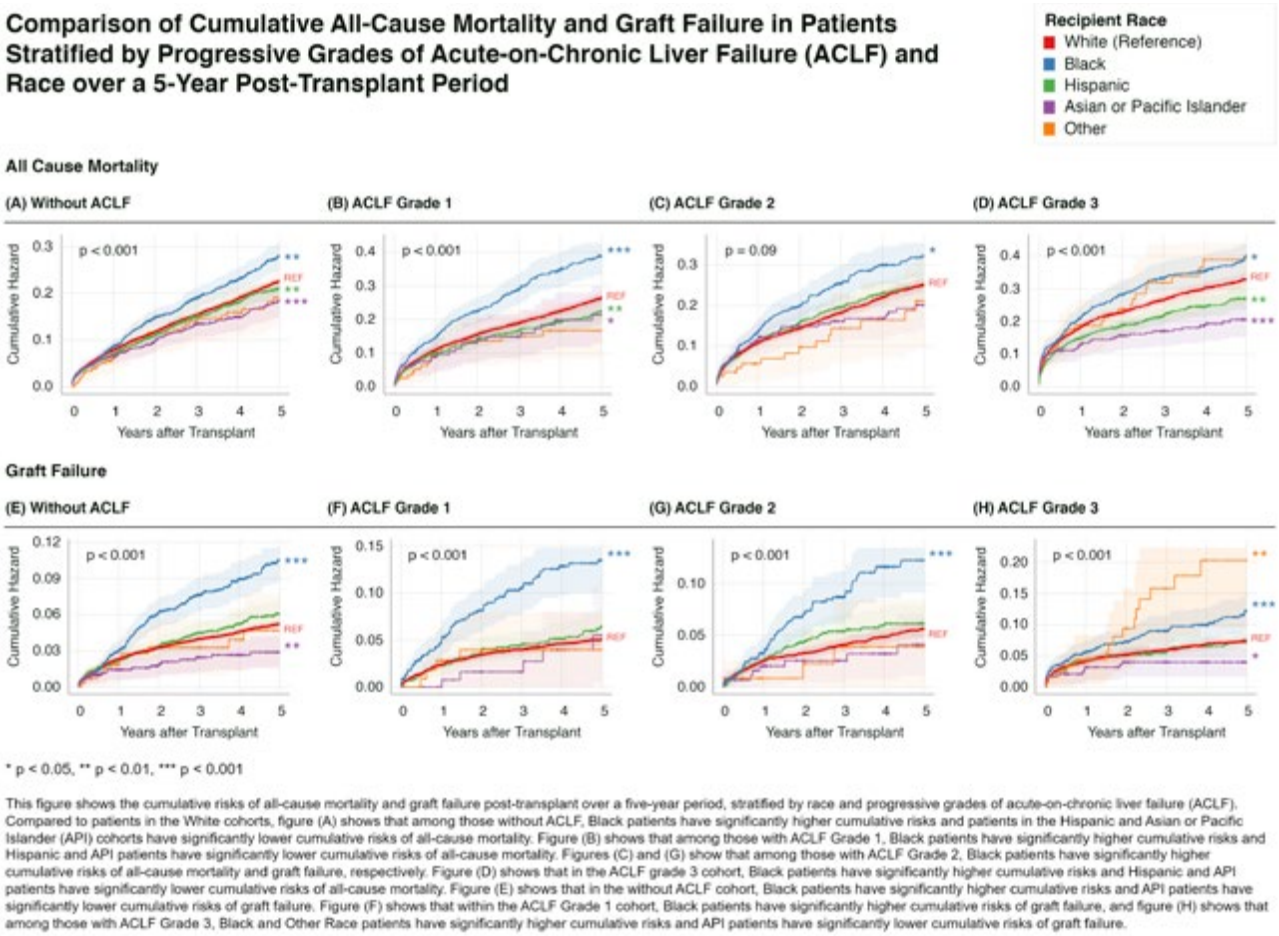

This figure shows the cumulative risks of all-cause mortality and graft failure post-transplant over a five-year period, stratified by race and progressive grades of acute-on-chronic liver failure (ACLF). Compared to patients in the White cohorts, figure (A) shows that among those without ACLF, Black patients have significantly higher cumulative risks and patients in the Hispanic and Asian or Pacific Islander (API) cohorts have significantly lower cumulative risks of all-cause mortality. Figure (B) shows that among those with ACLF Grade 1, Black patients have significantly higher cumulative risks and Hispanic and API patients have significantly lower cumulative risks of all-cause mortality. Figures (C) and (G) show that among those with ACLF Grade 2, Black patients have significantly higher cumulative risks of all-cause mortality and graft failure, respectively. Figure (D) shows that in the ACLF grade 3 cohort, Black patients have significantly higher cumulative risks and Hispanic and API patients have significantly lower cumulative risks of all-cause mortality. Figure (E) shows that in the without ACLF cohort, Black patients have significantly higher cumulative risks and API patients have significantly lower cumulative risks of graft failure. Figure (F) shows that within the ACLF Grade 1 cohort, Black patients have significantly higher cumulative risks of graft failure, and figure (H) shows that among those with ACLF Grade 3, Black and Other Race patients have significantly higher cumulative risks and API patients have significantly lower cumulative risks of graft failure.

Disclosures: David Lee: Nothing to Disclose, Sindhura Kolachana: Nothing to Disclose, Kimberly Schuster: Nothing to Disclose, Ki Jung Lee: Nothing to Disclose, Mohammed Shaik: Nothing to Disclose, Sharmitha Yerneni: Nothing to Disclose, Hannah Chou: Nothing to Disclose, Harrison Chou: Nothing to Disclose, Nathalie Urrunaga: Nothing to Disclose

2618 | THE EFFECTS OF RECIPIENT BODY MASS INDEX ON THE PROGNOSTIC OUTCOMES OF PATIENTS WITH ACUTE-ON-CHRONIC LIVER FAILURE UNDERGOING LIVER TRANSPLANTATION

David Lee[1] *Mohammed Shaik*[1] *Sharmitha Yerneni*[2] *Youngjae Cha*[1] *Nishat Anjum Shaik*[1] *Gregory Fan*[2] *Nathalie Urrunaga*[1]

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Background: Obesity is an independent risk factor for clinical decompensation and infection in patients with chronic liver disease. Recent studies have suggested that class III obesity (body mass index >40 kg/m2) is independently associated with the development of acute-on-chronic liver failure (ACLF). The increasing prevalence of ACLF in this group has driven up the demand for liver transplantation (LT). However, a significant gap persists in understanding how obesity influences LT outcomes in ACLF patients. **Methods:** Patients who underwent LT were selected from the UNOS-STAR transplant registry. They were categorized into four BMI groups and further stratified based on ACLF grade, using the modified European Association for the Study of the Liver-Chronic Liver Failure Consortium (EASL-CLIF) criteria. Cox regression analysis was utilized to assess primary outcomes, including post-transplant all-cause mortality and graft failure. **Results:** A total of 47,447 pre-transplant ACLF patients were stratified by ACLF grade (ACLF-0: 25,400; ACLF-1: 7,704; ACLF-2: 7,049; ACLF-3: 7,294). Patients in each grade were categorized by BMI as underweight (U), normal weight (N), overweight

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(Ow), and obese (O). The distribution was: G1 (N: 2,075, U: 129, Ow: 2,520, O: 2,980); G2 (N: 1,889, U: 135, Ow: 2,259, O: 2,766); G3 (N: 1,849, U: 141, Ow: 2,275, O: 3,029); G0 (N: 6,774, U: 366, Ow: 9,054, O: 9,206). In general, underweight patients tended to be younger, while overweight and obese patients were older compared to those with normal weight. Obese patients exhibited higher MELD scores while underweight patients had lower MELD scores. In terms of outcomes, overweight and obese patients with ACLF-0 and ACLF-2 had lower all-cause mortality rates compared to their normal weight counterparts. The exact incidence rates were: G0, Ow: 45.16 (HR: 0.85, 95% CI 0.79-0.90, p<0.001); G0, O: 45.67 (HR: 0.85, 95% CI 0.80-0.91, p<0.001); G2, Ow: 48.92 (HR: 0.84, 95% CI 0.74 - 0.95, p=0.007); and G2,O: 50.95 (HR: 0.87, 95% CI 0.77 - 0.99, p=0.04). No significant differences in all-cause mortality or graft failure were observed based on BMI for other ACLF grades. **Conclusion:** Higher BMI was linked to reduced mortality in post-LT patients with ACLF-0 and ACLF-2. However, there was no association between BMI and post-LT mortality with other ACLF grades. The underlying reasons are unclear and merit further investigation.

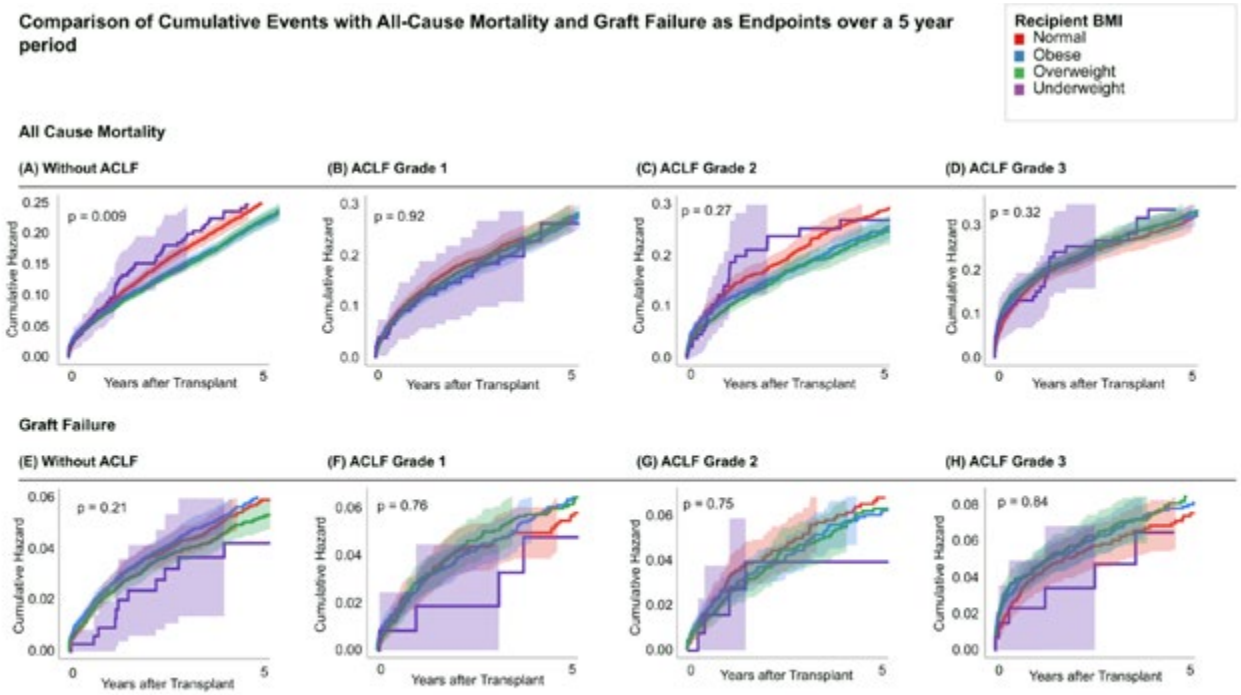

Figure 1 represents the cumulative hazard of all-cause death and graft failure across a 5-year span among transplant recipients with escalating grades of acute-on-chronic liver failure (ACLF): without ACLF or with ACLF grade 1/ ACLF grade 2/ ACLF grade 3. Graphs (A), (B), (C), and (D) illustrate the cumulative hazards for all-cause mortality among normal, underweight, overweight, and obese liver transplant recipients with increasing grades of ACLF over 5 years. Graphs (E), (F), (G), and (H) illustrate the cumulative hazards for graft failure among normal, underweight, overweight, and obese liver transplant recipients with escalating grades of ACLF over 5 years.

Disclosures: David Lee: Nothing to Disclose, Mohammed Shaik: Nothing to Disclose, Sharmitha Yerneni: Nothing to Disclose, Youngjae Cha: Nothing to Disclose, Nishat Anjum Shaik: Nothing to Disclose, Gregory Fan: Nothing to Disclose, Nathalie Urrunaga: Nothing to Disclose

2619 | ASSOCIATION OF CIRRHOTIC CARDIOMYOPATHY AND ITS ECHOCARDIOGRAPHIC MARKERS WITH INTRAOPERATIVE AND PERIOPERATIVE CARDIAC OUTCOMES IN TWO LARGE LIVER TRANSPLANT CENTERS

Alex Liu[1] Megan Ellis[1] Ashley Cozart[2] Ashley Spann[2] James Slaughter[2] Jeffrey Annis[2] Evan Brittain[2] Kymberly Watt[1] Manhal Izzy[2] Alexandra Anderson[1]

[1]Mayo Clinic Rochester, [2]Vanderbilt University Medical Center

Background: First defined in 2005, cirrhotic cardiomyopathy (CCM) has been hypothesized to be associated with liver transplant (LT) intraoperative course and outcomes. The defining echocardiographic criteria were revised in 2020 with advances in cardiac imaging. This study aims to evaluate the impact of CCM, based on revised diagnostic criteria, on intraoperative and perioperative LT cardiac outcomes. **Methods:** We performed a retrospective cohort study in two tertiary academic centers involving 308 adult liver only transplant recipients

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with sufficient echocardiographic data to define CCM. Presence of CCM and its echocardiographic markers on last pre-LT transthoracic echocardiography (TTE) were analyzed. Clinical data were collected in relation to occurrence of reperfusion syndrome (RPS) and incidence of major adverse cardiac events (MACE; heart failure, arrhythmia, cardiac arrest, and cardiac death) within 30 days post-transplant. **Results:** Overall, there was no statistically significant difference in 30-day MACE between patients who met criteria for the 2020 CCM definition and those who did not (19.4% vs 10.7%, p =0.99). Within individual CCM echocardiographic markers, increased left atrial volume index (LAVI) was associated with MACE (HR: 1.04 (1.01 – 1.07), p = 0.02) and arrythmia (HR: 1.04 (1.01 – 1.07), p = 0.015). Septal e'< 7 was associated with heart failure (HR: 4.7 (1.17-18.8) p = 0.03). RPS data were available in 189 patients of whom 38 (20%) had RPS. Age, sex, body mass index, prior smoking, and CCM were not associated with RPS. While LAVI was inversely associated with RPS on univariable analysis, LAVI did not retain significance on multivariable analysis adjusting for site and E/A ratio. No other echocardiographic marker of CCM showed a statistically significant association with RPS. **Conclusion:** Abnormal LAVI and septal e' are associated with perioperative arrythmia and heart failure, respectively. However, CCM did not predict intraoperative or perioperative outcomes. No clinical or echocardiographic predictors for RPS were identified in this study. This study challenges the paradigm that cirrhotic cardiomyopathy affects intraoperative and perioperative cardiovascular outcomes. It may also reflect improved intra-operative management of patients with CCM over time.

Disclosures: Alex Liu: Nothing to Disclose, Megan Ellis: Nothing to Disclose, Ashley Cozart: Nothing to Disclose, Ashley Spann: Bristol Myers Squibb Foundation: Grant/Research Support, James Slaughter: Nothing to Disclose, Jeffrey Annis: Nothing to Disclose, Evan Brittain: Nothing to Disclose, Kymberly Watt: Madrigal: Stock - publicly traded company, Viking: Stock - publicly traded company, Manhal Izzy: Nothing to Disclose, Alexandra Anderson: Nothing to Disclose

2620 | VALUE OF EDUCATIONAL COMPONENTS OF A PEER-TO-PEER MENTORING PROGRAM: A TRANSPLANT RECIPIENTS' INTERNATIONAL ORGANIZATION (TRIO) STUDY

Lorrinda Gray-Davis[1] Alexis Bobu[2] Wendy Balliet[3] Faith Parsons[4] Solaf Al Awadhi[4] Amy Waterman[4]

[1]Transplant Recipients International Organization, [2]Baylor Univeristy, [3]Medical University of South Carolina, [4]Houston Methodist Hospital

Background: Patient-led nonprofit organizations are designing peer-support programs to serve their members' needs. We conducted an exploratory mixed-methods evaluation of the value of different educational and support components of Transplant Recipients' International Organization's (TRIO) peer-to-peer mentoring program. **Methods:** Since 2020, the peer-to-peer mentoring program has been facilitated by transplant recipients, occurring twice a week online with each session focused on sharing about a single topic (e.g., navigating appointments). From July-Aug. 2023, we invited 57 members participating in the program from 6 TRIO chapters to complete an online survey measuring their demographic characteristics, number of mentoring sessions attended monthly, the importance of different educational topics and impacts on their behavior afterwards. We also asked if they would recommend the mentoring program to others. We conducted chi-squared analyses to assess differences in pre- and post-transplant patients' value of different topics and thematic analysis to assess benefits of peer mentoring. **Results:** TRIO peer support group members were predominantly female (53%) and had college level education or higher (58%). Most had received liver (77%) or kidney (11%) transplants and were ≤5 years post-transplant (69%). Mentoring participation ranged from 2-6 sessions monthly (median of 3 sessions), with coping, communication with physicians, and diet being the most valuable topics (Table). Most members reported improved mental health (96%), ability to manage stress (93%), feeling more prepared when going to doctor's visits (91%), and making improved lifestyle and dietary changes (86%), with thematic analyses revealing that participating patients reported becoming more hopeful, confident, and proactive. All participants would recommend the peer-to-peer mentoring program to others. **Conclusion:** Participation in peer support programs was highly recommended and valuable for preparing for and coping with the challenges of transplant. These programs should be integrated with transplant care and expanded to more patients managing the stressors of transplant.

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Transplant Recipients
International (TRIO) Study

Prioritization of Value of Transplant Educational Topics.
(Scores ranged from 1-11 with higher mean scores indicating greater value of the topic.)

Educational Topic	Overall, Mean Value (SD)	Pre-transplant Mean Value (SD)	Post-transplant Mean Value (SD)	p-value
Emotional Support & Coping Strategies	5.9 (3.1)	6.8 (2.6)	5.7 (3.2)	0.089
Post-transplant Life & Adjustment	5.7 (3.2)	4.5 (3.8)	6.1 (2.9)	0.440
Communication & Relationships with Doctors	5.6 (3.0)	5.5 (3.1)	5.6 (3.0)	0.943
Diet	5.5 (2.9)	4.9 (3.6)	5.6 (2.7)	0.300
Self-care	5.5 (2.8)	6.1 (3.3)	5.5 (2.7)	0.333
Mental Health	5.4 (3.1)	5.7 (2.4)	5.3 (3.3)	0.345
Health Care Management	4.6 (2.6)	3.4 (2.3)	4.8 (2.6)	0.140
Preparation for Transplant	4.6 (3.9)	5.7 (3.6)	4.4 (4.0)	0.794
Managing Medications	4.2 (2.5)	4.0 (1.8)	4.3 (2.7)	0.571
Communication & relationships with Family Members	4.0 (3.3)	5.2 (3.2)	3.7 (3.3)	0.554

Disclosures: Lorrinda Gray-Davis: Nothing to Disclose, Alexis Bobu: Nothing to Disclose, Wendy Balliet: Nothing to Disclose, Faith Parsons: Nothing to Disclose, Solaf Al Awadhi: Nothing to Disclose, Amy Waterman: Nothing to Disclose

2621 | THE IMPACT OF FUNCTIONAL STATUS ON THE POST-TRANSPLANT OUTCOMES OF PATIENTS WITH ACUTE-ON-CHRONIC LIVER FAILURE UNDERGOING LIVER TRANSPLANTATION

David Lee[1] Sharmitha Yerneni[2] Youngjae Cha[1] Andrew Yi[1] Gregory Fan[2] Nathalie Urrunaga[1]

[1]University of Maryland School of Medicine, [2]Tufts School of Medicine

Background: The recognition of acute-on-chronic liver failure (ACLF) has significantly influenced how liver transplant (LT) is approached. Given its notable effect on the prognosis after LT, it becomes essential to evaluate the factors before the LT that are linked to outcomes following surgery. This study aims to investigate the prognostic impact of functional status at the time of LT on post-LT outcomes in ACLF. **Methods:** We conducted a retrospective analysis on patients who underwent LT for ACLF between 2005 to 2019 using the UNOS-STAR registry. The severity of ACLF was based on the modified European Association for the Study of the Liver-Chronic Liver Failure Consortium (EASL-CLIF) criteria, with grade 0 (G0) indicating no ACLF. Functional status was evaluated through the Karnofsky Performance Status (KPS) score at hospital admission, categorized into no assistance (KPS 80-100%), some assistance (KPS 50-70%), and total assistance (10-40%). Outcomes measured were all-cause mortality (ACM) and graft failure (GF), and organ-specific causes of death, using Cox regression and comparing some and total assistance against no assistance. **Results:** A total of 46,434 LT recipients were investigated and stratified by ACLF grade (G0: 24,776; G1: 7,536; G2: 6,917; G3: 7,205) and further stratified by no assistance (G0: 6,750; G1: 986; G2: 422; G3: 160), some assistance (G0: 12,607; G1: 2,803; G2: 1,534; G3: 576), and total assistance (G0: 5,419; G1: 3,667; G2: 4,961; G3: 6,469). Higher ACM was seen in G0 only in both patients requiring some assistance (aHR 1.10, 95%CI 1.04-1.17, p=0.002) and total assistance (aHR 1.32, 95%CI 1.22-1.43, p<0.001). Higher rates of GF were only seen with G0 patients requiring total assistance (aHR 1.34, 95%CI 1.13-1.58, p<0.001). There were no statistically significant differences detected in ACM and GF rates in ACLF grades 1-3. Among G0 patients, etiologies of mortality were diverse, including cardiac in some assistance and total assistance patients, as well as graft rejection, infectious, and respiratory etiologies in those requiring

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total assistance. **Conclusion:** Functional status at the time of admission for LT significantly impacts outcomes on patients with non-ACLF indications for transplant. However, no prognostic differences were observed across different levels of functional status among ACLF patients.

Figure 1: Comparison of Cumulative Events with All-Cause Mortality and Graft Failure as Endpoints over a 5 year period

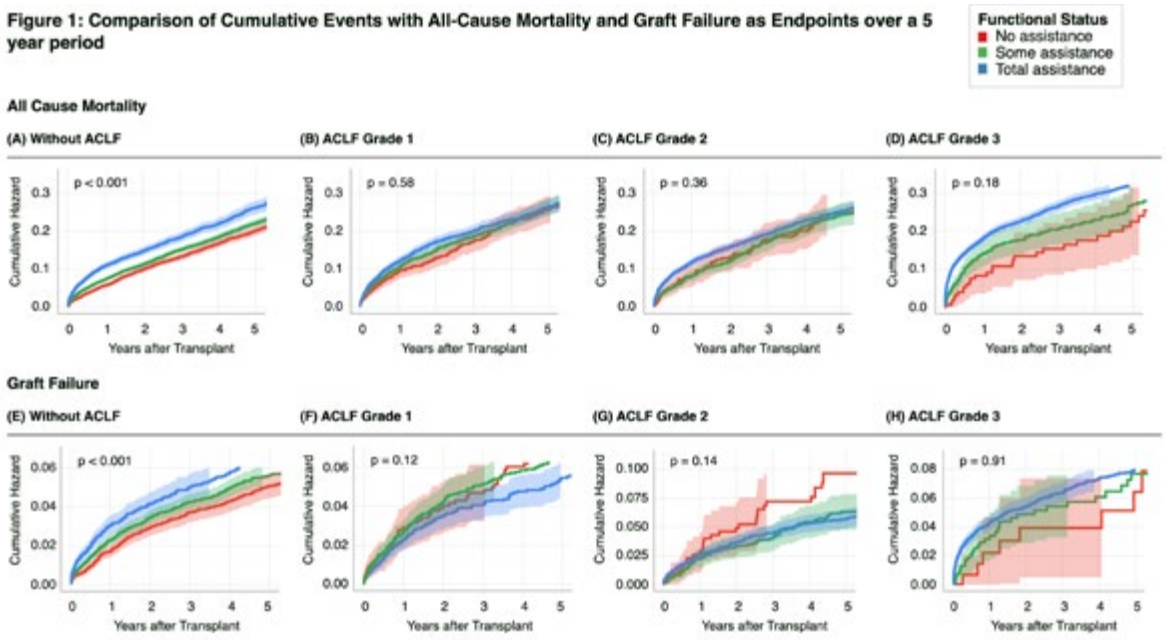

Figure 1 represents the cumulative hazard of all-cause death and graft failure among patients with escalating grades of acute on chronic liver failure (ACLF) over a 5 year period. Graphs (A), (B), (C), and (D) illustrate the cumulative hazard(s) for all-cause mortality in liver transplant recipients with no assistance, some assistance, and total assistance with increasing grades of ACLF over a 5 year period. Graphs (E), (F), (G), and (H) represent the cumulative hazard(s) for graft failure in liver transplant recipients with no assistance, some assistance, and total assistance with increasing grades of ACLF over a 5 year period.

Disclosures: David Lee: Nothing to Disclose, Sharmitha Yerneni: Nothing to Disclose, Youngjae Cha: Nothing to Disclose, Andrew Yi: Nothing to Disclose, Gregory Fan: Nothing to Disclose, Nathalie Urrunaga: Nothing to Disclose

2622 | DETERMINANTS OF CAREGIVING BURDEN; INTERIM RESULTS FROM THE MULTI-CENTER LIVCOG COHORT STUDY ◆

Marina Serper[1] Anna Gurian[2] Douglas Schaubel[2] Allison Novorita[3] Julia Yoshino Benavente[3] Jacqueline Theroux[2] Sumeet Asrani[4] Michael Wolf[3]

[1]University of Pennsylvania Health System, [2]University of Pennsylvania, [3]Northwestern University, [4]Baylor All Saints

Background: Liver transplant recipients (LTRs) have high burden of neurological complications and frailty. Care partners (CP) play a critical role in supporting LTRs, however, CP burden and patient and CP factors affecting it have not been thoroughly examined. **Methods:** This is an interim analysis of the prospective NIDDK-funded, LivCog cohort study which investigates longitudinal changes on LTR cognition and quality of life (QOL) as well as detailed CP characteristics. We report on CP-patient dyads (n=143) across 4 transplant centers. We investigated relationships between CP burden (Zarit Care Giver Burden (ZBI)), CP self-efficacy or confidence in managing medical information, caring for recipients, caring for oneself, and managing difficult interactions/ emotions. (Care Giver Inventory (CGI)), and CP health literacy (Newest Vital Sign (NVS)). Additionally, we assessed relationships between these CP characteristics and LTR outcomes, specifically global cognition (Montreal Cognitive Assessment (MoCA)), PROMIS anxiety, depression, and physical function. **Results:** For CPs, the median age was 56; 73**%** were women; 20**%** were non-white; 27% had 12 or fewer years of education; and 76% were married. Among CPs, 14% reported significant caregiver burden (ZBI >21); 20% had inadequate health literacy (NVS <4);A total 62**%** of CPs were spouses; 17**%** were adult children; 11**%** were parents; 9**%** were other family; and 6**%** were friends. Among LTRs, median age was 57; 34% were women; 23% were non-white; 45**%** had high school education or less; 71% were married; 45% had pre-transplant hepatic encephalopathy (HE); 55**%** had mild cognitive impairment (MoCA < 26)**;** and 29**%** were frail (LFI ≥ 4.5). Low CP self-efficacy was

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significantly associated with higher reported CP burden (OR 9.1, 95% CI 1.97-41.6) p<0.0001) as was history of pre-transplant HE (OR 5.9, 95% 1.80-19.4, p=0.003). Other factors associated with higher CP burden were high recipient pain scores and lower cognitive function by MoCA (OR 1.28, 95% CI 1.08-1.52, p<.001) **Conclusion:** Greater caregiver self-efficacy is associated with lower reported CP burden. This suggests that interventions aimed at enhancing CP skills, confidence, self-care, knowledge, and function could reduce burden. Future studies regarding CP characteristics and post-LT comes are currently underway.

Disclosures: Marina Serper: Grant/Research Support relationship with Grifols; Has not ended; Grant/Research Support relationship with Eurofins; Has not ended; Grant/Research Support relationship with Transplant Genomics; Has not ended, Anna Gurian: Nothing to Disclose, Douglas Schaubel: Nothing to Disclose, Allison Novorita: Nothing to Disclose, Julia Yoshino Benavente: Nothing to Disclose, Jacqueline Theroux: Nothing to Disclose, Sumeet Asrani: Nothing to Disclose, Michael Wolf: Nothing to Disclose

2624 | ABDOMINAL AORTIC CALCIFICATION SCORE IN LIVER TRANSPLANT RECIPIENTS: DOES IT PORTEND A WORSE PROGNOSIS?

Fernando Gil Lopez[1] Lydia Mercado[1] Abdullah Jebrini[1] Liu Yang[1] Houssam Farres[1] David Sella[1] Shennen Mao[2] Tambi Jarmi[1] Denise Harnois[1]

[1]Mayo Clinic, [2]Mayo Clinic Rochester

Background: Abdominal aortic calcification (AAC) is common among candidates for liver transplant (LT). Few studies have explored the relationship between AAC and clinical outcomes in solid organ transplant recipients, our aim was to determine the correlation between AAC and postoperative outcomes in deceased-donor liver transplant recipients. **Methods:** We conducted a retrospective cohort study of 516 patients who had LT at our center between January 2011 and March 2021. The most recent abdominal computer tomography scan performed before LT was used for analysis. A modified Agaston method was used to generate a scoring system on abdominal arteries (aorta, common iliac, external iliac and internal iliac) and results were expressed in mm^3. Wilcoxon rank-sum test was used for median comparison of AAC score between groups. For overall survival (OS), patients were divided according to AAC: low (<100 mm^3) or high calcium score (≥100 mm^3). **Results:** Patient demographics and baseline characteristics are depicted in Table 1. Median follow-up following LT was 59.5 months (range 0-158). Median BMI was 28.6 kg/m^2 (IQR 24.9-33.3). 87.4% were donation after brainstem death, 12.6% donation after circulatory death, 70% required ICU post-LT, and 32.4% CRRT. Overall median AAC score for all patients was 437.4 mm^3 (IQR: 0-1736.4). Diabetes mellitus [682 mm^3 (IQR 120.1-1948.9) vs. non-diabetic 240.1 mm^3 (IQR 0-1547.2), p=0.002] and smoking [1278.1 mm^3 (IQR 132.4-3713.2) vs. non-smokers 144.2 mm^3 (IQR 0-1059.5), p=0.000] were associated with a higher median AAC. Median OS was 153 months. There was no statistically significant difference in OS between the high and low calcium score groups (Log-Rank test X^2=2.61, p=0.10). ROC curve demonstrated an AUC=0.567 for AAC and mortality. Median hospital length of stay (LOS) post-LT was 11 days (IQR: 7-22). Median AAC was not significantly different between ≤7 and >7 days LOS groups [686.4 mm^3 (16.55-2347.4) vs. 363.7 mm^3 (IQR 0-1673.7), p=0.08]. Additionally, median AAC was not significantly different between patients requiring ICU care and those who did not [497 mm^3 (IQR 0-1942.7) vs. 361.7 mm^3 (IQR 3.3-1538.2), p=0.33], as well as in those who required CRRT [591.6 mm^3 (IQR 0-2430) vs. no CRRT 368.5 mm^3 (IQR 0-1533.5), p=0.170. **Conclusion:** Contrary to prior studies where an association was found between AAC and patients' survival in kidney transplant recipients, our study shows that AAC alone does not correlate with worse post-operative outcomes after LT.

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Variable	Total n (%)
Age (median)	64, range 22-83
Female	206 (39.9)
Male	310 (60.1)
Caucasian	444 (86)
African American	31 (6)
Another race	41 (8)
Hypertension	232 (45)
Diabetes mellitus	185 (36)
Hypercholesterolemia	112 (21.7)
Current smoker	21 (4.1)
Former smoker	189 (36.6)
Clinical coronary artery disease	57 (11)
Alcohol	190 (36.8)
NASH	142 (27.5)
ALD	114 (22)
HCV	145 (28)
HCC	114 (22)
BMI (median)	514, range 14.2-55.5
MELD Na (median)	23.5, range 6-49
Hospital LOS (days) (median)	11, IQR 7-22
AAC score (median)	437.45, IQR 0-1736.4

Table 1. Patient demographics and baseline characteristics.

Disclosures: Fernando Gil Lopez: Nothing to Disclose, Lydia Mercado: Nothing to Disclose, Abdullah Jebrini: Nothing to Disclose, Liu Yang: Nothing to Disclose, Houssam Farres: Nothing to Disclose, David Sella: Nothing to Disclose, Shennen Mao: Nothing to Disclose, Tambi Jarmi: Nothing to Disclose, Denise Harnois: Nothing to Disclose

2625 | IMPACT OF CLOSTRIDIOIDES DIFFICILE INFECTION ON OUTCOMES IN LIVER TRANSPLANT RECIPIENTS: A COMPREHENSIVE META-ANALYSIS

Ammad Chaudhary[1] Muhammad Shahzil[2] Fariha Hasan[3] Anza Muhammad[4] Diana Jomaa[1] Abdullah Ejaz[4] Muhammad Saad Faisal[1] Yara Dababneh[1] Palak Patel Rodrigues[1] Muhammad Ali Khaqan[5] Syed-Mohammed Jafri[1]

[1]Henry Ford Health System, [2]Penn State Health Milton S. Hershey Medical Center, [3]Cooper University Health Care, Camden, NJ, United States, [4]King Edward Medical University, [5]John H. Stroger, Jr. Hospital of Cook County

Background: Clostridioides difficile (C. difficile) is a Gram-positive, anaerobic, spore-producing bacillus common in the human gastrointestinal tract. Gastrointestinal dysbiosis, often due to antibiotic use, can lead to severe CDI, a frequent healthcare-associated complication, especially in liver transplant (LT) recipients. LT recipients are at higher risk due to compromised immune defenses and other factors. This meta-analysis aims to understand CDI mortality rates, hospital length of stay, MELD scores, PPI use, and CDI recurrence in LT recipients. **Methods:** This meta-analysis adhered to Cochrane guidelines and PRISMA standards. A comprehensive search was conducted across PubMed, MEDLINE, Embase, Scopus, and CENTRAL databases until October 2023. Inclusion criteria targeted RCTs and observational studies with LT patients. Data extraction followed PICOS criteria using Excel. Statistical analyses utilized RevMan with a random-effects model, considering results significant at $p < 0.05$. Risk of bias was assessed with the Newcastle-Ottawa Scale, and GRADE considerations determined evidence certainty. **Results:** Of 2144 screened studies, 10 studies with 1,216,500 LT patients were included:

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39,309 with CDI and 1,177,191 without CDI. Primary outcomes assessed were mortality and hospital length of stay (LOS). Mortality showed no significant difference (RR: 1.34; 95% CI: 0.38, 4.72). LOS was significantly longer in CDI patients (mean difference: 6.00 days; 95% CI: 2.83, 9.17). Secondary outcomes included PPI use and MELD scores. PPI use showed no significant association with CDI risk (RR: 2.18; 95% CI: 0.29, 16.27). MELD scores were significantly higher in CDI patients (mean difference: 2.77; 95% CI: 1.34, 4.20). CDI recurrence rate was 14.7%. Risk of bias was assessed with the Newcastle-Ottawa Scale, and evidence quality was evaluated using GRADE, showing moderate quality for most outcomes due to confounding bias and non-randomization. **Conclusion:** This meta-analysis shows that CDI significantly impacts morbidity and length of hospital stay in liver transplant recipients but does not affect mortality. Patients with CDI had longer hospital stays and higher preoperative MELD scores, highlighting the importance of vigilant postoperative monitoring. Further research is needed to identify specific risk factors and optimize patient outcomes through targeted interventions and preventive measures.

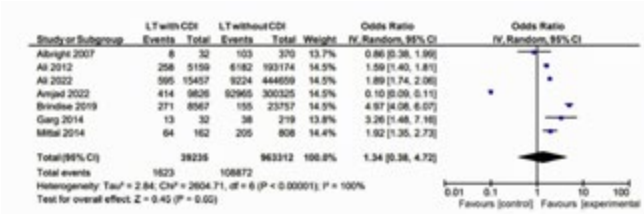

Figure 1: Comparative mortality in liver transplant recipients, CDI vs. non-CDI.

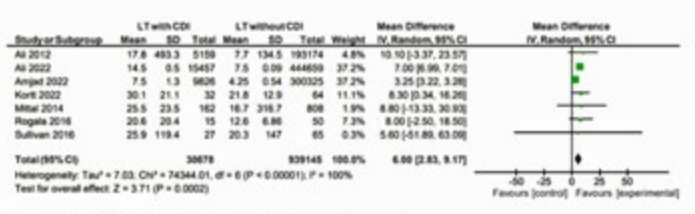

Figure 2: Hospital stay length: liver transplant with vs. without CDI.

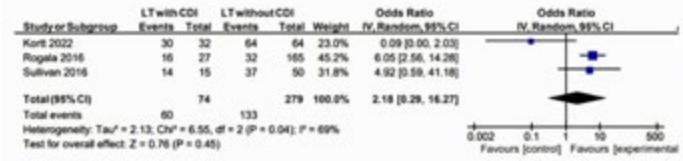

Figure 3: PPI therapy in liver transplant patients, CDI vs. non-CDI.

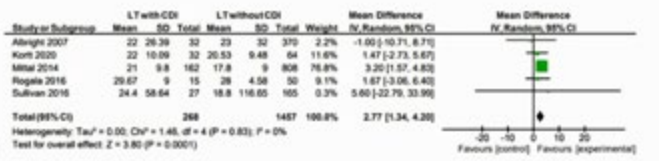

Figure 4: MELD score comparison, CDI vs. non-CDI LT recipients.

Disclosures: Ammad Chaudhary: Nothing to Disclose, Muhammad Shahzil: Nothing to Disclose, Fariha Hasan: Nothing to Disclose, Anza Muhammad: Nothing to Disclose, Diana Jomaa: Nothing to Disclose, Abdullah Ejaz: Nothing to Disclose, Muhammad Saad Faisal: Nothing to Disclose, Yara Dababneh: Nothing to Disclose, Palak Patel Rodrigues: Nothing to Disclose, Muhammad Ali Khaqan: Nothing to Disclose, Syed-Mohammed Jafri: Takeda: Speaking and Teaching, Gilead: Speaking and Teaching, Abbvie: Speaking and Teaching, Ironwood: Advisor, Intercept: Speaking and Teaching

2626 | MINIMIZATION OF IMMUNOSUPPRESSION BEYOND FIVE YEARS FOLLOWING LIVER TRANSPLANT: LONG TERM OUTCOMES ON REJECTION, MALIGNANCY, AND MORBIDITY

Abdulmalik Saleem[1] Saleh Al-Juburi[2] Muhammad Saad Faisal[3] Ammad Chaudhary[3] Ahmad Alomari[3] Mohammed Abusuliman[3] Avi Toiv[3] Momin Samad[3] Mahfujul Haque[4] Syed-Mohammed Jafri[5]

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Background: Post liver transplantation survival and graft preservation has substantially improved over the last few decades. Post-transplant management remains particularly challenging due to the intricate balance between immunosuppression and its adverse effects. Excess immunosuppression can be associated with metabolic disease, infection, and malignancy. Our study aims to delineate this balance to guide clinicians in their ability to safely minimize immunosuppression without predisposing to rejection. **Methods:** Our study included patients who have had a 10-year liver transplant course. Patients who underwent transplantation in 2013 and initiated tacrolimus were included. Patients who expired between 2018 – 2023 and those without adequate clinical data were excluded. Mean 5-year tacrolimus troughs 5 years after transplant (2018 – 2023) were calculated. A mean trough level of 4 was used as a cutoff to subcategorize our patients into those with a 5 year mean trough of ≤4 or >4. We compared the incidence of rejection, infection, malignancies, and hyperkalemia between the groups during this period. **Results:** 79 patients underwent liver transplants at our center in 2013. 33 expired or had

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inadequate data and were excluded. 44 patients met inclusion criteria, 17 Females (38%), 27 Males (61%). The mean age for our patients was 54.6 with a standard deviation of 8.9. Etiologies of cirrhosis were Hepatitis C (45.45%), Alcohol (18.18%), Nonalcoholic Steatohepatitis (18.8%), Cryptogenic (9.09%), Primary Biliary Cirrhosis (4.55%), Primary Sclerosing Cholangitis (2.27%), and Cystic Fibrosis (2.27%). 23 (52%) patients had a mean 5-year tacrolimus trough greater than 4 and 21 (48%) less than 4. 3 patients experienced rejection in the >4 group and 1 in the <4 group during this period. 2 patients in each group were hospitalized for infection. 2 patients developed a malignancy in the > 4 group and 3 in the < 4 group. No statistically significant relationship between the mean 5-year trough and incidence of rejection, hyperkalemia, and infection was found in our analysis (Table 1). **Conclusion:** Our findings underscore clinicians' abilities to down titrate tacrolimus levels without an associated increased risk of rejection. Conversely, higher tacrolimus levels were also not associated with an increased incidence of cancer, infections, or hyperkalemia. Our study's **Results:** may reassure providers regarding the safety of minimizing immunosuppression. This topic can benefit from larger sample sizes for increased generalizability in the future.

Hyperkalemia 2018 - 2023

	Hyperkalemia (2018-2023)		
Mean Trough (2018 - 2023)	Yes	No	Total
less than 4	3	18	21
	14.29	85.71	100.00
Greater than 4	0	23	23
	0.00	100.00	100.00
Total	3	41	44
	6.82	93.18	100.00

Pearson Chi2 = 3.53 Prob = 0.0604

The first row has *frequencies* and the second row has *row percentages*

Hospital Admission for Infection 2018 - 2023

	Infection (2018 - 2023)		
Mean Trough (2018 - 2023)	Yes	No	Total
less than 4	2	19	21
	9.52	90.48	100.00
Greater than 4	2	21	23
	8.70	91.30	100.00
Total	4	40	44
	9.09	90.91	100.00

Pearson Chi2 = 0.01 Prob = 0.9240

The first row has *frequencies* and the second row has *row percentages*

Malignancy 2018 - 2023

	Cancer 2018 - 2023		
Mean Trough (2018 - 2023)	Yes	No	Total
less than 4	3	18	21
	14.29	85.71	100.00
Greater than 4	2	21	23
	8.70	91.30	100.00
Total	5	39	44
	11.36	88.64	100.00

Pearson Chi2 = 0.34 Prob = 0.5595

The first row has *frequencies* and the second row has *row percentages*

Rejection experienced 2018 - 2023

	Hx of Rejection		
Mean Trough (2018 - 2023)	Yes	No	Total
less than 4	3	18	21
	14.29	85.71	100.00
Greater than 4	6	17	23
	26.09	73.91	100.00
Total	9	35	44
	20.45	79.55	100.00

Pearson Chi2 = 0.94 Prob = 0.3324

The first row has *frequencies* and the second row has *row percentages*

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Disclosures: Abdulmalik Saleem: Nothing to Disclose, Saleh Al-Juburi: Nothing to Disclose, Muhammad Saad Faisal: Nothing to Disclose, Ammad Chaudhary: Nothing to Disclose, Ahmad Alomari: Nothing to Disclose, Mohammed Abusuliman: Nothing to Disclose, Avi Toiv: Nothing to Disclose, Momin Samad: Nothing to Disclose, Mahfujul Haque: Nothing to Disclose, Syed-Mohammed Jafri: Takeda: Speaking and Teaching, Gilead: Speaking and Teaching, Abbvie: Speaking and Teaching, Ironwood: Advisor, Intercept: Speaking and Teaching

2627 | NEOADJUVANT IMMUNOTHERAPY IN PATIENTS UNDERGOING LIVER TRANSPLANTATION FOR PRIMARY LIVER CANCER AT A SINGLE CENTER

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Background: Primary liver cancers have rising incidence and mortality rates. Excellent outcomes can be achieved with liver transplantation (LT), and access improved by downstaging approaches. Immunotherapy regimens offer high response rates but may confer increased rejection and mortality risks post-LT. We examine our single center experience with immunotherapy pre-LT. **Methods:** Patients with hepatocellular carcinoma (HCC) and cholangiocarcinoma (CCA) undergoing LT at a single center between January 2008 and February 2024 were reviewed retrospectively. **Results:** Of 1777 LT performed, 13 patients received neoadjuvant immunotherapy. All LTs were performed between 2021 and 2024, including 10 patients with HCC and 3 with CCA. Patients were predominantly male (n=11), white (n=8), with median age 61 (IQR,59-68) and median biological MELD at transplant 20 (IQR,9-27). Only 1 patient received UNOS exception points. The most common immunotherapy was atezolizumab (n=7) followed by durvalumab (n=2). The number of systemic therapy lines per patient ranged from 1-5, with the plurality receiving 1 (n=5). The median duration of immunotherapy was 197 days (IQR,66-476), and median washout between last immunotherapy and LT was 177 days (IQR,74-291) days. Most patients (n=9) also received loco-regional therapies. Median waitlist time was 88 days (IQR,31-127). On final pathology, most tumors were multifocal (n=10), moderate (n=6) or high (n=4) grade, with median size 4.2 cm (IQR,3-9.5) and number 3 (2-4). A minority had LVI (n=4), and none had lymph node metastases. Majority had incomplete treatment effect, with median tumor necrosis 40% (IQR,24-76%). Median follow-up was 197 days (IQR,128-476). No patients experienced rejection on index admission, and there was no graft loss on follow up. Recurrence was seen in 4 patients, most commonly in the liver allograft (n=3) and/or lungs (n=3). Three patients died, most commonly of malignancy (n=2). Median survival was 23 months, and 1-year survival probability was 77%. **Conclusion:** This single-center study supports the safety of pre-LT immunotherapy in patients with liver cancer, given a sufficient washout period prior to transplant. Prospective clinical trials are ongoing at our center to further investigate the use of immunotherapy in the pre-transplant setting given its potential to increase LT accessibility for cancer patients.

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ID	Diagnosis	Neoadjuvant Immunotherapy	Washout Period (days)	LRT	Waitlist Time (days)	Histologic Treatment Effect
1	CCA	pembrolizumab	12	SBRT	201	incomplete response
2	HCC	atezolizumab	205	TACE, TARE	95	incomplete response
3	HCC	atezolizumab	122	SBRT	127	incomplete response
4	HCC	nivolumab, atezolizumab	77	TARE	3	incomplete response
5	HCC	nivolumab, ipilimumab	200	TACE, RFA, SBRT, hepatectomy	713	no response
6	HCC	atezolizumab	291	TARE, RFA	31	incomplete response
7	HCC	nivolumab	22	TARE	126	incomplete response
8	HCC	atezolizumab	74	TARE	340	incomplete response
9	HCC	atezolizumab	37	TARE	16	complete response
10	HCC	atezolizumab	313	-	4	incomplete response
11	CCA	durvalumab	313	-	44	incomplete response
12	HCC	atezolizumab	434	-	77	complete response
13	CCA	durvalumab	177	-	88	no response

CCA, cholangiocarcinoma; HCC, hepatocellular carcinoma; LRT, locoregional therapy; RFA, radiofrequency ablation; SBRT, stereotactic body radiotherapy; TACE, transarterial chemoembolization; TARE, transarterial radioembolization

Disclosures: Sudha Kodali: Advisor relationship with Astrazeneca; Has not ended; Speaking and Teaching relationship with Gilead; Has not ended; Advisor relationship with SIRTEX; Has not ended; Speaking and Teaching relationship with Gilead; Has ended; Advisor relationship with SIRTEX; Has ended; Consultant relationship with Astrazeneca; Has ended, Ashton Connor: Nothing to Disclose, Ahmed Elaileh: Nothing to Disclose, Khush Patel: Nothing to Disclose, Jason Todd: Nothing to Disclose, Tamneet Basra: Nothing to Disclose, David Victor: Nothing to Disclose, Caroline Simon: Nothing to Disclose, Yee Lee Cheah: Intuitive Surgical: Consultant, Mark Hobeika: Nothing to Disclose, Constance Mobley: Nothing to Disclose, Ashish Saharia: Nothing to Disclose, Sadhna Dhingra: Nothing to Disclose, Mary Schwartz: Nothing to Disclose, Anaum Maqsood: Nothing to Disclose, Kirk Heyne: Nothing to Disclose, Maen Abdelrahim: Nothing to Disclose, Elizabeth Brombosz: Nothing to Disclose, Ahmed Kaseb: Nothing to Disclose, Milind Javle: Nothing to Disclose, Jean-Nicolas Vauthey: Nothing to Disclose, Ahmed Gaber: Nothing to Disclose, R. Mark Ghobrial: TransMedics: Consultant, Sanofi: Consultant, LyGenesis: Advisory Board Member

2628 | EFFECTS OF A STRUCTURED, MODIFIED MEDITERRANEAN DIETARY INTERVENTION AFTER LIVER TRANSPLANTATION (MEDDIET): INTERIM ANALYSIS OF A RANDOMIZED, CONTROLLED TRIAL

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Background: Thirty to seventy percent of liver transplant recipients (LTR) become obese or overweight, with fastest weight gain occurring in the first year. This randomized, controlled trial evaluated a 12-week, virtual visit-based, modified Mediterranean (no alcohol or added fats) dietary intervention on post-transplant body weight and metabolic profile. **Methods:** Adult (age ≥18 years) primary LTRs with BMI ≥ 25 kg/m^2 were included. Exclusions included use of weight loss drugs, uncontrolled diabetes, significant proteinuria, severe allograft dysfunction, multi-organ transplant, previous bariatric surgery, and hepatocellular carcinoma outside Milan criteria on explant. Participants were randomized to dietary intervention (DI) or standard of care (SOC) arms and underwent baseline, 4-month and 12-month post-transplant evaluations of body composition, bloodwork, physical function, dietary compliance, and quality of life (SF-36). DI group received baseline one-on-one modified Mediterranean dietary counselling followed by virtual visits at 1, 2, 3, 4, 6, 8 and 10 weeks to review body weight and compliance. Primary outcome was post-transplant body weight/composition. Generalized estimating equations were used to assess trends within and between treatment arms. **Results:** At interim analysis, 22 participants were randomized to DI and 27 to SOC. At baseline, DI group had higher body fat mass (BFM), % body fat (PBF), and lower skeletal muscle to body fat mass ratio (MFR). Trends in body weight and BFM are shown (Figure 1). Compared to SOC,

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DI blunted the increase in PBF (4 months: p=0.03; 12 months: p=0.01), visceral fat area (12 months: p=0.04) and decrease in MFR (4 months: p=0.03; 12 months: p<0.01). From 4 to 12 months, HDL cholesterol decreased in SOC versus plateauing in DI (p=0.04). From baseline, LDL cholesterol rose in both groups, plateauing in DI and declining in SOC groups after 4 months (p=0.01). Both groups had comparable trends in blood pressure, HgbA1c, triglycerides, Karnofsky Performance, and quality of life scores. DI group maintained good compliance with the Mediterranean diet throughout the 4 months but not through the following 8 months. **Conclusion:** Mediterranean dietary counselling may mitigate weight gain in LTRs while they are closely followed and compliant with the diet. The intervention durably improved metabolic profiles by blunting gains in body weight and visceral fat, while resisting decreases in MFRs and HDL cholesterol.

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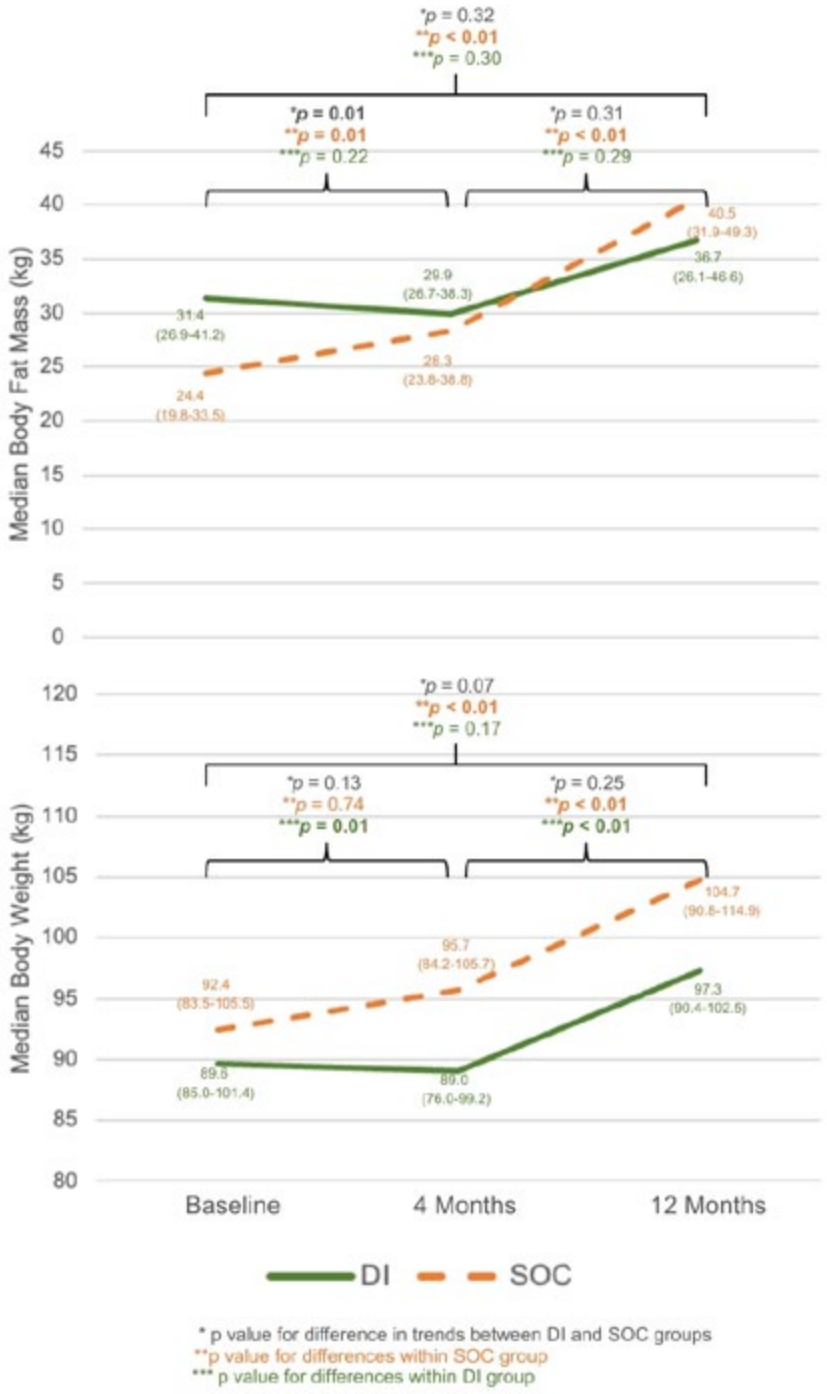

Figure 1 - Trends in body weight and body fat mass between DI and SOC groups

Disclosures: Mohammad Qasim Khan: Nothing to Disclose, Ahmed Elhawary: Nothing to Disclose, Bradley Busebee: Nothing to Disclose, Ummah Salma Nisar: Nothing to Disclose, Nikhita Chennaiah Gari: Nothing to Disclose, Sara DiCecco: Nothing to Disclose, Nickie Francisco-Ziller: Nothing to Disclose, Heather Bamlet: Nothing to Disclose, Kathryn Tiedtke: Nothing to Disclose, Kristin Cole: Nothing to Disclose, Kymberly Watt: Madrigal: Stock - publicly traded company, Viking: Stock - publicly traded company

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2629 | IMPACT OF ACUTE PRE-LIVER TRANSPLANTATION RENAL REPLACEMENT THERAPY ON POST-TRANSPLANTATION OUTCOMES IN ALCOHOL-RELATED LIVER DISEASE

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Background: Alcohol-related liver disease (ALD) has become the most frequent indication for liver transplantation (LT). Acute kidney injury is a frequent complication occurring in patients with ALD and often requires renal replacement therapy (RRT). It is unclear if pre-LT RRT impacts post-LT outcomes differently in ALD patients compared to non-ALD patients. We examined the association between pre-LT RRT and post-LT outcomes in ALD patients compared to non-ALD patients with metabolic dysfunction-associated steatohepatitis (MASH) and chronic hepatitis C virus (HCV) infection. **Methods:** All adult patients (≥18 years) who underwent deceased donor LT from 1/1/2017-12/31/2022 in United Network for Organ Sharing (UNOS) were analyzed. Patients were followed from the date of transplant to last follow-up. Patients who underwent previous LT, received MELD exception points, were waitlisted for multiorgan transplant, or had MELD <20 at the time of LT were excluded. Our primary outcome was 1-year post-LT mortality and secondary outcomes were post-LT length of stay (LOS), prevalence of post-LT chronic kidney disease (CKD), and rates of kidney transplantation (KT) within 1 year of LT. CKD was defined as eGFR <60. Multivariable Cox regression models adjusting for recipient age, sex, race/ethnicity, MELD, wait time, and donor risk index were used to assess the association between RRT by liver disease etiology and post-LT mortality. **Results:** Among 22,769 patients, 20.8% (n = 4,725) of LT recipients were undergoing RRT <6 weeks prior to LT. Patients with ALD were found to be significantly younger and had higher MELD scores compared to all other etiologies. Comparisons of post-LT outcomes by liver disease etiology can be found in Table 1. Rates of RRT at the time of LT were highest among those listed for ALD (ALD 23.8%, MASH 18.0%, HCV 17.6%; p<0.001). Overall, 1-year post-LT mortality was higher in recipients undergoing RRT compared to those without RRT across all etiologies (p<0.001). For patients undergoing RRT, recipients listed for ALD had the lowest 1-year post-LT mortality (ALD 7.4%, MASH 9.2%, HCV 14.4%; p<0.001). On multivariable analysis, compared to ALD, there was no difference in post-LT mortality for MASH, while HCV recipients had a higher risk for post-LT mortality [HR 1.32 (95%CI 1.08-1.61; p=0.006)]. No differences were observed for post-LT LOS between etiologies. The proportion of recipients with CKD 90-days post-LT was highest for those listed for MASH (ALD 62.0%, MASH 72.2%, HCV 63.8%; p<0.001), while rates of KT within 1 year of LT were highest for ALD (ALD 5.5%, MASH 4.5%, HCV 3.5%; p<0.001). **Conclusion:** Although the rates of RRT at the time of LT were highest among those listed for ALD, ALD patients had the lowest 1-year post-LT mortality. Further allocation adjustments may be needed to ensure equitable organ allocation in non-ALD patients requiring RRT.

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Table 1. Comparing characteristics and post-LT outcomes by etiology in recipients with and without RRT at the time of LT.

All recipients	**ALD (n = 9,819)**	**MASH (n = 5,298)**	**HCV (n = 1,304)**	**Other etiologies (n = 6,348)**	***P* value**
RRT at transplant, n (%)	2,334 (23.8)	953 (18.0)	229 (17.6)	1,209 (19.0)	< 0.001
1-year post-LT survival [95% CI]	-	-	-	-	-
RRT	92.6 [91.4 – 93.6]	90.8 [88.7 – 92.5]	85.6 [80.1 – 89.6]	90.4 [88.5 – 92.0]	< 0.001
No RRT	96.1 [95.6 – 96.5]	93.7 [92.9 – 94.4]	93.2 [91.5 – 94.6]	93.9 [93.2 – 94.6]	< 0.001
RRT	**ALD (n = 2,334)**	**MASH (n = 953)**	**HCV (n = 229)**	**Other etiologies (n = 1,209)**	***P* value**
1-year post-LT mortality univariable HR [95% CI], *P* value	Reference	1.277 [0.984 – 1.657], 0.065	1.405 [1.160 – 1.702], 0.001	1.082 [0.998 – 1.174], 0.056	-
1-year post-LT mortality multivariable HR [95% CI], *P* value[a]	Reference	1.037 [0.776 – 1.387], 0.807	1.321 [1.082 – 1.614], 0.006	1.077 [0.988 – 1.172], 0.090	-
Median LOS, days [IQR]	18 [18]	18 [21]	18 [20]	18 [20]	0.926
LOS > 20 days, n (%)	1,000 (42.8)	433 (45.4)	101 (44.1)	528 (43.7)	0.600
Creatinine > 1.5, n (%)[b]	1,137 (48.7)	478 (50.2)	105 (45.9)	476 (39.4)	< 0.001
CKD, n (%)[b]	1,447 (62.0)	688 (72.2)	146 (63.8)	686 (56.7)	< 0.001
KT ≤ 1 year following LT, n (%)	129 (5.5)	43 (4.5)	8 (3.5)	30 (2.5)	< 0.001

[a]Multivariable Cox proportional hazards models were adjusted for recipient age, sex, race/ethnicity, MELD, wait time, and donor risk index (DRI).
[b]Creatinine and eGFR measured 90-days post-LT.

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2630 | PRE-TRANSPLANT PHOSPHATIDYLETHANOL LEVELS ARE PREDICTIVE OF POST-TRANSPLANT RELAPSE RISK IN SHORT-TERM ABSTAINERS: A SINGLE-CENTER STUDY

Ethan Berman[1] Alex Chang[2] Fariha Ilyas[3] Maham Ghani[1] Alexa Giammarino[1] Talal Bhatti[3] Nishi Joshi[3] Cindy Law[3] James Park[3] Nabil Dagher[4] Sanjaya Satapathy[3]

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Background: Numerous studies have suggested that liver transplantation remains feasible for patients with limited or no prior alcohol abstinence, although the risk of post-transplant relapse may be elevated. Positive phosphatidylethanol (pETH) levels in these individuals can indicate recent alcohol consumption as well as the quantity of alcohol ingested. This study aims to explore the relationship between the most recent pre-transplant pETH levels and post-transplant outcomes in patients with less than three months of abstinence. **Methods:** 37 patients with a minimum follow-up of six months were transplanted at a single center between 2019 and 2023, having had less than three months of abstinence before transplantation. Data on the most recent pre-transplant pETH level, pre-operative characteristics, and post-transplant outcomes were gathered through retrospective chart review. Two patients were excluded due to unavailable pre-transplant pETH levels. Patients were categorized into three groups based on pre-transplant pETH levels: negative pETH, pETH level between 0 and 250, and pETH level above 250. Kaplan-Meier log-rank analysis, with a censoring point at six months, was employed to compare post-transplant relapse rates among the groups. **Results:** Kaplan-Meier log-rank analysis revealed a significant association between a pre-transplant pETH level of less than 250 or negative pETH and a reduced risk of relapse within six months post-transplant in patients with less than three months of abstinence ($p = .031$). Notably, there were no significant differences between the groups in terms of post-transplant infections, mortality, rejection, or graft failure. **Conclusion:** Elevated absolute pETH levels may signify recent alcohol consumption or higher alcohol intake. For patients with less than three months of abstinence prior to transplantation, our study highlights that the absolute pETH level may correlate with an increased risk of relapse within six months post-transplant. Future investigations should delve into not only the relationship between duration of abstinence and relapse risk but also the impact of alcohol consumption quantity on relapse risk.

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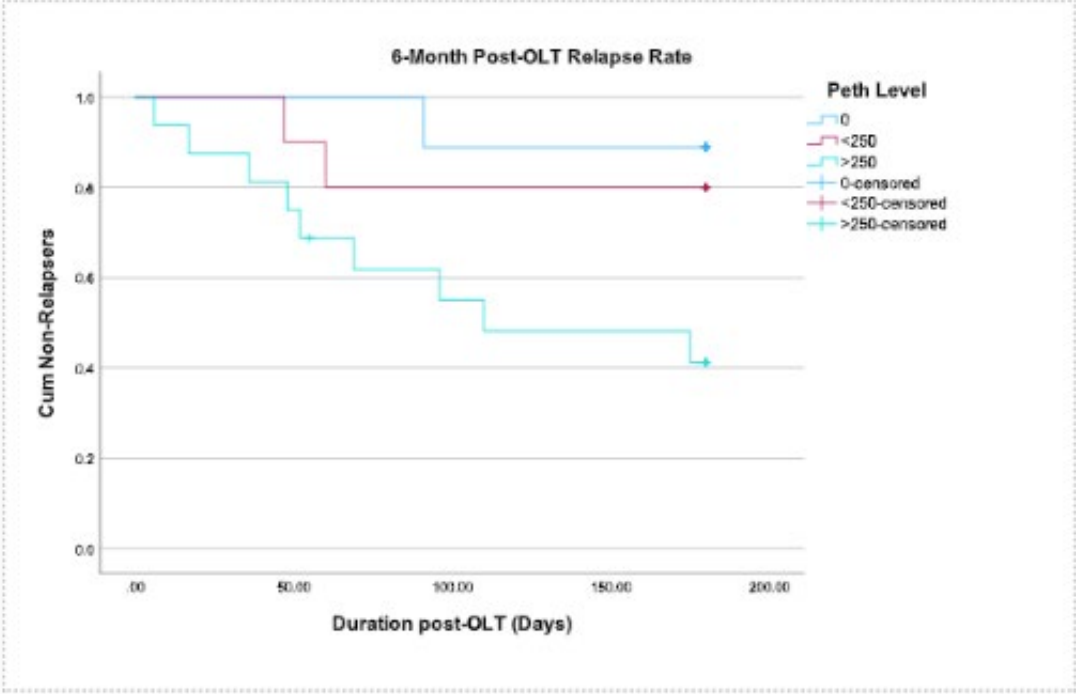

	Negative pETH (n = 9)	pETH 0 – 250 (n = 10)	pETH >250 (n = 16)	p-value
Age	51.4 (12.8)	46.2 (7.1)	47.1 (10.3)	.484
Sex **Male=** **Female=**	 7 2	 5 6	 14 2	.100
BMI	30.1 (4.4)	24.8 (3.5)	27.6 (6.0)	.079
MELD	31.8 (4.2)	30.7 (7.3)	33.3 (6.4)	.591
Bilirubin	15.0 (8.6)	20.7 (12)	25.0 (9.5)	.071
Relapse	1 (11.1%)	2 (20%)	9 (56.3%)	**.031**
Readmissions	1.3 (1.2)	1.4 (1.4)	1.0 (1.2)	.686
Infections (3 mo. Post-OLT)	3 (33.3%)	3 (30%)	5 (31.3%)	.876
Rejections	3 (33.3%)	3 (30%)	4 (25%)	.657
Graft Failure	0	1	0	-
Death	0	1	1	-

Disclosures: Ethan Berman: Nothing to Disclose, Alex Chang: Nothing to Disclose, Fariha Ilyas: Nothing to Disclose, Maham Ghani: Nothing to Disclose, Alexa Giammarino: Nothing to Disclose, Talal Bhatti: Nothing to Disclose, Nishi Joshi: Nothing to Disclose, Cindy Law: Nothing to Disclose, James Park: Nothing to Disclose, Nabil Dagher: Nothing to Disclose, Sanjaya Satapathy: Gilead Sciences: Grant/Research Support, Durect Pharma: Grant/Research Support, Fibronostics: Grant/Research Support, Novartis: Grant/Research Support, Zydus Pharma: Grant/Research Support, Boehringer Ingelheim: Grant/Research Support, Intercept Pharma: Grant/Research Support

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2631 | A PATH TO BETTER PATIENT SELECTION: A RISK SCORE TO PREDICT POST-TRANSPLANT SURVIVAL AMONG PATIENTS WITH HEPATOCELLULAR CARCINOMA

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Background: Utilization of liver transplantation (LT) for patients with hepatocellular carcinoma (HCC) and extended tumor criteria beyond Milan has been increasing. Multiple societies have endorsed a minimum threshold survival 5-years post-transplant of 60%. We aimed to develop a predictive score for post-LT survival using readily available pre-LT characteristics to guide selection of HCC candidates in clinical practice. **Methods:** Adults transplanted with HCC MELD exceptions in UNOS registry between 4/1/2012-12/31/2019 were included. Tumor characteristics included highest tumor burden (categorized as within Milan, down-staging (DS) within UNOS criteria (UNOS-DS), and all-comers DS), alpha-fetoprotein (AFP) category, and the size of largest lesion plus number of tumors. We additionally included age and lab MELD at time of transplant. A prediction score was built using these variables in a multivariable Cox regression model with primary outcome of post-LT survival up to 5 years, with follow-up until 3/31/2024. **Results:** 9783 patients transplanted for HCC (median age 62, 77% male) were included. Majority (N=8636, 88.3%) had highest tumor burden within Milan, followed by UNOS-DS (N=867, 8.9%) and all-comers (N=280, 2.9%). The frequency by AFP category was 77.5%, 15.5%, 5.7%, and 1.2% for AFP<20, 20-100, 101-500 and >500, respectively. Median lab MELD at LT was 11 (IQR 8-14). The median size of the largest lesion at LT was 1 cm (IQR 0-2.2) and tumor number was 1 (IQR 1-1). The 5-year post-LT survival was 79.5% (IQR 78.6-80.3%) and 5-year cumulative incidence of recurrence was 8.0% (IQR 7.4-8.6%). Based on the multivariable analysis (Figure), a risk score was developed with a median score of 2.1 (IQR 1.9-2.3). The subgroup with a score >2.7 (above 95th percentile) had 5-year survival below 60%, compared to >85% in the lower 25th percentile (Figure). In this high-risk subgroup (N=491), 23.8% had an AFP>500, 20.8% were AC-DS, and median sum of largest lesion size and number was 4.3. In comparison, the lower 25th percentile had 0.1% with AFP>500, 7.2% AC-DS, and median sum of largest lesion size and number of 3.2 (all P<0.01). **Conclusion:** We have developed a simple risk score based on five variables at time of LT that stratifies prognosis after LT for HCC. This risk score identifies a subgroup in whom LT should be withheld given a post-transplant survival below the minimal threshold of 60%.

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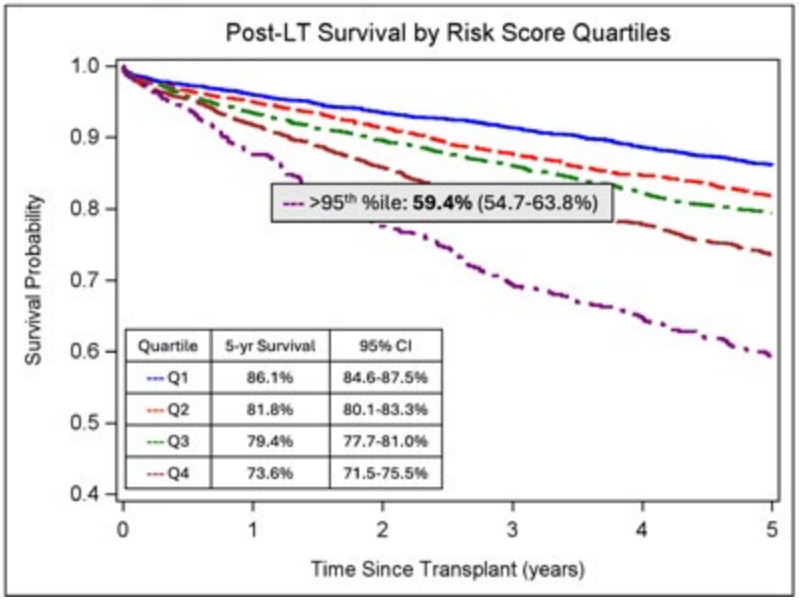
At Transplant	Coef	HR	95% LL	95% UL	P-value
Age	0.027	1.03	1.02	1.04	<0.001
AFP category					
<20	0	ref			
20-100	0.389	1.74	1.48	2.05	<0.001
101-500	0.555	1.48	1.31	1.66	<0.001
>500	1.117	3.06	2.30	4.06	<0.001
Lab MELD	0.016	1.02	1.01	1.03	<0.001
Lesion size + num	0.064	1.07	1.04	1.10	<0.001
Tumor burden					
Within Milan	0	ref			
UNOS-DS	0.145	1.62	1.30	2.03	<0.001
AC-DS	0.485	1.16	1.00	1.34	0.06

Risk score equation = (age x 0.027) + (0.389 if AFP 20-100) + (0.555 if AFP 101-500) + (1.117 if AFP >500) + (final lab MELD x 0.016) + (sum of largest lesion size plus number (capped at 7) x 0.064) + (0.145 if UNOS-DS) + (0.485 if all-comers DS)



Disclosures: Kali Zhou: Nothing to Disclose, Neil Mehta: Merck: Consultant, FujiFilm WAKO: Consultant, Sarah Razon: Nothing to Disclose, Jennifer Dodge: Nothing to Disclose, Francis Yao: Nothing to Disclose

2632 | EVALUATING THE PROGNOSTIC VALUE OF RIGHT VENTRICULAR DILATION IN LIVER TRANSPLANTATION

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[1]Ohio State University

Background: Patients with right ventricular dysfunction experience poor outcomes following liver transplantation, largely due to cardiovascular complications. Transplant surgeons and hepatologists rely on 2D echocardiograms to assess this risk prior to transplantation, looking at the right ventricular (RV) size and right ventricular systolic pressure (RVSP). We aimed to assess the significance of right ventricular dilation (RVD) as an independent predictor of peri- and post-transplant outcomes. **Methods:** We retrospectively examined demographics, echocardiograms (RV size, RVSP), and outcome data from liver transplant patients at The Ohio State University from January 2016 to April 2020. We excluded patients with acute liver failure, porto-pulmonary hypertension (PoPH) and end-stage renal disease (ESRD) undergoing hemodialysis. Only 2D echocardiograms conducted

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within one year before transplant were considered. Right Ventricular dilation was defined as a base diameter exceeding 42 mm, mid-cavity diameter surpassing 35 mm, or longitudinal diameter exceeding 86 mm. We used RV base diameter as surrogate for dilated RV for certain calculations. **Results:** The original dataset comprised 464 liver transplant recipients, 256 patients met inclusion criteria. Among them 28% were found to have right ventricular dilation (RVD). Majority were male (65%) and white (91%). Mean RV base size was 3.7 ± 0.6 cm, median RVSP was 28 (22.5,33). Though the group with dilated RV and non- dilated RV has significantly different RVSP's, the basal RV size correlated weakly with RVSP (r= 0.2, p= 0.0034) for the whole cohort, did not in those with RV base dilation (r=0.08, p=0.57). Table 1 compares demographics and outcomes between the RV dilated group and Non-dilated RV group. **Conclusion:** Right ventricular dilation is a common finding in cirrhosis patients undergoing liver transplantation excluding those with proven PoPH or those on HD. Right ventricular dilation did not have any prognostic value in short term post-transplant outcomes. Right Ventricular parameters correlate with RVSP at low values but when dilated the correlation appears to be lost, limiting its clinical applicability and in the absence of reported RVSP a dilated RV should not prompt a right heart catheterization.

Table 1: Comparison between dilated right ventricle and non-dilated right ventricle groups

Variable	Dilated RV (N = 71)	Non-dilated RV (N = 184)	P-value
Age (years, mean±SD)	54±8.9	54±11	0.6
Male sex (N(%))	59 (83)	116 (63)	0.1
RVSP (Median,(IQR))	30.66 (12,51)	27 (14,45)	0.02
length of stay (days, (Median,(IQR))	9 (2,30)	10 (3,49)	0.89
30-day readmission (N (%))	15 (21.1)	31 (16.8)	0.43
90-day readmission (N (%))	16 (22.5)	42 (22.8)	0.96
Graft loss during index admission (N (%))	2 (2.82)	4 (2.17)	0.76
90-day mortality (N (%))	2 (2.17)	3 (1.63)	0.55

Disclosures: Chathur Acharya: Nothing to Disclose, Hong Lin: Nothing to Disclose, Antonio Alvarez Castaneda: Nothing to Disclose, Khalid Mumtaz: Nothing to Disclose

2633 | MYOSTEATOSIS AND MUSCLE LOSS IMPACT LIVER TRANSPLANT OUTCOMES IN MALE PATIENTS WITH HEPATOCELLULAR CARCINOMA

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Background: Sarcopenia is associated with unfavorable long-term survival in patients undergoing liver transplantation (LT) for hepatocellular carcinoma (HCC). However, the impact of myosteatosis and muscle loss on patient prognosis has not been investigated. **Methods:** 756 HCC patients who received LT at 3 transplant centers were included. Computed tomography (CT) images of recipients were collected to measure skeletal muscle index (SMI) and skeletal muscle radiodensity (SMRA). The impact of myosteatosis on the prognosis of sarcopenic and non-sarcopenic patients was studied separately. Muscle status was evaluated based on the presence of sarcopenia and myosteatosis. The muscle loss of 342 males was calculated as the relative change of SMI between pre- and post-LT (around 1 month) evaluations. Cox regression models were used to identify predictors of overall survival (OS) and recurrence-free survival (RFS). **Results:** The study comprised 673 males and 83 females. The median follow-up time was 31 months (IQR, 19-43 months). Prior to LT, 267 (39.7%) and 187 (27.8%) males were defined as sarcopenic (low-SMI) and myosteatotic (low-SMRA), respectively. Sarcopenic recipients had decreased OS and RFS compared to the non-sarcopenic patients ($p<0.05$). For sarcopenic recipients, the presence of myosteatosis was followed by a 23.6% decrease in 5-y OS ($P < 0.001$) and a 15.0% decrease in 5-y RFS ($P = 0.014$). Univariate and multivariate analyses revealed that muscle status (defined by the existence of sarcopenia/myosteatosis) was an independent predictor of OS (HR, 1.569; 95% CI, 1.317-1.869; $P < 0.001$) and RFS (HR, 1.369; 95% CI, 1.182-1.586; $P < 0.001$). Post-transplant muscle loss (a decrease of

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SMI>14%) impaired outcomes of non-sarcopenic recipients (N = 209), and was an independent risk factor for poor OS (HR, 2.286; 95% CI, 1.358-3.849; P = 0.002) and RFS (HR, 2.219; 95% CI, 1.418-3.471; P < 0.001). **Conclusion:** Pre-transplant myosteatosis aggravated the adverse impact of sarcopenia on liver transplant outcomes in male HCC patients. Post-transplant muscle loss might assist in prognostic stratification of recipients without pre-existing sarcopenia, intriguing new insights into individualized management.

Disclosures: Di Lu: Nothing to Disclose, Zhihang Hu: Nothing to Disclose, Xiao Xu: Nothing to Disclose

2634 | TITLE: FACTORS ASSOCIATED WITH DEATH BEFORE LIVER TRANSPLANT WAITLISTING : THE CALIFORNIA LIVER NETWORK

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Background: Mortality before liver transplant (LT) waitlisting is not well understood, with national data capturing only post-waitlist mortality. California Liver Network (UCSF, UCLA, USC, UCSD, Stanford, and Cedars Sinai), a multicenter cohort of 6 transplant centers, was created to better characterize the LT referral and evaluation process and the purpose of this study is to identify factors associated with death before LT waitlisting. **Methods:** This is a retrospective cohort study of 6856 patients referred for LT evaluation to a transplant center within the California Liver Network (CLN). The primary outcome was death before waitlisting. Descriptive statistics were used to describe patient characteristics. Multivariable Fine-Gray model was performed to evaluate association between patient factors and death, with LT waitlisting considered as a competing event. Missing values were categorized as missing/unknown if >5% of the variable. **Results:** Of the 6856 patients referred for liver transplant evaluation, 4925 (72%) were evaluated and 2362 (34%) waitlisted. Of the evaluated patients, 791 (16%) patients died before waitlisting. These patients were male (62%), non-Hispanic White (35%), had public insurance (74%), had high school/GED or less (42%), social security income (25%), social support at time of evaluation (84%), ALD (46%) and MELD 15-29 (46%). In adjusted Fine-gray model, Medicaid insurance (vs Private insurance; sHR 1.40, 95% CI 1.13 - 1.73), Medicare (vs Private insurance; sHR 1.51 95% CI 1.22 - 1.86), Disability/Social Security (vs employed; sHR 1.40, 95% CI 1.10 - 1.78) and higher MELD categories (vs MELD < 15; p<0.001) were all associated with increased risk of mortality before listing (Table). Having social support (vs none, sHR 0.75, 95% CI 0.58 - 0.97) was associated with decreased risk of mortality before listing. There were also site variations. **Conclusion:** 16% of patients who were referred and evaluated at a transplant center died before waitlisting. Even after adjusting for disease severity, we found several non-medical risk factors of death before listing including insurance, education, income, and support. Identifying at risk patients at the time of referral can allow transplant centers to allocate appropriate resources, such as patient navigators.

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Variable	HR (95% CI)	p-value
Site		
A	0.61 (0.43, 0.86)	0.004
B	Ref	
C	0.71 (0.54, 0.92)	0.01
D	0.60 (0.44, 0.81)	0.001
E	0.71 (0.52, 0.98)	0.04
F	0.74 (0.55, 1.01)	0.06
Insurance at Evaluation		
Private	Ref	
Medicare	1.51 (1.22, 1.86)	<.001
Medicaid	1.40 (1.13, 1.73)	0.002
Social Support		
No	Ref	
Yes	0.75 (0.58, 0.97)	0.03
Unknown/Missing	1.32 (0.97, 1.80)	0.07
Education		
<High School	Ref	
High School/GED	0.97 (0.73, 1.28)	0.82
> High School	0.75 (0.55, 1.02)	0.07
Missing/Unknown	1.53 (1.07, 2.19)	0.02
Etiology		
ALD	Ref	
MASH	0.82 (0.67, 1.01)	0.06
Viral	0.92 (0.74, 1.16)	0.50
PBC/PSC/Autoimmune	0.88 (0.65, 1.20)	0.42
Other	0.86 (0.63, 1.18)	0.34
Income		
Employed	Ref	
Disability/Social Security	1.40 (1.10, 1.78)	0.007
None	1.20 (0.91, 1.58)	0.21
Pension/Retired	1.37 (1.01, 1.85)	0.05
Unknown/Missing	1.16 (0.77, 1.73)	0.48
MELD		
<15	Ref	
15-29	1.79 (1.49, 2.15)	<.001
30-35	2.51 (1.89, 3.34)	<.001
>35	4.44 (3.37, 5.85)	<.001
Unknown/Missing	1.24 (0.74, 2.10)	0.42

Model adjusted for site, race/ethnicity, language, insurance, marital status, income, social support, etiology, MELD; Competing event = waitlist

Disclosures: Mignote Yilma: Nothing to Disclose, Kali Zhou: Nothing to Disclose, Allison Kwong: Nothing to Disclose, Amy Shui: Nothing to Disclose, Connie Zhou: Nothing to Disclose, Sophie Ann Kupiec-Weglinski: Nothing to Disclose, Lynn Leng: Nothing to Disclose, Jasleen Singh: Nothing to Disclose, Ashley Jowell: Nothing to Disclose, Steven Wisel: Nothing to Disclose, Alexander Kuo: Nothing to Disclose, Aarshi Vipani: Nothing to Disclose, Tiffany Lim: Nothing to Disclose, Michie Adjei: Nothing to Disclose, James Daniels: Nothing to Disclose, Justin Steggerda: Nothing to Disclose, Lana Bridi: Nothing to Disclose, Monica Tincopa: Nothing to Disclose, Veeral Ajmera: Nothing to Disclose, Irine Vodkin: Nothing to Disclose, Chris Freise: Nothing to Disclose, Neil Mehta: Merck: Consultant, FujiFilm WAKO: Consultant, Ryutaro Hirose: Nothing to Disclose

2635 | RELATIONSHIP BETWEEN CENTER-LEVEL EXTENDED CRITERIA DONOR LIVER TRANSPLANTATION VOLUME AND RECIPIENT OUTCOMES

Peter Lymberopoulos[1] Raphael Kirou[1] Anwar Uddin[1] Aboud Kaliounji[1] Anjiya Shaikh[2] Madeleine Hines Salge[3] Patrick Boddie[3] Vinh Tran[3] Howard (Tzu-Hao) Lee[3] Kavish Patidar[3] Fasiha Kanwal[4] Anji Wall[5] Abbas Rana[3] George Cholankeril[3]

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Background: The use of extended criteria donors (ECDs) has increasingly become a strategy to expand the donor pool and reduce wait times. Understanding outcomes after ECD liver transplantation (LT) is crucial for determining the appropriate use of these allografts. It remains unclear if transplant centers with low ECD LT volume can achieve similar outcomes to high volume centers. This study aimed to assess the relationship between center-level ECD LT volume and recipient outcomes. **Methods:** Using the United Network for Organ Sharing (UNOS) registry, we analyzed all adult patients (≥ 18 years) who underwent deceased donor LT (DDLT) from May 1, 2019 through April 30, 2022, with follow-up through June 30, 2023. Patients who underwent previous transplant and those waitlisted for simultaneous organ transplant were excluded. Patients who were transplanted at centers that averaged less than 50 DDLT annually during the study period were also excluded. ECD was

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defined as 90th percentile donor risk index (DRI) or discard risk index (DSRI), greater than 30% macrovesicular steatosis, greater than 70 years old, donation after cardiac death (DCD), hepatitis C virus nucleic acid amplification testing positive (HCV NAT+) donors, and hepatitis B virus nucleic acid amplification testing positive (HBV NAT+) donors. Transplant centers were grouped into terciles (low, medium, high) based on total volume of ECD or DCD during the study period. We assessed 1- and 3-year post-LT outcomes using Kaplan-Meier survival analysis with log-rank testing. **Results:** During the study time period, the proportion of ECD LT was 28.7% (n = 4,761) of total LT volume. Among ECDs, 34.6% were in the 90th percentile DRI, 34.7% were in the 90th percentile DSRI, 7.3% had > 30% macrovesicular steatosis, 11.4% were from donors age > 70, 41.5% were DCD, 22.1% were HCV NAT+, and 1.7% were HBV NAT+. Furthermore, 24.7% of ECD allografts met 2 ECD criteria, and 14.0% met ≥ 3 ECD criteria. Table 1 shows 1- and 3-year post-LT outcomes in ECD and DCD among transplant centers grouped into terciles (low, medium, high) based on total volume of ECD or DCD. There was no difference in 1- and 3-year post-LT survival between low, medium, and high volume ECD centers when looking at total volume of ECD (3-year survival; low volume 84.3% vs medium volume 87.2% vs high volume 83.7%; $p = 0.646$). No difference in survival was observed between centers in the bottom 10th percentile and top 90th percentile of ECD volume (3-year survival; 10th percentile 86.0% vs 90th percentile 82.0%; $p = 0.493$). Likewise, survival outcomes were similar for DCD regardless of volume status of the transplant center. **Conclusion:** No differences in short- and medium-term post-LT survival were seen for ECD and DCD LT when comparing center-level volume. High volume ECD and DCD centers are expanding the donor pool without adversely impacting patient outcomes.

Table 1. Comparison of 1- and 3-year post-LT outcomes in ECD and DCD among transplant centers grouped into terciles (low, medium, high) based on total volume of ECD or DCD.

Total volume of ECD[a]				
	Low volume centers	**Medium volume centers**	**High volume centers**	**Log-rank *P* value**
1-year post-LT survival [95% CI]	94.4 [93.1 – 95.4]	93.9 [92.5 – 95.0]	94.2 [92.8 – 95.3]	0.831
3-year post-LT survival [95% CI]	84.3 [81.6 – 86.7]	87.2 [84.7 – 89.3]	83.7 [80.6 – 86.3]	0.646
	Bottom 10th percentile of total volume	-	**Top 90th percentile of total volume**	-
1-year post-LT survival [95% CI]	95.6 [93.1 – 97.1]	-	94.0 [91.3 – 95.9]	0.433
3-year post-LT survival [95% CI]	86.0 [80.5 – 90.0]	-	82.0 [75.4 – 87.0]	0.493
Total volume of DCD[b]				
	Low volume centers	**Medium volume centers**	**High volume centers**	**Log-rank *P* value**
1-year post-LT survival [95% CI]	94.9 [92.8 – 96.4]	93.6 [91.2 – 95.4]	93.9 [91.8 – 95.6]	0.688
3-year post-LT survival [95% CI]	89.1 [85.5 – 91.8]	84.2 [79.4 – 88.0]	83.3 [78.4 – 87.2]	0.321
	Bottom 10th percentile of total volume	-	**Top 90th percentile of total volume**	-
1-year post-LT survival [95% CI]	93.9 [89.6 – 96.5]	-	95.0 [90.6 – 97.4]	0.577
3-year post-LT survival [95% CI]	88.7 [82.6 – 92.7]	-	83.2 [73.0 – 89.8]	0.781

[a]Transplant center volume was categorized into terciles based on total volume of ECD by center during the study period. Low volume centers had ≤ 68 ECD LTs. Medium volume centers had between 69 – 109 ECD LTs. High volume centers had ≥ 110 ECD LTs. The bottom 10th percentile of centers by total volume had ≤ 42 ECD LTs. The top 90th percentile of centers by total volume had ≥ 196 ECD LTs.

[b]Transplant center volume was categorized into terciles based on total volume of DCD by center during the study period. Low volume centers had ≤ 36 DCD LTs. Medium volume centers had between 37 – 61 DCD LTs. High volume centers had ≥ 62 DCD LTs. The bottom 10th percentile of centers by total volume had ≤ 17 DCD LTs. The top 90th percentile of centers by total volume had ≥ 145 DCD LTs.

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Disclosures: Peter Lymberopoulos: Nothing to Disclose, Raphael Kirou: Nothing to Disclose, Anwar Uddin: Nothing to Disclose, Aboud Kaliounji: Nothing to Disclose, Anjiya Shaikh: Nothing to Disclose, Madeleine Hines Salge: Nothing to Disclose, Patrick Boddie: Nothing to Disclose, Vinh Tran: Nothing to Disclose, Howard (Tzu-Hao) Lee: Nothing to Disclose, Kavish Patidar: Madrigal Pharmaceuticals: Medical Advisory Board, Fasiha Kanwal: Nothing to Disclose, Anji Wall: Nothing to Disclose, Abbas Rana: Nothing to Disclose, George Cholankeril: Nothing to Disclose

2636 | FRAILTY AND SARCOPENIA PREDICT PERI-OPERATIVE OUTCOMES IN PATIENTS UNDERGOING LIVER TRANSPLANTATION: ANALYSIS OF NATIONAL INPATIENT SAMPLE 2016-2020

Aalam Sohal[1] Sheena Bhushan[1] Isha Kohl[2] Srinivasan Dasarathy[3] Kris Kowdley[4]

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Background: Frailty and sarcopenia contribute to adverse clinical outcomes in patients with cirrhosis awaiting and after liver transplantation (LT). However, the impact of sarcopenia/physical frailty on perioperative LT outcomes has not been reported. The impact of physical frailty and sarcopenia on outcomes in patients undergoing liver transplantation was evaluated in a nationwide dataset. **Methods:** Adult patients undergoing liver transplantation between 2016-2020 in the National Inpatient Sample database without/with frailty (HFRS score) and/or sarcopenia were analyzed. Patients were stratified into four groups including those without sarcopenia or frailty (sarcopenia/frailty), with sarcopenia alone, with frailty alone, and those with both sarcopenia and frailty. Univariate and multivariate logistic/linear regression analyses were performed to compare in-hospital mortality, perioperative organ system complications, length of stay, and costs during the LT hospitalization in patients with or without frailty and/or sarcopenia. Adjustments were made for patient demographics, hospital characteristics, modified Charlson Comorbidity index, etiology, and decompensation of liver disease. **Results:** The prevalence of frailty, sarcopenia, or both sarcopenia/frailty among the 34,405 LT recipients was 64.1%, 36.7% and 29.1% respectively. Patients with both sarcopenia and frailty had the highest rates of perioperative complications, non-home discharge and in-hospital mortality among the four groups (Figure 1).After adjusting for confounding factors compared to patients without sarcopenia and frailty, patients with both sarcopenia and frailty had a higher odds ratio for in-hospital mortality (aOR-2.79, 95% CI-1.68-4.64, p<0.001), perioperative complications (aOR-3.52, 95% CI-3.01-4.10, p<0.001), and non-routine discharge (aOR-3.55, 95% CI-2.97-4.24, p<0.001). A significantly longer length of stay (adj. Coeff-18.3 days, p<0.001) and higher hospitalization charges (adj. coeff-$430,966, 95% CI-$377,731-$484,202, p<0.001) was also noted in patients with both frailty and sarcopenia, compared to patients without either. **Conclusion:** Patients with frailty and sarcopenia independently or in combination, have significantly worse outcomes. Formally assessing sarcopenia and frailty pre-LT and utilizing them as objective prognostication tools can aid with risk stratification of patients who would benefit from more intensive nutritional supplementation, aggressive physical therapy programs pre-operatively.

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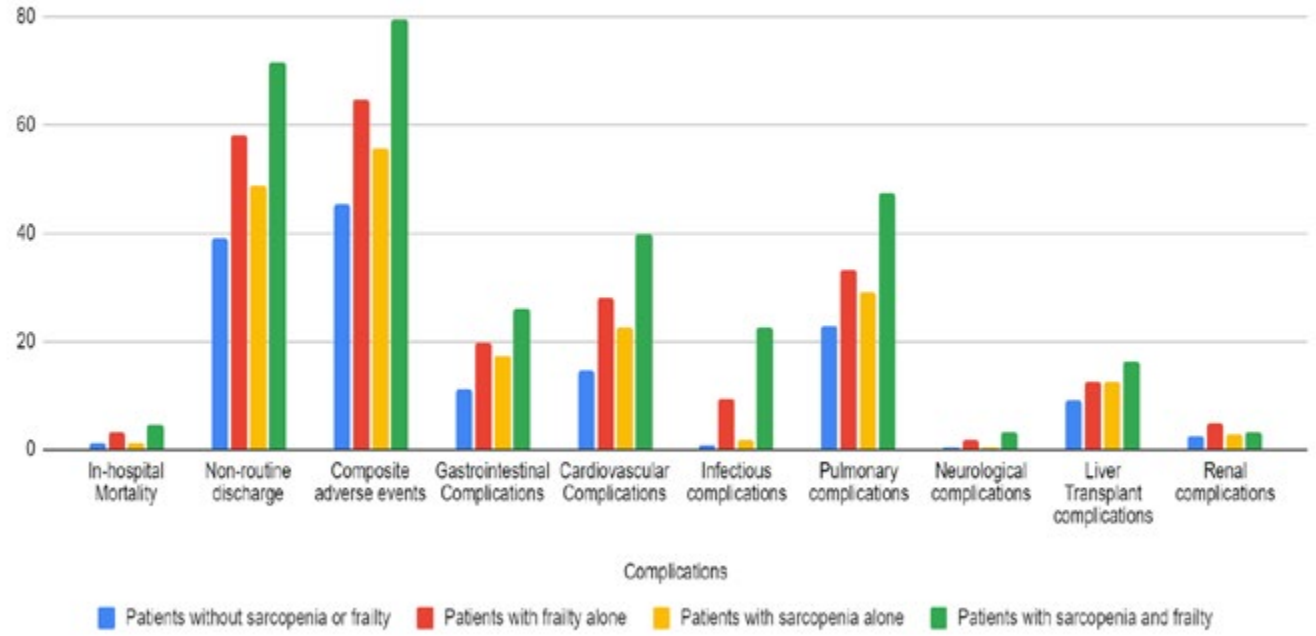
Figure 1- Complications, stratified into three groups based on presence of frailty and sarcopenia



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2637 | ADVANCING DIAGNOSIS, MANAGEMENT, TREATMENT, AND TRANSPLANTATION OF LIVER DISEASE IN TELOMERE BIOLOGY DISORDERS: PUBLICATION AND DISSEMINATION OF GUIDELINES ◆

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Background: Telomere Biology Disorders (TBDs), characterized by short telomeres and aberrations in telomere-related genes, are associated with a range of liver manifestations from mildly abnormal liver tests to advanced cirrhosis, portal hypertension, and hepatocellular carcinoma. Research from recent years has shown that the prevalence of liver disease in patients with TBDs is notably high. Importantly, the proper diagnosis of liver disease in the context of TBDs is essential to tailor management and treatment. Transplantation for liver

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disease in the context of TBDs requires particular attention given the systemic nature of TBDs, including careful evaluation, donor selection, and transplant management to optimize outcomes. Thus, the patient advocacy group Team Telomere Inc. aimed to develop comprehensive guidelines to be utilized by patients, caregivers, clinicians, and researchers that reflect an updated understanding of TBDs while filling important gaps within the hepatology field. **Methods:** The development of the Telomere Biology Disorders: Diagnosis and Management Guidelines resulted from a multi-disciplinary international collaboration spanning two years. The effort brought together 58 contributing authors and field experts from 34 institutions across seven countries, nine Community-Centric Review Committee members, fruitful inter-organizational collaboration, and the TBD community at large. **Results:** The second edition of the TBD Diagnosis and Management Guidelines are a comprehensive reference manual for patients, physicians, and researchers. They consist of 31 peer-reviewed, comprehensive chapters. Notably, Chapter 18 and Chapter 19 of the guidelines cover the topics of Hepatic Complications and Liver Transplantation, respectively. These chapters include an updated and comprehensive discussion on the range of TBD hepatic clinical presentations, monitoring for hepatic involvement, treatment options, and transplantation recommendations and management. Additional topics covered in the guidelines include underlying biology, genetics, TBD diagnostic criteria, major body and organ systems, routine care, and potential future field directions. To date, over 375 copies of the physical guidelines have been distributed, and over 30,000 individuals have been reached. Additionally, accessible one-page resource sheets are available on the topics of Hepatic Complications and Liver Transplantation. **Conclusion:** The second edition of the guidelines effectively addresses the management of liver disease in the context of TBDs. With this publication, we hope to see increased awareness of TBDs within the hepatology space, optimal screening and management, and better outcomes for TBD patients undergoing liver transplantation. The guidelines can be downloaded or requested at https://teamtelomere.org/diagnosis-management-guidelines/.

Disclosures: Heidi Carson: Nothing to Disclose, Hannah Raj: Nothing to Disclose, Heidi Carson: Nothing to Disclose, Sharon Savage: Nothing to Disclose, Suneet Agarwal: Cimeio Therapeutics: Consultant, Rejuveron: Consultant, Orbimed Advisors: Consultant

3001 | EVOLVING TRENDS AND OUTCOMES FOR ALCOHOL-ASSOCIATED HEPATITIS PATIENTS WITH SEVERELY HIGH MELD SCORES ON THE US LIVER TRANSPLANT WAITLIST

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Background: Over the past decade, the United States has witnessed significant changes in liver transplantation (LT) waitlisting, particularly with an increase in patients with alcoholic hepatitis (AH). This study aims to update the outcomes of AH patients on the waitlist following the COVID-19 pandemic and the implementation of the Acuity Circle policy. **Methods:** Conducted as a nationwide retrospective cohort study and utilizing the UNOS STAR file, this research examined LT candidates who were added to the waitlist from June 18, 2013, to May 31, 2023, focusing on adults listed for their first deceased donor LT. The study contrasted outcomes based on the etiology of end-stage liver disease (ESLD), specifically comparing AH with other causes. Primary outcomes were the removal from the waitlist due to death or deterioration; secondary outcomes considered post-transplant survival. Survival outcomes on the waitlist were modeled using Fine-Gray models, incorporating competing risks, and generalized linear mixed models (GLMM) with center- and date-of-listing-level random intercepts. Post-transplant survival was analyzed using Cox models, adjusted for clinical and donor variables. **Results:** During the study period, 8,156 liver transplant (LT) candidates with MELD scores ≥ 37 were analyzed, including 850 with AH. Candidates with AH, who were typically younger and predominantly white, demonstrated a significant increase in waitlist additions post-2019 (Figures A and B), with a lower probability of waitlist death or dropout due to clinical deterioration (11.1% in the AH group vs. 19.8% in others, $p<0.001$). Candidates with AH exhibited a reduced risk of waitlist mortality or dropout, with a sub-hazard ratio (sHR) of 0.72 (95% CI: 0.58, 0.90) from the Fine-Gray model and an adjusted odds ratio (aOR) of 0.66 (95% CI: 0.44, 0.99) from the GLMM when compared to other diagnoses, notably autoimmune hepatitis, metabolic dysfunction-associated fatty liver disease, and primary biliary cholangitis (Figure C) **Conclusion:** This study underscores the growing prevalence of alcoholic hepatitis (AH) post-COVID-19 and Acuity Circle among US liver transplant waitlist candidates with high MELD scores, revealing that AH patients face lower waitlist mortality and have access to quality allografts. It suggests a need to reconsider

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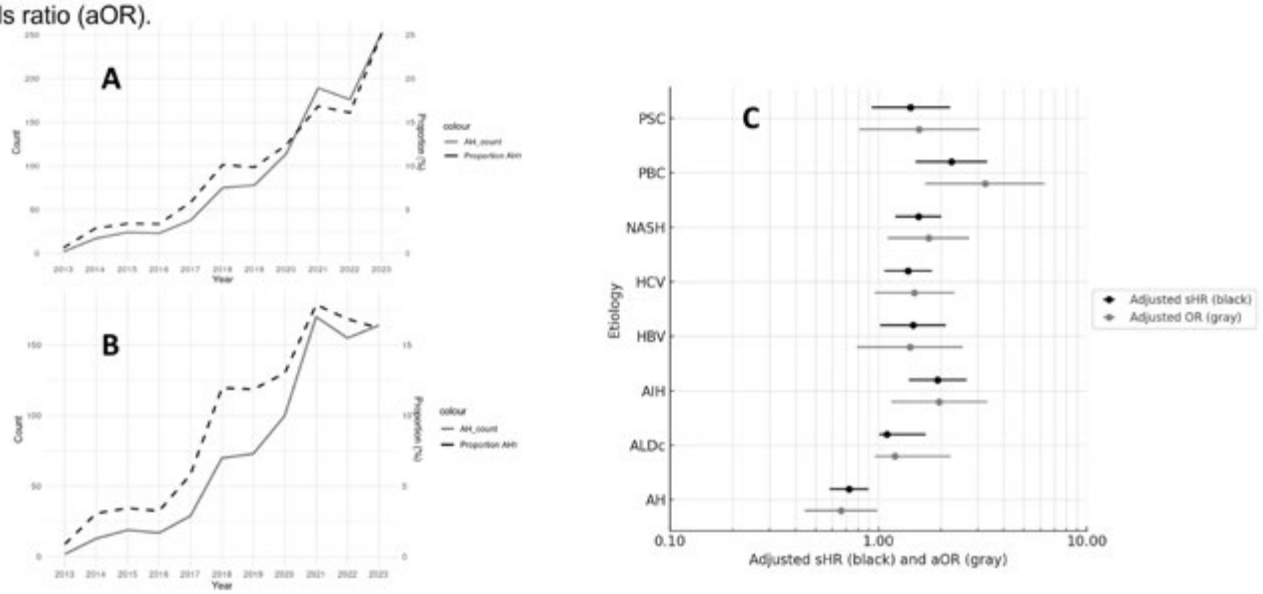
allocation policies for equitable organ distribution and emphasizes the importance of improving the identification of AH patients to potentially avoid unnecessary transplants.

Figure. Trend of alcoholic hepatitis, the absolute number of waitlisting and proportion among all the candidates listed with MELD ≥ 37 (A), the absolute number of liver transplantation and proportion among all the LT recipients with initial MELD at listing of ≥ 37 (B), and the outcomes of statistical analyses; the semiparametric competing risk survival model, indicated by the sub-hazard ratio (sHR), and the generalized linear mixed-effect model, represented by the adjusted odds ratio (aOR).



Disclosures: Tomohiro Tanaka: Nothing to Disclose, David Axelrod: Nothing to Disclose

3002 | IN-HOSPITAL OUTCOMES FOR ACUTE ALCOHOL ASSOCIATED CIRRHOSIS AND MAJOR CARDIAC ARRHYTHMIAS

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Background: Liver cirrhosis is one of the major risk factors for cardiac arrhythmias and outcomes of arrhythmias in liver cirrhosis patients are often fatal in nature. In the acute setting of alcohol associated cirrhosis, outcomes of arrhythmias have not been evaluated. The aim of present study is to examine the impact of major cardiac arrhythmias in patients admitted with acute alcohol associated cirrhosis. **Methods:** We used the Healthcare Cost and Utilization Project (HCUP) Nationwide Inpatient Sample (NIS) to identify adult patients admitted with acute alcohol associated cirrhosis (AC) during 2016 – 2020 using ICD-10-CM codes. We defined the acute alcohol associated cirrhosis as alcoholic cirrhosis with complications like ascites, variceal hemorrhage, hepatic encephalopathy, hepatorenal syndrome, and spontaneous bacterial peritonitis. We divided the patients into two groups based on concomitant diagnosis of major cardiac arrhythmias including atrial fibrillation/flutter (AF), Ventricular fibrillation/flutter (VF), and premature depolarization. Main outcomes were in-hospital mortality, length of stay (LOS), and hospital costs. We evaluate the association between arrhythmias and outcomes using survey based multivariate logistic regression models for in-hospital mortality, Poisson regression for LOS, and generalized linear model with gamma distribution and log link for hospitalization cost. Models were adjusted for age, sex, race and ethnicity, primary payer, Charlson comorbidity index, hospital bed size and hospital region. **Results:** We identified a total of 944,105 AC hospitalizations between 2016 and 2020 in the United States and 96,675 (10.2%) of them were associated with cardiac arrhythmias (Table 1). In-patient mortality was significantly higher in AC patients with arrhythmias (14.0% vs 8.6%, adjusted OR: 1.5, 95%CI: 1.45 - 1.59 P < 0.001, Table 2). AC patients with arrhythmias had an increased length of stay (8.5 ± 0.07 vs 6.9 ± 0.03 days, P < 0.001) and cost of hospitalization ($26,764 ± 324 vs $20,928 ± 169, P < 0.001, Table 2). **Conclusion:** Cardiac arrhythmias are

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common in patients with acute alcohol associated cirrhosis and are associated with higher in-hospital mortality, increased length of stay, and increased cost of hospitalization. Further studies will need to be conducted to investigate the relationship between cardiac arrhythmias and acute alcohol assoicated cirrhosis.

Table 1: Baseline characteristics of two groups (Acute Alcoholic Cirrhosis with Cardiac Arrhythmias vs Acute Alcoholic Cirrhosis without Cardiac Arrhythmias)

Characteristic	Overall, N = 944,105	No Cardiac Arrythmias, N = 847,430	Cardiac Arrythmias, N = 96,675	p-value
Age	55.6 (0.04)	54.6 (0.04)	63.9 (0.08)	<0.001
Age Category (%)				
18-40	97760 (10.4%)	95845 (11.3%)	1915 (2%)	<0.001
41-50	186005 (19.7%)	179390 (21.2%)	6615 (6.8%)	
51-60	314355 (33.3%)	291075 (34.3%)	23280 (24.1%)	
>61	345985 (36.6%)	281120 (33.2%)	64865 (67.1%)	
Female	288,130 (31%)	269,035 (32%)	19,095 (20%)	<0.001
Male	655,975 (70%)	578,395 (68%)	775,80 (80%)	
Race				<0.001
White	635,475 (67%)	562,040 (66%)	73,435 (76%)	
Black	83,435 (8.8%)	74,465 (8.8%)	8,970 (9.3%)	
Hispanic	163,385 (17%)	153,305 (18%)	10,080 (10%)	
Asian or Pacific Islander	12,030 (1.3%)	10,860 (1.3%)	1,170 (1.2%)	
Native American	22,530 (2.4%)	21,485 (2.5%)	1,045 (1.1%)	
Other	27,250 (2.9%)	25,275 (3.0%)	1,975 (2.0%)	
Insurance				<0.001
Medicare	297,285 (32%)	243,590 (29%)	53,695 (56%)	
Medicaid	322,085 (34%)	303,290 (36%)	18,795 (19%)	
Private	210,125 (22%)	192,800 (23%)	17,325 (18%)	
Other	113,110 (12%)	106,380 (13%)	6,730 (7.0%)	
Unknown	1,500	1,370	130	
Hospital bed size				0.094
Small	171,470 (18%)	153,340 (18%)	18,130 (19%)	
Medium	267,760 (28%)	240,260 (28%)	27,500 (28%)	
Large	504,875 (53%)	453,830 (54%)	51,045 (53%)	
Hospital region				<0.001
Northeast	159,845 (17%)	142,720 (17%)	17,125 (18%)	
Midwest	193,375 (20%)	170,805 (20%)	22,570 (23%)	
South	353,900 (37%)	319,635 (38%)	34,265 (35%)	
West	236,985 (25%)	214,270 (25%)	22,715 (23%)	
Charlson comorbidity index				<0.001
0-1	110,955 (12%)	106,165 (13%)	4,790 (5.0%)	
2	65,915 (7.0%)	58,465 (6.9%)	7,450 (7.7%)	
>=3	767,235 (81%)	682,800 (81%)	84,435 (87%)	
Ascites	799,130 (85%)	719,445 (85%)	79,685 (82%)	<0.001
Variceal hemorrhage	117,900 (12%)	111,825 (13%)	6,075 (6.3%)	<0.001
Hepatic encephalopathy	177,370 (19%)	152,125 (18%)	25,245 (26%)	<0.001
Hepatorenal syndrome or	102,535 (11%)	91,990 (11%)	10,545 (11%)	0.829
Spontaneous bacterial peritonitis	68,265 (7.2%)	62,580 (7.4%)	5,685 (5.9%)	<0.001
Mean (SE); n (%)				
Wilcoxon rank-sum test for complex survey samples; chi-squared test with Rao & Scott's second-order correction				

Table 2: Comparison of primary outcomes: Acute Alcoholic Cirrhosis with Cardiac Arrhythmias vs Acute Alcoholic Cirrhosis without Cardiac Arrhythmias

	Acute Alcohol Associated Cirrhosis		Adjusted OR / RR		
Characteristic	No Cardiac Arrythmias, N = 847,430	Cardiac Arrhythmias, N = 96,675	OR / RR	95% CI	p-value
In-hospital mortality - N (%)	73,065 (8.6%)	13,155 (14%)	1.52	1.45, 1.59	<0.001
LOS (days) - mean (SE)	6.9 (0.03)	8.5 (0.07)	1.24	1.22, 1.26	<0.001
Hospital Cost ($, 2020) - mean (SE)	20,927.5 (168.68)	26,764.0 (324.40)	1.33	1.30, 1.36	<0.001

Relative ratio is reported using Poisson regression model for LOS
Relative ratio is reported using generalized linear model with gamma distribution and log link for Hospital Cost; adjusted for inflation using Consumer Price Index (CPI) for Medical care services in U.S. city average, all urban consumers, chained, with 2018 as the reference point
Variables used for multivariate logistic regression: age, sex, race, insurance status, Charlson comorbidity index, hospital bed size, and hospital region

Disclosures: Anwar Uddin: Nothing to Disclose, Aboud Kaliounji: Nothing to Disclose, Peter Lymberopoulos: Nothing to Disclose, Rahat Uddin: Nothing to Disclose, Madia Ahad: Nothing to Disclose, Afgal Ahad: Nothing to

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Disclose, Rafat Uddin: Nothing to Disclose, Nazima Khatun: Nothing to Disclose, Besh Karki: Nothing to Disclose, Prashil Dave: Nothing to Disclose, Nazeera Ghanie: Nothing to Disclose, Sahil Chaddha: Nothing to Disclose

3003 | MORTALITY FROM ALCOHOL-ASSOCIATED LIVER DISEASE AND ALCOHOL USE DISORDER IS DECREASING GLOBALLY YET INCREASING IN THE UNITED STATES

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[1]Department of Internal Medicine, Texas Tech University Healt, [2]Chiang Mai university, [3]National University of Singapore, [4]National University Hospital, Singapore, [5]Saga University, [6]VA Palo Alto Healthcare System, [7]NIH, Baltimore and Bethesda, Maryland, [8]Cedars-Sinai Medical Center, [9]University of Michigan Medical Center, [10]Houston Methodist Hospital, [11]Pontificia Universidad Católica de Chile, [12]University of Western Ontario, [13]Indiana University, [14]University of Arizona College of Medicine-Phoenix

Background: The economic impact of alcohol-associated liver disease (ALD) is substantial, with estimates suggesting that between 2022 and 2040, the disease will incur a cost of $880 billion. Older adults with ALD typically experience more adverse outcomes compared to younger individuals with the same condition. Of particular concern is the aging population in the US, with projections indicating a significant increase in the number of individuals aged 65 and over by the year 2040. ALD is not solely a standalone hepatic condition but is intricately linked with addiction diseases such as alcohol use disorder (AUD). Our study aims to address this gap by examining temporal shifts in both the prevalence and mortality rates associated with ALD and AUD among the elderly population in the US. To achieve this, we draw on insights from the Global Burden of Disease (GBD) Study 2019. **Methods:** We gathered the ALD and AUD prevalence, mortality, and age-standardized rates (ASRs) from the Global Burden of Disease (GBD) Study 2019 between 2010 and 2019. We estimated the annual percent change (APC) with confidence intervals (CIs) for burden of ALD and AUD in the elderly (>70 years) in the US. The findings were contrasted with global estimates and further categorized by sex and state/ territory. **Results:** In 2019, there were approximately 556,340 cases of AUD, 112,560 cases of alcohol-associated cirrhosis, and 3,720 cases of primary liver cancer from alcohol among the elderly in the US. In contrast to declining ASRs of prevalence and mortality in the global burden, these parameters were increased in the US. From 2010 to 2019, mortality from AUD (APC +1.63%, 95% confidence interval [CI] 1.34 to 1.92%), cirrhosis (APC +0.56%, 95% CI 0.39 to 0.73%), and primary liver cancer from alcohol (APC +3.09%, 95% CI 2.81 to 3.37%) increased. Nearly half of the states in the US exhibited a rise in mortality from alcohol-associated cirrhosis. **Conclusion:** Our findings highlighted the increased prevalence and mortality of ALD and AUD among the elderly population in US. Public health strategies on ALD and AUD targeting the elderly are urgently needed.

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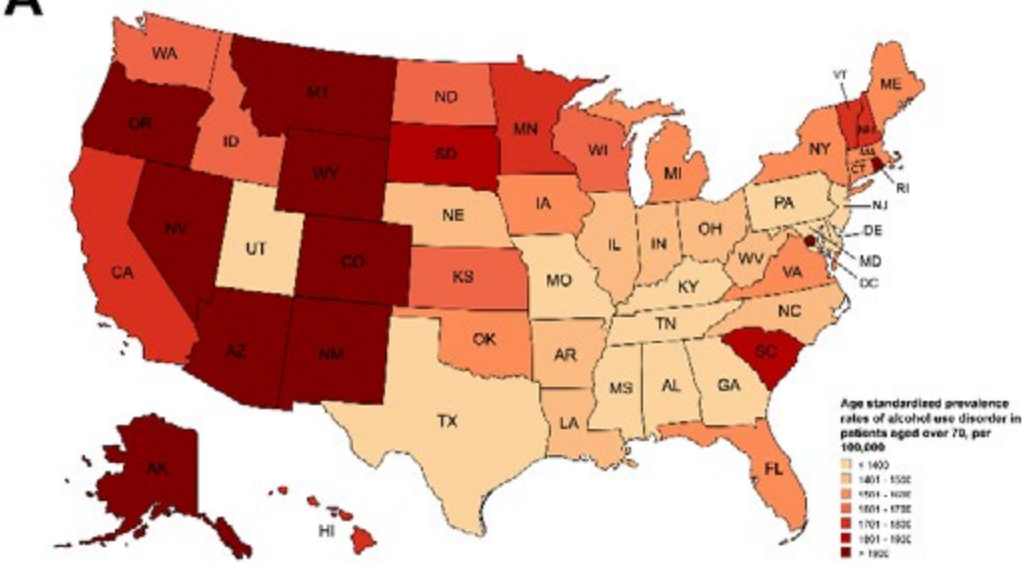

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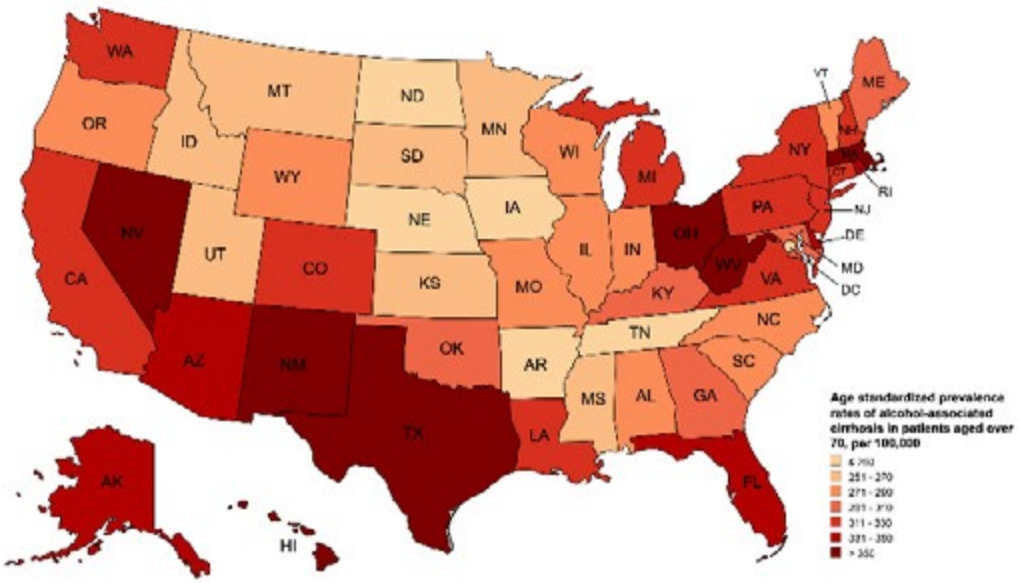

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Consultant relationship with Eisai; Has not ended; Consultant relationship with AstraZeneca; Has not ended; Consultant relationship with Exact Sciences; Has not ended, Vincent Chen: Site PI on industry-sponsored trial relationship with AstraZeneca; Has ended; site co-I on industry-sponsored trial relationship with Ipsen; Has not ended; site co-I on industry-sponsored trial relationship with Kowa; Has not ended, Mazen Noureddin: Principal Investigator for a Drug Study relationship with Viking; Has not ended; Consultant relationship with Eli Lilly; Has not ended; Consultant relationship with AstraZeneca; Has not ended; Consultant relationship with Boston Pharmaceuticals; Has not ended; Principal Investigator for a Drug Study relationship with Genfit; Has not ended; Principal Investigator for a Drug Study relationship with Galectin; Has not ended; Principal Investigator for a Drug Study relationship with Gilead; Has not ended; Principal Investigator for a Drug Study relationship with BMS; Has not ended; Principal Investigator for a Drug Study relationship with BI; Has not ended; Principal Investigator for a Drug Study relationship with Akero; Has not ended; Consultant relationship with Cytodyn; Has not ended; Consultant relationship with GSK; Has not ended; Consultant relationship with BI; Has not ended; Consultant relationship with Madrigal; Has not ended; Terns,Takeda, Zydus. relationship with Itimmune, BI, Cytodyn, 89BIO, GSK, Madrigal, Merck, Novo Nor; Has not ended; Principal Investigator for a Drug Study relationship with Allergan; Has not ended; Consultant relationship with Takeda; Has not ended; Consultant relationship with Terns; Has not ended; Terns, Corcept, Takeda, Madrigal, Novartis, Novo Nordisk, relationship with Allergan, Akero, BI, BMS, Gilead, Galectin, Zydus GSK; Has not ended; Consultant relationship with Novo Nordisk; Has not ended; Stock â€“ privately held company relationship with Rivus Pharma, Cytodyn, and ChronWell; Has not ended; Consultant relationship with Merck; Has not ended; Principal Investigator for a Drug Study relationship with Madrigal; Has not ended; Consultant relationship with Altimmune; Has not ended; Principal Investigator for a Drug Study relationship with Terns; Has not ended; Principal Investigator for a Drug Study relationship with Zydus; Has not ended; Stock â€“ privately held company relationship with Rivus Pharmaceuticals; Has not ended; Consultant relationship with Alligos; Has not ended; Stock - publicly traded company relationship with Cytodyn; Has not ended; Stock â€“ privately held company relationship with ChronWell; Has not ended; Speaking and Teaching relationship with Madrigal; Has not ended; Principal Investigator for a Drug Study relationship with Takeda; Has not ended; Principal Investigator for a Drug Study relationship with Shire; Has not ended; Principal Investigator for a Drug Study relationship with Novo Nordisk; Has not ended; Principal Investigator for a Drug Study relationship with Novartis; Has not ended; Principal Investigator for a Drug Study relationship with Enanta; Has not ended; Principal Investigator for a Drug Study relationship with Corcept; Has not ended; Principal Investigator for a Drug Study relationship with GSK; Has not ended; Principal Investigator for a Drug Study relationship with Conatus; Has not ended, Luis Antonio Diaz: Nothing to Disclose, Juan Pablo Arab: Nothing to Disclose, Suthat Liangpunsakul: DURECT: Consultant, Durect Corporation: Consultant, Surrozen: Consultant, Korro Bio: Consultant, Karn Wijarnpreecha: Nothing to Disclose

3004 | VITAMIN D DEFICIENCY EXACERBATES ALCOHOL-ASSOCIATED LIVER DISEASE VIA GUT BARRIER DYSFUNCTION AND HEPATIC OVERLOAD OF ENDOTOXIN IN MICE

KOSUKE KAJI[1] *NORIHISA NISHIMURA*[1] *Shinya Sato*[1] *Tadashi Namisaki*[1] *Hitoshi Yoshiji*[1]

[1]*Nara Medical University*

Background: Endogenous lipopolysaccharide (LPS) that translocates via the disrupted intestinal barrier plays an essential role in the progression of alcohol-related liver disease (ALD). Vitamin D deficiency is observed in ALD, and it participates in regulating gut barrier function. The current study aimed to examine the association between vitamin D deficiency and endotoxemia in patients with ALD-related cirrhosis. Moreover, the effect of vitamin D deficiency on ethanol (EtOH)- and carbon tetrachloride (CCl4)-induced liver injury relevant to gut barrier disruption in mice was investigated. **Methods:** Clinical study evaluated the serum 25(OH)D levels and endotoxin activity of patients with ALD-related cirrhosis. Retrospective observational study enrolled a single-center cohort at Nara Medical University Hospital. In total, 86 consecutive patients with ALD-related liver cirrhosis were enrolled. Basic study was performed to elucidate the impact of Vitamin D deficiency on the pathogenesis of ALD. We fed female C57BL/6J mice a liquid diet containing 2.5% EtOH and intraperitoneal injections of CCl4 twice weekly for 8 weeks. The mice were divided into vitamin D-deficient (vitamin D: 1.6 IU/kg) and vitamin D-sufficient (vitamin D: 54.4 IU/kg) groups. In addition, we cultured CaCo2 cells to examine the direct effects of vitamin D on intestinal cells. **Results:** The serum 25(OH)D level of patients with ALD-related cirrhosis was significantly lower, as evidenced by decreased hepatic reserve, than that of non-drinking controls. Meanwhile, the endotoxin activity of patients with ALD-related cirrhosis increased with decreased hepatic function. Based on these results, serum 25(OH) D levels were negatively correlated with endotoxin activity in total patients (R=−0.481, P<.0001). Moreover, we

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confirmed that the negative correlation between them were observed in the patients with Child-Pugh class A (R=−0.473, P<.001), class B (R=−0.847, P=.0162), and class C (R=−0.581, P =.0292). The EtOH/CCl4-treated mice developed hepatic steatosis, inflammation, and fibrosis, which were significantly exacerbated by vitamin D-deficient diet. Vitamin D deficiency enhanced gut hyperpermeability by reducing the intestinal expressions of tight junction proteins including ZO-1, occludin, and claudin-2/5/12/15 in the EtOH/CCl4-treated mice. Consequently, it induced Kupffer cell infiltration and LPS/toll-like receptor 4 signaling-mediated proinflammatory response in the liver. Based on the in vitro assay, vitamin D3-mediated vitamin D receptor activation inhibited EtOH-stimulated paracellular permeability and the downregulation of tight junction proteins in Caco-2 cells. **Conclusion:** Vitamin D deficiency exacerbates alcohol-associated liver disease via gut barrier dysfunction and hepatic overload of LPS.

Disclosures: KOSUKE KAJI: Nothing to Disclose, NORIHISA NISHIMURA: Nothing to Disclose, Shinya Sato: Nothing to Disclose, Tadashi Namisaki: Nothing to Disclose, Hitoshi Yoshiji: Nothing to Disclose

3005 | TARGETING MITOCHONDRION-NUCLEUS PDH1 TRANSFER SUPPRESSES SELF-RENEWAL AND EPIGENETIC *NANOG* REPROGRAMING OF LIVER TUMOR-INITIATING CELLS INDUCED BY ALCOHOL WESTERN DIET

Purva Kalel[1] Simran Mehta[1] Hye Yeon Choi[1] Gary Kanel[1] Cholsoon Jang[2] Ramachandran Murali[3] Hidekazu Tsukamoto[1] Keigo Machida[1]

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Background: Tumor-initiating stem-like cells (TICs) are implicated in hepatocellular carcinoma (HCC) therapy-resistance. The TCA enzyme pyruvate dehydrogenase (PDH1), translocates to the nucleus to supply acetyl-CoA from pyruvate and stimulates H3K27 acetylation (H3K27ac) in stem cells. The oncoprotein TBC1D15 activates and stabilizes NOTCH in TICs. *Aim:* We tested the hypothesis that NOTCH Intracellular Domain (NICD) supports TBC1D15-mitochondrial fission protein 1 (FIS1) interaction at the mitochondrional outer membrane (MOU), the nuclear import of PDH1, and H3K27ac modification of enhancers for the pluripotency factors NANOG. **Methods:** Gain or loss function approaches validated the tripartite complex NOTCH-TBC1D15-PDHA1 axis and epigenetic NANOG enhancer activation, self-renewal ability and oncogenesis. **Results:** Gain or loss function approaches validated the tripartite complex NOTCH-TBC1D15-PDHA1 axis mediates epigenetic NANOG enhancer activation through nuclear-PDH1-mediated H3K27 acetylation. Co-IP analysis demonstrated the nature of NICD interaction with TBC1D15 and FIS1 at MOU in TICs. This triple protein complex formation was dependent on NICD and was required for PDH1 nuclear-influx. O-linked β-N-acetylglucosamine modification (O-GlcNAcylation) of PDHA1 promoted its binding to HSP70 and HIKESHI proteins, and subsequent PDH1 nuclear translocation. NICD1 ChIP-seq analysis revealed reduced enrichments of H3K27ac at *Nanog* enhancer in *AlbCreERT;Tbc1d15$^{f/f}$;NA5A* mice deficient in hepatocyte TBC1D15 resulting in 7-fold decreased liver tumor burden vs. wild type *Tbc1d15$^{f/f}$;NA5A* mice. Similarly, PDH-E1 silencing also reduced H3K27ac on *Nanog* enhancers. A small molecule inhibitor which blocked the NICD-TBC1D15 interaction or a TBC1D15 deletion mutant of a NICD-TBC1D15 Canoe domain binding site, abrogated the NICD1-TBC1D15-FIS1 interaction required for achieving mitochondrion-nuclear spatial proximity for PDH1 nuclear uptake. CRISPR/Cas9 mutations of the FIS1/NUMB-binding site of TBC1D15 reduced the tumor initiation property of TICs in NSG mice, patient-derived HCC xenograft (PDX) growth in NSG mice, and liver tumor development in the humanized HCC model of *Fah-/-;Rag2-/-;Il2rgc-/-* (*FRG*) mice transplanted with human fetal liver cells bearing humanized immune system and hepatoblasts with *ARID1A* and/or *CTNNB1* mutations. **Conclusion:** Taken together, a novel epigenetic mechanism of NANOG upregulation and liver tumorigenesis mediated by mitochondrial PDH1, which becomes nuclear-translocated via NICD-TBC1D15-FIS1 interaction at MOM. This study addressed a novel therapeutic target for BASH (both alcohol and non-alcohol-associated steatohepatitis)-derived HCC which clinically is recognized as a major progressive form of HCC. Supported by NIH grants R01AA025204-01A1, R21AA025470-01A1, P50AA011999, pilot project funding (5P30DK048522-13), and R24AA012885.

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3006 | ADMINISTRATION OF POLYETHYLENE GLYCOL AMELIORATES INFLAMMATION OF LIVER AND GUT, AND HANGOVERS AGAINST ACUTE ALCOHOL CONSUMPTION

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Background: This study revealed the effectiveness of polyethylene glycol (PEG) for protection of liver and gut against inflammation and hangover symptoms with mouse model of binge drinking. **Methods:** 8-week-old male C57BL6J wild type mice with vehicle, binge drinking (4 g/kg body weight), or binge drinking plus PEG (2 g/kg body weight) were analyzed by blood concentration tests using gas chromatography, and behavior tests. H&E, immunohistochemistry, and immunofluorescence staining were conducted with the slides of liver and intestine of alcohol intoxicated mice. Quantitative real-time polymerase chain reaction (qRT-PCR) was utilized with tissue and mononuclear cells of liver and proximal jejunum. Also, PEG (2 g/kg body weight) or additional 4-Methylpyrazole (4-MP) (50 mg/kg, intraperitoneally) were administered after binge drinking for the precise study for molecular mechanism. **Results:** Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels and mRNA expressions of *Cyp2e1* and *Tnf* were increased in binge drinking group of mice, compared to controls. Aggravated damage of hepatocytes were observed by histologic finding in binge drinking group. Also, deteriorated intestinal barrier and activated cytochrome P450 2E1 (CYP2E1) and alcohol dehydrogenase (ADH) were shown in slides of proximal jejunum in acute alcohol consumption group, compared to the vehicle. Concentrations of ethanol and acetaldehyde in blood were also increased and impaired motor function was observed in behavior tests of mice in the binge group. Interestingly, PEG administration after alcohol consumption significantly decreased serum AST and ALT levels, and downregulated mRNA level of *Tnf* of liver tissue. Hepatic injury was recovered with liver of additional PEG-treated mice. Moreover, gut injury was ameliorated and expression of ADH and CYP2E1 in the gut barrier were decreased in histologic findings of intestine of PEG group. Upregulated blood concentration of ethanol and acetaldehyde and motor impairment after acute ethanol consumption were drastically recovered with PEG administration. Moreover, additional administration of 4-MP, which is an inhibitor of ADH, to the intervention of PEG after binge drinking increased the serum level of acetaldehyde and the blood concentration of acetaldehyde. **Conclusion:** PEG administration after acute binge drinking would be a novel therapeutic option for protection of liver and gut, and reducing hangover symptoms. The present study could suggest the concept of “intestinal drinking of alcohol” and removal of remnant alcohol with PEG within the gut lumen would be a protector against the damage of liver after binge drinking

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3007 | COGNITIVE INTERVIEWING OF EXPERTS AND PATIENTS TO DEVELOP AN ALCOHOL INSIGHT SCALE FOR PATIENTS WITH ALCOHOL-ASSOCIATED LIVER DISEASE

Victoria Gill[1] *Shivali Patel*[1] *Jessica Mellinger*[2] *Gerald Scott Winder*[1]

[1]*University of Michigan Medical Center,* [2]*University of Michigan Hospitals and Health Centers*

Background: Alcohol-associated liver disease (ALD) is the leading indication for liver transplantation (LT) in the US. LT teams often use alcohol-associated insight (AAI) in treatment planning and liver allocation, yet no standardized definition or measurement scale exists for this population. To address this gap, the authors developed a psychometric scale to assess AAI for use in early LT and elsewhere in the management of ALD. **Methods:** An initial 55-item AAI scale was developed by author GSW using established insight domains from the literature. Cognitive interviews were completed with 23 multidisciplinary LT experts. A revised scale was then presented to 12 patients with varying stages of ALD to obtain patient perspectives for further revisions. **Results:** 23 LT experts representing hepatology, psychiatry, psychology, and social work (52% male, 48% female, 57% White, 13% Black, 22% Asian) completed cognitive interviews. Feedback resulted in the removal of extreme language (i.e. “always”) from 7 items, confusing language (i.e. “relapse”) from 5 items, and stigmatized language (i.e. “addiction”) from 2 items. Ten items were redundant and 9 items too vague. Six items were adjusted from negative phrasing to positive alternatives. Authors incorporated expert input by consensus, resulting in an edited

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and shortened 35 item scale. This revised scale was then presented to 12 patients with liver disease (50% decompensated ALD, 17% compensated ALD, and 33% alcohol-associated hepatitis). Patients found most items to be clear, with only 3 items requiring modification after patient review; 2 of these items required simplification of the misunderstood term “unhealthy”. Scale items effectively and often prompted patients to share personal reflections and anecdotes regarding their experiences with and perceptions of alcohol, sobriety, and liver disease. One item was added based on patient feedback, resulting in a final 36-item AAI scale. **Conclusion:** We have developed the first psychometric AAI scale for use in patients with ALD. Cognitive interviews with multidisciplinary experts indicate that this tool fills a needed gap in ALD care and LT. Patients find the index clear and easy to engage with as part of their treatment. Next steps include further statistical testing of the AAI scale.

Disclosures: Victoria Gill: Nothing to Disclose, Shivali Patel: Nothing to Disclose, Jessica Mellinger: Nothing to Disclose, Gerald Scott Winder: GSK: Consultant, Alexion: Consultant

3008 | ATP-BINDING POCKET INHIBITOR FOR MIXED LINEAGE KINASE DOMAIN-LIKE PROTEIN (MLKL) ATTENUATED ALCOHOLIC LIVER DISEASE VIA NECROPTOSIS-INDEPENDENT PATHWAY

Dae Won Jun[1] Eileen Yoon[1] Ji Hyun An[2] HA IL KIM[1] Joo Hyun Sohn[1] Bo-Kyeong Kang[1] Chul-Min Lee[1] Hyo Young Lee[3] Hyun Woo Oh[4] Hye-Lin Kim[5] Sang Bong Ahn[6] Joo Hyun Oh[7]

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Background: MLKL is known to be a key molecule of necroptosis and the “RIP3–MLKL” axis is recognized as a key pathway of necroptosis-induced cell death. Recently, the RIP3-independent MLKL activation pathway was suggested, and the fate of cell death after necroptotic stimuli is known to differ according to the cell type.
In this study, we investigated the role of the ATP-binding pocket of MLKL and a possible novel necroptosis-independent pathway of MLKL. The purpose of this study was to investigate the necroptosis-independent role of MLKL and the role of the MLKL ATP-binding pocket in this cell death-independent pathway. In addition, we investigated the effects of this necroptosis-independent MLKL mechanism on various alcoholic and non-alcoholic liver diseases. **Methods:** Cell death following necroptosis was evaluated using cell proliferation assays, flow cytometry, and electron microscopy in various cells. To evaluate the anti-inflammatory efficacy of the MLKL ATP-binding inhibitor in a steatohepatitis liver organoid model, the steatohepatitis-induced organoid was treated with CPD for 1 d after necroptotic stimuli. Additionally, animal models of alcoholic and fatty liver diseases were used to determine whether MLKL ATP pocket inhibitors could attenuate liver injury. **Results:** Unlike HT29 cells, RAW 264.7 cells demonstrate resistance to cell death and instead become activated in response to necroptosis. Specifically, RAW 264.7 cells do not exhibit MLKL phosphorylation or oligomerization upon necrotic stimulation; however, they undergo necrosis-associated cell death following demethylation. While an MLKL ATP pocket-binding inhibitor did not prevent necroptosis-induced cell death in RAW 264.7 cells, it did reduce the necroptosis-led expression of CXCL2, ICAM, and VCAM. Notably, MLKL ATP pocket inhibitor diminishes the expression of CXCL2, ICAM, and VCAM by inhibiting the IκB kinase and NFκB pathways without inducing necroptosis-induced cell death in two-dimensional cell culture as well as the human-derived liver organoid system. CPD4-treated mice exhibited a reduction in lipid droplets, and reduced inflammation. CPD4-treated mice showed a decreasing ALT and AST. The mRNA levels of inflammatory factors CXCL2, ICAM, VCAM, MCP-1, and NLRP3 showed a decreasing in the ASH model. **Conclusion:** To date, research targeting MLKL has primarily concentrated on the N-terminal cysteine, which is implicated in MLKL-associated cell death. Conversely, the ATP pocket, which does not influence cell death or MLKL phosphorylation, has received relatively little attention. This study identified a novel necroptosis-independent, ICAM/VCAM-activated pathway of MLKL, in addition to the previously known MLKL-induced necroptosis cell death pathway.
MLKL ATP pocket-binding inhibitor exerted anti-inflammatory effects through the necroptosis-independent MLKL pathway in an animal model of alcoholic liver disease.

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Disclose, Hye-Lin Kim: Nothing to Disclose, Sang Bong Ahn: Nothing to Disclose, Joo Hyun Oh: Nothing to Disclose

3009 | COMPREHENSIVE PROFILING OF INFILTRATED CIRCULATING IMMUNE CELL TYPES AND THEIR SUBSET RESPONSIBLE FOR ALCOHOLIC STEATOHEPATITIS BY SCRNASEQ ANALYSIS

Dae Won Jun[1] Eileen Yoon[1] Ji Hyun An[1] HA IL KIM[1] Joo Hyun Sohn[1] Bo-Kyeong Kang[1] Chul-Min Lee[1] Hyo Young Lee[2] Hyun Woo Oh[3] Hye-Lin Kim[4] Sang Bong Ahn[5] Joo Hyun Oh[5]

[1]Hanyang University, [2]Sanggye Paik Hospital, Inje Univ., [3]Kangbuk Samsung, Sungkyunkwan Univ., [4]College of Pharmacy, Sahmyook Universit, [5]Nowon Eulji Medical Center, Eulji Univ.

Background: Alcoholic steatohepatitis (ASH) is primarily caused by inflammatory processes that occur after repeated exposure to alcoholic byproducts released into the bloodstream, causing circulating immune cells to infiltrate the liver and generate additional acute or chronic inflammatory reactions. Despite several investigations, little focus has been made to identifying immune cell type response on ASH at the single cell level. Therefore, in this study, we explored the heterogenous immune leukocytes from ALD induced and healthy control mouse groups that are responsible for ASH at a single cell level by high-dimensional single cell RNA sequencing (scRNAseq) analysis. **Methods:** In our study, t-distributed stochastic neighbor embedding (t-SNE) dimensionality reduction and 2D-visualization plot were used to visualize heterogenous immune cell types. Moreover, singleR was used for automated cell annotation to identify the cell types and differentially expressed genes (DEGs) from each cell type and their subsets were identified respectively. **Results:** In particular, we observed population decline in B cells and their subsets with up and downregulated genes denoted innate pro-inflammatory response as an important sign of alcoholic induced liver fibrosis. Similarly, neutrophils deficient in alcoholic-induced mouse group was another key finding of ASH, and an increase in eosinophils diverts further complications of liver fibrosis suggesting functional heterogeneity of granulocyte subsets. Overall, all these circulating immune cells were significantly reduced by frequent alcohol exposure, which may fail to protect the liver from pathogenic microbe or antigen infection. **Conclusion:** Our findings may assist in discovering potential ALD biomarker cell types and enhance our understanding of the circulating immune leukocytes that lead to alcoholic-induced liver fibrosis.

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3010 | CLINICAL OUTCOMES OF ALCOHOL-ASSOCIATED LIVER DISEASE IN A MEDICAL CENTER IN TAIWAN

Chun-Ming Hong[1] Tung-Hung Su[2] Shih-Jer Hsu[2] Tai-Chung Tseng[2] Chen-Hua Liu[2] Hung-Chih Yang[3] Shang-Chin Huang[1] Jia-Horng Kao[2] Chun Jen Liu[2] Pei-Jer Chen[2]

[1]National Taiwan University, [2]National Taiwan University Hospital, [3]National Taiwan Univeristy Hospital

Background: Alcohol use disorder (AUD) is becoming increasingly important and has caused liver-related disease and death globally. This issue has become even more serious after the COVID-19 pandemic. Public awareness of and managements towards major liver diseases including viral hepatitis or metabolic dysfunction-associated steatotic liver disease (MASLD) have been improving over the decades. In contrast to other etiologies of liver diseases, studies for alcohol-associated liver disease (ALD) are not easily conducted in Taiwan because of lack of effective therapies and of patient compliance. Our study tried to explore current epidemiology of ALD in Taiwan. **Methods:** We conducted a retrospective study by looking into Integrative Medical Database in National Taiwan University Hospital (NTUH-iMD) from 2006 to 2021. ICD-9 (International Classification of Diseases, ninth edition) and ICD-10 were used for disease coding. The inclusion criteria are patients whose diagnosis was made once at outpatient or inpatient and over 20 years old, while the exclusion criteria are those who had hepatocellular carcinoma (HCC), liver transplantation, or death before the index date. The index date was the first time when the

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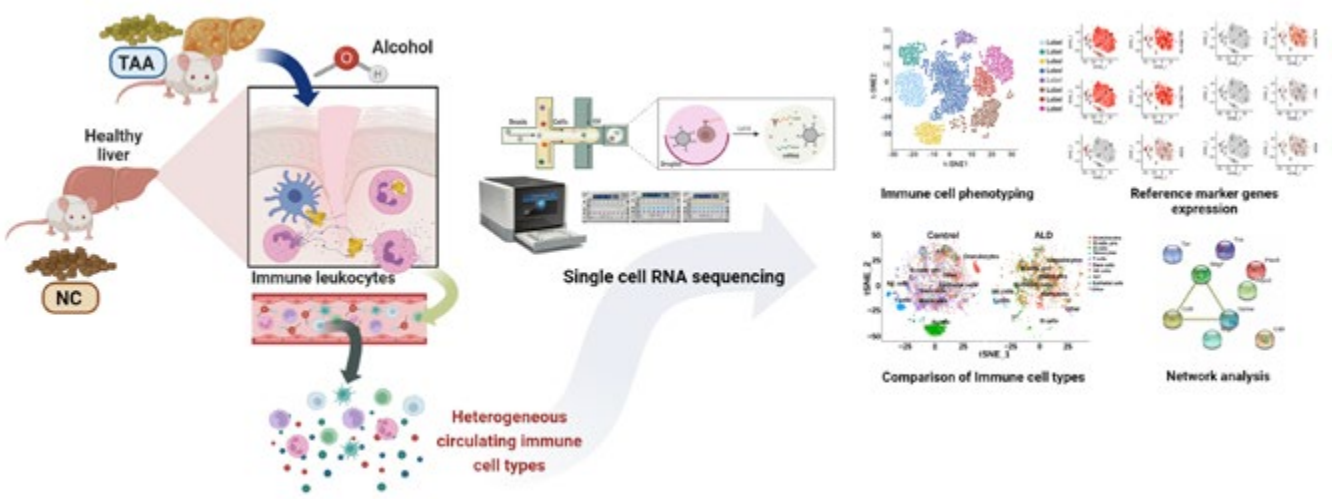
patient was diagnosed inpatient or outpatient. **Results:** From 2006 to 2021, 4403 patients were recruited from NTUH-iMD. 4001 patients were diagnosed at outpatient while 1330 patients were diagnosed when hospitalized. 3757 (85.33%) patients were male. However, the percentage of female patients in 20-30s (35.96%) was increasing than other age groups (10.53% to 19.20%). Mean total bilirubin was 2.69 mg/dL, mean ALT was 66.68 U/L, and the mean GGT was 277.19 U/L. The average of FIB-4 index was 5.43. 328 patients (7.45%) had HBV infection while 138 patients (3.13%) had HCV infection. 819 patients were ALBI grade 1, 915 patients were ALBI grade 2, and 410 patients were ALBI grade 3. 402 patients (9.13%) had psychiatric or neurologic comorbidity. 79 patients (1.79%) received liver transplantation, 162 patients (3.68%) developed HCC, and 1584 patients (35.98%) died. **Conclusion:** Our single-center retrospective study presents a preliminary epidemiology of ALD in urban areas in northern Taiwan. While over 85 percent of ALD patients were male, the percentage of young female ALD patients was increasing. Moreover, a high mortality suggested ALD awareness and managements as an important unmet need to be addressed.



Disclosures: Chun-Ming Hong: Nothing to Disclose, Tung-Hung Su: Nothing to Disclose, Shih-Jer Hsu: Nothing to Disclose, Tai-Chung Tseng: Nothing to Disclose, Chen-Hua Liu: Nothing to Disclose, Hung-Chih Yang: Nothing to Disclose, Shang-Chin Huang: Nothing to Disclose, Jia-Horng Kao: Nothing to Disclose, Chun Jen Liu: Nothing to Disclose, Pei-Jer Chen: Nothing to Disclose

3011 | TRENDS IN HOSPITALIZATIONS FOR ALCOHOL RELATED HEPATITIS IN THE PRE-COVID, COVID, AND POST-COVID ERA: A NATIONAL DATABASE STUDY

Regis Lee[1] Oluwaposi Omiwade[2] JOSEPH Alukal[3] Julio Gutierrez[4]

[1]HCA Riverside Community Hospital, [2]Scripps Mercy Hospital, [3]University of California, Riverside, [4]Scripps Clinic

Background: Alcoholic hepatitis (AH) is a severe form of alcohol-related liver disease (ALD) characterized by jaundice and systemic inflammation. During the COVID-19 pandemic it was well documented that there was a significant increase in the number of hospitalizations related to ALD. The objective of our study was to evaluate trends in hospitalizations and mortality for AH in the post-pandemic era (2022-23) in comparison to the pre-pandemic (2017–19) and pandemic era (2020–21) using a large national dataset. **Methods:** This was a retrospective study from 1/1/2017 to 12/31/2023 involving 186 HCA Healthcare hospitals throughout the US. The HCA Healthcare System is a large healthcare network comprising of medium- and large-sized community hospitals spread across 19 states that see approximately 37 million patient encounters annually. De-identified electronic health data was used to identify patients admitted with a primary diagnosis of AH. AH was diagnosed using a combination of ICD-10 codes and biochemical parameters (total bilirubin ≥ 3 mg/dL on admission, AST between 50-400 IU/L and AST/ALT > 1.5). Each year was divided into 4 quarters, and the Cochran-Armitage test was used to determine trends. **Results:** During this study period, we identified 10,864 patients hospitalized for AH with a median age of 49 years, a MELD score of 22, and a Maddrey score of 38. There were 3,594 admissions for AH in the pre-COVID era, accounting for just 0.007% of the total admissions, in contrast, 3,429 hospitalizations for AH were identified during the pandemic era, accounting for 0.012% of all admissions; and 3,841 admissions for

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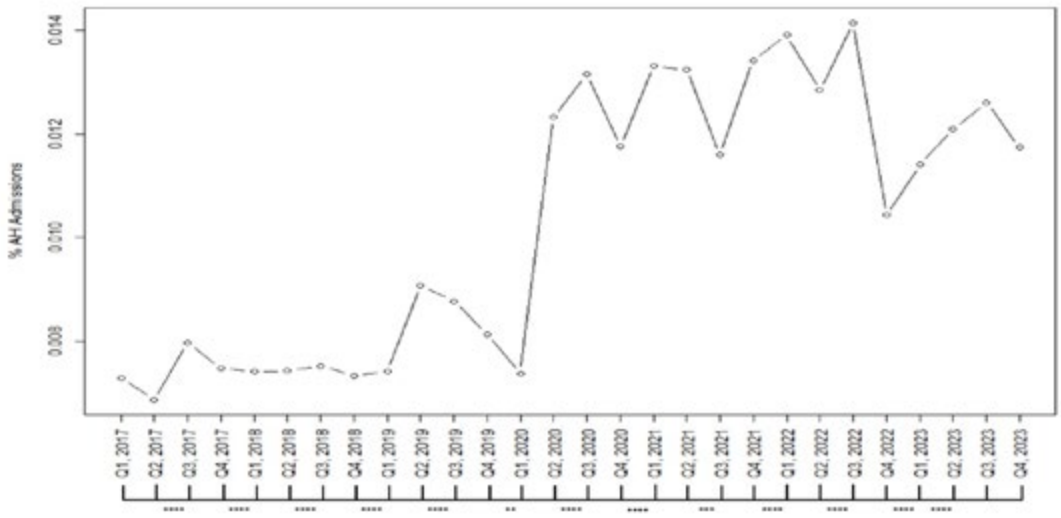
AH in the post-pandemic era, representing 0.012% of all admissions (Figure 1A). We noticed that the exponential spike in AH admissions started in the second quarter (Q2) of 2020, and this trend continued into Q2 and Q3 of the post-pandemic era (2022). Admissions began declining by the last quarter of 2022 (Q4). The Cochran-Armitage test of trend was significant, indicating a linear trend to the data ($p < 0.0001$). Pairwise comparisons (adjusted for multiple comparisons to control familywise error) indicated several significant differences between the sequential time points (e.g., Q2, 2017 to Q3, 2017) and are marked with asterisks in Figure 1B (*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$; ****$p < 0.0001$). **Conclusion:** Using a large national dataset, we were able to demonstrate that hospitalizations for AH have continued to rise both in the pandemic and post-pandemic eras. Admissions reached an all-time high during late 2021 and early 2022 and started declining in the last quarter of 2022. However, it appears that the rise in admissions may be reaching a plateau which is somewhat reassuring. Unlike data from large datasets such as the national inpatient sample (NIS), we believe our data are more accurate since we identified AH using a combination of ICD-10 codes and laboratory data, making it less susceptible to selection bias.

Figure 1A: Percentage of AH admissions over time



Figure 1B: Cochran-Armitage Test for trends in AH admissions by each quarter



Disclosures: Regis Lee: Nothing to Disclose, Oluwaposi Omiwade: Nothing to Disclose, JOSEPH Alukal: Nothing to Disclose, Julio Gutierrez: Altimmune: Consultant, AbbVie: Speaking and Teaching, Gilead: Speaking and Teaching, Alexion: Speaking and Teaching, Exelixis: Speaking and Teaching, Madrigal: Consultant, Intercept: Speaking and Teaching, Livivos: Stock – privately held company, Surozen: Advisor, Escient: DSMB Chairman

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3012 | IMPACTS OF SMOKING ON ALCOHOLIC LIVER DISEASE: A NATIONWIDE COHORT STUDY

Young Seok Kim[1]

[1]*Soon Chun Hyang University*

Background: Smoking is a preventable risk factor for morbidity and mortality in patients with liver disease. This study aims to explore the additional risks of smoking in the development of alcoholic liver disease (ALD), cirrhosis, and hepatocellular carcinoma (HCC) in high-risk drinkers. **Methods:** Data from the National Health Insurance Service, including claims and health check-up information spanning 2011 to 2017, were used. The overall alcohol consumption was calculated, and ALD was defined based on ICD-10 codes. High-risk drinking was defined as 7 or more drinks for men and 5 or more for women, twice weekly. Half of the high-risk drinkers were smokers, decreasing in men but stable at 20% for women. **Results:** ALD prevalence was 0.97% in high-risk drinkers and 1.09% in high-risk drinkers who smoked, higher than 0.16% in social drinkers. ALD incidence over 3-years was highest in high-risk drinkers who smoked (2.35%), followed by high-risk drinkers (2.03%) and social drinkers (0.35%). Cirrhosis and HCC followed similar patterns, with prevalence and incidence was highest in drinkers who smoked. 3-year mortality was 0.65% in high-risk drinkers who smoked, compared to 0.50% in high-risk drinkers and 0.24% in social drinkers. Smoking increased the incidence of ALD, cirrhosis, and HCC by 1.30, 1.50, and 1.45 times, respectively. **Conclusion:** Women's risk ratio for ALD, cirrhosis, and HCC increased more significantly with smoking compared to men. Smoking significantly raises the risk of ALD, cirrhosis, and HCC in high-risk drinkers, particularly impacting women more than men. Hence, smoking cessation is crucial for female ALD patients.

Disclosures: Young Seok Kim: Nothing to Disclose

3013 | PREVALENCE AND IMPACT OF CARDIOMETABOLIC RISK FACTORS IN ALCOHOL-RELATED LIVER DISEASE AND METALD

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[1]*Brigham and Women's Hospital,* [2]*Massachusetts General Hospital*

Background: Recent modifications to the categorization of steatotic liver disease have necessitated updated epidemiologic studies. Specifically, recognition of (1) "MetALD" where metabolic associated liver disease (MASLD) overlaps with heavy alcohol use and (2) alcohol-related liver disease (ALD) without metabolic risk creates new clinical phenotypes with undefined prevalence and clinical significance. **Methods:** We collected cross-sectional data from the Mass General Brigham Biobank. To capture all ALD and MetALD, we included adults (>18 years) with an ICD-10 diagnosis of ALD or both MASLD and alcohol use disorder. Cardiometabolic criteria of MetALD were defined as (1) hypertension or anti-hypertensive use, (2) dyslipidemia or anti-lipemic use, (3) diabetes mellitus or anti-glycemic use, and (4) peak BMI ≥25 kg/m^2. results were expressed as n (%), median (interquartile range), or odds ratio (OR) with 95% confidence interval (CI) and compared using Wilcoxon or Kruskal-Wallis rank sum tests or Chi-squared tests. **Results:** Among 4,057 patients, only 118 (2.9%) met 0 cardiometabolic criteria for MetALD (Fig 1A). This "pure ALD" phenotype was more commonly female (56% vs. 46%, 39%; p<0.01), younger [54 (43-63) vs. 57 (46-67), 68 (60-75) years; p<0.01], and had higher risk of cirrhosis (49% vs. 34%, 31%; p<0.01), hepatocellular carcinoma (10% vs. 6.2%, 4.6%; p=0.01), and death (21% vs. 16%, 19%; p=0.03) than ALD with 1-2 or 3-4 cardiometabolic criteria, respectively. Frequency of transplantation did not differ (4.2% vs. 5.3%, 4.2%; p=0.25). Compared to patients whose only cardiometabolic criterion was BMI 25-30 kg/m^2, patients with pure ALD were more often female (56%, 39%; p<0.01), but otherwise did not significantly differ (**Fig 1B**). Factors associated with cirrhosis in univariable analysis included male sex [OR 1.47 (1.29-1.67)], age [OR 1.08 per 10 years (1.03-1.13)], and diabetes [OR 1.21 (1.05-1.40)], but not BMI 25-30 kg/m^2 [OR 0.86 (0.64-1.14), relative to BMI <25 kg/m^2] or having BMI 25-30 kg/m^2 as the only cardiometabolic criterion [OR 0.94 (0.60-1.48), relative to meeting 0 criteria]. No significant differences in selected single nucleotide polymorphisms (*PNPLA3, GCKR, TM6SF2, MBOAT7,* or *HSD17B12*) were identified between groups. **Conclusion:** ALD without metabolic disease is uncommon. Effects of cardiometabolic risk factors varied, and BMI 25-30 kg/m^2 did not impact clinical features, raising the question of optimal BMI cutoff for MASLD. Further investigating these novel disease categories is essential for better understanding their biology and clinical impact.

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Fig 1A: Patients with alcohol-related liver disease.

# MetALD criteria met	N = 4,057
0	118 (2.9%)
≥1	3,939 (97%)
Peak BMI ≥25 kg/m²	3,797 (94%)
Hypertension	2,318 (54%)
Dyslipidemia	3,095 (72%)
Diabetes mellitus	1,086 (25%)
≥2	3,210 (79%)
≥3	2,169 (53%)
4	847 (21%)

Fig 1B: Patients with 0 MetALD criteria vs. only meeting criteria with peak BMI 25-30 kg/m².

Characteristic	0 criteria, n = 118	1 criterion (BMI), n = 214	p-value
Age (years)	54 (43, 63)	53 (41, 64)	0.55
Female	66 (56%)	83 (39%)	<0.01
White	109 (92%)	188 (88%)	0.20
ALT (U/L)	27 (20, 46)	30 (21, 44)	0.68
Total bilirubin (mg/dL)	0.6 (0.4, 1.1)	0.7 (0.4, 1.3)	0.44
Cirrhosis	58 (49%)	102 (48%)	0.90
Hepatocellular carcinoma	12 (10%)	15 (7.0%)	0.31
Liver transplant	5 (4.2%)	18 (8.4%)	0.15
Deceased	25 (21%)	36 (17%)	0.33

Disclosures: Wesley Dixon: Nothing to Disclose, Kathleen Corey: Advisor relationship with Intercept; Has not ended; Advisor relationship with Sagimet; Has ended; Speaking and Teaching relationship with Medscape; Has not ended; Consultant relationship with Theratechnology; Has ended, Jay Luther: Nothing to Disclose, Russell Goodman: Nothing to Disclose, Esperance Schaefer: Nothing to Disclose

3014 | DISTINCT NEUTROPHIL PHENOTYPES INFILTRATE THE LIVER IN DIFFERENT LIVER DISEASES

Noriyoshi Ogino[1] syeda zehra[1] Mateus Guerra[1] Emma Kruglov[1] Romina Fiorotto[1] Mario Strazzabosco[1] Michael Nathanson[1]

[1]Yale University

Background: Neutrophils are classically thought to engage in nonspecific digestion and killing of targets, but recent evidence suggests additional neutrophil phenotypes are found in various tissues, and highly specific and reversible interactions between neutrophils and hepatocytes or cholangiocytes have been reported. We investigated whether neutrophil phenotypes in the liver can differ in different liver diseases. **Methods:** The intrahepatic distribution of neutrophils was examined in three mouse models of liver disease: 1) An alcoholic hepatitis (AH) model with both hepatocellular injury and cholestasis, 2) Acetaminophen (APAP) treatment to induce hepatocellular injury, and 3) MDR2 KO mice, as a model of biliary injury. Single cell RNA sequencing (scRNAseq) was performed on neutrophils isolated from the liver and blood of these three models and from normal control blood. **Results:** In APAP liver injury, nearly all neutrophils were in the parenchyma around the central veins, whereas in MDR2 KO mice, most neutrophils were in close proximity to the bile ducts. Neutrophils were in both regions in the AH mouse. Gene signatures by scRNAseq analysis of neutrophils isolated from the liver were unique in each of the three mouse models. For each disease, IPA was performed for the gene groups of liver neutrophils that were significantly altered relative to blood neutrophils. In AH, there was decreased signaling in integrin, Rho, and PAK pathways, but increased RHOGDI and Th2 signaling, suggesting reduced adhesion and migration of neutrophils and enhanced anti-inflammatory responses. MRD2 KO also displayed increases in the Th2 pathway, plus boosted ROS production and phagocytosis. Phagocytosis also was elevated in APAP, but reductions were seen in nuclear receptor signaling (PARα/RXRα, PPAR, VDR/RXR). APAP also showed increased EIF2 signaling while MRD2 KO showed decreased senescence pathways, both suggesting longer lifespans for liver neutrophils than for those in circulation. **Conclusion:** Neutrophils infiltrating the liver have distinct, disease-specific transcriptional profiles, which furthermore differ from neutrophils in circulation. This may reflect a much greater, disease-specific repertoire of neutrophil behavior in the liver, an understanding of which may lead to more targeted treatment strategies.

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Disclosures: Noriyoshi Ogino: Nothing to Disclose, syeda zehra: Nothing to Disclose, Mateus Guerra: Nothing to Disclose, Emma Kruglov: Nothing to Disclose, Romina Fiorotto: Nothing to Disclose, Mario Strazzabosco: Nothing to Disclose, Michael Nathanson: Nothing to Disclose

3015 | TARGETED BREATH BIOPSY® PROFILING OF INDUCED BIOMARKERS UNVEILS A METABOLIC ADAPTATION IN CIRRHOSIS TOWARD ALCOHOL PRODUCTION

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Background: Subjects with chronic liver disease have shown higher circulating ethanol levels after fasting or carbohydrates ingestion. However, clinical functional data about the capability of the injured liver to cope with alcohols remain limited. In this study we used exhaled breath analysis to explore the conversion of an alcohol to the corresponding ketone, and a ketone to the corresponding alcohol, to establish the suitability of potential metabolic alterations and identify subjects with cirrhosis using a non-invasive breath test. **Methods:** We selected 2-butan**ol**, and 2-pentan**one** (the substrates) as an alcoh**ol** and a ket**one** based on their safe human consumption, reported hepatic metabolism, and presence in breath. Hepatic metabolism was confirmed by treating human suspension hepatocytes with 10 ng/µl of 2-butan**ol**, and 2-pentan**one** to measure their conversion to respectively 2-butan**one**, and 2-pentan**ol** (the bioproducts) by using headspace analysis coupled with gas-chromatography mass-spectrometry (GC-MS). Clinical metabolism was evaluated by analysing the breath profile of 14 subjects with cirrhosis and 14 controls before and at different timepoints (10 - 120 minutes) after ingestion of 2-butanol (100 mg) and 2-pentanone (100 mg), using Breath Biopsy® OMNI. **Results:** Bioproducts were present in primary hepatocytes treated with the substrates and absent in control conditions omitting primary hepatocytes or substrates. After an overnight fasting all the participants showed breath levels of investigated compounds with no differences between healthy and cirrhosis groups ($p > 0.05$). After ingestion of the substrates, all the subjects showed a > 100-fold increase of investigated compounds within 10 minutes. Subjects with cirrhosis showed higher levels of 2-butan**ol** and 2-pentan**ol** ($p < 0.05$) compared to controls between 20- and 90-minutes post-administration (Fig. 1). An exploratory classification model built on these breath-induced biomarkers at 20 minutes showed an area under the ROC curve of 0.85. **Conclusion:** 2-butan**ol** and 2-pentan**one** are metabolized to the corresponding ket**one** and alcoh**ol** in primary hepatocytes, supporting previous findings reporting hepatic metabolism. Cirrhosis subjects showed higher breath levels of secondary alcohols independently from administration of the alcoh**ol** or the corresponding ket**one**, suggesting that the hepatic function is more balanced toward alcoh**ol** production compared to controls. This metabolic adaptation may contribute to higher circulating ethanol levels observed in subjects with chronic liver disease and be exploited in a breath test for cirrhosis detection.

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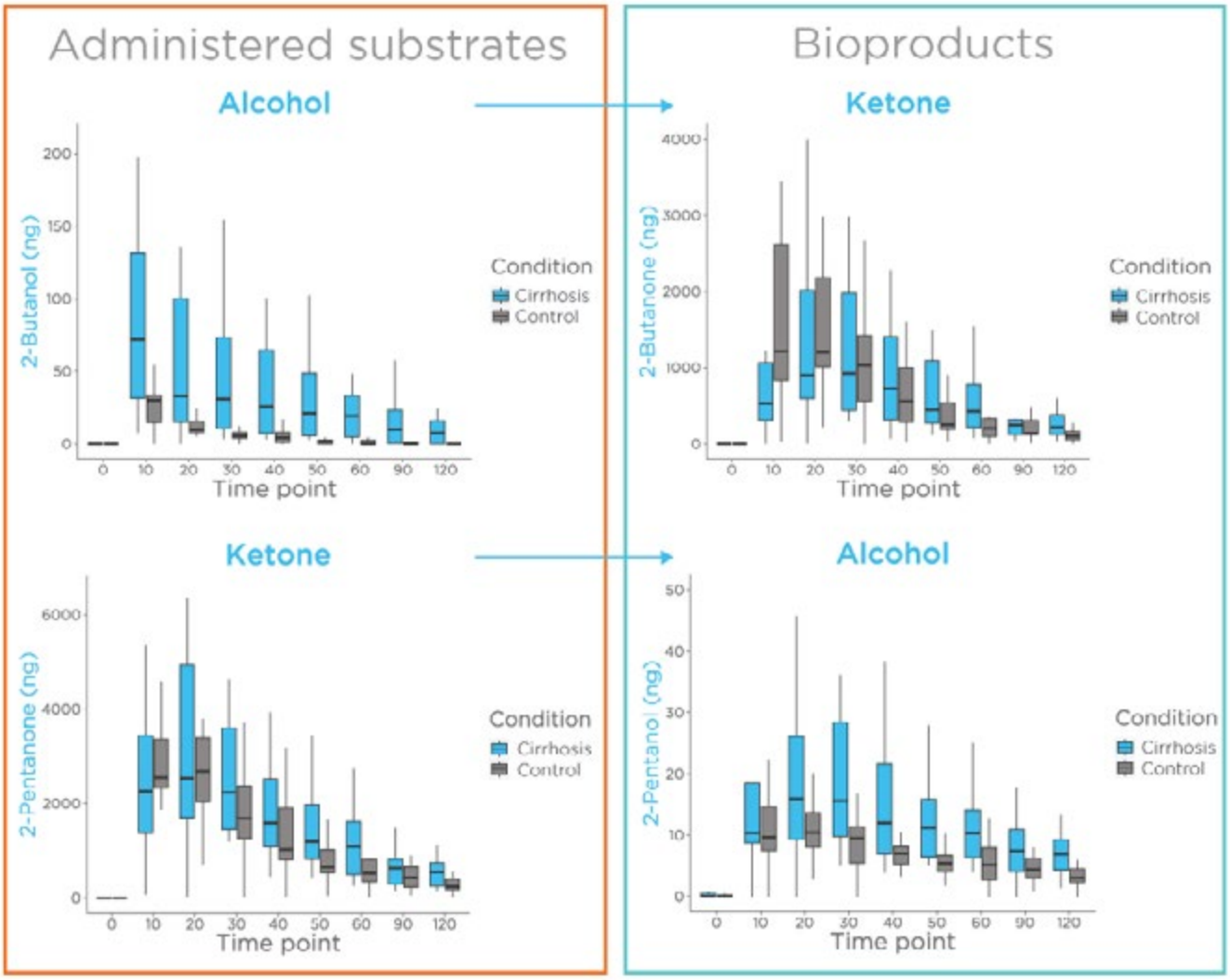

Disclosures: Giuseppe Ferrandino: Owlstone Medical: Employee, Federico Ricciardi: Nothing to Disclose, Antonio Murgia: Nothing to Disclose, Menisha Manhota: Nothing to Disclose, Daniela Fonseca: Nothing to Disclose, Louise Nicholson-scott: Nothing to Disclose, Chloe Fitzpatrick: Nothing to Disclose, Olga Gandelman: Nothing to Disclose, Max Allsworth: Nothing to Disclose, Billy Boyle: Nothing to Disclose, Smolinska Agnieszka: Nothing to Disclose, Alexandra Ginesta Frings: Nothing to Disclose, Jorge Contreras: Nothing to Disclose, Victor Gabrielli: Nothing to Disclose, Claudia Asenjo-Lobos: Nothing to Disclose, Francisca Bascur: Nothing to Disclose, Viviana Barrientos: Nothing to Disclose, Nataly Clavo: Nothing to Disclose, Melissa Jerez: Nothing to Disclose, Huw Davies: Owlstone Medical: Employee, Luis Méndez: Nothing to Disclose

3016 | THE IMPACT OF INTEGRATED CARE ON CLINICAL OUTCOMES IN PATIENTS WITH ALCOHOL-ASSOCIATED LIVER DISEASE: EARLY OUTCOMES FROM A MULTIDISCIPLINARY CLINIC

Shreya Sengupta[1] Akhil Anand[1] Meghan Reagan[1] Mariah Husted[1] Austin Minnick[1] Qijun Yang[1] Laura Nagy[2] Srinivasan Dasarathy[1] Omar Sims[2] Jessica Mellinger[3]

[1]Cleveland Clinic, [2]Cleveland Clinic Foundation, [3]University of Michigan Hospitals and Health Centers

Background: Integrated care models have the potential to provide optimal and coordinated care for patients who need simultaneous treatment of alcohol use disorder (AUD) and alcohol-associated liver disease (ALD). We analyzed early outcomes regarding the impact of our integrated ALD clinic on patients with ALD and alcohol use. **Methods:** We conducted a retrospective study of patients with ALD who were evaluated in our integrated clinic

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from 5/1/2022-12/31/2023. Non-transplant ALD patients and ALD patients' status-post liver transplant with active alcohol use were eligible. A total of 252 patients were referred; 102 patients accepted an appointment and were evaluated, and 66 patients declined an appointment. Primary outcomes included differences in baseline clinical/demographic data between patients who accepted versus declined an appointment and changes in severity of ALD, remission in AUD, alcohol consumption, functional status, and hospital utilization for evaluated patients. **Results:** Patients who declined appointments (n=66) had higher median no-show rates (15.0[8.0,30.0] vs. 8.5[3.25,15.0], p<0.001), social vulnerability index (0.53[0.26,0.79] vs. 0.38[0.17,0.63], p=0.033), and proportions of cirrhosis (78.8% vs. 59.8%, p=0.017) versus evaluated patients. Comparison of baseline to first-follow-up-visit for evaluated patients (n=102) demonstrated significant reductions in median aspartate-aminotransferase (AST) (59.5 [41.75, 89] vs. 44.5 [33.5,56.25], p<0.001), alanine-aminotransferase (ALT) (33.5 [20,45.25] vs. 26.5 [18.75,33.0], p=0.017), total bilirubin (1.6 [0.7,3.3] vs.1 [0.5,1.9], p,0.001), phosphatidylethanol (PEth) (263 [35,784] vs. 0 [0,163], p<0.001), Model-for-End-Stage-Liver-Disease (MELD-3.0 and Sodium) scores for patients with alcohol-associated hepatitis and cirrhosis (16 [11,18.75] vs.12 [9,14], p<0.001), 14 [9.25,17.75] vs.11 [8.5,14], p<0.001), and Child-Turcotte-Pugh (CTP) scores for patients with cirrhosis (9 [6,10.5] vs. 7[6,9], p<0.001). The proportion of patients with active-severe AUD significantly decreased (85.2% vs. 51.9%, p<0.001). Additionally, patients had significant reductions in inpatient utilization (incidence rate ratio of 0.64 emergency department visits/month (p=0.002) and 0.71 hospital admissions/month (p=0.025)). A subgroup analysis of evaluated patients who were previously established with a hepatology provider also showed significant reductions in AST, ALT, total bilirubin, PEth, MELD-3.0 and Sodium, and remission in AUD at follow-up. **Conclusion:** Our integrated approach led to reductions in liver injury, degree of liver decompensation, alcohol use, and inpatient utilization, as well as early and sustained remission in AUD in a population of both non-transplant ALD and post-transplant patients. Patients who declined an appointment in our multidisciplinary clinic had more social determinants of health barriers.

Disclosures: Shreya Sengupta: Nothing to Disclose, Akhil Anand: Nothing to Disclose, Meghan Reagan: Nothing to Disclose, Mariah Husted: Nothing to Disclose, Austin Minnick: Nothing to Disclose, Qijun Yang: Nothing to Disclose, Laura Nagy: Nothing to Disclose, Srinivasan Dasarathy: Nothing to Disclose, Omar Sims: Nothing to Disclose, Jessica Mellinger: Nothing to Disclose

3017 | AUTOPHAGY DEFICIENCY INDUCES THE EXPRESSION OF INTERFERON-STIMULATED GENES IN MOUSE LIVERS

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Background: Autophagy is an evolutionarily conserved cellular degradation process that is critical to maintaining metabolism homeostasis in the liver. Loss of autophagy-related genes (Atg), Atg5 and Atg7, cause chronic liver damage in mice. Continuous activation of nuclear factor erythroid 2-related factor 2 (NRF2) is attributed to autophagy deficiency-induced liver damage. However, the mechanism by which NRF2 activation induces injury in autophagy-deficient livers remains unclear. Evidence has shown that liver-specific knockout of Atg5 enhances liver injury induced by interferon γ (IFN-γ) in mice. We hypothesized that IFN-stimulated genes (ISGs) contribute to autophagy-related liver pathology. **Methods:** To examine the alteration of ISGs in mouse livers, microarray data from mice with liver-specific knockout of Atg5, Atg7, Atg5/Nrf2, and Atg7/Nrf2 were analyzed for IFN-related pathways and the expression of a set of ISGs. Single-cell RNA sequencing data from mice with inducible hepatocyte-specific knockout of Atg7 were analyzed for the expression of ISGs in hepatocytes. The cGAS-STING pathway was analyzed by immunoblotting. Autophagy, the expression of ISGs, and the cGAS-STING pathway were also examined in a mouse model representing alcohol-associated cholestasis and hepatitis (AlChoHep) to evaluate the disease relevance. **Results:** We found that IFN-related pathways were enriched in mouse livers with autophagy deficiency, and the enrichment was not improved by Nrf2 co-deletion, suggesting that autophagy deficiency may induce IFN-related pathways independent of Nrf2 activation. The expression of ISGs was increased in autophagy-deficient mouse livers. Single-cell RNA sequencing data suggests that the expression of ISGs was induced in autophagy-deficient hepatocytes. The cGAS-STING pathway was altered in autophagy-deficient livers and hepatocytes. In AlChoHep mouse livers, we observed an accumulation of an autophagy substrate, sequestosome 1 (SQSTM1/P62), indicating impaired autophagy. Similar to autophagy-deficient livers, the cGAS-STING pathway was altered in AlChoHep mouse livers with the expression of several ISGs induced.

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Conclusion: Taken together, our results suggest that autophagy deficiency induces the expression of ISGs in mouse hepatocytes, which may be a mechanism of alcohol-associated liver disease.

Disclosures: Shengmin Yan: Nothing to Disclose, Xiao-Ming Yin: Nothing to Disclose

3018 | SYMPATHETIC NERVOUS SYSTEM-BETA 3 ADRENERGIC RECEPTOR-MEDIATED LIPOLYSIS IN BINGE DRINKING-INDUCED FATTY LIVER DISEASE

Lin Jia[1]

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Background: Alcohol-associated liver disease (ALD) contributes significantly to the death and disability worldwide. There is an alarming rise in binge alcohol drinking in the US. Accumulating studies have shown that lipid homeostasis at the adipose-liver-axis plays an important role in the development of ALD. Specifically, alcohol drinking causes enhanced lipolysis in white adipose tissue (WAT), which increases circulating free fatty acid (FFA). These FFAs can enter the liver for triglyceride synthesis, contributing to alcoholic fatty liver disease. However, the molecular mechanisms by which alcohol induces hyper-lipolysis are not completely understood. **Methods:** C57BL/6J male mice were intraperitoneally injected with 6-hydroxydopamine hydrobromide (6-OHDA), a widely used drug that inhibits sympathetic nervous system (SNS), once a day for three days at 100mg/kg body weight (BW). On the fourth day, mice were treated with a single binge (5g/kg BW) (EtOH) or maltose dextrin (Control) by oral gavage. To investigate whether beta 3-adrenergic receptor (Adrb3) is responsible for binge drinking-induced hyper-lipolysis, we generated mice lacking Adrb3 selectively in adipose tissue ($Adrb3^{FKO}$) using Adrb3 floxed mice ($Adrb3^{fl/fl}$). These mice were subjected to binge drinking. Blood and livers were collected 6 hours after the oral gavage. In addition, ex vivo lipolysis experiments were performed using adipose tissues isolated from $Adrb3^{fl/fl}$ and $Adrb3^{FKO}$ exposed to Control and EtOH. **Results:** We found that alcohol binge-treated mice showed increased levels of circulating FFA, hepatic triglyceride and plasma alanine transaminase (ALT). However, binge drinking-associated lipolysis and liver injury were dramatically attenuated in mice exposed to systemic 6-OHDA administration. Compared to alcohol-fed $Adrb3^{fl/fl}$ mice, mice lacking Adrb3 in WAT had dramatically suppressed expression of WAT phosphorylated hormone-sensitive lipase (pHSL) and decreased plasma FFA levels. Importantly, this reduced lipolysis in alcohol-exposed $Adrb3^{FKO}$ mice was accompanied by significant decreases in hepatic contents of FFA and triglyceride as well as plasma ALT levels, suggesting that adipocyte Adrb3 deficiency protects mice from acute alcohol-induced liver damage. Furthermore, ex vivo lipolysis assay showed that epididymal WAT (eWAT) was the major adipose tissue that released FFA following binge drinking. And this ex vivo FFA release was dramatically suppressed by adipocyte Adrb3 ablation. **Conclusion:** Collectively, our data suggest that SNS-Adrb3 signaling plays an important role in binge drinking-induced adipose tissue lipolysis and fatty liver disease.

Disclosures: Lin Jia: Nothing to Disclose

3019 | BEER CONSUMPTION IS ASSOCIATED WITH LOW DIETARY QUALITY AMONG ALCOHOL USERS

Madeline Novack[1] *Peng-Sheng Ting*[1] *Wei-Ting Lin*[2] *Suthat Liangpunsakul*[3] *Chiung-kuei Huang*[1] *Hui-Yi Lin*[4] *Tung Sung Tseng*[4] *Po-Hung (Victor) Chen*[5]

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Background: Alcohol use and poor dietary quality are risk factors for steatotic liver disease. With the rise in alcohol consumption and metabolic syndrome, it is essential to understand how alcohol use patterns may be associated with dietary quality. Previous studies found that dietary quality declines with increasing alcohol consumption, but research is limited on whether different alcohol types may variably influence dietary habits and vice versa. We hypothesized that consuming different alcohol types is associated with variations in dietary quality. **Methods:** We included all alcohol drinkers from the National Health and Nutrition Examination Survey (NHANES) 2017-2020 cycle, identified based on responses to the alcohol use questionnaire and 24-hour dietary

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recall interviews. Alcohol drinkers were categorized as beer only, wine only, liquor/cocktails only, or multiple types. Dietary quality was assessed by the Healthy Eating Index (HEI), where a higher HEI score indicates better adherence to dietary guidelines and improved dietary quality. All analyses were performed using survey modules to account for the complex sampling design of NHANES. **Results:** A total of 1,917 alcohol drinkers were included. Beer-only drinkers (38.9%) composed the largest proportion of alcohol consumers, followed by wine-only (21.8%), liquor/cocktail-only (18.2%), and multiple types (21.0%). More beer-only drinkers were men (73.4%), while more wine-only drinkers were women (72.4%). Beer-only drinkers reported the highest total daily caloric intake when adjusted for body weight (29.6 kcal/kg) and the lowest prevalence of sufficient physical activity (42.2%). Wine-only drinkers were more likely than other groups to have high food security and less likely to report living below the poverty level. After adjusting for confounders, we found higher HEIs in wine-only drinkers (β=3.19) and liquor/cocktail-only drinkers (β=3.01) compared to beer-only drinkers. Stratifying by level of alcohol consumption, light wine-only and liquor/cocktail-only drinkers had higher HEIs compared to light beer-only drinkers (β=3.69 and β=3.91, respectively), whereas moderate drinkers of all groups had similar HEI scores. **Conclusion:** Beer-only drinkers may have the lowest dietary quality among consumers of different alcohol types. Clinicians and health policy officials should focus on promoting healthier dietary patterns among beer-only drinkers to mitigate the negative impact of their dietary habits.

Table 1 Demographic, lifestyle patterns, and HEI components among different types of alcohol drinkers

		Type of alcohol use				
	Total	**Beer only**	**Wine only**	**Liquor/ cocktails only**	**Multiple types[4]**	***P* value**
Raw population[1]	1917	798	394	379	346	
Survey-weighted[2]	100%	38.9%	21.8%	18.2%	21.0%	
Demographic factors						
Age (year), mean±se	46.8±0.8	44.8±1.1	53.4±1.2	46.1±1.2	44.2±1.6	<0.001
Sex (male)	56.5%	73.4%	27.6%	48.8%	62.1%	<0.001
Below poverty	9.2%	12.7%	5.7%	9.6%	6.0%	<0.001
Lifestyle patterns						
Current cigarettes smoker	19.9%	27.8%	10.0%	19.9%	15.3%	<0.001
Physical activity, hr/week (sufficient)[3]	50.3%	42.2%	59.8%	46.1%	59.3%	0.002
Metabolic syndrome	23.8%	27.7%	21.4%	27.3%	16.1%	0.045
Food security						
high	77.2%	71.7%	85.5%	72.9%	82.7%	0.012
very low	6.5%	9.0%	3.7%	8.0%	3.5%	
Dietary intake						
total energy, kcal	2314±33	2464±38	1981±52	2342±86	2358±85	<0.001
total energy intake per kg, kcal	28.8±0.5	29.6±0.6	26.9±0.7	28.6±1.4	29.3±1.0	0.047
total alcohol, gram	31.3±1.0	28.8±1.8	18.4±1.1	34.3±3.8	46.9±3.2	<0.001
Dietary components for HEI-2015 score (scale)						
Moderation components						
sodium (0-10)	4.9±0.1	4.9±0.2	4.7±0.2	4.9±0.2	5.2±0.3	0.564
refined grains (0-10)	6.9±0.1	6.5±0.1	7.0±0.2	7.4±0.2	6.8±0.3	0.011
saturated fats (0-10)	5.7±0.1	5.4±0.2	5.4±0.2	5.7±0.2	6.6±0.3	0.005
added sugar (0-10)	7.9±0.1	7.7±0.2	8.2±0.2	7.6±0.2	8.1±0.2	0.011
Adequacy components						
total vegetables (0-5)	3.0±0.1	2.9±0.1	3.3±0.1	3.0±0.1	3.0±0.2	0.020
greens and beans (0-5)	1.6±0.1	1.3±0.1	2.0±0.2	2.0±0.2	1.7±0.2	0.004
total fruits (0-5)	1.7±0.1	1.5±0.1	2.2±0.1	1.8±0.1	1.5±0.1	<0.001
whole fruits (0-5)	1.8±0.1	1.6±0.1	2.4±0.1	1.7±0.2	1.5±0.2	<0.001
whole grains (0-10)	2.2±0.1	2.0±0.1	3.0±0.3	2.1±0.2	1.7±0.2	0.003
total dairy (0-10)	4.4±0.1	4.5±0.1	4.5±0.2	4.8±0.2	3.8±0.3	0.008
total protein foods (0-5)	4.3±0.04	4.2±0.1	4.4±0.1	4.4±0.1	4.3±0.1	0.184
seafood and plant proteins (0-5)	2.4±0.1	2.0±0.1	2.9±0.2	2.5±0.2	2.5±0.2	<0.001
fatty acids (0-10)	5.1±0.1	4.7±0.1	5.1±0.2	5.0±0.2	5.8±0.2	0.006
Total HEI-2015 score	51.9±0.6	49.3±0.7	55.1±0.8	52.8±1.1	52.6±0.9	0.004

[1] Raw number of participants in this study without adjusted for sample survey design.
[2] Results were obtained after adjusting for sample weights and complex study design.
[3] Sufficient physical activity was defined according to World Health Organization guidelines for adults.
[4] Individuals who consumed multiple types of alcoholic beverage during the 24-hour dietary survey, including beer and wine, beer and liquor, wine and liquor or beer, wine and liquor.

Disclosures: Madeline Novack: Nothing to Disclose, Peng-Sheng Ting: Nothing to Disclose, Wei-Ting Lin: Nothing to Disclose, Suthat Liangpunsakul: DURECT: Consultant, Durect Corporation: Consultant, Surrozen: Consultant, Korro Bio: Consultant, Chiung-kuei Huang: Nothing to Disclose, Hui-Yi Lin: Nothing to Disclose, Tung

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Sung Tseng: Nothing to Disclose, Po-Hung (Victor) Chen: Gilead Sciences Research Scholars Program: Grant/ Research Support

3020 | CARDIOLIPIN TREATMENT IN HEPATOCYTE SPECIFIC *PTPMT1*$^{-/-}$ MICE IS HEPATOPROTECTIVE IN AN ANIMAL MODEL OF ALCOHOL-ASSOCIATED HEPATITIS

Josiah Hardesty[1] *Rui Treves*[1] *Tyler Gripshover*[1]

[1]*University of Louisville*

Background: Alcohol-associated hepatitis (AH) is a severe clinical condition with a high mortality. There are limited effective treatment options for AH and regenerative mechanisms are not well defined. We have demonstrated that mitochondrial phospholipid, cardiolipin (CL), synthesis is downregulated in AH liver. The key enzyme required for CL synthesis, PTPMT1, is also downregulated in liver tissue from AH patients. The objective of the current study is to determine if hepatocyte specific *Ptpmt1* knockout mice develop exacerbated AH and whether CL treatment ameliorates this phenotype. We hypothesize that *Ptpmt1* knockout mice will develop worsened AH injury, but CL will mitigate this effect and promote regeneration. **Methods:** Male and female C57BL/6J mice (n=10) were placed on the chronic-binge ethanol (EtOH) feeding paradigm. To produce a more severe phenotype that better mimics advanced human ALD, the mice were also challenged with galactosamine (GalN), which sensitizes the liver to gut-derived endotoxin leading to enhanced hepatocellular death. GalN was given at 500 mg/kg i.p. for three days prior to EtOH binge and CL (1 mg/kg per day) for the final 3 days. Mice were sacrificed at 9- and 48-hrs post EtOH-binge. Markers of liver injury, function, inflammation, and regeneration were evaluated. Data were statistically compared by a two-way ANOVA with a Tukey's post-hoc test. A $p<0.05$ was considered statistically signif **Results:** Female mice experienced less mortality and liver injury in this model of AH. Male mice treated with CL had reduced mortality as compared to male mice treated with vehicle. Both male and female mice had reduced markers of liver injury (Blood ALT, AST, and ALP activity) with CL treatment at 9-hr. Blood amylase (measure of pancreatic injury) was also reduced with CL treatment in both sexes. At 48-hr, mouse liver to body weight was significantly increased in both sexes with CL treatment. **Conclusion:** This study demonstrated that CL treatment reduced EtOH-GalN induced AH in hepatocyte-specific *Ptpmt1*$^{-/-}$ mice in males and females. Specifically, liver and pancreatic injury were reduced in both males and females with CL treatment. Further, liver mass was restored with CL treatment in both sexes indicative of enhanced liver regeneration. This study demonstrates that CL may serve as therapeutic agent for the treatment of AH.

Disclosures: Josiah Hardesty: Nothing to Disclose, Rui Treves: Nothing to Disclose, Tyler Gripshover: Nothing to Disclose

3021 | PATIENTS RECEIVING LIVER TRANSPLANTATION FOR ACUTE ON CHRONIC LIVER FAILURE AND KNOWN ALCOHOL RELATED LIVER DISEASE HAVE EQUIVALENT RELAPSE RISK COMPARED TO THOSE TRANSPLANTED FOR FIRST PRESENTATION OF SEVERE ALCOHOL RELATED HEPATITIS

Stephanie Zanowski[1] *Jenessa Price*[1] *Taylor Hallcox*[1] *Raj Prasad*[1] *Veronica Loy*[1]

[1]*Medical College of Wisconsin*

Background: Severe alcohol related hepatitis (SAH) is an accepted indication for liver transplantation (LT) for selected patients without sobriety, showing equivalent recidivism post-LT to patients with alcohol cirrhosis and demonstrated sobriety. Prior SAH studies excluded patients with known chronic liver disease, despite high short-term mortality risk for patients with acute on chronic liver failure (ACLF). Presence of cirrhosis on 70-95% of explants was noted in these studies. We investigated if post-LT recidivism differs between patients with prior known vs. unknown alcohol related liver disease and limited sobriety in a setting of careful selection aided by psychosocial risk stratification. **Methods:** We conducted prospective analysis of all patients evaluated for early LT for SAH/decompensated alcohol related liver disease (cirrhosis or previous SAH) at a single center from 4/1/15 to 4/30/24, as approved by IRB. Comprehensive inpatient evaluations, including psychosocial risk stratification by a psychologist, were completed for all patients. Patients were stratified into two groups: prior knowledge of liver disease (Group 1) and first presentation of liver disease (Group 2). Alcohol relapse was defined as any use

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post-LT based on serologic testing.ANOVAs and Chi-square tests examined potential group differences at the time of evaluation. Kaplan-Meier analyses estimated post-LT relapse and death by group, with survival curves compared using the log-rank test. Significance was set at $p \leq 0.05$. Analyses were conducted in SPSS version 28.0. **Results:** 300 patients met criteria for LT evaluation. 119 patients were listed; 67 received LT. 34 (50.7%) recipients comprised Group 1, and 33 (49.3%) comprised Group 2. Cirrhosis on explant was noted in 100% of Group 1 and 90.9% of Group 2. All in Group 1 met criteria for ACLF Grade 3. Groups did not differ for gender, racial/ethnic identity, and education. Group 1 had increased prior history of relapse ($x^2(1)=9.34$, $p=.002$) and longer length of abstinence (days) at time of evaluation ($F(1,65)=9.70$, $p=.003$). There were no other differences between groups for medical or substance use variables ($p=0.08$-0.97).Among those who survived to discharge post-LT (n=65),16 had alcohol relapse (17 to 817 days post-LT). Alcohol relapse did not differ between groups (8 each; Figure 1, log rank $p=0.96$), even when including prior history of relapse in the model (yes: $p=0.21$, no: $p=0.22$). One-year survival was 93% for Group 1 and 92% for Group 2 (p=0.22); 7 patients died (3 with relapse; $p=0.13$). **Conclusion:** Careful selection of patients with ACLF and known alcohol related liver disease for "early LT" provided equivalent rates of survival and alcohol relapse compared to patients with SAH and no prior knowledge of liver disease. Findings support the provision of equitable opportunities for evaluation, listing and LT in this patient population, particularly in the context of high risk for short-term mortality.

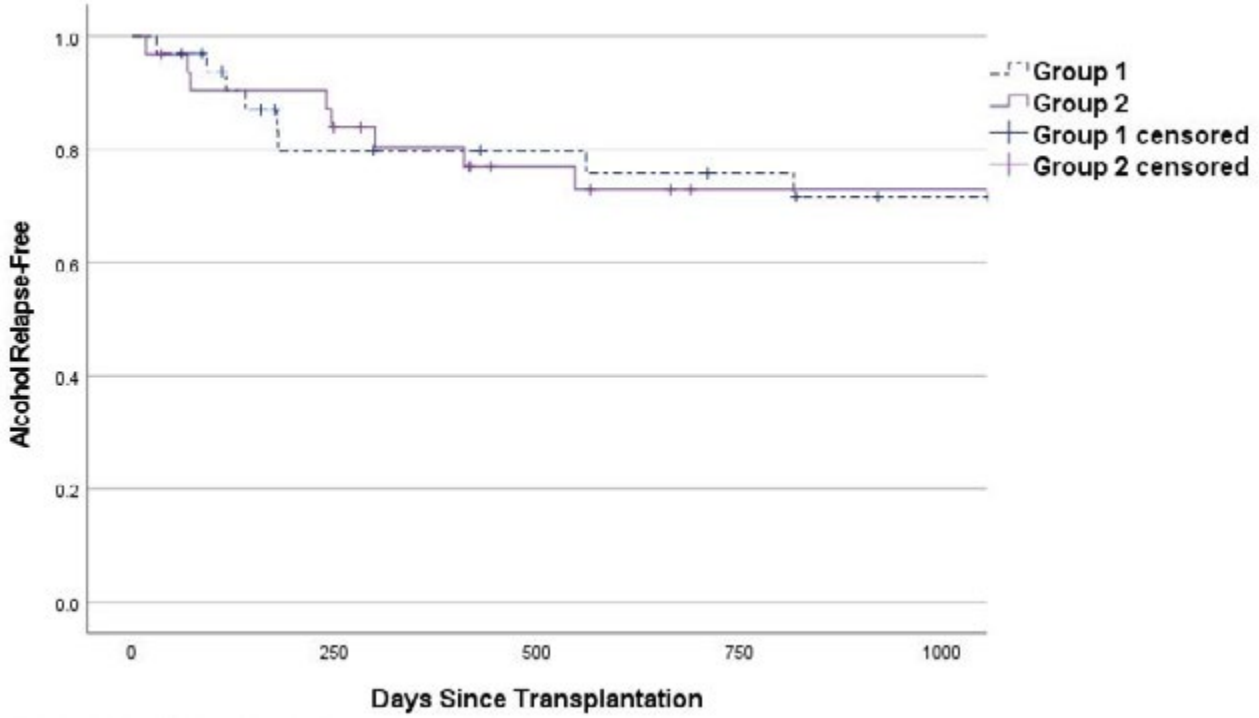

Figure 1. Kaplan-Meier estimates of proportion alcohol relapse-free after LT.

Disclosures: Stephanie Zanowski: Nothing to Disclose, Jenessa Price: Nothing to Disclose, Taylor Hallcox: Nothing to Disclose, Raj Prasad: Nothing to Disclose, Veronica Loy: Nothing to Disclose

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3022 | EFFECT OF DIABETES ON MORTALITY AND LIVER TRANSPLANTATION IN ALCOHOLIC LIVER CIRRHOTIC PATIENTS WITH ACUTE DECOMPENSATION

Sung-Eun Kim[1] JIHYE LIM[2] Ai Jeong Jo[3] Young Kul Jung[4] Do Seon Song[5] Sung Won Lee[5] Sang Gyune Kim[6] Jae Young Jang[7] Moon Young Kim[8] Young Joo Jin[9] Ki Tae Suk[1] Won Kim[10] Eileen Yoon[11]

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Background: Few studies have been published on the influence of diabetes in patients with alcoholic liver cirrhosis. This study aimed to determine the impact of diabetes on acute decompensation and adverse outcome (death or liver transplantation), utilizing real-world data. **Methods:** We analyzed prospective multicenter data collected from 31 hospitals in Korea from 2015 to 2019. We included 965 patients diagnosed with alcoholic liver cirrhosis who were admitted due to acute decompensation. A comparative analysis was conducted to assess the risk of major precipitating factors and the incidence of death or liver transplantation between patients with and without diabetes. Propensity score (PS) matching was employed at a 1:2 ratio for accurate comparisons. **Results:** The mean age of the entire cohort was 53.4 years, with 81.0% being male. Diabetes was prevalent in 23.6% of the cohort. Patients with diabetes had positive correlations with hepatic encephalopathy and upper gastrointestinal bleeding even though it did not reach statistical significance. Over a median follow-up of 903.5 person-years (PYs), 64 patients with diabetes and 171 patients without diabetes were dead or underwent liver transplantation, with an annual incidence of 33.6 and 24.0 per 100 PYs, respectively. In the PS-matched cohort, the incidence of death or liver transplantation was 36.8 per 100 PYs in the diabetic group and 18.6 per 100 person-years in the matched control. After adjusting for various factors, coexisting diabetes significantly increased the risk of death or liver transplantation for short-term and long-term, along with other factors such as prolonged prothrombin time, low serum albumin, elevated total bilirubin and creatinine, and decreased serum sodium levels. **Conclusion:** In patients with alcoholic liver cirrhosis, the presence of diabetes increases the risk of death or liver transplantation. Alongside appropriate medical treatment, it is imperative to educate and modify lifestyle targeting well-controlled diabetes.

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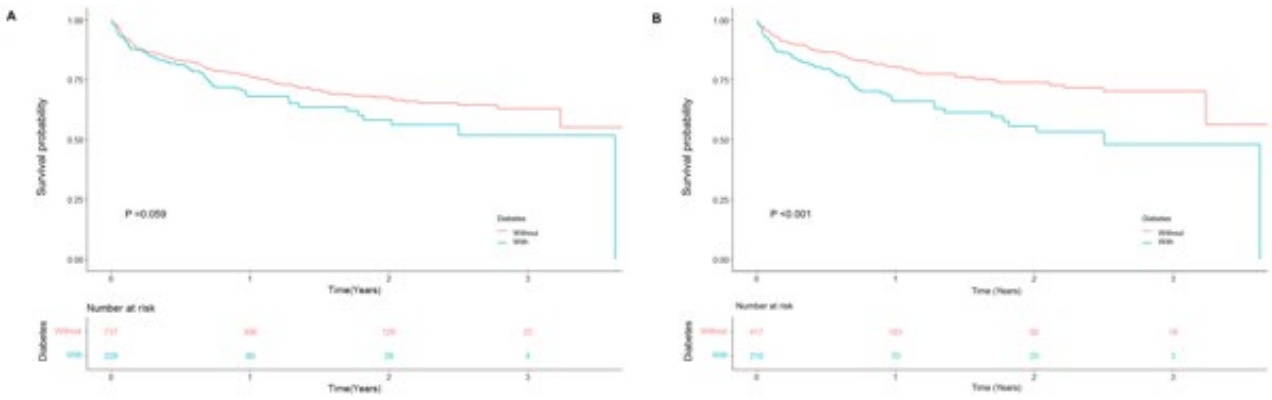

Figure 1. Cumulative risk of composite outcome in (A) the total and (B) propensity score-matched cohorts

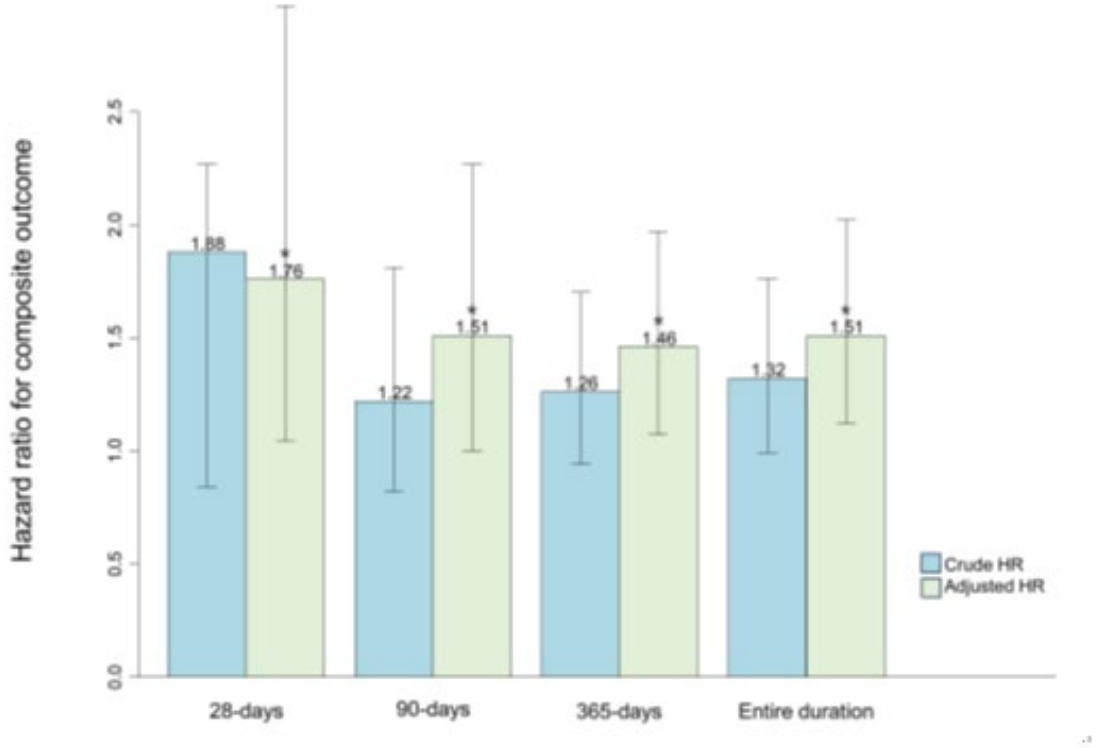

Figure 2. Diabetes and composite outcome by Cox regression analysis

* P≤ 0.05

Disclosures: Sung-Eun Kim: Nothing to Disclose, JIHYE LIM: Nothing to Disclose, Ai Jeong Jo: Nothing to Disclose, Young Kul Jung: Nothing to Disclose, Do Seon Song: Nothing to Disclose, Sung Won Lee: Nothing to Disclose, Sang Gyune Kim: Nothing to Disclose, Jae Young Jang: Nothing to Disclose, Moon Young Kim: Nothing to Disclose, Young Joo Jin: Nothing to Disclose, Ki Tae Suk: Nothing to Disclose, Won Kim: Nothing to Disclose, Eileen Yoon: Nothing to Disclose

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3023 | BODY MASS INDEX INFLUENCES LIVER-RELATED MORTALITY AFTER THE FIRST DECOMPENSATION EVENT IN PATIENTS WITH ALCOHOL-RELATED LIVER DISEASE

Noriyo Yamashiki[1] Miki Murata[1] Kanehiko Suwa[1] Masao Yamashina[1] Katsunori Yoshida[1] Syunichiro Ikeda[1] Toshihito Seki[1] Masaaki Shimatani[1] Shinji Shimoda[2] Makoto Naganuma[2]

[1]Kansai Medical University Medical Center, [2]Kansai Medical University

Background: Alcohol related liver disease (ALD) is the most common causes of liver cirrhosis and hepatocellular carcinoma (HCC). It is important to determine whether there are factor affecting prognosis that can be modifiable, as patients may only become aware of the need for lifestyle modifications only after hospitalization event. Drinking status post discharge, nutritional imbalance, and sarcopenia at the presentation can influence to prognosis of ALD patients with decompensation event. **Methods:** This retrospective study enrolled 104 patients with ALD who admitted to our hospital due to their first liver-related events other than HCC between 2016 and July 2023. Collected baseline characteristics included clinical and laboratory data, body mass index (BMI), and psoas muscle mass index (PMI) measured by manual trace methods on L3-level CT image taken within a week of admission. Drinking pattern after discharge was according to doctors' medical charts. Risk factors for all-cause mortality and liver-related death were analyzed using cox regression hazard model and competing risks analysis. The factors with p-values <0.1 were entered to multivariate analysis. **Results:** Patient age was 55±11 years, and 74 (71%) were male. BMI was 22.8± 4.4 kg/m^2; there was no correlation between BMI and degree of ascites (none/ mild-moderate/ severe: 34/28/42) (rho-0.0707, p=0.4756). PMI was 3.18±1.33 cm^2/m^2 and 63 (60.5%) met muscle volume loss (cutoff value for male 4.24 cm^2/m^2, for female 2.50 cm^2/m^2 according to Hiraoka A., Hep Res 2018). Aim of the first admission was refractory ascites 43(41%), acute-on-chronic liver failure in 12 (11%), alcoholic hepatitis in 13(12%), variceal bleeding in 10 (10%), hepatic encephalopathy in 6(6%), and other or combination events in 20 (19%).Patients' average daily alcohol consumption was 131±79g, and drinking behavior after discharge was abstinent in 31 (28%), reduced in 15 (14%), continued in 40 (38%), and unknown in 19 (18%). The median survival was 4.45 years, and 37 died; 27 were liver-related death, and 10 were from other causes. For all-cause mortality, BMI (HR 1.16 (95%CI: 1.08 - 1.24), p<.001), T-Bil (1.16 (1.05 - 1.28), p<.01), positive ascites (3.10 (1.34-7.17), p<.05), and post-discharge drinking (3.88 (1.64 - 9.17), p<.01) were independent predictors. By cause-specific competing risks analysis, BMI (p<.001), T-Bil (p<.05) and positive ascites (p<.05) were associated with liver-related mortality, but not related to mortality from other causes. **Conclusion:** BMI, T-Bil and post-discharge drinking behavior influence post-discharge prognosis in ALD patients with decompensation events.

Disclosures: Noriyo Yamashiki: Nothing to Disclose, Miki Murata: Nothing to Disclose, Kanehiko Suwa: Nothing to Disclose, Masao Yamashina: Nothing to Disclose, Katsunori Yoshida: Nothing to Disclose, Syunichiro Ikeda: Nothing to Disclose, Toshihito Seki: Nothing to Disclose, Masaaki Shimatani: Nothing to Disclose, Shinji Shimoda: Nothing to Disclose, Makoto Naganuma: Nothing to Disclose

3024 | POTENTIAL USE OF IPSC-DERIVED HEPATOCYTE-LIKE CELLS TO DEVELOP PRECISION MEDICINE FOR ASH

Samantha Hoey[1]

[1]National Institute on Alcohol Abuse and Alcoholism

Background: The possibility to create "off the shelf" iPSC therapies is attractive. We optimized the production of iPSCs from patient blood samples and their differentiation into hepatocyte-like cells (iHLCs). Genetic and environmental factors contribute to the development of risky drinking pattern or unhealthy eating behavior, which can result in the development of alcoholic steatohepatitis (ASH) or nonalcoholic steatohepatitis (NASH). iPSC-derived iHLCs from healthy subjects and ASH or NASH patients will be probed to understand the interplay of genetic and environmental factors in disease development. **Methods:** Blood samples were collected from healthy subjects and ASH patients, and iPSC clones were generated from CD4+ T cells isolated from the blood samples. iPSCs were sequentially treated with growth factors and activators to generate iHLCs, characterized by the expression of multiple markers as detected by RT-PCR, flow cytometry and confocal microscopy. Functional assays were also performed to probe lipid and glycogen accumulation and toxicity. Furthermore, transcriptome analyses were performed to understand the molecular signature of ASH. **Results:** Whole blood samples from

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healthy subjects and ASH patients were obtained from VCU and NIH. CD4+ T cells were purified and activated to generate iPSCs, which were characterized by the expression of SSEA4 and Tra-1-60. iHLCs generated from iPSCs isolated from healthy subjects were characterized by multiple markers including albumin and HNF4α. ASH cirrhotic (AC) patients derived hepatocytes are associated with increased lipid droplet (LD) formation. Increase LD formation in patients derived hepatocytes leads to increased senescence. Treatment with Aramchol, a fatty acid pathway modulator, led to decreased LD formation and senescence. **Conclusion:** iPSCs generated from whole blood can be induced to differentiate into iHLCs, which can be further characterized by transcriptome analyses. In vitro exposure of iHLCs to ethanol induced lipid accumulation and upregulated fatty acid synthesis pathways. iHLCs were also generated from ASH patients' blood samples and their further characterization may facilitate the development of precision therapeutics.

Disclosures: Samantha Hoey: Nothing to Disclose

3025 | THE ROLE OF C/EBPβ-SAA1/2 AXIS IN ALCOHOL-ASSOCIATED LIVER DISEASE RESOLUTION

Michael Schonfeld[1] *Steven Weinman*[1] *Irina Tikhanovich*[1]

[1]*University of Kansas Medical Center*

Background: Abstinence is an important therapeutic intervention for patients with alcohol-associted liver disease (ALD). However, fibrosis improvement after cessation is not uniform and some patients progress to cirrhosis even while abstinent. We aimed to study the mechanisms of ALD resolution using spatial transcriptomics combined with scATAC-seq analysis. **Methods:** Mice were fed high fat diet with 20% of alcohol in the drinking water for 20 weeks (alcohol) followed by 4 weeks of chow diet with plain water (resolution). Spatial transcriptomics analysis was performed using CosMx Nanostring 1000-plex assay. scATAC-seq dataset and Spatial dataset were analyzed using Seurat v5 R package. *Cebpb* floxed mice received AAV-TBG-Cre or AAV-control at the time of alcohol cessation. Hepatocyte – macrophage crosstalk was investigated using a transwell co-culture system. **Results:** Our previous studies suggest that alcohol-induced persistent epigenetic changes in hepatocytes prevent ALD resolution. To better understand the upstream regulators of gene expression in hepatocytes during ALD resolution we performed scATAC-seq analysis and analyzed differentially accessible regions in liver cells from control, ALD, and at 4 weeks after alcohol cessation followed by transcription factor motif enrichment analysis. We identified transcription factors that are predicted to be activated by alcohol and still activated 4 weeks after alcohol exposure. The top hit was C/EBPβ. *In vivo* data indicated that C/EBPβ was induced by alcohol and remained elevated after alcohol withdrawal. We found that hepatocyte specific *Cebpb* knockout at the time of alcohol cessation promoted fibrosis resolution. Using spatial transcriptomics we identified cellular composition and gene expression features of fibrolytic and fibrogenic niches in the liver of alcohol fed mice and mice after 4 weeks of alcohol cessation. Fibrolytic niche contained *Mmp12* ^{high} *Gpnmb* ^{high} macrophages, subsets of T-cells, B-cells, subset of endothelial cells and a unique population of *Saa1/2* $^{highCxcl9\ pos}$ hepatocytes. Since C/EBPβ is a known regulator of *Saa1* and *Saa2* gene expression, we examined *Saa1/2* gene expression in *Cebpb* KO mice. We found that both genes were induced about 10-fold in KO mice, which correlated with increased *Mmp12* and *Mmp13* gene expression and increased fibrosis resolution. *In vitro Cebpb* KO or *Saa1* overexpression in hepatocytes promoted *Mmp12* expression and fibrolytic properties of macrophages. **Conclusion:** C/EBPβ-SAA1/2 axis controls hepatocyte to macrophage crosstalk in the context of fibrolytic niche in the liver after alcohol cessation.

Disclosures: Michael Schonfeld: Nothing to Disclose, Steven Weinman: Nothing to Disclose, Irina Tikhanovich: Nothing to Disclose, Nothing to Disclose

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3026 | PREVALENCE OF INFECTION IN ALCOHOL-ASSOCIATED HEPATITIS AND IMPACT ON MORTALITY

Regis Lee[1] Oluwaposi Omiwade[2] JOSEPH Alukal[3] Julio Gutierrez[4]

[1]HCA Riverside Community Hospital, [2]Scripps Mercy Hospital, [3]University of California, Riverside, [4]Scripps Clinic

Background: Alcoholic-associated hepatitis (AH) is an acute inflammatory condition characterized by jaundice, liver failure, and short-term mortality. The reported prevalence of infections in AH varies between 20% and 50% and is a known risk factor for mortality. The objective of our study was to investigate the prevalence and type of infections in patients hospitalized with AH in the USA using a large electronic dataset and identify additional risk factors for mortality. **Methods:** This was a retrospective study from 1/2017 to 12/2023 involving 186 HCA Healthcare hospitals throughout the US, where de-identified electronic health data were used to identify patients admitted with AH. HCA Healthcare is a large healthcare network consisting of medium- and large-sized community hospitals spread across 19 states that oversees approximately 37 million patient encounters annually. AH was identified using a combination of ICD-10 codes and biochemical parameters (total bilirubin ≥ 3 mg/dL on admission, AST between 50-400 IU/L and AST/ALT > 1.5). We collected data on well-established biochemical parameters and mortality scores. Multivariable analysis was used to determine risk factors for mortality. **Results:** During this study period, we identified 10,864 patients with AH, of whom 2,678 (25%) had an infection. The most common infection was UTI (13%), followed by pneumonia (7.5%) and spontaneous bacterial peritonitis (SBP) (3%), while the prevalence of bacteremia, oral cavity, and skin infections were less than 1%. AH patients with infection had a higher MELD score (23 vs 21; $p < 0.0001$), MDF score (43 vs 37; $p < 0.0001$), higher prevalence of complications, and were more likely to be administered steroids (28% vs 24%; $p < 0.0001$) compared to those without infection. Table 1 shows important differences in the clinical features between the 2 groups. The multivariable analysis revealed MELD score (OR 1.2, 95% CI, 1.1-1.2), hepatic encephalopathy (OR 1.4, 95% CI, 1.1-1.8), infections (OR 2.5, 95% CI, 2.1-2.9) and GI bleed (OR 2.6, 95% CI, 2.1- 3.0) were independent risk factors for higher in-hospital mortality, while African Americans (OR 0.6, 95% CI, 0.4-0.8) and Hispanics (OR 0.6, 95% CI, 0.4-0.7) had lower mortality compared to Caucasians. Ascites did not have an impact on mortality (OR 1.1, 95% CI, 0.9–1.3). **Conclusion:** Using a large electronic health database we were able to demonstrate that 25% of patients admitted with AH had infections, with UTIs being the most common type. We also found that those with an infection were 2.5 times more likely to die compared to those without likely due to the severity in the setting of cirrhotic-associated immune dysfunction. Clinicians should have a high index of suspicion for infections in AH and initiate treatment promptly to improve clinical outcomes.

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Table 1: Demographics and clinical characteristics in AH with and without infection

VARIABLE		Total		INFECTION: Yes		No		p-value
		N	%	N	%	N	%	
Sex	Female	4043	37.2	1280	47.8	2763	33.8	<0.0001
	Male	6821	62.8	1398	52.2	5423	66.3	
Race	AA	636	5.85	168	6.27	468	5.72	0.457
	Hispanic	2177	20.0	548	20.5	1629	19.9	
	White	7174	66.0	1737	64.9	5437	66.4	
	Other	877	8.07	225	8.4	652	7.96	
Diabetes		1284	11.8	305	11.4	979	12.0	0.427
Ascites		7550	69.5	2027	75.7	5523	67.5	<0.0001
Hepatic Encephalopathy		597	5.5	171	6.39	426	5.2	0.020
Gastrointestinal bleed		2318	21.3	551	20.6	1767	21.6	0.268
Steroid use		2709	24.9	761	28.4	1948	23.8	<0.0001
Dialysis		257	2.37	135	5.04	122	1.49	<0.0001
Respiratory failure		1073	9.88	513	19.2	560	6.84	<0.001
Laboratory panel		M	SD	M	SD	M	SD	p-value
Age		49.1	11.2	49.3	11.4	49.1	11.2	0.484
Platelets		124.2	76.2	130.3	79.5	122.2	74.9	<0.0001
Maddrey's score		38.3	31.4	43.0	35.0	36.8	30.0	<0.0001
MELD score		21.5	6.33	22.8	6.99	21.1	6.03	<0.0001
Bilirubin		9.41	7.35	10.1	7.63	9.18	7.24	<0.0001
INR		1.81	0.54	1.89	0.61	1.78	0.52	<0.0001
Albumin		2.34	0.55	2.30	0.54	2.36	0.56	<0.0001
Creatinine		1.05	0.94	1.18	1.08	1.01	0.89	<0.0001

*M= median; SD= standard deviation

Disclosures: Regis Lee: Nothing to Disclose, Oluwaposi Omiwade: Nothing to Disclose, JOSEPH Alukal: Nothing to Disclose, Julio Gutierrez: Altimmune: Consultant, AbbVie: Speaking and Teaching, Gilead: Speaking and Teaching, Alexion: Speaking and Teaching, Exelixis: Speaking and Teaching, Madrigal: Consultant, Intercept: Speaking and Teaching, Livivos: Stock – privately held company, Surozen: Advisor, Escient: DSMB Chairman

3027 | CLINICAL IMPACT OF HARM REDUCTION IN PATIENTS WITH CHRONIC LIVER DISEASE AND ALCOHOL USE DISORDER BY BRIEF INTERVENTION IN A HEPATOLOGY OUTPATIENT UNIT

Nagisa Hara[1] Atsushi Hiraoka[2] Masato Nakai[3] Makoto Shiraki[4] Tadashi Namisaki[5] Hisamitsu Miyaaki[6] Takuro Hisanaga[7] Hirokazu Takahashi[1] Hideko Ohama[2] Fujimasa Tada[2] Naoya Sakamoto[8] Kazuhiko Nakao[6] Taro Takami[7] Yuichiro Eguchi[9] Hitoshi Yoshiji[10]

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Background: Both AASLD and EASL guidelines recommend appropriate interventions for harm reduction, such as brief intervention (BI), when managing patients with chronic liver disease (CLD) and harmful drinking habits.

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It has been reported that heavy drinkers who have undergone BI are approximately twice as likely to reduce alcohol consumption as those who have not (odds ratio 1.95) (J Gen Intern Med. 1997). However, there is limited evidence regarding BI's efficacy in CLD patients with alcohol use disorder. In this retrospective study, we aimed to evaluate BI's effectiveness in CLD patients affected by harmful alcohol use. **Methods:** From 2021 to 2023, 123 Japanese outpatients with CLD (hepatitis B virus [HBV], hepatitis C virus [HCV], alcoholic liver disease [ALD], other: 32:18:42:31, respectively) with harmful drinking habits at the time of the initial interview who had undergone a follow-up interview nine months later were enrolled in the present study. Harmful use of alcohol was defined as Alcohol Use Disorders Identification Test (AUDIT) score ≥8 . We retrospectively compared relevant data of patients who had and had not undergone BI. **Results:** There were no significant differences in clinical features other than CLD etiology (HBV, HCV, ALD, other: 20:17:37:27 vs. 12:1:5:4, respectively, P=0.028) and baseline AUDIT scores (median 10 [IQR 9–13] vs. 12 [IQR 10–17], P=0.016) between the BI and non-BI groups. However, AUDIT scores did not differ significantly between these groups at the second interview (median 11 [IQR 8–15] vs. 9 [IQR 6–13], P=0.156). There were significant improvements in items 1, 2, 3, 4, 5, 8, and 10 of AUDIT following BI (Table) (each P<0.05). Albumin–bilirubin scores at baseline and after 9 months did not differ significantly between the non-BI (−2.74±0.38 vs. −2.72±0.44, P=0.701) and BI (−2.76±0.38 vs. −2.75±0.42, P=0.951) groups. Similarly, there were no significant differences in Child–Pugh scores (5:6:7:8:9) between the non-BI (21:0:1:0:0 vs. 18:4:0:0:0, P=0.119) and BI (85:9:5:2 vs. 81:11:4:4:1, P=0.688) groups. **Conclusion:** Although there was no significant improvement in hepatic reserve function after BI because of the short duration of follow-up, both patients with alcohol use disorder and those with alcohol dependency who had undergone BI exhibited notable decreases in AUDIT scores. BI is a simple and cost-effective intervention for alcohol use disorders in patients with CLD.

Table. Changes in each item of AUDIT score in patients who underwent BI

	Questions of AUDIT (score)	Baseline (0:1:2:3:4)	After 9 months (0:1:2:3:4)	P value
Q1	How often do you have a drink containing alcohol? (0) Never, (1) Monthly or less, (2) 2 to 4 times a month, (3) 2 to 3 times a week, (4) 4 or more times a week	2:2:7:18:72	14:6:13:15:53	P<0.001
Q2	How many drinks containing alcohol do you have on a typical day when you are drinking? (0) 1 or 2, (1) 3 or 4, (2) 5 or 6, (3) 7, 8, or 9, (4) 10 or more	12:32:23:22:12	33:28:21:14:5	P<0.001
Q3	How often do you have 5 or more drinks on one occasion? (0) Never, (1) Less than monthly, (2) Monthly, (3) Weekly, (4) Daily or almost daily	22:9:16:26:28	44:11:12:21:13	P<0.001
Q4	How often during the last year have you found that you were not able to stop drinking once you had started? (0) Never, (1) Less than monthly, (2) Monthly, (3) Weekly, (4) Daily or almost daily	64:15:4:7:11	80:8:7:3:3	P=0.008
Q5	How often during the last year have you failed to do what was normally expected of you because of drinking? (0) Never, (1) Less than monthly, (2) Monthly, (3) Weekly, (4) Daily or almost daily	73:11:6:5:6	87:7:3:2:2	P=0.021
Q6	How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session? (0) Never, (1) Less than monthly, (2) Monthly, (3) Weekly, (4) Daily or almost daily	93:3:3:1:1	97:0:1:1:2	P=0.822
Q7	How often during the last year have you had a feeling of guilt or remorse after drinking? (0) Never, (1) Less than monthly, (2) Monthly, (3) Weekly, (4) Daily or almost daily	79:10:6:4:2	84:6:4:2:5	P=0.921
Q8	How often during the last year have you been unable to remember what happened the night before because of your drinking? (0) Never, (1) Less than monthly, (2) Monthly, (3) Weekly, (4) Daily or almost daily	67:19:8:3:4	84:10:4:1:2	P=0.005
Q9	Have you or someone else been injured because of your drinking? (0) No, (2) Yes, but not in the last year, (4) Yes, during the last year	89:NA:9:NA:3	86:NA:13:NA:2	P=0.835
Q10	Has a relative, a friend, a doctor, or another health care worker been concerned about your drinking or suggested you cut down? (0) No, (2) Yes, but not in the last year, (4) Yes, during the last year	18:NA:17:NA:66	31:NA:29:NA:41	P<0.001

NA: not applicable

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3028 | CARDIOMETABOLIC COMORBIDITIES ARE ASSOCIATED WITH LOWER RATES OF RECOMPENSATION AND TRANSPLANT FREE SURVIVAL IN PATIENTS WITH ACUTE ALCOHOL ASSOCIATED LIVER DISEASE

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Background: Early liver transplant (LT) for patients with alcohol associated liver disease (ALD) including those with alcohol associated hepatitis (AH) and limited sobriety is an increasingly common practice. Many of these patients have coexisting cardiometabolic comorbidities and there is increasing recognition of the possible combinatorial effects of metabolic dysfunction and alcohol on steatotic liver disease. We hypothesized that cardiometabolic (CM) risk factors would be associated with lower rates of recompensation and survival in patients referred for early LT for ALD. **Methods:** This multicenter, retrospective cohort study of six liver transplant centers (RESOLVE) assessed adult patients with ALD and less than six months of sobriety from alcohol who were evaluated for early liver transplant (LT) between 2018 and 2021. The outcomes were transplant free survival and hepatic recompensation. Hepatic recompensation was defined as being alive without transplant and having no decompensation events at 6, 12 and 24 months. Cox proportional hazards model was used to assess for the outcomes in patients with CM risk factors. Transplant status was factored into each variable. CM risk factors included a history of diabetes, hypertension, or hyperlipidemia. **Results:** 632 patients with a mean (+/- SD) age of 49 (+/- 11) years with a median MELD at referral of 25 (IQR 18-33) were included. The prevalence of diabetes, hypertension and hyperlipidemia in the cohort were 19%, 43%, and 17%, respectively. 311 (49%) patients had 0 CM risk factors, 275 (44%) patients had 1-2 CM risk factors and 46 (7%) patients had 3 CM risk factors. 166 (45%) patients had transplant free survival over a median 77 days of follow up (IQR 18-239). The 1-year mortality rate was 30%. Fifty-one (17%) patients had recompensation at six months and 66 (24%) patients had recompensation at 12 months. Patients with any cardiometabolic risk factors were less likely to have transplant free survival (HR=0.85, 95% CI 0.76-0.97; p=0.01) or recompensation at six months (HR=0.83, 95% CI 0.73-0.94; p=0.01), 12 months (HR=0.85, 95% CI 0.75-0.96; p=0.01), and 24 months (HR=0.86, 95% CI 0.76-0.97; p=0.01). Patients with three risk factors were less likely to have transplant-free survival or recompensation compared to patients with one or two CM risk factors (Table). **Conclusion:** Cardiometabolic risk factors including diabetes, hypertension and hyperlipidemia were associated with lower likelihood of recompensation and transplant free survival in patients evaluated for early LT for ALD. Our results support a possible contribution of metabolic dysfunction-associated steatosis to prognosis in ALD patients with limited sobriety.

Table: Survival and recompensation at 6, 12, and 24 months by number of cardiometabolic risk factors compared to 0 risk factors; HR (95% CI)

CM Risk	Transplant Free Survival	Recompensation at 6 months	Recompensation at 12 months	Recompensation at 24 months
1-2 factors	HR=0.90 (0.65-0.97)	HR=0.77 (0.63-0.95)	HR=0.82 (0.67-1.01)	HR=0.83 (0.68-1.02)
3 factors	HR=0.65 (0.45-0.93)	HR=0.60 (0.41-0.89)	HR=0.63 (0.43-0.92)	HR=0.65 (0.45-0.94)

Disclosures: Kelly Torosian: Nothing to Disclose, Allison Kwong: Nothing to Disclose, Kaleb Tesfai: Nothing to Disclose, Katherine Cooper: Nothing to Disclose, Deepika Devuni: Avania Medical: Grant/Research Support, Intercept: Grant/Research Support, Kawthar Mohamed: Nothing to Disclose, Nicholas Lim: Nothing to Disclose, Weiyu Wu: Nothing to Disclose, Anjana Rajan: Nothing to Disclose, Amanda Cheung: Nothing to Disclose, Kevin Wang: Nothing to Disclose, Hersh Shroff: Nothing to Disclose, Veeral Ajmera: Nothing to Disclose

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3029 | EARLY PHARMACOLOGIC TREATMENT OF ALCOHOL USE DISORDER AND PSYCHIATRY CONSULTATION ARE ASSOCIATED WITH IMPROVED OVERALL SURVIVAL IN SEVERE ALCOHOL-ASSOCIATED HEPATITIS

Claire Durkin Douglas Schaubel[1] Therese Bittermann[2]

[1]University of Pennsylvania, [2]Perelman School of Medicine

Background: Data are limited regarding the safety and efficacy of pharmacotherapies for the treatment of alcohol use disorder (AUD) in the acute setting of severe alcohol-associated hepatitis (SAH). **Methods:** This was a retrospective cohort study of first-time hospitalizations for SAH (Maddrey's Discriminant Function ≥32) admitted to the Veterans Health Administration between 1/3/2005-12/5/2020, evaluating the effect of pharmacologic therapies for AUD on overall survival. Admissions were identified via a validated algorithm using International Disease Classification discharge codes and laboratory values. Exposure to AUD pharmacotherapy was based on inpatient administration records and outpatient pharmacy fills within 28-days of admission for medications approved for the treatment of AUD: naltrexone, acamprosate, and disulfiram. Time-to-event analyses were conducted using Kaplan-Meier and multivariable Cox models, which were adjusted for baseline and admission characteristics, as well as shared frailty by center. Follow-up time started at 28-days following admission (to allow for medication exposure) until death, receipt of AUD pharmacotherapy (for the unexposed group), or end of the 1-year follow-up period. **Results:** There were 2,618 first-time admissions for SAH during the study period. Of the 1,801 (68.8%) Veterans who completed the AUDIT-C questionnaire prior to hospitalization, 1,349 (74.9%) screened positive for possible AUD (score ≥4 for males, ≥3 for females). Psychiatry was consulted during about half (52.8%) of admissions. Early treatment of AUD was limited with only 115 (4.4%) Veterans in receipt of pharmacotherapy, 143 (5.5%) admitted to inpatient psychiatry, and 289 (11.0%) attending an outpatient mental health visit within 28-days of hospitalization. Medications used to treat AUD were mostly commonly acamprosate (69.9%) and naltrexone (44.4%) with rare use of disulfiram (2.6%). Unadjusted survival for those in receipt vs non-receipt of AUD pharmacotherapy was 96.3% vs 86.4% at 28-days, 94.4% vs 76.2% at 90-days, and 88.3% vs 56.7% at 365-days during the follow-up period, respectively. AUD pharmacotherapy was associated with improved overall survival both unadjusted ($p<0.001$) and adjusted models (HR 0.26, $p<0.001$). Improved survival was also observed with psychiatry consultation during admission (HR 0.79, $p=0.002$). Determination of alcohol relapse following diagnosis was limited by missingness (<35% completed an AUDIT-C within 1 year). **Conclusion:** In a large, multicenter cohort of U.S. Veterans, behavioral and pharmacologic treatment of AUD following diagnosis of SAH remains limited. Early intervention with AUD pharmacotherapy and inpatient psychiatry consultation in this population was associated with improved overall survival. Additional research is needed to confirm these findings and understand how to increase the utilization of AUD therapies following SAH.

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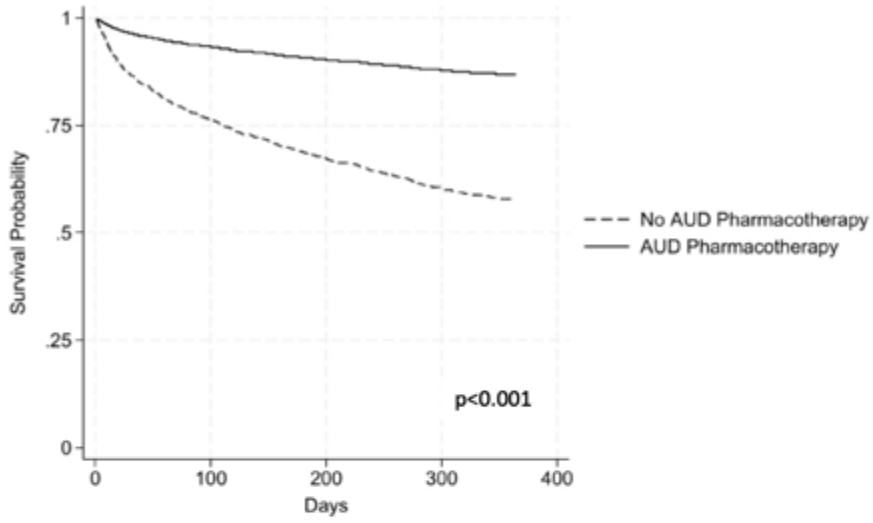
Figure:
A) Adjusted overall survival probability by receipt of pharmacotherapy for alcohol use disorder†



B) Multivariable Cox model adjusting for baseline and admission characteristics†

	Hazard ratio (95% confidence interval)	p-value
Mental health comorbidity	1.25 (1.02-1.53)	0.035
AUDIT-C score (per point)	1.00 (0.98-1.02)	0.941
Psychiatry consult	0.79 (0.68-0.92)	0.002
AUD pharmacotherapy	0.26 (0.18-0.36)	<0.001

*Abbreviations: AUD=alcohol use disorder, BMI=body mass index, AUDIT-C=Alcohol Use Disorders Identification Test, MELD=Model for End-Stage Liver Disease

†Follow-up time started at 28-days following admission. Adjusted for age, sex, race/ethnicity, BMI, cirrhosis, ascites, hepatic encephalopathy, cardiovascular disease, diabetes, chronic kidney disease, mental health comorbidity (depression, anxiety, post-traumatic stress disorder [PTSD], bipolar disorder, schizophrenia, and non-alcohol substance use disorder), critical care admission, antibiotic use, AUDIT-C score, Model for End Stage Liver Disease score, corticosteroid use, N-acetylcysteine use, pentoxifylline use, subspecialty consultation (gastroenterology, psychiatry, nutrition, palliative care), inpatient psychiatry admissions, and outpatient mental health visits, as well as shared frailty by center

Disclosures: Claire Durkin: Nothing to Disclose, Douglas Schaubel: Nothing to Disclose, Therese Bittermann: Nothing to Disclose

3030 | TREATMENT OF ALCOHOL USE DISORDER WITH MEDICATIONS AND WITH INTEGRATED CARE MODEL BENEFIT PATIENTS WITH ALCOHOL-ASSOCIATED LIVER DISEASE

Prabha Bhandari[1] Shaikhoon Mohammed[2] Akshay Shetty[3] Arpan Patel[4] Mohamed Abdallah[5] Vatsalya Vatsalya[1] Lorenzo Leggio[6] Ashwani Singal[1]

[1]University of Louisville, [2]Emory University, [3]University of California Los Angeles, [4]University of California, Los Angeles, [5]Cleveland Clinic, [6]John Hopkins University

Background: Alcohol-associated liver disease (ALD) imposes a significant healthcare burden. Alcohol use disorder (AUD) is the most important risk factor and determines the long-term outcomes of ALD patients. Risk of relapse to alcohol use remains in ALD patients including those who receive liver transplantation (LT). However,

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several barriers limit the wide use of AUD treatment in ALD patients. This meta-analysis pools data from studies outside and within LT settings to examine the impact of AUD treatment (behavioral and pharmacological) on alcohol relapse, liver disease, and patient outcomes. **Methods:** 22 eligible studies (11 outside and 11 in LT settings) were analyzed. Outcomes were abstinence, liver outcomes (decompensation, readmission), and patient mortality. Data were pooled using random effect model and presented as incidence rate ratio (IRR) of outcomes/person year (PY), with 95% confidence interval (CI). **Results:** Pooled IRR (95% CI) from seven out of the 11 studies (n=36,931, AUD treatment in 5520) looking at AUD treatment in ALD patients outside LT settings on alcohol relapse was 0.81 (0.29-1.33). Data from five randomized controlled trials (RCT, n=522) comparing placebo vs. medications for AUD (MAUD, n=347: baclofen in two and one each with fecal matter transplant, metadoxine, and LGG) showed IRR of 0.42 (0.24-0.73). Pooled IRR on liver outcomes were 0.68 (0.41-1.12) for readmission (three studies), 0.52 (0.39-0.68) for hepatic decompensation (two studies), and 0.71 (0.54-0.93) on patient mortality (six studies), (Fig.1A). Analysis of 11 studies in LT setting (n=1583, AUD treatment in 613) showed IRR on alcohol relapse of 0.80 (0.41-1.54), and this was 0.93 (0.40-2.17) among LT recipients on post-LT alcohol relapse from nine studies. IRR on alcohol relapse with integrated model (AUD treatment for dual pathology of liver disease and of AUD by respective specialists in one clinic) in four studies (addiction team integrated in LT center providing continuing AUD care from evaluation to post-LT follow up) was 0.42(0.28-0.64), and this was 0.78(0.41-1.48) in four studies using non-integrated AUD care. The IRR for patient mortality (three of studies) was 0.49 (0.27-0.87) (Fig. 1B). **Conclusion:** AUD treatment especially with MAUD reduces alcohol relapse and improve patient outcomes. However, this is rarely used with MAUD examined in only 347 patients in clinical trials. An integrated multidisciplinary model reduces alcohol relapse and patient mortality. Multicenter clinical trials are needed to examine MAUD and integrated care model with aim of improving long-term survival in patients with ALD.

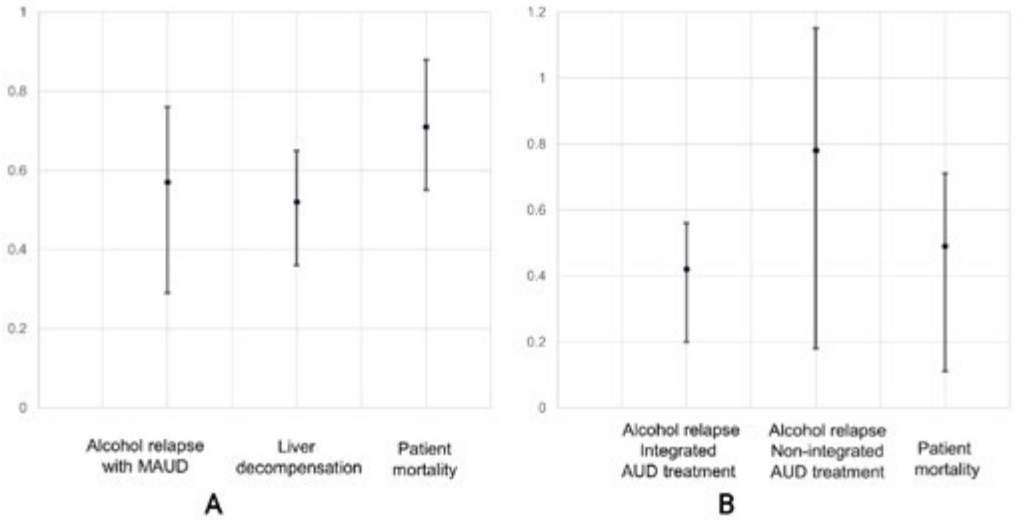

Fig: 1. Effect of alcohol use disorder treatment in patients with alcohol-associated liver disease outside (**A**) and within (**B**) liver transplant setting. The pooled data are expressed as incidence rate ratios (black circles) and 95% confidence intervals (error bars on the circle).

Disclosures: Prabha Bhandari: Nothing to Disclose, Shaikhoon Mohammed: Nothing to Disclose, Akshay Shetty: Nothing to Disclose, Arpan Patel: Nothing to Disclose, Mohamed Abdallah: Nothing to Disclose, Vatsalya Vatsalya: Nothing to Disclose, Lorenzo Leggio: Nothing to Disclose, Ashwani Singal: Advisor relationship with CLD Foundation; Has not ended; Speaking and Teaching relationship with Medical Speaker's Network; Has not ended; Speaking and Teaching relationship with Madrigal; Has not ended; Stock â€“ privately held company relationship with Pleiogenix; Has not ended; Consultant relationship with Pleiogenix; Has not ended; Advisor relationship with Durect; Has ended; Royalties or patent beneficiary relationship with Up-to-Date; Has not ended; Executive role relationship with Gastro Endo News; Has not ended; Grant/Research Support relationship with NIAAA; Has not ended; Employee relationship with Avera Medical Group; Has ended; Grant/Research Support relationship with GSK; Has not ended; Employee relationship with University of Louisville School of Medicine; Has not ended; Speaking and Teaching relationship with Medscape; Has not ended

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3031 | SURVIVAL BENEFIT FROM CORTICOSTEROIDS IN SEVERE ALCOHOL-ASSOCIATED HEPATITIS ATTRIBUTED TO CLINICAL AND TREATMENT DIFFERENCES IN A LARGE MULTICENTER COHORT

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[1]University of Pennsylvania, [2]Hospital of the University of Pennsylvania, [3]Perelman School of Medicine

Background: Corticosteroids are recommended by multiple society guidelines for the treatment of severe alcohol-associated hepatitis (SAH). However, their use remains controversial due to inconsistent studies regarding their survival benefit. **Methods:** This was a retrospective cohort study of first-time hospitalizations for SAH (Maddrey's Discriminant Function ≥ 32) admitted to the Veterans Health Administration between 1/3/2005-12/5/2020, evaluating the effect of corticosteroid therapy on all-cause survival and characterizing the clinical and psychosocial factors associated with corticosteroid use. Admissions were identified via a validated algorithm using International Disease Classification discharge codes and laboratory values. Corticosteroid exposure was based on inpatient administration records and outpatient pharmacy fills initiated within 7-days of admission for prednisolone, prednisone, and methylprednisolone. Time-to-event analyses were conducted Kaplan-Meier and multivariable Cox models, which were adjusted for demographics, clinical factors, subspecialty consults, other treatments, and shared frailty by center. Follow-up time started at 7-days following admission (to allow for medication exposure) until death, receipt of corticosteroids (for the unexposed group), or end of the 1-year follow-up period. **Results:** During the study period, 2,618 Veterans were admitted with SAH, of whom 1,083 (41.4%) received corticosteroids. Among those treated, 317 (29.3%), 316 (29.2%), and 449 (41.50%) had a duration of therapy of ≤7, 8-27, and ≥28-days, respectively. Patients who received corticosteroids vs no corticosteroids were less likely to be Black (11.2% vs 14.3%, p=0.042 for all pairs), reside in a low-income zip code (19.7% vs 24.4% for the lowest quintile, p=0.056 for all pairs), or have a mental health comorbidity (14.7% vs 17.5%, p=0.055), suggesting disparities in prescribing patterns. Unadjusted overall survival for patients treated with corticosteroids vs no corticosteroids was 80.9% vs 77.6% at 28-days, 69.0% vs 66.5% at 90-days, and 54.8% vs 50.4% at 365-days following admission. Although corticosteroid use was significantly associated with improved all-cause survival in the unadjusted model (p=0.022), no survival benefit from corticosteroids was observed in the adjusted model after accounting for baseline and admission characteristics (hazard ratio=1.01, p=0.818). Factors associated with worse survival included older age, male sex, cirrhosis, hepatic encephalopathy, higher Model for End-Stage Liver Disease score, need for critical care, pentoxifylline use, palliative care, and mental health comorbidity (all p<0.05). **Conclusion:** Despite being recommended by clinical guidelines for the treatment of SAH, corticosteroids have low utilization with no survival benefit after accounting for differences in patient characteristics and practice patterns.

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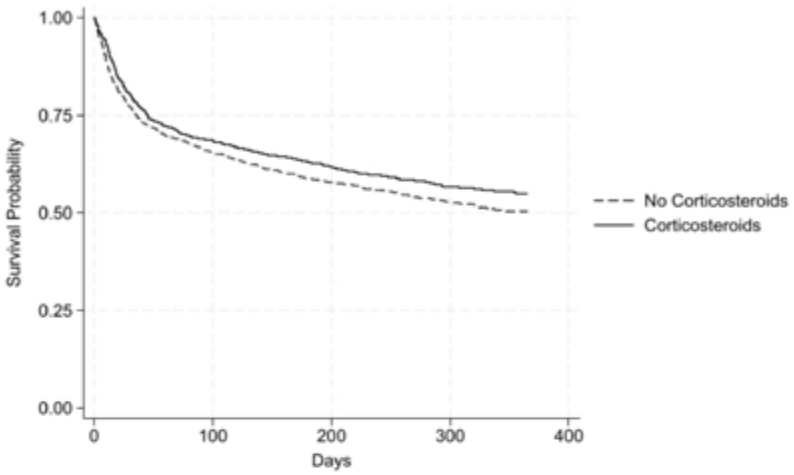
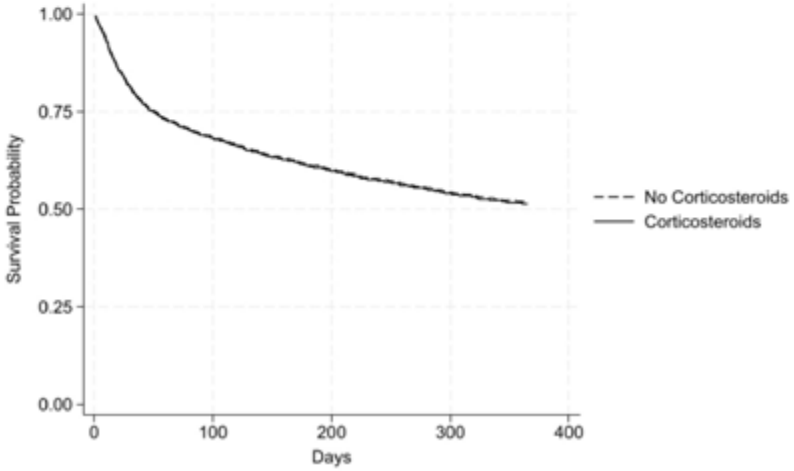
Figure: Unadjusted (A) and adjusted (B) all-cause survival following admission for severe alcohol-associated hepatitis by corticosteroid use

a)



	Number at risk			
	0 days	28 days	90 days	365 days
Corticosteroids	1064	863	734	583
No corticosteroids	1332	1033	853	601

b)



Disclosures: Claire Durkin: Nothing to Disclose, Douglas Schaubel: Nothing to Disclose, Nadim Mahmud: Nothing to Disclose, David Kaplan: Independent Contractor relationship with Roche Genentech; Has not ended; Grant/Research Support relationship with AstraZeneca Inc; Has not ended; Advisor relationship with AstraZeneca; Has ended; Advisor relationship with Exelixis; Has ended; Grant/Research Support relationship with Gilead; Has not ended; Advisor relationship with Sirtex; Has ended; Grant/Research Support relationship with Exact Sciences; Has not ended; Grant/Research Support relationship with Glycotest; Has ended, Therese Bittermann: Nothing to Disclose

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3032 | PROGNOSTIC SIGNIFICANCE OF SKELETAL MUSCLE MASS IN PATIENTS WITH ALCOHOLIC CIRRHOSIS

Tadashi Namisaki Shinya Sato[1] KOSUKE KAJI[1] NORIHISA NISHIMURA[1] Hitoshi Yoshiji[1]

[1]Nara Medical University

Background: Reduced hand grip strength (HGS) is predictive of poor survival in patients with cirrhosis (LC). Alcohol is a major risk factor of liver cirrhosis (LC). This study aimed to assess the prognostic significance of HGS and skeletal muscle mass in alcoholic LC. **Methods:** Out of 941 patients with LC, 619 were assessed for HGS and computed tomography based skeletal muscle mass index (CT-SMI). They were then divided into two groups: alcoholic cirrhosis (AC; n = 226) and non-alcoholic cirrhosis (NAC; n = 393). **Results:** The overall prevalence of sarcopenia was 16.4% (37/226) in group AC and 21.1% (83/393) in group NAC. Members of Group AC were significantly younger than those of Group NAC. Group AC showed significantly higher rates of male and incidence of esophageal varices and Type IV collagen 7S (T4C7S) levels along with significantly lower SMI in female and blood urea nitrogen (BUN) levels than Group NAC. In group AC, dead patients (D group) showed significantly lower hepatic function reserve (HFR), body mass index (BMI), SMI in female, and hemoglobin (Hb), serum levels of sodium (Na), albumin (ALB), cholinesterase (Ch-E), and prothrombin time (PT) along with significantly higher BUN levels, and the incidence of ascites and sarcopenia than alive patients (A group). In group NAC, D group shows significantly lower HFR, SMI and HSG in males, platelet counts (PLT), PT and serum levels of Hb, ALB, Ch-E and Na along with significantly higher rates of female, incidence of ascites and sarcopenia, and serum levels total bilirubin (T-Bil) and T4C7S. Multivariate regression analysis shows the prognostic factors for mortality were ALB < 3.7 (g/dL), sodium < 138 (mEq/L), low SMI [42 (cm²/m²), male, < 38 (cm²/m²), female] in AC group and incidence of ascites, lower ALB < 3.5 (g/dL), Ch-E < 200 (U/L), Na < 138 (mEq/L), low HGS [< 28 (kg), male, < 18 (kg), female] in NAC group. Kaplan-Meier curve shows that cumulative survival (CS) was significantly higher in patients with normal SMI and HGS than in patients with either normal HGS + low SMI (pre-sarcopenia) or normal SMI + low HGS (dynapenia) in group AC. CS was significantly lower in patients with low SMI + low HGS (sarcopenia) than in those with dynapenia. However, no significant differences in CS were found between those with pre-sarcopenia and those with sarcopenia in group AC. CS was significantly higher in patients those with normal SMI and HGS than those with dynapenia in group NAC. CS was significantly lower in patients with low SMI + low HGS (sarcopenia) than in those with pre-sarcopenia. However, no significant differences in CS were found between those with dynapenia and those with sarcopenia in group NAC. **Conclusion:** Sarcopenia is predictive of poor survival in patients with LC. Reduced SMI is associated with an increased risk of mortality in group AC. However, reduced HGS is associated with an increased risk of mortality in group NAC. SMI is found to be a more powerful predictor of survival than HGS in group AC.

Disclosures: Tadashi Namisaki: Nothing to Disclose, Shinya Sato: Nothing to Disclose, KOSUKE KAJI: Nothing to Disclose, NORIHISA NISHIMURA: Nothing to Disclose, Hitoshi Yoshiji: Nothing to Disclose

3033 | SCREENING OF COMPENSATED ALCOHOL-RELATED LIVER DISEASE: EFFICACY OF A HOLISTIC APPROACH (HEPATOLOGY VISIT, BRIEF INTERVENTION, AND NON-INVASIVE TEST) ON ALCOHOL ABSTINENCE AND RELAPSES

Ares Villagrasa[1] Anna Aguilar-Amorós[2] Sonia Carramiñana[3] Carla Morer[4] Mireia Valle[5] Marta Selvi Blasco[6] Maria Úbeda[7] Alba Jimenez-Massip[1] Marianela Guzman[8] Patricia Álvarez-López[3] Natalia Tumas[9] Francesc Belvis[9] Mariana Gutierrez-Zamora[9] Joan Benach[9] JuanManuel Pericàs[10] Meritxell Cots[10]

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Background: The asymptomatic forms of alcohol-related liver disease (ArLD) have been ignored worldwide leading to the late diagnosis of the disease. The main factor linked to progression and mortality among ArLD patients is the lack of abstinence. We aim to compare an intervention (i.e hepatology and psychology visit including brief intervention and assessment of the underlying liver disease with noninvasive test) with a historical control to establish a better strategy to promote abstinence **Methods:** Prospective interventional study (currently

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recruiting) including subjects ³30 years old with a diagnosis of alcohol use disorder or excessive alcohol consumption as well as ALT or AST > 1.5 UNL or GGT >100 mg/dL gathered from primary care and emergency department (ER). Patients with known liver disease were excluded. Patients from the historical cohort were gathered from the ER (discharge with the recommendation to cease drinking and control for either primary care and/or addiction center). Patients were followed for 1 year with an initial assessment of the underlying liver disease with Fibroscan® and thereafter visited every 3 months by the psychologist. Control patients (n=19) were followed for 1 year **Results:** Up to date 32 patients had been included in the intervention group and 21 completed 3 months follow up. In summary, most patients were men with a mean age of 51 vs 49 years old. The average of standard drink units/week was 83 [IQR= 33-129.6] for the intervention group vs 128.3 [IQR=67.7-189] in the control (p=0.2). Both groups presented similar Fib-4 score 4.02 vs 3.4, p=0.5, without relevant differences in the analytical parameters. At 3 months follow-up, 8 patients from the intervention group stopped drinking while only 5 of the control did (p=0.4). Of note, 16 patients in the intervention vs 7 in the control cohort achieved a ³ 50% reduction of baseline consumption (p=0.01). A reduction in total number of standard drink units/week among the intervention group was also observed 20.7 vs 65; p=0.02. While up to 6 patients from the control group required a second ER admission, none of the study group did (p=0.009). Finally, up to 40% patients from the study group presented advanced liver disease assessed by Fibroscan. **Conclusion:** Asymptomatic forms of advanced ArLD are common and frequently underdiagnosed. A holistic approach including hepatology, psychology and assessment of the underlying liver disease decreases alcohol consumption and promotes abstinence in patients with a suspected underlying ArLD as compared with a historical cohort

Disclosures: Ares Villagrasa: Nothing to Disclose, Anna Aguilar-Amorós: Nothing to Disclose, Sonia Carramiñana: Nothing to Disclose, Carla Morer: Nothing to Disclose, Mireia Valle: Nothing to Disclose, Marta Selvi Blasco: Nothing to Disclose, Maria Úbeda: Nothing to Disclose, Alba Jimenez-Massip: Nothing to Disclose, Marianela Guzman: Nothing to Disclose, Patricia Álvarez-López: Nothing to Disclose, Natalia Tumas: Nothing to Disclose, Francesc Belvis: Nothing to Disclose, Mariana Gutierrez-Zamora: Nothing to Disclose, Joan Benach: Nothing to Disclose, JuanManuel Pericàs: Nothing to Disclose, Meritxell Cots: Nothing to Disclose

3034 | OBESITY AND ACUTE ALCOHOL-ASSOCIATED HEPATITIS: ADDING INSULT TO INJURY

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Background: Alcohol-associated hepatitis (AH) has high morbidity and mortality. Obesity, a component of the metabolic syndrome (Met), is prevalent in AH and associated with lower short-term survival. However, the impact of obesity on long-term mortality (≥90-day (d)) is unclear. The NIAAA-supported Alcoholic Hepatitis Network (AlcHepNet) enrolled subjects with AH in a clinical trial and observational studies from 8 centers in the US. We aimed to determine the impact of BMI (normal <25, overweight 25-29.9, and obese ≥30 kg/m2) on disease severity at presentation and on 90 and 180-d survival. **Methods:** We analyzed combined data from two studies. We used the analysis of variance tests to compare the baseline MELD 3.0 in the three weight groups. Time to death was censored for those who survived the 90- and 180-d. Kaplan-Meier estimates and survival rates were compared using log-rank tests. Cox regression analysis was used to examine factors associated with 90- and 180-d mortality. We additionally examined baseline serum cytokine levels in 187 selected individuals using Cytokine 71-Plex Discovery Assay and compared their levels among the 3 weight groups. **Results:** Of the 779 subjects with available data, the mean (SD) age was 44.9 (10.5), 59% were male, and MELD 3.0 27.8 (3.4). Overweight (n=256; 33%) and obesity (n=310; 40%) were common. Overweight (mean BMI 27.3) and obese (mean BMI 36.6) compared with normal weight (n=213; mean BMI 22.1) were more likely male (65%, 62% vs 49%; p<.001), had higher MELD 3.0 (27.7, 28.8 vs 26.4; p=.009) higher rate of bacteremia (7.4%, 8.3% vs 1.9%; p=.03) and multiorgan failure (39%, 40% vs 26%; p=.03) with similar steroid use. Though 28-d survival was similar among the BMI groups, survival at both 90-d (Fig A) and 180-d (Fig B) was significantly lower in the obese cohort (75.2% and 69.7%) compared to overweight (80.1% and 77.7%) and normal weight (86.4% and 83.6%) (p=.007 and p<.001, respectively). In the multivariable Cox model, MELD score (HR=1.09; 95%CI [1.07-1.11], p<.001), steroid use (HR=0.51 [0.34-0.73], p<.001), and obesity (HR=1.43 [0.97-2.16] p=0.07) were associated with 180-d mortality. In the subset of 187 subjects with cytokine measurements, obese patients (n=74) had significantly higher circulating pro-inflammatory (IL-1ß, IL-33, IL-17A, IL-6), immunoregulatory cytokines (IL-12, IL-27, IL-21,

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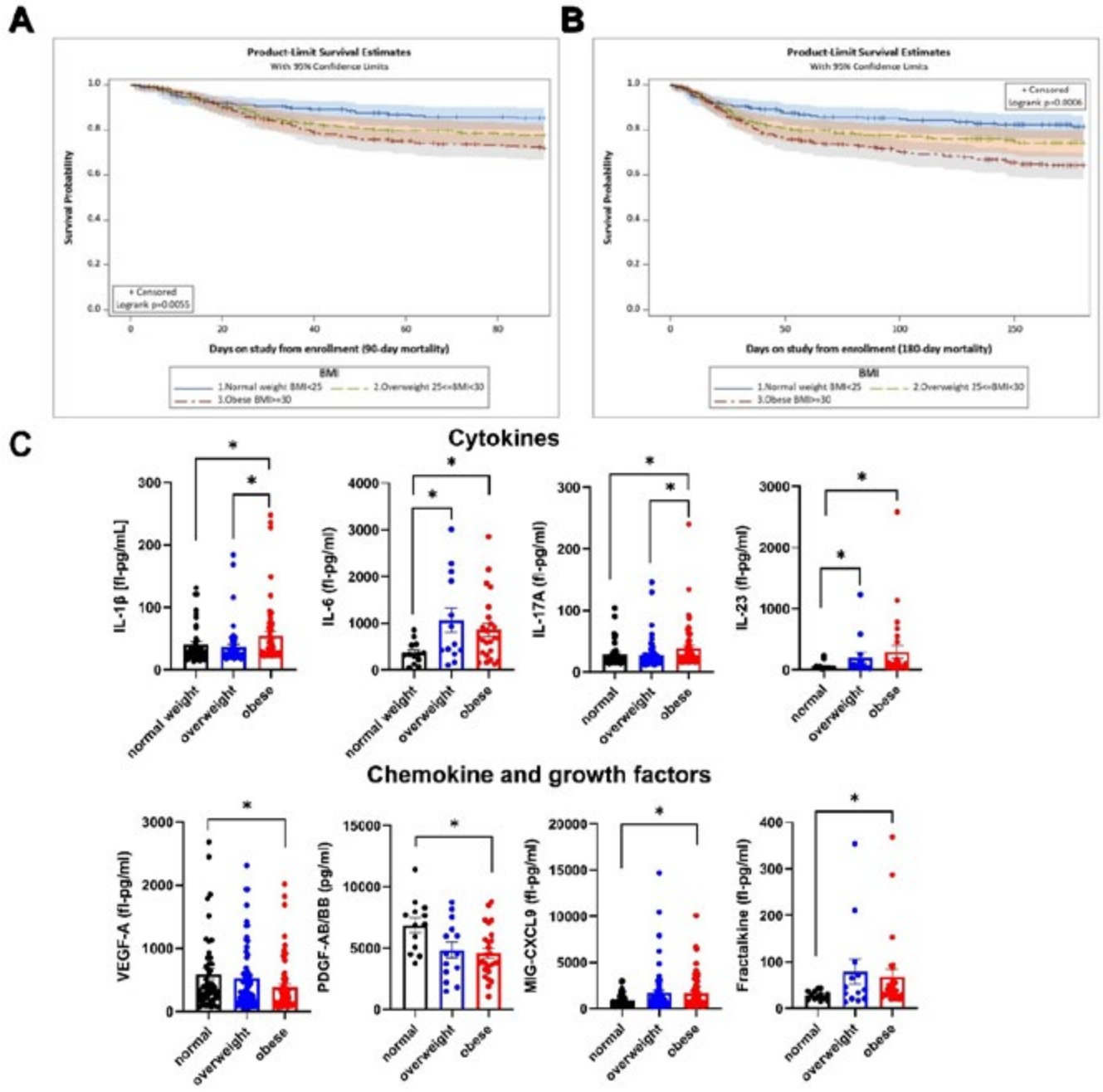
IL-23) and chemokines (CXCL9 and fractalkine) while VEGF and PDGF were reduced compared to normal weight patients (n=48) (Fig C). **Conclusion:** Obese patients with AH had higher MELD score and inflammatory cytokines profiles compared to normal-weight subjects with worse 90- and 180-d mortality. However, when adjusting for MELD and steroid use, obesity was not associated with reduced survival. Further studies are needed to better understand the causal pathways of the elevated risk of obesity and in MetAH.



(A-B) Kaplan-Meier curves of 90 and 180-day survival of alcohol-associated hepatitis (AH) patients according to different weight status, the p value corresponds to log-rank test. (C) Baseline serum cytokine, chemokine and growth factor levels in AH patients in different weight groups. * p<0.05 by non-parametric test.

Disclosures: Yun-Cheng Hsieh: Nothing to Disclose, Mrigya Babuta: Nothing to Disclose, Hannah Siegenberg: Nothing to Disclose, Yunpeng Yu: Nothing to Disclose, Wanzhu Tu: Nothing to Disclose, Richard Sterling: Grant/Research Support relationship with HCV Vax; Has not ended; Grant/Research Support relationship with GSK; Has not ended; Grant/Research Support relationship with Gilead; Has not ended; Grant/Research Support

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3035 | BILE ACID INDUCES RETINOL METABOLISM IN HEPATIC STELLATE CELLS TO ACTIVATE GLUTATHIONE SYNTHETIC MACHINERY FOR PROTECTION AGAINST ALCOHOL-ASSOCIATED STEATOHEPATITIS

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Background: Despite acetaldehyde being highly mutagenic and carcinogenic, early stage of alcohol-associated liver disease (ALD) is predominantly presented with hepatic steatosis and inflammation. We previously reported that hepatocytes and their neighboring hepatic stellate cells (HSCs) form a glutamate-mediated bidirectional loop pathway to induce steatosis, indicating the involvement of HSCs in ALD. This study aims to identify a novel role of bile acid (BA) in inducing retinol metabolism in HSCs which activates glutathione synthesis in hepatocytes with oxidative stress, forming a protective metabolic synapse in early ALD. **Methods:** Wild-type and alcohol dehydrogenase class 3 knockout (*ADH5* KO) mice were fed with pair- or EtOH diet. Serum biochemical assessment, including BA and retinoic acid (RA) measurement, was performed. Liver tissues were subjected to GeoMX spatial transcriptomics and bulk RNA-sequencing. Flow cytometry analysis was performed to assess the changes in liver mononuclear cells. Freshly isolated HSCs and hepatocytes were analyzed for gene expressions or subjected to *in vitro* experiments. **Results:** Following chronic alcohol consumption, serum levels of RA and BA were increased in EtOH-fed mice compared to pair-fed controls. In line with this, genes related to BA transporters (*Mrp3, Mrp4*), as well as RA-degrading enzyme (*Cyp26a1*), were elevated in EtOH-fed hepatocytes. Interestingly, only freshly isolated HSCs among hepatic cells from EtOH-fed liver showed the highest increase in genes related to retinol metabolism, which was parallel to the loss of retinol-storing lipid droplets observed. Moreover, *Nr1h4*, which encodes the BA receptor FXR, was upregulated in HSCs of EtOH-fed mice. *In vitro*, FXR stimulation in HSCs increased *Adh5* expression and RA production. In turn, direct treatment of RA to EtOH-exposed hepatocytes showed elevated expression of *Gss* and *Gsr*, which are involved in glutathione synthesis, whereas the expression of MYC and γ-H2AX was suppressed. In ADH3 KO mice, we observed an aggravation in steatosis and liver injury due to the lack of RA delivered to the hepatocytes, implicating the protective effect exerted by HSCs and their retinoids. **Conclusion:** Our study reveals that, upon chronic alcohol consumption, hepatocytes and HSCs form a metabolic synapse through metabolites, including BA and RA, by which hepatocytes may be protected against alcohol-induced steatosis and liver injury.

Disclosures: Sung Eun Choi: Nothing to Disclose, Kyurae Kim: Nothing to Disclose, Min Jeong Kim: Nothing to Disclose, Katherine Po Sin Chung: Nothing to Disclose, Eunmi Lee: Nothing to Disclose, Kwang Woo Lee: Nothing to Disclose, WON-IL JEONG: Nothing to Disclose

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3036 | INFLUENCE OF THE COVID-19 PANDEMIC AND ALCOHOL ON HOSPITALIZATIONS FOR DECOMPENSATED LIVER DISEASE

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Background: The COVID-19 pandemic has been associated with significant increases in both alcohol misuse and alcohol-related mortality, in part from complications of liver disease. Alcohol sales, a marker of population-based alcohol consumption, also increased during the initial stages of the pandemic. However, alcohol sales exhibited time-dependent and regional variability and its relation to hospitalizations for decompensated liver disease during this period has been relatively unexplored. The aim of this study was to test the hypothesis that COVID-19 pandemic-associated increases in alcohol sales would be paralleled by increases in hospitalizations for decompensated liver disease, specifically from alcohol-associated liver disease (ALD). **Methods:** We performed a retrospective review of admissions to the Adult Medicine and Medical Intensive Care Unit (ICU) services at the University of Vermont Medical Center in the years 2019 (pre-pandemic) and 2021 (during the pandemic). To track alcohol consumption, we utilized alcohol sales data extracted from the Annual Reports developed by the State of Vermont Department of Liquor and Lottery. **Results:** During the COVID-19 pandemic, hospital admissions increased from 6,981 in 2019 to 7,356 in 2021. Between 2019 and 2021, there was a 1.6% increase ($p < 0.001$) in admissions for decompensated liver disease and a 12.9% increase ($p < 0.01$) in ICU admissions for these patients. However, there were no significant differences among liver related admissions in 2021, compared with those in 2019, in inpatient mortality, hospital length of stay (median 4 days in each cohort), or 30-day readmission rate (Table 1). The majority of liver-related admissions were due to ALD (77.6% in 2019 and 81.5% in 2021). Over this time, alcohol sales in Vermont increased yearly from $82 million in 2019 to $95 million in 2021. The greatest rate of increase was during the COVID-19 pandemic (+6.49% in 2020 and +7.44% in 2021). **Conclusion:** There were significantly more hospitalizations for hepatic decompensation, particularly from ALD, in 2021 compared to 2019. This paralleled an increase in alcohol sales over the same time period. We speculate that the COVID-19 pandemic-associated increase in alcohol use, as evident by increase in sales, was the primary driver for increases in liver-related hospitalizations. Further research is warranted to elucidate the enduring consequences of the COVID-19 pandemic on long-term changes in alcohol use and future health burden of chronic liver disease.

Table 1. Hospital outcomes for decompensated liver disease in 2019 and 2021, compared by chi-square analysis

	2019 Cohort		2021 Cohort		p-value
	%	n	%	n	
Decompensated liver disease admissions among total admissions (n = 6,891 in 2019, n = 7,356 in 2021)	3.1	(210)	4.7	(346)	<0.001
ICU admissions among decompensated liver disease admissions	14.8	(27)	27.7	(93)	0.001
30-day readmissions among decompensated liver disease admissions	21.9	(46)	29.5	(102)	0.050
Inpatient mortality for decompensated liver disease admissions	9.5	(20)	9.5	(33)	0.996
30-day mortality for decompensated liver disease admissions	18.6	(39)	20.8	(72)	0.522
60-day mortality for decompensated liver disease admissions	24.3	(51)	25.1	(87)	0.820
1-year mortality for decompensated liver disease admissions	41.0	(86)	45.1	(156)	0.340

Disclosures: Erika Dorff: Nothing to Disclose, Aurasch Moaven: Nothing to Disclose, Bradley Tompkins: Nothing to Disclose, Steven Lidofsky: Gilead: Grant/Research Support, Exact Sceinces: Grant/Research Support, Gilead: Grant/Research Support, Intercept: Grant/Research Support, Inventiva: Grant/Research Support, Bausch Health: Grant/Research Support, Madrigal: Grant/Research Support, Exact Sciences: Grant/Research Support

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3037 | INCORPORATING SARCOPENIA TO ENHANCE MORTALITY PREDICTION IN SEVERE ALCOHOLIC HEPATITIS

Hyunseok Kim[1] Ally Hatcher[1] Vikrant Rachakonda[2] Linda Azab[1] Touseef Qureshi[1] Lixia Wang[1] Ji Hye Min[3] Polly Kirsch[1] Irene Kim[1] Yee Hui Yeo[1] Walid Ayoub[4] Alexander Kuo[4] Hirsh Trivedi[1] Aarshi Vipani[1] Yun Wang[1] Ekihiro Seki[4] Fasiha Kanwal[5] Stephen Pandol[1] Debiao Li[1] Shelly Lu[1] Ju Dong Yang[4]

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Background: Prognostication in severe alcoholic hepatitis (AH) remains challenging due to its dynamic and often rapidly deteriorating course. While the MELD score is used for prognostication of AH, its predictive performance remains suboptimal, especially in severe AH patients. Sarcopenia, a known adverse prognostic factor in chronic liver diseases, has not been extensively studied in the context of AH. This study aims to evaluate whether integrating sarcopenia into prognostic models can improve mortality prediction in severe AH patients. **Methods:** We conducted a retrospective analysis of 161 patients with severe AH (MELD >20) admitted between 01/2020 and 06/2023 at a tertiary liver transplant referral center. All patients had abdominal CT imaging on admission, while those who underwent liver transplantation were excluded. Sarcopenia was determined using the skeletal muscle index (SMI) at the L3 vertebral level, with cut-offs of 42 cm^2/m^2 for men and 38 cm^2/m^2 for women. The primary outcome was 6-month overall mortality. Predictive accuracy was assessed using the area under the receiver operating characteristic curve (AUC) for the following models: MELD 3.0, MELD-Sarcopenia (MELD + 10.35×Sarcopenia (Y or N)), MELD-L3 SMI (MELD - 0.3065× L3 SMI), Composite Model 1 (MELD 3.0 + age, sex, race/ethnicity, BMI, having insight into alcohol issues), and Composite Model 2 (MELD 3.0 & SMI + age, sex, race/ethnicity, BMI, having insight into alcohol issues). **Results:** The cohort had a mean age of 50.9 years [95% CI: 26.9-74.9], and 67% were male. About one-fourth of the patients were Non-Hispanic Whites (24.8%) and Hispanics (22.0%), while 5.6%, 2.0%, and 10% were Non-Hispanic Blacks, Asian Pacific Islanders, and other race/ethnicity, respectively. The mean BMI and MELD 3.0 were 27.2 [95% CI: 15.0-39.3] and 30.0 [95% CI: 16.0-44.3], respectively. Sarcopenia was present in 44.7% (72/161) of the patients, with a mean SMI of 42.5 cm^2/m^2 [95% CI: 22.6-62.5]. During the study follow-up until 6 months from the index date, 51 patients died (31.7%). The AUC values for MELD 3.0, MELD-Sarcopenia, MELD-SMI, Composite Model 1, and Composite Model 2 were 0.71 [95% CI: 0.62-0.79], 0.75 [95% CI: 0.67-0.84], 0.76 [95% CI: 0.67-0.84], 0.83 [95% CI: 0.76-0.89], and 0.86 [95% CI: 0.81-0.92], respectively (Table). Both models incorporating sarcopenia (MELD-L3 SMI and Composite Model 2) significantly enhanced predictive accuracy compared to MELD 3.0 alone (AUC: 0.71 vs. 0.76, p-value 0.03; and 0.83 vs. 0.86, p-value 0.02, respectively). **Conclusion:** Sarcopenia is common among severe AH patients, and its inclusion in prognostic models substantially improves mortality prediction. These findings suggest that routine assessment of sarcopenia via cross-sectional imaging could improve risk stratification and early management decisions, including considerations for liver transplantation and goals of care planning. Further external validation is warranted.

Table. Predictive Accuracy of Overall Mortality in Severe Alcoholic Hepatitis

	AUC	P-value
Model 1 (MELD 3.0 alone)	0.71 [95% CI: 0.62-0.79]	REF
Model 2 (MELD 3.0- Sarcopenia)	0.75 [95% CI: 0.67-0.84]	0.10
Model 3 (MELD 3.0-L3 SMI)	0.76 [95% CI: 0.67-0.84]	0.03
Composite Model 1 (MELD 3.0, age, sex, race/ethnicity, BMI, insight on alcohol issues)	0.83 [95% CI: 0.76-0.89]	REF
Composite Model 2 (MELD 3.0, SMI, age, sex, race/ethnicity, BMI, insight on alcohol issues)	0.86 [95% CI: 0.81-0.92]	0.02

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to Disclose, Ji Hye Min: Nothing to Disclose, Polly Kirsch: Nothing to Disclose, Irene Kim: Nothing to Disclose, Yee Hui Yeo: Nothing to Disclose, Walid Ayoub: Intercept: Speaking and Teaching, Mirum: Grant/Research Support, GSK: Consultant, GSK: Grant/Research Support, Madrigal: Grant/Research Support, Cymabay: Consultant, Ipsen: Grant/Research Support, Zydus: Grant/Research Support, Alexander Kuo: Nothing to Disclose, Hirsh Trivedi: Nothing to Disclose, Aarshi Vipani: Nothing to Disclose, Yun Wang: Nothing to Disclose, Ekihiro Seki: Nippon Zoki: Research Grant Support, Novonordisc: Consultant, Fasiha Kanwal: Nothing to Disclose, Stephen Pandol: Nothing to Disclose, Debiao Li: Nothing to Disclose, Shelly Lu: Nothing to Disclose, Ju Dong Yang: Consultant relationship with Fujifilm Medical Sciences; Has not ended; Consultant relationship with Exelixis; Has not ended; Consultant relationship with Eisai; Has not ended; Consultant relationship with AstraZeneca; Has not ended; Consultant relationship with Exact Sciences; Has not ended

3038 | INCIDENCE AND PREDICTORS OF LONG-TERM RISKS OF CIRRHOSIS AMONG VETERANS WITH ALCOHOL-ASSOCIATED LIVER DISEASE

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Background: Alcohol-associated liver disease (ALD) has rapidly emerged as the leading cause of end-stage liver disease requiring liver transplantation among U.S. adults. More than one in seven Veterans self-report high risk alcohol use. To better understand the long-term risks of cirrhosis and to identify factors that further increase this risk among Veterans with ALD is critical. We aim to evaluate long-term incidence and predictors of cirrhosis among a national cohort of US Veterans with ALD. **Methods:** Veterans with ALD were identified from 1/1/2010 to 12/31/2018 (with follow-up through 12/31/2023) using national Veterans Affairs (VA) data. ALD was defined as individuals with hepatic steatosis and high-level alcohol use (AUDIT-C >2 for women and >3 for men). Patients with other causes of chronic liver disease or with baseline cirrhosis or hepatocellular carcinoma were excluded. Incidence of cirrhosis (per 100 person-years (py)) was stratified by sex, race/ethnicity, tobacco use, and baseline FIB-4 score. Competing risks cumulative incidence functions and adjusted multivariable Cox proportional hazards models were utilized. **Results:** Among 305,692 Veterans with ALD (94.4% men, mean age 61.0±12.8, 69.5% non-Hispanic white (NHW), 19.6% Black/African American (AA), 8.7% Hispanic, 1.4% Asian-Pacific Islander (API), 0.8% American Indian/Alaska Native (AI/AK)), 59.9% were obese, 6.3% had diabetes, 43.7% reported active tobacco use, and 12.1% had baseline FIB-4 > 2.67. Overall incidence of cirrhosis was 0.66 per 100-py, which was significantly higher in men vs. women, and significantly higher in AI/AN and Hispanics vs. NHW (Figure). Patients with active tobacco use and higher baseline FIB-4 score also had significantly higher risk of cirrhosis. On regression analyses, compared to NHW, risk of cirrhosis was higher in Hispanics (aHR 1.12, 95% CI 1.04-1.20), but lower among AA (aHR 0.76, 95% CI 0.72-0.81). Compared to never smokers, active smokers had greater risk of cirrhosis (HR 1.28, 95% CI 1.22-1.36). Compared to baseline FIB-4 < 1.3, increasing FIB-4 score was associated with incrementally higher risk of cirrhosis (FIB-4 1.3-2.67: aHR 2.36, 95% CI 2.22-2.50; FIB-4 > 2.67: aHR 7.68, 95% CI 7.24-8.16). **Conclusion:** Among a large cohort of US Veterans with ALD, greater risk of cirrhosis was observed among Hispanics and lower risk among AA, when compared to NHW. ALD patients with baseline elevated FIB-4 scores as well as those with continued active tobacco use also have significantly greater risks of cirrhosis.

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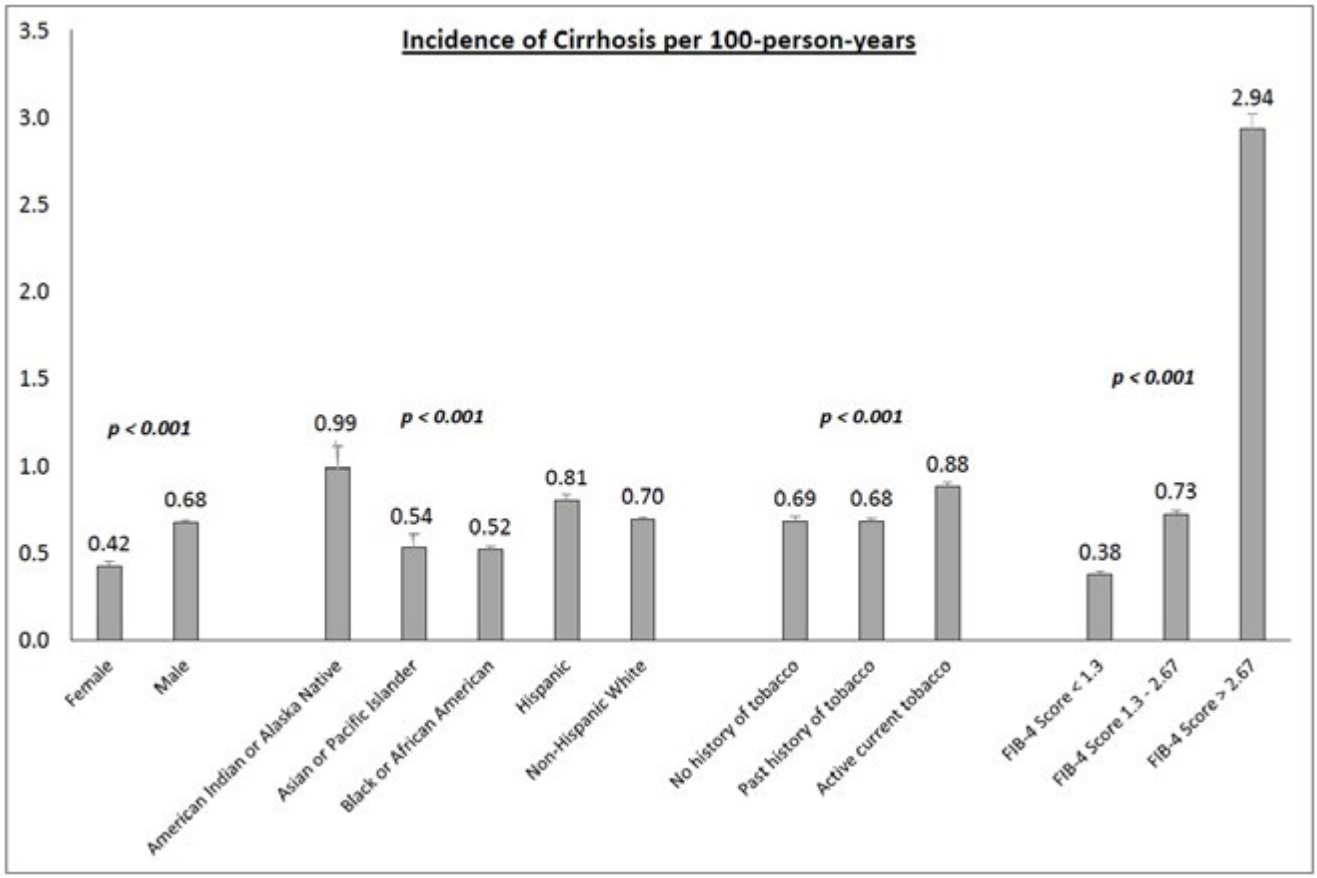

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3039 | DEVELOPMENT OF AN EHR-BASED ALGORITHM TO IDENTIFY RECOMPENSATION IN ALCOHOL-ASSOCIATED LIVER DISEASE

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Background: The development of decompensation, specifically ascites, hepatic encephalopathy, and/or variceal bleeding, represents a watershed point in cirrhosis and is the main indication for transplantation. The transition from compensated to decompensated cirrhosis has long been considered unidirectional. However, the Baveno VII consensus formalized the concept of recompensation in 2021 to describe the subset of patients who improve after initial decompensation when the inciting etiology is removed. Patients who are likely to recompensate can potentially avoid invasive procedures such as transjugular intrahepatic portosystemic shunts (TIPS) and even forego liver transplant evaluation. As such recompensation is of great research interest, but no validated approaches exist to identify recompensation in large datasets. This interest is magnified in alcohol-associated liver disease (ALD) – the leading reason for liver transplantation in the US. Therefore, we aimed to derive an algorithm based on EHR data to identify recompensation in patients with decompensated ALD. **Methods:** Using

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sequential application of validated ICD diagnosis code algorithms for cirrhosis, decompensation, and ALD to the University of Pennsylvania Health System EHR, we identified a cohort with decompensated ALD. Additional inclusion criteria applied were 1) a new diagnosis code for decompensation in the year 2021 (the latest full year of data available), 2) at least 6 months of documented follow-up with multiple GI clinic visits, and 3) residence in Philadelphia based on zip code. Patients with death, liver transplant, or TIPS within 18 months of decompensation were excluded. All medication orders as well as procedures were extracted for this subset. Those with initial evidence of ascites based on diuretics and/or paracentesis orders, or initial evidence of hepatic encephalopathy based on orders for Lactulose and/or Rifaximin, and subsequent absence of these within 1 year were labelled as recompensated. All recompensated individuals' charts were reviewed manually. **Results:** A total of 2,774 patients with decompensated ALD were identified. The analysis cohort was composed of 30 patients and our algorithm identified 6 possible recompensated patients. On manual chart review, 5 out of 6 were confirmed to be truly recompensated. This revealed a recompensation prevalence of 16.7% and gave our algorithm a positive predictive value (PPV) of 83.3%. **Conclusion:** We have successfully created a proof-of-concept algorithm to detect recompensation in patients with decompensated ALD using EHR-based medication and procedure codes. The prevalence of recompensation in our cohort was consistent with reports in prior studies. Although this algorithm has a good PPV, it will require further testing with measurement of PPV and sensitivity in a larger cohort to assess its overall generalizability in identifying recompensation in EHR datasets.

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3040 | A BALANCING ACT: THE LIFE-SAVING POTENTIAL AND DILEMMA OF LIVER TRANSPLANTATION AS AN ENDPOINT IN ALCOHOL-ASSOCIATED HEPATITIS TRIALS

Aparna Goel[1] Allison Kwong[1] Lance Stein[2] Alexandre Louvet[3] Sanjaya Satapathy[4] Ashwini Mehta[5] Steven Flamm[6] Costica Aloman[7] Julie Thompson[8] Amon Asgharpour[9] Daniel Ganger[10] Alexander Kuo[11] Fedja Rochling[12] Nikolaos Pyrsopoulos[13] Mitchell Shiffman[14] Christina Blevins[15] Julie Fergus[16] Deborah Scott[17] William Krebs[17] Jim Brown[17] Norman Sussman[15] WeiQi Lin[17]

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Background: Alcohol-associated hepatitis (AH) is an acute form of alcohol-associated liver disease (ALD) with a high 90-day mortality. Patients admitted with severe AH generally have high MELD scores, and may be referred for liver transplant (LT) evaluation. Without a mandatory pretransplant sobriety period, we have no reliable means of determining, either prospectively or retrospectively, whether liver transplant (LT) is/was necessary for an individual patient to survive. We present data on liver size and question whether patients with normal or large liver volumes might survive without LT. **Methods:** The AHFIRM study was a randomized trial of larsucosterol vs. placebo in the treatment of AH in which we enrolled 307 patients with severe AH. Entry criteria included Maddrey Discriminant Function (MDF) >32 and MELD score 21-30. Twenty-six subjects were waitlisted for LT and 20 received a LT. Demographic and clinical data included MELD scores at enrollment, at listing, and immediately prior to LT. Explant weights and histology were obtained from pathology reports. **Results:** 18/20 transplants were performed in the US and two in Europe. 19/20 (95%) transplant recipients survived 90 days post-LT. Median age was 41 yrs (range 28-61). Median MELD score at enrollment was 26 (21-30) and was 33 at both listing and LT (ranges 24-40 and 27-45 respectively). Six transplanted patients had MELD <30 at listing and 5 had MELD <30 at LT. Median time from the first dose of study drug to LT was 28.5 days (range 14-81), and explant weights varied from 708 to 4407 grams. Explant weight was inversely correlated with age. Six subjects were listed but

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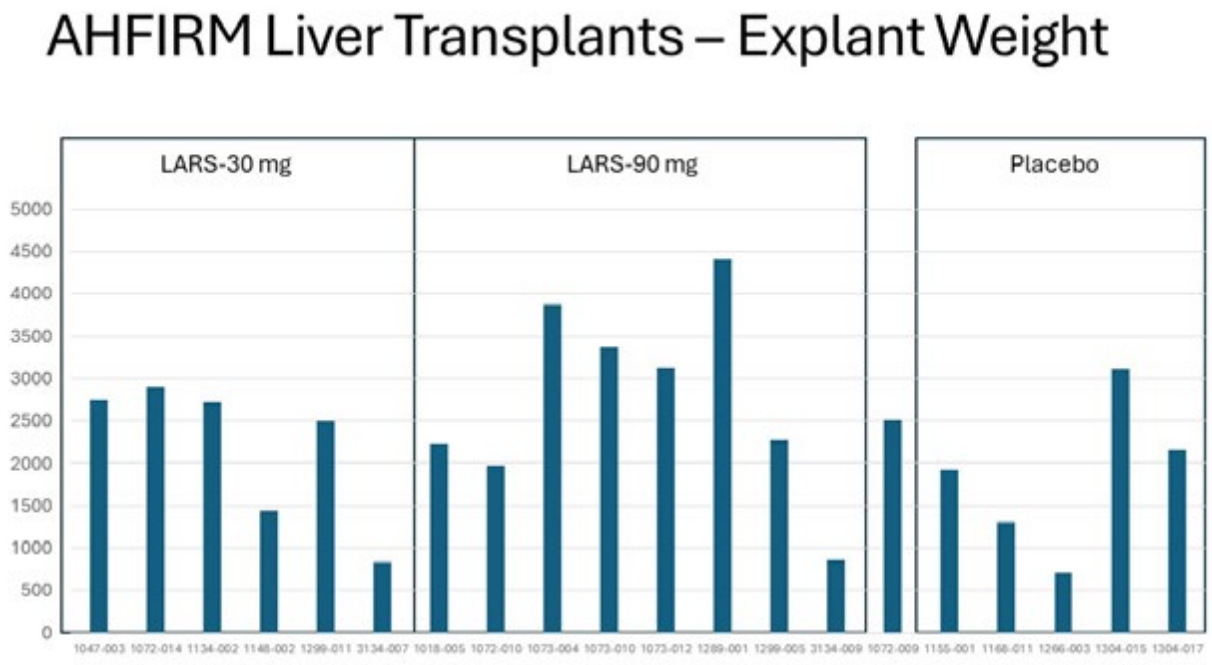
not transplanted; 2 died (both had MELD 30 at listing), one was de-listed, and 3 remained listed at day 90.
Conclusion: The clinical diagnosis of AH does not distinguish the acute inflammatory, and potentially reversible hepatitis that defines AH from severe decompensated cirrhosis. Liver biopsy is done routinely in certain centers, but is not typically performed prior to LT in the US since it has not been associated with improved survival. Small liver size may indicate a lower likelihood of recovery from an episode of severe AH and a large liver may indicate a better chance of hepatic recovery. Death is an undeniable risk in AH, but our results suggest that at least some of the patients transplanted in the AHFIRM study (e.g., those with larger livers) had the potential to recover without LT. Without tools to accurately predict recovery from AH, LT remains a confounding variable when assessing the therapeutic efficacy of drugs for AH. Thus, liver transplant cannot be equated with death, and OLT may confound interpretation of clinical trials. A drug that improves a patient with AH might equally increase or decrease the possibility of OLT.



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Julie Fergus: Nothing to Disclose, Deborah Scott: Nothing to Disclose, William Krebs: DURECT, Incorporated: Independent Contractor, RISE Therapeutics: Independent Contractor, Jim Brown: Durect Corporation: Employee, Norman Sussman: Durect Corporation: Employee, WeiQi Lin: Nothing to Disclose

3041 | COMBINATION OF HIGH-FAT DIET WITH CHRONIC ETHANOL CONSUMPTION IN MICE RESULTS IN EARLY-STAGE ALCOHOL-ASSOCIATED LIVER DISEASE

Marta Szydlowska[1] Misha Goswami[1] Maria Erlandsson[1] Anne-Christine Andréasson[1] Xiao-Rong Peng[1] David Baker[1] Rhianna Laker[1]

[1]AstraZeneca

Background: Alcohol-associated liver disease (ALD) represents a spectrum of liver conditions resulting from chronic, excessive alcohol consumption. It ranges from hepatic steatosis through steatohepatitis with various levels of fibrosis, to cirrhosis that is associated with high risk of mortality. Development of new therapies is limited by the lack of appropriate preclinical models to test drug candidates. The main limitation in rodents is a higher basal metabolism of ethanol, compared with humans, as well as lack of addictive behavior. As a result, *ad libitum* consumption of alcohol alone does not suffice to induce liver damage in mice. To overcome these limitations, we attempted to establish a mouse model of ALD by combining high-fat diet and ethanol consumption. **Methods:** 8-week-old C57Bl6/J male mice received either normal chow with drinking water, normal chow with ethanol, high-fat diet (HFD) with drinking water, or HFD with ethanol for 20 weeks. An additional group received Gubra-Amylin NASH (GAN) diet, known for inducing metabolic-associated steatohepatitis (MASH), for 24 weeks to serve as a positive control. The mice receiving ethanol alternated between 10% ethanol in drinking water from Monday to Wednesday, and 20% from Thursday to Sunday. Body weight was measured throughout, and liver damage was assessed by histology and plasma ALT and AST. **Results:** Mice fed HFD or GAN diet showed significant body weight gain, increased liver weight, and mildly elevated plasma ALT and AST compared with normal chow, regardless of ethanol consumption. The same animals developed advanced liver steatosis, measured via NMR and H&E assessment. Pathologist scoring of H&E detected moderate inflammation but almost no fibrosis development via PSR staining, the latter showing lower score in mice drinking alcohol. In addition, neutrophilic infiltration (Ly6G+) and minor biliary proliferation (CK19), frequently found in patients with ALD, were observed in both HFD groups with no additional effect of ethanol consumption. **Conclusion:** These findings confirm the presence of liver damage in mice fed HFD and ethanol, consistent with clinical observations in early ALD. However, the contribution of ethanol consumption beyond the HFD-induced liver damage is not apparent. Longer treatment time or an alternative mouse strain may be necessary.

Disclosures: Marta Szydlowska: AstraZeneca: Employee, Misha Goswami: Nothing to Disclose, Maria Erlandsson: Nothing to Disclose, Anne-Christine Andréasson: AstraZeneca: shareholdning, Xiao-Rong Peng: AstraZeneca RD Sweden: Employee, David Baker: Nothing to Disclose, Rhianna Laker: Nothing to Disclose

3042 | A NOVEL ROLE OF STARD10 IN ERBB2-MEDIATED LIPOGENESIS IN ALCOHOL-ASSOCIATED LIVER DISEASE

Manisha Dagar[1] Youngyi Lim[1] Swati Chandla[1] Monica Justo[1] Andrea Floris[1] Alfonso Darmawan[1] Maria Lauda Tomasi[1]

[1]Cedars Sinai Medical Center

Background: In developed countries, one of the most important risk factors for liver cirrhosis and HCC is alcoholic steatohepatitis (ASH). Recently, ErbB2 (transmembrane receptors with tyrosine kinase activity) has been described in ASH and correlated with severity of inflammation and signs of longstanding liver injury like liver fibrosis. ErBb2 has the ability to translocate into the nucleus and mediates survival effects in injured hepatocytes. StAR-related lipid transfer domain containing 10 (StarD10) is a phosphorylated protein that positively regulates ErBb2 signalling pathway. We recently reported that ethanol administration lowers StarD10 phosphorylation leading to increased plasma membrane fluidity and induced ErbB2 activity in breast cancer. This study aims to investigate whether phosphorylation of StarD10 regulates lipogenesis via ErbB2 in alcohol associated liver disease (ALD). **Methods:** NIAAA mice livers and primary mouse hepatocytes. Western blot

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and immunoprecipitation. Duolink PLA and immunofluorescence. Lipids binding and membrane fluidity assays. **Results:** We found increased protein levels of StarD10 and ErbB2 in NIAAA livers as well as in ethanol-treated hepatocytes. In addition, ethanol promoted StarD10 and ErbB2 co-immunoprecitation and co-localization in vitro and in vivo. StarD10 was found to bind all phosphatidylinositides species (PIPs) and ethanol treatment increased it further. Overexpression of StarD10 increased membrane fluidity in hepatocytes that presumably caused ErbB2 transactivation and nuclear translocation from plasma membrane. Also, StarD10 overexpression induced SERBP1 and its downstream target genes expression such as FASN and ACC, the de novo lipogenesis related gene. These findings suggest that StarD10 binds to, and may transport, PIPs influencing membrane lipid composition and lipids biosynthesis via ErbB2 pathway. **Conclusion:** This study suggests a potential role for StarD10-induced nuclear ErbB2 to cause liver steatosis upon alcohol treatment. It also opens a wide field of research about functional implications of StarD10 and nuclear ErbB2 cross-talk deducing possible therapeutic strategies in ALD.

Disclosures: Manisha Dagar: Nothing to Disclose, Youngyi Lim: Nothing to Disclose, Swati Chandla: Nothing to Disclose, Monica Justo: Nothing to Disclose, Andrea Floris: Nothing to Disclose, Alfonso Darmawan: Nothing to Disclose, Maria Lauda Tomasi: Nothing to Disclose

3043 | A NOVEL ROLE OF PHOSPHORYLATED UBIQUITIN CONJUGATING ENZYME 9 ON LIPOGENESIS IN ALCOHOL-ASSOCIATED LIVER DISEASE

Swati Chandla[1] Youngyi Lim[2] Andrea Floris[2] Alfonso Darmawan[2] Monica Justo[2] Manisha Dagar[2] Komal Ramani[3] Maria Lauda Tomasi[2]

[1]Cedars Sinai Medical Center, Los Angeles, [2]Cedars Sinai Medical Center, [3]Cedars-Sinai Medical Center

Background: Chronic alcohol consumption leads to hepatocellular injury and liver inflammation by increasing translocation of gut-derived endotoxins to the portal circulation and activating Kupffer cells (KCs). Activation of KCs induces SREBP-1c and CEBP-δ expression, the key players of de novo lipogenesis in hepatocytes, through the NF-κB mediated mechanism. We recently found that alcohol-induced phosphorylation of ubiquitin conjugating enzyme 9 (UBC9), the sole E2 conjugating enzyme for SUMOylation, leads to NF-κB activation in KCs. In this study, we revisited this crosstalk between KCs and hepatocytes to identify novel therapeutic strategies for alcoholic associated liver disease (AALD). **Methods:** We used primary mouse hepatocytes and KCs for in vitro studies followed by NIAAA mouse model for further validation. We also used human steatohepatitis livers (HAS) in the present study. The investigation into the role of phosphorylated UBC9 in AALD involved employing Phospho-peptide mapping, CRISPR/Cas9 UBC9 Y68 editing in vitro, proximity ligation assay (PLA), co-immunoprecipitation, western blot, ELISA, RT-PCR, Oil red O, and H&E stain. **Results:** Activated KCs in vitro and in vivo NIAAA model as well as in HAS revealed that Tyr68 (Y68) of UBC9 is phosphorylated specifically in KCs upon alcohol exposure, and this is mediated by SRC kinase. Alcohol-mediated liver injury and lipogenesis in NIAAA model were prevented by inhibition of SRC activity (PP1 inhibitor) and in vitro by CRISPR/Cas9 editing of UBC9 Y68 to F68 residue that prevented UBC9 phosphorylation and suppressed proinflammatory cytokines expression in KCs. Further, blocking UBC9 Y68 phosphorylation attenuated the levels of SREBP1-c and CEBPδ in hepatocytes and NIAAA mice livers. **Conclusion:** Phosphorylation of UBC9 at Y68 by SRC kinase promotes lipogenesis via SREBP1/CEBPδ induction, suggesting Y68 of UBC9 as a potential therapeutic target for AALD.

Disclosures: Swati Chandla: Nothing to Disclose, Youngyi Lim: Nothing to Disclose, Andrea Floris: Nothing to Disclose, Alfonso Darmawan: Nothing to Disclose, Monica Justo: Nothing to Disclose, Manisha Dagar: Nothing to Disclose, Komal Ramani: Nothing to Disclose, Maria Lauda Tomasi: Nothing to Disclose

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3044 | A ROLE FOR THE C5 COMPLOSOME IN KUPFFER CELL POLARIZATION IN ALCOHOL ASSOCIATED LIVER DISEASE

Shannon Twardy[1] Rebecca McCullough[2]

[1]University of Colorado, Anschutz Medical Campus, [2]Univeristy of Colorado, Anschutz Medical

Background: Complement activation and the resident macrophage Kupffer cells (KCs) play critical roles in the pathogenesis of alcohol associated liver disease (ALD). Ethanol increases production of C5a, a potent anaphylatoxin, leading to immune cell activation via C5a Receptor 1 (C5aR1). During ALD, KCs become hyperinflammatory and secrete proinflammatory cytokines, chemokines, and produce ROS, and in parallel, suppress phagocytosis of debris and pathogenic microbes. Despite the known role of KCs in ALD, the mechanisms of KC hyperinflammatory processes and disease progression are more complex. A newly described function of complement includes intracellular complement activation (complosome) which has been shown to mediate proinflammatory functions in macrophages, however the role for the complosome in KCs during ALD is unknown. We hypothesize that intracellular C5a binding to mitochondrial C5aR1 (mtC5aR1) contributes to hyperinflammatory phenotypes including macrophage polarization, mtROS production and impaired phagocytosis, following ethanol and LPS exposure. **Methods:** Here, immortalized mouse KCs (ImKCs) were sensitized to 50mM ethanol (18hrs) then challenged with 10ng/mL lipopolysaccharide (LPS) for up to 24 hours. CRISPR-Cas9 technologies to knockout C5 and C5aR1, along with cell permeable and impermeable C5aR1 antagonists, are used to elucidate the role of the complosome in expression of macrophage polarization markers, mtROS production, and phagocytosis. **Results:** Complosome component expression, including C5 and C5aR1, were increased following EtOH and LPS exposure and mtC5aR1 localization increased 50-fold following a 24 hour ethanol treatment. Ethanol and LPS exposure enhanced macrophage pro-inflammatory markers, including CD86 and iNOS, and suppressed anti-inflammatory marker CD206 and phagocytosis of pHrodo *E. coli* conjugated fluorescent beads. In turn, ImKCs deficient in C5 or C5aR1 suppressed ethanol- and LPS-induced pro-inflammatory polarization markers and increased anti-inflammatory marker and phagocytosis. Ethanol alone and in combination with LPS increased mtROS, which was significantly decreased by pre-treatment of cell permeable C5aR1 antagonist JPE1375, but not cell impermeable C5aR1 antagonist PMX205. **Conclusion:** These data potentially suggesting mtC5aR1 localization as an important sensitization step proceeding detection of pathogen-associated molecules (LPS) and the C5 complosome may be an important mediator of KC hyperinflammatory response in the context of ALD.

Disclosures: Shannon Twardy: Nothing to Disclose, Rebecca McCullough: Nothing to Disclose

3045 | TRENDS IN ALCOHOL-ASSOCIATED HEPATITIS AMONG U.S. VETERANS: EXPLORING ALTERNATIVE DEFINITIONS BEYOND SOLELY USING ICD-9/10 CODES TO IMPROVE ACCURATE ESTIMATES OF DISEASE BURDEN

Zeyuan Yang[1] Vicki Wing-Ki Hui[2] Ramsey Cheung[3] Che To Jimmy Lai[2] Terry Cheuk-Fung Yip[2] Vincent Wong[2] Grace Wong[2] Robert Wong[1]

[1]VA Palo Alto Healthcare System, [2]The Chinese University of Hong Kong, [3]Stanford University Medical Center

Background: The burden of alcohol-associated liver disease and alcohol-associated hepatitis (AH) has been exacerbated by increasing high-risk alcohol use during and following the COVID-19 pandemic. Accurate estimates of AH burden are lacking due to limitations of ICD-9/10 codes and lack of longitudinal alcohol use data in many datasets. We aim to evaluate trends in AH burden among U.S. Veterans and explore alternative definitions beyond solely using ICD-9/10 codes to better estimate true AH clinical burden. **Methods:** All Veterans utilizing Veterans Affairs healthcare facilities in the U.S. from 1/1/2010 to 12/31/2023 with ≥1 clinical encounter/year were included. AH (*Definition #1*) was identified using definitions from previously published studies and included both Criteria A (≥1 AH-related ICD-9/10 diagnosis code [571.1, K70.10, K70.11]) and Criteria B (≥3 of the following lab criteria: ALT or AST > 50 IU/L; AST:ALT ratio > 2; INR > 2; bilirubin > 3.0 mg/dL, within +/- 30 days). Two alternative AH definitions were evaluated that incorporated Criteria C (high risk alcohol use: AUDIT-C >2 for women, >3 for men): *Definition #2* (Criteria A+B or A+C) and *Definition #3* (Criteria A+B or B+C). Rates of AH (per 100,000 person-years (py)) were calculated annually and were stratified by age, sex, and race/ethnicity. Comparisons of AH trends utilized the trends test, and comparisons of rates between groups utilized the

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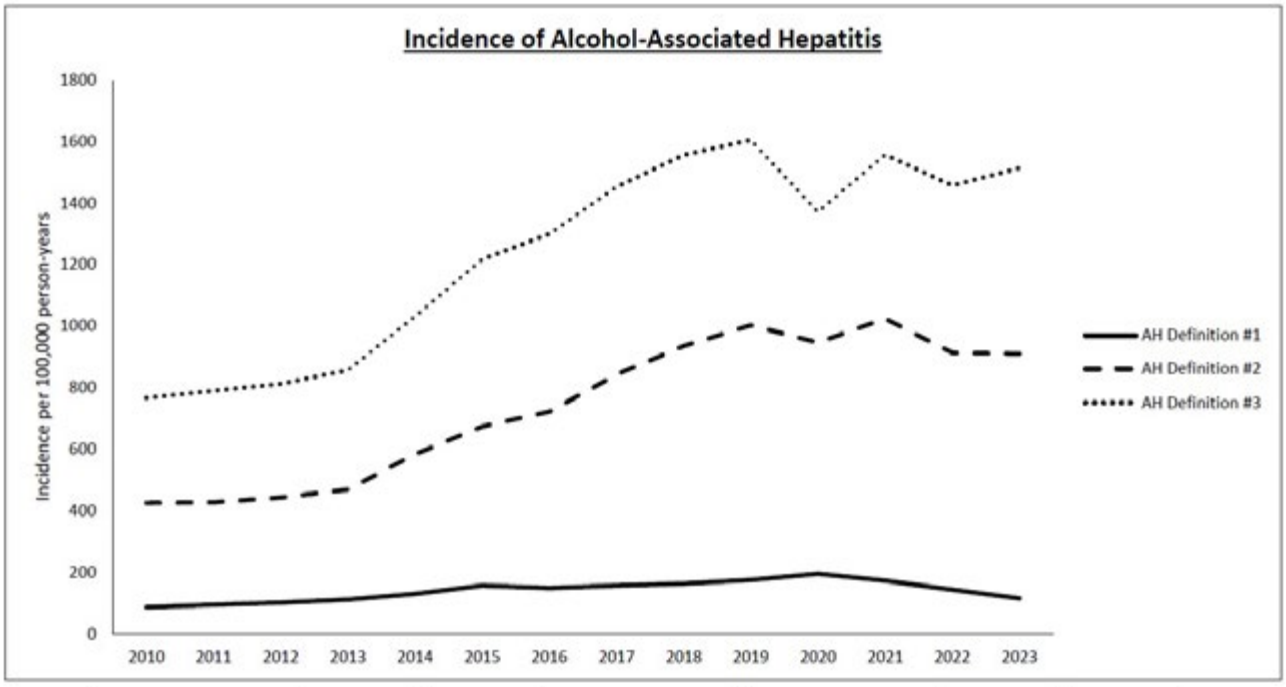
z-statistic. **Results:** Overall AH rates (Definition #1) increased from 86 to a peak of 195 per 100,000-py from 2010 to 2020, then declined to 115 per 100,000-py in 2023 (Figure). When evaluating alternative definitions, AH rates similarly rose rapidly, peaking 2020-2021, and then appeared to plateau (Definition #2:426 to 1,024 per 100,000-py (2010 to 2021), plateaued to 910 per 100,000-py in 2023; Definition #3: 767 to 1,558 per 100,000-py (2010 to 2021), plateaued to 1,515 per 100,000-py in 2023). Across all 3 definitions, AH rates in 2023 were significantly higher in women vs. men (e.g. Definition #3: 1,577 vs. 997 per 100,000-py, p<0.01) and highest in American Indian/Alaska Natives (e.g. Definition #3: 2,197 vs. 1,441 in non-Hispanic whites, p<0.01). When stratified by age, highest rates of AH were observed among Veterans age 50-69 years. **Conclusion:** Increasing rates of AH among Veterans appeared to have peaked in 2020-2021 and have since plateaued. Incorporating longitudinal alcohol use together with ICD-9/10 codes and lab data led to 8 times higher estimated clinical burden of AH.



	A	B	C
	ICD-9/10 Codes (571.1, K70.10, K70.11)	≥ 3 Laboratory Criteria: 1) ALT or AST > 50 IU/L; 2)AST:ALT ratio > 2; 3) INR > 2; 4) bilirubin > 3.0 mg/dL	AUDIT-C > 2 for women AUDIT-C > 3 for men
AH Definition #1	***A + B***		
AH Definition #2	***A+B or A+C***		
AH Definition #3	***A+B or B+C***		

Disclosures: Zeyuan Yang: Nothing to Disclose, Vicki Wing-Ki Hui: Nothing to Disclose, Ramsey Cheung: Nothing to Disclose, Che To Jimmy Lai: Nothing to Disclose, Terry Cheuk-Fung Yip: Gilead Sciences: Consultant, Gilead Sciences: Advisor, Gilead Sciences: Speaking and Teaching, Vincent Wong: Abbott: Speaking and Teaching, AbbVie: Advisor, AbbVie: Speaking and Teaching, Boehringer Ingelheim: Advisor, Echosens: Advisor, Echosens: Speaking and Teaching, Gilead Sciences: Advisor, Gilead Sciences: Speaking and Teaching, Gilead Sciences: Grant/Research Support, Intercept: Advisor, Inventiva: Advisor, Novo Nordisk: Advisor, Novo Nordisk: Speaking and Teaching, Pfizer: Advisor, Sagimet: Advisor, TARGET PharmaSolutions: Advisor, Unilab: Speaking and Teaching, Visirna: Consultant, Illuminatio Medical Technology: Stock – privately held company, Grace Wong: AstraZeneca: Advisor, Gilead Sciences: Advisor, Gilead Sciences: Speaking and Teaching, Janssen: Advisor, GSK: Advisor, GSK: Speaking and Teaching, Abbott: Speaking and Teaching, AbbVie: Speaking and Teaching, AstraZeneca, Gilead Sciences, GlaxoSmithKline and Janssen,: Advisor, Abbott, AbbVie, Ascletis, Bristol-Myers Squibb, Echosens, Gi: Speaking and Teaching, Gilead Sciences: Grant/Research Support, AstraZeneca, Gilead Sciences, GlaxoSmithKline and Janssen: Consultant, Abbott, AbbVie, Ascletis, Bristol-Myers Squibb, Echosens, Gi: Speaking and Teaching, AstraZeneca, Gilead Sciences, GlaxoSmithKline Pharmaceutical: Consultant, Gilead Sciences: Independent Contractor, AstraZeneca, Gilead Sciences, GSK and Janssen,: Advisor, Abbott, AbbVie, BMS, Gilead Sciences, GSK, Janssen, Roche: Speaking and Teaching, Gilead Sciences: Grant/Research

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3046 | UBC9 PHOSPHORYLATION REGULATES CYTOKINE SECRETORY SIGNALING IN ALCOHOLIC ASSOCIATED LIVER DISEASE

Youngyi Lim[1] Andrea Floris[1] Manisha Dagar[1] Swati Chandla[1] Maria Lauda Tomasi[1]

[1]Cedars Sinai Medical Center

Background: Alcohol metabolism-induced oxidative stresses result in hepatocyte injury, leading to the release of damage-associated molecular patterns (DAMPs) into the extracellular environment, which contributes to tissue inflammation. DAMPs are packaged in extracellular vesicles (EVs) and enable crosstalk between hepatocytes and non-parenchymal cells such as Kupffer cells (KCs). EVs have emerged to be implicated in the pathogenesis of alcoholic hepatitis. However, the underlying mechanisms of EVs in cell-to-cell communication and alcohol associated liver disease (AALD) pathogenesis are unknown. We demonstrated that Ubiquitin conjugating enzyme 9 (UBC9), the sole E2 enzyme essential for SUMOylation, plays a key role on inflammatory response and AALD development. The current study investigated whether the interaction between UBC9 and RABs may facilitate cytokine secretion and EV endocytosis, thereby causing KCs activation. **Methods:** NIAAA alcohol fed model and primary mouse hepatocytes. Co-immunoprecipitation, western blot, ELISA and Oil Red staining. **Results:** We found that UBC9 is phosphorylated at tyrosine 68 residue (Y68) in KCs from liver of NIAAA mice. Thus, we mutated UBC9 Y68 to phenylalanine (F68) using CRISPR-HDR gene editing technology that resulted in prevention of proinflammatory cytokine expression such as IL-1β, IL-6 and TNF-α, consistently with a strong inhibition of TNF-α secretion compared to control. This data suggests that phosphorylated UBC9 (pUBC9) might be involved in cytokine secretory signaling. This notion is further supported by proteomics data, which showed that pUBC9 interacted with several RAB family members which are scaffold proteins involved on the secretion of chemokines and cytokines by upregulating endocytosis and phagocytosis. We found that pUBC9 interacted with RAB1A, RAB5A, and RAB14 in alcohol-activated KCs compared with control cells from NIAAA mouse livers; similar results were obtained from LPS-activated KCs. UBC9 Y68 gene editing increases RAB1b SUMOylation and lowers TNF-α secretion in LPS-treated KCs. Inhibition of UBC9 Y68 phosphorylation in KCs prevented de novo lipogenesis in co-cultured, ethanol-treated hepatocytes. **Conclusion:** Our findings provide highly novel insights on the role of pUBC9 in RABs activity and/or expression that could impact on EVs internalization in AALD.

Disclosures: Youngyi Lim: Nothing to Disclose, Andrea Floris: Nothing to Disclose, Manisha Dagar: Nothing to Disclose, Swati Chandla: Nothing to Disclose, Maria Lauda Tomasi: Nothing to Disclose

3047 | ENGAGEMENT WITH ADDICTION MEDICINE POST-LIVER TRANSPLANT INCREASES TREATMENT FOR ALCOHOL USE DISORDER

Mounica Konjeti[1] Jessica Musto[1] Thomas Piasecki[1] John Rice[1]

[1]University of Wisconsin

Background: Alcohol-associated liver disease (ALD) is now the leading indication for liver transplant (LT). Understanding post-LT patterns of alcohol use and optimal alcohol use disorder interventions are important for positive post-LT outcomes. **Methods:** Single-center retrospective study of adult recipients of primary LT for ALD between 2015-2021, with follow-up through 2024. Detailed alcohol use, biomarker, and treatment data were gathered at 3 month intervals post-LT. Those who self-reported heavy alcohol use or had a PETH >200 without a period of sustained remission and actively drinking at last clinical contact were classified as engaging in high-risk drinking. Logistic regression was used to identify factors associated with relapse to alcohol use, remission after relapse, graft loss and mortality. **Results:** Of 217 patients who underwent LT for a primary indication of ALD, 76 (35%) relapsed to alcohol use post-transplant. Of the 76 patients who relapsed, 46 (60%) were classified as high risk and 16 (21%) lost their grafts. Patients with social support concerns pre-transplant were more likely to engage in high-risk alcohol use (OR 2.26, p=0.027) as well as those with a comorbid psychiatric diagnosis (OR 2.63, p=0.028). Transplant addiction medicine (AODA) reached out to patients that relapsed (median attempts 5,

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range 0-51) yielding a median of 2 contacts (range 0-43) per patient. Number of AODA contacts was a significant predictor of patients engaging in formal treatment (OR 1.58, p<0.001), attending peer support (OR 1.10, p=0.019) and using medications for alcohol use disorder (MAUD) (OR 1.34, p=0.001). Though the use of MAUD was not significantly associated with graft loss, of the 23 patients who used MAUD only 3 (13%) lost their grafts vs 13/53 (25%) of those who did not. Patients declining AODA contact was also not significantly associated with graft loss but of the 6 who refused contact 3 (50%) lost their grafts vs 13/70 (23%) of those who engaged with AODA. **Conclusion:** Relapse to alcohol use post-liver transplant is more common in patients with poor social support and comorbid psychiatric diagnoses. Contact with a dedicated transplant AODA counselor led to more engagement in treatment for alcohol use disorder in the form of counseling, peer support and medications for alcohol use disorder.

Disclosures: Mounica Konjeti: Nothing to Disclose, Jessica Musto: Nothing to Disclose, Thomas Piasecki: Nothing to Disclose, John Rice: Nothing to Disclose

3048 | THE HISTOLOGIC FEATURES OF SEVERE ALCOHOL-ASSOCIATED HEPATITIS UNDERGOING LIVER TRANSPLANTATION: AN EXPLANT STUDY

Chad Spencer[1] Michael Idowu[1] Kevin Houston[1] Nikita Chadha[1] Nikki Duong[2] David Bruno[1] Joel Wedd[1] Richard Sterling[1]

[1]Virginia Commonwealth University, [2]Stanford University

Background: Alcohol-related liver disease (ALD) is the leading indication for liver transplantation (LT) in the United States. Severe alcohol-associated hepatitis (AAH) can present with acute decompensation (i.e., ascites, hepatic encephalopathy, variceal bleeding) in patients without a known history of liver disease, often making it difficult to elucidate underlying chronic liver disease severity. Furthermore, many with AAH have extrahepatic organ failure similar to those with chronic ALD. However, AAH has not been classified as acute on chronic liver failure (ACLF). We evaluated explants to assess the histologic features in patients undergoing LT for severe AAH in order to identify the prevalence of cirrhosis and determine if these patients in fact had ACLF. **Methods:** A retrospective single-center review of clinical data and explant pathology in of 44 LT patients with severe AAH between 2019-2022 was conducted. Severe AAH was defined as MELD ≥ 20 or Maddrey Discriminant Function > 32 in the setting recent alcohol use, meeting the NIAAA definition. ACLF was defined by the North American Consortium for the Study of End-Stage Liver Disease. The explants were reviewed by an expert hepatic pathologist with focus on histologic fibrosis staging and microscopic features of AAH and steatohepatitis for steatosis grade, Mallory bodies, cytologic ballooning, lobular and portal inflammation, neutrophilic infiltration, bilirubinostasis, and megamitochondria. Continuous variables were described as means with standard deviations and categorical variables were described as percentages. **Results:** The mean MELD of the cohort was 36 +/- 7. Average age at the time of LT was 43 +/- 11.5 years. Fifty-nine percent of patients were male and 93% were white. Ninety-seven percent had ascites, 64% had hepatic encephalopathy, 9% had portal hypertensive bleeding, and 58% met the NACSELD definition of ACLF. The mean explant weight was 1933 +/- 721 g. On histologic evaluation (table 1), 59% of explants had macrosteatosis, 91% had Mallory bodies, 84% had cytologic ballooning, 95% had lobular inflammation, 98% had portal inflammation, 70% had neutrophilic infiltration, 97% had bilirubinostasis, and 25% had megamitochondria. Fibrosis assessment revealed cirrhosis in 43 of 44 explants (98%) and bridging fibrosis in 1 explant. **Conclusion:** We describe detailed histopathology in those undergoing LT. Almost all explants of LT patients with severe AAH had cirrhosis and histologic features of severe AAH. Given that features of ACLF and extrahepatic manifestations of ALD were common, these findings suggest that severe AAH should be classified as ACLF, which carries a high short-term mortality, portends a poor prognosis, and urgently warrants further study.

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Table 1

Clinical Characteristics and Explant Features of Patients Transplanted for Severe AAH (n = 44)

Patient Characteristics	Mean (standard deviation) or percentage
Age, years	43 (11.5)
Male	59%
Positive PEth	88%
MELD	36 (7)
Portal Hypertension	
Ascites	98%
Hepatic encephalopathy	66%
GI bleeding	9%
Gross Explant Features	
Weight, grams	1933 (721)
Volume, cm^3	4929 (2026)
Histologic Explant Features	
Fibrosis	
Cirrhosis	98%
Bridging	2%
Steatosis grade	
S0	41%
S1	30%
S2	11%
S3	18%
Mallory bodies	
None	9%
Few	32%
Many	59%
Ballooning	
None	16%
Few	34%
Many	50%
Lobular inflammation	
None	5%
2-4 foci/hpf	34%
>4 foci/hpf	61%
Portal inflammation	
None	2%
Mild	66%
> Mild	32%
Neutrophilic Infiltration	70%
Bilirubinostasis	97%
Megamitochondria	25%

Disclosures: Chad Spencer: Nothing to Disclose, Michael Idowu: Nothing to Disclose, Kevin Houston: Nothing to Disclose, Nikita Chadha: Nothing to Disclose, Nikki Duong: Nothing to Disclose, David Bruno: Nothing to Disclose, Joel Wedd: Nothing to Disclose, Richard Sterling: Grant/Research Support relationship with HCV Vax; Has not ended; Grant/Research Support relationship with GSK; Has not ended; Grant/Research Support relationship with Gilead; Has not ended; Grant/Research Support relationship with Roche; Has not ended; Grant/Research Support relationship with AbbVie; Has not ended; Grant/Research Support relationship with Abott; Has not ended; GI Specialty Board relationship with ABIM; Has not ended

3049 | GLOBAL LANDSCAPE OF SKELETAL MUSCLE MITOCHONDRIAL FUNCTIONAL AND STRUCTURAL PERTURBATIONS IN SARCOPENIA OF ALCOHOL RELATED LIVER DISEASE

Nicole Welch[1] Pugazhendhi Kannan[1] Saurabh Mishra[1] Annette Bellar[1] Laura Nagy[2] Srinivasan Dasarathy[1]

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Background: Skeletal muscle mitochondrial oxidative dysfunction and oxidative stress contribute to sarcopenia of in alcohol related liver disease. However, the global mitochondrial perturbations are not well described. We

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used a multiomics directed integrated experimental validation to identify the mechanisms of skeletal muscle mitochondrial dysfunction in alcohol related liver disease in a comprehensive array of models. **Methods:** A comprehensive array of multiomics data, including ATACseq, bulk RNAseq, untargeted proteomics, global acetylomics, phosphoproteomics, and untargeted metabolomics, was generated from multiple models of sarcopenia in ALD to identify global mitochondrial differentially expressed molecules (DEM). Complementary horizontal and vertical integration of DEM using supervised and unsupervised approaches were used to generate Upset plots, heatmaps, volcano plots, and pathway enrichments. Data from differentiated murine myotubes, human induced pluripotent stem cell-derived myotubes (hiPSCm), gastrocnemius muscle from mice with ALD (mALD), and rectus abdominis muscle from patients with ALD were evaluated. Targeted experimental validation was performed in murine myotubes/muscle tissue from mALD for mitochondrial oxidative function using high sensitivity respirofluorometry, structural evaluation of mitochondrial morphology using confocal microscopy, cristae morphology on 3D electron microscopy, HIF1a, and myostatin expression by immunoblots. Expression of critical components of electron transport chain complexes, HIF1a, and myostatin (regulates mTOR signaling) with mitochondrial Lactobacillus brevis NAD oxidase (MitoLbNOX) was quantified. **Results:** We noted distinct patterns of temporal clusters of DEM that included early transient, persistent, late, and pseudosilent. Global multiomics analyses showed enrichment of mitochondrial dysfunction and oxidative phosphorylation pathways in response to ethanol. Integrated pathway analyses showed enrichment of circadian rhythm, HIF1a, mTOR signaling in the early transient and while mitochondrial dysfunction was enriched in late and persistent response clusters. Experimentally, in hiPSCm, mitochondrial oxidative dysfunction was consistent with prior reports in murine myotube/muscle tissue (Fig1A). Mitochondria showed less fission, with concordant changes in Fis1 and MFF (less expression) on immunoblots (Fig1B). On 3D EM, mitochondrial cristae spacing was less with ET and consistently, on RNAseq, cristae formation geneset showed significant alterations (Fig1C). Expression of HIF1a and myostatin were higher with ET in myotubes and muscle tissue. In response to MitoLbNOX, increased HIF1a and myostatin expression with ET was reversed (Fig1D). Conclusion: Integrated multiomics analyses showed perturbations in skeletal muscle mitochondrial function and structure with stabilization of HIF1a and myostatin

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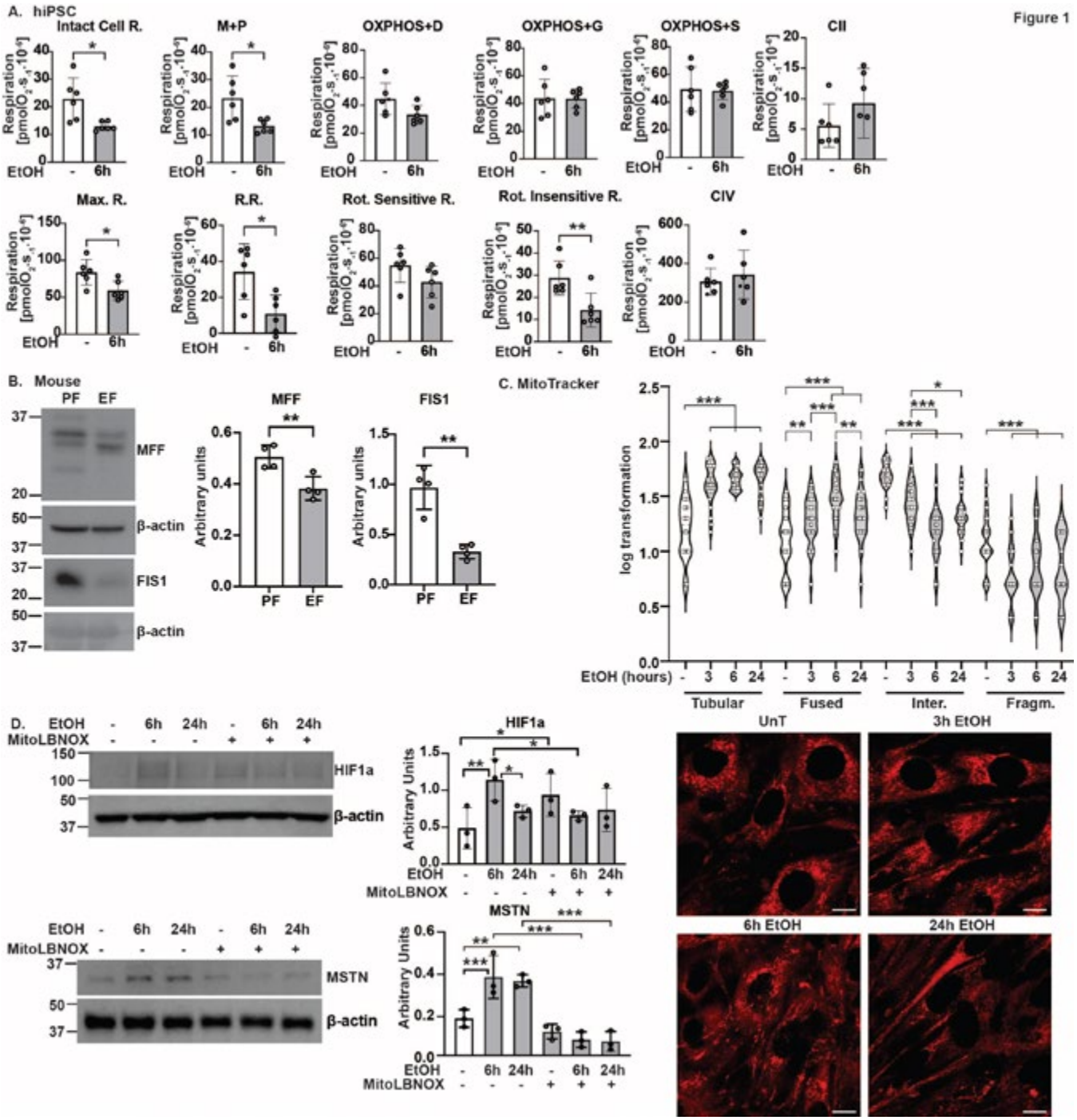

Disclosures: Nicole Welch: Nothing to Disclose, Pugazhendhi Kannan: Nothing to Disclose, Saurabh Mishra: Nothing to Disclose, Annette Bellar: Nothing to Disclose, Laura Nagy: Nothing to Disclose, Srinivasan Dasarathy: Nothing to Disclose

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3050 | THE ROLE OF PSYCHOTHERAPY ALONE IN REDUCING ALCOHOL RETURN TO DRINKING IN PATIENTS WITH CHRONIC LIVER DISEASES: A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

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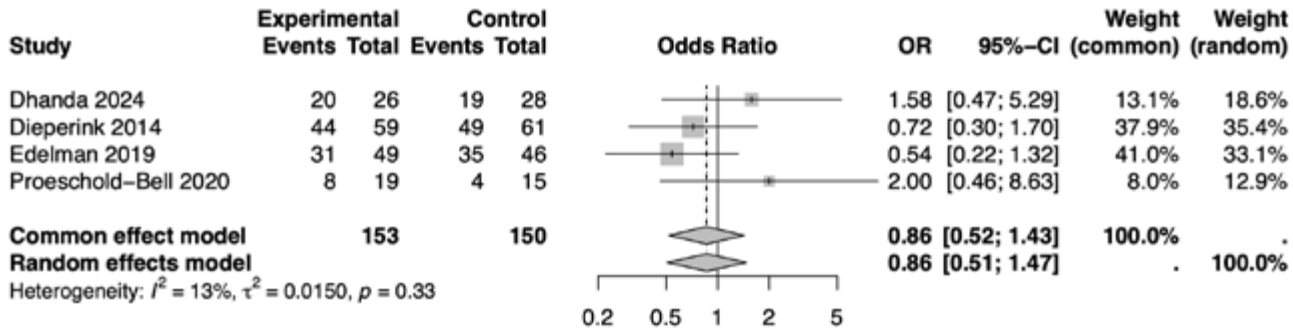
Background: Psychosocial interventions are effective in alcohol cessation, but many studies are conducted on alcohol use disorder (AUD) patients. Recent meta-analyses showed the effectiveness of pharmacotherapy in conjunction with psychosocial interventions to reduce the return to drinking in AUD, but there is limited data on psychosocial therapy alone. Thus, we aim to evaluate the effectiveness of psychosocial therapy in patients with chronic liver disease (CLD) with AUD. **Methods:** A systematic review, assisted by an NIH librarian and databases (PubMed, Embase, CENTRAL, APA PsycInfo), identified eligible RCTs and observational studies on psychosocial interventions for CLD with AUD. Search terms included various CLD and AUD terms, filtered for interventions like “cognitive behavioral therapy (CBT),” “motivational interview,” or “psychosocial intervention.” The primary outcome was return to drinking alcohol. Two reviewers independently reviewed and extracted data. Selected RCTs were included in the meta-analysis. Statistical analysis was performed using R-4.4.0 with “meta” and “metafor” packages. Odds ratios were calculated using the Mantel-Haenszel method with random and fixed effects models. Heterogeneity was assessed using the Q-test and quantified by I^2 and tau^2 statistics. **Results:** A total of 2,275 studies retrieved by March 25, 2024, were imported for screening, with only 50 studies eligible for full-text review. 25 studies were further excluded because the articles were not in English or had wrong interventions or endpoints. 25 studies were included, but ultimately 4 RCTs from 2014-2024 were included in the meta-analysis. A majority (3) of the studies were conducted in the US while one study was conducted in England. All studies evaluated return to drinking at 6 months, except one study had a 3-month follow-up. Most studies used motivational enhancement therapy (MET), one study combined MET with CBT, and only one used functional imagery training (FIT). Most of the studies compared psychotherapy to standard care, and in two studies, all participants received brief interventions. The odds ratio for the effect of psychosocial therapy on alcohol relapse for fixed and random effects model was 0.86 (95% CI 0.52-1.43, p=0.56) and 0.86 (95% CI 0.51-1.47, p=0.59), which were not statistically significant. The I^2 was 13.1% with little heterogeneity and Q test of heterogeneity p-value = 0.33. **Conclusion:** In this meta-analysis, psychosocial intervention alone was not statistically significant in reducing alcohol return to drinking when compared to the standard of care in patients with CLD with AUD. Given limited literature, more studies are needed to evaluate the effectiveness of psychosocial interventions alone in patients with CLD with AUD.



Disclosures: Christopher Sollenberger: Amphix Bio: Employee, Huai-En Chang: Nothing to Disclose, Mohammed Rifat Shaik: Nothing to Disclose, Hanna Blaney: Nothing to Disclose, Nancy Terry: Nothing to Disclose, Nancy Diazgranados: Nothing to Disclose, Christine Hsu: Nothing to Disclose

3051 | HEPATIC STELLATE CELLS AND ALCOHOL: INVESTIGATING CANONICAL WNT/ß-CATENIN SIGNALING IN MODELS OF ALCOHOL-ASSOCIATED LIVER DISEASE

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Lauren Rutt[1] *Rebecca McCullough*[2]

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Background: Alcohol-associated Liver Disease (ALD) is a leading cause of liver-related mortality and involves nearly 61 percent of the American population. Moreover, patients with progressive ALD have stage 3-4 fibrosis, yet there remains no effective antifibrotic therapies available for patients with fibrosis. Hepatic stellate cells (HSC) play a key role in the initiation and progression of liver fibrosis by secreting fibrogenic factors and accumulation of extracellular matrix. Despite this knowledge, detailed mechanisms driving HSC activation during fibrosis are highly complex and not well understood. Wnt proteins are morphogens that elicit a multitude of cellular responses via canonical ß-catenin-dependent and noncanonical, ß-catenin-independent signals and the association and release of YAP/TAZ from the ß-catenin destruction complex have been recently implicated in HSC activation. It is our working hypothesis that alcohol increases the expression of transducers of Wnts, leading to Wnt-dependent activation of ß-catenin, via activation of YAP/TAZ to promote HSC transdifferentiation in the liver during the early pathogenesis of fibrosis in ALD. **Methods:** To investigate this, we make use of murine models of chronic ethanol feeding (6%v/v, 25 days) and moderate ethanol (2%v/v) exposure superimposed with carbon tetrachloride (CCl_4) and models of culture-induced activation of primary mouse HSCs and human HSCs (LX2) cells. **Results:** *In vivo*, chronic ethanol feeding to mice increased Wnt3a and Wnt5a positive cells, which colocalize with hepatocyte nuclear factor-4 alpha (HNF4α). In models of moderate ethanol exposure superimposed with CCl_4 characterized by activated HSCs, the expression and nuclear localization of ß-catenin and YAP expression was increased by ethanol. *In vitro*, α-SMA protein expression was increased in primary mouse HSCs following exogenous challenge of Transforming Growth Factor ß, Wnt3a, and Wnt5a, which was further increased by the combination of ethanol. mRNA expression of the transducers of Wnts, Frizzled (*fzd2* and *fzd7)*, were increased by day 7 of culture, and was further increased by ethanol. Following ethanol challenge, expression of YAP/TAZ target genes, *ctgf* and *dkk-1*, were increased in human LX2s. **Conclusion:** These data reveal that ethanol induces Wnt-mediated activation of mHSCs *in vitro* and *in vivo,* and that Wnt/ß-catenin may play causative roles in HSC activation and regulating the fibrogenic program in ALD.

Disclosures: Lauren Rutt: Nothing to Disclose, Rebecca McCullough: Nothing to Disclose

3052 | NALTREXONE USE IN PATIENTS WITH COMBINED METABOLIC AND ALCOHOL-ASSOCIATED LIVER DISEASE (METALD), PROPENSITY SCORE MATCHED STUDY

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Background: Naltrexone has demonstrated efficacy in management of alcohol use disorder. Furthermore, Naltrexone combined with bupropion is approved therapy for weight management in patients with obesity. Thus, we hypothesize that long-term use of Naltrexone may benefit patients with combined metabolic and alcohol-associated liver disease (MetALD) with lower rates of decompensated liver disease. **Methods:** This is a retrospective cohort of patients with steatotic liver disease due to MetALD. Data is based on the National Eversana database. MetALD was defined based on presence of steatotic liver disease and a history of both metabolic dysfunction and excessive alcohol use. Metabolic dysfunction was defined as the presence of at least one out of five cardiometabolic risk factors [1-BMI >25, 2-Hgb A1c >5.7% or diagnosis of diabetes mellitus (DM), 3-blood pressure >130/80 or being on antihypertensive medication, 4-triglyceride >150 mg/dL or being on statin therapy, 5-HDL less than 40 mg/dL or being on statin]. Patients with a diagnosis of cirrhosis or decompensated liver disease were excluded at the time of entry to the study. Patients were categorized into intervention group with exposure to Naltrexone therapy for at least 3 months versus conventional therapy (no-Naltrexone exposure). Patients were followed for incidence of decompensated liver disease or death. Basic and propensity score (PS) matching were performed to limit confounding factors. **Results:** We identified 1,273 MetALD patients exposed to Naltrexone and 25,000 patients with no exposure to Naltrexone. There was no significant difference in demographic characteristics between the two groups. While patients in Naltrexone group had lower rate of comorbid conditions, the difference was balanced in PS-matched groups. Naltrexone use did not result in significant reduction in BMI, hemoglobin A1c, or serum transaminases. Among patients who received naltrexone, 90 (7.1%) patients developed incident decompensated cirrhosis, compared to 2683 (10.7%) patients in the no-Naltrexone group (p <0.01). In time-to-even analysis, Naltrexone use significantly decreased the long-term risk

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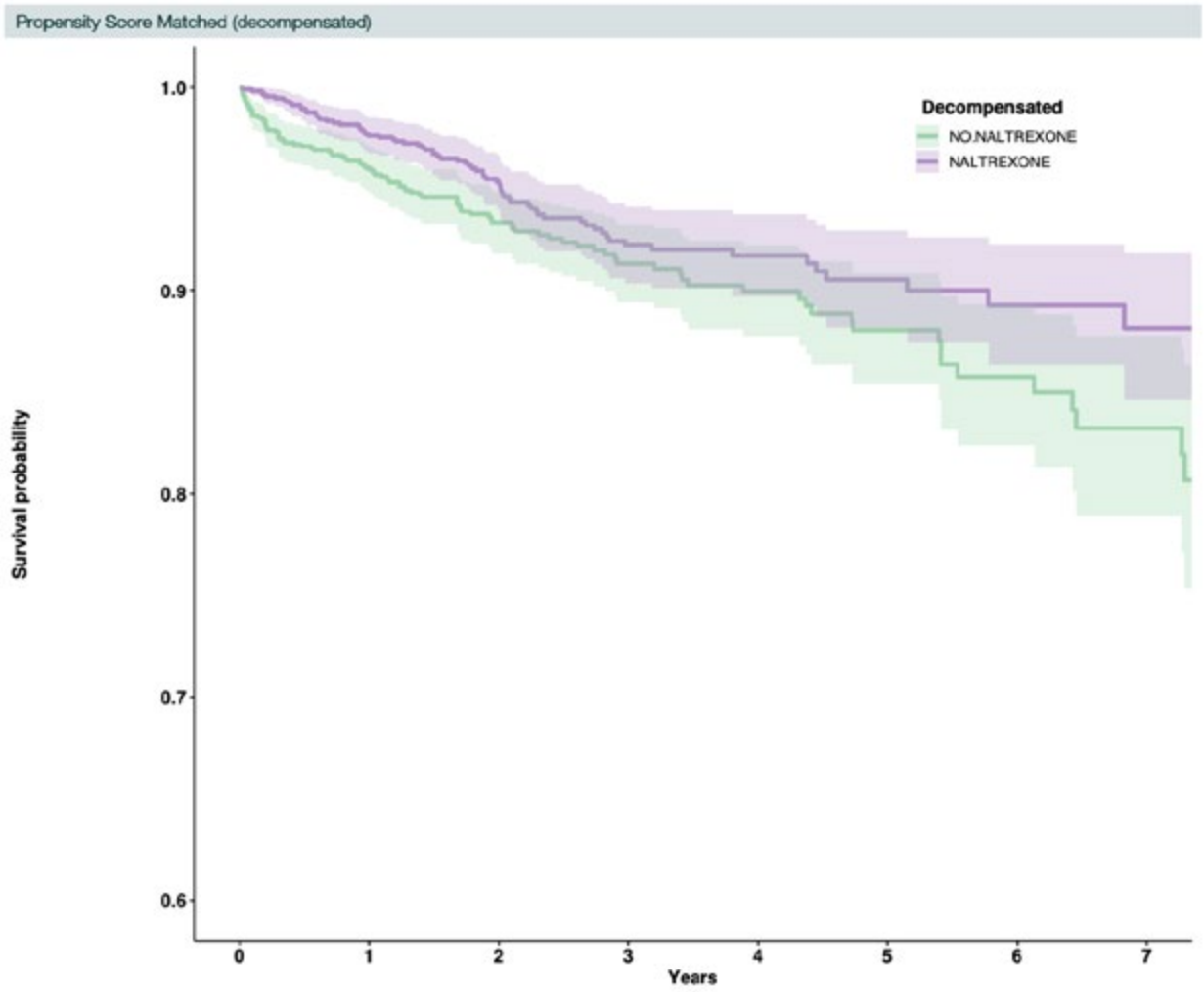
of decompensated liver disease (HR, 0.7; 95%CI, 0.53-0.8; p <0.01). After PS matching, the association remained significant. Naltrexone use was also associated with lower mortality in unmatched analysis (HR, 0.7; 95% CI, 0.5-0.09; p <0.01] and after PS matching (HR 0.66; 95%CI, 0.5-0.9; p=0.018). **Conclusion:** Naltrexone use in patients with non-cirrhotic MetALD was associated with reduction in risk of incident decompensated cirrhosis and mortality. Given no effect on BMI, the beneficial effect may be related to modulation of AUD. If our results are confirmed, randomized clinical trials are warranted to confirm the efficacy of Naltrexone use in patients with MetALD.



intervention	N	Events	HR (95% CI)	Median (95% CI)	RMST (95% CI)	pvalue	E-value
NO.NALTREXONE	1139	102	NA	Undefined	3706.6 (3633.5, 3779.7)	NA	NA
NALTREXONE	1139	75	0.72 (0.53, 0.97)	Undefined	3935.4 (3871.1, 3999.7)	0.03	1.2 (L)

Disclosures: Amir Hossein Gougol: Nothing to Disclose, Paul Kwo: Nothing to Disclose, C Pike: Nothing to Disclose, Saurabh Gombar: Nothing to Disclose, Gavin Hui: Nothing to Disclose

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3053 | PREDICTORS OF SURVIVAL AND HEPATIC RECOMPENSATION IN PATIENTS WITH ALD REFERRED FOR EARLY LIVER TRANSPLANTATION

Nicholas Lim[1] Giovanni Roldan[1] Kawthar Mohamed[1] Weiyu Wu[2] Gurpreet Judge[2] Katherine Cooper[3] Deepika Devuni[3] Kevin Wang[4] Hersh Shroff[5] Anjana Rajan[6] Amanda Cheung[7] Kaleb Tesfai[8] Veeral Ajmera[8] Allison Kwong[9]

[1]University of Minnesota, [2]Stanford University, [3]University of Massachusetts, [4]University of North Carolina, [5]UNC Chapel Hill, [6]Northwestern Medicine, [7]Northwestern Memorial Hospital/Northwestern University, [8]University of California, San Diego, [9]Stanford University Medical Center

Background: Alcohol-associated liver disease (ALD) is the leading cause of liver transplant (LT) in the United States, with increased acceptance of alcohol associated hepatitis (AH) as an indication for transplant and no minimum sobriety requirement. However, access to early LT for patients with recent sobriety — whether in the setting of AH or ACLF — is inconsistent, and some proportion of LT recipients might have recovered without LT. We evaluated predictors of survival and hepatic recompensation among patients with ALD who were referred for early LT. **Methods:** RESOLVE is a retrospective cohort of adults with ALD and <6 months from last alcohol use, who were referred for early LT between 2018 to 2021 at six transplant centers across the United States. A Fine-Gray subdistribution hazard model was used to evaluate predictors of death, with LT considered as a competing risk. Multivariable logistic regression was used to evaluate predictors of hepatic recompensation, defined as being alive without transplant and Child-Pugh class A after 12 months. **Results:** 618 patients with ALD were evaluated for early LT, 357 (57%) were listed and 246 (40%) transplanted. The median MELD was 27 (IQR 19-35); 47% met NIAAA criteria for AH; median time from last drink was 79 days (IQR 34-131), and 24% had a positive PETH or <30 days from their last drink (ultrashort sobriety). 52% (90/172) of patients with AH and available follow-up data had favorable Lille scores (<0.45), of whom 47% received transplant. The cumulative incidence of mortality without transplant was 23% at 6 months and 30% at 1 year. In the competing risk analysis, significant predictors of death included INR, renal dysfunction, and albumin, whereas bilirubin was not predictive (Table). Higher WBC was also associated with increased mortality risk. Among those not transplanted, 15% had recompensated at 6 months and 21% at 12 months. Predictors of Child-Pugh A status at 12 months included lower INR or creatinine, and higher albumin and platelet count. Meeting NIAAA AH criteria (vs not) did not predict survival or recompensation. **Conclusion:** In patients with ALD referred for early LT, INR and renal dysfunction were more predictive of outcome than bilirubin. Novel predictive models that consider alternative weights to the existing MELD 3.0 coefficients, as well as additional clinical variables, should be developed for this unique patient population — which will help to more accurately identify patients who may have the opportunity to recover without the need for transplant, establish medical selection criteria for this population, and improve utility of LT for this indication.

Table. (A) Competing risk analysis with death as event and liver transplant as a competing risk, and (B) logistic regression for recompensation at 12 months. Statistically significant effects are bolded.

	Mortality (competing risk analysis)		Alive & CTP A at 12 months	
	Univariable (sHR)	Multivariable (sHR)	Univariable (OR)	Multivariable (OR)
Age	1.01 (0.99-1.02)		1.01 (0.99-1.04)	
Sex	1.00 (0.74-1.37)		0.83 (0.48-1.45)	
Bilirubin	**1.01 (1.00-1.03)**	0.98 (0.97-1.00)	**0.96 (0.93-0.98)**	1.01 (0.98-1.05)
INR	**1.46 (1.24-1.71)**	**1.39 (1.12-1.72)**	**0.27 (0.15-0.50)**	**0.51 (0.25-1.02)**
Serum creatinine*	**1.37 (1.14-1.64)**	**1.32 (1.06-1.65)**	**0.52 (0.33-0.79)**	**0.55 (0.37-0.81)**
Serum sodium	1.01 (0.98-1.04)		1.00 (0.96-1.04)	
Serum albumin	**0.79 (0.63-0.99)**	0.80 (0.63-1.02)	**1.52 (1.01-2.29)**	**1.69 (1.03-2.77)**
ALT, per 10 U/L	1.01 (0.98-1.05)		0.99 (0.91-1.06)	
AST, per 10 U/L	1.01 (1.00-1.03)		0.99 (0.94-1.03)	
Platelet, per 10/L	**0.97 (0.95-1.00)**	0.98 (0.76-1.27)	**1.07 (1.04-1.10)**	**1.07 (1.03-1.11)**
log(ALKP)	0.90 (0.67-1.20)		0.65 (0.39-1.08)	
WBC	**1.03 (1.01-1.05)**	**1.03 (1.00-1.05)**	0.98 (0.95-1.02)	
NIAAA AH criteria	1.11 (0.82-1.50)		0.63 (0.36-1.10)	
Ultrashort sobriety	**1.51 (1.07-2.11)**	1.39 (0.93-2.07)	**0.40 (0.19-0.86)**	0.49 (0.19-1.24)

*Dialysis set to Cr 3 mg/dL

Disclosures: Nicholas Lim: Nothing to Disclose, Giovanni Roldan: Nothing to Disclose, Kawthar Mohamed: Nothing to Disclose, Weiyu Wu: Nothing to Disclose, Gurpreet Judge: Nothing to Disclose, Katherine Cooper: Nothing to Disclose, Deepika Devuni: Avania Medical: Grant/Research Support, Intercept: Grant/Research

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Support, Kevin Wang: Nothing to Disclose, Hersh Shroff: Nothing to Disclose, Anjana Rajan: Nothing to Disclose, Amanda Cheung: Nothing to Disclose, Kaleb Tesfai: Nothing to Disclose, Veeral Ajmera: Nothing to Disclose, Allison Kwong: Nothing to Disclose

3054 | BREWING BIAS: ALCOHOL BIOMARKER TESTING TRENDS FOR PATIENTS ON THE LIVER TRANSPLANTATION WAITLIST

Hamza Sadhra[1] Jessica Jang[2] Don Rockey[1] Clara Tow[1] Yael Belinkie[1] Rebecca Roediger[1] Lisa Teh[1]

[1]Montefiore Medical Center, [2]Albert Einstein College of Medicine

Background: Alcohol abstinence is an important consideration for individuals awaiting liver transplant (LT). The AASLD and AST recommend monitoring alcohol with toxicology screening through biomarkers such as urine ethyl glucuronide (EtG) and phosphatidylethanol (PEth) as they are more reliable than self-reporting and breath tests. However, there are no specific recommendations regarding the frequency of testing and the lack of standardization may lead to potential bias for certain groups who are being evaluated for LT. This study aimed to look at patterns of alcohol biomarker testing among patients with alcohol-related liver disease (ArLD) and in evaluation for LT. **Methods:** This retrospective study developed a cohort of patients who were evaluated for liver transplant for ArLD between January 2020 and March 2023 at a diverse major urban liver transplant health system in NYC. Demographic data and the number of EtG and PEth tests completed were collected. The primary outcome of interest was the total number of EtG and PEth tests performed. A linear regression analysis was done to assess the relationship between demographic variables such as age, sex, race, ethnicity, and location, and the average number of EtG and PEth tests performed. **Results:** Out of 164 patients included, those aged 25-39 years were tested an average of 23.2 times with either EtG or PEth, individuals aged 40-59 years were tested 12.6 times, and those aged 60 years and above were tested 6.2 times. Multivariate linear regression analysis revealed statistical differences between the age groups, when adjusting for race, ethnicity, sex, and location. Compared to the reference group (ages 60+), the 40-59 age group was tested more frequently with an odds ratio of 6.6 (p=0.026). This trend continued with the youngest 25-39 age group, who had nearly 4 times more testing with an odds ratio of 17.4 (p=0.001) (Table 1). **Conclusion:** This study observed a higher frequency of alcohol biomarker testing among younger patients (< 40 years) and may identify a potential selection bias during listing for LT. Opportunities to mitigate these biases may be well served by implementing a standardized approach to frequency and methods of testing for all patients with ArLD and in evaluation for LT. Future investigations on these interventions are warranted.

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	Average EtG and PEth tests	OR	p-value
Race			
Black	14.4		
Caucasian	12.2	6.4	0.263
American Indian or Alaskan Native	1	-9.4	0.495
Asian	22	11.6	0.396
Other	6	-1.4	0.841
Ethnicity			
Hispanic	12.1		
Not Hispanic	11.4	-2.7	0.573
Age			
25-39	23.2		
40-59	12.6	**-10.8**	**0.028**
60+	6.2	**-3.5**	**0.001**
Sex			
Male	12.2		
Female	11	-0.5	0.89
Location			
Bronx	11.3		
Brooklyn	4	-3.5	0.711
Manhattan	7	-4.6	0.719
Westchester	18.6	3.2	0.439
Rockland	19.5	6.0	0.374
Other NY	8.3	-7.0	0.12
NJ	7.8	-3.3	0.488
CT	13.5	1.6	0.822

Disclosures: Hamza Sadhra: Nothing to Disclose, Jessica Jang: Nothing to Disclose, Don Rockey: Grant/Research Support relationship with Versantis; Has not ended; Grant/Research Support relationship with AstraZeneca; Has not ended; Grant/Research Support relationship with Ipsen; Has not ended; Grant/Research Support relationship with Boehringer Ingelheim; Has not ended; Consultant relationship with WL Gore and Associates; Has not ended; Grant/Research Support relationship with Gilead; Has not ended; Grant/Research Support relationship with Durect; Has not ended; Consultant relationship with BD Medical; Has not ended; Consultant relationship with Cook Medical; Has not ended; Grant/Research Support relationship with Intercept; Has not ended; Grant/Research Support relationship with Inventiva; Has not ended; Grant/Research Support relationship with Madrigal; Has not ended; Grant/Research Support relationship with Ocelot; Has ended; Grant/Research Support relationship with Bio89; Has not ended; Grant/Research Support relationship with Salix; Has not ended; Grant/Research Support relationship with Novonordisk; Has not ended; Grant/Research Support relationship with Viking; Has ended; Grant/Research Support relationship with Galectin; Has not ended, Clara Tow: Nothing to Disclose, Yael Belinkie: Nothing to Disclose, Rebecca Roediger: Nothing to Disclose, Lisa Teh: Nothing to Disclose

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3055 | USING A HUMAN LIVER-ON-A-CHIP MODEL TO STUDY ALCOHOL-ASSOCIATED LIVER DISEASE BY TARGETING LSECS AND ALDH2

Takashi Tsuchiya[1] Michitaka Matsuda[1] Yuji Ishida[2] Takeshi Saito[3] Ekihiro Seki[1]

[1]Cedars-Sinai Medical Center, [2]Universoty of Southern California, [3]University of Southern California

Background: The current experimental approach for studying alcohol-associated liver disease (ALD) has limitations due to insufficient expression and activity of alcohol-metabolizing enzymes in hepatocytes using the standard cell culture system and animal models. We have developed a liver-on-a-chip using human liver cells, which express relevant levels of alcohol-metabolizing enzymes. Because we found ALDH2 is expressed in liver sinusoidal endothelial cells (LSEC) besides hepatocytes, and senescent LSECs reduced ALDH2 expression, we hypothesize that reduced ALDH2 in senescent LSECs contributes to ALD development through accumulation of acetaldehyde in the liver. We used a liver-on-a-chip model to test this hypothesis. **Methods:** Liver-on-a-chip with hepatocytes only and hepatocytes plus LSECs were treated with 0.2% ethanol (~43.5mM). Then, ALDH2 was silenced or pharmacologically activated (by Alda-1) in LSECs on liver-on-a-chip. AST, ALT, acetaldehyde, and ethanol levels in culture media were measured. Using single-cell RNA-seq data of human alcoholic cirrhosis and in vitro model of senescent LSECs, ALDH2 levels and senescence markers were measured. **Results:** Liver-on-a-chip model had high expression of albumin, ADH1, ALDH2, and CYP2E1 compared with the standard culture. Ethanol treatment increased AST and ALT release in liver-on-a-chip without LSECs but the chip with LSECs inhibited AST and ALT elevation, suggesting LSECs are protective against ethanol-induced hepatocyte damage. Silencing ALDH2 in LSECs increased AST/ALT levels whereas activation of ALDH2 by Alda-1 treatment reduced AST/ALT levels in liver-on-a-chip treated with ethanol, underscoring that ALDH2 in LSECs is crucial for protecting against ethanol-induced liver damage. Single-cell RNA-seq data of human cirrhosis showed reduced ALDH2 expression and increased senescence markers p21 and p16 in LSECs. Long-term acetaldehyde exposure induced LSEC senescence in the chip system and the senescent LSEC showed reduced ALDH2 expression. Taken together, these findings suggest that cirrhosis induces LSEC senescence and lowers ALDH2 expression and that in cirrhosis a large amount of ethanol exposure induces severe liver damage due to acetaldehyde accumulation by low ALDH2 in senescent LSECs, which might be a mechanism of severe alcoholic hepatitis occurs in patients with cirrhosis. **Conclusion:** A human liver-on-a-chip system is a useful tool to study ALD. Our study showed the importance of LSEC's ALDH2 in ALD.

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3056 | POPULATION BASED SCREENING FOR ALCOHOL ASSOCIATED LIVER DISEASE USING THE ELECTRONIC HEALTH RECORD

Kristina Folta[1] John Mendelson[2] Judith Prochaska[3] Kevin Hallgren[4] Weiyu Wu[3] Allison Kwong[5]

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Background: A screening modality that identifies patients with alcohol-associated liver disease (ALD) prior to symptom onset could improve outcomes and prognosis. As part of a clinical trial in partnership with Ria Health (NCT05747703), we deployed an EHR-wide screening program based on elevated liver enzymes, with linkage to care via the Ria Treatment Platform — a telehealth approach for alcohol use disorder (AUD) that incorporates medical assessment, medications, education, and coaching. Here, we evaluate the demographic yield of patients responding to this population-based screening effort for ALD. **Methods:** Patients were identified through the STAnford Research Repository (STARR), if they were ≥18 years old and had ALT, AST, or GGT greater than 45, 45, or 100 respectively within 90 days. Invitations were sent to potential participants via Epic MyHealth, explaining that their test results may be attributed to alcohol and providing a link to complete a screening questionnaire to enter a study to reduce alcohol use. Demographics and clinical data of respondents were extracted by chart review. **Results:** In the first phase of the study, 17,739 invitations were sent, and identifiable data were available for 39 of 93 patients who completed screening, with mean age of 46 years (SD 16), 23% female; 33% AST >45 U/L, 67% ALT >45 U/L, 11% GGT >100 U/L; and AUDIT-C score 4 (IQR 3-7). The average BMI was 29.4 kg/m2

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(SD 5.8); 33% had hypertension, 31% diabetes, and 82% hyperlipidemia; median FIB-4 0.83 (IQR 0.49-2.10). Eligible patients with AUDIT-C ≥3 (n=30) proceeded to structured MINI interview and TLFB; 83% met criteria for AUD (9% mild, 39% moderate, 35% severe), self-reporting a median 5 standard drinks per week (IQR 3-15) and PETH 41 ng/mL (IQR 14-160). Although steatosis was not confirmed by imaging, 89% would meet criteria for metALD based on reported amount of alcohol consumption (≤350 gm/week for women and ≤420 gm/week for men) rather than ALD. **Conclusion:** The population-based screening strategy based on elevated liver enzymes detected 93 patients with a desire to reduce their alcohol use. The majority of those with AUDIT-C ≥3 would classify as metALD rather than ALD on further alcohol intake history. Quantification of alcohol use would help to clarify thresholds for metALD vs ALD and enable treatment to be tailored appropriately. This is a promising strategy to detect early steatotic liver disease with linkage to timely and appropriate subspecialty care.

Disclosures: Kristina Folta: Nothing to Disclose, John Mendelson: Ria Health: Founder and CMO, Judith Prochaska: Achieve Life Sciences: Consultant, Oneleaf Health: Advisor, Kevin Hallgren: Nothing to Disclose, Weiyu Wu: Nothing to Disclose, Allison Kwong: Nothing to Disclose

3057 | CIRRHOSIS IS ASSOCIATED WITH WORSE OUTCOMES IN HOSPITALIZATIONS FOR ALCOHOL WITHDRAWAL

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Background: Alcohol cessation is critical to the prevention of further liver dysfunction and decompensation in patients with cirrhosis. However, alcohol withdrawal can complicate alcohol cessation and the clinical outcomes of alcohol withdrawal in patients with cirrhosis have not been adequately explored. **Methods:** This is a cross-sectional retrospective assessment of hospitalizations with a primary diagnosis of alcohol withdrawal within the National Inpatient Sample 2016-2019. Patients with a diagnosis of cirrhosis were compared to those without cirrhosis using multivariable regression analysis with assessed outcomes including mortality, mechanical ventilation, length of hospital stay and cost. Subgroup analysis was performed comparing those with decompensated cirrhosis to those without cirrhosis. Decompensated cirrhosis was defined as a history of esophageal varices, hepatic encephalopathy, hepatorenal syndrome, spontaneous bacterial peritonitis, or ascites. ICD-10 codes were used to establish diagnoses. **Results:** A total of 673,380 admissions for alcohol withdrawal were identified with 44,235 of those admissions being for patients with cirrhosis. Those with cirrhosis were older (mean age 50.8 vs 47.3 years, p<0.001) but had a similar proportion of female patients to those without cirrhosis (27.2% vs 27.1% respectively, p=0.877). Mortality was higher in patients with cirrhosis (0.4% vs 0.1%, aOR = 2.60, 95% CI: 1.67-4.05, p<0.001) as was the need for mechanical ventilation (2.2% vs 1.0%, aOR = 1.37, 95% CI: 1.15-1.62, p<0.001), mean length of hospital stay (4.78 vs 3.81 days, p<0.001) and mean cost ($9,104 vs $6,045, p<0.001). Mortality in those with decompensated cirrhosis was 1.0% and 3.9% of such patients required mechanical ventilation with both outcomes being significantly increased compared to patients without cirrhosis (aOR = 5.19, 95% CI: 2.99-9.01, p<0.001 and aOR = 1.93, 95% CI: 1.51-2.47, p<0.001, respectively). **Conclusion:** Patients with cirrhosis, particularly decompensated cirrhosis, are at increased risk for poor alcohol withdrawal outcomes. Increased vigilance for withdrawal in patients with cirrhosis and ongoing alcohol use and higher levels of care for those experiencing alcohol withdrawal may be warranted.

Disclosures: Yasmin Ali: Nothing to Disclose, Spencer Goble: Nothing to Disclose

3058 | SUBCUTANEOUS INJECTION OF GALANIN ATTENUATES ALCOHOLIC HEPATITIS AND ABDOMINAL ADIPOSE TISSUE INFLAMMATION INDUCED BY ETHANOL BINGE IN OB/OB MICE

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Background: Galanin is an endogenous neuropeptide known to regulate inflammation and metabolism. This study aims to explore the effects of galanin on alcoholic hepatitis in mice with metabolic dysfunction-associated

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steatotic liver disease(MASLD). **Methods:** Male ob/ob mice aged 10 weeks were randomly divided into four groups, namely water gavage + PBS (ob/ob), water gavage + Galanin (ob/ob+Gal), and ethanol gavage + PBS (ob/ob-binge), ethanol gavage + Galanin (ob/ob-binge+Gal). Galanin was administered at 8 μg/100g subcutaneously once daily for 10 days. On the morning of the 11th day, the alcohol treatment group was given a single dose of 5 g/Kg of 50% (v/v) alcohol by gavage. After 9 hours of gavage, the mice were euthanized and sampled. Hepatic pathological changes were detected by HE staining. Immunohistochemistry was performed to detect the expression of Ly6G-positive cells in the liver and F4/80 positive cells in abdominal adipose tissue. WB and qRT-PCR were performed to detect the expression of proteins and genes in inflammation and MAPK signaling pathways. In vitro, galanin receptor 2 (GalR2) inhibitor (M871) interfered with LPS or ethanol-induced mouse BV2 cell line. **Results:** Compared with the ob/ob binge group, the serum AST levels in the ob/ob binge+Gal group mice were significantly reduced. HE staining showed that the alcohol gavage+galanin intervention group did not significantly improve the degree of liver steatosis in mice. No significant change in the number of LY6G positive neutrophil infiltration in the liver of ob/ob binge+Gal group mice. In mice's ob/ob binge+Gal group, liver cytokines mRNA of Cxcl1, Cxcr2, Lcn2, and IL-1 were significantly reduced compared to the ob/ob binge group. Infiltration of F4/80 positive macrophage in adipose tissue in ob/ob-binge+Gal mice was also reduced. Mechanistically, galanin receptor 2(GalR2) inhibitor M871 can reverse the inhibitory effects of galanin on LPS or alcohol-induced phosphorylation of JNK, ERK, cJUN proteins, and expression of inflammatory factors in BV2 cells ($P<0.05$). **Conclusion:** The findings of this study suggest that the subcutaneous injection of galanin at 8 μg/100g body weight daily holds significant promise in attenuating alcoholic hepatitis and abdominal adipose tissue inflammation induced by ethanol binge in MASLD mice, potentially paving the way for a new therapeutic approach.

Disclosures: Yuanwen Chen: Nothing to Disclose, Yu-Qing Cheng: Nothing to Disclose, Yingwei Chen: Nothing to Disclose, Shuangzhe Lin: Nothing to Disclose

3059 | STATIN THERAPY MAY PROTECT AGAINST VARICEAL BLEEDING IN PATIENTS WITH ALCOHOL-ASSOCIATED LIVER DISEASE

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[1]University at Buffalo

Background: Patients with alcohol-related liver disease (ALD) frequently have risk factors for cardiovascular disease (CVD), but their long-term risk of CVD is not well-known. The 2018 American Heart Association recommends statin therapy in patients with chronic and stable liver disease for secondary prevention of atherosclerotic cardiovascular disease (ASCVD). However, the adequate intensity of statin for patients with ALD and their effects on decompensation remains unclear. This retrospective study aims to assess the impact of statins (high and moderate intensity) on the rates of alcohol-associated decompensation including hepatic encephalopathy (HE), variceal bleeding (EVB), ascites, and mortality in patients with ALD. **Methods:** 174 patients with ALD and active alcohol use were identified and stratified into two groups based on statin use on admission. Baseline characteristics, ASCVD risk, signs of decompensation, and 90-day mortality rates were compared between the two groups. In sub-group analysis, decompensation in persons on statin monotherapy without anti-hypertensives including non-selective beta-blockers (NSBB) was also investigated. Significance was assessed by analysis of variance (ANOVA) and $p<0.05$ was considered significant. Data were presented as mean±SEM. **Results:** The ASCVD risk for all patients was 14.92±1.2, with a MELD score of 11±0.7. In total 23.7% (n=41) presented with HE, 20.3% (n=35) had EVB, and 17.1% (n=31) had ascites on admission. In total, 31.6% (n=55) were on statins. Those with statin therapy had lower but not significantly different rates of EVB (18.5% vs 21.2%; p=0.3). Also, rates of HE (27.7% vs 21.84%; p=0.2) and ascites (20.37% vs 16.8%; p=0.3) were not significantly different between groups; however, EVB among patients on a high-intensity statin was considerably lower compared to those on moderate-intensity statins or no statin therapy (5% vs 26.47% vs 21.2%; $p<0.01$). Furthermore, in the absence of anti-hypertensives and NSBB, those on statins (moderate or high intensity) had significantly lower rates of EVB (11.76% vs 29.85%; $p<0.05$). Yet, the rates of HE and ascites remained unchanged regardless of statin dose. All-cause mortality was 14% (n=25); however, patients on a statin had a significantly improved 90-day mortality (7.31% vs 17.34%; $p<0.05$). **Conclusion:** Patients with ALD have an intermediate ASCVD risk. Those receiving statins had lower rates of bleeding and significantly lower rates of EVB with high-intensity statins. In the absence of NSBB, patients on statins demonstrated lower rates of EVB. Overall,

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statins did not improve other symptoms of decompensation including HE and ascites but demonstrated significant improvement in 90-day mortality. Given intermediate ASCVD risk, a dialogue between clinicians and ALD patients about statin therapy particularly those at high risk of EVB may be warranted. These findings may benefit the management of ALD and clinical outcomes.

Disclosures: Nariman Hossein-Javaheri: Nothing to Disclose, Blake Podger: Nothing to Disclose, Himaben Gohil: Nothing to Disclose, Ikjot Singh: Nothing to Disclose, Ali Aijaz: Nothing to Disclose, Leonard Palatnic: Nothing to Disclose, Anthony Martinez: Gilead: Consultant, Gilead: Speaking and Teaching, Abbvie: Consultant, Abbvie: Speaking and Teaching, Arbutus: Consultant, Braeburn: Speaking and Teaching, Sirtex: Consultant, Roche: Consultant, Syneos/VBI: Consultant, Madrigal: Speaking and Teaching, Altimune: Consultant

3060 | REAL-WORLD EVIDENCE OF EMERGING HEALTH DISPARITIES IN SEVERE ALCOHOLIC HEPATITIS INCIDENCE IN THE POST-COVID ERA

Jiangqiong Li[1] Shihui Jiang[1] Chi Nguyen[1] Yang Li[1] Ryan Healey[1] Wanzhu Tu[1] Suthat Liangpunsakul[1] Jing Su[1]

[1]Indiana University School of Medicine

Background: The COVID-19 pandemic has significantly altered social norms of work and life. These changes in socioeconomic stressors disproportionately affect populations with different social determinants of health (SDoHs) and trigger new health disparities. Severe alcoholic hepatitis (sAH) serves as a sensitive indicator of the new health disparities after the pandemic. We examined the longitudinal changes in sAH incidences from 2017 to 2023 and reported a real-world evidence of emerging health disparities in sAH risk in the post-COVID era. **Methods:** Optum's Clinformatics® Data Mart (CDM,V9,released 12/14/2023), derived from a database of administrative health claims for members of large commercial and Medicare Advantage health plans, is used. sAH events that involve emergency medicine or hospitalization are phenotyped among the insured members of Optum between 01/01/2017 and 02/28/2023. The SDoH domains examined in this work include age, sex, race and ethnicity, education, housing status, income, and insurance status. The COVID pandemic period is defined as between 01/10/2020 and 06/31/2021. Incidence rates are adjusted by the age composition with respect to February 2023. **Results:** The median monthly at-risk population was 16,843,674 [95% CI: 16,756,927 – 16,921,093]. The overall sAH incidence rate has been rising since the end of the COVID pandemic, increasing from 70.0 per million person-years in July 2021 to 79.1 in February 2023. This indicates a national trend of more risky drinking behaviors. Emerging health disparities in sAH incidences were observed across different housing statuses (Fig 1), race and ethnicity, educational levels, income, and geographic regions. The high-risk age group shifted from late middle-age (46–65 years) to early middle-age (31–45 years) after the pandemic. **Conclusion:** A national trend of fast-rising sAH since the end of the COVID-19 pandemic indicates a broader issue of increasing alcohol use disorders. This trend predicts upcoming alcohol-related health and social consequences. The emerging health disparities in sAH risk, particularly in housing status and other SDoH domains, suggest that individuals of different socioeconomic statuses and demographic characteristics exhibit differential vulnerability to new stressor patterns post-pandemic. This raises broader concerns about other substance use disorders and the mental health of these vulnerable groups that share similar socioeconomic stressors.

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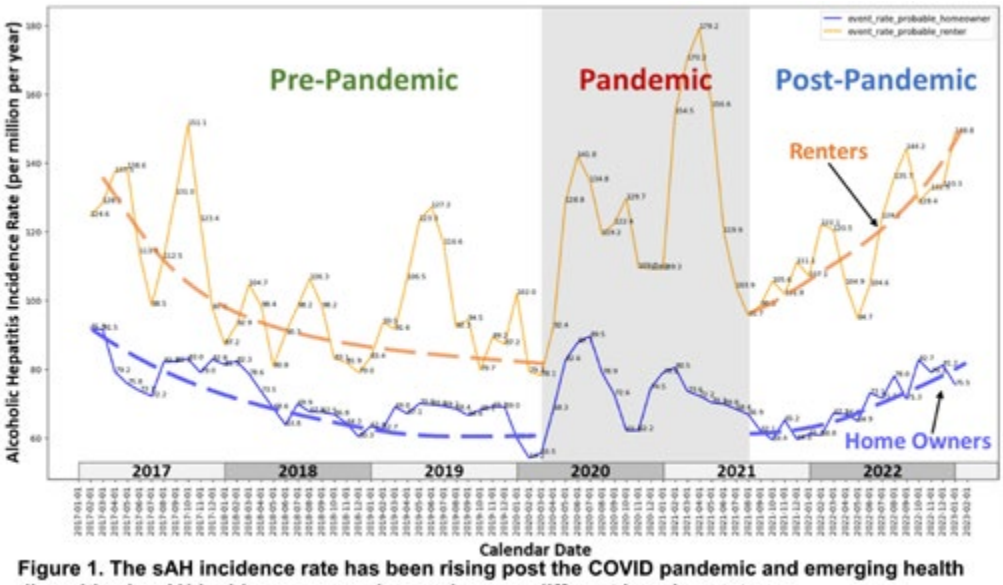

Figure 1. The sAH incidence rate has been rising post the COVID pandemic and emerging health disparities in sAH incidences were observed across different housing statuses

Disclosures: Jiangqiong Li: Nothing to Disclose, Shihui Jiang: Nothing to Disclose, Chi Nguyen: Pfizer: Stock - publicly traded company, Biomerica: Stock - publicly traded company, Yang Li: Nothing to Disclose, Ryan Healey: Nothing to Disclose, Wanzhu Tu: Nothing to Disclose, Suthat Liangpunsakul: DURECT: Consultant, Durect Corporation: Consultant, Surrozen: Consultant, Korro Bio: Consultant, Jing Su: Nothing to Disclose

3061 | WHAT IS THE CORRELATION BETWEEN AUDIT SCORE AND PHOSPHATIDYLETHANOL LEVEL BOTH TAKEN ON ADMISSION TO A TERTIARY LIVER UNIT? A CIRRHOSIS REGISTRY STUDY

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Lubomir Skladaný[1] Janka Ciefova[2] Svetlana Adamcova Selcanova[3] Daniela Zilincanova[3] Daniel Ján Havaj[4] Karolina Kristina Sulejova[3] Lukas Laffers[5] Jakub Gazda[6] Juan Pablo Arab[7]

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Background: The Alcohol Use Disorder Identification Test (AUDIT), introduced by Saunders and adopted by WHO, detects hazardous and harmful drinking. Its accuracy in various healthcare settings from primary to in-hospital care is high, with sensitivity and specificity above 0.9 and 0.8, respectively. However, data on its performance in in-patients with advanced chronic liver disease (ACLD) is lacking. Recently, an opportunity arose to scrutinize AUDIT against the new comparator - phosphatidylethanol (PEth); PEth is a direct serum biomarker of recent alcohol intake (3-4 weeks prior to testing). In the realm of alcohol use disorder-related care, PEth is aspiring for the position of a golden standard and is becoming increasingly availabile. In 2020, we have included PEth in the core dataset of our cirrhosis registry which is in operation since 2014. AIM: In this registry study, we have explored for the first time how AUDIT score correlates with PEth level in patients admitted to hospital with liver disease. **Methods:** We analyzed data from our cirrhosis registry RH7 (NCT 04767945) of consecutive adults admitted to a tertiary liver/transplant unit with ACLD, focusing on AUDIT and PEth at admission. Apart from analyzing AUDIT, AUDIT-C and PEth as a continuous variables, we have categorized results into tertiles for both AUDIT score (no/low risk drinking 0-7 points; hazardous drinking 8-14; harmful drinking 15+), and PEth levels (low intake <0.05 umol/L; medium intake 0.05-0.3; high intake >0.3). We excluded patients (pts) with missing data. **Results:** Inclusion/exclusion criteria were passed by 394 pts, aged 54 years (20-79); as a background etiology of ACLD, 68% had alcohol-associated liver disease (ALD), 11% MetALD, 8% metabolic dysfunction-associated steatotic liver disease (MASLD); 31% were female; median MELD was 20 (6-40). Median AUDIT, AUDIT-C, and PEth were 7 (0-36), 4 (1-7), and 0.00 (0.00-2.71), respectively. We found weak but statistically significant

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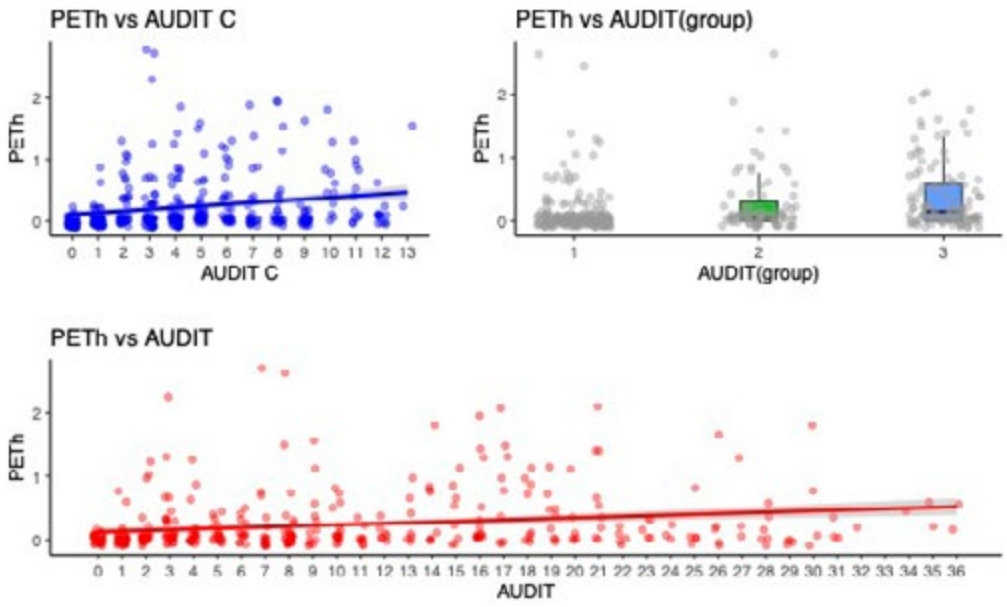
correlations between AUDIT and PEth and AUDIT-C and PEth in both continuous and categorical plots (Graph). One in four pts with the lowest AUDIT tertile showed elevated PEth, indicating false negativity of AUDIT; and 40% with AUDIT>8 had PEth<.05, indicating false positive AUDIT. **Conclusion:** Supposing PEth were the golden standard for recent alcohl use, AUDIT may misclasify considerable proportion of patients admitted to a tertiary liver/transplant unit. If externally corroborated, these results can have serious consequences for diagnosing ACLD etiology as well as for liver transplant listing and timely allocation of integrated addiction care.
While 25% false negativity of AUDIT fell in the range of expected results, AUDIT's 40% false positivity was a great surprise and has bacome THE focus of our further research.



Disclosures: Lubomir Skladaný: Worwag: Speaking and Teaching, ProMed: Speaking and Teaching, Abbvie: Speaking and Teaching, Gilead: Speaking and Teaching, RegPharm: Speaking and Teaching, Janka Ciefova: Nothing to Disclose, Svetlana Adamcova Selcanova: Nothing to Disclose, Daniela Zilincanova: Nothing to Disclose, Daniel Ján Havaj: Nothing to Disclose, Karolina Kristina Sulejova: Nothing to Disclose, Lukas Laffers: Nothing to Disclose, Jakub Gazda: Nothing to Disclose, Juan Pablo Arab: Nothing to Disclose

3062 | SHORT-TERM COSTS OF ALCOHOL-ASSOCIATED HEPATITIS CARE IN DIFFERENT CLINICAL SETTINGS

Chi Mai Nguyen[1] Jing Su[1] Ryan Healey[1] Yang Li[1] Shihui Jiang[1] Jiangqiong Li[1] Samer Gawrieh[1] Wanzhu Tu[1] Suthat Liangpunsakul[1]

[1]Indiana University School of Medicine

Background: Alcohol-associated hepatitis (AH) presents significant challenges due to its high mortality, and the substantial financial burden. Effective treatments are limited, necessitating a comprehensive understanding of the costs and key cost drivers for informed healthcare policy. This study aims to quantify the short-term medical costs within 30 days of AH diagnosis across different healthcare settings: outpatient (OP), emergency department (ED), and inpatient (IP). **Methods:** We conducted a retrospective cohort study using de-identified data from Optum's Clinformatics® Data Mart database. Individuals aged 21 years and older with diagnoses of AH from January 1, 2016, to September 30, 2023, were included. They were categorized based on their venue of care, OP, ED, or IP, to allow an assessment of medical costs across different care settings. Medical costs were calculated for the 30 days before and after AH diagnosis. Costs were inflation-adjusted to 2023-dollar values to provide a standardized comparison. Comorbidities were identified using the Elixhauser index. Multivariable linear regression models were employed to analyze the medical costs; they accounted for potential confounding variables and allowed for the identification of key factors driving the variation in medical costs among AH patients. **Results:** The study cohort included a total of 34,974 individuals with AH [8,048 (23%) OP, 2,736 (7.8%) ED, and 24,190 (69.2%) IP]. In the 30 days before the index AH diagnosis, average medical spending for OP, ED, and IP was $7,334, $5,740,

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and $14,458. In the 30 days following the index, the mean costs for OP jumped to $8,345, ED to $20,990, and IP to $88,655, representing increases by 14%, 266% and 413%, respectively. In IP, having moderate-to-severe liver disease and its sequelae (such as portal hypertension) was associated with a 39% increase in care cost (p<0.001), cardiovascular disease and metabolic syndrome and its sequelae (such as hypertension and diabetes) were associated with a 31% and 16% increase in care cost (p<0.001) respectively. Liver transplant and death within 30 days of AH diagnosis were respectively associated with 86% and 1.29 times increase in cost (p<0.001, Fig 1). **Conclusion:** The immediate cost associated with alcohol-associated hepatitis (AH) can be substantial, particularly for those who require inpatient care. Our study highlights the significant increase in care costs across all settings following AH diagnosis, with inpatient costs experiencing the most drastic escalation. Furthermore, our findings underscore the importance of improving treatment outcomes and effectively managing comorbidities in AH patients. Care costs escalate drastically in the presence of high-cost comorbidity clusters, such as moderate-to-severe liver disease, cardiovascular disease, and metabolic syndrome, emphasizing the need for comprehensive care approaches that address both AH and its associated conditions.

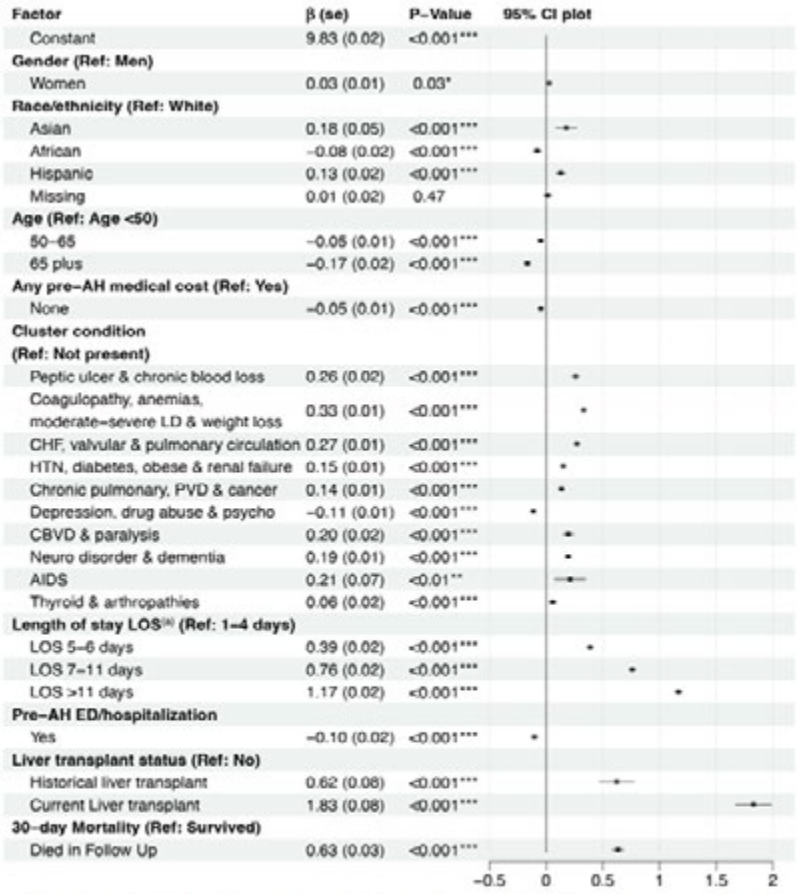

Fig 1. Risk factors associated with the 30-day medical costs post-AH diagnoses in those who received inpatient care (adjusted for the year of the diagnosis)

Disclosures: Chi Mai Nguyen: Nothing to Disclose, Jing Su: Nothing to Disclose, Ryan Healey: Nothing to Disclose, Yang Li: Nothing to Disclose, Shihui Jiang: Nothing to Disclose, Jiangqiong Li: Nothing to Disclose, Samer Gawrieh: Transmedics: Consultant, pfizer: Consultant, kowa: Consultant, spruce: Consultant, viking: Grant/Research Support, zydus: Grant/Research Support, dsm: Grant/Research Support, Sonicincytes: Grant/Research Support, Novo Nordisk: Consultant, Wanzhu Tu: Nothing to Disclose, Suthat Liangpunsakul: DURECT: Consultant, Durect Corporation: Consultant, Surrozen: Consultant, Korro Bio: Consultant

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3063 | IMPACT OF STEROIDS AND INFECTION ON MORTALITY IN ALCOHOL-RELATED HEPATITIS

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Background: Infections are common in alcohol-related hepatitis (AH) and are a well-established risk factor for mortality. Data on the benefits of steroids in AH is somewhat controversial, and some experts suggest against the use of steroids in AH, especially in the presence of an infection. We used a large electronic dataset to analyze the impact of steroids and infections on survival in this population. **Methods:** This was a retrospective study from 1/2017 to 12/2023 involving 186 HCA Healthcare hospitals throughout the US. The HCA Healthcare System is a large healthcare network comprising of medium- and large-sized community hospitals spread across 19 states that see approximately 37 million patient encounters annually. AH was diagnosed using a combination of ICD-10 codes and biochemical parameters (total bilirubin ≥ 3 mg/dL on admission, AST between 50-400 IU/L and AST/ALT > 1.5). Steroid use was defined as those who received any steroids (Prednisone, Methylprednisolone, Hydrocortisone, or Dexamethasone) for 3 or more consecutive days in the hospital. Infections were identified using ICD-10 codes. Multivariable analysis was used to determine the impact of steroids and other variables on mortality. The Sidak method was used for multiple pairwise comparisons. **Results:** During this study period, we identified 10,864 patients hospitalized for AH with a median MELD score of 22 and a Maddrey score of 38. We found that 25% of these patients had infections and 25% were administered steroids. The use of steroids in those with and without infections is shown in Table 1. On multivariable analysis, steroids did not impact in-hospital mortality (OR 0.9, 95% CI 0.82 - 1.12) (Table 2). Several pairwise comparisons were significant after adjusting for multiple comparisons using the Sidak method and are shown in Table 3. Patients with an infection who did not receive steroids were 2.6 times more likely to die compared to those who had no infection but did receive steroids (P<0.0001,95% CI 1.93 - 3.66). Additionally, patients with an infection who received steroids were 2.6 times more likely to die compared to those who had no infection but did receive steroids (P< 0.0001, 95% CI 1.82 - 3.85). We also found that patients who had an infection but received steroids did not have increased mortality compared to those with an infection but did not receive steroids (OR 1.00, 95% CI 0.71-1.4). Other differences between the groups are shown in Table 3. **Conclusion:** Data from our retrospective study indicates that infections are primarily responsible for the increased likelihood of mortality in those with alcohol-related hepatitis, rather than the administration of steroids. Steroids did not improve survival in our cohort. It was also interesting to observe that those who received steroids despite having an infection did not have increased mortality compared to those with an infection but did not receive steroids (in theory, this group should have higher mortality).

Table 1: Steroid use and infections in Alcohol related hepatitis

Variable	Level	Total		Mortality			
				No		Yes	
		N	*%*	*N*	*%*	*N*	*%*
Female		4043	37.21	3700	37.67	343	32.92
Male		6821	62.79	6122	62.33	699	67.08
Steroid	No	8155	75.06	7427	75.62	728	69.87
	Yes	2709	24.94	2395	24.38	314	30.13
Infection	No	8186	75.35	7617	77.55	569	54.61
	Yes	2678	24.65	2205	22.45	473	45.39
Infection*Steroid	Infection / No Steroid	1917	17.65	1601	16.30	316	30.33
	Infection / Steroid	761	7.00	604	6.15	157	15.07
	No Infection / No Steroid	6238	57.42	5826	59.32	412	39.54
	No Infection / Steroid	1948	17.93	1791	18.23	157	15.07

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Table 2: Multivariable analysis on mortality

Parameter	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq	Odds Ratio	95 % CI Lower	95 % CI Upper
Intercept	-9.7494	0.2716	1288.4516	<.0001			
Steroids	-0.0279	0.0847	0.1084	0.7420	0.972	0.824	1.148
Hep Encephalopathy	0.3880	0.1308	8.7949	0.0030	1.474	1.141	1.905
Ascites	0.1712	0.0930	3.3899	0.0656	1.187	0.989	1.424
MELD Score	0.1885	0.00559	1136.2790	<.0001	1.207	1.194	1.221
GI Bleed	0.9525	0.0822	134.2180	<.0001	2.592	2.206	3.046

Table 3: Adjustment for Multiple Comparisons: Sidak Method

Comparison	Reference	Standard Error	Z Value	Adjusted P value	Odds Ratio	Lower	Upper
Infection / No steroids	Infection / Steroids	0.1310	0.03	1.0000	1.0041	0.7113	1.4175
Infection / No Steroids	No Infection / Steroids	0.1209	8.11	<.0001	2.6653	1.9390	3.6637
Infection / No steroids	No Infection / No Steroids	0.09490	9.36	<.0001	2.4299	1.8930	3.1191
Infection / steroids	No Infection / Steroids	0.1422	6.86	<.0001	2.6544	1.8258	3.8590
Infection / steroids	No Infection/ No Steroids	0.1237	7.14	<.0001	2.4199	1.7477	3.3508
No Infection / Steroids	No Infection / No Steroids	0.1115	-0.83	0.9565	0.9117	0.6798	1.2226

Disclosures: Joseph Alukal: Nothing to Disclose, Regis Lee: Nothing to Disclose, Oluwaposi Omiwade: Nothing to Disclose, Julio Gutierrez: Altimmune: Consultant, AbbVie: Speaking and Teaching, Gilead: Speaking and Teaching, Alexion: Speaking and Teaching, Exelixis: Speaking and Teaching, Madrigal: Consultant, Intercept: Speaking and Teaching, Livivos: Stock – privately held company, Surozen: Advisor, Escient: DSMB Chairman

3064 | GROWTH DIFFERENTIATION FACTOR 15 AND ADRENERGIC RECEPTOR β2 REGULATES ANTI-INFLAMMATORY ADIPOSE FOAMY MACROPHAGES IN ALCOHOL-ASSOCIATED LIVER DISEASE

Min Jeong Kim[1] Kyurae Kim[1] Sung Eun Choi[2] Po Sin Chung[1] Eunmi Lee[1] Kwang Woo Lee[1] WON-IL JEONG[3]

[1]GSMSE,KAIST, [2]Korea Advanced Institute of Science and Technology, [3]KAIST

Background: The level of catecholamine increases leading to adipose tissue (AT) lipolysis and free fatty acids (FFAs) release from adipocyte in alcohol-related liver disease (ALD). It induces increase of foamy AT macrophages (ATMs), but the properties of foamy ATMs remain elusive. Recently, growth differentiation factor 15 (GDF15) and beta-2 adrenergic receptor (ADRB2) have been found to impose anti-inflammatory functions on macrophages. Thus, we investigated the effects of GDF15 and ADRB2 on foamy ATMs in ALD. **Methods:** Wild-type (WT) and macrophage-specific ADRB2 knockout (ADRB2 mKO) mice were fed liquid EtOH or control (Pair) diet. Biochemical, histopathological, and bulk RNA-sequencing analyses were performed. qPCR and flow cytometric analyses were performed using stromal vascular fractions (SVFs) from human and mouse AT, while single-cell RNA-sequencing (scRNA-seq) analysis was conducted using mouse SVFs. *In vitro* experiments, primary macrophages or RAW 264.7 cells were treated with recombinant GDF15 and an ADRB2 agonist for further analyses. **Results:** Chronic alcohol consumption increased levels of AT catecholamines and serum FFAs in EtOH-fed WT mice compared to controls. Bulk RNA-seq showed elevated expression of ADRB3 and lipolysis-related genes, suggesting catecholamine release in AT after alcohol consumption. Flow cytometric and scRNA-seq analyses revealed that frequency of fat-storing F4/80^{high}Trem2^{+} ATMs (foamy ATMs) was increased and characterized by elevated expression of *Cd36, Fabp5, Dgat1* and anti-inflammatory genes. In human AT and blood, cytoplasmic fat storing was mainly observed in CD14^{+}CD16^{+} intermediate monocytes. Moreover, qPCR and immunostaining showed increased GDF15 expression in adipocytes and elevated ADRB2 expression in ATMs near crown-like structures. *In vitro*, EtOH exposure increased GDF15 expression in adipocytes through alcohol metabolism-mediated oxidative stress. GDF15 treatment significantly increased *Cd36* expression, leading to fat storage in ATMs. Notably, F4/80^{high} foamy ATMs in EtOH-fed mice highly expressed ADRB2, suggesting increased anti-inflammatory features response to catecholamine. ADRB2 agonist suppressed pro-inflammatory genes including *Il1b* in ATMs, consequently leading to the formation of an anti-inflammatory foamy ATMs. **Conclusion:**

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Our findings highlighted the roles of GDF15 and ADRB2 in regulating fat storage and anti-inflammation in ATMs after chronic alcohol consumption. Thus, targeting GDF15 and ADRB2 might be therapeutics for ALD intervention.

Disclosures: Min Jeong Kim: Nothing to Disclose, Kyurae Kim: Nothing to Disclose, Sung Eun Choi: Nothing to Disclose, Po Sin Chung: Nothing to Disclose, Eunmi Lee: Nothing to Disclose, Kwang Woo Lee: Nothing to Disclose, WON-IL JEONG: Nothing to Disclose

3065 | DEVELOPMENT OF ALCOHOL-ASSOCIATED HEPATOCELLULAR CARCINOMA MOUSE MODEL

Wonhyo Seo[1] Jisoo Kang[2]

[1]Ewha Womans University, [2]Ewha Womans Univ

Background: Liver cancer represents an escalating global health issue, and liver cancer ranks as the sixth most prevalent cancer and the fourth leading cause of cancer-related mortality. The major causes of hepatocellular carcinoma (HCC) are chronic infections with viral infection (hepatitis B virus and hepatitis C virus), chronic alcohol consumption, and metabolic dysfunction-associated steatotic liver disease (MASLD) which can result in cirrhosis and subsequently increase the risk of developing HCC. Recently, the prevalence of viral infection mediated-HCC has gradually decreased, while the incidence of HCC due to chronic alcohol consumption and MASLD has been gradually increasing due to changes in diet and lifestyle. The number of people is suffering from advanced stage of liver disease (liver fibrosis, and cirrhosis) to end-stage of liver disease (HCC) with the excessive alcohol consumption worldwide. High demands for research on alcohol-associated liver cancer have been existed, however, there are no appropriate alcohol-associated HCC animal models which is able to reflect the pathophysiological changes in human alcoholic liver cancer patients. **Methods:** Therefore, we proposed a methodology to establish an animal model via the combination treatment of diethylnitrosamine (DEN) and carbon tetrachloride (CCl_4) for HCC development. In addition, 4.5% Lieber-DeCarli diet (13 weeks or 20 weeks) was further provided to those animals for acceleration of tumor development. **Results:** As a result of combination of DEN+CCl_4+Lieber DeCarli diet (4.5% alcohol), we were able to observe extensive tumor formation compared to DEN+CCl_4+pair fed diet. Besides of increased tumor size/number, we also found increased oxidative stress, inflammation, and extensive fibrosis, which encompass the clinical symptoms of advanced stages of liver damage. In addition, changes of chronic alcohol-associated microbiome were also evaluated in alcohol-associated HCC mouse models. **Conclusion:** Based on the results we obtained, the newly proposed HCC animal model effectively induces the formation of liver cancer in a relatively short period of time and encompass various pathophysiological changes. Therefore, it would be helpful in understanding the alcohol-associated HCC in humans using this mouse model.

Disclosures: Wonhyo Seo: Nothing to Disclose, Jisoo Kang: Nothing to Disclose

3066 | GENE ISOFORM TRANSCRIPT USAGE IS ASSOCIATED WITH HIGHER ALCOHOL-ASSOCIATED HEPATITIS SUSCEPTIBILITY IN FEMALES THAN MALES ◆

Alastair Kilpatrick[1] Daniel Rodrigo-Torres[1] Luke Tyson[2] Stephen Atkinson[2] Nikhil Vergis[2] Mark Thursz[2] Laura Martinez-Gili[2] Stuart Forbes[1]

[1]The University of Edinburgh, [2]Imperial College London

Background: Alcohol-associated hepatitis (AH) is an acute form of alcohol-related liver disease with high mortality. Females have higher risk of developing AH, but the underlying molecular mechanisms are not fully understood. Genes can be transcribed into different isoforms, affecting gene function. We investigated transcript usage between sexes in a cohort of severe AH (sAH) patients. **Methods:** Baseline liver tissue was biopsied from a subset of sAH patients (n=30; 46.7% female) enrolled in the ISAIAH clinical trial of canakinumab, an anti-IL-1β antibody. Tissue homogenate RNA was extracted and sequenced; differential transcript usage of gene isoforms was computed between sexes using the IsoformSwitchAnalyzeR Bioconductor package. Clinical data was compared with Welch two sample t-tests. False discovery rate (q) <0.05 was considered significant. **Results:** Mean alcohol intake was higher in males than females (156.3 vs 92.6 units/week; p=6.1E-3). However,

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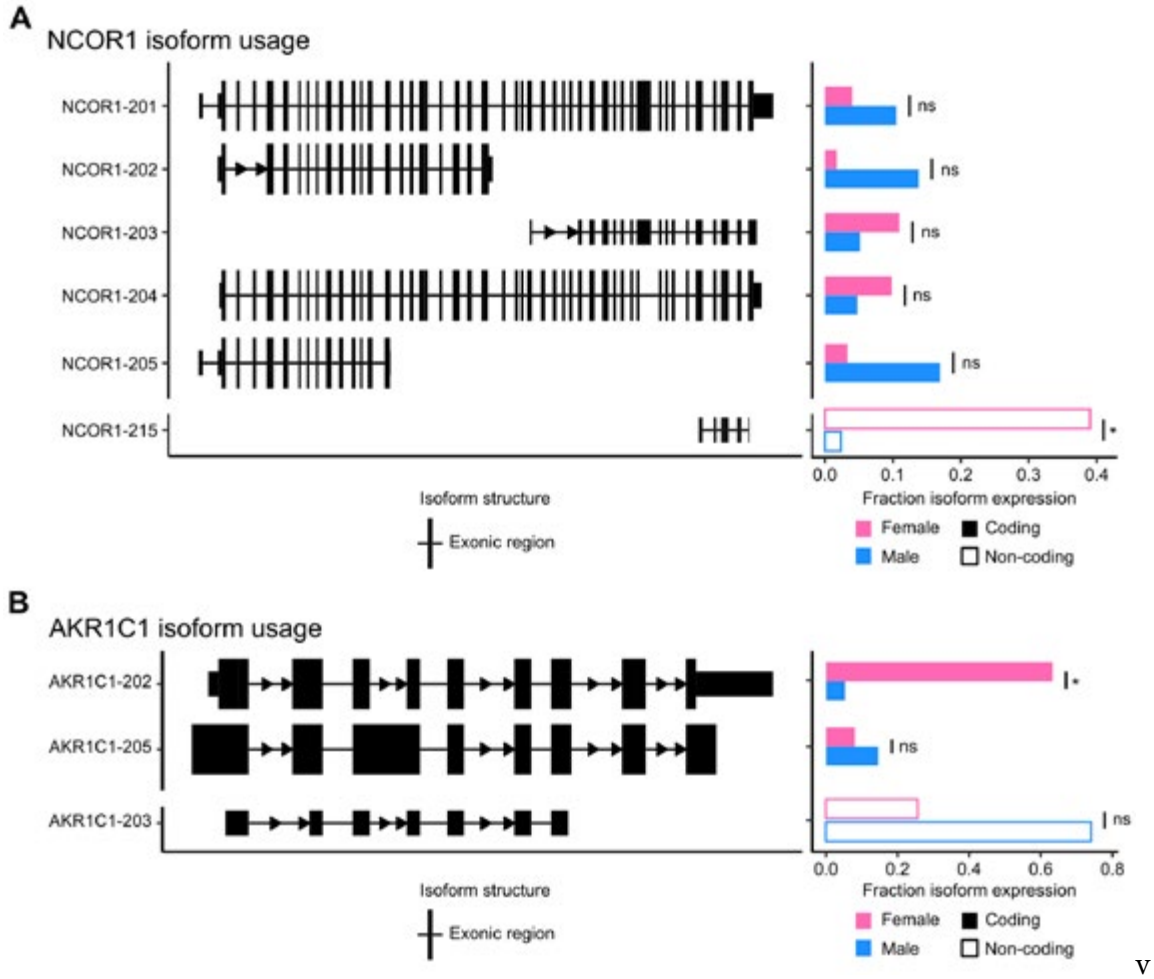
inflammation in males was significantly lower (CRP; 34.33 vs 49.00; p=3.45E-2). Mean MELD (male 23.54; female 22.46) and age (male 49.4 years; female 48.9 years) were not significantly different between sexes. We found 66 genes for which transcript usage differed significantly between sexes. 39.0% of nuclear receptor co-repressor 1 (NCOR1) expression in females was from a truncated non-coding transcript (NCOR1-215) (**Figure A**). NCOR1-215 expression was significantly lower in males (2.4%; q=0.015), who had higher expression of 3 coding transcripts of NCOR1. In mice, hepatic deletion of NCOR1 exacerbated alcohol induced liver damage; here, higher NCOR1-215 expression results in effective NCOR1 depletion in females, potentially worsening alcohol damage. Aldo-keto reductase family 1 member C1 (AKR1C1) catalyses the reduction of acetaldehyde to ethanol. Females had significantly higher expression of coding transcript AKR1C1-202 (63.3% vs 5.2% in males; q=0.036) (**Figure B**); males had higher expression of the truncated non-coding transcript AKR1C1-203 (25.7% vs 74.1%). Together, these suggest increased acetaldehyde recycling in females. **Conclusion:** Transcript usage of relevant genes may contribute to sex-specific pathological mechanisms in AH. In female AH patients, we identified significantly differential transcript usage that may worsen alcohol-induced damage, by prolonging exposure to ethanol and acetaldehyde toxicity and potentially increasing inflammation.



Disclosures: Alastair Kilpatrick: Nothing to Disclose, Daniel Rodrigo-Torres: Nothing to Disclose, Luke Tyson: Nothing to Disclose, Stephen Atkinson: Nothing to Disclose, Nikhil Vergis: Nothing to Disclose, Mark Thursz: Durect: Consultant, GSK: Consultant, Resolution Tx: Consultant, Intercept: Consultant, Galecto: Consultant, Durect: Consultant, Laura Martinez-Gili: Nothing to Disclose, Stuart Forbes: Resolution Therapeutics: Founder

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3067 | PROGNOSTIC UTILITY OF SYSTEMIC INFLAMMATORY RESPONSE SYNDROME CRITERIA IN ACUTE ALCOHOLIC HEPATITIS

Joseph Spengler[1] Geetha Ramalingam[2] Yiwei Hang[2] Rosa Yang[2] Marcus Healey[1] Ekaterina Smirnova[2] Amon Asgharpour[2] Vaishali Patel[2] Hannah Lee[2] Scott Matherly[2] Velimir Luketic[2] Mohammad Siddiqui[2] Joel Wedd[3] Arun Sanyal[2] Richard Sterling[2]

[1]Virginia Commonwealth University Health, [2]Virginia Commonwealth University, [3]Virginia Commonwealth University Hospital

Background: Acute alcoholic hepatitis (AAH) is a disorder of inflammation, associated with severe morbidity and mortality. Many with AAH have features of the Systemic Inflammatory Response Syndrome (SIRS). While Maddrey's Discriminant Function (MDF) and Model for End-Stage Liver Disease (MELD) are used to assess severity of AAH and guide treatment with steroids, the utility of the SIRS criteria in predicting outcomes remains unclear. Our aim is to assess the relationship between SIRS criteria and the severity and outcome of AAH. We hypothesize that AAH patients who have more SIRS criteria will have greater illness severity, be less likely to respond to steroids, and have worse 30-day survival. **Methods:** A retrospective analysis of clinical and demographic characteristics on 531 patients admitted between 1/1/2012 through 12/30/2019 with AAH who met SIRS criteria was performed. The patient cohort was stratified into two groups: those with ≥ 2 SIRS criteria (n=243) and those with < 2 criteria (n=288). Demographic profiles, laboratory parameters (e.g., aspartate aminotransferase, alanine aminotransferase, total bilirubin, international normalized ratio, prothrombin time, albumin, and creatinine), and scoring system measures (MDF on admission, MELD upon admission and discharge) were collected. The primary outcome assessed was 30-day (30-d) survival rate between the groups. **Results:** The mean age was 47 years; the majority were male and White (W). As seen in Table 1, there were no statistically significant differences in demographic or clinical characteristics between those with SIRS criteria ≥ 2 and those with < 2. Similarly, laboratory parameters, admission MDF and MELD, and steroid use were not significantly different between groups. Though not significant, there was a trend towards lower 30-d survival in patients who had ≥ 2 (87 vs 92%; p=.06). **Conclusion:** Our findings suggest that SIRS criteria may not serve as a reliable predictor of severity and 30-d survival in AAH patients treated with steroids. While there was a trend towards lower 30-d survival in those meeting ≥ 2 SIRS criteria, further investigations employing larger sample sizes is needed to confirm these observations and elucidate additional prognostic determinants influencing outcomes in this population. Enhanced scoring systems and more comprehensive outcome measures may be necessary to accurately assess the impact of treatment interventions, such as steroid therapy, on AAH prognosis.

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Contents	SIRS < 2	SIRS ≥ 2	Confidence Interval	P-value
Number of subjects	288	243	-	-
Age in years	47.5	46.5	-2.8352889, 0.9803506	0.34
Female/Male	106/182	125/118	-	-
Race (AA/W/multi/others/unknown)	74/185/1/16/12	59/166/0/9/10	-	-
Ethnicity % non-Hispanic	91.66%	92.59%	-	-
Weight in kg	84.7	80.7	-8.0275485, 0.0880774	0.05517
BMI kg/m2	28.3	29.6	-1.399655, 4.052526	0.3391
AST U/L	221	341	-85.26559, 325.62383	0.2504
ALT U/L	76.3	57.7	-12.28830, 33.00544	0.3687
Total bilirubin mg/dl	12.9	12.5	-2.340321, 1.564576	0.6965
Albumin g/dL	2.96	2.86	-0.2170845, 0.0131356	0.08239
PT sec	19.9	20.3	-0.667093, 1.466175	0.4621
INR	1.71	1.75	-0.079381, 0.1636119	0.4961
Creatinine mg/dl	1.04	1.09	-0.0992883, 0.2026986	0.5014
DF (using PT 13.5)	37.2	39.9	-3.117114, 10.287148	0.2938
MELD (admission)	20.3	21.3	-0.7691538, 2.5985580	0.2864
MELD (discharge)	23.7	23.3	-2.615000, 1.885391	0.7501
Thirty-day survival rate	92.01%	86.83%	0.9576114, 3.2256804	0.06268
Tachycardia	50.34%	98.35%	0.00446853, 0.04614357	< 2.2e-16
Tachypnea	3.8%	54.73%	0.01550867, 0.06417475	< 2.2e-16
Fever	0.35%	4.11%	0.00186901, 0.58007254	0.003467
Leukocytosis	10.4%	69.95%	0.06322916, 0.14801561	< 2.2e-16
Steroids	46.87%	46.09%	0.7223063, 1.4749754	0.8618

Table 1: Demographic, laboratory, and clinical characteristic comparison of those with SIRS ≥ 2 and < 2.

AA=African-American, W=White, %=percent, kg=kilograms, BMI=Body Mass Index, kg-kilograms, m2-meters squared, AST-Aspartate aminotransferase, U-Units, L-Liter, mg-milligrams, dL-deciliter, g-grams, ALT-Alanine aminotransferase, PT-Prothrombin time, INR-International Normalized Ratio, DF-Discriminant Function, MELD - Model for End-Stage Liver Disease

Disclosures: Joseph Spengler: Nothing to Disclose, Geetha Ramalingam: Nothing to Disclose, Yiwei Hang: Nothing to Disclose, Rosa Yang: Nothing to Disclose, Marcus Healey: Nothing to Disclose, Ekaterina Smirnova: Pfizer, Inc: Grant/Research Support, Amon Asgharpour: Galectin: Clinical Endpoint Committee, NovoNordisk: Advisor, Madrigal: Advisor, Vaishali Patel: Nothing to Disclose, Hannah Lee: Nothing to Disclose, Scott Matherly: Nothing to Disclose, Velimir Luketic: Nothing to Disclose, Mohammad Siddiqui: Grant/Research Support relationship with NovoNordisk; Has not ended; Advisor relationship with 89Bio; Has not ended; Advisor relationship with AMRA; Has not ended, Joel Wedd: Nothing to Disclose, Arun Sanyal: Genfit, Akarna, Tiziana, Durect, Inversago, Hemoshear, North: Stock - publicly traded company, Astra Zeneca (60K), Boston Pharmaceutical

3068 | ETHANOL INDUCED SKELETAL MUSCLE SENESCENCE CONTRIBUTES TO SARCOPENIA IN ALCOHOL RELATED LIVER DISEASE.

Nicole Welch[1] Pugazhendhi Kannan[1] Saurabh Mishra[1] Annette Bellar[1] Laura Nagy[2] Srinivasan Dasarathy[1]

[1]Cleveland Clinic, [2]Cleveland Clinic Foundation

Background: Sarcopenia in alcohol associated liver disease (ALD) is more frequent, severe, and progressive than in other etiologies of liver disease. We used a multiomics directed integrated molecular-metabolic approach to identify accelerated post-mitotic senescence in skeletal muscle in ALD. **Methods:** Vertical and horizontal integration of multiomics data and cluster analyses were performed on assay for transposase accessible chromatin sequencing (ATACseq), bulk RNAseq, untargeted proteomics, global acetylomics, phosphoproteomics, and untargeted

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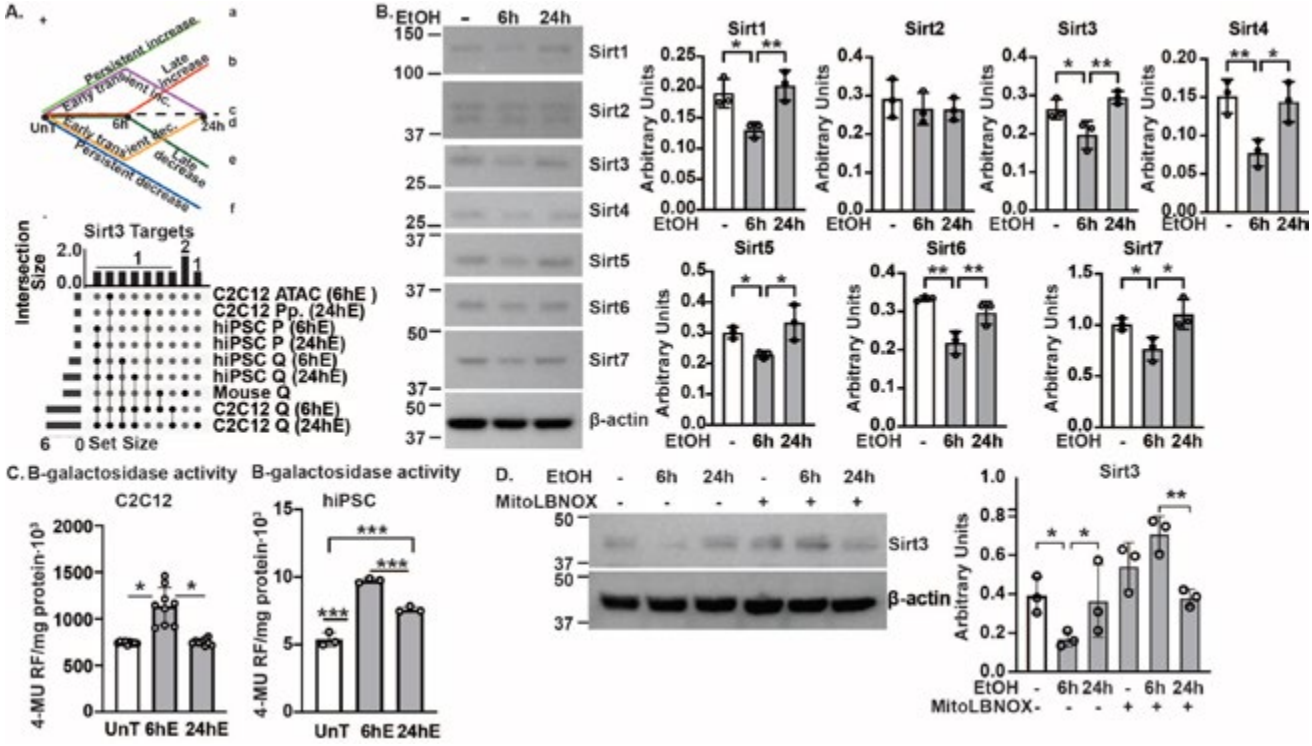
metabolomics from multiple models of sarcopenia in ALD to identify the global responses to ethanol treatment (ET). Models included differentiated murine myotubes, human induced pluripotent stem cell derived myotubes (hiPSCm), gastrocnemius muscle from mice with ALD (mALD), and rectus abdominis muscle from patients with ALD. Experimental validation was done in murine myotubes/muscle tissue from mALD for acetylated proteins in subcellular fractions, expression of sirtuins (lysine deacetylases), redox (NAD^+/NADH) measurements, post mitotic senescence markers (expression of p16,p21, phosphoryated/total p53, senescence associated b-galactosidase/ SABG, myotube diameter) and responses to reversing redox changes with mitochondria directed Lactobacillus brevis NAD^+ oxidase (MitoLbNOX) and mitochondrial free radical scavenger, MitoTEMPO. **Results:** Supervised and unsupervised UpSet plots, heatmaps, volcano plots, and pathway enrichments showed distinct clustering of DEM into Early Transient, Persistent, Late, and Pseudosilent patterns. Enrichment of sirtuin signaling and NAD signaling pathways in the early response and mitochondrial oxidative dysfunction, sirtuin and NAD signaling in the late response clusters (Fig1A). Untargeted metabolomics showed high pathway impact scores were noted for tryptophan and adenine dinucleotides that regulate cell senescence. Untargeted metabolomics Experimentally, redox ratio was less and acetylation in multiple cellular compartments was higher in ET myotubes and mALD muscle. Expression of Sirt1-7 (greater reduction of mitochondrial Sirt3,5) were decreased in multiple models (Fig1B). Measures of post-mitotic senescence including p16, p21, phosphorylated/total p53 were variably altered but SABG was consistently increased in myotubes/muscle (Fig1C). hiPSCm diameter was decreased with ethanol treatment. MitoLbNOX but not MitoTEMPO consistently reversed measures of post mitotic senescence (Fig1D). **Conclusion:** Multiomics directed experimental studies show that ethanol and ALD result in post-mitotic senescence that is caused by lower redox ratio but not mitochondrial free radical generation.



Disclosures: Nicole Welch: Nothing to Disclose, Pugazhendhi Kannan: Nothing to Disclose, Saurabh Mishra: Nothing to Disclose, Annette Bellar: Nothing to Disclose, Laura Nagy: Nothing to Disclose, Srinivasan Dasarathy: Nothing to Disclose

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3069 | RETINOIC ACID PATHWAY PROTECTS AGAINST OXIDATIVE STRESS IN ALCOHOL-ASSOCIATED LIVER DISEASES

Marta Melis[1] Xiao-Han Tang[1] Joseph Locker[2] Glen Pesola[1] Yue Yang[1] Lorraine Gudas[1]

[1]Weill Cornell Medicine, [2]University of Pittsburgh

Background: Oxidative stress critically drives the pathophysiology of alcohol-associated liver diseases (ALD). Previous research from our group and others demonstrated that both retinoic acid, a pan agonist of the retinoic acid receptors, and a retinoic acid receptor b2 (RARb2) synthetic agonist, more targeted toward one of the receptors, improved the liver pathology and decreased the levels of oxidative stress in metabolism-associated disorders, suggesting that retinoic acid signaling could help maintain cellular homeostasis. In support of these findings, our group recently demonstrated that oxidative stress and steatosis were increased in the livers of mice deficient for the retinoic acid receptor b (RARb), a critical retinoic acid signaling effector, fed an ethanol-based diet for 21 days. Based on these initial findings, our aim here was to further define the mechanisms whereby RARb preserves the liver against oxidative stress. **Methods:** We assessed the histopathology of female and male wild type (Wt) and hepatocyte RARb-deficient mice (AlbCre) (RARb-LKO) treated with the NIAAA/NIH Lieber DeCarli model (10 days+binge). Next, we performed *in vitro*experiments aimed to investigate the response to various stress challenges including ethanol and pro-inflammatory fatty acids in a human HepG2 RARb knockout (KO) cell line, made by using CRISPR/Cas9 technology. **Results:** A 10-day-long ethanol treatment caused increased steatosis levels in male and female RARb-LKO compared to Wt mice, confirming the higher susceptibility to lipid accumulation in RARb-LKO after a much shorter ethanol feeding model then the one used in previous studies. We next treated RARb KO hepatocytes with ethanol (100 mM) at different time points (24h and 72h) and found that reactive oxygen species (ROS) developed more rapidly than in ethanol-treated RARb KO vs parental cells. This response to ethanol was associated with greater increases in the levels of ATF4 and CHOP proteins, two key markers of a prolonged oxidative stress response known as the integrated stress response, in the RARb KO cells. Further experiments using palmitic acid to induce cellular stress again confirmed that the RARb KO hepatocytes were more susceptible to oxidative stress than parental cells. **Conclusion:** These data reveal that the retinoic acid pathway in hepatocytes, via RARb, is key for regulating the response to multiple stress signals associated with ALD pathogenesis. The protective role of RARb against ethanol-induced steatosis and stress could be leveraged to design therapies to prevent and limit ALD.

Disclosures: Marta Melis: Nothing to Disclose, Xiao-Han Tang: Nothing to Disclose, Joseph Locker: Nothing to Disclose, Glen Pesola: Nothing to Disclose, Yue Yang: Nothing to Disclose, Lorraine Gudas: Nothing to Disclose

3071 | CHOLESTEROL TOXICITY AND PON-1 LEVELS IN ALCOHOL-ASSOCIATED HEPATITIS CORRELATE WITH SEVERITY AND SURVIVAL ◆

Praveena Narayanan[1] Jiapeng Ruan[2] Saam Dilmaghani[3] Nima Fattahi[2] Sameet Mehta[2] Pramod Mistry[2] Shiny Nair[2]

[1]Mayo Clinic, [2]Yale University, [3]Mayo Clinic Rochester

Background: Severe alcohol-associated hepatitis (AH) is a life-threatening condition characterized by an inflammatory response to severe hepatic steatosis. We hypothesize that multisystemic organ dysfunction in AH is driven by bioactive lipid accumulation that triggers inflammation and disrupts membrane functions. To explore this, we performed comprehensive plasma lipidomics, investigated inflammatory biomarkers, conducted whole exome sequencing (WES), and mapped the single-cell landscape of liver biopsies. **Methods:** Peripheral blood samples from 50 AH patients and 11 healthy controls were analyzed. WES identified pathogenic variants. Shotgun lipidomic analysis of 16 lipid classes was conducted on plasma from 20 AH patients (MELD-Na >20, HDL <20mg/dL) and 20 controls. Key biomarkers included paraoxynase-1 (PON-1), lecithin cholesterol ester transferase (LCAT), cholesterol ester transfer protein (CETP), and macrophage migration inhibitory factor (MIF). Single-nuclear RNA sequencing (snRNA-seq) was performed on liver tissue from two AH patients and one control. The relationship between biomarkers and MELD-Na, survival, and 90-day mortality were assessed using Pearson correlation, Kaplan-Meier survival curves with logrank test, and multiple variable generalized linear models with binomial distribution, respectively. **Results:** Among the 50 AH patients (70% male, 82% Non-Hispanic White, mean age 46), mean MELD-Na score was 29, with a 30% 90-day mortality rate. Shotgun lipidomics revealed a significant increase in free cholesterol (FC) and decreased cholesteryl ester (CE) in AH plasma versus controls.

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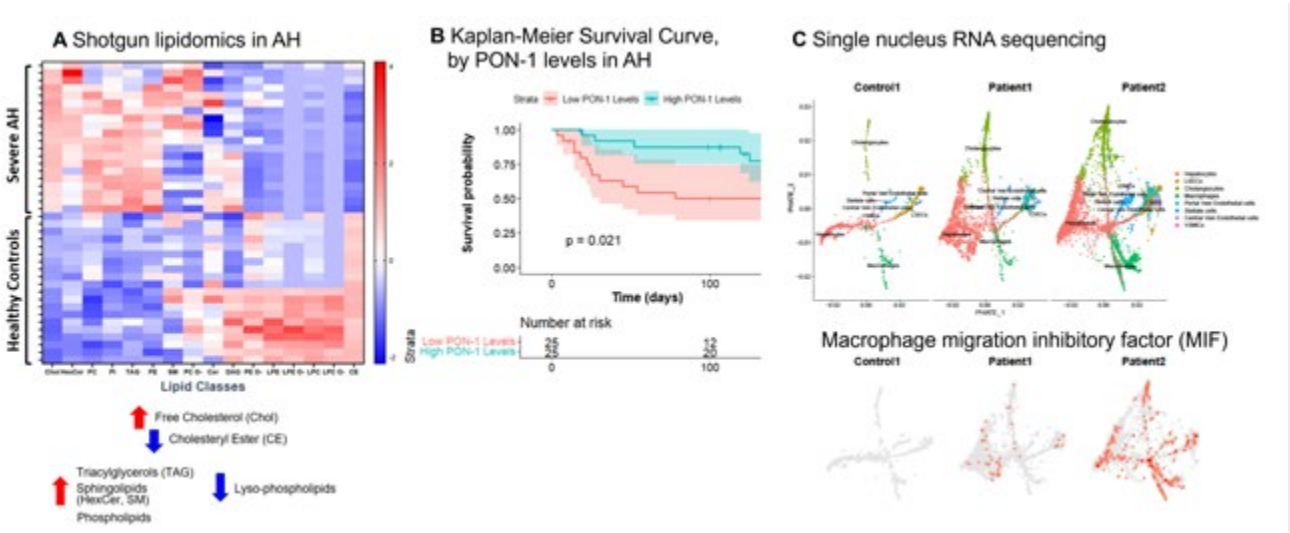
AH plasma also had higher levels of triacylglycerols, hexosylceramides, and total phospholipids, but lower levels of ceramides, sphingomyelin, and lysophospholipids (Fig1A). The ratio of FC to total phospholipids increased, indicating membrane integrity disruption. PON-1 emerged as a pathogenic variant on WES and reduced PON-1 levels in AH patients correlated with increased MELD-Na scores (*R*= -0.72, p= 4.3e-09). Lower PON-1 levels demonstrated worse transplant-free survival (p=0.021) (Fig1B), as did CETP levels (p=0.00024). LCAT activity was reduced in AH and correlated with MELD-Na, but not with survival. snRNA-seq revealed distinct inflammatory pathways mediated by different liver cells in AH patients. MIF levels were elevated in AH, with intense liver expression in Kupffer cells, SIECs, cholangiocytes, and hepatic stellate cells, associated with increased CD74 receptor expression (Fig1C). **Conclusion:** Severe AH is associated with extensive plasma lipidome disruption, contributing to membrane dysfunction and multiorgan failure. Genetic susceptibility to severe AH may involve significant lipid metabolism disruption and roles in innate immunity. Further research could help identify at-risk individuals and discover biomarkers for developing new therapies.



Disclosures: Praveena Narayanan: Nothing to Disclose, Jiapeng Ruan: Nothing to Disclose, Saam Dilmaghani: Nothing to Disclose, Nima Fattahi: Nothing to Disclose, Sameet Mehta: Nothing to Disclose, Pramod Mistry: Nothing to Disclose, Shiny Nair: Nothing to Disclose

3072 | US TRENDS IN ALCOHOL USE AFTER THE COVID-19 PANDEMIC: A NATIONAL CROSS-SECTIONAL STUDY

Divya Ayyala[1] Jennifer Dodge[2] Norah Terrault[2] Brian Lee[3]

[1]University of Southern California- Keck Medicine, [2]University of Southern California, [3]Keck School of Medicine

Background: Alcohol-associated liver disease related mortality increased during the COVID-19 pandemic, in part due to increased prevalence heavy alcohol use. Data regarding whether these changes have been sustained post-pandemic are lacking. **Methods:** Adults (age≥18) were included from the nationally-representative 2018-2022 National Health Interview Survey. We aimed to describe the prevalence (per 100 persons) of any alcohol (within 1 year of survey) and heavy alcohol (men: >5 drinks/day or 15 drinks/week; women>4 drinks/day or 8 drinks/week) use overall and stratified by sex, age, race, and Hispanic ethnicity over the study period. We tested for differences in national prevalence of current and heavy alcohol use by year compared to 2018 utilizing linear regression. **Results:** A total of 229,419,579 participants (any: 65.1%, heavy: 5.3%) were included in the study. Since 2018 [any: 68.3% (65.3-67.4%); heavy: 5.1% (4.8-5.4%)], there was an absolute increase in any and heavy alcohol use in 2020 [any: +2.7% (1.3-4.1%), p<0.001; heavy: +1.0% (0.6-1.5%), p<0.001] and in 2022 [any:+3.0% (1.6-4.3%), p<0.001; heavy:+1.2% (0.7-1.7%), p<0.001]. Compared to 2018, any and heavy alcohol use significantly increased in 2020 and 2022 in most subgroups **(Table)**. Increases (2020 vs 2018, 2022 vs 2018) were greatest among females [any: +3.2% (1.5-4.9%) p<0.001, +3.9% (2.1-5.6%) p<0.001; heavy: +0.9% (0.3-1.5%) p=0.006, +1.3% (0.6-1.9%) p<0.001], adults aged 50-64 [any: +2.4% (0.3-4.5%) p=0.03, +2.5% (0.4-4.6%) p=0.02; heavy: +1.3% (0.4-2.2%) p=0.005, +1.5% (0.5-2.5%) p=0.002], white race[any: +3.3% (1.8-4.8%)

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p<0.001, +3.4% (1.9-4.9%) p<0.0001; heavy: +1.4% (0.8-2.0%) p<0.001, +1.7% (1.1-2.3%) p<0.001], and Hispanic ethnicity [any: +6.1% (3.8-8.4%) p<0.001, +5.6% (3.7-7.5%) p<0.001; heavy: +1.3% (0.3-2.3%) p=0.01, +1.1% (0.2-2.1%) p=0.01]. **Conclusion:** Increases in any and heavy alcohol use observed during the COVID-19 pandemic continue to be sustained through 2022. Increases were observed in the overall population, especially among female sex, middle-aged adults, white race, and Hispanic ethnicity underscoring concerning public health disparities. These data should motivate public policy to limit alcohol consumption and promote alcohol use disorder treatment resources.

	Any Alcohol Use			Heavy Alcohol Use		
Overall	Prevalence per 100 person (95% CI)	mean difference between year and 2018 (95% CI)	P value	Prevalence per 100 person (95% CI)	mean difference between year and 2018 (95% CI)	P value
2018	66.3 (65.3-67.4)			5.1 (4.8-5.4)		
2020	69.0 (68.1-70.0)	2.7 (1.3-4.1)	<0.001	6.1 (5.8-6.5)	1 (0.6-1.5)	<0.001
2022	69.3 (68.4-70.2)	3.0 (1.6-4.3)	<0.001	6.3 (5.9-6.6)	1.2 (0.7-1.7)	<0.001
Female						
2018	62.4 (61.1-63.7)			5.2 (4.7-5.7)		
2020	65.6 (64.4-66.8)	3.2 (1.5-4.9)	<0.001	6.1 (5.6-6.5)	0.9 (0.3-1.5)	0.006
2022	66.3 (65.1-67.5)	3.9 (2.1-5.6)	<0.001	6.4 (6.0-6.9)	1.3 (0.6-1.9)	<0.001
Male						
2018	70.6 (69.3-71.8)			5.0 (4.6-5.5)		
2020	72.7 (71.7-73.9)	2.2 (0.4-3.9)	0.01	6.2 (5.6-6.7)	1.2 (0.5-1.9)	<0.001
2022	72.5 (71.4-73.6)	1.9 (0.2-3.6)	0.03	6.1 (5.6-6.6)	1.1 (0.4-1.8)	0.002
18-38 years						
2018	70.1 (68.5-71.8)			5.3 (4.7-5.9)		
2020	74.7 (73.3-76.2)	4.6 (2.4-6.8)	<0.001	6.3 (5.6-6.9)	1.0 (0.1-1.8)	0.02
2022	73.7 (72.4-75.1)	3.6 (1.5-5.7)	<0.001	5.8 (5.2-6.4)	0.5 (-0.3 to 1.4)	0.23
40-49 years						
2018	72.3 (70.4-74.3)			5.1 (4.3-6.0)		
2020	74.5 (72.7-76.3)	2.2 (-0.5 to 4.9)	0.11	6.5 (5.7-7.3)	1.3 (0.4-2.2)	0.005
2022	76.0 (74.4-77.7)	3.8 (1.2-6.3)	0.004	8.2 (7.2-9.2)	1.5 (0.5-2.5)	0.002
50-64 years						
2018	67.2 (65.6-68.8)			5.6 (5.0-6.2)		
2020	69.6 (68.2-71.1)	2.4 (0.3-4.5)	0.03	7.0 (6.3-7.6)	1.3 (0.4-2.2)	0.005
2022	69.7 (68.3-71.1)	2.5 (0.4-4.6)	0.02	7.2 (6.4-7.9)	1.5 (0.5-2.5)	0.002
>65 years						
2018	53.5 (51.9-66.2)			4.1 (3.6-4.6)		
2020	54.5 (53.0-56.0)	1 (-1.2 to 3.2)	0.39	4.8 (4.2-5.3)	0.7 (-0.1 to 1.4)	0.08
2022	56.6 (55.1-68.0)	3 (0.8-5.2)	0.008	4.8 (4.3-5.3)	0.7 (0.0-1.5)	0.06
White						
2018	69.2 (68.0-70.3)			5.7 (5.3-6.1)		
2020	72.5 (71.5-73.5)	3.3 (1.8-4.8)	<0.001	7.1 (6.7-7.6)	1.4 (0.8-2.0)	<0.001
2022	72.5 (71.5-73.5)	3.4 (1.9-4.9)	<0.001	7.3 (6.9-7.8)	1.7 (1.1-2.3)	<0.001
Black						
2018	56.8 (54.4-59.1)			2.8 (2.1-3.4)		
2020	60.5 (58.1-63.0)	3.8 (1.4-6.2)	0.002	3.2 (2.5-3.9)	0.5 (-0.5 to 1.5)	0.33
2022	62.7 (60.7-64.7)	5.9 (3.9-7.9)	<0.001	4.0 (3.2-4.7)	1.2 (0.2-2.3)	0.02
American Indian						
2018	53.5 (41.7-65.4)			7.2 (3.2-11.2)		
2020	61.6 (52.9-70.2)	8.0 (-0.6 to 16.7)	0.07	8.3 (4.8-11.8)	1.1 (-4.4 to 6.5)	0.7
2022	62.9 (54.9-71.0)	9.4 (1.3-17.5)	0.02	6.2 (3.3-9.1)	-1.1 (6.1 to 4.0)	0.68
Asian						
2018	52.2 (48.6-55.7)			2.1 (1.2-3.0)		
2020	54.7 (51.6-57.8)	2.5 (-0.6 to 5.6)	0.11	2.3 (1.4-3.1)	0.2 (-1.1 to 1.4)	0.80
2022	53.3 (50.5-56.1)	1.1 (-1.7 to 3.9)	0.44	1.7 (1.0-2.4)	-0.4 (-1.5 to 0.7)	0.47
Hispanic						
2018	59.1 (56.6-61.6)			2.6 (2.0-3.3)		
2020	65.2 (62.9-67.6)	6.1 (3.8-8.4)	<0.001	3.9 (3.1-4.7)	1.3 (0.3-2.3)	0.01
2022	64.7 (62.8-66.6)	5.6 (3.7-7.5)	<0.001	3.8 (3.1-4.4)	1.1 (0.2-2.1)	0.01
Non-Hispanic						
2018	67.8 (66.7-68.8)			5.6 (5.2-6.0)		
2020	69.8 (68.8-70.8)	2.1 (0.6-3.5)	0.006	6.6 (6.2-7.0)	1.0 (0.5-1.5)	<0.001
2022	70.3 (69.3-71.2)	2.5 (1.1-3.9)	<0.001	6.8 (6.4-7.2)	1.2 (0.7-1.8)	<0.001

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3073 | LONGITUDINAL OUTCOMES AND RECOVERY IN PATIENTS WITH DECOMPENSATED ALCOHOL ASSOCIATED LIVER DISEASE

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Background: Alcohol-associated liver disease (ALD) is associated with significant morbidity and mortality, but hepatic recovery is achievable, particularly with abstinence from alcohol. We evaluated longitudinal outcomes in patients with decompensated liver disease in the setting of recent alcohol use. **Methods:** This prospective cohort included adult patients hospitalized at our center with decompensated ALD and less than 6 months of abstinence from alcohol. Serial measurements were taken during follow-up over the 12 months after the index hospitalization, including (1) laboratory tests for liver function and alcohol intake,(2) CAP and liver stiffness (kPa) by vibration-controlled transient elastography (VCTE), (3) frailty, and (4) quality of life by SF-36. Relationships were evaluated by t-test, ANOVA, and Pearson's correlation. **Results:** Of 207 patients enrolled, 75 (36%) completed at least one outpatient follow-up visit in our hepatology clinic, with a median age of 44 years (37-52), 53% male, 38% White, and 44% Hispanic. Of the remainder, 34 (16%) died before being able to follow-up, 55 (27%) received liver transplant, and 43 (21%) were lost to follow-up. During the first year, the median MELD-Na improved from 26 to 10 ($p < 0.001$), and over half of the patients achieved Child-Pugh A status (Table); 19% died, 5% received liver transplant, and 25% reported return to alcohol use. Improvement in MELD-Na was associated with lower VCTE scores ($r=0.41$, $p<0.01$) and improved mid-arm muscle circumference ($r=-0.22$, $p=0.02$), as well as higher scores on physical functioning ($r=-0.32$, $p<0.01$) and physical role ($r=-0.31$, $p<0.01$) domains of the SF-36. Although there were improvements in physical functioning, physical role limitations, energy/fatigue, and general health, lesser gains were seen in the emotional role limitation, emotional well-being, and pain component subscales of the SF-36. **Conclusion:** Significant improvements in liver function, frailty, and physical function were observed within the first year after hospitalization for decompensated ALD, and the majority of patients were able to maintain abstinence from alcohol. However, elastography measurements remain elevated, and patients continue to report deficits in physical and emotional health, highlighting the ongoing need to support this high-risk population to achieve positive health outcomes.

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	Month 1 N = 66	Month 3 N = 48	Month 6 N = 38	Month 12 N = 24	p-value
Median MELD (IQR)	20 (15-24)	16 (11-19)	14 (10-18)	10 (8-14)	<0.001
Median MELD-Na (IQR)	22 (16-28)	16 (12-21)	17 (10-20)	10 (8-15)	<0.001
Child-Pugh class (%)					
A	13%	33%	28%	58%	0.001
B	24%	30%	45%	26%	
C	63%	37%	28%	16%	
Average SF-36 (SD)					
Physical Function	44 (29)	58 (30)	65 (28)	70 (31)	0.001
Physical Role Limitation	16 (28)	40 (42)	46 (45)	57 (45)	<0.001
Emotional Role Limitation	44 (43)	68 (41)	60 (41)	76 (37)	0.10
Energy/Fatigue	41 (25)	53 (22)	55 (27)	56 (29)	0.01
Emotional Wellbeing	65 (21)	74 (16)	69 (25)	69 (27)	0.19
Social Functioning	52 (32)	62 (28)	69 (27)	68 (29)	0.04
Pain	53 (29)	56 (34)	60 (33)	65 (35)	0.40
General Health	45 (21)	56 (21)	56 (27)	59 (26)	0.03
Liver Frailty Index (IQR)	4.20 (3.76-4.83)	4.04 (3.57-4.33)	3.78 (3.45-4.39)	3.34 (2.85-4.10)	0.003
Mid-arm muscle circumference, cm (IQR)	23.9 (20.8-29.4)	26.2 (20.9-30.0)	28.0 (21.2-30.0)	29.6 (25.5-31.2)	0.08
Fibroscan (IQR)					
Median kPa	63 (46-75)	48 (43-72)	46 (25-65)	47 (20-64)	0.01
Median CAP	222(191-250)	235 (199-268)	221 (207-231)	239 (201-261)	0.59
Reported alcohol use (%)	7%	23%	11%	17%	0.04

Disclosures: Weiyu Wu: Nothing to Disclose, Brianna Cavalla: Nothing to Disclose, Gurpreet Judge: Nothing to Disclose, Allison Kwong: Nothing to Disclose

3074 | BIASED AGONISM OF FPR1 SIGNALING IN NEUTROPHILS MITIGATES ALCOHOL-ASSOCIATED LIVER DISEASE

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Background: Individuals suffering from alcohol-associated liver disease (ALD) tend to develop an inflammatory state, as evidenced by elevated circulating levels of inflammatory cytokines and local neutrophil infiltration. Neutrophils, also known as polymorphonuclear cells, are the most abundant circulating leukocytes in humans and a dominant leukocyte population in experimental mice. It's well-known that neutrophils play a crucial role in the development of ALD. Several ongoing studies are currently focused on manipulating neutrophils for the treatment of a wide range of diseases. Formyl peptide receptor 1 (FPR1), a G-protein-coupled receptor (GPCR), is highly expressed in multiple immune cells such as neutrophils and macrophages and primarily regulates pro-inflammatory response, leading to chemotaxis, degranulation, and oxidative burst during infection. FPR1 interacts with various ligands, including bacteria-derived N-Formyl methionyl-leucyl-phenylalanine (fMLP), which stimulates neutrophil chemotaxis. However, whether and how neutrophilic FPR1 signaling affect the development of ALD remain unclear. **Methods:** In this study, we performed two approaches to induce FPR1 dysfunction: the use of a selective inhibitor of FPR1, Cyclosporin (CSH), and the generation of neutrophil-specific *Fpr1* knockout mice

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(*Fpr1*$^{f/f}$ S100a8-Cre+). The NIAAA model is achieved through chronic ethanol feeding (10 days of ad libitum oral feeding with the Lieber-DeCarli ethanol liquid diet) combined with a single binge ethanol feeding. Ultimately, after the initial screening process *in vitro*, where compounds are tested in a controlled laboratory environment, the selected compounds will be progressed to the next stage of evaluation in experimental mouse models. **Results:** Contrary to our expectation, administration of CsH led to greater liver injury and inflammation in both a chronic-plus-binge and a four-week chronic ethanol feeding models. Furthermore, neutrophil-specific *Fpr1* deficient mice were more susceptible to alcohol-induced liver disease compared with wild-type (WT) mice as demonstrated by higher levels of serum ALT and AST, greater lipid accumulation, elevated oxidative stress levels, and increased infiltration of immune cells. Transcriptomics analysis suggested that neutrophil-specific FPR1 signaling affected neutrophil maturation and differentiation. The flow cytometry **Results:** further showed that neutrophils from *Fpr1*-deficient mice exhibited a trend toward immaturity (decreased proportion of CXCR4+CD62L- and increased proportion of CD62L+CXCR2+ neutrophils). Interestingly, a high concentration of fMLP can induce the differentiation of neutrophils into a senescent phenotype, leading to an increase in the population of CXCR4+CD62L+ neutrophils. Most importantly, high concentrations of fMLP promoted CXCR4 upregulation in neutrophils in an ERK signaling-dependent manner, facilitating neutrophil homing to the bone marrow to be eliminated in ALD. Finally, we screened for biased agonists of FPR1 that selectively activated the ERK signaling pathway and upregulated the expression of CXCR4 in neutrophils. We will continue our drug screening work to discover additional potential compounds. These screened compounds will further undergo animal experiments to study their pharmacological properties. **Conclusion:** Taken together, our findings indicate that the biased activation of neutrophil-specific FPR1 elevates the surface expression of CXCR4 in neutrophils by activating the ERK signaling pathway to trigger neutrophil homing, thus alleviating ALD-related inflammation. Our findings not only identify a novel function of FPR1 but also may provide a novel strategy for the treatment of ALD.

Disclosures: Shengying Qian: Nothing to Disclose

3075 | ALCOHOL BINGE DRINKING IMPAIRS LIPID METABOLISM IN HEALTHY HAMSTERS AND AGGRAVATES LIVER LESIONS IN DIET-INDUCED OBESE MASH HAMSTERS

Francois Briand[1] *Natalia Breyner*[1] *Estelle Grasset*[1] *Thierry Sulpice*[1]

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Background: While mouse and rat are not convenient to study the effects of alcohol binge drinking, we previously observed that the golden Syrian hamster spontaneously shows a high preference for alcohol and may therefore represent a better animal model. Here we aimed to evaluate the effects of binge drinking (BD) in lean healthy hamsters and diet-induced obese MASH hamsters. **Methods:** The effects of alcohol BD (40% alcohol at 5mL/kg p.o., 3 times per week) were first evaluated for 4 weeks in lean healthy hamsters fed a control chow diet. Hamsters treated with saline were used as control. In a second set, obesity and MASH were induced with a free choice diet, which presents golden Syrian hamsters with a choice between control chow or high fat/cholesterol diet, and normal water or 10% fructose water. After a 20-week diet induction, animals were maintained on the same diet with the 10% fructose water supplemented with 5% alcohol, without (control) or with alcohol BD (40% alcohol at 5mL/kg p.o., 3 times per week) for 5 weeks. **Results:** Compared to control saline, BD in lean hamsters significantly reduced body weight gain, plasma triglycerides and total cholesterol levels. Fast protein liquid chromatography (FPLC) showed that BD lowered HDL-cholesterol levels, while it increased triglycerides levels in all lipoprotein fractions (i.e. VLDL, LDL and HDL). Although 4-week of BD did not induce any liver lesion, hepatic expression of genes involved in lipogenesis (ACC, Srebp-1c, SCD1, and DGAT2) were all significantly increased, while genes involved in alcohol metabolism (Cyp2E1, ADH1 and ALDH1) showed lower expression. Compared to respective control, BD in obese MASH hamsters led to higher plasma triglycerides levels in HDL fractions (as observed by FPLC) and significantly higher hepatic inflammation and ballooning scores. Compared to control, BD increased liver fibrosis, as measured with % Sirius Red labelling ($p<0.05$). BD reduced the hepatic expression of genes involved in alcohol metabolism (Cyp2e1 and ADH1) and significantly raised the expression of genes involved in lipogenesis (ACC and SCD1), inflammation (IL-1b, IL-6, and MCP-1), cell death (caspase 3) and fibrosis (a-SMA, Col1a1, Col3a1 and TIMP1). **Conclusion:** Alcohol binge drinking impairs lipid metabolism in healthy hamsters and aggravates liver lesions in diet-induced obese MASH hamsters. This preclinical model will help to evaluate drugs, in a context of moderate to heavy alcohol use, and their potential benefits in humans.

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Disclosures: Francois Briand: Physiogenex: Employee, Physiogenex: Stock – privately held company, Natalia Breyner: Nothing to Disclose, Estelle Grasset: Nothing to Disclose, Thierry Sulpice: Nothing to Disclose

3076 | DECIPHERING THE IMPACT OF MYELOID CELL-DERIVED OSTEOPONTIN IN ALCOHOL-ASSOCIATED LIVER DISEASE

Nithyananthan Subramaniyam[1] *Sukanta Das*[1] *Hui Han*[1] *Xiaodong Ge*[1] *Sai Santosh Babu Komakula*[1] *Chao Wang*[1] *Daniel Lantvit*[1] *Grace Guzman*[1] *Natalia Nieto*[1]

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Background: Alcohol use disorder (AUD) frequently results in alcohol-associated liver disease (ALD), a condition that initially manifests as hepatic steatosis and can advance to alcoholic steatohepatitis (ASH). Current treatment options are limited and include corticosteroid therapy, with liver transplantation in severe cases. Osteopontin (OPN, encoded by *SPP1*), a matricellular protein, has been shown to attenuate hepatic steatosis in ALD by diminishing liver inflammation and reducing intestinal permeability. Accumulating evidence suggests the existence of macrophage subsets expressing high OPN in various models of chronic liver disease. This study investigates the specific role of myeloid cell-derived OPN in the progression and mitigation of ALD. **Methods:** We analyzed publicly available human alcoholic hepatitis datasets for *SPP1* expression. To induce early ALD, 12-week-old male and female wild-type (WT), *Spp1*$^{KI\text{-}Mac}$, *Spp1*$^{\Delta Mac}$, *Spp1*$^{KI\text{-}KC}$, and Arg2$^{\Delta Hep}$ mice were fed a control or ethanol Lieber-DeCarli diet for six weeks. Liver histopathology, serum markers of liver injury, and hepatic triglycerides were analyzed. **Results:** Transcriptomics analysis of human ASH subjects demonstrated increased myeloid cell-specific expression of *SPP1*, confirmed by immunohistochemistry. Feeding of an alcohol diet to WT mice induced hepatic steatosis in the mid-zonal area. However, the overexpression of *Spp1* in macrophage decreased hepatic steatosis compared with WT mice, as evidenced by gross weight and histological and serum biochemical analysis. Meanwhile, *Spp1*$^{\Delta Mac}$ mice fed with ethanol exhibited significantly higher levels of hepatic steatosis than WT and *Spp1*$^{KI\ Mac}$ mice. Further, feeding an alcohol diet to Kupffer cells-specific OPN overexpressing mice displayed significant protection against ALD in the WT mice. Overexpression of OPN in the macrophage resulted in increased levels of hepatic oncostatin M, which is reported to activate Arg2. Feeding of alcohol diet to and Arg2$^{\Delta Hep}$ showed increased hepatic steatosis than the WT mice. **Conclusion:** The macrophage and Kupffer cell-specific overexpression of OPN results in the secretion of oncostatin M, which modulates the hepatic expression of Arg2 and offers protection against ALD.

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3077 | DYSREGULATED LYSOSOME BIOGENESIS AND ABNORMAL LYSOSOMAL ACTIVITY POTENTIALLY DRIVE HUMAN ALCOHOL-ASSOCIATED LIVER DISEASE

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Background: Lysosomes are critical for degrading cellular macromolecules, thereby maintaining cellular homeostasis. In rodents fed ethanol, lysosomes are downregulated, leading to accumulation of undegraded polymeric substrates. However, the connection between these changes in human alcohol-associated liver disease (ALD) is not fully understood. Here, we investigated lysosomal alterations in livers of human subjects with alcohol-induced hepatitis (AH) and cirrhosis (AC) to assess the role of lysosomes in ALD pathology. **Methods:** Livers of normal human subjects or those with AH or AC were subjected to immunostaining, RT-PCR, and Western blot (WB) analyses. **Results:** Compared with normal livers, mRNA levels encoding Transcription Factor EB (TFEB), which regulates autophagy and lysosome biogenesis, were elevated 4.5-fold in livers with AH and by 2.5-fold in those with AC. The upregulation of TFEB mRNA was associated with increased expression of two of its targets, *PGC1α* and *VAT6V1H* (acidifies lysosomes). In AH livers, mRNAs encoding the lysosomal-associated membrane proteins *LAMP1* and *LAMP2* were unchanged. However, in AC livers, both *LAMP1* and *LAMP2A*

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mRNA levels were elevated, compared with normal livers. WB analyses of AH and AC liver homogenates revealed significantly higher levels of TFEB, the lysosomal protease cathepsin B (Cat B), and the lysosome damage-sensing protein Galectin-3 (Gal-3). Compared with normal livers, LAMP1 levels were lower in AH livers but were higher in AC livers. Immunostaining showed enhanced TFEB expression in both the cytoplasm and nuclei of hepatocytes of AH livers. Additionally, Cat B, Gal-3, and the autophagosome marker LC3B, showed increased staining in hepatocytes of AH livers compared with normal livers. In normal livers, LAMP1/2 and Cat B appeared as small, punctate structures, whereas in AH livers, they were larger and aggregated. In AH livers, Cat B was widely distributed throughout the entire hepatocyte, and it exhibited enhanced interaction with lipid droplet (LD) membranes. Gal-3, LC3B, and P62 were also associated with LD membranes. High colocalization of cat B and LAMP2 with Gal-3 was observed in AH livers. **Conclusion:** Our findings suggest that in human ALD, there is enhanced lysosome biogenesis to process high volume of substrates like lipids. This abnormal substrate processing causes lysosome aggregation, damage, and leakage, leading to hepatocyte injury, thereby contributing to ALD pathogenesis.

Disclosures: Ahmed Bakheet: Nothing to Disclose, Paul Thomes: Nothing to Disclose, Murugadas Anbazhagan: Nothing to Disclose

3078 | BIOCHEMICAL AND HISTOLOGICAL CLUES IN METABOLIC DYSFUNCTION AND ALCOHOLIC ASSOCIATED LIVER DISEASE (METALD)

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Background: Metabolic syndrome and alcohol consumption are the two major causes of liver disease but one of the two conditions often predominates while the other acting as cofactor of morbidity/mortality in combined severe alcohol associated steatohepatitis (ASH) and non-alcoholic steatohepatitis (NASH). There is a limited data to define the contribution of each of the two pathologies and diagnosis of steatohepatitis due to a combination of the two. We undertook this study to discern possible histological clues in patients with the combined etiology.. **Methods:** We included 420 cases of histologically confirmed cases of NASH and ASH (Jan 2022-Dec 2023), and recorded metabolic disorders and alcohol intake of each patient. Cases were categorized in 3 groups: MAFLD (metabolic dysfunction associated fatty liver disease, n=201), MetALD (metabolic dysfunction alcoholic associated liver disease, n=124), ALD (alcohol associated liver disease, n=89) and studied for various histological and biochemical parameters. **Results:** Out of 201 patients of MAFLD, 68.8 % had obesity with body mass index (BMI) >25 kg/m^2, 9.2% had history of diabetes mellitus type 2 (DM-2), 6.4 % had history of hypertension, 62.41 % of the cases had dyslipidemia with 25.53% of cases of hypertriglyceridemia and 36.87% cases of low HDL levels. Out of 124 cases of MetALD, along with history of alcohol intake ; 54.8% had obesity, 26.6 % had history of DM-2, 16.1 % had history of hypertension, 66.93% of cases had dyslipidemia with 23.38% cases of hypertriglyceridemia and 43.54% cases of low HDL levels . High density lipoprotein (HDL) levels and HDL/TG ratio was found to be lowest in MetALD group (22.6 ± 14.1 and 0.20± 0.1) (p <0.001). Alanine aminotransaminase (ALT) was highest in MAFLD (68.9± 31.1 IU/L) and serum AST levels was found to be highest in MetALD (157±84.73 IU/L) (p=0.001, <0.001; respectively). Marked steatosis noted in 15.6% of cases of MAfLD as compared to 7.9 % of ALD and 13.7% of MetALD cases (p<0.001). MetALD cases (47.6%) cases show more frequent and prominent ballooning degeneration than ALD cases (40.4%) and MAFLD (23.2%) (p<0.001). Nuclear vacuolation was seen in majority of MAFLD (64.5%) and relatively less in MetALD (33.9%) and ALD (31.5%){p<0.001}. Marked ductular proliferation (>10 ductules/tracts) was most prominently noted in MetALD (89%) than others categories ALD (65%), and MAFLD (41.5%) (p <0.001) Mild or no fibrosis was seen in majority of MAFLD cases while 28.4% cases showed established cirrhosis in contrast to 55.6% cases of MetALD and 57.3% of ALD hadestablished cirrhosis (P value <0.001). **Conclusion:** MetALD cases showed the lowest high density lipoprotein (HDL) levels and HDL/TG ratio. Histologically MetALD had marked ductular reaction and most pronounced ballooning degeneration as compared to ALD, MAFLD.

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le 1: Comparison of various parameters in MAFLD, MetALD, and ALD

Parameters	Diagnosis			p value
	MAFLD (n = 201)	METALD (n = 124)	ALD (n = 89)	
Age (Years)	43.26 ± 14.73	42.52 ± 8.62	41.21 ± 9.85	0.059
Age***				<0.001
<20 Years	15 (10.6%)	0 (0.0%)	0 (0.0%)	
20-29 Years	13 (9.2%)	5 (4.0%)	6 (6.7%)	
30-39 Years	22 (15.6%)	49 (39.5%)	36 (40.4%)	
40-49 Years	36 (25.5%)	37 (29.8%)	32 (36.0%)	
50-59 Years	42 (29.8%)	31 (25.0%)	10 (11.2%)	
60-69 Years	12 (8.5%)	2 (1.6%)	5 (5.6%)	
70-79 Years	1 (0.7%)	0 (0.0%)	0 (0.0%)	
Gender***				<0.001
Male	108 (76.6%)	123 (99.2%)	88 (98.9%)	
Female	33 (23.4%)	1 (0.8%)	1 (1.1%)	
Height (cm)***	162.73 ± 11.10	168.08 ± 8.06	169.50 ± 7.78	0.014
Weight (kg)	79.89 ± 16.05	83.43 ± 12.90	76.30 ± 6.22	0.132
BMI (Kg/m²)	30.16 ± 5.26	29.47 ± 3.59	26.54 ± 0.27	0.356
BMI***				<0.001
<25 Kg/m²	44 (31.2%)	56 (45.2%)	86 (96.6%)	
>25 Kg/m²	97 (68.8%)	68 (54.8%)	3 (3.4%)	
Alcohol (Present)***	0 (0.0%)	124 (100.0%)	89 (100.0%)	<0.001
DM (Present)***	13 (9.2%)	33 (26.6%)	0 (0.0%)	<0.001
HTN (Present)***	9 (6.4%)	20 (16.1%)	0 (0.0%)	<0.001
S. HDL (mg/dL)***	39.36 ± 10.53	22.56 ± 14.14	48.92 ± 7.54	<0.0011
S.Triglycerides (mg/dL)	131.79 ± 54.91	156.68 ± 91.32	111.00 ± 25.17	0.4591
HDL/Triglycerides Ratio***	0.35 ± 0.16	0.20 ± 0.19	0.46 ± 0.15	<0.0011
Steatosis***				<0.0012
< 5%	1 (0.7%)	26 (21.0%)	15 (16.9%)	
5 To 33%	74 (52.5%)	52 (41.9%)	35 (39.3%)	
34 To 66%	44 (31.2%)	29 (23.4%)	32 (36.0%)	
>66%	22 (15.6%)	17 (13.7%)	7 (7.9%)	
Lobular Inflammation***				<0.0012
None	11 (7.8%)	11 (8.9%)	1 (1.1%)	
<2 Foci/20 X	102 (72.3%)	37 (29.8%)	34 (38.2%)	
2-4 Foci/20 X	27 (19.1%)	54 (43.5%)	38 (42.7%)	
>4 Foci/20 X	1 (0.7%)	22 (17.7%)	16 (18.0%)	
Ballooning***				<0.0012
None	11 (7.8%)	14 (11.3%)	8 (9.0%)	
Few	105 (74.5%)	51 (41.1%)	45 (50.6%)	
Many	25 (17.7%)	59 (47.6%)	36 (40.4%)	
Portal Inflammation***				<0.0012
None	2 (1.4%)	0 (0.0%)	0 (0.0%)	
Minimal	11 (7.8%)	0 (0.0%)	0 (0.0%)	
Mild	111 (78.7%)	84 (67.7%)	57 (64.0%)	
Moderate	17 (12.1%)	38 (30.6%)	31 (34.8%)	
Severe	0 (0.0%)	2 (1.6%)	1 (1.1%)	

Disclosures: Chhagan Bihari: Nothing to Disclose, Sujata Kumari Prasad: Nothing to Disclose, Archana Rastogi: Nothing to Disclose, Sherin Thomas: Nothing to Disclose, Harsh Tevethia: Nothing to Disclose, Shiv Kumar Sarin: Nothing to Disclose

3079 | THE IMPACT OF TYPE 2 DIABETES (T2D) ON THE OUTCOMES OF LIVER TRANSPLANTATION (LT) AMONG PATIENTS WITH ALCOHOL-ASSOCIATED LIVER DISEASE (ALD) IN THE UNITED STATES

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Background: ALD and metabolic dysfunction-associated steatotic liver Disease (MASLD) are top indications for LT in the U.S. T2D is closely associated with MASLD and can negatively impact outcomes of patients with chronic liver disease (CLD). Our aim was to assess the impact of pre-transplant T2D on the outcomes of LT

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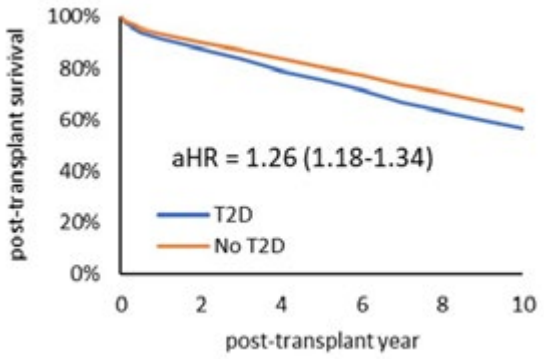
in ALD patients. **Methods:** We used Scientific Registry of Transplant Recipients (SRTR) 2008-2022 to collect data for all patients ≥18 years old who were listed or received LT with ALD in the U.S. The study outcomes were removal from LT list due to improvement or death/deterioration (on-the-list mortality) and time to post-LT mortality (cut-off date March 2, 2023). **Results:** We included 49,928 LT candidates with ALD: 54.2±9.4 years, 74% male, 20% covered by Medicare and 23% by Medicaid, 15% with superimposed CHC, 12% HCC, MELD score 22.2 ± 10.3. The share of ALD among LT listings steadily increased from 21% (2008) to 41% (2022). Among patients with ALD, 18% had pre-transplant T2D. ALD candidates with T2D had higher on-the-list mortality than those without T2D: cumulative 22% vs. 17% (p<0.0001). In contrast, 4.2% patients with T2D vs. 6.8% non-T2D were removed from the list due to improvement (p<0.0001). In multivariate regression analysis adjusted for socio-demographic factors, non-hepatic comorbidities and markers of severity (higher MELD score, decompensation, HCC, TIPSS, re-transplantation), having pre-transplant T2D was independently associated with a higher risk of on-the-list mortality in ALD: OR = 1.21 (1.13-1.29), p<.0001. Of the LT recipients with ALD (n=28,708) 21% died and 4% had graft failure during post-LT follow-up (median=45 months, IQR=19-85 months). The 1-, 3- and 5-year post-LT survival of patients with ALD was 93%, 86% and 79%, respectively. Post-LT mortality was higher in ALD patients with pre-transplant T2D (Figure). In multivariate survival analysis, pre-transplant T2D was independently associated with higher post-LT mortality: adjusted hazard ratio (aHR) (95% CI) = 1.26 (1.18-1.34) in all ALD, 1.30 (1.21-1.40) in ALD without HCC, 1.12 (0.96-1.30) in ALD with HCC. There was no association of T2D with the risk of graft failure (p>0.05). **Conclusion:** Overall, patients with ALD have good post-LT survival. However, presence of pre-transplant T2D in patients with ALD is independently associated with an increased risk of adverse waitlist and post-LT outcomes.



Disclosures: Maria Stepanova: Nothing to Disclose, Robert Wong: Theratechnologies: Grant/Research Support, Durect: Grant/Research Support, Gilead Sciences: Grant/Research Support, Exact Sciences: Grant/Research Support, Theratechnologies: Grant/Research Support, Durect Corporation: Grant/Research Support, Ashwani Singal: Nothing to Disclose, Veronica Nguyen: Nothing to Disclose, Linda Henry: Nothing to Disclose, Saleh Alqahtani: Nothing to Disclose, Zobair Younossi: Nothing to Disclose

3080 | PRIOR DIAGNOSIS OF DECOMPENSATED ALCOHOL-ASSOCIATED LIVER DISEASE DOES NOT INCREASE RISK OF ALCOHOL RELAPSE DURING TRANSPLANT EVALUATION AND MAY INCREASE RISK OF POST-TRANSPLANT ALCOHOL RELAPS

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Background: Access to liver transplant (LT) patients with alcohol-associated liver disease (ALD) has expanded in the past decade. ALD is now the leading indication for LT in the US, and most centers no longer have a strict 6-month abstinence rule. Some centers, however, may only consider patients with recent alcohol consumption for LT if they are presenting with their first hepatic decompensation. We sought to examine the impact of a prior diagnosis of decompensated ALD in patients referred for LT with < 6 months of alcohol abstinence on alcohol relapse during LT evaluation (LTE) and post-LT. **Methods:** RESOLVE-ALD is a multi-center retrospective cohort

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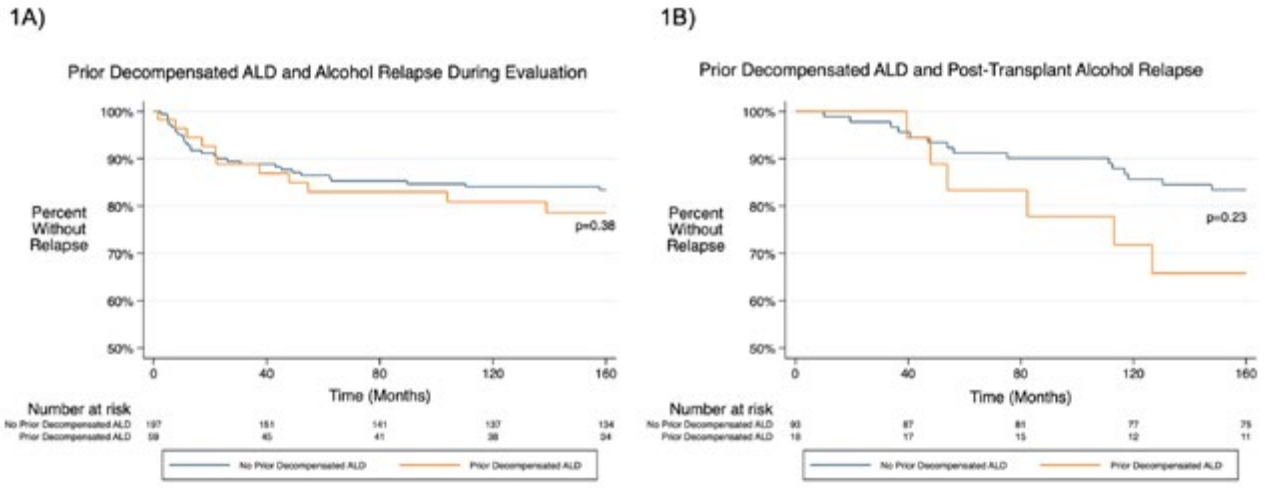
study of patients with ALD referred for LTE with < 6 months of alcohol abstinence. We compared patients with and without a "prior decompensated ALD diagnosis," defined as a previous diagnosis of alcohol-associated hepatitis (AAH) or hepatic decompensation secondary to cirrhosis with subsequent ongoing alcohol use. Alcohol relapse was defined as any use of alcohol after referral for LTE. Cox regression survival analyses adjusting for age, inpatient evaluations, sex, prior and current AUD treatment, psychiatric history, race and ethnicity, insurance status, quantity of alcohol consumption prior to referral, and MELD score evaluated the effect of prior decompensated ALD diagnosis on relapse during LTE and post-LT. Patient mortality was censored as appropriate. **Results:** 256 patients referred for LTE were included in our analyses. 59 (23%) patients had a prior diagnosis of decompensated ALD: 30 (12%) were diagnosed with AAH and 51 (20%) with a hepatic decompensation. Prior decompensated ALD was numerically higher in female patients (30%) than male patients (19%). Patients with prior decompensated ALD were more likely to be engaged in formal alcohol use disorder treatment (53% compared to 27%) and were less to undergo inpatient evaluation (24% versus 54%). 41 (16%) patients experienced alcohol relapse during LTE and 22 (20%) patients post-LT. A prior diagnosis of decompensated ALD was not associated with risk of alcohol relapse during LTE (HR 0.70, 95% CI 0.32-1.55), however we observed a trend toward increased relapse post-LT (HR 2.21, 95% CI 0.39-28.14); this was non-significant and limited by a small number of events. (Figure 1A and 1B). A sensitivity analysis including all prior liver disease diagnoses (including abnormal liver enzymes, compensated cirrhosis, and hepatic steatosis) demonstrated similar findings. **Conclusion:** In a multi-center cohort study of patients with ALD and <6 months of alcohol abstinence referred for transplant evaluation, a diagnosis of decompensated ALD prior to referral was not associated with increased risk of alcohol relapse during LTE, but may be associated with increased risk of relapse post-transplant, albeit this was limited by a small sample size.



Disclosures: Sasha Deutsch-Link: Nanbar Health: Consultant, Kevin Wang: Nothing to Disclose, Weiyu Wu: Nothing to Disclose, Allison Kwong: Nothing to Disclose, Kawthar Mohamed: Nothing to Disclose, Nicholas Lim: Nothing to Disclose, Katherine Cooper: Nothing to Disclose, Deepika Devuni: Avania Medical: Grant/Research Support, Intercept: Grant/Research Support, Anjana Rajan: Nothing to Disclose, Amanda Cheung: Nothing to Disclose, Kaleb Tesfai: Nothing to Disclose, Veeral Ajmera: Nothing to Disclose, Hersh Shroff: Nothing to Disclose

3081 | ALCOHOL-ASSOCIATED LIVER DISEASE (ALD) IS ASSOCIATED WITH LESS ADVERSE OUTCOMES COMPARED TO NON-ALCOHOL-ASSOCIATED LIVER DISEASE (NAALD) IN HOSPITALIZED PATIENTS WITH COVID-19

Jessica Musto[1] *Thomas Piasecki*[2] *Wendy Slutske*[2] *Michael Lucey*[1]

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Background: The interaction of liver disease with COVID-19 infection and the potential influence of alcohol has not been well described. This study utilized a prospective American multicenter cohort of patients hospitalized with COVID-19 to consider the impact of comorbid liver disease in general, and ALD in particular, on short-term patient outcomes. **Methods:** Data from all patients with COVID-19 who were hospitalized at 21 participating healthcare

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systems between February 1, 2020 and January 31, 2022 were examined. Subjects were followed until hospital discharge or death. The analyses used generalized linear mixed model logistic regression including random intercepts to account for the clustering of patients within healthcare systems. **Results:** Among 145,944 patients hospitalized for COVID-19, 7,951 (5.4%) had comorbid liver disease, among whom 1,153 (14.5%) had ALD, while 6,798 (85.5%) had non-alcohol-associated liver disease (NAALD). The presence of liver disease was associated with increased odds of all tested adverse outcomes in patients hospitalized with COVID-19, with increased odds of mortality (aOR 3.43, p<0.001), assisted ventilation (aOR 2.94, p<0.001) and ICU admission (aOR 2.27, p<0.001). [TP1] There was a clear gradient of mortality among severity of liver disease such that fibrosis OR < cirrhosis OR < decompensated cirrhosis OR. When compared to patients with NAALD, ALD was independently associated with reduced odds of mortality (aOR 0.30, p<0.001), assisted ventilation (aOR 0.31, p<0.001), and ICU admission (aOR 0.47, p<0.001). On multivariable analysis liver disease, male gender, increasing age, higher BMI and former smoking status, but not ALD, were associated with increased mortality from COVID-19. **Conclusion:** In this large, prospective, observational cohort of hospitalized COVID-19 patients, the presence of liver disease increased the odds of all adverse outcomes with a mortality gradient that correlated with severity of liver disease. When compared to liver disease not related to alcohol, ALD was associated with reduced odds of mortality, requiring assisted ventilation and ICU admission. The reasons for this apparent paradoxical protective effect of ALD among patients with comorbid liver disease and severe COVID-19 infection deserves further elucidation.

Disclosures: Jessica Musto: Nothing to Disclose, Thomas Piasecki: Nothing to Disclose, Wendy Slutske: Nothing to Disclose, Michael Lucey: Nothing to Disclose

3082 | UNDERSTANDING THE IMMUNE LANDSCAPE OF ALCOHOL-RELATED LIVER DISEASE THROUGH FIBRO-INFLAMMATORY SEROLOGICAL BIOMARKERS

Andressa de Zawadzki[1] Maja Thiele[2] Stine Johansen[2] Ida Villesen[2] Peter Andersen[2] Morten Karsdal[1] Aleksander Krag[3] Diana Julie Leeming[1]

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Background: Excessive alcohol consumption in alcohol-related liver disease (ALD) can progress to liver fibrosis, cirrhosis, and end-stage liver failure. Severe ALD patients exhibit disrupted gut microbiome, damaged gut barrier with bacterial translocation and impaired immune system. The extracellular matrix (ECM) provides potential markers for investigating inflammatory and fibrotic processes in gut-liver axis following ALD progression and may aid in understanding the immune landscape behind fibrosis using the novel concept of hot and cold fibrosis which refers to the presence of immune cells within the fibrotic tissues. Herein we aimed to investigate diagnostic and prognostic utility of ECM biomarkers reflecting fibrogenesis, fibrolysis and immune cell activity in ALD. **Methods:** Serum levels of ECM biomarkers PRO-C6 (endotrophin; type VI collagen formation) ; CTX-III (matrix metalloproteinase dedraged fragment of cross-linked type III collagen), neutrophil activity marker CPa9-HNE (calprotectin fragment degraded via neutrophil elastase), T-cell activity marker C4G (type IV collagen fragment degraded via granzyme-B) and PC3X (cross-linked N-terminal pro-peptide of type III collagen) were assessed in a cross-sectional cohort of 450 patients with biopsy-proven ALD and 147 matched healthy controls. Biomarkers levels were investigated in relation to histological scores and prediction performance for the risk of death and decompensation over a median of 5.9 years of follow-up. **Results:** ALD patients with advanced fibrosis (F3-F4) exhibited higher CPa9-HNE ($p < 0.001$), C4G ($p < 0.001$), PRO-C6 ($p < 0.001$) and PC3X ($p < 0.001$) serum levels in comparison to ALD patients with no or mild fibrosis (F0-F2). Kaplan-Meier curves showed that PRO-C6, C4G and PC3X provided prognostic value for all-cause mortality (PRO-C6, $p < 0.001$; C4G, $p = 0.016$; PC3X, $p < 0.001$) and risk of decompensation (PRO-C6, $p < 0.001$; C4G, $p < 0.001$; PRO-C6*C4G, $p < 0.001$; PC3X, $p < 0.001$) in ALD patients. **Conclusion:** The unique fibro-inflammatory aspects of the biomarkers used in this study provide evidence that changes in ECM composition related to liver fibrosis, gut barrier epithelial damage and activation of immune cells (neutrophils and T cells) occur in more severe stages of ALD. More data is needed for assessing their relation to disease progression, to the immune landscape within the gut-liver axis and for a better understanding their prognostic value for prediction of ALD-related outcomes.

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Nothing to Disclose, Aleksander Krag: Independent Contractor relationship with Siemens; Has ended; Speaking and Teaching relationship with Norgine; Has not ended; Advisor relationship with Boehringer Ingelheim; Has not ended; Advisor relationship with Novo Nordisk; Has not ended; Speaking and Teaching relationship with Nordic Bioscience; Has not ended, Diana Julie Leeming: Nordic Bioscience: Employee

3083 | THE ASSOCIATION OF DYSREGULATED SPHINGOLIPID METABOLISM AND MICRORNAS WITH ALCOHOL-ASSOCIATED LIVER DISEASES

Hongkun Lu[1] Grayson Way[1] Derrick Zhao[1] Jing Zeng[1] Yun-Ling Tai[1] Xuan Wang[1] Lianyong Su[1] Sayed Obaidullah Aseem[1] Arun Sanyal[1] Phillip Hylemon[1] Huiping Zhou[1]

[1]Virginia Commonwealth University

Background: Alcohol-associated liver disease (ALD) poses an increasing health burden, often needing liver transplantation due to limited therapeutics. Sphingolipid metabolism and signaling has been shown to have a key role in inflammation and the pathogenesis of metabolic diseases. However, their role in ALD and the development of alcohol-associated cirrhosis (AC) remains poorly understood and is the focus of this study. **Methods:** Liver tissues from 6 AC patients and 5 healthy controls (male, age 46-62) were obtained from the Liver Tissue Cell Distribution System in Minneapolis, MN. Total RNA was used for NanoString Metabolic Gene profiling and microRNA (miRNA) profiling using nCounter. Differentially expressed genes (DEGs) and miRNAs were identified using the Rosalind platform. Ingenuity Pathway Analysis (IPA) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses were used to identify the impacted biological pathways. mirNET was used to identify the potential targets of dysregulated miRNAs. The composite data was analyzed to visualize the miRNA-mRNA pathway interactome. **Results:** Metabolic gene profiling identified 96 DEGs, including key genes implicated in sphingolipid metabolism [sphingosine kinase 1 (SPHK1), hexosaminidase subunit alpha (HEXA), and sulfatase modifying factor 1 (SUMF1)]. KEGG analysis revealed significantly upregulated adipocytokine signaling and focal adhesion pathways. Integrated analysis of DEGs and predicted miRNA identified the miRNAs that target the identified 3 DEGs related to sphingolipid metabolism (hsa-mir-1-3p and hsa-mir-124-3p), miRNAs targeting both HEXA and SPHK1 (hsa-mir-155-5p and hsa-mir-484), and miRNAs targeting both SPHK1 and SUMF1 (hsa-mir-10b-5p, hsa-mir-21-3p, and hsa-mir-27a-5p). The NanoString miRNA profiling identified 89 differentially expressed miRNAs. Hsa-let-7a-5p, hsa-let-7b-5p, and hsa-let-7d-5p were found in both the miRNA profiling and the integrated analysis as predicted miRNAs to target SPHK1. IPA highlighted the predicted activation of key inflammatory and hepatic fibrosis signaling pathways. **Conclusion:** These results indicate that AC patients exhibit distinct gene and miRNA expression profiles compared to healthy controls. Our findings provide new insight into the association between sphingolipid metabolism, inflammation, and adhesion pathways in ALD. These findings provide novel information for the development of novel diagnostic and therapeutic strategies for ALD.

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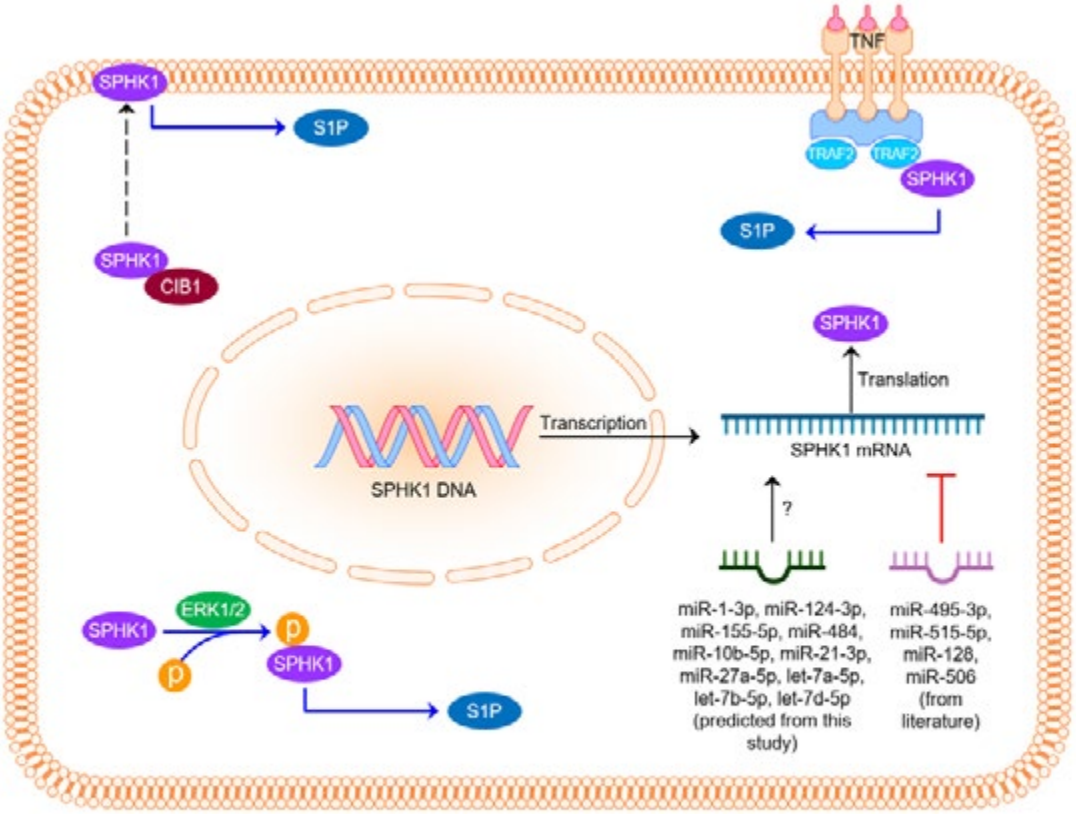

Figure 1. Mechanisms of SPHK1 regulation by miRNAs and genes from literature and predicted miRNAs targeting SPHK1 from this study.

Disclosures: Hongkun Lu: Nothing to Disclose, Grayson Way: Nothing to Disclose, Derrick Zhao: Nothing to Disclose, Jing Zeng: Nothing to Disclose, Yun-Ling Tai: Nothing to Disclose, Xuan Wang: Nothing to Disclose, Lianyong Su: Nothing to Disclose, Sayed Obaidullah Aseem: Galmed Pharmaceuticals: Grant/Research Support, Arun Sanyal: Genfit, Akarna, Tiziana, Durect, Inversago, Hemoshear, North: Stock - publicly traded company, Astra Zeneca (60K), Boston Pharmaceutical

3084 | A NATIONWIDE ANALYSIS OF THE OUTCOMES AMONG HOSPITALIZED CARDIOGENIC SHOCK PATIENTS WITH ALCOHOLIC CIRRHOSIS: A UNITED STATES POPULATION-BASED COHORT STUDY

Carlo Gabriel Casipit[1] *Bruce Adrian Casipit*[1] *Mikaela Nikkola Jara-Tantoco*[1] *Maxim Barnett*[1] *Tinsae Anebo*[1] *Phuuwadith Wattanachayakul*[1] *Arshi Syal*[1] *Yajur Arya*[1]

[1]*Jefferson-Einstein Hospital*

Background: Cardiac dysfunction associated with alcoholic liver cirrhosis was attributed to the hyperdynamic state of cirrhosis and the direct toxic effects of alcohol on the myocardium. These effects become extremely significant in hemodynamically compromised states such as in patients with cardiogenic shock. However, there is paucity of data regarding the outcomes of hospitalized cardiogenic shock patients with comorbid alcoholic cirrhosis. **Methods:** We utilized the National Inpatient Sample (NIS) to identify patients with alcoholic cirrhosis who were hospitalized for cardiogenic shock during the index hospitalization using appropriate ICD-10 codes between 2018-2020. We aim to investigate the impact of alcoholic cirrhosis among cardiogenic shock patients based on in-hospital mortality, risk for acute respiratory failure, and utilization of mechanical ventilation. A multivariable logistic regression analysis was used to calculate adjusted odds ratios (ORs) for the outcomes of interest. **Results:** A total of 501,738 hospitalized patients with cardiogenic shock were identified, of which 0.55% (2,760/501,738) had concomitant alcoholic cirrhosis during the index hospitalization. The overall in-hospital

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mortality rate among hospitalized patients with cardiogenic shock was 33.07% (165,925/501,738). Among those with concomitant alcoholic cirrhosis, the in-hospital mortality rate was deemed to be significantly elevated to 40.22% (1,110/2,760, p= <0.001) compared to those who did not have alcoholic cirrhosis. After adjusting for possible confounders, concomitant alcoholic cirrhosis among hospitalized cardiogenic shock patients was significantly associated with increased risk for in-hospital mortality (aOR 1.57; 95% CI, 1.31-1.90; p=<0.001) and utilization of mechanical ventilation (aOR 1.32; 95% CI, 1.10-1.58; p=0.003), however, it was not associated with increased risk for acute respiratory failure (aOR 1.99; 95% CI, 1.23-3.22; p=0.005). **Conclusion:** Our analysis showed that alcoholic cirrhosis among hospitalized cardiogenic shock patients was independently associated with increased risk for adverse in-hospital outcomes. This is likely due to the direct toxic effects of alcohol on the myocardium and the hyperdynamic circulation, diastolic dysfunction, and impaired contractile responsiveness to stress of patients with cirrhosis that negatively impact the hemodynamic profile of cardiogenic shock patients. These emphasize the importance of risk factor modification, early identification, risk stratification, and optimization of the hemodynamics of alcoholic cirrhosis patients especially in patients who are at high risk for hemodynamic compromise.

Table 1. Adjusted odds ratio of in-hospital outcomes among patients with cardiogenic shock and concomitant alcoholic cirrhosis

	Adjusted Odds Ratio	95% Confidence Interval	P value
In-hospital mortality	aOR 1.57	1.31-1.90	p=<0.001
Acute respiratory failure	aOR 1.99	1.23-3.22	p=0.005
Mechanical Ventilation	aOR 1.32	1.10-1.58	p=0.003

*Adjusted for age, gender, race, Charlson comorbidity index, median annual income, insurance type, hospital location, hospital bed size, hospital teaching status, hyperlipidemia, hypertension, diabetes mellitus, obesity, COPD, CAD, CKD, ESRD, tobacco use

Disclosures: Carlo Gabriel Casipit: Nothing to Disclose, Bruce Adrian Casipit: Nothing to Disclose, Mikaela Nikkola Jara-Tantoco: Nothing to Disclose, Maxim Barnett: Nothing to Disclose, Tinsae Anebo: Nothing to Disclose, Phuuwadith Wattanachayakul: Nothing to Disclose, Arshi Syal: Nothing to Disclose, Yajur Arya: Nothing to Disclose

3085 | NON-ENZYMATIC TARGETING OF METABOLIC-ALCOHOL-ASSOCIATED LIVER DISEASE AND CANCER ASSOCIATED WITH ALDH2 DEFICIENCY AND ALTERED TGF-BETA SIGNALING

Xiaochun Yang[1] *Krishanu Bhowmick*[1] *Kazufumi Ohshiro*[1] *Xiyan Xiang*[1] *Paolo Cifani*[2] *Lopa Mishra*[1]

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Background: Obesity, Alcohol-associated Liver Disease (ALD) and Metabolic syndrome (MetS) affect more than a third of the global population and are exacerbated in individuals with loss of functional aldehyde dehydrogenase 2 (ALDH2). Yet, current modalities of treatment are limited by toxicity, requiring new insight and options. An allelic mutation in ALDH2(ALDH2*2,) affects ~560 million people. This mutation destabilizes the tetrameric enzyme, diminishing lipid derived reactive aldehyde metabolism and alcohol metabolism. ALDH2 mutation is also associated with MetS, Alzheimer's and cancer, implicating reactive aldehydes that can drive these conditions. SPTBN1 is a crucial TGF-beta/SMAD3 adaptor protein. Sptbn1-/- embryos exhibit a phenotype resembling fetal alcohol syndrome, and embryonic death occurs following alcohol exposure. $Sptbn1^{+/-}/Smad3^{+/-}$ have raised levels of ALDH2, suggesting that SPTBN1/Smad3 regulates enzymes involved in alcohol and aldehyde metabolism. **Methods:** We crossed $Aldh2^{-/-}$ mice and $Sptbn1^{+/-}$ mice to explore these interactions further. Transcriptomic, metabolomic, lipidomic, and microbiome analyses were performed. Mass spectrometric, structural analyses were performed to identify 4-HNE protein adducts. Liver immune phenotypes were dissected by multiplex IF staining. **Results:** $Aldh2^{-/-}Sptbn1^{+/-}$ mice spontaneously develop characteristics of MetS and MASH on a normal chow diet. Dramatic changes were observed in liver metabolism, including increased amounts of reactive aldehydes, such as 4-HNE in mutant mice. We identified abnormally accumulated 4-HNE binding to SPTBN1, disrupting normal function of the SMAD3/4-SPTBN1 complex and disrupting TGF-beta signaling, thereby promoting injury and lipogenesis that ultimately manifest in metabolic syndrome and cancer. In addition, the microbiome and liver immune phenotypes were significantly altered. Strikingly, when we targeted SPTBN1 in mouse models and a

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human microfluidic culture MASH model, siRNA-mediated knockdown and genetic knockout SPTBN1 blocked reactive aldehyde toxicity, restored normal TGF-beta signaling, and significantly blocked lipid accumulation, tissue damage, and tumorigenesis. This treatment approach also caused normalization in the liver immune phenotypes and cell types regulated by TGF-beta signaling, such as regulatory T cell (FoxP3+) and infiltrated monocytes (CD11b+). **Conclusion:** Our studies support a decisive role for SPTBN1 as an important nonenzymatic target for treating ALD and MetS/MASH.

Disclosures: Xiaochun Yang: Nothing to Disclose, Krishanu Bhowmick: Nothing to Disclose, Kazufumi Ohshiro: Nothing to Disclose, Xiyan Xiang: Nothing to Disclose, Paolo Cifani: Nothing to Disclose, Lopa Mishra: Nothing to Disclose

3086 | FORMOTEROL PROMOTES MITOCHONDRIAL BIOGENESIS AND DECREASES LIVER INJURY AFTER CHRONIC-BINGE ETHANOL (CBE) TREATMENT IN MICE

Devadoss Samuvel[1] *John Lemaster*[1] *Zhi Zhong*[1]

[1]*Medical University of South Carolina*

Background: A pattern of chronic plus binge drinking is observed in many alcoholic hepatitis patients. Our previous studies showed that mitochondrial dysfunction occurs after chronic-binge ethanol treatment (CBE), which drives mitophagy and the development and progression of alcohol-associated liver disease (ALD). Mitochondrial biogenesis (MB) must occur after mitochondrial damage to restore mitochondrial homeostasis and recover mitochondrial function. This study examined whether stimulation of MB decreases CBE-induced liver injury and improves liver function. **Methods:** Mice were fed a liquid diet containing 5% ethanol for 10 days and then gavaged once with ethanol (5 g/kg) on day 11. Liver and blood were harvested 9 hours later. Formoterol (100 µg/kg, i.p.), a long-acting beta2-adrenergic receptor agonist and MB stimulator, was injected daily during feeding of ethanol-containing liquid diet and 30 min before gavage. **Results:** Serum ALT increased to 339 U/L after CBE. With formoterol treatment, ALT increased to only 78 U/L. After CBE, histology showed moderate hepatic steatosis, leukocyte infiltration, and scattered necrotic cell death. Moreover, cleaved caspase-3 (apoptosis marker) increased by 410%, and myeloperoxidase (neutrophil marker) increased by 680%. Formoterol attenuated histological alterations and markedly decreased apoptosis and inflammation. After CBE, PGC1α (master regulator of MB) and phospho-PGC1α (active form) decreased by 67% and 64%, respectively. Mitochondrial transcription factor-A (TFAM), which controls mitochondrial DNA (mtDNA) replication and transcription, decreased by 42%. ATP synthase-β and NADH dehydrogenase-3 (ND3), mitochondrial oxidative phosphorylation proteins encoded by nuclear and mitochondrial DNA, respectively, decreased by 46% and 67%, indicating suppressed MB. Formoterol blunted decreases of PGC1α, phospho-PGC1α, TFAM, ATP synthase-β, and ND3. Mitochondria is responsible for fatty acid beta-oxidation. CBE decreased hepatic fatty acid oxidation (FAO) by 74%, which formoterol totally recovered. **Conclusion:** Formoterol decreases liver injury and inflammation and recovers FAO after CBE, at least in part, by promoting MB. Hence, formoterol may serve as a novel drug for the treatment of ALD.

Disclosures: Devadoss Samuvel: Nothing to Disclose, John Lemaster: Nothing to Disclose, Zhi Zhong: Nothing to Disclose

3087 | POST-LIVER TRANSPLANT PETH MONITORING: POTENTIAL AS AN EARLY BIOMARKER FOR REJECTION AND GRAFT FAILURE

Muhammad Ali Butt[1] *Himsikhar Khataniar*[1] *Rahul Karna*[2] *Shahid Malik*[3] *Nabeeha Mohy-ud-din*[4]

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Background: Alcohol-associated liver disease (ALD) is the leading indication for liver transplantation (LT) in the United States. The estimated rates of post LT alcohol relapse are 20-30%. Serum phosphatidyl ethanol (PETH) is a highly specific and sensitive marker of alcohol use and can detect alcohol consumption up to 28 days prior. There is currently no guidance for incorporation of alcohol biomarker monitoring post LT. We aimed

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to elucidate current trends of post LT PETH monitoring and compare clinical outcomes, including rejection, hospital admissions and mortality, in patients who underwent LT for ALD with and without post-transplant PETH monitoring. We hypothesized that PETH can be an early biomarker for detection of rejection and is associated with higher mortality and risk of hospital admissions. **Methods:** We conducted a retrospective analysis using data from a large retrospective US database (Trinetx). We compared outcomes between two cohorts: patients with post-transplant PETH monitoring and patients without PETH monitoring. This data was acquired from multiple hospital systems. We utilized risk analysis and Kaplan Meier survival analysis. **Results:** A total of 2313 patients who underwent LT for ALD were included in the time frame between 2011 to 2024. Only 1.3% (n=32) patients had PETH monitoring post LT, out of which 28 patients had PETH > 10 ng/ml. Patients in whom PETH was checked were more likely to be younger (53.4 vs 60.4 [p=<0.03]) and non-white race (p<0.03). The group with PETH monitoring had higher incidence of rejection (OR: 2.3, 95% CI:1.0-4.9) and graft failure (OR:2.9, 95% CI:1.4-6.5), but no significant difference in hospital admissions (OR:1.1, 95% CI:0.5-2.2) and mortality (OR: 1.9, 95% CI: 0.9-4.2) **Conclusion:** Only 1% of patients who underwent LT for ALD had PETH monitoring post LT. A positive PETH test may be an early biomarker of predicting rejection and graft failure post LT. Proactive PETH monitoring post-LT can lead to early detection of alcohol relapse that can reduce risk of rejection and mortality if treated appropriately.

Table 1. Clinical Outcomes in Patients with Post-transplant monitoring of PETH

Outcome	Odds Ratio	95% CI for Odds Ratio
Transplant Rejection	2.3	1.0 - 4.9
Graft Failure	2.9	1.4 - 6.5
Hospital Admissions	1.1	0.5 - 2.2
Mortality	1.9	0.9 - 4.2

Disclosures: Muhammad Ali Butt: Nothing to Disclose, Himsikhar Khataniar: Nothing to Disclose, Rahul Karna: Nothing to Disclose, Shahid Malik: Nothing to Disclose, Nabeeha Mohy-ud-din: Nothing to Disclose

3088 | LIVER INJURY IN HEAVY DRINKING INDIVIDUALS IS ASSOCIATED WITH ELEVATED LEVELS OF PLASMA SOLUBLE EPOXIDE HYDROLASE

Irina Kirpich[1] *Dennis Warner*[1] *Craig McClain*[1]

[1]*University of Louisville*

Background: Long-term heavy alcohol consumption may result in alcohol use disorders including alcohol-associated liver disease (ALD). The mechanisms of ALD development, progression and severity are not well understood, and therapies are limited. Alterations in bioactive lipid mediators and associated enzymes/pathways, including soluble epoxide hydrolase (sEH), have been linked to ALD pathogenesis in animal models. The current study measured plasma sEH, an enzyme that converts bioactive lipid-derived epoxides to less active/inactive molecules, in heavy drinking individuals and to evaluate associations with liver injury and systemic inflammation. We hypothesized that sEH levels will differentiate heavy drinking individuals with ALD from those without **Methods:** The study was performed on archived plasma from heavy-drinking individuals (15 drinks/day) with or without ALD, based on plasma ALT levels: ALT<40 U/L, no liver injury, n=15 and ALT≥40 U/L, liver injury, n=33. The control group was 29 social-drinking but otherwise healthy volunteers. Plasma ALT, AST and full-length cytokeratin 18 (CK M65, indicator of cell death) were measured by standard laboratory procedures and by ELISA, respectively. Plasma sEH, IL-1β and TNF-α were measure by ELISA. Associations between various subject characteristics were assessed using Spearman's correlation analysis. **Results:** Plasma sEH levels were significantly higher in heavy drinking patients with mild liver injury (ALT = 98.6 ± 9.8 U/L) compared to healthy controls as well as to heavy drinking individuals without ALD (ALT = 26.5 ± 2.3 U/L). There was a moderate

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nonsignificant increase in sEH levels in heavy-drinking subjects without liver injury *vs* controls. To determine the true positivity of the findings, analysis of the receiver operating characteristic (ROC) curve was performed and revealed differentiation (difference of 0.8323, p = 0.0003) in plasma sEH levels between heavy drinking individuals with and without ALD. Proinflammatory cytokines were increased in subjects with ALD *vs* without and significantly elevated *vs* controls. Elevated sEH levels were positively correlated with ALT (p < 0.001, *r*=0.578), AST (p < 0.001, *r*=0.705), and CK M65 (p = 0.003, *r*=0.506) in heavy drinking subjects with mild liver injury. **Conclusion:** The current study provides evidence that heavy drinking individuals with mild ALD have elevated plasma sEH levels and that plasma sEH can distinguish individuals with ALD from those without.

Disclosures: Irina Kirpich: Nothing to Disclose, Dennis Warner: Nothing to Disclose, Craig McClain: Novo Nordisk: Grant/Research Support, Intercept Pharmaceuticals: Grant/Research Support, Altimmune: Grant/Research Support, Target Pharma Solutions: Grant/Research Support, NIH: Grant/Research Support, VAMC: Grant/Research Support

3089 | ASSESSMENT OF EARLY RETURN TO DRINKING IN PATIENTS WITH ALCOHOL-ASSOCIATED HEPATITIS

Thomas Cotter[1] Nicole Welch[2] Qing Tang[3] Wanzhu Tu[3] Samer Gawrieh[3] Lauren Nephew[3] Ramon Bataller[4] Vijay Shah[5] Naga Chalasani[6] Gyongyi Szabo[7] Craig McClain[8] Arun Sanyal[9] Laura Nagy[10] Mack Mitchell[11] Srinivasan Dasarathy[2]

[1]UT Southwestern Medical Center, [2]Cleveland Clinic, [3]Indiana University, [4]University of Pittsburgh, [5]Mayo Clinic Rochester, [6]Indiana University Medical Center, [7]Beth Israel Deaconess Medical Center, [8]University of Louisville, [9]Virginia Commonwealth University, [10]Cleveland Clinic Foundation, [11]University of Texas Southwestern Medical Center

Background: Recurrent alcohol use is a major determinant of liver-related outcomes in patients who survive an episode of alcohol-associated hepatitis (AH). However, the timing and predictors of return to drinking (RTD) following an episode of AH are not well studied. **Methods:** We examined the frequency of alcohol use within 6 months of diagnosis and baseline risk factors associated with RTD among patients diagnosed with AH as defined by an NIAAA consortium. Patients were enrolled in two concurrent AlcHepNet multi-center studies: a Phase 2b randomized controlled trial (RCT) and an observational (OBS) study. Moderate AH (mAH) was defined as MELD <20 and severe AH (sAH) as MELD ≥20. Demographics were similar in the 2 cohorts, but the RCT had only patients with sAH. Patients completed TimeLine FollowBack to assess drinking at each study visit. RTD was defined as any alcohol consumption since the previous visit. Cumulative incidence (Fine-Gray method) and associations with first recurrence of alcohol use (univariable- and multivariable-adjusted Cox proportional hazards regression model) were determined. **Results:** In 482 patients with AH alive at day 28, the 30-, 90- and 180-day cumulative incidences of RTD were 7.9%, 22.7%, 31.6% (Fig 1A). Those with mAH (n=95) had significantly higher 30-, 90- and 180-day cumulative incidences of RTD (9.6%, 35.9%, 48.5% respectively vs 7.5%, 19.4%, and 27.9% respectively in those with sAH (n=387; p<0.01) (Fig 1B). Those who RTD had higher AUDIT scores (mean 25.0 vs. 22.9; p=0.03); more family history of alcohol use disorder (AUD) (65.9 vs. 53.1%; p=0.04); lower levels of education (14.5 vs. 31.3% with college or higher; p<0.01), higher number of drinks/day (mean 12.0 vs. 9.4; p=0.01); more drinking days in past month (mean 20.9 vs. 14.2; p<0.01); lower MELD scores (mean 23.4 vs. 25.3; p=0.02); and lower rates of ascites (60.2 vs. 74.4%; p<0.01) compared with those who did not RTD. In the multivariable-adjusted model, those with college education had less risk of RTD (HR: 0.48, 95%CI: 0.27, 0.85) while those who had >20 drinking days in the past 30 days had higher risk of RTD (HR: 3.07, 95%CI: 1.97, 4.77). **Conclusion:** Return to drinking occurred in 23% within the first 90 days and 32% within 180 days after recovery from AH showing the need for early AUD interventions in AH. More than 20 drinking days in the past month and less than college education were associated with early RTD.

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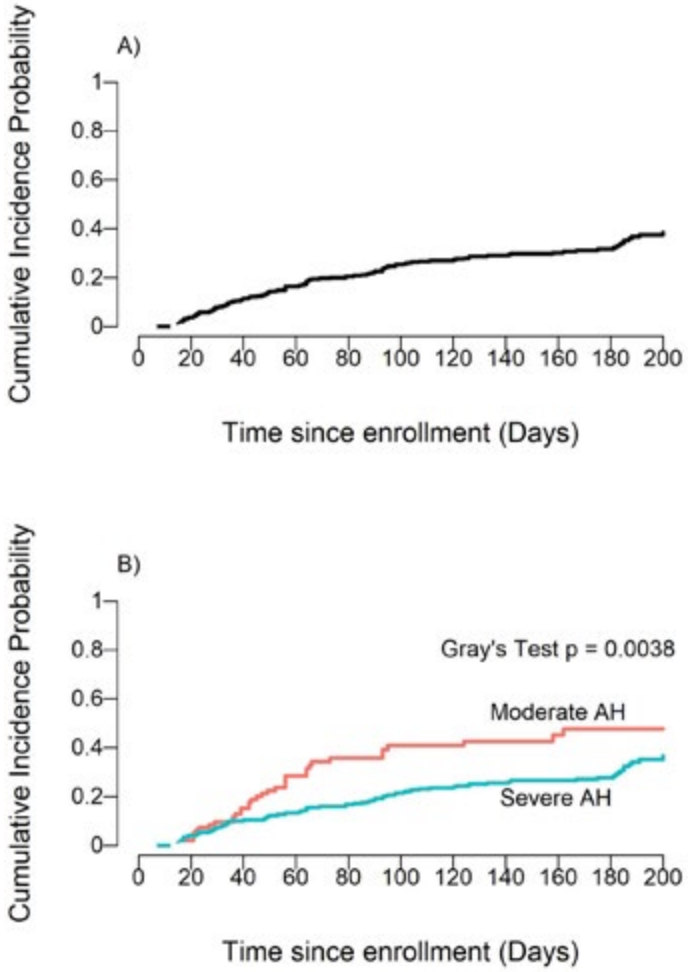

Disclosures: Thomas Cotter: Nothing to Disclose, Nicole Welch: Nothing to Disclose, Qing Tang: Nothing to Disclose, Wanzhu Tu: Nothing to Disclose, Samer Gawrieh: Transmedics: Consultant, pfizer: Consultant, kowa: Consultant, spruce: Consultant, viking: Grant/Research Support, zydus: Grant/Research Support, dsm: Grant/Research Support, Sonicincytes: Grant/Research Support, Novo Nordisk: Consultant, Lauren Nephew: Nothing to Disclose, Ramon Bataller: Nothing to Disclose, Vijay Shah: Boehringer Ingelheim: Consultant, GSK: Consultant, GENFIT SA: Consultant, Intercept Pharmaceuticals, Inc.: Advisor, Korro Bio, Inc.: Consultant, Mallinckrodt Pharmaceuticals: Advisor, Novo Nordisk A/S: Consultant, Resolution Therapeutics, Ltd.: Advisor, Seal Rock Therapeutics, Ltd.: Consultant, Surrozen: Advisor, Naga Chalasani: Madrigal: Consultant, Zydus, Ipsen, Pfizer, Merck, Altimmune, GSK: Consultant, Exact Sciences: Grant/Research Support, NIH: Grant/Research Support, Gyongyi Szabo: Advisor relationship with Glympse Bio, Inc (acquired by Sunbird Bio); Has not ended; Consultant relationship with Terra Firma; Has not ended; Consultant relationship with Pfizer; Has not ended; Consultant relationship with Pandion Therapeutics; Has ended; Consultant relationship with Merck; Has ended; Consultant relationship with Durect Corporation; Has ended; Advisor relationship with Satellite Biosciences; Has not ended; Consultant relationship with Zomagen Bioscience/Ventyx Biosciences; Has ended; Consultant relationship with CYTA Therapeutics; Has ended; Royalties or patent beneficiary relationship with Springer Nature Group; Has not ended; Royalties or patent beneficiary relationship with UpToDate Inc; Has not ended; Consultant relationship with LabCorp; Has not ended; Advisor relationship with Evive; Has not ended; Advisor relationship with Surrozen; Has not ended; Consultant relationship with Takeda; Has ended, Craig McClain: Novo Nordisk: Grant/Research Support, Intercept Pharmaceuticals: Grant/Research Support, Altimmune: Grant/Research Support, Target Pharma Solutions: Grant/Research Support, NIH: Grant/Research Support, VAMC: Grant/Research Support, Arun Sanyal: Genfit, Akarna, Tiziana, Durect, Inversago, Hemoshear, North: Stock - publicly traded company, Astra Zeneca (60K), Boston Pharmaceutical

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3090 | NATIONAL TRENDS IN METABOLIC RISK FACTORS AND ALCOHOL USE FROM 1999 TO 2018 IN EMERGING ADULTS AGED 20-25

Emmanuelle Hodara[1] *Jennifer Dodge*[2] *Norah Terrault*[3] *Brian Lee*[4]

[1]*Keck School of Medicine of USC,* [2]*Keck School of Medicine of University Southern of California,* [3]*University of Southern California,* [4]*Keck School of Medicine*

Background: Adults aged 25-34 with alcohol-associated liver disease (ALD) represent the fastest growing demographic contributing to liver-related deaths. Emerging adulthood (age 20-25), is a key developmental period marked by exploration and habit formation. We hypothesized changes in metabolic risk factors and alcohol use among emerging adults could be an important contributor to the surge in ALD-related mortality among young adults. **Methods:** Using NHANES (National Health and Nutrition Examination Survey), a continuous cross-sectional survey, we created weighted study samples representing noninstitutionalized U.S. adults aged 20 to 25 without viral hepatitis from 1999 to 2018. Alcohol use in the past 12 months was categorized as abstinent, non-heavy, or heavy (≥8 drinks/week for women or ≥15 drinks/week for men). We evaluated metabolic risk factors as defined by the National Cholesterol Education Program's Adult Treatment Panel III, including waist circumference (>102 cm for men or >88 cm for women), serum triglyceride levels (≥150 mg/dL), HDL cholesterol levels (<40 mg/dL for men or <50 mg/dL for women), blood pressure (≥130/85 mm Hg or on antihypertensive medications), and diabetes (fasting plasma glucose≥100 mg/dL or on diabetes medications). We estimated the survey-weighted prevalence of these risk factors for each 4-year interval from 1999 to 2018 based on category of alcohol use (heavy, non-heavy, abstinent). **Results:** Among 4,549 emerging adult respondents (heavy [n=364], non-heavy [n=3,146], abstinent [n=1,039]), the survey-weighted prevalence of elevated waist circumference and diabetes mellitus increased significantly from 28.6% (95%CI, 23.9-33.8) to 39.1% (32.8-45.7; p=0.01) and from 5.6% (4.0-7.9) to 16.9% (14.1-20.1; p<0.001), respectively, between 1999-2002 to 2015-2018. In contrast, the prevalence of elevated triglycerides, low HDL, and hypertension remained stable or decreased. Heavy alcohol use declined from 10.7% (95%CI 7.6-15.0) to 8.5% (95%CI 6.5-11.0) while non-heavy alcohol use rose from 64.3% (95%CI 58.7-69.5) to 75.7% (95%CI 71.1-79.7), between 1999-2002 to 2015-2018. Metabolic risk factors were stable over time across alcohol use subgroups, except for elevated waist circumference, which rose significantly among heavy alcohol users from 12.7% (95%CI 7.1-21.7) to 57.1% (95%CI 36.9-75.1), between 1999-2002 to 2015-2018. (FIG 1). **Conclusion:** In emerging adults aged 20 to 25, elevated waist circumference increased nearly 5-fold among heavy alcohol users. Increasing prevalence of metabolic risk factors (especially obesity) among emerging adults, in addition to heavy alcohol use, identifies an important risk group for ALD-related mortality among young adults. Addressing obesity among emerging adults may be an important intervention to address the ALD epidemic.

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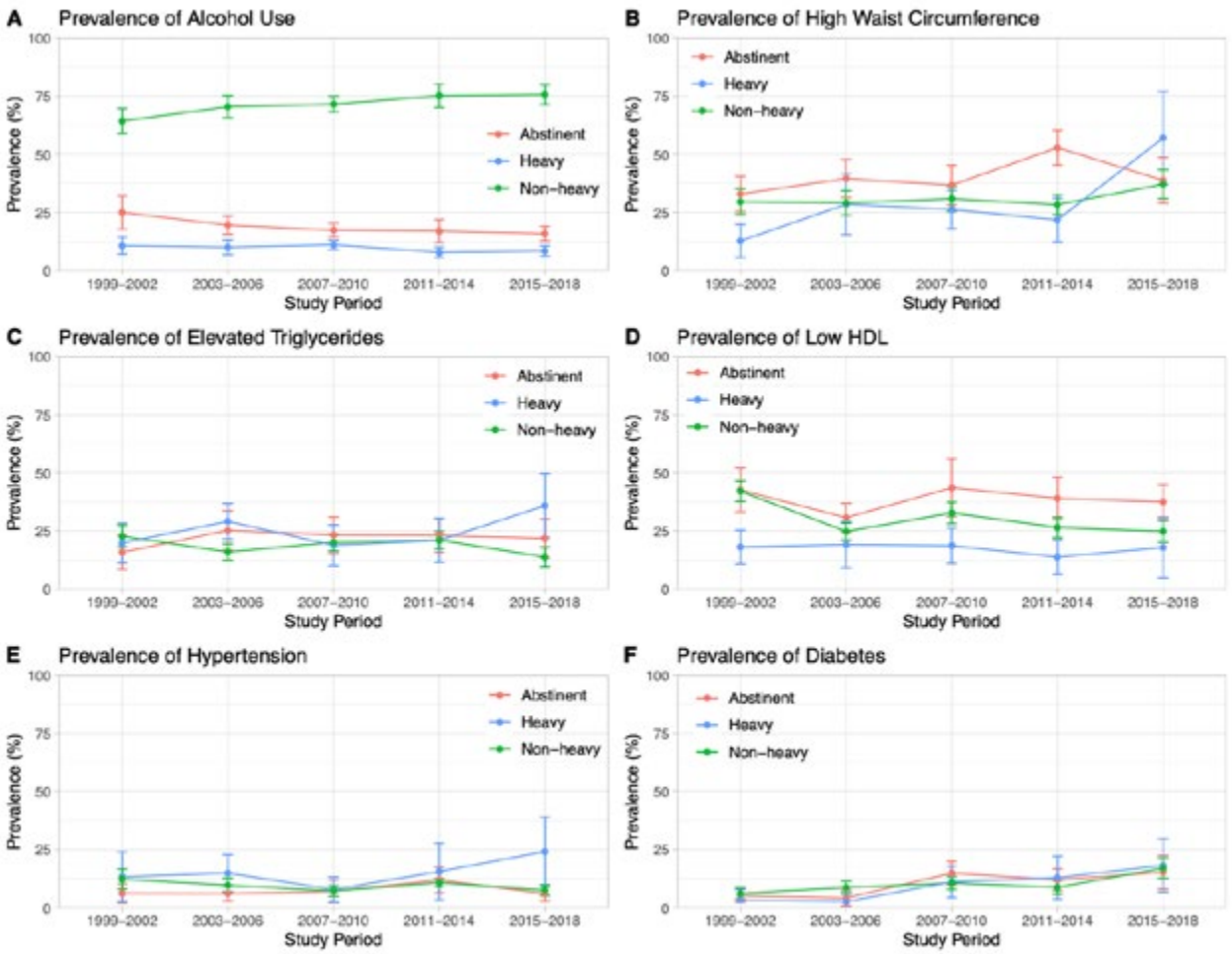

Figure 1. Prevalence of Metabolic Risk Factors categorized by alcohol use from 1999 to 2018 in emerging adult aged 20-25.

Disclosures: Emmanuelle Hodara: Nothing to Disclose, Jennifer Dodge: Nothing to Disclose, Norah Terrault: Grant/Research Support relationship with Eiger Pharmaceuticals; Has ended; Grant/Research Support relationship with GSK; Has not ended; Royalties or patent beneficiary relationship with Elseiver; Has not ended; Grant/Research Support relationship with Helio Health; Has ended; Grant/Research Support relationship with Durect Corp; Has ended; Executive role relationship with AASLD; Has not ended; Board member relationship with HBV Foundation; Has not ended; Grant/Research Support relationship with ImmunoCore; Has ended, Brian Lee: NIAAA: Grant/Research Support, Novo Nordisk: Advisor, GSK: Advisor, DURECT: Advisor, HepaTx: Advisor, CymaBay: Consultant, Ipsen: Consultant, Siemens Healthineers: Grant/Research Support, AltImmune: Advisor

3091 | PLASMA CELL-FREE MTDNA IS RELEASED IN ALCOHOL-RELATED LIVER DISEASE AND CORRELATES WITH LIVER INJURY

MARAM ALENZI[1] Pinzhu Huang[2] Heansika Matta[1] Disha Badlani[1] David GUARDAMINO OJEDA[3] Gloria Horta[1] Michelle Lai[3] Z. Gordon Jiang[3] Yury Popov[4]

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Background: Mitochondrial DNA (mtDNA) is a pro-inflammatory and pro-fibrogenic damage-associated molecular pattern (DAMP) with a pathogenic role in several inflammatory diseases. Due to common evolutionary origins, mtDNA shares many similarities with immunogenic bacterial DNA. We performed a pilot study to evaluate the potential significance of circulating mtDNA as a functional disease driver and biomarker in patients with alcohol-related liver disease (ALD). **Methods:** We collected EDTA-plasma and serum from 71 ALD patients (40

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alcohol-related hepatitis [AH] and 31 alcohol-related cirrhosis [AC]) and 27 healthy controls in our tertiary hospital Liver Center (BIDMC) and measured absolute copy number of circulating mtDNA using our novel in-house high sensitivity duplex digital droplet polymerase chain reaction (ddPCR) mtDNA assay via amplification of two unique highly conserved mtDNA regions (hDL, hND). The relationship between multiple clinically relevant AH parameters and mtDNA levels was assessed using linear regression analysis. **Results:** Plasma mtDNA levels were significantly increased in both AH (2219 ± 5445 copies/ul of plasma, P=0.01) and AC (1233 ± 1716 copies/ul of plasma, P=0.008) compared with healthy controls (387.6 ± 426.5 CI copies/ul of plasma) (Figure.1). In active AH, mtDNA levels were significantly higher compared to AC (P = 0.01). Plasma mtDNA level in alcohol-related hepatitis, but not alcohol associated cirrhosis, significantly correlated with parameters of liver injury - alanine aminotransferase (ALT, P<0.001) > alkaline phosphatase (ALK-P, P<0.001) > white cell count (WBC, P=0.02), and markers of abnormal lipid metabolism - triglycerides (TG, P=0.005) > lipoprotein X (LPX, P=0.01) > lipoprotein Z (LPZ, P=0.03) but not with aspartate aminotransferase (AST, P=0.06), and total bilirubin (TBILI, P=0.38). mtDNA levels in AH serum were about two-fold lower compared to those detected in plasma, and demonstrated similar pattern of significant, but weaker associations with above clinical parameters. **Conclusion:** Using our novel ddPCR assay for circulating mtDNA we show for the first time that proinflammatory and pro-fibrogenic mtDNA is released during active AH and correlates with parameters of alcohol-related liver injury and abnormal lipid metabolism. These results support multi-center disease biomarker validation studies. The potential pathogenic role of mtDNA in ALD should also be interrogated in follow-up mechanistic studies.

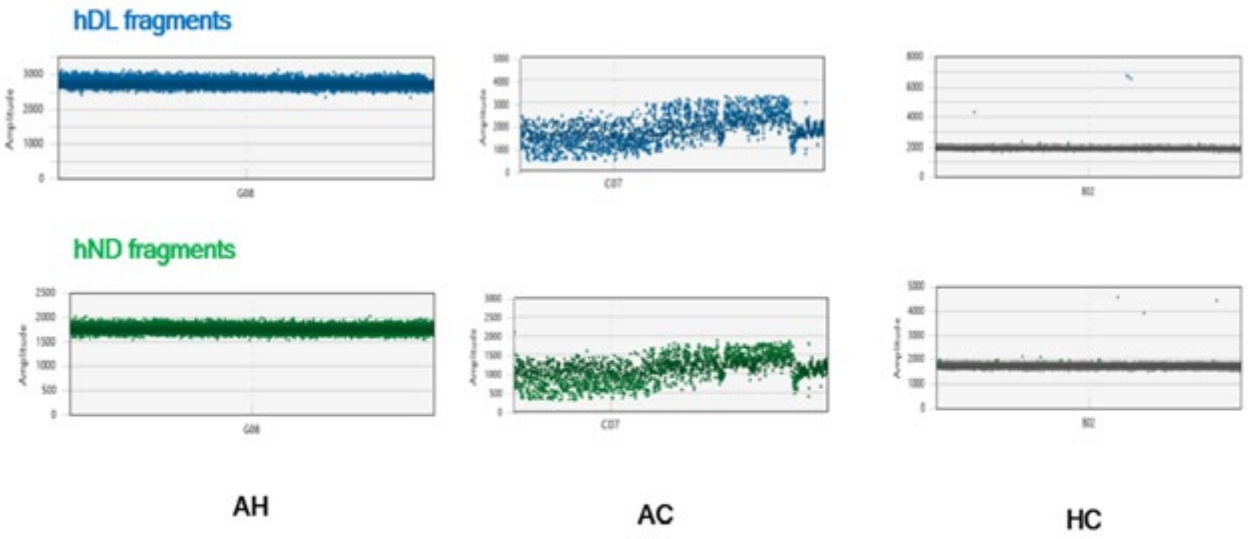

Figure1: ddPCR mtDNA amplitude plot quantification for the hDL fragment (*blue*) and the hND fragment (*green*) in patient with alcohol-related hepatitis, alcohol-related cirrhosis and heathy control.

Disclosures: MARAM ALENZI: Nothing to Disclose, Pinzhu Huang: Nothing to Disclose, Heansika Matta: Nothing to Disclose, Disha Badlani: Nothing to Disclose, David GUARDAMINO OJEDA: Nothing to Disclose, Gloria Horta: Nothing to Disclose, Michelle Lai: Nothing to Disclose, Z. Gordon Jiang: Nothing to Disclose, Yury Popov: Nothing to Disclose

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3092 | SEX DIFFERENCES IN CHARACTERISTICS AND OUTCOMES OF VETERANS WITH ALCOHOL-ASSOCIATED HEPATITIS

Anahita Rabiee[1] Eric DeRycke[2] Rachel Thompson[3] Ronald Hauser[1] Kathleen Akgün[1] Tamar Taddei[4]

[1]VA Connecticut Healthcare System; Yale School of Medicine, [2]VA Connecticut Healthcare System, [3]Yale New Haven Hospital, [4]Yale University

Background: While the role of sex in susceptibility, presentation and severity of alcohol related liver disease has been investigated, associations between sex and alcohol-associated hepatitis (AH) are unclear. We assessed the characteristics, severity, and outcomes of AH among men and women Veterans. **Methods:** All Veterans with first hospitalization for AH between 2017 and 2021 were included using the Veteran's Health Administrative (VA) data. AH ascertainment required laboratory criteria of total bilirubin >=3, AST>50, AST/ALT >1.5, AST and ALT<400 and AH ICD code within 6 months of the laboratory criteria. The index date was the date when laboratory criteria were first met. Women and men were matched 1:2 based on age group, race, body mass index>30, and history of hepatitis C. Continuous variables were compared using t test and categorical variables were compared via Chi square test. Several outcomes, such as decompensation, engagement in care, and mortality were evaluated during the first year of follow up. Cox regression was used to evaluate long term survival. **Results:** Among 16,502 Veterans with AH ICD code, 4037 (24%) met AH lab criteria; 291 (7%) were female. Men were significantly older and more likely to be white, obese and have a higher prevalence of medical comorbidities and hepatitis C. After matching, the cohort consisted of 289 women and 578 men. Women had a higher prevalence of mental health comorbidities (depression, anxiety, and post-traumatic stress disorder [all p<0.001]) and higher levels of military sexual trauma (42% vs 3%, p<0.0001). Baseline mental health and alcohol and substance use services utilization in the year prior to diagnosis of AH were higher among women. During follow-up, more women developed ascites (72% vs. 63%, p=0.007), however other decompensations were similar. One year mortality was high among both groups and did not vary by sex (33% women vs. 32% men, p=0.69). Engagement in care as measured by percentage of patients seeking mental health or substance use disorder clinics during the first year of follow up was higher among women (Table 1). Cox regression model in the matched cohort showed similar survival in men and women (HR 1.07 [0.84-1.38]). **Conclusion:** Among Veterans presenting with AH between 2017–2019, we observed a similar mortality between women and men. However, women with AH had a significantly higher prevalence of military sexual trauma and mental health comorbidities, which could be an important area for early interventions to address alcohol use disorder in this population.

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Sex differences in characteristics and outcomes of Veterans with alcohol-associated hepatitis

Alcohol associated hepatitis	Female	Male	P-Val
Demographics at the time of AH diagnosis (index date)	N=289	N=578	
Age (mean, SD)	47.9 (10.1)	51.5 (12.4)	<.0001
Age over 40	75.4	75.4	1
Race			1
White	57.4	57.4	
Black	20.1	20.1	
Other or missing	22.5	22.5	
Body mass index *(8%missing) over 30	20.4	20.4	1
Comorbidities at baseline (before the index date) (%)			
Comorbidity index >3+	29.8	31.5	0.21
Cirrhosis	15.2	15.1	0.94
Hepatitis C	5.9	5.9	1
Non alcoholic fatty liver	16.6	6.7	0.003
Hepatitis B	1.7	1.7	1
Bariatric surgery	5.5	0.9	<.0001
Diabetes	12.5	12.5	1
Alcohol use disorder	82.01	80.5	0.58
History of alcohol associated hepatitis	15.2	14.7	0.84
History of any alcohol related liver disease	64.4	58.1	0.077
Depression	60.9	43.6	<.0001
Anxiety	59.2	40.3	<.0001
Post traumatic stress disorder	46.4	36.7	0.006
Substance use disorder	43.3	43.9	0.84
Healthcare Utilization 1 year prior to diagnosis (%)			
Primary care visit	86.9	80.6	0.022
Mental health visit	74.1	60.6	<.0001
Any Alcohol or substance use Treatment visits	36.3	27.2	0.0056
Emergency room visits	64.1	58.8	0.14
Hepatology or Gastroenterology Clinic visits	31.8	25.1	0.035
Military sexual trauma screening done	94.8	97.6	0.03
Military sexual trauma (screened positive)	42.2	2.8	<.0001
Audit-C Positive (performed in 73% of women and 71% of men) Cut off of 3 for women, and 4 for men were used	70.4	68.5	0.62
Outcomes during first year of follow up (%)			
Cirrhosis diagnostic code	55.7	56.2	0.88
Hepatic encephalopathy	2.4	1	0.11
Ascites	71.6	62.5	0.007
Variceal bleeding	9.3	10	0.74
Liver transplant	3.1	3.3	0.89
Naltrexone use	14.5	11.9	0.28
Acamprosate use	13.5	13.13	0.89
Primary care visit	98.6	99.3	0.31
Mental health visit	86.6	78.4	0.004
Any alcohol/substance use treatment visit	58.9	49.5	0.009
Hepatology or Gastroenterology Clinic visits	73.8	68.9	0.13
Death (%)			
30 day mortality	8.3	9	0.75
90 day mortality	16.6	17.8	0.64
1 year mortality	33.1	31.8	0.69

Disclosures: Anahita Rabiee: Nothing to Disclose, Eric DeRycke: Nothing to Disclose, Rachel Thompson: Nothing to Disclose, Ronald Hauser: Nothing to Disclose, Kathleen Akgün: Nothing to Disclose, Tamar Taddei: Nothing to Disclose

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3093 | COMPARATIVE ANALYSIS OF PROGNOSTIC MODELS IN ALCOHOL-ASSOCIATED HEPATITIS

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Background: Despite the increasing prevalence and severity of alcohol-associated hepatitis (AAH), our understanding of its prognostication remains limited. We conducted a prognostic study to systematically compare the performance of various risk models for predicting short-term mortality in AAH. **Methods:** We identified all adult patients with AAH hospitalized at 130 Veterans Affairs hospitals between October 2017 and October 2022. Patients were identified based on at least one inpatient ICD-9/10 code for alcohol use disorder and a documented increase in serum bilirubin from a normal value in the 6 months prior to admission to an elevated value of >3 mg/dL on admission. We excluded patients with hepatitis B or C virus infection, other chronic liver disorders, biliary obstruction, metastatic cancer, or those with hospital stays less than 24 hours. We examined the accuracy of AAH definition by comparing it with diagnosis derived from medical record review in a random national sample of 100 patients with AAH. We calculated risk scores from five models: Model for End-Stage Liver Disease (MELD), MELD 3.0, Maddrey's Discriminant Function (MDF), Glasgow Alcoholic Hepatitis Score (GAHS), and Age, serum Bilirubin, INR, and serum Creatinine score (ABIC). We estimated the models' discrimination and calibration in predicting 30 and 90-day all-cause mortality. **Results:** The positive predictive value of AAH definition was 79%. Using this definition, we identified 3,991 patients with AAH (mean age, 55.2 years (SD, 11.8), 70% White, 12.5% Black). The mean AUDIT-C within 12 months prior to hospitalization was 6.5 (SD, 4.6). Patients had high comorbidity burden; 40% had a Deyo comorbidity index >3. Most patients presented with hepatic decompensation including ascites (67.6%), infection (47.7%), variceal bleeding (35.5%), and hepatic encephalopathy (25.6%). In total, 399 (10%) patients died within 30 days and 766 (19.2%) died within 90 days of hospitalization. AUCs for 30-day mortality were >0.70 for four of the five models. The AUC was the highest for the ABIC model (0.79, 95% CI, 0.77-0.81) followed by MELD 3.0 (0.76, 95% CI, 0.74-0.79), traditional MELD (0.76, 95% CI, 0.74-0.79), MDF (0.74, 95% CI, 0.72-0.77), and GAHS (0.63, 95% CI, 0.61-0.65). All models had lower discrimination for 90-day mortality, but the trends were similar (AUCs for ABIC: 0.76, 95% CI, 0.74-0.77, MELD 3.0: 0.73, 95% CI, 0.71-0.75, traditional MELD: 0.72, 95% CI, 0.71-0.75, MDF: 0.73, 95% CI, 0.71-0.75, and GAHS: 0.62, 95% CI, 0.61-0.64). MELD 3.0 demonstrated better calibration across all time points compared to other prognostic models. **Conclusion:** In this large cohort of patients with AAH, most published models performed well in predicting short-term mortality, although the ABIC model provided the highest predictive accuracy. However, MELD 3.0 had the best calibration, suggesting it may provide more reliable risk stratification in clinical practice.

	ABIC	MELD 3.0	MELD	MDF	GAHS
Median Score on admission [IQR]	7.8	21.2	18.9	47.5	8.7
Proportion with severe AAH	(Score>9) 23.5%	(Score>20) 55.4%	(Score>20) 37.8%	(Score>32) 62.1%	(Score>9) 69.1%
AUC at 30-days (95% CI)	0.788 (0.768, 0.809)	0.762 (0.739, 0.786)	0.761 (0.738, 0.785)	0.742 (0.719, 0.766)	0.629 (0.609, 0.649)
AUC at 90-days (95% CI)	0.756 (0.74, 0.771)	0.728 (0.711, 0.746)	0.724 (0.706, 0.742)	0.727 (0.71, 0.745)	0.623 (0.608, 0.638)

Disclosures: Ronald Samuel: Nothing to Disclose, Xian Yu: Nothing to Disclose, yumei Cao: Nothing to Disclose, Jennifer Kramer: Nothing to Disclose, George Cholankeril: Nothing to Disclose, Fasiha Kanwal: Nothing to Disclose

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3094 | IDENTIFICATION OF ALCOHOL-ASSOCIATED HEPATITIS USING ELECTRONIC MEDICAL RECORDS

Rachel Thompson[1] Eric DeRycke[2] Kathleen Akgün[3] Tamar Taddei[4] Anahita Rabiee[4]

[1]Yale New Haven Hospital, [2]VA Connecticut Health system, [3]VA Conneticut Health care system; Yale School of Medicine, [4]Yale University

Background: Alcohol-associated hepatitis (AH) is challenging to diagnose and inconsistently documented by International Classification of Diseases (ICD) codes in the electronic medical records (EMR). We developed a two-part algorithm using a combination of structured and accessible EMR variables to enhance identification of AH cases. **Methods:** This was a retrospective study to identify patients diagnosed with AH in the Veterans Affairs health system from 2017 to 2021. The reference standard for AH was established by chart review (definite, probable, or possible AH per AASLD/NIAAA (National Institute on Alcohol Abuse and Alcoholism) definition) or AH ICD code *and* meeting laboratory criteria (total bilirubin≥3, AST>50, AST/ALT>1.5, AST & ALT< 400 within 6 months of the ICD code). The initial sample included all patients meeting AH laboratory criteria *or* having AH ICD code. Part 1 of the algorithm included limiting the sample to patients with an AH ICD code *and* meeting lab criteria. Part 2 of the algorithm aimed to identify AH cases among patients meeting laboratory criteria but *without* AH ICD code. This algorithm used a combination of extended alcohol related liver disease, alcohol use disorder, and toxic liver injury ICD codes; it excluded patients with ICD codes for alternative causes of laboratory abnormalities (e.g., cholecystitis, pancreatic cancer, etc.). In addition, part 2 of the algorithm required a Clinical Institute Withdrawal Assessment (CIWA) note during admission, which indicates active alcohol use. A random sample of 118 charts identified using part 2 of the algorithm were manually reviewed. **Results:** We identified 16,502 patients with an AH ICD code and 26,956 meeting the lab criteria (irrespective of ICD codes). Using part 1 of the algorithm (AH ICD code + AH lab criteria overlap), 4,037 patients were classified as AH. Among 21,693 patients meeting laboratory criteria *without* AH ICD code, we used part 2 of the algorithm to identify 790 additional cases of AH (Figure 1). The positive predictive value of part 2 of the algorithm to identify AH among patients meeting laboratory criteria *without* AH ICD code, was 94%. Solely using AH ICD code for diagnosis resulted in very high number of false positive cases (misclassifying 12,465 cases as AH) and false negative cases (missing at least 790 cases with AH). **Conclusion:** Reliance on only AH ICD code for diagnosis of AH is inaccurate and has a very poor positive predictive value (24%). It also misses at least 16% of AH cases. Epidemiological studies on AH using only AH ICD codes for cohort definition should be interpreted with caution. Using a two-part algorithm incorporating lab values, an extended list of ICD codes, and CIWA notes in the EMR can improve the identification of AH.

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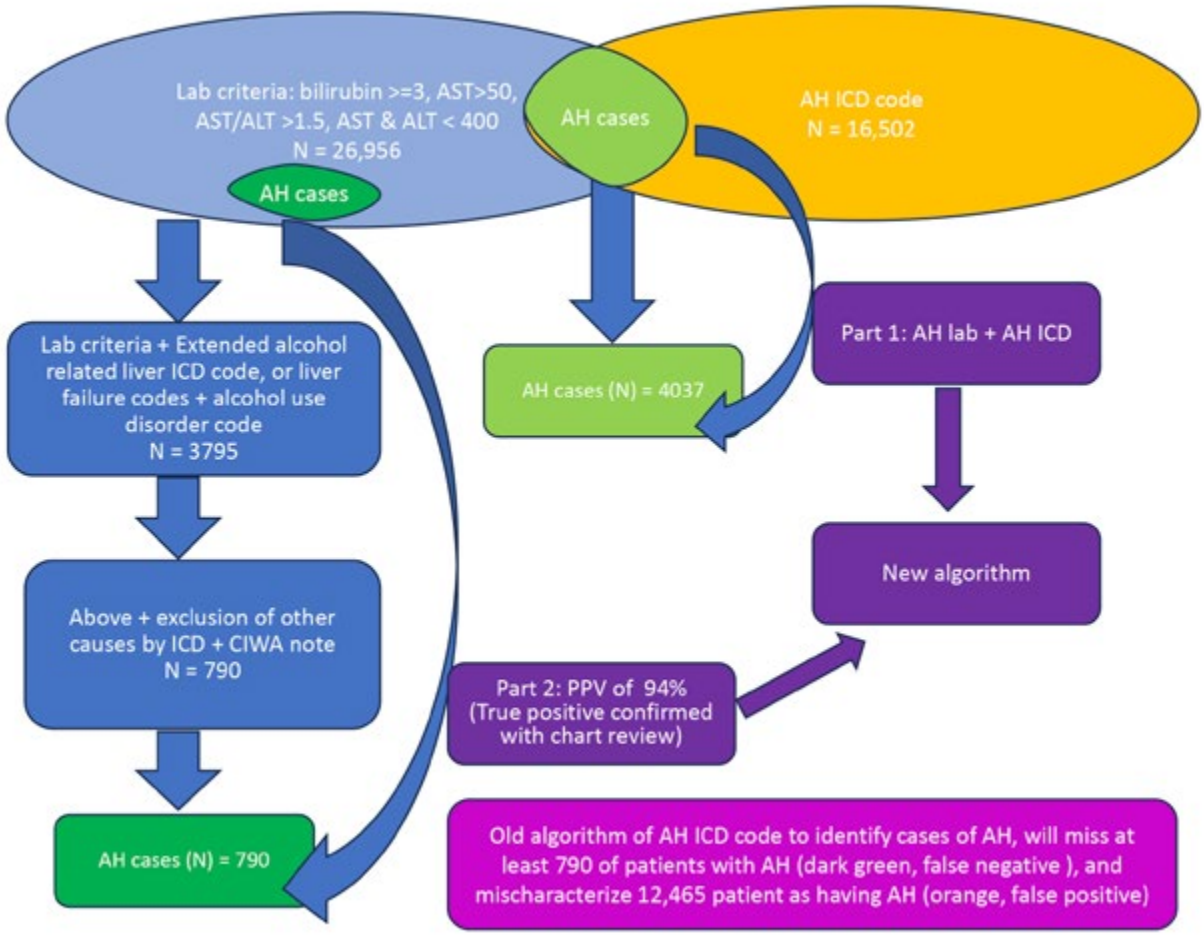
Figure 1: New algorithm to identify cases of alcohol associate hepatitis (AH)



Disclosures: Rachel Thompson: Nothing to Disclose, Eric DeRycke: Nothing to Disclose, Kathleen Akgün: Nothing to Disclose, Tamar Taddei: Nothing to Disclose, Anahita Rabiee: Nothing to Disclose

3095 | GLP-1 RECEPTOR AGONISM REDUCES INJURY, HEPATIC CYP2E1 ACTIVITY AND INCREASES ANTIOXIDANT ACTIVITY IN A MOUSE MODEL OF ALCOHOL-INDUCED ACUTE HEPATITIS

frhaan zahrawi[1] Suyavaran Arumugam[1] Bubu Banini[1] Mehal Wajahat[2]

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Background: We have previously reported that in vivo glucagon like peptide-1 receptor agonism (GLP-1RA) significantly reduces steatosis and inflammation in a murine model of alcohol-associated hepatitis (AH). This may occur in part due to reduced EtOH intake, but GLP-1RA in the brain may also induce sympathetic and hormonal effects on the liver. We conducted an in-depth analysis of hepatic changes due to GLP-1RA while controlling for EtOH intake. **Methods:** Liver tissue was obtained from mice on control or alcohol diets for 16 days with and without GLP-1RA (escalating dose of Semaglutide up to 30nmol/Kg sc daily), and separately from mice that were fasted for 16hrs with and without GLP-1RA. Histology, q-PCR and bulk RNA sequencing were performed. P-value <0.05 was considered significant. **Results:** GLP-1RA significantly reduced EtOH-induced microvascular steatosis. Differentially expressed genes (DEGs) were noted as follows: control vs control+GLP-1RA: 2164 DEGs;

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control vs alcohol: 2052 DEGs; alcohol vs alcohol+GLP-1RA**:** 2163 DEGs. GLP-1RA induced up-regulation of genes involved in glutathione and xenobiotic metabolism including cytochrome P450. Interestingly, GLP-1RA downregulated CYP2E1 mRNA in both control and EtOH groups ($p<0.001$). This was confirmed by immunostaining for CYP2E1**.** Alcohol+GLP-1RA vs. alcohol showed reduced ROS formation (4HNE Immune staining). Furthermore, alcohol+GLP-1RA vs**.** alcohol showed a reduction of aldehyde dehydrogenase (NAD+) pathway and ethanol oxidation genes (Adh5, Adh7, Adh4, Adh1a1). In fasted mice (controlling for PO intake), GLP-1RA significantly reduced liver CYP2E1 mRNA levels ($p<0.05$). **Conclusion:** GLP-1RA provides hepatoprotection in AH likely through reduced CYP2E1 activity and up-regulation of antioxidant genes. Our findings suggest direct hepatoprotection by GLP-1RA which would be expected to act in concert with any effects induced by the reduction in ethanol intake.

Disclosures: Frhaan Zahrawi: Nothing to Disclose, Suyavaran Arumugam: Nothing to Disclose, Bubu Banini: Boehringer Ingelheim: Advisor, Novo Nordisk: Advisor, Mehal Wajahat: Sagimet: Advisor

3096 | PREVALENCE, RISK FACTORS, AND OUTCOMES OF FUNGAL INFECTIONS IN PATIENTS WITH SEVERE ALCOHOL-ASSOCIATED HEPATITIS

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Background: Patients with severe alcohol-associated hepatitis (sAH) are at high risk of fungal infections. Fungal infections are associated with mortality in patients with sAH. However, studies vary widely regarding prevalence rates, risk factors, and outcomes of fungal infections. We aim to study the prevalence, risk factors, and outcomes of sAH with and without fungal infections. **Methods:** We used ICD 9th and 10th codes for ALD and AUD from 2012-2021, identifying 1287 cases. After detailed chart reviewing, we identified 298 patients that met the NIAAA definition of sAH. Demographic, clinical, treatment data, as well as complications of liver disease were extracted from the EMR. Mucosal fungal infections (MFI) were defined as candiduria or other mucosal fungal diseases. Invasive fungal infections (IFIs) were defined as fungemia, pulmonary, or peritoneal infections. Univariable, multivariable, and survival analyses were performed to compare those with and without fungal infections. Overall survival was also assessed via Kaplan-Meier estimation and the log-rank test. **Results:** The mean age of our cohort was 47 +/- 10.7 years. 62.8% of patients were male, 72.5% white, 7.4% African American, 10.7% Hispanic, and 9.4% identified as “other.” Spontaneous recovery occurred in 56.7%, whilst 35.9% died and 6.9% received a liver transplant. Of the 298 patients, 8.1% (n=24) developed any fungal infection. Amongst those who developed fungal infection, 7.1% (n=21) developed MFI whilst 1.68% (n=5) developed IFIs (ie fungemia or fungal peritonitis). In univariate analyses, fungal infections were associated with female sex (62.5% vs 35%, p=0.014), ascites (87.5% vs 64.6%, p=0.024), hepatic encephalopathy (HE) (62.5% vs 33.6%, p<0.01), esophageal variceal bleeding (EVB) (20.8% vs 6.6%, p=0.03), pentoxifylline administration (25% vs 9.1%, p=0.03), and recurrent infections (87.5% vs 37.6%, p<0.001). Multivariable analyses suggest that lower age (OR 0.79, 95% CI 0.63-0.97, p=0.03), female sex (aOR 2.6 95% CI 1.1-6.7, p=0.03), ascites (OR 3.6 95% CI 1.2-15.6 p=0.048), and EVB (OR 4.4 95% CI 1.2-13.9, p=0.02) are associated with fungal infections. Overall, there were no differences in survival among sAH patients with and without fungal infection (log-rank=0.76). **Conclusion:** Fungal infections in patients with sAH have a prevalence of 8.1% as MFIs make up the majority of cases, yet IFIs are just under 2%. Female sex and EVB are common risk factors for fungal infections. Corticosteroid or pentoxifylline administration did not increase risk of fungal infections. Fungal infections did not affect overall survival amongst patients with sAH.

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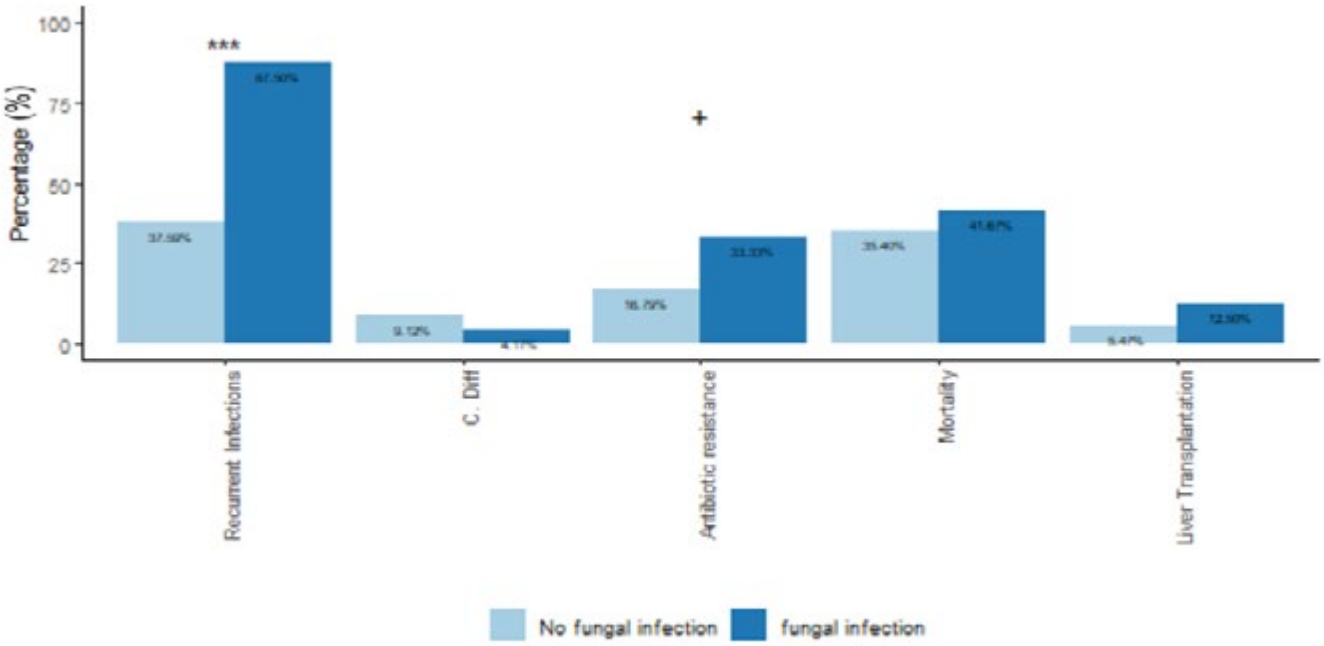

Figure 1: Clinical Outcomes by fungal infection status

Disclosures: Filippa Trikantzopoulou: Nothing to Disclose, Irena Helenowski: Nothing to Disclose, Fritzie Albarillo: Nothing to Disclose, Steven Scaglione: Nothing to Disclose

3097 | MOLECULAR TARGETS OF PXR-DEPENDENT ETHANOL-INDUCED HEPATOTOXICITY IN FEMALE MICE

Malvin Ofosu-Boateng[1] Sarah Kim[2] Daniel Nnamani[1] Lidya Gebreyesus[1] Elizabeth Twum[1] Julia Yue Cui[3]

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Background: Alcohol-associated liver disease (ALD) develops from excessive alcohol use and is more severe in both human and rodent females than their male counterparts. Women alcoholics also have higher death rate than men. However, the precise mechanism remains unknown. The pregnane X receptor (PXR, NR1I2), a xenobiotic-sensing nuclear receptor signaling potentiates ethanol (EtOH)-induced hepatotoxicity in male mice, however, how PXR signaling modulates EtOH-induced hepatotoxicity in female mice is unknown. **Methods:** Wild type (WT, C57BL/6J) and *Pxr*-null mice received 5% EtOH-containing diets or paired-fed control diets for 8 weeks followed by assessment of liver injury, EtOH elimination rates, histology, and gene and protein expression changes; microarray and bioinformatic analyses were also employed to identify PXR targets in chronic EtOH-induced hepatotoxicity. **Results:** In WT females, EtOH ingestion significantly increased serum ethanol and alanine aminotransferase (ALT) levels, hepatic *Pxr* mRNA, constitutive androstane receptor (CAR) activation, *Cyp2b10* mRNA and protein, oxidative stress, and endoplasmic stress (phospho-eIF2α) and pro-apoptotic (Bax) protein expression. Unexpectedly, EtOH-fed female *Pxr*-null mice displayed increased EtOH elimination and elevated levels of hepatic acetaldehyde detoxifying aldehyde dehydrogenase 1a1 (*Aldh1a1*) mRNA and protein, EtOH-metabolizing alcohol dehydrogenase 1 (ADH1), and lipid suppressing microsomal triglyceride transport protein (MTP) protein, aldo-keto reductase 1b7 (*Akr1b7*) and *Cyp2a5* mRNA, but suppressed CYP2B10 protein levels, with evidence of protection against chronic EtOH-induced oxidative stress and hepatotoxicity. While liver injury was not different between the two WT sexes, female sex may suppress EtOH-induced macrovesicular steatosis in the liver. Several genes and pathways important in retinol and steroid hormone biosynthesis, chemical carcinogenesis, and arachidonic acid metabolism were upregulated by EtOH in a PXR-dependent manner in both sexes. **Conclusion:** Taken together, these data establish that female *Pxr*-null mice are resistant to chronic EtOH-induced hepatotoxicity and provide insight into the PXR-dependent and -independent mechanisms that contribute to EtOH-induced hepatotoxicity.

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Disclosures: Malvin Ofosu-Boateng: Nothing to Disclose, Sarah Kim: Nothing to Disclose, Daniel Nnamani: Nothing to Disclose, Lidya Gebreyesus: Nothing to Disclose, Elizabeth Twum: Nothing to Disclose, Julia Yue Cui: Nothing to Disclose

3098 | IMPACT OF SOCIAL DETERMINANTS OF HEALTH ON TRANSPLANT CANDIDACY FOR ALCOHOL-ASSOCIATED LIVER DISEASE

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Background: Alcohol-associated liver disease (ALD) including alcoholic hepatitis (AH) is now a leading indication for liver transplantation (LT). While there are several factors that deem a patient with ALD not a suitable candidate for LT such as lack of social support and untreated psychologic disease, the impact of social determinants of health (SDOH) have on LT candidacy has been understudied. The social deprivation index (SDI) can be utilized to assess SDOH with higher scores indicating worse SDOH. This study aims to identify factors that impact candidacy decisions for listing on those with ALD. **Methods:** Medical and psychosocial factors were collected into a REDCap database via chart review of candidate evaluations between 2019-2023. All candidates underwent detailed medical and psychosocial evaluation. Pre-LT psychiatric testing included the Stanford Integrated Psychosocial Assessment for Transplant (SIPAT), General Anxiety Disorder-7 (GAD-7), and Patient Health Questionnaire-9 (PHQ-9). Risk of return to drinking by the Sustained Alcohol use post-LT (SALT) and High-Risk Alcohol Relapse (HRAR) scores. SDI was collected off generalized United States Postal Service zip codes called Zip Code Tabulation Area (ZCTA) using the Robert Graham Center's SDI data (range 1-100). Patients with ALD not approved for LT listing were compared to those who were approved. **Results:** Among those evaluated with ALD, 278 were listed while 56 were not (Table). While age, sex, alcohol use, SALT and HRAR were similar, there were significant differences in SIPAT, % AH, marital and employment status, race, insurance, and MELD-Na. There were no differences in SDI between listed and not listed patients. The main reasons for not listing were high risk alcohol use, lack of social support, psychological, and medical. Using multivariate logistic regression, statistically significant variables were MELD-Na (p = 0.0001), acute AH (p=0.0001), SIPAT Score (p=0.001), "Other" Psychiatric Illnesses (p=0.016), and Divorced (p=0.033) with an AUC of 0.856 for the model. **Conclusion:** While we did observe differences in several demographic, psychosocial factors, ALD disease severity, and presence of acute AH in our cohort of patients referred for LT with ALD, there was no difference in SDI between those listed and those who were not. Therefore, better indices of SDOH are needed to assess candidacy for LT for ALD.

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Table. Comparison of values between Not Listed and Listed patients:

	Not Listed *n=56*	Listed *n=278*	p
Age (median)	54	51	0.539
Female (%)	28.6%	37.8%	0.224
SDI (median)	35.5	37	0.878
Race (%)	*(n=52)*	*(n=277)*	
Asian	0	1.1	1.0
Black	13.5	7.6	0.176
Other	11.5	4.3	0.047
White	75.0	87	0.034
Insurance (%)	*(n=47)*	*(n=277)*	
Medicaid	51.1	24.9	0.0004
Medicare	14.9	12.3	0.635
Private	31.9	46.9	0.059
VA	2.1	15.9	0.010
Employment Status (%)	*(n=54)*	*(n=275)*	
Homemaker	0.0	1.5	1.0
Disability	14.8	6.2	0.044
Employed	14.8	35.3	0.003
Gov't Assistance	7.4	0	0.001
Retired	20.4	12.7	0.139
Unemployed	42.6	44.4	0.881
Job Type (%)	*(n=40)*	*(n=209)*	
Blue Collar	80	73.2	0.434
Homemaker	0	1.4	1.0
White Collar	20	25.4	0.551
Marital Status (%)			
Not married, in relationship	10.7	12.2	1.0
Divorced	28.6	18.3	0.099
Married	30.4	48.6	0.013
Not in relationship	21.4	14.0	0.159
Separated	5.4	5.0	1.0
Widowed	3.6	1.8	0.333
Disease Type (%)		*(n=276)*	
Liver Disease <6mo sobriety	37.5	51.4	0.078
Acute Alcohol Hepatitis	33.9	2.5	0.3e-10
Cirrhosis >6mo sobriety	28.6	46.0	0.018
MELD-Na (median)	26 *(n=55)*	30	0.002
Average # Drinks per Day (median)	10 *(n=48)*	9 *(n=269)*	0.929
Max. Reported >= 10drink/day (%)	66.0 *(n=47)*	54.4 *(n=270)*	0.155
Reported # Days Abstinence (median)	110 *(n=40)*	150 *(n=275)*	0.097
Alcohol-Related Legal Issues (%)	50.0 *(n=46)*	41.7	0.336
SALT Score (median)	3 *(n=44)*	4 *(n=271)*	0.743
HRAR Score (median)	2 *(n=39)*	2 *(n=270)*	0.325
SIPAT Score (median)	31.5 *(n=30)*	22 *(n=207)*	0.0001
Psychiatric Illness (%)			
Anxiety	23.2	34.5	0.119
Depression	39.3	35.3	0.647
Mood Disorder	10.7	6.5	0.261
Other	14.3	5.0	0.018
SDI (median)	35.5	37	0.878
Reason Declined (%)			
High Risk Alcohol use	48.2	-	-
Lack of Social Support	23.2	-	-
Psychological	16.1	-	-
Medical	30.4	-	-
Financial	7.1	-	-
Lost to Follow Up	8.9	-	-
Other	16.1	-	-

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3099 | COMPARATIVE EFFECTIVENESS OF DIFFERENT CORTICOSTEROIDS IN PREDICTING 30-DAY MORTALITY AND CLINICAL OUTCOMES IN SEVERE ALCOHOL-ASSOCIATED HEPATITIS

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Background: Alcohol-associated hepatitis is a serious condition resulting from excessive alcohol consumption, leading to liver inflammation and impaired function. Severe alcohol-associated hepatitis (AH) is characterized by high mortality, especially in patients with a MELD score >20. Corticosteroids are the primary therapy for SAH, but the effectiveness of different types of steroids (prednisone, methylprednisolone, and others) compared to prednisolone in predicting 30-day mortality remains unclear. This study evaluates the comparative effectiveness of these regimens in terms of response to corticosteroids and mortality among patients with AH. **Methods:** This was a retrospective analysis, collecting data from an international multicenter cohort study including adults with AH. We determined response to corticosteroids using the Lille score at day 7 and mortality over time. For this analysis, we performed a regression model to assess response to corticosteroids (Lille Day 7 score) and a competing-risk model, with liver transplantation as the competing risk. We pre-defined the variables to be included in models based on the main predictors of mortality in AH in the prior literature, including age, sex, history of cirrhosis, and MELD score at admission. **Results:** We included 1,829 patients with SAH. The median age was 47.3±11.2 years old and 69.2% of patients were male. The median MELD at admission was 25 [21–32] and 43% used corticosteroids, wherein 27.5% use prednisolone, 55.6% prednisone, 14.1% methylprednisolone, and 2.8% other steroids (including hydrocortisone and dexamethasone). Compared to prednisolone, prednisone (subdistribution hazard ratio [sHR] 0.735, 95%CI: 0.529–1.0412; p=0.083), methylprednisolone (sHR = 0.824, 95%CI: 0.529–1.283; p=0.392), and other steroids (sHR=1.045, p=0.928) did not significantly predict different 30-day mortality (Figure). Similarly, in the Lille score regression analysis, there were no significant differences: prednisone (p=0.214), methylprednisolone (p=0.427), and other steroids (p=0.869) were not significantly different from prednisolone in predicting Lille score (Day 7). In both models, age and MELD were significant predictors of mortality and corticosteroid response. **Conclusion:** Our study found no statistically significant comparative difference between prednisolone, prednisone, methylprednisolone, and other steroids in predicting 30-day mortality or Lille score (day 7) in patients with severe AH. These findings suggest that the choice of steroids may not influence short-term clinical outcomes in this patient population. Future research should focus on long-term effects, potential interactions with other treatments, and patient-specific factors to enable more personalized treatment approaches. Larger studies are needed to validate these results and explore underlying mechanisms.

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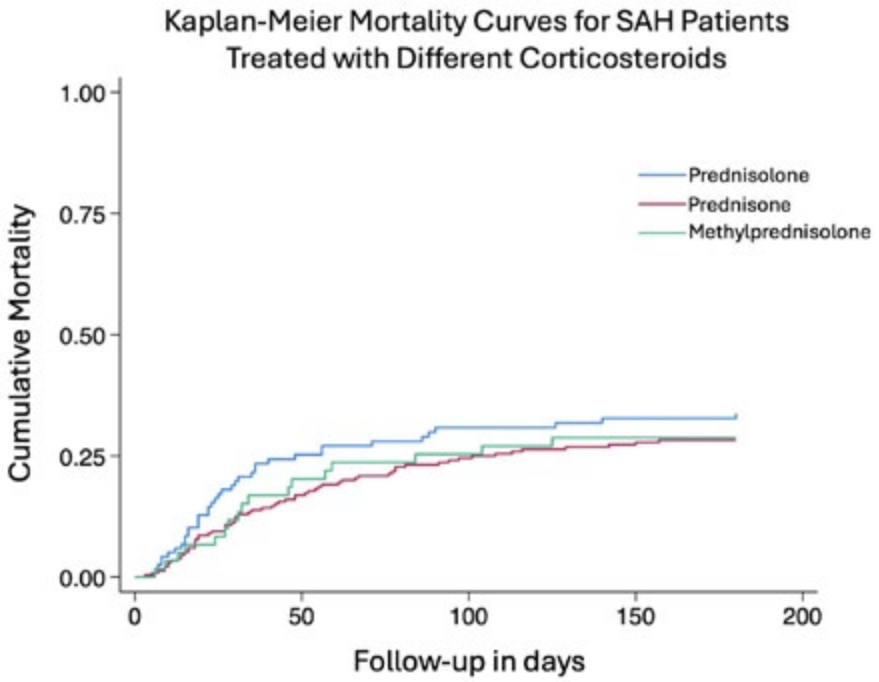

Disclosures: Alvi Islam: Nothing to Disclose, Luis Antonio Díaz: Nothing to Disclose, Francisco Idalsoaga: Nothing to Disclose, Rokhsana Mortuza: Nothing to Disclose, Winston Dunn: Nothing to Disclose, Yanming Li: Nothing to Disclose, Ashwani Singal: Advisor relationship with CLD Foundation; Has not ended; Speaking and Teaching relationship with Medical Speaker's Network; Has not ended; Speaking and Teaching relationship with Madrigal; Has not ended; Stock â€“ privately held company relationship with Pleiogenix; Has not ended; Consultant relationship with Pleiogenix; Has not ended; Advisor relationship with Durect; Has ended; Royalties or patent beneficiary relationship with Up-to-Date; Has not ended; Executive role relationship with Gastro Endo News; Has not ended; Grant/Research Support relationship with NIAAA; Has not ended; Employee relationship with Avera Medical Group; Has ended; Grant/Research Support relationship with GSK; Has not ended; Employee relationship with University of Louisville School of Medicine; Has not ended; Speaking and Teaching relationship with Medscape; Has not ended, Douglas Simonetto: Consultant relationship with BioVie; Has ended; Consultant relationship with Iota; Has ended; Consultant relationship with Mallinckrodt; Has ended; Consultant relationship with Resolution Therapeutics; Has ended; Consultant relationship with Evive; Has ended, Carolina Ramirez-Cadiz: Nothing to Disclose, Wei Zhang: Nothing to Disclose, Steve Qian: Nothing to Disclose, Joaquin Cabezas: Gilead: Advisor, Gilead: Speaking and Teaching, Abbvie: Speaking and Teaching, Gilead: Grant/Research Support, Ines Garcia: Nothing to Disclose, Shiv Kumar Sarin: Nothing to Disclose, Rakhi Maiwall: Nothing to Disclose, Prasun Jalal: Nothing to Disclose, Fatima Higuera-de-la-Tijera: Nothing to Disclose, Lubomir Skladaný: Worwag: Speaking and Teaching, ProMed: Speaking and Teaching, Abbvie: Speaking and Teaching, Gilead: Speaking and Teaching, RegPharm: Speaking and Teaching, Natalia Bystrianska: Nothing to Disclose, Ana Clemente: Nothing to Disclose, Diego Rincon: Nothing to Disclose, Kristina Chacko: Nothing to Disclose, Pamela Yaquich: Nothing to Disclose, Meritxell Cots: Nothing to Disclose, Guadalupe Garcia-Tsao: Nothing to Disclose, Juan Abraldes: Gilead: Grant/Research Support, 89bio: Consultant, Boston Pharmaceuticals: Consultant, Novo Nordisk: Consultant, Boehringer Ingelheim: Consultant, Astra Zeneca: Consultant, Agomab: Consultant, Terumo: Speaking and Teaching, Cook: Grant/Research Support, Patrick Kamath: Advisor relationship with Sequana; Has ended; Advisor relationship with NovoNordisk; Has ended, Marco Arrese: Aztra Seneca: Steering Commitee, Inventiva: Consultant, Vijay Shah: Boehringer Ingelheim: Consultant, GSK: Consultant, GENFIT SA: Consultant, Intercept Pharmaceuticals, Inc.: Advisor, Korro Bio, Inc.: Consultant, Mallinckrodt Pharmaceuticals: Advisor, Novo Nordisk A/S: Consultant, Resolution Therapeutics, Ltd.: Advisor, Seal Rock Therapeutics, Ltd.: Consultant, Surrozen: Advisor, Juan Pablo Arab: Nothing to Disclose

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3100 | ALCOHOL USE DISORDER TREATMENT DURING EVALUATION IN PATIENTS WITH ALD REFERRED FOR EARLY LIVER TRANSPLANT

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Background: With alcohol-associated liver disease (ALD) becoming the leading indication for liver transplant (LT) in the United States, many centers now offer LT for ALD without a minimum required period of sobriety. Still, LT centers encourage alcohol use disorder treatment pre-LT to reduce relapse risk. In persons with short sobriety undergoing LT evaluation (LTE), we describe characteristics associated with receipt of AUD treatment and its impact on listing decision. **Methods:** RESOLVE-ALD is a multi-center retrospective cohort study of patients with ALD and <6 months of sobriety referred for early LT between 2018 and 2021. Nested multiple logistic regression analysis was used to evaluate factors associated with participation in AUD treatment during LTE (inpatient rehab, intensive outpatient programs [IOP], pharmacotherapy, or psychotherapy). A multivariable logistic regression analysis was used to analyze the effect of AUD treatment on LT waitlisting. Interaction analyses were used to explore the effects of age, sex, race, and insurance on receipt of AUD treatment. **Results:** Of 632 patients evaluated for early LT, 24.8% (n=157) engaged in at least one AUD treatment during LTE (IOP: n=66, pharmacotherapy: n=25; outpatient psychotherapy: n=74; inpatient rehab: n=7). A majority of patients were white (77.5%) and male (60.6%) with no psychiatric comorbidities (65%) and no prior AUD treatment attempts (80.6%). Patients with age ≥ 50 (OR 0.53, 95% CI 0.35-0.96), Hispanic/Latino heritage (OR 0.51, 95% CI 0.26-0.96), and Medicaid/self-pay status (OR 0.61, 0.37-0.99) were less likely to receive AUD treatment. Prior AUD treatment attempts (OR 1.85, 95% CI 1.16-2.93) and history of alcohol-related illnesses (OR 2.12, 95% CI 1.39-3.26) increased odds of AUD treatment during LTE. Of patients listed for LT (37.4%, n=373), AUD treatment during evaluation increased odds of listing (OR 1.70, 95% CI 1.09-2.68). Conversely, Medicaid/self-pay status (OR 0.51, 95% CI 0.33-0.77) and history of prior AUD treatment attempts before evaluation (OR 0.49, 95% CI 0.32-0.75) reduced odds of listing. **Conclusion:** Older, underinsured, and Hispanic/Latino patients are less often supported with AUD treatment during LTE compared to their counterparts. Given that AUD treatment significantly increases listing odds for patients when controlled for sociodemographic variables, disparities in engagement with AUD treatment may be an area for centers to target to improve transplant candidacy in these patient populations.

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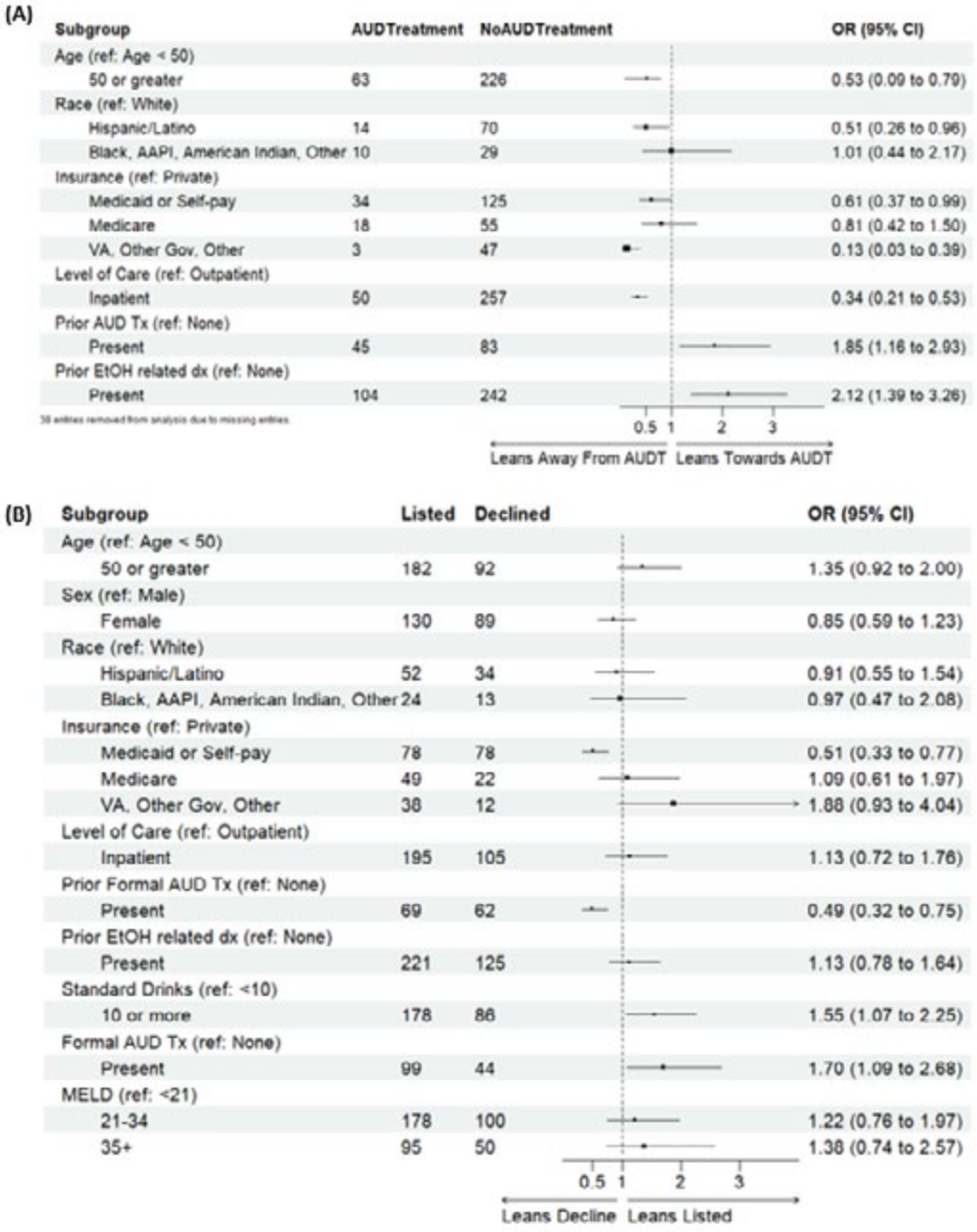

Figure 1: Multivariable logistic regressions of variables associated with (A) receipt of AUD treatment; n=36 missing because of missing entries. (B) listing decision for LT.

Disclosures: Kevin Wang: Nothing to Disclose, Sasha Deutsch-Link: Nanbar Health: Consultant, Weiyu Wu: Nothing to Disclose, Allison Kwong: Nothing to Disclose, Kawthar Mohamed: Nothing to Disclose, Nicholas Lim: Nothing to Disclose, Deepika Devuni: Avania Medical: Grant/Research Support, Intercept: Grant/Research Support, Katherine Cooper: Nothing to Disclose, Anjana Rajan: Nothing to Disclose, Amanda Cheung: Nothing to Disclose, Kaleb Tesfai: Nothing to Disclose, Veeral Ajmera: Nothing to Disclose, Hersh Shroff: Nothing to Disclose

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3101 | DEMOGRAPHIC DISPARITIES IN THE OUTCOMES OF PATIENTS ADMITTED WITH ALCOHOL-ASSOCIATED HEPATITIS: A CROSS-SECTIONAL STUDY

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Background: Alcohol associated hepatitis (AAH) is a significant burden on healthcare resource utilization and inpatient healthcare expenditures. Previous studies had demonstrated increased hospital costs in Hispanics compared to Blacks and Whites. However, there is paucity of data in recent trends of healthcare resource utilization associated with AAH hospital admissions. **Methods:** We conducted a cross -sectional study on the Nationwide Inpatient Sample (NIS). We included patients aged 18 years and older hospitalized in 2016-2019 with a principal International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) diagnosis of alcohol associated hepatitis (K70.1). Age, sex, race, Charlson Comorbidity Index (CCI), and primary insurance data were evaluated. In-hospital mortality was the primary outcome and the hospital length of stay (LOS) in days was the secondary outcome. Bivariate analysis was conducted to identify indicators of mortality and increased hospital LOS. Logistic regression was performed to determine the adjusted association of the indicators and the outcomes, in-hospital mortality and increased hospital length of stay. STATA version 18.0 software was used for data analysis. **Results:** We identified 70,420 subjects admitted for AAH between 2016-2019. The mean age was 46 years, and the majority of the subjects were White (72%), Table 1. Medicaid was the primary insurance for 40% of the cohort and 15% were self-pay. There were 2,115 (3%) inpatient deaths in the whole cohort. After multivariable regression analysis, self-pay status (OR: 1.94, p-value: 0.006) and CCI of 3 or more (OR: 1.34, p <0.01) were observed to have increased odds of mortality compared to Medicare patients and subjects with lower CCI, respectively. Compared to Whites, there was no significant differences among the different races in mortality. Overall, mean LOS was 6.1 days and mean hospital cost was $13,602. Compared to Whites, Blacks (-0.69, p <0.01) and Hispanics (-0.62, p <0.01) had shorter LOS. Females (0.4, p <0.01) and Medicaid patients (0.57, p<0.01) had longer LOS. **Conclusion:** We observed that 55% of the patients admitted with AAH had either self-pay or Medicaid insurance. Additionally, almost 30% of the population had an annual household income of less than $50,000, reflecting potential financial vulnerability inherent to this population. Self-pay status was associated with almost two-fold increase in mortality which may reflect suboptimal medical care provided to this vulnerable group. As expected, patients with higher morbidity burden as reflected by CCI also had increased mortality. We did not find a difference in mortality among different races. Our findings highlight the demographic disparities in outcomes of AAH patients and call for standardized management measures.

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Table 1. Comparison of demographic and baseline clinical characteristics of patients admitted with alcoholic hepatitis

Variable	
N= 70,420	
Female, %	41.2
Mean Age, years	46
Race, %	
White	72%
Black	9%
Hispanic	12%
Asian or Pacific Islander	1%
Native American	2%
Other	3%
CCI score, %	
0	0.0
1	43%
2	13%
>=3	43%
Primary payer, %	
Medicare	13%
Medicaid	39.6%
Private insurance	31.9%
Self-pay	14.9%

Abbreviations: N, Number, CCI, Charlson Comorbidity Index

Disclosures: Nehna Abdul Majeed: Nothing to Disclose, Abdel-Latif Ismail: Nothing to Disclose, Kirti Shetty: Nothing to Disclose

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3102 | DEVELOPMENT OF ALCOHOL-ASSOCIATED LIVER DISEASE IN YOUNG INDIAN ADULTS: AN OBSERVATIONAL STUDY OF CLINICAL AND SOCIO-DEMOGRAPHIC CORRELATES AND OPPORTUNITIES FOR EARLY INTERVENTION

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[1]Associate Professor, Institute of Liver and Biliary Sciences, [2]Institute of Liver and Biliary Sciences, [3]Director, Institute of Liver and Biliary Sciences

Background: The global trend indicates a decreasing age of onset for Alcohol Use Disorder (AUD) and alcohol-associated Liver Disease (ALD). This study aims to analyse the clinical and socio-demographic factors correlating with AUD in Indian patients with ALD diagnosed under 32 years of age. **Methods:** Over the past decade (2015-2024), a total of 888 patients diagnosed with ALD at our centre were under the age of 32, comprising 10.06% of all ALD cases. We incorporated retrospective data from young ALD patients with recent lapses who are currently undergoing follow-up in our Hepatology outpatient departments (n=62). Additionally, we prospectively included young ALD patients attending the AUD clinic over a six-month period (n=144) at our centre. We conducted ANOVA and correlation studies to analyse relevant factors. Young ALD was defined as ALD first diagnosed before the age of 32, supported by histological, radiological, or endoscopic evidences. Informed consent was obtained from all patients. **Results:** Two hundred six patients with AUD, 31.39 ± 2.8 years, 202 males, 98.1% with some form of decompensation, MELD (25.13 ± 6.83), CTP (10.13 ± 1.9) who presented with ALD were evaluated. There were 45.6% CLD-ALD, 39.8% ACLF (APASL definition) with AARC score of 9.35 ± 2.3 and 14.56% SAH. Metabolic traits were present in 61.6% patients and 59.7% had BMI ≥ 23. A positive correlation of Beck's Depression Inventory Score, BDI (r=0.207, p=0.009) was found with the quantity of alcohol consumed in grams/week. Binge drinking (df=2, p<0.01) and daytime drinking (df=2, p<0.01) were significant across the three diagnoses. Group-wise analysis revealed a positive correlation of quantity of alcohol intake (1000 ± 54.2 grams/week) with MELD (r=0.239, p=0.030), CTP (r=0.346, p=0.001) and AARC (r=0.259, p=0.019) score in the ACLF group. On the basis of ANOVA, MELD (F=15.14, p<0.00), CTP (F=13.38, p<0.00) and AARC (F=8892, p<0.00) were found significantly correlating with early onset liver disease. Duration of AUD [F=18.6, CI(11.68-12.6), p<0.00)] and BDI (F=3.4, p=0.03) were found to be significantly associated with the early onset of Alcohol-associated liver disease. However, age at first drink [CI(17.90-18.63) p=0.170] and age at AUD diagnosis [CI(29.16-29.83) p=0.102] could not reach statistical significance for our sample. **Conclusion:** Approximately one in ten ALD patients in India is under the age of 32, with 60% presenting metabolic traits. Furthermore, there is a positive correlation between Beck's Depression Inventory scores (BDI) and the progression of ALD. It is imperative to address AUD and associated psychiatric conditions, which can provide essential insights for developing preventive strategies and focused interventions to mitigate the early onset of ALD.

TABLE 1: ANOVA of factors correlating to young age of onset of AUD related ALD.

Parameters	F	95% CI	p
MELD- Na	15.142	24.19- 26.06	p<0.00
CTP	13.38	9.87- 10.39	p<0.00
AARC (ACLF)	-	8.83-9.87	p<0.00
CAP	0.911	251.87-261.96	0.404
LSM	8.168	69.31-72.21	P<0.00
SSM	1.503	64.70-69.86	0.225
Fib-4 Score	5.029	24.84-36.73	0.007
Age @ First Drink	1.789	17.90-18.63	0.17
Age @ AUD Diagnosis	2.305	29.16-29.83	0.102
AUD(Years)	18.636	11.68-12.60	P<0.00
Q (grams/week)	0.917	883.70-1028.48	0.401
CAGE	7.399	-	0.001
AUDIT	4.416	-	0.013
HAMA	0.011	-	0.989
BDI	3.454	-	0.034
CIWA- Ar	5.225	-	0.006
BMI	0.958	23.96-25.123	0.385

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Disclosures: Mohit Varshney: Nothing to Disclose, Aashmita Ajit: Nothing to Disclose, Vishnu Girish: Nothing to Disclose, Shiv Kumar Sarin: Nothing to Disclose

3103 | IMPACT OF COVID-19 ON ALCOHOLIC-RELATED HEPATITIS ADMISSIONS AT A MIDWEST TERTIARY CARE HOSPITAL

Padmavathi Mali[1] Siegfried Yu[1] Milan Folkers[1] Aditi Muduganti[2]

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Background: Alcoholic hepatitis is an acute, inflammatory liver disease associated with high morbidity and mortality. Wisconsin has the third highest rate of drinking in the United States with a consumption percentage of 64.8% compared to the national average of 55.1%. We aimed to determine the impact of the coronavirus disease 2019 (COVID-19) on hospitalizations for alcohol-related hepatitis at our community hospital system in La Crosse, Wisconsin. **Methods:** Our study included 68 hospital admissions with alcoholic hepatitis between March 16, 2018, and March 2022. Alcoholic hepatitis is defined by recent alcohol abuse within 3 months, aspartate transaminase (AST) /alanine transaminase (ALT) ratio > 1.5:1, total bilirubin > 1.2 mg/dL, AST >50, and AST <500 and ALT <500. The time interval from March 16, 2018, to March 15, 2020, is considered pre-COVID" while the interval from March 16, 2020, to March 15, 2022, is considered "post-COVID". Statistical comparisons were made using the Wilcoxon rank sum test, Fisher's exact test, and Pearson's Chi-squared test. **Results:** There were significantly more admissions with alcoholic hepatitis during the post-Covid period 77% (53/68) than pre-Covid 22% (15/68). There was an increase in admissions with age less than 40 years from 6.7% (1/15) in the pre-COVID to 32% (17/53) in the post-COVID period. We did not see significant changes in gender or ethnicity and the rate of comorbidities between the two groups. median MELD score showed an increase but the changes were not statistically significant. Complication rates including admission to the intensive care unit, readmission to hospital in 90 days, and death during admission did not differ significantly from pre- to post-COVID. **Conclusion:** Even though the complication rate in patients admitted with alcoholic hepatitis in pre- and post-COVID times did not differ, there were significantly more admissions in the post-COVID period compared to pre-COVID, especially in patients <40 years old. These findings have implications for supporting public health interventions targeted at alcohol use disorders and their related complications during future pandemics, to reduce the strain on already limited healthcare resources.

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Lab Values and Complications				
Characteristic	**Overall**, N = 68[1]	**Pre-COVID**, N = 15[1]	**Post-COVID**, N = 53[1]	**p-value**[2]
Average MELD score				0.073
Mean (SD)	23.83 (14.24)	17.64 (6.05)	25.73 (15.48)	
Median (IQR)	18.03 (15.75, 28.85)	16.65 (14.86, 18.55)	19.66 (16.18, 29.96)	
Unknown	4	0	4	
Average MELD NA score				0.093
Mean (SD)	26.57 (11.71)	21.62 (5.16)	28.08 (12.73)	
Median (IQR)	22.69 (19.19, 31.49)	20.05 (18.24, 23.38)	23.95 (19.31, 32.38)	
Unknown	4	0	4	
Mean albumin				0.2
Mean (SD)	2.32 (0.96)	2.08 (0.74)	2.37 (1.00)	
Median (IQR)	2.05 (1.74, 3.00)	1.75 (1.68, 2.28)	2.10 (1.86, 3.00)	
Unknown	24	7	17	
Mean bilirubin				0.5
Mean (SD)	14.80 (10.24)	12.87 (9.32)	15.34 (10.50)	
Median (IQR)	12.02 (6.63, 19.74)	8.93 (6.71, 15.56)	12.48 (6.68, 21.15)	
Mean INR				0.7
Mean (SD)	1.96 (0.60)	1.87 (0.49)	1.99 (0.63)	
Median (IQR)	1.84 (1.51, 2.23)	1.83 (1.57, 2.05)	1.87 (1.50, 2.27)	
Unknown	2	0	2	
Mean creatinine				**0.002**
Mean (SD)	4.49 (13.96)	0.69 (0.38)	5.61 (15.74)	
Median (IQR)	0.75 (0.61, 1.36)	0.63 (0.48, 0.70)	0.84 (0.68, 1.60)	
Unknown	2	0	2	
Endoscopy	12 (18%)	2 (13%)	10 (19%)	>0.9
Steroid use	30 (44%)	6 (40%)	24 (45%)	0.7
CCU admission	3 (4.4%)	1 (6.7%)	2 (3.8%)	0.5
Intubation				
No	68 (100%)	15 (100%)	53 (100%)	
Kidney injury	1 (1.5%)	0 (0%)	1 (1.9%)	>0.9
Acute kidney failure	1 (1.5%)	0 (0%)	1 (1.9%)	>0.9
Hemodialysis	5 (7.4%)	0 (0%)	5 (9.4%)	0.6
Death during admission	5 (7.4%)	0 (0%)	5 (9.4%)	0.6
Readmitted within 90 days	34 (50%)	8 (53%)	26 (49%)	0.8

[1] N (%)

[2] Wilcoxon rank sum exact test; Wilcoxon rank sum test; Fisher's exact test; Pearson's Chi-squared test

Disclosures: Padmavathi Mali: Nothing to Disclose, Siegfried Yu: Nothing to Disclose, Milan Folkers: Nothing to Disclose, Aditi Muduganti: Nothing to Disclose

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3104 | CARDIOMETABOLIC COMORBIDITIES INFLUENCE EARLY MORTALITY IN PATIENTS WITH ALCOHOL-ASSOCIATED HEPATITIS (AH)

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Background: Both alcohol and cardiometabolic risk factors (CMRFs) cause hepatic steatosis but the influence of CRMFs on alcohol-associated hepatitis (AH) is understudied. We hypothesized that CMRFs lead to a more severe presentation and lower likelihood of recovery from AH. **Methods:** Single-center retrospective study of adults (>18 years) with index hospitalization for possible/probable/definite AH (per NIAAA criteria) at an urban safety net hospital from 2017-2022. CMRFs at presentation (BMI, diabetes, dyslipidemia, hypertension) were identified and categorized as <1 and ≥1 for analysis. Primary outcome was 30-day mortality and secondary outcomes were 90-day mortality, 30-day and 90-day readmission. Multivariable logistic regression models evaluated CMRFs as the primary explanatory variable for mortality and readmission. **Results:** 384 patients diagnosed with AH were included (median age 43 (IQR: 36-52), 85% male, 86% Hispanic, MELD-Na 26 (IQR 21-31), MDF 51 (IQR (34-68), 66% had a diagnosis of cirrhosis, 26% required an ICU stay, 2.9% had hepatorenal syndrome (HRS), and 53% received corticosteroids. Of the 384 patients, 72 had a definite diagnosis of AH (per NIAAA criteria), 235 probable AH, and 77 possible AH. 40% had at least one CMRF: 77% were obese (BMI > 30) with median (IQR) BMI of 32 (30-34), 24% type-2 diabetes, 25% hypertension and 2% dyslipidemia. Overall, 30-day and 90-day mortality rates were 11% and 16% respectively; 30-day and 90-day readmission rates were 26% and 34%. There were no differences in disease severity in presentation in those with and without CMRF: presence of cirrhosis (67% vs 65%, p=0.41), median MELD-Na on admission (26 vs 26, p=0.22), MDF (51 vs 46, p= 0.85), % requiring ICU stay (25% vs 27%, p=0.33). Those with CMRF compared to those without had a significantly higher 30-day mortality (14% vs 8%, p=0.042) and a higher but not statistically significant 90-day mortality rate (20% vs 14%, p=0.09). The rates of 30-day readmission (26% vs 25%, p=0.42) and 90-day readmission (25% vs 34%, p=0.50) were similar. In multivariable models, CMRF >1 was significantly associated with higher 30-day mortality (AOR 2.2, 95% CI 1.00-4.74, p=0.05) but not higher 90-day mortality (AOR 1.7, 95% CI 0.90-3.15, p=0.10) (TABLE). **Conclusion:** Among adults with AH, CMRFs are prevalent and associated with a 2-fold higher 30-day mortality, even after adjustment for corticosteroid response. Strategies to improve short-term mortality need to consider both alcohol and metabolic-specific therapies.

Table: Factors Associated with 30-day and 90-day Mortality

	30-day Mortality		*90-day Mortality*	
Variable	***Univariable OR, 95% CI***	***P value***	***Univariable OR, 95% CI***	***P value***
CMRF > 1	**1.86 (0.98-3.51)**	**0.057**	**1.51 (0.87-2.61)**	**0.140**
	Multivariable OR*, 95% CI	***P value***	***Multivariable OR*, 95% CI***	***P value***
CMRF > 1	**2.18 (1.00-4.73)**	**0.05**	**2.69 (0.90-3.15)**	**0.103**
Age	1.04 (1.00-1.07)	0.038		
MELD-Na	1.15 (1.08-1.22)	< 0.001	1.10 (2.05-1.15)	< 0.001
Hepatorenal Syndrome	5.37 (1.17-24.7)	0.031	7.76 (1.85-31.5)	0.005
ICU	7.13 (3.23-15.7)	< 0.001	5.14 (1.05-1.15)	< 0.001
Steroid responder	0.20 (0.06-0.69)	0.011		
Hepatic encephalopathy			1.94 (0.99-3.80)	0.054

*Other variables evaluated in multivariable models but that were not significant were: BMI, whether patient received corticosteroids, and MDF upon presentation.

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3105 | INITIATION OF NALTREXONE IS ASSOCIATED WITH LOWER RATES OF SBP AND MORTALITY THAN ACAMPROSATE IN PATIENTS WITH DECOMPENSATED ALCOHOL-ASSOCIATED CIRRHOSIS

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Background: Naltrexone and acamprosate are FDA-approved medications for the treatment of alcohol use disorder (AUD). Data regarding their use in patients with alcohol-associated cirrhosis (AC) are limited. Historically, naltrexone has been avoided in patients with decompensated AC due to its hepatic metabolism and concern for potential hepatotoxicity. In contrast, acamprosate is renally excreted and is the preferred agent in this cohort. We aimed to compare further decompensation and mortality after initiation of naltrexone versus the current preferred agent, acamprosate, in patients with decompensated AC. **Methods:** Analysis was completed using a TriNetX query of US Collaborative Network – a research network of 60 healthcare organizations. We identified patients with AC with ascites and ongoing alcohol use who were either initiated on naltrexone (Cohort 1) or acamprosate (Cohort 2). Propensity Score Matching (PSM) was used to create cohorts matched for age, race, sex, ethnicity, and prior hepatic encephalopathy. Outcomes were assessed 30 days to 5 years after the initiation of pharmacotherapy. Patients with the outcome before the index event were excluded from individual analyses. The estimated risk of each outcome was reported as a percentage. Associations were reported as odds ratios (OR) and 95 % confidence intervals (95% CI). **Results:** 4122 patients were identified, including 2,274 patients who were initiated on naltrexone and 1,888 patients who were initiated on acamprosate. After PSM, 1800 patients were included in each group. Median follow-up time was slightly longer in the naltrexone cohort (449 days, IQR 842) compared to the acamprosate cohort (406 days, IQR 846). Naltrexone was associated with a comparable risk of alcoholic hepatitis (OR 1.082, [95% CI: 0.786-1.48[9, p=0.629), bleeding esophageal varices (OR 0.86 [0.657-1.128], p=0.277) and acute kidney injury (AKI) (OR 0.97, [0.80-1.19], p=0.820) relative to acamprosate. However, naltrexone was associated with significantly lower rates of spontaneous bacterial peritonitis (SBP) (OR 0.753 [0.583-0.972], p=0.029) and mortality (OR 0.858 [0.740-0.994], p=0.042) compared to those initiated on acamprosate. **Conclusion:** Our cohort study suggests that naltrexone may be associated with lower rates of further decompensation (e.g., SBP) and death in patients with AC decompensated by ascites and ongoing alcohol use, compared to acamprosate. These results may inform the growing literature on medication-assisted therapies in patients with co-morbid AUD and AC.

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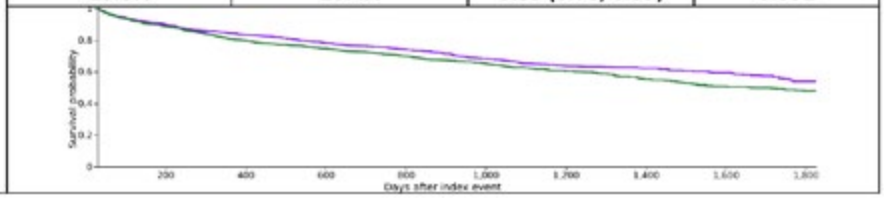
Table 1: Propensity score matching of variables, and outcomes with naltrexone vs acamprosate use

	Naltrexone (n=1800)	Acamprosate (n=1800)	p-value (before matching)	p-value (final cohort)
Age in years	50.6± 11	50.4±11	<0.001	0.868
Female sex	709 (38%)	671 (36%)	0.161	0.199
White	1,334 (74%)	1,383 (77%)	0.086	0.063
Black or African American	166 (9%)	153 (9%)	0.171	0.446
Hispanic or Latino	202 (11%)	172 (10%)	<0.001	0.101
Hepatic encephalopathy	334 (19%)	331 (18%)	<0.001	0.897
Outcomes				
Event	**Risk**	**Risk**	**OR (95% CI)**	**p-value**
Alcohol-associated Hepatitis (1st episode)	10.5 %	9.7%	1.10 (0.8, 1.5)	0.572
Variceal bleeding (1st episode)	6.9%	8.0%	0.86 (0.65, 1.12)	0.271
Acute kidney injury (1st episode)	26.6%	27.0%	0.98 (0.80, 1.20)	0.834
Spontaneous bacterial peritonitis (1st episode)	6.9%	9.0%	0.75 (0.58, 0.97)	0.029
Death	23.3%	26.4%	0.85 (0.73, 0.99)	0.031
				

Disclosures: Vinay Jahagirdar: Nothing to Disclose, Katherine Cooper: Nothing to Disclose, Deepika Devuni: Avania Medical: Grant/Research Support, Intercept: Grant/Research Support

3106 | PERFORMANCE OF URINE RAPID ETHYL GLUCURONIDE TESTING TO CHARACTERIZE RECENT AND UNHEALTHY ALCOHOL USE AT HIV CLINICS IN ZAMBIA

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Background: Emerging alcohol biosensors and biomarkers may improve the detection of harmful alcohol use in clinical care; however, the most sensitive and specific ones remain too expensive for widespread use. We leveraged a behavioral intervention trial for alcohol reduction at human immunodeficiency virus (HIV) clinics in Zambia to evaluate a low-cost urine rapid test for Ethyl glucuronide (EtG), an alcohol metabolite. **Methods:** The trial enrolled Zambian adults with HIV infection and who reported at least hazardous alcohol use disorder in the past 3 months based on the Alcohol Use Disorders Identification Test (AUDIT score of 4+/8+ points for women/ men). We also ascertained daily reports of alcohol use in the past 2 weeks via the alcohol timeline follow back (TLFB) in a subset. In dried whole blood spots, we measured phosphatidylethanol (sensitivity, 8 ng/dl; USDTL, Inc.), a metabolite of alcohol that can be detected for 3 weeks, using liquid chromatography tandem mass spectrometry. A fresh urine sample was rapid tested for presence of EtG (500 ng/ml threshold; CLIA waived, Inc.). We calculated the sensitivity and specificity of EtG testing for recent alcohol use by TLFB (any drink in past 3 days), by Peth (i.e., past 3 week use), and for a moderate-severe alcohol use disorder (AUD; AUDIT score of

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12+/16+ for women/men) in the past 3 months. **Results:** We analyzed 302 participants (107 women, 35%) who enrolled between January 2023 – April 2024. Median age was 41 years (range, 18-67), median AUDIT score was 23 (range, 4-39), and 153/197 (78%) reported alcohol use in past 3 days. 190/302 (63%) were EtG-positive and 277/302 (92%) were Peth-positive. EtG was 78% sensitive and 75% specific for past 3-day reported use, 68% sensitive and 88% specific for detectable Peth, and 66% sensitive and 59% specific for reported AUD. **Conclusion:** Among adults with HIV, reporting unhealthy alcohol use over the past 3 months, and joining an alcohol-focused clinical trial in Lusaka, Zambia, objective alcohol use was more frequently present via blood Peth than urine EtG biomarker testing. The accuracy of EtG rapid testing was moderate for recent alcohol use, but poor for longer term use.

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3107 | THERAPEUTIC INHIBITION OF BRUTON'S TYROSINE KINASE (BTK) ACTS ON BOTH IMMUNE CELLS AND HEPATOCYTES TO ATTENUATE IMMUNE CELL ACTIVATION AND STEATOSIS IN A MOUSE MODEL OF ALCOHOL-ASSOCIATED HEPATITIS ◆

Prashanth Thevkar Nagesh[1] Yuan Zhuang[2] Mrigya Babuta[2] Marti Ortega-Ribera[2] the AlcHepNet clinical investigators[2] Gyongyi Szabo[3]

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Background: Alcohol-associated hepatitis (AH) involves hepatic steatosis, neutrophil infiltration, neutrophil extracellular traps (NETs) formation and NLRP3 inflammasome activation in macrophages. Finding a therapeutic target that is common to these different cellular pathways has been a major challenge. Bruton's tyrosine kinase (BTK), a non-receptor tyrosine kinase, plays an important role in immune cell activation. However, its role in AH is unknown. We hypothesized that alcohol induces BTK phosphorylation (pBTK) and pharmacological inhibition BTK will attenuate AH. **Methods:** Female, C57BL/6J mice aged 12-14 weeks received Lieber-deCarli diet with alcohol for 10 days followed by one binge (AH model) or calorie matched control diet. Some mice received daily oral gavages of evobrutinib, a BTK inhibitor (BTKi), or DMSO on days 7-10. Serum ALT and proinflammatory cytokines were measured by ELISA. pBTK was assessed in human or mouse livers by Western blotting. NET markers (citrullinated histone H3, neutrophil elastase) were measured in liver lysates. Circulating and liver monocytes and neutrophils and ASC specs were evaluated by flow cytometry. Hepatic steatosis markers were determined by qPCR. Interaction between NLRP3 and BTK was tested in mouse bone marrow derived macrophages (BMDMs) by co-immunoprecipitation. **Results:** Circulating neutrophils and monocytes from AH patients showed increase in pBTK compared to healthy controls (n=8/group). *In vitro,* alcohol treatment rapidly induced pBTK both in primary human and mouse hepatocytes, neutrophils, and monocytes. *In vivo,* we found increased pBTK (Y223 and Y551) in human and mice liver with AH compared to controls. In a preclinical model of AH, treatment with BTKi significantly reduced pro-inflammatory cytokines and attenuated liver damage (ALT). Importantly, we discovered that alcohol-induced increase in liver infiltrated monocytes and neutrophils was associated with an increase in pBTK levels, which was significantly attenuated in BTKi treated mice. Furthermore, co-immunoprecipitation revealed that alcohol-induced pBTK interacted with NLRP3, stabilizing the inflammasome complex. Alcohol-induced ASC specs, which amplify inflammation, were significantly reduced after BTKi treatment in mice BMDMs, *in vitro*. Alcohol-induced increase in neutrophil activation and NETs was prevented in the livers of BTKi-treated mice. Finally, BTKi resulted in reduced hepatic lipid content expression of genes involved in steatosis: *Fasn*, *Fatp5, Pparα*. **Conclusion:** Our study demonstrates a central role of alcohol-induced BTK activation in regulating steatosis, inflammation, NLRP3 inflammasome activation and NETs formation in AH by acting on both hepatocytes and immune cells. Our novel findings highlight the therapeutic potential of BTK inhibition as a new potential strategy to treat AH.

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Nothing to Disclose, Gyongyi Szabo: Advisor relationship with Glympse Bio, Inc (acquired by Sunbird Bio); Has not ended; Consultant relationship with Terra Firma; Has not ended; Consultant relationship with Pfizer; Has not ended; Consultant relationship with Pandion Therapeutics; Has ended; Consultant relationship with Merck; Has ended; Consultant relationship with Durect Corporation; Has ended; Advisor relationship with Satellite Biosciences; Has not ended; Consultant relationship with Zomagen Bioscience/Ventyx Biosciences; Has ended; Consultant relationship with CYTA Therapeutics; Has ended; Royalties or patent beneficiary relationship with Springer Nature Group; Has not ended; Royalties or patent beneficiary relationship with UpToDate Inc; Has not ended; Consultant relationship with LabCorp; Has not ended; Advisor relationship with Evive; Has not ended; Advisor relationship with Surrozen; Has not ended; Consultant relationship with Takeda; Has ended

3108 | ELEVATED SYSTEMIC IGM ANTIBODIES TARGETING MALONDIALDEHYDE ADDUCTS PROMOTE ALCOHOL-ASSOCIATED LIVER DISEASE VIA COMPLEMENT ACTIVATION

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Background: Alcohol-associated liver disease (ALD) associates with elevated immunoglobulin type M (IgM) levels in circulation. Primarily via complement activation, secretory IgM fulfils efferocytosis and clearance functions upon recognition of presented epitopes, such as malondialdehyde (MDA) on dying cells. Interestingly, mice deficient for soluble IgM (*sIgM*$^{-/-}$), which display altered immunity and compensatory IgA titers, were previously found to be protected from early stages of ethanol-induced liver disease. Yet, the exact functional and mechanistic contribution of increased IgM levels to ALD remains incompletely understood. **Methods:** The development of ethanol-induced liver disease was assessed in *sIgM*$^{-/-}$ mice, mice deficient for the sialic acid-binding immunoglobulin-like lectin G (*Siglec-G*$^{-/-}$), resulting in specifically increased systemic IgM, and their corresponding wildtype littermates after receiving chronic-binge ethanol diet. To study the contribution of specific MDA-binding IgM antibodies to ALD, wildtype mice were injected with LR04 antibodies or isotype control IgM during chronic-binge ethanol feeding. *Siglec-G*$^{-/-}$ bone marrow transplantation into wildtypes or mice deficient for complement C3 (*C3*$^{-/-}$) was done to study the involvement of complement activation by elevated IgM in ALD. Anti-MDA IgM and IgG titers, and complement factors were assessed in serum of ALD patients. **Results:** Complementing reduced ethanol-induced liver injury in *sIgM*$^{-/-}$ mice, specifically increased systemic IgM levels and hepatic IgM deposition in *Siglec-G*$^{-/-}$ mice resulted in more liver damage and steatosis after ethanol feeding compared with wildtype littermates. Importantly, despite similar total IgM titers, LR04 administration aggravated ethanol-induced steatohepatitis compared with mice injected with isotype control IgM, indicating anti-MDA IgM antibodies promote murine ALD. Supporting our murine findings, serum titers of IgM targeting MDA exclusively positively correlated with liver injury and disease stage in patients with alcohol-associated hepatitis, while an inverse correlation was found with C3c and C4 levels, suggesting increased complement activation and consumption by MDA-binding IgM. In line, ethanol feeding in *Siglec-G*$^{-/-}$, which have elevated anti-MDA IgM, and LR04-treated mice resulted in more hepatic C3 deposition and hepatocyte cell death. Moreover, mice deficient for C3 displayed ameliorated ethanol-induced liver injury in the presence of high IgM antibody levels compared to wildtype controls. **Conclusion:** Elevated systemic IgM titers recognizing MDA facilitates complement recruitment which enhances cell death, thereby promoting alcohol-associated liver disease.

Disclosures: Dragana Rajčić: Nothing to Disclose, Beatriz Silva: Nothing to Disclose, Benedikt Simbrunner: Nothing to Disclose, Benedikt Hofer: Nothing to Disclose, Constanze Hoebinger: Nothing to Disclose, Nikolina Papac-Milicevic: Nothing to Disclose, Mattias Mandorfer: Ipsen: Consultant, Echosens: Speaking and Teaching, Echosens: Grant/Research Support, Ipsen: Grant/Research Support, Ipsen: Consultant, Takeda: Consultant, Takeda: Speaking and Teaching, W.L. Gore & Associates: Speaking and Teaching, Thomas Reiberger: Nothing to Disclose, Tim Hendrikx: Nothing to Disclose

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3109 | SINGLE-CELL RNA SEQUENCING ANALYSIS REVEALS SPECIFIC CELL SUBPOPULATIONS IN ALCOHOL-ASSOCIATED HEPATITIS CHARACTERIZED BY INFLAMMATORY, ANGIOGENIC AND FIBROGENIC PROFILE

Elisa Pose[1] Alicia Martínez[2] Aina Rill-Hinarejos[3] Jordi Gratacós Ginès[1] Silvia Ariño[2] Martina Pérez[1] Ana Rubio[2] Celia Martínez-Sánchez[2] Ramon Bataller[1] Pere Gines[1] Elisabetta Mereu[3] MAR COLL[2]

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Background: The phenotypic alterations of the different cell types through Alcohol-associated liver disease (ALD) progression are largely unknown. The aim of this work was to dissect the transcriptomic identity of cellular populations across ALD stages focusing in Alcohol-associated Hepatitis (AH). **Methods:** Liver biopsies were obtained from patients with compensated ALD (n=3), patients with AH (n=6) and healthy donors (n=3). Samples were processed by mechanical and chemical digestion and single cell RNA sequencing was performed using the 10X Genomics platform. Data were analysed with Seurat in R, and Reactome and Gene Ontology databases were used to describe biological functions. A validation with immunofluorescence of liver biopsies from controls and patients with ALD was done. **Results:** A total of 30,092 cells were clustered based on their expression pattern; 5 cell types (epithelial, mesenchymal, endothelial, myeloid and lymphoid) and 76 cell subpopulations with a unique transcriptomic identity were defined. Among epithelial cells, two subpopulations of hepatocytes (Hep(4) and Hep(5))were found enriched in AH, both of them characterized by inflammatory profile (increased expression of SAA1 (FC 3.5 and 4.3) and SAA2 (FC 4.8 and 5.8)) and one of them with an intermediate hepatobiliary cell genetic expression profile, with increased expression genes like SOX9 or LCN2 as compared to the rest of hepatocytes subpopulations. In the myeloid compartment, a subpopulation of macrophages with scar-associated profile was found in AH, with increased expression of genes as TREM2 and MMP19. In the endothelial compartment three subpopulations characteristic of AH were found, with increased expression of pro-inflammatory, pro-angiogenic and pro-fibrotic genes as ACKR1 and PLVAP. Using inmmunofluorescence, we found an increased expression of SAA1, SAA2 and SOX9 in hepatocytes, an overexpression of TREM2 and MMP19 in macrophages and an overexpression of ACKR1 and PLVAP in endothelial cells in the liver biopsies of patients with AH as compared to controls. **Conclusion:** This study unveils for the first time the transcriptomic identity of the liver cell populations during in the progression of ALD and specifically in AH at a single cell level. Moreover, we define specific AH subpopulations of hepatocytes with inflammatory and hepatobiliary cell profile, scar-associated macrophages and pro-fibrogenic endothelial cells, probably involved in the pathogenesis of AH.

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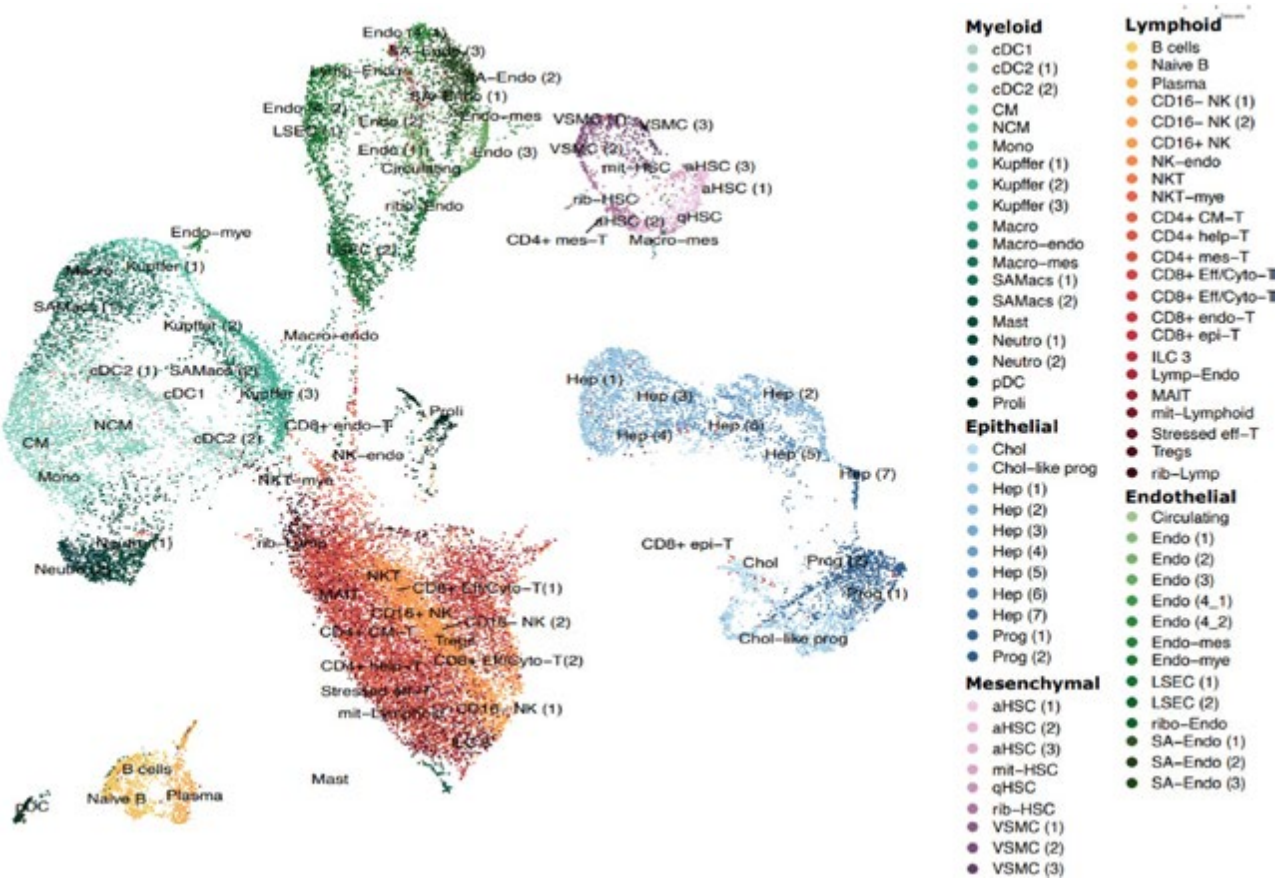

Disclosures: Elisa Pose: Nothing to Disclose, Alicia Martínez: Nothing to Disclose, Aina Rill-Hinarejos: Nothing to Disclose, Jordi Gratacós Ginès: Nothing to Disclose, Silvia Ariño: Nothing to Disclose, Martina Pérez: Nothing to Disclose, Ana Rubio: Nothing to Disclose, Celia Martínez-Sánchez: Nothing to Disclose, Ramon Bataller: Nothing to Disclose, Pere Gines: Gilead & Grifols: Grant/Research Support, SeaBeLife, Merck, Sharp and Dohme (MSD), Ocelot Bio, Roche Diagnostics Intern, Boehringer Ingelheim: Advisor, Pfizer: Speaking and Teaching, Gilead, RallyBio, Behring: Advisor, Pfizer: Speaking and Teaching, Elisabetta Mereu: Nothing to Disclose, MAR COLL: Nothing to Disclose

3110 | SURVIVAL OUTCOMES IN PATIENTS WITH SEVERE ALCOHOL-ASSOCIATED HEPATITIS RECEIVING DIALYSIS

Emily Stephenson[1] Alvi Islam[2] Luis Antonio Diaz[3] Rokhsana Mortuza[2] Leonardo Guizzetti[4] Francisco Idalsoaga[5] Winston Dunn[6] Ashwani Singal[7] Douglas Simonetto[8] Carolina Ramirez-Cadiz[9] Wei Zhang[10] Steve Qian[10] Joaquin Cabezas[11] Ines Garcia[11] Shiv Kumar Sarin[12] Rakhi Maiwall[13] Prasun Jalal[14] MARIA DE FATIMA HIGUERA DE LA TIJERA[15] Lubomir Skladaný[16] Natalia Bystrianska[17] Ana Clemente[18] DIEGO RINCON[18] Kristina Chacko[19] Pamela Yaquich[20] Merixtell Ventura Cots[21] Guadalupe García-Tsao[22] Juan Abraldes[23] Patrick Kamath[24] Marco Arrese[5] Vijay Shah[8] Juan Pablo Arab[1]

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Background: Acute kidney injury (AKI) increases mortality amongst patients with alcohol-associated hepatitis (AH). The impact of renal replacement therapy (RRT) on survival outcomes in patients with AH remains unclear. We aim to characterize survival outcomes to better guide the use of RRT in patients with severe AH and renal failure. **Methods:** This retrospective study analyzed adult hospitalized patients with AH and AKI across multiple centers. Key inclusion criteria included a diagnosis of severe AH per NIAAA criteria and severe AKI defined as uremia, metabolic acidosis, creatinine ≥4 mg/dL, or requiring RRT (ICA grade 3 criteria). Exclusion criteria included significant non-alcoholic liver diseases, malignancies, or severe extrahepatic conditions with estimated survival of less than six months. Baseline characteristics, overall mortality rates at 30 and 90 days, and survival curves were analyzed. A multivariable logistic regression model was used to determine the association between dialysis use and 90-day mortality, adjusting for clinical and patient characteristics at the time of admission. Cox proportional hazards regression modeling was also used. Propensity score matching was performed with a 1:1 ratio to balance the covariates between the RRT and non-RRT groups. **Results:** Among 507 patients with AKI, 140 received RRT. Kaplan-Meier analysis indicated significantly lower survival rates for the RRT group ($p<0.05$). Multivariable logistic and Cox regression models confirmed that use of RRT was an independent predictor of increased 90 day mortality (OR: 2.82; 95% CI: 1.78, 4.48; $p<0.0001$ and HR: 1.85; 95% CI: 1.39, 2.45; $p<0.0001$, respectively). Sensitivity analyses using propensity score matching yielded similar results, demonstrating that that the average treatment effect of dialysis was associated with a 22.5% higher risk of mortality (ATE 0.225; 95% CI: 0.103, 0.347). These results demonstrate that dialysis use independently predicts higher mortality in this population. Other predictors of 90-day mortality included age (OR: 1.04; 95% CI: 1.02, 1.06; $p<0.0001$), higher total bilirubin (OR: 1.02; 95% CI: 1.00, 1.05; $p=0.0324$), and longer prothrombin time (OR: 1.05; 95% CI: 1.01, 1.09; $p=0.0198$). **Conclusion:** Patients with severe AH and AKI who receive RRT have significantly higher 90 day mortality compared to those who do not. Other independent predictors of mortality include older age, higher total bilirubin, and longer prothrombin time. The reason for increased mortality amongst patients receiving RRT is unclear; potential factors may include increased susceptibility to infections, cardiovascular events, and dialysis-related hemodynamic instability. These results should not be used to withhold dialysis as further research is needed to improve treatment decisions and optimize patient outcomes.

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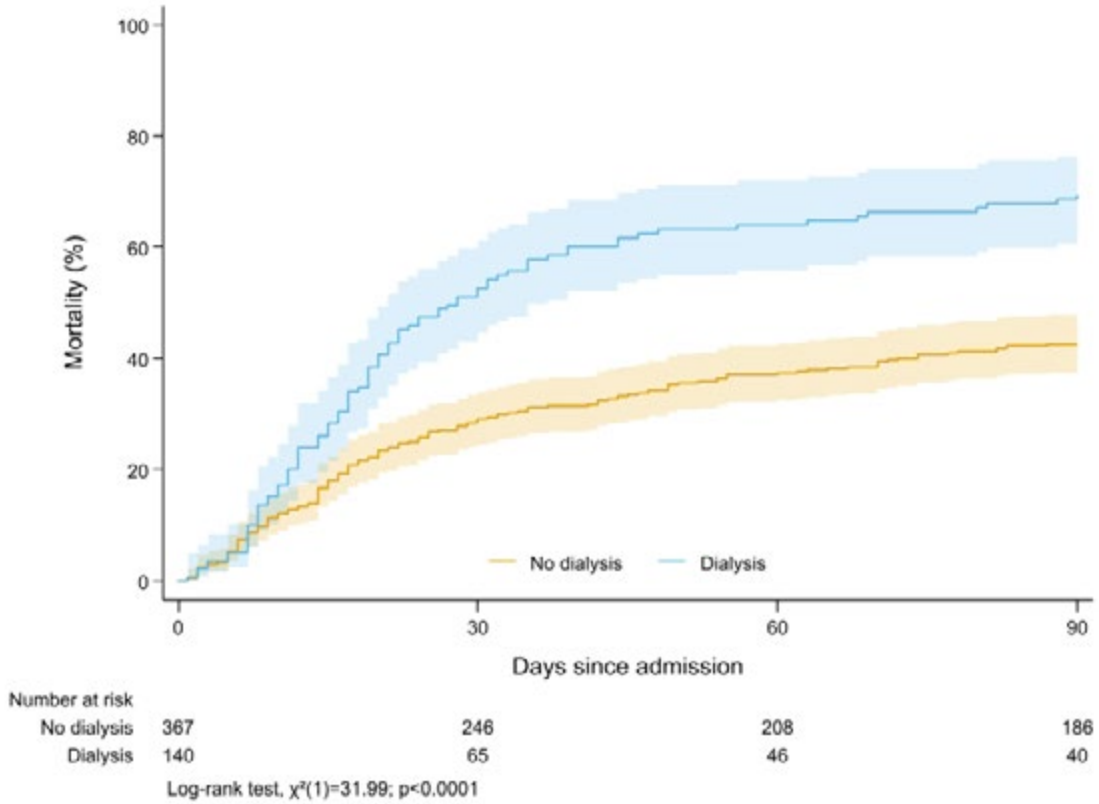

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3111 | MODULATION OF MAIT CELLS BY FMT AMELIORATES THE INTESTINAL AND HEPATIC INFLAMMATORY MILIEU, IMPROVES GUT BARRIER FUNCTION AND CLINICAL OUTCOMES IN SEVERE ALCOHOL ASSOCIATED HEPATITIS

Sukriti Baweja[1] Shvetank Sharma[1] SM Shastry[1] Rahul khajuria[1] Preeti Negi[1] Ashmit Mittal[1] Vibhuti Jakhmola[1] Chhagan Bihari[1]

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Background: Fecal Microbial Transplant (FMT) has shown promising results in severe alcohol associated hepatitis (SAH) patients; possibly by modulating gut bacteria, mucosal permeability and inflammation. We investigated the compartmentalisation of immune cell subsets,intrahepatic lymphocytes, cellular damage and their association with intestinal permeability before and after FMT. **Methods:** Altogether 55 SAH patients, histologically diagnosed, and undergoing FMT given through nasoduodenal tube were studied pre- and post-FMT. Flow cytometry based immune phenotyping was performed for monocytes, neutrophils, Th1, Th2, Th17, mucosal associated invariant T cells (MAITs), T-regulatory (Treg) and B-cell subsets, intracellular cytokines. Intestinal permeability was measured in duodenal biopsy obtained pre- and post-FMT, to investigate tight junction proteins, enteric lymphocytes. Further, intrahepatic MAITs were studied to understand the compartmentalisation. Genes associated with inflammation, gut permeability were analyzed by q-Real time PCR. Cellular injury was assessed by microvesicles (MV). MAITs and hepatocytes crosstalk, cocultures was performed with and without fecal administration. **Results:** Interestingly, in the peripheral blood in the SAH patients {mean age 46±16 years; all males, Maddrey's discriminant function score 72±26, MELD score 24.6±9.2}, compared to baseline, post-FMT, the T-cell subsets were significantly altered; the frequency of $CD3^+CD8^+$(p=0.026), $CD3^+CD4^-CD8^+$ MAITs ($CD161^+$ TCR $va7.2^+$)(p=0.000) and Th17 ($CD3^+CD4^+RoRg^+$) increased while that of $CD3^-CD19^+$ cells declined (p=0.002). Intracellular cytokines, IL-17A (p=0.000) and IFN- (p=0.00) released from MAITs were significantly reduced post-FMT. MAITs activation was found low $CD25^+$ (p=0.000) and $CD69^+$. The intrahepatic MAITs were also significantly reduced post-FMT at d28 (p<0.001). The tight junction proteins expression improved as the expression of ZO1(p=0.00) and Claudin1 (p=0.00) increased post FMT. The genes associated with permeability [*Epcam, Zo1, MUC1, Vcam1*] and inflammation [IL-17A, IL-22, FoxP3, RORg] (p<0.05) were also significantly decreased post-FMT. Microvesicles associated with enteric epithelial cells MV, significantly decreased (p=0.001) as a measure of cellular damage. Upon co-culture with SAH fecal, MAIT cells produced high levels of IL-17A and IFNg(p<0.001) and hepatocytes showed upregulation of Casp3 and Casp9 (p<0.001). **Conclusion:** FMT supresses the intrahepatic and circulatory inflammatory responses in patients with SAH, as evidenced by reduced frequency of T cell subsets (MAITs and Th17) and IL-17A and IFNg. FMT helps restore the gut integrity, lowers inflammation and improve clinical outcomes in SAH patients.

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3112 | PREDICTIVE VALUE OF NLR IN SHORT-TERM PROGNOSIS OF PATIENTS WITH SEVERE ALCOHOLIC HEPATITIS

Mincong Long[1] Hui Liu[1] Xinting li[1] Xiaobo Lu[1]

[1]The First Affiliated Hospital of Xinjiang Medical University

Background: To access the value of NLR in predicting the 28-day prognosis of patients with severe alcoholic hepatitis (SAH). **Methods:** A retrospective analysis was performed for 102 patients with SAH who were admitted to Center for Infectious Diseases-Hepatology, The first Affiliated Hospital of Xinjiang medical university,from June 2012 to June 2022, and according to the **Results:** of 28-day follow-up, they were divided into survival group (n = 75) and death group (n = 27); Related clinical data were collected within 24 hours after the diagnosis of SAH in our hospital, including

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routine blood test results, hepatic and renal function, blood coagulation function, and complications such as hepatic encephalopathy; The Glasgow alcoholic hepatitis score(GAHS), Maddrey's discriminant function(MDF), model for end-stage liver disease (MELD), ABIC (age, serum bilirubin, INR, and serum creatinine) scores were calculated . The t-test was used for the between-group comparison with the normal distribution, and the Mann-Whitney U test was used for the non-normally distributed between-group comparison. The χ2 test and Fisher's exact test were used for comparison between counting data groups. Binary logistic regression was used to analyze whether NLR was an independent risk factor for 28 days prognosis in patients with SAH. The receiver operating characteristic(ROC) curve was plotted to analyze whether NLR combined with each score could improve the predictive value of the existing model, and the Z-test was used for the comparison. **Results:** The percentage neutrophils(NEU%), serum total bilirubin (TBil) and ABIC scores in the death group were higher than those in the survival group, and the differences were statistically different (t=-3.417, -3.84, -4.431,all P < 0.05), respectively, white blood cell count(WBC), neutrophils(NEU), urea nitrogen(BUN), serum creatinine (CR), prothrombin time(PT), international normalized ratio(INR), procalcitonin(PCT), Neutrophil-to-lymphocyte ratio (NLR), GAHS, MDF and MELD score were higher than those in survival group, and Na+, albumin(ALB) and the activity of PT was lower than that of the survival group, and the differences were statistically significant (z= 2.435, -2.613, -4.532, -4.468, -2.2, -2.151, -4.328, -3.326, -3.422, -3.478, -5.078, -2.909, 2.388, 2.016, all P<0.05). Logistic analysis showed that hepatic encephalopathy(HE) (OR=0.142, 95% CI: 0.038-0.53, P=0.004), hepatorenal syndrome (HRS)(OR=0.075, 95% CI: 0.02-0.28, P<0.001), and NLR (OR=1.087, 95% CI: 1.013-1.167, P=0.021) were independent risk factors for the 28-day prognosis of patients with SAH. After combining NLR with existing models, the area under the ROC curve increased. **Conclusion:** NLR is an independent risk factor for the 28-day prognosis of patients with SAH, which has predictive value for the short-term prognosis of patients with SAH, and its combination with existing models may improve the predictive value.

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3113 | LIVER-RELATED COMPLICATIONS ARE ASSOCIATED WITH WORSE OUTCOMES IN PATIENTS WITH SEVERE ALCOHOL-ASSOCIATED HEPATITIS

Filippa Trikantzopoulou[1] Irena Helenowski[2] Tiange Zhang[1] Steven Scaglione[1]

[1]Loyola University Medical Center, [2]Loyola University Chicago

Background: The principal feature of severe alcohol-associated hepatitis (sAH) is jaundice after prolonged alcohol use. Patients can present with liver-related complications (LRCs), such as esophageal variceal bleeding (EVB), hepatic encephalopathy (HE), ascites, hepatorenal syndrome (HRS), and spontaneous bacterial peritonitis (SBP). Few studies explored the impact of LRCs in sAH. We aimed to examine prevalence, risk factors, and outcomes of patients with sAH who present with LRCs. **Methods:** We used ICD 9th and 10th codes for ALD and AUD between 2012-2021, identifying 1287 cases. After detailed chart review, we identified 298 patients that met the NIAAA definition of sAH. Demographics, clinical, and treatment variables were extracted from the EMR. LRCs were defined as presence of ascites, HE, EVB, SBP, or HRS. Outcomes included infections, mortality, and survival. Univariable, multivariable (MV), and survival analyses were performed comparing those with and without LRCs. **Results:** The median age was 47+/-10.7 yrs. 62.8% of patients were male, 72.8% white, 7.4% AAs, 10.7% Hispanic, and 9.4% identified as "other." Over a third (35.9%) died, whilst 6.9% received a liver transplant. LRCs occurred in 77% of patients, with 86.1% having ascites, 46.5% HE, 26.5% HRS, 10% EVB, and 5.2% SBP. Patients with LRCs had higher MELD-Na (31 vs 22.4, p<0.01) and Maddreys Discriminant function (mDF) (77.7 vs 28. 6, p<0.01), as well as higher rates of glucocorticoid administration (36.9% vs 19.1%, p=0.005) and antibiotic use (50.0% vs 30.1%, p<0.01). Patients with LRC had higher rates of recurrent infections (44.8% vs 30.8%, p=0.05), fungal infections (10% vs 1.5%, p=0.02), antibiotic resistance (20.9% vs 8.8%, p=0.03), and mortality (40.9% vs 19.1%, p<0.01). Patients with LRCs had lower one year survival (60.1% vs 88%, log rank p<0.01). There was a significant decrease in survival with increasing number of LRCs (log rank <0.001, see figure). SBP and EVB were associated with the lowest survival. MV analysis suggests that older age (aOR 1.18 95% CI 1.0-6.7, p=0.053), MELD-Na (aOR 1.11 95% CI 1.0-1.21, p=0.02), mDF (aOR 1.16 95% CI 1.1-1.3, p<0.01), and antibiotic use for clinical infection (aOR 2.29 95% CI 1.1-5, p=0.03) were associated with LRCs. **Conclusion:** LRCs occured in 77% of patients with sAH and were associated with higher rates of infections, antibiotic resistance, and mortality. Survival was lower with increasing number of LRCs, whilst SBP and EVB were associated with worse survival. Clinicians should be aware of the impact LRCs have on this critically ill patient population.

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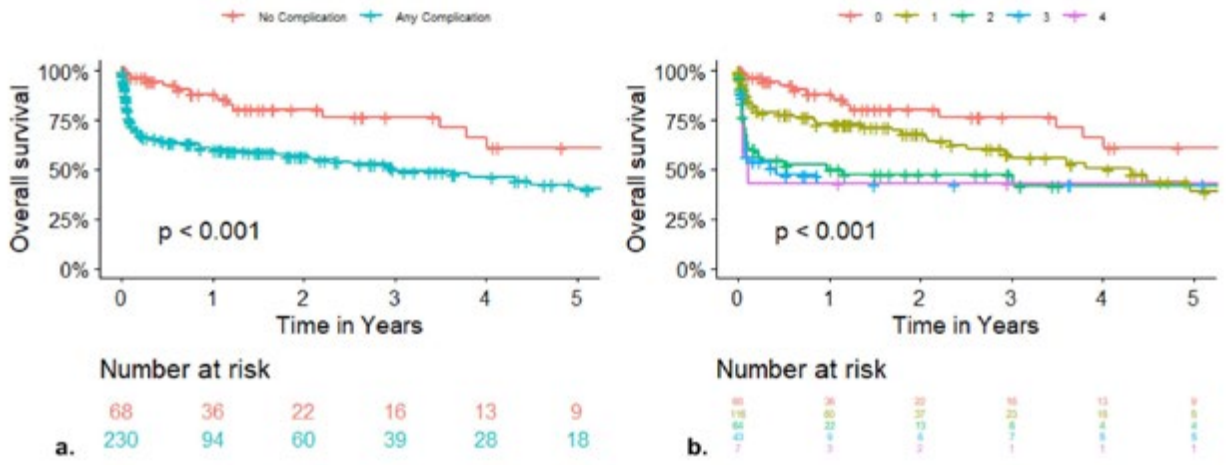

Figure 1: Kaplan-Meier curves and estimates are presented to summarize the overall survival rates by complication status at 1-, 2-, and 5 years. Differences between groups were assessed via the log-rank test. **1a.** Survival by any complication status **1b.** Survival by number of complications

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3114 | COMPLEMENT ACTIVATION IS ASSOCIATED WITH LOWER EGFR AND MARKERS OF KIDNEY INJURY IN PATIENTS WITH SEVERE ALCOHOL HEPATITIS

Luan Prado[1] Moyinoluwa Taiwo[1] Craig McClain[2] Mack Mitchell[3] Bruce Barton[4] Gyongyi Szabo[5] Srinivasan Dasarathy[1] Laura Nagy[1]

[1]Cleveland Clinic Foundation, [2]University of Louisville, [3]University of Texas Southwestern Medical Center, [4]University of Massachusets, [5]Beth Israel Deaconess Medical Center

Background: Mortality in patients with severe alcohol-associated hepatitis (sAH) is often associated with impaired kidney function and acute kidney injury (AKI). Complement activation has been implicated in both liver and kidney injury in multiple murine models and a recent meta-analysis of proteomic profiles from liver and circulation identified a complex perturbation of complement in patients with sAH. Of relevance to kidney function, serum collectin 11 (CL11) was strongly associated with sAH. In murine models of AKI, CL11 binds to tubular L-fucose and recruits mannan binding lectin-associated serine proteases to activate the lectin pathway and the development of kidney lesions. Kidney function can be indirectly measured by the estimated glomerular filtration rate (eGFR) and kidney injury markers, such as KIM-1, are indicative of impaired kidney function. Here we tested the hypothesis that CL11 would be positively associated and that uromodulin (Tamm-Horsfall protein - THP), a negative regulator of CL11 function, would be negatively associated with impaired renal function in patients with sAH. **Methods:** Plasma samples from 60 patients with sAH enrolled in the Defeat Alcoholic Steatohepatitis (DASH) were analyzed by commercial ELISA (Collectin 11, Uromodulin, KIM-1) and multiplex assays (complement components, ExSera). eGFR was calculated by the CKD-EPI creatinine equation. **Results:** eGFR at the entry of the study was normal in 31 (52%) of the patients with sAH and 29 (48%) had some degree of decline in eGFR. CL11 was negatively associated with eGFR and positively associated with KIM-1. CL11 was also positively correlated with C2 and C4b, complement components responsible for C3-convertase assembly in the classical and lectin pathways. Inversely, uromodulin negatively correlates C4b, which highlights its complement modulatory role. eGFR negatively correlated with CL11 and C2, but not with C4b. Components of the alternative pathway of complement activation, Factor D, Factor Ba and Factor Bb were also negatively associated with eGFR. **Conclusion:** Taken together, these data suggest that perturbed balance in the function of complement proteins in the classical, lectin and alternative pathways may contribute to impaired renal function in patients with sAH. An imbalance in the ratio of CL11 and its negative regulator uromodulin in patients with sAH points to potential novel targets for therapeutic intervention in patients with sAH.

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Grant/Research Support, Mack Mitchell: GlaxoSmithKline: Advisor, Amygdala Neuroscience: Consultant, Parvus Therapeutics: Advisor, HepaTX: Advisor, Durect: Grant/Research Support, Bruce Barton: Nothing to Disclose, Gyongyi Szabo: Advisor relationship with Glympse Bio, Inc (acquired by Sunbird Bio); Has not ended; Consultant relationship with Terra Firma; Has not ended; Consultant relationship with Pfizer; Has not ended; Consultant relationship with Pandion Therapeutics; Has ended; Consultant relationship with Merck; Has ended; Consultant relationship with Durect Corporation; Has ended; Advisor relationship with Satellite Biosciences; Has not ended; Consultant relationship with Zomagen Bioscience/Ventyx Biosciences; Has ended; Consultant relationship with CYTA Therapeutics; Has ended; Royalties or patent beneficiary relationship with Springer Nature Group; Has not ended; Royalties or patent beneficiary relationship with UpToDate Inc; Has not ended; Consultant relationship with LabCorp; Has not ended; Advisor relationship with Evive; Has not ended; Advisor relationship with Surrozen; Has not ended; Consultant relationship with Takeda; Has ended, Srinivasan Dasarathy: Nothing to Disclose, Laura Nagy: Nothing to Disclose

3115 | CHRONIC ETHANOL INSULT DAMAGES HEPATOCELLULAR LYSOSOMES

Sandhya Sen[1] Micah Schott[2] Paul Thomes[2] Carol Casey[2] Mark McNiven[3]

[1]Mayo Clinic, [2]University of Nebraska Medical Center, [3]Mayo Foundation for Medical

Background: Hepatocytes are well known to accumulate lipid into specific organelles or droplets (LDs) a process that is exacerbated by EtOH exposure by unknown mechanisms. We have recently described a process utilized by hepatocytes to degrade and catabolize its lipid stores via direct action of the lysosome. This “microlipophagic” process appears to be independent of the canonical autophagic pathway but instead may utilize direct fusion and engulfment of LDs by the lysosome. Thus, the function and structural integrity of the lysosome in reducing lipid stores is essential.Thus, the GOAL of this study was to assess and test the effects of EtOH exposure on lysosome integrity and repair. It is known that lysosomes have a sophisticated mechanism to undergo self-repair that is initiated by several adaptors and members of the ESCRT (endosomal complexes required for transport) machinery. **Methods:** VA13 cells expressing alcohol dehydrogenase were treated with 50 or 100mM doses of ethanol for 24 hours. To assess lysosomal damage by EtOH or the agent LLOMe, VA13 cells were transiently transfected with a Gal3-mCherry construct. Immunohistochemistry of liver sections from human ASH patients and control using anti-Galectin 3 antibody was performed to test lysosomal damage in human subjects. To assess the lysosomal repair process, control and ethanol treated VA-13 cells were co-incubated with1mM dose of LLOMe. **Results:** Ethanol treatment in VA13 cells resulted in substantial lysosomal damage as a 3-fold increase in lysosome-associated GAL3mCh puncta was observed compared to controls. Importantly, IHC of liver sections from human ASH patients showed a 2-fold increase in Gal3 staining, indicating EtOH-induced lysosome damage occurs in situ. To assess if EtOH might delay or prevent lysosome repair, the recruitment of ESCRT proteins to lysosomes was measured at 30 minute increments and revealed a 65 % increase in ESCRT repair proteins at a 4 hr time point. This suggests an accumulation of the repair machinery as a result of a faulty mending process. Finally, to test if the exogenous expression of resident lysosome proteins might act in a protective way we transfected VA-13 cells to express the lysosomal-associated membrane glycoprotein 1 (LAMP-1) prior to an EtOH insult and observed that this markedly reduced ESCRT recruitment. **Conclusion:** Taken together, these findings provide some of the first insights into structural damage of hepatocellular lysosomes by EtOH. Supported by RO1AA020735 to MAM and CAC.

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3116 | IMPACT OF AREA-LEVEL INCOME AND RESIDENCE ON IN-HOSPITAL MORTALITY AND INTENSIVE CARE UNIT ADMISSIONS AMONG PATIENTS WITH CIRRHOSIS AND ALCOHOL-RELATED HEPATITIS HOSPITALIZATIONS: A POPULATION-BASED STUDY

Liam Swain[1] Jenny Godley[1] Meng Wang[2] Jennifer Flemming[3] Mayur Brahmania[1] Juan Abraldes[4] Karen Tang[1] Abdel Shaheen[1]

[1]University of Calgary, [2]Alberta Health Services, [3]Queen's University, [4]University of Alberta

Background: Few studies have examined socio-economic factors as predictors of in-hospital mortality and admission to intensive care unit (ICU) for patients with alcohol-related cirrhosis (AC), alcohol-related hepatitis (AH), and non-alcohol-related cirrhosis (NAC). To address this knowledge gap, we examined the role of sex, age, area-level income, rural residency, and the COVID-19 pandemic on in-hospital mortality and ICU admission for AC, AH, and NAC from 2012-22 in Alberta, Canada. **Methods:** We examined all adult hospitalizations (>20 years) with AC/NAC/AH between 2012-2022 in Alberta using the Discharge Abstract Database (DAD). Our outcomes were in-hospital mortality and ICU admission. Exposure variables were sex, age group (20-34, 35-49, 50-64, ≥65 years), MELD sodium at admission, Charlson comorbidity index, rural/urban residency, and area-level income. Admissions were matched to the 2016 Census data, assigned their Dissemination Area (DA; 400-700 person regions) median after tax household income and placed into quartiles (Q1≤$62,976, Q2>$62,976 & ≤$77,995, Q3>$77,995 & ≤$96864, Q4>$96864). Predictors of in-hospital mortality and ICU admission were assessed using adjusted logistic regression. **Results:** During our study time, we identified 25,503 AC (64% male; median age 56 years), 17,815 NAC (55% male; median age 65 years), and 3,717 AH hospitalizations (59% male; median age 46 years). The odds of AC/NAC ICU admission was higher for younger age groups. The odds of NAC ICU admission was higher for those residing in areas with income Q3/4 than Q1, Table 1. The odds of AH ICU admission was lower during than before COVID-19 (OR 0.71, 95% CI 0.52-0.96). For all conditions, females and older age groups had a higher odds of in-hospital mortality, Table 1. The odds of AC in-hospital mortality was higher in area-level income Q1 than Q2-4, Table 1. Rural residency was associated with lower odds of in-hospital mortality for AH patients (OR 0.60, 95% CI 0.44-0.83). During the post COVID-19 era, patients with AC/AH had lower odds of in-hospital mortality, Table 1. Higher MELD sodium predicted ICU admission and in-hospital mortality for all conditions, Table 1. **Conclusion:** In this large Canadian cohort, we report that patients with NAC living in high-income areas had a higher likelihood of being admitted to the ICU, while in-hospital mortality for AC patients was higher among those living in low-income areas. Sustained efforts to minimize socioeconomic disparities in patient outcomes are needed.

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Table 1. Regression output for predictors of in-hospital mortality and admission to intensive care unit for alcohol-related cirrhosis, non-alcohol-related cirrhosis, and alcohol-related hepatitis hospitalizations from 2012-2022 in Alberta, Canada.

Variables	AC ICU Adjusted OR (95% CI)	AC in-hospital mortality Adjusted OR (95% CI)	NAC ICU Adjusted OR (95% CI)	NAC in-hospital mortality Adjusted OR (95% CI)	AH ICU Adjusted OR (95% CI)	AH in-hospital mortality Adjusted OR (95% CI)
Sex						
Male	Reference	Reference	Reference	Reference	Reference	Reference
Female	1.05 (0.98-1.13)	**1.10 (1.00-1.21)**	1.07 (0.96-1.20)	**1.15 (1.04-1.28)**	1.15 (0.93-1.44)	**1.47 (1.09-1.99)**
Age group						
20-34 years	Reference	Reference	Reference	Reference	Reference	Reference
35-49 years	**0.81 (0.70-0.95)**	**1.49 (1.16-1.91)**	0.83 (0.59-1.18)	1.17(0.64-2.17)	**0.66 (0.50-0.88)**	0.78 (0.48-1.25)
50-64 years	**0.75 (0.65-0.88)**	**2.72 (2.15-3.47)**	**0.69 (0.50-0.94)**	**2.07 (1.17-3.65)**	0.75 (0.55-1.01)	**2.30 (1.45-3.63)**
≥65 years	**0.44 (0.37-0.53)**	**5.30 (4.12-6.82)**	**0.32 (0.23-0.44)**	**4.44 (2.52-7.82)**	0.67 (0.40-1.13)	**4.05 (2.14-7.66)**
Income quartile						
Q1	reference	reference	Reference	Reference	Reference	Reference
Q2	**0.85 (0.77-0.94)**	**0.88 (0.78-0.98)**	1.04 (0.89-1.20)	0.88(0.77-1.02)	0.78 (0.58-1.04)	0.74 (0.48-1.25)
Q3	1.05 (0.95-1.15)	**0.80 (0.71-0.90)**	**1.23 (1.07-1.43)**	1.02 (0.88-1.17)	0.82 (0.61-1.09)	**0.65 (0.44-0.97)**
Q4	0.99 (0.89-1.10)	**0.83 (0.74-0.95)**	**1.27 (1.09-1.48)**	0.98 (0.84-1.14)	0.78 (0.58-1.06)	0.87 (0.58-1.30)
Residency						
Urban	Reference	Reference	Reference	Reference	Reference	Reference
Rural	0.99 (0.93-1.08)	0.94 (0.86-1.03)	0.97 (0.86-1.09)	0.94 (0.84-1.05)	1.23 (0.98-1.53)	**0.60 (0.44-0.83)**
COVID-19†						
Pre-Covid	Reference	Reference	Reference	Reference	Reference	Reference
Post-Covid	0.97 (0.90-1.05)	**0.86 (0.78-0.95)**	0.97 (0.86-1.09)	1.11 (0.99-1.24)	**0.75 (0.60-0.94)**	**0.71 (0.52-0.96)**
MELD sodium	**1.05 (1.04-1.05)**	**1.21 (1.21-1.22)**	**1.05 (1.04-1.06)**	**1.21 (1.20-1.22)**	**1.09 (1.07-1.10)**	**1.28 (1.25-1.31)**

*Adjusted ORs for sex, age, Dissemination Area (DA)-level after tax median household income, rural/urban residency, COVID-19, MELD sodium, and Charlson Comorbidity Index.
Abbreviations: Q1≤$62,976, Q2>$62,976 & ≤$77,995, Q3>$77,995 & ≤$96864, Q4>$96864: ICU, intensive care unit: IHM, in-hospital mortality: AC, alcohol-related cirrhosis: NAC: non-alcohol-related cirrhosis: AH, alcohol-related hepatitis: MELD, Model-for-End-Stage Liver Disease:

†Post-COVID era defined as implementation of pandemic social restrictions in Canada (March 1st 2020)

Disclosures: Liam Swain: Nothing to Disclose, Jenny Godley: Nothing to Disclose, Meng Wang: Nothing to Disclose, Jennifer Flemming: Nothing to Disclose, Mayur Brahmania: Nothing to Disclose, Juan Abraldes: Gilead: Grant/Research Support, 89bio: Consultant, Boston Pharmaceuticals: Consultant, Novo Nordisk: Consultant, Boehringer Ingelheim: Consultant, Astra Zeneca: Consultant, Agomab: Consultant, Terumo: Speaking and Teaching, Cook: Grant/Research Support, Karen Tang: Nothing to Disclose, Abdel Shaheen: Nothing to Disclose

3117 | THE EFFECT OF AREA-LEVEL MATERIAL AND SOCIAL DEPRIVATION ON CIRRHOSIS AND ALCOHOL-RELATED HEPATITIS HOSPITALIZATION RATES DURING THE COVID-19 PANDEMIC: A POPULATION-BASED STUDY

Liam Swain Abdel Shaheen[1] Meng Wang[2] Jennifer Flemming[3] Mayur Brahmania[1] Juan Abraldes[4] Karen Tang[1] Jenny Godley[1]

[1]University of Calgary, [2]Alberta Health Services, [3]Queen's University Cancer Research Institute, [4]University of Alberta

Background: Few studies have examined the impact of the COVID-19 pandemic on hospitalization rates for alcohol-related cirrhosis/hepatitis (AC/AH) and non-alcohol-related cirrhosis (NAC) in relation to the social determinants of health. We examined temporal changes in AC/NAC/AH hospitalization rates before the pandemic (2012-19) and during the pandemic (2020-22) in Alberta, Canada. We focused on comparing hospitalization rates for those living in materially and /or socially advantaged areas versus deprived areas. **Methods:** We selected all adult (≥18 years) AC/NAC/AH hospitalizations using validated administrative database case definitions from the 2012-22 Discharge Abstract Database. Each admission was matched to a 2016 Alberta Census Dissemination Area (DA; 400-700 person regions). Using the Material and Social Deprivation Index (MSDI) we classified each DA in relation to material and social deprivation. Material deprivation is operationalized using Census measures

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of education, employment, and income. Social deprivation is operationalized using Census measures of the proportion of people living alone, in single-parent families, and separated/divorced/widowed. Temporal trends in annual AC/NAC/AH hospitalization rates/100,000 at-risk Alberta population were assessed using Joinpoint analysis and annual percent change (APC) stratified by MSDI quintiles. **Results:** From 2012-22, we identified 25,506 AC (64% male; median age 56 years), 17,827 NAC (55% male; median age 65 years), and 3,722 AH hospitalizations (59% male; median age 46 years). AC hospitalization rates significantly increased during the pandemic for people living in areas that are both materially and socially deprived (APC 17.0%; 95% CI 13.3-20.8), and then decreased to pre-pandemic levels, Fig. 1A. For NAC, no inflection points occurred during the pandemic for any MSDI quintile, Fig. 1B. AH hospitalization rates increased during the pandemic for people living in regions that are both materially and socially deprived (APC 74.9%, 95% CI 19.5-117.6) and for those living in regions that are socially privileged but materially deprived (APC 86.2%, 95% CI 48.0-108.4), followed by a return to pre-pandemic levels, Fig. 1C. **Conclusion:** During the pandemic, AC hospitalization rates increased among those living in both socially and materially deprived areas, whereas AH hospitalization rates increased only for those residing in materially deprived areas, regardless of DA-level social deprivation. NAC hospitalization rate trajectories were not impacted by the pandemic.

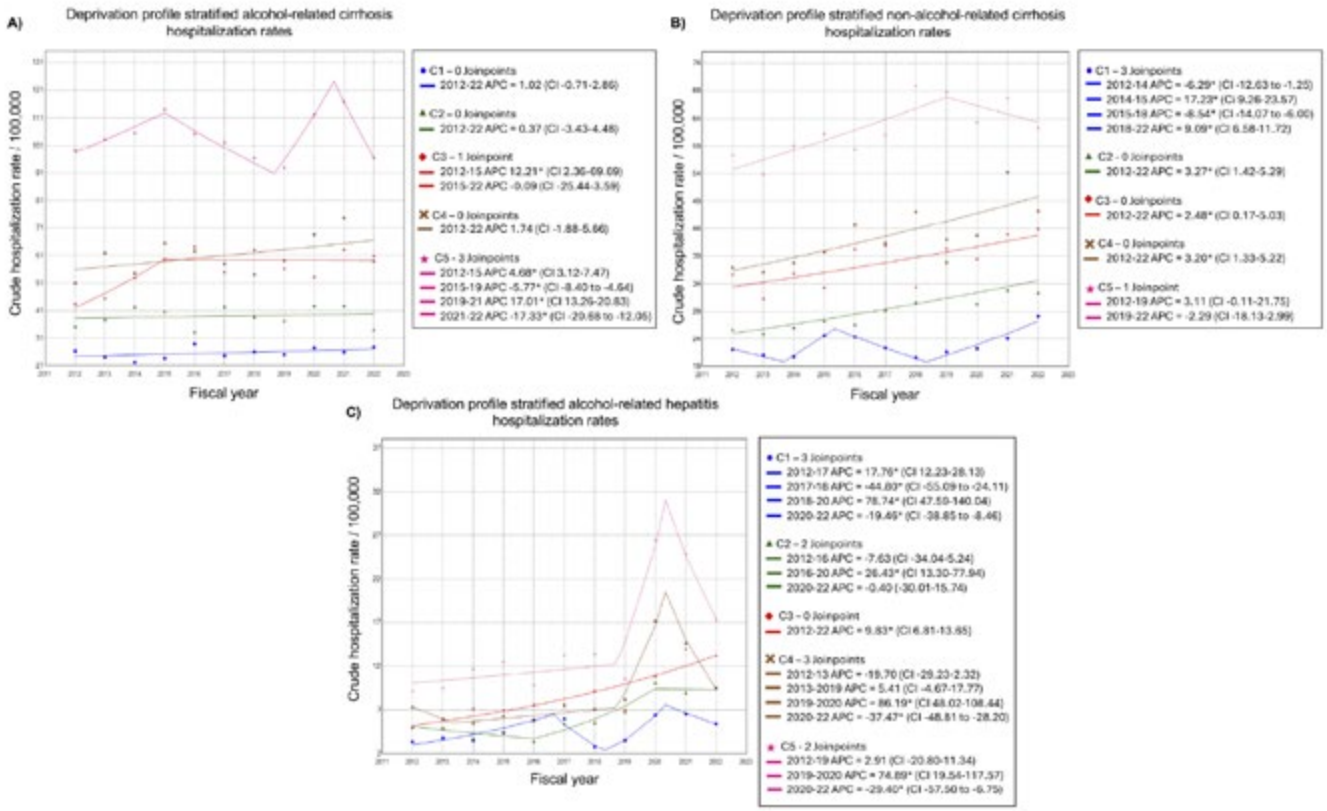

Figure 1. Temporal trends from April 1, 2012, to March 31, 2023, (i.e., fiscal years 2012-2022) for (A) alcohol-related cirrhosis (AC), (B) non-alcohol-related cirrhosis (NAC), and (C) alcohol-related hepatitis (AH) hospitalization rates per 100,000 Alberta population. Yearly changes in crude hospitalization rates are assessed using annual percent change (APC) stratified by the Material and Social Deprivation Index (MSDI) quintiles (i.e., C1, materially/socially privileged; C2, average material/social deprivation; C3, materially privileged but socially deprived; C4, socially privileged but materially deprived; C5, materially/socially deprived).

Disclosures: Liam Swain: Nothing to Disclose, Abdel Shaheen: Nothing to Disclose, Meng Wang: Nothing to Disclose, Jennifer Flemming: Nothing to Disclose, Mayur Brahmania: Nothing to Disclose, Juan Abraldes: Gilead: Grant/Research Support, 89bio: Consultant, Boston Pharmaceuticals: Consultant, Novo Nordisk: Consultant, Boehringer Ingelheim: Consultant, Astra Zeneca: Consultant, Agomab: Consultant, Terumo: Speaking and Teaching, Cook: Grant/Research Support, Karen Tang: Nothing to Disclose, Jenny Godley: Nothing to Disclose

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3118 | ENGINEERED HUMAN LIVER CO-CULTURES TO MODEL HEPATIC DYSFUNCTIONS IN METALD

Owen Lally[1]

[1]*University of Illinois Chicago*

Background: Metabolic dysfunction-associated liver disease (MASLD) with increased alcohol intake is characterized by symptoms of both MASLD and alcohol-associated liver disease (ALD), known as MetALD. Symptoms include hepatic steatosis and insulin resistance, predisposing patients to inflammation and fibrosis. Rodents fail to recapitulate the full MetALD spectrum, necessitating human *in vitro* models. However, such models often do not incorporate liver nonparenchymal cells (NPCs), which deposit excess collagen and cause inflammation. Furthermore, primary human hepatocytes (PHHs) rapidly lose function as 2D monocultures. Thus, we engineered a liver micropatterned co-culture (MPCC) platform to elucidate the effects of MetALD-like soluble triggers on hepatic dysfunctions. **Methods:** Micropatterned PHH islands, generated using soft lithography, were surrounded by 3T3-J2 fibroblasts (MPCC) +/- activated hepatic stellate cells (HSCs) to generate stellate cell-containing micropatterned tri-cultures (S-MPTCs). Next, co-cultures were treated with dietary triggers or combinations to induce hepatic steatosis, including glucose, fructose, and a mixture of saturated (palmitic, stearic) and unsaturated (oleic, linoleic) free fatty acids (FFAs, 300 or 500 µM). For MetALD, co-cultures were treated with dietary triggers plus ethanol (0.25% vol/vol). Hepatic cytochrome P450 (CYP450) expression, steatosis, insulin resistance, and inflammation were assessed. **Results:** Only ethanol and FFAs caused hepatic steatosis and loss of insulin sensitivity (Fig. 1a). The combination of FFAs and ethanol significantly increased CYP3A4 and CYP2A6 enzyme activities (Fig. 1b). Additionally, a two-fold increase in CYP2E1 staining was observed when FFAs and ethanol were combined compared to any individual trigger (Fig. 1c). S-MPTCs showed similar **Results:** as MPCCs, though HSCs were similarly activated irrespective of treatment condition. Furthermore, S-MPTCs containing activated HSCs showed significantly higher levels of inflammation than MPCCs, as measured via C-reactive protein (CRP) (Fig. 1d). **Conclusion:** We showed that engineered human liver co-cultures are useful in elucidating the effects of MetALD-like triggers on hepatic steatosis, insulin resistance, CYP450 metabolic activity, and inflammation. Future studies are focused on incorporating other liver NPCs to elucidate the effects of cellular crosstalk on MetALD-like dysfunctions and uncover novel pathways of progressive disease.

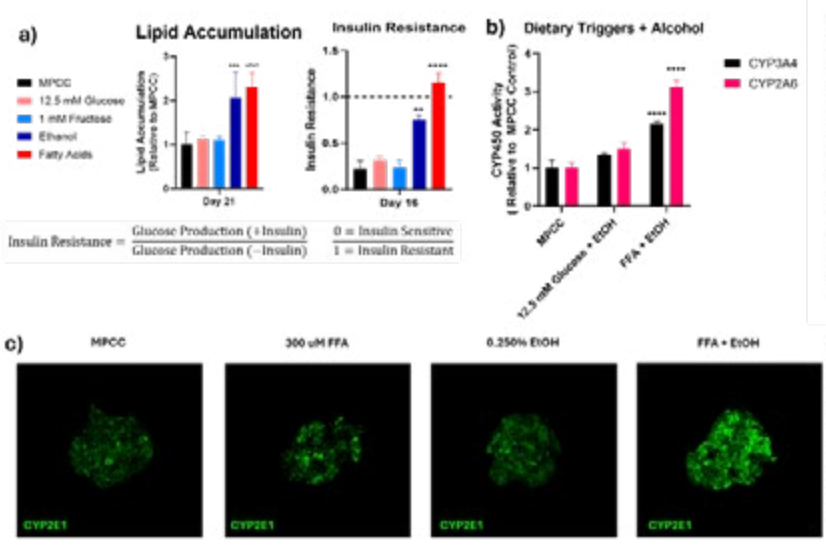

Figure 1: Hepatic steatosis and insulin resistance (a) and CYP450 activities (b) in MPCCs treated with soluble triggers of fatty liver disease. **(c)** Induction of CYP2E1 protein expression in MPCCs treated with FFAs, ethanol, or their combination. **(d)** Inflammation in MPCCs and S-MPTCs with FFA and ethanol treatment, as measured through hepatic CRP production.

Disclosures: Owen Lally: Nothing to Disclose

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3119 | IMPACT OF PRE-TRANSPLANT STEROID THERAPY ON EARLY POST-TRANSPLANT INFECTIONS IN ALCOHOL-ASSOCIATED HEPATITIS PATIENTS UNDERGOING LIVER TRANSPLANTATION

Alex Chang[1] Alexa Giammarino[1] Maham Ghani[1] Ethan Berman[1] Aditya Sood[1] Nishi Joshi[1] Alvin Htut[1] James Park[1] Nabil Dagher[1] Sanjaya Satapathy[1]

[1]Northwell Health

Background: The use of steroids in treating alcohol-associated hepatitis (AH) remains controversial due to infection risks and uncertain benefits, especially for steroid-non-responders. Although previous case series have indicated an increased infection risk in AH patients on steroids, few studies have examined whether receiving steroids just before liver transplantation raises the risk of post-surgical infections. This study aims to compare rates of post-surgical bacterial and fungal infections (<1 month post-transplant) in AH patients who did and did not receive steroids before transplant. **Methods:** We conducted a retrospective review of 29 AH patients who underwent liver transplantation at a single institution with at least 6 months of follow-up. Inclusion criteria encompassed AH diagnosis within two months before transplantation, excluding patients transplanted for alcohol-related liver disease without AH. Patients were divided into those receiving steroids for AH treatment and those not receiving steroids during the same period. Post-transplant bacterial and fungal infections were defined based on clinical treatment decisions, excluding donor-derived, latent, and viral infections. Post-transplant infection rates were compared using binary logistic regression, while pre-operative characteristics were compared using Mann-Whitney U test. **Results:** There was no significant difference in post-surgical infection rates between AH patients who received steroids and those who did not. Among the 10 patients with a 4-day steroid course (later determined non-responders), 3 developed post-surgical infections. None of the 5 patients with more than 4 days of steroids had post-surgical infections. Bacterial infections in the bloodstream, abdomen, and urinary tract were most common in the first post-transplant month. One fungal infection led to mortality in the steroid-treated group, while mortality in the non-steroid group was unrelated to infection. **Conclusion:** Short-term steroid treatment for alcohol hepatitis before liver transplantation does not appear to significantly raise the risk of early post-surgical bacterial or fungal infections.

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	Received Steroids (n =15)	Did not receive steroids (n = 14)	p-value
Age	46.2 (9.6)	48.6 (10.4)	.585
Sex Male = Female =	 12 (80%) 3 (20%)	 11 (78.6%) 3 (22.4%)	.924
BMI	26.7 (5.2)	27.2 (5.1)	.948
MELD	32.9 (6.5)	33.4 (4.6)	.844
Bilirubin	24.2 (8.3)	25.4 (10.6)	.631
Maddrey's Discriminant Function	101.2 (54.7)	111.9 (40.7)	.335
Steroid-Course 4-Day = >4-Day = Duration Between Last Day of Steroids and Transplant	 10 5 17.1 (11.7)	No Steroids	-
Patients with Post-Surgical Infections	**3 (20.0%)**	**4 (28.6%)**	.591
Unique Infections Abdominal (abscess, peritonitis, etc.) Respiratory tract (pneumonia, etc.) Urinary Tract GI Tract Wound Bloodstream Infection	**3 (20.0%)** 0 0 0 0 1 (6.7%) 2 (13.4%)	**6 (42.9%)** 2 (14.3%) 0 2 (14.3%) 1 (7.2%) 0 1 (7.2%)	.192
Death	1 (6.7%)	1 (7.2%)	.960
Re-Transplantation	2 (13.4%)	0	-

Disclosures: Alex Chang: Nothing to Disclose, Alexa Giammarino: Nothing to Disclose, Maham Ghani: Nothing to Disclose, Ethan Berman: Nothing to Disclose, Aditya Sood: Nothing to Disclose, Nishi Joshi: Nothing to Disclose, Alvin Htut: Nothing to Disclose, James Park: Nothing to Disclose, Nabil Dagher: Nothing to Disclose, Sanjaya Satapathy: Gilead Sciences: Grant/Research Support, Durect Pharma: Grant/Research Support, Fibronostics: Grant/Research Support, Novartis: Grant/Research Support, Zydus Pharma: Grant/Research Support, Boehringer Ingelheim: Grant/Research Support, Intercept Pharma: Grant/Research Support

3120 | RISING TRENDS OF CONCURRENT MOOD DISORDERS IN HOSPITALIZED PATIENTS WITH ALCOHOL-ASSOCIATED LIVER DISEASE BETWEEN 2014 AND 2023: A NATIONWIDE STUDY OF INSURED AND UNINSURED POPULATIONS

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[1]Department of Internal Medicine, Weiss Memorial Hospital, Chicago, IL, [2]Department of clinical medicine, the Second Affiliated Hospital of Xi'an Jiaotong University, Xi'an, [3]Karsh Division of Gastroenterology and Hepatology, Department of Medicine, Cedars-Sinai Medical Cent, [4]Tulane University School of Medicine

Background: Mood disorders significantly increase the risk of alcohol use disorder, complicating efforts toward alcohol cessation. Despite this, there is limited literature on the incidence and prevalence of comorbid mood disorders in patients with alcohol-associated liver disease (ALD). This study aims to assess the 10-year nationwide trends in the incidence of depression, anxiety, and suicidal ideation (SI) or homicidal ideation (HI) among hospitalized patients with ALD. **Methods:** This population-based longitudinal cohort study utilized de-identified electronic health records from the TriNetX network, which comprises of over 113 million patients in

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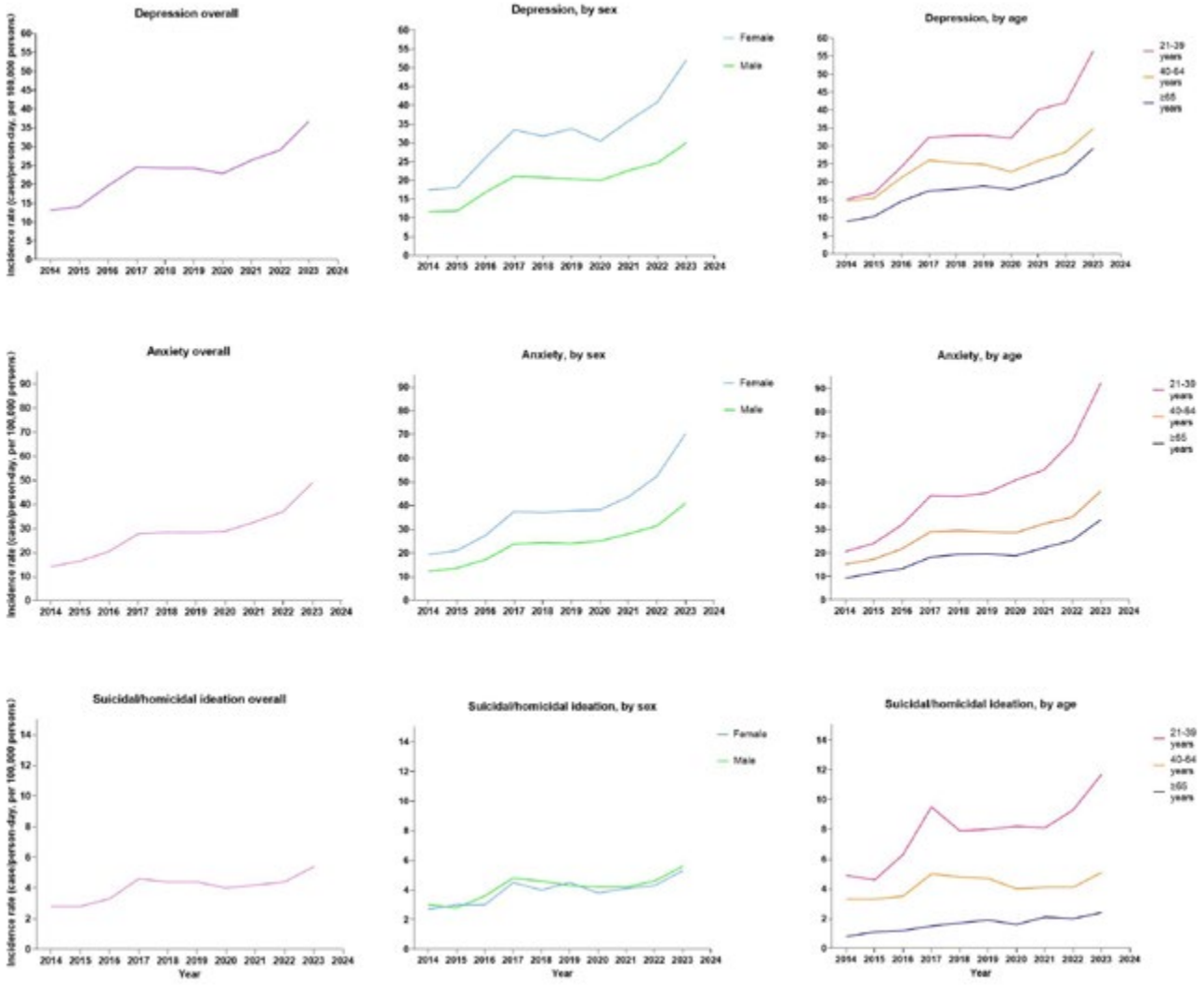
the U.S. We included patients hospitalized with ALD, alcoholic hepatitis or cirrhosis from 1/1/2014 to 12/31/2023. The incidence rate (IR) of mood disorders was calculated annually (case/person-day). Incident cases of depression, anxiety, SI/HI were identified by the new ICD-10 codes in ALD patients with no prior history of these conditions. Two subgroup analyses, stratified by gender and age, were conducted. Age stratification included three subgroups: 20-39, 40-65, and ≥65 years old. Piecewise regression and joinpoint analysis were utilized to determine annual percentage changes (APC) with 95% confidence intervals (CI) in the overall trends, identifying statistically significant shifts of the rates. **Results:** A total of 206,252 ALD patients were identified. Significant upward trends in the annual incidence rates of depression (APC 21.0%, 95% CI:8.05-49.37), anxiety (APC 21.84%, 95% CI: 10.35-44.28), and SI/HI (APC:16.68%, 95% CI: 2.94-46.63) were observed from 2014 to 2017. After 2017, the rate of increase moderated in depression, anxiety, and SI/HI, with the APCs declined to 5.92%, 9% and 2.35%, respectively (Figure 1**).** Subgroup analyses revealed consistently higher IR of depression and anxiety among women compared to men over the past decade, with significant increasing trends noted (depression: APC 10.76%, 95% CI 5.60-16.08; anxiety: APC 13.14%, 95% CI 8.47-17.91). However, no significant difference in the IR of SI/HI was found between the two genders. As for age comparison, significantly upward trends were noted in younger ALD patients across all three mood disorders. Surprisingly, even elderly ALD patients, with lowest IR compared to their counterparts, exhibited significant increases over a decade in anxiety (APC 12.82, 95% CI 9.47-16.28) and from 2014-2017 in SI/HI (APC 22.58, 95% CI 2.16-47.09). **Conclusion:** The current study demonstrated significant upward trends in depression, anxiety, and suicidal or homicidal ideation (SI/HI) incidence rates among ALD patients over past 10 years. These findings underline the importance of addressing comorbid psychiatric mood disorders among hospitalized ALD patients.



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Disclosures: Emily Shu-Yen Chan: Nothing to Disclose, Sikai Qiu: Nothing to Disclose, Natchaya Polpichai: Nothing to Disclose, Hyunseok Kim: Nothing to Disclose, Yee Hui Yeo: Nothing to Disclose, Peng-Sheng Ting: Nothing to Disclose

3121 | POST-TRANSPLANTATION OUTCOMES IN ALCOHOL-RELATED LIVER DISEASE: HIGHER RELAPSE RATES ASSOCIATED WITH ALCOHOL-ASSOCIATED HEPATITIS

Alex Chang[1] Alexa Giammarino[1] Maham Ghani[1] Ethan Berman[1] Nishi Joshi[1] Nitzan Roth[1] Esther Benamu[1] Ilan Berlinrut[1] Nabil Dagher[1] Sanjaya Satapathy[1]

[1]Northwell Health

Background: Among individuals with alcohol-related liver disease (ARLD), those with alcohol-associated hepatitis (AH) who do not respond to steroids face elevated mortality rates, necessitating liver transplantation as the definitive intervention. Given that many AH patients undergo transplantation without the traditional six-month abstinence period, there's a critical need to assess the risks of harmful relapse and adverse outcomes post-transplantation. This study aims to compare post-operative outcomes between patients transplanted for ARLD + AH and those transplanted for ARLD alone. **Methods:** We conducted a retrospective study involving 82 patients with a minimum 6-month follow-up, all transplanted for ARLD at a single institution between December 2019 and August 2023. Twenty-nine patients were classified under the ARLD + AH group due to severe AH (MDF > 32) within two months pre-transplantation, while 53 patients were transplanted for ARLD without AH. Patient characteristics pre-operatively and outcomes post-operatively were collected via chart review. Harmful relapse was defined as consuming >3 drinks per week post-transplantation or alcohol-related medical harm. Post-operative complications were compared using binary logistic regression, and relapse rates were assessed via Kaplan-Meier log-rank analysis. **Results:** Log-rank analysis revealed a significantly higher rate of harmful relapse ($p = .021$) and a trend towards higher any relapse rates ($p = .094$) in patients transplanted for ARLD + AH compared to those with ARLD alone. In the ARLD + AH group, one patient died from graft-versus-host disease (GVHD) and another from relapse-associated complications. One patient from the ARLD-only group died from hepatocellular carcinoma (HCC) complications. No significant differences were found in post-operative hospital readmissions, infections, or rejection rates between the two groups. On average, ARLD + AH patients had higher Model for End-Stage Liver Disease (MELD) scores ($p < .001$) and bilirubin levels ($p < .001$) at transplantation. **Conclusion:** Patients transplanted for ARLD + AH are generally more critically ill pre-transplantation and experience higher harmful relapse rates post-transplantation compared to those with ARLD alone. However, short-term outcomes regarding mortality, infection, hospital readmissions, and rejection rates are similar between the two groups. Further studies are warranted to explore relapse risk reduction strategies for AH patients undergoing transplantation. Nonetheless, our findings support the feasibility of transplanting patients with ARLD + AH based on a minimum of 6-month post-transplantation follow-up.

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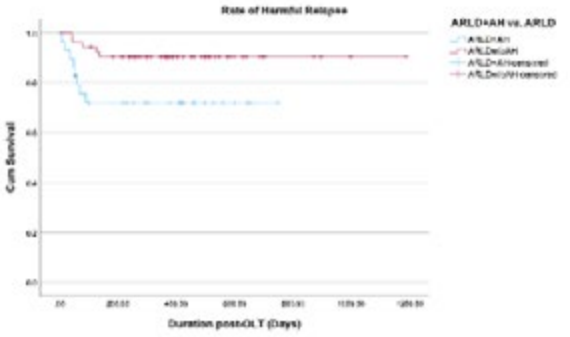

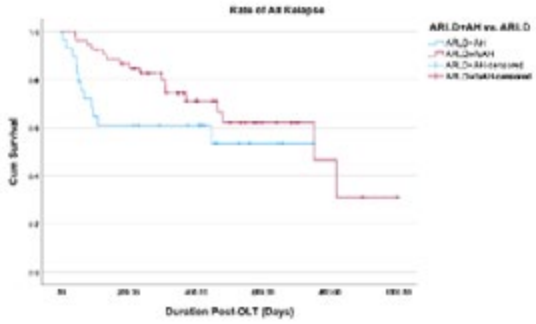

Patient Characteristic	ARLD + AH (n = 29)	ARLD (n = 53)	P-value
Age	47.4 (9.9)	54.9 (10.3)	.002
Sex			.564
Male =	23	40	
Female =	6	13	
BMI	26.9 (5.1)	28.5 (9.9)	.420
MELD	33.1 (5.5)	27.9 (5.3)	**<.001**
Bilirubin	24.8 (9.4)	8.7 (8.2)	**<.001**
Hospital LOS (Days)	20.7 (12.9)	19.0 (25.1)	.728
Harmful Relapse	8 (27.6%)	5 (9.4%)	**.039**
Slips	4 (13.8%)	12 (22.6%)	.338
Hospital Readmissions	1.2 (1.2)	1.5(1.5)	.358
Infections (first 3 months post-OLT)	8 (27.6%)	11 (20.8%)	.485
Unique Infections (first 3 months post-OLT)	10 (34.5%)	13 (24.5%)	.339
Abdominal (abscess, peritonitis, etc.)	1 (3.4%)	2 (3.8%)	
Respiratory tract (pneumonia, etc.)	0	2 (3.8%)	
Urinary Tract	3 (10.3%)	7 (13.2%)	
GI Tract	1 (3.4%)	0	
Wound	1 (3.4%)	0	
Bloodstream Infection	4 (13.8%)	2 (3.8%)	
Rejection	7 (24.1%)	19 (35.8%)	.451
Biopsy-Confirmed	4 (13.8%)	7 (13.2%)	
Thymoglobulin	1 (3.4%)	4 (7.6%)	
Graft Failure	1 (3.8%)	2 (3.6%)	.940
Death	2 (7.7%)	1 (1.7%)	.280
Dur. Of Follow-Up	404.3 (162.3)	494.6(270.7)	.105

Disclosures: Alex Chang: Nothing to Disclose, Alexa Giammarino: Nothing to Disclose, Maham Ghani: Nothing to Disclose, Ethan Berman: Nothing to Disclose, Nishi Joshi: Nothing to Disclose, Nitzan Roth: Nothing to Disclose, Esther Benamu: Nothing to Disclose, Ilan Berlinrut: Nothing to Disclose, Nabil Dagher: Nothing to Disclose, Sanjaya Satapathy: Gilead Sciences: Grant/Research Support, Durect Pharma: Grant/Research Support, Fibronostics: Grant/Research Support, Novartis: Grant/Research Support, Zydus Pharma: Grant/Research Support, Boehringer Ingelheim: Grant/Research Support, Intercept Pharma: Grant/Research Support

3122 | THE FOREVER CHEMICAL, PERFLUOROOCTANE SULFONATE (PFOS), ALTERS HEPATIC METABOLISM AND WORSENS ALCOHOL-ASSOCIATED LIVER DISEASE SEVERITY IN A CHRONIC-BINGE ETHANOL FEEDING MODEL

Frederick Ekuban[1] Tyler Gripshover[1] Paxton Ames[1] Oluwanifedmiesther Bolatimi[1] Banrida Wahlang[1] Joshua Abramson[1] Jianzhu Luo[1] Abigail Ekuban[1] Walter Watson[1] Jae Hwang[1] Juw Park[1] Kushal Biswas[2] Dhimiter Bello[2] Jennifer Schlezinger[3] Craig McClain[1] Matthew Cave[1]

[1]University of Louisville, [2]University of Massachusetts, Lowell, [3]Boston University

Background: MASLD has increasingly been associated with pollutant exposures including the ubiquitous 'forever chemical', PFOS (PMID:35475652). However, only limited environmental health data exist for alcohol-associated liver disease (ALD). We hypothesize that pollutants may disrupt hepatic metabolism to modify ALD severity. Recently, we developed a two-hit (ethanol plus pollutant) mouse model (PMID: 36377258, 38619879), enabling testing of this hypothesis. Here, we elucidate the metabolic and disease-modifying effects of PFOS in this model. **Methods:** Male C57BL/6J mice were fed isocaloric control or 5% EtOH Lieber-DeCarli diet for 15 days. From day 6 of feeding, mice were concurrently gavaged with 1 mg/kg PFOS or 2% tween-80 vehicle for 10 days, followed by a 5 g/Kg EtOH binge dose and sacrifice 5-6 hours later. Assessments included: liver disease and metabolic

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phenotyping; ethanol and PFOS exposure assessments; whole-liver RNA-Seq followed by Ingenuity Pathway Analysis (IPA); RT-PCR and immunoblotting. **Results:** PFOS exacerbated EtOH-induced hepatic steatosis and increased plasma VLDL and ALT. PFOS upregulated ethanol-metabolizing enzymes to decrease blood alcohol levels. Approximately 60% of the administered PFOS dose accumulated in liver. Alcohol-fed (*vs.* pair-fed) mice had decreased PFOS tissue levels which was largely a reflection of the weight-based PFOS dosing protocol. IPA Top Toxicity Functions/Lists associated with PFOS co-exposure in EtOH-fed mice included: fatty acid metabolism and liver steatosis; nuclear receptor activation, cytochrome P450, and ROS; apoptosis; liver fibrosis; and HCC. GO/KEGG analyses similarly revealed enrichment in fatty acid, xenobiotic, alcohol, or glutathione metabolic processes; and PPAR signaling. PFOS upregulated expression of several nuclear receptors (e.g., *Pparα, Car*, and *Pxr*) and their P450 target genes (e.g., *Cyp4a10*, *Cyp2b10*, and *Cyp3a11*) by RT-PCR or Western blot, confirming key IPA results. **Conclusion:** PFOS is a metabolism disrupting chemical that worsened ALD severity despite lower blood alcohol levels. PFOS activated hepatic nuclear receptors and enriched hepatic transcriptional pathways associated with steatosis, oxidative stress, cell death, fibrosis, and HCC. Key results were subsequently validated in a human study submitted to the Liver Meeting as a companion abstract. More data are required on environmental pollution as a disease modifying factor in ALD.

Disclosures: Frederick Ekuban: Nothing to Disclose, Tyler Gripshover: Nothing to Disclose, Paxton Ames: Nothing to Disclose, Oluwanifedmiesther Bolatimi: Nothing to Disclose, Banrida Wahlang: Nothing to Disclose, Joshua Abramson: Nothing to Disclose, Jianzhu Luo: Nothing to Disclose, Abigail Ekuban: Nothing to Disclose, Walter Watson: Nothing to Disclose, Jae Hwang: Nothing to Disclose, Juw Park: Nothing to Disclose, Kushal Biswas: Nothing to Disclose, Dhimiter Bello: Nothing to Disclose, Jennifer Schlezinger: Nothing to Disclose, Craig McClain: Novo Nordisk: Grant/Research Support, Intercept Pharmaceuticals: Grant/Research Support, Altimmune: Grant/Research Support, Target Pharma Solutions: Grant/Research Support, NIH: Grant/Research Support, VAMC: Grant/Research Support, Matthew Cave: Nothing to Disclose

3123 | RISK REDUCTION IS POSSIBLE IN PATIENTS WITH HIGH-RISK SIPAT SCORES UNDERGOING LIVER TRANSPLANTATION FOR ALCOHOL-RELATED LIVER DISEASE

Alex Chang[1] Ethan Berman[1] Maham Ghani[1] Alexa Giammarino[1] Nishi Joshi[1] Nazia Qazi[1] Jennifer Onwochei[1] James Park[1] Nabil Dagher[1] Sanjaya Satapathy[1]

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Background: Alcohol relapse following liver transplantation for alcohol-related liver disease is linked to adverse outcomes. The SIPAT score, ranging from 0 to 119, integrates various psychosocial risk factors to predict transplant outcomes and has demonstrated predictive value for alcohol relapse post-transplantation. However, few studies have investigated the efficacy of risk reduction interventions in preventing relapse among patients with high-risk SIPAT scores (>21). This study evaluates the effectiveness of post-transplant interventions in mitigating harmful relapse risk in high-risk SIPAT score patients. **Methods:** A retrospective analysis was conducted on 82 patients transplanted for alcohol-related liver disease between December 2019 and August 2023, with a minimum 6-month follow-up period. Pre- transplant SIPAT scores were prospectively gathered, categorizing 27 patients as high-risk (SIPAT ≥ 21) and 33 as low-risk (SIPAT < 21); 22 patients were excluded due to cognitive impairment. Post-transplant risk reduction interventions (medication-assisted treatment, pETH surveillance, and rehabilitation) were assessed retrospectively through chart review. Harmful relapse rates in high-risk and low-risk patients were compared using Kaplan-Meier log-rank analysis, defining harmful relapse as >3 drinks weekly or alcohol-related readmission post-transplant. **Results:** Within 6 months post-transplant, 18.2% (n = 6) of high-risk and 11.1% (n = 3) of low-risk patients experienced harmful relapse. Additionally, 6 patients in the low-risk group experienced slips post-transplant. Kaplan-Meier analysis revealed no significant differences in harmful relapse or overall relapse rates between high-risk and low-risk groups (p = .789 and .806, respectively). Enrollment in rehabilitation programs and post-transplant pETH surveillance frequency did not significantly differ between groups. However, more high-risk patients initiated medication-assisted therapy post-transplant compared to low-risk patients (p = .049). **Conclusion:** Prospective SIPAT score collection pre-transplant can guide clinicians in implementing risk reduction interventions post-transplant for high-risk patients. Despite higher initiation of medication-assisted therapy, high-risk patients showed similar 6-month relapse rates to low-risk patients, suggesting potential efficacy of medication-assisted therapy in mitigating relapse risk among high-risk individuals.

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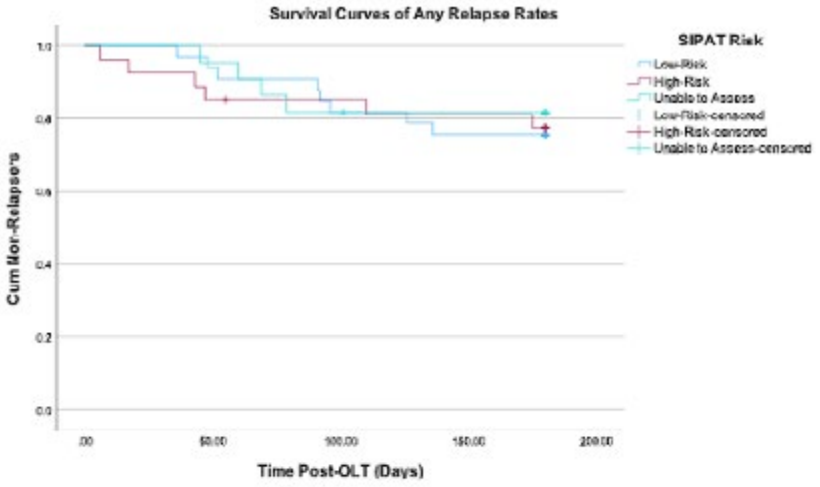

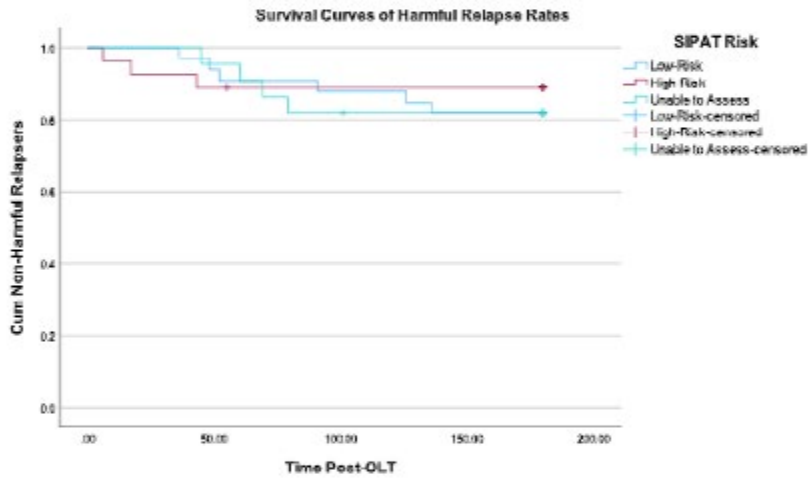

Post-Operative Intervention	Low-Risk (n = 33)	High-Risk (n = 27)	Unable to be assessed (n = 22)	P-value
Alcohol Rehab Prog.	26 (78.8%)	20 (74.1%)	13 (59.1%)	.668
Outpatient =	21 (63.6%)	16 (59.3%)	10 (45.5%)	
Inpatient =	0	2 (7.4%)	1 (4.5%)	
Virtual =	5 (15.2%)	2 (7.4%)	2 (9%)	
None =	7 (21.2%)	7 (25.9%)	9 (40.9%)	
Peth Surveillance				
Peth/Month	.93 (.31)	.81 (.40)	.67 (.41)	.152
First 3-Months	5.8 (2.8)	4.9 (2.7)	4.1 (2.9)	.193
First 6-Months	9.0 (3.8)	7.5 (4.5)	7.1 (4.6)	.152
MAT	3 (9.1%)	8 (29.6%)	1 (4.5%)	**.041**
Acamprosate	1 (3.0%)	3 (11.1%)	0	
Vivitrol	2 (6.0%)	5 (18.5%)	1 (4.5%)	

Disclosures: Alex Chang: Nothing to Disclose, Ethan Berman: Nothing to Disclose, Maham Ghani: Nothing to Disclose, Alexa Giammarino: Nothing to Disclose, Nishi Joshi: Nothing to Disclose, Nazia Qazi: Nothing to

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Disclose, Jennifer Onwochei: Nothing to Disclose, James Park: Nothing to Disclose, Nabil Dagher: Nothing to Disclose, Sanjaya Satapathy: Gilead Sciences: Grant/Research Support, Durect Pharma: Grant/Research Support, Fibronostics: Grant/Research Support, Novartis: Grant/Research Support, Zydus Pharma: Grant/Research Support, Boehringer Ingelheim: Grant/Research Support, Intercept Pharma: Grant/Research Support

3124 | TRENDS IN POST-DISCHARGE PHARMACOLOGICAL ALCOHOL CESSATION THERAPY AND PSYCHIATRIC REFERRALS FOR HOSPITALIZED PATIENTS WITH ALCOHOL-ASSOCIATED LIVER DISEASE (ALD) BETWEEN 2014 TO 2023: A NATIONWIDE STUDY ◆

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Background: Alcohol-associated liver disease (ALD) is associated with high rates of alcohol relapse and unfortunately many patients do not follow up after discharge for alcohol cessation therapy. Literature supports the use of pharmacological or psychiatric cessation therapies for ALD patients, albeit limited. This study aims to evaluate the 10-year nationwide trends in post-discharge pharmacological cessation therapies and psychiatric referrals for hospitalized patients with ALD. **Methods:** This population-based longitudinal cohort study utilized TriNetX network comprised of 113 million patients in the U.S. We included hospitalized patients with alcohol-associated liver disease, alcoholic hepatitis or cirrhosis from 1/1/2014 to 12/31/2023. The primary outcomes were post-discharge pharmacological cessation therapies (baclofen, naltrexone, acamprosate, disulfiram), psychiatric referrals or outpatient psychiatric encounters and mortality rate. Annual incidence and prevalence of these outcomes were calculated. Subgroup analysis was conducted by gender. Piecewise regression and joinpoint analysis determined annual percentage changes (APC) with 95% confidence intervals (CI), identifying significant shifts in trends. Pairwise comparisons using Average Annual Percent Change (AAPC) were also performed between three outcomes. **Results:** A total of 206,252 hospitalized ALD patients were reported. The incidence of pharmacological cessation therapies post-discharge increased from 3.38% (2014) to 9.97% (2023), with a more pronounced uptick starting in 2020 (APC:11.46% from 2014-2020 vs APC:15.51% from 2020-2023). Psychiatric referrals or outpatient follow-ups initially decreased from 2014 to 2018 (APC:-4.38%, 95% CI:-7.18 to -2.27) but then increased significantly after 2018 (APC:5.13%, 95% CI:3.47-7.32), reaching the highest incidence of 5.84% in 2023. There was no significant change in overall incidence or mortality rates among hospitalized ALD patients over the 10 years. Compared to psychiatric referral or mortality rate, the increase in pharmacological alcohol cessation therapies was pronounced (AAPC difference: 12.0%, p<0.001), (AAPC difference:13.24%, p<0.001), respectively. Subgroup analysis showed significant increases in pharmacological cessation therapies for both genders, with no changes in mortality. Women had a higher incidence of psychiatric follow-up than men **(**Figure 1**). Conclusion:** Our study revealed a significant increase in the rate of pharmacological cessation therapies for hospitalized ALD patients over the past decade. Despite this progress, the incidence of patients receiving post-discharge pharmacological alcohol cessation therapy and psychiatric follow-up remains a minority. Greater efforts and strategies are needed to support long-term alcohol cessation in ALD patients.

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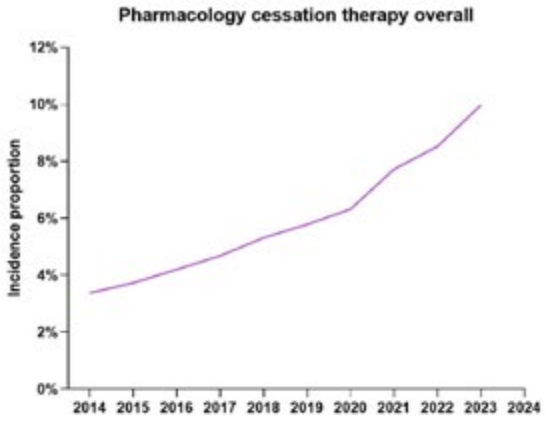

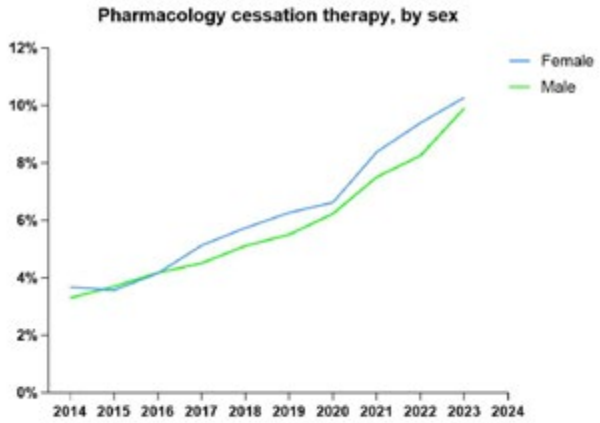

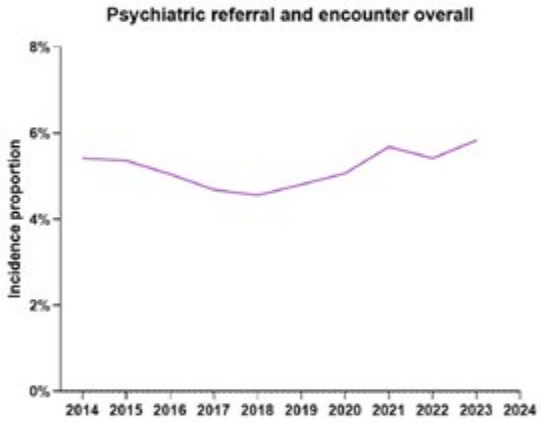

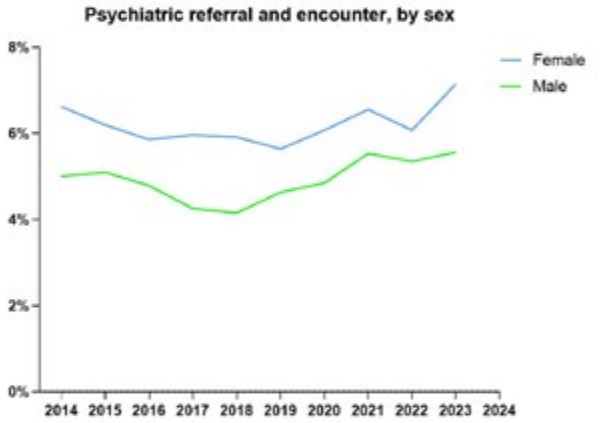

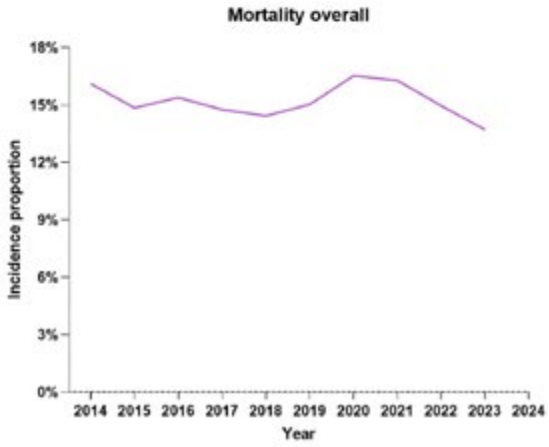

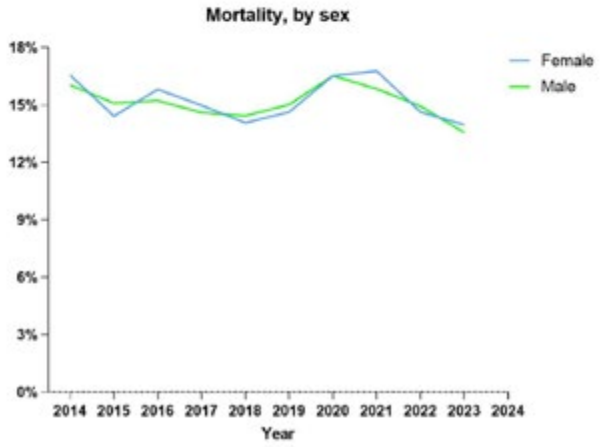

Disclosures: Emily Shu-Yen Chan: Nothing to Disclose, Yee Hui Yeo: Nothing to Disclose, Sikai Qiu: Nothing to Disclose, Hyunseok Kim: Nothing to Disclose, Peng-Sheng Ting: Nothing to Disclose

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3125 | THE ROLE OF KUPFFER CELL-DERIVED LET7A-5P IN REGULATING HEPATOCYTE DIFFERENTIATION DURING ALCOHOL-ASSOCIATED LIVER DISEASE

Sheetalnath Rooge[1] Isabel Aranzazu Pulido Ruiz[1] Marina Barmanova[2] Kyle Yuquimpo[1] KYO SASAKI[3] Priyanka Ghosh[1] Irina Tikhanovich[1] Ann Wozniak[1] Steven Weinman[1]

[1]University of Kansas Medical Center, [2]Liberty University, [3]Kawasaki Medical School

Background: Loss of hepatocyte differentiation is the key event leading to liver failure in alcohol-associated hepatitis (AH). Our previous work (PMID: 38687563) in the WDA mouse model of alcohol-associated liver disease (ALD) showed that selective KC ablation with diphtheria toxin (DT) caused a liver failure phenotype with hepatocytes transitioning toward a progenitor state. Analysis of upstream regulators showed that there was an increased expression of Let7 target genes in the WDA-DT KC ablation model. Since the Let7 miRNA family is known to suppress stemness and progenitor phenotype, we hypothesized that KCs might be an important source of Let7 in ALD. The Aims of this study were to determine if KC-derived Let7 was important for supporting liver function in the WDA model and if KC-derived EVs might be a vector for KC to hepatocyte Let7 transfer. **Methods:** C57BL/6J mice were fed a high-fat western diet with ad-libitum 10%-20% alcohol in drinking water for 16 weeks (WDA model). Clec4f-DTR mice on the WDA diet received injections of Diphtheria toxin every 3 days during the last 4 weeks to ablate KCs. Transcriptomic analysis was performed on whole liver tissue isolated from chow, WDA, and WDA-DT mice. Co-culture experiments with isolated hepatocytes and KCs were performed in trans-well plates. KCs and IMs were isolated using FACS to assess the cellular and extra-cellular vesicle (EV) content of Let7a-5p. **Results:** We used a hepatocyte-macrophage co-culture system to assess the impact of macrophages on hepatocyte differentiation status. Co-culture with WDA KCs enhanced hepatocyte albumin expression 2.7-fold but identical co-culture with chow KCs, WDA IMs, or WDA-DT KCs failed to increase albumin expression. Hepatocyte content of Let7a-5p decreased 2-fold over the course of WDA feeding compared to chow-fed mice and was decreased further after ablation of KCs. WDA KCs had 77-fold higher levels of Let7a-5p than chow KCs. EVs from WDA-KC had 2.5-fold higher amounts of Let7a-5p compared to that in EVs from chow KCs. **Conclusion:** Let7 undergoes dramatic shifts in distribution between hepatocytes and KCs during ALD. In response to alcohol, hepatocytes become depleted in Let7 while KC Let7 content and EV secretion are increased. In addition, alcohol KCs are better able to support hepatocyte differentiated function than KCs from chow-fed mice. These results are consistent with our hypothesis that Let7 is a key factor supporting liver differentiation in ALD, and KCs support liver function by delivering Let7 cargo to hepatocytes. Loss of this support can lead to liver failure and targeting relative Let7 deficiency might improve liver function in patients with ALD and AH.

Disclosures: Sheetalnath Rooge: Nothing to Disclose, Isabel Aranzazu Pulido Ruiz: Nothing to Disclose, Marina Barmanova: Nothing to Disclose, Kyle Yuquimpo: Nothing to Disclose, KYO SASAKI: Nothing to Disclose, Priyanka Ghosh: Nothing to Disclose, Irina Tikhanovich: Nothing to Disclose, Ann Wozniak: Nothing to Disclose, Steven Weinman: Nothing to Disclose

3126 | THE ROLE FOR KERATIN18 M30 AS A COMPANION DIAGNOSTIC FOR GLUCOCORTICOID THERAPY IN SEVERE ALCOHOL-ASSOCIATED HEPATITIS (SAH)

Jane Frimodig[1] Craig McClain[1] Vatsalya Vatsalya[1] Min Wang[1] Samer Gawrieh[2] Srinivasan Dasarathy[3] Wanzhu Tu[2] Patrick Kamath[4] Naga Chalasani[5] Ramon Bataller[6] Gyongyi Szabo[7] Qing Tang[2] Bruce Barton[8] Laura Nagy[9] Vijay Shah[10] Arun Sanyal[11] Mack Mitchell[12]

[1]University of Louisville, [2]Indiana University, [3]Cleveland Clinic, [4]Mayo Clinic, [5]Indiana University Medical Center, [6]University of Pittsburgh, [7]Beth Israel Deaconess Medical Center, [8]University of Massachusetts, [9]Cleveland Clinic Foundation, [10]Mayo Clinic Rochester, [11]Virginia Commonwealth University, [12]University of Texas Southwestern Medical Center

Background: Mortality for sAH remains high, even with glucocorticoid therapy. It is clear that some patients do not respond to glucocorticoid therapy, and the Lille stopping rule is designed to limit glucocorticoid exposure in such patients. Keratins, previously termed cytokeratins, are the major epithelial-specific subgroup of intermediated filament proteins, and K18 is released with cell death. During hepatocyte apoptosis, activated caspases cleave K18 which can be detected in plasma by the M30 ELISA, whereas the M65 ELISA detects both caspase-cleaved and uncleaved K18. Data from the STOPAH trial reported that K18M30 was diagnostic, prognostic and

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theragnostic in their large patient population with sAH. However, there have been no studies of K18M30 in sAH where the Lille stopping rule was followed and where follow-up data were available. **Methods:** The study included 66 individuals, aged 26-67, with sAH enrolled in the AlcHepNet study evaluating therapy with Anakinra+Zinc (A+Z) v. Prednisone (P). Patients were diagnosed using clinical/laboratory criteria described by the NIAAA consortium. All patients had baseline and at least one follow-up serum sample; patients were grouped as survivors/non-survivors at 180 days. Serum K18M30 was determined by ELISA assay (Diapharma Group, West Chester, OH). Statistical analysis was performed using t-tests. **Results:** There were 37 patients in the P group (4 non-survivors) and 29 patients in the A+Z group (6 non-survivors). Patients in both groups tended to be younger (mid-40s). Non-survivors in the P group (Lille Stopping Rule was used in all P-treated patients) had significantly lower baseline K18M30 (2340 vs. 5192, p=0.043) than survivors, while there was no difference between the A+Z survivors/non-survivors. Interestingly, patients in both groups had a slow resolution of the K18 levels, with major decreases not occurring until ~90 days. **Conclusion:** Patients with lower levels of K18M30 have less apoptotic cell death and are more likely to represent patients with decompensated cirrhosis and limited acute inflammation. These patients represent those unlikely to benefit from, and more likely to experience adverse effects of, glucocorticoids. Thus, the combination of the Lille stopping rule and low K18M30 could optimize glucocorticoid therapy. The slow improvement in cell death over time suggests that novel longer-term therapy may be needed.

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3127 | A NOVEL METALD SPHEROID MODEL REVEALS DIFFERENTIAL EFFECTS OF ETHANOL AND METABOLIC STRESSORS ON MITOCHONDRIAL RESPIRATION AND SYNERGISTIC INCREASES IN LIPID ACCUMULATION

Eden Gallegos[1] *Keishla Rodriguez-Graciani*[1] *Patricia Molina*[1] *Liz Simon*[1]

[1]*LSUHSC-New Orleans*

Background: Metabolic and alcohol-associated steatotic liver disease (MetALD) is more prevalent than ALD, yet differential cellular adaptations to the combination of metabolic dysregulation and alcohol are poorly defined. As there are no therapeutic interventions for alcohol-associated liver injury, identifying synergistic mechanisms of cellular dysfunction in MetALD is critical. The objective of this study was to use a HepaRG spheroid model to identify hepatocyte-specific metabolic and mitochondrial alterations resulting from exposure to ethanol, high sugars, and high fats. **Methods:** Differentiated HepaRG cells were seeded at 2000 cells per spheroid and incubated for 10 days

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in the following conditions: control (C), 50mM ethanol (E10), high sugars (11mM glucose and 11mM fructose) and fats (300uM oleic acid and 300uM palmitic acid; SF10), and ethanol, high sugars and high fats (ESF10). Control media contained 5.5mM glucose and vehicle (0.1% BSA). At endpoint, cholesterol, triglyceride, and secreted albumin concentrations were determined. The Agilent mitochondrial stress test was used to measure oxygen consumption rates using the Seahorse XF Pro. A two-way ANOVA was used with Fisher's LSD test for post hoc analyses; alpha was set to 0.05. **Results:** ESF10 increased spheroid triglyceride and cholesterol concentrations compared to all other groups ($p<0.0001$), and E10 increased cholesterol to a lesser extent compared to C ($p<0.0001$). There was a main effect of SF10 on decreased albumin secretion ($p<0.05$). Oxygen consumption rates (OCR) revealed a main effect of decreased ATP production and maximal respiration due to SF10 ($p<0.001$), but an increase in maximal respiration due to ethanol ($p<0.05$). There was an interaction between E10 and SF10 on non-mitochondrial oxygen consumption and spare respiratory capacity (%), which were elevated in the E10 group compared to all other groups ($p<0.01$) but not in the ESF10 group. **Conclusion:** These data suggest that ethanol and high sugars/fats synergistically increase lipid accumulation and differentially affect respiration in HepaRG spheroids. As cholesterol was increased by ethanol alone and further by ESF10, future experiments will test the relationship between cholesterol and the ability of the mitochondria to produce ATP by using atorvastatin to block cholesterol synthesis. This work is funded by the following NIAAA grants: F30AA030910 and P60AA009803.

Disclosures: Eden Gallegos: Nothing to Disclose, Keishla Rodriguez-Graciani: Nothing to Disclose, Patricia Molina: Nothing to Disclose, Liz Simon: Nothing to Disclose

3128 | ALCOHOL-INDUCED LIVER INJURY IS MEDIATED VIA &ALPHA;4 NICOTINIC ACETYLCHOLINE RECEPTORS EXPRESSED IN HEPATOCYTES

Walter Watson[1] Abigail Ekuban[1] Jeffrey Ritzenthaler[2] Jesse Roman[2]

[1]University of Louisville, [2]Thomas Jefferson University

Background: Our previous study demonstrated that alcohol induced the expression of the α4 subunit of nicotinic acetylcholine receptors (nAChRs) in the livers of wild type mice (WT) and that whole-body α4 nAChR knockout mice (α4KO) showed protection against alcohol-induced steatosis, inflammation, and injury. Based on these findings, we hypothesized that hepatocyte-specific α4 nAChRs may directly contribute to the detrimental effects of alcohol on the liver. **Methods:** Hepatocyte-specific α4 knockout mice (α4HepKO) were generated, and the absence of α4 nAChR was confirmed through PCR of genomic DNA. Female WT and α4HepKO mice were exposed to alcohol in the NIAAA chronic + binge model. After 10 days on the Lieber-DeCarli liquid diet containing 5% (vol/vol) alcohol or isocaloric maltose-dextrin, the mice were gavaged with a single dose of alcohol or isocaloric maltose-dextrin The mice were euthanized 9 hours later, and their organs harvested. Additionally, hepatocytes were isolated from WT, α4HepKO, α4floxed, and α4KO mice and either exposed to or left unexposed to alcohol (80 mM) in vitro for 24 hours. **Results:** Alcohol increased histological and biochemical features of steatosis, inflammation and injury in WT mice in WT mice. These effects were inhibited in α4HepKO mice. As enhanced lipid synthesis is known to contribute to alcohol-induced hepatic steatosis, we measured mRNA expression of genes involved in lipogenesis. Exposure of WT mice and primary mouse hepatocytes (PMH) to alcohol downregulated the expression of Sirt1 and upregulated the expression of lipogenic genes that are negatively regulated by Sirt1 such as Srebf1, Fasn, and Dgat2. Furthermore, alcohol increased the mRNA expression of inflammatory mediators such as TNFα, Cxcl5, Cxcl1, and Serpine1 in WT mice livers and PMH but not in the livers of α4HepKO mice or hepatocytes obtained from α4HepKO mice. **Conclusion:** α4 nAChRs expressed in hepatocytes mediate alcohol-associated hepatoxicity. Therefore, the development of therapeutic strategies targeting hepatocyte α4 nAChRs could help reduce the burden of ALD.

Disclosures: Walter Watson: Nothing to Disclose, Abigail Ekuban: Nothing to Disclose, Jeffrey Ritzenthaler: Nothing to Disclose, Jesse Roman: Nothing to Disclose

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3129 | IDENTIFICATION OF ENVIRONMENTAL POLLUTANTS AND METABOLIC PATHWAYS IN HUMAN SUBJECTS WITH ALCOHOL-ASSOCIATED HEPATITIS

Matthew Cave[1] Matthew Smith[2] Hao Zheng[1] Vatsalya Vatsalya[1] Jane Frimodig[1] Frederick Ekuban[1] Jianzhu Luo[1] Yongliang Liang[2] Sami Teeny[2] Walter Watson[1] Gyongyi Szabo[3] Srinivasan Dasarathy[4] Mack Mitchell[5] Laura Nagy[6] Bruce Barton[7] Young-Mi Go[2] Maiying Kong[1] Dean Jones[8] Craig McClain[1]

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Background: Little is known about the potential disease modifying effects of environmental pollution in alcohol-associated liver disease (ALD). Exposures to the 'forever chemicals', perfluoroalkyl and polyfluoroalkyl substances (PFAS), have been associated with hepatotoxicity in humans and MASLD in rodents. Recently, we demonstrated that some pollutants, including PFAS, worsened liver histology and disrupted metabolism in rodent models of ALD. This pilot study investigates the exposome and metabolome in human alcohol-associated steatohepatitis (ASH), with an initial focus on PFAS. **Methods:** Exposomics and metabolomics (LC-MS^2 & GC-MS^2) were performed in de-identified, archived plasma samples from consenting subjects with severe ASH (n=96), moderate ASH (n=28), or non-drinking healthy controls (n=11). Associations between log-transformed PFAS exposure biomarkers and ASH disease severity biomarkers were determined by linear regression in R. Metabolome-wide association studies (MWAS) were performed *vs.* disease group or *vs.* PFAS exposures in ASH using xMSPanda. Pathway analyses were performed using mummichog 2.0. **Results:** The mean age was 44.5±11.3 (SD) years, and subjects in the control group were younger. 57% of subjects were male and 87.4% were white. Demographic variables were similar between the ASH groups. 691 environmental pollutants were detected, including 6 PFAS (e.g., PFOS, PFOA, PFHxS, PFHpA, PFTrDA, and PFUnA). PFAS detection rates ranged from 94.1-100%. Compared to controls, subjects with ASH had higher PFOA levels (p=0.02). PFOS was positively associated with ABIC (β=0.061 [95% CI: 0.029, 0.092]) in an unadjusted model. MWAS *vs.* disease group yielded 3765 associated metabolic features (FDR<0.05) and enrichment of 30 pathways. Top pathways included Vit. D3; branched chain amino acids; bile acids; ascorbate; pentose and glucuronate; and butanoate. MWAS *vs.* PFOA, PFOS, or PFHxS yielded 3318, 806, or 721 associated features (p<0.05), respectively in ASH. These features corresponded to enrichment in 32, 7, or 29 pathways;13 of which were common to two PFAS. 19 pathways, including ascorbate and butanoate, were common to ASH and at least one PFAS. **Conclusion:** Subjects with ASH are exposed to a significant number of environmental pollutants, some of which were higher than in non-drinking controls. PFAS exposures were common and associated with metabolic disruption. Reverse causality cannot be excluded. Data analyses are ongoing.

Disclosures: Matthew Cave: Nothing to Disclose, Matthew Smith: Nothing to Disclose, Hao Zheng: Nothing to Disclose, Vatsalya Vatsalya: Nothing to Disclose, Jane Frimodig: Nothing to Disclose, Frederick Ekuban: Nothing to Disclose, Jianzhu Luo: Nothing to Disclose, Yongliang Liang: Nothing to Disclose, Sami Teeny: Nothing to Disclose, Walter Watson: Nothing to Disclose, Gyongyi Szabo: Advisor relationship with Glympse Bio, Inc (acquired by Sunbird Bio); Has not ended; Consultant relationship with Terra Firma; Has not ended; Consultant relationship with Pfizer; Has not ended; Consultant relationship with Pandion Therapeutics; Has ended; Consultant relationship with Merck; Has ended; Consultant relationship with Durect Corporation; Has ended; Advisor relationship with Satellite Biosciences; Has not ended; Consultant relationship with Zomagen Bioscience/ Ventyx Biosciences; Has ended; Consultant relationship with CYTA Therapeutics; Has ended; Royalties or patent beneficiary relationship with Springer Nature Group; Has not ended; Royalties or patent beneficiary relationship with UpToDate Inc; Has not ended; Consultant relationship with LabCorp; Has not ended; Advisor relationship with Evive; Has not ended; Advisor relationship with Surrozen; Has not ended; Consultant relationship with Takeda; Has ended, Srinivasan Dasarathy: Nothing to Disclose, Mack Mitchell: GlaxoSmithKline: Advisor, Amygdala Neuroscience: Consultant, Parvus Therapeutics: Advisor, HepaTX: Advisor, Durect: Grant/Research Support, Laura Nagy: Nothing to Disclose, Bruce Barton: Nothing to Disclose, Young-Mi Go: Nothing to Disclose, Maiying Kong: Nothing to Disclose, Dean Jones: Nothing to Disclose, Craig McClain: Novo Nordisk: Grant/Research Support, Intercept Pharmaceuticals: Grant/Research Support, Altimmune: Grant/Research Support, Target Pharma Solutions: Grant/Research Support, NIH: Grant/Research Support, VAMC: Grant/Research Support

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3130 | ACUTE-ON-CHRONIC LIVER FAILURE (ACLF) CRITERIA IN ALCOHOL-ASSOCIATED HEPATITIS: IMPLICATIONS FOR LIVER TRANSPLANTATION

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Background: Alcohol-associated hepatitis (AH) is a severe form of alcohol-associated liver disease with high mortality and morbidity, caused by excessive alcohol consumption. Severe AH is considered a common precipitant of acute-on-chronic liver failure (ACLF), and frequently complicates the clinical course of AH, posing substantial challenges in management and prognosis. This study aims to characterize the association between AH and ACLF, focusing on mortality across different ACLF grades. **Methods:** Multicenter prospective cohort study. We included patients admitted with severe AH between 2015–2022. Sociodemographic and clinical information were recorded. The main outcome was mortality over time according to the ACLF grade during admission. The analysis included survival analysis using Cox regression. We chose variables to adjust multivariable models based on the main predictors of mortality in prior studies. **Results:** 646 patients from 24 centers (8 countries: Mexico, Chile, Argentina, Brazil, Peru, Bolivia, Colombia, and Ecuador) were included. Age 49.9±11.7 years, 85.1% of men and 64.4% had a previous diagnosis of cirrhosis. Median MELD at admission was 25 [20-31] points, 46.5% of patients were treated with corticosteroids, and only 2.2% underwent liver transplantation (LT). Around 67.4% of patients fulfilled ACLF criteria: 10.1% grade 1, 19.2% grade 2, and 38.1% grade 3. The most frequent organ dysfunctions were 76.2% liver, 40.8% brain, 43.2% coagulation, 29.6% renal, 29.4% circulatory, and 18.9% lung failure. Survival at 180 days was 77.8% (95%CI: 72.1-82.6%) in those without ACLF grade 3 and 28.0% (95%CI: 20.5–36.0%) in those with ACLF grade 3 (p<0.001). In univariate analysis, ACLF grade 1 (HR 2.75, 95%CI: 1.55–4.88; p=0.001), grade 2 (HR 1.84, 95%CI: 1.10–3.08; p=0.021), and grade 3 (HR 7.44, 95%CI: 4.90–11.28; p<0.001) were associated with a higher mortality than those without ACLF. In the multivariable model adjusted by age, body mass index, and MELD score, individuals with ACLF grade 3 had lower survival than those

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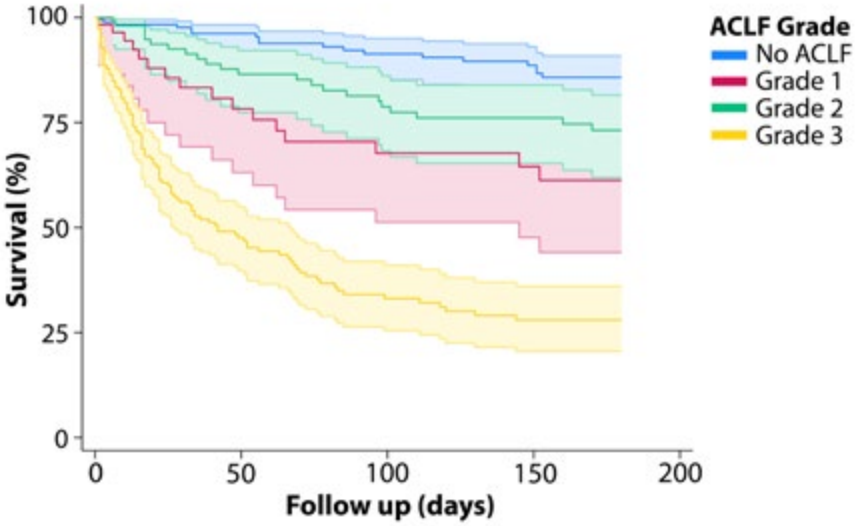
without ACLF (HR 2.67, 95%CI: 1.50–4.76; p=0.001). However, those with ACLF grade 1 (HR 1.50, 95%CI: 0.76–2.96; p=0.243) and grade 2 (HR 0.70, 95%CI: 0.31–1.56; p=0.380) were not associated with a higher mortality than those without ACLF. **Conclusion:** In AH, only ACLF grade 3 is a major determinant of morbimortality among patients with AH. Thus, patients who fulfill ACLF grade 3 should promptly be referred for early LT. Redefinition of ACLF in AH is essential to better quantify the severity and determine therapeutic goals.

Cumulative survival in patients with alcohol-associated hepatitis according to Acute-on-chronic (ACLF) grade



No at risk					
No ACLF	186	126	107	94	80
Grade 1	59	31	26	21	18
Grade 2	110	71	62	57	46
Grade 3	223	63	35	28	24

Disclosures: Luis Antonio Diaz: Nothing to Disclose, Paula Huerta: Nothing to Disclose, Renata Farias: Nothing to Disclose, Bastian Alcayaga: Nothing to Disclose, Francisco Idalsoaga: Nothing to Disclose, Gustavo Ayares: Nothing to Disclose, Jorge Arnold Alvarez: Nothing to Disclose, María Ayala-Valverde: Nothing to Disclose, Diego Perez: Nothing to Disclose, Jaime Gomez: Nothing to Disclose, Rodrigo Escarate: Nothing to Disclose, Eduardo Fuentes-López: Nothing to Disclose, Katherine Maldonado: Nothing to Disclose, Juan Pablo Roblero: Nothing to Disclose, Daniela Simian: Nothing to Disclose, Blanca Norero: Nothing to Disclose, Raul Lazarte: Nothing to Disclose, José Antonio Velarde: Nothing to Disclose, Jacqueline Córdova: Nothing to Disclose, Fátima Higuera-de-la-Tijera: Nothing to Disclose, Alfredo Servin-Caamaño: Nothing to Disclose, Jesús Varela: Nothing to Disclose, Scherezada Mejía Loza: Nothing to Disclose, Rita C M DA SILVA: Nothing to Disclose, Cristina Melo Rocha: Nothing to Disclose, Roberta C. Araujo: Nothing to Disclose, Gustavo Henrique Pereira: Nothing to Disclose, Claudia Alves Couto: Nothing to Disclose, Fernando Bessone: Nothing to Disclose, Mario Tanno: Nothing to Disclose, Gustavo Romero: Nothing to Disclose, Manuel Mendizabal: Nothing to Disclose, Sebastián Marciano: Nothing to Disclose, Gonzalo Gomez Perdiguero: Nothing to Disclose, Melisa Dirchwolf: Nothing to Disclose, Pedro Montes: Nothing to Disclose, Patricia Guerra Salazar: Nothing to Disclose, Geraldine Ramos: Nothing to Disclose, Susana Castro Sánchez: Nothing to Disclose, Juan Carlos Restrepo: Nothing to Disclose, Enrique Carrera: Nothing to Disclose, Mayur Brahmania: Nothing to Disclose, Ashwani Singal: Durect: DSMB, GSK: Grant/Research Support, Pleiogenix: Consultant, Pleiogenix: Stock – privately held company, Medscape: Speaking and Teaching, Medical Education Speaker's Network: Speaking and Teaching, CLD Foundation: Advisor, CLD Foundation: Speaking and Teaching, Madrigal: Speaking and Teaching, Up-to-Date: Royalties or patent beneficiary, NIAAA: Grant/Research Support, AASLD: Advisor, ACG: Speaking and Teaching, Winston Dunn: Nothing to Disclose, Ramon Bataller: Nothing to Disclose, Vijay Shah: Boehringer Ingelheim: Consultant, GSK: Consultant, GENFIT SA: Consultant, Intercept Pharmaceuticals, Inc.: Advisor, Korro Bio, Inc.: Consultant, Mallinckrodt Pharmaceuticals: Advisor, Novo Nordisk A/S: Consultant, Resolution Therapeutics, Ltd.: Advisor, Seal

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Rock Therapeutics, Ltd.: Consultant, Surrozen: Advisor, Patrick S. Kamath: Nothing to Disclose, Marco Arrese: Nothing to Disclose, Juan Pablo Arab: Nothing to Disclose

3131 | PRECISION CUT LIVER SLICE DISEASE MODEL RECAPITULATES HUMAN LIVER DISEASE BIOLOGY FOR PRECLINICAL DRUG DEVELOPMENT

Sofia Izunza Barba[1] *Denisse Rubio-Cruz*[1] *Hua Xu*[1] *Susmita Bhattarai*[1] *Z. Gordon Jiang*[1]

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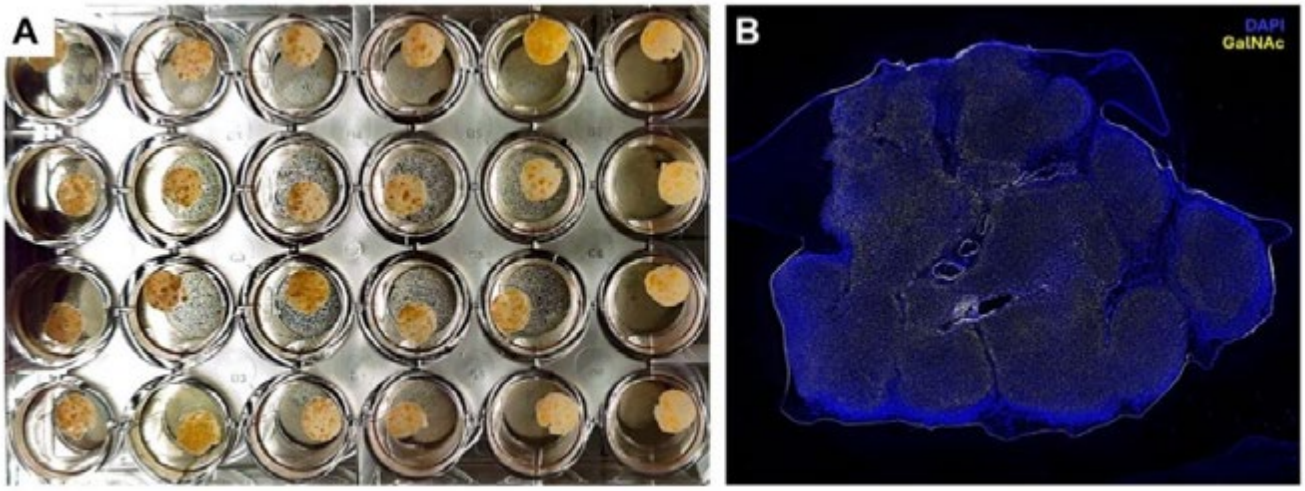
Background: Current liver research largely relies on murine models and immortalized human cells. Live human tissue-derived models are the “holy grails” for studying liver disease pathogenesis and validating drug targets in a human system. Functional and structural integrity in the liver tissue is essential to achieve high fidelity in preclinical drug testing in a human setting, leading to clinical trials. **Methods:** We have successfully developed a translational research program that uses the Precision Cut Liver Slice (PCLS) technology to develop human liver tissue culture models from both healthy and diseased livers. **Results:** Our PCLS program leverages an IRB-approved End-Stage Liver Disease Patient Registry at a regional transplant center and an academic Organ Procurement Organization. A streamlined patient enrollment and consent process enables effective liver tissue procurement from healthy and diseased donors with targeted phenotypes. To achieve the most efficient OR-to-Incubator standard operation protocol, significant efforts were made to optimize and standardize PCLS preparation during tissue procurement, tissue slicing, and tissue recovery with minimal ischemia time and maximal temperature control. We demonstrate the capability to generate PCLS from both healthy and diseased liver tissue and have significantly addressed issues of reproducibility (Fig. A). Tissue cultured under this protocol retains the disease feature of the donor patient for up to 14 days. PCLS preserved human liver architecture with native lobular morphology and multicellular environment by microscopic observations. Quantitative PCR demonstrates robust liver gene expression as well as mature hepatocyte differentiation and parenchymal cell phenotype. In addition, chemical analyzer measured metabolites in the culture media of PCLS aided to understand the functional state of the PCLS. Furthermore, hepatocyte-specific drug delivery was successfully fulfilled in the PCLS models, demonstrating robust GalNAc uptake with a physiological zonation gradient, indicating a high fidelity of human liver phenotype (Fig. B). Efficient gene regulation was observed in PCLS when treated with siRNA, suggesting PCLS can be utilized in siRNA drug testing. **Conclusion:** PCLS is a promising 3D human tissue model that captures human biology and disease pathology. Herein, we report a refined human PCLS model that is reproducible, disease-oriented, and suitable for both hypothesis testing and drug validation in a multicellular human tissue setting.



Disclosures: Sofia Izunza Barba: Nothing to Disclose, Denisse Rubio-Cruz: Nothing to Disclose, Hua Xu: Nothing to Disclose, Susmita Bhattarai: Nothing to Disclose, Z. Gordon Jiang: Nothing to Disclose

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3132 | INFLAMMATION DURING ALCOHOL ASSOCIATED HEPATITIS IS MEDIATED BY LIVER SINUSOIDAL ENDOTHELIAL CELL PRODUCTION OF GALECTIN-9 AND PD-L1

Benjamin Swartzwelter[1] Fiona Xhafi[1] Mengfei Liu[1] Tejasav Sehrawat[1] Vijay Shah[2] Shawna Cooper[3] Sheng Cao[2] Deijian Zhao[1]

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Background: Immune cell infiltration is a key driver of inflammation in alcohol-associated hepatitis (AH). Liver structural cells such as liver sinusoidal endothelial cells (LSECs) secrete chemokines and contribute to this process. Here we describe models for investigating LSEC-T cell interactions in the context of AH, using both single-cell RNA-seq and *in vitro* co-culture systems. **Methods:** Mice were subjected to a modified NIAAA chronic-binge model of AH, with the addition of LPS injection to better simulate the inflammatory response associated with human AH. Liver and peripheral blood were collected for single-cell RNA-seq. Bulk-RNA-seq was performed on livers of healthy control and AH human subjects. We stimulated LSECs with IFN?? and IFN?? and assessed LSEC activation profile by ELISA and qPCR. To identify the impact of LSECs on activated CD8+ T cells, we conducted a co-culture *in vitro* model and assessed the T cell activation profile by flow cytometry, in addition to cell viability. **Results:** In mouse single-cell RNA-seq analysis, Ingenuity Pathway Analysis of top differentially expressed genes identified increased T cell activation in mouse liver compared to peripheral blood in the pair-fed mice, but decreased T cell activation in mouse liver compared to blood in the ethanol-fed mice. In addition, the Programmed-Death (PD) pathway appeared upregulated in the AH liver compared to peripheral blood in AH mice. Through receptor-ligand analysis of LSEC-T cell interactions, we reveal that Galectin-9 (Gal-9) displayed the highest communication probability between LSECs and T cells in the AH liver. In RNA-seq of human AH livers, we found that both PD-L1 and Gal-9 expression are upregulated under AH conditions; the same holds true in mice for both total liver and LSECs. *In vitro,* we found that IFN?? is a strong activator of both Gal-9 and PD-L1 in LSECs. While LSEC-CD8+ T cell co-culture does not affect T cell viability or activation at rest, co-culture of PMA/Ionomycin activated T cells with LSECs significantly increased LSECs PD-L1 and Gal-9 expression and markedly increased CD8+ T cell death. **Conclusion:** AH pathogenesis occurs due in part to T cell infiltration and associated inflammation. We have found that the drivers of T cell senescence and/or apoptosis PD-L1 and Gal-9 are upregulated in LSECs during AH; thus revealing a potential mechanism by which LSECs attempt to regulate T cell signaling and associated inflammation in the AH-affected liver.

Disclosures: Benjamin Swartzwelter: Nothing to Disclose, Fiona Xhafi: Nothing to Disclose, Mengfei Liu: Nothing to Disclose, Tejasav Sehrawat: Nothing to Disclose, Vijay Shah: Boehringer Ingelheim: Consultant, GSK: Consultant, GENFIT SA: Consultant, Intercept Pharmaceuticals, Inc.: Advisor, Korro Bio, Inc.: Consultant, Mallinckrodt Pharmaceuticals: Advisor, Novo Nordisk A/S: Consultant, Resolution Therapeutics, Ltd.: Advisor, Seal Rock Therapeutics, Ltd.: Consultant, Surrozen: Advisor, Shawna Cooper: Nothing to Disclose, Sheng Cao: Nothing to Disclose, Deijian Zhao: Nothing to Disclose

3133 | THIRTY-DAY READMISSIONS AMONG PATIENTS WITH ALCOHOLIC HEPATITIS, RISK FACTORS, IMPACT ON MORTALITY AND HEALTHCARE RESOURCE UTILIZATION: A NATIONWIDE ANALYSIS

Shahryar Khan[1] Ahmad Khan[2] Aamer Ahmad[2] Mashal Alam Khan[2] Muhammad Abu Bakkar[2] Hafsa Parveen[2]

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Background: Alcoholic hepatitis (AH) is a distinct, acute, inflammatory liver disease, most often associated with prolonged, heavy alcohol consumption with a poor prognosis. Patients are associated with high rates of hospital admissions and mortality due to sudden liver decompensation or relapse to alcohol. We aimed to investigate hospitalization characteristics, the rate of hospital readmissions, and outcomes for 30-days readmissions of AH. **Methods:** We retrospectively analyzed the 2020 Nationwide Readmissions Database to identify patients hospitalized with Alcoholic hepatitis. Discharges were included if they were adults, urgent/emergent and had a principal ICD-10 CM code indicating Alcoholic hepatitis. A readmission was defined as the first admission to any hospital for any non-trauma diagnosis within 30 days of the index admission. Same day admissions and

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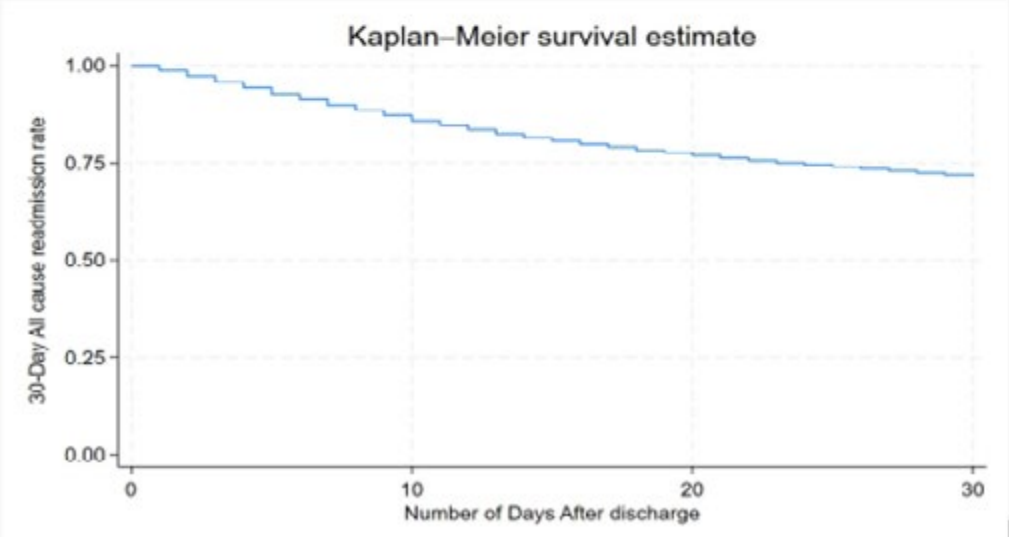
discharges were excluded. The primary outcome was 30-day readmission. We compared mortality during index hospitalization and during 30-day readmission, causes of readmissions, and resource utilization. Independent risk factors for readmission were identified using multivariate cox regression analysis. **Results:** The number of admissions for Alcoholic hepatitis was 32,658. The mean age was 49 years (48.8-49.4) and 38.8% of patients were female. Alcoholic Hepatitis specific 30-day readmission rates was 28.37%. The in-hospital and 30-day mortality rates were 6.9% and 8.5%, respectively. The in-hospital mortality rate for readmitted patients was 9.3%. The most common 5 principal diagnoses for readmissions were Ascites (24.7%), Alcoholic hepatic failure without coma (14%), Sepsis (7.8%), Alcohol withdrawal (2.2%), and Acute Kidney injury (1.72%). Figure 1 shows the Kaplan-Meier curve for 30-Day readmission. Independent predictors of readmission were comorbidities, diabetes, acute kidney injury, malnutrition, anemia, Medicaid, Private insurance, and length of Indexed hospital stay (Table 1). The mean length of stay associated with readmission was 6.9 days, with a total healthcare in-hospital economic burden of $7.33 billion. **Conclusion:** In our large real-life cohort, we found the rate of readmissions in patients with Alcoholic hepatitis are high and are associated with an increase in both mortality and resource utilization. These factors which contribute to higher readmissions can guide in orchestrating guidelines, treatment protocols, and policy changes in preventing readmissions in AH.

Table 1. Independent Predictors of 30-Day Readmission

Variable	Adjusted Hazard ratio (95% confidence interval)	*P* value
Insurance provider		
Medicare	Reference	Reference
Medicaid	1.15 (1.05-1.25)	0.001
Private	0.86 (0.79-0.95)	0.003
Uninsured	0.94 (0.84-1.05)	0.37
Charlson comorbidity score	1.10 (1.08-1.12)	<0.05
Malnutrition	1.09 (1.01-1.17)	0.02
Anemia	1.20 (1.11-1.29)	<0.05
Diabetes	1.21 (1.12-1.31)	<0.05
Acute Kidney Injury	1.13 (1.06-1.25)	<0.05
Length of Stay	1.004 (1.001-1.006)	0.002

Figure 1



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Disclosures: Shahryar Khan: Nothing to Disclose, Ahmad Khan: Nothing to Disclose, Aamer Ahmad: Nothing to Disclose, Mashal Alam Khan: Nothing to Disclose, Muhammad Abu Bakkar: Nothing to Disclose, Hafsa Parveen: Nothing to Disclose

3134 | PREVALENCE AND OUTCOME OF CONCOMITANT HEPATITIS B OR C INFECTION IN ALCOHOL ASSOCIATED LIVER DISEASE

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[1]Seth GS Medical College & KEM Hospital, [2]Department of Gastroenterology, Seth GS Medical College and KEM Hospital, Mumbai

Background: Prevalence of hepatitis B and C in alcohol associated liver disease (ALD) was 1.9%-8% and 3.8%-6% respectively. We aimed to study prevalence and implication of Hepatitis B and/or C infection in ALD. **Methods:** Prevalence of HBV and HCV was assessed in 4780 consecutive patients diagnosed with ALD seen in the liver OPD at presentation, recruited over a period of 5 years. **Results:** The median age was 45[29-78] years and 4380 (91.6%) were men. The presentations were decompensated cirrhosis [3465 (72%)], acute on chronic liver failure (ACLF) [385 (8%)] and alcoholic hepatitis [240 (5%)]. HBsAg, anti-HCV and isolated total Hepatitis B core antibody (anti-HBcAb) were positive in 155 (3.2%), 60(1.3%), 120 (2.5%) patients respectively. One patient was positive for both hepatitis B and C. The proportion of patients with CTP-C cirrhosis was higher in patients with HBV or HCV infection. More patients died with HBV or HCV infection as compared to those without or those with isolated anti-HBcAb. [Table] There was no difference in prevalence or outcomes in patients with ACLF or alcoholic hepatitis with or without HBV or HCV co-infection. **Conclusion:** HBV and HCV infection is present in 3.2% and 1.3% ALD cases respectively. Concomitant Hepatitis B or C infection but not isolated Anti-HBc positivity in ALD is associated with worse outcomes in patients with decompensated cirrhosis.

TOTAL patients n=4780	CTP C AT ADMISSION	MELD AT ADMISSION	In-Hospital Mortality
HbsAg positive ALD n=155(3.2%)	95 (61%), p<0.05	19, p<0.05	45 (29%), p<0.0001
Anti HCV positive ALD n=60(1.3%)	30 (50%), p<0.05	25, p<0.05	10 (16.6%) p=0.0263
Anti HBc Total Ab positive, n=120(2.5%)	40 (33%)	17	10 (8.3%) p=0.932
Hepatitis B and C negative ALD, n= 4445	1740 (39%)	17	380 (8.5%)

Disclosures: Akash Shukla: Nothing to Disclose, Gautam Jain: Nothing to Disclose, Arun Vaidya: Nothing to Disclose, Vaibhav Padole: Nothing to Disclose

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3135 | IL17 SIGNALING IN LIVER SINUSOIDAL ENDOTHELIAL CELLS MEDIATES INFLAMMATION IN ALCOHOL ASSOCIATED HEPATITIS ◆

Fiona Xhafi[1] Mengfei Liu[1] Benjamin Swartzwelter[1] Tejasav Sehrawat[1] Vijay Shah[2] Shawna Cooper[2] Deijian Zhao[1] Tejasav Sehrawat[1] Sheng Cao[2]

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Background: Alcohol-associated hepatitis (AH) is characterized by marked liver inflammation with dense immune cell infiltration. Numerous cytokines and chemokines are produced by immune cells and liver structural cells, such as liver sinusoidal endothelial cells (LSECs). We have previously shown that LSECs produce chemokines including CXCL1, which attracts neutrophils to the liver in AH models. Here, we aim to explore the upstream regulation of this immune activation, particularly the role of cytokine Interleukin-17 (IL17) in the pathogenesis of AH. **Methods:** RNA-sequencing was performed on liver tissue from patients with AH compared to healthy controls, and differentially expressed genes were analyzed via ingenuity pathway analysis (IPA). IL17 and TNFα stimulations of human primary LSECs were performed. The effect on CXCL1 expression after siRNA knockdown of IkBz with and without IL17 stimulation was assessed. To further explore IL17 signaling in a murine model, we employed the NIAAA chronic-binge model and modified it with an LPS injection in the AH group to better mimic human AH inflammation. **Results:** IPA analysis of the human AH liver RNA-seq data identified multiple IL17 signaling pathways to be upregulated in AH patients compared to control. IL17 significantly increases the expression of CXCL1 in LSECs, and this effect was synergistic with TNFα stimulation. In a murine AH model, mice fed an alcohol diet and given LPS injections demonstrated increased CXCL1 and IL17 expression and liver neutrophil infiltration compared to pair-fed controls. A transcription factor inhibitor of nuclear factor kBz (IkBz) has been implicated in keratinocytes as a key regulator of the IL17 pathway, but the regulation of the IL17 pathway in LSECs is unknown. We found that IkBz expression increases significantly when stimulated with IL17 and induced synergistically with TNFα. siRNA silencing of IkBz in LSECs attenuated the expression of CXCL1 after IL17 stimulation. **Conclusion:** IL17 may play an important role in the regulation of inflammation in AH, and this effect may be mediated through IL17 activation of LSECs. We also demonstrated the potential regulatory effects of a key transcription factor IkBz in the IL17 signaling cascade in LSECs. Delineating the LSEC IL17 signaling pathway may reveal novel targets for therapeutic intervention.

Disclosures: Fiona Xhafi: Nothing to Disclose, Mengfei Liu: Nothing to Disclose, Benjamin Swartzwelter: Nothing to Disclose, Tejasav Sehrawat: Nothing to Disclose, Vijay Shah: Boehringer Ingelheim: Consultant, GSK: Consultant, GENFIT SA: Consultant, Intercept Pharmaceuticals, Inc.: Advisor, Korro Bio, Inc.: Consultant, Mallinckrodt Pharmaceuticals: Advisor, Novo Nordisk A/S: Consultant, Resolution Therapeutics, Ltd.: Advisor, Seal Rock Therapeutics, Ltd.: Consultant, Surrozen: Advisor, Shawna Cooper: Nothing to Disclose, Deijian Zhao: Nothing to Disclose, Tejasav Sehrawat: Nothing to Disclose, Sheng Cao: Nothing to Disclose

3136 | PERTUBRATIONS IN THE PERIPHERAL T CELL NICHE OF PATIENTS WITH ALCOHOL-ASSOCIATED HEPATITIS PROVIDE MECHANISTIC INSIGHTS INTO IMMUNE PARALYSIS

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Background: Bacterial infections frequently complicate Alcohol-associated hepatitis (AH) and precipitate decompensation or death. The mechanisms of immune paralysis in AH are poorly understood. We analyzed the lymphocyte compartment of AH patients to gain mechanistic insights into how adaptive immune dysfunction may contribute to infection risk in AH patients. We hypothesized that AH patients at-risk for infection have significant perturbations within the T cell compartment that contribute to the immune paralysis phenotype. **Methods:** Peripheral blood mononuclear cells (PBMC) from patients enrolled in the AlcHepNet Observational Study were analyzed via CITE-seq (n = 17; >1x10^5 total cells), a single-cell sequencing modality that provides both transcriptome and surface protein data. T cell receptors (TCR) sequencing of patient-matched PBMC was also performed to fully characterize the T cell repertoire. AH patients at-risk for infection (AH-inf; diagnosed bacterial infection within 30 days of blood draw; n = 5) were compared to lower risk AH patients (AH-low; n = 5), heavy drinkers (HD; n = 3), and healthy controls (HC; n = 4). Bioinformatics analysis was performed with Seurat

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Packages (R) and Ingenuity Pathway Analysis (IPA). **Results:** AH patients had lower frequency of circulating total CD4 and CD8 T cells while B cell frequencies remained unchanged. Subset analysis of these lineages showed that memory T cells, particularly effector memory (T_{EM}) and central memory (T_{CM}), were depleted in AH-inf patients while naïve T cells were preserved. Of note, there was no significant difference between the average MELD of AH-inf (29±8) and AH-low (25±4) patients (p = 0.43). The transcriptomes of bulk CD4 and CD8 T cells from AH-inf and AH-low patients were compared, which revealed that AH-inf T cells had features suggestive of an exhausted phenotype. AH-inf CD4 T cells had lower predicted activity of IFN-γ /IL-1β/TNF signaling and higher activity of IL-10 signaling. Functional analysis predicted that AH-inf CD4 T cells had impaired inflammatory and proliferative responses and a phenotype like cancer-associated T cells. Notable genes that were more highly expressed in AH-inf CD4 T cells included SOCS3 and FOXP3, which are known to suppress cytokine production and promote T_{reg} development, respectively. Notable genes that were downregulated in AH-inf CD4 T cells compared to AH-low patients include IFNG, STAT1, IRF 2/5/7, and JAK2. These are genes involved in interferon signaling. **Conclusion:** Single-cell sequencing analysis of the lymphocyte compartment of AH patients at-risk for infection suggested that T cell exhaustion and depletion contribute to the immune paralysis that occurs in severe AH. The memory T cell niche may also harbor biomarkers of infection risk in the setting of AH. Further mechanistic studies and predictive modeling are warranted to validate these findings.

Disclosures: Brett McGettigan: Nothing to Disclose, Dawood Al Dawood: Nothing to Disclose, Harmeet Malhi: Nothing to Disclose, Vijay Shah: Boehringer Ingelheim: Consultant, GSK: Consultant, GENFIT SA: Consultant, Intercept Pharmaceuticals, Inc.: Advisor, Korro Bio, Inc.: Consultant, Mallinckrodt Pharmaceuticals: Advisor, Novo Nordisk A/S: Consultant, Resolution Therapeutics, Ltd.: Advisor, Seal Rock Therapeutics, Ltd.: Consultant, Surrozen: Advisor

3137 | HEPATIC METHYLTRANSFERASE PROTEINS MEDIATE PNPLA3-I148M-DRIVEN LIPID DROPLET DYNAMICS IN FATTY LIVER ◆

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Background: The accumulation of Lipid droplets (LDs) characterizes fatty liver in metabolic dysfunction-associated fatty liver disease (MAFLD) and alcohol-associated liver disease (ALD), closely tied to genetic variants, particularly *PNPLA3*-I148M. The methyltransferase-like (METTL) family proteins, important in various biological functions, have unclear roles in fatty liver. To determine whether liver specific METTL proteins plays a role in *PNPLA3*-I148M-driven LD dynamics in fatty liver. **Methods:** A bioinformatic analysis of transcriptome and proteome profiled METTL expression in livers from MAFLD and ALD patients, along with mouse studies. Phosphoproteomic analysis was performed on MAFLD patient livers. Human and mouse hepatocytes were treated with ethanol under METTL knockdown (KD) to study their role on LD formation, observed via confocal imaging. Molecular docking predicted interactions between *PNPLA3*-I148M and METTLs. Protein interactions were studied using protein truncation and immunoprecipitation-western blotting. **Results:** METTL7B and its human homolog, METTL7A, showed high and hepatic-specific expression among METTLs from both mouse and human, along with the validation in isolated primary hepatocytes. METTL7B formed a physical heterodimer with METTL7A with the requirement of its N-terminal region (1-23 aa) and protein binding domain (173-244aa). A significant increase in METTL7A phosphorylation, particularly at site METTL7A-S53 (P<0.001), was observed in liver tissues from biopsy-proven fatty liver patients (n=57) compared to healthy cohorts (n=10). The increase of METTL7A-S53 significantly correlated with ALT (P<0.05) and AST (P<0.05) levels, as well as clinical scores indicating steatosis (p<0.001), inflammation (p<0.001), and fibrosis (P<0.05). METTL7B KD**,** METTL7A KD, and the inactive mutation of METTL7A-S53A significantly suppressed ethanol induced LDs accumulation in hepatocyte cultures. Interestingly, molecular docking revealed *PNPLA3*-I148M interaction with METTL7A and METTL7B, yielding RMSD scores of 1.1 for METTL7A, 1.0 for METTL7B, 0.9 for METTL7A-S53, 26.7 for METTL7A-S53A, and 0.6 for METTL7A-S53D. Under ethanol stimulation, *PNPLA3*-I148M significantly increased LD accumulation compared to native *PNPLA3* (P<0.01). Additionally, METTL7A was found to co-localize with *PNPLA3*-I148M around LDs at the ER. METTL7A KD significantly attenuated the accumulation of LDs driven by *PNPLA3*-I148M (P<0.01). Under ethanol stimulation, PNPLA3I148M impaired the trafficking of LDs from Golgi to lysosomes, while METTL7A KD enhanced the clearance of LDs at lysosomes. **Conclusion:** Our study uncovers

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the importance of METTL family proteins, and the role of METTL7A in targeting fatty liver therapy. This finding holds promise for individuals with *PNPLA3*-I148M variant.

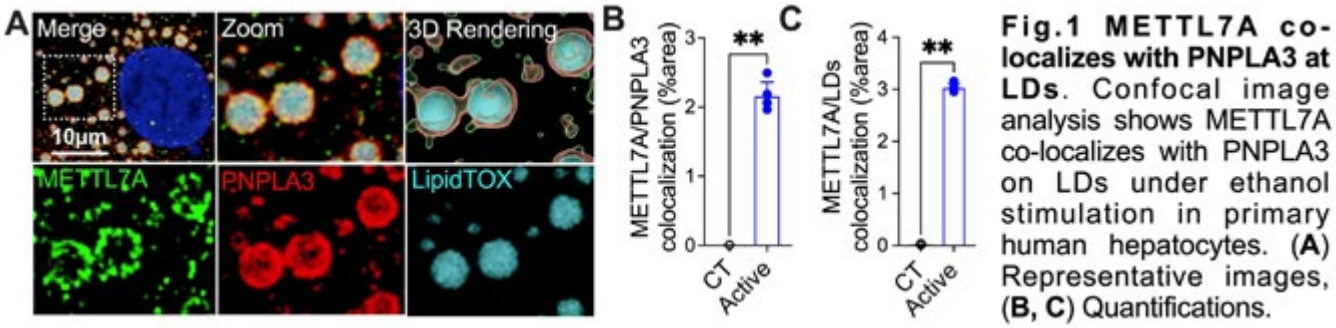

Fig.1 METTL7A co-localizes with PNPLA3 at LDs. Confocal image analysis shows METTL7A co-localizes with PNPLA3 on LDs under ethanol stimulation in primary human hepatocytes. (**A**) Representative images, (**B, C**) Quantifications.

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3138 | MEDICATIONS FOR AUD IN PATIENTS WITH ALCOHOL-ASSOCIATED CIRRHOSIS OR HEPATITIS: NO HEPATOTOXICITY, BUT SIDE-EFFECT RISKS AND DECOMPENSATION

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Background: Medications for alcohol use disorder (MAUD) are an under-utilized treatment, particularly in patients with alcohol-associated cirrhosis (AC) or alcohol-associated hepatitis (AH) due to a lack of data. The aim of this study is to examine the safety and tolerance of MAUD in patients with AC or AH receiving hepatology care. **Methods:** In this retrospective study, patients with clinically diagnosed AC and AH receiving hepatology care were identified at two centers: Massachusetts General Hospital (MGH) and Mount Sinai Hospital (MSH). At MGH, a database was used to identify patients from the Alcohol Liver Evaluation (ALivE) inpatient service with hepatology follow-up in an outpatient integrated clinic. At MSH, patients taking MAUD were identified by ICD-10 codes for AC and AH while receiving hepatology (non-integrated) care. The primary outcome of analysis was elevated liver tests after starting MAUD. Secondary outcomes examined were side-effects, hepatic decompensation events, and change in alcohol use. **Results:** From 2018 to 2024, 26 patients with AC (n=22) and AH (n=4) under hepatology care were started on MAUD. Median age was 54 years (IQR 48-60), 62% male, 35% White, 31% unmarried, and 62% with public insurance. Median MELD score at MAUD start was 14 (IQR 10-18), and 50% had a history of decompensation, most commonly ascites (50%), variceal hemorrhage (38%), and HE (29%). While median MELD scores were similar, 16 (IQR 10-20) for MGH v 12 (IQR 10-16) for MSH, p=0.08, history of decompensation was more common in MGH (80%) compared to MSH (50%). Most patients (82%) were not engaged in alcohol rehab at MAUD initiation. While MGH patients were more likely to start MAUD as an inpatient compared to MSH (76% v 13%, p<0.01), MAUD prescribing by hepatology providers was similar (80% v 77%, p=0.83). Gabapentin (39%), baclofen (21%) and naltrexone (21%) were the top MAUD prescribed. Median duration of MAUD (data censured after 6 months) was longer when started as outpatient compared to inpatient (6 months [2.75-6] v 2 months [0.625-5.5], p<0.01). Overall, baseline median AST, ALT, ALP, TB, and INR levels were 83 U/L, 32 U/L, 110 U/L, 2.6 mg/dL, and 1.4, respectively. Mean changes from baseline after MAUD were -5%, 9%, 11%, -10%, and 7%, respectively (Figure 1). Overall, 82% experienced MAUD side-effects, with fatigue, nausea, slow cognition being the most common. Side-effects led to MAUD cessation in 28% of MGH patients compared to 50% of MGH patients, p=0.19. Hepatic decompensation events after MAUD initiation were more frequent in MGH (30%) patients compared to MSH (0%, p<0.01). There were similar self-reported reductions in alcohol use at MGH (60%) and MSH (64%) while on MAUD. **Conclusion:** Medications for AUD in patients with alcohol-associated cirrhosis or hepatitis lack hepatotoxicity, but frequently cause side-effects. The practice setting of MAUD initiation, MELD, and prior decompensation may affect patient tolerance and risk of decompensation.

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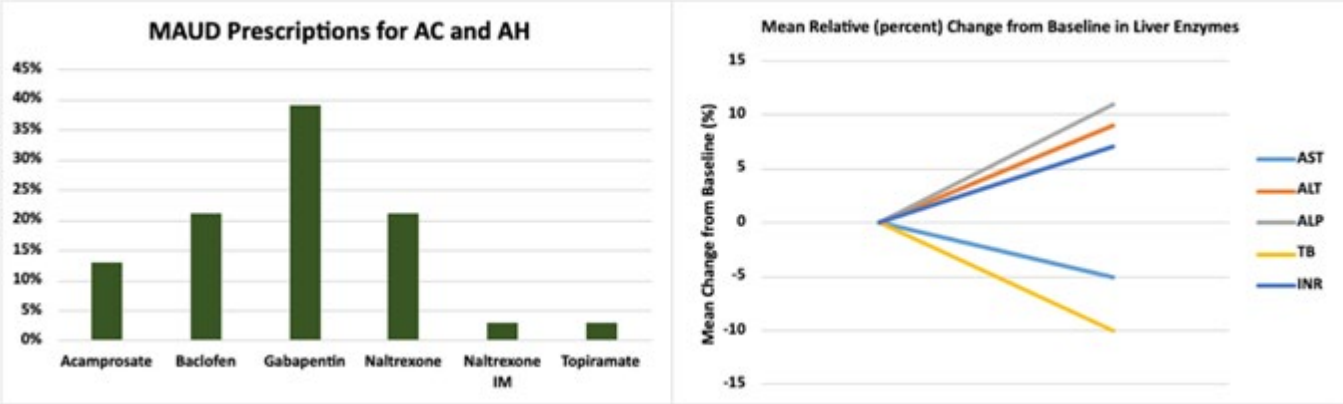

Disclosures: Gene Im: Consultant relationship with KorroBio; Has not ended; Device support for research relationship with Echosens; Has not ended; Advisor relationship with Novo Nordisk; Has not ended; Consultant relationship with Alimentiv; Has not ended, Michael Butler: Nothing to Disclose, Rohit Nathani: Nothing to Disclose, Manhal Izzy: Nothing to Disclose, Jay Luther: Nothing to Disclose, Esperance Schaefer: Nothing to Disclose

3139 | ROLE OF GHRELIN HORMONE IN THE DEVELOPMENT OF ALCOHOL-ASSOCIATED LIVER DISEASE VIA DYSREGULATING GLP-1 RECEPTOR-MEDIATED SIGNAL TRANSDUCTION

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Background: Metabolic dysfunction influences the development of several liver diseases of various etiologies, including alcohol-associated liver disease (ALD). It is known that organ crosstalk, specifically gut-pancreas-adipose-liver interplay, regulates major energy metabolic pathways such as lipid and carbohydrate metabolism via peptide hormones. Our previous studies revealed that the alcohol-induced rise in serum ghrelin reduces insulin secretion despite an increase in an incretin, glucagon-like peptide-1 (GLP-1). Such increase in GLP-1 was not observed in the ethanol-fed ghrelin receptor knockout (GHSR-KO) rats that were insulin-sensitive and resistant to ALD development. Further, *in vitro* studies identified that ghrelin inhibits GLP-1 analog-induced hepatic triglyceride breakdown, further suggesting that ghrelin/GHSR likely interferes with GLP-1 receptor (GLP-1R)-mediated signaling. This study was conducted to identify whether GHSR-GLP-1R dimerization is responsible for the observed reduced GLP-1 function. **Methods:** To identify the receptor interactions, hepatocytes transfected with fluorescently labeled GHSR (RFP) and GLP-1R (GFP) plasmids were treated with ghrelin for 4h followed by examination by Confocal microscopy. In addition, receptor-receptor interactions were examined by immunoprecipitating GLP-1R (by GFP) in the cellular lysates of these cells and subjecting them to further analyses. Furthermore, we used *bioluminescence resonance energy transfer* (BRET) assay to characterize the receptor-receptor dimerization. Simultaneously, *in-silico* prediction of protein-protein interaction was performed using Bio Luminate version 4.9. **Results:** Confocal microscopic examination revealed increased co-localization of GHSR and GLP-1R in transfected hepatocytes treated with ghrelin. This increased receptor interactions were also confirmed with Western Blot analysis of the GLP-1R immunoprecipitated sample. BRET assay further confirmed that indeed GLP-1R and GHSR dimerize that could be responsible for reduced GLP-1/GLP-1R-mediated protective downstream events. The *in-silico* studies revealed several possible sites of interaction between GHSR and GLP-1R that are currently being investigated using site-directed mutagenesis method. **Conclusion:** These results indicate a fundamental role of the alcohol-induced increases in ghrelin levels in impairing GLP-1/GLP-1R-mediated signal transduction in hepatocytes (and likely other organs such as pancreas and adipose) to promote the development of ALD.

Disclosures: Karuna Rasineni: Nothing to Disclose, Sundararajan Mahalingam: Nothing to Disclose, Ramesh Bellamkonda: Nothing to Disclose, Ojeshvi Ethiraj: Nothing to Disclose, Carol Casey: Nothing to Disclose, Kusum Kharbanda: Nothing to Disclose

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3140 | DRINKING BEHAVIOR IN THE AHFIRM TRIAL AS MEASURED BY PHOSPHATIDYL ETHANOL

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[1]Rush University Medical Center, [2]Bon Secours Liver Institute, [3]Stanford University Medical Center, [4]Piedmont Hospital Transplant Services, [5]Liver Institute Dallas, [6]Université Libre de Bruxelles, [7]University Hospital at Lille, [8]Northwell Health, [9]Cedars-Sinai Medical Center, [10]Northwestern Memorial Hospital, [11]Westchester Medical Center, [12]Eastern Health, [13]Prince Alfred Hospital and University of Sydney, [14]University of Texas Southwestern Medical Center, [15]Cleveland Clinic, [16]Royal Adelaide Hospital, [17]Imperial College London, [18]University of Louisville, [19]Durect

Background: Phosphatidyl ethanol (PEth) is a sensitive biomarker for alcohol consumption that can detect a single drinking episode for up to 12 days due to its prolonged bloodstream half-life (5.5 days average). Sensitive analytical methods such as LC/MS/MS can detect as little as 20 ng/mL. The aim of determining PEth concentrations in the AHFIRM study was to assess the level of alcohol consumption at trial entry and to detect episodes of relapse. **Methods:** AHFIRM was a phase 2b double-blind, placebo-controlled trial comparing 1 or 2 doses of larsucosterol 30mg or 90mg IV in patients with severe alcohol associated hepatitis (AH). 307 patients were enrolled and 301 received at least one dose of study drug or placebo. Entry criteria included daily consumption of >40 grams of alcohol for females and >60 grams for males with <8 weeks of abstinence and <8 days of systemic corticosteroids. PEth blood concentrations were measured at screening and on days-7, -14, -28, -60, and -90 after dosing. PEth was assayed at a central laboratory (NMS Labs) using a sensitive LC/MS/MS method with a lower limit of detection of about 20 ng/mL. **Results:** At the screening visit, PEth concentrations for all subjects were: [median, range] 400,15-3680 ng/mL, first & third quartiles [Q1&Q3] 30 & 586 ng/mL). 74 subjects had PEth >30ng/mL and 144 subjects had PEth >200ng/mL. PEth concentrations gradually decreased up to Day-28: median, range (15, 10-2560), Q1&Q3 (15, 15). At day-28,192 subjects had PEth >30 ng/mL and 10 subjects had PEth >200 ng/mL. Subjects then gradually relapsed; by day-60, 19 previously abstinent subjects had relapsed. On Day 90, an additional 18 subjects relapsed. 15 subjects never stopped drinking during the trial (positive PEth at each visit). For surviving subjects at day-90, the median, range (15, 10-4600), Q1&Q3 (15,25), 148 subjects had PEth >30 ng/mL and 39 subjects had PEth ≥200 ng/mL. There were no significant differences in PEth between treatment groups. None of the 20 subjects who received a liver transplant resumed drinking after transplant. 77 subjects received AUD drugs such as acamprosate, gabapentin, and naltrexone. **Conclusion:** Repeated PEth assay is a sensitive means of assessing drinking behavior. In AHFIRM subjects there was wide variability in alcohol consumption as measured by PEth. Many subjects were able to abstain from alcohol, but some subjects returned to drinking and a small minority continued drinking throughout the trial.

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3141 | SUSTAINING A-KINASE ANCHORING PROTEIN-12 EXPRESSION DURING ALCOHOL EXPOSURE MAINTAINS PKA SIGNALING AND REGULATES STEATOSIS

Chandana Thimme Gowda[1] MALLIKARJUNA SIRAGANAHALLI ESHWARAIAH[1] Nirmala Mavila[2] Jiaohong Wang[1] Maria Lauda Tomasi[1] Komal Ramani[2]

[1]Cedars Sinai Medical Centre, [2]Cedars-Sinai Medical Center

Background: Alcohol-associated liver disease (ALD) is associated with disrupted lipogenic signaling and fat accumulation in the liver. A-kinase anchoring protein 12 (AKAP12) is a scaffolding partner of protein kinase A (PKA). Activation of PKA by cAMP inhibits lipogenesis and facilitates fatty acid oxidation (FAO). Our preliminary analysis demonstrated that AKAP12's interaction with PKA was reduced in alcohol-exposed human hepatocytes and alcohol-fed mice (10-day +1 binge NIAAA model). AKAP12-PKA scaffold was reduced in human alcoholic steatosis subjects. PKAs lipogenic targets, acyl CoA carboxylase (ACC1) and pyruvate dehydrogenase (PDHA) interacted with AKAP12 in hepatocytes and interaction was suppressed by alcohol. We therefore hypothesized that AKAP12-PKA crosstalk sustains PKA activity and regulates alcoholic steatosis. The conceptual goal is to understand how modulation of AKAP12-PKA signalosome may influence ALD outcomes. **Methods:** AKAP12-PKA scaffold was examined by co-immunoprecipitation and proximity ligation. Lipid accumulation was evaluated by Nile red and triglyceride quantification. Liver injury was measured by ALT/AST levels. PKA activity was evaluated by ELISA. AKAP12's PKA interaction site was modified by CRISPR editing. **Results:** Alcohol suppressed AKAP12 expression, reduced its PKA scaffolding activity and inhibited PKA activity in human hepatocytes. Overexpression of *AKAP12* restored alcohol suppressed PKA activation and inhibited lipid accumulation, whereas silencing had the reverse effect. Since *AKAP12* sustained PKA activity, we evaluated whether the AKAP12-PKA scaffold was important in lipid homeostasis. Inhibition of AKAP12-PKA interaction by CRISPR mutation of AKAP12's PKA binding domain dramatically suppressed PKA activity, PKA-catalyzed inhibitory phosphorylation of its lipogenic substrate, ACC1, enhanced lipid accumulation and reduced FAO in hepatocytes. Mechanistically, we found that alcohol induced binding of PKA to an inhibitory kinase, STK25, that caused S77/S83 phosphorylation and inactivation of PKA and suppressed the AKAP12-PKA scaffold. Sustained phosphorylation of PKA by a S77E/S83E mimetic mutation suppressed PKA-AKAP12 interaction and induced lipid accumulation. Forced expression of *AKAP12* in alcohol-fed mice suppressed lipid accumulation and liver injury, further reiterating the role of AKAP12 in lipid homeostasis. **Conclusion:** The AKAP12-PKA scaffold controls lipogenic signaling, disruption of which favors steatosis during ALD.

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3142 | INTEGRATED HEPATOLOGY AND ADDICTION MEDICINE CONSULTATION FOR HOSPITALIZED PATIENTS WITH ALCOHOL USE DISORDER REDUCES FUTURE LIVER-RELATED DECOMPENSATING EVENTS

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Background: While multiple factors contribute to rising mortality seen with alcohol-associated liver disease (ALD), one deficiency is clear: most patients with ALD are diagnosed at an advanced stage. Accordingly, preventative strategies to diagnose and treat early-stage ALD are needed. To address this deficiency, we developed a novel hepatology-led inpatient consult team (ALivE) that works in concert with the inpatient addiction team to evaluate patients with AUD who have no past or current evidence of advanced liver disease. In this work, we sought to determine if ALivE impacts future liver-related outcomes. **Methods:** Included patients were hospitalized, had a diagnosis of alcohol use disorder (AUD), and had no prior history of liver disease and no signs of active liver disease during their hospitalization. We compared patients seen by the ALivE service (intervention) at Massachusetts General Hospital to those who received standard of care at our neighboring, tertiary-care hospital (Brigham and Women's Hospital) over the same time period of 2020-2024. We followed patients from time of consult (ALivE) or admission (control) to 05/01/24, examining for the development of any liver decompensating event (ascites, variceal bleeding, hepatic encephalopathy, hepatorenal syndrome, hepatocellular cancer, or death) as our primary outcome. Continuous variables were compared using an unpaired, 2-tailed t test with Welch correction, whereas categorical variables were compared using the Fisher exact test. We used Cox proportional hazards mulitvariable regression models to account for the follow-up duration, generating adjusted hazard ratios (HRs) for the development of a liver decompensating event. **Results:** 423 patients in the ALivE group and 96 patients in the control group met inclusion criteria. Patients shared similar demographic and clinical data, including age, sex, race, insurance status, admitting diagnoses, and serum albumin, coagulation, liver biochemical tests. While fibrosis assessment was not performed in the control group (not standard of care), 50/423 (12%) of patients evaluated by ALivE were found to have advanced fibrosis/cirrhosis on initial testing. More patients seen by ALivE were discharged on medical alcohol therapy (P<0.01). Total follow-up time was 1256 years. We found that patients seen by ALivE were less likely to develop a liver-related outcome during the follow-up period compared to controls (aHR: 0.50, 95%CI: 0.27-0.90, P:0.03). Specifically, ALivE patients were less likely to develop variceal bleeding (aHR: 0.13, 95%CI:0.03-0.51, P<0.005) and hepatic encephalopathy (aHR:0.24, 95%CI:0.08-0.73, P:0.01). There was no difference in ascites or HRS development, or mortality. **Conclusion:** These data support integrated hepatology and addiction care for hospitalized AUD patients without overt liver disease as a strategy to limit progression of underlying liver disease and hepatic decompensation.

Disclosures: Jay Luther: Nothing to Disclose, Paul George: Nothing to Disclose, Michael Butler: Nothing to Disclose, Prasanna Challa: Nothing to Disclose, Esperance Schaefer: Nothing to Disclose, Russell Goodman: Nothing to Disclose, Wei Zhang: Nothing to Disclose

3143 | PHOSPHODIESTERASE 4 INHIBITION MITIGATES ALCOHOL-INDUCED INTESTINAL DYSFUNCTION AND THE DEVELOPMENT OF ALCOHOL-ASSOCIATED STEATOHEPATITIS (ASH)

Mary Nancy Walter[1] DIEGO MONTOYA DURANGO[1] Walter Rodriguez-Alvarez[1] Yali Wang[1] Claudio Maldonado[1] Shirish Barve[2] Craig McClain[1] Leila Gobejishvili[1]

[1]University of Louisville, [2]University of Kentucky Medical Center

Background: Recent studies identified phosphodiesterases (PDEs) as pathogenic players in gastrointestinal disorders. However, their role in alcohol-induced intestinal barrier dysfunction and gut-liver axis is unknown. Hence, we examined the effect of alcohol on colonic and hepatic PDE expression changes in a mouse model of alcohol-associated steatohepatitis (ASH). We also evaluated the therapeutic effect of PDE4 inhibition on alcohol-induced intestinal barrier dysfunction and liver injury. **Methods:** Male C57Bl/6 mice were fed a high fat, high cholesterol diet with and without ethanol and a weekly alcohol binge in an eight-week Tsukamoto-French intragastric feeding model of ASH. Starting from week 4, mice were treated with a PDE4 inhibitor, rolipram,

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or placebo thrice a week. Liver damage was evaluated with plasma injury markers and immunohistochemical staining. Liver and colon tissue bulk RNA sequencing and differential expression analysis were performed, and the data were further analyzed using Clarivate Analytics MetaCore software. **Results:** Alcohol increased *Pde1b*, *Pde4a*, and *Pde8a* expression in the colon and *Pde1a, Pde4a/d, Pde5a*, and *Pde10a* in the liver. MetaCore pathway analysis showed that the greatest number of differentially expressed colonic genes were involved in the regulation of the actin cytoskeleton, which is crucial in maintaining intestinal barrier integrity. *Actr2, Rhoa, Dstn, Arpc2*, and *Myl12a* were among the genes significantly downregulated with alcohol feeding and upregulated with rolipram. Additionally, *Rhov, Myl12b, Rock2, Vcl*, and *Actb* were upregulated with rolipram, indicating that PDE4 inhibition was able to stabilize the cytoskeleton and gut barrier. Furthermore, the genes relevant to mucous layer composition, mucins 1, 3, and 13, and antimicrobial lectin *Reg3b* expression were increased with rolipram. Expression of tight junction protein Tjp2 and claudins 4, 7, and 8 was also increased with rolipram treatment, further supporting intestinal barrier integrity. PDE4 inhibition led to a marked attenuation of alcohol-induced hepatocyte apoptosis, inflammation, and fibrogenesis. **Conclusion:** Our findings demonstrate that chronic alcohol consumption alters PDE expression in both the colon and liver. PDE4 inhibition prevents destabilization of the actin cytoskeleton responsible for epithelial barrier integrity and modulates gut mucosal homeostasis in ALD. These observations also suggest that PDE4 inhibition mitigated the development of ASH by regulating the gut-liver axis.

Disclosures: Mary Nancy Walter: Nothing to Disclose, DIEGO MONTOYA DURANGO: Nothing to Disclose, Walter Rodriguez-Alvarez: Nothing to Disclose, Yali Wang: Nothing to Disclose, Claudio Maldonado: EndoProtech, Inc.: Stock – privately held company, EndoProtech, Inc.: Executive role, Shirish Barve: Nothing to Disclose, Craig McClain: Novo Nordisk: Grant/Research Support, Intercept Pharmaceuticals: Grant/Research Support, Altimmune: Grant/Research Support, Target Pharma Solutions: Grant/Research Support, NIH: Grant/Research Support, VAMC: Grant/Research Support, Leila Gobejishvili: Nothing to Disclose

3144 | IL-17 SIGNALING COORDINATES TNFR1-DEPENDENT NF-KB ACTIVATION IN HEPATOCYTES DURING ALD

Raquel Weber[1] Vivian Zhang[1] Gen Yamamoto[2] Ju Youn Kim[3] Ji Young Kim[4] Na Li[5] Hyun Young Kim[1] Wonseok Lee[1] Sadatsugu Sakane[6] Grant Miller[1] Michael Karin[1] David Brenner[7] Tatiana Kisseleva[8]

[1]UCSD, [2]Kyoto University, [3]Hanyang University, [4]Sungkyunkwan University, [5]5Shanghai University of Medicine & Health Sciences, [6]Osaka National Hospital, [7]Sanford Burnham Prebys, [8]University of California, San Diego

Background: Alcohol-associated liver disease (ALD) progresses from steatosis, to steatohepatitis, fibrosis, cirrhosis, and hepatocellular carcinoma (HCC). We have demonstrated that alcohol-injured IL-17RA$^{\Delta Hep}$ mice, devoid of IL-17RA in hepatocytes, were protected from steatosis and fibrosis, but inflammation is not changed. This effect was associated with suppression of IL-17 signaling cascade Act1-TRAF6, and unexpectedly downregulation of TNFRI in injured hepatocytes making them unresponsive to TNF stimulation. TNFRI is increased during ALD leading to the development of ER stress and *de novo* lipogenesis. TNF mediates its functions via activation of TNFRI-TRAF2/5-NF-κB. Here we investigate the relationship between IL-17 signaling and TNF-TNFRI activation of NF-kB. We hypothesized that overexpression of TNFR1 restores the wild type phenotype in ALD-injured IL-17RA$^{\Delta Hep}$ mice. **Methods:** Male IL-17RA$^{\Delta Hep}$ mice (generated by crossing Alb^{Cre} x IL-17RA$^{F/F}$ mice) and age-matched WT IL-17RA$^{F/F}$ littermates were i.p. injected with DEN (25 mg/kg, 14 days old). Mice were then i.v. injected with hepatocyte specific promoter-driven TNFR1-expressing-AAV8 adenovirus (AAV8-TGB-TNFR1) to overexpress TNFR1 in hepatocytes (or control AAV8-TBG-GFP). The mice were fed with high-fat and ethanol diet for 18 weeks. Steatosis, fibrosis and HCC were measured. To identify which of the TNFR1 signaling components were restored in IL-17RA$^{\Delta Hep+AAV8\text{-}TNFR1}$ mice, the protein expression of signaling molecules of IL-17 and TNF pathways were analyzed. **Results:** The overexpression of TNFR1 in IL-17RA$^{\Delta Hep}$ mice failed to restore steatosis and fibrosis but increased the development of HCC by 2-fold compared to IL-17RA$^{\Delta Hep+AAV8\text{-}GFP}$ control. The overexpression of TNFR1 did not restore components of IL-17 signaling, expression of TRAF6 and nuclear Act1. Remarkably, overexpression of TNFR1 failed to restore phosphorylation of IkB or p65 in hepatocytes from ALD IL-17RA$^{\Delta Hep+AAV8\text{-}TNFR1}$ mice. Meanwhile, TNFR1 overexpression induced the phosphorylation of JNK, ERK, p38, AKT, and the activation of STAT3 and STAT5. Our data suggest that IL-17 signaling is required to mount TNF-dependent NF-kB response in ALD hepatocytes. **Conclusion:** The overexpression of TNFR1 in IL-17RA$^{\Delta Hep}$ mice does not restore steatosis and fibrosis but increases HCC. IL-17RA is necessary for TNF mediated NF-kB activation in hepatocytes during ALD, while activation of TNF-STAT3/5 signaling does not depend on IL-17 signaling.

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Disclosures: Raquel Weber: Nothing to Disclose, Vivian Zhang: Nothing to Disclose, Gen Yamamoto: Nothing to Disclose, Ju Youn Kim: Nothing to Disclose, Ji Young Kim: Nothing to Disclose, Na Li: Nothing to Disclose, Hyun Young Kim: Nothing to Disclose, Wonseok Lee: Nothing to Disclose, Sadatsugu Sakane: Nothing to Disclose, Grant Miller: Nothing to Disclose, Michael Karin: Nothing to Disclose, David Brenner: Nothing to Disclose, Tatiana Kisseleva: Nothing to Disclose

3145 | THE DEVELOPMENT, FEASIBILITY, AND USABILITY OF AN ARTIFICIAL INTELLIGENCE-ENABLED CONVERSATIONAL AGENT IN VIRTUAL REALITY FOR PATIENTS WITH ALCOHOL-ASSOCIATED CIRRHOSIS

Yee Hui Yeo[1] Allistair Clark[1] Muskaan Mehra[1] Alexander Kuo[2] Itai Danovitch[1] Hyunseok Kim[1] Karen Osilla[3] Aarshi Vipani[1] Ju Dong Yang[2] Yun Wang[1] Walid Ayoub[2] Hirsh Trivedi[1] Joshua Hakimian[1] Zoe Krut[1] Karisma Suchak[1] Jamil Samaan[1] Rajsavi Anand[1] Tiffany Wu[4] Vijay Shah[4] Omer Liran[1] Brennan Spiegel[1]

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Background: Approximately half of cirrhosis cases are attributable to alcohol, yet most patients do not have access to effective interventions to prevent or reduce drinking. We aimed to develop and assess the feasibility of eXtended-Reality Artificial Intelligence Assistant (XAIA), an AI-enabled, virtual reality (VR)-based conversational intervention for patients with alcohol-associated cirrhosis. **Methods:** Our multidisciplinary research team trained XAIA to employ cognitive behavioral and motivational interviewing techniques derived from established relapse prevention protocols. Our procedures were HIPAA compliant, and our evaluations were IRB-approved. Participants with alcohol-associated cirrhosis engaged with XAIA privately for 30 minutes in one of the nine VR environments (Figure 1A), followed by a 45-minute semi-structured interview debrief session. The intervention usability scale (IUS) was used to measure usability. Thematic content analysis of the interview transcripts was conducted to extract key themes and insights. **Results:** Twenty participants were enrolled, with 65% being males, 45% being non-Hispanic White, 50% having active alcohol use (last drink within the past 3 months), 50% having a college degree or above, and 75% having little to no previous experience using VR. The median MELD 3.0 score was 22. All participants utilized all 30 minutes with XAIA with no severe adverse events reported. The IUS score was considered acceptable (i.e. a score of ≥75) in 78% of participants (Figure 1B). Thematic analysis distilled 509 first-level codes into 35 second-level codes, ultimately identifying 9 overarching themes. In most patients, XAIA quickly established rapport and provided positive reinforcement, actionable goals, and salient advice perceived as non-judgmental. There were 80% of participants stated feeling open towards XAIA, 85% reported the experience as beneficial, 85% noted belief in its potential efficacy, and 90% expressed interest in using XAIA further. Many participants indicated that the privacy, anytime availability, and immersive nature of VR-based psychotherapy were positive attributes of the system. While a minority of participants still preferred human therapists and noted shortcomings in XAIA's interactions and appearance, most patients would recommend it to others. **Conclusion:** Designed to fill an unmet need among patients with alcohol-associated cirrhosis, XAIA is perceived to be a safe, acceptable, easy-to-use, non-judgmental, and immersive VR psychotherapy modality. Studies to examine XAIA's impact on cessation are needed.

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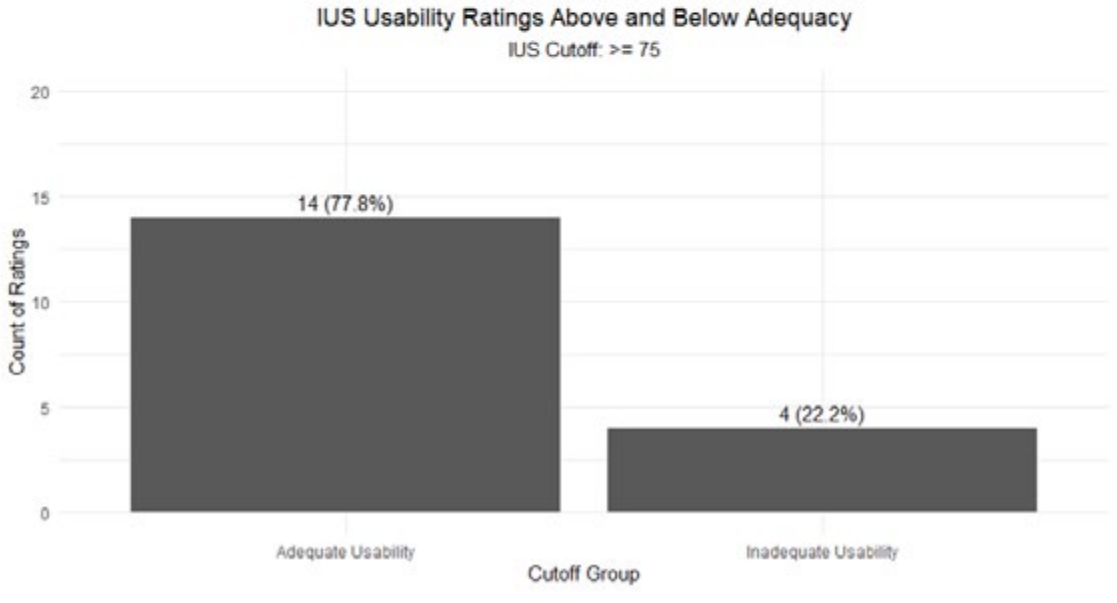
Figure 1 (A) The Virtual Reality Environment of eXtended-Reality Artificial Intelligence Assistant (XAIA) (B) Summary of the Intervention Usability Scale (IUS)

(A)



(B)



Disclosures: Yee Hui Yeo: Nothing to Disclose, Allistair Clark: Nothing to Disclose, Muskaan Mehra: Nothing to Disclose, Alexander Kuo: Nothing to Disclose, Itai Danovitch: Workit Health: No current relationship other than stock ownership, Bexson Biomedical: Board of Directors, Hyunseok Kim: Nothing to Disclose, Karen Osilla: Nothing to Disclose, Aarshi Vipani: Nothing to Disclose, Ju Dong Yang: Consultant relationship with Fujifilm Medical Sciences; Has not ended; Consultant relationship with Exelixis; Has not ended; Consultant relationship with Eisai; Has not ended; Consultant relationship with AstraZeneca; Has not ended; Consultant relationship with Exact Sciences; Has not ended, Yun Wang: Nothing to Disclose, Walid Ayoub: Intercept: Speaking and Teaching, Mirum: Grant/Research Support, GSK: Consultant, GSK: Grant/Research Support, Madrigal: Grant/Research Support, Cymabay: Consultant, Ipsen: Grant/Research Support, Zydus: Grant/Research Support, Hirsh Trivedi: Nothing to Disclose, Joshua Hakimian: Nothing to Disclose, Zoe Krut: Nothing to Disclose, Karisma Suchak: Nothing to Disclose, Jamil Samaan: Nothing to Disclose, Rajsavi Anand: Nothing to Disclose, Tiffany Wu: Nothing to Disclose, Vijay Shah: Boehringer Ingelheim: Consultant, GSK: Consultant, GENFIT SA: Consultant, Intercept Pharmaceuticals, Inc.: Advisor, Korro Bio, Inc.: Consultant, Mallinckrodt Pharmaceuticals: Advisor, Novo Nordisk A/S: Consultant,

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Resolution Therapeutics, Ltd.: Advisor, Seal Rock Therapeutics, Ltd.: Consultant, Surrozen: Advisor, Omer Liran: Nothing to Disclose, Brennan Spiegel: Nothing to Disclose

3146 | SOCIODEMOGRAPHIC DISPARITIES IN ACCESS TO LIVER TRANSPLANTATION WAITLIST IN PATIENTS WITH ALCOHOL ASSOCIATED LIVER DISEASES: A SINGLE CENTER STUDY

Islam Mohamed[1] Mohamad Ali Ibrahim[2] Nikita Rao[2] Bhavik Tadigotla[3] Ahmed El sabagh[2] Mazen ELsheikh[2] Prasun Jalal[2]

[1]Cleveland clinic foundation, [2]Baylor College of Medicine, [3]Baylor college of Medicine

Background: Alcohol- associated liver disease (ALD) has become the leading indication for liver transplantation in the USA. Selection criteria for liver transplantation are still porous due to favorable short-term survival. Racial and social disparities have been identified in patients with ALD. The aim of this study to assess the effect of social determinants of health in access to wait-list for patient with ALD referred for liver transplantation. **Methods:** In this retrospective cohort we included patients with alcohol associated liver disease (ALD) and/or alcoholic hepatitis (AH) referred for evaluation for liver transplantation in 2022 at Baylor College of Medicine. ALD was defined as cirrhosis in patients consuming > 3 drinks (40 g) a day for women and > 4 drinks (60 g) for men in the absence of concomitant liver disease. AH was defined according to the NIAAA diagnostic criteria. Retrospective chart review and collection of sociodemographic and clinical data were performed. Patients were divided into two groups depending on the outcome of the transplant evaluation: listed or not listed. Data was analyzed via Chi-square and Fisher's exact tests for categorical data, and t-test and Mann-Whitney test for continuous data. Multivariate analysis was performed to control confounders. **Results:** A total of 63 patients were included in the study (mean age 50.07 ± 10.86, female 40.3%). Patients were divided into two groups depending on the outcome of the transplant evaluation: not listed (n=24) or listed (n=38). On univariable analysis (table 1), gender, race, ethnicity (Hispanic vs non-Hispanic), and type of insurance (governmental vs non-governmental) did not differ between both groups (all p > 0.05).Similarly, the amount and duration of alcohol consumption and the area deprivation index showed non-statistically significant difference between the two groups. Patients in the listed group had significantly higher level of education (p = 0.023). Smoking and polysubstance use (p = 0.002 and p = 0.059, respectively) were significantly higher in the not listed group while diabetes (p = 0.033), hypertension (p = 0.023), portal hypertension (p = 0.008), and spontaneous bacterial peritonitis (p = 0.009) were more reported in the listed group. On multivariable analysis, only higher educational level (p = 0.039), hypertension (p = 0,039), and portal hypertension (p = 0.027) were significantly associated with the listed group. **Conclusion:** The results of this study showed that financial and social determinants of health doesn't play a fundamental role in access to waitlist in patient referred for liver transplantation. These findings highlight the importance of changing the provider attitude for referral to access transplant wait list for patient with ALD. Study with a larger sample size is warranted to test the association.

Disclosures: Islam Mohamed: Nothing to Disclose, Mohamad Ali Ibrahim: Nothing to Disclose, Nikita Rao: Nothing to Disclose, Bhavik Tadigotla: Nothing to Disclose, Ahmed El sabagh: Nothing to Disclose, Mazen ELsheikh: Nothing to Disclose, Prasun Jalal: Nothing to Disclose

3147 | POST-TRANSPLANT OUTCOMES IN PATIENTS WITH AND WITHOUT ALCOHOL RELAPSE FOLLOWING LIVER TRANSPLANTATION FOR ALCOHOLIC ASSOCIATED LIVER DISEASE

Rachana Punukollu[1] Nilofar Najafian[1] Suaka Kagbo-Kue[2] Laura budvytyte[1] Margaret Liu[1] Xingjie Li[1] Alyssa McGary[1] David Chascsa[3] Channa Jayasekera[3] Michele Barnhill[1] Blanca Lizaola-Mayo[3] Caroline Jadlowiec[3] Rolland Dickson[1]

[1]Mayo Clinic, [2]Intermountain Health, [3]Mayo Clinic Arizona

Background: Alcohol-associated liver disease (ALD) is the most common indication for liver transplantation (LT) in the US. We aim to identify predictive risk factors for relapse among patients receiving LT for ALD and assess post LT outcomes compared to LT for non-ALD indications **Methods:** Patients who underwent LT at Mayo

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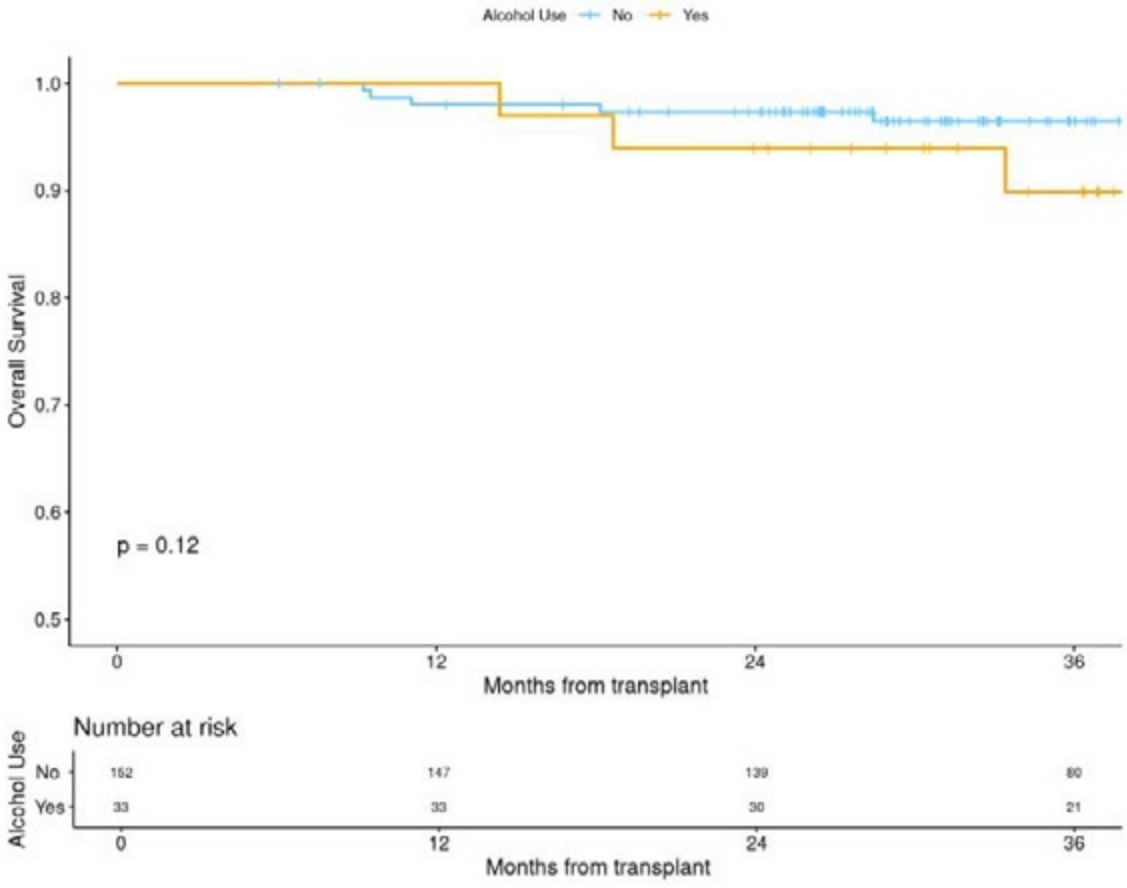
Clinic Arizona from 2019 to 2022 were reviewed retrospectively. Medical comorbidities, clinical and psychosocial characteristics were used to assess relapse in ALD patients. Patient and graft survival were assessed at 1 and 2 years based on relapse and by alcohol transplant pathway: Traditional (≥6 months of sobriety pre-LT); Expedited (cirrhotic patients < 6 months sobriety); Acute alcohol associated hepatitis (AH). results were compared to LT for non-ALD indications. **Results:** 209 patients underwent LT for ALD and 796 for non-ALD indications. 24 ALD patients were excluded given lack of alcohol screening. Overall, 162 (88%), 15(10%) and 4(3%) patients were transplanted via traditional, expedited and AH pathway respectively. Relapse occurred in 17.8%(n=33) with no difference between pathways (p=1.000). Significant factors for relapse vs no relapse included younger age, (mean age 52.8 vs 56.4 years, p=0.048), male sex (84% vs, 55%, p<0.001), shorter pre-LT sobriety (mean 1.7 vs 2.7 years, p=0.03), comorbid psychiatric disease (70% vs 33%, p<0.001), anxiety (36% vs 19%, p=0.038), depression (42% vs 22%, p=0.027) and higher initial SIPAT score (mean 31.9 vs 25.4, p=0.012).In those with recidivism, 48% had sustained alcohol use and 25% completed relapse therapy post-LT. Relapse was detected by alcohol testing alone in 23/33, by self-report in 2/33, both self-report and alcohol testing in 8/33 patients. In those that relapsed vs no relapse, overall survival at 1-year was 100% and 98%, and at 2 year 93.9% and 97.3% (p=0.12). Graft survival at 1-year was 93.9% and 96.7% and at 2 year 90.9% and 96% (p=0.31) respectively. There were no differences in patient (p=0.084) and graft survival (p=0.87) between ALD and non-ALD patients. **Conclusion:** Alcohol recidivism was seen in all transplant pathways and was associated with acceptable but trend toward lower overall patient and graft survival. Identification and modification of risk factors pre-LT such as psychiatric comorbidities and early identification of post LT recidivism with routine alcohol testing post LT to allow intervention is essential to improve long term outcomes for patients transplanted for ALD.

Figure : Overall Survival by Alcohol Use Post-Transplant



Disclosures: Rachana Punukollu: Nothing to Disclose, Nilofar Najafian: Nothing to Disclose, Suaka Kagbo-Kue: Nothing to Disclose, Laura budvytyte: Nothing to Disclose, Margaret Liu: Nothing to Disclose, Xingjie Li: Nothing to Disclose, Alyssa McGary: Nothing to Disclose, David Chascsa: Nothing to Disclose, Channa Jayasekera: Nothing to Disclose, Michele Barnhill: Nothing to Disclose, Blanca Lizaola-Mayo: Nothing to Disclose, Caroline Jadlowiec: Nothing to Disclose, Rolland Dickson: Nothing to Disclose

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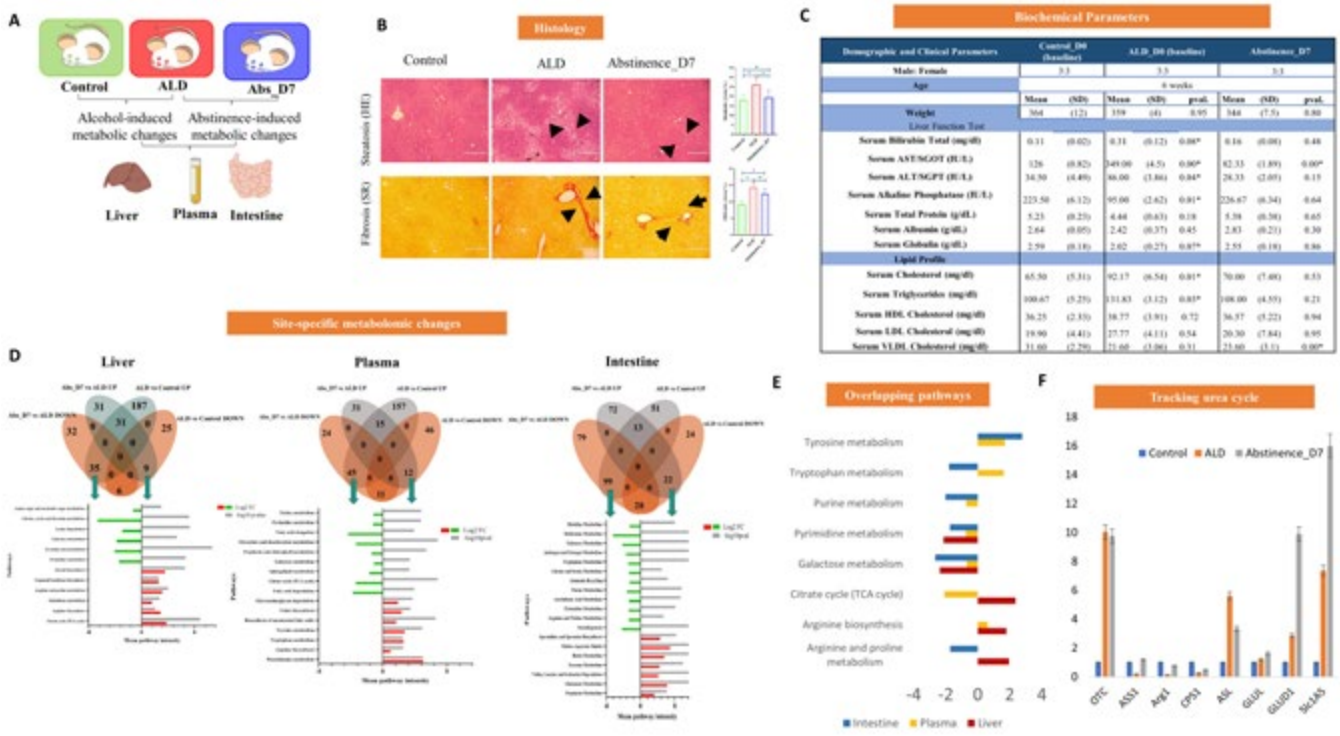
3148 | ABSTINENCE TRIGGERS SITE-SPECIFIC METABOLOMIC CHANGES IN THE RESOLUTION OF ALCOHOL-RELATED LIVER DISEASE ◆

NUPUR SHARMA[1] Sadam Bhat[1] Babu Mathew[1] Manisha Yadav[1] sushmita Pandey[1] Gaurav Tripathi[1] Vasundhra Bindal[1] Neha Sharma[1] Shiv Kumar Sarin[1] jaswinder singh Maras[1]

[1]Institute of Liver and Biliary Sciences

Background: Typically, alcohol damages and increases gut permeability, allowing translocation of several endotoxins. In blood, it signals inflammatory cells into circulation, further exacerbating liver steatosis, fibrosis, and neutrophil infiltration. This suggests that alcohol damage occurs in site-specific manner and the most efficacious treatment for this condition is alcohol abstinence. We aimed to find site-specific metabolomic changes upon alcohol abstinence to identify potential targets for the resolution of alcohol-associated liver disease (ALD). **Methods:** 6-8 week old male/female LE rats were randomized: The control group fed with Lieber Di Carli (LDC) control diet (n=6), while ALD (n=6), and abstinence groups (n=6) were fed LDC ethanol diet for 24 weeks. After 24 weeks, the abstinence group rats abstained from alcohol for 7 days. Liver, plasma, and intestine samples underwent metabolomic analysis. **Results:** Histology of the 24-week LDC model showed increased steatosis (28%) and fibrosis (15%) while abstinence resolved it to 19% ($p<0.05$) and 12%, respectively. Key serum markers including AST, ALT, total bilirubin, triglycerides, and cholesterol showed significant elevation in ALD but decreased in abstinence rats, indicating substantial liver injury and successful model development, with marked resolution upon alcohol abstinence. Liver-specific metabolomics showed induction of steroid biosynthesis, terpenoid backbone pathways upon abstinence to mitigate inflammation. Plasma specifically showed increased phenylalanine metabolism, and folate biosynthesis while reduced fatty acid metabolism. Moreover, intestinal malate aspartate shuttle and glutamate metabolism pathways were upregulated during abstinence. Site-integration analysis exhibited abstinence resolved increased pyrimidine and galactose metabolism metabolites in liver, plasma, and intestine. In-depth analysis revealed metabolic shift from pyrimidine to arginine synthesis resulting in increased urea synthesis. Further tracking of urea cycle showed increased GLUD1 and SLC1A5 mRNA in liver implicating its role in reducing alcohol toxicity. **Conclusion:** Alcohol abstinence induces alterations in energy metabolism and a metabolic shift from pyrimidine to arginine synthesis, promoting the proper functioning of the urea cycle. This process aids in removing ammonia from the body, facilitating the recovery from ALD. Consequently, targeting arginine biosynthesis and urea cycle (GLUD1 and SLC1A5) could be beneficial in treating ALD.



Disclosures: NUPUR SHARMA: Nothing to Disclose, Sadam Bhat: Nothing to Disclose, Babu Mathew: Nothing to Disclose, Manisha Yadav: Nothing to Disclose, sushmita Pandey: Nothing to Disclose, Gaurav Tripathi: Nothing

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to Disclose, Vasundhra Bindal: Nothing to Disclose, Neha Sharma: Nothing to Disclose, Shiv Kumar Sarin: Nothing to Disclose, jaswinder singh Maras: Nothing to Disclose

3149 | THE CLINICAL SIGNIFICANCE OF HOMELESSNESS ON THE HOSPITAL OUTCOMES OF PATIENTS ADMITTED WITH ALCOHOL-ASSOCIATED LIVER DISEASE

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[1]University of Maryland School of Medicine, [2]Tufts School of Medicine

Background: Alcohol use significantly contributes to the burden of liver disease among homeless individuals, who often face barriers in accessing medical and psychological care. This study examines the effect of homelessness on outcomes in patients with alcohol-associated liver disease (ALD). **Methods:** Patients hospitalized with ALD from 2012-2017 were selected from the National Inpatient Sample (NIS) and stratified into non-homeless as the reference group and homeless as the comparison group. Propensity score matching was then applied to create a matched cohort. The primary endpoints including mortality, length of stay (LOS), and hospitalization costs, and secondary endpoints including the hepatic complications of ascites, encephalopathy, varices, and sepsis, were analyzed using multivariate Cox regression analysis. Additional sub analyses were performed based on specific needs, such as inadequate housing or lack of material needs. **Results:** The NIS database contained 354,339 patients with ALD, of whom 340,714 (96.15%) were non-homeless and 13,625 (3.85%) homeless. For this study, the 13,625 homeless patients were matched with non-homeless counterparts. Homeless patients demonstrated lower mortality (aHR 0.36, 95% CI 0.30-0.43, p<0.001) and hospitalization costs (aHR 0.93, 95%CI 0.93-0.93, p<0.001), however had longer LOS (6.90 vs. 5.95d; aHR 1.18, 95%CI 1.16-1.19, p<0.001). In terms of hepatic complications, homeless patients experienced lower rates of ascites (aHR 0.36, 95%CI 0.27-0.48, p<0.001), varices (aHR 0.63, 95%CI 0.58-0.68, p<0.001), encephalopathy (aHR 0.78, 95%CI 0.71-0.85, p<0.001), and sepsis (aHR 0.76, 95%CI 0.69-0.83, p<0.001). Subanalyses for those with inadequate housing revealed no difference in mortality, higher LOS (5.89 vs. 4.21d; aHR 2.00, 95%CI 1.54-2.59, p<0.001), higher hospitalization costs (aHR 1.05, 95%CI 1.04-1.06, p<0.001), but lower rates of varices (aHR 0.08, 95%CI 0.01-0.73, p=0.03). Homeless patients with inadequate material resources had lower hospitalization costs (aHR 0.73, 95%CI 0.73-0.73, p<0.001), but no difference in the other outcomes. **Conclusion:** Despite being stigmatized as complex and resource-intensive, homeless patients with ALD in our study demonstrated lower mortality rates and hospitalization costs, likely due to fewer hepatic complications. Longer LOS was expected due to challenges with discharge planning. Future studies are needed to understand the inpatient needs of this vulnerable population.

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Figure 1: The multivariable forest plot using of all-cause mortality as the primary endpoint, with homeless status as the exposure variable



Covariates	Exposures	OR	95% CI	p value
Social Factors	Homeless	0.37	0.31 - 0.43	<0.001
	Social Housing Needs	0.36	0.30 - 0.43	<0.001
	Inadequate Material Resources	0.89	0.18 - 4.40	<0.001
	Combined Social Inequity	0.36	0.30 - 0.43	<0.001
Household Income Quartile 2 (vs. Quartile 1)	Homeless	1.24	1.04 - 1.49	0.019
	Social Housing Needs	1.27	1.06 - 1.52	0.008
	Inadequate Material Resources	1.51	0.32 - 7.16	0.606
	Combined Social Inequity	1.27	1.06 - 1.52	0.008
Household Income Quartile 3 (vs. Quartile 1)	Homeless	1.05	0.87 - 1.27	0.596
	Social Housing Needs	1.05	0.87 - 1.27	0.631
	Inadequate Material Resources	1.27	0.26 - 6.26	0.769
	Combined Social Inequity	1.05	0.87 - 1.27	0.631
Household Income Quartile 4 (vs. Quartile 1)	Homeless	1.07	0.87 - 1.31	0.534
	Social Housing Needs	1.12	0.91 - 1.37	0.292
	Inadequate Material Resources	1.45	0.27 - 7.85	0.668
	Combined Social Inequity	1.12	0.91 - 1.37	0.292
Hospital Bed Size: Medium (vs. Small)	Homeless	1.41	1.14 - 1.76	0.002
	Social Housing Needs	1.41	1.14 - 1.74	0.002
	Inadequate Material Resources	35204599.62	0.00 - Inf	0.990
	Combined Social Inequity	1.41	1.14 - 1.74	0.002
Hospital Bed Size: Large (vs. Small)	Homeless	1.49	1.22 - 1.82	<0.001
	Social Housing Needs	1.47	1.20 - 1.79	<0.001
	Inadequate Material Resources	31233333.37	0.00 - Inf	0.990
	Combined Social Inequity	1.47	1.20 - 1.79	<0.001
Hospital Location/Teaching Status: Urban Nonteaching	Homeless	1.50	1.02 - 2.19	0.022
	Social Housing Needs	1.56	1.07 - 2.29	0.022
	Inadequate Material Resources	44959985.44	0.00 - Inf	0.995
	Combined Social Inequity	1.56	1.07 - 2.29	0.022
Hospital Location/Teaching Status: Urban Teaching	Homeless	1.78	1.25 - 2.55	<0.001
	Social Housing Needs	1.83	1.28 - 2.62	<0.001
	Inadequate Material Resources	23574065.90	0.00 - Inf	0.995
	Combined Social Inequity	1.83	1.28 - 2.62	<0.001
Hospital Region: Midwest (vs. Northeast)	Homeless	1.36	1.13 - 1.64	0.003
	Social Housing Needs	1.32	1.10 - 1.59	0.001
	Inadequate Material Resources	1.30	0.20 - 8.43	0.782
	Combined Social Inequity	1.32	1.10 - 1.59	0.001
Hospital Region: South (vs. Northeast)	Homeless	1.37	1.12 - 1.69	0.001
	Social Housing Needs	1.42	1.16 - 1.74	0.001
	Inadequate Material Resources	1.23	0.17 - 8.67	0.838
	Combined Social Inequity	1.42	1.16 - 1.74	0.001
Hospital Region: West (vs. Northeast)	Homeless	1.45	1.16 - 1.80	0.001
	Social Housing Needs	1.45	1.17 - 1.80	0.001
	Inadequate Material Resources	0.57	0.05 - 6.28	0.650
	Combined Social Inequity	1.45	1.17 - 1.80	0.001

Disclosures: David Lee: Nothing to Disclose, Sharmitha Yerneni: Nothing to Disclose, Mohammed Shaik: Nothing to Disclose, Ki Jung Lee: Nothing to Disclose, Youngjae Cha: Nothing to Disclose, Gregory Fan: Nothing to Disclose, Nathalie Urrunaga: Nothing to Disclose

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3150 | NATIONAL TRENDS IN THE COSTS OF PATIENTS ADMITTED WITH ALCOHOL-ASSOCIATED LIVER DISEASE STRATIFIED BY PATIENT DEMOGRAPHICS: ANALYSIS OF NATIONAL HOSPITAL DATABASE

David Lee[1] Mohammed Shaik[1] Youngjae Cha[1] Ki Jung Lee[2] Gregory Fan[2] Andres Chavez-Barragan[1] Andrew Yi[1] Nathalie Urrunaga[1]

[1]University of Maryland School of Medicine, [2]Tufts School of Medicine

Background: Global increases in alcohol consumption have led to a significant rise in alcohol-associated liver disease (ALD). ALD often necessitates inpatient admission when complications such as alcoholic hepatitis, cirrhosis, or acute-on-chronic liver failure arise. This study aims to monitor national trends in ALD-related admission costs. **Methods:** Patients with ALD-admissions were selected using the 2016-2019 National Inpatient Sample and categorized based on age, sex, and race. Total and mean annual admission costs were determined using weighted charge data and inflation-adjusted charge-to-cost ratios. Multinomial regression curves were plotted for each year with R^2 and p-values for each trend. **Results:** All cost calculated have parentheses denoting (R^2, p). Combining all strata, total annual costs from 2016 to 2019 (in million dollars) were: 6,428.76, 6,582.47, 6,868.09, 7,401.04 (0.93, 0.03). By age; 18-34y: 379.27, 384.81, 426.11, 478.35 (0.91, <0.05). 35-49y: 1573.00, 1573.55, 1637.33, 1803.38 (0.80, 0.10). 50-64y: 3294.91, 3332.81, 3384.65, 3596.55 (0.84, 0.08). >65y: 1181.59, 1291.31, 1419.99, 1522.76 (1.00, <0.001). By sex; Male: 4515.80, 4679.99, 4837.56, 5166.04 (0.96, 0.02). Female: 1913.00, 1902.48, 2030.53, 2235.00 (0.84, 0.09). By race; White: 4215.99, 4327.24, 4514.09, 4850.40 (0.94, 0.03). Black: 681.35, 644.49, 682.90, 707.94 (0.34, 0.42). Hispanic: 1077.22, 1119.64, 1172.96, 1285.94 (0.94, 0.03). Asian or Pacific Islander (API): 99.81, 105.65, 108.28, 115.52 (0.97, 0.01). Other: 354.40, 385.46, 389.86, 441.25 (0.90, <0.05). The following were the mean annual costs (in dollars). By age; 18-34y: 13217.16, 12687.29, 12877.29, 13237.82 (0.01, 0.88). 35-49y: 14644.13, 14372.98, 14176.04, 14664.62 (0.01, 0.93). 50-64y: 15890.20, 15706.72, 15587.43, 16511.55 (0.30, 0.45). >65y: 16030.22, 16206.17, 16298.33, 16364.12 (0.95, 0.03). By sex; Male: 15408.50, 15418.30, 15299.79, 15867.91 (0.42, 0.44). Female: 15414.30, 14846.33, 14857.15, 15475.72 (0.01, 0.93). By race; White: 14808.01, 14885.60, 14783.82, 15264.82 (0.54, 0.27). Black: 15836.09, 14515.60, 14778.15, 14973.44 (0.28, 0.47). Hispanic: 16885.61, 16304.61, 16260.58, 17364.59 (0.12, 0.66). API: 20902.00, 19876.96, 20220.40,19381.75 (0.73, 0.15). Other: 16981.53, 17059.40, 16370.47, 17692.39 (0.12, 0.66). **Conclusion:** The cost burden of ALD-related hospitalizations has increased significantly among males, the youngest and eldest individuals, and across all racial groups except for Blacks.

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Figure 1a: Inflation-adjusted Total Costs Stratified by Age, Sex, and Race in Patients With Alcoholic Liver Disease

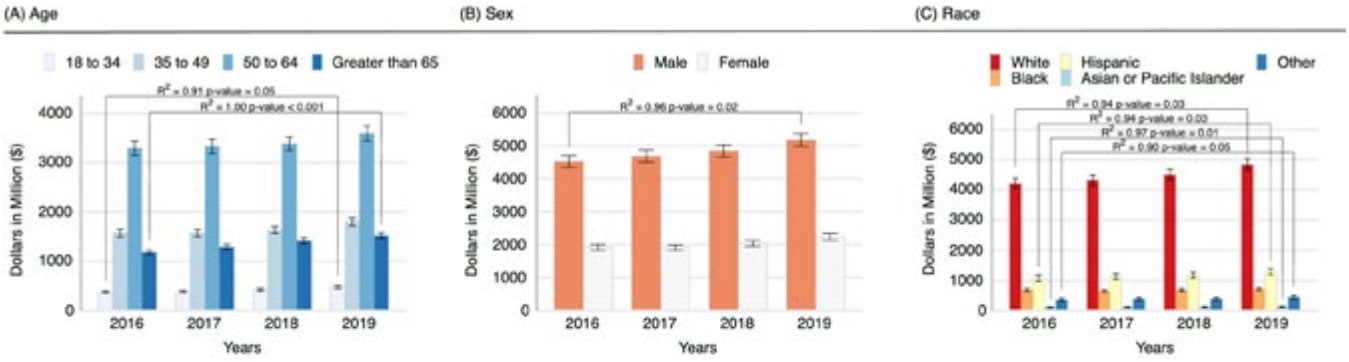
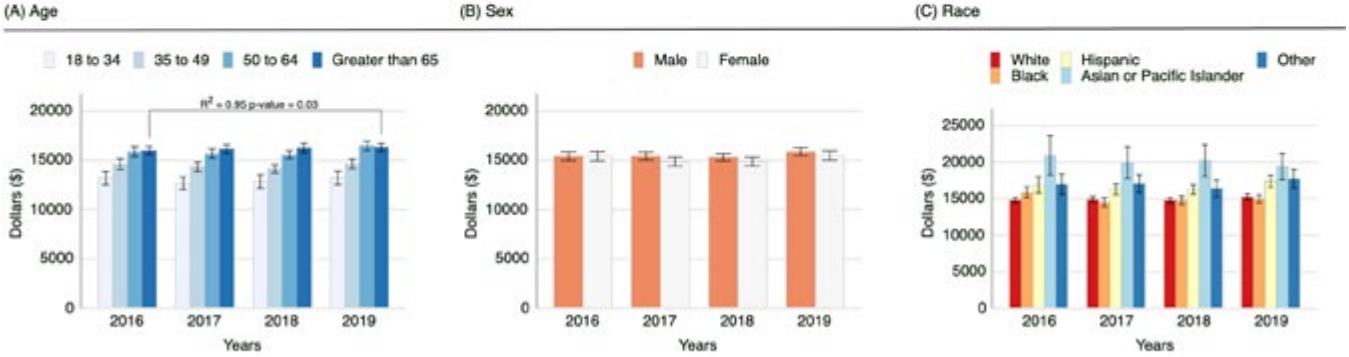


Figure 1b: Inflation-adjusted Mean Costs Stratified by Age, Sex, and Race in Patients With Alcoholic Liver Disease



These figures represent the total (figure 1a) and mean (figure 1b) costs of Alcoholic Liver Disease stratified by (A) age, (B) sex, and (C) race.

Disclosures: David Lee: Nothing to Disclose, Mohammed Shaik: Nothing to Disclose, Youngjae Cha: Nothing to Disclose, Ki Jung Lee: Nothing to Disclose, Gregory Fan: Nothing to Disclose, Andres Chavez-Barragan: Nothing to Disclose, Andrew Yi: Nothing to Disclose, Nathalie Urrunaga: Nothing to Disclose

3151 | NATIONAL TRENDS IN THE COSTS OF PATIENTS ADMITTED WITH ALCOHOL ASSOCIATED LIVER DISEASE STRATIFIED BY PSYCHIATRIC COMORBIDITIES AND SUBSTANCE USE: ANALYSIS OF NATIONAL HOSPITAL DATABASE

David Lee[1] Mohammed Shaik[1] Sharmitha Yerneni[2] Ki Jung Lee[2] Andres Chavez-Barragan[1] Andrew Yi[1] Gregory Fan[2] Nathalie Urrunaga[1]

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Background: Alcohol consumption is on the rise and can lead to liver damage, which is associated with high mortality and significant healthcare burden. We used the National Inpatient Sample (NIS) database to analyze trends in costs related to Alcohol-associated liver disease (ALD) admissions. **Methods:** Patients with ALD were identified using the NIS database from 2016 to 2019. The admission costs were determined using weighted charge data and adjusted for inflation through charge-to-cost ratios. Patient cohorts were categorized based on the spectrum of ALD, psychiatric comorbidities, and substance use, using weighted estimates and patient data. Multinomial regression curves were plotted and analyzed for each year from 2016 to 2019 to evaluate the goodness-of-fit. R2 and p-values were calculated for each trend. **Results:** All cost calculations have R^2 and p-values noted in parentheses as (R^2, p). Costs for the combined strata from 2016 until 2019 were (in million dollars): 6,428.80, 6,582.47, 6,868.09, 7,401.04 (0.93, 0.03). The strata-specific total costs were as follows. By ALD spectrum; alcoholic cirrhosis: 3614.53, 3,707.83, 3,861.68, 4,159.92 (0.94, 0.03). Alcohol-associated fatty liver disease: 156.96, 159.23, 151.71, 175.95 (0.37, 0.39). Alcohol-related hepatitis: 863.55, 898.84, 942.88, 990.59 (1.00, 0.002). Other: 474.88, 438.88, 433.76, 453.47 (0.24, 0.51). Mixed: 1,318.85, 1,377.69, 1,478.05, 1,621.12 (0.97, 0.02). By psychiatric comorbidities: Bipolar disorder: 117.63, 114.24, 118.55, 128.61 (0.60, 0.22). Depression: 594.27, 598.12, 572.80, 622.87 (0.14, 0.62). Anxiety disorder: 431.46, 451.72, 496.92, 554.96 (0.96,

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0.02). Schizophrenia: 94.57, 91.91, 102.54, 113.04 (0.81, 0.10). ≥ 2 Etiologies: 540.51, 565.24, 634.36, 730.06 (0.94, 0.03). None: 4,650.32, 4,761.24, 4,942.92, 5,251.49 (0.95, 0.02). By substance use; cocaine: 80.36, 85.25, 82.23, 95.64 (0.66, 0.19). Marijuana: 176.74, 181.85, 199.96, 207.80 (0.96, 0.02). Opioid: 195.81, 203.09, 210.23, 224.18 (0.97, 0.02). Stimulant use: 64.57, 71.39, 89.41, 99.62 (0.97, 0.01). ≥ 2 Etiologies: 102.34, 106.92, 106.82, 125.21 (0.76, 0.13). None: 5,808.94, 5,933.97, 6,179.44, 6,648.58 (0.93, 0.04). **Conclusion:** The burden of costs for ALD has increased significantly, notably among those with cirrhosis and fatty liver, multiple psychiatric comorbidities and concurrent substance use. Therefore, there is a need for comprehensive strategies to address the complex needs of this population.

Figure 1a: Inflation-adjusted Total Costs Stratified by Alcoholic Liver Disease Type, Psychiatric Disorders, and Substance Use Disorders in Patients With Alcoholic Liver Disease

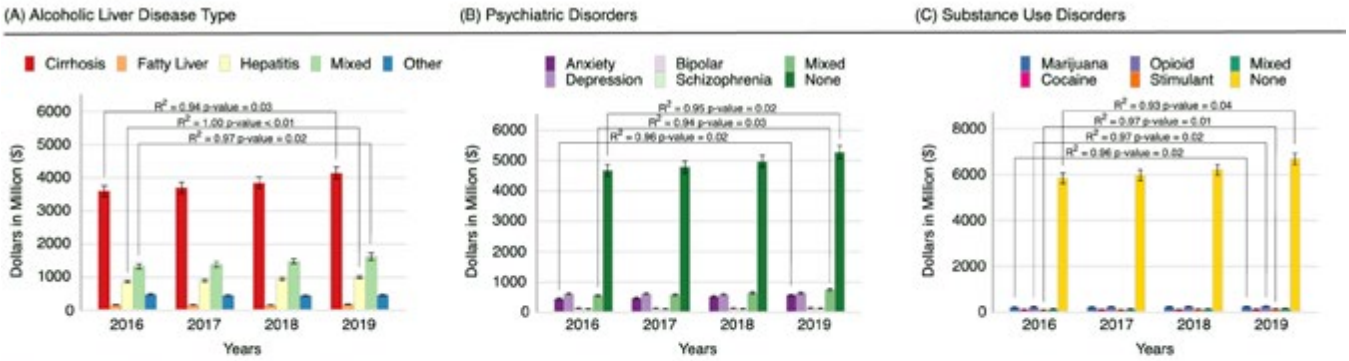
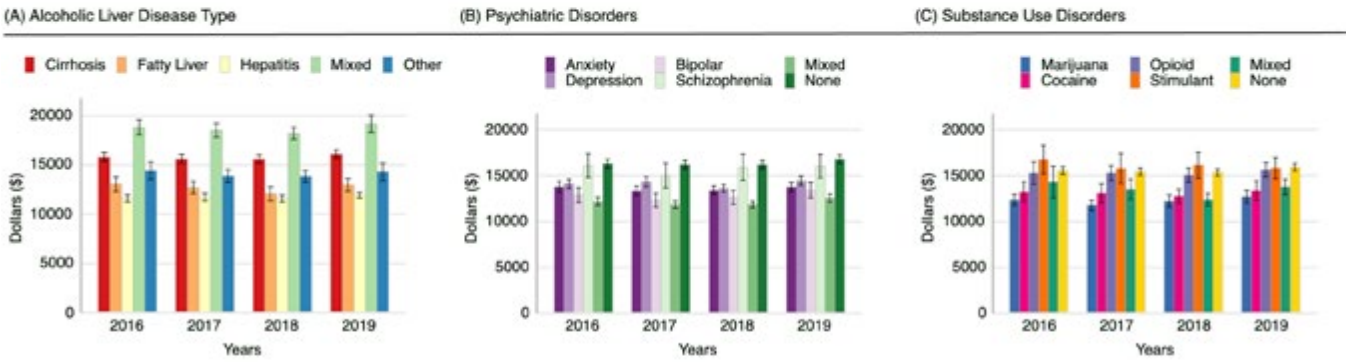


Figure 1b: Inflation-adjusted Mean Costs Stratified by Alcoholic Liver Disease Type, Psychiatric Disorders, and Substance Use Disorders in Patients With Alcoholic Liver Disease



These figures represent the total (figure 1a) and mean (figure 1b) costs of Alcoholic Liver Disease stratified by (A) Alcoholic Liver Disease Type, (B) Psychiatric Disorders, and (C) Substance Use Disorders.

Disclosures: David Lee: Nothing to Disclose, Mohammed Shaik: Nothing to Disclose, Sharmitha Yerneni: Nothing to Disclose, Ki Jung Lee: Nothing to Disclose, Andres Chavez-Barragan: Nothing to Disclose, Andrew Yi: Nothing to Disclose, Gregory Fan: Nothing to Disclose, Nathalie Urrunaga: Nothing to Disclose

3152 | IDENTIFYING RISK FACTORS FOR RETURN TO ALCOHOL USE IN POST-LIVER TRANSPLANT: THE ROLE OF SOBRIETY DURATION AND AGE

Natalia Rodriguez-Payan[1] *Maria P Cote*[1]

[1]*Massachusetts General Hospital*

Background: While sobriety is most often the goal for alcohol consumption after LT, approximately 30-40% of LT recipients will return to alcohol use within the first 5 years post-LT, increasing the risk of recurrent alcohol associated liver disease, and death. Estimating the risk of drinking in patients after LT remains a challenge that requires the consideration of multiple factors. We aim to identify clinical elements that can help predict return to alcohol use (RAU) in the LT population. **Methods:** We performed a retrospective chart review of patients who

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received a liver transplant for alcohol-related liver disease (ARLD) from 2016-2022 at a single institution. Patient demographics, sobriety duration at transplant, psychiatric comorbidities, family history of alcohol use disorder (AUD), relapse scores High Risk Alcoholism Relapse Scale and Geneva, and social supports were obtained from the EHR. We defined return to alcohol use (RAU) as the presence of a positive serum Phosphatidylethanol (PEth) or urine ethyl glucuronide (EtG)/ethyl sulfate (EtS) test at any point in the post-transplant period. We used Wilcoxon Rank Sum, and Fisher's exact test to compare continuous and categorical variables. **Results:** A cohort of 194 patients that received a LT for ALD was identified. Of those, 53 patients had RAU during the post-transplant period. Patient demographics, and social support elements were comparable amongst RAU and no RAU groups (Table 1). Shorter duration of sobriety at transplant, and younger age were significantly associated with return to alcohol use post-transplant ($p<.001$). Although not significantly associated with RAU, there was a high incidence of a family history of AUD in the cohort, regardless of RAU status. Finally, relapse scores (HRAR and Geneva) did not seem to predict higher risk of post-transplant RAU (Table 1). **Conclusion:** Sobriety duration at the time of transplant evaluation and younger age significantly predicted risk of return to alcohol use after transplant; however, other demographic variables, social factors, and relapse risk scores did not accurately predict RAU amongst our cohort. Commonly used relapse prevention scores (HRAR, Geneva Score) likewise offer inconsistent results, perhaps reflective of subjective nature of many of these measures and strong reliance on patient/family report rather than objective data. Estimating clinical risk factors to return to alcohol use in the post-liver transplant population is paramount to improve patient outcomes and generate targeted interventions for optimal care.

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Variable	RAU (n = 53)	No RAU (n = 141)	P value
Age	53 (42-60)	62 (52-67)	**<0.001**
Alcoholic Cirrhosis diagnosis for transplant	36 (67.9%)	89 (63.1%)	0.48
Male Sex	29 (54.7%)	111 (78.7%)	**0.001**
White Race	47 (88.7%)	129 (91.5%)	0.28
Hispanic Ethnicity	1 (1.89%)	7 (4.92%)	0.34
Married status	28 (52.8%)	84 (59.6%)	0.19
Insurance coverage present	52 (98.1%)	137 (97.2%)	0.71
Employment status	20 (37.7%)	50 (35.5%)	0.67
MELD	34 (30-39)	33 (29-39.5)	0.69
Sobriety time at listing (months) <6 months 6-12 12-24 >24	16 (30.2%) 21 (39.6%) 7 (13.2%) 8 (15.1%)	25 (17.7%) 27 (19.1%) 34 (24.1%) 55 (39.0%)	**<0.001**
Duration of heavy drinking prior to transplant (months) < 11 11-25 >25	28 (65.1%) 9 (21%) 6 (14%)	52 (36.9%) 25 (17.7%) 29 (20.6%)	0.14
Presence of psychiatric comorbidities	45 (85%)	107 (75.4%)	0.15
Family history of AUD	26 (49%)	61 (43%)	0.75
Social support pre-transplant 1 2 3 Unknown	5 (9.4%) 10 (18.8%) 38 (88.3%) 0 (0)	13 (9.2%) 28 (19.9%) 97 (68.8%) 3 (2.1%)	0.75
Living alone	7 (13.2%)	15 (10.6%)	0.73
HRAR Score <4 4 Unknown	38 (71.6%) 5 (9.4%) 10 (18.8%)	90 (63.8%) 10 (7.1%) 41 (29%)	0.71
Geneva Score 5% 18% 64% 100%	17 (39.5%) 18 (41.8%) 8 (18.6%) 0 (0)	58 (54.7%) 37 (34.9%) 10 (9.4%) 1 (0.94%)	0.21
Geneva score grouped <18% ≥18%	17 (39.5%) 26 (60.5%)	59 (55.1%) 48 (44.9%)	0.08
Pharmacotherapy for AUD	3 (5.7%)	7 (4.9%)	0.97

Table1.

Disclosures: Natalia Rodriguez-Payan: Nothing to Disclose, Maria P Cote: Nothing to Disclose

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3153 | INTEGRATED HEPATOLOGY AND ADDICTION CARE FOR HOSPITALIZED PATIENTS WITH ALCOHOL USE DISORDER IMPROVES MEDICAL ALCOHOL THERAPY ENGAGAMENT AT DISCHARGE

Jay Luther[1] Eric Barash[2] Benjamin Grobman[3] Peter Rentzepis[3] Russell Goodman[1] Esperance Schaefer[4] Michael Butler[2] Prasanna Challa[2] Wei Zhang[2]

[1]Massachusetts General Hospital, [2]MGH, [3]HMS, [4]BWH

Background: Hospitalizations for patients with alcohol use disorder (AUD) offer an opportunity to engage patients in medical treatment for alcohol use (MAT). Unfortunately, a minority of hospitalized patients with AUD are discharged on MAT, even when seen by addiction specialists. Novel strategies are critically needed to enhance MAT engagement amongst high-risk alcohol users to prevent the development and progression of ALD. While our initial data suggests improved rates of MAT at discharge for patients seen by an integrated hepatology and addiction consult service (ALivE) versus those seen by addiction medicine alone, certain questions remain regarding the validity of these results, predictive markers for success, and the influence it has on patients. In this work, we sought to investigate the effect of ALivE on MAT in a validation cohort of hospitalized patients with AUD while also performing prediction and patient-centered analyses to understand the mechanism driving the potential benefit. **Methods:** This single-center study performed at a tertiary academic center evaluated the performance of ALivE against a historical cohort of hospitalized patients with AUD who received standard of care (SOC) of addiction medicine consultation alone. Included patients had a diagnosis of AUD and no prior history of liver disease or active liver disease at the time of admission that would normally require hepatology consultation. The primary outcome was the presence of MAT at discharge. Patient questionnaires were completed using Likert scales. Continuous variables were summarized with means and compared using an unpaired, 2-tailed t test with Welch correction, whereas categorical variables were compared using the Fisher exact test. Ridge regression was used for predictive analyses. **Results:** We studied 161 patients in the ALivE cohort and 58 patients in the SOC group. Compared to SOC, patients evaluated by ALivE were more likely to be discharged on MAT (75.6% vs 56.9%, P<0.05), newly started on MAT at discharge (48.5% vs 24.14%, P<0.05), and have their preadmission MAT regimen altered at discharge (60.25% vs 31.0%, P <0.05). Predictors of MAT at discharge in the ALivE group included Hispanic ethnicity (coefficient: 0.16) and a primary discharge diagnosis related to alcohol (coefficient: 0.18) or falls (coefficient: 0.15), whereas homelessness, leaving against medical advice, and discharge diagnoses of infection and pancreatitis associated with a reduced likelihood of MAT. Patients interviewed suggested ALivE increased their understanding of the seriousness of AUD, the hepatotoxic effects of alcohol, and the positive effect of MAT on limiting progression of liver disease, while also increasing their trust with providers (Likert score >4). **Conclusion:** Integrated hepatology and addiction care of hospitalized patients with alcohol use disorder increases medical therapy at discharge and improves patients' understanding of ALD.

Disclosures: Jay Luther: Nothing to Disclose, Eric Barash: Nothing to Disclose, Benjamin Grobman: Nothing to Disclose, Peter Rentzepis: Nothing to Disclose, Russell Goodman: Nothing to Disclose, Esperance Schaefer: Nothing to Disclose, Michael Butler: Nothing to Disclose, Prasanna Challa: Nothing to Disclose, Wei Zhang: Nothing to Disclose

3154 | FEASIBILITY OF RADIOMICS IN PREDICTION OF OVERALL MORTALITY IN SEVERE ALCOHOLIC HEPATITIS: A PILOT STUDY ◆

Hyunseok Kim[1] Ally Hatcher[1] Vikrant Rachakonda[2] Linda Azab[1] Touseef Qureshi[1] Lixia Wang[1] Ji Hye Min[3] Polly Kirsch[1] Yee Hui Yeo[1] Walid Ayoub[4] Alexander Kuo[4] Hirsh Trivedi[1] Aarshi Vipani[1] Yun Wang[1] Stephen Pandol[1] Ju Dong Yang[4] Shelly Lu[1] Debiao Li[1]

[1]Cedars Sinai Medical Center, [2]University of Maryland, Baltimore, [3]Samsung Medical Center, [4]Cedars-Sinai Medical Center

Background: Radiomics, which involves extracting large amounts of quantitative features from medical images using advanced algorithms, has shown promise in enhancing diagnostic and prognostic accuracy in various medical fields. This pilot study evaluates the feasibility of using radiomics-based prediction models to predict overall mortality in patients with severe alcoholic hepatitis. **Methods:** This retrospective cohort study included 55 patients with severe AH (MELD 3.0 score >20) who were admitted to a tertiary liver transplant

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referral center and had abdominal CT scans with intravenous contrast upon admission between January, 2020 and June, 2023. Radiomic features were extracted from CT images of the whole liver, spleen, and portal vein. A total of approximately 5000 predefined radiomic features were analyzed, including morphological and textural characteristics such as size, shape, and pattern heterogeneity. The main outcome was 6-month overall mortality. Two machine learning models were developed: The first model utilized radiomic features from the liver alone, while the second model integrated radiomic features from the liver, spleen, and portal vein. The Nearest Neighbor classifier was chosen for binary classification due to its simplicity and effectiveness in dealing with high-dimensional data. The classifier's performance was evaluated using a three-fold cross-validation approach. **Results:** Several radiomic features were significantly different between patients who survived (n=38, 69%) and those who died (n=17, 31%) within 6 months. Features indicative of texture heterogeneity within the liver, spleen, and the diameter of the portal vein were particularly notable. For the model based on liver features alone, the sensitivity was 0.55, specificity was 0.66, accuracy was 0.58, and the area under the receiver operating characteristic curve (AUC) was 0.55. For the model integrating features from the liver, spleen, and portal vein, the sensitivity was 0.67, specificity was 0.77, accuracy was 0.60, and the AUC was 0.73. The second model demonstrated superior performance, suggesting that integrating features from structures associated with portal hypertension provides a more accurate prediction of mortality in severe AH patients. **Conclusion:** This pilot study demonstrates the potential of radiomics to serve as a non-invasive tool for risk stratification in severe AH. If validated in larger, prospective studies, these radiomic biomarkers could be integrated into clinical practice to enhance the management of severe AH by providing personalized risk assessments. Further research is needed to validate these findings and explore the integration of radiomics with other clinical and laboratory data to enhance predictive accuracy.

Disclosures: Hyunseok Kim: Nothing to Disclose, Ally Hatcher: Nothing to Disclose, Vikrant Rachakonda: Nothing to Disclose, Linda Azab: Nothing to Disclose, Touseef Qureshi: Nothing to Disclose, Lixia Wang: Nothing to Disclose, Ji Hye Min: Nothing to Disclose, Polly Kirsch: Nothing to Disclose, Yee Hui Yeo: Nothing to Disclose, Walid Ayoub: Intercept: Speaking and Teaching, Mirum: Grant/Research Support, GSK: Consultant, GSK: Grant/Research Support, Madrigal: Grant/Research Support, Cymabay: Consultant, Ipsen: Grant/Research Support, Zydus: Grant/Research Support, Alexander Kuo: Nothing to Disclose, Hirsh Trivedi: Nothing to Disclose, Aarshi Vipani: Nothing to Disclose, Yun Wang: Nothing to Disclose, Stephen Pandol: Nothing to Disclose, Ju Dong Yang: Consultant relationship with Fujifilm Medical Sciences; Has not ended; Consultant relationship with Exelixis; Has not ended; Consultant relationship with Eisai; Has not ended; Consultant relationship with AstraZeneca; Has not ended; Consultant relationship with Exact Sciences; Has not ended, Shelly Lu: Nothing to Disclose, Debiao Li: Nothing to Disclose

3155 | HEPATOCYTE-SPECIFIC DELETION OF BETAINE HOMOCYSTEINE METHYLTRANSFERASE PROMOTES AGE-DEPENDENT PROGRESSION OF LIVER DISEASE

Poonam Sagar[1] Sathish Perumal[1] Ramachandran Rajamanickam[1] Natalia Osna[1] Karuna Rasineni[1] Kusum Kharbanda[2]

[1]University of Nebraska Medical Center, [2]Department of Veterans Affairs, Veterans Affairs Nebraska-Western Iowa Health Care System

Background: Betaine homocysteine methyltransferase (BHMT), an enzyme involved in one-carbon metabolism, plays a critical role in maintaining liver health. Our laboratory has made seminal contributions in demonstrating that by virtue of removing the two detrimental metabolites, homocysteine and S-adenosylhomocysteine (SAH), BHMT-mediated catalysis serves an important role in preventing the development of alcohol-associated liver disease. To further define the crucial role of BHMT in maintaining liver function, we generated BHMT floxed and liver specific BHMT knockouts (LKO) mice. This study investigates the influence of liver specific deletion of BHMT on age-dependent progression of liver disease. **Methods:** One-year-old male and female C57BL/6 BHMT floxed and liver-specific BHMT knockout (BHMT LKO) mice were fed a standard chow diet and housed under ambient conditions. The liver tissues were harvested and subjected to histopathological and biochemical analyses. **Results:** Loss of liver BHMT leads to a compensatory increase in 5-methyltetrahydrofolate-homocysteine methyltransferase (MTR) protein level by ~2.5 fold ($p<0.01$). However, despite a rise in MTR expression, over 7-fold ($P<0.005$) increased hepatocellular SAH and a corresponding decrease in S-adenosylmethionine

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(SAM):SAH ratio was observed. Histological analysis revealed macro and microvesicular steatosis in LKOs which was corroborated by increased CD36 expression ($p<0.01$) and loss of FABP1 ($p<0.05$). We also observed increased indices of inflammation in BHMT LKOs as revealed by elevated CCL2 ($p<0.05$), IL1-β ($p<0.05$), IL10 ($p<0.05$) expression levels and by the presence of higher number of CD68 positive cells ($P<0.01$). Picrosirius red staining showed evidence of fibrosis, which was confirmed by increased expression of TGF-β ($p< 0.05$), PDGFR-β ($p<0.05$) and type I collagen ($p<0.05$) in the BHMT LKOs. Additionally, we observed increased HDAC9 ($p<0.05$) expression in BHMT LKOs. **Conclusion:** Liver-specific deletion of BHMT leads to increased expression of MTR, an alternate enzyme involved in homocysteine remethylation. However, despite this adaptive increase, we observed increased indices of liver injury with aging in both male and female BHMT LKO mice. These data suggests that the patients with the loss-of-function polymorphism in BHMT have the potential to develop spontaneous liver damage with age and more serious liver injury with second hits, such as alcohol, high-caloric intake, viral infections.

Disclosures: Poonam Sagar: Nothing to Disclose, Sathish Perumal: Nothing to Disclose, Ramachandran Rajamanickam: Nothing to Disclose, Natalia Osna: Nothing to Disclose, Karuna Rasineni: Nothing to Disclose, Kusum Kharbanda: Nothing to Disclose

3156 | EXPLORING THE INTERPLAY OF GRADED ALCOHOL USE AND EXCESS WEIGHT ON ATHEROGENIC LIPID PROFILES AMONG LATINOS WITH UNDERLYING CHRONIC LIVER DISEASE

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Background: Unhealthy alcohol use, excess weight, and chronic hepatitis C (HCV) have been linked to atherogenic lipid profiles and disproportionately affect Latinos. In this study, we aimed to describe the atherogenic lipid and lipoprotein profiles and assess the interplay between graded alcohol use and other pre-specified variables, including excess weight, on small dense low-density lipoprotein (sdLDL) and lipoprotein-associated phospholipase A2 (Lp-PLA2) levels among Latinos with and without HCV. **Methods:** One hundred fifty non-diabetic Latinos (58 HCV+, 92 HCV-) underwent lipid and lipoprotein measurements and genetic testing (% African and Native American ancestry and PNPLA3 polymorphisms). Alcohol use within the last 12 months was categorized as none, moderate (≤1 drink/day for women and ≤2 drinks/day for men), and heavy (not moderate). Two sets of linear regression models each adjusting for age, sex, and graded alcohol use and including one other pre-specified variable, assessed associations with sdLDL and Lp-PLA2, respectively. **Results:** Patient demographics were as follows: median age 44 years, 64% men, 25% obese (42% overweight), 19% heavy (47% moderate and 34% none) alcohol use, PNPLA3 (29% CC, 49% CG, 22% GG), median% Native American and African ancestry were 42% and 4%, respectively. Overall, median sdLDL was 22 mg/dL and Lp-PLA2 was 150 nmol/min/mL. Median high-density lipoprotein (47 vs. 42 vs. 41 mg/dL) and Apolipoprotein A-1 levels (146 vs. 137 vs. 128 mg/dL) differed significantly, with higher values for heavier alcohol use than moderate or none, while Lp-PLA2 levels (139 vs. 149 vs. 163 nmol/min/mL) were lower for heavier alcohol use. On multivariable analysis, HCV was associated with lower sdLDL (estimate -9.39; 95% CI -12.57 to -6.21). While overweight (estimate 6.19; 95% CI 2.52 to 9.85) and obesity (estimate 4.20; 95% CI 0.19 to 8.22) were associated with higher sdLDL, the effect of overweight on sdLDL was increased among patients with moderate (interaction 8.32; 95% CI 0.44 to 16.20) and heavy (interaction 11.92; 95% CI 1.91 to 21.93) alcohol use (vs. none). Overweight (estimate 14.90; 95% CI 2.85-26.95) and obesity (estimate 16.86; 95% CI 3.58 to 30.14) each were associated with higher Lp-PLA2, however alcohol use did not modify these relationships. These BMI associations also remained significant when additionally controlling for HCV. **Conclusion:** Unhealthy alcohol use exacerbates the impact of excess weight on atherogenic lipid profiles, specifically among overweight individuals. These findings are especially relevant to patients with combined metabolic dysfunction and unhealthy alcohol use as they may be more susceptible to atherogenic lipid profiles. In addition to improving cardiometabolic health and weight loss, curbing alcohol use is important to mitigate atherogenic risk.

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pharmaceuticals: Consultant, Intercept pharmaceuticals: Grant/Research Support, Gilead Sciences Inc: Consultant

3157 | DIFFERENCES IN ALCOHOL USE DISORDER TREATMENT AND RETURN TO DRINKING ACCORDING TO SEVERITY OF ALCOHOL-ASSOCIATED HEPATITIS

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Background: Alcohol use disorder (AUD) treatment to facilitate sustained abstinence is crucial for improving long-term survival in patients who recover from an episode of alcohol-associated hepatitis (AH). We aimed to evaluate AUD treatment utilization and timing of return to drinking after index AH diagnosis, between patients with mild or moderate AH (mAH) and severe AH (sAH). **Methods:** We performed a cohort study of consecutive patients from Olmsted County, MN, hospitalized with AH at Mayo Clinic Rochester between January 1st, 2000, and December 31st, 2020. Patients were screened using ICD-9/10 codes and the diagnosis of AH was confirmed on manual review using NIAAA criteria. Severe AH was defined as MELD score ≥21. AUD treatment included outpatient or inpatient rehabilitation and/or pharmacotherapy. Return to drinking was defined as any amount of alcohol consumption based on clinical documentation or alcohol biomarkers, either early (<1 year) or late (>1 year). **Results:** 163 patients met inclusion criteria, of which 73 (44.8%) had mAH and 90 (55.2%) had sAH (table). Within 1 year following the index AH hospitalization, AUD treatment adoption was similar amongst patients with sAH and mAH (35.6% versus 28.8%, respectively; p=0.65). Among mAH 21/73 (28.8%) patients opted for AUD treatment (95% received behavioral inpatient or outpatient therapy, 5% received pharmacotherapy in addition to behavioral therapy and no one received pharmacotherapy alone), among sAH 32/90 (35.6%) were enrolled in AUD treatment (81% behavioral inpatient or outpatient treatment, 16% pharmacotherapy alone and 3% received both). 4 patients with mAH and 3 patients with sAH opted for only sober support group (i.e AA meetings) without any AUD treatment. Despite similar AUD treatment rates, patients with sAH were significantly more likely to achieve early alcohol abstinence (82.2% versus 65.8%, p=0.016), and less likely to return to drinking when compared to patients with mAH (54.1% versus 72.9%; p=0.039). Median time to relapse was similar in both cohorts of around one year. Median survival was 4.6 years in mAH and 3.8 years in sAH (p=0.04). **Conclusion:** Patients hospitalized with severe AH had a similar rate of AUD treatment compared to mild-moderate AH, but significantly higher 1-year and overall abstinence. Future studies are needed to understand factors that affect patient perception and completion of AUD treatment, which may differ based on severity of disease.

Demographics			
	Mild/Moderate AH (mAH)	Severe AH (sAH)	p-value
Total patients	73	90	
Sex, M	46 (63.0%)	58 (64.4%)	0.85
Race, white	65 (89.0%)	83 (92.2%)	0.48
Median Age (IQR)	48 (41-56)	49 (42-57)	0.43
Median BMI (IQR)	27.4 (24.5-32.9)	27.2 (23.3-30.9)	0.58
Median MELD (IQR)	17 (15-19)	26 (23-30)	<0.001
No or unknown social support	16 (21.9%)	17 (18.9%)	0.63
Outcomes			
AUD treatment <1 year	21 (28.8%)	32 (35.6%)	0.65
Alcohol abstinence, <1 year	48 (65.8%)	74 (82.2%)	0.016
Return to drinking	35/48 (72.9%)	40/74 (54.1%)	0.039
Median time to relapse in patients, years (IQR)	1.2 (0.5-2.0)	1 (0.4-1.9)	0.93
Median survival, years (IQR)	4.6 (2.9-7.7)	3.8 (1.1-7.3)	0.04

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3158 | A PROSPECTIVE STUDY EVALUATING THE PREVALENCE OF STEATOTIC LIVER DISEASE AND ADVANCED FIBROSIS AND CIRRHOSIS IN OVERWEIGHT AND OBESE INDIVIDUALS IN THE UNITED STATES

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Background: In 2023, new steatotic liver disease (SLD) nomenclature was introduced to include metabolic dysfunction-associated liver disease (MASLD), alcohol-associated liver disease (ALD), and the entity metabolic dysfunction and alcohol-associated liver disease (MetALD) accounting for those with both metabolic risk factors and significant alcohol use. There are limited prospective studies data among overweight and obese individuals on the prevalence of advanced fibrosis, and cirrhosis using standardized advanced imaging technologies in the United States. This study aimed to fill that gap in knowledge by prospectively determining the prevalence of SLD and its subcategories, advanced fibrosis, and cirrhosis among overweight and obese individuals residing in the United States. **Methods:** This cross-sectional analysis of prospectively enrolled overweight or obese adults aged 40-75 years from primary care and community-based settings in Southern California. Participants were classified as having SLD if MRI-PDFF≥5% or CAP≥288db/m (if MRI-PDFF not available) and subclassified as MASLD, MetALD, and ALD consistent with the new nomenclature guidance per AASLD – EASL – ALEH. Advanced fibrosis and cirrhosis were defined as MRE≥3.63 kPa (VCTE≥8.6kPa if MRE is not available) and MRE≥4.67 kPa (VCTE≥13.1kPa if MRE is not available), respectively. **Results:** The cohort included 539 participants with a mean (±SD) age of 51.5 (±13.1) years and BMI of 32.6 (±6.2) kg/m^2, respectively. The prevalence of SLD, advanced fibrosis, and cirrhosis was 75%, 10.8%, and 4.5%, respectively. (Figure 1) The prevalence of MASLD, MetALD, and ALD was 67.3%, 4.8%, and 2.6%, respectively. There was no difference in advanced fibrosis and cirrhosis prevalence among the SLD subcategories. Those with advanced fibrosis had higher BMI, hemoglobin A1c, AST, ALT, total bilirubin, and lower platelet and albumin. **Conclusion:** Utilizing advanced imaging methods, including MRI-PDFF and MRE, in a prospectively enrolled cohort of overweight and obese adults, the prevalence of cirrhosis was 4.5%. The most common SLD subcategory was MASLD, with 67% of individuals, whereas MetALD and ALD were less common. This study highlights the importance of systematic screening for advanced fibrosis among overweight/obese adults, and further studies to understand the effects of alcohol use and metabolic risk factors on liver fibrosis are imperative.

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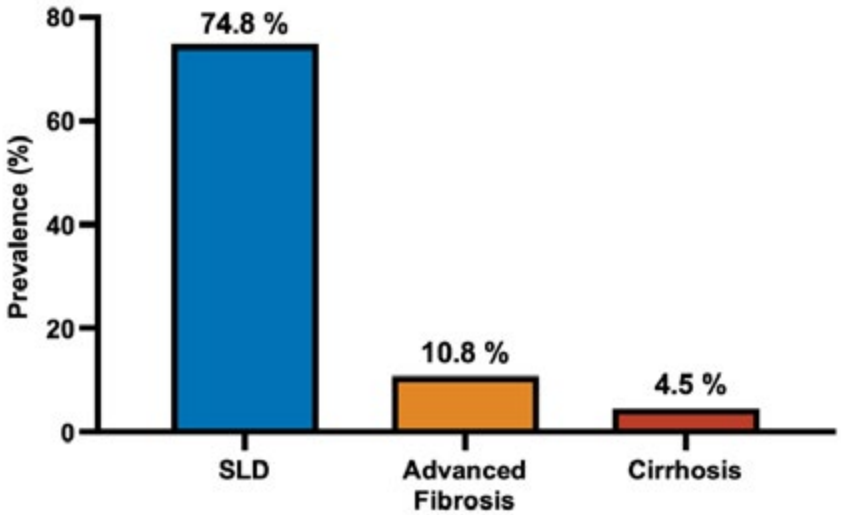

Disclosures: Alexander Yang: Nothing to Disclose, Monica Tincopa: Nothing to Disclose, Federica Tavaglione: Nothing to Disclose, Veeral Ajmera: Nothing to Disclose, Lisa Richards: Nothing to Disclose, Maral Amangurbanova: Nothing to Disclose, Christian Butcher: Nothing to Disclose, Christie Hernandez: Nothing to Disclose, Egbert Madamba: Nothing to Disclose, Seema Singh: Nothing to Disclose, Ricki Bettencourt: Nothing to Disclose, Bernd Schnabl: Grant/Research Support relationship with Prodigy Biotech; Has not ended; Grant/Research Support relationship with CymaBay Therapeutics; Has ended; Consultant relationship with Surrozen; Has ended; Grant/Research Support relationship with Intercept Pharmaceuticals; Has not ended; Stock â€“ privately held company relationship with Nterica Bio; Has not ended; Grant/Research Support relationship with Axial Biotherapeutics; Has ended; Consultant relationship with Ambys Medicines; Has ended; Grant/Research Support relationship with ChromoLogic; Has not ended; Consultant relationship with Mabwell Therapeutics; Has not ended, Claude Sirlin: Nothing to Disclose, Rohit Loomba: Eli Lilly and Company: Consultant, 89bio: Consultant, Aardvark Therapeutics: Consultant, Altimmune: Consultant, Alnylam/Regeneron: Consultant, Amgen: Consultant, Arrowhead Pharmaceuticals: Consultant, AstraZeneca: Consultant, Bristol Myers Squibb: Consultant, CohBar: Consultant, Eli Lilly: Consultant, Galmed Pharmaceuticals: Consultant, Gilead: Consultant, Glympse Bio: Consultant, Hightide: Consultant, Inipharma: Consultant, Intercept: Consultant, Inventiva: Consultant, Ionis: Consultant, Janssen, Inc.: Consultant, Madrigal Pharmaceuticals: Consultant, Merck, Metacrine, Inc.: Consultant, NGM Biopharmaceuticals: Consultant, Novartis: Consultant, Novo Nordisk: Consultant, Pfizer: Consultant, Sagimet Biosciences: Consultant, Terns Pharmaceuticals: Consultant, Theratechnologies and Viking Therapeutics: Consultant, 89bio: Stock options, Sagimet Biosciences: Stock options, Arrowhead Pharmaceuticals: Research grant, AstraZeneca: Research grant, Boehringer Ingelheim: Research grant, Bristol Myers Squibb: Research grant, Eli Lilly: Research grant, Galectin Therapeutics: Research grant, Galmed Pharmaceuticals: Research grant, Gilead: Research grant, Hanmi: Research grant, Intercept: Research grant, Inventiva: Research grant, Ionis: Research grant, Janssen, Inc.: Research grant, Madrigal Pharmaceuticals: Research grant, Merck: Research grant, NGM Biopharmaceuticals: Research grant, Novo Nordisk: Research grant, Pfizer: Research grant, Sonic Incytes: Research grant, Terns Pharmaceuticals: Research grant, LipoNexus, Inc.: Co-founder

3159 | THE CARE OF ACUTE ALCOHOL ASSOCIATED HEPATITIS AT A LARGE TERTIARY CARE AND LIVER TRANSPLANT CENTER: ASSESSING KNOWLEDGE GAPS

Alessandro Colletta[1] *Katherine Cooper*[1] *Deepika Devuni*[1]

[1]*UMass Chan Medical School*

Background: Acute alcohol associated hepatitis (AAH) is a clinical syndrome that occurs in patients with sustained alcohol use and has high mortality index. Diagnosis of AAH requires rapid onset of jaundice, bilirubin ≥ 3 mg/dL, elevated transaminases < 400 U/L, in the context of severe alcohol use > 6 months. An algorithm about pharmacological and nutritional recommendations for patients with AAH exists. Yet, patients with AAH are at times managed inconsistently, possibly leading to worse outcomes. We analyzed the diagnosis and management of AAH patients to identify barriers to a standardized approach and designed an anonymous survey

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to measure providers' knowledge about the management of AAH. **Methods:** The electronic medical record was queried for patients admitted between 1/1/21-6/31/21 with diagnosis of AAH at our institution. Laboratory data and management plans were collected. An anonymous survey assessing internal medicine (IM) residents and attendings' knowledge about AAH diagnosis and management was conducted. Questions on diagnosis, work-up, and management were asked in the format "select all that apply". Confidence in making the diagnosis of AAH was queried on a numeric scale [1 = least confident, 10 = most confident]. Variables were compared between residents and attendings using Chi squared tests and student's t tests. **Results:** 114 patients with diagnosis of AAH were identified, of which 47.4% met true criteria for AAH (24.6% severe and 22.8% non-severe). Maddrey's discriminant function (MDF) was calculated for 59.3% patients. Of those with AAH (n=54), 26 were seen by hepatology (3/26 non severe and 23/28 severe) and 28 were seen by nutrition. 68 IM providers completed the survey (53 residents and 15 attendings). 2 providers (2.9%) appropriately selected answers for the following questions: criteria for AAH diagnosis, AAH work-up and, contraindications to prednisolone treatment. Attendings were more knowledgeable than residents on: 1) the labs needed to calculate MDF 2) the need for hepatology consult in moderate/severe AAH 3) the right pharmacological regimen and 4) the need for GI follow-up within 4 weeks of discharge (table 1). Providers with confidence ≥ 7 in diagnosing AAH were more likely to know 1) the need for hepatology consult in moderate/severe AAH 2) the adequate pharmacological regimen. 83% of providers chose that time to steroid initiation affects outcomes. **Conclusion:** The results suggest inconsistent diagnosis and management approach for AAH across the institution. There is significant room to improve clinicians' knowledge regarding the diagnosis and management of AAH. Further education and use of a standardized management algorithm on admission are needed to best treat patients with AAH and prevent poor outcomes.

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	N Resident (%)	N Attending (%)	p	N Confidence ≥ 7 (%)	N Confidence < 7 (%)	p
Subject number	53 (22.1)	15 (77.9)	-	38	30	
Elements chosen as necessary to make AAH diagnosis						
serum bili >3 mg/dL	25 (47.2)	7 (46.7)	1.0	21 (55.3)	11 (36.7)	0.5
Heavy alcohol use > 6 mo	26 (49.1)	5 (33.3)	0.38	18 (45.6)	13 (43.3)	1.0
Scleral icterus or jaundice	26 (49.1)	4 (26.7)	0.15	17 (44.7)	13 (43.3)	1.0
AST and ALT > 50 and < 400	25 (47.2)	6 (40)	0.77	16 (42.1)	15 (50)	0.63
Maddrey's for AAH severity	45 (84.9)	15 (100)	1.0	35 (92.1)	25 (83.3)	0.45
Labs chosen to assess AAH severity score						
Bilirubin	53 (100)	14 (93.3)	0.22	37 (97.4)	30 (100)	1.0
Prothrombin time	31 (58.8)	11 (73.3)	0.38	25 (65.8)	17 (56.7)	0.46
Hepatology Consult	24 (45.3)	11 (73.3)	**0.08**	27 (71.1)	8 (26.7)	**<0.01**
Prednisolone for treatment & correct length of therapy	21 (39.6)	10 (66.7)	**0.08**	22 (57.9)	9 (30)	**0.03**
Early pharmacologic therapy affects outcomes	44 (83)	12 (80.0)	0.44	33 (87)	25 (83.3)	0.74
Prednisolone before hepatology recs in severe AAH	43 (81.2)	13 (86.8)	1.0	31 (81.6)	25 (83.3)	1.0
Tests to be done prior to starting prednisolone for AAH						
Blood culture	39 (73.6)	10 (66.7)	0.75	27 (71.1)	22 (73.3)	1.0
Urinalysis/Urine culture	30 (56.6)	11 (73.3)	0.37	24 (63.2)	17 (56.7)	0.63
BMP	25 (47.2)	8 (53.3)	0.77	16 (42.1)	17 (57)	0.33
Lipase	14 (26.4)	4 (26.7)	1.0	10 (14.7)	8 (26.7)	1.0
CXR	17 (32.1)	9 (60)	**0.05**	14 (20.6)	12 (40)	0.81
Diagnostic Paracentesis	32 (58.5)	12 (80)	0.22	28 (74)	15 (50)	**0.08**
CT Abdomen	4 (7.5)	1 (6.7)	1.0	1 (1.5)	4 (5.9)	0.16
Selected absolute contraindications to prednisolone therapy for AAH						
Active infection	15 (100)	46 (86.8)	0.33	35 (92.1)	26 (86.7)	0.69
AKI with Cr ≥ 4	10 (18.9)	3 (20)	1.0	7 (18.4)	6 (20)	1.0
Current GI bleeding	21 (39.6)	7 (46.7)	0.77	18 (47.4)	10 (33.3)	0.32
Pancreatitis	5 (9.4)	4 (26.7)	**0.1**	0	1 (3.3)	0.44
Nutrition consult for AAH	47 (90.4)	13 (86.7)	0.65	31 (83.8)	29 (96.7)	0.12
Nutrition recommendations selected as appropriate for AAH (protein and calorie intake)						
High protein (1.5+ g/kg/day)	38 (71.7)	12 (80)	0.74	24 (63.2)	26 (86.7)	**0.05**
High cal (≥30 kcal/kg/day)	17 (32.1)	6 (40)	0.55	14 (37)	9 (30)	0.61
Moderate/severe AAH must have outpatient GI f/up	46 (86.8)	15 (100)	0.33	35 (92.1)	26 (86.7)	0.69
GI f/up ≤ 4 wks post discharge	34 (64.2)	15 (100)	**<0.01**	29 (76.3)	20 (66.7)	0.42

Table 1. Summary of choice selection to anonymous survey by IM providers based on title (residents versus attendings) and declared confidence level (≥ 7 or < 7) for diagnosis of AAH at our institution. Required elements for diagnosis and treatment of AAH have been bolded.

Disclosures: Alessandro Colletta: Nothing to Disclose, Katherine Cooper: Nothing to Disclose, Deepika Devuni: Avania Medical: Grant/Research Support, Intercept: Grant/Research Support

3160 | REAL-WORLD OUTCOMES OF CORTICOSTEROID USE IN SEVERE ALCOHOLIC HEPATITIS POST-STOPAH TRIAL: A PROPENSITY MATCHED COHORT STUDY

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Background: Alcohol associated hepatitis (AH) presents a significant medical challenge, with severity ranging from mild to severe, with high short- and long-term mortality and morbidity. The use of corticosteroids in AH treatment remains controversial. The STOPAH trial reported a statistically non-significant survival benefit at 28-days, while a 2021 study indicated improved 30-day mortality rates with steroid use. This study aims to explore the real-world utilization of corticosteroids in severe AH since the STOPAH trial in 2015, examining both short- and long-term outcomes. **Methods:** We conducted a retrospective cohort study utilizing the TriNetX database to

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evaluate short- and long-term outcomes of patients with severe AH (Maddrey's score >32) on steroids compared to those not on steroids between 2015 and 2023. The primary aim was to assess all-cause mortality, incident hepatic decompensating events (ascites, hepatic encephalopathy, variceal bleed, liver failure), and the incidence of liver transplant within 7 days, 30 days, and 6 months. Patients with absolute contraindications to steroids, HCC, HIV, viral hepatitis, and HbA1c>10 were excluded. Patients with prior outcomes likely to skew results were also excluded. 1:1 propensity score matching was performed for age, gender, race, comorbidities, liver-related characteristics, BMI, and malignancies between the cohorts, with risk expressed as adjusted odds ratios (aOR) with 95% confidence intervals (CI). **Results:** Our study included 416 patients on steroids and 890 patients not on steroids. Patients on steroids had a mean age of 42.9 ± 10.9 years, 77.4% were white, and 41.11% were female. Patients not on steroids had a mean age of 45.5 ± 11.1 years, 72.58% were white, and 38.54% were female. No significant differences were observed in mortality, liver transplant, liver failure, variceal bleed, or hepatic encephalopathy between the two groups. At the end of 7 days, patients on steroids had a lower incidence of ascites (6.20% vs. 11.10%, aOR 0.52, 95% CI 0.31-0.87, p=0.01), and shorter length of stay at 7 days (3.53 ± 2.05 vs. 4.13 ± 1.98, p=0.05), 30 days (4.7 ± 4.3 vs. 5.7 ± 4.7, p=0.01), and 180 days (4.9 ± 4.7 vs. 6.33 ± 5.6, p=0.004). **Conclusion:** Our study reinforces the results from the STOPAH trial in a real-world setting, where the impact of steroids on overall survival and severe liver complications in patients with severe alcohol related hepatitis (AH) remains inconclusive. Given the increased risk of infections depicted in multiple studies, the use of steroids remains controversial. These findings highlight the need for cautious consideration before prescribing steroids.

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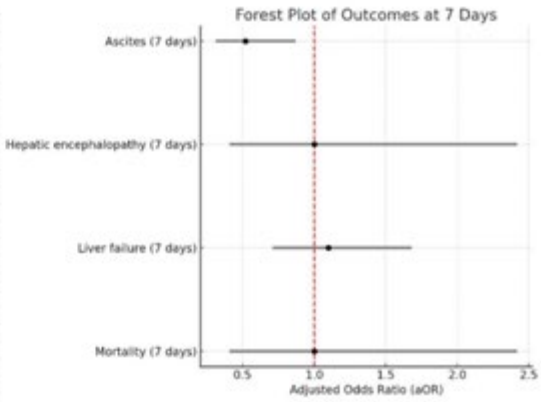
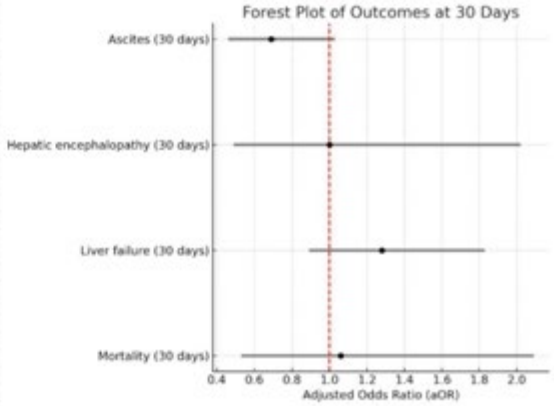
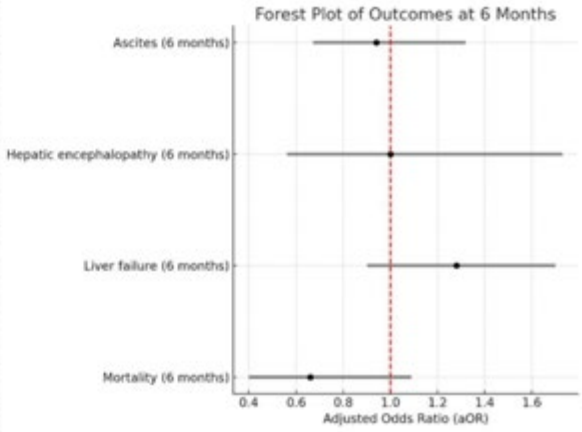
Severe AIH on steroids	416					
Severe AIH not on steroids	890					
*between 2016-2021 for cohort identification						
Severe AIH on steroids						
Mean age	42.9 ± 10.9					
White	77.40%					
Female sex	41.11%					
Severe AIH not on steroids						
Mean age	45.5 ± 11.1					
White	72.58%					
Female sex	38.54%					
Outcomes	**Time duration**	**N**	**%**	**aOR**	**95% CI**	**p value**
Mortality	7 days	10	2.49%	1	0.41-2.42	1
		10	2.49%			
	30 days	18	4.47%	1.06	0.53-2.09	0.8
		17	4.22%			
	6 months	29	7.20%	0.66	0.4-1.09	0.1
		42	10.44%			
Liver transplant	7 days	0	0.00%			
		0	0.00%			
	30 days	10	2.48%			
		0	0.00%			
	6 months	10	2.48%			
		0	0.00%			
Liver failure	7 days	50	12.43%	1.099	0.71-1.68	0.1
		46	11.44%			
	30 days	82	20.30%	1.28	0.89-1.83	0.17
		67	16.60%			
	6 months	102	25.30%	1.28	0.9-1.7	0.13
		84	20.80%			
Variceal bleed	7 days	0	0.00%			
		10	2.48%			
	30 days	0	0.00%			
		10	2.48%			
	6 months	0	0.00%			
		10	2.48%			
Hepatic encephalopathy	7 days	10	2.48%	1	0.41-2.42	1
		10	2.48%			
	30 days	16	3.98%	1	0.49-2.02	1
		16	3.98%			
	6 months	25	6.20%	1	0.56-1.73	1
		25	6.20%			
Ascites	7 days	25	6.20%	0.52	0.31-0.87	**0.01**
		45	11.10%			
	30 days	48	11.94%	0.69	0.46-1.03	0.72
		66	16.40%			
	6 months	82	20.30%	0.94	0.67-1.32	0.72
		86	21.30%			
Lenghth of stay	7 days	3.53+/-2.05				**0.05**
		4.13+/-1.98				
	30 days	4.7+/-4.3				**0.01**
		5.7+/-4.7				
	180 days	4.9+/-4.7				**0.004**
		6.33+/-5.6				







Disclosures: Himsikhar Khataniar: Nothing to Disclose, Aakash Desai: Nothing to Disclose, Muhammad Ali Butt: Nothing to Disclose, Michael Babich: Abbvie: Speaking and Teaching, Gilead pharma: Speaking and Teaching, Salix pharma: Speaking and Teaching, Intercept pharma: Speaking and Teaching, Madrigal pharma: Speaking and Teaching, Nabeeha Mohy-ud-din: Nothing to Disclose

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3161 | HEPATOCYTE-SPECIFIC DELETION OF BETAINE HOMOCYSTEINE METHYLTRANSFERASE PROMOTES ALCOHOL-INDUCED LIVER INJURY

Ramachandran Rajamanickam[1] Sathish kumar Perumal[1] Poonam Sagar[1] Natalia Osna[1] Karuna Rasineni[1] Kusum Kharbanda[2]

[1]University of Nebraska Medical Center, [2]Department of Veterans Affairs, Veterans Affairs Nebraska-Western Iowa Health Care System

Background: Alcohol-associated liver disease (ALD) remains a significant health concern globally. The development of ALD depends on several factors, including genetics. Our laboratory previously reported that chronic alcohol consumption alters liver methionine metabolism and the consequent reduction in the methylation potential leads to the generation of hallmark features of ALD. We further showed that treatment with a methyl donor, betaine, prevent ALD development via its utilization by betaine homocysteine methyltransferase (BHMT)-mediated catalysis to remove the two detrimental metabolites, homocysteine and S-adenosylhomocysteine (SAH). Since there are several common loss-of-function single-nucleotide polymorphisms in the human *BHMT* gene, we investigated whether the liver-specific loss of BHMT would promote more severe liver injury in an experimental model of ALD. **Methods:** We generated BHMT floxed and liver specific BHMT KO (LKO) mice that were housed in an AAALAC-accredited animal facility at the Omaha VA Medical Center. Eight-week-old male and female C57BL/6 BHMT floxed and LKO mice were subjected to chronic + binge (10+1) feeding. Nine hours after the gavage, the mice were sacrificed. Blood and liver were collected and subjected for histopathological and biochemical analyses. **Results:** We observed elevated serum AST level ($p<0.05$) in both male and female BHMT LKO ethanol-fed mice. BHMT LKO mice fed control or the ethanol diet exhibited over 10-fold increase in hepatocellular S-adenosylhomocysteine levels. However, the lowest methylation potential (i.e., S-adenosylmethionine (SAM):SAH ratio) was seen in the ethanol-fed BHMT LKO of either gender. Liver triglycerides revealed highest level in the ethanol-fed male and female BHMT LKO mice, which was further confirmed by histological assessment revealing massive macro- and microvesicular steatosis and parenchymal inflammation compared to BHMT floxed ethanol-fed mice. Highest mRNA expression of perilipin 2, CIDEC, TNFα, IL1-β, CCL2 and TGFβ indicating increased steatosis, inflammation and fibrosis was observed in both male and female ethanol-fed BHMT LKO mice compared to the rest of the groups. Only female BHMT LKO ethanol-fed mice exhibited significantly lower lysosomal cathepsin B, cathepsin L, proteasomal trypsin-like and chymotrypsin-like activities compared to the rest of the groups. **Conclusion:** These results indicate that BHMT has an important role in one-carbon metabolism and is key hepatoprotective enzyme to reduce liver damage with alcohol administration.

Disclosures: Ramachandran Rajamanickam: Nothing to Disclose, Sathish kumar Perumal: Nothing to Disclose, Poonam Sagar: Nothing to Disclose, Natalia Osna: Nothing to Disclose, Karuna Rasineni: Nothing to Disclose, Kusum Kharbanda: Nothing to Disclose

3162 | PSYCHIATRIC COMORBIDITIES AND RISK OF RETURN TO DRINKING AMONGST LIVER TRANSPLANT RECIPIENTS

Sienna Li Maria Cote[1] Natalia Rodriguez-Payan[1] Kelly Hsu[2] Katherine Specht[1] Maria Diaz Soto[3] Eric Przybyszewski[1] Ana Ivkovic[1] Mladen Nisavic[1] Wei Zhang[1] Leigh Anne Dageforde[1] Sofia Baptista[1] Heidi Yeh[1] Emily Bethea[1]

[1]Massachusetts General Hospital, [2]Tufts Medical School, [3]Beth Israel Deaconess

Background: Currently, alcohol-related liver disease (ARLD) is the leading indication for liver transplantation (LT) in the US. Alcohol use disorder (AUD) carries a high rate of comorbidity with other psychiatric diagnoses, and comorbid psychiatric illness is a known risk factor for return to alcohol use (RAU) post-transplant. While alcohol use management after transplant involves a multidisciplinary approach, little is known about RAU risk factors, especially regarding specific mental health diagnoses. We aim to understand if patients with specific psychiatric comorbidities have a higher risk of RAU after LT. **Methods:** We performed a retrospective chart review of patients receiving a liver transplant for ARLD from 2016-2022 in a single institution. Electronic medical records were reviewed for psychiatric diagnoses including mood disorders (MDD, bipolar disorder), anxiety, PTSD, and substance use disorders other than AUD. Patient charts were also screened for protracted grief. We

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defined return to alcohol use (RAU) as the presence of a positive serum Phosphatidylethanol (PEth) or urine Ethyl glucuronide (EtG)/Ethyl sulfate (EtS) test at any point in the post-transplant period. We used descriptive statistics for patient demographics and comorbidities, and Chi2 to assess the differences in prevalence of psychiatric comorbidities among those with RAU or not. **Results:** A cohort of 194 patients (72% male, median age 59, median MELD 33) received a liver transplant for ARLD. A total of 150 (77.3%) of patients had at least one psychiatric comorbidity. For patients actively grieving a significant loss, the risk of RAU was significantly higher. Approximately 40.6% of patients had 1-2 psychiatric comorbidities, and 30.7% had 3-5 beyond AUD. Fifty-three (27.2%) patients were identified as having RAU post-transplant. RAU post-transplant was significantly associated with depression (p=.002), generalized anxiety disorder (p=.030), PTSD (p=.007), and grief (p=.040), while no association was found with bipolar or unspecified mood disorders (Table 1). **Conclusion:** Comorbid psychiatric illness is highly prevalent amongst AUD patients and plays a significant role in patients status post LT for ALRD. Diagnosis of depression, generalized anxiety, grief, and PTSD at the time of transplant evaluation are significantly associated with RAU after transplant. Further studies should assess the relationship between potential therapies used for psychiatric conditions and how they impact RAU prevention after LT.

Table 1

Variable	RAU (n=53)	Non-RAU(n=141)	P value
Psychiatric comorbidities			0.09
Yes	45 (84.9%)	102 (72.3%)	
No	8 (15%)	39 (27.7%)	
Depression	22 (41.5%)	28 (19.8%)	**0.002**
Bipolar disorder	0 (0%)	2 (1.41)	0.39
Generalized anxiety	20 (37.7%)	32 (22.6%)	**0.03**
Unspecified mood disorder	8 (15.09%)	11 (7.8%)	0.12
Substance abuse, non-alcohol (nicotine, cocaine, cannabis, opioids)	33 (62%)	83 (58.8%)	0.63
PTSD diagnosis	21 (39.62%)	29 (20.56%)	**0.007**
Active grief process	12 (22.64%)	21 (14.8%)	**0.04**
Number of psych comorbidities +/- active grief process			0.18
0	8 (15.1%)	38 (26.9%)	
1-2	20 (37.7%)	59 (41.8%)	
3-5	21 (39.6%)	37 (26.2%)	
6+	2 (3.8%)	7 (4.9%)	

Disclosures: Sienna Li: Nothing to Disclose, Maria Cote: Nothing to Disclose, Natalia Rodriguez-Payan: Nothing to Disclose, Kelly Hsu: Nothing to Disclose, Katherine Specht: Nothing to Disclose, Maria Diaz Soto: Nothing to Disclose, Eric Przybyszewski: Nothing to Disclose, Ana Ivkovic: Nothing to Disclose, Mladen Nisavic: Nothing to Disclose, Wei Zhang: Nothing to Disclose, Leigh Anne Dageforde: Nothing to Disclose, Sofia Baptista: Nothing to Disclose, Heidi Yeh: Nothing to Disclose, Emily Bethea: Nothing to Disclose

3163 | ALTERED LIPIDS IN PATIENTS AND HUMANIZED MICE WITH ALCOHOLIC HEPATITIS MODULATE LIVER IMMUNE RESPONSES ◆

Eleana Kaffe[1] *Wajahat Mehal*[2] *Richard Flavell*[3]

[1]*University of Pennsylvania,* [2]*Yale School of Medicine, Yale University,* [3]*Yale University*

Background: Acute alcoholic Hepatitis (AH) has a high mortality and effective treatment options are very limited. High alcohol consumption leads to lipid deposition in hepatocytes (steatosis) and in AH progress to severe liver inflammation and defective immune responses against infections. Alcohol increases lipid synthesis and lipid overload in hepatocytes; but the metabolic fate of these lipids and whether the metabolic products of accumulated lipids result in altered immune responses associated with AH progression is not known. **Methods:** We performed flow cytometry and lipidomic with HPLC-MS/MS in the plasma and liver of mice with humanized livers undergoing a model of AH, and we compared them with the lipidomic data in patients with AH. We treated wild-type mice with the top altered lipids found in humanized mice and patients with AH and we performed flow cytometry for all

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immune populations in the liver and blood, liver histology and we measured plasma ALT. **Results:** Humanized mice with AH are characterized by increased liver granulocyte infiltration and decreased NK-T cells in comparison to non-treated humanized and alcohol treated regular mice. These results in humanized mice are consistent with humans with AH. In the livers and plasma of humanized mice with AH there was elevation of N-acyl-taurine (a fatty acid derivative) and sulfatide (a ceramide derivative). Similar results were found in the plasma of patients with AH in comparison to healthy controls or heavy drinkers. Treatment of regular mice with alcohol and with these lipids increased plasma ALT, liver granulocytes and decreased NKT to the levels of humanized mice. **Conclusion:** The metabolism of lipids to other lipid derivatives in AH may be responsible for the dysregulation of immune responses in AH.

Disclosures: Eleana Kaffe: Nothing to Disclose, Wajahat Mehal: Sagimet: Advisor, Sagimet: Advisor, Richard Flavell: Nothing to Disclose

3164 | IMPACT OF ALCOHOL USE DISORDER REMISSION ON OUTCOMES POST-TIPS PROCEDURE: A RETROSPECTIVE COHORT STUDY

Himsikhar Khataniar[1] Muhammad Ali Butt[1] Aakash Desai[2] Michael Babich[1] Nabeeha Mohy-ud-din[1]

[1]Allegheny General Hospital, [2]Mayo Clinic Jacksonville

Background: Transjugular Intrahepatic Portosystemic Shunt (TIPS) is a procedure used to manage complications from portal hypertension including refractory ascites and endoscopically untreatable variceal hemorrhage. A TIPS procedure results in lowering of portal pressure, however, we hypothesized that persistent alcohol use post TIPS may lead to higher risk of complications of portal hypertension by raising portal pressures. **Methods:** We conducted a retrospective cohort study utilizing the TriNetX database to evaluate short- and long-term outcomes of AUD patients undergoing TIPS who achieved remission post-procedure compared to those who did not, between 2010 and 2020. The primary aim was to assess the incidence of hepatic decompensation events (ascites, hepatic encephalopathy, variceal bleed), sepsis, and all-cause mortality. Propensity score matching (1:1) was performed for age, sex, race, comorbidities, liver-related characteristics, common indications for TIPS, prior decompensation events, BMI, malignancies, and commonly used medications between the cohorts. The risk was expressed as adjusted odds ratios (aOR) with 95% confidence intervals (CI). **Results:** Our study included patients with AUD undergoing TIPS who were in remission (n=833) versus those not in remission (n=1,406). Patients in remission had a mean age of 54.7 ± 9.4 years, 82.82% were white, and 28.40% were female. Patients not in remission had a mean age of 53.8 ± 9.69 years, 79.30% were white, and 22.40% were female. At the end of 12 months, patients in remission had a significantly lower risk of variceal bleed (9.30% vs. 13.30%, aOR 0.66, 95% CI 0.4-0.95, p=0.02), hospitalization, (59.40% vs. 75.90%, aOR 0.46, 95% CI 0.36-0.59, p<0.0001), mortality (16.80% vs. 35.20%, aOR 0.37, 95% CI 0.28-0.48, p<0.0001), and a non-statistically significant lower rate of new onset ascites (53.90% vs. 56.50%, aOR 0.9, 95% CI 0.7-1.1, p=0.3). No significant differences were found in new onset hepatic encephalopathy (19.60% vs. 17.10%, aOR 1.17, 95% CI 0.88-1.57, p=0.2) at 12 months. **Conclusion:** This study demonstrates that remission from alcohol use disorder (AUD) post-TIPS procedure is associated with significantly better outcomes, including lower rates of variceal bleeding, hospital visits and mortality. These findings emphasize the importance of achieving and maintaining remission in patients with AUD undergoing TIPS to improve clinical outcomes.

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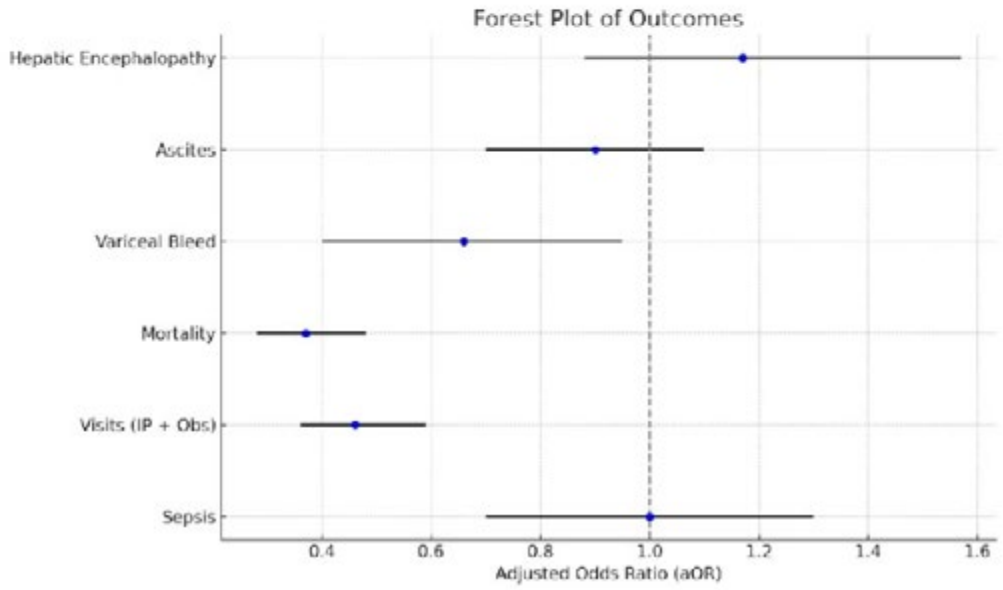
AUD TIPS - in remission	833					
AUD TIPS - not in remission	1,406					
*between 2010-2020 for cohort identification						
AUD TIPS - in remission						
Mean age	54.7 +/- 9.4					
White	82.82%					
Female sex	28.40%					
AUD TIPS - not in remission						
Mean age	53.8+/- 9.69					
White	79.30%					
Female sex	22.40%					
Outcomes	**Time duration**	**N**	**%**	**aOR**	**95% CI**	**p value**
Hepatic Encephalopathy	12 months	120	19.60%	1.17	0.88-1.57	0.2
		105	17.10%			
Ascites	12 months	330	53.90%	0.9	0.7-1.1	0.3
		348	56.50%			
Variceal Bleed	12 months	57	9.30%	0.66	0.4-0.95	**0.02**
		82	13.30%			
Mortality	12 months	103	16.80%	0.37	0.28-0.48	**<0.0001**
		216	35.20%			
Visits (IP + Obs)	12 months	364	59.40%	0.46	0.36-0.59	**<0.0001**
		465	75.90%			
Sepsis	12 months	89	14.50%	1	0.7-1.3	1
		89	14.50%			



Disclosures: Himsikhar Khataniar: Nothing to Disclose, Muhammad Ali Butt: Nothing to Disclose, Aakash Desai: Nothing to Disclose, Michael Babich: Abbvie: Speaking and Teaching, Gilead pharma: Speaking and Teaching, Salix pharma: Speaking and Teaching, Intercept pharma: Speaking and Teaching, Madrigal pharma: Speaking and Teaching, Nabeeha Mohy-ud-din: Nothing to Disclose

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3165 | LIVER TRANSPLANTATION IN ALCOHOLIC HEPATITIS AND ACLF: REDEFINING SELECTION AND SOBRIETY CRITERIA

Parvez Mantry[1]

[1]*Methodist Dallas Medical Center*

Background: Acute Alcoholic Hepatitis (AAH) and Acute and Chronic Liver Failure (ACLF) secondary to alcohol use disoreder remain the leading indications of Liver Transplantation in the United States in the last 4 years impacted by the Covid Era. We adopted a policy and protocol finalized in 2022 to allow patients with AH or ACLF with sobriety less than 6 monthsto be listed for liver transplantation. The psychosocial and medical criteria were finalized by Hepatologists/Transplant surgeonsi in concert and with guidance from our transplant psychologist and social workers and adopted as a policy for our institution . We present data **Methods:** We studied the charts of 160 consecutive patients who were transplanted for AAH or ACLF from 2017- 2024. There were 108 patients pre protocol and 52 patients post protocol implementation that fell into the respective cohorts. The protocol included simplified criteria adopted by other institutions and recognized as reliable to predict long term sobriety. These included - first time severe event related to alcohol, lack of major medical comorbidities, age less than 65, strong family support, lack of polysubstance use, lack of relapses and documented commitment to pursuing a recovery program or Intensive outpatient program for prevention of relapse. **Results:** 160 patients transplanted during this time met the above criteria- 108 patients transplanted pre protocol were 73% male with a median age of 55 a median MELD of 25 at transplant had an overall graft loss of 1 patient and 1 year mortality rate of 12%. The 52 patients transplanted post protocol were also 73% male with a median age of 54 but with a median MELD of 31 at transplant and had an overall graft loss rate of 0 with 1 year mortality of 0%. The rate of alcohol relapse in the pre protocol group was 19% vs 12% in the post protocol group. Readmission rates were half in the post protocol group. **Conclusion:** Institution of a carefully vetted protocol for transplantation of patients with AAH and ACLF resulted in superior graft survival and improvement in 1 year mortality even after removing the sobriety period and leads to a higher net benefit of life. Post Transplant Relapse prevention strategies and patient selection are the key to successful outcomes.

Disclosures: Parvez Mantry: Nothing to Disclose

3166 | ALCOHOL INTERVENTION AFTER ACUTE VARICEAL BLEEDING: REDUCES ALCOHOL CONSUMPTION, BUT REMAINS UNDERUTILIZED IN REAL-WORLD SETTING

Yu Jun Wong[1] *Alyssa SIM*[2] *Margaret Teng*[3] *Marianne De Roza*[4] *Fria May Manejero*[1] *Jason Chang*[5] *Guan Wee Wong*[6]

[1]*Changi General Hospital, Singapore,* [2]*Tan Tock Seng General Hospital, Singapore,* [3]*National University Hospital, Singapore,* [4]*Sengkang General Hospital, Singapore,* [5]*Singapore General Hospital, Singapore,* [6]*Division of Gastroenterology, Ng Teng Fong Hospital, Singapore*

Background: The prevalence of alcohol-associated (ALD) cirrhosis is rising globally. While pharmacological treatments are safe to prevent relapse and promote abstinence in patients with cirrhosis, the real-world utility and clinical impact of alcohol intervention in decompensated cirrhosis patients remained unclear. We aimed to investigate the real-world utility and clinical impact of alcohol intervention following acute variceal bleeding (AVB). **Methods:** This is a post-hoc analysis of the Singapore Nationwide Acute Variceal Bleeding (AVB) Audit. Alcohol intervention is defined as either the use of pharmacological treatment (Naltrexone, acamprosate, baclofen and gabapentin), or referral to psychologists or addiction service. Favourable alcohol use was defined as a reduction in individuals' alcohol use at one year after AVB compared to baseline (ie: 6-week after AVB). Patients who were demised within 6 weeks of AVB were excluded. **Results:** From a total of 989 cirrhosis patients included in this

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nationwide AVB audit (2015 to 2021), 153 (15.5%) patients with ALD cirrhosis were included for analysis. Patients with ALD cirrhosis have a mean age of 57 (SD: 11) years and were predominantly male (93.5%). The median (IQR) of CTP and MELD scores were 7 (7-8) and 14 (11-19), respectively. The real-world utility of pharmacological treatment for ALD and ALD intervention was low at only 5.4% and 23.1%, respectively. AUD intervention was more common in patients who were younger (51 vs 59, p<0.001) and reported binge drinking (32% vs 17%, p=0.048). Both ALD treatment (19% vs 5%, p=0.065) and intervention (50% vs 23%, p=0.032) were associated with reduced alcohol use at 1 year. Similar findings in subgroup analysis among patients with CTP class A and B: ALD treatment: (20% vs 5%, p=0.078), AUD intervention: (53% vs 21%, p=0.021). The commonest AUD treatment used was naltrexone (38%) and baclofen (38%), with no adverse events and early discontinuation reported from AUD treatment. **Conclusion:** Alcohol intervention was associated with a reduction in alcohol use among ALD cirrhosis patients in the real-world setting. Given the potential of patients with decompensated ALD cirrhosis to recompensate after alcohol abstinence, our findings highlight the gap in improving the uptake of AUD intervention in this cohort.

Disclosures: Yu Jun Wong: Nothing to Disclose, Alyssa SIM: Nothing to Disclose, Margaret Teng: Nothing to Disclose, Marianne De Roza: Nothing to Disclose, Fria May Manejero: Nothing to Disclose, Jason Chang: Boehdringer-Ingelheim: Advisor, Guan Wee Wong: Nothing to Disclose

3167 | SGLT2 INHIBITORS SUPPRESSED THE ONSET OF ESOPHAGEAL VARICES AND EXTRAHEPATIC CANCER COMPARED TO DPP4 INHIBITORS IN TYPE 2 DIABETIC PATIENTS WITH MASLD: A NATIONWIDE MEDICAL CLAIMS DATABASE STUDY IN JAPAN

Takumi Kawaguchi[1] Yoshiyuki Fujishima[2] Fusayo Io[2] Yuri Sato[2] Saeko Uchida[2] Yukiko Kitajima[2]

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Background: Sodium-glucose transporter 2 inhibitors (SGLT2i) were reported to improve hepatic steatosis in patients with type 2 diabetes mellitus (T2DM) and metabolic dysfunction-associated steatotic liver disease (MASLD). However, it remains unclear the effects of SGLT2i on the onset of serious events in patients with T2DM and MASLD. We aimed to investigate the impact of SGLT2i on the incidence of liver-related events including esophageal varices and extrahepatic cancer compared with dipeptidyl-peptidase 4 inhibitors (DPP4i) using a nationwide medical claims database in Japan. **Methods:** We conducted a retrospective cohort study using the Medical Data Vision database. From T2DM patients prescribed SGLT2i or DPP4i (n=1,628,656), eligible patients were classified into SGLT2i (n=4,204) and DPP4i (n=4,204) groups after adjustment by propensity score matching. Effects of SGLT2i on the following outcomes were compared to DPP4i: Outcome 1) changes in HbA1c and ALT levels after 6 months, 2) changes in hepatic fibrosis indexes including FIB-4 index and aspartate aminotransferase to platelet ratio index (APRI) over 12 months, 3) the incidence of newly diagnosed liver-related events (liver cancer, cirrhosis, liver failure, esophageal varices) and extrahepatic cancer during 12 months. **Results:** Outcome 1) After 6 months, DPP4i significantly decreased HbA1c levels than SGLT2i (P<0.01). In contrast, SGLT2i significantly decreased ALT levels than DPP4i (P<0.01). Outcome 2) SGLT2i significantly decreased various hepatic fibrosis indexes including FIB-4 index (P<0.001) and APRI (P<0.001) than DPP4i over 12 months. Outcome 3) There was no significant difference in the overall incidence of liver-related events between the SGLT2i and DPP4i groups during 12 months. In the analysis for each liver-related event, no significant difference in the incidence of HCC, liver cirrhosis, and liver failure between the two groups. However, SGLT2i significantly reduced the incidence of esophageal varices compared to DPP4i (HR 0.12, 95%CI 0.01-0.95). Moreover, SGLT2i significantly reduced the incidence of extrahepatic cancer than DPP4i (HR 0.5, 95%CI 0.30-0.84). We further performed a stratified analysis to identify patients' characteristics associated with SGLT2i-caused suppression of the incidence of extrahepatic cancer. SGLT2i significantly suppressed the incidence of extrahepatic cancer in patients aged ≥65 years, ALT >30 U/L, FIB-4 index ≥1.3, eGFR <60 mL/min/1.73m^2, HbA1c <7.0%, triglyceride ≥150 mg/dL, and HDL-cholesterol ≥40 mg/dL. **Conclusion:** SGLT2i was more beneficial than DPP4i in improving hepatic inflammation and fibrosis indexes. Moreover, SGLT2i suppressed the incidence of esophageal varices and extrahepatic cancer compared to DPP4i. Thus, SGLT2i may be beneficial to improve the prognosis of patients with T2DM and MASLD.

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3168 | IDENTIFICATION OF CANDIDATES FOR MASLD TREATMENT WITH INDETERMINATE VIBRATION-CONTROLLED TRANSIENT ELASTOGRAPHY

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Background: A noteworthy proportion of patients with metabolic dysfunction-associated steatotic liver disease (MASLD) have an indeterminate vibration-controlled transient elastography (VCTE). Among these patients, we aimed to identify candidates for MASLD treatment by diagnosing moderate-to-advanced fibrosis. **Methods:** Real-world prospective multicenter study including a large cohort of MASLD patients with paired VCTE and liver biopsy (n=950). Data was divided in a training (n=250) and validation (n=700) set. In patients with indeterminate liver stiffness measurements (LSM: 8-12 kPa), a diagnostic algorithm was developed and validated to identify significant fibrosis, defined as histological fibrosis stage ≥F2. Statistical analysis was performed using gaussian mixture model (GMM) and k-means unsupervised clusterization. The proposed diagnostic algorithm was applied to the American Gastroenterological Association (AGA) Clinical Care Pathways to evaluate its performance. **Results:** From the eligible population, 33% and 29% had indeterminate VCTE in the training and validation samples, respectively. Control attenuation parameter (CAP) had the best diagnostic performance to differentiate the GMM clusters (AUC: 0.89 [95%CI: 0.86-0.97], with a cut-off of 280 dB/m. Within patients with <280 dB/m, a LSM <9.0 kPa excluded significant fibrosis with a 93% sensitivity. Among patients with ≥280 dB/m, a LSM ≥10.3 kPa diagnosed significant fibrosis with a 91% specificity. The diagnostic algorithm was validated with a 90% sensitivity and 87% specificity. Applying the developed algorithm within the AGA Clinical Care Pathway, 36% of the indeterminate VCTE were possibly re-allocated into low and high-risk groups, correctly classifying 88% of these cases (Figure). Of the 499 participants with initial low-risk (< 8 kPa), 18% had significant fibrosis (13% F2, 5% F3). Among re-allocated low-risk (n=49 with CAP <280 dB/m + LSM <9 kPa), 10% had significant fibrosis (4% F2, 4% F3, 2% F4). Of the 166 participants with initial high-risk (>12 kPa), 83% had significant fibrosis (15% F2, 40% F3, 28% F4). Among re-allocated high-risk (n=53 with CAP ≥280 dB/m + LSM ≥10.3 kPa), 87% had significant fibrosis (36% F2, 34% F3, 17% F4). Initial and re-allocated risk groups also shared similar clinical characteristics. **Conclusion:** To identify candidates for MASLD treatment among indeterminate VCTE, an algorithm-based on the sequential combination of LSM and CAP thresholds can optimize the diagnosis of moderate-to-advanced fibrosis.

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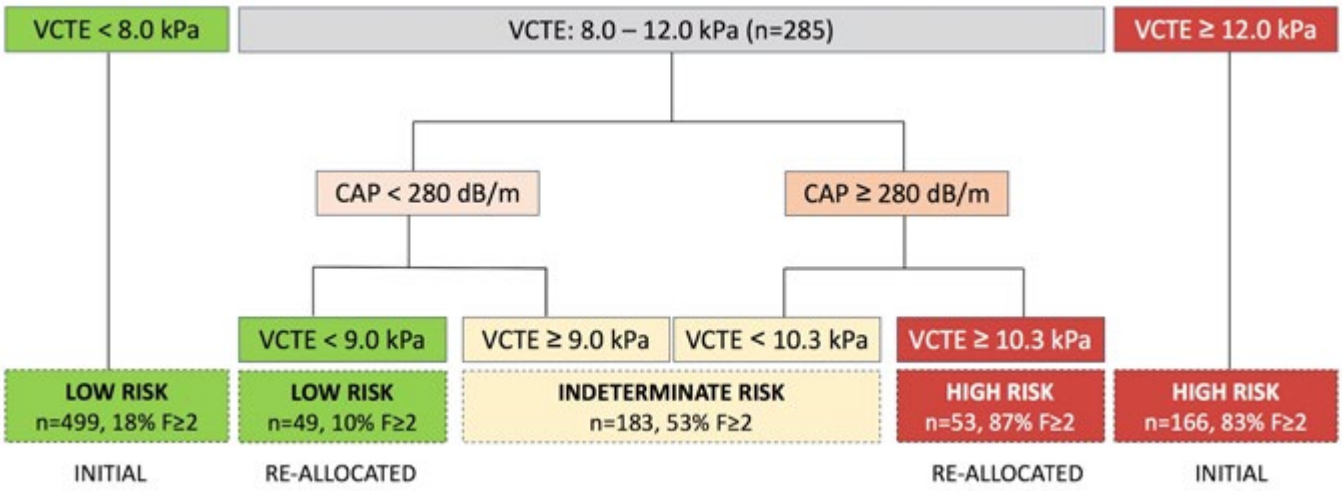

Disclosures: David Marti-Aguado: Nothing to Disclose, Jose Miguel Carot Sierra: Nothing to Disclose, Aida Villalba Ortiz: Nothing to Disclose, Rose Marie Vallejo Vigo: Nothing to Disclose, Carmen Lara Romero: Nothing to Disclose, Marta Martín-Fernández: Nothing to Disclose, Matias Fernandez Paton: Nothing to Disclose, Clara Alfaro-Cervello: Nothing to Disclose, Ana Crespo: Nothing to Disclose, Elena Coello-Cordoba: Nothing to Disclose, Victor Merino Murgui: Nothing to Disclose, Salvador Benlloch: Nothing to Disclose, Judith Perez-Rojas: Nothing to Disclose, Victor Carlos Puglia Puglia: Nothing to Disclose, Antonio Ferrandez: Nothing to Disclose, Victoria Aguilera: Nothing to Disclose, Cristina Montón: Nothing to Disclose, M Desamparados Escudero: Nothing to Disclose, PALOMA LLUCH GARCIA: Nothing to Disclose, rocio aller: Nothing to Disclose, Manuel Romero-Gómez: Nothing to Disclose, Luis Marti-Bonmati: Nothing to Disclose

3169 | EFFECTS OF LUSEOGLIFLOZIN ON MASLD IN PATIENTS WITH TYPE 2 DIABETES MELLITUS: A POOLED META-ANALYSIS OF PHASE III CLINICAL TRIALS

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Background: Luseogliflozin, a sodium-glucose cotransporter 2 inhibitor, potentially exerts pleiotropic effects on the liver. However, sufficient evidence is still lacking on its effect on MASLD. We aimed to investigate the effects of luseogliflozin on hepatic steatosis, fibrosis, and cardiometabolic risk factors in diabetic patients by a pooled meta-analysis. **Methods:** In this pooled meta-analysis, we enrolled diabetic patients who participated in phase III clinical trials of luseogliflozin (luseogliflozin group n=302, placebo group n=191). The primary outcomes were changes in fatty liver index (FLI) and Hepamet fibrosis score (HFS) after 24 weeks. The secondary outcomes were changes in cardiometabolic risk factors and liver function tests after 24 weeks. Statistical analysis was performed using propensity scoring analysis by the inverse probability of treatment weighting method. **Results:** Primary outcomes: Luseogliflozin significantly decreased FLI compared to placebo after 24 weeks (adjusted coefficient -5.423, 95%CI -8.760 to -2.086, P=0.0016). There was no significant difference in changes in HFS between the two groups. However, luseogliflozin significantly decreased HFS compared to placebo in diabetic patients with ALT >30 U/L (adjusted coefficient -0.039, 95%CI -0.077 to -0.001, P=0.0438) and with FIB-4 index >1.3 (adjusted coefficient -0.0453, 95%CI -0.075 to -0.016, P=0.0026). Secondary outcomes: Luseogliflozin significantly decreased HbA1c level, HOMA-IR value, BMI, and uric acid level, and increased HDL-cholesterol level compared to placebo. Moreover, luseogliflozin significantly decreased AST, ALT, and γ-GT levels and increased albumin levels after 24 weeks. **Conclusion:** This pooled meta-analysis demonstrated that 24-week treatment with luseogliflozin improved hepatic steatosis and fibrosis indexes in diabetic patients, especially those with liver injury. Furthermore, luseogliflozin improved various cardiometabolic risk factors as well as liver function tests. Thus, luseogliflozin may be useful for improving MASLD in diabetic patients.

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3170 | CHANGING PRESCRIPTION PATTERN OF ANTI-DIABETIC MEDICATIONS AND IMPROVEMENT IN GLYCEMIC CONTROL IN PATIENTS WITH T2DM, WITH AND WITHOUT CIRRHOSIS: A TERRITORY-WIDE COHORT STUDY IN HONG KONG FROM 2000-2023

Mary Yue Wang[1] Sherlot Juan Song[1] Grace Wong[1] Vincent Wong[1] Terry Cheuk-Fung Yip[1]

[1]The Chinese University of Hong Kong

Background: We aimed to compare the secular trends of glycemic control and anti-diabetic medication use in patients with type 2 diabetes mellitus (T2DM), with and without cirrhosis in a retrospective cohort in Hong Kong. **Methods:** We identified patients with T2DM, with or without cirrhosis between January 2000 and December 2023 and excluded patients without demographic data, <18 years old at T2DM diagnosis, or type 1 diabetes. Secular trends were analyzed in five consecutive periods, i.e., 2000-2004, 2005-2009, 2010-2014, 2015-2019, and 2020-2023. The percentage of patients with and without cirrhosis who achieved time-weighted average hemoglobin A1c (HbA_{1c}) <7% were compared. Differences in proportion of patients using different anti-diabetic medications in each period were examined. **Results:** Of 1,206,233 patients with T2DM from 2000 to 2023, 63,200 (5.3%) (mean age 63.1 years, 52.0% male) had cirrhosis. Between the periods 2000-2004 and 2020-2023, the proportion of patients achieving HbA_{1c} <7% increased from 44.3% to 76.0% in patients with cirrhosis, and from 40.1% to 66.6% in patients without cirrhosis. Sulfonylurea, metformin and insulin were the most commonly used medications in patients with T2DM. More patients with cirrhosis used insulin, and its trend increased from 24.8% to 37.5% (Figure 1A), compared to 16.3% to 20.4% in those without cirrhosis (Figure 1B). The use of sulfonylurea consistently declined in both groups throughout the study period, whereas the trend of metformin use remained relatively stable over the years. Notably, a significantly higher proportion of patients without cirrhosis used metformin compared to those with cirrhosis (61.1% vs 37.4% in 2020-2023, p<0.001). The use of thiazolidinediones and dipeptidyl peptidase-4 inhibitors also experienced a huge increase. The adoption of novel anti-diabetic medication, including sodium glucose co-transporter-2 inhibitors and glucagon-like-peptide 1 receptor agonists, has significantly increased recently. **Conclusion:** Glycemic control improved over time in 1.2 million patients with T2DM in Hong Kong and was more prominent among patients with cirrhosis. The use of metformin was less common in patients with cirrhosis, while they had a higher prevalence of insulin use. There has been an increasing use of new classes of anti-diabetic medications in recent years. The correlations between the change in prescription patterns and glycemic controls need to be further explored.

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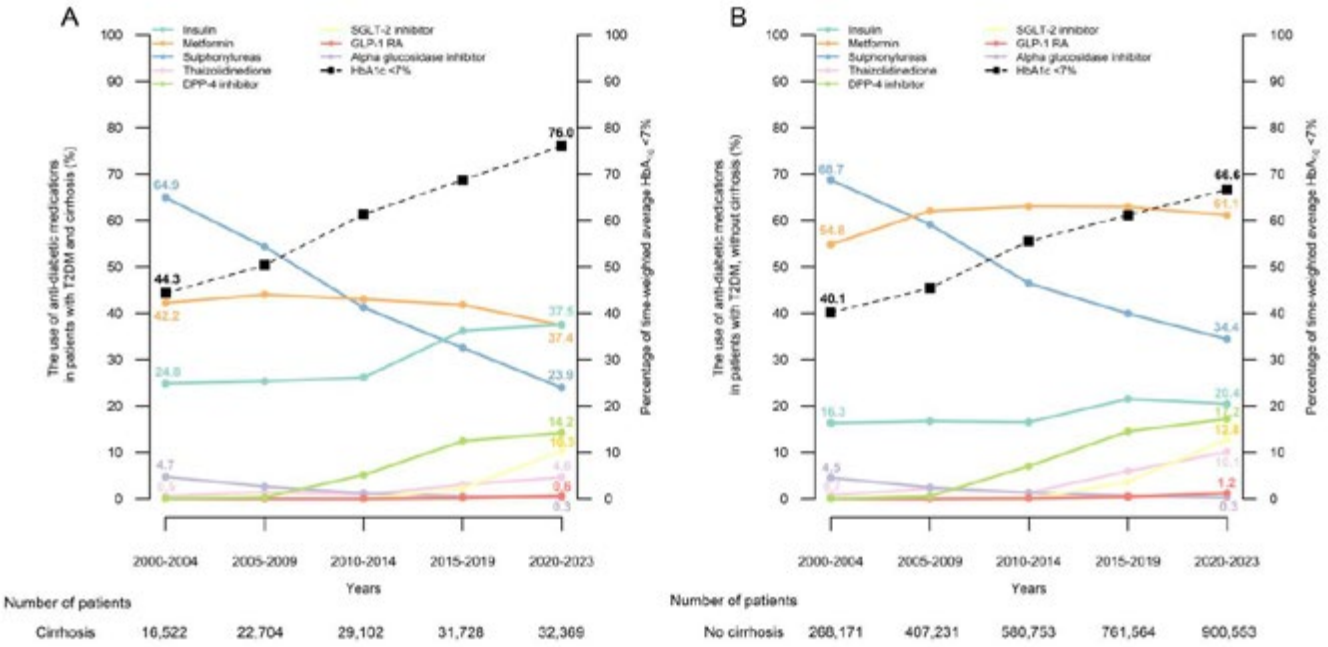

Disclosures: Mary Yue Wang: Nothing to Disclose, Sherlot Juan Song: Nothing to Disclose, Grace Wong: AstraZeneca: Advisor, Gilead Sciences: Advisor, Gilead Sciences: Speaking and Teaching, Janssen: Advisor, GSK: Advisor, GSK: Speaking and Teaching, Abbott: Speaking and Teaching, AbbVie: Speaking and Teaching, AstraZeneca, Gilead Sciences, GlaxoSmithKline and Janssen,: Advisor, Abbott, AbbVie, Ascletis, Bristol-Myers Squibb, Echosens, Gi: Speaking and Teaching, Gilead Sciences: Grant/Research Support, AstraZeneca, Gilead Sciences, GlaxoSmithKline and Janssen: Consultant, Abbott, AbbVie, Ascletis, Bristol-Myers Squibb, Echosens, Gi: Speaking and Teaching, AstraZeneca, Gilead Sciences, GlaxoSmithKline Pharmaceutical: Consultant, Gilead Sciences: Independent Contractor, AstraZeneca, Gilead Sciences, GSK and Janssen,: Advisor, Abbott, AbbVie, BMS, Gilead Sciences, GSK, Janssen, Roche: Speaking and Teaching, Gilead Sciences: Grant/Research Support, Vincent Wong: Nothing to Disclose, Terry Cheuk-Fung Yip: Gilead Sciences: Consultant, Gilead Sciences: Advisor, Gilead Sciences: Speaking and Teaching

3171 | EVALUATION OF MASH DRUG EFFICACY USING LIVER ORGANOIDS BASED ON DRUG TARGET PATHWAYS

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Background: Metabolic dysfunction-associated steatohepatitis (MASH) is a disease characterized by passive lipotoxicity leading to activation of hepatic stellate cells (HSCs) and Kupffer cells (KCs), resulting in fibrosis. The conventional in vitro model such as HepG2 cells has limitations in evaluating drug efficacy in fibrosis due to the absence of HSCs and KCs. Liver organoids (miniature livers in vitro) consist of diverse liver-specific cell types, including HSCs and KCs, which better mimic the native liver. Here, we compare HepG2 cell line and induced pluripotent stem cell (iPSC)-derived liver organoids to determine which in vitro model is more suitable to evaluate drug efficacy against lipid accumulation and fibrosis. **Methods:** Human iPSCs are sequentially differentiated into endoderm, posterior foregut, and liver organoids. We established a liver organoid bank and were able to produce uniform organoids using ECM hydrogel (Matrigel® or Regenix™) in three weeks. The expression of liver-specific markers in HepG2 and organoids was detected by quantitative real-time polymerase chain reaction (qRT-PCR). HepG2 and liver organoids were treated with fatty acids and glucose to induce MASH. Then, we administered the following drugs alone or in combination: Resmetirom (10 μM), Lanifibranor (80 μM), Firsocostat (20 μM) and Liraglutide (20 μM). Change in gene expression associated with lipid oxidation, lipogenesis, and fibrosis were evaluated using qRT-PCR. Hepatic lipid accumulation was examined by triglyceride measurement and inflammation was evaluated by the expression of proinflammatory cytokines. **Results:** Liver organoids exhibited higher expression of hepatocyte, HSCs, and KCs markers compared to HepG2 cells. When the liver organoids

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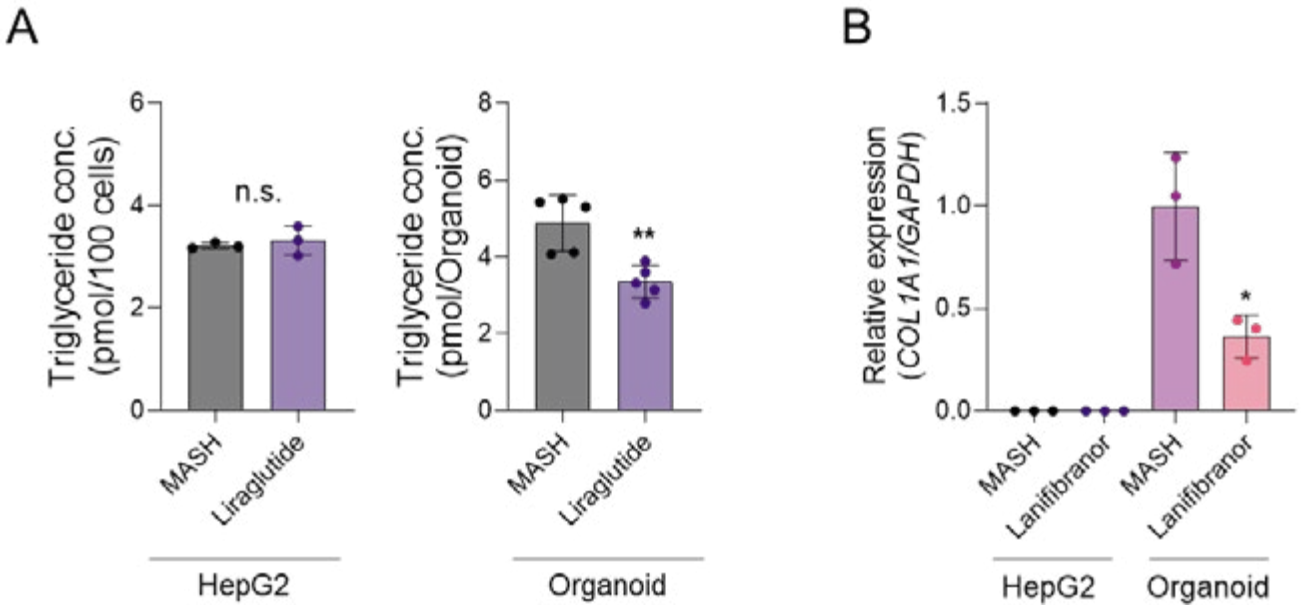
were treated with fatty acids and glucose to induce MASH, the formation of lipid droplets was confirmed by immunostaining and triglyceride assay. Additionally, increases in fibrosis markers (α-SMA, collagen 1a1) and inflammatory cytokine (IL-6) was observed. In MASH organoid model, Liraglutide or Firsocostat alone had minimal effect on lipid reduction, but when combined with drugs like FGF19 and FGF21 analogs, they significantly reduced triglyceride levels. Applying the same conditions to the MASH HepG2 model showed no effect on triglyceride level change (Figure A). The inhibitory effect of Lanifibranor on HSC activation was confirmed by decreased collagen gene expression in the MASH organoid model. In contrast, in MASH HepG2 model lacking HSCs, we were unable to assess collagen changes upon Lanifibranor treatment (Figure B). **Conclusion:** Although accurately reproducing the lipid metabolism of actual patients is difficult, the organoid model was shown to be more appropriate for evaluating drug efficacy than the existing in vitro 2D cell models.



Disclosures: Yeonjoo An: Cellartgen: Employee, Anthony Mukhtar: Cellartgen: Employee, Jiseon Kim: Nothing to Disclose, Jihye Choi: Nothing to Disclose, Seung-Woo Cho: Nothing to Disclose, Suran Kim: cellartgen: Employee

3172 | LONG-TERM OUTCOMES OF GLP-1 ANALOGUES TREATMENT IN MASLD PATIENTS WITH TYPE 2 DIABETES

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Background: Glucagon like peptide-1 (GLP-1) analogue is one of the diabetes agents available on the market. An important advantage of GLP-1 analogue is its favorable effect on the reduction of body weight (BW). The aim of this study is to analyze the long-term outcomes of GLP-1 analogues as treatment for metabolic dysfunction associated steatotic liver disease (MASLD) patients with type 2 diabetes mellitus (T2DM). **Methods:** This is a single arm prospective observational study (UMIN000004512). We prospectively enrolled consecutive 182 Japanese MASLD patients with T2DM who were administered GLP-1 analogues between 2010 June 1 and 2022 December 31. The last follow-up date was 2023 December 31. We compared the changes of laboratory data including liver inflammation and fibrosis score after administration of GLP-1 analogues. The primary end point was normalization of ALT level (less than 40 IU/l). The secondary endpoints were alteration of liver fibrosis score and re-exacerbation of ALT level (equal to or over 40 IU/l). **Results:** The median follow-up period was 5.1 years. The median age was 54.7 years old and 132 (72.5%) patients were male. The median ALT level was 66 IU/l. After administration of GLP-1 analogues, normalization of ALT level was observed in 135 (74.2%) patients at the end of follow-up, and the cumulative normalization rate of ALT was 6 months, 1 year and 2 years of 23.3%, 40.5%, and 60.9%, respectively. Fibrosis score (FIB-4 index) also significantly improved (1.29 to 1.09, P < 0.01). Multivariate analysis indicated that BW reduction (HR: 0.98 per 1kg, 95%CI: 0.97-0.99, P=0.024), presence of hypertension (HR: 1.56, 95%CI: 1.10-2.21, P=0.012), and alteration of T2DM (HR: 0.61, 95%CI: 0.43-0.86, P<0.01) as

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independent factors related to the normalization of ALT level. During the follow-up period, 84 of 135 patients (62.2%) who had achieved improvement of ALT level experienced re-exacerbation. BW gain was independently related to re-exacerbation after normalization of ALT level (HR: 1.09 per 1 kg gain of BW, 95%CI: 1.05-1.13, P<0.01). No severe side effects exceeded CTCAE grade 2 were occurred. During the observational period, 2 patients died of malignancy, and 4 patients lost their lives to ischemic cardiovascular diseases. Malignancies were detected in 9 patients; 4 hepatocellular carcinoma, 3 breast cancer, 1 pancreas cancer, and 1 cholangiocellular carcinoma. **Conclusion:** The administration of GLP-1 analogue led not only good glycaemic control but also normalization of ALT level with a favorable effect of BW reduction. Maintenance of BW after normalization of ALT level was also very important to avoid re-exacerbation of liver inflammation and fibrosis.

Disclosures: Takamasa Ohki: Nothing to Disclose

3173 | REAL WORLD DATA SHOWS MEANINGFUL IMPROVEMENT IN LIVER FIBROSIS IN VETERANS ENROLLED IN MULTI-DISCIPLINARY LIVER WEIGHT MANAGEMENT CLINIC ON GLP-1 RECEPTOR AGONISTS

Paul Henderson[1] Craig Casella[2] Jennifer Kerns[3] Atoosa Rabiee[4] Shruti Gandhi[3] Sabyasachi Sen[3] Marianna Papademetriou[3] Jessica Davis[4]

[1]Georgetown University, [2]Department of Veteran Affairs - DC, [3]DC VA Medical Center, [4]Washington DC VA Medical Center

Background: For patients with comorbid obesity, the prevalence rate of metabolic dysfunction associated steatotic liver disease (MASLD) is as high as 90%. Only 1% of patients eligible for anti-obesity medications receive pharmacotherapy. A multidisciplinary liver weight management clinic was established at the Washington DC Veterans Affairs Medical Center in 2022 with a goal of improving access to pharmacotherapy, lifestyle counseling and bariatric interventions for veterans with MASLD. This study aimed to assess the impact of GLP-1 receptor agonists (GLP-1 RA) on metabolic parameters and hepatic fibrosis for patients enrolled in the liver weight management clinic. **Methods:** Authors conducted a single-center retrospective cohort study of patients seen in the DC VA Medical Center liver weight management clinic from June 2022 to June 2023 who were prescribed GLP-1 RA. The impact of treatment on weight and metabolic parameters was evaluated. Baseline and follow-up hepatic fibrosis and steatosis were obtained in patients who underwent non-invasive (NIV) testing with serial transient elastography. Baseline measurements were defined as the pre-treatment value that was closest in proximity to the medication start date, within at least 24 months of the medication start date. Recent measurements were defined as the most recent value in the defined time period with at least 6 months duration from the time of the baseline value. **Results:** From June 2022 to June 2023, 66 new patients were seen in the weight management clinic. Thirty-nine (59%) patients were prescribed GLP-1 RA. Semaglutide (n=38) was the predominant therapy in conjunction with liraglutide (n=1). The average age was 53 years, and 82% of patients were male with a mean baseline BMI of 38.8. Thirteen (33%) patients had comorbid diabetes. At baseline, sixteen patients had F0:F1 fibrosis, sixteen F2, three F3, and four F4. Patients (n=33) lost an average of 19.7 lbs (SD 15.5), which translated to an overall mean total body weight loss of 8.1% (SD 6.8) (table 1). Among patients with both baseline and follow-up fibroscans (n=11), there was an average kPa change of -1.9 (SD 1.7, range +1.1 to -4.1) and average CAP change of -57 (SD 45, range -10 to -131). **Conclusion:** This real-world data shows clinically meaningful changes with the use of GLP-1 RA for a veteran population with MASLD in the context of a multidisciplinary weight management clinic. Patients with serial elastography moved from an average of 8 kPa, corresponding with F2 fibrosis, a population identified by AASLD as “at risk” given worse outcomes, to 6.1 kPa, consistent with F0:F1 fibrosis. This significant improvement in liver fibrosis on NIV testing among participants underscores the importance of GLP-1 RA in the treatment and management of MASLD. Future studies are needed to evaluate real-world performance of GLP-1 RA in MASLD as well as expand the role of NIV testing in assessment of medication response.

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Baseline Demographics (n=39)			
Age, mean (SD)	53 (10)	**Number of patients on GLP – 1 dose**	
Sex, female %	17.9 (7/39)	**Sem 2.4**	18
Race, %		**Sem 2.0**	1
NHB	43.6 (17/39)	**Sem 1.7**	3
NHW	30.8 (12/39	**Sem 1**	4
HIS	12.8 (5/39)	**Sem 0.5**	8
NHA	2.5 (1/39)	**Sem 0.25**	4
UNK	10.3 (4/39)	**Lira 0.6**	1
Comorbid DM	33.3% (13/39)		
Metabolic Parameters (n=39)			
	Baseline (SD)	**Recent (SD)**	**Mean Change (SD)**
Weight (lbs)	258.5 (49.5)	235.1 (46.2)	-19.7 (15.5)
BMI (kg/m²)	38.8 (5.3)	35.8 (5.4)	
A1c (%)	6.1 (0.8)	5.6 (0.5)	-0.5 (0.6)
LDL (mg/dL)	110.0 (35.7)	97.9 (35.0)	-17 (27)
TG (mg/dL)	152 (82)	128 (71)	-23 (69)
Transient Elastography (n=11)			
Median stiffness (kPA)	8.0 (2.9)	6.1 (3.5)	-1.9 (1.7)
CAP (dB/m)	351 (46)	294 (59)	-57 (45)

Table 1. Baseline demographics and changes in metabolic parameters and fibrosis for patients enrolled in multidisciplinary liver weight management clinic who were prescribed GLP-1 agonist.

Disclosures: Paul Henderson: Nothing to Disclose, Craig Casella: Nothing to Disclose, Jennifer Kerns: Nothing to Disclose, Atoosa Rabiee: Nothing to Disclose, Shruti Gandhi: Nothing to Disclose, Sabyasachi Sen: Nothing to Disclose, Marianna Papademetriou: Nothing to Disclose, Jessica Davis: Nothing to Disclose

3174 | THE ASSOCIATION BETWEEN LEVOTHYROXINE AND ITS POTENTIAL PREVENTATIVE EFFECT ON LIVER CONDITIONS, PARTICULARLY IN MASLD AND MASH

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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is a prevalent yet underdiagnosed condition, affecting approximately 30% of the global population. The inflammatory progression of MASLD is classified as metabolic dysfunction-associated steatohepatitis (MASH). Recent research highlights the role of thyroid hormones in the pathogenesis of both MASLD and MASH. Novel agents, such as Resmetirom, a thyroid hormone receptor beta agonist have received approval in the United States for the treatment of noncirrhotic MASH. Levothyroxine, a T4 thyroid hormone used in managing primary hypothyroidism, may play a role in treating these liver disorders. Our study investigates the potential relationship between levothyroxine and the prognosis of liver disease, providing new insights into therapeutic strategies. **Methods:** Propensity score matching was used to match UK Biobank patients without prior liver disease, based on criteria including age, gender, alcohol consumption, ethnicity, hypothyroidism, type 2 diabetes and disorders of lipoprotein. These criteria were selected in accordance with the new classification for steatotic liver disease to minimize potential confounding variables. The study compared outcomes among 46,395 patients who were either levothyroxine users or non-users after matching using a Cox regression model in R. Incident liver disease was defined as any new diagnosis of K70-K77 post the baseline assessment. Fibrosis and cirrhosis of liver was defined using ICD-10 code K74, inflammatory liver diseases by K75. Based on ICD-10 code K75.8 was formerly classified as non-alcohol steatohepatitis, which has been redefined as MASH. Other diseases of liver was classified as per ICD 10 code as K76. Fatty liver disease, now known as MASLD was defined using former ICD-10 code classification as K76.0. **Results:** In the UK Biobank levothyroxine users showed a 25% risk reduction in developing new liver disease (HR_{UKB}=0.751, 95% CI, 0.678-0.833; p=<.001), a 24% lower risk of developing fibrosis and cirrhosis of the liver (HR_{UKB}=0.756, 95% CI, 0.582-0.983; p=0.037), a 35 % risk reduction in developing hepatosteatosis

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or MASH (HR_{UKB}=0.645 95% CI0.423-0.987; p=0.043). The most notable and statistically significant finding is the association between levothyroxine use and a 29% reduction in developing non-alcoholic fatty liver disease or MASLD (HR_{UKB}=0.708, 95% CI, 0.617-0.813; p=<0.001) **Conclusion:** Recent studies have clinically linked intrahepatic hypothyroidism to the progression of MASLD and MASH. These studies suggest that a decreased intrahepatic conversion of T4 to T3 promotes the progression of MASH. Our study demonstrates, however, that use of levothyroxine, a T4 hormone might be an effective option for the prevention of liver diseases. In conclusion, our results emphasizes the need for further research to comprehensively understand the impact of levothyroxine on liver disease outcomes.

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Table: Levothyroxine users compared with non-users at baseline and development of liver disease, fibrosis and cirrhosis, inflammatory liver disease, MASH and MASLD

Disease and Treatment Group	No with Disease/Total No. Patients	HR	95% CI	P-value
Incident liver Disease (K70-K77) **				
No Levothyroxine intake	1176/26,536	1.00	(reference)	-
Levothyroxine intake	774/19,859	0.751	0.678-0.833	<0.001
Subgroups***				
Fibrosis and cirrhosis of liver (K74)	117//19,859	0.756	0.582-0.983	0.037
Inflammatory liver diseases (K75)	95/19,859	0.738	0.552-0.988	0.041
Non-alcoholic steatohepatitis (K75.8)****[1]	41/19,859	0.646	0.423-0.987	0.043
Other diseases of liver (K76)	638/19,859	0.737	0.659-0.825	<0.001
Fatty liver disease (K76.0) ****[2]	399/19,859	0.708	0.617-0.813	<0.001

HR = Hazard Ratio, CI = Confidence Interval
MASLD = Metabolic dysfunction-associated steatotic liver disease
MASLD = metabolic dysfunction associated steatohepatitis

*Matching was performed at a ratio of 1:2
**We defined incident liver disease as the occurrence of any new diagnosis of K70-K77 after baseline
***For sub diagnoses (K74-K76.0) only individuals taking levothyroxine are listed, with HR and P-values calculated consistently compared with individuals not taking levothyroxine
****[1]K75.8 is classified according to ICD-10 code as non-alcoholic steatohepatitis (NASH), currently redefined as MASH
****[2]K76.0 according to ICD-10 code was formerly classified as non-alcoholic fatty liver disease, (NAFLD) which as per ICD-11 code has been reclassified to MASLD

Disclosures: Joel Joy: Nothing to Disclose, Mara Sophie Vell: Nothing to Disclose, Kai Markus Schneider: Nothing to Disclose, Carolin Victoria Schneider: Nothing to Disclose

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3175 | EFFECTS OF SAROGLITAZAR IN COMPENSATED MASLD CIRRHOSIS: A MAGNETIC RESONANCE ELASTOGRAPHY-BASED (MRE) BASED SINGLE ARM PROSPECTIVE STUDY

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Background: Saroglitazar, dual peroxisome proliferator-activated receptor α/γ agonist, has been shown to be promising in metabolic dysfunction-associated steatotic liver disease (MASLD). However, its safety and efficacy in MASLD-compensated cirrhosis (CC) remain relatively unexplored. **Methods:** In a single-center, prospective single-arm study, we assessed the safety of Saroglitazar (4mg for 24 weeks) in MASLD-CC, and evaluated the effects on anthropometric indices, biochemical measurements, liver fat content (LFC) by Magnetic resonance Imaging Proton Density Fat Fraction (MRI-PDFF) and liver stiffness measurement (LSM) by Magnetic resonance elastography (MRE). To discern measurement error from real changes, a threshold of 0.75kPa for MRE-LSM was used to compare LSM-progressors and regressors **Results:** Out of 37 individuals with MASLD-CC, 26 [age 61(58-64) years, 61.5% females, body mass index 28.7±3.3kg/m^2,88.4% obese, 76.9% diabetes] completed 24 weeks follow up. Body weight [69.5(64-75)vs68.3(66-71 Kg),p=0.02], ALT[42.5(30-61)vs. 22.5(20-36)U/L], AST [53(39-74) vs. 40(33-49)U/L],fasting blood sugar [109(100-129.5)vs. 100.5(96.3-108.3)mg/dl], total cholesterol (157(139.5-171) vs. 140(120-167)mg/dl],triglycerides [121(95-153)vs. 100(94.113.5)mg/dl] and LFC (7.2(6.9-11.1) vs 5.1(3.5-6.1)%]decreased with Saroglitazar(p=<0.01 for all). MRE-LSM [5.4(4.9-6.2) vs. 5.1(4.9-5.8_] decreased in the overall cohort (p=0.04). 4(15.3%) and 2 (7.6%) showed MRE-LSM regression and progression of ≥0.75 kPa respectively. No differences were noted between regressors and progressors using the 0.75kPa threshold (23.5% vs 22.2%, p=0.91). 2 patients (pruritis, increased urine frequency) reported adverse events not requiring medication discontinuation **Conclusion:** Saroglitazar use in MASLD-CC appears safe, and is associated with improved biochemical parameters and LFC, but may not translate to clinically meaningful LSM changes.

Disclosures: Akash Roy: Nothing to Disclose, Surabhi Jajodia: Nothing to Disclose, Usha Goenka: Nothing to Disclose, Arka De: Nothing to Disclose, Awanish Tewari: Nothing to Disclose, Nikhil Sonthalia: Nothing to Disclose, Uday Ghoshal: Nothing to Disclose, Mahesh Goenka: Nothing to Disclose

3176 | REAL-WORLD ASSESSMENT OF GLUCAGON-LIKE PEPTIDE 1 RECEPTOR AGONIST (GLP-1RA) IN THE MANAGEMENT OF PATIENTS WITH MASLD WITH DIFFERENT STAGES OF LIVER FIBROSIS

Dalton Caviness[1] Malcolm Chapman[1] Joshua Fricker[1] Fernando Bril[1] Meagan Gray[1]

[1]University of Alabama at Birmingham

Background: Background: While weight loss remains the backbone of MASLD therapy, the number of patients achieving significant weight loss with lifestyle modifications is quite low. GLP-1RA can play an important role facilitating weight loss, however, several factors preclude widespread utilization of these agents in Hepatology clinics. Therefore, we sought to assess the use and efficacy of GLP-1RA in a hepatology-driven multidisciplinary clinic managing patients with MASLD. **Methods:** Patients who established care at the University of Alabama at Birmingham's Multidisciplinary MASLD clinic from 2/2022 to 1/2024 with at least one follow-up visit were included in the study. Presence of MASLD was defined based on available evidence at the time of chart review. GLP1-RA use was defined as an available prescription for a GLP-1RA during the course of follow-up. Participants with excessive alcohol consumption, alternative etiologies of liver disease, and/or steatogenic medications were excluded. **Results:** A total of 191 adults were included (52 ± 14 years old; 42% male, 73% Non-Hispanic White, 14% Non-Hispanic Black; BMI: 34.8 ± 6.8kg/m2; type 2 diabetes: 39%). Mean follow-up was 17 ± 12 months. A total of 76 patients (40%) had GLP-1RA use reported and follow-up was similar for users and non-users. Patients prescribed GLP1-RA had higher BMI and more T2D (Table 1). At follow-up, GLP1-RA users had achieved significantly higher weight loss (-5.5 ± 9.1% vs. -1.1 ± 7.8%, p < 0.001) than non-users. Moreover, a significantly higher percentage achieved ≥10% body weight loss (27.6% vs. 9.8%, p = 0.001). GLP-1RA use was associated with a significant reduction of AST (-12 ± 31 vs. -4 ± 26 U/L, p=0.049) and A1c among the subgroup of patients with T2D (-0.5 ± 1.2 vs. +0.3 ± 1.7, p=0.030). Response in weight among GLP-1RA was not significantly different

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when patients were divided in quartiles of liver fibrosis based on US or magnetic resonance elastography. **Conclusion:** Conclusions: In a multidisciplinary MASLD clinic, the use of GLP1RA is still relatively low (40%), but it led to significantly more weight loss, and to a higher percentage of patients achieving 10% body weight loss than non-users. Moreover, response was similar across all stages of liver fibrosis based on US or magnetic resonance elastography. These data aid to a growing body of literature recommending more coverage for GLP1-RA and higher use in MASLD patients.

	GLP-1RA users (n = 76)	Non users of GLP-1RA (n = 115)	p-value
Age (years)	53 ±12	52 ± 16	0.67
Gender (% male)	49%	37%	0.122
Race Non-Hispanic White Non-Hispanic Black	 74% 16%	 73% 13%	
Body mass index (kg/m^2)	36.1 ± 5.8	33.9 ± 7.3	0.024
ALT (U/L)	53 ± 45	48 ± 40	0.50
AST (U/L)	39 ± 34	35 ± 22	0.33
Presence of T2D (%)	64%	27%	p<0.001
A1c (%)	6.3 ± 1.3	5.8 ± 0.9	0.007
Mean follow-up time (months)	18 ± 12	17 ± 12	0.60
Mean Weight loss (%)	-5.5 ± 9.1%	-1.1 ± 7.8%	p<0.001
Rate of patients achieving ≥10% weight loss	27.6%	9.8%	p=0.001
Change in ALT (U/L)	-17 ± 40	-10 ± 45	p=0.28
Change in AST (U/L)	-12 ± 31	-4 ± 26	p=0.049
Change in A1C in patients with T2D (%)	-0.5 ± 1.2	0.3 ± 1.7	p=0.030

Disclosures: Dalton Caviness: Nothing to Disclose, Malcolm Chapman: Nothing to Disclose, Joshua Fricker: Nothing to Disclose, Fernando Bril: NovoNordisk: Consultant, NovoNordisk: Speaking and Teaching, Boehringer Ingelheim: Speaking and Teaching, Boehringer Ingelheim: Advisor, Meagan Gray: NovoNordiesk: Consultant

3177 | A REAL-WORLD EVIDENCE, PHASE 4, MULTICENTER, OPEN-LABEL, SINGLE-ARM STUDY TO EVALUATE THE SAFETY AND EFFICACY OF SAROGLITAZAR 4 MG IN PATIENTS WITH NON-ALCOHOLIC FATTY LIVER DISEASE WITH OBESITY, TYPE 2 DIABETES MELLITUS, DYSLIPIDEMIA, OR METABOLIC SYNDROME

Deven Parmar[1] *Arun Sanyal*[2] *Kevin Kansagra*[3] *Rahul Shrivastava*[3]

[1]*Zydus Therapeutics Inc,* [2]*Virginia Commonwealth University,* [3]*Zydus Research Center*

Background: Non-alcoholic fatty liver disease (NAFLD) is a common disease and has a prevalence of 13-32% globally and 5-28% in Asian countries, including India. NAFLD is a hepatic component of the metabolic syndrome, which is a clinical syndrome characterized by obesity, dyslipidemia, type 2 diabetes mellitus (T2DM), and hypertension. Saroglitazar is a dual peroxisome proliferator-activated receptor alpha/gamma agonist and is approved in India for the treatment of NAFLD and non-cirrhotic non-alcoholic steatohepatitis. Although previous phase II and III studies have demonstrated that saroglitazar 4 mg dose leads to significant reduction in liver fat, liver enzymes, and liver stiffness in patients with NAFLD, a real-world evidence (RWE) study for saroglitazar in Asian population with NAFLD and comorbidities is lacking. Hence, a phase 4, RWE study was planned with the aim to evaluate the safety and efficacy of saroglitazar 4 mg in patients with NAFLD with comorbidities (obesity, dyslipidemia, T2DM, and metabolic syndrome) in India. Here, we present the design and plan of this ongoing study with initial safety and efficacy data. **Methods:** This RWE, open-label, single-arm study is being conducted at multiple centers in India, with a target patient size of 1500. The study consists of a screening period of up to 4

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weeks, a treatment period of 52 weeks, and end of the study assesssment on completion of 364 days/52 weeks of the treatment. The major safety endpoints include frequency and severity of treatment-emergent adverse events (AEs)/serious AEs (SAEs), whereas the main efficacy endpoints comprise the change in liver stiffness measurement (LSM) from baseline to week 24 and 52. **Results:** At present, more than 450 patients have been screened at various centers across India; of these, enrolled patients had LSM ≥8 kPa and/or serum ALT ≥45 U/L. The mean (±SD) age and BMI of first 322 enrolled and analyzed patients were 46 ± 12 years and 29.8 ± 4.5 kg/m^2, respectively; the men to women ratio was 228:94. Among 65 patients who completed 6-month treatment (24 weeks), a significant improvement in LSM (p<0.001) and serum ALT and AST levels (p<0.05) was observed compared with those at baseline; in addition, triglyceride levels also demonstrated significant improvements. Three AEs (in two patients) have been observed among enrolled population thus far, and all observed AEs were successfully resolved. **Conclusion:** This ongoing RWE, phase 4 study helps establish the role of saroglitazar 4 mg in decreasing liver injury and stiffness in patients with NAFLD and comorbidities. Results also demonstarted that saroglitazar 4 mg improved hepatic status without any safety issues.

Disclosures: Deven Parmar: Zydus Therapeutics Inc: Employee, Arun Sanyal: Genfit, Akarna, Tiziana, Durect, Inversago, Hemoshear, North: Stock - publicly traded company, Astra Zeneca (60K), Boston Pharmaceutical

3178 | THE 5-YEAR MORTALITY RATE IN MASLD PATIENTS UNDERGOING PHARMACOLOGIC VERSUS BARIATRIC INTERVENTIONS

Leith Ghani[1] Qumber Ali[1] Majd Aboona[1] Pooja Rangan[2] Jay Kumar[1] Moises Nevah Rubin[3] Karn Wijarnpreecha[4] Mike Fallon[5] Farah Husain[6] Ma Ai Thanda Han[7]

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Background: The mortality rate of MASLD patients is rising. Comparison of mortality in MASLD patients who underwent bariatric surgery versus Glucagon-Like Peptide 1 receptor agonist (GLP-1 RA) or Sodium-Glucose Cotransport 2 inhibitor (SGLT2i) is lacking in the literature. Understanding the comparative effectiveness of these interventions in the context of mortality is crucial for informing evidence-based strategies for managing MASLD population. **Methods:** This is a retrospective, multicenter study across the Banner Health System of MASLD patient cohort which was identified with an ICD code for non-alcoholic fatty liver disease and 1 of 5 metabolic criteria. We included individuals who followed for 12 months or more after intervention and had at least one of the interventions: bariatric surgery alone, GLP-1 RA, SGLT2i, or combination of more than one therapy. We compared the 5-year mortality dependent on different interventions. To identify 5-year mortality, we selected patients who died between 12 and 60 months after the intervention. We conducted medication reconciliation to ascertain the use of GLP-1 RA and SGLT2i. For bariatric surgeries, we utilized ICD codes to initially identify relevant procedures and further refined our dataset by including only those surgeries performed by bariatric surgeons. A Cox regression model was used to compare the 5-year mortality in each group to bariatric surgery alone after adjusting for tobacco use, age, BMI, sex, race, HTN, HLD, and DM. The Kaplan-Meier survival curve was produced. **Results:** The cohort included 8,619 patients, 5.8% of patients underwent bariatric surgery, 39.3% of patients received GLP-1 RA, 23.4% of patients treated with SGLT2i, and 31.5% of patients received more than one therapy. When compared to bariatric surgery alone, patients taking GLP-1RA had an adjusted Hazard Ratio (aHR) of 2.99 (P < 0.001), those taking SGLT2i had an aHR of 2.96 (P < 0.001), and the combination therapy group had an aHR of 1.78 (P < 0.001). The Kaplan-Meier survival curve for 5-year mortality suggested patients who underwent bariatric surgery had a better survival than those received treatment with GLP-1 RA, SGLT2i, or combination therapy (Figure 1). **Conclusion:** In this multicenter study, bariatric surgery appears to be superior compared to GLP-1 RA, SGLT2i, or combination therapy when studying the 5-year mortality. Patients treated with GLP-1 RA and SGLT2i therapies may be at a higher risk of mortality due to underlying metabolic disorders or cardiovascular disease. Further prospective investigation is warranted.

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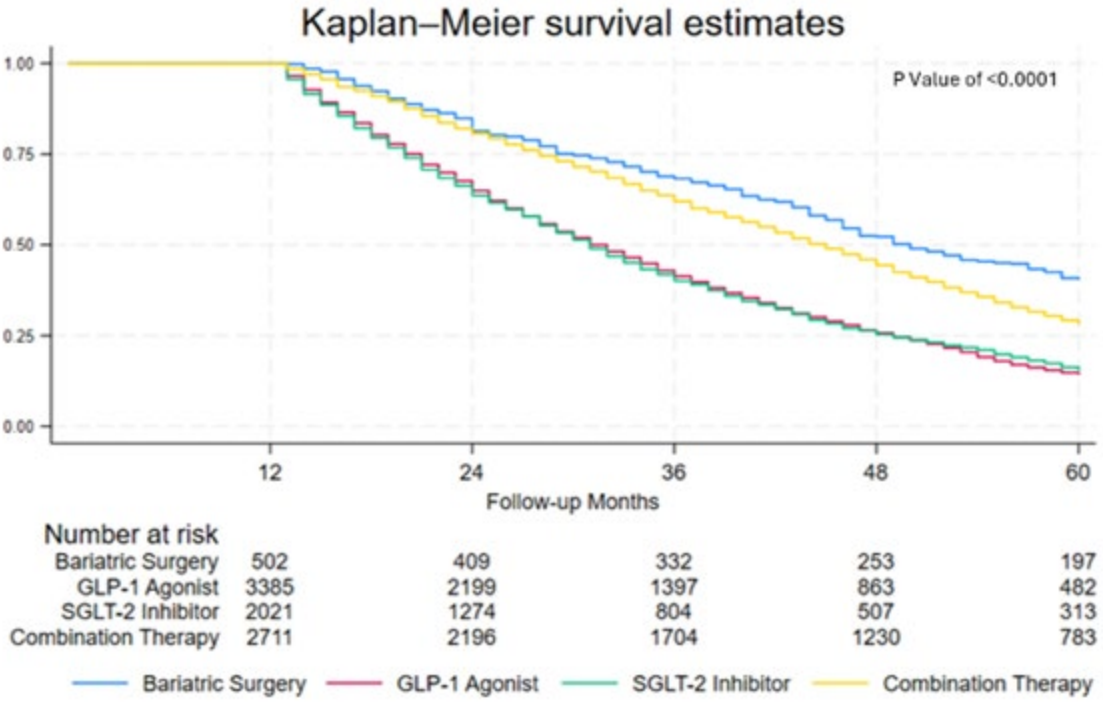

Disclosures: Leith Ghani: Nothing to Disclose, Qumber Ali: Nothing to Disclose, Majd Aboona: Nothing to Disclose, Pooja Rangan: Nothing to Disclose, Jay Kumar: Nothing to Disclose, Moises Nevah Rubin: Nothing to Disclose, Karn Wijarnpreecha: Nothing to Disclose, Mike Fallon: Nothing to Disclose, Farah Husain: J&J Ethicon: Speaking and Teaching, W.L. Gore: Speaking and Teaching, Ma Ai Thanda Han: Nothing to Disclose

3179 | A PHASE I TRIAL TO DETERMINE LOWEST EFFECTIVE DOSE OF BETAINE FOR IMPROVEMENT OF ALT IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE

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[1]*VA Long Beach Healthcare System*

Background: Betaine is an inexpensive nutraceutical that has improved ALT and liver histology in some but not all clinical trials of MASH when administered at 20 g/day. Betaine at a dose of 4 g/day and 8 g/day for 12 weeks improved ALT among subjects with a clinical diagnosis of MASLD. The aim of this phase I trial was to determine the lowest effective dose of betaine for treatment in MASLD. **Methods:** 26 subjects with clinically diagnosed MASLD and ALT>50 IU/L received betaine 1 g/d (n=10) or 2g/d (n=16) for 24 weeks. Primary outcome was % change in abnormal ALT (ie, ALT greater than 30 IU/L) between Week 0 and Week 24. Laboratory tests and clinical assessments were performed at 4, 12, and 24 weeks, and at 12 and 24 weeks after stopping treatment. Paired-t-tests were used to assess improvement in abnormal ALT and lab tests between baseline and Week 24. **Results:** Age (37±11 in 1g/d, 38±10 in 2g/d), gender (10 males:0 females in 1g/d, 15 males:1 female in 2g/d), BMI (33.2±4.9 in 1g/d, 38.3±4.6 in 2g/d), A1c (5.7±0.86 in 1g/d, 6.0±.91 in 2g/d; 2 patients in 1g and 5 patients in 2g had T2DM), LDL (127±35 in 1g/d, 125±35 in 2g/d), and ALT (99±42 in 1g/d, 96±39 in 2g/d) did not differ between groups at baseline. Hs-CRP (2.5±2.7 in 1g/d, 5.4±3.8 in 2g/d) differed between groups at baseline. At Week 24, betaine 1 g/day did not improve ALT, but betaine 2 g/day significantly improved ALT and CK18-M30. Mean weight loss was 0±4.3 kg in 1g/d and 2.6±3.7 kg in 2g/d, and did not differ between groups (p<0.15). Betaine 2 g/day increased HDL by 3±5 mg/dL (p<0.05) while LDL decreased 6mg/dL. Betaine 2 g/day non-significantly decreased A1c and hs-CRP. ALT increased towards baseline after stopping betaine. Adverse events were primarily mild GI upset (20% of patients); no patient had to decrease betaine dosage. **Conclusion:** Betaine at a dose of 2 g/day for 24 weeks improved ALT, HDL and cytokeratin-18 among subjects with a clinical diagnosis of MASLD and an elevated ALT. Betaine 2g/d non-significantly decreased in A1c, LDL, and hs-CRP. Betaine 1 g/day did not improve

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ALT. Given the low cost and minimal adverse event profile, additional trials of betaine treatment of MASLD should be considered.

Variable	1g Baseline	1g End of Treatment	P-value	2g Baseline	2g End of Treatment	P-value
Age	37±11	--	--	38±10	--	--
BMI	33.2±5.0	33.3±5.2	0.76	38.3±4.6	37.5±5.0	0.062
Gender (Male:Female)	10:0	--	--	15:1	--	--
ALT	99±42	92±38	0.60	96±39	61±23	0.0030*
% Change in Abnormal ALT	--	5.39%	0.82	--	-45.6%	0.00062*
A1c	5.74±0.86	5.87±0.94	0.033	6.0±0.91	5.9±0.84	0.45
HDL	39±7	38±7	0.83	38±8	42±8	0.026*
LDL	127±35	124±33	0.44	125±35	119±51	0.66
Hs-CRP	2.5±2.7	2.4±2.4	0.79	5.4±3.8	4.2±2.3	0.33
CK18-M30	--	--	--	659±303	469±280	0.036*

Disclosures: Andrew Lim: Nothing to Disclose, Timothy Morgan: Nothing to Disclose, Aliya Asghar: Nothing to Disclose

3180 | PATTERNS OF PRACTICE FOR SCREENING AND MANAGEMENT OF METABOLIC DYSFUNCTION ASSOCIATED STEATOTIC LIVER DISEASE (MASLD). REPORT OF A GLOBAL SURVEY

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[1]University of Iowa hospitals and clinics, [2]University of Iowa School of Medicine

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most common chronic liver disease globally. The American Association for the Study of Liver Diseases (AASLD) published an updated Practice Guidance on the Clinical Assessment and Management of MASLD in May 2023 highlighting the use of biomarkers and noninvasive tools to assess the likelihood of significant fibrosis, disease progression, and therapeutic advancements. Following a rigorous consensus process, a change in the nomenclature to steatotic liver disease and its subcategories was subsequently implemented. The practice guidance and new MASLD nomenclature have significantly influenced the approach towards managing this condition globally. Our aim is to describe patterns of screening and management of MASLD amongst members of the AASLD. **Methods:** An Institutional Review Board approved survey was emailed to AASLD members, through a secure web-based tool, Research Electronic Data Capture. Responses were anonymous. **Results:** All AASLD members were invited to participate, 460 submitted responses. Regarding the new nomenclature, 59% of participants apply the new MASLD guidelines in their daily practice and 44% believe the new nomenclature is less stigmatizing and more inclusive, 43% expect the new nomenclature will bring a positive impact on MASLD management and public health. Most respondents were hepatologists, affiliated with academic centers, 29% see more than 50 patients with MASLD per month. For primary risk assessment of fibrosis, 74% calculate FIB-4 in patients with hepatic steatosis, in cases with a FIB-4 score less than 1.3 who have T2DM or ≥ 2 metabolic risk factors, 75% reevaluate patients every 6-12 months. 89% of participants use Fibroscan to screen for advanced fibrosis, 86% periodically screen MASLD patients for alcohol intake, quantification of weekly intake is the primary means of assessment.

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With regards to treatment of MASH without cirrhosis, dietary and lifestyle modifications remain first line therapy (92%). 55% of respondents prescribe GLP-1 agonists to “at-risk” MASH patients with obesity, 44% refer eligible MASH patients without cirrhosis to bariatric surgery; most often with a BMI of 35-40. Notably, 68% of participants have a weight management center on site. **Conclusion:** To our knowledge, this is the largest survey on the patterns of screening and management of MASLD directed to a large group of liver specialists, since the release of the MASLD nomenclature and updated practice guidance.

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3181 | COMPARING MAJOR ADVERSE CARDIOVASCULAR EVENT (MACE) INCIDENCE IN MASLD PATIENTS UNDERGOING PHARMACOLOGIC VERSUS BARIATRIC INTERVENTIONS

Qumber Ali[1] Leith Ghani[2] Pooja Rangan[3] Majd Aboona[1] Jay Kumar[1] Moises Nevah Rubin[4] Karn Wijarnpreecha[5] Mike Fallon[6] Farah Husain[7] Ma Ai Thanda Han[8]

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Background: Patients with Metabolic Dysfunction Associated Liver Disease (MASLD) have a higher propensity of experiencing major adverse cardiovascular events (MACE). Bariatric surgery, Glucagon-Like Peptide-1 receptor agonists (GLP-1 RA), and Sodium-Glucose Cotransporter 2 inhibitors (SGLT2i) therapy have all been shown to reduce the incidence of MACE. But there is no study yet comparing their effects on the incidence of MACE in the MASLD population, specifically. Thus we compare the incidence of MACE among patients with MASLD, dependent on intervention, to aid in the management of cardiovascular disease in this population **Methods:** This retrospective, multicenter study spanned across the Banner Health System. The MASLD patient cohort was identified with an ICD code for non-alcoholic fatty liver disease and 1 of 5 metabolic criteria. To identify MACE, we used ICD codes for coronary artery disease, cerebrovascular disease, and congestive heart failure. Only patients who received at least one intervention and followed up 12 months or more after intervention were included. Interventions included bariatric surgery, GLP-1 RA, SGLT2i, or any combination of more than one therapy. We conducted medication reconciliation to ascertain the use of SGLT2i and GLP-1 RA. The bariatric surgery population was identified using relevant procedure ICD codes and refined by including only procedures performed by bariatric surgeons. Competing risk analysis was used to compare the incidence of MACE after 12 months of intervention in each group vs bariatric surgery alone after adjusting for confounders. **Results:** This study includes 8,622 patients: 5.8% underwent bariatric surgery, 39.3% received therapy with GLP-1 RA, 23.4% were treated with SGLT2i, and 31.5% received more than one therapy. Both univariate and multivariate competing risk analysis showed the bariatric surgery alone group had a significantly lower MACE incidence compared to either GLP1-RA, SGLT2i, or combination therapy groups. [Table 1] **Conclusion:** Bariatric surgical interventions appear to be superior as compared to GLP-1 RA and SGLT2i therapy or combination therapy when studying the incidence of MACE after 12 months of therapy. Patients being treated with GLP-1 RA and SGLT2i therapies could be at risk for MACE due to underlying metabolic disorders or cardiovascular disease. Further investigation could identify additional risk factors which place this population at higher risk.

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Table 1.

Intervention	12-Month MACE Incidence			
	HR (95% CI)	p-value	aHR (95% CI)	p-value
Bariatric Surgery	Reference			
Glucagon-Like Peptide-1 Agonist (GLP-1 RA)	2.79 (2.12, 3.65)	<0.001	1.83 (1.37, 2.44)	<0.001
Sodium-Glucose Cotransporter 2 Inhibitor (SGLT2i)	2.72 (2.06, 3.61)	<0.001	1.72 (1.27, 2.33)	<0.001
Combination Therapy	2.69 (2.05, 3.52	<0.001	1.91 (1.43, 2.56)	<0.001

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

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3182 | THERAPEUTIC HORIZONS IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE(MASLD) & METABOLIC DYSFUNCTION ASSOCIATED STEATOHEPATITIS(MASH): A SYSTEMATIC REVIEW OF CURRENT TREATMENT OPTION

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Background: NIH data indicates that about 24% of U.S. adults have MASLD and 1.5% to 6.5% has MASH. This growing epidemic has limited treatment options. Current standards of care include GLP-1 agonists, bariatric surgery, lifestyle interventions, and herbal remedies like Berberine. Our systematic review(SR) highlights their effectiveness in improving liver health. **Methods:** This SR follows PRISMA guidelines and is registered with PROSPERO. We searched databases like PubMed, Elsevier, and Google Scholar through March 31, 2024, for randomized trials on lifestyle interventions, Berberine, GLP-1 agonists, and bariatric surgery for MASLD and MASH. We included adults with evident steatosis via biopsy, MRI, or ultrasound. Studies are selected based on their relevance and methodological rigor, with the risk of bias assessed using the Cochrane Risk of Bias tool. **Results:** Study results are comprehensively mentioned in Table 1 with key findings summarized as below: GLP-1 agonists**:** Analyzing 13 trials with 1,476 patients, Semaglutide reduced liver fat by 73% (P<0.05), and other agonists like Liraglutide and Efinopegdutide also significantly decreased liver fat and improved fibrosis markers (P<0.001); Lifestyle interventions:12 trials with 1,032 patients showed significant liver marker improvements with the Mediterranean diet(P<0.001), calorie restriction with pentadecanoic acid(P<0.001), intermittent fasting with exercise (P<0.05), and technology-assisted interventions (P<0.001); Berberine: 4 trials with 415 patients demonstrated Berberine's effectiveness in reducing liver fat and improving LFTs (P<0.05), especially at higher doses and in combination with Ursodeoxycholic acid. Women saw greater reductions; Bariatric Surgery: 4 trials with 484 patients showed substantial improvements in liver biochemical markers and hepatic fibrosis with both Roux-en-Y gastric bypass and sleeve gastrectomy. Roux-en-Y showed superior results in improving liver stiffness and fibrosis scores (P<0.05). **Conclusion:** Our SR shows that GLP-1 agonists are effective on liver fat reduction. Bariatric surgery is highly effective for MASLD and MASH but requires careful consideration of indications and potential early and long-term complications. Lifestyle interventions are cost-effective, although their efficacy is challenging to quantify. While herbal supplements like Berberine are effective, they are not standardized. Emerging treatments like Resmetirom, highlight the value of such SR in guiding clinical care for MASLD patients.

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Table:1 Comparative Effectiveness of Therapeutic Interventions in MASLD/MASH

GLP-1 Agonists				
Drug	**Study Description**	**Reduction (%)**	**P-value**	**Additional Notes**
Efocipegtrutide	Triple agonist, placebo-controlled	23% difference	<0.001	Superior in reducing liver fat by MRI-PDFF
Efinopegdutide	Dual agonist, active-controlled	72% to 65%	<0.001	Significant improvement compared to Semaglutide
Semaglutide	Dual agonist, active-controlled	73% to 72%	<0.05	Slight effect in reducing liver fat content
Tirzeputide	Novel trial	-	<0.05	Significant decrease in apoptosis and fibrosis markers
Liraglutide	Multiple studies, various settings	Up to 60%	<0.001	Significant reduction in liver fat and steatohepatitis
Lifestyle Interventions				
Intervention	**Study Description**	**Reduction/Improvement**	**P-value**	**Additional Notes**
Mediterranean Diet	Multiple studies	Significant improvement	<0.001	Effective in improving overall liver health
Calorie Restriction + Pentadecanoic Acid	Active-controlled, MR spectroscopy diagnosed MASLD	10.3 ± 5.9 (control group)	<0.001	Significant improvement with supplementation
Intermittent Fasting + Exercise	Active-controlled, multiple comparators	-1.30% (exercise only)	<0.05	Significant reduction in combination group
Text Messaging for Diet and Lifestyle	Technology-assisted intervention	Significant improvement	<0.001	Highlighted potential of modern tools in managing liver diseases
Berberine				
Intervention	**Study Description**	**Reduction/Improvement**	**P-value**	**Additional Notes**
Berberine Monotherapy	500mg twice daily, active-controlled	55.1% reduction in liver fat content	<0.001	Significant improvement in serum transaminases and HDL levels
Berberine High Dose	1000mg twice daily, placebo-controlled	Compared to 2% decrease in placebo group	<0.05	Favorable response to higher Berberine dose
Gender-Specific Effects	0.5g three times daily, active-controlled	Women: −19.95 ± 17.59 decrease in liver fat content	<0.05	Greater effect in women compared to men
Berberine with Ursodeoxycholic Acid	1000mg Berberine + Ursodeoxycholic acid, twice daily	-	<0.05	Improved outcomes in combination therapy
Bariatric Surgery				
Surgical Intervention	**Study Type**	**Results**	**P-value**	**Additional Notes**
Sleeve Gastrectomy	Active-controlled, MRI-guided biopsy	3.67 times higher likelihood of resolving MASH	<0.001	Compared to lifestyle modifications
Roux-en-Y Gastric Bypass	Active-controlled, MRI-guided biopsy	3.60 times higher likelihood of resolving MASH	<0.001	Superior to lifestyle modifications
Bariatric Surgery (General)	Trial post-surgery liver biopsy	Liver markers improved significantly post-surgery	<0.05	Initial increase in markers, followed by a significant drop
Roux-en-Y Gastric Bypass (Germany)	Study with baseline correction	Improved liver stiffness; AST/ALT ratio increased	<0.05	Demonstrated superior results over sleeve gastrectomy

Disclosures: Pratiksha Moliya: Nothing to Disclose, Hasan Al-Obaidi: Nothing to Disclose, Pranav Patel: Nothing to Disclose, Raj Patel: Nothing to Disclose, Charmy Parikh: Nothing to Disclose, Melvin Joy: Nothing to Disclose

3184 | VALIDATING PRE-IDENTIFIED MORPHOLOGICAL BASELINE FEATURES FOR PREDICTING FIBROSIS PROGRESSION IN MAESTRO-NASH

Jörn Schattenberg[1] Rebecca Taub[2] Dominic Labriola[2] Hang Zhang[2] Dean Tai[3] Elaine Chng[3] Yayun Ren[3] Rohit Loomba[4] Mazen Noureddin[5]

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Background: Fibrosis staging remains the pinnacle predictor of clinical outcomes in metabolic-associated steatohepatitis (MASH) clinical trials. Despite liver biopsies being the gold standard, their ability to reflect dynamic fibrotic changes during interventions is debated. Various non-invasive tests (NITs) have been developed but have yet to replace biopsies. This study uses qFibrosis, an AI-driven fibrosis assessment tool, to validate whether specific pre-identified fibrotic features can predict fibrosis progression in MAESTRO-NASH, a 54-month phase 3 trial which achieved NASH resolution and fibrosis reduction. **Methods:** Based on sample availability at baseline, 845 patients had qFibrosis assessment and corresponding selected NITs (VCTE, MRE, ProC3, AST, GGT and platelets), except for MRE where there were only 495 patients. 30 fibrosis features previously identified from SteatoSITE are used in this analysis and Spearman correlation against pathologist scores. Using univariate analyses and random forest model with baseline fibrosis stage as the outcome, 6 fibrosis features (5 from portal tract region, 1 from zone 2) were chosen for exploration with clinical data and subsequent validation. **Results:** NITs showed modest correlation with pathologist scores; MRE was the highest (0.489), followed by VCTE (0.309). Quantitative readouts of the 6 selected fibrosis features from baseline samples also showed weak to modest correlations with NITs (ranging from 0.05 to 0.46). Notably, the zone 2 feature (number of short strings) demonstrated a negative correlation (-0.07 to -0.324), while others showed positive correlations. Baseline MRE

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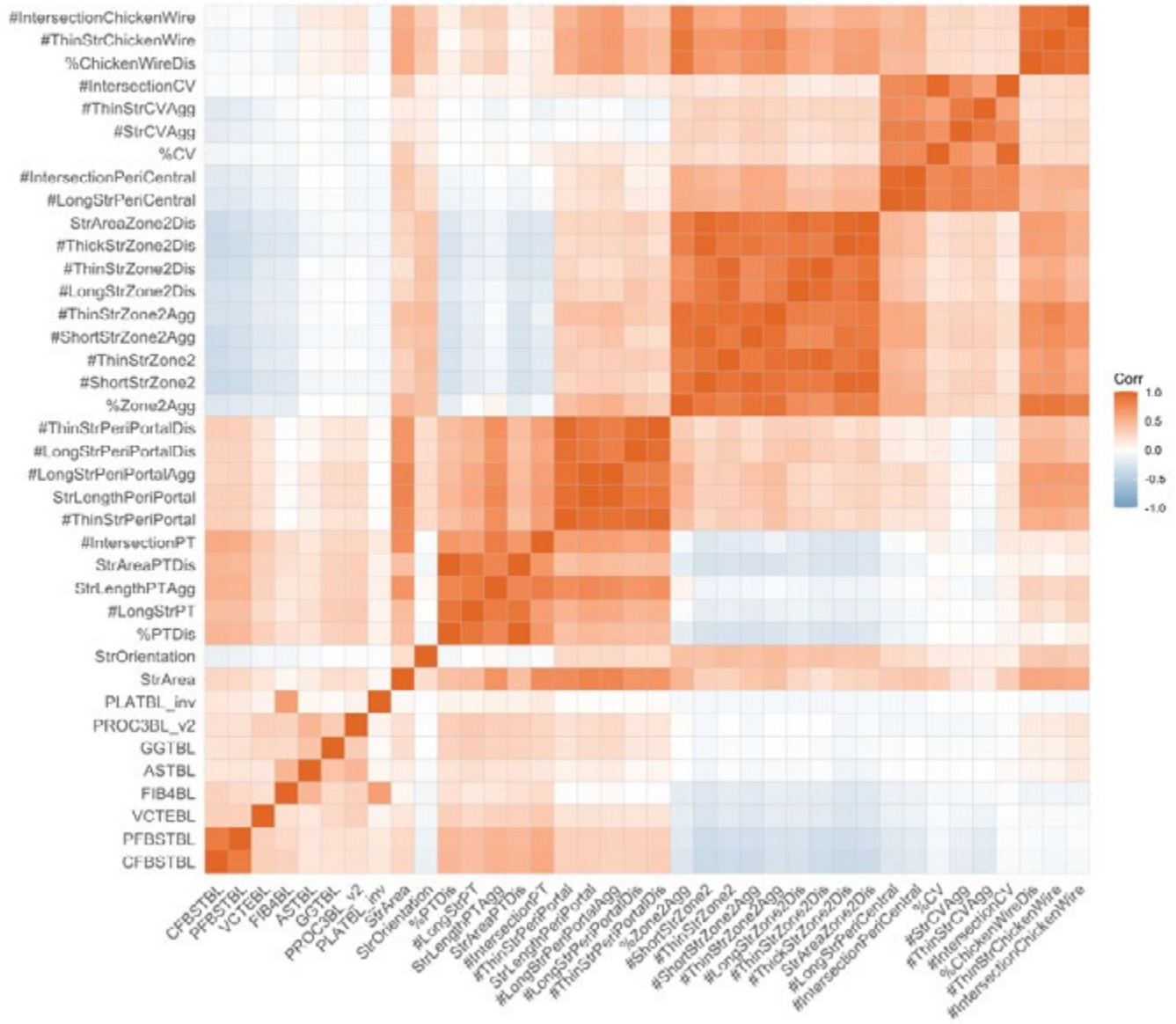
and VCTE correlations with these 6 features closely matched with pathologist baseline scores, ranging from 0.393 to 0.464 with MRE, and 0.233 to 0.342 with VCTE, suggesting they are nuanced markers of fibrosis progression. Note that the correlation of zone 2 fibrosis feature to MRE and VCTE are -0.324 and -0.255, respectively. Across 6 fibrosis features, the data at week 52 indicates that resmetirom treatment at 80mg and 100mg shows more frequent improvement in fibrosis compared to placebo, across consensus baseline fibrosis stages F1b, 2 and 3. **Conclusion:** Pre-identified fibrosis features from SteatoSITE were validated in MAESTRO-NASH where the week 52 data suggests that resmetirom treatment consistently reduces the progression of MASH-related fibrosis more effectively than placebo, across all baseline stages. The identification of negatively correlating features reveals the complexity of fibrosis progression markers, emphasizing the need for a composite NIT approach that integrates both positively and negatively correlating fibrosis features. Confirmation of clinical relevance will require further analyses of month 54 biopsies and subsequent clinical outcomes.

Figure: Spearman correlation heatmap of 845 patients with qFibrosis assessment with selected NITs and pathologist baseline fibrosis stages.



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Disclosures: Jörn Schattenberg: Consultant relationship with Intercept Pharmaceuticals; Has ended; Speaking and Teaching relationship with MedicalTribune, MedPublico GmbH, MedScape,; Has not ended; Consultant relationship with Ipsen, Inventiva Pharma, Madrigal Pharmaceuticals; Has not ended; Consultant relationship with Apollo Endoscopy, Boehringer Ingelheim, Gilead Sciences; Has not ended; Speaking and Teaching relationship with Forum fÃ¼r Medizinische Fortbildung (FOMF), Gilead Sciences; Has not ended; Speaking and Teaching relationship with Boehringer Ingelheim, Echosens; Has not ended; Speaking and Teaching relationship with AbbVie, Academic Medical Education (AME),; Has not ended; Consultant relationship with Novo Nordisk, Pfizer, Roche, Sanofi, and Siemens Healthineer; Has not ended; Consultant relationship with Madrigal Pharmaceuticals, Lilly, MSD, Northsea Therapeutics,; Has not ended; Consultant relationship with Boehringer Ingelheim, Gilead Sciences, GSK, Ipsen, Inventiva; Has not ended; 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Study relationship with GSK; Has not ended; Principal Investigator for a Drug Study relationship with Conatus; Has not ended

3185 | RESMETIROM PROTECTS AGAINST DIET-INDUCED MASLD AND REDUCES ATHEROSCLEROSIS DEVELOPMENT IN OBESE LDLR-/-.LEIDEN MICE

Eveline Gart[1] Geurt Stokman[1] Robert Kleemann[1] Martine Morrison[2]

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Background: Resmetirom (a thyroid hormone receptor-β agonist) is the first approved medicine for metabolic dysfunction-associated steatotic liver disease (MASLD). Interestingly, Resmetirom was also found to lower plasma LDL-cholesterol in clinical trials, which suggests that it could improve cardiovascular disease (CVD), the primary cause of mortality in MASLD patients. In the present study we studied the effect of resmetirom on progression of atherosclerosis, in addition to its effects on MASLD-associated liver fibrosis in diet-induced obese Ldlr-/-.Leiden mouse model. **Methods:** Ldlr-/-.Leiden mice underwent an initial 18-week period of fast-food diet (FFD) feeding to establish early stages of MASLD and atherosclerosis. After this run-in period, one group of mice was terminated as a start-of-treatment reference. The remaining mice were maintained on FFD and received vehicle (FFD + vehicle controls) or 3 mg/kg resmetirom (FFD + Resmetirom) by oral gavage for an additional 10 weeks after which they were terminated at t=28 weeks. Chow-fed mice were included as a healthy reference group. Plasma parameters, liver and heart tissues, were analyzed in the study. **Results:** FFD-fed mice developed obesity, dyslipidemia with an increase in atherogenic (V)LDL-C, and MASLD associated liver fibrosis as compared to chow-fed controls. Therapeutic treatment with resmetirom lowered atherogenic risk factors, i.e. TG in VLDL and cholesterol in (V) LDL-sized particles. In line with the strong reduction in circulating lipids, resmetirom significantly reduced the FFD-induced atherosclerosis lesion area. Lesion severity analysis according to the American Heart Association scoring system revealed that resmetirom exhibits its most significant impact on the lesion area of severe type V lesions. Notably, all effects were observed independent of changes in body weight, adiposity, and food intake, as resmetirom did not impact these factors. Furthermore, FFD-induced circulating liver injury markers ALT and AST were significantly reduced upon resmetirom treatment, and reduced to that in the chow-fed group. Consistent with this data, MASLD-associated liver fibrosis was attenuated with resmetirom relative to the FFD control group, as hepatic collagen content corrected for total liver weight was significantly reduced with resmetirom. **Conclusion:** Our findings demonstrate that in Ldlr-/-.Leiden mice, treatment with resmetirom has additional protective effects on cardiovascular risk factors and attenuated atherosclerosis development, on top of its effects on MASLD.

Disclosures: Eveline Gart: Sagimet: Independent Contractor, Mead Johnson: Independent Contractor, Geurt Stokman: Nothing to Disclose, Robert Kleemann: Nothing to Disclose, Martine Morrison: Nothing to Disclose

3186 | ACCURATE PREDICTION OF LIVER FAT REDUCTIONS ACROSS RANGE OF WEIGHT LOSS BY QUANTITATIVE SYSTEMS PHARMACOLOGY MODELING

Scott Siler[1] Christina Battista[1] Celeste Vallejo[1] Michael Kelley[1] Zackary Kenz[1]

[1]Simulations Plus

Background: Weight loss (WL) has positive effects on reducing hepatic lipid burden in MASH patients. Reports using various drugs have shown reductions of liver fat with WL (1-4). Mechanistically, reduced food intake and WL lead to declines in adipose fatty acid (FA) release and hepatic de novo lipogenesis (DNL; 5,6). NAFLDsym, a quantitative systems pharmacology (QSP) model (7), was used to characterize the relationship between WL and steatosis. The overall effects of WL on steatosis reductions in NAFLDsym were calibrated with data from clinical studies with liraglutide (1), canagliflozin (2), and retatrutide (3). Simulation results were validated with clinical data from semaglutide studies (4). Moreover, prospective predictions of WL (8) and liver fat reductions with tirzepatide were performed. **Methods:** A simulated cohort (SimCohorts) of 200 MASH patients was included in simulations with NAFLDsym where daily caloric intake was adjusted from isocaloric amounts for each individual simulated patient. Clinically-observed WL was simulated by increasing (3%) or decreasing food intake (7%-30%) daily for 48 weeks. Relative reductions in liver fat were predicted as a result of altered adipose FA release and hepatic DNL. Clinical data from liraglutide, canagliflozin, and retatrutide were used to calibrate the simulated steatosis changes.

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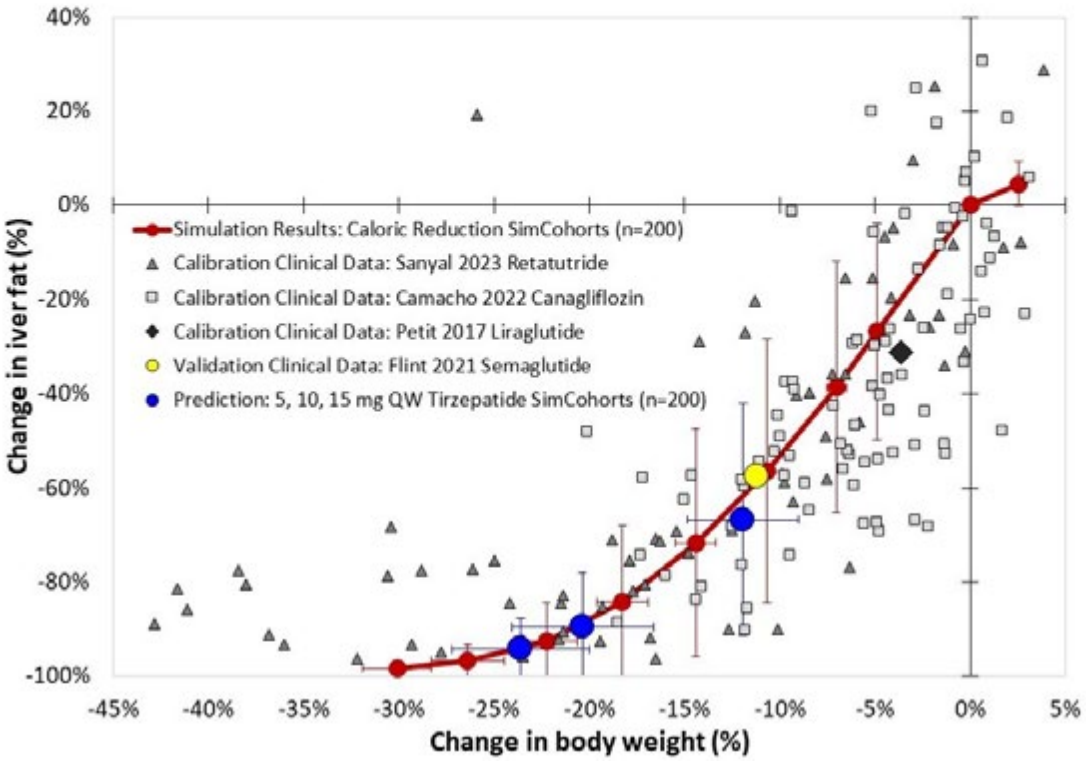
Clinical data from semaglutide studies were used to validate the simulation results. Tirzepatide administration (5, 10, or 15 mg QW including uptitration) and exposures were directly simulated using a two compartment PK model. Simulated WL in the SimCohorts over 48 weeks agreed with clinical data, and steatosis reductions were predicted. **Results:** Simulations of reduced caloric intake were predicted to elicit WL and reductions in steatosis that align with clinical data from several drugs that elicit WL (Figure 1). The predicted relationship between WL and liver fat is linear between 5-15% WL, and it plateaus between 15-30% WL. The predicted effects of tirzepatide on WL and liver fat reduction also aligned with the simulation **Results:** generated via consistent daily caloric reduction. Uptitration of tirzepatide does not appear to influence the magnitude of liver fat after 48 weeks of simulated treatment. **Conclusion:** WL in excess of 10% has substantial, positive effects on reducing hepatic lipid burden and steatosis. References: (1) Petit 2017; (2) Camacho 2022; (3) Sanyal 2023; (4) Flint 2021; (5) Mittendorfer 2009; (6) Smith 2020; (7) Siler 2022; (8) Jastreboff 2022

Figure 1: The quantitative relationship between weight loss and liver fat reductions in MASH patients, as expressed with both NAFLDsym simulation results and clinical data. Clinical data from retatrutide, canagliflozin, and liraglutide studies were used to calibrate the quantitative relationship within NAFLDsym, while clinical data from a semaglutide study was used to validate the simulation. Predictions of steatosis reductions with tirzepatide treatment (5, 10, 15 mg QW, with uptitration) are also included.



Disclosures: Scott Siler: Nothing to Disclose, Christina Battista: Nothing to Disclose, Celeste Vallejo: Nothing to Disclose, Michael Kelley: Nothing to Disclose, Zackary Kenz: Nothing to Disclose

3187 | SCREENING AND COMPARISON OF CURRENT CLINICAL CANDIDATES IN MASH USING HUMAN LIVER SPHEROIDS

Francisco Verdeguer[1] Philipp Vonschallen[1] Thomas Hofstetter[1] Radina Kostadinova[1] Jesus Glaus[1] Angelina Freitag[1] Joel Zvick[1]

[1]InSphero

Background: Metabolic dysfunction-associated steatohepatitis (MASH) is a progressive severe disease characterized by hepatic lipid accumulation, inflammation, and fibrosis which lacks any approved drug therapy. Novel approaches to identify therapeutic candidates that predict clinical responses are needed. Human

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pre-clinical models, including organoids/spheroids, are powerful models for drug testing and discovery. Pre-clinical models combining fast, robust, high-throughput compatible, and predictive outputs are still a limiting factor in identifying novel clinical therapies. We aimed to compare the efficacy of existing clinical candidates for MASH using a human-derived 3D spheroid model. **Methods:** We used a previously developed a human-derived 3D spheroid model, containing primary human hepatocytes, Kupffer cells, liver endothelial cells, and stellate cells from healthy donors. Incubation with a MASH-inducing cocktail during 10 days lead to the recapitulation the main hallmarks of MASH including steatosis, inflammation, and fibrosis. We screened simultaneously the toxicity and efficacy of 20 current clinical candidates in a dose-dependent manner. We selected secreted lactate dehydrogenase (LDH), intracellular triglycerides (TGs) and secreted pro-collagen 1 (PC-1) as surrogate markers of cytoxicity, steatosis and fibrosis. LDH was measured at day 3, 5, 7 and 10, TGs at day 10 and PC-1 at day 7 and 10. **Results:** The screen of 20 clinical candidates comprised different modalities including small molecules, antibodies, and antisense oligos (ASOs) targeting different mechanisms of action. The majority of compounds did not show signs of toxicity at lower doses but some lead to high LDH release at higher doses. We generated a matrix of anti-steatotic versus anti-fibrotic effects to plot the comparison of all tested clinical candidates. We show that the HTD1801 (berberine ursodeoxycholate, an ionic salt of berberine and ursodeoxycholic acid) reduces significantly the secretion of PC-1. **Conclusion:** We show for the first time a screening platform that combines toxicity and MASH efficacy readouts. We show the translational capacity of this platform of several clinical candidates by predicting clinical outcomes.

Disclosures: Francisco Verdeguer: InSphero: Employee, Philipp Vonschallen: Nothing to Disclose, Thomas Hofstetter: Nothing to Disclose, Radina Kostadinova: Nothing to Disclose, Jesus Glaus: Nothing to Disclose, Angelina Freitag: Nothing to Disclose, Joel Zvick: Nothing to Disclose

3188 | THE IMPACT OF LIRAGLUTIDE ON PATIENTS WITH METABOLIC DYSFUNCTION ASSOCIATED FATTY LIVER DISEASE

Hye Won Lee[1] Jae Eun So[1] Sang Hoon Ahn[1] Seung Up Kim[1]

[1]Yonsei University College of Medicine

Background: Metabolic dysfunction associated steatotic liver disease (MASLD) is a prevalent condition associated with obesity and metabolic syndrome. Liraglutide, a glucagon-like peptide-1 receptor agonist has shown promise in improving metabolic parameters and liver histology in patients with MASLD. **Methods:** This study involved a cohort of patients diagnosed with MASLD. We evaluated the efficacy of liraglutide in patients with MASLD compared to untreated controls, focusing on liver fat content, body weight, liver enzyme levels, and body composition. **Results:** At baseline, the incidence of obesity and the levels of aspartate transaminase (AST) and alanine transaminase (ALT) were higher in the liraglutide group than in the control group. Patients treated with liraglutide had a significant reduction in steatosis evaluated by hepatic steatosis index (mean 43.2, 37.9, 37.1 vs. 41.4, 38.8, 38.3 at baseline, 2 months after beginning treatment and 6 months after beginning treatment, respectively, $p<0.001$). Body weight tended to be lower in the liraglutide group than in the control group (87.9, 85.0, 85.3kg vs. 81.3, 80.3, 82.4g, $p<0.001$). ALT levels decreased significantly in the liraglutide group compared to the control group (ALT; 62.1, 40.8, 44.3 IU/L vs. 66.6, 42.7, 39.1 at baseline, 2 months and 6 months after, $p= 0.046$). Additionally, patients treated with liraglutide had significant reductions in visceral fat area (153.1, 140.5, and 145.2 cm2 vs. 137.4, 132.5, and 130.3 cm2, $p<0.001$) without effects on sarcopenia (ratio of appendicular skeletal muscle to body mass index: 0.76, 0.78, and 0.76 vs. 0.76, 0.77, and 0.78, $p=0.002$). **Conclusion:** Liraglutide significantly improved liver fat content, liver enzyme levels, and visceral fat of MASLD. These findings suggest that liraglutide may be a beneficial therapeutic option for managing MASLD, particularly in patients with obesity and metabolic syndrome. Further long-term studies are needed to confirm these benefits and assess the effects on liver-related morbidity and mortality.

Disclosures: Hye Won Lee: Nothing to Disclose, Jae Eun So: Nothing to Disclose, Sang Hoon Ahn: Nothing to Disclose, Seung Up Kim: Nothing to Disclose

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3189 | PEMAFIBRATE IMPROVES LIVER FUNCTION WITH ALTERATION OF BILE ACID COMPOSITION IN PATIENTS WITH STEATOTIC LIVER DISEASE

Kota Tsuruya[1] Yusuke Mishima[1] Yoshitaka Arase[1] Hajime Takei[2] Hiroshi Nittono[2] Tatehiro Kagawa[1]

[1]Tokai University, [2]Junshin Clinic Bile Acid Institute

Background: Currently, there are no effective therapeutic drugs for steatotic liver disease (SLD). Pemafibrate, a selective PPAR-alpha agonist, is a new drug for dyslipidemia and may be effective for SLD. In this study, we performed a single-arm prospective trial to investigate the efficacy and safety of pemafibrate in SLD patients, and also analyzed the alteration of bile acid composition and gut microbiota. **Methods:** Twenty SLD patients with dyslipidemia received 0.1 mg of pemafibrate twice a day for 6 months. Liver fat content evaluated by MRS, body composition, liver function, fibrosis markers, lipid metabolism, arteriosclerosis markers, serum bile acid composition, and gut microbiota were analyzed and compared before and 6 months after administration. Comparisons before and after treatment were performed using a paired t-test. **Results:** Twenty patients (7 females) with 45.2 ± 14.2 (mean ± SD) years old received pemafibrate. In comparison before and after pemafibrate treatment (before/6 months later), body weight (79.4±18.5/78.9±17.6kg, P=0.397), body fat percentage (35.6±7.4/35.6±7.7%, P=0.847), and liver fat (19.6±6.2 /21.7±10.8%, P=0.305) did not change, whereas serum liver enzymes and fibrosis markers significantly decreased (P<0.05); ALT (99.1 ± 55.9/72.6 ± 53.6 IU/L), ALP (146.7 ± 92.4/107.3 ± 78.2 IU/L), GGT (105.3 ± 82.2/59.1 ± 52.7 IU/ L), total bilirubin (0.85 ± 0.43/0.64 ± 0.26 mg/dL), type IV collagen/7S (4.4 ± 1.7/4.0 ± 1.3 ng/mL), and M2BPGi (0.89 ± 0.51/0.73 ± 0.50 C.O.I). Regarding lipid metabolism, serum triglyceride (217.1 ± 81.0/150.8 ± 64.9 mg/dL), LDL-cholesterol (C) (140.7 ± 28.7/126.6 ± 28.4 mg/dL), RLP-C (10.2 ± 4.4/6.5 ± 3.8 mg/dL), small dense LDL-C (48.7 ± 18.4/32.8 ± 17.0 mg/dL), and apolipoprotein C-III (13.5 ± 5.5/9.4 ± 2.9 mg/dL) improved significantly (P<0.01). The percentage of glucuronidated or sulfated chenodeoxycholic acid at the C-3 position (CDCA-3G or 3S) in total serum bile acids increased from 2.8 to 4.4 (P<0.001). Alpha diversity (Shannon index) of gut microbiota significantly increased (P<0.05). No adverse effects were observed during treatment. **Conclusion:** Pemafibrate treatment for 6 months significantly improved liver function, fibrosis markers, and arteriosclerosis markers in SLD patients with dyslipidemia, although body composition and liver fat content did not change. The increase of hydrophilic bile acids such as CDCA-3G or 3S might contribute to the beneficial effects of pemafibrate.

Disclosures: Kota Tsuruya: Eisai Co., Ltd.: Speaking and Teaching, Eisai Co., Ltd.: Speaking and Teaching, Eisai Co., Ltd.: Speaking and Teaching, Takeda Pharmaceutical Co., Ltd.: Speaking and Teaching, Kowa Company, Ltd.: Speaking and Teaching, Chugai Pharmaceutical Co., Ltd.: Speaking and Teaching, ASKA Pharmaceutical Co., Ltd.: Speaking and Teaching, AbbVie GK: Speaking and Teaching, Yusuke Mishima: Nothing to Disclose, Yoshitaka Arase: Nothing to Disclose, Hajime Takei: Nothing to Disclose, Hiroshi Nittono: Nothing to Disclose, Tatehiro Kagawa: Nothing to Disclose

3190 | USE OF NON-INVASIVE TESTS TO DIAGNOSE AND FOLLOW NASH WITH LIVER FIBROSIS PATIENTS TREATED WITH RESMETIROM ◆

Naim Alkhouri[1] Rebecca Taub[2] Sam Moussa MD[3] Dominic Labriola[2] Arun Sanyal[4] Mazen Noureddin[5]

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Background: MAESTRO-NASH (NCT03900429) is an ongoing 54-month, randomized, double-blind, placebo-controlled Phase 3 trial evaluating the efficacy of resmetirom in patients with biopsy-confirmed nonalcoholic steatohepatitis (NASH/MASH) and fibrosis. 966 patients with biopsy-confirmed NASH were randomized 1:1:1 to resmetirom 80 mg, resmetirom 100 mg, or placebo administered once daily. Dual primary endpoints at Week 52 were achieved with both resmetirom 80 mg and 100 mg: NASH resolution with no worsening of fibrosis (NR) or ≥1-stage improvement in fibrosis with no worsening of NAS (FI). Both Week 52 liver biopsy endpoints, NR and FI, were achieved. Resmetirom was recently approved for the treatment of adult patients with noncirrhotic NASH and liver fibrosis consistent with F2 to F3 stages. Accuracy of NASH/fibrosis diagnosis and followup of resmetirom treated patients long-term using real-world, readily available non-invasive testing were assessed. **Methods:** Machine learning models evaluated the relative importance of MAESTRO patients' intrinsic characteristics and screening/baseline biomarkers in 1247 patients who had F0-F4 on liver biopsy. The Random Forrest (RF) model

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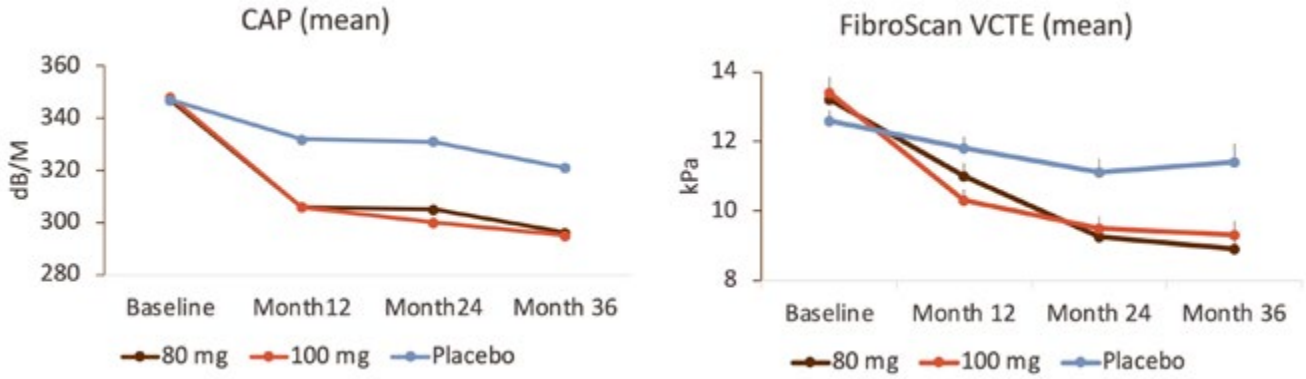
was selected due to its predictive performance. For this model, only readily available tests including FibroScan, ELF and standard blood chemistries were used to determine the accuracy in diagnosing NASH patients consistent with F2 to F3. Long-term effects of resmetirom on non-invasive tests and biomarkers out to 3 years post randomization were evaluated. **Results:** In the F2 to F3 population (n=888) FibroScan VCTE was 12 (10,15) median kPa (Q1, Q3) and ELF 9.7 (9.2, 10.4). Using 23 baseline clinical characteristics, standard labs, FibroScan and ELF, the random forest model determined that the most important markers that distinguished F2 to F3 from either F0/1 or F4, in order, were FibroScan VCTE, platelets, FIB-4, FAST and ELF. The AUC (SD) for separation from F0/F1 or F4 were 0.76 (0.03) and 0.90 (0.03), respectively. 58% of F2 to F3 were correctly predicted to be F2/F3; 26% were incorrectly predicted to be F0/F1 and 16% were incorrectly predicted to be F4. Of F4 patients, 72% were correctly predicted to be F4 and 19% were predicted to be F2/F3. The addition of MRE/MRI-PDFF increased diagnostic accuracy for F2/F3 to 68% and F4 to 81%. Resmetirom showed improvement relative to placebo on multiple responses at Week 52 including MRI-PDFF (the most predictive of a biopsy response), liver enzymes, lipids and FibroScan CAP and VCTE. Resmetirom responses on liver enzymes, lipids and FibroScan (Figure) were durable/increased at Years 2 and 3 relative to placebo. **Conclusion:** Reasonably accurate identification of NASH F2/F3 patients was achieved with FibroScan VCTE, ELF and readily available blood tests. F4 patients were effectively ruled out. Long term followup of resmetirom patients with noninvasive tests showed durability of responses relative to placebo.



Disclosures: Naim Alkhouri: Madrigal: Grant/Research Support, Madrigal: Speaking and Teaching, Novo Nordisk: Consulting, Novo Nordisk: Grant/Research Support, Gilead: Grant/Research Support, Corcept: Grant/Research Support, Boehringer Ingelheim: Grant/Research Support, Echosens: Speaking and Teaching, Perspectum: Consultant, Cima: Consultant, Fibronostics: Consultant, 89Bio: Grant/Research Support, Inventiva: Grant/Research Support, Merck: Grant/Research Support, Pfizer: Grant/Research Support, Ipsen: Speaking and Teaching, Intercept: Speaking and Teaching, Madrigal: Consulting, Research Funding, Novo Nordisk: Consulting, Research Funding, Inventiva: Research Funding, Boehringer Ingelheim: Consulting, Research Funding, Corcept: Research Funding, Ipsen: Consulting, Research Funding, Gliead: Consulting, Research Funding, Speaking, Perspectum: Consulting, Research Funding, Cima: Advisor, 89Bio: Consulting, Research Funding, Akero: Grant/Research Support, Arbutus: Grant/Research Support, GSK: Grant/Research Support, Regeneron: Grant/Research Support, AstraZeneka: Grant/Research Support, Rebecca Taub: Madrigal Pharmaceuticals: Employee, Madrigal Pharmaceuticals: Stock - publicly traded company, Madrigal Pharmaceuticals: Executive role, Sam Moussa MD: Madrigal Pharmaceutical: Stock - publicly traded company, Dominic Labriola: Nothing to Disclose, Arun Sanyal: Genfit, Akarna, Tiziana, Durect, Inversago, Hemoshear, North: Stock - publicly traded company, Astra Zeneca (60K), Boston Pharmaceutical

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3191 | DIFFERENTIAL CLASS EFFECTS OF ORAL ANTI-DIABETIC DRUGS ON CARDIOVASCULAR EVENTS IN PATIENTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE

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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most prevalent chronic liver disease worldwide and is associated with a high risk of cardiovascular events. Despite some research on the potential benefits of certain oral antidiabetic drugs (OADs) in mitigating MASLD, there is currently a paucity of comprehensive, large-scale studies elucidating which OAD is the most effective in reducing the incidence of cardiovascular events in this patient population. **Methods:** We conducted a nationwide cohort study using the National Health Information Database of the Korean population. The study included patients with MAFLD and type 2 diabetes prescribed a combination of metformin and either sodium-glucose cotransporter 2 (SGLT2) inhibitors, TZDs, or dipeptidyl peptidase-4 (DPP-4) inhibitors for ≥80% of a 90-day period from January 2015 to December 2020. We used the Fine and Gray model to analyze subdistribution hazard ratios for major adverse cardiovascular events (MACE), cardiovascular disease-related mortality, and heart failure hospitalization in each OAD group compared to sulfonylureas, adjusting for baseline differences using inverse probability of treatment weighting. **Results:** Among 218,066 patients, the risk of MACE was significantly lower in the SGLT2 inhibitors, TZDs, and DPP-4 inhibitors groups compared to sulfonylureas, with adjusted subdistribution hazard ratios (aSHRs) of 0.52 (95% CI, 0.41–0.67), 0.60 (95% CI, 0.42–0.86), and 0.68 (95% CI, 0.60–0.78), respectively. Cardiovascular disease-related mortality was significantly lower only in the SGLT2 inhibitors group (aSHR = 0.30; 95% CI, 0.14–0.64), while no statistically significant associations were observed in the TZDs and DPP-4 inhibitors groups (aSHRs = 0.73; 95% CI, 0.28–1.93 and 0.76; 95% CI, 0.52–1.09, respectively). The risk of hospitalization for heart failure was significantly lower only in the SGLT2 inhibitors group (aSHR = 0.60; 95% CI, 0.40–0.91). **Conclusion:** In this nationwide cohort study of patients with MASLD and type 2 diabetes, SGLT2 inhibitors, TZDs, and DPP-4 inhibitors were associated with a lower risk of MACE compared to sulfonylureas. However, only SGLT2 inhibitors were associated with a significantly reduced risk of cardiovascular disease-related mortality and hospitalization for heart failure, suggesting their potential as a preferred treatment option for reducing cardiovascular risk in this population.

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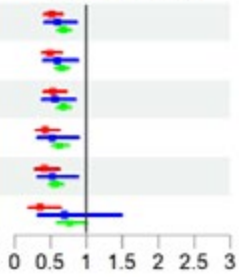
A. Major adverse cardiovascular events

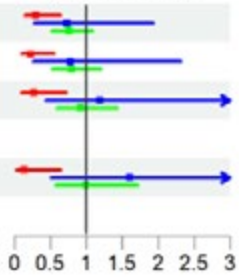
Index date	SGLT2 inhibitors	Thiazolidinediones	DPP-4 inhibitors	ASHR (95% CI)
80% of 90 consecutive days	0.52 (0.41 to 0.67)	0.60 (0.42 to 0.86)	0.68 (0.60 to 0.78)	
100% of 90 consecutive days	0.50 (0.38 to 0.66)	0.60 (0.40 to 0.88)	0.66 (0.57 to 0.76)	
80% of 180 consecutive days	0.54 (0.41 to 0.72)	0.57 (0.38 to 0.85)	0.68 (0.59 to 0.78)	
100% of 180 consecutive days	0.43 (0.30 to 0.62)	0.53 (0.32 to 0.89)	0.63 (0.53 to 0.76)	
80% of 365 consecutive days	0.42 (0.29 to 0.62)	0.53 (0.32 to 0.88)	0.57 (0.48 to 0.68)	
100% of 365 consecutive days	0.36 (0.20 to 0.64)	0.70 (0.33 to 1.49)	0.77 (0.59 to 1.01)	



Group vs Sulfonylureas SGLT2 inhibitors Thiazolidinediones DPP-4 inhibitors

B. Cardiovascular disease-related mortality

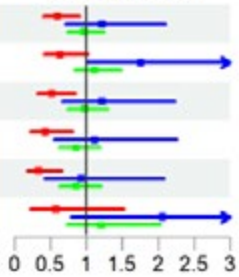
Index date	SGLT2 inhibitors	Thiazolidinediones	DPP-4 inhibitors	ASHR (95% CI)
80% of 90 consecutive days	0.30 (0.14 to 0.64)	0.73 (0.28 to 1.93)	0.76 (0.52 to 1.09)	
100% of 90 consecutive days	0.23 (0.10 to 0.55)	0.78 (0.26 to 2.31)	0.80 (0.53 to 1.20)	
80% of 180 consecutive days	0.27 (0.10 to 0.72)	1.19 (0.44 to 3.20)	0.92 (0.59 to 1.43)	
100% of 180 consecutive days	Non-event	Non-event	Non-event	
80% of 365 consecutive days	0.14 (0.03 to 0.64)	1.61 (0.51 to 5.12)	0.99 (0.57 to 1.72)	
100% of 365 consecutive days	Non-event	Non-event	Non-event	



Group vs Sulfonylureas SGLT2 inhibitors Thiazolidinediones DPP-4 inhibitors

C. Hospitalization for heart failure

Index date	SGLT2 inhibitors	Thiazolidinediones	DPP-4 inhibitors	ASHR (95% CI)
80% of 90 consecutive days	0.60 (0.40 to 0.91)	1.22 (0.71 to 2.10)	0.97 (0.74 to 1.25)	
100% of 90 consecutive days	0.64 (0.41 to 1.02)	1.76 (1.01 to 3.04)	1.12 (0.84 to 1.49)	
80% of 180 consecutive days	0.52 (0.32 to 0.85)	1.22 (0.67 to 2.23)	0.98 (0.74 to 1.30)	
100% of 180 consecutive days	0.43 (0.22 to 0.81)	1.12 (0.55 to 2.26)	0.86 (0.62 to 1.19)	
80% of 365 consecutive days	0.34 (0.18 to 0.66)	0.93 (0.42 to 2.08)	0.86 (0.62 to 1.21)	
100% of 365 consecutive days	0.58 (0.22 to 1.52)	2.06 (0.79 to 5.37)	1.21 (0.73 to 2.03)	



Group vs Sulfonylureas SGLT2 inhibitors Thiazolidinediones DPP-4 inhibitors

Disclosures: Heejoon Jang: Nothing to Disclose, Yoo Kyoung Lim: Nothing to Disclose, Yeonjin Kim: Nothing to Disclose, Dong Hyeon Lee: Nothing to Disclose, Sae Kyung Joo: Nothing to Disclose, Bokyung Koo: Nothing to Disclose, Woojoo Lee: Nothing to Disclose, Won Kim: Nothing to Disclose

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3192 | COMPARISON OF BARIATRIC SURGERY VS. GLP-1 RECEPTOR AGONISTS ON CARDIOVASCULAR OUTCOMES AND MORTALITY IN PATIENTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE, DIABETES, AND OBESITY: A LARGE POPULATION-BASED COHORT STUDY ◆

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[1]Apex Institute of Medical Sciences, [2]RWTH Aachen University, [3]Johns Hopkins University School of Medicine

Background: Cardiovascular disease (CVD) is the leading cause of mortality in patients with metabolic dysfunction-associated steatotic liver disease (MASLD). Bariatric surgery (BS) has been shown to reduce cardiovascular risk factors. Conversely, glucagon-like peptide-1 receptor agonists (GLP-1RA) have shown effects on reducing liver fat, progression of MASLD, and lowering CVD as a promising therapeutic avenue. However, comparative evidence for the effects of BS and GLP-1RA on cardiovascular outcomes has not been well characterized. The present study aimed to determine the incidence of major CVD among patients with MASLD, type 2 diabetes (T2D), and obesity without a history of CVD treated with BS versus GLP-1RA. **Methods:** This large population-based, retrospective cohort study was conducted using the TriNetX database. All adult patients (>18 years) diagnosed with MASLD, diabetes, and obesity with no prior history of CVD between 2012 and 2022. were identified after excluding other chronic liver disease etiologies. We performed a 1:1 propensity score matching (PSM) for demographics, BMI, comorbidities, laboratory parameters, and medications. Cohort entry for GLP-1 RAs (control group) was defined as the first-ever prescription date. We used a lag of 6 months to minimize protopathic bias. The primary outcome was the first occurrence of heart failure (HF), major adverse CV events (MACE), or cerebrovascular disease. The secondary outcome was all-cause mortality. Sensitivity analyses assessed the robustness of the findings. Cox proportional hazard models were used to estimate hazard ratio (HR). **Results:** A total of 167,895 individuals with MASLD, T2D, and obesity were identified. Of those, 6898 patients had a history of BS, whereas 49,767 individuals had newly received GLP-1RAs; following PSM, both cohorts are well matched (n=6430). At 1 year, the new incidence of HF (HR 0.67; 95% CI, 0.51-0.82); MACE (HR 0.75; 95% CI, 0.62-0.89); or cerebrovascular diseases (HR 0.59; 95% CI, 0.43-0.78) was significantly lower in the BS group. However, there was no difference in mortality (HR 0.92; 95% CI, 0.77-1.02) at 1 year in the GLP-1RA group. Overall, in the adjusted analysis (Table 1), the risks of MACE (HR, 0.87), HF (HR, 0.67), and cerebrovascular disease (HR, 0.70) were significantly lower for BS than new users of GLP-1RA. Similarly, BS was also associated with a lower incidence of all-cause mortality (HR, 0.34) and a composite outcome of major CVD. These outcomes were consistent at 3-, 5-, and 7-year follow-ups. The sensitivity analysis results were consistent. **Conclusion:** In individuals with MASLD, T2D, and obesity, BS was associated with a significantly lower risk of CVD and all-cause mortality compared with GLP-1RA. These initial results should be confirmed in a larger randomized clinical trial to optimize therapeutic strategies for this growing patient population.

Table 1: Cardiovascular Outcomes and All-Cause Mortality among patients with MASLD, obesity type-2 diabetes between bariatric surgery and GLP-1RA.

Outcomes	BS (n=6430) Patients with events, N	GLP1-RA (n=6430) Patients with events, N	Hazard Ratio (95% CI)
Primary outcome (cardiovascular diseases)			
Composite MACE[1]	413	593	0.81 (0.71-0.92)
HF	143	170	0.67 (0.54-0.84)
Composite Cerebrovascular disease*	324	397	0.70 (0.61-0.82)
Secondary outcome			
All-Cause Mortality	83	52	0.34 (0.21-0.56)

Abbreviations: BS, bariatric surgery, HF, heart failure, MACE, major adverse cardiovascular events ; MASLD, metabolic dysfunction-associated steatotic liver disease; GLP-1RA, glucagon-like peptide-1 receptor agonists.

[1]A composite endpoint of MACE was defined occurrence of myocardial infarction (ST-segment elevation myocardial infarction and non-ST-elevation myocardial infarction), unstable angina, and ischemic heart disease.

*A composite endpoint of cerebrovascular disease was defined as the occurrence of stroke, carotid stenosis, transient ischemic attack, and carotid interventions or surgeries)

Disclosures: Arunkumar Krishnan: Nothing to Disclose, Diptasree Mukherjee: Nothing to Disclose, Carolin Schneider: Nothing to Disclose, Tinsay Woreta: Nothing to Disclose, Saleh Alqahtani: Nothing to Disclose

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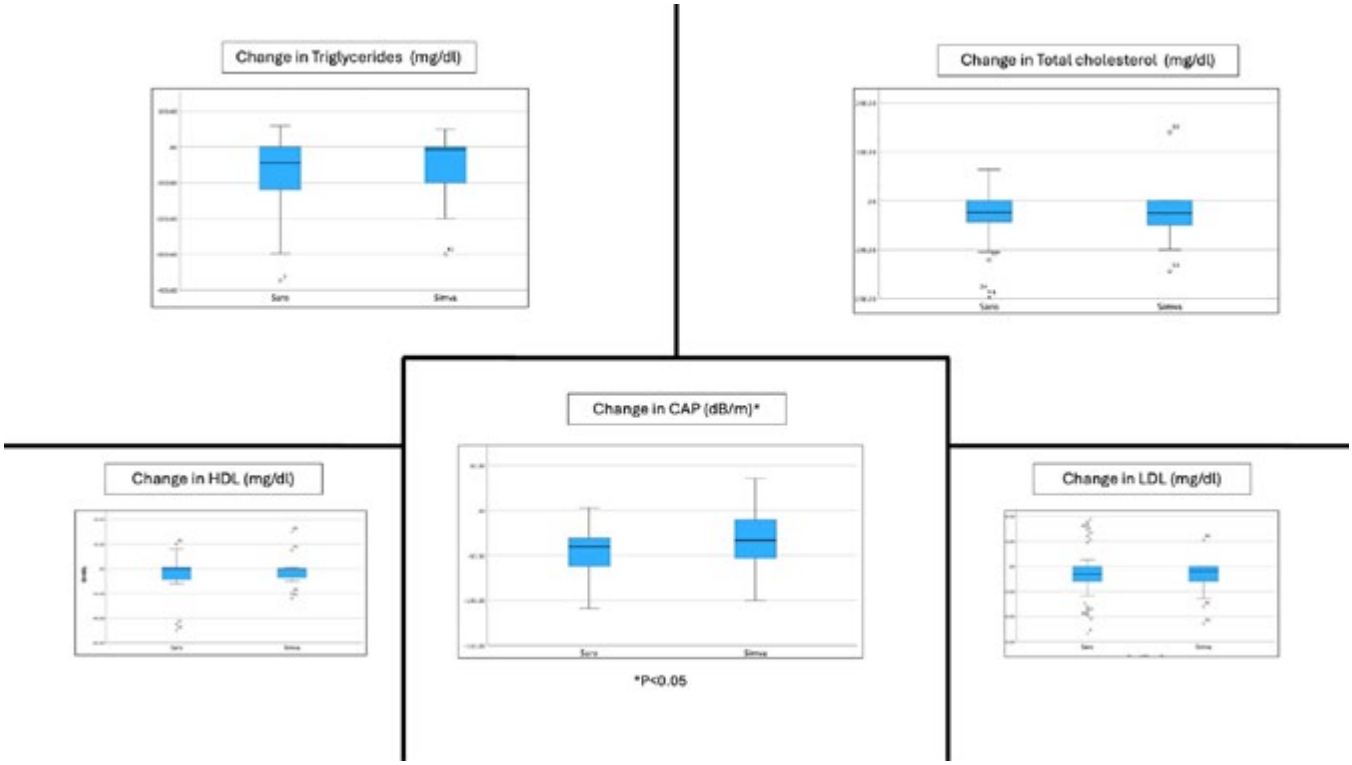
3193 | SAROGLITAZAR IS MORE EFFECTIVE THAN SIMVASTATIN IN REDUCING STEATOSIS IN PATIENTS WITH MET-ALD

Anand Kulkarni[1] Ramyasri Ramagundam[2] Zaid Mohammed Gangdany[2] Mithun Sharma[3] Manasa Alla[2] Shantan Venishetty[2] Sowmya T R[2] Padaki Nagaraja Rao[2] Nageshwar Reddy[2]

[1]Asian Institute of Gastroenterology, [2]AIG Hospitals, [3]ASIAN INSTITUTE OF GASTROENTROLOGY PVT LTD

Background: MetALD is the new term proposed to identify patients with steatotic liver disease, who concomitantly consume alcohol (210-420 g/week). The use of lipid-lowering drugs is common in these patients with cardiometabolic diseases. No studies have compared the use of saroglitazar (PPAR-a/g agonist) with simvastatin (HMG CoA reductase inhibitor) for patients with MetALD which we aimed to assess. **Methods:** In this retrospective study, we included patients with MetALD. The primary objective was to compare changes in transient elastography, lipid profile and glycosylate hemoglobin among patients receiving saroglitazar (Gr.A) and simvastatin (Gr.B). **Results:** Of the 102 patients (age-42.1 years; males-100%; BMI-25.8±3.9; duration of alcohol intake-16.5 years) with alcohol use disorder (AUD) who received saroglitazar or simvastatin, 99% satisfied cardiometabolic criteria of MASLD. Among these patients, 43.1% had satisfied 3 criteria, 16.7% each had satisfied 1, 2 and 4 criteria, while only 6% had satisfied all the five criteria. Fifty-seven patients received saroglitazar at 4 mg/day and 45 received simvastatin at 10 (10-20) mg/day. The median duration of therapy was 6 months in both groups. Twenty eight percent in Gr.A and 31.1% of patients in Gr.B had alcohol relapse, and the remaining were abstinent (P=0.73). Twenty six percent in Gr.A and 31.1% in Gr.B had at least 5% weight loss in 6 months (P=0.59) The median controlled attenuation parameter was 288 (195-400) dB/m in Gr.A and 287 (170-381) dB/m in Gr.B (P=0.42) at baseline. The liver stiffness measurement was also similar among both groups (Gr.A: 8.9 [4.5-30] kPa and Gr.B: 9.8 [4-25];P=0.39). Lipid profile, including total cholesterol, triglycerides, and high, low and very low-density lipoprotein, were similar among both groups. The median change in CAP score after 6 months of therapy was significantly more in Gr.A (-40 [-109 to 3] dB/m) than Gr. B (-33 [-100 to 36] dB/m; P=0.04). While the change in LSM was similar among both groups (Gr.A: -1.9 [=19.5 to 26.3] kPa vs. Gr.B: -0.8 [-12 to 9] kPa; P=0.21). The change in lipid profile parameters was also similar. (Figure) However, the change in HbA1c was higher in Gr.A (-0.1 [-3.6 to 0]) than Gr.B (0 [-1.2 to 0.8] P=0.02) There were no adverse events in both groups except fatigue and abdominal discomfort in two patients taking saroglitazar. **Conclusion:** Saroglitazar is safe and more effective than simvastatin in reducing steatosis in patients with Met-ALD.



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3194 | LONG-TERM HEPATOPROTECTIVE EFFECTS OF GLP-1RA IN OBESE PATIENTS WITH TYPE 2 DIABETES: A RETROSPECTIVE COHORT STUDY

Himsikhar Khataniar[1] Ashni Dharia[1] Aakash Desai[2] Muhammad Ali Butt[1] Michael Babich[1] Nabeeha Mohy-ud-din[1]

[1]Allegheny General Hospital, [2]Mayo Clinic Jacksonville

Background: There is an increasing incidence of glucagon-like peptide-1 receptor agonist (GLP-1RA) use for type 2 diabetes mellitus (T2DM) and weight management. It may also benefit patients with liver diseases, specifically patients with MASLD, where it can improve steatosis and may provide cardiovascular benefit. **Methods:** We conducted a retrospective cohort study utilizing the TriNetX database to evaluate long-term outcomes of patients with T2DM and obesity on GLP-1RA compared to those not on GLP-1RAbetween 2010 and 2019. The primary aim was to assess whether regular use of GLP-1RAis associated with a reduction in incidence of liver disease, particularly cirrhosis, hepatocellular carcinoma (HCC), and all-cause mortality. Rare but serious side effects of GLP-1RA were also evaluated as secondary outcomes. Patients with pre-existing liver diseases before 2009, including HCC and HbA1c > 10, were excluded from the study. Patients needed to be on GLP-1RA for at least 6 months to be included. 1:1 propensity score matching was performed for age, gender, race, comorbidities, liver-related characteristics, BMI, malignancies, and commonly used medications between the cohorts, with risk expressed as adjusted odds ratios (aOR) with 95% confidence intervals (CI). **Results:** Our study included obese patients with T2DM using GLP-1RA(n=40,223) and those not using GLP-1RA (n=1,156,237) from 2010 to 2019. Patients using GLP-1RA had a mean age of 56 ± 11.4 years, with 15.80% African American and 52.50% female, while non-users had a mean age of 60.5 ± 14.2 years, with 18.45% African American and 50.10% female. At 5 years, patients using GLP-1RA had significantly lower rates of non-alcohol related cirrhosis (1.59% vs. 1.86%, aOR 0.83, 95% CI 0.75-0.93, p=0.001), alcohol related cirrhosis (0.15% vs. 0.35%, aOR 0.45, 95% CI 0.33-0.61, p<0.0001), HCC (0.12% vs. 0.21%, aOR 0.57, 95% CI 0.4-0.82, p=0.002), and all-cause mortality (4.10% vs. 9.90%, aOR 0.39, 95% CI 0.37-0.41, p<0.0001). Adverse outcomes included higher rates of drug-induced myopathy (0.16% vs. 0.07%, aOR 2.2, 95% CI 1.4-3.4, p=0.0003) and thyroid cancer (0.84% vs. 0.65%, aOR 1.29, 95% CI 1.09-1.52, p=0.002). **Conclusion:** Our study highlights the potential hepatoprotective benefits of GLP-1RA in reducing incidence of liver disease in high-risk populations, though the increased risk of certain adverse effects necessitates careful consideration. Further research is needed to confirm these benefits and fully elucidate the risk profile of GLP-1 agonists in this patient population.

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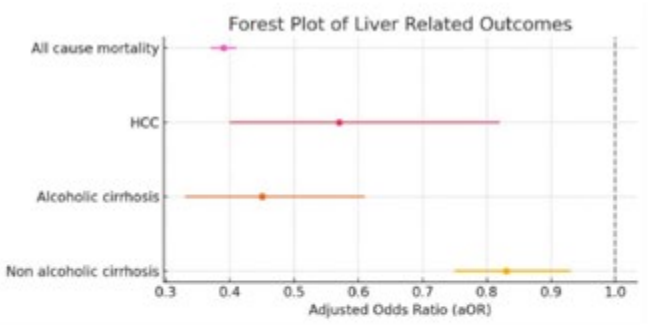
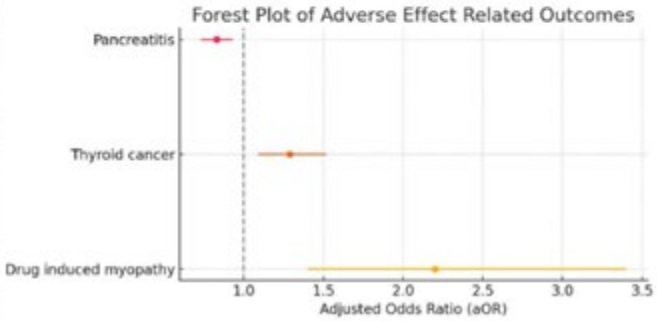
T2DM+Obese w GLP-1	40,223				
T2DM+Obese	1,156,237				
*between 2010-2019 for cohort identification					
T2DM+Obese w GLP-1					
Mean age	56+/-11.4				
African American	15.80%				
Female sex	52.50%				
T2DM+Obese					
Mean age	60.5+/-14.2				
African American	18.45%				
Female sex	50.10%				
5 year - outcomes	**N**	**%**	**aOR**	**95% CI**	**p value**
Liver related outcomes					
Non alcoholic cirrhosis	613	1.59%	0.83	0.75-0.93	**0.001**
	730	1.86%			
Alcoholic cirrhosis	61	0.15%	0.45	0.33-0.61	**<0.0001**
	135	0.35%			
HCC	47	0.12%	0.57	0.4-0.82	**0.002**
	82	0.21%			
All cause mortality	1600	4.10%	0.39	0.37-0.41	**<0.0001**
	3811	9.90%			
Adverse effect related outcomes					
Drug induced myopathy	64	0.16%	2.2	1.4-3.4	**0.0003**
	29	0.07%			
Thyroid cancer	326	0.84%	1.29	1.09-1.52	**0.002**
	253	0.66%			
Pancreatitis	521	1.35%	0.83	0.73-0.93	**0.002**
	625	1.62%			





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3195 | DENIFANSTAT SIGNIFICANTLY IMPROVES LIVER FIBROSIS IN DIFFICULT-TO-TREAT METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS (MASH) PATIENTS. RESULTS FROM CONVENTIONAL AND AI-BASED PATHOLOGY FROM THE PHASE 2B FASCINATE-2, A 52-WEEK RANDOMIZED, DOUBLE BLIND, PLACEBO-CONTROLLED TRIAL OF FATTY ACID SYNTHASE (FASN) INHIBITOR DENIFANSTAT, IN F2/F3 MASH ◆

Rohit Loomba[1] Eduardo Martins[2] Katharine Grimmer[2] Wen-Wei Tsai[2] Marie O'Farrell[2] William McCulloch[2] George Kemble[3] Pierre Bedossa[4] Jose Cobiella[5] Eric Lawitz[6] Madhavi Rudraraju[7] Stephen Harrison[8]

[1]University of California, San Diego, [2]Sagimet Biosciences, [3]BioScience Communications, [4]Liverpat, [5]Global Research Associates, [6]The Texas Liver Institute, [7]Pinnacle Clinical Research, [8]University of Oxford

Background: New therapies are needed for MASH, in particular drugs that improve liver fibrosis, the main predictor of poor clinical outcomes. Denifanstat directly blocks stellate cell activation and collagen production, inflammatory cell activation and hepatocyte fat synthesis by inhibition of FASN, an enzyme required by these 3 cell types for MASH pathogenesis. In FASCINATE-2, a phase 2b, multicenter, double blind, randomized, placebo (pbo)-controlled trial, denifanstat met primary and multiple secondary endpoints, including fibrosis improvement without worsening of MASH. Here we report denifanstat's impact on fibrosis in the overall study population and difficult-to-treat subsets by conventional histopathology and second harmonic generation AI-based digital pathology (SGH, HistoIndex). **Methods:** 168 patients with biopsy-confirmed MASH and F2/F3 fibrosis were randomized 2:1 to once daily oral denifanstat 50 mg or pbo for 52 weeks. 126 had both pre- and post-treatment biopsies (mITT), 70 (55.6%) F3 fibrosis, 16 (12.7%) on a stable dose GLP1, and 82 (65.1%) type 2 diabetes (T2D). Biopsies were read by an expert liver pathologist using the NASH CRN system, and a separate slide by SHG. Mean (SD) SHG baseline qFibrosis values for denifanstat and pbo were, respectively: qFibrosis continuous 2.6 (0.75) vs. 2.5 (0.64), and qFibrosis stages 2.8 (0.72) vs. 2.8 (0.61). **Results:** At the end of treatment denifanstat led to fibrosis improvement by ≥1 stage without worsening of MASH: 40.7% vs. 17.8% for pbo (p = 0.0051). Evaluation of at-risk subsets using this same endpoint showed: • F3 fibrosis: denifanstat 48.9% vs. 13% pbo, p = 0.0016 • GLP1: denifanstat 42% vs. 0% pbo, p = 0.034 • T2D: denifanstat 40% vs. 18.5% pbo, p

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= 0.0382 • PNPLA3 I148M carrier: denifanstat 30% vs. 6% pbo, p=0.022 • SHG confirmed denifanstat's fibrosis improvement with qFibrosis results as follows – LS mean (90% CI) % change from baseline (BL): • qFibrosis continuous value: denifanstat -6.1% (-10.62, -1.65) vs. 4.6% (-1.14, 10.43) pbo, p = 0.0071 • Steatosis corrected qFibrosis continuous value: denifanstat -20.7% (-25.86, -15.57) vs. 0.8% (-5.84, 7.41), p < 0.0001 • qFibrosis stage: denifanstat -6.5% (-11.84, -1.09) vs. 2.9% (-4.04, 9.83) pbo, p = 0.0370 • Steatosis corrected qFibrosis stage: denifanstat -19.4% (-25.46, -13.31) vs. 0.2% (-7.64, 8.02) pbo, p = 0.00006. Post-hoc analysis of 16 patients with baseline SHG qFibrosis stage 4 showed 1-stage improvement in fibrosis by the central pathologist (NASH CRN) in 39% of denifanstat patients vs. 0% pbo. Denifanstat was generally well tolerated, with no drug related grade ≥3 AEs and no drug related SAEs. **Conclusion:** Denifanstat demonstrated clinically meaningful and statistically significant improvement in liver fibrosis without worsening of MASH, including in difficult-to-treat MASH. Fibrosis improvement was also demonstrated by AI-based pathology.

Disclosures: Rohit Loomba: Eli Lilly and Company: Consultant, 89bio: Consultant, Aardvark Therapeutics: Consultant, Altimmune: Consultant, Alnylam/Regeneron: Consultant, Amgen: Consultant, Arrowhead Pharmaceuticals: Consultant, AstraZeneca: Consultant, Bristol Myers Squibb: Consultant, CohBar: Consultant, Eli Lilly: Consultant, Galmed Pharmaceuticals: Consultant, Gilead: Consultant, Glympse Bio: Consultant, Hightide: Consultant, Inipharma: Consultant, Intercept: Consultant, Inventiva: Consultant, Ionis: Consultant, Janssen, Inc.: Consultant, Madrigal Pharmaceuticals: Consultant, Merck, Metacrine, Inc.: Consultant, NGM Biopharmaceuticals: Consultant, Novartis: Consultant, Novo Nordisk: Consultant, Pfizer: Consultant, Sagimet Biosciences: Consultant, Terns Pharmaceuticals: Consultant, Theratechnologies and Viking Therapeutics: Consultant, 89bio: Stock options, Sagimet Biosciences: Stock options, Arrowhead Pharmaceuticals: Research grant, AstraZeneca: Research grant, Boehringer Ingelheim: Research grant, Bristol Myers Squibb: Research grant, Eli Lilly: Research grant, Galectin Therapeutics: Research grant, Galmed Pharmaceuticals: Research grant, Gilead: Research grant, Hanmi: Research grant, Intercept: Research grant, Inventiva: Research grant, Ionis: Research grant, Janssen, Inc.: Research grant, Madrigal Pharmaceuticals: Research grant, Merck: Research grant, NGM Biopharmaceuticals: Research grant, Novo Nordisk: Research grant, Pfizer: Research grant, Sonic Incytes: Research grant, Terns Pharmaceuticals: Research grant, LipoNexus, Inc.: Co-founder, Eduardo Martins: Sagimet Biosciences: Employee, Sagimet Biosciences: Employee, Sagimet Biosciences: Stock - publicly traded company, Katharine Grimmer: Nothing to Disclose, Wen-Wei Tsai: Sagimet: Stock share holder, Gordian: paid consultant service, Marie O'Farrell: Nothing to Disclose, William McCulloch: Nothing to Disclose, George Kemble: Sagimet Biosciences: Salary, stock ownership, Pierre Bedossa: Nothing to Disclose, Jose Cobiella: Nothing to Disclose, Eric Lawitz: Nothing to Disclose, Madhavi Rudraraju: Nothing to Disclose, Stephen Harrison: Nothing to Disclose

3196 | THERAPEUTIC ACTIVITY OF RESOLVIN D1 (RVD1) IN MURINE MASH

Bishuang Cai[1]

[1]*Icahn School of Medicine at Mount Sinai*

Background: Recent studies have highlighted the beneficial effect of resolvin D1 (RvD1), a DHA-derived specialized pro-resolving mediator, on metabolic dysfunction-associated steatohepatitis (MASH), but the underlying mechanisms are not well understood. Our study aims to determine the mechanism by which RvD1 protects against MASH progression. **Methods:** RvD1 was administered to mice with experimental MASH, followed by bulk and single-cell RNA sequencing analysis. Primary cells including bone marrow–derived macrophages (BMDMs), Kupffer cells, T cells, and primary hepatocytes were isolated to elucidate the effect of RvD1 on inflammation, cell death, and fibrosis regression genes. **Results:** Hepatic tissue levels of RvD1 were decreased in murine and human MASH, likely due to an expansion of pro-inflammatory M1-like macrophages with diminished ability to produce RvD1. Administering RvD1 reduced inflammation, cell death, and liver fibrosis. Mechanistically, RvD1 reduced inflammation by suppressing the Stat1-Cxcl10 signaling pathway in macrophages and prevented hepatocyte death by alleviating ER stress-mediated apoptosis. Moreover, RvD1 induced *Mmp2* and decreased *Acta2* expression in hepatic stellate cells (HSCs), and promoted *Mmp9* and *Mmp12* expression in macrophages, leading to fibrosis regression in MASH. **Conclusion:** RvD1 reduces Stat1-mediated inflammation, mitigates ER stress-induced apoptosis, and promotes MMP-mediated fibrosis regression in MASH. This study highlights the therapeutic potential of RvD1 to treat MASH.

Disclosures: Bishuang Cai: Nothing to Disclose

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3197 | A GENOME-FIRST APPROACH TO CODING VARIANTS IN *GPAM* REVEALS AN INCREASED RISK OF STEATOTIC LIVER DISEASE IN THE PRESENCE OF ALTERED LIPOPROTEIN PROFILES ACROSS THREE BIOBANKS

Helen Huang[1] *Anastasia Raptis*[2] *David Zhang*[3] *Cecilia Vitali*[3] *Joseph Park*[4] *Nicholas Hand*[3] *Kai Markus Schneider*[5] *Carolin Schneider*[2] *Daniel Rader*[3]

[1]*Royal College of Surgeons in Ireland,* [2]*University Hospital RWTH Aachen,* [3]*University of Pennsylvania,* [4]*Weill Cornell Medical Center,* [5]*University Hospital Aachen*

Background: Genetic risk is becoming a key contributor to steatotic liver disease (SLD) progression. Recent genome-wide association studies associated missense variants of *GPAM* with hepatic steatosis and elevated aminotransferases. Utilizing a genome-first approach, interrogating large disease-agonistic biobanks can permit deeper phenotyping of *GPAM* variants to understand its relevance with steatosis for therapeutic targets. **Methods:** We leveraged whole exome-sequencing data from the Penn Medicine Biobank (PMBB, N=37,891) and interrogated 180 non-synonymous missense variants in *GPAM* for associations with imaging-proven steatosis on CT scans derived from natural language processing methods. Significant variants were further analyzed in the United Kingdom Biobank (UKB, N=488,089) and All of Us cohort (N=230,016) as well as a publicly available GWAS from the Global Lipids Genetic Consortium (GLGC). Participants without clinically-diagnosed chronic hepatitis B/C and alcohol-related disorders were included. Analyses are fitted for age, sex, BMI and principal components of ancestry 1-10, with **Results:** being statistically significant if p<0.05. **Results:** One coding variant in *GPAM* (rs2792751, p.Ile43Val) were associated with a higher risk of imaging-proven steatosis (p<0.05, OR:1.00[1.00-1.01]) in the PMBB. Carriers were predominantly males of European ancestry and exhibited significantly lower BMI than non-carriers. These findings corresponded with carriers exhibiting elevated CT-derived hepatic fat scores (p<0.05, OR: 1.37 [1.02-1.88]) based off mean spleen-liver attenuation as well as an increased risk in ICD-diagnosed steatohepatitis (p<0.05, OR: 1.0[1.00-1.02]). In the UKB and All of Us cohort, we replicated significant associations with steatohepatitis and noted homozygotes to exhibit a higher risk of advanced liver disease phenotypes such as fibrosis/cirrhosis and hepatocellular carcinoma (p<0.05). Specific to the UKB, we identified a higher risk of hepatic steatosis defined as proton density fractionated fat of >5% on MRI and metabolic dysfunction-associated steatotic liver disease (p<0.0001, OR:1.23[1.17-1.41]). Carriers in all cohorts exhibited significantly higher alanine aminotransferases and high-density lipoprotein cholesterol (HDL-C) as well as moderate elevations in low-density lipoproteins (LDL) and total cholesterol in the GLGC. The metabolomics analysis in the UKB shows carriers exhibiting significantly higher apolipoprotein B (ApoB) and lower ketone bodies across carriers. **Conclusion:** *GPAM* rs2792751 carriers are at a higher risk of steatotic liver disease and advanced liver disease in the presence of higher circulating HDL-C, ApoB and transaminases despite exhibiting relatively lower BMI. These finding suggests that *GPAM* rs2792751 may be an independent risk factor for hepatic steatosis and could act as a promising therapeutic target to ameliorate these phenotypes.

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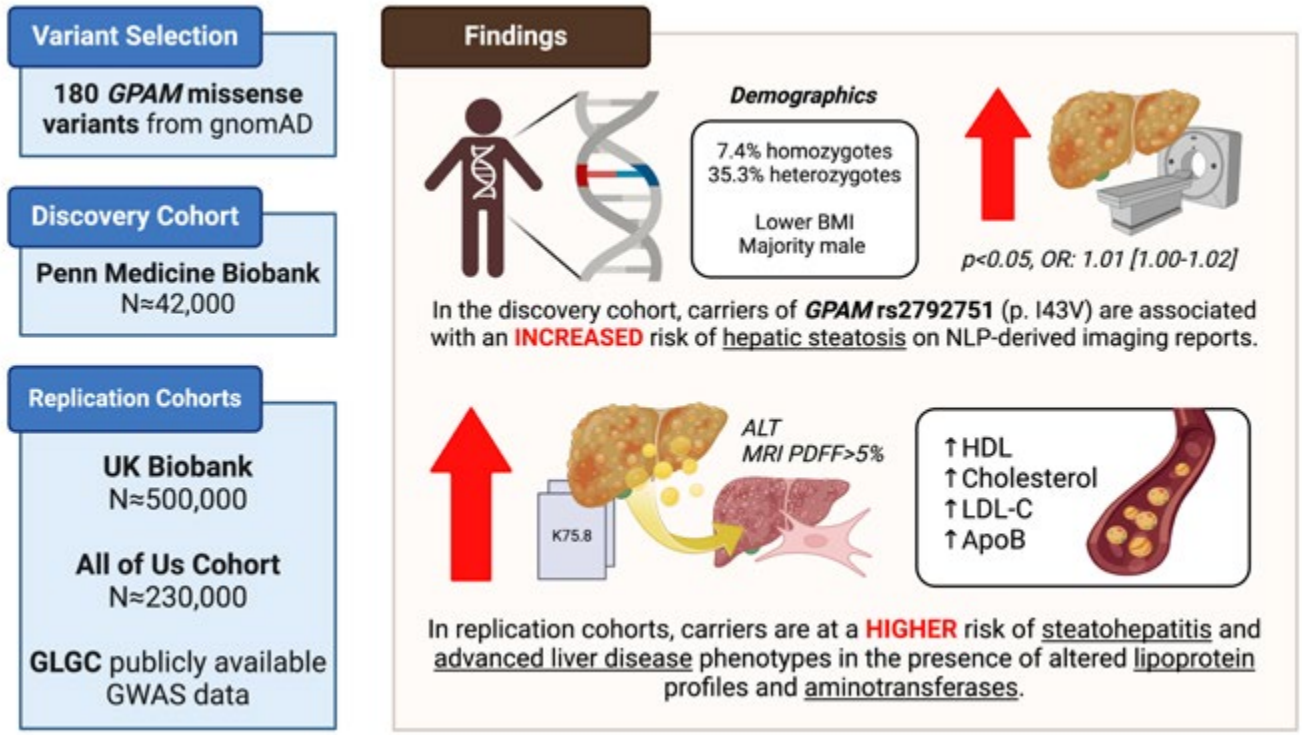

Disclosures: Helen Huang: Nothing to Disclose, Anastasia Raptis: Nothing to Disclose, David Zhang: Nothing to Disclose, Cecilia Vitali: Nothing to Disclose, Joseph Park: Nothing to Disclose, Nicholas Hand: Nothing to Disclose, Kai Markus Schneider: Nothing to Disclose, Carolin Schneider: Nothing to Disclose, Daniel Rader: Nothing to Disclose

3198 | COMPARATIVE EFFICACY OF PHARMACOLOGIC THERAPIES FOR MASH IN REDUCING LIVER FAT CONTENT: SYSTEMATIC REVIEW AND NETWORK META-ANALYSIS

EN YING TAN Benjamin Koh[1] Cheng Han Ng[2] Pojsakorn Danpanichkul[3] Benedix Kuan Loon Sim[1] Benjamin Nah[2] Margaret Teng[4] Karn Wijarnpreecha[5] Yuya Seko[6] Mei Chin Lim[2] Hirokazu Takahashi[7] Atsushi Nakajima[8] Mazen Noureddin[9] Mark Muthiah[2] Daniel Huang[2] Rohit Loomba[10]

[1]Yong Loo Lin School of Medicine, [2]National University Hospital, Singapore, [3]Department of Internal Medicine, Texas Tech University Healt, [4]National University Hospital, [5]University of Arizona College of Medicine-Phoenix, [6]Kyoto Prefectural University of Medicine, [7]Saga University, Japan, [8]National Hospital Organization Yokohama Medical Center, [9]Houston Methodist Hospital, [10]University of California, San Diego

Background: Metabolic dysfunction-associated steatohepatitis (MASH) is a leading cause of liver disease. Liver biopsy is the gold standard for assessment of treatment response in MASH but is limited by sampling variability and its invasive nature. Reductions in magnetic resonance imaging (MRI) proton-density-fat fraction (PDFF), particularly a 30% decline in PDFF, are associated with MASH resolution. We aimed to determine the relative efficacy of therapeutic agents for reducing hepatic fat, assessed by MRI-PDFF. **Methods:** In this systematic review and network meta-analysis, we searched MEDLINE and Embase from inception until Dec 26, 2023, for published randomized-controlled trials (RCTs) comparing pharmacological interventions to each other or to placebo, in MASH patients, which assessed changes in MRI-PDFF. The primary outcome was absolute change in MRI-PDFF. The secondary outcome was a ≥30% decline in MRI-PDFF. A surface under-the-curve cumulative ranking probabilities (SUCRA) analysis was performed. **Results:** Of 1550 records, a total of 39 RCTs comprising 3311 participants met the inclusion criteria. By comparison of absolute MRI-PDFF decline at 24 weeks, aldafermin (SUCRA: 83.65), pegozafermin (SUCRA: 83.46), and pioglitazone (SUCRA: 71.67) were the most efficacious interventions. Efinopegdutide (SUCRA: 67.02), semaglutide + firsocostat (SUCRA: 62.43), and

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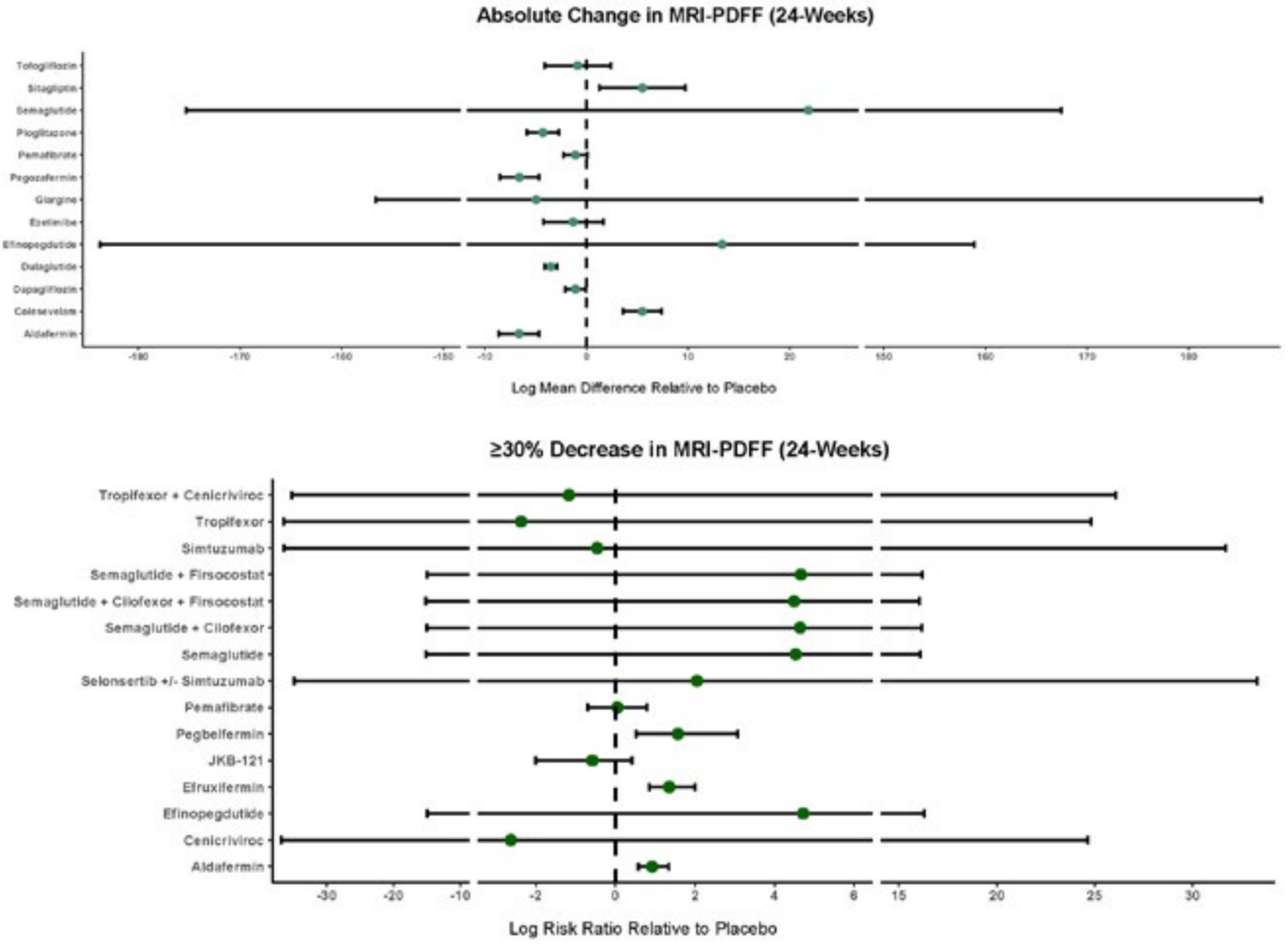
pegbelfermin (SUCRA: 61.68) were the most efficacious interventions for achieving ≥30% decline in MRI-PDFF at 24 weeks. Semaglutide monotherapy was less efficacious than these interventions. Efruxifermin, aldafermin and pegozafermin were the most efficacious for MRI-PDFF decline at 12 weeks by both the absolute decline and achieving ≥30% decline in MRI-PDFF. At 48 weeks, Cilofexor + firsocostat, selonternib + firsocostat and cilofexor were most efficacious in absolute reduction in MRI-PDFF, while semglutide, tropifexor and tropifexor + cenicriviroc were most efficacious in achieving ≥30% decline in MRI-PDFF. FGF-21 analogues were not included in the 48 week analysis. **Conclusion:** This study provides an updated, relative rank-order efficacy of therapies for MASH in reducing hepatic fat as assessed by MRI-PDFF. These data may help inform the design and sample size calculation of future clinical trials and assist selection of combination therapy.



Disclosures: EN YING TAN: Nothing to Disclose, Benjamin Koh: Nothing to Disclose, Cheng Han Ng: Nothing to Disclose, Pojsakorn Danpanichkul: Nothing to Disclose, Benedix Kuan Loon Sim: Nothing to Disclose, Benjamin Nah: Nothing to Disclose, Margaret Teng: Nothing to Disclose, Karn Wijarnpreecha: Nothing to Disclose, Yuya Seko: AbbVie GK: Speaking and Teaching, Novo Nordisk Pharma Ltd: Speaking and Teaching, Merck & Co., Inc.: Speaking and Teaching, Gilead Sciences, Inc.: Speaking and Teaching, Mitsubishi Tanabe Pharma Corporation: Speaking and Teaching, Mei Chin Lim: Nothing to Disclose, Hirokazu Takahashi: Sysmex: Grant/Research Support, Novo Nordisk: Speaking and Teaching, Kowa: Speaking and Teaching, Taisho: Speaking and Teaching, Takeda: Grant/Research Support, Atsushi Nakajima: Nothing to Disclose, Mazen Noureddin: Principal Investigator for a Drug Study relationship with Viking; Has not ended; Consultant relationship with Eli Lilly; Has not ended; Consultant relationship with AstraZeneca; Has not ended; Consultant relationship with Boston Pharmaceuticals; Has not ended; Principal Investigator for a Drug Study relationship with Genfit; Has not ended; Principal Investigator for a Drug Study relationship with Galectin; Has not ended; Principal Investigator for a Drug Study relationship with Gilead; Has not ended; Principal Investigator for a Drug Study relationship with BMS; Has not ended; Principal Investigator for a Drug Study relationship with BI; Has not ended; Principal Investigator for a Drug Study relationship with Akero; Has not ended; Consultant relationship with Cytodyn; Has not ended;

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3199 | A THERAPEUTIC HUMAN PLASMA FRACTION REVERSES LIVER AGING AND STEATOSIS TRANSCRIPTOME AND IMPROVES LIVER REGENERATION

Benson Lu[1]

[1]*Alkahest*

Background: The regenerative capacity of the aging liver diminishes, particularly in the presence of steatosis. Heterochronic parabiosis studies in mice have shown that exposure of aged liver to young circulation can restore hepatocyte proliferation, suggesting a potential for enhancing liver regeneration by modulating the plasma proteome. However, in order to translate this approach into a therapeutic, the effect must be replicated through the administration of human plasma proteins. Here, we employed a manufacturing-scale human plasma subfraction approach to identify a human plasma fraction (PF) capable of enhancing liver regeneration in a mouse model of hepatectomy and acetaminophen (APAP)-induced liver injury. Additionally, we outline some of the mechanisms responsible for rejuvenating aged hepatocytes with the PF. **Methods:** Twenty-month-old C57/B6 mice were fed with either a high fat diet or normal chow for 6 weeks before intravenous administration of PF. 70% partial hepatectomy was performed, and liver regeneration was assessed by measuring the proliferation index. Single-nuclei RNA-seq (snRNA-seq) was conducted to profile liver transcriptome following PF treatment. In the APAP-induced liver injury model, mice aged 10 weeks received intraperitoneal injections of 450 to 650 mg/kg of APAP followed by PF treatment. Mortality and serum alanine aminotransferase (ALT) levels were

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analyzed to assess the hepatoprotective effects of PF. **Results:** PF administration increased liver regeneration and reduced senescence following hepatectomy in aged mice with steatosis. snRNA-seq revealed that PF reversed transcriptomic signatures associated with steatosis and liver aging in hepatocytes. Pathway analysis revealed that PF primarily reversed genes in fatty acid metabolism, protein homeostasis, and complement and coagulation cascades. In the APAP-induced liver injury model, PF treatment resulted in increased survival rates and significantly reduced serum ALT levels, suggesting a decrease in hepatocyte death. **Conclusion:** Here we present a clinically relevant approach to reverse age- and steatosis-induced decline in liver regeneration by modulating the plasma through PF administration. Additionally, PF treatment demonstrated beneficial effects in APAP-induced liver injury. Moreover, improvement in hepatocyte functions, including fatty acid and protein homeostasis, as well as complement and coagulation pathways, likely underlie the mechanisms through which PF enhances liver regeneration.

Disclosures: Benson Lu: Grifols: Employee

3200 | CVI-2742, A NOVEL THR-BETA SELECTIVE AGONIST, EXHIBITS ENHANCED LIVER-TARGETING PROPERTIES IN NON-HUMAN PRIMATES AND POTENT ANTI-NASH ACTIVITY IN MOUSE NASH MODEL

Jingwen Liu[1] *Zhenyu Wang*[1] 德鸣 徐[2]

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Background: Resmetirom has shown promising results in treating non-alcoholic steatohepatitis (NASH) by selectively activating thyroid hormone receptor-beta (THR-β) in liver tissue. Our previous studies in rodent models have introduced CVI-2742 as a highly potent and liver-targeted new generation THR-β selective agonist with superior liver-targeting capabilities compared to Resmetirom. Here we investigated tissue partition profiles of CVI-2742 and Resmetirom in non-human primates and assessed the anti-NASH activity of CVI-2742 in a DIO-CCl4 mouse NASH model. **Methods:** CVI-2742 and Resmetirom were orally administered to Cynomolgus monkeys (n=3 per group) at 5 mg/kg. Plasma samples were collected at different time point after a single dosing and were analyzed by LC/MS-MS. After 1 week washing period, Monkeys were orally given CVI-2742 or MGL-3196 at 5 mg/kg the second time and plasma and liver biopsy samples were collected at 4 hours post dosing. Male C57BL/6J mice were fed a high fat diet for 12 weeks to induce obesity prior to daily oral drug treatment and biweekly intraperitoneal carbon tetrachloride treatment. CVI-2742 doses were 0.5 mg/kg, 1 mg/kg and 3 mg/kg. Resmetirom was included in the study at 10 mg/kg. On day 28 of treatment, animals were euthanized for liver weight measurement and liver sample collections for lipid, histology, and gene expression analyses (RT-qPCR). **Results:** In this investigation, CVI-2742 and Resmetirom were administered to Cynomolgus monkeys, showing significantly 4.6 fold higher liver tissue/plasma drug concentration ratios for CVI-2742 (54.9±33.7) than Resmetirom (12.0±4.4), demonstrating CVI-2742's enhanced liver-targeting property. In the DIO-CCl4 mouse NASH model, CVI-2742 displayed remarkable anti-NASH activity, reducing NASH scores, hepatocyte ballooning, liver fibrosis, and hepatic lipid levels at low efficacious doses. Additionally, CVI-2742 upregulated THR-β target genes in the liver, indicating its selective hepatic action. **Conclusion:** These findings highlight CVI-2742 as a promising candidate for NASH therapy due to its liver-targeted mechanism and potent anti-NASH effects in preclinical models. The excellent pharmacokinetic profiles observed in non-human primates and rodent models support the further development of CVI-2742 towards human clinical studies for NASH treatment.

Disclosures: Jingwen Liu: Nothing to Disclose, Zhenyu Wang: Nothing to Disclose, 德鸣 徐: Nothing to Disclose

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3201 | SKQ1, A MITOCHONDRIA-TARGETED FERROPTOSIS INHIBITOR, DEMONSTRATES EFFICACY AGAINST STEATOSIS, BALLOONING AND FIBROSIS IN PRECLINICAL MODELS OF MASH

Anton Petrov[1] Maxim Skulachev[1] Natalia Perekhvatova[2]

[1]Mitotech Ltd, [2]Mitotech

Background: SkQ1 is a small molecule that efficiently accumulates in mitochondria and has dual mode of efficacy: mild mitochondrial uncoupling and anti-ferroptosis action. With combined potential effect of weight loss via uncoupling mechanism and direct protection of the liver from ferroptosis SkQ1 may be an ideal candidate for next-generation treatment of MASH. **Methods:** To examine the effects of SkQ1 in DIO mouse model of obesity and fatty liver male C57BL/6J mice were exposed to the high fat diet for circa 32 weeks. SkQ1 was administered at doses of 0.5 and 1.0 mg/kg QD for four weeks. Animals were monitored daily for body wight and food intake. Liver histology was performed at the end of the study. To evaluate the effect of SkQ1 in STAM model of MASH, male C57BL/6J mice were subcutaneously injected with a low dose of streptozotocin solution 2 days after birth and were fed with high fat diet after 4 weeks of age. SkQ1 was administered at the dose of 3 mg/kg BID for four weeks. **Results:** SkQ1 induced 15% weight loss in DIO mice over the course of treatment with no impact on muscle mass. This weight loss was accompanied by significant reduction of triglycerides ($p<0.001$ vs. vehicle) and lipid deposition ($p<0.05$ vs. vehicle) in the liver. NAFLD activity score composed of steatosis, inflammation and ballooning scores was also significantly reduced ($p<0.001$ vs. vehicle). In the STAM model study no weight loss was observed, as in that model MASH was induced in lean animals. The study demonstrated SkQ1-induced reduction of both steatosis and ballooning in the liver ($p<0.05$ vs. vehicle for both), as well as reduction of the combined NAFLD activity score ($p<0.01$ vs. vehicle). Interestingly, these effects were accompanied by a significant reduction in fibrosis grade in the liver ($p<0.05$ vs. vehicle). SkQ1 induced 15% weight loss in DIO mice over the course of treatment with no impact on muscle mass. This weight loss was accompanied by significant reduction of triglycerides ($p<0.001$ vs. vehicle) and lipid deposition ($p<0.05$ vs. vehicle) in the liver. NAFLD activity score composed of steatosis, inflammation and ballooning scores was also significantly reduced ($p<0.001$ vs. vehicle). In the STAM model study no weight loss was observed, as in that model MASH was induced in lean animals. The study demonstrated SkQ1-induced reduction of both steatosis and ballooning in the liver ($p<0.05$ vs. vehicle for both), as well as reduction of the combined NAFLD activity score ($p<0.01$ vs. vehicle). Interestingly, these effects were accompanied by a significant reduction in fibrosis grade in the liver ($p<0.05$ vs. vehicle). **Conclusion:** The effect of SkQ1 on hepatocyte ballooning – the hallmark of human MASH – and reduction of fibrosis highlighted SkQ1 potential as a candidate for next-generation treatment of MASH.

Disclosures: Anton Petrov: Mitotech Ltd: Employee, Maxim Skulachev: Nothing to Disclose, Natalia Perekhvatova: Nothing to Disclose

3202 | FIBROSIS REGRESSION AFTER TIRZEPATIDE TREATMENT OF NON-CIRRHOTIC MASH FOR 52 WEEKS OCCURRED IN A ZONE-DEPENDENT MANNER

Arun Sanyal[1] Vlad Ratziu[2] Cindy Behling[3] Oscar Cummings[4] Yukti Choudhury[5] Elaine Chng[5] Yuanyuan Tang[6] Dean Tai[5] Mark Hartman[6] Rohit Loomba[7]

[1]Virginia Commonwealth University, [2]Sorbonne Université, [3]Pacific Rim Pathology, [4]Indiana University School of Medicine, [5]HistoIndex Pte., [6]Eli Lilly and Company, [7]University of California - San Diego

Background: Tirzepatide (TZP) is a long-acting GIP/GLP-1 receptor agonist. In the SYNERGY-NASH trial (NCT04166773), the proportion of participants who completed treatment and achieved ≥1-stage fibrosis improvement was 32.5% for placebo (PBO), and 59.2%, 53.4% and 54.3% for TZP 5, 10 and 15 mg, respectively. This post hoc analysis explored zonal changes in fibrosis using quantitative second harmonic generation (SHG)/two-photon excited fluorescence (TPEF) microscopy imaging with an artificial intelligence-based algorithm. **Methods:** 144 paired biopsy samples (baseline [BL] and week 52 [W52]) from SYNERGY-NASH were imaged using SHG/TPEF microscopy. Because fibrosis burden may be underestimated in the setting of steatosis and TZP induced large liver fat reductions, a steatosis correction was applied: the steatosis area (by SHG/TPEF) was subtracted from the total liver tissue area to remove the confounding effect of changes in steatosis. Changes in fibrosis were assessed for the whole sample (qFibrosis) and for 5 zones: portal, peri-portal (zone

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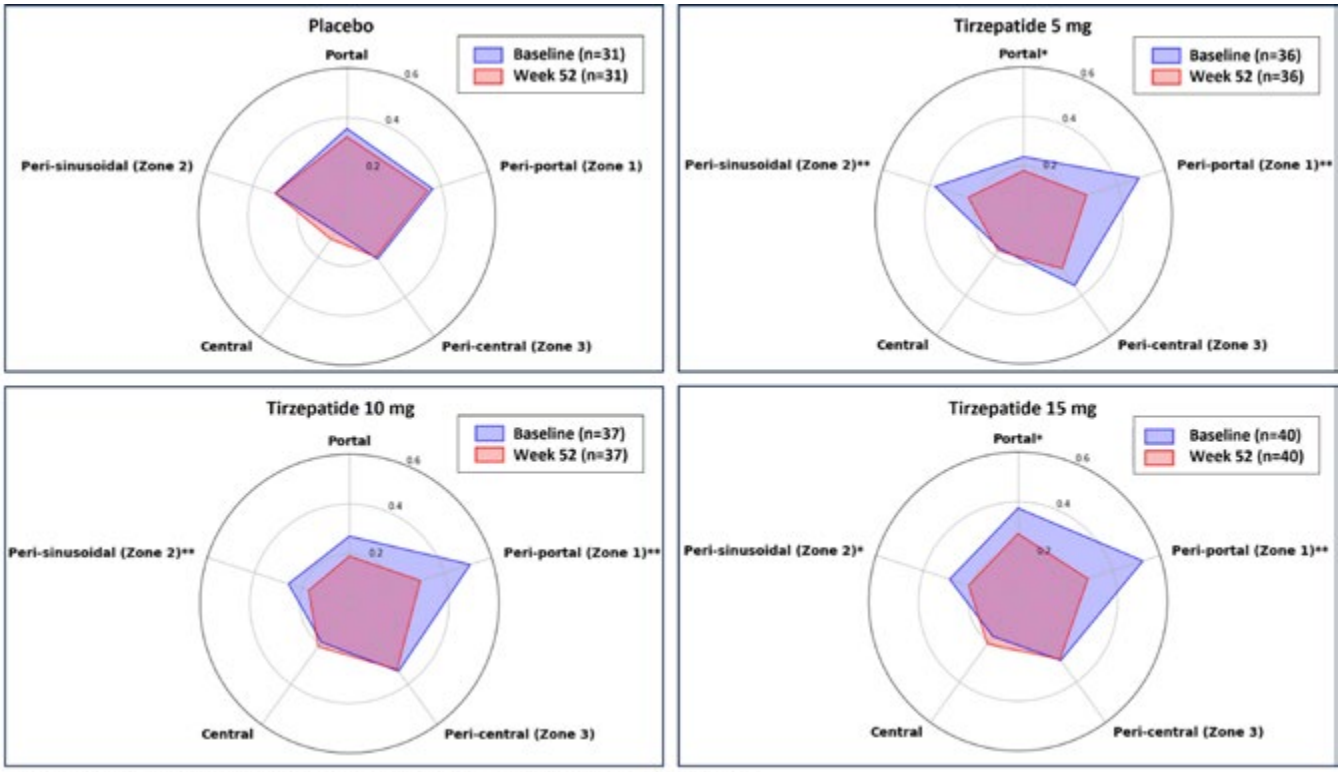
1), peri-sinusoidal (zone 2), central and peri-central (zone 3). **Results:** Changes from BL in qFibrosis (steatosis-corrected) values at W52 did not differ significantly between TZP groups and PBO. When zonal analysis of collagen area was applied, statistically significant decreases in fibrosis between BL and W52 were observed in zone 1, zone 2 and the portal zone with TZP 5mg and 15mg and in zone 1 and zone 2 with TZP 10mg but not with PBO. No significant changes were observed in zone 3 and the central zone (Figure). Among participants with ≥1 stage fibrosis improvement according to the pathologists, significant ($p<0.05$) fibrosis regression with TZP was seen in zones 1, 2 and portal zone with 5mg, zones 1 and 2 with 10mg and zone 1 with 15mg. TZP-treated participants with no change in fibrosis staging by the pathologists showed significant ($p<0.05$) fibrosis regression in zone 1 (10mg and 15mg) and portal zone (15mg). Among TZP-treated participants with a ≥1 stage increase in fibrosis (by pathologists), a non-significant trend toward worsening of fibrosis was observed in the portal/peri-central/central zones. **Conclusion:** Fibrosis regression with TZP treatment of MASH for 52 weeks occurred in zones 1 and 2 but not in zone 3 of the liver lobule, which was different from fibrosis regression in PBO. This suggests the potential for distinct mechanisms of fibrosis regression triggered by TZP, to be evaluated in longer studies.



* for $p<0.05$, and ** for $p<0.001$ for comparison between baseline and Week 52

Disclosures: Arun Sanyal: Genfit, Akarna, Tiziana, Durect, Inversago, Hemoshear, North: Stock - publicly traded company, Astra Zeneca (60K), Boston Pharmaceutical

3203 | DUAL SILENCING OF *YAP1*/*WWTR1* AS A NOVEL THERAPEUTICAL APPROACH FOR LIVER FIBROSIS

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[1]*Nitto Denko Corporation*

Background: Metabolic dysfunction-associated steatohepatitis (MASH) is the leading cause of liver fibrosis worldwide, and no approved therapies exist to treat advanced fibrosis in MASH. It is known that YAP (Yes-associated protein, encoded by *YAP1*)/TAZ (transcriptional coactivator with PDZ-binding motif, encoded by *WWTR1*) contribute to fibrogenesis in the various organs including liver. However, there are no reports

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demonstrating the therapeutic effects for MASH by pharmacological blockade of YAP/TAZ. The present study aimed to explore the therapeutic potential of *YAP1*/*WWTR1* silencing in the choline-deficient L-amino-acid defined high fat diet (CDAHFD)-fed mice with advanced fibrosis. **Methods:** Expression levels of *YAP1*/*WWTR1* and their responsive genes were explored in the publicly available datasets of bulk-RNA sequence from the MASH patients. *In vitro* study, negative control siRNA (siNC), siRNA targeting *YAP1* and/or *WWTR1* were transfected in HepG2 (human hepatoma cell line) and LX-2 (human hepatic stellate cell line) cells, and then gene expression levels were determined. A siNC or siRNA targeting *YAP1*/*WWTR1* (siYW) was encapsulated in lipid nanoparticle (LNP), and each formulation and control buffer were single dosed at 3 mg/kg in mice fed with CDAHFD for 2 weeks to determine the target genes silencing *in vivo*. Each formulation was also dosed at 3 mg/kg bi-weekly for 8 weeks in mice fed with CDAHFD for 12 weeks to explore the efficacy for advanced fibrosis. Gene and protein expressions, biochemistry and histology were evaluated. **Results:** In the two different cohorts of MASH (GSE135251, GSE162694), expression levels of YAP/TAZ responsive genes (*CCN1*, *CCN2*, *AMOTL2*, *THBS1*, *PXMP2*, *FLNA*) were significantly varied depending on the METAVIR stages (F0-F2 vs. F3-F4). Dual silencing of *YAP1*/*WWTR1* suppressed the transcriptions of YAP/TAZ responsive genes (*CCN1*, *CCN2*, *ANKRD1*) synergistically compared to single silencing of each in HepG2 and LX-2 cells. Single dosed siYW/LNP decreased the hepatic mRNA levels of *YAP1* and *WWTR1* by 81% and 85%, the protein levels of YAP and TAZ by 96% and 85%, respectively, 7 days after administration in comparison to control. Therapeutical dosing of siYW/LNP suppressed the levels of hepatic triglyceride, hydroxyproline, picrosirius red and collagen 1 positive area by 45%, 31%, 39% and 67%, respectively, in comparison to control. In addition, the expressions of genes related to *de novo* lipogenesis (*Srebf1*, *Scd*1, *Dgat2*), fibrogenesis (*Ccn1*, *Col1a1*, *Timp1*, *Tgfb1*) and inflammatory response (*Adgre1*, *Il1b*, *Ccl2*, *Tnfa*) were significantly decreased by siYW/LNP compared to control. **Conclusion:** Dual silencing of *YAP1*/*WWTR1* suppressed YAP/TAZ pathway synergistically *in vitr*o, and ameliorated steatosis and fibrosis in the liver of CDAHFD fed mice with advanced fibrosis. These findings suggest that dual silencing of YAP/TAZ would be a novel therapeutical approach for advanced fibrosis in MASH.

Disclosures: Masayuki Sugimoto: Nitto Denko Corporation: Employee, Tatsuki Sato: Nothing to Disclose, Kaito Ueda: Nothing to Disclose, Yuki Yamada: Nothing to Disclose, Misa Yoshida: Nothing to Disclose, Tomonari Mizuno: Nothing to Disclose, Kazuki Hashiba: Nothing to Disclose, Hiroyuki Tanaka: Nothing to Disclose, Kenjiro Minomi: Nothing to Disclose, Hiroshi Yamada: Nothing to Disclose

3204 | EFFICACY AND ADVERSE EVENTS OF RESMETIROM 80 MG IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS (MASH): A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: Metabolic dysfunction-associated steatohepatitis (MASH) affects 3-5% of the global population and poses a significant socioeconomic burden due to its complications. Resmetirom, the first Food and Drug Administration (FDA)-approved treatment for MASH, is an oral, liver-directed thyroid hormone receptor beta (THR-ß) agonist. Given the unmet therapeutic needs in MASH, the FDA granted accelerated conditional approval for Resmetirom. This study aims to systematically review and perform a meta-analysis to evaluate the efficacy and safety of Resmetirom in adults with MASH. **Methods:** A systematic search of electronic databases (PubMed, EMbase, Cochrane Central Register of Controlled Trials) from 2013 to February 2024 yielded 250 studies. After rigorous screening, 25 relevant articles were reviewed, and data were extracted from 3 studies (N=2,060) that met inclusion criteria. Pooled proportions were calculated using fixed and random-effects models with a 95% confidence interval (CI). The primary endpoint was the reduction in liver steatosis, measured by Magnetic Resonance Imaging - Proton Density Fat Fraction (MRI-PDFF), with Resmetirom 80 mg. Secondary endpoints included assessing adverse events (graded according to the Common Terminology Criteria for Adverse Events) and dyslipidemia in the Resmetirom group. **Results:** The analysis included three double-blind randomized controlled trials (RCTs) conducted across 16 countries and 113 sites. Among the 2,060 participants, 90.5% were Caucasian, 46.4% were male (SD ±9.2), with a mean BMI of 35.2. Hypertension and Type 2 diabetes mellitus (T2DM) were prevalent in 68.16% and 51.73% of participants, respectively. There were 733 patients in the Resmetirom 80 mg group and 680 in the placebo group. The Resmetirom 80 mg group showed a significant reduction in hepatic steatosis compared to the placebo group (Pooled Hedges' g -0.88 [-1.01, -0.76], p<0.001,

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I^2 = 0.0%). Additionally, Resmetirom 80 mg significantly decreased levels of low-density lipoprotein (LDL), Apolipoprotein B (Apo B), triglycerides (TG), and lipoprotein (a) [Lp(a)] compared to placebo: LDL (-0.69 [-1.08, -0.29], p<0.001), Apo B (-0.96 [-1.52, -0.40], p<0.001), TG (-0.43 [-0.73, -0.13], p=0.005), and Lp(a) (-0.51 [-0.88, -0.14], p=0.007) (Table 1). The incidence of mild, moderate, and severe adverse events was 32% vs. 27%, 47% vs. 45%, and 0.0% vs. 0.0% for the Resmetirom and placebo groups, respectively. **Conclusion:** Resmetirom significantly reduces hepatic fat fraction and improves lipid profiles (LDL, Apo B, TG, Lp(a)) in patients with MASH, with a favorable safety profile and no significant increase in severe adverse events compared to placebo. Further research and randomized trials are warranted to continue exploring the therapeutic potential of THR-ß agonists in MASH.

Outcome	k	Pooled Hedges' g	95% CI		p-values	Cochrane's Q	I^2
MRI % CFB	3	-0.88	-1.1	-0.076	<0.001	0.79	0.0%
LDL % CFB	3	-0.69	-1.08	-0.29	<0.001	7.87	81.8%
ApoB % CFB	3	-0.96	-1.52	-0.4	<0.001	13.81	90.8%
TG % CFB	3	-0.43	-0.73	-0.13	0.005	5.14	67.1%
Lp(a) % CFB	3	-0.51	-0.88	-0.14	0.007	10.42	83.4%

Note: k = number of studies. Pooled Hedges' g = pooled standardized mean difference. CI = confidence interval. Cochrane's Q = observed variation. I^2 =percentage variation across studies due to heterogeneity. CFB = Change from baseline

Disclosures: Ankita Nekkanti: Nothing to Disclose, Ishaan Vohra: Nothing to Disclose, Harishankar Gopakumar: Nothing to Disclose, Sonu Dhillon: Nothing to Disclose, Neil Sharma: Nothing to Disclose, Srinivas Puli: Nothing to Disclose

3205 | METABOLOMIC AND LIPIDOMIC ANALYSIS OF PATIENTS WITH PRESUMED METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS (MASH) TREATED WITH THE SELECTIVE GLUCOCORTICOID RECEPTOR MODULATOR MIRICORILANT

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Background: Patients (pts) with presumed MASH treated with miricorilant (MIRI, a liver-active nonsteroidal selective glucocorticoid receptor modulator [SGRM]) in a phase 1b trial had rapid liver fat content (LFC) decrease, occasionally accompanied by efficacy-associated alanine aminotransferase (ALT) increase. Responders (pts with ≥30% LFC decrease from baseline [BL]) with rise in ALT levels to >3x the upper limit of normal (ULN) lost LFC twice as fast in the first 6 weeks (wks) as responders without significant ALT rise. The aim of this metabolomics study is to explore MIRI's mechanism of reducing liver fat. **Methods:** Plasma samples were collected from a phase 1b, open-label trial (NCT05117489) of adult pts with MASH who received MIRI 30–200 mg intermittently or daily for 12 or 24 wks. Samples were grouped as: standard responders without ALT rise (SR, n=11); rapid responders with ALT rise >3x ULN (RR, n=9); and non-responders (NR, minimal changes in LFC from BL; n=11). Changes in serum metabolomics profiles were assessed at different time points by liquid chromatography/mass spectrometry (Metabolon). **Results:** Both groups of responders showed notably lower levels of acylglycerols such as triacylglycerols at wk 6 compared to NRs (SR: +2.6%, P<0.0001; RR: -26.8%, P<0.0001; vs NR: +10.8%). Most long-chain fatty acids (FAs), including polyunsaturated FAs (omega-3 and -6), were significantly reduced at wk 6 vs BL in both responder groups (SR: -5.3%, P<0.01; RR: -16.6%, P<0.0001), with minimal changes in NRs (+0.6%, non-significant [ns]). Many short- to medium-chain acylcarnitine species were reduced in RRs vs NRs (3.3% at wk 6, ns). Several 3-hydroxy FA species were reduced in RRs vs NRs at wk 6 (12.7% from BL, P<0.05). RRs trended towards elevated bile acids vs NRs at wk 6 (+21.5%, P=0.06). Secondary bile acids were significantly increased at wk 6 in RRs but not in SRs (RR: +34.6%, P<0.05; SR: +17.3%, ns; from BL). **Conclusion:** This study highlights the potential of MIRI as a MASH treatment and suggests that pts who respond

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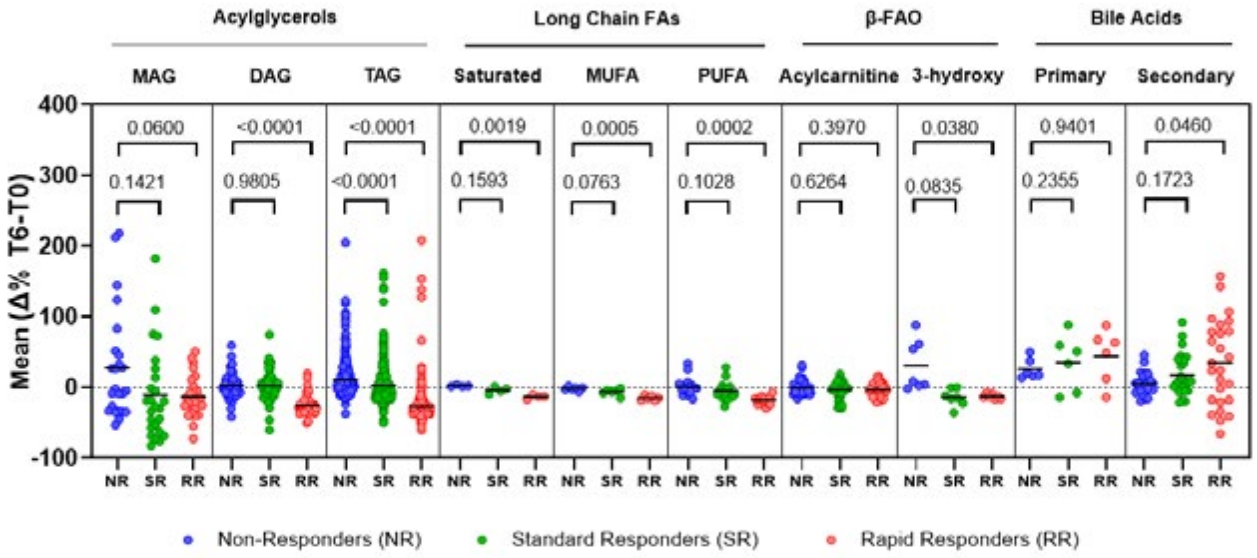
to MIRI, especially those with rapid LFC reduction and efficacy-associated rise in ALT (RRs), had a significant enhancement in metabolic clearance of FAs. The changes may indicate an increase in cellular FA beta-oxidation, which, despite contributing to transient hepatic stress in some pts, signals improved metabolic regulation and liver health. The ongoing MONARCH phase 2b trial (NCT06108219) will provide further insights into MIRI's efficacy.

Figure. Change in metabolites from baseline to week 6 in patients with presumed MASH treated with miricorilant



3-hydroxy, 3-hydroxy FA species; β-FAO, beta-fatty acid oxidation; DAG, diacylglycerols; FA, fatty acid; MAG, monoglycerides; ns, non-significant; MUFA, monounsaturated fatty acid; NR, non-responder; PUFA, polyunsaturated fatty acid; RR, rapid responder; SR, standard responder; TAG, triacylglycerols. Statistical analysis: one-way ANOVA vs. NR; matched Sidak multiple comparisons test, with individual variances computed for each comparison.

Disclosures: Kris Kowdley: Boston Scientific: Grant/Research Support, Corcept: Grant/Research Support, CymaBay: Grant/Research Support, Genfit: Grant/Research Support, Gilead: Grant/Research Support, GSK: Grant/Research Support, Hanmi: Grant/Research Support, Intercept: Grant/Research Support, Ipsen: Grant/Research Support, Janssen: Grant/Research Support, Madrigal: Grant/Research Support, Mirum: Grant/Research Support, Novo Nordisk: Grant/Research Support, NGM: Grant/Research Support, Pfizer: Grant/Research Support, Pliant Therapeutics: Grant/Research Support, Terns: Grant/Research Support, Viking: Grant/Research Support, Zydus: Grant/Research Support, 89bio Inc: Grant/Research Support, UpToDate: Royalties or patent beneficiary, CymaBay: Consultant, Enanta: Consultant, Genfit: Consultant, Gilead: Consultant, HighTide: Consultant, Inipharm: Consultant, Intercept: Consultant, Ipsen: Consultant, Madrigal: Consultant, Mirum: Consultant, NGM: Consultant, Pliant Therapeutics: Consultant, Pfizer: Consultant, Protagonist: Consultant, Zydus: Consultant, 89bio Inc: Consultant, AbbVie: Payment or honoraria, Gilead: Payment or honoraria, Intercept: Payment or honoraria, US Department of Justice: Payment for expert testimony, CTI: Advisor, Medpace: Advisor, Labcorp: Advisor, Worldwide Clinical Trials: Advisor, Inipharm: Stock – privately held company, Velacur: Received equipment, materials, drugs, medical writing, gifts, Mazen Noureddin: Principal Investigator for a Drug Study relationship with Viking; Has not ended; Consultant relationship with Eli Lilly; Has not ended; Consultant relationship with AstraZeneca; Has not ended; Consultant relationship with Boston Pharmaceuticals; Has not ended; Principal Investigator for a Drug Study relationship with Genfit; Has not ended; Principal Investigator for a Drug Study relationship with Galectin; Has not ended; Principal Investigator for a Drug Study relationship with Gilead; Has not ended; Principal Investigator for a Drug Study relationship with BMS; Has not ended; Principal Investigator for a Drug Study relationship with BI; Has not ended; Principal Investigator for a Drug Study relationship with Akero; Has not ended; Consultant relationship with Cytodyn; Has not ended; Consultant relationship with GSK; Has not ended; Consultant relationship with BI; Has not ended; Consultant relationship with Madrigal; Has not ended; Terns,Takeda, Zydus. relationship with Itimmune, BI, Cytodyn, 89BIO, GSK,

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3206 | THE SAFETY AND EFFICACY OF RESMETIROM FOR MASH: A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

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Background: Metabolic Dysfunction-Associated Steatohepatitis (MASH) remains without an optimal pharmacological solution. Resmetirom is an oral, thyroid hormone receptor beta-selective agonist being developed for the treatment of MASH. **Methods:** A systematic review and meta-analysis identified relevant randomized controlled trials (RCTs) investigating the efficacy and safety of resmetirom for treating MASH. PubMed, EMBASE, Web of Science, and SCOPUS were searched up to February 8th, 2024. The meta-analysis was conducted utilizing (RevMan 5.4.1). PROSPERO ID: CRD42024517326. **Results:** Our meta-analysis included three RCTs with a total of 2.231 participants. Resmetirom was significantly associated with decreased

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MRI-PDFF change (MD: -6.02 with 95% CI [-6.92, -5.13], P<00001). However, there was no significant difference between resmetirom and placebo in MASH resolution without fibrosis worsening (RR: 2.09 with 95% CI [-0.96, 4.55], P= 0.06). Resmetirom was also effective in decreasing LDL cholesterol (MD: -16.29 with 95% CI [-19.57, -13.01], P< 0.00001). Also, there was no significant difference between resmetirom and placebo in the incidence of any adverse events (AEs) (RR: 1.05 with 95% CI [0.96, 1.16], P= 0.28), any serious AEs (RR: 1.01 with 95% CI [0.75, 1.35], P= 0.95). **Conclusion:** Resmetirom showed a statistically significant reduction in hepatic fat, but no significant difference was observed in MASH resolution without worsening fibrosis compared to placebo. Additionally, resmetirom appeared to be safe and well-tolerated. However, further research is required to comprehensively understand its long-term effects and efficacy in managing MASH, particularly with a focus on clinical outcomes and advanced stages of the disease.

Disclosures: Fouad Jaber: Nothing to Disclose, Obieda Altobaishat: Nothing to Disclose, Ahmed Amin: Nothing to Disclose, omar bataineh: Nothing to Disclose, Rana Youssef: Nothing to Disclose, Yazan Sallam: Nothing to Disclose, Mustafa Turkmani: Nothing to Disclose, Mohamed Abuelazm: Nothing to Disclose

3207 | ORAL MANNOSE SUPPLEMENTATION DAMPENS LIVER FIBROSIS IN MURINE MASH MODEL BY REDUCING ACTIVATED HEPATIC STELLATE CELLS

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Background: Metabolic dysfunction associated steatohepatitis (MASH) is the most common liver disease, yet there are limited treatment options for MASH-induced fibrosis. We have previously shown that mannose, a simple sugar, can dampen hepatic stellate cell activation *in vitro*, but its role in MASLD and MASH has not been studied. **Methods:** We used the well-validated FAT-MASH model (Tsuchida et al, J. Hepatology 2018). Mice were fed normal diet or FAT-MASH regimen (high fat, fructose, and cholesterol, and low dose carbon tetrachloride) for 12 weeks. Mannose was supplied in drinking water at low (5%) or high (20%) concentrations for either the full 12 weeks to assess for preventive effects, or after a 6-week delay when MASH-induced fibrosis is already present. Liver tissue was collected for histopathological examination, mRNA extraction for qPCR analysis, and protein extraction for western blotting. We used an unbiased, AI-based approach to quantify fibrosis phenotypes in liver sections (FibroNest™). To further characterize hepatic stellate cells, we used immunofluorescence staining and single nuclear RNA-sequencing (snRNAseq). **Results:** Mannose supplementation decreased the Sirius Red staining in all treatment groups (low and high doses in both prophylactic and disease treatment groups). AI-based histological assessment confirmed the previous finding, as mannose supplementation improved phenotypic fibrosis composite score in all treatment groups ($p<0.05$). Prophylactic high dose mannose treatment decreased Col1a1 expression by western blot ($p<0.05$). Immunofluorescence staining showed prophylactic mannose treatments to decrease desmin$^+$ cell population with low and high doses and αSMA$^+$ cell population with low dose. Prophylactic low dose mannose treatment decreased the relative proportion of activated hepatic stellate cells with snRNAseq analysis. **Conclusion:** Our findings uncover a novel role for mannose in MASLD as a potential anti-fibrotic therapy. Ongoing studies will test the role of mannose in liver fibrosis.

Disclosures: John Hong: Nothing to Disclose, Joshaya Trotman: Nothing to Disclose, Mariel Glass: Nothing to Disclose, Yvette Carbajal: Nothing to Disclose, Victoria Sclar: Nothing to Disclose, Isaac Alter: Nothing to Disclose, Peng Zhang: Nothing to Disclose, Liheng Zhang: Nothing to Disclose, Li Chen: Nothing to Disclose, Mathieu Petitjean: Nothing to Disclose, Scott Friedman: 89 Bio: Consultant, Boehringer Ingelheim: Consultant, Boston Pharmaceutical: Consultant, Bristol Myers Squibb: Consultant, Merck: Consultant, Glycotest: Consultant, Morphic Therapeutics: Consultant, HepGene: Consultant, North Sea Therapeutics: Consultant, Pfizer Pharmaceuticals: Consultant, Sagimet: Consultant, Scholar Rock: Consultant, Prosciento: Consultant, Seal Rock: Consultant, Surrozen: Consultant, Takeda Pharmaceuticals: Consultant, Junevity: Consultant, Therasid Bio: Consultant, Merck: Consultant, Ochre Bio: Consultant, Gordian Biotechnology: Consultant, Abalone Bio: Grant/Research Support, Prosciento: Consultant, Charles DeRossi: Nothing to Disclose, Jaime Chu: Nothing to Disclose

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3208 | EFFICACY AND SAFETY OF RESMETIROM IN TREATING PATIENTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD): A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD), affecting approximately a quarter of the global population, has become the leading cause of chronic liver disease and the second leading reason for liver transplants. Given this significant public health burden, effective treatment options are urgently needed. This systematic review and meta-analysis investigate the efficacy and safety of resmetirom as a potential treatment for MASLD. **Methods:** We searched on 9th February in PubMed, Google Scholar, VHL, Cochrane Library, Scopus, Web of Science, and ClinicalTrials.gov for randomized clinical trials (RCTs) studies comparing resmetirom versus placebo in treating MASLD. We extracted data on its effects on hepatic fat, liver enzymes, inflammation, and fibrosis. We analyzed the data using odds ratios (OR) and 95% confidence intervals (CI) for categorical variables and mean difference (MD) and 95% CI for continuous variables. **Results:** Out of 446 studies initially pooled for screening, we included 3 studies that met the inclusion criteria for our meta-analysis, comprising a total of 1,413 patients. This analysis investigates the effects of resmetirom versus placebo in patients with metabolic dysfunction-associated steatohepatitis (MASH). The study population included 54.7% females, 56.7% individuals with type 2 diabetes, and 74.6% with hypertension. Our analysis showed resmetirom to might be an effective (p-value <0.01) compared to placebo, significantly lowering several key markers. This includes low-density lipoprotein cholesterol (LDL-C), particularly for those with a baseline LDL-C exceeding 100 mg/dL. Additionally, reductions were observed in apolipoprotein B (again, more pronounced in those with higher baseline LDL- C ≥ 100 mg/dL), triglycerides (if baseline levels were above 150 mg/dL), lipoprotein(a) (especially for individuals with elevated baseline Lp(a) > 10 nmol/L), cytokine 18, alanine transaminase (ALT), and reverse T3. Beyond these blood markers, resmetirom also demonstrated some positive effects on liver health. It reduced magnetic resonance imaging-proton density fat fraction (MRI-PDFF) by -20.266 (95% CI: -35.806 to -4.726, P=0.01) and decreased enhanced liver fibrosis score (baseline ≥9) by -0.234 (95% CI: -0.441 to -0.027, P=0.03). Resmetirom showed increased in both high-density lipoprotein cholesterol (HDL-C) and adiponectin (all with p-value <0.01). Importantly, there was no significant difference in treatment-related side effects or serious adverse events between the resmetirom and placebo groups (p-value >0.05). **Conclusion:** Among (MASLD) patients, resmetirom might significantly reduce hepatic fat, inflammation, liver enzymes, lipoprotein (a), and atherogenic lipids, which are markers of inflammation and fibrosis in MASLD patients, in addition, we need more studies to see the difference more clearly.

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3209 | GENETIC AND PHARMACOLOGICAL TARGETING OF HEPATIC OXALATE OVERPRODUCTION AMELIORATES METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS

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Background: Metabolic dysfunction-associated steatohepatitis (MASH) is on the rise, and with limited pharmacological therapy available, identification of new metabolic targets is urgently needed. Oxalate is a terminal metabolite produced from glyoxylate by hepatic lactate dehydrogenase (LDHA). The liver-specific alanine-glyoxylate aminotransferase (AGXT) detoxifies glyoxylate, preventing oxalate accumulation. While oxalate effects in the kidneys are well known, they have not been systematically studied in hepatocytes, the primary cells responsible for its formation. Also, the causative role of oxalate in MASH, its underlying mechanisms, and the therapeutic potential of targeting oxalate overproduction are unknown. **Methods:** We assessed dysregulated oxalate metabolism in multiple cohorts of patients and mice with MASH through unbiased transcriptomics, molecular and biochemical analyses. Hepatic DNA methylation was assessed by reduced representation bisulfite sequencing. Genetic approaches to manipulate hepatic oxalate metabolism included generation of *Agxt*$^{-/-}$ mice using CRIPSR/Cas9 and hepatocyte-specific overexpression of AGXT using AAV8-TBG-AGXT during diet-induced MASH. Pharmacological inhibition of LDHA and glycolate oxidase was achieved using the salicylic acid derivative, MDMG-935P. MASH severity was assessed by histopathology, RNA-seq, and lipidomics. The effects of oxalate overload and lowering on cellular energetics, lipid metabolism, and the inflammatory response were assessed in primary hepatocytes, HepG2 cells, and human primary blood monocytes. **Results:** In livers of humans and mice with MASH, AGXT was suppressed due to promoter hypermethylation, and LDHA activity was enhanced, leading to a marked increase in hepatic oxalate in association with disease severity. In *Agxt*$^{-/-}$ mice, hepatic oxalate was increased, and MASH was accelerated with suppressed fatty acid β-oxidation (FAO) and induced proinflammatory pathways. In hepatocytes, oxalate overload caused mitochondrial dysfunction and lipid accumulation by inhibiting the transcription of peroxisome proliferator-activated receptor α and blocking mitochondrial FAO. Oxalate overload also upregulated C-C motif chemokine ligand 2 to induce monocyte chemotaxis. Genetic (AAV8-TBG-AGXT) and pharmacological (MDMG-935P) lowering of oxalate production ameliorated MASH by enhancing hepatic FAO and lowering monocyte infiltration to the liver. **Conclusion:** These findings highlight hepatic oxalate overproduction as a new target for the treatment of MASH.

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Nothing to Disclose, Jifeng Zhang: Nothing to Disclose, Wayne Orr: Nothing to Disclose, Wanqing Liu: Nothing to Disclose, Monica Diaz-Gavilan: Nothing to Disclose, Eugene Chen: Nothing to Disclose, Nirav Dhanesha: Nothing to Disclose, Paul Thevenot: Boston Scientific: Grant/Research Support, FUJIFILM: Grant/Research Support, Helio Genomics: Grant/Research Support, Ari Cohen: Nothing to Disclose, Arif Yurdagul: Nothing to Disclose

3210 | A SMALL MOLECULE INHIBITOR OF FIBROBLAST ACTIVATION PROTEIN (FAP) BLOCKS ENZYMATIC ACTIVITY AND IMPROVES LIVER HISTOPATHOLOGY IN CYNOMOLGUS MONKEYS WITH MASH AND F1/F2 FIBROSIS

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Background: Fibrosis severity is associated with liver-related outcomes and mortality for metabolic dysfunction-associated steatohepatitis (MASH). FAP expression increases with pathogenic fibroblasts in fibrotic niche in livers. FAP may promote fibrosis via cleaving multiple proteins regulating extracellular matrix turnover and metabolism, *e.g.* collagens, alpha2-antiplasmin (a2-AP) and fibroblast growth factor 21 (FGF21). Human, but not mouse, a2-AP, FGF21 and collagens are effectively cleaved by FAP in ex-vivo conditions, which limits mouse models for the evaluation of pharmacological effects of FAP inhibitors. **Methods:** We have developed a potent oral FAP inhibitor AZD2389, which blocks the cleavage of human a2-AP, FGF21 and collagens *ex vivo*. Cynomolgus monkeys were selected to explore the therapeutic potential of our molecule. Male monkeys (aged 8-20 years) with diet induced, biopsy confirmed MASH (F1/2 fibrosis) were randomized based on baseline body weight, FAP levels and fibrosis stage, to orally administered vehicle (n=20) or AZD2389 (n=25) for 29 weeks. FAP activity, compound exposure, a2-AP, FGF21, safety and metabolic parameters were monitored throughout the study. Effects on histology were compared between baseline and end of treatment biopsies from the same animal and scored by expert pathologists using the NASH CRN scoring criteria. **Results:** AZD2389 was well tolerated without notable safety signals and resulted in complete inhibition of FAP activity during the treatment period, returning to baseline after washout. Concordantly, intact a2-AP increased 34% in the active arm compared to 6% for vehicle ($p<0.0001$), and intact/total FGF21 ratio also increased (estimated effect size=0.16) at week 4 ($p=0.036$) and week 29 ($p=0.029$) in the active arm compared vehicle. AZD2389 treatment resulted in improved NAFLD activity score in 48% of animals with an increased odds ($p=0.0008$) in active arm vs 20% in vehicle arm. Similarly, AZD2389 arm showed increased odds of histological fibrosis improvement ($p=0.01$) with 16% of animals with improvement in active vs 5% vehicle, independent of age and body weight, as analyzed by the proportional-odds model. **Conclusion:** To our knowledge, this is the first study demonstrating that FAP inhibition leads to increased intact a2-AP *in vivo* in a physiologically relevant disease model. Importantly, histological improvement of MASH and fibrosis, underline the therapeutic potential of our compound in the treatment of fibrotic liver diseases.

Disclosures: Xiao-Rong Peng: AstraZeneca RD Sweden: Employee, Mathias Liljeblad: AstraZeneca: Employee, AstraZeneca: Stock - publicly traded company, David Janzén: Nothing to Disclose, Tasso Miliotis: Nothing to Disclose, Eva Töppner Carlsson: Nothing to Disclose, Jianming Liu: Nothing to Disclose, Peter Konings: AstraZeneca AB: Employee, Magnus Söderberg: AstraZeneca: Employee, Anne-Christine Andréasson: AstraZeneca: shareholdning, Jens Petersen: Nothing to Disclose, Anneli Nordqvist: Nothing to Disclose, Mahssa Karimi: Nothing to Disclose

3211 | TGF-β SIGNALING TARGETING PEPTIDE BTI615 ATTENUATED LIVER FIBROSIS BY MODULATING FIBROTIC NICHE IN CCL_4-INDUCED MOUSE-MODEL

Qiu Jiang[1] Xiaomei Li[1] Rui Chen[1] Zhengwen Zhu[1] Jiabao Yue[1] Yi Ding[1]

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Background: The importance of fibrosis progression and regression in predicting outcomes in Metabolic Dysfunction-associated Steatohepatitis (MASH) has been highlighted. Dysregulated TGF-β activity orchestrates liver fibrotic niche formation which can suppress hepatic regeneration and homeostasis recovery. Targeting abnormal TGF-β activity would be a critical anti-fibrotic approach to MASH and thus enable the structural

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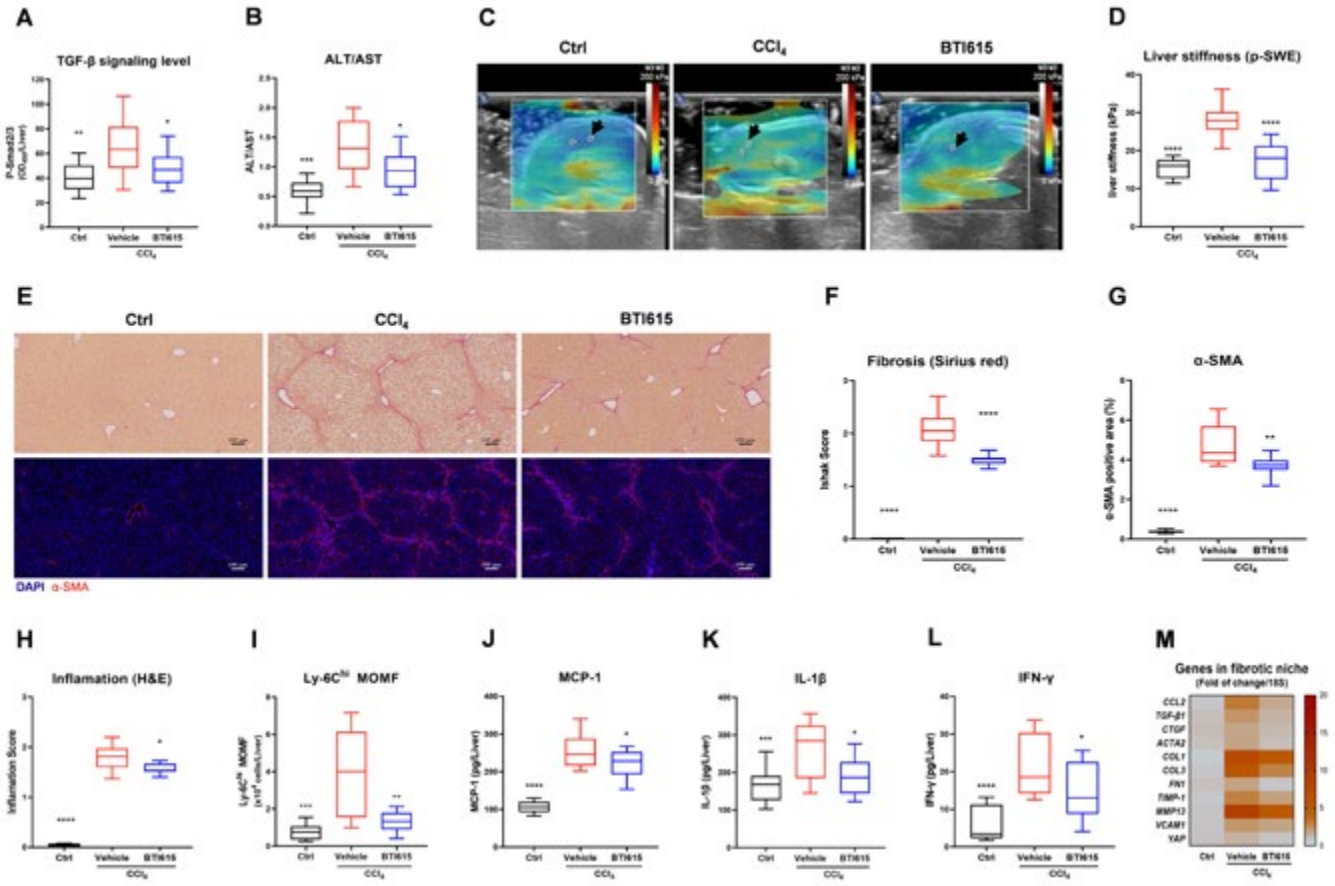
resolution and functional recovery of the liver. We verified the efficacy of BTI615, a synthetic peptide regulating TGF-β activity, on the improvement of liver fibrosis, tissue regeneration and ALT/AST level in a CCl_4-induced mouse liver fibrosis model. **Methods:** Male C57BL/6J mice (8-week-old) were administered with 0.4 mL/kg of CCl_4 (diluted in oil,1:4) via intraperitoneal injection twice a week for 4 weeks. Control animals were treated with oil only at the same time intervals. From Day 6, the mice were administered with 40 mg/kg BTI615 or same volume of vehicle via intraperitoneal injection every other day for 3 weeks. At the end of experiment, *in vivo* liver stiffness measured by point quantification shear-wave elastography (p-SWE), and bloods and liver tissues were used for histopathologic evaluation and biochemical analyses. **Results:** BTI615 suppressed P-Smad2/3 level in liver (A). Liver function reflected by serum ALT/AST levels were significantly improved in BTI615 treated group (B). Of note, BTI615 profoundly ameliorated liver stiffness measurements with p-SWE (C, D), extracellular collagen deposition (Sirius Red), and the production of α-SMA (E-G). Moreover, BTI615 inhibited tissue inflammatory cells infiltration, in which Ly6C^{hi} monocyte-derived macrophages (MoMFs), and cytokines such as MCP-1, IL-1β and IFN-γ were dramatically reduced (H-L). Finally, BTI615 decreased the expression of critical pro-inflammatory and pro-fibrotic genes driving liver fibrotic niche progression (M). **Conclusion:** BTI615 showed the great potential to attenuate liver fibrotic niche progression by suppressing aberrant TGF-β signaling, and it would be an anti-fibrotic MASH pharmacotherapy worthy for further clinical investigation.



Disclosures: Qiu Jiang: Nothing to Disclose, Xiaomei Li: Nothing to Disclose, Rui Chen: Nothing to Disclose, Zhengwen Zhu: Nothing to Disclose, Jiabao Yue: Nothing to Disclose, Yi Ding: Nothing to Disclose

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3212 | ASSESSMENT OF RESMETIROM EFFICACY (80 MG VS. 100 MG) STRATIFIED BY BASELINE BODY MASS INDEX AND WEIGHT IN PATIENTS FROM THE MAESTRO-NASH TRIAL

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Background: MAESTRO-NASH (NCT03900429) is an ongoing 54-month, randomized, double-blind, placebo-controlled Phase 3 trial evaluating the efficacy of resmetirom in patients with biopsy-confirmed nonalcoholic steatohepatitis (NASH) and fibrosis. 966 patients with biopsy-confirmed NASH were randomized 1:1:1 to resmetirom 80 mg, resmetirom 100 mg, or placebo administered once daily. Histologic endpoints were assessed after 52 weeks. Dual primary endpoints at Week 52 were achieved with both resmetirom 80 mg and 100 mg: NASH resolution with no worsening of fibrosis (NR) or ≥1-stage reduction in fibrosis with no worsening of NAS (FI). Body weight is the major factor influencing exposure to resmetirom in patients with NASH/MASH. This post-hoc analysis was performed to provide additional evidence of a relationship between resmetirom dose, baseline body weight and body mass index (BMI). **Methods:** To assess the impact of baseline body weight and BMI on resmetirom response, we stratified resmetirom efficacy data on the dual endpoints based on baseline patient body weight (≤100 and >100 kg) and BMI (≥35 and <35 kg/m^2). **Results:** For patients treated with resmetirom 80 mg who weighed ≤100 kg, the 30% PDFF response was 66.9%; and in patients with a Week 52 biopsy, 35.4% showed fibrosis improvement (FI) compared with 32% who showed no worsening of fibrosis (NR). In patients >100 kg, the 30% PDFF response was 56.7%; FI=22.5%; and NR=27%. For patients who received resmetirom 100 mg who were ≤100 kg, the 30% PDFF response was 71.7%; FI was 33.6% and NR was 35.8%; for patients >100 kg, PDFF=72.5%; FI=32.5%; NR=35.8%. Increases in FI were noted relative to placebo for patients who received resmetirom 80 mg (mITT population) who had BMI <35: 13.0% (5.2, 20.8); NR=33.4% (14.2, 30.6); and in patients with BMI ≥35: FI=7.0% (-0.7, 14.7); NR=9.8% (3.1, 16.6). Increases were also noted relative to placebo for patients who received 100 mg of resmetirom (mITT population) who had a BMI <35: FI=11.8% (4.2, 19.4) NR=21.0% (13.4, 28.7); for patients with BMI ≥35: FI=11.1% (3.4, 18.9); NR=20.0% (12.3, 27.7). **Conclusion:** As shown in these stratified data, resmetirom 100 mg was consistently more effective than 80 mg in achievement of the dual primary endpoints in the sample of patients who had higher baseline body weight and BMI. In patients with a lower BMI, there was no observed difference in efficacy between the 80 and 100 mg resmetirom doses.

Disclosures: Mazen Noureddin: Principal Investigator for a Drug Study relationship with Viking; Has not ended; Consultant relationship with Eli Lilly; Has not ended; Consultant relationship with AstraZeneca; Has not ended; Consultant relationship with Boston Pharmaceuticals; Has not ended; Principal Investigator for a Drug Study relationship with Genfit; Has not ended; Principal Investigator for a Drug Study relationship with Galectin; Has not ended; Principal Investigator for a Drug Study relationship with Gilead; Has not ended; Principal Investigator for a Drug Study relationship with BMS; Has not ended; Principal Investigator for a Drug Study relationship with BI; Has not ended; Principal Investigator for a Drug Study relationship with Akero; Has not ended; Consultant relationship with Cytodyn; Has not ended; Consultant relationship with GSK; Has not ended; Consultant relationship with BI; Has not ended; Consultant relationship with Madrigal; Has not ended; Terns,Takeda, Zydus. relationship with Itimmune, BI, Cytodyn, 89BIO, GSK, Madrigal, Merck, Novo Nor; Has not ended; Principal Investigator for a Drug Study relationship with Allergan; Has not ended; Consultant relationship with Takeda; Has not ended; Consultant relationship with Terns; Has not ended; Terns, Corcept, Takeda, Madrigal, Novartis, Novo Nordisk, relationship with Allergan, Akero, BI, BMS, Gilead, Galectin, Zydus GSK; Has not ended; Consultant relationship with Novo Nordisk; Has not ended; Stock â€“ privately held company relationship with Rivus Pharma, Cytodyn, and ChronWell; Has not ended; Consultant relationship with Merck; Has not ended; Principal Investigator for a Drug Study relationship with Madrigal; Has not ended; Consultant relationship with Altimmune; Has not ended; Principal Investigator for a Drug Study relationship with Terns; Has not ended; Principal Investigator for a Drug Study relationship with Zydus; Has not ended; Stock â€“ privately held company relationship with Rivus Pharmaceuticals; Has not ended; Consultant relationship with Alligos; Has not ended; Stock - publicly traded company relationship with Cytodyn; Has not ended; Stock â€“ privately held company relationship with ChronWell; Has not ended; Speaking and Teaching relationship with Madrigal; Has not ended; Principal Investigator for a Drug Study relationship with Takeda; Has not ended; Principal Investigator for a Drug Study relationship with Shire; Has not ended; Principal Investigator for a Drug Study relationship with Novo Nordisk; Has not ended; Principal Investigator for a Drug Study relationship with Novartis; Has not ended; Principal Investigator

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3213 | IMPACT OF RESMETIROM ON STATIN PHARMACOKINETICS AND SAFETY IN PHASE 1 STUDIES AND MAESTRO-NASH

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Background: Resmetirom was approved by FDA and is indicated for treatment of adults with non-alcoholic steatohepatitis (NASH) with moderate to advanced liver fibrosis (consistent with stages F2 to F3). In MAESTRO-NASH, 49% of enrolled patients were taking statins, including 13% on high intensity statins (rosuvastatin 20 mg; atorvastatin 40 mg), and 36% on moderate or low intensity statins; therefore, the study population included approximately 95% of the statin dose regimens in use by NASH patients. **Methods:** To assess the potential impact of administration of statins on the pharmacokinetics of resmetirom, drug interaction studies of resmetirom with commonly prescribed statins (simvastatin 20 mg, rosuvastatin 10 mg, pravastatin 40 mg, and atorvastatin 20 mg) were performed. Statin levels were measured in patients in MAESTRO-NASH and safety was assessed in patients according to statin therapy. **Results:** Simvastatin: Simvastatin (an OATP1B1 and OATP1B3 substrate) Cmax increased 1.4-fold and area under the curve (AUC) 1.7-fold following concomitant use of a single oral dose of simvastatin (20 mg) with resmetirom at steady state (100 mg/day) in healthy subjects.
Rosuvastatin: Rosuvastatin (BCRP, OATP1B1, and OATP1B3 substrate) AUC 1.8-fold following concomitant use of a single oral dose of rosuvastatin (10 mg) with 200 mg resmetirom at steady state (two times the highest recommended dosage) in healthy subjects. Pravastatin: Pravastatin (OATP1B1 and OATP1B3 substrates) Cmax increased 1.3-fold and AUC 1.4-fold following concomitant use of a single oral dose of pravastatin (40 mg) with resmetirom at steady state (100 mg/day) in healthy subjects. Atorvastatin: Atorvastatin (BCRP, OATP1B1, and OATP1B3 substrates) Cmax was unchanged and AUC increased 1.4-fold following concomitant use of a single oral dose of atorvastatin (20 mg) with resmetirom at steady state (100 mg/day) in healthy subjects. Statin PK assessment in MAESTRO-NASH demonstrated that the levels of statins were within the range of normal variability. Assessment of statin safety parameters including muscle AEs and liver AEs showed no serious

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AEs and no increase in AEs with resmetirom alone or in combination with statins. **Conclusion:** Simvastatin, rosuvastatin, pravastatin, and atorvastatin co-administered with resmetirom (100 mg) demonstrated relatively weak pharmacokinetic interactions. No safety findings were noted in MAESTRO-NASH in which half the patients took statins. The study population included 95% of the statin dose regimens in use by NASH patients, including high intensity statins. Dose adjustment in patients prescribed resmetirom will be uncommon.

Disclosures: Seth Baum: Nothing to Disclose, Naim Alkhouri: Madrigal: Grant/Research Support, Madrigal: Speaking and Teaching, Novo Nordisk: Consulting, Novo Nordisk: Grant/Research Support, Gilead: Grant/Research Support, Corcept: Grant/Research Support, Boehringer Ingelheim: Grant/Research Support, Echosens: Speaking and Teaching, Perspectum: Consultant, Cima: Consultant, Fibronostics: Consultant, 89Bio: Grant/Research Support, Inventiva: Grant/Research Support, Merck: Grant/Research Support, Pfizer: Grant/Research Support, Ipsen: Speaking and Teaching, Intercept: Speaking and Teaching, Madrigal: Consulting, Research Funding, Novo Nordisk: Consulting, Research Funding, Inventiva: Research Funding, Boehringer Ingelheim: Consulting, Research Funding, Corcept: Research Funding, Ipsen: Consulting, Research Funding, Gliead: Consulting, Research Funding, Speaking, Perspectum: Consulting, Research Funding, Cima: Advisor, 89Bio: Consulting, Research Funding, Akero: Grant/Research Support, Arbutus: Grant/Research Support, GSK: Grant/Research Support, Regeneron: Grant/Research Support, AstraZeneka: Grant/Research Support, Rebecca Taub: Madrigal Pharmaceuticals: Employee, Madrigal Pharmaceuticals: Stock - publicly traded company, Madrigal Pharmaceuticals: Executive role, Dominic Labriola: Nothing to Disclose, Jesse Fishman: Nothing to Disclose, Mazen Noureddin: Principal Investigator for a Drug Study relationship with Viking; Has not ended; Consultant relationship with Eli Lilly; Has not ended; Consultant relationship with AstraZeneca; Has not ended; Consultant relationship with Boston Pharmaceuticals; Has not ended; Principal Investigator for a Drug Study relationship with Genfit; Has not ended; Principal Investigator for a Drug Study relationship with Galectin; Has not ended; Principal Investigator for a Drug Study relationship with Gilead; Has not ended; Principal Investigator for a Drug Study relationship with BMS; Has not ended; Principal Investigator for a Drug Study relationship with BI; Has not ended; Principal Investigator for a Drug Study relationship with Akero; Has not ended; Consultant relationship with Cytodyn; Has not ended; Consultant relationship with GSK; Has not ended; Consultant relationship with BI; Has not ended; Consultant relationship with Madrigal; Has not ended; Terns,Takeda, Zydus. relationship with Itimmune, BI, Cytodyn, 89BIO, GSK, Madrigal, Merck, Novo Nor; Has not ended; Principal Investigator for a Drug Study relationship with Allergan; Has not ended; Consultant relationship with Takeda; Has not ended; Consultant relationship with Terns; Has not ended; Terns, Corcept, Takeda, Madrigal, Novartis, Novo Nordisk, relationship with Allergan, Akero, BI, BMS, Gilead, Galectin, Zydus GSK; Has not ended; Consultant relationship with Novo Nordisk; Has not ended; Stock â€“ privately held company relationship with Rivus Pharma, Cytodyn, and ChronWell; Has not ended; Consultant relationship with Merck; Has not ended; Principal Investigator for a Drug Study relationship with Madrigal; Has not ended; Consultant relationship with Altimmune; Has not ended; Principal Investigator for a Drug Study relationship with Terns; Has not ended; Principal Investigator for a Drug Study relationship with Zydus; Has not ended; Stock â€“ privately held company relationship with Rivus Pharmaceuticals; Has not ended; Consultant relationship with Alligos; Has not ended; Stock - publicly traded company relationship with Cytodyn; Has not ended; Stock â€“ privately held company relationship with ChronWell; Has not ended; Speaking and Teaching relationship with Madrigal; Has not ended; Principal Investigator for a Drug Study relationship with Takeda; Has not ended; Principal Investigator for a Drug Study relationship with Shire; Has not ended; Principal Investigator for a Drug Study relationship with Novo Nordisk; Has not ended; Principal Investigator for a Drug Study relationship with Novartis; Has not ended; Principal Investigator for a Drug Study relationship with Enanta; Has not ended; Principal Investigator for a Drug Study relationship with Corcept; Has not ended; Principal Investigator for a Drug Study relationship with GSK; Has not ended; Principal Investigator for a Drug Study relationship with Conatus; Has not ended

3214 | ENGINEERED MACROPHAGES EXPRESSING FIBROSIS-MODIFYING TRANSGENES AMELIORATE LIVER FIBROSIS IN PRECLINICAL MODELS

David Sloas[1] Yumi Ohtani[1] Julia Smith[1] MacKenzie Villano[1] Nancy Carson[1] Angela Mosebarger[1] James Montgomery[1] Lauren Shaw[1] Joanna Schmidt[1] Sascha Abramson[1] Thomas Condamine[1] Michael Klichinsky[1] Bradley Zinker[1]

[1]Carisma Therapeutics, Inc.

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Background: Liver fibrosis is associated with progressive organ dysfunction in metabolic dysfunction-associated steatohepatitis (MASH) and other chronic hepatic pathologies and represents a significant unmet medical need. Macrophage-based cell therapies represent an opportunity to target fibrosis. Macrophages (Mϕs) are innate immune cells capable of regulating inflammation and promoting tissue remodeling. We sought to evaluate whether Mϕs can be genetically engineered to express anti-fibrotic transgenes, and to assess whether engineered Mϕs can ameliorate collagen deposition in multiple models of liver fibrosis, including CCl_4-induced liver fibrosis and preclinical MASH models. **Methods:** Primary human and murine Mϕs were genetically engineered to overexpress fibrosis-modifying transgenes such as IL10, Relaxin, or a dominant negative (DN) TGFβR2. Engineered Mϕ phenotype, viability, and transgene expression were confirmed through flow cytometry and secretome analyses. The ability of engineered Mϕs to inhibit fibroblast activation or to clear apoptotic debris was demonstrated using *in vitro* assays. Anti-fibrotic efficacy was evaluated *in vivo* using the classical CCl_4-induced liver fibrosis model (Mϕs dosed IV at week 4; takedown at week 6; n=9/group) or a westernized diet (WD) with low-dose CCl_4 (WD-MASH; Mϕs dosed IV at weeks 21, 23, 25; takedown at week 26; n=9-12/group). Primary fibrotic readouts included histological and biochemical analyses. **Results:** Mϕs were efficiently engineered to produce high levels of anti-fibrotic transgenes. Mϕs could traffic to tissues of interest and detectably express encoded proteins for at least 2 weeks *in vivo*. A single dose of Mϕs co-expressing IL10 and Relaxin significantly reduced fibrotic area in a CCl_4-induced model (116% reduction vs. control). Systemic administration of engineered Mϕs also reduced fibrotic area in the WD-MASH model (45% reduction vs. control). Importantly, engineered Mϕs induced a larger reduction in fibrosis than non-engineered cells. Mϕs engineered to express additional disease-modifying constructs were analyzed in additional *in vitro* and *in vivo* fibrotic models. **Conclusion:** Mϕs engineered to express fibrosis-modifying transgenes improved liver fibrosis in multiple preclinical models. These results demonstrate preclinical proof-of-concept using Mϕ cell therapies for the treatment of liver fibrosis and potentially represent a vertical advance in the use of cell therapy for chronic fibrotic disease.

Disclosures: David Sloas: Nothing to Disclose, Yumi Ohtani: Carisma Therapeutics Inc.: Employee, Julia Smith: Nothing to Disclose, MacKenzie Villano: Nothing to Disclose, Nancy Carson: Nothing to Disclose, Angela Mosebarger: Nothing to Disclose, James Montgomery: Nothing to Disclose, Lauren Shaw: Nothing to Disclose, Joanna Schmidt: Carisma Therapeutics: Employee, Sascha Abramson: Nothing to Disclose, Thomas Condamine: Carisma Therapeutics: Employee, Michael Klichinsky: Nothing to Disclose, Bradley Zinker: Nothing to Disclose

3215 | METABOLISM AND THERAPEUTIC EFFECTS OF N-ACYL AMINO ACIDS IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS (MASH) AND ATHEROSCLEROSIS

SUMIT KUMAR ANAND[1] Sandeep Das[1] Jennifer Lee[1] Koral Richard[2] Peyton McKinney[1] Sumati Rohilla[1] Nilesh Pandey[1] Dhananjay Kumar[1] Brenna Pearson-Gallion[1] Lu Wang[3] Alexandra Finney[1] Jifeng Zhang[3] Duxin Sun[3] Wanqing Liu[4] Eugene Chen[3] Wayne Orr[1] Nirav Dhanesha[1] Arif Yurdagul[1] Oren Rom[1]

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Background: One of the major causes of death in patients with MASH is atherosclerotic cardiovascular disease, independent of traditional risk factors. Thus, there is an urgent need to identify new pathways for simultaneous targeting of MASH and atherosclerosis. While lipid and amino acid metabolism are commonly dysregulated in MASH and atherosclerosis, the crosstalk between these metabolic pathways remains unknown. N-acyl amino acids (NAAs) lie in the crosshair of lipid and amino acid metabolism. Yet, little is known about the metabolic regulation of NAAs in MASH and atherosclerosis. **Methods:** We developed an LC-MS method to measure endogenous NAAs. We used unbiased transcriptomics, qPCR, and immunoblotting analyses to study the metabolism of NAAs in livers from humans and mice with MASH and in lipid-loaded primary hepatocytes and hepatic cell lines. We developed *Ppara*^{HKO} mice (hepatocyte specific loss of peroxisome proliferator activated receptor alpha, PPARα) and overexpressed specifically in hepatocytes, a key regulator of NAA metabolism, peptidase M20 domain containing 1 (PM20D1), using AAV8-TBG-PM20D1. We employed Seahorse, luciferase, histopathology, and biochemical assays to explore the mechanisms of action by which the NAA N-oleoyl leucine (C18:1-Leu) ameliorates MASH and atherosclerosis. **Results:** We uncovered suppression of known NAA biosynthetic genes and upregulation of NAA degradative genes in livers from humans and mice with MASH and in lipid-loaded primary hepatocytes and hepatic cell lines. Accordingly, a marked reduction of hepatic NAAs was

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found in MASH. Hepatic NAAs, particularly C18:1-Leu, inversely correlated with MASH and inflammatory indices. PM20D1 overexpression in mice with MASH reduced disease severity. C18:1-Leu activated PPARα and induced fatty acid β-oxidation (FAO) and when administered to mice with established MASH reduced steatohepatitis, hepatic macrophage accumulation and fibrosis. RNA-seq confirmed induction of hepatic FAO and suppression of proinflammatory pathways aligned with reduced liver and plasma C-C motif chemokine ligand 2 (CCL2). This was partially dependent on PPARα activation as indicated by studies in *Pparα*^{HKO} mice. In atherosclerotic *Apoe*$^{-/-}$ mice, C18:1-Leu lowered hepatic steatosis and CCL2, while reducing lesional macrophages and atherosclerosis. **Conclusion:** Our findings uncover a newly identified metabolic pathway linking MASH and atherosclerosis and a novel potential therapy for simultaneously treating these two prominent diseases.

Disclosures: SUMIT KUMAR ANAND: Nothing to Disclose, Sandeep Das: Nothing to Disclose, Jennifer Lee: Nothing to Disclose, Koral Richard: Nothing to Disclose, Peyton McKinney: Nothing to Disclose, Sumati Rohilla: Nothing to Disclose, Nilesh Pandey: Nothing to Disclose, Dhananjay Kumar: Nothing to Disclose, Brenna Pearson-Gallion: Nothing to Disclose, Lu Wang: Nothing to Disclose, Alexandra Finney: Nothing to Disclose, Jifeng Zhang: Nothing to Disclose, Duxin Sun: Nothing to Disclose, Wanqing Liu: Nothing to Disclose, Eugene Chen: Nothing to Disclose, Wayne Orr: Nothing to Disclose, Nirav Dhanesha: Nothing to Disclose, Arif Yurdagul: Nothing to Disclose, Oren Rom: Diapin Therapeutics: Scientific Advisor

3216 | FIRST-IN-HUMAN PHASE 1 STUDY OF THE SAFETY AND PHARMACODYNAMIC EFFECTS OF OA-235I, A PAR2 PEPDUCIN, IN ADULTS WITH METABOLIC-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD) AND STEATOHEPATITIS (MASH)

Athan Kuliopulos[1] Manal Abdelmalek[2] Marina Takawy[3] Susan Turner[1] Christopher Kigongo[3] Nga Nguyen[4] Lidija Covic[1]

[1]Oasis Pharmaceuticals, [2]Mayo Clinic Rochester, [3]Mayo Clinic, [4]Tufts Medical Center

Background: MASH, the progressive form of MASLD, is characterized by steatosis and necroinflammation with or without hepatic fibrosis. Resmetirom, a thyroid hormone-derived metabolic drug, recently received conditional FDA approval based on its safety and efficacy on surrogate endpoints of MASH resolution and fibrosis regression. However, there remains an unmet need for more effective therapies to mitigate MASH fibrosis and its associated metabolic comorbidities which contribute to disease progression and poor clinical outcomes. Cell surface protease-activated receptor 2 (PAR2) drives several critical pathways of MASH progression, fibrosis and metabolism. Liver PAR2 expression increases with diabetes and hepatic fibrosis in patients with MASH and in preclinical models of MASH, diabetes and obesity. **Methods:** In a Phase 1a/1b randomized, placebo-controlled study, OA-235i, a Pepducin™ inhibitor which targets the cytoplasmic surface of the PAR2 receptor, was evaluated for safety, pharmacokinetics and target engagement in adults with MASH/MAFLD. 15 subjects received OA-235i (sc) in 5 ascending single-dose cohorts (4-40 mg) and 9 subjects were randomized to OA-235i or placebo (3:1) in a 7-day multi-dose (20-40 mg) study. **Results:** OA-235i was well tolerated with no hemodynamic, laboratory adverse events, SAEs, nor GI side-effects observed following daily single or multi-doses. There was a dose-dependence of both mean Cmax and drug exposure, peaking at the 30-40 mg doses. OA-235i rapidly appeared in blood at the 30 min time point, reached Cmax at 4-6 h, with high drug levels maintained for at least 24 h with no drug detected in urine. Consistent with pre-clinical studies, improvements in blood glycemic indices, and ketones indicating stimulation of fatty acid beta-oxidation, was observed at both day 1 and after 7 days of multi-dosing. OA-235i caused a 25% reduction in plasma triglycerides and 13-18% increases in HDL-cholesterol levels from days 1-9. **Conclusion:** OA-235i, a PAR2 inhibitor, is safe and well-tolerated. Early efficacy signals on metabolic parameters justify further investigation of PAR2 as a therapeutic target for treatment of MASH.

Disclosures: Athan Kuliopulos: Oasis Pharmaceuticals: Executive role, Manal Abdelmalek: Madrigal: Advisor, Madrigal, Gilead, Inventiva, Hanmi, Oasis, 89BIo: Grant/Research Support, Madrigal, Inventiva, Novo Nordisk, 89Bio, Intercept: Advisor, Hanmi: Consultant, 89BIo: Advisor, Marina Takawy: Nothing to Disclose, Susan Turner: Oasis Pharmaceuticals, LLC: Employee, Christopher Kigongo: Nothing to Disclose, Nga Nguyen: Nothing to Disclose, Lidija Covic: Nothing to Disclose

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3217 | ETX-312, A GALOMIC™ SIRNA, FOR THE TREATMENT OF MASH

Natalie Pursell[1] Gaye Saginc Giannoustas[1]

[1]e-therapeutics plc

Background: Metabolic associated steatohepatitis (MASH) is a chronic liver disease with high unmet need despite recent therapeutic advances. e-therapeutics (ETX) uniquely combines computation and RNAi therapeutics to discover and develop life-transforming medicines. ETX's proprietary RNAi chemistry platform, GalOmic™, enables generation of specific, potent, and long-acting siRNA therapeutics for effective silencing of novel gene targets in hepatocytes. ETX's HepNet™ computational platform drives forward development of GalOmic™ therapies and was used to identify ETX-312's novel target as a key factor in MASH. Potent siRNAs designed *in silico* were tested *in vivo* and the lead siRNA tested in the industry-leading Gubra DIO-MASH mouse model to assess its impact on MASH pathophysiology. **Methods:** Candidate siRNAs were tested in male C57BL/6 mice and non-human primates. For evaluation in the Gubra DIO-MASH mouse model, male C57BL/6 mice were fed the GAN diet high in fat, fructose, and cholesterol for 34 weeks prior to study start. A liver biopsy was collected 4 weeks prior to study start for confirmation of liver pathology and mice randomized based on quantitative liver fibrosis staining. ETX-312 was tested as a monotherapy and in combination with emerging MASH treatments, including a GLP-1 receptor agonist and a THR-β agonist. Body weight was measured weekly and histopathological pre-to-post individual assessment of NAFLD activity score (NAS) was performed. Other terminal endpoints included quantitative liver histology and plasma biomarkers of MASH disease. **Results:** ETX-312 was selected as a highly active siRNA for the treatment of MASH with a long duration of action. Treatment of DIO-MASH mice with ETX-312 resulted in significant improvements in NAFLD activity score (NAS), liver biomarkers (ALT and AST), and lobular inflammation. The combination of ETX-312 with emerging treatments, including a GLP-1 receptor agonist and a THR-β agonist, resulted in additive improvement in NAS compared to either therapy alone including up to 5-point improvement in NAS in the combination groups. **Conclusion:** High unmet need remains despite recent advances in treatments of MASH. These results highlight the potential of ETX-312 as an effective treatment for MASH as a monotherapy with a desirable quarterly subcutaneous dosing regimen; or as part of a combination regimen, to further improve the efficacy of emerging therapies. ETX-312 has been selected for clinical development and is being evaluated in IND-enabling studies.

Disclosures: Natalie Pursell: Nothing to Disclose, Gaye Saginc Giannoustas: Nothing to Disclose

3218 | EVALUATION OF EFFICACY OF BERBERINE URSODEOXYCHOLATE (HTD1801) COMPARED TO ONGOING USE OF GLP-1 RECEPTOR AGONISTS IN PATIENTS WITH MASH AND T2DM

Stephen Harrison[1] Guy Neff[2] Nadege Gunn[3] Abigail Flyer[4] Leigh MacConell[5]

[1]Pinnacle Clinical Research, [2]Covenant Metabolic Specialists, LLC, [3]Velocity Clinical Research, [4]Pacific Northwest Statistical Consulting, [5]HighTide Therapeutics

Background: HTD1801 is a gut-liver anti-inflammatory metabolic modulator with a unique molecular structure which has been shown to significantly reduce liver fat content (LFC) as determined by MRI-PDFF and important cardiometabolic endpoints in an 18-Week, placebo-controlled Phase 2 study in patients with MASH and T2DM (NCT03656744). GLP-1 receptor agonists (RA) are widely used for the treatment of T2DM and obesity and are under investigation for treatment of MASH. The purpose of this post-hoc comparative efficacy analysis was to evaluate ongoing GLP-1RA use compared to newly initiated HTD1801 treatment. **Methods:** 100 patients were randomized and treated with HTD1801 1000 mg BID (n=34), HTD1801 500 mg BID (n=33), or placebo (n=33) for 18 weeks. The primary endpoint was change in LFC. This analysis included patients who were randomized to HTD1801 and were not treated concomitantly with GLP-1RA or placebo randomized patients who were receiving ongoing GLP1RA. **Results:** At baseline, 39% of placebo patients were utilizing GLP-1RA compared with 18% of patients randomized to HTD1801. Baseline characteristics were balanced across groups with the exception of ALT. Dose-dependent improvements were observed at Week 18 with HTD1801 treatment in LFC, ALT, HbA1c, and weight. Furthermore, reductions in each of these parameters were greater with HTD1801 1000 mg BID vs ongoing GLP-1RA. **Conclusion:** This data suggests newly initiated HTD1801 provides greater benefit than ongoing GLP-1RA use. Utilization of GLP-1RA continues to grow and may be confounding in studies of MASH.

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This has resulted in their exclusion from some new studies of MASH which is unlikely to be reflective of real-world use. In order to address this concern, GLP-1RA utilization is a stratification factor in the ongoing Phase 2b study of HTD1801.

Table 1. Baseline and Change from Baseline in Key Hepatic and Cardiometabolic Parameters

Mean (SD)	HTD1801 1000 mg BID (n=28)	HTD1801 500 mg BID (n=27)	GLP-1RA (n=13)
LFC, (%)	19.6 (7.5)	19.0 (6.6)	19.7 (5.0)
Δ to Week 18	-4.5 (4.4)	-3.2 (4.4)	-2.9 (4.0)
ALT, U/L	62.7 (34.2)	46.2 (28.6)	43.1 (17.0)
Δ to Week 18	-16.7 (28.6)	-4.6 (18.6)	-4.5 (13.8)
HbA1c, (%)	7.3 (1.2)	6.9 (0.9)	7.4 (1.0)
Δ to Week 18	-0.4 (0.9)	-0.4 (0.7)	-0.04 (1.0)
Weight, (kg)	99.4 (17.9)	100.4 (22.5)	101.1 (19.2)
Δ to Week 18	-3.7 (5.1)	-1.4 (3.2)	-1.9 (3.4)

Disclosures: Stephen Harrison: Nothing to Disclose, Guy Neff: Nothing to Disclose, Nadege Gunn: Nothing to Disclose, Abigail Flyer: Nothing to Disclose, Leigh MacConell: Nothing to Disclose

3219 | TIME COURSE OF ONSET, INCIDENCE AND PREVALENCE OF GASTROINTESTINAL ADVERSE EVENTS WITH HTD1801 (BERBERINE URSODEOXYCHOLATE) IN PATIENTS WITH MASH AND T2DM

Guy Neff[1] Stephen Harrison[2] Nadege Gunn[3] Abigail Flyer[4] Kui Liu[5] Alexander Liberman[6]

[1]Covenant Metabolic Specialists, LLC, [2]Pinnacle Clinical Research, [3]Velocity Clinical Research, [4]Pacific Northwest Statistical Consulting, [5]Shenzhen HighTide Biopharmaceuticals Ltd, [6]HighTide Therapeutics

Background: HTD1801 is a gut-liver anti-inflammatory metabolic modulator consisting of an ionic salt combination including berberine and ursodeoxycholic acid. The unique molecular structure has been shown to significantly reduce liver fat content (LFC) as determined by MRI-PDFF. Clinically, HTD1801 has shown improved multiple cardiometabolic endpoints in an 18-Week, placebo-controlled Phase 2 study in patients with metabolic dysfunction-associated steatohepatitis (MASH) and Type 2 Diabetes (T2DM) (NCT03656744). HTD1801 is safe and well-tolerated. Overall adverse events (AEs) in studies of HTD1801 across several indications have been mild to moderate gastrointestinal (GI) AEs, primarily diarrhea and nausea. The purpose of this post-hoc analysis is to present time course and severity of GI AEs in patients with MASH and T2DM treated with HTD1801 for 18 weeks. **Methods:** One hundred patients were randomized and treated with HTD1801 1000 mg BID (n=34), HTD1801 500 mg BID (n=33), or placebo (n=33) for 18 weeks. Onset was defined as the first occurrence of an event for each subject; incidence was defined as any new event within a visit window; and prevalence was defined as any new or ongoing event within a visit window. As AEs can occur at any time, they are assigned to scheduled visits using the following windows based on the study day: Day 0: Day 0; Week 2: Day 1- 28; Week 6: Day 29-56; Week 10: Day 57-84; Week 14: Day 85-112; Week 18: Day 113 onward. **Results:** Treatment with HTD1801 resulted in significant reductions in LFC, HbA1c, weight, and liver biochemistry compared to placebo. GI AEs were experienced by 10%, 42%, and 56% of patients randomized to placebo, HTD1801 500 mg BID and HTD1801 1000 mg BID, respectively; all of which were mild or moderate in severity. Four subjects in the HTD1801 1000 mg BID group and 1 subject in the HTD1801 500 mg BID group discontinued study drug due to a GI AE. As shown in Figure 1, the incidence or GI AEs peaks within the first 4 weeks of treatment and then rapidly declines with ongoing treatment with HTD1801. Furthermore, the prevalence of GI AEs also declines with ongoing treatment. Diarrhea and nausea were the most commonly occurring GI AEs. As shown in the figure, they follow a consistent trend with all GI AEs, they are early onset, mild or moderate, with a decreasing incidence and prevalence over the course of treatment. **Conclusion:**

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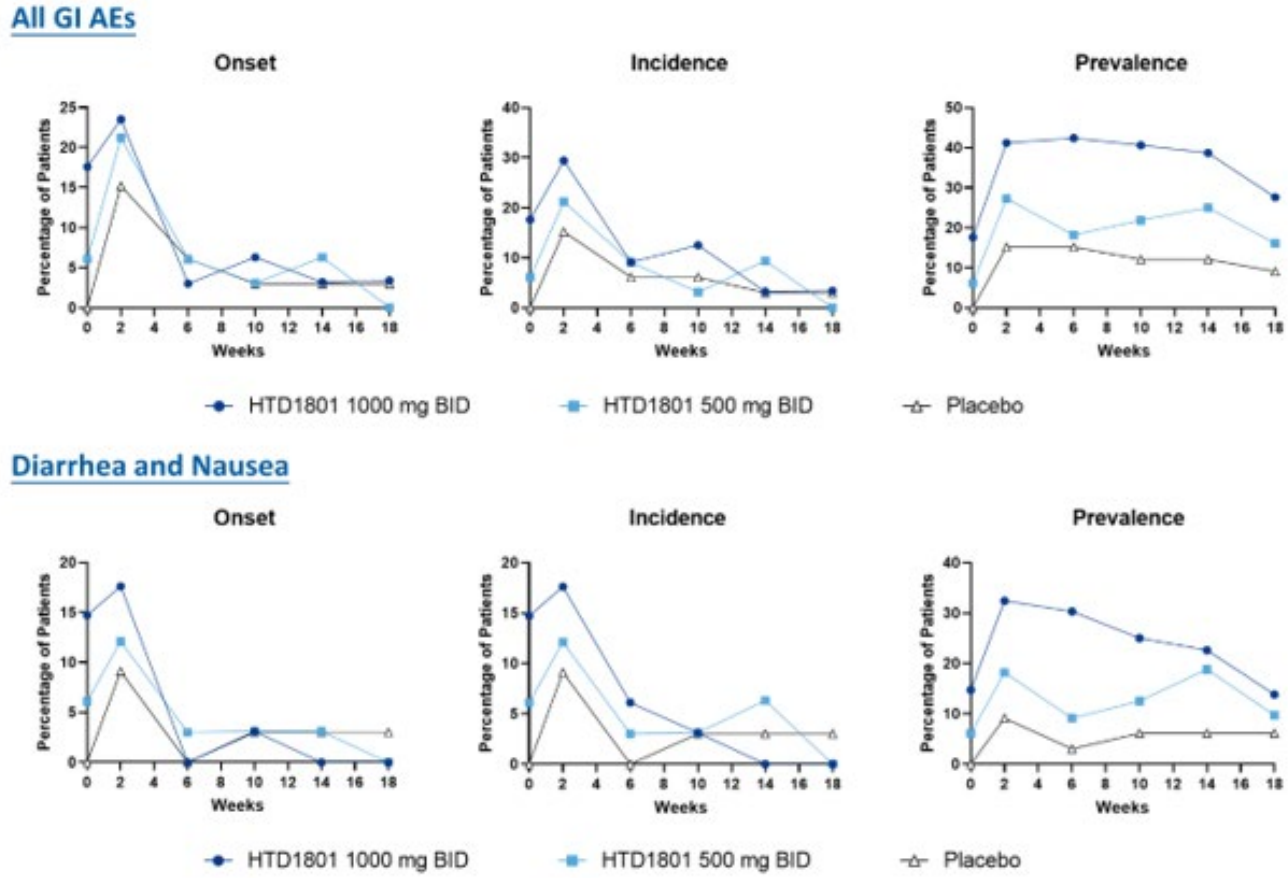
HTD1801 was found to be generally safe and well tolerated in this study. Although most commonly occurring AEs in studies involving HTD1801 are GI related and are typically mild to moderate in severity with decreasing incidence over time. The above data indicates subject tolerability to HTD1801 which improves over the course of treatment.

Figure 1. Time Course of Gastrointestinal Adverse Events over 18 Weeks of Treatment with HTD1801



Disclosures: Guy Neff: Nothing to Disclose, Stephen Harrison: Nothing to Disclose, Nadege Gunn: Nothing to Disclose, Abigail Flyer: Nothing to Disclose, Kui Liu: Nothing to Disclose, Alexander Liberman: Nothing to Disclose

3220 | LIVER ENZYMES REDUCTIONS FROM BASELINE OVER TIME IN RESMETIROM TREATED PATIENTS IN A PHASE 3 STUDY, MAESTRO-NASH

Seth Baum[1] Rebecca Taub[2] Dominic Labriola[2] Naim Alkhouri[3] Mazen Noureddin[4]

[1]Florida Atlantic University, Flourish Research, [2]Madrigal Pharmaceuticals, [3]Arizona Liver Health, [4]Houston Methodist Hospital

Background: Resmetirom was approved by FDA in March 2024 and is indicated for the treatment of adults with noncirrhotic nonalcoholic steatohepatitis (NASH) with moderate to advanced liver fibrosis (consistent with stages F2 to F3). Liver enzyme data from the 52-week MAESTRO-NASH study was analyzed in patients who received resmetirom 80 or 100 mg or placebo co-administered with a statin, or who were not co-administered a statin. **Methods:** Patients randomized to resmetirom 80 or 100 mg were monitored for changes from baseline in alanine aminotransferase (ALT), aspartate aminotransferase (AST) and gamma-glutamyl transferase (GGT) over a period of 52 weeks and changes in liver enzymes were assessed according to statin treatment at baseline. **Results:** A total of 473 patients were on a statin at baseline (49.0% of total population of 966 patients), including 223 (23.1%) patients were on atorvastatin, 7 (0.7%) on lovastatin, 3 (0.3%) on pitavastatin, 63 (6.5%) on pravastatin, 114 (11.8%) on rosuvastatin, and 64 (6.6%) on simvastatin. This group also included 13% on high-intensity statin

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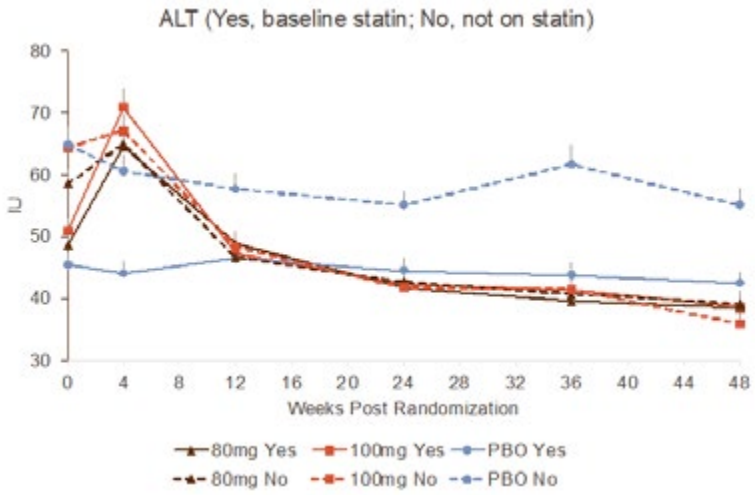
therapy (rosuvastatin 20 mg and atorvastatin 40 mg) and 36% on moderate- to low-intensity statins. A total of 149 (46.2%) patients received resmetirom 80 mg, 166 (51.4%) resmetirom 100 mg, and 158 (49.2%) received placebo. NASH patients on statins had lower ALT and AST at baseline than NASH patients who were not on statins. There was a mild and transient increase in AST and ALT (<1.5-fold baseline) at Week 4 in patients on statins compared with patients not on statins that did not exceed the level of ALT or AST at 4 weeks in patients not on statins. The elevations resolved by Week 8; liver enzymes declined thereafter (see Figure). At Week 48, in patients with ALT ≥30 at baseline ALT declined from baseline by 20% and 24% at 80 and 100 mg; respectively, in patients on statins and declined by 37% and 43% at 80 and 100 mg; respectively, in patients not on statins (all p<0.0001 relative to placebo). **Conclusion:** Transient increases in liver enzymes ALT and AST of <1.5-fold baseline occurred at week 4 in patients co-dosed with resmetirom and statins. Patients on statins had lower baseline liver enzymes and elevations resolved by Week 8. GGT declined from the time resmetirom treatment was initiated. Liver enzymes declined significantly in resmetirom treated patients relative to placebo beginning at Week 12.



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3221 | A SYSTEMATIC REVIEW ON RESMETIROM: ARRESTING MASH/MASLD PROGRESSION

Charmy Parikh[1] Raj Patel[2] Henil Upadhyay[3] Maurya Patel[4] Parameswaran Ramnath[5] Shubham Kumar Singh[3]

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Background: Resmetirom, a thyroid hormone receptor agonist with remarkable selectivity for thyroid hormone receptor subtype β (THR-β), primarily acts on the liver by enhancing mitochondrial β-oxidation and improving hepatocyte mitochondrial function. By targeting hepatic metabolic pathways, Resmetirom effectively reduces intra-hepatic lipids, thereby addressing the underlying pathology of MASH/MASLD. Its specificity for THR-β offers the advantage of minimizing systemic effects associated with excessive thyroid hormone activity, potentially reducing adverse effects in non-hepatic tissues. The significant reduction in hepatic fat fraction and histopathological improvements observed in clinical trials underscore Resmetirom's efficacy in treating MASH/MASLD and highlight its mechanistic role in ameliorating liver dysfunction. **Methods:** A thorough review using an advanced search strategy and relevant MeSH keywords was done across databases like PubMed, Europe PMC, Science Direct, Web of Science, Cochrane, and Google Scholar for articles investigating the role of resmetirom in preventing MASH/MASLD progression. The initial search yielded a total of 1,283 articles. Adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines, we selected 5 RCTs for inclusion. **Results:** 2629 patients with a mean age of 52.08 years were included in our study from the five selected RCTs. Both Phase 2 & 3 trials demonstrated significant reductions in % hepatic fat fraction [-37.3(T) vs -8.9(P), -45.8(T) vs -52(T+P) at 36 weeks in Phase 2 alongside -35.4(T) & -46.6(T) vs -8.7 (P); -38.6(T), -33.9(T), & -47.8(T) vs -9.9(P) at 52 weeks in Phase 3], LDL, ALT, cytokeratin, and adiponectin levels with histopathological improvements in MASH/MASLD patients treated with Resmetirom group (T) (80 mg and 100 mg) compared to the placebo group (P). Further numerical details are demonstrated in the chart given below. Adverse events, predominantly gastrointestinal symptoms, were mild and self-limited. **Conclusion:** Resmetirom recently approved by the US FDA emerges as a promising pharmacological intervention for MASH/MASLD, offering significant reductions in hepatic fat and histopathological improvements with manageable adverse effects. Further research is warranted to elucidate its long-term safety and efficacy, particularly in high-risk MASH/MASLD populations.

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Study	Design	Total number of Patients	Mean age (years)	Males	Females	Treatment arms		% change in MRI PDFF		% change in LDL		% change in ALT		Change in Cytokeratin (Units/L)	Change in Adiponectin	Adverse effect
								Week 12	Week 36	Week 12	Week 36	Week 12	Week 36			
(NCT02912260)	Phase-2, double-blind, randomized controlled trial	125	49.5	62	63	Placebo	41	-10.4	-8.9	6.2		-5.2	11	-101	0.24 Mg/L	diarrhea, nausea, headaches, urinary tract infections, dizziness, fatigue
						Resmetirom 80 mg	80	-32.9	-37.3	-11.2		-8.2	-15.4	-272	1.31 Mg/L	
Open-Label Extension (OLE) of NCT02912260	Phase 2 Extension study	31	48.2	16	15	Placebo + Resmetirom	14	-39.9	-52	-23.4	-26.1	-16.8	-31.7		0.84 Mg/L(at 12 weeks)	N/A
						Resmetirom + Resmetirom	17	-33.5	-45.8			-14.4	-16.4		-0.039 Mg/L (at 12 weeks)	N/A
HQRL study	Phase-2, double-blind, randomized controlled trial	125	50	62	63	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
								Week 16	Week 52	Week 24	Week 48	Week 48	Week 52			
MAESTRO-NASH (NCT03900429)	Phase 3, double-blind, placebo-controlled	966	56.7	425	541	Placebo	321	N/A	-8.7	0.1		-6.9			No significant change	Covid-19 Nausea Arthralgia Back pain Urinary tract infection Fatigue Pruritus Vomiting
						Resmetirom 80 mg	322	N/A	-35.4	-13.6		-26.6			Improvement	
						Resmetirom 100 mg	323	N/A	-46.6	-16.3		-33.2			Improvement	
MAESTRO-NAFLD-1 (NCT04197479)	Phase 3, Randomized, double-blind, placebo-controlled	1143	56	418	554	Placebo	320	-6.2	-9.9	-1.3	-1.4		-1.1	4.15	0.42	Covid-19, diarrhea, nausea, abdominal pain, Arthralgia, UTI, BAck pain, fatigue, headache, headache, pain in extremity,
						Resmetirom 80 mg		-41.2	-38.6	-12.4	-10.6		-10.8	-87.2	1.12	
						Resmetirom 100 mg	325	-38.6	-33.9	-13.9	-13.4		-11.9	-78.4	0.9	
						Open Label Resmetirom 100mg	171	-47.8	-51.8	-19.4	-20.5		-14.3	-174.2	1.61	

Disclosures: Charmy Parikh: Nothing to Disclose, Raj Patel: Nothing to Disclose, Henil Upadhyay: Nothing to Disclose, Maurya Patel: Nothing to Disclose, Parameswaran Ramnath: Nothing to Disclose, Shubham Kumar Singh: Nothing to Disclose

3222 | EFFICACY AND SAFETY OF PEGBELFERMIN IN MASH CIRRHOSIS – A META-ANALYSIS AND SYSTEMATIC REVIEW OF RANDOMIZED CONTROLLED TRIALS

Muhammad Shahzil[1] Fariha Hasan[2] Kanza Kazmi[1] Umm E Salma Shabbar Banatwala[3] Ammad Chaudhary[4] Muhammad Saad Faisal[4] Muhammad Ali Khaqan[5] Manesh Gangwani[6] Kathy Williams[7] Babu Mohan[8] Christina Tofani[7]

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Background: Metabolic dysfunction-associated steatohepatitis (MASH), an advanced form of fatty liver disease, is characterized by liver inflammation and fibrosis, affecting 1.5-6.5% of adults globally. Lifestyle changes and medications are primary management options, with an emerging interest in fibroblast growth factors (FGF) like FGF21 and its analogs, particularly pegbelfermin (PGBF). This systematic review and meta-analysis evaluates the efficacy and safety of pegbelfermin in treating MASH-related cirrhosis. **Methods:** This meta-analysis followed Cochrane guidelines and PRISMA standards. A comprehensive search of CENTRAL, PubMed, MEDLINE, Embase, and Scopus databases up to January 2023 focused on RCTs comparing pegbelfermin to placebo for MASH. Two reviewers independently extracted data, and bias was assessed using the RoB 2.0 tool. Meta-analyses, performed with RevMan 5.4 using a random-effects model, set statistical significance at $p < 0.05$ and evaluated heterogeneity with Chi-square and Higgins I^2 tests. **Results:** Data from 452 participants across three RCTs were analyzed, with 227 in the PGBF group (113 received 10 mg, 114 received 20 mg). Significant improvements in adiponectin concentration were observed in both the 10 mg (MD = 18.23, 95% CI: 6.35-30.11, P = 0.003) and 20 mg (MD = 18.09, 95% CI: 5.88-30.31, P = 0.004) PGBF groups compared to placebo. Significant reductions in PRO-C3 concentration were noted in both the 10 mg (MD = -25.50, 95% CI: -43.95 to -7.05, P = 0.007) and 20 mg (MD = -19.54, 95% CI: -33.33 to -5.76, P = 0.005) groups indicating hepatic benefits and reduced fibrosis. Significant improvement in MASH was seen in the 10 mg group (RR = 2.84, P = 0.02), but not in the 20 mg group (RR = 3.24, P = 0.15). No significant improvements in liver stiffness (10 mg: RR = 1.31, P =

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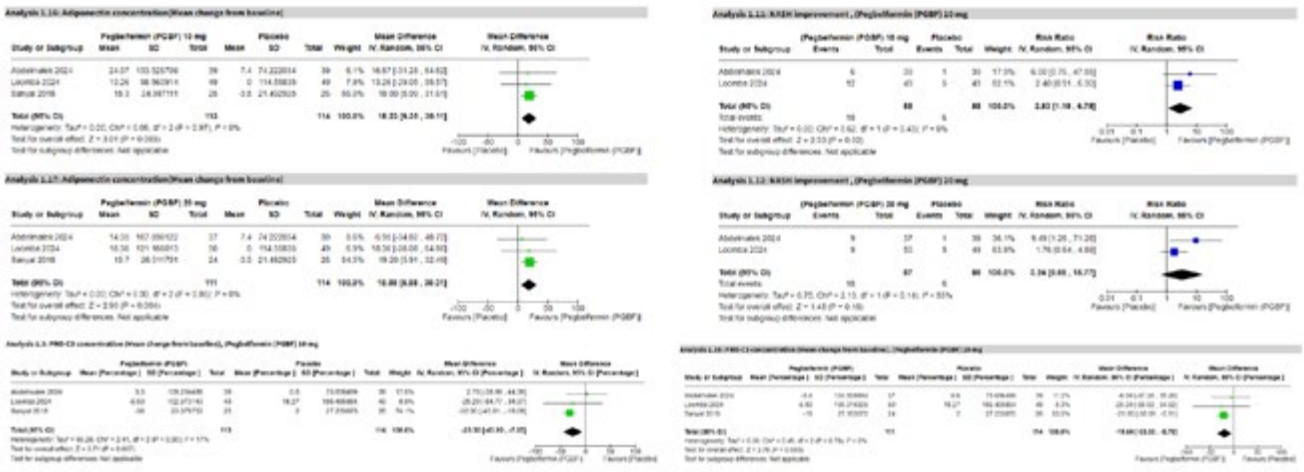
0.23; 20 mg: RR = 1.41, P = 0.07), Modified Ishak scores (10 mg: RR = 1.25, P = 0.37; 20 mg: RR = 1.01, P = 0.98), or collagen proportionate area (10 mg: RR = 0.87, P = 0.63; 20 mg: RR = 0.88, P = 0.38) were observed in either the 10 mg or 20 mg groups compared with placebo. ALT and AST levels showed no significant reductions in either group. There was no significant risk of treatment-emergent adverse events (TEAEs) in either group, except for diarrhea in the 20 mg group (RR = 2.28, P = 0.005). **Conclusion:** Pegbelfermin, a promising therapy for MASH cirrhosis, has demonstrated effectiveness at 10 mg, significantly improving MASH and biomarkers such as adiponectin and PRO-C3. Despite mild gastrointestinal side effects, it maintains a generally safe profile. Further research with larger randomized controlled trials and extended follow-up is warranted to explore Pegbelfermin's role in enhancing MASH and liver fibrosis outcomes, particularly in combination with Resmetirom.



Disclosures: Muhammad Shahzil: Nothing to Disclose, Fariha Hasan: Nothing to Disclose, Kanza Kazmi: Nothing to Disclose, Umm E Salma Shabbar Banatwala: Nothing to Disclose, Ammad Chaudhary: Nothing to Disclose, Muhammad Saad Faisal: Nothing to Disclose, Muhammad Ali Khaqan: Nothing to Disclose, Manesh Gangwani: Nothing to Disclose, Kathy Williams: Nothing to Disclose, Babu Mohan: Nothing to Disclose, Christina Tofani: Nothing to Disclose

3223 | ENHANCEMENT OF DE NOVO NAD+ BIOSYNTHESIS BY ACMSD INHIBITION COUNTERS DNA DAMAGE IN MASLD/MASH

Yasmine Liu[1] Masaki Kimura[2] Xiaoxu Li[3] Jonathan Sulc[3] Qi Wang[3] Sandra Rodríguez-López[4] Angelique Scantlebery[5] Keno Strotjohann[3] Hector Gallart Ayala[6] Archana Vijayakumar[7] Rob Myers[7] Julijana Ivanisevic[6] Riekelt Houtkooper[5] Mani Subramanian[7] Takanori Takebe[8] Johan Auwerx[9]

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Background: The enzyme α-amino-β-carboxymuconate-ε-semialdehyde decarboxylase (ACMSD), primarily expressed in liver and kidney, acts as a modulator for *de novo* NAD+ synthesis. Augmenting NAD+ levels with novel ACMSD inhibitors has been shown to improve fibrosis and inflammation in a mouse model of MASLD/MASH. In human MASLD/MASH, hepatocyte DNA damage resulting from genome instability, oxidative stress and replication stress is evident and may underlie the disease condition. Here, we characterized the genome-protective effects of ACMSD inhibition in mouse primary hepatocytes (mPH), MASLD/MASH mouse models, and induced pluripotent stem cell (iPSC)-derived human liver organoids (HLOs). **Methods:** mPH were treated with 1 mM doxorubicin ± 5 mM ACMSD inhibitor TLC-065 for 24 h. HLOs were exposed to 5 mM doxorubicin for 24 hours ± 10 mM TLC-065. C57BL/6J mice fed a western diet (WD) or chow were housed at thermoneutrality (TN; 30°C) for 23 wk and treated with TLC-065 (25 mg/kg/day dosed in WD) from wk 9-23. DNA damage was assessed by immunofluorescence, immunoblotting of p-H2A.X and p-53BP1, canonical makers of DNA strand breaks in mPH and HLOs, and immunohistochemistry of liver sections. **Results:** Inhibiting ACMSD with TLC-065

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decreased doxorubicin-induced DNA strand breaks in mPH, as measured by TUNEL staining and immunoblotting of p-H2A.X (Fig. a-b). TLC-065 reversed the DNA damage response (increased p-H2A.X+ cells and poly-ADP ribosylation (PARylation)) observed in livers of WD/TN mice (Fig. c-d) To verify the genome-protective effects of TLC-065 in humans, HLOs treated with 5 mM doxorubicin caused significant accumulation of DNA strand breaks, detected by the formation of p-53BP1 puncta in nuclei and this was reduced by TLC-065 (Fig. e, f). **Conclusion:** Inhibition of ACMSD enhances genome stability in hepatocytes in a diet-induced mouse model of MASLD/MASH which may contribute to beneficial effects on liver inflammation and fibrosis. These genome-protecting effects are also recapitulated in human liver organoid models. Our data support evaluation of ACMSD inhibition as a treatment for MASLD/MASH.

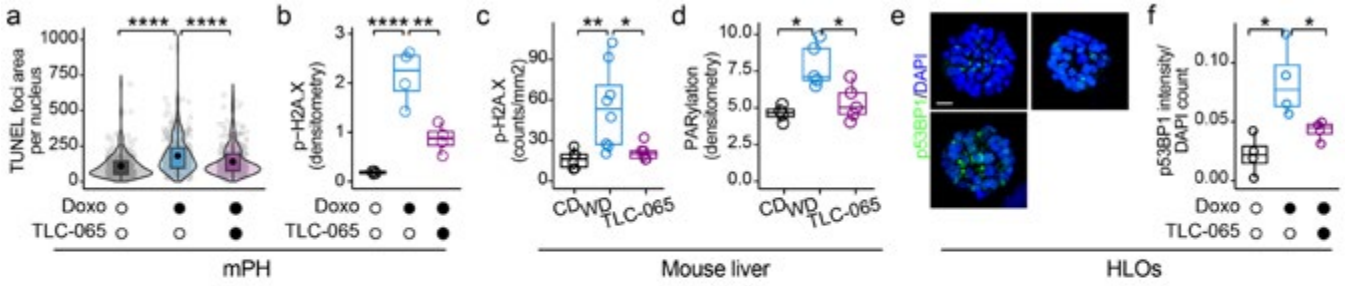

Figure a. Quantification of TUNEL foci area per nucleus in mPH.
b. Quantification of the band densitometry of p-H2A.X at Ser139 normalized to H2A.X in mPH exposed to doxorubicin (Doxo) ± TLC-065.
c. Quantification of p-H2A.X positive nuclei in liver sections of CD, WD and TLC-065-treated mice.
d. Band densitometry quantification of PARylation of liver proteins normalized to HSP90 from CD, WD and TLC-065 treated mice.
e-f. Representative images and quantification of DNA damage signal p-53BP1 Ser1778 in HLOs exposed to 5 μM Doxo for 24-h ±10 μM TLC-065.

Disclosures: Yasmine Liu: Nothing to Disclose, Masaki Kimura: Nothing to Disclose, Xiaoxu Li: Nothing to Disclose, Jonathan Sulc: Nothing to Disclose, Qi Wang: Nothing to Disclose, Sandra Rodríguez-López: Nothing to Disclose, Angelique Scantlebery: Nothing to Disclose, Keno Strotjohann: Roche: Intern, Hector Gallart Ayala: Nothing to Disclose, Archana Vijayakumar: Nothing to Disclose, Rob Myers: Nothing to Disclose, Julijana Ivanisevic: Nothing to Disclose, Riekelt Houtkooper: Nothing to Disclose, Mani Subramanian: Nothing to Disclose, Takanori Takebe: Nothing to Disclose, Johan Auwerx: Nothing to Disclose

3224 | MIMERET, A NOVEL MITOCHONDRIAL-TARGETED DRUG, IMPROVES HEPATIC STEATOSIS BY STIMULATING MITOCHONDRIAL FATTY ACID BETA-OXIDATION TO PREVENT LIPID ACCUMULATION

Seong Jin Kim[1] Kwiyeom Yoon[2] Dongwoo Kang[2] HeeJae Choi[2] Jinhwan Kim[2]

[1]Medpacto Inc./ GILO Foundation Research Institute, [2]Medpacto Inc.

Background: Metabolic dysfunction-associated steatohepatitis (MASH) is a common liver disease associated with metabolic syndrome, characterized by hepatic steatosis, inflammation, and fibrosis. Although Resmetirom was recently approved by the FDA, it still has limitations and new treatment approaches are needed. This study was conducted in an amylin diet-induced mouse model of MASH to evaluate the effectiveness of Mimeret, a novel mitochondrial-targeted therapeutic, in improving liver histology, function, and inflammation. **Methods:** Male C57BL/6J mice were fed an amylin diet to induce MASH and randomized into four groups: vehicle, Resmetirom, Mimeret 4 mg/kg, and Mimeret 8 mg/kg, with a normal diet group serving as a control. Drugs were administered orally once daily for 8 weeks. Efficacy was assessed by analyzing liver function, serum lipid profiles, inflammatory cytokine expression, and histology of steatosis, inflammation, and fibrosis in liver tissue. Changes in body weight and body fat mass were also measured. RNA sequencing was performed to identify gene expression signatures associated with treatment response. **Results:** Mimeret significantly improved liver histology, NAS score, and fibrosis score compared to the control group ($p<0.01$), demonstrating similar efficacy to Resmetirom. Mimeret improved liver function and reduced pro-inflammatory marker expression. Notably, Mimeret induced weight loss and improved adiposity without decreasing appetite due to its ability to promote fatty acid mitochondrial beta-oxidation and inhibit lipid accumulation. RNA sequencing revealed distinct gene expression patterns of Mimeret compared to Resmetirom, suggesting a unique mechanism for Mimeret and raising its potential as a novel liver disease treatment. **Conclusion:** Mimeret has demonstrated promising efficacy in ameliorating

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MASH pathology, with similar improvements to Resmetirom in an amylin-induced mouse model; however, unlike Resmetirom, Mimeret induces weight loss and has a unique gene expression profile, indicating its potential as a comprehensive treatment option for MASH. Importantly, Mimeret did not cause any significant adverse events. These findings support the potential of Mimeret as a novel treatment for MASH, highlighting its dual efficacy in improving MASH pathology and obesity, as well as its favorable safety profile.

Disclosures: Seong Jin Kim: Medpacto Inc.: Executive role, Kwiyeom Yoon: Medpacto Inc.: Employee, Dongwoo Kang: Medpacto,Inc: Employee, HeeJae Choi: Medpacto Inc.: Employee, Medpacto Inc.: Employee, Jinhwan Kim: Medpacto, Inc: Employee

3225 | SIGMA1 REGULATION OF HEPATIC LIPID METABOLISM IN RESPONSE TO DIET-INDUCED OBESITY

Luis Martinez[1] Nathalia Tancler[1] Bach Tran[1] Zhijiu Zhong[1] Wei Jiang[1] Paola Castagnino[1] Justin Myers[1] Halley Oyer[1] Alexandra Steck[1] Lila Busser[1] Amy Shaver[1] Grace Lu-Yao[1] Dina Halegoua-DeMarzio[1] Felix Kim[1]

[1]Thomas Jefferson University

Background: Metabolic dysfunction associated steatotic liver disease (MASLD) has a highly variable natural history reflected by different progression rates among individuals and heterogeneous clinical manifestations. The cellular factors involved in the natural history of MASLD and cellular mechanisms driving disease progression are not well defined. Sigma1 (gene name *SIGMAR1*) is a unique ligand-operated intracellular integral membrane scaffolding protein enriched in the endoplasmic reticulum (ER). The liver expresses among the highest levels of *SIGMAR1* mRNA, however, a role for Sigma1 in liver physiology and pathophysiology has not been established. Here we demonstrate a role for Sigma1 in hepatic lipid metabolism associated with obesogenic diet induced MASLD. **Methods:** To evaluate Sigma1 in MASLD, we made a *SIGMAR1* knockout (KO) mouse and compared the impact of obesogenic diet on the liver and on other obesity associated phenotypes of wild-type (WT) and KO mice. We performed histopathology to characterize and quantify changes in liver phenotypes and RNAseq analysis to identify differential hepatic gene expression patterns. We developed a novel Sigma1 selective inhibitor to evaluate whether pharmacological inhibition of Sigma1 would phenocopy the genetic KO. Using WT and KO cells and a hepatocyte cell line, we elucidated the mechanism of action of Sigma1 inhibition in regulating hepatic lipid metabolism. **Results:** Weight gain and adiposity increased similarly in *SIGMAR1* KO and WT mice fed the obesogenic diet. However, hepatic steatosis was significantly mitigated in KO mice. Transcriptomic analysis revealed differential hepatic gene expression in WT and KO mice fed the obesogenic diet, including genes involved in lipid droplet metabolism, ER stress response, fatty acid metabolism, and AMPK signaling pathway. Our Sigma1 inhibitor phenocopied key aspects of the KO. Treatment with the Sigma1 inhibitor accelerated recovery from hepatic steatosis, suggesting Sigma1 is a druggable target in MASLD. Finally, we found that *SIGMAR1* mRNA levels are elevated in the liver of people with early MASLD through MASH (metabolic dysfunction associated steatohepatitis). Gene set enrichment analysis revealed that changes in *SIGMAR1 mRNA* corresponded with multiple metabolic pathways directly involved in MASH. **Conclusion:** This work reveals a central role for Sigma1 in regulating hepatic lipid metabolism, and it establishes a novel mouse model to investigate new factors involved in MASLD pathophysiology. Furthermore, it suggests Sigma1 as a potential therapeutic target in MASLD.

Disclosures: Luis Martinez: Nothing to Disclose, Nathalia Tancler: Nothing to Disclose, Bach Tran: Nothing to Disclose, Zhijiu Zhong: Nothing to Disclose, Wei Jiang: Nothing to Disclose, Paola Castagnino: Nothing to Disclose, Justin Myers: Nothing to Disclose, Halley Oyer: Johnson and Johnson Innovative Medicine: Employee, Alexandra Steck: Nothing to Disclose, Lila Busser: Nothing to Disclose, Amy Shaver: Nothing to Disclose, Grace Lu-Yao: Nothing to Disclose, Dina Halegoua-DeMarzio: Grant/Research Support relationship with Viking; Has ended; Advisor relationship with Novo Nordisk; Has not ended; Advisor relationship with Madigral; Has not ended; Grant/Research Support relationship with Galectin; Has not ended; Grant/Research Support relationship with Akero; Has not ended; Advisor relationship with Madigral; Has not ended; Grant/Research Support relationship with Novo Nordisk; Has not ended; Grant/Research Support relationship with Intercept; Has ended

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3226 | NONCLINICAL TOXICOLOGY PROFILE OF ALG-055009, A NOVEL AND POTENT THYROID HORMONE RECEPTOR β AGONIST, FOR THE TREATMENT OF METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS (MASH)

Dinah Misner[1] Kusum Gupta[2] Kha Le[3] Doug Clark[1] Xuan Luong[1] Meenakshi Venkatraman[1] David Smith[1] Tse-I Lin[1] Julian Symons[2] Lawrence Blatt[1] Sushmita Chanda[1]

[1]Aligos Therapeutics, Inc., [2]Aligos Therapeutics, [3]Aligos Therapeutic s

Background: MASH is characterized by hepatic inflammation/damage as a reaction to build-up of fat in the liver. Recently, Rezdiffra™ (resmetirom) was approved to treat MASH, demonstrating the utility of thyroid hormone receptor β (THRβ) agonists in MASH. Additional THRβ agonists have demonstrated reduced liver fat, restored liver function and reversed inflammation/fibrosis in clinical trials. Here we present the preclinical development of ALG-055009, a second-generation THRβ agonist with improved potency and favorable selectivity. **Methods:** ALG-055009 was profiled in in vivo pharmacokinetic and toxicology studies across species. In vivo pharmacokinetic studies were conducted in mice, rats, rabbits, dogs, and non-human primates. Repeat-dose toxicology studies were conducted in rats and dogs using once daily (QD) oral gavage administration, up to 6 months in rats and 9 months in dogs. Clinical pathology endpoints including thyroid hormones were assessed at 6-, 13-, 26-, and 39-weeks (dogs only), as well as following 4-weeks of recovery. Pharmacodynamic endpoints included total/LDL cholesterol, liver enzymes, and thyroid hormones. **Results:** ALG-055009 showed favorable pharmacokinetic properties across species following single or repeat doses. ALG-055009 was well tolerated in both rats and dogs in repeat dose toxicology studies up to the highest doses tested. Dose-dependent changes in lipid parameters were observed in repeat-dose toxicology studies, whereas changes in total circulating thyroid hormones levels were observed at supratherapeutic exposures. These changes demonstrated reversibility following a 4-week recovery period. **Conclusion:** ALG-055009 is a potent and selective THR-β agonist with favorable in vitro safety and ADME properties and repeat-dose toxicity profile in rats and dogs. ALG-055009 also dose-dependently reduced levels of atherogenic lipids. Combined, this profile indicates ALG-055009 has the potential to be a best-in-class THR-β agonist for the treatment of MASH. Enrolment for the HERALD study has been completed, and the Phase 2a study is ongoing with topline data expected by the end of 2024.

Disclosures: Dinah Misner: Nothing to Disclose, Kusum Gupta: Nothing to Disclose, Kha Le: Nothing to Disclose, Doug Clark: Nothing to Disclose, Xuan Luong: Nothing to Disclose, Meenakshi Venkatraman: Nothing to Disclose, David Smith: Nothing to Disclose, Tse-I Lin: Nothing to Disclose, Julian Symons: Nothing to Disclose, Lawrence Blatt: Nothing to Disclose, Sushmita Chanda: Nothing to Disclose

3227 | MASSIVELY PARALLEL SINGLE NUCLEUS TRANSCRIPTOMICS-BASED *IN VIVO* SCREENING IDENTIFIES NOVEL DRUG TARGETS TO TREAT MASH

Joanne Hsieh[1] Caroline Duwaerts[1] Hikaru Miyazaki[1] Vinay Kartha[1] Chris Carrico[1] Jesi Nonora[1] Daniel Fuentes[1] Linda Chio[1] Jingshu Chen[1] Smitha Shambhu[1] Dimitry Popov[1] Ian Driver[1] Kimberly Mackenzie[1] Chris Towne[1] Francisco LePort[1] Martin Borch Jensen[1]

[1]Gordian Biotechnology

Background: As evidenced by the success of direct-acting antivirals for HCV and the recent FDA approval of a thyroid hormone receptor beta (THRB) agonist for MASH, hepatocyte-targeting therapies have great potential to induce fibrosis regression in addition to metabolic improvements. However, such an anti-fibrotic effect necessitates intercellular communications between hepatocytes and non-parenchymal cells that are yet to be completely defined and are poorly recapitulated in *in vitro* systems. **Methods:** We administered a low dose of a pool of 350 different adeno-associated virus-based gene therapies to mice fed the Gubra-Amylin NASH diet for 58 weeks, resulting in a mosaic liver with an average of 7% of hepatocytes receiving a single therapy each. The targets encompassed a wide range of biology, from metabolic enzymes to transcription factors to cytokines. The response to each intervention was assessed at the single nucleus level based on expression of gene sets designed to capture multiple pathways of MASH pathogenesis, various aspects of liver function, as well as signatures of active disease recovery. Select interventions that exhibited desirable directionality in many features were delivered in saturating amounts to mice fed a MASH diet for 48 weeks. **Results:** Overexpression of PNPLA3 I148M in hepatocytes resulted in decreased expression of hepatocyte function genes and increased signals of endoplasmic reticulum stress and DNA damage.

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Overexpression of *PPP1R3B*, a gene in which higher hepatic transcript levels were associated with chronically elevated serum ALT in human GWAS, showed upregulation of a number of pathogenic modules and downregulation of hepatocyte function. *THRB* overexpression exhibited signs of decreased sterol regulatory element binding protein 1 transactivation and less apoptotic signaling. Overexpression of inflammatory cytokines such as *IL6* and *CCL3* clustered among interventions with a deleterious transcriptomic profile in our screens. Modeling toll-like receptor 4 (TLR4) antagonism with dominant-negative *TLR4* overexpression predicted the disappointing performance in the clinical trial. Interim pre-necropsy sampling indicated that within 4 weeks, one of the 6 selected novel interventions already significantly decreased ALT and low density lipoprotein cholesterol levels relative to the control. **Conclusion:** By examining many pathways of liver disease and health at the single cell level in a preclinical model of disease, we can predict the human response to therapeutic interventions. The ability to query hundreds of interventions in a single animal renders it feasible to test expensive models more resemblant of human disease, such as the non-human primate model included in our next steps.

Disclosures: Joanne Hsieh: Gordian Biotechnology: Employee, Caroline Duwaerts: Gordian Biotechnology: Employee, Hikaru Miyazaki: Nothing to Disclose, Vinay Kartha: Nothing to Disclose, Chris Carrico: Gordian Biotechnology: Employee, Jesi Nonora: Nothing to Disclose, Daniel Fuentes: Nothing to Disclose, Linda Chio: Gordian Biotechnology: Employee, Gordian Biotechnology: Stock – privately held company, Jingshu Chen: Nothing to Disclose, Smitha Shambhu: Nothing to Disclose, Dimitry Popov: Nothing to Disclose, Ian Driver: Nothing to Disclose, Kimberly Mackenzie: Nothing to Disclose, Chris Towne: Nothing to Disclose, Francisco LePort: Nothing to Disclose, Martin Borch Jensen: Nothing to Disclose

3228 | DURABLE UPREGULATION OF P1-ISOFORM HEPATOCYTE NUCLEAR FACTOR 4 ALPHA (HNF4α) USING NOVEL EPIGENOMIC CONTROLLERS

Amy McCurley[1] Christopher Pedigo[1] Joseph Newman[1] Charles O'Donnell[1] Justin Chen[1] Yaoyu Wang[1]

[1]Omega Therapeutics

Background: Hepatocyte nuclear factor 4 alpha (HNF4α) is a nuclear receptor and master regulator of liver development and function. The HNF4α gene is driven by two promoters, with isoforms derived from the P1 promoter associated with therapeutic benefit. HNF4α expression is dysregulated in fibrotic liver disease, with an HNF4α P1-P2 expression imbalance in favor of P2, potentially driven by TGFβ signaling. Omega Therapeutics has developed a modular platform for design of programmable mRNA medicines, termed epigenomic controllers (ECs), that precisely tune gene expression by site-specifically modulating epigenetic state. Using an EC to induce selective upregulation of the HNF4α P1 isoform to correct the disease-state dysregulation represents a novel therapeutic strategy for the treatment of fibrotic liver disease. **Methods:** Epigenetic control of the human *HNF4A* gene was investigated and an EC was designed to modulate its expression. Hepatic stellate cells (LX-2) and primary human hepatocytes were transfected with LNP-encapsulated ECs (HNF4α-EC) and qPCR or western blot was performed to assess HNF4α expression. To evaluate gene expression changes following HNF4α upregulation, LX-2 cells were transfected with HNF4α-EC, cells were collected over 10 days and RNA-seq was performed. To characterize the interaction between TGFβ and HNF4α signaling, primary human hepatocytes were treated with TGFβ, transfected with HNF4α-EC and qPCR was performed to evaluate isoform-specific HNF4α and target gene expression. **Results:** A single treatment with an HNF4α-EC in primary human hepatocytes led to durable upregulation of P1-HNF4α mRNA levels for up to 14 days. This coincided with minimal changes to P2-HNF4α mRNA expression, demonstrating the intended P1 isoform-specific induction of HNF4α. HNF4α-EC treatment of LX-2 cells resulted in robust upregulation of HNF4α mRNA expression, with corresponding increases in HNF4α protein levels. RNA-Seq profiling shows HNF4α target genes were differentially expressed throughout the treatment window (10 days). Gene set enrichment analysis reveals modulation of multiple pathways, including hormone receptor signaling, cholesterol homeostasis, and fatty acid metabolism. Treatment of heptaocytes with TGFβ resulted in substantial downregulation of P1-HNF4α and HNF4α-EC treatment was able to restore normal P1-HNF4α levels. **Conclusion:** We demonstrate the ability to durably increase the expression of HNF4α with EC treatment in a P1 isoform-specific manner. We showed that increasing HNF4α expression regulates HNF4α target genes and induces multiple downstream pathways. TGFβ treatment induced a dysregulation of HNF4α P1-P2 expression and treatment with the HNF4α-EC restored HNF4α-P1 expression levels. Future studies will test the efficacy of this treatment in liver disease models and further explore the therapeutic potential of epigenomic targeting of HNF4α in liver disease.

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Disclosures: Amy McCurley: Omega Therapeutics: Employee, Christopher Pedigo: Omega Therapeutics: Employee, Joseph Newman: Nothing to Disclose, Charles O'Donnell: Nothing to Disclose, Justin Chen: Omega Therapeutics: Employee, Omega Therapeutics: Stock - publicly traded company, Yaoyu Wang: Nothing to Disclose

3229 | REAL WORLD DATA ASSESSING THE IMPACT OF GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE ◆ ★

Reeti Gulati[1] Rachel Lee[2] Lucas Collins[2] Berline Francis[1] Alice Parish[1] Donna Niedzwiecki[1] Amreen Dinani[1]

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Background: Glucagon-like peptide-1 receptor agonists (GLP-1RA) are an effective treatment for Type 2 Diabetes (T2D) and obesity and have shown promise in improving metabolic dysfunction-associated steatotic liver disease (MASLD). The aim of this study is to determine the effect of GLP-1RA on liver health in patients with T2D and MASLD. **Methods:** Adult patients with a diagnosis of T2D (ICD-10 E11.XX) and MASLD (IDC-10 K75.8X, K76.0, or histological diagnosis) with atleast 12 months of treatment with GLP-1RA were identified at a tertiary care medical center from 01/2015 - 10/2022. Other causes of liver diseases were excluded. Demographics, medical comorbidities, and medications were collected. Liver enzymes, liver function tests, lipids, and HbA1c were recorded at baseline and 12 months after initiation of GLP-1RA (within 3 months of each time point). The primary outcome is the change in ALT from baseline to 12 months. Secondary outcomes include the change in FIB-4, BMI, HbA1c, LDL, HDL, TG, and AST from baseline to 12 months. Wilcoxon signed rank tests were used to test for significant differences between baseline and 12 months. **Results:** A total of 4742 patients with T2D and MASLD prescribed GLP-1RA were identified in this dataset. At the time of analysis, 409 patients had complete data for baseline and 12 months. Mean age was 59 years (SD 10.4), 63% were female, 70% identified as White, 25.5% identified as Black, 4% identified as Hispanic or Latino, 53% had private insurance, and 63% were married. There was a significant decrease in ALT by 1.0 IU/L ($p=0.039$) and an increase in FIB-4 by 0.02 ($p=0.005$) from baseline to 12 months (Table 1). A significant decrease was observed in AST (median Δ=-2.0 IU/L; $p=0.006$), HbA1c (median Δ=-0.6 %; $p<0.001$), BMI (median Δ=-0.8 kg/m^2; $p<0.001$), and LDL (median Δ=3.0 mg/dL; $p=0.047$). There was a noteworthy although insignificant decrease in TG by 9 mmol/L ($p=0.058$). No difference was observed in HDL ($p=0.11$). Hispanic patients had higher baseline ALT (78 IU/L; 95% CI: 53, 103) than non-Hispanic patients, and had a significant decrease in ALT at 12 months that was not observed in non-Hispanic patients. **Conclusion:** In this analysis, prescription of GLP1-RA illustrates early improvement in markers of liver inflammation and metabolic parameters. The change observed in FIB-4 was likely influenced by increase in age after 12 months. These results provide evidence of a potentially beneficial impact of GLP-1RA on liver metabolic health.

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Table 1: Laboratory Values at Baseline and 12 Months with GLP1-RA				
	Baseline	12 Months	Δ 12-Baseline	p-value
ALT, median (Q1, Q3)	29.0 (21.0, 46.0)	29.5 (21.0, 44.0)	-1.0 (-10.0, 6.0)	**0.039**
N	324	304	255	
FIB-4, median (Q1, Q3)	1.18 (0.85, 1.77)	1.17 (0.84, 1.75)	0.02 (-0.03, 0.03)	**0.005**
N	267	263	263	
BMI, median (Q1, Q3)	36.6 (32.1, 41.8)	35.8 (31.1, 41.0)	-0.8 (-2.2, 0.5)	**<0.001**
N	388	366	352	
TG, median (Q1, Q3)	158.0 (115.5, 229.0)	152.0 (111.0, 219.0)	-9.0 (-59.0, 33.5)	0.058
N	292	255	204	
LDL, median (Q1, Q3)	83.0 (59.0, 114.0)	84.0 (60.0, 112.0)	-3.0 (-19.0, 11.0)	0.047
N	289	247	195	
HDL, median (Q1, Q3)	41.0 (35.0, 48.0)	40.0 (35.0, 50.0)	0.0 (-3.0, 4.4)	0.110
N	292	255	204	
AST, median (Q1, Q3)	27.0 (20.0, 38.0)	26.0 (21.0, 37.0)	-2.0 (-8.0, 4.0)	**0.006**
N	322	299	251	
HBA1C, median (Q1, Q3)	8.0 (6.9, 9.5)	7.0 (6.3, 8.4)	-0.6 (-1.8, 0.1)	**<0.001**
N	391	355	344	

Disclosures: Reeti Gulati: Nothing to Disclose, Rachel Lee: Nothing to Disclose, Lucas Collins: Nothing to Disclose, Berline Francis: Nothing to Disclose, Alice Parish: Nothing to Disclose, Donna Niedzwiecki: Toray Industries, Inc.: DSMB member, Cancer Prevention and Research Institute of Texas: Scientific Reviewer, Amreen Dinani: Madrigal Pharmaceuticals: Consultant, Novo Nordisk: Consultant, Guidepoint: Consultant

3230 | IMPROVEMENTS IN NON-INVASIVE MARKERS OF MASH AND FIBROSIS WERE ASSOCIATED WITH HISTOLOGICAL MASH RESOLUTION WITH TIRZEPATIDE TREATMENT OF NON-CIRRHOTIC MASH ◆

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Background: Tirzepatide (TZP) is a long-acting GIP/GLP-1 receptor agonist. The SYNERGY-NASH trial (NCT04166773) randomized 190 patients with biopsy-confirmed MASH, stage 2 or 3 fibrosis and NAS ≥ 4 to receive once-weekly s.c. TZP (5 mg, 10 mg or 15 mg) or placebo (PBO) for 52 weeks. Among 155 participants who completed the study on treatment with evaluable liver biopsies (efficacy analysis set; EAS), MASH resolution

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without worsening of fibrosis was achieved by 51.8%, 62.8% and 73.3% with TZP 5, 10, and 15 mg, respectively, and by 13.2% with PBO. This post hoc analysis explored the relationship between changes in non-invasive tests (NITs) and responder status for this histological endpoint **Methods:** Comparisons among treatment groups for NITs were analyzed with a mixed model for repeated measures based on participants with available data in the EAS. Chi-square test and T-test were used to analyze changes in NITs by histological responder status; all treatment groups, including PBO, were pooled for this analysis. **Results:** Statistically significant reductions in ALT, AST, GGT, NIS4®, ELF (Enhanced Liver Fibrosis), Pro-C3 (type III collagen formation), cytokeratin-18 (CK-18; M30 and M65 antigens), FIB-4, MRI proton density fat fraction (PDFF), iron-corrected T1 (cT1), and VCTE liver stiffness measure (LSM) were observed across all 3 TZP treatment groups compared with PBO (P<0.01 for all NITs). Reductions in ALT, AST, GGT, NIS4®, MRI-PDFF, and cT1 were significantly greater among participants achieving MASH resolution without worsening of fibrosis (responders) compared with those not achieving this endpoint (non-responders). In contrast, changes in CK-18, Pro-C3, ELF, FIB-4 and VCTE LSM did not differ significantly between responders and non-responders (Table). The proportion of patients achieving the high specificity cutoff of the MASH Resolution Index (comprising MRI-PDFF, ALT and AST; doi: 10.1136/gutjnl-2023-331401) was significantly higher in responders (78.7%) than non-responders (40.4%; P<0.001). **Conclusion:** In the SYNERGY-NASH trial, significant reductions in multiple NITs were observed with TZP compared with PBO. MASH resolution without worsening of fibrosis was associated with significantly greater improvements in NITs that assessed liver injury, liver fat and MASH disease activity compared to non-responders. Despite significant TZP treatment effects, changes in fibrosis NITs were not consistently associated with MASH resolution.

NIT	MASH resolution responder Mean (95% CI)	MASH resolution non-responder Mean (95% CI)	P value
ALT (% change)*	-57.3 (-62.4, -52.2)	-22.1 (-33.1, -11.0)	<0.001
AST (% change)*	-45.7 (-51.8, -39.6)	-16.9 (-29.1, -4.8)	<0.001
GGT (% change)*	-46.5 (-53.1, -39.8)	-15.0 (-25.5, -4.6)	<0.001
NIS4® (absolute change)	-0.45 (-0.52, -0.38)	-0.18 (-0.25, -0.12)	<0.001
MRI-PDFF, % (absolute change)	-11.1 (-13.0, -9.2)	-5.5 (-7.7, -3.4)	<0.001
MRI-PDFF (% change)	-62.4 (-68.7, -56.0)	-22.9 (-39.1, -6.7)	<0.001
cT1, msec (absolute change)	-102.3 (-122.6, -82.0)	-62.3 (-90.3, -34.3)	0.020
CK-18 (M30), U/L (absolute change)	-319.5 (-405.9, -233.2)	-216.6 (-362.2, -71.0)	0.223
CK-18 (M65), U/L (absolute change)	-608.8 (-757.2, -460.3)	-379.12 (-587.4, -170.9)	0.074
Pro-C3, µg/L (absolute change)	-47.1 (-59.7, -34.6)	-29.3 (-47.3, -11.2)	0.106
ELF (absolute change)	-0.48 (-0.64, -0.32)	-0.31 (-0.51, -0.10)	0.170
FIB-4 (absolute change)	-0.24 (-0.34, -0.13)	-0.15 (-0.31, 0.00)	0.379
VCTE LSM, kPa (absolute change)	-3.5 (-4.6, -2.4)	-2.6 (-3.8, -1.5)	0.289

Data are presented as mean (95% CI) unless otherwise stated. *Due to skewed distributions, liver enzymes were analyzed after log transformation and reported as percentage change.

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3231 | SELECTIVE INHIBITION OF NTRK3 ON HEPATIC STELLATE CELLS BY A SMALL MOLECULE (LOXO195) ATTENUATES HCC AND FIBROSIS IN ADVANCED MOUSE MASH AND HUMAN LIVER SLICES

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Background: We previously uncovered a novel role of Ntrk3 in driving autocrine HSC signaling in advanced fibrosis (Wang, Sci Trans Med, 2023). In this study, we explored the inhibitory activities of an NTRK3 inhibitor, LOXO195, in a well-established murine model (FAT-MASH) induced by diet and carbon tetrachloride (CCl_4), which develops advanced fibrosis and hepatocellular carcinoma. We also investigated the effects of LOXO195 in human precision-cut liver slices (hPCLS) generated from explant livers of patients with MASH or viral hepatitis. **Methods:** (1) Male wild-type black mice were maintained on a Western diet (WD) and sugar water (SW) combined with a low dose of weekly intraperitoneal injections of CCl_4 for 24 weeks to induce cirrhosis and HCC. From week 18 to week 24, animals were orally administered either LOXO195 (10 mg/kg) or vehicle (1.5% Carboxymethylcellulose in water) once daily for 5 days/week. LOXO195 is a small molecule NTRK3 inhibitor. After 24 weeks the animals were sacrificed, liver and blood samples were harvested. (2) Human precision-cut liver slices (hPCLS) were treated with either LOXO195 (0.5 or 1.0 μM dosing) or vehicle (DMSO) for 48 hours. The liver slices and conditioned media were collected. **Results:** (1) In advanced FAT-MASH, LOXO195 treatment reduced the number and size of liver surface tumors despite a short, 6 wk treatment interval. Hepatic Col1a1 and Acta2 protein and gene expression were significantly downregulated by LOXO195, associated with reduced HSC activation (Figure 1). LOXO195 suppressed MASH-associated fibrosis in the tumor stroma based on morphometry of Sirius red staining. (2) In hPCLS, LOXO195 treatment significantly reduced Col1a1 and Acta2 mRNA expression associated with significantly reduced Col1a1 secretion by ELISA. **Conclusion:** These findings establish, for the first time, that specific, HSC-directed therapy can attenuate HCC development without directly targeting the tumor. This is a major conceptual advance that introduces the possibility of HSC-directed therapy that antagonizes Ntrk3 for use in human HCC prevention and/or treatment.

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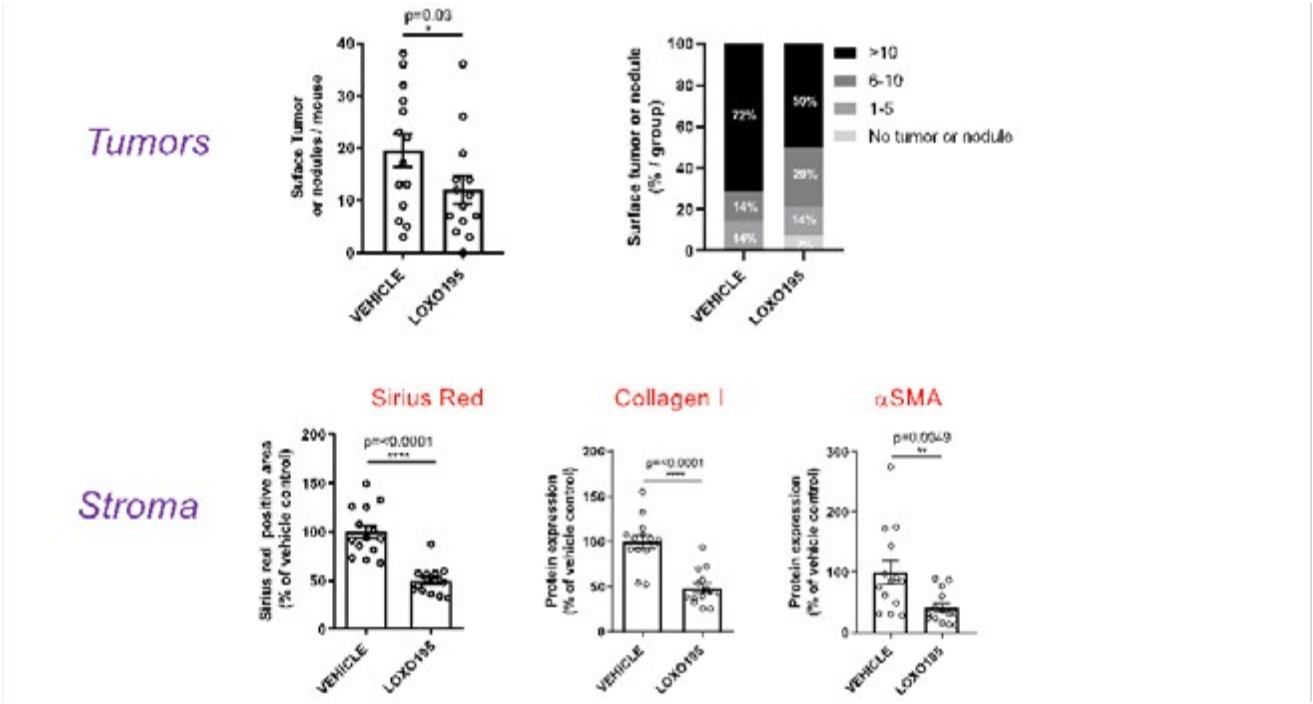

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3232 | FUNCTIONAL DYNAMICS OF MASH REGRESSION ASSOCIATED MACROPHAGES (RAM)

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Background: While macrophage (MF) heterogeneity in Metabolic dysfunction-associated steatohepatitis (MASH) is well-documented, how MF diversity and functionality are altered during MASH regression remains obscure. We elucidate the MF heterogeneity and their functional dynamics during MASH progression and compare them to that in MASH regression. Understanding the signaling pathways that drive MASH/fibrosis resolution will lead to the identification of novel therapeutic targets and strategies. **Methods:** MASH Regression was modeled by switching 12w western diet-fed Alms1$^{-/-}$ (Foz/Foz) mice to normal chow for an additional 8w. We employed a multifaceted approach, integrating single-cell RNA sequencing (scRNAseq), single-nucleus RNA sequencing (snRNAseq), flow cytometry, biochemical assays, and immunostaining techniques to understand the MF behavior during MASH progression and regression. **Results:** During MASH, embryonic liver resident Kupffer cells (EmKCs) are lost and are replaced by four distinct monocyte-derived MF subclusters: 1) Ly6c^{hi} 2) Mac1 (Itgax^{hi}) 3) Lipid-associated MF (LAM) (Spp1^{hi}, Gpnmb^{hi}) and 4) Monocyte-derived Kupffer cells (MoKC) (Vsig^{+}, Clec4f^{+}, Clec1b^{+} but Timd4^{-}). Both LAM and MoKC highly express Trem2. During MASH regression, hepatic stellate cells (HSCs) underwent either apoptosis or transitioned to an inactivated phenotype, thereby forming a distinctive cluster in scRNAseq analyses. In contrast, no new clusters emerged in scRNAseq analysis of the RAMs. RAMs mostly co-localized with MASH-associated MF. MoKC and LAM were enriched in disease-resolving pathways and expressed high levels of restorative MF gene signatures. Interestingly, while MoKC was the most abundant MF population during MASH,

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they shrunk during regression and LAM became the dominant MF subtype during regression and maintained high Trem2 expression. Trem2 not only protects against MASH progression but is also essential for effective MASH resolution. These findings suggest that the RAMs, which maintain LAM gene signatures including high Trem2 expression, perform critical reparative functions during MASH regression. Moreover, the absence of Trem2 promotes the emergence of the pro-inflammatory Ly6c^{hi} MF while restricting the emergence of beneficial LAMs. **Conclusion:** This study elucidates several previously unexplored aspects of MF behavior in MASH regression. For example, it shows that the healthy liver EmKCs that are lost during MASH do not come back promptly during regression. Furthermore, RAMs that retain the LAM gene signature, particularly high Trem2 expression, are enriched in restorative MF gene signatures. Trem2 is critical for effective MASH resolution. Finally, Trem2 functions partly by promoting the emergence of the restorative LAM and by restricting the inflammatory Ly6c^{hi} MF population, in addition to its role in collagen degradation.

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3233 | MASH 2B TRIALS- A SYSTEMATIC REVIEW

Bipneet Singh[1] Sruthi Ramanan[1] Gurleen Kaur[2] Waryaam Singh[3] Merritt Bern[1]

[1]Henry Ford Health Jackson, [2]GMCH Amritsar, [3]DMCH Ludhiana

Background: Non-alcoholic fatty liver disease (NAFLD), now termed metabolic dysfunction-associated fatty liver disease (MAFLD), is the leading cause of chronic liver disease in the U.S., encompassing conditions from simple steatosis to cirrhosis and hepatocellular carcinoma. Early symptoms like fatigue and abdominal pain are non-specific, often delaying diagnosis until advanced stages. Systemic insulin resistance leads to lipid accumulation in the liver, triggering inflammatory responses. The gut microbiome and gut-liver axis also play significant roles. Diagnosis uses the NAFLD Activity Score (NAS) and the NASH Clinical Research Network (CRN) fibrosis score to assess disease activity and progression. Treatments emphasize weight loss and lifestyle changes, with promising pharmacological options targeting insulin sensitivity, lipid metabolism, and inflammation. These include PPAR agonists, SGLT-2 inhibitors, GLP-1 inhibitors, and the recently approved Resmetirom. Current research focuses on phase 2b trials to evaluate the efficacy and safety of these treatments. **Methods:** This study follows PRISMA-2020 guidelines. Three researchers conducted a literature search across multiple databases for phase 2b trials from the past 5 years. Studies were selected using PICO criteria and data were extracted per the Cochrane Handbook. Quality assessment was done using the Cochrane Risk of Bias Tool (2.0). **Results:** This study includes 11 randomized control trials (RCTs), all double-blinded, with 10 being placebo-controlled, involving adults with histologically confirmed NASH. The trials ranged from 100 to 392 participants. PPAR agonists were tested in the EMMINENCE and NATIVE trials, with NATIVE showing significant fibrosis and NASH resolution at higher doses. FGF21 and FGF19 pathways were targeted in six trials. The Harmony trial with efruxifermin showed significant fibrosis improvement, while the Enliven trial with pegozafermin also demonstrated significant fibrosis reduction at higher doses. The Falcon trials with pegbelfermin did not achieve significant primary outcomes. Alpine 2/3 and Alpine 4 trials with aldafermin showed mixed results, with significant fibrosis improvement only in specific doses. The TANDEM trial, comparing Tropifexor and Cenicriviroc, focused on safety and efficacy, showing ALT, AST, and GGT reductions. ICONA trial with Icosabutate showed potential in NASH patients with T2DM. Belapectin, a galectin-3 inhibitor, did not significantly reduce portal pressure. Outcomes frequently measured NAS or SAF score improvements, highlighting potential in combined drug mechanisms and specific comorbidities. **Conclusion:** RCTs in NASH treatment showed mixed outcomes. Lanifibranor and icosabutate showed promise, especially in T2D patients. FGF21 analogues like efruxifermin improved fibrosis, while FGF19 trials had variable results. Further research is needed.

Disclosures: Bipneet Singh: Nothing to Disclose, Sruthi Ramanan: Nothing to Disclose, Gurleen Kaur: Nothing to Disclose, Waryaam Singh: Nothing to Disclose, Merritt Bern: Nothing to Disclose

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3234 | SURGE IN INCIDENCE AND PREVALENCE OF AUTOIMMUNE HEPATITIS SINCE THE COVID-19 PANDEMIC ◆

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Background: The COVID-19 pandemic, emerging in early 2020, has profoundly reshaped global health landscapes. The virus infection, as well as the new vaccine technologies, may impact immune system dynamics and leading to a surge in autoimmune diseases like autoimmune hepatitis (AIH). Understanding the pandemic's influence on AIH incidence is essential for guiding clinical and public health strategies. **Methods:** We conducted retrospective analysis comparing AIH (ICD-10 code K75.4) incidence rates and prevalence during the pandemic (2020-2023) with pre-pandemic rates (2016-2019) using data from TrinetX, a global federal health research network including 84 large healthcare organizations. Statistical methods assessed changes in incidence rates over time. **Results:** Analysis of 80,704,920 patients' data revealed a notable increase in AIH incidence rate and prevalence since the pandemic. The incidence rate nadir in 2020 at 0.032 cases/100,000 person-day, which nearly doubled by 2023 (0.073 cases/100,000 person-day), and has not yet peaked. Prevalence steadily rose, with a significant slope increase after 2021, reaching 93.3 per 100,000 people in 2023, nearly double the pre-pandemic rate (56.3 per 100,000 people in 2019).Stratification by race/ethnicity showed potential disparities, notably in the American Indian/Alaska Native patient population, with incidence rate and prevalence both surpassing the second largest patient population, Asians. While the incidence rate of American Indians/ Alaska Natives was 54.85% compared to Asians in 2016, it increased to 3.5-fold in 2023. Correspondingly, the prevalence of AIH in Indians/Alaska Natives increased from 54.7 to 169.4 per 100,000 people, which is a more than threefold increase. **Conclusion:** Our study reveals a concerning AIH incidence rise since the pandemic, emphasizing the need for heightened awareness, proactive screening strategies, patient education, and ensuring continued access to healthcare services amidst pandemic-related disruptions. Further research should explore underlying mechanisms driving the observed increase in AIH incidence and develop targeted interventions aimed at reducing disease burden and improving patient outcomes. Addressing the impact of the COVID-19 pandemic on autoimmune diseases such as AIH is crucial for optimizing clinical management and public health responses in the post-pandemic era.

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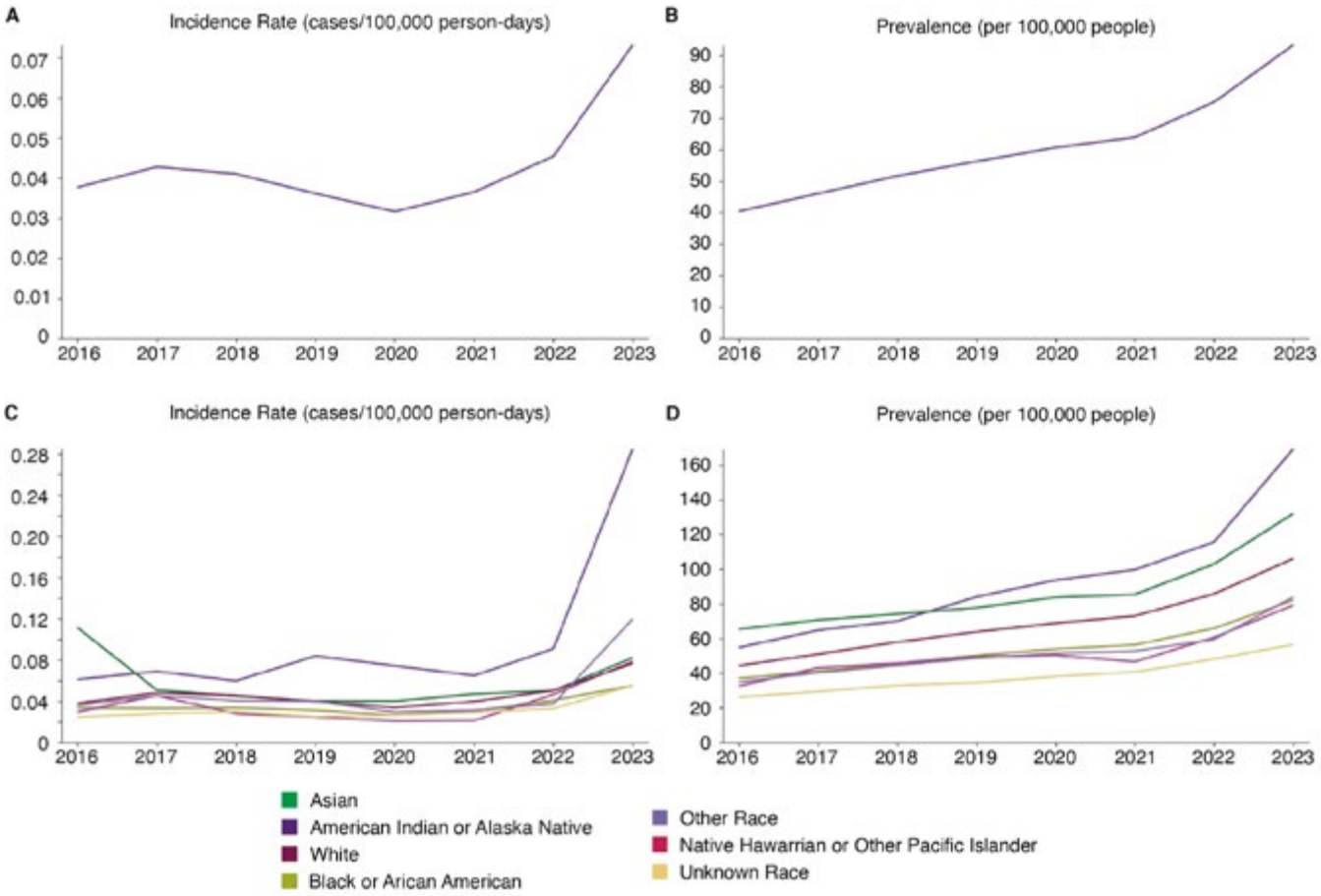

Disclosures: Yuting Huang: Nothing to Disclose, Yichen Wang: Nothing to Disclose, Liu Yang: Nothing to Disclose

3235 | QUALITY IMPROVEMENT FOR VIBRATION CONTROLLED TRANSIENT ELASTOGRAPHY USING A NOVEL ANALYSIS ALGORITHM

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Background: Vibration controlled transient elastography (VCTE) is a non-invasive modality for fibrosis staging and risk stratification in chronic liver disease with rapidly increasing use. However, correlation of reported liver stiffness measurement (LSM) with histologic fibrosis stage remains imperfectly defined, particularly at intermediate degrees of fibrosis and subject to variability by etiology of disease. In March 2023, the Cleveland Clinic updated VCTE outputs to report LSM as a certain probability of underlying fibrosis across a distribution (F1-2, F3-4, F4), stratified by etiology of liver disease. This study sought to obtain feedback from ordering providers about this new reporting algorithm and its implications for patient care. **Methods:** We conducted an email-based, 9-item survey of hepatology providers at Cleveland Clinic (Figure 1). The Likert questions ranged from 1 to 5 (strongly disagree to strongly agree). Responses ≥4 were defined as favorable (i.e., positive), and each question was aggregated to create 3 categories: favorable, neutral, and not favorable. **Results:** A total of 26 providers completed the survey (response rate: 84%). The majority of providers rated the new reporting algorithm more favorably than the conventional algorithm in the following areas (Table 1): ease of explanation to patients (50%, median [IQR]): 3.5 [2.25-4.0]); ease of understand patients' stage of fibrosis (69%, 4 [3-4]); ease of monitoring fibrosis progression (62%, 4 [3-4]); ease of communication with referring provider (62%, 4 [3-4]); and format desirability (77%, 4 [4-4]). The majority of providers rated patients' preferability for the new reporting algorithm as neutral (60%, 3 [3-3]). Similarly, patients' ease of understanding was overall split, with 38% favorable, 23% neutral, and 38% non-favorable (3[2-4]) responses. However, the majority rated favorably that the new reporting

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algorithm caused less confusion for patients than the conventional algorithm reporting method when biopsy and VCTE results are divergent (73%, 4[3.25-4]). **Conclusion:** Overall, hepatology providers find a probabilistic reporting of LSM on VCTE to more favorably facilitate their understanding of patients' fibrosis, communication with referring providers, and longitudinal surveillance; patients find it most helpful when biopsy and VCTE are not concordant. Nonetheless, refinements to this reporting output are needed to enhance patients' understanding of test results.

Table 1. Comparative Thoughts and Preferences between Probabilistic Vs. Conventional Algorithm Reporting

Question Item	Favorable	Neutral	Not Favorable	
	n (%)	n (%)	n (%)	Median [IQR]
Providers' Thoughts and Preferences	83 (64%)	26 (20%)	21 (16%)	
Ease of explanation to patients	13 (50 %)	6 (23%)	7 (27%)	3.5 [2.25-4]
Ease of understanding patient's stage of fibrosis	18 (69%)	4 (15%)	4 (15%)	4 [3-4]
Ease of monitoring fibrosis progression	16 (62%)	8 (31%)	2 (8%)	4 [3-4]
Ease of communication with referring provider	16 (62%)	6 (23%)	4 (15%)	4 [3-4]
Preference of format providers	20 (77%)	2 (8%)	4 (15%)	4 [4-4]
Patients' Thoughts and Preferences from the Perspective of Providers	35 (45%)	23 (30%)	19 (25%)	
Ease of understanding by patient	10 (38%)	6 (23%)	10 (38%)	3 [2-4]
Clarity with discordant biopsy results	19 (73%)	2 (8%)	5 (19%)	4 [3.25-4]
Patients' preferability	6 (24%)	15 (60%)	4 (16%)	3 [3-3]

Disclosures: Jeffrey Schwartz: Nothing to Disclose, Shalini Tripathi: Nothing to Disclose, Omar Sims: Nothing to Disclose, William Carey: Nothing to Disclose, Dian Chiang: Nothing to Disclose

3236 | TIMELY POST-DISCHARGE FOLLOW-UP AFTER A FIRST DIAGNOSIS OF CIRRHOSIS IS ASSOCIATED WITH REDUCED MORTALITY AND REHOSPITALIZATION IN A LARGE NATIONAL COHORT

Max Schechter[1] Linnea Widman[2] Axel Wester[2] Ying Shang[2] Per Stål[2] Don Rockey[3] Hannes Hagström[2]

[1]University of Pennsylvania, [2]Karolinska Institutet, [3]Montefiore Medical Center

Background: Timely transition of care among patients with a first diagnosis of cirrhosis in a hospital to an outpatient visit is important. We evaluated rates of outpatient follow-up after a first diagnosis of cirrhosis in an inpatient setting, and its association with the subsequent rates of rehospitalization and mortality. **Methods:** We conducted a population-based cohort study identifying all hospitalized patients in Sweden diagnosed with a new diagnosis of cirrhosis between 2002 and 2020 from the Swedish National Patient Register. The primary outcome was defined as an outpatient visit related to cirrhosis within 90 days after hospital discharge. Secondary outcomes were rates of rehospitalization and mortality within 1 year of discharge in patients receiving outpatient follow-up within 90 days or not, starting follow-up at 90 days after initial discharge. A sensitivity analysis examined 30-day follow-up instead of 90 days. Cox regression was used for all analyses and incidence rates per 1000 person-years were calculated for mortality and rehospitalization. **Results:** Of 8,852 patients, 3,759 (42%) had outpatient follow-up within 90 days of discharge, with higher rates of early follow-up during the later study period (57% in 2017-2020 vs 33% in 2002-2006, aHR=2.08, 95%CI=1.89-2.29). Patients who received follow-up within 90 days of discharge were younger (median age 62 vs. 65, p<0.001), had a higher level of education (18.8% vs. 14.2% with 12+ years education, p<0.001), and were more likely to have liver decompensation or HCC (54% vs 43%, p<0.001) compared to those without timely follow-up. In an unadjusted analysis, follow-up within 90 days was associated with lower rates of one year mortality (HR=0.78, 95%CI=0.66–0.92) and rehospitalization (HR=0.89, 95%CI=0.81–0.97). After adjusting for age, sex, year of diagnosis, country of birth, education, cirrhosis etiology,

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baseline healthcare utilization, and the presence of decompensation or HCC, these estimates were attenuated for mortality (aHR=0.86, 95%CI=0.72–1.02) and rehospitalization (aHR=0.95, 95%CI=0.87–1.05). Similar trends were found when examining outpatient follow-up within 30 days. **Conclusion:** In Sweden, 42% of hospitalized patients with newly diagnosed cirrhosis receive outpatient follow-up within 90 days of their hospital discharge. These patients may experience lower mortality and lower rehospitalization rates within one year. Further investigation in novel healthcare delivery models to help improve transitions of care are needed for this vulnerable population.

Table 1: 1-year rehospitalization and 1-year mortality amongst patients with cirrhosis with follow-up compared to patients without follow-up. Incidence rates per 1000 person-years, and hazard ratio and adjusted hazard ratios of patients with follow-up compared to patients without follow-up. Included are all studied definitions of early follow-up looking at 30 days, 90 days, and different cirrhosis-relating coding. Adjusted hazard ratios were adjusted for age, sex, year of diagnosis, country of birth, education, cirrhosis etiology, baseline healthcare utilization, and the presence of decompensation or HCC.

	Rehospitalization within 1 year			Mortality within 1 year		
Early Follow-Up Definition	N	Hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)	N	Hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)
Within 90-days	4,023			4,037		
Cirrhosis related code as primary diagnosis		0.89 (0.81 – 0.97)	0.95 (0.87 – 1.05)		0.78 (0.66 – 0.92)	0.86 (0.72 – 1.02)
Any outpatient visit		0.97 (0.87 – 1.08)	0.99 (0.89 – 1.10)		0.72 (0.60 – 0.86)	0.76 (0.63 – 0.92)
Within 30-days	5,886			5,932		
Cirrhosis related code as primary diagnosis		0.92 (0.86 – 0.99)	0.97 (0.90 – 1.05)		0.84 (0.74 – 0.95)	0.93 (0.82 – 1.05)
Any outpatient visit		1.01 (0.95 – 1.08)	1.00 (0.94 – 1.07)		0.88 (0.79 – 0.98)	0.91 (0.82 – 1.02)

Disclosures: Max Schechter: Nothing to Disclose, Linnea Widman: Nothing to Disclose, Axel Wester: Nothing to Disclose, Ying Shang: Nothing to Disclose, Per Stål: AstraZeneca: Speaking and Teaching, Don Rockey: Grant/Research Support relationship with Versantis; Has not ended; Grant/Research Support relationship with AstraZeneca; Has not ended; Grant/Research Support relationship with Ipsen; Has not ended; Grant/Research Support relationship with Boehringer Ingelheim; Has not ended; Consultant relationship with WL Gore and Associates; Has not ended; Grant/Research Support relationship with Gilead; Has not ended; Grant/Research Support relationship with Durect; Has not ended; Consultant relationship with BD Medical; Has not ended; Consultant relationship with Cook Medical; Has not ended; Grant/Research Support relationship with Intercept; Has not ended; Grant/Research Support relationship with Inventiva; Has not ended; Grant/Research Support relationship with Madrigal; Has not ended; Grant/Research Support relationship with Ocelot; Has ended; Grant/Research Support relationship with Bio89; Has not ended; Grant/Research Support relationship with Salix; Has not ended; Grant/Research Support relationship with Novonordisk; Has not ended; Grant/Research Support relationship with Viking; Has ended; Grant/Research Support relationship with Galectin; Has not ended, Hannes Hagström: Nothing to Disclose

3237 | PATIENT PERCEPTIONS OF UNDERGOING ROUTINE VIRAL HEPATITIS SCREENING AND RECEIVING A HEPATITIS C (HCV) DIAGNOSIS WHILE INCARCERATED: A QUALITATIVE STUDY

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Background: Justice-involved individuals are disproportionately impacted by hepatitis C (HCV), with 16-41% having a positive HCV antibody and 12-35% being chronically infected, compared with only one percent of the overall

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United States population having HCV antibodies present. The most common risk factor for HCV transmission in correctional settings is injection drug use. Significant barriers to HCV screening remain in correctional facilities, including short lengths of stay and population turnover, varied resources among facilities, and onsite healthcare capacity. Prior research conducted within the Santa Clara County (SCC) Jail showed that knowledge of HCV, perception of individual risk, and perceived coercion to participate in such a program impacted an individual's willingness to participate in routine HCV screening. The purpose of this study was to understand patient perceptions of undergoing routine viral hepatitis screening and receiving a diagnosis of HCV while incarcerated. **Methods:** A qualitative design was employed using a 13-item semi-structured interview guide to assess patient perceptions of routine testing, feelings about diagnosis of HCV, HCV knowledge and confidence in ability to follow-up. Interviews were conducted among individuals newly diagnosed with HCV via routine screening in the SCC Jail between March – November 2023. Data were analyzed using thematic analysis. **Results:** Of the 15 participants, most were within the 35-44 (47%) and 25-34 (40%) age ranges, White or Caucasian (47%), and all were male. Nine themes emerged: (1) risk perception as motivator for testing; (2) testing convenience to maintain health; (3) minimal to no prior testing experience; (4) mixed experiences testing in the jail; (5) negative to neutral reactions to HCV diagnosis; (6) intrinsic motivation to get treated; (7) basic HCV knowledge after diagnosis; (8) seamless treatment experience in the jail; and (9) perceived barriers to continuing care upon release. Patients expressed positive perceptions of the HCV screening program implemented within the SCC Jail, stating ease and convenience as major reasons for undergoing HCV screening upon admission. Patients also expressed positive experiences receiving health education and counseling upon diagnosis to better understand their HCV diagnosis and treatment and care options. **Conclusion:** Routine HCV screening as an evidence-based intervention reduced barriers to testing; correctional facilities may consider offering similar programming to their populations.

Figure 1 - Flow Diagram of the Routine HCV Screening Program for Patients Newly Diagnosed with HCV in the Santa Clara County Jail



Disclosures: Harit Agroia: Nothing to Disclose, Kristin Walsh: Nothing to Disclose, Rajvinder Gill: Nothing to Disclose

3238 | HOPE FOR THE BEST, PREPARE FOR THE WORST: INTEGRATING PALLIATIVE CARE WITH LIVER TRANSPLANT CANDIDATE EVALUATION AND MANAGEMENT

Jesslyn McMahon[1] *David Kramer*[1] *Ajay Sahajpal*[1]

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Background: Liver transplantation (LT) presents a paradox of hope and fear as decompensation brings patients simultaneously closer to transplantation and closer to death. Historically, palliative care (PC) is involved late

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in the care of these patients, if at all, because of the misperception that it stands in opposition to the effort dedicated by transplant clinicians to achieve successful patient care and transplant outcomes. Clinicians are focused on identifying and eliminating obstacles to liver transplantation. However, this intensity may overwhelm the patient's understanding of their medical condition and risk, benefit and burden assessment of the proposed care. Significant emotional, psychological, financial, and physical distress for patients and their caregivers may result but remain unrecognized and unsupported. A PC specialist could alleviate some of this distress as well as assist with communication, support, and planning. **Methods:** The LT and PC services agreed to integrate a palliative care provider with a background in liver disease and surgical ICU practice into the liver transplant evaluation. This PC provider evaluated all potential transplant candidates irrespective of etiology or severity of liver disease, inpatient or outpatient setting, or insurance status. Patient comprehension and values were assessed, and PC provider collaborated with transplant teams to communicate bidirectionally the plan of care and patient preferences to facilitate timely advance care planning. Patient wishes, insight, and preparedness were discussed with patients and caregivers and presented to the Transplant Selection Committee for incorporation in the full evaluation discussion. PC continued to follow as indicated for ongoing discussions throughout their clinical trajectory regardless of whether the patient was declined, deferred, or listed. **Results:** During an 11-month period (12/2022-10/2023) there were 234 overall PC visits in LT candidates, including 189 inpatient and 45 outpatient visits. Early integration of palliative medicine with the transplant medicine and surgery services was well received and increased overall acceptance and utilization of PC. The process has improved the consistency of messaging and understanding for the patients and the transplant clinicians. **Conclusion:** Early integration of PC in the evaluation and management of patients with liver failure was welcomed by patients and transplant clinicians without compromise of patient outcomes. Integrating PC with the advanced liver disease population provides benefit to the patient, caregivers, and healthcare, regardless of transplant candidacy. We now have the opportunity to investigate the impact of integration of palliative care and transplant services with respect to completion of candidate evaluation, waitlist mortality, transplant rate as well as patient and clinician satisfaction.

Disclosures: Jesslyn McMahon: Nothing to Disclose, David Kramer: Nothing to Disclose, Ajay Sahajpal: Boston Scientific: Speaker

3239 | RISING PROPORTION OF HISPANICS AND WOMEN WITH STEATOTIC LIVER DISEASE-RELATED END-STAGE LIVER DISEASE AND HEPATOCELLULAR CARCINOMA AWAITING LIVER TRANSPLANTATION IN THE UNITED STATES

Shyam Patel[1] Wei Zhang[2] Ashwani Singal[3] Ramsey Cheung[4] Robert Wong[5]

[1]California Pacific Medical Center, [2]Massachusetts General Hospital, [3]University of Louisville, [4]Stanford University Medical Center, [5]VA Palo Alto Healthcare System

Background: Steatotic liver disease (SLD), including alcohol-associated liver disease (ALD) and metabolic-dysfunction associated steatotic hepatitis (MASH), is the most common indication for liver transplantation (LT) in the U.S. We aim to assess trends in the changing epidemiology of LT waitlist registrants with SLD in the U.S. in the last decade. **Methods:** Using data from the 2014-2023 United Network for Organ Sharing registry, adult LT waitlist registrants (≥18 years old) with SLD were identified using primary and secondary diagnosis codes. Changes in the proportion of patients with SLD by age groups, gender, race/ethnicity were evaluated overall as well as stratified by those with and without hepatocellular carcinoma (HCC). Statistical analyses utilized the z-statistic and trends test. **Results:** From 2014 to 2023, out of all WL registrants, the proportion of those with SLD increased from 39.9% to 68.6%. Of 65,675 adults with SLD awaiting LT [median age [IQR] 57 years [50-64], 65.1% men, 75.0% non-Hispanic White, 3.2% African American, 17.9% Hispanic, 2.5% Asian/Pacific Islander, 1.1% American Indian/Alaska Native, 17.2% HCC], 55.5% had ALD and 44.5% had MASH. Among registrants with SLD, there was a significant increase in the proportion of younger adults (18-49 years old) (19.5% in 2014 to 29.4% in 2023, p<0.01) and Hispanics (16.1% in 2014 to 20.0% in 2023, p<0.01). Similar patterns were observed among SLD waitlist registrants without HCC. Among those with MASH, a growing proportion were older adults (≥60 years old) (55.4% in 2014 to 61.8% in 2023, p<0.01) and Hispanics (16.6% in 2014 to 22.5% in 2023) (Figure 1). Among non-HCC MASH registrants, a significant rise in the proportion of women was observed, such that the majority of non-HCC MASH waitlist registrants in 2023 were women (46.9% in 2014 to 51.8% in 2023). Among those with ALD, we observed an increase in the proportion of younger adults (26.7% in 2014 to 40.7% in 2023, p<0.01) and women (25.2% in 2014 to 30.9% in 2023, p<0.01). Similar trends were observed among ALD

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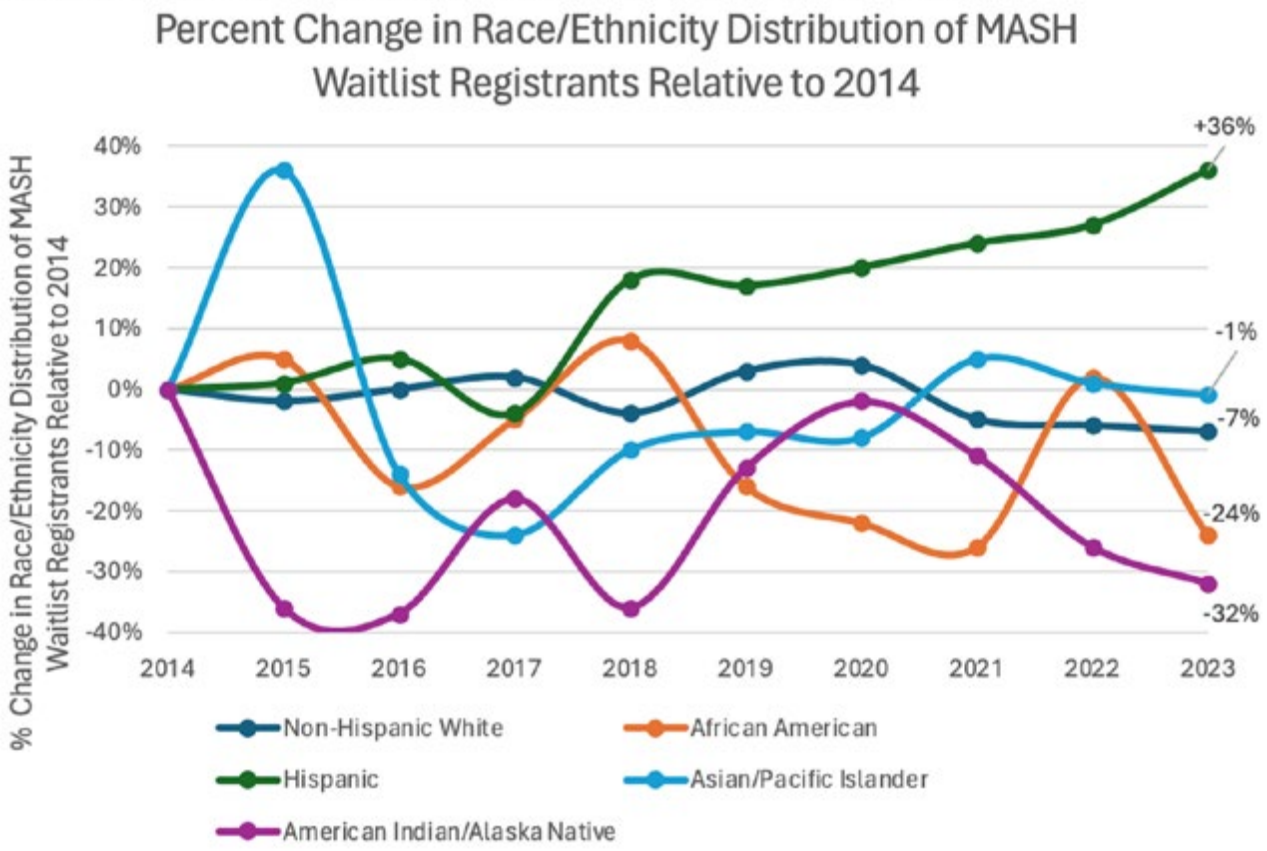
sub-groups with or without HCC. **Conclusion:** Among LT registrants with SLD, there is an increasing proportion of younger adults and Hispanics. An increasing proportion of LT registrants with MASH are older adults and Hispanics. Conversely, a growing proportion of LT registrants with ALD are younger adults and women. These findings emphasize the need to enhance cardiometabolic health and curb unhealthy alcohol use among these populations.

Figure 1. Percent change in race/ethnicity distribution of MASH waitlist registrants relative to 2014



Disclosures: Shyam Patel: Nothing to Disclose, Wei Zhang: Nothing to Disclose, Ashwani Singal: Advisor relationship with CLD Foundation; Has not ended; Speaking and Teaching relationship with Medical Speaker's Network; Has not ended; Speaking and Teaching relationship with Madrigal; Has not ended; Stock â€“ privately held company relationship with Pleiogenix; Has not ended; Consultant relationship with Pleiogenix; Has not ended; Advisor relationship with Durect; Has ended; Royalties or patent beneficiary relationship with Up-to-Date; Has not ended; Executive role relationship with Gastro Endo News; Has not ended; Grant/Research Support relationship with NIAAA; Has not ended; Employee relationship with Avera Medical Group; Has ended; Grant/Research Support relationship with GSK; Has not ended; Employee relationship with University of Louisville School of Medicine; Has not ended; Speaking and Teaching relationship with Medscape; Has not ended, Ramsey Cheung: Nothing to Disclose, Robert Wong: Theratechnologies: Grant/Research Support, Durect: Grant/Research Support, Gilead Sciences: Grant/Research Support, Exact Sciences: Grant/Research Support, Theratechnologies: Grant/Research Support, Durect Corporation: Grant/Research Support

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3240 | POOR ACCESS TO ANTI-OBESITY MEDICATIONS IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE

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Background: Weight loss has been the cornerstone therapy for MASLD. Incretin medications (IM) including glucagon-like peptide 1 receptor agonists (GLP-1 RAs) and glucose dependent insulinotropic polypeptide/ GLP-1 RAs have been FDA approved for weight management. While effective for weight loss, these medications can often be difficult for patients to access. This study sought to determine accessibility to IM in the MASLD population. **Methods:** A 10-month, single center retrospective chart review was conducted for patients referred to clinical pharmacist practitioner (CPP) for review of pharmacological weight loss options as part of a multidisciplinary MASLD team between 3/2023 -12/2023. Fibrosis stage as measured by vibration controlled transient elastography and approval or denial from various payers (Commercial, Medicare, Medicaid, noninsured) were compared. Access to care was determined by patient starting on IM. Chi Square test was used where appropriate. **Results:** A total of 42 patients with MASLD were referred to the CPP for medical weight loss therapy. Payor types included 28 with commercial plans (67%), 10 Medicare (24%), 2 Medicaid (5%), and 2 uninsured (5%). Fibrosis stage was F0-F1=36%, F2=12%, F3=14%, F4=38%. Forty patients (95%) had BMI >30 and 13 (31%) had diabetes. Weight loss medications were plan exclusions for 17 patients (41%). Initial approval was granted for 11 patients (26%). Final approval after prior authorization (PA), appeal, or failure of an alternative medication (e.g. metformin) was achieved in 27 patients (64.2%). Among the 13 patients with diabetes, 4 (31%) were initially approved for IM, and 11 (85%) received final approval. After insurance approval, 22 (52%) patients received and started IM after a mean 30.1 (range 1-136) day delay. Overall, there were no differences in initiating IM by insurance type (p=0.22), or fibrosis score (p=0.61) (Table 1). **Conclusion:** In an academic MASLD clinic with a dedicated CPP, only 52% of patients were able to start IM. Neither payor status nor fibrosis stage was associated with starting IM. Many insurers excluded IM or required PA, some with step up therapy, which added to staff time, effort, and delays in starting therapy. Some patients were unable to start treatment even after insurance approval due to unaffordable copays and shortages of these medications. Incretin therapies are a beneficial option for patients with MASLD complicated by obesity and diabetes, but access needs to be improved.

Table 1: Access and initiation of incretin medications (IM) by insurance provider and fibrosis status.

Payors	Initial Approval	Final Approval	Started IM
Commercial n=28	4 (14.3%)	16 (57.1%)	13 (46.4%)
Medicare n=10	6 (60%)	8 (80%)	6 (60%)
Medicaid n=2	0 (0%)	2 (100%)	2 (100%)
Uninsured n=2	1 (50%)	1 (50%)	1 (50%)
Total n=42	11 (26.2%)	27 (64.2%)	22 (52.4%) p=0.44
Fibrosis			
F0-1 n=15	0	8 (53.3%)	7 (46.7%)
F2 n=5	2 (40%)	4 (80%)	3 (60%)
F3 n=6	0	2 (33.3%)	2 (33.3%)
F4 n=16	9 (56.3%)	13 (81.3%)	10 (62.5%)
Total n=42	11 (26.2%)	27 (64.2%)	22 (52.4%) p=0.61

Disclosures: Jane Giang: Nothing to Disclose, Sophia Hurr: Nothing to Disclose, Alfred Barritt IV: Merck (Any division): Advisor, Madrigal: Consultant, Life Edit: Consultant, Boehringer Ingelheim: Consultant, Target-RWE: Consultant

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3241 | ASSESSING TRANSITIONS OF CARE AMONGST INPATIENTS WITH CIRRHOSIS DISCHARGED FROM A DIVERSE, URBAN LIVER TRANSPLANT CENTER: THE IMPORTANCE OF HEPATOLOGY INVOLVEMENT AND DISCHARGE DESTINATION

Max Schechter[1] Katherine Ni[2] Zoe Verzani[3] Kimberline Chew[2] Jang Hyun Kim[2] Lewis Paulino[2] Danielle Garfunkel[2] Lital Aliasi-Sinai[4] Daniel Alvarez[2] Adejoke Johnson[2] Soaptarshi Paul[2] Hamza Sadhra[2] Clara Tow[2] Don Rockey[2]

[1]Albert Einstein College of Medicine, [2]Montefiore Medical Center, [3]Weill Cornell Medicine, [4]American Medical Prgm Tel Aviv Universit

Background: Hospitalized patients with cirrhosis are at risk of readmission due to the severity and complexity of their disease. The AASLD Practice Metrics Committee recommends patients have a post-discharge hepatology appointment within 30 days of discharge. The impact of this, however, remains uncertain among patients with cirrhosis seen at a diverse, urban healthcare system. This study's primary outcome is to determine predictors of discharged patients with cirrhosis attending a hepatology follow-up visit within 30 days. Additionally, the study examines whether 30-day follow-up attendance leads to lower 90-day readmission rates. **Methods:** We retrospectively analyzed 474 consecutively hospitalized adult patients with cirrhosis between January 2021 and December 2021 at a major, diverse, urban liver transplant health system. We collected demographic, laboratory, and hospital data during the index admission of the 2021 calendar year as well as readmission and follow-up appointment data. Pearson's Chi-squared test, Fisher's exact test, and one-way ANOVA were used to characterize differences between patients who followed up within 30-days of discharge and patients that did not. Cox regression analysis was used to determine the impact of follow-up on the rate of rehospitalization within 90 days accounting for death and transplant as competing risks. **Results:** Of the 474 patients admitted to the hospital, 168 (35%) had hepatology follow-up within 30 days of discharge scheduled of which 128 (27%) attended these appointments. Patients who did not attend 30-day follow-up were older, had Medicaid insurance, had less severe liver disease (based on Child Pugh Score and MELD 3.0), and had more cardiovascular comorbidities compared to patents that did attend follow-up within 30 days (Table 1). Furthermore, patients who did follow-up within 30 days were more often admitted for a liver-related event, had hepatology involvement during the hospital stay, and were discharged to home rather than nursing facilities or acute rehab. Interestingly, lack of follow-up within 30 days of discharge did not lead to a significant impact on the 90-day rehospitalization rate (35% rate for both groups, HR=1.16, 95%CI=0.83-1.64, p=0.4). After adjusting for significant covariates from the univariate analysis, the impact of not having 30-day follow-up on the 90-day readmission rate remained non-significant (sHR=1.13, 95%CI=0.74-1.72, p=0.6). **Conclusion:** Older patients with cardiovascular comorbidities, not seen by a hepatology consultant, and discharged to nursing facilities were less likely to attend hepatology follow-up within 30 days of discharge yet did not experience higher 90-day rehospitalization rates. The present study highlights the need for future quality improvement research to determine the ideal timing of post-discharge follow-up and discharge processes for patients with cirrhosis so to reduce early readmissions and improve care.

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Table 1: Baseline patient demographics and admission characteristics in inpatients with cirrhosis, stratified by patients that attended follow-up within 30 days of discharge and patients that did not (regardless of whether follow-up was scheduled or not). Data reported as n (%) or mean (standard deviation).

	Overall N = 474	Follow-up within 30 days N = 128	No Follow-up within 30 days N = 346	p-value
Demographics				
Sex				0.2
Female	176 (37%)	54 (42%)	122 (35%)	
Age Groups				**0.050**
18-54	128 (27%)	43 (34%)	85 (25%)	
55-65	179 (38%)	50 (39%)	129 (37%)	
>65	167 (35%)	35 (27%)	132 (38%)	
Primary Insurance				**0.021**
None, self-pay, or emergency Medicaid	24 (5.1%)	7 (5.5%)	17 (4.9%)	
Medicaid	191 (40%)	52 (41%)	139 (40%)	
Medicare	197 (42%)	43 (34%)	154 (45%)	
Private	62 (13%)	26 (20%)	36 (10%)	
Child Pugh Class				**<0.001**
A	129 (33%)	22 (19%)	107 (39%)	
B	155 (40%)	51 (43%)	104 (38%)	
C	105 (27%)	45 (38%)	60 (22%)	
Unknown	85	10	75	
Meld 3.0	18 (7)	19 (7)	17 (7)	**0.002**
Unknown	93	11	82	
Comorbidities				
CKD not on dialysis	45 (9.5%)	7 (5.5%)	38 (11%)	0.069
ESRD on dialysis	13 (2.7%)	2 (1.6%)	11 (3.2%)	0.5
CAD, AFib, stroke, or PVD	104 (22%)	19 (15%)	85 (25%)	**0.023**
Congestive heart failure	45 (9.5%)	3 (2.3%)	42 (12%)	**0.001**
Advanced lung disease	14 (3.0%)	0 (0%)	14 (4.0%)	**0.015**
Malignancy within past 5 years	60 (13%)	25 (20%)	35 (10%)	**0.006**
Diabetes	172 (36%)	41 (32%)	131 (38%)	0.2
Clotting disorder	10 (2.1%)	2 (1.6%)	8 (2.3%)	>0.9
Rheumatologic	14 (3.0%)	2 (1.6%)	12 (3.5%)	0.4
Admission Characteristics				
Index Admission Reason				
Liver-related event	188 (40%)	74 (58%)	114 (33%)	**<0.001**
Non-SBP Infection	91 (19%)	18 (14%)	73 (21%)	0.084
AKI/Renal Failure	31 (6.5%)	9 (7.0%)	22 (6.4%)	0.8
Alcohol-related	19 (4.0%)	5 (3.9%)	14 (4.0%)	>0.9
Cardiovascular	31 (6.5%)	3 (2.3%)	28 (8.1%)	**0.025**
Oncologic	14 (3.0%)	6 (4.7%)	8 (2.3%)	0.2
Other	277 (58%)	64 (50%)	213 (62%)	**0.023**
Hepatology Involvement	246 (52%)	106 (83%)	140 (40%)	**<0.001**
Discharge Location				**0.001**
Home	384 (81%)	118 (92%)	266 (77%)	
AMA/Eloped	20 (4.2%)	1 (0.8%)	19 (5.5%)	
SNF	47 (9.9%)	8 (6.3%)	39 (11%)	
Acute rehab	23 (4.9%)	1 (0.8%)	22 (6.4%)	
Liver Transplantation Status				**<0.001**
Addressed	152 (32%)	68 (53%)	84 (24%)	
Not addressed	322 (68%)	60 (47%)	262 (76%)	

Disclosures: Max Schechter: Nothing to Disclose, Katherine Ni: Nothing to Disclose, Zoe Verzani: Nothing to Disclose, Kimberline Chew: Nothing to Disclose, Jang Hyun Kim: Nothing to Disclose, Lewis Paulino: Nothing to Disclose, Danielle Garfunkel: Nothing to Disclose, Lital Aliasi-Sinai: Nothing to Disclose, Daniel Alvarez: Nothing to Disclose, Adejoke Johnson: Nothing to Disclose, Soaptarshi Paul: Nothing to Disclose, Hamza Sadhra: Nothing to Disclose, Clara Tow: Nothing to Disclose, Don Rockey: Grant/Research Support relationship with Versantis; Has not ended; Grant/Research Support relationship with AstraZeneca; Has not ended; Grant/Research Support relationship with Ipsen; Has not ended; Grant/Research Support relationship with Boehringer Ingelheim; Has not ended; Consultant relationship with WL Gore and Associates; Has not ended; Grant/Research Support

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3242 | EARLY PALLIATIVE CARE (PC) IN END-STAGE LIVER DISEASE (ESLD) PATIENTS SIGNIFICANTLY IMPROVES HEALTH-RELATED QUALITY OF LIFE (HRQOL)

Shirley Bong[1] Calvin Koh[1] Jonathan Lee[1] Mark Muthiah[1] Guan Huei Lee[1] Lin Liu[2] Yin Mei Lee[1]

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Background: ESLD is characterized by recurrent complications and repeated visits to the emergency room (ER) and hospital admissions. Early PC in cancer patients was shown to reduce ER visits and hospital admissions and a better QOL. The barriers to early PC in ESLD patients include a poor understanding of the progressive nature of ESLD and the benefits of palliative care. Palliative care is commonly stigmatized in Asia and often misconceived as synonymous with end-of-life care. Our study aims to investigate the effect of early palliative care in Asian ESLD patients with a first episode of decompensation on healthcare outcomes of ER visits, hospital admissions, and HRQoL. **Methods:** This is a prospective controlled cohort study of patients aged 21 years old and above, with liver cirrhosis irrespective of etiology who develop a first episode of decompensation of either ascites, spontaneous bacterial infection, hepatic encephalopathy, recurrent gastrointestinal bleeding, or a combination of the above. Patients in the control group were managed with a standard of care. Patients in the study group received education in symptom control and natural history of ESLD using visual aids. The study patients received advance care planning and 3 monthly clinic consults with early referral to the medical social worker and dietitian. At each visit, patients in the study group and control group answered the Chronic Liver Disease Questionnaire (CLDQ) which is well-validated for HRQoL for chronic liver disease regardless of severity and etiology. The questionnaire consists of 29 items categorized into 6 domains, each item scored 1-7, with an overall HRQoL score, which is a summation of scores of all items. A higher score indicates a higher quality of life. The student t-test was used for continuous variables and Chi-square test for categorical variables. **Results:** There were 13 patients enrolled and followed up for one year (9 in the study group and 4 controls). The mean age of the group was 75.7 years (68-86). There were no differences between the 2 groups in age, gender, etiology of liver disease, MELD scores, or HRQoL scores at entry. At 12 months, the average HRQoL score in the study group was significantly higher than in the controls (5.60 vs 4.37 p=0.027). However, there was no difference between the 2 groups in the number of ER visits and hospital admissions. There were 2 deaths in each group at the end of the study. **Conclusion:** Our pilot study is one of few prospective studies on early palliative care in ESLD. Early introduction of palliative care after a first episode of liver decompensation resulted in significantly better HRQoL at 1 year compared with the standard of care. Secondly, it was shown that with education, symptom control, good communication, and support, cultural barriers to PC can be overcome. These results need to be further validated by large randomized controlled trials.

Disclosures: Shirley Bong: Nothing to Disclose, Calvin Koh: Nothing to Disclose, Jonathan Lee: Nothing to Disclose, Mark Muthiah: Lerna Bio: Stock – privately held company, Olympus: Speaking and Teaching, Boston Scientific: Speaking and Teaching, Novo Nordisk: Grant/Research Support, Echosens: Grant/Research Support, Gilead: Advisor, Guan Huei Lee: Nothing to Disclose, Lin Liu: Nothing to Disclose, Yin Mei Lee: Nothing to Disclose

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3243 | LIVER CIRRHOSIS AND ITS IMPACT ON CLINICAL OUTCOMES IN ADULT RESPIRATORY SYNCYTIAL VIRUS PNEUMONIA: A RETROSPECTIVE ANALYSIS OF THE NATIONAL INPATIENT SAMPLE

Raghav Bassi[1] Zubair Bodla[2] Mariam Hashmi[2] Fatima Niaz[3] Muhammad Khalil[4] Yaseen Perbtani[2] Tony Brar[2]

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Background: Respiratory syncytial virus (RSV) pneumonia is a significant cause of mortality, especially among adults with underlying comorbidities. Liver cirrhosis can impair the body's immune response and its ability to fight infections, increasing rates of severe infections. However, there is limited literature addressing the interplay between RSV pneumonia and liver cirrhosis in the adult population. The aim of this study is to elucidate the impact of liver cirrhosis on clinical outcomes in adults diagnosed with RSV pneumonia. **Methods:** Retrospective analysis using the 2020 national inpatient sample dataset, and utilizing relevant ICD-10-CM codes to identify adults aged 18 years and older who were hospitalized with RSV pneumonia. From this cohort, we derived two distinct groups by examining the presence or absence of liver cirrhosis. Age odds ratio (AOR) was calculated to identify predictors of mortality **Results:** We identified 10,875 adult patients diagnosed with RSV pneumonia with 255 (2.34%) with underlying cirrhosis. These cirrhosis patients were younger (mean age of 63.76 years vs. 70.03). Furthermore, cirrhosis patients with RSV pneumonia had a markedly higher prevalence of severe comorbidities with 49.02% having a Charlson Score of ≥5, compared to 24.53% in the non-cirrhosis group. The in-patient mortality rate among patients with cirrhosis was substantially higher at 17.64% (CI: 9.68%-30.0%) than those without cirrhosis (7.34%) (Table 1). After adjusting for confounders, patients with liver cirrhosis had more than twice the odds of in-patient mortality (AOR 2.28, p=0.036). The average length of hospital stay was also comparable between the two groups (AOR -0.86 days, p=0.503). In terms of resource utilization, total charges (p=0.780) and cost of hospitalizations were statistically similar (p=0.611). A multivariate analysis revealed that being of Asian, Pacific Islander, or Native American race independently predicted mortality (AOR 1.93, p=0.020). Additionally, having a Charlson Score greater than 5 was also associated with a higher risk of mortality (AOR 1.58, p=0.037). However, factors such as age, gender, hospital bed size, hospital region, location, teaching status, insurance category, and median household income for zip did not exhibit a statistically significant impact on mortality outcomes in patients with RSV pneumonia and cirrhosis. **Conclusion:** Systemic inflammation and immunodeficiency are important components of immune dysfunction in patients with cirrhosis. Our study highlights the clinical implications of liver cirrhosis in adults diagnosed with RSV pneumonia. It underscores the pressing need for prophylactic strategies, most notably RSV vaccination which can serve as a crucial tool in reducing the disease burden, especially in high-risk populations like those with cirrhosis.

Outcomes: Mortality and resource utilization

Outcome	RSV Pneumonia without liver cirrhosis	RSV Pneumonia with liver cirrhosis	Adjusted Odds Ratio (AOR)	P-Value
In-Patient Mortality	7.34% (6.35-8.48)	17.64% (9.68-30.0)	2.28 (1.06-4.92)	0.036
Length of stay (Days)	8.46 (7.97- 8.95)	8.55 (6.44- 10.66)	-0.86* (-3.37, 1.65)	0.503
Total Charge (USD)	107611 (96777- 118445)	128262 (73410-183115)	8991* (-54219, 72201.89)	0.780
Total Cost (USD)	28447 (25363-31531)	34661 (16819-52504)	5342* (-15233, -25917)	0.611

**- Adjusted mean difference.*

RSV: Respiratory syncytial virus, *USD: United States Dollar*

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Disclosures: Raghav Bassi: Nothing to Disclose, Zubair Bodla: Nothing to Disclose, Mariam Hashmi: Nothing to Disclose, Fatima Niaz: Nothing to Disclose, Muhammad Khalil: Nothing to Disclose, Yaseen Perbtani: Nothing to Disclose, Tony Brar: Nothing to Disclose

3244 | ACTIVITY METRICS MEASURED BY WEARABLE TECHNOLOGY CORRELATES WITH PATIENT-REPORTED WELLBEING IN CIRRHOSIS

Brian McSteen[1] Jessica Siguencia[1] Russell Rosenblatt[2] Arun Jesudian[2] Ana Krieger[2] Avesh Thuluvath[3] Robert Schwartz[4] Robert Brown[2] Adam Buckholz[5]

[1]NewYork-Presbyterian, Weill Cornell Campus, [2]Weill Cornell Medicine, [3]Northwestern University Feinberg School of Medicine, [4]Weill Cornell Medical College, [5]New York Presbyterian Hospital Program

Background: Inactivity is associated with progressive sarcopenia, worse transplant outcomes and increased mortality in cirrhosis; activity, exercise and energy level are accepted surrogates of health-related quality of life (HRQoL). Activity assessment has historically relied largely on subjective survey data and most research in activity levels in cirrhosis is in advanced disease. Wearable technology offers the potential to assess and monitor activity levels longitudinally in an objective manner, which could allow for targeted diagnosis and intervention to improve outcomes. **Methods:** We prospectively enrolled 12 low MELD (<10) participants with cirrhosis in a pilot study. We collected baseline clinical data, assessed wellbeing via the validated Chronic Liver Disease Questionnaire (CLDQ) responses and collected the subsequent 14 days of activity using the Oura Ring wearable. Our primary outcome was correlation assessed by Pearson correlation coefficient (PCC) between measured activity metrics (inactive time, average METs, average steps, moderate/vigorous exercise time) and CLDQ total and subdomain scores. **Results:** Of 12 participants who enrolled and completed the baseline CLDQ, there were 164 days of activity tracked (98% of total possible days). Mean age was 53.5 (sd 8.4) and average MELD was 5.5. One participant had active ascites, 2 had diuretic-controlled ascites, and 3 had CHE by PHES. The mean global CLDQ score was 4.33 (SD 1.15) with 5 participants reporting high overall HRQoL (CLDQ>5). Participants averaged 6610 steps/day (SD 3453), with lower average steps (5341 vs 9536, p<0.01) and more daily inactive time (531 vs 431 min, p<0.01) among those with a below-average global CLDQ. Among individual CLDQ domains, daily inactivity time was significantly inversely correlated to Activity/Energy (PCC = -0.24, p=0.002) and Worry (PCC = -0.18, p=0.02). Average exercise time was positively correlated to Abdominal Symptoms (PCC = 0.33, p<0.001) and Activity/Energy (PCC = 0.18, p=0.02). Inactive time decreased with age (b=-4.52 min, p<0.01) and was higher in men (b=55 min, p=0.04). Adjusting for individual variation, age and gender, low CLDQ remained associated with inactive time (b=185 min, p<0.01). **Conclusion:** These pilot findings suggest that dynamic activity monitoring using wearable technology correlates with subjective wellbeing data. Even in a relatively-well group of patients with cirrhosis, more than half reported low HRQoL associated with wearable-measured activity metrics reflecting fewer steps and more inactive time. Further work can help establish the probable bidirectional relationship, whereby worse wellbeing results in less activity, worsening wellbeing/outcomes. However, this analysis indicates that wearable-measured activity data may have utility in identifying patients at risk for poor outcomes, such as sarcopenia, or in monitoring the impact of interventions to increase physical activity.

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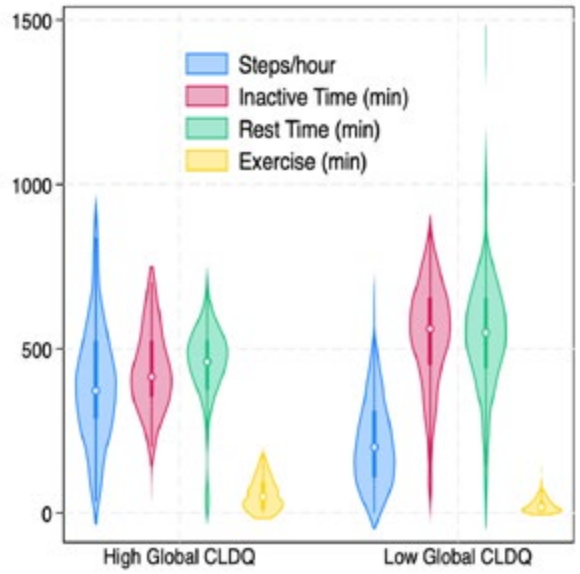

Figure: Activity Metrics Collected by Oura Ring (Steps/Hour, Inactive Time (min), Rest Time (min), Exercise Time (min)) in patients reporting High Global CLDQ (>5) vs Low Global CLDQ (<5) scores

Disclosures: Brian McSteen: Nothing to Disclose, Jessica Siguencia: Nothing to Disclose, Russell Rosenblatt: Nothing to Disclose, Arun Jesudian: Salix Pharmaceuticals: Consultant, Salix Pharmaceuticals: Speaking and Teaching, Madrigal Pharmaceuticals: Speaking and Teaching, Novo Nordisk: Consultant, Orphalan: Consultant, Ana Krieger: Nothing to Disclose, Avesh Thuluvath: Nothing to Disclose, Robert Schwartz: Miromatrix Inc: Advisor, Lime Therapeutics: Advisor, Otsuka Inc.: Grant/Research Support, Alnylam Pharmaceuticals: Speaking and Teaching, Alnylam Pharmaceuticals: Consultant, Robert Brown: Consultant relationship with Intercept; Has not ended; Consultant relationship with Gilead; Has not ended; Consultant relationship with Abbvie; Has not ended; Consultant relationship with Madrigal; Has not ended; Consultant relationship with GSK; Has not ended; Consultant relationship with eGenesis; Has not ended; Consultant relationship with mirum; Has not ended, Adam Buckholz: Nothing to Disclose

3245 | PSYCHOMETRIC PROPERTIES OF A NOVEL TOOL TO MEASURE GOAL CONCORDANT CARE (GCC) FROM PATIENTS WITH END STAGE LIVER DISEASE, AND THEIR CAREGIVERS

Manisha Verma[1] Bryce Reeve[2] Sofia Jakab[3] Michael Volk[4] Li Lin[2] Andrzej Kosinski[5] Victor Navarro[6]

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Background: Measuring the extent to which care delivered is concordant with patients' goals and preferences is an important aspect of palliative care (PC) research and practice. However, there are currently no gold standard instruments to assess goal concordant care (GCC) from patients with end stage liver disease (ESLD) and their caregivers. We describe the psychometric properties of a novel GCC measurement tool. **Methods:** We developed a questionnaire with direct input from clinicians, PC researchers, ESLD patients, and caregivers. Part 1 of the questionnaire (5 items) assesses how much of the care received is concordant with patient preferences, and part 2 (7 items) assesses components of goals of care conversations such as prognosis discussion and linkage of care with personal goals. The psychometric properties are assessed using baseline data from PAL-LIVER trial. We analyzed the factor structure using confirmatory factor analysis with fit criteria of the comparative fit index (CFI; ≥0.90), Tucker-Lewis Index (TLI; ≥0.90), and root-mean squared error of approximation (RMSEA; <0.08). For each unidimensional scale, we estimated Cronbach's coefficient alpha of reliability (threshold of 0.70 for group-level assessment). Higher scores reflect better GCC. We examined the scales' ability to differentiate between patients and caregivers who reported they did or did not receive medical treatment they did not want. **Results:** 882 patients and 527 caregivers are enrolled in this ongoing study. Mean age of patients is 62.5 (SD=10), 70% male, 79% white, and 70% Medicare/ Medicaid beneficiaries. 38% with alcohol-related liver disease, 22% HCV, 22% MASH and 28% had HCC. Mean age of caregivers is 57.3 years, 77% females, 52% spouses. Factor analysis found satisfactory model fit for a single factor for part 1 (patient (P): RMSEA=.06,

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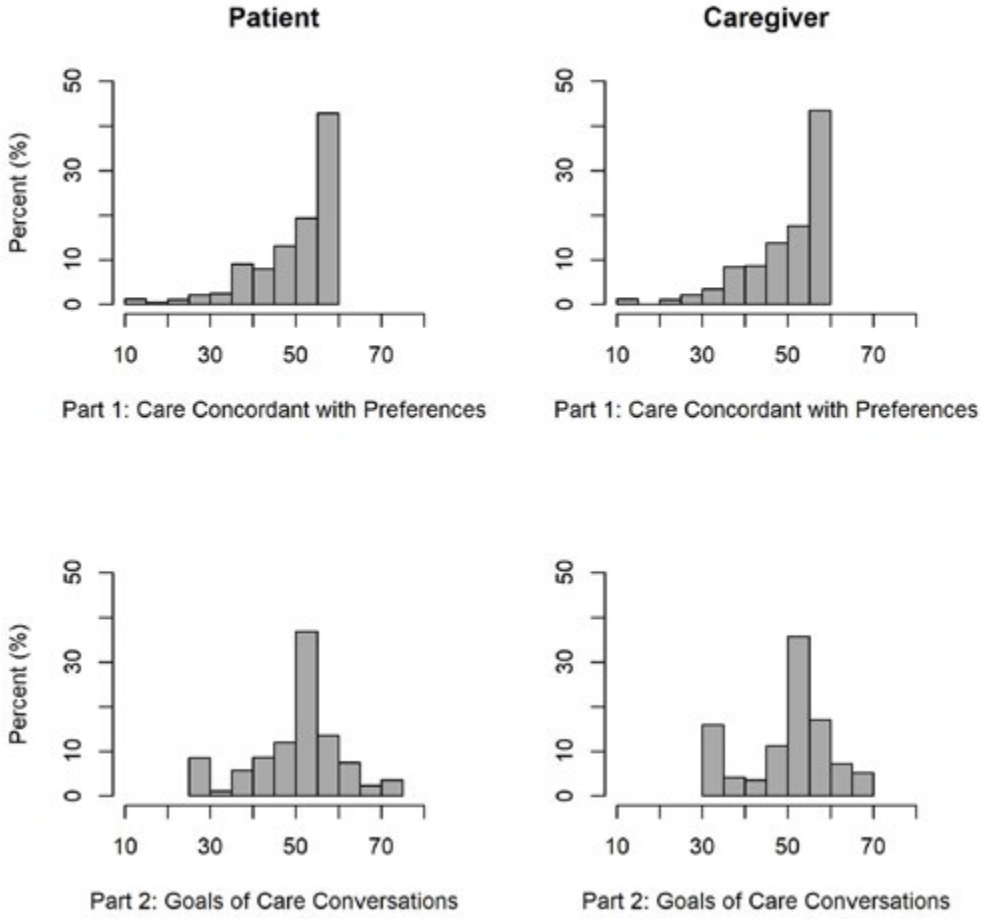
CFI=0.99, TLI=0.98; caregiver(**C**): RMSEA=.12, CFI=0.97, TLI=0.94); and for part 2 (P: RMSEA=.13, CFI=0.94, TLI=0.92; C: RMSEA=.07, CFI=0.99, TLI=0.99). Reliability was satisfactory for both part 1 (P a=0.87; C a=0.85) and part 2 (P a=0.79; C a=0.85). Figure shows the distribution of scores for both GCC scales. Only a minority of respondents (77 out of 747 patients, 34 out of 451 caregivers) reported they received medical treatment that was not what they wanted. There were no statistically significant differences between those who did receive and those who didn't receive care they didn't want for Part 1 (P, *p*=0.15; C, *p*=0.41), and for part 2 for patients (*p*=0.98) but was statistically significant for caregivers (*p*=0.03). **Conclusion:** We have designed two multi-item GCC scales: a 5-item measure of how well clinicians provide care concordant with patient preferences, and a 7-item measure assesses components of goals of care conversations. Both scales cluster on a single factor and demonstrate excellent reliability. The majority of patients and caregivers in the sample report receiving care consistent with their preferences.



Disclosures: Manisha Verma: Nothing to Disclose, Bryce Reeve: Nothing to Disclose, Sofia Jakab: Nothing to Disclose, Michael Volk: Nothing to Disclose, Li Lin: Nothing to Disclose, Andrzej Kosinski: Nothing to Disclose, Victor Navarro: Nothing to Disclose

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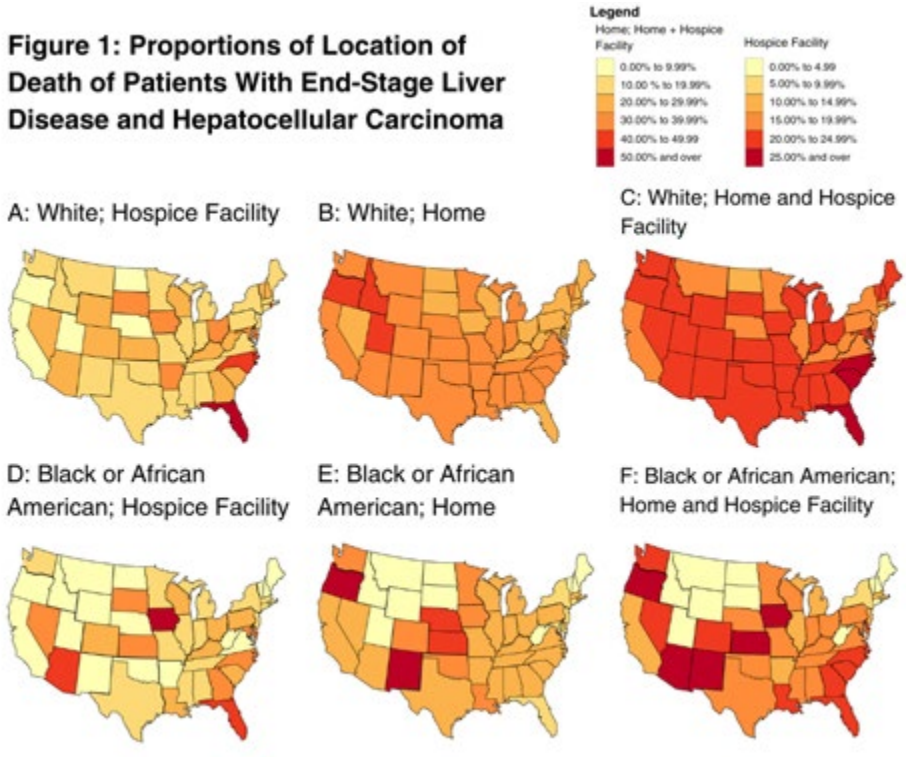
3246 | STATE-LEVEL VARIABILITY AND DISPARITIES IN LOCATION OF DEATH OF PATIENTS WITH END-STAGE LIVER DISEASE: A RETROSPECTIVE CROSS-SECTIONAL ANALYSIS ◆

Julia Meguro[1] *Michael Huber*[2] *David Goldberg*[2]

[1]*University of Miami Miller School of Medicine,* [2]*Univ. of Miami Miller School of Medicine*

Background: Deaths of patients with end-stage liver disease (ESLD) and hepatocellular carcinoma (HCC) in the United States are increasingly occurring at home or in hospice facilities, a trend that is in line with providing appropriate and patient-centered end-of-life care. Nevertheless, hospice care uptake has not been homogenous across the country and remains underutilized at the end of life. This study aimed to investigate state-level variability and disparities in the locations of death for patients with ESLD and HCC, with a specific focus on comparing outcomes between Black or African American and White patients. **Methods:** A retrospective cross-sectional analysis was conducted using data from the Centers for Disease Control and Prevention Wide-Ranging OnLine Data for Epidemiologic Research spanning 2018 to 2021. The percentage of patients with ESLD, HCC, and both conditions who died at home, in hospice facilities, or in a combination of both settings was calculated for Black or African American and White patients. Mapping was utilized to compare the proportions of locations of death for these categories across the US. **Results:** Variability was observed in the proportions of patients dying at home and in hospice facilities across different regions of the country for both White and African American patients. Patients with HCC exhibited the highest uptake of hospice care and had the highest rates of dying at home, with notable disparities noted between White and Black or African American patients. Southern states generally had higher rates of home deaths for patients with ESLD than other areas of the country. Disparities in the proportion of deaths at home between racial groups were more apparent and homogenous than disparities in hospice facility utilization. **Conclusion:** Future research should explore factors contributing to interstate variability and racial disparities in end-of-life care for patients with ESLD and HCC and surrogate measures of hospice accessibility. Strategies to address these disparities and improve access to high-quality end-of-life care for all patients, especially those who are Black or African American, should also be identified.

Figure 1: Proportions of Location of Death of Patients With End-Stage Liver Disease and Hepatocellular Carcinoma



Disclosures: Julia Meguro: Nothing to Disclose, Michael Huber: Nothing to Disclose, David Goldberg: Nothing to Disclose

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3247 | HEALTHCARE CONTACT DAYS PRE- AND POST-LIVER TRANSPLANT IN PATIENTS WITH CIRRHOSIS: A NATIONAL COHORT STUDY

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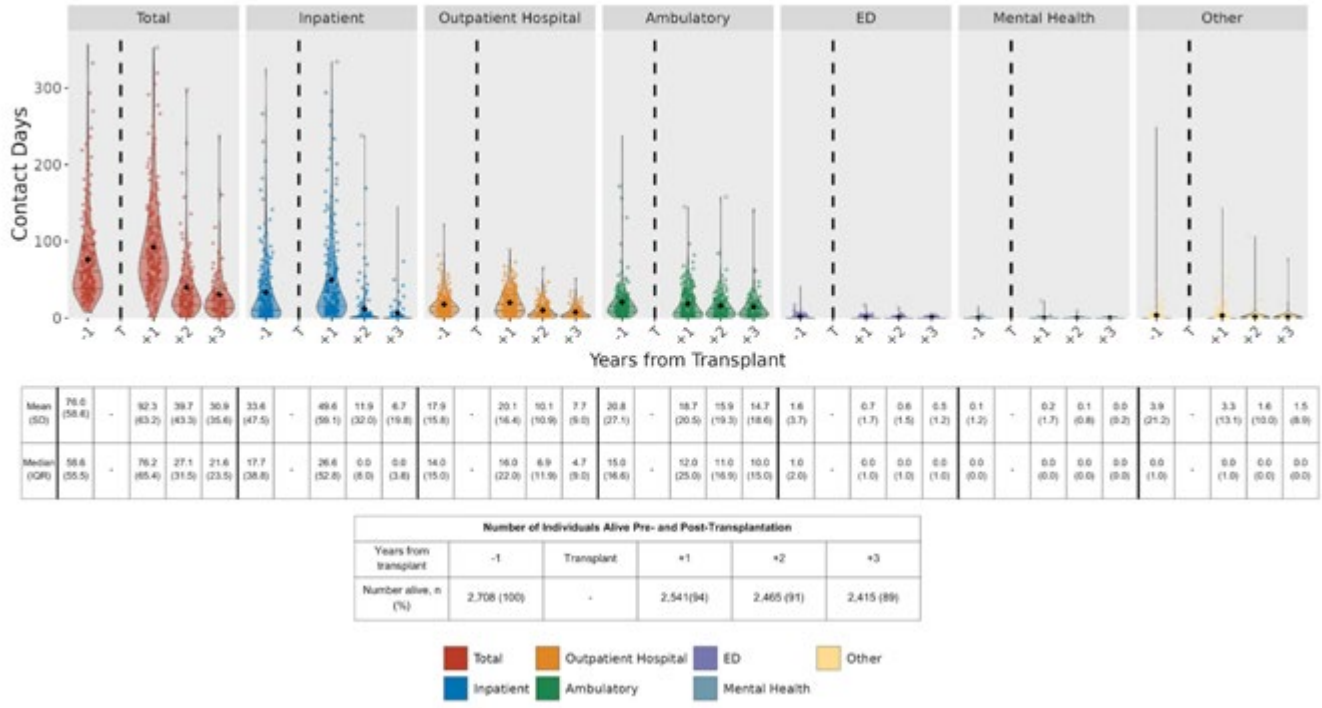
Background: “Healthcare contact days” is a patient-centered quantitative proxy for quality of life and time toxicity, which can be informative for liver transplant (LT) decision-making. We aimed to (i) quantify contact days in patients with cirrhosis pre- and post-LT; (ii) identify clinical and demographic features associated with contact days. **Methods:** Using Optum’s de-identified Clinformatics® Data Mart Database (CDM), we calculated healthcare contact days (inpatient, outpatient hospital [e.g. observation], ambulatory, emergency, mental health, other) for patients with cirrhosis who underwent liver transplantation between 2008-2023. We calculated healthcare contact days before and after LT. We used Poisson regression, adjusted for demographic and clinical features, to assess characteristics associated with pre- and post-transplant contact days. **Results:** 2,708 patients underwent LT (median age 59[IQR 52-65], 66% male, 68% non-Hispanic white). Total mean contact days were 76.0(SD,58.6) 1-year pre-LT, increasing to 92.3(SD,63.2) 1-year post-LT, then decreasing to 39.7(SD,43.3) and 30.9(SD,35.6) 2- and 3-years post-LT, respectively. Mean inpatient contact days were 33.6(SD,47.5) 1-year pre-LT, increasing to 49.6(SD,59.1) 1-year post-LT, then decreasing to 11.9(SD,32.0) and 6.7(SD,19.8) 2- and 3-years post-LT, respectively. In multivariable analysis, pre-LT contact days were not associated with post-LT days (incidence rate ratio [IRR] 1.00[1.00-1.00]). Post-LT, female gender (IRR 1.09[1.03-1.15]), Black race (IRR 1.11[1.00-1.23]), and pre-LT dialysis (IRR 1.21[1.10-1.34]) were associated with increased total contact days. Years post-LT (2- vs 1-, [IRR 0.50[0.49-0.50]], 3- vs 1-, [IRR 0.40[0.39-0.40]]), hepatocellular carcinoma (IRR 0.92[0.86-0.99]), and simultaneous liver-kidney transplant (IRR 0.85[0.73-0.99]) were associated with decreased total contact days. **Conclusion:** “Healthcare contact days” increased 1-year post-LT (vs. 1-year pre-LT) but declined 2- and 3-years post-LT. Healthcare contact days provide interpretable prognostic information to inform expectations regarding LT for cirrhosis, and can be useful for patients, providers, and policymakers alike.



Disclosures: Gurmehr Brar: Nothing to Disclose, Gurmehr Brar: Nothing to Disclose, Jennifer Dodge: Nothing to Disclose, Brian Lee: NIAAA: Grant/Research Support, Novo Nordisk: Advisor, GSK: Advisor, DURECT: Advisor, HepaTx: Advisor, CymaBay: Consultant, Ipsen: Consultant, Siemens Healthineers: Grant/Research Support, AltImmune: Advisor

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3248 | A QUALITATIVE INQUIRY INTO THE EXPERIENCES OF PARTICIPANTS AND NURSES IN THE AUSTRALIAN LIVER FAILURE TRIAL

Jeyamani Ramachandran[1] anuradha pati[2] luisa wigg[3] sharon lawn[4] Sumudu Narayana[5] Kate Muller[6] Alan Wigg[1]

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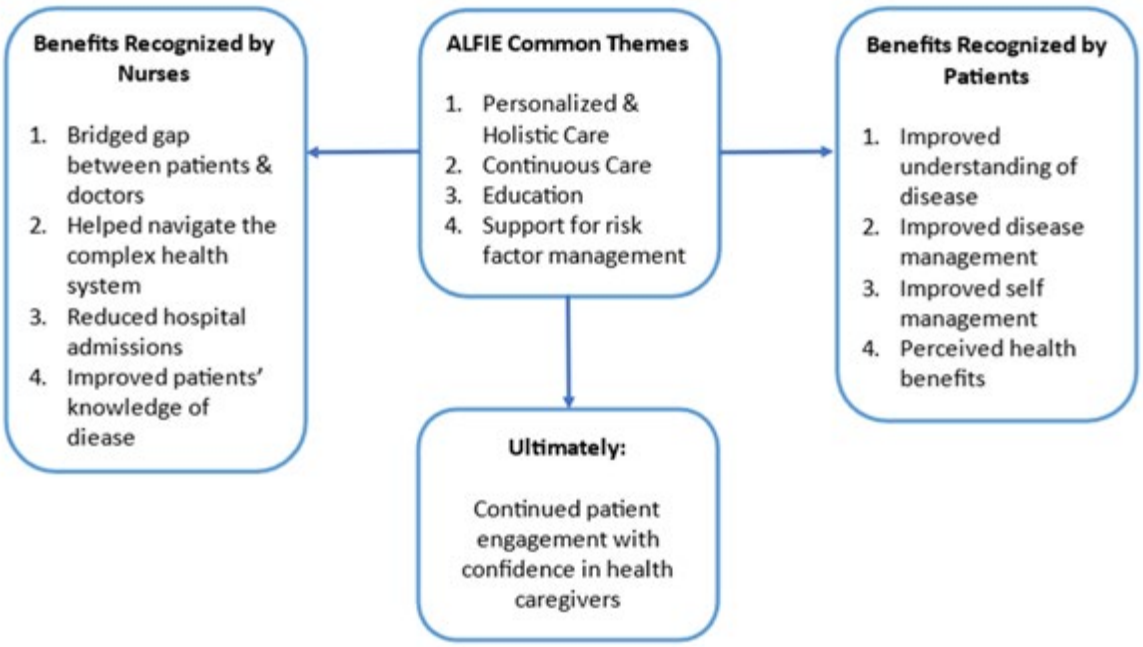
Background: The Australian Liver FallurE (ALFIE) trial, a multicentre randomized controlled, trial assessed the efficacy of a nurse-coordinated model of care to reduce liver-related emergency admissions (LREAs) in patients with decompensated cirrhosis (DC). The model of care was delivered by a specialist nurse and included intensive post-discharge monitoring, linkage to multidisciplinary care, rapid access to care pathways, enhanced education, and self-management support. **Objective:** To examine the experiences of participants and staff involved in the ALFIE trial to understand the impact, barriers, and areas for improvement. **Methods:** A qualitative semi-structured interview analysis nested within the ALFIE trial. **Participants**: A purposive sample of 15 patients,14 controls, and 12 staff. **Intervention:** Thematic analysis of interview transcripts. **Results:** Intervention participants appreciated the dedicated, ongoing management outside of the hospital. ALFIE provided a point of contact to navigate the busy hospital system. Simplified presentation of clinical updates and tailored nutritional and medication education helped them understand and manage their symptoms better. This translated to confidence in care and perceived health improvement. In contrast, control participants missed having personal contact to deal with emergencies that resulted in hospital presentations. They expressed the need for better follow-up plans and education on symptoms, complications, or self-management. The need for easily accessible psychological support was expressed by both participant groups. The nurses were happy with the training provided and wanted to continue with the MOC. Regular monitoring of participants' weight, blood tests, and titration of medications seemed to reduce unplanned admissions and the burden of clinic visits. Providing psychosocial, emotional, and dietetic support enabled the development of robust therapeutic relationships and trust that promoted patient engagement and risk-factor modification. However, the care of participants with DC was demanding on the nurses. Barriers identified were poor patient engagement due to ongoing alcohol use, unstable social circumstances, and lack of mental-health referral pathways. Systemic issues identified were limited hospital bed availability and staffing. Suggestions to improve the MOC included increased staffing, phones with caller ID, better communication pathways with primary care providers, and the use of technological support. **Conclusion:** ALFIE trial was well received by nurses and pati participants ents . It met the needs of both participants, through personalised, holistic, ongoing care and the health system by helping to navigate the system more effectively. Nurses served as a bridge between doctors and patients. The study identified barriers and systemic improvement areas



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Disclosures: Jeyamani Ramachandran: Nothing to Disclose, anuradha pati: Nothing to Disclose, luisa wigg: Nothing to Disclose, sharon lawn: Nothing to Disclose, Sumudu Narayana: Nothing to Disclose, Kate Muller: CSL Behring: Advisor, NovoNordisk: Advisor, AstraZeneca: Advisor, Chiesi: Advisor, Eisai: Speaking and Teaching, Alan Wigg: Nothing to Disclose

3249 | THE PERCEIVED PSYCHOLOGICAL BENEFITS AND HARMS OF UNDERGOING HCC SCREENING AMONG CHEROKEE NATION PATIENTS – A PATIENT PERSPECTIVE

Nicole Kim[1] Ruby Fried[2] Kendra Lewis[3] Sabrina Omer[1] Jorge Mera[3] George Ioannou[1]

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Background: Hepatocellular carcinoma (HCC) disproportionately affects American Indian persons. HCC screening promotes early HCC detection. We investigated the patient experience of undergoing abdominal ultrasound (US) vs. abbreviated MRI (aMRI) for HCC screening within the Cherokee Nation Health Services (CNHS). **Methods:** We administered a patient survey (Psychological Consequences Questionnaire [PCQ]) to CNHS patients enrolled in an ongoing randomized clinical trial (RCT) assessing the feasibility of using US vs. aMRI for HCC screening. The PCQ measures several aspects of perceived psychological benefit and distress related to cancer screening, and was completed at study enrollment and after each screening test during the RCT. A subset of patients were invited for a semi-structured interview after the first screening test. Fisher's exact test and rapid matrix-based analysis were used to analyze PCQ and interview data. **Results:** 48 patients completed the PCQ at enrollment and after their first screening test. Median age was 59.5 yrs (IQR 55-65.5), 100% had cirrhosis (56% MASLD/MASH, 27% cured HCV, 19% ALD), 60% were female, and patients were equally randomized to US vs. aMRI. Before HCC screening, 25% reported feeling nervous, or worried about their future related to HCC. After screening, 60-67% reported feeling more relaxed, less anxious, and reassured they don't have HCC (Figure 1). Patients who received US were more likely to report trouble sleeping (63% vs. 33%; p=0.04) and difficulty with meeting work/other commitments (58% vs. 21%; p=0.02) than patients who received aMRI. There were no other significant differences in the psychological benefits and harms reported by imaging modality. 15 patients (26%) were interviewed and several key themes emerged from the data: patients feel nervous or anxious before receipt of screening (33%), feel a sense of relief after screening (60%), and believe screening is important to complete despite logistical barriers (e.g., travel time/cost, lost wages; 53%). **Conclusion:** Among CNHS patients with cirrhosis, a third reported feeling nervous or worried before HCC screening, while two-thirds reported a sense of relief after completing screening. Patients who received aMRI reported fewer psychological harms and similar psychological benefits as patients who received US. Further analyses are needed to assess whether these findings persist over recurrent screening episodes, as it may affect patient acceptance of testing.

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Figure 1.



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3250 | HEPATOLOGY CLINICIAN PERSPECTIVES ON ADDICTION STIGMA IN THE CARE OF PATIENTS WITH LIVER DISEASE AND ADDICTION

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Background: Chronic liver diseases, including alcohol-associated liver disease and hepatitis C virus infection, co-occur with addiction, however patients with both conditions rarely receive evidence-based addiction treatment. Although hepatology clinicians are well-positioned to address addiction among patients seen in hepatology clinics, many do not feel comfortable providing addiction treatment due to lack of knowledge or training. There has been increased attention to the potential role that addiction stigma may play in this treatment gap. Little is known regarding the impact of addiction stigma on provision of integrated care for chronic liver disease and addiction. To foster implementation research, we aimed to assess the perspectives of hepatology clinicians regarding addiction stigma and its impact on addiction treatment in hepatology clinics. **Methods:** Hepatology clinicians, including hepatologists, trainees, nurses, advanced practice and behavioral health providers, caring for patients with chronic liver disease at six sites within an academic medical center in Connecticut were invited to participate in semi-structured in-depth interviews grounded within the Promoting Action on Research Implementation in Health Services (PARIHS) framework as part of a formative evaluation of attitudes and preferences toward

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treating addiction in hepatology clinics between July-September 2022. A codebook for qualitative data analysis was developed and refined iteratively, and thematic analysis was conducted to generate themes. **Results:** Among the 35 clinicians who participated in interviews (70% participation rate), 14 hepatology attendings, 9 trainees, 5 advanced practice providers, 4 nurse coordinators, and 3 behavioral health clinicians were included. Major themes related the impact of addiction stigma within the PARIHS domains are shown in the table. Within the domain of Evidence, themes included: 1. stigma affects clinician perspectives and quality of patient care; 2. chronic disease model of addiction can help mitigate stigma. Within the domain of Context, themes were: 1. stigma prevents patients from receiving evidence-based liver care; 2. stigma affects uptake of addiction treatment among patients; 3. stigma is heightened in the context of liver transplantation; 4. stigma influences resource allocation and systems-level investment in the care of this patient population. Within the domain of Facilitation, the major theme was: 1. hepatology-clinician driven care models that incorporate addiction treatment as part of liver disease care may reduce stigma. **Conclusion:** Addiction stigma may lead to barriers to care on multiple levels. Integrated care models may help destigmatize addiction treatment for patients with chronic liver disease.

Table: Themes and Representative Quotes form Qualitative Interviews

PARIHS Domain	Themes	Representative Quotes
Evidence	*Stigma associated with alcohol-associated liver disease affects clinician attitudes and can impact the quality of care that patients receive.*	*"They come in, alcoholic cirrhosis, alcoholic hepatitis, and nurses, residents...stop thinking. I have seen again and again, people miss hemochromatosis, alpha-1-antitrypsin, all sorts of things - they just stop thinking... There is that burnt out attitude of what am I doing with my life? I'm looking after alcoholics - that is not a glamorous aspect of medicine... they are covered in this kind of stigma in a punitive healthcare system."*
	Emphasizing the definition of addiction as a chronic medical condition rather than a moral issue may help address stigma and its impact on addiction treatment uptake among patients.	*"From my perspective I think what's really important is to kind of step away from the judgment and the shame - I'm using that word very deliberately - and for patients to understand that at least from my point of view, this is a sort of this medical issue and has to be treated medically and obviously with behavioral support. Wrapping it into their medical care, I think, maybe I would hope would make it more accessible and allow patients to feel more open and receptive to it."*
Context	*Stigma related to addiction may prevent patients from receiving treatment for their liver disease.*	*"I really don't think that we should be holding up the moral yardstick to patients with respect to eligibility for liver transplantation... I just think it's wrong to do that, to deny somebody the ultimate therapy for their disease because they have the disease."*
	Experiencing stigma can prevent patients from seeking addiction treatment.	*"Coming into transplant with liver disease, it is very, very difficult for patients to acknowledge their alcohol use or their substance use. That's often a very difficult thing, and they are afraid of being judged or criticized or thought less than. And so their acceptance of recommendations or treatment for relapse prevention really relies on acknowledging that there's a problem, to begin with and feeling comfortable enough to say that that this is a problem that I'm having, and that I need help with."*
	Stigma related to alcohol and other substance use may be heightened in the context of liver transplantation due to implications for eligibility.	*"In some ways, I think having a hepatology clinic that is somewhat connected but somewhat removed from the transplant center might actually be helpful. Embedded substance abuse treatment within the transplant center can have an impact on their ability to be listed, so I think that makes it harder actually for them to be honest, so if there was a group that's sort of active but separate from transplant where we really are just there to treat the whole person, and we want, we encourage and invite you, to be honest, and this is not, you know, we're not going to withhold treatment for your liver disease or your substance use just because you're struggling or something like - I think in some ways that might be helpful."*
	Recurrence of alcohol-associated liver disease after liver transplantation is stigmatized relative to other etiologies.	*"Let's say you complete all the requirements that we asked but it so happens that you have non-alcoholic steatohepatitis or primary sclerosing cholangitis again... we can do redo transplants provided you still meet the criteria, but for alcoholic, that's noncompliance. We told you not to drink, and you're drinking, so that's outright noncompliance."*
	Stakeholders may not prioritize resources for patients with chronic liver disease and addiction due to stigma.	*"Oh, I think with all the stigma associated with liver disease, there are more barriers than just the logistical. A lot of people, because of their personal biases, especially the stakeholders, they rather spend the money somewhere else."* *"I think there's still probably a lot of, I don't know if I should say like bias, or prejudice, but something similar to that, where people still feel like, maybe people with substance use disorder, they don't really consider it a disease, and they feel like, why should we be investing so much money to help these people when they're not strong enough to, and that's in quotes, not strong enough to stop using whatever substance it is that they're using? Why are we investing so much money and helping these people?"*
Facilitation	*Integrated care for chronic liver disease and addiction may help address stigma associated with addiction treatment for patients.*	*"If they can just stay a bit longer in clinic and discuss with the addiction specialist, or just be called later on, I don't think that is the same burden in terms of the stigma of having addiction or having to go to the substance use disorder clinic - I think it's a good way to introduce patients to this area of medicine and sort of destigmatize and that's why to me it seems like the acceptance is much higher if all this is done in an integrative way."* *"I think that there is a sense by many patients of being judged, there still is substantial stigma as it relates to addiction more broadly, and I think that to the degree to which active engagement of clinicians in this process of treating addiction can help affirm that we as clinicians are not passing judgment at all, but rather really trying to partner in their care and that we that we address this as a medical disease, this is something that can really be very hopefully reassuring and affirming for patients."* *"Having a multidisciplinary approach really takes away the stigma that, you know, you are an alcoholic, and you need treatment for that... it's more like you have really bad liver disease, alcohol is contributing, so you need treatment for that."*

Disclosures: Lamia Haque: Nothing to Disclose, Hye Young Choi: Nothing to Disclose, Marissa Justen: Nothing to Disclose, E. Jennifer Edelman: Nothing to Disclose, David Fiellin: Nothing to Disclose

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3251 | PATIENTS WITH NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD) AND METABOLIC DYSFUNCTION ASSOCIATED STEATOTIC LIVER DISEASE (MASLD) HAVE SIMILAR CLINICAL, NON-INVASIVE TESTS (NITS) AND PATIENT-REPORTED OUTCOMES (PROS) PROFILE

Zobair Younossi[1] Yusuf Yilmaz[2] Ling-Lung Yu[3] Vasily Isakov[4] Marlen Ivon Castellanos Fernandez[5] Vincent Wong[6] Yuichiro Eguchi[7] Manuel Romero-Gómez[8] Ajay Duseja[9] Elisabetta Bugianesi[10] Wah Kheong Chan[11] Khalid Alswat[12] Saeed Hamid[13] Ashwani Singal[14] Jian-Gao Fan[15] George Papatheodoridis[16] Stuart Gordon[17] Mohamed El-Kassas[18] Ziad Younes[19] Stuart Roberts[20] NAHUM NAHUM MENDEZ-SANCHEZ[21] Caglayan Keklikkiran[2] Aijaz Ahmed[22] Brian Lam[23] Fatema Nader[24] Linda Henry[1] Maria Stepanova[1] Saleh Alqahtani[25]

[1]The Global NASH Council, [2]Recep Tayyip Erdoğan University, [3]National Sun Yat-Sen University, [4]Federal Research Center of Nutrition Bio, [5]University of Medical Sciences of Havana, [6]The Chinese University of Hong Kong, [7]Loco Medical General Institute, [8]Virgen del Rocío University Hospital, [9]Postgraduate Institute of Medical Education & Research, [10]University of Torino, [11]University of Malaya, [12]King Saud University/KKUH, [13]Aga Khan University, [14]University of Louisville, [15]Shanghai Jiaotong University, [16]National/Kapodistrian University of Athe, [17]Henry Ford Health System, [18]Helwan University, [19]Gastro One, [20]Alfred Hospital, [21]National Autonomous University of Mexico, [22]Stanford University School of Medicine, [23]Beatty Liver and Research Program, [24]Center for Outcomes Research in Liver Diseases, CORLD, [25]King Faisal Specialist Hospital & Research Center, Riyadh, Saudi Arabia

Background: NAFLD was recently renamed as MASLD. Given changes in the definition, there have been concerns about the applicability of previous NAFLD evidence on MASLD. Our aim was to compare PROs and NITs between NAFLD and MASLD. **Methods:** Using our Global NASH Registry and NAFLD Databases, patients with established diagnosis of NAFLD and NASH were included. MASLD and MASH were defined according to the new criteria (Rinella, Hepatology 2023). We calculated the concordance of definitions for MASH and NASH or NAFLD and MASLD. We also evaluated NIT scores and PRO scores (by CLDQ-NAFLD or FACIT-F or WPAI instruments) according to NAFLD and MASLD. **Results:** 11,600 NAFLD patients were included (age 53±12 years, 45% male, BMI 34.0±8.0, and T2D 48%). Of the entire NAFLD group, 97.2% fulfilled the criteria for MASLD; among participants with biopsy-proven NASH, 99.97% also met the definition of MASH. Subjects with MASLD and NAFLD had similar FIB-4 scores (1.58 ± 1.52 vs. 1.58 ± 1.51) and liver stiffness by transient elastography (12.0 ± 9.8 kPa vs. 11.8 ± 9.7 kPa). Of the entire NAFLD sample, 71% had PRO scores recorded. The CLDQ-NAFLD and FACIT-F scores were similar between MASLD and NAFLD groups: total CLDQ-NAFLD 5.16 ± 1.14 vs. 5.17 ± 1.14 (range 1-7), total FACIT-F 114.1 ± 26.2 vs. 114.5 ± 26.2 (range 0-160). However, for subjects with NAFLD who did not fulfil the criteria for MASLD (2.8% of all NAFLD), NIT scores were significantly lower (FIB-4 1.39 ± 1.32 vs. 1.58 ± 1.52, liver stiffness 5.73 ± 3.22 kPa vs. 12.0 ± 9.8 kPa) while their PRO scores were significantly higher (CLDQ-NAFLD 5.70 ± 0.84 vs. 5.16 ± 1.14, FACIT-F 125.1 ± 23.4 vs. 114.1 ± 26.2) in comparison to subjects with MASLD. In multivariate regression analysis, independent predictors of PRO scores were similar in patients with NAFLD and MASLD and included age, sex, enrollment setting (tertiary care vs. real-world), BMI, FIB-4 score, and the presence of non-hepatic comorbidities ($p<0.05$). **Conclusion:** Over 97% of NAFLD patients meet the criteria for MASLD with similar NIT and PRO profile. NAFLD patients who do not meet MASLD criteria seem to have milder disease as manifested via lower NIT scores and higher PRO scores. These data provide evidence that NAFLD and MASLD, NASH and MASH can be used interchangeably.

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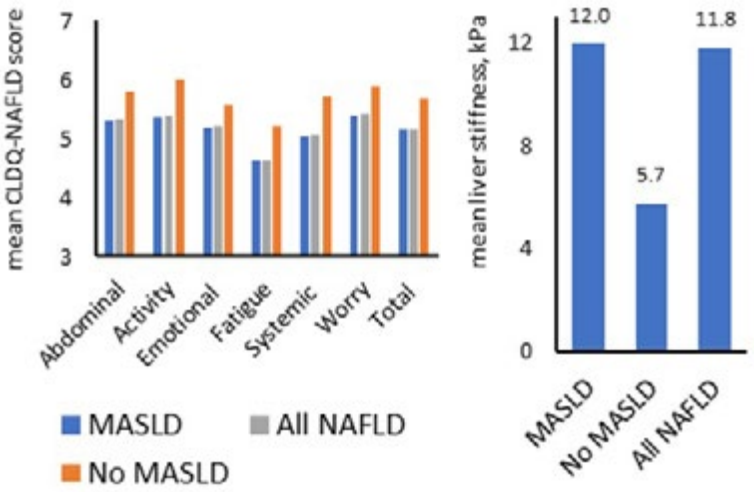

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3252 | THE LONG-TERM FOLLOW-UP STATUS OF 3,643 PATIENTS ACHIEVING SVR AFTER DAAS, MANAGED BY SPECIALISTS IN HEPATOLOGY; NATIONWIDE SURVEY

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[1]Hokkaido University Hospital, [2]Osaka Metropolitan University, [3]Saitama Medical University, [4]Hirosaki University, [5]Gunma University, [6]Hamamatsu University, [7]Ehime University, [8]Oita University, [9]Tohoku University, [10]University of Miyazaki, [11]Saga University, [12]Kanazawa University, [13]NTT East Sapporo Hospital, [14]Tokyo Medical University, [15]Kurume University Medical Center, [16]Graduate School of Medicine Hokkaido University, [17]NCGM

Background: Treatment of hepatitis C virus (HCV) infection with direct-acting antivirals (DAAs) has demonstrated high rates of viral clearance, however strategies for post-sustained viral response (SVR) follow-up remain

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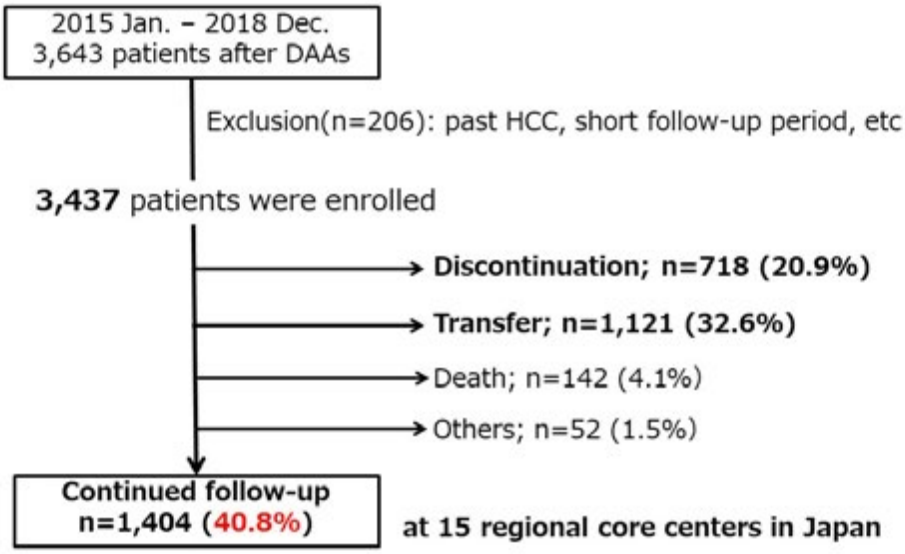
uncertain. We investigated the long-term follow-up status and factors associated with continuation of follow up among patients treated for HCV by specialist at Japanese regional core centers for the management of liver disease. **Methods:** Patients who received DAAs (SOF/LDV, SOF/RBV, OMV/PTV/r±RBV, EBR+GZR, GLE/PIB) for HCV infection at 15 regional core centers for the management of liver disease in Japan between 2015 and 2018 were screened. Those with a confirmed SVR12 and no history of hepatocellular carcinoma before DAAs treatment or within six months after DAAs treatment were included. The main survey items included blood test data at end of treatment, prognosis, history of hypertension, diabetes, dyslipidemia, and presence of liver cancer, follow-up status. Patients were classified into three groups: continued follow-up at regional core centers, transfer to another facility, and discontinuation of follow-up. **Results:** Of the 3,643 HCV patients who underwent DAAs treatment, 3,437 met the inclusion criteria. Among these, 1,404 (40.8%) patients continued regular follow-up (median follow up period, 7.0 years, 95%CI 3.0-8.4), and 1,121 (32.6%) patients transferred to another facility (median 2.3 years, 95%CI 2.0-2.6), and 718 (20.9%) patients discontinued regular follow-up (median 2.6 years, 95%CI 2.3-3.7), 142 (4.1%) died, and 52 (1.5%) were categorized as other. Comparison of patient characteristics among the three groups revealed that the patients with discontinuation of follow-up were younger than those with the continuation, while the patients with transfer to another facility were older than those with the continuation, and those with discontinuation had lower FIB4-index values. Multivariable logistic regression models were used to identify the factors associated with the continuation of follow-up. The development of liver cancer (odds ratio 6.97, 95%CI 3.15-15.40, P<0.001), treatment for dyslipidemia (odds ratio 1.48, 95%CI 1.01-2.15, P=0.043), and serum albumin ≥ 4 g/dl (odds ratio 1.54, 95%CI 1.25-1.91, P<0.001) were identified as significant factors associated with continued follow-up. Conversely, FIB-4 index ≤ 1.3 (odds ratio 0.66, 95%CI 0.50-0.87, P=0.003), Serotype 2 (odds ratio 0.60, 95%CI 0.49-0.73, P<0.001), hypertension treatment (odds ratio 0.63, 95%CI 1.01-2.15, P=0.043), and chronic hepatitis (odds ratio 0.48, 95%CI 0.35-0.66) were extracted as factors that did not significantly contribute to continued outpatient care. **Conclusion:** Achieving continued follow-up for all patients treated at regional core centers is challenging, highlighting the importance of individualized decision-making by specialists in hepatology.



Disclosures: Masatsugu Ohara: Nothing to Disclose, Ritsuzo Kozuka: Nothing to Disclose, Yoshihito Uchida: Nothing to Disclose, Chikara Iino: Nothing to Disclose, Hiroki Tojima: Nothing to Disclose, Kazuhito Kawata: Nothing to Disclose, Satoru Kakizaki: Nothing to Disclose, Yoshio Tokumoto: Nothing to Disclose, Mizuki Endo: Nothing to Disclose, Jun Inoue: Nothing to Disclose, Kenji Nagata: Nothing to Disclose, Hirokazu Takahashi: Sysmex: Grant/Research Support, Novo Nordisk: Speaking and Teaching, Kowa: Speaking and Teaching, Taisho: Speaking and Teaching, Takeda: Grant/Research Support, Tetsuro Shimakami: Nothing to Disclose, Koji Ogawa: Nothing to Disclose, Masaru Enomoto: Nothing to Disclose, Tadashi Ikegami: Nothing to Disclose, TATSUYA IDE: Nothing to Disclose, Naoya Sakamoto: Gilead Sciences, Eisai, AbbVie, Chugai: Speaking and Teaching, Masaaki Korenaga: Nothing to Disclose

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3253 | THE QUALITY OF CARE PROVIDED TO PATIENTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE IN THE DEPARTMENT OF VETERANS AFFAIRS

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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most common cause of chronic liver disease. Evidence-based guidelines define the standards of care for patients with MASLD, ranging from screening, diagnosis, and referral to management-related care. However, the extent to which patients with MASLD receive care that meets these standards is unknown. **Methods:** We conducted a retrospective cohort study of 470,951 patients with MASLD, identified based on previously validated algorithms, who sought primary care at any of the 130 Veterans Affairs hospitals and affiliated clinics between 1/01/2022 and 12/31/2022 with follow up through 12/31/2023. We used clinical and administrative data to evaluate the quality of MASLD care, measured by 11 guideline-based quality indicators (2 measured screening/risk stratification, 3 diagnosis/referral, and 6 clinical outcomes). For each indicator, we calculated the percentage of patients who received the recommended care or met the desired outcome among those who were eligible for the indicator. We used a hierarchical logistic regression model to assess the associations between patients and characteristics. **Results:** Mean age was 58.9 year (SD 14.2 years), 67.3% were white, and 15.4% were African American. Proportions of patients meeting quality indicators varied widely. In total, 10.9% of patients with an elevated FIB-4 underwent a second-tier test with either transient elastography, MRE, or liver biopsy, and 9.6% were seen by liver specialists. Fewer than 17% had a documented diagnosis code for MASLD (NAFLD) in the medical record, and fewer than 19% of those with documented MASLD cirrhosis underwent HCC screening. Although 80% of patients with MASLD and diabetes received medications for diabetes or saw an endocrinologist, less than 45% had adequate glycemic control. Only 14.9% achieved at least 5% weight loss during the study period. Adherence to treatment-related care was higher than adherence to screening and diagnosis-related care. **Conclusion:** Health care quality, measured by whether patients received recommended services or achieved outcome targets, was suboptimal for patients with MASLD. We found that only 1 out of 10 primary care patients with MASLD undergo risk stratification or receive liver specialty care. Without systemic change targeting routine screening and risk stratification, the care of patients with MASLD will continue to suffer.

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Table 1: Rates of Quality Indicators, Defined as Percentage of Eligible Patients Who Received the Care (Numerator) Among Those Who Were Eligible for the Care (Denominator). First visit with the primary care physician between Jan 1, 2022 and Dec 31, 2022 was defined as the index date.

Quality Indicator*	Rate, % (95% CI) (denominator)
Processes of Care	
Among patients with MASLD and Fib-4 > 1.3, % who had either transient elastography, MRE, or liver biopsy 1 year before to 1 year after index date	10.9 (10.74-11.06) (151854)
Among patients with MASLD and cirrhosis or Fib-4>2.67, % with HCC screening (ultrasound with or without AFP) 1 year before to 1 year after index date	18.3 (17.78-18.77) (23736)
Among patients meeting criteria for MASLD, % with documented ICD diagnosis of MASLD/NAFLD in medical record	16.3 (16.18-16.40) (447656)
Among patients with MASLD and Fib-4 > 1.3, % seen by GI or hepatologist 1 year before to 1 year after index date	9.7 (9.50-9.80) (153529)
Among patients with MASLD and diabetes, % prescribed medication for diabetes or seen by endocrinologist 1 year before to 1 year after index date	80.0 (79.48-79.87) (165914)
Outcomes of Care	
Among patients with MASLD, % of patients with weight loss of at least 5% of body weight over 1 year	14.9 (14.76-15.03) (280,150)
Among patients with MASLD and diabetes, % with adequate glycemic control (meeting individualized A1C targets) at index date	44.7 (44.43-44.92) (160044)
Among patients with MASLD and hypertension, % with adequate blood pressure control 1 year before to 1 year after index date	41.9 (41.76-42.13) (265735)
Among patients with MASLD and dyslipidemia, % with adequate LDL-C control 1 year before to 1 year after index date	50.5 (50.35-50.72) (283729)
Among patients with MASLD and no history of major cardiac events, % on statin with LDL < 100 mg/dl 1 year before to 1 year after index date	51.3 (51.11-51.57) (186799)
Among patients with MASLD and a history of major cardiac events, % on statin with LDL > 70 mg/dl 1 year before to 1 year after index date	33.3 (32.72-33.81) (28661)

*patients with missing lab values, weights, or blood pressures were excluded from the denominator for the QIs relevant to the missing values

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3254 | RACIAL DIFFERENCES IN PERCEPTION OF HEALTHCARE EXPERIENCES AMONG PATIENTS WITH ALCOHOL-ASSOCIATED LIVER DISEASES: A CROSS-SECTION ANALYSIS OF THE ALL OF US DATABASE

Nicole Ng[1] *Subhanik Purkayastha*[1] *Xiaohan Ying*[1] *Russell Rosenblatt*[1] *Catherine Lucero*[1] *Arun Jesudian*[1]

[1]*Weill Cornell Medicine*

Background: Adverse healthcare experiences and negative patient-provider interactions are key contributors to health disparities among minority groups and can lead to worse health outcomes. Due to increased needs in longitudinal care, lifestyle modifications, and medication adherence, patients with chronic diseases are

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particularly at risk. Our study aims to evaluate how perception of care differs amongst patients with alcohol-associated liver disease (ALD) from different demographic backgrounds. **Methods:** This cross-sectional study analyzed survey data from participants with ALD who enrolled in the *All of Us* Research Program, an NIH-funded, national, epidemiologic study that collects health records from diverse participants with specific efforts to recruit underrepresented groups in biomedical research. The primary outcome was favorable healthcare experiences, as defined by whether providers were easy to understand, asked for patients' opinion, or demonstrated respect. The secondary outcome was unfavorable healthcare experiences, as defined by whether patients felt providers were not listening, provided poorer service, or treated them with less courtesy. Outcomes were assessed based on binarized questionnaire answers with "always" and "most of the time" set as a positive response. We compared the healthcare experience between self-identified race and demographic variables using multivariable logistic regression that were adjusted for *a priori* covariates. **Results:** 2805 patients with ALD were evaluated. 60.1% identified as male, 53.9% White, and 83.4% were US-born. The average age was 54. Half of the patients reported income at or below $35k, and 47.5% reported education of high school and below. After controlling for age and income, Asian and foreign-born patients both reported lower odds of feeling respected by providers when compared to White patients and US-born patients, respectively (OR 0.13, CI 0.02-0.70, p=0.02 and OR 0.35, CI 0.13-0.93, p=0.04). Black and Hispanic patients did not feel less respected by providers. Patients' race did not affect the odds of finding doctors easy to understand. Compared to those with annual income above $150k, patients with less than $10k reported higher odds of feeling that providers were not listening (OR 4.0, CI 1.25-12.6, p=0.02), that they were treated with less courtesy (OR 14.9, CI 1.81-122.3, p=0.01), and received worse service (OR 8.8, CI 1.04-75.3, p=0.04). Female patients reported higher odds of provider not listening (OR 1.98, CI 1.20-3.26, p=0.01) compared to males. **Conclusion:** Perception of healthcare interactions varies between patients of different backgrounds. Asian and foreign-born patients had lower odds of favorable experiences. Our findings pinpoint potential targets for interventions to decrease disparities among patients with ALD by improving patient-provider relationships and reinforcing inclusive clinical settings.

Disclosures: Nicole Ng: Nothing to Disclose, Subhanik Purkayastha: Nothing to Disclose, Xiaohan Ying: Nothing to Disclose, Russell Rosenblatt: Nothing to Disclose, Catherine Lucero: Nothing to Disclose, Arun Jesudian: Salix Pharmaceuticals: Consultant, Salix Pharmaceuticals: Speaking and Teaching, Madrigal Pharmaceuticals: Speaking and Teaching, Novo Nordisk: Consultant, Orphalan: Consultant

3255 | SOCIOECONOMIC FACTORS IMPACT THE PERCEPTION OF CARE IN PATIENTS WITH CIRRHOSIS: FINDINGS FROM THE *ALL OF US* DATABASE

Nicole Ng[1] *Subhanik Purkayastha*[1] *Xiaohan Ying*[1] *Arun Jesudian*[1] *Russell Rosenblatt*[1]

[1]*Weill Cornell Medicine*

Background: Suboptimal patient-provider relationships have been identified as a significant contributor to healthcare disparities. Minority populations report less favorable interactions, which may lead to poorer health outcomes and engagement in future care. Vulnerable patients with chronic diseases are especially at risk. Thus, we aimed to study perceptions of healthcare providers and experience among subpopulations with cirrhosis. **Methods:** The *All of Us* database was queried for adults with cirrhosis. This NIH-funded, national dataset compiles health records from diverse participants with an emphasis on recruiting those underrepresented in biomedical research. The primary outcome was favorable healthcare experience, as defined by whether providers asked for the patient's opinion, demonstrated respect, and were easy to understand. The secondary outcome was unfavorable healthcare experience, as defined by whether patients felt they were treated with less courtesy, received poorer service, or not listened to. Outcomes were assessed based on binarized survey answers with "always" and "most of the time" set as a positive response. We compared the healthcare experience between income levels and demographic variables. Multivariable logistic regression was adjusted for *a priori* covariates. **Results:** 5467 patients with cirrhosis were included with an average age of 57. 51.3% were male, 52.8% White, and 84.8% were US-born. 47.1% reported income below $35k, and 44.3% reported education of high school and below. Compared to those with annual income over $150k, when controlled for age, patients with $10-35k and with <$10k annual income reported lower odds of finding doctors easy to understand (OR 0.38, CI 0.16-0.92, p=0.03 and OR 0.35, CI 0.14-0.89, p=0.03) and higher odds of receiving worse service (OR 3.20, CI 1.10-9.31, p=0.03 and OR 4.44, CI 1.40-14.05, p=0.01), respectively. The <$10k group had higher odds of feeling providers were not listening (OR 2.26, CI 1.12-4.54, p=0.02). Compared to White patients, Black patients had lower odds of feeling respected by providers (OR 0.46, CI 0.23-0.94, p=0.03). Compared to male patients, female and

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non-binary patients reported higher odds of feeling providers were not listening (OR 2.01, CI 1.47-2.76, *p*<0.01 and OR 3.51, CI 1.08-11.33, *p*=0.04 respectively). Foreign-born patients had lower odds of feeling providers were not listening, when compared to US-born counterparts (OR 0.50, CI 0.27-0.95, *p*=0.03). **Conclusion:** Patients with cirrhosis from various socioeconomic and demographic backgrounds report substantially different experiences with healthcare providers. In particular, those with lower income endorsed more unfavorable interactions. Our findings identified areas for interventions to strengthen the patient-provider relationship and promote inclusive therapeutic environments, with the goal of mitigating disparities among patients with chronic liver disease.

Disclosures: Nicole Ng: Nothing to Disclose, Subhanik Purkayastha: Nothing to Disclose, Xiaohan Ying: Nothing to Disclose, Arun Jesudian: Salix Pharmaceuticals: Consultant, Salix Pharmaceuticals: Speaking and Teaching, Madrigal Pharmaceuticals: Speaking and Teaching, Novo Nordisk: Consultant, Orphalan: Consultant, Russell Rosenblatt: Nothing to Disclose

3256 | EFFECTIVENESS OF POLYENE PHOSPHATIDYLCHOLINEIN IMPROVING LIVER FUNCTION FOR PATIENTS WITH NON-HEPATITIS B CHRONIC LIVER DISEASE: A REAL-WORLD STUDY

Ning Lin Jinghang Xu[1] Yifan Han[1] Zhan Zeng[1] yanyan yu[1] Xiaoyuan Xu[1]*

[1]Peking University First Hospital

Background: Polyene phosphatidylcholine (PPC) injection is commonly used as a hepatoprotective medication for a variety of liver diseases in China. We previously reported real-world evidence about the effectiveness of lowering ALT and AST levels in patients with hepatitis B virus (HBV) infection, which was comparable with classical glutathione and magnesium isoglycyrrhizinate treatments. The aim of the study is to further examine the heterogenous treatment effects of PPC among different liver diseases other than HBV infection and evaluate the effect of different dosages. **Methods:** Data was extracted from a multicenter registry database in China, which were collected from 264 hospitals in 16 provinces from October 2018 to September 2019. Patients with abnormal liver function and at least one follow-up liver function test after PPC treatment were included in the analysis cohort. Patients with HBV infection or concomitant treatment with other hepatoprotective drugs were excluded. Totally 1454 patients were eligible. The parameters evaluated included ALT, AST, GGT, total bilirubin, prothrombin activity (PTA), globulin, and albumin. Linear mixed-effects growth curve analysis was conducted to compare the slope differences in change of liver function with covariate adjustment for age and sex. A similar analysis was conducted to compare the effects of different dosages. Statistical significance was set at $p < 0.05$. **Results:** The median age of patients was 52 years old among 1454 Patients and the majority of patients were male (63.8%). In the entire cohort, PPC treatment significantly lowered ALT (-9.0 U/L per day, p<0.001), AST (-7.0 U/L per day, p<0.001), GGT (-6.0 U/L per day, p<0.001) and total bilirubin levels (-0.9 mM/L per day, p=0.02), without impacting PTA and globulin. PPC also increased albumin level significantly (0.7 g/L per day, p< 0.001). Patients with DILD had a significantly higher ALT level at baseline ($p < 0.05$) and their ALT level decreased significantly faster compared to those without DILD ($p < 0.05$). ALT ($p < 0.05$) and AST ($p < 0.05$) levels were lower in patients with cirrhosis at baseline and decreased significantly more slowly during PPC treatment compared to those without cirrhosis. Patients with AIH showed similar recovery in ALT and AST levels compared to those without AIH (Figure 1). ALD patients had a much faster decline in GGT after PPC treatment compared to other patients ($p < 0.001$) (Figure 2). Dose analysis revealed that patients with higher ALT levels received higher doses of PPC. The time for normalizing ALT was shown in Figure 3. **Conclusion:** During PPC treatment,ALT and AST levels decline rapidly in patients with AIH and in patients without cirrhosis . ALT level decreased significantly faster in patients with DILD and GGT level decreased significantly faster in patients with ALD. Patients with higher ALT level received higher doses of PPC. The time for normalizing ALT was consistent across different dose regimens.

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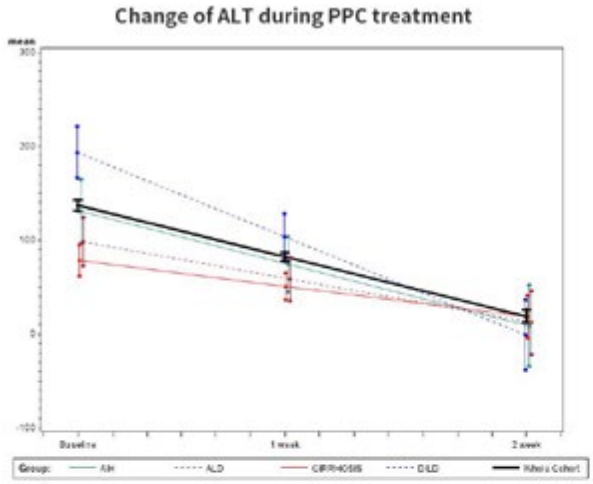

Figure 1. Change of ALT level in patients with chronic live diseases
Change of ALT level in patients with chronic live diseases using mixed effects growth curve analysis. AIH (n=17): autoimmune hepatitis. ALD (n=51): alcoholic liver disease. CIRRHOSIS (n=117). DILD (n=31): drug-induced liver damage.

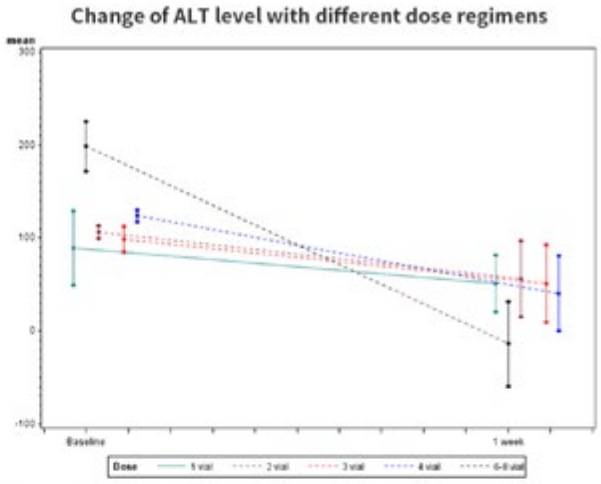

Figure 3. Change of ALT level in patients with different dose regimens
Change of ALT level in patients with different dose regimens using mixed effects growth curve analysis. 1 vial: n=15; 2 vial: n=653; 3 vial: n=189; 4 vial: n=552; 6-8 vial: n=42.

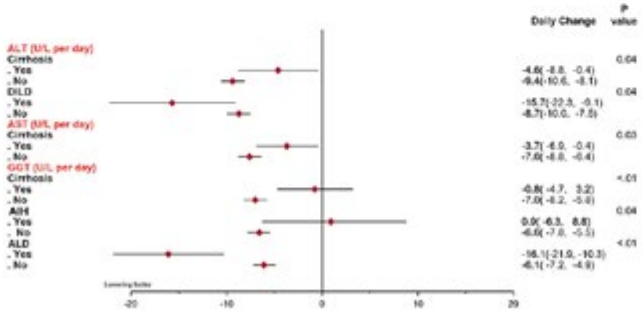

Figure 2. Effect modification on slope of ALT changes by different chronic liver disease.

Disclosures: Ning Lin: Nothing to Disclose, Jinghang Xu: Nothing to Disclose, Yifan Han: Nothing to Disclose, Zhan Zeng: Nothing to Disclose, yanyan yu: Nothing to Disclose, Xiaoyuan Xu*: Nothing to Disclose

3257 | IMPACT OF DISTANCE FROM LIVER TRANSPLANT CENTRE ON OUTCOMES FOLLOWING LIVER TRANSPLANTATION – AN AUSTRALIAN SINGLE CENTRE STUDY

Ken Liu[1] *Simone Chin*[2] *Charlotte Kench*[1] *Rena Cao*[1] *Christina Lee*[1] *Claire West*[1] *Susan Virtue*[1] *Talal Valliani*[1] *David Bowen*[1] *Simone Strasser*[1] *GEOFF McCaughan*[1]

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Background: Access to liver transplantation (LT) is affected by geographic disparities. Higher waitlist mortality is observed in patients residing further away from LT centres but impact of distance on post-LT outcomes is unclear. We aimed to evaluate whether the distance LT recipients reside from their LT centre impacts on graft and patient outcomes. **Methods:** We retrospectively studied consecutive adults who underwent deceased-donor LT from 2006-2021 at Royal Prince Alfred Hospital (RPAH), the only LT centre in the state of New South Wales (NSW), Australia. The state covers an area of 801,150km^2. Those residing outside of NSW at time of transplant were excluded. Donor and recipient data were collected from a prospective LT database. Patients' regional area code (0 = least remote, 4 = most remote) and socioeconomic code (1 = relatively greater disadvantage, 5 = relative lack of disadvantage) were obtained from the Australian Bureau of Statistics. Patients were grouped based on their distance from LT centre at time of transplant (≤100km vs. >100km). For survival analyses, patients were censored if they moved to a new residential address during follow-up. **Results:** During the study period, 973 patients underwent LT (69.7% male, median age 55.6 years (IQR 49.0-60.6)). The median distance from patient residence to LT centre was 44.9km (IQR 21.9-168.0). 64.2% of patients lived ≤100km from RPAH. 77.6% of patients were

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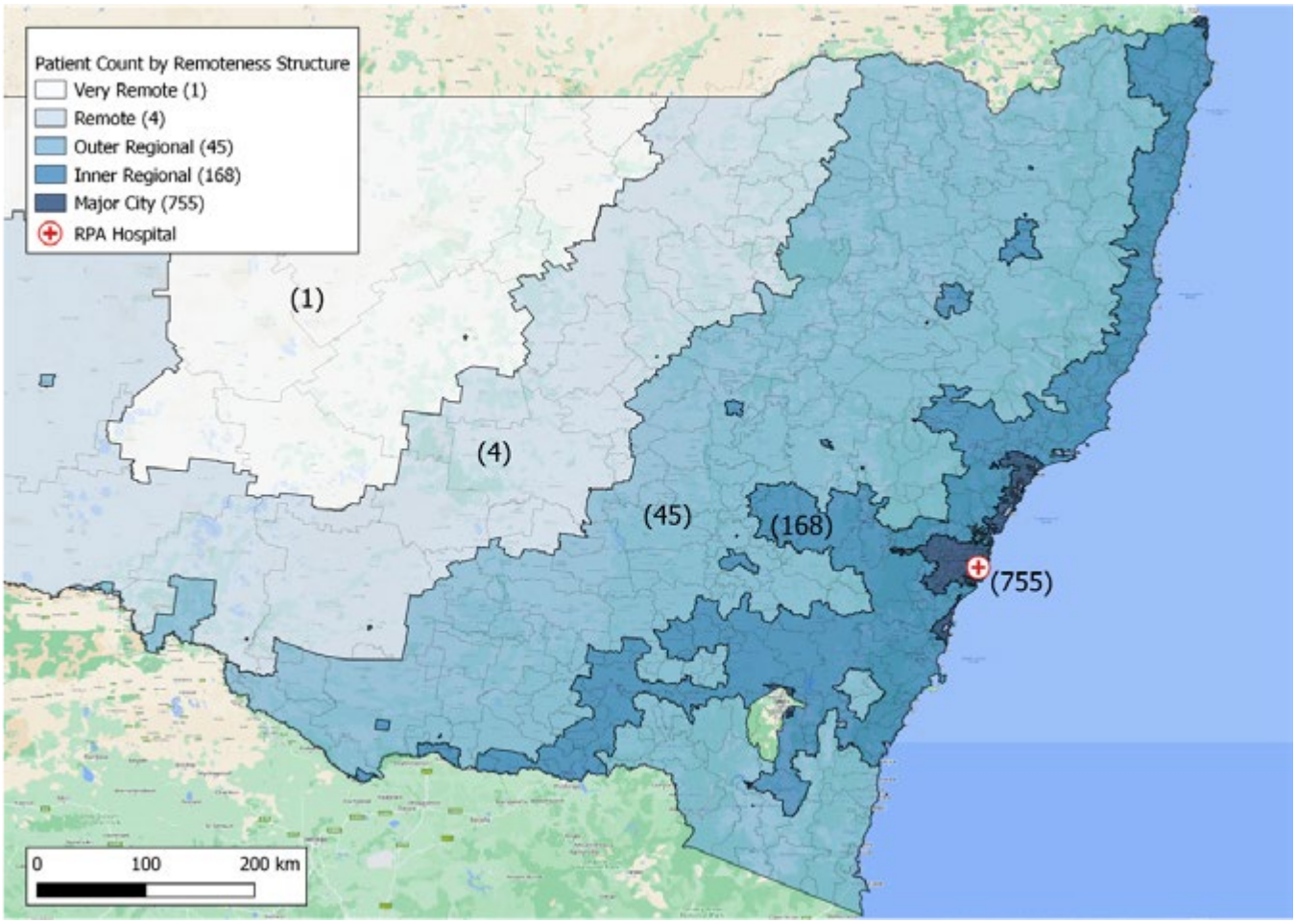
from regional area code 0 (Figure 1). The distribution of LT recipients across the five socioeconomic codes was similar (17.9-20.2%). Compared to patients living ≤100km from RPAH, those living >100km away were less likely to: be male (64.0% vs. 72.7%, p = 0.004); have chronic hepatitis B (3.5% vs. 12.6%, p = 0.001) or viral hepatitis (35.7% vs. 42.2%, p = 0.049) as their cause of liver disease; or have hepatocellular carcinoma as their primary indication for LT (23.3% vs. 32.1%, p = 0.004). Patients living >100km away had higher body mass indices (27.1 vs. 26.0 kg/m^2, p = 0.01) compared to those living closer. At a median follow-up of 47.1 months (IQR 13.5-93.7), there were 190 deaths and 42 retransplants. Living >100km from the LT centre was associated with fewer face-to-face clinic visits in the first year after LT (10 vs. 11 visits, p < 0.001) and fewer overall readmissions to the LT centre (32.4% vs 67.6%, p < 0.001). Distance from LT centre, regional code, and socioeconomic code did not impact on long-term graft or patient survival based on Kaplan-Meier survival analysis (Log-Rank p all >0.1). There was a trend towards increased likelihood of biopsy-proven rejection in patients living >100km away (p = 0.069). **Conclusion:** In this single centre Australian study, patients living further away from their LT centre had different demographics and fewer face-to-face visits during follow-up. Despite this, distance from the LT centre was not associated with long-term inferior graft or patient survival post-LT.



Disclosures: Ken Liu: Nothing to Disclose, Simone Chin: Nothing to Disclose, Charlotte Kench: Nothing to Disclose, Rena Cao: Nothing to Disclose, Christina Lee: Nothing to Disclose, Claire West: Nothing to Disclose, Susan Virtue: Nothing to Disclose, Talal Valliani: Nothing to Disclose, David Bowen: Nothing to Disclose, Simone Strasser: Chiesi: Advisor, Roche Diagnostics: Advisor, Roche Therapeutics: Advisor, Norgine: Speaking and Teaching, Abbott Diagnostics: Advisor, CSL Behring: Advisor, Novo Nordisk: Advisor, Astra Zeneca: Advisor, Sirtex: Speaking and Teaching, Eisai: Speaking and Teaching, GEOFF McCaughan: Nothing to Disclose

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3258 | MORTALITY IMPROVEMENT IN CIRRHOTIC AND HEPATOCELLULAR CARCINOMA PATIENTS WITH MAJOR DISCREPANCIES ACCORDING TO ETIOLOGY: A 10-YEAR NATIONWIDE STUDY ◆

Claire DELACOTE[1] Xavier Lenne[2] Alexandre Louvet[3] Line Ntandja Wandji[4] Amélie BRUANDET[5] Sylvie Deuffic-Burban[6] Philippe Mathurin[4]

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Background: Use of direct antiviral agents (DAA), growing burden of metabolic syndrome (MS) and changes in alcohol per capita require to investigate evolution of mortality in patients with cirrhosis and / or hepatocellular carcinoma (HCC). **Methods:** Data of patients hospitalized between 2012 and 2021 with at least one ICD-10 code of cirrhosis and / or HCC were extracted from the French national medicalized information system program. To overcome over or under diagnosis in 2012, analyses were conducted over 2013-2021. Overall and liver-related deaths (related to HCC or liver failure), age-standardized mortality rates (ASMR, per 100 000), age at death and years of life lost (YLL) were assessed according to etiology (viral [VIR], alcohol [ALC], MS, autoimmune, genetic, other). **Results:** Death occurred in 149,539 out of 380,789 cirrhotic / HCC patients (91.5% related to ALC, VIR and MS). Regardless of etiology, 2/3 deaths were liver-related. Liver-related deaths were mainly HCC-related in VIR (57.9%) and MS (58.5%), but liver failure-related in ALC (65.8%). In VIR, alcohol use disorder (AUD) increased proportion of liver failure-related deaths to 53.2% (vs. 36.6% without AUD, p=0.02). Between 2013 and 2021, overall and liver-related ASMRs decreased in VIR (from 3.0 to 2.5, p=0.01 and from 2.4 to 1.6, p<0.01) and increased in MS (from 2.5 to 3.8, p<0.01 and from 1.9 to 2.3, p=0.02) (Fig A/B). In ALC, overall ASMR remained stable (from 17.1 to 18.1, p=0.11) and liver-related ASMR decreased (from 11.9 to 11.0, p=0.01) (Fig A/B). ALC remained the leading contributor of liver-related ASMR (~67%). MS became the second leading cause (from 10.9 % to 14.1%, p=0.03) and VIR decreased (from 13.6% to 9.7%, p<0.01). Similar trends were observed for overall ASMR. Age at death increased from 62.4 to 66.1 years (p<0.01) in VIR and from 65.5 to 67.8 years (p<0.01) in ALC but remained stable (from 74.2 to 75.1 years, p=0.06) in MS (Fig C). In VIR, AUD decreased age at death (58.4 vs. 68.1 years, p<0.01). The total number of YLL was 2,034,174 (ALC 71.0%, VIR 13.8%, MS 7.5%). YLL per individual were around twice higher in VIR (16.8 years) and ALC (14.3 years) compared to MS (7.9 years). **Conclusion:** Deaths occurred mainly from liver failure in ALC and from HCC in VIR and MS. Therapeutic improvement and earlier patient care management may explain the decrease in liver-related mortality. In VIR, liver-related mortality decreased by 33% thanks to DAA. The years of life lost per individual remained high in ALC and VIR.

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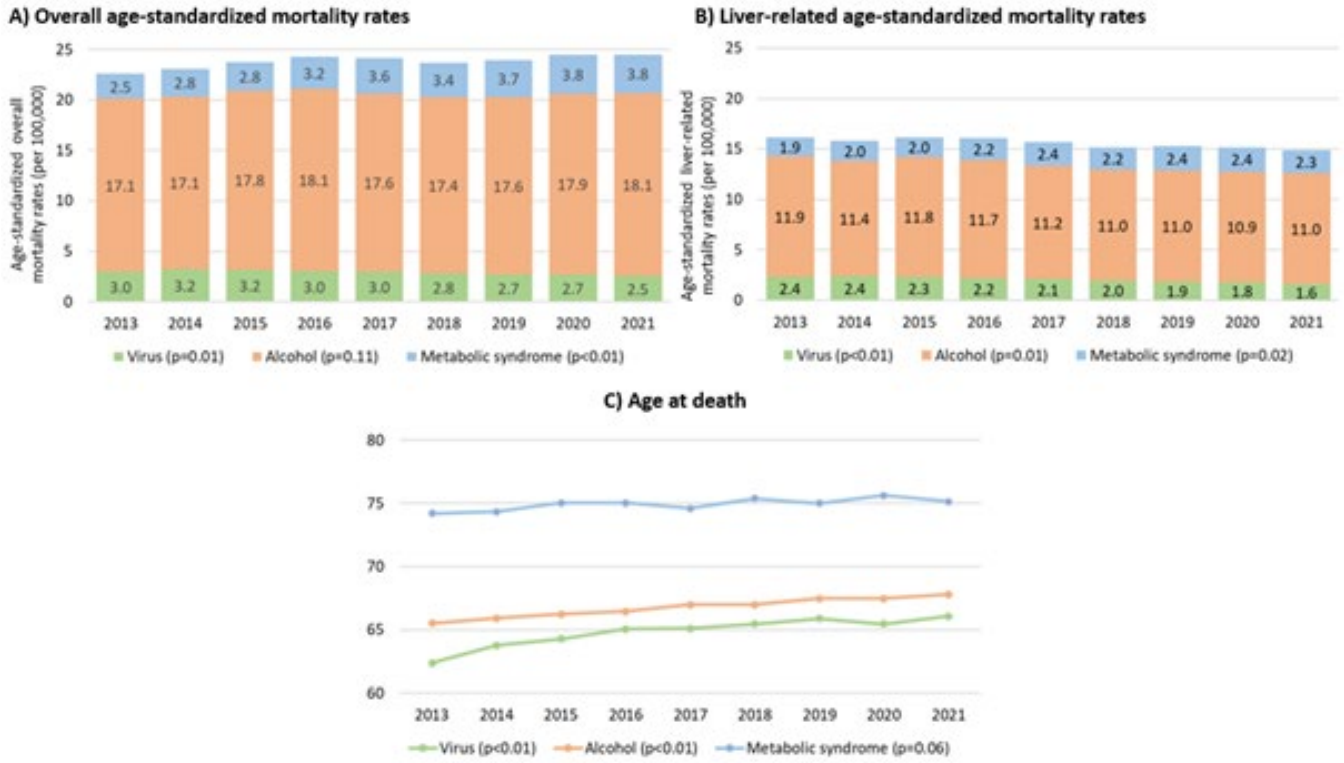

Disclosures: Claire DELACOTE: Nothing to Disclose, Xavier Lenne: Nothing to Disclose, Alexandre Louvet: Consultant relationship with Glaxo-Smith-Kline; Has not ended; Consultant relationship with Ipsen; Has not ended; Speaking and Teaching relationship with Astra-Zeneca; Has not ended; Speaking and Teaching relationship with Gilead; Has not ended; Speaking and Teaching relationship with AbbVie; Has not ended, Line Ntandja Wandji: Nothing to Disclose, Amélie BRUANDET: Nothing to Disclose, Sylvie Deuffic-Burban: Nothing to Disclose, Philippe Mathurin: Nothing to Disclose

3259 | POPULATION-BASED HEPATITIS C SCREENING IN COUNTRY WITH MODERATE SEROPREVALENCE: 21-MONTH RESULTS OF THE PROGRAM IN LITHUANIA

Limas Kupcinskas[1] Egle Čiupkeviciene[1] Alexis Voeller[2] Devin Razavi-Shearer[3] John Ward[4] Ligita Jancoriene[5] Gediminas Urbonas[1] Viktorija Basyte-Bacevice[1] Janina Petkeviciene[1]

[1]Lithuanian University of Health Sciences, [2]Center for Disease Analysis Foundation, [3]Center for Disease Analysis Foundation, [4]Viral Hepatitis Action Coalition, [5]Vilnius University

Background: Lithuanian HCV screening program started on May, 2022. State health authorities pay general practitioners (GPs) a special promoting fee for performing serological tests for HCV antibodies: 1. For the population born in 1945-1994 (once per life) and 2. For people who inject drugs (PWID) or are HIV-infected (annual HCV testing). Such an initiative is the first in Central and Eastern Europe. This study aimed to evaluate **Results:** of the first 21-month of the program and different scenarios to achieve WHO 2030 targets. **Methods:** GPs invited people to perform a serum blood test for HCV antibodies. Anti-HCV (+) patients were referred to a gastroenterologist or infectologist for HCV RNA testing, and if result was positive, direct-acting antiviral (DAA) therapy was prescribed. Information about patients was obtained from the database of the National Health Insurance Fund. The Markov disease progression model elaborated by the CDA Foundation was used to assess HCV elimination progress. The data from the 2022-2023 screening were used as inputs. Three scenarios were developed: the 'Base' scenario - return to pre-screening program level in 2023 and 2 scenarios with different extents of treatment. **Results:** At the beginning of 2022, about 1.8 million people born in 1945-1994 lived in Lithuania. Between May 5, 2022 and January 31, 2024, from this population 1145121 people (63,6%) were tested for HCV antibodies. Positive test results were found in 1.23% of cases. In the risk group, 9604 PWID and HIV+ people were screened, and 30,1% were seropositive. Viremia was detected in 58 %. During 21-month period 4811 patients were treated with DAA. The number of treated patients during 21 months of program increased 2,8 times

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in comparison to previous 21 month before the program (Aug 2020 - Apr 2022). Treatment delay for 48% of HCV patients was related to organizational problems (consultation waiting line; fibrosis restrictions were removed only on May, 2024). By the end of 2024 we expect to perform HCV antibody testing in 80% of the target population and treatment of 80% of RNA-positive individuals, further aiming to cure most of infected patients by 2030. The Markov disease progression model to assess HCV elimination showed the following scenarios: Scenario 1: if the same number of patients are treated as before the screening, the WHO targets will not be reached. Scenario 2: treating 70% of infected patients will meet most but not all WHO targets. Scenario 3: by treating all infected patients by 2030, the WHO target will be met by saving 150 lives and preventing 90 new cases of decompensated cirrhosis and 120 cases of hepatocellular carcinoma. **Conclusion:** Our data show that in European country with moderate HCV seroprevalence a population-based screening program can be feasible, screening near 64 % (more than 1,1 million) of the population born between 1945 and 1994 during the first 21 months of the program. WHO 2030 goals can be achievable in Lithuania.

Disclosures: Limas Kupcinskas: Abbvie: Honorarium for lecture, Egle Čiupkeviciene: Nothing to Disclose, Alexis Voeller: Nothing to Disclose, Devin Razavi-Shearer: Nothing to Disclose, John Ward: Grant/Research Support relationship with Dynavax, Merck, Cepheid,; Has not ended; Grant/Research Support relationship with Abb Vie, Abbott, Gilead, Siemens, Roche, Pharco, Virion,; Has not ended, Ligita Jancoriene: Nothing to Disclose, Gediminas Urbonas: Nothing to Disclose, Viktorija Basyte-Bacevice: Nothing to Disclose, Janina Petkeviciene: Nothing to Disclose

3260 | EXPLORING THE IMPACT OF WEEKEND ADMISSION AND RURALITY ON OUTCOMES AND PRACTICES IN HOSPITALIZED PATIENTS WITH DECOMPENSATED CIRRHOSIS: A NATIONWIDE CROSS-SECTIONAL STUDY

Ahamed Khalyfa[1] *Betty Tu*[1] *Qianyi Shi*[1] *Tomohiro Tanaka*[1]

[1]*University of Iowa School of Medicine*

Background: In patients with decompensated cirrhosis, prior studies have illustrated an equivocal effect from weekend admission on mortality, while others have shown increased odds of mortality associated with admission to rural hospitals. We aimed to investigate the impact of hospital-level rurality and weekend admissions, as well as their effect modification, in hospitalized patients with decompensated cirrhosis in the United States in the recent era. **Methods:** We performed a cross-sectional study using National Inpatient Sample (NIS) of hospital admissions for decompensated cirrhosis between 2016 and 2020. Logistic regression models were fitted to evaluate the impact of rurality, weekend admission, and their interaction on the outcomes of in-hospital mortality (primary outcome), chances to receive certain procedures (esophagogastroduodenoscopy, paracentesis, Transjugular Intrahepatic Portosystemic Shunt [TIPS]), and time to first procedure for each complication (secondary outcomes). Models were adjusted for sex, age, race, etiology of liver disease, severity of the clinical condition (APRDRG Risk Mortality), and socioeconomic factors. **Results:** In total, 2,369,041 hospitalizations with decompensated cirrhosis were included in the analysis. Hospitalization in rural hospitals was associated with a lower odds of in-hospital death (odds ratio [OR] 0.84; 99% CI: 0.80-0.86) compared to non-rural hospitals. However, hospitalization in rural centers was associated with a higher probability of being transferred to other tertiary care centers (7.2% vs 2.8%, Chi-square test, p<0.001), particularly for those with highest APRDRG mortality score (OR 1.72; 1.59-1.86). Weekend admission had lower odds of death (OR 0.99; 0.975-0.998). No significant interaction between rurality and weekend was observed in any of the models. Hospital rurality was associated with lower odds of receiving procedures of interest (95% CIs <1) but not with days to procedures except for hemodialysis (-1.35 days; -2.59 - -0.11). Weekend admission was not significantly associated with the chance to receive a procedure except for paracentesis (OR 0.94; 0.88-0.94). **Conclusion:** This study showed a novel finding that admission to a rural hospital with decompensated cirrhosis in recent years was associated with lower odds of mortality, which could be partially explained by a higher probability of being transferred to tertiary care centers. The discrepancy between the lower probability of receiving life-saving procedures for complications of decompensated cirrhosis, and the non-significant difference in the days until those procedures are received, suggests variability in practice patterns and activity among rural hospitals. Weekend hospitalization was associated with reduced mortality regardless of hospital-level rurality, though the effect size was modest and may be due to unmeasured confounders.

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Disclosures: Ahamed Khalyfa: Nothing to Disclose, Betty Tu: Nothing to Disclose, Qianyi Shi: Nothing to Disclose, Tomohiro Tanaka: Nothing to Disclose

3261 | COMPENSATED ADVANCED CHRONIC LIVER DISEASE MANAGEMENT IN PRIMARY CARE: GOOD QUALITY WITH THE RIGHT MODEL

Alvin Lee[1] Jeyamani Ramachandran[1] Kate Muller[2] Rachel Wundke[1] Kylie Bragg[1] Alan Wigg[1]

[1]Flinders Medical Centre, [2]Flinders Medical Center

Background: Despite an increasing global emphasis on the adoption of care pathways for chronic liver disease (CLD) in the primary care setting, CLD has not yet been incorporated within the spectrum of chronic diseases that are managed by primary care physicians (PCPs) in Australia. Therefore, at a tertiary hospital in South Australia, a de-centralised model of care (MOC) was developed in consultation with PCPs to transition patients with stable compensated advanced CLD (cACLD) back to their PCPs. The aim of this study was hence to examine the quality of care received by patients with cACLD following transition to this new MOC. **Methods:** We conducted a retrospective analysis of all adult patients at our centre who transitioned to this new MOC with a greater than 12-month follow-up period. Quality outcome measures that were assessed included adherence to surveillance for hepatocellular carcinoma (HCC) and hepatic osteodystrophy, as well as appropriate titration of beta-blocker prophylaxis for patients with clinically significant portal hypertension (CSPH). The transition to primary care was supported by PCP protocols outlining care requirements, including triggers for referral back to the tertiary care system. Hepatology nurses provided ongoing annual reviews with vibration-controlled transient elastography too. **Results:** 172 patients with cACLD were included in this study, with a median follow-up period of 15.1 months (IQR 13.9-17.3). The average age was 66 years (SD 10.7) with 59.9% being male, and the predominant aetiologies for their cACLD included alcohol-related liver disease (41.9%), metabolic-associated fatty liver disease (32.6%), and Hepatitis C virus (22.7%). Adherence to 6-monthly ultrasounds and serum Alpha-Fetoprotein testing was 79.7% and 79.1% respectively. In addition, adherence to 2-yearly Bone Mineral Density scans and serum Vitamin D testing was 74.4% and 75.6% respectively. Of the 79 patients with CSPH, 65 (82.3%) were being appropriately managed on Carvedilol by their PCP. Promisingly, of the five patients who met triggers for referral back to a hepatology unit, all were appropriately referred back by their PCP. Significantly, no patients experienced any preventable presentations or admissions to hospital from their underlying cirrhosis. However, one patient suffered a serious adverse event in primary care related to a missed diagnosis of HCC, which was due to non-adherence to ultrasound surveillance. **Conclusion:** Preliminary results from this pilot study suggest that transition of patients with cACLD to primary care based on this MOC is feasible and associated with an acceptable quality of care. Moreover, this MOC may provide a sustainable solution to the growing clinical burden of cACLD in tertiary care hepatology clinics. Further evaluation of this MOC with long-term follow-up data, as well as assessment of the acceptability by PCPs and patients, is required before additional recommendations can be made.

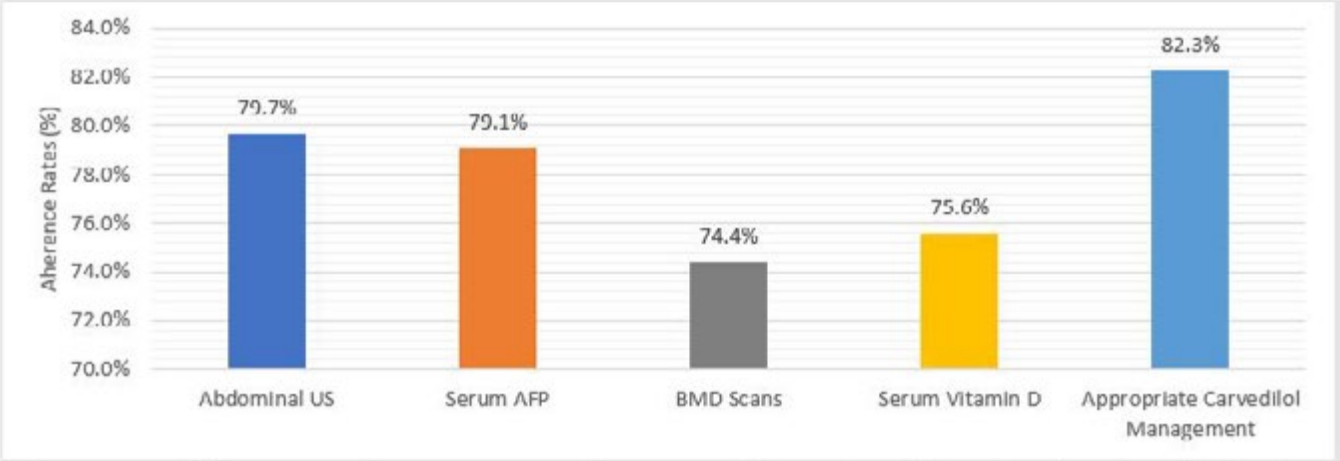

Figure 1: *Rates of adherence to quality outcome measures for patients with chronic advanced chronic liver disease (cACLD) within this new model of care; US, ultrasound; AFP, Alpha Fetoprotein; BMD, bone mineral density*

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Disclosures: Alvin Lee: Nothing to Disclose, Jeyamani Ramachandran: Nothing to Disclose, Kate Muller: CSL Behring: Advisor, NovoNordisk: Advisor, AstraZeneca: Advisor, Chiesi: Advisor, Eisai: Speaking and Teaching, Rachel Wundke: Nothing to Disclose, Kylie Bragg: Nothing to Disclose, Alan Wigg: Nothing to Disclose

3262 | THE EFFECT OF IMPLEMENTATION INTERVENTION (GILEAD FOCUS PROGRAM) ON LINKAGE TO HEPATITIS C CARE TIME AT A COMMUNITY HEALTH CENTER IN DEEP SOUTH ◆

Adelero Adebajo[1]

[1]*Cooperative Health, Columbia SC*

Background: To eliminate Hepatitis C (HCV) by 2030, people with HCV should be identified and promptly linked to care after diagnosis. An implementation intervention, the Frontline of Communities in the United States (FOCUS) program, highlighted by four pillars (normalization of routine testing, promotion of testing based on electronic medical records [EMR], procedure overseed by bridge coordinator, and quality improvement training/feedback among staff), has been conducted in a community health center in South Carolina since 2018. We aim to assess the impacts of this intervention on linkage to care time and its sustainability. **Methods:** The EMR data from a cohort (n=580) of adults who received HCV care services from the Cooperative Health Center (January 2012 to April 2024) were used. Descriptive analysis was employed for outcome (linkage to care days) and sociodemographic variables (i.e., race, sex, age, health insurance). Socio-demographics and average LTC days were compared by subgroups (patients before vs. after the intervention). Multivariate linear regressions were conducted on LTC days, controlling relevant covariates. **Results:** Most of the cohort were male (59%) and African Americans (60%), with a mean age of 45 years (SD=13.64) and without health insurance (57%). The average LTC days have significantly declined since the FOCUS was implemented (396 days vs. 34 days). The FOCUS intervention was associated with a decrease of 551 days in linkage to care time (p=.002, 95%CI [-893, -209]) controlling demographics. The impacts of the implementation intervention were not affected by gender, age, race/ethnicity, or health insurance status. Although the HCV testing uptakes decreased during the COVID-19 pandemic (2020-2023), the LTC days remained low except in 2022. **Conclusion:** Since its implementation, the FOCUS program has significantly shortened the days of linkage to care for people with HCV. Patients' socio-demographic characteristics did not affect the positive impacts and were sustainable through the COVID-19 pandemic.

Disclosures: Adelero Adebajo: Nothing to Disclose

3263 | BISPHOSPHONATE EFFECTIVENESS IN PATIENTS WITH CIRRHOSIS: AN EMULATED CLINICAL TRIAL

Beanna Martinez[1] *Xi Chen*[1] *Elliot Tapper*[2] *Neehar Parikh*[2]

[1]*University of Michigan,* [2]*University of Michigan Medical Center*

Background: Falls and fractures are common and morbid for patients with cirrhosis. Osteoporosis increases the risk of fractures. Bisphosphonates are recommended for the prevention of fractures in cirrhosis; however, data supporting effectiveness are lacking for effectiveness. We sought to emulate a clinical trial of bisphosphonates in cirrhosis. **Methods:** We used national Medicare data (2008-2020) to examine the risk of fractures in patients who did or did not receive bisphosphonates with a new-user design among people diagnosed with cirrhosis and osteoporosis. We balanced treated and untreated with inverse probability of treatment weighting, evaluated intention-to-treat and as-treated effects, and examined both control exposures (statin use) and outcomes (decompensation) to test causal relationships. The primary outcome was fractures incurred over 5 years. Secondary outcomes included falls requiring hospitalization, decompensation, and death/transplant. **Results:** There were 253 and 1,428 new users and non-users of bisphosphonates, respectively. The mean age was 75 years. The most common bisphosphonate used was alendronate (73.6%). Bisphosphonates reduced fractures (28.5% versus 45.3%), sHR 0.74 95%CI(0.66,0.83). Arm fractures had the greatest reduction with bisphosphonate use (17.1% versus 30.9%, p <0.0001). Overall, bisphosphonate users spent more time on drug (28.4% of person-years), but crossover occurred (non-users spent 15.1% of person-years on bisphosphonates). As treated, bisphosphonates as a time-varying covariate reduced fractures sHR 0.82 95%CI(0.74,0.92). Similar

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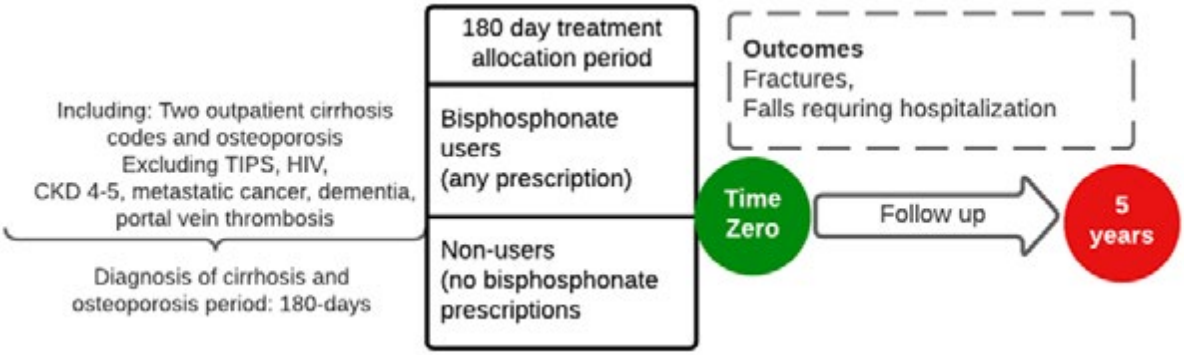
as-treated effects on fracture risk were not observed with statin therapy. **Conclusion:** In our target trial emulation of a nationally representative cohort of elderly patients with cirrhosis bisphosphonates reduced fracture risk in patients with cirrhosis.



Disclosures: Beanna Martinez: Nothing to Disclose, Xi Chen: Nothing to Disclose, Elliot Tapper: Nothing to Disclose, Neehar Parikh: Grant/Research Support relationship with Exact Sciences; Has not ended; Consultant relationship with AstraZeneca; Has not ended; Consultant relationship with Exelixis; Has not ended; Grant/Research Support relationship with Exelixis; Has ended; Advisor relationship with Fujifilm Medical; Has ended; Grant/Research Support relationship with Genentech; Has ended; Consultant relationship with Exact Sciences; Has not ended

3264 | DIGESTIVE DISEASE BURDEN AND HEALTHCARE DISPARITIES IN SUB-SAHARAN AFRICA OVER THREE DECADES

Omar Al Ta'ani[1] Yazan Al-Ajlouni[2] Wesam Aleyadeh[3] Mohammad Tanashat[4] Basile Njei[5]

[1]Allegheny Health Network, [2]Montefiore Medical Center, [3]Toronto Centre for Liver Disease/Cleveland Clinic Akron General Hospital, [4]Yarmouk University, [5]Yale University

Background: Digestive diseases (DD), such as cirrhosis, upper digestive diseases, inflammatory bowel disease, and pancreatitis, pose a significant public health challenge in Sub-Saharan Africa (SSA). The prevalence and impact of these conditions vary widely, highlighting the difficulties in managing DD within diverse health systems and sociocultural contexts. Despite their severe impact on morbidity and mortality, they have not received as much attention as diseases like HIV/AIDS or malaria. This study utilizes the Global Burden of Disease (GBD) dataset to provide a comprehensive epidemiological overview of DD in SSA, aiming to address gaps in current research and inform effective health policies and interventions. **Methods:** Our study utilized data from the GBD dataset spanning 1990 to 2019, which offers extensive information on mortality, incidence, and disability-adjusted life years (DALYs) across 204 countries. We analyzed trends in the prevalence, deaths, and DALYs of DD, calculating percentage changes and estimated annual percentage changes (EAPCs) in age-standardized rates. Linear regression was employed to compute EAPCs, while Pearson correlation analyses were used to assess the relationships between EAPCs and socio-demographic indices. All analyses and figures were generated using R programming version 4.3.3. **Results:** Our study documented a significant increase in the total cases of digestive diseases from 1990 to 2019, with prevalence rising by 95.7% for males and 103.5% for females. However, age-standardized prevalence rates per 100,000 individuals declined by 6.9% for males and 7.2% for females. Age-standardized DALY rates for all digestive diseases decreased by 23.7%, while age-standardized death rates fell by 20.6% for males and 22.1% for females. Specific conditions, such as cirrhosis, showed substantial declines in both DALY and death rates, with reductions of 25.9% and 30.7% for DALYs, and 25.6% and 27.6% for death rates in males and females, respectively. The analysis revealed a significant negative correlation between the EAPCs of DALYs and the Universal Health Coverage (UHC) effective coverage index, with a Pearson correlation coefficient of -0.38 (p-value: 0.008). **Conclusion:** Our study revealed significant changes in the prevalence of digestive diseases in Sub-Saharan Africa, with decreases in conditions like cirrhosis and increases in inflammatory bowel disease, driven by risk factors such as high BMI and drug use. These findings highlight the urgent need for tailored health policies and interventions that address both declining and emerging health challenges. By enhancing public health strategies, these measures can ultimately improve health outcomes in the region.

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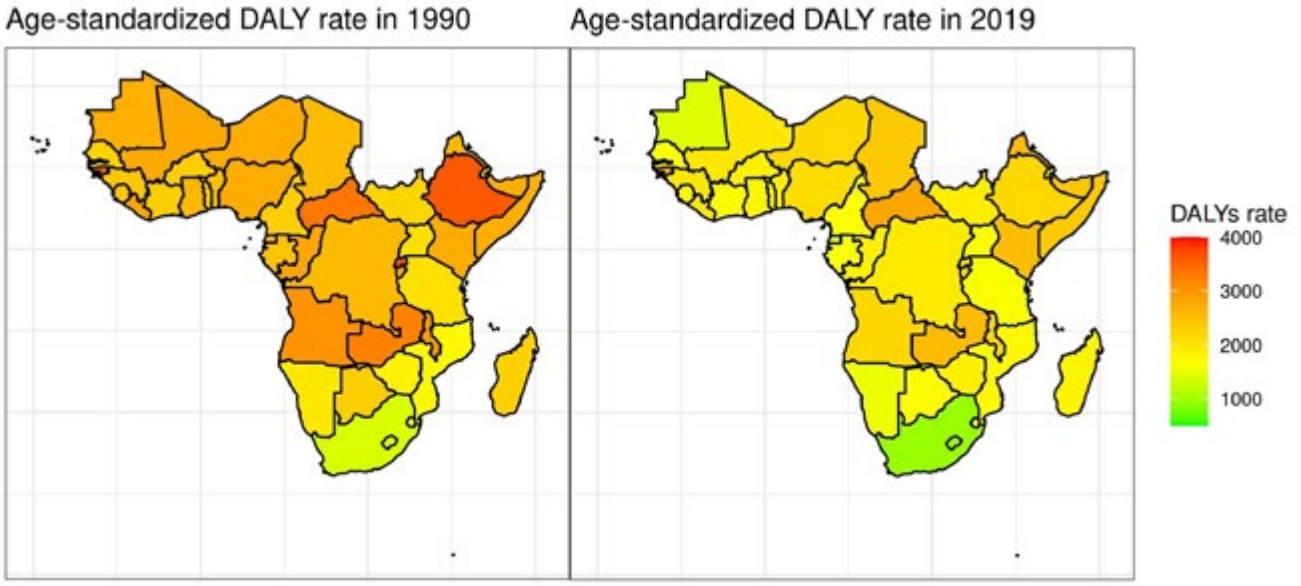

Disclosures: Omar Al Ta'ani: Nothing to Disclose, Yazan Al-Ajlouni: Nothing to Disclose, Wesam Aleyadeh: Nothing to Disclose, Mohammad Tanashat: Nothing to Disclose, Basile Njei: Nothing to Disclose

3265 | ANNUAL OUT-OF-POCKET MEDICAL COSTS AND FINANCIAL BURDEN AMONG TRANSPLANT RECIPIENTS IN THE UNITED STATES

Gabrielle Jutras[1] *Jennifer Lai*[1] *Sharad Wadhwani*[2]

[1]*University of California, San Francisco,* [2]*UCSF Benioff Children's Hospital*

Background: Solid organ transplantation, including liver transplantation, involves significant financial costs. While studies have quantified costs to the United States (U.S.) healthcare system, the risk of financial toxicity on transplant recipients remains poorly characterized. We assessed annual out-of-pocket (OOP) medical expenses for transplant recipients and characterized their risk of financial toxicity. **Methods:** We identified solid-organ or bone marrow transplant recipients from the Medical Expenditure Panel Survey (MEPS) survey 2016–2020. We calculated total OOP healthcare expenditures, including yearly costs for medical care, medications, and insurance premiums. Financial toxicity was defined as (1) "high" if the total OOP healthcare expenses exceeded 20% of household income, and as (2) "catastrophic" if it exceeded 40%. Sample weights estimated national prevalence. **Results:** There were N=200 transplant recipients during the survey period, representing 466,016 U.S. adults nationally. The annual mean OOP healthcare expenses was $4,034 (95%CI, $3,218, $4,851), with health insurance premiums and medications being the largest categories of cost. Among transplant recipients, 12% (SE 3) experienced high financial burden while 6% (SE 2) faced catastrophic financial burden. Low-income patients (income ≤ 200% of the poverty line) were ~8-fold more likely to experience high burden (OR 7.6, p=0.001) and ~3-fold more likely to face catastrophic burden (OR 3.2, p=0.01) than high-income patients. Low-income patients with private insurance faced the highest risk of financial toxicity (OR 7.4, p=0<0.001). Among patients with private insurance, those facing financial toxicity were less educated, more likely to live in the northeast or south regions, and had a higher prevalence of high cholesterol (p<0.05 of all). In the overall transplant recipients population, those with high financial burden reported poorer health (29% vs 9%, p=0.05) and more frequent episodes of nervousness (51% vs 20%, p<0.01). Among recipients with financial toxicity, 10% (SE 6) delayed medication due to costs, versus 3% (SE 1) of those without financial toxicity. **Conclusion:** Transplant is costly for patients, especially for low-income patients with private insurance, leading to financial toxicity associated with poorer health. Tailoring health system and policy interventions to address financial toxicity in transplant recipients may be one strategy to improve transplant outcomes.

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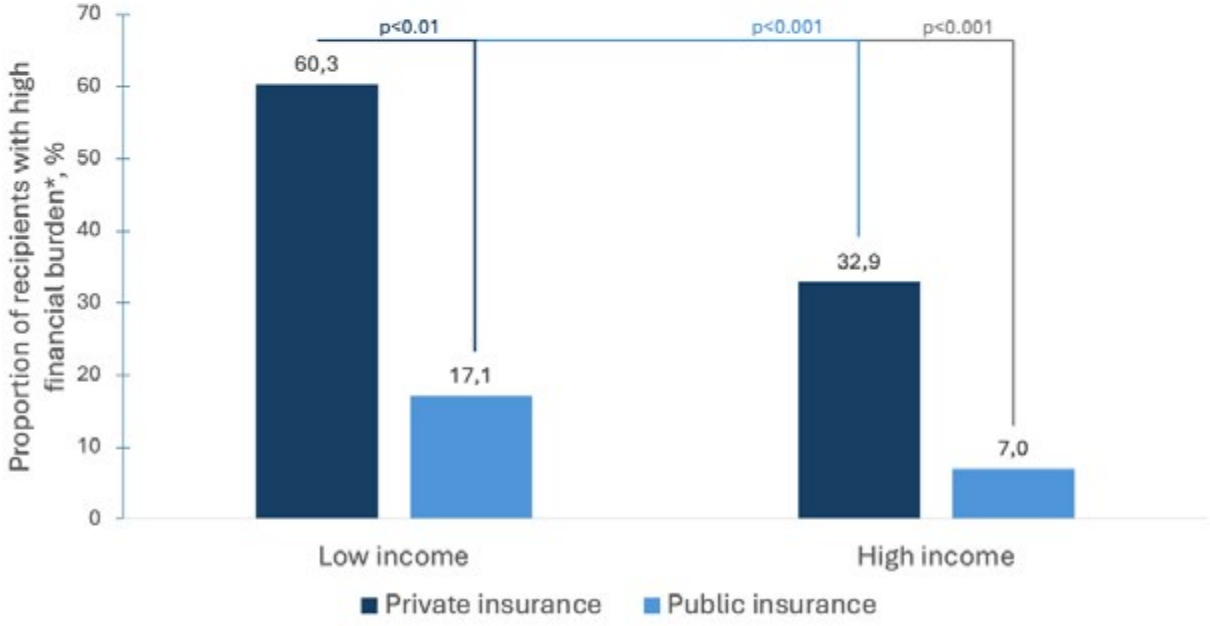
Table 1: Out-of-Pocket Healthcare Expenses, Overall and by Income Category

Annual OOP* Expenditure Category, mean (95% CI)	Overall (n=466,017)	Low income (n=110,504)	Middle/High income (n=355,513)	p-value
Total	4034 [3218-4851]	2537 [1210-3864]	4500 [3493-5506]	**0.02**
Insurance premiums	2005 [1214-2796]	926 [0-1912]	2340 [1331-3350]	**0.05**
Office visits	503 [360-646]	191 [43-340]	600 [424-778]	**0.00**
Outpatient facilities	88 [48-128]	100 [4-195]	85 [41-128]	0.78
Emergency visits	36 [5-66]	19 [0-44]	41 [1-80]	0.36
Inpatient stays	44 [15-73]	57 [0-137]	40 [11-70]	0.69
Dental care	313 [133-489]	493 [0-1167]	258 [143-373]	0.50
Medication	810 [543-1076]	614 [6-1222]	871 [585-1156]	0.44
Medical supplies	131 [56– 206]	115 [0-248]	136 [46-225]	0.80

*OOP: out-of-pocket

Figure 1. Proportion of transplant recipients with high financial burden, by income and insurance category



$$\text{*High financial burden} = \frac{\text{Total annual out-of-pocket expenses}}{\text{Household income}} \geq 20\%$$

Disclosures: Gabrielle Jutras: Nothing to Disclose, Jennifer Lai: Nestle Nutrition Institute: Grant/Research Support, Novo Nordisk: Consultant, Genfit: Consultant, Boehringer Ingelheim: Advisor, Sharad Wadhwani: Mirum: Advisory Board

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3266 | TREATMENT PERSISTENCE AND DISCONTINUATION AMONG CHRONIC HEPATITIS B PATIENTS INITIATING ANTIVIRAL TREATMENT

Dilip Makhija[1] Benjamin Chastek[2] Mary Johnson[2] Aileen Chi[1] Alice Hsiao[1] Marvin Rock[1]

[1]Gilead Sciences, [2]Optum

Background: This study aimed to describe treatment persistence, discontinuation, switch, and restart of nucleos(t)ide analogues in treatment naïve CHB patients. **Methods:** This was a retrospective study using administrative claims from the Optum Research Database for commercial and Medicare Advantage Part D (MAPD) health plan enrollees. Treatment-naïve CHB patients initiating tenofovir alafenamide fumarate (TAF), entecavir (ETV), or tenofovir disoproxil fumarate (TDF) between 01Nov2016 and 30Nov2022 were identified. Treatment initiation was considered the index date. Persistence was measured as time to the earlier of discontinuation (gap in therapy >30 days), switch, or end of follow-up. Adherence was measured as proportion of days covered during the variable length follow-up. Descriptive analysis, Kaplan-Meier analysis, and Cox Proportional Hazards models adjusting for demographics, clinical characteristics, and baseline cost and utilization were conducted. **Results:** Of the CHB patients identified (N=14,935), 4067 adults had evidence of treatment and at least 6 months baseline and follow-up enrollment in the claims database. A total of 1384 treatment-naïve patients met inclusion criteria. On index 338(24%) patients initiated TAF, 477(35%) ETV, and 567(41%) TDF. Mean (SD) age (years) was 55(14) for ETV, 54(15) TAF and 52(14) TDF. Using Kaplan-Meier analysis, median persistence (months) with the index therapy was longest for TAF (23.3), followed by ETV (11.5) and TDF (9.2). Among patients 65+, median persistence (months) with TAF was 38.0, 9.0 for ETV and 6.9 for TDF. Across all three cohorts, persistence was more likely to end due to discontinuation vs. switching; TAF: 49% vs. 7.4%; ETV: 60% vs. 3.6%; TDF: 64% vs. 7.6%. Following discontinuation, most patients (56%-60%) restarted their index therapy. Compared to TAF, adjusting for covariates, the rate of discontinuation/switch was higher for ETV (HR=1.34, p<0.01) and TDF (HR=1.62, p<0.01). Mean adherence with the index medication was highest for TAF (0.74) followed by ETV (0.63) and TDF (0.59). **Conclusion:** TAF was found to have higher adherence and longer persistence versus ETV and TDF, especially among patients 65+ years old. While half to two-thirds of patients discontinued the index therapy, most restarted before the end of the follow-up. These findings have clinical implications for patient engagement, therapy selection, and achieving long-term treatment success and warrant further investigation.

Disclosures: Dilip Makhija: Gilead Lifesciences: Employee, Benjamin Chastek: Optum: Employee, Mary Johnson: Optum: Holds stock, Aileen Chi: Gilead Scienes Inc.: Employee, UCB Inc.: Employee, Savara: Stock – privately held company, Transmedics: Stock – privately held company, UCB Inc.: Employee, Alice Hsiao: Gilead Sciences, Inc.: Employee, Marvin Rock: Nothing to Disclose

3267 | EARLY DETECTION OF LIVER FIBROSIS IN PATIENTS WITH ALCOHOL USE DISORDER IMPROVES LONG-TERM ABSTINENCE ◆

Amelia Orgill[1] Michael Jew[2] MARYAM SOLTANI[1] Heather Patton[1]

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Background: Excessive alcohol consumption contributes to millions of deaths worldwide, with 25% of deaths being associated with liver cirrhosis. With both alcohol use disorder (AUD) and alcohol-associated liver disease on the rise, there is a need for collaboration between psychiatry and hepatology disciplines to augment early identification of advanced liver disease prior to symptoms and decompensation. In this study, we utilize Fibroscan to establish the prevalence of advanced fibrosis and cirrhosis in veterans with severe AUD without known liver disease and assess the effect of early screening on alcohol consumption. **Methods:** All veterans with AUD admitted to the Substance Abuse Residential Rehabilitation Treatment Program (SARRTP), a residential treatment program within the San Diego VA, between January 2021 and June 2023 were offered liver health screening via blood tests and Fibroscan. Patients with liver stiffness measurement (LSM) ≥ 8 kPa were offered liver clinic follow-up and repeat Fibroscan in three to six months. The severity of AUD was assessed for each patient using the condensed Alcohol Use Disorders Identification Test (AUDIT-C) prior to admission, within a year after admission, and over a year after admission. Patients' demographic information, alcohol consumption patterns, laboratory and Fibroscan results, and longitudinal outcomes were collected. **Results:** Of 220 patients

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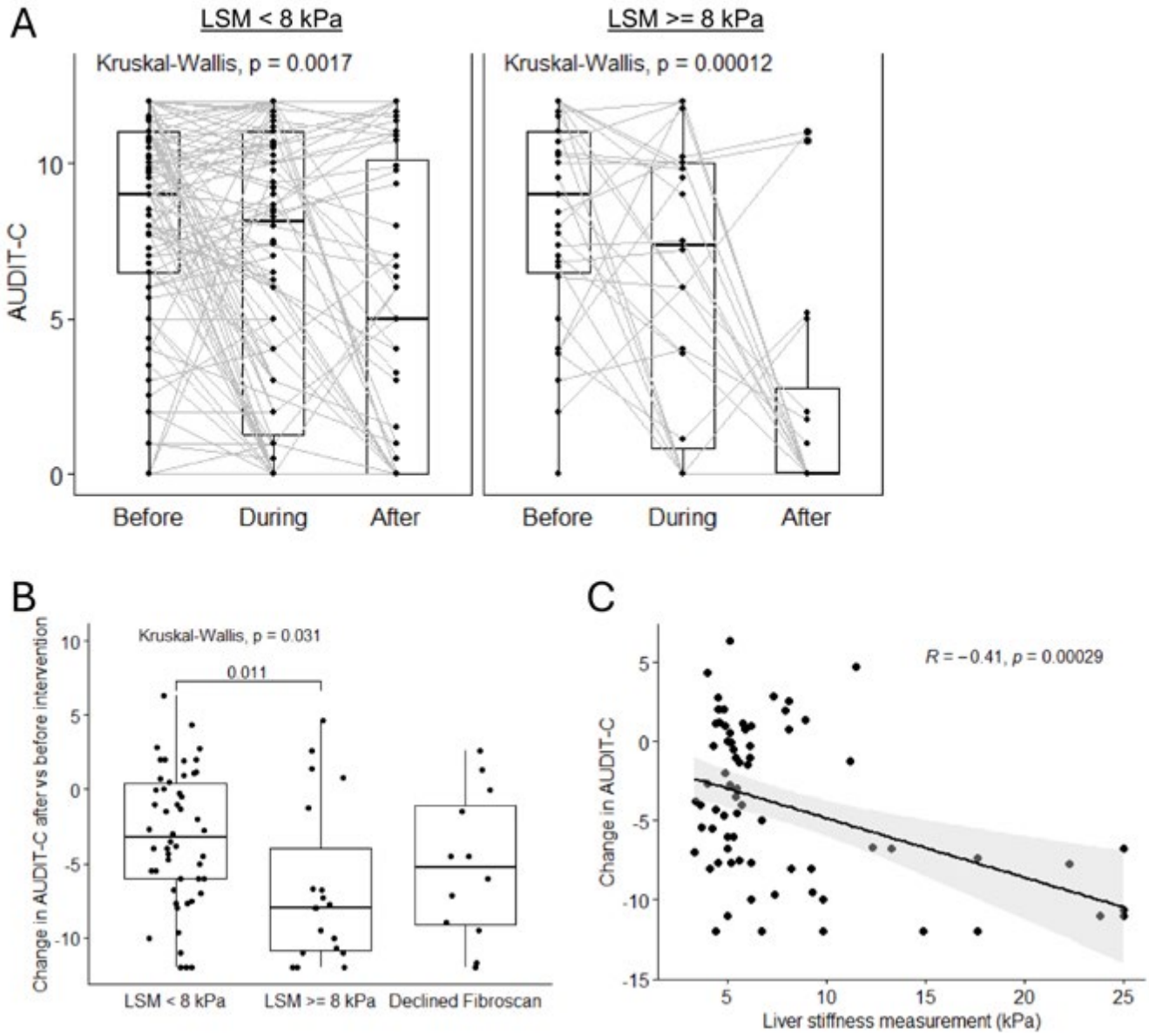
with AUD without known liver disease enrolled in SARRTP, 35 patients were identified by Fibroscan to have LSM ≥ 8 kPa. Patients with LSM ≥ 8 kPa had a significantly lower AUDIT-C score after one year compared with patients with LSM < 8 kPa and patients who did not undergo Fibroscan (median AUDIT-C score of 0 vs 6 and 3, respectively, p = 0.012, Figure 1A). Patients with LSM ≥ 8 kPa also had a significantly greater change in AUDIT-C scores before and after Fibroscan, compared to patients who declined FibroScan or those with LSM < 8 kPa (p = 0.031, Figure 1B). The change in AUDIT-C score before and after Fibroscan was negatively correlated with LSM (Figure 1C). 29% of patients with elevated LSM at baseline encounter were identified to have cirrhosis on follow-up and incorporated into regular hepatology care. **Conclusion:** Our findings highlight that implementation of liver health screening with noninvasive testing, such as Fibroscan, in high-risk populations assists in early diagnosis of advanced liver disease and promotes abstinence in patients with AUD and advanced fibrosis.



Disclosures: Amelia Orgill: Nothing to Disclose, Michael Jew: Nothing to Disclose, MARYAM SOLTANI: Nothing to Disclose, Heather Patton: Nothing to Disclose

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3268 | LIVER CANCER RISK IN INDIVIDUALS UNDER 35 AND PM2.5 EXPOSURE: A GLOBAL ANALYSIS OF 179 COUNTRIES FROM 1990 TO 2019, WITH PROJECTIONS TO 2035

Wang Zixing[1] Zilong Wang[2] Xiaoxiao Wang[2] Huiying Rao[2] Feng Liu[2] Liying Ren[2] Hongsong Chen[2]

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Background: Since the 1990s, the widespread administration of hepatitis B vaccines to newborns has brought about significant shifts in the risk factors for liver diseases worldwide. Despite the increasing divergence in air quality over the past three decades, the impact of PM2.5 exposure on liver cancer risk in the new generation remains uncertain. **Methods:** Our analysis encompassed PM2.5 data from 1990 to 2019 across 179 countries, which were classified into four trajectory groups. We assessed the risk of liver cancer among individuals aged 10–35 years old within each group in 2022. By identifying the most critical exposure window, we calculated the relative risks of liver cancer based on the World Health Organization's Interim Targets 1 to 4 for PM2.5 (35, 25, 15, 10 μg/m3, respectively). Moreover, we projected the population attributable fraction of liver cancer from 2025 to 2035 by considering the ongoing trends of PM2.5 exposure in each major continent. **Results:** We found significant differences in the risk of liver cancer based on the specific PM2.5 trajectory groups. Specifically, the high minor decrease group (60 countries, with PM2.5 levels decreasing from 49 to 48 μg/m3), continuously moderate group (40 countries, with levels averaging approximately 27 μg/m3), moderate dramatic decrease group (33 countries, with levels decreasing from 24 to 16 μg/m3), and low minor decrease group (46 countries, with levels decreasing from 14 to 13 μg/m3) exhibited mean (SE) incidence rates of 8.16 (1.38), 4.82 (0.91), 2.49 (0.61), and 2.44 (0.57) per million population in 2022, respectively. Notably, no significant differences were observed in the latter two groups across gender and age categories. The analysis identified the maximum PM2.5 concentration over the past 10 years as the most critical exposure window. After adjusting for age, gender, smoking, alcohol consumption, and hepatitis B vaccine coverage, the relative risks for PM2.5 levels corresponding to World Health Organization Interim Targets 1-4 (compared to levels below 10 μg/m3) were 1.168 (95% CI: 0.483, 2.824), 2.258 (1.017, 5.012), 3.720 (1.631, 8.483), and 5.912 (2.648, 13.197), respectively. During 2025–2035, the estimated fractions of new liver cancer cases attributable to PM2.5 exposure were 0.4% (stable) for North America, 34.4–7.1% for Latin America and the Caribbean, 79.4% (stable) for Africa, 79.2–77.3% for Asia, 24.1–<0.1% for Europe, and 6.9% (stable) for Oceania. **Conclusion:** These findings underscore the ongoing role of air pollution as a driver of global disparities in liver cancer among the new generation, emphasizing the imperative for coordinated efforts in environmental protection and cancer prevention.

Disclosures: Wang Zixing: Nothing to Disclose, Zilong Wang: Nothing to Disclose, Xiaoxiao Wang: Nothing to Disclose, Huiying Rao: Nothing to Disclose, Feng Liu: Nothing to Disclose, Liying Ren: Nothing to Disclose, Hongsong Chen: Nothing to Disclose

3269 | CAREGIVERS OF LIVER TRANSPLANTATION RECIPIENTS EXPERIENCE SIGNIFICANT ANXIETY PRE-TRANSPLANT AND DECREASED INFORMATIONAL SUPPORT POST-TRANSPLANT

Meena Tadros[1] Alvaro Noriega Ramirez[1] Jennifer Cardin[1] Dyanna Gregory[1] Prajwal Gowda[1] Nneka Ufere[2] Madhukar Patel[1] Arjmand Mufti[1] Lisa VanWagner[1] Amit Singal[1] Sarah Lieber[1]

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Background: Despite the essential care provided by caregivers to liver transplantation recipients (LTRs), caregiver experiences remain understudied. We aimed to describe longitudinal experiences, specifically caregiver burden, psychological health, and financial distress, before and after LT. **Methods:** Dyads of caregivers and LTRs were assessed at a large academic U.S. transplant center both on the waitlist (baseline) and post-LT (1 month). At baseline and post-LT, sociodemographic and clinical comorbidities, as well as caregiver reported outcomes were assessed, including the following constructs: anxiety, depression, social isolation, emotional and informational support, caregiver preparedness, caregiver and financial burden (Table 1). For surveys administered to caregivers, higher scores indicate more of the concept tested, except COST-FACIT, where higher scores indicate lower financial burden. Descriptive statistics and bivariate analyses were performed to assess changes

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in caregiver reported outcomes pre- vs. post-LT. **Results:** A total of 88 caregivers have been enrolled thus far; 40 completed data pre-LT and 1-month post-LT, a majority (70%) of whom were female, White (92.5%) married (74.4%) and the spouse/partner (60%) of the LTR (Table 1). Just under a third (30%) of caregivers were Hispanic. Over half of caregivers (59.4%) had an income of <$75K with 41% having less than or equal to a high school degree. At baseline, caregivers had higher anxiety scores compared to national T scores using PROMIS, with decreased anxiety post-LT (p=0.001). Overall, caregiver preparedness was high (median score 3.0 IQR 2.4-3.8); 38.0% reported mild/moderate caregiver burden, with 13.9% having high burden at baseline. Financial burden was moderate post-LT (median COST FACIT score 25.3 (IQR 15.4, 29.7); 10.3% of caregivers reported transportation issues and delays. Caregivers had lower levels of informational support post-LT compared to pre-LT (p=0.03). **Conclusion:** A total of 88 caregivers have been enrolled thus far; 40 completed data pre-LT and 1-month post-LT, a majority (70%) of whom were female, White (92.5%) married (74.4%) and the spouse/partner (60%) of the LTR (Table 1). Just under a third (30%) of caregivers were Hispanic. Over half of caregivers (59.4%) had an income of <$75K with 41% having less than or equal to a high school degree. At baseline, caregivers had higher anxiety scores compared to national T scores using PROMIS, with decreased anxiety post-LT (p=0.001). Overall, caregiver preparedness was high (median score 3.0 IQR 2.4-3.8); 38.0% reported mild/moderate caregiver burden, with 13.9% having high burden at baseline. Financial burden was moderate post-LT (median COST FACIT score 25.3 (IQR 15.4, 29.7); 10.3% of caregivers reported transportation issues and delays. Caregivers had lower levels of informational support post-LT compared to pre-LT (p=0.03).

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Table 1. Characteristics of Caregivers for Adult Liver Transplant Recipients at a large U.S. Transplant Center at Baseline and Post-LT (N=40)

VARIABLE		FREQUENCY^ N (%) / Median (IQR)		
Age		51 (44.5, 62)		
Female		28 (70%)		
Race	*White*	37 (92.5%)		
	Black	2 (5.0%)		
	Other	1 (2.5%)		
Ethnicity	*Hispanic*	12 (30%)		
	Non-Hispanic	28 (70%)		
Education Level	*<= Highschool*	16 (41.0%)		
	Undergraduate	13 (33.3%)		
	>=Graduate	10 (25.6%)		
Income Level	*<$25,000*	7 (18.9%)		
	$25,000 - $74,999	15 (40.5%)		
	>=$75,000	15 (40.5%)		
Marital Status	*Married*	29 (74.4%)		
	Single/Divorced/Separated	2 (5.1%)		
	Prefer not to answer	8 (20.5%)		
Relationship to LT Candidate	*Spouse / Partner*	24 (60%)		
	Family (Sibling, Child)	16 (40%)		
Employed / Work for Pay		23 (57.5%)		
Transportation Issues		4 (10.3%)		
Delays in Care Due to Transportation		1 (2.5%)		
Charlson Comorbidity Index (CCI)	0	5 (20%)		
	1-3	13 (52%)		
	>3	7 (28%)		
Preparedness for Caregiving Scale (Range 0-4)		3.0 (2.4, 3.8)		
LT Indication	*Alcohol*	17 (44.7%)		
	MASLD	15 (39.5%)		
	Other	6 (15.8%)		
HCC in LT Candidate		4 (10.5%)		
MELD-Na at LT		27.3 (18.9, 32.3)		
LT Hospitalization Duration		6 (5, 7)		
Waitlist Time (median days, IQR)		33.5 (8.5, 168)		
CAREGIVER REPORTED OUTCOMES PRE- AND POST-LT				
SURVEY INSTRUMENT		**PRE-LT**	**POST-LT**	**p-value**
Zarit Caregiver Burden (Range 0-48)		10.0 (4.0, 16.0)	9.0 (5.0, 17.0)	0.36
	0-10 (no/mild)	38 (48.1%)	19 (51.4%)	
	10-20 (mild/moderate)	30 (38.0%)	14 (37.8%)	
	(>20 high)	11 (13.9%)	4 (10.8%)	
COST-FACIT (Range 0-44) [low = worse burden]		24.8 (14.9, 30.8)	25.3 (15.4, 29.7)	0.71
PROMIS-Emotional Support (T score 24.7-63.5)		55.7 (49.1, 63.4)	55.2 (48.8, 63.4)	0.65
PROMIS-Informational Support (T score 23.7-69.1)		65.6 (50.6, 65.6)	52.3 (50.2, 65.6)	**0.03**
PROMIS-Social Isolation (T score 34.8-74.2)		45.9 (34.8, 49.4)	47.9 (34.8, 52.3)	0.25
PROMIS-Depression (T score 37.1-81.1)		48.6 (37.1, 53.4)	45.8 (37.1, 54.5)	0.23
PROMIS-Anxiety (T score 36.3-82.7)		54.0 (47.0, 61.3%)	48.1 (36.3, 57.8)	**0.001**

** Frequencies including n/% are provided for categorical variable. Median and interquartile ranges (IQR) are provided for continuous scores.*

Abbreviations: Comprehensive Score for Financial Toxicity-Functional Assessment of Chronic Illness Therapy (COST-FACIT), Hepatocellular Carcinoma (HCC), Metabolic Dysfunction Associated Steatotic Liver Disease (MASLD), Liver Transplantation (LT), Model for End-Stage Liver Disease (MELD-Na), Patient Reported Outcome Measurement Information System (PROMIS)

Disclosures: Meena Tadros: Nothing to Disclose, Alvaro Noriega Ramirez: Nothing to Disclose, Jennifer Cardin: Nothing to Disclose, Dyanna Gregory: Nothing to Disclose, Prajwal Gowda: Nothing to Disclose, Nneka Ufere: Nothing to Disclose, Madhukar Patel: Nothing to Disclose, Arjmand Mufti: Nothing to Disclose, Lisa VanWagner: Consultant relationship with Gerson Lehrman Group; Has not ended; Consultant relationship with AlphaSights; Has not ended; Consultant relationship with Slingshot Insights; Has not ended; Grant/Research Support relationship with Madrigal Pharmaceuticals; Has not ended; Grant/Research Support relationship with

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W.L. Gore & Associates; Has not ended, Amit Singal: Consultant relationship with AstraZeneca; Has not ended; Consultant relationship with Sirtex; Has not ended; Consultant relationship with Boston Scientific; Has not ended; Consultant relationship with Bayer; Has not ended; Consultant relationship with Eisai; Has not ended; Consultant relationship with FujiFilm Medical Sciences; Has not ended; Consultant relationship with Elevar; Has not ended; Consultant relationship with Exact Sciences; Has not ended; Consultant relationship with Glycotest; Has not ended; Consultant relationship with Exelixis; Has not ended; Consultant relationship with Merck; Has not ended; Consultant relationship with Genentech; Has not ended; Consultant relationship with HistoSonics; Has not ended, Sarah Lieber: Nothing to Disclose

3270 | TRENDS IN PRESCRIBER CHARACTERISTICS OF ORAL HEPATITIS B MEDICATIONS IN THE UNITED STATES

Xiaohan Ying[1] Russell Rosenblatt[2] Nicole Ng[3] Catherine Lucero[2] Arun Jesudian[2]

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Background: Chronic hepatitis B (CHB) is a major cause of global liver-related morbidity and mortality, and affects approximately 1.6 million individuals in the United States. Studies have shown that individuals with CHB are often underdiagnosed and undertreated, with only a third of the treatment-eligible patients receiving antiviral therapy, exposing many patients to high risk of cirrhosis and hepatocellular carcinoma. We aim to better characterize prescriber characteristics for patients with CHB to ultimately address gaps in treatment for patients with CHB. **Methods:** Publicly available Medicare part D data (2013-2021) were analyzed to determine the number of 30-day CHB anti-viral prescriptions, total drug spending, as well as prescriber characteristics such as specialty and geography. Prescriber specialties were categorized into 1. Primary Care Provider (PCP), 2. Gastroenterology (GI), 3. Infectious Diseases (ID), 4. Advanced Practice Provider (APP), and 5. Other. Microsoft Excel was used for data analysis, and JoinPoint Regression Program was used for annual percent change (APC) and trends analysis. **Results:** Five oral medications were included in this study: tenofovir DF (Viread® and generic), entecavir (Baraclude® and generic), and tenofovir alafenamide (Vemlidy®). Between 2013 and 2021, over 17,000 prescribers prescribed over 2.1 million 30-day prescriptions of these CHB therapies. Over the study period, the number of 30-day prescriptions increased by 5.4% annually (95% CI 4.4% to 6.4%). The number of 30-day prescriptions by GI increased by 12.5% a year (95% CI 10.0% to 15.1%), followed by APPs (APC 12.2%, 95% CI 10.5% to 13.8%), and finally PCPs (APC 2.9%, 95% CI 1.8% to 4.1%). However, number of prescriptions prescribed by ID physicians fell by 14.0% a year (95% CI -16.2% to -11.6%). (Figure 1a) In terms of share of prescriptions ordered, PCPs accounted for 36.6% of all prescriptions, followed by GI (31.0%), APP (16.6%), and ID (11.6%). In 2013, GI accounted for 22.0% of all prescriptions, but accounted for 35.2% by 2021 (APC 6.9%, 95% CI 4.7% to 9.1%); similarly, APPs grew from 12.9% in 2013 to 20.6% (APC 6.3%, 95% CI 5.7% to 7.0%). On the contrary, PCP's share shrank by 2.4% annually (95% CI -3.1% to -1.6%) and ID's share shrank by 18.0% annually from 21.7% to 4.8% (95% CI -19.8% to -16.3%). P<0.001 for all trends noted above. (Figure 1b) **Conclusion:** Since 2013, the number of prescriptions for CHB grew steadily at ~5% annually. These prescriptions are increasingly written by GIs and APPs and less so by PCPs and ID physicians. As we continue to strive for viral hepatitis elimination, it is crucial to develop deeper understanding of the specific providers who are engaged in treating CHB on a national level and associated barriers to CHB treatment.

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Figure 1a

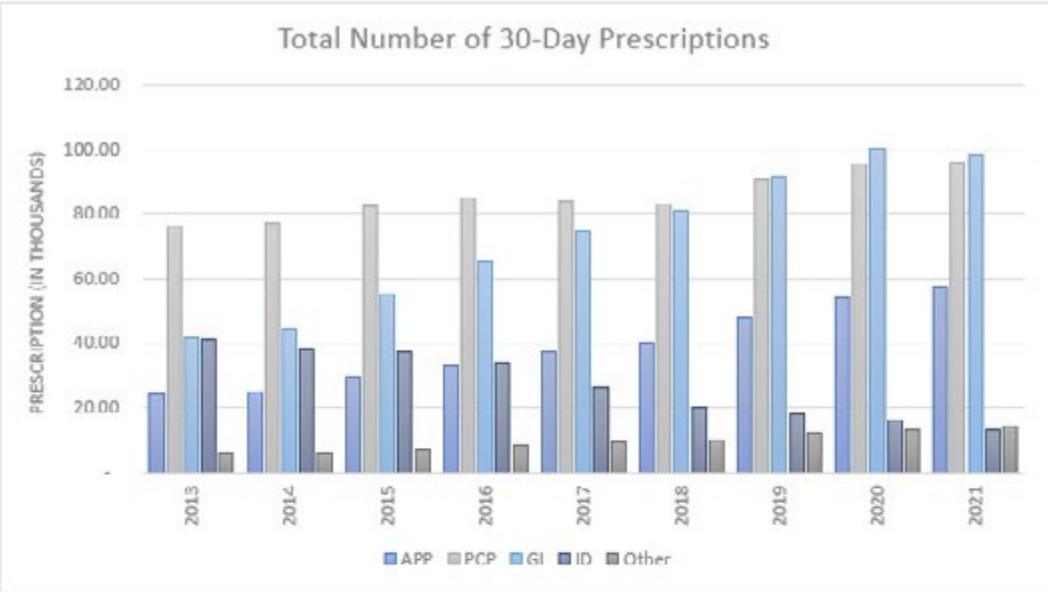
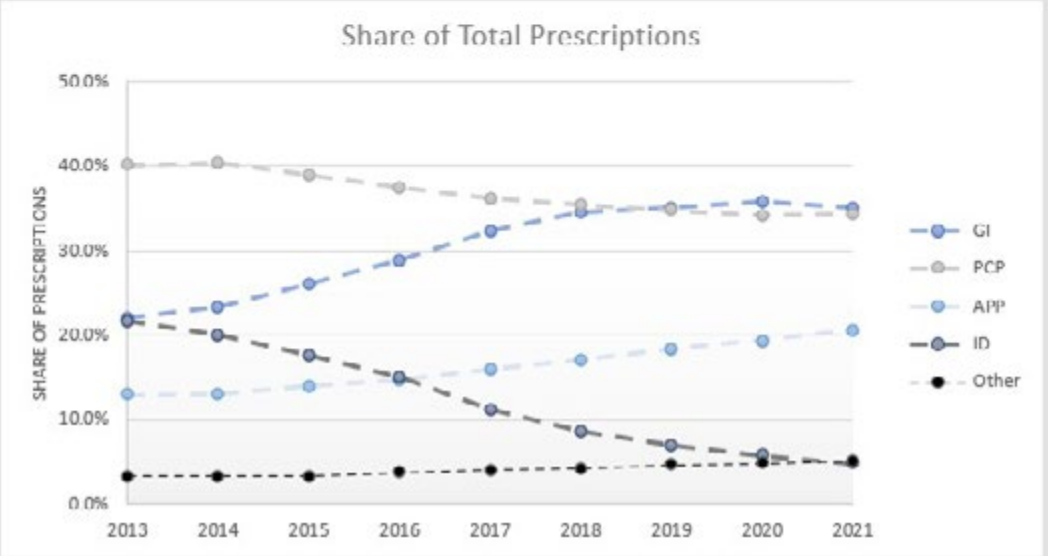


Figure 1b



Disclosures: Xiaohan Ying: Nothing to Disclose, Russell Rosenblatt: Nothing to Disclose, Nicole Ng: Nothing to Disclose, Catherine Lucero: Nothing to Disclose, Arun Jesudian: Salix Pharmaceuticals: Consultant, Salix Pharmaceuticals: Speaking and Teaching, Madrigal Pharmaceuticals: Speaking and Teaching, Novo Nordisk: Consultant, Orphalan: Consultant

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3271 | IMMUNOGENICITY OF SARS-COV-2 VACCINE IN PATIENTS WITH CHRONIC LIVER DISEASE

Asif Hitawala[1] Elizabeth Wright[2] Gavin Nee[1] Graciela Galvez[1] Harish Gopalakrishna[3] Maria Mironova[1] Gian Rodriguez Franco[1] Yaron Rotman[3] Theo Heller[1] Shani Scott[1] Anna Liza Rivero[1] Valeria De Giorgi[4] Sarah Porche[5] Zillay Saleem[5] Heather Kalish[5] Emily Ricotta[6] Marc Ghany[1]

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Background: The CDC recommends vaccination against SARS-CoV-2 virus for patients with chronic liver disease (CLD) due to a higher risk of worse outcomes. However, response rates to vaccinations have been reported to be lower among patients with CLD, especially cirrhosis. Whether this is true for newer mRNA vaccines is uncertain. **Aim:** To compare the SARS-CoV-2 spike protein anti-IgG antibody (anti-Spike-Ab) response 1- year after initial vaccination between patients with CLD and healthy persons. **Methods:** A retrospective-prospective, single center study was conducted. Patients completed a questionnaire to provide demographic data, SARS-CoV-2 vaccination history, COVID-19 history and alcohol and tobacco use. Stored sera, from 1-year ± 3 months post-first dose of the SARS-CoV-2 vaccine (primary analysis timepoint), were serially diluted to measure concentration of anti-Spike-Ab using an in-house ELISA assay. Unpaired t-test and chi-square test were used to compare numerical and categorical variables, respectively. Linear regression was used to identify factors (age, gender, COVID infection or receipt of a vaccine dose within 90 days of primary endpoint, presence/absence of liver disease, presence of cirrhosis, smoking and alcohol use between patients with and without cirrhosis) associated with higher antibody level. P value <0.05 was considered statistically significant. **Results:** Of 262 patients with CLD approached for enrollment, 29 declined. Amongst 233 enrollees, 71 were excluded (2 withdrew consent, 16 never vaccinated, 52 lacked stored sera and 1 had missing data), leaving 162 patients with CLD for analysis. Additionally, 63 healthy persons in another COVID vaccination trial served as a comparison group; 36/63 had samples available at the primary analysis timepoint. Baseline characteristics are provided in Table 1. 99% of both cohorts received mRNA vaccine; 76% of CLD patients and 64% of healthy controls received ≥3 vaccine doses at the time of primary analysis. There was no difference in alcohol or tobacco use between patients with and without cirrhosis- data unavailable for healthy persons. At 1-year post-initial SARS-CoV-2 vaccine, mean concentration of anti-Spike-Ab was similar in CLD patients and healthy persons (7.93±8.32 vs 7.29±7.27 mg/mL, p-value=0.67) and among patients with and without cirrhosis (8.3±8.26 vs 6.61±8.54, p-value=0.32). On linear regression, receipt of a vaccine dose within 90 days of the primary endpoint resulted in statistically higher anti-Spike Ab concentrations, but the mean concentration of anti-Spike Ab between the groups remained similar. **Conclusion:** Patients with CLD have similar response to vaccination against SARS-CoV-2 as healthy persons. Moreover, among patients with CLD, those with cirrhosis have similar immune responses as those without cirrhosis, likely due to greater immunogenicity of mRNA vaccines.

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Table 1: Baseline Characteristics and Results

VARIABLES	NON-CIRRHOTIC	CIRRHOTIC	TOTAL	P-VALUE*	CONTROLS	P-VALUE**
	N=126	N=36	N=162		N=36	
Age	56±14	60±12	58±14	0.17	40±20	<0.0001
Male gender	72 (57%)	21 (58%)	93 (57%)	0.90	13 (36.11%)	0.021
Race				0.70		0.0008
American Indian/Alaska Native	1 (1%)	0 (0%)	1 (1%)		1 (3%)	
Asian	52 (41%)	6 (17%)	58 (36%)		2 (6%)	
Black	17 (13%)	12 (33%)	29 (18%)		3 (8%)	
White	48 (38%)	15 (42%)	63 (39%)		25 (69%)	
Multiple	3 (2%)	1 (3%)	4 (2%)		3 (8%)	
Unknown	5 (4%)	2 (6%)	7 (4%)		2 (6%)	
Hispanic	10 (8%)	6 (17%)	16 (10%)	0.20	2 (6%)	0.42
Active alcohol use	38 (30%)	9 (25%)	47 (29%)	0.55		
Current smoker	11 (9%)	4 (11%)	15 (9%)	0.66		
Liver disease				0.67		
Viral hepatitis	87 (69%)	26 (72%)	113 (70%)			
MASLD or ALD	20 (16%)	6 (17%)	26 (16%)			
AIH or PBC	15 (12%)	2 (6%)	17 (10%)			
Other	4 (3%)	2 (6%)	6 4%)			
Number of doses				0.80		0.50
1	1 (1%)	1 (3%)	2 (1%)		0 (0%)	
2	28 (22%)	8 (22%)	36 (22%)		13 (36%)	
3	89 (71%)	26 (72%)	115 (71%)		21 (58%)	
4-5	8 (6%)	1 (23%)	9 (6%)		2 (6%)	
No. of Days from first vaccine dose	357±48	358±53	387±48	0.88	382±49	0.0057
COVID within 1 yr	34 (27%)	7 (19%)	41 (25%)	0.36	11 (31%)	0.52
COVID within 90 days of endpoint	10 (8%)	0 (0%)	10 (6%)	0.12	5 (14%)	0.16
Booster dose within 90 days of endpoint	41 (33%)	12 (33%)	53 (33%)	0.93	10 (28%)	0.57
Spike Protein IgG Antibody Positive	115 (91.27%)	34 (94.44%)	149 (91.98%)	0.73	36 (100%)	0.13
Concentration of Spike Protein IgG (µg/mL)	8.3±8.26	6.61±8.54	7.93±8.32	0.32	7.29±7.27	0.67

AIH: autoimmune hepatitis; ALD: alcoholic liver disease; MASLD: metabolic-dysfunction associated steatotic liver disease; PBC: primary biliary cholangitis
*: comparison between CLD with and without cirrhosis
**: comparison between healthy controls and CLD patients

Disclosures: Asif Hitawala: Nothing to Disclose, Elizabeth Wright: Nothing to Disclose, Gavin Nee: Nothing to Disclose, Graciela Galvez: Nothing to Disclose, Harish Gopalakrishna: Nothing to Disclose, Maria Mironova: Nothing to Disclose, Gian Rodriguez Franco: Nothing to Disclose, Yaron Rotman: Astra Zeneca: My spouse is an employee, Theo Heller: Nothing to Disclose, Shani Scott: Nothing to Disclose, Anna Liza Rivero: Nothing to Disclose, Valeria De Giorgi: Nothing to Disclose, Sarah Porche: Nothing to Disclose, Zillay Saleem: Nothing to Disclose, Heather Kalish: Nothing to Disclose, Emily Ricotta: Nothing to Disclose, Marc Ghany: Nothing to Disclose

3272 | CREATION OF A NEW VA TRANSPLANT CENTER INCREASED ACCESS AND REDUCED WAIT TIMES FOR LIVER TRANSPLANT

Jessica Davis[1] *Suzanne Robertazzi*[1] *Melissa Kaltenbach*[1] *Rohit Satoskar*[2] *Atoosa Rabiee*[1]

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Background: The Veterans Health Administration (VHA) has a nationwide organ transplantation network to coordinate veteran transplant care. Given the complexity of care required to support transplantation, centers are limited with only seven VHA liver transplant centers (VATC) nationwide. Transplant outcomes are worse

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for veterans who live farther from VATC. Debate continues about whether the best way to expand transplant among veterans is to increase the number of VATC versus distribute care to providers outside of VHA. The Washington DC VA Medical Center (DCVAMC) became a liver VATC in fall 2022. This study assessed the impact of the newest liver VATC on veteran access to liver transplantation. **Methods:** Retrospective chart review was performed of veterans who were referred for liver transplant at the DCVAMC. Data from five years prior to activation of the transplant center (11/11/2017-11/10/2022) were compared to data from the first year post-activation (11/11/2022-12/31/2023). Patient demographics as well as quantity and timeliness of referrals were reviewed. **Results:** Pre-activation, there were 30 total liver transplant referrals for DC, an annual average of 6 referrals (Table 1). In the 1-year period post-activation, there were 39 referrals to DC VATC. Within the local geographic region, there were 136 liver transplant referrals pre-activation, an average of 27 referrals per year, versus 41 referrals in the first year post-activation. Pre-activation, 73% of referred patients were evaluated versus 95% post-activation. Pre-activation, a total of 10 patients were transplanted, 2 patients per year. In the first year post activation 11 patients were transplanted. Pre-activation, 60% of referrals were referred outside of VHA vs 2.5% of referrals post-activation. Time from referral to evaluation decreased from a mean of 19 days pre-activation to 13 days post-activation. Time from referral to listing decreased from a mean 123 days to 56 days. Time from referral to transplant decreased from 284 to 148 days and time from listing to transplant decreased from 167 to 97 days. **Conclusion:** Activation as a new transplant center created a unique opportunity to compare access and timeliness before and after this transition. Creation of a new VATC in Washington DC improved access to liver transplantation for veterans with an increase in referrals seen at the DC VATC as well as within the geographic service area. Timeliness of transplant improved as well despite this increased volume of referrals. Both access and timing can have a significant mortality impact on this cohort of patients with advanced disease. These data support creation of VATC to increase transplant access for veterans and is in line with other data that support keeping veteran care within the VHA. Future studies should evaluate transplant metrics for veterans transplanted in the community to ensure quality and outcome standards are maintained when veterans leave the VHA umbrella.

	Pre-activation	Post-activation
DC VA mean annual referrals (n)	6	36
"VISN" (DC/WV/MD) mean annual referrals (n)	27	41
Referred outside of VHA care (%)	60%	2.5%
mean annual listed (n)	3.6	17.6
mean annual transplanted (n)	2	11
mean time referral to listing (days)	123	56
mean time listing to transplant (days)	167	97

Table 1. Comparison of transplant referral number and timeliness pre- and post-activation of the DC VA Liver Transplant Center. (VISN: Veteran Integrated Service Network; VHA: Veteran's Health Administration)

Disclosures: Jessica Davis: Nothing to Disclose, Suzanne Robertazzi: Nothing to Disclose, Melissa Kaltenbach: Nothing to Disclose, Rohit Satoskar: Nothing to Disclose, Atoosa Rabiee: Nothing to Disclose

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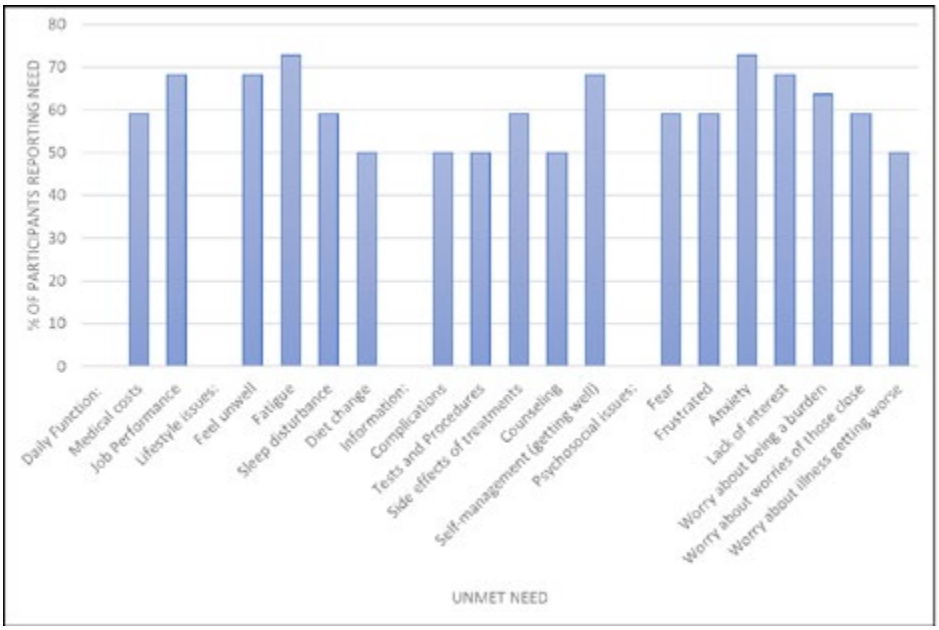
3273 | THE SUPPORTIVE NEEDS ASSESSMENT TOOL IN CIRRHOSIS IS A FEASIBLE TOOL FOR IDENTIFYING UNMET NEEDS IN A US ACADEMIC COHORT

Cristal Brown[1] Nazan Aksan[2] Elizabeth Kvale[3] Rebecca Sudore[4] Andrew Muir[5]

[1]University of Texas at Austin Dell Medical School, [2]UT Austin Dell Medical School, [3]Baylor College of Medicine, [4]UC San Francisco, [5]Duke University

Background: Patients with end-stage liver disease (ESLD) experience high rates of morbidity associated with complications of advanced liver disease and psychosocial distress that have deleterious effects on quality of life. The Supportive Needs Assessment tool in Cirrhosis (SNAC) is a validated survey developed in Australian patients identifying unmet needs. Objective: Evaluate feasibility of obtaining SNAC with systematic resource linkage in patients with ESLD in a US academic center. **Methods:** Pilot study 30 adult patients with ESLD. Patients completed the 39 question SNAC assessing 4 domains: practical and physical needs, lifestyle changes, psychosocial issues, and information needs. Participants could self-administer the REDCap survey remotely or do an in-person visit for assistance with survey completion. Each positive response prompted a 4-point Likert scale (no help, a little, some, a lot) allowing clarification of the additional help needed to address the concern. Prior to study enrollment, a hepatologist, social worker and nutritionist developed a systematic algorithm linking each response to available resources.This included self-care and symptom management handouts for physical symptoms, 10-60-minute social work visit for practical and psychosocial support and nutrition counseling for malnutrition needs. Participants were called with the recommendations for additional resources with voluntary scheduling of appointments to receive these resources in-person or via telehealth. Quality of life, anxiety/depression and caregiver burden was concurrently assessed with plan to follow participants over a 6-month period. **Results:** Preliminary data for 22 enrolled participants is reported. 17/22 chose self-administered survey completion. Participants had a mean age of 54 years (SD=11), 81% White, 30% Hispanic, and 47% women. Mean MELD score was 10 (SD=5) with range of 6-25. All enrolled participants had complete data for the baseline SNAC survey. The table below displays 18 out of 39 variables in which at least 50% of the participants reported needing assistance in their care.The greatest needs included fatigue, anxiety, lack of interest, feeling unwell, job performance, worry about being a burden and information for self-management.18/22 participants reported needing “some” or “a lot” of help for at least one item. **Conclusion:** SNAC is a feasible tool identifying patient-reported needs in a US academic cohort. Preliminary data shows overwhelming need for resources in all 4 domains with very high psychosocial and informational needs. This data also highlights the importance of multidisciplinary care with a wide range of needs spanning multiple domains.



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3274 | DIAGNOSIS OF HEPATITIS C IN BABY BOOMERS THROUGH AN AUTOMATIC NOTIFICATION IN THE GREEK PRESCRIPTION SYSTEM

Anthie Chatziioannou[1] Emmanouil Smyrnakis[2] Magda Gavana[2] Christos Gkiourtzidis[1] Theodoros Bougas[3] VANGELITSA CHARTAMPA[3] Vasiliki Voskidou[3] Dimitra Iosifina Papageorgiou[3] Evelin Fachouri[3] Katerina Vogiatzi[3] Maria Dragasaki[3] Areti Rountou[3] Melpomeni Tsanaktsidou[3] Lia Gulitasvili[3] Charis Birtsou[3] Foteini Boutzikou[3] MARTHA ANDREOU[3] Elpida Lavrentiadou[3] Emmanouil Sinakos[1]

[1]Aristotle University Of Thessaloniki, Greece, [2]Laboratory of Primary Health Care, General Practice and Health Services Research, [3]Aristotle University of Thessaloniki Primary Health Care Research Network

Background: Efforts have been made in different countries to tackle underdiagnosis of hepatitis C in the general population level. The Hellenic National Action Plan for viral hepatitis elimination has introduced an automatic notification for HCV testing (pop-up message) whenever a visit is generated in the online prescription system for all individuals born between 1945 and 1980. Our study assessed the effectiveness of this measure for the diagnosis of hepatitis C in Primary Healthcare Units (PHCU). **Methods:** PHCU are the cornerstone of the primary healthcare system in Greece. The Primary Healthcare Research Network (AUTH.PHC.RN) is aimed to promote research in primary healthcare in Greece and to collaborate with academic hospitals. In this study physicians from the participating PHCU (n=15), who were members of the AUTH.PHC.RN, proposed HCV testing in response to the pop-up message to every visiting patient regardless of the reason of the visit. Only patients that consented to testing (n=941) along with their basic clinical and epidemiological data were recorded. HCV positive patients were referred to the academic hospital that coordinated the study for evaluation and treatment. The study was approved by the Ethics Committee of the Aristotle University of Thessaloniki. **Results:** The average age of the patients (44.6% males) was 61.2 years. Five patients (0.53%) were current or former intravenous drug users and 17 patients (1.8%) had undergone blood transfusions before 1992. 96.7% of the patients that consented actually performed the testing and 92.6% of the total patients finally submitted the results to their physicians. Six patients (0.64%) tested positive for HCV consisting of three men and three women with average age of 58 and 60 years, respectively. Notably, 2/5 drug users and 1/17 patients that had undergone blood transfusions tested positive. 4/6 positive patients were referred for evaluation and treatment. **Conclusion:** Our study confirms the low prevalence of HCV infection in the general population of Greece. Physicians in PHCU can contribute significantly in the efforts for HCV elimination in Greece. The extensive implementation of the automatic notification for HCV testing can increase the rates of diagnosis in baby boomers as this measure seems effective and easy to perform.

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3275 | TECHNOLOGY UTILIZATION AND HEALTH LITERACY ASSESSMENT IN PATIENTS WITH CHRONIC LIVER DISEASE (TULAP-CLD)

Zoe Post[1] Jonathan Day[1] Ashley Cawthon[1] Sierra Anderson[1] Ana Maria Davila Morales[1] Sujit Janardhan[1]

[1]Rush University Medical Center

Background: Chronic liver diseases (CLD) are a leading cause for mortality and morbidity in the United States. Chronic Disease Management (CDM) models that utilize mobile technology for patient self-management have been shown to improve disease outcomes. To efficiently deliver mobile technologies to CLD patients, it is imperative to understand their level of literacy and technology utilization. We therefore aimed to measure technology utilization and health literacy in CLD patients. **Methods:** English-speaking CLD patients aged 18 or older, at a single tertiary center were included. Informed consent was obtained. Demographics including age, sex, race/ethnicity, level of education, and CLD data were collected. The Rapid Estimate of Adult Literacy in Medicine Short Form (REALM-SF) was used to assess health literacy. Technology utilization was measured using a novel

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survey instrument based in part on questions modified from Pew Research Center's Internet and American Life Project. **Results:** 52 patients were included. Most were female (60%) and Caucasian (33%). 64% reported a high school diploma or higher. Metabolic dysfunction-associated steatotic liver disease (MASLD) (40%) or alcohol-associated liver disease (ALD) (25%) were the most common CLD represented with 48% having cirrhosis. Based on REALM-SF, 30% have a 7-8th grade reading level. 90% of patients use the internet, mostly through smartphone (69%). Receptive or simple interactive activities (text messages and checking weather/traffic) had high engagement (>90%). More complex receptive/interactive activities (emailing and video chat) showed slightly less engagement (>80%). The most complex interactive or proactive activities (posting online and purchasing products) showed lowest engagement (49-64%) (Table 1). Frequency of use was similar between patients with and without cirrhosis. Engagement with health-related technology showed similar results with higher engagement (>85%) for receptive activities (researching conditions and treatments) and less engagement (22-39%) for proactive activities (support groups and sending medical information to providers). **Conclusion:** We show that while most CLD patients use the internet, they are more likely to engage in simple receptive tasks rather then complex interactive or proactive tasks. Limited literacy in this population should also inform patient focused interactions. This pilot study demonstrates the importance of understanding the capabilities of each individual population for which CDM interventions are being designed.

Table 1. Frequency of engaging in general activities and health-related activities that require internet using any device (including laptop, desktop computer, tablet, smartphone). Percentages shown for the activities are based only on records that have data entered for the specific activity (yes versus no); the frequency of engaging in the activity represents the patient population that reported to engage in the activity. Frequent = once a day or multiple times per day, Intermittent = at least once per week or once per month, Rarely = once every three months or less

Task	All (n=52)	Cirrhosis (n=24)	Non-cirrhosis (n=28)
GENERAL ACTIVITIES			
Receive/send text message	40 (100%)	19 (100%)	21 (100%)
Frequent, daily+	95%	89%	100%
Intermittent	2.5%	5%	0%
Rarely 3 months or less	2.5%	5%	0%
Participant in video call/chat	39 (87%)	18 (86%)	21 (88%)
Frequent	23%	22%	24%
Intermittent	56%	67%	48%
Rarely	21%	11%	29%
Read/send email	39 (87%)	18 (81%)	22 (92%)
Frequent	77%	82%	73%
Intermittent	18%	18%	18%
Rarely	5%	0%	9%
Check the weather/traffic	42 (93%)	20 (95%)	22 (92%)
Frequent	83%	85%	82%
Intermittent	14%	10%	18%
Rarely	2%	5%	0%
Social networking*	39 (87%)	19 (90%)	20 (83%)
Frequent	92%	100%	85%
Intermittent	8%	0%	15%
Rarely	0%	0%	0%
Find product/business information	42 (93%)	20 (95%)	22 (92%)
Frequent	38%	35%	41%
Intermittent	57%	60%	55%
Rarely	5%	5%	5%
Get directions	41 (91%)	18 (86%)	23 (96%)
Frequent	17%	22%	13%
Intermittent	68%	67%	70%
Rarely	15%	11%	17%
Post online (blog, social media, photos)	22 (49%)	9 (43%)	13 (54%)
Frequent	36%	44%	31%
Intermittent	45%	44%	46%
Rarely	18%	11%	23%
Online banking	34 (76%)	15 (71%)	19 (79%)
Frequent	24%	27%	21%
Intermittent	76%	73%	79%
Rarely	0%	0%	0%
Online grocery/product shopping	29 (64%)	13 (62%)	16 (67%)
Frequent	7%	8%	6%
Intermittent	72%	92%	56%
Rarely	21%	0%	38%
HEALTH RELATED ACTIVITIES			
Learn about medical condition	37 (90%)	15 (79%)	22 (100%)
Frequent	14%	7%	18%
Intermittent	62%	73%	55%
Rarely	24%	20%	27%
Learn about treatments for medical condition	36 (88%)	15 (79%)	21 (95%)
Frequent	14%	7%	19%
Intermittent	61%	67%	57%
Rarely	25%	27%	24%
Communicate with other patients/support groups	9 (22%)	3 (16%)	6 (27%)
Frequent	11%	33%	0%
Intermittent	33%	33%	33%
Rarely	56%	33%	67%
Look up personal health information	39 (95%)	19 (100%)	20 (91%)
Frequent	10%	11%	10%
Intermittent	64%	63%	65%
Rarely	26%	26%	25%
Participate in e-visits with provider	28 (68%)	13 (68%)	15 (68%)
Frequent	0%	0%	0%
Intermittent	11%	23%	0%
Rarely	89%	77%	100%
Send personal medical information to provider	16 (39%)	10 (53%)	6 (27%)
Frequent	0%	0%	0%
Intermittent	31%	50%	0%
Rarely	69%	50%	100%

*Facebook 72%, Instagram 36%, Youtube 59%, Twitter 7.7%, Pinterest 23%, Linkedin 13%

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Disclosures: Zoe Post: Nothing to Disclose, Jonathan Day: Nothing to Disclose, Ashley Cawthon: Nothing to Disclose, Sierra Anderson: Nothing to Disclose, Ana Maria Davila Morales: Nothing to Disclose, Sujit Janardhan: Nothing to Disclose

3276 | ESTIMATING THE PREVALENCE OF CHRONIC HEPATITIS B IN THE UNITED STATES BY STATE USING MEDICARE DATA

Stephen Congly[1] Mayur Brahmania[1] Conar O'Neil[2] Karen Doucette[2] Mang Ma[2] Carla Coffin[1]

[1]University of Calgary, [2]University of Alberta

Background: Current prevalence estimates of patients living with chronic hepatitis B (CHB) in the United States (0.35%) are predominantly based on NHANES survey data which may underestimate at-risk populations. Medicare Part D is a voluntary drug plan for patients aged >65 years or with disabilities providing coverage for CHB treatment. Using the number of recipients of nucleos(t)ide analogues (NA) in Medicare Part D, the prevalence of CHB can be calculated based on the estimated proportion of the CHB population receiving therapy. **Methods:** The 2021 Medicare Part D database was accessed and the number of recipients receiving any NA specific to CHB [lamivudine, adefovir, entecavir, tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide (TAF)] were extracted by state. Exact numbers of patients >65 years was not available for all states/medications due to data suppression so the national proportion of patients >65 years was utilized for calculation of state rates. Estimates of the prevalence of CHB by state for patients over 65 were created using a range of potential treatment rates of the CHB population (0.1-25%). This was subsequently extrapolated to the general population using the proportion of the state population covered by Medicare Part D. **Results:** In total, there were 51,009 Medicare Part D beneficiaries who received NA with 39,686 over the age of 65 (77.8%). Data was unavailable for Montana nor Wyoming due to data suppression. The most common NAs were entecavir (20,098), TDF (15,454) and TAF (11,719). The potential CHB prevalence for patients >65 years ranged from 159,000-39 million and for the overall population from 1.1-27 million. Although the exact treatment rate of CHB is unknown, a 15% rate suggests 340,000 patients >65 and 1.8 million overall are living with CHB, comparable to previous estimates. The top 5 states (proportionally) with residents who received NA via Medicare Part D were the District of Columbia, New York, California, Hawaii and Massachusetts. The states with the highest number of residents receiving NA were California (N=14,056), New York (N=8,911), Texas (N=3,240), Florida (N=2,887), and Pennsylvania (N=1,911). **Conclusion:** There is a significant burden of CHB in the US and this study highlights geographic variations by state seen beyond differences in population. Further study into factors affecting these differences would be important for further understanding of the epidemiology of this disease.



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3277 | VARIATION IN NULEOS(T)IDE ANALOGUE USE IN MEDICARE PART D THROUGHOUT THE UNITED STATES

Stephen Congly[1] Conar O'Neil[2] Karen Doucette[2] Mang Ma[2] Mayur Brahmania[1] Carla Coffin[1]

[1]University of Calgary, [2]University of Alberta

Background: Treatment for chronic hepatitis B (CHB) with nucleos(t)ide analogues (NA) suppresses viral replication and prevents progression to fibrosis and liver cancer. All US states offer Medicare Part D prescription drug plan coverage for NA in patients aged >65 years or living with disabilities, however the coverage may vary between state and program. Given potential geographic disparity, we aimed to analyze NA utilization by state in Medicare Part D. **Methods:** The Centers for Medicare & Medicaid Services Medicare Part D database was accessed for the most recent year (2021). Data on different NA agents prescribed were extracted and analyzed for each state and the District of Columbia (DC). The analysis included types of NA used [lamivudine, adefovir, entecavir, tenofovir disoproxil fumarate (TDF), and tenofovir alafenamide (TAF)], stratified into originator (n=6) and generic (n=5) forms, as well as access to highly potent NA (entecavir, TDF and TAF). **Results:** All states offered access to highly potent NA with the exception of TAF coverage in Alaska. The mean number of NA use per state, generic NA usage, and number of originators was 6.1 (range 1-9), 3.6 (range 1-5) and 2.5 (range 1-5), respectively. All but one state (Wyoming) used generic entecavir and TDF. Lamivudine was used in 43 states plus the DC, and adefovir was available in 40 states. Originator TDF was used in 57% of the 50 states and the DC (n=29) while originator entecavir usage was less frequent (n=29, 43%). A minority of the 50 states and the DC used originator adefovir (n=10, 20%) and lamivudine (n=18, 35%). **Conclusion:** There is considerable variation in NA utilization throughout the US although notably all states/regions provide access to highly potent NA. Formulary adjustment to a preferred generic CHB treatment strategy in the Medicare Part D program could offer cost-savings.

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3278 | THE COST OF DILI: EXPLORING HOW DRUG INDUCED LIVER INJURY BURDENS THE U.S. HEALTHCARE SYSTEM

Danielle Zolotnitsky[1] Victor Navarro[2] Dina Halegoua-De Marzio[3]

[1]Sidney Kimmel Medical College, [2]Jefferson-Einstein Medical Center, [3]Thomas Jefferson University at Sidney Kimmel Medical College

Background: Drug-induced liver injury (DILI) represents a significant patient and health system level concern, thus necessitating a precise understanding of its economic impact. This analysis aims to examine healthcare related parameters of DILI using the Vizient database as a representation of DILI care across the United States (US). These parameters include the number of admissions, associated length of stay (LOS), readmission rates, mortality index, and total cost of care. **Methods:** The Vizient database comprises information from 782 hospitals across the U.S. and provides data analytics, insights, and advisory services to its members. These include hospitals, health systems, and academic medical centers (AMCs). Vizient subscribers use the platform to access benchmarking data aimed at enhancing operational efficiency, clinical outcomes, and financial performance in healthcare delivery. For the purposes of this analysis, we used Vizient data from March 2019 to January 2024, including patients aged 18 and above who were admitted with billing codes MS-DRGs 441 & 442 and the following ICD10 codes: K710, K711, K712, K716, K719, K720, K729, K759, and K762. Percent of inpatient admissions, LOS, 30-day readmissions, mortality indices, and mean direct cost vs. risk-adjusted expected cost were collected. The data was then stratified between AMCs and community health centers (CHCs) for further analysis, as these venues would capture the majority of patients with DILI severe enough to require hospitalization. **Results:** A total of 8117 patients in Vizient were admitted with a diagnosis of DILI during March 2019-January 2024, accounting for <1% of all admissions in the database (54.5 million). Compared to expected values, the DILI admissions showed an increase in LOS (+0.724 days) and mortality (+0.515%) as well as a 15.4% increase in overall 30-day readmissions. The top 3 states with the most DILI admissions were California, New York and Pennsylvania. The majority of hospitalizations occurred at AMCs (54%) compared to CHCs (9.1%). Also, higher observed mortality rates were noted in the former (+3.63% vs +1.62%) (Figure 1). Among DILI cases, 1.7% required a liver transplant. Reviewing the data over time, there is a trend of increased cases of DILI from 2019 to 2024 (R^2= 0.88). Cost of DILI admission on average (CHC and AMC) was $785 higher than expected. Specifically, at AMCs the excess spend was observed at $1270. **Conclusion:** This is the first analysis to show the rate of hospital admissions for DILI in the US. The percent of overall hospital admissions for DILI in the US is low. However, the inpatient admissions for DILI are complicated by increased LOS, increased mortality index, high readmission rate, and associated high costs particularly at AMCs

Figure 1: Comparison of DILI Admissions at Academic Medical Centers (AMCs) and Community Health Centers (CHCs)

	AMC	CHC
Number of Admissions	4,463	762
LOS (mean)	7.286 days	4.65 days
Mortality Index (mean)	1.17	0.93
Readmission rates (mean)	15.2%	3.4%
Total Cost (mean)	$10,426.33	$5,179.16

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3279 | SYMPTOM BURDEN AND MANAGEMENT IN PATIENTS WITH END STAGE LIVER DISEASE VERSUS PANCREATIC CANCER: A COMPARATIVE ANALYSIS

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Background: Patients with end-stage liver disease (ESLD) have a high symptom burden similar to other serious chronic illnesses including advanced malignancy, but management is often different for patients with ESLD versus cancer. The aim of our study was to compare symptom burden and management of patients with ESLD and pancreatic ductal adenocarcinoma (PDAC). **Methods:** We performed a single center retrospective comparative analysis of patients removed from the liver transplant (LT) wait list (population 1) and patients who were diagnosed with PDAC (population 2) from 2018-2022. Outcomes of interest included reported symptoms, frequency of untreated pain, and the impact of a palliative care (PC) consult on treatment of pain. Analysis was completed within and between groups utilizing Chi squared tests. **Results:** A total of 270 patients (170 ESLD and 100 PDAC) were included. Patients with ESLD were younger (61 years vs 68 years, p<0.01) more likely to be male (68.8% vs 52.0%, p<0.01). Fewer patients with ESLD than PDAC reported pain as a symptom in the last year of life (82.0% vs 61.2%, p<0.001). Of those that reported pain (ESLD n=104, PDAC n=82), untreated pain was more common in ESLD patients compared to PDAC patients (81.7% vs 13.4%, p < 0.001) (Figure 1). Patients with ESLD who reported pain were less likely to be prescribed an opioid (18.3% vs 86.6%, p <0.001) or neuropathic analgesic (17.3% vs 31.7%, p=0.022) compared to patients with PDAC (Figure 1). Patients in either group who reported pain and had a PC consult were more likely to receive either an opioid or neuropathic medication compared to those without a PC consult (73.0% vs 41.2%, p<0.001). However, the association between a PC consult and treated pain was not significant on stratified analyses for ESLD or PDAC patient groups and was not statistically significant when only evaluating opioid prescription rates. Patients with ESLD who were prescribed an antidepressant for depression were less likely to experience untreated pain compared to those who were not prescribed antidepressants (36.2% vs 55.3%, p=0.026). This was not observed in PDAC patients (p=0.463). All patients with untreated pain were more likely to die in the hospital compared to patients with treated pain (70.5% vs 47.6%, p=0.005). Those with untreated pain were also more likely to undergo an invasive intervention (such as intubation or admission to an intensive care unit) in the last 30 days of life (75.3% vs 30.5%, p<0.001) (Figure 2). **Conclusion:** This comparative analysis demonstrates that pain is common in patients with ESLD and PDAC, but patients with ESLD are less likely to be prescribed pharmacotherapy. Untreated pain is associated with invasive interventions at the end of life and death in the hospital, but a PC consult may mitigate these outcomes. These results can inform clinical practices on pain management in patients with ESLD.

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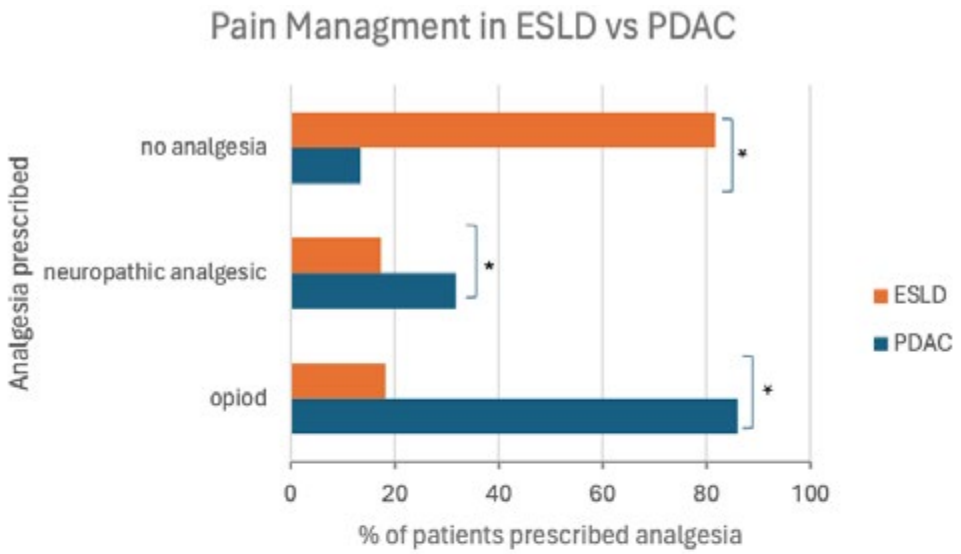

***Figure 1*: Pharmacologic therapy for patients with ESLD and PDAC who reported pain. * p<0.05.**

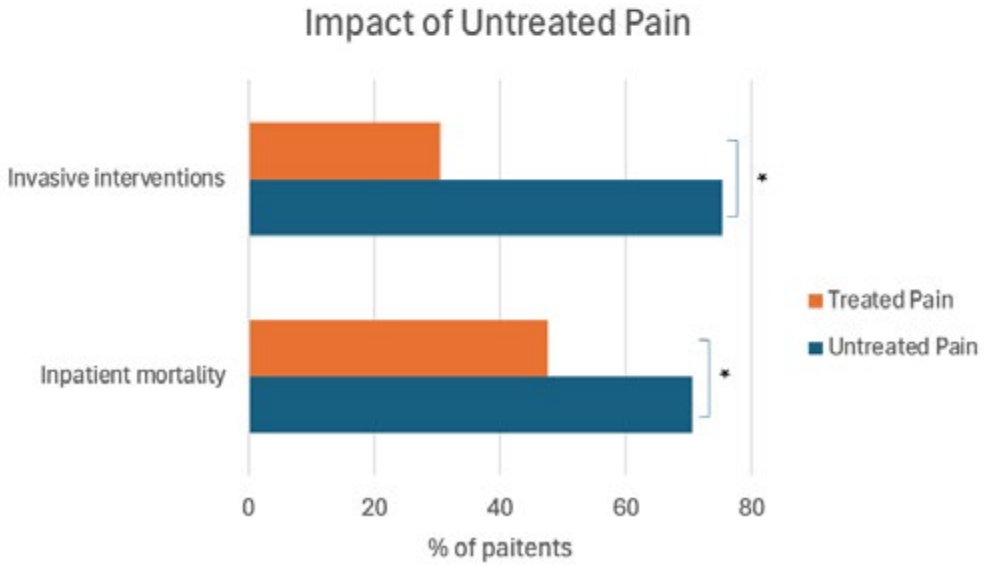

***Figure 2*: Outcomes for patients with either ESLD or PDAC who had untreated pain. * p <0.05.**

Disclosures: Mary Bassaly: Nothing to Disclose, Katherine Cooper: Nothing to Disclose, Navine Nasser-Ghodsi: Boston Scientific: Consultant, Neil Marya: Nothing to Disclose, Kai-Lou Yue: Nothing to Disclose

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3280 | GENDER DISPARITIES IN LISTING AND TRANSPLANTATION IN PATIENTS WITH ALD REFERRED FOR EARLY LIVER TRANSPLANTATION

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Background: The rate of alcohol use is increasing, particularly in younger women. Women are more susceptible to the toxic effects of alcohol compared to men and experience reduced access to liver transplant (LT). The aim of this analysis was to evaluate gender differences in presentation and access to LT in patients with alcohol associated liver disease (ALD) referred for early LT. **Methods:** RESOLVE-ALD is a multi-center retrospective cohort of patients with ALD referred for early LTE (≤ 6 months of abstinence) at six US centers between 2018-2021. The rate of listing and LT were compared between men and women. Stratified analyses were performed by MELD-Na (< 25 vs. ≥ 25) and age (≤ 50 vs. > 50 years). Multi-variable logistic regression was used to evaluate for association between gender and 1) waitlisting and 2) LT, adjusted for MELD-Na, albumin, days since last drink, race, marital status, children, employment, and substance use. Models were repeated using MELD-3.0 to account for current allocation protocols. **Results:** There were 632 patients referred for early LT (39% women, 61% men). The median time from last drink was 80 days (IQR 35-132). Women were younger and were less likely to have a prior diagnosis of liver disease (28% vs. 38%, p=0.010). A similar proportion were married (p=0.85), had minor children (p=0.43), and had prior substance use disorder (p=0.28). MELD-Na scores were similar between men and women (p=0.51). Of the 632 patients referred, 132 (21%) died prior to potential listing, 372 (59%) were listed, and 263 (42%) underwent LT. The reasons for which patients were not listed did not differ by gender (psychosocial p=0.163; medically too well, p=0.358; medical contraindication p=0.876; death, p=0.581). Overall, women were both less likely to be listed (53% vs. 62%, p=0.03) and less likely to undergo LT (34% vs. 47%, p=0.002) compared to men. In patients with MELD-Na < 25 (n=274), women were less likely to be listed (46% vs. 62%, p=0.01) and undergo LT (20% vs. 39%, p=0.02) compared to men; but no differences in listing and LT were observed with MELD-Na ≥ 25. Similarly, the gender disparity in listing and LT was noted among those < 50 years (n=346), but not those >50 years (n=284). On multivariable analyses, women had 32% lower odds of being listed for LT (aOR 0.68, 95% CI 0.49-0.97, p=0.03). Once listed for LT, women had 45% lower odds of undergoing LT (aOR 0.54, 95% CI 0.33-0.89, p=0.02). The associations between gender and listing (aOR 0.64, 95% CI 0.46-0.91, p=0.01) and LT (aOR 0.49, 95% CI 0.29-0.81, p=0.005) persisted when repeating analyses with MELD 3.0 instead of MELD-Na. **Conclusion:** We observed reduced LT access among women with ALD referred for early LT evaluation. Younger women and women with MELD-Na < 25 experienced the greatest disparities in waitlisting and transplant. The gender disparity was alleviated but persisted when modeling with MELD 3.0, which suggest greater impact of psychosocial than biologic factors in this cohort.

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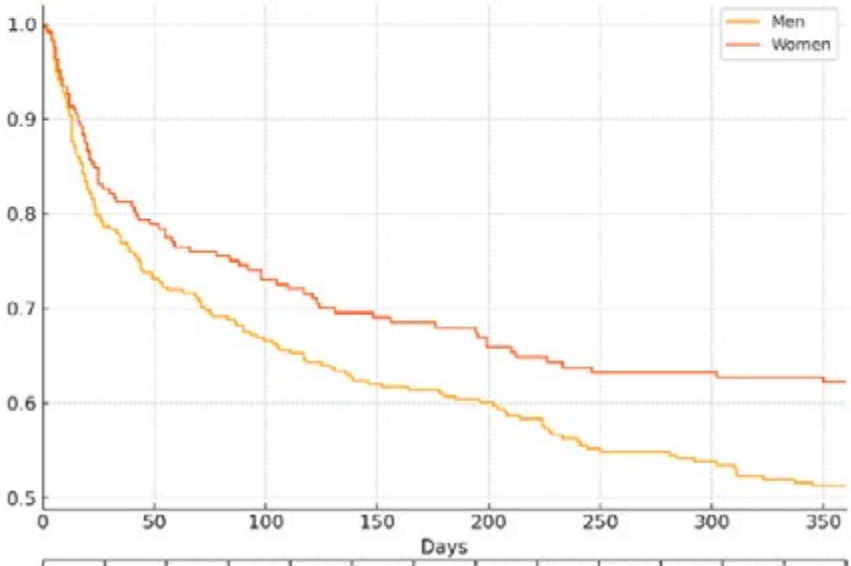
	Men (n=383)	Women (n=249)	p-value
Age (years)	51 (41,58)	49 (39,55)	0.044
MELD-Na (points)	28 (19,36)	27 (20,33)	0.507
Abstinence (days)	79 (34,131)	82 (35,133)	0.955
Race (%)			0.156
White, non-Hispanic	78.1	81.1	
White, Hispanic	16.2	10.8	
Black/African American	1.6	3.2	
Other/More than one	4.2	4.8	
Psychosocial factors (%)			
Married	45.4	46.2	0.853
Minor children	29.5	32.5	0.420
Unemployed at referral	27.9	41.0	<0.001
Marijuana use history	20.1	16.9	0.309
Substance use history	17.8	14.5	0.275
Outcomes (%)			
Waitlisted	62.4	53.4	0.025
Died prior to LT	26.1	26.5	0.912
Transplanted	46.5	34.1	0.002

Figure 1b: Time to transplant by gender for patients transplanted within 1 year. Men were significantly more to have undergone LT at 1 year compared to women (Log rank=0.022)



	0	30	60	90	120	150	180	210	240	270	300	330	360
Men	383	267	234	214	200	188	183	172	162	155	148	143	141
Women	249	182	160	152	142	135	130	126	121	118	117	116	114

Disclosures: Katherine Cooper: Nothing to Disclose, Alessandro Colletta: Nothing to Disclose, Ami Patel: Nothing to Disclose, Kawthar Mohamed: Nothing to Disclose, Nicholas Lim: Nothing to Disclose, Weiyu Wu: Nothing to Disclose, Allison Kwong: Nothing to Disclose, Anjana Rajan: Nothing to Disclose, Amanda Cheung: Nothing to Disclose, Kaleb Tesfai: Nothing to Disclose, Veeral Ajmera: Nothing to Disclose, Kevin Wang: Nothing to Disclose, Hersh Shroff: Nothing to Disclose, Deepika Devuni: Avania Medical: Grant/Research Support, Intercept: Grant/ Research Support

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3281 | LESS RESTRICTIVE MEDICAID POLICIES FOR DAA ACCESS ARE ASSOCIATED WITH GREATER DECLINES IN HCC-RELATED DEATHS

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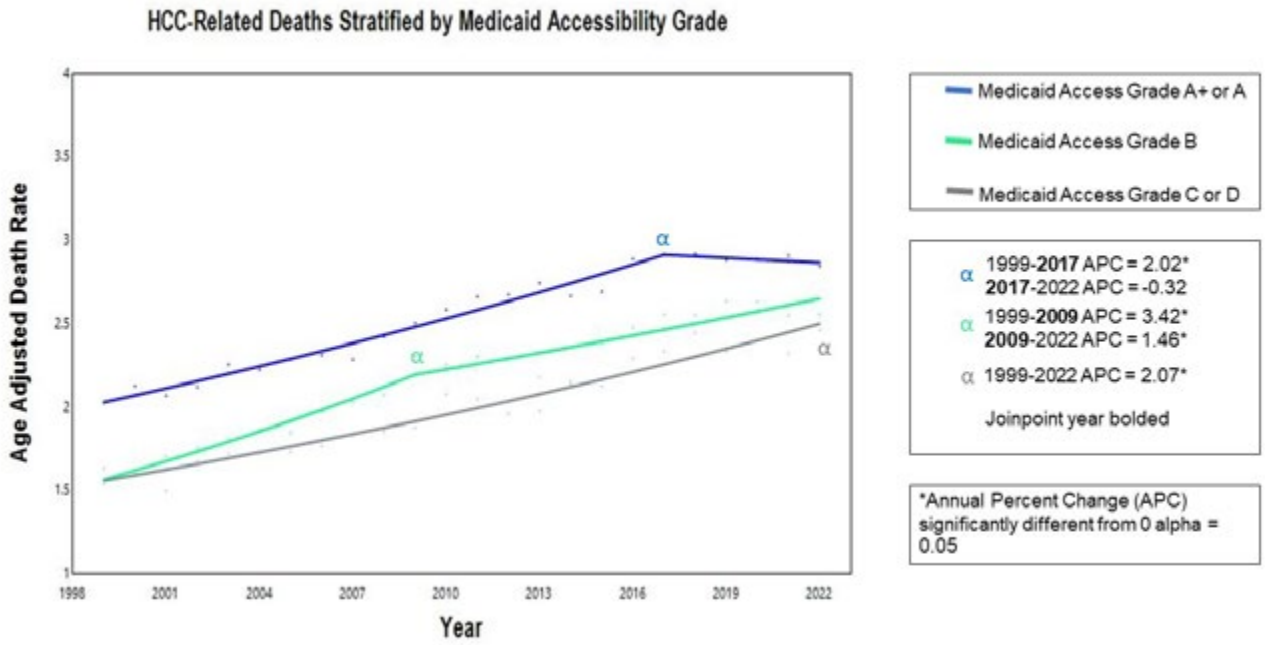
Background: In the US, chronic hepatitis C virus (HCV) remains the most common underlying liver disease etiology leading to hepatocellular carcinoma (HCC). Direct acting antivirals (DAAs) cure up to 95% of patients and decrease the risk of HCC development. Medicaid is a major payor for HCV treatment, but access to DAAs varies by state. Medicaid recipients with access restrictions are significantly less likely to receive timely treatment with DAAs. We aimed to assess if Medicaid DAA policies were associated with trends in HCC-related deaths. **Methods:** CDC WONDER is a publicly available database that collects death certificate data for all US residents. We determined age-adjusted death rate with a primary cause of death from HCC (C22.0) from 1999-2022 (all years included in the database) stratified by state Medicaid accessibility grade. We used the publicly available "Hepatitis C: State of Medicaid Access (2024)" state-by-state scoring system developed by the National Viral Hepatitis Roundtable and Harvard Center for Health Law and Policy Innovation. This system grades states with an A+ to F letter grade scale based on prior authorization (PA) restrictions. A+ grade states have PA removed for most patients, and F grade states have PA required for all patients with harsh restrictions. We grouped states based on their 2024 PA grade classification into 3 categories: A+/A (n=28), B (n=11), and C/D (n=12). There were no F grade states. We then assessed trends in age-adjusted death rate from 1999-2022 using the NCI Joinpoint analysis software to calculate annual percent change (APC). **Results:** In 1999, the age-adjusted HCC-related death rate for the three groups was: 2.03 per 100,000 in group A+/A, 1.54 in group B, and 1.63 in group C/D. Prior to 2017, HCC-related death rates were increasing in all states: group A+/A (APC 2.02 1999-2017), group B (APC 3.42 1999-2009; APC 1.46 2009-2022), and group C/D (APC 2.07 1999-2022). After 2017, the APC became negative only in group A+/A states (APC -0.32). From 1999-2022, group C/D states showed a consistent positive APC in age-adjusted HCC-related deaths (APC 2.07). **Conclusion:** We observed different trajectories of HCC-related deaths between the 3 groups of Medicaid accessibility. States with A+/A grade had a dramatic change from positive to negative APC in age-adjusted HCC deaths in 2017, while grade B and grade C/D states had a positive APC from 1999-2022. High baseline death rates may have led to less restrictive Medicaid policies in grade A+/A states, which likely contributed to a subsequent decrease in HCC-related deaths. Increased access to DAAs may have reduced HCC deaths by decreasing HCC incidence, preventing HCC recurrence or liver-related decompensation in patients with HCC, and improving linkage to subspecialty care and HCC surveillance. The results of this study indicate that less restrictive Medicaid access for DAAs is associated with reductions in HCC-related deaths.



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Disclosures: Gabriel Lupu: Nothing to Disclose, Alfred Barritt IV: Merck (Any division): Advisor, Madrigal: Consultant, Life Edit: Consultant, Boehringer Ingelheim: Consultant, Target-RWE: Consultant, Sasha Deutsch-Link: Nanbar Health: Consultant, Jane Giang: Nothing to Disclose, Ellen Green: Nothing to Disclose, Oren Fix: Nothing to Disclose, Neil Shah: GSK: Advisor, Ipsen: Advisor, Hersh Shroff: Nothing to Disclose, Andrew Moon: TARGET RWE: Consultant, DCN Diagnostics: Grant/Research Support, Intercept Pharmaceuticals: Consultant, Intercept Pharmaceuticals: DSMB, IDEOlogy: Consultant

3282 | ADVANCED CARE PLANNING IN ADVANCED LIVER DISEASE REMAINS DISMALLY LOW IN SINGAPORE: LESSONS LEARNED FROM EXAMINING REFERRALS AMONGST A COHORT OF HOSPITALIZED PATIENTS WITH CIRRHOSIS

Chanda Ho[1] Marianne De Roza[2] Wei Quan Teo[2] Jun Xian Wee[2] Amber Chung[2] Hiang Keat Tan[1] Rahul Kumar[3] Prema Raj[1] Jason Chang[1]

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Background: Implementation of advanced care planning (ACP) remains challenging in Asia. In response to an aging population where citizens > 65 comprise nearly 20% of the population, Singapore launched a national ACP program in 2011. While enrollment increases annually, ACP uptake remains quite low. Furthermore, its adoption amongst patients with advanced liver disease has not been well studied. Given low uptake amongst patients with liver disease even in countries where ACP adoption is more mainstream, we hypothesized that ACP uptake among liver disease patients in Singapore would be even lower. However, the burden of liver disease in Singapore is significant with the recent Singapore burden of disease survey ranking liver cancer as 8th and cirrhosis as 20th in years of life lost. **Methods:** We performed a retrospective cohort study among patients admitted to a large tertiary public hospital in Singapore from January 1-December 31, 2018 with validated ICD-10 codes for cirrhosis. We performed a qualitative study to better understand barriers to ACP uptake. All ACP chart notes were reviewed to identify themes based on the referral documentation. **Results:** Of 937 patients with cirrhosis, only 15 patients had an ACP referral. Of the 15 referrals, 3 patients completed an ACP. Most patients had incomplete referrals where the coordinator initiated contact with the patient but no full discussion took place. The average number of contact points between the ACP coordinator and the patient was 1.75. The most common themes to emerge were that 1) The patient did not feel ready or that they were contacted at a bad time (n= 6) and 2) At the time of referral, the patient was documented to have altered mental status either from their current medical condition or dementia (n=4). The other common theme to emerge was the importance of family members in the medical decision making process. In 11 out of 15 charts, family members were involved in the decision making process, and this was documented in the ACP referral. **Conclusion:** In a sample of 937 patients with cirrhosis, we found a low number of ACP referrals and an even lower number of completed ACPs. These data are consistent with relatively low adoption of ACP despite nationwide efforts but underscores the need for more ACP planning especially among patients with advanced liver disease. With regard to next steps, we have designed a pathway entitled Palliate End-stage and Advanced Cirrhotics Early (PEACE) to address this care gap with plans for implementation in July 2024.

Disclosures: Chanda Ho: Nothing to Disclose, Marianne De Roza: Nothing to Disclose, Wei Quan Teo: Nothing to Disclose, Jun Xian Wee: Nothing to Disclose, Amber Chung: Nothing to Disclose, Hiang Keat Tan: Nothing to Disclose, Rahul Kumar: Nothing to Disclose, Prema Raj: Nothing to Disclose, Jason Chang: Boehdringer-Ingelheim: Advisor

3283 | LIVER TRANSPLANTATION (LT) IS NOT COMMONLY BROACHED AMONGST A COHORT OF PATIENTS WITH DECOMPENSATED LIVER DISEASE IN SINGAPORE

Chanda Ho[1] Adam Quek Rop Fun[1] Amber Chung[1] Wei Quan Teo[1] Jun Xian Wee[1] Marianne De Roza[2] Thinesh Krishnamoorthy[1] Hiang Keat Tan[1] Rahul Kumar[3] Prema Raj[1] Jason Chang[1]

[1]Singapore General Hospital, [2]SingHealth, [3]Changi General Hospital

Background: Low rates of LT in Singapore have been attributed to decreased awareness of organ donation and cultural, religious, and social beliefs. While these factors may account for insufficient donors, they do not

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completely explain the relatively low uptake of LT by patients as treatment. We aimed to understand how often LT is broached among patients with decompensated cirrhosis. **Methods:** Patients admitted to a large tertiary public hospital in Singapore from January 1-December 31, 2018 with validated ICD-10 codes for cirrhosis were captured. Various outcomes were tracked via manual chart abstraction by two independent investigators, including hepatic decompensation (inclusive of hepatocellular carcinoma (HCC)) until December 31, 2022. Patients with both a decompensated episode and gastroenterology progress notes were identified. These notes were scanned for keywords: “transplant,” “LDLT”, “DDLT”, or “LTx” and examined from oldest to newest to determine if LT was broached. Entries where keywords were used in a different context were parsed out. **Mixed Methods:** analyses were conducted to evaluate the context of LT discussions and to determine if there were any differences between patients for whom LT was broached vs. not-broached. **Results:** Of 1733 patient records, 377 met inclusion criteria. LT was broached for 75 (17.5%) patients. Patients in the broached group were younger (mean age 59.4 vs. 70.1; p<0.001) at study inclusion and at decompensation (mean age 57.4 vs. 69.6; p<0.001). There was no significant difference in sex, ethnicity, MELD score, HCC rates, or liver disease etiology between the groups. Of the 377 patients, 11 patients underwent LT and 2 remain listed. Patients in the broached category had improved survival (from decompensation to death) compared to the not-broached with 1-year survival (88.7% vs. 75.8%) and 5-year survival (65.6% vs. 49.7%). **Conclusion:** LT was broached in < 25% of patient visits in a retrospective cohort study of cirrhosis patients. The improved survival in the broached group is most likely due to the younger age. More interestingly, these data suggest that there are a cohort of patients with decompensated liver disease who may have been eligible for LT who did not end up pursuing LT. Additional studies are needed to better understand barriers to LT uptake in Singapore. This study also underscores there is an opportunity to encourage LT as treatment option in eligible patients.

Disclosures: Chanda Ho: Nothing to Disclose, Adam Quek Rop Fun: Nothing to Disclose, Amber Chung: Nothing to Disclose, Wei Quan Teo: Nothing to Disclose, Jun Xian Wee: Nothing to Disclose, Marianne De Roza: Nothing to Disclose, Thinesh Krishnamoorthy: Nothing to Disclose, Hiang Keat Tan: Nothing to Disclose, Rahul Kumar: Nothing to Disclose, Prema Raj: Nothing to Disclose, Jason Chang: Boehdringer-Ingelheim: Advisor

3284 | HIGH CIRRHOSIS SURGICAL VOLUME CENTERS ARE ASSOCIATED WITH REDUCED POSTOPERATIVE MORTALITY IN PATIENTS WITH CIRRHOSIS UNDERGOING SURGERY: A VETERANS AFFAIRS COHORT STUDY

Bachir Ghandour[1] *David Kaplan*[1] *Nadim Mahmud*[1]

[1]*Hospital of the University of Pennsylvania*

Background: Patients with cirrhosis have increased postoperative risks as compared to the general population. It has been demonstrated across different surgical specialties that higher surgical volumes are associated with improved postoperative outcomes. However, data specific to patients with cirrhosis undergoing major surgeries remains limited. We aimed to assess the impact of cirrhosis surgical volume on postoperative mortality in patients with cirrhosis undergoing surgery. **Methods:** This was a retrospective cohort study of patients with cirrhosis in the Veterans Health Administration who underwent major surgery between 1/2009 and 3/2022. We limited our analysis to patients with American Society of Anesthesiology (ASA) classification 3 or 4. A rolling surgical volume indicator was created such that the center’s number of surgeries on patients with cirrhosis in the 1 year prior to each surgery was captured. This was categorized as low (<10 surgeries), medium (10-20 surgeries), or high (>20 surgeries) volume. We then used unadjusted Kaplan-Meier and multivariable Cox regression analysis (adjusted for age, sex, race, surgery type, ASA class, Child-Turcotte-Pugh Score, and MELD-Na) to evaluate the association between center surgical volume and postoperative mortality through 3 months. **Results:** A total of 14,806 patients across 110 different centers were included. The median rolling surgical volume for centers was 12 surgeries in the past year (IQR 7, 18). High volume centers had a higher proportion of ASA 4 patients as compared to medium and low volume centers (31.5% vs 27.1% and 27.4% respectively, p <0.001). In Kaplan-Meier analysis, no significant differences were observed in postoperative survival among the different surgical volume categories (Figure 1**).** However, in adjusted Cox regression the hazard of postoperative mortality at 3 months was significantly reduced at high volume centers (hazard ratio [HR], 0.72; 95% confidence interval [CI], 0.55-0.95) as compared to low volume centers. No significant differences were observed between medium and low volume centers (HR, 0.91; 95% CI, 0.73-1.10). **Conclusion:** Performance of major surgery in patients with cirrhosis at high-volume centers was associated with a reduced risk of postoperative mortality in adjusted

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analysis. This suggests that referral to high surgical volume centers might improve postoperative outcomes of patients with cirrhosis independent of patient specific factors.

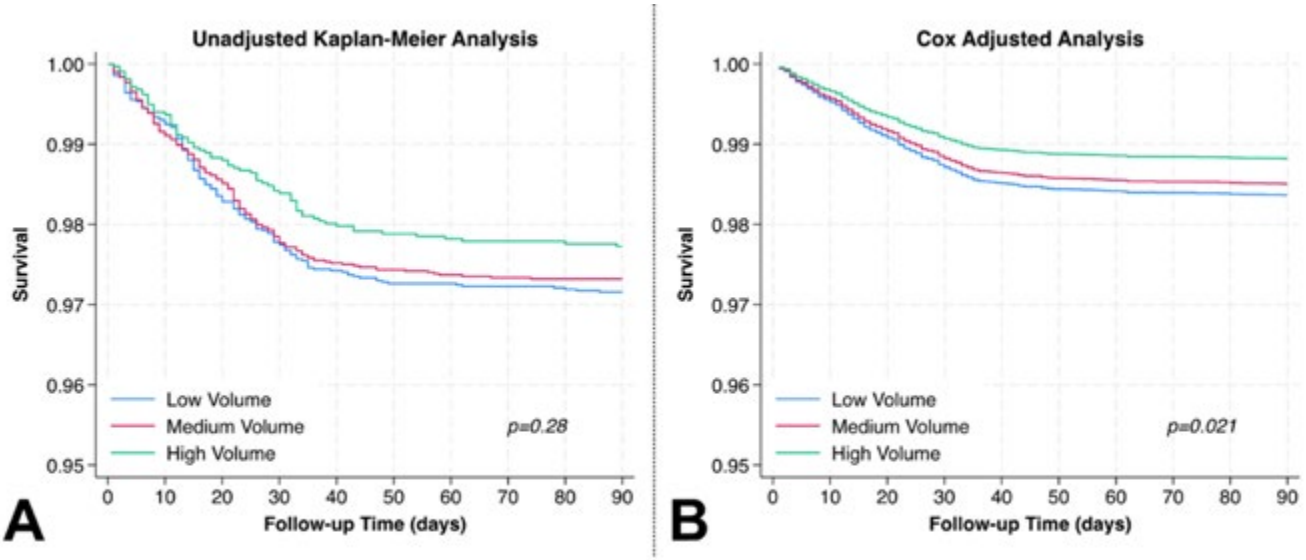

Figure 1: Association between Center Cirrhosis Surgical Volume and Post-operative survival through 3 Months in (A) Unadjusted Kaplan-Meier and (B) Cox Adjusted Analyses in Patients with Cirrhosis Undergoing Surgery

Disclosures: Bachir Ghandour: Nothing to Disclose, David Kaplan: Independent Contractor relationship with Roche Genentech; Has not ended; Grant/Research Support relationship with AstraZeneca Inc; Has not ended; Advisor relationship with AstraZeneca; Has ended; Advisor relationship with Exelixis; Has ended; Grant/Research Support relationship with Gilead; Has not ended; Advisor relationship with Sirtex; Has ended; Grant/Research Support relationship with Exact Sciences; Has not ended; Grant/Research Support relationship with Glycotest; Has ended, Nadim Mahmud: Nothing to Disclose

3285 | PATIENT VOICE IN MASH INITIATIVE: FOUNDATIONAL PRINCIPLES FOR THE CONDUCT OF PATIENT-CENTRIC MASH RESEARCH

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[1]Fatty Liver Alliance, [2]European Liver Patients Association, [3]Prometheus, [4]NASH kNOWledge, [5]Global Liver Institute, [6]Amigos del Hígado AC, [7]Thermo Fisher Scientific, [8]Thermo Fisher Scientific,

Background: Recognizing the growing global burden of metabolic dysfunction-associated steatohepatitis (MASH) and the need for treatment innovation, a diverse and representative group of worldwide patient leaders in metabolic dysfunction-associated fatty liver disease (MAFLD) and MASH advocacy came together with subject matter experts in liver disease and clinical trials to identify barriers to participation in MASH clinical studies and opportunities to make MASH trials more efficient, effective and patient-centric. **Methods:** Following a landscape analysis of MASH advocacy groups and literature, a patient engagement plan aligned with the Patient Focused Medicines Development Quality Guidance for meaningful patient engagement was developed. Leaders from six global patient advocacy groups focused on steatotic liver disease and MASH were invited to form the Patient Voice in MASH patient advisory board (PAB). Through a series of one-to-one and group meetings, the PAB identified barriers to and facilitators of patient participation and retention in MASH clinical research. Recommendations were mapped to existing trial supports and services to identify areas for potential investment of resources to enhance the patient-centricity of MASH trials and improve the patient experience in participation. **Results:** In partnership with subject-matter experts within the PPD clinical research business of Thermo Fisher Scientific, the Patient Voice in MASH PAB identified barriers to successful MASH research that were clustered into three key areas, and then identified facilitators and patient needs to address these barriers. Five foundational principles for the design and conduct of patient-centric MASH trials were identified. These principles state that all MASH research should be: 1. Transparent; 2. Whole person focused; 3. Created in partnership with patients; 4.

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Family- and caregiver-aware. Responsive to patient needs **Conclusion:** The Foundational Principles of Patient-centric MASH Research provide tangible guidance for how to better meet the needs of individuals living with MASH within clinical trials. These principles highlight concrete ways in which the planning and implementation of trials can be optimized in partnership with patients to increase the patient-centricity and likely success of studies. Future research is needed to assess feasibility and effectiveness of implementing these principles and their impact on study recruitment, retention and patient satisfaction.

Foundational Principles of Patient-centric MASH Research

Foundational Principle	Examples of Principles in Practice
Transparent	• Study materials should be written in a patient-friendly and culturally conscious way.
	• In placebo-controlled trials, clarity on whether, when and how participants randomized to placebo will receive the active comparator should be provided to patients at the time of consent.
	• Lay summaries of research findings should be developed and made available to all trial participants.
Whole person focused	• All trials should embrace the ethos of patients as partners rather than subjects.
	• Comfort, respect, awareness, flexibility, agility and collaboration are essential facets to ensure a trial remains cognizant of the evolving circumstances of a person with liver disease.
Created in partnership with patients	• Patient insights should be sought and integrated into each phase of trial planning and implementation, from initial protocol development through dissemination efforts.
	• Opportunities to partner with both PAGs and lay patients should be pursued in all MASH trials, and efforts to create materials in partnership with patients and PAGs must be prioritized.
Family- and caregiver-aware	• Consideration must be given to the role that family members and caregivers play in helping patients decide whether to participate in a trial, and in the likelihood that they will remain in a trial once they have enrolled. Engaging family members and caregivers (in addition to patients) in the planning of MASH trials can help to anticipate patient and caregiver needs, and design the trial around them.
	• In patients with MASH, the role of family members and caregivers will become increasingly important as disease progresses. Integrating the perspective of family members and caregivers into the protocol development for MASH studies, creating patient- and family-facing outreach materials, selecting sites, and determining which support services to provide will add great value.
Responsive to patient needs	• The experience of trial participants should be evaluated as the study progresses. Participant feedback should be integrated into trial operations in real time.
	• Participant experience data should routinely be collected at timepoints throughout each study. In addition to implementing changes into active studies, an evaluation of what worked well and where improvements could have been made should be conducted at the conclusion of each study. These learnings should be applied to the design and implementation of future studies.

Abbreviations: MASH = metabolic dysfunction-associated steatohepatitis; PAG = patient advocacy group

Disclosures: Michael Betel: Grant to Fatty Liver Alliance for charity work relationship with Regeneron Pharmaceuticals; Has not ended; Grant to Fatty Liver Alliance for charity work relationship with Siemens Healthineers; Has not ended; Grant to Fatty Liver Alliance for charity work relationship with Merck Pharmaceuticals; Has ended; Grant to Fatty Liver Alliance for charity work relationship with Pfizer Pharmaceuticals; Has not ended; Grant to Fatty Liver Alliance for charity work relationship with Echosens; Has not ended; Grant to Fatty Liver Alliance for charity work relationship with Madrigal Pharmaceuticals; Has not ended; Grant to Fatty Liver Alliance for charity work relationship with Aegle Medical; Has not ended; Grant to Fatty Liver Alliance for charity work relationship with Pfizer Pharmaceuticals; Has not ended; Consultant relationship with Regeneron Pharmaceuticals; Has not ended; Grant to Fatty Liver Alliance for charity work relationship with Inventiva Pharmaceuticals; Has not ended; Grant to Fatty Liver Alliance for charity work relationship with Novo Nordisk Pharmaceuticals; Has not ended; Consultant relationship with Madrigal Pharmaceuticals; Has not ended; Speaking and Teaching relationship with PPD; Has not ended, Julio Berman: Nothing to Disclose, George Kalamitsis: Nothing to Disclose, Gina Madison: Nothing to Disclose, Jeff McIntyre: Nothing to Disclose, Jorge Luis Poo: Nothing to Disclose, Kimberly Bailey: Nothing to Disclose, Sigrunn Blacoe: Nothing to Disclose, Soren Skovlund: Nothing to Disclose, Paola Figueroa Barojas: Nothing to Disclose

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3286 | COST-EFFECTIVENESS OF EXPANDING ELIGIBILITY FOR ANTIVIRAL PROPHYLAXIS TO ALL HBSAG-POSITIVE PREGNANT WOMEN INACCESSIBLE TO HBV DNA OR HBEAG TESTING IN CHINA ◆

Xueru Yin[1] Xin Liang[2] Zhihua Liu[3] Jinlin Hou[3]

[1]Nanfang Hospital, Southern Medical University, [2]Southern Medicial University, [3]Nanfang Hospital, Southern Medicial University

Background: The World Health Organization (WHO) 2024 hepatitis B virus (HBV) guideline expanded antiviral prophylaxis to all hepatitis B surface antigen (HBsAg) positive pregnant women in settings where neither HBV DNA nor hepatitis B e antigen (HBeAg) testing is available. We aimed to assess the cost-effectiveness of the WHO new recommendation based on the Shield Program (Yin XR, et al, Nature Medicine, 2024;30(2):455-462). **Methods:** A decision tree and a lifetime Markov model were constructed to compare the cost-effectiveness of two strategies in pregnant women with HBV infection: 1) existing strategy: antiviral prophylaxis for HBsAg-positive pregnant women with HBV DNA ≥200,000 IU/mL or HBeAg positive in addition to universal infant immunization with at least three doses of the hepatitis B vaccine; and 2) expanding strategy: administer antiviral prophylaxis to all HBsAg-positive pregnant women who have no access to the test of HBV DNA or HBeAg serology based on existing strategy. Model parameters were obtained from the Shield Program and literature research. Outcome measures were the total cost saved and quality-adjusted life-year (QALY) gained. The incremental cost-effectiveness ratio (ICER) between the two strategies was calculated. **Results:** In China, the expanding strategy decreased cost by $1,509, gaining incremental QALYs by 0.08 years, compared with the existing strategy. The ICER of expanding strategy was -$19,456/QALY. The expanding strategy could reduce 11,787 newborns' infection of HBV per 1,000,000 pregnant women, compared with the existing strategy. The probabilistic sensitivity analysis indicated that at a willingness-to-pay threshold of the three times gross domestic product (GDP) per capita in China, the probability of expanding strategy being cost effective was 94%. One-way deterministic sensitivity analyses showed the robustness of the results. **Conclusion:** Expanding eligibility for antiviral prophylaxis during pregnancy to prevent mother-to-child transmission of HBV is cost-effective in China and may contribute to eliminating hepatitis B.

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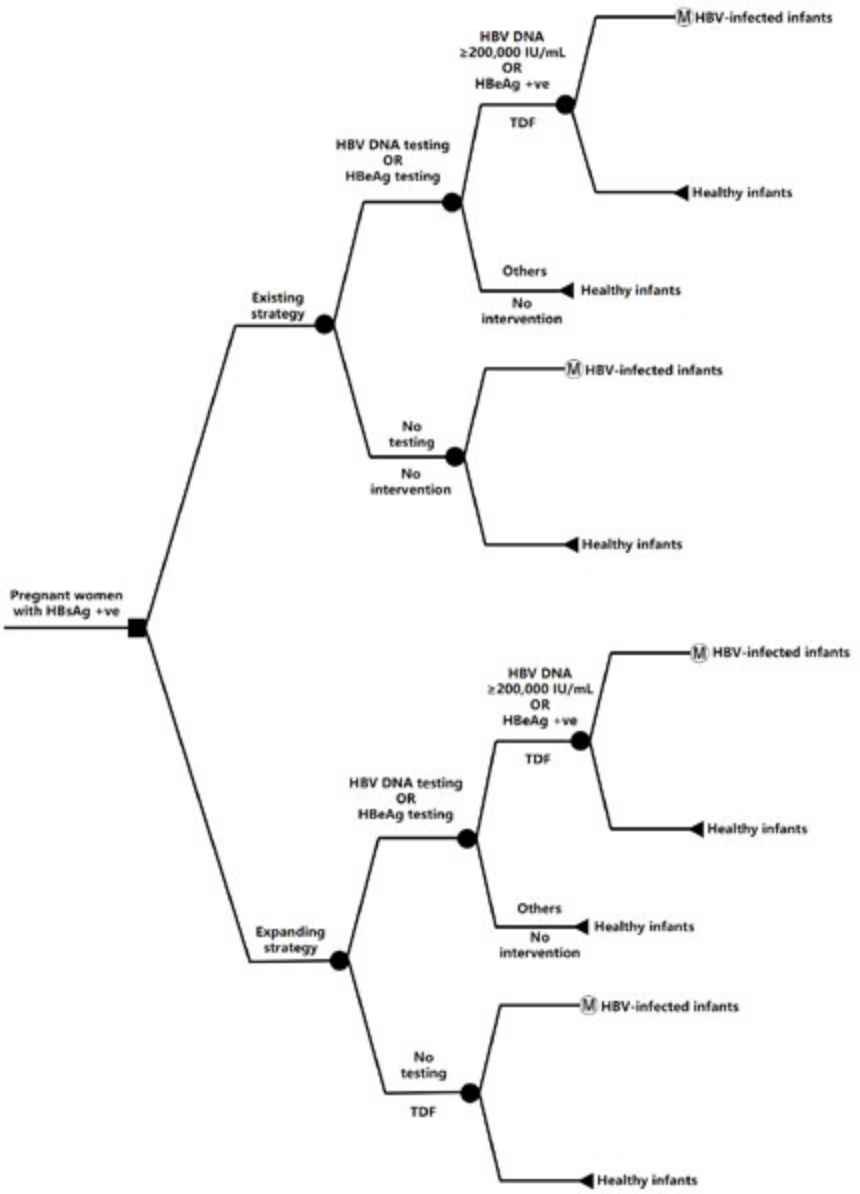

Disclosures: Xueru Yin: Nothing to Disclose, Xin Liang: Nothing to Disclose, Zhihua Liu: Nothing to Disclose, Jinlin Hou: Nothing to Disclose

3287 | COMPARATIVE EVALUATION OF STANDARD MACHINE LEARNING MODELS FOR LIVER FIBROSIS PREDICTION

Marcus Buchwald[1] Pascal Memmesheimer[1] Arash Dooghaie Moghadam[1] Ines Tuschner[1] Laura Alejandra Santamaria Suarez[1] Jimmy Daza[1] Timo Itzel[2] Christoph Antoni[1] Catharina Gerhards[1] Michael Neumaier[1] Christoph Brochhausen-Delius[1] Matthias Ebert[1] Jürgen Hesser[1] Andreas Teufel[1]

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Background: The progression of liver fibrosis to cirrhosis is a common pathway in chronic liver diseases. The development of liver cirrhosis, in particular, can lead to significant functional impairments and complications. Therefore, early detection of fibrotic changes is essential in assessing chronic liver diseases. However, existing serological markers remain inadequate, prompting the analysis of explainable machine learning-based models that we have compared against a standard cohort of liver biopsies. **Methods:** Between 06.23.1999 and 03.04.2022, 655 patients underwent liver biopsies at Mannheim University Hospital. The corresponding clinical

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and laboratory parameters were retrospectively extracted from the respective hospital information systems. For the analysis of machine learning methods used to classify liver fibrosis as a binary task as well as a three-stage classification, a variety of classical machine learning models and state-of-the-art deep neural networks were implemented, hypertrained, and tested on the collected data. **Results:** The accuracy of standard machine learning models for predicting liver fibrosis using blood markers was robust, with accuracies reaching up to 88.04%. The tree-based models, namely LightGBM, XGBoost, and Random Forest consistently performed the best across various classification tasks with a range of 81.07% to 88.04% for binary classification and 69.64% to 73.04% for three-stage classification, significantly outperforming the traditional FIB-4 score. SHAP analysis of the best ensemble models consistently identified thrombocyte count, MCV, INR, and Quick as the most influential biomarkers, with models using only these four parameters achieving comparable performance to those using the full set of biomarkers (accuracy up to 89.46%). These findings suggest that simplified diagnostic tools using established ML algorithms focusing on these key biomarkers could be highly effective for liver fibrosis prediction. **Conclusion:** Machine learning models can significantly improve the prediction of liver fibrosis compared to serum-based tests alone. Platelets, MCV, INR, and Quick are significantly more important than previously thought. Providing an internet-based analysis tool for our predictive algorithm offers an opportunity for clinical use and validation.

Disclosures: Marcus Buchwald: Nothing to Disclose, Pascal Memmesheimer: Nothing to Disclose, Arash Dooghaie Moghadam: Nothing to Disclose, Ines Tuschner: Nothing to Disclose, Laura Alejandra Santamaria Suarez: Nothing to Disclose, Jimmy Daza: Nothing to Disclose, Timo Itzel: Nothing to Disclose, Christoph Antoni: Nothing to Disclose, Catharina Gerhards: Nothing to Disclose, Michael Neumaier: Nothing to Disclose, Christoph Brochhausen-Delius: Nothing to Disclose, Matthias Ebert: Nothing to Disclose, Jürgen Hesser: Nothing to Disclose, Andreas Teufel: Nothing to Disclose

3288 | NEW DIAGNOSIS OF CIRRHOSIS IS COMMON IN THE EMERGENCY DEPARTMENT AND ASSOCIATED WITH HIGHER HEALTHCARE UTILIZATION

Swetha Parvataneni[1] Qing Tang[1] Yara Sarkis[1] Michelle Haugh[1] Brittany Baker[1] Lauren Nephew[1] Marwan Ghabril[1] Naga Chalasani[2] Raj Vuppalanchi[1] Eric Orman[1] Nicholas Harrison[1] Archita Desai[1]

[1]Indiana University, [2]Indiana University Medical Center

Background: In a recent study, we observed that up to 20% of patients with cirrhosis have their first diagnosis of cirrhosis made in the emergency department (ED) when they are presented for acute care. The characteristics of such patients is not known. We therefore conducted a study to describe individuals newly diagnosed with cirrhosis (NDC) during an ED visit and compare their outcomes with patients with known diagnosis of cirrhosis (KDC) attending the ED. **Methods:** We conducted a study of adults with cirrhosis who presented to the ED between January 2021 and December 2021 in a large, state-wide healthcare system affiliated with a tertiary care liver transplant center (n=2124, 16 ED sites) and did not have a history of liver transplant. Charts were reviewed to determine if cirrhosis diagnosis was established or newly diagnosed during the ED visit. Cirrhosis diagnosis was based on clinical documentation, imaging, and/or liver biopsy. We collected baseline demographics, ED visit characteristics, subsequent ED visits, hospitalizations, and mortality up to 90 days . NDC were compared to KDC using Chi-square test or Fisher's exact test for categorical variable and two sample t-test for continuous variables. Additionally, within the NDC group, we compared the characteristics of those who had a ED revisit within 90-days vs. not. **Results:** Among the overall cohort, 391 (18%) patients were NDC, with 49% of these diagnoses confirmed clinically and 94% through imaging. The Table shows comparisons between the NDC and KDC groups. The NDC and KDC groups had similar sociodemographic characteristics. Compared to the KDC group, the NDC group had similar MELD-Na (both p>0.05) but had significantly lower Elixhauser comorbidity index (7.3 ± 4.0 vs. 5.3 ± 3.8p<.001). The NDC group also had lower prior healthcare utilization, including fewer inpatient encounters and outpatient visits (p < 0.05). Active alcohol or substance use was more common in the NDC vs. KDC group (22% vs. 11%, p<.001[CNP1]). Compared to KDC group, ED visits in the NDC group were more commonly for abdominal pain, nausea, vomiting, ascites, and GI bleeding (p<0.05). During the initial ED visit, the NDC group underwent more ED interventions such as lab draw, blood cultures, imaging, and GI consultations. The NDC group was more likely to be hospitalized (78% vs. 56%, p<.001). 90-day ED revisit rates were similar between the 2 groups, however, the NDC group returned to the ED or hospital sooner, and 20% had more than two ED visits during the 90-day period. **Conclusion:** Individuals who were newly diagnosed with cirrhosis in the ED were hospitalized more often despite similar severity of liver disease, experienced more interventions in the ED and

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returned to the ED sooner than the known diagnosis group. More studies are needed to better understand why the health care utilization (HCU) is higher in this group and strategies to mitigate such higher HCU.

Table: Baseline demographics and ED visit characteristics of individuals with new and known diagnosis of cirrhosis

	Known diagnosis of cirrhosis (n=1733) N (%)	New diagnosis of cirrhosis (n=391) N (%)	p-value
Age*	61.3 ± 12.5	61.3 ± 14.5	0.969
Gender: Male	916 (53%)	214 (55%)	0.509
Race: White	1544 (91%)	356 (92%)	0.426
Insurance: Medicare	914 (53%)	193 (49%)	0.117
HCU 12 months prior to the initial ED visit*			
ED encounters	0.6 ± 1.7	0.5 ± 1.4	0.162
Inpatient encounters	0.5 ± 1.2	0.4 ± 1.1	0.005
Outpatient encounters	4.9 ± 7.9	2.0 ± 4.0	<.001
Cirrhosis characteristics at time of ED visit:			
Etiology: Undetermined/Unknown	213 (12%)	160 (41%)	<.001
Ascites	867 (50%)	162 (42%)	0.003
Hepatic encephalopathy	612 (35%)	63 (16%)	<.001
Varices	649 (38%)	71 (18%)	<.001
Hepatocellular carcinoma	134 (8%)	14 (4%)	0.014
MELD-Na Score*	18.0 ± 7.9	18.2 ± 8.2	0.680
Elixhauser Comorbidity Score*	7.3 ± 4.0	5.3 ± 3.8	<.001
Reasons for ED visit:			
Abdominal pain	325 (19%)	113 (29%)	<.001
Ascites/Abdominal distension	247 (14%)	94 (24%)	<.001
Nausea/vomiting	147 (9%)	58 (15%)	<.001
GI bleed	125 (7%)	43 (11%)	0.012
ED interventions:			
Lab draw	1555 (90%)	377 (96%)	<.001
Urine studies	311 (18%)	104 (27%)	<.001
Blood cultures	109 (6%)	39 (10%)	0.010
Imaging:			
Abdominal CT	508 (30%)	240 (61%)	<.001
Chest CT	199 (12%)	83 (21%)	<.001
Abdominal US	80 (5%)	41 (11%)	<.001
Procedures: Paracentesis	66 (4%)	18 (5%)	0.466
Consults: GI	71 (4%)	25 (7%)	0.048
Disposition:			<.001
Home	709 (41%)	75 (19%)	
Hospital	967 (56%)	306 (78%)	
Return to ED in 90 days	729 (42%)	167 (43%)	0.815
Time to return to ED*	30.3 ± 25.6	22.5 ± 21.0	<.001
Return to Hospital in 90 days	573 (33%)	141 (36%)	0.257
Time to return to Hospital*	25.7 ± 26.8	16.1 ± 23.1	<.001
30- day mortality	159 (9%)	40 (10%)	0.518
90-day mortality	271 (16%)	73 (19%)	0.412

*Mean(SD)

Disclosures: Swetha Parvataneni: Nothing to Disclose, Qing Tang: Nothing to Disclose, Yara Sarkis: Nothing to Disclose, Michelle Haugh: Nothing to Disclose, Brittany Baker: Nothing to Disclose, Lauren Nephew: Nothing to Disclose, Marwan Ghabril: Nothing to Disclose, Naga Chalasani: Madrigal: Consultant, Zydus, Ipsen, Pfizer, Merck, Altimmune, GSK: Consultant, Exact Sciences: Grant/Research Support, NIH: Grant/Research Support, Raj Vuppalanchi: Eli LIlly: Advisor, GSK: Advisor, Madrigal: Advisor, Zydus Therapeutics: Grant/Research Support, Galectin Therapeutics: Grant/Research Support, Kowa: Grant/Research Support, Takeda: Grant/Research Support, GSK: Consultant, UBC: Consultant, Eric Orman: Sitero: Consultant, Biovie: Advisor, Nicholas Harrison: Nothing to Disclose, Archita Desai: Nothing to Disclose

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3289 | MEDICARE PART D COVERAGE RESTRICTIONS FOR DRUGS COMMONLY PRESCRIBED FOR HEPATITIS B TREATMENT, 2019-2023

Misha Gautam[1] *Utkarsh Goel*[2] *Babu Mohan*[3]

[1]*University of Missouri Kansas City School of Medicine, Kansas City, MO, USA,* [2]*Cleveland Clinic, Cleveland, OH, USA,* [3]*Orlando Gastroenterology PA, Orlando, FL, USA*

Background: Payors increasingly ration care by imposing utilization management strategies such as quantity limits and prior authorizations. Unreasonably restrictive strategies, along with placing drugs on higher cost sharing tiers are barriers to persons with Hepatitis B infection accessing prescription drugs. **Methods:** We evaluated 5 antiviral drugs (8 unique formulations) commonly prescribed for chronic hepatitis B treatment using the Medicare Part D Prescription Drug Plan Formulary Files and analyzed the mean formulary tier placement, the proportion of stand-alone Medicare Part D plans adopting prior authorizations, and the proportion of plans imposing quantity limits for each formulation for the first quarters of 2019-2023. **Results:** An antiviral drug formulation on average was covered by 697 plans/year (range 14-1007). The proportion of plans requiring prior authorization remained mostly unchanged for most formulations (Figure 1A). However, for certain formulations- Vemlidy and Baraclude, the proportion of plans requiring prior authorization varied greatly, with coverage being most restrictive in 2021. The pattern of prior authorizations also varied with different formulations of the same drug. For example, while no plans required prior authorization for Viread (tenofovir disoproxil fumarate), 8.6-42.2 % plans required a prior authorization for Vemlidy (tenofovir alafenamide). We found that the mean formulary tier placement overall was on a lower tier for generic and brand name lamivudine (range 3-3.6), as compared to other brand name drugs (range 4.3-5, Figure 1B). The proportions of plans imposing quantity limits varied greatly across formulations (range 0-100%) but were mostly similar for respective individual formulations over the study period (Figure 1C). **Conclusion:** Payer-imposed utilization management strategies limit access to prescription drugs at various levels. Our assessment and comparison of current coverage restrictions on antiviral drug formulations commonly used for hepatitis B treatment revealed no improvement in these restrictions from 2019-2023. These strategies can delay or restrict necessary care, and lead to higher cost-sharing for patients. We emphasize the need for urgent advocacy, legislative efforts, and policy changes to ensure affordable, equitable, and timely access to treatment for Part D beneficiaries.

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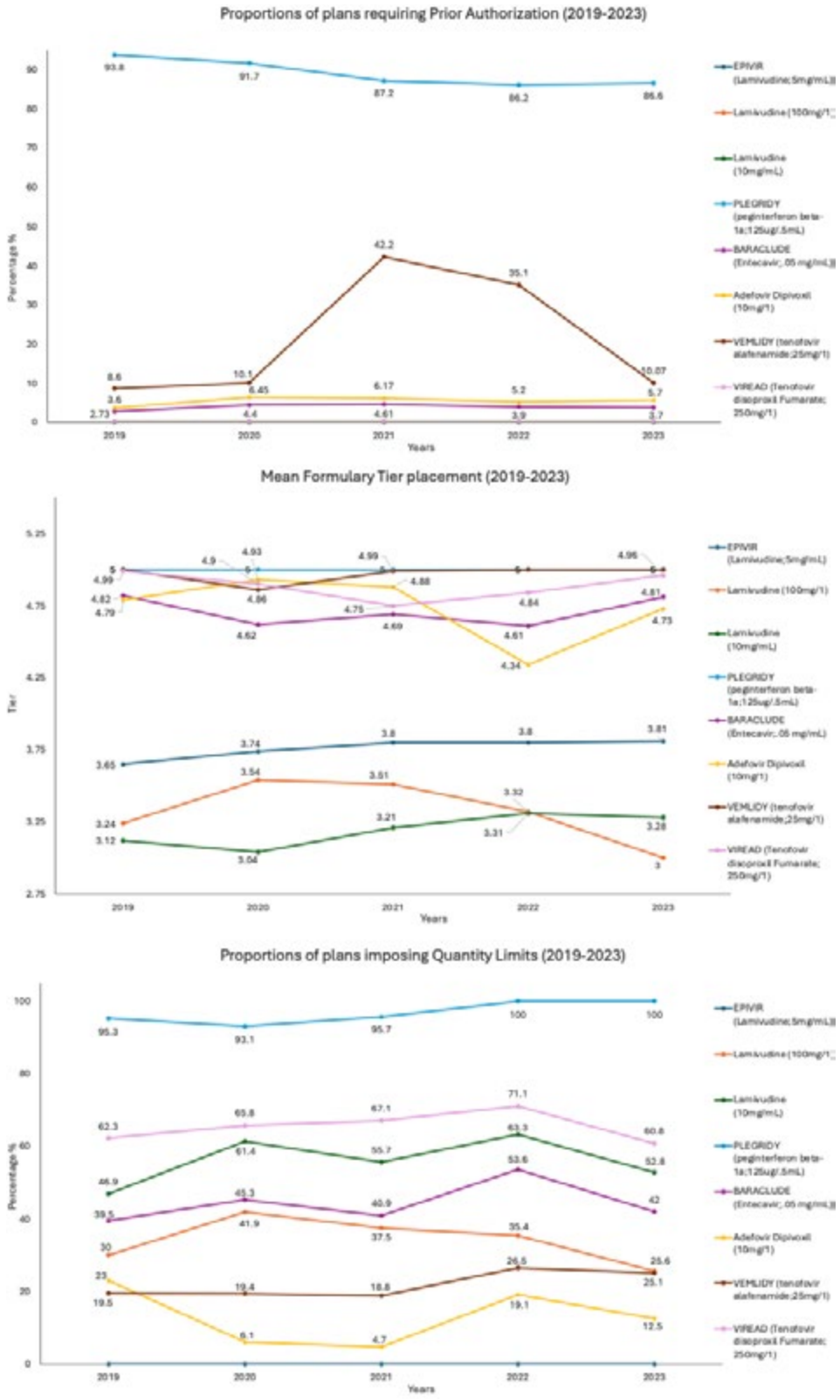

Disclosures: Misha Gautam: Nothing to Disclose, Utkarsh Goel: Nothing to Disclose, Babu Mohan: Nothing to Disclose

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3290 | MEDICARE PART D COVERAGE RESTRICTIONS FOR DRUGS COMMONLY PRESCRIBED FOR HEPATITIS C TREATMENT, 2019-2024

Misha Gautam[1] *Utkarsh Goel*[2] *Babu Mohan*[3]

[1]*University of Missouri Kansas City School of Medicine, Kansas City, MO, USA,* [2]*Cleveland Clinic, Cleveland, OH, USA,* [3]*Orlando Gastroenterology PA, Orlando, FL, USA*

Background: Payors increasingly ration care by imposing utilization management strategies such as quantity limits and prior authorizations. Unreasonably restrictive strategies, along with placing drugs on higher cost sharing tiers are barriers to persons with Hepatitis C infection accessing prescription drugs. **Methods:** We evaluated 8 unique antiviral drug formulations commonly prescribed for chronic hepatitis C treatment using the Medicare Part D Prescription Drug Plan Formulary Files and analyzed the mean formulary tier placement, the proportion of stand-alone Medicare Part D plans adopting prior authorizations, and the proportion of plans imposing quantity limits for each formulation for the first quarters of 2019-2024. **Results:** Hepatitis C antiviral formulations on average were covered by 424 (range 16-1005) plans/year. All plans (100%) required prior authorization from 2019-2024, both for brand name and generic formulations. The mean formulary tier placement was on a relatively higher Part D cost sharing tier (tier 5) and remained constant from 2019-2024 for most formulations (Figure 1A). For certain formulations like Epclusa and Harvoni, tier placement became more restrictive with time (mean 4.8 in 2019 to 5.0, 2020 and onwards). The proportions of plans imposing quantity limits varied across formulations; however, the quantity limits themselves (units/time-period, e.g., 30 tablets/month) remained largely unchanged. For most brand name formulations- Sovaldi, Epclusa, Harvoni, Vosevi and Mavyret, the trend became increasingly restrictive over the years, with a higher proportion of plans imposing quantity limits each year. For certain generic formulations, there was a slight improvement in the proportion of plans imposing these limitations (Figure 1B). **Conclusion:** Over the 6-year study period, access to hepatitis C treatments via Medicare Part D plans remained restrictive, with all plans requiring a prior authorization, and most plans placing these drugs on higher cost sharing tiers. Over the years, a higher proportion of plans imposed quantity limits for brand name hepatitis C formulations. With our findings, we highlight the need for urgent advocacy, legislative efforts, and policy initiatives to ensure affordable, equitable, and timely access to treatment for Part D beneficiaries with Hepatitis C.

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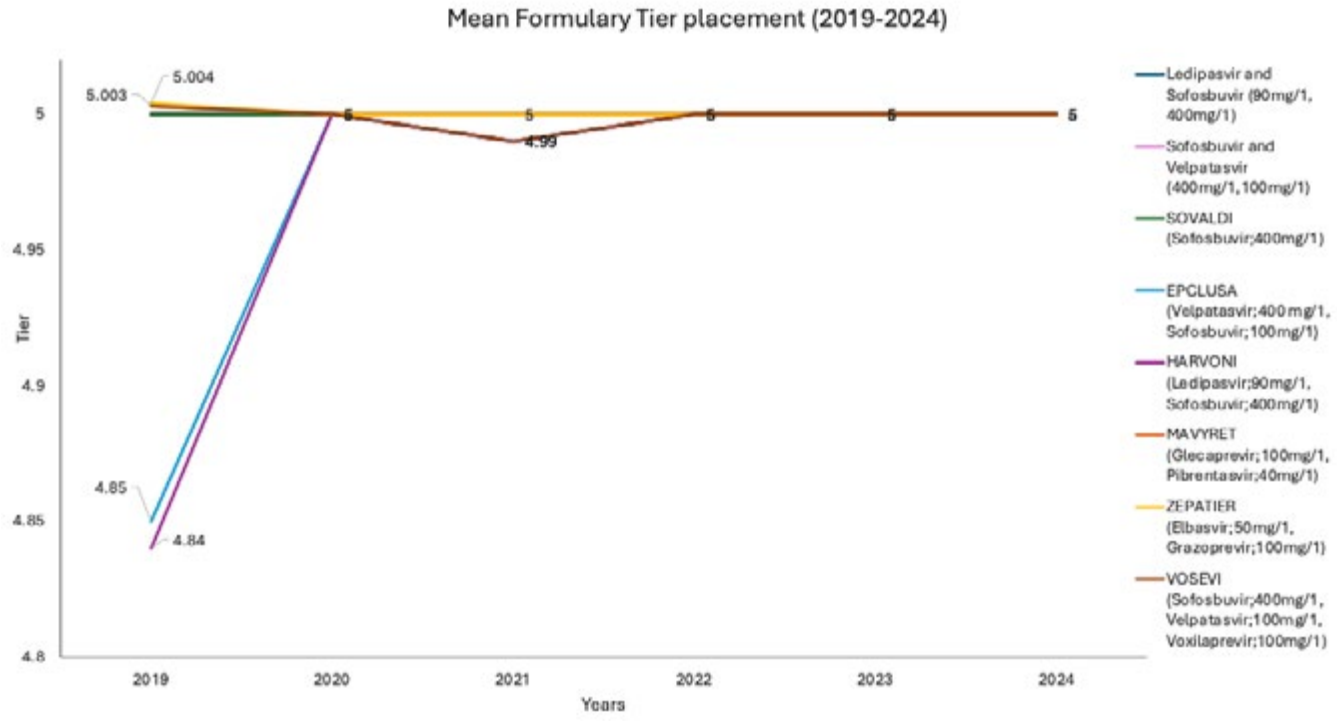

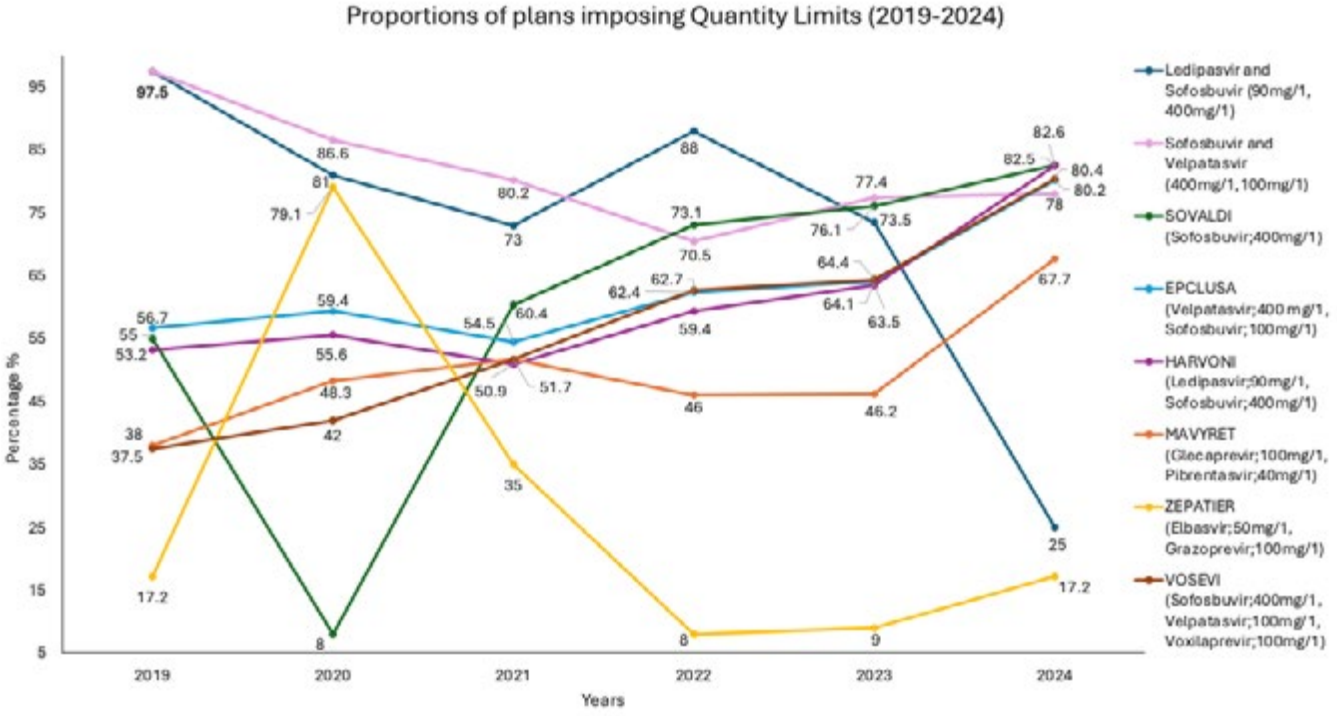

Disclosures: Misha Gautam: Nothing to Disclose, Utkarsh Goel: Nothing to Disclose, Babu Mohan: Nothing to Disclose

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3291 | INCREASING READINESS AND SELF-EFFICACY FOR SERIOUS ILLNESS COMMUNICATION ENGAGEMENT IN PATIENTS WITH ESLD

Cristal Brown[1] Nazan Aksan[2] Elizabeth Kvale[3] Andrew Muir[4] Rebecca Sudore[5]

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Background: Serious illness communication (SIC) is a series of conversations between providers, patients and families that facilitates prognostic understanding, elicits patient values and aligns goals of care with the stated patient values. Patients with ESLD have low rates of SIC. It is unknown if high-quality SIC supports the delivery of goal concordant care and improves patient-reported quality of life in patients with ESLD. Appropriate measures of goal concordant care have not been established in this patient population. **Objective:** Evaluate the feasibility of an outpatient intervention of SIC for patients with ESLD measuring quality of communication and feasibility testing measurements of goal concordant care **Methods:** Recruitment of 30 participants with ESLD completing baseline assessment of demographics and clinical data with planned 3 and 6-month follow-up. Participants completed the 9-item Advance Care Planning (ACP) engagement survey, a validated tool measuring patient readiness and self-efficacy on a 5-point Likert scale for SIC engagement. An increase of 0.2 demonstrates clinically significant improvement in engagement. Participants were asked 2 potential measures of goal concordant care: 1. Do they feel heard and understood by their medical providers? 2. Would they choose a medical plan to extend life or avoid discomfort? Participants were then scheduled for a standard of care hepatology outpatient clinic and offered an additional 30-minute SIC discussion. The SIC discussion was conducted by a trained hepatologist. Participants completing the SIC discussion were provided a literacy-sensitive advance directive and encouraged to complete ACP documentation. The ACP engagement survey was repeated immediately after the visit to assess quality of communication and compare to baseline measure. **Results:** 22 participants have enrolled. Ages range from 30-79 years with mean of 54 years (SD=11). Self-identified female gender is 47% (N=10). Race/ethnicity is 81% White (N=17), 30% Hispanic (N=6). MELD-Na scores range from 6-25 with mean 10 (SD=5).Baseline ACP engagement score for readiness was 2.94 (SD=1.37) and self-efficacy was 3.89 (1.17). Immediately following SIC visit (N=14), readiness was 4.12 (SD=0.80) and self-efficacy 4.5 (0.78). Mixed linear models show the difference from pre to post SIC to be significant for both readiness and self-efficacy, $p < .05$. Figure 1 shows mean and SEs in both scales pre and post SIC. 16/22 report feeling completely or mostly Heard and Understood. Equal 50% result (N=11) for participants desiring a medical plan of prolonging life and avoiding discomfort. **Conclusion:** Our pilot shows feasibility for an outpatient serious illness communication intervention with clinically significant increase in ACP engagement after one visit. We have also collected goal concordant care data, novel for this patient population. We will determine durability of this response over a 6-month period.

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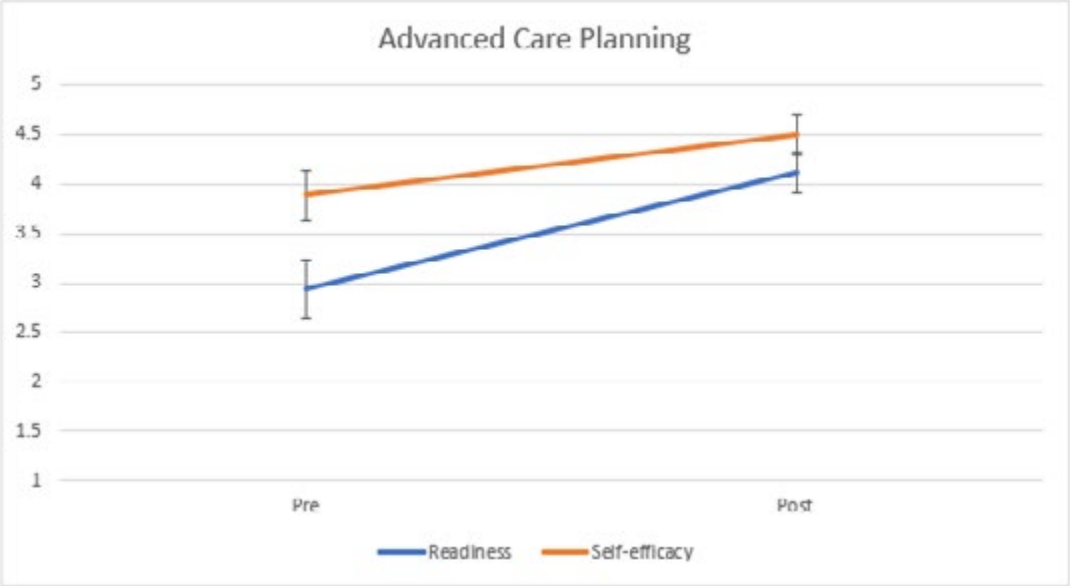
Figure 1 Pre and post-ACP engagement survey score following Serious Illness Communication visit



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3292 | THE INDIAN METABOLIC AND LIVER DISEASE (IMELD) STUDY: UTILIZING EPIDEMIOLOGY AND IMPLEMENTATION SCIENCES TO STRATIFY POPULATION RISK FOR NAFLD

Kanica Kaushal[1] Sumridhi Gautam[2] Dr.Priyanka Aggarwal[3] GURESH KUMAR[4] Anamika Tomar[5] Manoj Sharma[6] Shiv Kumar Sarin[7]

[1]Assistant Professor, ILBS, [2]Project Officer, [3]Senior Resident, [4]Consultant Statistics, [5]Assistant Professor, [6]Professor, ILBS, [7]Senior Professor, ILBS

Background: Most Non-Alcoholic Fatty Liver Disease (NAFLD) risk scores are developed in hospitals, which may introduce selection bias and include biomarkers. In India, the National Program for Prevention and Control of Non-Communicable Diseases (NP NCD) uses waist circumference (WC) or diabetes mellitus (DM) as risk assessment criteria for NAFLD. This can result in excess false positives. Region-specific risk prediction scores are needed in a diverse country like India. The Indian Metabolic and Liver Disease (IMELD) study aims to create a screening equation/risk score for population risk stratification of NAFLD in India with due contextualization for inter-site variation. **Methods:** IMELD is a cross-sectional design with multi-stage stratified random sampling to select adults from the selected nine villages based on probability proportional to size from three tehsils in Jaipur district, Rajasthan. The sample size was 3128, calculated with a ratio of unexposed to exposed of 0.059, a confidence level of 99%, power of 90%, design effect of two, and a non-response rate of 10%. All eligible participants were interviewed using pretested e-questionnaires, followed by blood sampling and fibro scan. Scores were assigned based on multinomial logistic regression's nearest odds ratio value. The dataset was divided into derivative and validation cohorts in a 60:40 ratio for internal validation. **Results:** For the achieved sample of 3194 (63% females, 46% between 18-39 years), the prevalence rate of NAFLD was 37.19% (95% CI; 35.51 - 38.87), diabetes mellitus 19.3% (95% CI; 17.96%—20.73%), hypertension 40.23% (95% CI; 38.30%—41.70%), dyslipidemia 76.02% (95% CI; 73.5%-76.5%), and metabolic syndrome 34.82% (95% CI; 33.3%-36.7%) using standard definitions. A primary screening equation *[10*(0.55*age if age is 40-59 years or 0.73*age if age is ≥60 years + 0.78*BMI if BMI=23-24.9 or 1.41*BMI if BMI is ≥25 + 0.25* WC + 0.33* Hypertension + 0.59* Personal History of DM) – 1.77]* was derived. Table 1 outlines a scoring system for community NAFLD risk assessment where a score of six or higher indicates high risk, requiring specialist evaluation. Figures 1a & 1b show the Receiver Operating Curves (ROC) and Area Under the Curve (AUC). Score cut-off of ≥6 had 64.2% sensitivity, 70.5% specificity and 76% negative predictive

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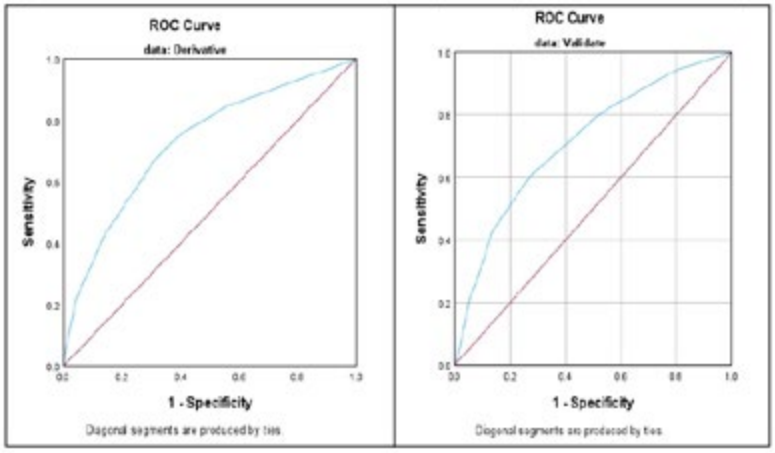
value. **Conclusion:** To address the pressing issue of NAFLD, which affects roughly 40% of the rural population in northwestern India, the IMELD risk score can serve as an effective means of early self-risk stratification. It is the first to be based on personal history and anthropometric measurements without including any biomedical markers. It is directly applicable in NP NCD, enabling frontline workers to screen individuals for NAFLD noninvasively at the community level. Subsequent field testing based on implementation research principles and leveraging mHealth will follow.

Table 1: IMELD Risk Score based on history & anthropometric measurements for community NAFLD risk assessment

I	Age	Score
	<40 years	0
	40-59 years	2
	≥60 years	3
II	**Body Mass Index (BMI)**	
	<23	0
	23-24.9	3
	≥25	5
III	**Waist circumference (WC)**	
	<90 cm (Males), <80 cm (females)	0
	≥90cm (Males), ≥80cm (females)	2
IV	**Hypertension**	
	Yes	2
	No	0
V	**Personal History of Diabetes (DM)**	
	Yes	2
	No	0
	Maximum Score	**14**

Figure 1a & 1b: ROC for derivation data (n=1912) and validation data (n=1282)



Cohort	Area under Curve	P-value	95% Confidence Interval	
			Lower Bound	Upper Bound
Derivation (n=1912)	72.8	<0.001	70.4	75.1
Validation (n=1282)	71.4		68.5	74.3

Disclosures: Kanica Kaushal: Nothing to Disclose, Sumridhi Gautam: Nothing to Disclose, Dr.Priyanka Aggarwal: Nothing to Disclose, GURESH KUMAR: Nothing to Disclose, Anamika Tomar: Nothing to Disclose, Manoj Sharma: Nothing to Disclose, Shiv Kumar Sarin: Nothing to Disclose

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3293 | THE PATIENT EXPERIENCE OF A NEW REFERRAL PATHWAY FOR LIVER DISEASE IN THE SOMERSET LIVER IMPROVEMENT PROJECT

Christina Owen[1] Timothy Jobson[1]

[1]Somerset NHS Foundation Trust

Background: The Somerset Liver Improvement Project uses unique software to identify patients at risk of undiagnosed liver disease by analysing trends in prior blood tests. This is outside the traditional pathway in the UK of patient referral to secondary care. We intended to contact patients directly rather than waiting for a referral from their General Practitioner. The aim of this part of the project was to maximise patient engagement and understand emotional responses within the new pathway, ensuring that unnecessary anxiety was minimised. **Methods:** Our public and patient reference group (PPRG) were consulted in a workshop and followed by an iterative process to co-design communication materials, an invitation letter and information leaflet. PPRG members were asked via a structured questionnaire to a) predict emotional responses, b) determine whether sufficient information had been relayed and c) provide insight into the format and style of the material. Real world letters were developed and sent to patients in the post inviting them to book a clinical review. Patients who attended clinic were sent a feedback form incorporating the same structured questions, along with an opportunity for bespoke feedback. **Results:** The PPRG preferred the initial communication to be via letter as opposed to email, phone or text. All wanted a formal letter style. Most felt a clinic appointment via phone or face to face of equal value. Of 66 patients subsequently called to clinic, 31completed feedback forms. The overall experience rated 4.8 out of 5. Patients on average scored 4.3 out of 5 for clarity of the information received on initial contact. After reading the invite letter the emotional descriptive words which scored the highest were ‘Interested’, ‘Grateful’, ‘Supported’ and ‘Concerned’. Patients scored ‘Supported’, ‘Grateful’, ‘Interested’ and ‘Relieved’ the highest after a clinical encounter. **Conclusion:** New referral pathways which communicate with patients outside of traditional approaches need to consider the emotional impact on patients to avoid doing any harm. Public and patient involvement in developing communication materials was effective, with patients engaging positively with this programme of work. Patients found it acceptable to be contacted directly without the need for a primary care referral. Many extremely positive free text comments emphasised the perceived benefit of proactive preventative medicine.

Disclosures: Christina Owen: Nothing to Disclose, Timothy Jobson: Predictive Health Intelligence Ltd: Executive role, Predictive Health Intelligence Ltd: Stock – privately held company

3294 | ASSESSING ECONOMIC BURDEN AMONG UNIQUE PATIENT SEGMENTS IN AN HDV-INFECTED POPULATION

Prajakta Bhounsule[1] Norah Terrault[2] Elizabeth Kinter[1] Michael Chattergoon[1] Nancy Reau[3] Pallavi Mudumby[4] Yazid Barhoush[4]

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Background: Hepatitis delta virus (HDV) has a heightened risk of liver fibrosis progression and increases the risk of hepatocellular carcinoma and hepatic decompensation compared to chronic HBV monoinfection. This study aims to characterize key HDV patient groups defined by comorbidities to understand their influence on healthcare utilization through machine learning (ML) driven cluster analysis. **Methods:** This is a retrospective claims analysis that used the STATinMED RWD Insights database. The index date (index) is the earliest known HDV diagnosis claim (2015-2022). Eligible patients were ≥18 years old with ≥ one HDV inpatient or two HDV outpatient claims ≥30 days apart, ≥12 months of continuous capture pre- and post-index, and a claim for HBV-related care in the 12-month pre-index period. Patients were segmented using ML cluster analysis, determining optimal clusters via the Elbow method and hierarchical clustering. Disease characteristics and economic burden in total, inpatient (IP), outpatient (OP) and pharmacy costs were determined for all clusters. **Results:** A total of 17,960 HDV infected patients met eligibility criteria. Cluster analysis yielded five segments, named for dominant comorbidities: 1) Hypertension (n=5,291, high incidence of hypertension (100% vs. 43% overall); 2) Liver Conditions (n = 1,608, high incidence of liver transplant, compensated and decompensated Cirrhosis (81% vs.21% overall); 3) Substance Dependency (n = 932, high incidence of alcohol abuse disorder or substance abuse (94% vs. 19%

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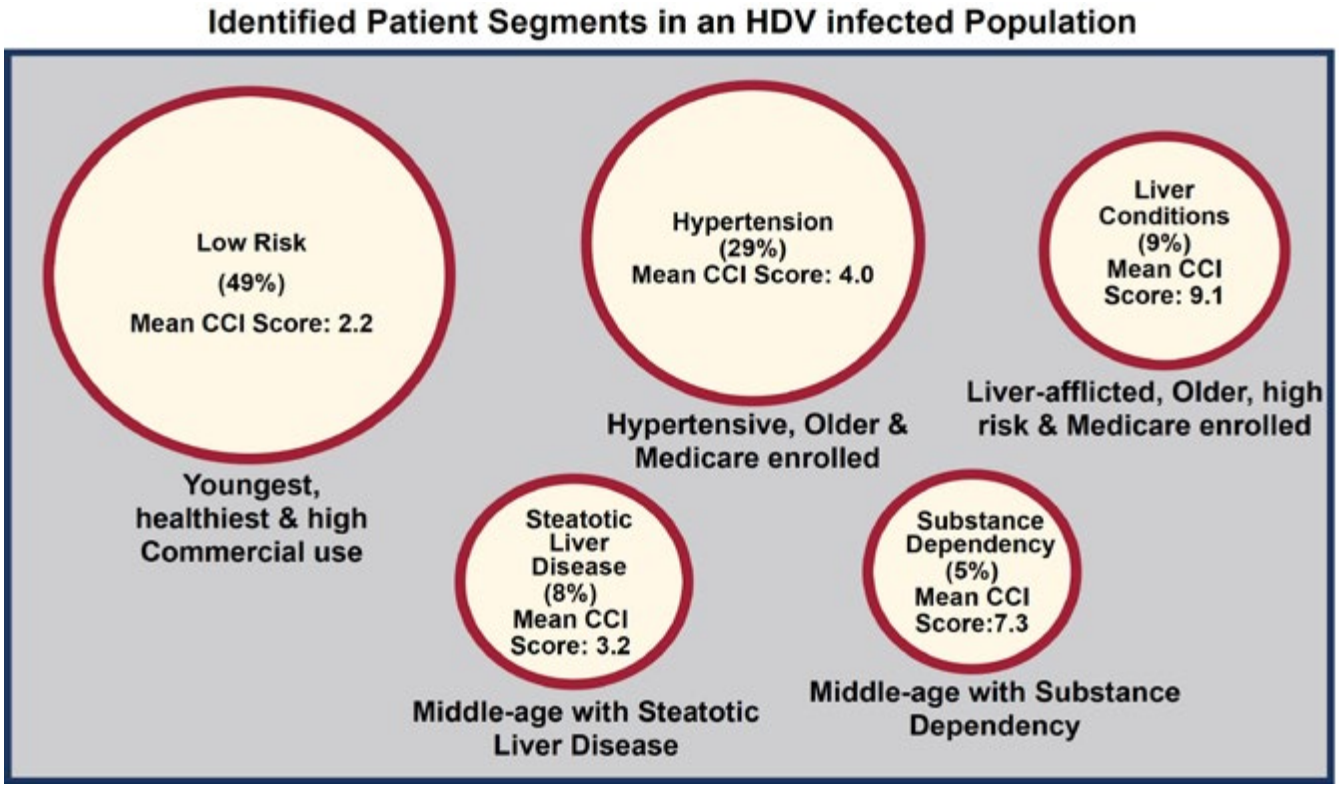
overall); 4) Steatotic Liver Disease (n = 1,399, high incidence of MASH or MASLD (78% vs. 18% overall); 5) Low Risk (n = 8,730, low incidence of liver conditions or substance dependency). At the 12-month follow-up, HDV infection patients with liver conditions and HDV infection patients with substance dependency have significantly higher total ($71,553 and $68,819 vs. $28,258), IP ($17,518 and $16,328 vs. $4,396), OP ($11,929 and $12,344 vs. $5,853), and pharmacy ($14,481 and $13,850 vs. $9,780) costs compared to overall HDV infection patients, respectively (all p<.0001). **Conclusion:** HDV patients experience high healthcare resource utilization. Higher resource utilization clusters include patients with cirrhosis, needing a liver transplant, and with substance abuse. These results highlight the importance of early diagnosis to prevent cirrhosis and the need for increased awareness of comorbidities like alcohol or substance use to improve outcomes.



Disclosures: Prajakta Bhounsule: Nothing to Disclose, Norah Terrault: Nothing to Disclose, Elizabeth Kinter: Nothing to Disclose, Michael Chattergoon: Nothing to Disclose, Nancy Reau: Gilead: Grant/Research Support, eiger: Grant/Research Support, abbott: Consultant, Arbutus: Consultant, Gilead: Consultant, VIR: Consultant, Salix: Consultant, Salix: Grant/Research Support, AbbVie: Grant/Research Support, Pallavi Mudumby: Nothing to Disclose, Yazid Barhoush: Nothing to Disclose

3295 | UTILIZING TECHNOLOGY TO RISK STRATIFY PATIENTS WITH MASLD AND INCREASE RATES OF IDENTIFICATION OF CLINICALLY SIGNIFICANT LIVER FIBROSIS

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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most common chronic liver disease worldwide. Due to the silent nature of disease progression, many patients present with advanced stages of disease. FIB-4 is a non-invasive test (NIT) to risk stratify patients and determine likelihood of clinically meaningful fibrosis and has been validated in MASLD patients. Our healthcare system needs strategies to identify patients earlier in the disease course such as implementation of a clinical support tool in primary care clinics. **Methods:** A best practice alert (BPA) was developed in the electronic medical record (EMR) to provide guidance to primary care clinicians. We needed an NIT that uses variables typically available in the primary care context; thus, we chose the FIB-4 score which requires only 4 variables (age, AST, ALT, platelet) typically checked at

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annual health exams. Patients were identified by the BPA based on ICD-10 diagnosis codes related to hepatic steatosis. If the variables to calculate FIB-4 were not checked within the past year, clinicians received a prompt to order the appropriate bloodwork. If the FIB-4 was less than 1.3, clinicians were provided instructions for patient counseling and the BPA will launch again in 3 years. If the FIB-4 was greater than 1.3, clinicians were instructed to order transient elastography (TE) for further diagnostic staging. Due to low BPA utilization in the first three months, educational interventions were implemented including personalized messages in the EMR and emails to primary care clinicians, educational conferences for internal medicine residents and gastroenterology fellows, and primary care grand rounds in multiple regions of the healthcare system. Following these interventions, the subsequent three months of data were analyzed. Fisher exact test analysis was performed to analyze for significant difference between the two groups; P-values <0.05 were considered statistically significant. **Results:** From March 2023 to June 2023, there were 1271 patients (291 patients had FIB-4 1.3-2.67, 57 patients had FIB-4 >2.67, and 272 patients had FIB-4 unable to be calculated). Following the educational interventions, from November 2023 to February 2024. there were 1588 patients (368 patients had FIB-4 1.3-2.67, 70 patients had FIB-4 >2.67, and 370 patients had FIB-4 unable to be calculated). Additional TEs were ordered independent of the BPA which was not accounted for in these totals. Between the two cohorts, BPA utilization increased significantly from 5.3% to 9.4% (p<.005, OR 1.85, 95% CI 1.19 to 2.91). **Conclusion:** MASLD with advanced liver disease will continue to rise and burden the healthcare system if we are unable to identify these patients earlier in disease course. Technology may be used to our advantage, but we found that additional education efforts were necessary to achieve greater engagement and further optimize care pathways.

FIB-4 Score	Pre-Intervention # of patients (% of total)	Pre-Intervention: Orders placed (% of total possible orders)	Post-Intervention: # of patients (% of total)	Post-Intervention Orders placed (% of total possible orders)
<1.3	651 (51)	N/A	780 (49.1)	N/A
1.3-2.67	291 (23)	12 (4.1)	368 (23.2)	36 (9.8)
>2.67	57 (21)	2 (3.5)	70 (4.4)	5 (7.1)
Unable to calculate	272 (4)	20 (7.4)	370 (23.3)	35 (9.5)
Total	**1271 (100)**	**33 (5.3)**	**1587 (100)**	**76 (9.4)**

Disclosures: Rachel Orbuch: Nothing to Disclose, Justin Boike: W. L. Gore and Associates: Grant/Research Support, Eurofins Transplant Genomics: Advisor, Echosens: Consultant, Amanda Cheung: Nothing to Disclose

3296 | COMPARATIVE ANALYSIS OF TWO METHODS OF FIB-4 CALCULATION IN PRIMARY CARE TO IDENTIFY ADVANCED FIBROSIS IN PATIENTS WITH DIABETES: IMPLICATIONS FOR ADHERENCE TO THE AASLD MASH CARE PATHWAY

Anna Mageras[1] Rohit Nathani[2] Jake DeBroff[3] Rama Hussein[4] Rahul Anand[5] Carolina Villarroel[3] Silpa Yarra[3] Theresa Mack[4] Nina Priven[4] Heather Viola[4] Stephanie Wang[4] Fernando Carnavali[4] Meena Bansal[1]

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Background: Despite the AASLD recommendation for screening for advanced fibrosis in patients with type 2 diabetes using FIB-4, compliance with the care pathway in the Mount Sinai Health System (MSHS) was low at baseline. To address this care gap, hepatologists partnered with primary care champions to test two methods to calculate FIB-4 scores and track requisite referrals. **Methods:** Two primary care clinics participated in a comparative intervention. For arm 1, we created an EMR “SmartPhrase,” which calculates a patient’s FIB-4 score from their most recent lab results when the provider types “.FIB4SCORE” into their encounter note, and it provides recommended follow-up based on FIB-4: < 1.3 repeat in a year; 1.3 – 2.67 referral to VCTE; > 2.67 referral to hepatology evaluation. For arm 2, we extracted patient data from our EMR-based diabetes registry, calculated FIB-4 scores in Excel, and provided guideline-based recommendations to the clinic’s medical director, who assigned outreach to staff. We calculated rates of providers’ SmartPhrase utilization in arm 1 and referrals

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in both arms and compared them using chi-square tests in SAS. **Results:** From 1/2023 to 2/2024, 3,804 adult patients with diabetes had an encounter with arm 1 clinics. Providers used the SmartPhrase at least once for 12% of them, exceeding our 10% goal. For the arm 2 clinic, labs to calculate FIB-4 scores were available for 99% of eligible patients. Based on FIB-4 scores, 46% of both arm 1 and 2 patients needed a referral to VCTE or hepatology evaluation. Of these, 63% in arm 1 and 85% in arm 2 were offered at minimum a VCTE referral ($p < .0001$). Among 96% of patients who accepted a referral, 58% of arm 1 patients completed their evaluation, compared to 32% of arm 2 patients ($p < .0001$). Among these, 10% of arm 1 and 11% of arm 2 patients were confirmed with advanced fibrosis or cirrhosis. **Conclusion:** Backend (arm 2) FIB-4 calculation streamlined identification of patients for outreach, leading to higher screening and referral rates compared to provider-driven arm 1. However, referral completion was higher in the provider-driven arm, indicating benefits to both methods. In-person conversations with a primary care provider may encourage referral completion, but further exploration is needed. The rates of advanced fibrosis/cirrhosis found underscore the clinical importance of implementing the MASH care pathway systematically. Next steps include assessing the impact of age-adjusted FIB-4 scores on referral rates; embedding the FIB-4 calculator in the health maintenance tab of the EMR; and building an EMR provider dashboard.

Table 1: Adherence to the AASLD MASH Care Pathway across Two Arms of a FIB-4 Intervention

Care Pathway Milestone	*Arm 1* *N (% of Previous Milestone)*	*Arm 2* *N (% of Previous Milestone)*	*P-Value*
Eligible	3,804	540	
Screened	459 (12%)	533 (99%)	**<.0001**
Needed VCTE	181 (39%)	219 (41%)	0.6
Needed Hepatology Evaluation	30 (7%)	26 (5%)	0.26
Offered Referral	133 (63%)	209 (85%)	**<.0001**
Accepted Referral	128 (96%)	200 (96%)	0.8
Completed Referral	74 (58%)	64 (32%)	**<.0001**
F2	8 (11%)	7 (11%)	0.98
F3	5 (7%)	2 (3%)	0.33
F4	2 (3%)	5 (8%)	0.17

Disclosures: Anna Mageras: The Kinetix Group: Advisor, Novo Nordisk: Speaking and Teaching, Gilead Sciences: Grant/Research Support, Rohit Nathani: Nothing to Disclose, Jake DeBroff: Nothing to Disclose, Rama Hussein: Nothing to Disclose, Rahul Anand: Nothing to Disclose, Carolina Villarroel: Nothing to Disclose, Silpa Yarra: Nothing to Disclose, Theresa Mack: Nothing to Disclose, Nina Priven: Nothing to Disclose, Heather Viola: Nothing to Disclose, Stephanie Wang: Nothing to Disclose, Fernando Carnavali: Nothing to Disclose, Meena Bansal: Advisor relationship with Madrigal; Has not ended; Advisor relationship with Fibronostics; Has not ended; Advisor relationship with NOVO Nordisk; Has not ended; Advisor relationship with GSK; Has not ended; Advisor relationship with Merck; Has not ended; Advisor relationship with Boeheringer-Ingelheim; Has not ended; Advisor relationship with Boston Pharma; Has not ended; Advisor relationship with The Kinetix Group; Has not ended

3297 | DEVELOPMENT OF A SEXUAL FUNCTION ASSESSMENT TOOL IN MEN AND WOMEN WITH LIVER DISEASE AND LIVER TRANSPLANTATION

Yooyun Chung[1] *Deepak Joshi*[1] *Niloufar Safinia*[1] *Michael Heneghan*[1]

[1]*King's College Hospital*

Background: Patients with liver disease (LD) or liver transplantation (LT) may experience sexual dysfunction (SD). The existing tools to assess SD are not specific to LD/LT and our aim was to develop a liver specific sexual function (SF) assessment tool. **Methods:** This was a cross sectional study to assess SD in 262 male and 171 female patients with LD/LT at King's College Hospital. A preliminary SF assessment tool in LD/LT for men (SFLM) and for women (SFLW) were developed through a literature search, input from a multidisciplinary panel of experts

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and patient group feedback. The international index of erectile function (IIEF) for men, female sexual function index (FSFI) and female sexual distress scale (FSDS) for women were used as gold standard, non-disease specific SF assessment tools. Chronic liver disease questionnaire (CLDQ) was used as a liver specific quality of life assessment tool. Clinical data was gathered from patient medical records. Exploratory factor analysis (EFA) was used to assess the SFLM and SFLW scales. **Results:** EFA reduced both the SFLW and SFLM to a 12-item scale with good internal consistency reliability (α=0.94 and α=0.96 respectively). Criterion validity using Spearman's coefficient showed the SFLW and SFLM to significantly correlate with FSFI/ FSDS and IIEF respectively. The SFLW and SFLM had stronger correlation with the CLDQ compared to the IIEF, FSFI and FSDS demonstrating construct validity. The prevalence of SD in women with LD/LT was 51% and in men was 48% with 33% experiencing moderate to severe symptoms. The prevalence and severity of SD were higher in women with cirrhosis compared to non-cirrhosis and LT patients. The SFLW scale showed women with cirrhosis and LT experienced SD related to changes in body image and fear of intimacy. Men with cirrhosis and LT recipients were more likely to experience severe SD. Multiple regression analysis identified age and feeling of depression as predictors of both female and male SD. For women, the presence of cirrhosis was also significant whereas for men the duration of liver disease and Childs Pugh score were relevant. **Conclusion:** Approximately 50% of patients with LD/LT experience some degree of SD. The new 12-item SFLW and SFLM demonstrated significant correlation with the gold standard SF assessment tools and the liver specific CLDQ. Patients with cirrhosis and LT recipients are most at risk of SD and the new SF scales may aid assessment.

Disclosures: Yooyun Chung: Nothing to Disclose, Deepak Joshi: Nothing to Disclose, Niloufar Safinia: Nothing to Disclose, Michael Heneghan: Advanz: Speaking and Teaching

3298 | RECOMMENDATIONS FOR METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS (MASH) DISEASE MANAGEMENT: A MODIFIED DELPHI PANEL ◆

Anna Watzker[1] Mark Delegge[2] Gail Fernandes[1] Matthew Melaragno[1] Rhys Williams[2] Fátima Godinho[2] Kyriaki Drymaliti[2] Samuel Engel[1]

[1]Merck & Co., Inc., Rahway, NJ, USA, [2]IQVIA

Background: Metabolic dysfunction-associated steatohepatitis (MASH) is a progressive form of metabolic dysfunction-associated steatotic liver disease (MASLD) which can lead to cirrhosis and liver-related morbidity and mortality. While clinical practice guidelines exist, MASH disease management may vary globally. The aim of this modified Delphi panel was to gain consensus and make recommendations on MASH disease management including screening, diagnosis, treatment, and monitoring. **Methods:** Hepatologists in the United States (US) and Europe (France [FR], Germany [DE], and United Kingdom [UK]) participated in a three-round modified Delphi panel between December 2023-February 2024. Panelists were required to be actively managing ≥5 MASH patients per year, be proficient in English, and not have participated in a clinical trial in the past three years. Panelists expressed agreement/disagreement for 59 statements across five topics (screening [n=11], diagnosis/referral [n=13], lifestyle modification [n=7], treatments currently in clinical practice guidelines [n=20], treatment practices [n=8]). Before dissemination, two independent hepatologists reviewed all statements. Two rounds were administered as online surveys, followed by a live, online discussion (Figure). The threshold for consensus was 80%. The study was double blinded until completion of all rounds and received an IRB exemption (2023-0338). **Results:** Recommendations highlight the need for increased awareness, education, and improved collaboration between specialties. Non-invasive tests, including imaging and biomarkers, are recommended for screening, diagnosis, and monitoring. Liver biopsy may be used in patients with inconclusive diagnosis. The panel recommended that patients with suspected MASH or diagnostic uncertainty be referred to a hepatologist for diagnosis, while monitoring may be a shared responsibility with primary care. In addition, there was consensus on lifestyle modification as the initial treatment approach, and that diagnosed MASH patients should be considered for available pharmacologic treatment. Dose increase, alternative or additional treatments may be considered for progressing MASH. **Conclusion:** This modified Delphi panel of hepatologists made recommendations for MASH disease management based on current knowledge. As the Delphi panel was conducted prior to any approved treatments for MASH, future studies may explore the strength of evidence to support utilization of these treatments.

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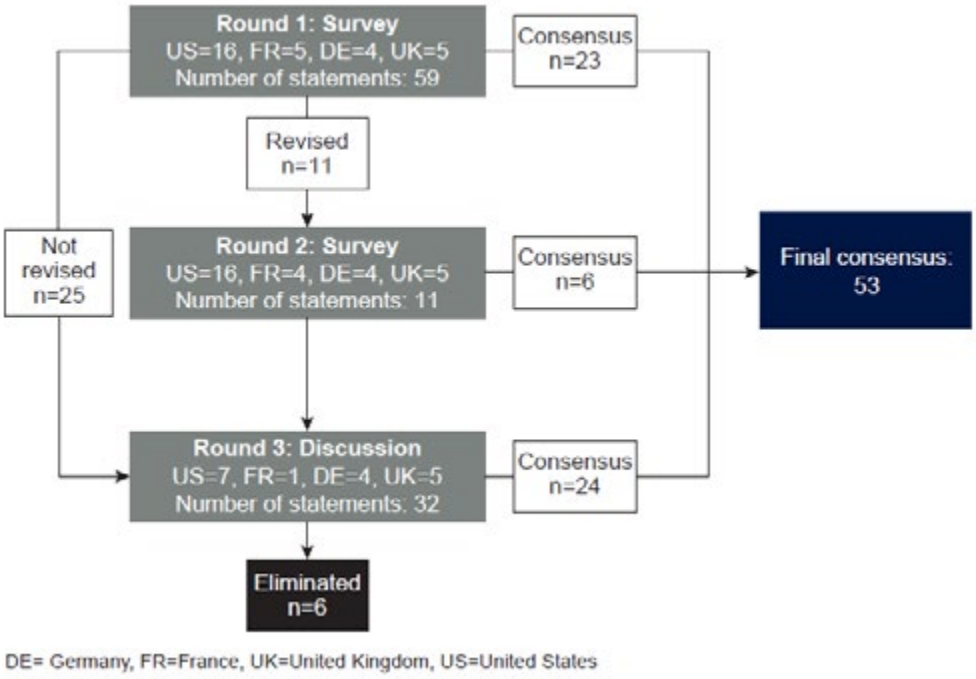

Disclosures: Anna Watzker: Merck & Co., Inc.: Employee, Mark Delegge: Nothing to Disclose, Gail Fernandes: Merck & Co., Inc: Hold Stocks, Merck & Co., Inc: Employee, Merck & Co., Inc: Stock - publicly traded company, Matthew Melaragno: Merck & Co., Inc.: Stock ownership, Merck & Co., Inc.: Employee, Merck & Co., Inc.: Stock - publicly traded company, Rhys Williams: Nothing to Disclose, Fátima Godinho: Nothing to Disclose, Kyriaki Drymaliti: Nothing to Disclose, Samuel Engel: Merck Sharp Dohme: Employee

3299 | ACHIEVEMENTS AND CHALLENGES OF HCV MASS SCREENING GRANTED BY THE ITALIAN MINISTRY OF HEALTH DEDICATED FUNDS

Loreta Kondili[1] Sabrina Valle[2] Maria Giovanna Quaranta[1] Francesco Maraglino[2]

[1]Istituto Superior Di Sanita (ISS), [2]Italian Ministry of Health

Background: Before the wide use of direct-acting antiviral therapy (DAA) for chronic HCV infection, Italy was the country with the highest HCV-related mortality in the European Union. Italy reports over 263.000 patients with chronic HCV infection treated with DAA (the highest number of treated patients in Europe). Since 2021, a dedicated fund of 71.5 million Euros was allocated by the government to implement HCV screening for specific key populations (people who use drugs and those with dependencies and inmates) and the 1969-1989 general population's birth cohorts. This work aims to determine the progress made in the country following this political action during the last two years. **Methods:** The 'point of care' strategy that guarantees simplified testing and immediate linkage to care in the key populations was recommended. General practitioners and local health care centers' involvement, and opportunistic HCV screening were also recommended to be implemented for HCV screening in each Italian Region.The last results of HCV screening by December 31st, 2023 are reported. **Results:** Of 21 Italian Regions, 7 (33%) have not yet implemented the 1969-1989 HCV general population birth cohort screening. Of the Regions that have implemented the birth cohort screening, the screening coverage (tested/target population) was 11% (very low rate), the uptake (tested/invited population) was 21%. The anti-HCV positivity was 0.8%. The active infection rate of those tested anti–HCV positive was 23% (the expected rate, was 50- 60%). This suggests that the current screening and treatment efforts are not reaching all infected individuals. Overall, among 1.550.357 individuals tested, 2.314 (0.15%) had an active infection. The reported linkage to care was 60%. The active HCV screening of the key populations addressed in these two years has been implemented in 16 (76.2%) Regions. The screening coverage rate in drug users and people with dependencies was 39%, the uptake was 64%. The anti-HCV prevalence was 20%; the active infection rate of those anti-HCV positive was 44%. The linkage to care was 49%. Of the 99.118 people with dependencies tested, 8.504 (8.6%) had an active

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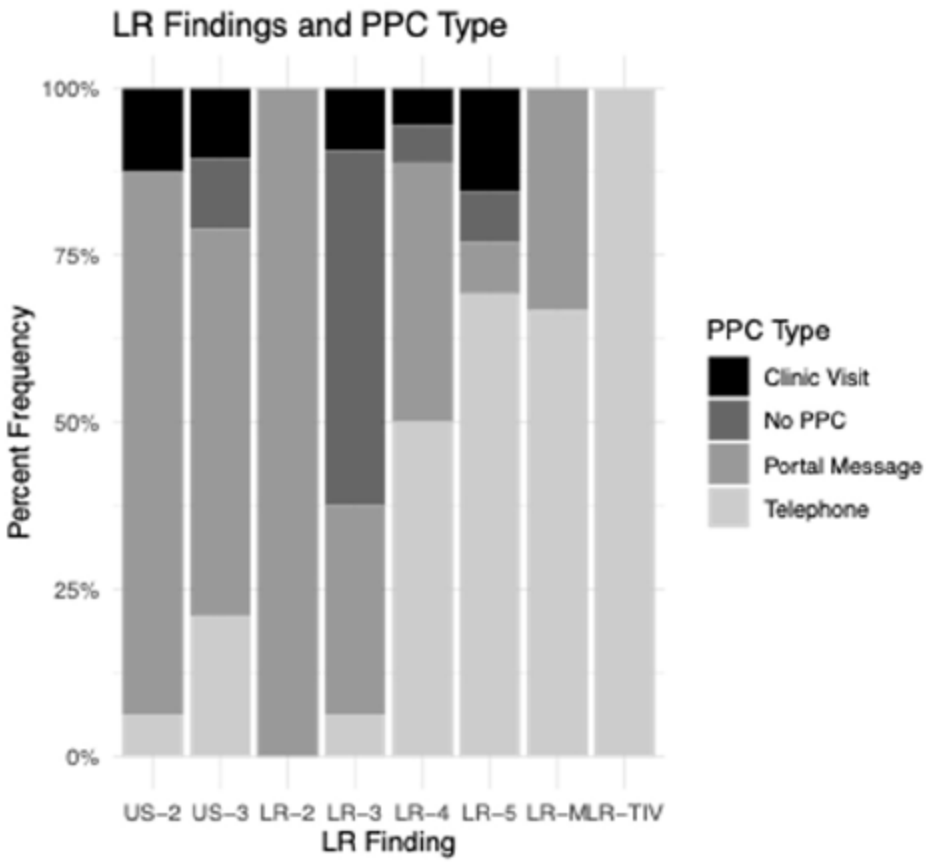
infection. The inmate population's screening coverage rate was 70%,the uptake rate was 79%. The anti-HCV infection rate was 9%, and the active infection rate of those who were anti-positive was 53%. Of the 52.251 inmates screened, 2.250 (4.3%) had an active infection; the reported linkage to care was 60%. Thanks to the mass screening in the last two years in Italy, 13.068 individuals were detected with active infection, and over 6.800 were successfully linked to care to eradicate HCV infection. **Conclusion:** The three target populations had a lower-than-expected active infection rate. Although political will and funded HCV screening are in place for general and key populations in Italy, the road to elimination is still hurdled due to the low perceived risk, lack of effective communications strategies, and complex models of care

Figure 1: Patient-Provider Communication Type by LI-RADS Finding:



Disclosures: Loreta Kondili: Nothing to Disclose, Sabrina Valle: Nothing to Disclose, Maria Giovanna Quaranta: Nothing to Disclose, Francesco Maraglino: Nothing to Disclose

3300 | INITIAL DISCLOSURE OF ABNORMAL HEPATOCELLULAR CARCINOMA SURVEILLANCE RESULTS VIA THE PATIENT PORTAL: A SHIFT IN COMMUNICATION

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Background: The 21st Century Cures Act requires the immediate release of test results to patients electronically. Patients with cirrhosis frequently review radiology results beforetheir providers; however, the interval between patient result review and patient-provider communication (PPC) remains unknown. Herein, we characterized the interval between patient review of abnormal HCC surveillance results and result-related PPC. **Methods:** We identified patients with cirrhosis enrolled in the patient portal who had a new liver lesion seen on ambulatory ultrasound or triphasic CT/MRI. Indeterminate results includedUS-2 or US-3 on ultrasound or LR-2 or LR-3 on CT/MRI; abnormal results includedLR-4, -5, -M, or -TIV on CT/MRI. Patients were excluded if the finding was

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previously present or they had a prior LR-4 or higher lesion. We extracted when the result was released and reviewed by the patient. PPC time was defined as any liver clinic visit and result-related telephone call or patient portal message occurring within 14 days of result release. We calculated the median (IQR) time to patient review and result PPC. In a sensitivity analysis, we imputed a PPC time of 14 days for studies with no identified PPC time. **Results:** We identified 104 patients, with median age 61 years (51-69), 59.6% male, and 21.2% Hispanic ethnicity. Imaging findings included 16 US-2, 19 US-3, 1 LR-2, 32 LR-3, 18 LR-4, 13 LR-5, 3 LR-M, and 2 LR-TIV. Seven results were never reviewed by the patient, and 21 (20.2%) results had no documented PPC within 14 days. PPC for abnormal results was predominantly via telephone calls (61.1%) and portal messages (25.0%), with only 5.6% having no PPC (Figure 1). PPC for indeterminate results was mainly via portal messages (51.5%), with 27.9% studies having no PPC. Median time to patient review was 3.6 hours (0.85-21.4), compared to median time to PPC of 47.9 hours (19.5-119.2). In sensitivity analysis after imputing 14 days for results with no PPC, the median PPC was 71.3 hours (115.6 for indeterminate and 48.2 hours for abnormal results). **Conclusion:** The initial disclosure of abnormal and cancerous results to patients often occurs days prior to patient-provider communication. Studies are needed to examine the potential for psychological distress and other harms related to this shift in result release to patients.

Disclosures: Beverly Kyalwazi: Nothing to Disclose, John Deng: Nothing to Disclose, Jonathan Melendez-Torres: Nothing to Disclose, Elliot Tapper: Nothing to Disclose, Amit Singal: Consultant relationship with AstraZeneca; Has not ended; Consultant relationship with Sirtex; Has not ended; Consultant relationship with Boston Scientific; Has not ended; Consultant relationship with Bayer; Has not ended; Consultant relationship with Eisai; Has not ended; Consultant relationship with FujiFilm Medical Sciences; Has not ended; Consultant relationship with Elevar; Has not ended; Consultant relationship with Exact Sciences; Has not ended; Consultant relationship with Glycotest; Has not ended; Consultant relationship with Exelixis; Has not ended; Consultant relationship with Merck; Has not ended; Consultant relationship with Genentech; Has not ended; Consultant relationship with HistoSonics; Has not ended, Jeremy Louissaint: Nothing to Disclose

3301 | A HEPATITIS C (HCV) SURVEILLANCE SYSTEMS EVALUATION TO IMPROVE UNDERSTANDING OF LOCAL HCV DISEASE BURDEN AND ITS EFFECTS ON IMPACTED COMMUNITIES IN SANTA CLARA COUNTY, CALIFORNIA ◆

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Background: California has experienced a dramatic increase of chronic HCV infection in recent years. In Santa Clara County, more than 1,500 residents are reported to be newly diagnosed with chronic HCV infection each year; however, this local data may be underreported and therefore ineffectively communicating the true burden of HCV given programmatic changes to data collection processes, workflows and systems that affect HCV surveillance. The County of Santa Clara Public Health Department's (SCCPHD)'s HCV linkage to care program is comprised of health care providers and navigators that work to identify and link HCV diagnosed individuals to care; program success depends on an accurate understanding of the local disease burden of HCV infection and its effects on impacted communities. Key components of surveillance data that are important for successful program delivery include race and ethnicity, patient address, and provider name and address fields. **Methods:** The purpose of this project was to perform an evaluation to understand the strengths and limitations of current HCV surveillance data systems to inform future improvement efforts. External consultants performed an assessment of SCCPHD's HCV program and surveillance system through eleven virtual key informant interviews with staff and HCV provider organizations. Informants were asked to provide insight on successes and challenges in capturing surveillance data and to offer recommendations for improvements. These questions were guided by a Strengths, Weaknesses, Opportunities, and Threats (SWOT) Analysis framework which was also the framework used to organize results. **Results:** The following were identified surveillance system strengths: (1) there are dedicated staff in epidemiology, outreach, prevention, and leadership with designated responsibilities that contribute to HCV surveillance; (2) there is an onsite and mobile clinic offering harm reduction services which presents unique opportunity to identify individuals for HCV testing and linkage to care; and (3) there is an established HCV testing program at the local jail. The following were identified as areas of improvement: (1) need for investigation and follow-up with a subset of chronic HCV cases who may have more complex needs, (2) need for leveraging existing hospitalization connections through ICD-10 codes to increase data quality

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and completeness, and (3) integration of data from other sources into the surveillance system for improved completeness. Consultants recommended: (1) expanded case investigation and follow-up by considering other priority populations for intervention, such as pregnant persons or chronic cases <30 years old and (2) in partnership with epidemiologists, conducting data matching from different data systems to improve data quality and completeness. **Conclusion:** These recommendations may improve local provider ability to promptly identify and treat HCV diagnosed individuals.

Disclosures: Amelia Salmanson: Nothing to Disclose, Danica Kuncio: Nothing to Disclose, Isabel Lechuga: Nothing to Disclose, Wen Lin: Nothing to Disclose, Harit Agroia: Nothing to Disclose

3302 | CAREGIVER INVOLVEMENT AND CHARACTERISTICS ARE ASSOCIATED WITH PATIENT QUALITY OF LIFE: BASELINE ANALYSES FROM THE PAL LIVER TRIAL

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Background: Patients with end stage liver disease often receive physical aid and emotional comfort from caregivers, but the impact of caregiver characteristics and roles on patients is unknown. We aimed to examine the associations between patient quality of life (QOL) and caregiver involvement and characteristics in this population. **Methods:** We performed a cross-sectional analysis of patients with end stage liver disease and their caregivers enrolled in a cluster-randomized trial at 19 sites in the US from Jan 2018-Mar 2023. We compared patient QOL (assessed by FACT-Hep: higher = better QOL) in those with and without caregiver co-enrollment and among different caregiver characteristics (age, sex, employment, caregiver burden (assessed by Zarit Burden Interview[ZBI]-12), and patient-caregiver relationship). **Results:** A total of 890 patients were included, including 531 (60%) with a co-enrolled caregiver. The mean patient age of the overall cohort was 63, 71% were male, 79% were White, mean MELD was 11, 65% had ascites, 44% had HE, and 47% had HCC. Co-enrolled patients were older (mean age 63 vs. 62, p=0.04) with greater disease severity (MELD 12 vs. 11, p=0.01; Child-Pugh B/C 60%/26% vs. 55%/23%, p=0.02; ascites 68% vs. 61%, p=0.05; HE 50% vs. 36%, p<0.001), and were less likely to be Black (13% vs. 20%, p=0.02). QOL was similar in those with and without caregiver co-enrollment (mean 117 vs. 115, p=0.29; Table). Those with co-enrollment had lower physical wellbeing (17 vs. 18, p=0.04) and higher social wellbeing (21 vs. 18, p<0.001). QOL comparisons were similar regardless of the presence of ascites, HE, or HCC. Caregivers had a mean age of 57, 77% were female, and 51% were employed. 56% of caregivers were spouses/partners, and 18% were the patient's child. 33% reported ZBI-12 ≥ 12 (high burden). Patients with older caregivers had numerically higher QOL (quartile 1: 113, quartile 4: 122, p=0.06) with significant associations with higher physical and social wellbeing. Patients with caregivers who reported low burden (ZBI-12 <12) had higher QOL (121 vs. 109, p<0.001) with significant differences among all subscales. Caregiver sex, employment status, and relationship to the patient were not associated with patient QOL. **Conclusion:** Caregiver co-enrollment is associated with greater social wellbeing. Older caregiver age and lower caregiver burden are associated with greater patient QOL. Reducing caregiver burden may benefit both caregivers and patients.

Quality of Life in Patients With and Without Caregiver Co-Enrollment

	Co-Enrollment (N=531)	No Co-Enrollment (N=359)	p-value
FACT-Hep Total	117 (27)	115 (30)	0.29
Physical Wellbeing	17 (6)	18 (7)	0.04
Social Wellbeing	21 (6)	18 (7)	<0.001
Emotional Wellbeing	16 (5)	16 (6)	0.16
Functional Wellbeing	14 (6)	14 (7)	0.47
Hepatobiliary Cancer Subscale	49 (11)	49 (12)	0.44

*Values are mean (SD)

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Disclosures: Eric Orman: Sitero: Consultant, Biovie: Advisor, Amy Johnson: Nothing to Disclose, Marina Serper: Grant/Research Support relationship with Grifols; Has not ended; Grant/Research Support relationship with Eurofins; Has not ended; Grant/Research Support relationship with Transplant Genomics; Has not ended, Don Rockey: Grant/Research Support relationship with Versantis; Has not ended; Grant/Research Support relationship with AstraZeneca; Has not ended; Grant/Research Support relationship with Ipsen; Has not ended; Grant/Research Support relationship with Boehringer Ingelheim; Has not ended; Consultant relationship with WL Gore and Associates; Has not ended; Grant/Research Support relationship with Gilead; Has not ended; Grant/Research Support relationship with Durect; Has not ended; Consultant relationship with BD Medical; Has not ended; Consultant relationship with Cook Medical; Has not ended; Grant/Research Support relationship with Intercept; Has not ended; Grant/Research Support relationship with Inventiva; Has not ended; Grant/Research Support relationship with Madrigal; Has not ended; Grant/Research Support relationship with Ocelot; Has ended; Grant/Research Support relationship with Bio89; Has not ended; Grant/Research Support relationship with Salix; Has not ended; Grant/Research Support relationship with Novonordisk; Has not ended; Grant/Research Support relationship with Viking; Has ended; Grant/Research Support relationship with Galectin; Has not ended, Victor Navarro: Nothing to Disclose, Manisha Verma: Nothing to Disclose

3303 | PREVALENCE OF ALCOHOL USE DISORDER AND ALCOHOL-RELATED LIVER DISEASE IN WOMEN UNDERGOING CERVICAL CANCER SCREENING: A MISSED OPPORTUNITY TO SCREEN? ◆

Mary Thomson[1] *Katelyn Tessier*[1] *Nicholas Lim*[1]

[1]*University of Minnesota*

Background: Early intervention for alcohol use disorder (AUD) is key to preventing alcohol-related liver disease (ARLD). Women may only follow with a provider for their reproductive health needs, specifically cervical cancer screening. We hypothesize that the prevalence of AUD and its downstream consequences are high enough to warrant focused screening for AUD during these visits. **Methods:** We performed a retrospective observational study of adult women aged 18-65 who underwent cervical cancer screening using claims data from the Truven MarketScan Database between 7/1/2013 and 12/31/2021. This database contains medical claims from several employer covered private insurance plans with a smaller cohort of Medicaid enrollees. **Results:** 11,965,683 women had cervical cancer screening in this nationwide cohort. Mean age was 40.7 (S.D. 12.9). Average follow-up period was 6.0 years (SD 2.3) and mean number of visits for cervical cancer screening was 2.1 (S.D. 1.6) during the follow-up period.2.1% (n=248,860) of women undergoing cervical cancer screening had coding for AUD: 46.4% were age <40. 0.5% (n=63,384) of the entire cohort had an AUD-related hospitalization. 8.9% of patients hospitalized for AUD had concurrent ARLD. 30.1% of those hospitalized for AUD did not have outpatient encounters for AUD. After a woman had been diagnosed with AUD as an outpatient, the 8-year incidence of hospitalization for AUD and ARLD was 13.2% (95% CI 13.0-13.3) and 1.5% (95% CI 1.4-1.5), respectively (Figure 1a-b).3.2% of those with AUD had evidence of ARLD and 4.9% had cirrhosis. Patients with ARLD were older than those without (mean age 48.7 v. 40.7, P<0.001). Only 18.7% of ARLD diagnoses were under age 40. For the patients hospitalized for ARLD (0.05%, n=5,496), 37.7% had not had outpatient encounters related to this. **Conclusion:** In a privately insured cohort, approximately one in fifty patients undergoing cervical cancer screening had AUD and one in 200 had an AUD-related hospitalization, which may be higher in a real-world setting. A notable proportion of patients admitted for complications of AUD or ARLD did not have these issues addressed in outpatient clinic, despite receiving other outpatient care. Visits for cervical cancer screening in women may represent a missed opportunity for screening and intervention to prevent future hospitalizations for AUD and ARLD.

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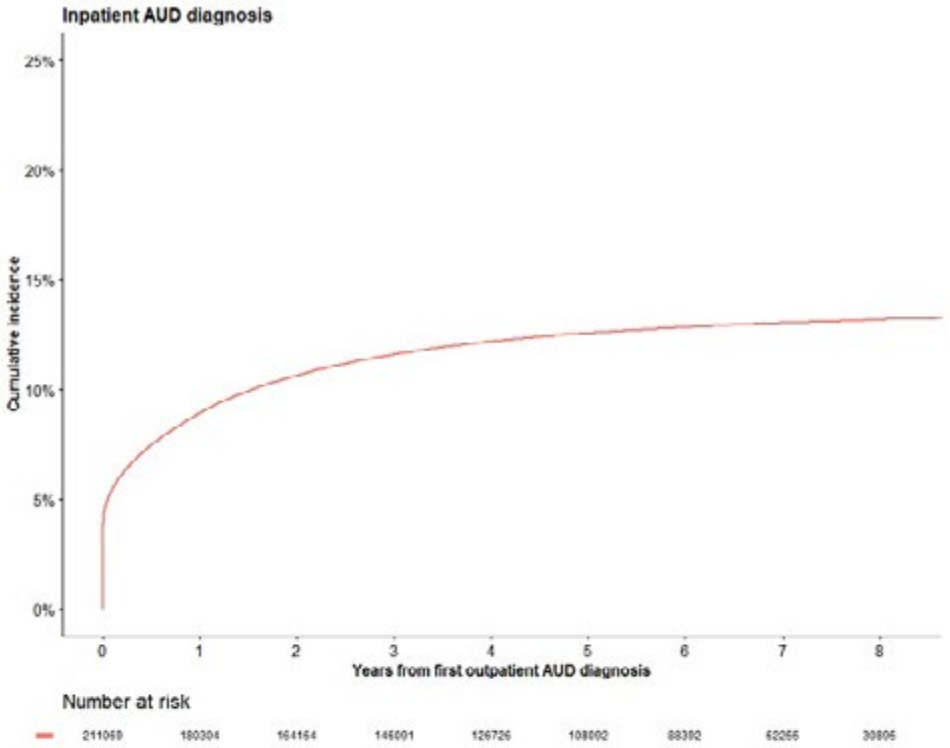

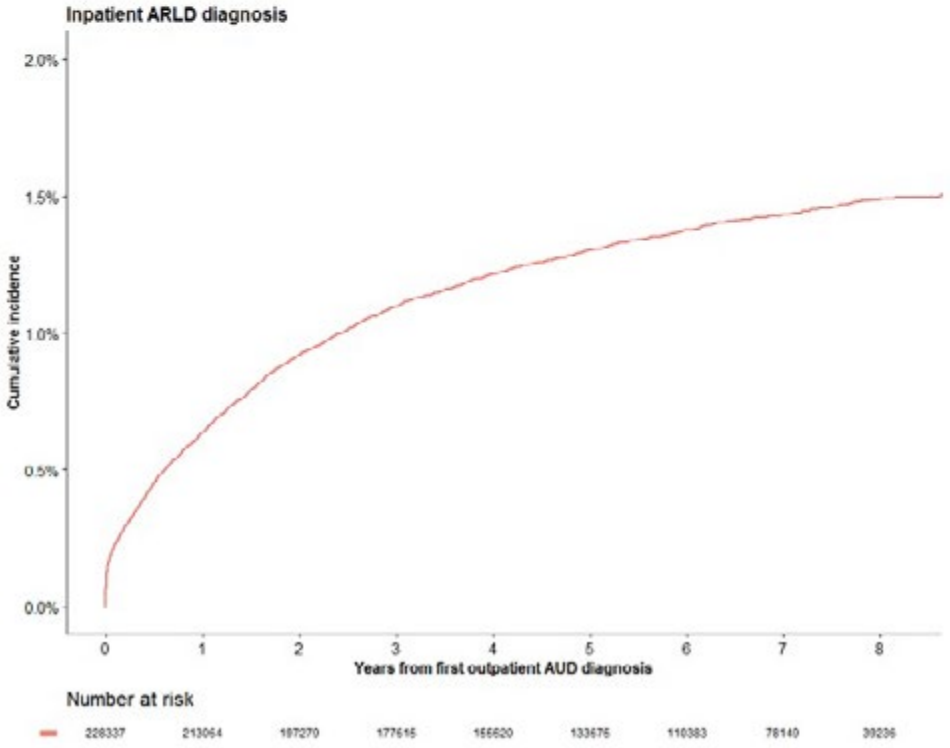

Disclosures: Mary Thomson: Nothing to Disclose, Katelyn Tessier: Nothing to Disclose, Nicholas Lim: Nothing to Disclose

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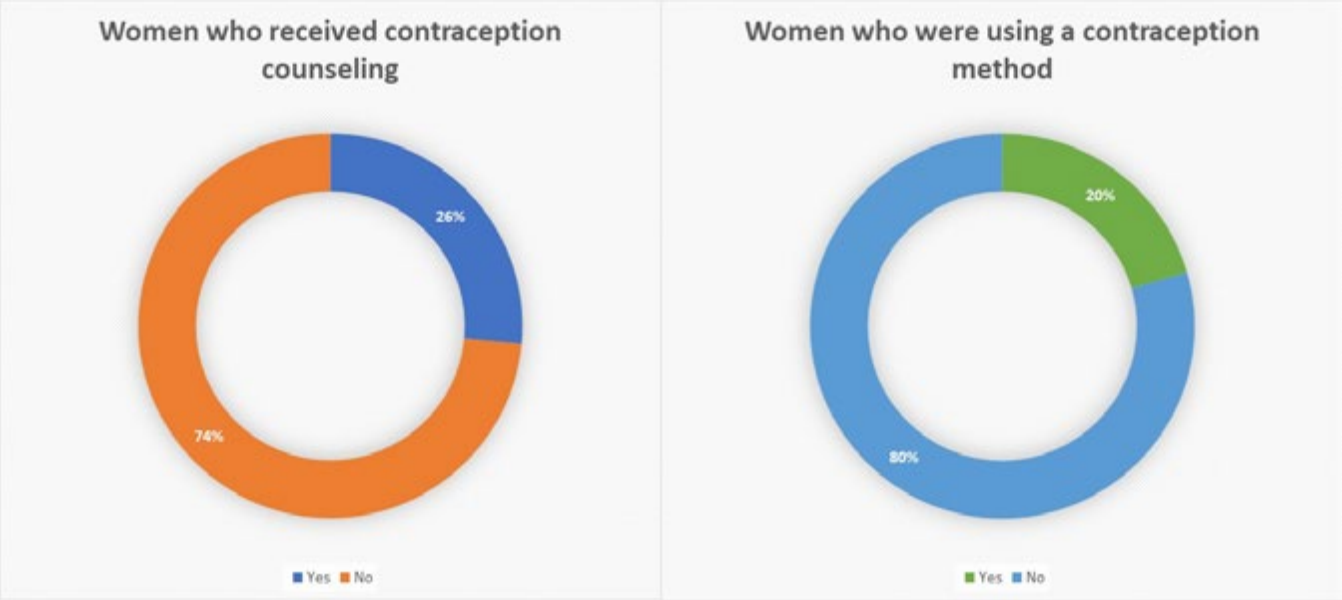
3304 | CONTRACEPTION COUNSELING AND PREGNANCY AFTER LIVER TRANSPLANTATION: A SINGLE CENTER EXPERIENCE

Juan Gonzalez[1] *Divya Devabhaktuni*[1] *Hannah Zuercher*[1] *Katarina Pittman*[1] *Ismael Media*[1]

[1]*University of Florida*

Background: Contraceptive counseling is critical for women of reproductive age (15-49 years) who have undergone liver transplantation due to the potential risks associated with unplanned pregnancy in this population, including graft rejection, maternal complications and teratogenic effects of immunosuppression medications. Current guidelines recommend avoiding pregnancy at least one-year post-transplant with at least two reliable forms of contraception to ensure stable graft function and minimize complications. There is limited data on the prevalence and quality of counseling provided to these patients. **Methods:** This retrospective study involved a comprehensive chart review of female patients aged 18-49 who underwent liver transplantation at a tertiary care center between January 2017 and December 2023. The primary objective was to determine documentation of contraceptive counseling during the post-transplant follow-up visits within 12 months of liver transplantation. Secondary objectives included identifying demographics, contraceptive methods, subsequent pregnancies and their outcomes. **Results:** Between 2017 and 2023, 194 patients aged 18-49 underwent liver transplantation at our center. Among them, 83 (42.8%) were women with an average age of 38.1 years. The ethnic distribution was predominantly White (73.5%), followed by Black (14.5%), Hispanic (8.4%), and three patients with other ethnic backgrounds. Twenty-two (26.5%) of these women received contraception counseling at the transplant clinic visit within 12 months post-transplantation. Seventeen patients were using one form of contraception, with intrauterine devices (IUDs) and oral contraceptives being the most common methods used. None were on two forms of contraception. Post-transplant, four patients experienced pregnancies: two resulted in live births, and two ended in miscarriages. **Conclusion:** This study highlights a significant gap in contraceptive counseling for women of reproductive age who have undergone liver transplantation, with less than one-third of patients with documented counseling. These findings underscore the need for standardized contraceptive counseling protocols in post-transplant care to improve reproductive health outcomes. Future research should focus on targeted interventions to ensure comprehensive contraceptive counseling is consistently provided.



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3305 | THE SELF-RATING SCALE ITEM IS A VALID MEASURE OF LACTULOSE ADHERENCE IN PATIENTS WITH HEPATIC ENCEPHALOPATHY

Stacey Tam[1] Nicole Garcia[1] Archita Desai[1] Lauren Nephew[1] Marwan Ghabril[1] Naga Chalasani[2] Fangqian Ouyang[1] Elliot Tapper[3] Noll Campbell[4] Eric Orman[1]

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Background: Lactulose is the backbone of hepatic encephalopathy (HE) treatment, but adherence is difficult, and poor adherence leads to poor outcomes. Valid measures of lactulose adherence are lacking. We adapted a single item self-report adherence measure – the Self-Rating Scale Item (SRSI) – for lactulose, and examined its relationship with clinical events, cognition, and symptoms. **Methods:** We prospectively enrolled patients with HE taking lactulose seen at a referral center from June to Dec 2023. Patients were approached nonjudgmentally and responded to the SRSI: "Over the past 2 weeks, rate your ability to take your lactulose as prescribed." Clinical history was obtained, as was bowel movement response. Symptoms and cognition were collected using PROMIS-29+2, and PROPr was calculated to estimate overall health utility (0=dead; 1=full health). The relationships between the SRSI and other measures were assessed. **Results:** 74 patients were enrolled. The median age was 60, and 58% were female. Cirrhosis was due to MASH in 46% and alcohol in 31%; median MELD-Na was 15. By SRSI, adherence was ≤good in 31 (42%), very good in 21 (28%), and excellent in 22 (30%). Across the 3 groups, self-reported skipped lactulose doses in the prior week occurred in 84%, 24%, and 18%, respectively (p<0.01), with median number of skipped doses of 3 (IQR 1-7) vs. 0 (0-2) vs. 0 (0-0) (p<0.01). Across the groups, median number of days in the prior week with 2-4 bowel movements daily was 4 (3-7), 7 (6-7), and 7 (5-7) (p=0.02) with 39%, 71%, and 68% reporting 2-4 bowel movements on all 7 days (p=0.03). PROMIS-29+2 results are shown in the Table. Sleep disturbance was significantly lower in those with better adherence (p=0.01). Fatigue and pain interference trended lower in those with better adherence, and cognitive function trended higher. PROPr was numerically greater in those with excellent adherence (0.28 vs. 0.21). Median number of days since HE-related hospitalization or emergency visit was greater and borderline significant in those with better adherence: 24 (4-139) vs. 90 (23-278) vs. 96 (39-365) (p=0.06). **Conclusion:** The SRSI is associated with other measures of lactulose adherence, bowel movement response, symptoms, cognition, and healthcare utilization. With further prospective validation, adopting the SRSI into clinical practice may be a feasible and patient-centered way to improve lactulose dosing, adherence, and health outcomes.

PROMIS-29+2 Comparisons Across Levels of Lactulose Adherence

	≤ Good	Very Good	Excellent	p-value
Physical function	38 (8.5)	39 (6.5)	39 (10.9)	0.89
Anxiety	56 (11.1)	53 (9.9)	50 (9.6)	0.21
Depression	53 (11.0)	50 (8.9)	49 (9.2)	0.38
Fatigue	61 (7.7)	60 (9.9)	55 (8.1)	0.08
Sleep disturbance	58 (10.0)	57 (9.9)	50 (7.8)	0.01
Ability to participate in social roles	44 (9.9)	45 (12.2)	46 (12.7)	0.86
Pain interference	61 (8.4)	58 (8.8)	56 (9.8)	0.08
Pain intensity	5 (2.6)	4 (3.1)	4 (3.4)	0.25
Cognitive function	45 (7.6)	48 (7.7)	49 (8.6)	0.11
PROPr	0.21 (0.19)	0.21 (0.14)	0.28 (0.23)	0.33

Disclosures: Stacey Tam: Nothing to Disclose, Nicole Garcia: Nothing to Disclose, Archita Desai: Nothing to Disclose, Lauren Nephew: Nothing to Disclose, Marwan Ghabril: Nothing to Disclose, Naga Chalasani: Madrigal:

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Consultant, Zydus, Ipsen, Pfizer, Merck, Altimmune, GSK: Consultant, Exact Sciences: Grant/Research Support, NIH: Grant/Research Support, Fangqian Ouyang: Nothing to Disclose, Elliot Tapper: Nothing to Disclose, Noll Campbell: Nothing to Disclose, Eric Orman: Sitero: Consultant, Biovie: Advisor

3306 | THE HOSPITAL FRAILTY RISK SCORE PREDICTS OUTCOMES IN PATIENTS WITH HEPATIC FIBROSIS OR CIRRHOSIS

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Background: Cirrhosis is the leading liver-related cause of death worldwide and significantly contributes to global morbidity and mortality. Frailty frequently accompanies chronic liver disease due to persistent inflammation, disrupted protein metabolism, and the toxic effects of ammonia on muscles. The Hospital Frailty Risk Score (HFRS) is a validated tool designed to predict outcomes in acutely ill hospitalized patients by assessing their frailty. In this study, we applied the HFRS to predict outcomes in hospitalized patients with liver fibrosis or cirrhosis. **Methods:** The National Inpatient Sample Database was queried from 2016 to 2019 to identify patients with a primary or secondary diagnosis of fibrosis or cirrhosis of the liver using International Classification of Diseases Tenth Edition Revision (ICD-10) codes. Patients less than 18 years of age were excluded. Using HFRS, patients were divided into having low frailty (HFRS<5), medium frailty (HFRS 5-15), or high frailty scores (HFRS>15). Chi-squared tests and independent t-tests were used for categorical data and continuous data, respectively. Multivariate logistic regression was utilized to assess the relationship between HFRS categories and outcomes, including length of stay (LOS), intensive care unit (ICU) admission, shock, and mortality after adjusting for confounding variables. **Results:** A total of 438,558 patients were admitted and had hepatic fibrosis or cirrhosis. Among these, 193,295 patients (44.08%) had low frailty scores, 230,101 (52.47%) had medium frailty scores, and 15,162 (3.46%) had high frailty scores. As shown in the table, patients with medium and high frailty scores had significantly higher adjusted odds ratios (aOR) for mortality [aOR 5.39 (CI 5.17-5.62) and aOR 9.68 (CI 9.10-10.31), respectively, P < 0.001], ICU admission [aOR 7.12 (CI 6.84-7.40) and aOR 17.73 (CI 16.76-18.75), respectively, P < 0.001], and shock [aOR 5.84 (CI 5.66-6.01) and aOR 13.37 (CI 12.77-14.01), respectively, P < 0.001] compared to those with low frailty scores. Additionally, patients with medium and high frailty scores had longer lengths of stay [2.94 days (CI 2.90-2.98) and 6.75 days (CI 6.63-6.86), respectively, P < 0.001] compared to patients with low frailty scores. **Conclusion:** As measured by the Hospital Frailty Risk Score (HFRS), frailty significantly increases the length of stay, ICU admissions, and mortality in hospitalized cirrhosis patients. Utilizing the HFRS is a low-cost method to predict these outcomes effectively.

	Mortality aOR (95% CI)	P-value	ICU Admission aOR (95% CI)	P-value	Shock aOR (95% CI)	P-value	LOS Coefficient (95% CI)	P-value
Low Frailty	1	(reference)	1	(reference)	1	(reference)	0	(reference)
Medium Frailty	5.39 (5.17 - 5.62)	<0.001	7.12 (6.84 - 7.40)	<0.001	5.84 (5.66 - 6.01)	<0.001	2.94 (2.90 - 2.98)	<0.001
High Frailty	9.68 (9.10 - 10.31)	<0.001	17.73 (16.76 - 18.75)	<0.001	13.37 (12.77 - 14.01)	<0.001	6.75 (6.63 - 6.86)	<0.001

Disclosures: Imran Qureshi: Nothing to Disclose, Yazan Abboud: Nothing to Disclose, Ritik Mahaveer Goyal: Nothing to Disclose, Shivani Patel: Nothing to Disclose, Kaveh Hajifathalian: Nothing to Disclose, Ahmed Al-Khazraji: Nothing to Disclose

3307 | TERLIPRESSIN IS ASSOCIATED WITH DECREASED HEALTHCARE RESOURCE UTILIZATION COMPARED WITH MIDODRINE/OCTREOTIDE AMONG PATIENTS WITH HEPATORENAL SYNDROME

Alexandra DeSousa Tanvi Goyal[1] David Kaplan[1] Jonathan Nahas[1]

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Background: Hepatorenal syndrome (HRS) is a decompensation of end-stage liver disease and portal hypertension associated with significant healthcare resource utilization, frequently culminating in in-hospital mortality. Terlipressin (T), a synthetic vasopressin analogue, recently became the first FDA-approved treatment for HRS. T has a significantly higher cost per use relative to the prior off-label standard of care, midodrine/

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octreotide (MO). The aim of this study was to determine how the introduction of T changed inpatient resource utilization among hospitalized patients when compared with MO. **Methods:** We performed a retrospective cohort study utilizing medical records review of inpatients admitted to our health system with a diagnosis of HRS in the 7 months prior to terlipressin formulary approval (December 2022-June 2023) and the 7 months following its introduction (July 2023-January 2024). We collected laboratory values 48h prior, at the time of initiation, 48h after, and at maximal change in kidney function, length of stay (LOS) on medical floor and intensive care unit (ICU), and need for renal replacement therapy (RRT). We used non-parametric statistics and chi-square tests to compare demographic characteristics and outcomes of interest. Linear and logistic regression models were used to evaluate the association of treatment assignment and outcomes adjusting for key baseline covariates. **Results:** 38 patients received MO and 10 patients received T within the specified timeframes. There was no significant difference in group demographics and ALD was the dominant disease etiology. At the time of initiation of therapy, MO patients had higher average creatinine (3.1 mg/dL vs 2.3 mg/dL, p=0.011) and MELD-Na (32.1 vs 24.6, p=0.002) compared to T. Mean total LOS did not differ between patients receiving T versus MO (17.2 days vs 18.3 days, p=0.758). However, for the MO group, mean floor LOS was lower (11.5 days vs 17.0 days, p= 0.034) and ICU LOS was higher (5.7 days vs 1.3 days, p=0.026), therefore the percentage of floor LOS is lower in the MO group (80% vs 100%, p=0.002). **Conclusion:** Our single center experience demonstrated that T appears to be associated with greater improvements of creatinine, decreased RRT, and decreased ICU days compared to MO. While T's higher upfront cost per dose remains a barrier to adoption by some institutions, there is a possibility that changes in RRT and ICU LOS may mitigate these costs. Ongoing work will assess the effect of T utilization on total hospitalization costs.

		Midodrine/Octreotide	Terlipressin	p
Median age, *years*		59	62	0.21
Male sex, %		47	60	0.49
Race, %				
	Asian	10.5	0	
	Black	10.5	10	
	Hispanic	15.8	0	
	White	52.6	80	
	Unknown	10.5	10	
Etiology of Liver Disease, %				
	ALD	52.6	60	
	MASH	18.4	10	
	MetALD	7.9	0	
	Other*	21.1	30	
Mean Initial Cr (SD), *mg/dL*		3.1 (1.4)	2.3 (0.7)	0.011
Mean Post-Treatment Cr (SD), *mg/dL*		3.2 (1.8)	1.5 (0.6)	<0.001
Mean Initial MELD-Na (SD)		32.1 (6.9)	24.6 (6.5)	0.002
Mean Post-Treatment MELD-Na (SD)		30.4 (9.9)	21.5 (8.1)	0.006
Need for RRT, %		39.5	10	0.088
Mean Total LOS (SD), *days*		17.2 (11.7)	18.3 (9.8)	0.758
Mean Floor LOS (SD), *days*		11.5 (8.2)	17.0 (7.1)	0.034
Mean ICU LOS (SD), *days*		5.7 (10.4)	1.3 (3.1)	0.026
Percent of Hospitalization on Floor, %		0.8 (0.3)	1.0 (0.1)	0.002

*Other includes A1AT, AIH, ALD/HCV, HBC, HCV, cryptogenic, MASH/HH

Disclosures: Alexandra DeSousa: Nothing to Disclose, Tanvi Goyal: Nothing to Disclose, David Kaplan: Independent Contractor relationship with Roche Genentech; Has not ended; Grant/Research Support relationship with AstraZeneca Inc; Has not ended; Advisor relationship with AstraZeneca; Has ended; Advisor relationship with Exelixis; Has ended; Grant/Research Support relationship with Gilead; Has not ended; Advisor relationship with Sirtex; Has ended; Grant/Research Support relationship with Exact Sciences; Has not ended; Grant/Research Support relationship with Glycotest; Has ended, Jonathan Nahas: Nothing to Disclose

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3308 | ASSOCIATION BETWEEN CIRRHOSIS AND LIVER INJURY AND TOXIC METALS EXPOSURES

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Background: Data from model systems link exposure to toxic metals such as cadmium (Cd) and arsenic (As) to liver injury and chronic liver disease; however, human data are inconsistent. The aim of this study was to examine the association between toxic metal blood levels, liver enzyme levels and cirrhosis using data from the Southern Liver Health Study (STRIVE). **Methods:** We measured toxic metal blood levels in whole blood collected from participants (pts) aged 40-75 years enrolled in STRIVE, a longitudinal study of pts with cirrhosis and otherwise healthy controls residing in NC or GA, between 2021-22. Using Inductively Coupled Plasma-Mass Spectrometry (ICP-MS), we measured toxic metals As, lead (Pb), gadolinium (Gd) and Cd, and trace metals magnesium (Mg), iron (Fe) and copper (Cu). We used regression models to determine if toxic metal concentrations were associated with cirrhosis, and/or levels of alanine aminotransferase (ALT), aspartate aminotranferase (AST), and triglycerides (TG). **Results:** Metal blood levels were measured in 366 pts (n=155 with cirrhosis). The mean age of the cohort was nearly 60 years, 64% were female and 58% non-Hispanic White (Table 1). 18 of the 155 pts with cirrhosis died during follow up and those pts had higher blood levels of As (p=0.048), Cd, Gd, and Pb than cirrhosis patients remaining alive. Low Mg levels associated with significantly higher As (β=-0.1262, p=0.0035) and Pb (β=-0.1758, p=0.0001) concentrations. Elevated Pb (β=2.8941, p=0.0007) associated with elevated levels of Cu even after adjustment for age, cigarette smoking, obesity, sex, and race/ethnicity. Elevated Pb (β=1.2952, p=0.0024) and Gd (β=1.6204, p<0.0001) levels associated with cirrhosis. To assess possible confounding of Gd levels by magnetic resonance imaging exposure among cirrhotic pts, we analyzed liver/metabolic dysfunction indicators. Elevated Pb levels remained associated with elevated ALT (β=1.2952, p=0.0024) and AST (β=1.2952, p=0.0024), and Cd with AST (β=1.2952, p=0.0024), but there was no association of elevated liver enzymes with Gd (p>0.05) (Table 2). **Conclusion:** We found that elevated toxic metals levels in blood associated with cirrhosis and liver injury compared to otherwise healthy controls in our cohort. Toxic metals also associated with co-exposure to trace metals like Cu and Mg. While this is a small study and cannot assess causation, these findings warrant further investigation into the role of metals and their co-exposure in the initiation and progression of liver disease.

Table 1 Characteristics of participants

Characteristics	Overall N=366	%	Cirrhosis N=155	%	Non-Cirrhosis N=211	%
Sex						
Male	131	35.79%	75	48.39%	56	26.54%
Female	235	64.21%	80	51.61%	155	73.46%
Race/Ethnicity						
Non-Hispanic Black	93	25.41%	21	13.55%	72	34.12%
Non-Hispanic White	212	57.92%	120	77.42%	92	43.60%
Hispanic	11	3.01%	4	2.58%	7	3.32%
Native American	2	0.55%	2	1.29%	0	0.00%
Asian	7	1.91%	2	1.29%	5	2.37%
Other	1	0.27%	0	0.00%	1	0.47%
Unknown	40	10.93%	6	3.87%	34	16.11%
BMI category						
<25	78	21.31%	29	18.71%	49	23.22%
25-29	78	21.31%	32	20.65	46	21.80%
30-34	82	22.40%	24	15.48	58	27.49%
35-39	45	12.30%	20	12.90%	25	11.85%
40+	44	12.01%	19	12.26%	25	11.85%
Unknown	39	10.66%	31	20.00%	8	3.79%
Smoking Status						
Yes	26	7.10%	14	9.03%	12	5.69%
No	198	54.10%	76	49.03%	122	57.82%
Unknown	142	38.80%	65	41.94%	77	36.49%
	N	**Mean, STD**	**N**	**Mean, STD**	**N**	**Mean, STD**
Enrollment Age	356	59.8, 9.5	155	60.7, 8.4	211	59.17, 10.3
Laboratory Parameters						
Alanine Transaminase (U/L)**	341	15.8, 15	145	16.9, 11.9	196	14.9, 16.9
Aspartate Aminotransferase (U/L)	341	37, 30.9	145	44.3, 31.1	196	31.8, 29.8
Triglyceride (U/L)	346	135, 76.4	146	123.4, 69.5	200	143.5, 80.2

*RUCA is Rural – Urban Commuting Area Codes. RUCA larger than or equal to 4 are micropolitan low commuting areas, small town, and rural areas.

**The mean and standard deviation of ALT was calculated using values of limit of detection (LOD) divided by 2 when < LOQ.

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Table 2. Risk factors and metabolic parameters for high level of metals

Risk Factors	Arsenic (As)*		Cadmium (Cd)*		Gadolinium (Gd)*		Lead (Pb)*	
	Estimate	P-Value	Estimate	P-Value	Estimate	P-Value	Estimate	P-Value
	N=221		N=221		N=221		N=221	
NHB	-0.2679	0.6805	0.6463	0.3894	-0.6520	0.3705	-0.2117	0.7878
NHW	-0.9704	0.1111	0.1966	0.7818	-0.9261	0.1664	-0.4270	0.5528
Sex (Female)	0.2329	0.5190	0.7962	**0.0436**	-0.7178	**0.0364**	0.0199	0.9599
Smoking (Yes)	-1.3077	0.0531	1.5262	**0.0012**	-0.1528	0.7674	0.5358	0.3219
BMI	-0.0387	0.1128	-0.0475	0.0595	0.0169	0.4627	-0.0571	**0.0379**
Cirrhosis (Yes)	-0.0439	0.9068	0.7195	0.0619	1.6204	**<.0001**	1.2952	**0.0024**
Magnesium (Mg)**	-0.1262	**0.0035**	-0.0199	0.6288	0.0232	0.5484	-0.1758	**0.0001**
Iron (Fe)**	0.0477	0.2253	0.0292	0.4183	-0.0317	0.3742	-0.0196	0.6654
Copper (Cu)**	0.3589	0.6250	-0.1846	0.8044	-0.5514	0.4748	2.8941	**0.0007**

Metabolic Parameters	N	Arsenic (As)***		Cadmium (Cd)***		Gadolinium (Gd)***		Lead (Pb)***	
		Estimate	P-Value	Estimate	P-Value	Estimate	P-Value	Estimate	P-Value
ALT U/L****	206	0.1828	0.6200	0.8823	**0.0276**	-0.2896	0.4817	1.1633	**0.0022**
AST U/L ******	206	0.0226	0.9391	0.3365	0.2963	0.0703	0.8303	0.9108	**0.0026**
TG mg/dL******	211	0.0596	0.8215	-0.1185	0.6838	-0.1425	0.6280	-0.1175	0.6666

*As, Cd, Gd, and Pb were dichotomized by 3rd quartile.
**Mg, Fe, and Cu were logarithm transformed.
*** As, Cd, Gd, and Pb were dichotomized by 3rd quartile. Adjusted by age at enrollment, sex, smoking status, race/ethnicity, interaction term for race/ethnicity and metal.
****Adjusted by age at enrollment, sex, smoking status, race/ethnicity, interaction term for race/ethnicity and metal.

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3309 | THE OTAGO EXERCISE PROGRAM IMPROVES LIVER FRAILTY IN PRE-TRANSPLANT CANDIDATES

Neil Shah[1] *Kathryn Bridgens*[2] *Jyotsna Gupta*[1] *Deborah Givens*[1]

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Background: Outpatient pre-habilitation has effectively improved the frailty of candidates for liver transplant (LT). However, LT centers vary in their recommendations and use of physical activity-based interventions. The Otago Exercise Program (OEP) focuses on balance, strength, and fall prevention and is individually tailored to the participant by a physical therapist (PT). This pilot study explores if the OEP improves the health status of pre-frail patients undergoing LT evaluation. **Methods:** Between March 2022 and April 2024, candidates for LT who were "pre-frail" by the liver frailty index (LFI) were recruited. Participants who agreed were referred to PTs trained in the OEP and were familiar with the LFI. The PTs evaluated the participants and personalized the home-based OEP, providing home-based exercises. Participants returned every 3 months for reassessment. tailored exercise changes and progression in the program. Outcome measures included LFI and the 10-meter walk test (10 MWT). **Results:** A total of 22 patients were identified, 3 declined, and 2 died before initial intake. The remaining 17 patients were 62% male (median MELD 3.0 of 16). The initial median LFI was 4.11. The average change in 3-month LFI was -0.19 (improvement in frailty) with the largest increase occurring from 3 to 6 months (-0.35). Initial average 10 MWT was 0.70 m/s (fast speed) with early worsening to 0.81 m/s by 3 months and then slight improvement to 0.69 m/s by 9 months. During the study period, 3 patients were lost to follow-up, 4 underwent liver transplantation, and 3 died on the waitlist. Those that underwent liver transplantation had an average improvement in LFI by 0.73. No significant changes were seen in MELD 3.0 during the study period. **Conclusion:** The OEP improved frailty in candidates for LT deemed pre-frail. OEP offers a standardized approach to pre-habilitation amongst transplant centers. Future directions will include longer-term follow-up and post-transplant outcomes.

Disclosures: Neil Shah: GSK: Advisor, Ipsen: Advisor, Kathryn Bridgens: Nothing to Disclose, Jyotsna Gupta: Nothing to Disclose, Deborah Givens: Nothing to Disclose

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3310 | COST-EFFECTIVENESS OF UNIVERSAL PEDIATRIC SCREENING OF HEPATITIS C VIRUS IN THE UNITED STATES

Jessica Frankeberger[1] Melissa Choz[1] Tatyana Kushner[2] Nancy Reau[3] Adriane Wynn[1] Natasha Martin[4]

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Background: In the United States, approximately 5 in 1,000 children are exposed to Hepatitis C Virus (HCV) perinatally each year. Although universal HCV screening in adults starting at age 18 and in pregnancy is now recommended, many pediatric cases remain undiagnosed and untreated. This study examines the cost-effectiveness of universal HCV screening among children by age 2. **Methods:** An HCV natural history Markov model was developed to evaluate the cost-effectiveness of universal HCV pediatric screening by age 2 compared to the currently recommended risk-based screening of children born from mothers with HCV. We adopted a healthcare provider perspective and lifetime horizon. We assumed HCV chronic prevalence of 0.73% among pregnant persons and a 7.2% vertical transmission rate, leading to a 0.05% HCV chronic prevalence in children. In the status-quo risk-based scenario, we assumed 23% of children with prenatal HCV exposure were screened by age 2 based on published data. We assessed costs (USD) and quality-adjusted life years (QALYs) and calculated the incremental cost-effectiveness ratio (ICER, $ per QALY gained) compared to a willingness-to-pay threshold (WTP) of $50,000/QALY. We also assessed the impact of varying HCV chronic prevalences among children. As guidelines have recently changed to recommend risk-based HCV screening at age 2-6 months, we conducted a sensitivity analysis with increased HCV screening rates (to 74%) based on published data of well-child visits during this period in the status-quo scenario. **Results:** Universal pediatric HCV screening was cost-effective (ICER=$15,767/QALY gained) compared to the status quo risk-based screening. The lowest HCV chronic prevalence in which universal pediatric screening remained cost effective under a WTP of $50,000/QALY was 0.020% (ICER=$41,874/gained). Given increased testing in pregnancy and updated pediatric guidelines, it is likely more prenatally exposed infants will be recognized and tested in the risk-based scenario. Universal screening remained cost-effective when increasing risk-based screening to 74% (ICER=$21,182/gained) and was cost-effective at the lowest HCV chronic prevalence in children of 0.025% (ICER=$44,976/gained). **Conclusion:** Universal HCV screening in early childhood is cost-effective. Guidelines should consider recommendation of universal screening in the pediatric population, particularly if it can be conducted at the time of routine pediatric blood draws, such as lead testing.

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3311 | ESTIMATING LOCAL TRANSMISSION DYNAMICS OF HEPATITIS A VIRUS INCREASED INCIDENCE AMONG MEN WHO HAVE SEX WITH MEN IN NEW YORK CITY AND CALIFORNIA, 2016-2019

Oluwatosin Jegede[1] Ravi Goyal[1] Christl Donnelly[2] Megan Hofmeister[3] Lauren Stockman[4] Olivia Arizmendi[4] HaeNa Waechter[5] Julia Latash[5] Natasha Martin[1]

[1]University of California San Diego, [2]University of Oxford, UK, [3]Centers for Disease Control and Prevention, USA, [4]California Department of Public Health, [5]New York City Department of Health and Mental Hygiene

Background: Hepatitis A is a vaccine-preventable disease. Vaccination against hepatitis A has been recommended for men who have sex with men (MSM) in the United States since 1996; however, vaccination coverage rates among MSM are low, putting this population at risk for hepatitis A outbreaks. During 2016–2019, increased incidence of hepatitis A among MSM was observed in New York City (NYC) and California (CA). To better understand the role of local transmission dynamics versus the role of imported cases, we estimated the effective time-varying reproduction number (Rt) for these two hepatitis A clusters among MSM. **Methods:** We analyzed data from reported hepatitis A cases among MSM in NYC and CA diagnosed during 2016–2019

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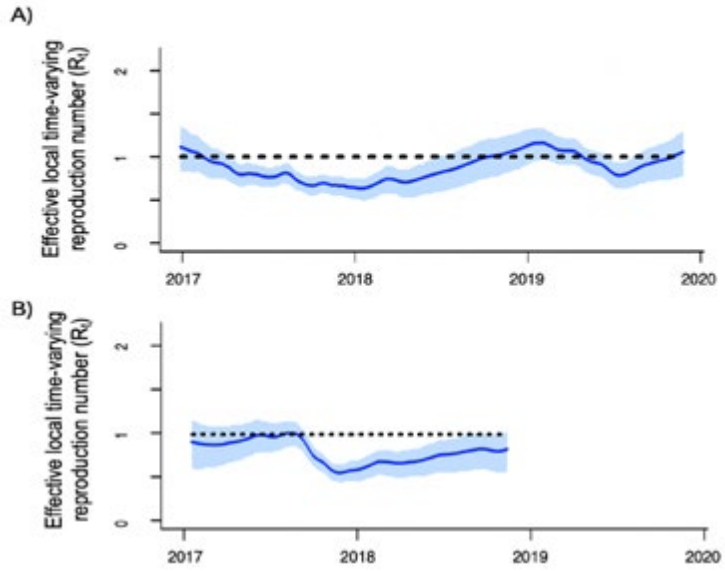
and 2017–2018, respectively. We excluded cases with missing information on illness onset date and travel history. Rt was estimated using a Bayesian recursive filtering and smoothing renewal model optimized for low case incidence; if Rt is <1.0 the epidemic is unsustainable. It accounts for local versus imported cases through modeling incident cases as a Poisson process incorporating an exogenous force of infection from imported cases; both types of cases can drive future local infections. We defined imported cases as those with a reported history of recent international travel (i.e., during their exposure period), and local cases as those without a reported history of recent international travel. **Results:** After excluding cases with missing information (n=2 in NYC and n=2 in CA), we analyzed 124 hepatitis A cases among MSM from NYC and 61 cases among MSM from CA. Thirty-two (26%) cases in NYC and 20 (33%) cases in CA reported recent international travel. Accounting for importation, mean R_t for hepatitis A virus (HAV) infection among MSM hovered at or below 1.0 for most of the time period in NYC and CA (Fig 1). R_t peaked at 1.15 (95% CI: 0.97–1.33) at the beginning of 2019 in NYC. **Conclusion:** During 2016–2019, the effective time-varying reproduction numbers in hepatitis A clusters among MSM in NYC and CA hovered at or below the threshold required to sustain local transmission, suggesting that the increased incidence observed was potentially driven by recurring importation of internationally-acquired HAV infections rather than local transmission. In line with Advisory Committee on Immunization Practices recommendations, efforts should ensure continued routine hepatitis A vaccination of MSM.

Figure 1: Effective local time-varying reproduction number of hepatitis A virus infection among men who have sex with men in (A) New York City and (B) California. Blue line represents the mean, shading representing the 95% confidence interval.



Disclosures: Oluwatosin Jegede: Nothing to Disclose, Ravi Goyal: Nothing to Disclose, Christl Donnelly: Nothing to Disclose, Megan Hofmeister: Nothing to Disclose, Lauren Stockman: Nothing to Disclose, Olivia Arizmendi: Nothing to Disclose, HaeNa Waechter: Nothing to Disclose, Julia Latash: Nothing to Disclose, Natasha Martin: Nothing to Disclose

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3312 | TO ACHIEVE FUNCTIONAL CURE FOR CHRONIC HEPATITIS B INFECTION- NEW THERAPY VS EXPANDING THE EXISTING THERAPY ◆

George Lau[1] Jing Chen[2] Ji-Dong Jia[3] Jin Mo Yang[4] Tawesak Tanwandee[5] Diana Payawal[6] Saeed Hamid[7] Shiv Kumar Sarin[8] Masao Omata[9] George Lau[10]

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Background: Chronic Hepatitis B (CHB) remains a significant global health challenge, necessitating effective and cost-effective therapeutic strategies. This study evaluated the impact and cost-effectiveness of different therapeutic strategies on HBsAg loss and related complications, and estimated the cost to achieve a HBsAg loss from the perspective of healthcare provider in the Asia-Pacific (AP) region. **Methods:** A Markov state-transition model was used to evaluate cost-effectiveness of three strategies of antiviral treatment, i.e. infinite nucleos(t)ide analogues (NA, entecavir) treatment, add-on PegIFN to stop NA (PegIFN+NA), and add-on new therapy to stop NA (New+NA). The model simulated chronic HBV infection status of 10,000 patients (aged 50+ years, NA-suppressed, HBeAg-) with virological and clinical relapse, and retreat in AP. The health outcomes and costs were discounted at 3.5%. One-way sensitivity analysis and probability sensitivity analysis were conducted to explore the parameters and model uncertainty. **Results:** PegIFN+NA is estimated to reduce HCC and HBV-related deaths by 34.4% and 23.3%, respectively, by 2050, compared to infinite NA treatment; while the reduction with New+NA is 1.2% and 0.7%, respectively. The reduction is more prominent in low-income than high-income countries. PegIFN+NA is generally cost-effective in AP, with an incremental cost-effectiveness ratio (ICER) of 6,363 USD/QALY, under one GDP per capita. The ICER is ranging from 10,765 USD/QALY in high-income countries/areas to 5,398 USD/QALY in low-income countries and all are below one GDP per capita. The ICERs are sensitivity to the rate of HBsAg loss and HBsAg seroreversion, and cost of different therapies. To achieve an ICER under 3 times GDP per capita, the cost for a new therapy must not exceed a one-time treatment cost of USD3000, 7300, and 38500 in low-, middle-, and high-income countries in AP. The probability of New+NA being cost-effective compared to infinite NA treatment is below 8% in AP. **Conclusion:** New antiviral therapies exhibit a low probability of being cost-effective, while combination therapy may serve as a cost-effective strategy in achieving HBsAg loss. Disparities exist in HBV treatment among high-, middle-, and low-income countries, where compared strategies yield higher health gains but are less affordable for low-income countries.

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3313 | DATA DRIVEN CLINICAL TRIAL RECRUITMENT - FROM THE COMMON TO THE RARE

Robert Miller[1] Christina Owen[1] Timothy Jobson[1]

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Background: Approximately 85% of clinical trials fail to reach recruitment goals and recruitment in the UK has fallen by 44% between 2017 and 2022. This has significant consequences for patients suffering from diseases with limited treatment options. Hepatology trials are particularly affected by this decline exacerbated by high levels of screen failure. Hepatology studies often have complex eligibility criteria including co-morbidities and laboratory abnormalities which limits patient recruitment. In addition, more deprived communities are less likely to participate in clinical trials. Common conditions such as Metabolic dysfunction Associated Steatotic Liver Disease (MASLD), as well as rarer conditions such as Primary Biliary Cholangitis (PBC) are the focus of drug trials currently in the recruitment phase. In Somerset UK, we developed a case-finding search engine which allows rapid analysis of

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patterns in blood tests to identify cohorts of patients. Here we evaluated the potential of an approach using this database for clinical trial recruitment. **Methods:** We identified clinical trials currently recruiting PBC and MASLD patients using the NIH database (at www.clinicaltrials.gov). We assessed the recruitment targets, number of centres recruiting for each study and eligibility criteria (EC). We then assessed an alternative approach for recruitment using our database as an analytical tool to identify patients for these studies. It is anticipated the database will soon cover 10 million population. We assessed the potential power of recruitment by extrapolating from our current to our proposed footprint. **Results:** 4 studies in MASLD and 4 in PBC were selected for analysis (Fig. 1). Those EC which were based upon biomarkers were rapidly assessed to identify large numbers of potential recruits using the database. Conventional approaches aimed to recruit on average 2.42 patients per research site. In contrast, our approach (based on 10M footprint) would identify on average 1,819 patients per trial. With 10% enrolment of eligible patients, our approach would yield the equivalent of 70 (S.D. 44) conventional sites per 10M footprint. **Conclusion:** Our approach led to the rapid identification of a group of patients eligible for clinical trials in MASLD and PBC compared to traditional approaches. Specifically, this approach does not rely on waiting for a clinical encounter and does not rely on historic coded data. Far reaching implications of undertaking this approach include widening access to and increasing participation in clinical trials leading to more rapid availability of therapeutics.

	MASLD				PBC			
Eligibility Criteria	**1**	**2**	**3**	**4**	**1**	**3**	**4**	**9**
Inclusion Criteria	**Lanifibranor in F2-3**	**NNC0194-0499 with Semaglutide**	**Lanifibranor +/- Empagliflozin**	**Semaglutide**	**Obeticholic Acid Phase 4**	**GKT137831**	**Elafibranor with UCDA**	**Seladelpar**
Diagnosis	N- Histological	N- Histological	N- Histological	N- Histological	Y - Biochemical & Histological	Y - Biochemical & Histological	Y - Biochemical & Histological	Y - Biochemical & Histological
Metabolic Risk Factors	P		P					
Age	Y	Y	Y	Y	Y	Y	Y	Y
Exclusion Criteria								
Alternative aetiology	Y	Y	Y	Y	Y	Y	Y	Y
Complications	Y	Y	Y					
Decompensation & MELD Scoring		P		P	P	P	P	P
HIV Positivity	Y	Y	Y	Y	Y	Y	Y	
Biochemistry & Haematology	Y		Y		Y	Y	Y	Y
Treatments	N	N	N	N	N	N	N	N
Other Co-morbidities	N	N	N	N	N	N	N	N
Participation in other trials or recent surgery	N	N	N	N	N		N	
Recruitment Target	1000	672	63	1200	334	111	161	500
Geographical Area	International	International	International	International	International	International	International	International
Number of Recruitment Centres	455	186	40	454	181	61	115	118
Recruitment Target per Site	2.20	3.61	1.58	2.64	1.85	1.82	1.40	4.24
Database Patients identified	131	269	98	142	22	17	22	135
10 Million Footprint Extrapolation	1,980	4,798	1,748	2,533	392	303	392	2,408
Ratio of eligible patients identified (10 Million Database Footprint) to global target	1.98	7.14	27.75	2.11	1.17	2.73	2.44	4.82
Database Recruitment per Patient per Site	901	1328	1110	958	213	167	280	568
Database site equivalence (10% convertion rate)	90	133	111	96	21	17	28	57

Key:
N = Not assessable using the database
Y = Assessable entirely using the database
P = Assessable via a proxy measure using the database
MASLD = Metabolic-Associated Steatotic Liver Disease
PBC = Primary Biliary Cholangitis

Disclosures: Robert Miller: Nothing to Disclose, Christina Owen: Nothing to Disclose, Timothy Jobson: Predictive Health Intelligence Ltd: Executive role, Predictive Health Intelligence Ltd: Stock – privately held company

3314 | ADVANCE CARE PLANNING COMPLETION RATES AND PERCEPTIONS AMONG ADULTS WITH END-STAGE LIVER DISEASE IN A POPULATION-BASED COHORT

Arpan Patel[1] Anne Walling[1] Rebecca Sudore[2] Douglas Bell[1] Chi-Hong Tseng[1] Christine Ritchie[3] Ron Hays[1] Maryam Rahimi[4] Lisa Gibbs[4] Fernando Sanz Vidorreta[1] Neil Wenger[1]

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Background: Single-center studies report low participation in advance care planning (ACP) activities among adults with end-stage liver disease (ESLD). Understanding how the ACP perspectives of patients with ESLD differ from those of other patients with advanced illnesses can inform intervention development. **Methods:** This secondary analysis of data from the UC Health Care Planning study, a multi-site trial of ACP interventions in seriously ill primary care patients. A validated electronic health record algorithm used encounter and clinical data to identify patients with six advanced illnesses (21% mortality over two years). The full sample contained data

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regarding advance directive (AD) completion rates (population cohort). A sub-sample of individuals completed surveys assessing characteristics and ACP perceptions (research cohort). We compared ESLD patients with those with other advanced illnesses using *t*-tests and χ^2 tests. Multivariate logistic regression assessed independent predictors of AD completion. **Results:** The 539 patients with ESLD in the population cohort were racially and ethnically diverse (White: 42%, Hispanic: 38%, Asian 9%, Black: 3%), had a mean age of 62 (SD: 13, range: 22-90) years and a quarter preferred a language other than English. Patients with ESLD had similar 2-year mortality (18% vs. 21% p=0.14) but lower AD/POLST completion (22% vs. 34%, p<0.001) compared to other conditions. In multivariable analysis, older age (odds ratio [OR]: 1.02, 95% confidence interval [CI]: 1.00-1.04) and Hispanic ethnicity (OR: 0.51, 95% CI: 0.26-0.97) were independently associated with higher and lower AD completion, respectively. In the research subsample (demographics similar to the main cohort), patients with ESLD vs. those without ESLD, reported higher baseline levels of anxiety and depression and greater preference for aggressive care, but similar levels of ACP engagement and preference for life support if death were imminent (Table). **Conclusion:** AD completion is low among patients with ESLD, particularly Hispanic and younger adults. Mental health and perceptions about aggressiveness of care may be factors worth addressing to improve ACP engagement and AD completion rates in this population.

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Table: Characteristics and Preferences of Research Cohort with and without ESLD

	ESLD cohort	Non-ESLD cohort	p-value
N	74	1025	
Age in years, mean (SD)	62.4 (12.4)	70.5 (15.3)	**0.000**
Gender, N (%)			
Female	34 (46.0%)	493 (48.1%)	0.726
Male	40 (54.1%)	533 (52.0%)	
Race/Ethnicity, N (%)			
Hispanic	34 (46.0%)	164 (16.0%)	
White	32 (43.2%)	633 (61.7%)	**0.000**
Asian	1 (1.4%)	99 (9.7%)	
Black	3 (4.1%)	70 (6.8%)	
Other	4 (5.4%)	60 (5.9%)	
Language spoken, N (%)			
English	55 (74.3%)	864 (84.2%)	**0.001**
Spanish	17 (23.0%)	96 (9.4%)	
Other	2 (2.7%)	66 (6.4%)	
Marital status, N (%)			
Married or committed	43 (58.1%)	615 (59.9%)	0.784
Not	30 (40.5%)	404 (39.3%)	
N/A	1 (1.4%)	7 (0.7%)	
Education Level, N (%)			
High school or less	30 (40.6%)	229 (22.3%)	
Some college	24 (32.4%)	286 (27.9%)	**0.000**
College graduate	7 (9.5%)	218 (21.3%)	
Graduate degree	11 (14.9%)	286 (27.9%)	
N/A	2 (2.7%)	7 (0.7%)	
Insurance, N (%)			
Commercial	13 (17.6%)	297 (29.0%)	
Managed/HMO	6 (6.8%)	55 (5.4%)	**0.000**
Medicaid	30 (40.5%)	175 (17.1%)	
Medicare	25 (33.8%)	395 (38.5%)	
Other	1 (1.4%)	104 (10.1%)	
Quality of life, physical, mean (SD)	44.3 (6.7)	45.5 (7.3)	0.09
Quality of life, mental, mean (SD)	49.9 (6.28)	50.3 (5.84)	0.53
Anxiety, mean (SD)	54.8 (8.78)	52.6 (8.61)	**0.04**
Depression, mean (SD)	53.9 (7.90)	51.3 (8.56)	**0.01**
Desired Aggressiveness of Care, N (%)			
Extend life	25 (33.9%)	236 (23%)	
Relieve pain	21 (28.4%)	506 (49.3%)	**0.007**
Not sure	26 (35.1%)	265 (25.9%)	
If may die soon, prefer, N (%):			
Stay on life support	10 (13.5%)	100 (9.8%)	
Do a trial of life support	34 (46.0%)	437 (42.6%)	0.51
Focus on comfort	22 (29.7%)	359 (35.0%)	
Not sure	8 (10.8%)	108 (10.5%)	
Doctor communication scale, mean (SD)	3.66 (0.50)	3.58 (0.55)	0.18
ACP Engagement (Sudore4), mean (SD)	3.48 (1.13)	3.48 (1.23)	0.99
Advance care planning engagement (TotlevelB), N (%)			0.51
Never heard of ACP	8 (11.1%)	111 (11.3%)	
Heard of ACP	28 (38.9%)	343 (35.1%)	
Wrote/discussed surrogate	16 (22.2%)	161 (16.5%)	
Discussed with doctor	11 (15.3%)	187 (19.1%)	
Wrote preferences/goals	9 (12.5%)	176 (18.0%)	
TotlevelB, mean (SD)	1.79 (1.21)	1.97 (1.31)	0.25
Confidence in receiving desired end of life care, mean (SD)	3.07 (0.69)	3.03 (0.76)	0.63

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3315 | ETIOLOGICAL TRANSITIONS IN PATIENTS WITH LIVER CIRRHOSIS AND HEPATOCELLULAR CARCINOMA: A SINGLE-CENTER STUDY FROM AN INSTITUTION LOCATED IN A DISTRICT WITH A HIGH PREVALENCE OF VIRAL HEPATITIS

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Background: In Japan, viral hepatitis is the main cause of chronic liver diseases, including liver cirrhosis (LC) and hepatocellular carcinoma (HCC). Due to the availability of highly effective antiviral drugs in combination with anti-hepatitis measures, Japan has become one of the most successful countries in the world with regard to hepatitis virus elimination. A recent nationwide survey has shown that the contribution of viral hepatitis as an etiology of LC is suggested to have been decreasing (Hepatol Res. 2024, in press). Our institution is located in a district with a markedly high prevalence of viral hepatitis, including a particularly high number of hepatitis virus C (HCV)-infected patients. We thus investigated the details of inpatients, focusing on the contribution of viral hepatitis-related cirrhosis and HCC. **Methods:** We classified inpatients of our department into four groups (diagnosed in -2007, 2008-2012, 2013-2017, and 2018-2021) and analyzed the changing trends in the etiologies of LC (N=1568) and HCC (N=980). **Results:** Regarding the transition in the etiologies of LC, the contribution of viral hepatitis-related cirrhosis decreased from 81.1% to 58.9%. In particular, HCV-related cirrhosis was found to have dropped from 70.2% to 43.0%. In contrast, the ratios of alcohol-associated liver disease (ALD)-related LC and NASH-related LC increased (from 9.9% to 18.0% and from 0.3% to 10.8%, respectively). Regarding the etiologies of HCC, the contribution of viral hepatitis-related HCC remarkably decreased from 91.8% to 74.9%. HCV-related HCC was found to have also declined from 82.6% to 54.7%. The ratios of ALD-related LC and NASH-related LC increased (from 3.6% to 11.7% and from 0.0% to 10.1%, respectively). **Conclusion:** Our data in daily practice from an institution located in a district with a high prevalence of viral hepatitis was consistent with the recent nationwide survey regarding the etiologies in LC and HCC, depicting a decreasing trend in viral hepatitis and increasing trend in non-viral liver diseases.

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3316 | PATIENTS WITH HEPATITIS DELTA VIRUS INCUR INCREASED HEALTHCARE RESOURCE UTILIZATION AND COSTS POSTDIAGNOSIS: RESULTS FROM A LARGE HEALTHCARE PROVIDER IN ISRAEL

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Background: Patients with hepatitis delta virus (HDV) infection are at greater risk of liver disease progression compared to patients with HBV monoinfection. Using a large healthcare provider database in Israel, this study compared healthcare resource utilization (HCRU) and costs for adult patients with HDV infection before and after HDV diagnosis. **Methods:** This retrospective cohort study used anonymized data from Maccabi Healthcare Services covering 2.7 million patients. Diagnosis and laboratory data were used to identify a subset of patients with chronic HBV (via *ICD-9* claims code or positive laboratory test) who met HDV diagnostic criteria from

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2005–2021. Adult patients 18 years or older diagnosed with HDV (index date = date of earliest: HDV claims code or positive HDV test result) were included in this study and were continuously enrolled for at least 12 months pre- and post-index; patient characteristics were described at index date. HCRU was reported as the number (%) of patients with at least 1 visit (hospitalizations, emergency room visits, physician visits, nursing visits) and as the number of visits per patient per year (PPPY). Total costs were reported in 2022 US dollars PPPY and based on unit costs from the Israel Ministry of Health. HCRU and total costs were compared for the 12-month periods pre- and post-index. **Results:** Of 1.8 million adult patients, 155 with HDV were included with a median (quartile [Q]1, Q3) age at index of 42.5 (33.1, 53.1) years; 52.3% were male. Socioeconomic status was classified as low, mid, or high in 9.7%, 71.6%, and 18.1% of patients, respectively. Baseline prevalence rates for HIV, hepatitis C virus RNA+, and drug dependence were 4.5%, 5.8%, and 6.5%, respectively. The median number of primary care practitioner (PCP), overall outpatient (OP) visits, and OP specialist visits were higher in the 12 months post-index vs pre-index; however, there were no differences in the median number of hospitalizations or ER visits (Table). Mean pharmacy costs PPPY ($1,625 vs $1,192; *P* <.001) and mean total costs PPPY ($5,293 vs $4,912; *P* = .009) were higher in the 12-months post-index vs pre-index, respectively. **Conclusion:** In a large healthcare database in Israel, patients with HDV had increased HCRU and total costs after vs before HDV diagnosis. The higher costs were driven primarily by the increased number of PCP and OP visits and increased pharmacy costs. These findings underscore the need for effective treatments to ease the economic burden of HDV infection.

Table. HCRU and Costs in the 12-Month Periods Pre- vs Post-Index Among Patients With HDV

Characteristic	Pre-Index (n = 155)	Post-Index (n = 155)	P-value
N with ≥1 visit, n (%)			
PCP	152 (98.1)	153 (98.7)	0.7
OP overall	153 (98.7)	154 (99.4)	0.6
OP specialists	132 (85.2)	138 (89.0)	0.3
Gastroenterologists	81 (52.3)	96 (61.9)	0.085
ER	40 (25.8)	31 (20.0)	0.2
Hospitalization (≥1 admission)	32 (20.6)	32 (20.6)	>0.9
HCRU PPPY, median (Q1, Q3)			
PCP visits	7.0 (4.0, 12.0)	8.0 (5.0, 13.0)	**0.027**
OP overall visits	11.0 (6.5, 18.5)	14.0 (8.0, 20.5)	**0.003**
OP specialist visits	3.0 (1.0, 6.0)	4.0 (1.0, 8.5)	**0.043**
ER visits	0.0 (0.0, 1.0)	0.0 (0.0, 0.0)	0.8
Hospitalization length of stay	6.5 (2.0, 13.5)	7.0 (3.0, 15.2)	0.05
Cost PPPY, USD, mean (SD)			
IP costs	2,460.3 (13,391.0)	2,239 (8,562.0)	0.8
OP costs	1,101.4 (808.9)	449.0 (441.6)	**<0.001**
Pharmacy costs	1,192.0 (5,311.5)	1,625.2 (3,250.3)	**<0.001**
Total costs	4,912.1 (14,746.2)	5,293.3 (9,957.0)	**0.009**

Bold P-values indicate statistical significance.
ER, emergency room; HCRU, healthcare resource utilization; HDV, hepatitis delta virus; IP, inpatient; OP, outpatient; PCP, primary care practitioner; PPPY, per person per year; Q, quartile.

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3317 | HEPATIC ENCEPHALOPATHY AND ACUTE KIDNEY INJURY LARGELY DRIVE TRANSFER OF PATIENTS TO HIGHER CENTERS OF CARE: A NATIONAL ANALYSIS

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Background: Selected patients with decompensated cirrhosis (DC) are referred from smaller to larger centers for specialized care including liver transplantation. Amongst the various decompensations, hepatic encephalopathy (HE), acute kidney injury (AKI) and ascites are the most common reason for admission/readmission. We aimed to study the rate and reasons of transfer of cirrhosis patients from a smaller center to a larger center based on

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the presence of decompensation(s) of cirrhosis. **Methods:** Using the 2017-2020 Nationwide Inpatient Sample (NIS) database, non-pregnant patients ≥18 years of age with a primary diagnosis of cirrhosis were identified using ICD-10 codes. HCUP's standard definition of hospital size was used to classify small/medium and large centers. Multivariable logistic regression was used to identify predictors of transfer-out from small/medium sized hospitals to a larger center. Analyses were weighted to reflect national estimates and performed using SAS v9.4. **Results:** A total of 80,845 DC patients were alive at discharge in larger centers between 2017-2020. Only 2.3% were "transferred out". Those not transferred tended to be older 57 +/-12.3 yrs vs 55+/-11.6 yrs (p-value<0.001). Minorities, such as Blacks (8.1% vs 7.7%) and Hispanics (19.5% vs 13.4%) were "transferred out" less frequently (p <0.001). Patients with lower income and Medicaid/Medicare insurance were also "transferred out" less frequently (p <0.001). The multivariable prediction model found the odds of "transfer out" were significantly higher amongst younger patients (OR: 0.95; 95% CI: 0.93-0.97), with a lower AHRQ (OR: 0.94; 95%: 0.90-0.98), AKI/ metabolic abnormalities (OR: 1.99; 95% CI: 1.64-2.42), HE (OR: 1.33; 95%: 1.19-1.48), hepatitis C (OR: 3.13; 95%: 1.42-6.91), pneumonia (OR: 1.69; 1.37-2.08), or SBP (OR: 1.91; 95% CI: 1.59-2.28). The presence of HE and AKI predominantly increased the odds of "transferring out" (Table 1). **Conclusion:** The rate of transfer of patients with DC from small/medium center to large center appears to be relatively low, and largely driven by the presence of decompensations. The presence of HE, AKI, and increasing number of decompensations increased the odds of transferring out. Moreover, patients from minority race and lower SES are less likely be transferred out indicating a disparity in health care access.

Table 1. Comparing the odds of "transfer-out" for HE patients with different risk factors; confidence intervals were adjusted for multiple comparisons using Bonferroni correction

	HE + AKI	HE + Infection	HE + EV bleeding	HE + Ascites
HE + AKI				
HE + Infection	1.38 (1.00, 1.92) p=0.009			
HE + EV bleeding	1.39 (1.03, 1.87) p=0.004	1.00 (0.81, 1.24) p=0.98		
HE + Ascites	1.94 (1.42, 2.65) p<0.001	1.40 (1.11, 1.77) p<0.001	1.40 (1.14, 1.72) p<0.001	

Findings: HE patients with AKI had significantly higher odds of transfer out compared to those with infection (p=0.009), EV bleeding (p=0.004), and ascites (p<0.001).
HE patients with infection had significantly higher odds of transfer out compared to those with ascites (p<0.001), but the odds of transfer out between EV bleeding and infection was not significantly different (p=0.98).
Lastly, those with EV bleeding had significantly higher odds of transfer out compared to those with ascites (p<0.001).

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3318 | A NATIONWIDE CROSS-SECTIONAL SURVEY IN VIRAL HEPATITIS SCREENING FOR JAPANESE WORKERS AND CONSULTATION BEHAVIOR OF POSITIVE PATIENTS FOR HCV ANTIBODY -13.7 MILLION GENERAL CHECKUP APPLICANTS

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Background: Although more than 20 million community residents have been provided an opportunity to undergo hepatitis B virus and hepatitis C virus (HCV) screening by the Japanese government, there is no publicly funded screening for hepatitis virus infections among workers. The aim of this study was to investigate the national number of viral hepatitis screening tests in the workplace and how many of those found to be positive patients have been followed up with examinations and hospital treatment. **Methods:** We conducted a nationwide survey to

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estimate these parameters using data from approximately 13.7 million workers (7.3 million insured and 6.3 million dependents) who underwent mandatory health examinations in their workplaces between April 2016 and 2019. The main outcome measure was attendance rates in HCV screening which were examined Anti-HCV antibody (HCVAb) and we analyzed how many workers who were positive for HCVAb visited to physicians by medical prescription system. **Results:** There was a significant difference in general checkup applicants rates between insured (n=5,433,743 74%) and dependents (n=6,428,225 15%; p<0.001). However, there was no differences in viral hepatitis screening attendance rates between the groups (insured: n=325,597 6.0% and dependents: n=65,012 6.8%, respectively). One thousand six hundred sixty-eight were positive of HCVAg (0.42%) and only two hundred forty-one with HCVAb positive (14%) confirmed to visit specialists within one year after the screening. Sixty-three with HCVRNA positive (26%) were treated with IFN-free direct-acting antivirals. **Conclusion:** There were still many positive patients with viral hepatitis at work sites in Japan. Promoting hepatitis virus screening for workers at general checkup can rescue hepatitis virus carriers who are unaware of their infection and require to therapy for viral elimination.

		2015		2016		2017		2018		2019	
general checkup applicants		number	rate	number	rate	number	rate	number	rate	number	rate
Insured		798544	65.65%	927149	70.21%	1108242	72.60%	1273547	80.37%	1315261	80.66%
dependents		157675	14.05%	176835	14.72%	200175	14.86%	213158	15.48%	204447	14.81%
viral hepatits screeening		number	rate	number	rate	number	rate	number	rate	number	rate
Insured		43920	5.50%	47977	5.17%	65706	5.93%	83584	6.56%	84410	6.42%
dependents		9445	5.99%	10653	6.02%	13546	6.77%	16422	7.70%	14946	7.31%
Insured	Age										
	~19 y.s	93	7.38%	124	6.75%	145	5.31%	174	4.79%	189	3.73%
	20~29y.s	2693	4.61%	2832	3.52%	3068	2.91%	3764	2.56%	3208	1.89%
	30~39y.s	8955	9.25%	9143	7.22%	11009	6.65%	15140	6.54%	13033	5.17%
	40~49y.s	16904	5.64%	17625	5.28%	25112	6.55%	31171	7.73%	31166	7.89%
	50~59y.s	11657	5.05%	13620	5.26%	19218	6.20%	23853	7.06%	26054	7.61%
	60~69y.s	3442	3.19%	4534	3.75%	6777	5.04%	8742	6.15%	9932	7.00%
	70~74y.s	176	4.87%	99	2.26%	377	5.95%	740	9.53%	828	9.62%
dependents	Age										
	~19 y.s									1	25.00%
	20~29y.s	29	2.29%	24	1.33%	22	1.22%	29	1.62%	17	0.93%
	30~39y.s	1119	6.89%	1484	7.96%	1680	7.97%	1951	8.53%	1312	6.12%
	40~49y.s	3904	6.27%	4263	6.10%	5144	6.66%	6089	7.61%	5312	7.18%
	50~59y.s	3160	6.10%	3599	6.27%	4671	6.96%	5725	7.81%	5572	7.69%
	60~69y.s	1148	4.88%	1223	4.65%	1871	6.38%	2363	7.58%	2455	8.03%
	70~74y.s	85	3.21%	60	2.12%	158	4.41%	264	6.50%	277	6.69%
Positive of HCV antibody		number	rate	number	rate	number	rate	number	rate	number	rate
		376	0.76%	227	0.48%	243	0.45%	418	0.71%	258	0.40%

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3319 | EXPLORING CAMPAIGN PREFERENCE STYLES AND TRUSTED INFORMATION SOURCES REGARDING HEPATITIS B AND HEPATOCELLULAR CARCINOMA AMONG ADULTS IN THE MIDWEST: A CROSS-SECTIONAL SURVEY WITH VISUAL AIDS

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Background: Effective health communication campaigns are essential for promoting public health messages, especially regarding hepatitis B(HBV)vaccination and hepatocellular carcinoma (HCC) prevention. This study aimed to investigate the differences in campaign preference styles and trusted sources of information between younger (age <40) and older (age ≥40) adults attending the Minnesota State Fair using visual aids. **Methods:** A cross-sectional structured survey was conducted among 481 adults attending the 2023 Minnesota State Fair. Participants were shown images of different HBV and HCC prevention campaigns from various organizations

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and asked to rank their preferences. Images were grouped as emotionally evocative and factually informative for analysis purposes. Tied cases were excluded, and differences among groups based on age were analyzed. Respondents were also asked about trusted sources of health information and self-reported aspects of campaign preferences they considered important. Chi-square test was used to compare differences between groups. **Results:** In the survey population, 48.4% of respondents were younger adults (age <40), and 51.6% were older adults (age ≥40). Females comprised 62.6% of the sample. When shown campaign images for HCC prevention, younger adults showed a trend towards preferring emotionally evocative campaign styles compared to older adults (55.0% vs. 45.0%, p=0.07). For HBV campaigns, older adults were more likely to prefer factually informative styles (59.4% vs. 40.6%, p=0.02). No significant differences in campaign preference were observed based on race, gender, metropolitan status, or being US/foreign-born. In self-reported preferences, younger adults reported that memorable or messages interpreted as “funny” were more important than older adults (50.6% vs. 37.9%, p=0.005). Both groups reported similar rates of importance for seeing facts and statistics (49.4% vs. 50.6%, p=0.48). Regarding trusted sources of information, both younger and older adults highly trusted their healthcare providers (96.1% vs. 92.7%, p=0.10). However, younger adults were more likely to trust family members (33.0% vs. 21.0%, p=0.003), community leaders (8.2% vs. 2.0%, p=0.002), and the Centers for Disease Control (CDC) (63.9% vs. 56.0%, p=0.07) compared to older adults. Social media was the least trusted source for both younger and older adults (5.2% vs. 3.2%, p=0.29). **Conclusion:** The findings of this study emphasize the importance of tailoring health communication campaigns to the preferences and trusted sources of different age groups. Trust levels were notably lower among older adults compared to younger adults. Public health organizations should consider these age-related differences when designing targeted health communication strategies to maximize engagement and impact.

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3320 | PREMATURE MORTALITY FOR THE SPECTRUM OF STEATOTIC LIVER DISEASE (SLD) IN THE US POPULATIONS

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Background: The new consensus nomenclature of SLD emphasizes presence of cardiometabolic risks (CMRs). Our aim was to assess the risk of mortality associated with the spectrum of SLD using population-based data. **Methods:** National Health and Nutrition Examination Survey (1988-1994 and 1999-2006) with linked mortality data were utilized. Premature mortality was defined as death occurring before age 80 years. Steatosis was defined as based on ultrasound and fatty liver index for the US population (US FLI). The spectrum of SLD and metabolic dysfunction (MetD) were classified according to the recent consensus. **Results:** 20,026 adults [N=12,214 (NHANES III) and N=7,812 (NHANES 1999-2006)] were included. Of these, 79.5% (NHANES III) and 86.0% (NHANES 1999-2006) were found to have at least one CMR. The prevalence of different subtypes of SLD is summarized in the Table. Subjects from NHANES III had a median follow-up of 23.1 years (257,210 person-years) with 2,875 premature deaths. The highest premature mortality rate (per 1,000 person-years) was observed in VH with MetD (28.94), followed by cryptogenic SLD with MetD (25.83), MetALD (31.24), ALD with MetD (13.12), and MASLD (12.53). In MASLD, premature death rates increased with the number of CMRs, ranging from 4.48 per 1,000 PY for one CMR to 24.04 per 1,000 PY for those with 5 CMRs (P<0.001 for trend). Subjects from NHANES 1999-2006 were followed for a median of 12.5 years (95,549 person-years) with 729 premature deaths. Again, the highest premature mortality rate (per 1,000 PYs) was observed in individuals with VH with MetD (25.99), followed by MetALD (23.47), ALD with MetD (16.35), MASLD (9.29), and cryptogenic SLD with MetD (9.28). Similarly, premature death rates increased with the number of CMRs, ranging from 6.02 for one CMR and 20.43 for 5 CMRs (P<0.001 for trend). **Conclusion:** Presence of MetD superimposed on various liver diseases increases mortality. Increasing number of CMRs is associated with the higher the risk of mortality.

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Table. Prevalence of Spectrum of Steatotic Liver Disease (SLD) in US populations

	NHNAES III	NHANES 1999-2006
MASLD	15.04%	25.80%
MetALD	0.34%	0.11%
ALD with MetD	1.93%	1.19%
Viral hepatitis with MetD	0.47%	0.99%
Cryptogenic SLD with MetD	0.28%	0.28%
Other CLD without MetD	4.53%	0.77%

Disclosures: James Paik: Nothing to Disclose, Zaid Younossi: Nothing to Disclose, Carey Escheik: Nothing to Disclose, Wisna'Odom Keo: Nothing to Disclose, Manirath Shirshord: Nothing to Disclose, Zobair Younossi: Nothing to Disclose

3321 | IMPROVEMENT IN TIME TO HEPATITIS C VIRUS TREATMENT IN NEW MEXICO STATE PRISONS, 2020-2023

Paulina Deming[1] Gaelyn Archer[1] Laura Tomedi[1] Karla Thornton[1]

[1]University of New Mexico

Background: New Mexico (NM) state prisons have one of the highest HCV rates and NM has the highest rate of chronic liver disease and cirrhosis in the United States. Delayed treatment for HCV can result in reduced quality of life, cirrhosis, liver cancer, and decreased life expectancy. Early detection and treatment halts disease progression and saves lives. ECHO (Extension for Community Healthcare Outcomes) began a collaboration with the NM Corrections Department (NMCD) in 2004 to establish an HCV treatment program using the ECHO model. In 2020, ECHO, NMCD, and NMCD's medical vendor Wexford Health Services (WHS) revised their HCV treatment guidelines to significantly increase the number of people receiving HCV treatment. **Methods:** The unit of analysis is the initial intake date of a patient. "Time to treatment" is the time in days from a patient's intake to the time that the patient first receives treatment for HCV. For patients with multiple intake or start of treatment dates, only the first date was used. Year was categorized based on the initial start of treatment date. Gender was categorized by patient's facility type (e.g., male or female facility). Cirrhosis status was determined by the ECHO team after reviewing transient elastography and/or baseline lab work. Kaplan-Meier curves were used to calculate the probability of treatment over time and were adjusted by age group, gender, and cirrhosis status. Log-rank tests were used to test for differences between the survival curves for each year. Cox proportional hazards regression was used to calculate the adjusted hazard ratio. **Results:** From 11/2020 to 12/2023, 1,233 patients received HCV treatment. In 2020, it took approximately 230 days to treat 50% of patients; treatment for 50% of patients took 50 days in 2023. Most patients who received treatment were aged 30-44 (60.10%), and male (92.05%). Overall, time to treatment was 67 times faster in 2023 compared to 2020 ($p < 0.001$) when adjusted by age group, gender, and cirrhosis status. **Conclusion:** Initially, HCV time to treatment in NMCD was slow, risking HCV transmission and worsening of liver disease in many HCV-infected people. NMCD, ECHO, and WHS met regularly to address issues and revise clinical guidelines. The collaborative effort and the ECHO model improved time to treatment for HCV patients. Expanding HCV treatment and improving time to treatment is critical in reducing the risk of HCV transmission and improving quality of life for patients.

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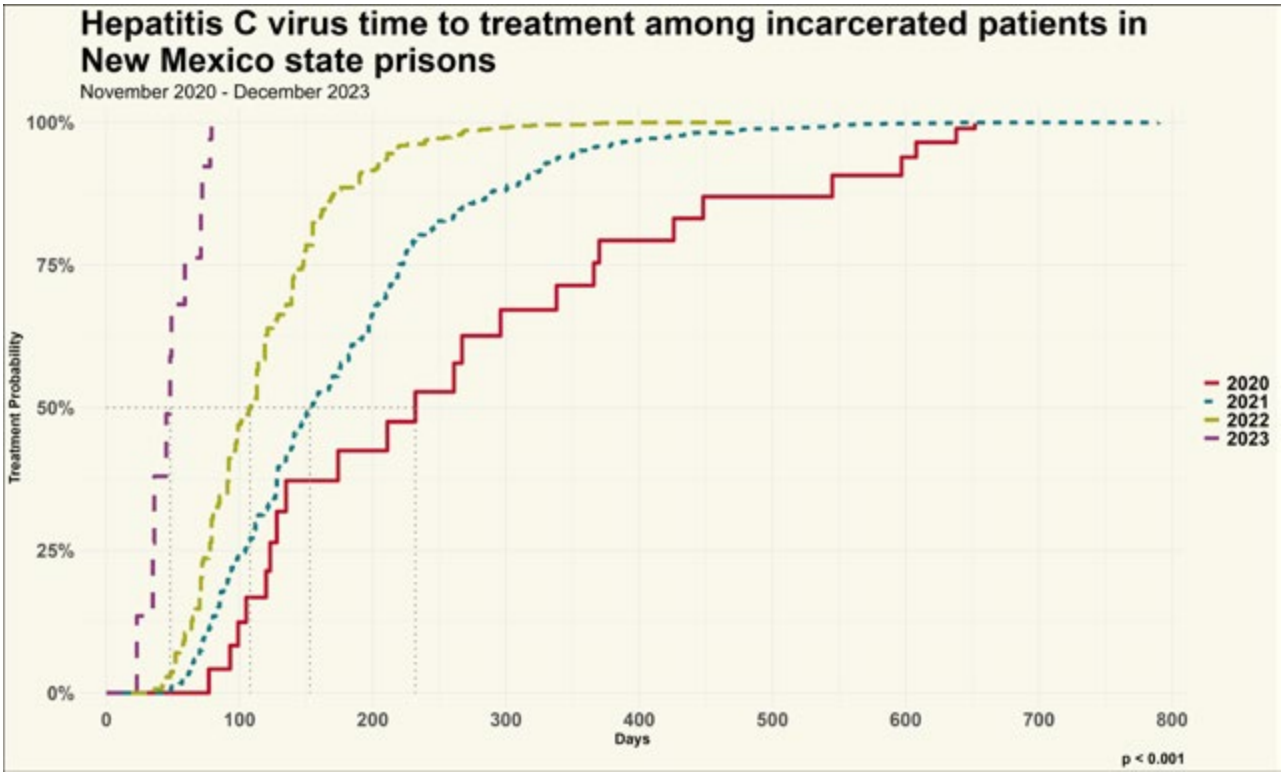

Disclosures: Paulina Deming: Nothing to Disclose, Gaelyn Archer: Nothing to Disclose, Laura Tomedi: Nothing to Disclose, Karla Thornton: Nothing to Disclose

3322 | IMPACT OF HOSPICE UTILIZATION IN ACUTE HOSPITAL CARE OF PATIENTS ADMITTED WITH DECOMPENSATED CIRRHOSIS AND HEPATOCELLULAR CARCINOMA – A SYSTEMATIC REVIEW AND META-ANALYSIS

Shahryar Khan[1] Ahmad Khan[2] Amina Arif[3] Muhammad Abu Bakkar[2] Aamer Ahmad[2] Mashal Alam Khan[2]

[1]University of Kansas Medical Center, [2]Khyber Medical University, [3]University of Nevada, Reno school of Medicine

Background: Patients with Decompensated Cirrhosis (DC) and Hepatocellular carcinoma (HCC) are associated with high symptom burden, poor quality of life, life threatening complications, and higher healthcare utilization. Palliative services and Hospice care guide patients to help them understand their healthcare goals and improve health related quality of life in advanced diseases such as DC and HCC. Our review aimed to assess the impact of palliative care services on resource utilization, and in-hospital treatments for patients hospitalized for HCC and DC**. Methods:** MEDLINE and Embase were searched to include studies which addressed the utilization of Palliative care services for adults with DC and HCC. The main outcomes measured were ICU admissions, Hospital admissions, In-hospital all-cause mortality, Healthcare resource utilization includes CPR, Intubation, Dialysis, and Endoscopy. We used a random effects model to calculate the Odds ratio (OR) and the corresponding 95% confidence intervals of our desired outcomes. A p value of < 0.05 was considered statistically significant. Heterogeneity was assessed using the I2 Index. (I2 values >50% implied the presence of significant heterogeneity). Qualities of studies were assessed using the ROBINS-1 tool. Data analysis was performed using the Revman software (version 5.4.1). **Results:** In our meta-analysis, 7 studies were included with a total population of 83220, of whom 25165 (30%) received Hospice care. Participants comprise an average age of 67.1 in Hospice care (HC) and 65.8 in Usual care (UC). Female comprised 33.8% in HC and 34% in UC. Compared to UC, HC is associated with lower rates of ICU admissions (OR 0.13, $I^2 = 90\%$, $P < 0.05$, Figure 1), In-Hospital all-cause mortality (OR 0.42, $I^2 = 100\%$, $P < 0.05$), Endoscopies (OR 0.81, $I^2 = 79\%$, $P < 0.05$), CPR (OR 0.34, $I^2 = 85\%$, $P < 0.05$), Mechanical ventilation (OR 0.18, $I^2 = 96\%$, $P < 0.05$), Dialysis (OR 0.79, $I^2 = 98\%$, $P < 0.05$). Hospice care was not associated with a lower admission rate (OR 0.50, $I^2 = 100\%$, $P=0.42$, Figure 2). **Conclusion:** Palliative care and Hospice services remain underutilized for patients with decompensated cirrhosis

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and hepatocellular carcinoma. The use of palliative care services was associated with reduced healthcare resource utilization.

Figure 1. ICU Admissions

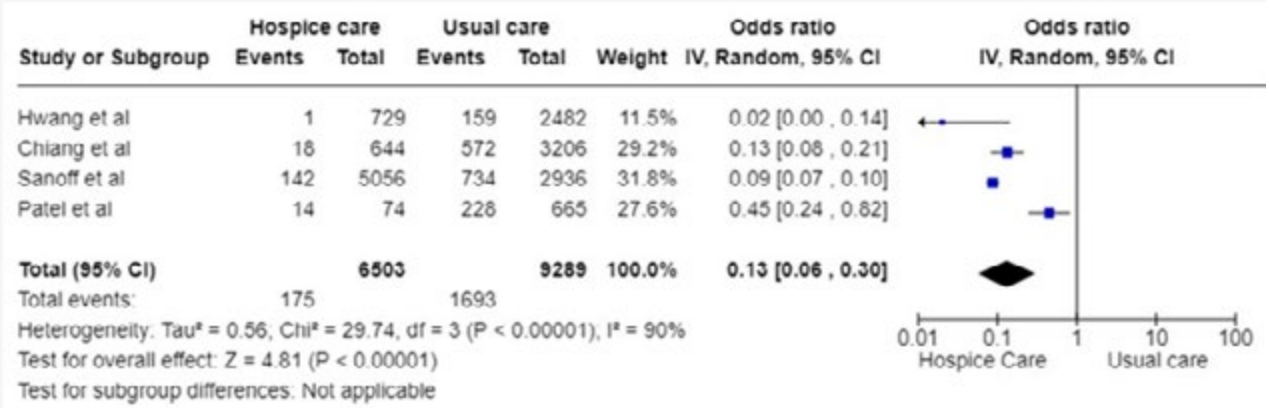
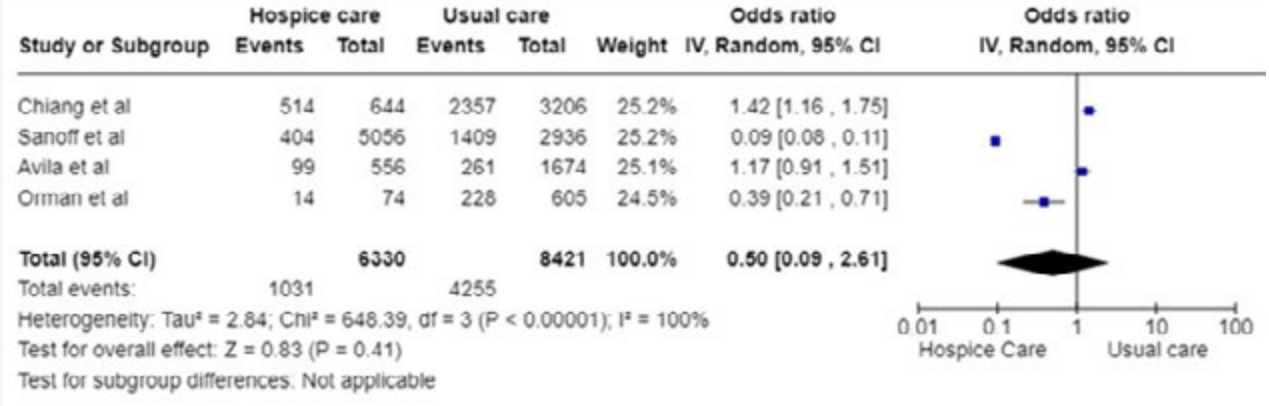


Figure 2. Hospital Admissions



Disclosures: Shahryar Khan: Nothing to Disclose, Ahmad Khan: Nothing to Disclose, Amina Arif: Nothing to Disclose, Muhammad Abu Bakkar: Nothing to Disclose, Aamer Ahmad: Nothing to Disclose, Mashal Alam Khan: Nothing to Disclose

3323 | NATIONAL HEPATITIS PROFILES: A GLOBAL HBV REPORT

Jana Manning[1] Lindsey Hiebert[2] John Ward[3]

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Background: To reach elimination goals for HBV incidence and related deaths, countries must develop strategic information, plans, and policies to prevent, detect, and treat HBV. To assess and compare national disease burden, policies, and service delivery, the Coalition for Global Hepatitis Elimination developed profiles for 33 countries from six WHO regions representing the majority of persons with HBV globally. **Methods:** Profiles were developed for countries with a large HBV burden and others on request. Data were collected by reviewing the scientific literature, government reports, and other sources (e.g. WHO). Local stakeholders from government, clinical practice, and civil society validated the collected data and provided additional data sources. **Results:** Of the 33 profiled countries (PC), 24 (73%) have HBV action plans with elimination goals.

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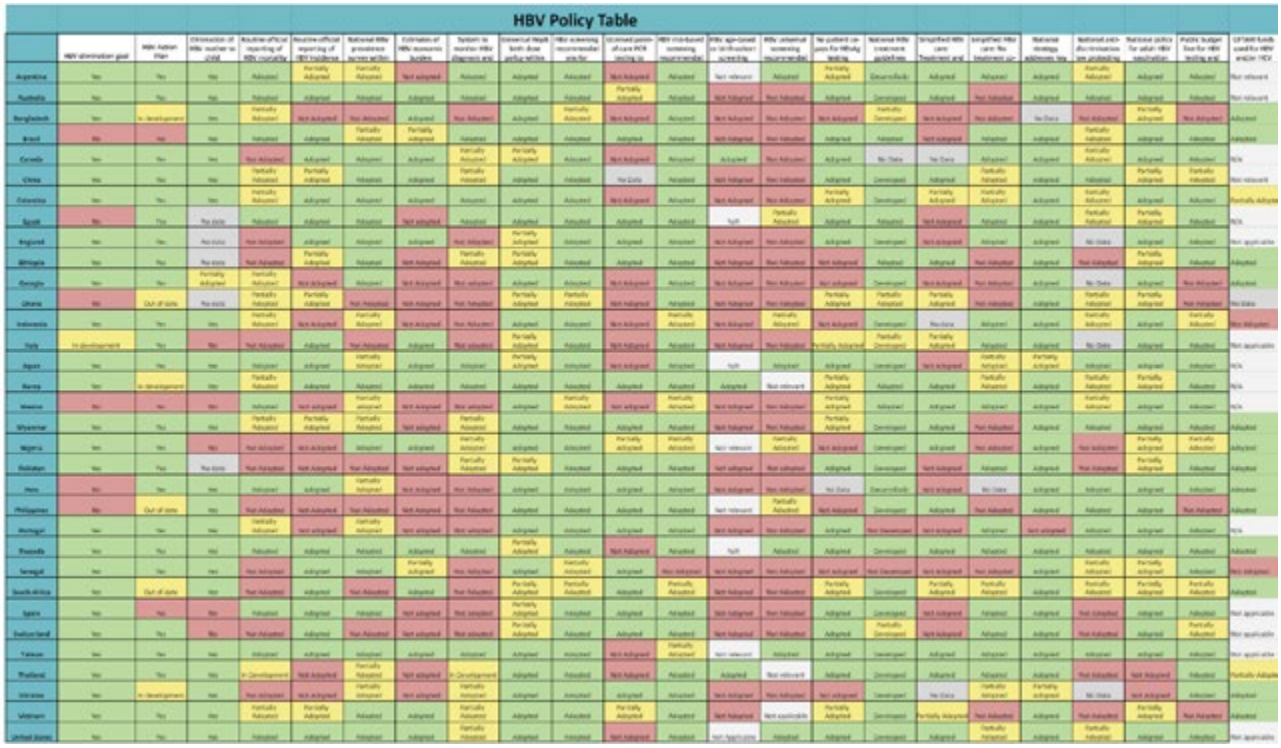
Strategic information systems: HBsAg prevalence ranged from 0.1% (Mexico) to 12.3% (Ghana), with 22 PCs (66%) meeting the WHO 2025 interim target of <0.5% for children under 5. However, few PCs routinely track and report HBV death rates (33%) or incidence (48%). Among the 16 PCs (48%) with data, HBsAg+ testing coverage ranged from <1% (Myanmar) to 82.9% (Republic of Korea), and appropriate treatment of diagnosed persons ranged from 0.25% (Georgia) to 80% (Argentina). Prevention of new infections: Most PCs have policies for HBV screening of pregnant women (85%) and for universal, HepB birth dose (BD) vaccination (67%). Most PC who have not reached interim WHO targets, have yet to implement HepB BD vaccination. A total of 22 (67%) PCs have prevention policies for persons who inject drugs, and 16 (48%) have decriminalized needle/syringe (N/S) possession. Of the PC 60% have policies for adult hepatitis B vaccination. Testing and treatment: Most PCs have adopted risk-based screening (80%) but only 4 of 13 PCs with >2% HBsAg prevalence have universal or age-based testing policies. Fifteen PCs (45%) cover all patient costs for HBsAg testing, and 9 (27%) do so for low-income populations. Licensure for point-of-care virologic tests is limited (45% of PC). While 26 (79%) PCs have local HBV treatment guidelines, only 39% have guidelines for primary care providers. For PCs, the proportion of people with HBV diagnosed ranges from 0.7% (Ghana) to 82.9% (Korea). The proportion of diagnosed HBV persons receiving appropriate treatment is 0.25% (Georgia) - 45.71% (Egypt). **Financing:** Although 70% of PCs have national budget lines for HBV testing and treatment, more PC funds are needed to scale up programs. **Conclusion:** Most PCs report good progress in preventing perinatal HBV transmission, but improvements are needed in certain African and Asian PCs. While many have action plans with testing and treatment policies, large-scale HBV testing policies are lacking, and treatment barriers remain. Increased global and national funding for research and programs to enhance vaccination, testing, and treatment is needed.



Disclosures: Jana Manning: Nothing to Disclose, Lindsey Hiebert: Nothing to Disclose, John Ward: Grant/ Research Support relationship with Dynavax, Merck, Cepheid,; Has not ended; Grant/Research Support relationship with Abb Vie, Abbott, Gilead, Siemens, Roche, Pharco, Virion,; Has not ended

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3324 | EVALUATING THE ROLE OF PALLIATIVE CARE IN HEPATOCELLULAR CARCINOMA USING THE NATIONAL INPATIENT SAMPLE: COST SAVINGS, REDUCED INTERVENTIONS, AND RACIAL DISPARITIES

Amir Sultan Seid[1] *Spencer Goble*[2] *Jose Debes*[1]

[1]*University of Minnesota,* [2]*Hennepin Healthcare*

Background: There is a lack of data on the use of palliative care related and its impact on those hospitalized with hepatocellular carcinoma (HCC). We conducted a large-scale nationwide analysis of United States (US) hospital data to quantify the potential cost savings, reductions in invasive interventions, and variations across socioeconomic groups that palliative care consultation could confer in this setting. **Methods:** We analyzed all hospitalizations of patients with HCC in the 2016-2019 National Inpatient Sample, the largest publicly available national sample of inpatient admissions in the US. Multivariable linear and logistic regressions were utilized to assess the relationship between palliative care encounters, demographic factors, invasive interventions and hospitalization cost controlling for confounding patient and hospital factors. The median income within a patient's ZIP code was used to determine the patient's income quartile based on United States national data. **Results:** There were a total of 217,060 admissions with HCC nationwide, of which 21,075 were terminal. Females accounted for 26.1% of admissions and mean age was 65 years (SD 11.3). Palliative care was utilized in 57.8% of terminal admissions and 13.8% of non-terminal admissions. Adjusted regression analysis showed palliative care was associated with $2,126 (CI 1270-2983, p<0.001) savings per admission for all hospitalized HCC patients and $8,556 (CI 4353-12758, p<0.001) cost savings per terminal admission. Palliative care encounter among terminal admissions was also associated with significantly lower mechanical ventilation, tracheostomy, blood transfusion, central line placement, and cardiopulmonary resuscitation(CPR). Compared to white patients, black patients had higher odds of CPR OR 2.57 (CI 1.83-3.61, p<0.001), mechanical ventilation OR 1.38 (CI 1.14-1.67, p=0.001), and dialysis OR 1.65 (CI 1.18-2.30, p= 0.003). Hispanic patients had significantly higher use of mechanical ventilation OR 1.31 (CI 1.06-1.61, p= 0.01) and RRT OR 1.62 (CI 1.16-2.26, p= 0.005) compared to white patients. When comparing outcome parameters across income quartiles, no significant differences were found for rates of palliative care encounter, CPR, and mechanical ventilation between higher and lower income groups. **Conclusion:** Palliative care consultations significantly decrease healthcare expenditures and intensity of interventions for both non-terminal and terminal hospitalizations in patients with HCC. Racial differences exist in terms of the intensity of care among terminal patients, indicating a potential domain for future interventions.

	Palliative care encounter	No palliative care encounter	Odds ratio (95% CI)	P-Value
DNR order	79.7%	47.8%	4.28 (3.71-4.94)	<0.001
Mechanical ventilation	26.8%	42.5%	0.50 (0.43-0.57)	<0.001
Tracheostomy	0.4%	1.1%	0.33 (0.15-0.72)	0.005
Upper GI endoscopy	5.1%	6.3%	0.80 (0.62-1.05)	0.105
Paracentesis	26.9%	22.3%	1.28 (1.11-1.48)	0.001
Enteral nutrition	2.1%	1.9%	1.10 (0.71-1.70)	0.682
Transfusion	14.7%	21.1%	0.64 (0.55-0.76)	<0.001
RRT	7.1%	8.4%	0.82 (0.65-1.04)	0.099
Central line	6.2%	11.1%	0.53 (0.42-0.66)	<0.001
CPR	2.8%	10.2%	0.26 (0.19-0.34)	<0.001

Table 1. Rates of interventions among patients with terminal HCC hospitalization. N=21075

Disclosures: Amir Sultan Seid: Nothing to Disclose, Spencer Goble: Nothing to Disclose, Jose Debes: Nothing to Disclose

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3325 | TITLE: IMPACT OF A SPECIALTY PHARMACY CLINIC ON THE MANAGEMENT AND OUTCOMES OF PATIENTS WITH CIRRHOSIS

Michael Jew[1] Seo Kim[1] Christina Villagran[2] Elaine Kim[2] Cynthia Hsu[1] Zachary Gitto[3] Heather Patton[4]

[1]UC San Diego, [2]VA San Diego Healthcare System, [3]UC San Diego Hospital Medicine, [4]VA San Diego Healthcare

Background: Patients with decompensated cirrhosis (DC) have substantial health care costs, morbidity, and mortality. Prevention of complications from DC reduces healthcare utilization and costs. The addition of clinical pharmacists to the management of other chronic conditions, such as chronic kidney disease, reduces cost of care while improving medication adherence and clinical outcomes. To our knowledge, specialty pharmacy clinic (SPC) implementation has not been studied in the care of patients with DC. Our aim is to evaluate the impact of SPC on healthcare utilization outcomes including number of hospitalizations and number of emergency department (ED) visits. **Methods:** Retrospective chart review was performed comparing the health outcomes of patients with DC 6 months prior to (control, T1) and 6 months after (intervention, T2) first specialty pharmacy clinic (SPC) visit. Indications for referral to SPC included initiation of pharmacotherapy for complications of cirrhosis and assistance with titration to therapeutic goals or switching medications. A clinical pharmacist followed protocols created for this clinic based on national guidelines. The medications managed included diuretics, antibiotics, beta-blockers, lactulose, acamprosate and naltrexone. Patients referred to SPC continued to receive routine care in hepatology clinic. Veterans were provided blood pressure monitors, digital scales, and paper logs for tracking vitals at home. **Results:** A total of 44 patients were seen in SPC from August 2021 to July 2023. Patient characteristics and results are shown in Table 1. Of the clinical outcomes evaluated, there was a significant decrease in active alcohol use, decrease in body weight, decreased number of large volume paracenteses performed, and an increase in serum creatinine. Overall, no decrease in the number of ED visits, number of admissions, total number of admission days, or change in MELD 3.0 score was observed. However, when comparing T1 and T2 by etiology of cirrhosis, there was a significant reduction in number of ED visits and total number of admission days for patients with alcohol-related cirrhosis. Furthermore, among patients referred for diuretic management or for multiple indications, there was a significant reduction in body weight suggesting improvement in volume overload. **Conclusion:** Patients with DC due to alcohol-associated liver disease had significant improvements in outcomes after SPC visits compared to other etiologies, including a reduction in the total number of hospitalization days and ED visits. The benefit in this population may be related to decreased alcohol use, potentially facilitated by pharmacotherapy to reduce craving. These findings may help guide resource allocation to provide multidisciplinary and higher value care for patients with decompensated cirrhosis.

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Table 1. Characteristics and Results of Patients Referred to Specialty Pharmacy Clinic

Category	Control (T1) (N=41)	Post-Intervention (T2) (N=41)	P-value
Median Age (years) (range)	70 (40-82)		N/A
Sex (male) (%)	38 (93%)		N/A
Race			
White (%)	34 (84%)		N/A
Asian and Native Hawaiian or Other Pacific Islander (%)	2 (4%)		N/A
Unknown (%)	5 (12%)		N/A
Etiology of Cirrhosis			
Alcohol-Associated Liver Disease (%)	18 (41%)		N/A
Metabolic Dysfunction-Associated Steatotic Liver Disease (%)	8 (18%)		N/A
Viral Hepatitis C (%)	3 (6%)		N/A
Viral Hepatitis B (%)	2 (5%)		N/A
Combination	13 (30%)		N/A
Indications for Referral to SPC			
Beta-Blocker Use	21 (48%)		N/A
Diuretic Use	8 (18%)		N/A
Lactulose Use	3 (7%)		N/A
Combination	12 (27%)		N/A
Number of Hepatology Clinic Visits (%)			0.051
0	2 (4.5%)	11 (25%)	
1	23 (52%)	17 (39%)	
2	13 (30%)	7 (16%)	
3	3 (6.8%)	5 (11%)	
4	1 (2.3%)	1 (2.3%)	
5	1 (2.3%)	3 (6.8%)	
6	1 (2.3%)	0 (0%)	
Number of Pharmacy Clinic Visits, Median (range)	N/A	3 (1-10)	N/A
Clinical Outcomes (Median (IQR))			
Weight (pounds	204 (171, 261)	194 (167, 237)	**0.008**
Active Alcohol Use (%)	23 (52%)	13 (30%)	**0.048**
MELD 3.0 score	14.0 (10.0, 17.8)	14.2 (5.5)	0.8
ALT Lab Value	30 (23, 47)	29 (19, 35)	0.083
AST Lab Value	41 (29, 70)	36 (25, 52)	0.12
Total Bilirubin Lab Value	1.40 (0.88, 1.95)	1.20 (0.83, 1.90)	0.5
ALP Lab Value	87 (69, 136)	89 (63, 124)	0.062
Creatinine Lab Value	0.99 (0.85, 1.26)	1.12 (0.82, 1.43)	**0.025**
INR Lab Value	1.20 (1.18, 1.40)	1.20 (1.10, 1.48)	0.5
Platelet Count Lab Value	114 (81, 157)	121 (85, 162)	0.7
Albumin Lab Value	3.35 (2.78, 3.90)	3.60 (3.03, 3.98)	0.2
Number of Large Volume Paracenteses			**0.034**
0	37 (84%)	42 (95%)	
1	7 (16%)	1 (2.3%)	
2	0 (0%)	1 (2.3%)	
Number of Emergency Department Visits (%)			0.3
0	17 (40%)	22 (51%)	
1	11 (26%)	12 (28%)	
2	8 (19%)	5 (12%)	
3+	7 (16.3%)	4 (9.2%)	
Number of Admissions			0.5
0	25 (57%)	27 (61%)	
1	10 (23%)	11 (25%)	
2	5 (11%)	4 (9.1%)	
3+	4 (9.1%)	2 (4.6%)	
Number of Total Admission Days, Median (IQR)	0.0 (0.0, 4.0)	0.0 (0.0, 3.0)	0.3
Death (%)	N/A	8 (20%)	N/A

Disclosures: Michael Jew: Nothing to Disclose, Seo Kim: Nothing to Disclose, Christina Villagran: Nothing to Disclose, Elaine Kim: Nothing to Disclose, Cynthia Hsu: Nothing to Disclose, Zachary Gitto: Nothing to Disclose, Heather Patton: Nothing to Disclose

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3326 | PRISMA (PATIENT RESONANCE INTELLIGENCE SUPPORTING MEDICAL ANALYSIS): AN AI ALGORITHM IN DE-CIPHERING LIFESTYLE FACTORS EFFECTS ON LIVER DISEASE

Mustafa Behan[1] Jutta Kurz[1] Victoria Aksakovska[1] Michael Tunkelrott[1] Fatma Barakat[2] Julian Diaz-Moreno[3] Emmanuel Gorospe[4] Tarek Hassanein[3]

[1]Amsety Gmbh, [2]SCTI Research Foundation, [3]Southern California Liver Centers, [4]Great Lakes Research Network

Background: Over 100 million Americans are affected by fatty liver. With diagnostic and treatment options being more available, we need to understand the impact of lifestyle factors on the development and progression of MASLD. **Objective**: Identify the key risk factors and their individual risk contribution to MASLD to improve selection for screening and targeting of lifestyle interventions. **Methods:** The Amsety database has over 600,000 subjects with chronic liver disease. 6022 subjects were included in the analysis based on evaluability of a complete set of data from a self-reported population diagnosed with MASLD. The analysis is based on the self-reported answers patients provided. We built groups based on different lifestyle/risk profiles and then understood the topology for the entire groups and subsets. We used Amsety's PRISMA AI-Model to understand the impact of life-style factors on Liver disease progression. The PRISMA Model understands connected correlations of data in multi-dimensional, non-linear spaces. As a practical outcome, we developed the PRISMA-Score for each single influence factor. Each influence factor comprised of 1) what is the negative impact if the respective influence factor is handled unfavorably (e.g. poor diet) and 2) what is the positive impact if the respective influence factor is handled favorably (e.g. good diet). The PRISMA-Score is normalized on a scale from 0 (low negative impact of the risk factor) to 100 (high negative impact of the risk factor). **Results:** We calculated the PRISMA-Score for 6 influence factors: Diet, Hydration, Sleep, Routine Health Services, Alcohol Intake, and Exercise; Looked at the topology of the surveyed respondents and analyzed risk factors age group (table). 96% manage alcohol intake well, specifically as they get older. Attention to diet was reported in only 32% of all respondents. Adequate sleep and routine health services were reported in 81% and 79% of respondents, respectively. However, sleep quality decreased with age, while compliance with medical care increased with age. The most populous groups share poor management of diet, poor sleep, and good/strong alcohol handling. Sleep disturbance has a double impact on liver health. **Conclusion:** In a self-reported database, involving over 6000 patients with MASLD, our AI-based analysis showed: Poor sleep habits is common among patients with MASLD. The key indicator for liver disease – and an early warning sign, is a disturbance in sleep quality, even above an unhealthy diet. Importantly, alcohol intake plays a role in liver disease but is less useable as an early indicator compared to sleep. The PRISMA-Score is a viable tool to understand topologies in larger patient populations. It can be applied to lifestyle factors as well as laboratory data to identify influence of single drivers.

Disclosures: Mustafa Behan: Amsety GmbH: Founder and Co-Owner, Jutta Kurz: Nothing to Disclose, Victoria Aksakovska: Amsety: Employee, Michael Tunkelrott: Nothing to Disclose, Fatma Barakat: Nothing to Disclose, Julian Diaz-Moreno: Nothing to Disclose, Emmanuel Gorospe: Nothing to Disclose, Tarek Hassanein: Nothing to Disclose

3327 | OPIOID USE AFTER ADULT LIVER TRANSPLANTATION: PREDICTING INCIDENCE, HIGH-RISK USE, AND OPIOID-RELATED COMPLICATIONS IN A NATIONAL COHORT

Olgert Bardhi[1] Yue Jiang[2] Alex Jones[1] Prajwal Gowda[1] Madhukar Patel[1] Parsia Vagefi[3] Steven Hanish[1] Van Ngo[1] Mary Olumesi[1] Jessica Francois Whitt[1] Raelene Trudeau[1] Arjmand Mufti[1] Lisa VanWagner[1] Amit Singal[1] Sarah Lieber[1]

[1]University of Texas Southwestern Medical Center, [2]Duke University, [3]UT Southwestern Medical Center

Background: Opioid use disorder significantly impacts morbidity and mortality. Liver transplant recipients (LTRs) are vulnerable due to pre-existing substance use, psychiatric conditions, and post-operative pain. Nationally, limited data exists on opioid use burden in LT. We describe prevalence and new opioid use, factors linked to high-risk use, and opioid-related complications among LTRs. **Methods:** We identified adult LTRs from 2006-2021 using IQVIA PharMetrics® Plus for Academics, a database representing commercially insured US individuals. Opioid use was assessed >30 days post-LT; high-risk use was defined as >50 morphine milligram equivalents per day or concurrent opioid-benzodiazepine (BZD) use. Chronic opioid use was defined as 10 opioid prescription refills,

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or at least 120-day supply dispensed during any 365-day period >30 days post-LT.Factors associated with high-risk use were analyzed using multivariable logistic regression. Landmark survival analysis with a multivariable proportional hazards regression model assessed opioid use 30-120 days post-LT and subsequent opioid-related complications (i.e., depression, anxiety, substance use disorder, chronic pain syndrome, altered mental status, or fractures/falls). We also compared opioid prescriptions between LTRs and kidney transplant recipients (KTRs). **Results:** Among 1,338 LTRs, 899 (67.2%) received opioid prescriptions >30 days post-LT, with 13.5% having high risk use and 41% incident use (Table 1). Incident opioid use >30 days post-LT was associated with higher pre-LT comorbidity (Charlson comorbidity index (CCI) >3) and psychiatric disorder. Chronic opioid use was associated with pre-LT psychiatric disorder and opioid use. High-risk use was associated with female sex, pre-LT CCI >3, opioid use, and psychiatric disorder. Similar associations were seen for incident high-risk use. LTRs had higher opioid use at 30-120 days post-LT (9%) vs. KTRs (3%) ($p<0.001$), with a higher incidence of high-risk use (67.1% vs. 38.4%). At 1 year, 70% of LTRs with opioid use developed new opioid-related complications versus 49% of non-opioid users ($p<0.001$). High-risk users had a 1.85 times higher risk of opioid-related complications at 120 days post-LT vs. non-users. **Conclusion:** Two-thirds of LTRs were prescribed opioids >30 days post-LT, with 14% identified as high-risk users. Opioid-related complications were prevalent, particularly among high-risk users. Opioid prescriptions should be avoided, especially high doses or in combination with BZDs among LTRs, particularly those with psychiatric comorbidities and pre-existing pain conditions.

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Table 1: Sociodemographic and Clinical Characteristics of Adult Liver Transplant Recipients Stratified by Opioid Use Post-LT* (N=1,338)

Variable	Total LT Recipients (N = 1,338)	Opioid Use >30 Days Post-LT (N = 899)		No Opioid Use >30 Days Post-LT (N = 439)	p Value
		High Risk* (n = 122)	Non-High Risk (n = 777)		
Age at Transplant	55 (49 – 60)	55 (49 – 60)	55 (49 – 59)	56 (48 – 60)	0.932
Male	905 (68%)	69 (57%)	533 (69%)	303 (69%)	**0.023**
U.S. Region^					
Northeast	269 (20%)	29 (24%)	163 (21%)	77 (18%)	0.079
Midwest	426 (32%)	35 (29%)	227 (29%)	164 (37%)	
South	301 (22%)	26 (21%)	188 (24%)	87 (20%)	
West	342 (26%)	32 (26%)	199 (26%)	111 (25%)	
Primary Insurance Type					
Commercial	1,054 (79%)	87 (71%)	618 (80%)	349 (79%)	**0.002**
Medicare	134 (10%)	23 (19%)	80 (10%)	31 (7%)	
Other	149 (11%)	12 (10%)	78 (10%)	59 (13%)	
Primary Enrollment Type					
HMO	329 (25%)	37 (30%)	190 (24%)	102 (23%)	**0.016**
PPO	852 (64%)	76 (62%)	507 (65%)	269 (61%)	
Other	153 (11%)	8 (7%)	78 (10%)	67 (15%)	
Follow-Up in Database Post-LT (insurance-covered months)	33 (19 – 56)	33 (21 – 48)	38 (21 – 71)	25 (17 – 47)	**<0.001**
Indication for LT					
Alcohol	191 (14%)	13 (11%)	108 (14%)	70 (16%)	0.078
MASLD	299 (22%)	29 (24%)	180 (23%)	90 (21%)	
Viral	358 (27%)	35 (29%)	225 (29%)	98 (22%)	
Other/Unknown	446 (33%)	38 (31%)	243 (31%)	165 (38%)	
SLK Transplant	92 (7%)	12 (10%)	57 (7%)	23 (5%)	0.141
LT Hospital LOS (Median Days)	10 (7 – 18)	10.5 (7 – 21.25)	10 (8 – 21)	9 (7 – 15)	**<0.001**
PRE-LT CHARACTERISTICS					
Pre-LT Modified CCI**					
<3	866 (65%)	72 (59%)	487 (63%)	307 (70%)	**0.015**
≥3	472 (35%)	50 (41%)	290 (37%)	132 (30%)	
Pre- LT HCC	477 (36%)	50 (41%)	273 (35%)	154 (35%)	0.435
Pre-LT Hepatic Encephalopathy	573 (43%)	42 (34%)	351 (45%)	180 (41%)	0.053
Pre-LT Psychiatric History					
Substance Use Disorder	681 (51%)	70 (57%)	406 (52%)	205 (47%)	0.057
Depression	246 (18%)	44 (36%)	138 (18%)	64 (15%)	**<0.001**
Anxiety	159 (12%)	31 (25%)	87 (11%)	41 (9%)	**<0.001**
Pain Disorder	77 (6%)	17 (14%)	53 (7%)	7 (2%)	**<0.001**
Pre-LT Opioid Use^	428 (32%)	66 (54%)	280 (36%)	82 (19%)	**<0.001**
POST-LT CHARACTERISTICS					
Opioid Use LT-30 Days Post-LT	714 (53%)	78 (64%)	445 (57%)	191 (44%)	**<0.001**
Incident Opioid Use‖	553 (41%)	56 (46%)	497 (64%)	-	**<0.001**
Concomitant Opioid-BDZ Use >30 days post-LT	369 (28%)	117 (96%)	187 (24%)	65 (15%)	**<0.001**
Chronic Opioid Use¶	210 (16%)	49 (40%)	161 (21%)	0 (0%)	**<0.001**
Pain Treatments > 30 Days Post-LT					
NSAIDs	114 (9%)	13 (11%)	69 (9%)	32 (7%)	0.401
Tricyclic Antidepressant	31 (2%)	4 (3%)	19 (2%)	8 (2%)	0.531
SSRI/SNRI	250 (19%)	38 (31%)	160 (21%)	52 (12%)	**<0.001**
Anticonvulsants	6 (0%)	1 (1%)	2 (0%)	3 (1%)	0.330
Interventional Pain Management	27 (2%)	3 (2%)	22 (3%)	2 (0%)	**0.007**
Opioid-Related Complications	848 (63%)	100 (82%)	531 (68%)	217 (49%)	**<0.001**

Abbreviations: ALD, alcoholic liver disease; BZD, benzodiazepine; LT, liver transplant; MME, morphine milligram equivalents; SLK, simultaneous liver kidney; CCI, Charlson comorbidity index; HCC, hepatocellular carcinoma; HE, hepatic encephalopathy; NSAID, non-steroidal anti-inflammatory drugs; SSRI/SNRI, serotonin-reuptake inhibitor/serotonin-norepinephrine reuptake inhibitor.

** Opioid use was assessed using outpatient claims for the entire population >30 days post-LT until end of follow-up in the database. High risk opioid use defined based on MME or concomitant opioid-benzodiazepine exposure between 30-120 days post-LT.*

*** Pre-LT conditions including a modified Charlson comorbidity index (CCI), psychiatric comorbidity, and substance use history evaluated 6 months prior through 30 days after transplant index date. Pre-LT psychiatric disorders included ICD/10 codes for depression, anxiety, pain disorder, and substance abuse.*

^ Pre-LT opioid use was evaluated 6 months prior through the day before index transplant to avoid capturing opioid use for transplant.

‖ Incident opioid use defined as no opioid claims 6 months pre-LT.

¶ Chronic opioid use defined as >10 opioid fills or >120 supplied days (or both) during any 365-day interval beyond 30 days post-LT.

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3328 | INADEQUATE VIRAL HEPATITIS IMMUNIZATION AND TESTING AMONGST VULNERABLE PATIENTS IN THE AMBULATORY SETTING

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Background: This study addresses the goal set by the WHO to eliminate viral hepatitis as a public health threat by 2030, emphasizing the need for continued efforts despite recent declines in hepatitis A and B infections in the United States. A key component of the elimination strategy is increased rates of testing and immunization against Hepatitis A (HAV) and Hepatitis B (HBV), both of which can have severe consequences, especially in vulnerable, vaccine-priority populations. **Methods:** This retrospective chart review was conducted at a tertiary care center in New York City. It included adult patients seen in the gastroenterology and transplant hepatology fellow trainee clinic from January 2021 to November 2023. Patients had to be seen at least once, with additional analysis performed on those with multiple visits. We defined vulnerable, vaccine-priority populations as those recommended by the CDC to receive vaccination. For HAV this includes the elderly, those with chronic liver disease (CLD), and those immunosuppressed. For HBV, this includes those with CLD, immunosuppression, on hemodialysis, with diabetes, with HIV, or with a history of IV drug use. Other groups recommended for HBV vaccination were not included, neither was this reflective of the 2022 CDC update for all adults to be immunized. **Results:** Of the 2845 patients included, 54% were vulnerable to HAV, but 58% were not tested for immunization status. Similarly, 13% were vulnerable to HBV and 27% were not tested. Of those with documented immunization, only 12% (13/106) of vulnerable HAV patients and 28% (13/47) of vulnerable HBV patients received vaccination. Among patients with multiple visits, 57% (398/696) of vulnerable HAV patients and 17% (27/158) of vulnerable HBV patients were not tested for immunization status. There were significant differences in testing status amongst vulnerable groups based on age, ethnicity, and insurance (Table 1). **Conclusion:** The study found significant gaps in testing and vaccination for hepatitis among vulnerable, vaccine-priority patients in a New York City tertiary care fellows clinic. Improving testing and vaccination strategies is crucial to eliminate viral hepatitis, especially among underserved populations. Future interventions should focus on increasing awareness among healthcare providers and patients to improve vaccination rates and work to eliminate barriers to compliance with interventions that will be required to reduce the burden of viral hepatitis.

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	Tested	Not Tested	Chi Square	p-value
HAV Vulnerable				
Sex				
Male	111	121	3.2928	0.06958
Female	187	277		
Age				
Age 19-64	75	14	69.695	<0.01
Age 65+	223	384		
Race				
Asian	3	3	1.7718	0.7776
Black	57	70		
Declined	23	33		
Other	180	255		
White	35	37		
Ethnicity				
Declined	13	22	3.3531	0.3403
Hispanic or Latino	217	303		
Not Hispanic or Latino	68	72		
Unknown	0	1		
Insurance				
Commercial	69	62	13.392	<0.01
Medicaid	106	118		
Medicare	123	218		
Not Vaccinated	26	13		
HBV Vulnerable				
Sex				
Male	68	13	0.020885	0.8851
Female	63	14		
Age				
Age 19-64	77	15	0.0090121	0.9244
Age 65+	54	12		
Race				
Asian	2	0	6.521	0.1635
Black	37	13		
Declined	11	0		
Other	68	13		
White	13	1		
Ethnicity				
Declined	8	0	6.6083	0.03673
Hispanic or Latino	86	13		
Not Hispanic or Latino	37	14		
Insurance				
Commercial	36	6	0.83283	0.6594
Medicaid	65	16		
Medicare	30	5		
Not Vaccinated	10	0		

Disclosures: Chip Bowman: Nothing to Disclose, Elizabeth Verna: Nothing to Disclose

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3329 | OPTIMAL TREATMENT DURATION OF RESMETIROM FOR METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE: A COST-EFFECTIVENESS ANALYSIS

Phuc Le[1] William Herman[2] Srinivasan Dasarathy[1] Wen Ye[3] Victoria Criswell[1] Nicole Welch[1] Michael Rothberg[1]

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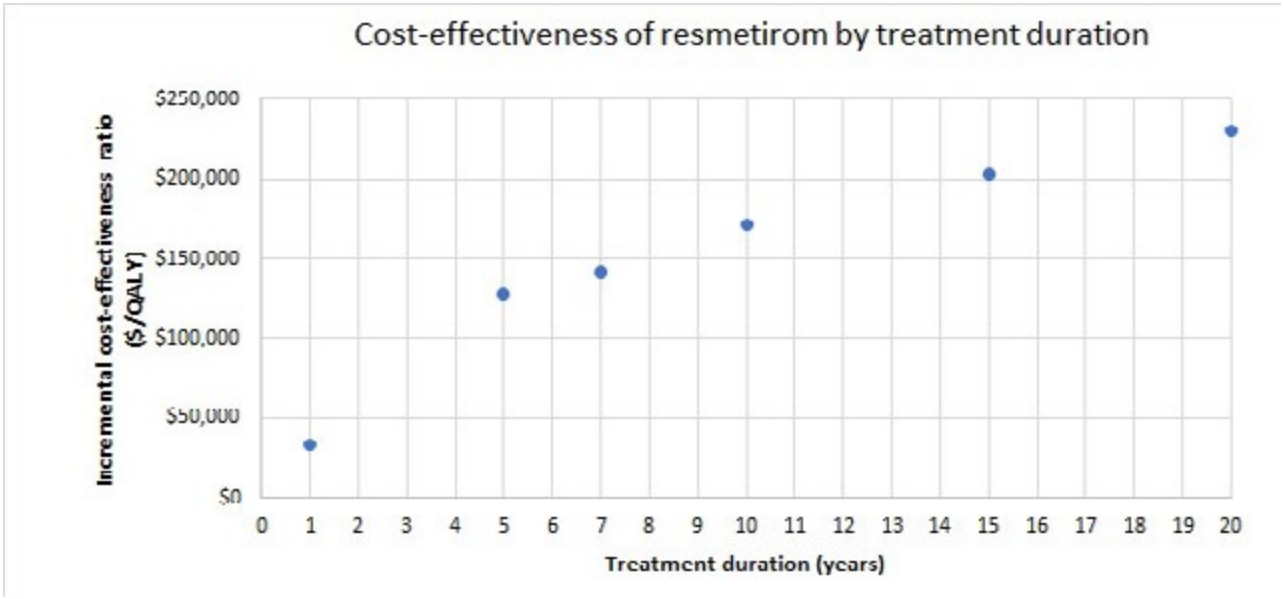
Background: With recent approval from the US Food and Drug Administration, resmetirom is the first pharmacotherapy for metabolic dysfunction-associated steatohepatitis (MASH) and significant fibrosis (F2-F3). However, the imperative for lifelong treatment raises significant economic considerations due to its potentially high price. Using cost-effectiveness analysis, we determined the optimal treatment duration for resmetirom. **Methods:** We developed an agent-based state transition model with 16 histologically defined health states including no steatosis, metabolic dysfunction-associated steatotic liver (MASL) or F0, MASH, fibrosis F1-F3 with or without MASH, cirrhosis (F4), decompensated cirrhosis, liver cancer, transplant, and liver-related and other-cause death. The model has yearly cycles and follows patients lifelong. We compared no treatment to treatment for different durations (from 1 year to lifetime). Patients discontinued treatment when entering F4 or more advanced liver disease. Treatment group had higher rates of fibrosis regression and MASH resolution and lower rates of fibrosis progression compared to no treatment. We derived model inputs from published data and used a drug price of $19,011/year in base-case. Outcomes included costs (in 2023$), quality-adjusted life years (QALYs), and incremental cost-effectiveness ratio (ICER) (incremental costs divided by incremental QALYs). We also estimated the maximum price corresponding to different treatment durations based on the $150,000/QALY threshold. We conducted analyses from the health system perspective and used a discount rate of 3% per year. **Results:** With lifetime treatment, resmetirom had a total cost of $283,280 and saved 0.8215 QALY/patient, resulting in an ICER of $286,441/QALY compared to no treatment. Treatment for shorter durations produced fewer QALYs overall but was also less expensive and more cost-effective (figure). At the base-case drug price, treatment was cost-effective at $150,000/QALY threshold only if used for 7 years or less. For treatment to be cost-effective for 20 years, the annual drug price could not exceed $13,774. **Conclusion:** Lifetime treatment with resmetirom was not cost-effective at a willingness-to-pay threshold of $150,000/QALY. At the current placeholder price, the optimal treatment duration was 7 years. Longer treatment duration would be cost-effective only if the price were lowered.



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3330 | CLINICAL OUTCOMES OF UTILIZING AN INTERACTIVE CARE PLAN (ICP) IN PATIENTS WITH CIRRHOSIS

Kathryn Schmidt[1] Jessica Grimm[1] Devin Copley[1] Daniel Penrice[1] Barbara Copeland[1] William Harmsen[1] Rachel Gullerud[1] Winnie Fan[1] Jordan Coffey[1] Julianne Lunde[1] Sarah Harper[1] Hugo Vargas[2] Blanca Lizaola-Mayo[2] Douglas Simonetto[1]

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Background: Patients with cirrhosis face an increased risk of disease-related symptoms and complications, leading to reduced quality of life. To address this challenge, an interactive care plan (ICP) was developed and implemented, leveraging a smartphone-enabled self-care application with an emphasis on education and symptom-based management. **Methods:** A longitudinal virtual self-care program was developed by a multidisciplinary team of hepatologists, specialty nurses, data scientists and developers from Mayo Clinic Rochester and Arizona, and the Center for Digital Health Care Anyplace team. Patients 18 or older receiving longitudinal care for cirrhosis at Mayo Clinic Rochester or Arizona were eligible for enrollment. The ICP program delivered symptom-based questionnaires, and self-management education through patients' Mayo Clinic app on their personal smartdevices. Data were abstracted from the ICP dashboard and EMR over the enrollment period. **Results:** 96 patients with cirrhosis were enrolled in the program between February 2021 and August 2022 in Minnesota and Arizona. The median age of participants was 62.5 years, and 63.5% were female. Alcohol-associated liver disease and metabolic dysfunction-associated liver disease accounted for 37.5% and 38.5% of cases, respectively. The median duration in the program was 372 days (IQR 159-431 days). Nearly a third of patients reported significant cirrhosis-related symptoms requiring escalation to the nurse care team while in the program. The most common symptoms prompting escalation were peripheral edema and abdominal distention (16.7%). Among patients with compensated cirrhosis, overall symptoms reported included fluid overload (24.5%), melena (1.9%), and confusion (5.7%). Patients with decompensated cirrhosis experienced greater symptom burden with fluid overload (37.2%), melena (2.3%) and confusion (6.9%). Three patients reported active alcohol consumption, and one patient sought assistance to quit drinking. Medication concerns and poor adherence to low sodium diet were reported by 31 (32%) patients throughout the program. A total of 36 emergency department visits were reported resulting in 14 hospital admissions. Time to first ED visit from ICP enrollment was 152 days. **Conclusion:** The cirrhosis ICP is a unique, longitudinal outpatient program that allows for proactive monitoring of cirrhosis-related symptoms, compliance issues and for delivery of education content. In future studies, the potential impact of interactive self-care plans on quality of life and cirrhosis-related outcomes should be explored.

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3331 | PREVALENCE OF COMPENSATED ADVANCED CHRONIC LIVER DISEASE (CACLD) IN THE UNITED STATES: INSIGHTS FROM NHANES 2017-2020

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Background: Compensated Advanced Chronic Liver disease (cACLD) is described in the Baveno VI consensus which defines it as a continuum of severe fibrosis and cirrhosis as these patients are clinically inseparable. People without cACLD have <1% three-year risk of decompensation and liver-related deaths while patients with cACLD should undergo further workup. There is a paucity of epidemiological literature on cACLD, hence we aim to calculate the prevalence of cACLD in the United States (US) and describe demographic and clinical comorbidities in these patients. **Methods:** We identified adults with complete transient elastography (TE) examinations using the National Health and Nutrition Examination Survey (NHANES) data set from 2017 to March 2020. We used Baveno VII's recommended Liver Stiffness Measure (LSM) cut-offs of 10kPa and 15kPa to rule out and rule in cACLD respectively and LSM 10-15kPa was considered as possible cACLD. We accounted for NHANES' complex sampling design by using recommended sample weights in our analysis. For categorical variables, the chi-square test was used, and for continuous variables, the ANOVA test. **Results:** Of the 15,560 participants in the NHANES during the 2017– March 2020 cycle, 8318 adult participants had completed a TE, of which 222 had cACLD, and 312 had possible cACLD. In our analysis, the weighted prevalence estimate of cACLD among US adults was 2.40% (CI, 1.76-3.03%) and that of possible cACLD was 3.46% (CI, 2.62-4.3%). Of the possible cACLD and cACLD patients, 86.54% (77.69%-95.39%) and 86.66% (80.09-93.23%), respectively, did not know they had liver disease. Amongst cACLD patients, 65.87 % (CI, 56.03-75.71%) were males, 40.84% (CI, 32.59-49.10%) were diabetic, 81.55% (CI, 73.38-87.64) were obese and 67.15% (CI, 57.58-76.73%) had hypertension. In cACLD patients, the prevalence of metabolic dysfunction-associated steatotic liver disease (MASLD), excessive alcohol use, hepatitis C, and hepatitis B was 79.72% (CI, 73.14-86.29%), 43.42% (CI, 30.44-56.40%), 7.11% (CI, 3.77-10.45%) and 2.86% (0.19-30.71%) respectively. **Conclusion:** Around 8 million people in the US are affected by cACLD in addition to the 11.5 million people who have possible cACLD. A majority of cACLD patients tend to be male, diabetic, hypertensive, and obese. More than 80% of individuals are unaware of their liver disease which can be attributed to the indolent nature of compensated liver disease. Improved screening, surveillance, and referral of these patients are required to enhance early detection, prevent decompensation events, and improve overall liver-related outcomes.

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Participant Factors	LSM<10kPa (No cACLD) Prevalence%(CI)	LSM = 10-15kPa (Possible cACLD) Prevalence%(CI)	LSM>15kPa (cACLD) Prevalence%(CI)	p-value
Weighted Prevalence	94.15% (92.81%-95.48%)	3.46% (2.62%-4.3%)	2.4% (1.76%-3.03%)	
Mean Age (years)	46.93	52.84	52.03	<0.001
Males	48.60%(46.92-50.29)	57.89%(47.83-67.94)	65.87%(56.03-75.71)	<0.05
Race				0.23
White	62.25%(57.76-66.74)	67.51%(56.51-78.50)	65.57%(53.34-77.81)	
Black	11.31%(8.61-14.02)	9.88%(5.21-14.55)	9.73%(5.08-14.38)	
Asian	5.97%(4.16-7.77)	3.50%(1.20-5.81)	3.90%(1.41-6.39)	
Mexican American	8.69%(6.31-11.07)	9.12%(5.14-13.09)	7.56%(4.35-10.78)	
Other Hispanic	7.72%(6.31-9.14)	7.25%(3.26-11.24)	5.55%(2.99-8.12)	
Multiracial	4.06%(3.35-4.78)	2.75%(0.18-5.31)	7.68%(1.25-14.11)	
Have been told that they have liver disease	4.05%(3.22-4.87)	13.46%(4.61-22.31)	13.34%(6.77-19.91)	<0.001
Mean BMI (SE)	29.02 (0.17)	37.78 (0.79)	40.07 (0.92)	<0.001
BMI Categories				<0.001
BMI<18.5	1.61%(1.18-2.19)	0.90%(0.18-4.38)	0.25% (0.03-1.93)	
BMI 18.5-24.9	29.32%(25.4-29.32)	4.53%(1.97-10.09)	5.83%(3.01-10.98)	
BMI 25-29.99	32.59%(30.94-34.28)	15.75% (10.6-22.75)	12.37%(7.88 - 18.9)	
BMI > 30	38.48%(35.87-41.16)	78.82%(68.28-86.55)	81.55% (73.38-87.64)	
Current Smoker	40.65%(37.02-44.28)	31.57%(22.14-40.99)	28.19%(18.48-37.89)	<0.05
Diabetes Mellitus	13.01% (12.02-14.00)	37.06%(27.35-46.77)	40.84%(32.59-49.10)	<0.001
Hypertension	44.71%(42.06-47.36)	71.04%(62.66-79.42)	67.15%(57.58-76.73)	<0.001
MASLD	32.02%(29.79-34.24)	73.60%(66.89-80.32)	79.72%(73.14-86.29)	<0.001
Excess Alcohol Intake	50.72%(47.87-53.56)	59.05%(46.20-71.90)	43.42%(30.44-56.40)	0.26
Hep B positive	5.6%(3.89 - 8)	3.7%(0.45 - 24.58)	2.86%(0.19 - 30.71)	0.69
Hep C positive	1.77%(0.96-2.58)	7.81%(0.33-15.29)	7.11%(3.77-10.45)	<0.001

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3332 | ASSESSING LIVER BIOPSY METHODS COMPARING ADEQUACY AND SAFETY. A REAL-WORLD SINGLE-CENTER EXPERIENCE

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Background: Liver biopsy (LBx) remains the gold standard in assessing histology along the spectrum of liver disease, from acute injury of unclear etiology to chronic liver diseases and post-transplant tissue assessment. In recent years, endoscopic ultrasound guided (EUS) liver biopsy has emerged as an alternative to percutaneous and transvenous biopsy approaches but is not yet established in society guidelines as a standard method for tissue acquisition. There is limited data and experience comparing the three different LBx approaches for sample adequacy and procedure safety. **Methods:** A retrospective review of all LBx performed at a tertiary care center between January 2021 and April 2024 was performed. Cases were randomly selected and matched in number, and categorized by biopsy approach, into percutaneous LBx (PCLBx), transvenous LBx (TVLBx) and EUS LBx (ELBx). The primary objective was to compare the tissue adequacy for interpretation, defined as LBx adequate for

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evaluation by the pathologist by sufficient number of portal tracts regardless of sample size. Secondary objectives included complication rates post LBx. Electronic medical records were reviewed to assess complications including abdominal pain, intra-abdominal bleeding, hospitalization, and mortality within 7 days post LBx. Chi square statistical analysis was performed using Excel. **Results:** A total of 216 LBx done at our tertiary care center were randomly selected. The mean age of patients was 58.9 years with 56.5% being female. Indications for LBx included abnormal liver function tests (59.3%), suspected steatotic liver disease (15.7%), abnormal imaging (12.5%), concern for cirrhosis (8.8%), and heart related liver disease (3.7%). LBx for heart related liver disease were exclusively performed via TVLBx route, while all other indications were similarly distributed among the three approaches. The tissue inadequacy rates were 5.6%, 5.6% and 13.9% for TCBLx, TVBLx, and ELBx, respectively, without a statistically significant difference (P value 0.11). Follow up admission or phone calls occurred in 5.1% of cases with reasons including abdominal pain in seven cases, bleeding in three, bruising in two and confusion in one case. Follow up imaging occurred in 7.9% of cases with confirmed bleeding in 1.9% and mortality in 1.9%, with no significant difference observed among the three approaches (Table 1). **Conclusion:** LBx remains a valuable tool in assessing liver disease with any of the three approaches available to obtain tissue. Despite the difference in gauge size, all three modalities have similar success rates with good tissue acquisition and safety profile.

	Total (216)	PCLBx (72)	TVLBx (72)	ELBx (72)	P-Value
Device Gauge	-	16G	18G	19G, 20G, 22G	-
Median # passes	-	1	3	1.5	-
Tissue inadequacy	18/216 (8.3%)	4/72 (5.6%)	4/72 (5.6%)	10/72 (13.9%)	0.11
Tissue fragmentation	84/216 (38.9%)	22/72 (30.6%)	28/72 (38.9%)	34/72 (47%)	0.12
Follow up admission or phone calls	11 (5.1%)	2 (2.8%)	5 (6.9%)	4 (5.6%)	0.92
Abdominal imaging	17 (7.9%)	5 (6.9%)	7 (9.7%)	5 (6.9%)	0.77
Bleeding	4 (1.9%)	2 (2.8%)	0	2 (2.8%)	0.36
Mortality	4 (1.9%)	0	2 (2.8%)	2 (2.8%)	0.70

Table 1: Sample Adequacy and Complication Rates Following Liver Biopsy
PCLBx: percutaneous liver biopsy, TVLBx: transvenous liver biopsy, ELBx: endoscopic ultrasound guided liver biopsy

Disclosures: Divya Devabhaktuni: Nothing to Disclose, Juan Gonzalez: Nothing to Disclose, Katarina Pittman: Nothing to Disclose, Hannah Zuercher: Nothing to Disclose, Anand Gupte: Nothing to Disclose, Consuelo Soldevila-Pico: Nothing to Disclose, Media Ismael: Nothing to Disclose

3333 | HEPATITIS DELTA TESTING AND POSITIVITY RATES ARE INCREASED IN MORE HIGHLY RESOURCED COMMUNITIES IN A LARGE, URBAN COHORT: AN ANALYSIS OF THE INSIGHT PCORNET DATABASE IN NEW YORK CITY ◆

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Background: Hepatitis delta virus (HDV) is the most severe form of viral hepatitis and is associated with rapid progression to advanced liver disease. New York City (NYC) is a US hotspot for HDV, possibly due to its high immigration rate from hepatitis B virus (HBV)- and HDV-endemic countries. We evaluated the impact of neighborhood resource scarcity on HDV testing and positivity in a large NYC cohort. **Methods:** Data were derived from the INSIGHT database, a robust PCORnet research network containing EHR data from five NYC academic health centers. All patients with hepatitis B surface antigen (HBsAg) positivity and/or an HBV diagnosis code were identified. Rates of HDV testing (defined as the presence of an HDV Ab, RNA, and/or Ag laboratory test in the EHR) and HDV positivity (defined as an HDV Ab, RNA, and/or Ag laboratory test with a "positive" or "reactive" qualitative result; HDV Ab >0 IU/mL; HDV RNA ≥20 IU/mL; or HDV Ag >0 IU/mL) were determined. Mean community deprivation index (CDI), a marker of neighborhood resources based on American Community Survey data, was calculated stratified by HDV testing and positivity status. CDI ranges from 0 to 1, with higher

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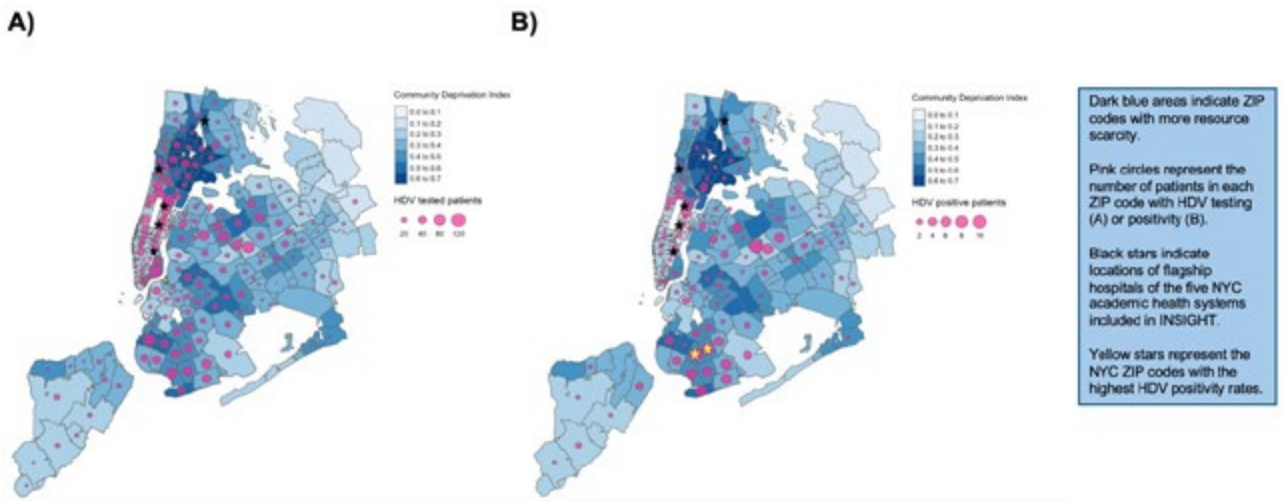
values indicating more resource scarcity. **Results:** A total of 106,210 patients with HBV were identified, among whom 5,388 (5%) received HDV testing; 294 (6%) were HDV positive. Those with HDV testing were a median age of 44; 58% male, 42% Asian, 29% white, 28% Black, and 10% Hispanic. Mean CDI for patients with HDV testing was lower than for those without (0.39 vs. 0.46, p<0.01), indicating less resource scarcity among those tested. Individuals with HDV testing were more likely to have a CDI below the 2018 mean NYC and US CDI compared to those without (p<0.01). HDV positive patients were a median age of 47; 34% male, 33% Asian, 47% white, 20% Black, and 5% Hispanic. Mean CDI for patients with HDV was lower than for those without (0.37 vs. 0.39, p=0.04), demonstrating less resource deprivation among HDV positive individuals. Patients with HDV were more likely to have a CDI below the 2018 mean NYC CDI compared to those without (p<0.01). HDV testing occurred more often in patients living near flagship hospitals; the two residential ZIP codes with the highest HDV positivity rates were both in Brooklyn (Figure 1). **Conclusion:** In a NYC cohort, only 5% of patients with HBV received HDV testing; 6% were HDV positive. Residence in higher resource areas was associated with higher likelihood of HDV testing and positivity. HDV tested patients appeared to live near NYC academic health systems. HDV positive patients primarily lived in Brooklyn, as has been shown in other studies. Efforts to increase HDV testing in communities with lower resources and decreased healthcare access will be essential to improve HDV screening rates.

Figure 1. CDI and NYC ZIP code-level rates of A) HDV testing and B) HDV positivity



Disclosures: Lauren Alpert: Nothing to Disclose, Xiaotao Zhang: Nothing to Disclose, Rachel Smith: Nothing to Disclose, Tatyana Kushner: Advisor relationship with Gilead; Has ended; Advisor relationship with GSK; Has ended; Advisor relationship with Eiger; Has ended; Grant/Research Support relationship with Gilead; Has not ended

3334 | EMERGENCY DIAGNOSIS OF HEPATOCELLULAR CARCINOMA IN SEER-MEDICARE BENEFICIARIES: DISPARITIES AND UNDERTREATMENT

Ellen Green[1] Andrew Moon[1] Sara Lyon[2] Gabriel Lupu[1] Yuelin He[2] Sharon Peacock Hinton[3] Caroline Thompson[3]

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Background: While ideally screened and diagnosed in outpatient settings, patients at-risk of hepatocellular carcinoma (HCC) may receive diagnosis through emergency department presentation (EP). In a recent safety-net hospital study, 32% of HCC cases were diagnosed by EP and were more often male, Black/Hispanic, of lower socioeconomic status (SES), and presented with advanced stage disease. However, population-based evidence on emergency diagnosis of HCC and its impact on treatment cascades is needed. **Methods:** We analyzed SEER-Medicare (2008-2017) patients with non-metastatic HCC, 66+ years old, alive at diagnosis, and enrolled in Medicare 1 year prior to diagnosis. Patients were EPs if they had ED contact within 30-days of their first cancer-related claim, subclassified by subsequent inpatient admission (EP-IP) or outpatient medical visit (EP-OP). Risk

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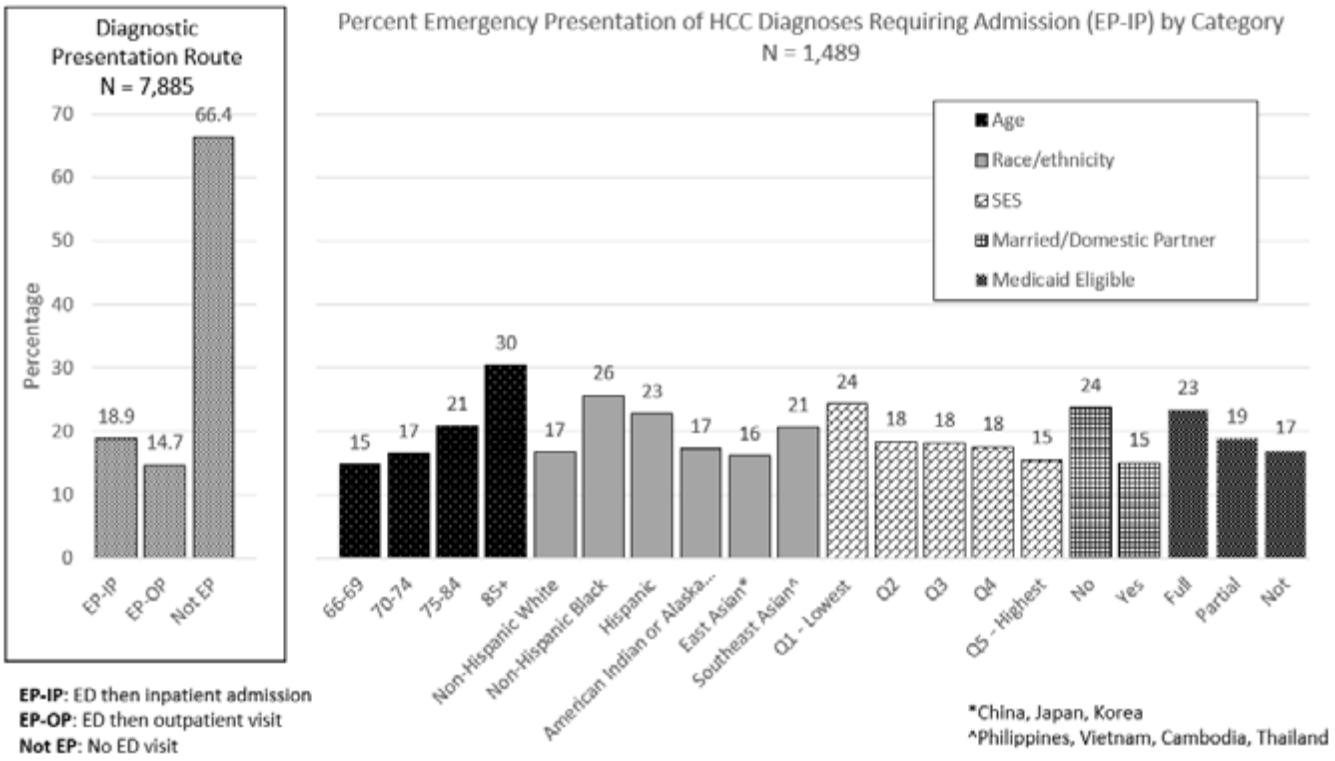
of no cancer-directed treatment (surgery, systemic, or radiotherapy) was estimated using regression models and inverse probability weights (IPWs) to account for non-treatment due to death within 90-days. **Results:** Among 7,885 Medicare beneficiaries with non-metastatic HCC, 18.9% were diagnosed as EP-IPs, 14.7% as EP-OPs, and 66.4% via traditional pathways. EP-IP was higher for patients who were older (30% for 85+ v.15% for 66-69), female (20% v.18% male), non-Hispanic Black (26%), Hispanic (23%), SE Asian (21%) v. non-Hispanic whites (17%) or East Asian (16%), living in metropolitan counties (19% v.17% non-metro), living in the lowest quintile neighborhood SES (24% v.15% in the highest), unmarried (24% vs.15% married), or Medicaid eligible (23% v. 17% non-eligible). EP-OP was more common in rural patients (28% v.14% metro), but racial and SES differences were less pronounced. Compared to non-EPs, risk ratios for no treatment were 2.2 (95% CI 2.0-2.3) for EP-IP and 1.6 (95% CI 1.5-1.7) for EP-OP, and essentially unchanged when analysis restricted to those who survived >90 days with IPWs. **Conclusion:** Optimal HCC outcomes depend on diagnosis in routine settings to facilitate care coordination. Patients with HCC who receive their diagnosis via EP are at 1.5-to-2-fold higher risk of receiving no cancer directed treatment, even after adjustment and accounting for non-treatment due to early death. This underscores the importance of understanding patient populations who preferentially access medical care through emergency departments and novel pathways to better integrate recipients of EP HCC diagnoses into standard, evidence-based oncologic management.



Disclosures: Ellen Green: Nothing to Disclose, Andrew Moon: TARGET RWE: Consultant, DCN Diagnostics: Grant/Research Support, Intercept Pharmaceuticals: Consultant, Intercept Pharmaceuticals: DSMB, IDEOlogy: Consultant, Sara Lyon: Nothing to Disclose, Gabriel Lupu: Nothing to Disclose, Yuelin He: Nothing to Disclose, Sharon Peacock Hinton: Nothing to Disclose, Caroline Thompson: Nothing to Disclose

3335 | CREATININE KINASE MEASUREMENT AND GASTROENTEROLOGY CONSULTATIONS IN PATIENTS ON STATINS WITH ELEVATED TRANSAMINASES

Faris Shweikeh[1] Rajshri Joshi[1] Margaret McGuigan[2] Anjali Nidhaan[3] Amandeep Singh[4]

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Background: Some of the most commonly reported side effects of statin drugs are muscle injury and hepatic dysfunction. Transaminases (ALT and AST) are makers of liver injury and creatine kinase (CK) level in the blood

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assesses statin-induced myopathy. In addition, apart from the liver, skeletal muscles also produce transaminases. It is important to diagnose these statin induced pathologies at an early stage in order to prevent further worse complications. We explored how frequently clinicians check CK in patients with elevated transaminases to look for muscle injury as well as the frequency of gastroenterology consultations. **Methods:** This was a retrospective chart review conducted in the various outpatient departments of Cleveland Clinic Foundation in Ohio and Florida over a 5-year period, from May 2017 to May 2022. We randomly selected 731 patients taking statins and diagnosed with elevated transaminases via ICD-10 codes. Then, we reviewed the records to ascertain if the subjects had a CK level checked within 1 month of diagnosis of elevated transaminases. Records were also reviewed for patients who did not have their CK level measured within 1 month of the diagnosis but had a gastroenterology consult placed within 2 months of the diagnosis. We labeled transaminases and CK as elevated when they were flagged high per the laboratory cut off values. **Results:** Among 731 patients, only 169 (23%) had their CK level measured within one month of diagnosis of elevated transaminases. Of these 169 subjects, 26 patients, or 15%, had an elevated CK level. Hence, 3.5 % of the total study population had elevated CK levels. The other 562 patients (77%) did not have their CK checked. Of these patients, 20 patients, or 3.5 % had a gastroenterology consult placed within 2 months of diagnosis for further liver status workup. **Conclusion:** We found that at our institution, the majority of patients on statins with elevated transaminase levels did not have their CK checked in a timely fashion. Finding an elevated CK may prevent further unnecessary testing of liver status, reduce healthcare costs and allow for earlier treatment of statin-induced muscle damage. Efforts to train physicians to appropriately check biomarker enzymes of injury in patients on statins should be undertaken.

Disclosures: Faris Shweikeh: Nothing to Disclose, Rajshri Joshi: Nothing to Disclose, Margaret McGuigan: Nothing to Disclose, Anjali Nidhaan: Nothing to Disclose, Amandeep Singh: Nothing to Disclose

3336 | NATIONAL HEPATITIS PROFILES: A GLOBAL HCV REPORT

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Background: To reach elimination goals for HCV incidence and related deaths, countries must develop strategic information, plans, and policies to prevent, detect, and treat HCV. To assess and compare national disease burden, policies, and service delivery, the Coalition for Global Hepatitis Elimination developed profiles for 33 countries from six WHO regions representing the majority of persons with HCV globally. **Methods:** Profiles were developed for countries with large HCV burden and others on request. Data were collected through a review of the scientific literature, government reports, and other sources (e.g. WHO). Local stakeholders from government, clinical practice, and civil society validated collected data and provided additional data sources. **Results:** Of the 33 profiled countries (PC), 29 (88%) have HCV action plans with elimination goals. Two PC are developing action plans. **Strategic information (SI)** Only 7 (21%) profile countries (PC) reported HCV incidence rates. Death rates (DR) varied from 0.22/ 100,00 (Argentina) to 15.1/100,000 (Chinese Taipei). HCV DR declined in the 8 high income PCs versus only 3 of 25 low- middle income PCs. DR in 10 PCs appear to meet WHO 2025 interim target (< 3/100,00). Most PCs do not routinely track and report HCV mortality (33%), and incidence (48%); 18 (54%) have HCV case registries Testing and Treatment: For HCV screening, 30 (90%) PCs direct testing to risk populations (pop) and 22 (67%) to pregnant women. A total 15 (45%) PC cover testing costs for all patients and 12 (36%) PCS for low income and other pop. Licensed point-of-care PCR testing is limited to 48% of PCs. Treatment policies are avialble in 30 (91%) PC. In 19 (58%) PCs, non-specialists can treat HCV. Policies for sobriety and genotype testing persist in 24% and 27% PCs, respectively. Harm Reduction (HR): A total of 22 (67%) PCs have HR policies for persons who inject drugs (PWID); 16 (48%) have decriminalized needle/ syringe (N/S) possession. Only 3 PCs provide clean N/S in federal prisons. Financing: There are national budget lines for the testing and treatment of HCV in 24 (73%) PCs. **Conclusion:** Most PCs have action plans with testing and treatment policies. Some PCs have reached interim targets. However, SI is sparse. Large-scale HCV testing is rare. Treatment barriers remain. HR access is mostly inadequate. Increases in global and national financing are needed.

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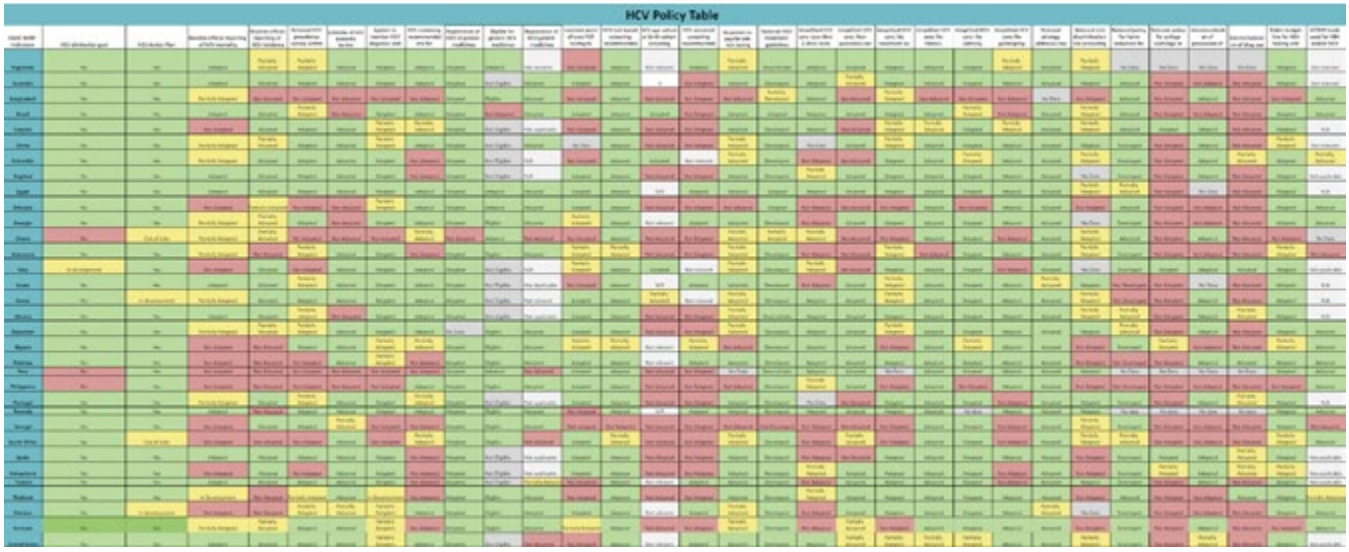

Disclosures: Jana Manning: Nothing to Disclose, John Ward: Grant/Research Support relationship with Dynavax, Merck, Cepheid,; Has not ended; Grant/Research Support relationship with Abb Vie, Abbott, Gilead, Siemens, Roche, Pharco, Virion,; Has not ended, Lindsey Hiebert: Nothing to Disclose

3337 | MISSED DIAGNOSIS OF AMBULATORY COMMUNITY ACUTE KIDNEY INJURY IS COMMON AND ASSOCIATED WITH MAJOR ADVERSE KIDNEY EVENTS IN PATIENTS WITH CIRRHOSIS

Kavish Patidar[1] Yan Liu[1] Ruben Hernaez[1] Thomas Taylor[1] George Cholankeril[1] Jennifer Kramer[1] Prasun Jalal[1] Tzu-Hao Lee[1] Avegail Flores[1] Guiseppe Cullaro[2] Andrew Allegretti[3] Pere Gines[4] Hardeep Singh[1] Fasiha Kanwal[5]

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Background: Patients with cirrhosis frequently experience acute kidney injury (AKI). We showed that AKI can first present in an ambulatory community setting (community-acquired AKI, CA-AKI) and is associated with major adverse kidney events (MAKE). Diagnostic errors, especially missed diagnosis of CA-AKI, can contribute to patient harm, although few data exist to describe their prevalence or underlying causes among patients with cirrhosis. **Methods:** We conducted a retrospective cohort study in a random sample of patients with cirrhosis seen in the national Veterans Affairs healthcare system who developed CA-AKI between 1/01/2018 and 12/31/2022. CA-AKI was defined by meeting International Club of Ascites AKI criteria in an ambulatory setting. We conducted a structured review of each medical record to determine whether a diagnostic error occurred (missed diagnosis), identify diagnostic process faults, and classify harms, including progression to MAKE. We used multivariable models to examine the association between missed diagnosis and subsequent harm (MAKE). **Results:** Of 250 patient records at 86 hospitals that underwent review (median age 67 years; 58% white, 30% African American], 104 (42%) patients had experienced a missed diagnosis. In total, 10% events were preventable and 23% (n=58) were ameliorable (events where severity of injury could have been substantially reduced if different actions was performed). Common precipitants were volume depletion due to diuretics or GI losses (n=63, 40%), nephrotoxic medication use (n=37, 15%), and hypotension (n=33, 15%). The most common process faults were related to problems with follow up and monitoring (64%) and appropriate assessment (42%).Patients with missed diagnosis had significantly higher median MELD 3.0 scores (12.6 vs. 9.0, p=0.003), were more likely to have ascites (52% vs. 43%, p=0.014), CKD (37% vs. 13%, p<0.001) and had higher severity of AKI at diagnosis (stage 1B, 2, 3: 68%, 15%, 2% vs 29%, 5%, 1%; p<0.001) compared to patients without missed diagnosis (Table). On multivariable analysis, missed diagnosis was independently associated with MAKE, OR 4.23 [95% 1.67-10.74, p<0.001] after adjusting for age, MELD 3.0, ascites, and co-morbidities. **Conclusion:** CA-AKI is often underdiagnosed and undertreated in ambulatory patients with cirrhosis. Interventions focusing on timely diagnosis and cirrhosis specific treatment algorithms of CA-AKI could improve outcomes in this population.

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Table: Comparisons Between Patients With Timely and Missed CA-AKI Diagnosis

	Chart Review N=250	Timely CA-AKI Dx N=146	Missed CA-AKI Dx N=104	p-value
Age, median (25-75%)	67.0 (62.0-70.0)	66.5 (62.0-70.0)	67.0 (62.5-70.0)	0.999
Sex, n (%) male	241 (96.40)	141 (96.58)	100 (96.15)	0.999
Race, n (%)				
White	145 (58.0)	82 (56.2)	63 (60.6)	0.609
Black	74 (29.6)	45 (30.8)	29 (27.9)	
Other	31 (12.4)	19 (13.0)	12 (11.5)	
Cirrhosis etiology				
HCV	26 (10.4)	17 (11.6)	9 (8.7)	
Alcohol	81 (32.4)	50 (34.3)	31 (29.8)	0.748
HCV and alcohol	87 (34.8)	50 (34.3)	37 (35.6)	
MASLD	54 (21.6)	28 (19.2)	26 (25.0)	
Other	2 (0.80)	1 (0.6)	1 (0.9)	
Ascites, n (%)	107 (42.8)	53 (36.3)	54 (51.9)	**0.014**
HE	18 (7.2)	14 (9.6)	4 (3.9)	0.083
HCC	50 (20.0)	28 (19.2)	22 (21.2)	0.700
Esophageal varices	71 (28.4)	41 (28.1)	30 (28.9)	0.895
MELD 3.0, median (25%-75%)	10.1 (7.1-14.4)	9.0 (6.6-13.5)	12.6 (9.0-15.9)	**0.003**
CKD (eGFR <60)	57 (22.8)	19 (13.01)	38 (36.5)	**<0.001**
Diabetes	135 (54.0)	81 (55.5)	54 (51.9)	0.578
Hypertension	223 (89.2)	127 (87.0)	96 (92.3)	0.182
CHF	48 (19.2)	25 (17.1)	23 (22.1)	0.323
AKI stage, n (%)				
1A	109 (43.6)	94 (64.3)	15 (14.4)	
1B	113 (45.2)	42 (28.8)	71 (68.3)	**<0.001**
2	24 (9.6)	8 (5.5)	16 (15.4)	
3	4 (1.6)	2 (1.4)	2 (1.9)	

Disclosures: Kavish Patidar: Madrigal Pharmaceuticals: Medical Advisory Board, Yan Liu: Nothing to Disclose, Ruben Hernaez: Nothing to Disclose, Thomas Taylor: Nothing to Disclose, George Cholankeril: Nothing to Disclose, Jennifer Kramer: Nothing to Disclose, Prasun Jalal: Nothing to Disclose, Tzu-Hao Lee: Nothing to Disclose, Avegail Flores: Nothing to Disclose, Guiseppe Cullaro: Nothing to Disclose, Andrew Allegretti: Nothing to Disclose, Pere Gines: Gilead & Grifols: Grant/Research Support, SeaBeLife, Merck, Sharp and Dohme (MSD), Ocelot Bio, Roche Diagnostics Intern, Boehringer Ingelheim: Advisor, Pfizer: Speaking and Teaching, Gilead, RallyBio, Behring: Advisor, Pfizer: Speaking and Teaching, Hardeep Singh: Nothing to Disclose, Fasiha Kanwal: Nothing to Disclose

3338 | ADVANCED LIVER DISEASE COORDINATOR IMPROVES HEPATOCELLULAR AND VARICEAL SURVEILLANCE ACROSS A DIVERSE VETERANS AFFAIRS HEALTHCARE NETWORK

Melissa Kaltenbach[1] *Jessica Davis*[1] *Jennifer Bonair*[1] *Atoosa Rabiee*[1]

[1]*Washington DC VAMC*

Background: Guidelines recommend that all individuals with cirrhosis undergo biannual hepatocellular carcinoma (HCC) surveillance, and those with evidence of portal hypertension should have additional variceal surveillance. In clinical practice, adherence to these guidelines remain low. The aim of this project was to optimize HCC and variceal surveillance across multiple Veterans Affairs (VA) medical centers. **Methods:** We conducted a quality improvement (QI) study to assess the impact of an advanced liver disease (ALD) coordinator on HCC and variceal surveillance across Veterans Integrated Service Network (VISN) 5, a network of 6 heterogenous VA medical centers serving Veterans across the mid-Atlantic. A VISN 5 Advanced Liver Disease Coordinator position was established June 4, 2023, to provide support to all medical sites in the VISN through weekly provider driven emails identifying patients overdue for surveillance, biweekly site meetings to discuss local process

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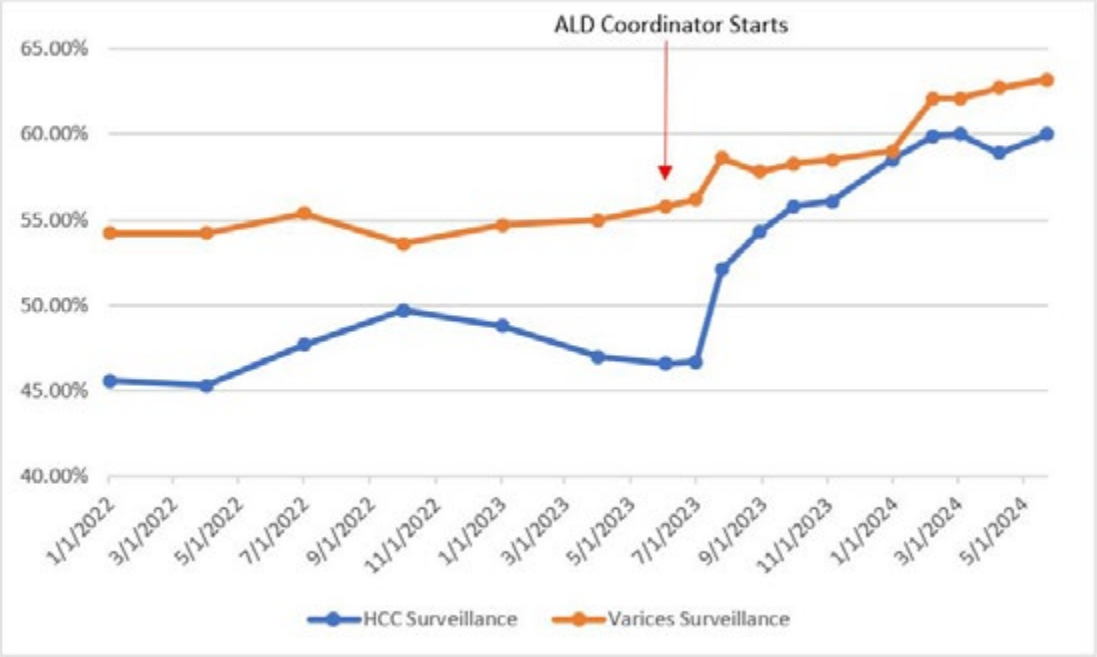
improvements, and monthly VISN debriefs and educational lectures. HCC and variceal surveillance rates were tracked using the ALD Dashboard, a previously validated tool used to accurately identify patients with cirrhosis overdue for surveillance from the VHA Corporate Data Warehouse. Surveillance rates were tracked in real time and iterative plan-do-study-act cycles were used to improve metrics. **Results:** At baseline, there was a 46.6% and 55.8% HCC and variceal surveillance rate in VISN 5, respectively (Figure 1). Ten months after start of the intervention, rates improved to 60.0% and 63.2% HCC and variceal surveillance rates, respectively. All 6 sites saw improvements in both HCC and variceal surveillance from baseline. The largest gains were in HCC surveillance from 2 lower performing sites with one site improving rates from 38.6% to 50.9%, and another from 42.1% to 57.7%. VISN 5 performs above the national rate for HCC (60.0% vs 49.8%) and variceal surveillance (63.3% vs 61.4%) and has the second highest HCC and 7th highest variceal surveillance rate out of 18 VISNs. **Conclusion:** An ALD coordinator improved surveillance rates across all medical centers within the VISN, despite diversity across each healthcare site in terms of patient mix, subspecialty access, and academic affiliation. The role of a dedicated ALD coordinator may provide a potential model for other healthcare systems looking to enhance cirrhosis population health management.

Figure 1. VISN 5 HCC and Variceal Surveillance Rates Before and After Intervention



Footnote: VISN= Veterans Integrated Service Network; HCC= Hepatocellular Carcinoma; ALD= Advanced Liver Disease

Disclosures: Melissa Kaltenbach: Nothing to Disclose, Jessica Davis: Nothing to Disclose, Jennifer Bonair: Nothing to Disclose, Atoosa Rabiee: Nothing to Disclose

3339 | COMPARING HEALTH RELATED-QUALITY OF LIFE OF PATIENTS BETWEEN COMPENSATED AND DECOMPENSATED CIRRHOSIS - A SYSTEMATIC REVIEW AND META-ANALYSIS ◆

Shahryar Khan[1] Mashal Alam Khan[2] Fatma Hussain[2] Nimra Ehsan[2] Fahad Rahman[2] Hoor Umar Afridi[2] Hafsa Parveen[2]

[1]University of Kansas Medical Center, [2]Khyber Medical University

Background: Chronic Liver Disease (CLD) is being recognized as an important cause of chronic diseases worldwide with consistently impaired health related quality of life (HRQoL). Patients with CLD have distinct physical and cognitive symptoms that interfere with their quality of life which correlates with reduced compliance, poor treatment outcomes, and prognosis. We aimed to investigate and compare components of HRQoL between

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Compensated (CC) and Decompensated Cirrhosis (DC). **Methods:** A literature search was conducted identifying studies published since inception till May 2024. We included Studies that compared HRQoL between CC and DC. In all studies, HRQoL was assessed with Short-form 36 (SF-36) survey that provides a composite of General Health (GH), Physical functioning (PF), bodily pain (BP), Physical Role (PR), Social Role (SR), Mental Health, Emotional role (ER), vitality (VT), Physical Component Summary Score (PCSS), and Mental Component Summary Score (MCSS). Severity of CLD was assessed using Pugh's modification of Child's grading system with Class A, Class B as CC, and Class C as DC. The main outcomes were assessed comparing differences with each component of SF-36 between CC and DC. The random effects model was used to calculate the pooled Mean effect and Mean difference (MD) with the corresponding 95% confidence intervals of our desired outcomes. A p value of < 0.05 was considered statistically significant. Heterogeneity was assessed using the I2 Index. (I2 values >50% implied the presence of significant heterogeneity). Qualities of studies were assessed using the ROBINS-1 tool. Data analysis was performed using the Revman software (version 5.4.1). **Results:** In our review, 12 Studies were included with 4454 patients, 44.2% with CC, and 19.4% with DC. CC group comprised 39.1% with Class A, and 60.9% with Class B. The average age of 53.9 in CC group, and 54.5 in DC group; Female comprised 34% in CC group, and 31% in DC group. Regarding the cause of Cirrhosis in these patients, 35% from Alcohol use in CC, and 42% in DC. In comparing CC with DC, decompensation is significantly associated with worsening components of SF-36 including PCSS (MD of 6.79, 95% CI of 4.54 to 9.05, random effect, $I2 = 87\%$, $P < 0.05$, Figure.1), MCSS (MD of 4.58, 95% CI of 2.92 to 6.23, random effect, $I2 = 69\%$, $P < 0.05$, Figure.2), PF (MD of 13.32, 95% CI of 8.51 to 18.14), PR (MD of 15.60, 95% CI of 10.82 to 20.38), BP (MD of 8.58, 95% CI of 4.76 to 12.40), GH (MD of 9.95, 95% CI of 6.27 to 13.63), VT (MD of 9.37, 95% CI of 5.86 to 12.88), SR (MD of 11.92, 95% CI of 7.69 to 16.15), ER (MD of 10.95, 95% CI of 7.79 to 14.1), and MH (MD of 6.41, 95% CI of 3.17 to 9.65). **Conclusion:** This study showed significantly impaired quality of life including Physical and Psychological aspects in the stages of Advanced Liver disease. Along with clinical indications of CLD, focusing on these components of HRQoL with a timely and multidisciplinary approach can improve the disease-related quality of life.

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Figure 1. Physical Component Summary Score

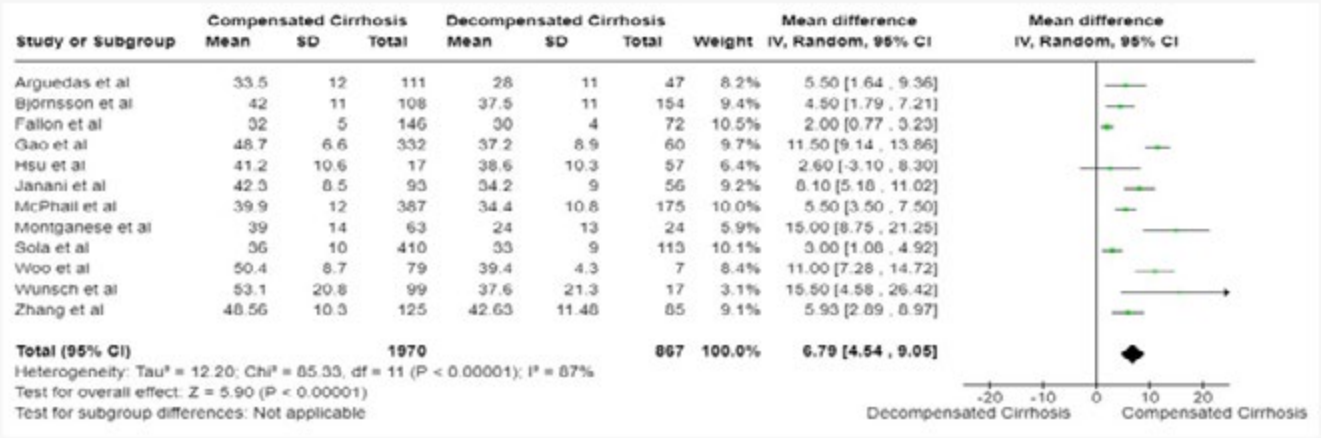
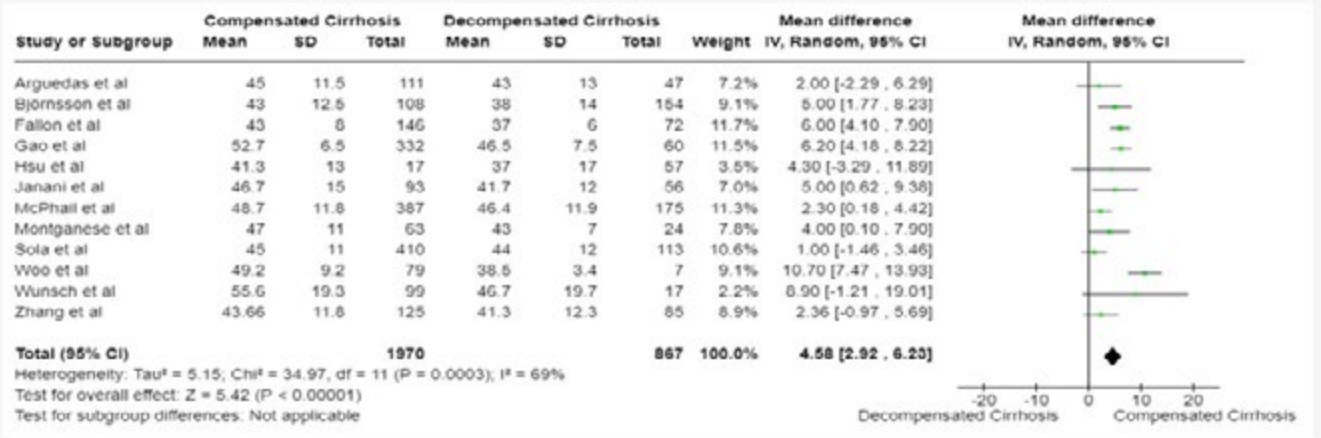


Figure 2 Mental Component Summary Score



Disclosures: Shahryar Khan: Nothing to Disclose, Mashal Alam Khan: Nothing to Disclose, Fatma Hussain: Nothing to Disclose, Nimra Ehsan: Nothing to Disclose, Fahad Rahman: Nothing to Disclose, Hoor Umar Afridi: Nothing to Disclose, Hafsa Parveen: Nothing to Disclose

3340 | BREAKING DOWN BARRIERS: INVESTIGATING TRANS ARTERIAL CHEMO EMBOLISM (TACE) AS A PALLIATIVE MEASURE FOR UNRESECTABLE HCC ALONG THE US-MEXICO BORDER

Swati Mahapatra[1] Shivangini Duggal[2] Sparsha Reddy Duvvuru[1] Alan Guzman[1] M Ammar Kalas[1] Bhavi Trivedi[1] Alok Dwivedi[3] Ricardo Badillo[1]

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Background: Trans arterial chemo embolism (TACE) is currently the first line of treatment for patients with unresectable, multinodular tumors without vascular invasion or extrahepatic spread; most commonly hepatocellular carcinoma (HCC). It has gained momentum over the years as a palliative treatment for those with HCC due to prolonged survival. To evaluate the use of TACE as a palliative treatment for HCC, we aimed to assess mortality rates in those with HCC that have underwent TACE procedures, recurrence of TACE, and insurance status. Our aim was to illustrate the use of TACE as a palliative measure for those with unresectable HCC along the US-Mexico border. **Methods:** We conducted a retrospective analysis of TACE performed in the inpatient at the county hospital (Jan 1, 2017 – Jan 1, 2022). Variables considered were: patient demographics (age, race, gender, insurance, zip code), procedure type, recurrence, and associated complications. Charts were

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analyzed for repeated visits for TACE and oncologic follow up dependent on insurance status. **Results:** The demographics showed that majority of our studied patients were male and Hispanic. Over 40% of our patients were un-insured (Table 1). Our study revealed patients undergoing TACE were seen to have a worsening in MELD over the timeline of five years. The initial mean being 11.95 to the final mean 18.45 (p<.01). However, there was a significant loss of follow-up reported. Of those treated with TACE, mortality was 26.9% within the five-year interval. Complications associated were minimal, with only five individuals having a reported complication, which varied from sepsis to renal failure to GI bleed. Of note, no complications of acute cholecystitis, which is the most common complication of TACE, was noted. Progression of MELD score over the five-year period was similar despite funding (p=0.01). **Conclusion:** While TACE may be a palliative approach to those with suffering with unresectable HCC, there are significant underlying factors that determine the effectiveness of its therapy like funding, follow-up, and associated complications. Our data illustrated that there may be a significant mortality benefit of TACE. However, the trend remains ambiguous due to the lack of follow-up reported in those undergoing TACE treatments along with an increase in uninsured status, as seen in our border community. Further analysis must be done to identify and correct for issues related to poor follow-up such as cost, funding, and insurance status.

Table 1: Demographics of those with TACE in the setting of HCC

Factor	Value
N	39
Age, mean (SD)	60.5 (8.3) (n=39)
Male	
0	8 (20.5%)
1	31 (79.5%)
Hispanic	
1	39 (100.0%)
Insurance	
Charity	5 (12.8%)
Medicaid	7 (17.9%)
Medicare	16 (41.0%)
No Insurance	11 (28.2%)

Disclosures: Swati Mahapatra: Nothing to Disclose, Shivangini Duggal: Nothing to Disclose, Sparsha Reddy Duvvuru: Nothing to Disclose, Alan Guzman: Nothing to Disclose, M Ammar Kalas: Nothing to Disclose, Bhavi Trivedi: Nothing to Disclose, Alok Dwivedi: Nothing to Disclose, Ricardo Badillo: Nothing to Disclose

3341 | COST-EFFECTIVENESS OF THE HEPQUANT DUO TEST FOR THE MANAGEMENT OF PATIENTS AT RISK FOR LARGE ESOPHAGEAL VARICES

Gregory Everson[1] Shailesh Chavan[2] Kelly Pitts[3] Michael McRae[4]

[1]HepQuant, [2]HepQuant LLC, [3]HepQuant, LLC, [4]Custom DX Solutions, LLC

Background: The dual-sample oral cholate challenge test (HepQuant DuO) quantifies liver function and portal-systemic shunting. Herein we report the economic impact of the use of the HepQuant DuO Disease Severity Index (DSI) in the clinical management of patients with chronic liver disease suspected of having large esophageal varices. **Methods:** A Markov health state transition model of 100,000 patients with chronic liver disease suspected of having varices was populated with previously reported epidemiological, utility, and price data to assess the cost-effectiveness of employing the HepQuant DuO test (DSI cutoff 18.3) against the standard of care (SOC) (Figure 1) at a fixed price of $3250 per HepQuant DuO test. The model examined the clinical and economic impact of three management decisions, based on a DSI cutoff of 18.3, all three decisions taken at once: (1) avoidance of endoscopy (DSI ≤18.3), (2) reduction in clinical follow-up (DSI ≤18.3), and (3) improved adherence to SOC guidelines (DSI >18.3). Each year, direct medical costs and health effects denominated in

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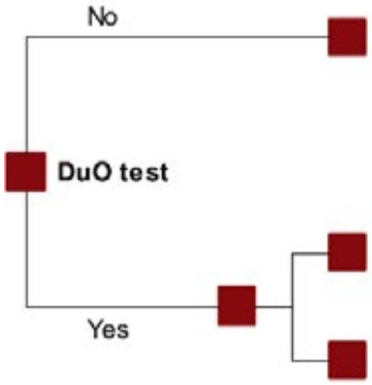
quality-adjusted life years (QALYs) were calculated, and incident cases of decompensated cirrhosis (DC) and mortality were estimated. **Results:** In the target population, the combined strategy of healthcare management decisions based on DSI results would be highly cost-effective within two years and cost-saving within three years at the fixed price per HepQuant DuO test. Over five years, these management decisions would result in 3498 incident cases of DC averted in the HepQuant DuO arm relative to the SOC, as well as 2740 lives saved — with 4342 QALYs gained. Over the same period, a total of $236M in direct medical costs would be saved. Maintaining all three management decisions at a variable test price, a "what-if" analysis revealed that employing HepQuant DuO would be highly cost-effective relative to SOC within a range of 3–9 years for a price range of $3500–5000 per test. **Conclusion:** Clinical decisions related to avoidance of endoscopy, reduction in follow-up, and adherence to SOC guidelines based on DSI from HepQuant DuO are highly cost-effective in the management of patients with chronic liver disease suspected of having large esophageal varices. The HepQuant DuO test offers a simplified approach that could enhance clinical and research utility of liver function testing.



		Annual tests					
			EGD				
	DuO test	No varices	Small varices	Large varices	Lab tests & AFP	Ultrasound
Std of care	0	0.5	1	2	2	2
DSI > 18.3	0	0.5	1	2	2	2
DSI ≤ 18.3	1	0	0	0	1	0.5

Disclosures: Gregory Everson: HepQuant LLC: Executive role, Shailesh Chavan: Nothing to Disclose, Kelly Pitts: Nothing to Disclose, Michael McRae: HepQuant, LLC: Consultant

3342 | EXPANDING ACCESS TO LIVER TRANSPLANTATION: EFFECTIVENESS OF A SINGLE-CENTER TARGETED OUTREACH PROGRAM

Sudha Kodali[1] Analisa Lopez[1] Marcela Velazquez[1] Nicole Hinton[1] John Ontiveros[1] Riki Graves[1] Julie Luczon[1] Elizabeth Brombosz[1] Linda Moore[1] Christian Valverde[1] Susan Zylicz[1] Kelly Maresh[1] Chukwuma Egwim[2] Julie Corkrean[1] R. Mark Ghobrial[3]

[1]Houston Methodist Hospital, [2]Liver Associates of Texas, [3]Houston Methodist JC Walter Transplant Center

Background: Liver transplantation (LT) is often the only cure for patients with end-stage liver disease (ESLD), but access to LT can be limited by socioeconomic factors. Hispanic patients experience ESLD at higher rates than other ethnicities due to a combination of genetic and environmental factors, but they often have limited access to LT. In mid-2021, our center instituted a targeted outreach program to increase referrals of Hispanic patients to our LT program. Outreach activities included meetings with clinicians and lectures for patients throughout the state of Texas, as well as the creation of new Spanish-language brochures and signage. Center representatives also made monthly trips to clinics in the Rio Grande Valley, a Hispanic-majority area with high rates of end-stage liver disease. **Methods:** Records of patients referred for LT between 1/2018 and 12/2019 ("pre-outreach") were compared to patients referred between 7/2021 and 6/2023 ("post-outreach") were retrospectively reviewed. Fisher's exact, Chi-square, and Kruskal-Wallis tests were utilized to make comparisons between eras, with $p<0.05$ considered statistically significant. **Results:** A greater proportion of patients referred in the post-outreach era identified as Hispanic ($p=0.004$), but they were similarly likely to prefer Spanish as a primary language ($p=0.37$).

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The patients' area deprivation index (ADI) was significantly lower in the post-outreach era (p<0.001), indicating post-outreach referrals were less socioeconomically disadvantaged. There was a corresponding increase in referrals of patients with private insurance post-outreach (p<0.001). The proportion of referred patients from the Rio Grande Valley increased significantly (p<0.001), more than doubling from 2.1% to 5.3%. A significantly lower proportion of referrals went on to waitlisting (p<0.001), although the absolute number of patients waitlisted increased by 23% (n=554 vs 684). Most patients who were ineligible for LT had financial contraindications (33.1%). **Conclusion:** Our center's targeted outreach program was very successful at increasing the number and proportion of Hispanic patients referred for LT, particularly from the Rio Grande Valley. Most of the growth in referrals came from patients from moderate ADI areas with private insurance. Outreach programs can effectively increase access to LT for Hispanic patients, although more work is needed to overcome financial barriers to transplantation.

	Pre-Outreach (n=1013)	Post-Outreach (n=1546)	p
Age, median (IQR)	59.1 (50.2, 65.8)	57.8 (46.0, 65.7)	**0.01**
Male sex, n (%)	422 (41.7%)	651 (42.1%)	0.82
Race, n (%)			**0.001**
White	766 (75.6%)	1127 (72.9%)	
Black	108 (10.7%)	132 (8.5%)	
Asian	43 (4.2%)	58 (3.8%)	
Other	96 (9.5%)	229 (14.8%)	
Ethnicity, n (%)			**0.004**
Non-Hispanic	730 (72.1%)	1029 (66.6%)	
Hispanic	235 (23.2%)	405 (26.2%)	
Unknown	48 (4.7%)	112 (7.2%)	
Primary language, n (%)			0.37
English	891 (88.0%)	1340 (86.7%)	
Spanish	59 (5.8%)	112 (7.2%)	
Other	63 (6.2%)	94 (6.1%)	
Etiology, n (%)			**<0.001**
Alcohol-associated	306 (30.2%)	655 (42.4%)	
MASLD/MASH	167 (16.5%)	271 (17.5%)	
Malignancy	237 (23.4%)	259 (16.8%)	
Viral Hepatitis	88 (8.7%)	78 (5.0%)	
Other	215 (21.2%)	283 (18.3%)	
Insurance type, n (%)			**<0.001**
Private	412 (40.7%)	799 (51.7%)	
Public	526 (51.9%)	572 (37.0%)	
Other/Not provided	75 (7.4%)	175 (11.3%)	
Waitlisted, n (%)	554 (54.7%)	684 (44.2%)	**<0.001**
ADI, median (IQR)	70 (53, 85)	52 (33, 70)	**<0.001**
From Rio Grande Valley, n (%)	21 (2.1%)	82 (5.3%)	**<0.001**

ADI, area deprivation index; IQR, interquartile range; MASLD, metabolic dysfunction-associated steatotic liver disease; MASH, metabolic dysfunction-associated steatohepatitis

Disclosures: Sudha Kodali: Advisor relationship with Astrazeneca; Has not ended; Speaking and Teaching relationship with Gilead; Has not ended; Advisor relationship with SIRTEX; Has not ended; Speaking and Teaching relationship with Gilead; Has ended; Advisor relationship with SIRTEX; Has ended; Consultant relationship with Astrazeneca; Has ended, Analisa Lopez: Nothing to Disclose, Marcela Velazquez: Nothing to Disclose, Nicole Hinton: Nothing to Disclose, John Ontiveros: Nothing to Disclose, Riki Graves: Nothing to Disclose, Julie Luczon: Nothing to Disclose, Elizabeth Brombosz: Nothing to Disclose, Linda Moore: Nothing to Disclose, Christian Valverde: Nothing to Disclose, Susan Zylicz: Nothing to Disclose, Kelly Maresh: Nothing to Disclose, Chukwuma Egwim: Gilead Sciences: Speaking and Teaching, Julie Corkrean: Nothing to Disclose, R. Mark Ghobrial: TransMedics: Consultant, Sanofi: Consultant, LyGenesis: Advisory Board Member

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3343 | OUTCOMES OF MANAGEMENT OF PATIENTS WITH CIRRHOSIS IN A COMMUNITY CLINIC

Deanna Oliver[1] Ahmed Atalla[1] Usman Gul[1] Julian Diaz-Moreno[1] Ayisha Aziz[1] Lita Petcharaporn[1] Fatma Barakat[2] James Johnson[1] Anna Hefner[1] Tarek Hassanein[1]

[1]Southern California Liver Centers, [2]SCTI Research Foundation

Background: Cirrhosis is a public health burden with over 5 million affected individuals in the US, with over 350,000 hospitalizations per year. It is ranked as the 7th age-stratified analysis of disability-adjust life-years amongst 50-74 year olds. Cirrhosis leads to Hepatocellular Carcinoma and decompensation, which is associated with increased hospitalizations and in turn economic burden. The primary goal of managing patients with cirrhosis is to prolong the compensated state and quick recovery from episodes of decompensation. This is a report on the outcomes of managing patients with cirrhosis in a non-academic, community-based liver center serving predominately Hispanic as well as economically and educationally disadvantaged patients. **Methods:** Between January 2010 and December 2022, 36,615 patients were followed by a single liver center with multiple clinics. 5,352 had cirrhosis. Patients with cirrhosis were managed according to standardized protocol tailored to each patient's individual needs following the published guidelines. Standard of care parameters including information on primary liver disease, co-morbidities, medications, vital signs, outpatient visits, hospital admission, laboratory, and imaging studies were analysed. To date, analysis was completed on 500 consecutive patients. The focus of this abstract is on the outcomes and disposition. **Results:** *Demographics and etiology:* 50.7% males. Mean age was 65.5 ± 9.9 years. 52.1% Hispanics and 79.1% whites. Underlying etiology of liver disease was primarily history of HCV (40.7%), Alcoholic liver disease (23.3%), and MASLD/MASH (17.3%). *Outpatient Visits:* Median follow-up: 4.2 years (0.08-12). Median number of outpatient visits at Hepatology practice is 15 visits (2-117). *Complications and hospitalizations:* Refer to table for results on complications. 56.4% were hospitalized. Mean number of hospitalizations was 3.0±5.93. Only 37% of hospitalizations was due to liver disease. *Disposition and transplant status:* 83.6% alive. 5.4% referred to Hospice. 2.7% received a liver transplant. 90.9% not listed for transplant mainly because of lack of criteria. **Conclusion:** Closely following patients with cirrhosis and tailoring the management of their comorbidities including eliminating primary liver injury resulted in 1) decreasing the frequency of hospitalizations and length of stay per hospitalization, 2) decreasing need for listing for liver transplantation, and 3) early detection and lower rate of Hepatocellular Carcinoma. In a non-academic, community-based liver center, having a dedicated program to managing patients in a tailored manner had a major impact on lowering morbidity and improving complications-free survival. This ultimately decreased the cost of cirrhosis care.

Table: N=500 patients with cirrhosis

Varices	No varices	44.7%
	Trace or Grade 1	46.4%
	Grades 2 or 3	8.9%
GI Bleed	No	98.8%
	Yes	1.2
Sepsis	No	86.1%
	Yes	13.9%
HRS	No	89.7%
	Yes	10.3%
TIPS	No	90.2%
	Yes	9.8%
HCC	No	92.2%
	Yes	7.8%

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Disclosures: Deanna Oliver: Nothing to Disclose, Ahmed Atalla: Nothing to Disclose, Usman Gul: Nothing to Disclose, Julian Diaz-Moreno: Nothing to Disclose, Ayisha Aziz: Nothing to Disclose, Lita Petcharaporn: Nothing to Disclose, Fatma Barakat: Nothing to Disclose, James Johnson: Nothing to Disclose, Anna Hefner: Nothing to Disclose, Tarek Hassanein: Nothing to Disclose

3344 | QUALITY OF LIFE AMONG VETERANS WITH CIRRHOSIS

Paarth Kapadia[1] Timothy Morgan[2] vera yakovchenko[3] Carolyn Lamorte[1] Brittney Neely[1] Sandra Gibson[1] Monica Merante[1] Rachel Gonzalez[2] Patrick Spoutz[4] Shari Rogal[5]

[1]VA Pittsburgh Healthcare System, [2]VA Long Beach Healthcare System, [3]VA Bedford Healthcare System, [4]VA Northwest Network, [5]University of Pittsburgh

Background: Patient reported outcomes (PROs) have been emphasized by the AASLD as essential quality measures in the care of people with cirrhosis. While PROs are critical for understanding patient experiences, they can be challenging to collect. We aimed to evaluate PROs across multiple facilities in the Veterans Health Administration (VA), which cares for over 80,000 veterans with cirrhosis annually nationwide. **Methods:** As a part of an ongoing cirrhosis care improvement initiative, we mailed paper surveys to a random sample of patients with cirrhosis across 23 VA facilities, every 6 months for two years. The survey included the Veterans RAND 12-Item Health Survey (VR-12), an instrument validated in measuring patient-reported indices of physical health ("Physical Component Score", or "PCS") and mental health ("Mental Component Score", or "MCS"). We then used clinical data from the VA Corporate Data Warehouse (CDW) to identify parameters associated with PCS and MCS. **Results:** In this cohort of 1,659 Veterans, the average PCS score was 33 and the average MCS score was 43 (scored 0-100, with higher values representing better perceived health and 50 representing the average American). Scores were stable across repeated measures in the same patient. PCS and MCS scores were not substantially correlated with each other (R^2 0.07), Model for End-stage Liver Disease (MELD) 3.0 score (PCS R^2 0.01; MCS R^2 <0.01), Charleson Comorbidity Index (CCI) (PCS R^2 0.03, MCS R^2 0.01), or site-level measures of care quality. Multivariable regression found that PCS and MCS were statistically significantly associated with patient age, education level, disease uncertainty, key self-reported symptoms (confusion and inability to walk were good proxies for the total MCS and PCS, respectively), and the self-administered Comorbidity Questionnaire (SCQ) scores (*see figure*). **Conclusion:** These findings identified persistently low MCS and PCS that did not correlate with site performance metrics, MELD, or electronic medical record comorbidity scores, but rather with *self-reported* comorbidity scores, disease uncertainty, and education. These findings suggest that asking two key questions may substitute for lengthier QoL assessments and identify important aspects of living with cirrhosis that cannot be found from chart data alone.

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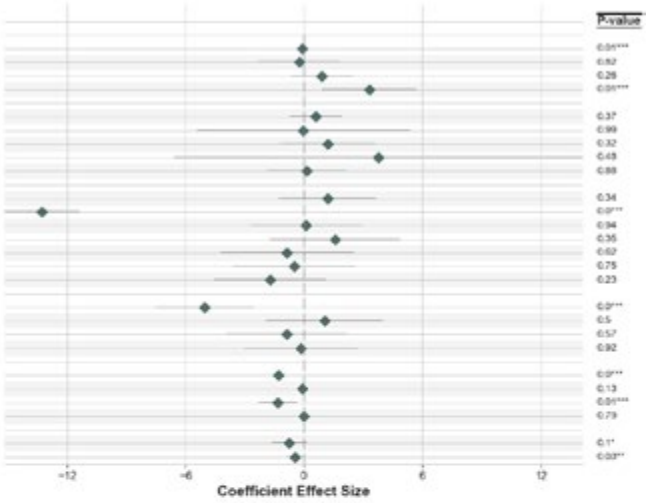
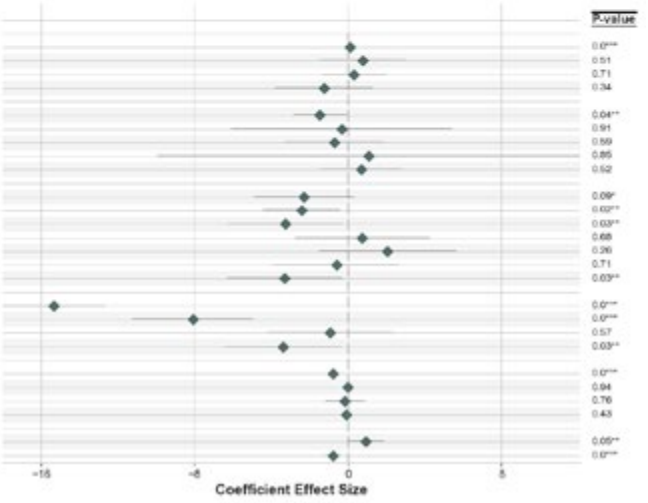
Multivariable Linear Regression for Physical Component Score

Variable	Coefficient (95% Confidence Interval)	P-value
Patient Demographics		
Patient Age	-0.08(-0.15 to -0.02)	0.01**
Male Sex	-0.24(-2.33 to 1.85)	0.82
Hispanic Ethnicity	0.91(-0.68 to 2.49)	0.26
Patient Education Level	3.32(0.92 to 5.72)	0.01**
Patient Race (Ref=White)		
Black	0.61(-0.72 to 1.94)	0.37
Asian	-0.03(-5.46 to 5.39)	0.99
American Indian/Alaskan Native	1.22(-1.20 to 3.64)	0.32
Native Hawaiian/Pacific Islander	3.77(-6.59 to 14.13)	0.48
Other	0.15(-1.84 to 2.14)	0.88
Patient-Reported Physical Symptoms		
Difficulty Taking Deep Breaths	1.21(-1.25 to 3.67)	0.34
Difficulty Breathing After Walking 2-3 Minutes	-13.27(-15.16 to -11.38)	0.0***
Difficulty Eating Due To 'Stomach' Issues	0.10(-2.72 to 2.93)	0.94
Difficulty Laying Due To 'Stomach' Issues	1.57(-1.71 to 4.87)	0.35
Difficulty Moving Due To 'Stomach' Issues	-0.86(-4.24 to 2.52)	0.62
Report Of Stomach Bloating	-0.49(-3.58 to 2.59)	0.75
Report Of 'Heavy Stomach'	-1.72(-4.55 to 1.11)	0.23
Patient-Reported Cognitive Symptoms		
Difficulty Concentrating Or Thinking	-5.04(-7.53 to -2.55)	0.0***
Report Of Confusion	1.04(-1.94 to 4.01)	0.5
Report Of Trouble With Memory	-0.88(-3.95 to 2.18)	0.57
Difficulty Remembering Conversations	-0.14(-3.04 to 2.76)	0.92
Clinical Factors		
Self Administered Comorbidity Questionaire Score	-1.29(-1.53 to -1.05)	0.0***
Model For End-Stage Liver Disease 3.0 Score	-0.09(-0.21 to 0.03)	0.13
Decompensated Cirrhosis	-1.31(-2.29 to -0.34)	0.01***
Charlson Comorbidity Index	-0.02(-0.21 to 0.16)	0.79
Misc.		
Site Performance	-0.75(-1.64 to 0.14)	0.1*
Uncertainty Regarding Survey Questions	-0.46(-0.87 to -0.05)	0.03**



Multivariable Linear Regression for Mental Component Score

Variable	Coefficient (95% Confidence Interval)	P-value
Patient Demographics		
Patient Age	0.11(0.05 to 0.18)	0.0***
Male Sex	0.75(-1.48 to 2.97)	0.51
Hispanic Ethnicity	0.32(-1.36 to 2.01)	0.71
Patient Education Level	-1.24(-3.80 to 1.31)	0.34
Patient Race (Ref=White)		
Black	-1.47(-2.89 to -0.06)	0.04**
Asian	-0.33(-6.10 to 5.44)	0.91
American Indian/Alaskan Native	-0.71(-3.29 to 1.86)	0.59
Native Hawaiian/Pacific Islander	1.07(-9.95 to 12.10)	0.85
Other	0.69(-1.43 to 2.81)	0.52
Patient-Reported Physical Symptoms		
Difficulty Taking Deep Breaths	-2.28(-4.90 to 0.33)	0.09*
Difficulty Breathing After Walking 2-3 Minutes	-2.42(-4.43 to -0.40)	0.02**
Difficulty Eating Due To 'Stomach' Issues	-3.25(-6.26 to -0.24)	0.03**
Difficulty Laying Due To 'Stomach' Issues	0.74(-2.77 to 4.25)	0.68
Difficulty Moving Due To 'Stomach' Issues	2.06(-1.53 to 5.66)	0.26
Report Of Stomach Bloating	-0.61(-3.90 to 2.67)	0.71
Report Of 'Heavy Stomach'	-3.29(-6.31 to -0.28)	0.03**
Patient-Reported Cognitive Symptoms		
Difficulty Concentrating Or Thinking	-15.33(-17.98 to -12.68)	0.0***
Report Of Confusion	-8.09(-11.26 to -4.92)	0.0***
Report Of Trouble With Memory	-0.93(-4.18 to 2.32)	0.57
Difficulty Remembering Conversations	-3.40(-6.49 to -0.31)	0.03**
Clinical Factors		
Self Administered Comorbidity Questionaire Score	-0.79(-1.04 to -0.54)	0.0***
Model For End-Stage Liver Disease 3.0 Score	0.00(-0.12 to 0.13)	0.94
Decompensated Cirrhosis	-0.16(-1.20 to 0.88)	0.76
Charlson Comorbidity Index	-0.08(-0.27 to 0.12)	0.43
Misc.		
Site Performance	0.94(-0.01 to 1.90)	0.05**
Uncertainty Regarding Survey Questions	-0.80(-1.24 to -0.36)	0.0***



Disclosures: Paarth Kapadia: Nothing to Disclose, Timothy Morgan: Nothing to Disclose, vera yakovchenko: Nothing to Disclose, Carolyn Lamorte: Nothing to Disclose, Brittney Neely: Nothing to Disclose, Sandra Gibson: Nothing to Disclose, Monica Merante: Nothing to Disclose, Rachel Gonzalez: Nothing to Disclose, Patrick Spoutz: Nothing to Disclose, Shari Rogal: Nothing to Disclose

3345 | LIVER FRAILTY INDEX, NOT SIX-MINUTE WALK DISTANCE, IS ASSOCIATED WITH LIVER TRANSPLANT WAITLIST DROPOUT ◆

Tania Larsen[1] Erica Lo[1] Tracy Fuller[2] Kristin Morris[2] Corinne Weernink[2] Anouar Teriaky[1] Karim Qumosani[1] David Hudson[1] Mayur Brahmania[3] Juan Pablo Arab[1] Mohammad Qasim Khan[1]

[1]University of Western Ontario, [2]London Health Sciences Centre, [3]University of Calgary

Background: There remains uncertainty as to which objective tools should be incorporated to accurately assess frailty and sarcopenia, as well as predict clinical outcomes, in liver transplant candidates (LTC). We aimed to evaluate associations of Liver Frailty Index (LFI) and 6-Minute Walk Distance (6MWD) on waitlist dropout, death on the waitlist, and transplantation, in a cohort of LTCs in London, ON, Canada. **Methods:** In this retrospective cohort study, adult (age ≥18 years) LTCs listed for transplant between December 1, 2021, and March 31, 2023,

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with at least one measure of LFI and 6MWD were included. Patients with hepatopulmonary syndrome and portopulmonary hypertension were excluded. Patients were followed until waitlist dropout, death on the waitlist, transplantation, or last follow-up. Categorical data were presented as frequencies and percentages. Continuous data were presented as medians with minimum and maximum ranges. Multi-state survival analyses were conducted using Aalen-Johnson estimators for competing risks. Multi-state Cox-proportional hazards models were used to estimate associations between LFI and 6MWD, among other predictors, on risk of waitlist dropout, death on the waitlist, and transplantation. **Results:** Overall, 105 waitlisted LTCs were identified but after complete case evaluation, 59 were included in the final analysis. Of these, 9 (15.3%) dropped out, 6 (10.2%) died on the waitlist, 39 (66.1%) survived to transplant, and 5 (8.5%) remained on the waitlist. Two-thirds of LTCs were male. Median biological MELDNa was 13.5 (6-40), median LFI was 3.74 (2.57-5.30) and median 6MWD was 418 m (192-570 m). Higher LFI scores were associated with increased waitlist dropout, increased death on the waitlist, and decreased survival to liver transplant (Figure 1). On multi-state Cox-proportional hazards analysis, LFI significantly increased the hazards of waitlist dropout (log HR: 0.82, 95% CI: 0.06-1.58), but not death on the waitlist (log HR: 0.44, 95% CI: -0.64-1.52), or transplantation (log HR: -0.36, 95% CI: -1.09-0.38). Age, sex, baseline body weight, height, MELDNa and 6MWD did not significantly increase the *hazards* of waitlist dropout, death on the waitlist, or transplantation. **Conclusion:** LFI, not 6MWD, is significantly associated with waitlist dropout in liver transplant candidates, independent of MELDNa. A graded relationship was seen with rising LFI and increased waitlist dropout, death on the waitlist, and decreased survival to transplant.

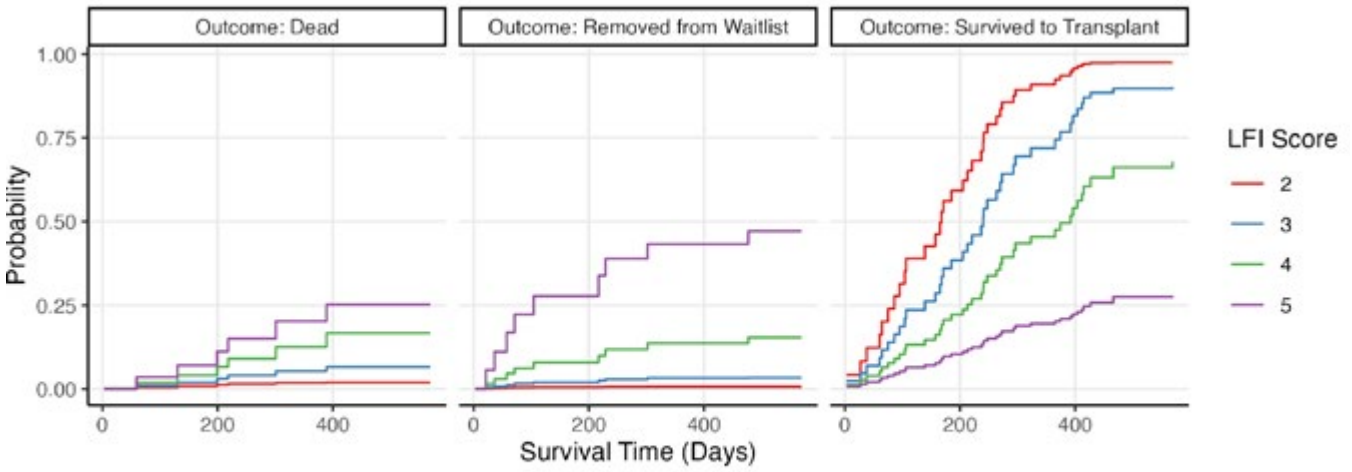

Figure 1 - Effect of Liver Frailty Index (LFI) on Death on the Waitlist, Waitlist Dropout, and Survival to Liver Transplant

Disclosures: Tania Larsen: Nothing to Disclose, Erica Lo: Nothing to Disclose, Tracy Fuller: Nothing to Disclose, Kristin Morris: Nothing to Disclose, Corinne Weernink: Nothing to Disclose, Anouar Teriaky: Nothing to Disclose, Karim Qumosani: Nothing to Disclose, David Hudson: Nothing to Disclose, Mayur Brahmania: Nothing to Disclose, Juan Pablo Arab: Nothing to Disclose, Mohammad Qasim Khan: Nothing to Disclose

3346 | UNVEILING CHANGES IN RACIAL, ETHNIC, AND SOCIOECONOMIC DISPARITIES IN ACCESS TO CRITICAL INTERVENTIONS FOR HOSPITALIZED PATIENTS WITH CIRRHOSIS AND PORTAL HYPERTENSION COMPLICATIONS IN THE U.S. IN 2021

Miriam Sanchez[1] Chris Sabillon[2] Carolina De la Porte[1] Kevin Sanchez[3] Anunaya Aashish[4] Chukwuma Egwim[5] Richard Ward[6]

[1]Texas Health Resources HEB/Denton, [2]IEEE, [3]Universidad Catolica de Honduras, [4]Texas Health HEB/Denton, [5]Liver Associates of Texas, [6]Texas Health HEB/ Denton

Background: In the U.S., cirrhosis remains the 12th leading cause of death. The disease leads to severe complications, including hepatocellular carcinoma (HCC), ascites, hepatic encephalopathy, and variceal bleeding (VH). Prior research by Nephew et al. (2023) highlighted racial and ethnic disparities in the receipt of lifesaving procedures from 2009 to 2018, but there is limited information on socioeconomic disparities in such interventions

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for decompensated cirrhosis patients. This study aims to identify trends in racial, ethnic, and socioeconomic disparities in receiving critical interventions among U.S. patients with decompensated cirrhosis in 2021. **Methods:** We conducted a retrospective cross-sectional analysis using 2020-2021 National Inpatient Sample data. Inclusion criteria were hospital discharges for individuals aged 18 years and older with at least one cirrhosis-related ICD-10 code and one complication-related ICD-10 code. Exclusion criteria included patients without complete demographic data or those with confounding conditions (e.g., heart failure for TIPS, alcoholic cirrhosis for LT). We collected data on demographic variables (age, gender, race, ethnicity, insurance status) and comorbid conditions. Outcomes of interest were the receipt of procedures such as esophagogastroduodenoscopy (EGD) for VH, transjugular intrahepatic portosystemic shunt (TIPS) for VH and ascites, hemodialysis for acute kidney injury (AKI) or hepatorenal syndrome (HRS), and liver transplantation (LT). Statistical analyses included multivariable logistic regression to calculate odds ratios (ORs) for receiving these procedures, adjusting for potential confounders. Chi-square tests were used to assess differences in categorical variables. Annual standardized procedure rates (ASPRs) per 1000 admissions were also calculated. The significance level was set at $p<0.05$ for all analyses. **Results:** Out of 165,407 patients with cirrhosis, 107,059 have complicated cirrhosis. These patients average 20.5 diagnoses and 2.53 procedures, with median lengths of stay and total charges at 5 days and $54,780, respectively. The average age is 60.48 years. Demographically, 66.04% are White, 17.38% Hispanic, 9.82% Black, and 6.76% Other. Age distribution shows 47.78% aged 60-79, 37.81% aged 40-59. Gender distribution is 60.48% male and 39.52% female. Significant disparities were found across all procedures in 2020. White and Hispanic individuals were more likely than Black individuals to undergo EGD for VH (OR=1.289, 95% CI: 1.160-1.433; OR=1.339, 95% CI: 1.194-1.501, respectively). However, Hispanics had higher odds compared to White of accessing TIPS for VH (OR=1.301, 95% CI: 1.161-1.458). Regarding TIPS for ascites, White patients were more likely than Black and Hispanic (OR=1.770, 95% CI: 1.528-2.051; OR=1.128, 95% CI: 1.032-1.234, respectively). For HD for HRS/AKI, Black individuals had higher odds compared to White (OR=1.221, 95% CI: 1.169-1.275). White and Hispanic individuals were more likely than Black individuals to have access to liver transplants for overall decompensated cirrhosis (OR=1.626, 95% CI: 1.460-1.811; OR=1.402, 95% CI: 1.241-1.584, respectively). Disparities based on insurance type were also found. Those with Medicare had higher odds compared to those with Private/HMO for EGD for VH (OR=1.149, 95% CI: 1.069-1.236). For TIPS for VH, Private/HMO had higher odds compared to those with Medicare (Private/HMO: OR=1.510, 95% CI: 1.336-1.708). Patients with Private/HMO insurance had higher odds compared to those with Medicaid and Medicare for LT (OR=3.907, 95% CI: 3.633-4.201; OR=4.257, 95% CI: 4.003-4.527, respectively). **Conclusion:** The study reveals significant disparities in medical procedure utilization across demographic groups where Black individuals have the lowest odds to undergo EGD, TIPS, and LT. Black individuals have the highest odds for HD. Insurance type further impacts access, with Private/HMO insurance holders having higher odds of undergoing procedures compared to those with Medicare or Medicaid. These findings highlight the need for targeted interventions to address healthcare inequities.

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Complication	Procedure	Comparison	Odds Ratio (95% CI)	P-Value	ASPR Comparison
VH	EGD	White vs. Black	1.289 (1.160-1.433)	<0.001	White: 852.09, Black: 817.86
VH	EGD	Hispanic vs. Black	1.339 (1.194-1.501)	<0.001	Hispanic: 856.09, Black: 817.86
VH	EGD	Medicare vs. Private/HMO	1.149 (1.069-1.236)	<0.001	Medicare: 844.23, Private/HMO: 860.04
VH	TIPS	Male vs. Female	1.115 (1.012-1.228)	0.028	Male: 49.18, Female: 44.22
VH	TIPS	Hispanic vs. White	1.301 (1.161-1.458)	<0.001	Hispanic: 39.67, White: 51.33
VH	TIPS	White vs. Black	1.306 (1.063-1.606)	0.011	White: 51.33, Black: 39.29
VH	TIPS	Private/HMO vs. Medicare	1.510 (1.336-1.708)	<0.001	Private/HMO: 55.90, Medicare: 37.97
VH	TIPS	Private/HMO vs. Other	1.754 (1.482-2.076)	<0.001	Private/HMO: 55.90, Other: 33.60
HRS/AKI	Hemodialysis	Male vs. Female	1.051 (1.022-1.081)	<0.001	Male: 88.02, Female: 84.16
HRS/AKI	Hemodialysis	Black vs. White	1.221 (1.169-1.275)	<0.001	Black: 97.78, White: 81.07
HRS/AKI	Hemodialysis	Medicaid vs. Medicare	1.430 (1.382-1.480)	<0.001	Medicaid: 99.32, Medicare: 72.08
HRS/AKI	Hemodialysis	Private/HMO vs. Medicare	1.632 (1.576-1.690)	<0.001	Private/HMO: 111.82, Medicare: 72.08
Any Complication	LT	White vs. Black	1.626 (1.460-1.811)	<0.001	White: 12.25, Black: 7.51
Any Complication	LT	Hispanic vs. Black	1.402 (1.241-1.584)	<0.001	Hispanic: 10.48, Black: 7.51
Any Complication	LT	Male vs. Female	1.146 (1.086-1.210)	<0.001	Male: 12.31, Female: 10.78
Any Complication	LT	Private/HMO vs. Medicaid	3.907 (3.633-4.201)	<0.001	Private/HMO: 29.63, Medicaid: 7.72
Any Complication	LT	Private/HMO vs. Medicare	4.257 (4.003-4.527)	<0.001	Private/HMO: 29.63, Medicare: 7.10
Ascites	TIPS	White vs. Black	1.770 (1.528-2.051)	<0.001	White: 12.18, Black: 6.91
Ascites	TIPS	Medicaid vs. Medicare	1.364 (1.259-1.479)	<0.001	Medicaid: 13.12, Medicare: 9.70
Ascites	TIPS	White vs. Hispanic	1.128 (1.032-1.234)	0.008	White: 12.18, Hispanic: 10.76
Ascites	TIPS	Private/HMO vs. Medicare	1.431 (1.314-1.559)	<0.001	Private/HMO: 13.69, Medicare: 9.70
Ascites	TIPS	Hispanic vs. Black	1.569 (1.333-1.846)	<0.001	Hispanic: 10.76, Black: 6.91

Disclosures: Miriam Sanchez: Nothing to Disclose, Chris Sabillon: Nothing to Disclose, Carolina De la Porte: Nothing to Disclose, Kevin Sanchez: Nothing to Disclose, Anunaya Aashish: Nothing to Disclose, Chukwuma Egwim: Gilead Sciences: Speaking and Teaching, Richard Ward: Nothing to Disclose

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3347 | REFINING MEDICATION RECONCILIATION IN LIVER CLINICS: EVIDENCE FROM A GI CONTINUITY CLINIC

Hammad Ashraf[1] Abdul Nadir[2] Mustafa Ashraf[3] Sara Akar[4] Adnan Malik[5]

[1]Midwestern University Consortium - Verde Valley Medical Center, [2]nadir, [3]Zia Uddin Medical College, [4]Grand Canyon University, [5]Mountain Vista Medical Center

Background: Medication reconciliation is the cornerstone of patient care, it ensures accurate documentation of a patient's current medications. This is particularly important in GI and liver clinics, where medications that are prescribed by non-GI physicians, notably beta-blockers and antidepressants, can significantly affect GI processes. Inaccuracies in medication lists can lead to ineffective treatments, higher healthcare costs and increased adverse effects. Our study aimed to objectively evaluate and improve medication list accuracy in a GI-fellow continuity clinic. **Methods:** This quasi-experimental study was conducted at a GI fellow liver clinic. Follow-up patients were given a printed medication list which they reviewed and corrected. This list was then compared to the list found in the patient's chart. Data was collected for 6 weeks pre and 6 weeks post intervention. The intervention included educating staff and providers to ensure at least one person reviewed and updated each patient's medication list in the EMR during each visit. The patient corrected medication lists were also scanned into the EMR. Statistical analysis was performed using chi-square tests and logistic regression. **Results:** One hundred seventy-three patients were surveyed pre-intervention and 190 post-intervention. Initially 73% of patients reported inaccuracies; the specific type of inaccuracies, which ranged from 6-29%, were a combination of missing medications, inaccurate dosages and extra medications. Medication class inaccuracies, such as beta-blockers, ranged from 19-33%. Table A details the specific variations of inaccuracies, exact medication classes, frequencies and statistical analyses. Notable findings included 38% of patients that had beta-blocker inaccuracies also had liver disease, 23% of patients that had antidepressant inaccuracies also had IBS or IBD, and patients who had private insurance had 20% fewer inaccuracies compared to those with government-funded insurance. Statistical analysis showed a statistically significant reduction in total inaccuracies ($p < 0.001$). **Conclusion:** Our study demonstrated that a structured intervention significantly improves the accuracy of medication lists in a GI continuity clinic. The findings highlight the critical need for accurate medication reconciliation, particularly in a GI clinic where medications such as beta-blockers, commonly used to manage gastric varices and portal hypertension in liver disease, and antidepressants, which affect the gut-brain axis, are often prescribed by non-GI providers. Socioeconomic status also played a role in medication management, likely due to differences in medical literacy. Continued efforts in accurate and frequent medication reconciliations, along with patient education, are essential for effective treatment plans, reduced adverse events, lower healthcare costs, and overall better patient care in the outpatient GI setting.

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Table A: Statistical Analysis of Medication Inaccuracies Pre- and Post-Intervention

Category	Pre-Intervention (n=173)	Post-Intervention (n=190)	Type of Analysis	Odds Ratio (OR)	Confidence Interval (CI)	P-value	Statistical Significance
Total Patients	173	190	Descriptive	-	-	-	-
Inaccuracies Reported	126 (72.8%)	80 (42.1%)	Chi-square, Logistic Regression	0.27	0.17-0.42	<0.001	Yes
Extra Medications	49 (28.3%)	51 (26.8%)	Chi-square	-	-	0.45	No
Incorrect Dosages	10 (5.8%)	8 (4.2%)	Chi-square	-	-	0.60	No
Missing Medications	50 (28.9%)	56 (29.5%)	Chi-square	-	-	0.89	No
Extra and Missing Medications	22 (12.7%)	23 (12.1%)	Chi-square	-	-	0.88	No
Extra, Missing, and Incorrect Dosages	17 (9.8%)	16 (8.4%)	Chi-square	-	-	0.71	No
Incorrect Dosages and Extra Medications	10 (5.8%)	11 (5.8%)	Chi-square	-	-	1.00	No
Incorrect Dosages and Missing Medications	14 (8.1%)	15 (7.9%)	Chi-square	-	-	0.94	No
Beta-blocker Inaccuracies	41 (32.6%)	61 (32.1%)	Chi-square	-	-	0.93	No
Biologics Inaccuracies	29 (23.2%)	44 (23.2%)	Chi-square	-	-	1.00	No
NSAIDs Inaccuracies	45 (36.0%)	69 (36.3%)	Chi-square	-	-	0.96	No
Antipsychotics Inaccuracies	28 (22.0%)	42 (22.1%)	Chi-square	-	-	0.98	No
Antidepressants Inaccuracies	40 (32.0%)	61 (32.1%)	Chi-square	-	-	0.98	No
Diuretics Inaccuracies	23 (18.0%)	34 (17.9%)	Chi-square	-	-	0.97	No
Laxatives Inaccuracies	38 (30.2%)	56 (29.5%)	Chi-square	-	-	0.89	No
Steroids Inaccuracies	25 (19.7%)	38 (20.0%)	Chi-square	-	-	0.94	No
Private Insurance Inaccuracies	30 (57.7%)	19 (33.3%)	Logistic Regression	0.57	0.33-0.98	0.04	Yes
Government Insurance Inaccuracies	88 (72.7%)	56 (42.1%)	Logistic Regression	0.35	0.22-0.56	<0.001	Yes

Disclosures: Hammad Ashraf: Nothing to Disclose, Abdul Nadir: Nothing to Disclose, Mustafa Ashraf: Nothing to Disclose, Sara Akar: Nothing to Disclose, Adnan Malik: Nothing to Disclose

3348 | USE OF GLP1RA IN A MASLD CLINIC IS INFLUENCED BY TYPE OF INSURANCE COVERAGE

Meagan Gray[1] *Fernando Bril*[1]

[1]*University of Alabama at Birmingham*

Background: Recent guidance recommends use of GLP1RA in patients with MASLD with T2D and/or obesity, as these agents may also reduce liver fat and resolve steatohepatitis. Despite these recommendations, the access to GLP1RA remains challenging even for patients who meet standard criteria for use. Therefore, we sought to assess the use and efficacy of GLP1RA in a hepatology-driven multidisciplinary clinic managing patients with MASLD based on insurance status. **Methods:** Patients who established care at the University of Alabama at Birmingham's Multidisciplinary MASLD clinic from 2/2022 to 1/2024 with at least one follow-up visit were included

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in the study. GLP1RA use was defined as an available prescription for a GLP1RA during the course of follow-up. Participants with excessive alcohol consumption, alternative etiologies of liver disease, and/or steatogenic medications were excluded. Patients who were self-pay (n = 3) were excluded. **Results:** A total of 188 adults were included, 141 (75%) with commercial insurance and 47 (25%) with Medicare/Medicaid (MM). Those with commercial insurance were younger (50 ± 13 vs. 60 ± 15, p<0.001) and had lower prevalence of T2D (33 vs. 59%, p=0.002) and lower A1c (5.9 ± 1.0% vs. 6.4 ± 1.3%, p=0.016) than those with MM, but were similar in terms of gender, presence of obesity, and cirrhosis (Table 1). There were significant racial differences between the groups with less Non-Hispanic Blacks in the commercial group (p = 0.006). Use of GLP1RA was significantly higher in those with T2D and commercial insurance compared to MM (72% vs. 48%, p=0.037), though use was similar in those with obesity without T2D. Patients with commercial insurance had more significant weight loss (-3.8 ± 8.7% vs. MM -0.5 ± 7.7%, p=0.027) and higher likelihood of achieving 10% body weight loss (21 vs. 7%, p=0.030) after a mean follow-up of 17 ± 12 months. **Conclusion:** In a multidisciplinary MASLD clinic, there remain a significant number of patients eligible for GLP1RA treatment based on the presence of T2D and/or obesity who are not receiving it. Despite higher prevalence of T2D and higher A1c values, less patients with MM and T2D were on GLP1RA compared to commercially insured patients. Patients with commercial insurance were able to achieve more significant weight loss and were more likely to achieve the 10% body weight loss target. While safe and effective GLP1RA therapy is available for patients with MASLD, issues remain regarding access, with significant disparities seen in patients with MM.

	Commercial insurance (n = 141)	Medicare/Medicaid (n = 47)	*p*-value
Age (years)	50 ± 13	60 ± 15	<0.001
Gender (% male)	43%	38%	0.55
Race Non-Hispanic White (%) Non-Hispanic Black (%)	 77 9	 64 30	0.006
Body mass index (kg/m^2)	34.6 ± 6.9	35.2 ± 6.8	0.64
Presence of Obesity (%)	73	82	0.21
Presence of T2DM (%)	33	59	0.002
Hemoglobin A1C (%)	5.9 ± 1.0	6.4 ± 1.3	0.016
Presence of cirrhosis (%)	11	20	0.12
Use of GLP1RA in T2DM (%)	72	48	0.037
Use of GLP1RA in T2DM and Obesity (%)	76	55	0.11
Use of GLP1RA in Obesity without T2DM	37	13	0.061
Mean Weight loss (%)	-3.8 ± 8.7	-0.5 ± 7.7	0.027
Rate of patients achieving ≥10% weight loss	21	7	0.030

Disclosures: Meagan Gray: NovoNordiesk: Consultant, Fernando Bril: Nothing to Disclose

3349 | AFFORDABLE HEPATOLOGY: EXPLORING THE POTENTIAL BENEFITS OF THE MARK CUBAN COST PLUS DRUG COMPANY MODEL FOR LIVER DISEASE TREATMENTS

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Background: The prevalence of liver diseases is increasing, fueling the demand for treatments and expanding the U.S. liver disease therapeutics market from $9.7 billion in 2022 to an expected $13 billion by 2030, with a compound annual growth rate (CAGR) of 3.7%. The U.S. generic drugs market is set to grow from $133.59 billion in 2023 to about $188.44 billion by 2033. Despite this growth, high generic drug prices from limited price transparency and administrative inefficiencies burden liver patients. Launched in 2022, the Mark Cuban Cost Plus Drug Company (MCCPDC) aims to reduce these costs. This study assesses MCCPDC's potential to provide cost savings for liver disease patients compared to other pharmacies and to reduce Medicare expenditures. **Methods:**

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We calculated potential national cost savings by analyzing data gathered on total dosage units, pharmacy and shipping fees, and the cost per dose from MCCPDC compared to Medicare spending. Our analysis focused on the proportions of 30-day and 90-day prices attributable to pharmacy and shipping fees, evaluating their impact on overall spending and potential savings. **Results:** In 2022, Medicare spent approximately $638 million on 15 commonly used generic hepatology drugs, with a significant portion of these expenditures coming from pharmacy and shipping costs. Our analysis reveals potential savings of $490 million (76% of total) on 13 of these drugs under the most conservative estimate, and $531 million (83%) on 14 drugs under a less conservative estimate. The impact of pharmacy and shipping fees varied widely; for instance, Furosemide's fees accounted for 83% of its 30-day price, while Adefovir's fees were only 2%. Notable savings were identified for Tenofovir and Entecavir, each offering over $17 million in potential 30-day savings. In contrast, Prednisolone and Lactulose showed potential cost increases over 90 days, leading to negative savings. The total Medicare Part D spending for these drugs in 2022 was roughly $637.99 million, with significant expenses on drugs like Spironolactone and Ursodiol. **Conclusion:** The U.S. generic hepatology drug market offers significant potential for cost savings through increased competition, reduced administrative costs, and patient advocacy for price comparison. MCCPDC provides a cost-effective option, particularly for 90-day supplies, demonstrating potential savings for liver patients. This study highlights the impact of pharmacy and shipping fees on Medicare expenditures and underscores the need for policy interventions to optimize these costs. We encourage hepatologists to advocate for legislative changes to promote price transparency and enhance liver health affordability.

Generic name	Total dosage units 2022	Percentage of 30-day based price attributable to pharmacy and shipping fees (%)	Estimated savings per MCCPDC 30 Day prices	Percentage of 90-day based price attributable to pharmacy and shipping fees (%)	Estimated savings per MCCPDC 90 Day prices	Total medicare part D 2022 spending
Tenofovir	3859518	50	$17,636,091	25	$17,638,950	$17,644,754
Entecavir	5484202	24	$29,497,849	9	$30,716,560	$37,194,012
Lamivudine	2241586	15	$4,403,008	6	$4,407,989	$4,453,070
Adefovir	127661	2	$3,133,986	1	$3,136,823	$3,378,372
Pentoxifylline	39210514	43	$13,640,939	20	$13,662,723	$13,716,746
Prednisolone	8205078	2	-$23,197,111	1	-$22,832,441	$1,308,722
Azathioprine	46675471	8	$29,243,838	3	$29,347,561	$31,182,426
Penicillamine	107192	1	$10,750,578	0	$10,750,673	$10,760,724
Trientine	101965	9	$5,586,320	3	$5,586,411	$5,587,864
Ursodiol	57645975	43	$107,553,932	20	$107,579,552	$107,643,091
Spironolactone	479313487	65	$91,257,472	38	$92,322,613	$93,717,948
Furosemide	1520827293	83	$132,035,548	65	$136,450,172	$139,703,052
Propranolol	301182366	92	$69,079,130	40	$69,388,678	$70,447,000
Nadolol	20798613	63	$23,483,138	36	$23,540,912	$23,621,795
Lactulose	1486169286	49	-$23,924,048	24	$9,101,936	$77,630,853
			$490,180,669		**$530,799,113**	**$637,990,428**

Disclosures: Pratiksha Moliya: Nothing to Disclose, Hasan Al-Obaidi: Nothing to Disclose, Hasan Al-Obaidi: Nothing to Disclose, Omar Saab: Nothing to Disclose, Hima Voruganti: Nothing to Disclose

3350 | HIGHER RISK OF PROTEINURIA IN ATEZOLIZUMAB PLUS BEVACIZUMAB THAN LENVATINIB AS A FIRST-LINE SYSTEMIC TREATMENT IN UNRESECTABLE HEPATOCELLULAR CARCINOMA

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Background: Proteinuria presents a challenging complication during systemic therapy for hepatocellular carcinoma (HCC). This study aims to identify risk factors for proteinuria in patients with HCC treated with atezolizumab plus bevacizumab (Atezo/Bev) or lenvatinib (LEN) as first-line systemic treatment. **Methods:** A retrospective analysis was conducted of 604 consecutive patients with unresectable HCC who received Atezo/Bev or LEN as first-line systemic treatment between October 2013 and October 2022. Cumulative incidence

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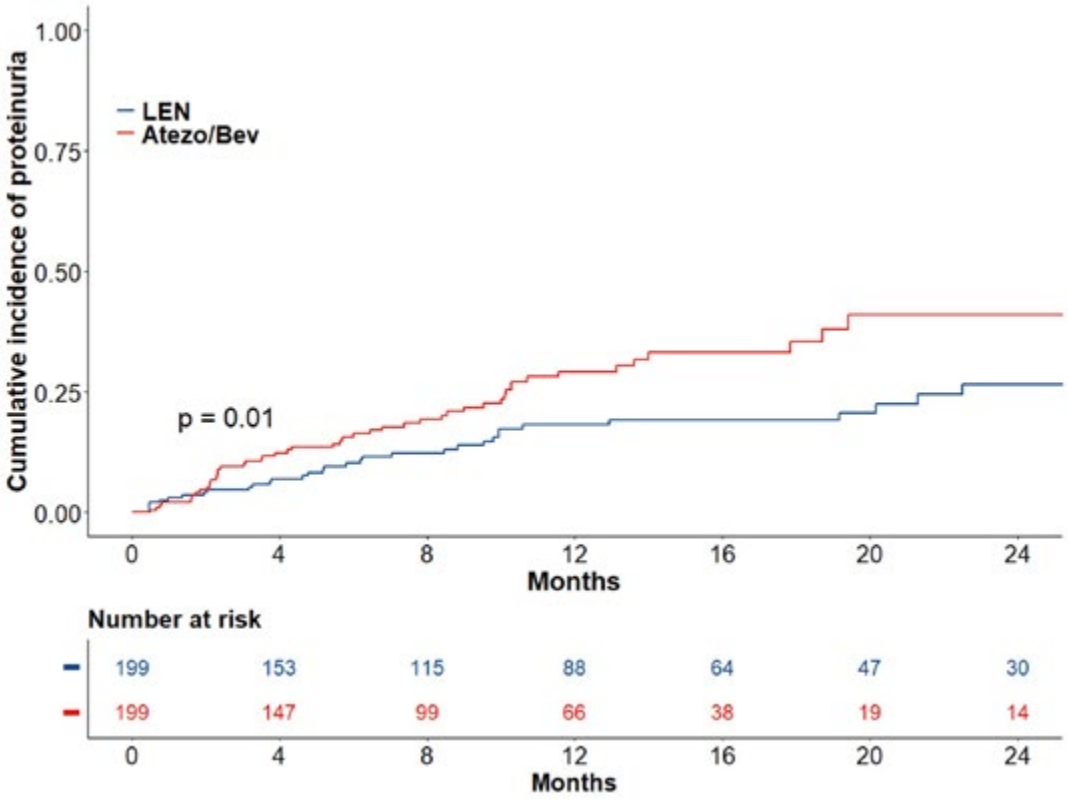
of proteinuria was estimated using Kaplan–Meier curves and compared using log-rank tests. Risk factors for proteinuria were identified using Cox proportional hazard models, along with propensity score-matched and subgroup analyses. **Results:** Among 349 patients treated with Atezo/Bev and 255 with LEN, the cumulative incidence of proteinuria at 12 months was 25.4%. In the multivariable analysis, Atezo/Bev treatment (hazard ratio [HR], 1.73; 95% confidence interval [CI], 1.21–2.47; *P*=0.003), diabetes (HR, 1.52; 95% CI, 1.04–2.24; *P*=0.03), Child–Pugh class B (HR, 3.56; 95% CI, 1.46–8.72; *P*=0.01), macrovascular invasion (MVI; HR, 1.51; 95% CI, 1.06–2.14; *P*=0.02), and an estimated glomerular filtration rate ≤60 mL/min/1.73 m^2 (HR, 3.31; 95% CI, 2.02–5.41; *P*<0.001) were identified as risk factors for proteinuria. A higher risk of proteinuria in Atezo/Bev patients compared with LEN was consistently observed in the PS-matched cohort, particularly pronounced in subgroups with MVI (HR, 3.15; 95% CI, 1.52–6.52; *P*=0.002) compared with those without MVI (HR, 1.25; 95% CI, 0.73–2.15; *P*=0.42). **Conclusion:** Patients treated with Atezo/Bev as first-line systemic treatment for HCC exhibited a higher risk of proteinuria compared with those with LEN, particularly when accompanied by MVI.



Disclosures: Jiwon Yang: Nothing to Disclose

3351 | LOCOREGIONAL TREATMENTS FOR BRIDGING PATIENTS WITH HEPATOCELLULAR CARCINOMA TO LIVER TRANSPLANTATION

Grace Lee[1] *Kelsey Lau-Min*[1] *Elizabeth Walsh*[1] *Hannah Roberts*[1] *Theodore Hong*[1] *Nahel Elias*[1] *Jennifer Wo*[1]

[1]*Massachusetts General Hospital*

Background: Locoregional treatments (LRT) can bridge patients with hepatocellular carcinoma (HCC) to liver transplantation (LT) which offers the best chance of cure. Here, we aimed to determine the efficacy and safety of various LRT modalities used pre-LT and evaluate the outcomes post-LT. **Methods:** A retrospective review identified patients with HCC who received LRT(s) pre-LT between 2015-2023. Tumor response, local failure (LF), distant recurrence (DR), and hepatotoxicity (per CTCAE v5 G3+ liver function tests and/or 2+ Child-Turcotte Pugh [CTP] score increase) within 6 months post-LRT were compared between LRT modalities. Surgical complications, disease free survival (DFS), and overall survival (OS) post-LT were evaluated. **Results:** 122 patients received a total of 209 LRTs pre-LT. Cumulative number of LRT was 1 in 50%, 2 in 33%, 3+ in 17%. LRT modalities included microwave/radiofrequency ablation (MWA/RFA; n=119), transarterial chemoembolization (TACE; n=66),

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transarterial radioembolization (TARE; n=16), and external beam radiation (EBRT; n=8). There was an increased use of TARE and MWA in recent years. 39% of LRT resulted in pathologic complete response (pCR) with highest rate post EBRT (63%) and MWA/RFA (47%) compared to TACE (23%) and TARE (38%). 13% had LF at a median time of 8 months and 29% had DR (all intrahepatic) at a median time of 7 months post-LRT, with no significant difference between LRT modalities. 27% of LRTs were associated with hepatotoxicity, with no significant difference in LRT modalities. Median time to LT was 13 months from initial listing. Median follow up post-LT was 49 months. Pre-LT, 32% of patients had radiographic residual HCC. Upon LT, 31% of patients had pCR while 69% had residual HCC (26% outside Milan criteria). Post-LT, 36% had surgical complications (19% re-operation), with no significant difference in LRT modalities received. LRT-related hepatotoxicity was a significant predictor of surgical complications (OR=2.3 [95% CI 1.08-5.02], p=0.03). Post-LT, DFS was 83% and OS was 87% at 4-years, with no significant difference in LRT modalities received. Higher MELD and AFP pre-LT, higher pathologic T stage, nodal involvement, and major vessel invasion were associated with worse DFS and OS. **Conclusion:** While EBRT and MWA/RFA were associated with higher pCR, other outcomes such as hepatotoxicity, surgical complications, and DFS/OS post-LT were comparable across LRT modalities. Future studies should evaluate individualized LRT strategies in HCC management.

Disclosures: Grace Lee: Nothing to Disclose, Kelsey Lau-Min: Nothing to Disclose, Elizabeth Walsh: Nothing to Disclose, Hannah Roberts: Nothing to Disclose, Theodore Hong: Nothing to Disclose, Nahel Elias: Nothing to Disclose, Jennifer Wo: Nothing to Disclose

3352 | ANALYSIS OF FACTORS PREDICTING THE REAL-WORLD EFFICACY OF ATEZOLIZUMAB AND BEVACIZUMAB IN PATIENTS WITH ADVANCED HEPATOCELLULAR CARCINOMA

CHANG WON HA[1] *Yong-Han Paik*[1] *Byeong Geun Song*[1]

[1]*Samsung Medical Center*

Background: Atezolizumab and bevacizumab has shown promising efficacy in clinical trials for advanced hepatocellular carcinoma (HCC). This study aims to validate these findings with comprehensive real-world data on their efficacy and safety in advanced HCC patients. **Methods:** We conducted a retrospective cohort study at a tertiary cancer center in Korea, including 111 patients with advanced HCC treated with atezolizumab and bevacizumab as first-line therapy from May 2022 to June 2023. We assessed overall survival (OS), progression-free survival (PFS), objective response rate (ORR), disease control rate (DCR) according to RECIST v1.1, and safety profile. **Results:** Of the patients, 38% had macrovascular invasion and 33% presented high risk features, including extensive portal vein tumor thrombosis, bile duct invasion, and significant liver infiltration (over 50%). The median OS was reported at 10.6 months (95% confidence interval 8.9-13.1 months). The ORR and DCR were 27% and 63%, respectively. Albumin-Bilirubin (ALBI) grade and Alpha-fetoprotein (AFP) levels were significant predictors of OS, with AFP also associated with PFS and ORR. Combined radiotherapy positively impacted PFS and ORR. Patients with peritoneal seeding exhibited a favorable response. The safety profile was consistent with that observed in clinical trials. **Conclusion:** The real-world application of atezolizumab and bevacizumab for advanced HCC has validated its efficacy. The study identified ALBI grade, AFP levels, combined radiotherapy, and the presence of peritoneal seeding as significant prognostic factors affecting clinical outcomes.

Disclosures: CHANG WON HA: Nothing to Disclose, Yong-Han Paik: Nothing to Disclose, Byeong Geun Song: Nothing to Disclose

3353 | DEVELOPING AND VALIDATING A MACHINE LEARNING MODEL FOR LONG-TERM PROGNOSIS PREDICTION IN PATIENTS WITH BCLC0-A STAGE LIVER CANCER

Yi Zhang[1] *Xianbo Wang*[1] *Fangyuan Gao*[1]

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Background: The mortality and recurrence rates of hepatocellular carcinoma (HCC) remain high, making early treatment and clinical management crucial for patients. Despite this, there is a significant lack of effective

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predictive tools in clinical practice. This study aims to develop a new prognostic model using machine learning techniques to help physicians identify patients with BCLC stages 0-A HCC who are at a higher risk of long-term mortality. **Methods:** A total of 993 patients with hepatocellular carcinoma (HCC) hospitalized at Beijing Ditan Hospital, Capital Medical University, were selected for this study. These patients were randomly divided into a training group and a validation group at a 2:1 ratio. The prognostic model, termed LRA, was developed using a multifactorial Cox regression, random forest, and artificial neural networks. The performance and clinical utility of the LRA model were assessed by comparing it with other classical liver cancer scoring systems. The model's accuracy was evaluated using the area under the receiver operating characteristic curve (AUC), calibration curves, and decision curves, and was validated in the validation cohort. Finally, Kaplan-Meier survival analysis was used to compare survival outcomes among patients with high, medium, and low risk, and the performance of the LRA model was assessed across different subgroups. **Results:** Among all prognostic models evaluated, the LRA model demonstrated superior predictive performance, with AUCs of 0.81 (95% CI: 0.74-0.87), 0.80 (95% CI: 0.75-0.84), and 0.85 (95% CI: 0.82-0.87) at 1, 3, and 5 years, respectively. In the validation cohort, the corresponding AUCs were 0.76 (95% CI: 0.64-0.88), 0.72 (95% CI: 0.66-0.78), and 0.79 (95% CI: 0.74-0.85). The LRA model significantly outperformed other classic models such as the random forest model, multifactorial Cox regression, and JIS, OKUDA, CLIP, CUPI staging systems in both training and validation sets ($p<0.001$). According to the LRA model, patients were categorized into high, medium, and low-risk groups. The survival rates for high and medium-risk patients were significantly lower than those for the low-risk group ($p<0.0001$). Compared with low-risk patients, the hazard ratios for 5-year overall survival (OS) for the high and medium-risk groups were 6.95 (95% CI: 4.76-9.20) and 3.81 (95% CI: 3.10-6.24), respectively ($P<0.0001$). The 1, 3, and 5-year survival rates for the low-risk group were 97.8%, 88.7%, and 70.9%, respectively. **Conclusion:** A non-invasive, low-cost model has been developed, utilizing artificial neural networks. This model exhibits strong predictive performance in assessing the five-year survival rates of patients with early-stage hepatocellular carcinoma. It assists clinicians in identifying high-risk patients with poor prognosis, thereby supporting enhanced clinical monitoring and early intervention.

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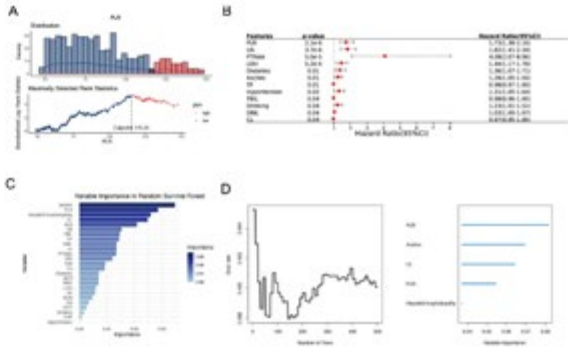
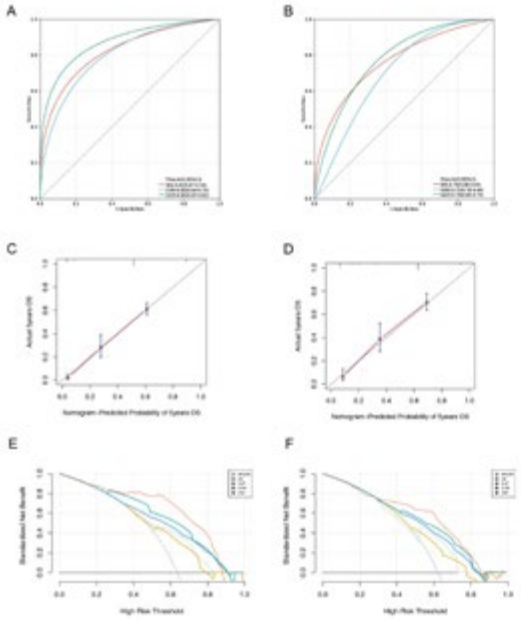
Random Grouping of Patients

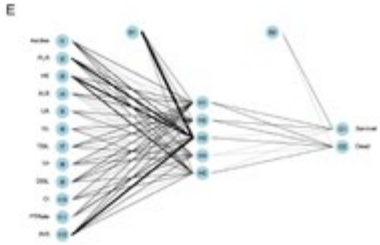


Prognostic Model Construction

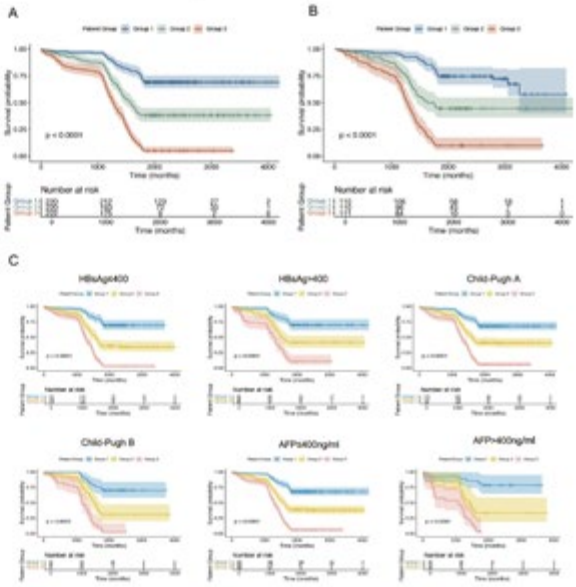


Predictive Performance of the LRA Machine Learning Model

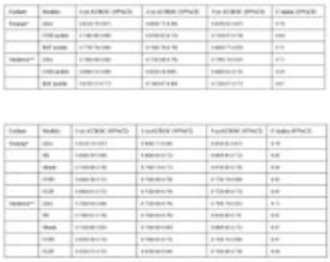




Subgroup Analysis of Patients



Comparison of LRA with Other Models



Disclosures: Yi Zhang: Nothing to Disclose, Xianbo Wang: Nothing to Disclose, Fangyuan Gao: Nothing to Disclose

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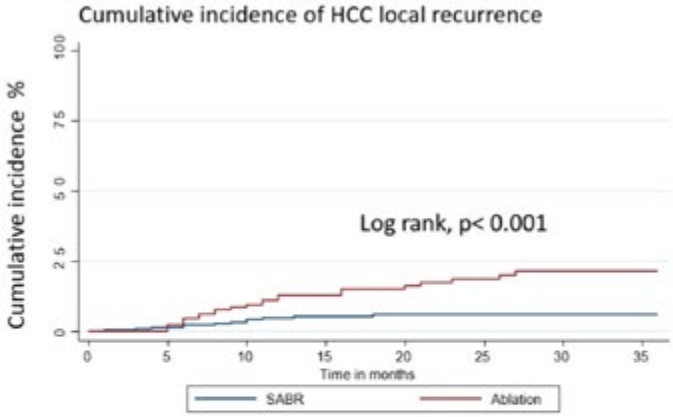
3354 | STEREOTACTIC ABLATIVE BODY RADIOTHERAPY VERSUS ABLATION FOR THE TREATMENT OF EARLY-STAGE HEPATOCELLULAR CARCINOMA

Darragh Egan[1] Fadak Mohammadi[2] Lauren Andersson[3] William Ormiston[1] Jonathan Tibballs[1] Shaun Samuelson[1] Matthys Van Wyk[1] Matthew Clifford[1] Luis Calzadilla Bertot[4] Hien Le[5] Michael Wallace[1] Alan Wigg[2]

[1]Sir Charles Gairdner Hospital, [2]Flinders Medical Centre, [3]St Vincent's Hospital Melbourne, [4]University of Western Australia, [5]Royal Adelaide Hospital

Background: Stereotactic ablative body radiotherapy (SABR) shows promise as a curative therapy for early-stage hepatocellular carcinoma (HCC) by delivering high dose, targeted radiation. Its use is limited by a lack of high-quality comparative data with current standard of care treatments. The aim of this study was therefore to assess the efficacy of SABR compared to percutaneous ablation (PA) in a large Australian cohort, with the primary outcome of local recurrence. **Methods:** This was a retrospective cohort study from two Australian quaternary referral centers from May 2012 to February 2024 of 276 patients (369 tumors treated) who underwent SABR or PA (MWA and RFA) with a minimum 1-year follow-up. Cox proportional hazard regression analysis was performed per tumor treated. Adverse events (AEs) were recorded according to the Common Terminology Criteria for Adverse Events (CTCAE), Version 5. **Results:** A total of 235 episodes of SABR and 134 episodes of PA in 276 patients were included. The cohorts had a similar median age (65 vs 63) and similar percentage of male patients (80% vs 82%). Most common aetiology for both cohorts was hepatitis C followed by alcohol associated liver disease. Clinical characteristics that differed significantly between SABR and PA groups included ECOG score of 0 (70% vs 95%; p<0.0001), prior HCC treatment (71% vs 46%; p<0.0001), tumors >3cm (22% vs 5%; p<0.0001) The mean dose of radiation in the SABR group was 43.9 Gy delivered in a mean of 3.8 fractions. Local recurrence in the SABR cohort were 4.6% (95 % CI 2.5-8.4%), 6.0% (CI 3.2-10%) and 6.0% (95% CI 3.2-10%) at 1, 2 and 3 years respectively. Local recurrence rates in the ablation cohort were 11% (95% CI 6.8-18%), 18% (95 %CI 12-27%) and 21% (95 %CI 14.8-31%) at 1, 2 and 3 years respectively (p<0.001) (Figure). After adjustment for age, sex, MELD, previous HCC treatment, tumor size, AFP and BCLC stage, the SABR cohort had an 85% reduced risk of recurrence compared to the PA cohort (HR 0.15; 95 % CI 0.06-0.37, p<0.01). For progression events outside the radiation field there was a similar rate for SABR and PA 50.2% versus 46.3% respectively (p=0.466). Rate of treatment related adverse events (AE) was identical in both groups (43%). There was only one Grade 3 AE, an hepatic abscess 4 months post SABR. **Conclusion:** This is the largest study of early HCC treated with SABR in Australia. SABR demonstrated excellent local tumor control compared to PA, and a low rate of serious AEs. Our observational study is further justification for ongoing randomized controlled trials investigating primary treatment with SABR vs standard of care for early-stage HCC.



	1 year (95% CI)	2-year (95% CI)	3-year (95% CI)
SABR	4.6 (2.5-8.4)	6.0 (3.4-10)	6.0 (3.4-10)
Ablation	11 (6.8-18)	18 (12-27)	21 (14.8-31)

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Disclosures: Darragh Egan: Nothing to Disclose, Fadak Mohammadi: Nothing to Disclose, Lauren Andersson: Nothing to Disclose, William Ormiston: Nothing to Disclose, Jonathan Tibballs: Nothing to Disclose, Shaun Samuelson: Nothing to Disclose, Matthys Van Wyk: Nothing to Disclose, Matthew Clifford: Nothing to Disclose, Luis Calzadilla Bertot: Nothing to Disclose, Hien Le: Nothing to Disclose, Michael Wallace: Nothing to Disclose, Alan Wigg: Nothing to Disclose

3355 | THE ASAP SCORE DEMONSTRATES HIGH SENSITIVITY FOR HEPATOCELLULAR CARCINOMA (HCC) AND IS FEASIBLE FOR USE IN HCC SURVEILLANCE – A PROSPECTIVE STUDY ◆

Chee-Kiat Tan[1] Si-Yu Tan[1] Kaina Chen[1] Jason Pik Eu Chang[1] Thinesh Krishnamoorthy[1] Claire Chen[2] Chin-Pin Yeo[1] Wei-Lun Liou[1]

[1]Singapore General Hospital, [2]Abbott Diagnostics

Background: Hepatocellular carcinoma (HCC) surveillance with liver ultrasound and alpha-fetoprotein (AFP) has limitations of accuracy and patients' poor adherence with ultrasound examination. The ASAP score is a HCC risk algorithm based on Age, Sex, AFP, and Protein Induced by Vitamin K Antagonist-II (PIVKA-II) that may allow for a personalized surveillance protocol. We studied the performance of the ASAP score in a prospective cohort of patients undergoing HCC surveillance. **Methods:** Patients without prior HCC undergoing HCC surveillance in Singapore General Hospital Department of Gastroenterology and Hepatology between December 2017 to October 2018 were enrolled. Baseline AFP and PIVKA-II (Abbott ARCHITECT®) were assayed and prediction from the ASAP score was calculated using the published model. The patients continued HCC surveillance with semi-annual ultrasound and AFP. **Results:** There were 612 patients (60.9% male). Median age was 65 years (IQR 58-72). Most common liver disease was Hepatitis B (90%). By February 2023, after a median follow-up of 52.2 months (IQR 48.3-54.5), 15 patients developed HCC with 13 in BCLC stage 0/A. ASAP score had the highest AUROC (0.767) for HCC detection, compared to AFP or PIVKA-II alone (0.743 and 0.672 respectively). The ASAP score's sensitivity, specificity, negative predictive value (NPV), AUROC for HCC developing within 1 and 2 years of biomarker assessment were 100%, 87.3%, 100%, 0.946 and 83%, 87.3%, 99.8%, 0.889, respectively. **Conclusion:** The ASAP score demonstrated high sensitivity, specificity and NPV for HCC detection in a prospective cohort of patients undergoing HCC surveillance. In view of patients' poor adherence to ultrasound imaging during surveillance of HCC, it may be feasible to substitute ultrasound with regular assessment of the ASAP score instead.

Disclosures: Chee-Kiat Tan: Eisai: Advisor, Abbott Laboratories: Advisor, Gilead Sciences: Advisor, Roche Diagnostics: Advisor, Fujifilm: Advisor, Si-Yu Tan: Nothing to Disclose, Kaina Chen: Nothing to Disclose, Jason Pik Eu Chang: Boehringer Ingelheim: Advisor, Thinesh Krishnamoorthy: Nothing to Disclose, Claire Chen: Abbott Laboratories: Employee, Chin-Pin Yeo: Nothing to Disclose, Wei-Lun Liou: Nothing to Disclose

3356 | UCSF CRITERIA AND LIVER DYSFUNCTION PREDICT HEPATOCELLULAR CARCINOMA (HCC) RECURRENCE AFTER SURGERY FOR HCC: A LARGE MULTICENTRE STUDY

Conner Blackmore[1] Ian Lockart[2] Yueh Yeoh[3] Ciara Flynn[3] Gregory Dore[4] mark danta[2] Jacob George[5] Maryam Alavi[6] Basheer Alshiwanna[7] Behzad Hajarizadeh[6] Miriam Levy[7]

[1]Liverpool Hospital Australia, [2]St Vincents Hospital, Sydney Australia, [3]Faculty of Medicine, UNSW Australia, [4]The Kirby Institute, [5]The University of Sydney, [6]Kirby Institute, Sydney Australia, [7]Liverpool Hospital, Sydney Australia

Background: Primary liver cancer is the third leading cause of cancer-related death worldwide, with hepatocellular carcinoma (HCC) accounting for 80% of primary liver cancers. Liver resection is a curative treatment for early HCC (more than 2cm or when inaccessible to locoregional ablation), however there is a paucity of literature on predicting the likelihood of HCC recurrence following resection. We evaluated factors related to recurrence following primary HCC resection with curative intent. **Methods:** We retrospectively reviewed the electronic medical records of patients with HCC who underwent primary resection at three tertiary referral hospitals in Australia between January 2008 and May 2022. Baseline and follow-up characteristics, including

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liver disease, patient, and tumour characteristics were collected. The incidence rate of HCC recurrence following curative resection, and the factors associated with recurrence risk was evaluated. **Results:** A total of 242 patients underwent surgical resection with a median follow up of 36.6 months (IQR: 13.8 - 60.5). The overall survival rate at 3 years was 54%, with total disease-free survival at 3 years 29%. Underlying HCC aetiology was hepatitis C virus (HCV) in 73 (30%), hepatitis B virus (HBV) in 98 (41%) and non-viral in 71 (29%). Clear histological margins and complete post-operative radiological response was achieved in 190 (79%) patients with 1 (0.4%) 90-day mortality. Recurrence occurred in 94 (39%) with median time to recurrence of 18.8 months (IQR: 8.6 - 35]). The incidence rate of recurrence was 10.5 per 100 person-years (95% CI: 8.6 – 12.9). Multivariate Cox regression analysis identified an increased risk of HCC recurrence was independently associated with: MELD score ≥ 7 (aHR: 2.36; 95% CI: 1.20 - 4.63; p = 0.012), Alpha-fetoprotein (AFP) ≥ 400 (aHR: 4.76; 95% CI: 2.07 - 10.91; p < 0.001), albumin-bilirubin (ALBI) grade ≥ 2 (aHR: 1.71; 95% CI: 1.00 - 2.90; p = 0.049) and if tumour was outside UCSF criteria (aHR: 2.09; 95% CI: 1.08 - 4.04; p = 0.029). HCC aetiology was not associated with recurrence risk. **Conclusion:** HCC recurrence in those having liver resection is more likely in those with worse liver function and those with tumours outside the UCSF criteria. Enhanced post-surgical interval surveillance could be considered for patients with this risk profile.

Factors associated with recurrence of hepatocellular carcinoma among patients who underwent liver resection as their first management. (n=242)

		Unadjusted model		Adjusted model 1*		Adjusted model 2*
Characteristics	**Rate of recurrence (95% CI) - Per 100 person years**	**HR (95% CI)**	**P-value**	**HR (95% CI)**	**P-value**	**HR (95% CI)**
Aetiology of HCC						
- HBV	8.7 (6.2 – 12.3)	1.00				
- HCV	14.5 (10.4 – 20.0)	**1.74 (1.08 – 2.81)**	**0.022**	1.19 (0.69 – 2.05)	0.535	1.25 (0.72 – 2.17)
- MAFLD/ETOH	9.4 (6.4 – 13.9)	1.27 (0.74 – 2.16)	0.386	0.88 (0.48 – 1.62)	0.686	0.92 (0.50 – 1.68)
Age, year	N/A	**1.02 (1.01 – 1.05)**	**0.016**	**1.03 (1.01 – 1.06)**	**0.004**	**1.03 (1.01 – 1.06)**
Age, years						
- 1-39	5.1 (0.4 – 21.7)	1.00				
- 40-49	8.5 (4.1 – 17.6)	3.37 (0.41 – 27.76)	0.260			
- 50-59	10.4 (7.1 – 15.1)	4.18 (0.56 – 31.20)	0.163			
- 60-69	10.1 (7.2 – 14.2)	4.97 (0.66 – 37.24)	0.119			
- 70-79	13.7 (8.9 – 21.0)	7.03 (0.92 – 53.68)	0.060			
- 80-89	14.0 (5.8 – 33.7)	6.94 (0.79 – 60.94)	0.081			
Sex						
- Male	10.4 (8.2 – 13.0)	1.00				
- Female	11.3 (7.3 – 17.5)	1.15 (0.70 – 1.89)	0.576			
Country of birth						
- Australia	10.9 (7.1 – 16.5)	1.00				
- Outside Australia	10.3 (8.2 – 13.0)	0.83 (0.51 – 1.35)	0.446			
Aboriginal or Torres Strait Islander - unable to analyse due to small sample size						
Diabetes (T2DM)						
- Nil diabetes	10.7 (8.4 – 13.6)	1.00				
- T2DM	10.2 (7.0 – 14.8)	1.09 (0.69 – 1.71)	0.715			
Child Pugh						
- No cirrhosis	7.9 (5.7 – 11.0)	1.00				
- AS	11.7 (8.7 – 15.7)	**1.87 (1.17 – 2.97)**	**0.008**	**2.50 (1.41 – 4.43)**	**0.002**	
- >/=AS	19.7 (12.1 – 32.2)	**3.28 (1.78 – 6.04)**	**<0.001**	**2.60 (1.20 – 5.62)**	**0.015**	
MELD score						
- No Cirrhosis	7.7 (5.5 – 10.8)	1.00				
- 6	7.6 (4.0 – 14.7)	1.25 (0.60 – 2.64)	0.557			1.22 (0.50 – 2.96)
- 7	12.6 (8.0 – 19.8)	**1.94 (1.10 – 3.43)**	**0.023**			**2.36 (1.20 – 4.63)**
- >7	17.6 (12.5 – 24.9)	**3.33 (1.99 – 5.57)**	**<0.001**			**3.51 (1.93 – 6.40)**
AFP						
- <400 (n=193)	10.0 (8.0 – 12.5)	1.00				
- >/=400 (n=24)	**18.3 (9.2 – 36.7)**	**2.12 (1.02 – 4.44)**	**0.045**	**5.09 (2.22 – 11.70)**	**0.000**	**4.76 (2.07 – 10.91)**
Detection of initial HCC						
- Incidental/symptomatic	11.5 (8.3 – 15.9)	1.00				
- Surveillance	9.5 (7.2 – 12.5)	0.71 (0.46 – 1.11)	0.132			
Platelet count						
- </= 150	9.9 (6.6 – 15.0)	1.00				
- >150	10.8 (8.5 – 13.6)	1.09 (0.68 – 1.75)	0.721			
ALBI grade						
- 1	9.1 (7.1 – 11.7)	1.00				
- >/= 2	14.9 (10.6 – 21.0)	**2.24 (1.43 – 3.52)**	**<0.001**	**1.79 (1.00 – 3.19)**	**0.050**	**1.71 (1.00 – 2.90)**
UCSF Criteria						
- In (n = 198)	10.0 (8.0 – 12.5)	1.00				
- Out (n= 44)	14.2 (8.7 – 23.2)	**1.81 (1.04 – 3.15)**	**0.035**	**2.12 (1.08 – 4.18)**	**0.029**	**2.09 (1.08 – 4.04)**

* "MELD score" was not included in this model due to collinearity with "Child Pugh"; ** "Child Pugh" was not included in this model due to collinearity with "MELD score".

Disclosures: Conner Blackmore: Nothing to Disclose, Ian Lockart: Nothing to Disclose, Yueh Yeoh: Nothing to Disclose, Ciara Flynn: Nothing to Disclose, Gregory Dore: Nothing to Disclose, mark danta: Nothing to Disclose, Jacob George: Nothing to Disclose, Maryam Alavi: Nothing to Disclose, Basheer Alshiwanna: Nothing to Disclose, Behzad Hajarizadeh: Nothing to Disclose, Miriam Levy: Nothing to Disclose

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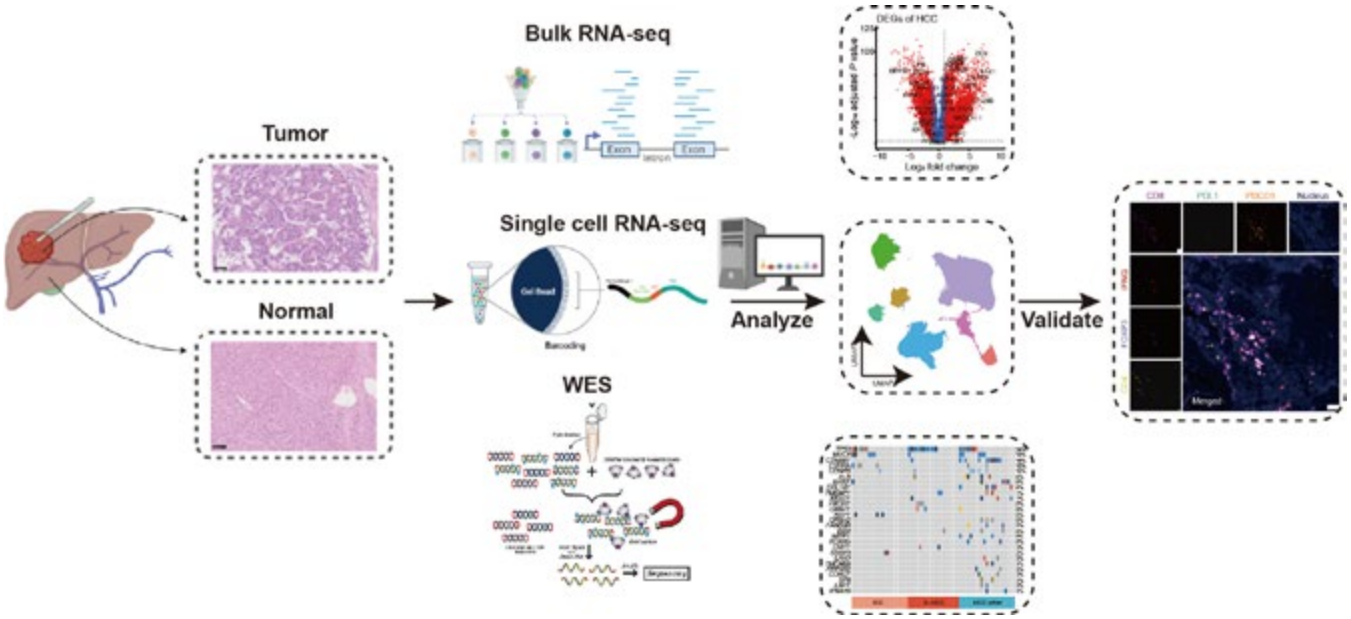
3357 | MULTI-OMICS ANALYSES IDENTIFY A NOVEL HCC SUBTYPE WITH WORSE PROGNOSIS AND BETTER RESPONSE TO IMMUNE CHECKPOINT INHIBITOR BASED THERAPIES

Junjie Xu[1]

[1]*Zhejiang University*

Background: The overall comprehensive treatment effect is less than satisfactory for HCC patients. There is a crucial need to identify different molecular subtypes for precise diagnosis and treatment. **Methods:** Whole transcriptome sequencing was performed on tumor and adjacent non-tumor tissues across 242 patients with hepatocellular carcinoma (HCC) and 51 patients with intrahepatic cholangiocarcinoma (ICC). Whole exome sequencing was performed in selected samples of each cancer subtype. Single-cell RNA sequencing was performed on fresh primary tumor samples from 15 HCC patients and 8 ICC patients. **Results:** The HCC tumors were clustered into four subtypes, among which ICC-like HCC (IL-HCC) is a novel subtype that is transcriptionally similar to ICC rather than the other HCC subtypes. IL-HCC and ICC showed significant metabolic and immunological commonalities, including high levels of glycan biosynthesis, reduced levels of glucose/lipid metabolism, increased hypoxia, and high immune cell infiltration with exhausted CD8+ T cells and activated mast cells. Single-cell RNA sequencing further suggested an exhausted immune microenvironment in IL-HCC tumors. Whole exome sequencing revealed that IL-HCC and ICC had a significantly lower tumor mutation burden. TP53, PIK3R1, OR6P1, and CHIT1 were identified as the driver genes of the IL-HCC subtype. A 29-gene expression signature was developed and external validated to distinguish IL-HCC subtype. Importantly, this subtype was characterized by a considerably worse prognosis but better response to immune checkpoint inhibitor based therapies. **Conclusion:** Our analysis revealed broad similarities between IL-HCC and ICC in metabolism, immune infiltration, gene mutations, and overall survival. These results provide a more accurate basis for precision medicine-based treatments of HCC.



Disclosures: Junjie Xu: Nothing to Disclose

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3358 | FGF18,A POTENTIAL PREDICTIVE MARKERS OF IMMUNE COMBINED WITH TARGETED THERAPY FOR PRIMARY LIVER CANCER

Hua Xu[1] *Zhi Zhou*[1]

[1]*the Second Affiliated Hospital, CQMU*

Background: This study plans to collect peripheral blood specimens of patients with primary liver cancer before targeted immunotherapy to explore new circulating biomarkers. **Methods:** Blood specimens were collected from patients before treatment, and peripheral blood mononuclear cell (PBMC) was isolated for transcriptome sequencing. Bioinformatics analysis was conducted to screen for differentially expressed genes based on sequencing results. The expression of differentially expressed gene was detected at the gene and protein levels in patients with different efficacy groups. The potential as predictive factor was evaluated through survival analysis. Transgenic mice overexpressing target genes or control genes was created, and a liver cancer xenograft model was established using Hepa1-6 mouse liver cancer cells. Subsequently, targeted immunotherapy will be administered to both groups of mice. PBMCs and tumor tissues will be collected before and after treatment from both groups of mice. The expression of differentially expressed gene and the downstream pathway-related proteins were detected. **Results:** In this study, a total of 30 peripheral blood specimens were obtained, comprising 14 in the durable clinical benefit (DCB) group and 16 in the non-durable clinical benefit (NDB) group. Notably, the expression of fibroblast growth factor 18 (FGF18) exhibited significant correlations with both PFS and OS in patients, leading to its identification as the target biomarker. Validation analysis conducted on patients' peripheral blood specimens demonstrated an upregulation of FGF18 mRNA and protein expression levels in the DCB group compared to the NDB group. Survival analysis further confirmed that patients with elevated FGF18 expression experienced longer PFS compared to those with lower FGF18 expression. The FGF18 overexpression group had higher infiltration of CD4+T cells and CD8+T cells but lower infiltration of FOXP3+T cells compared to the control group. After treatment, both groups showed an increase in Treg cells and exhausted T cells, with a higher increase observed in the control group than in the FGF18 overexpression group. Additionally, after treatment, both groups showed increased IFN-γ expression levels in CD8+T cells, with the FGF18 overexpression group exhibiting higher levels than the control group. Furthermore, results showed that there was no significant difference in the levels of FGFR expression after treatment. Finally, after treatment, the FGF18 overexpression group showed higher total expression levels, phosphorylation (Tyr701) levels of STAT1, and PD-L1 expression compared to the control group. **Conclusion:** This study highlights serum FGF18 as a promising circulating biomarker for predicting immune therapy efficacy. The mechanism through which FGF18 influences targeted immunotherapy efficacy may involve the suppression of activated FGF/FGFR pathways post-treatment.

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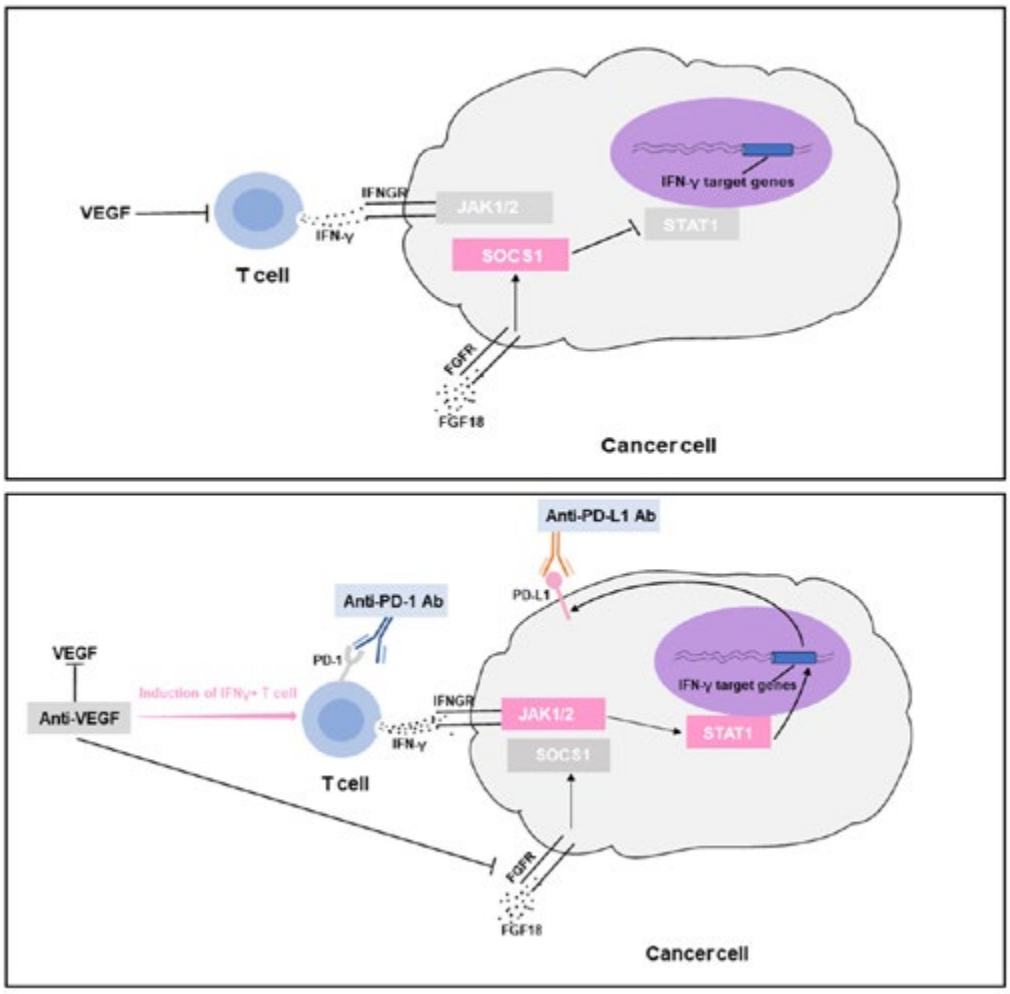

Disclosures: Hua Xu: Nothing to Disclose, Zhi Zhou: Nothing to Disclose

3359 | NO IMPACT OF SARCOPENIA ON PROGNOSIS OF TRANSARTERIAL CHEMOEMBOLIZATION FOR HEPATOCELLULAR CARCINOMA

Chun-Ming Hong[1] Chih-Horng Wu[1] Tung-Hung Su[1] Shih-Jer Hsu[1] Tai-Chung Tseng[1] Chen-Hua Liu[1] Hung-Chih Yang[1] Jia-Horng Kao[1] Pei-Jer Chen[1] Shang-Chin Huang[2] Chun Jen Liu[1]

[1]National Taiwan University Hospital, [2]National Taiwan University

Background: Chronic liver diseases are associated with poor nutritional status especially when progress to advanced liver disease or liver cirrhosis, and such status is related to development of hepatocellular carcinoma (HCC). Sarcopenia, loss of skeletal muscle mass, strength, and function, is related to poor nutritional status and adversely affects clinical outcomes. Sarcopenia is common in 65-100% of liver cirrhotic patients with advanced liver disease and its occurrence is irrespective of etiology.Transarterial chemoembolization (TACE) is a standard of care for intermediate-stage HCC, although treatment response varies. Whether sarcopenia affect prognosis of TACE remains unclear. **Methods:** We recruited 161 adult HCC patients who were TACE-naive from 2015 to 2018 in National Taiwan University Hospital. Skeletal muscle index (SMI), a height squared-adjusted cross-section area of the muscles at the third lumbar vertebra on CT or MRI, is an indicator of sarcopenia. The mean of measurements on two adjacent CT slices at L3 level was used to calculate the L3 skeletal muscle index (L3 SMI) by correcting it for height. Sarcopenia is defined as a L3 SMI<41cm2/m2 in women, <43cm2/m2 in men with a body mass index (BMI) of <25 and <53cm2/m2 in men with a BMI of >25. **Results:** Among these 161 patients, 118 were male and 43 were female. The average age was 67 years old. 32 male patients (27.1%) had sarcopenia and 23 female patients had sarcopenia (53.5%). 156 patients (96.9%) had liver cirrhosis. 41 patients (25.5%)

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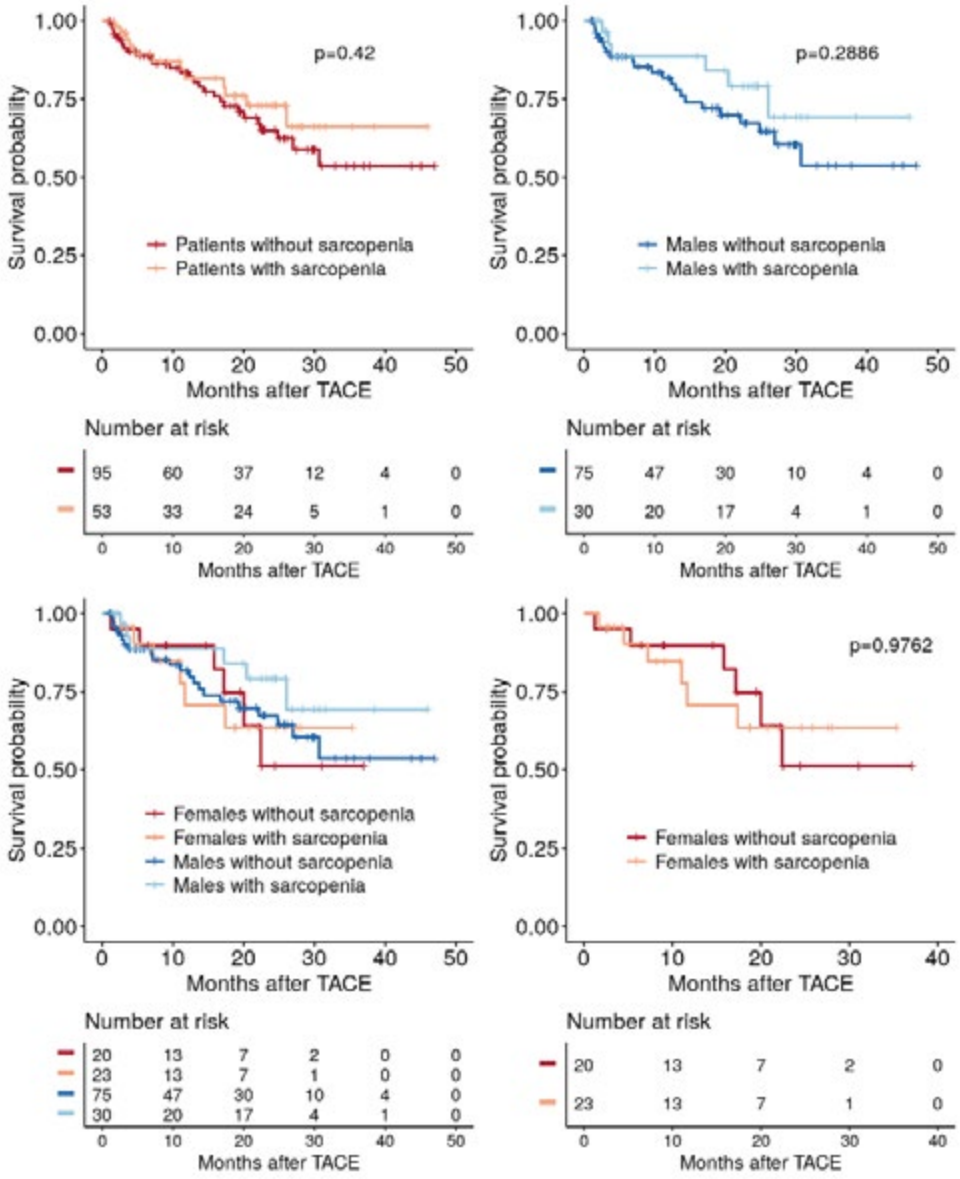
had infiltrative type HCC. The average tumor number was 5.4. 111 patients (68.9%) received conventional TACE while 50 patients (31.1%) had drug-eluting bead TACE. In univariate Cox regression analysis, infiltrative type, vascular invasion, necrosis, tumor number, largest tumor size, and post-TACE AFP had impact on OS (overall survival). While in multivariate Cox regression analysis, only vascular invasion had statistical significance on OS. Sarcopenia did not have statistical significance in both univariate and multivariate Cox regression analysis. **Conclusion:** Our data suggest that sarcopenia has no impact on the prognosis of TACE for intermediate-stage HCC.



Disclosures: Chun-Ming Hong: Nothing to Disclose, Chih-Horng Wu: Nothing to Disclose, Tung-Hung Su: Nothing to Disclose, Shih-Jer Hsu: Nothing to Disclose, Tai-Chung Tseng: Nothing to Disclose, Chen-Hua Liu: Nothing to Disclose, Hung-Chih Yang: Nothing to Disclose, Jia-Horng Kao: Nothing to Disclose, Pei-Jer Chen: Nothing to Disclose, Shang-Chin Huang: Nothing to Disclose, Chun Jen Liu: Nothing to Disclose

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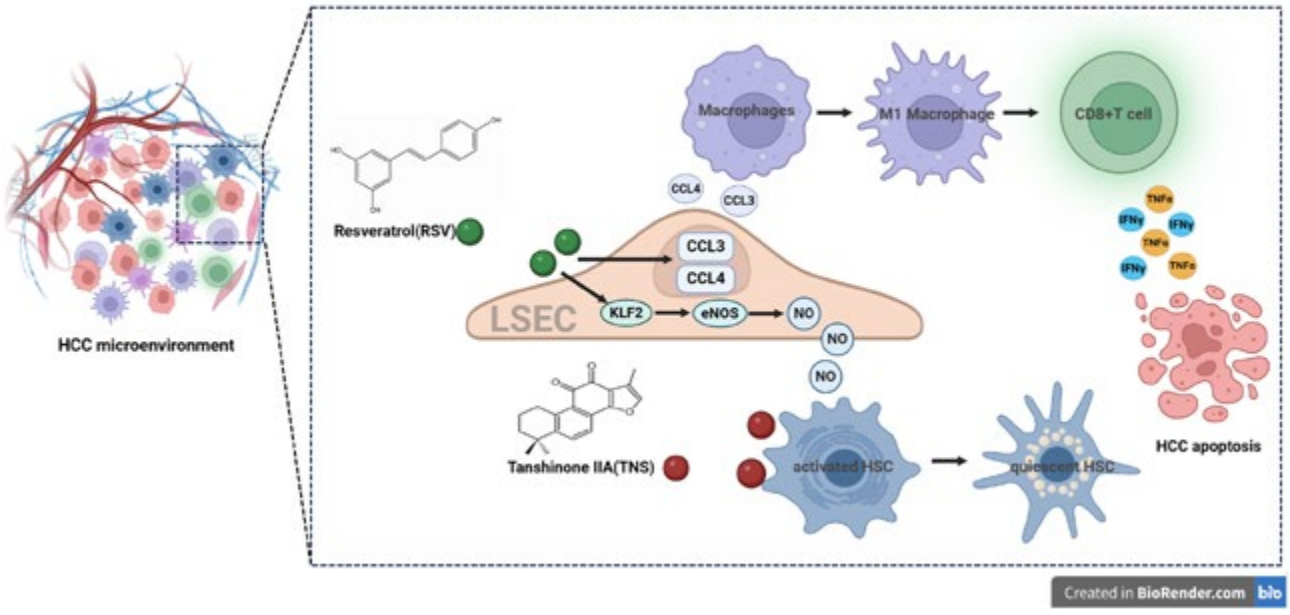
3360 | RESVERATROL AND TANSHINONE IIA SYNERGIZE TO SUPPRESS HEPATOCELLULAR CARCINOMA BY MODULATING STROMAL CELLS TO REMODEL TUMOR MICROENVIRONMENT

Jia Shi[1] Xuemei Zhang[1] Xiaona Lu[1] Shihan Yu[1] Wenlan Zheng[1] Hai Feng[1] Zhuo Yu[2]

[1]Shuguang hospital Affiliated to SHUTCM, [2]Shuguang Hospital Affiliated to Shanghai University of TCM

Background: Hepatocellular carcinoma (HCC) is usually insensitive to immunotherapy due to the aggravated immunosuppressive statue in context of liver fibrosis. Activation of hepatic stellar cells (HSCs) is one of the major events responsible for fibrotic progression, whereas liver sinusoidal endothelial cells (LSECs) play a crucial role in inhibiting the activity of HSCs and stimulating immune response. Traditional Chinese medicines resveratrol (RSV) and tanshinone IIA (TNS) exert the effect on liver protection by separately improving the functions of LSECs and HSCs, however their advanced efficiency in liver disease has been uninvestigated. We here evaluated the effect of the combination of RSV and TNS on fibrotic HCC, and explored the underlying mechanism based on the regulation of LSECs and HSCs. **Methods:** The phenotype, morphology and molecules in signaling pathway of LSECs treated by RSV were examined by immunofluorescence, scanning electron microscope, qPCR, immunoblotting. mRNA sequencing profile was performed in RSV-treated LSECs, and immunoregulatory candidates were identified by qPCR, immunoblotting and immunofluorescence. HSCs were treated with LSEC-originated supernatant or TNS, and the effect on HSC activation was evaluated through the detection of related marks and phenotypes. RSV- and TNS-loading nanoparticles, separately targeting LSECs and HSCs, were made, and their synergistic effect on HCC growth was assessed in mouse fibrotic HCC model. The regulation of RSV and TNS on the fibrosis and immune response in tumor lesions was evaluated by immunohistochemistry. **Results:** RSV inhibited CD31 expression and capillarization of LSECs, and promoted LSECs to release NO by stimulating the activity of KLF2-eNOS signaling pathway, which suppressed the expression of αSMA and collagen1 in HSCs, indicating that RSC blocked the activation of HSCs through the upregulation of KLF2-eNOS signaling in LSECs. Comparatively, TNS directly inhibited the activity of HSCs, as evidenced by the suppression of αSMA and collagen1 expression. Moreover, RSV promoted LSECs to express and release CCL3 and CCL4, the chemokines that recruit and activate M1 macrophages to exert immune modification. Nano-targeted delivery of RSV to LSECs and that of TNS to HSCs synergistically suppressed HCC growth in mouse fibrotic HCC models, accompanied with the alleviation of fibrosis and the increased infiltration of M1 macrophages and effector CD8+ T cells in tumor lesions, suggesting that RSV and TNS exert anti-HCC effect by improving tumor immune suppressive microenvironment. **Conclusion:** Our finding demonstrates that RSV and TNS synergize to suppress the development of liver fibrosis and HCC by targeting LSECs and HSCs respectively, and stimulating immune response to cancer cells, giving rise to a new strategy for HCC immunotherapy by remodeling tumor immunosuppressive microenvironment on the basis of the regulation of mesenchymal cells.



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Disclosures: Jia Shi: Nothing to Disclose, Xuemei Zhang: Nothing to Disclose, Xiaona Lu: Nothing to Disclose, Shihan Yu: Nothing to Disclose, Wenlan Zheng: Nothing to Disclose, Hai Feng: Nothing to Disclose, Zhuo Yu: Nothing to Disclose

3361 | RISK OF BLEEDING IN HEPATOCELLULAR CARCINOMA PATIENTS TREATED WITH ATEZOLIZUMAB/BEVACIZUMAB: A SYSTEMATIC REVIEW AND META-ANALYSIS

Young Seok Kim[1]

[1]*Soon Chun Hyang University*

Background: The combination of atezolizumab/bevacizumab has emerged as an effective first-line treatment for advanced hepatocellular carcinoma (HCC). However, this therapy is potentially associated with bleeding complications, warranting a comprehensive analysis of their incidence and severity. This meta-analysis aims to synthesize available evidence from clinical trials and observational studies to quantify the prevalence of bleeding following atezolizumab/bevacizumab administration. **Methods:** This meta-analysis focused on HCC treatment using atezolizumab/bevacizumab, particularly examining bleeding complications. It determined the prevalence of bleeding post-administration and compared the risk ratio with tyrosine kinase inhibitors (sorafenib or lenvatinib). Risk factors for bleeding complications were also evaluated. **Results:** From 28 studies involving 3,895 patients, the pooled prevalence of bleeding side effects was 8.42% (95% CI 5.72-11.54). Grade III or IV bleeding occurred in 4.42% (95% CI 2.64-6.10) of patients, with grade V bleeding observed in 2.06% (95% CI 0.56-4.22). Gastrointestinal bleeding, predominantly variceal, was the most common, with a prevalence of 5.48% (95% CI 3.98-7.17). Subgroup analysis indicated variability in bleeding rates based on study design and geographical location. Atezolizumab/bevacizumab treatment exhibited a 2.11 times higher prevalence of bleeding compared to tyrosine kinase inhibitors (95% CI 1.21-3.66). Meta-regression identified high body mass index (BMI) and higher proportion of albumin-bilirubin (ALBI) grade 3 as significant risk factors for bleeding complications. **Conclusion:** Atezolizumab/bevacizumab therapy for advanced HCC carries a heightened risk of gastrointestinal bleeding, exceeding that of tyrosine kinase inhibitors. High BMI and higher ALBI grade are key predictors of bleeding complications, emphasizing the need for cautious patient selection and monitoring.

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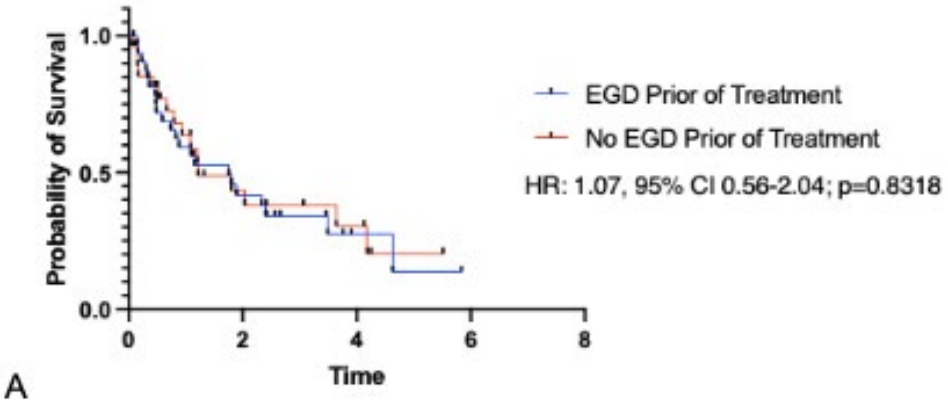

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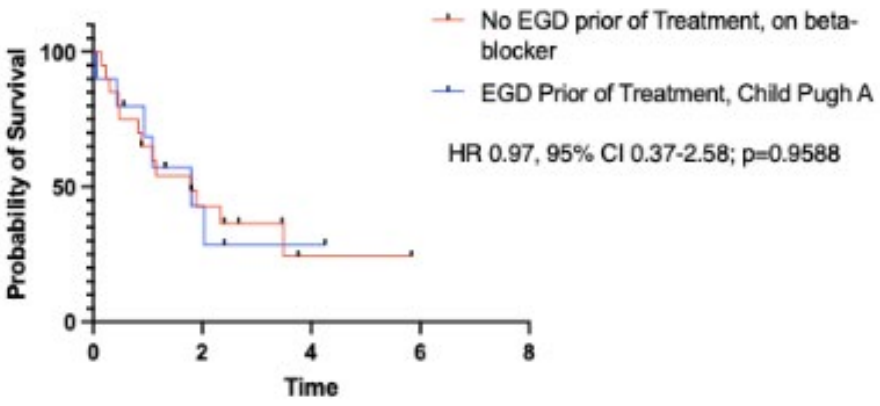

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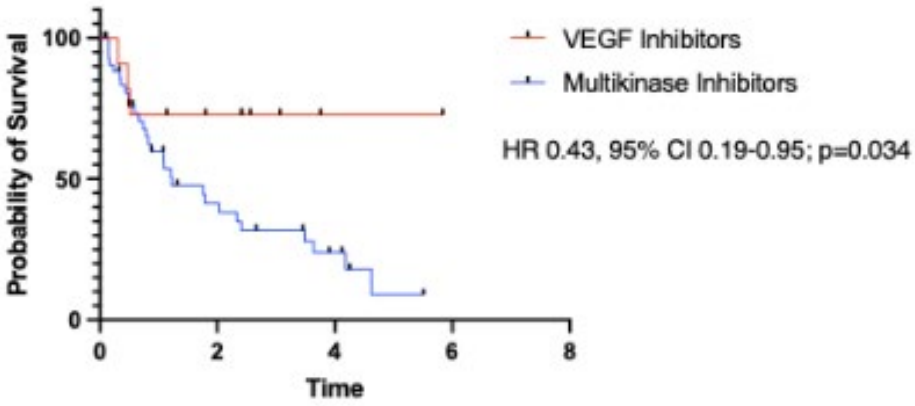

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3362 | EVALUATION OF PROPHYLACTIC ESOPHAGOGASTRODUODENOSCOPY VERSUS BETA BLOCKADE IN HEPATOCELLULAR CARCINOMA PATIENTS UNDERGOING ANTI-ANGIOGENIC CANCER TREATMENTS

Panayiotis Kontoyiannis[1] *Camila Ayerbe*[1] *Kok Hoe Chan*[1] *Julie Rowe*[1]

[1]*McGovern Medical School*

Background: Gastrointestinal (GI) bleeding is common among hepatocellular carcinoma (HCC) patients, often linked to comorbid decompensated cirrhosis or anti-angiogenic therapies. Despite studies addressing bleeding risks in cirrhotic patients undergoing chemotherapy, comprehensive analysis of cumulative risks is limited. Additionally, the comparative effectiveness of bleeding prevention strategies, specifically receipt of beta blockers (BBs) versus prophylactic esophagogastroduodenoscopy (EGD) before therapy initiation, is not fully understood. **Methods:** This retrospective study of cirrhotic HCC patients spanned January 1, 2018 to December 31, 2022 at our institution. Data on demographics, clinical findings, and treatment outcomes were analyzed. Fisher's exact and Wilcoxon rank-sum tests identified significant differences, with p <0.05 deemed statistically significant. The Cox proportional-hazards model compared overall survival (OS) between treatment groups. **Results:** The cohort (n=63) had a median age of 66 years, mostly males (n=45), and 40 non-Hispanic individuals. Most liver pathologies were hepatitis C (46%) and alcoholic cirrhosis (27%). Medication-related bleeding risks were assessed, with 48% of patients receiving therapies such as low-dose aspirin, clopidogrel, and apixaban. Patients had stage 3 (49%) or stage 4 (38%) liver cancer; 65% were Child-Pugh A (CPA) status. Initial chemotherapy included VEGF-R (n=12) and multikinase inhibitors (MKI) (n=45). In all, 27 received BBs, 6 of whom were on or prescribed BB at HCC presentation, and 9 receiving BBs at their cirrhosis diagnosis. 33 patients underwent EGD within 6 months before treatment, revealing varices that required banding for 12 patients. Eight of these 12 patients experienced bleeding within 3 months of chemotherapy initiation. Four of the 8 resulted in deaths. Among CPA patients, no significant difference in bleeding outcomes was observed based on prophylactic EGD (p=0.597). No significant difference was seen in bleeding outcomes between patients who received BBs but did not undergo EGD versus those who only had EGD (p>0.999). No statistical difference in bleeding outcomes was identified in patients receiving VEGF-R vs. MKI (p=0.193). VEGF-R inhibitor use showed a significantly higher probability of survival versus use of MKI (HR 0.43, 95% CI 0.19–0.95; p=0.034). **Conclusion:** In Child Pugh A patients, prophylactic EGD prior to treatment did not affect bleeding outcomes. Similarly, no disparity in bleeding outcomes was noted between the use of VEGF-R and MKI. More studies are essential to elucidate the survival benefits of prophylactic EGD vs. BBs prior to HCC therapy. The survival advantage of VEGF-R inhibitors versus MKI is still unclear, but our cohort showed a higher probability of survival among those treated with VEGF-R inhibitors.

Disclosures: Panayiotis Kontoyiannis: Nothing to Disclose, Camila Ayerbe: Nothing to Disclose, Kok Hoe Chan: Nothing to Disclose, Julie Rowe: Nothing to Disclose

3363 | CHOLANGIOCYTES' PRIMARY CILIA REGULATES DNA DAMAGE RESPONSE AND REPAIR ◆ ★

Estanislao Peixoto[1] *Seth Richard*[2] *Kishor Pant*[2] *Sergio Gradilone*[3]

[1]*Hormel Institute, University of Minnesota,* [2]*Hormel Institute,* [3]*The Hormel Institute and Masonic Cancer Center. University of Minnesota*

Background: Primary cilia have been implicated in various cancers, including cholangiocarcinoma (CCA), functioning as a tumor-suppressing organelle. Despite previous demonstrations of their suppressive role, the specific mechanisms through which primary cilia protect against cancer remain to be fully elucidated. Known components of carcinogenesis triggers related to failures in DNA damage response (DDR) and repair have been linked to the primary cilium and its basal body. To further our understanding of primary cilia's function in CCA, we investigated whether the loss of primary cilia affects DNA damage response (DDR) and DNA repair processes. **Methods:** Using human cholangiocyte cell lines, we investigated the colocalization of DNA repair proteins at the cilia base and examined how experimental deciliation affects DNA repair pathways, leveraging RNA sequencing data for comprehensive insight. Deciliation was induced in cells via CRISPR-mediated knockout of IFT20, IFT88, and KIF3A, followed by assessment of cellular survival in response to cisplatin, methyl methanesulfonate (MMS), and irradiation challenges. Further analyses included evaluations of cell cycle dynamics and apoptosis rates.

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To quantify DNA damage, we employed comet assays and γH2AX quantification. Additionally, we measured the levels of key DNA damage response (DDR) proteins using Western blot analysis, providing a multi-dimensional perspective on the impact of cilia loss on cellular DNA repair mechanisms. **Results:** RAD51 was observed at the base of the cilia, whereas PARP1 and CHK1 exhibited localization within the cilia itself. In deciliated cells, we noted dysregulation in critical pathways, including DNA damage checkpoints, DNA double-strand break repair, and MGMT-mediated DNA damage reversal. Exposure to genotoxic agents resulted in reduced survival, increased S arrest, and elevated apoptosis in deciliated cells compared to their normal counterparts. Furthermore, deciliated cells subjected to genotoxic challenges displayed significantly higher DNA damage, as evidenced by enhanced γH2AX signals and comet assay findings. Additionally, key DNA damage response (DDR) proteins, including ATM, phosphorylated ATM (pATM), and p53, were downregulated in deciliated cells post-irradiation. **Conclusion:** Our findings highlight the significant role of primary cilia in modulating DNA damage response and repair mechanisms. Given the urgent need for novel therapeutic approaches for cholangiocarcinoma, elucidating the intricate relationship between primary cilia and nuclear processes unveils a promising new avenue for therapeutic development.

Disclosures: Estanislao Peixoto: Nothing to Disclose, Seth Richard: Nothing to Disclose, Kishor Pant: Nothing to Disclose, Sergio Gradilone: Nothing to Disclose

3364 | RESTAGING PATIENTS WITH EARLY INTRAHEPATIC OR SYSTEMIC RECURRENCE OF HEPATOCELLULAR CARCINOMA (HCC) FOLLOWING THERAPIES WITH A CURATIVE INTENT: IS BCLC THE IDEAL SYSTEM?

Spyridon Pantzios[1] ANTONIA SYRIHA[2] Ioanna Stathopoulou[2] Orestis Sidiropoulos[2] Sofia Rellou[2] Georgia Barla[2] Nikolaos Ptohis[2] Ioannis Elefsiniotis[2]

[1]National and Kapodistrian University of Athens, [2]National Kapodistrian University Athens

Background: HCC recurrence is observed in 50-70% of patients treated either with liver resection (LR) or radiofrequency ablation (RFA) with curative intent within the first 5 years. The pattern of HCC recurrence is either intrahepatic and/or systemic and the efficacy of Atezolizumab-Bevacizumab (A-B) treatment, as early therapy after recurrence has not been extensively evaluated. Moreover, registrational trials included patients with advanced (BCLC-C) HCC, either initially diagnosed or progressed to this stage following LR/RFA. **Methods:** We evaluated 32 patients (group A) under active surveillance after curative LR/RFA, with early HCC recurrence (within 2 years) and 24 patients (group B) initially diagnosed in BCLC-C stage, all treated with A-B. Group A patients were subdivided in group A1 [14 patients with macrovascular invasion and/or extrahepatic disease (BCLC-C)] and group A2 [18 patients with multifocal, diffuse, or infiltrative intrahepatic disease not amenable to further locoregional therapy (BCLC-B)]. **Results:** Groups A1 and A2 were comparable for all baseline parameters (age, gender, BMI, diabetes presence, ALBI, cirrhosis and varices presence, AFP values and morphomolecular histological status). Objective response, according to mRECIST criteria, was observed in 2/14 (14.3%) and 6/18 (33.3%) patients of group A1 and A2, respectively. Median overall survival (mOS) as well as median progression free survival (mPFS) were comparable between the two groups. It is important to note that mOS was better than that observed in IMBRAVE150 (22m and 26m for group A1 and A2, respectively, p=0.71), whereas mPFS was longer in group A1 patients (15m vs 6m, p=0.126), although not significantly. Moreover, we evaluated the efficacy of A-B among patients with advanced disease (groups A1 and B). The two groups were comparable for all baseline parameters evaluated. Despite the unremarkable objective response rates, mOS was significantly higher in group A1 compared to group B patients (26m vs 6m for OS, p<0.001), whereas a significant trend for mPFS was observed (6m vs 3m, p=0.086). **Conclusion:** Early initiation of A-B treatment after recurrence diagnosis results in high and comparable survival rates (22-26m) in treated patients, irrespective of the pattern of recurrence, a finding that needs further investigation in large scale studies. The efficacy of A-B in patients initially diagnosed in BCLC-C stage is significantly different from those who progressed to this stage following therapies with a curative intent.

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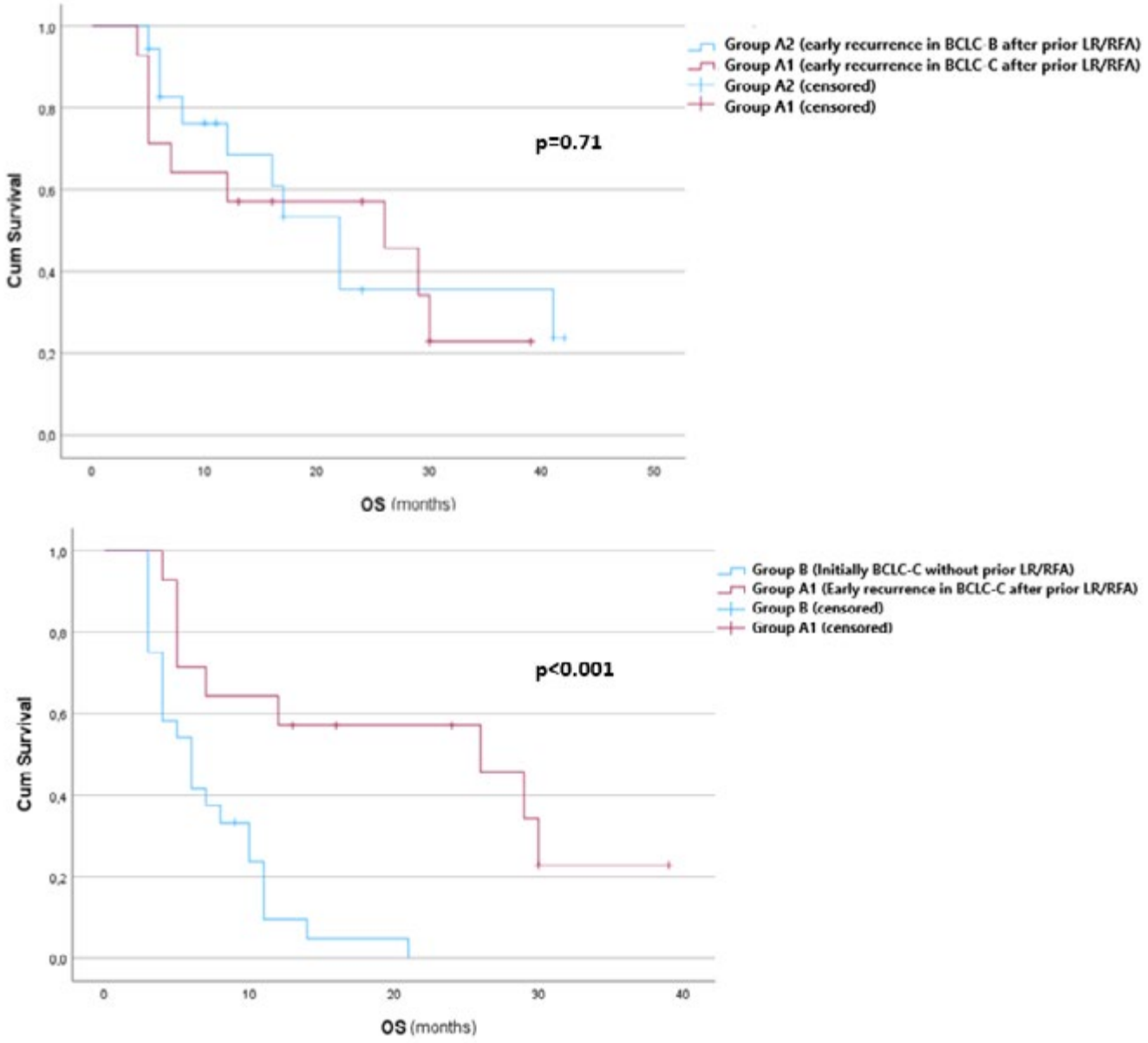

Disclosures: Spyridon Pantzios: Nothing to Disclose, ANTONIA SYRIHA: Nothing to Disclose, Ioanna Stathopoulou: Nothing to Disclose, Orestis Sidiropoulos: Nothing to Disclose, Sofia Rellou: Nothing to Disclose, Georgia Barla: Nothing to Disclose, Nikolaos Ptohis: Nothing to Disclose, Ioannis Elefsiniotis: Nothing to Disclose

3365 | DIGITALIZED PRECISE SCREENING AND RISK STRATIFIED MANAGEMENT IMPROVE EARLY DIAGNOSIS OF HEPATOCELLULAR CARCINOMA (HCC) IN CHINA: A MULTI-CENTER REAL-WORLD STUDY

Honglian Gui[1] Jiao-jian Lv[2] Wei Shao[1] Hai-guang Xin[1] Simin Guo[1] Hui-juan Zhou[1] XIAOLIN WANG[1] Xiaogang Xiang[1] Ruidong Mo[1] Wei-liang Tang[1] Bao-yan An[1] Zhujun Cao[1] shaowen jiang[1] Yan Huang[1] Qing Xie[1]

[1]Ruijin Hospital, [2]Lishui People's Hospital

Background: Previous data have demonstrated that early screening and standardized follow-up improve outcomes in patients with high risk of HCC. However, the dominant etiology of liver disease in China has been diversified and changing from viral hepatitis to MAFLD, making the traditional one-size-fits-all screening and follow-up strategy inapplicable. Besides, the sensitivity of ultrasound or AFP in identifying early HCC requires to be improved. These challenges represent the major unmet needs in HCC screening and surveillance in China.

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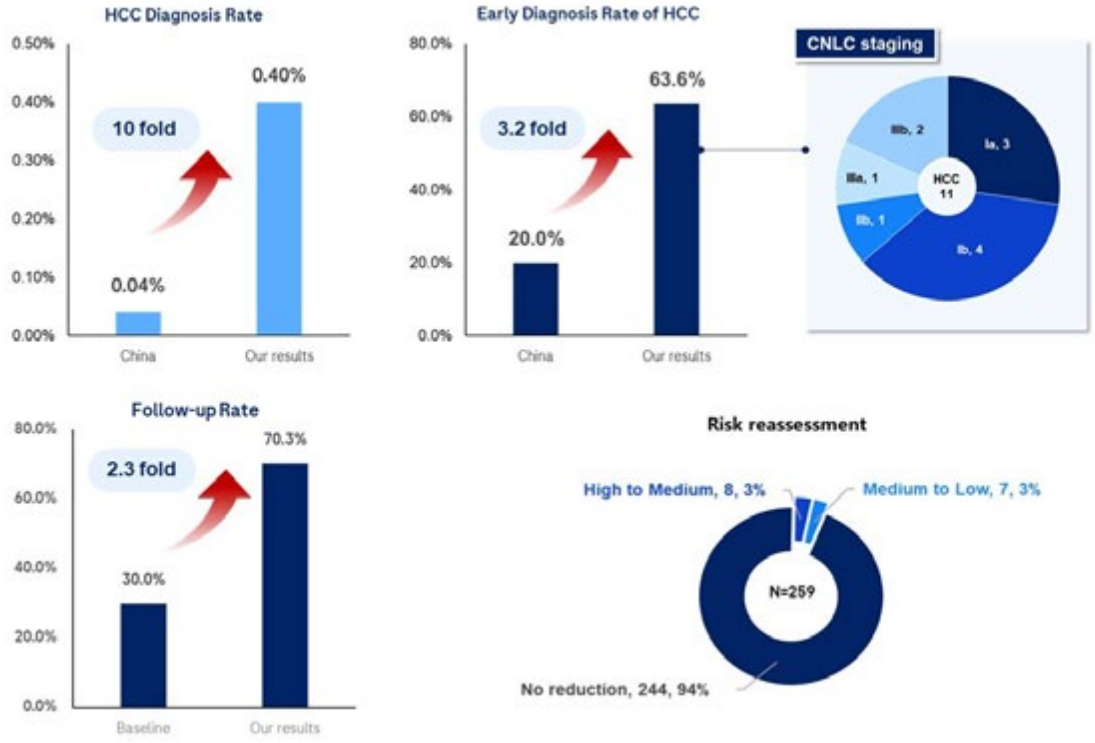
Therefore, we aim to develop an innovative procedure and validate its value in real-world practice. **Methods:** The prospective, multi-center real-world study enrolled eligible patients with chronic liver disease from Ruijin Hospital and LiShui People's Hospital since May 2023. Each patient underwent an initial HCC screening with abdominal ultrasound exam, serum tests for AFP and PIVKA-II. A digital platform was adopted to collect and synthesize the screening results, in which those with abnormal results followed standard HCC diagnosis work-up. For patients not suspicious of HCC, the digital platform would individually assign a risk-dependent follow-up plan for HCC surveillance after classifying them into different risk groups based on local guidelines and established risk stratification models. Moreover, the digital platform provided service on smart phone including patient education, Q&A and re-visit reminder to improve patient compliance. Early diagnosis of HCC was defined as Stage Ia, Ib, and IIa according to Chinese National Liver Cancer (CNLC) criteria. **Results:** A total of 3,832 patients were enrolled, of which 2,775 (72.4%) completed the screening and assessment process. The top three most common etiologies were chronic hepatitis B (77.0%), cirrhosis (18.0%), and fatty liver with fibrosis (10.9%). HCC was confirmed in 11 patients (0.4%) and 7 were diagnosed as early-stage, with a remarkably higher early diagnosis rate of 63.6% compared with the average level (20.0%) in China. Considering the HCC surveillance, the patient compliance measured by follow-up rate was increased from 30.0% to 70.3%. Risk reduction was observed in 15 (5.8%) of patients with risk reassessment during the follow-up. **Conclusion:** By applying precise screening approach, digital platform and risk stratified management, we successfully improved the effectiveness and efficiency of HCC screening and surveillance. Most importantly, the high early diagnosis rate could transform into significant survival benefit, which is essential to address the public health issue of liver cancer burden in China.



Disclosures: Honglian Gui: Nothing to Disclose, Jiao-jian Lv: Nothing to Disclose, Wei Shao: Nothing to Disclose, Hai-guang Xin: Nothing to Disclose, Simin Guo: Nothing to Disclose, Hui-juan Zhou: Nothing to Disclose, XIAOLIN WANG: Nothing to Disclose, Xiaogang Xiang: Nothing to Disclose, Ruidong Mo: Nothing to Disclose, Wei-liang Tang: Nothing to Disclose, Bao-yan An: Nothing to Disclose, Zhujun Cao: Nothing to Disclose, shaowen jiang: Nothing to Disclose, Yan Huang: Nothing to Disclose, Qing Xie: Nothing to Disclose

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3366 | THE HISTONE LYSINE ACETYLTRANSFERASE KAT2B INHIBITS CHOLANGIOCARCINOMA GROWTH: EVIDENCE FOR INTERACTION WITH SP1 TO REGULATE NF2-YAP SIGNALING

Wenbo Ma[1] Jinqiang Zhang[2] Weina Chen[2] Nianli Liu[2] Tong Wu[3]

[1]Tulane University School of Medicine, [2]Tulane University, [3]Tulane Medical Center

Background: Cholangiocarcinoma (CCA) is a highly malignant cancer of the biliary tract with poor prognosis. Further mechanistic insights into the molecular mechanisms of CCA are needed to develop more effective target therapy. **Methods:** The expression of the histone lysine acetyltransferase KAT2B in human CCA was analyzed in human CCA tissues. CCA xenograft was developed by inoculation of human CCA cells with or without KAT2B overexpression into SCID mice. Western blotting, ChIP-qPCR, qRT-PCR, protein immunoprecipitation, GST pull-down and RNA-seq were performed to delineate KAT2B mechanisms of action in CCA. **Results:** We identified KAT2B as a frequently downregulated histone acetyltransferase in human CCA. Downregulation of KAT2B was significantly associated with CCA disease progression and poor prognosis of CCA patients. The reduction of KAT2B expression in human CCA was attributed to gene copy number loss. In experimental systems, we demonstrated that overexpression of KAT2B suppressed CCA cell proliferation and colony formation in vitro and inhibits CCA growth in mice. Mechanistically, forced overexpression of KAT2B enhanced the expression of the tumor suppressor gene NF2, which is independent of its histone acetyltransferase activity. We showed that KAT2B was recruited to the promoter region of the NF2 gene via interaction with the transcription factor SP1, which led to enhanced transcription of the NF2 gene. KAT2B-induced NF2 resulted in subsequent inhibition of YAP activity, as reflected by reduced nuclear accumulation of oncogenic YAP and inhibition of YAP downstream genes. Depletion of NF2 was able to reverse KAT2B-induced reduction of nuclear YAP and subvert KAT2B-induced inhibition of CCA cell growth. **Conclusion:** This study provides the first evidence for an important tumor inhibitory effect of KAT2B in CCA through regulation of NF2-YAP signaling and suggests that this signaling cascade may be therapeutically targeted for CCA treatment.

Disclosures: Wenbo Ma: Nothing to Disclose, Jinqiang Zhang: Nothing to Disclose, Weina Chen: Nothing to Disclose, Nianli Liu: Nothing to Disclose, Tong Wu: Nothing to Disclose

3367 | RBM39 ENHANCES CHOLANGIOCARCINOMA GROWTH THROUGH EZH2-MEDIATED WNT7B/β-CATENIN PATHWAY

Nianli Liu[1] Jinqiang Zhang[1] Weina Chen[1] Wenbo Ma[2] Tong Wu[3]

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Background: The RNA-binding motif protein 39 (RBM39) functions as both an RNA-binding protein and a splicing factor in a variety of cancer types. However, the function of RBM39 in cholangiocarcinoma (CCA) remains undefined. In this study, we aimed to investigate the role of RBM39 in CCA and explore its potential as a therapeutic target. **Methods:** The expression of RBM39 in CCA was investigated by analyzing human CCA tumor specimens. CRISPR/Cas9 or shRNA-mediated depletion of RBM39 was performed in vitro and in vivo to document the oncogenic role of RBM39 in CCA. The anti-tumor effect of the RBM39 inhibitor Indisulam in combination with the EZH2 degrader MS177 was assessed in vitro and in vivo. **Results:** RBM39 is significantly increased in human CCA tissues and associated with a poor prognosis in CCA patients. Depletion of RBM39 by CRISPR/Cas9 or shRNA inhibited CCA cell proliferation in vitro and prevented CCA development and tumor growth in mice. Mechanistically, our results showed that depletion of RBM39 suppressed EZH2 expression via disrupting its mRNA splicing. RBM39-regulated EZH2 controls WNT7B/β-catenin activity. Pharmacological co-targeting of RBM39 (with Indisulam) and EZH2 (with MS177) resulted in a synergistic antitumor effect, both in vitro and in vivo. **Conclusion:** This study discloses a novel RBM39-EZH2-β-catenin signaling axis that is crucial for CCA growth. Our findings suggest that simultaneous inhibition of RBM39 and EZH2 presents a promising therapeutic strategy for CCA treatment.

Disclosures: Nianli Liu: Nothing to Disclose, Jinqiang Zhang: Nothing to Disclose, Weina Chen: Nothing to Disclose, Wenbo Ma: Nothing to Disclose, Tong Wu: Nothing to Disclose

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3368 | NON-VIRAL HEPATOCELLULAR CARCINOMA HAS SIMILAR PROGNOSIS AFTER RADICAL TREATMENT AS VIRAL HCC: ANALYSIS OF A NATIONWIDE REGISTRY FOR ADVANCED LIVER DISEASES (REAL)

Kazuya Okushin[1] Ryosuke Tateishi[1] Shinya Hirakawa[2] Hisateru Tachimori[2] Koji Uchino[1] Ryo Nakagomi[1] Tomoharu Yamada[1] Takuma Nakatsuka[1] Tatsuya Minami[1] Masaya Sato[1] Mitsuhiro Fujishiro[1] Kiyoshi Hasegawa[1] Yuichiro Eguchi[3] Tatsuya Kanto[4] Hitoshi Yoshiji[5] Namiki Izumi[6] Masatoshi Kudo[7] Kazuhiko Koike[8]

[1]The University of Tokyo, [2]Keio University School of Medicine, [3]Saga University, [4]National Center for Global Health and Medicine, [5]Nara Medical University, [6]Musashino Red Cross Hospital, [7]Kindai University Faculty of Medicine, [8]Kanto Central Hospital

Background: Tumor stage and liver function determine the prognosis of patients with hepatocellular carcinoma (HCC) and are also used to guide treatment. However, the natural course of underline liver disease also affect survival. This study aims to analyze the nationwide REgistry for Advanced Liver diseases (REAL) in Japan to clarify the difference in the prognosis of HCC patients by etiology. **Methods:** We enrolled patients initially diagnosed with HCC and curatively treated with resection or ablation between January 2018 and December 2021 from the REAL. The endpoints were overall survival (OS) and decompensation-free survival (DFS). Patients were grouped into hepatitis B (HBV), hepatitis C (HCV) and others (non-B, non-C). Considering the differences in patient characteristics between etiologies, we applied inverse probability of treatment weighting (IPTW) to draw adjusted Kaplan–Meier curves. The weights were based on propensity scores calculated using a logistic regression based on age, sex, tumor size, number of intrahepatic tumors, and laboratory data. **Results:** Of the 4,568 patients who met the inclusion criteria, 3,546 and 1,022 were treated with resection and ablation, respectively. Median follow-up times in the HBV, HCV, and non-B, non-C groups was 2.0, 2.1, and 1.9 years, respectively. Among those who were treated with resection (13.9% HBV, 29.4% HCV, and 56.0% non-B, non-C), the 3-year OS rates in the HBV, HCV, and non-B, non-C groups were 91.1%, 88.7%, and 85.7%, respectively. However, the adjusted OS showed no significant difference between non-B, non-C vs HBV (Figure 1A, p = 0.57 by log-rank test) and non-B, non-C vs HCV (Figure 1B, p =0.68). The adjusted DFS was also similar between non-B, non-C vs. HBV and non-B, non-C vs. HCV (p = 0.63 and p = 0.66, respectively). Among the 1,022 patients treated with ablation (11.1% HBV, 44.2% HCV, and 43.9% non-B, non-C), the 3-year OS in the HBV, HCV, and non-B, non-C groups were 90.4%, 93.5%, and 93.0%, respectively. There was also no significant difference in adjusted OS (Figure 1C and 1D) and DFS between etiologies. **Conclusion:** The prognosis of patients with HCC were similar among etiologies after adjustment for tumor stage and liver function, regardless of treatment modality.

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Figure 1

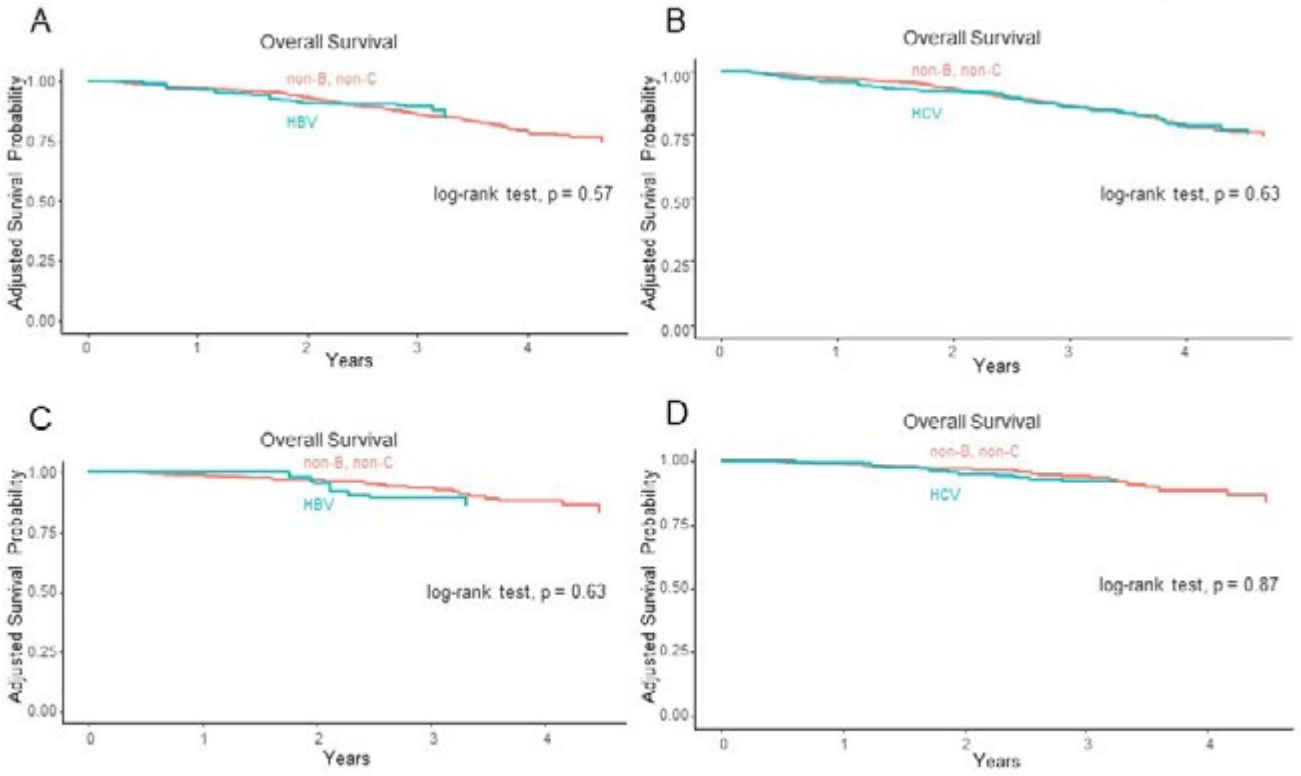

Figure 1. Adjusted overall survivals for curatively treated HCC patients
A. non-B, non-C vs HBV in resection cohort B. non-B, non-C vs HCV in resection cohort
C. non-B, non-C vs HBV in ablation cohort D. non-B, non-C vs HCV in ablation cohort

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3369 | TGF-β SIGNALING MOLECULES IN CIRCULATING TUMOR CELLS AS PROGNOSTIC BIOMARKER IN PATIENTS WITH UNRESECTABLE HEPATOCELLULAR CARCINOMA TREATED WITH ATEZOLIZUMAB PLUS BEVACIZUMAB

Yosuke Murata[1] Takuto Nosaka[1] Tomoko Tanaka[1] Yu Akazawa[1] Kazuto Takahashi[1] Tatsushi Naito[1] Masahiro Ohtani[1] Yasunari Nakamoto[1]

[1]University of Fukui

Background: Circulating tumor cells (CTCs) derived from peripheral blood have a notable advantage in that they are noninvasive and real-time biomarker and have attracted attention in monitoring therapeutic efficacy. Combination immunotherapy has promising outcomes in patients with unresectable hepatocellular carcinoma (HCC). However, there is no reliable biomarker for predicting disease progression. In this study, CTCs were serially collected from HCC patients undergoing combination immunotherapy, Atezolizumab plus Bevacizumab (Atezo+Bev) or Tremelimumab plus Durvalumab (STRIDE). Changes in molecular profiles of CTCs were analyzed to identify effective biomarkers. **Methods:** We obtained 5mL of peripheral blood from 28 HCC patients treated with Atezo+Bev (n=22) or STRIDE (n=6) between September 2020 and April 2024. Treatment response was assessed by RECIST ver.1.1. CTCs were isolated with RosetteSep Human CD45 Depletion Cocktail and the enriched cells were stained with monoclonal antibodies targeting the cell surface antigens including Pan-CK and CD45. Then, CD45 negative and Pan-CK positive cells were defined as CTCs by flow cytometry using a FACSAria II. CTC-derived RNA underwent targeted RNA sequencing of 373 genes with next-generation sequencing (NGS) on Illumina Miseq and qRT-PCR. Gene set enrichment analysis (GSEA) was also performed. **Results:** CTC counts significantly correlated with the Barcelona clinic liver cancer (BCLC) stages. CTC counts of PR/SD group during combination immunotherapy decreased at response evaluation, compared with baseline (207 ± 23 vs. 104 ± 26, $p < 0.05$) and increased at PD responses, reflecting changes in tumor burden. In NGS analysis of Atezo+Bev group, unsupervised hierarchical clustering classified into two clusters A and B. The median PFS was significantly prolonged in cluster B than in cluster A, with a tendency towards improved OS in cluster B. GSEA revealed enrichment of the TGF-β signaling pathway in cluster A, and the apoptosis-related signaling pathway was enriched in cluster B in clinical course ($p < 0.05$). Furthermore, TGF-beta signaling molecules including CDKN2B, GRB2 and PIK3R1 changed earlier, 3weeks after starting Atezo+Bev, significantly correlating with therapeutic response ($p < 0.05$), although this was not significant in STRIDE. **Conclusion:** In HCC patients treated by combination immunotherapy, CTC numbers accurately reflects changes in tumor burden at response evaluation. NGS analysis showed that patients with elevated expression of genes related to TGF-β signaling in CTCs exhibit a poor therapeutic response to Atezo+Bev and changes of TGF-β signaling molecules, specifically CDKN2B, GRB2, and PIK3R1, in CTCs may be biomarkers reflecting treatment response early and accurately. Molecular profiling in CTCs may serve as prognostic biomarkers in HCC patients undergoing Atezo+Bev.

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3370 | DIAGNOSTIC ACCURACY OF BLOOD PLASMA SPECTROSCOPY FOR EARLY LIVER CANCER DIAGNOSTICS IN OBESE PATIENTS

Petr Hříbek[1] Ondřej Vrtělka[2] Kateřina Králová[2] Johana Klasová[1] Markéta Fousková[2] Lucie Habartová[2] Vladimír Setnička[2] Petr Urbánek[1]

[1]Military University Hospital Prague, [2]University of Chemistry and Technology

Background: Hepatocellular carcinoma (HCC) represents one of the most common cancers worldwide, with a high mortality rate. A considerable proportion of HCC cases is caused by cirrhosis related to metabolic dysfunction-associated steatohepatitis (MASH). It is expected that the increasing prevalence of metabolic syndrome in general population will be accompanied by subsequent increase in MASH-related HCC prevalence. Currently, HCC screening relies on liver ultrasonography which sensitivity reaches only 23% in obese patients, making its early diagnosis a global problem. To date, no studied blood-based biomarker has shown sufficient accuracy for screening purposes. Our aim (hypothesis was that unique combination of spectroscopic methods will provide a distinct spectra of blood plasma in patients with and without HCC) was to evaluate the combination

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of spectroscopic methods as a potential cheap, fast and accurate biomarker of HCC in plasma of obese patients. **Methods:** We employed a combination of conventional and chiroptical spectroscopic methods (infrared and Raman spectroscopy, electronic circular dichroism, and Raman optical activity) to identify differences between the blood plasma of obese cirrhotic patients with and without HCC. We enrolled twenty subjects with diagnosed HCC (70% males) and seventeen controls (65% males). The inclusion criteria were confirmed liver cirrhosis and a BMI ≥ 30. The mean BMI for HCC patients and controls was 33 and 35, respectively. The mean age in the cohort was 64 years. The distribution of Barcelona Clinic Liver Cancer (BCLC) stages among the patients was 40% A, 35% B, 15% C, and 10% D. **Results:** We analyzed spectra from each spectroscopic method to differentiate between HCC and non-HCC samples. Sensitivity and specificity for HCC diagnosis were as follows: infrared spectroscopy (0.725, 0.747, AUROC: 0.734), Raman spectroscopy (0.673, 0.650, AUROC: 0.748), electronic circular dichroism (0.775, 0.738, AUROC: 0.823), and Raman optical activity (0.660, 0.740, AUROC: 0.745). By selecting distinctive variables, we constructed targeted models with improved sensitivity and specificity: infrared (0.780, 0.905), Raman (0.700, 0.767), electronic circular dichroism (0.840, 0.743), and ROA (0.805, 0.923). Combining all spectroscopies yielded a sensitivity of 0.810, specificity of 0.857, and the highest AUROC of 0.961. **Conclusion:** The presented data suggest that spectroscopic methods may represent a valuable diagnostic tool for HCC, and their accuracy, especially when combined, might reach acceptable accuracy for the screening of high-risk obese patients. The high values of sensitivity and specificity, 81% and 86%, respectively confirmed our hypothesis that spectroscopy represent a promising screening tool of HCC in obese patients for whom the sensitivity of the currently used USG examination is significantly reduced.

Disclosures: Petr Hříbek: Eisai: Speaking and Teaching, Roche: Speaking and Teaching, Ondřej Vrtělka: Nothing to Disclose, Kateřina Králová: Nothing to Disclose, Johana Klasová: Nothing to Disclose, Markéta Fousková: Nothing to Disclose, Lucie Habartová: Nothing to Disclose, Vladimír Setnička: Nothing to Disclose, Petr Urbánek: Nothing to Disclose

3371 | OUTCOMES BY BASELINE LIVER FUNCTION IN EMERALD-1: A PHASE 3, RANDOMIZED, PLACEBO-CONTROLLED STUDY OF TRANSARTERIAL CHEMOEMBOLIZATION WITH DURVALUMAB WITH/WITHOUT BEVACIZUMAB IN PARTICIPANTS WITH EMBOLIZATION-ELIGIBLE UNRESECTABLE HEPATOCELLULAR CARCINOMA

Stephen Chan[1] Thomas Decaens[2] Masatoshi Kudo[3] Joseph Erinjeri[4] Riccardo Lencioni[5] Mohamed Bouattour[6] Valeriy Breder[7] Jeong Heo[8] Vincenzo Mazzaferro[9] Joong-Won Park[10] Alejandro Molina Alavez[11] Kwong Ming Kee[12] Aibing Xu[13] Yoshitaka Inaba[14] Farshid Dayyani[15] Magdalena Zotkiewicz[16] Carrie McCoy[17] Mallory Makowsky[18] Bruno Sangro[19]

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Background: In the Phase 3 EMERALD1 study (NCT03778957), durvalumab (D) + bevacizumab (B) + transarterial chemoembolization (TACE) significantly improved progression-free survival (PFS) versus placebos (PBOs) + TACE. In unresectable hepatocellular carcinoma (uHCC), liver function is often impaired; TACE may further deteriorate liver function and the underlying liver disease. Here, we evaluated the efficacy and safety

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of D + B + TACE by liver function in uHCC. **Methods:** Participants (pts) with embolization-eligible uHCC were randomized 1:1:1 to the D + B + TACE, D + TACE, or PBOs + TACE (TACE) arms. Pts received D (1500 mg) or PBO for D (Q4W) + TACE. After completion of last TACE, pts received D (1120 mg) + PBO for B, D (1120 mg) + B (15 mg/kg), or PBOs for D and B (Q3W). PFS and time to progression (TTP) in pts in the D + B + TACE and TACE arms of the intent-to-treat population, and safety in pts who received D + B + TACE or TACE in the safety analysis set (pts who received ≥1 dose of study treatment, by treatment received, regardless of randomization) are reported by albumin-bilirubin (ALBI) grade 1 or 2 at baseline (no pts had ALBI grade 3 in the D + B + TACE or TACE arms). **Results:** Baseline characteristics were generally consistent across treatment arms, regardless of ALBI grade. PFS and TTP improved with D + B + TACE versus TACE in the ALBI grade 1 and 2 groups (Table). The rates of treatment-emergent hepatic events were numerically higher in pts treated with D + B + TACE versus TACE in the ALBI grade 1 (37.8% vs 19.5%) and 2 (48.4% vs 28.6%) groups, consistent with the longer median duration of exposure to D with D + B + TACE versus TACE (Table); however, these events were predominantly low-grade. Rates of treatment-related grade 3 or 4 hepatic events were comparable across treatment arms regardless of baseline ALBI grade; no treatment-related grade 5 hepatic events occurred in pts treated with D + B + TACE. **Conclusion:** These results support a favorable risk-benefit profile with D + B + TACE in embolization-eligible uHCC regardless of baseline ALBI grade. Previously presented at ESMO GI Congress 2024, FPN: 166P, Stephen L. Chan *et al.* - Reused with permission.

	ALBI grade 1		ALBI grade 2	
ITT	**D + B + TACE (n=117)**	**TACE (n=126)**	**D + B + TACE (n=87)**	**TACE (n=79)**
Median PFS*, months (95% CI)	17.4 (12.5–22.1)	9.2 (6.9–13.6)	11.1 (7.2–15.7)	7.2 (6.7–11.1)
PFS HR versus TACE (95% CI)	0.76 (0.56–1.05)		0.76 (0.52–1.09)	
Median TTP*, months (95% CI)	22.1 (16.6–27.6)	9.5 (7.0–14.1)	19.4 (13.9–25.1)	10.0 (6.9–16.3)
TTP HR versus TACE (95% CI)	0.65 (0.47–0.92)		0.57 (0.36–0.88)	
SAS	**D + B + TACE (n=90)**	**TACE (n=123)**	**D + B + TACE (n=64)**	**TACE (n=77)**
mDoE to D or PBO for D, months	17.28	9.79	10.89	7.75
mDoE to B or PBO for B, months	11.84	8.87	6.62	7.59

*Assessed by blinded independent central review per RECIST v1.1.
ALBI, albumin-bilirubin; B, bevacizumab; CI, confidence interval; D, durvalumab; HR, hazard ratio; mDoE, median duration of exposure; PBO, placebo; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; SAS, safety analysis set; TACE, transarterial chemoembolization; TTP, time to progression.

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Speaking and Teaching, Sirtex: Speaking and Teaching, Takeda: Speaking and Teaching, Magdalena Zotkiewicz: Nothing to Disclose, Carrie McCoy: Nothing to Disclose, Mallory Makowsky: Nothing to Disclose, Bruno Sangro: Nothing to Disclose

3372 | INTRAINDIVIDUAL COMPARISON OF PROGNOSTIC IMAGING FEATURES OF HEPATOCELLULAR CARCINOMAS BETWEEN MRIS WITH EXTRACELLULAR AND HEPATOBILIARY CONTRAST AGENTS: FOCUS ON MICROVASCULAR INVASION AND EARLY RECURRENCE

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Background: Beyond an accurate and unified diagnostic approach for hepatocellular carcinoma (HCC), accumulating evidence suggests that certain imaging features may have prognostic implications. Accordingly, standardized terms and definitions for prognostic imaging features have recently been proposed by an expert consensus. This study aimed to perform direct intraindividual comparisons of MRIs with extracellular contrast agent (ECA-MRI) and hepatobiliary agent (HBA-MRI) for prognostic imaging features of HCC including the use of standardized terms and definitions, and to compare the prediction of microvascular invasion (MVI) and subsequent early recurrence between the two MRIs. **Methods:** The present study included 102 prospectively enrolled at-risk patients (median age, 61.0 years; 83 men) with surgically resected single HCC who underwent both preoperative ECA-MRI and HBA-MRI between July 2019 and June 2023. The McNemar test was used for the comparison of each prognostic imaging feature between the two MRIs. Significant imaging features associated with MVI were identified by multivariable logistic regression analysis, and early recurrence rates (< 2 years) were compared between the two MRIs. **Results:** The frequencies of prognostic imaging features were not significantly different between the two MRIs (P = 0.07 to > 0.99). Non-smooth tumor margin (ECA-MRI, odds ratio [OR] = 5.30; HBA-MRI, OR = 7.07) and peritumoral arterial phase hyperenhancement (ECA-MRI, OR = 4.26; HBA-MRI, OR = 4.43) were independent factors significantly associated with MVI on both MRIs. Two-trait predictor of venous invasion on ECA-MRI (OR = 11.24) and peritumoral HBP hypointensity on HBA-MRI (OR = 20.42) were other predictors of MVI on each of the two MRIs. Early recurrence rates of any two or more significant imaging features (49.8% on ECA-MRI vs 51.3% on HBA-MRI, P = 0.75) were not significantly different between the two MRIs. **Conclusion:** Prognostic imaging features of HCC may be comparable between ECA-MRI and HBA-MRI.

Disclosures: Sunyoung Lee: Nothing to Disclose, Ja Kyung Yoon: Nothing to Disclose

3373 | MECHANISM OF HEPATOCARCINOGENESIS DUE TO HEPATITIS B VIRUS GENOME INTEGRATION INTO HOST KMT2B LOCUS

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Background: Hepatitis B virus (HBV)-DNA integration into the host genome contributes to the development of hepatocellular carcinoma (HCC). KMT2B is the second most frequent site of HBV-DNA integration in HCC. However, the oncogenic mechanism of HBV integration into the KMT2B locus (HBV-*KMT2B* integration) in HCC remains unclear. In this study, we aimed to elucidate the oncogenic mechanism of HBV-*KMT2B* integration by identifying the integrated HBV-DNA sequences in an HCC specimen with HBV-*KMT2B* integration and reproducing the integration in human induced pluripotent stem cells (iPSCs). We analyzed the functional significance of HBV-*KMT2B* integration in HBV-related HCC by differentiating them into hepatic lineages. **Methods:** We selected the sample with HBV-*KMT2B* integration through next-generation sequencing analysis of in-house HCC samples, determined the sequence information, and analyzed the transcripts by RNA sequencing analysis (approved by the Ethical Review Committee). We reproduced the HBV-*KMT2B* integration in iPSCs with an intact genome derived from a healthy person using the CRISPR/Cas9 system. The phenotype of HBV-*KMT2B*

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integration was analyzed in iPSC-derived hepatic progenitor cells (HPCs). **Results:** The reproduced HBV-*KMT2B* integration significantly upregulated the proliferation of the iPS-derived HPCs, whereas proliferation of *KMT2B*-deficient HPCs was decreased. Comprehensive analysis revealed an enhanced expression of cell cycle-related genes in HBV-*KMT2B*-integrated HPCs due to enhancement of histone methylation (H3K4me3). These data indicated that HBV-*KMT2B* integration induces gain-of-function of *KMT2B* in host cells. Long-read RNA sequence analysis using the HCC sample and the HBV-*KMT2B* integrated HPCs revealed a common N-terminal truncated *KMT2B* transcript variant. Overexpression of the transcript variant significantly enhanced proliferation of normal HPCs. Additionally, replication stress and DNA damage were significantly induced in HBV-*KMT2B* integrated HPCs, indicating that our genome-edited iPSC model involves the oncogenic processes in HCC. Consistent with our *in vitro* data, gene set variation analysis (GSVA) using RNAseq data from public databases of clinical HCC samples revealed that the high enrichment score of pathways related to replication stress in HBV-*KMT2B* integrated HCC. **Conclusion:** This study demonstrates that HBV-*KMT2B* integration contributes to oncogenic processes through replication stress, mediated by abnormal cell proliferation through the enhancement of histone methylation-related KMT2B function.

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3374 | METTL3-MEDIATED M6A MODIFICATION REGULATES THE POLYCOMB REPRESSIVE COMPLEX 1 (PRC1) COMPONENTS BMI1 AND RNF2 IN HEPATOCELLULAR CARCINOMA CELLS

Weina Chen Jinqiang Zhang[1] Wenbo Ma[1] Nianli Liu[1] Tong Wu[1]

[1]Tulane University

Background: Methyltransferase-like 3 (METTL3) is a primary RNA methyltransferase that catalyzes N6-methyladenosine (m6A) modification which is implicated in several human cancers including hepatocellular carcinoma (HCC), although its mechanism of action remains to be further defined. The current study aims to further delineate the effect and mechanism of METTL3 in HCC. **Methods:** Stable METTL3 knockdown human HCC cell lines (Huh7 and PLC/PRF/5) were established by shRNA. Cell growth features were evaluated using cell proliferation assay, colony formation and trans-well cell invasion assay. The role of METTL3 in vivo was evaluated by plasmid-based murine HCC models. Immunohistochemistry staining was performed for YAP1, METTL3, Ki67 and HCC markers (Glypican3 and CK19). N6-methyladenosine-sequencing (m6A-Seq) and RNA sequencing (RNA-Seq) were used to explore the potential targets of METTL3. The efficacy of METTL3 inhibitor STM2457 was evaluated *in vitro* and in a mouse model of HCC. **Results:** We observe that METTL3 expression is significantly upregulated in human HCC tissues which is associated with poor patient survival. By using a murine model of hepatocellular cancer development induced via hydrodynamic tail vein injection, we showed that METTL3 enhanced HCC development. In cultured Huh7 and PLC/PRF/5 cells, we observed that stable knockdown of METTL3 by shRNA significantly decreased tumor cell proliferation, colony formation and invasion, *in vitro*. When Huh7 and PLC/PRF/5 cells with shRNA knockdown of METTL3 were inoculated into the livers of SCID mice, we found that METTL3 knockdown significantly inhibited the growth of HCC xenograft tumors. These findings establish METTL3 as an important oncogene in HCC. Through m6A-Seq and RNA-Seq together with subsequent validation studies, we identified BMI1 and RNF2, two key components of the polycomb repressive complex 1 (PRC1), as direct downstream targets of METTL3 in HCC cells. Our data showed that METTL3-mediated m^6A modification of BMI1 and RNF2 mRNAs led to increased mRNA stability and this process involved the m6A reader proteins IGF2BP1/2/3 in HCC cells. Furthermore, we observed that pharmacological inhibition of METTL3 by its inhibitor, STM2457, significantly inhibited HCC cell growth *in vitro* and in mice. **Conclusion:** Our study provides novel evidence that METTL3 promotes HCC development and progression through m6A modification of BMI1 and RNF2. Our findings suggest that the METTL3-m6A-BMI1/RNF2 signaling axis may represent a new therapeutic target for the treatment of HCC.

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3375 | COMPARISON OF LIVER FUNCTION INJURY IN INTERMEDIATE AND ADVANCED HEPATOCELLULAR CARCINOMA PATIENTS TREATED WITH HEPATIC ARTERIAL INFUSION CHEMOTHERAPY VERSUS TRANSCATHETER ARTERIAL CHEMOEMBOLIZATION COMBINED WITH IMMUNE CHECKPOINT INHIBITORS AND TYROSINE KINASE INHIBITORS ◆

Mengya Zang[1] Peilin Zhu[1] Qingxian Cai[2] Haojie Liao[3] Dayong Zheng[4] Feng Shi[5] Hualang Cai[6] Xuan Wu[7] Qi Li[1] Huajin Pang[1]

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Background: Interventional therapy serves as the primary treatment for intermediate and advanced hepatocellular carcinoma (HCC), with liver function injury being a common adverse effect. This study aimed to compare the postoperative liver function injury of intermediate and advanced HCC patients who underwent either hepatic arterial infusion chemotherapy (HAIC) or transcatheter arterial chemoembolization (TACE) combined with immune checkpoint inhibitors (ICIs) and tyrosine kinase inhibitors (TKIs). **Methods:** This retrospective study enrolled intermediate and advanced HCC patients who received HAIC/TACE combined with ICIs and TKIs therapy from January 2019 to November 2023 across five institutions. The liver function indices within one week before treatment and within one week after intervention were recorded, and then were graded according to the common terminology criteria for adverse events 5.0 (CTCAE 5.0). Propensity score matching (PSM) was employed to minimize confounding bias. The tumor response was evaluated according to RECIST 1.1 criteria. **Results:** A total of 348 HCC patients were included in this study (HAIC group, n=210; TACE group, n=138). After PSM, 176 patients (HAIC group, n=88; TACE group, n=88) were analyzed. The postoperative occurrence of elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST) in the HAIC group was significantly lower than that in the TACE group (46.59% vs. 69.32%, P=0.002; 62.50% vs. 81.82%, P=0.003). Additionally, fewer patients in the HAIC group experienced grade 3 or 4 elevations in ALT and AST compared to the TACE group (6.8% vs. 20.7%, P=0.008; 14.8% vs. 23.0%, P =0.165). There were no significant differences in the frequency of hyperbilirubinemia, hypoalbuminemia and increased international standardized ratio between the two groups. The median progression-free survival (PFS) was 11.0 months in the HAIC group versus 7.05 months in the TACE group (P=0.0045). There was no significant difference in median overall survival (OS) (22.0 vs. 19.8 months, P=0.22) between the two groups. Objective response rate (ORR) was 53.95% in the HAIC group and 48.75% in the TACE group (P=0.516), while disease control rate (DCR) was 90.79% in the HAIC group versus 83.75% in the TACE group (P=0.189). **Conclusion:** The incidence of liver injury events was higher in the TACE group compared to the HAIC group.

Postoperative liver injury condition

	HAIC (n=88)	TACE (n=88)	*P*
Elevated ALT			0.002
No	47(53.40%)	26(29.90%)	
Yes	41 (46.60%)	61 (70.10%)	
Elevated AST			0.003
No	33 (37.50%)	15 (17.20%)	
Yes	55 (62.50%)	72 (82.80%)	
Hypoalbuminemia			1.000
No	10 (11.40%)	9 (10.30%)	
Yes	78 (88.60%)	78 (89.70%)	
Elevated TBIL			0.148
No	53 (60.90%)	43 (50.00%)	
Yes	34 (39.10%)	43 (50.00%)	
Elevated INR			0.492
No	70 (81.40%)	64 (77.10%)	
Yes	16 (18.60%)	19 (22.90%)	
Level of ALT elevation (≥3)	6 (6.80%)	18 (20.70%)	0.008
Level of AST elevation (≥3)	13 (14.80%)	20 (23.00%)	0.165
Level of hypoalbuminemia(≥2)	22 (25.00%)	23 (26.40%)	0.828
Level of TBIL elevation (≥3)	5 (5.70%)	2 (2.30%)	0.450
Level of INR elevation (≥3)	1(1.20%)	0 (0%)	0.324

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3376 | THE HIPPO PATHWAY EFFECTOR TAZ IS REQUIRED FOR NOTCH-DRIVEN CHOLANGIOCARCINOGENESIS VIA METTL3-MEDIATED M6A MODIFICATION

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[1]Tulane University School of Medicine, [2]Tulane University, [3]Tulane Medical Center

Background: Notch and TAZ are implicated in cholangiocarcinogenesis, but whether and how these oncogenic molecules interact remain unknown. **Methods:** The development of CCA was induced by hydrodynamic tail vein (HDTV) injection of oncogenes (NICD/AKT) to the FVB/NJ mice. CCA xenograft was developed by inoculation of human CCA cells into the livers of SCID mice. Tissues and cells were analyzed using qRT-PCR, Western blotting analyses, Immunohistochemistry, ChIP-qPCR and WST-1 cell proliferation Assay. **Results:** Our experimental findings show that TAZ is indispensable in NICD-driven cholangiocarcinogenesis. Notch activation induces the expression of METTL3 (Methyltransferase like-3) which catalyzes N6-methyladenosine (m6A) modification of TAZ mRNA and that this mechanism plays a central role in the crosstalk between Notch and TAZ in CCA cells. Mechanistically, Notch regulates the expression of METTL3 through the binding of NICD to its downstream transcription factor CSL in the promoter region of METTL3. METTL3 in turn mediates m6A modification of TAZ mRNA which is recognized by the m6A reader YTHDF1 to enhance TAZ protein translation. We observed that inhibition of Notch signaling decreased the protein levels of both MELLT3 and TAZ. Depletion of METTL3 by shRNAs or by the next generation GapmeR antisense oligonucleotides (ASOs) decreased the level of TAZ protein and inhibited the growth of human CCA cells *in vitro* and in mice. **Conclusion:** This study describes a novel Notch-METTL3-TAZ signaling cascade which is important in CCA development and progression. Our experimental results provide new insight into how the Notch pathway cooperates with TAZ signaling in CCA, and the findings may have important therapeutic implications.

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3377 | PERFORMANCE OF A MULTI-CANCER EARLY DETECTION (MCED) TEST FOR DETECTION OF HEPATOCELLULAR CARCINOMA (HCC) IN PATIENTS WITH CIRRHOSIS

Darine Daher[1] Purva Gopal[1] Marie Coignet[2] Vivian Xiao[2] Kathryn Kurtzman[2] Amit Singal[1]

[1]UT Southwestern Medical Center, [2]GRAIL, LLC

Background: HCC is the leading cause of cancer death in patients with cirrhosis, largely due to frequent late-stage diagnosis, underscoring a need for novel surveillance strategies. In this pilot study, we explored the potential of the MCED test to detect HCC at an early stage in patients with cirrhosis. **Methods:** In this case-control study, biobanked plasma was processed from patients aged >18 years with cirrhosis, without (controls) and with (cases) treatment-naïve HCC. Cases and controls were matched on liver disease etiology and Child Pugh score. The MCED test uses a targeted methylation assay and machine learning classifiers to detect a shared cancer signal and predict cancer signal origin (CSO) using circulating cell-free DNA across cancer types, and it was validated in the third and final Circulating Cell-Free Genome Atlas substudy. Test performance was assessed blinded to case-control status. We performed exploratory subgroup analyses, stratified by liver disease etiology, Barcelona Clinic Liver Cancer (BCLC) stage, and HCC treatment response (per modified RECIST). **Results:** Cases (n=27) and controls (n=17) were similar in demographics (median age, 63 years; male, 60%). Patients were diverse regarding race/ethnicity (36% non-Hispanic White, 36% Hispanic, 27% Black), cirrhosis etiology (50% hepatitis C virus, 25% nonalcoholic steatohepatitis, 20% alcohol), and tumor stage (41% early-stage BCLC stage 0/A and 59% BCLC stage B, with 41% being within Milan Criteria). Two-thirds had Child Pugh A cirrhosis. MCED test sensitivity and specificity was 78% and 100%, respectively. CSO prediction accuracy was 100%; all cases with a cancer signal detected had a CSO prediction of liver/bile duct. Cancer signal was detected in 55% of cases with early-stage (BCLC stage 0/A) HCC and 94% of those with BCLC stage B. Sensitivity

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and specificity was similar between patients with viral and non-viral etiologies of liver disease. The MCED test detected a cancer signal in 67% of cases with an objective response to transarterial chemoembolization and 87% of those with progressive disease. When stratified by BCLC stage, sensitivity continued to appear higher in patients with progressive disease than those with objective response (0/A: 67% vs 40%, respectively; B: 100% vs 86%, respectively). **Conclusion:** The MCED test shows promise as a noninvasive blood test for HCC surveillance in high-risk patients. Larger longitudinal studies are warranted to confirm these results.

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3378 | PROSPECTIVE STUDY ON THE IMPROVEMENT OF PROGNOSIS AND SUPPRESSION OF CANCER DEVELOPMENT AFTER ADMINISTRATION OF ZINC PREPARATION IN PATIENTS WITH LIVER CIRRHOSIS ◆

Atsushi Hosui[1] *Naoki Hiramatsu*[1] *Tomohide Kurahashi*[1]

[1]*Osaka Rosai Hospital*

Background: Serum zinc levels decrease with the progression of fibrosis in patients with chronic liver disease and low zinc levels are a risk factor for hepatocellular carcinoma (HCC) development. In a retrospective study, we demonstrated that the incidence of events such as hepatic encephalopathy and death, and the incidence of HCC were significantly lower in the zinc-treated group than in the zinc-untreated group. The aim of this study was to clarify in prospective study whether long-term zinc supplementation improves prognosis, inhibits HCC development, and suppresses deterioration of liver function in patients with cirrhosis after administration of zinc acetate (Novelzin), which can be used in daily clinical practice. **Methods:** Among 1067 consecutive patients diagnosed as cirrhosis between May 2018 and October 2023, 563 patients were investigated after exclusion due to history of HCC, observation period of less than 3 months, or failure to obtain consent, and were divided into zinc-taking group (n=130) and zinc-non-taking group (n=433). The trend of blood tests, survival rates, and the incidence of cancer development in the two groups were examined. **Results:** The clinical background of all patients was as follows: mean age 70.4±12.3 years, male/female 343/220, etiology alcohol/HBV/HCV/NASH 231/53/123/105, total bilirubin 1.8±2.5 mg/dL, albumin (Alb) 3.23±0.73 g/dL, prothrombin time (PT) 70.9±20.1, serum zinc 56. 3±20.3 μg/dL, and the mean observation period was 17.7±18.5 months. In the zinc group, serum zinc levels, Alb, and PT at the time of 6 months after zinc treatment were significantly higher than before (90.7→99.8 μg/dL, 3.48→3.66 g/dL, and 72.7→77.3% (all p-value <0.01). Survival rate and the incidence of cancer development were significantly better in the zinc-taking group than in the zinc-non-taking group (3-year survival rate: 69.0% vs. 56.2%, p=0.035; 3-year incidence of cancer development: 1.5% vs. 8.1%, p=0.043). **Conclusion:** As in the retrospective study, the zinc group showed significantly improved liver function, lower incidence of cancer development, and improved survival rates in the prospective study. These results indicate that administration of zinc preparations may be effective as one of the treatments for cirrhosis irrespective of etiology.

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3379 | FEVER AFTER THE ADMINISTRATION OF ATEZOLIZUMAB AND BEVACIZUMAB PREDICTS LIVER INJURY IN PATIENTS WITH UNRESECTABLE HEPATOCELLULAR CARCINOMA: A PROSPECTIVE OBSERVATIONAL ANALYSIS USING A MULTIPLEX BEAD-BASED IMMUNOASSAY

Takanori Ito[1] Takafumi Yamamoto[1] Kazuki Nishida[2] Yumiko Kobayashi[2] Kazuyuki Mizuno[2] Shinya Yokoyama[1] Norihiro Imai[1] yoji ishizu[1] Takashi Honda[1] Masatoshi Ishigami[1] Toshinari Koya[3] Sayori Nakashima[4] Takehito Naito[5] Satoshi Yasuda[6] Teiji Kuzuya[7] Hidenori Toyoda[6] Yuichi Ando[2] Sachiyo Yoshio[8] Hiroki Kawashima[1]

[1]Nagoya University, [2]Nagoya University Hospital, [3]Tosei General Hospital, [4]Kariya Toyota General Hospital, [5]Toyohashi Municipal Hospital, [6]Ogaki Municipal Hospital, [7]Fujita Health University, [8]National Center for Global Health and Me

Background: Liver injury as a treatment-related adverse event (liver-TRAE), which includes immune-related adverse events, is one of the most common complications induced by atezolizumab and bevacizumab (Atez/Bev) when treating unresectable hepatocellular carcinoma (uHCC). Previous studies have shown that fever after immune checkpoint inhibitor (ICI) administration may predict ICI-induced liver injury in various types of malignancies. However, the association between fever and liver-TRAE in uHCC patients treated with Atez/Bev has not been investigated. Therefore, we prospectively evaluated the relationship between the onset of liver-TRAE and preceding fever, and sought to identify circulating biomarkers that predict liver injury in Atez/Bev-treated uHCC patients. **Methods:** The primary outcome of this prospective, multicenter study was the association between liver-TRAE (≥ grade 2 based on CTCAE v.5.0) and the presence of ICI-induced fever before the onset of liver injury. We excluded patients from the liver-TRAE group if they had liver injury due to tumor progression or fever due to infection. We used a multiplex bead-based immunoassay to evaluate 40 circulating proteins in sera before and 1, 3, and 6 weeks after initial Atez/Bev treatment. **Results:** Among 99 patients receiving Atez/Bev, liver-TRAE (≥ grade 2) occurred in 10 (10.1%) during the follow-up period (median, 14.7 months). The incidences of liver-TRAE associated with the presence of fever before liver injury were 27.8% (n=5/18) and 6.2% (n=5/81) in the fever and non-fever groups, respectively. Multivariable analysis showed that the presence of fever was a significant risk factor for liver-TRAE (odds ratio 7.57; 95% confidence interval, 1.83–33.89; P=0.006). Furthermore, the prognosis tended to be worse in the liver-TRAE (≥ grade 2) group (P=0.065 for progression-free survival and P=0.074 for overall survival). Among patients with preceding fever, the liver-TRAE group had significantly higher levels of CXCL-5 before treatment, IL-6 at 1 and 3 weeks, and CXCL-5, IFNγ, and IL-10 at 6 weeks (P<0.05). **Conclusion:** Fever during Atez/Bev treatment may predict liver-TRAE, which leads to poor prognosis in patients with uHCC. Altered levels of inflammatory cytokines and chemokines may help predict liver-TRAE in patients with fever after Atez/Bev therapy.

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3380 | ANALYSIS OF VARIX BLEEDING COMPLICATION AFTER ATEZOLIZUMAB PLUS BEVACIZUMAB FOR ADVANCED HEPATOCELLULAR CARCINOMA PATIENTS

Hee Kim[1] Ahlim Lee[1] Sung Won Lee[1] Haelim Lee[1] Jung Hyun Kwon[1] Chang Wook Kim[2] Se Hyun Cho[1] Heechul Nam[1] Hyun Yang[3] Do Seon Song[1] U Im Chang[1] SOON WOO NAM[1] Soon Kyu Lee[1] Seok-Hwan Kim[1] Myeong Jun Song[1] Pil Soo Sung[1] Ji Won Han[1] Jeong Won Jang[1] SI HYUN BAE[1] Jongyoung Choi[1] Seung Kew Yoon[1]

[1]The Catholic University of Korea, [2]Uijeongbu St. Mary's Hospital, [3]Seoul St. Mary's Hospital

Background: Following the IMbrave150 trial, atezolizumab plus bevacizumab (AteBeva) emerged as the gold standard for unresectable hepatocellular carcinoma (HCC). However, given the exclusion criteria of the trial, including no history of acute variceal bleeding or high-risk esophageal varices, real-world data on AteBeva's efficacy and safety in patients with such histories remain scarce. We aimed to assess the therapeutic effect and safety of AteBeva and identify risk factors for AVB during treatment in Korea. **Methods:** This retrospective study enrolled all patients diagnosed with advanced HCC who received AteBeva from seven centers of the Catholic Medical Center between September 2020 and December 2022. Patients were followed up until December 2023, and therapeutic efficacy, safety, and AteBeva-related variceal bleeding were analyzed. Time-to-event analyses were conducted using Kaplan-Meier and Cox models. **Results:** One hundred fifty-four patients treated with AteBeva were included. Baseline characteristics revealed a median age of 64.0 years (range: 56.0-73.0), with 85.1% male. The most common etiologies were hepatitis B virus infection (62.2%) and alcohol-related liver disease (26.5%). The Objective Response Rate was 38.3%, and the Disease Control Rate was 70.9%. Median overall survival (OS) was 14.0 months (95% CI: 8.5-19.5), median progression-free survival was 5.0 months (95% CI: 3.9-6.1), and median time-to-progression was 3.0 months (95% CI: 2.3-3.7). Multivariable analysis identified variables associated with OS and varix bleeding after AteBeva. In multivariable analysis, variables associated with OS were the Eastern Cooperative Oncology Group performance scale, liver cirrhosis, Child-Pugh class, largest intrahepatic tumor size, and treatment duration. Among the patients who underwent all grades of gastrointestinal bleeding events after AteBeva, 40 (26.0%) were affected, including varix bleeding (n=23, 14.9%). In multivariable analysis, variables associated with varix bleeding after AteBeva were Child-Pugh score and ulceration from prophylactic endoscopic band ligation (EBL) before AteBeva. **Conclusion:** Child-Pugh score at baseline and ulceration from prophylactic EBL before AteBeva were identified as risk factors for varix bleeding. Monitoring and managing ulceration post-EBL are essential for patients receiving AteBeva, particularly those with prophylactic EBL. Further large-scale studies are warranted to validate these findings.

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3381 | HYPOCRELLIN A, A NATURAL SMALL COMPOUND, EXERTS ANTI-TUMOR EFFECTS VIA MULTI-TARGET INHIBITION OF THE PI3K-AKT-MTOR, MAPK, AND STAT3 SIGNALING PATHWAYS IN INTRAHEPATIC CHOLANGIOCARCINOMA

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Background: Intrahepatic cholangiocarcinoma (ICC) is an aggressive and highly lethal cancer lacking available effective treatment regimens, with an increasing incidence worldwide. Hypocrellin A (HA), a natural small compound isolated from S. bambusicola, has multiple biomedical activities, including anticancer activity. We aimed to investigate the therapeutic effect of HA on ICC and explored the underlying mechanisms. **Methods:** RBE and HuccT1 cell lines were utilized for in vitro experiments. CCK8 assay, colony formation analysis, RTCA, and immunofluorescence staining of ki67 were performed to evaluate the inhibitory effects of HA on the proliferation. The inhibitory effects of HA on cell migration and invasion were assessed using transwell and wound healing assays, while Hoechst 33258 staining was employed to evaluate apoptosis. Additionally, we

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performed transcriptome sequencing and molecular docking for targeting identification, and immunoblotting and immunofluorescence of key molecules for validation. HuccT1 xenografts and primary ICC model (KRAS/P19/SB) by hydrodynamic tail-vein injection were implemented for vivo experiments. Multiplex immunohistochemistry (mIHC) was employed to illustrate the multi-target inhibition effects of HA. **Results:** CCK8 assay determined that the IC50 of HA against RBE and HuccT1 cells were 4.612 μM and 10.01 μM for 24 hours. Our results confirmed that HA significantly repressed the proliferation, migration, invasion, and promoted apoptosis of ICC cells. Moreover, HA exerts its anti-tumor effects through multi-target inhibition of the PI3K-AKT-mTOR, MAPK, and STAT3 signaling pathways. This inhibitory effect can be rescued by recilisib, an activator of PI3K-AKT-mTOR. Animal studies suggested that HA strongly inhibits the tumor growth of xenografts ICC models, and repressed the tumor number and size in the liver of primary ICC models, also through inhibition of these three crucial pathways. **Conclusion:** HA demonstrated promising therapeutic efficacy against ICC through its multi-target inhibition effects on the PI3K-AKT-mTOR, MAPK, and STAT3 signaling pathways. Moreover, it exhibited notable therapeutic benefits in primary ICC model (KRAS/P19/SB), positioning it as a novel therapeutic agent for treating ICC.

Disclosures: Bo Chen: Nothing to Disclose, Qiwen Chen: Nothing to Disclose, Na Zheng: Nothing to Disclose, Gang Chen: Nothing to Disclose

3382 | MULTI-OMICS ANALYSIS OF PATIENTS WITH HEPATOCELLULAR CARCINOMA TREATED WITH ANTI-PD-L1 PLUS ANTI-CTLA-4 AND LOCOREGIONAL THERAPY: CORRELATIVE STUDY OF PHASE2 TRIAL

Yuta Myojin[1] Sepideh Babei[2] Christoph Hoffman[2] Noemi Kedei[1] Benjamin Ruf[1] Mohamed-Reda Benmebarek[1] Kylynda Bauer[1] Patrick Huang[1] Rajiv Trehan[1] Chi Ma[1] Cecilia Monge[1] Changqing Xie[1] Paul Armstrong[3] Austin Duffy[3] Firouzeh Korangy[1] Manfred Claassen[2] Tim Greten[1]

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Background: Hepatocellular carcinoma (HCC) is a significant contributor to cancer-related mortality, with immunotherapy utilizing durvalumab (Dur) and tremelimumab (Trem) now established as standard treatment for advanced cases. However, comprehensive studies on immune responses are lacking. This study aimed to investigate immune responses in HCC patients using clinical samples. **Methods:** In a phase 2 trial, 41 HCC patients were enrolled and administered Dur and Trem in combination with intervention therapies. Blood and tumor samples were collected pre- and post-treatment. Peripheral blood mononuclear cells (PBMC) and serum samples from 28 patients were analyzed. Tumor biopsies from 24 patients underwent RNA sequencing, whole exon sequencing, single-cell RNA sequencing and 37-plexed immunofluorescence (CODEX). Orthotopic liver tumor mouse models were utilized to assess responses to anti-PD-L1 and anti-CTLA4 therapy. **Results:** Patients exhibited median progression-free survival (PFS) and overall survival (OS) of 4.9 and 20.2 months, respectively. Patient characteristics, including liver function and tumor stage, related with treatment response. Tissue RNA sequencing demonstrated enhancement of interferon responses in both responder and non-responder groups, with a more pronounced effect in responders. The antigen presentation gene signature was enhanced in responders and TGF-beta late signature was enriched in non-responders. To examine immune cells in the tumor microenvironment by spatial context, we developed a 37-plexed CODEX panel. The cellular composition observed in the images matched with predictions from RNA sequencing. Analysis of cellular neighborhoods revealed regulatory T cells enriched in tumor neighborhoods. scRNAseq showed that, in non-responders, ITGB1 expression in Treg increased after the treatment. In the peripheral blood analysis, levels of monocytes in PBMC increased in responders, while regulatory T cells in PBMC increased in non-responders. Serum cytokine analysis indicated elevated IL18 and CCL22 levels in responders and increased IL6 and TNFa levels in non-responders. Random forest analysis using tissue and blood features revealed that some features related to the prognosis. Animal studies showed reductions in tumor size, T cell infiltration, an increase of cytotoxicity in tumors and liver, and an increase in monocytes in PBMC with combination therapy. **Conclusion:** We utilized and combined multiple analysis **Methods:** to analyze the tumor immune environments from a clinical trial.

Disclosures: Yuta Myojin: Nothing to Disclose, Sepideh Babei: Nothing to Disclose, Christoph Hoffman: Nothing to Disclose, Noemi Kedei: Nothing to Disclose, Benjamin Ruf: Nothing to Disclose, Mohamed-Reda Benmebarek: Nothing to Disclose, Kylynda Bauer: Nothing to Disclose, Patrick Huang: Nothing to Disclose, Rajiv Trehan: Nothing to Disclose, Chi Ma: Nothing to Disclose, Cecilia Monge: Nothing to Disclose, Changqing Xie: Nothing to

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Disclose, Paul Armstrong: Nothing to Disclose, Austin Duffy: Nothing to Disclose, Firouzeh Korangy: Nothing to Disclose, Manfred Claassen: Nothing to Disclose, Tim Greten: Nothing to Disclose

3384 | LIVER TRANSPLANTATION IS THE MAJOR DETERMINANT IN ACHIEVING OVER 10-YEAR SURVIVAL FOR PATIENTS WITH EARLY-STAGE HEPATOCELLULAR CARCINOMA ◆

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Background: Hepatocellular carcinoma (HCC) is a leading cause of cancer-related mortality, with prognosis heavily dependent on the stage at diagnosis and treatment modalities. For patients with early-stage HCC, curative intent treatments, including ablation, resection, or liver transplantation (LT), are recommended. This study aimed to identify factors achieving >10-year survival for HCC patients, with a particular emphasis on the type of treatment in early-stage patients. **Methods:** We conducted a retrospective cohort study using the National Cancer Database (NCDB), encompassing HCC patients diagnosed between 2004 and 2022. Patients with at least 10 years of follow-up or who died within 10 years were included and were stratified by length of survival (≤5 years, 5-10 years, >10 years). Multivariable logistic regression and decision tree analysis were employed to identify factors predicting >10 years survival (vs.≤5 years), adjusting for confounding factors, including age, sex, race/ethnicity, tumor size, comorbidities, and socioeconomic status. **Results:** Out of 196,139 patients, 9,907 (5.1%), 14,232 (7.3%), and 17,580 (9.0%) patients received LT, surgical resection, and ablation. Among 9,761 (5.0%) patients who achieved >10-year survival, 4,276 (43%), 1,960 (14%), and 1,040 (5.9%) patients received LT, surgical resection, and ablation. Multivariable analysis revealed that younger age, female sex, Hispanic and Asian ethnicity, smaller tumor size, lower AJCC stage, lower comorbidity score, higher income, academic facility treatment, and undergoing LT were significant predictors of achieving > 10-year survival. In the subgroup of 54,706 early-stage HCC patients (AJCC T1), LT remained the most effective treatment, significantly improving the odds of >10-year survival (OR: 11.47, 95% CI: 10.35-13.09, p<0.001) compared to ablation. Resection was also associated with higher odds of >10-year survival compared to ablation, but to a lesser extent (OR: 3.16, 95% CI: 2.72-3.50, p<0.001). The decision tree analysis supported these findings, highlighting LT as the most critical determinant of long-term survival for both the overall cohort and T1 patients. **Conclusion:** Our study demonstrates that LT offers the highest probability of achieving >10-year survival for HCC patients, likely due to substantial mortality reduction from cancer recurrence and hepatic failure. However, prioritizing LT for HCC patients should be carefully weighed against the necessity to provide equitable organ access for decompensated cirrhosis patients awaiting LT.

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Predictors of 10-year survival in patients with early-stage HCC (AJCC T1)

Characteristic	Univariate			Multivariable		
	OR[1]	95% CI[1]	p-value	OR[1]	95% CI[1]	p-value
Age (10 Years)	0.49	0.47, 0.51	<0.001	0.55	0.53, 0.57	<0.001
Sex						
Male	—	—		—	—	
Female	1.04	0.97, 1.11	0.308	1.30	1.20, 1.42	<0.001
Race / Ethnicity						
White	—	—		—	—	
Hispanic	1.12	1.02, 1.24	0.023	1.27	1.15, 1.46	<0.001
Black	0.85	0.76, 0.94	0.002	0.88	0.77, 0.99	0.041
Asian + Others	2.44	2.22, 2.68	<0.001	2.15	1.89, 2.40	<0.001
Tumor Size (cm)	0.85	0.84, 0.87	<0.001	0.90	0.89, 0.91	<0.001
Comorbidity						
0	—	—		—	—	
1	1.19	1.10, 1.28	<0.001	1.08	0.99, 1.19	0.099
2	0.88	0.79, 0.98	0.020	0.88	0.78, 1.02	0.047
3	0.90	0.83, 0.99	0.025	0.72	0.65, 0.81	<0.001
Insurance						
Medicaid/Medicare	—	—		—	—	
Private	3.66	3.46, 3.94	<0.001	1.81	1.69, 1.98	<0.001
Not Insured	0.85	0.68, 1.05	0.152	0.75	0.59, 0.95	0.019
Other	1.38	1.07, 1.72	0.007	1.29	0.97, 1.66	0.061
Education (% NO HSD)						
15.3% +	—	—		—	—	
9.1% - 15.2%	1.04	0.94, 1.12	0.410	0.95	0.87, 1.07	0.302
5.0% - 9.0%	1.18	1.09, 1.29	<0.001	0.95	0.87, 1.10	0.384
< 5.0%	1.46	1.31, 1.58	<0.001	1.01	0.89, 1.19	0.910
Income						
< $46,277	—	—		—	—	
$46,277 - $57,856	1.15	1.01, 1.25	0.008	1.10	0.95, 1.21	0.124
$57,857 - $74,062	1.40	1.23, 1.50	<0.001	1.21	1.03, 1.32	0.004
$74,063 +	2.04	1.83, 2.19	<0.001	1.57	1.31, 1.72	<0.001
Facility Type						
Non Academic	—	—		—	—	
Academic	2.38	2.22, 2.55	<0.001	1.56	1.44, 1.70	<0.001
Location						
Northeast	—	—		—	—	
Midwest	0.73	0.67, 0.81	<0.001	0.73	0.65, 0.82	<0.001
South	0.66	0.60, 0.72	<0.001	0.70	0.64, 0.79	<0.001
West	0.89	0.82, 0.98	0.013	0.82	0.75, 0.93	<0.001
MELD (10 Units)	0.85	0.79, 0.85	<0.001	0.86	0.79, 0.86	<0.001
Fibrosis						
No cirrhosis	—	—		—	—	
Cirrhosis	0.70	0.64, 0.74	<0.001	0.63	0.54, 0.65	<0.001
AFP						
Negative	—	—		—	—	
Positive	0.74	0.70, 0.79	<0.001	0.81	0.75, 0.88	<0.001
Treatment						
Ablation	—	—		—	—	
Resection	3.03	2.72, 3.38	<0.001	3.16	2.72, 3.50	<0.001
Transplant	**14.37**	**12.91, 16.04**	**<0.001**	**11.47**	**10.35, 13.09**	**<0.001**
Non-curative management	0.41	0.37, 0.45	<0.001	0.55	0.50, 0.61	<0.001

[1] OR = Odds Ratio, CI = Confidence Interval

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relationship with Exelixis; Has ended; Advisor relationship with Fujifilm Medical; Has ended; Grant/Research Support relationship with Genentech; Has ended; Consultant relationship with Exact Sciences; Has not ended, Amit Singal: Consultant relationship with AstraZeneca; Has not ended; Consultant relationship with Sirtex; Has not ended; Consultant relationship with Boston Scientific; Has not ended; Consultant relationship with Bayer; Has not ended; Consultant relationship with Eisai; Has not ended; Consultant relationship with FujiFilm Medical Sciences; Has not ended; Consultant relationship with Elevar; Has not ended; Consultant relationship with Exact Sciences; Has not ended; Consultant relationship with Glycotest; Has not ended; Consultant relationship with Exelixis; Has not ended; Consultant relationship with Merck; Has not ended; Consultant relationship with Genentech; Has not ended; Consultant relationship with HistoSonics; Has not ended, Ju Dong Yang: Consultant relationship with Fujifilm Medical Sciences; Has not ended; Consultant relationship with Exelixis; Has not ended; Consultant relationship with Eisai; Has not ended; Consultant relationship with AstraZeneca; Has not ended; Consultant relationship with Exact Sciences; Has not ended

3385 | INTERACTION OF SOLUTE CARRIER FAMILY 39 MEMBER 1 AND DYNAMIN RELATED PROTEIN 1 TO FACILITATE DEVELOPMENT OF HEPATOCELLULAR CARCINOMA BY IMPAIRING MITOCHONDRIAL QUALITY CONTROL

Rui Li[1] Zhe Wang[1] Lixin Cheng[2] Zhiqiang Cheng[3] Qiong Wu[4] Qingxian Cai[5] Yijin Wang[1]

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Background: Despite rapid advances in HCC therapy, patients undergoing surgical resection have a poor prognosis with recurrence in the short-term. We have previously shown that solute carrier family 39 member 1 (SLC39A1) is involved in HCC recurrence.This study aimed to investigate the mechanism of SLC39A1 in the regulation of hepatocarcinogenesis and recurrence. **Methods:** Liver samples from non-relapsed and relapsed HCC patients after surgically resection, were collected for RNA sequencing. Liver-specific SLC39A1 knockout mice (SLC39A1^{lko}) were generated by crossing Alb-Cre mice and SLC39A1$^{f/f}$ mice. Liver samples were analyzed for inflammation, fibrosis and proliferation. Mitochondrial dynamics, autophagy, ROS and MMP, were detected. Co-IP and molecular docking identified protein interactions. Targeting 1-28 peptide of SLC39A1 was designed. **Results:** Upregulated SLC39A1 was associated with poor survival. Knockdown of SLC39A1 inhibited cell proliferation, migration and arrested cell cycle, but promoted cell apoptosis, which suppressed autophagic flux. Since SLC39A1 is localized in mitochondria, we then detected mitochondrial function and dynamics. MMP hyperpolarization, ROS production and Cytochrome C activation, and mitochondrial aggregation, consistent with a marked increase upregulated OPA1 and MFN1 and downregulated of Fis1 and DRP1, were observed in SLC39A1-silenced cells. Co-immunoprecipitation and molecular docking analysis implied SLC39A1 was bind to DRP1. Genetic or pharmacological inhibition of DRP1 potently abolished SLC39A1-induced mitochondrial division and MMP depolarization, while overexpression DRP1 can reverse SLC39A1 silence induced mitochondrial fusion and hyperpolarization MMP, accompanied by recuperative cell proliferation. Taken together, SLC39A1/DRP1/MCU axis were critical for MMP reduction, mitochondrial fragmentation. SLC39A1^{lko} mice displayed reduced tumor number in DEN-CCL4 model compared with SLC39A1$^{flox/flox}$ mice, evidenced by reduced liver damage, hepatocyte proliferation (Ki-67), inflammation (TGF-β), and fibrosis (Masson), accompanied by increased ROS accumulation and decreased LC3 and Lamp1. Finally, we designed specific peptide to target 1-28 fragment of SLC39A1 to interfere combination of full-length SLC39A1 and DRP1. Treatment with 1-28 fragment significantly decreased tumor volume and weight in subcutaneous mouse models. **Conclusion:** SLC39A1 was significantly upregulated in HCC relapsed patients. SLC39A1 interacted with DRP1 to impair mitochondrial quality control, promote autophagy and reduce MMP and ROS production, thereby promoting cell proliferation and inhibiting apoptosis. Targeting SLC39A1 and 1-28 peptide offer a promising novel strategy for HCC treatment.

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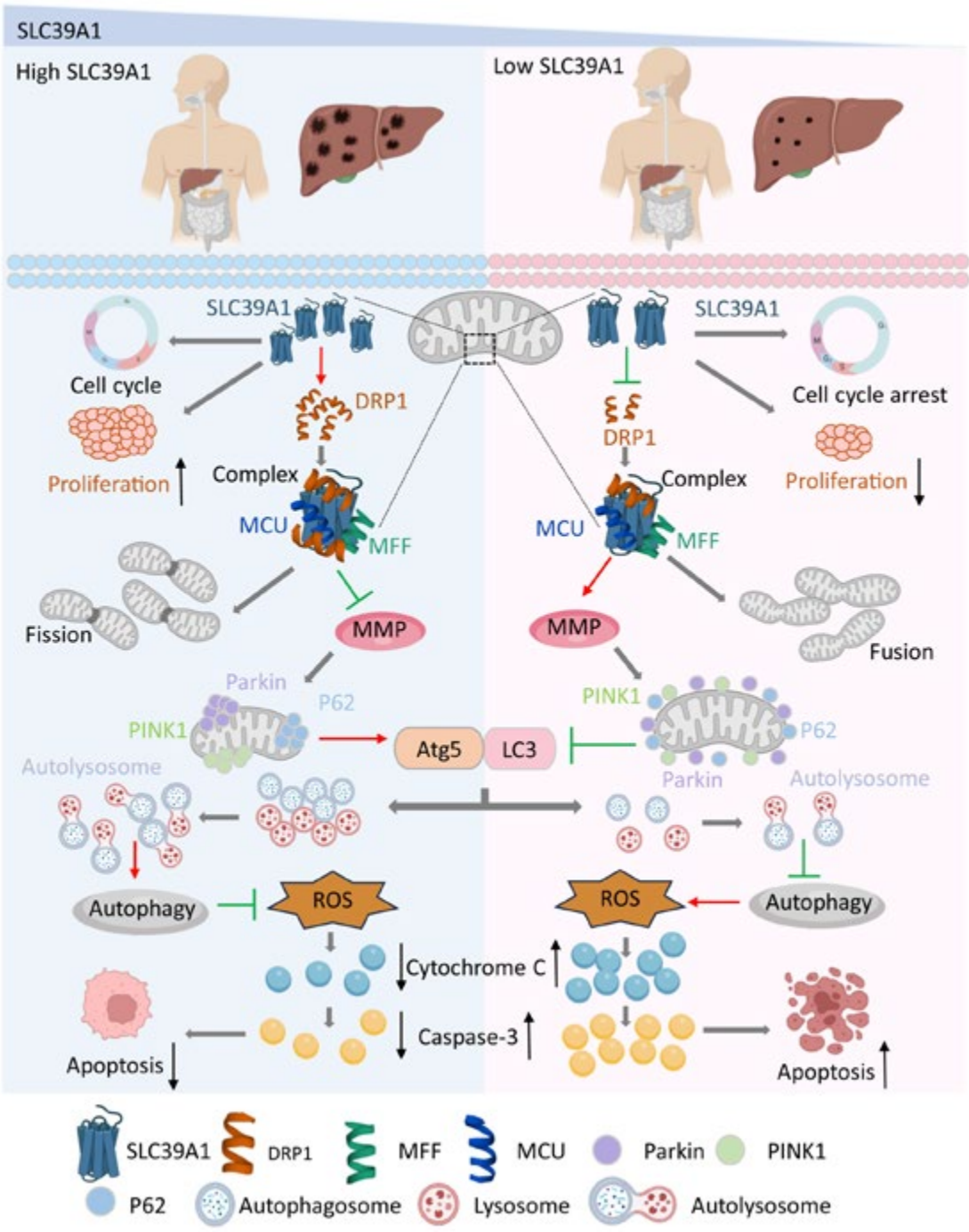

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3386 | MAINTENANCE OF GOOD LIVER FUNCTION IS IMPORTANT FOR GOOD POST-PROGRESSION SURVIVAL WITH ATEZOLIZUMAB/BEVACIZUMAB IN ADVANCED HEPATOCELLULAR CARCINOMA

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Background: Atezolizumab/bevacizumab (Atz/Bev) has been widely used in patients with advanced hepatocellular carcinoma (HCC). However, there is little information about the post-progression survival (PPS) of Atz/Bev. The aim of this study was to investigate the post-progression treatment switching rate and prognostic factors associated with PPS in patients with advanced HCC treated with Atz/Bev. **Methods:** We included 121 patients with HCC who had Child-Pugh A and Eastern Cooperative Oncology Group performance status (ECOG-PS) 0/1 at the start of Atz/Bev. Median age was 75 years, 101 were male, 81 had non-viral HCC, 94 had PS 0, 85 had Child-Pugh score 5, and 60 had BCLC stage C. Median follow-up was 15.3 months. **Results:** The best antitumor response according to RECIST was 34.7% for ORR and 79.3% for DCR. Median OS and PFS were 21.9 and 9.2 months, respectively. Median PFS for the 88 patients with radiologically confirmed progression was 9.2 months. Significant and independent prognostic factors at PD associated with favorable PFS were ECOG PS score 0 and Child-Pugh A. The rate of switching to post-progression treatment for the 69 patients with both Child-Pugh A and ECOG-PS score 0/1 at PD was 92.8% and the median PFS was 17.5 months, both significantly better than the remaining 19 patients (36.8% and 2.0 months, respectively). The only significant predictive factor contributing to both Child-Pugh A and PS of 0/1 at PD was Child-Pugh score 5 at the start of Atz/Bev treatment. **Conclusion:** Good liver function at baseline and at PD in patients treated with Atz/Bev would be expected to be associated with a higher rate of switching to post-progression treatment and better PPS. To prolong the prognosis of patients with advanced HCC who receive sequential treatment with systemic agents, it is important to start systemic therapy with good liver function at induction and maintain good liver function during treatment by appropriately managing adverse events.

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3387 | A COMPARATIVE VALIDATION OF CLINICAL PREDICTION SCORES FOR HEPATOCELLULAR CARCINOMA IN STEATOTIC LIVER DISEASE WITHOUT CIRRHOSIS

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[1]Yale University

Background: Many clinical risk scores to predict hepatocellular carcinoma (HCC) have been assessed in cohorts without known cirrhosis or viral hepatitis, whose HCC risk is driven by steatotic liver disease (SLD). Although differences in HCC incidence are observed across predictive score values, the clinical utility of a risk score depends on its ability to inform clinical decisions in the target population. **Methods:** For adults engaged in Veterans Affairs care for at least 18 months without evidence of prior HBV, HCV, or hepatic decompensation, we randomly selected a visit and calculated HCC risk scores using clinical and laboratory data. A sub-sample with likely SLD was identified based on the presence of two or more elevated ALT values at least 180 days apart with no diagnosis codes for alternate primary liver diseases. Patients were followed until the earliest of HCC diagnosis, death, or 6 months after last contact. We compared the performance of eight scores to predict 10-year risk of HCC. Six were liver disease staging scores (FIB-4, APRI, ALBI, aMAP, BARD, NFS) and two were novel HCC risk scores (Hung and Sinn). We evaluated previously utilized thresholds and score values corresponding to 10-year HCC risk thresholds from 0.25% to 5.0% using Cox proportional hazards regression. **Results:** The sample included 6,509,288 patients, 15,142 (0.2%) of whom developed HCC during follow-up. In all, 891,599 individuals met criteria for likely SLD, 2,104 (0.2%) of whom developed HCC. Mean age was 63.6 years. The sample was 92.9% men, 68.9% non-Hispanic White race, 15.0% non-Hispanic Black race, and 5.3% Hispanic ethnicity. Previously tested risk score thresholds yielded positive predictive values (PPV) for incident HCC ≦ 1%. For example, FIB-4 ≥ 2.67 yielded a sensitivity of 40%, specificity of 90%, and PPV of 1.0% and aMAP score

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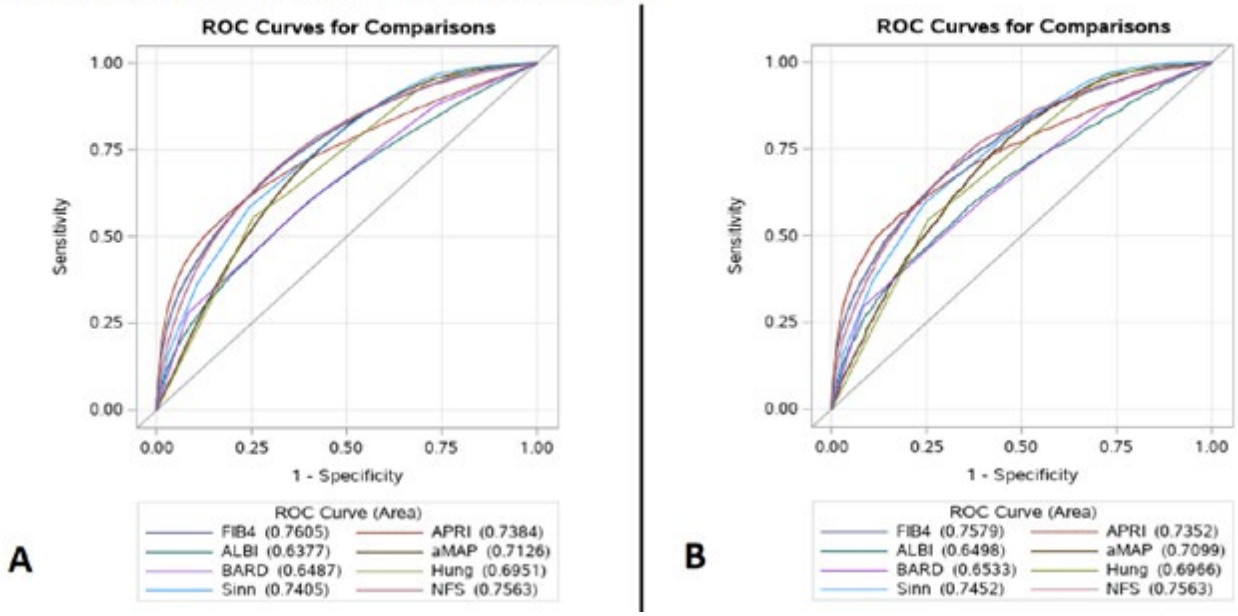
≥ 60 provided a sensitivity of 66%, specificity of 63%, and PPV of 0.4%. Risk score thresholds that provided sensitivity 80% (NFS -5.69, Hung 9, Sinn 9, BARD 2, and ALBI -3.07) had poor specificity (0%, 22%, 32%, 28%, and 22%, respectively) and PPVs were ≦ 0.3%. The C statistics for 10-year incident HCC ranged from 0.64 (ALBI) to 0.76 (FIB-4 and NFS) in the total sample and 0.65 (ALBI) to 0.76 (FIB-4 and NFS) in the subsample with likely SLD. **Conclusion:** In a general patient cohort where HCC risk is driven largely by SLD, eight clinical risk scores showed poor applicability for use in clinical decision-making. Further research is needed to identify novel predictors of HCC in non-cirrhotic SLD with an emphasis on translation to clinical practice.

Overlay of receiver operating curves for 8 HCC prediction scores in the total sample (A) and subsample with likely steatotic liver disease (B)



Disclosures: Catherine Mezzacappa: Nothing to Disclose, Janet Tate: Nothing to Disclose, Tamar Taddei: Nothing to Disclose, Amy Justice: Nothing to Disclose

3388 | OPTIMAL SUBSEQUENT THERAPY FOR UNRESECTABLE HEPATOCELLULAR CARCINOMA PATIENTS PROGRESSED ON ATEZOLIZUMAB PLUS BEVACIZUMAB THERAPY, APPROPRIATE TO THE RADIOLOGICAL PROGRESSION PATTERNS

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Background: We evaluated the impact of the radiological progression patterns integrated with tumor-related characteristic at progression on the prognosis of unresectable hepatocellular carcinoma patients (uHCC) who progressed on atezolizumab plus bevacizumab therapy (Atezo/Bev) and considered the optimal subsequent therapy. **Methods:** Between December 2018 and March 2023, 161 uHCC with Child-Pugh score of 5-7 and performance status (PS) of 0-1 received Atezo/Bev in our hospitals. Among them, 102 patients who had radiological progression (1st line: n=66) were enrolled (median observation periods: 17.4 months). The factors associated with post progression survival (PPS) and achievement of objective response (OR) by subsequent therapy were analyzed. **Results:** Median PPS was 12.5 months. Tumor-related characteristics at progression included maximal tumor size>6cm (n=26), tumor number≥7 (n=37), vascular invasion (VI) (n=23) and extrahepatic spread (EHS) (n=37). The radiological progression patterns included intrahepatic growth (IHG: n=70).

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extrahepatic growth (EHG: n=26), new intrahepatic lesion (NIL: n=38) and new EHS (nEHS: n=11) and expression or progression of VI (nVI: n=13). Molecular targeted therapy (MTT: n=56), the combination of locoregional therapy (LT) and MTT (n=22), catheter therapy (n=5), liver resection (n=1) and best supportive care (BSC: n=18) were performed as subsequent therapies, and OR rate assessed by mRECIST was 12.5%, 77.3%, 20.0%, 100.0% and 0.0%. Tumor number >6 with NIL (hazard ratio [HR], 4.0) and tumor number>6 without NIL (HR, 2.3) were associated with unfavorable PPS, with tumor number ≤6 without NIL used as a reference. EHS with EHG and/or nEHS was associated with unfavorable PPS (HR, 3.1), with abscence of EHS used as a refrence. Achievement of OR was contributed to favorable PPS (HR, 0.048) with BSC used as a reference. Combination of LT and MTT (odds ratio, 23.8) was contributed to achievement of OR, with MTT used as a reference, especially in the situation with IHG and without EHG (OR rate: 87.5% and 84.2%). **Conclusion:** Prognosis after progression on Atezo/Bev in uHCC could be stratified in detail by integrated evaluation of tumor-related characteristic at progression and radiological progression pattern. Combination of LT and MTT would be a subsequent therapy aiming at achievement of OR, especially in the situation with radiological progression pattern of IHG or without radiological progression pattern of EHG.

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3389 | UBE2D3 NEGATIVELY REGULATES HEPATOCARCINOGENESIS VIA SUPPRESSION OF STAT3 SIGNALING

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Background: Pharmacotherapy for hepatocellular carcinoma (HCC) has progressed markedly in recent years, with many drugs becoming available. However, its prognosis is still dismal, and further understanding of the hepatocarcinogenesis mechanism is desired. We identified UBE2D3 as a candidate tumor-suppressor gene in the liver by cancer gene screening using transposon insertional mutagenesis. We thus investigated the role of UBE2D3 in HCC. **Methods:** We investigated the clinical relevance of UBE2D3 abnormality in human HCC from multiple cohorts. We suppressed or forced expression of UBE2D3 by shRNA transfection in murine immortalized liver progenitor cell lines (LPCs) or cDNA transfection in human HCC cell line SNU-387, respectively. We investigated their effects on cell proliferation by WST-8, apoptosis by Caspase-3/7 activity, sphere formation, and tumour formation as well as signalling pathways regulating these phenotypes. We generated liver-specific Ube2d3 knockout mice and investigated the effect of Ube2d3-deletion on hepatocarcinogenesis. **Results:** Significant copy number loss in UBE2D3 gene locus was observed in human HCC, resulting in significant downregulation of UBE2D3 mRNA levels compared to non-tumor liver tissue. UBE2D3 gene expression levels were inversely correlated with patient survival. UBE2D3 Inhibition suppressed apoptosis, enhanced cell proliferation, and sphere formation in LPCs, and significantly increased the rate of allograft tumour formation. In contrast, forced expression of UBE2D3 resulted in increased apoptosis, decreased cell proliferation and sphere formation in SNU-387, and decreased xenograft tumorigenicity. STAT3 phosphorylation was negatively regulated by UBE2D3 in these cells and STAT3 inhibition mitigated the *in vitro* oncogenic phenotypes induced by UBE2D3 inhibition in LPCs. Genetic ablation of hepatic Ube2d3 increased hepatic STAT3 phosphorylation and promoted hepatocarcinogenesis in the mice with steatohepatitis induced by CDAA-HFD feeding or liver-specific PTEN deletion. **Conclusion:** UBE2D3 is a novel tumor suppressor gene that regulates hepatocarcinogenesis via STAT3 pathway.

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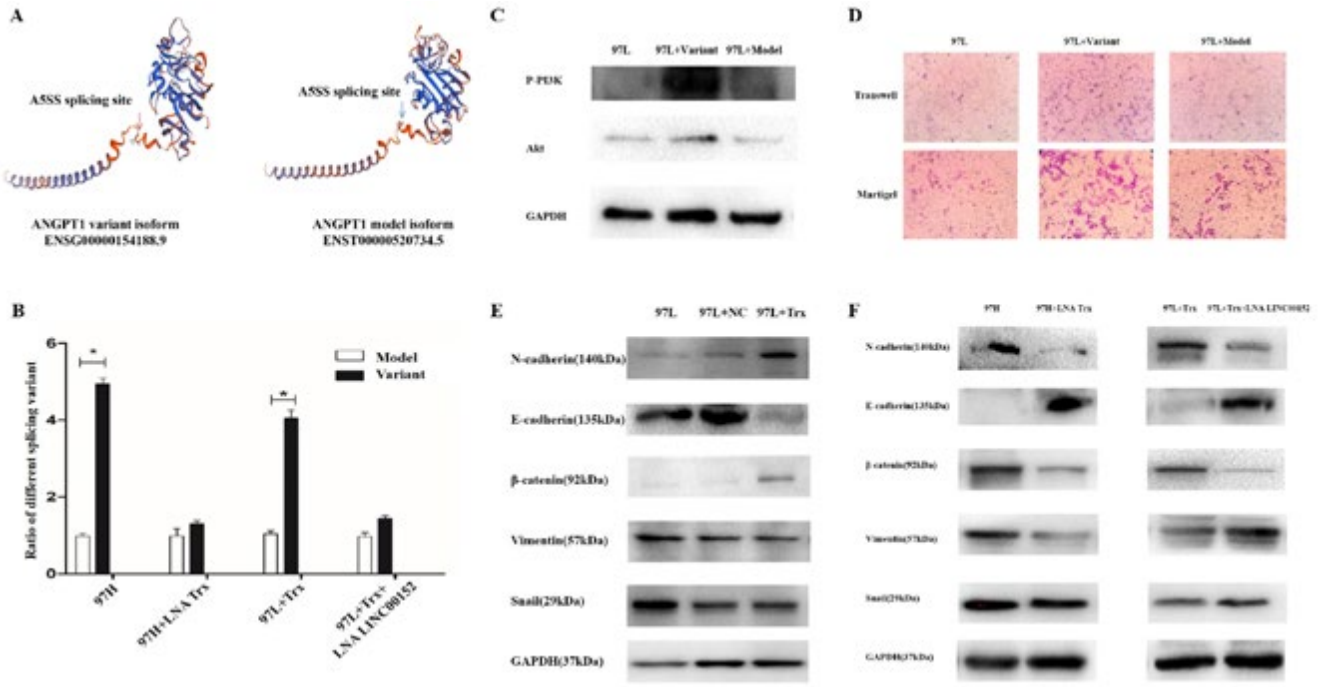
3390 | RNA-BINDING PROTEIN TRX REGULATES ALTERNATIVE SPLICING AND PROMOTES METASTASIS OF HCC VIA INTERACTING WITH LINC00152

Xiangnan Teng[1] *Jin Shang*[2] *Lingyao Du*[1] *Hong Tang*[1] *Lang Bai*[1]

[1]*West China Hospital, Sichuan University,* [2]*Sichuan Cancer Hospital & Institute*

Background: Hepatocellular carcinoma (HCC) is one of the most common malignant tumors worldwide, and metastasis being a major cause of recurrence and death. Epithelial-mesenchymal transition (EMT) is central to HCC metastasis, in which RNA-binding proteins (RBPs) play a key role. This study explores the mechanism by which RBPs promote hepatocellular carcinoma metastasis and provides theoretical support for new therapeutic targets. **Methods:** To explore the role of RBPs in metastasis of hepatocellular carcinoma (HCC), whole transcription sequencing was conducted to identify differential RBPs between HCC with metastasis or without metastasis. The influence of RBPs on metastasis of HCC was verified by in vitro and in vivo experiments. Interaction of RBPs with non-coding RNAs was evaluated by RNA immune-precipitation and pull-down assay. RNA-seq whole genome sequencing and alternative splicing analysis were further performed to clarify post-transcription regulation mechanisms. **Results:** Whole transcription sequencing results showed that expression of Thioredoxin (Trx) was significantly up-regulated in HCC patients with metastasis. Trx was also found to be associated with poor prognosis in HCC patients. Over-expression of Trx could promote migration and invasion of HCC cells in vitro and increase the rate of lung metastasis of HCC cells in vivo. Moreover, binding assays showed that Trx could bind to LINC00152. As a result, LINC00152 was verified to determine the pro-metastasis function of Trx by knockdown assay. Furthermore, we revealed that Trx could regulate metastasis-associated alternative splicing program. Specifically, ANGPT1 was the splicing target, the splicing isoform switching of ANGPT1 could activate PI3K-Akt pathway, up-regulate EMT-associated proteins and promote migration and invasion of HCC cells. **Conclusion:** Trx interacts with LINC00152 to promote HCC metastasis via alternative splicing regulation, suggesting Trx as a novel therapeutic target for HCC treatment. This study provides new insights into the molecular mechanisms of HCC metastasis and potential pathways for therapeutic intervention.



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3391 | A CLINICOPATHOLOGICAL AND ARTIFICIAL INTELLIGENCE-DERIVED SCREENING MODEL AS A TOOL FOR DISTINGUISHING PATIENTS WITH NON-HODGKIN LYMPHOMAS FROM INFLAMMATORY HEPATIC DISEASES: A MULTICENTRIC LEARNING APPROACH

Mina Farag[1] Andre Lametti[1] Ajay Rajaram[1] Nadine Demko[1] Pari Jafari[2] Ruoji Zhou[3] Alison Xiaotang Du[3] Pierre Fiset[1] Amine Benmassaoud[4] Farhad Maleki[5] Victoria Marcus[1] Rene P MICHEL[1] Amy Chadburn[6] John Hart[2] Greta Evaristo[7]

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Background: Primary hepatic non-Hodgkin lymphomas (NHL) are rare, with nonspecific and often subtle clinical presentations. Differentiating NHL from an inflammatory process represents a diagnostic challenge, requiring an extensive workup, which can delay management and lead to rapid clinical deterioration. A reliable method for triaging cases with a higher likelihood of NHL is critical for rapid evaluation. We investigated a multimodal approach using several clinicopathological parameters and artificial intelligence (AI) as an innovative avenue for expedited identification of hepatic NHL. **Methods:** Patients with NHL and other conditions inducing prominent inflammatory responses from four North American academic centers were reviewed for different clinical parameters and liver biopsy findings. For AI-based analysis, whole slide images (WSI) of H&E-stained slides were randomly assigned to training (70%) and validation (30%) sets. A weakly supervised learning paradigm derived from attention-based multiple-instance learning was applied to the training set. The performance of the trained model was tested on the validation group. **Results:** Between 2016 and 2023, 146 patients were included. The mean (SD) age was 59.9 (16.8) years, and 53% were male. NHL cases comprised 53% diffuse large B-cell, 11% T-cell, 9% marginal, 8% follicular, and 19% other lymphomas. Non-NHL controls, used as negative ground truth in the AI training, comprised of 60% inflammatory liver diseases, 15% non-NHL tumors, 15% normal biopsies, and 10% other diagnoses. In clinically unsuspected cases, NHL had significantly worse survival compared with non-NHL (mean [CI] 22 [17-28] vs. 40[29-51] months; p=0.02). ALT and ALP (xULN) were significantly lower in NHL compared with non-lymphoma (mean [SD] 1.9 [4.0] vs 6.6 [6.2]; p<0.001 and 1.5 [1.4] vs 2.2 [1.7]; p=0.03). ALT <x3 ULN showed 93% specificity and 75% NPV in NHL patients. The area under the ROC curve for discriminating NHL by ALT was 0.803 (95% CI: 0.7-0.9; p<0.001). The AI-trained model investigating liver biopsies without hyperparameter optimization was 73% accurate in classifying patients in the validation set, with the area under the ROC curve of 0.851. **Conclusion:** This multicenter study outlined clinicopathologic features of hepatic NHL that can potentially be used along with low/no-annotation AI models as an efficient and reliable triaging tool to prioritize hepatic NHL diagnosis. Further integration of biochemical parameters will allow for model optimization.

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3392 | OUTCOMES BY COMORBIDITIES WITH TREMELIMUMAB AND DURVALUMAB IN THE PHASE 3 HIMALAYA STUDY IN UNRESECTABLE HEPATOCELLULAR CARCINOMA

Lorenza Rimassa[1] Farshid Dayyani[2] Robin Kate Kelley[3] Bruno Sangro[4] Stephen L. Chan[5] Carrie L McCoy[6] Michael J. Paskow[7] Mallory Makowsky[8] Charu Gupta[9] Di Ran[10] Alejandra Negro[8] Ghassan Abou-Alfa[11]

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Background: In the 4-year analysis of HIMALAYA, STRIDE (Single Tremelimumab Regular Interval Durvalumab) sustained an overall survival (OS) benefit versus sorafenib and showed further improvement in participants (pts) who achieved disease control (Sangro et al. *Ann Oncol* 2024). Cardiovascular and metabolic comorbidities are often found in people with hepatocellular carcinoma and can impact treatment options and outcomes. This exploratory analysis assessed outcomes in pts with cardiovascular or metabolic comorbidities in HIMALAYA. **Methods:** Comorbidities were based on medical history reported at baseline and qualified using preferred terms from cardiovascular or metabolic Standardised MedDRA Queries. Pts with >1 comorbidity were counted once. OS by comorbidities was assessed in the full analysis set (FAS; pts randomized to STRIDE, durvalumab, or sorafenib), including long-term survivors (pts alive ≥36 months beyond randomization). Within-arm OS hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using the unstratified Cox models. Safety was assessed in the safety analysis set (SAS; pts who received ≥1 dose of study drug). Data cut-off was Jan 23, 2023. **Results:** Of the FAS, hypertension was the most common cardiovascular comorbidity (STRIDE, 212 [54%]; durvalumab, 163 [42%]; sorafenib, 197 [51%]), and type 2 diabetes was the most common metabolic comorbidity (STRIDE, 141 [36%]; durvalumab, 104 [27%]; sorafenib, 110 [28%]). In the STRIDE arm, OS HRs (95% CI) in pts with versus without comorbidities were 0.86 (0.68–1.08) for cardiovascular comorbidities and 1.16 (0.92–1.47) for metabolic comorbidities (Table). 36- and 48-months OS rates were higher with STRIDE versus sorafenib in pts with comorbidities (Table). Higher proportions of pts with comorbidities were long-term survivors with STRIDE versus sorafenib (Table). For STRIDE, rates of serious treatment-related adverse events were similar in pts with comorbidities (21%) and all pts in the SAS (18%; Table). **Conclusion:** Pts with comorbidities experienced similar OS benefits from STRIDE as those without comorbidities, and long-term survival was achieved in more pts with STRIDE than sorafenib, irrespective of comorbidity presence. No new safety signals were observed. Findings continue to support the unprecedented long-term benefits of STRIDE in a broad population reflective of unresectable hepatocellular carcinoma globally. Previously presented at ESMO GI Congress 2024, FPN: 169P, Lorenza Rimassa *et al.* - Reused with permission.

	STRIDE N=393		Durvalumab N=389		Sorafenib N=389	
	Cardiovascular (n=216)	Metabolic (n=159)	Cardiovascular (n=172)	Metabolic (n=130)	Cardiovascular (n=207)	Metabolic (n=135)
OS HR (95% CI) in pts with versus without comorbidities	0.86 (0.68–1.08)	1.16 (0.92–1.47)	0.98 (0.78–1.23)	1.05 (0.83–1.33)	0.93 (0.74–1.16)	0.86 (0.68–1.08)
Landmark OS, % (95% CI)						
36-months	33 (27–39)	26 (19–33)	24 (18–31)	22 (15–30)	19 (14–24)	21 (14–29)
48-months	28 (22–34)	20 (14–27)	19 (13–25)	16 (10–24)	15 (10–21)	16 (10–23)
Long-term survivors, n (%)	61 (28)	36 (23)	33 (19)	21 (16)	34 (16)	21 (16)
Hypertension,* n/N (%)	61/212 (29)	–	32/163 (20)	–	34/197 (17)	–
Type 2 diabetes mellitus,† n/N (%)	–	31/141 (22)	–	17/104 (16)	–	17/110 (15)
Serious TRAEs, n/N (%)‡	45/215 (21)	33/157 (21)	12/172 (7)	16/132 (12)	19/201 (10)	14/131 (11)

Percent calculated of pts with *hypertension, †type 2 diabetes mellitus, or the ‡SAS.
CI, confidence interval; HR, hazard ratio; OS, overall survival; pts, participants; SAS, safety analysis set; STRIDE, Single Tremelimumab Regular Interval Durvalumab; TRAE, treatment-related adverse event.

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Hengrui, Incyte, Ipsen, IQVIA: Consultant, AstraZeneca, Bayer, BMS, Guerbet: Speaking and Teaching, Incyte, Ipsen, Roche, Servier: Speaking and Teaching, Agios, AstraZeneca, BeiGene, Eisai, Exelixis, Fibrogen: Grant/Research Support, Incyte, Ipsen, Lilly, MSD, Nerviano Medical Sciences: Grant/Research Support, Roche, Servier, TransThera Sciences, Zymeworks: Grant/Research Support, Farshid Dayyani: Astellas: Speaking and Teaching, Astrazeneca: Consultant, Eisai: Consultant, Exelixis: Consultant, Ipsen: Speaking and Teaching, Jazz: Consultant, Servier: Speaking and Teaching, Sirtex: Speaking and Teaching, Takeda: Speaking and Teaching, Robin Kate Kelley: Astra Zeneca: Grant/Research Support, Bayer: Grant/Research Support, Eli Lilly: Grant/Research Support, Exelixis: Grant/Research Support, Genentech/Roche: Grant/Research Support, Kinnate: Consultant, Merck: Grant/Research Support, Partner Therapeutics: Grant/Research Support, Regeneron: Consultant, Agios: Grant/Research Support, BMS: Grant/Research Support, QED: Grant/Research Support, Tyra: Grant/Research Support, Taiho: Grant/Research Support, Surface: Grant/Research Support, Servier: Grant/Research Support, GSK: Consultant, moderna: Consultant, J Pharma Inc.: Consultant, Relay Therapeutics: Grant/Research Support, Bruno Sangro: Nothing to Disclose, Stephen L. Chan: MSD: Honoraria recipient, research grants, Ipsen: Honoraria recipient, research grants, Astra-Zeneca: Speaking and Teaching, Eisai: Speaking and Teaching, Roche: Speaking and Teaching, Carrie L McCoy: Nothing to Disclose, Michael J. Paskow: Nothing to Disclose, Mallory Makowsky: Nothing to Disclose, Charu Gupta: Astrazeneca: Employee, Di Ran: Nothing to Disclose, Alejandra Negro: Nothing to Disclose, Ghassan Abou-Alfa: Agenus, Arcus, Astra Zeneca, BioNtech, BMS, Elicio, Genentec: Grant/Research Support, Abbvie, Alligator Astra Zeneca, Autem, Berry Genomics, BioNt: Consultant

3393 | TRENDS IN HCC DEATHS AND CONTRIBUTING CHRONIC LIVER DISEASE ETIOLOGIES – A CONTEMPORARY ANALYSIS OF NATIONAL DEATH CERTIFICATE DATA ◆

Andrew Moon[1] Sasha Deutsch-Link[2] Ellen Green[1] Gabriel Lupu[1] Hanna Sanoff[1] Ted Yanagihara[1] Nima Kokabi[1] David Mauro[1] Alfred Barritt IV[1]

[1]University of North Carolina, [2]UNC Chapel Hill

Background: The availability of effective therapies for viral hepatitis and an increasing burden of metabolic dysfunction-associated steatotic liver disease (MASLD) and alcohol-associated liver disease (ALD) have led to changes in the underlying etiologies of hepatocellular carcinoma (HCC). We utilized CDC WONDER to assess trends in age-adjusted HCC mortality and etiologies contributing to HCC deaths. **Methods:** CDC WONDER is a publicly available database of death certificate data for all US residents. We determined the age-adjusted death rate from HCC (C22.0) between 2005-2022, assessing temporal changes in age-adjusted HCC death rates using the NCI's Joinpoint program. This program calculates annual percentage change (APC) and identifies significant changes in the trends of death rates. We calculated the numbers of deaths with a primary cause of death from HCC and HCC-related deaths with a contributing cause of death from ALD (K70), MASLD (K75.8, K76.0), viral hepatitis (B18) and cholestatic/autoimmune liver disease (K74.3, K75.4, K83.0). We performed a sensitivity analysis that included all alcohol-related conditions (defined by CDC NCHS) for ALD and included diabetes (E11) and obesity (E66) for MASLD. We computed the percentage of HCC deaths attributable to each liver disease for the eras identified from the Joinpoint analysis. **Results:** From 2005-2022, there were 174,391 deaths from HCC with an overall increase in age-adjusted death rate [average APC of +1.6 (95% CI +1.4, +1.9) per 100,000 population]. The Joinpoint analysis yielded three temporal changes in the age-adjusted death rate from HCC. From 2005 to 2009, the APC for age-adjusted HCC-related deaths was +3.1 (95% CI +2.0, +6.2) from 2009 to 2018, the APC was +1.7 (95% CI +0.4, +2.5) and, from 2018 to 2022, the APC was -0.2 (95% CI -2.4, +0.9). From Era 1 (2005-2009), Era 2 (2009-2017) and Era 3 (2018-2022), the percentage of HCC deaths with viral hepatitis listed as a contributing cause decreased from 82% to 77% to 65%. From Eras 1-3, HCC deaths with ALD increased from 14% to 19% to 26% and those with MASLD increased from 1% to 3% to 7% (Figure 1). In the sensitivity analysis, ALD accounted for 20%, 20% and 25% of HCC deaths and MASLD accounted for 11%, 11% and 19% HCC deaths in Eras 1, 2 and 3, respectively. The percentage of HCC deaths with a contributing cause from autoimmune/cholestatic causes remained low (1-2%) in all Eras. **Conclusion:** After a decade of increasing age-adjusted death rate from HCC, deaths from HCC have plateaued from 2018-2022. Decreased healthcare access during this era due to the COVID-19 pandemic may have affected HCC diagnosis and deaths. The proportion of HCC deaths attributable to viral hepatitis is declining while HCC deaths from ALD and MASLD are increasing. There is still a need to continue efforts to screen and treat viral hepatitis, which remains the predominant driver of HCC, while also addressing the rising burden of metabolic risk factors and alcohol use.

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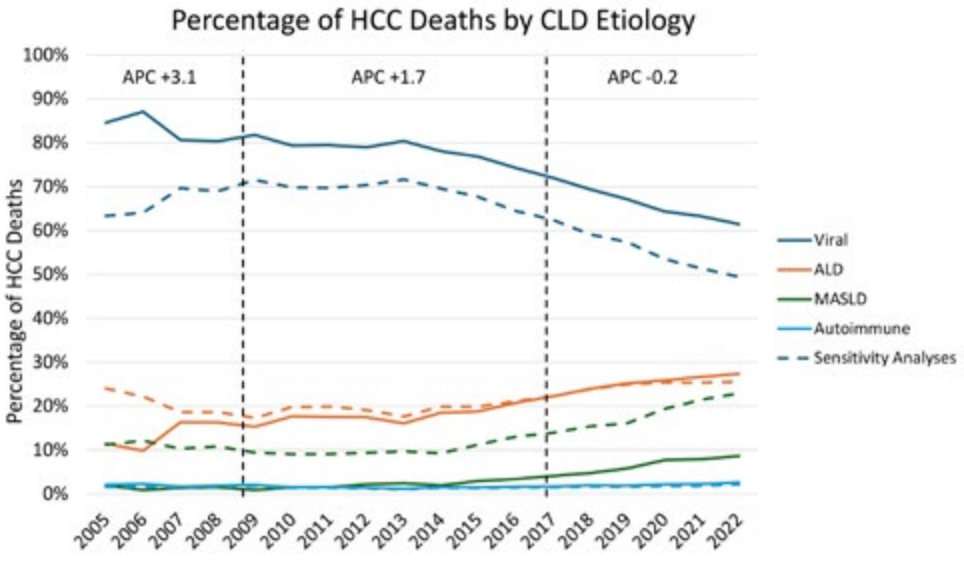

Figure 1. Deaths with an underlying cause from HCC and a contributing cause from various etiologies of liver disease in primary (solid lines) and sensitivity (dashed lines) analyses. Vertical black dotted lines denote Joinpoints with statistically significant changes in annual percentage change (APC) in age-adjusted HCC death rate.

Disclosures: Andrew Moon: TARGET RWE: Consultant, DCN Diagnostics: Grant/Research Support, Intercept Pharmaceuticals: Consultant, Intercept Pharmaceuticals: DSMB, IDEOlogy: Consultant, Sasha Deutsch-Link: Nanbar Health: Consultant, Ellen Green: Nothing to Disclose, Gabriel Lupu: Nothing to Disclose, Hanna Sanoff: Nothing to Disclose, Ted Yanagihara: Nothing to Disclose, Nima Kokabi: Nothing to Disclose, David Mauro: Nothing to Disclose, Alfred Barritt IV: Merck (Any division): Advisor, Madrigal: Consultant, Life Edit: Consultant, Boehringer Ingelheim: Consultant, Target-RWE: Consultant

3394 | VALIDATION OF A RISK-STRATIFIED APPROACH TO SCREENING FOR HEPATOCELLULAR CARCINOMA FOLLOWING LIVER TRANSPLANTATION

Wesley Dixon[1] Shaun Chandna[2] Stephen Zucker[1] Jordan Sack[1]

[1]Brigham and Women's Hospital, [2]Olive View-UCLA Medical Center

Background: Hepatocellular carcinoma (HCC) recurs in 8-20% of patients following liver transplantation (LT) and it is common practice to screen all recipients for HCC recurrence after LT. We previously developed simple criteria that identify recipients at very low-risk of HCC recurrence in whom post-LT screening provides marginal benefit. We apply these criteria to a validation cohort from an alternate transplant center. **Methods:** We retrospectively analyzed adults with HCC who underwent LT at Mass General Brigham between 2015-2022 (validation cohort). Patients at high-risk for HCC recurrence satisfied any of the following criteria originally developed at the University of Cincinnati Medical Center: 1) outside Milan criteria by imaging at LT, 2) alpha fetoprotein (AFP) >200 ng/mL at LT (after downstaging following locoregional therapy), 3) prior hepatectomy for HCC with vascular invasion or unknown histology, 4) extrahepatic involvement at LT, or 5) explant histology with vascular invasion or >3 lesions. Criteria performance was compared with the RETREAT score. **Results:** Among 188 adult LT recipients, 82% were male, median age at LT was 62 (interquartile range 57-66) years, and AFP at LT was 5.2 (3.1-11) ng/mL. HCC recurred in 15 (8%) over 4.3 (2.0-6.2) years of follow-up. Recurrence occurred at 1.6 (0.6-2.6) years, most commonly in the lung or bone (44% each). Diagnosis was driven by symptoms (50%), routine screening imaging (38%), or rising AFP (12%). A total of 74 (39%) patients met ≥1 high-risk criterion, 15 (20%) of whom developed recurrent HCC. Of those classified as low-risk, 1 (0.9%) experienced HCC recurrence. These results validate the findings of the original development cohort (N=132, Figure 1). By comparison, 141 (75%) were high-risk by RETREAT score >0 and 39 (21%) by RETREAT >2. Our risk stratification criteria had favorable sensitivity and specificity (94%, 68%) for 5-year recurrence compared to RETREAT >0 (94%, 27%) and >2 (44%, 81%). By our criteria, the number of high-risk patients needed to screen to detect an HCC recurrence was 5, compared to 12 for RETREAT >0 and 8 for RETREAT >2. **Conclusion:** The present study validates previously developed criteria

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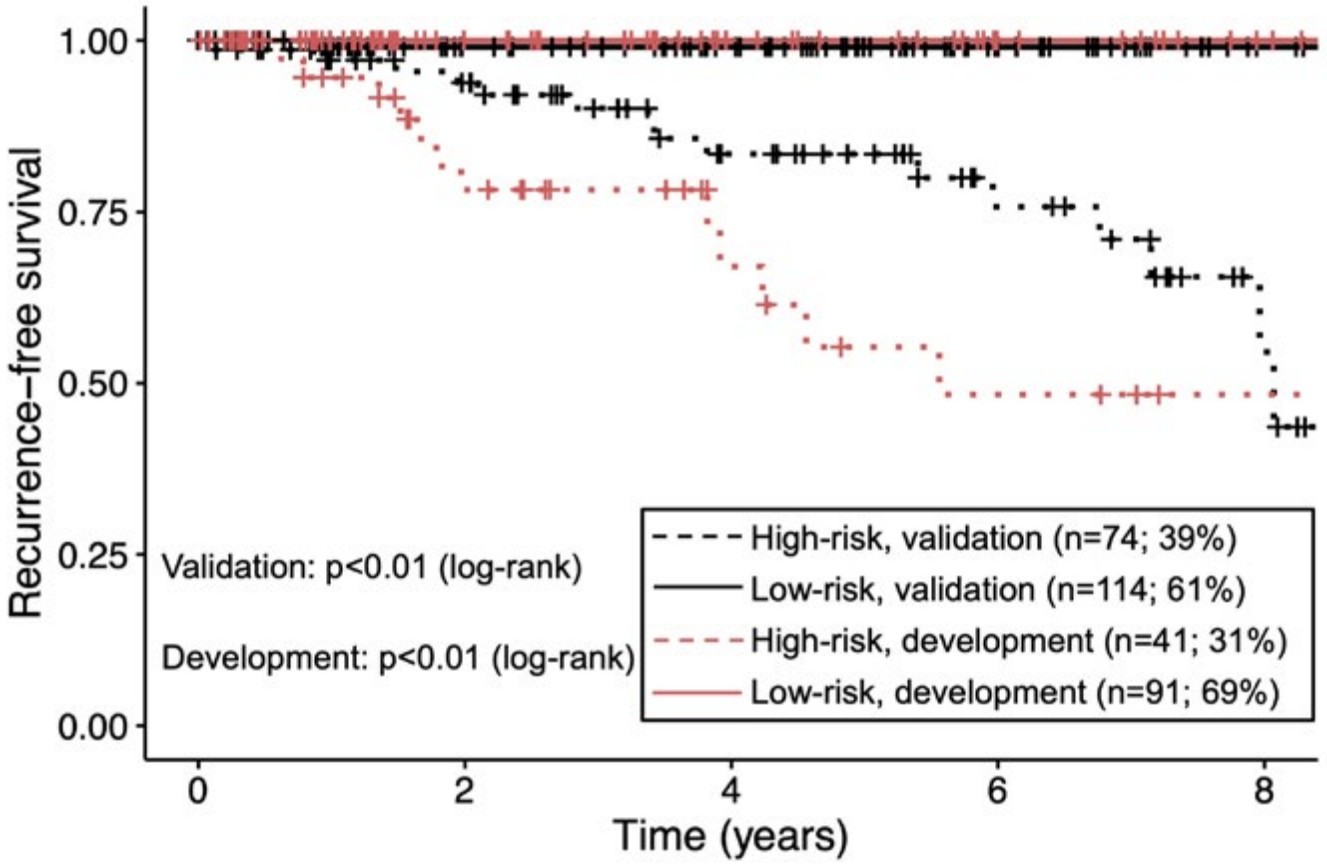
that effectively stratify LT recipients with HCC into low- and high-risk for recurrence. Using these simple criteria, surveillance targeting only high-risk patients could reduce the cost and potential harm of excess screening.

Figure 1: Recurrence-free survival by risk criteria in development and validation cohorts.



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3395 | LOSS OF BAP1 CONFERS RESISTANCE TO FERROPTOSIS AND PROMOTES CHOLANGIOCARCINOMA DEVELOPMENT

Peyton Classon[1] Sophia Jaramillo[1] Danielle Carlson[1] Irene Yan[2] Sumera Ilyas[1] Rory Smoot[1] Gregory Gores[1] Tushar Patel[2] Davide Povero[1]

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Background: Cholangiocarcinoma (CCA) is a lethal epithelial cell malignancy of the biliary tract. Tumor suppressor BRCA1-Associated Protein 1 (BAP1) is mutated in up to 25% of human CCAs and has been found to promote ferroptosis, an iron-dependent form of cell death driven by phospholipid peroxidation. Our project aims to uncover the mechanisms by which loss of BAP1 function confers resistance to ferroptosis, thereby promoting CCA development. **Methods:** CCA cell lines and normal cholangiocytes were treated with ferroptosis inducers (RSL3, erastin) followed by assessment of cell viability, cellular and mitochondrial iron levels, and phospholipid peroxidation. Mitochondrial structure and function were assessed by fluorescent microscopy and Seahorse. Gain- and loss-of-function strategies were employed for functional studies and malignant transformation. Subcutaneous xenograft and orthotopic, syngeneic murine models of CCA were treated with RSL3 or vehicle followed by assessment of tumor burden and ferroptosis markers. EpCAM-aptamer coated nanoparticles (MNPs)

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packaged with siRNA were employed to induce tumor-specific ferroptosis. **Results:** BAP1 mutational inactivation or downregulation protects CCA cells from RSL3-induced mitochondrial iron overload, phospholipid peroxidation, and ferroptosis, as compared to BAP1 wild-type (WT). Following exposure to ferroptosis inducers, BAP1-mutant CCA cells exhibited normal mitochondrial respiration, membrane potential and ultrastructure, as compared to marked functional and structural damage observed in WT CCA cells. Lipid peroxidation inhibitor ferrostatin-1 failed to rescue mitochondrial respiration in RSL3-treated BAP1 WT CCA cells, suggesting mitochondrial iron overload is an upstream event in the ferroptosis pathway. BAP1 knockdown via siRNA rendered CCA cells resistant to ferroptosis, while re-expressing BAP1 in mutant CCA cells re-sensitized them ferroptosis. Stable BAP1 KO in cholangiocytes promoted anchorage-independent growth and colony formation, as compared to BAP1 WT. *In vivo,* RSL3-induced ferroptosis inhibited tumor growth in CCA-bearing mice and increased lipid peroxidation markers (oxPAPC, 4HNE). Lastly, MNPs containing siRNA against ferroptosis suppressor glutathione peroxidase 4 (GPX4) induced marked cell viability loss *in vitro*, and *in vivo* showed tumor enrichment, target engagement and reduced tumor burden. **Conclusion:** Our findings suggest that BAP1 mutational inactivation confers cholangiocyte resistance to ferroptosis thus promoting malignant transformation, and that ferroptosis exerts therapeutic benefits *in vivo* in CCA.

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3396 | T CELL RECEPTOR AND IMMUNE GENE EXPRESSION PHARMACODYNAMICS FOR DURVALUMAB MONOTHERAPY AND IN COMBINATION WITH TREMELIMUMAB OR BEVACIZUMAB IN UNRESECTABLE HEPATOCELLULAR CARCINOMA (UHCC)

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Background: Study 22 (NCT02519348), a Phase 2 trial of immune checkpoint inhibitor (ICI) monotherapy and combination regimens in uHCC, showed higher rates of objective response (ORR) with STRIDE (Single Tremelimumab [T] Regular Interval Durvalumab [D]) or D+bevacizumab (B) than with D. Pharmacodynamic analyses showed that improved efficacy with STRIDE versus (vs) D was associated with increased expansion of T cell clones at the end of cycle 1 (C1) vs D. We performed further T cell clone analyses to include D+B and compared gene expression signatures (GES) associated with each treatment arm to explore commonalities and differences in mechanistic biomarkers underpinning the efficacies associated with STRIDE and D+B. **Methods:** Participants (pts) with uHCC and no prior ICI therapy received STRIDE (T 300 mg + D 1500 mg [1 dose during C1] then D 1500 mg once every 4 weeks [Q4W]), T75+D (T 75 mg + D 1500 mg Q4W [4 doses] then D 1500 mg Q4W), D (1500 mg Q4W), T (750 mg Q4W [7 doses] then Q12W), or D+B (D 1120 mg + B 15 mg/kg Q3W). DNA and RNA were isolated from PAXgene®-preserved whole blood collected at baseline and at the end of C1. CDR3 sequencing of T cell receptor β using the immunoSEQ® Assay (Adaptive Biotechnologies, Seattle, WA) and RNA sequencing (Q Squared Solutions, Morrisville, NC) were performed. ImmunoSeq results and immunologic gene expression changes were reported with ORR across treatment arms. **Results:** ImmunoSeq did not show significant differences in baseline T cell clonality across treatment arms. In contrast to STRIDE vs D, the number of expanded T cell clones at the end of C1 for D+B vs D was unchanged, and no association between expanded T cell clones and ORR was observed (Table). While increases in Type I and II interferon and mitotic GES were seen for both STRIDE and D+B, more changes in immune-related peripheral GES, with greater magnitude of change, were associated with STRIDE. Significant changes in CD8 T cell, M1 macrophage, and Treg GES were only observed for STRIDE. **Conclusion:** While STRIDE and D+B both had higher ORRs than D monotherapy in uHCC, only STRIDE was associated with an increased expansion of T cell clones vs D. This, in addition to the differences in magnitude and type of GES changes, suggest that STRIDE and D+B have distinct and potentially complementary mechanisms of action. © 2024 American Society of Clinical Oncology, Inc. Reused with permission. This abstract was accepted and previously presented at the 2024 ASCO Annual Meeting. All rights reserved.

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3397 | EMERALD-Y90: A PHASE 2 STUDY TO EVALUATE TRANSARTERIAL RADIOEMBOLIZATION (TARE) FOLLOWED BY DURVALUMAB (D) AND BEVACIZUMAB (B) FOR THE TREATMENT OF PARTICIPANTS (PTS) WITH UNRESECTABLE HEPATOCELLULAR CARCINOMA (UHCC) ELIGIBLE FOR EMBOLIZATION

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Background: Intermediate HCC is often treated with locoregional therapy (LRT), such as transarterial chemoembolization (TACE) or TARE. Despite advances in TACE and TARE delivery, median progression-free survival (PFS) following treatment is <1 year, highlighting a need for new treatment options. **Methods:** Immune checkpoint inhibitor combinations (tremelimumab+D and atezolizumab+B) have shown promise as first-line treatments for uHCC not eligible for LRT. The Phase 3 EMERALD-1 study is evaluating the efficacy and safety of TACE+D±B vs TACE alone in pts with uHCC eligible for embolization. TARE and TACE are recommended in pts with uHCC in the US; a need exists for evidence to support additional treatment options in settings where TARE is the preferred treatment. The EMERALD Y-90 study will evaluate the efficacy and safety of TARE with D monotherapy, followed by D+B in pts with uHCC eligible for embolization. **Results:** EMERALD-Y90 (NCT06040099) is a Phase 2, single-arm study that will enroll ~100 pts aged ≥18 years with uHCC (Child-Pugh class A, ECOG 0–1) amenable to embolization who are ineligible for or have declined treatment with resection and/or ablation or liver transplant. Exclusion criteria include prior LRT (TACE, TARE, or SBRT associated with curative setting ≥6 months prior to study, and radiofrequency ablation if target lesion not treated or subsequently progressed, are permitted), prior systemic therapy, evidence of extrahepatic spread, or major portal vein invasion. Pts will receive partition-based dosing of TARE using Y-90 glass microspheres. Following TARE, pts will receive D 1500 mg (one dose) followed by D 1120 mg + B 15 mg/kg every 3 weeks until study completion or discontinuation criteria are met. **Conclusion:** The primary endpoint is PFS (time from start of TARE until date of disease progression [investigator (INV)-assessed per modified Response Evaluation Criteria in Solid Tumors (mRECIST)] or death due to any cause [DAC]). Secondary endpoints include safety and tolerability, and 6-, 12-, and 24-month PFS, objective response rate (% of pts with confirmed complete or partial response [INV-assessed per mRECIST]), OS (time from start of TARE until DAC), and duration of response (time from date of first documented response until date of progression or DAC). An early safety review is planned when ≥30 pts complete ≥2 cycles of D+B. Study enrollment will occur at ~20 US sites. This abstract was originally presented at the 2024 Society of Interventional Oncology Annual Scientific Meeting.

Disclosures: Riad Salem: Nothing to Disclose, Anne Noonan: Nothing to Disclose, Ben Spieler: Nothing to Disclose, Sarah White: Cook: Consultant, Medtronic: Consultant, Merck: Advisor, Penumbra: Speaking and Teaching, Trisalus: Advisor, Laura Kulik: Nothing to Disclose, Dex Underwood: Nothing to Disclose, Eric Heilbron: AstraZeneca: Employee, Binh Nguyen: AstraZeneca: Employee, Graham Wetherill: AstraZeneca: Consultant, Renuka Iyer: Nothing to Disclose

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3398 | NON-VIRAL ETIOLOGY SUBGROUP OF THE PHASE 3 HIMALAYA STUDY OF TREMELIMUMAB PLUS DURVALUMAB IN UNRESECTABLE HEPATOCELLULAR CARCINOMA

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Background: STRIDE (Single Tremelimumab Regular Interval Durvalumab) improved overall survival (OS) versus sorafenib in unresectable hepatocellular carcinoma (uHCC) overall and across hepatitis B virus (HBV), hepatitis C virus, and other (no active viral hepatitis) etiologies in the Phase 3 HIMALAYA study (Sangro et al. *Ann Oncol* 2024). Non-viral uHCC etiology prevalence is increasing worldwide. Thus, we aimed to further characterize the non-viral uHCC etiology subgroup in HIMALAYA. **Methods:** This exploratory analysis assessed STRIDE, durvalumab, or sorafenib in participants with non-viral etiology, here, more specifically defined as no active viral hepatitis or prior HBV infection. Self-reported alcohol use (yes [former/current] vs no [never]), history of metabolic/diabetes comorbidities, OS, and safety were assessed. OS hazard ratios and 95% confidence intervals were calculated using a Cox proportional hazards model. Data cut-off was Jan 23, 2023. **Results:** The non-viral subgroup included 388 participants randomized to STRIDE, durvalumab, or sorafenib; 245 (63%) participants reported alcohol use (Table). Baseline characteristics were generally balanced across treatment arms. Non-viral etiology and alcohol use were more common in Western countries than in Asia, per known trends. History of metabolic/diabetes comorbidities were observed in 147/245 (60%) participants with and 64/142 (45%) participants without alcohol use. OS was improved, and 36- and 48-months OS rates were higher for STRIDE and durvalumab versus sorafenib in the non-viral subgroup. Grade 3/4 treatment-related adverse events were lower for STRIDE and durvalumab versus sorafenib in the non-viral subgroup (Table) and were consistent with previously reported rates. **Conclusion:** STRIDE continued to demonstrate an OS benefit in a more strictly defined non-viral etiology subgroup of participants. 36- and 48-months OS rates remained higher in participants treated with STRIDE versus sorafenib, with no new safety signals observed. As rates of non-viral etiology for HCC rise, these data further support the benefits of STRIDE in a diverse population consistent with uHCC globally. Previously presented at ESMO GI Congress 2024, FPN: 167P, Maria Reig *et al.* - Reused with permission.

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	Non-viral etiology N=388		
	STRIDE N=132	Durvalumab N=122*	Sorafenib N=134
Alcohol use, n (%)			
Yes	88 (67)	74 (61)	83 (62)
No	44 (33)	47 (39)	51 (38)
Geographic region, n (%)			
Asia (excluding Japan)	15 (11)	19 (16)	17 (13)
Alcohol use – Yes	8 (6)	7 (6)	10 (7)
Rest of World (including Japan)	117 (89)	102 (84)	117 (87)
Alcohol use – Yes	80 (61)	67 (55)	73 (54)
OS HR (95% CI) versus sorafenib	0.62 (0.47–0.81)	0.69 (0.53–0.91)	
OS rates, % (95% CI)			
36 months	32 (24–40)	26 (19–35)	12 (7–18)
48 months	26 (18–34)	20 (13–29)	8 (4–14)
Grade 3/4 TRAEs, n/N (%)†	42/129 (33)	12/121 (10)	54/131 (41)

*One participant with missing alcohol status was excluded from the yes/no alcohol use subsets. †Percentages were calculated from the safety analysis set.
CI, confidence interval; HR, hazard ratio; OS, overall survival; STRIDE, Single Tremelimumab Regular Interval Durvalumab; TRAE, treatment-related adverse event.

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3399 | STATIN USE REDUCES TUMOR RECURRENCE IN HEPATOCELLULAR CARCINOMA AFTER CURATIVE RADIOFREQUENCY ABLATION: A PROPENSITY-MATCHED ANALYSIS

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Background: Radiofrequency ablation (RFA) is a minimally invasive procedure that is commonly employed in the treatment of small hepatocellular carcinomas (HCC). The use of statins as adjuvant therapy has been associated with a lower risk of HCC recurrence after curative resection. Yet, the effect of statin use on HCC recurrence after RFA remains unknown. Our study aim was to evaluate the impact of statin use on recurrence after curative

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RFA among patients with HCC. **Methods:** We retrospectively identified 301 patients with HCC who underwent RFA between January 2011 and July 2022 at the University Hospital. We excluded subjects who had any of the following within three months of RFA: HCC recurrence, liver transplantation, or death. Patients were stratified according to the cumulative defined daily dose (cDDD) for statin. Patients taking a statin cDDD of more than 28 were assigned to the statin group. The primary outcome was to evaluate the effect of statin exposure on HCC recurrence after RFA. Propensity score matching (PSM) was applied to reduce selection bias between the study groups. The Kaplan-Meier method was used to plot the recurrence-free survival (RFS) and the overall survival (OS) curves stratified by statin use and the curves were compared using the log-rank test. **Results:** Among the 301 patients, 113 (37.5%) were assigned to the statin group. After 1:1 case propensity score matching, 77 patients in the statin group and 77 in the non-statin group were analyzed. The baseline characteristics were balanced between the matched groups (SMD < 0.2 and p > 0.05 for all variables). Statin use was significantly associated with a reduced risk of HCC recurrence after PSM (p=0.01; Figure 1). The OS rate was not significantly different between the groups after PSM (P=0.42; Figure 1). **Conclusion:** Patients with significant statin exposure were associated with a reduced risk of HCC recurrence after RFA. Therefore, statin may exert a chemo-preventive effect on HCC recurrence post-RFA. Further prospective randomized trials are needed to confirm the ideal dose, efficacy, and long-term safety of statin as a chemo-preventive agent for HCC after RFA.

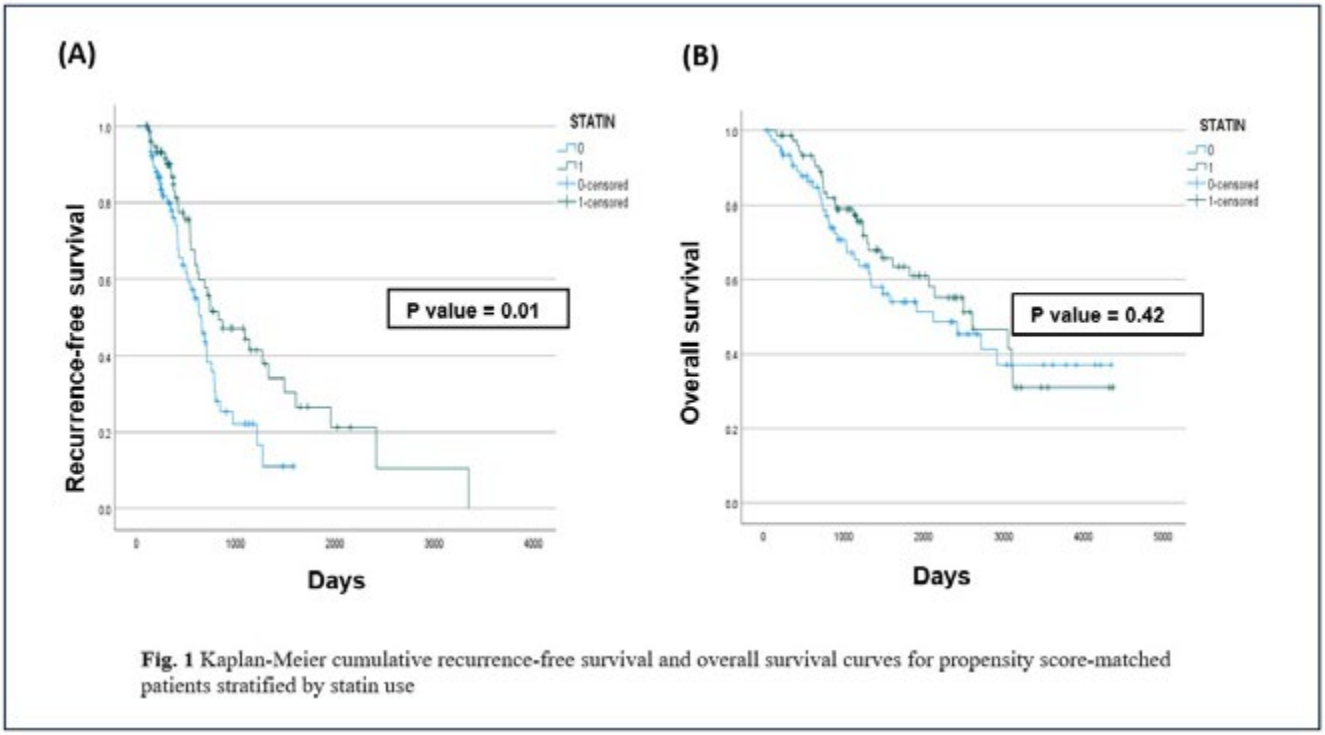

Fig. 1 Kaplan-Meier cumulative recurrence-free survival and overall survival curves for propensity score-matched patients stratified by statin use

Disclosures: Mazen Almasry: Nothing to Disclose, Elizabeth Townsend: Nothing to Disclose, Hiep Phan: Nothing to Disclose, Adnan Said: Mallinckrodt: Speaking and Teaching

3400 | DEVELOPMENT OF AN ULTRA-SENSITIVE TERT PROMOTER MUTANT DNA DETECTION METHOD AND ITS APPLICATION IN LIQUID BIOPSY

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Background: TERT promoter mutation is highly prevalent in HCC, and cell free DNA (cfDNA) with this mutation is a potential target for liquid biopsy. Mutant DNA is difficult to detect because TERT promoter mutation exists in a GC-rich region and most of cfDNAs are derived from white blood cells. **Methods:** We developed a new digital PCR (dPCR) method using an MGB-probe to specifically detect the TERT promoter C228T mutation and

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a peptide nucleic acid probe (PNA-probe) to prevent PCR of the wild allele (PNA-MGB clamp method). The accuracy was compared with the conventional TaqMan method.
Serial dilutions of 2921 bp plasmid DNA containing the TERT promoter C228T mutated region were made to 10, 100 and 1000 copies/µl of Mutant DNA and 10,000 and 50,000 copies/µl of Wild DNA. Using plasmid DNAs of each copy number as template, TERT promoter mutant DNAs were absolutely quantified using a plate-based dPCR and chip-based dPCR (ThermoFisher Scientific). Each diluted plasmid DNAs were assayed 10 times; cfDNAs derived from five tyrosine kinase inhibitor cases and four radiofrequency ablation cases were analyzed to validate the accuracy of the PNA-MGB method. **Results:** Quantitative analysis of wild-type plasmid DNA showed no suspect positives for the PNA-MGB and TaqMan methods; median Mutant DNA copies quantified for 10, 100 1000 copies of mutant plasmid DNA were 9.7, 71.9 and 836.4 copies for the PNA-MGB method and 5.1, 66.9, 892.0 copies for the TaqMan method, with a significant difference in the quantification of 10 copies (P=0.0049). Analyzed mixed 10 copies of Mutant DNA and 50,000 copies of Wild DNA by the PNA-MGB and TaqMan method, the median quantified mutant DNA copies were 5.7 copies and 0 copy respectively (P<0.001). The median quantified mutant DNA copies of clinical cases were 33.9 and 10.8 copies, respectively, with significantly better sensitivity of the new detection method (P = 0.0077). **Conclusion:** The PNA-MGB clamp method is particularly useful in detecting small amounts of TERT promoter Mutant DNA in large amounts of Wild DNA and has potential application in liquid biopsy.

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3401 | THE OPTIMAL AFP THRESHOLD FOR HCC SCREENING SHOULD BE LOWER THAN 20 NG/ML IN CURED HEPATITIS C, ALD, AND MASLD

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Background: Alpha-fetoprotein (AFP) testing is a key component of hepatocellular carcinoma (HCC) screening in patients with cirrhosis. AFP≥20 ng/mL is considered a positive screening test, but AFP levels vary by liver disease etiology. We investigated the performance of AFP as an HCC screening test in patients with cirrhosis. **Methods:** Using national Veterans Affairs electronic health records, we identified all patients diagnosed with cirrhosis who were alive and without HCC as of 1/1/2019. Patients were categorized as “cases” if they developed HCC during calendar year 2019 and had an AFP test within 6 months of diagnosis. Patients were categorized as “controls” if they had an AFP test in 2019 but no HCC diagnosis in 2019 or within 1 year following the AFP test. We used the cases and controls to determine the sensitivity and specificity of AFP at different thresholds (e.g. >5, >10, >15, >20 ng/mL) by liver disease etiology (active hepatitis C [HCV], cured HCV, alcohol-associated liver disease [ALD], and metabolic-dysfunction-associated steatotic liver disease [MASLD]). **Results:** Of 28,170 patients, 1,029 had incident HCC (cases) and 27,141 did not (controls). Mean age was 60.9 years (SD 8.4), 96.4% were male, 69.1% were White, 21.9% were Black, and 8.9% were Hispanic. HCV was the most common etiology (52.4%; 42.8% cured, 9.6% active), followed by ALD (24.3%) and MASLD (13.7%). At an AFP threshold >20 ng/mL, sensitivity was highest in active HCV (42.3%), followed by cured HCV (33.7%), ALD (23.8%), and MASLD (21.7%) (Table 1). At an AFP >10 ng/mL, sensitivity improved and was highest in active HCV (60.7%), followed by cured HCV (42.5%), ALD (33.3%), and MASLD (29.9%). When lowering the AFP threshold from >20 to >10 ng/mL, the false positive rate increased from 8.5% to 17.8% in active HCV and 1.5-2.0% to 4.1-6.0% in all other etiologies. At 90% specificity, AFP had the highest accuracy in active HCV (50.8%), followed by cured HCV (48.4%), ALD (41.3%), and MASLD (41.2%). The AFP threshold was also highest in active HCV (>16.99 ng/mL), followed by cured HCV, ALD, and MASLD (>7.80, >7.38, >6.20 ng/mL). The AUROC was highest in active and cured HCV (0.76), followed by ALD (0.72), and MASLD (0.70). **Conclusion:** AFP performs better as an HCC screening test in active HCV than in other etiologies of cirrhosis. In patients with cured HCV, ALD, and MASLD, lowering the AFP threshold from >20 to >10 ng/mL would provide greater sensitivity with minimal reduction in specificity to detect HCC.

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Table 1. Performance characteristics of AFP for HCC screening at AFP>20 ng/mL, AFP>10 ng/mL, 80% specificity, and 90% specificity by liver disease etiology

	AFP>20 ng/mL		AFP>10 ng/mL		80% Specificity		90% Specificity		
	Sensitivity	Specificity	Sensitivity	Specificity	AFP value	Sensitivity	AFP value	Sensitivity	AUROC (95% CI)
HCV (active)	42.3%	91.5%	60.7%	82.2%	8.99	61.7%	16.99	50.8%	0.76 (0.72, 0.80)
HCV (cured)	33.7%	98.5%	42.5%	94.2%	5.72	58.5%	7.80	48.4%	0.76 (0.73, 0.78)
ALD	23.8%	98.0%	33.3%	94.0%	5.31	53.4%	7.38	41.3%	0.72 (0.67, 0.76)
MASLD	21.7%	98.5%	29.9%	95.9%	4.70	52.6%	6.20	41.2%	0.70 (0.64, 0.70)

AFP: alpha-fetoprotein. ALD: alcohol-associated liver disease. AUROC: area under the receiver operating characteristic curve. HCV: hepatitis C infection. MASLD: metabolic dysfunction-associated steotic liver disease.

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3402 | THE CHEMOPROTECTIVE EFFECTS OF GENISTEIN IN A RAT MODEL OF CIRRHOSIS AND HEPATOCELLULAR CARCINOMA

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Background: Liver cancer is the sixth most common cancer and the third most common cause of cancer-related mortality worldwide. Despite its prevalence, chemoprotective agents for hepatocellular carcinoma (HCC) are still lacking. Genistein, a phytoestrogen, has previously been shown in *in vitro* studies to suppress the growth of liver cancer cells. Due to the scarcity of data regarding the chemoprotective effects of genistein in *in vivo* studies, the aim of the study was to determine whether genistein could reduce the incidence and tumor burden of HCC in a rat model. **Methods:** Thirty-three male Sprague Dawley rats were divided into 3 groups (n=11 per group). In the control group, rats did not receive any interventions. In the HCC group, rats received weekly intraperitoneal (i.p.) injection of 70 mg/kg diethylnitrosamine (DEN) for 16 weeks, and between week 8 and 16, rats received once-daily oral gavage of dimethyl sulfoxide (DMSO) 1 mL for 8 weeks. In the genistein (GEN) group, rats received weekly i.p. injection of 70 mg/kg DEN for 16 weeks, and between week 8 and 16, rats received once-daily oral gavage of genistein 50 mg/kg for 8 weeks. At 16 weeks, liver was harvested to determine the incidence of HCC, the size, and the number of tumors in each group. Liver tissue was used for histopathological diagnosis of HCC. Serum was obtained to measure the levels of total bilirubin, alanine aminotransferase (ALT), alpha-fetoprotein (AFP), and p53. Continuous variables were compared using one-way ANOVA, while categorical variables were compared using Chi-square test. **Results:** The incidence of HCC was 0%, 100%, and 77.8% in control, HCC, and GEN groups, respectively. The mortality rate was 18.2% in both HCC and GEN groups and 0% in the control group. The mean number of tumors was 0, 3.56±0.41, and 2.11±0.54 in control, HCC, and GEN groups, respectively (p<0.001). The tumor burden score was 0, 4.16±0.53, and 2.28±0.54 in control, HCC, and GEN groups, respectively (p<0.001). Serum AFP levels were 0.88±0.72, 382.78±6.58, 138.56±1.68 ng/mL in control, HCC, and GEN groups, respectively (p<0.001). Serum p53 levels were 84.62±0.47, 380.88±6.76, 151.33±1.05 pg/mL in control, HCC, and GEN groups, respectively (p<0.001). Serum total bilirubin levels were 6.76±0.40, 27.07±0.72, 12.46±0.48 mg/dL in control, HCC, and GEN groups, respectively (p<0.001). Serum ALT levels were 27.18±0.72, 382.78±6.58, 138.56±1.68 U/L in control, HCC, and GEN groups, respectively (p<0.001).

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Conclusion: In conclusion, genistein significantly reduced HCC tumor burden and improved serum markers of HCC and liver injury in rats with DEN induced cirrhosis.

Variables	Control	HCC	Genistein	p-value
Tumor burden scores	0	4.16±0.53	2.28±0.54	0.002*, 0.018**
Serum AFP (ng/mL)	0.88±0.72	382.78±6.58	138.56±1.68	*<0.001, **<0.001
Serum p53 (pg/mL)	84.62±0.47	380.88±6.76	151.33±1.05	*<0.001, **<0.001
Total bilirubin (mg/dL)	6.76±0.40	27.07±0.72	12.46±0.48	*<0.001, **<0.001
ALT (U/L)	27.18±0.72	382.78±6.58	138.56±1.68	*<0.001, **<0.001

*Comparison between HCC and Control groups; ** Comparison between HCC and Genistein groups

Disclosures: Maneerat Chayanupatkul: Nothing to Disclose, Duangporn Werawatganon: Nothing to Disclose, Natcha Wanpiyarat: Nothing to Disclose

3403 | NUCLEOS(T)IDE ANALOGUES IN THE TREATMENT OF LONG-TERM PROGNOSIS IN PATIENTS WITH HEPATITIS B VIRUS-RELATED HEPATOCELLULAR CARCINOMA AFTER RADICAL SURGERY: INTERIM ANALYSIS OF THE PHASE 3 MULTI-CENTER PROSPECTIVE TRIAL

Zhongguo Zhou[1] Tianqing Wu[1] Li Huang[2] Chunhui Qiu[3] Guolin Li[4] Dandan Hu[1] Yaojun Zhang[1] Li Xu[1] Minshan Chen[1]

[1]Sun Yat-sen University Cancer Center, [2]The First Affiliated Hospital of SYSU, [3]The Third Affiliated Hospital of SYSU, [4]The Sixth Affiliated Hospital of SYSU

Background: Hepatitis B virus (HBV) infection is the main cause of hepatocellular carcinoma (HCC) in China. Studies have suggested that nucleos(t)ide analogues (NUCs) are associated with lower risk of tumor recurrence in HBV-related HCC patients after radical surgery, while the superiority of entecavir (ETV), tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide fumarate (TAF) remains uncertain. Therefore, we conducted a prospective trial evaluating different kinds of NUCs after curative resection in HBV-related HCC patients.
Methods: In this prospective, multi-center, phase III study, 329 eligible HCC patients (BCLC 0 or A) were divided into three groups, receiving the following treatments: the ETV group (0.5 mg ETV once a day), the TDF group (300 mg TDF once a day), and the TAF group (25 mg TAF once a day). The primary endpoint is recurrence-free survival (RFS) in the intention-to-treat population. The Secondary endpoint include overall survival, virological response and biochemical response. This study is registered on Clinical Trials.gov, identifier: NCT04392700.
Results: As of November 27, 2023, 163 patients were randomized to ETV group, 165 to TDF/TAF group. Baseline characteristics were balanced between groups. The median RFS was 41.7 months in the ETV group, 37.3 months in the TDF group, and not yet available in the TAF group (ETV vs TDF: HR 1.13 [95% CI 0.73-1.76]; ETV vs TAF: 0.93 [0.69-1.24]; TDF vs TAF: 0.75 [0.41-1.37]; p=0.65). The 1-year and 2-year RFS rate for ETV, TDF and TAF groups were 82.2%, 78.1% and 82.0% (p=0.68) and 74.8%, 72.4% and 77.0% (p=0.79), respectively. The median OS was not yet available in each group (ETV vs TDF: HR 0.96 [95% CI 0.37-2.47]; ETV vs TAF: NA; TDF vs TAF: NA; p=0.17). After 1 month, 3 months, 6 months, 12 months of surgery, the HBV DNA level of each group was similar. Additionally, there was no significant difference in changes of serum alanine aminotransferase (ALT), serum aspartate transaminase (AST) and serum creatinine between groups.
Conclusion: This interim analysis demonstrated ETV, TDF and TAF showed similar efficacy in preventing tumor recurrence after radical surgery, reducing HBV DNA level and maintaining liver and renal function in HBV-related HCC.

Disclosures: Zhongguo Zhou: Nothing to Disclose, Tianqing Wu: Nothing to Disclose, Li Huang: Nothing to Disclose, Chunhui Qiu: Nothing to Disclose, Guolin Li: Nothing to Disclose, Dandan Hu: Nothing to Disclose, Yaojun Zhang: Nothing to Disclose, Li Xu: Nothing to Disclose, Minshan Chen: Nothing to Disclose

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3404 | THE ROLE OF HBV PREGENOMIC RNA IN INFLUENCING THE DEVELOPMENT OF HEPATOCELLULAR CARCINOMA

Yifan Han[1] *Zhan Zeng*[1] *Ning Lin*[1] *Xiaoyuan Xu**[1]

[1]*Peking University First Hospital*

Background: Our previous research indicated that pregenomic RNA (pgRNA) of the hepatitis B virus (HBV) could serve as a potential biomarker for the prediction of the recurrence of HBV-related advanced hepatocellular carcinoma (HCC) in patients. However, the specific mechanism in which pgRNA affects the development of HCC remains unclear. **Methods:** Huh7 and HepG2 cell lines with overexpressed pgRNA were constructed through lentivirus infection, along with their negative controls. A series of in vitro and in vivo functional experiments were performed, including CCK-8, EdU, transwell, scratch test, invasion test, subcutaneous tumour formation and others, in order to explore the effects of pgRNA on the biological behavior of HCC cells. A transcriptome sequencing analysis was conducted with the objective of exploring the potential mechanisms by which pgRNA affects HCC development. **Results:** The CCK8 and EdU assays revealed that pgRNA increased the proliferation of hepatocellular carcinoma cells, and the enhanced proliferation may be mainly due to the increased DNA synthesis. The expression of pgRNA significantly enhanced the clone formation and tumorigenesis of hepatocellular carcinoma cells, as demonstrated by the results of the clone formation and subcutaneous tumorigenesis assay. The Transwell and scratch assays suggest that pgRNA increases the cell migration rate of hepatocellular carcinoma cells. Additionally, the cell invasion assay shows a significant increase in the invasive ability of hepatocellular carcinoma cells after the expression of pgRNA. The results of the transcriptome sequencing showed a significant reduction in the expression of the oncogene B-cell translocation gene 2 (BTG2) in pgRNA-expressing hepatocellular carcinoma cells and tissues. The expression of BTG2 in hepatocellular carcinoma cells expressing pgRNA was significantly lower than in their negative control group, as confirmed by qPCR and immunohistochemistry experiments. This suggests that pgRNA may affect the development and progression of HCC by influencing the expression of BTG2. **Conclusion:** The expression of pgRNA has been found to enhance the proliferation, migration, and invasive ability of hepatocellular carcinoma cells. The mechanism by which pgRNA affects the biological behavior of these cells and promotes hepatocarcinogenesis and progression may be achieved by inhibiting BTG2 expression.

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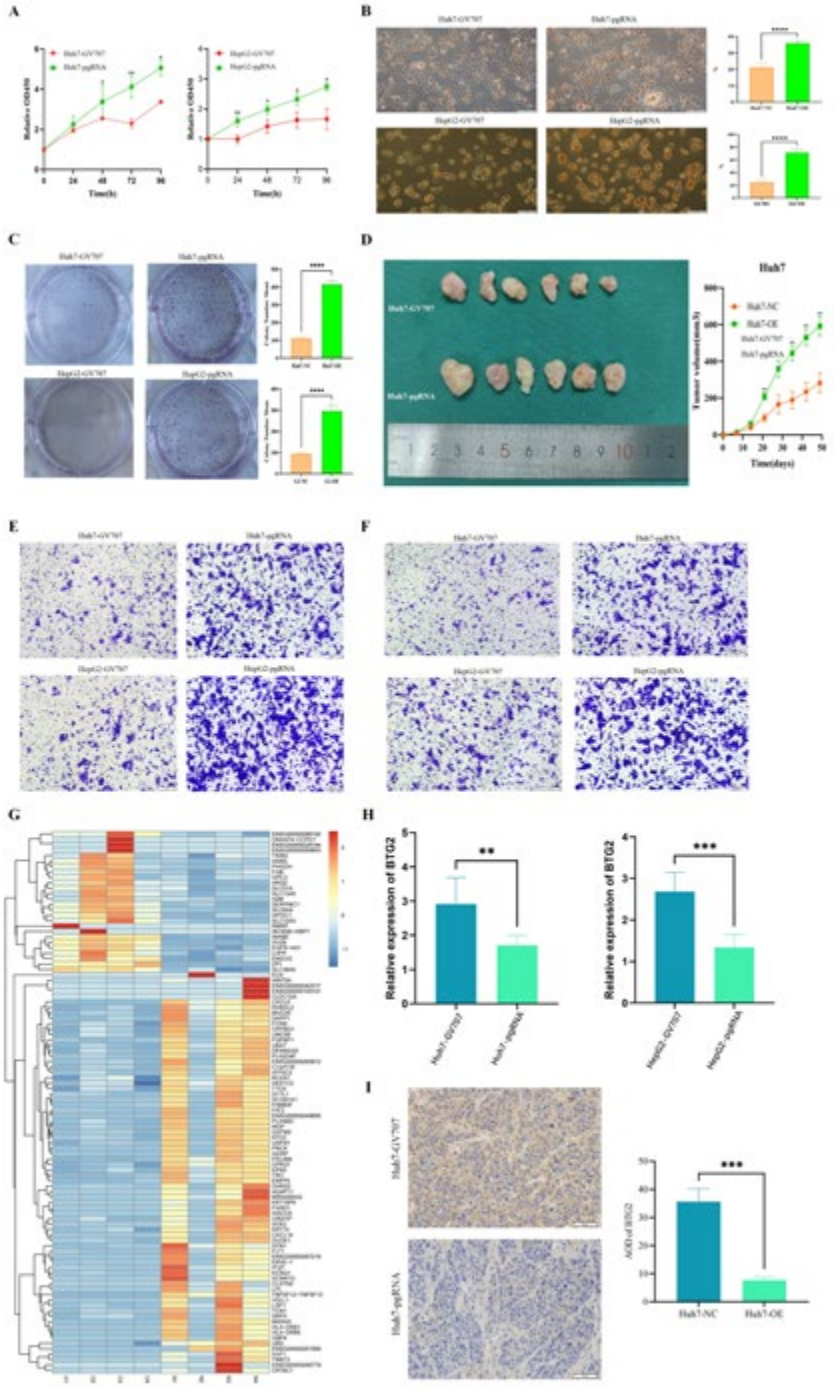

Figure1. Overexpressing pgRNA increases the proliferation, migration, and invasion abilities of HCC cells in vitro and in vivo. CCK-8 assays(A), EdU-DAB staining (B), the clone formation experiment (C) and subcutaneous tumorigenesis assay(D) were performed to measure cell proliferation. Transwell assay(E) and invasion assay(F) were performed to evaluate migration and invasion abilities of cell. Atranscriptome sequencing analysis(G) suggested the expression of BTG2 was lower after overexpression of pgRNA and qPCR(H) and immunohistochemistry experiments(I) confirmed the BTG2 was down-regulated after overexpression of pgRNA in vitro and in vivo.

Disclosures: Yifan Han: Nothing to Disclose, Zhan Zeng: Nothing to Disclose, Ning Lin: Nothing to Disclose, Xiaoyuan Xu*: Nothing to Disclose

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3405 | IDENTIFICATION OF PRMT5 AS A THERAPEUTIC TARGET IN CHOLANGIOCARCINOMA

Jasmin Elurbide[1] Leticia Colyn[2] Maria Ujue Latasa[1] Iker Uriarte[1] Stefano Mariani[3] Amaya Lopez-Pascual[4] Emiliana Valbuena[2] Borja Castello-Uribe[2] Robert Arnes Benito[5] Elena Adan-Villaescusa[2] Mikel Azkargorta[6] Felix Elortza[6] Hanghang Wu[7] Marcin Krawczyk[8] Kai Markus Schneider[9] Bruno Sangro[10] Luca Aldrighetti[11] Francesca Ratti[11] Andrea Casadei-Gardini[11] Jose Marin[12] Irene Amat[13] Jesus Urman[13] Maria Arechederra[14] Maria Martinez-Chantar[15] Christian Trautwein[16] Meritxell Huch[17] Francisco Javier Cubero[18] Carmen Berasain[19] Maite Fernandez-Barrena[14] Matías Ávila[14]

[1]CIMA,CCUN,University of Navarra;CIBERehd, [2]CIMA, CCUN, University of Navarra, [3]CIMA,CCUN,Univ. of Navarra; AOU Cagliari, [4]CIMA, CCUN, University of Navarra;IdiSNA, [5]Max Plank Institute CBG, [6]CIC bioGUNE - BRTA, [7]IOO - UCM, [8]Saarland University Hospital, [9]University Hospital Aachen, [10]CCUN; CIBERehd; IdiSNA, [11]IRCCS San Raffaele Scientific Institute, [12]HEVEPHARM, IBSAL, [13]Navarra University Hospital, [14]CIMA, CCUN; CIBERehd; IdiSNA, [15]CICbioGUNE-BRTA; CIBERehd, [16]Technical University Dortmund (IfADo), [17]Max Plankk Institute CBG, [18]IOO, UCM; CIBERehd, [19]CIMA, CCUN, Univ. of Navarra; CIBERehd

Background: Cholangiocarcinoma is a very difficult to treat cancer. Chemotherapies are little effective and the response to immune checkpoint inhibitors is poor. Therefore, new therapeutic strategies must be identified. We characterized the enzyme protein arginine-methyltransferase 5 (PRMT5) as a novel therapeutic target in cholangiocarcinoma. **Methods:** We evaluated the expression of PRMT5, its functional partner MEP50 and methylthioadenosine phosphorylase (MTAP), an enzyme that modulates the sensitivity of PRMT5 to pharmacological inhibitors, in human CCA tissues. PRMT5-targeting drugs currently tested in clinical trials for other malignancies were assessed in human CCA cell lines and organoids, as well as in two immunocompetent cholangiocarcinoma mouse models. Transcriptomic, proteomic and functional analyses were performed to explore the underlying antitumoral mechanisms. **Results:** PRMT5 and MEP50 proteins were correlatively overexpressed in most cholangiocarcinoma tissues. MTAP was absent in >20% of intrahepatic cholangiocarcinomas. PRMT5-targeting drugs markedly inhibited CCA cells proliferation, synergizing with cisplatin and gemcitabine, and hindered the growth of cholangiocarcinoma organoids. PRMT5 inhibition blunted the expression of oncogenic genes involved in chromatin remodeling and DNA repair, consistently inducing the formation of RNA-loops and promoting DNA damage. Treatment with PRMT5-targeting drugs significantly restrained the growth of experimental cholangiocarcinoma without adverse effects, and concomitantly induced the recruitment of CD4 and CD8 T cells to shrinking tumoral lesions. **Conclusion:** PRMT5 and MEP50 are frequently upregulated in human cholangiocarcinoma, and PRMT5-targeting drugs have significant antitumoral efficacy in clinically-relevant cholangiocarcinoma models. Our findings support the evaluation of PRMT5 inhibitors in clinical trials, including their combination with cytotoxic and immune therapies.

Disclosures: Jasmin Elurbide: Nothing to Disclose, Leticia Colyn: Nothing to Disclose, Maria Ujue Latasa: Nothing to Disclose, Iker Uriarte: Nothing to Disclose, Stefano Mariani: Nothing to Disclose, Amaya Lopez-Pascual: Nothing to Disclose, Emiliana Valbuena: Nothing to Disclose, Borja Castello-Uribe: Nothing to Disclose, Robert Arnes Benito: Nothing to Disclose, Elena Adan-Villaescusa: Nothing to Disclose, Mikel Azkargorta: Nothing to Disclose, Felix Elortza: Nothing to Disclose, Hanghang Wu: Nothing to Disclose, Marcin Krawczyk: Nothing to Disclose, Kai Markus Schneider: Nothing to Disclose, Bruno Sangro: Nothing to Disclose, Luca Aldrighetti: Nothing to Disclose, Francesca Ratti: Nothing to Disclose, Andrea Casadei-Gardini: Nothing to Disclose, Jose Marin: Nothing to Disclose, Irene Amat: Nothing to Disclose, Jesus Urman: Nothing to Disclose, Maria Arechederra: Nothing to Disclose, Maria Martinez-Chantar: Nothing to Disclose, Christian Trautwein: Nothing to Disclose, Meritxell Huch: Nothing to Disclose, Francisco Javier Cubero: Nothing to Disclose, Carmen Berasain: Nothing to Disclose, Maite Fernandez-Barrena: Nothing to Disclose, Matías Ávila: Nothing to Disclose

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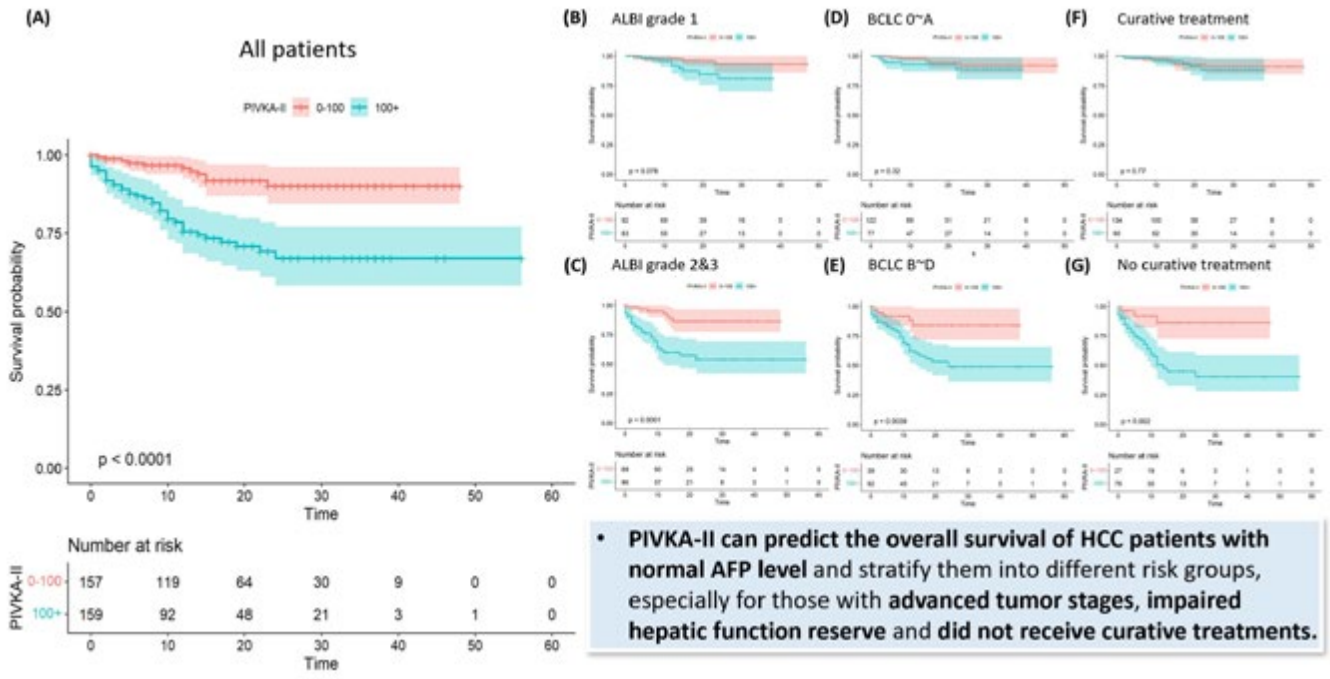
3406 | PIVKA-II AS A PROGNOSTIC FACTOR FOR PATIENTS WITH HEPATOCELLULAR CARCINOMA AND WITH NORMAL SERUM ALPHA-FETOPROTEIN LEVELS

Chun-Ting Ho[1] Elise Chia-Hui Tan[2] Tzu-Han Ma[3] Yi-Hsiang Huang[1] Ming-Chih Hou[1] Jaw-Ching Wu[3] Chien-Wei Su[1]

[1]Taipei Veterans General Hospital, [2]China Medical University, [3]National Yang Ming Chiao Tung University

Background: Hepatocellular carcinoma (HCC) patients with normal serum alpha-fetoprotein (AFP) levels (< 20 ng/mL) may exhibit distinct characteristics, yet there is a lack of serum biomarkers to predict their prognosis. Protein induced by vitamin K absence or antagonists-II (PIVKA-II) has emerged as a tumor marker for HCC, demonstrating its potential for HCC surveillance and diagnosis. However, its prognostic value remains unclear. This study aimed to investigate the prognostic ability of PIVKA-II in HCC patients with normal serum AFP levels. **Methods:** This retrospective study included 330 consecutive treatment-naïve HCC patients with normal serum AFP levels from 2020 to 2023. Patients were categorized based on their serum PIVKA-II levels. Prognostic factors were analyzed using a multivariate Cox proportional hazards model. **Results:** Among these patients, 169 (51.2%) patients had serum PIVKA-II levels > 100 mAU/mL. These patients exhibited more aggressive tumor characteristics including larger tumor size, more multiple tumors, and increased presence of extra-hepatic metastasis and vascular invasion than those with serum PIVKA-II levels ≤ 100 mAU/mL. Liver functional reserves were comparable between the two groups. Additionally, patients with higher serum PIVKA-II levels underwent curative treatment less frequently than those with lower levels (53.3% vs.83.2%, p<0.001). After a median follow-up of 17 months (interquartile range 8.0-27.0), 50 patients had died, with a 3-year overall survival rate of 77%. The 3-year overall survival rates for the high and low PIVKA-II groups were 54.9% and 87.1%, respectively. Multivariate analysis identified higher serum PIVKA-II level as an independent risk factor for poorer overall survival (hazard ratio HR 2.422, 95% confidence interval CI 1.128-5.198, p=0.023), along with presence of vascular invasion, higher serum creatinine levels (> 1.2 mg/dL), larger prothrombin time international normalized ratio (> 1.1), higher serum alkaline phosphatase levels (> 100 U/L), and non-curative treatment. **Conclusion:** Serum PIVKA-II level was an independent prognostic factor for HCC patients with normal serum AFP levels and could efficiently stratify patients into different risk groups.



Disclosures: Chun-Ting Ho: Nothing to Disclose, Elise Chia-Hui Tan: Nothing to Disclose, Tzu-Han Ma: Nothing to Disclose, Yi-Hsiang Huang: Nothing to Disclose, Ming-Chih Hou: Nothing to Disclose, Jaw-Ching Wu: Nothing to Disclose, Chien-Wei Su: Nothing to Disclose

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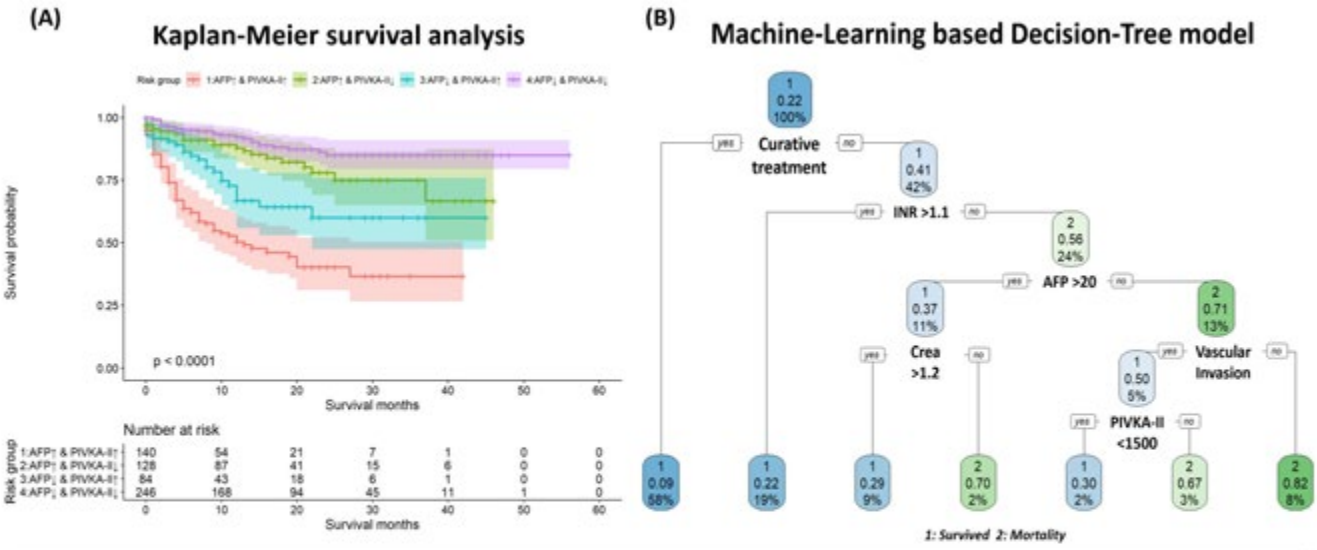
3407 | MACHINE LEARNING-BASED DECISION-TREE MODEL DEMONSTRATING THE PROGNOSTIC VALUE OF PIVKA-II AND AFP IN PATIENTS WITH HEPATOCELLULAR CARCINOMA ◆

Chun-Ting Ho[1] Elise Chia-Hui Tan[2] Tzu-Han Ma[3] Yi-Hsiang Huang[1] Ming-Chih Hou[1] Jaw-Ching Wu[3] Chien-Wei Su[1]

[1]Taipei Veterans General Hospital, [2]China Medical University, [3]National Yang Ming Chiao Tung University

Background: Protein induced by Vitamin K absence or antagonists-II (PIVKA-II) and alpha-fetoprotein (AFP) are two widely used tumor markers for the surveillance and diagnosis of hepatocellular carcinoma (HCC). However, their prognostic value remains unclear. The study aimed to evaluate the prognostic ability of PIVKA-II and AFP for HCC patients and develop a machine learning-based decision-tree model to predict patient outcomes. **Methods:** The retrospective study enrolled 598 consecutive treatment-naïve HCC patients diagnosed from 2020 to 2023. Patients were categorized into four groups based on their serum PIVKA-II (cut-off value 1500 mAU/mL) and AFP (cut-off value 20 ng/mL) levels at diagnosis. The cohort was randomly divided into a training cohort (n=479) and a validation cohort (n=119). A Cox proportional hazards model was used to identify independent risk factors for overall survival (OS). A machine learning-based decision-tree analysis was then performed on the training cohort to develop a model predicting OS, which was subsequently validated in the validation cohort. **Results:** The four groups showed significant differences in tumor characteristics, including tumor stage, size, number of tumors, presence of extra-hepatic metastasis and vascular invasion, as well as liver functional reserve. After a median follow-up of 16.0 months (interquartile range 5.0-22.0), 141 patients had died, with a 3-year OS rate of 63.0%. The 3-year OS rates for the four groups (high AFP & high PIVKA-II, high AFP & low PIVKA-II, low AFP & high PIVKA-II, low AFP & low PIVKA-II) were 31.7%, 67.3%, 51.6%, and 70.0%, respectively (p<0.001). Multivariate analysis revealed higher serum AFP levels, high PIVKA-II levels, lower serum albumin levels, higher serum creatinine levels, higher serum alkaline phosphatase levels, larger prothrombin time international normalized ratio (PT INR), presence of vascular invasion, and non-curative treatment as independent risk factors for poor OS in the training set. The machine learning-based decision-tree model included AFP, PIVKA-II, vascular invasion, serum creatinine level, PT INR, and treatment modalities as important factors, demonstrating an accuracy rate of 78.2% in predicting OS in the validation cohort. **Conclusion:** The machine learning-based decision-tree model, utilizing both serum PIVKA-II and AFP levels, accurately predicted the outcomes of HCC patients.



Highlight:

- The **combination use** of **PIVKA-II** and **AFP** on predicting overall survival of HCC patients
- Implication of **machine-learning** on survival analysis and model developing

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Disclosures: Chun-Ting Ho: Nothing to Disclose, Elise Chia-Hui Tan: Nothing to Disclose, Tzu-Han Ma: Nothing to Disclose, Yi-Hsiang Huang: Nothing to Disclose, Ming-Chih Hou: Nothing to Disclose, Jaw-Ching Wu: Nothing to Disclose, Chien-Wei Su: Nothing to Disclose

3408 | FACTORS ASSOCIATED WITH TYPE OF FIRST-LINE TREATMENT RECEIVED FOR UNRESECTABLE HEPATOCELLULAR CARCINOMA IN THE ERA OF IMMUNOTHERAPY

Amie Tan[1] *Spencer Cheng*[1] *Tu My To*[1] *Robert Schuldt*[1]

[1]*Genentech*

Background: In 2020, the landscape of 1L therapy for unresectable hepatocellular carcinoma (uHCC) shifted with the approval of the first immunotherapy (IO), atezolizumab plus bevacizumab (A+B), replacing tyrosine kinase inhibitors (TKIs) as the standard of care. Despite this shift, real-world (RW) data indicates that TKIs are still being used in the 1L setting. We aim to identify factors associated with use of TKIs relative to A+B in the US community oncology setting. **Methods:** This was a retrospective cohort study of uHCC patients (pts) who received 1L therapy with A+B (A+B cohort), or sorafenib or lenvatinib (TKI cohort) between Jun 2020 and Jul 1, 2023, using nationwide Flatiron Health electronic health record (EHR)–derived data. Pt characteristics, including area-level socioeconomic status (SES), were compared between cohorts. Multivariate logistic regressions were used to evaluate the association between pt characteristics and the choice of A+B as 1L therapy vs oral TKIs. **Results:** Among the 780 eligible pts with uHCC (81% male, mean [SD] age at diagnosis: 68.8 [8.9] y), 81% (n=634) and 19% (n=146) pts received A+B and TKIs, respectively. Compared with the TKI cohort, the A+B cohort was younger (mean age: 68.4 vs 70.2 y; *P*=0.043), had lower proportion of albumin-bilirubin (ALBI) grade 3 (9.5% vs 20.6%; *P*=0.001), history of ascites (22.8% vs 32.2%; *P*=0.017), and encephalopathy (3.7% vs 8.2%; *P*=0.019). In the regression model, covariates that were significantly associated with a lower likelihood of 1L A+B use vs TKI include: better performance status (ECOG 0 vs 2+; odds ratio [OR], 0.34; 95% CI: 0.12, 0.83), worse liver function (ALBI grade 3 vs 1; OR, 0.29; 95% CI: 0.13, 0.67), and history of ascites (vs not reported; OR, 0.51; 95% CI: 0.29, 0.89). While not statistically significant, there was a trend of pts in areas with lower SES being less likely to receive A+B vs TKIs. Those living in an area with the lowest (vs highest) quintile of SES were less than half as likely to receive A+B (OR, 0.47; 95% CI:0.18, 1.09; *P*=0.088). **Conclusion:** In this RW cohort of uHCC pts treated at US community oncology practices, a non-negligible proportion of pts continued to receive TKIs despite the availability of more effective IO. Factors including performance status, liver function, ascites, and potentially SES are associated with the treatment choice. Future studies with larger sample sizes are warranted to elucidate barriers to IO initiation, including SES-based disparities.

Disclosures: Amie Tan: Genentech: Employee, Genentech: Stock - publicly traded company, Spencer Cheng: Nothing to Disclose, Tu My To: Genentech: Employee, Robert Schuldt: Nothing to Disclose

3409 | DIAGNOSIS MODE AND OUTCOMES OF HEPATOCELLULAR CARCINOMA IN ELDERLY PATIENTS WITH IMPLICATIONS FOR SURVEILLANCE

Aryoung Kim[1] *Dong Hyun Sinn*[2]

[1]*Inje University Ilsan Paik Hospital,* [2]*Samsung Medical Center*

Background: Hepatocellular carcinoma (HCC) surveillance is recommended by international liver societies for individuals who are at high risk of developing HCC. While previous studies have demonstrated the benefits of surveillance for middle-aged individuals, its necessity for older individuals is unclear. This study aimed to evaluate the benefits of HCC surveillance in the elderly. **Methods:** This is a single-center retrospective cohort study of elderly patients aged 75 years or older who were newly diagnosed with HCC between January 2009 and December 2021. Patients were grouped into two groups: those diagnosed with HCC during surveillance (*n* = 235, surveillance group) and those diagnosed with HCC due to symptoms (*n* = 184, symptomatic group). The study outcome was overall survival. It was compared in the overall cohort and a propensity score (PS)-matched cohort. **Results:** Early-stage diagnosis was more frequent in the surveillance group compared to the symptomatic group (mUICC stage I/II: 72.3% vs. 39.1%, $p < 0.001$). The overall survival rate was better in the surveillance group than in the symptomatic group (median 4.4 vs. 2.1 years, log-rank $p < 0.001$). In multivariable-adjusted

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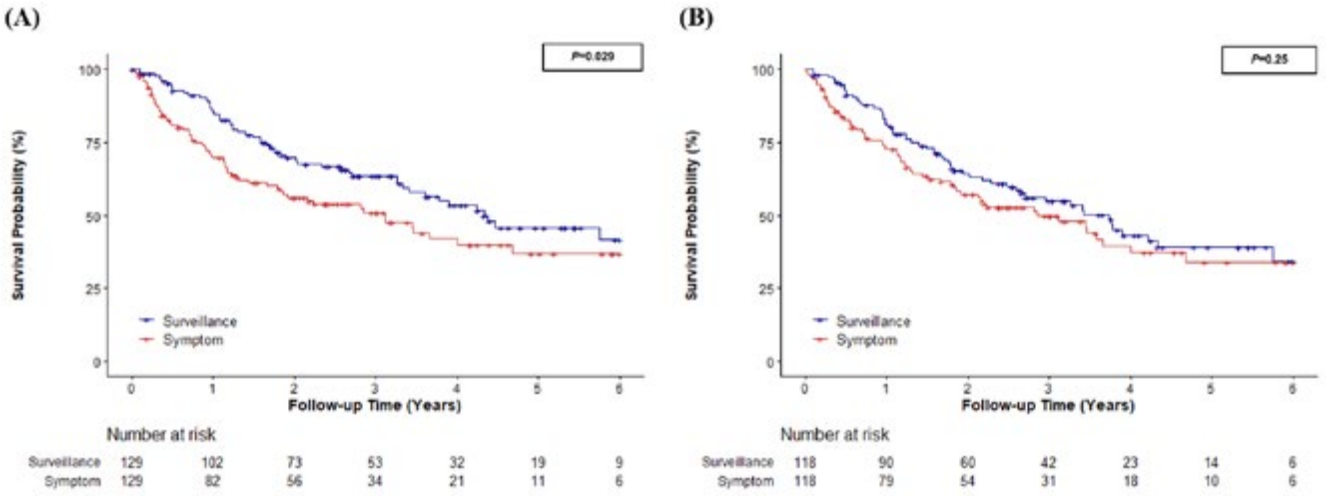
models, the hazard ratio (HR) of mortality of the surveillance group compared to the symptomatic group was 0.64 (95% confidence interval (CI): 0.47 – 0.87). However, further adjustment for the tumor stage markedly attenuated this association, which was no longer statistically significant (adjusted HR = 0.75; 95% CI: 0.54 – 1.02). In the PS-matched cohort analysis, outcomes were better for the surveillance group when PS matching variables did not include the tumor stage (HR = 0.67; 95% CI: 0.47 – 0.96). However, when the PS matching variables included the tumor stage, the difference in outcomes between the two groups was no longer significant (HR = 0.81; 95% CI: 0.57 – 1.16). **Conclusion:** The surveillance group of elderly patients showed better survival than the symptomatic group, which was mainly explained by earlier tumor stage at diagnosis. This implies that, even in patients aged 75 and older, HCC surveillance has shown a considerable advantage in terms of improving survival rates, and hence active surveillance should be carried out in this age group.

Figure. Kaplan-Meier estimates of survival in elderly patients according to diagnosis mode in matched group (over 75 years old) (A) propensity score matched cohort that did not include mUICC stage (B) propensity score matched cohort included mUICC stage



Disclosures: Aryoung Kim: Nothing to Disclose, Dong Hyun Sinn: Nothing to Disclose

3410 | RPL41 PROMOTES HCC METASTASIS VIA TRANSCRIPTION FACTORS RUNX2-MEDIATED EMT MECHANISM

Shen Neng[1] *Liu Li*[1]

[1]*Chongqing University Cancer Hospital*

Background: Hepatocellular carcinoma (HCC) is the most common malignant tumor worldwide with high morbidity and mortality rates. We aimed to examine the expression of ribosomal protein L41 (RPL41) in HCC and analyze its correlation with clinicopathological features of HCC patients. Moreover, the role of RPL41 in the HCC cell proliferation, invasion and metastasis and the potential mechanism underlying HCC metastasis were also investigated. **Methods:** We used quantitative polymerase chain reaction (qRT-PCR) and Western blot to evaluate the expression levels of RPL41 in HCC cell lines. Furthermore, the expression of RPL41 in HCC and the adjacent non-tumor tissues was assessed by immunohistochemistry (IHC). Cell proliferation was evaluated using MTT assay, cell migration and invasion were measured using wound healing and transwell assays. Finally, we detected the expression of target proteins in HCC cell lines transfected with RPL41 overexpression plasmid or RPL41 shRNA plasmid by Western blot. **Results:** We found that the expression of RPL41was increased in 280 cases of HCC tissues compared that in adjacent non-tumor tissues. HCC patients with high RPL41 expression had a higher tendency to have high growth rate, strong invasion ability, high clinical stage and poor tumor differentiation. Functional study demonstrated that the upregulation of RPL41 promotes proliferation, migration and invasion of HCC cells while silencing RPL41 in HCC cells significantly inhibited cell proliferation, migration and invasion. Furthermore, RPL41 could accelerate the EMT process in HCC cells by upregulating the expression of RUNX2. **Conclusion:** RPL41 played an important role in the process of tumorigenesis and progression in HCC

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and enhanced the invasion and metastasis ability of HCC cells through regulating transcription factors RUNX2-mediated EMT mechanism, which indicated that the protein could serve as a novel therapeutic target for the treatment of HCC.

Disclosures: shen neng: Nothing to Disclose, liu li: Nothing to Disclose

3411 | ASSOCIATIONS BETWEEN METABOLIC SYNDROME AND CHOLANGIOCARCINOMA RISK: A LARGE-SCALE POPULATION-BASED PROSPECTIVE STUDY

Mei-Hsuan Lee[1] Tzu-I Chen[1] Ming-Huang Chen[2] Szu-Ching Yin[1] Yi-Ting Chen[1] Xia-Rong Liu[1] Yun-Zheng Gao[1] Chih-Jo Lin[1] Hsuan-Yu Chen[3] Jill Koshiol[4]

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Background: Cholangiocarcinoma is a rare cancer with poor survival rates. Identifying risk factors is crucial for early prevention. This large-scale, population-based prospective study aimed to examine the associations between metabolic syndrome and the risk of cholangiocarcinoma, including its intra- and extra-hepatic forms. **Methods:** A total of 4,932,211 adults aged 40 years and older participated in a government-initiated health checkup program from 2012 to 2017. This program collected lifestyle data through standardized questionnaires, anthropometric measurements, and biochemical tests. Follow-up continued until the end of 2020. Data linkage with the National Cancer Registration and Death Certification System was performed to ascertain the occurrence of cholangiocarcinoma and obtain vital status information. Cox proportional hazards models were used to estimate adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) for metabolic syndrome and its individual components associated with cholangiocarcinoma risks. **Results:** During 35,879,371 person-years of follow-up, 6,117 new cases of cholangiocarcinoma were identified, with an incidence rate of 17.05 (95% CI: 15.90-18.20) per 100,000 person-years. Individuals with metabolic syndrome had significantly higher incidences of both intra- and extra-hepatic cholangiocarcinoma (p<0.0001). The multivariate-adjusted HR for metabolic syndrome was 1.20 (95% CI: 1.14-1.27) in relation to cholangiocarcinoma risk, compared to those without metabolic syndrome. An increasing number of metabolic risk factors was associated with elevated cholangiocarcinoma risks, with adjusted HRs ranging from 1.14 (95% CI: 1.04-1.25) for one risk factor to 1.63 (95% CI: 1.41-1.89) for five risk factors (p for trend <0.0001). Individual components such as central obesity, abnormal HDL, hypertension, and impaired fasting glucose were also linked to increased cholangiocarcinoma risk (p<0.0001). Prediabetes and diabetes increased cholangiocarcinoma risk with adjusted HRs of 1.08 (95% CI: 1.01-1.15) and 1.41 (95% CI: 1.33-1.49), respectively, compared to normal fasting glucose. Stratification analyses by age, sex, liver enzyme levels, and comorbidities consistently showed that metabolic syndrome increased the risk for cholangiocarcinoma. Overall, the presence of metabolic syndrome, the number of metabolic factors, and most individual metabolic components consistently heightened the risks for both intra- and extra-hepatic cholangiocarcinoma (p<0.001). **Conclusion:** The positive association between metabolic syndrome and cholangiocarcinoma risk suggests that managing metabolic risk factors might reduce the occurrence of both intra- and extra-hepatic cholangiocarcinoma.

Disclosures: Mei-Hsuan Lee: Nothing to Disclose, Tzu-I Chen: Nothing to Disclose, Ming-Huang Chen: Nothing to Disclose, Szu-Ching Yin: Nothing to Disclose, Yi-Ting Chen: Nothing to Disclose, Xia-Rong Liu: Nothing to Disclose, Yun-Zheng Gao: Nothing to Disclose, Chih-Jo Lin: Nothing to Disclose, Hsuan-Yu Chen: Nothing to Disclose, Jill Koshiol: Nothing to Disclose

3412 | SERUM SOLUBLE DR5 AS A NOVEL BIOMARKER PREDICTS EARLY RECURRENCE OF HEPATOCELLULAR CARCINOMA IN TACE-TREATED PATIENTS WITH CHRONIC HEPATITIS B

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Background: This study aimed to determine if serum Death receptor 5(sDR5)levels, a member of the tumor necrosis factor receptor superfamily (TNFRSF), was associated with the length of recurrence-free survival of hepatocellular carcinomas (HCC) patients after transcatheter arterial chemoembolization (TACE) and may

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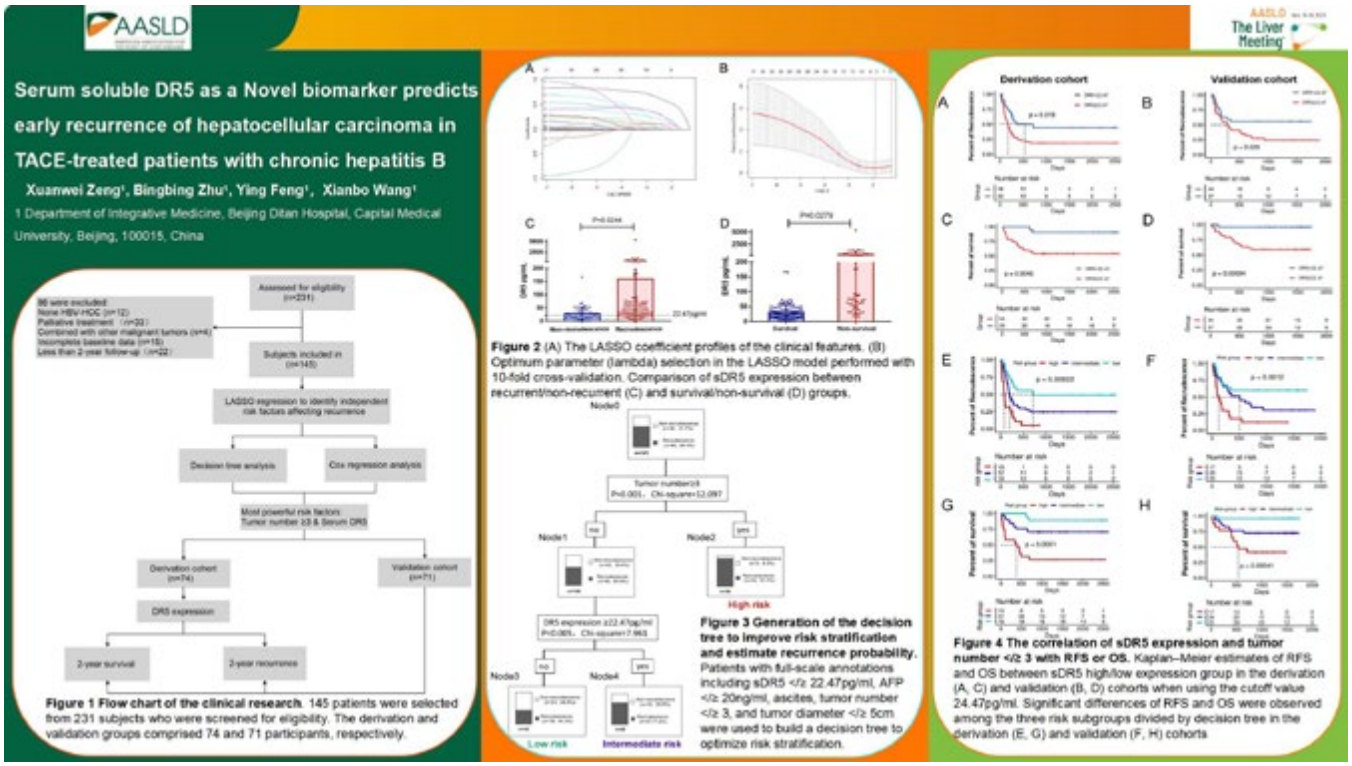
help to predicting the risk of 2-year recurrence-free survival (RFS). **Methods:** A total of 145 patients with HBV-HCC after TACE were recruited. Individual risk factors for 2-year recurrence were selected using LASSO-COX regression and decision tree analysis. Then the patients were divided into derivation and validation cohorts (74 and 71 patients, respectively). In the derivation cohort, The predicted probability of recurrence risk was obtained from decision tree analysis. The results were validated in a validation cohort. **Results:** Serum sDR5, AFP levels and tumor number (< 3/≥ 3) were identified as independent risk factors for recurrence in patients with HBV-HCC. Using the decision tree, three different risk subgroups were defined based on two major components, tumor3+/− and sDR5+/− (cutoff: 22.47pg/ml). Patients with serum DR5 levels ≥22.47pg/ml and tumor number ≥3 had a distinctly poor prognosis. **Conclusion:** High sDR5 levels correlated with shorter RFS in patients with HBV-HCC undergoing TACE. Execution of sDR5-based decision tree analysis can assist in early identification and prompt management of HCC patients at a high risk of recurrence in 2 years.



Disclosures: Xuanwei Zeng: Nothing to Disclose, Bingbing Zhu: Nothing to Disclose, Ying Feng: Nothing to Disclose, Xianbo Wang: Nothing to Disclose

3413 | FIVE-YEAR OVERALL SURVIVAL AND OVERALL SURVIVAL BY TUMOR RESPONSE MEASURES FROM THE PHASE 3 HIMALAYA STUDY OF TREMELIMUMAB PLUS DURVALUMAB IN UNRESECTABLE HEPATOCELLULAR CARCINOMA

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Background: In the Phase 3 HIMALAYA study (NCT03298451) in unresectable hepatocellular carcinoma (uHCC), STRIDE (Single Tremelimumab Regular Interval Durvalumab) significantly improved overall survival (OS) versus sorafenib in the primary analysis (Abou-Alfa et al. *NEJM Evid* 2022) and demonstrated durable long-term survival with a 4-year OS rate of 25.2% (Sangro et al. *Ann Oncol* 2024). Here, we report the first 5-year OS analysis in uHCC and evaluate survival by multiple tumor response measures. **Methods:** Participants with uHCC were randomized to STRIDE, durvalumab monotherapy, or sorafenib. OS, 5-year OS rates, OS by disease control, changes in tumor size and depth of response (Osgood et al. *J Clin Oncol* 2019), and serious adverse events (SAEs) were assessed. Extended long-term survivors were described. Data cut-off was March 1, 2024. **Results:** The OS hazard ratio for STRIDE versus sorafenib was 0.76 (95% confidence interval, 0.65–0.89) (Table). The 5-year OS rate was 19.6% with STRIDE versus 9.4% with sorafenib (rate ratio, 2.09) and was further improved in participants who achieved disease control (28.7% vs 12.7%; rate ratio, 2.26). OS rates for participants who achieved ≥G2 (>25%) tumor shrinkage were 58.0% (57 participants at risk) versus 36.0% (8 participants at risk) at 48 months and 50.7% (34 participants at risk) versus 26.3% (4 participants at risk) at 60 months for STRIDE versus sorafenib, respectively. The rate of treatment-related SAEs with STRIDE did not change from the primary analysis. **Conclusion:** STRIDE demonstrated an unprecedented 5-year survival rate, with no additional serious safety events in the extended follow-up. The improved OS outcomes observed across multiple tumor response evaluations, including disease control and depth of response, provide novel insights on the clinical benefit of dual immune checkpoint inhibition beyond conventional measures of response. These results set a new benchmark in uHCC, with 1 in 5 participants alive with STRIDE at 5 years.
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	STRIDE (n=393)	Durvalumab (n=389)	Sorafenib (n=389)
Median follow-up duration (95% CI), months	62.5 (59.5–64.8)	62.7 (60.8–63.8)	59.9 (58.3–61.5)
OS HR (95% CI)	0.76 (0.65–0.89)	0.85 (0.73–1.00)	
OS rates (95% CI), %			
48 months	25.2 (20.9–29.7)	19.0 (15.1–23.3)	15.1 (11.5–19.1)
60 months	19.6 (15.6–23.8)	14.4 (10.9–18.4)	9.4 (6.5–13.0)
OS rates in participants with disease control (95% CI), %			
48 months	36.3 (30.0–42.5)	28.9 (22.7–35.4)	20.2 (15.1–25.9)
60 months	28.7 (22.8–34.9)	21.8 (16.1–28.0)	12.7 (8.4–17.9)
Treatment-related SAEs, n/N (%)	68/388 (17.5)	33/388 (8.5)	37/374 (9.9)

CI, confidence interval; HR, hazard ratio; OS, overall survival; SAE, serious adverse event.

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3414 | IMMUNE-RELATED LIVER INJURY IS A GOOD PROGNOSTIC FACTOR IN PATIENTS WITH HEPATOCELLULAR CARCINOMA UNDER ATEZOLIZUMAB PLUS BEVACIZUMAB THERAPY ◆

Tai-Chi Wu[1] Wei Teng[1] Po-Ting Lin[1] Eric Yi-Liang Shen[1] Chung-Wei Su[1] Yi-Chung Hsieh[1] Wei-Ting Chen[1] Tsung-Han Wu[1] Chen-Chun Lin[1] Chun-Yen Lin[1] Shi-Ming Lin[1]

[1]Linkou Chang Gung Memorial Hospital

Background: Atezolizumab plus bevacizumab therapy is the standard first-line therapy for unresectable hepatocellular carcinoma (HCC), and immune-related liver injury (IrLI) is commonly observed in these treated patients, especially with underlying chronic liver disease. However, the association between IrLI and clinical outcome remains unknown. This study aimed to investigate the prognostic value of IrLI on patients with HCC undergoing atezolizumab plus bevacizumab therapy. **Methods:** One hundred and sixteen patients who received atezolizumab plus bevacizumab and fulfilled the IMBrave150 inclusion criteria for unresectable HCC in Chang Gung Memorial Hospital, Linkou Medical Center from 2020-2023 were enrolled for analyses. Radiologic evaluation was based on modified Response Evaluation Criteria in Solid Tumors (mRECIST). Treatment-related adverse event (TrAE) was graded according to the National Cancer Institute CTCAE v5.0. IrLI was defined as an increase in ALT or AST serum levels attributed to the treatment. **Results:** Of the 116 patients, the best objective response rate (ORR) and disease control rate (DCR) were 38.8% and 67.2%, respectively. Forty-eight patients (41.4%) died during the median follow-up of 9.8 months. The overall occurrence rate of any grade of TrAE was 69.0%, and that of grades 3 and 4 was 15.5%. IrLI was the most common AE among these patients (52.6%), and the median time to the onset was 1.7 months. The development of grade ≥2 IrLI was associated with longer OS (19.7 vs. 11.0 months; log-rank p=0.039) and PFS (6.7 vs. 3.5 months; log-rank p=0.027). However, patients with

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grade ≥ 2 elevated bilirubin had shorter OS (4.5 vs. 16.7 months; log-rank p<0.001) and PFS (2.3 vs. 5.0 months; log-rank p<0.001). Prior loco-regional therapy is the only predictor of the occurrence of grade ≥ 2 IrLI (OR 2.667; 95% CI:1.022-7.710, p=0.040). **Conclusion:** In patients with HCC who receive atezolizumab plus bevacizumab, the development of grade ≥ 2 IrLI correlates with improved outcomes, while prior loco-regional therapy may be associated with the occurrence of grade ≥ 2 IrLI.

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3415 | ROLE OF MYELOID-CELL DERIVED OSTEOPONTIN IN HEPATOCELLULAR CARCINOMA

Chao Wang[1] *Hui Han*[1] *Sai Santosh Babu Komakula*[1] *Xiaodong Ge*[1] *Romain Desert*[1] *Nithyananthan Subramaniyam*[1] *Daniel Lantvit*[1] *Grace Guzman*[1] *Natalia Nieto*[1]

[1]*University of Illinois at Chicago*

Background: Hepatocellular carcinoma (HCC) is the most common liver cancer. Surgery remains the only curable treatment, even though remarkable progress has been made in early diagnosis and perioperative management. The overall prognosis remains low regardless of advances in immunotherapy and targeted therapy. Osteopontin (OPN, encoded by *SPP1*) regulates cell proliferation and migration. Previous research showed the contribution of OPN to tumor growth, tumor grade, metastasis, and recurrence in several malignancies. However, the contribution of myeloid-derived OPN to HCC is unknown. We hypothesize that enhancing OPN expression in myeloid cells protects against HCC development. **Methods:** *Spp1*$^{fl/fl}$ and *Spp1.Stop*$^{fl/fl}$ mice were bred with *Lyz2.Cre* mice to generate myeloid-specific knockout (*Spp1*$^{\Delta Mye}$) and knockin (*Spp1*$^{KI\ Mye}$) mice. To induce HCC in these mice, we used three models. First, we injected diethylnitrosamine (25 mg/kg body weight) to 14-day-old mice and sacrificed them at 10 months. Second, we altered two cancer driver genes in 6-week-old mice. We overexpressed *MYC*, a well-established oncogene involved in HCC, and we altered *CTNNB1, a* gene frequently mutated in HCC. To achieve this, a transposon-derived *MYC* gene and a CRISPR sgRNAs *CTNNB1* were delivered by hydrodynamic tail-vein injection to target hepatocytes and induce HCC. Mice were sacrificed 50 days later. Third, to provoke MASH-induced HCC, we i.p. injected a low-dose of carbon tetrachloride (0.2 µl/g/week) to 9-week-old mice to create a profibrogenic environment. Mice were fed control or high-fat, fructose, and cholesterol diet (40% of calories from fat, 20% from fructose, and 18 g/kg cholesterol) for 8 months. **Results:** *Spp1*$^{\Delta Mye}$ showed accelerated onset HCC, presenting larger total tumor volume, number of tumors, and tumor/liver weight than *Spp1*$^{KI\ Mye}$ and *Lyz2.Cre* mice. Moreover, *Spp1*$^{KI\ Mye}$ mice showed reduced histopathological scores, including inflammation, necrosis, and fibrosis. The tumor staging in *Spp1*$^{\Delta Mye}$ mice was more advanced than in *Spp1*$^{KI\ Mye}$ and *Lyz2.Cre* mice. **Conclusion:** Enhancing OPN expression in myeloid cells protects from developing HCC in mice.

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3416 | CIRCULATING TUMOUR DNA MARKERS FOR PREDICTION OF SUSTAINED RESPONSE FOLLOWING THE CESSATION OF TARGETED THERAPY AND IMMUNOTHERAPY IN HEPATOCELLULAR CARCINOMA (HCC)

Qi Li[1] *Peilin Zhu*[1] *wenli li*[1] *Mengya Zang*[1] *Guosheng Yuan*[1] *Xiaoyun Hu*[1] *Yongru Chen*[1]

[1]*Nanfang Hospital*

Background: The combination of targeted therapy and immunotherapy has significantly improved the treatment outcomes for unresectable hepatocellular carcinoma (uHCC), with some patients even having achieved complete response (CR). However, the optimal timing for medication cessation remains unknow. Circulating tumour DNA

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(ctDNA) carrying cancer-specific genetic and epigenetic aberrations may assist in the diagnosis and monitoring of HCC. This study aims to assess the sensitivity and effectiveness of ctDNA to predict sustained response after the discontinuation of targeted therapy and immunotherapy in HCC. **Methods:** This retrospective study reviewed 27 patients with initially uHCC at BCLC stage B and C, who underwent the combination of targeted therapy and immunotherapy with or without transarterial therapies. Tumor response was evaluated using the mRECIST criteria. Radiologic CR (rCR) and ctDNA were evaluated. The detection of ctDNA was conducted within 1 week after achieving rCR. Discontinue medication for ctDNA-negative patients, whereas continue medication for ctDNA-positive patients. Progression-free survival (PFS) and overall survival (OS) were compared between ctDNA negative group and positive group. **Results:** Between March 2019 and July 2022, 32 patients planned to discontinue medication due to rCR or safety and underwent ctDNA tests. Finally, we enrolled 27 patients (25 men and 2 women; median age, 56 years) meeting the inclusion criteria, including 24 patients who achieved rCR and 3 patients who achieved PR with drug withdrawal due to safety. 8 patients were ctDNA-positive and 19 patients were ctDNA-negative. As of May 24, 2024, the median follow-up was 44.40 months. At the time of ctDNA testing,the median duration of medication for ctDNA-negative patients and ctDNA-positive patients were 27.13 months and 27.65 months, respectively. Even with continued medication, 50.00% (4 of 8) ctDNA-positive patients observed progressive disease (PD). After drug withdrawal, 5.26% (1 of 19) ctDNA-negative patients experienced PD. The risk of PD was significantly lower in the ctDNA-negative group compared to the ctDNA-positive group (HR=0.001, p<0.0001). 1 (12.50%) ctDNA-positive patient died. There were no deaths in the ctDNA-negative patients. The risk of death between the two groups has shown no significant difference. **Conclusion:** Watch and wait strategy in selective patients who achieve rCR after conversion therapy can achieve organ preservation and improve the quality of life. The ctDNA detection could serve as a prognostic marker for drug withdrawal decision.

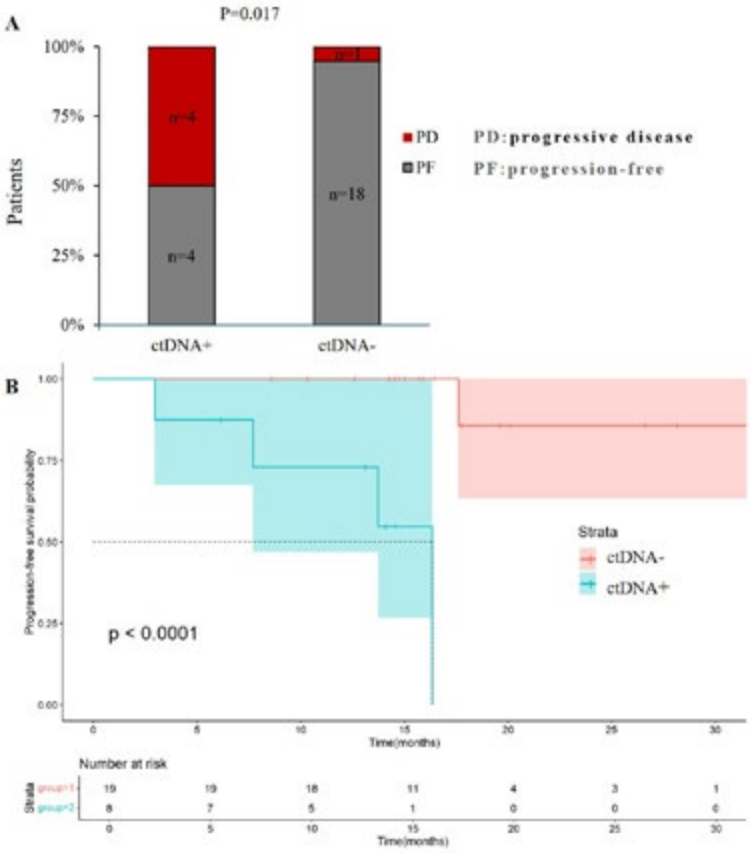

Fig. The relationship between ctDNA status and the risk of PFS in HCC patients. (A) Comparison of PFS proportion between ctDNA-positive and ctDNA-negative patients. (B) Kaplan-Meier curves for progression-free survival (PFS) for patients stratified by ctDNA status. Discontinue medication for ctDNA-negative patients, whereas continue medication for ctDNA-positive patients.

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3417 | THE ALBUMIN-BILIRUBIN SCORE AS AN INDICATOR OF EFFECTIVE IMMUNOTHERAPY IN ELDERLY PATIENTS WITH UNRESECTABLE HEPATOCELLULAR CARCINOMA

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Background: Background/Aim: The global population is aging, and patients with hepatocellular carcinoma (HCC) are no exception. The elderly population recruited in clinical trials may not accurately represent real-world elderly patients with HCC. There are few reports on the efficacy and safety of immunotherapy in the elderly that reflect the real-world population distribution. Therefore, we aimed to clarify the actual conditions of immunotherapy, as well as the prognostic factors and indicators in elderly patients with HCC. **Methods:** A total of 286 patients (242 patients aged ≥65 years) who received atezolizumab + bevacizumab or durvalumab + tremelimumab as first-line immunotherapy from November 2020 to January 2024 at 16 hospitals were enrolled in this retrospective study. The baseline characteristics and prognosis were analyzed by subdividing the patients based on age into three groups: under elderly (UE; ≤64 years), early elderly (EE; ≥65 and ≤74 years), and late elderly (LE; ≥75 years). **Results:** The proportion of patients was 44 (15.4%), 125 (43.7%), and 117 (40.9%) in UE, EE, and LE, respectively, with any adverse events occurring in 45.4%, 38.4%, and 46.1% of patients. Regarding actual characteristics, the UE patients had higher AFP (median ng/mL: 131.45 vs. 15.45), higher ALT levels (median U/L: 50.5 vs. 26.0), and lower disease control rate (59.1% vs. 77.7%) compared to the EE and LE patients. The LE patients had a lower albumin-bilirubin (ALBI) score (median: -2.478 vs. -2.296), higher performance status score (0/1/2 n; 82/32/3 vs. 143/25/1), and experienced more proteinuria (21.3%) compared to the UE and EE patients. Multivariate analysis for prognosis identified the ALBI score as an independent factor (HR 2.005, 95% CI 1.44–2.790, P < 0.001). The modified ALBI grade divided into 1/2a and 2b/3 (cut-off: -2.27) demonstrated the highest discrimination for 1- and 2-year survival prediction. Based on these results, when the analysis was limited to the ALBI 1/2a, there was no significant difference in overall survival among UE, EE, and LE patients (median months: 22.2, 19.7, 30.4, P=0.40). Fine-Gray competing risk model analysis revealed no significant difference in liver-related and other deaths (P=0.34). **Conclusion:** Immunotherapy should be administered to elderly HCC patients considering their liver function and overall condition. Appropriate evaluation of the ALBI score can lead to a better prognosis even in elderly patients with HCC.

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3418 | LONGITUDINAL TRENDS IN FRAILTY AMONG PATIENTS WITH HEPATOCELLULAR CARCINOMA ◆

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Background: Functional status impairments are common in patients with cirrhosis and have been shown to predict poor pre- and post-liver transplant outcomes. Hepatocellular carcinoma (HCC) is a common indication for transplantation, but it is unknown whether functional status in these patients changes over time after

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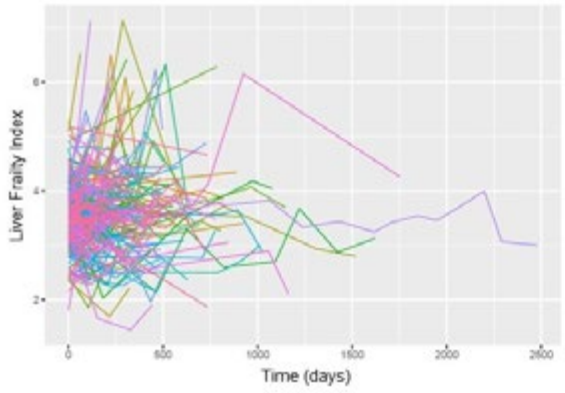
initial transplant evaluation, including after receiving locoregional therapy (LRT). **Methods:** We conducted a retrospective study of patients with HCC enrolled in the FrAILT study. Liver Frailty Index (LFI) assessments were captured at initial liver transplant evaluation and then longitudinally until transplant, loss to follow-up, or death. Our primary outcome was change in LFI over time. We also analyzed the subgroup of patients with at least one pre-LRT and one post-LRT LFI assessment to investigate the impact of LRT on frailty. Linear mixed effects modeling was used to evaluate for changes in LFI while adjusting for covariates considered *a priori* to be potential confounders. Logistic regression was used to investigate factors in the LRT subgroup associated with a moderate increase (≥0.5) in LFI. **Results:** There were 361 patients with HCC in our study, with a median baseline LFI of 3.58 (SD 0.73) and median follow-up time of 363 days (SD 303). A spaghetti plot of LFIs over time did not show any clear longitudinal trends (Fig. 1A). This was confirmed through a linear mixed effects model, in which time did not significantly affect LFI (estimated coefficient $3.4x10^{-5}$ per 30 days; p=0.64; Fig. 1B). Of the remaining factors tested, tumor number was the only variable to be significantly associated with worsening LFI (est. coefficient 0.25, p=0.03; Fig. 1B). 86 patients who received LRT had both pre- and post-treatment LFI scores, with these assessments occurring after a median of 89 and 96 days, respectively. Among these patients, a linear mixed effects model again showed that there was no significant effect of time on LFI (est. coefficient -0.001 per 30 days; p=0.58). MELD (OR 1.14 for each 1 unit increase, p=0.038) and female sex (OR 3.76, p=0.058) were associated with LFI increasing by ≥0.5. **Conclusion:** Our data show that LFI in patients with HCC typically remains stable, implying that patients are overall unlikely to experience substantial decline in functional status during the 6 month waiting period for MELD exception points. Furthermore, LFIs pre- and post-LRT were stable, suggesting that LRT is overall a well-tolerated intervention that does not negatively impact functional status.

A



B

	Estimate	95% CI	p-value
(Intercept)	2.72	(1.21, 4.23)	0.00
30 days time lapsed	0.00	(-0.004, 0.007)	0.59
Female sex	0.19	(-0.16, 0.55)	0.29
Age	-0.01	(-0.03, 0.02)	0.63
Hispanic ethnicity	0.03	(-0.29, 0.36)	0.85
Hypertension	0.19	(-0.10, 0.48)	0.20
Diabetes	0.09	(-0.21, 0.39)	0.55
BMI	0.02	(-0.002, 0.047)	0.07
MELD-Na	0.02	(-0.011, 0.053)	0.21
Number of tumors	0.25	(0.025, 0.46)	0.03
Largest tumor diameter	-0.08	(-0.19, 0.023)	0.13
Prior treatment for HCC	-0.14	(-0.41, 0.13)	0.31

Disclosures: Madeleine Hu: Nothing to Disclose, Steven Chiou: Nothing to Disclose, Molly Delk: Nothing to Disclose, Cynthia Fenton: Nothing to Disclose, Jennifer Lai: Nestle Nutrition Institute: Grant/Research Support, Novo Nordisk: Consultant, Genfit: Consultant, Boehringer Ingelheim: Advisor, Michael Li: Nothing to Disclose

3419 | PERFORMANCE OF THE LI-RADS-BASED MILAN CRITERIA AND ITS PROGNOSTIC IMPLICATION IN POTENTIAL TRANSPLANT CANDIDATES WITH HEPATOCELLULAR CARCINOMA ◆

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[1]*Asan medical center*

Background: Given the limited availability and feasibility for pathologic confirmation of every hepatic lesion, imaging diagnosis is primarily used to assess Milan criteria in candidates for liver transplantation (LT) with hepatocellular carcinoma (HCC). There is little data on the correlation between explant pathology and radiologic measurement based on LI-RADS in determining LT eligibility in HCC patients. This study aimed to investigate the radio-pathologic correlation of Milan criteria using LI-RADS-based diagnosis, and also to identify factors affecting discordance and its prognostic impact. **Methods:** This retrospective study included 267 patients who had any hepatic lesion identified on dynamic liver CT within 3 months prior to LT and/or in the explant livers at Asan Medical Center. Two radiologists reviewed CT examinations, evaluating nodules and the Milan criteria based on

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LI-RADS v2018. Analyses were performed on a per-lesion and per-patient basis, comparing radiologic lesions with their matched pathology. LR-5 or LR-TR-V nodules were regarded as HCC to determine LI-RADS Milan criteria (MC). Overall survival (OS) and recurrence-free survival (RFS) were measured according to LI-RADS MC and pathologic MC, applying a competing risk analysis to 259 patients, excluding cases of in-hospital mortality. **Results:** In per-lesion analysis, among 79 LR-5 lesions and 48 LR-3/LR-4 lesions, 72 lesions (91.1%) and 37 (77.1%) were identified as HCCs, respectively. The 189 LR-TR-V lesions were matched with 176 HCCs (93.1%) in pathology. According to per-patient analysis, an overall concordance rate of 87.3% was presented between LI-RADS MC and pathologic MC. These concordances were not affected by pre-LT chemoembolization and type of LT. The 5-year OS and RFS were significantly greater for patients meeting the MC, compared to the counterparts: 96% vs. 86% and 90% vs. 62% for pathologic MC; and 96% vs. 76% and 90% vs. 45% for LI-RADS MC, respectively (Ps3). When cases meeting LI-RADS MC and pathologic MC were compared, there were no significant differences in OS and RFS. Multivariate Cox-proportional hazard models indicated that being outside LI-RADS MC independently predicted OS and RFS (hazard ratios, 6.51 and 6.34; 95% confidence intervals: 2.37-17.86 and 3.38-11.88, respectively). The presence of nodules other than LR-5/LR-TR-V did not affect survivals. **Conclusion:** The LI-RADS-based radiology presented high concordance and comparable prognostic performance with explant pathology in determining the MC. LT eligibility could likely be judged by CT LI-RADS in patients with HCC.

Disclosures: Yeongseok Hwang: Nothing to Disclose

3420 | STEM CELL GROWTH FACTOR-β AS A PREDICTIVE BIOMARKER OF RESPONSE TO CHEMOTHERAPY AND PROGNOSIS IN PATIENTS WITH ADVANCED-STAGE HEPATOCELLULAR CARCINOMA: A RETROSPECTIVE STUDY

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[1]*Tokyo Metropolitan Cancer and Infectious*

Background: The prognosis for hepatocellular carcinoma (HCC) patients is generally poor. Current treatment protocols, including the combination of atezolizumab (Atz) and bevacizumab (Bev), have shown varying levels of efficacy. Chronic inflammation is known to significantly increase the risk of HCC development. Various serum biomarkers have been investigated to predict treatment outcomes, but specific indicators for chemotherapy response remain underexplored. This study focuses on the potential role of serum stem cell growth factor beta (SCGF-β) as a biomarker for predicting therapeutic response and prognosis in patients with advanced-stage HCC undergoing Atz/Bev combination therapy. **Methods:** This retrospective study analyzed data from patients treated with Atz/Bev at our institution between October 2020 and November 2023. Pre- and post-treatment serum SCGF-β levels were measured and analyzed in relation to treatment outcomes and overall survival (OS). Patients were stratified into three groups based on the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines: partial response (PR), stable disease (SD), and progressive disease (PD). The study included various demographic and clinical characteristics, such as sex, age, etiology, laboratory metrics, and disease classification. Serum levels of 48 different cytokines, chemokines, and growth factors were quantified using a Bio-Plex Pro Human Cytokine Screening 48-Plex Panel. **Results:** Initially, 48 different cytokines, chemokines, and growth factors were quantified in serum samples from 12 healthy volunteers without liver disease and 34 patients with HCC. Before initiating Atz/Bev combination therapy, patients with HCC exhibited significantly elevated serum levels of Eotaxin, HGF, IL-2Ra, IL-8, IL-16, IP-10, M-CSF, MIG, SCF, SCGF-β, and SDF-1α compared with the healthy volunteers. Pearson's correlation analysis revealed a notable distinction in SCGF-β levels; the PD group displayed significantly elevated SCGF-β levels before treatment when compared with the PR group ($p = 0.045$). Analyzing overall survival (OS) with a SCGF-β threshold of 163,295 pg/ml, patients with SCGF-β levels above the cutoff had significantly lower OS than patients with SCGF-β levels below the cutoff level (hazard ratio [HR] 0.448; 95% confidence interval [CI] 0.208–0.965; $P = 0.012$) [Figure 1]. Specifically, the median OS of patients with SCGF-β levels exceeding the 163,295 pg/ml threshold was 12.03 months, whereas patients with SCGF-β levels at or below the 163,295 pg/ml value had a median OS of 28.87 months. **Conclusion:** Our study suggests that serum SCGF-β levels can serve as a predictive marker for treatment response and prognosis in patients with advanced-stage HCC undergoing Atz/Bev combination therapy.

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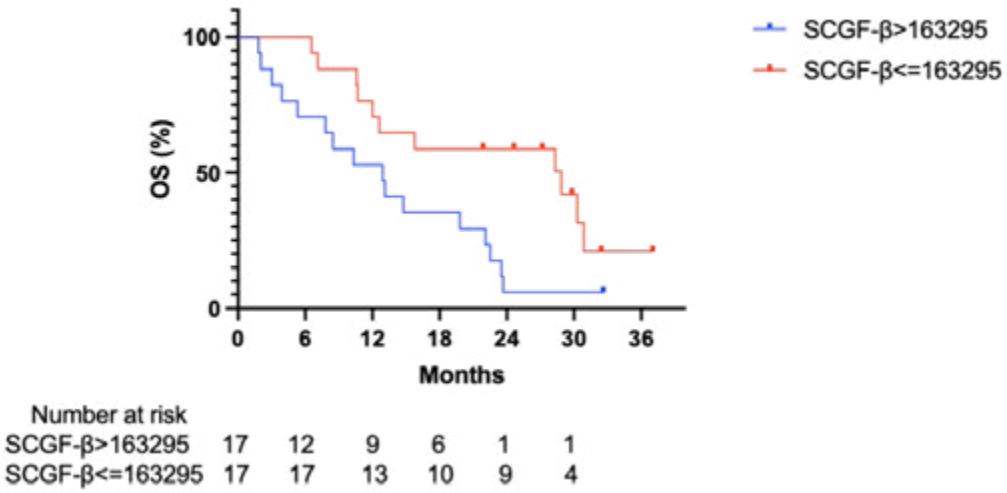

Disclosures: Masamichi Kimura: Nothing to Disclose, Yumi Otoyama: Nothing to Disclose, Jun Imamura: Nothing to Disclose, Kiminori Kimura: Nothing to Disclose

3421 | INVESTIGATION FOR A ROLE OF NON-APOPTOTIC CELL DEATH IN THE DEVELOPMENT OF HEPATOCELLULAR CARCINOMA

Yoshinobu Saito Hayato Hikita[1] Tomoya Hamabe[2] Yoichi Sasaki[2] SHINNOSUKE KUDO[2] Kazuhiro Murai[3] Takahiro Kodama[4] Tetsuo Takehara[4]

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Background: Hepatocyte death is involved in the progression of chronic liver disease. We previously reported that sustained hepatocyte apoptosis is linked to hepatocarcinogenesis, and that non-apoptotic cell death is associated with the progression of metabolic dysfunction-associated steatotic liver disease. However, the role of non-apoptotic cell death in the progression of hepatocellular carcinoma (HCC) remains unclear. Recently, Dfna5 is reported to regulate the secondary necrosis of apoptotic cells, but its role in hepatocyte death and HCC progression has not been elucidated. Therefore, we aim to investigate the significance of non-apoptotic death and the role of Dfna5 in HCC progression. **Methods:** We used siRNA to suppress DFNA5 and induced hepatocyte apoptosis by administering ABT737, a Bcl-xL inhibitor in Huh7, a human HCC cell line. To create hepatocyte-specific Dfna5-deficient mice, we administered AAV8-TBG-Cre into Dfna5 fl/fl mice and then treated them with FasL. We used Alb-Cre Mcl-1 fl/fl (Mcl-1 L-KO) mice as a model of a chronic liver disease, where sustained spontaneous apoptosis leads to hepatocarcinogenesis. Prognostic analysis was conducted using the TCGA-LIHC cohort. **Results:** In Huh7 cells, ABT737 administration led to an increase in caspase-3/7 activity in the supernatant and Dfna5 fragmentation, which is reported to be essential for the induction of secondary necrosis. siRNA-mediated knockdown of Dfna5 did not alter caspase-3/7 activity but decreased LDH activity in the supernatant. Dfna5 L-KO mice exhibit no remarkable phenotype under physiological conditions. After FasL injection to induce apoptosis, L-KO mice had significantly lower serum ALT levels and fewer TUNEL-positive hepatocytes compared to wild-type mice, along with a significant reduction in *Tnfa* expression. Phagocytic cells release inflammatory cytokines, including TNF-α, when engulfing cells undergoing non-apoptotic cell death. To investigate the role of TNF-α, we used Mcl-1 L-KO mice because they also showed an increase in *Tnfa* expression in the liver at 6 weeks of age. Deletion of Kupffer cells using clodronate liposomes completely suppressed *Tnfa* expression in Mcl-1 L-KO mice, suggesting that Kupffer cells engulfed non-apoptotic cells and secrete *Tnfa*. Mcl-1 L-KO mice developed HCC spontaneously in 100% (17/17) in 1.5 years. TNFα KO in Mcl-1 L-KO mice significantly suppressed HCC incidence to 47.8% (11/23) (p=0.0008). There was no significant difference in serum ALT levels or caspase-3/7 activity between hepatocyte-specific Mcl-1 L-KO mice and Mcl-1/TNF double KO mice at 6 weeks of age, indicating no difference in hepatocyte apoptosis. In TCGA-LIHC cohort, patients with high DFNA5 expression had a significantly worse prognosis compared to those with low expression

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(HR=1.72 [1.21-2.44], p=0.002). **Conclusion:** Non-apoptotic cell death is suggested to contribute to the progression of HCC.

Disclosures: Yoshinobu Saito: Nothing to Disclose, Hayato Hikita: Nothing to Disclose, Tomoya Hamabe: Nothing to Disclose, Yoichi Sasaki: Nothing to Disclose, SHINNOSUKE KUDO: Nothing to Disclose, Kazuhiro Murai: Nothing to Disclose, Takahiro Kodama: Chugai Pharmaceuticals: Speaking and Teaching, Astrazeneca: Speaking and Teaching, Eisai Co Ltd: Speaking and Teaching, Tetsuo Takehara: Nothing to Disclose

3422 | PROGNOSTIC VALUE OF COMBINATION OF NEUTROPHIL TO LYMPHOCYTE RATIO AND ALBUMIN- BILIRUBIN GRADE IN PATIENTS WITH HEPATOCELLULAR CARCINOMA UNDERGOING TRANSARTERIAL CHEMOEMBOLIZATION

Young Mi Hong[1] Joo Yeon Jang[2] Hwaseong Ryu[2]

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Background: Transarterial chemoembolization (TACE) is recommended for HCC patients ineligible for curative treatment with heterogeneous outcomes observed in real-world practice. Therefore, determining the prognosis is crucial for managing and planning treatment. In this study, we aimed to develop a new model to predict the prognosis of hepatocellular carcinoma **Methods:** A total of 642 treatment naïve HCC patients undergoing TACE as the initial treatment were included in this study. Factors associated with survival were analysed. Univariate and multivariate analyses were used to determine the risk factors of overall survival (OS). Patients were stratified into high and low neutrophil to lymphocyte ratio (NLR) groups based on the cut-off value using receiver operating characteristic (ROC) analysis. The clinicopathologic characteristics and OS were compared between stratified groups. **Results:** The univariate analysis indicated etiology, Barcelona Clinic Liver Cancer (BCLC) stage, tumor size, tumor number, albumin-bilirubin (ALBI) grade, protein induced by vitamin K absense or antagonist-II and NLR were significant indicators of OS. However, only BCLC stage, ALBI grade and NLR were identified as independent predictors of OS in the multivariable analysis. The combination of NLR and ALBI grade enhances the predictive ability for survival after TACE with an area under the curve (AUC) of 0.645. Patients with higher NLR and ALBI grade showed worse OS compared to those with lower NLR and ALBI grade (p<0.001). **Conclusion:** The combination of NLR-ALBI grade showed a better prognostic performance in patients with HCC treated with TACE. As a simple marker reflecting both systemic immune status and reserve liver function, it provides evidence to help distinguish between patients who will benefit from TACE and those who need a more personalized treatment strategy.

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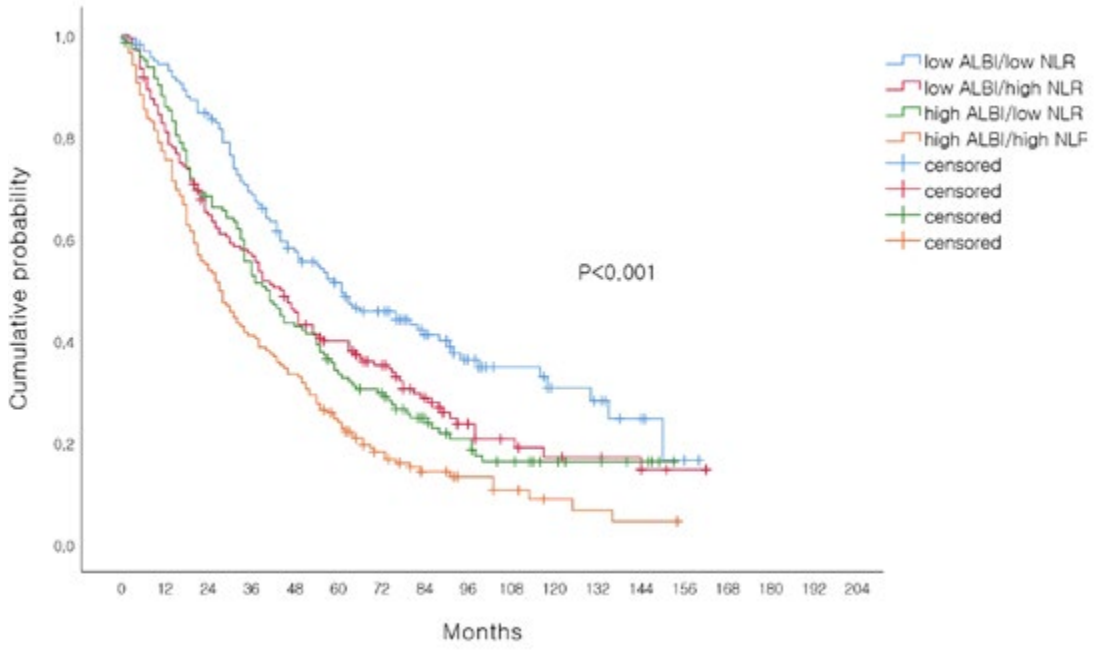

Disclosures: Young Mi Hong: Nothing to Disclose, Joo Yeon Jang: Nothing to Disclose, Hwaseong Ryu: Nothing to Disclose

3423 | REAL-WORLD STUDY OF ADJUVANT THERAPY AFTER COMPLETE RESECTION OF EARLY-STAGE HEPATOCELLULAR CARCINOMA

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[1]Guizhou Provincial People's Hospital, [2]Guizhou Provincial People's Hospital

Background: The recurrence rate after complete surgical resection of early-stage liver cancer can be as high as 50-70% within five years. Current AASLD guidelines recommend postoperative adjuvant therapy for early liver cancer patients with high-risk factors to reduce the risk of postoperative recurrence. However, there is currently a lack of high-quality evidence-based research on high-risk factors, potentially leading to the underestimation of high-risk factors in some patients. This study analyzes real-world data on postoperative adjuvant therapy for early-stage hepatocellular carcinoma, providing new support for the selection of postoperative adjuvant therapy for early liver cancer patients. **Methods:** A retrospective analysis was made on 138 patients with hepatocellular carcinoma (HCC) who underwent complete surgical resection. These patients conformed to a single nodule (stage 0 or stage A) in the BCLC staging system. Patients were stratified based on whether they received postoperative adjuvant therapy, and differences between the recurrence group and non-recurrence group within two years were compared. A COX regression model (SMD) was constructed, and patients were divided into low, moderate, and high-risk groups based on quartile ranges. Recurrence differences after postoperative adjuvant therapy in patients from different risk groups were analyzed using the Kaplan-Meier method (log-rank test). **Results:** Among 138 patients, 42.5% of the patients in the postoperative adjuvant therapy group relapsed, while 64.4% of the patients in the non-postoperative adjuvant therapy group relapsed. Tumor diameter, baseline AFP levels, and sarcopenia were identified as high-risk factors for recurrence within two years in patients with early hepatocellular carcinoma. The risk factors of recurrence in AASLD guidelines can clearly indicate the high-risk group of recurrence, but postoperative adjuvant therapy can increase the recurrence-free survival time (RFS) of high-risk and low-risk patients in our study. while the low-risk group based on the stratification by our cox-model (SMD), the decision to undergo postoperative adjuvant therapy does not affect RFS. However, for patients categorized as moderate or high-risk according to SMD, postoperative adjuvant therapy significantly enhances RFS. **Conclusion:** Following complete surgical resection of early-stage liver cancer, patients categorized as low-risk based on SMD may not require postoperative adjuvant therapy.

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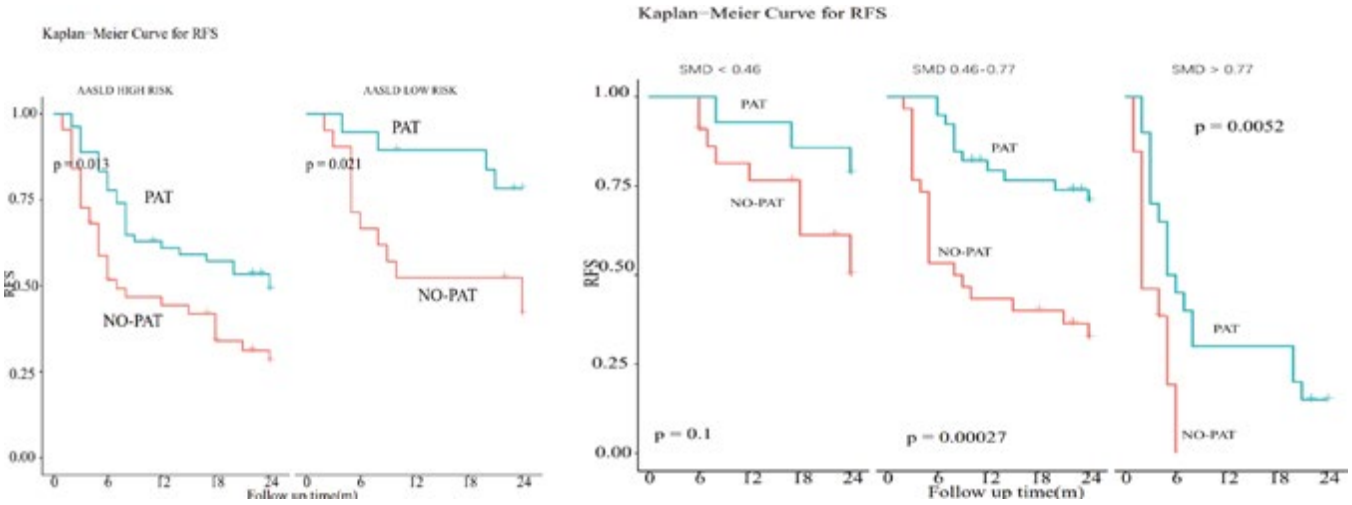

Disclosures: Yue Huang: Nothing to Disclose, Hong Peng: Nothing to Disclose, Siyi Lei: Nothing to Disclose, Qian Zhang: Nothing to Disclose, Qing Zhang: Nothing to Disclose, Li Long: Nothing to Disclose, Xinhuo Luo: Nothing to Disclose

3424 | CAUSAL ASSOCIATION OF CHOLESTEROL METABOLISM-RELATED PROTEINS IN HCC AND MASLD: MENDELIAN RANDOMIZATION AND DRUG REPOSITIONING

Han Zheng[1]

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Background: Abnormal cholesterol metabolism plays a pivotal role in the development of liver diseases such as hepatocellular carcinoma (HCC) and metabolic dysfunction-associated steatotic liver disease (MASLD). The pathogenesis of these diseases is complicated and involves a variety of proteins and signaling pathways. Therefore, an in-depth and sound understanding of the role of cholesterol metabolism-related proteins in HCC and MASLD is of theoretical and practical significance for revealing the molecular mechanism of diseases and finding potential therapeutic targets. **Methods:** An innovative two-sample Mendelian randomization (MR) analysis combined with network-based drug repositioning was used to explore the causal link between cholesterol metabolism-related proteins and HCC or MASLD. Based on the results of MR analysis, we further applied drug repositioning and molecular docking methods to identify potential therapeutic agents targeting HCC and MASLD. For key proteins that had been validated in publicly available datasets, we used bioinformatics methods to further explore their potential value of clinical application from four dimensions: differential expression, patient survival, treatment response, and single-cell analysis. **Results:** A total of 14 proteins were included in MR analysis. By combining the analysis results of two datasets, we confirmed a significant causal association between APOE and HCC (OR: 1.710, 95% CI: 1.220-2.400; P < 0.01), and between APOE and MASLD (OR: 1.490, 95% CI: 1.280-1.740; P < 0.01). Drug repositioning showed that there were some certain drugs with potential therapeutic effects in clinical studies of HCC or MASLD. Molecular docking testified the potential binding efficacy between these drugs and APOE. Compared with that in normal liver tissue, the mRNA expression levels of APOE in HCC samples (TCGA dataset, P < 0.05) or MASLD samples (GEO dataset, P = 0.023) was significantly higher. As for the survival of HCC, patients in the APOE high-expression group had a significantly longer median survival time (log-rank P < 0.05) compared with the low-expression group. Treatment response analysis exhibited that high expression of the APOE gene may indicate stronger stem-cell properties and probable resistance to certain targeted drugs. In single-cell analysis, the APOE gene expression was significantly high in macrophage subsets in both HCC and MASLD group. **Conclusion:** This study reveals the potential roles of cholesterol metabolism-related proteins, especially APOE, in HCC and MASLD. The findings suggest that the upregulation of APOE expression level is associated with the increased risk of these two liver diseases and has a potential causal association. New therapeutic strategies based on drug repositioning and molecular docking technologies would lay a theoretical foundation for future clinical applications.

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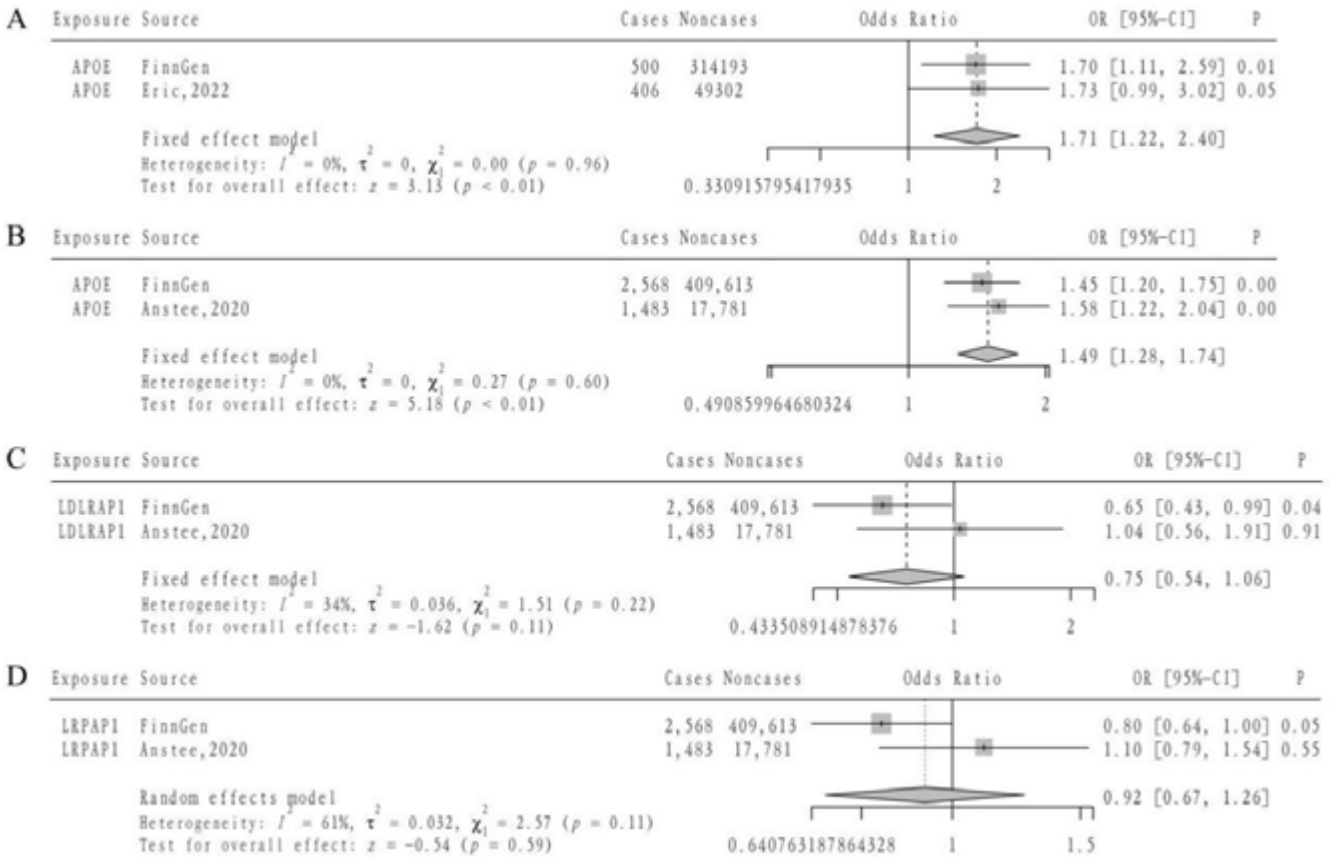

Disclosures: Han Zheng: Nothing to Disclose

3425 | IMPACT OF LOW LEVEL VIREMIA ON THE EFFICACY OF IMMUNE CHECKPOINT INHIBITORS THERAPY IN PATIENTS WITH UNRESECTABLE HEPATOCELLULAR CARCINOMA

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Background: The efficacy of immune checkpoint inhibitors (ICIs) therapy in HBV-related hepatocellular carcinoma (HCC) patients with low level viremia (LLV) remains unclear. This study aimed to explore the impact of LLV on the efficacy of ICIs-based treatment in patients with unresectable HCC (uHCC). **Methods:** We performed a multicenter retrospective cohort study of ICIs-based therapy from January 2019 and December 2022 in patients with uHCC who were seropositive for hepatitis B surface antigen and received nucleos(t)ide analogues antiviral therapy before ICIs involvement. LLV was defined according to either persistent or intermittent episodes of <2,000 IU/mL detectable HBV DNA after 48 weeks of antiviral therapy. **Results:** A total of 329 patients were enrolled in the analysis. The patients had a mean age of 56 years, and 304 (92.4%) were male. The patients were categorized as LLV and maintained virological response (MVR) groups according to their virological response status following antiviral therapy. It was found that the LLV group exhibited lower objective response rate (ORR) and disease control rate (DCR) than the MVR group (21.2% vs. 36.5%, P=0.002; 78.8% vs. 92.5%, P<0.001). Additionally, the LLV group demonstrated shorter median progression-free survival (mPFS) and median overall survival (mOS) than the MVR group (7.6 vs. 12.6 months, P<0.001; 22.8 vs. 40.0 months, P<0.001). Patients with persistent LLV exhibited lower mPFS and mOS compared to those with intermittent LLV (7.1 vs. 7.7 months, P=0.049; 15.7 vs. 25.5 months, P=0.003). Propensity score matching (PSM) was conducted to identified 124 matched pairs of patients with comparable level of gender, age, BCLC stage, cirrhosis and Child-Pugh grade at baseline. The consistent results was demonstrated after PSM (Figure1). Furthermore, multivariate Cox regression

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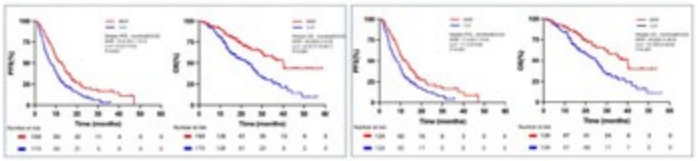
analysis showed that LLV was the independent negative prognostic factor for OS (HR 0.522, 95% CI, 0.348-0.781; P=0.002) after adjusting age, previous treatment, platelet count, Child-pugh grade, baseline HBV DNA load and local regional therapy. **Conclusion:** LLV paly an important role in the anti-tumor efficacy among uHCC patients undergoing ICIs-based treatment.

Table 1. Baseline patient characteristics and tumor response.

Characteristics		Before PSM			After PSM		
		MVR	LLV	*P*	MVR	LLV	*P*
Patients		159	170		124	124	
Male sex		147(92.5)	157(92.4)	0.973	114(91.9)	115(92.7)	1.000
Age≥60 years		65(40.9)	59(34.7)	0.248	46(37.1)	46(37.1)	1.000
ECOG performance[1]				0.174			0.759
	0	122(76.7)	122(71.8)		92(74.2)	95(76.6)	
	1	36(22.6)	42(24.7)		31(25.0)	27(21.8)	
	2	1(0.6)	6(3.5)		1(0.8)	2(1.6)	
Previous treatment		80(50.3)	86(50.6)	0.960	63(50.8)	57(46.0)	0.497
BCLC (C)		103(64.8)	130(76.5)	0.020	86(69.4)	87(70.2)	1.000
Extrahepatic Metastasis		65(40.9)	90(52.9)	0.029	60(48.4)	53(42.7)	0.427
Embolus		64(40.3)	78(45.9)	0.303	48(38.7)	53(42.7)	0.603
Number of tumors ≥2		134(84.3)	137(80.6)	0.380	101(81.5)	101(81.5)	1.000
Tumor diameter ≥10cm		31(19.5)	47(27.6)	0.082	25(20.2)	31(25.0)	0.430
Ascites		39(24.5)	45(26.5)	0.686	29(23.4)	34(27.4)	0.533
Cirrhosis		126(79.2)	132(77.6)	0.725	99(79.8)	96(77.4)	0.749
Diabetes		29(18.2)	29(17.1)	0.779	23(18.5)	22(17.7)	1.000
ALT levels ≥40U/L		51(32.1)	73(42.9)	0.042	48(38.7)	47(37.9)	1.000
Platelet count ≥100x10^9/L		119(74.8)	135(79.4)	0.324	94(75.8)	96(77.4)	0.880
Child-Pugh grade (A)		128(80.5)	139(81.8)	0.770	100(80.6)	100(80.6)	1.000
Serum AFP ≥400ng/ml		53(33.3)	72(42.4)	0.092	42(33.9)	49(39.5)	0.392
HBV DNA ≥2000IU/mL		26(16.4)	44(25.9)	0.035	26(21.0)	27(21.8)	1.000
HBeAg positive		17(10.7)	31(18.2)	0.053	16(12.9)	19(15.3)	0.678
Anti-viral therapy				0.784			0.446
	ETV	105(66.0)	103(60.6)		81(65.3)	72(58.1)	
	TDF	14(8.8)	17(10.0)		12(9.7)	13(10.5)	
	TAF	34(21.4)	43(25.3)		26(21.0)	32(25.8)	
	TMF	6(3.8)	7(4.1)		5(4.0)	7(5.6)	
Local Regional therapy				0.269			0.489
	None	52(32.7)	63(37.1)		44(35.5)	45(36.3)	
	HAIC	43(27.0)	47(27.6)		36(29.0)	34(27.4)	
	TACE	41(25.8)	40(23.5)		29(23.4)	30(24.2)	
	Ablation	15(9.4)	7(4.1)		12(9.7)	9(4.0)	
	Radiotherapy	8(5.0)	13(7.6)		4(3.2)	10(8.1)	
Immune therapy[2]				0.415			0.543
	Camrelizumab	50(31.4)	52(30.6)		35(28.2)	42(33.9)	
	Sintilimab	25(15.7)	35(20.6)		21(16.9)	27(21.8)	
	Tislelizumab	48(30.2)	36(21.2)		37(29.8)	24(19.4)	
	Atezolizumab	12(7.5)	16(9.4)		9(7.3)	11(8.9)	
	Pembrolizumab	10(6.3)	10(5.9)		8(6.5)	6(4.8)	
	Toripalimab	10(6.3)	18(10.6)		10(8.1)	11(8.9)	
	Durvalumab	4(2.5)	3(1.8)		4(3.2)	3(2.4)	
Targeted therapy[3]				0.936			0.553
	Lenvatinib	79(49.7)	88(51.8)		63(50.8)	61(49.2)	
	Sorafenib	15(9.4)	20(11.8)		14(11.3)	11(8.9)	
	Donafenib	14(8.8)	11(6.5)		11(8.9)	8(6.5)	
	Bevacizumab	26(16.4)	25(14.7)		20(16.1)	20(16.1)	
	Apatinib	12(7.5)	10(5.9)		8(6.5)	10(8.1)	
	Anlotinib	9(5.7)	10(5.9)		5(4.0)	10(8.1)	
	Regorafenib	4(2.5)	6(3.5)		3(2.4)	4(3.2)	
Tumor response							
	Partial response (PR)	58(36.5)	36(21.2)		46(37.1)	26(21.0)	
	Stable disease (SD)	89(56.0)	98(57.6)		68(54.8)	72(58.1)	
	Progressive disease (PD)	12(7.5)	36(21.2)		10(8.1)	26(21.0)	
	ORR	58(36.5)	36(21.2)	0.002	46(37.1)	26(21.0)	0.005
	DCR	147(92.5)	134(78.8)	<0.001	114(91.9)	98(79.0)	0.004

Note：[1]: Fisher's exact test, others used χ^2 tests



A: before PSM B: after PSM

Figure.1 PFS and OS curves for the patients

Disclosures: Jinzhang Chen: Nothing to Disclose, Rong Li: Nothing to Disclose, Zhanzhou Lin: Nothing to Disclose, Qing Yang: Nothing to Disclose, Yujuan Guan: Nothing to Disclose, Guosheng Yuan: Nothing to Disclose, Rong Fan: Nothing to Disclose, Jinlin Hou: Nothing to Disclose

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3426 | UTILITY OF THE GAAD ALGORITHM IN HEPATOCELLULAR CARCINOMA SURVEILLANCE AMONG A HIGH-RISK COHORT

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Background: Early HCC diagnosis is essential to improve patients' survival. International guidelines recommend ultrasound (US) surveillance every 6 months for at-risk patients. This US-based strategy has several barriers and limited sensitivity in detecting early-stage tumors. Biomarkers such as AFP, L3-AFP, and DCP (also called PIVKA) support HCC diagnosis. Their diagnostic efficiency is improved (AUROCs >90%) when combined into algorithms as GALAD (Gender, Age, AFP, L3-AFP, DCP) and GAAD (Gender, Age, AFP, DCP). No prospective studies have addressed these algorithms in the surveillance setting. **Methods:** Prospective, 3-year study starting in Feb/2023. Consecutive patients from a tertiary center under HCC surveillance per 2018 EASL Guideline were included. Main exclusion criteria were Child-Pugh C, vitamin K deficiency, pregnancy, and obstructive jaundice. US findings (Canon Aplio i800) were categorized per US LIRADS 2018 as US1: no observation or definitely benign; US2: observation <10 mm not definitely benign; US3: observation ≥10 mm not definitely benign or new thrombus in vein. Visualization limitations were also recorded (no/minimal, moderate, severe). Concurrently with US, AFP, L3-AFP, and DCP were measured (Cobas E-601), and Elecsys® GAAD and GALAD calculated (Roche Dialog; predefined cut-offs in diagnosis [range 0-10]: GAAD <2.57, GALAD <2.47). Patients were followed biannually if US1 and GAAD <2.57, and quarterly if US2 or GAAD ≥2.57. HCC work-up (CT, MRI, and/or biopsy) was performed if US3 category. HCC diagnosis followed 2018 EASL's BCLC criteria. The study was approved by the Ethics Committee. **Results:** Four hundred twenty-two patients were included: mean age 63.2 years, 68% male, 88% white, 81.5% cirrhosis, 18.5% non-cirrhotic HBV (per PAGE-B criteria), BMI 27.3 kg/m². Main etiologies were: HCV (35%), alcohol (28%), MASLD (25%). After a median follow-up of 6.7±5.2 months (range 2-14.8), 18.5% of US were sorted as US2/US3, and 30.3% had moderate/severe limitations; 18.5% had GAAD ≥2.57 and 19.7% had GALAD ≥2.47. Twelve HCC cases were diagnosed: 9 (75%) BCLC-0/A, 1 (8.3%) BCLC-B, and 2 (16.7%) BCLC-C. For BCLC-0/A patients, US sensitivity was 77.8%. Biomarkers and GAAD/GALAD were independently associated with HCC (p≤0.001). Performance data are shown in Table 1. US1 category combined with GAAD <2.57 had a 100% NPV. **Conclusion:** Our results suggest a high performance of GAAD and GALAD in HCC surveillance. The simpler GAAD algorithm shows similar efficacy to GALAD.

Table 1	AUROC (CI95%)	P	Sens (%)	Sp (%)	PPV (%)	NPV (%)
Full set						
AFP	0.78 (0.65 - 0.91)	0.001	41.7	100	100	98.3
L3-AFP	0.76 (0.59 - 0.94)	0.002	41.7	98.3	41.7	98.3
DCP/PIVKA	0.89 (0.82 - 0.98)	<0.001	91.7	69.1	8.1	99.6
GAAD	0.96 (0.92 - 0.99)	<0.001	91.7	83.7	14.3	99.7
GALAD	0.96 (0.92 - 0.99)	<0.001	91.7	82.4	13.4	99.7
BCLC 0/A						
AFP	0.72 (0.57 - 0.85)	0.032	22.2	100	100	98.3
L3-AFP	0.69 (0.47 - 0.91)	0.050	33.3	98.3	30	98.5
DCP/PIVKA	0.88 (0.77 - 0.99)	<0.001	88.9	69.1	6	99.6
GAAD	0.95 (0.90 - 0.99)	<0.001	88.9	83.7	10.7	99.7
GALAD	0.94 (0.90 - 0.98)	<0.001	88.9	82.4	10.1	99.7

ULN: AFP <20 ng/mL, L3-AFP <2.3 ng/mL, DCP/PIVKA <28.4 ng/mL, GAAD <2.57, GALAD <2.47.

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Disclose, Irene González: Nothing to Disclose, Carmen Amor: Nothing to Disclose, Clara Amiama: Nothing to Disclose, Rafael Gayoso: Nothing to Disclose, Paula Torrijos: Nothing to Disclose, Alberto Cerpa: Nothing to Disclose, Rubén Fernández-Martos: Nothing to Disclose, Yolanda Zarauza: Nothing to Disclose, Patricia Mayor: Nothing to Disclose, Marta Cuadros: Nothing to Disclose, María Sánchez-Azofra: Nothing to Disclose, José Erdozain: Nothing to Disclose, Miriam Romero: Nothing to Disclose, Pilar Castillo: Nothing to Disclose, Araceli García-Sánchez: Nothing to Disclose, Francisco García-Samaniego: Nothing to Disclose, Susana Cano: Nothing to Disclose, Verónica Ucle: Nothing to Disclose, Sonia Álvarez: Nothing to Disclose, Mariana Serres: Nothing to Disclose, María Sanz de Pedro: Nothing to Disclose, Antonio Buño: Nothing to Disclose, Antonio Olveira: Roche: Grant/Research Support, Canon: Speaking and Teaching

3428 | IDENTIFICATION OF ITGB2 AS A NOVEL MHC-II NEOANTIGEN USING HEPATOCELLULAR CARCINOMA ORGANOIDS

Deyuan Zhong[1] *Jin Shang*[1] *Yuxin Liang*[1] *Xiaolun Huang*[1] *Hongtao Yan*[1]

[1]*Sichuan cancer hospital*

Background: Immunotherapy has achieved breakthrough in hepatocellular carcinoma (HCC). Representatively, immune checkpoint inhibitors (ICIs) form the basis of HCC anti-tumor therapy. Recently, neoantigens emerged as promising immunotherapeutic targets to overcome the immune suppressive microenvironment. However, neoantigens had not been clearly identified in HCC. The aim of this study was to discovery and validate HCC neoantigens. **Methods:** Fresh tissues from HCC patients were obtained for organoid establishment. Next, combination of proteomic analysis and HLA affinity prediction was performed to discovery potential neoantigens using exosomes from tumor organoids and normal liver organoids. At last, the immunogenicity of specific neoantigen was verified via in vivo and vitro experiments. **Results:** Tumor organoids and matched normal liver organoids from 3 HCC patients were firstly established, autologous killing assay showed that HCC organoid-derived exosomes could significantly activate immune cells. Next, proteomic analysis results showed that differential expression proteins mainly participated in immune-related processes such as MHC class II receptor binding, CD4 receptor binding, antigen processing and presentation. Next, among the potential neoantigens via netMHC software analysis, ITGB2 showed high MHC-II affinity. Moreover, ITGB2 showed significantly immune activation effect and prognosis predictive value in TCGA cohort database.In further validation experiments, ITGB2 loaded DCs could enhance the cytotoxicity of effector T cells when co-culturing with autologous primary liver cancer cells. Consistently, ITGB2 loaded DCs could also control the tumor growth in hu-PBMC SCID mice. In regard to concrete mechanism of ITGB2 on $CD4^+$ T cells. Cytometric bead array results showed that ITGB2 loaded DCs could increase the release of Th1 $CD4^+$ T cells specific cytokines including IL-2, IL-1β, TNF-α and IFN-γ. Peripheral bloods collected from hu-PBMC SCID mice were also analyzed via flow cytometry. results showed that ITGB2 loaded DCs significantly improve $CD4^+$ T cell infiltration, with a higher expression of Th1 polarization. These results showed that ITGB2 could enhance anti-tumor immunity via activating Th1 polarization of $CD4^+$ T cells. **Conclusion:** Our study revealed a HCC neoantigen landscape via tumor organoid application. HCC organoid-derived exosomes enriched neoantigens such as ITGB2 and exhibited anti-tumor immunogenicity. Furthermore, our study identified ITGB2 as a novel MHC-II neoantigen and verified its activation effect on Th1 polarization of $CD4^+$ T cells. These findings suggested that the therapeutic potential of MHC-II neoantigen ITGB2 is worth exploring in tumor vaccine or ICIs combination therapy.

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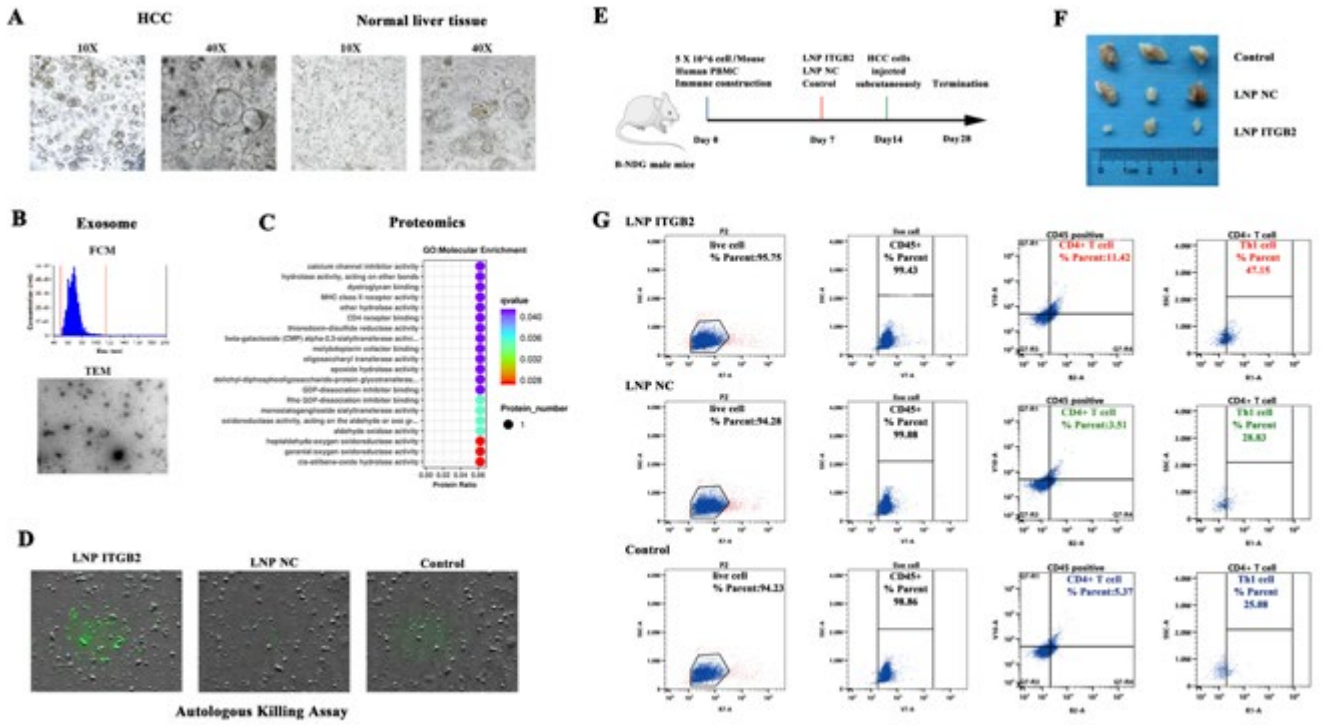

Disclosures: Deyuan Zhong: Nothing to Disclose, Jin Shang: Nothing to Disclose, Yuxin Liang: Nothing to Disclose, Xiaolun Huang: Nothing to Disclose, Hongtao Yan: Nothing to Disclose

3429 | PERIPHERAL BLOOD INFLAMMATORY SCORE USING A CYTOKINE MULTIPLEX ASSAY PREDICTS CLINICAL OUTCOMES IN UNRESECTABLE HCC PATIENTS TREATED WITH ATEZOLIZUMAB/BEVACIZUMAB

Hee Sun Cho[1] *Ji Won Han*[1]

[1]*The Catholic University of Korea*

Background: Several serum cytokines have been proposed as biomarkers for predicting outcomes in hepatocellular carcinoma (HCC) patients receiving tyrosine kinase inhibitors. However, their role in Atezolizumab/Bevacizumab (AB) treatment is unclear. **Methods:** We examined serum cytokines, including interferon-γ (IFN-γ), interleukin-10 (IL-10), IL-12, IL-17, IL-2, IL-6, and tumor necrosis factor (TNF), using a Luminex cytokine multiplex assay before AB treatment in prospectively-enrolled 116 AB-treatment patients. We collected baseline characteristics, including neutrophil-lymphocyte ratio (NLR) and C-reactive protein (CRP), and prospectively observed clinical outcomes. **Results:** Among various peripheral blood inflammatory markers, high NLR, CRP, IL-2, and IL-12 were significantly associated with poor progression-free survival (PFS) and overall survival (OS). Optimal cut-offs identified by Cox-regression analysis were as follows; NLR >3.5, CRP >0.13 mg/dL, IL-2 >3.2 pg/mL, and IL-12 >11.6 pg/mL. With the sensitivity analysis, we could define a high peripheral blood inflammatory score (PBIS) group who had 2 or more factors among high NLR, CRP, IL-2, and IL-2. High PBIS was an independent risk factor associated with poor OS, PFS, and objective response rate (ORR) in the multivariate analyses. However, it was not a predictive factor regarding OS, PFS, and ORR in lenvatinib-treated patients. The low PBIS group (n=54) showed 1-year OS, median PFS, and ORR of 76.5%, 297 days, and 37.0%, whereas the high PBIS group (n=62) showed 1-year OS, median PFS, and ORR of 47.7%, 97 days, and 17.7%, respectively. **Conclusion:** These results suggest that the cytokine-multiplex assay-based scoring system significantly predicts clinical outcomes in AB-treated HCC patients. This non-invasive blood base biomarker needs to be validated in multicenter, large-sized cohorts.

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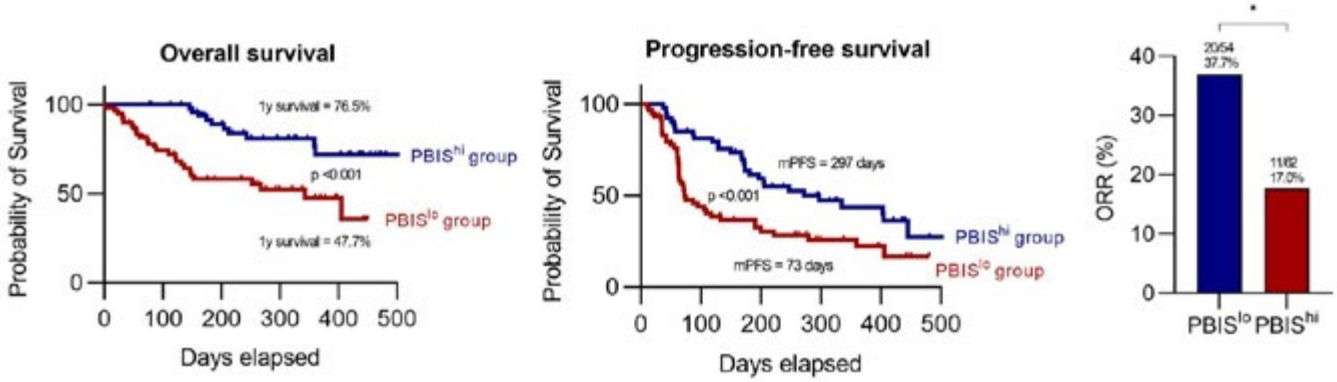

Disclosures: Hee Sun Cho: Nothing to Disclose, Ji Won Han: Nothing to Disclose

3430 | CHANGES IN BRIDGING THERAPY FOR HEPATOCELLULAR CARCINOMA (HCC) BY REGION IN THE U.S. FROM 2018-2023:

Parth Patel[1] Abdulrahman Alhajahjeh[2] Francis Nugent[1] Alyson Kaplan[1] Ahmed Abdulelah[3] Mohammad Almeqdadi[1] Fredric Gordon[4]

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Background: Bridging therapies (BTs) are standard care for patients with hepatocellular carcinoma (HCC) awaiting liver transplantation (LT). This study examines the evolution of BT utilization across the United States (US) over the past five years. **Methods:** Data from the United Network of Organ Sharing (UNOS) database (2018-2023) was analyzed to assess changes in the use of thermal ablation (ABL), transarterial radioembolization (TARE), and transarterial chemoembolization (TACE) across U.S. regions, patient characteristics, and over time. **Results:** Of the 7,754 patients identified with BTs, 4,787 (61.7%) received LT. The median age was 64 years, 24.7% were female, and 62.0% were white non-Hispanic. Median tumor size was 2.6 cm2 (IQR 2.10-3.60), and 10.4% had multifocal disease. The median time from BTs to LT was 9.6 months (IQR 6.4-14.5). TARE use increased significantly from 21.1% in 2018 to 41.3% in 2023 (p<0.001), while TACE decreased from 35.7% to 25.6% (p<0.001) and ABL from 43.2% to 33.1% (p<0.001). TARE was more common in tumors >3 cm2 (53.4% vs. 40.5% TACE, 29.2% ABL, p<0.001). TACE was more frequent in multifocal disease (12.7% vs 10.2% TARE, 8.69% ABL, p<0.001). Median time to LT was shorter with TACE (8.9 months vs. 9.3 TARE, 10.5 ABL, p<0.001). Significant regional variation in BT utilization was observed. (Figure 1). **Conclusion:** Despite BTs being standard care for HCC before LT, their utilization patterns across U.S. regions, patient subgroups, and temporal trends have been understudied. A clear rise in TARE use across all regions has been identified, but the impact on overall patient survival warrants further investigation.

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Table: General Characteristics and Univariable difference between different bridging therapy.

	Total N=7754	Chemoembolization *N=2283*	Radiation microspheres *N=2411*	Thermal ablation *N=3060*	P-value
Time from BT to transplant	288 [192;434]	266 [180;382]	280 [188;416]	316 [206;486]	**<0.001**
Size:					**<0.001**
Smaller Than 2 Cm	436 (9.89%)	132 (10.6%)	103 (7.48%)	201 (11.3%)	
Between 2-3	2209 (50.1%)	611 (48.9%)	538 (39.1%)	1060 (59.5%)	
Larger Than 3 Cm	1763 (40.0%)	506 (40.5%)	736 (53.4%)	521 (29.2%)	
Age	64.0 [59.0;68.0]	64.0 [59.0;67.0]	65.0 [60.0;68.0]	64.0 [59.0;68.0]	**<0.001**
ETHCAT:					**0.043**
White, non-Hispanic	4808 (62.0%)	1396 (61.1%)	1531 (63.5%)	1881 (61.5%)	
Black, non-Hispanic	489 (6.31%)	147 (6.44%)	143 (5.93%)	199 (6.50%)	
Hispanic/Latino	1781 (23.0%)	566 (24.8%)	528 (21.9%)	687 (22.5%)	
Asian, non-Hispanic	565 (7.29%)	135 (5.91%)	180 (7.47%)	250 (8.17%)	
Amer Ind/Alaska Native, Non-Hispanic	53 (0.68%)	18 (0.79%)	14 (0.58%)	21 (0.69%)	
Native Hawaiian/other Pacific Islander, Non-Hispanic	18 (0.23%)	8 (0.35%)	4 (0.17%)	6 (0.20%)	
Multiracial, Non-Hispanic	39 (0.50%)	13 (0.57%)	10 (0.41%)	16 (0.52%)	
Regions:					**<0.001**
Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, Eastern Vermont	386 (4.98%)	76 (3.33%)	66 (2.74%)	244 (7.97%)	
Delaware, District of Columbia, Maryland, New Jersey, Pennsylvania, West Virginia, Northern Virginia	851 (11.0%)	368 (16.1%)	158 (6.55%)	325 (10.6%)	
Alabama, Arkansas, Florida, Georgia, Louisiana, Mississippi, Puerto Rico	904 (11.7%)	243 (10.6%)	405 (16.8%)	256 (8.37%)	
Oklahoma, Texas	1089 (14.0%)	350 (15.3%)	230 (9.54%)	509 (16.6%)	
Arizona, California, Nevada, New Mexico, Utah	1583 (20.4%)	437 (19.1%)	473 (19.6%)	673 (22.0%)	
Alaska, Hawaii, Idaho, Montana, Oregon, Washington	259 (3.34%)	57 (2.50%)	96 (3.98%)	106 (3.46%)	
Illinois, Minnesota, North Dakota, South Dakota, Wisconsin	681 (8.78%)	138 (6.04%)	324 (13.4%)	219 (7.16%)	
Colorado, Iowa, Kansas, Missouri, Nebraska, Wyoming	415 (5.35%)	173 (7.58%)	101 (4.19%)	141 (4.61%)	
New York, Western Vermont	531 (6.85%)	117 (5.12%)	216 (8.96%)	198 (6.47%)	
Indiana, Michigan, Ohio	439 (5.66%)	121 (5.30%)	162 (6.72%)	156 (5.10%)	
Kentucky, North Carolina, South Carolina, Tennessee, Virginia	616 (7.94%)	203 (8.89%)	180 (7.47%)	233 (7.61%)	

Disclosures: Parth Patel: Nothing to Disclose, Abdulrahman Alhajahjeh: Nothing to Disclose, Francis Nugent: Nothing to Disclose, Alyson Kaplan: Nothing to Disclose, Ahmed Abdulelah: Nothing to Disclose, Mohammad Almeqdadi: Nothing to Disclose, Fredric Gordon: Allurion Technologies: Stock - publicly traded company, Gilead Pharmaceuticals: Speaking and Teaching, Ipsen: Speaking and Teaching, Ipsen: Consultant, Madrigal: Speaking and Teaching

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3432 | REDUCTION IN HEPATOCELLULAR CARCINOMA RISK WITH SGLT2 INHIBITORS IN PATIENTS WITH CO-EXISTING HEPATITIS C AND TYPE 2 DIABETES: A GLOBAL MULTICENTER PROPENSITY-MATCHED STUDY

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Background: Chronic Hepatitis C infection (CHC) and Diabetes Mellitus Type 2 (T2DM) are independent risk factors for the development of Hepatocellular Carcinoma (HCC). Preclinical studies suggest that Sodium-glucose cotransporter-2 receptor inhibitors (SGLT2i) regulate pathways implicated in HCC progression and may inhibit oncogenesis. However, clinical studies are lacking. Using a large research network, this study aimed to evaluate the effect of SGLT2i on the incidence of HCC in patients with concomitant T2DM and CHC. **Methods:** In this retrospective cohort study and time-to-event analysis, we utilized the TriNetX electronic health records network, encompassing over 120 million patients from January 1, 2005, to December 31, 2022. We included patients aged 18 years or older diagnosed with co-existing T2DM and chronic hepatitis C who had received either previous or current antiviral treatment. Patients with and without SGLT2 inhibitor treatment were matched using propensity scores for age, gender, race, comorbidities, liver-related characteristics, BMI, and background medications. Patients with a prior history of HCC, liver transplant, type 1 diabetes mellitus, or end-stage renal disease were excluded. Using a Cox proportional hazards regression model, we evaluated the association between SGLT2i use and the incidence of HCC in both groups. **Results:** We identified 1,478 patients in the SGLT2i group and 14,044 patients in the non-SGLT2i group. A total of 1,448 patients were included after propensity matching from both groups. Table 1 contains the baseline demographics, comorbid conditions, and baseline medications before and after propensity matching. The incidence of HCC was 6.63% in the SGLT2i group vs. 10.42% in the non-SGLT2i group (RR = 0.64, 95% CI(0.49–0.81), P<0.01). This association remained significant regardless of age, gender, ethnicity, diabetes, hypertension, cirrhosis, and background diabetic medications (metformin, sulfonylurea, glitazone, DPP4i,alpha-glucosidase inhibitors, glucagon-like peptide 1 receptor agonists, and insulin). **Conclusion:** Based on a large global retrospective study of patients with co-existing CHC and T2DM, SGLT2i use was associated with a significantly lower risk of HCC. However, confirmation through future large-scale prospective studies is required.

Baseline Characteristics

	Before propensity matching			After propensity matching		
	SGLT2i Group (N=1478)	non-SGLT2i Group (N=14044)	P value	SGLT2i Group (N=1448)	non-SGLT2i Group (N=1448)	P value
Characteristics:						
Age, y, mean ± SD	60.69 ± 8.71	59.37 ± 8.90	<0.01	60.66 ± 8.73	60.37 ± 8.42	0.72
Male, n(%)	944 (63.87%)	8827 (62.85%)	0.44	922 (63.67%)	941 (64.99%)	0.46
Female, n (%)	520 (35.18%)	5043 (35.91%)	0.58	512 (35.36%)	493 (34.05%)	0.46
Race, n (%)						
White	626 (42.36%)	6383 (45.45%)	0.02	614 (42.4%)	638 (44.06%)	0.37
Black or African American	505 (34.17%)	4758 (33.88%)	0.82	497 (34.32%)	446 (30.8%)	0.04
Hispanic or Latino	160 (8.01)	49 (5.81)	0.04	60 (7.11)	49 (5.81)	0.28
Unknown Race	280 (18.90%)	2223 (15.80%)	0.01	272 (18.80%)	302 (20.90%)	0.16
Comorbid Conditions:						
Hypertensive diseases	1266 (85.66%)	10125 (72.1%)	<0.01	1236 (85.36%)	1227 (84.74%)	0.64
Disorders of lipoprotein metabolism and other lipidemias	974 (65.9%)	5639 (40.15%)	<0.01	948 (65.47%)	794 (54.83%)	0.77
Cirrhosis of liver	697 (47.16%)	6227 (44.34%)	0.04	684 (47.24%)	637 (43.99%)	0.08
Overweight and obesity	662 (44.79%)	4060 (28.91%)	<0.01	642 (44.34%)	504 (34.81%)	0.82
Chronic lower respiratory diseases	550 (37.21%)	4331 (30.84%)	<0.01	530 (36.6%)	527 (36.4%)	0.91
Ischemic heart diseases	533 (36.06%)	2971 (21.16%)	<0.01	517 (35.7%)	450 (31.08%)	0.01
Heart failure	405 (27.4%)	1689 (12.03%)	<0.01	379 (26.17%)	402 (27.76%)	0.34
Alcoholic liver disease	133 (9%)	1542 (10.98%)	0.02	129 (8.91%)	135 (9.32%)	0.70
Medications:						
Insulins	966 (65.36%)	5651 (40.24%)	<0.01	937 (64.71%)	951 (65.68%)	0.58
Biguanides	1080 (73.07%)	5446 (38.78%)	<0.01	1053 (72.72%)	1022 (70.58%)	0.20
Sulfonylureas	594 (40.19%)	2476 (17.63%)	<0.01	577 (39.85%)	571 (39.43%)	0.82
Dipeptidyl peptidase 4 (DPP-4) inhibitors	356 (24.09%)	1062 (7.56%)	<0.01	345 (23.83%)	362 (25%)	0.46
Glucagon-like peptide-1 (GLP-1) analogues	328 (22.19%)	486 (3.46%)	<0.01	298 (20.58%)	276 (19.06%)	0.31
Thiazolidinediones	114 (7.71%)	349 (2.49%)	<0.01	107 (7.39%)	111 (7.67%)	0.78

Disclosures: Abdullah Sohail: Nothing to Disclose, Mujtaba Bhinder: Nothing to Disclose, Aysha Aslam: Nothing to Disclose, Ammad Chaudhary: Nothing to Disclose, Kyle Brown: Nothing to Disclose

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3433 | SYSTEMIC IMMUNE PROFILING IDENTIFIES PREDICTIVE BIOMARKERS FOR RESPONSE TO COMBINATION IMMUNOTHERAPY IN HEPATOCELLULAR CARCINOMA

Akira Nishio[1] Takahiro Kodama[1] Kazuki Maesaka[1] Kazuma Daiku[1] Akira Doi[1] Yuki Tahata[1] Kazuhiro Murai[1] Hayato Hikita[1] Tomohide Tatsumi[1] Tetsuo Takehara[1]

[1]Osaka University

Background: Immune checkpoint inhibitors have revolutionized therapy for advanced hepatocellular carcinoma (HCC). Two combination immunotherapy regimens, Atezolizumab plus Bevacizumab (Atez/Bev) and Durvalumab plus Tremelimumab (Dur/Tre), are approved as first-line therapy. However, precise immune characteristics correlating with clinical response remain elusive. This study investigates the systemic immune response in HCC patients receiving combination immunotherapy using single-cell RNA sequencing (scRNAseq). **Methods:** Peripheral blood mononuclear cells (PBMCs) were collected before or at 6 weeks after starting combination immunotherapy in HCC patients from a multicenter study. scRNAseq and single-cell T cell receptor (TCR) sequencing were conducted on 20 PBMC samples from 5 responders and 5 non-responders to Atez/Bev, and 14 PBMC samples from 4 responders and 5 non-responders to Dur/Tre. UMAP clustering and cell type annotation, differentially expressed genes, and TCR repertoire diversity were analyzed. **Results:** 231,383 cells from 20 PBMC samples of 10 Atez/Bev-treated patients were clustered into 24 subpopulations. Responders had a higher frequency of LEF1+CD4T cells at pretreatment, while non-responders had a higher frequency of LYZ+monocytes at both pretreatment and during therapy. CD8T cell clusters were not significantly different between the two groups, but gene ontology analysis revealed higher CD8T cell activation in responders at pretreatment. Responders showed greater expression of cytotoxicity-associated genes before therapy, whereas non-responders had increased expression of T cell exhaustion-related genes post-therapy. TCR repertoire diversity in CD8T cells decreased upon Atez/Bev therapy in responders. In Dur/Tre-treated patients, none of the phenotypes observed in Atez/Bev responders were present. The ratio of LEF1+CD4T cells to LYZ+monocytes stratified progression-free survival (PFS) during Atez/Bev treatment. Patients with a higher ratio had longer PFS with Atez/Bev compared to Dur/Tre, but not in those with a lower ratio. **Conclusion:** The immune cells in peripheral blood may represent distinct immune profiles between responders and non-responders in HCC patients receiving Atez/Bev therapy, which could be used to stratify combination immunotherapies.

Disclosures: Akira Nishio: Nothing to Disclose, Takahiro Kodama: Chugai Pharmaceuticals: Speaking and Teaching, Astrazeneca: Speaking and Teaching, Eisai Co Ltd: Speaking and Teaching, Kazuki Maesaka: Nothing to Disclose, Kazuma Daiku: Nothing to Disclose, Akira Doi: Nothing to Disclose, Yuki Tahata: Nothing to Disclose, Kazuhiro Murai: Nothing to Disclose, Hayato Hikita: Nothing to Disclose, Tomohide Tatsumi: Nothing to Disclose, Tetsuo Takehara: Nothing to Disclose

3434 | PHASE I CLINICAL TRIAL OF ADJUVANT THERAPY UTILIZING SIX TUMOR-ASSOCIATED ANTIGEN-DERIVED PEPTIDES AND AUTOLOGOUS DENDRITIC CELLS FOR HEPATOCELLULAR CARCINOMA

Hidetoshi Nakagawa[1] Hidenori Kido[1] Noboru Takata[1] Takeshi Terashima[1] Eishiro Mizukoshi[1] Taro Yamashita[1]

[1]Kanazawa University

Background: We have previously discovered that anti-tumor immunity is induced by radiofrequency ablation (RFA) (Mizukoshi et al. Hepatology 2013). Moreover, we have reported that combining dendritic cell vaccination therapy with RFA can lead to clinical benefit (Kitahara et al., Transl Oncol. 2020). Additionally, based on the extension of recurrence-free survival observed in cases showing tumor antigen-specific immune responses (Mizukoshi et al., Nat Commun. 2022; Nakagawa et al. AASLD TLM, 2024), we are currently developing dendritic cell therapy incorporating antigen peptides. In this study, we evaluated the feasibility, safety, and immune responses of immunotherapy using dendritic cells loaded with a mixture of six tumor-associated antigen-derived peptides. **Methods:** Monocyte-derived autologous dendritic cells pulsed with six antigen peptides ($SART2_{889}$, $SART3_{109}$, $MRP3_{765}$, AFP_{403}, AFP_{357}, $hTERT_{461}$) were prepared as regenerative medical products using GM-CSF, IL-4, and OK-432, then subcutaneously administered three times at 2-week intervals to patients with hepatocellular carcinoma who underwent RFA. The primary endpoint was the occurrence of severe adverse events, while secondary endpoints included recurrence-free survival, immune responses, and adverse events.

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The planned enrollment was 6 cases with HLA-A24. **Results:** Six cases were enrolled, comprising 2 females and 4 males, with a median age of 69 years (range: 47–80 years). All cases were recurrent with previous HCV infection or HBV infection (5 cases and 1 case, respectively), including cirrhosis in 5 cases and chronic hepatitis in 1 case. The median interval from RFA to the first administration of dendritic cells was 27 days. A Grade 4 cerebrovascular ischemia (lacunar infarction) requiring hospitalization was observed during the protocol treatment in 1 case who fully recovered. The causality with the treatment was denied. The median follow-up period was 526.5 days, with recurrence observed in 2 cases. Other severe adverse events were not observed, while Grade 2 or lower fever, fatigue, and injection site reactions were observed in 1, 3, and 5 cases, respectively. Delayed-type skin reactions were performed in 4 cases both before and after treatment, with enhancement of reactions observed in all 4 cases. IFNγ-ELISpot assay revealed immune inductions of at least one peptide were detected in four out of five patients. **Conclusion:** We confirmed the feasibility, safety, and induction of immune responses with dendritic cell vaccination with six tumor-associated antigen-derived peptides. Future studies will involve further clinical trials testing the efficacy of the treatment.

Disclosures: Hidetoshi Nakagawa: Nothing to Disclose, Hidenori Kido: Nothing to Disclose, Noboru Takata: Nothing to Disclose, Takeshi Terashima: Nothing to Disclose, Eishiro Mizukoshi: Nothing to Disclose, Taro Yamashita: Nothing to Disclose

3435 | DISRUPTION OF FGL2 INDUCED TFEB-DEPENDENT LYSOSOMAL DEGRADATION OF PD-L1 AND ENHANCED THE EFFICACY OF ANTI-PD-1 THERAPY IN HEPATOCELLULAR CARCINOMA

Meiwen Han[1] Qianting Guan[2] Fangfei Yan[2] Qinghao Guo[2] Ming Wang[2] Dong Xi[2] Qin Ning[2]

[1]Tongji Hospital, Tongji Medical College, HUST, [2]Tongji Hospital, Tongji Medical College

Background: Tumor cells evaded T cell-mediated immune surveillance via ligation of programmed death-1 ligand 1 (PD-L1) on tumor cells to programmed cell death-1 (PD-1) expressed on T cells. Immune checkpoint blockade (ICB) therapies targeting PD-1 and PD-L1 have been approved for several cancers, with durable clinical benefit. However, the majority of patients with hepatocellular carcinoma (HCC) are unresponsive, which highlight the need to investigate the molecular regulation of PD-L1. **Methods:** Gene expression profiling interactive analysis (GEPIA) was used to analyze the correlation between fibrinogen-like protein 2 (FGL2) and immune checkpoints in liver cancer patients. Loss- and gain-of-function approaches were employed to investigate the impact of FGL2 on the regulation of PD-L1 expression and associated molecular pathways in Huh7 and MHCC97H cell lines. Hepa1-6 cells were inoculated subcutaneously or orthotopically in C57BL/6J wild type (WT) mice and fgl2 gene knockout ($fgl2^{-/-}$) mice, and combined interference with antibody against PD1 and FGL2 was investigated. Growth of tumors was measured, and tumor tissues were separated for further analysis by flow cytometry. **Results:** In liver cancer patients, GEPIA database showed that FGL2 was significantly positively correlated with PD1, PD-L1, programmed cell death ligand 2 (PD-L2) and cytotoxic T lymphocyte-associated protein 4 (CTLA4). In mouse models, the growth of transplanted hepatomas was inhibited in $fgl2^{-/-}$ mice and those treated with FGL2 antibody. In the tumor microenvironment, PD-L1, PD-L2 expression on tumor cells and PD1, CTLA4 expression on T cells were significantly lower in $fgl2^{-/-}$ mice than those in WT mice ($P<0.05$). Mechanistically, FGL2 deficiency remarkably increased the level of nuclear transcription factor EB (TFEB), thus promoting lysosome biogenesis and the degradation of PD-L1 in tumor cells. Furthermore, compared with anti-PD-1 monotherapy, combined interference with antibody against PD1 and FGL2 showed synergistic antitumor effects in the mouse HCC models. Histologically, flow cytometric analysis revealed up-regulated expression of interferon-γ and down-regulated expression of PD1, CTLA4 on $CD8^+$ T cells, along with reduced expression of CTLA4 on regulatory T cell in combined interference. **Conclusion:** FGL2 promoted the progression of HCC by mediating TFEB dependent lysosomal degradation of PD-L1 in tumor cells. Interventions targeting against FGL2 might enhance the effectiveness of anti-PD-1 treatment for HCC.

Disclosures: Meiwen Han: Nothing to Disclose, Qianting Guan: Nothing to Disclose, Fangfei Yan: Nothing to Disclose, Qinghao Guo: Nothing to Disclose, Ming Wang: Nothing to Disclose, Dong Xi: Nothing to Disclose, Qin Ning: Nothing to Disclose

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3436 | SOLUBLE FGL2-FC&GAMMA;RIIB AXIS DRIVED MEMORY CD8+ T CELLS DYSFUNCTION IN HEPATOCELLULAR CARCINOMA

Qianting Guan[1] Meiwen Han[1] Fangfei Yan[1] Qinghao Guo[1] Ming Wang[1] Dong Xi[1] Qin Ning[2]

[1]Tongji Hospital, Tongji Medical College, [2]Huazhong University of Science and Technology

Background: Soluble fibrinogen-like protein 2 (sFGL2), a pro-cancer molecule, expressed at high levels in tumor tissues and peripheral blood of patients with hepatocellular carcinoma (HCC). sFGL2 significantly reduced the activity of dendritic cells and suppressed $CD8^+$ T cells subsequently, thereby dampening anti-tumor immunity. FcγRIIB, receptor of sFGL2, was expressed on memory $CD8^+$ T cells and promoted the growth of melanoma. However, the features of FcγRIIB expression and direct inhibitory effects of sFGL2 on $CD8^+$ T cells in HCC remained unclear. Here, our aim is to elucidate the role of FcγRIIB, specifically sFGL2-FcγRIIB axis, in directly suppressing memory $CD8^+$ T cells in HCC. **Methods:** Murine HCC models were established by subcutaneous or orthotopic injection of Hepa1-6 cells in Wild-type, *fcgr2b*-knockout or *fgl2*-knockout C57BL/6J mice. The expression of FcγRIIB on memory $CD8^+$ T cells from tumors, peri-tumor liver tissues, lymph nodes, peripheral blood and spleen and its immunosuppressive effects in memory subsets were characterized by flow cytometry. Tumor tissues were analyzed by multiplex immunohistochemistry and co-immunoprecipitation to evaluate the interactions between sFGL2 and FcγRIIB. Moreover, functional markers closely related to sFGL2-FcγRIIB axis in memory $CD8^+$ T cells were screened out by flow cytometry. **Results:** FcγRIIB was mainly expressed on tumor-infiltrating effector memory $CD8^+$ T cells ($CD8^+$ TEMs) and resident memory $CD8^+$ T cells ($CD8^+$ TRMs), whereas Naïve $CD8^+$ T cells didn't express FcγRIIB. Compared to FcγRIIB$^-$ $CD8^+$ TEMs and TRMs, FcγRIIB$^+$ $CD8^+$ TEMs and TRMs showed a significant decrease in proliferation and cytotoxicity, and an increase in apoptosis and expression of several inhibitory receptors. However, knockout of *fcgr2b* significantly limited tumor growth, increased the number of tumor-infiltrating $CD8^+$ TRMs and improved effector function of $CD8^+$ TEMs and TRMs. Besides, ELISA showed a high level of sFGL2 in tumor tissues. There was an interaction and co-localization between sFGL2 and FcγRIIB in tumor tissues. Furthermore, knockout of *fgl2* effectively enhanced expression of Ki67 and Granzyme B and reduced the expression of Caspase3, Caspase7 and T cell immunoglobulin domain and mucin domain-3 in FcγRIIB$^+$ TEMs and TRMs. **Conclusion:** FcγRIIB might be a novel immune checkpoint in HCC. FcγRIIB severely impaired effector function of memory $CD8^+$ T cells partly by sFGL2-FcγRIIB axis.

Disclosures: Qianting Guan: Nothing to Disclose, Meiwen Han: Nothing to Disclose, Fangfei Yan: Nothing to Disclose, Qinghao Guo: Nothing to Disclose, Ming Wang: Nothing to Disclose, Dong Xi: Nothing to Disclose, Qin Ning: Nothing to Disclose

3437 | INVESTIGATION FOR DIAGNOSTIC VALUE OF CIRCULATING TUMOR DNA FOR THE EARLY HBV-DERIVED HCC BY PROFILING FRAGMENTATION ★

Tom Ryu[1] Sung Hwan Yoo[2] HyoJu Kim[1] Young Chang[1] Jeong-Ju Yoo[1] Sang Gyune Kim[1] Do Seon Song[3] Young Sun Lee[4] Su Jong Yu[5] Sae Hwan Lee[1] Hyuk Soo Eun[6] Won Kim[5] JAE YOUNG JANG[1] Young Seok Kim[1] Hong Soo Kim[1] So-Young Jin[1] Hyun Woong Lee[2] Soung Won Jeong[1]

[1]Soonchunhyang University, [2]Yonsei University, [3]The Catholic University of Korea, [4]Korea University, [5]Seoul National University, [6]Chungnam National University

Background: It is difficult to detect the hepatocellular carcinoma (HCC) within the diameter of 3 centimeters, even though there have been a step forward for the diagnostic tools such as radiologic modalities and tumor markers. Here, we report that profiling fragmentation and target gene enrichment of peripheral blood would be one of the effective diagnostic tools for detecting the early hepatitis B virus (HBV) derived HCC, with an operability. **Methods:** The multi center prospective study enrolled 7 patients with liver cirrhosis as control and 21 patients with HBV induced HCC (tumor size ≤ 3cm). For variants analysis, we designed 19 targeted genes, and which were selected based on previous studies. Peripheral blood was obtained and circulating tumor DNA (ctDNA) was extracted before and after operation from the plasma. Also, genomic DNA (gDNA) was isolated from formalin-fixed paraffin-embedded tissue blocks. Isolated DNA were handled for capture probes utilizing target enrichment kit and target panel Next Generation Sequencing analysis was used for further analysis. **Results:** Mean diameter of the tumors was 2.05 cm and the numbers of patients with liver cirrhosis and previous medication of antiviral agents were 16 and 16, respectively. Median value of alpha-fetoprotein and protein induced

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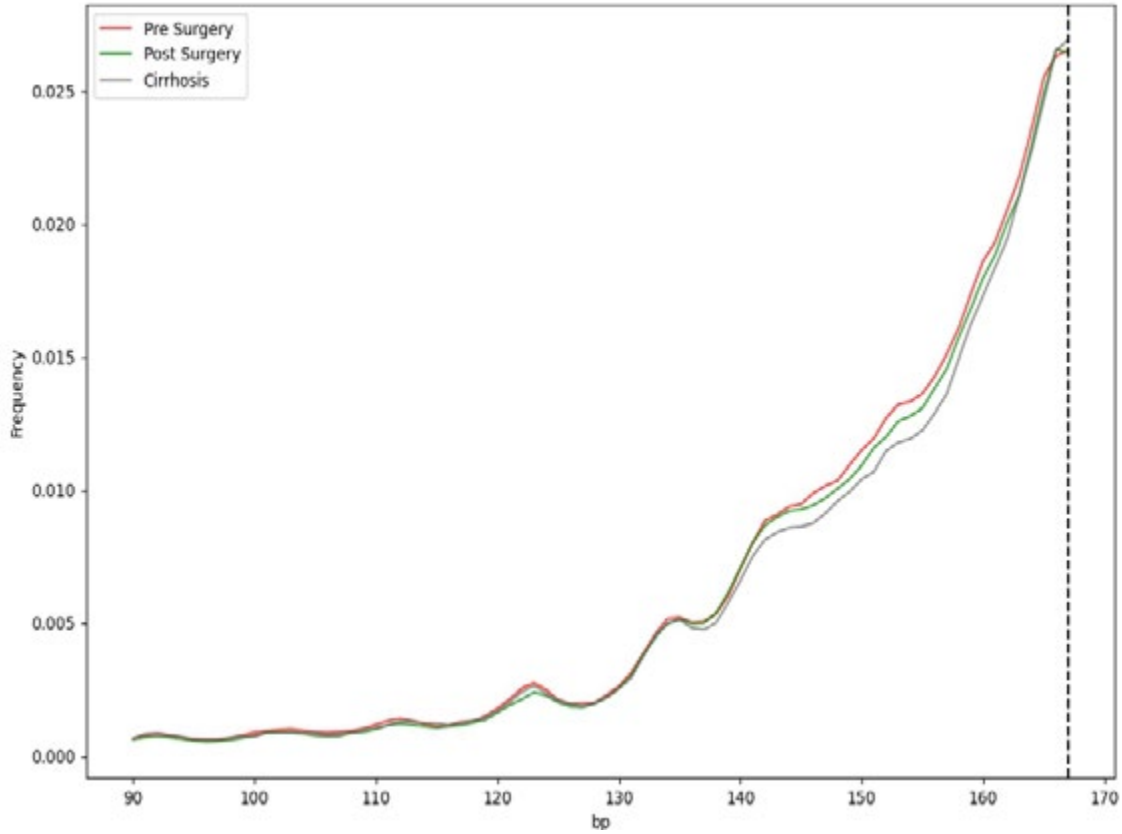
by vitamin K absence or antagonist-II was 17.1 ng/mL and 30.85 mAU/mL, respectively. *APOB*, *ARID1A*, *ERBB2,* and *KMT2B* were 4 representative frequently mutated genes in pre-operative blood and cancer tissue of HBV-HCC derived cancer patients. High variant allele frequency (VAF) was shown in pre-operative ctDNA, while low VAF was presented in the blood of patients with cirrhosis and post-operative ctDNA. HBV host DNA integration analysis showed the attached HBV reference genome with a part of human hg38 reference genome. In addition, fragment length frequency showed significant high frequency of ctDNA in pre-operative blood samples compared to post-operative blood samples. Also those of both pre and post blood samples were higher than that of patients with cirrhosis. **Conclusion:** For earlier stage of HBV-HCC, using blood samples by profiling fragmentation of ctDNA would be one of the leading diagnostic methods.



Disclosures: Tom Ryu: Nothing to Disclose, Sung Hwan Yoo: Nothing to Disclose, HyoJu Kim: Nothing to Disclose, Young Chang: Nothing to Disclose, Jeong-Ju Yoo: Nothing to Disclose, Sang Gyune Kim: Nothing to Disclose, Do Seon Song: Nothing to Disclose, Young Sun Lee: Nothing to Disclose, Su Jong Yu: Nothing to Disclose, Sae Hwan Lee: Nothing to Disclose, Hyuk Soo Eun: Nothing to Disclose, Won Kim: Nothing to Disclose, JAE YOUNG JANG: Nothing to Disclose, Young Seok Kim: Nothing to Disclose, Hong Soo Kim: Nothing to Disclose, So-Young Jin: Nothing to Disclose, Hyun Woong Lee: Nothing to Disclose, Soung Won Jeong: Nothing to Disclose

3438 | MULTI-OMIC RISK PREDICTION FOR CHOLANGIOCARCINOMA

Felix Van Haag Jan Clusmann[1] Paul-Henry Koop[2] Kai Markus Schneider[2] Carolin Victoria Schneider[2]

[1]Institute for Clinical Artificial Intelligence, EKFZ for Digital Health, TU Dresden, [2]Uniklinik RWTH Aachen

Background: Cholangiocarcinoma (CCA) is a highly malignant cancer of the bile ducts. Characterized by its late presentation and rapid progression, CCA remains a formidable challenge in oncology and hepatology, particularly in early detection and surveillance strategies. Unlike Hepatocellular carcinoma (HCC), where liver disease represents a clear population at risk, there is currently no method to pre-select patients at higher risk of developing CCA. This deficiency in early detection tools not only limits therapeutic options but also dramatically worsens patient prognosis. Utilizing data from the United Kingdom Biobank (UKB), this study aims to assess

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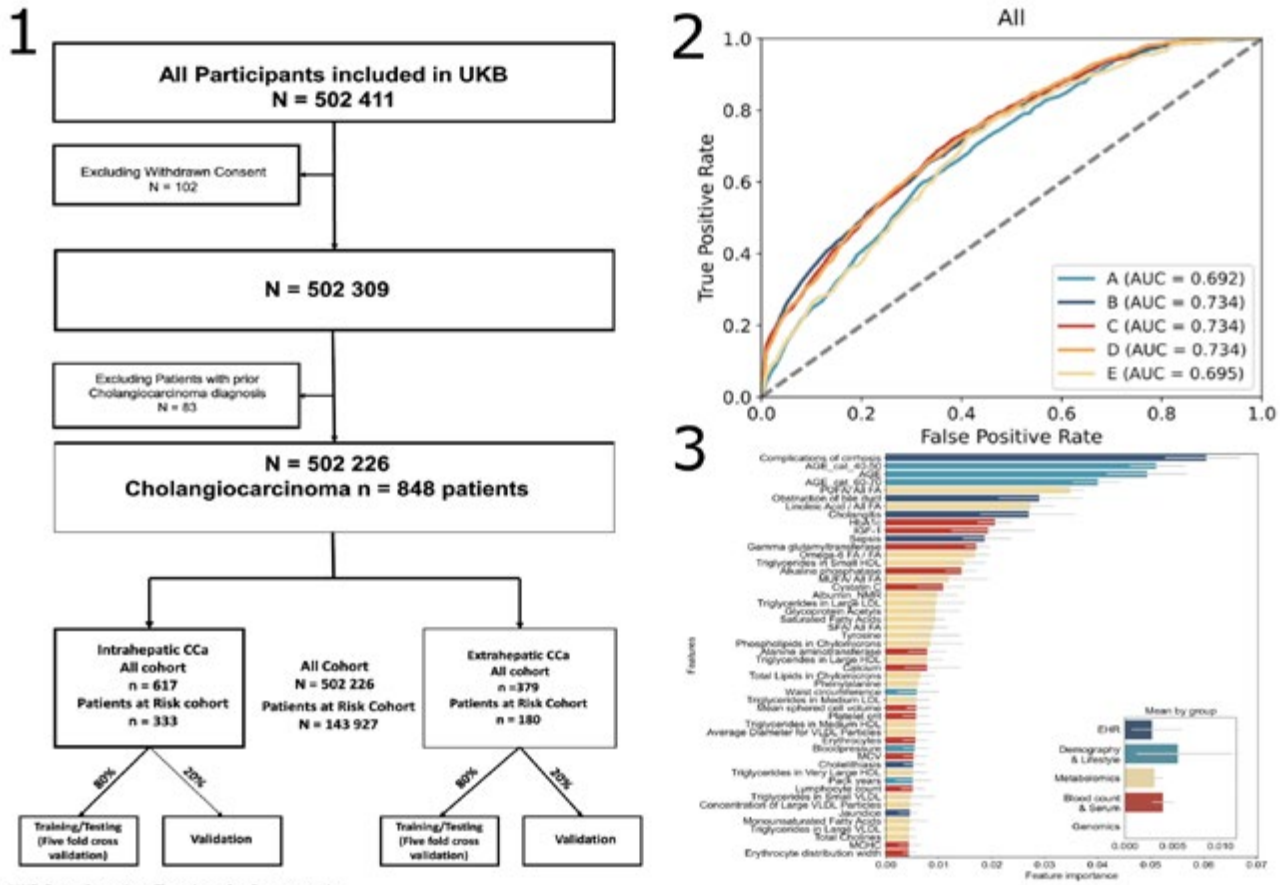
multiple data modalities for their potential to identify at-risk individuals. This could transform CCA screening and significantly impact patient outcomes. **Methods:** The UKB is a comprehensive nationwide prospective cohort study, comprising data from over 500,000 participants. This dataset encompasses an extensive range of data modalities, including detailed lifestyle and medical histories, precise physical measurements, and biological samples suited for advanced metabolomic and genetic analyses. After rigorous preprocessing, we trained machine learning algorithms such as Random Forest Classifier and X Gradient Boost. Training was performed in a five-fold cross-validation on data from England, with testing done on data from Wales and Scotland. To simulate different clinical scenarios, we incrementally increased the amount of data given to the model, evaluating added benefit to the model. Analyses were performed for the whole population of UKB and several subgroups such as e.g. patients with history of cholelithiasis or biliary tract diseases. Genetic analyses were performed on 18 SNPs relevant to CCA. **Results:** Evaluation of models on the withheld test set revealed AUROCs between 0.69 (Model A, Demographics only) and 0.74 (Model B (A + Diagnosis), with only minimal changes in AUROCs for Model C (+ Blood), D (+SNPs), E (+ Metabolomics), (0.73, 0.73, 0.7). Feature importance analyses revealed a high relevance of demographic data (e.g. age) and EHR items (e.g. Complications of Cirrhosis, Cholelithiasis, or Cholangitis). Interestingly, genomic parameters showed little to no relevance for the models. As intra- and extrahepatic CCA (iCCa/eCCa) have different phenotypes and populations at risk, we are currently developing specific models for both entities. Preliminary results show that this approach might enhance prediction accuracy. **Conclusion:** The trained models using RFC could give good indications on the risk of CCA, even though their accuracy is still underwhelming. Integration of more sophisticated machine learning algorithms and systematic hyperparameter tuning could improve the model's accuracy or redirect the attention to potential new risk factors for CCA, which we will validate on the US-American "All Of Us" Cohort.



1: UKB Data Overview Flowchart for Preprocessing
2: Model performance on the Random Forest Classifier All cohort as receiver operating characteristic (ROC) curves and corresponding area under the curve (AUC) for incrementally increased scenarios (A-E). Each line represents performance of one majority vote model from five-fold cross-validation. Dotted grey line represents AUC of 0.5.
3: Relative Feature Importance Barplot for Random Forest Classifier Model E in the All Cohort, Mean feature Importance by Group added to Bottom right corner

Disclosures: Felix Van Haag: Nothing to Disclose, Jan Clusmann: Nothing to Disclose, Paul-Henry Koop: Nothing to Disclose, Kai Markus Schneider: Nothing to Disclose, Carolin Victoria Schneider: Nothing to Disclose

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3439 | ANALYSIS OF ATEZOLIZUMAB ANTIDRUG ANTIBODY IN HCC PATIENTS TREATED WITH ATEZOLIZUMAB AND BEVACIZUMAB

Ouchi Keishi[1] Jun Inoue[2] Masashi Ninomiya[2] Akitoshi Sano[3] Mio Tsuruoka[4] Kosuke Sato[2] Satoko Sawahashi[2] Masazumi Onuki[2]

[1]Tohoku University Graduate School of Medicine, Japan, [2]Tohoku University Graduate School of Med, [3]Mayo Clinic, Rochester, [4]Tohoku University Hospital

Background: Atezolizumab+Bevacizumab (Atezo+Bev) is positioned as first-line chemotherapy for unresectable hepatocellular carcinoma (HCC). Although immune checkpoint inhibitors (ICIs) may induce an antidrug antibody (ADA), there is a lack of evidence for the relationship between ADA against Atezo (ATZ-ADA) levels and treatment outcome. In this study, we assayed ATZ-ADA levels and analyzed its association with therapeutic outcome in advanced HCC patients who were treated with Atezo+Bev. **Methods:** Thirty-eight patients with unresectable HCC treated with Atezo+Bev between 2020 and 2024 were included in this study. ATZ-ADA was assayed with ELISA using the stored serum samples at the time of 3 courses of treatment or the earliest time point. **Results:** The backgrounds of 38 patients were as follows: male/female=28/10, median age 74 years, HCV/HBV/non-B, C=10/8/20, BCLC stage B/C=20/18, Child-Pugh score 5/6=28/10, ALBI grade 1/2=10/28. Portal vein tumor thrombus was observed in 8 cases (21%), and extrahepatic spread was observed in 10 cases (26%). Atezo+Bev was administered for a median of 3 courses, and the best responses with mRECIST were CR/PR/SD/PD=2/13/13/10. ATZ-ADA levels were assayed at 3/4-6/7-12/13-20 course administration (24/7/3/4 cases, respectively). The median ADA level (OD value) was 0.037 and did not correlate with the number of treatment courses. The median ADA level in each response group was CR/PR/SD/PD=0.031/0.036/0.037/0.044. Since ADA levels were lower in CR, PR, and SD and higher in PD, we compared ADA levels in CR+PR+SD and PD with no treatment effect by Wilcoxon signed-rank test. The mean (standard deviation) of CR+PR+SD was 0.036 (0.006) and that of PD was 0.047 (0.013), showed a statistical difference in ADA levels (p=0.0087). The AUS of ROC curve was 0.78, and the cut-off value was 0.041, with (sensitivity and specificity) of (0.70 and 0.86). Interestingly, a PD patient had the highest ATZ-ADA level (0.079). His treatment was switched to the STRIDE regimen with Tremelimumab+Durvalumab resulting in CR. **Conclusion:** Although ATZ-ADA levels in this study was generally low, there was a significant difference between cases with and without treatment effect, suggesting that the ATZ-ADA levels may reflect the treatment effect. It was suggested that patients with high ATZ-ADA should consider treatment switch as soon as possible.

Disclosures: Ouchi Keishi: Nothing to Disclose, Jun Inoue: Nothing to Disclose, Masashi Ninomiya: Nothing to Disclose, Akitoshi Sano: Nothing to Disclose, Mio Tsuruoka: Nothing to Disclose, Kosuke Sato: Nothing to Disclose, Satoko Sawahashi: Nothing to Disclose, Masazumi Onuki: Nothing to Disclose

3440 | ACC2: A NOVEL BIOMARKER FOR METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE-INDUCED HEPATOCELLULAR CARCINOMA WITH SEVERE STEATOSIS

Fatima DAHBOUL[1] JIHAN SUN[1] Benjamin Buchard[2] Delphine Weil-Verhoeven[3] Vincent Di Martino[3] Aicha Demidem[4] Armand Abergel[5]

[1]CLERMONT AUVERGNE UNIVERSITY, [2]Hepato-Gastroenterology Unit, University Hospital Estaing, [3]Hepatology and digestive intensive care unit, [4]Clermont-Auvergne University, [5]CHU Clermont Ferrand

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) affects 25% of the world's population and is a leading cause of cirrhosis and hepatocellular carcinoma (HCC) (Huang *et al.,* 2020). We previously reported the existence of two phenotypes of MASLD-HCC based on fibrosis severity (Buchard *et al.,* 2021). We recently demonstrated that fatty acid oxidation (FAO) and de novo lipogenesis (DNL) are simultaneously and exclusively activated in MASLD-HCC but not in Virus-HCC (Dahboul *et al.,* 2023 submitted). The present study aims to identify tissue biomarkers for MASLD-HCC according to the degree of differentiation and steatosis grade by exploring the metabolic pathways involved in lipid metabolism (LM), DNL, and FAO. **Methods:** Our cohort comprises 86 pairs of HCC and non-tumor (NTT) tissues (CRB Foie). A qRT-PCR analysis focusing on the expression of 29 genes involved in the 3 metabolic pathways: DNL, LM and FAO was conducted. For each group, HCC was compared to NTT. The study was approved by the Ethic Committee (agreement

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number AU887). **Results:** The transcriptomic analysis (figure 1) of a panel of 29 genes reveals: Depending on the degree of differentiation (well vs. moderate), MASLD-HCC differs in the expression of a unique gene: MBOAT7, which is involved in the remodeling pathway of phosphatidylinositol (PI), is up-regulated in MASLD-HCC with moderate differentiation. This result is consistent with previous data indicating that PI (16:0, 18:1) accumulates in MASLD-HCC. Our observation suggests that MBOAT7 emerges as a candidate marker in MASLD-HCC exhibiting moderate differentiation. Considering the degree of steatosis (low *vs.* severe), we observed that the gene encoding for ACC2, a mitochondrial enzyme involved in DNL, is up-regulated exclusively in MASLD-HCC with severe steatosis, despite the expression of the genes encoding for ACC1 and FASN remaining unchanged regardless of the degree of steatosis. Consequently, our findings indicates that ACC2 may serve as a clinical marker in MASLD-HCC with severe steatosis (>30%). This result aligns with findings from studies using an ACC inhibitor (GS-0976) in NASH (Loomba *et al.,* 2018). ACC inhibitors show promise in addressing various aspects of NASH pathology. **Conclusion:** The transcriptomic analyses in this study suggest that AAC2 inhibitors could be evaluated in combination with tyrosine kinase inhibitors and/or immunotherapy treatment for MASLD-HCC in patients with severe steatosis.

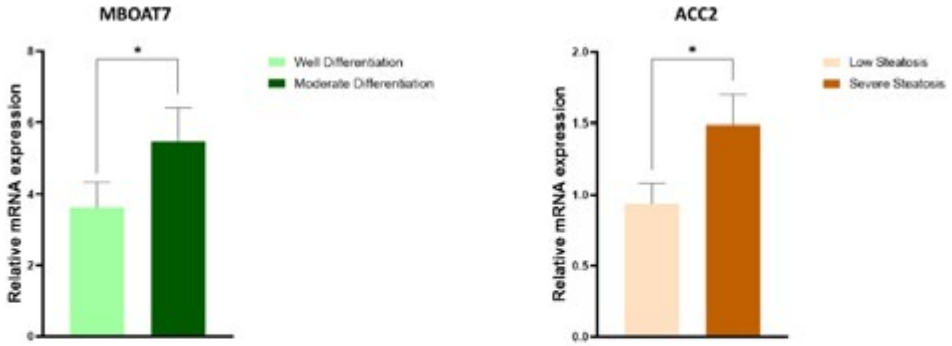

Figure 1. (A) Comparison of MBOAT7 expression in MASLD-HCC compared between well and moderately differentiated tumors **(B)** Comparison of ACC2 expression in MASLD-HCC compared between low and severe steatosis degrees using Quantitative real-time PCR (qRT-PCR). Data are expressed as mean ± S.E.M. *p < 0.05 (Wilcoxon test).

Disclosures: Fatima DAHBOUL: Nothing to Disclose, JIHAN SUN: Nothing to Disclose, Benjamin Buchard: Nothing to Disclose, Delphine Weil-Verhoeven: Nothing to Disclose, Vincent Di Martino: Nothing to Disclose, Aicha Demidem: Nothing to Disclose, Armand Abergel: Nothing to Disclose

3441 | RADIOMICS-BASED PREDICTION OF HCC RESPONSE TO ATEZOLIZUMAB/ BEVACIZUMAB

Isaac Israel Rodriguez Salazar[1] Andreas Teufel[1] Abhinay Vellala[1] Timo Itzel[1] Jimmy Daza[1] Michael Vácha[1] Manuel Debic[2] De-Hua Chang[3] Michael Dill[2] Max Seidensticker[4] Gerd Oswald Stefan Schönberg[1] Lukas Müller[5] Julia Mayerle[4] Stefan Munker[4] Peter Galle[5] Arndt Weinmann[5] Dietmar Tamandl[6] Matthias Pinter[6] Marino Venerito[7] Matthias Ebert[1] Matthias Froelich[1] Maciej Pech[7] Friedrich Sinner[7] Bernhard Scheiner[6]

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Background: Atezolizumab/bevacizumab has emerged as a breakthrough therapy for advanced hepatocellular carcinoma (HCC). However, as not all patients respond equally to immunotherapy, predicting treatment response remains an important issue in order to stratify and optimize treatment. **Methods:** We investigated 103 HCC patients treated with atezolizumab/bevacizumab, and either disease control (DC) or progressive disease (PD) based on their response to therapy. Radiomics features were extracted from baseline MRI scans. Predictive models using radiomics variables and clinical variables were developed separately and ultimately also integrated to create a composite predictive model. Hyper-parameter tuning and stratified K Fold cross-validation were employed to optimize predictive accuracy and ensure robustness. **Results:** While clinical parameters alone showed limited predictive accuracy (40% accuracy, AUC 0.62), radiomics features demonstrated modest

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performance (55% accuracy, AUC 0.79). However, the hybrid model combining both clinical and radiomics data exhibited significantly improved predictive efficacy, with an overall accuracy of 88% and an AUC of 0.98 for predicting disease progression. **Conclusion:** Machine learning significantly enhances the development of hybrid models capable of predicting response to atezolizumab/bevacizumab by leveraging both clinical and radiomics features. Our hybrid model clearly outperformed models solely based on clinical/serological parameters or radiomics features.

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3442 | SPATIAL OMICS ANALYSIS OF THE PROXIMITY OF PD-L1(+) TUMOR-ASSOCIATED MACROPHAGE AND CD8T CELL INTERACTION PROMOTING HEPATOCELLULAR CARCINOMA PROGRESSION

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

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Background: Spatial omics technology enables visualization of the tumor immune microenvironment and analysis of immune cell interactions. We have reported tumor-associated macrophages (TAMs) promoting the proliferative potential of hepatocellular carcinoma (HCC) cells (J Immunol. 2018, Biomed phar. 2023). Herein, we examine proximity of PD-L1(+)TAMs and immune cells, based on spatial location and their association with prognosis using multiplex immunohistochemistry (mIHC). Further, we investigate factors related to interaction of immune cells and mechanism of cancer progression in a mouse model. **Methods:** mIHC (OPAL: CD8, CD68, CD163, CD11c, PD-L1, and DAPI) was performed on 88 resected HCC specimens. Cell distribution and spatial location in the tumor center, tumor border, non-tumor border, and non-tumor area were determined using inForm (Akoya). Intercellular distances were measured using Phenoptr, and the interaction variable (proportion of target cells within 25 μm) was calculated. The mouse HCC cell line, BNL, transfected with GM-CSF vector was intraportally injected into Balb/c mice. Anti-GM-CSF antibody (αGM-CSF) and/or αPD-L1 were injected intraperitoneally into the mice. **Results:** Spatial analysis of HCC tissue showed that higher interaction variable of PD-L1(+) TAMs and CD8T cells in the tumor center had significantly worse in recurrence and survival rates [HR=3.0, $p<0.05$]. The interaction variable correlated positively with the number of GM-CSF-positive cells, but not with M-CSF. PanCK(+) tumor cells were expressed GM-CSF. In a mouse model, GM-CSF-transfected BNL cells increased tumor size and the interaction variable of TAM-CD8T, and decreased the number of granzyme B(+) CD8T cells. αGM-CSF Ab reduced tumor size and interaction variable of PD-L1(+)TAM and CD8T and the combination with αPD-L1 Ab further significantly reduced tumor size. qRT-PCR analysis of TAM and CD8T cells from tumors revealed that αGM-CSF Ab decreased PD-L1 in TAM, and decreased PD1 and increased GZMB expression in CD8T. **Conclusion:** Spatial omics analysis revealed significant correlation of proximity between PD-L1(+)TAMs and CD8T cells with recurrence rate and overall survival. Tumor cell-derived GM-CSF expression correlated with the proximity and may promote PD-L1 expression in TAMs and CD8T exhaustion. GM-CSF, which regulates TAM-CD8T interactions, and PD-L1 may serve as a new therapeutic target to regulate tumor progression in cancer microenvironment.

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Nothing to Disclose, Kazuto Takahashi: Nothing to Disclose, Tatsushi Naito: Nothing to Disclose, Yasunari Nakamoto: Nothing to Disclose

3443 | CRITICAL OUTCOMES IN PATIENTS WITH HEPATOBILIARY NEOPLASIA DURING COVID-19: UNITED STATES NATIONWIDE ANALYSIS

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Background: Hepatobiliary cancers are the second leading cause of cancer related death worldwide and the sixth leading cause of cancer related death among men in developed countries. Recent data showed the detrimental effects of COVID-19 infection on gastroenterological conditions, causing increase mortality rates and complications. However, limited information exists on the specific impacts of COVID-19 infection in patients hospitalized for hepatobiliary cancers. **Methods:** We analyzed the 2020 U.S. National Inpatient Sample (NIS) to investigate the effects of COVID-19 infection on cases primarily admitted due to hepatobiliary cancers. Adjusted odds ratios (aORs) for specified outcomes were calculated through multivariable logistic and linear regression analyses. The primary outcome was inpatient mortality, with secondary outcomes including system-based complications. **Results:** We identified 27,730 patients with a primary discharge diagnosis of hepatobiliary cancers, excluding age < 18 years and elective hospitalization. The mean age was 66.1 years; 61.6% were male. Caucasians accounted for 59%, followed by African Americans. Of these, 0.52% (145/27,730) had a concurrent diagnosis of COVID-19 infection. COVID-19 infection was associated with higher in-hospital mortality (aOR 6.87; 95% CI 2.49, 18.95, p < 0.001), shock (aOR 5.82; 95% CI (1.86, 18.22), p = 0.002), sepsis (aOR 5.18; 95%CI (1.66, 16.16), p = 0.005), acute respiratory failure (aOR 5.26; 95% CI (1.81, 15.23), p = 0.002) and mental status change (aOR 4.12; 95% CI (1.41, 11.98), p = 0.009). We observed non-significant, but increased, risks of acute kidney injury, coagulopathy, liver failure and mechanical ventilation, as well as, length of stay and total hospitalization costs in COVID-19 positive patients. **Conclusion:** COVID-19 infection is associated with higher in-hospital mortality and increased risks of various critical outcomes in patients diagnosed with hepatobiliary cancers. Additional studies are warranted to comprehensively assess the causation of these clinical outcomes in this population.

Table 1: Outcomes in hepatobiliary neoplasia with COVID-19 infection

Outcome	aOR (95% CI)	P-value
Inpatient mortality	**6.87 (2.49, 18.59)**	**<0.001***
Mean length of stay (days)	10.11 (-0.06, 20.29)	0.051
Mean total hospital charge (USD)	90,454.26 (-50,996.29, 231,904.80)	0.210
Mean total hospital cost (USD)	29,608.74 (-16,848.24, 76,065.72)	0.211
Shock	**5.82 (1.86, 18.22)**	**0.002***
Sepsis	**5.18 (1.66, 16.16)**	**0.005***
Acute kidney injury	1.87 (0.74, 4.75)	0.184
Acute respiratory failure	**5.26 (1.81, 15.23)**	**0.002***
SIRS	**6.48 (1.16, 36.02)**	**0.033***
Mechanical ventilation usage	2.69 (0.46, 15.69)	0.270
Coagulopathy	2.79 (0.89, 8.73)	0.076
Mental status change	**4.12 (1.41, 11.98)**	**0.009***
Liver failure	2.33 (0.41, 13.58)	0.330

Adjusted for age, gender, hospital location, hospital region, insurance status, patient location, hospital size, hospital type and co-morbidities

*Denotes significant value at p<0.05

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3444 | MISCLASSIFICATION ANALYSIS OF A MULTIMODAL IMAGE-BASED DEEP-LEARNING MODEL FOR PREDICTING POST-OPERATIVE HCC RECURRENCE: IMPLICATIONS FOR MODEL IMPROVEMENT

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Background: Image-based deep-learning models have been studied for hepatocellular carcinoma (HCC) prognostication, yet their lack of explainability may hinder model optimization. We performed misclassification analysis on our model – Recurr-NET, aiming to identify measures to improve model performance. **Methods:** We trained, validated and externally tested Recurr-NET, a multimodal residual-network random survival forest deep-learning model that incorporates pre-treatment computed tomography (CT) and clinical parameters to predict HCC recurrence within 5 years after curative surgery. Our model classified patients as high or low-risk for recurrence. True-positive (High-risk patient who recurred) or true-negative (Low-risk patient who did not recur) predictions were defined as correct predictions, whereas false-positive (High-risk patient who did not recur) or false-negative (Low-risk patient who recurred) predictions were defined as model misclassification. Logistic regression was used to assess imaging, clinical and histology parameters associated with model misclassification in the external cohort of our study. **Results:** We included 560 patients with resected histology-confirmed HCC (Mean age 62.1, 80.5% male, mean MELD score 7.9). At year 2, the model achieved area-under curve (AUROC) 0.781, sensitivity 0.699 and specificity 0.764 for predicting HCC recurrence. Year 2 misclassification occurred in 140 patients (25.0%; 75 [13.4%] false-positives, 65 [11.6%] false-negatives). Ascites on CT (OR 4.316, 95%CI 1.502-12.405, p=0.007) and MELD score (OR 1.097, 95%CI 1.002-1.201, p=0.045) were both independent predictors of year 2 misclassification. At year 5, the model achieved AUROC 0.760, sensitivity 0.556 and specificity 0.841 for predicting recurrence. Year 5 misclassification occurred in 163 patients (29.1%; 27 [4.8%] false-positives, 136 [24.3%] false-negatives). Predictors of year 5 misclassification were ascites on CT (OR 3.600, 95%CI 1.186-10.926, p=0.024), Barcelona Clinic Liver Cancer (BCLC) staging (OR 2.042 in BCLC-0 vs higher stages, 95%CI 1.048-3.976, p=0.036) and histological microvascular invasion (OR 0.615, 95%CI 0.403-0.939, p=0.024). Ascites on CT was the only independent predictor of year 5 misclassification in multivariate analysis (OR 3.690, 95%CI 1.208-11.271, p=0.022), predominantly being false-negative. **Conclusion:** Presence of ascites on CT affected the prediction accuracy of both early and late HCC recurrence in our image-based deep-learning model, possibly due to its interference with image segmentation. Algorithm enhancements may enhance deep learning predictability to facilitate post-resection prognostication of HCC.

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3445 | PHASE II STUDY OF ATEZOLIZUMAB PLUS BEVACIZUMAB COMBINATION THERAPY IN PATIENTS WITH UNRESECTABLE HEPATOCELLULAR CARCINOMA AND CHILD-PUGH B: CHALLENGE TRIAL

Takeshi Terashima[1] Masafumi Ikeda[2] Tatsuya Yamashita[3] Takuji Okusaka[4] Hiroshi Imaoka[2] Satoshi Kobayashi[5] Sadahisa Ogasawara[6] Tomokazu Kawaoka[7] Atsushi Hiraoka[8] Masahito Nakano[9] Fumio Nagashima[10] RIE SUGIMOTO[11] Michihisa Moriguchi[12] Yoshitaka Inaba[13] Satoru Shinoda[14] Makoto Ueno[5] Naoya Kato[15] Masatoshi Kudo[16] Junji Furuse[5] Hiroaki Nagano[17]

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Background: Recently, atezolizumab plus bevacizumab combination therapy (Atezo+Bev) has successfully developed and been introduced into clinical practice as a standard of care for patients with unresectable hepatocellular carcinoma (HCC) and Child-Pugh A; however, there is no established treatment for those with Child-Pugh B. This study aimed to evaluate the safety and efficacy of Atezo+Bev in patients with advanced HCC with Child-Pugh B. **Methods:** In this multicenter, open-labeled, single-arm, phase II trial, CHALLENGE trial (jRCTs031210355), advanced HCC patients with Child-Pugh score 7 or 8 and no prior systemic therapy were enrolled to receive a dose of 1,200mg of atezolizumab plus 15mg/kg of bevacizumab every three weeks. The primary endpoint was the frequency of severe adverse events (SAEs). The secondary endpoints included the objective response rate, progression-free survival, time to progression, overall survival, and frequency of adverse events. The threshold and expected frequency of SAEs were 68.5% and 42%, respectively, and the minimum required sample size was 27 patients considering a one-sided significance level of 0.025 and a statistical power of 80%. **Results:** A total of 31 patients were enrolled between December 2021 and April 2023. Child-Pugh score was 7 points in 25 patients (80.6%) and 8 points in 6 patients (19.4%), and BCLC stage was C in 14 patients (45.2%). Of them, 30 eligible patients were included in this analysis. The frequency of SAEs was 23.3% (95% confidence interval [CI] 9.9-42.3, p-value <0.0001), including gastric ulcer in 2 patients, and hepatic failure, lung infection, anorexia, hepatic encephalopathy, pneumonitis, enterocolitis infectious in a patient each. Main Grade 3 or more severe adverse events were blood bilirubin increased (n=3), hypoalbuminemia (n=2), proteinuria (n=2), and hypertension (n=2), and occurred in 13 patients (43.3%). One patient died of atezolizumab-induced pneumonitis. The mean Child-Pugh score (±SD) at the start of treatment was 7.2±0.4, which changed to 7.0±1.0, 7.2±0.9, and 7.6±1.8 at the third and fifth cycles and the end of treatment. **Conclusion:** Atezo+Bev was well-tolerated, and the liver functional reserve was maintained during treatment in patients with unresectable HCC and Child-Pugh B in this cohort. Patients continue to be followed for efficacy endpoints, which will be analyzed after one year from the last patient enrollment.

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3446 | HEPATOCELLULAR CARCINOMA RISK IN HISPANICS WITH CHRONIC HEPATITIS B

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Background: There is a paucity in literature investigating hepatocellular carcinoma (HCC) risk among Hispanic populations with chronic hepatitis B (HBV) in the United States (US), a population with differing risk profiles and disease co-factors. We are addressing this notable gap in research by building a multicenter cohort to estimate the cumulative incidence of HCC among US Hispanic patients with HBV. **Methods:** This is a preliminary analysis of data from two sites of an ongoing retrospective multicenter cohort study of Hispanic adults with chronic HBV. Patients were identified by a positive surface antigen test and self-reported Hispanic ethnicity. Demographic, clinical and laboratory data were abstracted from the electronic health record. Primary outcome was incident HCC diagnosed by usual radiographic or histologic criteria. We estimated the cumulative incidence (CI) of HCC after excluding prevalent HCC defined as diagnosed within 3 months of HBV diagnosis using Kaplan-Meier analysis. **Results:** Our cohort included 369 Hispanic patients with chronic HBV with a median age of 50 years (IQR 41-59); 60% were male and 78% Medicaid-insured. Among those with known birthplace, 52% were born in Mexico, followed by 16% in Central America and 10% in the US. Majority (85%) were HBeAg negative with median HBV DNA of 76 IU/mL. 69% of patients were inactive carriers, 30% were on antiviral therapy, and 16% had cirrhosis. Secondary chronic liver disease was common: 23% with MASLD, 11% with AUD, and 7% with hepatitis C (HCV) co-infection; 17% had HIV co-infection. Thirteen patients developed HCC over median follow-up of 3.2 months (IQR .17-103.2). Of note, 6 patients had prevalent HCC and were incidentally diagnosed with HBV after their HCC diagnosis. Those with HCC were more likely to have cirrhosis (82% vs 14%), higher liver tests, lower platelets, and HCV co-infection (23% vs 8%) (P<0.01). The 1-, 5-, and 10-year CI of HCC was 0.4%, 1.4%, and 3.7%, respectively (Figure). Of HCC patients, 15%, 15%, and 69% were classified as low, medium, and high-risk PAGE-B group. **Conclusion:** In this observational study, the risk of HCC in Hispanics with chronic HBV was comparable to other racial/ethnic groups at ~0.5% per year. Nearly half were diagnosed with HBV concurrent with their HCC diagnosis, a concerning finding suggesting inadequate HBV screening. HCV co-infection and cirrhosis

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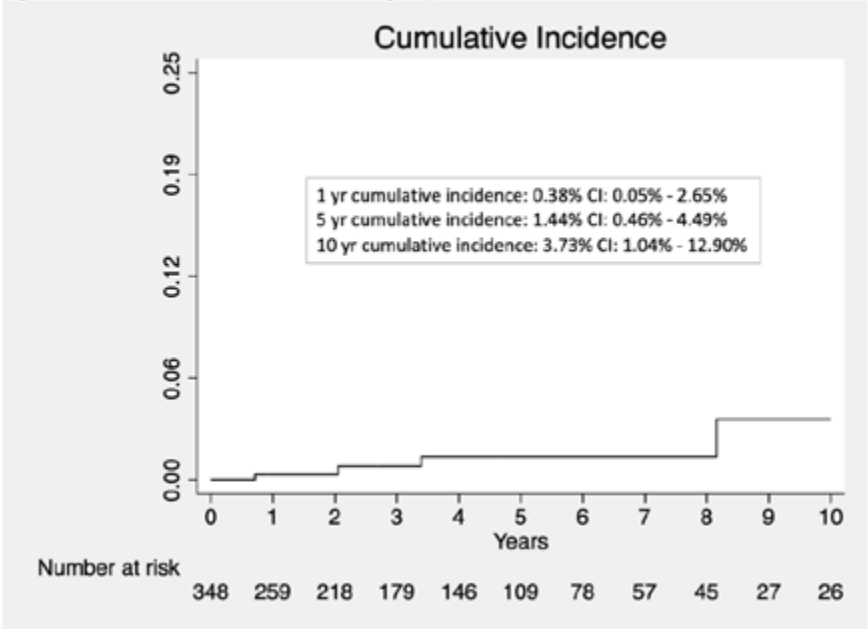
were usual risk factors. However, the low-risk PAGE-B group did not have negligible risk, justifying the need for a larger multicenter cohort to validate existing HCC risk scores in this distinct, understudied population with HBV.

Figure: Cumulative Incidence of HCC among Hispanics with HBV



Disclosures: Ariel Lee: Nothing to Disclose, Phillip Chung: Nothing to Disclose, Jung Jung: Nothing to Disclose, Christopher Wong: Nothing to Disclose, Kali Zhou: Nothing to Disclose

3447 | IMPACT OF PRIOR LOCOREGIONAL THERAPY (LRT) ON OUTCOME OF PATIENTS TREATED WITH SINGLE-DOSE TREMELIMUMAB INDUCTION REGULAR DURVALUMAB (STRIDE) THERAPY FOR UNRESECTABLE HEPATOCELLULAR CARCINOMA (UHCC) IN A REAL-WORLD COHORT

Shalini Bansal[1] *Priya Amin*[2] *Stephen Valerio*[2] *David Kaplan*[3]

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Background: HIMALAYA demonstrated that STRIDE improved overall survival (OS) and 4-year landmark OS in patients with uHCC compared to sorafenib. There have been concerns that prior locoregionally may impair liver function and reduce benefit of systemic therapy in uHCC. **Methods:** In this retrospective cohort study, we identified all patients within the Veterans Affairs Medical System diagnosed with uHCC from 1/1/2015-3/31/2024 who had received at least one dose of the STRIDE regimen using the VA Corporate Data Warehouse. Demographics, etiology of liver disease, baseline lab parameters, and concomitant medications were extracted. BCLC staging, prior treatments, number of treatment cycles and adverse events (AE) were manually abstracted using REDCAP. Survival outcomes were evaluated using Kaplan-Meier methodologies. **Results:** Of 117 patients diagnosed with uHCC receiving at least one cycle of the STRIDE regimen, 87 (74.4%) had undergone prior LRT/resection while 30 (25.6%) received systemic therapy in the first line. For the prior treatment group, the first treatment was resection(10; 12%), ablation(20; 23%), TA(C)E (45; 54%), and TARE(12; 14%), with a median of 2 [IQR 1-3] prior treatments. Compared to those receiving LRT, those not receiving LRT were younger (69 [IQR 66-75] vs 73 [69-76, p = 0.04]) with no statistical difference between groups regarding sex (all male), race/ethnicity, BMI, underlying liver disease etiology, baseline CP score, or mALBI class. Compared to those who received LRT/resection, those without LRT or resection had a higher largest tumor size (8.5 [IQR 4.8 – 11.9] vs. 3.0 [IQR 1.8 – 6.5], p<0.0001), larger total tumor diameter (13.4 [IQR 8.2 – 24.0] vs. 5.8 [IQR 2.8 – 14.0], p = 0.0008) and a higher rate of macrovascular invasion (17 (56.7%) vs. 25 (28.7%), p=0.011). There was no significant difference in presence of malignant lymph nodes, local invasion, distant metastases, or baseline AFP. Median duration of STRIDE treatment was not different, 3 cycles [IQR 2-5]. Reasons for treatment discontinuation differed, with higher rates of discontinuation for death and disease progression in those with prior LRT, while

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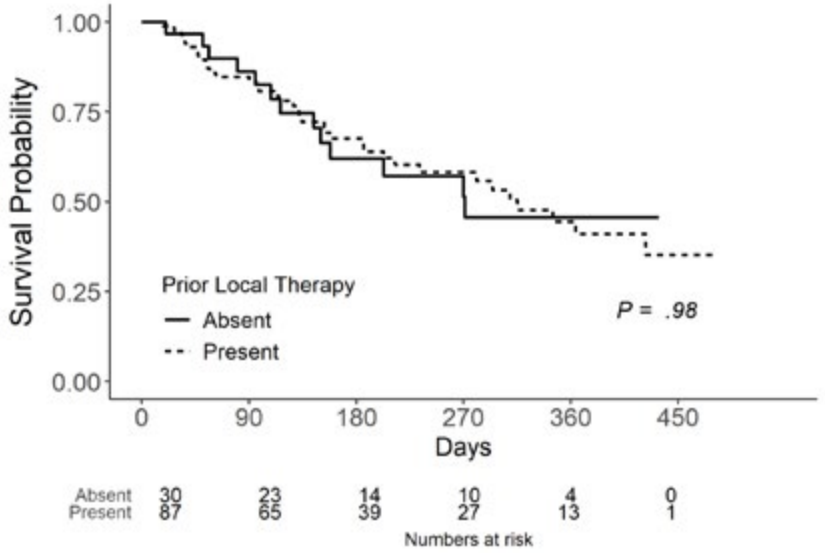
discontinuation due to patient preference was more common with no prior LRT. AE rates were similar, all grades 39 to 52% leading to discontinuation in 19 and 17%. Kaplan-Meier analysis demonstrated no significant difference in survival between the two groups (see Figure). During a maximum follow-up of 450 days, median OS in the prior LRT group was 11.3 months [IQR 7.6 – NA] vs 9.7 [IQR 5.6 – NA] in the no prior LRT group (p=0.98). **Conclusion:** Among veterans receiving STRIDE for uHCC, those that had not undergone prior LRT started STRIDE with greater degrees of intrahepatic tumor burden and greater macrovascular invasion while those with prior LRT manifested greater extrahepatic disease. However, patients with prior LRT manifested similar tolerability and OS as those started in 1L after starting STRIDE for uHCC.



Disclosures: Shalini Bansal: Nothing to Disclose, Priya Amin: AstraZeneca: Employee, Stephen Valerio: AstraZeneca Pharmaceuticals: Stock, Publicly Traded Company, Speaking, Astrazeneca Pharmaceuticals: Employee, Stock, Publicly Traded Company, Speaking, David Kaplan: Independent Contractor relationship with Roche Genentech; Has not ended; Grant/Research Support relationship with AstraZeneca Inc; Has not ended; Advisor relationship with AstraZeneca; Has ended; Advisor relationship with Exelixis; Has ended; Grant/Research Support relationship with Gilead; Has not ended; Advisor relationship with Sirtex; Has ended; Grant/Research Support relationship with Exact Sciences; Has not ended; Grant/Research Support relationship with Glycotest; Has ended

3448 | VIRAL VERSUS NON-VIRAL ETIOLOGY DOES NOT IMPACT OUTCOMES OF UNRESECTABLE HEPATOCELLULAR CARCINOMA (UHCC) PATIENTS TREATED WITH SINGLE TREMELIMUMAB REGULAR INTERVAL DURVALUMAB (STRIDE) IN A REAL-WORLD SETTING

Shalini Bansal[1] *Priya Amin*[2] *Stephen Valerio*[2] *David Kaplan*[3]

[1]*Thomas Jefferson University,* [2]*AstraZeneca Inc.,* [3]*University of Pennsylvania*

Background: The HIMALAYA trial demonstrated that STRIDE significantly improved overall survival (OS) in patients with uHCC vs sorafenib. There is conflicting data as to the impact of viral etiology on response to immunotherapy in uHCC. In IMBRAVE 150, patients with viral etiology of uHCC had better outcomes than those with non-viral etiology when treated with atezolizumab+bevacizumab, consistent with RWE data from the Veterans Affairs (VA) Medical System reporting OS of 16.3 mo vs 6.1 mo, respectively. In HIMALAYA no association was seen between etiology and outcomes. The aim of this study was to further evaluate the potential interaction of disease etiology and treatment response with STRIDE in a real-world cohort. **Methods:** In this retrospective cohort study using the VA Corporate Data Warehouse, we identified all patients within the VA Medical System diagnosed with uHCC from 1/1/2015-3/31/2024 who had received at least 1 dose of the STRIDE regimen. Demographics, liver disease etiology, baseline laboratory parameters, and concomitant medications were extracted. ECOG performance status, BCLC staging, prior treatments, number of treatment cycles and

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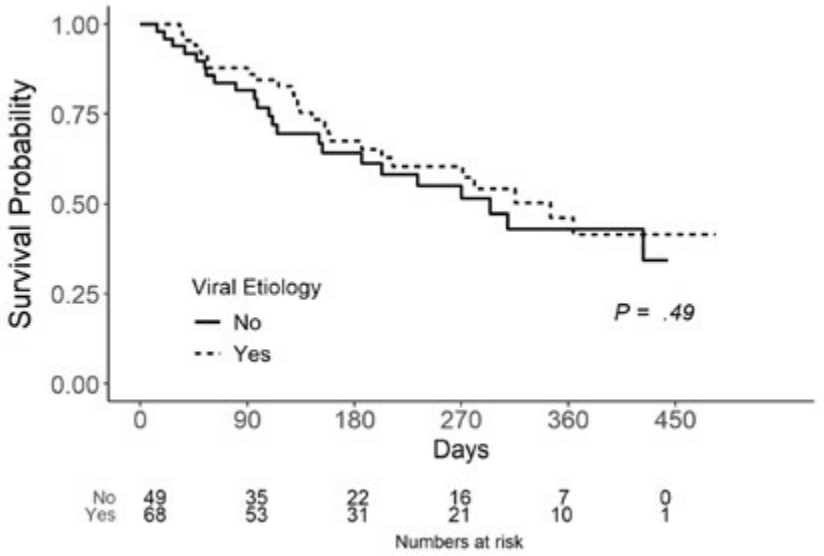
adverse events (AE) were manually abstracted by a single chart reviewer using REDCAP. Survival outcomes were evaluated using Kaplan-Meier methodologies. Cox Proportional Hazards was employed to evaluate this association, with observations adjusted for age, BCLC stage and prior locoregional (LRT). **Results:** Of the 117 uHCC patients (all male) who received STRIDE, 68 (58%) had a viral etiology (1 HBV, 38 HCV, 29 HCV + ALD) while 49 (42%) were non-viral (17 ALD, 29 MASH, 3 other). Patients with a viral etiology were slightly younger (median age 70.8 yr [67.9 – 76.1] vs 75.4 [70.2 – 77.3, p<0.001]), were more likely to be Black (vs White or Hispanic, p=0.05), and current smokers than non-viral patients. Both groups has similar baseline CP score, ECOG performance status, mALBI class, BCLC stage distribution, tumor number 3 [IQR 1-5], largest tumor size (4.1 cm [IQR 2.2-8.7], total tumor diameter, presence of MVI (36%), malignant LN (31%), and distant metastases (22%). Similar fractions had undergone prior resection or LRT (74%). Both groups received a median of 3 cycles of STRIDE [IQR 2-5]. Non-viral patients were more likely to discontinue therapy due to death or progressive disease, whereas viral patients were more likely to discontinue due to AEs or patient preference (p=0.005). Comparing patients with viral and non-viral etiologies, no difference in median OS was observed: 12.3 months [IQR 6.6 - NA] for the viral cohort and 10.5 months [IQR 7.6 - NA] for the non-viral cohort, p = 0.49. **Conclusion:** Among patients with uHCC receiving STRIDE in this real-world veteran cohort, viral versus non-viral disease etiology manifested no observable impact on OS.



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3449 | UNRAVELING IMMUNE-ACTIVATED TUMOR MICROENVIRONMENT CORRELATED WITH CLINICAL RESPONSE TO ATEZOLIZUMAB PLUS BEVACIZUMAB IN ADVANCED HEPATOCELLULAR CARCINOMA

MyungJi Goh Yong-Han Paik[1] Wonseok Kang[1] BYEONGGEUN SONG[1] Joon Hyeok Lee[1] Moon Seok Choi[1] Dong Hyun Sinn[1] Geum-Youn Gwak[1]

[1]samsung medical center

Background: In advanced hepatocellular carcinoma (HCC), tumor microenvironment (TME) can significantly influence cancer progression and treatment response. Although atezolizumab plus bevacizumab has shown treatment efficacy, mechanisms and prognostic biomarkers for such combined treatment remain unclear.

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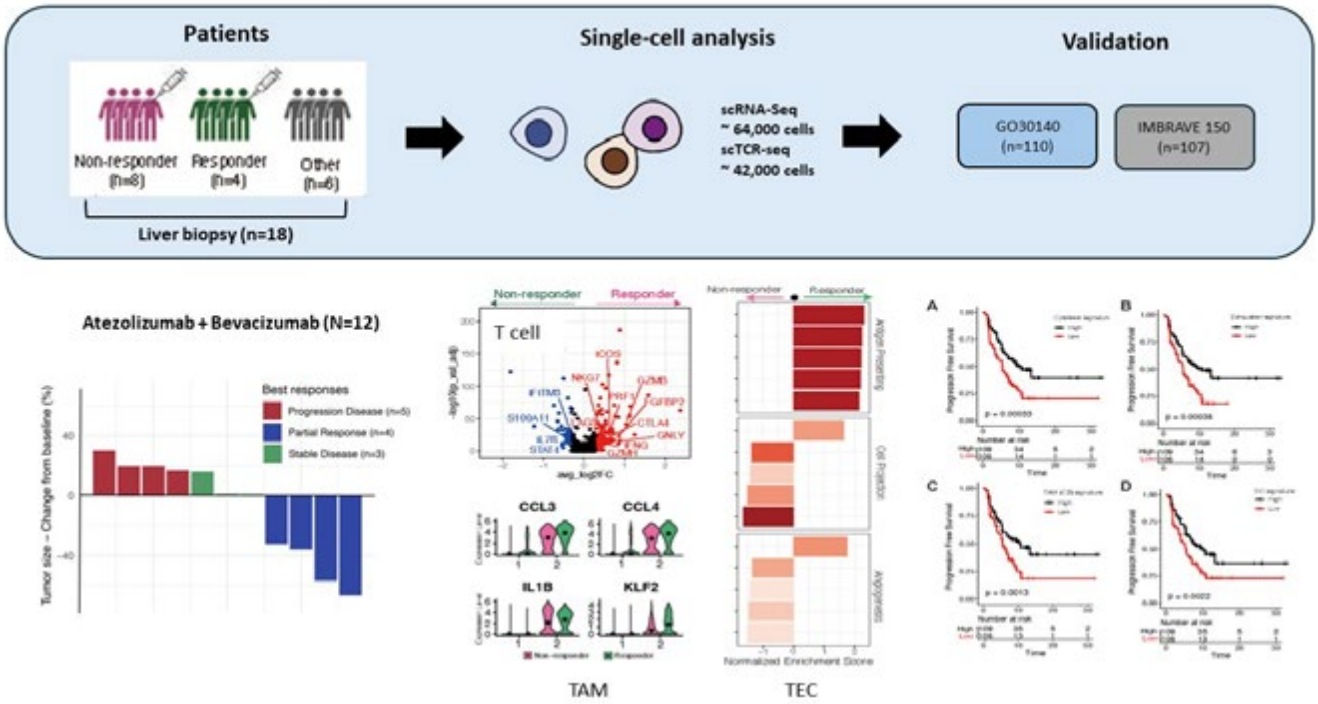
Methods: We analyzed single-cell transcriptomic and T-cell receptors sequencing data from 18 HCC patients including 12 patients undergoing atezolizumab plus bevacizumab. **Results:** Patients who responded to combination therapy with atezolizumab and bevacizumab demonstrated an immune-activated TME marked by enhanced cytotoxicity and the presence of tissue-resident T cells. Furthermore, these patients exhibited an increased population of cDC2 cells, elevated chemokine levels, including CCL3, in tumor-associated macrophages and activated the antigen-presenting function in tumor endothelial cells. These findings were validated in an independent cohort as to their prognostic significance. **Conclusion:** The existence of an activated immune TME prior to treatment is crucial for patients undergoing atezolizumab and bevacizumab to achieve a favorable clinical response. These findings could be helpful in identifying patients with advanced HCC who would benefit from this combination therapy.



Disclosures: MyungJi Goh: Nothing to Disclose, Yong-Han Paik: Nothing to Disclose, Wonseok Kang: Nothing to Disclose, BYEONGGEUN SONG: Nothing to Disclose, Joon Hyeok Lee: Nothing to Disclose, Moon Seok Choi: Nothing to Disclose, Dong Hyun Sinn: Nothing to Disclose, Geum-Youn Gwak: Nothing to Disclose

3450 | IDENTIFICATION OF ERZHU JIEDU RECIPE AND ITS MOLECULAR MECHANISM UNDERLYING INHIBITED HUMAN HEPATOMA CELLS BY UHPLC-MS/MS AND NETWORK PHARMACOLOGY

Yang Cheng[1]

[1]*Shuguang Hospital affiliated to Shanghai University of TCM*

Background: Erzhu Jiedu recipe (EZJDR) can relieve the condition of the HCC patients after partial hepatectomy. This formula consists of five herbs, A macrocephala Koidz (Baizhu, BZ), Atractylodes DC (Cangzhu, CZ), Scutellaria barbata D.Don (Banzhilian, BZL), Hedyotis diffusa (Baiuhuashecao, BHSSC) and Salvia miltiorrhiza (Danshen, DS). Our group has noticed the clinical efficacy of EZJDR on HBV cirrhosis with hyperalphafetoproteinemia, and has also demonstrated its preventive intervention on liver precancerous lesions. We previously reported that EZJDR exerted a therapeutical effect on the advanced-stage HCC patients in combination with antiviral therapy, such as entecavir and tenofovir. EZJDR treatment is not based on a single chemical component, but is based on multiple components due to holistic nature of TCM. However, the active components of EZJDR and its action mechanism underlying the liver diseases still remain important questions. **Methods:** UHPLC-MS/MS was used to identify the chemical constituent of EZJDR and their distribution in the

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serum and liver of mose. Together with experimental investigations, the network pharmacology revealed the molecular mechanism of components of EZJDR underlying the inhibited Hep3B cells. **Results:** A total of 138 compounds derived from 18 components were found in EZJDR aqueous extract. Among these was the tricyclic-diterpenoid, which exhibited a highest content in the serum (74.5%) and liver (94.7%) of mouse. The network pharmacology revealed that multiple components of EZJDR targeted key node genes involved in apoptosis, proliferation, migration and metabolism through various signaling pathways, including ligand binding and protein phosphorylation. In vitro experiments demonstrated that 6 tricyclic-diterpenoids, 2 anthraquinones and 1 flavonoid inhibited the viability of Hep3B cells, with IC50 values ranging from 3.81 μM to 37.72 μM. Among the diterpenoids was dihydrotanshinone I with the most potent bioactivity, which arrested the S phase and induced apoptosis. This compound changed the expression of proteins, including Bad, Bax, Bcl-2, Bal-x, caspase and catalase, which were associated with mitochondria-mediated apoptotic pathways. Moreover, dihydrotanshinone I increased the levels of p21 proteins, but decreased the phosphorylated p53, suggesting accumulation of p53 protein prevented cell cycle progression of Hep3B cells with damaged DNA. **Conclusion:** These results suggested that multiple components of EZJDR—diterpenoid, anthraquinone and flavonoid—could be the effective material for the treatment of HBV-HCC. This research provided valuable insights into the molecular mechanism of action underlying the therapeutic effects of EZJDR.

Disclosures: Yang Cheng: Nothing to Disclose

3451 | DNA DEMETHYLATION IN PROMOTER REGION RESTORES CYGB EXPRESSION AND ATTENUATES HEPATOCELLULAR CARCINOMA PROGRESSION

Hoang Hai[1] Le Thuy[2] Minh Phuong Dong[3] Nguyen Thi Ha[2] Duc Pham[2] Shoji Kubo[2] Akihiro Tamori[2] Atsushi Hagihara[2] Etsushi Kawamura[2] Sawako Uchida-Kobayashi[2] Masaru Enomoto[2] Norifumi Kawada[2]

[1]Osaka Metropolitan University Graduate School of Medicine, [2]Osaka Metropolitan University, [3]Loma Linda University

Background: Cytoglobin (*CYGB*) acts as a tumor suppressor gene and DNA methylation in the *CYGB* promoter region have been reported in various types of cancers such as non-small cell lung, oral, and breast. This study aims to investigate whether methylation in *CYGB* promoter associates with hepatocellular carcinoma (HCC) and demethylation restores CYGB expression and attenuates HCC. **Methods:** Forty-two pairs of tumor and adjacent non-tumor tissues from liver cancer patients with chronic hepatitis C virus infection were evaluated for *CYGB* promoter methylation using Ion GeneStudio S5. Truncated mutation analysis of human *CYGB* promoter region was performed. Restoration of CYGB expression was implemented in four HCC cell lines treated with 5-aza-2'- deoxycytidine (DAC). DAC-treated and untreated Huh7 cells (control) were subcutaneously injected into the right and left flanks in 9 nude mice, respectively. **Results:** Methylation frequency in tumors was significantly higher than that in non-tumor tissues at all of 33 CpG sites ($p = 1.02E-8$) in promoter region. Reversely, *CYGB* mRNA expression in tumor was significantly lower than that in non-tumor tissues (–60%, $p < 0.05$). Almost no methylation was found in human hepatic stellate cells that correspond to positive CYGB expression. In contrast, high methylation frequency and no CYGB expression at RNA and protein levels were found in HCC cells (HepG2, Huh7, SNU-387, HLE) and myofibroblast LX-2 cells. The truncated *CYGB* promoter region spanning from –994 to –639 positions related to translational starting site exhibited a significant decrease in promoter activity. Interestingly, DAC treatment time- and dose-dependently restored CYGB expression at both mRNA and protein levels in SNU-387, HLE and Huh7, and at mRNA level in HepG2 cells while no change in those of LX-2. Notably, after inducing CYGB expression in SNU-387, discontinuation of DAC treatment resulted in regressing of CYGB expression at both mRNA and protein levels. In vivo experiment, after 6 weeks of injection into the nude mice, DAC treatment reduced the probability of tumor occurrence compared with untreated Huh7 (log-rank test, $p < 0.0001$). The mean tumor volume in left flanks injected with Huh7 was 3570 mm^3, significantly higher than that of 61 mm^3 in right flanks injected with DAC-treated Huh7 ($p < 0.05$). **Conclusion:** Down-regulation of CYGB through promoter methylation is associated with HCC progression. Demethylation of *CYGB* gene promoter may lead to cancer regression.

Disclosures: Hoang Hai: Nothing to Disclose, Le Thuy: Nothing to Disclose, Minh Phuong Dong: Nothing to Disclose, Nguyen Thi Ha: Nothing to Disclose, Duc Pham: Nothing to Disclose, Shoji Kubo: Nothing to Disclose, Akihiro Tamori: Nothing to Disclose, Atsushi Hagihara: Nothing to Disclose, Etsushi Kawamura: Nothing to

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Disclose, Sawako Uchida-Kobayashi: Nothing to Disclose, Masaru Enomoto: Nothing to Disclose, Norifumi Kawada: Nothing to Disclose

3452 | RE-CLASSIFICATION OF COMBINED HEPATOCELLULAR-CHOLANGIOCARCINOMA AND SMALL DUCT TYPE INTRAHEPATIC CHOLANGIOCARCINOMA BY GENETIC ALTERATIONS

Motoko Sasaki[1] *Yasunori Sato*[1] *yasuni nakanuma*[2]

[1]*Kanazawa University,* [2]*Fukui Saiseikai Hospital*

Background: Combined hepatocellular-cholangiocarcinoma (cHCC-CCA) shares various features such as cholangiolocellular carcinoma (CLC) components, etiologies and possible cell origin with small duct type intrahepatic cholangiocarcinoma (SmD-iCCA). Therefore, it may be difficult to draw a clear line between these 2 entities. We addressed to re-classify primary liver carcinoma including cHCC-CCA and CLC/SmD-iCCA. **Methods:** We examined genetic alterations of hTERT promoter (hTERT), IDH1 or 2 (IDH1/2), KRAS, fibroblast growth factor receptor 2 (FGFR2), methylthioadenosine phosphorylase (MTAP), ARID1A, PBRM1, ARID2, BAP1, p53 by PCR and direct sequence or immunohistochemical staining in 103 primary liver carcinomas diagnosed as cHCC-CCA or CLC/SmD-iCCA in 100 patients (28 women and 72 men, mean 67 yrs.). Primary liver carcinomas were divided into clusters using a cluster analysis on the R software. The clinicopathological features including nestin expression in each cluster were analyzed. **Results:** The primary liver carcinomas were divided into 5 clusters; 19 tumors (18%) in Cluster-1 (alterations in hTERT and/or p53-prone), 24 (23%) in Cluster-2 (FGFR2 and/or p53-prone), 13 (13%) in Cluster-3 (IDH2 or null), 19 (18%) in Cluster-4 (MTAP and/or FGFR2-prone), 28 (27%) in Cluster-5 (ARID1A and/or PBRM1-prone), being based on genetic alterations. Cluster-1 and Clusters-2 to- 5 formed distinct 2 groups. Cluster-1 was characterized by significantly bigger size ($p<0.05$), rich hepatocellular carcinoma (HCC) component ($p<0.01$), high histological grade of HCC component ($p<0.01$), less CLC-component ($p<0.01$), less ductal plate malformation pattern ($p<0.05$) and less bile duct adenoma in the background livers ($p<0.01$). No CLC/SmD-iCCAs and cHCC-CCAs with predominant CLC was included in Cluster-1, whereas they distributed similarly in Clusters 2-5. Cluster-4 was characterized by higher prevalence of hepatitis B ($p<0.05$) and higher histological diversity scores ($p<0.05$). There was no significant difference in the expression of nestin and AFP among the Clusters 1-5. **Conclusion:** Primary liver carcinomas diagnosed as cHCC-CCA and CLC/SmD-iCCA could be divided into 5 clusters based on genetic alterations. Cluster-1 was HCC-like cluster characterized by hTERT alteration, HCC-component-rich, high grade of HCC and bigger size. Clusters-2-5 may be iCCA-like clusters characterized by different genetic alterations. cHCC-CCA in Cluster-1 and Clusters-2-5 should be handled separately for further analysis and treatment.

Disclosures: Motoko Sasaki: Nothing to Disclose, Yasunori Sato: Nothing to Disclose, yasuni nakanuma: Nothing to Disclose

3453 | MARIJUANA USE IS NOT INDEPENDENTLY ASSOCIATED WITH THE INCIDENCE OF HEPATOCELLULAR CARCINOMA IN PATIENTS WITH CIRRHOSIS

Tae Hoon Lee[1] *Kristel Hunt*[1] *David Kaplan*[2] *Tamar Taddei*[3]

[1]*Icahn School of Medicine at Mount Sinai,* [2]*University of Pennsylvania,* [3]*Yale University*

Background: Use of marijuana continues to expand in the United States, yet its effects on patients with cirrhosis are largely unknown. This study analyzed the Veterans Outcomes and Costs Associated with Liver Disease (VOCAL) cohort retrospectively from Veterans Health Administration (VA) Informatics and Computing Infrastructure (VINCI) to determine any effects of marijuana use on the incidence of hepatocellular carcinoma (HCC). **Methods:** The VOCAL cohort is comprised of veterans with cirrhosis, receiving their care at the VA. Patients' urine and serum toxicology reports were utilized to define study groups: if a patient had any positive result for marijuana, the patient was classified as a marijuana user (THC_User). All negative results classified the patient as a nonuser (THC_Nonuser) and someone who had never been tested was classified as no test group (Not_Tested). The cumulative incidence of HCC was compared between marijuana use groups with Gray's test. A Cox Proportional Hazard regression was performed to investigate the effect of marijuana use on HCC

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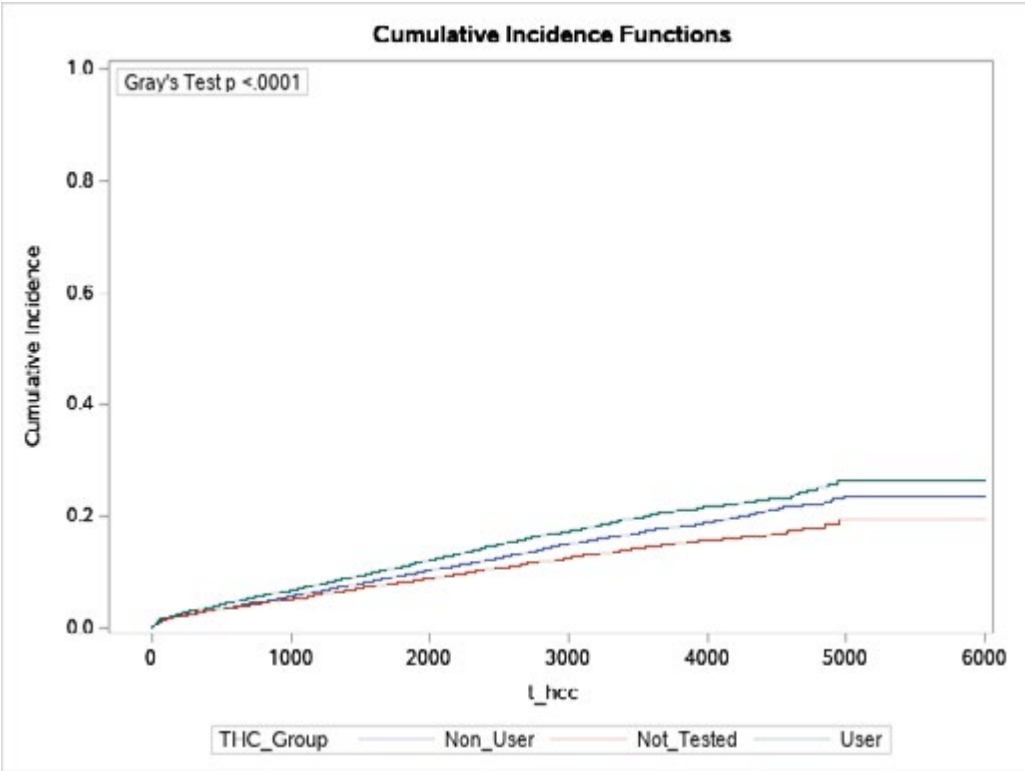
incidence after adjusting for multiple variables. **Results:** Out of 90,683 cirrhotic veterans who did not have a diagnosis of HCC at baseline, 8,903 patients (9.82%) developed HCC during the follow up period. THC_User group (2,659 patients [12.52%]) had a higher incidence of HCC than THC_Nonuser (4,365 patients [9.83%]) and Not_Tested group (1,879 patients [7.55%]) ($p<0.01$, Figure 1) After adjusting for age, gender, BMI, race, tobacco use, hypertension, diabetes/impaired fasting glucose, congestive heart failure, chronic kidney disease, COPD, and baseline MELD score in the Cox proportional hazard model, Not_Tested group (HR=0.691, $p<0.001$) and THC_Nonuser group (HR= 0.849, $p<0.001$) had significantly lower HCC incidence compared to the THC_User group. After adjustment for key baseline covariates and specifically the etiology of cirrhosis, marijuana use was no longer significantly associated with HCC incidence. (Not_Tested group: HR=0.972, 95%CI 0.906 - 1.042; THC_Nonuser group: HR=1.037, 95%CI 0.985 - 1.091). Instead, HCV etiology (HR=2.463, 95%CI 1.229 - 4.934) and Alcohol+HCV etiology (HR=4.232, 95%CI 2.112 - 8.487) were independently associated with HCC incidence. **Conclusion:** Patients with cirrhosis due to viral rather than non-viral causes were much more likely to be marijuana users (36.58% vs 14.41%). After adjusting for etiology of liver disease, marijuana use no longer had an independent effect on HCC incidence. Further studies should address the relationship between viral hepatitis, marijuana, and HCC risk.



Disclosures: Tae Hoon Lee: Merck & Co., Inc.: Chapter Authorship of Merck Manual, Salix Pharmaceuticals, Inc. an affiliate of Bausch Health US: Grant/Research Support, Kristel Hunt: Nothing to Disclose, David Kaplan: Independent Contractor relationship with Roche Genentech; Has not ended; Grant/Research Support relationship with AstraZeneca Inc; Has not ended; Advisor relationship with AstraZeneca; Has ended; Advisor relationship with Exelixis; Has ended; Grant/Research Support relationship with Gilead; Has not ended; Advisor relationship with Sirtex; Has ended; Grant/Research Support relationship with Exact Sciences; Has not ended; Grant/Research Support relationship with Glycotest; Has ended, Tamar Taddei: Nothing to Disclose

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3454 | INCORPORATING GERIATRIC NUTRITIONAL RISK INDEX WITH ALBI GRADE IMPROVES RISK STRATIFICATION IN PATIENTS WITH HEPATOCELLULAR CARCINOMA: BASED ON KOREA CENTRAL CANCER REGISTRY DATABASE ◆

Heechul Nam[1] Sung Won Lee[1] Chang Wook Kim[2] SI HYUN BAE[1]

[1]The Catholic University of Korea, [2]Uijeongbu St. Mary's Hospital

Background: Despite its prognostic impact, nutritional status is not integrated into staging of hepatocellular carcinoma (HCC). This study investigated the association between geriatric nutritional risk index (GNRI) and survival in patients with HCC using nationwide registry database. **Methods:** The study utilized data from the Korea Central Cancer Registry from 2008 to 2019. Overall survival (OS) was analyzed according to albumin–bilirubin (ALBI) grade, Barcelona Clinic Liver Cancer (BCLC) stage, GNRI, and other prognostic factors. Restricted cubic spline regression was conducted to apply different GNRI cut-off values within each ALBI grade. **Results:** The study enrolled 16,416 naïve HCC patients, with a median age of 61 years, of whom 79.2% were male. Patients were categorized into ALBI grades as follows: 7,409 in grade 1, 7,445 in grade 2, and 1,562 in grade 3. Patients were distributed across BCLC stages: 5,132 in stage 0/A, 2,608 in stage B, 5,289 in stage C, and 968 in stage D. Median OS for all patients was 3.1 years (95% CI; 3.0-3.2) and significantly differed according to the incorporation of ALBI grade and GNRI (P<0.001). The impact of the combination of ALBI and GNRI was further assessed within each BCLC stage. This risk stratification based on incorporation of ALBI and GNRI showed a significant correlation with OS in each stage (all P<0.001), except for BCLC stage D (refer to Figure 1). Multivariate analysis revealed that the combination of favorable ALBI grade and high GNRI was independently associated with decreased mortality risk (refer to Table 1). **Conclusion:** GNRI showed a significant correlation with OS within each respective ALBI grade and BCLC stage. Incorporating ALBI grade with GNRI may provide enhanced risk stratification for patients with HCC.

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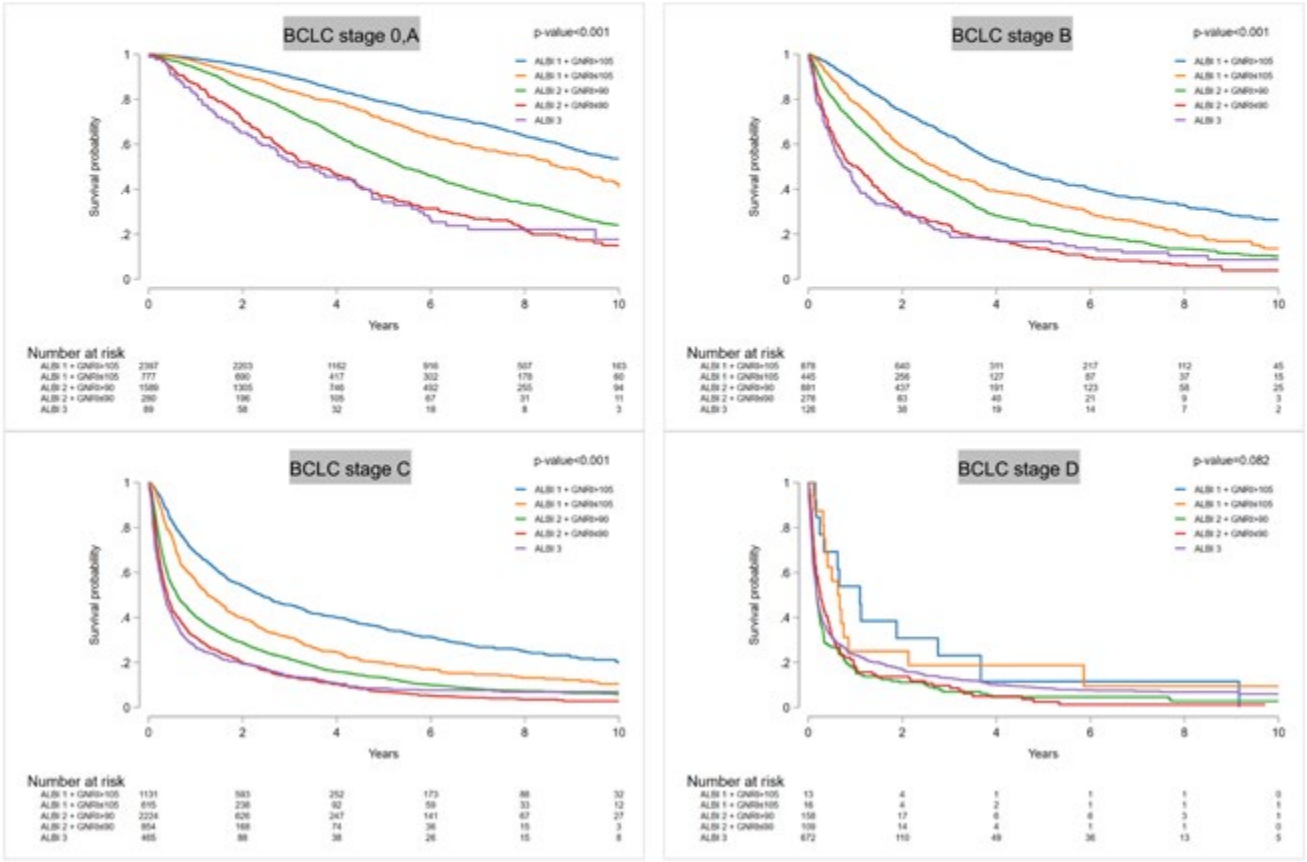
Table 1. Univariate and multivariate analyses of association between GNRI and survival

	Model 0		Model 1		Model 2	
Variable	Crude HR (95% CI)	Crude P	Adjusted HR (95% CI)	Adjusterd P	Adjusted HR (95% CI)	Adjusterd P
GNRI						
low	reference		reference		reference	
high	0.714 (0.685-0.744)	<0.001	0.732 (0.702-0.763)	<0.001	0.800 (0.760-0.842)	<0.001
ALBI + GNRI						
ALBI 3	reference		reference		reference	
ALBI 2 + GNRI≤90	0.783 (0.728-0.842)	<0.001	0.715 (0.665-0.769)	<0.001	0.887 (0.812-0.968)	0.007
ALBI 2 + GNRI>90	0.495 (0.466-0.526)	<0.001	0.471 (0.443-0.501)	<0.001	0.717 (0.665-0.773)	<0.001
ALBI 1 + GNRI≤105	0.306 (0.283-0.330)	<0.001	0.288 (0.267-0.311)	<0.001	0.420 (0.382-0.460)	<0.001
ALBI 1 + GNRI>105	0.193 (0.181-0.207)	<0.001	0.186 (0.173-0.199)	<0.001	0.311 (0.286-0.338)	<0.001

Model 0: Not adjusted; Model 1: Adjusted for age and sex; Model 2: Adjusted for age, sex, BMI, platelet count, ALBI grade, BCLC stages, etiology, and alpha fetoprotein.
Abbreviations: GNRI, geriatric nutritional risk index; HR, hazard ratio; CI, confidence interval; ALBI, albumin to bilirubin; BMI, body mass index; BCLC, Barcelona Clinic Liver Cancer.



Disclosures: Heechul Nam: Nothing to Disclose, Sung Won Lee: Nothing to Disclose, Chang Wook Kim: Nothing to Disclose, SI HYUN BAE: Nothing to Disclose

3455 | OUTCOMES OF COMBINED HEART AND LIVER TRANSPLANTS IN PATIENTS WITH CONGESTIVE HEPATOPATHY AND HCC: ANALYSIS OF US NATIONAL DATABASE

Fadl Zeineddine[1] *Efstathia Polychronopoulou*[2] *Prasun Jalal*[3]

[1]*Houston Methodist Hospital,* [2]*University of Texas Medical Branch,* [3]*Baylor College of Medicine*

Background: Liver nodules are common in presence of congestive hepatopathy, especially in patients with congenital heart disease. A diagnosis of HCC in such patients is difficult and prognosis is poor. Combined heart and liver transplant probably offers the best treatment choice in such patients. We aim to study outcomes of patients with the diagnosis of HCC undergoing simultaneous heart and liver transplantation. **Methods:** We

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retrospectively analyzed United Network for Organ Sharing (UNOS/OPTN) database for patients with heart and liver transplants between April 1, 2012 and June 31, 2023. HCC patients were identified if listed with the diagnosis and/or had exception points for HCC. Pre-transplant radiology characteristics and histology on explant were outlined. Post-transplant patient survival was compared with patients receiving combined heart and liver transplants without HCC. **Results:** A total of 863 patients were listed for combined heart and liver transplant; 43 had diagnosis of HCC. 427 underwent simultaneous heart and liver transplant during the period and 18 had a diagnosis of HCC. Six out of 18 patients had exception points for HCC and explant confirmed HCC in all six patients. Median number of tumors on explant was 2 (range 1-4); median size of tumors on explant was 2.9 cm (range 1.5 cm-4.2 cm). Seven out of 18 received locoregional treatment pre-transplant. 1 had microvascular invasion post-transplant. When compared to non-HCC group, median age was similar (43 yrs. vs 48 yrs., p=0.68); 55.56% (n=10) in HCC group had congenital heart disease compared with 35.69% (n=146) in non-HCC group (p=0.08). Unadjusted 1-year mortality rate between the HCC and non-HCC groups was: 93.75% (95% CI, 63.23%-99.1%) vs. 82.95% (95% CI, 78.6%-86.5%), p=0.30. 3-year mortality rate between HCC and non-HCC groups was 85.23% (95% CI, 51.9%-96.18%) vs. 74.98% (95% 69.4%- 79.69%), p=0.52. 5-year mortality rate between the two groups was 85.23% (95% CI, 51.9%-96.18%) vs. 74.98% (95% CI, 69.4%-79.69%), p=0.47. HCC recurrence occurred in 2 patients after 118 and 152 days. **Conclusion:** Patients undergoing simultaneous heart and liver transplant with a diagnosis of HCC had comparable survival outcomes compared to those without HCC and should be considered as a therapeutic strategy.

Disclosures: Fadl Zeineddine: Nothing to Disclose, Efstathia Polychronopoulou: Nothing to Disclose, Prasun Jalal: Nothing to Disclose

3456 | CAUSAL ASSOCIATION AND PROGNOSTIC VALUE OF TERTIARY LYMPHOID STRUCTURE-RELATED GENE SIGNATURES IN HCC

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Background: Tertiary lymphoid structures (TLS) are organized aggregates of immune cells that form in a chronic inflammatory or tumor environment. However, the causal association of TLS with the onset of hepatocellular carcinoma (HCC) and its prognostic value after the onset remain unknown. **Methods:** Gene cards and IEU GWAS databases were used to obtain TLS-related Genes (TLSG), eqtl data, and HCC GWAS data (ieu-b-4953), and the Inverse Variance Weighted method was used to perform Mendelian randomization (MR) analyses. The TCGA database was used to obtain RNA-seq from HCC patients and conduct differentially expressed genes (DEGs) analysis, and the genes identified by MR analysis were intersected with DEGs. A TLSG-related prognostic signature (TLSGPS) was constructed using univariate and multivariate COX analysis, and prognostic analyses were performed. Additionally, we performed biological function and immune infiltration analyses based on TLSGPS. **Results:** 21 intersecting genes were obtained from 194 genes causally associated with HCC and 2421 DEGs. Among them, HM13 (HR=1.595, P=0.002), CSTB (HR=1.46, P=0.005), CDCA7L (HR=1.363, P=0.02), SUPT3H (HR=1.86, P=0.007), and S100A10 (HR=1.25, P=0.008) correlated with the survival of HCC patients and were used to construct TLSGPS. In addition, MR analysis revealed that HM13 (OR=0.9997, P=0.01), CSTB (OR=0.9997, P=0.04), SUPT3H (OR=0.9996, P=0.002), S100A10 (OR=0.9996, P=0.02) negatively correlated with the risk of HCC, while CDCA7L (OR=1.0004, P=0.01) was the opposite. TLSGPS exhibited better predictive ability (AUC=0.656) than other clinical phenotypes, and had good predictive ability at 1 (AUC=0.739), 3 (AUC=0.656), and 5 (AUC=0.673) years. There was a significant difference in overall survival between the TLSGPS-based high-risk group (HRG) and low-risk group (LRG), and the mortality rate increased with the increase of risk. The biological functions and pathways that differed between HRG and LRG involved cell proliferation and differentiation. The abundance of T cells CD4 memory resting, Monocytes, and Dendritic cells resting was significantly lower in the HRG than in LRG, while the opposite was true for T cells CD4 memory activated. **Conclusion:** Each of the five TLSGs (HM13, CSTB, CDCA7L, SUPT3H, and S100A10) was causally associated with the risk of HCC and was a prognostic biomarker for predicting HCC.

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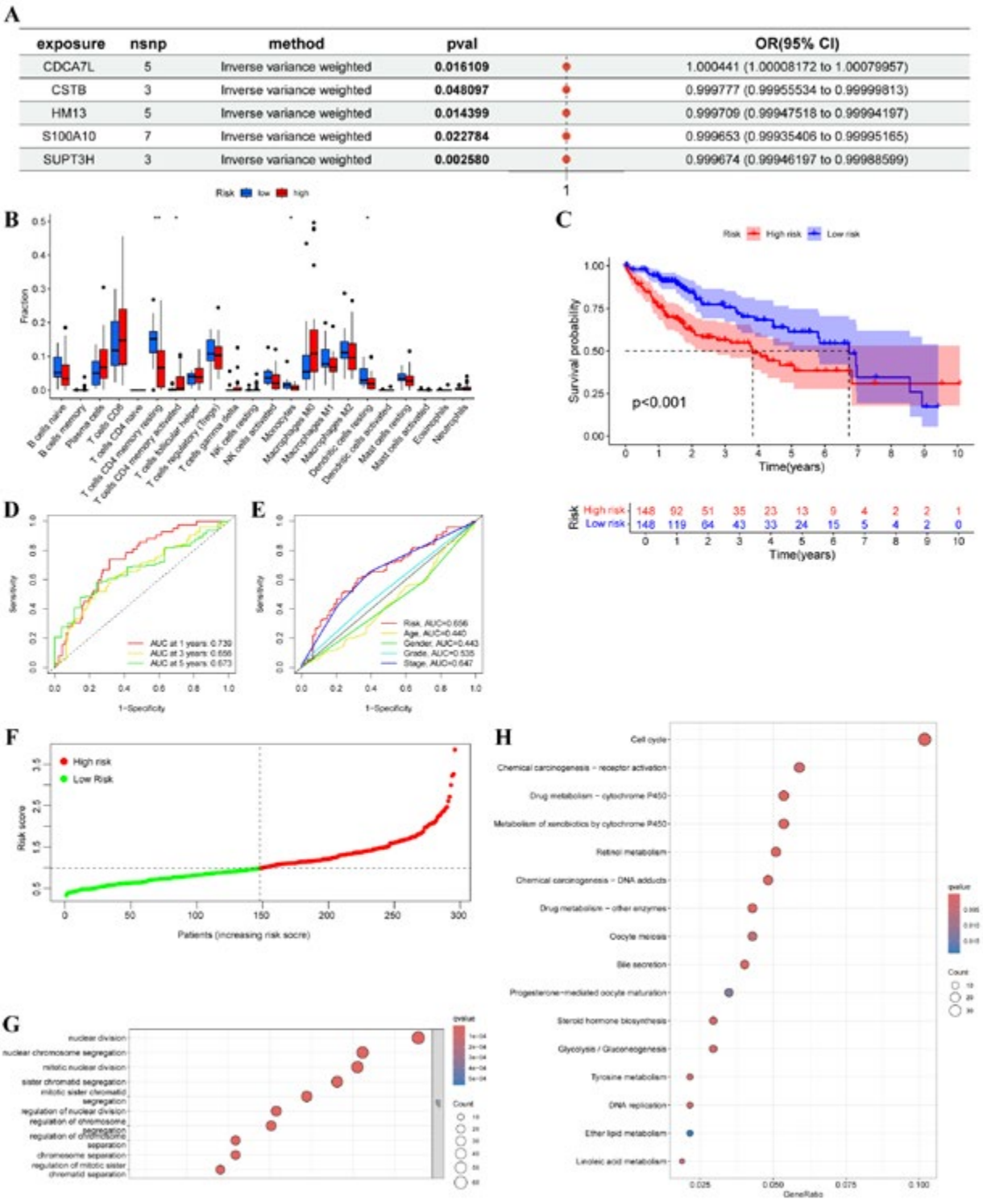

Disclosures: Lei Pu: Nothing to Disclose, Cheng Pu: Nothing to Disclose, Xiaoyan Zhang: Nothing to Disclose

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3457 | NOVEL MIRNA METHYLATION PATTERNS SPECIFIC TO HEPATOCELLULAR CARCINOMA IN THE POST-SVR PATIENTS

Takehisa Watanabe[1] Katsuya Nagaoka[1] Shintaro Ogawa[1] Satoshi Narahara[1] Hiroki Inada[1] Sanae Hayashi[1] takayuki tokunaga[1] Etsuko Iio[1] Yoko Yoshimaru[1] Hiroko Setoyama[1] Takehito Ohshiro[2] Ishii Hideshi[2] Yasuhito Tanaka[1]

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Background: Liver carcinogenesis post-SVR is a significant concern. This study explores miRNAs that predict hepatocellular carcinoma (HCC) in post-SVR patients and investigates their methylation. **Methods:** With informed consent, we extracted miRNA from stored serum at SVR 24 in 43 cases of post-SVR HCC (Case group) and 37 controls (Control group). Comprehensive RNA-seq analysis and intergroup comparison identified miRNAs with significant changes (≥2-fold) and stable measurability. LASSO regression analysis via AI selected candidate miRNAs as potential post-SVR HCC predictive markers. Validation was performed using q-PCR on a separate cohort of 68 cases and 224 controls. Additionally, single-molecule quantum sequencing, which allows base-specific methylation modification analysis, was used to assess the methylation of miRNAs in the serum of 10 cases and 10 controls around SVR 24. **Results:** Four candidate miRNAs were identified from the RNA-seq results. Validation with the separate cohort indicated significant differences in serum miR-x13 levels between groups ($p<0.001$) and a similar trend for miR-x7 ($P=0.067$). The AUROC for miR-x13 was 0.76 ($p=0.002$), suggesting its potential as a predictive marker for post-SVR HCC. Moreover, adenine (A) methylation in miRNAs was increased in the HCC group compared to the Control group, and the miRNA methylation patterns differed between groups, indicating post-SVR HCC-specific methylation patterns. Comparative analysis of the miRNA methylation in stored serum from five cases each of post-SVR HCC and non-viral HCC identified five specific methylation patterns unique to post-SVR HCC, including the methylation of the sixth adenine in miR-x13, which was absent in the Control group. Conversely, miR-x7 did not exhibit any specific methylation patterns in post-SVR HCC. **Conclusion:** miR-xx13 has the potential to predict post-SVR HCC. A specific miRNA methylation pattern for post-SVR HCC in miR-xx13 existed, necessitating further functional analysis to understand its biological significance.

Disclosures: Takehisa Watanabe: Nothing to Disclose, Katsuya Nagaoka: Nothing to Disclose, Shintaro Ogawa: Nothing to Disclose, Satoshi Narahara: Nothing to Disclose, Hiroki Inada: Nothing to Disclose, Sanae Hayashi: Nothing to Disclose, takayuki tokunaga: Nothing to Disclose, Etsuko Iio: Nothing to Disclose, Yoko Yoshimaru: Nothing to Disclose, Hiroko Setoyama: Nothing to Disclose, Takehito Ohshiro: Nothing to Disclose, Ishii Hideshi: Nothing to Disclose, Yasuhito Tanaka: Nothing to Disclose

3458 | PREVALENCE OF CHRONIC LIVER DISEASE IN CHOLANGIOCARCINOMA: A META-ANALYSIS

Ethan Kai Jun Tham[1] Ryan Lim[2] Darren Jun Hao Tan[1] Wen Hui Lim[3] Cheng Han Ng[4] Pojsakorn Danpanichkul[5] Karn Wijarnpreecha[6] Mark Muthiah[7] Alfred Kow[8] Jia Hao Law[7] Daniel Huang[9]

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Background: Chronic liver disease (CLD) is a known risk factor for cholangiocarcinoma but It is unclear the proportion of patients with CCA have concurrent CLD. This meta-analysis aims to evaluate the prevalence of CLDs in patients with cholangiocarcinoma. **Methods:** In this single-arm meta-analysis, we searched MEDLINE and EMBASE from inception to 6th June 2023 for articles in English containing data for cholangiocarcinoma with and without CLDs. Population data was pooled to obtain the prevalence of different CLDs, with further stratification by geographical location and tumor location. **Results:** In total, 119,022 individuals with cholangiocarcinoma [A1] and 16,102 individuals with both cholangiocarcinoma and CLD were included. A pooled analysis of 100 studies determined that CLD prevalence was 24.08% (95% CI: 19.52 – 29.31%; I^2=99.0%), and 9.16% (6.84% – 12.16%; I^2=98.7%) of CCA patients had cirrhosis. CLDs were associated with intrahepatic CCAs, compared to extrahepatic CCAs (RR: 2.72, CI: 2.62 – 2.82, $p < 0.0001$). This was observed across all etiologies

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of liver disease, except for primary sclerosing cholangitis which was associated with extrahepatic CCAs (RR: 0.49; CI: 0.43 – 0.57, p < 0.0001) **Conclusion:** Around one in four people with cholangiocarcinoma are known to have CLDs. CLDs were more likely to be associated with intrahepatic CCAs.

Disclosures: Ethan Kai Jun Tham: Nothing to Disclose, Ryan Lim: Nothing to Disclose, Darren Jun Hao Tan: Nothing to Disclose, Wen Hui Lim: Nothing to Disclose, Cheng Han Ng: Nothing to Disclose, Pojsakorn Danpanichkul: Nothing to Disclose, Karn Wijarnpreecha: Nothing to Disclose, Mark Muthiah: Lerna Bio: Stock – privately held company, Olympus: Speaking and Teaching, Boston Scientific: Speaking and Teaching, Novo Nordisk: Grant/Research Support, Echosens: Grant/Research Support, Gilead: Advisor, Alfred Kow: Nothing to Disclose, Jia Hao Law: Nothing to Disclose, Daniel Huang: Nothing to Disclose

3459 | HEPATOMA-DERIVED GROWTH FACTOR (HDGF) IS AN ONCOGENE ON CHROMOSOME 1Q IN LIVER CANCER

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Background: Chromosome 1q is frequently amplified and a plausible hot spot of oncogenes in hepatocellular carcinoma (HCC). *Hepatoma-derived growth factor* (*HDGF*) is located on chromosome 1q23 and its nuclear overexpression is associated advanced stages and poor prognosis in HCC. However, the incidence and oncogenic potential of HDGF in HCC remains unclear. The present study employed multiple-disciplined approaches to delineate the oncogenic role of HDGF in liver cancer. **Methods:** The Cancer Genome Atlas (TCGA) cohort study was used to explore molecular significance and outcome in liver cancer. A cohort of 90 resected HCC specimens consisting of paired non-tumor and tumor tissues were employed for immunoblot analysis to investigate the prevalence of HDGF overexpression and its relationship with other clinical parameters by statistical analysis. Adenovirus gene delivery was utilized to investigate the influence of HDGF overexpression/knockdown on tumorigenic behaviors of HCC cells *in vitro* and *in vivo*. **Results:** TCGA analysis revealed that elevated *HDGF* mRNA level was correlated with disease progression, shorter survival and earlier recurrence in HCC patients. Moreover, the *HDGF* copy number is highly amplified in liver cancer. By using resected paired HCC specimens, immunoblot analysis found that HDGF overexpression is highly frequent event (about 60-70%). Besides, patients with HDGF overexpression exhibited significantly shorter survival rates and disease-free survival. Multivariate analysis indicated HDGF overexpression constitute an independent prognostic factor for the overall survival and recurrence of HCC patients after surgery. By adenovirus gene delivery, it was shown that HDGF overexpression promotes the proliferation, invasion and colonies formation of HCC cells and growth of xenografted HCC in SCID mice. In contrast, HDGF knockdown effectively attenuated the tumorigenesis of HCC *in vitro* and *in vivo*. **Conclusion:** TCGA and immunoblot analysis support that *HDGF* is an oncogene located on chromosome 1q and amplified during liver carcinogenesis. Besides, HDGF upregulation in resected HCC specimens may constitute a useful biomarker for prognosis of HCC patients after surgery. Finally, HDGF targeting may perturb the malignant progression of HCC, thereby facilitating a novel strategy to combat HCC.

Disclosures: Tsung-Hui Hu: Nothing to Disclose

3460 | ESCALATING BURDEN OF MASH ASSOCIATED HCC. AN UPDATED ANALYSIS OF GLOBAL BURDEN OF DISEASE 2021

Cheng Han Ng[1] *EN YING TAN*[1] *Darren Jun Hao Tan*[2] *Wen Hui Lim*[2] *Ethan Kai Jun Tham*[2] *Pojsakorn Danpanichkul*[3] *Karn Wijarnpreecha*[4] *Mark Muthiah*[1] *Daniel Huang*[1]

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Background: Metabolic dysfunction-associated steatohepatitis (MASH) is a progressive form of metabolic dysfunction associated steatotic liver disease (MASLD) that can lead to liver cancer. With increasing prevalence due to rising rates of obesity and metabolic syndrome, understanding trends in MASH-related liver cancer is crucial for public health planning and resource allocation. **Methods:** We analyzed data on liver cancer incidence,

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mortality, and disability-adjusted life years (DALYs) from 2010 to 2021. We focused on MASH-related liver cancer across different regions, socio-demographic indexes (SDIs), and sexes. Age-standardized incidence (ASIR), death (ASDR), and DALYs (ASDALYs) rates per 100,000 persons were calculated with their respective 95% uncertainty intervals (UI). Temporal trends were assessed using annual percentage change (APC) and associated 95% confidence intervals (CIs). **Results:** From 2010 to 2021, the global incidence of MASH-related liver cancer increased from 29,147 (95% UI: 24,027-35,167) to 42,291 (95% UI: 34,033-51,129), with the ASIR rising from 0.46 (95% UI: 0.38-0.55) to 0.49 (95% UI: 0.40-0.60) per 100,000, reflecting an APC of 0.68% (95% CI: 0.62-0.73, $p < 0.001$). This is in contrast to the reduced incidence of liver cancer of any etiology, with an APC of -0.52% (95% UI: 0.59-0.45, $p < 0.001$). The proportion of liver cancers that were reported as MASH-related increased from 7.02 to 8.05%. The number of deaths due to MASH-related liver cancer increased from 28,259 (95% UI: 23,212-34,209) to 40,925 (95% UI: 32,961-49,610), with ASDR rising from 0.45 (95% UI: 0.37-0.54) to 0.48 (95% UI: 0.39-0.58) per 100,000, reflecting an APC of 0.63% (95% CI: 0.37-0.88, $p < 0.001$). Similarly, DALYs due to MASH-related liver cancer increased from 712,890 (95% UI: 581,915-858,291) to 995,475 (95% UI: 808,799-1,201,789), with the ASDALYs rate increasing from 10.84 (95% UI: 8.9-12.97) to 11.5 (95% UI: 9.39-13.84) per 100,000, reflecting an APC of 0.56% (95% CI: 0.38-0.73, $p < 0.001$). **Conclusion:** The significant increase in MASH-related liver cancer over the past decade underscores the growing public health challenge posed by metabolic diseases. Rising trends in incidence, mortality, and DALYs highlight the need for enhanced screening, preventive measures, and targeted interventions to address the burden of MASH and its progression to liver cancer. Future research should focus on developing effective therapies and public health strategies to mitigate the impact of this escalating health concern.

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3461 | REAL-WORLD CLINICAL CHARACTERISTICS AND TREATMENT PATTERNS AMONG PATIENTS WITH UNRESECTABLE HEPATOCELLULAR CARCINOMA (UHCC) AMENABLE TO LOCOREGIONAL THERAPY (LRT) IN THE UNITED STATES (US)

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Background: LRT, including transarterial chemoembolization (TACE), transarterial radioembolization (TARE), and transarterial embolization (TAE), is commonly used in patients with uHCC amenable to LRT; however, disease recurrence often occurs within 1 year of treatment. Data on real-world treatment patterns and outcomes following LRT in patients with uHCC are limited. We aimed to describe demographics, clinical characteristics, and treatment patterns in patients with uHCC treated with LRT in the US. **Methods:** We performed a retrospective observational study using Optum's de-identified Market Clarity Data. Adults treated with LRT (TACE, TARE, or TAE) between July 2016 and Sept 2022 following HCC diagnosis were included. Patients were followed from index (date of first LRT) until death, end of continuous eligibility, or end of study period (Sept 2023), whichever is earlier. Demographics, clinical characteristics, and treatment patterns were described. **Results:** Of the 1458 patients included, 33.5%, 41.8%, and 24.6% of patients received TACE, TARE, or TAE at index, respectively. At index, TACE was the most common LRT between 2016 and 2017, and TARE was the most common LRT between 2018 and 2022. The median age at index was 65 years; 74.6% of patients were male and 66.6% of patients were White. Most patients had liver cirrhosis (80.5%), were ALBI Grade ≥2 (70.0%; n/N=704/1005), with an AFP ≤400 ng/mL (82.2%; n/N=626/762) and a Charlson Comorbidity Index of ≥3 (75.9%; primary malignancies/metastatic solid tumors not counted). Overall, 63.2% of patients received ≥1 subsequent treatment post-index;

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the most common first subsequent treatment was embolization (Table). The median (95% CI) time from index to first subsequent treatment or death was 5.9 (5.5–6.3) months (Table). At any time post-index, 40.5% of patients received embolization, 21.7% of patients received curative-intent therapy, and 24.1% of patients received systemic therapy (Table). **Conclusion:** In this real-world cohort of patients with uHCC treated with LRT, TARE was the most common treatment received at index during the study period. Most patients received ≥1 subsequent treatment post-index, with embolization as the most common first subsequent treatment received. The median time to first subsequent treatment or death was less than 6 months. These findings highlight the unmet need for patients with uHCC amenable to LRT, which warrants further clinical investigation.

Table. Treatment patterns during the follow-up period

	Received TACE at index (N=489)	Received TARE at index (N=610)	Received TAE at index (N=359)	Overall (N=1458)
Received ≥1 subsequent treatment post-index, n (%)	345 (70.6)	380 (62.3)	196 (54.6)	921 (63.2)
First subsequent treatment(s) received*,†	**N=345**	**N=380**	**N=196**	**N=921**
Embolization, n (%)	**184 (53.3)**	**220 (57.9)**	**107 (54.6)**	**511 (55.5)**
TACE	130 (37.7)	41 (10.8)	17 (8.7)	188 (20.4)
TARE	29 (8.4)	124 (32.6)	19 (9.7)	172 (18.7)
TAE	24 (7.0)	50 (13.2)	70 (35.7)	144 (15.6)
TACE + TARE	NA	5 (1.3)	NA	7 (0.8)
Curative-intent therapy, n (%)	**78 (22.6)**	**61 (16.1)**	**33 (16.8)**	**172 (18.7)**
Ablation	32 (9.3)	21 (5.5)	13 (6.6)	66 (7.2)
Liver transplant	26 (7.5)	30 (7.9)	9 (4.6)	65 (7.1)
Hepatic resection	11 (3.2)	10 (2.6)	11 (5.6)	32 (3.5)
Hepatic resection + liver transplant	9 (2.6)	NA	NA	9 (1.0)
Systemic therapy, n (%)	**53 (15.4)**	**82 (21.6)**	**35 (17.9)**	**170 (18.5)**
Sorafenib	23 (6.7)	36 (9.5)	17 (8.7)	76 (8.3)
Atezolizumab + bevacizumab	10 (2.9)	14 (3.7)	5 (2.6)	29 (3.2)
Nivolumab	6 (1.7)	14 (3.7)	6 (3.1)	26 (2.8)
Lenvatinib	8 (2.3)	5 (1.3)	5 (2.6)	18 (2.0)
Atezolizumab	NA	6 (1.6)	NA	10 (1.1)
Bevacizumab	NA	NA	NA	5 (0.5)
Radiation therapy, n (%)	**27 (7.8)**	**16 (4.2)**	**20 (10.2)**	**63 (6.8)**
SBRT	24 (7.0)	7 (1.8)	15 (7.7)	46 (5.0)
EBRT	NA	9 (2.4)	5 (2.6)	17 (1.9)
Median (95% CI) time from index to first subsequent treatment or death, months	5.7 (4.9–6.5)	6.7 (6.0–7.6)	5.1 (4.5–5.6)	5.9 (5.5–6.3)
Received any subsequent treatment post-index‡				
Any embolization, n (%)	217 (44.4)	251 (41.2)	122 (34.0)	590 (40.5)
Any curative-intent therapy, n (%)	143 (29.2)	116 (19.0)	58 (16.2)	317 (21.7)
Any systemic therapy, n (%)	124 (25.4)	159 (26.1)	68 (18.9)	351 (24.1)
Any radiation therapy, n (%)	55 (11.3)	52 (8.5)	44 (12.3)	151 (10.4)

*Results were not presented or noted as 'NA' for variables where the number of patients was <5 to protect patient identity.
†Percentages were calculated in patients who received ≥1 subsequent treatment post-index in each embolization cohort or the overall cohort.
‡Percentages were calculated in patients in each embolization cohort or the overall cohort.
CI, confidence interval; EBRT, external beam radiation therapy; NA, not applicable; SBRT, stereotactic body radiation therapy; TACE, transarterial chemoembolization; TAE, transarterial embolization; TARE, transarterial radioembolization.

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3462 | DNA METHYLATION-REGULATED TIPIN PROMOTES HEPATOCELLULAR CARCINOMA METASTASIS

Penghong Song

Zheijang Univ. School of Medicine

Background: Hepatocellular carcinoma (HCC) ranks as the third most fatal cancer globally. Despite surgical resection being the primary treatment for early-stage HCC, recurrence and metastasis occur in some patients within five years post-surgery. Therefore, there is a pressing need to elucidate the mechanisms underlying liver cancer metastasis and identify potential interventions. DNA methylation, a chemical modification of DNA, plays a pivotal role in modulating genetic function without altering the DNA sequence. Numerous studies have underscored the significance of DNA methylation in the initiation and progression of liver cancer. Timeless-interacting protein (TIPIN), a protein involved in DNA replication fork stability, has been implicated in tumorigenesis and tumor metastasis in prior research. **Methods:** Utilizing the TCGA database, we examined the differential expression of TIPIN between cancerous and normal tissues. Additionally, we analyzed the correlation between TIPIN expression and clinical data using the same database. Lentivirus-mediated techniques were employed to construct TIPIN-knockdown and TIPIN-overexpression HCC cell lines. Subsequently, we employed transwell and wound healing assays to assess the impact of TIPIN on HCC metastasis. To further investigate its role, we established a mouse model of lung colonization via tail vein injection of lentivirus-stabilized TIPIN-overexpressing HCC cells. **Results:** Our findings revealed that DNMT1 regulates the DNA methylation status of TIPIN, with AZA treatment significantly inhibiting TIPIN methylation and upregulating its expression in HCC cell lines. TIPIN exhibited heightened expression in HCC tissues compared to normal tissues and was closely associated with prognosis and various clinical features of HCC. Patients with elevated TIPIN expression tended to experience poorer prognoses, with TIPIN expression levels correlating with tumor stage and malignancy grade. Notably, individuals with high TIPIN expression and microvascular metastasis exhibited worse prognoses. Both in vitro and in vivo experiments demonstrated that TIPIN overexpression facilitated HCC cell metastasis. Furthermore, TIPIN influenced tumor cell adhesion and extracellular matrix remodeling processes. **Conclusion:** Our study elucidates the regulatory role of DNA methylation in TIPIN expression and highlights its significantly elevated expression in HCC tissues compared to normal tissues. Alterations in TIPIN expression profoundly impact tumor cell migration, invasion, and lung colonization. Moreover, we demonstrate the influence of TIPIN expression on cell adhesion and extracellular matrix remodeling, underscoring its potential as a novel therapeutic target for HCC metastasis.

Disclosures: Penghong Song: Nothing to Disclose

3463 | MANZAMINE A INHIBITS PROLIFERATION OF HUMAN HEPATOCELLULAR CARCINOMA CELLS BY SUPPRESSION OF MITOCHONDRIAL AND GLYCOLYTIC METABOLISM

Kenji Takemoto[1] Masataka Asagiri[2] Menny Benjamin[1] Mark Hamann[1] John Lemasters[1]

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Background: Manzamine A, a marine alkaloid isolated from sea sponges, has antiproliferative activity and is of interest as a potential cancer therapeutic. Manzamine A inhibits sine oculis homeobox homolog 1, which is overexpressed in many cancer cell lines and promotes the Warburg effect. Manzamine A also induces caspase-dependent apoptotic cell death in human colorectal carcinoma cells. The aim of this study was to characterize the mechanism of manzamine A metabolic suppression in human hepatocellular carcinoma cells. **Methods:** Human hepatocellular carcinoma cells, Huh7, were studied. Cell viability was assessed at 24 and 48 h after manzamine A treatment using a tetrazolium reduction assay. Oxygen consumption rate (OCR) and extracellular acidification rate (ECAR) were measured with a Seahorse analyzer. Mitochondrial morphology was imaged with the ΔΨ-indicating fluorophore, tetramethylrhodamine methylester (TMRM) using a Zeiss LSM 880 Airyscan confocal microscope. Fluorogenic 2',7'-dichloromethyldihydrofluorescein diacetate (cmH_2DCF-DA) was used to assess the formation of reactive oxygen species (ROS). **Results:** After 0 to 10 μM manzamine A, cell viability decreased in a dose-and time-dependent manner. After 10 μM manzamine A, viability decreased to 5% and 4%, respectively, after 24 and 48 h, whereas 1 μM manzamine A caused half-maximal cell killing after 24 h. Injection of 5 μM manzamine A into

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Seahorse wells decreased maximal and ATP production-linked respiration by 45% and 22%, respectively, within an hour prior to loss of cell viability, whereas proton leak-linked respiration increased by 245%. Moreover, glycolysis of glucose and maximal glycolytic capacity after OXPHOS inhibition decreased by 60% and 63%, respectively. Swelling and fragmentation of mitochondria occurred progressively during the first hour after 5 μM manzamine A. ROS-indicating cmDCF-DA fluorescence also increased by 2.8-times at 1 h after 10 μM manzamine A. **Conclusion:** The results indicate that cancer cells treated with manzamine A experience mitochondrial respiratory disruption with ROS generation together with suppression of glycolysis in the short-term response preceding progression to loss of cell viability. These changes may underlie the antiproliferative effects of manzamine A on cancer cells.

Disclosures: Kenji Takemoto: Nothing to Disclose, Masataka Asagiri: Nothing to Disclose, Menny Benjamin: Nothing to Disclose, Mark Hamann: Nothing to Disclose, John Lemasters: Nothing to Disclose

3464 | MAFLD ETIOLOGY AND MULTIDISCIPLINARY TREATMENT COULD ACHIEVE A GOOD SURVIVAL IN ADVANCED HCC WITH CIRRHOSIS - A LARGE RETROSPECTIVE DATA FROM INDIA

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Background: Hepatocellular Carcinoma (HCC) is often associated with a poor outcome due to delayed presentation, impaired liver functions and unsuitability for curative therapies. We aimed to study the presentation, feasibility of treatment and survival outcomes in HCC patients from India. **Methods:** Electronically maintained medical records of HCC patients with cirrhosis seen at the ILBS from January 2010 to April 2024 were screened. The etiology, presentation, profile and treatment offered were analyzed and a competing risk analysis was done for the survival in relation to liver disease severity and liver transplant. **Results:** A total of 4079 cases of HCC, nearly all (96.62%) with cirrhosis, age (60±10.9 years), predominantly male (85.5%), decompensated at presentation (91.2%, 3631), mean CTP (8.08±1.6) and MELD (14.7±5.6) score. Ascites (52.9%), Jaundice (27.7%), HE (13.7%), Sepsis (13.5%) and Hydrothorax (11.7%) were common presenting symptoms. The etiology for CLD and associated HCC was MAFLD (41.4%, 1649), viral (1644, 41.3%) followed by alcohol (643, 16%). Patients often presented in advanced stages, only 10.9% (n=415) in BCLC O/A, 41.8% (n=1664) in B, 538(n=13.5%) and 34.3% (n=1365) in C and D. Only 22.7% (902) patients were within the Milan criteria. The median tumor number was 3(range 1-7) with 48% having 4 or more lesions. PVTT was noted in 39.4% (n=1570) with 92.2% being VP3/4 tumor thrombus. Hepatic vein (277, 7%), right atrium extension (162, 4.1%), bile duct invasion (162, 4.1%) and infiltrative pattern (400, 10%) noted. Because of the advanced disease, the curative therapy could be offered to a small proportion {LT (2.6%, 107), resection (3.8%, 156)}, and locoregional therapy (LRT) to 16.6% (679), LRT with systemic therapy to 13.1% (536) and systemic therapy only to 26.2% (1070 cases). Best supportive care offered to37.5% (1531) cases. One year survival was 76.5% cases with a median follow up of 137 (range30-4886) days**.** Competing risk analysis was done with consideration CTP>12 & MELD Score >25, liver transplant or resection, age >80 years and survival less than 1 month. The independent predictors for mortality were Index presentation with HCC [HR-1.65, 95 CI (1.44-1.90), p<0.001], non-MAFLD etiology [HR-1.27, 95 CI (1.14-4.41), p<0.001], presence of PVTT [HR-1.18, 95 CI (1.05-1.34), p<0.01], number of HCC tumor [HR-1.13, 95 CI (1.04-1.17), p<0.001], and serum albumin [HR-0.81, 95 CI (0.74-0.89), p<0.01]. **Conclusion:** The presentation of HCC among patients of cirrhosis in India is changed from viral to metabolic liver disease, often in advanced stages, with decompensation and with limited curative therapy. Three fourth patients could survive one year with multi-modal therapy, and was influenced by non-MAFLD etiology, index presentation as HCC with multifocal tumor and portal vein invasion independent of liver synthetic function. A routine surveillance suggested for early detection and curative therapy.

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Parameters	HR	95CI	P
BCLC 0/A/B	0.95	0.83-1.08	0.48
Non-MAFLD etiology	1.27	1.14-4.41	<0.001
HCC as index presentation	1.65	1.44-1.90	<0.001
Portal vein Tumor Thrombus	1.18	1.05-1.34	0.007
Tumor number of HCC Tumor	1.13	1.09-1.17	<0.001
Serum Albumin	0.81	0.74-0.89	<0.001
Combined therapy	0.91	0.79-1.04	0.17

Competing Risk Model (Multivariate)

Disclosures: Ashok Kumar Choudhury: Nothing to Disclose, Akhil Deshmukh: Nothing to Disclose, Vishnu Girish: Nothing to Disclose, Tushar Madke: Nothing to Disclose, Manasi Shringarpure: Nothing to Disclose, Amar Mukund: Nothing to Disclose, Deepti Sharma: Nothing to Disclose, Guresh Kumar: Nothing to Disclose, Manoj Kumar Sharma: Nothing to Disclose, Shiv Kumar Sarin: Nothing to Disclose

3465 | RECOMBINANT HUMAN THROMBOPOIETIN (RHTPO) AND PLATELET TRANSFUSION IN PATIENTS WITH SEVERE THROMBOCYTOPENIA (STCP) UNDERGONG LIVER CANCER ABLATION PROCEDURES: A RETROSPECTIVE STUDY

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Background: Liver cancer with severe thrombocytopenia (sTCP) usually require prophylactic platelet transfusion before ablation procedures to reduce bleeding risk. Identifying effective medicant to increase platelet count (PLT) is of great clinical significance for reducing platelet transfusion. Recombinant human thrombopoietin (rhTPO) is safe and effective for patients with tumor chemotherapy related thrombocytopenia, but there is few study in patients with liver cancer undergoing ablation therapy. **Methods:** Retrospective collection 1739 cases with HCC undergoing percutaneous thermal ablation at Tianjin Third Central Hospital between January 2020 and December 2023. Excluding rhTPO treatment period < 5 days, 137 patients with sTCP (PLT < 50 ×109/L) were finally enrolled and divided into five groups: control group (no platelet elevation therapy, n=25), rhTPO group (n=13), combined treatment group (rhTPO and platelet transfusion, n=25), PLT group (platelet transfusion, n=52) and multiple treatment group (rhTPO, platelet transfusion, rhIL-11, CSF, alone or overlap theatment, n=22). Evaluation indicators include response rate (PLT ≥ 50 ×109/L within 48 hours after ablation), complete blood count, liver function, and adverse events. **Results:** No difference in baseline characteristics among the treatment groups. In control group, PLT decreased from 46.20±3.16 ×109/L to 40.52±8.10 ×109/L after ablation. The treatment response rates were respectively 12.0%(3/25), 92.3%(12/13), 80.0%(20/25), 48.1%(25/52) and 54.5%(12/22) (P<0.05) (FIG 1A). The postoperative PLT in rhTPO group was higher (75.85 ± 25.79×109/L) than the other groups(P<0.05) (FIG 1B). It is worth noting that the ALT levels in the rhTPO group (60.38 ± 35.8 U/L) was significantly lower than the other groups (FIG 1C), which was partly due to the liver protective effect of rhTPO. No significant adverse events was observed related to rhTPO. **Conclusion:** In HCC patients with sTCP undergoing

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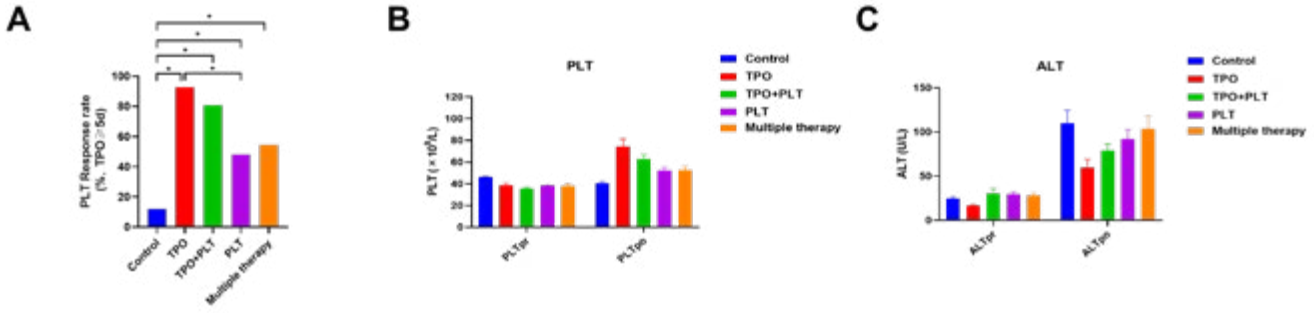
thermal ablation, standard dose and course (5 days and more) rhTPO treatment can effective increase platelet count, reducing platelet transfusion rate and improving perioperative safety.



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3466 | SAFETY ANALYSIS BY TREATMENT PERIODS FROM EMERALD-1: A PHASE 3, RANDOMIZED, PLACEBO-CONTROLLED STUDY OF TRANSARTERIAL CHEMOEMBOLIZATION WITH DURVALUMAB WITH/WITHOUT BEVACIZUMAB IN PARTICIPANTS WITH EMBOLIZATION-ELIGIBLE UNRESECTABLE HEPATOCELLULAR CARCINOMA

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Background: The global Phase 3 EMERALD-1 study (NCT03778957) primary endpoint was met: durvalumab (D) + bevacizumab (B) + transarterial chemoembolization (TACE) significantly improved progression-free survival versus placebos (PBOs) + TACE (median 15.0 vs 8.2 mo; HR 0.77; 95% CI 0.61–0.98; p=0.032 [threshold 0.0435]) in participants (pts) with embolization-eligible unresectable hepatocellular carcinoma (uHCC) with a manageable safety profile. This post hoc, exploratory analysis assessed safety in the study's two treatment periods: D-TACE (D-T) and D-B. **Methods:** Pts were randomized 1:1:1 to D + TACE, D + B + TACE, or PBOs + TACE. In the D-T period, pts received 1–4 TACE (cTACE or DEB-TACE [investigator choice]) plus D (1500 mg Q4W) or PBO for D. In the D-B period, post-last TACE, pts received D (1120 mg Q3W) plus PBO for B, D (1120 mg Q3W) plus B (15 mg/kg Q3W), or PBOs for D and B. Adverse events (AEs), start/end date, maximum/change in CTCAE grade, and causality were assessed in the D-T and D-B periods in pts who received any study

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treatment in the arm to which they were randomized, until end of follow-up. **Results:** The Table shows duration of exposure. In the D + TACE, D + B + TACE, and PBOs + TACE arms, AEs were reported by 144 (74.6%), 139 (72.0%), and 148 (74.0%) pts in the D-T period and 133 (68.9%), 147 (76.2%), and 132 (66.0%) pts in the D-B period; were possibly related to study treatment in 59 (30.6%), 56 (29.0%), and 41 (20.5%) pts in the D-T period and 76 (39.4%), 114 (59.1%), and 69 (34.5%) pts in the D-B period; and were provoked by TACE in 72 (37.3%), 90 (46.6%), and 85 (42.5%) pts in the D-T period and 16 (8.3%), 18 (9.3%), and 21 (10.5%) pts in the D-B period, respectively. **Conclusion:** D + B + TACE had a manageable safety profile across the D-T and D-B periods, consistent with the individual agents and underlying disease. These data further support D + B + TACE as a new potential standard of care in embolization-eligible uHCC. © 2024 American Society of Clinical Oncology, Inc. Reused with permission. This abstract was accepted and previously presented at the 2024 ASCO Annual Meeting. All rights reserved.

	D + TACE D-T period (n=193)	D + B + TACE D-T period (n=193)	PBOs + TACE D-T period (n=200)	D + TACE D-B period (n=193)	D + B + TACE D-B period (n=193)	PBOs + TACE D-B period (n=200)
Median (range) DoE to D or PBO, months	2.76 (0.2–30.8)	2.76 (0.2–25.3)	2.76 (0.9–26.1)	6.93 (0.7–45.5)	10.51 (0.3–38.1)	8.31 (0.7–43.0)
Median (range) DoE to B or PBO, months	–	–	–	6.92 (0.7–45.5)	9.35 (0.3–36.5)	8.31 (0.7–43.0)
Any AE, n (%)						
Max Grade 3/4	29 (15.0)	29 (15.0)	26 (13.0)	36 (18.7)	60 (31.1)	22 (11.0)
Possibly related to study treatment, max Grade 3/4*	4 (2.1)	6 (3.1)	4 (2.0)	10 (5.2)	38 (19.7)	8 (4.0)
With outcome of death	*9 (4.7)*	*6 (3.1)*	*5 (2.5)*	*6 (3.1)*	*16 (8.3)*	*6 (3.0)*
*Possibly related to study treatment**	*0*	*2 (1.0)†*	*1 (0.5)†*	*1 (0.5)‡*	*0*	*2 (1.0)‡*
Provoked by TACE	0	0	1 (0.5)	0	0	0
Leading to discontinuation of study treatment	11 (5.7)	7 (3.6)	5 (2.5)	13 (6.7)	42 (21.8)	10 (5.0)
*Possibly related to study treatment**	*1 (0.5)*	*3 (1.6)*	*2 (1.0)*	*5 (2.6)*	*18 (9.3)*	*4 (2.0)*

*Excluding TACE. †Possibly related to D or placebo for D. ‡Possibly related to B or placebo for B.
AE, adverse events; B, bevacizumab; D, durvalumab; DoE, duration of exposure; D-T, D-TACE; PBO, placebo; pd, period; pos rel, possibly related; TACE, transarterial chemoembolization; tx, treatment.

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3467 | RISKS OF VARICEAL BLEEDING IN PATIENTS WITH HEPATOCELLULAR CARCINOMA RECEIVING IMMUNE CHECKPOINT INHIBITORS AND/OR TYROSINE KINASE INHIBITORS (TIKS)

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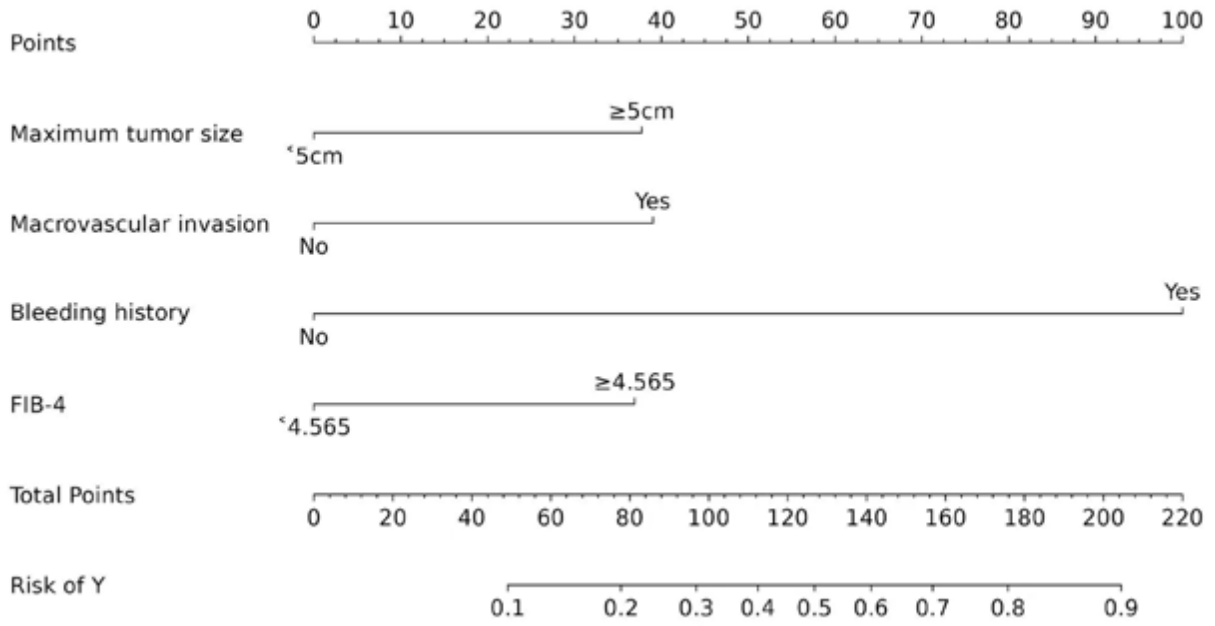
Background: In recent years, the application of immune checkpoint inhibitors (ICIs) and/or tyrosine kinase inhibitors (TIKs) has provided additional therapeutic opportunities for HCC patients; however, it may further increase the risk of gastrointestinal bleeding. Once a bleeding event occurs, it can be life-threatening and negatively impact subsequent cancer treatment. Therefore, assessing the risk of bleeding events before administering ICIs and/or TKIs is crucial for HCC patients. We aimed to identify predictive factors of acute variceal bleeding (AVB) in patients receiving ICIs. **Methods:** This retrospective cohort study included 286 HCC patients who received immune checkpoint inhibitors (ICIs). Patients hospitalized from January 2020 to December 2021 were grouped into a training cohort (n=184) to develop the new score, and those hospitalized from January 2022 to December 2022 were grouped into a validation cohort (n=102) to validate the score. Patients in the training cohort were divided into bleeding or non-bleeding groups based on the presence of a bleeding event. General information, etiological data, laboratory indicators, tumor staging, systemic treatment drugs, variceal bleeding history, and endoscopic treatment history were compared between the two groups. Risk factors for acute variceal bleeding (AVB) were identified and used in establishing the logistic regression model for predicting bleeding, and the model was further validated. **Results:** The proportion of PLT≥100×109/L, AFP≥400ng/ml, maximum tumor diameter ≥5cm, macrovascular invasion, ascites, bleeding history, endoscopic treatment history, ALBI Level 2-3, FIB-4 ≥ 4.565 and PNI<42.125 in the bleeding group was significantly higher than that in the non-bleeding group. A multivariate logistic regression analysis was conducted, and the results showed that the maximum tumor diameter ≥5cm, macrovascular invasion, bleeding history, and high FIB-4 were all statistically significant (P<0.05) in the model, all of which were risk factors affecting bleeding. A logistic regression model was established to predict AVB. The area under the curve (AUC) of the training and validation models were 0.861 and 0.816, respectively, indicating a high predictive value of the model for bleeding. **Conclusion:** Patients with a history of bleeding before receiving ICIs have a significantly increased risk of recurrent bleeding during immunotherapy, which is 16.9 times higher than those without bleeding history. Special caution should be exercised. In addition, FIB-4, as a commonly used fibrosis evaluation method, can also serve as a predictive factor for AVB in patients with HCC receiving ICIs.



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3468 | A PATIENT-DERIVED HEPATOCELLULAR CARCINOMA SPHEROID SYSTEM HARNESSING PATIENT SERUM TO MODEL THE TUMOR MICROENVIRONMENT AND TREATMENT RESPONSE

Emilie Crouchet[1] Nuno Almeida[2] Sarah Durand[2] Marie Parnot[2] Marine Oudot[2] Fabio Giannone[3] Cloé Gadenne[2] Natascha Roehlen[2] Antonio Saviano[4] Emanuele Felli[3] Patrick Pessaux[3] Hideki Ohdan[5] Hiroshi Aikata[6] Kazuaki Chayama[7] Thomas Baumert[2] Catherine Schuster[2]

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Background: Hepatocellular carcinoma (HCC) is the third leading and fastest rising cause of cancer-related death worldwide. The discovery and preclinical development of compounds targeting HCC is hampered by the absence of authentic tractable systems recapitulating the heterogeneity of patient HCC tumors and the tumor microenvironment (TME). **Methods:** Here, we established a novel, simple and robust patient-derived multicellular tumorspheroid model based on clinical HCC tumor tissues. HCC tissues were processed using enzymatic and mechanical dissociation. Cells were grown in 3D in optimized medium for the culture of tumorsphere and in presence of autologous patient serum. Characterization of the tumorspheroid cell populations was performed by flow cytometry, immunohistochemistry and functional assays. As a proof of concept, we treated patient-derived spheroids with FDA approved anti-HCC compounds. **Results:** The model was successfully established independently from cancer etiology and grade. We show that the use of autologous patient serum was essential for the TME function and to maintain cell viability. The tumorspheroids comprised the main cell compartments including epithelial cancer cells as well as all major cell populations of the TME (cancer-associated fibroblasts, macrophages and T cells, endothelial cells). Cell type proportions were variable between tumorspheroids reflecting HCC heterogeneity. Moreover, we observed differential responses to FDA HCC approved drugs (including tyrosine kinase and checkpoint inhibitors as well as VEGF-targeting agents) between donors as in patients. **Conclusion:** This patient HCC serum-tumorspheroid model provides novel opportunities for drug discovery and development as well mechanism of action studies including compounds targeting the TME. This model will likely contribute to improve the dismal outcome of patients with HCC.

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3469 | PFAS EXPOSURE AS A RISK FACTOR FOR HEPATOCELLULAR CARCINOMA: ARE ALL PFAS THE SAME?

Ana Maretti-Mira[1] Matthew Salomon[1] Chikako Matsuba[1] Veronica Setiawan[1] Brittney Baumert[1] Jesse Goodrich[1] Sarah Rock[1] Lida Chatzi[1] Lucy Golden-Mason[1]

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Background: Several epidemiological studies have linked PFAS, particularly PFOS and PFOA, to cancer development. While these studies report associations between PFAS levels in the blood and disease occurrence, the specific contribution of each individual PFAS to cancer development remains unclear due to the widespread presence of multiple PFAS in the environment and the human body. Here, we used an innovative in vitro model to assess the impact of PFAS commonly found in human blood on liver metabolism and hepatocellular carcinoma (HCC) development. **Methods:** We utilized multi-donor 3D InSight™ human liver spheroids (InSphero) and single-cell transcriptomics (scRNAseq) within an in vitro/in silico framework to test PFAS impact on HCC-related pathways. Spheroids were composed of hepatocytes and other non-parenchymal cells. Liver spheroids were exposed to PFOS, PFOA, PFNA, PFHxS, or PFHpA for 7 days in low glucose (lean) media at a non-cytotoxic concentration of 20µM. Spheroids cultured in lean medium for the same time served as controls. We dissociated spheroids with Trypsin, generating a single-cell suspension suitable for 10x Genomics scRNAseq (kit 3' v3.1).

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Results: Among the five PFAS tested, PFOS and PFNA demonstrated the most significant upregulation of HCC-related genes. PFOS upregulated CTNNB1, GLUL, IDH1, and TP53, while PFNA upregulated ARID1A, MDM4, and VEGFA, all recognized as markers of HCC progression, and several of which are drug targets for HCC. PFOS and PFNA also triggered several pathways in hepatocytes that might contribute to HCC development. PFOS exposure activated pathways related to oxidative stress and mitochondrial dysfunction, immune evasion, and Wnt/β-catenin signaling. PFNA induced cell cycle activation, oxidative stress, and TNF and VEGFA signaling in addition to dysfunction of Hedgehog signaling and p53-dependent regulatory pathways. Conversely, PFOA, PFHpA, and PFHxS did not induce cancer-related pathways in liver spheroids. **Conclusion:** Our findings suggest that not all PFAS exhibit carcinogenic traits. Exposure to PFOS and PFNA activates pathways that might contribute to HCC progression. Understanding the distinct effects of individual PFAS may provide novel insight into predicting disease progression and identifying those individuals at high risk of HCC development due to PFAS exposure.

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3470 | RISK FACTORS FOR POST-TRANSARTERIAL CHEMOEMBOLIZATION HEPATIC FAILURE IN PATIENTS WITH HEPATOCELLULAR CARCINOMA: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: Hepatic failure is a potentially fatal complication in patients with hepatocellular carcinoma (HCC) undergoing transarterial chemoembolization (TACE). However, there is a lack of clear predictive factors for hepatic failure after TACE in HCC patients. This study aimed to investigate the risk factors associated with post-TACE hepatic failure in HCC patients. **Methods:** We identified potentially eligible studies from Embase and Medline databases from inception to January 2024. Eligible study must report patient characteristics who developed hepatic failure and those who did not, among HCC patients undergoing TACE. The study must provide either the number of patients in each group for the particular outcome or odds ratio (OR) with its associated 95% confidence interval (95% CI). We extracted such data from each study to calculate mean difference (MD) or OR. Pooled MD or OR were determined using the generic inverse variance method. The random-effects model was used instead of the fixed-effects model due to the varied population characteristics and protocols across the included studies. **Results:** From 2,680 screened studies, nine were included in the meta-analysis, encompassing a total of 1,654 patients. The analysis revealed significantly lower levels of albumin with a pooled MD of -0.34 g/dl (95%CI -0.62-(-0.06), I^2 85%), lower platelet count with a pooled MD of -15.82 x 10^3/mm^3 (95%CI -20.91-(-10.72), I^2 9%), higher total bilirubin (TB) with a pooled MD of 0.65 mg/dl (95%CI 0.01-1.28, I^2 99%), higher alpha fetoprotein (AFP) with a pooled MD of 74.05 ng/ml (95%CI 64.12-83.99, I^2 0%), higher Model for End-Stage Liver Disease (MELD) with a pooled MD of 3.4 (95%CI 1.33-5.48, I^2 97%), higher Child-Pugh score (CTP score) with a pooled MD of 1.06 (95%CI 0.84-1.28, I^2 85%), higher CTP class with a pooled OR of 4.64 (95%CI 1.2-17.96, I^2 0%), larger tumor size with a pooled MD of 7.75 cm (95%CI 6.87-8.63, I^2 0%), higher prevalence of portal vein thrombosis with a pooled OR of 1.78 (95%CI 1.19-2.67, I^2 0%), and higher values of indocyanine green retention test after 15 minutes (ICG-R15 test) with a pooled MD of 16.58 % (95%CI 11.92-21.24, I^2 91%) in the hepatic failure group compared to the non-hepatic failure group. **Conclusion:** This meta-analysis identified several factors associated with hepatic failure in HCC patients undergoing TACE, including low albumin and platelets, high TB and AFP levels, elevated MELD score, elevated CTP score and class, large tumor size, presence of portal vein thrombosis, and high value of ICG-R15 test. These factors can assist clinicians in treatment planning, patient counseling, and postprocedural monitoring.

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Risk factors for hepatic failure after TACE	No. of studies	Total no. of patients	Pooled effect size (95%CI)	I^2 (%)
Albumin (g/dl)	5	571	Pooled MD -0.34 ((-0.62) - (-0.06))	85
TB (mg/dl)	5	571	Pooled MD 0.65 (0.01 - 1.28)	99
Platelet (10^3/mm^3)	4	529	Pooled MD -15.82 ((-20.91) - (-10.72))	9
AFP (ng/ml)	3	300	Pooled MD 74.05 (64.12 - 83.99)	0
MELD	5	458	Pooled MD 3.4 (1.33 - 5.48)	97
CTP score	4	442	Pooled MD 1.06 (0.84 - 1.28)	85
CTP class	5	534	Pooled OR 4.64 (1.2 – 17.96)	0
Tumor size (cm)	2	102	Pooled MD 7.75 (6.87 - 8.63)	0
Portal vein thrombosis	2	1019	Pooled OR 1.78 (1.19 – 2.67)	0
ICG-R15 test (%)	3	268	Pooled MD 16.58 (11.92 - 21.24)	91

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3471 | TGF-BETA/SMAD3 DEPENDENT AND SMAD3 INDEPENDENT ROLES OF SIRT6 REGULATION IN BLOCKING HCC

Xiyan Xiang[1] Xiaochun Yang[1] Krishanu Bhowmick[1] Kazufumi Ohshiro[2] Lopa Mishra[3]

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Background: Obesity driven liver cancer (HCC) is rising alarmingly in the United States. Yet, key signaling mechanisms underlying this obesity-driven HCC remain unclear. SIRT6 is a NAD+-dependent deacetylase that limits the activity of the lipogenic transcription factors SREBP1/2 and TGF-beta signaling. Reduced SIRT6 is associated with human fatty liver and HCC. We found that TGF-beta/SMAD3 signaling and SREBP1/2 are modulated by SPTBN1, and a mutation in human HCC-D1089Y abrogates SMAD3 binding (Gastro 2018). In stressed hepatocytes, SPTBN1 promotes lipogenesis through interactions between caspase-cleaved forms of both SREBP1 and SPTBN1(Sci TM 2021). Liver-specific knockout of SPTBN1 blocks fatty liver and HCC. Here we explored the extent of SPTBN1-D1089Y regulation of SIRT6 expression through SMAD3, and the combined roles of SIRT6 and SPTBN1 in human HCC. **Methods:** We generated a SPTBN1-D1089Y mutant mouse and examined SIRT6 expression in liver tissues and MEFs. Four-month-old $Sptbn1^{D1089Y/-}$ mutant and WT male mice were injected with DEN/CCl4 and fed on WD. TGF-beta/Smad3 pathway activity was analyzed via western blot and RNA-seq. SIRT6 expression was examined in mouse MASLD/MASH. Structure-based molecular docking simulations using structural coordinates of human SIRT6 and SPTBN1 from the AlphaFold database. **Results:** SIRT6 expression is significantly decreased in liver macrophages from mice with MASLD/MASH. $Sptbn1^{D1089Y/-}$ mice receiving DEN/CCl4 plus WD displayed significantly more tumor nodules with severe liver injury, steatosis, and inflammation. TGF-beta/SMAD3 pathway activity is suppressed in SPTBN1-D1089Y mutant MEFs with decreased phospho-SMAD3 levels. SIRT6 levels are decreased in Huh7 cells overexpressing SPTBN1-D1089Y and the mutant mouse liver tissues. Structural modeling predicts SIRT6 binding sites of SPTBN1 (R429-S439) is close to the region mediating SREBP1/SPTBN1 interaction. In HepG2 cells, overexpression of SIRT6 deacetylates SPTBN1; SMAD3 and SPTBN1 co-immunoprecipitate with SIRT6 upon TGF-beta treatment; SIRT6 knockdown increases nSREBP1, SCD1, and SPTBN1. **Conclusion:** Our data indicates a SMAD3 dependent as well as a SMAD3 independent role of SPTBN1 in regulating SIRT6. Sptbn1-D1089Y heterozygous loss aggravates liver carcinogenesis. Sptbn1-D1089Y together with SIRT6 deficiency may increase the susceptibility to MASH/HCC via regulating the crosstalk between macrophage and hepatocytes.

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Disclosures: Xiyan Xiang: Nothing to Disclose, Xiaochun Yang: Nothing to Disclose, Krishanu Bhowmick: Nothing to Disclose, Kazufumi Ohshiro: Nothing to Disclose, Lopa Mishra: Nothing to Disclose

3472 | COMPOUND SARCOPENIA AND PHYSICAL FRAILTY ADVERSELY IMPACT OUTCOMES IN HOSPITALIZED PATIENTS WITH HEPATOCELLULAR CARCINOMA IN AN AGE DEPENDENT MANNER

Arnav Rao[1] Nicole Welch[1] Amy Attaway[1] Pratham Bhashyakarla[1] Annette Bellar[1] jaividhya dasarathy[2] Joe Zein[3] Lopa Mishra[4] Srinivasan Dasarathy[1]

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Background: Sarcopenia (defined by a muscle loss phenotype/MLP) and muscle contractile dysfunction of physical frailty (PF) adversely impact outcomes in patients with hepatocellular carcinoma (HCC). MLP and PF are frequent in cirrhosis but their prevalence and impact on clinical outcomes in hospitalized patients with HCC are not known. The prevalence of HCC increases with age placing these patients at risk for compound sarcopenia (both primary sarcopenia of aging and secondary sarcopenia of chronic disease) and PF. **Methods:** The Nationwide Inpatient Sample (2010-2014) data were analyzed to evaluate the association of sarcopenia and/or PF with hospitalization outcomes, adjusting for sex, race, and comorbidities (acute kidney injury, congestive heart failure, anemia, alcohol abuse, coagulopathy, hypertension, and diabetes). Key outcomes of interest were: length of stay (LOS), hospitalization cost, discharge to a non-home setting, and inpatient mortality. Multivariate logistic and log-transformed linear regression analyses were performed to determine the impact of sarcopenia/PF on outcomes in patients stratified by age: ≤50, 51-64, 65-75, and >75 years. **Results:** Of the 35,073 patients with HCC, there were 25,499 (72.70%) males and mean (SD) age was 63.22 (11.27). Patients with PF alone (n=9893, 28.2%) and PF with MLP (2337; 6.7%) were more frequent with increasing age (p<0.001) while MLP alone (n=1989; 5.7%) did not change with age while the numbers of patients with neither PF nor MLP (20854; 59.5%) showed a decrease with age (p<0.001). In the overall HCC population, LOS was not different in the different age strata while hospitalization costs were highest in those aged 51-64y (p<0.001). Discharge to a non-home setting was more frequent with increasing age (p<0.001). Hospital mortality (overall 8.4%) was not different in the various age strata (p=0.393). Logistic regression showed that HCC patients with PF and PF with MLP had worse outcomes (LOS, costs, non-routine discharge, mortality) in all age strata (p<0.01 or less) while MLP alone adversely affected only LOS and non-routine discharge in all age group (p<0.01 or less). Absence of PF or MLP significantly improved all studied outcomes in all age groups (Table 1). **Conclusion:** PF without/with MLP/compound sarcopenia is more frequent with increasing age and adversely impacts hospitalization outcomes in HCC patients including cost of stay and decreases the likelihood of discharge to home. Compound sarcopenia/MLP alone adversely affected only LOS and discharge disposition in hospitalized patients with HCC.

Table 1.	Age ≤50 years	P-value	Age 51-64 years	P-value	Age 65-75 years	P-value	Age >75 years	P-value
Frailty & MLP								
Charge of hospitalization	1.74 (1.46-2.08)	<0.001	1.60 (1.50-1.71)	<0.001	1.43 (1.31-1.55)	<0.001	1.35 (1.24-1.48)	<0.001
Hospital mortality	3.24 (2.08-4.93)	<0.001	2.41 (2.04-2.83)	<0.001	2.16 (1.70-2.72)	<0.001	1.72 (1.30-2.26)	<0.001
Length of stay	1.62 (1.44-1.82)	<0.001	1.57 (1.50-1.64)	<0.001	1.59 (1.50-1.69)	<0.001	1.50 (1.41-1.59)	<0.001
Discharge to home	2.34 (1.57-3.50)	<0.001	3.00 (2.60-3.46)	<0.001	3.36 (2.74-4.14)	<0.001	4.05 (3.11-5.35)	<0.001
Frailty alone								
Charge of hospitalization	1.37 (1.25-1.50)	<0.001	1.39 (1.34-1.45)	<0.001	1.27 (1.21-1.33)	<0.001	1.16 (1.10-1.22)	<0.001
Hospital mortality	3.83 (2.88-5.09)	<0.001	3.27 (2.92-3.66)	<0.001	2.56 (2.18-3.01)	<0.001	2.01 (1.65-2.44)	<0.001
Length of stay	1.34 (1.26-1.42)	<0.001	1.37 (1.34-1.41)	<0.001	1.39 (1.35-1.44)	<0.001	1.24 (1.20-1.29)	<0.001
Discharge to home	2.15 (1.76-2.62)	<0.001	2.13 (1.97-2.31)	<0.001	2.22 (2.00-2.47)	<0.001	1.90 (1.67-2.16)	<0.001
MLP alone								
Charge of hospitalization	0.92 (0.77-1.09)	0.329	0.93 (0.87-1.00)	0.045	0.97 (0.88-1.06)	0.469	0.97 (0.87-1.07)	0.542
Hospital mortality	0.69 (0.32-1.31)	0.301	0.97 (0.77-1.21)	0.773	1.05 (0.75-1.44)	0.772	0.83 (0.53-1.24)	0.386
Length of stay	1.10 (0.98-1.24)	0.101	1.13 (1.08-1.18)	<0.001	1.17 (1.10-1.25)	<0.001	1.19 (1.11-1.28)	<0.001
Discharge to home	1.49 (1.02-2.14)	0.034	1.68 (1.47-1.93)	<0.001	1.80 (1.47-2.19)	<0.001	2.28 (1.76-2.99)	<0.001
Without frailty and MLP								
Charge of hospitalization	0.69 (0.64-0.75)	<0.001	0.68 (0.66-0.70)	<0.001	0.74 (0.71-0.77)	<0.001	0.79 (0.75-0.83)	<0.001
Hospital mortality	0.19 (0.14-0.26)	<0.001	0.22 (0.18-0.23)	<0.001	0.28 (0.24-0.34)	<0.001	0.39 (0.31-0.48)	<0.001
Length of stay	0.69 (0.65-0.73)	<0.001	0.66 (0.64-0.67)	<0.001	0.63 (0.61-0.65)	<0.001	0.68 (0.66-0.70)	<0.001
Discharge to home	0.40 (0.33-0.48)	<0.001	0.34 (0.32-0.37)	<0.001	0.32 (0.29-0.35)	<0.001	0.32 (0.28-0.36)	<0.001

Disclosures: Arnav Rao: Nothing to Disclose, Nicole Welch: Nothing to Disclose, Amy Attaway: Nothing to Disclose, Pratham Bhashyakarla: Nothing to Disclose, Annette Bellar: Nothing to Disclose, jaividhya dasarathy:

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Nothing to Disclose, Joe Zein: Nothing to Disclose, Lopa Mishra: Nothing to Disclose, Srinivasan Dasarathy: Nothing to Disclose

3473 | PREDIAGNOSTIC CT RADIOMICS FEATURES FOR HEPATOCELLULAR CARCINOMA (HCC) RISK STRATIFICATION AMONG PATIENTS WITH CIRRHOSIS

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Background: Hepatocellular carcinoma (HCC) is a leading cause of cancer-related death worldwide, largely because many patients still present at advanced, incurable stages. Most HCC cases arise in patients with cirrhosis. Risk stratification of HCC in cirrhosis may allow the identification of patients at high HCC risk who could benefit from close surveillance. Radiomics, defined as the analysis of quantitative image features, may have a role in risk prediction of HCC. We hypothesized that radiomics features of liver and body composition metrics extracted from pre-diagnostic CT images could be used to differentiate patients who did or did not progress to HCC. **Methods:** We identified patients with cirrhosis enrolled into the Baylor College of Medicine site of the Texas HCC Consortium Cohort between February 10, 2017 and September 22, 2022 who had a prediagnostic arterial phase abdominal CT imaging study. Automatic segmentations of the liver, visceral fat, and subcutaneous fat were extracted and radiomics features were obtained using PyRadiomics. We removed any features with a correlation coefficient > 0.7. A Wilcoxon signed rank test was performed on the remaining features and the three lowest p-values were selected from each segmentation region for input into the HCC predictive model (total of 9 features). A random forest model was built, trained, and tested using R library “Rattle” using 250 seeds with data split (80/0/20) for training, validation, and testing. We analyzed CT scans from 123 unique patients with cirrhosis including 15 unique patients who progressed subsequently to HCC diagnosis (avg. 1048 days after the prediagnostic scan) while the remaining 108 patients did not develop HCC as of January 10, 2024. The median age of the analysis cohort was 60 years (range: 23-85), 62 (50.4%) were women; active HCV was present in 8.1%, cured HCV was present in 21.1%, NAFLD in 32.5%, and alcoholic liver disease in 17.1%. A total of 261 radiomics features were obtained from the segmentations of all the study scans. **Results:** The final HCC predictive model contained 9 segmentation features and was adjusted for age, sex, and race. The model discriminated well between cases and controls with a mean area under the receiver operator curve of 0.87 ± 0.1, mean sensitivity of 0.89 ± 0.17, mean specificity of 0.90 ± 0.13, mean accuracy of 0.90 ± 0.05, and mean F1 score of 0.64 ± 0.15. **Conclusion:** Our results suggest that we can differentiate patients who did or did not develop HCC using radiomics features extracted from visceral fat, subcutaneous fat and liver segmentations on routine pre-diagnostic abdominal CT scans. Further validation of the HCC risk stratification value of these findings is warranted and ongoing.

Characteristics, N %	Controls (n=108)	Cases (n=15)
Age in years, Median (Range)	60 (23-85)	63 (35-73)
Gender		
Male	51 (47.2)	10 (66.6)
Female	57 (52.7)	5 (33.3)
Race/Ethnicity		
Non-Hispanic (NH) white	67 (62.0)	11 (73.3)
NH-Black	12 (11.1)	-
Hispanic	27 (25.0)	4 (26.6)
Other	2 (1.8)	-
Etiology of liver disease		
Cured HCV	23 (21.3)	3 (20.0%)
Active HCV	6 (5.5)	4 (26.6)
Autoimmune hepatitis	11 (10.1)	-
Nonalcoholic fatty liver disease	36 (33.3)	4 (26.6)
Others (HBV, PBC, PSC)	14 (12.9)	1 (6.6)

Disclosures: David Martinus: Nothing to Disclose, David Fuentes: Nothing to Disclose, Michelle Luster: Nothing to Disclose, Uma Ramamurthy: Nothing to Disclose, Fasiha Kanwal: Nothing to Disclose, Saira Khaderi: Nothing to Disclose, Hashem El-Serag: Nothing to Disclose, Eugene Koay: Nothing to Disclose

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3474 | MULTISTEP ACCUMULATION OF MISMATCH REPAIR DEFICIENCY-ASSOCIATED MUTATIONAL SIGNATURE DURING THE HEPATOCARCINOGENESIS REVEALED BY WHOLE-GENOME SEQUENCING ANALYSIS

Haruhiko Takeda[1] Atsushi Takai[1] Masayuki Ueno[1] Yosuke Fujii[1] Masako Mishima[1] Tadashi Inuzuka[1] Hiroshi Seno[1]

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Background: Mismatch repair deficiency (dMMR) is one of the established biomarkers predicting the efficacy of immune checkpoint inhibitors. While the immunotherapies show the favorable antitumor effect on a certain population with unresectable hepatocellular carcinoma (HCC), HCC of mismatch repair deficiency (dMMR) phenotype has been reported rare by conventional immunohistochemistry methods. Considering this discrepancy, we examined whether HCCs harbor any dMMR features through the genome-wide mutational analysis. **Methods:** We analyzed the whole-genome sequencing (WGS) data of a total of 768 samples including 529 multi-regional WGS data from 26 patients with or without HCC (cohort 1:in house and public data) and 239 bulk WGS data from 228 patients with HCC (cohort 2: ICGC database). We first extracted six types of Catalogue of Somatic Mutations in Cancer (COSMIC) single nucleotide variant signatures associated with dMMR (Sig^{dMMR}), and calculated the contribution rate of Sig^{dMMR} among the total somatic mutations in each sample. We obtained single nucleotide variants data with allele frequencies of more than 0.15, and the mutational signature analysis was conducted by MutationalPatterns package on R software. In the cohort 1, we phylogenetically analyzed the Sig^{dMMR} of noncancerous liver tissues and early step of carcinogenesis. Then in the cohort 2, we compared the Sig^{dMMR} of HCCs of Stages I, II, III and IV (N=36, 107, 71 and 25) **Results:** In the cohort 1, we found numbers of somatic mutations in noncancerous livers, however, never detected Sig^{dMMR} in them. Phylogenetical analysis of multi-regional WGS on HCCs demonstrated that the trunk mutations rarely harbored Sig^{dMMR}, while branch or progressor mutations had higher rate of Sig^{dMMR}. Interestingly, even in HCCs without classical dMMR features in immunohistochemistry, dMMR associated mutational changes were detected as a subclonal alterations. In the cohort 2, dMMR-associated signatures were present in 86 (36.0%) samples. And a high proportion of dMMR-associated signatures was associated with more advanced tumor stages. These results suggest that the dMMR-associated somatic mutations accumulate in the later stage of hepatocarcinogenesis. **Conclusion:** In this study, we extracted Sig^{dMMR} as the simple value representing the dMMR-associated mutational feature from the complicated big data of WGS of each HCC or liver tisssue sample. Different from the conventional methodologies, WGS-based analyses demonstrated that dMMR-associated signatures mainly increase at a later phase of HCC progression, especially in unresectable HCCs. It might be the clue to examine the dMMR-associated clinical biomarkers predicting the anti-tumor efficacy of immunotherapies for the patients with unresectable HCC.

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3475 | HIGH PROXIMITY OF TREG-CD8T/CD4T CELL INTERACTIONS IN SPATIAL OMICS ANALYSIS REGULATING CANCER PROGRESSION IN PATIENTS WITH HEPATOCELLULAR CARCINOMA

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

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Background: The tumor immune microenvironment influences clinical outcome, but the spatial relationships between immune cells in hepatocellular carcinoma (HCC) are not well elucidated. In this study, we analyzed the distribution of immune cells in tumor/non-tumor areas of HCC by spatial omics analysis using multiplex immunohistochemistry, and evaluated the proximity between immune cells. We also integrated next-generation sequencing (NGS) data to investigate immune cell interactions and regulation of cancer progression. **Methods:** Multiplex immunohistochemistry (OPAL™, CD3, CD4, CD8, Foxp3, CD68, CD163, CD11c, CD56, CD66b, CD20, CD11b, DAPI) was performed on 55 resected HCC tissues, and 4 areas of tumor/tumor border/non-tumor border/non-tumor were obtained with Mantra™. Immune cell phenotypes were machine-learned and analyzed

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by inForm™ and intercellular distances were calculated by phenoptr™. Interaction variable (Interact. Var.; the percentage of target immune cells with an intercellular distance of less than 25 μm) and touching cell counts (the number of pairs of target immune cells in contact) were evaluated. In addition, RNA of the tumor/non-tumor areas was extracted from formalin-fixed paraffin-embedded (FFPE) samples and targeted RNA sequencing of 629 genes related to tumor immunity was analyzed by Miseq (Illumina). **Results:** In the distribution of immune cells in the 4 areas, recurrence free survival (RFS) and overall survival (OS) were worse in cases with a high number of regulatory T cells (Treg: CD3+CD4+Foxp3+) in the tumor area (HR=3.1, p<0.05). In the proximity analysis between immune cells, RFS and OS were worse in cases with high Interact. Var. of Treg-CD8 T cell (CD8T: CD3+CD8+)/CD4 T cell (CD4T:CD3+CD4+) or high touching cell counts of Treg-CD4T in the tumor area (HR=2.9, p<0.05). Gene set enrichment analysis in RNA-NGS data showed that immune infiltration in cancer pathway and costimulation by the CD28 family pathway were enhanced in cases with abundant CD8T and low Interact. Var. of CD8T-Treg in the tumor area. **Conclusion:** Spatial location of immune cells and NGS analysis in HCC tissues revealed that patients with higher proximity of Treg-CD8T/CD4T in the tumor area had poor clinical outcomes and decreased expression of signaling molecules such as costimulation by the CD28 family. Spatial omics analysis of the immune microenvironment in HCC may provide insight into the regulation of cancer progression by immune cell interactions.

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3476 | IMPACT OF CRAFITY SCORE ON EFFICACY AND SAFETY OF FIRST-LINE ATEZOLIZUMAB PLUS BEVACIZUMAB THERAPY: MULTI-CENTER RETROSPECTIVE STUDY

Masayuki Ueno[1] Haruhiko Takeda[1] Atsushi Takai[1] Hiroki Morimura[1] Norihiro Nishijima[2] Satoru Iwamoto[3] Shunsuke Okuyama[4] Makoto Umeda[5] Takeshi Seta[6] Atsuyuki Ikeda[7] Tomoyuki Goto[8] Hiroyuki Marusawa[9] Etsuro Hatano[1] Hiroshi Seno[1]

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Background: Atezolizumab plus bevacizumab (Atezo/Bev) therapy has been used as the preferred first-line treatment for advanced hepatocellular carcinoma (HCC). Several studies have revealed that the CRP and AFP in immunotherapy (CRAFITY) score is associated with the efficacy of Atezo/Bev therapy, but its impact on the toxicity of this treatment remains unknown. Here we investigated the impact of the CRAFITY score on the efficacy and safety of first-line Atezo/Bev therapy. **Methods:** We retrospectively analyzed 214 patients with advanced HCC who received first-line Atezo+Bev therapy between October 2020 and September 2022 across nine hospitals in Japan. The CRAFITY score was calculated based on baseline values of AFP ≥ 100 ng/mL and CRP ≥ 1 mg/dL, with each parameter assigned 1 point. Best objective response (BOR) was assessed using the RECIST criteria (version 1.1). Treatment-associated adverse events (TRAEs) were assessed according to the CTCAE criteria (version 5.0). We investigated the associations between the CRAFITY score and objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), overall survival (OS), and frequencies of all-grade and grade ≥3 TRAEs. **Results:** The median age was 73 years; 160 (74.8%) patients were male; and 103 (48.1%) patients had viral hepatitis. The CRAFITY score effectively stratified ORRs (35.4%/27.7%/10.5% for CRAFITY scores of 0/1/2 points, p = 0.027) and DCRs (70.8%/47.7%/15.8%, p <0.001). The median PFS was 12.4/9.5/1.5 months (p <0.001) and median OS was not reached/16.7/6.2 months (p <0.001). The frequencies of all-grade and grade ≥3 TRAEs were 85.4%/86.2%/73.7% (p = 0.367) and 33.8%/35.4%/15.8% (p = 0.296), respectively. **Conclusion:** The CRAFITY score was significantly associated with the efficacy of first-line Atezo/Bev therapy for advanced HCC but not with the frequencies of all-grade and grade ≥3 TRAEs. Alternative therapies are warranted to overcome the limited treatment efficacy in CRAFITY-2 patients.

Disclosures: Masayuki Ueno: Nothing to Disclose, Haruhiko Takeda: Nothing to Disclose, Atsushi Takai: Nothing to Disclose, Hiroki Morimura: Nothing to Disclose, Norihiro Nishijima: Nothing to Disclose, Satoru Iwamoto:

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Nothing to Disclose, Shunsuke Okuyama: Nothing to Disclose, Makoto Umeda: Nothing to Disclose, Takeshi Seta: Nothing to Disclose, Atsuyuki Ikeda: Nothing to Disclose, Tomoyuki Goto: Nothing to Disclose, Hiroyuki Marusawa: Nothing to Disclose, Etsuro Hatano: Nothing to Disclose, Hiroshi Seno: Nothing to Disclose

3477 | STATIN USE AND HEPATOCELLULAR CARCINOMA IN PARTICIPANTS WITH HEPATIC FIBROSIS IN THE *ALL OF US* RESEARCH PROGRAM

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Background: Hepatocellular carcinoma (HCC) is a growing and major cause of cancer-related death in the U.S. Because HCC predominantly arises on a background of liver cirrhosis, cure of HCC requires transplantation, a largely impractical solution. Therefore, HCC prevention strategies are needed. Statins (particularly lipophilic statins), metformin, and aspirin are commonly prescribed medications proposed to reduce HCC risk. Despite these findings, data are limited for populations from the U.S. and with risk factors other than chronic viral hepatitis. We sought to assess the odds of HCC according to statin, metformin, and aspirin use in people with a diagnosis of hepatic fibrosis/cirrhosis. **Methods:** We conducted a case-control, cross-sectional analysis of data from the *All of Us* Research Program, an NIH precision-medicine initiative that collects data from adult volunteer participants residing in the U.S. For this study, we used electronic health record data from the "*All of Us* Controlled Tier Dataset v7". Diagnoses were defined by the presence of ICD-10 codes and medication use by prescription start date. Inclusion criteria required that participants have a diagnosis of hepatic fibrosis/cirrhosis and age, race, and sex data. Cases and controls were defined by the presence and absence of HCC, respectively. Data were analyzed with Python. Univariable analyses were performed to compare baseline characteristics and multivariable logistic regression to control for confounders. **Results:** 3,677 participants met inclusion criteria. Per univariable analyses, the HCC cohort (n=94), compared to control (n=3,583), had higher mean age (64 vs. 58 years), more men (64.1% vs. 50.0%), differed in racial composition, and had a higher proportion of participants with chronic HBV (9.6% vs. 2.5%) and HCV (36.2% vs 20.5%) (all p≤0.01). Multivariable logistic regression analyses controlling for age, race, sex, chronic HCV, and chronic HBV, showed a decreased odds of HCC in participants with exposure to lipophilic statins (p<0.05), particularly atorvastatin (p=0.02), and simvastatin (p=0.04) (Table 1). **Conclusion:** Use of lipophilic statins is associated with lower odds of HCC in participants with a diagnosis of hepatic fibrosis/cirrhosis. Study limitations include lack of data on statin doses, treatment length, and serologic/imaging data to confirm fibrosis/cirrhosis. Despite these limitations, our results provide rationale for further trials of lipophilic statins for chemoprevention in HCC.

Table 1. Logistic Regressions for Participants with a Diagnosis of HCC and Medication Use Controlling for Age, Race, Sex, Chronic HBV, and Chronic HCV*

Statin	Odds Ratio	95% Confidence Intervals	p-value
Any statin	1.05	0.50-1.17	0.22
Any lipophilic statin**	0.64	0.41-1.00	**<0.05**
Any hydrophilic statin	1.14	0.68-1.93	0.61
Atorvastatin	0.59	0.37-0.93	**0.02**
Simvastatin	0.46	0.22-0.97	**0.04**
Fluvastatin	0.84	0.30-2.38	0.75
Lovastatin	1.05	0.06-3.22	0.41
Pitavastatin***	-	-	-
Rosuvastatin	1.09	0.57-2.08	0.80
Pravastatin	1.51	0.84-2.71	0.17
Aspirin	0.88	0.58-1.35	0.56
Metformin	1.02	0.63-1.64	0.95

** Abbreviations- HCC= hepatocellular carcinoma; HBV= hepatitis B virus; HCV= hepatitis C virus.** Confidence interval from 0.4146-0.9972 but described differently due to rounding. ***Unable to calculate.*

Disclosures: Erik Almazan: Nothing to Disclose, Raymond Chung: Nothing to Disclose

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3478 | EXPLORING THE INFLUENCE OF ASPIRIN ON HEPATOCELLULAR CARCINOMA : A NATIONWIDE INPATIENT ANALYSIS

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[1]The Brooklyn Hospital Center, [2]Jacobi Medical Center, [3]Creighton University Health Sciences, [4]Cape Coral - FSU, [5]University of Texas Southwestern, [6]St. Barnabas Hospital Health System, [7]st Barnabas hospital

Background: Hepatocellular carcinoma [HCC] is the most common liver cancer and accounts for more than 80% of primary liver cancers and is the second most common cause of cancer-related death in the world. There were prior experimental and clinical studies suggesting that aspirin use influences the proliferation, apoptosis and metabolism of HCC through prevention of platelet degranulation, modulation of bioactive lipids and inhibition of pro-inflammatory COX2 enzyme. In this study we tried to establish the outcomes of aspirin use in HCC using the national inpatient sample database. **Methods:** A retrospective analysis was performed by utilizing the National Inpatient Sample database 2016-2020 and the ICD10 codes to identify the patients >18 years old with the principal diagnosis of HCC. Effect of Aspirin was studied on primary and secondary outcomes. Categorical variables were compared using the chi-square test, and continuous variables were compared using the t- test. Multivariable regression analyses were performed adjusting for demographics, hospital-level characteristics and relevant comorbidities. Confounding variables were adjusted using multivariate logistic and linear regression analyses. These included: gender, race, Charlson Comorbidity Index, Chronic liver diseases, toxin exposure, coronary artery disease, chronic kidney disease, alcohol use disorder, smoking and various patient and hospital characteristics. **Results:** A total of 236,985 hospitalized adults with HCC were identified, of which 8.3% were using aspirin. In hospitalized people with HCC, the mean age was 64.8 years without aspirin use and 69.3 years with aspirin use, of which 25.4% were females. In HCC hospitalisations, Patients with Aspirin use had 5.4 % in-hospital mortality, while 11 % for patients without aspirin use. After adjusting for confounders, aspirin use showed lower odds of mortality OR 0.55 [CI 0.47 - 0.64, p- value 0.00] compared to people without aspirin use. Compared to people using aspirin, hospitalized HCC patients using aspirin also had a lower odds of occurrence of acute liver failure, hepatic encephalopathy, variceal bleed, portal vein thrombosis. However the effect on obstructive jaundice was not statistically significant (Table 1). **Conclusion:** Aspirin use had a significant effect in lowering the mortality and morbidity outcomes in patients with HCC. Given the prevalence of HCC, further prospective studies are required to establish this relationship as aspirin could potentially be used in patients to prevent further complications.

Table 1: Comparison of influence of Aspirin use in outcomes of hospitalized patients with HCC

Outcomes of Hepatocellular carcinoma	With Aspirin Use %	Without Aspirin Use %	Multivariate Adjusted Odds Ratio OR	P-value
Acute liver failure	3.7	7.6	0.58	0.00
Hepatic encephalopathy	1.2	2.8	0.49	0.00
Variceal Bleeding	2.7	4.9	0.76	0.01
Portal vein thrombosis	11.7	15.9	0.87	0.02
Ascitis	37.8	72.7	0.98	0.00
Obstructive Jaundice	3.1	2.9	1.08	0.43

Disclosures: Manasa Ginjupalli: Nothing to Disclose, Anuj Sharma: Nothing to Disclose, Fnu Vikash: Nothing to Disclose, Vikash Kumar: Nothing to Disclose, Gautam Maddineni: Nothing to Disclose, Arnold Nongmoh Forlemu: Nothing to Disclose, Jayalekshmi Jayakumar: Nothing to Disclose, Camelia Ciobanu: Nothing to Disclose, Ali Wakil: Nothing to Disclose, Amr Dokmak: Nothing to Disclose, Vijay Bhaskar Reddy Gayam: Nothing to Disclose, Praneeth Bandaru: Nothing to Disclose, Khalid Home: Nothing to Disclose, Raissa Nana Sede Mbakop: Nothing

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to Disclose, Lisnaldy Ramirez: Nothing to Disclose, Denzil Etienne: Nothing to Disclose, Madhavi Reddy: Nothing to Disclose

3479 | MUTATED-β-CATENIN DRIVES SUPPRESSION OF AN IMMUNE-REGULATORY MODULE OF TRANSCRIPTION FACTORS ALTERING EXPRESSION OF KEY CHEMOKINES INVOLVED IN IMMUNE RESPONSE IN HEPATOCELLULAR CANCERS

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Background: Hepatocellular carcinoma (HCC) is the third-leading cause of cancer-related mortality worldwide. β-catenin (encoded by CTNNB1) is mutated in 26-38% of all HCC and exhibit immune cell exclusion leading to limited clinical benefit to first-line immunotherapy (IO). Tumor cell-intrinsic mechanisms underlying such phenotype remain poorly understood and were the subject of this study. **Methods:** Bulk RNA-sequencing (RNA-seq) of preclinical mouse models of HCC comparing β-catenin-mutated tumors (β-MUT) to β-catenin wild-type tumors (β-WT) identified upstream regulators influencing a β-catenin-driven immune excluded tumor microenvironment. Key transcription factors (TFs) were overexpressed in β-catenin-Nrf2 (β-N) and β-catenin-hMet (β-M) models and monitored for HCC development and immune infiltration was assessed via fluorescence-activated cell sorting, histology, and RNA-seq. **Results:** To understand dysregulated tumor cell-intrinsic signaling, promoter enrichment analysis on differentially expressed genes (DEGs) in β-MUT compared to β-WT identified notable suppression of an immune-regulatory module of TFs with IRF2 and POU2F1 ranked among the top candidates. IRF2 and POU2F1 signaling was also significantly downregulated in CTNNB1-mutated HCC TCGA patients. As such, forced expression of either IRF2 or POU2F1 in both the β-N and β-M HCC models resulted in a significant delay in tumor development, which coincided with immune infiltrate demonstrating re-engaged adaptive immune surveillance with enrichment of lymphocyte activation and proliferation, along with organization of immune cells into peri-tumoral lymphoid aggregates. Additionally, CD3+ immune cell depletion via a-CD3 antibody especially in the β-M-POU2F1 model reversed the phenotype, suggesting a strong immune dependence of these TFs in promoting tumor clearance. Lastly, to investigate downstream mechanisms, CXCL13, a known POU2F1 target gene, was significantly downregulated in CTNNB1-mutated HCC patients from three independent cohorts. Thus, enforced expression of CXCL13 significantly reduced tumor burden in the β-M model, and was associated with CD4+ and CD8+ T cell infiltration. **Conclusion:** We have identified an immune-regulatory module of TFs uniquely repressed in CTNNB1-mutated HCC limiting effective immune infiltration to promote anti-tumor immunity. Modulation of such TFs may provide novel therapeutic opportunities in β-catenin mutated HCC and may also improve their response to IO.

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3480 | EXOSOMAL MIRNA AS A VALUABLE INDICATOR FOR PREDICTING THE RESPONSE OF ATEZOLIZUMAB AND BEVACIZUMAB COMBINATION THERAPY IN PATIENTS WITH ADVANCED HEPATOCELLULAR CARCINOMA

Eunho Choi[1] Young-Sun Lee[1] Jeong-An Gim[2] Wonhyo Seo[3] Ha Seok Lee[1] Youngwoo Lee[1] Yang Jae Yoo[1] Seong Hee Kang[1] Sun Young Yim[1] Young Kul Jung[1] Ji Hoon Kim[1] Yeon Seok Seo[1] Hyung Joon Yim[1] Jong Eun Yeon[1] Kwan Soo Byun[1]

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Background: Atezolizumab and bevacizumab combination therapy is the frontline treatment for advanced hepatocellular carcinoma, but identifying a reliable biomarker for predicting treatment response remains elusive. This study aimed to identify exosomal miRNA biomarkers that could forecast favorable responses to this combination therapy. **Methods:** Blood samples were collected from patients with advanced hepatocellular carcinoma before initiating the atezolizumab and bevacizumab treatment Patients were categorized into responders (those exhibiting stable disease, partial, or complete response) and non-responders (those showing disease progression). Serum was concentrated using a qEV concentration and isolation kit, followed by extraction of exosomal RNA for small RNA sequencing via next-generation sequencing (NGS). Decision tree analysis was employed to identify miRNAs from the top 100 most expressed that effectively differentiated between responders and non-responders. The results were validated using a t-test. **Results:** The study comprised eight patients in each group, predominantly male, with seven out of eight patients in both groups having viral-induced hepatocellular carcinoma. NGS yielded 1076 miRNAs, among which 12 exhibited significant differential expression between responders and non-responders. Three miRNAs were notably elevated, while nine were decreased in the responder group. Notably, let7c-5p, miR-30a-5p, and miR192-5p were significantly increased in responders. Decision tree analysis identified 30 miRNAs from the top 100, with miR-30a-5p showing significantly higher levels in responders ($p = 0.0047$). Quantitative reverse transcription PCR validation confirmed the increased expression of miR-30a-5p in responders compared to non-responders. Additionally, transfection of miR-30a-5p into HepG2 cells resulted in decreased migration and proliferation **Conclusion:** Exosomal miRNAs hold promise as biomarkers for predicting response to atezolizumab-bevacizumab therapy.

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3481 | THE COMPOSITION OF CIRCULATING IMMUNE CELLS FOLLOWING TREATMENT WITH ATEZOLIZUMAB AND BEVACIZUMAB IN ADVANCED HEPATOCELLULAR CARCINOMA

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[1]Korea University College of Medicine

Background: Currently, combination therapy of atezolizumab and bevacizumab is used as a first-line therapy for advanced hepatocellular carcinoma. Numerous studies were performed to predict the response to this combination therapy, but it is still unknown. **Methods:** Patients with advanced hepatocellular carcinoma undergoing atezolizumab and bevacizumab combination therapy were enrolled in this study. Blood samples were collected on days 0 and 14 of the first administration of atezolizumab and bevacizumab. Peripheral blood mononuclear cells (PBMC) were isolated from blood samples. Eight patients were selected after the first response study; 4 showed complete response or partial response, and 4 showed progressive disease response. scRNA-seq was performed using previously collected PBMC samples. **Results:** Before treatment, patients with a positive prognosis typically showed elevated frequencies of γδ T cells, CD4+ T cells, classical monocytes, CD8+ T cells, and non-classical monocytes in their PBMCs compared to those with a less favorable prognosis.

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Additionally, a notable increase in proliferating lymphocytes was observed post-treatment among patients with a favorable prognosis. In the CD8+ T cell subset, cluster 4, characterized by high expression of the proliferation marker MKI67 and inhibitory checkpoint genes like PDCD1, HAVCR2, and CTLA4, is more prevalent in patients with favorable prognosis in PBMCs before treatment. Moreover, patients with better prognosis exhibit a notable increase in the frequency of this cluster after treatment. **Conclusion:** The landscape of heterogenous circulating immune cells of patients with advanced hepatocellular carcinoma before and after atezolizumab and bevacizumab treatment was identified in this study. A subgroup of CD8+ T cells can be a biomarker for predicting the response to combination treatment.

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3482 | IN VIVO EXPERIMENTS AND OMICS ANALYSIS TO EXPLORE THE EFFECT AND MECHANISM OF ANLUOHUAXIAN PILLS IN ALLEVIATING THE PROCESS OF HEPATITIS TO HEPATOCELLULAR CARCINOMA

Xiaobin Zao[1] Xu Cao[1] Yijun Liang[2] Ruijia Liu[1] Wenying Qi[1] Yue Chen[1] Yong'An Ye[1]

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Background: Hepatocellular carcinoma (HCC) is one of the most common malignant tumors worldwide and has a moderate treatment outcome. The Chinese herbal AnLuoHuaXian pills (ALHX), as a medicine already on the market, have a good therapeutic effect on hepatitis in clinical trials and in vivo experiments. Here, we aimed to explore the effect and mechanism of ALHX in preventing the transformation of hepatitis to HCC. **Methods:** We constructed the rat HCC model via intraperitoneal injection with diethylnitrosamine for 16 weeks. From the ninth week, the treatment group was given with ALHX aqueous solution by gavage (Figure A). After treatment, the rat' s serum was used to detectaminotransferase (ALT), aspartate aminotransferase (AST), total bile acid (TBA), and creatinine (CREA). The rat' s liver tissues were used to perform pathological examinations, second-generation sequencing (RNA-seq), and proteomics analysis. The differentially expressed genes (DEGs) and differentially expressed proteins (DEPs) were obtained between groups, and the Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses of the DEGs and DEPs were performed. **Results:** We constructed the rat HCC model via intraperitoneal injection with diethylnitrosamine for 16 weeks. From the ninth week, the treatment group was given with ALHX aqueous solution by gavage (Figure A). After treatment, the rat' s serum was used to detectaminotransferase (ALT), aspartate aminotransferase (AST), total bile acid (TBA), and creatinine (CREA). The rat' s liver tissues were used to perform pathological examinations, second-generation sequencing (RNA-seq), and proteomics analysis. The differentially expressed genes (DEGs) and differentially expressed proteins (DEPs) were obtained between groups, and the Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses of the DEGs and DEPs were performed. **Conclusion:** Our study showed that ALHX treatment could effectively alleviate the progression of HCC in rats. The mechanism is closely related to the regulation of fatty acid metabolism, PPAR signaling pathway, and ferroptosis.

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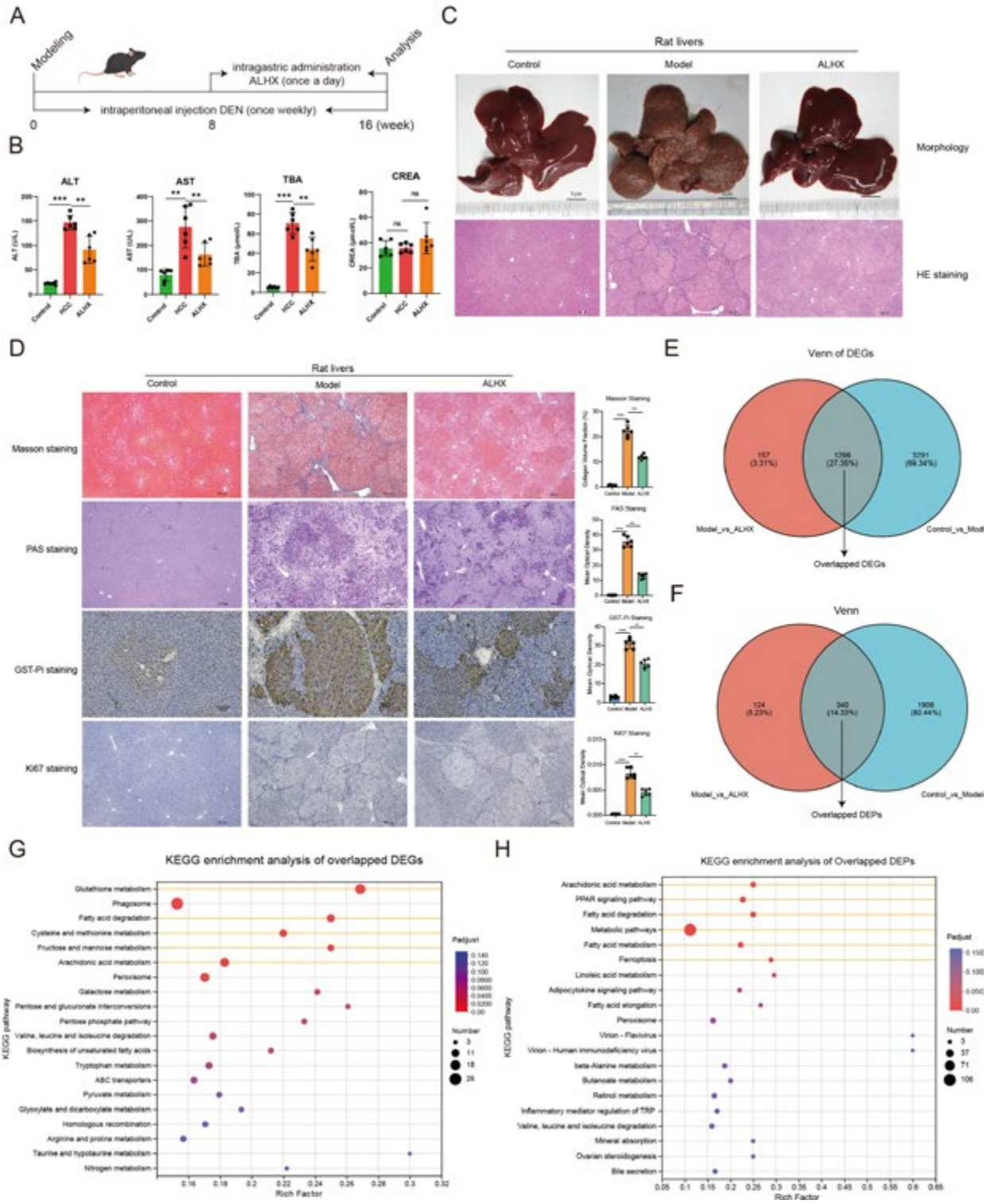

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3483 | IMPACT OF COVID-19 ON PRIMARY LIVER CANCER-RELATED MORTALITY IN THE UNITED STATES

Young Eun Chon[1] Mohammad Saeid Rezaee-Zavareh[2] Yee Hui Yeo[3] Hyunseok Kim[3] Alexander Kuo[3] Walid Ayoub[3] Hirsh Trivedi[3] Yun Wang[3] Aarshi Vipani[3] Cristina Ferrone[3] Kambiz Kosari[3] Nicholas Nissen[3] Nicole Rich[4] Neehar Parikh[5] Amit Singal[4] Ju Dong Yang[3]

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Background: Disruptions in health care during the COVID-19 pandemic may have affected the mortality trends of primary liver cancer. We aimed to characterize the trends of liver cancer related mortality during the peri-COVID-19 era. **Methods:** Primary liver cancer-related mortality (multiple cause of death [MCD], underlying cause of death [UCD], and COVID-19 related death) from 2018 to 2023 was extracted from the US Centers for Disease Control WONDER data set. We analyzed the annual age-standardized mortality rate of hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (iCCA). HCC and iCCA mortality trends with average annual percent change (AAPC) were estimated using the joinpoint analysis. **Results:** From 2018 to 2023, annual age-standardized UCD-mortality (from 7.4 to 7.1 per 100,000 person-years; AAPC, -0.88%; P=0.06) and MCD-mortality (from 8.3 to 8.1 per 100,000 person-years; AAPC, -0.35%, P=0.17) for HCC was not significantly changed. COVID-19 related deaths among HCC decedents were rare: 261 (1.1% among total deaths), 266 (1.2%), 187 (0.8%), and 59 (0.3%) cases in 2020, 2021, 2022 and 2023, respectively. Conversely, annual age-standardized UCD-mortality (from 2.9 to 3.4 per 100,000 person-years; AAPC, +3.17%; P<0.001) and MCD-mortality (from 3.3 to 3.7 per 100,000 person-years; AAPC, +4.04%; P<0.001) for iCCA significantly increased. There were 55 (0.6%), 65 (0.7%), 53 (0.6%), and 18 (0.2%) of COVID-19 related deaths among iCCA decedents in 2020, 2021, 2022 and 2023, respectively. **Conclusion:** There was little change in HCC mortality rates, while mortality rates of iCCA increased between 2018 and 2023 in the US. COVID-19 infection had minimal impact on the mortality of patients with HCC or iCCA.

Table. Mortality rate for primary liver cancer among US adults ≥ 25 years in 2018-2023

Hepatocellular carcinoma (ICD code: C22.0, C22.9)						
			Contributing cause of death		MCD-mortality rate	UCD-mortality rate
Year	MCD (total), n	UCD, n (%)	COVID-19 related death, n (%)	Non-COVID-19 death, n (%)	Age-adjusted mortality rate, /100,000 persons-years (95% CI)	Age-adjusted mortality rate, / 100,000 persons-years(95% CI)
2018	22,482	20122 (89.5)	0	2360 (10.5)	8.3 (8.2 - 8.4)	7.4 (7.3 - 7.5)
2019	22,480	20017 (89.0)	0	2463 (11.0)	8.1 (8.0 - 8.2)	7.2 (7.1 - 7.3)
2020	22,997	20142 (87.6)	261 (1.1)	2594 (11.3)	8.2(8.1 - 8.3)	7.2 (7.1 - 7.3)
2021	23,062	20038 (86.9)	266 (1.2)	2758 (11.9)	8.2 (8.1 - 8.3)	7.1 (7.0 - 7.2)
2022	23,268	20216 (86.9)	187 (0.8)	2865 (12.3)	8.1 (8.0 - 8.2)	7.0 (6.9 - 7.1)
2023 (provisional)	23,405	20397 (87.1)	59 (0.3)	2949 (12.6)	8.1 (8.0 - 8.2)	7.1 (7.0 - 7.2)
Intrahepatic cholangiocarcinoma (ICD code: C22.1)						
			Contributing cause of death		MCD-mortality rate	UCD-mortality rate
Year	MCD (total), n	UCD, n (%)	COVID-19 related death, n (%)	Non-COVID-19 death, n (%)	Age-adjusted mortality rate, /100,000 persons-years (95% CI)	Age-adjusted mortality rate, /100,000 persons-years (95% CI)
2018	7,967	7459 (93.6)	0	508 (6.4)	3.0 (3.0 - 3.1)	2.9 (2.8 - 2.9)
2019	8,364	7807 (93.3)	0	557 (6.7)	3.1 (3.1 - 3.2)	2.9 (2.9 - 3.0)
2020	8,589	7955 (92.6)	55 (0.6)	579 (6.8)	3.2 (3.1 - 3.2)	2.9 (2.9 - 3.0)
2021	9,259	8554 (92.4)	65 (0.7)	640 (6.9)	3.4 (3.3 - 3.5)	3.2 (3.1 - 3.2)
2022	9,594	8609 (89.7)	53 (0.6)	932 (9.7)	3.4 (3.4 - 3.5)	3.1 (3.0 - 3.2)
2023 (provisional)	10,452	9372 (89.7)	18 (0.2)	1062 (10.1)	3.7 (3.7 - 3.8)	3.4 (3.3 - 3.4)

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3484 | INSIGHTS INTO THE ROLE OF HEPATOCYTE MLKL IN MASLD-DRIVEN LIVER CANCER

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Background: Hepatocellular carcinoma (HCC), the primary liver tumor, is the second leading cause of cancer-related mortality with a five-year survival rate of about 18%. Metabolic dysfunction-associated steatotic liver disease (MASLD) has recently emerged as a significant contributor to HCC development. Chronic inflammation, driven by necroptosis, plays a key role in HCC progression, with MLKL (Mixed Lineage Kinase Domain-Like Protein) as a crucial effector in this pathway. Our research showed increased MLKL expression in a mouse model of diet-induced MASH-related HCC, and blocking MLKL (Mlkl-/- mice) reduced inflammation, tumor multiplicity, and volume. Given that hepatocytes primarily express MLKL, we hypothesized that hepatocyte MLKL is a key mediator in MASLD-driven HCC. **Methods:** To test our hypothesis, we developed and characterized hepatocyte specific MLKL knockout ($MLKL^{HepKO}$) mice by injecting AAV8-TBG-iCre ($MLKL^{HepKO}$) or AAV8-TBG-Null (Control) virus. The mice were fed a normal chow diet (CD) or MASLD-inducing western diet (WD; 43.7% fat (majorly from lard), 36.6% carbohydrate,19.7% protein and 0.2% cholesterol) diet for 15 months, starting at 2 months of age. **Results:** In the WD diet fed $MLKL^{HepKO}$ mice, the body weight and liver weight remained comparable between the corresponding study groups. Strikingly, WD diet feeding in control mice resulted in 80% tumor incidence when compared to 37.5% in the $MLKL^{HepKO}$ group fed the same diet. Remarkably, the control group when fed with WD exhibited greater tumor multiplicity (1.9$\pm$0.48) and tumor volume (4.4$\pm$1.04mm), while $MLKL^{HepKO}$ had reduced tumor burden (tumor multiplicity:0.5$\pm$0.26; tumor volume: 1.6$\pm$1.1). Additionally, there was a larger number of tumor foci in the control group (9.1$\pm$4.3) when compared to $MLKL^{HepKO}$ mice (5.1$\pm$1.3). *In vitro* studies using a human liver cancer cell line, HepG2, showed that blocking MLKL reduced cell proliferation and sphere formation compared to corresponding controls, as confirmed through genetic (siRNA) and pharmacological (necrosulfonamide) inhibition. RNA sequencing analysis revealed that cell cycle regulation is the most significantly downregulated pathway following MLKL inhibition. Thus, our data underscore a critical role of hepatocyte MLKL in diet-induced liver cancer, potentially by modulating the cell cycle, suggesting a non-necroptotic function of MLKL in HCC. **Conclusion:** Our study sheds light on the critical role of hepatocyte MLKL in tumor initiation and progression. By demonstrating reduced tumor burden and incidence in MLKLHepKO mice, we highlight MLKL as a promising therapeutic target for hepatocellular carcinoma associated with MASLD. Furthermore, our findings suggest that MLKL exerts non-necroptotic functions in promoting cancer cell survival and proliferation, offering new insights into HCC pathogenesis and potential treatment strategies.

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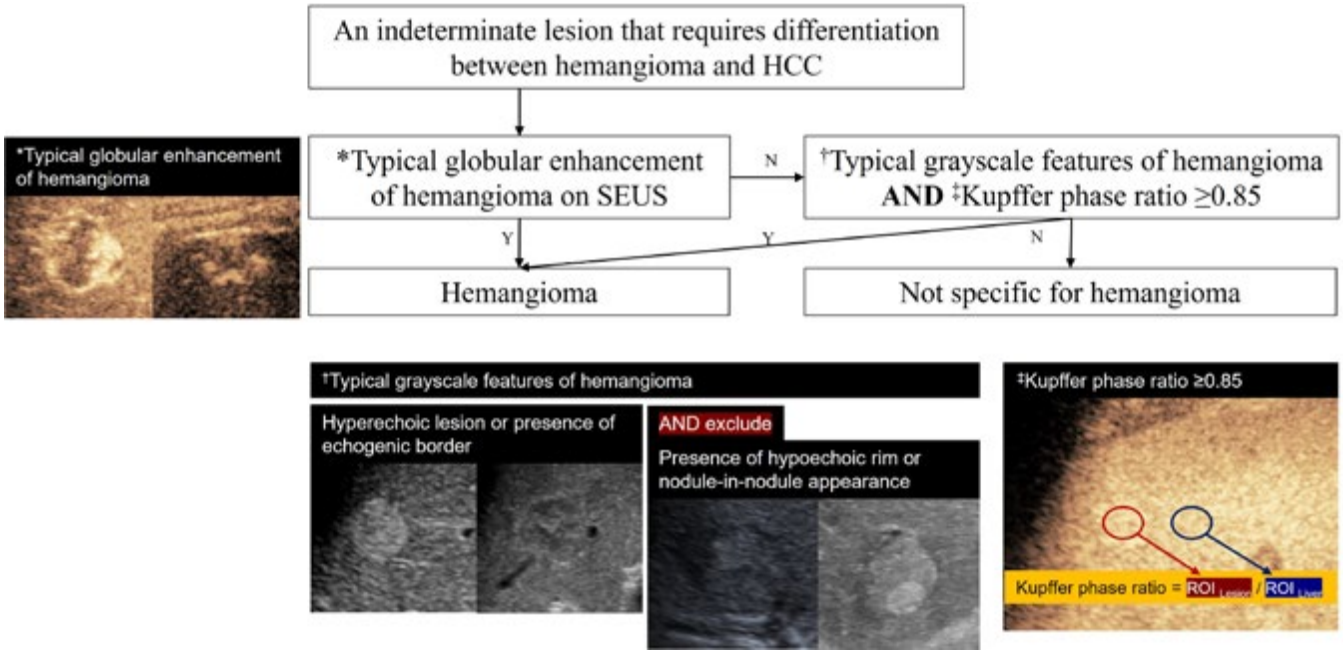
Disclosures: Deepa Sathyaseelan: Nothing to Disclose, Sabira Mohammed Jazir: Nothing to Disclose, Chao Jiang: Nothing to Disclose, Phoebe Ohene-Marfo: Nothing to Disclose

3485 | DIFFERENTIATING HEMANGIOMAS FROM HEPATOCELLULAR CARCINOMAS USING SONAZOID-ENHANCED ULTRASONOGRAPHY: A PROPOSED TWO-STEP DIAGNOSTIC ALGORITHM ◆

Jeong Ah Hwang[1] *Taewon Han*[1] *Woo Kyoung Jeong*[1] *Seungchul Han*[1]

[1]*Samsung Medical Center*

Background: There are several pitfalls in application of Sonazoid-enhanced ultrasonography (SEUS) to differentiate hemangioma and hepatocellular carcinoma (HCC). This study aims to develop a diagnostic algorithm for hemangioma in differentiating from HCC using SEUS. **Methods:** We retrospectively analyzed SEUS examinations of 159 patients with 110 hemangiomas or 49 HCCs from Jan. 2011 to Dec. 2022. Presence of lesion hyperechogenicity, typical grayscale features of hemangioma (hyperechoic or echogenic border without hypoechoic rim, nodule-in-nodule or mosaic appearances) and typical globular enhancement of hemangioma were evaluated. On Kupffer phase, we calculated the lesion-to-liver ratio (KP ratio) and performed receiver operating characteristic analysis to determine an optimal KP ratio to predict hemangioma. We proposed a diagnostic algorithm for hemangioma, and diagnostic performance between the proposed algorithm and typical globular enhancement of hemangioma was compared through McNemar's test. **Results:** The optimal KP ratio for predicting hemangioma was 0.85. The proposed two-step diagnostic algorithm, which diagnoses hemangioma based on typical globular enhancement initially, and then applies typical grayscale features and KP ratio ≥0.85 for negative cases. Proposed algorithm showed higher sensitivity (90.0% vs. 81.8%, p = 0.008) and accuracy (93.1% vs. 87.4%, p = 0.008) than typical globular enhancement of hemangioma, with same specificity (100%). The algorithm showed higher performance than typical globular enhancement of hemangioma in subgroup analysis for hyperechoic lesions (sensitivity; 91.9% vs. 77.4%, accuracy; 92.8% vs. 79.7%; p = 0.008). **Conclusion:** The two-step diagnostic algorithm using typical globular enhancement and grayscale features, along with the KP ratio, enhance the diagnostic performance of differentiating hemangioma from HCC.



Disclosures: Jeong Ah Hwang: Nothing to Disclose, Taewon Han: Nothing to Disclose, Woo Kyoung Jeong: Nothing to Disclose, Seungchul Han: Nothing to Disclose

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3486 | CURATIVE TREATMENT AFTER IMMUNOTHERAPY LEADS TO EXCELLENT OUTCOMES IN PATIENTS WITH HEPATOCELLULAR CARCINOMA ◆

Gwang Hyeon Choi[1] Michael Luu[2] Hyunseok Kim[2] Alexander Kuo[3] Walid Ayoub[3] Hirsh Trivedi[2] Yun Wang[2] Aarshi Vipani[2] Pin-Jung Chen[2] Steven Miles[2] Emily Kaymen[2] Andrew Hendifar[2] Tsuyoshi Todo[2] Todd Brennan[2] Georgios Voidonikolas[2] Steven Wisel[2] Justin Steggerda[2] Cristina Ferrone[2] Kambiz Kosari[2] Nicholas Nissen[2] Neehar Parikh[4] Amit Singal[5] Ju Dong Yang[3]

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Background: The high response rates observed with immunotherapy may allow subsequent curative treatment after systemic therapy in hepatocellular carcinoma (HCC). This study aims to investigate 1) the proportion of patients who switched to curative treatment after immunotherapy, 2) the prognostic impact of curative treatment after immunotherapy, and 3) factors related to curative treatment receipts. **Methods:** We identified patients with HCC who received immunotherapy as a first-line treatment during 2017-2023 from the US National Cancer Database. Patients were classified into two groups: 1) immunotherapy with subsequent curative treatment (resection, transplantation, local ablation) and 2) immunotherapy without subsequent curative treatment. Multivariable Cox regression analysis was performed to determine the factors associated with OS, followed by propensity-score (PS) matching and inverse probability of treatment weighting (IPTW) adjusted analysis. **Results:** Of 4,329 HCC patients (median age 66, 81% male, 33% T4, 22% N1, and 32% M1 stage) who received immunotherapy as a first-line treatment, 138 (3.2%) patients received curative treatment after immunotherapy, with a mean interval of 129 days between two treatments. Median survival was not reached vs. 10 months for those with and without subsequent curative treatment, respectively (Figure). OS was significantly longer in the group with subsequent curative treatment (hazard ratio [HR] 0.20, 95% CI 0.14–0.29) (Figure 1A). This result was consistent in multivariable Cox-regression (HR 0.19, 95% CI 011-0.21), PS matching (HR 0.20, 95% CI 0.13-0.30) (Figure 1B), and IPTW adjusted (HR 0.20, 95% CI 0.14-0.29) analyses. Independent predictors of subsequent curative treatment were lower T stage (HR 0.35, 95% CI 0.15-0.83 for T2; HR 0.20, 95% CI 0.09-0.46 for T3; HR 0.15, 95% CI 0.05-0.39 for T4 with reference of T1), absence of node metastasis (HR 0.16, 95% CI 0.02-0.55) and receiving care at an academic hospital (HR 3.41, 95% CI 1.69-7.41, p=0.001). **Conclusion:** Curative treatment after immunotherapy was infrequent but associated with significantly improved survival. After adjusting for tumor burden, care at an academic center increased the probability of receiving subsequent curative treatment.

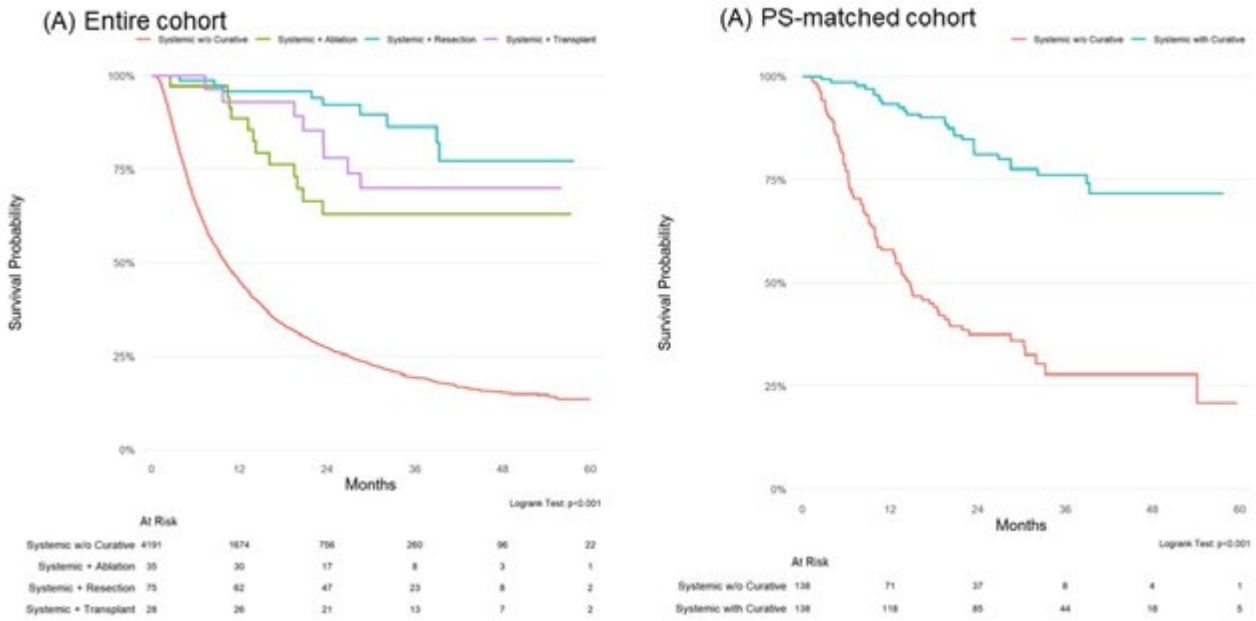

Figure 1. KM curve according to treatment

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3487 | IDENTIFICATION OF CYTOKINES PREDICTING THE INEFFECTIVENESS OF ATEZOLIZUMAB PLUS BEVACIZUMAB THERAPY

Satoshi Narahara[1] takayuki tokunaga[1] Toshinori Toyota[1] Kentaro Tanaka[1] Hiroki Inada[1] Etsuko Iio[1] Yoko Yoshimaru[1] Takehisa Watanabe[1] Katsuya Nagaoka[1] Hiroko Setoyama[1] Takanori Suzuki[2] kentaro matsuura[2] Masaya Onishi[3] Yasuhito Tanaka[1]

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Background: Atezolizumab plus bevacizumab therapy (Atezo+Bev) has been used in advanced hepatocellular carcinoma (HCC), but there is no useful biomarker that can predict the response before starting the treatment. In this study, we searched for biomarkers that predict response using tissue before starting Atezo+Bev and serum before and after the start of Atezo+Bev. **Methods:** We investigated the factors involved in the PD of Atezo+Bev using VISIUM in six HCC biopsy samples (best treatment effect CR/PR/SD: R group, PD: NR group) before starting Atezo+Bev. First, we investigated the association between the protein obtained by VISIUM and the best therapeutic effect using serum before and after the start of treatment in 40 patients (group R: 25 patients, group NR: 15 patients) treated with Atezo+Bev. We further validated this result in 60 patients treated with Atezo+Bev. **Results:** We found from the VISIUM results that cytokine X was uniformly highly expressed in the tumor in the NR group. When cytokine X, a secreted protein, was assessed in our pre-treatment serum, it was significantly elevated in the NR group (P = 0.033). When dichotomized by the median value, the high cytokine X group had significantly shorter OS (P = 0.001) and TTP (P = 0.024). A cut-off value was then set using ROC analysis and in the pre-treatment serum of Validation cases, this cytokine X tended to be higher in the NR group (P = 0.086) and when dichotomized by the cut-off value set above, the high group showed a trend towards shorter TTP (P = 0.084). In addition, when the log change in cytokine X was assessed using the serum before and 3 weeks after treatment to eliminate the influence of patient background, the high change group had a significantly shorter TTP (P = 0.012). **Conclusion:** We identified that high serum cytokine X levels before the start of Atezo+Bev significantly contributed to PD and shorter TTP. Future work is needed to develop a more accurate prediction equation combining clinical laboratory values.

Disclosures: Satoshi Narahara: Nothing to Disclose, takayuki tokunaga: Nothing to Disclose, Toshinori Toyota: Nothing to Disclose, Kentaro Tanaka: Nothing to Disclose, Hiroki Inada: Nothing to Disclose, Etsuko Iio: Nothing to Disclose, Yoko Yoshimaru: Nothing to Disclose, Takehisa Watanabe: Nothing to Disclose, Katsuya Nagaoka:

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Nothing to Disclose, Hiroko Setoyama: Nothing to Disclose, Takanori Suzuki: Nothing to Disclose, kentaro matsuura: Nothing to Disclose, Masaya Onishi: Nothing to Disclose, Yasuhito Tanaka: Nothing to Disclose

3488 | FUNCTIONAL ROLE OF MICRORNA-491 IN LENVATINIB RESISTANCE IN HEPATOCELLULAR CARCINOMA

Mari Satoh[1] Takayuki Kogure[1] Takehito Ito[1] Masanori Takahashi[1] Ryusuke Ouchi[1] Kensuke Usui[1] Kouji Okada[1] Kennichi Satoh[1]

[1]Tohoku Medical and Pharmaceutical University

Background: Lenvatinib, a multi-kinase inhibitor, has demonstrated superior efficacy in treating hepatocellular carcinoma (HCC) compared to other available agents. Nevertheless, its overall survival is non-inferior to sorafenib, suggesting the potential acquisition of resistance during the treatment. Lenvatinib induces severe hypoxia in the tumor by inhibiting VEGF receptors, which may be a critical factor in acquiring resistance. This study aimed to elucidate the mechanism of lenvatinib-resistance under hypoxia in HCC. **Methods:** Human HCC cell lines were cultured in a humidified atmosphere of 95% air and 5% CO_2 (normoxia) or 94% N_2 with 1% O_2 and 5% CO_2 (hypoxia). The anchorage-dependent proliferation was evaluated using the MTS assay. Genome-wide profiling of microRNAs and mRNAs was conducted in HCC cells using 3D-Gene® Human miRNA Oligo chips or 3D-Gene® Human mRNA Oligo chips (Toray Industries). HCC cells were transfected with synthetic precursors of microRNAs to force the expression. An anti-argonaute RIP-Chip assay was performed to identify mRNAs to which a microRNA binds directly. **Results:** Human HCC cell lines PLC/PRF/5, Huh7, Hep3B, and HepG2 were cultured under normoxic or hypoxic conditions. Hypoxia increased HIF1α expression without significantly affecting cell growth until 96 hours. Lenvatinib inhibited cell growth in a concentration-dependent manner, but this cytotoxicity was reduced under hypoxia, indicating resistance acquisition. MicroRNA profiling revealed that 48 microRNAs were differentially expressed in lenvatinib-treated PLC/PRF/5 cells under normoxia (42 increased, 6 decreased). Of the 42 increased microRNAs, 28 showed decreased expression in lenvatinib-treated PLC/PRF/5 cells under hypoxia. Among these, miR-491 exhibited the most significant change in expression. Forced expression of miR-491 partially restored lenvatinib cytotoxicity under hypoxia. Similar results were observed in all tested cell lines. Genome-wide mRNA profiling identified 168 genes commonly altered by miR-491 forced expression in PLC/PRF/5, Huh7, and HepG2, associated with RNA splicing, cell cycle, and cell adhesion pathways. The results of the RIP-Chip assay on RNA extracted from HepG2 cells with forced expression of miR-491 demonstrated a significant increase of 192 mRNAs compared to a negative control. A screening of the 192 mRNAs using the TargetScan algorithm identified 10 mRNAs with sequences complementary to the miR-491 seed region. **Conclusion:** miR-491 plays a role in hypoxia-induced lenvatinib resistance in HCC, and modulating its expression could partially restore lenvatinib cytotoxicity. These findings indicate the potential of targeting microRNAs to overcome lenvatinib resistance.

Disclosures: Mari Satoh: Nothing to Disclose, Takayuki Kogure: Nothing to Disclose, Takehito Ito: Nothing to Disclose, Masanori Takahashi: Nothing to Disclose, Ryusuke Ouchi: Nothing to Disclose, Kensuke Usui: Nothing to Disclose, Kouji Okada: Nothing to Disclose, Kennichi Satoh: Nothing to Disclose

3489 | EPIGENETIC REGULATION OF ACSM5 EXPRESSION IN HEPATOCELLULAR CARCINOMA

Lei Yang[1] Kien Pham[1] Yibo Xi[1] Shaoning Jiang[1] Chen Liu[1]

[1]Yale University

Background: Hepatocellular carcinoma (HCC) is characterized by dysregulated lipid metabolism, with acyl-CoA synthetase medium-chain family member 5 (ACSM5) involved in this process. Our recent studies have demonstrated the critical role of ACSM5 downregulation in promoting HCC progression. However, the underlying mechanisms driving this downregulation remain unclear. In this study, we investigate the potential role of DNA methylation in regulating ACSM5 expression in HCC. **Methods:** We analyzed the relationship between ACSM5 expression and DNA methylation levels in DNMIVD. Huh7 cells were treated with 5-Azac, a DNMT1 inhibitor, and the ACSM5 mRNA and protein expression levels were assessed by qRT-PCR and western blot, respectively. The

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methylation status of the ACSM5 promoter was determined by methylation-specific PCR (MSP). **Results:** Web-based analysis revealed a strong negative correlation between ACSM5 expression and DNA methylation levels. Treatment with the DNMT1 inhibitor significantly increased mRNA and protein levels of ACSM5 in Huh7 cells. Furthermore, MSP analysis showed increased promoter methylation levels of ACSM5 in 5-Azac-treated Huh7 cells, suggesting that promoter methylation leads to ACSM5 downregulation in HCC. **Conclusion:** Our findings provide evidence of promoter methylation-mediated downregulation of ACSM5 expression in HCC. Understanding the epigenetic regulation of ACSM5 may offer insights into the pathogenesis of HCC and provide potential targets for therapeutic intervention.

Disclosures: Lei Yang: Nothing to Disclose, Kien Pham: Nothing to Disclose, Yibo Xi: Nothing to Disclose, Shaoning Jiang: Nothing to Disclose, Chen Liu: Nothing to Disclose

3490 | DENDRITIC CELL EXOSOMES DECORATED WITH HEPATOCELLULAR CARCINOMA-SPECIFIC ANTIGENIC PEPTIDES COMBINED WITH ANTI PD-L1 BOOST CANCER IMMUNOTHERAPY

Weihua Li *Shumin Luo*[1]

[1]*capital medical university*

Background: Immunotherapy has shown great potential in the treatment of hepatocellular carcinoma (HCC). However, patients with HCC have immunosuppression, which makes immunotherapy unable to provide great therapeutic efficacy. Consequently, one key tactic for HCC immunotherapy is to boost and stimulate immune activity in individuals with the disease. We designed a new dendritic cell exosome (DEX) vaccine for HCC, which can effectively activate the body to produce HCC specific immune response and achieve good clinical efficacy. **Methods:** We designed a DEX vaccines decorated with HCC-specific antigenic peptides and immune adjuvant N1ND, in combination with anti-PD-L1 (DEXAGN+aPD-L1), which effectively elicit immunogenic tumor cell death. Investigation involved experiments conducted in HCC cell lines (in vitro), humanized HCC-CDX (human HCC cell line HepG2-Derived Xenograft) mice models (in vivo), and primary patient-derived tumor cells (clinically). **Results:** DEXAGN+aPD-L1 vaccine effectively activate CD8+ T cells by enhance the expressions of CD107a and cytokine IFN-γ, which could effectively boost specific cytotoxicity against HCC (the cytotoxicity on other types of tumor cells is general). It produced effective tumor suppression in the subcutaneous HCC mouse model, humanized HCC-CDX mice model, patient-derived tumor cells, demonstrating commendable immunotherapeutic efficacy against HCC. **Conclusion:** The new findings demonstrate that new DEX vaccination (DEXAGN+aPD-L1) exhibits better antitumor activity, improves HCC-specific CD8+ T-cell responses by promoting T-cell activation, and provides a rationale for the development of DEXAGN+aPD-L1 vaccines targeting HCC. Besides, DEXAGN+aPD-L1 vaccines have the potential to trigger the body to generate effective immune responses against other cancers by replacing dominant epitope peptides in other cancers, providing a promising reference for immunotherapy of other cancers.

Disclosures: Weihua Li: Nothing to Disclose, Shumin Luo: Nothing to Disclose

3491 | ATEZOLIZUMAB COMBINED WITH BEVACIZUMAB VERSUS SORAFENIB AND LENVATINIB FOR PATIENTS WITH UNRESECTABLE HEPATOCELLULAR CARCINOMA: A SYSTEMIC REVIEW AND META-ANALYSIS FOR RANDOMIZED CONTROLLED TRIALS

Sakditad Saowapa[1] *Natchaya Polpichai*[2] *Pojsakorn Danpanichkul*[3] *Thanathip Suenghataiphorn*[4] *Narathorn Kulthamrongsri*[5] *Maireigh McCullough*[3] *Lukman Tijani*[3] *Apichat Kaewdech*[6]

[1]*Texas Tech University Health Sciences Center, Lubbock, TX, USA,* [2]*Weiss Memorial Hospital, Chicago, IL, USA,* [3]*Texas Tech University Health Science Center, Lubbock, TX, USA,* [4]*Griffin Hospital, Derby, CT, USA,* [5]*John A. Burns School of Medicine, University of Hawaii, Honolulu, Hawaii, USA,* [6]*Faculty of Medicine, Prince of Songkla University, Songkhla, Thailand*

Background: Hepatocellular carcinoma (HCC) ranks 7th rank incidence and 4th in mortality among cancers, with a vast majority of patients present with unresectable HCC, which has a poorer prognosis. Sorafenib, Lenvatinib, and Atezolizumab combined with Bevacizumab (ATEZO/BEV) have received approval as first-line treatments for

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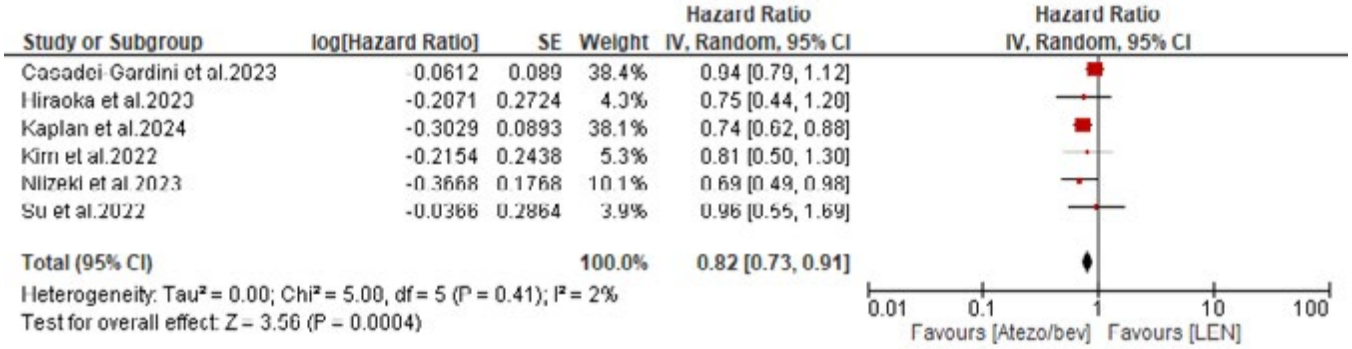
unresectable HCC. **Objective:** The primary objectives were to compare the overall survival (OS) and progression-free survival (PFS) in patients with unresectable HCC treated with ATEZO/BEV compared with sorafenib and lenvatinib. The secondary objectives were to compare the object response rate (ORR), disease control rate (DCR) and safety. **Methods:** PubMed, MEDLINE and Google Scholar databases were searched for records published until May 31, 2024. Records comparing ATEZO/BEV to Sorafenib or Lenvatinib were included. Studies published in languages other than English, case reports, and letters to the editor were excluded. Statistical analyses were performed using the Review Manager software. **Results:** Eight studies with 6855 unresectable HCC patients were included. The pooled analysis showed significantly higher OS and PFS in the ATEZO/BEV group compared to the Lenvatinib group (HR: 0.82; 95% CI: 0.73 – 0.91; p=0.0004 and HR: 0.76; 95% CI: 0.64 – 0.90; p=0.002, respectively). The subgroup analysis suggested that the OS is prolonged by ATEZO/BEV in viral patients (HR: 0.77; 95% CI: 0.63 – 0.95; p=0.01), while Lenvatinib was associated with prolonged OS in non-viral patients (HR: 1.36; 95% CI: 1.13 – 1.65; p=0.001). PFS was higher among non-viral patients receiving Lenvatinib than ATEZO/BEV (HR: 1.46; 95% CI: 1.04 – 2.05; p=0.03). The pooled analysis did not show any significant difference in ORR and DCR between ATEZO/BEV and Lenvatinib groups (OR: 0.91; 95% CI: 0.65 – 1.27; p=0.56 and OR: 1.34; 95% CI: 0.92 – 1.94; p=0.13, respectively). Regarding safety, ATEZO/BEV was associated with significantly lower incidences of grade ≥3 adverse events than Lenvatinib (OR: 0.43; 95% CI: 0.36 – 0.51; p=0.03). Conversely, the pooled data suggested that patients receiving ATEZO/BEV have significantly higher OS and PFS than Sorafenib (HR: 0.68; 95% CI: 0.57 – 0.81; p<0.00001 and HR: 0.67; 95% CI: 0.57 – 0.77; p<0.00001, respectively). **Conclusion:** ATEZO/BEV has better survival outcomes than Sorafenib and Lenvatinib and better safety than Lenvatinib in treating unresectable HCC. However, Lenvatinib might be an appropriate treatment option for patients with non-viral HCC.



Disclosures: Sakditad Saowapa: Nothing to Disclose, Natchaya Polpichai: Nothing to Disclose, Pojsakorn Danpanichkul: Nothing to Disclose, Thanathip Suenghataiphorn: Nothing to Disclose, Narathorn Kulthamrongsri: Nothing to Disclose, Maireigh McCullough: Nothing to Disclose, Lukman Tijani: Nothing to Disclose, Apichat Kaewdech: Nothing to Disclose

3492 | A MACHINE LEARNING MODEL TO PREDICT THE TREATMENT RESPONSE OF ATEZOLIZUMAB PLUS BEVACIZUMAB IN PATIENTS WITH HEPATOCELLULAR CARCINOMA

Moon Haeng Hur[1] Bo Hyun Kim[2] Byeong Geun Song[3] Dong Hyun Sinn[3] Hyunjae Shin[2] Yuri Cho[2] Youngsu Park[1] JEAYEON PARK[1] Yunmi Ko[1] Yun Bin Lee[1] Eun Ju Cho[4] Su Jong Yu[1] Yoon Jun Kim[1] Jung-Hwan Yoon[1] Jeong-Hoon Lee[4]

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Background: Although the number of patients receiving atezolizumab plus bevacizumab (Atezo/Bev) for advanced hepatocellular carcinoma (HCC) is increasing, there is a lack of reliable models to predict treatment response in advance. We aimed to aimed to develop machine learning models that can predict the effectiveness of Atezo/Bev therapy. **Methods:** A total of 477 consecutive patients with HCC who received Atezo/Bev as a

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first-line systemic therapy between 2020 and 2023 were included from 3 referral centers in Korea. Patients were randomly assigned to either the training (n=318) or test cohort (n=159) at a 2:1 ratio. Blood test results, including alpha-fetoprotein (AFP) and protein induced by vitamin K absence-II (PIVKA-II), were collected right before initiating Atezo/Bev treatment and at the first imaging follow-up visit 6–9 weeks after the first Atezo/Bev administration. Gradient boosting machine and random survival forest algorithms were employed to develop the Model 1 forecasting objective response (complete response or partial response) and the Model 2 predicting progression-free survival (PFS), respectively. **Results:** During a median follow-up of 9.6 (interquartile range [IQR]=5.7–14.1) months, 123 patients (25.8%) achieved objective response. Although baseline characteristics were comparable between those who experienced an objective response and those who did not, the former showed significantly lower MoRAL score (2x√AFP + 11x√PIVKA-II; 148.8 [IQR=75.9–423.8] vs. 394.9 [IQR=133.4-1,168.3], *P*<0.001), albumin-bilirubin score (ALBI score; -2.7 [IQR=-2.9–-2.4] vs. -2.4 [IQR=-2.8–-2.0], *P*<0.001), and neutrophil-to-lymphocyte ratio (NLR; 2.2 [IQR=1.5–3.2] vs. 2.6 [IQR=1.9–4.0], *P*=0.001) and a higher eosinophil count (178 /μL [IQR=88–303] vs. 119 /μL [IQR=61–218], *P*<0.001) at the first imaging follow-up. The Model 1 was developed using eight variables (MoRAL score, ALBI score, NLR, and eosinophil count at the first imaging follow-up and change in these variables from baseline) and demonstrated an area under the receiver operating characteristic curve of 0.779 (95% confidence interval [CI]=0.753–0.817) in the training cohort and 0.779 (95% CI=0.696–0.855) in the test cohort. Model 2 was built by adding the Barcelona Clinic Liver Cancer stage to these eight variables and showed a c-index of 0.802 (95% CI=0.770–0.834) and 0.666 (95% CI=0.609–0.723) in the training and test cohorts, respectively. **Conclusion:** Using the **Results:** of several blood tests, these machine learning models can predict treatment response in advance and help determine future treatment plans for patients with HCC receiving Atezo/Bev therapy.

Disclosures: Moon Haeng Hur: Nothing to Disclose, Bo Hyun Kim: Nothing to Disclose, Byeong Geun Song: Nothing to Disclose, Dong Hyun Sinn: Nothing to Disclose, Hyunjae Shin: Nothing to Disclose, Yuri Cho: Nothing to Disclose, Youngsu Park: Nothing to Disclose, JEAYEON PARK: Nothing to Disclose, Yunmi Ko: Nothing to Disclose, Yun Bin Lee: Nothing to Disclose, Eun Ju Cho: Nothing to Disclose, Su Jong Yu: Nothing to Disclose, Yoon Jun Kim: Nothing to Disclose, Jung-Hwan Yoon: Bayer: Grant/Research Support, Daewoong Pharmaceutical: Grant/Research Support, Bukwang Pharmaceutical: Grant/Research Support, Jeong-Hoon Lee: Nothing to Disclose

3493 | RISK STRATIFICATION CATEGORY IS ASSOCIATED WITH DIFFERENTIAL RISK-TO-BENEFIT RATIO OF LIVER CANCER SURVEILLANCE PROGRAMS

Elena Gavrila[1] Manasa Narasimman[1] Darine Daher[1] Sruthi Yekkaluri[1] Karim Seif El Dahan[1] Yujin Hoshida[1] Ruben Hernaez[2] Amit Singal[1]

[1]University of Texas Southwestern Medical Center, [2]Baylor College of Medicine

Background: The overall value of hepatocellular carcinoma (HCC) surveillance is driven by a balance of benefits and potential harms, which may differ by underlying HCC risk in patients with cirrhosis. **Methods:** We leveraged a prospective cohort study of 2142 patients with cirrhosis followed for 3 years at 3 large health systems (tertiary care referral system, safety-net health system, and Veterans Affairs health system). Patients were stratified into low, intermediate, and high risk of developing HCC categories based on three validated risk scores: aMAP, ADRESS-HCC, and Toronto risk score. We used KNN imputation for missing lab data in 714 patients. Across risk categories, we calculated the incidences of primary liver cancer and screening-related physical harms. Primary liver cancer included HCC (LR-5 or biopsy-confirmed) or cholangiocarcinoma (LR-M or biopsy confirmed). Physical harms were defined as diagnostic evaluation for abnormal or indeterminate screening results, with moderate-severe harm defined as repeated diagnostic imaging or any invasive evaluation (e.g., biopsy). We used Fine-Gray regression analysis, with death and liver transplantation as competing outcomes, to evaluate for differences in incidence rates between risk groups. **Results:** The median age of the cohort was 59.3 years, and 58.1% were male. The cohort was diverse regarding race and ethnicity (30.3% White, 27.4% Black, 38.6% Hispanic) and etiology of cirrhosis (49.6% hepatitis C, 21.6% alcohol-related, and 17.4% MASLD). During the study period, 98 (4.6%) patients developed primary liver cancer (of whom 70.4% had early-stage tumors), whereas 8.4% experienced any physical harms (of which 42.5% was moderate to severe). The incidence of primary liver cancer significantly increased with higher risk category. The 3-year cumulative incidences of HCC for low, intermediate, and high-risk groups were 0%, 0.9%, and 5.0% for aMAP (p=0.01), 1.7%, 4.3%, and 5.8% for ADRESS (p=0.001), and 0%, 3.0%, and 6.5% by the Toronto score (p<0.001). Conversely, physical harms

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did not significantly increase by HCC risk category, including 3-year incidences of 7.7%, 11.8%, and 8.0% for aMAP (p=0.16), 10.7%, 8.9%, and 7.3% for ADRESS (p=0.06), and 14.6%, 8.6%, and 7.6% for Toronto (p=0.06). **Conclusion:** HCC incidence significantly increases by risk category, although physical harms do not significantly vary. Risk-based surveillance can help optimize the overall benefit-to-harm ratio of HCC surveillance programs.

Disclosures: Elena Gavrila: Nothing to Disclose, Manasa Narasimman: Nothing to Disclose, Darine Daher: Nothing to Disclose, Sruthi Yekkaluri: Nothing to Disclose, Karim Seif El Dahan: Nothing to Disclose, Yujin Hoshida: Advisor relationship with Espervita Therapeutics; Has not ended; Advisor relationship with Helio Genomics; Has not ended; Stock - privately held company relationship with Alentis Therapeutics; Has not ended; Stock â€“ privately held company relationship with Espervita Therapeutics; Has not ended; Advisor relationship with Elevar Therapeutics; Has ended; Advisor relationship with Roche Diagnostics; Has ended, Nothing to Disclose, Ruben Hernaez: Nothing to Disclose, Amit Singal: Consultant relationship with AstraZeneca; Has not ended; Consultant relationship with Sirtex; Has not ended; Consultant relationship with Boston Scientific; Has not ended; Consultant relationship with Bayer; Has not ended; Consultant relationship with Eisai; Has not ended; Consultant relationship with FujiFilm Medical Sciences; Has not ended; Consultant relationship with Elevar; Has not ended; Consultant relationship with Exact Sciences; Has not ended; Consultant relationship with Glycotest; Has not ended; Consultant relationship with Exelixis; Has not ended; Consultant relationship with Merck; Has not ended; Consultant relationship with Genentech; Has not ended; Consultant relationship with HistoSonics; Has not ended

3494 | DPP4 INHIBITION AUGMENTS THE ANTI-TUMOR EFFECT OF COMBINED ANTI-PD-1 ANTIBODY/REGORAFENIB IN HEPATOCELLULAR CARCINOMA ◆ ★

Heejoon Jang[1] Yoo Kyoung Lim[1] Youngsu Park[2] Yunmi Ko[2] JEAYEON PARK[2] Moon Haeng Hur[2] Yun Bin Lee[3] Eun Ju Cho[4] Jeong-Hoon Lee[4] Su Jong Yu[2] Yoon Jun Kim[2] Jung-Hwan Yoon[2]

[1]Seoul Metropolitan Government-Seoul National University Boramae Medical Center, [2]Seoul National University College of Medicine, [3]Seoul National University, [4]Seoul National University Hospital

Background: Hepatocellular carcinoma (HCC) is one of the major causes of cancer-related deaths worldwide. Given that DPP4 inhibitors prevent the truncation of CXCL10 and enhance chemotaxis, combining ICIs with DPP-4 inhibitors may further enhance immune cell recruitment and treatment efficacy. We aim to explore the potential synergistic effects of these combinations in HCC using mouse models. **Methods:** Twenty mice (six-week-old male, C57BL/6) were injected subcutaneously with 8 × 10^5 RIL-175 cells to establish hepatocellular carcinoma models. Tumor growth was monitored bi-weekly, and treatments began when tumors reached an average volume of 150–200 mm^3. Mice were divided into four treatment groups: control, sitagliptin, anti-PD-1 antibody/regorafenib, and a combination of anti-PD-1 antibody/regorafenib and sitagliptin. After two weeks of treatments, tumors were harvested. Tumor volume measurement, blood tests, flow cytometry, and immunohistochemistry were performed. **Results:** The mean volume of the tumors in the control and sitagliptin group was 3180.1 ± 1204.1 mm^3 and 3383 ± 959.8 mm^3, respectively. The mean volume of the tumors in the anti-PD-1 antibody/regorafenib/sitagliptin group was 141± 43.9 mm^3, significantly lower than that in the anti-PD-1 antibody/regorafenib group which, was 1483.6 ± 434.3 mm^3 (P = 0.0001). No significant difference observed in body or liver weight and serum ALT and AST levels among the groups. Flow cytometry showed that an increased proportion of effector cell populations ($CD4^+$ T, $CD8^+$ T, NK, and NKT cells) in groups that contain sitagliptin compared with other groups. The proportion of NKT cells was significantly increased in the combination of anti-PD-1 antibody, regorafenib, and sitagliptin group compared to controls and other treatment arms. Immunohistochemistry confirmed that combination with sitagliptin significantly increased the proportion of NK and NKT cells, with enhanced NK cell activation markers and decreased inhibition markers. **Conclusion:** This study demonstrates that a DPP4 inhibitor augments the anti-tumor effect of the immune-based combination therapy of anti-PD-1 antibody and regorafenib by recruiting an increased proportion of effector immune cells, notably NKT cells, in the tumor microenvironment without causing hepatotoxicity.

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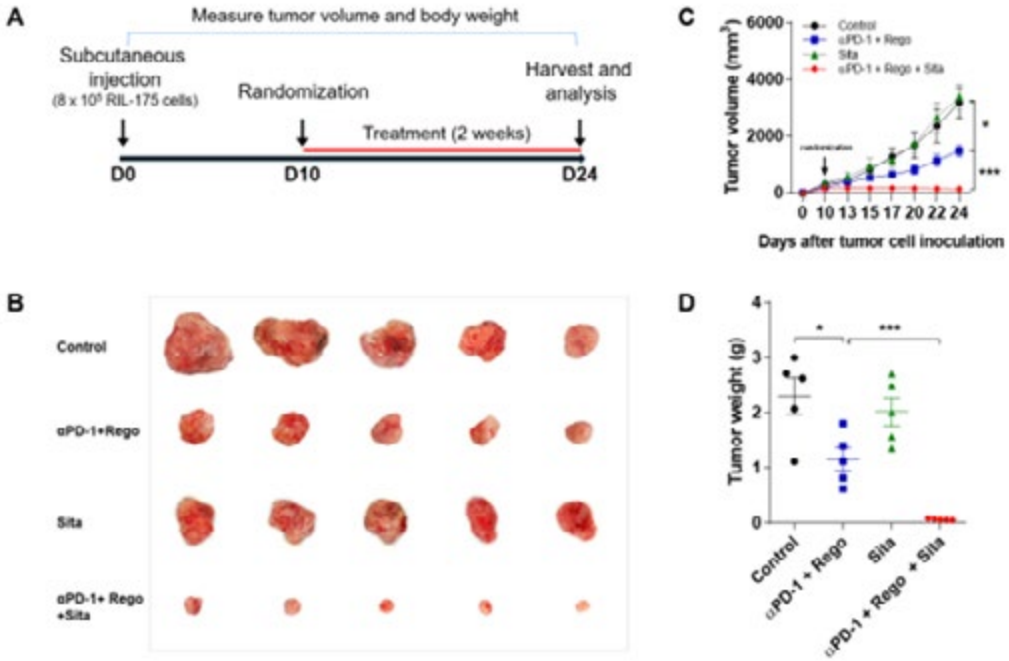

Disclosures: Heejoon Jang: Nothing to Disclose, Yoo Kyoung Lim: Nothing to Disclose, Youngsu Park: Nothing to Disclose, Yunmi Ko: Nothing to Disclose, JEAYEON PARK: Nothing to Disclose, Moon Haeng Hur: Nothing to Disclose, Yun Bin Lee: Nothing to Disclose, Eun Ju Cho: Nothing to Disclose, Jeong-Hoon Lee: Nothing to Disclose, Su Jong Yu: Nothing to Disclose, Yoon Jun Kim: Nothing to Disclose, Nothing to Disclose, Jung-Hwan Yoon: Bayer: Grant/Research Support, Daewoong Pharmaceutical: Grant/Research Support, Bukwang Pharmaceutical: Grant/Research Support

3495 | PREDICTING END-STAGE HEPATOCELLULAR CARCINOMA WITH THE ECHO SCORE: REFINING THE DEFINITION OF BARCELONA CLINIC LIVER CANCER STAGE D DISEASE IN PATIENTS TREATED WITH IMMUNE CHECKPOINT INHIBITORS ◆

Michael Li[1] *Robin Kate Kelley*[1] *Madeleine Hu*[1] *Jocelin Chen*[1] *Neil Mehta*[1] *Francis Yao*[1] *Lawrence Fong*[1] *Jennifer Lai*[1]

[1]*University of California, San Francisco*

Background: The BCLC criteria recommends best supportive care instead of cancer treatment in hepatocellular carcinoma (HCC) patients with 90-day expected survival (stage D or “end-stage” HCC). Currently, stage D is defined as Child-Pugh (CP) class C liver disease or ECOG performance status≥3. However, the major immune checkpoint inhibitor (ICI) trials in HCC were limited to highly-optimized patients (CP class A, ECOG 0-1), and therefore do not inform real-world practice with sicker patients. **Methods:** We conducted a single-center study of ICI-treated HCC patients. The primary outcome was early death (within 90 days of ICI initiation). ALBI scores, a measure of liver function, were calculated as: log10(total bilirubin*17.1)*0.66 + albumin*-0.85. LASSO regression was employed to develop a prediction model for early death, which was internally validated using bootstrapping and cross-validation. **Results:** In the 283 study patients, the median MELD was 11, 37% were CP class B/C, and 15% had ECOG scores >1. Although only 23 patients (8%) met current BCLC stage D criteria, 60 (21%) experienced early death. All measures of liver function (median MELD 17 vs 10; median CP points 8 vs 6, median ALBI score -0.71 vs -1.70) were worse in the early death group, as was performance status (RR 1.7 for each 1 unit increase in ECOG).The novel ECHO (Early Complications in HCC immunOncology) score was derived, and the formula for log odds of early death was: *-2.100 + 0.574*(ECOG score) + 1.000*(ALBI score) + 0.124*(CP points) + 0.748*(presence of metastases or macrovascular invasion).*ECHO had significantly better discrimination for early death compared to current BCLC stage D criteria (c-statistic 0.90 vs 0.63, p<0.001). The mean c-statistics for the ECHO score over 1000 bootstrap samples and on 10-fold cross-validation were 0.90 and 0.89, respectively. A 30% predicted risk of early death was the optimal cutoff based on maximizing Youden’s index; this

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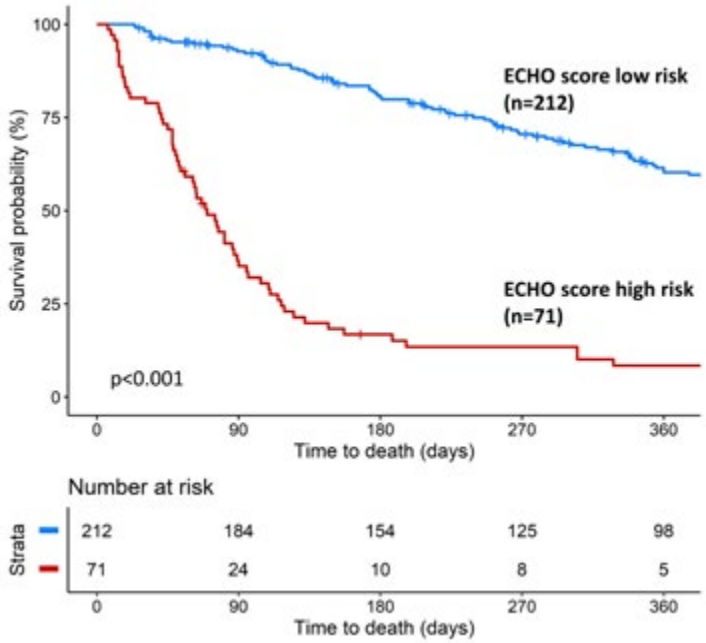
cutoff had a sensitivity of 77% and a specificity of 88%. Patients exceeding this cutoff had poor survival (median 70 vs 477 days, p<0.001; **Figure**). **Conclusion:** The ECHO score has excellent discrimination for death within 90 days of starting ICI therapy for HCC and can be applied using pre-treatment data to identify high-risk patients who are unlikely to benefit from treatment. This score also represents an improved definition of end-stage HCC than the current BCLC stage D criteria and warrants validation in an independent dataset.



Disclosures: Michael Li: Nothing to Disclose, Robin Kate Kelley: Astra Zeneca: Grant/Research Support, Bayer: Grant/Research Support, Eli Lilly: Grant/Research Support, Exelixis: Grant/Research Support, Genentech/Roche: Grant/Research Support, Kinnate: Consultant, Merck: Grant/Research Support, Partner Therapeutics: Grant/Research Support, Regeneron: Consultant, Agios: Grant/Research Support, BMS: Grant/Research Support, QED: Grant/Research Support, Tyra: Grant/Research Support, Taiho: Grant/Research Support, Surface: Grant/Research Support, Servier: Grant/Research Support, GSK: Consultant, moderna: Consultant, J Pharma Inc.: Consultant, Relay Therapeutics: Grant/Research Support, Madeleine Hu: Nothing to Disclose, Jocelin Chen: Nothing to Disclose, Neil Mehta: Merck: Consultant, FujiFilm WAKO: Consultant, Francis Yao: Nothing to Disclose, Lawrence Fong: Nothing to Disclose, Jennifer Lai: Nestle Nutrition Institute: Grant/Research Support, Novo Nordisk: Consultant, Genfit: Consultant, Boehringer Ingelheim: Advisor

3496 | CIRCULATING EXOPD-L1 PREDICTS THE OUTCOME OF PATIENTS WITH HCC WHO RECEIVED ATEZOLIZUMAB-BEVACIZUMAB

Yu Rim Lee[1] Gyeonghwa Kim[2] Young Oh Kweon[3] Won Young Tak[4] Soo Young Park[3] Se Young Jang[3] Jeong Hwa Lee[5] Min Hwa Park[3] Jung Gil Park[6] Min Kyu Kang[6] Jeong Eun Song[7] Keun Hur[2]

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Background: Hepatocellular carcinoma (HCC) is a highly aggressive disease that is usually diagnosed at an advanced stage. Advanced HCC has limited treatment options and often has a poor prognosis. Atezolizumab-bevacizumab significantly improved survival rates as a first-line treatment and became the new standard of care. The interaction between the programmed cell death receptor 1 (PD-1) and its ligand (PD-L1) contributes to immune evasion and exosomal PD-L1 is a marker of poor outcome after surgery or chemotherapy in patients with various types of cancers. However, the role of PD-L1-containing exosomes in patients with advanced HCC

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receiving atezolizumab-bevacizumab is remains to be elucidated. We therefore determined the prognostic significance of circulating exosomal PD-L1 in advanced HCC patients receiving atezolizumab-bevacizumab. **Methods:** This study enrolled 28 HCC patients receiving atezolizumab-bevacizumab between Dec 2020 and Jan 2023. Exosomes were extracted from serum samples using the ExoQuick Exosome Precipitation Solution. Exosomal PD-L1 was detected by Exocounter. **Results:** The total number of exosomes and PD-L1 positive exosomes increased significantly as the mUICC stage of HCC progressed (P<0.05). Comparing between the early and advanced stage, the number of Exosomal PD-L1 significantly increased in the advanced stage. The overall survival and progression-free survival were significantly lower in patients with lower circulating levels of exosomal PD-L1 (log-rank test: P=0.015 and 0.007, respectively). **Conclusion:** In conclusion, this study has provided strong evidence that circulating exosomal PD-L1 are novel prognostic markers and therapeutic targets for advanced HCC who received atezolizumab-bevacizumab.

Figure 1. The total number of exosomes and PD-L1 positive exosomes increased significantly as the mUICC stage of HCC progressed

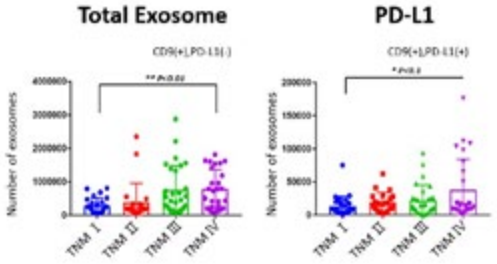
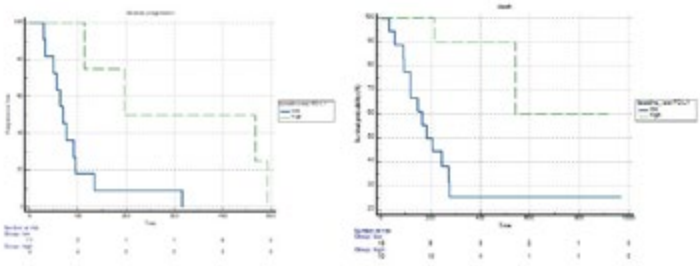


Figure 2. The overall survival and progression-free survival were significantly lower in patients with lower circulating levels of exosomal PD-L1 (log-rank test: P=0.015 and 0.007, respectively).



Disclosures: Yu Rim Lee: Nothing to Disclose, Gyeonghwa Kim: Nothing to Disclose, Young Oh Kweon: Nothing to Disclose, Won Young Tak: Nothing to Disclose, Soo Young Park: Nothing to Disclose, Se Young Jang: Nothing to Disclose, Jeong Hwa Lee: Nothing to Disclose, Min Hwa Park: Nothing to Disclose, Jung Gil Park: Nothing to Disclose, Min Kyu Kang: Nothing to Disclose, Jeong Eun Song: Nothing to Disclose, Keun Hur: Nothing to Disclose

3497 | BURDEN OF LIVER CANCER AND OTHER MAJOR GASTROINTESTINAL CANCERS IN THE EASTERN MEDITERRANEAN REGION

Saleh Alqahtani[1] Saleh Alessy[1] Eileen Morgan[2] Mariam Zahwe[2] Ariana Znaor[2]

[1]King Faisal Specialist Hospital & Research Center, [2]The International Agency for Research on Cancer

Background: The Eastern Mediterranean Region (EMR) is economically and culturally diverse and poses unique challenges regarding healthcare. The World Health Organization (WHO) warns that EMR may encounter the most significant increase in incidence in the coming decades owing to the rise in related risk factors. We aim to provide an overview of the current patterns of incidence and mortality estimates of liver cancer and other major gastrointestinal (GI) cancers in 2022 in the region. **Methods:** We extracted the estimated number of cases and deaths of liver cancer and other GI cancers, such as esophageal, gastric, colorectal, and pancreatic cancers, from the GLOBOCAN database, developed and quality-assured by the International Agency for Research on Cancer, Lyon, France, and presented the corresponding age-standardized rate (ASR) for incidence and mortality per 100,000 person-years for 2022 within the EMR. **Results:** An estimated 173,000 new cancer cases and 139,000 deaths occurred in the EMR in 2022 for esophageal, gastric, liver, colorectal, and pancreatic cancers, with corresponding incidence and mortality ASRs (for all five cancers combined) being 29.6 and 24.1 per 100000 person-years, respectively. The five cancers accounted for 22.2% of all new cancer cases and 28.7% of all cancer deaths estimated in the EMR. Out of all cancers (for both sexes combined), colorectal ranked third (6.9%; ASR 8.9), followed by liver cancer (6.2%; ASR 8.4) in terms of incidence, while liver cancer (9.6%; ASR 8.1), and stomach cancer (6.4%; ASR 5.5) were the third and fourth leading cause of cancer deaths in the region. There were large variations in cancer incidence and mortality rates between countries, with liver cancer most pronounced in Egypt and stomach cancer in Iran, with more than 10-fold differences in rates across countries. Excluding colorectal cancer, the patterns of mortality followed those for incidence in the region, reflecting the poor prognosis of esophageal, gastric, liver, and pancreatic cancers. The EMR ranked second among other WHO

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regions in terms of both liver cancer incidence and death. **Conclusion:** Liver and other GI cancers currently account for a significant fraction of the overall cancer burden in the EMR and are projected to increase due to population aging in the coming decades continuously, if not offset by current cancer prevention measures.

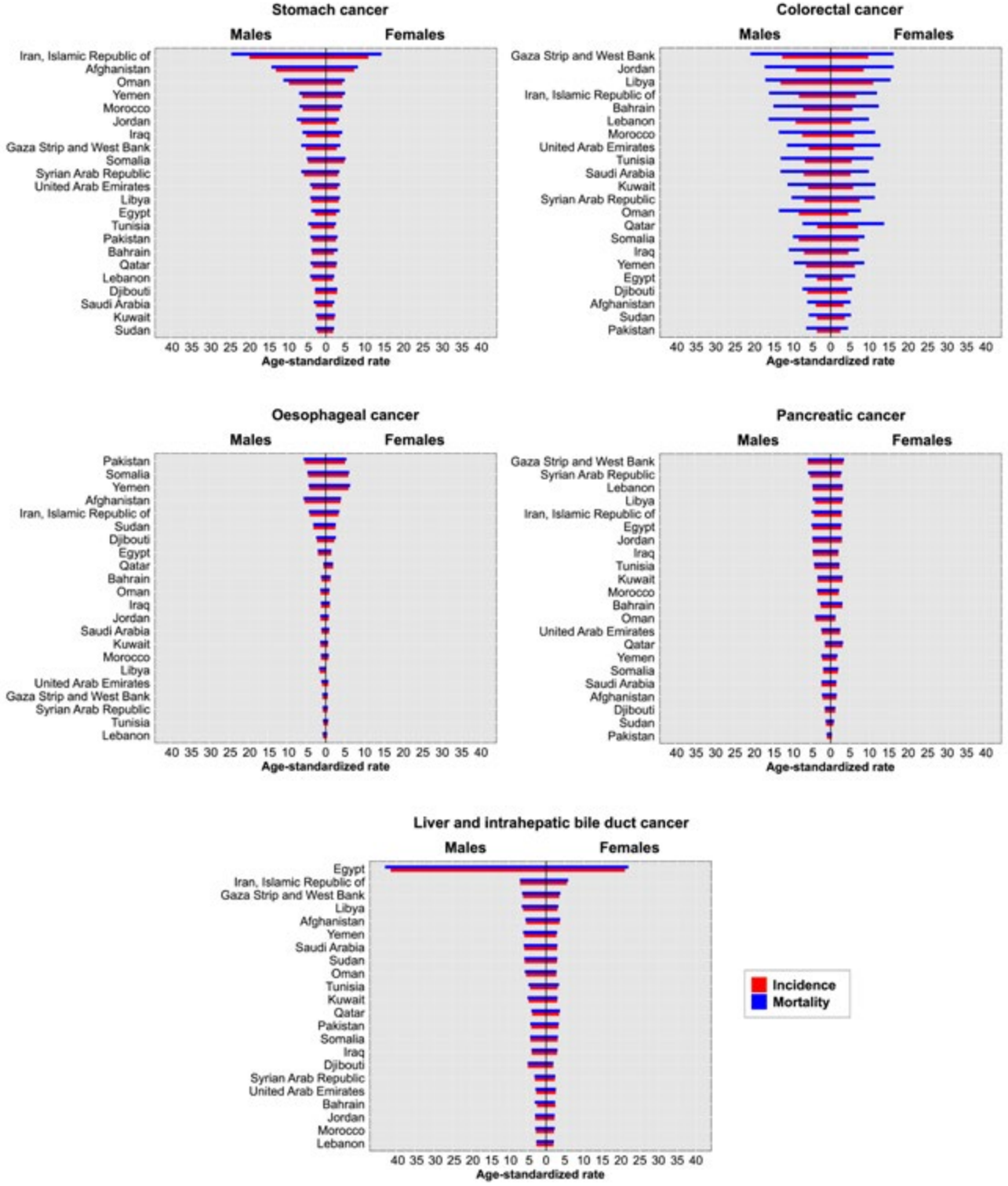

Figure 1: Age-standardized Rates (ASR) for five GI cancer incidences and deaths (by gender) across the 22 countries in the EMR.

Disclosures: Saleh Alqahtani: Nothing to Disclose, Saleh Alessy: Nothing to Disclose, Eileen Morgan: Nothing to Disclose, Mariam Zahwe: Nothing to Disclose, Ariana Znaor: Nothing to Disclose

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3498 | BENEFICIAL EFFECT OF COMBINED RADIATION THERAPY IN ATEZOLIZUMAB PLUS BEVACIZUMAB TREATMENT OF HEPATOCELLULAR CARCINOMA PATIENTS WITH MAIN PORTAL VEIN TUMOR THROMBOSIS OR BILE DUCT INVASION

Hyun Young Woo[1] Jeong Heo[1] SANGYOUN HWANG[2] Ga Ram You[3] Yu Rim Lee[4] Hyung Jun Kim[2] Young Joo Kim[1] Kiyoun Yi[1] Jae hyun Yoon[5] Soo Young Park[4] Woo Jin Chung[6] Byoung Kuk Jang[6] Sung Bum Cho[3] Won Young Tak[7]

[1]College of Medicine, Pusan National University, Pusan National University Hospital, [2]Dongnam Institute of Radiologic & Medical Sciences, [3]Chonnam National University Hwasun Hospital and Medical School, [4]School of Medicine, Kyungpook National University, Kyungpook National University Hospital, [5]Chonnam National University Hospital and Medical School, [6]Keimyung University School of Medicine, [7]College of Medicine, Kyungpook National University

Background: Previously, the authors showed that radiation therapy combined with atezolizumab (ATE) plus bevacizumab (BEV) treatment might be helpful to improve progression-free survival (PFS) and overall survival (OS) in high-risk patients. In this study, we aim to investigate the subgroup among high-risk patients who can benefit from radiation therapy combined with ATE+BEV. **Methods:** This is a multicenter retrospective cohort study. Between July 2020 to Dec 2023, 474 patients treated for advanced HCC with at ATE+BEV from five tertiary hospitals were analyzed. High-risk patients were those with grade Vp4 portal vein tumor thrombus (PVTT), bile duct invasion, or more than 50% liver infiltration and 203 (42.8%) was the high risk patients. Tumor response was evaluated with the Response Evaluation Criteria in Solid Tumors (version 1.1.). **Results:** Among high risk patients, 114 (56.2%) have HCC more than 50% liver infiltration, 112 (55.2%) have Vp4 PVTT and 46 (22.7%) patients have bile duct invasion. 141 (69.6%) have one of 3 high risk features 54 patients (26.6%) have two of them and 8 have all of them. Child-Pugh class was A in 173 (85.2%) and B in 30 (14.8%). 107 (52.7%) had received radiation treatment. In high-risk patients, objective response rate was 20.2%. disease control rate was 61.6%. The median PFS was 5.70 months (95% CI, 4.25-7.15) and median OS was 8.43 months (95% CI, 7.06-9.80). Multivariate analysis indicated that radiation therapy, number of high-risk features and ECOG performance status were associated with OS. Median OS was 10.3 months (95% CI, 7.76-12.84) in patients with radiation and 6.17 months (95% CI, 4.06-8.28) in patients without radiation. In the Vp4 PVTT group and the bile duct invasion group, combined radiation therapy significantly improved the survival rate (p=0.017, p=0.004), but in the more than 50% liver infiltration group, the survival rate did not improve with combined radiation therapy (p=0.282). Additionally, radiation therapy did not improve the survival rate in patients with one high-risk feature (p=0.184) but did improve the survival rate in patients with two or more high-risk features (p=0.007, p=0.003). **Conclusion:** In high-risk patients, radiation therapy combined with atezolizumab plus bevacizumab treatment might be helpful to improve OS in the Vp4 PVTT group and the bile duct invasion group, not in the in the more than 50% liver infiltration group. Additionally, radiation therapy helped improve survival rate as the number of high-risk features increased.

Disclosures: Hyun Young Woo: Nothing to Disclose, Jeong Heo: Gilead: Grant/Research Support, Roche: Speaking and Teaching, Roche: Speaking and Teaching, Yuhan: Speaking and Teaching, Abbvie: Speaking and Teaching, AstraZeneca: Advisor, Oncolys Japan: Grant/Research Support, Surrozen: Advisor, MedVir: Advisor, SANGYOUN HWANG: Nothing to Disclose, Ga Ram You: Nothing to Disclose, Yu Rim Lee: Nothing to Disclose, Hyung Jun Kim: Nothing to Disclose, Young Joo Kim: Nothing to Disclose, Kiyoun Yi: Nothing to Disclose, Jae hyun Yoon: Nothing to Disclose, Soo Young Park: Nothing to Disclose, Woo Jin Chung: Nothing to Disclose, Byoung Kuk Jang: Nothing to Disclose, Sung Bum Cho: Nothing to Disclose, Won Young Tak: Nothing to Disclose

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3499 | MACHINE LEARNING CAN ACCURATELY STRATIFY RISK OF HEPATOCELLULAR CARCINOMA IN REAL-WORLD DATA ◆

Jan Clusmann[1] Paul-Henry Koop[2] David Zhang[3] Felix Van Haag[2] Omar el Nahhas[1] Kai Markus Schneider[4] Jakob Nikolas Kather[1] Carolin Victoria Schneider[2]

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Background: Hepatocellular carcinoma (HCC) is a highly fatal malignancy. A growing proportion of HCCs is caused by the obesity-related Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD), expanding the population at risk of HCC. Risk constellations for HCC are well characterized, encompassing liver diseases, serum parameters, lifestyle and hereditary risk. Nonetheless, current screening strategies are exclusive for patients with liver cirrhosis. Stratifying patients in terms of risk of HCC poses a major clinical challenge. This can be addressed through systematic, multi-modal risk stratification methods on the foundation of machine learning and big data. **Methods:** We trained random forest classifiers (RFCs) on data of > 500.000 participants of the UK Biobank (UKB). UKB is a population-based database with electronic health records (EHR), death registers, lifestyle, physical and biological measures as well as genomics (n~500k each) and metabolomics data (n=250k), with over 15 years of follow up. Models were trained on multimodal data via five-fold cross-validation on 80 % of UKB (n=410 HCC cases, 18 of 22 centers), with independent testing on 128 HCC cases from remaining UKB centers from Scotland and Wales. Reflecting the step-by-step nature of clinical data gathering, we incrementally enriched the training data for different clinical scenarios from basic physical measurements and patient history, to routinely available blood counts and serum markers, and finally sophisticated methods such as genomics and metabolomics. **Results:** Our models achieved high predictive accuracies in the independent test set, outperforming few-parameter risk scores such as the widely recognized aMAP-score by far. Specifically, model accuracies ranged from AUROCs of 0.8 (lifestyle/demographics) to 0.88 after addition of serum information, which had the highest predictive capacities and feature importance. Interestingly, the inclusion of metabolomic or genomic data did not significantly enhance performance. Further validation of our model is currently performed on 333 HCC cases (+ 146446 controls) from the All-Of-Us Research Program, and will be presented at “The Liver Meeting” 2024. **Conclusion:** Our study reveals robust predictive capacities of explainable machine learning models when applied to risk stratification using real-world data. This establishes machine learning as a potential game-changer in HCC risk assessment.

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3500 | TARGETING UBE2I-MEDIATED PROTEIN HYPER-SUMOYLATION HALTS CHOLANGIOCARCINOMA PROGRESSION AND REWIRES THE TUMOR-STROMA CROSSTALK

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Background: Cholangiocarcinoma (CCA) includes a diverse range of biliary malignant tumours characterized by dismal prognosis. Although alterations in post-translational modifications have been reported to contribute to abnormal protein dynamics, cellular disturbances, and disease, how protein SUMOylation benefits CCA

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progression and modulates the interaction between transformed biliary cells and the tumour microenvironment (TME) remains unexplored. In this study, we investigate how protein SUMOylation favours CCA progression and reshapes the TME, and we explore its potential as a therapeutic target. **Methods:** Using a combination of human CCA cells and primary tumours, we analysed the levels and function of protein SUMOylation, identifying deregulated SUMOylated proteins by immunoprecipitation and mass spectrometry analysis. The response to genetic (*UBE2I*^{KD}) or pharmacological (ML792 and SAMe) inhibition of SUMOylation was assessed *in vitro* and in two *in vivo* models of CCA. By performing co-culture experiments between wild-type or *UBE2I*^{KD} cancer cells and CCA-derived cancer-associated fibroblasts (CAFs), human endothelial cells or monocytes, we have unveiled the impact of SUMOylation in the crosstalk between CCA cells and the TME. **Results:** Analysis of human CCA cells and primary tumours revealed increased expression and activity of the SUMOylation machinery, correlating with unfavourable clinical outcomes. Critically, we identified that the majority of SUMOylated proteins deregulated in CCA were involved in cell proliferation, survival or cell homeostasis. Depleting SUMOylation effectively halted tumorigenesis in subcutaneous and oncogene-driven models of CCA *in vivo*. The genetic and pharmacological inhibition of SUMOylation reduced CCA cell proliferation and hindered the formation of cell colonies *in vitro*, and it encompasses a profound impact on the establishment of the TME, inhibiting the growth of CAFs and vascular cells, while reducing the immunosuppressive tumour envvironment. **Conclusion:** Aberrant protein SUMOylation contributes to cholangiocarcinogenesis by promoting cell survival and proliferation, and contributes to the conformation of the TME. Impairing SUMOylation halts CCA growth and, thus, may represent a potential novel therapeutic strategy for patients with CCA for whom current targeted therapies are limited.

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3501 | THE INVOLVEMENT OF MICRORNA-1297 IN LENVATINIB RESISTANCE IN HEPATOCELLULAR CARCINOMA CELLS

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Background: Lenvatinib for treating hepatocellular carcinoma (HCC) has a superior response rate, although its overall survival is non-inferior to sorafenib, suggesting tumor cells may acquire resistance during therapy. Hypoxia in the tumor microenvironment has been reported to play a critical role in the acquisition of drug resistance. Tyrosine kinase inhibitors with inhibitory effects on VEGF prevent tumor angiogenesis, resulting in significant hypoxia in the tumor. We aimed to elucidate the mechanism of lenvatinib resistance and the involvement of microRNAs under hypoxia in HCC. **Methods:** HCC cell lines, PLC/PRF/5, HepG2, and Huh7 were cultured in 95% air and 5% CO_2 (normoxia) or in 94% N_2 with 1% O_2 and 5% CO_2 (hypoxia). Anchorage-dependent proliferation was assessed using a metabolic assay, and the induction of apoptosis was evaluated morphologically and through caspase-3/7 activation. A genome-wide profiling was conducted using 3D-Gene miRNA/mRNA Oligo chips to identify altered microRNAs in acquiring resistance to lenvatinib. An argonaute2-based RIP assay was performed, followed by genome-wide profiling of mRNA to identify direct miRNA targets. **Results:** Lenvatinib demonstrated a concentration-dependent inhibition of cell growth. The IC_{50} of lenvatinib (72 hrs), as determined by MTS assay, was significantly increased under hypoxic conditions in all cell lines tested, suggesting the acquisition of lenvatinib resistance. Under hypoxia, the number of morphologically determined apoptotic cells induced by lenvatinib was 22.4% and 19.6% decreased, and caspase-3/7 activity was 26.4% and 18.7% decreased compared to normoxia in PLC/PRF/5 and HepG2, respectively. A genome-wide profiling showed 42 microRNAs increased in PLC/PRF/5 treated with lenvatinib under normoxia, and 28 of these showed decreased expression under hypoxia. Among these, we focused on miR-1297 for further investigation. Following forced expression of miR-1297, the viability of PLC/PRF/5 cells treated with lenvatinib (12.5 and 25 μM) under hypoxia was 76.6%

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and 51.4%, respectively. This was significantly lower than the negative control, which was 88.3% and 76.8%. A genome-wide profiling of mRNA was conducted in PLC/PRF/5 under forced expression of miR-1297. 27 genes decreased more than 2-fold, and network analysis of these genes suggested that miR-1297 regulates a group of genes with TGF-β receptor1 as a hub. The results of the RIP assay on RNA extracted from PLC/PRF/5 cells with forced expression of miR-1297 demonstrated a significant increase of 88 mRNAs compared to negative control. A screening of these mRNAs using the TargetScan identified *TMSB10* mRNA with sequences complementary to miR-1297 seed region. **Conclusion:** miR-1297 may play a role in lenvatinib resistance induced by hypoxia by regulating TGF-β signaling through TMSB10. These observations indicate that microRNAs may represent an attractive target for overcoming lenvatinib resistance.

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3502 | ACTIVATION OF COAGULATION FACTORS AND IMPAIRED FIBRINOLYSIS IN PATIENTS WITH PRIMARY SCLEROSING CHOLANGITIS AND CHOLANGIOCARCINOMA

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Background: Venous thromboembolism (VTE) is the most common presentation of the cancer-associated hypercoagulable state. In cholangiocarcinoma (CCA), the risk of VTE and the role of the tumor cell in the abnormal activation of the blood coagulation cascade are underestimated. Primary sclerosing cholangitis (PSC) is burdened by a high incidence of CCA. Recent data indicate a role for the components of coagulation cascade in carcinogenesis and a prognostic significance of their expression levels. Starting from these observations, our aim was to analyze the expression of components of coagulation and fibrinolysis pathways in CCA and PSC. **Methods:** Archival formalin-fixed, paraffin-embedded tissues from surgical resection for PSC, intrahepatic CCA (iCCA), and biopsies from implanted grafts (controls) (all n=10) were stained by immunohistochemistry (IHC) or immunofluorescence with the coagulant factors tissue factor (TF), factor (F) XI, FXIIIA, von Willebrand factor (vWF), fibrinogen and endothelial protein C receptor (EPCR). IHC results was correlated with fibrin deposition (sign of portal vein microthrombosis, PVMT) assessed by Martius Scarlet Blue (MSB) staining. Real-time PCR of the same factors was performed in patient-derived organoids from PCS (n=10) and iCCA (n=10). **Results:** Activation of coagulation mechanisms was detected in PSC and iCCA samples but not in controls. iCCA showed a higher expression of coagulation factors with respect to PSC. TF was upregulated in cholangiocytes and stromal cells, on the contrary to FXI. Fibrinogen was diffuse throughout the stroma, while fibrin decorates stroma and tissue margins. Fibrin within the portal vein lumen (PSC, n=4/10 and iCCA, n=2/10), consistent with PVMT, was found in samples with the highest expression of TF. FXIIIA was expressed by cholangiocytes and macrophages. Endothelial expression of EPCR was significantly weaker in tumor than in PSC and controls, while vWF expression was increased in the endothelial cells of PSC and iCCA. This phenotypic expression was confirmed in patient-derived organoids from both PSC and iCCA. **Conclusion:** PSC and iCCA showed features of activation of procoagulation cascade and impaired fibrinolysis, regardless of the development of PVMT. Future studies are needed to understand the role of coagulation perturbation in PSC and in CCA progression, to possibly provide the rationale for testing modulatory agents of blood coagulation/fibrinolytic system in PSC and CCA patients.

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3503 | TRANSPOSON-BASED ONCOGENES INTEGRATION IN ABCB4 *(MDR2)-/-* MICE RECAPITULATES HIGH SUSCEPTIBILITY TO CHOLANGIOCARCINOMA IN PRIMARY SCLEROSING CHOLANGITIS

Pinzhu Huang[1] Guangyan Wei[1] Jesse Kirkpatrick[2] MARAM ALENZI[1] Yi Lin[1] Li Tan[1] Disha Badlani[1] Li Chen[3] Mathieu Petitijean[3] Kahini Vaid[1] Shuangshuang Zhao[1] Alicia Iugovskoy[1] xin chen[4] Gregory Gores[4] Yury Popov[1]

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Background: Cholangiocarcinoma (CCA) is a dreaded complication of primary sclerosing cholangitis (PSC), difficult to diagnose and associated with high mortality. Lack of animal models of CCA recapitulating the hepatic microenvironment of progressive sclerosing cholangitis hinders development of novel treatments. Here we sought to develop and characterize such PSC-associated CCA model in mice. **Methods:** Ten-week-old *Mdr2*-/- mice with congenital PSC-like progressive biliary disease, and healthy wild-type littermates (WT) mice enrolled as control fed with chow diet or DDC (3,5-diethoxycarbonyl-1,4-dihydrocollidine) were subjected to either modified retrograde biliary instillation or hydrodynamic tail vein injection of sleeping beauty transposon-transposase plasmid system with activated forms of AKT (myr-AKT) and Yap (YapS127A) protooncogenes (SB AKT/YAP1). ALK5 inhibitor (SB-525334, 300 mg/kg in diet) or placebo diet was administered into *Mdr2-/-* tumor-bearing mice to interrogate the functional role of TGFβ signaling in our model. Tumor phenotype, burden and desmoplastic reaction were analyzed based on histological staining in combination with transcriptomic analysis. **Results:** Hydrodynamic tail vein injection of SB AKT/YAP1 resulted in robust tumorigenesis in all fibrotic *Mdr2*-/- mice with high CCA burden relative to healthy mice. This model was duplicated in the context of biliary injury induced by DDC diet. Tumors expressed CK19, and exhibited a profound desmoplastic reaction, and high density of p-Smad2. Transcriptomic analysis indicated that tumorigenic mechanism of CCA.*Mdr2-/-* was dramatically different from CCA.WT. Pharmacological pan-TGFβ inhibition via ALK5 inhibitor reduced nontumor fibrosis, both tumor burden and desmoplastic tumor stroma compared to placebo. **Conclusion:** We established a new high-fidelity cholangiocarcinoma model in mice, termed SB CCA.*Mdr2-/-*, which recapitulates the increased susceptibility to CCA in the setting of progressive biliary injury and fibrosis observed in PSC. Furthermore, pharmacological targeting of ALK5 in our model suggests that TGFβ signaling functionally drives CCA tumorigenesis and promotes desmoplastic reaction.

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3504 | EVALUATING TREATMENT STRATEGIES IN HEPATOCELLULAR CARCINOMA: A LONGITUDINAL ANALYSIS OF BCLC RECOMMENDATIONS AND PATIENT OUTCOMES

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Background: In 2022 the BCLC staging and treatment algorithm for hepatocellular carcinoma (HCC) management has been updated (BCLC_2022), granting for higher flexibility and customized management for HCC patients as compared to the 2018 version. Aim of the study was to evaluate the feasibility of BCLC_2022 in daily clinical practice (BCLC_2018 as benchmark), its impact on response to treatment and on overall survival (OS). **Methods:** We retrospectively evaluated data of 798 prospectively followed (year 2006 to 2022) patients with de novo HCC: 187 0, 371 A, 132 B, 87 C and 21 D, according to BCLC. First line treatment allocations were discussed by a multidisciplinary team (MTD), following updated recommendations. All patients were followed until death or end of follow-up (12/2022). **Results:** Overall, the feasibility of the BCLC algorithm increased from

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51% for BCLC_2018 to 69% for BCLC_2022 (p<0.001): 56% to 73% stage 0 (p=0.001), 45% to 72% stage A (p<0.001), 51% to 65% stage B (p=0.02), while no changes were registered for stage C and D. Among BCLC 0/A patients, 130 (23%) were treated with a “lower priority option” according to BCLC_2022, reducing the rate of “downward stage migration” from 33% to 16%, p<0.001. However, patients treated with a “lower priority option” had a lower proportion of complete response (82% vs 60%, p=0.01 in BCLC 0 and 74% vs 20%, p<0.001 in BCLC A) and a shorter OS [33 (IQR 23-61) vs 74 months (IQR 42-137) p<0.001 in BCLC A] as compared to those undergoing first choice treatments in early stages. “Downward stage migration” without curative intent was associated with a lower proportion of complete response to first line treatment in the early stages (0% vs 77%, p=0.003 in BCLC 0; 0% vs 57%, p=0.001 in BCLC A) and to a shorter OS [6 months (IQR 2-16) vs 82 months (IQR 42-132), p<0.001 in BCLC 0] as compared to BCLC_2022. In BCLC B and C, an “upward stage migration” was associated to a higher achievement of complete response (17% vs 52%, p<0.001 in BCLC B and 2% vs 41% p<0.001 in BCLC C), and granted a longer OS [(63 months (IQR 36-72) vs 28 (IQR 18-44), p=0.003 in BCLC B and 21 months (IQR 15-44) vs 11 months (IQR 4-25) in BCLC C] as compared to BCLC 2022. In BCLC 0 and A, undergoing a “downward stage migration” without curative intent was an independent predictor of mortality [HR 6.94 (95% CI 2.27-21.20) p=0.001], alongside with age [HR 1.08 (95% CI 1.06-1.13), p<0.001] and ALBI grade 3 [HR 9.34 (95% CI 1.21-72.19), p=0.03]. Conversely, “upward stage migration” was independently associated to a lower mortality risk both in BCLC B [HR 0.46 (95% CI 0.27-0.80), p=0.006] and C [HR 0.50 (95% CI 0.27-0.92) p=0.03]. **Conclusion:** The BCLC_2022 updated version of HCC staging and treatment system allowed a greater adherence to the algorithm in clinical practice. When feasible, best survival is ensured by choosing treatment with curative intent in BCLC 0/A or opting for ‘upward stage migration’ in BCLC B/C, according to either the algorithm or tumor board evaluation.

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3505 | VALIDATION OF PREDICTION MODELS FOR HEPATITIS B VIRUS-RELATED HEPATOCELLULAR CARCINOMA BASED ON THE TYPE OF ANTIVIRAL AGENTS

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Background: In the HCC risk prediction model for patients with CHB using antiviral drugs, many studies have focused on patients using first-line drugs (ETV or TDF), while some have exclusively considered patients using ETV. Our goal is to compare predictive capabilities based on the types of antiviral agents, especially to analyze whether these models can also be applied in the TDF or TAF treatment group. **Methods:** Using a retrospective cohort of 2,090 CHB patients undergoing antiviral therapy (ETV = 1148, TDF = 692, TAF = 250), we assessed the performances of conventional HCC prediction models (PAGE-B, modified PAGE-B, REAL-B, CAMD, AALC, HCC rescue score) and the modified REACH-B (mREACH-B), CAMPAS, PAGE-B^{LS} using liver stiffness (LS) value. **Results:** During the follow-up (median, 56.5 months), HCC developed in 124 (5.9%) patients. REAL-B (0.77), CAMD (0.76), AALC (0.76), HCC rescue score (0.76) had higher areas under the receiver operating characteristic curves (AUC) for the prediction of HCC development compared with PAGE-B (0.70), respectively, with statistical significances (all P values <0.05). Among models using LS value, the CAMPAS score (0.78) demonstrated the highest prediction performance compared with mREACH-B (0.72; P <0.01) and PAGE-B^{LS} (0.75; P = 0.04). CAMPAS (0.77) and PAGE-BLS (0.78) showed the highest discrimination with AUCs in the ETV group in subgroups according to the type of antiviral agents. In contrast, the CAMPAS score (0.79) had the highest performance in the TDF group. The TAF group exhibited lower discrimination with AUC values ranging from 0.62 to 0.69 for conventional HCC prediction models, whereas the CAMPAS score still demonstrated a high prediction performance with 0.79. **Conclusion:** In this undergoing antiviral treatment, most HCC prediction models performed well even when applied during treatment with TDF or TAF, particularly REAL-B, CAMD, AALC, HCC rescue score, and CAMPAs model.

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Disclosures: Seong Hee Kang: Nothing to Disclose, Young Kul Jung: Nothing to Disclose, Hyung Joon Yim: Nothing to Disclose, Seung Kak Shin: Nothing to Disclose, Yim Sun Young: Nothing to Disclose, Young-Sun Lee: Nothing to Disclose, YEON SEOK SEO: Nothing to Disclose, Ji Hoon Kim: Nothing to Disclose, Jong Eun Yeon: Nothing to Disclose, Oh Sang Kwon: Nothing to Disclose, Yang Jae Yoo: Nothing to Disclose

3507 | INITIAL TRANS-ARTERIAL CHEMO-EMBOLIZATION (TACE) IS ASSOCIATED WITH SIMILAR SURVIVAL OUTCOMES AS COMPARED TO UPFRONT PERCUTANEOUS ABLATION IN THOSE WITH SINGLE HEPATOCELLULAR CARCINOMA (HCC) ≤ 3CM: RESULTS OF A REAL-WORLD PROPENSITY-MATCHED MULTI-CENTRE AUSTRALIAN COHORT STUDY

Jonathan Abdelmalak[1] Simone Strasser[2] Natalie Ngu[2] Claude Dennis[2] Marie Sinclair[3] Avik Majumdar[4] Kate Collins[3] Katherine Bateman[3] Anouk Dev[5] Joshua Abasszade[5] Zina Valaydon[6] Daniel Saitta[6] Kathryn Gazelakis[7] Susan Byers[6] Jacinta Holmes[8] Alexander Thompson[9] Dhivya Pandiaraja[9] Steven Bollipo[10] Suresh Sharma[11] Merlyn Joseph[11] Amanda Nicoll[12] Rohit Sawhney[3] Stephen Riordan[13] Nicholas Hannah[7] James Haridy[14] Siddharth Sood[14] Eileen Lam[15] Elysia Greenhill[15] Myo Tang[1] John Lubel[1] Will Kemp[1] Ammar Majeed[1] Zalcberg John[15] Stuart Roberts[1]

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Background: Percutaneous ablation is recommended in Barcelona Clinic Liver Cancer (BCLC) stage 0/A patients with HCC ≤3cm as a curative treatment modality alongside surgical resection and liver transplantation. Trans-arterial chemo-embolization (TACE) is commonly used in the real-world as an initial treatment in patients with single small HCC in contrast to widely-accepted clinical practice guidelines which typically describe TACE as a treatment for intermediate-stage HCC. We performed this real-world propensity-matched multi-centre cohort study in patients with single HCC ≤ 3cm to assess for differences in survival outcomes between those undergoing initial TACE and those receiving upfront ablation. **Methods:** Patients with a new diagnosis of BCLC 0/A HCC with a single tumour ≤3cm first diagnosed between 1 January 2016 and 31 December 2020 who received initial TACE or ablation were included in the study. **Results:** A total of 348 patients were included in the study, with 147 patients receiving initial TACE and 201 patients undergoing upfront ablation. After propensity score matching using key covariates including age, sex, liver disease aetiology, diabetes, smoking, Charlson comorbidity index, Child-Pugh score, platelet count and tumour size, 230 patients were available for analysis with 115 in each group. There were no significant differences in overall survival (log-rank test p=0.652) or liver-related survival (log-rank test p=0.495) over a median follow up of 3 years. Failure to achieve CR during follow-up was similar between the initial TACE and upfront ablation groups (20.0% vs 13.9%, p=0.219). Of those in the initial TACE group who went on to achieve CR, 71.4% did so immediately after the initial TACE, 12.1% required 2 or more TACE, 15.2% required TACE with subsequent ablation and 2.2% required TACE with subsequent transplantation. In the upfront ablation group, 93.5% of patients who achieved CR did so after the initial ablation, with 6.5% requiring 2 or more ablation treatments, 5.4% required ablation and subsequent TACE and 1.1% required SBRT after ablation. Comparing those who achieved CR in the initial TACE and upfront ablation groups, there was similar recurrence-free survival (log-rank test p=0.379) and local recurrence-free survival (log-rank test p=0.390). **Conclusion:** Our study provides valuable real-world evidence that TACE is a reasonable initial management strategy in very-early/early-stage HCC where further treatment can be offered as appropriate during follow-up, with similar survival outcomes as compared to those managed with upfront ablation. Further work is needed to better define the role for TACE in BCLC 0/A HCC.

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3508 | EFFICACY AND SAFETY OF STEREOTACTIC BODY RADIATION THERAPY IN ELDERLY PATIENTS WITH CIRRHOSIS AND LARGE ADVANCED HEPATOCELLULAR CARCINOMA

Deepti Sharma[1] *Babu Lal Meena*[1] *Hanuman Prasad Yadav*[1] *Shiv Kumar Sarin*[1]

[1]*Institute of Liver and Biliary Sciences*

Background: To evaluate the safety and efficacy of stereotactic body radiation therapy (SBRT) for 70 years or older patients with advanced hepatocellular carcinoma (aHCC). **Methods:** This observational retrospective study was done between May 2020 and March 2023. The data of 24 elderly patients with advanced HCC treated with stereotactic body radiation therapy (SBRT), was collected from the hospital electronic records. Patients with Child- Turcotte- Pugh status (CTP) A5 to B8 and a functional liver reserve of ≥ 700cc were included. Local control (LC), overall survival (OS), progression-free survival (PFS) and post-procedure adverse events were recorded. **Results:** The median follow-up period of the study cohort was thirteen months (range: 3-36 months). The median age was 75 years (range: 70-84 years) with CTP A (70.8%) and CTP B (29.2%). NASH was the commonest etiology (n=15, 62.5%). The median tumour diameter was 8.5 cm (range, 5-16). Portal vein and IVC tumour thrombosis were seen in 21 (87.5%) and 4(16.67%) patients. The median SBRT dose of 35Gy (range 30-45 Gy) was delivered in 5 fractions. Though the median AFP level was reduced from 136.5 (range 3.7 - 27533) to 34.5 (range 3 - 4964) ng/ml the difference was not significant. Median PIVKA II level was significantly decreased from 2702 (range 23.8 - 385454) to 189 (range 15 - 56262) mAU/ml, p=0.05. The estimated local control rates at 12 and 18 months were 90% and 62% respectively. The 1-year estimated overall survival and progression-free survival rates were 58% and 42%, respectively. The mOS and mPFS were 14 months (95% CI, 8.5-19.4) and 9 months (95% CI, 5.5-12.4) respectively. On multivariate analysis, baseline Geriatric 8 (G8) score ≤ 9 and CTP B were the predictors of poor OS. SBRT was found to be generally safe in patients with geriatric 8 score > 9 with post-procedure decompensation (increased CTP score by 2 points) in only one (4.16%) patient. **Conclusion:** SBRT is a safe and effective locoregional therapy in elderly subjects with cirrhosis and locally advanced HCC. In elderly patients, with limited transplant and other therapeutic options, SBRT is safe and provides improved local disease control, overall survival, and progression-free survival.

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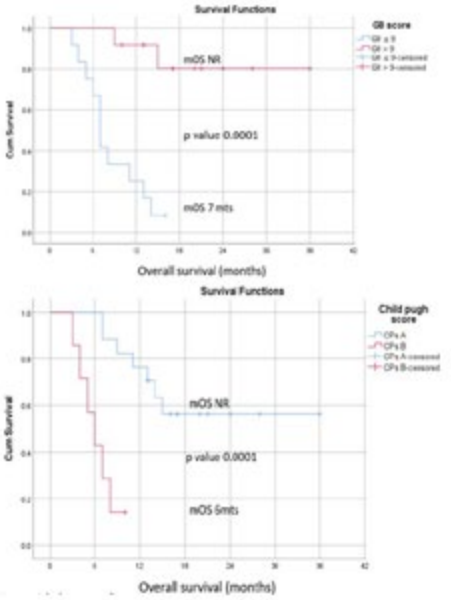
Baseline characteristics of the patients

Variables	N (%)
Sex	
• Male	20(83.33%)
• Female	4(16.67%)
Etiology	
• Hepatitis C	1(4.17%)
• Alcohol-related	8(33.33%)
• NASH	15(62.5%)
Diabetes mellitus, no. (%)	19 (79.16 %)
Hypertension, no. (%)	12 (58.33%)
BMI	
• <25	12(50%)
• ≥25	12(50%)
ECOG	
• 1	12 (50%)
• 2	12 (50%)
Tumour size median (range) cm	8.5 (5-16)
Multi focal tumour	19(79.16%)
Nodal metastasis	10(41.66%)
Distant metastasis	
• Lung	5 (20.83%)
• Bone	1 (4.17%)
ALBI grade	
• Grade I	6 (25%)
• Grade II	17 (70.8%)
• Grade III	1 (4.2%)

figure depicting overall survival (OS)



Disclosures: Deepti Sharma: Nothing to Disclose, Babu Lal Meena: Nothing to Disclose, Hanuman Prasad Yadav: Nothing to Disclose, Shiv Kumar Sarin: Nothing to Disclose

3509 | THE ROLE OF ADJUVANT THERAPY IN HCC TREATED WITH CURATIVE INTENT ABLATION: A STEP TOO FAR?

Natalie Commins[1] Rohit Gupta[1] Andrew Sloss[1] Tehara Wickremeratne[1] Roger Wilson[1] Jonathan Langton[1] Brooke Gaggin[1] James O'Beirne[1]

[1]Sunshine Coast University Hospital

Background: The IMBRAVE050 study demonstrated improved recurrence-free survival (RFS) in patients with high-risk hepatocellular carcinoma (HCC) receiving adjuvant atezolizumab and bevacizumab post curative treatment (ablation or liver resection) compared to active surveillance. Resection was the predominant curative treatment in the IMBRAVE050 cohort, and the majority of patients were of Asian background with chronic liver disease (CLD) secondary to Hepatitis B infection. This differs from the Australian context, where the majority of patients undergo microwave ablation, and the prevalence of Hepatitis B-associated CLD is much lower. This study aimed to explore the demographics, prevalence and outcomes of patients with high and low-risk HCC using the IMRAVE050 protocol. The primary outcomes were RFS and OS in the high and low-risk cohorts undergoing microwave ablation or liver resection. **Methods:** The study design was a retrospective cohort study over a 5 year period between 2019 to 2024. The inclusion criteria were patients over the age of 18, first diagnosis of HCC, and curative intent treatment with either microwave ablation or liver resection. Patients were risk-stratified into high-risk and low-risk groups according to the IMBRAVE050 criteria. Statistical analysis was completed using the Wilcoxon signed rank and Kaplan-Meier method. **Results:** 52 patients met the inclusion criteria. The median age was 68 (IQR 60-74). The most common causes of underlying CLD were Hepatitis C (34.6%), alcoholic-related liver disease (32.7%) and metabolic-associated fatty liver disease (17.3%). The majority of patients had a single lesion (84.6%) and were Barcelona Clinic Liver Cancer (BCLC) Grade 0/A at time of diagnosis. The initial treatment was microwave ablation in 76.9% (n=40) of patients. There were no procedure-related deaths. The majority of patients fulfilled high-risk criteria as defined by IMBRAVE050 (55% undergoing microwave ablation and 75% undergoing liver resection). The majority of patients were followed up to 1 year (90%). 1-year RFS in patients who underwent liver resection was 77.8% in high-risk and 100% in low-risk patients, respectively. In patients who underwent microwave ablation, 1-year RFS was 90% in the high-risk cohort and 66.7% in the low-risk cohort (Figure 1) p=NS. Overall Survival at 1-year was 100% in all cohorts. **Conclusion:** Applying the IMBRAVE050 risk stratification to Australian patients undergoing curative treatment for HCC did not correlate with a significant

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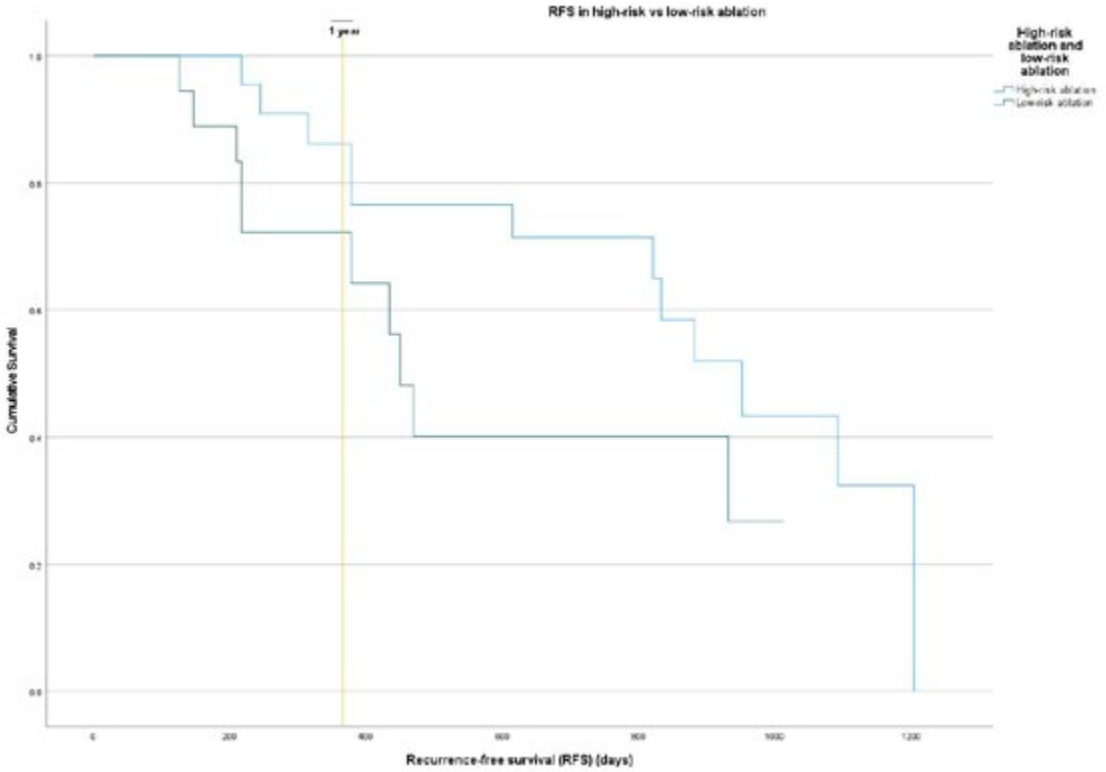
difference in either RFS or OS at 1 year or across the study period. This is likely due to the inherent differences in the Australian population of patients diagnosed with HCC compared to the IMBRAVE050 cohort. Further research is needed in this context to determine which patients may benefit from adjuvant therapy.



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3510 | RELATIONSHIP BETWEEN IMMUNE CELL INFILTRATION AND OUTCOMES IN CHOLANGIOCARCINOMA

Keiko Iwaisako[1] Hiroaki Fuji[2] Momoko Fujita[3] Reina Sawabu[3] Shoko Tsukamoto[4] Masaki Yamamoto[5] Ryo Tofukuji[5] Masataka Asagiri[6] Daichi Nakamura[7] Keisuke Okura[7] Takahiro Nishio[8]

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Background: Among primary liver cancers, hepatocellular carcinoma (HCC) resulting from chronic viral hepatitis is declining in developed countries due to advances in clinical management, while the number of patients with intrahepatic cholangiocarcinoma (ICC) is increasing. The prognosis of unresectable ICC is poor. Recently, immunotherapy, including immune checkpoint inhibitors, has been applied clinically, and complete responses have been achieved in some ICC patients. The purpose of this study is to investigate the relationship between intratumoral immune cell infiltration and prognosis in ICC and to expand research for the development of more effective therapies. Immunohistochemical analysis was performed on resected ICC specimens (n=74) to quantify immune cell infiltration and its association with prognosis. **Methods:** This is a single-center, retrospective, observational study. The study protocol was approved by the Ethics Committee of Kyoto University Graduate School of Medicine (G1023).Seventy-four patients who underwent liver resection for ICC between 2004 and 2016 were included in this study. Serial FFPE sections of ICC cancer tissues were used for immunohistological

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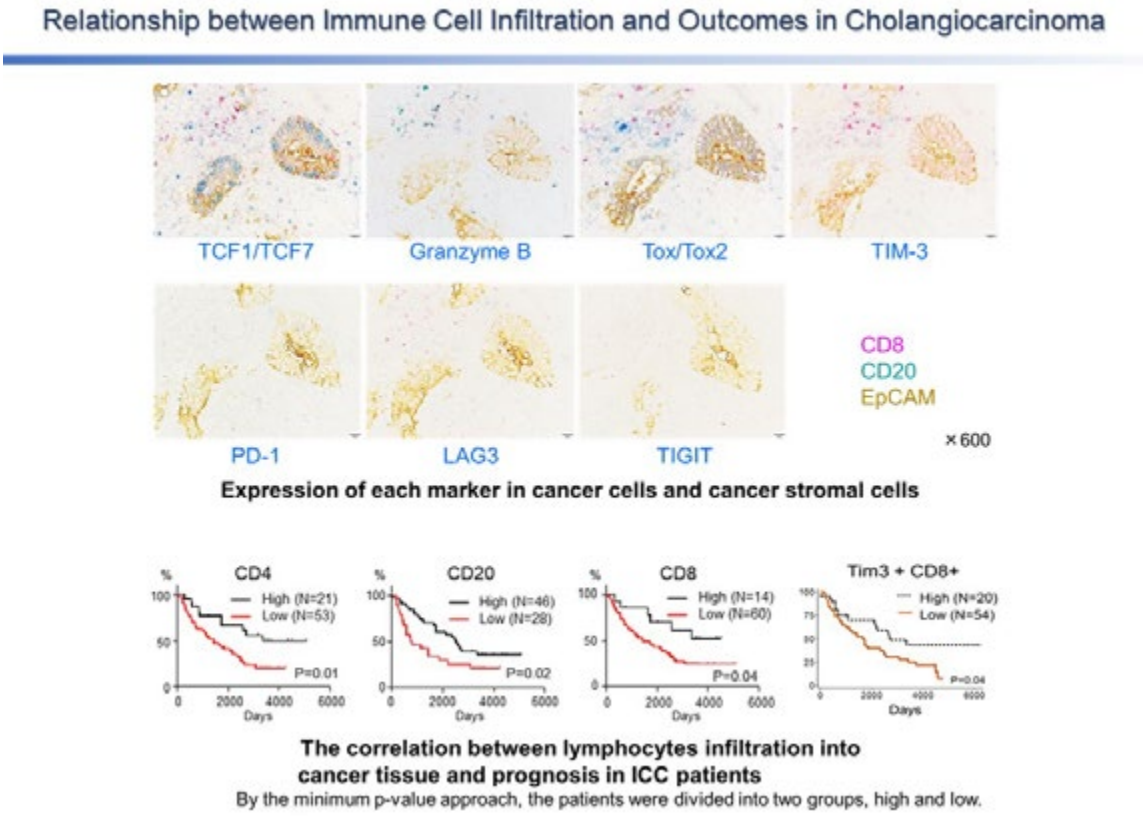
examination and immunostained for CD4, CD20, CD8 and marker molecules reported to be associated with killer T cell activation or exhaustion. Image J was used to quantify each marker-positive cell in the tissue area, and the density of infiltrating cells per unit area and prognosis were analyzed. **Results:** The number of cells positive for each marker infiltrating the cancer stroma was counted per unit area. Granzyme B, reported to be expressed on activated killer T cells, the transcription factor Tox/Tox2, reported to be involved in T cell exhaustion, and the co-repressor receptor TIM-3 were found at sites of CD8+ T cell infiltration, whereas PD-1, LAG3, and TIGIT-positive cells were rarely observed in the tissue. For CD4, CD20, and CD8, the more positive the cells, the better the prognosis; we analyzed the relationship between the amount of infiltration of CD8+ and granzyme B+ cells, CD8+ and Tox/Tox2+ cells, and CD8+ and TIM-3+ cells and prognosis. Surprisingly, higher infiltration of CD8+ and TIM-3+ cells, which are considered exhausted T cells, was associated with significantly longer overall survival. **Conclusion:** Cancers with low lymphocyte infiltration, such as the so-called immune desert or immune cold, are considered to have a poor prognosis. CD8+ and TIM-3+ T cells were considered exhausted killer T cells, and we expected that patients with high numbers of such T cells in cancer tissue would have a poor prognosis, but surprisingly, the prognosis was better. The high number of CD8+ and TIM-3+ T cells may be the result of an immune response to the cancer. In other words, it is possible that acquired immunity was established against cancer cells that were present prior to resection.



Disclosures: Keiko Iwaisako: Nothing to Disclose, Hiroaki Fuji: Nothing to Disclose, Momoko Fujita: Nothing to Disclose, Reina Sawabu: Nothing to Disclose, Shoko Tsukamoto: Nothing to Disclose, Masaki Yamamoto: Nothing to Disclose, Ryo Tofukuji: Nothing to Disclose, Masataka Asagiri: Nothing to Disclose, Daichi Nakamura: Nothing to Disclose, Keisuke Okura: Nothing to Disclose, Takahiro Nishio: Nothing to Disclose

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3511 | NRF2-MEDIATED IMMUNE COLD TUMOR MICROENVIRONMENT CONTRIBUTES TO RESISTANCE TO ATEZOLIZUMAB AND BEVACIZUMAB IN ADVANCED HEPATOCELLULAR CARCINOMA

Shuhei Yamamoto[1] Takahiro Kodama[1] Kazuki Maesaka[1] Akifumi Kuwano[2] kenta Motomura[2] Kumiko Shirai[1] Akira Doi[1] Kazuhiro Murai[1] Yuki Tahata[1] Yoshinobu Saito[3] Hayato Hikita[3] Tomohide Tatsumi[1] Tetsuo Takehara[1]

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Background: Atezolizumab/bevacizumab (Atezo/Bev) combination immunotherapy is the first-line treatment for advanced hepatocellular carcinoma (HCC), but around 20% of patients do not respond initially. We investigated resistance mechanisms by examining the tumor immune microenvironment (TIME) in mice and humans. **Methods:** Two immunocompetent HCC models were used: an endogenous genetically heterogeneous HCC model created via hydrodynamic tail vein injection of a 10-oncogene cDNA library, and a subcutaneous syngeneic model using the Hep55.1c cell line. RNA sequencing (RNA-seq) was performed on 23 pretreatment tumor biopsy specimens from advanced HCC patients treated with Atezo/Bev to examine the association between TIME and treatment response. Spatial transcriptomics were conducted on pre-treatment and post-progression samples from two HCC patients. **Results:** In the genetically heterogeneous HCC model, combination immunotherapy inhibited angiogenesis, increased intratumor CD8+ T cells, and extended survival. Resistant tumors had few tumor-infiltrating lymphocytes (TILs) and showed activation of the NRF2 pathway. In vitro, NRF2 overexpression in murine HCC cells activated the COX2/PGE2/EP4 pathway and upregulated TGFβ and VEGF-A. While NRF2 overexpression did not affect syngeneic HCC tumor growth, it significantly reduced the efficacy of anti-VEGF/PD-L1 antibodies in vivo. NRF2-expressing tumors had higher Vegf and lower Cd8, Cd4, and Itgax levels than control tumors. RNA-seq of human HCC tissues revealed that genes related to T cell migration, activation, and exhaustion were significantly lower in non-responders compared to responders. Gene set enrichment analysis showed NRF2 pathway activation and inactivation of antigen processing and presentation mechanisms, Jak/Stat signaling, B cell and T cell signaling, and chemokine signaling in non-responders. Spatial transcriptomics showed reduced intratumor T cells and the activation of NRF2 pathway in post-progression samples. **Conclusion:** Our TIME analysis suggests that an NRF2-mediated immune cold tumor microenvironment contributes to resistance to atezolizumab and bevacizumab in advanced HCC.

Disclosures: Shuhei Yamamoto: Nothing to Disclose, Takahiro Kodama: Chugai Pharmaceuticals: Speaking and Teaching, Astrazeneca: Speaking and Teaching, Eisai Co Ltd: Speaking and Teaching, Kazuki Maesaka: Nothing to Disclose, Akifumi Kuwano: Nothing to Disclose, kenta Motomura: Nothing to Disclose, Kumiko Shirai: Nothing to Disclose, Akira Doi: Nothing to Disclose, Kazuhiro Murai: Nothing to Disclose, Yuki Tahata: Nothing to Disclose, Yoshinobu Saito: Nothing to Disclose, Hayato Hikita: Nothing to Disclose, Tomohide Tatsumi: Nothing to Disclose, Tetsuo Takehara: Nothing to Disclose

3512 | LIPOPHILIC STATIN INCREASES SENSITIVITY FOR LENVATINIB BY SUPPRESSING YAP/TAZ IN HEPATOCELLULAR CARCINOMA CELL LINES AND PATIENT-DERIVED ORGANOIDS ◆

Jae Seung Lee[1] Kyung Joo Cho[2] Hye Jung Park[2] Hye Won Lee[1] Mi Na Kim[1] Beom Kyung Kim[1] Do Young Kim[1] Sang Hoon Ahn[1] Jun Yong Park[1]

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Background: Elevated expression of the transcription factors Yes-associated protein (YAP) and its paralogue, transcriptional co-activator with PDZ-binding motif (TAZ), contributes to drug resistance and adverse prognosis in patients with hepatocellular carcinoma (HCC). Recent studies have highlighted the potential of statin use in reducing the incidence of diverse cancers, potentially achieved through YAP/TAZ suppression via the mevalonate pathway inhibition in vitro. Accordingly, this study aimed to assess the effect of statins on YAP/TAZ inhibition in HCC cell lines and drug-resistant organoid models. **Methods:** We established cell lines with increased YAP/TAZ expression and evaluated their sensitivity to lenvatinib, with or without the concurrent administration of lipophilic atorvastatin. Additionally, we cultured HCC organoids derived from patient tissues and selected those that exhibited elevated YAP/TAZ levels. Lenvatinib was administered along with varying atorvastatin doses to assess changes in lenvatinib sensitivity by analyzing half-maximal inhibitory concentration (IC_{50}) values. **Results:** Hep3B and YAP-transfected

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SNU449 cells exhibited elevated IC50 values for lenvatinib (9.14 and 16.93 μM, respectively), which reduced to 4.89 and 5.25 μM, respectively, with two μM atorvastatin co-administration. Among ten established HCC organoids, six with elevated YAP/TAZ expression displayed higher lenvatinib IC50 values than their low-YAP/TAZ counterparts. Dose-dependent atorvastatin administration decreased lenvatinib IC50 values in organoids. Co-administration of lenvatinib and atorvastatin suppressed the YAP/TAZ target genes, an effect that was not observed with lenvatinib alone. Lenvatinib inhibited cell proliferation and apoptosis in an organoid model with low YAP/TAZ expression, and co-administration of atorvastatin restored the inhibitory effect of lenvatinib on cell proliferation and apoptosis by suppressing YAP/TAZ expression in an organoid model with high YAP/TAZ expression. **Conclusion:** Increased protein expression of YAP/TAZ in HCC cell lines and organoid models is correlated with lenvatinib resistance. Atorvastatin enhances the anticancer efficacy of lenvatinib by interfering with YAP/TAZ expression in HCC cell lines and organoids.

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3513 | TRIMETHYLAMINE N-OXIDE (TMAO) AS A NOVEL PREDICTIVE BIOMARKER IN GALLSTONE DISEASE AND GALLBLADDER CANCER: INSIGHTS FROM HUMAN AND MICE STUDY

Vipin Yadav[1] Deepti Sharma[1] Ragini Kilambi[1] Nihar Ranjan Mohaptra[1] Archana Rastogi[1] Viniyendra Pamecha[1] Vaishali Yadav[1] Khushboo Agrawal[1] ELAPAKATTU THOMAS[1] GURESH KUMAR[1] Nirupma Trehanpati[2] Shiv Kumar Sarin[1] Gayatri Ramakrishna[1]

[1]Institute of Liver and Biliary Sciences, [2], Institute of Liver and Biliary Sciences

Background: India has high incidence of gallstone disease and gallbladder cancer, accounting for 10% of global burden. Due to low diagnosis rates, gallbladder cancer has poor prognosis. We employed targeted and untargeted metabolomics of human plasma and a mice model to investigate metabolites linked to gallstone disease and gallbladder cancer as potential biomarkers. **Methods:** Metabolomic profiling was done for 100 plasma samples in discovery cohort:14 Healthy (HC), 30 gallstone disease (GSD), and 56 gallbladder cancer (CaGB) patients. Targeted metabolomics evaluated the significantly altered metabolite (TMAO) in the validation cohort (N=37). TMAO (0.3%) was then fed to mice along with lithogenic diet to assess its impact on the gallstone disease progression. **Results:** One-way ANOVA identified 90 significantly ($p<0.05$) altered metabolites in discovery cohort. Group-wise analysis (HC vs GSD and GSD vs CaGB) identified 15 commonly upregulated metabolites. TMAO was a common metabolite significantly increased in both groups ($p<0.001$). ROC curve-based multi metabolite model showed TMAO and pipecolic acid had an AUC value: 0.96 ($p<0.05$) to predict gallstones. Further, TMAO in association with N-acetyl neuraminic acid had the highest prediction by AUC: 0.91 ($p<0.01$) in gallbladder cancer. Targeted metabolomics in the validation cohort (N=37) showed increased plasma TMAO in gallbladder cancer (413.281±188.35ng/ml) ($p=0.08$) compared to gallstone (165.13±100.7ng/ml) ($p=0.014$) and healthy (115.37±41.49ng/ml) individuals. C57BL/6J mice fed with a lithogenic diet and 0.3% TMAO showed early appearance and higher gallstone frequency than those fed with a lithogenic diet alone. At 12 weeks, TMAO-supplemented mice had 20% (2/10) gallstone formation, while only 10% (1/10) animals showed gallstones on lithogenic diet alone. By 20 weeks 73.68% (14/19) of TMAO-supplemented mice developed gallstones, compared to 62.5% (10/16) of lithogenic diet-fed animals ($p=0.05$). Additionally, the TMAO-supplemented mice exhibited gallbladder metaplasia, indicating increased cellular proliferation. **Conclusion:** Elevated TMAO levels can influence the formation and progression of gallstone disease in human and mice model. Combining TMAO levels with metabolites like pipecolic acid and N-acetyl neuraminic acid demonstrated an increased sensitivity and specificity in predicting gallstone and gallbladder cancer respectively. As TMAO is produced in liver, the study also suggests the Liver-Gallbladder axis in gallstone-associated disease.

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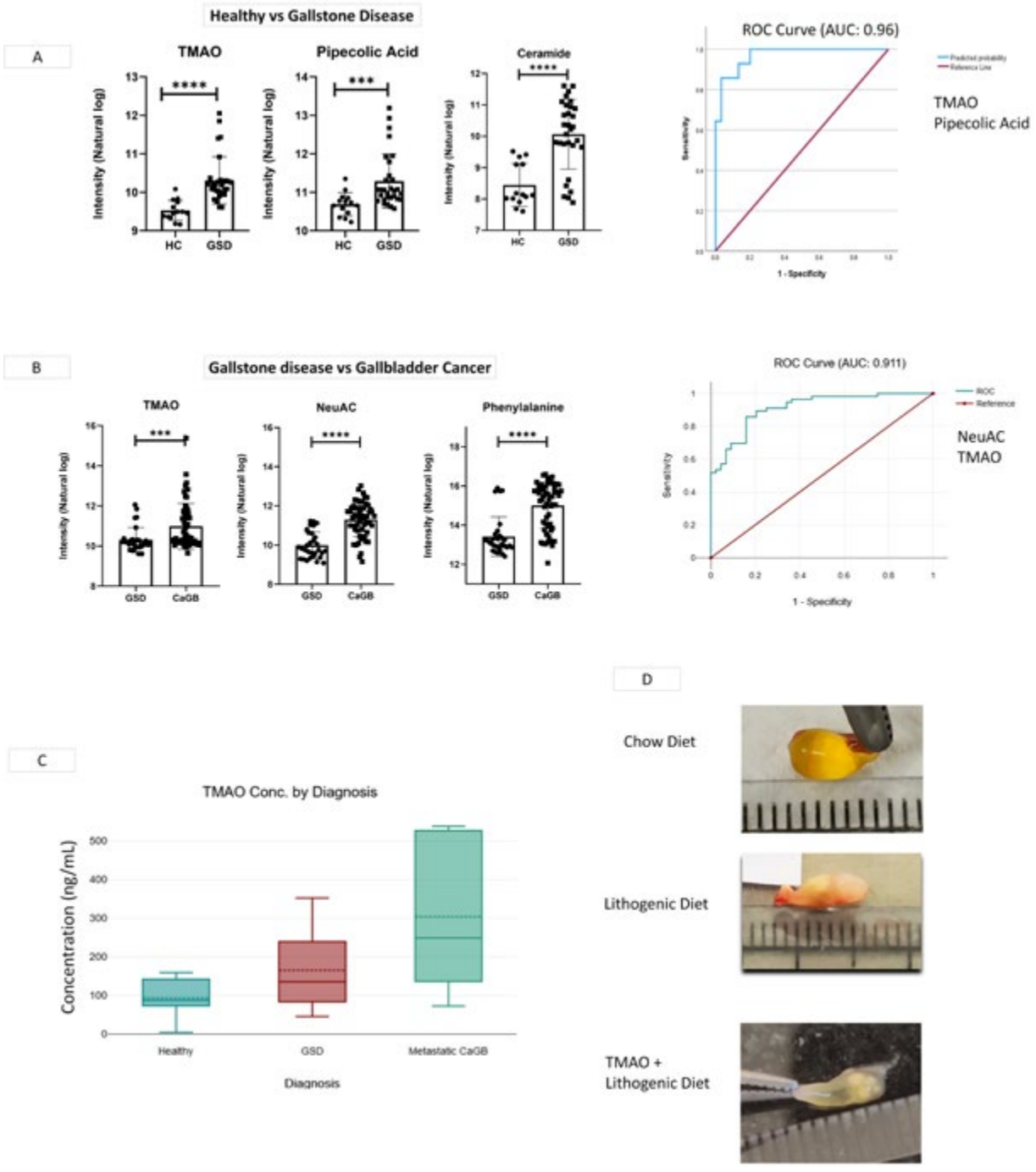

Disclosures: Vipin Yadav: Nothing to Disclose, Deepti Sharma: Nothing to Disclose, Ragini Kilambi: Nothing to Disclose, Nihar Ranjan Mohaptra: Nothing to Disclose, Archana Rastogi: Nothing to Disclose, Viniyendra Pamecha: Nothing to Disclose, Vaishali Yadav: Nothing to Disclose, Khushboo Agrawal: Nothing to Disclose, ELAPAKATTU THOMAS: Nothing to Disclose, GURESH KUMAR: Nothing to Disclose, Nirupma Trehanpati: Nothing to Disclose, Shiv Kumar Sarin: Nothing to Disclose, Gayatri Ramakrishna: Nothing to Disclose

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3514 | NOVEL TH17 LYMPHOCYTE POPULATIONS, TH17.1 PREDICTS SURVIVAL OF PATIENTS WITH HEPATITIS B VIRUS - ASSOCIATED HEPATOCELLULAR CARCINOMA

Xinhui Wang[1] *Zhiyun Yang*[1]

[1]*Capital Medical University Affiliated Beijing Ditan Hospital*

Background: Hepatitis B virus related hepatocellular carcinoma(HBV-HCC) account for the majority of liver cancer in China. And its mortality rate was higher than other types of liver cancer. The role of Th17 cells in liver cancer is still controversial and may be related to its plasticity. Th17.1 cells was recognized a new subset of classical Th17 cells. It is a phenotype of transdifferentiation from Th17 cells into pro-inflammatory Th1 cells. And clarifying its role helps us to understand the paradox of Th17 cell functions in HBV-HCC. **Methods:** By 10X Genomics single-cell transcriptome sequencing and GSE149614 data we found Th17.1 cells in the peripheral blood and liver cancer tissue in HBV-HCC patients. Detection of the ratio and density of Th17.1 cells in liver cancer tissue by multi-color immunofluorescence staining. Detection of Th17.1 ratio in PBMCs by multi-color flow cytometry, and we compared of 1-year survival rates of patients with different levels of Th17.1 cells by log rank tests. **Results:** Transcriptomic analysis revealed the presence of Th17.1 cells in the peripheral blood and liver cancer tissues in patients with HBV-HCC, which possess both Th1 and Th17 phenotypes and functions. The immunofluorescence showed a lower density of Th17.1 in tumor than peritumor. Liver cancer patients have an increased number of Th17.1 cells compared to normal individuals. The number of Th17.1 cells is significantly positively correlated with Th1 cells. The 1-year survival rate of patients with high level of Th17.1 cells was significantly higher, especially in the subgroup of patients with HBV-HCC ($P<0.05$). **Conclusion:** Our research has found that there was a novel lymphocyte populations, Th17.1 cell, in the peripheral blood and tumor tissue of patients with HBV-HCC. The higher ratio of Th17.1 cells is related to the short-term survival of patients with liver cancer, which is mainly in the population of patients with HBV-HCC. It predicated that promoting the production of Th17.1 cells can improve the short-term prognosis of patients. Furthermore, potential targets and related pathways regulating Th17.1 cell formation were explored, providing potential therapeutic targets for the development of subsequent new drugs.

Disclosures: Xinhui Wang: Nothing to Disclose, Zhiyun Yang: Nothing to Disclose

3515 | CHARACTERISTICS OF HBV INTEGRATION IN PATIENTS WITH AND WITHOUT HEPATOCELLULAR CARCINOMA

Yan Han[1] *Zhiwei Chen*[1] *Jing Tang*[1] *Na Wu*[1] *Hong Ren*[1]

[1]*Second Affiliated Hospital of Chongqing Medical University*

Background: Several studies have elucidated the distinct patterns of HBV integration in patients with hepatocellular carcinoma (HCC) by analyzing both tumor tissues (TT) and adjacent non-tumor liver tissues (ANTLT) from each patient. However, the characteristics of HBV integration in patients with and without HCC remain elusive. **Methods:** Clinical data and liver tissues were obtained from 36 patients with chronic hepatitis B (25 with HCC and 11 without HCC) who underwent liver resection between August 2023 and March 2024 at our hospital. A probe-based capture strategy was employed to analyze HBV integration in these samples. **Results:** Among the 36 patients, the majority were male (77.8%) and received antiviral therapy (86.1%). The mean age, HBsAg level, and ALT level were 53.5 years, 956.6 IU/mL, and 33.2 U/L, respectively. There were no significant differences in clinical characteristics between patients with and without HCC (all $P>0.05$). A total of 3848 HBV integration sites were identified in 61 samples. The average number of integration sites was found to be 46.9, 66.6, and 91.8 in TT group, ANTLT group, and normal liver tissues (NLT) group respectively. HBV integration events were more frequently detected in subgroups with higher levels of HBV DNA and HBsAg, while they were less commonly observed in subgroups with cirrhosis or those who received antiviral therapy. Regarding age, younger patients exhibited a higher number of HBV integration sites in both the TT and ANTLT groups, whereas the opposite trend was observed in the NLT group. In terms of gender, female patients had a higher number of HBV integration sites in the ANTLT and NLT groups, but a lower number in the TT group. In addition, the HBV integration sites were predominantly located on chromosomes 1-6 and 8 within host genomes (48.2%), as well as at regions 3198-3215nt, 1819-1827nt, and 6-10nt within HBV genome (1.6%). Compared to the NLT group, LOC100507412, CSMD1, KMT2B, LTBR AKAP6, and FN1 showed a higher prevalence in both the TT and ANTLT

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groups; notably APOBEC3G was specifically enriched in the TT group compared to both ANTLT and NLT groups. **Conclusion:** Distinct patterns of HBV integration were observed in patients with and without HCC, providing valuable insights into the mechanisms underlying HBV integration and its association with HCC occurrence.

Disclosures: Yan Han: Nothing to Disclose, Zhiwei Chen: Nothing to Disclose, Jing Tang: Nothing to Disclose, Na Wu: Nothing to Disclose, Hong Ren: Nothing to Disclose

3516 | INCREASED PD-1+TIGIT+TIM-3+ IN PERIPHERAL CIRCULATING CELLS PREDICTS OUTCOMES AND TREATMENT RESPONSE IN HCC PATIENTS WITH TRANSARTERIAL CHEMOEMBOLIZATION

Xiaoli Liu[1] Huiwen Yan[1] Lihua Yu[1] Yixin Hou[1] Tingting Jiang[1] Xianbo Wang[1] Jiang Yuyong[1] Yaxian Kong[2] Zhiyun Yang[1]

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Background: Transarterial chemoembolization (TACE) is an important treatment option for patients with unresectable hepatocellular carcinoma (HCC) and good liver function. Previous studies have shown that TACE can block the blood supply, leading to necrosis of the tumor tissue and activation of tumor-specific antigen release, thereby promoting a tumor-specific immune response. However, the specific changes in the immune microenvironment remain unclear. This study aims to explore the prognostic value of exhausted T cells in HCC patients undergoing TACE. **Methods:** We prospectively and consecutively enrolled 168 HCC patients under TACE hospitalized in Beijing Ditan Hospital, Capital Medical University, of whom 140 (83.3%) had hepatitis B infection. We used flow cytometry to detect the expression of T cell subsets and immune checkpoint molecules like PD-1, TIGIT, TIM-3, LAG-3, CTLA-4,in the peripheral blood mononuclear cells (PBMC) of patients with HCC under TACE. Then clinical indicators and inhibitory molecular expression were incorporated into Cox regression to analyze the impact on overall survival and progression of HCC. **Results:** In HCC patients who experience progression after TACE treatment, the proportion of PD-1, TIGIT, TIM-3, $CD8^+PD\text{-}1^+TIGIT^+TIM\text{-}3^+$T cells was higher than those without progression. COX univariate and multivariate regression analysis showed that, portal tumor thrombus (PVTT) (HR=1.87), neutrophil-to-lymphocyte ratio (HR=1.21), γ-GGT (HR=1.01), tumor size ≥5cm (HR=1.7), proportion of effect memory T cells (HR=1.08) and $CD8^+PD\text{-}1^+TIGIT^+TIM\text{-}3^+$T cells (HR=1.13) were independent risk factors for survival of HCC patients. Compared with low level of $CD8^+PD\text{-}1^+TIGIT^+TIM\text{-}3^+$T cells, the hazard ratios of overall survival of high level group were 1.75 (95% CI: 1.25-2.81) in the KM curve analysis. Additionally, we found that high post-TACE $CD8^+PD\text{-}1^+TIGIT^+TIM\text{-}3^+$T cell levels are also associated with a higher recurrence rate. **Conclusion:** High levels of $CD8^+PD\text{-}1^+TIGIT^+TIM\text{-}3^+$T cells in both pre-TACE and post-TACE was associated with poor outcome and tumor response of HCC. This insight provide a basis for accurately identifying patients who would benefit most from TACE treatment and for subsequent sequential immunotherapy.

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3517 | SARCOPENIA IMPACTS TREATMENT TOLERANCE AND SURVIVAL OF PATIENTS WITH HEPATOCELLULAR CARCINOMA IN CIRRHOSIS

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Background: Hepatocellular carcinoma(HCC) is the most common primary liver malignancy and the third leading cause of cancer-related mortality worldwide. Sarcopenia has been described as a significant prognostic factor in various malignancies. We looked at the prevalence and prognostic influence of sarcopenia on cirrhosis patients with HCC. **Methods:** Prospective observational study of 106 patients with cirrhosis and newly diagnosed HCC. Blood investigations, anthropometric measures, ultrasound, and CT abdomen were taken at baseline, 6 and 12 months. Skeletal muscle area at L3 was calculated using NIH image J software, and skeletal muscle index was calculated. Sarcopenia was defined according to the Japanese Society of Gastroenterology guidelines (SMI

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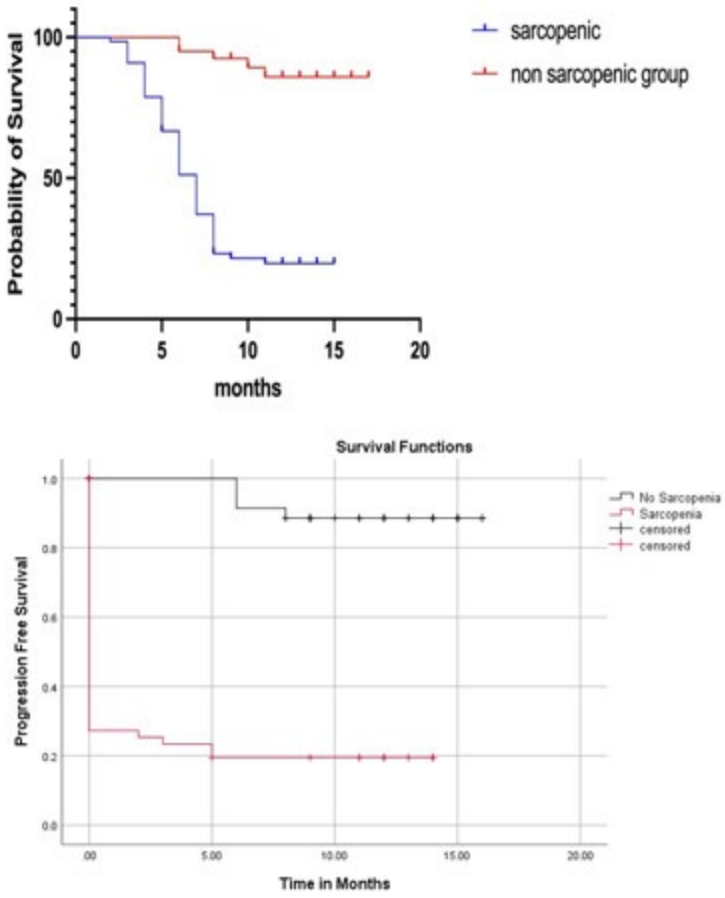
< 42 cm^2/m^2 in men and < 38 cm/m^2 in women). Patients were treated according to the BCLC stage, and were monitored for survival, treatment response, and adverse events. **Results:** 87 (82.1 %) patients were male. The most common aetiologies were MASLD (31.1%), HBV (28.3%), ALD (26.4%), and HCV (9.4%). 27.4%, 34.9%, 23.6% and 14.2% were BCLC A, B, C and D respectively. 35 patients received weight-based treatment with Sorafenib and 49, with Lenvatinib. 39 patients underwent Trans arterial chemoembolization (TACE), of which 31 had combined TACE and systemic therapy. 14 patients received palliative care only. Sarcopenia was present in 66 patients (62.3%). Mean SMI at 0, 6 and 12 months were 43.6, 41.7 and 40.6 cm^2/m^2 in the non-sarcopenic group, and 39.72, 39.0 and 37.63 $cm2/m^2$ in the sarcopenic group, Mortality was higher in the sarcopenic group, with a median overall survival of 7 months ($p < 0.001$). The non-sarcopenic group had a higher progression-free survival ($p< 0.01$). Non-sarcopenic patients had a treatment response by mRECIST of 58.9% and 42.5% at 6 and 12 months respectively ($p<0.003$). 77% of survivors at 6 months and 71% at 12 months had progressive disease(PD) in the sarcopenic group. 0 and 28% of survivors in the non-sarcopenic group had PD ($p<0.003$). In the first six months, adverse events were more common in the sarcopenic group($p< 0.001$). The common adverse events were Hypertension(52.5%), Proteinuria(42.5%) and Palmoplantar erythrodysesthesia(17.5%). Survival analysis showed better overall survival in those with adverse events between 6 - 12 months($p-< 0.001$). Early adverse events (at less than six months) led to treatment discontinuation and had no survival advantage. There was no significant difference between Sorafenib and Lenvatinib regarding overall survival and adverse events. **Conclusion:** Sarcopenia has an excellent predictive value for overall survival, progression-free survival, and the development of early adverse events. Weight-based administration of systemic treatment may increase the occurrence of adverse events and early treatment discontinuation. Risk stratification and dosing according to sarcopenia can prolong survival and avoid early adverse events.



Disclosures: Krishnadas Devadas: Nothing to Disclose, Akhil Visruthakumar: Nothing to Disclose

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3518 | THE RELATIONSHIP BETWEEN FATTY ACID COMPOSITION AND PROGNOSIS IN PATIENTS WITH HEPATOCELLULAR CARCINOMA: ESTABLISHMENT OF A NEW NUTRITIONAL PROGNOSTIC SCORE ◆

Akitoshi Sano[1] Jun Inoue[1] Eiji Kakazu[2] Masashi Ninomiya[1] Mio Tsuruoka[3] Kosuke Sato[3] Satoko Sawahashi[1] Masazumi Onuki[1] Keishi Ouchi[1] Kotaro Doi[1] Kengo Watanabe[1] Atsushi Masamune[1]

[1]Tohoku University Graduate School of Medicine, [2]National Center for Global Health and Medicine, [3]Tohoku University Hospital

Background: Hepatocellular carcinoma (HCC) is frequently accompanied by nutritional disorders such as protein-energy malnutrition. However, the relationship between fatty acid (FA) profiles and the prognosis of HCC has not been extensively investigated. This study aims to examine the association between blood FA profiles and the prognosis of HCC and to develop a novel nutritional prognostic score. **Methods:** This is a single-center retrospective study including 455 patients with HCC who were admitted to our department. Blood samples were collected in the morning, in a fasting state. Kaplan-Meier analysis and multivariate Cox proportional hazards models were used to assess the relationship between overall survival and levels of FAs. A prognostic score was constructed based on multiple nutritional factors associated with prognosis, and the accuracy of the score was validated using receiver operating characteristic (ROC) curves and Kaplan-Meier analysis. **Results:** A total of 353 patients were included in the analysis, excluding cases with missing data. The group with low levels of saturated FAs exhibited a significantly superior prognosis by the Kaplan-Meier curve (Log-rank: $p = 0.005$). Conversely, groups with lower levels of n-3 polyunsaturated fatty acids (PUFAs) and n-6 PUFAs showed better prognosis (Log-rank: $p = 0.01$ and $p = 0.002$, respectively). The multivariate Cox proportional hazards model identified low albumin levels (HR: 2.1, 95% CI: 1.3-3.1, $p < 0.001$), low n-6 PUFA levels (HR: 2.0, 95% CI: 1.3-3.1, $p = 0.001$), and low n-3 PUFA levels (HR: 1.6, 95% CI: 1.1-2.5, $p = 0.02$) as independent factors associated with poor prognosis regarding nutritional factors. Random forest and logistic regression analyses indicated that low albumin levels, high nervonic acid (NA) levels, and low arachidonic acid (AA) levels were associated with an unfavorable prognosis. The ROC curves demonstrated that both albumin levels (cut-off: 3.4, AUC: 0.74, $p < 0.001$) and the AA/NA ratio (cut-off: 4.04, AUC: 0.74, $p < 0.001$) exhibited good diagnostic performance for poor prognosis. The combination of these factors into a scoring system, the Albumin-Fatty Acids Index, permitted the stratification of prognosis via Kaplan-Meier curves (log-rank: $p < 0.001$). **Conclusion:** This study indicates that FA composition is associated with the prognosis of patients with HCC. The combination of FA profiles with albumin levels enhances the accuracy of nutritional prognostic predictions.

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3519 | THE STEATOSIS- ASSOCIATED FIBROSIS ESTIMATOR (SAFE) SCORE PREDICTS HEPATOCELLULAR CARCINOMA IN A COHORT OF CHRONIC LIVER DISEASE OF MIXED ETIOLOGY

Mai Sedki[1] Channa Jayasekera[2] Ajitha Mannalithara[1] Allison Kwong[1] W. Ray Kim[3]

[1]Stanford University Medical Center, [2]Mayo Clinic Arizona, [3]Stanford University School of Medicine

Background: The Steatosis Associated Fibrosis Estimator (SAFE) score was developed to distinguish clinically significant liver fibrosis among subjects with metabolic dysfunction-associated steatotic liver disease (MASLD). The score incorporates additional variables (diabetes, body mass index and serum globulin) to those of the FIB-4 (Fibrosis-4) index, a well established non-invasive measures of liver fibrosis. Since these factors have been associated with the risk of hepatocellular carcinoma (HCC), we examined whether the SAFE score is predictive of HCC among individuals with chronic liver disease and advanced fibrosis. **Methods:** From the Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis (HALT-C) cohort (n=1,500), we selected subjects who were included in the randomized trial portion of the study (n=1,050). The cohort enrolled adults with chronic hepatitis C with evidence of advanced

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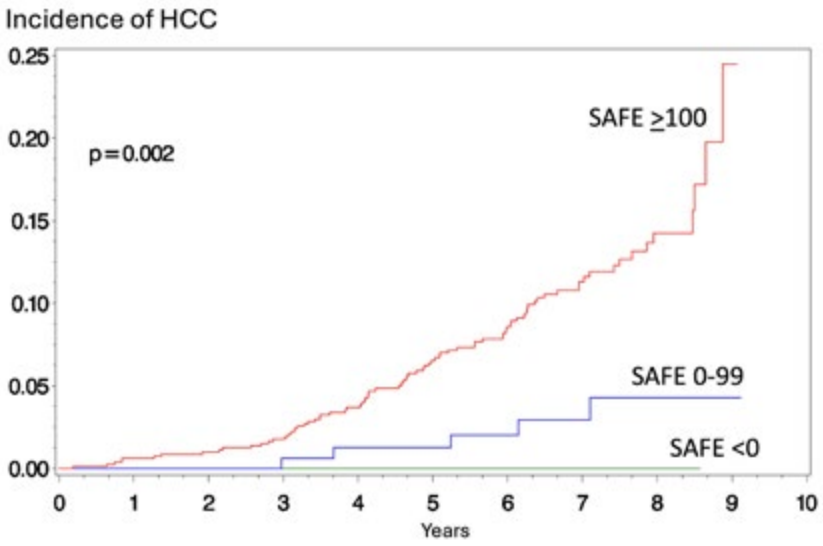
fibrosis or cirrhosis determined by liver biopsy. From the baseline data, we extracted demographic, clinical, laboratory and histological data and calculated the SAFE score. Outcome events during the follow-up included development of HCC (definite or presumed)[1], liver transplantation and death. Multivariable Cox regression analysis was conducted to model the occurrence of HCC. **Results:** The study sample included 428 (41%) subjects with cirrhosis, 872 (83%) with steatosis and 263 (25%) with diabetes. Although all subjects had ongoing hepatitis C infection, 81% met the criteria for steatotic liver disease, including 59% with MASLD, 11% with met-ALD and another 11% with alcohol-associated liver disease. The mean age was 49.0 years and 71% were men. As expected from the enrollment criteria, majority of the subjects (n=839, 80%) had a high-risk SAFE score (≥100). The Table describes low-, intermediate and high-risk SAFE score groups. After a median follow-up of 108 months, 88 patients developed HCC, including 5 from the intermediate risk group (SAFE:0-100) and 83 from the high risk group, whereas none of the low risk group (SAFE<0) did. The Figure depicts the incidence of HCC in the three groups. In the Cox regression models, steatosis had no impact on HCC, whereas the SAFE score and many of its individual variables were associated with HCC. The two most important predictors of HCC in the multivariate analysis included cirrhosis (hazard ratio [HR]: 1.67, 95% confidence interval [95%CI]: 1.10-2.56) and SAFE score ≥100 (HR:3.70, 95%CI: 1.49-9.23). **Conclusion:** Although the HALT-C cohort consisted of subjects with hepatitis C, there was a high prevalence of cardiometabolic risk factors and SLD, suggesting that the data may be extrapolated today's subjects with advanced chronic liver disease from mixed etiologies. The SAFE score was independently predictive of HCC. In particular, subjects with SAFE ≥100 had well over 10% risk of HCC over 10 years, whereas none of the subjects with SAFE <0 developed HCC.

	SAFE < 0 (n=27)	SAFE 0-99 (n=184)	SAFE ≥ 100 (n=839)
Age, median*	45	47	50
BMI, median*	27.3	27.4	29.7
Diabetes (%)*	0.0%	6.5%	29.9%
Cirrhosis (%)*	11.1%	15.8%	47.2%
Steatosis (%)*	66.7%	73.4%	85.7%
MASLD, n (%)*	48.1%	49.5%	61.5%
Met-ALD, n (%)	7.4%	10.9%	11.4%
ALD, n (%)	3.7%	10.9%	11.3%
HCC (%)*	0%	2.7%	9.9%
Death (%)*	3.7%	3.3%	15.6%
Liver Transplant (%)*	0%	1.1%	10.0%

*p<0.05



Disclosures: Mai Sedki: Nothing to Disclose, Channa Jayasekera: Nothing to Disclose, Ajitha Mannalithara: Nothing to Disclose, Allison Kwong: Nothing to Disclose, W. Ray Kim: Nothing to Disclose

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3520 | A COMPREHENSIVE STUDY EMPLOYING COMPUTATIONAL ANALYSIS AND MENDELIAN RANDOMIZATION HAS REVEALED THE IMPACT OF KEY GENES ON LIVER CANCER

Size Li[1] Wenying Qi[1] Xu Cao[1] Yue Chen[1] Shihao Zheng[1] Wei Wang[1] Qiyao Liu[1] Yong'An Ye[1] Xiaoke Li[1] Xiaobin Zao[1]

[1]Dongzhimen Hospital, Beijing University of Chinese Medicine

Background: This approach aims to provide a clearer understanding of liver cancer's genetic structure by using Mendelian randomization (MR) to identify causal links between specific genetic variants and liver cancer risk. **Methods:** We employed MR to pinpoint potential therapeutic targets for liver cancer. Differentially expressed genes (DEGs) were identified from the GEO database and cross-referenced with genes causally associated with liver cancer through MR analysis. Enrichment analysis explored the functions of overlapping DEGs. Additionally, immune cell infiltration profiles were examined to understand the interactions between identified genes and immune cells in liver cancer patients. We established a liver cancer rat model by administering diethylnitrosamine via intraperitoneal injection for 16 weeks and collected rat serum to detect levels of alanine aminotransferase and aspartate aminotransferase. The rats' liver tissues were used to perform hematoxylin and eosin staining, Masson's trichrome staining, immunohistochemical staining of Ki67, transcriptomics, and phosphoproteomics. **Results:** Mendelian randomization analyses (Figure D-I) validated the causal relationships between these genes and liver cancer, using methods like inverse variance weighting and MR-Egger regression to ensure robust results (Figure A-I). And our integrated analyses further identified two key genes, EHD4 and PPARGC1A, significantly linked to liver cancer onset and progression. EHD4 was primarily associated with Macrophages M0, while PPARGC1A was linked with resting and activated mast cells (Figure J, K). The rat HCC model was successfully constructed (Figure L, M). The transcriptomic and proteomic analyses of rat livers revealed that, compared to the normal group, EHD4 is significantly upregulated in liver cancer tissues both in mRNA and protein levels (Figure N, O). **Conclusion:** EHD4 and PPARGC1A are critical to liver cancer progression and serve as promising therapeutic targets. The MR approach underscores their significance, providing insights into liver cancer's molecular mechanisms and potential pathways for personalized treatment strategies.

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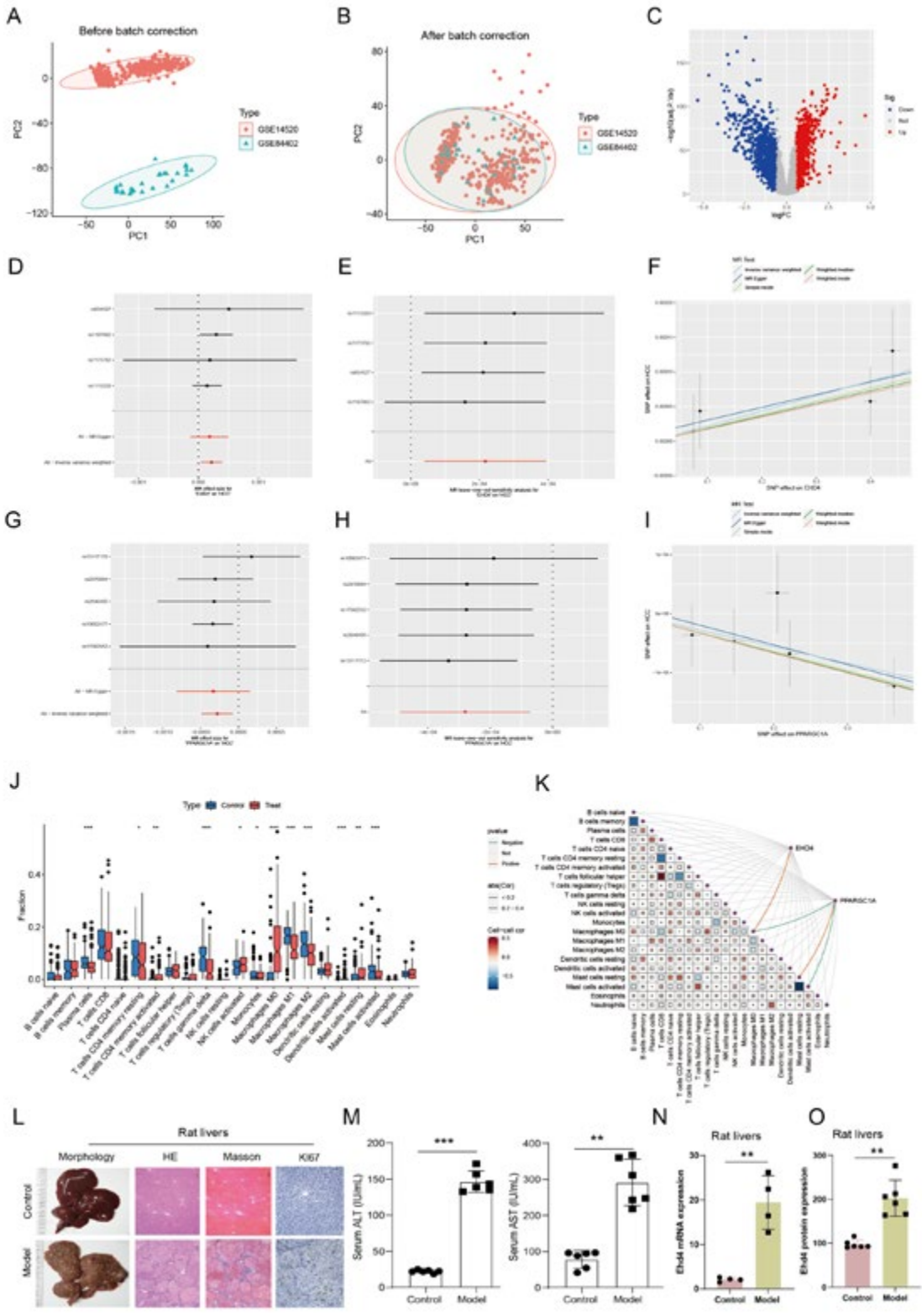

Disclosures: Size Li: Nothing to Disclose, Wenying Qi: Nothing to Disclose, Xu Cao: Nothing to Disclose, Yue Chen: Nothing to Disclose, Shihao Zheng: Nothing to Disclose, Wei Wang: Nothing to Disclose, Qiyao Liu: Nothing to Disclose, Yong'An Ye: Nothing to Disclose, Xiaoke Li: Nothing to Disclose, Xiaobin Zao: Nothing to Disclose

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3521 | GENOMIC PROFILING AND PATHOLOGICAL DIFFERENCES IN MASLD-RELATED HEPATOCELLULAR CARCINOMA WITH AND WITHOUT CIRRHOSIS

Ajay Duseja[1] Priya Singh[2] Amanjit Bal[2] Suvradeep Mitra[2] Naveen Kalra[2] SUNIL TANEJA[2] Arka De[2] Divya Khosla[2]

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Background: Metabolic dysfunction associated steatotic liver disease (MASLD) earlier called non-alcoholic fatty liver disease (MASLD) has increased as a cause of hepatocellular carcinoma (HCC) over the years. In comparison to other etiologies, more patients with MASLD-HCC develop HCC without cirrhosis. MASLD-HCC with and without cirrhosis do have certain clinical and radiological differences but the data regarding the genomic and histological differences among these two cohorts is lacking. This study aimed to elucidate the comprehensive genomic alterations and histological differences among MASLD-related HCC with and without underlying cirrhosis. **Methods:** In a prospective case-control study data was analyzed in 43 patients with MASLD-related HCC, categorized as having HCC with cirrhosis (n=35) and HCC without cirrhosis (n=8). In addition to clinical and radiological differences, the data was analyzed for the pathological differences and genomic alterations in the tumor tissue obtained from two groups. Biopsies were taken from the HCC nodules and histological grading of the tumor was assessed according to the Edmondson-Steiner criteria, and tumor subtypes were classified based on the 2019 WHO classification. Tumor samples taken from HCC nodules were subjected to Next-Generation Sequencing (NGS) for genomic profiling and the presence of pathogenic mutations. **Results:** MASLD-related HCC patients without cirrhosis were younger (average age 54.74 vs. 67.8 years; p<0.05) and had fewer metabolic comorbidities than patients with MASLD-HCC with cirrhosis. Tumors without cirrhosis in MASLD-related HCC predominantly presented as large, solitary masses, often with advanced local invasion but without extrahepatic spread.The histological analysis revealed that MASLD-related HCC with cirrhosis frequently displayed well-differentiated (Grade I) tumors, with prevalent subtypes including clear cell and macro trabecular massive, unlike the mixed histological features seen in non-cirrhotic cases. This distinction underscores the heterogeneity and possibly different oncogenic pathways influencing tumor development in cirrhotic and non-cirrhotic patients. Key genomic differences included a higher frequency of pathogenic mutations in genes UBXN11, MUC4, and MAP2K3 in patients without cirrhosis, which correlated with more aggressive tumor phenotypes. Significant mutations included Pro489_Gly514del in UBXN11 and Val3305_Ser3336del in MUC4, suggesting these as potential biomarkers for non-cirrhotic MASLD-HCC. **Conclusion:** The preliminary results of our study highlights not only the significant clinico-radiological differences between MASLD related HCC with and without cirrhosis but also differences in pathology and pathogenic mutations among the two groups.

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3522 | ROLE OF ALBI SCORE IN PATIENTS WITH HEPATOCELLULAR CARCINOMA UNDERGOING TRANSARTERIAL CHEMOEMBOLIZATION IN CHILD-PUGH CLASS A AND LOW MELD SCORE

Won Sohn[1] Jung Hee Kim[2] Hyun Woo Oh[1] Ju-Yeon Cho[3] Jae Yoon Jeong[4] Yongkyun Cho[1] Byung Ik Kim[1]

[1]Kangbuk Samsung Hospital, [2]Hallym University Dongtan Sacred Heart Hospital, [3]Chosun University Hospital, [4]National Medical Center

Background: This study was to investigate the role of Albumin-Bilirubin (ALBI) grade as a predictive factor for mortality in patients with hepatocellular carcinoma (HCC) undergoing transarterial chemoembolization (TACE). In particular, we investigated the effect of high ALBI grade on overall survival in Child-Pugh class A and low MELD score (<10) receiving TACE. **Methods:** A total of 267 HCC patients with Child-Pugh class A and low MELD score (<10) undergoing TACE as an initial treatment were analyzed. Predictive factors for overall survival in patients receiving TACE were investigated. High ALBI grade is defined as ALBI grade ≥2 (ALBI score > -2.60). **Results:** The mean age was 61.4 years. Of 267 patients, death was observed in 86 patients (32%). High ALBI grade was observed in 163 patients (61%). Multivariable analysis showed that the risk factors for mortality were BCLC stage C (hazard ratio [HR] 3.26 with 95% confidence interval [CI] 2.04-5.18, *p*<0.001), serum AFP ≥100 ng/mL (HR 1.57

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with 95% CI 1.00-2.46, *p*=0.049), and high ALBI grade (HR 2.84 with 95% CI 1.63-4.95, *p*<0.001). Overall survival was significantly different according to ALBI grade (*p*<0.001). The 24-month, 48-month, 72-month, and 96-month survival rates of patients were 94.6%, 87.9%, 82.6%, and 75.0%, respectively, in patients with low ALBI grade; and 94.3%, 81.1%, 71.7%, and 67.3%, respectively, in patients with high ALBI grade. **Conclusion:** High ALBI grade is associated with increased mortality in Child-Pugh class A and low MELD score receiving TACE for HCC. ALBI grade can be a predictive factor for overall survival in patients with relatively favorable liver function and HCC undergoing TACE.

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3523 | IMPACT OF THE SARS-COV-2 PANDEMIC ON THE DIAGNOSIS AND FOLLOW-UP OF PATIENTS WITH HEPATOCELLULAR CARCINOMA AT RÍO HORTEGA UNIVERSITY HOSPITAL

Natalia Marcos-Carrasco[1] Isabel Cañibano Liquete[2] Isabel Ruiz Nuñez[3] Jorge Ruiz Rodríguez[3] Irene Peñas[3] Carolina Almohalla[3] FELIX GARCIA PAJARES[3] Gloria Sanchez Antolín[3]

[1]Río Hortega University Hospital, [2]Valladolid University, [3]Rio Hortega University Hospital

Background: Hepatocellular carcinoma (HCC) is the 3rd leading cause of cancer death. Screening in cirrhotic patients with semi-annual ultrasound has proven effective in early detection. The SARS-CoV-2 pandemic caused difficulty in patient access to the healthcare system, but its effect on the stage at which HCC is diagnosed remains unknown. OBJECTIVE: To determine whether the COVID-19 pandemic caused a delay in the stage at HCC diagnosis. **Methods:** A retrospective, observational, single-center study was conducted, including patients with a new diagnosis of HCC between 2018 and 2023. The pre-pandemic period was defined as 2018-2020 and the post-pandemic period as 2021-2023. The characteristics of these patients were evaluated, comparing the main events between the two periods. **Results:** 167 patients were included, the majority of them being male (83%) with a median age of 66 years (IQR 60-71). 141 patients were cirrhotic and the most common cause was alcohol (50,35%) followed by HCV (19%). There was a trend to earlier diagnosis in cirrhotic patients (p<0.002). Median tumoral size in cirrhotic patients vs. non-cirrhotic was 5.09±3.87 cm SD vs 8,94±4,75 cm SD (p<0,001). Patients with AFP >400 had more advanced stages and larger tumor sizes (p<0.001). In the group of patients diagnosed after the pandemic period, a trend toward more advanced diagnoses was identified, though this was not statistically significant. Overall mortality was 47.9%. We did not find statistically significant diferences between both groups in the overall mortality. 92 patients relapsed during this period, with a shorter relapsed- free time in the pre-pandemic group (703 vs 760 p=0.02). We identified a higher mortality rate in patients with more advanced HCC (619 vs 1606 days survival, p<0.01) and in those who received not-curative treatment (858 vs 1723 days survival, p<0.01). **Conclusion:** According to our results, no negative impact of the pandemic on the diagnosis of HCC has been observed, with those diagnosed after 2021 showing a longer recurrence-free period. This underscores the importance of adapting and maintaining screening in these patients to improve their quality of life and survival. However, these results should be validated with larger number of patients and by including data from other centers.

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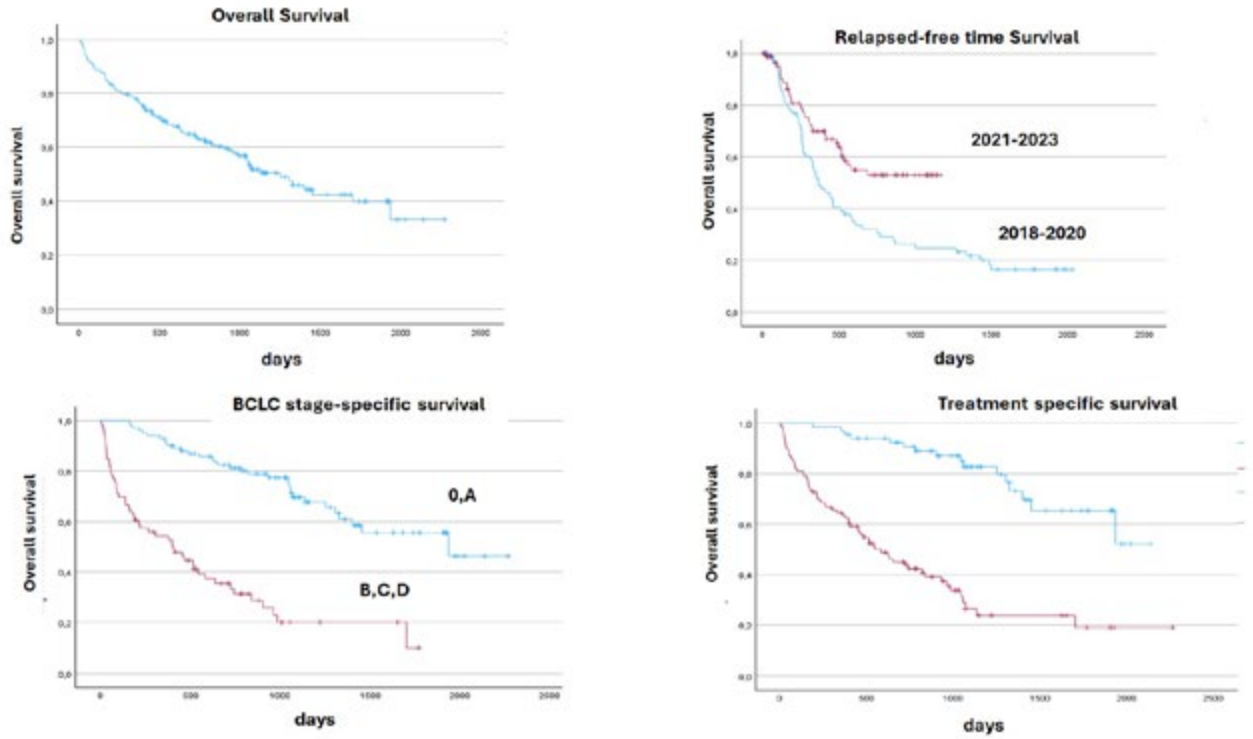

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3524 | ASAP SCORE PREDICTS HCC RECURRENCE AFTER COMPLETE RADIOLOGICAL RESPONSE TO LOCOREGIONAL TREATMENTS

Lorenzo Canova[1] Massimo Iavarone[1] Eleonora Alimenti[1] Riccardo Perbellini[1] Sara Renteria[1] Roberta D'Ambrosio[1] Elisabetta Degasperi[1] Floriana Facchetti[1] Anna Ierardi[1] Angelo Sangiovanni[1] Ferruccio Ceriotti[1] Pietro Lampertico[2]

[1]Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy, [2]CRC "A. M. and A. Migliavacca" Center for Liver Disease, University of Milan, Milan, Italy

Background: Alpha fetoprotein (AFP) and prothrombin induced by vitamin K absence/antagonist II (PIVKA-II) are biomarkers for hepatocellular carcinoma (HCC), which have been extensively studied in the diagnosis of HCC, while their use in the prognosis prediction remains poorly assessed. Recently, a new algorithm (ASAP) - including age, gender, AFP and PIVKA-II - has been validated as an alternative to GALAD for prediction of HCC development, with a cut-off of 0.56. The identification of predictors of HCC recurrence after curative treatment has always been relevant to patients' management, and now may have further utility with the arrival of adjuvant therapies. The aim of our study was to evaluate the predictive role of AFP and PIVKA-II alone or combined in the ASAP score for HCC recurrence in patients who achieved a complete response (CR) after locoregional treatment. **Methods:** In this single-center, observational study, we have enrolled consecutive patients with first diagnosis of HCC treated by ablation (MWTA) or chemoembolization (TACE) with a successful achievement of CR, which was evaluated by CT-scan 1 month after treatment. Patients were then evaluated every three months by CT-scan, clinical and biochemical features until recurrence, death or last follow up. PIVKA-II and AFP levels were measured at the day of treatment by Fujirebio assays, Japan. **Results:** 127 patients with HCC and available serum sample who achieved CR after the first treatment were included: median age 66 (38-88); 79% men, 78% with viral etiology, 85% Child-Pugh A, 86% BCLC 0/A, 60% MWTA. The day of treatment, the median AFP was 6.6 ng/mL (1.3-3,537), median PIVKA-II was 144 (16-17,772) mAU/mL, median ASAP score was 0.6 (-3.44-6.64; 52% with ASAP value > 0.56). During follow up, HCC recurred in 71 (56%) patients [median time to recurrence

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was 14.6 (0.9-82.4) months after achieving CR]. The ASAP score [HR 1.19 (95%CI 1.05-1.35), p=0.006] was the only independent predictor of recurrence in a multivariable model including only scores and algorithms. Milan's Criteria [HR 0.49 (95%CI 0.25-0.95), p=0.037] were the only independent predictor of HCC early recurrence (<12 months). Adopting the ASAP cut-off of 0.56, the algorithm independently predicted HCC recurrence [HR 2.527 (95%CI 1.39-3.71), p=0.001], but did not predict early recurrence. Calculating Receiver Operating Characteristic (ROC) curves and utilizing the Youden index method we identified the ASAP cutoff 0.547 to predict HCC recurrence (sensitivity 66%, specificity 62%), performing slightly better than adopting the 0.56 cut-off (sensitivity 64% specificity 62%). **Conclusion:** The ASAP algorithm may accurately predict HCC recurrence after complete radiological response, deserving further studies to refine the model. A cut-off of 0.547 might be more effective in predicting HCC recurrence.

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3525 | SURVIVAL AFTER REMOVAL FROM LIVER TRANSPLANT WAITLIST FOR HEPATOCELLULAR CARCINOMA PROGRESSION: EFFECTS OF IMMUNOTHERAPY AND THERAPY TYPE

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Background: Hepatocellular carcinoma (HCC) is an increasingly common primary malignancy, with liver transplantation (LT) providing better long-term survival outcomes than resection, systemic, or locoregional therapies. Unfortunately, some patients have progressive disease while on the LT waitlist and are no longer transplant eligible. The goal of this study was to determine whether post-delisting therapy type affects patient survival. **Methods:** Medical records of patients with who met exception criteria for HCC at listing, but who were ultimately removed from the LT waitlist between 4/2020 and 4/2024 were retrospectively reviewed. Differences in survival were analyzed using Kaplan-Meier analysis and log-rank tests. **Results:** During the study period, 23 patients were delisted for HCC progression, 15 (65.2%) of whom received cancer-directed therapy after delisting. Of those, 12 received any immunotherapy (IO), most frequently combination atezolizumab/bevacizumab (n=8). One patient received atezolizumab alone, 1 received regorafenib alone, and 2 received lenvatinib alone. Receiving immunotherapy with other locoregional or radiation therapy did not affect post-delisting survival (p=0.37; Figure 1), thought only one patient received only immunotherapy. **Conclusion:** For patients well enough to receive post-delisting therapy, survival is low, with 51.2% 1-year survival. Prognosis is generally poor; however, this cohort shows meaningful survival in a small group of patients beyond prior survival expectations. Optimum therapy of patients for HCC after delisting needs further study.

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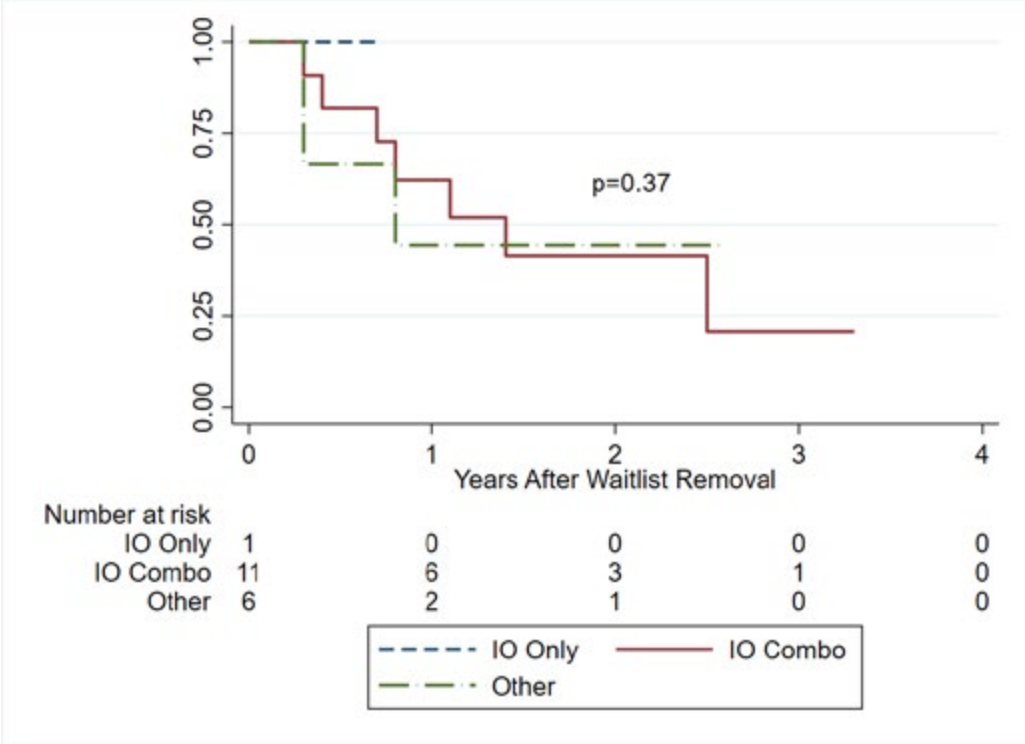

Disclosures: David Victor: Nothing to Disclose, Sudha Kodali: Advisor relationship with Astrazeneca; Has not ended; Speaking and Teaching relationship with Gilead; Has not ended; Advisor relationship with SIRTEX; Has not ended; Speaking and Teaching relationship with Gilead; Has ended; Advisor relationship with SIRTEX; Has ended; Consultant relationship with Astrazeneca; Has ended, Ashton Connor: Nothing to Disclose, Maen Abdelrahim: Nothing to Disclose, Elizabeth Brombosz: Nothing to Disclose, Tamneet Basra: Nothing to Disclose, Michelle Jones-Pauley: Nothing to Disclose, Mazen Noureddin: Principal Investigator for a Drug Study relationship with Viking; Has not ended; Consultant relationship with Eli Lilly; Has not ended; Consultant relationship with AstraZeneca; Has not ended; Consultant relationship with Boston Pharmaceuticals; Has not ended; Principal Investigator for a Drug Study relationship with Genfit; Has not ended; Principal Investigator for a Drug Study relationship with Galectin; Has not ended; Principal Investigator for a Drug Study relationship with Gilead; Has not ended; Principal Investigator for a Drug Study relationship with BMS; Has not ended; Principal Investigator for a Drug Study relationship with BI; Has not ended; Principal Investigator for a Drug Study relationship with Akero; Has not ended; Consultant relationship with Cytodyn; Has not ended; Consultant relationship with GSK; Has not ended; Consultant relationship with BI; Has not ended; Consultant relationship with Madrigal; Has not ended; Terns,Takeda, Zydus. relationship with Itimmune, BI, Cytodyn, 89BIO, GSK, Madrigal, Merck, Novo Nor; Has not ended; Principal Investigator for a Drug Study relationship with Allergan; Has not ended; Consultant relationship with Takeda; Has not ended; Consultant relationship with Terns; Has not ended; Terns, Corcept, Takeda, Madrigal, Novartis, Novo Nordisk, relationship with Allergan, Akero, BI, BMS, Gilead, Galectin, Zydus GSK; Has not ended; Consultant relationship with Novo Nordisk; Has not ended; Stock â€“ privately held company relationship with Rivus Pharma, Cytodyn, and ChronWell; Has not ended; Consultant relationship with Merck; Has not ended; Principal Investigator for a Drug Study relationship with Madrigal; Has not ended; Consultant relationship with Altimmune; Has not ended; Principal Investigator for a Drug Study relationship with Terns; Has not ended; Principal Investigator for a Drug Study relationship with Zydus; Has not ended; Stock â€“ privately held company relationship with Rivus Pharmaceuticals; Has not ended; Consultant relationship with Alligos; Has not ended; Stock - publicly traded company relationship with Cytodyn; Has not ended; Stock â€“ privately held company relationship with ChronWell; Has not ended; Speaking and Teaching relationship with Madrigal; Has not ended; Principal Investigator for a Drug Study relationship with Takeda; Has not ended; Principal Investigator for a Drug Study relationship with Shire; Has not ended; Principal Investigator for a Drug Study relationship with Novo Nordisk; Has not ended; Principal Investigator for a Drug Study relationship with Novartis; Has not ended; Principal Investigator for a Drug Study relationship with Enanta; Has not ended; Principal Investigator for a Drug Study relationship with Corcept; Has not ended; Principal Investigator for a Drug Study relationship with GSK; Has not ended; Principal Investigator for a Drug Study relationship with Conatus; Has not ended, Ashish Saharia: Nothing to Disclose, Constance Mobley: Nothing to Disclose, Mark Hobeika: Nothing to Disclose, Yee Lee Cheah:

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Intuitive Surgical: Consultant, Caroline Simon: Nothing to Disclose, Kirk Heyne: Nothing to Disclose, R. Mark Ghobrial: TransMedics: Consultant, Sanofi: Consultant, LyGenesis: Advisory Board Member

3526 | EFFICACY AND SAFETY OF FGFR INHIBITORS IN CHOLANGIOCARCINOMA, A SYSTEMATIC REVIEW AND META ANALYSIS

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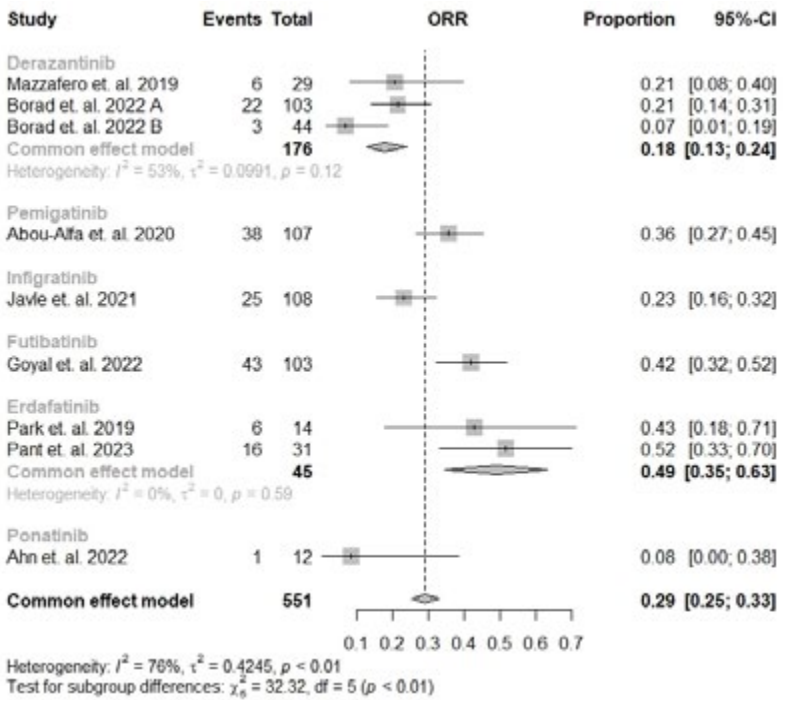
Background: Cholangiocarcinoma is one of the insidious and aggressive cancers often diagnosed late in the disease stage. Current treatment strategies include surgery, radiation and chemotherapy consisting mainly of 5-fluorouracil, gemcitabine and cisplatin. Targeted therapies towards Isocitrate Dehydrogenase (IDH) 1/2 and Fibroblast Growth Factor Receptor (FGFR) are being investigated for the treatment of cholangiocarcinoma. We attempted to perform a systematic review and meta-analysis of clinical trials of fibroblast growth factor receptor (FGFR) inhibitors for cholangiocarcinoma. **Methods:** We performed a systematic search on Pubmed, Clinicaltrials.gov, Embase, Cochrane, and google scholar from January 2010 to October 2023 using "Cholangiocarcinoma" AND "FGFR inhibitors". We focused on the phase II trials on FGFR inhibitors in cholangiocarcinoma population with fusion or amplification mutations of FGFR. Pooled Objective response rate (ORR) and Disease control rate (DCR) were calculated using R software. **Results:** A total of 1086 articles were screened and we included 9 clinical trials(3 Derazantinib, 1 Pemigatinib, 1 Infigratinib, 1 Futibatinib, 2 Erdafatinib, 1 Ponatinib). A total of 551 patients with cholangiocarcinoma received FGFR inhibitors. Pooled ORR was 0.29 (95% CI 0.25-0.33, I2=76%). The pooled DCR was 0.84 (95% CI 0.80-0.87, I2 =0%). Median progression free survival was noted to be 5.7- 8.3 months, 6.93 months, 7.3 months, 9 months, 4.2-5.59 and 2.4 months in trials for Derazantinib, Pemigatinib, Infigratinib, Futibatinib, Erdafatinib, and Ponatinib, respectively. Severe adverse events were noted in 10-58% of the patients in these trials and commonly reported serious adverse events were stomatitis, diarrhea, hyperphosphatemia, eye related toxicity, colangitis, anemia, sepsis and others. **Conclusion:** FGFR inhibitors present a promising targeted approach adding to the arsenal of drugs available for the treatment of cholangiocarcinoma. Continued research efforts and Phase 3 trial data are crucial to understand the efficacy, outcomes and safety profile of these novel drugs.



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Disclosures: Yashwitha Sai Pulakurthi: Nothing to Disclose, Praneeth Reddy Keesari: Nothing to Disclose, Gautam Maddineni: Nothing to Disclose, Wajeeha Aiman: Nothing to Disclose, Muhammad Ashar Ali: Nothing to Disclose, Muhammad Hussain: Nothing to Disclose, Mehul Shah: Nothing to Disclose, Hamid Shaaban: Nothing to Disclose

3527 | AGAP-APRI AS A PROPOSED ALTERNATIVE TO GALAD OR LIVER US WITH AFP FOR HCC SCREENING IN FILIPINOS

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Background:
Hepatocellular carcinoma is a leading cause of cancer death in Filipinos. GALAD is a statistical model utilizing clinical details and 3 tumor markers to diagnose HCC in patients with chronic liver disease. We aimed to create alternative screening tools for HCC using only AFP and PIVKA II together with other clinical and laboratory parameters. **Methods:** Data from 726 patients of the Early Cancer Detection in the Liver of Filipinos with Chronic Hepatitis B using AI-Driven Integration of Clinical and Genomic Biomarkers (CANDLE) Study were reviewed. 62 of the patients had HCC. The dataset was further divided into testing and training datasets. Four models utilizing AFP, PIVKA, AST and Platelet count together with age and gender were created. AST and platelets were used as alternatives for the first model (AGAP-PA), and AST to Platelet Ratio Index (APRI) was used for other three models (AGAP-APRI, AGA-APRI, AGP-APRI). These models were validated on the testing dataset and their AUROCs, sensitivities and specificities at the optimum cut-off points derived. These were compared with the performance of published models (GALAD, GAAP) and liver ultrasound with AFP. **Results:** The cohort was predominantly HBsAg+ (77.41%). 53.97% of the 61 patients had HCC were HBsAg +. All four newly derived models performed well, with AUROCs, sensitivities, and specificities comparable to GALAD and GAAP. The AGAP-APRI had the best AUROC at 0.986. None of the four models had a significantly different AUROC from either GALAD or GAAP. Sensitivities of the four models were comparable to GALAD, but AGP-APRI and AGA-APRI had better sensitivity than the GAAP(Sn= 80.3%; p-value = 0.046). AGP-APRI and AGA-APRI had better senstivity compared with ultrasound + AFP. No statistically significant was found between sensitivity of ultrasound + AFP compared to AGAP-PA and AGAP-APRI. **Conclusion:** The AGAP-PA, AGAP-APRI, AGA-APRI, and AGP-APRI models were comparable to GALAD in diagnosing HCC from non-HCC patients in the overall cohort of predominantly Hepatitis B patients. These models are cost-effective options for HCC screening. Among the four, we propose AGAP-APRI as a blood based screening testfor at risk patients. This model surpasses the performance of AFP + Ultrasound as a screening test. In addition, versions of the model using only either AFP or PIVKA have better sensitivity versus Liver ultrasound +AFP.

MODELS	AUROC	Difference from GALAD	Difference from GAAP	Spec	Sens	Difference of Sensitivity from GALAD	Difference of Sensitivity from GAAP	Difference of Sensitivity from AFP+US
Established								
GALAD(Age, Gender, AFP,AFP L3, PIVKA II)	0.983	-	*ns*	0.933	0.951	-	*	*
GAAP (Age, Gender, AFP, PIVKA II)	0.895	*ns*	-	0.974	0.803	*	-	*ns*
AFP + Ultrasound	-	-	-	0.957	0.797	*	*ns*	-
Newly developed								
AGAP-PA (Age,Gender, AFP,PIVKA II,AST, Platelet)	0.978	*ns*	*ns*	0.939	0.917	*ns*	*ns*	*ns*
AGAP-APRI (Age, Gender, AFP, PIVKA II, APRI)	0.986	*ns*	*ns*	0.962	0.917	*ns*	*ns*	*ns*
AGP-APRI (Age, Gender, PIVKA II, APRI)	0.981	*ns*	*ns*	0.916	1.000	*ns*	*	*
AGA-APRI (Age, Gender, AFP, APRI)	0.957	*ns*	*ns*	0.832	1.000	*ns*	*	*

* *Significant at α = 0.05*
[ns] *Not significantly different between datasets or subgroup counterpart*
1-tailed test of proportion used for comparison of Sens

Disclosures: Edhel Tripon: Roche: Speaking and Teaching, Dannah Zemirah Junio: Nothing to Disclose

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3528 | GALNAC-CONJUGATED ANTISENSE OLIGONUCLEOTIDES TARGETING DDR1 INHIBIT HEPATOCELLULAR CANCER

Wonseok Lee[1] Hyun Young Kim[1] Sue Murray[2] Karin Diggle[1] Debanjan Dhar[3] Michael Karin[1] Tatiana Kisseleva[1] David Brenner[3]

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Background: Liver cancer usually occurs in the setting of liver fibrosis, where type I collagen produced by activated hepatic stellate cells (HSCs) accumulates in the extracellular matrix (ECM). Cleaved type I collagens activate discoidin domain receptor 1 (DDR1)-NF-κB-p62-NRF2 signaling to induce macropinocytosis and promote hepatocellular cancer (HCC). Antisense oligonucleotides (ASOs) are a therapeutic approach to block mRNAs, and N-acetylgalactosamine (GalNAc) conjugation to ASOs mediates selective uptake by hepatocytes and HCC via their asialoglycoprotein receptor (ASGPR). Here, we investigated the role of DDR1 in collagenolysis-dependent HCC growth and assessed the effect of GalNAc-ASO targeting DDR1 (DDR1 GalNAc-ASOs). **Methods:** The pLKO.1-puro-DDR1 vector was used to delete DDR1 in HepG2, PLC/PRF/5 (PLC) and Hepa1-6 cells by CRISPR-Cas9. Primary fibroblasts were isolated from mouse ear tissues of wild-type and $Col^{r/r}$ mice, which have mutations in the collagenase cleavage site in collagen-α1(I) gene that block DDR1 signaling. Wild-type or $Col^{r/r}$ fibroblasts were seeded, cultured for 5 days, and removed to prepare ECM-coated dishes. To generate multicellular tumor spheroids (MCTS), HepG2 or PLC cells and purified human HSCs were mixed at a 1:1 ratio. GFP-labeled Hepa1-6 cells and DDR1-knockout Hepa1-6 cells were transplanted via intrasplenic injection following 2 weeks (twice a week) of CCl_4 administration to induce orthotropic liver cancer in mice. **Results:** Deletion of DDR1 inhibited HepG2 or PLC cell proliferation on wild-type ECM-coated dishes, with no difference on $Col^{r/r}$ ECM-coated dishes. Malignant markers of liver cancer and macropinocytosis-related genes were decreased in the DDR1 knockout cells (vs wild-type cells). MCTS generated using DDR1 knockout cells (HepG2 or PLC cells) showed a marked decrease in the size of spheroids. Likewise, intrasplenic injection of DDR1 knockout Hepa1-6 cells reduced the development of liver cancer (vs wild-type Hepa1-6 cells injection). Next, DDR1 GalNAc-ASOs were used to treat HCC cells and MCTS. DDR1 GalNAc-ASOs treatment significantly decreased HCC proliferation and spheroid growth. DDR1 GalNAc-ASOs treatment also inhibited the expression of malignant markers and macropinocytosis-related genes. **Conclusion:** We demonstrated that genetic deletion of DDR1 or targeting DDR1 by GalNAc-ASOs inhibits collagenolysis-dependent development of HCC. Our findings support DDR1 GalNAc-ASOs as a potential therapeutic approach to target HCC through its ASGPR.

Disclosures: Wonseok Lee: Nothing to Disclose, Hyun Young Kim: Nothing to Disclose, Sue Murray: Nothing to Disclose, Karin Diggle: Nothing to Disclose, Debanjan Dhar: Nothing to Disclose, Michael Karin: Nothing to Disclose, Tatiana Kisseleva: Nothing to Disclose, David Brenner: Nothing to Disclose

3529 | COMPARATIVE ANALYSIS OF IMAGING MODALITIES FOR HEPATOCELLULAR CARCINOMA SURVEILLANCE

Ahmed El sabagh[1] Mazen ELsheikh[2] Ahmed Elhariri[2] Mohamad Ali Ibrahim[2] Megha Bhongade[2] Prasun Jalal[2]

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Background: The superior sensitivity and specificity of contrast enhanced computed tomography (CT) or magnetic resonance imaging (MRI) make them preferred modalities for surveillance in high-risk populations for hepatocellular carcinoma (HCC) in many centers. While guidelines recommend ultrasound (US)for the surveillance for easier access and cost, it is not known whether CT or MRI offers superiority in early detection and impacts the management of HCC compared with US. **Methods:** Between January 2011 and June 2021, 1,954 patients diagnosed with HCC at Baylor Saint Luke's Medical Center Hospital were identified via ICD-9 and ICD-10 codes. Diagnosis confirmation utilized LIRADS-5 imaging. Surveillance eligibility required strict adherence to imaging intervals recommended in HCC surveillance guidelines and consistent use of the same imaging, along with serum AFP. Patients were classified by imaging modality. Descriptive statistics characterized the study population and identified independent associations between imaging modalities and HCC outcomes. Hazard ratios (HR) and 95% CIs were calculated using Cox proportional hazard models after considering the duration of surveillance. **Results:** We identified 183 incident patients with HCC who met the inclusion criteria.

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Contrast enhanced MRI-diagnosed patients predominated (N=115), compared with contrast enhanced CT and US (N=34 each). The median time between initiation of surveillance and HCC diagnosis was 28 months, with no significant difference among imaging modalities (P=0.73). At the time of diagnosis, 75.4% of patients had solitary hepatic lesions, with a median tumor size of 2.4 cm. Most patients (68.9%) were diagnosed at a late stage (BCLC B/C/D); macrovascular invasion was observed in 6% of cases as shown in (Table 1). 53.6% of patients received curative surgical treatment (resection/transplant). After adjusting for age, sex, and race, the use of CT or MRI for surveillance was associated with statistically insignificant decrease in time to receive surgical treatment (HR 2.6 for CT, 2.4 for MRI, P=0.4) and detection of smaller tumor sizes (HR 2.4 for CT, 1.9 for MRI, P= 0.2) when compared to US. **Conclusion:** Surveillance for HCC using contrast enhanced MRI and CT showed no superiority for detecting small tumors and time to curative surgical therapy compared with US. A prospective study with a larger sample size is needed to determine if MRI and CT offer substantial benefits over US for HCC surveillance programs.

Variable	All patients N= 183	US N= 34 (%)	CT N= 34 (%)	MRI N=115 (%)	P value
Age, Median (IQR), y	61 (57,67)	62 (57,69)	62.5 (58 66)	60 (56, 66)	0.229
Sex, Male, No. (%)	120 (65.6%)	22 (64.7%)	19 (55.9%)	79 (68.7%)	0.394
Race, No. (%)					
White	101(56.1)	11(33.3)	12(35.3)	78(69)	<0.001
Hispanics	45(25)	10(30.3)	15(44.1)	20(17.7)	
African Americans	17(9.4)	7(21.2)	7(20.6)	3(2.7)	
Other	17(9.4)	5(15.2)	.	12(10.6)	
Time from surveillance start to HCC diagnosis, Median (range), months	28 (6-105)	26(6-105)	25(6-83)	33(6-84)	0.73
Tumor Size, No. (%)					
< 2 cm	68 (37.2%)	10 (29.4%)	12(35.3%)	46 (40%)	0.438
2-3 cm	79 (43.2%)	14 (41.2%)	14(41.2%)	51(44.3%)	
>=3 cm	36 (19.7%)	10 (29.4%)	8(23.5%)	18 (15.7%)	
Vasoular Invasion, No. (%)	11 (6%)	1 (2.9%)	6 (17.6%)	4 (3.5%)	0.007
BCLC stage, No. (%)					
Early Stage (0/A)	57 (31.1%)	12 (35.3%)	8 (23.5%)	37 (32.2%)	0.535
Advanced Stage (B/C/D)	126 (68.9%)	22 (64.7%)	26 (76.5%)	78 (67.8%)	
Surgioal Curative Treatment, No. (%)	98(53.6)	17(50)	16(47)	65(56.5)	0.584

Table 1: Baseline Patient Characteristics and Clinical Variables Comparison Across Different Imaging Modalities for HCC Screening

Disclosures: Ahmed El sabagh: Nothing to Disclose, Mazen ELsheikh: Nothing to Disclose, Ahmed Elhariri: Nothing to Disclose, Mohamad Ali Ibrahim: Nothing to Disclose, Megha Bhongade: Nothing to Disclose, Prasun Jalal: Nothing to Disclose

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3530 | TRANSARTERIAL CHEMOEMBOLIZATION OFFERS SURVIVAL ADVANTAGE OVER RADIOEMBOLIZATION IN EARLY-STAGE UNRESECTABLE HEPATOCELLULAR CARCINOMA

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Background: Transarterial radioembolization (TARE) with Yttrium-90 resin microspheres is an established treatment option for patients with unresectable hepatocellular carcinoma (HCC). However, clinical efficacy and optimizing treatment application over transarterial chemoembolization (TACE) remain challenging. **Methods:** All consecutive, unselected patients undergoing treatment with TARE (n=106) or TACE (n=176) at four academic institutions were reviewed retrospectively. Those with metastatic disease or with high-grade locally advanced (Vp3/4 portal vein invasion) disease, had non-selective TARE or TACE, or with Child-Pugh (CP) class C disease were excluded. Patient characteristics and treatment-related data were collected at baseline; adverse events and time-to-event data (median overall survival [mOS], and objective response rates [by modified Response Evaluation Criteria in Solid Tumors; mRECIST]) were collected over a median follow-up duration of 27 (interquartile range [IQR] 13-50) months. **Results:** The mean age of the overall cohort was 66.8 ± 10.5 years, and 209 (73.9%) were male. More BCLC 0/A patients received TACE (42.9%) vs. TARE (29.3%). Between groups, patients were similar in age, performance status (ECOG), CP class, HCC etiology, presence of DM (P>0.05 for all), and minor vascular invasion (P=0.220). The mOS was longer in HCC patients undergoing TACE (40.0 months) vs. TARE (24.2 months; hazard ratio [HR] 1.70, 95% CI:1.2-2.5, P=0.006). BCLC 0/A patients receiving TACE had longer mOS (61.2 vs. 25.0 months; HR 2.2 [95% CI:1.1-4.5], P=0.029). Although longer survival was seen with TACE in BCLC B patients (38.1 vs. 24.0 months), this did not reach statistical significance (HR 1.4, 95% CI:0.9-2.3, P=0.143). The TACE group showed a higher complete response rate (57 [32.8%] vs. 22 [20.8%]; P=0.0015) but similar rates of progressive disease (32 [18.4%] vs. 20 [18.9%]) than patients in the TARE group. **Conclusion:** TACE is superior to TARE in treating HCC patients, particularly in early-stage disease, with improved OS and objective response rates. The utilization of TARE as a treatment option in early or intermediate-stage HCC must be evaluated in larger, randomized, controlled clinical trials.

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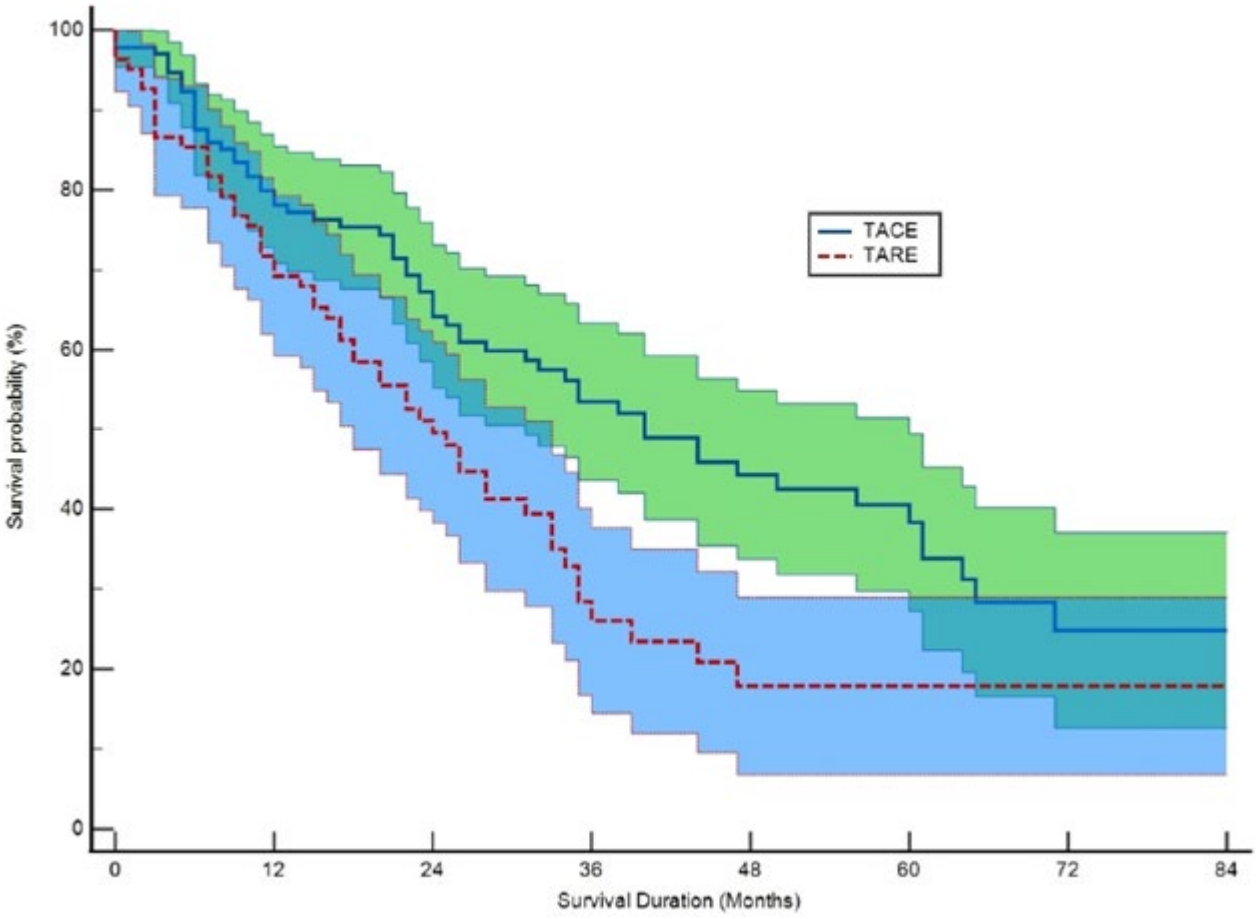

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3531 | ALTERED CELLULAR ENERGETICS AND DYSREGULATION OF NK CELLS IN HEPATOCELLULAR CARCINOMA

Pushpa Yadav[1] Anupama Kumari[1] Prabhjyoti Pahwa[1] Aesha Rehan[1] Viniyendra Pamecha[1] Shiv Kumar Sarin[1] Nirupma Trehanpati[1]

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Background: In tumor microenvironment (TME) of HCC, functional natural Killer (NK) cells are important, but their metabolic modulation in this environment has not been adequately explored. We investigated the cellular energetics in all developmental stages of NK cells in HCC. **Methods:** In the human study, 27 end stage liver disease patients (12 HCC and 15 CLD) were included. In the experimental study, CCl_4 induced mouse model of HCC and cirrhosis was developed in B6C3F1 mice. Group I received single dose of DEN (1 mg/kg), Group II was administered with CCl_4 (0.2 ml/kg) twice a week from 8 to 30 weeks old and Group III received a single dose of DEN (2 weeks old) and CCl_4 (twice/week) starting at 8 weeks up to 30 weeks old. Group IV was administered olive oil+1% PBS and served as control. Isolated PBMCs from the blood and liver infiltrated lymphocytes (LILs) from liver tissues of patients and mice models were used for immune-metabolic analysis using high dimensional

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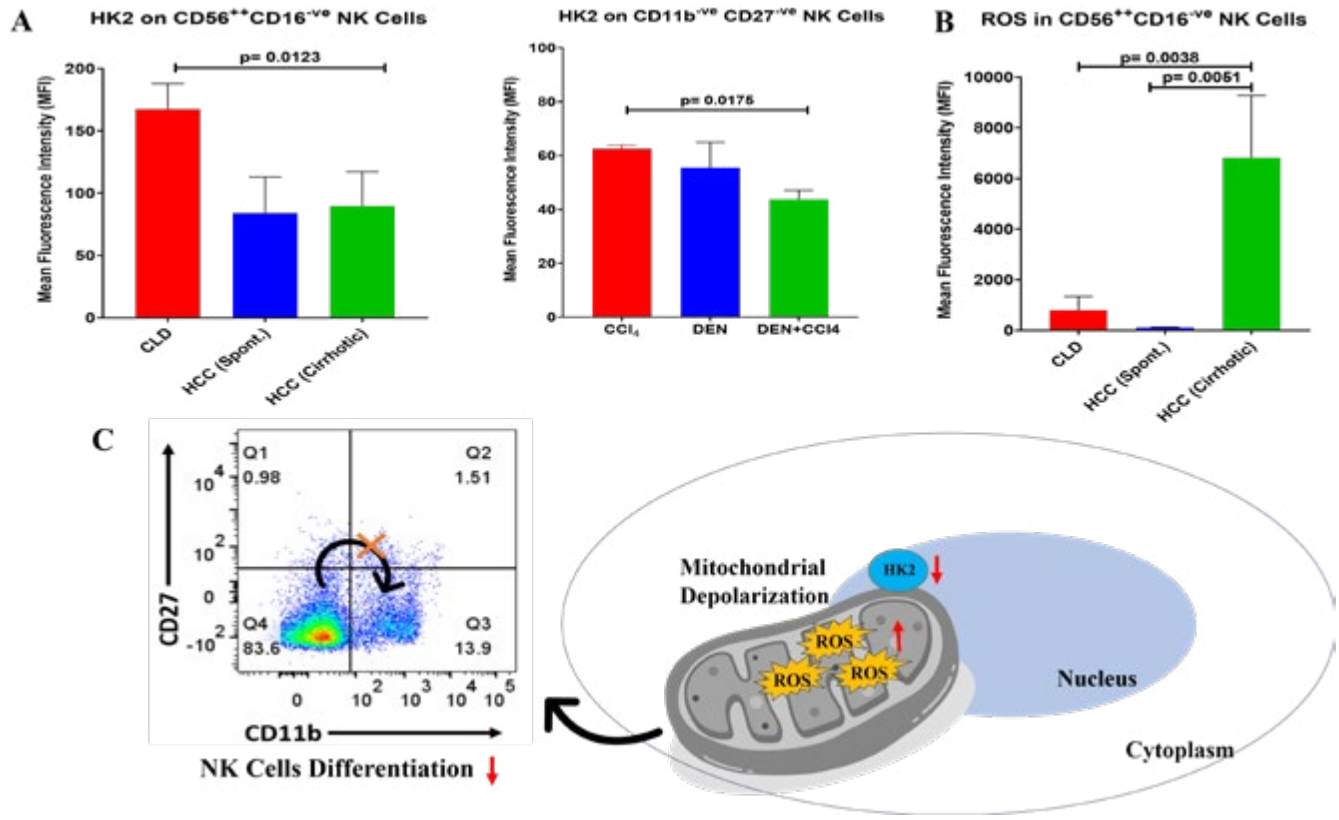
flow cytometry phenotyping. **Results:** In animal model of HCC, PB and TME shows elevation in total NK cells and CD11b^{-ve} CD27^{-ve} (least developed) phenotypes. Similarly, patient samples also showed, increased frequency of immature (CD56^{++}CD16^{-}) NK cells and reduced mature (CD56^{+}CD16^{+}) NK cells, along with diminished expression of maturation marker, CD57. PBMCs showed decreased expression of hexokinase 2 in the immature NK cell subsets i.e. CD11b^{-ve} CD27^{-ve} NK cells (p value = 0.0176) in mice and CD56^{++} CD16^{-ve} NK cells (p value =0.0123) in humans with HCC when compared to their respective cirrhotic controls [Fig A]. ROS production was also found to be increased in the CD56^{++} CD16^{-ve} NK cell subset (p value = 0.0038) of HCC patients when compared to CLD [Fig B]. **Conclusion:** Our results indicate metabolic reprogramming of NK cells and perturbation of their developmental stages in hepatocellular carcinoma (HCC). Decreased frequency of mature NK cells, coupled with reduced HK2 and heightened ROS production suggests mitochondrial depolarization. These metabolic alterations may contribute to the dysregulation of NK cell developmental stages in HCC.



Disclosures: Pushpa Yadav: Nothing to Disclose, Anupama Kumari: Nothing to Disclose, Prabhjyoti Pahwa: Nothing to Disclose, Aesha Rehan: Nothing to Disclose, Viniyendra Pamecha: Nothing to Disclose, Shiv Kumar Sarin: Nothing to Disclose, Nirupma Trehanpati: Nothing to Disclose

3532 | BASELINE LIVER HISTOLOGICAL CHARACTERISTICS IN PATIENTS WITH CHRONIC HEPATITIS B WHO DEVELOPED INTO HCC 3- 5 YEARS LATER

Haina Fan[1] *Yangqing Ma*[1]

[1]*Shuguang Hospital*

Background: Liver fibrosis is a vital risk factor for hepatocellular carcinoma (HCC). Consequently, the identification of risk indicators for the onset of HCC at the stage of liver fibrosis is of particular significance. In this study, we compared the clinical and histopathological of patients with and without HCC in a cohort of CHB liver fibrosis to understand the risk factors and possible mechanisms for the development of HCC. **Methods:** A case-control study design was employed to match HCC and non-HCC patients with balanced gender, age, BMI, and degree of liver fibrosis through the propensity score matching method. All patients underwent liver biopsy before receiving the relevant treatment and 80% patients underwent a second biopsy after 48-week treatment. Second

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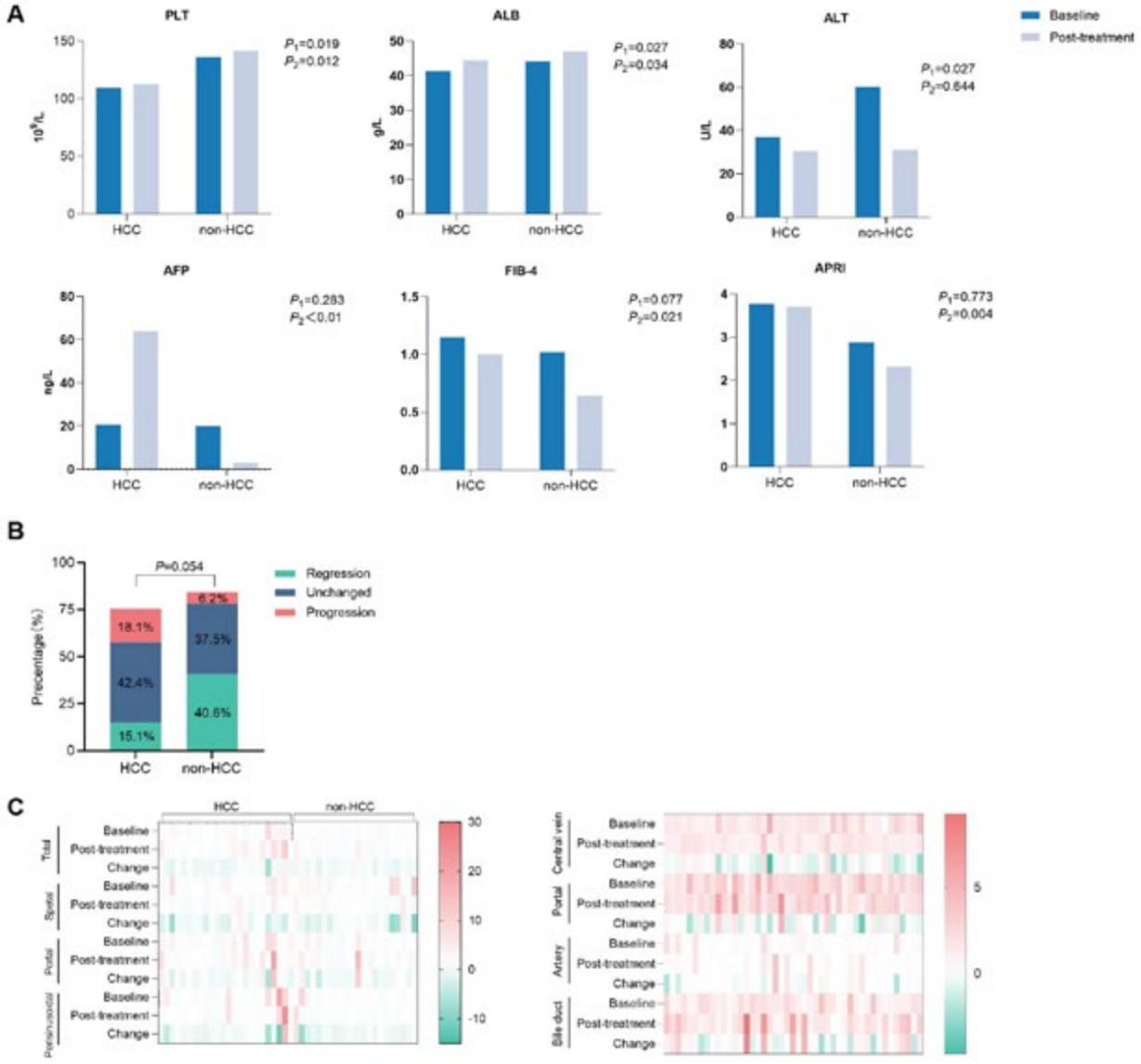
harmonic generation (SHG) was used to evaluate the distribution of collagen deposition and to identify lumen classes and distribution in liver tissue. **Results:** A total of 64 patients (32 patients in HCC and non-HCC group, respectively) were enrolled in the study. Patients who developed HCC had lower levels of ALT (median 34 vs 47 U/L), PLT (109.15 ± 66.72 vs 136.13 ± 65.21×10^9/L), and Alb (41.43±5.67 vs 44.2±4.02 g/L) at baseline than non-HCC group (P < 0.05, Fig.1A). After 48 weeks of treatment, PLT and Alb remained lower in the HCC group while AFP was higher than non-HCC group (P < 0.05). Meanwhile, APRI and FIB-4 were also higher in HCC group (P=0.021 and 0.004, respectively, Fig.1A). At baseline, there was no difference in the degree of liver fibrosis between the two groups. In the group without HCC, 13 cases (40.6%) occurred fibrosis regression and only 2 cases (6.2%) progressed after treatment (Fig.1 B). Overall collagen deposition was greater in the HCC group than non-HCC group at baseline (P=0.037); further analysis showed that the difference may be mainly concentrated in the perisinusoidal area (Fig.1 C). There was no difference in lumen distribution between the two groups before and after treatment. Collagen deposition was found to be decreased in both groups compared to baseline and was more significant in the group with HCC, especially perisinusoidal area. It was found that the number of total central veins in non-HCC group was significantly decreased (P=0.044, Fig.1 C) compared to baseline. The number of arteries in HCC group increased, but the difference was not statistically significant. **Conclusion:** In patients with hepatitis B liver fibrosis, PLT, Alb and ALT were lower at baseline in those who developed HCC. The lower level of PLT may be associated with portal venous pressure. Perisinusoidal collagen deposition or activated hepatic stellate cells may be involved in the development of HCC.



Disclosures: Haina Fan: Nothing to Disclose, Yangqing Ma: Nothing to Disclose

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3533 | CLINICAL AND IMAGING FACTORS ASSOCIATED HCC PROGRESSION ON THE LIVER TRANSPLANTATION WAITLIST

Amanda Su[1] Celestina Tolosa[1] Harry Luu[1] Ghazal Zandieh[1] Iman Yazdani Nia[1] Shadi Afyouni[1] Kanako Yoshida[1] Lisa Yanek[1] Ahmet Gurakar[2] Ihab Kamel[1] Amy Kim[1]

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Background: Approximately 20% of patients with hepatocellular carcinoma (HCC) awaiting liver transplantation (LT) have HCC progression, making them ineligible for LT. This 'drop-out' from the waitlist has been associated with baseline imaging tumor characteristics and liver decompensation. The utility of HCC treatment response in predicting drop-out has not been elucidated. This study investigated clinical and imaging factors associated with HCC progression and drop-out using a prospectively collected longitudinal database. **Methods:** Patients with HCC listed for LT between 2009–2023 who were removed from the waitlist due to HCC progression (Drop-out cohort) were included in this study. Clinical data and tumor characteristics were obtained at the time of HCC diagnosis, LT listing, and every 3 months thereafter. The Transplanted cohort comprised 50 patients who were listed with HCC and underwent LT. In addition to imaging reports, baseline and post-1st transarterial chemoembolization (TACE) imaging were reviewed by radiology for 35 Drop-out patients and 42 Transplanted patients, and evaluated for lesion number, size and edge definition. **Results:** 44 patients with HCC were included in the Drop-out cohort. Mean time to drop-out or LT was 264 days and 269 days, respectively. There was no difference between groups in age, sex, or underlying liver disease etiology. There were more White patients in the Transplanted cohort (80.0%) compared to the Drop-out cohort (59.1%) (p=0.027). At baseline, 70.5% and 100.0% were within Milan criteria in Drop-out and Transplanted cohorts, respectively, and at listing 70.7% and 85.7% were within Milan criteria, respectively. At baseline, listing and 3 and 6 months after listing, larger lesion size and higher alpha fetoprotein (AFP) were associated with Drop-out, compared to the Transplanted cohort. Lesion number differed between groups at 3 months (p<0.001) and 6 months (p=0.005). Neutrophil-to-lymphocyte ratio was higher in the Drop-out cohort at 6 months (p=0.025). On imaging analysis, poor lesion edge definition at baseline was associated with higher likelihood of Drop-out compared to the Transplanted cohort (p=0.007). Response to TACE therapy differed between Drop-out and Transplanted cohorts based on mRECIST (p=0.001) and EASL (p<0.001) criteria, with higher partial response or stable disease in the Transplanted cohort. Based on multivariable cox proportional hazards model, larger lesion size (p=0.026) and non-White race (p=0.050) were associated with the Drop-out cohort, compared to the Transplanted cohort. **Conclusion:** Imaging response to initial TACE was significantly different between the Drop-out and Transplanted cohorts. Larger HCC size, higher AFP, and non-White race were also risk factors for drop-out. This suggests that early TACE response may be helpful in guiding use of adjuvant therapies or more aggressive liver directed treatments, to reduce drop-out from the waitlist.

Disclosures: Amanda Su: Nothing to Disclose, Celestina Tolosa: Nothing to Disclose, Harry Luu: Nothing to Disclose, Ghazal Zandieh: Nothing to Disclose, Iman Yazdani Nia: Nothing to Disclose, Shadi Afyouni: Nothing to Disclose, Kanako Yoshida: Nothing to Disclose, Lisa Yanek: Nothing to Disclose, Ahmet Gurakar: Grant/Research Support relationship with DURECT; Has ended; Advisor relationship with Orphalan; Has ended, Ihab Kamel: Nothing to Disclose, Amy Kim: Nothing to Disclose

3534 | CHEMICAL INHIBITION OF PHOSPHOGLYCERATE MUTASE 5 ATTENUATES HEPATOCELLULAR CARCINOMA VIABILITY

Andrea Johnston[1] Chin-Chi Liu[1] Ganesan Muthusamy[1]

[1]Louisiana State University

Background: Hepatocellular carcinoma (HCC) is the 4th leading cause of cancer death worldwide. Phosphoglycerate mutase 5 (PGAM5) is a Ser/His/Thr phosphatase that regulates mitochondrial homeostasis. Overexpression of PGAM5 in HCC is correlated with a reduced survival time. Silencing of PGAM5 in HCC attenuates cell growth, promotes apoptosis, & dysregulates lipid metabolism. LFHP-1c is a small molecule inhibitor of PGAM5, which has recently been found to be protective in ischemic stroke. We aimed to determine if chemical inhibition of PGAM5 would attenuate HCC viability *in vitro*. **Methods:** Human HCC (HuH7) and hepatoma (HepG2) cell lines were treated with LFHP-1c at micromolar concentrations. Cell growth and viability

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were quantified using live-cell bright field microscopy, Caspase 3/7 assay, and the CellTiter-Glo luminescent assay. Protein expression was assessed with Western blot and quantified by densitometric analysis. Lipid droplet accumulation was measured by spectrophotometric quantification Oil Red O. Reactive oxygen species generation was quantified using the Reactive Oxygen Species fluorometric assay kit. **Results:** We found that the inhibition of PGAM5 by LFHP-1c resulted in a minimal but significant reduction in HCC cell growth and ATP production in a dose dependent manner (4 micromolar - 10 micromolar) compared to DMSO treated cells at 12 and 24 hours post treatment. LFHP-1c promoted ROS production and induced apoptotic cell death beginning 3 hours post treatment and reaching maximal effect at 24 hours post exposure in HuH7 and HepG2 cells. Finally, chemical inhibition of PGAM5 reduced long chain fatty acid uptake and downregulated FABP1 expression at a dose of 2 micromolar. **Conclusion:** Collectively, LFHP-1c exhibited a dose dependent impact on HuH7 and HepG2 growth and viability, resulting in increased ROS production and apoptotic cell death. Targeting PGAM5 therapeutically may be adjunctive to chemotherapic treatment of HCC.

Disclosures: Andrea Johnston: Nothing to Disclose, Chin-Chi Liu: Nothing to Disclose, Ganesan Muthusamy: Nothing to Disclose

3535 | SARCOPENIA AND PHYSICAL FRAILTY RESULT IN WORSE OUTCOMES IN HOSPITALIZED PATIENTS WITH HEPATOCELLULAR CARCINOMA THAN OTHER SOLID ORGAN CANCERS OR HOSPITALIZED PATIENTS WITHOUT CANCER

Nicole Welch[1] Arnav Rao[1] Amy Attaway[1] Annette Bellar[1] Pratham Bhashyakarla[1] jaividhya dasarathy[2] Joe Zein[3] Lopa Mishra[4] Srinivasan Dasarathy[1]

[1]Cleveland Clinic, [2]MetroHealth, [3]Mayo Clinic, [4]Feinstein Institutes for Medical Research & Cold Spring Harbor Laboratory

Background: Sarcopenia (defined by a muscle loss phenotype; MLP) and muscle contractile dysfunction (physical frailty; PF) contribute to adverse outcomes in patients with cancers including hepatocellular carcinoma (HCC). However, it is not known whether the adverse impact is different between HCC and other solid organ cancers (SOC). We tested our hypothesis that sarcopenia/PF contributes to worse outcomes in hospitalized patients with HCC than non-HCC SOC or patients without cancers. **Methods:** The National Inpatient Sample (2010-2014) was used to identify hospitalized patients with HCC. Comparisons were made with equivalent numbers of a random sample (2.5%) of non-pancreas SOC, and a random sample (0.25%) of the entire general medical population (GMP) without cancers. Patients with pancreas cancer were excluded because of the rapid course of illness and consistent association with the most severe sarcopenia/cachexia. MLP was defined by ICD9 codes as reported by us. PF was defined by ICD9 codes with specific weights that formed a Hospital Frailty Risk Score as reported by others. Impact on outcomes of MLP alone, PF alone, both MLP and PF, and neither MLP nor PF were compared between HCC,tother SOC patients, and GMP. Outcomes of interest included length of stay (LOS), hospital charges, discharge disposition (home or non-home setting), and inpatient mortality. Multivariate logistic and log-transformed linear regression analyses were performed with confidence interval (CI) set at 95%. **Results:** There were 35,073 patients with HCC, 46,393 with SOC, and 66,489 in the GMP. Mean(SD) age was 63.22(11.27), 62.35(16.32), and 46.68(21.06), respectively. Males were the majority in the HCC group (n=25,499; 72.7%) but not in the GMP (n=26,128; 39.3%) or SOC (n=19,283; 41.6%). The percent of Whites/Blacks was 56.5/14.9(HCC), 67.8/16.1(SOC), and 67.1/15.0(GMP). The most common primary payor in all groups was Medicare (HCC, SOC, GMP: 47.8, 48.6,47.5%). Percent of patients with both PF and MLP was highest in the HCC group (n=2337; 6.7%) compared to SOC (n=1936; 4.2%) and GMP (n=1857; 2.8%), while SOC (n=32,465; 70%) and GMP (n=45,712; 68%) were more likely to have neither PF nor MLP. Logistic and linear regression showed that HCC patients with PF alone and PF and MLP had worse outcomes (LOS, charges, non-routine discharge, mortality) than GMP and other SOC patients ($p<0.001$) while MLP alone adversely affected LOS and non-routine discharge in HCC patients when compared to GMP and other SOC patients ($p<0.001$) (Table1). Absence of PF or MLP significantly improved LOS, charges, non-routine discharge, and mortality ($p<0.001$) in HCC when compared to the GMP and improved all outcomes of interest except charges compared to SOC patients (Table1). **Conclusion:** HCC patients with PF and MLP have higher hospitalization charges, mortality rates, and longer hospital stays, with a reduced likelihood of discharge to home, compared to patients with other SOC and the GMP.

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Outcome	Frailty & MLP (Adj.OR(95% CI))	P-value	Frailty Alone (Adj.OR(95% CI))	P-value	MLP Alone (Adj.OR(95% CI))	P-value	Without Frailty & MLP (Adj.OR(95% CI))	P-value
HCC vs GMP								
Length of stay	1.54 (1.50-1.58)	<0.001	1.29 (1.28-1.31)	<0.001	1.15 (1.12-1.19)	<0.001	0.83 (0.82-0.84)	<0.001
Charge of hospitalization	1.64 (1.58-1.71)	<0.001	1.42 (1.39-1.45)	<0.001	1.09 (1.04-1.14)	<0.001	1.07 (1.04-1.08)	<0.001
Discharge to home	3.61 (3.26-4.00)	<0.001	2.08 (1.98-2.18)	<0.001	2.00 (1.82-2.20)	<0.001	0.64 (0.61-0.66)	<0.001
Hospital mortality	3.27 (2.91-3.67)	<0.001	4.29 (3.98-4.62)	<0.001	1.49 (1.25-1.75)	<0.001	0.75 (0.69-0.81)	<0.001
HCC vs SOC								
Length of stay	1.49 (1.45-1.54)	<0.001	1.25 (1.23-1.26)	<0.001	1.12 (1.08-1.15)	<0.001	0.78 (0.77-0.79)	<0.001
Charge of hospitalization	1.48 (1.42-1.54)	<0.001	1.25 (1.22-1.28)	<0.001	0.95 (0.91-0.99)	0.014	0.85 (0.84-0.86)	<0.001
Discharge to home	3.46 (3.13-3.83)	<0.001	2.08 (1.98-2.18)	<0.001	1.92 (1.75-2.12)	<0.001	0.60 (0.58-0.62)	<0.001
Hospital mortality	2.76 (2.46-3.10)	<0.001	3.36 (3.12-3.61)	<0.001	1.22 (1.03-1.43)	0.021	0.54 (0.50-0.59)	<0.001

Disclosures: Nicole Welch: Nothing to Disclose, Arnav Rao: Nothing to Disclose, Amy Attaway: Nothing to Disclose, Annette Bellar: Nothing to Disclose, Pratham Bhashyakarla: Nothing to Disclose, jaividhya dasarathy: Nothing to Disclose, Joe Zein: Nothing to Disclose, Lopa Mishra: Nothing to Disclose, Srinivasan Dasarathy: Nothing to Disclose

3536 | CHARACTERIZATION OF THE IMMUNE MICROENVIRONMENT IN HEPATOCELLULAR CARCINOMA BEFORE SELECTIVE INTERNAL RADIATION THERAPY AND ITS PROGNOSTIC ROLE IN TREATMENT EFFICACY

Maria Stella Franzè[1] Paul Vigneron[2] Stefano Caruso[2] helene regnault[3] Anna Sessa[2] Pascale MAILLE[2] Massimo Iavarone[4] Eric Nguyen Khac[5] Rami Rhaiem[6] Jean Charles Nault[7] Manon Allaire[8] Marie Lequoy[9] Mohamed bouattour[10] Daniele Sommacale[2] Alain Luciani[2] Jean-Michel Pawlotsky[2] Vincent Leroy[2] Julien Calderaro[2] Giuliana Amaddeo[2]

[1]Team 18 INSERM U955; Université Paris-Est Créteil, France; University of Messina, Italy, [2]Team 18 INSERM U955; Université Paris-Est Créteil; Henri Mondor University Hospital, Créteil, France, [3]Team 18 INSERM U955; Henri Mondor University Hospital, Créteil, France, [4]Foundation IRCCS Ca' Granda-Ospedale Maggiore Policlinico, Milano, Italy, [5]Amiens University Hospital, Amiens, France, [6]Team 18 INSERM U955, Créteil;Robert Debré University Hospital, Reims, France, [7]Avicenne Hospital, AP-HP, Bobigny, France, [8]Pitié-Salpêtriére University Hospital, AP-HP, Paris, France, [9]Saint Antoine University Hospital, AP-HP, France, [10]Beaujon University Hospital, AP-HP, Clichy, France

Background: Selective internal radiation therapy (SIRT) is a validated treatment of hepatocellular carcinoma (HCC), but the role of local immune response remains elusive. The aim of the study was to characterize the HCC immunological status before SIRT and its impact on therapeutic response (primary endpoint) and overall survival (OS). **Methods:** One hundred and three patients from 8 University Hospitals (7 French, 1 Italian) affected by histologically proven HCC and treated with SIRT were enrolled. Clinical/biological/radiological data were collected at the diagnosis of HCC and during follow-up. Patients were defined as "responders" and "non-responders" based on radiological tumor response evaluated 3 and 6 months after SIRT with mRECIST criteria. RNA sequencing was analyzed to study differentially expressed genes (DEGs) in the intratumoral microenvironment. **Results:** Thirty patients (83.3% male, median age 67 years, 67% with cirrhosis) were analyzable for primary endpoint. HCC distribution across BCLC stage was: 5 A (16.7%), 11 B (36.7%), 14 C (46.6%). Eleven patients were responders (1 complete/10 partial response), 19 non-responders (3 stable/16 progressive disease). According to RNA sequencing analysis, unsupervised hierarchical clustering identified two clusters (13 C1, 17 C2) of patients (most responders in C2, p=ns) with DEGs. Clusters differed in AFP levels (p=0.03) and histological differentiation (p=0.02). A supervised analysis for DEGs showed 594 genes down- and 1268 over-expressed in C1 compared to C2. Gene set enrichment analysis with MSigDB showed that C1 was associated with immune response genes, while C2 with genes involved in proliferation/differentiation liver cells. The MCP counter analysis showed higher immune infiltrates (monocytes, myeloid dendritic cells, neutrophils, T and B cells) and fibroblasts in C1 than C2. The comparison between responder and non-responder patients at 6 months showed no differences for intratumoral immune infiltrate, but non-responders predominantly exhibited bilobar and multinodular HCC (p=0.03, p=0.003), with a significantly shorter OS (p=0.004). Cox-univariate analysis showed a reduced death risk

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for responders at 3 months (p=0.001), confirmed in a multivariate model adjusted for cluster, AFP, sex, age (HR 0.11, 95%CI 0.03-0.42, p=0.001). The intratumoral immune infiltrate in deceased patients revealed significantly lower levels of B cells and cytotoxic lymphocytes compared to living patients (p=0.03, p=0.05, respectively). **Conclusion:** SIRT, like external radiotherapy, may trigger the release of pro-inflammatory mediators and increase tumor-infiltrating immune cells, potentially enhancing efficacy when combined with immunotherapy.

Disclosures: Maria Stella Franzè: Nothing to Disclose, Paul Vigneron: Nothing to Disclose, Stefano Caruso: Nothing to Disclose, helene regnault: Boston scientific: Consultant, sirtex: Consultant, Anna Sessa: Nothing to Disclose, Pascale MAILLE: Nothing to Disclose, Massimo Iavarone: Nothing to Disclose, Eric Nguyen Khac: Nothing to Disclose, Rami Rhaiem: Nothing to Disclose, Jean Charles Nault: Nothing to Disclose, Manon Allaire: Nothing to Disclose, Marie Lequoy: Nothing to Disclose, Mohamed bouattour: Bayer: Consultant, BMS: Consultant, ROCHE: Consultant, MSD: Consultant, Sirtex Medical: Consultant, Daniele Sommacale: Nothing to Disclose, Alain Luciani: Nothing to Disclose, Jean-Michel Pawlotsky: Abbvie: Speaker, Abbott: Advisor, Gilead: Speaking and Teaching, GSK: Advisor, Vincent Leroy: Nothing to Disclose, Julien Calderaro: Nothing to Disclose, Giuliana Amaddeo: Nothing to Disclose

3537 | RISING DISPARATE TRENDS IN HEPATOCELLULAR CARCINOMA INCIDENCE: A 22-YEAR ANALYSIS OF NATIONAL CENTERS FOR DISEASE CONTROL AND PREVENTION DATA

Khawaja Abdul Rehman[1] Waqas Rasheed[2] Syed Adeel Hassan[2] Mohamed Elsayed[2] Ruben Plentz[2]

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Background: Despite advancements in diagnostic and therapeutic modalities, hepatocellular carcinoma (HCC) imposes a significant burden on cancer-related mortality in the United States (US). While literature supports increasing incidence of HCC, evidence delineating trends by specific demographic characteristics remains limited. Herein, we aim to assess temporal trends in HCC incidence across a spectrum of demographic, racial and geographic factors. **Methods:** We analyzed HCC specific incidence from the CDC WONDER database from January 1, 1999, to December 31, 2020, for patients aged 15-85+. Age-adjusted incidence rate (AAIR) per 100,000-person, annual percentage change (APC), average annual percentage (AAPC), 95% confidence intervals were calculated and stratified by age, gender, race, regions and state. Temporal trends were examined using Joinpoint Regression by fitting log-linear regression models and weighted Bayesian information criterion. Slopes were considered increasing or decreasing if the estimated slope differed significantly from zero. Absolute percentage change was calculated by comparing AAIR between 1999-2020 (Table 1).The statistical significance was determined by 2-sided t testing (P≤0.05). **Results:** Annual AAIRs increased from 5.12 in 1999 to 7.72 in 2020 (AAPC:2.04,95%CI:1.87-2.28, p<0.000001). Highest AAIR was noted in patients aged 75-85+ (AAIR:26.33, 95%CI:26.17-26.48), 60-74 (AAIR:24.91,95%CI:24.80-25.02) and 45-59 (AAIR:10.04,95%CI:9.99-10.01). Cases increased in ages 45-59 (11.55%), 60-74 (98.54%), 75-85+ (40.96%) and decreased in ages 15-29 (-9.52%) and 30-44 (-22.92%). AAIR was highest in males (AAIR:12.85,95%CI:12.80-12.89) versus females (AAIR:3.84,95%CI:3.81-3.86). AAIR increased more in males (AAPC:2.09, 95%CI:1.87-2.38, p<0.000001) versus females (AAPC:1.76, 95%CI: 1.50-2.03, p<0.000001). Asian or Pacific Islanders (AAIR:14.96, 95%CI: 14.8-15.11) and Hispanics (AAIR:14, 95%CI:13.80-14.10) had the highest incidence while African Americans (AAIR:10.9,95%CI:10.82-10.98) and Whites (AAIR:7.15, 95%CI:7.13-7.18) had the lowest. AAPC increased across all racial subgroups except Asians (AAPC:-2.04,95%CI:-2.34,-1.67,p<0.000001). AAIR varied by census regions (West:9.1, South: 8.3, Northeast: 7.9, Midwest: 6.6). States with the highest AAIR include District of Columbia (12.01, 95%CI:11.37-12.69), Texas (11.59, 95%CI:11.48-11.69) and Hawaii (11.42, 95%CI:11.02-11.82). **Conclusion:** This investigation identifies disparities in HCC incidence by age, race, ethnicity, state and regions. Targeted policy adjustment for these high-risk individuals must aim to improve equitable access to preventative and therapeutic interventions.

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Stratification Variable	Age Adjusted Incidence Rate per 100,000 Population						AAPC (%)	95% Confidence Interval	Absolute % Change in Incidence	P-Value
	Year: 1999	95% Confidence Interval	Year: 2020	95% Confidence Interval	Overall: 1999-2020	95% Confidence Interval				
Annual Trend	5.12	5.02-5.22	7.72	7.62-7.81	8.01	7.98-8.03	+2.04	1.87-2.28	+50.7%	< 0.000001
Gender:										
Males	7.97	7.79-8.15	12.25	12.08-12.43	12.85	12.80-12.43	+2.09	1.87-2.38	+53.7%	< 0.000001
Females	2.80	2.70-2.89	3.79	3.70-3.88	3.84	3.81-3.86	+1.76	1.50-2.03	+35.3%	< 0.000001
Age:										
15-29 years	0.21	0.18-0.26	0.19	0.16-0.23	0.18	0.18-0.19	+0.48	-0.60, 1.58	-9.5%	0.38
30-44 years	0.96	0.88-1.04	0.74	0.67-0.81	0.89	0.88-0.91	-0.92	-1.30, -0.47	-22.91%	0.0008
45-59 years	5.80	5.59-6.02	6.47	6.27-6.66	10.04	9.99-10.1	+0.77	0.45-1.19	+11.55%	< 0.000001
60-74 years	14.42	13.98-14.86	28.63	28.17-29.1	24.91	24.80-25.02	+3.36	3.09-3.66	+98.54%	< 0.000001
75-85+ years	19.53	18.85-20.22	27.53	26.85-28.23	26.33	26.17-26.48	+1.79	1.56-2.14	+40.96%	< 0.000001
Race:										
American Indian/Alaskan Native	6.24	4.73-8.04	10.89	9.76-12.11	11.37	11.06-11.69	+2.51	1.72-3.57	+74.51%	< 0.000001
Asian or Pacific Islander	16.44	15.42-17.5	10.10	9.63-10.59	14.96	14.80-15.11	-2.04	-2.34,-1.68	-38.56%	< 0.000001
African American	6.8	6.44-7.18	8.81	8.51-9.12	10.90	10.82-10.98	+1.53	1.21-1.90	+29.55%	< 0.000001
White	4.49	4.39-4.59	7.17	7.07-7.27	7.15	7.13-7.18	+2.31	2.14-2.54	+59.68%	< 0.000001
Hispanic	10.60	10-11.3	12.10	11.70-12.50	14	13.80-14.10	+0.73	0.41-1.15	+14.15%	< 0.000001
Census Regions:										
Northeast	5.50	5.30-5.70	7.10	6.90-7.30	7.90	7.90-8	+1.30	1.05-1.56	+29%	< 0.000001
Midwest	4.50	4.30-4.70	6.40	6.20-6.60	6.60	6.50-6.60	+1.85	1.56-2.18	+42.22%	< 0.000001
South	4.70	4.50-4.90	8.50	8.30-8.60	8.30	8.30-8.30	+2.85	2.62-3.16	+80.85%	< 0.000001
West	6.20	6-6.40	8.10	7.90-8.30	9.10	9-9.10	+1.59	1.30-1.92	+30.6%	< 0.000001

Disclosures: Khawaja Abdul Rehman: Nothing to Disclose, Waqas Rasheed: Nothing to Disclose, Syed Adeel Hassan: Nothing to Disclose, Mohamed Elsayed: Nothing to Disclose, Ruben Plentz: Nothing to Disclose

3538 | HEPATOCELLULAR ADENOMAS: MALIGNANT TRANSFORMATION AND SURGICAL OUTCOMES IN A HIGH-VOLUME CENTER ◆

Mateo Noriega[1] *Gala Cygiel*[1] *Juan Rocca*[1] *Benjamin Samstein*[1]

[1]*Weill Cornell Medicine*

Background: Hepatocellular adenomas (HCAs) are uncommon benign tumors in the liver that have potential for malignization and a high risk of bleeding. It is more prevalent in Western Countries, with an incidence of 3-4 cases/100,000 in North America. Clinical presentation can vary from asymptomatic presentation or abdominal pain to a palpable liver mass or hemorrhage in case of rupture. However, they are most often encountered as incidental findings during imaging for unrelated reasons. In the present study, we review the instances of HCA treated at our institution. **Methods:** We conducted a retrospective chart review for patients referred to our institution over a 10-year period (January 2014-December 2023) with suspected hepatic adenomas, who then underwent hepatectomy. There were 896 hepatic resections performed during this period for various conditions and among them we identified 35 cases of HCA, accounting for approximately 3.9% of all cases. Demographic and clinicopathological data (including gender, age, tumor characteristics, number of lesions) and outcomes of HCA (including pathology results, recurrence, malignization) were analyzed. **Results:** HCA constituted 3.9% of all hepatic resection cases during the study duration. The median age of patients was 37±15.2 years, with 24 patients (68%) being female. Among surgical pathology findings, 5 (14%) patients were diagnosed with hepatocellular carcinoma (HCC). Four of these patients had previously undergone percutaneous liver biopsy with findings consistent with adenoma. Resection with clear margins (R0) was achieved in all 35 patients, with minimally invasive techniques utilized in 29 cases (83%), including laparoscopic (57%) and robotic (26%) procedures. The median tumor size was 7±4.2 cm, and most patients (25 patients/71%) presented with a single tumor. At present, all patients remain alive with a median follow-up period of 24.6±22.7 months. Of the patients diagnosed with HCC 3 (60%) had no recurrence, 2 (40%) patients had HCC recurrence. 1 patient had multifocal recurrence and was listed for liver transplant. 1 patient had metastatic and peritoneal recurrence and is undergoing chemotherapy. **Conclusion:** While surgical resection is indicated for diagnostic ambiguity, growing tumor or symptomatic mass, the risk of tumor recurrence and malignant transformation makes long-term follow-up a necessity.

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	N or Median	% or IQR
Sex		
Female	24	68.50%
Age	37	28-51
BMI	27	21.9-31.8
Surgical Technique		
Open	6	17%
Laparoscopic	20	57%
Robotic	9	26%
Pathology Results		
HepatoCelullar Adenoma	26	74%
HCC	5	14%
Biliary Adenoma	3	9%
Inflammatory Adenoma	1	3%
Type Of Liver		
Normal	32	91.40%
Diseased	3	8.60%
Number of Tumors		
Solitary	25	71.40%
Multiple	10	28.60%
Tumor Size	7	5-8.8
Resection Margins		
R0	35	100%
R1	0	0%

Disclosures: Mateo Noriega: Nothing to Disclose, Gala Cygiel: Nothing to Disclose, Juan Rocca: Nothing to Disclose, Benjamin Samstein: Nothing to Disclose

3539 | OPTIMAL TREATMENT STRATEGIES FOR HEPATOCELLULAR CARCINOMA: A META-ANALYSIS COMPARING TRANSARTERIAL CHEMOEMBOLIZATION (TACE) PLUS MICROWAVE ABLATION (MWA) VERSUS MICROWAVE ABLATION ALONE

Muhammad Shahzil[1] Fariha Hasan[2] Sechme Khan[3] Nimra Afzal[4] Diana Jomaa[5] Abdullah Sohail[6] Muhammad Saad Faisal[5] Muhammad Ali Khaqan[7] Yara Dababneh[5] Reena Salgia[5]

[1]Penn State Health Milton S. Hershey Medical Center, [2]Cooper University Health Care, Camden, NJ, United States, [3]Federal Medical College, Islamabad, Pakistan, [4]King Edward Medical University, Lahore, Pakistan, [5]Henry Ford Health System, [6]The University of Iowa Hospitals and Clinics, [7]John H. Stroger, Jr. Hospital of Cook County

Background: Hepatocellular carcinoma (HCC) is a leading cause of cancer-related deaths, with a rising incidence due to non-alcoholic steatohepatitis. Microwave ablation (MWA) is the preferred thermal ablation technique for its larger, more homogeneous ablation zones. Combining transarterial chemoembolization (TACE) with MWA enhances treatment efficacy by reducing heat-sink effects and delivering cytotoxic drugs to microscopic HCCs. This is the first meta-analysis comparing the efficacy of TACE plus MWA versus MWA alone in HCC patients, aiming to optimize treatment strategies for HCC. **Methods:** This meta-analysis adhered to Cochrane guidelines and PRISMA standards, comparing the effectiveness of TACE plus MWA versus MWA alone for HCC treatment. A comprehensive search was conducted across PubMed, MEDLINE, Embase, Scopus, and CENTRAL databases until May 2024. Inclusion criteria targeted RCTs and observational studies with adult HCC patients receiving TACE plus MWA or MWA alone. Data extraction followed PICOS criteria and was performed using Excel. Statistical analyses utilized RevMan with a random-effects model, considering results significant

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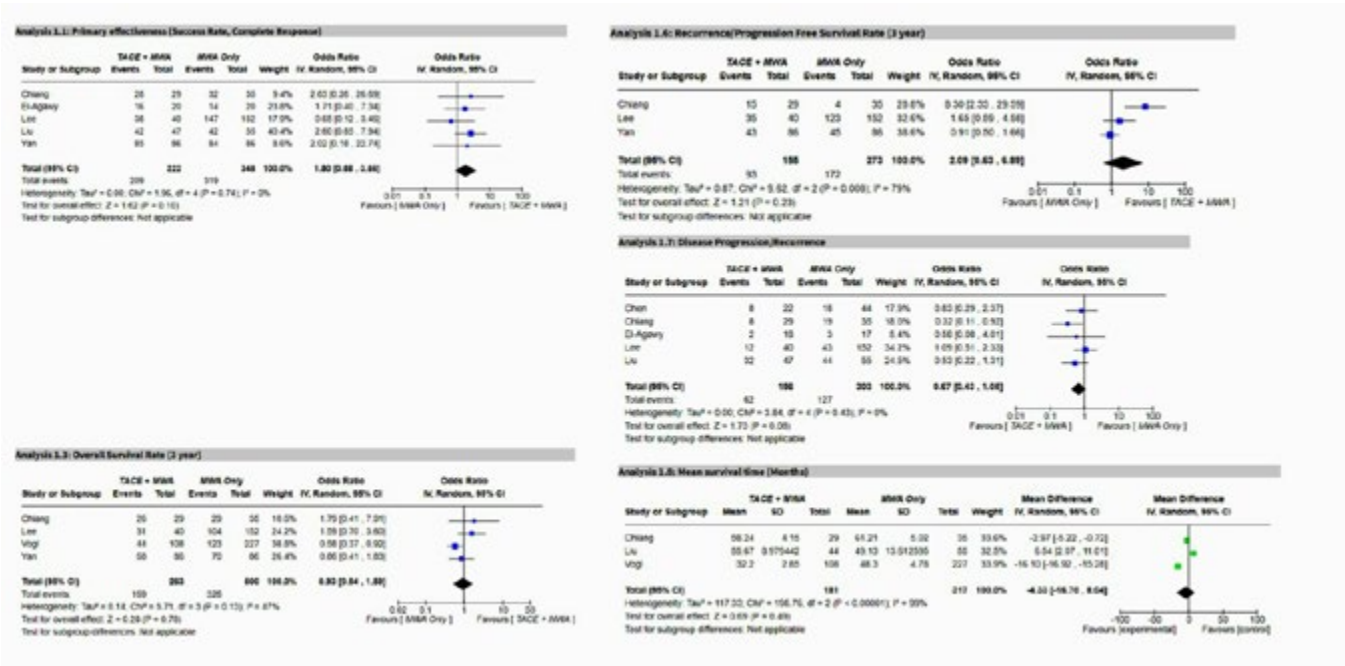
at p < 0.05. **Results:** Of 485 screened studies, seven studies with 971 HCC patients were included. The TACE plus MWA group had 352 patients, and the MWA group had 619. Primary outcomes assessed included primary effectiveness, overall survival rates, and recurrence/progression-free survival rates. Primary effectiveness showed no significant improvement (OR: 1.80; 95% CI: 0.88, 3.66). One-year overall survival (OR: 1.14; 95% CI: 0.55, 2.35), three-year overall survival (OR: 0.93; 95% CI: 0.54, 1.59), and five-year overall survival (OR: 0.58; 95% CI: 0.28, 1.21) showed no significant differences. Recurrence/progression-free survival at one year (OR: 1.18; 95% CI: 0.73, 1.92) and three years (OR: 2.09; 95% CI: 0.63, 6.89) also showed no significant differences. Secondary outcomes included disease progression/recurrence (OR: 0.67; 95% CI: 0.43, 1.05) and mean survival time (MD: -4.33 months; 95% CI: -16.07, 8.04), both of which were not significantly different. Adverse events, including intra-abdominal bleeding (OR: 0.72; 95% CI: 0.25, 2.11), GI symptoms (OR: 1.54; 95% CI: 0.21, 11.08), overall adverse events (OR: 2.56; 95% CI: 0.24, 26.79), and fever (OR: 3.65; 95% CI: 0.88, 15.20), showed no significant differences. **Conclusion:** This meta-analysis shows that combining TACE with MWA does not significantly improve primary effectiveness, overall survival, or recurrence/progression-free survival rates compared to MWA alone in treating HCC. Both treatments have similar safety profiles. Future research should identify subpopulations that may benefit from combined therapy, conduct larger randomized controlled trials, and assess the impact of transarterial radioembolization (TARE) with ablation, given the increasing use of radiation-based HCC treatments in the US.



Disclosures: Muhammad Shahzil: Nothing to Disclose, Fariha Hasan: Nothing to Disclose, Sechme Khan: Nothing to Disclose, Nimra Afzal: Nothing to Disclose, Diana Jomaa: Nothing to Disclose, Abdullah Sohail: Nothing to Disclose, Muhammad Saad Faisal: Nothing to Disclose, Muhammad Ali Khaqan: Nothing to Disclose, Yara Dababneh: Nothing to Disclose, Reena Salgia: Eisai: Speaking and Teaching, AstraZeneca: Advisor

3540 | ASSESSING TREATMENT RESPONSE IN HEPATOCELLULAR CARCINOMA (HCC) AFTER TRANS-ARTERIAL CHEMO-EMBOLISATION (TACE) - INCORPORATING DEGREE OF TUMOR NECROSIS TO PREDICT SURVIVAL OUTCOMES

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Background: Transarterial Chemoembolization (TACE) is the standard-of-care therapy for intermediate-stage (BCLC stage B) Hepatocellular Carcinoma (HCC). At present, the association between tumour necrosis measured by modified Response Evaluation Criteria in Solid Tumors (mRECIST) and patient survival is poorly defined.

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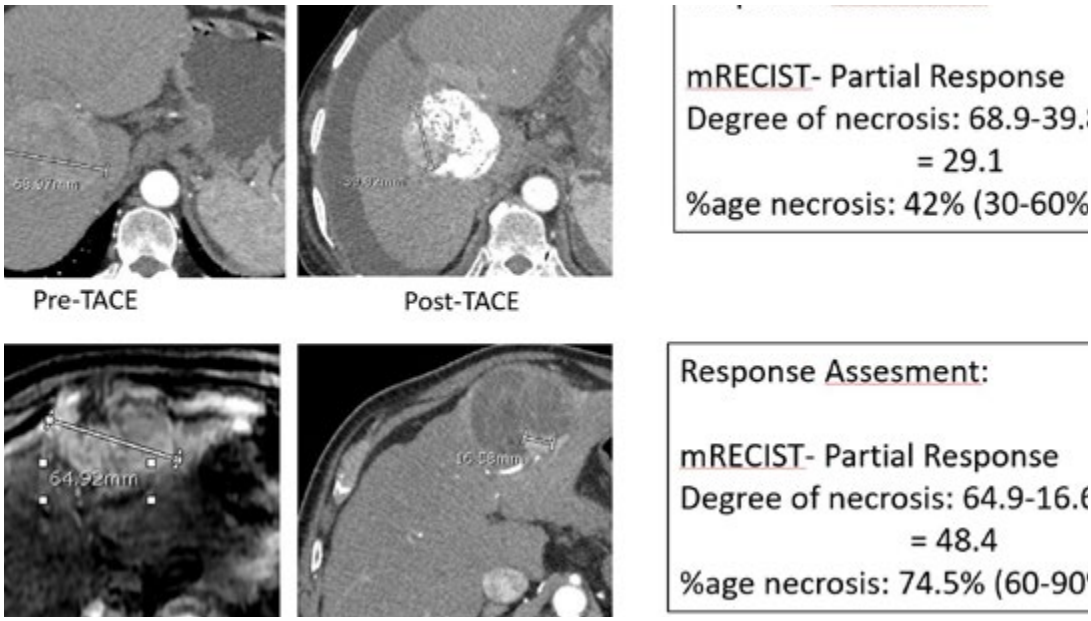
Partial Response is defined as atleast a 30% reduction in enhancing tumor diameter. Hence lesions showing 30% or 90% necrosis are categorized into this broad category without considering different survival outcomes. The purpose of this study was to determine short-term survival outcomes [3-year Overall Survival (3-yr OS) and Progression free-survival (PFS)] among patients who achieved variable degrees of tumour necrosis after the first session of TACE. **Methods:** TACE interventions were retrospectively reviewed. Response assessment was done using mRECIST criteria. The percentage of necrosis after TACE was stratified into five groups- 0%-30%, 30%-60%, 60%-90%, 90%-100% and 100% necrosis. Additional relevant clinical data was also recorded. **Results:** The Median Overall Survival (OS) was significantly higher in the complete response versus partial response group [27.4 months versus 17.6 months, p=0.01]. Based on the degree of tumour necrosis, tumours having 60%-90% tumour necrosis after the first TACE session had a short medial OS and progression-free survival (PFS) as compared to those with >90% tumour necrosis [Median OS 17.5 months vs 27.7months, PFS 15.3 months vs 17.9 months). Tumor size >5cm (vs <5cm, p= 0.02), higher MELD Na score (P-0.03) and presence of post-embolization syndrome (p-0.02) were associated with reduced overall survival and progression-free survival. Multivariate Cox-regression analysis showed that the degree of tumour necrosis >60% (vs <60% HR-0.169, p=0.002), tumour size (HR-1.1, p=0.013) and MELDNa score (HR- 1.07, p=0.01) were independent risk factors for overall survival. Subgroup analysis of tumours <5cm revealed that patients having initial tumour necrosis >60% after 1st TACE had better overall survival than those with <60% initial tumour necrosis (18.4 months vs 28.8 months, p= 0.002). **Conclusion:** We demonstrated that the degree of the initial response to TACE in the form of tumour necrosis had an impact on the overall survival of patients with those having >90% tumour necrosis had higher overall survival and near progression free survival than those with <90% survival. The main factors affecting the overall survival apart from the degree of tumor necrosis were baseline tumor size and MELD score. Interestingly no significant difference in the survival outcomes was noted among those with 90%- <100% necrosis as compared to those with complete response (100% necrosis). These results imply that near complete tumor necrosis could be a favourable end point especially in patients with compromised liver functions. These findings may inform treatment decision following first TACE.



Disclosures: Rishabh Jain: Nothing to Disclose, Amar Mukund: Nothing to Disclose, Yashwant Patidar: Nothing to Disclose, Shiv Kumar Sarin: Nothing to Disclose

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3541 | HEPATOCYTE SPECIFIC ATP1A1 KNOCK-OUT MICE DEVELOPS SPONTANEOUS PRIMARY LIVER MALIGNANCY ASSOCIATED WITH THE METABOLIC DISTURBANCES OF MASH- RELATED HCC

Utibe-Abasi Udoh[1] PRADEEP RAJAN[1] Juan Sanabria[2] Mathew Schade[2] Jacqueline Sanabria[2] Sandrine Pierre[2] Juan Sanabria[3]

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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD), including its inflammatory subtype, steatohepatitis (MASH), affects over 30% of the world population as the highest contributor to the global burden of chronic liver diseases. MASH can lead to cirrhosis, liver failure and hepatocellular carcinoma (HCC). HCC is the most common type of liver cancer and the fastest growing cause of cancer-related death worldwide. Nevertheless, there is a gap of knowledge on both its molecular pathogenesis and effective therapy, especially for advanced disease, resulting in its dismal prognosis. Our group described the role of the α1-Na/K-ATPase (ATP1A1) as a tumor suppressor in MASH-related HCC. ATP1A1 dysregulated signaling that follows oxidative stress leads to the activation of the PI3K-Akt pro-survival pathway, conducive to upregulation of the anti-apoptotic protein survivin, a potent driver of cell division and tumorigenesis. Therefore, we hypothezised that hepatocyte specific deletion of the *Atp1a1* gene will induce the development of HCC emulating MASH associated protein and metabolic disturbances. **Methods:** Hepatocyte- specific ATP1A1 conditional knock out (KNO) mice were generated by Cre/LoxP method. A two-step crossing was performed between a transgenic mouse expressing Cre recombinase under the control of the mouse albumin promoter (Albumin-Cre, Stock No: 003574, Jackson Laboratory, Bar Harbor, CA), and a mouse in which *Atp1a1* alleles have been flanked (floxed) at the LoxP sites. The floxed mice were designed to have exon 15-18 excised when crossed with the Cre-expressing mice. Gene deletion was confirmed by PCR genotyping and ATP1A1 expression was measured by immunofluorescence staining, confocal microscopy, and western blotting. RNA sequencing was performed for signaling pathways. Survivin and proteins expression were elucidated by ELISA and standard immunoblotting. Liver morphology was evaluated on H&E slides. **Results:** Mice present hepatocyte-specific reduction of more than 90% of ATP1A1 (*Fig. 1*). The level of survivin in the liver tissues of the APT1A1 KNO mice was significantly higher when compared to wild type counterparts ($p<0.01$). The RNA sequencing data showed decreased expression of *Atp1a1*, increased expression of *Birc5* (that encodes Survivin), *Rps6kl1* (that encodes Ribosomal protein S6) and genes that play key roles in the PI3K-Akt pathway. Our histology results revealed the presence of malignancy in the livers of the ATP1A1 KNO mice at 7-9 weeks of age (*Fig.1*), with the presence of Mallory- Denk bodies (emulating MASH-related HCC). **Conclusion:** Hepatocyte specific deletion of the *Atp1a1* gene increases ATP1A1 signalling with the development of malignancy that emulates MASH-related HCC. Our findings uncover the unequivocal mechanistic role of the ATP1A1 protein and its signalling pathway in MASH-related HCC, revealing a novel potential for ATP1A1- targeted therapy for clinical HCC.

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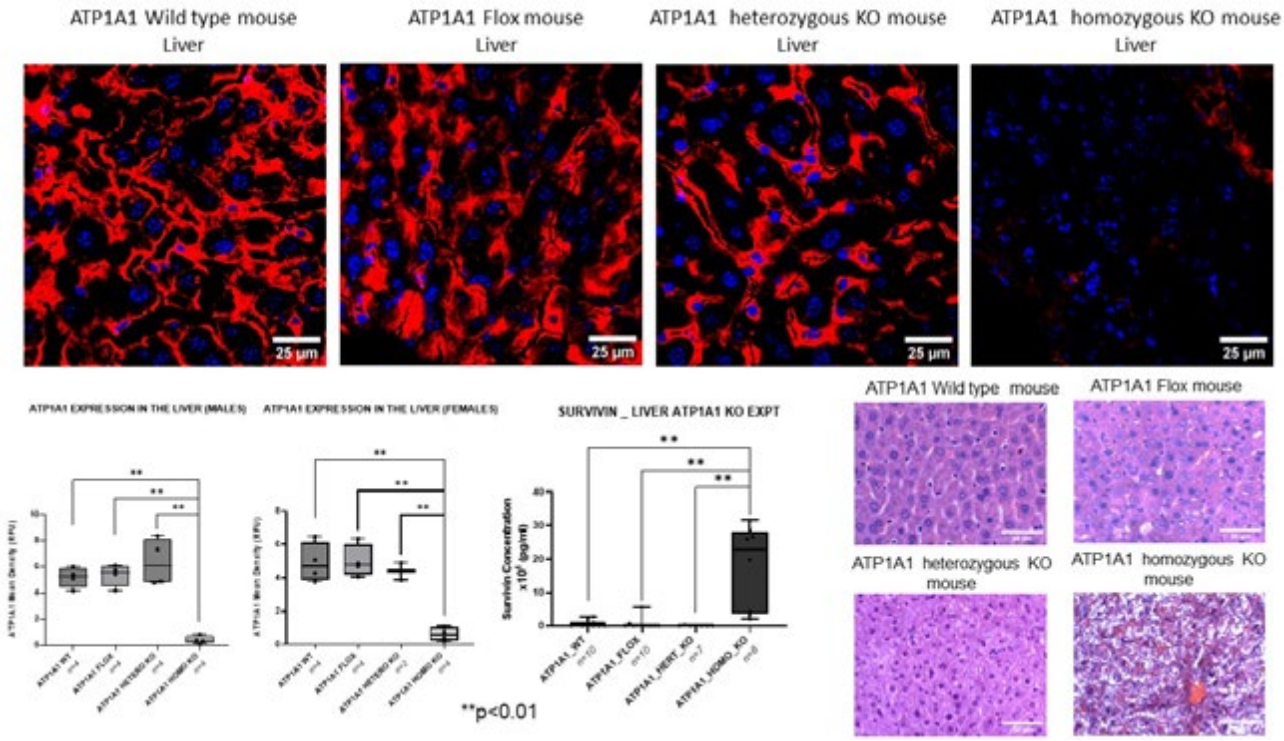

Disclosures: Utibe-Abasi Udoh: Nothing to Disclose, PRADEEP RAJAN: Nothing to Disclose, Juan Sanabria: Nothing to Disclose, Mathew Schade: Nothing to Disclose, Jacqueline Sanabria: Nothing to Disclose, Sandrine Pierre: Nothing to Disclose, Juan Sanabria: Nothing to Disclose

3542 | NONVIRAL HCC IS INDEPENDENTLY ASSOCIATED WITH POORER SURVIVAL AS COMPARED TO VIRAL HCC: A U.S. POPULATION-BASED STUDY

Elizabeth Garcia[1] *Nicholas Chien*[2] *Yee Hui Yeo*[3] *Mindie Nguyen*[2] *Ramsey Cheung*[2]

[1]*Stanford University,* [2]*Stanford University Medical Center,* [3]*Cedars-Sinai Medical Center*

Background: HCC remains one of the most common cancer deaths in the U.S. with a changing epidemiology due to the rise of obesity-related metabolic liver disease. Prior studies from single or referral centers have report disparities of HCC mortality due to viral versus nonviral etiologies, but U.S. population-based and trend data are limited. We aimed to evaluate temporal changes in survival rates of HCC patients related to viral versus nonviral etiologies. **Methods:** The study cohort included patients ≥ 67 years from the SEER-Medicare linked database with HCC diagnosed via the International Classification of Diseases-Oncology-3 codes, site: C22.0 and histology: 8170-8175 and excluded those without HCC prior to Medicare coverage, prior malignancies, or death certificates. We used joinpoint analysis and annual percentage change (APC) to evaluate trends in median survival rates of HCC patients. **Results:** We analyzed 47,113 HCC patients, 20,127 (42.7%) with viral (2,199 HBV, 14,374 HCV, 2873 HBV/HCV) and 26,986 (57.3%) with nonviral HCC (11,149 NAFLD, 5,453 ALD, and 9,313 other). The cohort was overall 71.6% male, 17.8% Hispanic, 72.3% White, 11.5% Black, 14.3% Asian, 1.42% other race, 66.1% from urban area, 46.9% cirrhosis (14.3% compensated, 32.6% decompensated), 10.5% with HCC surveillance history, and with mean age of 71.2 (SD 9.5) years and mean CCI (SD 7.4) 7.02. Patients with nonviral HCC (vs. viral HCC) were older (73.8±8.7 vs. 67.6±9.3), more likely White (81.0% vs. 61.7%), noncirrhotic (64.9% vs. 37.2%), and without history of HCC surveillance (94.3% vs. 82.9%), all P<0.001. Nonviral (vs. viral) HCC patients were also more likely to present with larger tumors (7.1 vs. 5.1 cm), extrahepatic metastasis (32.4 vs. 26.1%), less likely to receive liver transplant (1.9 vs. 8.2%), liver resection (4.9 vs. 6.4%), and much more likely to have no or unknown HCC treatment (69.7 vs. 45.3%), all P<0.001. Between 2000 and 2017, median survival rates have increased significantly for noncirrhotic as well as cirrhotic patients in both the viral (Fig 1A, APC 3.74 and 2.45) and nonviral (Fig 1B, APC 8.58 and 5.96) HCC groups, all P<0.05. However, survival remained poor for both groups (5-year cumulative survival 16.4% for viral and 12.0% for nonviral overall). On multivariable

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Cox's regression analysis adjusting for age, sex, race and ethnicity, socioeconomic status, urbanization, CCI, tumor stage, cirrhosis status, HCC treatment, time period (pre and post 2010), nonviral etiology (vs viral) was independently associated with 30% lower survival (adjusted HR=0.70, 95%CI 0.68-0.72, (*P*<0.001). **Conclusion:** Survival rates have increased over time for both viral and nonviral but they remained dismal. Nonviral HCC was independently associated with 30% lower survival as compared to viral HCC patients. Further efforts are needed to improve HCC surveillance and treatment especially for nonviral HCC.

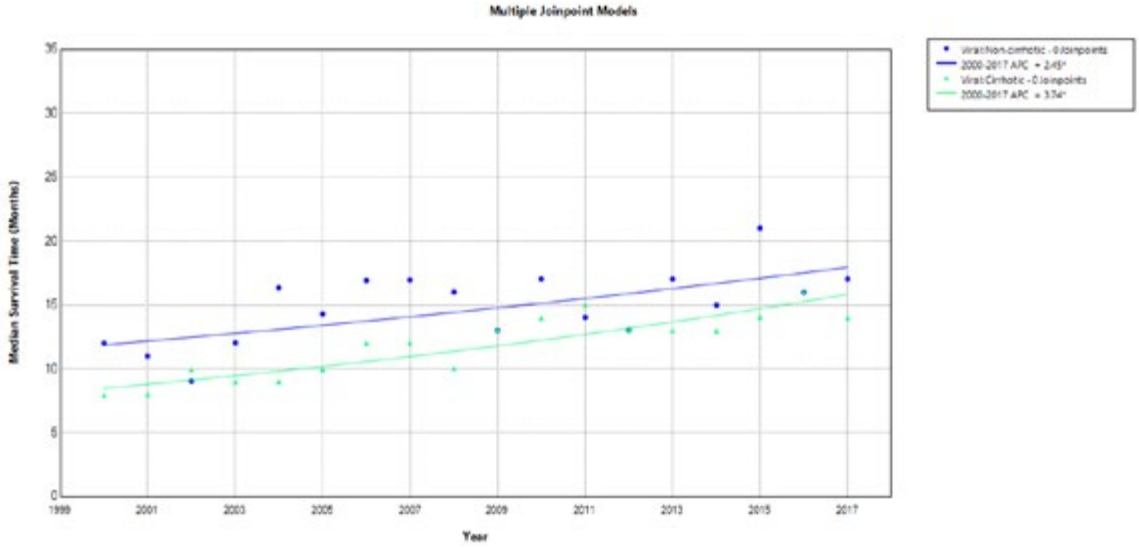

Figure 1A. Multiple joinpoint model and average annual percent change of median survival of viral non-cirrhotic vs cirrhotic patients from 2000-2017

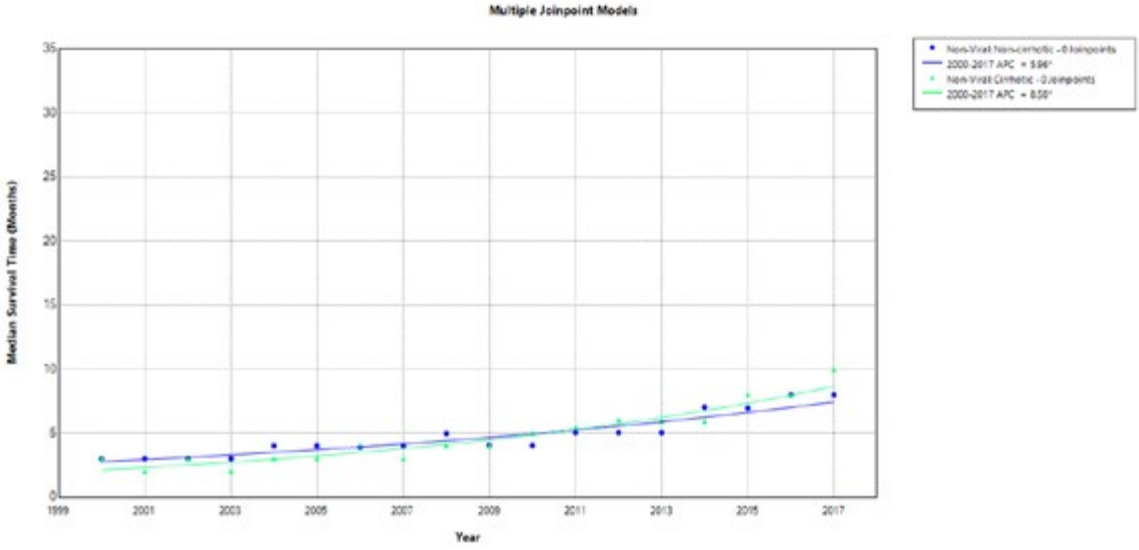

Figure 1B. Multiple joinpoint model and average annual percent change of median survival of non-viral non-cirrhotic vs cirrhotic patients from 2000-2017

Disclosures: Elizabeth Garcia: Nothing to Disclose, Nicholas Chien: Nothing to Disclose, Yee Hui Yeo: Nothing to Disclose, Mindie Nguyen: Nothing to Disclose, Ramsey Cheung: Nothing to Disclose

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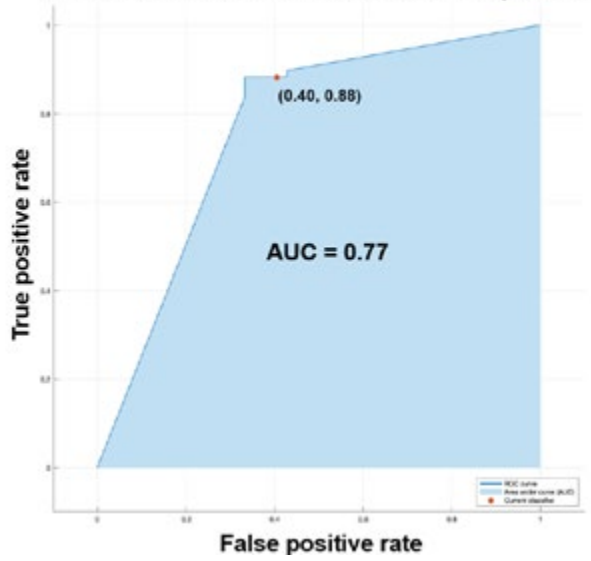
3543 | PREDICTION OF IMMUNE CHECKPOINT INHIBITOR TREATMENT RESPONSE IN HEPATOCELLULAR CARCINOMA USING CT RADIOMICS

Ji Hye Min[1] Pin-Jung Chen[2] Touseef Qureshi[2] Yibin Xie[2] Linda Azab[2] Lixia Wang[2] Hyunseok Kim[3] Debiao Li[2] Ju Dong Yang[4]

[1]Samsung Medical Center, Sungkyunkwan University School of Medicine, [2]Cedars-Sinai Medical Center, [3]Baylor College of Medicine, [4]Cedars-Sinai Medical Center

Background: Immune checkpoint inhibitor (ICI)-based immunotherapy has become a new standard of care for hepatocellular carcinoma (HCC). Understanding predictive biomarkers for treatment response to ICI is crucial for improving patient selection and maximizing clinical benefit. We aim to examine the artificial intelligence-guided radiomic features in pre-treatment computed tomography (CT) images of responders and non-responders to HCC treatment and develop a model for predicting ICI treatment response in HCC patients. **Methods:** This retrospective study included 55 consecutive patients with HCC who received ICI treatment (Pembrolizumab, Nivolumab, Atezolizumab, Durvalumab, and tremelimumab) between June 2016 and October 2023 at a tertiary liver transplant referral center. We assessed triphasic CT images within 3 months of ICI initiation. Radiomics features of the entire liver were extracted from arterial and portal venous phase CT images. The radiomic features of the responder group were compared to those of the non-responder group, and a prediction model was developed through a machine learning algorithm. The Nearest Neighbor classifier was trained to perform binary classification and tested using a three-fold cross-validation. **Results:** The cohort had a median age of 69 (IQR 63-73) years and 76.4% were male. The median ICI treatment duration was 19 (IQR 10-52) weeks, and 35 (63.6%) patients received combination therapies. Among them, 36 (65.5%) patients had a previous treatment history, while 19 (34.5%) were treatment-naive. The pre-treatment Barcelona Clinic Liver Cancer stages were A in 4 patients, B in 16 patients, C in 30 patients, and D in 5 patients. Following ICI treatment, 38.2% of patients (21/55) were responders (complete or partial response), and the remaining 61.8% (34/55) were non-responders. More than 5000 predefined radiomic features were extracted, with nearly 200 found predictive of HCC treatment response. Only 10 randomly selected significant features were used for the classification model. The performance of the Nearest Neighbor Machine algorithm estimatmed a sensitivity, specificity, and accuracy, as 77.9%, 76.2%, and 77.3%, respectively. **Conclusion:** In this pilot study, we extracted conventional CT radiomic features and developed a machine learning model using pre-treatment CT images of HCC patients. The model can predict treatment response in HCC patients following ICI treatments. These findings indicate that radiomic features have the potential to enhance patient selection, thereby maximizing clinical benefits. As promising predictive imaging biomarkers, radiomic features could play a significant role in the future. Larger scale validation is planned after integrating clinical factors to develop a comprehensive prediction model to improve the model accuracy.

Figure. ROC Curve for Classifying Responders vs. Non-Responders in HCC Patients Treated with Immune Checkpoint Inhibitor



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3544 | TUMOR-DERIVED CIRCULATING CARBONIC ANHYDRASE 9 AS A PREDICTOR OF RESISTANCE TO ATEZOLIZUMAB AND BEVACIZUMAB IN ADVANCED HEPATOCELLULAR CARCINOMA

Yu Sato[1] Takahiro Kodama[1] Machiko Kai[1] Kazuki Maesaka[1] Ryo Takahashi[1] Shuhei Yamamoto[1] Kumiko Shirai[1] Akira Doi[1] Kazuhiro Murai[1] Yuki Tahata[1] Yoshinobu Saito[2] Hayato Hikita[2] Tomohide Tatsumi[1] Tetsuo Takehara[1]

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Background: Immunotherapy has revolutionized hepatocellular carcinoma (HCC) treatment, but survival benefits remain limited. This study aimed to identify novel blood-based biomarkers and molecular mechanisms of resistance to atezolizumab and bevacizumab (Atez/Bev) therapy for advanced HCC patients. **Methods:** Using Proximity Extension Assay (PEA) technology from O-link, we profiled 184 pre-treatment plasma proteins from immune-oncology and metabolism panels in 69 unresectable HCC patients undergoing Atez/Bev therapy. We sought proteins associated with initial progressive disease (PD) by the Response Evaluation Criteria in Solid Tumors (RECIST). A candidate protein was overexpressed in the murine HCC cell line Hep55.1c, and its impact on anti-VEGF/PD-L1 antibody efficacy was assessed in a subcutaneous syngeneic model in immunocompetent mice. Pre-treatment plasma levels of the candidate protein were evaluated by Enzyme-Linked Immunosorbent Assay (ELISA) in 109 HCC patients treated with Atez/Bev, examining their association with clinical outcomes **Results:** PEA identified higher levels of circulating proteins, including Carbonic anhydrase 9 (CA9), IL-8, CCL20, CSF-1, and IL-6, in patients with initial PD compared to non-PD patients. Plasma CA9 levels correlated positively with tumoral CA9 mRNA levels in 34 surgically resected human HCC patients. Single-cell transcriptome analysis of human HCC tissue revealed CA9 was mainly expressed in malignant cells. Overexpression of CA9 in murine HCC cells did not affect their syngeneic tumor growth but reduced the efficacy of anti-VEGF/PD-L1 antibodies. In the validation cohort of 109 HCC patients who underwent Atez/Bev therapy, the disease control rate (DCR) was 63.0% by RECIST with median progression-free survival (PFS) and overall survival (OS) of 126 and 598 days, respectively. Pre-treatment plasma CA9 levels were significantly higher in PD patients. High CA9 levels were linked to a significantly higher PD rate (56.4 vs. 31.9%, p=0.013) compared to low CA9 levels. The median PFS (78 vs. 245 days, p=0.0010) and OS (355 vs. 598 days, p=0.0002) were significantly shorter in patients with high CA9 levels. Multivariate COX proportional hazard analysis showed plasma CA9 level as an independent predictor of shorter PFS. **Conclusion:** Tumor-derived CA9 conferred resistance to anti-VEGF/PD-L1 antibodies in HCC. Plasma CA9 levels predicted clinical outcomes in advanced HCC patients treated with Atez/Bev therapy.

Disclosures: Yu Sato: Nothing to Disclose, Takahiro Kodama: Chugai Pharmaceuticals: Speaking and Teaching, Astrazeneca: Speaking and Teaching, Eisai Co Ltd: Speaking and Teaching, Machiko Kai: Nothing to Disclose, Kazuki Maesaka: Nothing to Disclose, Ryo Takahashi: Nothing to Disclose, Shuhei Yamamoto: Nothing to Disclose, Kumiko Shirai: Nothing to Disclose, Akira Doi: Nothing to Disclose, Kazuhiro Murai: Nothing to Disclose, Yuki Tahata: Nothing to Disclose, Yoshinobu Saito: Nothing to Disclose, Hayato Hikita: Nothing to Disclose, Tomohide Tatsumi: Nothing to Disclose, Tetsuo Takehara: Nothing to Disclose

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3545 | TRENDS IN THE UTILIZATION OF SYSTEMIC THERAPY FOR TREATMENT AND PALLIATION IN PATIENTS WITH ADVANCED HCC IN THE ERA OF IMMUNOTHERAPY

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Background: Modern immunotherapy with checkpoint inhibitors revolutionized cancer treatment and outcomes. This study aims to demonstrate how immunotherapy has impacted the landscape of systemic treatment and palliative care in patients with advanced hepatocellular carcinoma (HCC) in modern times. **Methods:** Retrospective analysis using the National Cancer Database (NCDB) was performed for patients with clinical stages T3b/T4 and stage IV HCC treated from 2010 to 2021. A multivariable analysis was performed using the Cox proportional hazard for survival comparisons and a logistic regression model to study immunotherapy use. **Results:** There was a total of 54,285 patients. There was an increase in the use of immunotherapy from 0.27% in 2010 to 33.80% in 2021. The median overall survival (OS) was 2 months among patients who did not receive any therapy and 11.79 months among patients who received both chemotherapy and immunotherapy. The group of patients receiving only chemotherapy and only immunotherapy had median survivals of 7.20 and 7.46 months, respectively. Multivariable hazard regression analysis demonstrated significantly better survival in patients who received immunotherapy (HR 0.59, 95% CI 0.57-0.62). Factors impacting no receipt of immunotherapy included older age, higher comorbidities, Hispanic ethnicity, lack of insurance, treatment at community hospitals, and residential regions of low-income levels in our multivariable logistic regression. About 13.43% of patients received some form of palliative care (n=7,290). Among these patients, the proportion treated with systemic therapy for palliation (n=1,543) almost doubled, from 14.41% in 2010 to 25.32% in 2021. Compared to surgical palliation, both radiation (HR 0.61, 95% CI 0.52-0.71) and systemic palliative (HR 0.59, 95% CI 0.51-0.69) therapies were associated with significantly better survival. **Conclusion:** There was a significant increase in the use of immunotherapy for patients with advanced HCC from 2010 to 2021, and its use was associated with significant OS benefits in patients with advanced HCC. Contemporaneous with the rise of immunotherapy use, we observed a large shift toward systemic therapy use for palliative care and a significant OS benefit of systemic palliative therapy compared to those who undergo surgical modality of palliation. Notable social factors associated with not receiving immunotherapy included Hispanic ethnicity, residential areas of low-income levels, and lack of insurance.

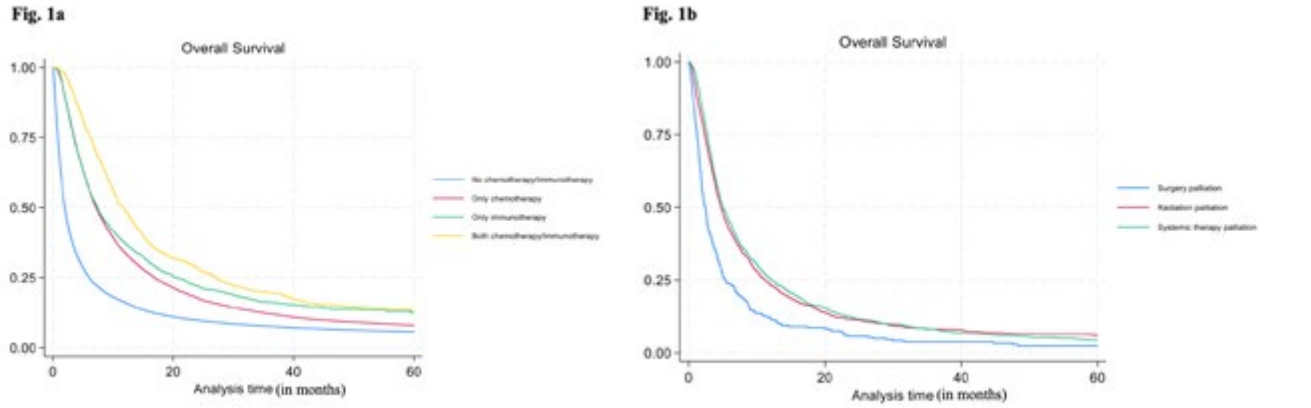

Figure 1. Overall survival difference by receipt of chemotherapy and/or immunotherapy (1a) and by type of palliative therapy among those undergoing palliation (1b)

Disclosures: Aryanna Sousa: Nothing to Disclose, Qusai Al Masad: Nothing to Disclose, Paola Pena: Nothing to Disclose, Ponnadai Somasundar: Nothing to Disclose, Thaer Abdelfattah: Nothing to Disclose, Steve Kwon: Nothing to Disclose

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3546 | ADVANCING SURVIVAL: A 45-YEAR ANALYSIS SHOWING IMPROVEMENT IN HEPATOCELLULAR CARCINOMA TREATMENT OUTCOMES

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Background: Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer and represents a major global health burden. The incidence of HCC has been increasing worldwide, largely due to the persistent prevalence of chronic liver diseases such as hepatitis B, hepatitis C, and metabolic liver disease. These underlying conditions contribute to the complexity and difficulty in managing HCC. Historically, the survival rates for HCC patients have been dismally low due to the cancer's aggressive nature and the limited efficacy of older treatment modalities.Over the past several decades, there has been a paradigm shift in the management of HCC, driven by advancements in medical imaging, a deeper understanding of the disease's molecular biology, and the development of novel therapeutic approaches. This study specifically examines the impact of these evolving treatment strategies on the long-term survival outcomes of HCC patients. This study aimed to explore long-term trends in survival outcomes for HCC patients, assessing the evolution of treatment modalities over the last 45 years. **Methods:** Utilizing data from the Surveillance, Epidemiology, and End results (SEER) database, this study examined survival trends for 40,465 HCC patients diagnosed from 1975 to 2020. Various treatment modalities, including chemotherapy, different forms of radiation therapy, and surgical interventions, were analyzed using a Cox proportional hazards model. **Results:** The survival analysis demonstrated consistent improvements across each five-year cohort from 1975-1979 to 2020+, with the most notable improvement in survival observed in the 2015-2019 cohort (HR 0.24, p <0.001). Chemotherapy was associated with a 28% improvement in survival outcomes (HR of 0.72, p <0.001). Further analysis of radiation therapy techniques showed significant survival benefits with the use of radioactive implants and radioisotopes post-1988. **Conclusion:** The dramatic improvements in survival outcomes over time align with advancements in HCC treatment protocols, particularly post-2015. The analysis confirms the crucial role of chemotherapy and innovative radiation therapies in enhancing survival rates, highlighting the progress made in oncological care of HCC. Further studies are needed to identify the key factors contributing to the improved survival during this time frame, guiding future research and optimizing effective strategies.While our results are promising, limitations due to data censoring and missing staging data need to be acknowledged. Further studies are required to consolidate our findings and expand on the long-term outcomes for the most recent cohorts.

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Table 1. Cox Proportional Hazards Model (n=40,465)

Characteristic	HR[1]	95% CI[1]	p-value
Year Group			
1975-1979	—	—	
1980-1984	0.85	0.78, 0.93	**<0.001**
1985-1989	0.75	0.69, 0.81	**<0.001**
1990-1994	0.66	0.61, 0.71	**<0.001**
1995-1999	0.59	0.55, 0.64	**<0.001**
2000-2004	0.49	0.46, 0.53	**<0.001**
2005-2009	0.42	0.39, 0.45	**<0.001**
2010-2014	0.39	0.36, 0.42	**<0.001**
2015-2019	0.24	0.22, 0.26	**<0.001**
2020+	0.23	0.21, 0.25	**<0.001**
Chemotherapy Treatment			
No/Unknown	—	—	
Yes	0.72	0.70, 0.74	**<0.001**
Radiation Treatment			
None/Unknown	—	—	
Beam radiation	1.04	0.98, 1.10	0.2
Combination of beam with implants or isotopes	0.88	0.60, 1.28	0.5
Other than beam radiation (1973-1987 cases only)	0.52	0.07, 3.68	0.5
Radiation, NOS method or source not specified	0.66	0.48, 0.90	**0.010**
Radioactive implants (includes brachytherapy) (1988+)	0.71	0.65, 0.78	**<0.001**
Radioisotopes (1988+)	0.56	0.52, 0.61	**<0.001**
Recommended, unknown if administered	0.79	0.64, 0.98	**0.030**
Refused (1988+)	0.98	0.84, 1.14	0.8
Histologic Type			
8170/3: Hepatocellular carcinoma, NOS	—	—	
8171/3: Hepatocellular carcinoma, fibrolamellar	0.61	0.50, 0.75	**<0.001**
8172/3: Hepatocellular carcinoma, scirrhous	0.62	0.38, 1.02	0.058
8173/3: Hepatocellular carcinoma, spindle cell variant	2.68	1.67, 4.31	**<0.001**
8174/3: Hepatocellular carcinoma, clear cell type	0.98	0.82, 1.17	0.9
8175/3: Hepatocellular carcinoma, pleomorphic type	0.62	0.16, 2.49	0.5
Race			
White	—	—	
Black	1.00	0.97, 1.04	0.9
Other (American Indian/AK Native, Asian/Pacific Islander)	0.90	0.87, 0.92	**<0.001**
Unknown	0.58	0.46, 0.74	**<0.001**

[1]HR = Hazard Ratio, CI = Confidence Interval

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3547 | COMPLEMENTING LOCOREGIONAL THERAPIES WITH IMMUNE CHECKPOINT INHIBITORS IN PATIENTS WITH ADVANCED HCC IS TOLERABLE AND IMPROVES DISEASE-FREE SURVIVAL: REAL-WORLD DATA AND EXPERIENCE

Tarek Hassanein[1] Julian Diaz-Moreno[1] Ahmed Atalla[1] Usman Gul[1] Noha Abdelgelil[1] Amir Hassanein[1] Fatma Barakat[2] Anna Hefner[1] Deanna Oliver[1]

[1]Southern California Liver Centers, [2]SCTI Research Foundation

Background: The prevalence and incidence of HCC continues to be on the rise in the US. The US FDA has approved several combinations of Immune Checkpoint Inhibitors (ICI) for the treatment of advanced unresectable HCC. Locoregional treatment are established in the guidelines as part of the management of advanced HCC. We report on the use and significant impact of complementing locoregional therapies (LRT) with ICIs ± VEGF Inhibitors in patients with HCC in a non-academic, community-based single Liver center. **Methods:** Between May 2018 and April 2024, 430 patients (pts) diagnosed with HCC were seen. Treatment with ICI was initiated in 119 patients with HCC as adjunctive therapy to LRT (primarily TACE ± RFA and Y-90). Of those, 100 received at least 2 doses and are the subjects of this analysis. ICI was infused per the package insert and pts were followed per standard of care. Labs, imaging, further locoregional interventions, disease progression, transplantation candidacy, and survival were analyzed. **Results:** 82.4% were males. 69.8% Hispanic, 90.8% white. Mean age was 64.8±7.6 years. Over 85% had History of HCV. All were Child-Pugh A or B. Almost 60% of pts were BCLC A3 or B prior to ICI start. *ICI treatment:* 52% were treated with nivolumab (nivo) only, 26% with nivolumab/ipilimumab (nivo/ipi), 13% with atezolizumab/bevacizumab (ate/bev), and 9% with durvalumab/tremelimumab (Imf/Imj). 6 pts received two different ICI regimens with 3-6 months washout period in between e.g. ate/bev followed by nivo. 1 pt receeived 3 ICI regimens. *Safety and Tolerability:* Liver enzymes and MELD score were stable throughout treatment. Across all regimens, pts experienced manageable side effects such as nausea, vomiting, and fatigue. However, pts with ate/bev had the most permanent discontinuation of their ICI due to severe side effects (see table). It was noted that in a subset of pts on nivo significant rash leading to holding nivo presented later in their treatment course (>2 years). Recurrence was in 4 pts while on ICI and 8 pts after ICI discontinuation. 8% received a liver transplant. 12% of pts became MILAN eligible post ICI. Median duration on ICI was 15 (1-58) months. There was a statistically significant (p-values <0.05) decrease in the average number of viable lesions as well as the average size of viable lesions post ICI treatment. *Survival:* 78.5% alive. Median survival from HCC diagnosis was over 4 years and 2 years with HCC-free survival. **Conclusion:** In a community-based single center Liver clinic, the most tolerated ICI regimen with the least discontinuations was nivolumab only followed by nivolumab/ipilimumab. Atezolizumab/bevacizumab regimen was the least tolerated. More real-world data is needed on the side effects of durvalumab/tremelimumab. The combination of LRT and ICI in HCC re-confirms that it is: 1) safe and well-tolerated, 2) more effective than LRT alone with fewer need of LRT, and 3) prolongs disease stability and overall transplant-free survival.

	Number of patients	Rate of ICI regimen discontinuation	Reasons for discontinuation
Nivo only	52	8%	Rash, lymphedema
Nivo/Ipi	26	15.4%	Rash, severe immune reaction
Ate/Bev	13	92.3%	Abdominal bleeding, rash, and/or immune reaction
Imf/Imj	9	44.4%	Rash, cardiac-related

Disclosures: Tarek Hassanein: Nothing to Disclose, Julian Diaz-Moreno: Nothing to Disclose, Ahmed Atalla: Nothing to Disclose, Usman Gul: Nothing to Disclose, Noha Abdelgelil: Nothing to Disclose, Amir Hassanein: Nothing to Disclose, Fatma Barakat: Nothing to Disclose, Anna Hefner: Nothing to Disclose, Deanna Oliver: Nothing to Disclose

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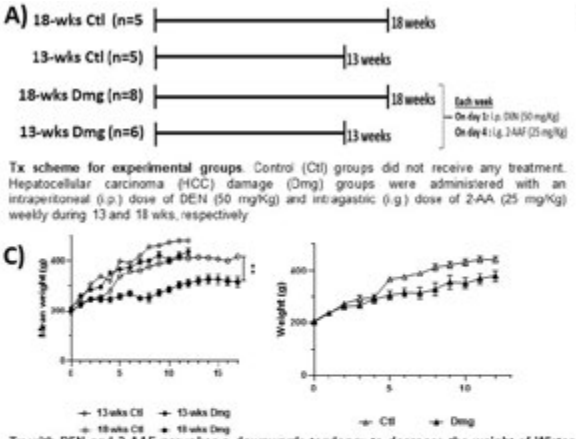
3548 | EVOLUTION OF HEPATOCARCINOGENESIS INDUCED WITH CHRONIC ADMINISTRATION OF DEN AND 2-AAF DURING 13 AND 18 WEEKS IN WISTAR RATS

LAURA SANCHEZ-OROZCO[1] Marina Campos-Valdez[1] Jaime Sánchez-Meza[1] José Domínguez-Rosales[1] Juliana Godínez-Rubí[1] Sarai Rodríguez-Reyes[1] Erika Martínez-López[1] Carmen Gurrola-Díaz[1] Adriana Salazar-Montes[1]

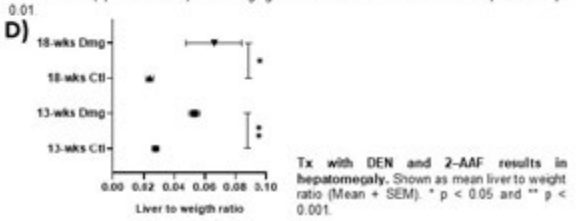
[1]Universidad de Guadalajara

Background: Among the models in liver cancer studies, *in vivo* induction of hepatocellular carcinoma (HCC) through the administration of carcinogenic agents, such as diethylnitrosamine (DEN) and N-(2-Fluorenyl) acetamide (2-AAF) are commonly used. Aim: to evaluate the changes caused by the chronic administration of DEN and 2-AAF during 13 and 18 weeks (wks) in Wistar rats. **Methods:** Male Wistar rats (180-200 g) were distributed into 4 groups: 1) Control 18 wks (18-wk Ctl), 2) Damage 18 wks (18-wk Dmg), 3) Control 13 wks (13-wk Ctl), and 4) Damage 13 wks (13-wk Dmg). 13-wk Dmg and 18-wk Dmg were weekly treated: DEN (50 mg/Kg, i.p) and 2-AAF (25 mg/Kg, i.g.) were administered on day one and third day, respectively. Treatment (Tx) was maintained during 13 and 18 wks respectively (Figure 1A). Subsequently, the animals were sacrificed and liver tissue and serum were collected for histological, biochemical and gene expression change analysis. Statistical analysis was carried out in the program GraphPad Prism version 8, with Mann–Whitney U test or t-test. A p value of < 0.05 was considered significant. **Results:** Tx with DEN and 2-AAF affected survival; in the 18-wk Dmg group, survival decreased to 62.5% (n=8) at the tenth week. When the 13-wk Dmg group was included (with a 100% survival) the survival percentage until thirteenth wk was 78.5% (n= 14) (Figure 1B). Tx with DEN and 2–AAF tended to decrease total weight (Figure 1C), and changes in the liver tissue were observed, such as pale coloration, differentiated nodules, and hepatomegaly (in a lesser degree in the 13-wk Dmg group) (Figure 1D). It is important to highlight that there was heterogeneity in damage severity among the animals in both groups, which was also observed at the histological level with loss of normal hepatocyte architecture (lobular structure disorder), increase in atypical cells, and collagen accumulation. In the 18-wk Dmg group, a probable lung metastasis (evident macroscopic damage and histological alterations) was found. Indicators of hepatic function (ALT, AST, ALKP, GGT, and total proteins) were significantly altered in both Dmg groups. At the gene expression level, Tx significantly changed the expression of *CAT, SOD, COL1A,* and *TGFB1*; *IL6* had significant changes only in the 18-wk Dmg group. **Conclusion:** 13-wk DEN and 2-AAF Tx is enough to find important macroscopic, histological, and gene expression alterations in all animals. However, 18-wk Tx shows a probable lung metastasis; in case of such results are proven, this could be a model to study the metastasis stage. The heterogeneity in the liver damage severity found in this model may seem like a disadvantage; however, heterogeneity of liver cancer among patients is observed in real life.

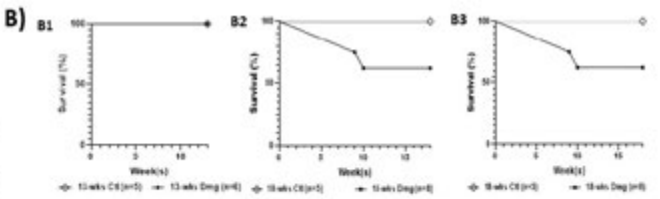


Tx scheme for experimental groups. Control (Ctl) groups did not receive any treatment. Hepatocellular carcinoma (HCC) damage (Dmg) groups were administered with an intraperitoneal (i.p.) dose of DEN (50 mg/Kg) and intragastric (i.g.) dose of 2-AA (25 mg/Kg) weekly during 13 and 18 wks, respectively

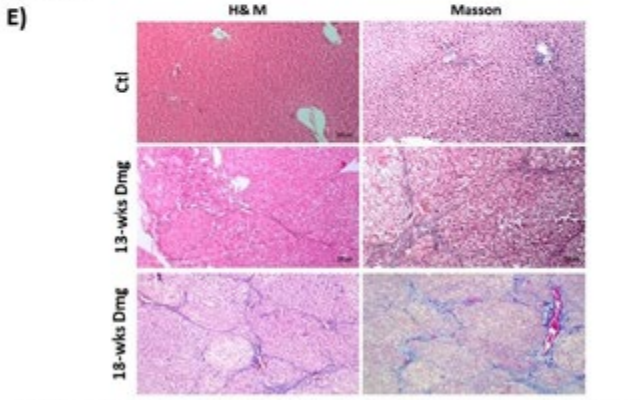
Tx with DEN and 2-AAF provokes a downwards tendency to decrease the weight of Wistar rats. On the left, weekly mean weights (Mean + SEM) during 18 and 13 weeks. The right graph shows results (up to 13 weeks) after merging data of animals from both treatment periods. ** $p > 0.01$



Tx with DEN and 2-AAF results in hepatomegaly. Shown as mean liver to weight ratio (Mean + SEM). * $p < 0.05$ and ** $p < 0.001$.



Survival rate in Wistar rats with liver injury induction by DEN and 2-AAF. Graphs B1) and B2) represent survival rate (%) after treatment during 13 and 18 weeks. B3) Survival rate (%) when the four groups were taken together.



Tx with DEN and 2-AAF provokes characteristic atypia of neoplastic cells. Loss of normal hepatocyte architecture (lobular structure disorder), increase in atypical cells and collagen accumulation.

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3549 | RELIABILITY RATE OF SPLEEN STIFFNESS MEASUREMENT IS ASSOCIATED WITH THE PRESENCE OF CIRRHOSIS OR PORTAL HYPERTENSION IN PATIENTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE

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Background: A reliability criterion for liver stiffness measurement (LSM) is currently applied to ensure that clinical decisions are not based on unreliable values. However, such criteria are not yet applied to spleen stiffness measurements (SSM). In the current study, we applied the same reliability criteria to SSM in patients with metabolic dysfunction-associated steatotic liver disease (MASLD) to estimate the frequency of unreliable scans and its association with severity. **Methods:** As currently applied to LSM (Boursier J et al. Hepatology 2013), SSM values were classified as very reliable when interquartile range (IQR)/median (M) is ≤10%, reliable when IQR/M is 10-30%, and unreliable when IQR/M is >30% in those with ≥ 10 valid measurements. A prospective, IRB-approved protocol with informed consent facilitated enrollment of 154 consecutive MASLD patients presenting to the Hepatology Clinic between November 2020 and May 2022 for simultaneous LSM and SSM measurements. Of these, 85 individuals had an upper endoscopy as standard of care within one year of SSM. The reliability of SSM was evaluated across various subgroups of the study population, including the presence or absence of cirrhosis, esophageal varices, thrombocytopenia, and LSM cut-offs as defined by the AASLD guidelines for advanced liver fibrosis (LSM ≥ 12 kPa) and Baveno VII criteria for compensated advanced chronic liver disease (cACLD) (LSM ≥ 15 kPa). LSM and SSM were performed using FibroScan 630 Expert by a single technician. **Results:** The median age of participants was 59 years (range 24-79 years), with a BMI of 33.7 ± 5.9 kg/m², and 46% were male. Among them, 125 had valid SSM measurements with an IQR/M of ≤30%, resulting in an unreliable rate of 22.4%. Patients with MASH cirrhosis were more likely to have a very reliable SSM than those without cirrhosis (21.3% vs 4.4%, p value 0.001) (Table 1). The presence of esophageal varices was associated with increased rates of **very reliable** SSM compared to those without esophageal varices (31.6% vs 6.4%, p value 0.004) (Table 1). Thrombocytopenia defined as platelet count < 150 k/cumm was associated with higher very reliable SSM rates compared to those with platelet counts ≥ 150 k/cumm (20.3% vs 4.9%, p value 0.007). The LSM cut-offs designated for ruling in advanced fibrosis and ruling in cACLD were not associated with predicting SSM reliability rates (p values 0.093 and 0.497, respectively) (Table 1). BMI across any of the subgroups were not statistically significantly different (Table 1). **Conclusion:** The likelihood of obtaining very reliable SSM is highest in patients with advanced MASLD, notably, in those with cirrhosis, esophageal varices, and/or thrombocytopenia. Although there is no statistical significance, there is a higher probability of unreliable SSM in those with lower LSM. Additionally, body mass index does not influence the reliability of SSM.

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Table 1. Reliability Rates of Spleen Stiffness Measurements Determined by Liver Disease Severity. SSM values were classified as **very reliable** when interquartile range (IQR)/median (M) is ≤10%, **reliable** when IQR/M is 10-30%, and **unreliable** when IQR/M is >30% in those with ≥ 10 valid measurements as currently applied to LSM.

Reliability Criteria	Cohort	Category		P value
-Cirrhosis		**Absent (n= 45)**	**Present (n= 80)**	0.001
Unreliable	28 (22.4)	17 (37.8)	11 (13.8)	
Reliable	78 (62.4)	26 (57.8)	52 (65.0)	
Very Reliable	19 (15.2)	2 (4.4)	17 (21.3)	
BMI, kg/m², mean ± SD	33.7 ± 5.9	34.3 ± 6.8	33.4 ± 5.4	0.385
-Esophageal Varices		**Absent (n= 47)**	**Present (n=38)**	0.004
Unreliable	14 (16.5)	11 (23.4)	3 (7.9)	
Reliable	56 (65.9)	33 (70.2)	23 (60.5)	
Very Reliable	15 (17.6)	3 (6.4)	12 (31.6)	
BMI, kg/m², mean ± SD	34.0 ± 6.0	34.4 ± 6.9	33.5 ± 4.8	0.503
-Platelet Count		**Platelets < 150 k/cumm (n= 64)**	**Platelets ≥ 150 k/cumm (n=41)**	0.007
Unreliable	24 (22.9)	9 (14.1)	15 (36.6)	
Reliable	66 (62.9)	42 (65.5)	24 (58.5)	
Very Reliable	15 (14.3)	13 (20.3)	2 (4.9)	
BMI, kg/m², mean ± SD	33.5 ± 5.9	33.1 ± 5.6	34.1 ± 6.3	0.398
-LSM		**< 12 kPa (n= 40)**	**≥ 12 kPa (n= 80)**	0.093
Unreliable	27 (22.5)	12 (30.0)	15 (18.8)	
Reliable	77 (64.2)	26 (65.0)	51 (63.8)	
Very Reliable	16 (13.3)	2 (5.0)	14 (17.5)	
BMI, kg/m², mean ± SD	33.7 ± 5.9	33.5 ± 6.4	33.9 ± 5.7	0.778
		< 15 kPa (n= 53)	**≥ 15 kPa (n=67)**	0.497
Unreliable	27 (22.5)	15 (28.3)	12 (17.9)	
Reliable	77 (64.2)	31 (58.5)	46 (68.7)	
Very Reliable	16 (13.3)	7 (13.2)	9 (13.4)	
BMI, kg/m², mean ± SD	33.7 ± 5.9	33.2 ± 6.2	34.2 ± 5.7	0.349

Disclosures: Elizabeth Williams: Nothing to Disclose, Regina Weber: Nothing to Disclose, Archita Desai: Nothing to Disclose, Raj Vuppalanchi: Eli LIlly: Advisor, GSK: Advisor, Madrigal: Advisor, Zydus Therapeutics: Grant/Research Support, Galectin Therapeutics: Grant/Research Support, Kowa: Grant/Research Support, Takeda: Grant/Research Support, GSK: Consultant, UBC: Consultant

3550 | UNLOCKING EPHX1-MEDIATED ALTERATIONS IN EICOSATRIENOIC ACID METABOLISM: NOVEL THERAPEUTIC TARGETS IN LIVER FIBROSIS ★

Hiroko Ikenaga[1] Tsutomu Matsubara[1] Masaru Enomoto[1] Misako Sato-Matsubara[1] Le Thi Thanh Thuy[1] NINHQUOC DAT[1] Truong Huu Hoang[1] Ngo Vinh Hanh[1] Chiho Kadono[1] Hideki Fujii[1] Sawako Uchida-Kobayashi[1] Shogo Tanaka[1] Shoji Kubo[1] Takeaki Ishizawa[1] Daisuke Oikawa[1] Fuminori Tokunaga[1] Akihiro Tamori[1] Sergi Guixé-Muntet[2] Jordi Gracia-Sancho[2] Frank Gonzalez[3] Kazuo Ikeda[1] Norifumi Kawada[1]

[1]Osaka Metropolitan University, [2]IDIBAPS, [3]National Cancer Institute

Background: Chronic liver diseases cause liver fibrosis, which can lead to cirrhosis and cancer. Although many kinds of lipid metabolites involved in chronic liver disease have been reported, it is not fully understood how these metabolites are associated with the pathogenesis of liver fibrosis. Herein, we aimed to discover metabolic pathogenesis of liver fibrosis in common to human and rodent. **Methods:** We performed serum lipidome analysis in two independent cohorts of 102 metabolic dysfunction–associated steatotic liver disease (MASLD) and 123 chronic hepatitis C (CHC) patients, and immunohistochemical quantification with the livers of 90 patients. Human liver microsomal fractions were used for hydrolysis assay. Liver fibrosis mouse models were generated by high-fat, high-cholesterol diet or methionine- and choline-deficient diet. We investigated the feature of enzyme expression using RNA-sequencing data of MASLD patients and single-cell RNA-sequencing data of MASLD model mice. Human hepatic stellate cells (HHSteCs) and LX-2 cells were used for in vitro experiments. **Results:**

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Serum dihydroxyeicosatrienoic acid (DHET) levels were significantly elevated in the patients with advanced fibrosis in original and propensity matching cohort. Of enzymes that converts epoxyeicosatrienoic acids (EETs) to DHETs, the levels of microsomal epoxide hydrolase (EPHX1) positively correlated with fibrosis stage, but not soluble epoxide hydrolase (EPHX2). Multivariate logistic regression analysis indicated EPHX1 expression was associated with advanced fibrosis in patients with MASLD and CHC (odds ratio [OR], 5.50, p = 0.01; OR, 4.02, p = 0.006, respectively). Human liver microsomal fractions that include EPHX1 substantially catalysed EETs to DHETs compared with cytosolic fractions that include EPHX2 at less than 100 nM. In fibrotic model mice, hepatic EPHX1 and DHET levels were increased and EET levels were decreased. RNA-sequencing data indicated hepatic *EPHX1* level in MASLD patients was significantly higher than healthy control, and significantly correlated with transforming growth factor-β1 (*TGFB1*) and collagen type 1 alpha 1 (*COL1A1*). Interestingly, abundant EPHX1 expression in hepatic stellate cells (HSCs), but no EPHX2 expression, was shown by western blotting with mouse primary HSCs and single-cell RNA-sequencing data, suggesting that EPHX1 preferentially participates in EET hydrolysis in HSCs. We confirmed EPHX1 expression in human HSCs (desmin-positive cells) by immunofluorescence staining. In human HSCs, 11,12-EET suppressed TGFβ-induced COL1A1 production in a dose-dependent manner while 11,12-DHET increased that. **Conclusion:** This study revealed that EPHX1 plays a key promoter in liver fibrosis through eicosatrienoic acid metabolism. DHETs are promising markers of advanced liver fibrosis, and EPHX1 and EET metabolism are novel therapeutic targets for liver fibrosis.

Disclosures: Hiroko Ikenaga: Nothing to Disclose, Tsutomu Matsubara: Nothing to Disclose, Masaru Enomoto: Nothing to Disclose, Misako Sato-Matsubara: Nothing to Disclose, Le Thi Thanh Thuy: Nothing to Disclose, NINHQUOC DAT: Nothing to Disclose, Truong Huu Hoang: Nothing to Disclose, Ngo Vinh Hanh: Nothing to Disclose, Chiho Kadono: Nothing to Disclose, Hideki Fujii: Nothing to Disclose, Sawako Uchida-Kobayashi: Nothing to Disclose, Shogo Tanaka: Nothing to Disclose, Shoji Kubo: Nothing to Disclose, Takeaki Ishizawa: Nothing to Disclose, Daisuke Oikawa: Nothing to Disclose, Fuminori Tokunaga: Nothing to Disclose, Akihiro Tamori: Nothing to Disclose, Sergi Guixé-Muntet: Nothing to Disclose, Jordi Gracia-Sancho: Independent Contractor relationship with Oncomatryx; Has not ended; Independent Contractor relationship with Quinton; Has not ended; Independent Contractor relationship with Inventiva; Has ended; Independent Contractor relationship with Novo Nordisk; Has not ended; Independent Contractor relationship with Gilead Sciences; Has ended; Stock â€“ privately held company relationship with Barcelona Liver Bioservices; Has not ended, Frank Gonzalez: Nothing to Disclose, Kazuo Ikeda: Nothing to Disclose, Norifumi Kawada: Nothing to Disclose

3551 | VALIDATION OF THE NOVEL GLAS ALGORITHM AS AN AID IN THE DETECTION OF LIVER FIBROSIS AND CIRRHOSIS BASED ON GP73, LG2M, AGE, AND SEX

Philip Hemken[1] Lori Sokoll[2] Laurel Jackson[1] Susan Gawel[1] Toru Yoshimura[1] Hideki Kinukawa[1] Shaohua Ning[1] Juru Miao[1] Daniel Chan[2] Gerard Davis[1]

[1]Abbott Laboratories, [2]The Johns Hopkins University

Background: Diagnosis of liver disease at earlier stages can improve outcomes and reduce the risk of progression to malignancy. Liver biopsy is the gold standard for diagnosis of liver disease, but is invasive and sample acquisition errors are common. Serum biomarkers for liver function and fibrosis, combined with patient factors, may allow for noninvasive detection of liver disease. In this pilot study, we tested and validated the performance of an algorithm that combines GP73 and LG2m serum biomarkers with age and sex (GLAS) to differentiate between patients with liver disease and healthy individuals in two independent cohorts. **Methods:** To develop the algorithm, prototype automated immunoassays were used to measure GP73 and LG2m in residual serum samples collected between 2003 and 2016 from patients with staged fibrosis and cirrhosis of viral or non-viral etiology (n = 260) and healthy subjects (n = 133). The performance of five predictive models using combinations of age, sex, GP73, and/or LG2m from the development cohort were tested. Residual samples from a separate cohort with liver disease (fibrosis, cirrhosis, or chronic liver disease; n = 395) and healthy subjects (n = 106) were used to validate the best performing model. **Results:** GP73 and LG2m concentrations were higher in patients with liver disease than healthy controls and higher in those with cirrhosis than fibrosis in both the development and validation cohorts. The best performing model included both GP73 and LG2m plus age and sex (GLAS algorithm), which had an AUC of 0.92 (95% CI: 0.90–0.95), a sensitivity of 88.8%, and a specificity of 75.9%. In the validation cohort, the GLAS algorithm had an estimated an AUC of 0.93 (95% CI: 0.90–0.95), a sensitivity of 91.1%, and a specificity of 80.2%. In both cohorts, the GLAS algorithm had high predictive probability for distinguishing between patients with liver disease versus healthy controls. **Conclusion:** GP73 and LG2m

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serum biomarkers, when combined with age and sex (GLAS algorithm), showed high sensitivity and specificity for detection of liver disease in two independent cohorts. The GLAS algorithm will need to be validated and refined in larger cohorts and tested in longitudinal studies for differentiating between stable versus advancing liver disease over time.

Disclosures: Philip Hemken: Nothing to Disclose, Lori Sokoll: Nothing to Disclose, Laurel Jackson: Abbott Laboratories: Employee, Susan Gawel: Nothing to Disclose, Toru Yoshimura: Abbott Japan: Employee, Abbott Laboratories: Stock - publicly traded company, Hideki Kinukawa: Nothing to Disclose, Shaohua Ning: Nothing to Disclose, Juru Miao: Nothing to Disclose, Daniel Chan: Nothing to Disclose, Gerard Davis: Nothing to Disclose

3552 | XCT⁺ MONOCYTE-DERIVED MACROPHAGES MEDIATE LIVER FIBROSIS RESOLUTION THROUGH EFFEROCYTOSIS ◆

Kyurae Kim[1] Sung Eun Choi[1] Min Jeong Kim[1] Katherine Po Sin Chung[1] Eunmi Lee[1] Kwang Woo Lee[1] WON-IL JEONG[1]

[1]GSMSE, KAIST

Background: Hepatic macrophages are key regulators of liver fibrosis progression and regression. Recent studies have reported a subset of TREM2⁺CD9⁺ monocyte-derived macrophages (MDMs) in fibrotic livers, but the factors steering MDM properties remain unidentified. Here, we investigated the mechanisms by which cystine and retinoids induce the restorative properties of xCT⁺ MDMs in liver fibrosis. **Methods:** Liver fibrosis was induced by carbon tetrachloride in wild-type and myeloid-specific xCT-deficient mice (*Slc7a11*$^{\Delta LysM}$). Single-cell RNA sequencing (scRNA-seq) analyses, spatial transcriptomic (GeoMX), and adoptive transfer of eGFP⁺ macrophages were performed in fibrotic mouse livers. Integrated public resources of human scRNA-seq were analyzed. Reactive oxygen species (ROS) and efferocytosis of MDMs were assessed by flow cytometry. Differentiated MDMs were subjected to *in vitro* experiments or cultured with hepatic stellate cells (HSCs). **Results:** scRNA-seq analysis revealed that a subset of MDMs expressed tissue restoration-related genes (*Arg1*, *Il10*, and matrix metalloproteases), referred to as restorative MDMs, which highly expressed *Slc7a11* encoding the cystine/glutamate antiporter (xCT) in both mouse and human. They were also enriched in gene sets with cysteine and retinoid metabolism. Notably, *Slc7a11*$^{\Delta LysM}$ MDMs showed not only reduced efferocytosis with GSH shortage and ROS elevation but also increased inflammatory features and glycolytic capacity compared to xCT⁺ MDMs, indicating impaired tissue clearance and characteristic acquisition in restorative macrophages. Accordingly, *Slc7a11*$^{\Delta LysM}$ mice showed decreased frequency of restorative MDMs and aggravated fibrosis compared to wild-type mice. Moreover, spatial transcriptomic analysis and adoptive transfer of eGFP⁺ macrophages confirmed that restorative MDMs were co-localized with activated HSC sparing retinoids within the fibrotic septa, suggesting interaction with activated HSCs. Furthermore, differentiated MDMs co-cultured with HSCs or retinoids significantly increased the expression of genes related to retinoid responses (*Rara*, *Stra6l*), tissue resolution, xCT, and GSH synthesis pathway, along with reduced cellular ROS levels. **Conclusion:** We suggested that xCT and retinoids are indispensable for determining the efferocytosis and restorative characteristics of MDMs in fibrotic liver. Therefore, understanding the metabolic modulation of xCT⁺ MDMs may be beneficial in the development of antifibrotic therapy.

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3553 | THE CAUSAL LINKAGE BETWEEN AGING AND CIRRHOSIS: RESULTS FROM NHANES AND MENDELIAN RANDOMIZATION STUDY

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Background: Liver cirrhosis is a global health challenge caused by various liver diseases. This study aimed to evaluate the effect of aging on the development of cirrhosis. **Methods:** We conducted a Mendelian randomization

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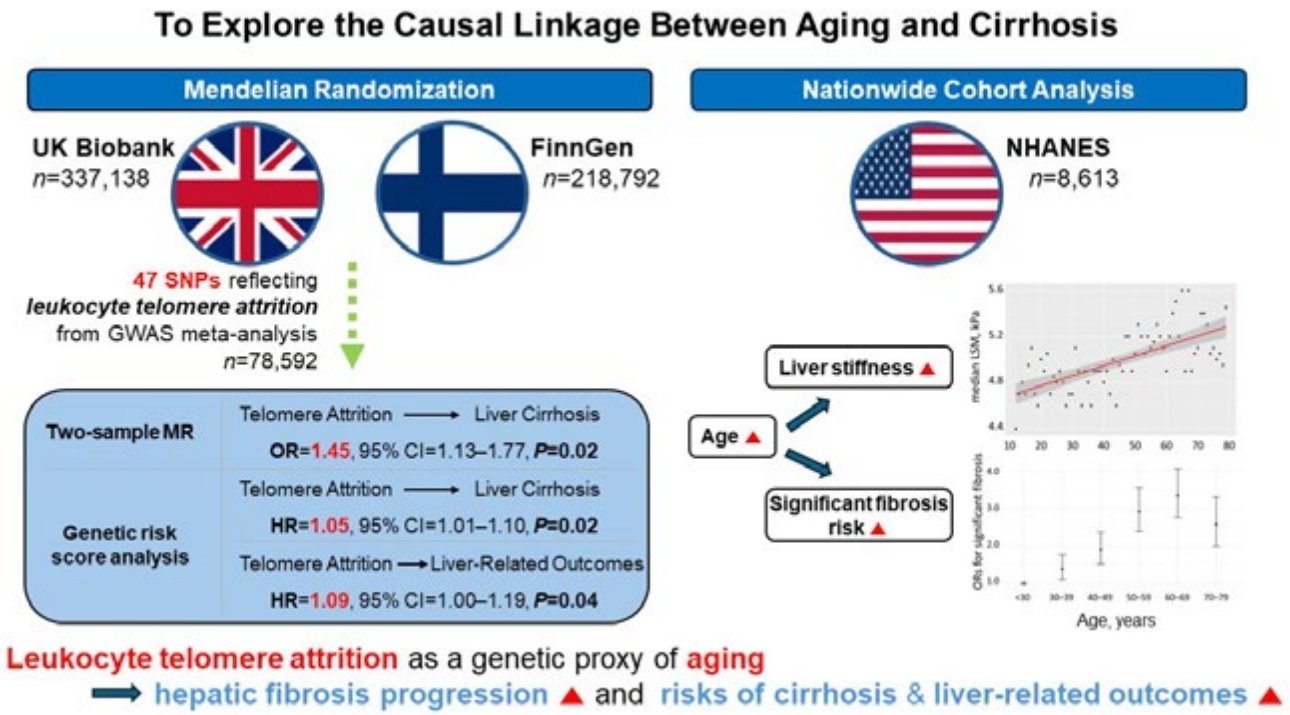
(MR) study using leukocyte telomere length as a genetic proxy for aging. The study included a two-sample bidirectional MR and a one-sample genetic risk score (GRS)-based MR analysis, utilizing the UK Biobank (n=337,138) and FinnGen data (n=218,792). We analyzed 47 single-nucleotide polymorphisms (SNPs) related to telomere attrition and 5 SNPs linked to liver cirrhosis. In parallel, the relationship between age and liver stiffness measurement (LSM) was explored using the 2017–2020 National Health and Nutrition Examination Survey (NHANES, n=8,613). **Results:** The inverse variance-weighted MR (MR–IVW) analysis indicated a significant increase in liver cirrhosis risk owing to leukocyte telomere attrition (per 1 *Z*-score increase, odds ratio [OR]=1.45, 95% confidence interval [CI]=1.13–1.77; *P*=0.02). No significant directional pleiotropy was observed (MR–Egger intercept *P*=0.54). A higher GRS for leukocyte telomere attrition was correlated with increased risks of liver cirrhosis and liver-related outcomes (*P*=0.02 and *P*=0.04, respectively). The reverse MR–IVW analysis showed no significant effect of the genetic predisposition of liver cirrhosis on leukocyte telomere attrition (OR=1.00, 95% CI=0.99–1.00; *P*=0.3). The NHANES data showed a positive linear correlation between age and LSM values (coefficient=0.009, R^2=0.43, *P*<0.001). The prevalence of cirrhosis (LSM ≥17.6 kPa) was significantly higher in individuals aged 60 and older compared to those under 30 (2.4% vs. 0.4%: OR=2.91, 95% CI=1.59–5.76; *P*<0.001). **Conclusion:** These findings establish a causal link between leukocyte telomere attrition and liver cirrhosis, underscoring aging itself as a significant risk factor for cirrhosis.



Disclosures: Hyunjae Shin: Nothing to Disclose

3554 | DEVELOPMENT AND VALIDATION OF A HOME-BASED (LIVERHOME) SCORE TO PREDICT ADVANCED FIBROSIS AND LONG-TERM OUTCOMES IN THE GENERAL POPULATION: AN INTERNATIONAL, MULTI-COHORT STUDY ◆

Xiaolong Qi[1] Shanghao Liu[2] Jie Shen[3] Jingli Gao[4] Xuanwei Jiang[5] Heng Wan[3] Xingdong Chen[6] Chuan Liu[1] Qing-Lei Zeng[7] Shuairan Zhang[8] Chengfu Xu[9] Zhenqiu Liu[6] Xiaozhong Jiang[4] Jiawei Zhang[1] Yuping Chen[1] Ling Yang[10] Lan Liu[3] Hua Liang[3] Xuan Liang[11] Zhenyu Dai[12] Yijun Tang[13] Yang Bu[14] Min Zhao[15] Yong Zhou[16] Jiajun Zhao[17] Junming Han[17] Jitao Wang[18] Dongfang You[19] Ming-Hua Zheng[20] Wanguang Zhang[21] Junliang Fu[22] Xiao Liang[23] Hui Shi[24] Qian Yu[1] Jie Li[25] Victor W. Zhong[5] Vincent Wai-Sun Wong[26] Gao-Jun Teng[1]

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Hospital of Shenyang, [12]Yancheng Third People's Hospital, [13]Taihe Hospital, [14]People's Hospital of Ningxia Autonomous, [15]The Third People's Hospital of Taiyuan, [16]Qingdao Sixth People's Hospital, [17]Shandong Provincial Hospital, [18]Xingtai People's Hospital, [19]Nanjing Medical University, [20]Wenzhou Medical University, [21]Tongji Medical College, [22]Chinese PLA General Hospital, [23]Sir Run-Run Shaw Hospital, [24]The First People's Hospital of Liangyung, [25]Nanjing Drum Tower Hospital, [26]The Chinese University of Hong Kong

Background: Universal disease screening is of great significance for reducing the burden of disease. As the precursor to cirrhosis, the prevalence of liver fibrosis in the general population ranges from 2% to 19%. Unfortunately, cirrhosis is often diagnosed only after an individual develops complications of liver disease. A fundamental shift must occur with health promotion, proactive case-finding, and early recognition of advanced fibrosis. To drive the paradigm shift, we aimed to develop and validate a home-based, zero-cost tool to predict advanced fibrosis and long-term outcomes in the general population. **Methods:** The LiverHome score was derived from a prospective Chinese cohort, to detect advanced fibrosis (i.e. liver stiffness measurement ≥10 kPa in transient elastography), then validated in two prospective cohorts. Moreover, we determined the prognostic value of the LiverHome score in the prediction of long-term outcomes in three prognosis cohorts (all median follow-up more than 10 years). **Results:** We enrolled 615185 participants from the general population; 15457 individuals were in the cross-sectional cohorts (6120 in derivation cohort, 2624 in test cohort, and 6713 in US validation cohort), while 599728 individuals were in the prognosis cohorts (96869 in Chinese prognosis cohort, 48238 in US prognosis cohort, and 454621 in UK prognosis cohort). The LiverHome score (https://chess.nuist.edu.cn/consult/gzconsult/LiverHome) included waist circumference, diabetes, and viral hepatitis history, and low-(score<0) and high-risk (score≥0) groups were created. Compared to the fibrosis-4 index, the LiverHome score had higher accuracy and screening performance in identifying advanced fibrosis in the three cross-sectional cohorts (Figure 1A). Furthermore, compared to the low-risk group, the high-risk group had a higher risk of liver cancer, liver-related mortality, and all-cause mortality in the prognosis cohorts (Figure 1B-1C). The predictive accuracy and risk stratification of the LiverHome score remained robust across subgroup analyses by (age<50, 50-60, and >60), sex (male and female), and ethnicity (white, black, and other races). **Conclusion:** The home-based, zero-cost LiverHome score can better assess advanced liver fibrosis and long-term outcomes in the general population. The LiverHome score is suitable for universal fibrosis screening and has the potential to reduce the burden of chronic liver disease.

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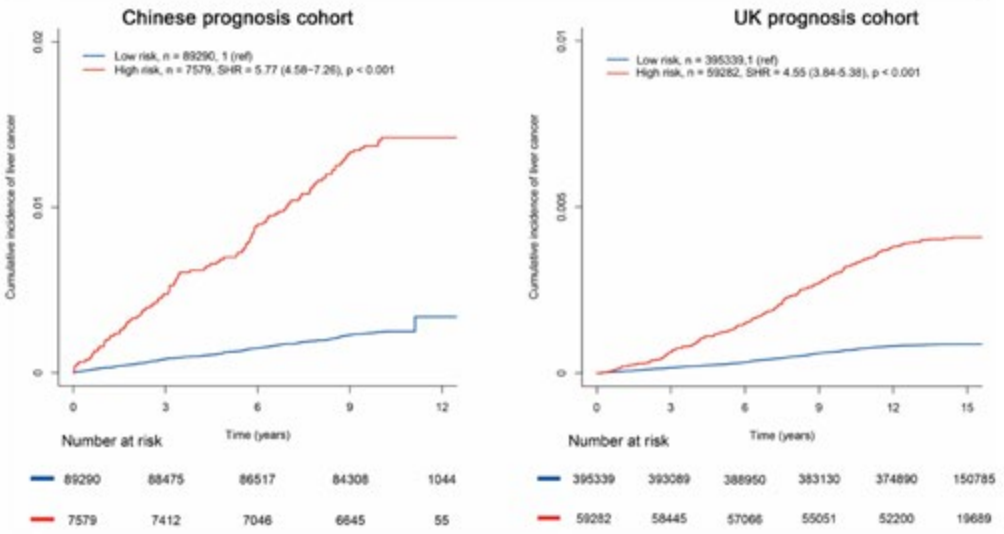
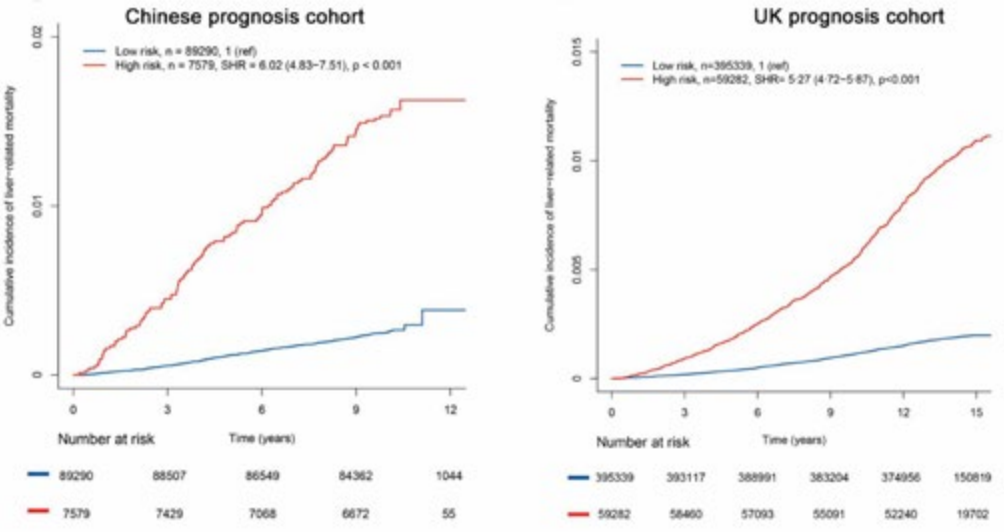
A

	AUC (95% CI)	Cut-off	Youden index	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	p value*
Derivation cohort								
LiverHome	0.77 (0.72-0.82)	0	0.40	48.8	91.3	10.5	98.8	1 (ref)
FIB-4	0.64 (0.58-0.70)	1.3	0.23	44.8	78.2	4.1	98.6	<0.001
Test cohort								
LiverHome	0.76 (0.70-0.83)	0	0.35	42.9	92.0	11.7	98.5	1 (ref)
FIB-4	0.63 (0.55-0.71)	1.3	0.20	41.3	78.3	4.5	98.2	0.010
US validation cohort								
LiverHome	0.84 (0.82-0.86)	0	0.51	86.7	64.4	13.1	98.7	1 (ref)
FIB-4	0.65 (0.62-0.68)	1.3	0.20	42.6	77.3	10.3	95.6	<0.001

B



C



Disclosures: Xiaolong Qi: Nothing to Disclose, Shanghao Liu: Nothing to Disclose, Jie Shen: Nothing to Disclose, Jingli Gao: Nothing to Disclose, Xuanwei Jiang: Nothing to Disclose, Heng Wan: Nothing to Disclose, Xingdong Chen: Nothing to Disclose, Chuan Liu: Nothing to Disclose, Qing-Lei Zeng: Nothing to Disclose, Shuairan Zhang: Nothing to Disclose, Chengfu Xu: Nothing to Disclose, Zhenqiu Liu: Nothing to Disclose, Xiaozhong Jiang: Nothing to Disclose, Jiawei Zhang: Nothing to Disclose, Yuping Chen: Nothing to Disclose, Ling Yang: Nothing to Disclose, Lan Liu: Nothing to Disclose, Hua Liang: Nothing to Disclose, Xuan Liang: Nothing to Disclose, Zhenyu Dai: Nothing to Disclose, Yijun Tang: Nothing to Disclose, Yang Bu: Nothing to Disclose, Min Zhao: Nothing to

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Disclose, Yong Zhou: Nothing to Disclose, Jiajun Zhao: Nothing to Disclose, Junming Han: Nothing to Disclose, Jitao Wang: Nothing to Disclose, Dongfang You: Nothing to Disclose, Ming-Hua Zheng: Nothing to Disclose, Wanguang Zhang: Nothing to Disclose, Junliang Fu: Nothing to Disclose, Xiao Liang: Nothing to Disclose, Hui Shi: Nothing to Disclose, Qian Yu: Nothing to Disclose, Jie Li: Nothing to Disclose, Victor W. Zhong: Nothing to Disclose, Vincent Wai-Sun Wong: Nothing to Disclose, Gao-Jun Teng: Nothing to Disclose

3555 | ACTIVATED HEPATIC STELLATE CELLS (AHSCS) ARE REQUIRED FOR RECOVERY FROM TOXIC LIVER INJURY IN MICE

Sadatsugu Sakane[1] Hiroaki Fuji[2] Animesh Singh[1] Hyun Young Kim[1] Mojgan Hosseini[3] Yusuke Kimura[1] Raquel Weber[1] Wonseok Lee[1] Kanani Hokutan[1] Souradipta Ganguly[3] Karin Diggle[1] Xiao Liu[1] Debanjan Dhar[4] Linda Burkly Burkly[5] David Brenner[4] Tatiana Kisseleva[3]

[1]University of California San Diego, [2]Department of Gastroenterological Surgery, Hyogo College of Medicine, Hyogo, Japan, [3]University of California, San Diego, [4]Sanford Burnham Prebys Medical Discovery Institute, La Jolla, CA, [5]Editas Medicine Inc. Cambridge, MA, USA.

Background: Activated Hepatic Stellate Cells (aHSCs) are the major source of fibrogenic myofibroblasts in the liver in response to toxic liver injury. We investigated the role of aHSCs in the development and recovery from carbon tetrachloride (CCl_4)-induced liver fibrosis. For this purpose, human Diphtheria Toxin Receptor (DTR, which is not expressed in mice) was overexpressed in Collagen Type I and Lrat expressing activated HSCs, so that administration of Diphtheria Toxin-α (DTA) to CCl_4-injured mice induced cellular death of $DTR^+Col1a1^+Lrat^+$ aHSCs. **Methods:** $Col1a1^{fl\text{-}stop\text{-}fl\text{-}DTR}$ mice were generated by knocking in the floxP-stop-floxP-DTR cassette into *col1a1* genetic locus. $Col1a1^{fl\text{-}stop\text{-}fl\text{-}DTR}$ mice were crossed with $Lrat^{Cre}$ mice, which express Cre in HSCs in the liver, to generate $Lrat^{Col1a1\text{-}DTR}$ mice. To visualize all HSCs, $Lrat^{Col1a1\text{-}DTR}$ and $Lrat^{Cre}$ mice were crossed to $Rosa26^{fl\text{-}stop\text{-}fl\text{-}YFP}$ mice. $Lrat^{YFP\text{-}Col1a1\text{-}DTR}$ mice were subjected to CCl_4 (25 µl/200 µl of corn oil, oral gavage) liver injury. Administration of DTA (50 ng/g, i.p.) to CCl_4-injured $Lrat^{YFP\text{-}Col1a1\text{-}DTR}$mice caused ablation of $Lrat^+Col1a1^+$ aHSCs compared to $Lrat^{YFP}$ mice (treated under the same conditions), or uninjured $Lrat^{YFP\text{-}Col1a1\text{-}DTR}$ mice (n≧10 per group). **Results:** The YFP reporter was expressed in 95% of $Lrat^{YFP}$ mice. CCl_4-injured $Lrat^{YFP\text{-}Col1a1\text{-}DTR}$ and $Lrat^{YFP}$ mice induced expression of Col1a1 and other fibrogenic genes in YFP^+ aHSCs (vs uninjured mice). Administration of DTA (25 or 50 ng/g, 2 x, i.p.) to CCl_4-injured $Lrat^{YFP\text{-}Col1a1\text{-}DTR}$ mice caused ablation of aHSCs within 24h in a dose dependent manner (60% to 90%, respectively), as shown by the disappearance of $YFP^+Desmin^+$ cells, and downregulation of Col1a1, YFP, DTR, and Cre mRNA, and attenuation of liver fibrosis at 3 days. Meanwhile, the number of YFP^+ HSCs was not changed in the livers of DTA-treated CCl_4-injured $Lrat^{YFP}$ mice, or uninjured $Lrat^{YFP\text{-}Col1a1\text{-}DTR}$ mice. Remarkably, DTA-CCl_4-injured $Lrat^{YFP\text{-}Col1a1\text{-}DTR}$ mice developed visible signs of distress. At day 7, mice exhibited the loss of body weight (»20%) and liver weight (»50%). 55% of DTA-CCl_4-injured $Lrat^{YFP\text{-}Col1a1\text{-}DTR}$ mice died within 2 weeks after aHSC ablation, the surviving 45% of DTA-CCl_4-injured $Lrat^{YFP\text{-}Col1a1\text{-}DTR}$ mice showed gradual weight gain and histological improvement. The loss of liver mass in recovering DTA-CCl_4-injured $Lrat^{YFP\text{-}Col1a1\text{-}DTR}$ mice was attributed to the marked shrinkage of hepatocyte cytoplasm, decrease of hepatocyte proliferation and abnormal hepatocyte differentiation in the absence of HSCs. At day 28, the liver volume returned to normal due to increased hepatocyte mass, and this effect was associated with HSC proliferation and restoration of HSC numbers in the livers of DTA-injected CCl_4-injured $Lrat^{YFP\text{-}Col1a1\text{-}DTR}$ mice. **Conclusion:** Ablation of HSCs reduces liver fibrosis but affects hepatocyte proliferation causing a defect in liver regeneration.

Disclosures: Sadatsugu Sakane: Nothing to Disclose, Hiroaki Fuji: Nothing to Disclose, Animesh Singh: Nothing to Disclose, Hyun Young Kim: Nothing to Disclose, Mojgan Hosseini: Nothing to Disclose, Yusuke Kimura: Nothing to Disclose, Raquel Weber: Nothing to Disclose, Wonseok Lee: Nothing to Disclose, Kanani Hokutan: Nothing to Disclose, Souradipta Ganguly: Nothing to Disclose, Karin Diggle: Nothing to Disclose, Xiao Liu: Nothing to Disclose, Debanjan Dhar: Nothing to Disclose, Linda Burkly Burkly: Editas Medicine: Employee, David Brenner: Nothing to Disclose, Tatiana Kisseleva: Nothing to Disclose

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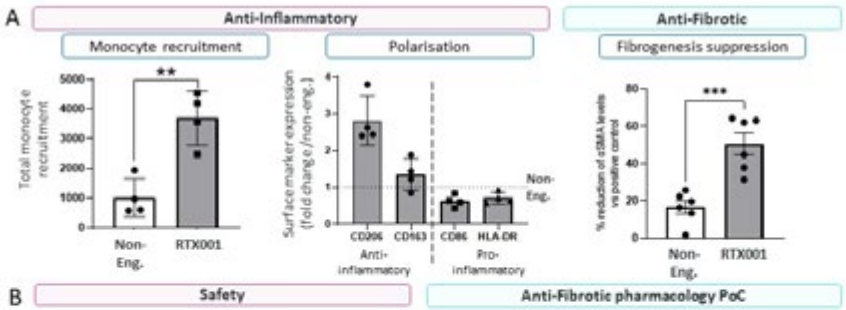
3556 | PRECLINICAL PROOF OF CONCEPT OF SAFETY AND EFFICACY FOR RTX001, A NOVEL AUTOLOGOUS MACROPHAGE CELL THERAPY PRODUCT FOR END-STAGE LIVER DISEASE

Moony Su[1] Olivia Matthews[1] Mark Cant[1] Anna Hoy[1] Niya Aleksieva[1] Rachel Lopera[1] Philip Starkey Lewis[1] Alejandro Armesilla-Diaz[1] Keith Sutton[1] Kayleigh Thirlwell[1] Lara Campana[1]

[1]Resolution Therapeutics

Background: Patients with end-stage liver disease (ESLD) have extensive fibrosis and inflammation, which cause loss of organ function, resulting in decompensation events and limited life expectancy. Currently, there are no licensed therapies to treat ESLD. Macrophages with a pro-regenerative phenotype control inflammation and promote fibrosis remodelling, thereby coordinating liver regeneration and offering a potential therapeutic avenue in these patients. Autologous, non-engineered, pro-regenerative macrophages have been tested in patients with cirrhosis in the academic MATCH clinical studies, displaying excellent safety and efficacy. Further enhancement of pro-regenerative macrophage potency via engineering is needed to ensure durable clinical responses in a more severe patient population with ESLD. **Methods:** After the conclusion of our candidate screening program, the best-in-class genes for anti-inflammation and anti-fibrosis were IL10 and MMP9, respectively. They were combined in a single mRNA construct to engineer our lead candidate, RTX001, using our proprietary platform. RTX001 was further characterised *in vitro* and *in vivo*, including in a GLP toxicology study, to enable initiation of a Phase 1/2 study in the UK and Europe. **Results:** RTX001 showed an increased anti-inflammatory effect as measured by its ability to attract monocytes (4x vs non-engineered; Fig1A left panel) and polarise them to pro-regenerative macrophages (2.6x CD206 expression vs non-engineered) *in vitro* (Fig1A middle panel). Furthermore, the combination of IL10-MMP9 resulted in enhanced ability to limit the activation of hepatic stellate cells (2.5x vs non-engineered) *in vitro* (Fig1A, right panel). These data supported the nomination of an IL10-MMP9 engineered macrophage as the lead product, RTX001. When tested *in vivo*, including in a GLP toxicology study, RTX001 primarily distributed to the lung and liver following intravenous administration, with persistence for up to a week in the liver. No safety concern was reported (Fig 1B, left panel). In a pharmacology study in a liver fibrosis model, RTX001 dosing promoted a reduction in fibrosis score *vs* vehicle control (Fig 1B, right panel), thereby supporting the intended pharmacology. **Conclusion:** RTX001 is superior to non-engineered macrophages for its anti-inflammatory and anti-fibrotic ability, and it has an excellent tolerability profile when tested *in vivo*. Overall, the preclinical package detailed above will support the initiation of a Phase 1/2 study, with first patient dosed planned for Q4 2024.



Safety	Uninjured (GLP)	CCl4
Adverse events (e.g. embolism)	None	None
Early deaths	None	None
Biodistribution in gonads	None	None
Histological findings in any organs	None	None

Disclosures: Moony Su: Nothing to Disclose, Olivia Matthews: Resolution Therapeutics: Employee, Resolution Therapeutics: Stock – privately held company, Mark Cant: Nothing to Disclose, Anna Hoy: Resolution Therapeutics: Employee, Resolution Therapeutics: Employee, Resolution Therapeutics: Stock – privately

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held company, Niya Aleksieva: Nothing to Disclose, Rachel Lopera: Nothing to Disclose, Philip Starkey Lewis: Resolution Therapeutics Ltd: Employee, Resolution Therapeutics Ltd: Stock – privately held company, Alejandro Armesilla-Diaz: Nothing to Disclose, Keith Sutton: Resolution Therapeutics: Employee, Kayleigh Thirlwell: Nothing to Disclose, Lara Campana: Resolution Therapeutics: Employee

3557 | HEPATIC STELLATE CELLS FACILITATES AMMONIA DETOXIFICATION THROUGH GPT1-MEDIATED ALANINE SYNTHESIS IN HEPATOCELLULAR CARCINOMA

Thi Nga Ha[1] Hyon-Seung Yi[1] Dong Wook Choi[2]

[1]Chungnam National University, [2]Korea University

Background: Targeting metabolic reprogramming during the activation of hepatic stellate cells (HSCs) has recently been highlighted as an emerging strategy for mitigating hepatic diseases. The activation process of HSCs is well-known to induce inflammation and fibrogenesis in the liver. However, the roles of HSCs in liver injury and diseases are still not fully elucidated. This study elucidates the previously unexplored role of alanine synthesis in activated HSCs for protecting against liver diseases via ammonia detoxification. **Methods:** Mouse primary HSCs were cultured to measure de novo alanine synthesis using U-C^{13}-glucose and N^{15}-NH4Cl for metabolic flux analysis. Furthermore, we phenotyped *Pdgfrb-Cre-Gpt1*$^{flox/flox}$ mice, where ammonia levels were measured to define the correlations with alanine levels, and evaluated liver cancer phenotypes in mouse models induced by diethylnitrosamine injection combined with a choline deficient and high fat diet. **Results:** Glutamic-pyruvic transaminase (GPT1) expression in activated HSCs is increased, leading to augmented alanine synthesis and secretion. scRNA-seq analysis of human liver revealed that GPT1 expression was significantly elevated in HSCs within liver cancer samples. A significant increase in the fractional abundance of $U^{13}C$ alanine and ^{15}N alanine isotopomers over the time of activation, leading to intracellular alanine accumulation, was observed. In order to elucidate the GPT1's role in HSCs during the progression of liver cancer, an in vivo analysis was conducted in mice bearing liver cancer induced by diethyl-nitrosamine administration in conjunction with a choline-deficient high-fat diet. Decreased alanine synthesis in HSCs upon *Gpt1* depletion results in elevated ammonia levels, which may contribute to the exacerbation of liver cancer. **Conclusion:** Our findings reveal novel mechanisms by which HSCs manage elevated ammonia levels in the context of liver damage. We highlight the significant role of the coordinated activity of GPT1, whereby the resultant alanine acts as a nitrogen sink for ammonia detoxification in liver cancer.

Disclosures: Thi Nga Ha: Nothing to Disclose, Hyon-Seung Yi: Nothing to Disclose, Dong Wook Choi: Nothing to Disclose

3558 | HEPATOCYTE-DERIVED FIBROBLAST GROWTH FACTOR 18 PROMOTES HEPATIC FIBROGENESIS UNDER DIETARY STEATOHEPATITIS IN HEPATOCYTE-SPECIFIC *CFLAR* DEFICIENT MICE

Kyoko Fukuhara[1] Yuichi Tsuchiya[2] SHUNHEI YAMASHINA[1] Xingchen Liu[1] Kazuyoshi Kon[1] Akira Uchiyama[1] Reiko Yaginuma[1] Kei Ishizuka[1] Hiroyasu Nakano[3] Kenichi Ikejima[1]

[1]Juntendo University School of Medicine, [2]Department of Biochemistry Toho University Faculty of Pharmaceutical sciences, [3]Department of Biochemistry Toho University School of Medicine

Background: Fibroblast growth factors (FGFs) play a pivotal role in tissue remodeling through regulation of various cellular responses such as proliferation, survival, migration and differentiation. Previous results suggested that members of the FGF family attenuate or exacerbate liver fibrosis. Here we investigated the role of FGF18 in hepatic fibrogenesis associated with dietary steatohepatitis in hepatocyte-specific *Cflar* deficient (*Cflar*^{LKO}) mice. **Methods:** We crossed *Cflar*^{FF}*;Alb-Cre* mice with *Fgf18*^{FF} mice, resulting in the generation of hepatocyte-specific *Cflar* and *Fgf18* double-deficient (*Cflar*^{LKO}*;Fgf18*^{LKO}) mice. We also generated transgenic mice expressing *Fgf18* in hepatocytes (*Fgf18* Tg mice). Some mice were fed a choline-deficient, ethionine supplemented (CDE) diet for 4 weeks. Liver pathology was evaluated with H&E and Sirius Red staining. The expression of *Col1a2, Col3a1, Acta2, Ccnd1, Fgf18* was determined by qPCR assays. Isolated HSCs from mice were plated and simulated with FGF18 (100 ng/mL) or TGFβ1 (1 ng/mL). Cell viability was determined by the WST assay. **Results:** We compared

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the extent of liver injury and fibrosis among *Fgf18*^{LKO}, *Cflar*^{LKO}, and *Cflar*^{LKO}*;Fgf18*^{LKO} mice following 4 weeks of CDE diet feeding. Serum ALT levels were elevated in both *Cflar*^{LKO} and *Cflar*^{LKO}*;Fgf18*^{LKO} mice but not *Fgf18*^{LKO} mice. The Sirius Red+ areas were elevated in the livers of *Cflar*^{LKO} mice; however, *Fgf18* deficiency reduced the Sirius Red+ areas. Accordingly, the expression of *Col3a1* and *Acta2* was elevated in the livers of *Cflar*^{LKO} mice but attenuated in the livers of *Cflar*^{LKO}*;Fgf18*^{LKO} mice. Serum ALT levels did not differ between non-Tg and *Fgf18* Tg mice. Interestingly, Sirius Red+ areas were elevated in the livers of *Fgf18* Tg mice compared to non-Tg mice. The expression of *Col1a2, Col3a1*, or *Acta2* in isolated HSCs was upregulated by treatment with TGFβ1 but not FGF18. Surprisingly, FGF18 stimulated the proliferation of HSCs and upregulated the expression of *Ccnd1*, encoding cyclin D1, which is involved in cell cycle progression. **Conclusion:** Deletion of Fgf18 in hepatocytes attenuated CDE-induced hepatic fibrogenesis; conversely, overexpression of *Fgf18* facilitated progression of liver fibrosis by increasing the number of HSCs. Mechanistically, FGF18 stimulated the proliferation of HSCs. Collectively, these findings clearly indicated that FGF18 promotes hepatic fibrogenesis, anticipating a novel therapeutic target for prevention and treatment of liver fibrosis.

Disclosures: Kyoko Fukuhara: Nothing to Disclose, Yuichi Tsuchiya: Nothing to Disclose, SHUNHEI YAMASHINA: Nothing to Disclose, Xingchen Liu: Nothing to Disclose, Kazuyoshi Kon: Nothing to Disclose, Akira Uchiyama: Nothing to Disclose, Reiko Yaginuma: Nothing to Disclose, Kei Ishizuka: Nothing to Disclose, Hiroyasu Nakano: Nothing to Disclose, Kenichi Ikejima: Nothing to Disclose

3559 | TARGETING TEAD1 ACTIVE ISOFORM TO ALLEVIATE LIVER FIBROSIS IN PRIMARY SCLEROSING CHOLANGITIS

Roi Isaac[1] *Jinyue Wang*[1] *Sion Kang*[1] *Victoria Nguyen*[1] *Charles McWherter*[2] *Jerrold Olefsky*[1]

[1]*University of California, San Diego,* [2]*CymaBay Therapeutics*

Background: Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease characterized by inflammation and fibrosis of the bile ducts, leading to progressive liver damage. Hepatic stellate cells (HSCs) and portal fibroblasts (PFs) play a crucial role in PSC-induced liver fibrosis. Recently, we showed that TEAD1, a Hippo pathway component, regulates HSC activation in metabolic dysfunction-associated steatohepatitis (MASH). TEAD1 activity is modulated by alternative splicing (AS), with the exclusion of the inhibitory exon 5, resulting in increased expression and activity of TEAD1^{DeltaEx5}, leading to HSC activation (See scheme). The splicing factor hnRNPU binds to TEAD1 pre-mRNA and facilitates exon 5 exclusion. Notably, this hnRNPU/TEAD1 regulatory system does not function in hepatocytes or nonparenchymal cells (NPCs). In this study, we investigated the role of TEAD1 AS in PSC-induced liver fibrosis. **Methods:** We used an antisense oligonucleotide (ASO 56) to target the TEAD1 pre-mRNA upstream of exon 5, blocking hnRNPU binding and reducing TEAD1^{DeltaEx5} expression (See scheme). The human HSC line, LX-2, portal fibroblasts, and H69 cholangiocyte cell line were transfected with ASO 56 or control. To assess HSC, PF, and cholangiocyte activation, we measured gene expression for TGFß-induced fibrogenesis or proliferation markers was measured. Finally, we administered ASO 56 to the PSC mouse model, Mdr2KO mice, and measured liver inflammation and fibrosis. **Results:** ASO 56 reduced the expression of TEAD1^{DeltaEx5}, Acta2, and Il-6 in HSCs and PFs compared to the control, but it did not alter TEAD1^{DeltaEx5} in cholangiocytes. Interestingly, cholangiocyte proliferation was reduced when exposed to conditioned media from LX-2 cells transfected with ASO 56 compared to control. When injected into Mdr2KO mice, ASO 56 mitigated HSC activation *in vivo*, reduced levels of circulating proinflammatory cytokines such as IL-6, and decreased F4/80 protein levels in the liver compared to control mice. Moreover, ASO 56 treatment reduced blood alanine aminotransferase (ALT) levels and attenuated PSC-induced liver fibrosis, characterized by ‘onion skin’ fibrosis, and detected by Sirius red staining. Importantly, our results indicate that ASO 56 also reduces cholangiocyte proliferation in Mdr2KO mice. **Conclusion:** Our findings revealed a pivotal role of TEAD1^{DeltaEx5} in HSC and PF activation, emphasizing the potential of ASO 56 targeting TEAD1 AS as a new approach to treat PSC.

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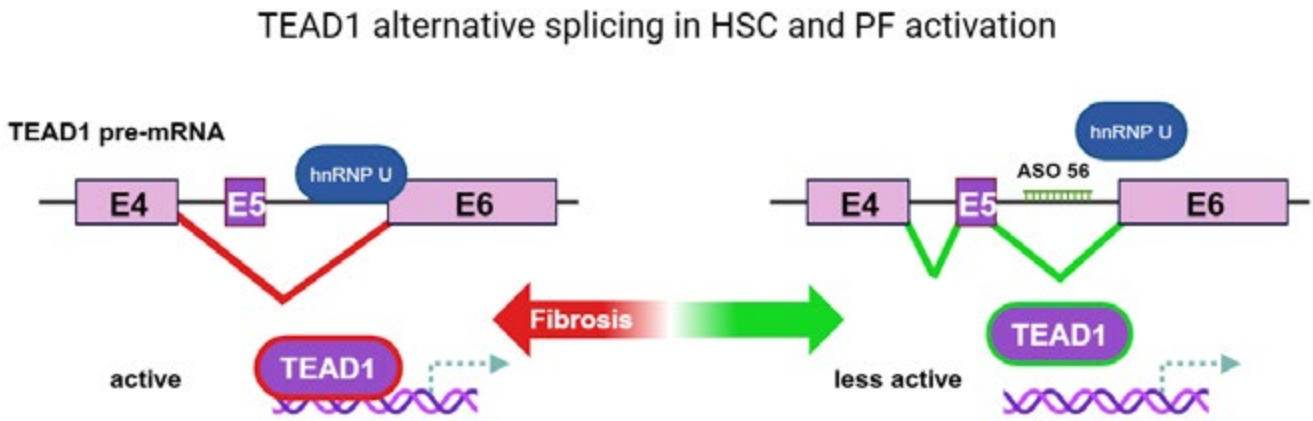

Disclosures: Roi Isaac: Cymabay therapeutics: Consultant, Jinyue Wang: Nothing to Disclose, Sion Kang: Nothing to Disclose, Victoria Nguyen: Nothing to Disclose, Charles McWherter: Nothing to Disclose, Jerrold Olefsky: Nothing to Disclose

3560 | ANTI-FIBROTIC MICRORNAS ENRICHED IN EXTRACELLULAR VESICLES DERIVED FROM MESENCHYMAL STEM CELLS SUPPRESS FIBROGENESIS OF HEPATIC STELLATE CELLS BY DOWNREGULATION OF RHOA SIGNALING

Daiki Kawamoto[1] Toshihiko Matsumoto[2] Tsuyoshi Fujioka[2] Naoki Yamamoto[1] Taro Takami[1]

[1]Yamaguchi University Graduate School of Medicine, [2]Yamaguchi University Graduate School

Background: We have been developing a liver regeneration therapy for decompensated liver cirrhosis (DLC) using cultured autologous bone marrow mesenchymal stem cells (BMSCs). Currently, we are conducting a clinical trial (jRCT2063200014), in which hepatic arterial infusion of cultured autologous BMSCs has improved liver function and fibrosis in DLC patients. However, the mechanism of anti-fibrotic action of BMSCs remain to be fully determined. We therefore identified anti-fibrotic microRNAs (miRNAs) enriched in extracellular vesicles derived from MSCs (MSC-EVs) and examined the underlying mechanisms that suppress extracellular matrix production by hepatic stellate cells (HSCs). **Methods:** We used a microarray to perform a comprehensive analysis of miRNA expression profiles and compared miRNA expression profiles in MSC-EVs derived from patients with DLC in our clinical trial and HSCs. To identify the anti-fibrotic miRNAs enriched in MSC-EVs, each mimic of miRNAs that highly expressed in MSC-EVs and lowly expressed in HSCs was transfected into HSCs and fibrosis-related gene expression determined. We performed pathway analysis based on the RNA sequence data of HSCs transfected with anti-fibrotic miRNAs cocktail. Furthermore, RhoA activity and cell motility of HSCs were evaluated by G-LISA and time-lapse cell migration assay. **Results:** Eleven miRNAs were extracted from the microarray data that showed normalized intensity of >1,000 in MSC-EVs from DLC patients in our clinical trial and 100-fold higher than that of HSCs. Each miRNA mimic of the eleven miRNAs was transfected into HSCs and we identified five miRNAs (miR204-3p, miR7977, miR5787, miR6089 and miR1237-5p) which suppressed expression of any of fibrosis-related genes (ACTA2, COL1A1, COL1A2, COL3A1 and ELN). Interestingly, transfection of the five miRNAs cocktail into HSCs decreased expression of all fibrosis-related genes. KEGG pathway analysis revealed downregulation of RhoA signaling pathway and RhoA activity measured by G-LIZA was downregulated in HSCs transfected with the miRNAs cocktail. Time-lapse cell migration assays also showed that transfection of miRNA cocktails inhibited HSC migration. **Conclusion:** This study identified five anti-fibrotic miRNAs enriched in MSC-EVs and revealed a mechanism for the suppression of fibrosis via down-regulation of RhoA signaling by MSC-EVs.

Disclosures: Daiki Kawamoto: Nothing to Disclose, Toshihiko Matsumoto: Nothing to Disclose, Tsuyoshi Fujioka: Nothing to Disclose, Naoki Yamamoto: Nothing to Disclose, Taro Takami: Nothing to Disclose

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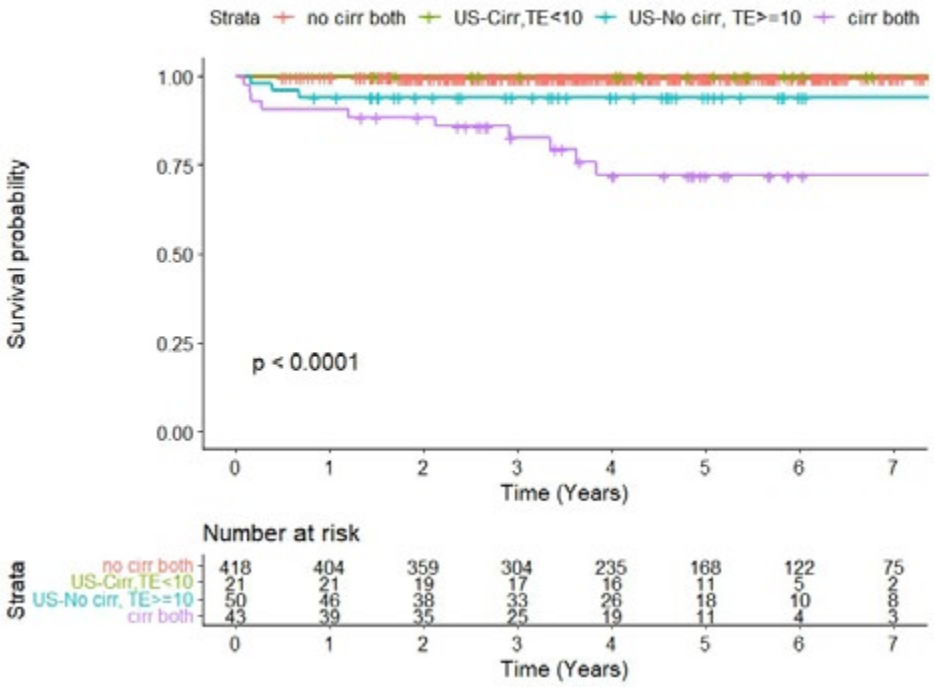
3561 | DISCORDANCE BETWEEN ULTRASONOGRAPHY AND TRANSIENT ELASTOGRAPHY (TE) IN THE DIAGNOSIS OF CIRRHOSIS: TE IS BETTER IN PREDICTING LONG-TERM OUTCOMES

Navavee Uman[1] *Pimsiri Sripongpun*[1] *Apichat Kaewdech*[1] *Naichaya Chamroonkul*[1]

[1]*Prince of Songkla University*

Background: Accurate assessment of fibrosis and cirrhosis is crucial to guide treatment and HCC surveillance in patients with chronic liver disease. Liver biopsy is the gold standard, but its invasiveness is the major limitation. Ultrasonography (USG) is a well-known imaging used in the diagnosis of cirrhosis. Transient elastography (TE) is developed to assess fibrosis and has been widely used now. The discordance between USG and TE results is frequently encountered in hepatology clinics. We aimed to evaluate long-term liver related events (LRE) in patients with concordant and discordant results of USG and TE regarding their cirrhosis status. **Methods:** This retrospective study included all chronic hepatitis B patients who underwent TE between 2014 and 2021 at a university hospital in Thailand. Patients with unreliable TE results, follow up <6 months, no USG results within 6 months of TE, or history of hepatic decompensation prior to TE were excluded. Cirrhosis diagnosed by TE was defined as LSM ≥10 kPa, and by USG as per radiologists' reports. LRE was defined as the development of HCC and/or cirrhosis complication(s). Kaplan-Meier and multivariable cox regression analysis were used to evaluate the risk of LRE in patients with concordant and discordant USG and TE results, adjusted by age, sex, and HBV DNA controlled status. **Results:** A total of 532 patients were eligible. Discordant results were found in 71 patients (13%), 418 (78.6%) had no cirrhosis by both tests [Group 1], 21 were reported having cirrhosis by USG but LSM<10 kPa [Cirrhosis by USG but not TE; Group 2], 50 had no cirrhosis by USG but LSM≥10 kPa [Cirrhosis by TE but not USG; Group 3], and 43 patients (8.1%) had concordant results of cirrhosis [Group 4]. The mean age appeared to be higher in group 2 than in other groups. Mean FIB-4 levels were 1.03, 1.4, 1.6, and 2.13 in group 1, 2, 3, 4, respectively (p<0.001). The LRE-free survivals of each group are shown in the Figure. The 5-year LRE-free survivals were 99.3%, 100%, 94%, and 72.1% in group 1, 2, 3, 4, respectively. In the Cox regression analysis, only group 3 and 4 had an increased risk of LREs (adjusted hazard ratio of 10.80 [95%CI 2.07-56.43] for group 3, p=0.005, and 46.23 [95%CI 10.87-196.61] for group 4, p<0.001), whereas group 2 were not different from those without cirrhosis. **Conclusion:** Discordant results in the diagnosis of cirrhosis between USG and TE was found in 13%. Those with both tests confirming cirrhosis had the highest risk of LREs. In those with discordant results, the TE was better than USG in predicting LREs.



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Disclosures: Navavee Uman: Nothing to Disclose, Pimsiri Sripongpun: Nothing to Disclose, Apichat Kaewdech: Nothing to Disclose, Naichaya Chamroonkul: Nothing to Disclose

3562 | TARGETING THE ANGPTL4-EIF2A AXIS IMPROVES FIBROTIC MASH BY MODULATING T CELL ACTIVATION

Damien Chua[1] *Hong Sheng Cheng*[1] *Nguan Soon Tan*[1]

[1]*Nanyang Technological University*

Background: The risk for liver-related mortality increases exponentially with advancing fibrosis stages in MASH, yet treatment options remain limited, revealing a significant clinical gap. Dietary insults contribute to a complex intrahepatic immune landscape driving fibrotic MASH. Angiopoietin-like protein 4 (Angptl4), a matricellular protein known for its roles in vascular leakiness are involved in many inflammatory-related diseases such as cardiovascular diseases. However, its role in fibrosis remains unclear. **Methods:** We used a human-relevant diet-induced MASLD model (LIDPAD) to profile and analyze the temporal intrahepatic immune landscape through multiparameter flow cytometry and single-cell transcriptomics. Anti-Angptl4 immunotherapy was administered intraperitoneally to LIDPAD mice with fibrosis as a therapeutic intervention. Guided by a systems biology approach, we elucidated the mechanism of Angptl4-associated T cell activation through kinomic analysis, adoptive transfer experiments, and flow cytometry. **Results:** Temporal profiling revealed a peak in the intrahepatic innate immune response during early steatotic stages and a peak in the adaptive immune response during fibrotic stages. Intrahepatic T cell numbers significantly increased during fibrosis development, particularly at weeks 8 and 12. Therapeutic targeting of Angptl4 with monoclonal antibodies ameliorated fibrosis in MASLD mice, highlighting the potential of anti-Angptl4 therapy. Further analysis, including kinomic profiling, showed Angptl4-dependent T cell activation via UPR and Eif2a signaling. **Conclusion:** Our findings highlight the pivotal role of Angptl4-mediated UPR in driving immune responses and underscore the promising therapeutic potential of Angptl4-mAb treatment in mitigating fibrosis in MASH.

Disclosures: Damien Chua: Nothing to Disclose, Hong Sheng Cheng: Nothing to Disclose, Nguan Soon Tan: Nothing to Disclose

3563 | LIVER SINUSOIDAL ENDOTHELIAL CELL-DERIVED EXTRACELLULAR VESICLES CONTAIN CATALASE THAT INDUCES SENESCENCE OF ACTIVATED HEPATIC STELLATE CELLS

Junyu Wang[1] *Jia Li*[1] *Manon Buist-Homan*[1] *Martin Harmsen*[1] *Han Moshage*[1]

[1]*University Medical Center Groningen*

Background: Liver sinusoidal endothelial cells (LSECs) are key to maintaining hepatic stellate cell (HSC) homeostasis. The intricate intercellular crosstalk between HSCs and LSECs is fundamental in modulating HSC quiescence and activation. Previous studies have identified LSEC-derived extracellular vesicles (EVs) as primary mediators in this regulatory process. However, the mechanisms through which LSECs and their EVs modulate the activated phenotype of HSCs (aHSCs) remain unclear. This study aims to investigate how LSEC-EVs influence HSC activation during liver fibrosis. **Methods:** Primary rat LSECs and HSCs were isolated from male Wistar rats. A primary cell transwell co-culture system of HSCs and LSECs was established to dissect the intercellular signaling mechanisms. EVs were isolated from LSEC-derived conditioned medium (CM) through differential centrifugation and characterized by nanoparticle tracking analysis, transmission electron microscopy, and EV-marker determination. Proteins present in EVs were identified by proteomic analysis. EVs and CM as well as selected proteins (catalase) in EVs were added to HSCs for 24 - 72 hours. Gene expression was determined by qPCR, protein expression by Western blot and immunofluorescence, and cell proliferation by Xcelligence and BrdU assay. **Results:** LSEC-derived EVs induced increased expression of components of the senescence-associated secretory phenotype (SASP), like IL-1 and senescence markers like senescence-associated β-galactosidase activity in aHSCs, while decreasing aHSC proliferation. These effects were also observed in the LSEC-aHSC transwell co-culture system. Catalase was identified in LSEC-derived EVs via proteomics. Since previous studies showed that exogenous catalase inhibits the activation of HSCs, we further investigated the

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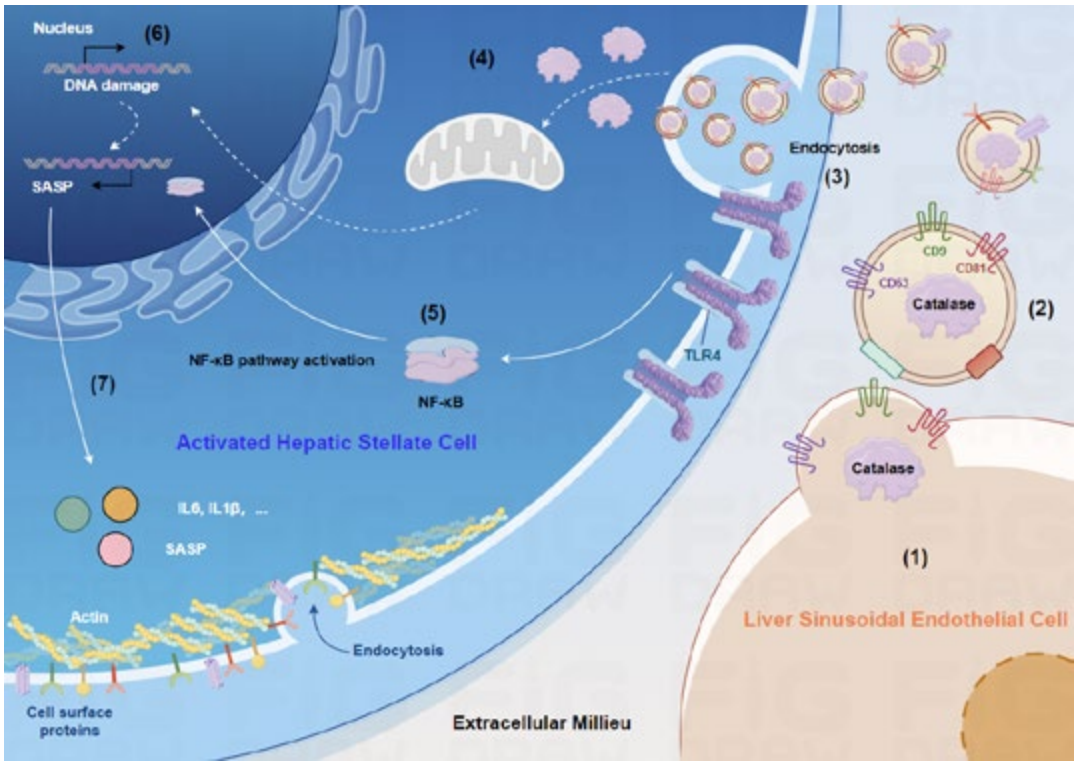
role of catalase. The presence of catalase in LSEC-derived EVs was confirmed by Western blot. Furthermore, the effects of LSEC-derived EVs on HSCs were mimicked by pegylated (cell permeable) catalase. **Conclusion:** Catalase-rich extracellular vesicles from liver sinusoidal endothelial cells reduce activation of HSCs by inducing senescence.



Disclosures: Junyu Wang: Nothing to Disclose, Jia Li: Nothing to Disclose, Manon Buist-Homan: Nothing to Disclose, Martin Harmsen: Nothing to Disclose, Han Moshage: Nothing to Disclose

3564 | TNFAIP3 MEDIATES JNK-DEPENDENT CHEMOKINE EXPRESSION IN HEPATIC STELLATE CELLS

Keiya Watakabe[1] *Masato Miyoshi*[1] *Sei Kakinuma*[1] *Ayako Sato*[1] *Kento Inada*[1] *Tomohiro Mochida*[1] *Taro Shimizu*[1] *Jun Tsuchiya*[1] *Tsubasa Nobusawa*[1] *Shun Kaneko*[1] *Fukiko Kawai-Kitahata*[1] *Miyako Murakawa*[1] *Mina Nakagawa*[1] *Yasuhiro Asahina*[1] *Ryuichi Okamoto*[1]

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Background: Hepatic stellate cells (HSCs) are activated under hepatic inflammation and play an important role in hepatic fibrosis. TNFAIP3 (A20) exhibit a lot of important functions in a variety of biological responses, including both regulation of inflammation and cell death and enhancement of autophagy. Loss of TNFAIP3 function in hepatocytes is involved in the development of metabolic dysfunction-associated steatohepatitis, however, the function of TNFAIP3 in HSCs is completely unknown. In this study, we analyzed the function of TNFAIP3 in HSCs. **Methods:** Mesenchymal cell-specific TNFAIP3 knockout (TNFAIP3 CKO) mice were generated by mating with *A20 flox/flox* mice with *Twist2-Cre* mice. The phenotype of TNFAIP3 CKO mice was assessed and comprehensive transcriptome data using HSCs derived from such mice was analyzed. The function of TNFAIP3 in HSCs was validated using human HSC line, LX-2. **Results:** Cre recombination was detetced in ~80-90% of HSCs in *Twist2-Cre* mice crossed with reporter mice. Our data showed that apparent inflammatory cell infiltration was observed in the liver of naïve TNFAIP3 CKO mice (without any treatment of liver damage). Sirius red staining showed the significantly increased liver fibrosis in the CKO mice. Comprehensive analysis showed upregulation of chemokine and cytokine signaling pathway in the liver. RNA sequence using HSCs isolated from TNFAIP3 CKO mice demonstrated the significantly upregulated the expression of chemokines, including Cxcl1 and Ccl2. Knockdown of TNFAIP3 in LX-2 induced the upregulation of chemokine expression and JNK phosphorylation. In contrast,

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overexpression of TNFAIP3 decreased chemokine expression in LX-2. JNK phosphorylation was also upregulated in HSCs in TNFAIP3 CKO mice. Further analysis from RNA sequencing indicated that inhibition of a TNFAIP3-target gene suppressed JNK phosphorylation and decreased chemokine expression. **Conclusion:** TNFAIP3 suppresses chemokine expression from HSCs under the condition without liver injury, and its dysfunction induces chemokine expression from HSCs and induces increased liver inflammation and fibrosis.

Disclosures: Keiya Watakabe: Nothing to Disclose, Masato Miyoshi: Nothing to Disclose, Sei Kakinuma: Nothing to Disclose, Ayako Sato: Nothing to Disclose, Kento Inada: Nothing to Disclose, Tomohiro Mochida: Nothing to Disclose, Taro Shimizu: Nothing to Disclose, Jun Tsuchiya: Nothing to Disclose, Tsubasa Nobusawa: Nothing to Disclose, Shun Kaneko: Nothing to Disclose, Fukiko Kawai-Kitahata: Nothing to Disclose, Miyako Murakawa: Nothing to Disclose, Mina Nakagawa: Nothing to Disclose, Yasuhiro Asahina: Nothing to Disclose, Ryuichi Okamoto: Nothing to Disclose

3565 | A NOVEL FGFR INHIBITOR BF12 ATTENUATES LIVER FIBROSIS BY SUPPRESSING THE PI3K/AKT AND ECM-RECEPTOR INTERACTION PATHWAYS

Dongke Yu[1] Ling Chen[2] Qi Liang[1] Linshen Xie[3] Yonghe Hu[2] Jianyou Shi[1]

[1]Sichuan Provincial People's Hospital, [2]Southwest Jiaotong University, [3]West China Fourth Hospital

Background: Liver fibrosis is an excessive accumulation of extracellular matrix that can lead to impaired function and liver failure. Currently, no cure exists, making a new treatment urgent. Fibroblast growth factor receptor (FGFR) has been shown to be a promising therapeutic target for liver fibrosis. Therefore, our group has designed and synthesized a novel isoindoline FGFR inhibitor F12 and investigated its effect on liver fibrosis and its mechanism. **Methods:** The cytotoxic effects of the FGFR inhibitor F12 on LX-2 cells were determined by the CCK-8 assay; the liver fibrosis model was successfully established in vitro using TGF-β1-induced LX-2 cells, and the mRNA expression of s of fibrosis-related protein, such as α-smooth muscle actin (ACTA2), collagen type I protein (COL1A1), and matrix metalloproteinase inhibitor (TIMP1), were detected by RT-qPCR. The pharmacokinetic properties of F12 were evaluated in vivo; the safety of F12 in vivo was evaluated by maximum tolerated dose (MTD). The effect of F12 on the protein expression of fibrosis-related markers in vitro was detected by Western blot. Additionally, the pathways predominantly influenced by the variation in gene expression across the study groups were elucidated through RNA-sequencing analysis, further substantiated by subsequent validation processes. **Results:** F12 inhibited LX2 cell proliferation by 60% at a 5 μM dose. The RT-qPCR results showed that F12 significantly inhibited the mRNA expression of α-Sma, Col1a1, and Timp1. According to the pharmacokinetic data, F12 had better pharmacokinetic characteristics in vivo. In the F12 group, administered at the MTD of 150 mg/kg in BALB/c mice, there was no notable reduction in body weight. Additionally, histological examination of vital organs including the heart, liver, spleen, lung, and kidney did not reveal any evidence of pathological alterations. Western blot results showed that F12 significantly inhibited the protein expression of COL1A1 and decreased the protein expression of TGF-β1, p-Smad2/3, p-PLCγ1, p-FRS2, and p-FGFR1 in the TGF-β1-induced LX-2 cells. RNA sequencing revealed that F12 notably reduced the activity of genes associated with fibrosis. The genetic differences between the TGF-β1 exposed group and the controls, as well as between F12 treated and TGF-β1 control groups, were predominantly linked to signaling pathways such as "TGF-beta signaling", "PI3K-Akt signaling", and "ECM-receptor interaction", all of which play crucial roles in the development of liver fibrosis. **Conclusion:** The compound F12, a novel FGFR inhibitor derived from isoindoline, has demonstrated significant effectiveness in a laboratory model of liver fibrosis. With advantageous pharmacokinetic properties and a reassuring safety profile, F12 emerges as a potential therapeutic agent for managing liver fibrosis.

Disclosures: Dongke Yu: Nothing to Disclose, Ling Chen: Nothing to Disclose, Qi Liang: Nothing to Disclose, Linshen Xie: Nothing to Disclose, Yonghe Hu: Nothing to Disclose, Jianyou Shi: Nothing to Disclose

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3566 | SCHISTOSOMIASIS-INDUCED LIVER FIBROSIS IS MORE SEVERE IN MICE INFECTED AT A YOUNG AGE DUE TO A HIGHER EGG BURDEN

Frederik Stettler[1] Verena von Buelow[1] Jan Straßmann[1] Maximilian Hagen[1] Max Möscheid[1] Christoph Grevelding[2] Elke Roeb[1] Martin Roderfeld[1]

[1]Justus Liebig University Giessen, [2]Justus Liebig University

Background: Schistosomiasis, a parasitic helminth infection, affects over 250 million people worldwide with highest infection rates at the age of 10-14 years. The influence of the host's age during infection on the severity of hepatic damage is unclear. Therefore, we systematically investigated the effect of host age at the time of infection on the hepatic impact of schistosomiasis. **Methods:** C57BL/6J/Crl mice were infected with *S. mansoni* in a water bath at the age of 8, 14, and 20 weeks. Hepatic damage, inflammation and fibrosis were analyzed by RT-qPCR, western blotting, ELISA, immunohistochemistry, and functional assays. Mechanistic aspects were investigated in co-culture experiments of *S. mansoni* eggs with human hepatic stellate cells (HSC) in a transwell-system. **Results:** We found that hepatomegaly, hepatic granulomas, egg load, inflammation, as well as fibrosis all improved with increasing host age at the time of infection. However, serum ALT levels were lowest in mice infected at a young age. Notably, *S. mansoni* eggs stimulated HSCs to an alternatively activated phenotype (GFAP+/desmin+/αSMA-), that secretes IL-6 and MCP-1. **Conclusion:** The formation of hepatic collagen-rich granulomas in mice infected with *S. mansoni* is age-dependent, with young mice affected most severely. Less severe fibrosis in mice infected at 20 weeks likely depends on the fine-tuning of regulatory and inflammatory cytokines as well as on alternative HSC activation. Finally, *S. mansoni* egg-induced alternative HSC activation may be crucial for parasite-induced hepatic fibrogenesis.

Disclosures: Frederik Stettler: Nothing to Disclose, Verena von Buelow: Nothing to Disclose, Jan Straßmann: Nothing to Disclose, Maximilian Hagen: Nothing to Disclose, Max Möscheid: Nothing to Disclose, Christoph Grevelding: Nothing to Disclose, Elke Roeb: Nothing to Disclose, Martin Roderfeld: Nothing to Disclose

3567 | CHEMOTHERAPEUTIC DRUGS INDUCE HEPATIC STELLATE CELL ACTIVATION IN HEPATOCELLULAR CARCINOMA VIA ROS-DEPENDENT PI3K PATHWAY

Qi Ruan[1] Lu Cao[2] Haotian Yang[2] Leslie Burke[2] Kim Bridle[2] Darrell Crawford[2] Xiaowen Liang[2]

[1]Gallipoli medical research/Frazer Institute, [2]Gallipoli Medical Research

Background: Chemotherapeutic drugs are widely used for transarterial chemoembolization (TACE) in hepatocellular carcinomas (HCC) patients. It has been reported that TACE and chemotherapy exacerbate liver fibrosis while the underlying mechanism is still unknown. As hepatic stellate cells (HSCs) are the main origin of cancer associated fibroblasts (CAFs) in liver cancer, we investigated the molecular mechanisms underlying HSC activation induced by chemotherapeutic drugs to identify the potential targets for improving liver cancer prognosis. **Methods:** HSC activation induced by chemotherapeutic drugs was examined by conditioned medium (CM) of cisplatin or doxorubicin pretreated Huh7 (human HCC cell line) in vitro. RNA sequencing and intracellular ROS level were investigated in HSCs exposed in different CM to identify the pathway involved in HSC activation. To verify the results, three HCC orthotopic models representing different stages of liver fibrosis was conducted, including orthotopic HCC mouse model, HCC mouse model with fibrosis background induced by thioacetamide acid, and spontaneous HCC model using 11 month-Mdr2 knockout mice. Chemotherapeutic drugs, cisplatin or doxorubicin, were given a total of four doses after 9 days of surgery. Tumour tissues were collected for immunofluorescence staining and western blot. Alpelisib, a PI3K α-specific inhibitor, was assessed its inhibitory effect on cisplatin-induced HSC activation. **Results:** The paracrine effect of cisplatin pretreated Huh7 cells significantly induced HSC activation, which was further confirmed in the orthotopic mouse models with normal and fibrotic liver background treated with cisplatin. Doxorubicin cannot further trigger HSC activation in vitro and in vivo. Moreover, we did not observe HSC activation by cisplatin in the cirrhotic liver background as the activation marker, a smooth muscle actin (aSMA), strongly expressed throughout the untreated tumour tissues. Regarding to the mechanism, intracellular ROS level was observed in LX2 cells cultured in cisplatin CM, but not doxorubicin CM. Oxidative stress led to PI3K activation in HSCs. We used the tumour tissues to confirm the PI3K activation induced by cisplatin treatment in all three HCC orthotopic models. Blocking PI3K p110a significantly suppressed its downstream Akt phosphorylation and resulted in inhibiting HSC activation induced by ROS and cisplatin CM.

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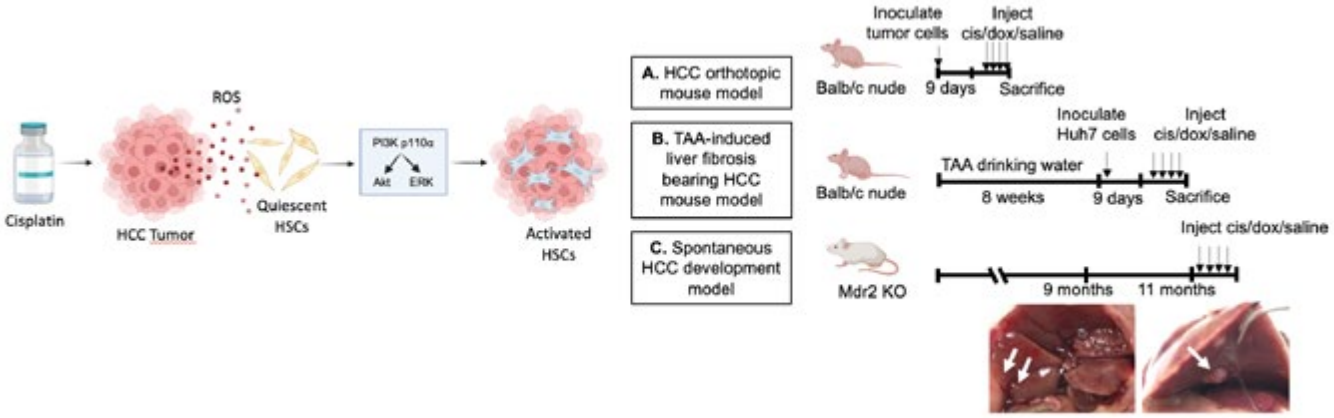
Conclusion: In the present study, we confirm that cisplatin induces HSC activation through paracrine factors of HCC cells through ROS-mediated PI3K pathway. The findings were verified in the orthotopic mouse models of normal and fibrotic liver background. The fibrosis condition can be considered for the therapeutic drug choice for HCC patients and targeting HSC activation can be a promising therapeutic strategy for improving the treatment efficacy.



Disclosures: Qi Ruan: Nothing to Disclose, Lu Cao: Nothing to Disclose, Haotian Yang: Nothing to Disclose, Leslie Burke: Nothing to Disclose, Kim Bridle: Nothing to Disclose, Darrell Crawford: Nothing to Disclose, Xiaowen Liang: Nothing to Disclose

3568 | THE IMPACT OF IQR/MEDIAN ON THE ACCURACY OF LIVER STIFFNESS MEASUREMENT PREDICTING ADVANCED FIBROSIS ON LIVER BIOPSY

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[1]*Virginia Commonwealth University*

Background: Vibration controlled transient elastography (VCTE) for liver stiffness measurements (LSM) is increasingly used to evaluate advanced fibrosis (AF). For a valid LSM, the interquartile range to median ratio (IQR/med) should be <30%. However, the impact of IQR/med on LSM across the acceptable range (1-30%) is not well defined. We hypothesized that a lower IQR/med would improve the diagnostic performance of VCTE by predicting AF (F3-4) proven by biopsy. **Methods:** This was a retrospective cohort study of 129 patients age 18 or older with chronic liver disease who underwent liver biopsy and VCTE 2016-2020; 19% with chronic HCV, 60% MASH, 20% other. Patients were excluded if they had a history of liver transplant, liver cancer, interquartile range/median > 30%, infiltrative disease on liver biopsy, or pregnant. Clinical and liver biopsy data was collected. All VCTE evaluated LSM and controlled attenuated parameter (CAP) for steatosis. Liver histology for fibrosis by Ishak score was assessed, blinded to LSM. The diagnostic performance VCTE and impact of IQR/med, both continuous and by tertile (1-10, 11-20, 21-30%) on LSM to identify AF by histology was assessed. **Results:** The mean (SD) age was 54 (12), 60% were female, and 71% had AF by biopsy. The average LSM was 15.8 (9.2) kPa and CAP 293 (85) dB/m with IQR/med ranged from 2-32% with 27% IQR/med 1-10, 46% 11-20, and 26% 21-30. Those with AF by biopsy had higher LSM (21 vs. 12 kPa; p<.0001) with similar IQR/med (16%) and IQR/med tertile distribution (Table). Using LSM threshold of 12 kPa for AF, specificity (Sp), positive predictive value (PPV) and accuracy were similar with high sensitivity (Sp) and negative predictive value (NPV) similar across the IQR/med tertiles for AF on biopsy (Table). Adjusting for age, sex, and CAP, LSM remained significantly associated with AF (p<.0001) with an AUROC of 0.80 while IQR/med or tertile was not associated with AF on liver biopsy. **Conclusion:** In this retrospective study, we observed that LSM highly correlated with AF in patients with biopsy proven fibrosis. We did not find an impact of IQR/med on the diagnostic performance of VCTE to identify AF by liver histology. Our results validate the threshold IQR/med of <30% in VCTE for LSM used in clinical practice and that LSM performs as well across the acceptable IQR/med range and was not better in those with low IQR/med (≤10%) compared to those with high IQR/med (21-30%).

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Table: Diagnostic performance of LSM by IQR/med of entire cohort and by tertile to predict F3-4 on biopsy.

IQR/Med %	N	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
1-30	129	98	46	54	97	66
1-10	35	100	65	68	100	80
11-20	60	95	40	44	94	58
21-30	34	100	38	59	100	67

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3569 | EVALUATION OF HIV-INDUCED LIVER INFLAMMATION AND FIBROSIS USING A NOVEL *EX VIVO* HUMAN LIVER MODEL

Yongtao Wang[1] Shadi Salloum[2] Ben Leaker[3] Mozhdeh Sojoodi[2] Ibrahim Eissa[2] Wenyu Lin[2] Min Xu[2] Nadia Alatrakchi[2] James Reed[2] Eliana Epstein[2] Jonathan Eddy[2] Oizoshimoshiofu Dimowo[2] Cecilie Siem Bach-Nielsen[2] Kenneth Tanabe[2] Georg Lauer[2] Raymond Chung[2]

[1]Massachusetts General Hospital and Harvard Medical School, [2]Massachusetts General Hospital, [3]Massachusetts Institute of Technology

Background: The most commonly used non-human primates and other animal models do not effectively recapitulate HIV infection and pathology in humans, including liver pathology. Suitable and tractable models for HIV-related liver researchare urgently needed. The *ex vivo* precision cut liver slice (PCLS) enables liver research in a setting that retains the architecture of liver from humans, and faithfully models the signal transduction pathways between different cell types including resident macrophages that produce cytokines to drive liver damage. **Methods:** The TCGA analysis of *in vivo* patient liver samples infected with HIV was performed. PCLS with a thickness of 250 μm from human livers were prepared. These slices were subsequently subjected to HIV virus infection alongside supplementary treatment protocols. Molecular assessment was further performed. **Results:** TCGA analysis unveiled significant insights into the impact of HIV infection on patient liver resident Kupffer macrophages *in vivo*. HIV infection led to a decrease in liver function signatures while inducing inflammatory and profibrogenic markers, alongside heightened immune activity and upregulation of EGFR and its downstream genes. Utilizing the *ex vivo* PCLS model, MTS assays showed its viability slightly decreased after 96 hours in culture. Consistently, HIV Gag mRNA expression post-infection validated the successful establishment of a PCLS-HIV model for subsequent studies. HIV infection in PCLS triggered the upregulation of inflammatory and profibrogenic gene expression. Notably, this phenotype exhibited a time-dependent relationship with HIV infection, particularly pronounced in PCLS derived from livers afflicted with metabolic dysfunction-associated steatotic liver disease (MASLD). Moreover, the reprogramming of resident M1 and M2 macrophages was observed upon HIV infection in PCLS. Intriguingly, erlotinib, an EGFR inhibitor previously identified as an antifibrotic agent, demonstrated efficacy in mitigating HIV-induced inflammatory and profibrogenic responses in PCLS. Furthermore, the reprogramming of M1 and M2 macrophages was further augmented following erlotinib treatment in HIV-infected PCLS. **Conclusion:** These data suggest that PCLS is a novel and robust *ex vivo* human liver model to evaluate HIV-induced liver inflammation and fibrosis, which are in line with the principles of Replacement, Reduction and Refinement (3Rs).

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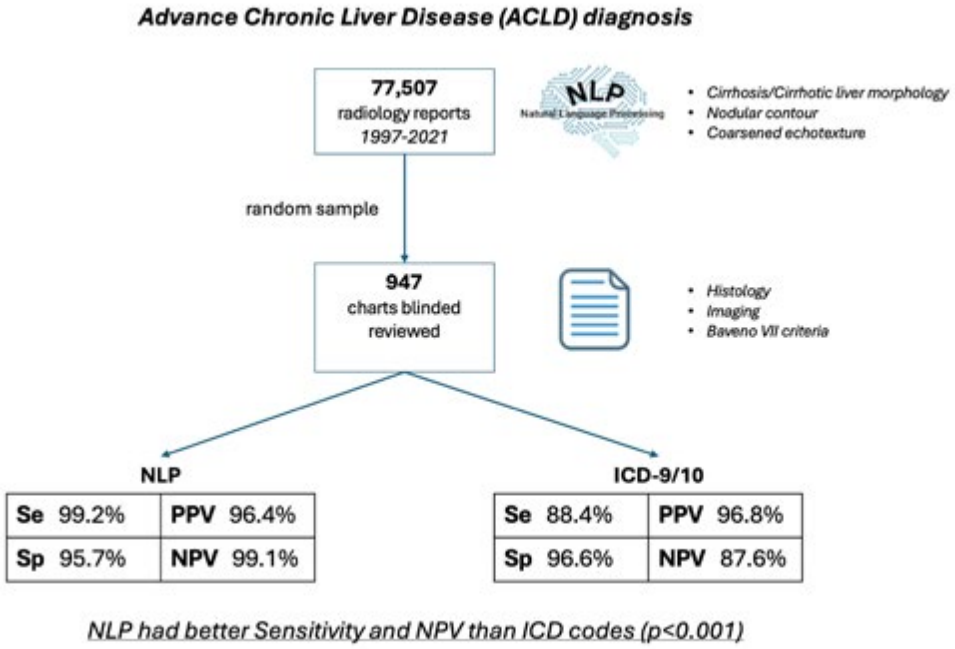
Disclose, Cecilie Siem Bach-Nielsen: Nothing to Disclose, Kenneth Tanabe: Nothing to Disclose, Georg Lauer: GSK: Grant/Research Support, GSK: Consultant, Raymond Chung: Nothing to Disclose

3570 | VALIDATION OF A NATURAL LANGUAGE PROCESSING MODEL FOR THE DETECTION OF ADVANCED CHRONIC LIVER DISEASE

Alberto Calleri[1] Puru Rattan[2] Blake Kassmeyer[1] Ryan Lennon[1] Patrick Kamath[1] Vijay Shah[1] Douglas Simonetto[1]

[1]Division of Gastroenterology and Hepatology, Mayo Clinic, [2]Division of Gastroenterology and Hepatology, University of Pennsylvania Perelman School of Medicine

Background: The International Classification of Diseases (ICD) coding system is commonly utilized to generate datasets from electronic health records. However, its accuracy relies on code assignment, and can vary over time. Natural language processing (NLP) represents a promising artificial intelligence (AI) tool for extracting data from medical records, yet its validity in hepatology remains untested. This study aims to validate the NLP methodology and to compare NLP against ICD in identifying patients with advanced chronic liver disease (ACLD). **Methods:** The MedTagger NLP tool was utilized to analyze radiology reports (US, CT, MR) performed at Mayo Clinic sites between 1997 and 2021, utilizing specific terms as “cirrhotic liver morphology,” “coarsened hepatic echotexture,” “nodular contour,” “consistent with cirrhosis,” “cirrhosis,” and “cirrhotic.” The performance of NLP was validated against information extracted by blinded manual chart review (gold standard) and compared to ICD-9/10 (two cirrhosis codes 30 day apart were required to be considered a diagnosis). The diagnosis of ACLD was confirmed through histology, imaging or according to Baveno VII criteria. Percentages are reported with 95% confidence intervals (CI) according to the Agresti-Coull method. **Results:** A total of 77,507 reports were analyzed by NLP and 947 patients were then randomly selected stratified on NLP/ICD results to maintain power for chart review, among whom 513 (54.2%) were identified as having ACLD while 434 (45.8%) had no history of liver disease. NLP correctly classified 511 out of 513 ACLD patients and 417 out of 434 controls, while ICD codes correctly identified 455 out of 513 ACLD patients and 421 out of 434 controls. The sensitivity was 99.2% (95% CI, 98.5-100) for NLP and 88.4% (95% CI, 85.6-91.2) for ICD (p<0.001). Specificity was 95.7% (95% CI, 93.8-97.6) for NLP and 96.6% (95% CI, 94.9-98.3) for ICD, p=0.21. PPV was 96.4% (95% CI, 94.9-98.0) for NLP and 96.8% (95% CI, 95.3-98.4) for ICD (p=0.47), while NPV was 99.1% (95% CI, 98.2-100) for NLP and 87.6% (95% CI, 84.6-90.5) for ICD (p<0.001). **Conclusion:** NLP correctly identified patients with ACLD and outperformed ICD codes, demonstrating significantly higher sensitivity and NPV while maintaining similar specificity and PPV. AI tools, such as NLP, are valuable for extracting data from health records and could enhance the performance of ICD codes. However, NLP accuracy should be tested broadly in hepatology to better understand the extent of its capabilities.



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Disclosures: Alberto Calleri: Nothing to Disclose, Puru Rattan: Nothing to Disclose, Blake Kassmeyer: Nothing to Disclose, Ryan Lennon: Nothing to Disclose, Patrick Kamath: Advisor relationship with Sequana; Has ended; Advisor relationship with NovoNordisk; Has ended, Vijay Shah: Boehringer Ingelheim: Consultant, GSK: Consultant, GENFIT SA: Consultant, Intercept Pharmaceuticals, Inc.: Advisor, Korro Bio, Inc.: Consultant, Mallinckrodt Pharmaceuticals: Advisor, Novo Nordisk A/S: Consultant, Resolution Therapeutics, Ltd.: Advisor, Seal Rock Therapeutics, Ltd.: Consultant, Surrozen: Advisor, Douglas Simonetto: Consultant relationship with BioVie; Has ended; Consultant relationship with Iota; Has ended; Consultant relationship with Mallinckrodt; Has ended; Consultant relationship with Resolution Therapeutics; Has ended; Consultant relationship with Evive; Has ended

3571 | PERFORMANCE AND CLINICAL VALUE OF SHEAR WAVE ELASTOGRAPHY (SWE) IN DIAGNOSING ADVANCED LIVER FIBROSIS BY COMPARING WITH LIVER BIOPSY AND OTHER NON-INVASIVE FIBROSIS TESTS (NIFTS)

Ke-Qin Hu[1] *Hien Lau*[1]

[1]*University of California, Irvine*

Background: Elastography is a standard for staging liver fibrosis. Two models, transient and shear wave elastography (TE and SWE), are currently used. Compared to TE, the performance and clinical value of SWE in diagnosing advanced liver fibrosis, i.e., F3-4 is less studied. This study assessed the performance of SWE in diagnosing F3-4 and its association with the clinical presentation, liver biopsy and other NIFTs. **Methods:** A single-center retrospective study on 438 patients followed at the UC Irvine Medical Center Liver Clinic for various chronic liver diseases (CLDs) with biopsy and histological stage of liver fibrosis, Supersonic SWE measurements, several NIFTs, and clinical and laboratory data. **Results:** The mean age was 57 ± 14; 217 (49.5%) were male; 260 (59.4%) had a BMI ≥ 25; 83 (19.2%), 85 (19.6%), and 124 (28.6%) had chronic hepatitis C, B, and metabolic dysfunction-associated steatotic liver disease (MASLD), respectively. Using histological F3-4 as the reference, the sensitivity and specificity of SWE was 73.8% and 68.6% for F3-4, respectively. Compared to F0-2 by SWE, 210 (47.9%) had F3-4 by SWE, that were significantly associated with age ≥ 50 (81.9% vs. 72.4%, p=.02), BMI ≥ 25 (64.8% vs. 54.4%, p=.03), diabetes mellitus (49.3% vs. 26.8%, p<.01), albumin < 3.5 g/dL (22.7% vs. 8.6%, p<.01), INR ≥ 1.2 (25.5% vs. 7.2%, p<.01), platelets ≤ 120 x 10^9/L (29.3% vs. 16.0%, p<.01), clinical evidence of cirrhosis (77.1% vs. 21.1%, p<.01), and hepatic decompensation (HD, 29.3% vs. 5.1%, p<.01). Multivariate analysis showed that F3-4 by SWE was significantly associated with INR ≥ 1.2 (95% CI 1.2-6.2, p=.019) and clinical cirrhosis (95% CI 5.1-16.2, p<.001), independent to platelets ≤ 120 x 10^9/L, albumin < 3.5 g/dL, and HD. Compared to F0-2 by SWE, F3-4 by SWE was also significantly associated with histological F3-4 (59.9% vs. 19.5%, p<.01), MELD score ≥ 10 (39.3% vs. 20.8%, p<.01), Child score > 6 (43.5% vs. 23.9%, p<.01), APRI score > 1 (36.3% vs. 20.8%, p<.01), FIB-4 score > 2.67 (50.0% vs. 24.5%, p<.01), and clinically significance portal hypertension (CSPH) by endoscopic ultrasound guided portal pressure gradient (EUS-PPG) measurement ≥ 10 mmHg (30.3% vs. 10.7%, p=.04). Multivariate analysis showed that F3-4 by SWE was significantly associated with histological F3-4 (95% CI 2.9-38.4, p<.001) and MELD score ≥ 10 (95% CI 1.4-19.4, p=.015), independent to Child score > 6, FIB-4 score > 2.67, APRI score > 1, and CSPH. **Conclusion:** SWE is sensitive and specific in diagnosing F3-4, independently and significantly associated with histological F3-4, MELD score ≥ 10, clinical cirrhosis, and elevated INR. These results indicated that SWE provides additional clinical value to NIFTs for diagnosing advanced liver fibrosis in various CLDs.

Disclosures: Ke-Qin Hu: Medrigal: honomarium, Hien Lau: Nothing to Disclose

3572 | S100A6 REGULATED BY PATZ1 PROMOTES LIVER FIBROSIS BY ACTIVATING HEPATIC STELLATE CELLS

Qian Xue[1] *Liang Deng*[1] *Jinqiu Zhao*[1] *Fengling Peng*[1] *Youping Zhou*[1] *Li Zhong*[1] *Lu Huang*[1] *Shan Li*[1] *Chunhong Guo*[1]

[1]*Chongqing Medical University*

Background: Hepatic fibrosis, characterized by increased extracellular matrix deposition, stems from various factors such as viral infections, alcohol abuse, and metabolic disorders. The transition of hepatic stellate cells

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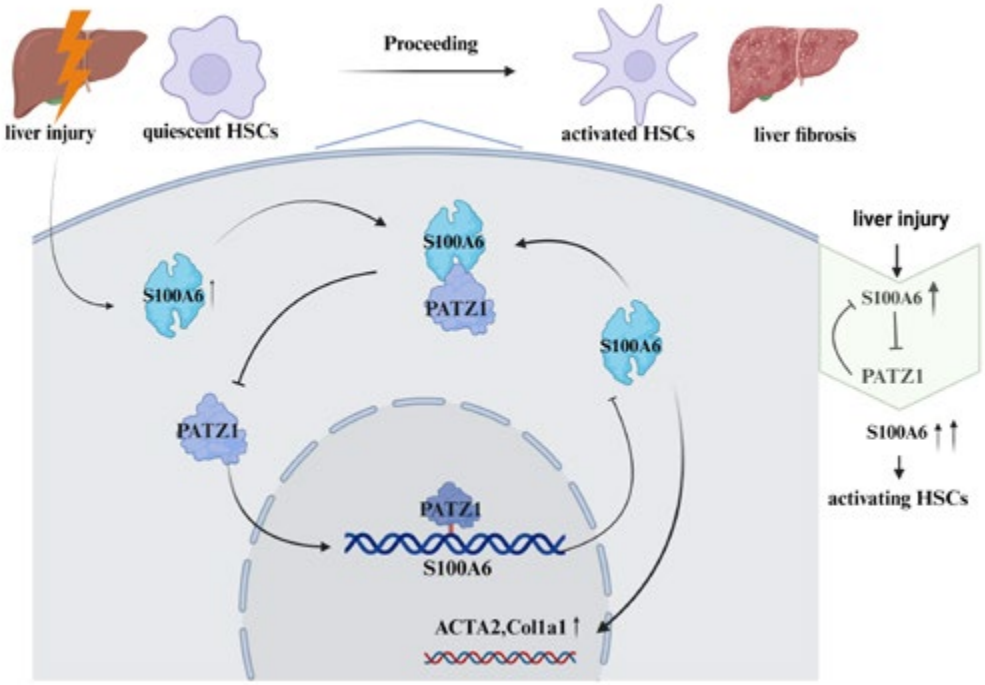
(HSCs) from a quiescent state to active myofibroblasts is pivotal in the progression of this disease. While S100A6, a member of the S100 protein family, and PATZ1, a transcriptional regulator, are speculated to play crucial roles in the fibrotic process, their specific functions and interactions in the context of liver fibrosis remain incompletely understood. **Methods:** Our study utilized C57BL/6 mice models for hepatic fibrosis induced by both CCl4 administration and a high-fat diet, mimicking metabolic dysfunction-associated steatohepatitis (MASH). Adenovirus and HBAAV were employed to knock down S100A6 and overexpress PATZ1. Primary HSCs were isolated from mice, cultured, and subjected to RNA interference. RNA sequencing (RNA-seq) and Electrophoretic Mobility Shift Assay (EMSA) were conducted to explore the interactions between S100A6 and PATZ1. **Results:** Analysis of data from the GEO database revealed that PATZ1 expression was significantly decreased in liver cirrhosis patients, negatively correlated with fibrosis severity. Overexpression of PATZ1 inhibited HSCs activation and alleviated liver fibrosis in vivo, as evidenced by reduced expression of fibrotic markers and decreased fibrotic areas in a CCl4-induced mouse model. Mechanistically, PATZ1 negatively regulated S100A6 expression, impairing HSC-activated signaling pathways. Conversely, S100A6 expression was progressively upregulated during liver fibrosis progression, particularly in activated HSCs, indicating its potential as a diagnostic marker. Knockdown of S100A6 inhibited HSCs activation and alleviated liver fibrosis in both in vitro and in vivo models. Additionally, S100A6 acted downstream of PATZ1 in regulating HSC activation. EMSA experiments confirmed PATZ1's binding to the S100A6 promoter, further elucidating its regulatory mechanism. **Conclusion:** Overall, our findings highlight the inhibitory role of PATZ1 on HSCs activation through suppression of S100A6 expression, offering potential therapeutic avenues for liver fibrosis management. Further research is warranted to explore the clinical implications of PATZ1 and S100A6 in liver fibrosis diagnosis and prognosis assessment.



Disclosures: Qian Xue: Nothing to Disclose, Liang Deng: Nothing to Disclose, Jinqiu Zhao: Nothing to Disclose, Fengling Peng: Nothing to Disclose, Youping Zhou: Nothing to Disclose, Li Zhong: Nothing to Disclose, Lu Huang: Nothing to Disclose, Shan Li: Nothing to Disclose, Chunhong Guo: Nothing to Disclose

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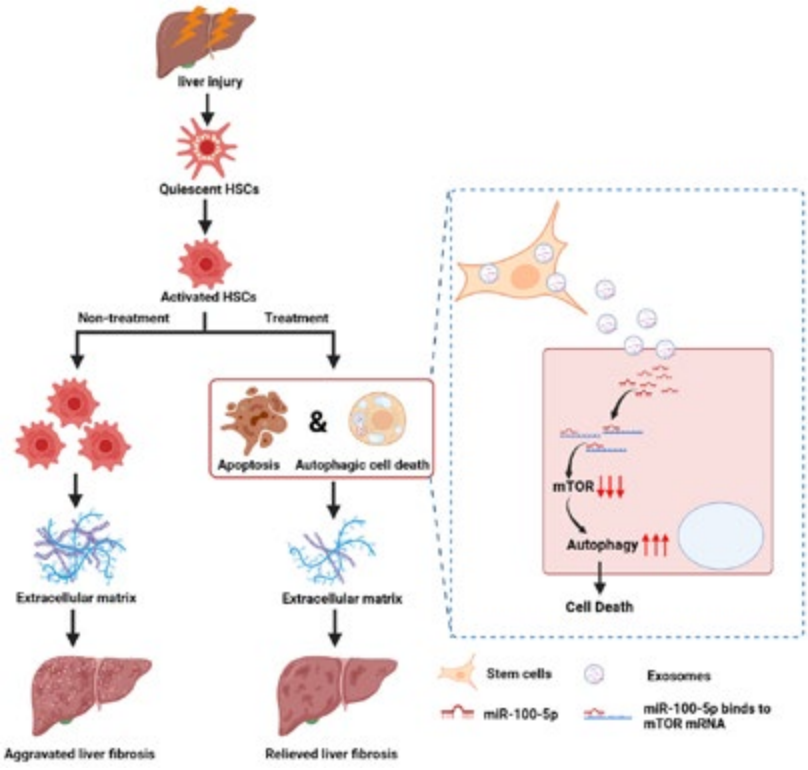
3573 | HUC-MSCS EXOSOME-DERIVED MIR-100-5P ALLEVIATES LIVER FIBROSIS BY INDUCING AUTOPHAGIC DEATH OF HEPATIC STELLATE CELLS

yonghong wang[1] *Menglan Wang*[1] *Yachao Tao*[1] *dongbo wu*[1] *enqiang Chen*[1] *hong Tang*[1]

[1]*West China hospital, Sichuan University*

Background: The incidence of end-stage liver disease is very high in the late stage of liver fibrosis,so early treatment of liver fibrosis is of great significance. Stem cell derived exosomes may play a role in treating disease by carrying various factors.The purpose of this study was to explore the therapeutic effect of stem cell exosomes on liver fibrosis and its mechanism. **Methods:** The therapeutic effects of exosomes on liver fibrosis were investigated in vivo and in vitro.The expression profiles of microRNA(miRNA) in exosomes were analyzed by sequencing, and the miRNA with the most significant anti-hepatic fibrosis effect were screened and verified in vitro. Overexpression and interference of miR-100-5p in exosomes and comparison of the therapeutic effects of exosomes on liver fibrosis. Finally, the target genes of miR-100-5p were screened and the mechanism of anti-liver fibrosis was further explored. **Results:** Exosomes can inhibit the expression of fibrosis-related factors a-SMA and COL1α1 in LX-2 cells. In liver fibrosis mice, exosome therapy improved liver histopathology, liver function, and decreased α-SMA expression in liver tissue. The highly expressed miR-100-5p in exosomes was screened by sequencing. MiR-100-5p can significantly inhibit the proliferation of LX-2 cells and the expression of α-SMA, COL1α1 and TIMP-1 in vitro.The exosomes overexpressing miR-100-5p could significantly improve the liver histopathology, liver function and inflammation-related indicators in liver fibrosis mice. However, interfering with miR-100-5p expression in exosomes significantly attenuated this therapeutic effect. The target gene of miR-100-5p was identified as mTOR. In liver fibrosis mice, the expression of mTOR in liver tissue was significantly increased, while exosomes overexpressing miR-100-5p significantly down-regulated the expression of mTOR in liver tissue. Meanwhile, it was found that exosomes overexpressing miR-100-5p can significantly inhibit the proliferation of LX-2 cells and promote their apoptosis, which is influenced by autophagy inhibitors. Overexpression of miR-100-5p in exosomes significantly inhibited the expression of mTOR, but enhanced the expression of autophagy associated proteins LC3II and Beclin-1. Exosomes overexpressing miR-100-5p can induce significant apoptosis in LX-2 cells, and the addition of chloroquine can significantly reduce the proportion of apoptotic cells. **Conclusion:** HUC-MSCs exosome-derived miR-100-5p alleviates liver fibrosis by inhibiting the expression of mTOR and inducing autophagic death of hepatic stellate cells.



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Disclosures: yonghong wang: Nothing to Disclose, Menglan Wang: Nothing to Disclose, Yachao Tao: Nothing to Disclose, dongbo wu: Nothing to Disclose, enqiang Chen: Nothing to Disclose, hong Tang: Nothing to Disclose

3574 | IMPROVEMENT OF LIVER CIRRHOSIS USING HEPATOCYTE-DERIVED LIVER PROGENITOR-LIKE CELLS (HEPLPCS): A PROSPECTIVE, OPEN LABEL, SINGLE ARM, SAFETY TRIAL

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Background: The escalating demand for liver transplantation, coupled with the scarcity of donor organs and inherent transplantation risks, underscores the urgent need for innovative cirrhosis treatments. **Methods:** To address this, we have developed a protocol for transforming human primary hepatocytes into expandable Hepatocyte-Derived Liver Progenitor-Like Cells (HepLPCs).This study comprises a pre-clinical phase and an inaugural clinical trial involving nine cirrhosis patients to assess the feasibility and safety of HepLPC treatment. This investigator-initiated clinical study, generously funded by Shanghai Cryowise Technology Co., Ltd., marks a significant advancement in addressing the unmet medical needs of liver cirrhosis patients. The study for both donors and recipients received ethical approval from the Ethics Committee of Renji Hospital, Shanghai Jiao Tong University School of Medicine (KY2020-084), and is meticulously registered on both ClinicalTrials.gov (NCT04806581) and the Chinese Clinical Trial Registry (ChiCTR2000032383). **Results:** In animal models, these cells exhibited anti-fibrotic properties and facilitated liver regeneration. The HepLPCs infusion was well-tolerated, devoid of transfusion reactions or dose-limiting toxicities. Primary outcome measures, encompassing safety and feasibility, were successfully met. Notably, the results revealed enhanced liver function following HepLPCs infusion, indicating significant improvements in cirrhosis indicators over a 6-month observation period. **Conclusion:** These promising findings advocate for the therapeutic potential of HepLPCs as an innovative strategy for liver cirrhosis, warranting further exploration through clinical trials, particularly in decompensated cirrhosis and acute-on-chronic liver failure patients.

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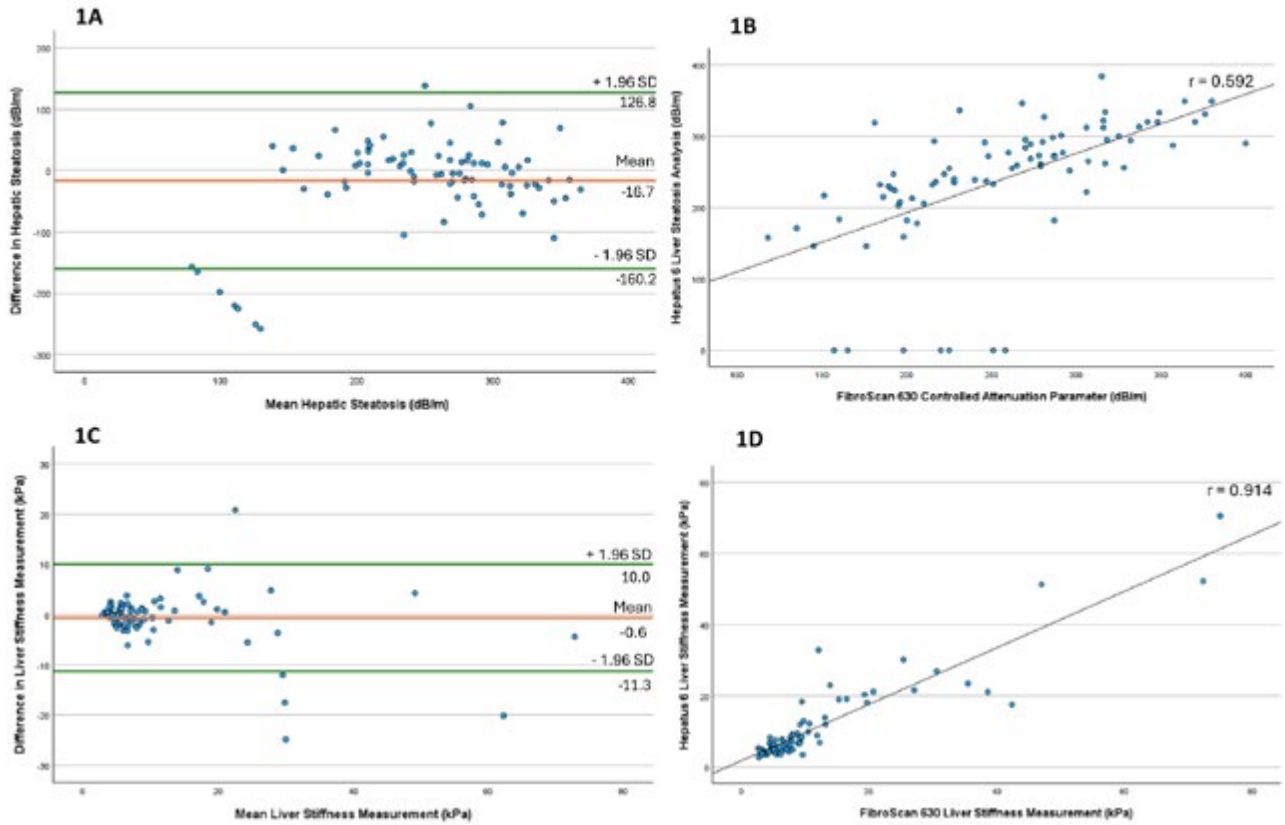
Figure 1. Comparison of Hepatic Steatosis (1A, 1B) and Liver Stiffness Measurement (1C, 1D) of Hepatus 6 and FibroScan 630 Expert, respectively.



Disclosures: hexin Yan: Nothing to Disclose

3575 | COMPARATIVE EVALUATION OF DIAGNOSTIC ULTRASOUND ELASTOGRAPHY WITH GUIDED VIBRATION-CONTROLLED TRANSIENT ELASTOGRAPHY IN PATIENTS WITH CHRONIC LIVER DISEASE

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Background: Non-invasive evaluation of hepatic steatosis and fibrosis is increasingly standard in evaluating and managing patients with chronic liver disease. Our study compared two clinic-based devices: Guided Vibration-Controlled Transient Elastography (Guided VCTE™) by FibroScan630 Expert (Echosens, USA) and Transient Elastography with diagnostic ultrasound by Hepatus 6 (Mindray, USA). We aimed to compare measurements of hepatic steatosis—using liver steatosis analysis (LiSA) with Hepatus 6 and continuous controlled attenuation parameter (continuous CAP) with Guided VCTE™—and liver stiffness measurement (LSM). **Methods:** In an IRB-approved study, 82 study participants with liver disease [steatotic liver disease (n=30), chronic hepatitis B (n=4), chronic hepatitis C (n=6), autoimmune hepatitis (n=5), primary biliary cholangitis (n=3), hemochromatosis (n=2), alcohol liver disease (n=6), liver transplant (n=6), other (n=20)] underwent evaluation with Guided VCTE™ followed by Hepatus 6 during the same visit. Descriptive statistics, Pearson correlation coefficient, and Bland-Altman plot analyses were performed to compare the differences between the measurements obtained by the two elastography devices. **Results:** The median age of participants was 54.5 years (range 21-86 years) and 52% were males. The mean LiSA and CAP scores, as determined by the Hepatus 6 and FibroScan 630, were 240.5 ± 89.8 dB/m and 257.2 ± 64.1 dB/m (p-value 0.173), respectively. There were seven patients with LiSA values of 0 dB/m, all of which occurred when CAP values were in the normal range (157 to 258 dB/m) (Figure 1A and 1B). There was a strong correlation between LiSA and CAP (r = 0.592, p = <0.001) (Figure 1B). Compared to the

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FibroScan 630 Expert, the Hepatus 6 underpredicted the degree of hepatic steatosis in patients with low CAP values (Figure 1B). The mean LSM determined by the Hepatus 6 and FibroScan 630 were 10.9 + 11.6 kPa and 11.5 + 13.3 kPa, respectively (p-value = 0.756). There was more variance in LSM at higher values (Figure 1C and 1D), but they were otherwise strongly correlated (r = 0.914, p = <0.001). **Conclusion:** Measures of hepatic steatosis and fibrosis obtained by the Hepatus 6 and FibroScan 630 Expert show a strong correlation; however, there appears to be a divergence in values outside the normal range.

Disclosures: Elizabeth Williams: Nothing to Disclose, Regina Weber: Nothing to Disclose, Samer Gawrieh: Transmedics: Consultant, pfizer: Consultant, kowa: Consultant, spruce: Consultant, viking: Grant/Research Support, zydus: Grant/Research Support, dsm: Grant/Research Support, Sonicincytes: Grant/Research Support, Novo Nordisk: Consultant, Niharika Samala: Novo Nordisk: Consultant, Naga Chalasani: Madrigal: Consultant, Zydus, Ipsen, Pfizer, Merck, Altimmune, GSK: Consultant, Exact Sciences: Grant/Research Support, NIH: Grant/Research Support, Raj Vuppalanchi: Eli LIlly: Advisor, GSK: Advisor, Madrigal: Advisor, Zydus Therapeutics: Grant/Research Support, Galectin Therapeutics: Grant/Research Support, Kowa: Grant/Research Support, Takeda: Grant/Research Support, GSK: Consultant, UBC: Consultant

3576 | FIBROMODULIN SELECTIVELY ACCELERATES ACTIVATED HEPATIC STELLATE CELLS APOPTOSIS IN LIVER FIBROSIS BY UPREGULATING INTERLEUKIN 1β EXPRESSION

Yichun Yang[1] Chunhong Guo[1] Shan Li[1] Lu Huang[1] Jinqiu Zhao[1] Xiaoxiao Pang[1] Liang Deng[1]

[1]Chongqing Medical University

Background: Hepatic stellate cells (HSC) activation into myofibroblasts exhibits a pivotal role during the progression of liver fibrosis. Targeting myofibroblasts apoptosis have been considered to be a therapeutic strategy for liver fibrosis. Interestingly, we previously found that fibromodulin (FMOD) could selectively induce cutaneous myofibroblast apoptosis to reduce skin fibrosis, which brings us a question if similar effects could be observed in the liver. Thus, in this study, we intend to investigate the role and the underlying mechanism of FMOD in liver fibrosis. **Methods:** The expression of FMOD in the human and mouse liver fibrosis or cirrhosis was analyzed by GEO database, and verified by immunohistochemistry (IHC). CCl_4 was used to induce liver fibrosis in wild type C57BL/6J mice and FMOD knockout mice ($FMOD^{-/-}$). Additionally, different concentrations (1mg/kg, 2mg/kg, 5mg/kg) of recombinant human FMOD protein (rhFMOD) were intraperitoneally injected into mice. rhFMOD was utilized in TGF-β1-induced activation of human hepatic stellate cells (LX2) or mouse HSC. Masson staining and IHC were stained in liver tissues, RT-qPCR and Western blot were performed to detect fibrotic factors and IL-1β, TUNEL staining and flow cytometry were used to detect the apoptosis rate**. Results:** The expression of FMOD in human and mouse liver fibrosis was significantly increased, and the up-regulation was positively correlated with the severity of liver fibrosis (P< 0.05). We found that knock out of FMOD dramatically enhanced liver fibrosis, which is inconsistent with previous reports, suggesting that FMOD might be a protective factor in liver fibrosis. rhFMOD could significantly alleviate liver fibrosis in CCl_4-induced and $FMOD^{-/-}$ mice, partially restore the established liver fibrosis, and did not damage liver function, in which low dose of rhFMOD (2 mg/kg) has the most significant anti-fibrosis effect (P < 0.001). In vitro, rhFMOD could significantly promote the apoptosis of activated HSC (P < 0.001), mechanistically, FMOD promoted the expression of IL-1β to increase the apoptosis of activated HSC. **Conclusion:** FMOD is a protective factor for liver fibrosis, and moderate exogenous administration of FMOD can alleviate, and even reverse liver fibrosis. Consequently, our results strongly suggest that FMOD could be a potential therapeutic protein for liver fibrosis. We aim to develop a novel mimic peptide as an anti-liver fibrosis medicine.

Disclosures: Yichun Yang: Nothing to Disclose, Chunhong Guo: Nothing to Disclose, Shan Li: Nothing to Disclose, Lu Huang: Nothing to Disclose, Jinqiu Zhao: Nothing to Disclose, Xiaoxiao Pang: Nothing to Disclose, Liang Deng: Nothing to Disclose

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3577 | ALTERED CHROMATIN ACCESSIBILITY IN HEPATIC STELLATE CELLS REVEALS MECHANISMS OF LIVER FIBROSIS

Tingting Jia[1] *Yi Shen*[1] *Kunyi Ba*[1] *Li Yang*[1]

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Background: The treatments for liver fibrosis are still in need so far. As the crucial initiators of liver fibrosis, activated hepatic stellate cells (aHSCs) undergo a series of epigenetic changes. The study intends to explore transcription factors (TFs) that facilitate HSCs activation and provide novel therapeutic targets for liver fibrosis. **Methods:** Three distinct HSCs activation models were established in present study (Fig. 1A). Firstly, in vitro activation involved isolating primary HSCs from normal rats and culturing them for 2 days (n=5) and 7 days (n=5), namely natural activation model. Secondly, in vivo activation entailed isolating primary HSCs from bile duct ligated rats (n=4) and normal controls (n=4), followed by culturing until the next day. Lastly, transforming growth factor-β (TGF-β, 2.5ng/ml) (n=10) or control buffer (n=10) were added to the human HSCs cell line LX2 and cultured for 24 hours. Assay for transposase-accessible chromatin using sequencing (ATAC-seq) was conducted on the abovementioned cells, along with motif enrichment and footprint analysis. RNA sequencing (RNA-seq) was employed to analyze gene expression profiles of primary HSCs in the natural activation model (n=4) and controls (n=4). The integration of ATAC-seq and RNA-seq further identified potential key TFs. RT-qPCR and differential expression analysis of public datasets was utilized to confirm the dysregulation of TFs. Finally, enrichment of these genes was validated by H3K27Ac and H3K4me3 chromatin immunoprecipitation followed by sequencing (ChIP-seq) of human activated HSCs. **Results:** For ATAC-seq, primary HSCs exhibited higher chromatin accessibility after activation compared with the controls. (Fig. 1C) After peak annotation, the up-regulated peaks (Fig. 1B) were mainly located in the promoter region, uncovering the dynamic transcriptional regulation during HSC activation. (Fig. 1D) The three models shared 10 aHSCs related TFs, namely *Runx-aml*, *Runx1*, *Runx2*, *Atf2*, *Atf4*, *Atf7*, *c-Jun-Cre*, *Creb5*, *Smad3* and *CArG* (Fig. 1E, 1F); and 19 qHSCs related TFs. Footprint analysis validated the alteration of accessibility in *Atf2*, *Atf4*, *Atf7*, *Creb5* (Fig. 1G). Integration of ATAC-seq and RNA-seq showed that gene expression was significantly correlated with chromatin accessibility, among which *Runx2*, *Creb5* (Fig. 1H), and *Smad3* were significantly upregulated in aHSCs at transcription level. The dysregulation of *Creb5* was further verified in fibrotic liver (Fig. 1I) and fibrotic model of human induced pluripotent stem cells (Fig. 1J). Finally, H3K27Ac and H3K4me3 ChIP-seq validated our results. **Conclusion:** We generated chromatin accessibility profiles of different HSCs activation models, highlighting the significance of *Creb5* as the key TF mediating HSCs activation. These findings proposed the TF as a promising target for future liver fibrosis treatment.

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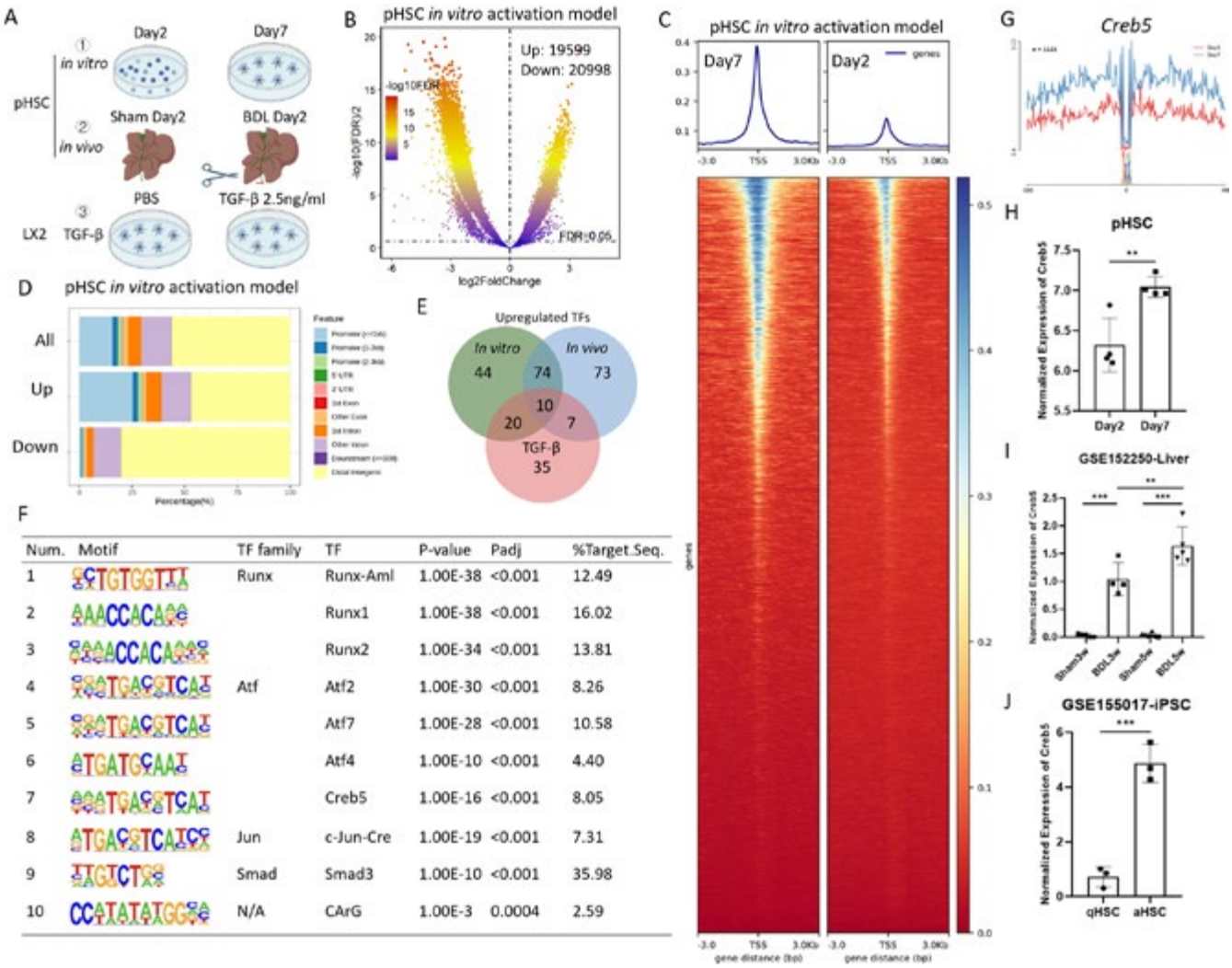

Disclosures: Tingting Jia: Nothing to Disclose, Yi Shen: Nothing to Disclose, Kunyi Ba: Nothing to Disclose, Li Yang: Nothing to Disclose

3578 | CBP/B-CATENIN SIGNALING IN HEPATOCYTES PLAYS PIVOTAL ROLES IN MMP-7-MEDIATED LIVER FIBROSIS IN A MASH MOUSE MODEL

Yumi Otoyama[1] *Masamichi Kimura*[1] *Koji Nishikawa*[1] *Jun Imamura*[1] *Kiminori Kimura*[1]

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Background: We have previously reported the importance of CBP/b-catenin signaling in hepatic stellate cells and macrophages as one of the mechanisms of action in liver fibrosis. In this study, we focused on CBP/b-catenin signaling in hepatocytes and investigated its involvement with fibrosis in a MASH model using CDAHFD.
Methods: Alb-Cre/CBPKO mice lacking hepatocyte-specific CBP ($CBP^{hep\text{-}KO}$), its counterpart P-300, Alb-Cre/P300KO mice ($P300^{hep\text{-}KO}$) and Alb-Cre mice were fed CDAHFD for 4 months, and liver tissue was used for H.E, Sirius Red, Sudan IV, and aSMA stainings. Serum was used to measure ALT, cytokines, and chemokines, and RNA was extracted from the livers and analyzed for fibrosis-related gene expression using rt-PCR, Microarray, PCR array, and RNA-seq analysis. Next, MMP-7KO and control mice were fed CDAHFD for 4 months, and fibrosis was assessed by liver histology and gene analysis as mentioned above. Furthermore, C57BL/6 mice were fed CDAHFD, and at 3 months after the start of the diet, AAV8/ShMMP-7 and AAV8/control (2×10^{12} copies/mouse)were injected twice at 2-week intervals, and fibrosis was assessed by liver histology and gene analysis. Finally, serum MMP-7 levels were measured in patients with MASH (n=54) and healthy volunteers (n=70).
Results: After 4 months of feeding CDAHFD to control mice (n=22), $CBP^{hep\text{-}KO}$ mice (n=20), and $P300^{hep\text{-}KO}$ mice

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(n=22), CBP$^{hep\text{-}KO}$mice showed a significant decrease in fibrosis area compared to other mice. On the other hand, P300$^{hep\text{-}KO}$ mice showed a significant increase in fibrosis area. Serum IL-6 and IL-10 levels were significantly decreased in CBP$^{hep\text{-}KO}$ mice, while serum IL-6, IL-10, IL-11 and TGF-b3 levels were significantly increased in P300$^{hep\text{-}KO}$ mice. Gene expression analysis of the livers also showed that the expression of Col1A1, Col1A2 and Col3A1 was significantly decreased in CBP$^{hep\text{-}KO}$ mice. Furthermore, microarray and RNA-seq analysis revealed a significant difference in MMP-7 expression between CBP$^{hep\text{-}KO}$ and P300$^{hep\text{-}KO}$ mice. Furthermore, analysis of liver histology from MMP-7KO mice showed a significant decrease in fibrosis area after 4 months of feeding CDAHFD. In addition, AAV8/ShMMP-7 treatment also reduced fibrosis area and the expression of Col1A1 and Col3A1 in the liver of CDAHFD fed mice. Finally, a significant increase in MMP-7 levels was observed in the serum of patients with MASH. **Conclusion:** CBP/b-catenin signaling in hepatocytes was implicated in MASH fibrosis via MMP-7, suggesting MMP-7 as a potential target for new fibrosis drugs.

Disclosures: Yumi Otoyama: Nothing to Disclose, Masamichi Kimura: Nothing to Disclose, Koji Nishikawa: Nothing to Disclose, Jun Imamura: Nothing to Disclose, Kiminori Kimura: Nothing to Disclose

3579 | THE CLINICAL CHARACTERISTICS ANALYSIS AND ETIOLOGICAL EXPLORATION OF CRYPTOGENIC CIRRHOSIS

yali Liu[1]

[1]*The first hospital of Jilin university*

Background: Cryptogenic Cirrhosis (CC) is a clinically complex disease, and its etiology and pathogenesis have not been fully understood, which brings great difficulties to clinical diagnosis and treatment. On one hand, we conducted a retrospective analysis of clinical data from 213 patients diagnosed with CC, allowing for a comprehensive understanding of the clinical characteristics of this condition through statistical analysis. On the other hand, we endeavored to infer and discuss the potential etiology of CC, aiming to provide a scientific foundation for the diagnosis, treatment, and prevention of this disease. **Methods:** A retrospective analysis was conducted on a cohort of 213 patients diagnosed with CC at the hepatology department of the first hospital of Jilin university, spanning from January 1, 2014, to December 31, 2023. The data were processed and analyzed using SPSS software and Excel. Genetic DNA was extracted from peripheral blood samples, and ALDH2-rs671 genotypes as well as susceptibility genes associated with fatty liver were analyzed using KASP technology. Additional investigation was carried out on PNPLA3-rs738409, TM6SF2-rs58542926, GCKR-rs1260326, MBOAT7-rs641738, and HSD17B13-rs72613567 to delve deeper into the potential etiology of CC. **Results:** 1. Compared with the male to female ratio in general liver cirrhosis (61.8% : 38.2%), the proportion of women in CC patients was relatively high (51.17% : 48.83%). 2. The proportion of CC patients complicated with diabetes mellitus is high, suggesting that diabetes mellitus may be related to the occurrence of CC. 3. Compared with CC patients and healthy people, the proportion of ALDH2-rs671 homozygous AA genotype in CC patients is relatively high, suggesting that ALDH2-rs671 homozygous mutation may be related to the occurrence and development of CC. The proportion of homozygous TT genotype at rs641738 locus of MBOAT7 gene in CC patients is relatively high, suggesting that the occurrence of CC may be related to the homozygous mutation at rs641738 locus. 4. In CC patients, compared with ALDH2 deficiency group, ALDH2 non-deficiency group had higher levels of AST, GGT and TBA ($P<0.05$), and lower levels of ALB and UA ($P<0.05$). 5. TM6SF2 mutant and absence of HSD17B13 gene group may be associated with lower serum LDL, may be the protection of liver disease. **Conclusion:** Patients with cryptogenic cirrhosis have a higher proportion of females and more comorbid metabolic factors, and pure mutations at the ALDH2-rs671 locus and MBOAT7-rs641738 locus may be associated with the development of cryptogenic cirrhosis.In the future, genetic and metabolic factors can be applied to predict the occurrence and development of cirrhosis.

Disclosures: yali Liu: Nothing to Disclose

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3580 | PROTON DENSITY FAT FRACTION STRATIFIES PROGNOSIS IN LIVER DISEASE WITH ADVANCED FIBROSIS

Tsubasa Nobusawa[1] Shun Kaneko[1] Miyako Murakawa[1] Kento Inada[1] Tomohiro Mochida[1] Keiya Watakabe[1] Taro Shimizu[1] Jun Tsuchiya[1] Masato Miyoshi[1] Fukiko Kawai-Kitahata[1] Sayuri Nitta[1] Koichiro Kimura[1] Mitsuhiro Kishino[1] Ukihide Tateishi[1] Mina Nakagawa[1] Sei Kakinuma[1] Ryuichi Okamoto[1] Yasuhiro Asahina[1]

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Background: In Japanese hospital cohorts, antiviral therapy has enabled the suppression of both hepatitis B virus (HBV) and hepatitis C virus (HCV). Recently, criteria for metabolic dysfunction-associated steatotic liver disease (MASLD) have been clarified, emphasizing the importance of quantifying liver fat and evaluating fibrosis not only in non-viral chronic liver disease but also in viral hepatitis. However, there is insufficient knowledge regarding the optimal fat quantification method. This study aimed to clarify the utility of liver fat quantification for predicting decompensation and prognosis in liver disease with advanced fibrosis. **Methods:** This study retrospectively recruited 393 patients who underwent MR elastography (MRE) and the IDEAL-IQ method for proton density fat fraction (PDFF) from June 2020 to October 2023. Decompensated events analyzed included ascites, encephalopathy, and esophagogastric varices. Additionally, we compared the prognostic predictive ability of PDFF and the controlled attenuation parameter (CAP) in patients with advanced liver fibrosis who also underwent FibroScan within one year of MRE. **Results:** The study population included 61 patients (15.5%) with HBV, 82 (20.9%) with HCV, and 250 (63.6%) with non-viral hepatitis. The breakdown of non-viral liver diseases was as follows: Alcoholic Liver Disease (ALD), MASLD, MetALD, Cryptogenic SLD, and non-SLD (n=9, 81, 23, 15, 122). The median age was 65 years, with 228 males (58.0%) and a median BMI of 24.4. Median liver stiffness and PDFF were 2.917 kPa and 4.61%, respectively. Decompensation was observed in 117 cases (29.7%). Multivariate logistic regression analysis showed that liver stiffness and PDFF were significant factors. The optimal cut-off for predicting decompensation was 3.034 kPa (AUROC 0.829, 95% CI 0.787-0.871) for liver stiffness and 2.94% (AUROC 0.648, 95% CI 0.59-0.707) for PDFF. Patients with advanced fibrosis and lower fat content as evaluated by MRE (E ≥ 3.034 kPa, PDFF < 2.94%) had poorer 2-year cumulative survival rates at 85.2% compared to other groups (p=0.0027). In subgroup analysis by viral and non-viral advanced liver disease (E ≥ 3.034 kPa, PDFF < 2.94%), the significantly poorer 2-year cumulative survival rates were 84.5% and 85.3%, respectively (p=0.04, 0.02). Additionally, we compared the predictive ability of PDFF and CAP in 171 cases who underwent both tests. In advanced fibrosis, PDFF but not CAP demonstrated significant discrimination for decompensation (p=0.001). **Conclusion:** In chronic liver disease with advanced fibrosis, lower liver fat as evaluated by PDFF is associated with more decompensated events and poorer prognosis. Liver fat quantification using PDFF is important for managing liver disease progression in all etiologies.

Disclosures: Tsubasa Nobusawa: Nothing to Disclose, Shun Kaneko: Nothing to Disclose, Miyako Murakawa: Nothing to Disclose, Kento Inada: Nothing to Disclose, Tomohiro Mochida: Nothing to Disclose, Keiya Watakabe: Nothing to Disclose, Taro Shimizu: Nothing to Disclose, Jun Tsuchiya: Nothing to Disclose, Masato Miyoshi: Nothing to Disclose, Fukiko Kawai-Kitahata: Nothing to Disclose, Sayuri Nitta: Nothing to Disclose, Koichiro Kimura: Nothing to Disclose, Mitsuhiro Kishino: Nothing to Disclose, Ukihide Tateishi: Nothing to Disclose, Mina Nakagawa: Nothing to Disclose, Sei Kakinuma: Nothing to Disclose, Ryuichi Okamoto: Nothing to Disclose, Yasuhiro Asahina: Nothing to Disclose

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3581 | A SMALL MOLECULE MIMICKING TCF21, A DEACTIVATION FACTOR OF HEPATIC STELLATE CELLS, ACCELERATES REPAIR OF INJURED LIVER BY ORCHESTRATING CROSSTALK BETWEEN DEACTIVATED STELLATE CELLS AND OTHER TYPES OF CELLS IN THE FIBROTIC TISSUE

Takayo Yanagawa[1] Harumi Ogawa[1] Sachie Nakao[1] Mayumi Watanabe[1] Hideaki Sumiyoshi[1] Hiromi Miura[1] Masato Ohtsuka[1] Masayuki Tanaka[1] Yumi Iida[1] Misaki Higashiseto[2] Shigeyuki Shichino[3] Kouji Matsushima[3] Kota Tsuruya[1] Yoshitaka Arase[1] Tatehiro Kagawa[2] Noriaki Hirayama[1] Yutaka Inagaki[1]

[1]Tokai University School of Medicine, [2]Tokai University Schoole of Medicine, [3]Tokyo University of Science

Background: Despite the recent approval of the first treatment for metabolic dysfunction-associated steatohepatitis (MASH), there is no drug available that directly suppresses fibrogenesis in MASH. We previously identified Tcf21 as a hepatic stellate cell (HSC)-specific deactivation factor implicated in the regression of liver fibrosis. Administration of Tcf21-overexpressing adeno-associated viruses not only suppressed progression of steatohepatitis and fibrosis, but also restored the hepatic lobular architecture and function. Subsequently, we identified several small molecules that mimic the ternary structure of the functional peptide sequence of Tcf21 and act as Tcf21 agonists to suppress progression of liver fibrosis. However, it was unknown whether and how deactivated HSCs *per se* caused repair of the fibrotic liver. In the present study, using cell fate tracing mice and single cell transcriptome analysis, we explored the molecular link between HSC deactivation and the repair of fibrotic liver. **Methods:** Using the genome editing method, Cre recombinase and estrogen receptor fusion gene was introduced into the 4th intron of endogenous type I α2 collagen gene (ColCreER mice). Single cell RNA sequencing was performed using Cre-mediated recombined mTFP1-positive cells and other types of cells obtained from CCl_4-injected mice with or without Tcf21 mimetic treatment. Alterations in signal pathways were analyzed comprehensively using the gene expression array data. **Results:** In mice obtained by crossing ColCreER and lox-stop-lox mTFP1 mice, activated HSCs were specifically and permanently labeled with mTFP1 following fibrogenic stimuli and tamoxifen injections. Administration of a Tcf21 mimetic into mice with liver fibrosis remarkably decreased expression of α-smooth muscle actin gene, a representative target of Tcf21. It also suppressed the MASH signatures such as *Adamtsl2*, *Thbs2*, and *Igfbp7* as well as gene expression of neurotrophin 3, an autocrine fibrogenic signal, in the major HSC population. Furthermore, a novel HSC subpopulation with decreased MMP2 expression and reduced epithelial to mesenchymal transition potential emerged following Tcf21 mimetic treatment. Administration of the Tcf21 mimetic also induced a unique subset of macrophages exhibiting tissue repair and angiogenic properties, and increased the number of sinusoidal endothelial cells that expressed vascular endothelial growth factor receptors. Consequently, peroxisome proliferator-activated receptor (PPAR), Wnt, and Hippo pathways were upregulated in hepatocytes from Tcf21 mimetic-treated mice. **Conclusion:** Administration of a Tcf21 mimetic not only suppressed progression of liver fibrosis but also accelerated tissue repair of the fibrotic liver. These combinatorial effects were exerted by orchestrating crosstalk between deactivated HSCs, a direct target of Tcf21, and neighboring other types of cells in the fibrotic liver.

Disclosures: Takayo Yanagawa: Nothing to Disclose, Harumi Ogawa: Kyowa kirin: Stock - publicly traded company, Sachie Nakao: Nothing to Disclose, Mayumi Watanabe: Nothing to Disclose, Hideaki Sumiyoshi: Nothing to Disclose, Hiromi Miura: Nothing to Disclose, Masato Ohtsuka: Nothing to Disclose, Masayuki Tanaka: Nothing to Disclose, Yumi Iida: Nothing to Disclose, Misaki Higashiseto: Nothing to Disclose, Shigeyuki Shichino: ImmunoGeneTeqs: Exective role, ImmunoGeneTeqs: Stock – privately held company, Kouji Matsushima: Nothing to Disclose, Kota Tsuruya: Nothing to Disclose, Yoshitaka Arase: Nothing to Disclose, Tatehiro Kagawa: Nothing to Disclose, Noriaki Hirayama: Nothing to Disclose, Yutaka Inagaki: AbbVie Inc.: Speaking and Teaching, Kyowa-Kirin Co. Ltd.: Advisor, Immunogenetics, Inc.: Stock – privately held company, Kyowa-Kirin Co. Ltd.: Grant/Research Support, Ono Phamaceutical, Co. Ltd.: Grant/Research Support, AbbVie Inc.: Speaking and Teaching

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3582 | ITACONATE MITIGATES LIVER FIBROSIS BY ELEVATING GDF15 PRODUCTION ◆

ningning Ma[1]

[1]*Shanghai Institute of Materia Medica CAS*

Background: Liver fibrosis is a common consequence of chronic liver injury and is characterized by the deposition of extracellular matrix (ECM). Activation of hepatic stellate cells (HSCs) caused by chronic inflammatory damage plays a key role in the development of liver fibrosis. Although the expansive knowledge about the cellular and molecular biology of liver fibrogenesis, its precise mechanisms remain obscure and effective therapies are lacking. During the development of liver fibrosis, immune cells and HSCs synthesize and secrete various chemical mediators in the presence of chronic liver injury, constituting a dynamic immune microenvironment composed of immune cell-mediator-HSC network system. As a highly heterogeneous group of immune cells in the liver immune microenvironment, macrophages play a key role in the occurrence and development of liver fibrosis. Itaconate is an important anti-inflammatory and antioxidant substance produced by aconitic acid decarboxylase (ACOD1) in the tricarboxylic acid cycle of macrophages. Accumulating studies indicate that itaconate and its derivatives have therapeutic potential in preclinical models of sepsis, viral infection, gout, ischemia/reperfusion injury and pulmonary fibrosis. However, whether and how itaconate affects the development and progression of liver fibrosis remain largely unknown. **Methods:** Carbon tetrachloride (CCl_4) and bile duct ligation (BDL)-induced liver fibrosis models was used to evaluate the ameliorated effect of itaconate derivative 4-octyl itaconate (4-OI). *Acod1* knockout (KO) mice and wild-type littermates were generated and subjected to different experimental liver fibrosis models. Liquid chromatography-mass spectrometry (LC-MS/MS) was performed to measure the serum amount of itaconate. The key roles of GDF15 in itaconate in alleviating liver fibrosis was further explored by generating different cell-specific *Gdf15* deficient mice (Alb-cre^{+}GDF15$^{f/f}$,Lrat cre^{+}GDF15$^{f/f}$ and Lyz2 cre^{+}GDF15$^{f/f}$). **Results:** 4-OI and itaconate significantly inhibited HSC activation and alleviated CCl_4 and BDL-induced liver fibrosis. *Acod1* deficient mice were more susceptible to liver fibrogenesis in three different experimental liver fibrosis models. Transcriptomic analysis suggested that itaconate not only significantly inhibited the activation of TGF-β/Smad signaling pathway, but also remarkedly upregulated the expression of growth differentiation factor 15 (GDF15). Indeed, itaconate elevated GDF15 production in HSCs, which suppressed HSC activation and TGF-β/Smad signaling pathway. **Conclusion:** In conclusion, itaconate and its derivative may provide a promising option to treat liver fibrosis by elevating anti-fibrotic GDF15 production.

Disclosures: ningning Ma: Nothing to Disclose

3583 | EXPLORING THE MECHANISM OF ACTION OF YGXJ IN THE TREATMENT OF LIVER CIRRHOSIS THROUGH ANIMAL EXPERIMENTS AND INTESTINAL FLORA

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Background: Globally, liver cirrhosis (LC) has a high prevalence and has become one of the most common liver diseases today. The YiGan XiaoJi formula (YGXJ) is a Chinese medicine formula that is mainly used for the treatment of LC and precancerous liver lesions. However, the specific mechanism of action of YGXJ in LC is not fully understood. **Methods:** The LC mice model was established by intraperitoneal injection of 20% CCl4 of olive oil mixture for 9 weeks. From the 6th week, the treatment group was given YGXJ granule aqueous solution by gavage. After treatment, the mice's body weight was recorded, and the mice's serum was used to detect biochemical indicators including aspartate aminotransferase (AST) and alanine aminotransferase (ALT). The rats' liver tissues were used to perform pathological examinations including Masson staining, HE staining, and Sirius red staining. After 4 weeks of treatment, specimens of feces and intestinal contents were retained from each group of mice before sampling for intestinal flora testing, and the OTU number, alpha diversity, and beta diversity of fecal bacterial samples from mice were detected, to observe the effects of YGXJ treatment of cirrhosis mouse model on intestinal flora. **Results:** Compared to the control group, after modeling, the weight of the model mice was significantly decreased. Compared to the model group, significantly lower levels of serum AST and ALT in the YGXJ group than in the model were observed. The HE staining, Sirius red staining, and Masson staining showed less inflammatory damage and collagen production after YGXJ treatment compared to the model. Through

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the detection and analysis of intestinal flora, it was found that the model group had the highest abundance of Bacteroides immitis, and the abundance of Bacteroides immitis gradually declined in the model, control, and YGXJ groups; whereas, Bacillota had the highest abundance in the YGXJ group, and the lowest abundance in the model group; the species diversity of the model group was significantly higher than that of the other two groups, and there was no significant difference in the intestinal flora of the three groups with regard to the species abundance and homogeneity. **Conclusion:** YGXJ exerted a reversion effect on the LC in mice. YGXJ modulates the disease process of liver cirrhosis by improving the state of hepatic inflammatory infiltration in mice, and also modulates the structure and abundance of intestinal flora in a mouse model of liver cirrhosis.

Disclosures: Shihao Zheng: Nothing to Disclose, Siyuan Gou: Nothing to Disclose, Jinchi Xie: Nothing to Disclose, Yongan Ye: Nothing to Disclose, Wenying Qi: Nothing to Disclose, Xiaobin Zao: Nothing to Disclose, Qiyao Liu: Nothing to Disclose, Peng Zhang: Nothing to Disclose

3584 | TARGETING JAK2/STAT1 SIGNALING TO REGULATE CX3CL1 EXPRESSION IN BILIARY EPITHELIAL CELLS FOR INTERVENTIONAL THERAPY IN LIVER FIBROSIS ◆

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Background: Liver cirrhosis, marked by progressive fibrosis, represents a significant medical challenge that necessitates a deep understanding of complex cellular and molecular mechanisms to improve treatment.. Our previous studies have demonstrated the positive therapeutic effects of modulating CX3CR1+ macrophage phenotypes through the administration of CX3CL1. However, the cellular origin and production mechanism of CX3CL1 in fibrotic livers remain unclear. This study aims to identify the major cellular sources of CX3CL1 in liver fibrosis and delineate the underlying molecular mechanisms involved, thereby paving the way for targeted therapies in the management of liver cirrhosis. **Methods:** This study examined liver samples from cirrhotic patients and healthy donors to analyze CX3CL1 expression and location using immunohistochemistry. CX3CL1 was assessed in various liver cell types in vitro, including human intrahepatic biliary epithelial cells (HIBEpiC), hepatocytes (L-02), monocyte-derived macrophages (THP-1), hepatic sinusoidal endothelial cells (HHSEC), and hepatic stellate cells (LX-2). HIBEpiC were exposed to IFN-γ to observe CX3CL1 expression changes via Western Blot. Transcriptome sequencing explored the molecular mechanisms of CX3CL1 production. The JAK2/STAT1 pathway's involvement in CX3CL1 generation was examined using a STAT1 inhibitor (Fludarabine) and agonist (Poly I:C). The role of the JAK2/STAT1/CX3CL1 axis was subsequently confirmed in vivo using a CCl4-induced mouse model of liver fibrosis. **Results:** Immunohistochemistry revealed elevated CX3CL1 in cirrhotic liver tissues, with notable localization on biliary epithelial cells. This was further supported by PCR results showing the highest expression of CX3CL1 in HIBEpiC. Introduction of IFN-γ to HIBEpiC cultures led to a significant increase in CX3CL1 expression. Transcriptome sequencing identified the JAK2/STAT1 pathway as the pivotal mediator for intracellular expression of CX3CL1. Western blot analysis affirmed the enhancement in phosphorylation of both JAK2 and STAT1 proteins following IFN-γ stimulation. Interestingly, the use of Fludarabine decreased STAT1 phosphorylation, thereby reducing CX3CL1 expression, highlighting STAT1's crucial role. Conversely, activation of STAT1 with Poly I:C potentiated its phosphorylated state, promoting the expression of CX3CL1 protein within cells. In line with in vitro findings, the CCl4-induced mouse model of liver fibrosis also showcased increased expression of CX3CL1 and heightened phosphorylation of JAK2 and STAT1 proteins in liver tissues. **Conclusion:** Our study highlights the increased expression of CX3CL1 in biliary epithelial cells in fibrotic livers and elucidates the regulatory mechanism through the JAK2/STAT1 signaling pathway. This mechanism may provide a new target for therapeutic intervention in liver fibrosis by modulating CX3CR1+ macrophages.

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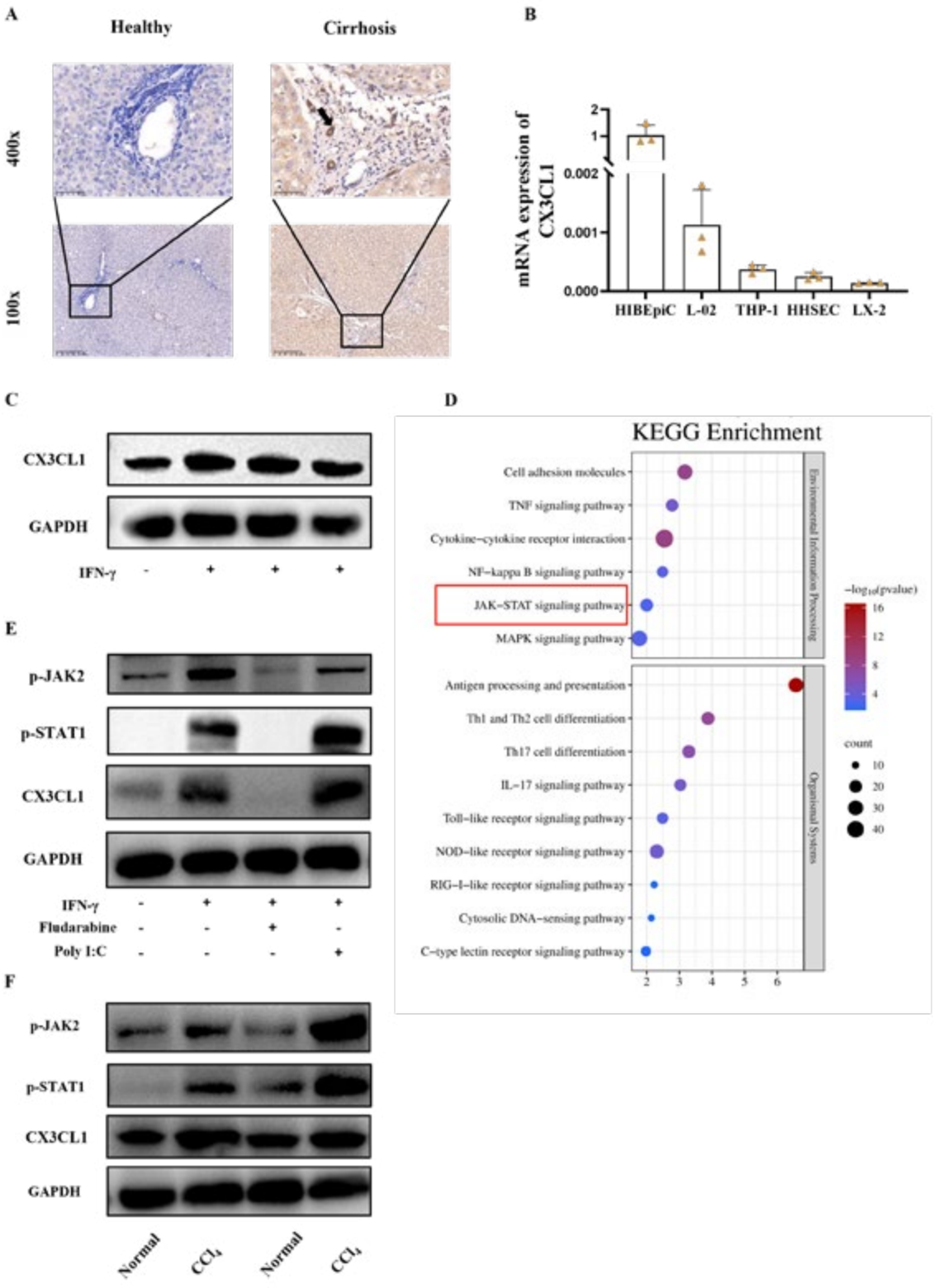

Disclosures: Dabing Ping: Nothing to Disclose, Xin Sun: Nothing to Disclose, Kai Huang: Nothing to Disclose, Xudong Hu: Nothing to Disclose, Chenghai Liu: Nothing to Disclose

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3585 | THERAPEUTIC POTENTIAL OF MIR-660-5P AND MIR-125A-5P ANTAGONISTS IN ATTENUATING LIVER FIBROSIS: INSIGHTS FROM NEXT-GENERATION SEQUENCING AND EXPERIMENTAL VALIDATION ◆ ★

Young Chang[1] *JAE YOUNG JANG*[1] *Soung Won Jeong*[1]

[1]*Soonchunhyang University*

Background: Exosomal microRNAs (miRNAs) have emerged as significant biomarkers and potential therapeutic targets in various diseases, including liver fibrosis. This study aimed to identify exosomal miRNAs associated with liver fibrosis stages and to evaluate the therapeutic potential of specific miRNA modulators for liver fibrosis in steatohepatitis. **Methods:** Patients with steatotic liver disease (n=20) was selected from a larger group undergoing liver biopsy. Next-generation sequencing (NGS) was conducted on blood exosomal miRNAs to identify those associated with liver fibrosis stages. In a steatohepatitis cell model, hepatocytes (Huh7) and hepatic stellate cells (LX-2) were co-cultured, treated with free fatty acids, and induced with LPS to simulate fibrosis. Specific miRNA modulators were transfected, and fibrosis markers were compared to controls using western blot and real-time RT-PCR.. In a steatohepatitis animal model, mice were divided into control and treatment groups, receiving intraperitoneal injections of specific miRNA modulators (3 mg/kg, twice weekly) for 12 weeks. Liver tissues were pathologically analyzed using special staining techniques, and fibrosis markers (collagen 1A, α-smooth muscle actin (SMA), fibronectin, transforming growth factor (TGF)-β) were assessed via western blot. **Results:** NGS of circulating exosomal miRNAs identified miR-660-5p and miR-125a-5p as significantly associated with liver fibrosis stages. In the steatohepatitis cell model, fibrosis markers significantly increased by LPS treatment were reduced by miR-660-5p and miR-125a-5p antagonists. Real-time RT-PCR results showed reduced mRNA levels of fibrosis markers in cells treated with these antagonists. Western blot analysis demonstrated consistent findings, showing decreased protein levels of collagen 1A, α-SMA, fibronectin, and TGF-β in the treated cells. In the steatohepatitis animal model, miR-660-5p and miR-125a-5p antagonist-treated groups showed a significant reduction in liver fibrosis compared to controls. Sirius Red and α-SMA staining of the liver confirmed reduced fibrosis in these groups. Western blot analysis of liver tissue also revealed markedly decreased expressions of collagen 1A, α-SMA, fibronectin, and TGF-β in the treated groups. **Conclusion:** The study demonstrates that miR-660-5p and miR-125a-5p antagonists significantly reduce fibrosis markers in both animal and cell models, highlighting their potential as therapeutic agents for liver fibrosis.

Disclosures: Young Chang: Nothing to Disclose, JAE YOUNG JANG: Nothing to Disclose, Soung Won Jeong: Nothing to Disclose

3586 | AI-DRIVEN COLLAGEN SEGMENTATION AND UNSUPERVISED FEATURE EXTRACTION FOR LIVER FIBROSIS EVALUATION

Davide Panzeri[1] *Reha Akpinar*[2] *Donato Inverso*[3] *Luca Di Tommaso*[2] *Laura Sironi*[1]

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Background: The assessment of pathological fibrosis stage is a process characterized by limited sensitivity in the identification of changes in disease or response to treatment. Aim of this work is to provide an Artificial Intelligence (AI) based method able to automatically segment collagen deposition in a series of Sirius Red (SR)-stained biopsies of patients treated in a single center. Moreover, collagen features were extracted and related to fibrosis progression by means of unsupervised AI methods. **Methods:** To segment the SR-stained collagen matrix we employed a deep-learning-based supervised approach. A U-Net 3+ architecture was exploited for whole slide images segmentation. The latent-space features were extracted and mapped in a 2D representation through a dimensionality reduction algorithm (tSNE). The obtained clustering representations were then correlated with explainable features of the original images. **Results:** The U-Net3+ architecture was successfully trained and achieved an accuracy higher than 95% in collagen segmentation. The clusters obtained from the latent-space features encode for explainable features of the original images, such as the average hue or the amount and architecture of collagen. Moreover, the extracted features correlate with the fibrosis stage progression assessed by pathologists. **Conclusion:** Here, we propose an automated method, based on neural networks, for collagen segmentation and characterization in whole-slide images related to liver fibrosis. Furthermore, we successfully

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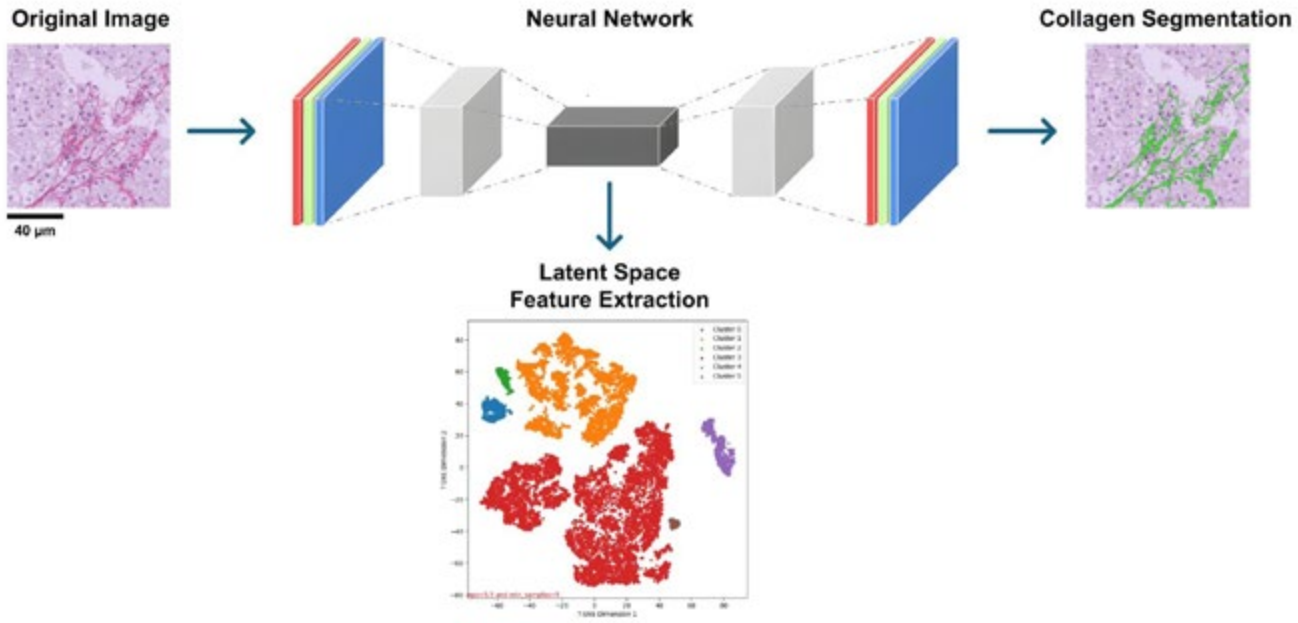
adapt an unsupervised approach for the extraction and characterization of novel features related to fibrosis progression.



Disclosures: Davide Panzeri: Nothing to Disclose, Reha Akpinar: Nothing to Disclose, Donato Inverso: Nothing to Disclose, Luca Di Tommaso: Nothing to Disclose, Laura Sironi: Nothing to Disclose

3587 | ATP-CITRATE LYASE ENABLES HEPATIC STELLATE CELL ACTIVATION: IMPLICATIONS FOR FIBROGENESIS

Shi Su[1] Ray Mastriani[2] Stephen Pinkosky[2] David Cohen[3]

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Background: Hepatic stellate cell activation in response to liver injury plays a key role in fibrogenesis. ATP-citrate lyase (ACLY) is a ubiquitous enzyme that converts citrate to acetyl-CoA, a key lipogenic substrate in cellular metabolism. Because lipogenesis is integral to proliferative responses of cells to external stimuli, we hypothesized that ACLY plays a pivotal role in hepatic stellate cell activation. The aim of this study was to determine whether knockdown of ACLY in hepatic stellate cells impairs their activation and responses to cellular stress. **Methods:** Small interfering RNA (siRNA) was leveraged to knock down ACLY expression in the LX-2 human hepatic stellate cell line. LX-2 cells stimulated with TGFβ were subjected to measurements of rates of oxygen consumption (OCR), which reflect mitochondrial respiration, as well as rates of extracellular acidification (ECAR), which reflect glycolysis, using a Seahorse XF Extracellular Flux Analyzer. Gene and protein expression of hepatic stellate cell-selective activation markers were measured using real-time quantitative PCR and immunoblotting, respectively. **Results:** siRNA treatment achieved greater than 75% reduction of the ACLY protein expression in LX-2 cells. ACLY knockdown respectively reduced the basal and maximal values of OCR by 30% and 26%, and of ECAR values by 19% and 17%. TGFβ activation increased the gene and protein expression of ACLY along with basal and maximal values of both ECAR and OCR. Knockdown of ACLY blunted the expression of activation markers, including αSMA, as well as the TGFβ-induced increases in OCR and ECAR values. **Conclusion:** ACLY promotes mitochondrial respiration and glycolytic activity in LX-2 cells, along with their metabolic responses to activation by TGFβ. We speculate that the intracellular citrate accumulation in response to ACLY knockdown leads to allosteric inhibition of glycolytic enzymes, thereby decreasing TCA cycle activity and hence the energy state of the LX-2 cells. These findings suggest that the activity of ACLY is integral to hepatic stellate cell activation and represents a potential therapeutic target in fibrogenesis.

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Disclosures: Shi Su: Nothing to Disclose, Ray Mastriani: Nothing to Disclose, Stephen Pinkosky: Nothing to Disclose, David Cohen: Nothing to Disclose

3588 | HGF UPREGULATED THE EXPRESSION OF HEPATOCYTE NRP-1 VIA RARA TO EXACERBATE LIVER FIBROSIS

Han Ding[1] Huanran Lv[1] Songbo Zhao[2] Jianni Qi[2] Le Wang[2] Qiang Zhu[2]

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Background: Liver fibrosis is a common feature of sustained liver injury, which can lead to irreversible cirrhosis and death. Previously, our team discovered that neuropilin-1 (NRP-1) on hepatic stellate cells and hepatic sinusoidal endothelial cells enhanced liver fibrosis via profibrogenic and proangiogenesis signaling pathways, respectively. However, the role of NRP-1 in hepatocytes during liver fibrosis still remains unclear. **Methods:** The correlation between NRP-1 expression and liver fibrosis degree was evaluated in both human and murine cirrhotic liver tissues by immunohistochemical staining, quantitative real-time PCR, and western blotting. In vivo, hepatocyte-specific NRP-1 knockdown mice were produced by injecting adeno-associated virus-8. The role and mechanism of NRP-1 in regulating fibrosis were identified in primary mouse hepatocytes and the Huh7 cell line in vitro. Additionally, we used ELISA to analyze TGF-β and VEGF levels and we utilized western blotting to identify the downstream signaling pathways in hepatocytes. ChIP and the Dual-Luciferase Reporter Assay were applied to test transcription factor binding to the NRP-1 promoter. **Results:** NRP-1 expression was significantly increased in hepatocytes during liver fibrosis and was positively correlated with c-Met expression and the degree of fibrosis. Blocking NRP-1 significantly alleviated extracellular matrix deposition and pathological angiogenesis in mice. In vitro, NRP-1 knockdown suppressed the expression of phosphorylated c-MET (p-MET) and reduced the release of TGF-β and VEGF in hepatocytes. Notably, we provided novel experimental findings demonstrating that NRP-1 was not only able to work as a co-receptor of HGF/c-MET but that the expression of NRP-1 in transcript and protein levels could be elevated by HGF in hepatocytes. Mechanistically, HGF upregulated the transcription factor RARA, which bound to the NRP-1 promoter region between 199 and 279 bp and initiated NRP-1 gene transcription. Ultimately, we confirmed that hepatocyte NRP-1 exerted its profibrotic effects through the Met/Erk pathway. **Conclusion:** Hepatocyte NRP-1, elevated by HGF via the transcription factor RARA binding to its promotor region between 199 and 279 bp, promoted liver fibrosis through the c-Met/ERK pathway. NRP-1 may be a viable target for therapeutic intervention in the management of liver fibrosis.

Disclosures: Han Ding: Nothing to Disclose, Huanran Lv: Nothing to Disclose, Songbo Zhao: Nothing to Disclose, Jianni Qi: Nothing to Disclose, Le Wang: Nothing to Disclose, Qiang Zhu: Nothing to Disclose

3589 | CCL2-CCR2 AXIS INHIBITION REDUCES LIVER FIBROSIS BY RESTORING THE IMMUNE CELL LANDSCAPE

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Background: C-C motif chemokine ligand 2 (CCL2), the most upregulated chemokine in injured LSECs, leads to hepatic CCR2+ monocyte-derived macrophage accumulation. Therefore, we performed pharmacological CCL2-CCR2 inhibition and examined how CCL2-CCR2 inhibition restored hepatic immune landscapes related to fibrogenesis. **Methods:** Liver injury and liver fibrosis were induced by carbon tetrachloride (CCl4) in wild-type mice, LSEC-specific Ccl2 deficiency mice, and Ccr2 knockout mice. Murine intrahepatic leukocytes were isolated from olive oil/CCl4-treated wild-type mice for mass cytometry by time-of-flight (CyTOF) analysis. Liver and primary mouse LSEC gene expression was analyzed using a PCR array and RNA sequencing. Cenicriviroc (CVC) was administrated to fibrotic mice in prevention and treatment models. Single-cell RNA sequencing (scRNA-seq) was performed on the livers of olive oil/CCl4/CVC-treated mice. **Results:** CCL2 was the most upregulated chemokine in injured LSECs compared to control LSECs. The CCL2 secreted by injured LSECs leads to CCR2+ monocyte-derived macrophage accumulation in CCl4-induced murine livers as determined by CyTOF. However,

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CCl4-mediated liver fibrosis and macrophage accumulation were reduced in LSEC-specific Ccl2 deficiency and CCR2 knockout mice. Thus, the CCL2-CCR2 angiocrine signaling axis is related to liver fibrogenesis, and the CVC was applied to block the CCL2-CCR2 angiocrine signaling axis. CVC was demonstrated to alleviate liver fibrosis by restoring the FSCN1+ macrophage and HERC6+ neutrophil landscape. Pathway analysis indicated that the STAT1, NFκB, and ERK signaling pathways might be involved in the anti-fibrotic effects of CVC. Consistently, both CVC treatment and Ccr2 knockout decreased the levels of phosphorylated STAT1, NFκB, and ERK in the fibrotic liver. In vitro, CVC could transcriptionally suppress crucial profibrotic genes (Xaf1, Slfn4, Slfn8, Ifi213, and Il1β) in macrophages by inactivating the STAT1/NFκB/ERK signaling pathways.In summary, activation of the angiocrine signal CCL2 in injured LSECs recruits CCR2+ monocyte-derived macrophages to the liver, leading to liver fibrosis. CVC restores the hepatic immune cell landscape by inhibiting profibrotic gene transcription via the CCR2-STAT1/NFκB/ERK signaling pathways. **Conclusion:** In summary, activation of the angiocrine signal CCL2 in injured LSECs recruits CCR2+ monocyte-derived macrophages to the liver, leading to liver fibrosis. CVC restores the hepatic immune cell landscape by inhibiting profibrotic gene transcription via the CCR2-STAT1/NFκB/ERK signaling pathways.

Disclosures: Yangkun Guo: Nothing to Disclose, Jinhang Gao: Nothing to Disclose, Chengwei Tang: Nothing to Disclose

3590 | RISK STRATIFICATION OF CIRRHOSIS TOWARDS HCC CAN BE PREDICTED BY MYOSTATIN, SMAD3 AND TGF-BETA MEMBERS, WITH METABOLIC AND IMMUNE MARKERS SUCH AS PKM2 AND HMGB1

Kazufumi Ohshiro[1] Krishanu Bhowmick[2] Xiyan Xiang[2] Shivani Kapoor[1] Richard Amdur[1] Srinivasan Dasarathy[3] Adrian Krainer[4] Lopa Mishra[2]

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Background: Sarcopenia or skeletal muscle loss, as well as metabolic alterations, are frequent and progressive comorbidities in patients with cirrhosis and hepatocellular carcinoma (HCC). Myostatin, a TGF-Beta superfamily member expressed primarily in skeletal muscle, inhibits muscle growth and causes sarcopenia in cirrhosis. Previously, we had observed liver-specific knockout of the SMAD3 adaptor, βII-spectrin -*Sptbn1* (βS-LSKO) or siRNA targeting βII-spectrin blocks sarcopenia, fatty liver disease-MASH, and HCC [Sci TM 2021], suggesting that βII-spectrin may be a viable strategy for identifying mechanisms and new biomarkers of MASH and HCC. **Methods:** 1. SPTBN1^{Flox} (control) and liver-specific βII-spectrin knockout (SPTBN1^{LSKO}) mice were fed a Western diet (WD) and treated with Diethylnitrosamine (DEN) for obesity-associated HCC. Muscle mass, body weight and multiple enzymes involved in glycolysis and sarcopenia were measured in mutant mice. 2. In tumors, pyruvate kinase isozyme M2 (PKM2), a rate-limiting enzyme in glycolysis, mediates inflammation and aerobic glycolysis in the Warburg effect. Therefore, we further examined TGF-Beta pathway-enriched biomarkers such as Myostatin and PKM2 for markers of HCC and whether these could stratify risk in patients with cirrhosis for HCC in a four-institution cohort (n=157) compared to cirrhosis patients (n=380). **Results:** 1. Similar to human fatty liver disease, obese mutant mice develop marked sarcopenia with increased PKM2 and Myostatin levels with decreased p-RPS6/total-RPS6 ratio (indicating mTOR signaling inhibition) in striated muscle tissue. In contrast, levels are restored to normal in the liver-specific knockout of SPTBN1. 2. Using the 108 markers as well as PKM2 and myostatin (MSTN), we found 31 markers with false discovery rate (FDR) p values < 0.10 from univariable Kruskal-Wallis tests for the associations of markers with HCC vs cirrhosis. 3. Using unsupervised clustering analysis, we found that higher expression of immune marker HMGB1 together SMAD3, and TGFBR2 in cirrhosis patients (83.3%) that are diagnosed as HCC within 5-year follow up. **Conclusions:** Our results reveal that SMAD3 adaptor, βII-spectrin liver-specific knockout decreases Myostatin and PKM2 expression, providing new insight into molecular mechanisms in MASH and HCC. These studies reflect that biologically functional circuits could provide new serum markers, such as Myostatin, PKM2 and HMGB1 for risk stratification of HCC.

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3591 | SUSTAINED IMPROVEMENT OF AMINOTRANSFERASE LEVELS IN PATIENTS WITH LYSOSOMAL ACID LIPASE DEFICIENCY TREATED WITH SEBELIPASE ALFA ENZYME REPLACEMENT THERAPY: LONGITUDINAL DATA FROM THE INTERNATIONAL LYSOSOMAL ACID LIPASE DEFICIENCY REGISTRY

WILLIAM BALISTRERI[1] Jennifer Evans[2] Florian Abel[2] Lorenzo D'Antiga[3]

[1]Cincinnati Children's Hospital Medical Center, [2]Alexion, AstraZeneca Rare Disease, [3]Hospital Papa Giovanni XXIII; University of Milano - Bicocca

Background: Serum alanine and aspartate aminotransferase (ALT, AST) levels chronically above the upper limit of normal (ULN) have been associated with more severe liver damage in patients with lysosomal acid lipase deficiency (LAL-D). This analysis evaluated ALT and AST in patients with LAL-D treated with sebelipase alfa (KANUMA®; Alexion, AstraZeneca Rare Disease) enzyme replacement therapy (ERT) and in untreated patients. **Methods:** This observational study included adults and children who were enrolled in the International LAL-D Registry (NCT01633489) and had baseline and longitudinal measures of ALT and AST (data cut: Oct 2, 2023). Patients who started sebelipase alfa at age <6 months were excluded. A subanalysis included data from patients with 3 consecutive annual follow-up measures of ALT and AST after baseline. **Results:** Of 186 patients who met inclusion criteria, 125 were treated. Median age at LAL-D diagnosis was 9.1 years for treated patients and 20.6 years for untreated patients. Among treated and untreated patients, baseline ALT levels were ≥1.5 x ULN in 65% (13/20), 78% (42/54), 75% (21/28), and 50% (30/60) of patients aged 0 to <6, 6 to <12, 12 to <18, and ≥18 years, respectively; Results were similar for AST. Among treated patients with 3 consecutive annual ALT measures (n=53), levels were ≥1.5 x ULN in 77% at baseline and in 25% after 1 year of treatment. Among untreated patients (n=22), the percentage with ALT ≥1.5 x ULN increased from 50% at baseline to 64% after 1 year of follow-up. Among treated patients with 3 consecutive annual AST measures (n=51), levels were ≥1.5 x ULN in 53% at baseline and in 16% after 1 year of treatment. A similar proportion of untreated patients (n=19) had AST levels ≥1.5 x ULN at baseline (32%) and after 1 year of follow-up (26%). Results were generally sustained throughout 3 years of follow-up for ALT and AST among treated and untreated patients. Most adverse events (AEs) were mild to moderate in severity. Of 21 serious AEs, 1 (non-severe anaphylaxis that resolved the same day) was deemed related to ERT. **Conclusion:** Liver injury in patients with LAL-D is common early in life, as demonstrated by baseline ALT and AST levels. Sustained reduction of aminotransferases was observed in patients receiving ERT. Further longitudinal studies are needed to evaluate disease progression and the effects of sebelipase alfa in patients with LAL-D.

Disclosures: WILLIAM BALISTRERI: Alexion, AstraZeneca Rare Disease: Consultant, Otsuka: Consultant, Mirum: Consultant, Alexion, AstraZeneca Rare Disease: International LAL-D Registry Scientific Advisory Board, Jennifer Evans: Alexion, AstraZeneca Rare Disease: Employee, Alexion, AstraZeneca Rare Disease: Stock - publicly traded company, Florian Abel: Alexion AstraZeneca Rare Disease: Employee, AstraZeneca: Stock - publicly traded company, Gilead Sciences: Stock - publicly traded company, Lorenzo D'Antiga: Selecta: Advisor, Vivet: Advisor, Spark: Advisor, Genespire: Advisor, Tome: Advisor, Mirum: Advisor, Ipsen/Albireo: Advisor, Intercept/Advanz Pharma: Advisor, Alexion/Astra Zeneca: Advisor

3592 | GENERATION OF COLEC11-CREERT2 KNOCK-IN MICE: A NOVEL TAMOXIFEN REGULABLE *CRE*-DRIVER MOUSE SPECIFIC TO HEPATIC STELLATE CELLS

Bruno Cogliati[1] Shuang Wang[1] Chittampalli Yashaswini[2] fanglin ma[1] Joana Almeida[1] Dipankar Bhattacharya[1] Erin Bresnahan[3] José Javier Bravo-Cordero[3] Hao Zhu[4] Scott Friedman[2]

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Background: Hepatic stellate cells (HSCs) are the major source of extracellular matrix during liver fibrogenesis. Currently there are very few mouse models for HSC-specific gene expression, and they are either not regulable and/or lack specificity to the liver. We have addressed this need by generating a regulable, highly restricted HSC-specific transgenic mouse driving Cre. **Methods:** To identify a suitable Cre driver, we reviewed publicly

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available single-nucleus RNA sequencing datasets from control and MASH mice to identify a gene locus that is highly and selectively activated in HSCs. This approach identified *collectin11* as among the most highly expressed genes in HSCs in normal and injured liver. Cross-validation against several other datasets, including our own, confirmed that *collectin11* is selectively expressed in HSCs in the liver and minimally expressed in other tissues. Using the easiCRISPR method, we successfully knocked-in the CreER^{T2} gene into the 5› UTR of the *collectin11* endogenous locus, which we sequence-verified using a PCR-based genotyping strategy and functionally confirmed by demonstrating regulable expression following administration of tamoxifen (TAM). These mice were crossed with ZsGreen1 reporter mice. Chow and high-fat diet-induced MASH males and females of Colec11-CreER^{T2}:ZsGreen1 mice were treated with TAM (75 mg/kg/day, i.p.) for 5 consecutive days and euthanized at 12, 35, 70, and 140 days after the first injection. Livers were analyzed by second harmonic generation with two-photon microscopy. Tissues were fixed in 4% paraformaldehyde, cryopreserved in 20% sucrose solution, and embedded in OCT. Frozen sections were used to evaluate immunofluorescence of Desmin, CD31, CD68, and F4/80. **Results:** TAM treatment of Colec11-CreER^{T2}:ZsGreen1 mice led to Cre-mediated recombination in HSCs in normal and MASH mice at all time points, whereas other cell types lacked Cre recombination. Immunofluorescence specifically co-localized ZsGreen1 and Desmin in HSCs, with no ZsGreen expression in macrophages or endothelial cells, using cell-specific markers. Utilizing two-photon microscopy, second harmonic generation visualized extracellular matrix that co-localized with ZsGreen1^{+} HSCs in regions of fibrosis in MASH mice. **Conclusion:** We have generated a powerful new mouse model with regulable gene expression selectively in HSCs. Colec11-CreER^{T2} mice will create new opportunities for time-dependent and lineage-tracing studies in vivo in liver fibrosis and cancer models.

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3593 | ASSOCIATION OF BIOMARKERS WITH HEPATIC COLLAGEN QUANTIFICATION IN PATIENTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD)

Daisong Tan[1] Aaron Koenig[1] Sean Felix[1] Michael Estep[1] Fanny Monge[2] Brian Lam[1] Andrei Racila[1] Maria Stepanova[2] Zachary Goodman[2] Zobair Younossi[3]

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Background: Hepatic collagen quantification measured as percent of hepatic collagen (PHC) can provide an accurate assessment of hepatic fibrosis. Although NITs for fibrosis correlate with semi-quantitative assessment of hepatic fibrosis using pathologic staging, association of NITs with PHC in patients with MASLD has not been well established. Our aim was to associate PHC with common fibrosis NITs in MASLD. **Methods:** Liver biopsy slides of MASLD patients were stained with Sirius red; PHC and % morphometric hepatic fat quantification (PHF) were evaluated using computer-assisted morphometry. The histologic stages of fibrosis (F0-F4) and grade of steatosis (S0-S3) were evaluated using semi-quantitative scoring. Serum samples collected at the time of biopsy were used to measure FIB-4, ELF, Hepatis Steatosis Index (HSI), and Fatty Liver Index (FLI) non-invasive test scores. DNA extracted from whole blood and was used to genotype *PNPLA3* rs738409 polymorphism. **Results:** 478 MASLD patients were included: age 46±12 years, 28% male, 95% obese (BMI>30), 37% type 2 diabetes, 53% hyperlipidemia, 59% hypertension, 51% MASH, 48% with *PNPLA3* rs738409 CG or GG genotype (linked to higher risk), 58% histologic F1, 22% F2, 13% F3, 7% F4; mean (SD) FIB-4 score 1.18 (1.82) with 75% having

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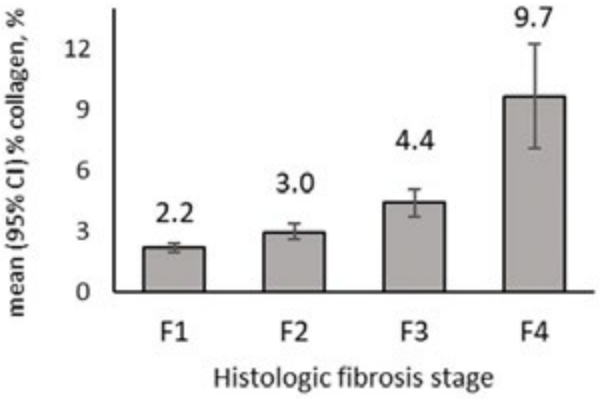
FIB-4 <1.30 (low-risk); mean (SD) ELF score 9.2 (1.3) with 69% having ELF<9.8 (low-risk). The mean (SD) PHC was 3.16 (3.41) % and mean (SD) PHF was 13 (10) %. There was a strong association between PHC with histologic stage of fibrosis (trend p<0.0001) (Figure). Pooled together, patients with advanced fibrosis (F3-F4) had significantly higher PHC than patients with mild or moderate fibrosis: 6.22 (5.51) % vs. 2.40 (2.02) % in F1-F2 (p<0.0001). Among NITs, there were modest but significant correlations of PHC with FIB-4 (r=+0.27) and ELF (r=+0.28) scores (all p<0.01). Patients with elevated ELF (≥9.8) had higher PHC than those with low-risk ELF: 4.7 (4.3) % vs. 2.9 (4.1) %, p=0.0001. Similarly, patients with elevated FIB-4 (≥1.30) had higher PHC than those with low-risk FIB-4: 5.11 (5.32) % vs. 2.53 (2.18) %, p<0.0001. Patients with high-risk *PNPLA3* rs738409 genotype (CG/GG) had higher PHC than those with the CC genotype: 3.32 (2.77) % vs. 2.47 (2.43) %, p=0.0015. The PHF correlated with histologic steatosis grade (r=+0.52), HSI (r=+0.15) and FLI (r=+0.43) scores (p<0.05). **Conclusion:** In MASLD patients, morphometric assessment of histologic steatosis and fibrosis correlate with semi-quantitative assessment by histology as well as some commonly used NITs.



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3594 | DEEP PROTEOMIC ANALYSIS OF PLASMA FROM MICE WITH REVERSAL OF ESTABLISHED LIVER FIBROSIS FOLLOWING TREATMENT WITH SELADELPAR

Edward Cable[1] *Yun-Jung Choi*[1] *Jeffrey Johnson*[1] *Xia Wu*[1] *Jiangao Song*[1] *Charles McWherter*[1]

[1]*CymaBay Therapeutics*

Background: Previously, CymaBay presented data demonstrating a reduction in liver fibrosis in the carbon tetrachloride (CCl_4) fibrosis mouse model. Seladelpar reduced established fibrosis during the final three weeks of on-going CCl_4 administration (8w total). Using archival plasma samples from the CCl_4 model, we performed a proteomic analysis using the Seer Proteograph Product Suite. Seer nanoparticles enable better detection of low abundance proteins within plasma and biofluids. **Methods:** Neat plasma from mice were provided to Seer's Technology Access Center. Seer's automated Proteograph XT workflow was used to generate MS ready peptides. A direct digest of plasma without nanoparticle enrichment was performed on a subset of the same samples. LC-MS was completed on a Thermo Scientific Vanquish Neo UHPLC system equipped with a Thermo Fisher Orbitrap Astral. Peptides were mapped using the DIA-NN search engine and the Uniprot mouse database using a 1% FDR cutoff. **Results:** Each plasma sample provided over 4400 individual proteins. There were no overall differences in intensity distributions by sample. PCA analysis demonstrated two clear groups, mapping to the treated and vehicle animals. After statistical filtering by removing peptide/proteins with complete missing values in at least one group and median normalization of raw intensity values, 4970 protein groups were identified, and 52 protein groups were significantly different comparing seladelpar treatment with vehicle. Nine protein groups were decreased and 43 were increased by treatment. In the decreased protein groups, several are associated with fibrosis including Insulin-like growth factor 1, CD248, and platelet-derived growth factor receptor A. In the induced groups several PPAR-responsive proteins were detected including acyl-CoA thioesterase 1, 2 and 6, Peroxisomal acyl-coenzyme A oxidase 1, 3-Ketoacyl-CoA thiolase, and Enoyl-CoA hydratase/3-hydroxyacyl

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CoA dehydrogenase. **Conclusion:** Seer proteomic analysis of plasma samples from animals that decreased established fibrosis in the presence of the fibrotic stimulus, demonstrates significant changes that are associated with both target engagement as well as related to decreases in fibrosis. IGF1, CD248 and PDGFRA are positively associated with liver fibrosis and their decrease in plasma demonstrate an association with a pharmacological decrease in liver fibrosis. Known PPAR inducible proteins being increased in plasma demonstrate target engagement within the animal.
Disclosures: Edward Cable: CymaBay Therapetics: Employee, Yun-Jung Choi: Nothing to Disclose, Jeffrey Johnson: CymaBay Therapeutics: Consultant, Xia Wu: CymaBay Therapeutics: Employee, Jiangao Song: Nothing to Disclose, Charles McWherter: Nothing to Disclose

3595 | HEPATIC STELLATE CELL-DERIVED NEUROTROPHIN-3 SUPPORTS LIVER REGENERATION AFTER PARTIAL HEPATECTOMY

Ting-Fang Lee[1] Kevin Ray[1] Vincent Quoc-Huy Trinh[1] Sara Lemoinne[2] Maria Ybanez[2] Mary Washington[1] Seth Karp[1] Scott Friedman[3] Kemal Akat[1] Youngmin Lee[1]

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Background: We recently reported that hepatic stellate cells (HSCs) maintain midzonal hepatocyte differentiation and liver cell mass in healthy adult mouse livers. HSC-derived neurotrophin-3 (Ntf3), a neuronal growth factor, induced hepatocyte proliferation through paracrine tropomyosin receptor kinase B (Trkb) signaling. Given Ntf3's proliferative properties in liver homeostasis, we sought to clarify the role of HSCs and Ntf3's potential in promoting liver regeneration. **Methods:** We used a murine HSC-depletion model resulting in near complete depletion of HSCs. HSC depletion was induced by adoptive transfer of GFP-specific CD8 T cells (Jedi T cells) into *Pdgfrb*-GFP transgenic mice. HSC-depleted mice and controls underwent partial hepatectomy (PH). Wildtype (WT) mice underwent PH and were treated daily with Ntf3 or vehicle-only. We assessed survival, liver/body weight ratio, hepatic histology, and hepatocyte proliferation by immunostaining for Ki67. We also assessed proliferative potential of Trkb ligands brain-derived neurotrophic factor (Bdnf), 7,8-DHF, LM22A-4, and N-acetyl-serotonin (NAS) in primary mouse hepatocytes and/or human hepatic organoids (HHO). Hepatocyte growth factor (HGF) was used as positive control. Pan-TRK inhibitor taletrectinib was used to assess if effects were TRK-dependent. Mouse livers and mouse and human HSC cell lines were assessed for Bdnf protein expression by IF and WB. **Results:** HSC-depletion led to marked decreased survival after PH compared to controls. Liver/body weight ratio and Ki67+ hepatocytes in surviving animals was markedly decreased compared to controls. WT animals that had been treated with Ntf3 showed significantly increased liver/body weight ratios and Ki67+ hepatocytes compared to vehicle-only treated animals and serum albumin and ALT levels were comparable. In primary mouse hepatocytes, only Bdnf and NAS, increased proliferation. Bdnf protein was expressed in mouse livers by IF and in human and mouse HSC cell lines by WB. Human hepatic organoids (HHO) cultured with Bdnf, Ntf3 or HGF significantly increased number of EdU+ cells compared to controls. Co-incubation of HHOs with Ntf3/taletrectinib decreased EdU+ cells suggesting TRK-mediated proliferation. **Conclusion:** Human and mouse HSCs release both Ntf3 and Bdnf which have similar proliferative properties towards hepatocytes. Ntf3 treatment accelerated liver regeneration in mice and proliferation in HHO. These findings underscore the beneficial roles of HSCs in liver regeneration and merit further investigation of TRK ligands to assess their potential for clinical translation.
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3596 | UNRAVELING THE IMPACT OF HEPATIC STELLATE CELL-DERIVED CXCL12 ON LIVER FIBROSIS: A STUDY OF TGFβ-MEDIATED REGULATION AND SPATIAL REDISTRIBUTION

Maria Hernandez-Tejero[1] Xie Man[1] Sofia Jerez[1] Shawna Cooper[1] Nidhi Jalan-Sakrikar[1] Usman Yaqoob[1] Maeeha Farheen Kalaiger[1] Papawee Sutthirat[1] Shalil Khanal[1] Brett McGettigan[1] Luke Doskey[1] Markcus A. Lee[1] Clifford M. Csizmar[1] Ningling Kang-Decker[1] Enis Kostallari[1] Moira Hilscher[1] Sheng Cao[1] Vijay Shah[1]

[1]Mayo Clinic Rochester

Background: Chemokines are secreted proteins crucial for stimulating immune cell migration. CXCL12, a highly conserved chemokine, is encoded by a gene with alternative splicing that produces five isoforms in humans and three in mice. It is secreted by mesenchymal stromal cell types, with hepatic stellate cells (HSCs) being the primary stromal cell population in the liver. The role of CXCL12 in HSCs remains largely unexplored. **Methods:** Gene expression was assessed using RNA-sequencing (RNA-seq) and single cell RNA-sequencing (RNA-seq) in primary human HSCs (hHSCs) and CCl4-murine models. hHSCS were treated with TGFβ and analyzed by qPCR, agarose gel electrophoresis, and Western blotting. RNA-fluorescence in situ hybridization (RNA-ISH) on mouse livers was used to investigate CXCL12 spatial distribution. Smad3 occupancy analysis at specific DNA loci in LX-2 cells treated with TGFβ was performed using *in silico* chromatin immunoprecipitation sequencing (ChIP-seq) data via Integrative Genomics Viewer. **Results:** *In silico* analysis showed that CXCL12 is primarily expressed in the liver by HSCs. RNA-seq analysis of hHSCs and murine models treated with TGFβ (vs. vehicle) revealed decreased CXCL12 expression (p=0.0385 and p=0.0012, respectively). scRNA-seq from HSCs isolated from vehicle and CCl4-injected mice indicated CXCL12 downregulation in a collagen-enriched HSCs subset ([Log2(FC)=-0.4, *P*<0.01). These findings were confirmed *in vitro* by qPCR, where TGFβ decreased total CXCL12 and isoforms 1-3 transcripts by 60% in hHSCs (p<0.0001). We further explored TGFβ's canonical signaling pathways to understand the transcriptional regulation of CXCL12. Interestingly, *in silico* analysis of ChIP-seq data from TGFβ-treated LX-2 cells suggested that unlikely COL1A1, CXCL12 is regulated by TGFβ through a SMAD3-independent pathway. Additionally, RNA-ISH in murine models showed that CXCL12 mRNA transcripts were predominantly redistributed along the fibrotic septae compared to the homogenous distribution in the vehicle. To gain further functional insight, Jurkat cells (human T lymphocytes) were treated with CXCL12, which led to an increased phosphorylation of ERK/MAPK, as observed by Western blot analysis. **Conclusion:** The TGFβ-mediated downregulation of HSCs-derived CXCL12 and its striking spatial redistribution highlights its critical role in directing cell trafficking to the fibrotic septae. TGFβ-mediated transcriptional regulation of CXCL12 likely occurs through a non-canonical SMAD3-independent manner. Current investigations are focused on understanding the redistribution of the CXCL12 and its isoforms, the TGFβ-mediated transcriptional regulation, and CXCL12-mediated cellular response in T cells.

Disclosures: Maria Hernandez-Tejero: Nothing to Disclose, Xie Man: Nothing to Disclose, Sofia Jerez: Nothing to Disclose, Shawna Cooper: Nothing to Disclose, Nidhi Jalan-Sakrikar: Nothing to Disclose, Usman Yaqoob: Nothing to Disclose, Maeeha Farheen Kalaiger: Nothing to Disclose, Papawee Sutthirat: Nothing to Disclose, Shalil Khanal: Nothing to Disclose, Brett McGettigan: Nothing to Disclose, Luke Doskey: Nothing to Disclose, Markcus A. Lee: Nothing to Disclose, Clifford M. Csizmar: Nothing to Disclose, Ningling Kang-Decker: Nothing to Disclose, Enis Kostallari: Nothing to Disclose, Moira Hilscher: Nothing to Disclose, Sheng Cao: Nothing to Disclose, Vijay Shah: Boehringer Ingelheim: Consultant, GSK: Consultant, GENFIT SA: Consultant, Intercept Pharmaceuticals, Inc.: Advisor, Korro Bio, Inc.: Consultant, Mallinckrodt Pharmaceuticals: Advisor, Novo Nordisk A/S: Consultant, Resolution Therapeutics, Ltd.: Advisor, Seal Rock Therapeutics, Ltd.: Consultant, Surrozen: Advisor

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3597 | EPIGENETIC MARKS ARE RESTORED BY PROLONGED-RELEASE PIRFENIDONE IN DAA-RESPONDERS HCV PATIENTS PRESENTING RESIDUAL FIBROSIS

Eira Cerda-Reyes[1] Ricardo de la Rosa-Bibiano[2] Ana Sandoval-Rodriguez[2] Rebeca Rosas-Campos[2] Rebeca Escutia-Gutiérrez[2] Ángel Vázquez-Esqueda[2] Stefanny Cornejo-Hernández[1] Alejandro Gutiérrez-Átemis[1] Salvador Amezquita-Pérez[1] Jorge Luis Poo[3] Gildarno Agustin Garrido-Sanchez[4] Juan Ramón-Aguilar[1] Juan Armendariz-Borunda[5]

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Background: Patients with residual liver fibrosis after hepatitis C virus-infection clearance represent an important challenge due to the risk of progression and hepatocarcinoma development. The primary end of this study was to evaluate epigenetic marks in DAA-responders HCV hispanic patients with remaining fibrosis and treated with prolonged-release pirfenidone (PR-PFD). **Methods:** Forty-four DAA-responders HCV patients presenting remaining fibrosis (73% women, 59 ± 9 years) received PR-PFD (1200 mg/day) for 12 months. Six patients dropped out. Liver biopsies and serum samples were analyzed, liver stiffness was assessed (shear wave elastography) and patients were classified as regressive fibrotic profile (RFP), stable fibrosis profile (SFP), or progressive fibrotic profile (PFP) based on liver stiffness behavior (± 30 % variation). Six non-fibrotic controls were included to compare epigenetics marks. Clinical trial number: NCT05542615. **Results:** After 12 months 38 patients completed the treatment, 29% of patients showed a reduction in at least 1 fibrosis stage based on liver biopsies, while 57 % experienced fibrosis improvement according to transient elastography reflected by a progress in liver stiffness (13.25 ± 6.26 vs 9.25 ± 4.36, p= 0.001). According to the fibrosis evolution profile, 15 patients had RFP (16.50 ± 7.72 vs 8.11 ± 3.73), 15 patients had SFP (10.56 ± 3.8 vs 9.00 ± 3.14) and 4 patients progressed PFP (13.55 ± 3.27 vs 20.50 ± 4.03). Bilirubin, alkaline phosphatase, AST, INR, and APRI values significantly decreased, and only minor adverse events were evident. Profibrogenic miRNAs displayed a significant increase in expression in advanced fibrosis versus controls without fibrosis. Noteworthy, PR-PFD treatment induced their decrease and restored the expression of miR-34a, miR-16, miR-192, miR-200a and miR-122 correlating with the downgrade of fibrosis stage after PR-PFD. Specific PDGFalpha CpGs hypermethylation in both cell-free-DNA and liver biopsies were found in both mild and advanced fibrosis. Interestingly, four CpGs in PPARdelta promoter were hypomethylated versus controls. PR-PFD treatment resulted in hypermethylation in three TGFbeta1-CpGs after 12 months, suggesting down-regulation of this profibrogenic cytokine. **Conclusion:** These findings suggest, for the first time, that PR-PFD might exert its therapeutic effects in hispanic patients with residual fibrosis by modulating the expression of miRNAs and methylation of specific CpG sites.
Disclosures: Eira Cerda-Reyes: Nothing to Disclose, Ricardo de la Rosa-Bibiano: Nothing to Disclose, Ana Sandoval-Rodriguez: Nothing to Disclose, Rebeca Rosas-Campos: Nothing to Disclose, Rebeca Escutia-Gutiérrez: Nothing to Disclose, Ángel Vázquez-Esqueda: Nothing to Disclose, Stefanny Cornejo-Hernández: Nothing to Disclose, Alejandro Gutiérrez-Átemis: Nothing to Disclose, Salvador Amezquita-Pérez: Nothing to Disclose, Jorge Luis Poo: Nothing to Disclose, Gildarno Agustin Garrido-Sanchez: Nothing to Disclose, Juan Ramón-Aguilar: Nothing to Disclose, Juan Armendariz-Borunda: Nothing to Disclose

3598 | HEPATIC STELLATE CELL-INTRINSIC ROLE FOR CYTOPLASMIC STRESS GRANULE PROTEINS IN IRF3-MEDIATED FIBROGENIC RESPONSES TO TGFβ

Jared Travers[1] Jianguo Wu[1] Laura Nagy[1]

[1]Cleveland Clinic Foundation

Background: Anti-viral defense pathways, such as nucleic acid-induced activation of the transcription factor interferon regulatory factor 3 (IRF3), have been implicated in sterile metabolic liver diseases. Furthermore, hepatic stellate cell-intrinsic IRF3 activity promotes transforming growth factor-beta (TGFβ)-induced fibrogenesis. Cytoplasmic stress granules are large, organized conglomerates of untranslated mRNAs, stalled ribosomes, and RNA-binding proteins that form in response to various conditions of cellular stress, including RNA virus infection. Their assembly requires the actions of nucleating proteins such as G3BP stress granule assembly factor 1 (G3BP1), its functional homolog G3BP2, and cell cycle associated protein 1 (CAPRIN1). Cytoplasmic

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stress granules promote anti-viral defense, but their potential involvement in fibrosis is unknown. **Methods:** A mass spectrometry-based proteomic analysis was performed in the human hepatic stellate cell line LX2 to identify novel IRF3-interacting proteins. Protein expression and subcellular location were assessed by immunoblotting and immunofluorescence, respectively. The presence of cytoplasmic double-stranded RNA (dsRNA) was assessed by immunofluorescence and flow cytometry. Quantitative real-time polymerase chain reaction was used to determine gene expression after pharmacologic inhibition or short interfering RNA (siRNA)-mediated gene silencing. **Results:** Gene ontology analysis of IRF3-binding proteins revealed striking enrichment in RNA metabolism and cellular responses to stress. Several component proteins of cytoplasmic stress granules were identified, most notably G3BP1, G3BP2, and CAPRIN1. TGFβ increased cytoplasmic dsRNA, assessed by flow cytometry and immunofluorescence. Immunofluorescence revealed cytoplasmic co-localization of IRF3 with both G3BP1 and CAPRIN1 after stimulation with the dsRNA analogue poly(I:C) or TGFβ. Pharmacologic inhibition of G3BP1 activity with (−)-epigallocatechin gallate (EGCG) or G3BP1/G3BP2 dual gene silencing decreased TGFβ-induced collagen 1A1 (COL1A1) and α-smooth muscle actin (ACTA2) gene expression, phenocopying IRF3 gene-silencing. **Conclusion:** Collectively, these results identify that cytoplasmic stress granule proteins contribute to the pro-fibrogenic response of hepatic stellate cells to TGFβ.

Disclosures: Jared Travers: Nothing to Disclose, Jianguo Wu: Nothing to Disclose, Laura Nagy: Nothing to Disclose

3599 | SUPPRESSING MASH FIBROTIC PROGRESSION BY BLOCKING SUCCINATE-GPR91 SIGNALING AXIS IN HEPATIC STELLATE CELLS

Jian Wu[1] *Li Xie*[1] *Hui Chen*[1] *Li Zhang*[1] *Yong-Yu Yang*[1] *Xiu-Ping Liu*[1]

[1]*Fudan University Shanghai Medical College*

Background: Succinate receptor GPR91 is one of G protein-coupled receptors (GPCRs), and its natural ligand is succinate. It is exclusively expressed in hepatic stellate cells (HSC), and its expression is enhanced in MASH-fibrotic progression (Liver Int. 2020;40:830-843). However, there is no convincing in vivo data available regarding whether this signaling pathway plays a critical role in MASH fibrotic progression. The present study aims to investigate whether depletion of GPR91 would block MASH fibrotic progression in murine models. **Methods:** Wild-type (WT) mice and HSC-specific GPR91 receptor knockout mice (HSC-GPR91-KO) were fed a high-fat and high-calorie diet with high fructose and glucose in drinking water (HFCD-HF/G) for 24 weeks to induce MASH fibrotic progression. **Results:** Peritoneal injection of succinate in mice fed choline-deficient amino acid-defined (CDAA) diet exacerbated fibrosis, presenting a positive correlation with GPR91 expression levels. Both WT and HSC-GPR91-KO mice exhibited a substantial elevation in hepatic succinate levels upon HFCD-HF/G diet feeding. However, in comparison to WT mice fed with HFCD+HF/G, hepatic fibrosis was markedly ameliorated in HSC-GPR91-KO mice, as evidenced by diminished hepatic hydroxyproline content. Masson staining and semi-quantitative analysis demonstrated a significant reduction in collagen deposition in HSC-GPR91-KO mice compared to their WT counterparts. Levels of hepatic smooth muscle α-actin (α-SMA) and connective tissue growth factor (CTGF) proteins were notably lower in HSC-GPR91-KO mice than in WT mice. Furthermore, gene expression profiling revealed significant upregulation of α-SMA, CTGF, fibronectin-1, and collagen type I-α1 in WT mice fed with HFCD+HF/G, whereas these markers were downregulated in the HSC-GPR91-KO group. GPR91 knockout profoundly inhibited succinate-induced expression of α-SMA and GRP91 expression at mRNA and protein levels in primary HSCs. Further mechanistic experiments suggest that succinate-mediated GPR91-Gαi signaling leads to diminished cAMP levels, contributing to HSC activation, and that NF-κB activity was activated by succinate-GPR91-AMP axis, thereby it suppressed HSC apoptosis in NASH fibrotic progression. **Conclusion:** HSC-specific GPR91 receptor knock-out effectively halted hepatic fibrosis in HFCD-HF/G-fed mice. This inhibition is mediated probably through two distinct signaling pathways: suppressing the succinate-GPR91-Gβγ-ERK/c-jun-Smad3 axis that positively regulates HSC activation, and abrogating the GPR91-Gαi-cAMP-NF-κB pathway that hinders HSC apoptosis. These findings underscore the critical role of this transmembrane protein in the pathogenesis of MASH fibrotic progression, shed light on the sophisticated interplays between hepatocytes and HSCs, and confer a promising target for molecular interventions in MASH-fibrotic progression.

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3600 | IN VIVO ANTI-FAP CAR T CELLS THAT TARGET FIBROGENIC HEPATIC STELLATE CELL SUBSETS AMELIORATE MURINE (MASH) LIVER FIBROSIS

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Background: Hepatic fibrosis in chronic liver disease is the main predictor of mortality and is generated from pro-fibrogenic subsets of hepatic stellate cells (HSCs). In cardiac fibrosis, targeting fibroblast activation protein (FAP) on activated cardiac myofibroblasts by generating chimeric antigen receptor (CAR) T cells in vivo reduces cardiac fibrosis (Aghajanian et al., 2019; Rurik et al., 2022), however it is not known if this approach is effective in liver. **Methods:** We sought to determine the efficiency and efficacy of LNP-mediated in vivo anti-FAP CAR T generation in murine MASH following tail vein injection, by assessing their impact on fibrosis in the murine FAT-MASH model after the disease is established, and on the distribution of specific immune and resident cell subsets. To do so we utilized flow cytometry, single nuclear RNA sequencing (snRNAseq), immunostaining and Sirius red morphometry. **Results:** Anti-CD5 coated LNPs carrying anti-FAP mRNA specifically target splenic and hepatic CD5+ immune cells, leading to generation of anti-FAP CD4+ and CD8+ CAR T cells in the spleen and liver. Hepatic fibrosis in mice with MASH was significantly reduced after 10 weeks total of the model and 4 weeks after CAR T LNP administration but not control LNPs. Based on snRNAseq, these in vivo CAR T cells reduce *Fap* RNA in HSCs, deplete fibrogenic HSC subsets – specifically the quiescent precursors of activated HSCs, and activated HSCs – and genetically alter hepatocytes in a way that may favor MASH resolution. Flow cytometry analysis shows alterations to hepatic immune cell populations following anti-FAP CAR T therapy – these effects on hepatic immunity may also favor MASH resolution. **Conclusion:** In vivo generated anti-FAP CAR T therapy significantly reduces MASH fibrosis, depletes only pro-fibrogenic HSC subsets, and leads to hepatocyte subset redistribution and immune microenvironment remodeling that may further abrogate MASH pathogenesis and progression.

Disclosures: Chittampalli Yashaswini: Nothing to Disclose, Bruno Cogliati: Nothing to Disclose, Tianyue Qin: Nothing to Disclose, Joel Rurik: Nothing to Disclose, Thomas Williamson: Nothing to Disclose, Tyler Papp: Nothing to Disclose, Kenneth Li: Nothing to Disclose, Hamideh Parhiz: Nothing to Disclose, Shuang Wang: Nothing to Disclose, Jonathan Epstein: Nothing to Disclose, Scott Friedman: 89 Bio: Consultant, Boehringer Ingelheim: Consultant, Boston Pharmaceutical: Consultant, Bristol Myers Squibb: Consultant, Merck: Consultant, Glycotest: Consultant, Morphic Therapeutics: Consultant, HepGene: Consultant, North Sea Therapeutics: Consultant, Pfizer Pharmaceuticals: Consultant, Sagimet: Consultant, Scholar Rock: Consultant, Prosciento: Consultant, Seal Rock: Consultant, Surrozen: Consultant, Takeda Pharmaceuticals: Consultant, Junevity: Consultant, Therasid Bio: Consultant, Merck: Consultant, Ochre Bio: Consultant, Gordian Biotechnology: Consultant, Abalone Bio: Grant/Research Support, Prosciento: Consultant

3601 | THE HIDDEN LINK BETWEEN LIVER STIFFNESS AND HEART FAILURE: NEW INSIGHTS FROM NHANES

Saleha Aziz[1] Arsalan Hamid[1] Michael Hall[1] Mark Pedersen[2] Jan Petrasek[1]

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Background: Heart failure (HF) is associated with increased liver fibrosis. We investigated the relationship between HF and liver fibrosis, as measured by liver stiffness using ultrasound. **Methods:** We analyzed data from the 2017 to 2020 National Health and Nutrition Examination Survey (NHANES), including 3,064 adults age 20 years and older (representing a weighted total of 84,796,953) with available liver ultrasound data. We used logistic regression models to assess the relationship between liver stiffness and prevalent HF, adjusting for age, gender, and race. **Results:** The mean age was 47±17 years, 49.6% were women, 63.7% were white adults, and 1.8% had prevalent HF. The median liver stiffness was 5.6 kPa. We found that both liver stiffness and liver stiffness ratio were associated with prevalent HF, with each 1 kPa increase in liver stiffness associated with a 6% increase in the odds of having prevalent HF. Cirrhosis (liver stiffness >14 kPa) was significantly associated with prevalent HF. While severe liver scarring (10.0 to 13.9 kPa) showed an association with prevalent HF in unadjusted models, this was not significant after adjustment. **Conclusion:** Our findings indicate that liver stiffness

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is associated with prevalent HF, and the risk increases with each unit increase in liver stiffness. This relationship becomes particularly significant at the level of cirrhosis. These results highlight the connection between prevalent HF and liver scarring in the development of liver cirrhosis.

Table. Participant odds of prevalent HF

	Odds Ratio (95% Confidence Interval)			
	Unadjusted	**p-value**	**Adjusted***	**p-value**
Median Liver Stiffness, kPa	1.06 (1.03 to 1.1)	0.001	1.06 (1.02 to 1.11)	0.004
Stiffness ratio (IQRe/median E)	1.08 (1.04 to 1.13)	0.001	1.06 (1.02 to 1.11)	0.005
Stiffness levels				
Normal stiffness	Ref	Ref.	Ref	Ref.
Moderate scarring	1.22 (0.26 to 5.75)	0.790	1.08 (0.23 to 5.13)	0.919
Severe scarring	3.48 (1.06 to 11.45)	0.041	2.41 (0.63 to 9.26)	0.191
Cirrhosis	5.26 (2.29 to 12.06)	p<0.001	3.74 (1.57 to 8.94)	0.005

*Model adjusts for age, gender, and race

Disclosures: Saleha Aziz: Nothing to Disclose, Arsalan Hamid: Nothing to Disclose, Michael Hall: Nothing to Disclose, Mark Pedersen: Nothing to Disclose, Jan Petrasek: Nothing to Disclose

3602 | HEPATIC STELLATE CELL-DERIVED THBS2 PROMOTE INTRAHEPATIC INFLAMMATORY INFILTRATION BY REGULATING SPP1 SECRETION DURING LIVER FIBROGENESIS

Hong Li[1] Ning Zhang[2] Wen Zhang[1] Wenyue Wu[1] Yameng Sun[1] Shuyan Chen[1] Qi Han[1] Xuzhen Yan[3] Aiting Yang[1] Hong You[1] Wei Chen[1]

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Background: Our previous study demonstrated that Thrombospondin-2 (THBS2) plays a critical role in hepatic stellate cells (HSCs) activation and the progression of liver fibrosis through TLR4-FAK/TGF-β signaling. However, its connection with chronic intrahepatic inflammation during liver fibrogenesis remains unclear. This study aims to explore the pro-inflammatory roles and mechanisms of THBS2 during the progression of liver fibrosis. **Methods:** The adeno-associated virus vector (serotype 6, AAV6) containing short hairpin RNAs targeting *Thbs2*, under the regulatory control of smooth muscle α-actin (αSMA) promoter, was utilized to specifically inhibit HSCs-derived *Thbs2* gene (AAV6-αSMA-sh*Thbs2*). Liver fibrosis was induced using CCl4 administered through intraperitoneal injection for 6 weeks. Single nucleus RNA sequencing (snRNA-seq), Western blot, immunofluorescence, and in vitro experiments using HSC and THP-1 cell lines were conducted. **Results:** Selective interference of *Thbs2* in HSCs attenuated chronic intrahepatic inflammatory infiltration in CCl4 mouse models. Analysis of frozen liver tissues via snRNA-seq revealed a marked decrease in the number of intrahepatic Kupffer cells in AAV6-αSMA-sh*Thbs2* mice compared to their controls. Cell chat analysis further demonstrated a significant weakening of the SPP1-CD44 interaction axis in AAV6-αSMA-sh*Thbs2* mice. Western blot and immunofluorescence showed a pronounced reduction in SPP1 expression in HSCs from AAV6-αSMA-sh*Thbs2* mice. *Thbs2* knockdown in HSCs significantly inhibited Spp1 expression, while its overexpression notably promoted Spp1 expression and secretion. Co-incubation with the conditioned medium from HSCs with *Thbs2* knockdown or overexpression perturbed the recruitment of monocytes and affected their differentiation into monocyte-derived macrophages (MoMFs). Additionally, treatment of THP-1 cells with recombinant human SPP1 protein increased the marker gene expression of macrophage activation. **Conclusion:** HSC-derived THBS2 facilitated intrahepatic inflammatory infiltration by promoting SPP1 expression and secretion, subsequently recruiting monocytes and inducing their differentiation into liver resident macrophages

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3603 | PREDICTING LIVER RELATED MORBIDITY AND MORTALITY IN NON-CIRRHOTIC CHRONIC LIVER DISEASE: EARLY RESULTS FROM THE ELUCIDATE TRIAL

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Background: Biomarkers have been validated for the prediction of adverse events in chronic liver disease (CLD) patients with a diagnosis of cirrhosis. We have investigated the performance of serum biomarkers to predict liver related events (LRE) in a secondary care cohort of patients diagnosed with CLD and thought not to have cirrhosis. **Methods:** Patients in the prospective ELUCIDATE trial (ELF to Uncover Cirrhosis as an Indication for Diagnosis and Action for Treatable Events) were recruited from secondary care clinics from 37 centres in the United Kingdom. Patients were reviewed at least every 6 months over the first 36 months of the trial to assess for the development of LRE including liver related death, hepatocellular carcinoma, large varices requiring therapy, ascites, spontaneous bacterial peritonitis and encephalopathy. Eligibility for the study included a registration ELF score of >8.37, age 18-75 and a 6 month history of abnormal liver function tests due to any aetiology of CLD. Patients were excluded if they had clinical, laboratory or histologic results corroborating a diagnosis of cirrhosis. The published thresholds for ELF (9.8 and 11.3) and FIB4 (1.3 and 3.25) for advanced fibrosis were validated for their ability to predict both all LRE and LRE related to portal hypertension (PHTN-LRE). **Results:** Of 873 patients who were randomised, 56% were male with a mean age 53 years (range 22-74). The primary diagnosis at randomisation was viral hepatitis (40%), MASLD (27%), alcohol-related liver disease (8%) and 'unknown/other' (26%). A BMI>30 was recorded for 63% of the 'unknown/other' group. LRE occurred in 28 patients including 5 liver related deaths with 11 HCC and 17 PHTN-LRE. All 873 patients had an ELF test at baseline of which 819 had available blood tests to allow FIB4, APRI and AST:ALT ratio to be calculated; 24 of the 819 patients had an LRE. The AUC for ELF (n=873) at predicting LRE was 0.85 and PHTN-LRE was 0.91. Comparative AUC (n=819) for predicting LRE were 0.84 (ELF), 0.79 (FIB4), 0.74 (APRI), 0.67 (AST:ALT ratio) and for PHTN-LRE were 0.90 (ELF), 0.85 (FIB4), 0.81 (APRI), 0.75 (AST:ALT ratio). Of note, all 3 of patients with ELF <9.8 and LRE (2 HCC) and were diagnosed with viral hepatitis. **Conclusion:** In this cohort of patients with CLD without a clinical diagnosis of cirrhosis both ELF and FIB4 performed well at predicting LRE during a follow up of up to 36 months. Most patients in this cohort had either a low or indeterminate FIB4 score (91%) with more than half of all LRE developing in patients with these scores. Regardless, ELF at the 9.8 threshold identified 79% of patients with either a low or indeterminate FIB4 score who would develop LRE, rising to 100% in patients without viral hepatitis. In keeping with recent studies, an ELF score >13.0 was associated with a very high risk of developing LRE and these patients should be subject to enhanced follow up.

Table 1

FIB4	n=819	LRE (n=24)	of which ELF>9.8
<1.3	328 (40%)	3	3 (100%)
1.3-3.25	421(51%)	11	8 (73%)
>3.25	70 (9%)	10	10 (100%)

Table 2

ELF	n=873	LRE (n=28)	PHTN-LRE (n=17)
<9.8	568 (65%)	3	1
>9.8	305 (35%)	25	16
>11.3	63 (7%)	14	11
>13.0	10 (1%)	4	4

Disclosures: Sudeep Tanwar: Nothing to Disclose, Walter Gregory: Nothing to Disclose, The ELUCIDATE Investigators: Nothing to Disclose, Peter Selby: Nothing to Disclose, William Rosenberg: Nothing to Disclose

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3604 | SERUM THROMBOSPONDIN 2 AND INSULIN-LIKE GROWTH FACTOR BINDING PROTEIN 7 PREDICT ADVANCED LIVER FIBROSIS IN PATIENTS WITH COMMON VARIABLE IMMUNODEFICIENCY

Rambabu Surabattula[1] Valentina Strohmeier[2] Anna-Maria Globig[2] Sudha Myneni[1] Maximilian Heeg[2] Gerhard Kindle[2] Sigune Goldacker[2] Caroline von Spee-Mayer[2] Michele Proietti[3] Birke Bausch[2] Dominik Bettinger[2] Michael Schultheiß[2] Robert Thimme[2] Klaus Warnatz[2] Detlef Schuppan[1]

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Background: Timely detection of segmental fibrosis and portal hypertension as a manifestation in a significant subgroup of patients with CVID (Common Variable Immunodeficiency) is a challenge, as it is usually not associated with classic liver cirrhosis. To date, there are no standard biomarkers for the diagnosis of portal hypertension in patients with CVID. To identify relevant markers, we assessed elastography and novel serum markers of fibrogenesis and liver metabolism/inflammation in a well-defined cohort of patients with CVID. **Methods:** Sandwich ELISAs to measure the matricellular fibrosis markers thrombospondin-2 (TSP2) and thrombospondin-4 (TSP4) as well as the metabolism/inflammation/fibrosis related markers insulin-like growth factor binding protein-7 (IGFBP7), CD163 and a disintegrin and metalloprotease thrombospondin like-9 (ADAMTS9) were developed in-house using combinations of recombinantly expressed proteins as well as commercial and self-produced monoclonal and polyclonal antibodies. Sensitivity and specificity were optimized, with intra- and Inter assay variations for serum or plasma below 10% and 15%, respectively. We included 39 CVID patients, 27 of whom had clinically significant portal hypertension defined by the presence of either esophageal varices, hypertensive gastropathy or ascites. In most patients, the measured liver stiffness (LSM) was above 6.5 kPa, indicating significant fibrosis. **Results:** Patients with an LSM above 6.5 kPa compared to an LSM below 6.5 kPa had significantly higher serum levels of TSP2 (118 vs. 69 ng/ml) and IGFBP7 (187 vs. 135 ng/ml). No significant differences were found for TSP4, ADAMTS9 and CD163. Both TSP2 and IGFBP7 correlated well with LSM levels. The underlying biochemistry as well as the results support a prominent role of TSP2 in liver fibrogenesis due to CVID, and of IGFBP7 in fibrogenic inflammation. Both parameters differentiated patients with LSM above 6.5 kPa and signs of portal hypertension from those with LSM below 6.5 kPa with an AUROC of 0.87 (TSP2) and 0.85 (IGFBP7) and outperformed PRO-C3 (0.65). In addition, the combination of TSP2 and IGFBP7 showed the highest AUROC value (0.91). **Conclusion:** The matricellular serum marker TSP2 and the metabolic/fibrosis-related marker IGFBP7 predicted advanced fibrosis and portal hypertension in CVID patients. The new markers could support early antifibrotic treatment of CVID. Confirmation of these results in a larger, prospective cohort is on the way.

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3605 | LOXL1 G153D MUTATION IS ASSOCIATED WITH NON-REGRESSION OF LIVER FIBROSIS DURING VIRAL CLEARANCE IN CHRONIC HBV INFECTION ◆

Wen Zhang[1] Wei Chen[1] Yameng Sun[1] Ning Zhang[1] Hong Li[1] Wenyue Wu[1] Xiaoning Wu[1] Xuzhen Yan[1] Qi Han[1] Aiting Yang[1] Hong You[1]

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Background: Lysyl oxidase like-1 (LOXL1), a member of the lysyl oxidase family, is responsible for cross-linking and stabilizing extracellular matrix (ECM) structural proteins. Previous studies have indicated that single nucleotide polymorphisms (SNPs) in the LOXL1 gene are closely associated with disorders resulting from abnormal elastin assembly. However, the relationship between LOXL1 SNPs and liver fibrosis remains unclear. **Methods:** Genomic DNA from 168 patients with liver fibrosis due to chronic hepatitis B virus (CHB) infection was collected to analyze LOXL1 SNPs using PCR and Sanger sequencing. Blood biochemistry indexes, LSM values, and histological Ishak scores were systematically compared between mutation and wildtype patients

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pre- and post-antiviral treatment. In vitro experiments were conducted to investigate the biological functions of the identified LOXL1 SNPs. **Results:** Patients with the heterozygous LOXL1 G153D mutation exhibited reduced reversibility after 78 weeks of antiviral treatment (26.3% and 52.4% reversal rates in heterozygous mutated and non-mutated patients, respectively, p=0.025). Subsequent analysis of blood biochemical data revealed significantly elevated levels of serum ALT and GGT, as well as increased LSM values and Ishak scores in patients with the heterozygous LOXL1 G153D mutation compared to non-mutant patients post-antiviral treatment. In vitro experiments demonstrated that the LOXL1 protein notably translocated to the cell membrane or extracellular space following transient transfection of hepatic stellate cells with the LOXL1 G153D mutant plasmid. This suggests that the LOXL1 G153D mutation promotes extracellular secretion of LOXL1 protein, leading to increased crosslinking and deposition of ECM structural proteins, thereby hindering the reversal of liver fibrosis. **Conclusion:** Our study reveals that CHB patients with the heterozygous LOXL1 G153D mutation tend to exhibit limited regression after HBV clearance. This sheds light on a genetic basis explaining why antiviral treatment is inadequate for achieving remission in all liver fibrosis patients with CHB.

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3606 | LYSYL OXIDASE INHIBITOR AMELIORATES ECM CROSS-LINKING AND INFILTRATING MACROPHAGES IN HEPATOCELLULAR CARCINOMA WITH FIBROSIS/ CIRRHOTIC BACKGROUND

Basundhara Das[1] Sachin Sharma[2] Maryam Shaikh[3] Bornika Roy[1] Sampa Ghose[4] Subhrajit Biswas[1]

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Background: During onset of hepatocellular carcinoma (HCC) in fibrosis/ cirrhotic microenvironment, secretion of extracellular matrix (ECM) proteins from hepatic stellate cells (HSCs) and cross-linking of ECM proteins by Lysyl Oxidase (LOX) are associated with endothelial cells (ECs) and infiltration of bone marrow derived macrophages. The aim of our study is to target LOX-mediated cross linking and macrophage polarity to inhibit HCC progression. **Methods:** The C57BL6 mice were treated with CCl_4 followed by directly injecting mice specific HCC, Hepa1-6 cells in injured liver. Expression of LOX family members were examined with publicly available database of NCBI-GEO, in the αSMA+ HSCs of portal and periportal region of human liver biopsies with increasing METAVIR score, cultural activated freshly isolated qHSCs *ex vivo*, TGFβ1 activated human HSCs (LX2) *in vitro* during interaction with HCC, ECs and human monocyte THP1- derived polarized macrophage subsets. **Results:** LOX expressions were enhanced in advance cirrhosis stage and HCC in cirrhotic background in compare with mild cirrhosis and HCC. Pro-fibrotic cytokine TGFβ1 secreted from M2 polarized macrophages enhanced HCC migration and the activation of HSCs. Angiogenic factors, VEGF-A and VEGFR1 were increased in ECs due to the influence of ECM. In activated HSCs, LOX expression was enhanced after interaction with HCC cells. As compared with non-metastatic set up, LOX expression in human HCC cells was significantly enhanced in metastatic set up after interaction with polarized macrophages *in vitro*. There was no change in viability among human HCCs, Hepa-1-6, TGFβ1 activated LX2 cells after treatment with beta-aminopropionitrile (BAPN), LOX inhibitor. However, the migration of LX2 under influence of Hep3B was significantly reduced with BAPN, indicating it's the possible effect on *in vivo* tumor microenvironment. Collagen contraction of HCC cells influenced with LX2 conditional media reduced with BAPN treatment. Treatment of ECs with BAPN blocked the hypoxia induced EMT and inhibited their invasion and migration capacities. BAPN treatment showed altered distribution of $F4/80^+$ and $CD68^+$ cells in the fibrotic septa and modulated infiltrating polarized M1 and M2 macrophage specific markers in orthotropic HCC mice with injured liver. **Conclusion:** HCC cells and tumor-associated stromal cells produce excessive LOX that not only provides a suitable niche for the tumor cells but also aids in cancer progression.

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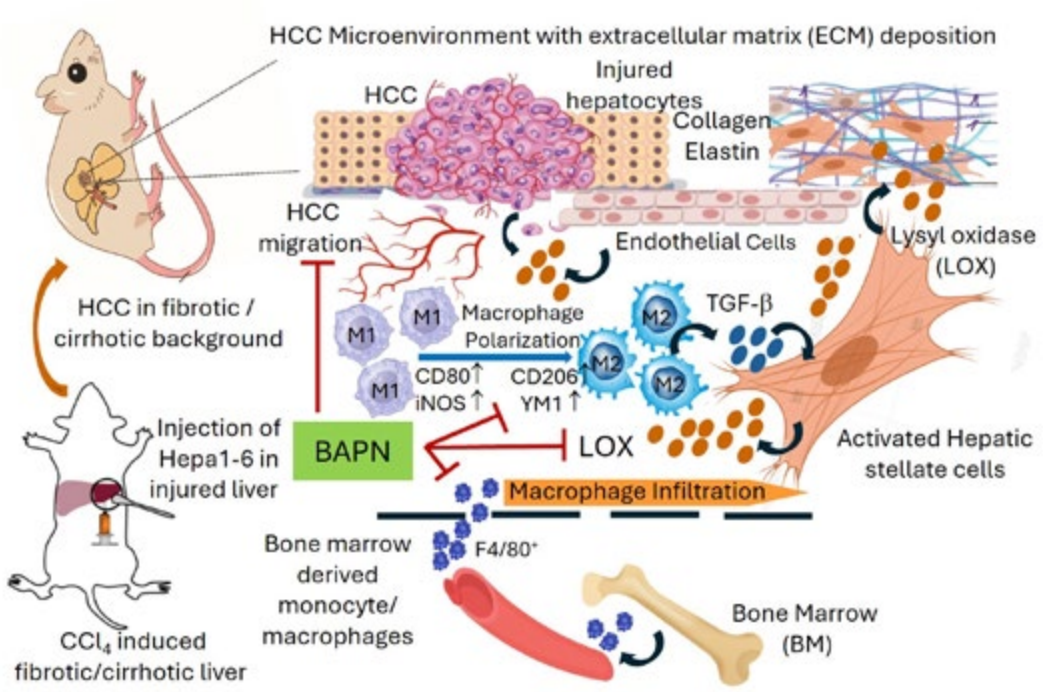

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3607 | *MFAP2* ABLATION RETARDS HEPATIC FIBROSIS REGRESSION BY ORCHESTRATING EXTRACELLULAR MATRIX AND INFLAMMATION

Wen Zhang[1] Wenyue Wu[1] Ning Zhang[1] Hong Li[1] Yameng Sun[1] Xiaodong Ge[2] Hui Han[2] Shuyan Chen[1] Anjian Xu[1] Sai Santosh Babu Komakula[2] Chao Wang[2] Nithyananthan Subramaniyam[2] Qi Han[1] Xuzhen Yan[1] Aiting Yang[1] Natalia Nieto[2] Hong You[1] Wei Chen[1]

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Background: Microfibril-associated glycoprotein 1 (MAGP-1) is a glycoprotein involved in extracellular matrix (ECM) remodeling. However, its role in liver fibrosis remains poorly understood. **Methods:** Human tissue microarrays and dynamic liver fibrosis mouse models were utilized to investigate MAGP-1 expression patterns. MAGP-1 gene deficiency (*Mfap2*$^{-/-}$) or overexpression mice were subjected to carbon tetrachloride (CCl_4) injection or bile duct ligation (BDL) to induce liver fibrosis. Histological, biochemical, bulk or single cell RNA-sequencing (scRNA-seq), matrisomal proteomic, and *in vitro* analyses were conducted to elucidate the roles and mechanisms of MAGP-1 in liver fibrogenesis and fibrolysis. **Results:** MAGP-1 (*Mfap2*) was predominantly enriched in activated hepatic stellate cells (HSCs) and upregulated in advanced liver fibrosis. Knocking it out had minimal impact on the histology of liver fibrosis under CCl_4 stimulation but significantly exacerbated intrahepatic inflammatory infiltration in lobular areas, accelerated ECM remodeling characterized by an upregulation of insoluble matrisome members within the ECM, and activated focal adhesion (FAK) signal in HSCs, hindering liver fibrosis regression after CCl_4 cessation. In BDL mouse models, *Mfap2* deficiency notably worsened liver fibrosis with no discernible effect on intrahepatic inflammation. Additionally, overexpression of *Mfap2* exhibited contrasting effects compared to *Mfap2* ablation in both models. Mechanically, inhibiting *Mfap2* enhanced the interaction strength within HSCs, leading to increased matrisome production and subsequent ECM remodeling, while weakening interactions across HSCs and Kupffer cells via reducing macrophage migration inhibitory factor (MIF) derived from HSCs in CCl_4 but not BDL mouse models. **Conclusion:** HSCs-derived MAGP-1 counteracts ECM remodeling and intrahepatic inflammation aggravation by inhibiting matrisome production and accelerating MIF secretion during liver fibrogenesis, thereby favoring liver fibrosis regression post-etiology removal.

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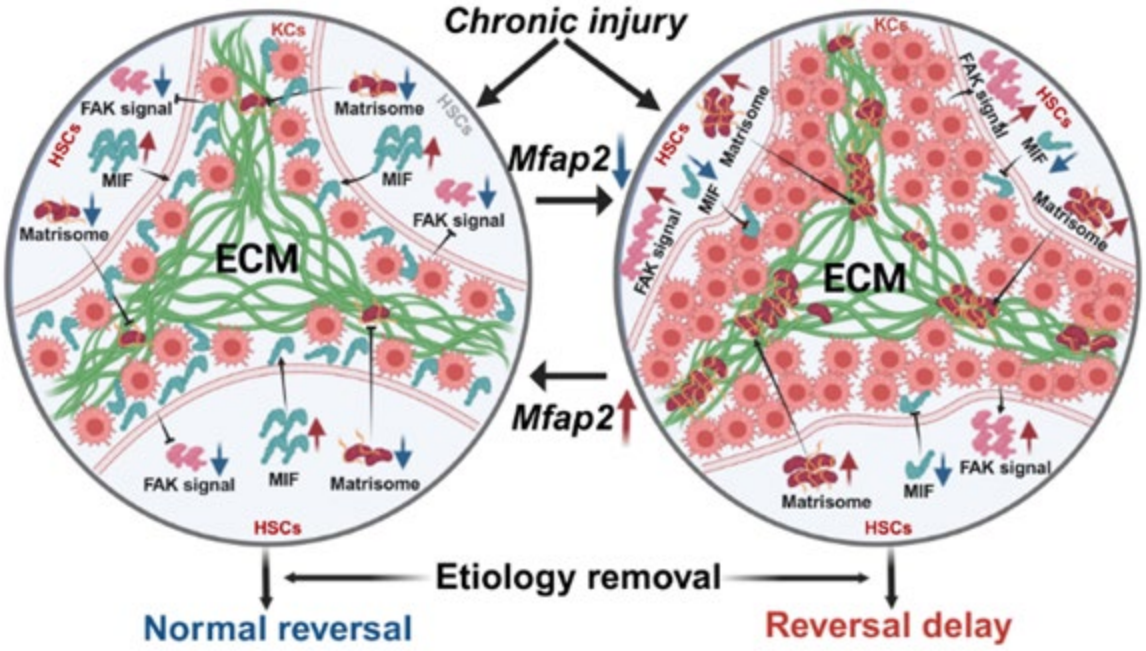

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3608 | NOVEL BLOOD-BASED BIOMARKER MODEL FOR DIAGNOSIS OF HEPATIC FIBROSIS IN MASLD

Eveline Gart Lars Verschuren[1] Anne Mak[2] Andre Boonstra[3] Joanne Verheij[4] Lise Lotte Gluud[5] Adriaan Holleboom[2] Maarten Tushuizen[6]

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Background: Considering the escalating prevalence of metabolic dysfunction-associated steatotic liver disease (MASLD) and related fibrosis, accurate non-invasive biomarkers for diagnosis and staging of fibrosis are urgently needed. This study applied a translational approach with the aim to develop a blood-based biomarker panel for fibrosis detection in MASLD. **Methods:** A first set of candidate biomarkers was identified using a translational diet-induced MASLD mouse model (LDLr-/-.Leiden), focused on the mechanism of collagen deposition using hepatic gene expression and new extracellular matrix deposition, as detected by dynamic D2O-labeling. To translate these findings to humans, gene expression profiles and biomarkers were analyzed in liver biopsies and serum samples from patients with histologically characterized MASLD and variable degrees of fibrosis and validated in two independent patient cohorts **Results:** A panel of blood-based fibrosis biomarkers was identified consisting of IGFBP7, SSc5D and Sema4D. The accuracy of the biomarker panel was validated in a separate cohort of 128 patients with histologically characterized MASLD across different stages of fibrosis. Light Gradient Boosting Machine (LightGBM) modelling demonstrated that fibrosis stage can be predicted in MASLD (F0/F1: AUC = 0.82; F2: AUC = 0.89; F3/F4: AUC = 0.87). Additionally, by validation in an independent second patient cohort (n=156), we successfully replicated the high-performance predictions for F0/F1 and F3/F4 fibrosis stages with an AUC of 0.84. Although the AUC for predicting F2 fibrosis was modest at 0.62 the overall accuracy of the model outperformed the FIB-4 and Fibroscan predictions. **Conclusion:** Using a translational approach to identify novel biomarkers mechanistically related to the dynamics of collagen synthesis, we developed a blood-based biomarker panel with three biomarkers which is able to identify MASH patients with mild (F0/F1) or advanced (F3/F4) hepatic fibrosis with high accuracy.

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3609 | EMPAGLIFLOZIN REDUCES LIVER FIBROSIS CAUSED BY CCL4: UNDERSTANDING THE MECHANISM

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Background: Liver fibrosis is a reversible response to liver damage and inflammation caused by chronic factors. However, currently, there is no approved chemical drug or biological preparation for liver fibrosis. Empagliflozin has antioxidative and anti-inflammatory effects, suggesting that it may alleviate liver inflammation and consequently reduce liver fibrosis. This study aims to determine if Empagliflozin can improve liver fibrosis in non-diabetic mice with CCl4-induced liver fibrosis and understand how it works. **Methods:** Mice were divided into normal control group, liver fibrosis group, and treatment group. Liver function,intraperitoneal insulin tolerance test and histological changes of liver tissues in each group were analyzed. SPSS 26.0 statistical software was used for data analysis. Measurement data were expressed as mean ± standard deviation (mean ± SD). One-way analysis of variance was used for comparison of multiple groups with normal distribution. LSD test was used for pairwise comparison of means between multiple groups when variance was homogeneous, and Mann-Whitney U test was used for comparison when variance was heterogeneous. **Results:** There was no statistically significant difference in liver weight/body weight ratio among 3 groups. ALT and AST levels were significantly elevated in the liver fibrosis group, but there was no statistically significant difference between the treatment group and the liver fibrosis group. In the insulin tolerance test, blood glucose levels in the treatment group mice were slightly higher than the other 2 groups only at 60 min. HE staining of liver tissue showed reduced inflammation and necrosis in the treatment group compared to the liver fibrosis group. Analysis of Sirius Red staining showed significantly less fibrosis in the treatment group compared to the fibrosis group. There were no significant differences in TNF-α, IL-2, and IL-6 levels among the three groups. Quantitative analysis of liver tissue enzyme activities of superoxide dismutase, malondialdehyde, and glutathione peroxidase showed no statistically significant differences among the three groups; however, hepatic catalase activity was significantly decreased in the liver fibrosis group and treatment group ($P < 0.01$). In all enzyme assays, the treatment group levels were closer to the normal control group than the liver fibrosis group. There was a trend of further reduction in the number of Keap1-positive cells in the treatment group compared to the liver fibrosis group. **Conclusion:** Empagliflozin could alleviate the degree of diffuse necrosis in liver cells and the extent of liver fibrosis induced by CCl4, possibly through modulation of the Keap1-Nfr2 signaling pathway, thereby reducing oxidative stress in liver tissues.

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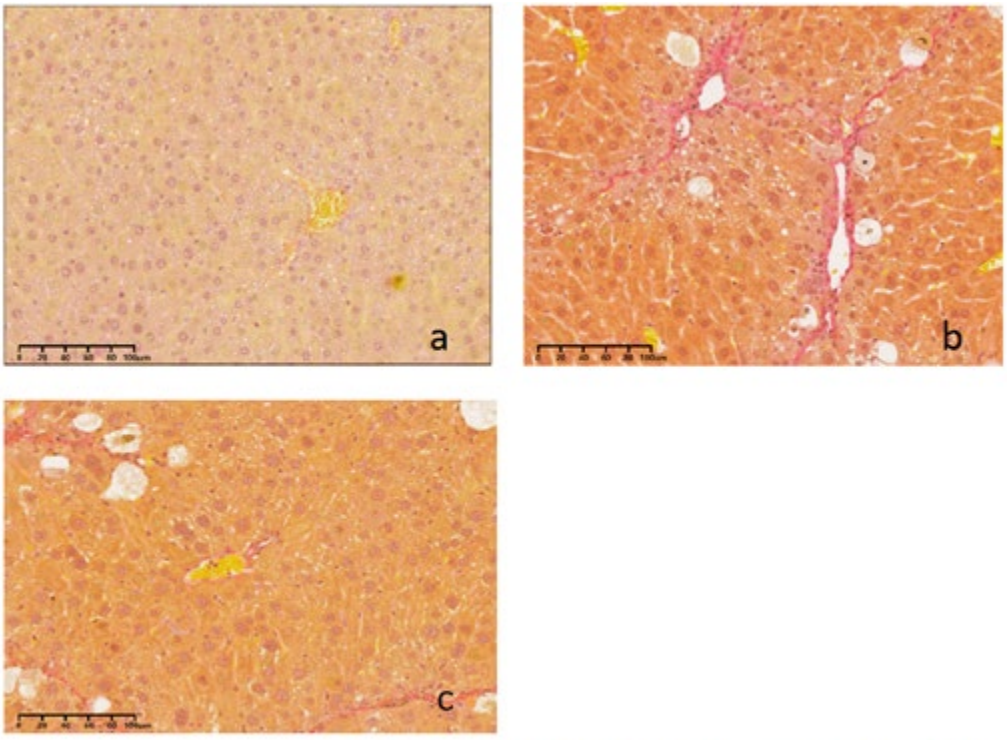

Figure. Liver Sirius red staining (×100).a is the normal control group; b is the hepatic fibrosis group: c is the treatment group

Disclosures: Fushuang Ha: Nothing to Disclose, Tao Han: Nothing to Disclose, Junjun Cai: Nothing to Disclose, Junqing Yan: Nothing to Disclose, Yin Gu: Nothing to Disclose

3610 | POLARIZATION OF CANCER ASSOCIATED FIBROBLASTS AND ACTIVATED MYOFIBROBLASTS IN THE TUMOR MICROENVIRONMENT OF HEPATOCELLULAR CARCINOMA

Daichi Nakamura[1] Takahiro Nishio[1] Yukinori Koyama[2] Kojiro Taura[1] Keiko Iwaisako[3] Keisuke Okura[1] Xuefeng Li[1] Etsuro Hatano[1]

[1]Kyoto university, [2]University of California, San Diego, [3]Doshisha university

Background: Hepatocellular carcinoma (HCC) develops in the setting of chronic liver diseases such as viral hepatitis, alcohol-associated liver disease (ALD) and metabolic steatotic liver disease (MASLD). Liver fibrosis, driven by activated myofibroblasts derived from hepatic stellate cells (HSCs) and portal fibroblasts, progresses through excessive extracellular matrix production, leading to cirrhosis and HCC. The tumor microenvironment (TME), composed of diverse stromal cells including cancer-associated fibroblasts (CAFs), influences tumor growth and invasion. The functions of CAF subpopulations in the TME and their association with activated non-tumor myofibroblasts are not fully understood. The aim of this study was to investigate fibroblast polarization to explore novel therapeutic strategies for HCC targeting myofibroblasts in the fibrotic liver and CAFs in the TME. **Methods:** Human HCC specimens were obtained from 8 patients who underwent liver resection for HCC. Spatial transcriptomics was used to identify gene expression markers related to the functions of myofibroblast/CAF subpopulations and to assess cellular interaction with a focus on fibroblast polarization in the TME. **Results:** The underlying liver diseases of the HCC specimens included 3 cases of MASLD, 2 cases of hepatitis C, 1 case of hepatitis B, 1 case of ALD and 1 case of adenoma (used as control). Spatial transcriptomics on human HCC revealed 21 clusters, which were categorized into tumor, non-tumor, and stromal regions. By re-clustering fibroblast-specific spots identified by ACTA2 and COL1A1 expression, it was found that fibroblast populations infiltrating intra-tumor, tumor septa, and fibrous scar in the non-tumor area. The gene expression profiles of CAFs were associated with tumor progression, showing high expression of Wnt/β-catenin signaling (POSTN, CTHRC1, SFRP4) and immunomodulation (CXCL13).In addition, CAFs showed high expression of genes related

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to detoxification and metabolism(AMACR, ALDH3A), with a strong association to retinol metabolism (RBP1, UGT1A1, ADH1) pathways, showing a similar signature to HSCs. In the tumor septa, fibroblasts were clustered into 3 subpopulations, including 2 clusters in the peritumor area expressing genes related to extracellular matrix organization (SPP1, AQP1, CXCL6, MMP7, MUC6), and the other close to the non-tumor parenchyma showing enrichment of T-cell-related genes (CCL7, IL7R, CD37, CXCR4). **Conclusion:** Spatial transcriptomics of human HCC identified the distinct roles of fibroblast-derived clusters, including myofibroblasts and CAFs. The results of this study suggest that CAFs resemble the signature of HSCs and contribute to tumor progression and immunomodulation by forming tumor septa with polarization, providing prospects for a therapeutic strategy for HCC targeting CAFs and myofibroblasts.

Disclosures: Daichi Nakamura: Nothing to Disclose, Takahiro Nishio: Nothing to Disclose, Yukinori Koyama: Nothing to Disclose, Kojiro Taura: Nothing to Disclose, Keiko Iwaisako: Nothing to Disclose, Keisuke Okura: Nothing to Disclose, Xuefeng Li: Nothing to Disclose, Etsuro Hatano: Nothing to Disclose

3611 | ECM1HIHSC SUBPOPULATION: AS A MASTER REGULATOR IN THE REVERSAL OF LIVER FIBROSIS ◆

Aiting Yang[1] *Xuzhen Yan*[1] *Qi Han*[1] *Hong You*[1]

[1]*Beijing Friendship Hospital, Capital Medical University*

Background: Studies utilizing single-cell transcriptomics techniques have revealed marked heterogeneity among hepatic stellate cells (HSC), with distinct subpopulations displaying unique gene expression signatures and functions. However, our knowledge of their cell biology is far from complete, especially the distinct functions of HSC subpopulations in liver fibrogenesis and their contribution to progression and regression. **Methods:** Genetic inhibition proliferation, or depletion of HSC in CCl4 and CDAA mouse models of experimental liver fibrosis revealed their overall role during fibrogenesis. Fibrosis- and inflammation-related parameters were determined biochemically, by quantitative immunohistochemistry, polymerase chain reaction, and transcriptomics. **Results:** Firstly, we studied PDGFRA, the key mediator of HSC proliferation. As expected, we observed that genetic inhibition of HSC proliferation by LratCre-mediated Pdgfra deletion (PdgfraΔHSC) decreased liver fibrosis in CCl4-induced fibrosis. But, surprisingly, PdgfraΔHSC mice exhibited increased Col1a1 mRNA and hepatic collagen deposition and exacerbated fibrogensis in CDAA-induced fibrosis, a well-established model of NASH related fibrosis. Secondly, genetic HSC depletion in transgenic mice expressing LratCre, and Cre-induced diphtheria toxin receptor (iDTR) efficiently reduced Lrat+HSC and HSC marker genes, and strongly suppressed CCl4-induced liver fibrosis development in comparison to DT-treated LratCre+, iDTR-littermates. Surprisingly, consistent with inhibition of HSC proliferation, depletion of Lrat+HSC results in aggravation from CDAA-induced liver fibrosis. Collectively, our data based on genetic HSC proliferation inhibition, or depletion approaches in different models of fibrosis demonstrated that distinct roles of HSC in CCl4 and CDAA induced fibrosis. Mechanistically, RNA-seq analysis indicated that extracellular matrix protein 1 high expression (Ecm1hi) HSC subpopulation protects hepatic fibrosis from fibrosis. In particular, the colocalization of ECM1 and LRAT was decreased in HSCs from CCl4 treated mice. Moreover, HSC specific Ecm1 knock-in mice showed reduced hepatic inflammation, and significant fibrosis regression compared to control mice in a CCl4 model. **Conclusion:** Inhibition hepatic stellate cells proliferation or depletion of activated hepatic stellate cells protects the progression of CCl4-induced fibrosis, surprisingly, HSC are required for fibrosis resolution in CDAA diet induced fibrosis. ECM1hiHSC subpopulation promotes liver fibrosis resolution, which may offer a promising strategy for the prevention and treatment of fibrotic liver diseases.

Disclosures: Aiting Yang: Nothing to Disclose, Xuzhen Yan: Nothing to Disclose, Qi Han: Nothing to Disclose, Hong You: Nothing to Disclose

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3612 | IN VIVO EXPERIMENTS AND NON-TARGET METABOLOME ANALYSIS TO EXPLORE THE EFFECT AND MECHANISM OF SHUXUENING INJECTION IN TREATING LIVER CIRRHOSIS

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Background: Liver cirrhosis (LC) has been a serious threat to the health of people all over the world which has no effective treatment for now. Traditional Chinese medicine (TCM) has shown a good therapeutic effect for LC. The ShuXueNing injection (SXN), the main component of Ginkgo biloba extract, is a commonly used TCM that is already on the market to dilate blood vessels and improve microcirculation. However, the effect and mechanism of SXN in treading LC is unclear. **Methods:** The LC mice model was established by intraperitoneal injection of 10% CCl4 of olive oil mixture for 12 weeks. From the seventh week, the treatment group was given SXN granule aqueous solution by intraperitoneal injection. After treatment, the mice's body weight, liver weight, and spleen weight were recorded, and the mice's serum was used to detect biochemical indicators including alanine aminotransferase (ALT), aspartate aminotransferase (AST), and hyaluronic acid (HA). The rats' liver tissues were used to perform pathological examinations, immunohistochemical staining, and non-target metabolomics assays. **Results:** Compared to the model group, after SNX treatment, the liver and spleen indexes of mice were both significantly decreased. Compared to the model group, significantly lower levels of serum ALT, AST, and HA in the SXN group than in the model were observed. The HE staining, Sirius red staining, and Masson staining showed less inflammatory damage and collagen production after SXN treatment compared to the model. The IHC staining results showed that SXN treatment significantly reduced production of α-SMA and COL1A1, and decreased positive-F4/80 cells. By non-target metabolomics assays, we obtained 182 differentially expressed metabolites (DEM) and the KEGG pathway enrichment analysis of these DEM showed that the SXN treatment was significantly associated with the Lysine degradation, Glycerophospholipid metabolism, and Choline metabolism in the liver. **Conclusion:** SXN exerted a reversion effect on the progress of earlier LC in mice. Its molecular mechanism may be related to the regulation of the lysine, glycerophospholipid, and choline metabolism in liver.

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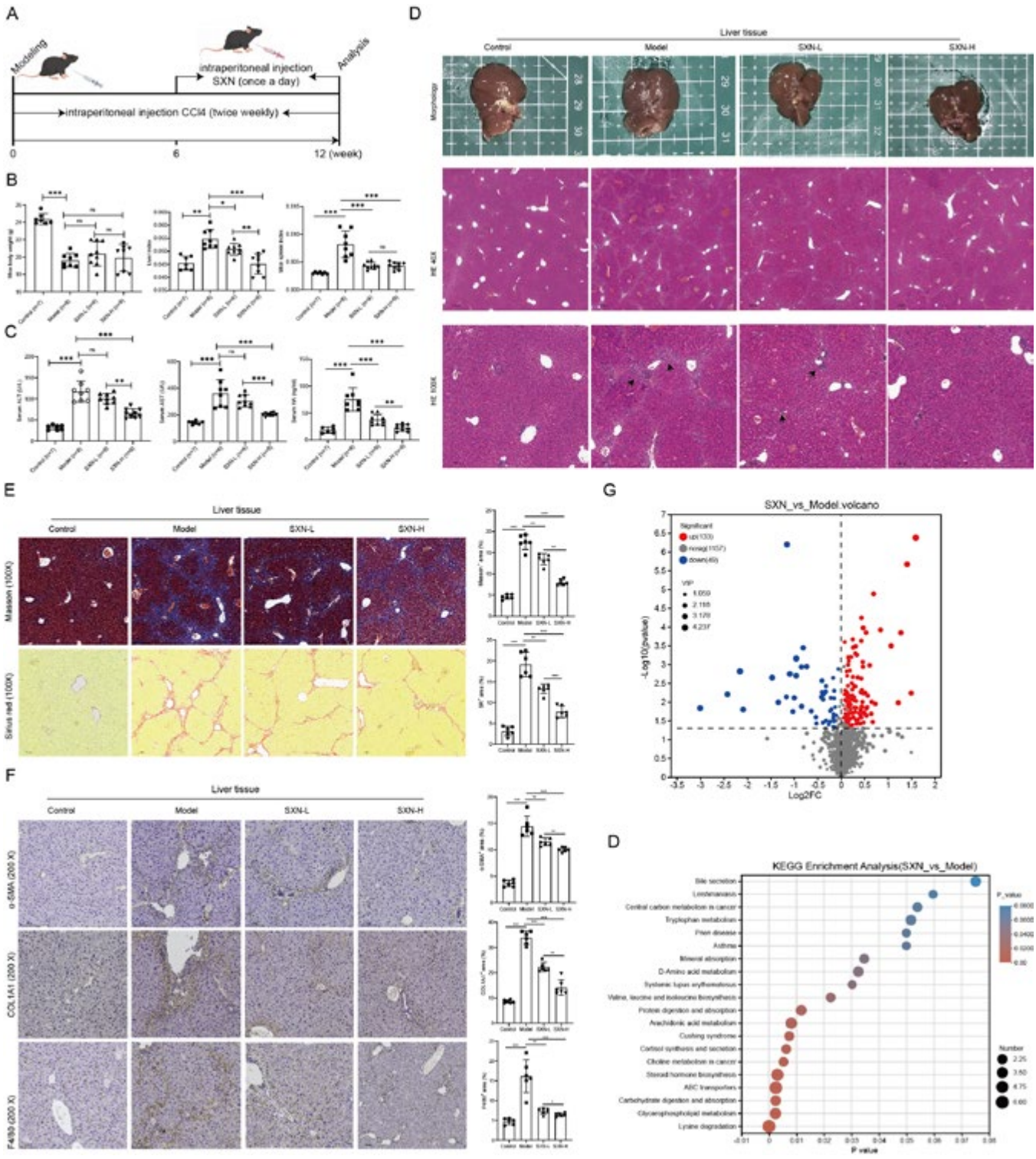

Disclosures: Zhang Tingyu: Nothing to Disclose, Xin Sun: Nothing to Disclose, Shihao Zheng: Nothing to Disclose, Wenying Qi: Nothing to Disclose, Yue Chen: Nothing to Disclose, Xiaoke Li: Nothing to Disclose, Xiaobin Zao: Nothing to Disclose

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3613 | CARFILZOMIB SHOWS THERAPEUTIC POTENTIAL FOR REDUCTION OF LIVER FIBROSIS BY TARGETING HEPATIC STELLATE CELL ACTIVATION

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[1]*Kyoto Prefectural University of Medicine*

Background: Advanced liver fibrosis eventually progresses to cirrhosis, which is directly related to a high incidence of mortality and hepatocellular carcinoma. An urgent need still exists for the development of effective drugs without significant adverse effects to treat liver fibrosis. Because hepatic stellate cells (HSCs) play a major role in fibrosis, we focused on HSCs as a potential target for the treatment of liver fibrosis. **Methods:** In this study, we attempted to identify drug candidates from 441 compounds to reduce HSC (LX-2) viability (CellTiter-Glo luminescent cell viability assay). Primary HSCs isolated from C57BL/6 mouse livers were treated with carfilzomib for 24 hours to evaluate cell viability, cell toxicity (LDH cytotoxicity assay) and suppression of fibrogenic activity (real-time qPCR assay). Carbon tetrachloride (CCl_4) -liver fibrosis model was induced by intraperitoneal injections of CCl_4 for 10 weeks. Then mice were injected intravenously with 5 mg/kg CZM or control phosphate-buffered saline at 6 to 10 weeks of the CCl_4 treatment period, and liver enzymes and liver fibrosis (picro-sirius red staining) were evaluated. RNA sequence analysis was conducted with primary HSCs isolated from mice to evaluate the effects of CZM on HSCs. **Results:** We found that proteasome inhibitors (PIs; carfilzomib (CZM), bortezomib, epoxomicin and MG132) reduced HSC viability at a low concentration of 0.4 μM. Among the PIs, a second-generation PI, CZM suppressed the mRNA expression of hallmarks of HSC activation and hepatic fibrogenesis, *Alpha smooth muscle actin 2, Collagen type I alpha 1, Collagen type IV alpha1,* and *Tissue inhibitor 1 of metalloproteinase 1* in primary murine HSCs at low concentrations of 5 or 10 nM. CZM was not toxic to HSCs up to a concentration of 12.5 nM. CZM achieved a clear reduction in liver fibrosis in the CCl_4-treated mice without worsening of liver injury. Mechanistically, RNA sequence analysis of primary HSCs revealed that CZM inhibits mitosis in HSCs. **Conclusion:** Our findings reveal that multiple PIs reduce HSC viability, specifically CZM which is widely used in clinical practice as anti-tumor drugs for the treatment of multiple myeloma, strongly suppress the viability of HSCs without toxicity at a low concentration, and attenuate liver fibrosis in a fibrosis model mouse. Together, CZM and next-generation PIs in development could be potential therapeutic agents for the treatment of liver fibrosis via inactivation of HSCs without liver injury. (Proteasome inhibitors including carfilzomib are not labeled for the use under discussion.)

Disclosures: Atsushi Umemura: Nothing to Disclose, Kanji Yamaguchi: Nothing to Disclose, Yoshito Itoh: Novo Nordisk Pharma LTD: Speaking and Teaching, ZERIA PHARMACEUTICAL CO., LTD.: Speaking and Teaching, Otsuka Pharmaceutical Co., Ltd.: Speaking and Teaching, Viatris Inc.: Speaking and Teaching, ASKA Pharmaceutical Co., Ltd.: Speaking and Teaching, Astelas Pharma Inc.: Speaking and Teaching, AstraZeneca K.K.: Speaking and Teaching, Gilead Sciences Inc.: Speaking and Teaching, Mitsubishi Tanabe Pharma Corporation: Speaking and Teaching, EA Pharma Co. Ltd.: Speaking and Teaching, Kowa Company Ltd.: Speaking and Teaching, CHUGAI PHARMACEUTICAL CO., LTD.: Speaking and Teaching, Takeda Pharmaceutical Company Limited.: Speaking and Teaching, ONO PHARMACEUTICAL CO., LTD.: Speaking and Teaching, AbbVie Inc.: Speaking and Teaching, Novartis Pharma Inc.: Speaking and Teaching, MYYARISAN Phramaceutocal Co.: Speaking and Teaching, Eli Lilly and Co.: Speaking and Teaching, Olympus Co.: Speaking and Teaching, AbbVie Inc.: Grant/Research Support, Otsuka Pharmaceutical Co., Ltd.: Grant/Research Support, CHUGAI PHARMACEUTICAL CO., LTD.: Grant/Research Support, SHIONOGI & CO., LTD.: Grant/Research Support, Eisai Co., Ltd.: Grant/Research Support, Mitsubishi Tanabe Pharma Corporation: Grant/Research Support, EA Pharma Co. Ltd.: Grant/Research Support, Sumitomo Pharma Co. Ltd.: Grant/Research Support, ASKA Pharmaceutical Co. Ltd.: Grant/Research Support, Eli Lilly and Co.: Grant/Research Support, Astra Zeneca plc.: Grant/Research Support, Pfizer Inc.: Grant/Research Support, Merk Sharp and Dohme: Grant/Research Support, Bristol-Myers Squibb Co.: Grant/Research Support, GSK plc.: Grant/Research Support, AbbVie Inc: Grant/Research Support

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3614 | HUMAN UMBILICAL CORD-DERIVED MESENCHYMAL STEM CELLS IN COMBINATION WITH SMALL EXTRACELLULAR VESICLES IMPROVE SURVIVAL AND DRAMATICALLY REDUCE FIBROSIS AND CIRRHOSIS IN WISTAR RATS RECEIVING CCL4

Naga Chalasani[1] Sairam Atluri[2] Ravi Kumar[2] Mohini Sridevi K[3] Ajay Duseja[4] Navneet Boddu[5] Marwan Ghabril[1] Jiayi Ma[1]

[1]Indiana University School of Medicine, Indianapolis, IN, [2]Tulsi Therapeutics, Hyderabad, India, [3]Cology Biosciences, Hyderabad, India, [4]3PGIMER, Chandigarh, India, [5]Scripps Health, Torrance, CA

Background: Umbilical cord-derived mesenchymal stem cells (UC-MSCs) exert potential anti-inflammatory properties and in previous studies have shown anti-fibrotic effects in animal models of liver fibrosis and cirrhosis. In this proof-of-concept, first in animal study, we examined the effect of human UC-MSCs combined with small extracellular vesicles (SEVs) on liver fibrosis in a rat model of fibrosis and cirrhosis. **Methods:** Human UC-MSCs were cultured via a xenofree, explant process with modifications to passage 3 and SEVs were obtained from supernatant of the cultured UC-MSCs. Two groups, each of 14 Wistar male rats, aged 7-8 weeks, received oral CCL4 with olive oil (1ml/kg) twice weekly for a total of 6 weeks from week 1 to week 6. Starting at week 4, after all animals in both groups received 6 induction doses of CCL4, one group of 14 animals received three weekly IV doses of UC-MSC + SEV at a dose of 1 million MSCs and 5 billion SEV each. All animals alive at week 7 were sacrificed. 14 animals who received CCL4 alone from weeks 4-7 were control animals. The primary objectives were to examine the survival differences between two groups of animals and the effect of UC-MSC + SEV on fibrosis stage by Trichrome and Sirius Red. **Results:** Six animals in the control group died before week 6 whereas all 14 animals in the US-MSC + SEV were alive at week 6. The survival difference at 6 weeks was significant between two groups (100% with UC-MSC + SEV vs 57%, p=0.0066). The necropsy of 6 dead animals in the control group showed cirrhosis in all 6 animals. The comparison between 8 animals in the control group and 14 animals receiving US-MSC + SEV is shown in Table1. Notably, liver fibrosis stage by both Trichrome and Sirius Red was significantly lower in the UC-MSC + SEV group. While there were no animals in the UC-MSC + SEV group had cirrhosis, there were 12 animals in the control group with cirrhosis. There were corresponding favorable liver biochemistry and liver immunohistochemistry changes in the UC-MSC +SEV group (Table). **Conclusion:** Human UC-MSCs cultured to passage 3 in combination with SEV significantly improved the survival of the animals receiving low-dose CCL4. UC-MSC + SEV dramatically reduced the development of fibrosis and cirrhosis induced by CCL4. Further studies are needed to validate our observations and to test the combination of UC-MSC + SEV in other animal models and in humans with fibrotic liver diseases and liver failure.

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Table: Selected characteristics of CCL4 fed animals with and without US-MSC + SEV treatment

	CCL 4 (N=8) (Mean±S.E)	CCL4 UC-MSC+ SEV (N=14) (Mean±S.E)	P. Value
Body weight(gm)	404.500 ±14.6470	429.357± 14.2785	0.271
Feed intake(gm)	21.750 ±1.1378	26.929 ±0.9677	0.003
Liver Index (g/100g of BW)	5.3924 ±0.18765	4.0001 ±0.09214	0.0001
Serum AST (U/L)	215.663 ±16.0369	220.393± 16.2959	0.851
Serum ALT (U/L)	214.850± 37.5172	97.214 ±5.2280	0.001
Serum ALP (U/L)	396.350±39.0886	270.171 ±27.3007	0.014
Serum Total Bilirubin (mg/dL)	0.2013 ±0.01093	0.1857 ±0.01147	0.381
Liver Histology			
- Fibrosis by Masson trichome	3.929±0.0714	1.071±0.2864	0.0001
- Fibrosis by Sirus red	3.929±0.0714	1.000±0.2568	0.0001
- Cirrhosis %	85%	0	0.0001
Liver IHC			
-Liver Collagen	3.429±0.1727	1.214±0.1869	0.0001
-Liver a-SMA	3.571±0.1373	0.714±0.1634	0.0001
-Liver CK18	1.964±0.2312	0.250±0.0869	0.0001
-Liver CK19	2.464±0.1333	0.179±0.0664	0.0001
Mortality (%)	**43**	**0**	**0.007**

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3615 | TRANSLATIONAL POTENTIAL ROLE OF ZEB2 IN LIVER FIBROSIS AND NAFLD

Qian Wen Zhao[1] *Fajuan Rui*[2] *Jie Li*[1]

[1]*Nanjing Drum Tower Hospital, Affiliated Hospital of Medical School, Nanjing University,* [2]*Nanjing Drum Tower Hospital Clinical College of Nanjing University of Chinese Medicine*

Background: Myofibroblasts, characterized by the expression of the matricellular protein periostin (*Postn*), mediate the pro-fibrogenic response during NAFLD. Previous studies have demonstrated that endothelial deficiency in zinc-finger E-box-binding homeobox 2 (Zeb2) attenuates liver fibrosis in mice. In the present study, we investigated the myofibroblast-specific role of Zeb2 in liver fibrosis during the development of NAFLD and the underlying mechanism. **Methods:** We generated myofibroblasts Zeb2 knockdown mice, by injecting AAV6-*Postn*-sh*Zeb2* virus, and then established BDL and HFD-diet model to investigate the role of Zeb2 in pro-fibrogenic response during liver fibrosis and NAFLD. RNA-seq was performed to detect the underlying mechanism of myofibroblast Zeb2 in liver fibroblasts. The genemania predicted upstream gene of Zeb2 was also verified. **Results:** Zeb2 knockdown retarded the fibroblast-myofibroblast transition (FMyT) in vitro and dampened liver fibrosis in mice. We also report that myofibroblast conditional deletion of Zeb2, achieved through injecting AAV6-*Postn*-sh*Zeb2* virus, led to amelioration of liver fibrosis. RNA-seq detect the underlying mechanism of myofibroblast Zeb2 in liver fibroblasts. Moreover, genemania predicted PTPRD is the upstream gene of Zeb2. Slicing PTPRD expression significantly upregulate the level of Zeb2 and then promote the development of NAFLD. **Conclusion:** Accordingly, our data unveil a novel PTPRD-Zeb2 axis that can potentially contribute to

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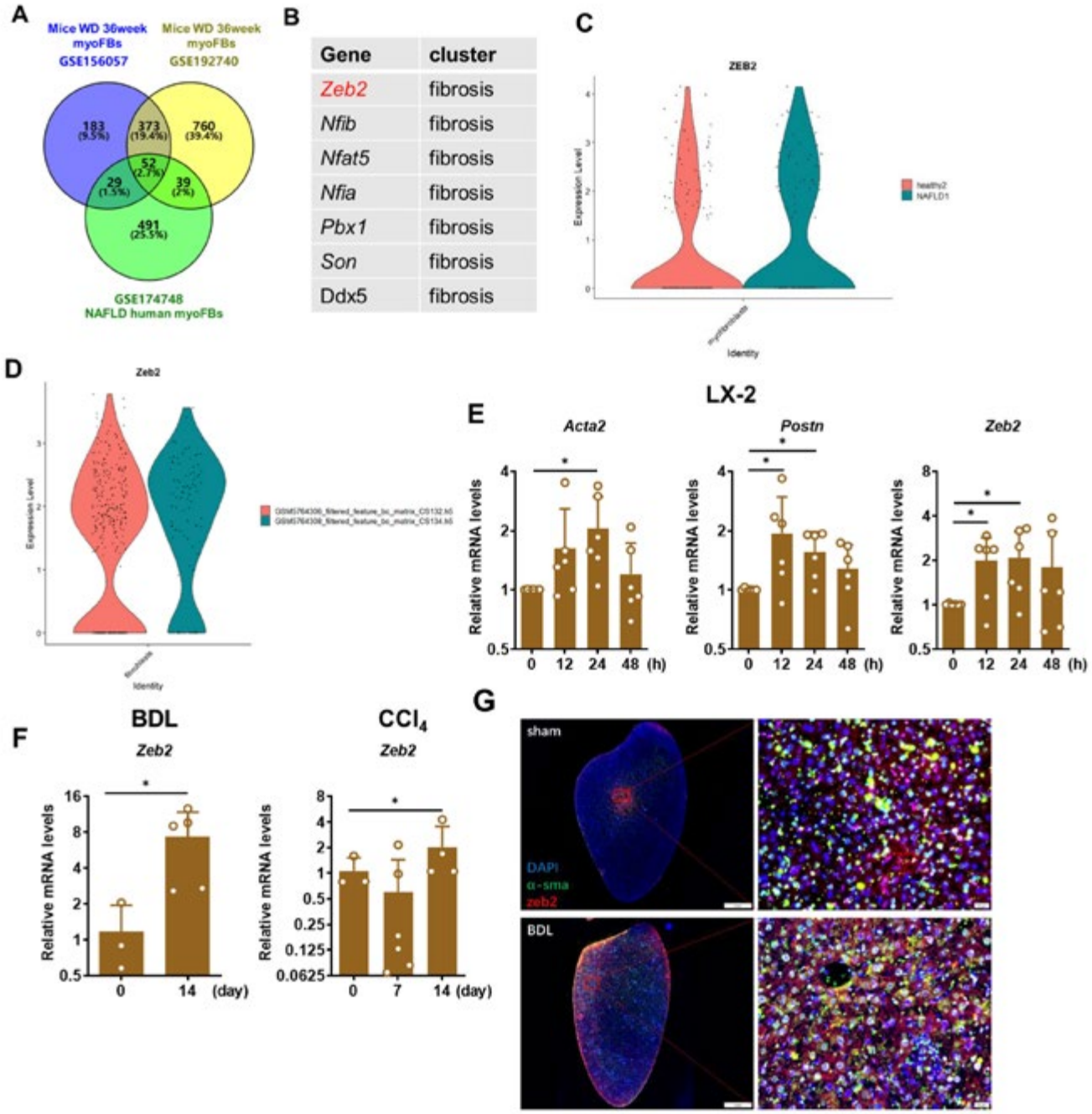
fibroblast-myofibroblast transition and NAFLD. Screening for small-molecule compounds that target this axis may yield therapeutic options for the mollification of NAFLD.



Disclosures: Qian Wen Zhao: Nothing to Disclose, Fajuan Rui: Nothing to Disclose, Jie Li: Nothing to Disclose

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3616 | EVALUATION AND VALIDATION OF ENDOSCOPIC ULTRASOUND GUIDED ELASTOGRAPHY FOR DIAGNOSIS OF ADVANCED LIVER FIBROSIS USING LIVER BIOPSY AS GOLD STANDARD

Shivani Patel Michael Bebawy[1] Cathy Tan[1] Zaid Tafesh[1] Mumtaz Niazi[1] Ahmed Al-Khazraji[1] Kaveh Hajifathalian[1]

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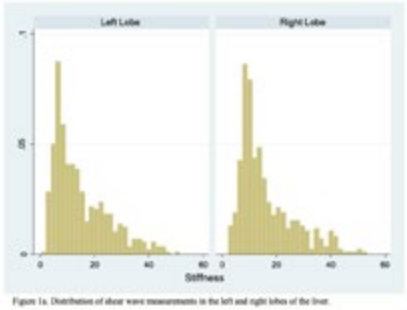
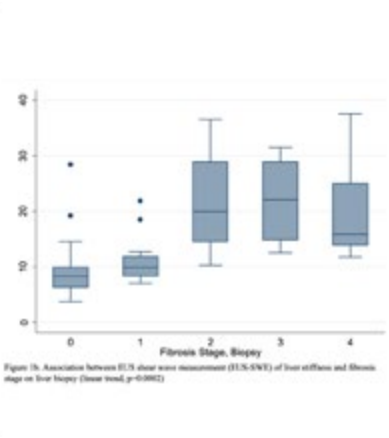
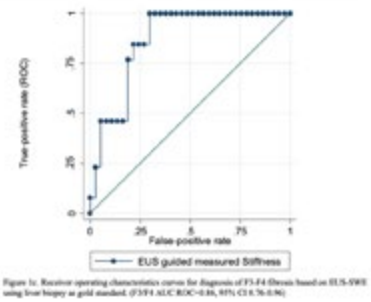
Background: Endohepatology is a growing field with multiple applications. Endoscopic ultrasound guided shear wave elastography (EUS-SWE) is a technique that allows for the evaluation of tissue stiffness, using acoustic forces and measurement of the propagation speed of the shear waves. This procedure allows for real-time evaluation of liver parenchyma, however currently and diagnostic values for EUS-SWE are not well defined. **Methods:** This is a prospective study, using a EUS-SWE and same session EUS guided liver biopsy as gold standard at a liver transplant center to evaluate diagnostic accuracy of EUS-SWE for diagnosis of advanced fibrosis. The study population was divided randomly into training and validation sets to independently find and test cutoff values for EUS-SWE. **Results:** A total of 61 patients were included in the study cohort. Of the 61 patients, 54 patients had complete biopsy data at the time of final analysis. The mean age was 51 years (± 13 years) and 54% were female (N=29). There was a median MELD-Na score of 9 (±4, median 8, IQR 6-10) and 5% of patients with a MELD-Na greater than 21. The median stiffness between the left lobe and right lobe were not statistically different (p=0.1029, Figure 1a). EUS-SWE had a statistically significant and consistent association with fibrosis seen on liver biopsy (linear trend, p=0.0002, Figure 1b). EUS-SWE values were also significantly higher with evidenceof portal hypertension on endoscopy (p=0.0139). EUS-SWE had an 86% accuracy in identifying patients with F3 or F4 fibrosis (AUC ROC = 0.86, 95% CI 0.76-0.96). A median stiffness of equal to or greater than 12.71 kPa was the optimal cutoff for diagnosis of F3 or F4 fibrosis with a sensitivity of 100% and specificity of 71% in the training subset. This cutoff value was then tested in the independent validation subset and showed a sensitivity of 100% and specificity of 67% for diagnosis of F3 or F0 fibrosis (X^2 test, p=0.003). **Conclusion:** EUS-SWE demonstrates excellentaccuracy for diagnosis of advanced liverfibrosis with a sensitivity of 100%. EUS-SWEcan be used to assistin decision-making during endoscopy by offering real time assessment of liver parenchyma.







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3617 | AMNIOTIC FLUID REDUCES EPITHELIAL-TO-MESENCHYMAL TRANSITION AND MYOFIBROBLAST ACTIVATION IN HEPATIC STELLATE CELLS

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Background: Hepatic stellate cells (HSCs) can transform from a quiescent to an activated state in response to liver damage. This is characterized by HSC proliferation, myofibroblast activation (MFA), and an increase in the epithelial-mesenchymal transition (EMT). Activated HSCs are the effector cells of liver fibrosis, as they directly secrete excessive extracellular matrix (ECM) which forms the fibrotic lesion; therefore, strategies to intercept HSC activation represent a major unmet need. Full-term cell-free amniotic fluid (cfAF) is a biofluid that is used to treat patients with chronic wounds. In vitro modeling indicate this is mediated in part through repressing EMT and MFA in fibroblasts and myoblasts. Thus we hypothesize that cfAF will prevent and/or reverse HSC activation. **Methods:** We measured HSC activation in different model systems including LX2 hepatic stellate cell culture, three-dimensional hepatic spheroids, and mouse models of acute (DMN) or chronic (CCl4) liver damage. We assessed EMT using the scratch test assay, and EMT and MFA by measuring RNA and protein expression, including multiomics analyses from hepatic stellate cell culture- and mouse model-based approaches. **Results:** Cell-free AF significantly reduced LX2 HSC migration, EMT, and TGFb-stimulated MFA, as assessed by multiomic analyses. Hepatic spheroids with or without ethanol exposure then treated with cfAF showed reduced Col1A1 protein levels, and a dose-dependent reduction in smooth muscle actin RNA levels. In vivo studies indicated that human cfAF treatment rescued normal weight gain in mice treated with DMN or CCl4 for the duration of each study and caused no adverse effects in immune competent mice; standard histological analyses revealed a slight reduction of fibrosis and preserved liver architecture. Gene expression profiling and immunostaining indicated that EMT- and MFA-associated gene expression and biomarker abundance were partially rescued in CCl4 mice treated with cfAF. Transcriptome analyses showed significant changes in the levels of some liver metabolism-associated transcripts with up-regulation of Arginase (Arg1) and down-regulation serum amyloid A (Saa1/2) in cfAF treated mice. **Conclusion:** Our data indicate that cfAF represses HSC activation by reducing MFA and EMT. Intriguingly, our transcriptome and proteome studies suggest cfAF may also have a protective effect on hepatocytes. Collectively, we conclude that cfAF may be a safe and effective treatment for fibrotic liver disease, by dampening HSC activation and preserving hepatocyte metabolic function.

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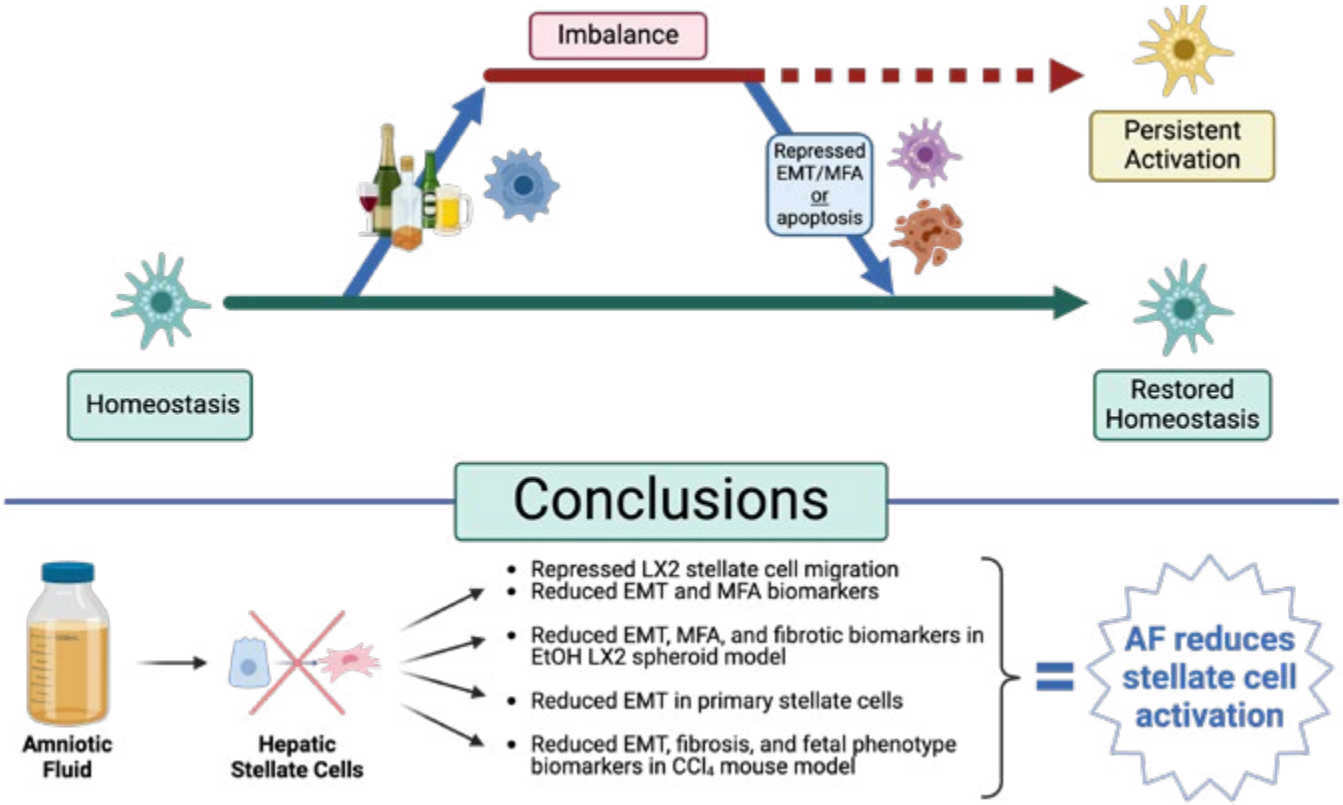

Disclosures: Charles Bowen: Nothing to Disclose, Frederick Ditmars: Nothing to Disclose, Naiyou Liu: Nothing to Disclose, Jose Abril: Nothing to Disclose, Heather Stevenson-Lerner: Nothing to Disclose, Eliseo Eugenin: Nothing to Disclose, Jeffrey Fair: Nothing to Disclose, W. Samuel Fagg: Nothing to Disclose

3618 | ASSOCIATION BETWEEN STATINS AND CHRONIC LIVER DISEASE PROGRESSION

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Background: Statin medications are associated with a reduced risk of portal hypertension complications and mortality in patients with cirrhosis. However, their impact on patients with chronic liver disease (CLD) before developing advanced fibrosis remains unclear. **Methods:** We performed a retrospective cohort study of primary care electronic health record (EHR) data from 2012-2021. Included were patients with a diagnosis of CLD who had lab inputs for a Fibrosis-4 Index (FIB-4) calculation and no prior diagnoses of cirrhosis or hepatocellular carcinoma (HCC) preceding the index FIB-4. We performed two analyses: (1) patients with an index FIB-4 <3.25 were followed until the occurrence of a FIB-4 >3.25 (indicating high-risk for advanced fibrosis) or the end of the study period; (2) all cohort patients were followed from the index FIB-4 until the occurrence of a severe liver disease (a composite of cirrhosis, a cirrhosis complication, or HCC), or the end of the study period. A statin prescription was the primary exposure. We developed unadjusted and adjusted Cox regression models for each outcome. **Results:** The cohort included 2,957 patients with CLD, with a mean index FIB-4 of 1.2. Analysis 1: 2,587 patients with an index FIB-4 <3.25 were followed for a mean of 5.4 (±2.6) years. 862 (33%) received a statin prescription and 627 (24%) progressed to a high-risk FIB-4. A statin prescription was associated with a lower hazard of progressing to FIB-4 >3.25 (adjusted HR 0.37; 95% CI 0.30-0.44). Analysis 2: 2,957 patients were followed for a mean of 3.8 (±2.7) years. 892 (30%) received a statin prescription and 463 (16%) experienced a severe liver disease outcome. Statin prescription was associated with a lower hazard of developing the composite severe liver disease outcome (adjusted HR 0.61; 95% CI 0.46-0.82). **Conclusion:** In a primary care population, statin prescriptions were associated with a lower hazard of progressive fibrosis or a severe liver disease outcome.

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Table 1. The estimated hazard ratios and 95% confidence intervals for statin prescription in the unadjusted and adjusted Cox regression models with the outcomes of time to a severe liver disease outcome and time to a FIB-4 ≥ 3.25, at high-risk for advanced fibrosis.

Outcome: Time to a severe liver disease outcome.				
	Model 1	Model 2	Model 3	Model 4
	Unadjusted	Adjusted for index FIB-4	Adjusted for demographics	Adjusted for comorbidities
	HR 95% CI	HR 95% CI	HR 95% CI	HR 95% CI
Statin Rx	0.53 0.41-0.67	0.84 0.64-1.09	0.60 0.45-0.80	0.61 0.46-0.82
Outcome: Time to a FIB-4 ≥ 3.25, at high-risk for advanced fibrosis.				
	Model 1	Model 2	Model 3	Model 4
	Unadjusted	Adjusted for index FIB-4	Adjusted for comorbidities	Adjusted for demographics
	HR 95% CI	HR 95% CI	HR 95% CI	HR 95% CI
Statin Rx	0.63 0.53 – 0.75	0.53 0.44 – 0.63	0.54 0.45 – 0.65	0.37 0.30 – 0.44

Models 1 are the unadjusted Cox regression models. Models 2 are Models 1 with adjustment for index FIB-4 score as a continuous variable. Models 3 are Models 2 with adjustment for comorbidity variables. Models 4 are Models 3 with additional adjustment for demographic and BMI variables.

Disclosures: Nicholas Smith: Nothing to Disclose, Andrew Schreiner: Nothing to Disclose, David Koch: Nothing to Disclose

3619 | DIFFERENTIATING EARLY-STAGE CIRRHOSIS FROM NON-CIRRHOTIC PORTAL HYPERTENSION USING NON-INVASIVE DIAGNOSTIC TESTS

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Background: This study aims to evaluate the effectiveness of non-invasive diagnostic tests, including Fibroscan, FIB-4, APRI, and MR elastography, in distinguishing between patients with non-cirhotic portal hypertension and cirhotic patients with Child-Pugh A. **Methods:** Our study included 7 patients with non-cirrhotic portal hypertension (NCPH) and 7 patients with non-cholestatic early-stage liver cirrhosis who were followed up in our center. These patients had their transient elastography (Fibroscan) and MRI elastography values measured simultaneously (within a 1-month interval). The APRI, FIB-4, MRI elastography, and TE values of these patients were compared. Patients with NCPH who developed cirrhosis and decompensated were excluded. The aim was to identify the non-invasive methods with the highest accuracy to distinguish cirrhotic patients with Child-Pugh score A from patients with NCPH. **Results:** The median age for patients was 28.0 years (IQR: 21.0- 40.0), significantly lower than the cirrhotic patients who had a median age of 48.0 years (IQR: 44.0 - 58.5), with a p-value of 0.017. Patients had a median stifness score of 6.7 kpA (IQR: 5.9-8.2), which was significantly different from the cirrhotic patients who had a median score of 32.3 kpA(IQR: 16.1 - 74.5)(p=0.004). FIB-4: The median Fib-4 score for patients was 1.07 (IQR: 0.95-1.37), compared to 2.39 (IQR: 1.62 - 3.45) in cirrhotic patients, with a p-value of 0.031. There was no significant difference in the APRI scores between patients with NCPH (median: 0.6, IQR: 0.4 - 0.7) and cirrhotic (median: 0.7, IQR: 0.5 - 0.75, p= 0.522). The median value of MR elastography value for cirrhotic patients (3.1 kPa vs. 6.05 kPa, p=0.04) was significantly higher compared to NCPH patients. The results indicated no significant difference in gender distribution between patients wtih cirrhosis and patients with NCPH (female 77.8 % vs. 71.4%, p = 0.608). **Conclusion:** Distinguishing between early-stage cirrhosis and non-cirrhotic portal hypertension using non-invasive methods can be challenging. The heterogeneous structure of the liver contributes to this difficulty, making the location of the biopsy crucial. However, even with precise biopsy locations, the results may not always provide the expected clarity. Therefore, while non-invasive methods such as APRI, FIB-4, MRI elastography, and transient elastography offer valuable insights, the role of liver biopsy remains significant in the accurate diagnosis and differentiation of these conditions. In conclusion, the combination of Fibroscan and MR elastography tests provides the best differentiation between the two groups, although further

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validation with more data is recommended to confirm these findings. In this ongoing study, analyses with a larger number of patients will more clearly evaluate the role of the combination of non-invasive tests in distinguishing early-stage cirrhosis from NCPH patients.

Disclosures: Dilara Turan Gokce: Nothing to Disclose, Derya Arı: Nothing to Disclose, Ilkay Idilman: Nothing to Disclose, Meral Akdogan: Nothing to Disclose

3620 | DELETION OF ETS1 IN HEPATIC STELLATE CELLS ACCELERATES DEVELOPMENT OF LIVER FIBROSIS ◆ ★

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Background: In response to chronic liver injury, quiescent Hepatic Stellate Cells (HSCs) activate into Collagen Type-I-producing myofibroblasts (activated HSCs), leading to the development of hepatic fibrosis. Recently, ETS1/2 (E26 transformation-specific transcription factor 1/2) were identified as lineage-specific transcription factors that play a key role in the maintenance of quiescent HSC phenotype, and *in vitro* deletion of ETS1/2 in HSCs was shown to accelerate HSC activation. In this study, we aimed to determine the *in vivo* role of ETS1 in HSCs during the development and regression of liver fibrosis. **Methods:** We generated HSC-specific Ets1 knockout mice ($HSC^{\Delta Ets1}$) by crossing Lrat-Cre with Ets1-floxed mice. Liver fibrosis was induced in Lrat-Cre and Ets1-floxed mice by oral administration of carbon tetrachloride (CCl_4) for 6 weeks, followed by regression of liver fibrosis for 2 weeks. To translate our findings in mice to humans, we generated 3D human liver spheroids that contain all liver cell types in physiological concentrations. Human HSCs were transfected with dsiETS1 RNA or scrambled dsiRNA (negative control, dsiNC) and used for the generation of human liver spheroids. Liver fibrosis was induced in human liver spheroids by exposure to a metabolic dysfunction-associated steatohepatitis (MASH)-cocktail that contains oleate, palmitate, glucose, fructose, LPS, and TGFβ1. **Results:** We investigated the role of ETS1 in the pathogenesis of liver fibrosis in mice, and its role in fibrosis regression and inactivation of HSCs. Deletion of Ets1 in HSCs exacerbated CCl_4-induced liver fibrosis in $HSC^{\Delta Ets1}$mice compared to control mice ($Ets1^{flox/flox}$). Moreover, regression of liver fibrosis was decreased in $HSC^{\Delta Ets1}$ mice compared to $Ets1^{flox/flox}$ mice. Knockdown of ETS1 in human HSCs increased the expression of TGFβ1-induced fibrogenic genes. Knockdown of ETS1 in HSCs significantly upregulated the expression of fibrogenic genes in MASH-induced human liver spheroids (vs. MASH-induced human liver spheroids containing dsiNC-transfected HSCs). Regression of metabolic liver injury in spheroids was achieved by exchanging the MASH-cocktail for normal growth medium. Knockdown of ETS1 in human HSCs suppressed fibrosis regression and inactivation of human HSCs in human liver spheroids. **Conclusion:** In this study, we demonstrate that HSC-specific deletion of ETS1 exacerbates liver fibrosis and suppresses fibrosis regression. ETS1 may become a novel target for anti-fibrotic therapy.

Disclosures: Wonseok Lee: Nothing to Disclose, Xiao Liu: Nothing to Disclose, Hyun Young Kim: Nothing to Disclose, Karin Diggle: Nothing to Disclose, David Brenner: Nothing to Disclose, Tatiana Kisseleva: Nothing to Disclose

3621 | ADAMTSL2 SECRETED BY HEPATIC STELLATE CELLS PROMOTES LIVER FIBROSIS THROUGH REGULATION OF MICROFIBRIL ASSEMBLY

Man Xie[1] Usman Yaqoob[1] Maria Hernandez-Tejero[1] Sofia Jerez[1] Shawna Cooper[1] Nidhi Jalan-Sakrikar[1] Maleeha Farheen Kalaiger[1] Papawee Sutthirat[1] Shalil Khanal[1] Brett McGettigan[1] Luke Doskey[1] Markcus A. Lee[1] Enis Kostallari[1] Moira Hilscher[1] Sheng Cao[1] Vijay Shah[1]

[1]Mayo Clinic Rochester

Background: Metalloproteinase with thrombospondin motifs-like 2 (ADAMTSL2) is a secreted glycoprotein crucial for regulating the extracellular matrix (ECM) by modulating pro-collagen and fibrillin, thereby affecting the bioavailability of transforming growth factor-β (TGF-β). Primarily produced by hepatic stellate cells (HSCs), ADAMTSL2 is a recognized biomarker in liver diseases, though its specific role and transcriptional regulation are not well understood. **Methods:** Gene expression was analyzed using RNA sequencing (RNA-seq), single-cell

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RNA sequencing (scRNA-seq), and 10x spatial transcriptomics in primary human hepatic stellate cells (hHSCs) and a CCl4-liver fibrosis induced murine model. hHSCs treated with TGFβ were evaluated using qPCR and Western blotting. Immunofluorescence (IF) was used to investigate the spatial distribution of ADAMTSL2, collagen, and fibrillin in mouse livers. Smad3 occupancy at specific DNA loci (COL1A1 and ADAMTSL2) in TGFβ-treated LX-2 cells was assessed using chromatin immunoprecipitation sequencing (ChIP-seq) data from public datasets. **Results:** In silico analysis identified HSCs as the primary source of ADAMTSL2 and fibrillin-1 in the liver. RNA-seq of TGFβ-treated hHSCs and spatial transcriptomics of CCl4-murine models showed increased ADAMTSL2 expression (log FC 5.8, p=2.37E-91, n=3). scRNA-seq of HSCs from vehicle and CCl4-injected mice confirmed ADAMTSL2 upregulation in a collagen-enriched subset (Log2(FC)=0.8, P<0.0001). These findings were validated by qPCR and Western blotting, showing a TGFβ-induced increase in ADAMTSL2 transcripts by 40% in hHSCs (Vehicle 1±0 vs. TGFβ 43.44±7.9, p<0.005, n=3) and 20% in bulk murine liver (Vehicle 1±0.01 vs. CCl4 4.4±1.13, p<0.05, n=3). IF confirmed higher ADAMTSL2 expression in CCl4-injected mice, colocalizing it with PDGFRβ (n=4, p<0.05). siRNA-mediated inhibition of ADAMTSL2 resulted in significantly increased expression of ECM proteins collagen1 and fibrillin, highlighting its regulatory role in ECM composition. Notably, ChIP-seq analysis indicated that, unlike COL1A1, ADAMTSL2 regulation by TGFβ occurs via a SMAD3-independent pathway. **Conclusion:** ADAMTSL2 is predominantly expressed by activated HSCs and plays a pivotal role in ECM organization in liver fibrosis driven by TGF-β signaling. These findings suggest that ADAMTSL2 could be a promising therapeutic target for mitigating liver fibrosis by modulating ECM assembly and reducing fibrotic ECM deposition.

Disclosures: Man Xie: Nothing to Disclose, Usman Yaqoob: Nothing to Disclose, Maria Hernandez-Tejero: Nothing to Disclose, Sofia Jerez: Nothing to Disclose, Shawna Cooper: Nothing to Disclose, Nidhi Jalan-Sakrikar: Nothing to Disclose, Maleeha Farheen Kalaiger: Nothing to Disclose, Papawee Sutthirat: Nothing to Disclose, Shalil Khanal: Nothing to Disclose, Brett McGettigan: Nothing to Disclose, Luke Doskey: Nothing to Disclose, Markcus A. Lee: Nothing to Disclose, Enis Kostallari: Nothing to Disclose, Moira Hilscher: Nothing to Disclose, Sheng Cao: Nothing to Disclose, Vijay Shah: Boehringer Ingelheim: Consultant, GSK: Consultant, GENFIT SA: Consultant, Intercept Pharmaceuticals, Inc.: Advisor, Korro Bio, Inc.: Consultant, Mallinckrodt Pharmaceuticals: Advisor, Novo Nordisk A/S: Consultant, Resolution Therapeutics, Ltd.: Advisor, Seal Rock Therapeutics, Ltd.: Consultant, Surrozen: Advisor

3622 | LARP6 REGULATES TRANSLATION OF COLLAGEN TYPE I/III MRNAS IN ACTIVATED HEPATIC STELLATE CELLS (HSCS) FROM PATIENT LIVERS WITH MASH AND METALD

Hyun Young Kim[1] Orel Mizrahi[1] Wonseok Lee[1] Sara Brin Rosenthal[1] Cuijuan Han[1] Brian Yee[1] Steven Blue[1] Jesiel Diaz[1] Jyotiprakash Jonnalagadda[1] Kanani Hokutan[1] Haeum Jang[1] Karin Diggle[1] Branko Stefanovic[2] Tatiana Kisseleva[1] Gene Yeo[1] David Brenner[3]

[1]University of California, San Diego, [2]Florida State University, [3]Sanford Burnham Prebys Medical Discovery Institute

Background: Excessive alcohol consumption results in development of liver fibrosis, which is characterized by increased Collagen Type I deposition, produced by activated Hepatic Stellate Cells (HSCs). Targeting collagen production in activated HSCs is an important strategy to halt liver fibrosis. La-related protein 6 (LARP6), an RNA-binding protein which binds to the 5' stem-loop region of collagen mRNAs, was implicated to facilitate Collagen Type I synthesis. Here, we investigate the role of LARP6 on HSC activation in fibrotic livers of metabolic dysfunction-associated steatohepatitis (MASH) or metabolic and alcohol-associated liver disease (MetALD) patients. **Methods:** Gene expression profiles of human HSCs were analyzed using single nucleus (sn)RNA-sequencing of NORMAL, MASL, MASH, and MetALD livers. To determine the role of LARP6 in HSC activation, isolated primary human HSCs were transfected with LARP6-specific (or control) dsiRNA and used to generate human liver spheroids. Human liver spheroids were composed of human liver cells in physiological ratios: 57% hepatocytes, 28% NPCs, and 15% dsiRNA-transfected HSCs. Upon formation of spheroids at day 7, human liver spheroids were cultured in MASH- or MetALD-cocktails for an additional 7 days. The MASH-cocktail contained palmitate, oleate, fructose, glucose, LPS, and human TGFβ-1, while MetALD cocktail was prepared by adding 100 mM ethanol to the MASH-cocktail. **Results:** snRNA-sequencing identified LARP6 as one of the most highly induced genes in activated human HSCs from MASH and MetALD livers (vs NORMAL or MASL

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HSCs). The binding of LARP6 to collagen mRNA was validated using enhanced CLIP (eCLIP) assay, with eCLIP peaks enriched at the 5'UTR regions of *COL1A1*, *COL1A2*, and *COL3A1*, demonstrating the specific binding of LARP6 to Collagen Type I/III mRNAs. Ribosome profiling revealed a significant reduction in the translation of *COL1A1*, *COL1A2*, and *COL3A1* in LARP6-knockdown human HSCs. Next, the development of liver fibrosis was examined in human liver spheroids which contained LARP6-knocked down human HSCs. Knockdown of *LARP6* suppressed TGFβ1-induced expression of fibrogenic genes in human HSCs and markedly reduced Collagen Type I/III deposition in MASH-or MetALD-induced human liver spheroids. **Conclusion:** LARP6 regulates the activation of human HSCs from MASH or MetALD livers through specific binding to Collagen Type I/III mRNAs. Our results suggest that targeting LARP6 in human HSCs may provide new strategies for anti-fibrotic therapy.

Disclosures: Hyun Young Kim: Nothing to Disclose, Orel Mizrahi: Nothing to Disclose, Wonseok Lee: Nothing to Disclose, Sara Brin Rosenthal: Nothing to Disclose, Cuijuan Han: Nothing to Disclose, Brian Yee: Nothing to Disclose, Steven Blue: Nothing to Disclose, Jesiel Diaz: Nothing to Disclose, Jyotiprakash Jonnalagadda: Nothing to Disclose, Kanani Hokutan: Nothing to Disclose, Haeum Jang: Nothing to Disclose, Karin Diggle: Nothing to Disclose, Branko Stefanovic: Nothing to Disclose, Tatiana Kisseleva: Nothing to Disclose, Gene Yeo: Nothing to Disclose, David Brenner: Nothing to Disclose

3623 | ETHANOL METABOLITES ENHANCE TGF-B SIGNALING IN HEPATIC STELLATE CELLS VIA MITOCHONDRIAL DNA RELEASE AND CGAS-STING-IRF3 PATHWAY

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Background: Very little is known about the direct pro-fibrogenic effects of ethanol. We examined the ability of ethanol to activate hepatic stellate cells (HSC), and its potential to enhance HSC activation through conventional signal pathways like TGF-b. We further examined the mechanism under ethanol-induced functional changes. **Methods:** Primary HSC were isolated from C57BL/6J mice and were exposed to 50mM ethanol in DMEM media for 16 h and were assayed for the transcriptional and metabolic changes. In parallel human HSC cell line of LX-2 cells was examined. Blockers of ethanol metabolic enzymes were tested in the LX-2 cells prior to ethanol stimulus. Inhibitors for VDAC (VBIT4 10μM), STING (IFM-4490 at 20μM) were used as per experimental target. Mitochondrial proteins from LX-2 cells were analyzed for phosphorylation via LCMS/MS LTQ-Orbitrap technique. **Results:** Ethanol exposure resulted in the activation of primary mouse HSC and human LX-2 cells at high concentrations (50mM) while enhancing TGF-b (2.5ng/ml) mediated activation at lower levels (10mM). Ethanol resulted in mtDNA release, which was blocked by knockdown of alcohol dehydrogenase 5 (ADH5). The released mtDNA was positive for 8-OH deoxyguanosine, indicating oxidative damage due to ethanol or a metabolite. Pretreatment with a mitochondrial antioxidant (mitoTEMPO 2μM) was able to attenuate 8-OHdG signal and block mtDNA release. Proximity ligation assay confirmed that mtDNA is released via mitochondrial outer membrane VDAC3 channels. Exposure to acetaldehyde (200μM) induced changes similar to ethanol (50mM). The alcohol dehydrogenase inhibitor (4 methylpyrazole, 5μM) blocked LX-2 activation, while an aldehyde dehydrogenase inhibitor (disulfuram, 20mM) accentuated the activation. Upon ethanol stimulation STING colocalized to Golgi-complex ($p<0.001$) and phospho-IRF3 translocation into nucleus reflecting transcriptional activation. Knockdown of STING/IRF3 as well as STING inhibitor treatment in LX-2 cells significantly suppressed IRF3 phosphorylation (S396) as well as the expression of extracellular matrix proteins (EM) upon ethanol stimulation (****$P<0.0001$, ***$P<0.001$, *$P<0.5$). Moreover, the mitochondrial phosphoproteome data showed SLC25A6 (ANT3), VDAC1 and SAM50 as the significant modified proteins indicating the activation of mitochondrial permeability transition pore in ethanol treated LX-2 cells. **Conclusion:** Ethanol metabolism to acetaldehyde in HSC results in oxidative mtDNA damage and release via VDAC3 channels on outer mitochondrial membrane, activating the c-GAS-STING-IRF3 pathway. IRF3 mediates transactivation of a panel of genes leading to trans-differentiation of HSC and fibrosis progression. These findings provide novel insights into ethanol metabolite mediated fibrogenic activation of HSCs and potential therapeutic targets for hepatic fibrosis in ALD.

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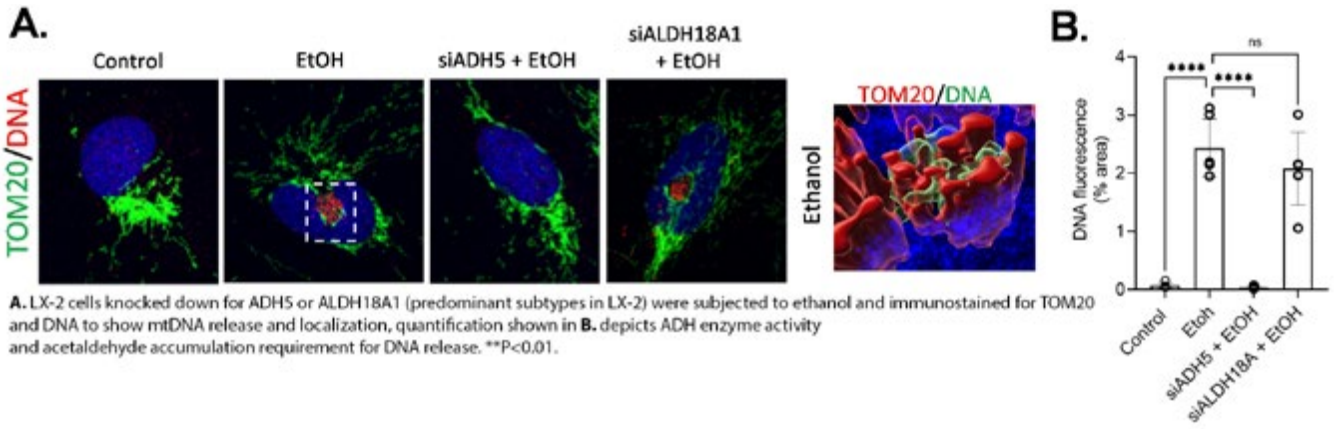

A. LX-2 cells knocked down for ADH5 or ALDH18A1 (predominant subtypes in LX-2) were subjected to ethanol and immunostained for TOM20 and DNA to show mtDNA release and localization, quantification shown in **B.** depicts ADH enzyme activity and acetaldehyde accumulation requirement for DNA release. **P<0.01.

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

3624 | GLYCOLYSIS IN HEPATIC STELLATE CELLS INDUCES EPIGENETIC HISTONE 3 LYSINE 9 ACETYLATION (H3K9AC) TO PROMOTE LIVER FIBROSIS

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Background: Activated hepatic stellate cells (HSCs) are the key drivers of liver fibrosis. HSC activation correlates with increased glycolysis, a metabolic process that generates acetyl groups. Histone acetylation is an epigenetic process that regulates gene transcription and cell behavior. Nevertheless, how glycolysis affects the epigenetic mechanisms in HSCs and *in vivo* liver fibrosis is elusive and is the aim of this study. **Methods:** *In vitro,* primary human HSCs were analyzed by targeted metabolomics, immunofluorescence (IF), western blot (WB), qPCR and RNAseq (GSE119606). *In vivo,* C56Bl/6 mice were treated with lysine acetyltransferase (KAT) inhibitor CPTH6, and liver fibrosis was induced by carbon tetrachloride (CCl_4). Livers were analyzed by spatial transcriptomics (GSE259363), WB and IF. Patient biopsies were analyzed by IF. **Results:** In our previous study, PDGF treatment increased glycolysis in HSCs. Here, after an epigenetic screen in HSCs, glycolysis inhibition by hexokinase 2 (HK2) shRNA decreased PDGF-mediated histone 3 lysine 9 acetylation (H3K9ac), suggesting that PDGF-dependent glycolysis promotes histone acetylation. Congruently, PDGF increased acetyl-CoA levels (targeted metabolomics, FC=2, n=5, p=0.0159), a metabolite necessary for histone acetylation. To understand how H3K9ac is mediated, we analyzed deposited transcriptomics datasets for the enzymes responsible for H3K9ac. PDGF increased *KAT2B* expression in HSCs (RNAseq, n=3, p=0.0013). In addition, both *Kat2a* and *Kat2b* were enriched in the fibrogenic pericentral areas during CCl_4-mediated liver fibrosis in mice (spatial transcriptomics, adj.p<0.05). Our findings prompted us to study the impact of H3K9ac on HSC activation *in vitro* and subsequent liver fibrosis *in vivo.* KAT2 inhibition by CPTH6 reduced PDGF-mediated collagen 1 (COL1) and KI67 expression (WB, n=3, p<0.05), suggesting that H3K9ac promotes HSC activation. Next, we assessed the therapeutic potential of CPTH6 to treat liver fibrosis. In this regard, CPTH6 treatment decreased CCl_4-induced COL1A1 and COL3A1 (IF, p=0.0038), alpha-smooth muscle actin (α-SMA) (WB, p=0.0002) and H3K9ac (WB, p=0.0012) levels by 2-fold (5-8 mice/group). Finally, liver biopsies from patients with cirrhosis presented a 3-fold increase in H3K9ac levels as compared to healthy liver (IF, n=5, p<0.05), suggesting a correlation between H3K9ac and chronic liver fibrosis. **Conclusion:** Our results suggest that glycolysis-dependent H3K9ac promotes HSC activation to amplify liver fibrosis.

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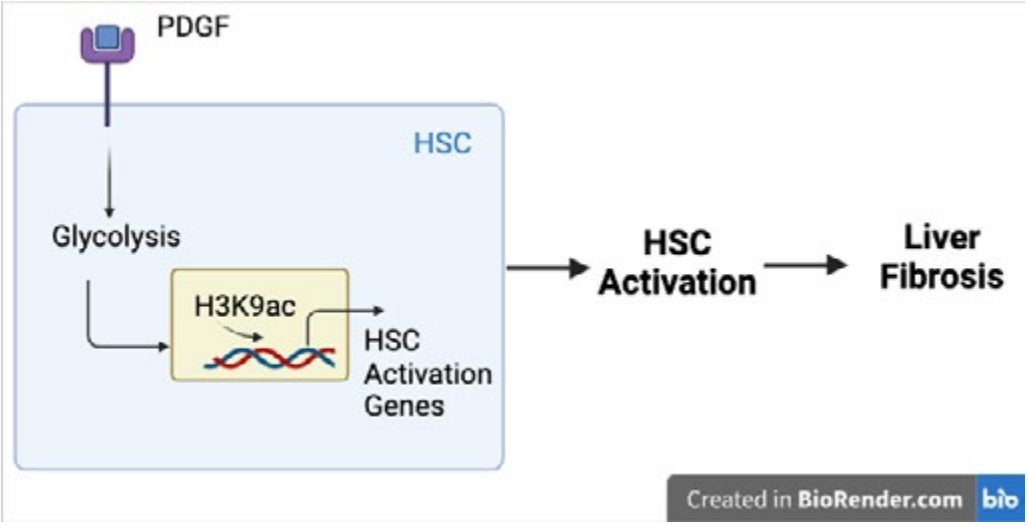

Disclosures: Alexander Washington: Nothing to Disclose, Shalil Khanal: Nothing to Disclose, Lulu Lyu: Nothing to Disclose, Taro Hitosugi: Nothing to Disclose, Enis Kostallari: Nothing to Disclose

3625 | SELECTED HISTAMINE 2 RECEPTOR ANTAGONISTS ARE ASSOCIATED WITH LOWER NON-INVASIVE FIBROSIS INDICES: A US NATIONWIDE POPULATION ANALYSIS

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Background: Liver fibrosis is the driver for life-threatening complications of chronic liver disease, including hepatocellular carcinoma (HCC). A recent in silico screen revealed that nizatidine, a histamine 2 receptor antagonist (H2RA), is associated with a favorable liver transcriptomic signature for HCC (Crouchet et al., Nat. Comm., 2021). In murine models, nizatidine reduced liver fibrosis and HCC burden. To explore the impact of H2RA on liver fibrosis in humans, we investigated their association in a nationwide database. **Methods:** We analyzed the National Health and Nutrition Examination Survey III (NHANES III, 1988-1994) to evaluate the association between H2RA use (cimetidine, famotidine, nizatidine, ranitidine) and non-invasive measures of liver fibrosis (FIB-4, APRI, NFS). Among 14,468 eligible participants of ages 21–70, 2,326 were excluded due to missing data. Among 12,142 eligible participants, 143, 32, 24, and 193 used cimetidine, famotidine, nizatidine, and ranitidine respectively for ≥30 days. Based on structural similarity, cimetidine/famotidine (CF; n = 170) and nizatidine/ranitidine (NR; n = 211) users were grouped. Propensity score (PS) matching was used to identify matched non-users. **Results:** PS-matched cohorts (CF users vs. non-users & NR users vs. non-users) showed no difference in covariates (age, sex, race, alcohol use, BMI, education, diabetes, HBV and HCV status). CF use was not associated with a significant difference in FIB-4, APRI, or NFS compared to non-use (Figure 1. Mean ± SEM; FIB-4 1.16 ± 0.0643 vs. 1.19 ± 0.0767, p = 0.69; APRI 0.261 ± 0.0143 vs. 0.315 ± 0.0516, p = 0.33; NFS -1.65 ± 0.117 vs. -1.55 ± 0.101, p = 0.48). In contrast, NR use was associated with significantly lower FIB-4, APRI, or NFS compared to non-use (FIB-4 1.02 ± 0.0335 vs. 1.31 ± 0.0944, p = 0.0043; APRI 0.245 ± 0.0109 vs. 0.362 ± 0.0568, p = 0.046; NFS -1.87 ± 0.104 vs. -1.56 ± 0.104, p = 0.011). For FIB-4, NR use was associated with a trend toward lower likelihood of probable fibrosis. **Conclusion:** In US population, use of nizatidine or ranitidine, but not cimetidine or famotidine, is associated with lower non-invasive fibrosis indices (FIB-4, APRI, NFS). Further investigation of this association using additional markers of liver fibrosis progression, larger cohorts, and prospective outcomes is warranted.

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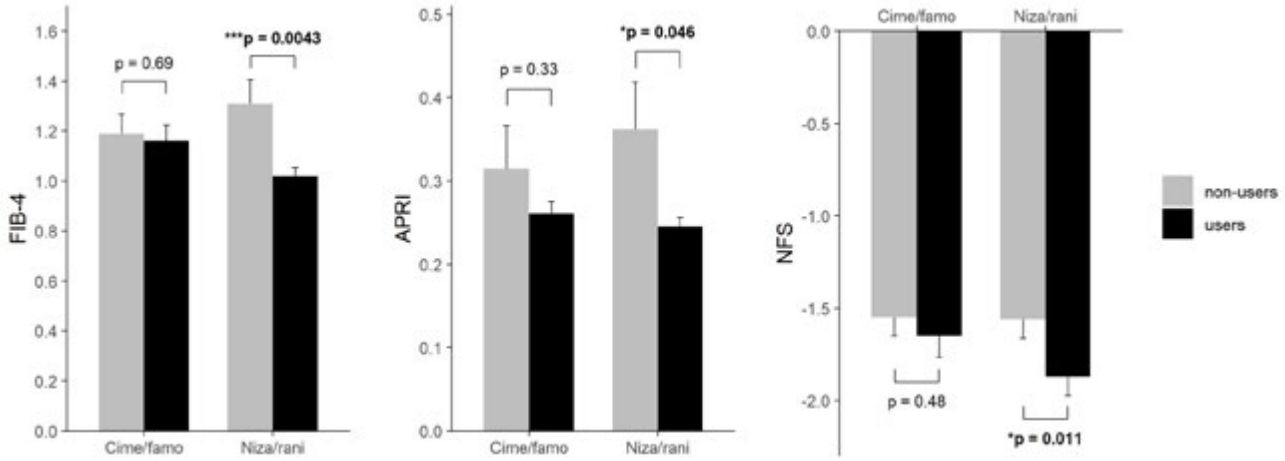

Disclosures: Jiunn Song: Nothing to Disclose, Margaret Selesky: Nothing to Disclose, Emilie Crouchet: Nothing to Disclose, Yujin Hoshida: Advisor relationship with Espervita Therapeutics; Has not ended; Advisor relationship with Helio Genomics; Has not ended; Stock – privately held company relationship with Alentis Therapeutics; Has not ended; Stock â€“ privately held company relationship with Espervita Therapeutics; Has not ended; Advisor relationship with Elevar Therapeutics; Has ended; Advisor relationship with Roche Diagnostics; Has ended, Thomas Baumert: Nothing to Disclose, Raymond Chung: Nothing to Disclose

3626 | "PROGNOSTIC VALUE OF THE PERIOPERATIVE PLATELET FUNCTION AND PLATELET COUNT IN RELATION TO LIVER REGENERATION AFTER LIVER RESECTION- AN EXPLORATIVE COHORT TRIAL (VOLUTHROMB-TRIAL)"

Carina Riediger[1] *Marie Groß*[1] *Oliver Tiebel*[1] *Felix Schön*[1] *Johannes Schweipert*[1] *Kühn Jens- Peter*[1] *Tibor Schuster*[2] *Jürgen Weitz*[1]

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Background: Liver surgery evolved over the last decades, but postoperative liver failure remains a serious problem after extended liver surgery, mostly due to small liver remnants. Despite hemostasis, platelets are multiplayers and said to play a key role in liver regeneration and tissue repair as platelets contain several growth factors, cytokines and chemokines. Clinical analyses of platelet function in liver surgery are lacking. This hypothesis-generating clinical trial was conducted to elaborate the effect of platelet function on postoperative liver regeneration and outcome. **Methods:** Patients undergoing oncological liver surgery between 2019 and 2021 at our surgical department were screened and prospectively included. Clinical data as well as radiological images (CT/MRI) including volumetry obtained preoperatively and 7 days after surgery were recorded for evaluation of hypertrophy. Laboratory tests were taken preoperatively before anesthesia and on days 1,3,5 and 7. Thrombocyte aggregation was tested within thrombocyte-rich plasma after stimulation with collagen, ADP, ristocetin arachidon acid. In addition, flow cytometric analyses were performed to get further information about the specific granule (a,b,d; lysosomes) and its release. For flow-cytometric tests, surface markers as CD41, PAC-1, CD62P, CD63 were used as well as Mecaprin uptake and release – each as basic test and after stimulation with TRAP-6 and ADP. **Results:** n= 51 out of 95 screened patients with a median age of 67 years (range 38-81) were included in final analyses. Underlying diagnosis for surgery were cholangiocarcinoma (10 %), hepatocellular carcinoma (20%) and metastases (70%) and treated by 21 major and 30 minor hepatectomies. Preoperative platelet count (median 216 GPT/l) and volume (10.9 fl) were normal in 80% of patients, but preoperative platelet function was altered in any functional test for aggregation as well as granule (release). However, preoperative altered platelet's function was not associated with postoperative morbidity, but massive further change from pre- to postop day 1 was associated with significantly higher morbidity. Platelet function was worst 1 to 4 days after surgery. Interestingly, platelet function was more altered after minor than major resections. Factors significantly affecting aggregation tests were HCC, cardiovascular disease, diabetes and liver cirrhosis. Risk factors for lysosomal function were diabetes and cardiovascular disease; steatosis was the only factor influencing d-granule. Perioperative impaired

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tests for d-granule showed correlation with liver hypertrophy. **Conclusion:** Most patients undergoing hepatic surgery present with impaired thrombocyte function with risk for reduced liver regeneration and impaired outcome.

Disclosures: Carina Riediger: Nothing to Disclose, Marie Groß: Nothing to Disclose, Oliver Tiebel: Nothing to Disclose, Felix Schön: Nothing to Disclose, Johannes Schweipert: Nothing to Disclose, Kühn Jens- Peter: Nothing to Disclose, Tibor Schuster: Nothing to Disclose, Jürgen Weitz: Nothing to Disclose

3627 | NOVEL CHRONIC LARGE ANIMAL MODEL OF LIVER CONGESTION TO STUDY FONTAN-ASSOCIATED LIVER DISEASE

John Kelly[1] Jingru Che[2] Joseph Leland[1] James Reinhardt[1] Xinlei Li[1] Joshua Spiess[1] Cameron Deshetler[1] Jennifer Kievert[1] Michael Davis[3] Christopher Breuer[1] David Brigstock[1]

[1]Nationwide Children's Hospital, [2]Nationwide Children's Hospital, [3]Georgia Institute of Technology and Emory University

Background: Single ventricle heart disease is a group of congenital cardiac lesions that result in one functioning ventricle. Surgical palliation by the Fontan procedure allows for direct pumping of blood to the body by the single ventricle while directly connecting the venous return to the pulmonary arteries without the aid of a ventricular pump. Fontan-associated liver disease (FALD) is a complication that involves congestion and fibrosis which may progress to cirrhosis and hepatocarcinoma. Current diagnosis of FALD is inadequate and there are no treatments beyond heart and liver transplant. To better understand the effects of venous congestion on the liver and associated aspects of FALD, we have developed a novel chronic large animal model of systemic venous hypertension. **Methods:** A model of IVC congestion was created in sheep with normal biventricular circulation (N= 9 [5M, 4F]; mean age 7.5±4.5 mo) by anastomosing a graft from the IVC to the main pulmonary artery and ligating the IVC-RA junction. An unoperated control group was followed for comparison (N=10 [5M, 5F]; mean age 3.6±2.3 mo). Model hemodynamics were evaluated by catheterization and MRI at 8.5±5.0 mo (surgery grp) or 3.6±2.3 mo (ctrl grp). Liver stiffness was measured by MR elastography. Liver sections were assessed by H&E and picrosirius red staining at 10 mo (N=3) or 20 mo (N=1) (surgery grp) or 3.6±2.3 mo (ctrl grp). Liver fibrosis was scored by modified Ishak congestive hepatic fibrosis (ICHF) score. Fluorescent immunostaining for HNF4α, collagen I, αSMA, desmin, or PDGFRβ was visualized by confocal microscopy. **Results:** 7/9 animals survived surgery. Compared to controls, model hemodynamics demonstrated a significant elevation in IVC pressure (17.2 ± 1.7 mmHg vs. 1.6 ± 1.8; p=0.008), liver stiffness (3.6 ± 0.8 kPa vs. 2.1±36; p=0.005), and ICHF score (3.8 ± 1.5 vs 0). Liver sections from the surgery cohort revealed loss of HNF4α from hepatocytes and enhanced staining for pro-fibrotic and HSC markers in the interstitial, periportal or pericentral areas, with co-localization of αSMA, desmin, collagen 1, and PDGFRβ1 to presumptive activated HSC. **Conclusion:** A novel chronic large animal model of venous congestion has been established that shows congestive and fibrotic similarities to FALD in humans. This unique model will be invaluable for detailed pre-clinical studies of FALD progression and assessment of novel diagnostics or treatments.

Disclosures: John Kelly: Nothing to Disclose, Jingru Che: Nothing to Disclose, Joseph Leland: Nothing to Disclose, James Reinhardt: Nothing to Disclose, Xinlei Li: Nothing to Disclose, Joshua Spiess: Nothing to Disclose, Cameron Deshetler: Nothing to Disclose, Jennifer Kievert: Nothing to Disclose, Michael Davis: Nothing to Disclose, Christopher Breuer: Nothing to Disclose, David Brigstock: Nothing to Disclose

3628 | DEGENERATION OF LIVER SYMPATHETIC INNERVATION ACCELERATES LIVER INJURY AND METABOLIC DYSREGULATION DUE TO IMPAIRED NEURONAL COMMUNICATION WITHIN THE LIVER ◆

Sadam Bhat[1] NUPUR SHARMA[1] Csaba Adori[2] Anupma Kumari[1] Babu Mathew[1] Adil Bhat[3] Hamid Hemati[4] Ravinder Singh[5] sushmita Pandey[1] Gaurav Trepathi[1] Neha Sharma[1] Vasundhra Bindal[1] Manisha Yadav[1] Nilesh Patil[1] Monika Adori[6] Viniyendra Pamecha[1] Rakhi Maiwall[1] Chaggan Bihari[1] Tore Bengtsson[7] Roshan Koul[1] Savneet kaur[1] Manoj Kumar[1] Jaswinder Singh[1]

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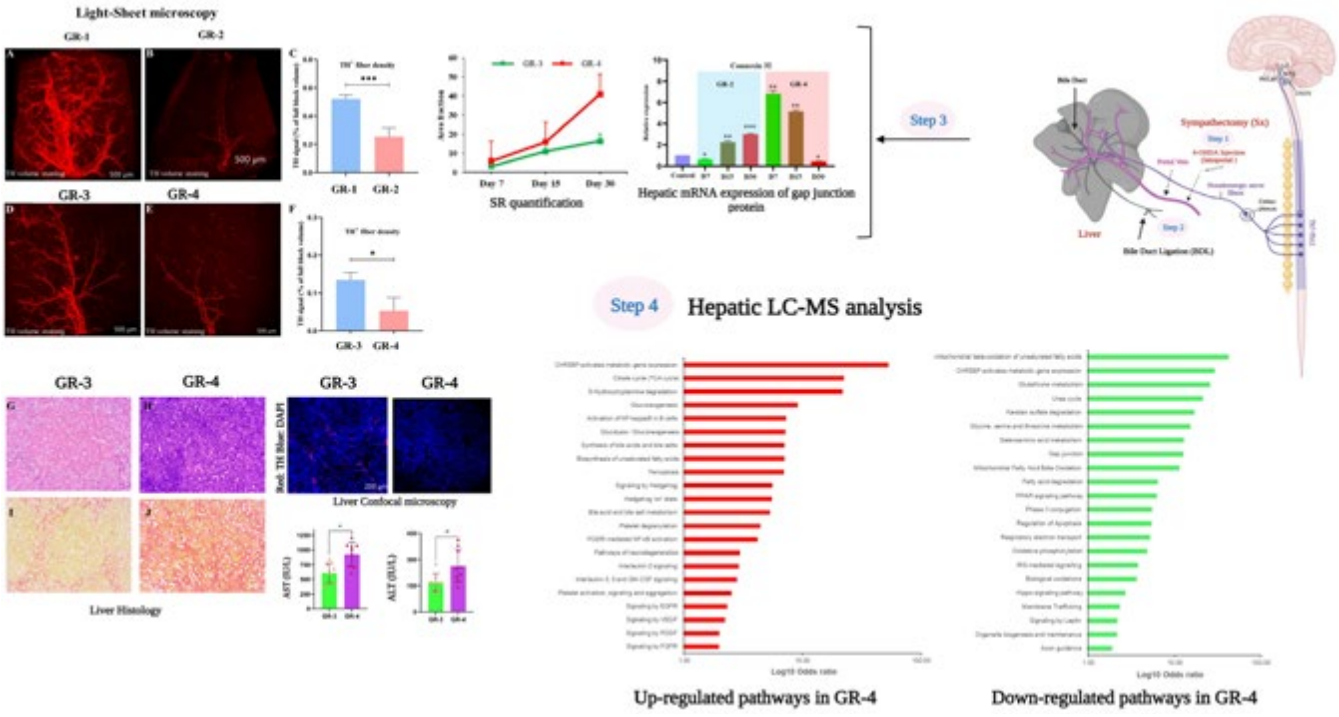
Background: Liver is primarily innervated by the sympathetic nervous system, originating from the T7 to T12 segments of the spinal cord. This innervation is crucial for regulating various liver functions, such as metabolism and regeneration. Damage to sympathetic nerves affects these hepatic functions, though the specific roles they play in disease progression and the associated molecular pathways remains unclear. We aimed to identify the neuronal structures and molecular pathways altered by sympathetic neuronal damage and their association with liver injury. **Methods:** Liver-specific sympathetic denervation (Sx) model was developed through intraportal injection of 6-OHDA hydrobromide in male Sprague Dawley rats, 8–10 weeks old. Four distinct groups were established: GR-1 (Veh; n=21), rats with intact nerves; GR-2 (Sx; n=24), sympathectomized rats; GR-3 (Veh+BDL; n=30), rats with intact hepatic sympathetic nerves and bile duct ligation (BDL); and GR-4 (Sx+BDL; n=51), sympathectomized rats with BDL. Histological analysis, confocal microscopy, serum AST/ALT measurements, and proteomic analysis were conducted at baseline, Day 7 (D7), Day 15 (D15), and Day 30 (D30) for all groups. **Results:** Sx in GR-2 and GR-4 was validated by change in urine color, ptosis, and absence of sympathetic nerves marker (tyrosine hydroxylase; TH) in the liver sections. At D7 and D15, GR-2 exhibited mild steatosis and inflammation, but no significant difference in AST and ALT levels compared to GR-1. Histologically, increased fibrosis and inflammation was observed in GR-4 versus GR-3 ($p<0.05$). Remarkably, at D15, fibrosis in GR-4 resembled that in GR-3 at D30 ($p<0.05$). GR-4 displayed elevated AST and ALT values versus GR-3 ($p<0.05$). GR-3 exhibited progressive disorganization of sympathetic nerves correlating with fibrosis severity and inflammation. Hepatic adrenergic receptors and gap junction proteins showed a gradual decrease in gene expression in GR-4 ($p<0.05$), suggesting an impaired hepatic neuronal communication. Hepatic proteome revealed a significant difference between groups. These differentially expressed proteins were involved in the activation of both fibrogenic (TNFR2, Wnt, FGF) and inflammatory (NLRP3, MAPK, PDGF) pathways ($p<0.05$). Interestingly, we also observed a significant metabolic dysregulation with the upregulation of TCA cycle ($p<0.05$) and downregulation of urea cycle ($p<0.05$) not only in GR-4 vs GR-3 but also in GR-2 vs GR-1, suggesting the role of sympathetic fibers in metabolic regulation in both healthy and diseased liver. **Conclusion:** The degeneration of sympathetic innervation may lead to impaired hepatic neuronal communication, which is associated with increased liver inflammation, fibrosis, and metabolic dysregulation, ultimately exacerbating liver injury.



Disclosures: Sadam Bhat: Nothing to Disclose, NUPUR SHARMA: Nothing to Disclose, Csaba Adori: Nothing to Disclose, Anupma Kumari: Nothing to Disclose, Babu Mathew: Nothing to Disclose, Adil Bhat: Nothing to Disclose, Hamid Hemati: Nothing to Disclose, Ravinder Singh: Nothing to Disclose, sushmita Pandey: Nothing to Disclose, Gaurav Trepathi: Nothing to Disclose, Neha Sharma: Nothing to Disclose, Vasundhra Bindal: Nothing to Disclose, Manisha Yadav: Nothing to Disclose, Nilesh Patil: Nothing to Disclose, Monika Adori: Nothing to

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3629 | NETWORK PHARMACOLOGY AND MOLECULAR DOCKING REVEAL THE MECHANISM OF GINKGO BILOBA EXTRACT AGAINST LIVER CIRRHOSIS

Liu Qiyao[1] Tingyu Zhang[2] Xin Sun[2] Xiaoke Li[2] Xiaobin Zao[2]

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Background: Liver cirrhosis (LC) has long posed a significant threat to public health. Ginkgo biloba extract (GBE), a well-established medication, has been extensively utilized in the treatment of cirrhosis. Here, we aim to elucidate the mechanism of GBE in the treating LC. **Methods:** We first obtained target genes of GBE and LC from public databases. Then we constructed a protein-protein interaction network of the key targets and screened out the hub genes. The LC rat model was constructed by intraperitoneal injection of diethylnitrosamine. The hub genes' expression was further verified in the LC rats' liver tissues with RNA-squencing approach. We performed the pathway enrichment analysis of the key targets and hub genes. We subsequently used a CCl4-induced liver cirrhosis mouse model treated with GBE. **Results:** After mining databases, we identified 368 overlapping genes between GBE's targets and LC's targets. These overlapping genes were further used to construct PPI network and screen the hub genes. With the rat LC model, we next detected the mRNA expression of the hub genes in the liver tissues. And the results showed that compared with the control, the expression of MAPK14, EGFR, and NR3C1 was significantly down regulated in LC; while the expression of AR, CASP3, and CCND1 was just the reverse. Subsequently, the KEGG pathway enrichment analysis results showed that the key targets and hub genes were significantly correlated to the PI3-AKT and MAPK signaling pathways. Furthermore, employing a mouse liver fibrosis model, we confirmed that GBE significantly reduced liver lesions in CCl4-treated mice, prevented liver parenchymal necrosis, improved liver collagen accumulation, and reduced macrophage infiltration. **Conclusion:** GBE shows potential as a therapeutic candidate for liver cirrhosis, likely modulating the PI3K-AKT and MAPK signaling pathways through identified overlapping genes and hub genes.

Disclosures: Liu Qiyao: Nothing to Disclose, Tingyu Zhang: Nothing to Disclose, Xin Sun: Nothing to Disclose, Xiaoke Li: Nothing to Disclose, Xiaobin Zao: Nothing to Disclose

3630 | LONGITUDINAL ANALYSIS OF FIBROSIS-4 INDEX AND PREDICTION OF TRANSITION TO INTERMEDIATE OR HIGH RISK – A POPULATION LEVEL STUDY OF 48,466 INDIVIDUALS WITH DIABETES

Daniel Yan Zheng Lim[1] Siyuan Yin[1] Charlene Tan Hui Ru[1] Jeanette Ng[1] Chee-Kiat Tan[1] George Boon Bee Goh[1]

[1]Singapore General Hospital

Background: Metabolic associated steatotic liver disease (MASLD) is highly prevalent in patients with type 2 diabetes mellitus (T2DM). The Fibrosis-4 (FIB-4) Index is a non-invasive biomarker that can be used to stratify the risk of advanced fibrosis and prompt referral to a hepatologist. However, the longitudinal stability of FIB-4 risk categories is not known, and no well validated prediction models exist for progression to a higher risk category. This study aims to assess the above in a large cohort of patients with diabetes. **Methods:** This study analyzed data from the SingHealth Diabetes Registry, a large retrospective cohort of all diabetes patients from 2013 to 2021 within the largest health system in Singapore. Adults >18 years old with valid FIB-4 scores were included. FIB-4 scores were aggregated on a quarterly basis, and categorized into low (<1.3), indeterminate (1.3-2.67), and high (>2.67) risk groups. Further data on patient demographics and comorbidities was extracted. We performed Markov chain analysis of changes in FIB-4 risk category. We performed logistic regression using demographic information, clinical measurements, laboratory results, and comorbidity data to predict a transition to a lower FIB-4 risk category in the subsequent year. **Results:** Data from 48,466 participants (average age 63 years; 53% female) was analysed. 31.1% of individuals initially at low risk (FIB-4 < 1.3) transitioned to moderate or high risk, with 17.9% of those at moderate risk (FIB-4 between 1.3 and 2.67) progressing to high risk (FIB-4 > 2.67). The Markov

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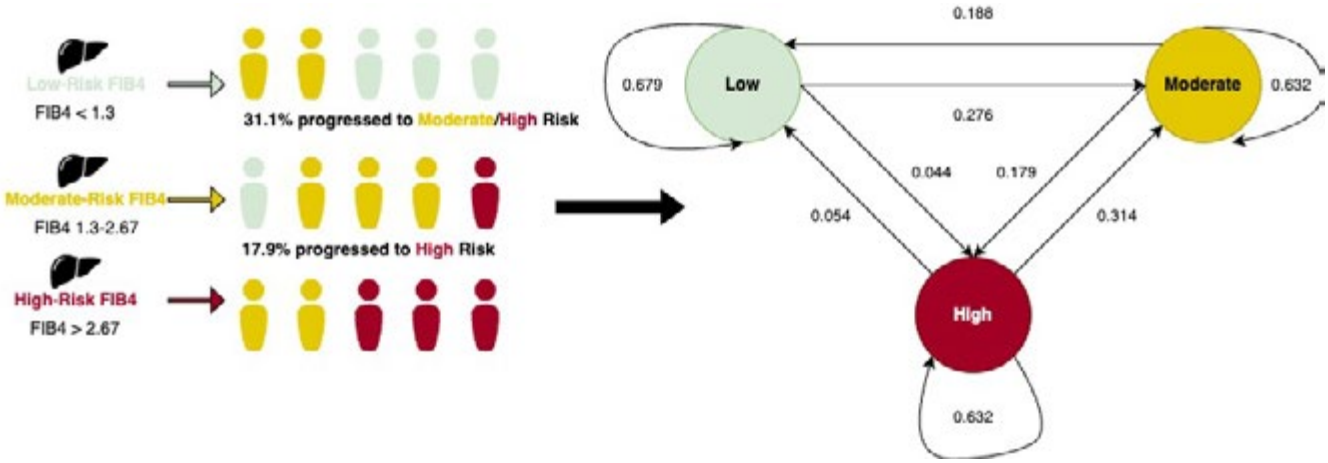
chain model showed that although majority of patients in the high risk category will stay there (0.63 likelihood), a fair proportion will transition back to the intermediate risk category (0.31 likelihood). The logistic regression model had an AUC of 0.79, indicating good discriminatory power. Significant predictive factors were age, BMI, ALT, AST, platelet count, and comorbid conditions such as hypertension and hypercholesterolemia. **Conclusion:** High FIB-4 scores may spontaneously regress and there may be a role to monitor such individuals, rather than referring them to a gastroenterologist. A logistic regression score may be used to stratify the risk.



Disclosures: Daniel Yan Zheng Lim: Nothing to Disclose, Siyuan Yin: Nothing to Disclose, Charlene Tan Hui Ru: Nothing to Disclose, Jeanette Ng: Nothing to Disclose, Chee-Kiat Tan: Eisai: Advisor, Abbott Laboratories: Advisor, Gilead Sciences: Advisor, Roche Diagnostics: Advisor, Fujifilm: Advisor, George Boon Bee Goh: Nothing to Disclose

3631 | MULTIPLEXED *IN VIVO* SCREENING REVEALS THE DELETERIOUS EFFECTS OF FIBROGENIC FACTORS ON HEPATOCYTES

Joanne Hsieh[1] Vinay Kartha[1] Hikaru Miyazaki[1] Christopher Carrico[1] Linda Chio[1] Daniel Fuentes[1] Dimitry Popov[1] Ian Driver[1] Chris Towne[1] Francisco LePort[1] Martin Borch Jensen[1]

[1]Gordian Biotechnology

Background: Hepatocyte injury and death promotes fibrosis deposition, but the ramifications of extracellular matrix composition on hepatocytes is less understood. There is evidence that higher liver stiffness is predictive of HCC development due to HCV infection or MASH, suggesting that high matrix content of fibers such as collagen type I could be detrimental to hepatocyte health. **Methods:** To increase fibrosis in the immediate environment of a particular hepatocyte, overexpression of fibrogenic factors were targeted to hepatocytes by adeno-associated virus (AAV) vector. The fibrogenic interventions were overexpression of *Ccn1*, *Ccn2*, *Fgf18*, *Pdgfrb*, *Serpine1*, *Spp1*, *Tgfb1*, *Tgfb2*, and *Tgfb3* and administered as a pool to a diet-induced obese mouse model of MASH. Since mesenchymal cells could be situated in apposition to multiple hepatocytes, to avoid detecting a hepatocytic response to more than one intervention, the dose of the AAV cocktail was titrated to transduce only 7% of the hepatocytes, leaving 93% of hepatocytes unperturbed. The transcriptomic response to these interventions was then characterized at the single nucleus level according to curated gene sets, which we've deemed "disease features." **Results:** As expected, overexpression of *Tgfb1*, *Tgfb2* or *Tgfb3* increased transcriptional activity of the TGFbeta signaling gene set. In general, the fibrogenic interventions increased expression of genes associated with focal adhesion, which was shown in the SteatoSITE cohort of Kendall and Fallowfield *et al*. to be activated in the transition from F2 to F3 fibrosis. Other fibrosis features also showed elevated expression. There was also some evidence of decreased thyroid hormone receptor beta signaling. The directionality of multiple tumorigenicity features suggests that a fibrogenic milieu is conducive to malignancy. However, there was also substantial heterogeneity in how each fibrogenic factor affected the hepatocyte transcriptome. **Conclusion:** Single nucleus RNA-sequencing suggests that it is possible to detect a fibrotic local environment at the hepatocyte level. The hepatocyte transcriptome may offer clues as to how stiffness could be pro-tumorigenic.

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Disclosures: Joanne Hsieh: Gordian Biotechnology: Employee, Vinay Kartha: Nothing to Disclose, Hikaru Miyazaki: Nothing to Disclose, Christopher Carrico: Nothing to Disclose, Linda Chio: Gordian Biotechnology: Employee, Gordian Biotechnology: Stock – privately held company, Daniel Fuentes: Nothing to Disclose, Dimitry Popov: Nothing to Disclose, Ian Driver: Nothing to Disclose, Chris Towne: Nothing to Disclose, Francisco LePort: Nothing to Disclose, Martin Borch Jensen: Nothing to Disclose

4001 | HYDROPHOBIC SECONDARY BILE ACIDS INDUCE PRIMARY SCLEROSING CHOLANGITIS THROUGH THE LIVER-LARGE INTESTINE AXIS IN A *CYP2C70*$^{-/-}$/*CYP2A12*$^{-/-}$ MOUSE WITH HUMAN-TYPE BILE ACID COMPOSITION ◆

Teruo Miyazaki[1] *Hajime Ueda*[1] *Tadashi Ikegami*[1] *Akira Honda*[1]

[1]*Tokyo Medical University Ibaraki Medical Center*

Background: Primary sclerosing cholangitis (PSC) is characterized by fibrosis around the large bile duct (onion-skin lesions) and frequently complicates inflammatory bowel diseases (IBD). Bile acids (BAs) have primarily been associated with PSC; however, there is no conclusive evidence due to unestablished mouse models and species differences in BAs. In the last Liver Meeting, we presented the data showing the development of onion-skin lesions in a *Cyp2c70/Cyp2a12* double KO (DKO) mouse with human-type BA composition, and this condition was aggravated upon chronic oral treatment with lithocholic acid (LCA), a human-type secondary BA. The present study compared the effects of hydrophobic secondary BAs, LCA and deoxycholic acid (DCA) on PSC onset and large intestine damage in the DKO mice. **Methods:** Male DKO mice (5-week old) were treated with LCA or DCA (75 mg/L) in drinking water for 15 weeks, while nontreated (NT)-DKO and C57BL/6J wild-type (WT) mice were untreated with BA. Liver and fecal BA profiles, histopathological and gene expression changes in the liver and large intestine, and serum lipopolysaccharide (LPS) levels were analyzed. FITC-dextran loading test was performed to evaluate intestinal permeability. **Results:** The liver of the DKO mice exhibited a marked increase in the secondary BA levels (LCA 15% and DCA 40%). DCA treatment further increased the DCA level while LCA treatment had no effect on the BA profile in these mice. Furthermore, LCA treatment caused onion-skin lesions in all DKO mice, while only 63% of the NT-DKO and 50% of the DCA-DKO mice developed this condition. The fibrotic area around the bile duct in the liver of the DKO mice was significantly increased upon LCA or DCA treatment. In the feces, BA profiles of DKO mice (approximately 75% LCA and 15% DCA) were not significantly altered by BA treatment. No symptoms of IBD such as diarrhea were observed in the DKO mice even after BA treatment. However, in the FITC-dextran loading test, compared to the WT mice, serum FITC level was higher in the NT-DKO group and significantly higher in the LCA- and DCA-DKO mice groups. Serum LPS levels were comparable among the NT-DKO, DCA-DKO, and WT mice; however, the levels were significantly increased by LCA treatment. The mRNA levels of *Tnfα*, *Tgfβ*, and *Tlr4* were significantly higher in the LCA- and DCA-DKO mice livers compared to the WT and NT-DKO mice livers. Moreover, the hepatic mRNA expression of the adhesion molecules *Itgαv* and *Itgβ6,* which are expressed in PSC patients and activate TGFβ (a master regulator of fibrosis), were significantly increased following LCA treatment. **Conclusion:** The hydrophobic secondary BAs are the major factors that induce PSC via the liver-large intestine axis by promoting periductal fibrosis and large intestinal leakage.

Disclosures: Teruo Miyazaki: Nothing to Disclose, Hajime Ueda: Nothing to Disclose, Tadashi Ikegami: Nothing to Disclose, Akira Honda: Nothing to Disclose

4002 | HISTONE DEACETYLASE INHIBITOR MS-275 REDUCES LIVER INJURY, INFLAMMATION, AND FIBROSIS IN A MOUSE MODEL OF CHOLESTATIC LIVER DISEASE

Tony (Chun-Cheng) Chiang[1] *Donghun Shin*[1] *Shuchang Liu*[1] *Satdarshan (Paul) Monga*[1] *Kari Nejak-Bowen*[1]

[1]*University of Pittsburgh*

Background: Liver transplantation remains the sole life-extending option for patients suffering from end-stage cholestatic liver disease thus a therapeutic alternative is urgently needed. Chemical screening in zebrafish models showed that a histone deacetylase (HDAC) inhibitor MS-275 can facilitate hepatocyte-to-cholangiocyte (HC-to-CC) transdifferentiation after injury. HDAC inhibitors were developed as treatments for oncologic diseases

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given the ability to inhibit cell growth and induce apoptosis, while their value in hepatobiliary disease is unknown. To evaluate the compound's effects on mammals, we aimed to validate the drug responses in mice subject to DDC-induced biliary injury. Additionally, we wanted to study the drug's underlying mechanism to determine if it is related to transdifferentiation. **Methods:** Rosa26: loxP-STOP-loxP-EYFP mice were given AAV8-TBG-Cre to permanently label HC with EYFP. Mice were given 0.1% DDC diet for 4 weeks. Starting at 3 weeks after DDC, mice were given either DMSO or MS-275 at 2 different doses with DDC for 7 days and sacrificed 4 weeks after DDC. Serum and liver were collected at experiment endpoints. Real-time quantitative PCR was used to determine mRNA levels of biliary markers, inflammatory cytokines, fibrosis markers, and cell cycle genes and to validate target genes found in zebrafish studies. RNA-seq was performed to identify the differential gene expression and pathways. Immunostainings were applied to validate RNA-seq results and fate-trace labeled HC after DDC injury. **Results:** MS-275 significantly reduced serum liver enzymes and bilirubin levels in the mouse model, and alleviated liver pathological changes like hepatitis and fibrosis. Though mouse gene expression analysis did not reveal similar changes in target genes as in zebrafish, MS-275 decreased G1/S cyclins including cyclin D1 and cyclin E1. Early biliary markers Sox9 and EpCAM were decreased after MS-275 compared to DDC alone, while mature biliary marker CK19 was comparable with and without MS-275. Interestingly, the absence of reprogrammed HC in MS-275-treated livers suggested that drug responses in mice may not directly act through HC-to-CC transdifferentiation. Cluster analysis and differential gene expression indicated that MS-275 normalized DDC-injured livers toward baseline controls. Enrichment analysis disclosed gene expression changes in cell cycle, senescence, bile acid secretion, oxidative phosphorylation, and immune cell activation pathways between DDC alone and MS-275 groups, providing insights for future studies. **Conclusion:** MS-275 exerts hepatoprotective effects against DDC-induced biliary injury in mice and causes phenotypic changes. MS-275 induces quiescence in mouse liver by downregulating cell cycle genes. The compound also reduces the senescence pathway and p21 expression. Further studies are expected to elucidate the molecular drivers and liver cell types involved.

Disclosures: Tony (Chun-Cheng) Chiang: Nothing to Disclose, Donghun Shin: Nothing to Disclose, Shuchang Liu: Nothing to Disclose, Satdarshan (Paul) Monga: Surrozen: Independent Contractor, Mermaid Bio: Advisor, Vicero: Advisor, AntlerA: Advisor, Genentech: Speaking and Teaching, Alnylam: Grant/Research Support, Alnylam: Consultant, UbiquiTx: Consultant, Mermaid Bio: Consultant, Fog Pharmaceuticals: Grant/Research Support, Surrozen: Consultant, Genentech: Independent Contractor, Kari Nejak-Bowen: Nothing to Disclose

4003 | 3D RECONSTRUCTION OF BILIARY SYSTEM IN THE BIOENGINEERED LIVERS USING DECELLULARIZED SCAFFFOLDS

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Background: The function of bioengineered livers generated by recellularization of cells that construct the liver such as hepatocytes, cholangiocytes and vascular endothelial cells has been investigated, but the reconstruction of functional biliary system in liver scaffolds has not been achieved. In this study, we aimed to reconstruct 3D biliary system in the bioengineered livers by recellularization of rat primary hepatocytes and liver ductal organoids. **Methods:** Liver harvesting, liver decellularization and isolation of rat primary hepatocytes were performed according to our previous report. Rat liver ductal organoids were prepared and cultured according to the previously described protocol of mouse. GFP-expressing liver ductal organoids were prepared using a lentiviral vector. Those organoids were recellularized into liver scaffolds via bile duct after dissociation into 3-5 x 10^6 single cells and cultured with an expansion medium using a circulation device for 5 days. The circulation device was connected to the cannula of portal vein and placed in a 37°C customized chamber. Next, 5 x 10^7 primary hepatocytes were recellularized via bile duct and cultured with co-culture medium for another 2 days. Drainage fluid from the bile duct was collected, and the concentration of total bile acids in the drainage fluid and culture medium were compared using ELISA. After total 7 days perfusion culture, the recellularized scaffolds were retrieved and fixed for histological analysis. **Results:** Histological analyses of this recellularized liver revealed the appropriate cell distribution of GFP-negative primary hepatocytes into the parenchymal space and GFP-positive liver ductal organoid cells into the bile duct. In the immunofluorescence analysis, repopulated primary hepatocytes expressed ALB, and repopulated liver ductal organoid cells expressed KRT19. Certain repopulated primary hepatocytes in the proximity of bile ducts reconstructed by liver ductal organoids expressed MRP2, one

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of the bile acid transporters, and ZO-1 in membranous area. Transmission electron microscope examination revealed that the bile canalicular-like structure was identified consistent with the expression regions of MRP2 and ZO-1 in repopulated hepatocytes. In addition, repopulated liver ductal organoids were revealed to have microvilli structures on the luminal side of the bile duct. Furthermore, the concentration of total bile acids in drainage fluid from the bile duct of liver grafts during perfusion culture tended to be higher than that of the culture medium (2.59 vs 6.35nmol/10^6cells; p = 0.100; n = 3, respectively). **Conclusion:** The bioengineered livers generated by recellularization of primary hepatocytes and liver ductal organoids exhibited biliary structure similar to native livers. Furthermore, it was suggested that the bile excretion pathway could be reconstructed in the bioengineered livers.

Disclosures: Hiroshi Horie: Nothing to Disclose, Ken Fukumitsu: Nothing to Disclose, Kentaro Iwaki: Nothing to Disclose, Fumiaki Munekage: Nothing to Disclose, Kenta Makino: Nothing to Disclose, Katsuhiro Tomofuji: Nothing to Disclose, Hidenobu Kojima: Nothing to Disclose, Elena Uebayashi: Nothing to Disclose, Satoshi Ogiso: Nothing to Disclose, Takamichi Ishii: Nothing to Disclose, Etsuro Hatano: Nothing to Disclose

4004 | THE PPAR-DELTA AGONIST SELADELPAR NORMALIZES PRIMARY BILIARY CHOLANGITIS-LIKE FEATURES IN HUMAN CHOLANGIOCYTES AND REDUCES PATHOLOGICAL IMMUNE ACTIVATION

Francisco Caballero-Camino[1] Irune Lasa[2] Ainhoa Lapitz[1] Xia Wu[3] Pedro Rodrigues[1] Noelia Pastor-Toyos[1] Laura Izquierdo-Sanchez[1] Jiangao Song[3] Edward Cable[3] Jeffrey Johnson[3] Yun-Jung Choi[3] Charles McWherter[3] Jesus Banales[1]

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Background: Primary biliary cholangitis (PBC) is a chronic cholestatic and immune-mediated liver disease characterized by the progressive impairment and destruction of bile duct epithelial cells (i.e., cholangiocytes). Overexpression of miR-506 in cholangiocytes leads to multiple PBC-like features, including impaired cell proliferation and adhesion, sensitization to bile acid-induced apoptosis, impaired energy metabolism, PDC-E2 overexpression and mislocation into the plasma membrane, and immune activation. Seladelpar, a novel delpar (selective PPAR-delta agonist), demonstrated therapeutic efficacy in the phase 3 clinical trial RESPONSE. Here, we investigated the cellular and molecular effects of seladelpar on normal and PBC-like human cholangiocytes. **Methods:** H69 human cholangiocytes, along with H69 cells stably overexpressing miR-506 (H69-miR-506) or a miRNA-negative control sequence (H69-miR-neg), were cultured in the absence or presence of seladelpar (10 μM). High-throughput proteomic analysis was performed using mass spectrometry. Mitochondrial respiration was assessed using Seahorse technology. Cholangiocyte apoptosis, and activation and proliferation of human peripheral blood mononuclear cells (PBMCs), were analyzed with flow cytometry. **Results:** Seladelpar treatment resulted in a profound remodeling of the dysregulated proteome of PBC-like cholangiocytes (H69-miR-506) compared with control cells (178 upregulated and 91 downregulated). Among those, expression of 31 proteins were normalized in H69-miR-506, involving processes such as cell adhesion and biliary differentiation (DSCL1, WNT5A), autophagy (NED4L), resistance to apoptosis (NSD2), and inhibition of immune cell recruitment (JAM3, IFI16). Importantly, seladelpar corrected the pathological mitochondrial respiration of H69-miR-506 cholangiocytes, leading to normalized maximal and ATP-linked respiration levels and increased ATP production, compared with control cells. Furthermore, seladelpar protected both control and PBC-like cholangiocytes from apoptosis, and reduced H69-miR-506-triggered activation and proliferation of PBMCs. **Conclusion:** Our results indicate that the therapeutic benefit of seladelpar in PBC may involve direct pharmacodynamic effects on cholangiocytes, including normalization of disease-related processes such as mitochondrial dynamics and bioenergetics, as well as protection from apoptosis and against pathological immune activation.

Disclosures: Francisco Caballero-Camino: Nothing to Disclose, Irune Lasa: Nothing to Disclose, Ainhoa Lapitz: Nothing to Disclose, Xia Wu: CymaBay Therapeutics: Employee, Pedro Rodrigues: Nothing to Disclose, Noelia Pastor-Toyos: Nothing to Disclose, Laura Izquierdo-Sanchez: Nothing to Disclose, Jiangao Song: Nothing to Disclose, Edward Cable: CymaBay Therapetics: Employee, Jeffrey Johnson: CymaBay Therapeutics: Consultant, Yun-Jung Choi: Nothing to Disclose, Charles McWherter: Nothing to Disclose, Jesus Banales: Nothing to Disclose

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4005 | REGULATION OF HEPATIC MULTIDRUG RESISTANCE-ASSOCIATED PROTEIN 3/ ATP-BINDING CASSETTE SUBFAMILY C MEMBER 3 (MRP3/ABCC3) BY PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR (PPAR): A NOVEL MECHANISM TO REDUCE BILE ACID INJURY DURING CHOLESTASIS

Colleen Hayes[1] *Gina Gallucci*[1] *James Boyer*[2] *David Assis*[2] *Nisanne Ghonem*[1]

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Background: Cholestatic liver diseases are characterized by the accumulation of toxic bile acids. Adjunct treatment with fenofibrate (145-160 mg/d), a PPARα agonist, increases serum bile acid glucuronides to reduce bile acid toxicity during refractory cholestasis in PBC and PSC vs. UDCA monotherapy (13-15 mg/kg/d). Bile acid glucuronides are substrates for the multidrug resistance-associated protein 3 (MRP3/ABCC3), an efflux transporter located on the basolateral membrane of hepatocytes that transports bile acid glucuronides out of the liver for urinary excretion, e.g., bile acid detoxification. Newer PPAR agonists are currently under investigation to treat PBC and PSC, however, their comparative efficacy is unknown. This study investigated the ability of PPAR agonists to transactivate hepatic MRP3 to reduce bile acid-induced injury during cholestasis. **Methods:** Hepatic MRP3 mRNA and protein expression were assessed in HepG2 cells treated with the following PPAR agonists: fenofibrate (α), elafibranor (α, β/δ) saroglitazar (α, γ), seladelpar (β/δ), and bezafibrate (pan-PPAR). The human *MRP3* promoter was analyzed *in silico* for potential peroxisome proliferator response elements and fragments spanning 10 kb upstream of the transcription start site were cloned into human *MRP3*-luciferase reporter constructs. HepG2 cells were co-transfected with human PPAR (α, β/δ, or γ)/RXRα and MRP3 promoter constructs, then treated with PPAR agonists for 24 hours to determine the effects of PPAR agonists on MRP3 transactivation. **Results:** HepG2 treatment with fenofibrate (125 μM), elafibranor (30 μM), and seladelpar (3 μM), significantly increased hepatic *MRP3* mRNA expression by an average of 2.1- (p<0.0001), 3.2- (p<0.01), and 1.4-fold (p<0.05) vs. DMSO (n=4-8), respectively. Similarly, fenofibrate (125 μM), seladelpar (30 μM), and bezafibrate (125 μM) increased MRP3 protein expression by an average of 1.5- (p<0.05), 1.7- (p<0.01), and 2.5-fold (p<0.01) vs. DMSO (n=3), respectively, while elafibranor did not (0.8-fold vs. DMSO). Luciferase reporter assays showed that fenofibrate stimulated *MRP3* promoter activity within the p-1,964/+163 region by 2-fold vs. DMSO (p<0.05), whereas bezafibrate stimulated the p-6,019/-4,060 region by 1.9-fold vs. DMSO (p<0.0001). **Conclusion:** PPAR agonists upregulate hepatic MRP3 mRNA and protein expression, and some of the agonists transactivate the *MRP3* promoter in HepG2 cells, with varying efficacy. Identifying the novel transcriptional regulation of hepatic *MRP3* by PPAR adds to the mechanistic understanding of PPAR in reducing BA toxicity. This novel mechanism emphasizes the clinical relevance of PPAR agonism to treat cholestatic liver diseases.

Disclosures: Colleen Hayes: Nothing to Disclose, Gina Gallucci: Boehringer Ingelheim: Employee, James Boyer: Mirum Pharmaceuticals: grant recipient, David Assis: Nothing to Disclose, Nisanne Ghonem: Nothing to Disclose

4006 | EXPERIMENTAL SCLEROSING CHOLANGITIS: PARADOXICAL EFFECTS OF AN ANTI-FIBROTIC STRATEGY

Richard Gilbert[1] *Yanling Zhang*[1] *Kerri Thai*[1] *Linda Nghiem*[1] *Hai Wang*[1]

[1]*St. Michael's Hospital*

Background: Primary sclerosing cholangitis (PSC) is an orphan liver disease with no known therapies and frequent recurrence after transplantation. It is characterised by fibrosis that begins in the bile ducts but progresses to advanced cirrhosis with cholestasis and liver failure. The magnitude of fibrosis correlates closely with the extent of the 'ductular reaction' in which cells expressing biliary markers proliferate, frequently forming small ductules. In the present study, we sought to examine the effects of an anti-fibrotic strategy on liver function and structure including the extent of both fibrosis and the ductular reaction. **Methods:** Experimental PSC was induced in mice by adding 3,5-diethoxycarbonyl-1,4-dihydrocollidine (DDC) to their diet, resulting in cholestasis, biliary inflammation (cholangitis), portal tract fibrosis and ductular reaction. Nineteen mice were randomly assigned to receive regular diet or 0.1% DDC diet with or without the transforming growth factor-ß receptor type 1 kinase (ALK5) inhibitor, SB431542 60 mg/kg bid over a 3-4 week period. The following parameters were assessed by: (1) Cholestasis: plasma alkaline phosphatase (ALP), serum icterus score; (2) Fibrosis by picrosirius red staining and

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semi-quantitative scoring; and (3) Ductular reaction by cytokeratin-7 (CK-7) immunolabelling and quantification. **Results:** DDC mice developed cholestasis (raised ALP and icterus score) with extensive portal fibrosis and ductular reaction. ALK5 inhibition attenuated the extent of fibrosis and biochemical evidence of cholestasis while increasing both liver size and the extent of the ductular reaction (Table). **Conclusion:** In a model of in experimental primary sclerosing cholangitis, TGF-ß antagonism using an ALK5 inhibitor ameliorated the extent of fibrosis and biochemical evidence of cholestasis. This strategy, however, also led to hepatomegaly and ductular reaction. Whether these latter two seemingly paradoxical responses are, in fact, unrecognised components of the reparative process or whether, alternatively, they are specific to blocking the effects of TGF-ß, remain to be determined.

	Vehicle	DDC diet	DDC + ALK5i
liver weight (g)	1.11 ± 0.07	0.77 ± 0.04*	1.59 ± 0.08*†
ALP (U/l)	83 ± 5	2186 ± 129*	776 ± 203*†
Icterus score	0 (IQR: 0-0)	4 (IQR: 4-4)	0.5 (IQR: 0-1.75)
Fibrosis score	3.4 ± 1.5	2 (IQR: 2-3)	1.75 (IQR: 1.25-2)
CK-7 (% area)	0.2 ± 0.03	2.3 ± 0.3*	6.2 ± 0.6*†

Data as mean ± SEM except for icterus and Metavir scores as median (IQR).
* p <0.001 versus vehicle, † p <0.001 versus DDC diet

Disclosures: Richard Gilbert: Fibrocor Therapeutics: Stock – privately held company, Certa Therapeutics: Stock – privately held company, Fibrocor Therapeutcs: Executive role, OccuRx: Stock – privately held company, Yanling Zhang: Nothing to Disclose, Kerri Thai: Nothing to Disclose, Linda Nghiem: Nothing to Disclose, Hai Wang: Nothing to Disclose

4007 | CHOLESTEROL-DEPENDENT MITOCHONDRIAL GSH STATUS DETERMINE THE HEPATOTOXICITY OF BILE ACIDS IN CHOLESTASIS ◆

Laura Fàbrega[1] *Laura Conde de la Ros*[1] *Susana Nuñez*[1] *Carmen Garcia-Ruiz*[1]

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Background: Cholestatic liver diseases (CLD) can cause hepatocellular injury, fibrosis, and cirrhosis due to the intracellular accumulation of solutes that cannot be excreted into bile, such as bile acids (BAs). Besides their role in fat digestion and intestinal absorption of lipids and lipophilic vitamins, BAs are involved in several physiological functions, including their role as signaling molecules for the regulation of gene expression by targeting nuclear and membrane receptors. However, when BAs concentration rise in the liver above certain concentrations, such as in CLD, they can cause liver injury that can lead to progressive liver damage and subsequent liver failure. The molecular mechanisms whereby BAs accumulation induces hepatocyte damage are not completely understood. Previous results reported that primary mouse hepatocytes (PMH) were resistant to a mix of BAs mimicking the induction seen in bile duct ligation (BDL) model, leading to the proposal that they are act as inflammagens and not as cytotoxic mediators in CLD. As CLD also leads to cholesterol accumulation, we hypothesize that cholesterol trafficking to mitochondria can deplete mitochondrial GSH (mGSH), which could sensitize PMH to BAs. Thus, our aim was to determine the role of mGSH in BAs-mediated cytotoxicity. **Methods:** Mice were subjected to BDL for 14 days to determine mGSH levels, mitochondrial cholesterol trafficking and BAs profile by mass spectrometry. PMH were treated with 3-hydroxy-4-pentenoate (HP), which is biotransformed in a Michael acceptor by 3-hydroxybutanoate dehydrogenase followed by its conjugation with GSH in mitochondrial matrix. HP-treated PMH were challenged with a mix of BAs mimicking the profile seen in BDL to determine cell viability by Sytox Green, inflammatory gene expression and DNA damage by comet assay. **Results:** BDL induced the depletion of GSH both in total homogenate (42%) and in mitochondrial fraction (59%) in parallel with a marked increase in mitochondrial cholesterol (3 fold). BDL increased by about 100-fold the total liver BAs pool, particularly reflected in the increase in TCA, bMCA and TbMCA. To address the specific role of mGSH in BAs hepatotoxcity, PMH were preincubated with HP to deplete mGSH and then challenged with the BAs mix mimicking the profile seen in BDL. HP depleted mGSH levels by 60-74% and BAs mix induced a significant decrease in cell viability (45-62%) compared to control PMH. Furthermore, HP-pretreated PMH exhibited a parallel increased expression of *Il-1b*,

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Il6, Ly6c and *Icam-1*. Similar results were observed when HP-pretreated PMH were challenged with GCDCA, leading to increased cell death compared to control PMH. Moreover, comet assays indicated that HP sensitized PMH to bMCA+TCA induced DNA damage. **Conclusion:** Thus, cholesterol-dependent mGSH depletion unmasks the sensitivity of hepatocytes to BAs-induced hepatotoxicity, inflammation and DNA damage, emerging as a key player in CLD.

Disclosures: Laura Fàbrega: Nothing to Disclose, Laura Conde de la Ros: Nothing to Disclose, Susana Nuñez: Nothing to Disclose, Carmen Garcia-Ruiz: Nothing to Disclose

4008 | REGENERATION OF BILE DUCT BY REPLACING ARTIFICIAL BILE DUCT MADE OF GELATINE HYDROGEL NONWOVEN FABRIC (GHNF) IN PIG

Daichi Nakamura[1] Takahiro Nishio[1] Yusuke Uemoto[2] Kojiro Taura[1] Yukinori Koyama[3] Etsuro Hatano[1] Motohiko Satou[1] Yuuichi Takamatsu[1] Makoto Kurimoto[1] Keisuke Okura[1] Shuhei kanda[1] Rei Toda[1]

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Background: Cholangectomy is necessary for conditions such as biliary tract cancer, bile duct injury during cholecystectomy, benign biliary stricture, refractory common bile duct lithiasis, and common bile duct cysts. Current reconstruction methods, like bile duct jejunal anastomosis, are complex and prone to complications. Artificial bile ducts made from gelatin, known for its biocompatibility and degradability, have been explored as a potential solution. Initial experiments with gelatin hydrogel nonwoven fabric (GHNF) in rats showed promising results in promoting cell infiltration and bile duct regeneration. This study extends the evaluation of GHNF-based artificial bile ducts to pigs. **Methods:** Nine pigs underwent replacement surgery of their bile ducts with artificial bile ducts made of GHNF. The common bile duct was cut, and a tube made of polyglycolic acid (PGA) was inserted and sutured into place. The PGA tube was then wrapped with GHNF sheets. Post-surgery, the pigs were monitored, and their bile ducts were evaluated through contrast fluoroscopy to assess function. Histological examinations, including hematoxylin and eosin staining, Sirius red staining, and immunohistochemistry with Cytokeratin 19, were conducted to confirm bile duct epithelial regeneration. **Results:** In case 8, the artificial bile duct consisted of a 2-layer structure: an inner PGA knit layer sutured to the bile duct transection and an outer GHNF sheet. A 5 Fr stent was placed through the lumen. Postoperatively, the pig's T-bil levels were elevated until day 13 but normalized thereafter. AST, ALT, and LDH levels were initially high but decreased over time. At 105 days post-surgery, the pig was sacrificed to evaluate bile duct regeneration. Fluoroscopy confirmed that the contrast agent flowed through the reconstructed bile duct to the intrahepatic bile ducts. The artificial bile duct and the normal bile duct were smoothly connected. Histological examination showed that the artificial bile duct was continuous with the normal bile duct, with the presence of CK19-positive bile duct epithelium indicating successful regeneration. The regenerated bile duct epithelium in the artificial bile duct area was structurally similar to the normal bile duct. **Conclusion:** The study demonstrated that GHNF-based artificial bile ducts could effectively promote bile duct regeneration in pigs, showing high biocompatibility and excellent cell adhesion properties. Further studies are needed to refine these materials and techniques for clinical applications.

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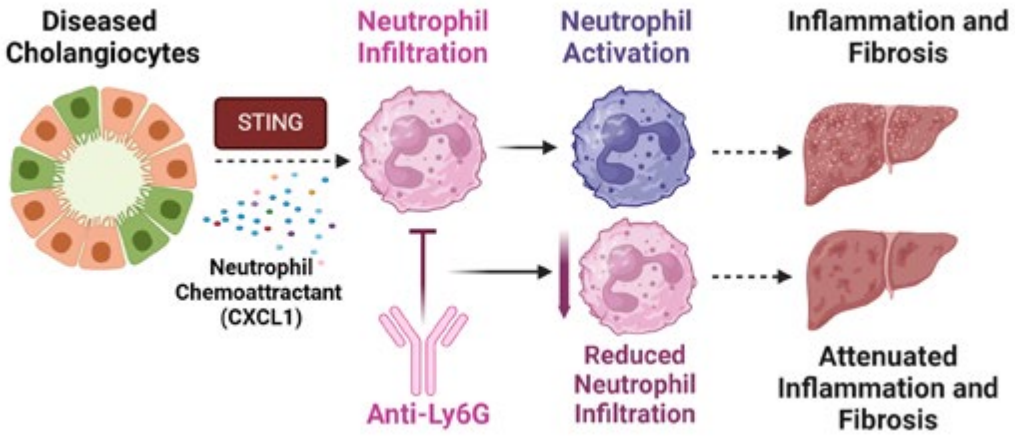
4009 | REDUCING NEUTROPHIL INFILTRATION IS PROTECTIVE IN PRIMARY SCLEROSING CHOLANGITIS

Sofia Jerez[1] Abid Anwar[1] Kaitlin Friesland[1] Maleeha Farheen Kalaiger[1] Usman Yaqoob[1] Vijay Shah[2] Robert Huebert[2] Nidhi Jalan-Sakrikar[2]

[1]Mayo Clinic, [2]Mayo Clinic Rochester

Background: Primary Sclerosing Cholangitis (PSC) manifests with an inflammatory milieu that can contribute to fibrotic scarring of the liver. Human PSC bile ducts are enriched with myeloid cells suggesting a role for the innate immune system, which has not been rigorously explored. The stimulator of interferon genes (STING) signaling pathway regulates the innate immune responses via the release of cytokines, including neutrophil chemoattractants. We aim to investigate the mechanism and impact of peribiliary neutrophil infiltration observed in PSC. **Methods:** Primary cholangiocytes isolated from WT and mouse models of PSC (3,5-Diethoxycarbonyl-1,4-Dihydrocollidine (DDC)-fed mice and Mdr2-/- mice) were analyzed by RNA-sequencing. Intrahepatic leukocytes (IHL) isolated from WT and Mdr2-/- were evaluated for neutrophil abundance and activation state by flow cytometry and RT-PCR. Anti-Ly6G antibody mediated neutrophil depletion in Mdr2-/- mice was analyzed by immunofluorescence (IF), histology, and cytometry by time-of-flight (CyTOF). Cholangiocytes stimulated with LPS (to induce an inflammatory phenotype) were analyzed for neutrophil chemoattractants upon genetic and pharmacological inhibition of STING. **Results:** RNA-seq analysis of primary cholangiocytes from PSC mouse models demonstrated enrichment in inflammatory and neutrophil degranulation pathways. Congruently, flow cytometry analysis on $CD45^+$ IHL revealed an increase in the neutrophil population ($Ly6^+$ $Cd11b^+$) in Mdr2-/- mice compared to WT (8.7% vs 2.5%, FC=3.48, *p<0.0001*). These neutrophils displayed an activated phenotype with increased expression of Cxcr1 and Cxcr2. Correspondingly, anti-Ly6G-mediated peripheral depletion of neutrophils in Mdr2-/- mice alleviated liver injury and inflammation (57.6% and 59.2% reduction in ALT and AST, respectively). IF and histology revealed a substantial reduction in peribiliary neutrophil infiltration and reduced bridging fibrosis in neutrophil-depleted Mdr2-/- mice livers. Interestingly, CyTOF analysis of IHL revealed a significant reduction in CD8+ T cells upon neutrophil depletion, implying a role for neutrophils in attracting CD8+ T cells to the liver. Mechanistically, the LPS-mediated increase in neutrophil chemoattractant, CXCL1, in cholangiocytes was abrogated with both pharmacological and genetic inhibition of STING. **Conclusion:** Our findings suggest that activation of the STING pathway in cholangiocytes in cholestatic liver disease triggers an immune response resulting in peri-portal neutrophil infiltration. The sustained presence of these activated neutrophils engages the adaptive immune system to perpetuate the inflammation and fibrosis seen in PSC.



Disclosures: Sofia Jerez: Nothing to Disclose, Abid Anwar: Nothing to Disclose, Kaitlin Friesland: Nothing to Disclose, Maleeha Farheen Kalaiger: Nothing to Disclose, Usman Yaqoob: Nothing to Disclose, Vijay Shah: Boehringer Ingelheim: Consultant, GSK: Consultant, GENFIT SA: Consultant, Intercept Pharmaceuticals, Inc.: Advisor, Korro Bio, Inc.: Consultant, Mallinckrodt Pharmaceuticals: Advisor, Novo Nordisk A/S: Consultant, Resolution Therapeutics, Ltd.: Advisor, Seal Rock Therapeutics, Ltd.: Consultant, Surrozen: Advisor, Robert Huebert: Nothing to Disclose, Nidhi Jalan-Sakrikar: Nothing to Disclose

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4010 | ALTERED EXPRESSION OF TIGHT JUNCTION PROTEINS CLAUDIN 2 AND 3 PROTECTS THE LIVER FROM CHOLESTATIC INJURY

James Boyer[1] Nikolai Arefyev[1] Scott Roberts[1] Mingqiao Li[2] Jin Chai[2] Alan Yu[3] David Assis[1] Yasuko Iwakiri[1] James Boyer[1]

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Background: Tight junctions (TJ) between hepatocytes and cholangiocytes are the only barrier between blood and bile. Claudin (Cldn) 2 and 3 are the two major TJ barrier proteins in the liver. Cldn3 is expressed throughout the hepatic lobule and bile ducts while Cldn2 expression is limited to pericentral zone 3 hepatocytes. Both Cldn 2 and 3 play an important role in bile formation as Cldn2 is a water pore while Cldn3 prevents leakage of bile acids from the bile lumen. Cldn2-/- mice produce less bile but have normal bile acid excretion while Cldn3-/- mice have increases in bile flow and efflux bile acids into blood. Whether Cldn2 and 3 play a role in the pathogenesis of cholestasis is unknown. The aim of this study is to determine whether Cldn2 and Cldn3 undergo an adaptive regulation in murine and human cholestasis and if these alterations are functionally significant. **Methods:** 7-day bile duct ligation in WT, Cldn2-/- and Mdr2-/- mice were studied. Protein and mRNA expression was determined by Western blot and Q-PCR, respectively. Liver sections were analyzed by H&E, Sirius Red staining and immunofluorescent (IF) labeling. Human liver specimens were obtained from patients with obstructive cholestasis, PBC, and PSC and assessed for CLDN2 and 3 expression. **Results:** Cldn2 mRNA and protein expression were significantly increased in the livers from 7-day BDL mice and Mdr2-/- mice, while IF staining increased in zone 2 and 3 and intrahepatic bile ducts compared with sham-operated mice. In contrast, Cldn3 protein expression was significantly decreased in both BDL and Mdr2-/- livers, while IF labeling decreased in zone 3 and intrahepatic bile ducts in 7-day BDL livers. Furthermore, ALT significantly increased in Cldn2-/- mice after 7-day BDL compared to WT BDL mice and more necrosis was also seen in Cldn2-/- liver sections. Analysis of human liver specimen from patients with common bile duct obstruction, PBC and PSC revealed a significant increase of CLDN2 and decrease of CLDN3 expression. **Conclusion:** Tight junction proteins Cldn2 and Cldn3 undergo adaptive regulation in cholestatic murine and human livers, significantly reducing liver injury in mice models. Upregulation of Cldn2 increases water movement into bile while downregulation of Cldn3 reduces hepatic tissue levels of bile acids. Pharmacological manipulations of Cldn2 and Cldn3 expression is a novel strategy to treat cholestasis.

Disclosures: James Boyer: IPSEN: Clinical Evenets Committee for clinical trial, Nikolai Arefyev: Nothing to Disclose, Scott Roberts: Nothing to Disclose, Mingqiao Li: Nothing to Disclose, Jin Chai: Nothing to Disclose, Alan Yu: Janssen: Consultant, Regulus Therapeutics: Consultant, Calico Biosciences: Consultant, Sarepta: Consultant, Amgen: Stock - publicly traded company, CVS: Stock - publicly traded company, Gilead: Stock - publicly traded company, Gilead: Stock - publicly traded company, Ionic: Stock - publicly traded company, Pfizer: Stock - publicly traded company, Vertex: Stock - publicly traded company, David Assis: Nothing to Disclose, Yasuko Iwakiri: Nothing to Disclose, James Boyer: Mirum Pharmaceuticals: grant recipient

4011 | THALAMIC VOLUME REDUCTION AND NEURAL CIRCUIT ALTERATIONS IN CHOLESTATIC MICE PARALLEL CHANGES IN PATIENTS WITH PRIMARY BILIARY CHOLANGITIS

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Background: Fatigue is a common symptom in patients with the cholestatic liver disease (CLD) primary biliary cholangitis (PBC). We recently described decreased thalamic size and altered neural connectivity in PBC patients using functional MRI; changes associated with fatigue severity [PMID: 30735529]. Therefore, we used a mouse model to examine the impact of CLD on thalamic volume and associated changes in thalamic neurotransmitter gene expression signatures. **Methods:** Male C57BL/6 mice (Jackson; 10 wks) had either bile duct ligation (BDL; to induce CLD) or sham surgery. Ten days post-surgery mice underwent brain MRI (9.4T; Bruker cryoprobe). In additional mice, thalamic gene expression signatures were evaluated using mRNA-seq and data analyzed

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using Ingenuity Pathway Analysis software (IPA; Qiagen). Key gene expression changes in RNA-Seq data were validated using real-time PCR (PCR). **Results:** Thalamic volume was reduced by 4.33% ($p \leq 0.0008$; n=10mice/grp) in BDL vs sham mice (Fig. 1) in conjunction with significantly reduced neurotrophin gene expression with a 6.6-fold decrease in MKI67 (Ki67, cell proliferation marker; $p \leq <0.0001$) and a 1.9-fold decrease in BDNF (Brain-Derived Neurotrophic Factor; $p \leq 0.0001$) in BDL vs sham mice. These changes were associated with altered thalamic neurotransmitter pathway gene expression profiles, including the *Glutaminergic Receptor Signaling Pathway* (z score = -3.73, B-H p-value $\leq 1.23 \times 10^{-10}$) and *GABAergic Receptor Signaling Pathway* (z score = 0.143, B-H p-value $\leq 9.77 \times 10^{-7}$); main brain excitatory and inhibitory neurotransmitter systems, respectively. Neurotransmitter gene expression changes were confirmed by PCR (e.g., *glutamate receptor Grin2b*, 1.83-fold decrease, $p \leq 0.0007$; *glutamate transporter SLC1A1*, 1.50-fold decrease, $p \leq 0.012$; *GABA receptor Gabra1*, 1.44-fold decrease, $p \leq 0.0024$; *GABA receptor Gabra2*, 1.77-fold decrease, $p \leq 0.0002$; *GABA receptor subunit rho-2*, 5.4-fold increase, $p \leq 0.0082$)(n=6 mice/grp). In addition, BDL mice exhibited a specific gene expression profile indicating microglia activation (i.e., 5.0-fold decrease in *P2Y12 receptor* gene expression, $p \leq 0.0001$; 1.57-fold decrease in *TMEM119* gene expression, $p \leq 0.0026$) and a 137-fold increase in gene expression for the key neuroinflammation-regulating protein, lipocalin 2 ($p \leq 0.0116$). **Conclusion:** Mice with CLD exhibit reduced thalamic volume and neurotrophin gene expression paralleled by altered excitatory/inhibitory neurotransmission and neuroinflammation gene expression signatures, findings congruent with observations in PBC patients. Therefore, the BDL model could serve as a valuable tool to investigate pathophysiological mechanisms driving thalamic changes in CLD's that lead to altered behaviors, including fatigue.

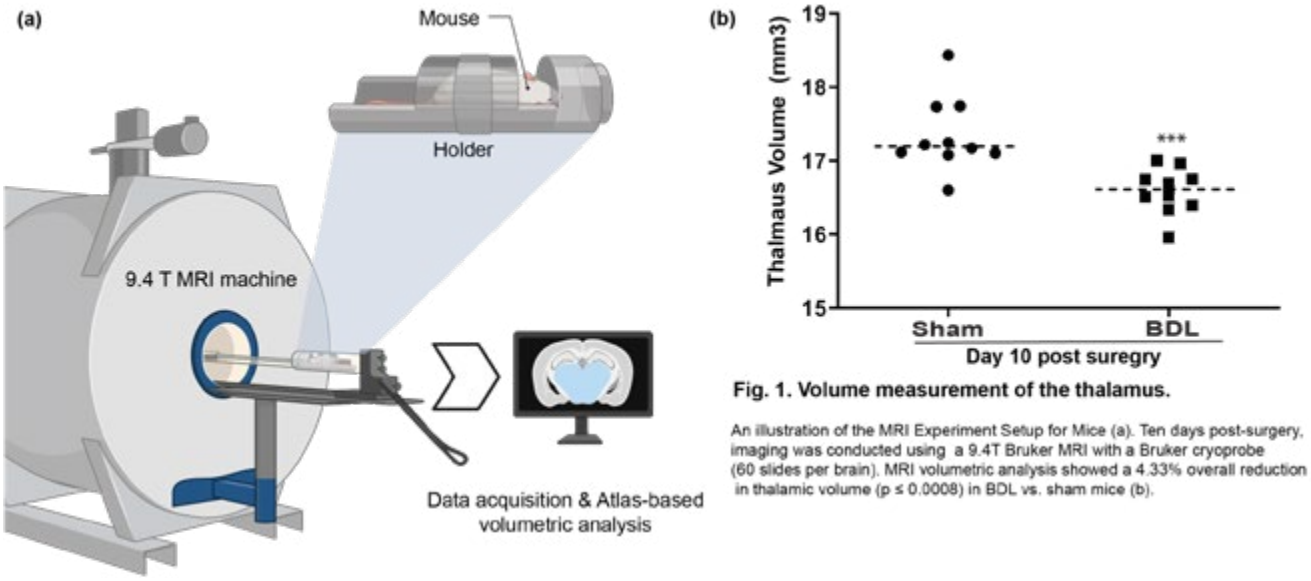

Fig. 1. Volume measurement of the thalamus.

An illustration of the MRI Experiment Setup for Mice (a). Ten days post-surgery, imaging was conducted using a 9.4T Bruker MRI with a Bruker cryoprobe (60 slides per brain). MRI volumetric analysis showed a 4.33% overall reduction in thalamic volume ($p \leq 0.0008$) in BDL vs. sham mice (b).

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4012 | ARAMCHOL, A STEAROYL-COA DESATURASE INHIBITOR, ATTENUATES THE TGFβ-STIMULATED FIBROINFLAMMATORY SIGNALS IN CHOLANGIOCYTE MODELS OF PRIMARY SCLEROSING CHOLANGITIS

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Background: Primary sclerosing cholangitis (PSC) is characterized by biliary fibrosis and inflammation, driving disease-related complications. In biliary fibrosis, cholangiocytes activated by transforming growth factor-β (TGFβ) communicate with immune cells and activate hepatic myofibroblasts to deposit the extracellular matrix. However, the mechanisms of TGFβ regulation of cholangiocyte lipid signaling milieu have not been fully investigated. TGFβ may regulate stearoyl-CoA desaturase (SCD), which catalyzes the synthesis of monounsaturated fatty acids, in stimulating fibroinflammatory lipid signaling. **Methods:** Transformed human cholangiocyte cells (H69) and mouse large biliary epithelial cells (MLEs) were used to test the effects of the SCD inhibitor, Aramchol, at varying doses on TGFβ-mediated expression of fibroinflammatory signals and confirmed in PSC-derived cholangiocytes (PSC-Cs) using ELISA, qPCR and Western blot analyses. Untargeted lipidomics was performed using high-performance liquid chromatography tandem mass spectrometry. **Results:** SCD mRNA is significantly increased in TGFβ-treated H69 cells (2-fold, $p<0.05$). Aramchol in a dose-dependent manner significantly attenuated the increased expression of the fibrotic marker, plasminogen activator inhibitor-1 (PAI-1/SERPINE1) and hepatic stellate cell-activating, vascular endothelial growth factor A (VEGFA) in TGFβ-activated H69 and MLEs (62% and 54% respectively, $p<0.05$). Aramchol also markedly reduced the expression of the inflammatory cytokine, interleukin 6 (IL6) (46%, $p<0.05$). SCD siRNA knockdown produced similar results in H69 cells. Furthermore, in PSC-Cs, the basal expression of SCD, VEGFA and IL6 were significantly reduced with Aramchol (43%, 73% and 53%, $p<0.05$). The expression of the anti-fibroinflammatory factor, peroxisome proliferator-activated receptor (PPAR)-γ was modestly increased in MLEs along with increased expression of PPARγ-responsive genes and increased nuclear PPARγ binding of its DNA PPAR response elements with Aramchol cotreatment compared to TGFβ only. Untargeted lipidomic analysis of TGFβ-stimulated H69 cells yielded significant changes in multiple lipid species (fold change ≥ 2, p-value <0.05) requiring further investigation to identify signaling pathways. **Conclusion:** Aramchol, an SCD inhibitor, attenuates the TGFβ-stimulated activation of the fibroinflammatory response in cholangiocytes partly through activating PPARγ. These findings warrant further investigation in PSC including *in vivo* models.

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4013 | ALCOHOL CONSUMPTION IN MICE LACKING THE BILE ACID RECEPTOR TGR5

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Background: Benign hepatic steatosis can progress to serious liver disease. In the liver, bile acids are made from cholesterol and aid in nutrient absorption. They also regulate hepatic metabolism by binding to receptors like Takeda G protein-coupled receptor 5 (Tgr5) expressed in the liver, gut, adipose, and brain. Our previous research indicated that $Tgr5^{-/-}$ mice had altered fibroblast growth factor 21 signaling which may have protected them from alcohol-induced liver damage. This hormone suppresses alcohol consumption, therefore we aimed to determine whether Tgr5 plays a role in alcohol consumption. **Methods:** Female C57BL/6J wild type mice (WT) and $Tgr5^{-/-}$ mice were fed a high fat (40% kcal), high fructose diet (HFS) plus 10% ethanol in drinking water for 20 weeks. Separate cohorts of mice were subjected to a 2-bottle choice paradigm to determine ethanol consumption (10% v/v in water) and preference with oral gavage of the specific Tgr5 agonist BAR-501 (30 mg/kg/day) for two weeks. Metabolic phenotypes were characterized through examination of bile acid metabolism in

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the liver and Fgf21-mediated feedback pathways in liver, adipose tissue, and brain. **Results:** Body weight and food intake were similar between WT and Tgr5$^{-/-}$ mice; however, Tgr5$^{-/-}$ mice consumed less ethanol than WT mice. This likely contributed to the reduced body fat and greater lean mass in Tgr5$^{-/-}$ mice after 20 weeks HFS + ethanol. Tgr5$^{-/-}$ mice given ethanol also had reduced liver enzymes, reduced serum free fatty acids, and reduced Sirius red-positive staining in liver. *Cyp7a1* mRNA expression was significantly reduced by ethanol consumption in all mice, indicating alcohol disrupts the hepatobiliary system. To determine a reduced preference for ethanol, mice were subjected to a two-bottle choice protocol. Tgr5$^{-/-}$ mice drank less ethanol without a change in water consumption, and this was accompanied with elevated *Fgf21* expression in liver. mRNA expression of glucose transport genes, TCA cycle genes, and leptin homeostasis were significantly reduced in hypothalamus of Tgr5$^{-/-}$ mice drinking ethanol. Lastly, the administration of the Tgr5 agonist BAR-501 for two weeks increased voluntary ethanol consumption in WT mice. Taken together, these data indicate a potential role for Tgr5 in the gut-brain crosstalk that controls alcohol consumption. **Conclusion:** Tgr5 may regulate ethanol consumption and its use as a metabolic fuel.

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4014 | THE INVOLVEMENT OF LECT2 IN THE FIBROSIS MECHANISM OF PRIMARY SCLEROSING CHOLANGITIS

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Background: Primary sclerosing cholangitis (PSC) shows onion-skin fibrosis around the bile duct (basolateral side), but the pathological mechanism has not been elucidated. LECT2 is a multifunctional protein produced mainly by hepatocytes, and it has been reported to be associated with liver fibrosis formation. We establish an in vitro experimental system that allowed separation of the apical side/ basolateral side by culturing H69 on an insert in a cell culture plate and adding bile acid stimulation to the insert, and reproduced the chronic bile acid exposure environment. Proteomic analysis of the basolateral EVs in the bottom of the insert confirmed that the fibrosis-inducing protein LECT2 contained in the basolateral EVs of the bile acid-stimulated group. In this study, we investigate the possibility that the bile acid-stimulated basolateral EVs and the contained protein LECT2 are involved in onion-skin fibrosis pathology specific to PSC by acting on fibrosis-related cells around the bile duct. **Methods:** The inserts were divided into a bile acid-stimulated group, in which bile acids were added to the inserts, and a non-stimulated group. The culture medium corresponding to the basolateral side of the lower part of the inserts was collected, and EVs were extracted by ultracentrifugation. The basolateral EVs of the bile acid-stimulated group and the basolateral EVs of the non-stimulated group were added to fibrosis-related cells, human hepatic stellate cells LX-2 and human fibroblasts KMST-6, and the expression of fibrosis markers (TGF-β, PDGF, ACTA2, COL1A1) was examined. In addition, LX-2 and KMST-6 were stimulated with LECT2, and the expression of fibrosis markers was examined by RT-PCR. Furthermore, immunostaining of LECT2 was performed on liver biopsy samples of PSC, and the expression of LECT2 in bile duct epithelial cells was examined. **Results:** In the stimulation of the basolateral EVs in the bile acid-stimulated group, the expression of TGF-β and COL1A1 was significantly increased in LX-2 compared to the stimulation of the basolateral EVs in the control group. In KMST-6, the expression of TGF-β and ACTA2 was significantly increased compared to the stimulation of the basolateral EVs in the control group. In the bile acid-stimulated group, the expression of the apical EVs did not increase significantly compared to the stimulation of the apical EVs in the control group. In the stimulation of the recombinant human LECT2, the expression of TGF-β, ACTA2, and COL1A1 was significantly increased in LX-2, and the expression of TGF-β, PDGF, ACTA2, and COL1A1 was significantly increased in KMST-6. Immunostaining for LECT2 confirmed that the expression of LECT2 increased in bile duct epithelial cells and fibrosis-related cells around the bile duct. **Conclusion:** In the bile acid-stimulated group, the basolateral EVs and the EV-containing protein LECT2 activated fibrosis-related cells (LX-2, KMST-6). Immunostaining confirmed thatthe expression of LECT2 increased in bile duct epithelial cells and fibrosis-related cells around the bile duct. It was suggested that the expression of LECT2 in EVs-containing proteins on the basolateral side of bile duct epithelial cells increased under bile acid exposure, and that LECT2 has the potential to be related to fibrosis formation of PSC.

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Disclosures: Keita Maki: Nothing to Disclose, Tomohiro Katsumi: Nothing to Disclose, Hiroaki Haga: Nothing to Disclose, Kyoko Hoshikawa: Nothing to Disclose, Fumiya Suzuki: Nothing to Disclose, Fumi Uchiyama: Nothing to Disclose, Yoshiyuki Ueno: Nothing to Disclose

4015 | AGMB-101, A FULL AGONISTIC ANTIBODY OF MET, ACHIEVES DEEP SUPPRESSION OF CHOLESTATIC DISEASE IN MDR2 KO MICE THROUGH A PLEIOTROPIC MECHANISM OF ACTION

Virginia Morello[1] Damiana Sattanino[1] Manuela Cazzanti[1] Luca Rossi[1] Aniko Meijer[2] Caroline Meers[1] Torsten Dreier[1] Maarten Van Roy[1] Reginald Brys[1] Paolo Michieli[1]

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Background: Primary sclerosing cholangitis (PSC) is a severe cholestatic liver disease characterized by persistent inflammation and fibrosis of the bile ducts. In view of its pleiotropic activities in liver, the therapeutic potential of an agonistic antibody of the HGF/MET pathway was tested in the mouse Mdr2 KO model for PSC. **Methods:** The signalling induced by AGMB-101, a MET agonistic antibody, was characterized in human and mouse primary hepatocytes using ELISAs for MET, ERK and AKT phosphorylation. 8-week-old male Mdr2 KO mice received 3 s.c. AGMB-101 injections (0.3 and 3 mg/kg, QW). Serum parameters reflecting cholestasis and liver damage were measured on samples collected 48h after the last injection. Differential gene expression analysis of RNAseq data generated from liver was performed to assess the impact of AGMB-101 on disease. **Results:** Characterization of AGMB-101-induced signalling in human and mouse primary hepatocytes revealed activation of the same core pathways as HGF across species, with MET, ERK and AKT phosphorylation induced (EC50s of 0.13, 0.05 and 0.03 nM, respectively (human) and 0.34, 0.11, 0.15 nM, respectively (mouse)). AGMB-101 effectively attenuated disease in the Mdr2 KO model already at a dose of 0.3 mg/kg. Serum markers related to cholestasis (ALP, bile acids) and liver damage (ALT, AST) were markedly reduced compared to vehicle-treated mice. AGMB-101 also increased albumin levels reflecting liver protective and regenerative effects. In a longer version of the Mdr2 KO model, AGMB-101 also showed reduction of tissue fibrosis (histology, collagen content). Liver transcriptomic profiling revealed strong impact on disease, with expression of 62% of disease-induced genes reversed by AGMB-101. MET agonism reduced the expression of genes related to inflammation, fibrosis and bile acid synthesis/response. **Conclusion:** Profiling of AGMB-101 in human and mouse primary hepatocytes confirmed potent, HGF-like signalling across species. Treatment of Mdr2 KO mice with the MET agonist at low dose induced strong suppression of disease, as revealed by serum markers and a reversal of the overall liver disease signature. Liver transcriptomic profiling revealed the pleiotropic mechanisms underlying efficacy. Overall, these data support the clinical evaluation of AGMB-101 in advanced liver disease.

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4016 | INCREASED INCIDENCE OF RECTAL PROLAPSE IN FGF15 TRANSGENIC MICE IS CAUSED BY CHRONIC DIARRHEA AND ELECTROLYTE IMBALANCE

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Background: Fibroblast growth factor (FGF) 15 (human homolog, FGF19) is highly expressed in the small intestine, and acts as an endocrine hormone to regulate bile acid homeostasis. Our previous studies demonstrated that overexpression of FGF15 in both liver and intestine promotes liver regeneration in mice directly through activating Fibroblast Growth Factor Receptor 4 (FGFR4), and indirectly by reducing bile acid (BA) toxicity after partial hepatectomy. Moreover, a high incidence of rectal prolapse was observed in these FGF15 transgenic mice. However, the etiology is unclear. A variety of factors including weakness of sphincters, chronic diarrhea and constipation, intestinal inflammation and colitis, and pathogenic bacteria are suggested to be involved in the development of rectal prolapse. **Methods:** Group-housed wild-type (WT), FGF15 transgene

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mice with (Tg-prolapse) and without rectal prolapse (Tg) from the same cage were selected for the study. Intestine and colon tissues were collected. Histology and immunohistochemistry were performed by standard procedures. Transcriptome in both intestine and colon was analyzed by RNA sequencing and further confirmed by quantitative real-time PCR. **Results:** Compared to WT, morphological abnormalities of tissue architecture including intestinal and colonic dilation and enteric crypts alterations were observed in Tg mice, which tended to be worse in Tg-prolapse mice. H&E staining showed muscle thickness was reduced in both Tg and Tg-prolapse mice compared to WT, which was further evident by the decreased expression levels of myosin related genes. However, no significant difference in inflammation was found between WT and Tg mice. Increased weight of wet feces was also observed in Tg mice, and relative expression levels of transporters involved in colonic electrolyte secretion and absorption were disturbed as well, indicating imbalance between luminal secretion and absorption of fluids and ions in the Tg mice. **Conclusion:** FGF15 overexpression in mice increased the incidence of rectal prolapse. BA and FGF15 related increase of chronic diarrhea and weakness of sphincter muscles, but not the inflammation might drive the disease progression. Imbalance between the secretion and absorption of water and salts contributes to the chronic diarrhea. However, the underline mechanisms need to be further investigated.

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4017 | PPARδ ACTIVATION WITH SELADELPAR REGULATES MULTIPLE INFLAMMATORY CHECKPOINTS IN THE HUMAN CHOLANGIOCYTE CELL LINE H69

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Background: In primary biliary cholangitis (PBC), cholangiocytes are considered key drivers of disease pathogenicity, amplifying bile duct injury signals and enhancing immune cell infiltration in the cholestatic liver. The phase 3 RESPONSE trial in PBC patients demonstrated that seladelpar, a novel delpar (selective PPARδ agonist) decreased cholestatic and liver injury markers including alkaline phosphatase, gamma-glutamyl transpeptidase and alanine aminotransferase, and downregulated expression of the pruritogenic cytokine, IL-31, with concomitant alleviation of pruritus. The activation of PPARδ alters the inflammatory phenotype of Kupffer cells and adipose tissue macrophages in mice. Here, we investigated the effect of seladelpar on key inflammatory transcription factors (TFs) and cytokines in the human cholangiocyte cell line H69. **Methods:** H69 cells were cultured under basal or inflammatory conditions with 10 ng/ml of IFN-γ, or TNF-α, in the presence or absence of 10 μM seladelpar. RNA levels of TFs including STATs, NF-κBs, and IRFs, and interferon stimulated genes (ISGs) were analyzed with qRT-PCR. Secreted cytokines in H69 cell culture supernatants were measured by Meso Scale Discovery assays. **Results:** IFN-γ treatment alone induced TFs from 1.7- to 7.6-fold, and ISGs from 6.7- to 45.5-fold (Table 1). The IFN-γ+TNF-α combined treatment further elevated mRNA levels of TFs, from 2.8- to 11.3-fold, and ISGs from 34.7- to 10861.9-fold. Consistent with the enhanced inflammation activation, greater cytokine levels of IL-6, IL-8, IL-1β, and IFN-β and IFN-λ1 were detected with the IFN-γ+TNF-α co-treatment, compared with IFN-γ alone. Importantly, seladelpar attenuated the IFN-γ-mediated up-regulation of STAT1, STAT2, and NFKB1 at mRNA levels. Likewise, seladelpar also significantly attenuated the IFN-γ+TNF-α -mediated up-regulation of STAT1, STAT2, NFKB1, RELA, IRF1 and IRF9 mRNA (Table 1). Furthermore, seladelpar significantly decreased the IFN-γ stimulated secreted IFN-β, and the IFN-γ+TNF-α stimulated secreted IFN-β and IFN-λ1 in H69 culture supernatants. The induction of ISGs including MX1, IFIT1, CCL5 and CXCL10 were also attenuated in the presence of seladelpar (Table 1). **Conclusion:** Seladelpar treatment decreased mRNA levels of inflammatory TFs and ISGs as well as the levels of key cytokines in the supernatants of cultured H69 cells. These results provide further evidence of the anti-inflammatory effects of seladelpar and are consistent with its therapeutic benefits in PBC.

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Table 1 Seladelpar attenuation of inflammatory genes and proteins

Genes/ Proteins	IFN-γ			IFN-γ + TNF-α		
	fold induction	seladelpar effect		fold induction	seladelpar effect	
		magnitude of attenuation	P< 0.05		magnitude of attenuation	P< 0.05
Transcription factors (TFs)						
STAT1	5.5	19%	yes	10.4	31%	yes
STAT2	4.9	27%	yes	9.7	43%	yes
NFKB1	2.3	18%	yes	5.3	37%	yes
RELA	1.7	10%	no	2.8	34%	yes
IRF1	7.6	-3%	no	11.3	32%	yes
IRF9	2.6	10%	no	4.9	39%	yes
Interferon-stimulated genes (ISGs)						
MX1	11.4	38%	yes	36.4	42%	yes
IFIT1	6.7	40%	yes	34.7	55%	yes
CCL5	13.6	60%	yes	47.3	38%	no
CXCL10	45.5	59%	yes	10861.9	61%	yes
Interferon proteins						
IFN-β	13.3	53%	yes	251.9	57%	yes
IFN-λ1	1.9	12%	no	23.5	15%	yes

Statistical analysis is based on two-tailed unpaired t test.

Disclosures: Xia Wu: CymaBay Therapeutics: Employee, Yen-Wen Chen: Nothing to Disclose, Jiangao Song: Nothing to Disclose, Edward Cable: CymaBay Therapetics: Employee, Jeffrey Johnson: CymaBay Therapeutics: Consultant, Joanne Elliott: Nothing to Disclose, Francisco Caballero-Camino: Nothing to Disclose, Xin Chen: Nothing to Disclose, Robert Martin: Nothing to Disclose, Jeffrey Stebbins: Nothing to Disclose, Jesus Banales: Nothing to Disclose, Charles McWherter: Nothing to Disclose

4018 | ABCB4/MDR2 HAPLOINSUFFICIENCY PREDISPOSES MICE TO BILIARY INJURY AND SECONDARY CHOLESTASIS AND DEFINES A TRANSLATIONAL MODEL OF TOXIC BILE INDUCED HEPATOBILIARY INJURY IN HUMAN CHOLANGIOPATHY

Eric Bell Jennifer Truong[1] Youhwa Jo[1] Bharat Reddy[1] Adrianne Kolpak[1] John Miller[1] Robert Hughes[1] Alastair Garfield[1]

[1]Rectify

Background: Bile composition is tightly controlled to buffer the toxicity of monomeric bile acids (BA) within bile ducts, preventing biliary system injury and the development of cholangiopathies and cholestatic disease. The Mdr2 KO mouse, a genetic model of PFIC3, has altered bile composition and serves as a model of toxic bile induced bile duct injury with sclerosing cholangitis. In rare hepatobiliary diseases like PSC, a two-hit hypothesis has been proposed, suggesting that the presence of a first hit genetic variant sensitizes the system to injury from a second environmental hit, thereby promoting development of hepatobiliary disease. To generate a more clinically relevant model for BA induced bile duct damage to support drug discovery and translational research, we generated a two-hit model utilizing the toxic bile of the Mdr2 heterozygous mouse. **Methods:** Eight- to ten-week-old female wild-type (WT) and heterozygous (HET) Abcb4 FVB/J littermates were provided lithogenic diet containing 15% fat, 1.25% cholesterol, and 0.5% cholic acid for 1- 4 and 6 weeks prior to takedown. The animals were analyzed for changes in peripheral markers of liver function, endpoints related to cholestasis, and for the development of biliary injury, cholangitis, and fibrosis. **Results:** Abcb4 HET mice are preferentially susceptible to diet induced liver injury as early as one week on diet. WT animals did not present with any phenotype. Clinically relevant hepatotoxic markers ALT, AST, and TBIL are all increased in HET mice compared with WT mice. Moreover, HET animals displayed changes in clinically relevant cholestatic endpoints sTBA and ALP compared to WT littermates. Liver gene expression demonstrated increased levels of inflammation and fibrosis, which was

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corroborated by histology. Finally, HET animals presented with hepatomegaly, as well as increased incidence of calculi formation in the gallbladder. **Conclusion:** Haploinsufficiency of the canalicular transporter Abcb4 sensitizes animals to diet induced injury, phenocopying Mdr2 KO mice on normal diet. The lack of phenotype in WT animals supports the notion that toxic bile composition contributes to cholangitis and cholestasis seen in a number of hepatobiliary diseases. Thus, this model serves as a useful tool for testing therapeutics impacting bile composition for the treatment of hepatobiliary diseases like PSC.

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4019 | HEPATOBILIARY-RESTRICTED *DCDC2* DELETION SERVES AS A GENETIC MOUSE MODEL OF CHOLANGIOPATHY AND RAPIDLY PROGRESSIVE LIVER FIBROSIS

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Background: Neonatal sclerosing cholangitis is a rare pediatric liver disease that manifests liver fibrosis. The ciliary gene doublecortin domain-containing 2 (*DCDC2*), which functions to stabilize the ciliary axoneme, has been implicated in disease pathogenesis. However, the relationship between *Dcdc2* and liver fibrosis is not known. We aim to investigate the role of the ciliary gene *Dcdc2* in liver fibrosis development. **Methods:** *Dcdc2*-knockout mice (C57/BL6 background) were generated with either loxP sites flanking exon 2 (*Dcdc2*$^{fl/+}$) or deletion of exon 2 (*Dcdc2*$^{+/-}$). *Dcdc2*$^{fl/fl}$ mice were crossed with *Albumin-Cre* (*Alb-Cre*) mice to generate mice with prenatal hepatobiliary-specific homozygous deletion (*Dcdc2*$^{fl/fl}$*; Alb-Cre)*. Phenotypic and histological analysis of hepatobiliary tissue from knockouts and controls (ctrl, *Dcdc2*$^{fl/fl}$ or wildtype mice) were performed during the neonatal period (p7-10) and at weaning (P28). Age-matched males and females were used in our analysis. **Results:** Liver appearance, liver histology, and serum chemistries were normal in heterozygous *Dcdc2*-knockout mice (*Dcdc2*$^{+/-}$ and *Dcdc2*$^{fl/+}$*;Alb-Cre* mice), which lacked a discernible phenotype. Homozygous whole-body deletion (*Dcdc2*$^{-/-}$) resulted in embryonic lethality. *Dcdc2*$^{fl/fl}$*;Alb-Cre* serum chemistries were notable for significantly increased AST (354.6 v. ctrl 147.8 (*p<0.05*)), ALT (123.4 v. ctrl 40 (*p<0.05*)), and total bilirubin (1.25 v. ctrl 0.3 (*p<0.01*)). Extrahepatic bile ducts from *Dcdc2*$^{fl/fl}$*;Alb-Cre* mice were patent on histological evaluation. Notably, livers from *Dcdc2*$^{fl/fl}$*;Alb-Cre* mice were visibly fibrotic with a nodular surface. *Dcdc2*$^{fl/fl}$*;Alb-Cre* livers demonstrated ductular plate malformation at portal tracts and significantly increased proliferation (45.54.8 v. ctrl 14.362.1 Ki67^{+} cells/hpf, *p<0.0001*). *Dcdc2*$^{fl/fl}$*;Alb-Cre* livers also exhibited significant periportal and bridging fibrosis (corrected fibrosis area 11.9% v. ctrl 1.4%, *p<0.0001*). Additionally, expression of the extracellular matrix remodeling genes *Mmp7* (26.04 v. ctrl 1.0 log fold change, *p<0.0001*) and *Mmp15* (4.74 v. ctrl 1.01 log fold change, *p<0.001*) was significantly increased. Finally, *Dcdc2*$^{fl/fl}$*;Alb-Cre* livers lacked primary cilia. **Conclusion:** *Dcdc*$^{fl/fl}$*;Alb-Cre* mice manifest cholestasis and exhibit early onset liver fibrosis with exceptionally rapid progression as evident by the nodularity and bridging fibrosis seen in the neonatal period and at the time of weaning. The important role of *Dcdc2* in cholangiocytes was evident by biliary dysmorphogenesis and ductal plate malformation seen in *Dcdc2*-knockouts. These data suggest that homozygous loss of *Dcdc2* is a driver of liver fibrosis and the mechanism(s) through which *Dcdc2* triggers liver fibrosis will be the focus of future studies.

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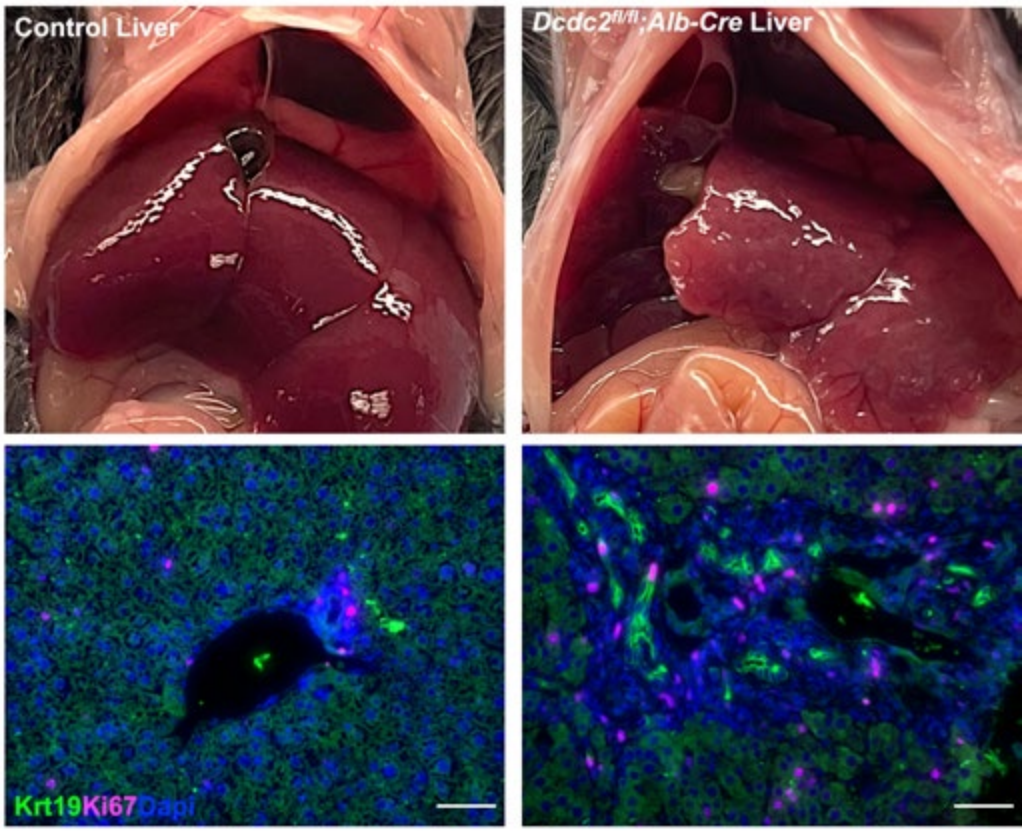

Disclosures: Natasha Corbitt: Nothing to Disclose, Yi Zou Lim: Nothing to Disclose

4020 | PROTECTIN DX EXERTS PROMISING ANTI-INFLAMMATORY, ANTIOXIDANT AND ANTI-FIBROTIC PROPERTIES IN LIVER CELLS

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Background: Primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC) are cholestatic autoimmune liver diseases (CALD) characterized by the accumulation of toxic bile acids (BA) in liver cells. These acids promote inflammation, fibrosis, cirrhosis, and ultimately liver failure, making their reduction an important pharmacological target for CALD treatment. Currently, ursodeoxycholic acid (UDCA) and obeticholic acid (OCA) are the only two drugs approved for the treatment of PBC, while no drugs are available for PSC. However, a significant proportion of PBC patients do not respond to or are intolerant to UDCA and/or OCA. Therefore, novel therapeutic options are urgently needed. The present study explores whether protectin DX (PDX), an omega-3 derivative with anti-inflammatory properties, can protect liver cells against BA accumulation and BA-induced inflammation, ER stress and fibrosis. **Methods:** HepG2 cells were treated with vehicle (0.01% Ethanol) and 5 µM PDX for 24H. To induce ER stress and fibrosis, HepG2 cells received the same treatments, with an additional 400 µM of toxic BA for 24H and 2 ng/mL of TGF-β for 72H, respectively. Finally, for inflammation, differentiated THP-1 cells were treated with 100 ng/mL of LPS, in addition to the previous treatments for 24H. Transcriptomic (qRT-PCR), proteomic (Western blot), or metabolomic targeted (LC-MS/MS) approaches were then employed to assess the effects of PDX. **Results:** In HepG2 cells, PDX exposure significantly reduced BA synthesis by inhibiting the CYP27A1 gene ($p<0.05$) and decreasing CDCA secretion ($p<0.05$). PDX also enhanced BA detoxification by increasing mRNA expression of the BA transporters OSTα and OSTβ ($p<0.001$) and the conjugating enzyme SULT2A1 ($p<0.001$). Additionally, PDX inhibited the: *i)* LPS-induced gene expression of the pro-inflammatory

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cytokines TNFα (p<0.001), MCP-1 (p<0.001), IL-6 (p<0.05), and IL-1β (p=0.0643) in THP-1 macrophages; *ii)* BA-induced expression of ER stress-related markers BIP (p<0.010) and CHOP (p=0.101) and TGF-β dependent stimulation of the fibrosis-related gene COL1A1 (p<0.001) mRNA in HepG2 cells. **Conclusion:** These findings suggest that PDX reduces hepatic BA levels and helps to mitigate inflammation, ER stress, and fibrosis in liver cells and macrophages. Given the role of BA buildup in the pathogenesis of PBC and PSC, PDX may provide a pharmacological option for these diseases. Further *in vivo* analyses are, however, required to validate this hypothesis.

Disclosures: Audrey-Anne Lavoie: Nothing to Disclose, Laurence Constantin: Nothing to Disclose, Mélanie Verreault: Nothing to Disclose, Jocelyn Trottier: Nothing to Disclose, René Maltais: Nothing to Disclose, Jean-Yves Sancéau: Nothing to Disclose, Donald Poirier: Nothing to Disclose, André Marette: Nothing to Disclose, Olivier Barbier: Nothing to Disclose

4021 | NOVEL ETIOLOGY FOR CHOLESTATIC CHOLANGIOPATHIES CAUSED BY MRP9 DEFICIENCY

Chunyue Yin[1] Akanksha Sharma[1] RAMESH KUDIRA[1] Bryan Donnelly[2] Annika Yang Vom Hofe[1] Hannah Nartker[2] Manavi Singh[2] Michelle Damen[2] Maria Moreno-Fernandez[2] Alexander Miethke[1]

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Background: Cholangiopathies, conditions characterized by cholangiocyte injury, are major contributors to liver diseases. One-third of patients with suspected inherited cholestasis, including many with cholangiopathies, lack pathogenic variants in known disease-causing genes, impeding the investigation into disease pathogenesis and the development of personalized treatments. We recently identified a biallelic frameshift variant in *ABCC12* in a patient with intrahepatic cholestasis and bile duct paucity. *ABCC12* encodes the ATP-binding cassette protein MRP9 with unknown function. Previous studies in zebrafish and mice indicated that MRP9 loss sensitizes cholangiocytes to bile acid-induced cell death, though the underlying mechanism is unclear. **Methods:** We applied three experimental models to study MRP9 function in cholangiocyte: *Abcc12* knockout zebrafish and mice, and human H69 cell line homozygous for the index patient variant. Immunofluorescent staining was performed to determine the subcellular localization of MRP9 in human cholangiocytes. Transcriptomes of cholangiocytes from adult wildtype and *abcc12-/-* mutant zebrafish were compared. Transmission electron microscopy was used to examine the ultrastructure of cholangiocytes from neonatal mice and larval zebrafish. Mitochondrial function in neonatal mouse cholangiocytes and H69 cells was assessed using the Seahorse assay. **Results:** MRP9 was localized close to the mitochondria in human cholangiocytes. Ultrastructural analysis of larval zebrafish and neonatal mice revealed mitochondrial damage in mutant cholangiocytes, but not in hepatocytes. The Seahorse assay indicated impaired mitochondrial energetic metabolism in MRP9-deficient mouse cholangiocytes and H69 cells. Transcriptomic analysis showed dysregulation of the porphyrin metabolism pathway, which is closely linked to mitochondrial function, in *abcc12-/-* zebrafish cholangiocytes. We observed ectopic accumulation of the heme intermediate protoporphyrin IX (PPIX) in the bile ducts of *abcc12-/-* larval zebrafish. Restoring wildtype MRP9 expression in cholangiocytes, but not in hepatocytes, suppressed PPIX accumulation and rescued bile duct loss in the mutant zebrafish. Consistent with zebrafish findings, MRP9-deficient neonatal mouse cholangiocytes and H69 human cholangiocytes accumulated more PPIX when treated with the heme precursor δ-aminolevulinic acid (ALA) compared to wildtype cells. They also showed reduced viability and increased cell death upon ALA treatment. **Conclusion:** Our study identify mitochondrial damage due to dysregulation of porphyrin homeostasis as a potential cause of cholangiocyte death in MRP9-deficient models, revealing a novel mechanism for cholestatic cholangiopathies.

Disclosures: Chunyue Yin: Nothing to Disclose, Akanksha Sharma: Nothing to Disclose, RAMESH KUDIRA: Nothing to Disclose, Bryan Donnelly: Nothing to Disclose, Annika Yang Vom Hofe: Nothing to Disclose, Hannah Nartker: Nothing to Disclose, Manavi Singh: Nothing to Disclose, Michelle Damen: Nothing to Disclose, Maria Moreno-Fernandez: Nothing to Disclose, Alexander Miethke: Mirum Pharmaceutical Inc: Grant/Research Support, Mirum Pharmaceutical Inc: Consultant, Ipsen: Speaking and Teaching

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4023 | SAFETY AND EFFICACY OF CENTRIFUGAL SEPARATION PLASMA EXCHANGE WITH ACD-A ON ACUTE LIVER FAILURE AND ACUTE ON CHRONIC LIVER FAILURE: A SINGLE CENTER RETROSPECTIVE STUDY

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[1]*Huashan Hospital, Fudan University*

Background: The purpose of this retrospective study is to compare the efficacy and safety of the centrifugal separation therapeutic plasma exchange (TPE) using citrate anticoagulant (cTPEc) with membrane separation TPE using heparin anticoagulant (mTPEh) in liver failure patients. **Methods:** The patients treated by cTPEc were defined as cTPEc group and those treated by mTPEh were defined as mTPEh group, respectively. Clinical characteristics were compared between the two groups. Survival analyses of two groups and subgroups classified by the model for end-stage liver disease (MELD) score were performed by Kaplan–Meier method and were compared by the log-rank test. **Results:** In this study, there were 51 patients in cTPEc group and 18 patients in mTPEh group, respectively. The overall 28-day survival rate was 76% (39/51) in cTPEc group and 61% (11/18) in mTPEh group (P > .05). The 90-day survival rate was 69% (35/51) in cTPEc group and 50% (9/18) in mTPEh group (P > .05). MELD score = 30 was the best cut-off value to predict the prognosis of patients with liver failure treated with TPE, in mTPEh group as well as cTPEc group. **Conclusion:** Our study concludes that there was no statistically significant difference in survival rate and complications between cTPEc and mTPEh groups. The liver failure patients tolerated cTPEc treatment via peripheral vascular access with the prognosis similar to mTPEh. The prognosis in patients with MELD score < 30 was better than in patients with MELD score ≥ 30 in both groups. In this study, the patients with acute liver failure (ALF) and acute on chronic liver failure (ACLF) treated with cTPEc tolerated the TPE frequency of every other day without significant clinical adverse event of hypocalcemia with similar outcomes to the mTPEh treatment.

Disclosures: Jian-Ming Zheng: Nothing to Disclose, Xin-Fang Zhu: Nothing to Disclose, Bing-Yao Wang: Nothing to Disclose

4024 | ARTIFICIAL LIVER SUPPORT SYSTEMS IS ASSOCIATED WITH IMPROVED SHORT-TERM AND MEDIUM-TERM OUTCOMES IN PATIENTS WITH HEPATITIS B-RELATED ACUTE-ON-CHRONIC LIVER FAILURE: A RETROSPECTIVE COHORT STUDY

Kunping Cui[1] *Lang Bai*[2] *hong Tang*[2] *xiangnan teng*[2] *Changhai Liu*[2] *Yuanji Ma*[2] *Fang Chen*[2]

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Background: Hepatitis B-related acute-on-chronic liver failure (HBV-ACLF) is a rapidly progressive and life-threatening syndrome with a still high mortality rate. Early and rapid improvement of liver function is crucial for improving survival rates. Artificial liver support systems (ALSS) are commonly used to remove toxins and metabolites from the body, helping patients with liver failure to recover liver function, but their effectiveness is often questioned. This study investigated the impact of ALSS on the short-term and medium-term prognosis of HBV-ACLF. **Methods:** A retrospective cohort study was conducted to collect clinical data of patients with HBV-ACLF who were hospitalized in the center for infectious diseases of West China Hospital, Sichuan University, from December 2015 to May 2021. The patients with HBV-ACLF were identified by the Asian Pacific Association for the Study of the Liver criteria. Patients were divided into two groups based on their use of ALSS. The mortality rates at 28-day, 60-day, and 90-day after admission were recorded for each group. The Boruta algorithm was used for feature selection. The univariate and multivariate Logistic and COX regression models were employed to explore the association between ALSS and the 28-day, 60-day, and 90-day mortality rates among patients with HBV-ACLF. **Results:** A total of 940 patients (median [IQR] age, 48.00 [39.00-54.00] years; 121 [12.87%] females) were enrolled in this study. The mortality rates at 28-day, 60-day, and 90-day were 19.89%, 27.87% and 30.74%, respectively. The patients were divided into ALSS group (n = 610) and standard medicine treatment (SMT) group (n = 330). Compared with the SMT group, the mortality rate of the ALSS group was significantly decreased within 28 days (17.70% vs. 23.94%), while no significant difference was observed at 60 days (28.03% vs. 27.58%) and

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90 days (31.15% vs. 30.00%). In the unadjusted univariate COX regression analysis, the ALSS only showed significant advantages in reducing 28-day mortality (HR, 0.69, 95%CI: 0.51, 0.94). To more accurately evaluate the actual impact of the ALSS on patient survival, we constructed multiple models for verification. Among them, the adjusted multivariate COX regression analysis based on variables screened by the Boruta method showed that the ALSS could reduce the 28-day (aHR, 0.81, 95%CI: 0.73, 0.88), 60-day (aHR, 0.89, 95%CI: 0.83, 0.97), and 90-day (aHR, 0.9, 95%CI: 0.84, 0.97) mortality rates. In addition, the results of other model analyses were also consistent with this. **Conclusion:** ALSS has a positive impact on the short-term and medium-term prognosis of patients with HBV-ACLF, and can reduce mortality. ALSS remains an effective treatment for HBV-ACLF.

Table 1. Primary and secondary outcome analyses with different models for cohort.

	p-value	Result
28-day mortality		
Log-rank [HR (95% CI)][1]	**<0.05**	**0.69 (0.51, 0.94)**
Cox model adjusted with all covariates [HR (95% CI)][1]	**<0.001**	**0.5 (0.36, 0.70)**
Cox model adjusted with covariates selected by uni-variable analyses [HR (95% CI)][1]	**<0.001**	**0.83 (0.75, 0.91)**
Cox model adjusted with covariates selected by selected by random forest algorithm [HR (95% CI)][1]	**<0.001**	**0.81 (0.73, 0.88)**
Logistic model adjusted with all covariates [OR (95% CI)][1]	**<0.001**	**0.46 (0.29, 0.73)**
Logistic model adjusted with covariates selected by uni-variable analyses [OR (95% CI)][1]	**<0.001**	**0.48 (0.31, 0.74)**
Logistic model adjusted with covariates selected by selected by random forest algorithm [OR (95% CI)][1]	**<0.001**	**0.42 (0.27, 0.64)**
60-day mortality		
Log-rank [HR (95% CI)][1]	0.754	0.96 (0.74, 1.24)
Cox model adjusted with all covariates [HR (95% CI)][1]	**<0.01**	**0.89 (0.82, 0.96)**
Cox model adjusted with covariates selected by uni-variable analyses [HR (95% CI)][1]	**<0.01**	**0.9 (0.83, 0.97)**
Cox model adjusted with covariates selected by selected by random forest algorithm [HR (95% CI)][1]	**<0.01**	**0.89 (0.83, 0.97)**
Logistic model adjusted with all covariates [OR (95% CI)][1]	**<0.05**	**0.64 (0.41, 0.97)**
Logistic model adjusted with covariates selected by uni-variable analyses [OR (95% CI)][1]	**<0.05**	**0.65 (0.43, 0.98)**
Logistic model adjusted with covariates selected by selected by random forest algorithm [OR (95% CI)][1]	**<0.05**	**0.61 (0.41, 0.91)**
90-day mortality		
Log-rank [HR (95% CI)][1]	0.925	0.99 (0.77, 1.26)
Cox model adjusted with all covariates [HR (95% CI)][1]	**<0.01**	**0.9 (0.83, 0.97)**
Cox model adjusted with covariates selected by uni-variable analyses [HR (95% CI)][1]	**<0.05**	**0.91 (0.85, 0.98)**
Cox model adjusted with covariates selected by selected by random forest algorithm [HR (95% CI)][1]	**<0.01**	**0.9 (0.84, 0.97)**
Logistic model adjusted with all covariates [OR (95% CI)][1]	**<0.05**	**0.64 (0.42, 0.97)**
Logistic model adjusted with covariates selected by uni-variable analyses [OR (95% CI)][1]	**<0.05**	**0.67 (0.45, 1.00)**
Logistic model adjusted with covariates selected by selected by random forest algorithm [OR (95% CI)][1]	**<0.05**	**0.64 (0.43, 0.93)**

Statistical analyses of different models with p-value < 0.05 were displayed in bold.

[1]OR = Odds Ratio, HR = Hazard Ratio, CI = Confidence Interval

Disclosures: Kunping Cui: Nothing to Disclose, Lang Bai: Nothing to Disclose, hong Tang: Nothing to Disclose, xiangnan teng: Nothing to Disclose, Changhai Liu: Nothing to Disclose, Yuanji Ma: Nothing to Disclose, Fang Chen: Nothing to Disclose

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4025 | ACTIVATION OF HEPATOCYTE P53 TRIGGERS ACUTE LIVER FAILURE WITH MULTIPLE ORGAN INJURY

Jihyun Sung[1] Hayato Hikita[1] Yuki Makino[1] Seiya Kato[1] Yoichi Sasaki[1] Kenji Fukumoto[1] Kazuhiro Murai[1] Yoshinobu Saito[1] Takahiro Kodama[1] Tomohide Tatsumi[1] Tetsuo Takehara[1]

[1]Osaka University

Background: Acute liver failure (ALF) is characterized by massive hepatocyte cell death in the short term, for which no effective treatment exists except liver transplantation. We previously reported that constitutive activation of p53 in hepatocytes caused hepatocyte cell death resulting in liver fibrosis and carcinogenesis. However, its impact on ALF remains unknown. This work aims to study the role of p53 in ALF. **Methods:** The analysis of RNA-seq in human ALF liver (GDS4387) was performed using the Gene Expression Omnibus (GEO) dataset. Acetaminophen (APAP) or concanavalin A (ConA) were used to induce ALF in mice. We generated tamoxifen-inducible, hepatocyte-specific knockout mice of Mdm2, a negative regulator of p53 (Mdm2Δhep mice), to analyze the impact of acute activation of hepatocyte p53. p53 was further deleted in Mdm2Δhep mice. Human ALF serum and liver tissues were obtained to assess p53 and inflammatory cytokines. **Results:** In silico analysis using GEO datasets, hepatic cdkn1a, a representative target of p53, was upregulated in ALF patients compared with normal liver samples. C57B6J mice administered with APAP or ConA showed upregulation of p21 mRNA and p53 protein in the liver, indicating the activation of the p53 pathway. After tamoxifen injection, Mdm2Δhep mice showed depletion of Mdm2 in their hepatocytes, leading to the activation of p53 signaling with extensive cell death in hepatocytes, and elevated serum ALT and bilirubin levels. Also, multiple organ injury was noted as the increase of TUNEL-positive cells and inflammatory cells in the kidney, heart, colon, and lung. All Mdm2Δhep mice died within 168 hours after tamoxifen injection. Of note, further deletion of hepatocyte p53 negated all of these findings in Mdm2Δhep mice. Multiplex cytokine assay and liver RNA-seq in Mdm2Δhep mice showed the elevation of multiple inflammatory cytokines. Among them, we focused on leukemia inhibitory factor (LIF), which was the most elevated inflammatory cytokine in RNA-seq of Mdm2Δhep mice liver. In Mdm2Δhep mice, LIF mRNA was elevated in multiple organs and serum levels. Also, human LIF mRNA in liver and serum LIF was significantly upregulated in ALF patients compared with non-hepatitis liver and serum samples. In vitro experiments, LIF increased by nutlin-3, an inhibitor of Mdm2, in CL2 and HepG2 (hepatocyte cells), indicating that LIF is a direct target of p53 in hepatocytes. Finally, recombinant LIF administration upregulated inflammatory cytokines, including LIF itself in LX-2 (hepatic stellate cells), TMNK-1 (hepatic sinusoidal endothelial cells), and HK2 (renal proximal tubule epithelial cells), which suggests the possibility of a LIF-mediated systemic inflammatory reaction. **Conclusion:** Acute activation of hepatocyte p53 triggers an inflammatory reaction and ALF leading to multiple organ injury. Activated p53 may represent a novel therapeutic target for ALF.

Disclosures: Jihyun Sung: Nothing to Disclose, Hayato Hikita: Nothing to Disclose, Yuki Makino: Nothing to Disclose, Seiya Kato: Nothing to Disclose, Yoichi Sasaki: Nothing to Disclose, Kenji Fukumoto: Nothing to Disclose, Kazuhiro Murai: Nothing to Disclose, Yoshinobu Saito: Nothing to Disclose, Takahiro Kodama: Chugai Pharmaceuticals: Speaking and Teaching, Astrazeneca: Speaking and Teaching, Eisai Co Ltd: Speaking and Teaching, Tomohide Tatsumi: Nothing to Disclose, Tetsuo Takehara: Nothing to Disclose

4026 | EFFECT OF PLASMA ADSORPTION PLUS HALF-VOLUME PLASMA EXCHANGE ON INTRACRANIAL PRESSURE IN ACUTE-ON-CHRONIC LIVER FAILURE

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Background: Patients with liver failure may be accompanied by cerebral edema and elevated intracranial pressure (ICP). The effect of plasma adsorption (PA) and half-volume plasma exchange (hvPE) on ICP were unclear. **Methods:** A prospective observational cohort study was conducted in patients with acute-on-chronic liver failure (ACLF) receiving PA followed immediately by hvPE. ICP was measured by transcranial doppler and flash visual evoked potential. ICP, mean arterial pressure (MAP) and cerebral perfusion pressure (CPP) were measured repeatedly, and their differences were evaluated by generalized estimation equation. **Results:** A total of 31 patients with ACLF were enrolled. The median MELD 3.0 was 27.8 (25.7~29.4). Compared with ICP before PA, the mean (95% CI) changes in ICP after PA, after hvPE, and 2 hour after hvPE were 0.5 (-1.8~2.9)

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mmHg (P =0.625), 0.7 (-1.7~3.1) mmHg (P =0.540), and 1.1 (-1.1~3.4) mmHg (P =0.304) (overall P for pairwise comparisons =0.777; P for trend =0.394). The mean MAP after hvPE (P for pairwise comparisons 0.99). **Conclusion:** PA and hvPE might have no effect on ICP in patients with ACLF, while hvPE rather than PA could improve MAP and CPP.

Disclosures: Yuanji Ma: Nothing to Disclose, Fang Chen: Nothing to Disclose, Lingyao Du: Nothing to Disclose, Lang Bai: Nothing to Disclose, hong Tang: Nothing to Disclose

4027 | ASSOCIATION BETWEEN SYSTEMIC IMMUNE-INFLAMMATION INDEX AND SHORT-TERM PROGNOSIS OF ACUTE-ON-CHRONIC LIVER FAILURE

Yuanji Ma Fang Chen[1] Lingyao Du[1] Lang Bai[1] hong Tang[1]

[1]West China Hospital, Sichuan University

Background: The systemic immune-inflammatory index (SII) has been identified as an independent prognostic factor for multiple diseases. However, the impact of SII on outcome of acute-on-chronic liver failure (ACLF) is scant. **Methods:** A retrospective study enrolled patients with ACLF treated with artificial liver support system. Restricted cubic spline (RCS) (knots at the 5th, 35th, 65th, and 95th percentiles) and Cox proportional hazards models were applied to investigate the relationship between SII and 90-day mortality in patients with ACLF. **Results:** A total of 258 patients were included. The SII was 465.5 (277.3-804.4). Patients with SII ≥480 had more serious condition and 90-day mortality (53.2% vs. 30.3%, P 1.00, all P **Conclusion:** Our findings suggested SII was positively associated with poor short-term prognosis of ACLF.

Disclosures: Yuanji Ma: Nothing to Disclose, Fang Chen: Nothing to Disclose, Lingyao Du: Nothing to Disclose, Lang Bai: Nothing to Disclose, hong Tang: Nothing to Disclose

4028 | ASSOCIATION BETWEEN PLATELET LEVELS AND BLEEDING EVENTS IN PATIENTS WITH ACUTE-ON-CHRONIC LIVER FAILURE TREATED WITH ARTIFICIAL LIVER SUPPORT SYSTEM

Yuanji Ma li yang[1] Lingyao Du[1] Lang Bai[1] hong Tang[1]

[1]West China Hospital, Sichuan University

Background: Platelet (PLT) reduction increases bleeding risk in patients with chronic liver disease. However, the association between PLT levels and bleeding events in patients with liver failure treated with artificial liver support system (ALSS) remains unclear. **Methods:** A retrospective study was conducted in patients with acute-on-chronic liver failure (ACLF) received ALSS therapy. Logistic regression analysis and linear regression analysis were employed to assess the association between PLT levels and bleeding events during hospitalization, and the relationship between sessions of ALSS therapy and PLT reduction rate. **Results:** A total of 262 patients were included, 56 (21.4%) patients experienced bleeding events during hospitalization. Baseline PLT levels in patients with bleeding events were lower than that in patients without bleeding events (59.0 (39.0~89.3) ×109/L vs. 88.5 (57.0~121.0) ×109/L; P0.05). Compared with patients with baseline PLT grade 0, the bleeding risks increased in patients with baseline PLT grade 1 (adjusted OR: 3.14~3.76, 95% CI: 1.16~9.50, all P0.05). **Conclusion:** Patients with ACLF and lower baseline PLT levels had higher bleeding risks during hospitalization.

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4029 | THERAPEUTIC DOSING OF DOUBLE PLASMA MOLECULAR ADSORPTION SYSTEM IN THE TREATMENT OF SEVERE LIVER DISEASE

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Background: The appropriate therapeutic dosing for double plasma molecular adsorption system (DPMAS) in the treatment of severe liver disease remains unclear. **Methods:** A prospective observational cohort study was conducted to provide reference for establishing reasonable therapeutic dosing for DPMAS treatment for patients with severe liver disease. Total bilirubin was used as an evaluation indicator, and it was detected repeatedly at 4 different time and different therapeutic dosing of DPMAS treatment (at 0.0 h (0 mL); at 2.0 hour (3000 mL); at 2.5h (3750 mL); at 3.0h (4500 mL)). The treatment was divided into 2 subgroups: patients with total bilirubin **Results:** Twenty nine patients with 75 sessions of DPMAS treatment were enrolled. The total bilirubin levels and their reduction rates in all patients (75 sessions), or patients with total bilirubin **Conclusion:** The therapeutic dosing of DPMAS treatment could be more than 4500 mL, especially for those with higher height or lower albumin.

Disclosures: Yuanji Ma: Nothing to Disclose, Lingyao Du: Nothing to Disclose, Lang Bai: Nothing to Disclose, hong Tang: Nothing to Disclose

4030 | MORTALITY AND OUTCOMES OF ACUTE LIVER INJURY IN CRITICALLY ILL PATIENTS: AN OBSERVATIONAL STUDY

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Background: Acute liver injury (ALI) are frequently observed in critically ill patients in intensive care units and are associated with high morbidity and mortality. The aim of present study is to examine the outcomes and prevalence of ALI among critically ill patients national database. **Methods:** The Healthcare Cost and Utilization Project (HCUP) Nationwide Inpatient Sample (NIS) was used to identify adult patients admitted with ALI during 2016 – 2020 using ICD-10-CM codes. We defined critically ill patients as having either major or extreme loss of function as per 3M All Patient Refined DRGs (APR-DRGs). Main outcomes were in-hospital mortality, length of stay (LOS), and hospital costs. We evaluate the risk factors associated with outcomes using survey based multivariate logistic regression models for in-hospital mortality, Poisson regression for LOS, and generalized linear model with gamma distribution and log link for hospitalization cost. Models were adjusted for age, sex, race and ethnicity, primary payer, Charlson comorbidity index, hospital bed size, hospital region and hospital teaching status. **Results:** We identified a total of 1,566,295 hospitalizations associated with ALI in critically ill patients between 2016 and 2020 in the United States with 656,090 (41.9%) of them having major loss of function and 910,205 (58.1%) having extreme loss of function. In-patient mortality was significantly higher in patients having extreme loss of function (39.0% vs 4.5%, adjusted OR: 12.6, 95%CI: 12.3 – 13.0, P < 0.001, Table 1). ALI patients with extreme loss of function had an increased length of stay (11.7 ± 0.06 vs 6.0 ± 0.02 days, P < 0.001) and cost of hospitalization ($51.118 ± 477 vs $15,425± 96, P < 0.001, Table 1). Increasing age, female gender, Black and Asian or Pacific Islander race, having Medicaid and private insurance, admission into hospitals with medium and large bed size had higher odds of in-hospital mortality while Hispanic race, having 2 or higher Charlson comorbidity index, hospital regions of Midwest, South, and West and admission into rural and urban non-teaching hospitals had lower odds of in-hospital mortality. **Conclusion:** APR-DRG risk severity highly correlate with in-hospital mortality, LOS, and hospitalization cost in critically ill acute liver injury patients.

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Table 1. Factors associated with in-hospital mortality, length of stay and hospitalization cost

	In-hospital mortality			Length of Stay			Hospitalization Cost		
Characteristics	OR	95% CI	p-value	IRR	95% CI	p-value	IRR	95% CI	p-value
APRDRG Severity Category									
Major loss of function	1	1	1	1	1	1	1	1	1
Extreme loss of function	12.6	12.3, 13.0	<0.001	1.94	1.92, 1.96	<0.001	3.02	2.99, 3.06	<0.001
Age	1.02	1.02, 1.02	<0.001	1	1.00, 1.00	<0.001	0.99	0.99, 1.0	<0.001
Gender									
Male	1	1	1	1	1	1	1	1	1
Female	1.03	1.01, 1.05	<0.001	0.96	0.95, 0.96	<0.001	0.92	0.91, 0.93	<0.001
Race									
White	1	1	1	1	1	1	1	1	1
Black	1.33	1.29, 1.37	<0.001	1.13	1.12, 1.15	<0.001	1.13	1.12, 1.15	<0.001
Hispanic	0.95	0.92, 0.98	0.002	1.05	1.04, 1.07	<0.001	1.07	1.05, 1.09	<0.001
Asian or Pacific Islander	1.17	1.11, 1.23	<0.001	1.12	1.09, 1.16	<0.001	1.27	1.24, 1.31	<0.001
Native American	1.04	0.95, 1.13	0.4	0.95	0.91, 0.98	0.006	0.92	0.87, 0.96	<0.001
Other	1.19	1.12, 1.26	<0.001	1.09	1.06, 1.12	<0.001	1.18	1.14, 1.22	<0.001
Insurance									
Medicare	1	1	1	1	1	1	1	1	1
Medicaid	1.05	1.02, 1.08	0.002	1.09	1.08, 1.11	<0.001	0.99	0.98, 1.01	0.2
Private	1.09	1.06, 1.12	<0.001	1.05	1.04, 1.06	<0.001	1.16	1.14, 1.17	<0.001
Other	1.54	1.48, 1.61	<0.001	0.94	0.92, 0.96	<0.001	0.91	0.89, 0.93	<0.001
Charlson comorbidity index									
0-1	1	1	1	1	1	1	1	1	1
2	0.88	0.85, 0.92	<0.001	1.1	1.08, 1.13	<0.001	1.14	1.12, 1.17	<0.001
>=3	0.68	0.66, 0.70	<0.001	1.05	1.03, 1.07	<0.001	0.93	0.92, 0.95	<0.001
Hospital bedsize									
Small	1	1	1	1	1	1	1	1	1
Medium	1.05	1.01, 1.09	0.01	1.11	1.09, 1.12	<0.001	1.12	1.09, 1.14	<0.001
Large	1.11	1.08, 1.15	<0.001	1.28	1.26, 1.30	<0.001	1.4	1.37, 1.43	<0.001
Hospital region									
Northeast	1	1	1	1	1	1	1	1	1
Midwest	0.81	0.78, 0.84	<0.001	0.85	0.83, 0.87	<0.001	0.83	0.81, 0.86	<0.001
South	0.85	0.83, 0.89	<0.001	0.92	0.90, 0.94	<0.001	0.81	0.78, 0.83	<0.001
West	0.86	0.83, 0.89	<0.001	0.86	0.84, 0.88	<0.001	1.1	1.06, 1.14	<0.001
Hospital Teaching Status									
Urban teaching	1	1	1	1	1	1	1	1	1
Rural	0.89	0.85, 0.93	<0.001	0.7	0.69, 0.71	<0.001	0.66	0.65, 0.68	<0.001
Urban nonteaching	0.92	0.89, 0.95	<0.001	0.84	0.83, 0.85	<0.001	0.76	0.75, 0.78	<0.001

Relative ratio is reported using Poisson regression model for LOS
Relative ratio is reported using generalized linear model with gamma distribution and log link for Hospital Cost; adjusted for inflation using Consumer Price Index (CPI) for Medical care services in U.S. city average, all urban consumers, chained, with 2020 as the reference point
Variables used for multivariate logistic regression: age, sex, race, insurance status, Charlson comorbidity index, hospital bed size, and hospital region

Disclosures: Anwar Uddin: Nothing to Disclose, Nazeera Ghanie: Nothing to Disclose, Madia Ahad: Nothing to Disclose, Rafat Uddin: Nothing to Disclose, Afgal Ahad: Nothing to Disclose, Rahat Uddin: Nothing to Disclose, Prashil Dave: Nothing to Disclose, Peter Lymberopoulos: Nothing to Disclose, Dipsa Shastri: Nothing to Disclose, Sahil Chaddha: Nothing to Disclose

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4031 | ENHANCING ASPP2 PROMOTES ACUTE LIVER INJURY THROUGH INFLAMMATORY IMMUNOREGULATORY MECHANISM

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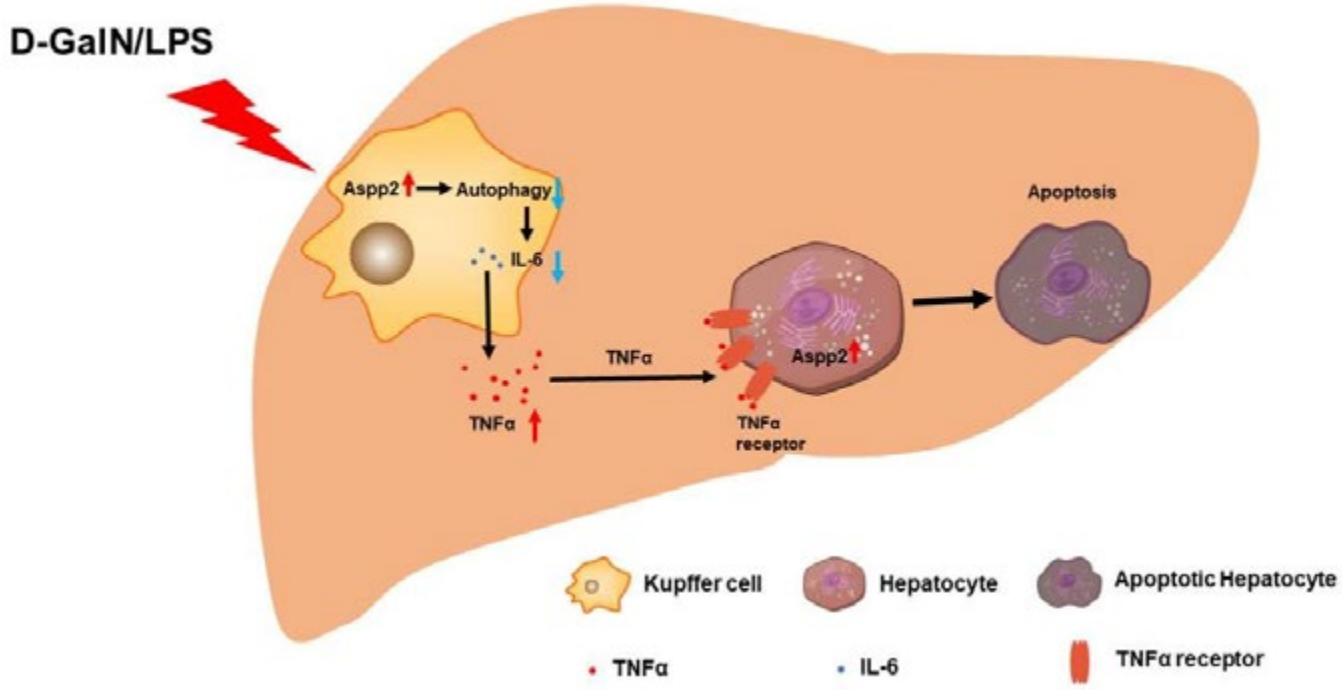
Background: Acute liver injury (ALI), which is a type of inflammation-mediated hepatocellular injury, is a clinical syndrome that **Results:** from hepatocellular apoptosis and hemorrhagic necrosis. Apoptosis stimulating protein of p53-2 (ASPP2) is a proapoptotic member of the p53 binding protein family. However, the role of ASPP2 in the pathogenesis of ALI and its regulatory mechanisms remain unclear. **Methods:** The expression of ASPP2 were compared between liver biopsies derived from patients with CHB, patients with ALI, and normal controls. Acute liver injury was modelled in mice by administration of D-GalN/LPS. Liver injury was demonstrated by serum transaminases and histological assessment of liver sections. ASPP2-knockdown mice (ASPP2+/−) were used to determine its role in acute liver injury. Mouse bone marrow macrophages (BMMs) were isolated from wildtype and ASPP2+/- mice and stimulated with LPS, and the supernatant was collected to incubate with the primary hepatocytes. Quantitative real-time PCR and western blot were used to analyze the expression level of target. **Results:** The expression of ASPP2 was significantly upregulated in the liver tissue of ALI patients and acute liver injury mice. ASPP2+/- mice significantly relieved liver injury through reducing liver inflammation and decreasing hepatocyte apoptosis. Moreover, the conditioned medium (CM) of ASPP2+/- bone marrow-derived macrophages (BMMs) protected hepatocytes against apoptosis. Mechanistically, we revealed that ASPP2 deficiency in BMMs specifically upregulated IL-6 through autophagy activation, which decreased the level of TNF-α to reduce hepatocytes apoptosis. Furthermore, up-regulation of ASPP2 sensitizes hepatocytes to TNF-α-induced apoptosis. **Conclusion:** Our novel findings show the critical role of ASPP2 in inflammatory immunoregulatory mechanism of ALI and provide a rationale to target ASPP2 as a refined therapeutic strategy to ameliorate acute liver injury.



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4032 | CHARACTERISTICS OF ACUTE LIVER FAILURE IN THE ELDERLY IN JAPAN: A CROSS-SECTIONAL STUDY

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Background: Certain patients with acute liver failure (ALF) require liver transplantation as a life-saving measure. But the number of livers that can be transplanted is limited in Japan. Also, old age is considered a poor prognostic factor in acute liver failure. Now, elderly people are not eligible for liver transplantation. In order to clarify the characteristics of the elderly patients with ALF, we carried out this study. **Methods:** In a cohort of elderly patients with ALF (elderly than 60 years old), we aimed to identify the difference between younger patients with ALF (between 0-59 years old). We identified patients admitted with ALF between 2005 and 2023 at a single institution in Sapporo, Japan. Subjects were divided into two groups: those aged 60 years or older (elderly group) and those aged less than 60 years (younger group). And we performed a retrospective chart review to describe the backgrounds, the risk factors and outcomes. **Results:** The authors identified 55 elderly patients with ALF and 101 younger patients with ALF. Of these, the average age was 65 years old in the elderly group and was 41.5 years old in the younger group. In the elderly group, there were 26 male and 29 female and, younger group, there were 54 male and 48 female. Compared to the younger group, the elderly group tended to have some underlying disease (19.6% vs 61.8%) (p-value<0.001). Ischemic hepatitis was most common etiology of ALF in the elderly group (26%) followed by autoimmune hepatitis (18.2%), hepatitis E virus (14.5%). On the other hand, hepatitis B virus was most common etiology in the younger group (22.5%) followed by autoimmune hepatitis (16.7%), hepatitis E virus (16.7%). However, there was no statistical difference significantly. Survival rate without liver transplantation was 66.0% the elderly group and 68.6 % in the younger group (Including cases of survival from liver transplantation, survival rate was 76.5% in younger group). There was no significant difference between two group statistically. However, the elderly patients with ALF due to ischemic hepatitis had better prognosis compared to the younger patients with ALF due to ischemic hepatitis (P=0.04) With logistic regression analysis, we found that PTINR was only related to their prognosis (OR=0.77) in the elderly group. However, in the younger group, not only PTINR but also total bilirubin were related to the prognosis. **Conclusion:** Since liver failure due to ischemic hepatitis requires a different treatment approach than other acute hepatitis, and the most common cause of ALF in elderly patients, it was important to diagnose the disease at an early stage and determine a treatment plan. Except ALF with ischemic hepatitis, survival rate was not good in the elderly group, thus we may consider indication of liver transplantation for elderly patients. But further discussion is required to make effective use of society's limited resources.

Disclosures: Ryosuke Minami: Nothing to Disclose, Takeshi Matsui: Nothing to Disclose, kazunari Tanaka: Nothing to Disclose

4033 | MELATONIN MITIGATES SLEEP DEPRIVATION-EXACERBATED ACUTE LIVER INJURY THROUGH PER2-MEDIATED ENDOPLASMIC RETICULUM STRESS

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Background: Sleep deprivation (SD) exacerbated acute liver injury (ALI) by the accumulation of reactive oxygen species and oxidative stress. Its well-documented that melatonin has strong antioxidant effects. However, the role of melatonin in the pathogenesis of ALI exacerbated by SD remains incompletely elucidated. The aim of this study is to elucidate the role and the mechanism of melatonin during liver injury. **Methods:** Mice were housed in a multiple platform water bath to induce SD. Meanwhile, the mice were intraperitoneally administered with melatonin. The degree of histologic inflammation, inflammatory mediators and Endoplasmic Reticulum Stress (ERS) levels were assessed in SD mice in LPS/ D-GalN induced ALI. **Results:** It was observed that SD markedly elevates the mortality rate, hepatocyte apoptosis, and ERS linked to ALI, whereas melatonin therapy mitigated ALI, resulting in a notable reduction in hepatocyte apoptosis, pro-inflammatory cytokines, and accumulation of reactive oxygen species. SD upregulates the expression of GRP78 and p-PERK in ALI, whereas melatonin supplementation can ameliorate ER stress. PER2 was markedly decreased in liver tissues exposed to ALI SD mice, while supplementation with melatonin can effectively increase PER2 expression. Knockdown of PER2

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lead to a notable increase in the expression of GRP78 and p-PERK in hepatocytes and hepatic macrophages. Administration of melatonin results in heightened PER2 expression and a significant decrease in p-PERK levels. **Conclusion:** Melatonin alleviates the exacerbation of acute liver injury by SD through the upregulation of PER2 in the liver, leading to the inhibition of p-PERK expression and subsequent attenuation of ERS.

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4034 | EXPANDABLE AND FUNCTIONAL HEPATOCYTES DERIVED FROM PRIMARY CELLS WITH ROBUST LIVER REPOPULATION CAPACITY

Sophie Cazanave[1] soujanya karanth[1] Abhijith Kudva[1] Timothy Norman[1] Maxwell Van Buskirk[2] Joseph Marturano[1] Andrew Hashkes[1] Esha Uddin[3] Mehar Cheema[1] Lindsay Tomczak[1] Aarohi Thakkar[1] David Broderick[1] William Scholl[1] Kevin Macera[1] Michael Ret[1] Christopher Steele[1] Julie Morse[1] Christopher Wilson[1] Eric Vanderploeg[1] Tom Lowery[1] Sunil Mallanna[1] Arnav Chhabra[1] Alireza Rezania[1]

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Background: Cellular therapy holds significant potential for treating severe liver failure, yet this approach has been hampered by the lack of a sustainable source of highly functional hepatocytes. To address this critical gap, we generated REGEN-HEPS, a unique source of primary cell-derived hepatocytes that combines expansive growth with retention of mature hepatocyte phenotype and functions. We tested their therapeutic potential in a rodent model of liver disease. **Methods:** Primary human hepatocytes (PHHs) from 11 donors were subjected to our expansion protocol. Immunohistochemistry, RNA-seq, ELISA and enzyme activity assays were used to query hepatic identity and functions across axes of synthesis, metabolism, and detoxification. REGEN-HEPS, PHHs, and iPSC-Heps were injected through the spleen into FRG mice (Fah-/-/, Rag2-/-/, IL-2RG-/-), followed by controlled cycles of NTBC administration. Engraftment was confirmed by human albumin secretion up to 4 months after transplantation. Liver damage upon NTBC withdrawal was evaluated by liver injury biomarkers (ALT, AST, Bilirubin, and Ammonia) and animal survival. **Results:** Our process effectively expanded primary human hepatocytes from several different donors, with 36% (4 out of 11) of the donors showing more than 20-fold expansion in the first passage and over a 1,000-fold expansion over two passages for one donor. Post-expansion, the cells retained key hepatocyte lineage markers, HNF4α and albumin, ensuring preservation of cellular identity. When cultured in chemically-defined media, REGEN-HEPS exhibited a transcriptional profile and functional capacities closer to PHHs in both synthetic and metabolic functions. In the FRG mouse model, REGEN-HEPS demonstrated robust liver repopulation, with a mean albumin level of 3.2 mg/mL at day 120, and further matured in vivo, significantly outperforming iPSC-Heps. REGEN-HEPS improved liver functions upon complete withdrawal of NTBC and offered a survival advantage comparable to PHHs (64% vs. 55%, p = 0.87), significantly outperforming control cells that failed to engraft (64% vs. 20%, p = 0.02). **Conclusion:** REGEN-HEPS represent a scalable and cGMP-compatible source of hepatocytes that preserve hepatic identity during expansion and demonstrate functionality equivalent to primary hepatocytes, both in vitro and in a rodent model of liver disease.

Disclosures: Sophie Cazanave: Nothing to Disclose, soujanya karanth: Nothing to Disclose, Abhijith Kudva: Nothing to Disclose, Timothy Norman: Nothing to Disclose, Maxwell Van Buskirk: Nothing to Disclose, Joseph Marturano: Nothing to Disclose, Andrew Hashkes: Nothing to Disclose, Esha Uddin: Nothing to Disclose, Mehar Cheema: Nothing to Disclose, Lindsay Tomczak: Nothing to Disclose, Aarohi Thakkar: Nothing to Disclose, David Broderick: Nothing to Disclose, William Scholl: Satellite Bio: Employee, Kevin Macera: Nothing to Disclose, Michael Ret: Nothing to Disclose, Christopher Steele: Nothing to Disclose, Julie Morse: Nothing to Disclose, Christopher Wilson: Satellite Biosciences: Employee, Eric Vanderploeg: Satellite Biosciences: Employee, Satellite Bio: Employee, Tom Lowery: Nothing to Disclose, Sunil Mallanna: Nothing to Disclose, Arnav Chhabra: Nothing to Disclose, Alireza Rezania: Nothing to Disclose

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4035 | COST-EFFECTIVENESS ANALYSIS OF DOUBLE PLASMA MOLECULAR ADSORPTION SYSTEM WITH SEQUENTIAL LOW VOLUME PLASMA EXCHANGE VERSUS PLASMA EXCHANGE IN EARLY HBV-ACLF ◆

Liang Peng[1] Jia Chen[1] Qiumin Luo[1] Lu Wang[2] Lihua Zheng[1] Yeqiong Zhang[1] Ying Liu[1] Wenxiong Xu[1]

[1]Sun Yat-sen University, [2]Binzhou Medical University

Background: The economic comparison between double plasma molecular adsorption system with sequential low volume plasma exchange (DPMAS+LPE) and traditional plasma exchange (PE) remains unclear, despite evidence demonstrating improved short-term survival rates in patients with hepatitis B-related acute-on-chronic liver failure (HBV-ACLF) using DPMAS+LPE. **Methods:** In this retrospective study, 215 early-stage HBV-ACLF patients were included. After propensity score matching (PSM), 101 patients each were assigned to the DPMAS+LPE group and the PE group. A 90-day follow-up was conducted to compare survival rates and direct medical costs between the two groups at 30 days and 90 days. The willingness-to-pay threshold (WTP) was set at 1-3 times China's 2023 per capita GDP. Univariate sensitivity analysis and probabilistic sensitivity analysis were performed to assess parameter uncertainty. **Results:** At 30 days, the survival rates in the DPMAS+LPE group and PE group were 99.01% and 97.01%, respectively. The average total costs were $10,510 and $9,607, with an incremental cost effectiveness ratio(ICER) of 45,150, exceeding the upper cost threshold, and an incremental net monetary benefit (INMB) of -161. At 90 days, the DPMAS+LPE group showed a 7.97% improvement in survival rate. For every 1 % increase in survival rate, an additional $2,886 would be required, and the INMB is 2,719. In the 30 % ≤ prothrombin activity(PTA) ≤ 40 % subgroup, the 90-day average total medical cost of the DPMAS + LPE group was lower than that of the PE group. For the PTA> 40% subgroup and 30%≤PTA≤40% subgroup, the ICER for DPMAS+LPE treatment were 10,284 and -928, with positive INMB values. At a WTP of 1 times per capita GDP, the economic probabilities for DPMAS+LPE at 30 days and 90 days were 14% and 75%, respectively. At a WTP of 3 times per capita GDP, the economic probabilities were 45% and 90% for 30 days and 90 days, respectively. The INMB value at 90 days was sensitive to patient survival rates and treatment frequency. **Conclusion:** Compared to PE, DPMAS+LPE improves the 90-day survival rate in early-stage HBV-ACLF patients and is cost-effective. Additionally, the 90-days economic benefits of DPMAS+LPE treatment surpass the short-term benefits observed at 30 days, particularly among patients with PTA 30%-40%. DPMAS+LPE may serve as an ideal artificial liver model for early HBV-ACLF.

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Group	Cost($) Mean[95%CI]	Effectiveness(%) Mean[95%CI]	CER	**ICER**	NMB	**INMB**
30-day economic evaluation						
DPMAS+LPE	10510 [10040, 10966]	99.01 [94.10, 1.00]	10615	**45150**	26123	**-161**
PE	9607 [8916, 10285]	97.01 [90.10, 99.01]	9903		26284	
90-day economic evaluation						
DPMAS+LPE	12340 [11401, 13278]	91.04 [84.17, 95.05]	13554	**2886**	21357	**2719**
PE	12110 [10803, 13416]	83.07 [73.27, 89.11]	14578		18638	

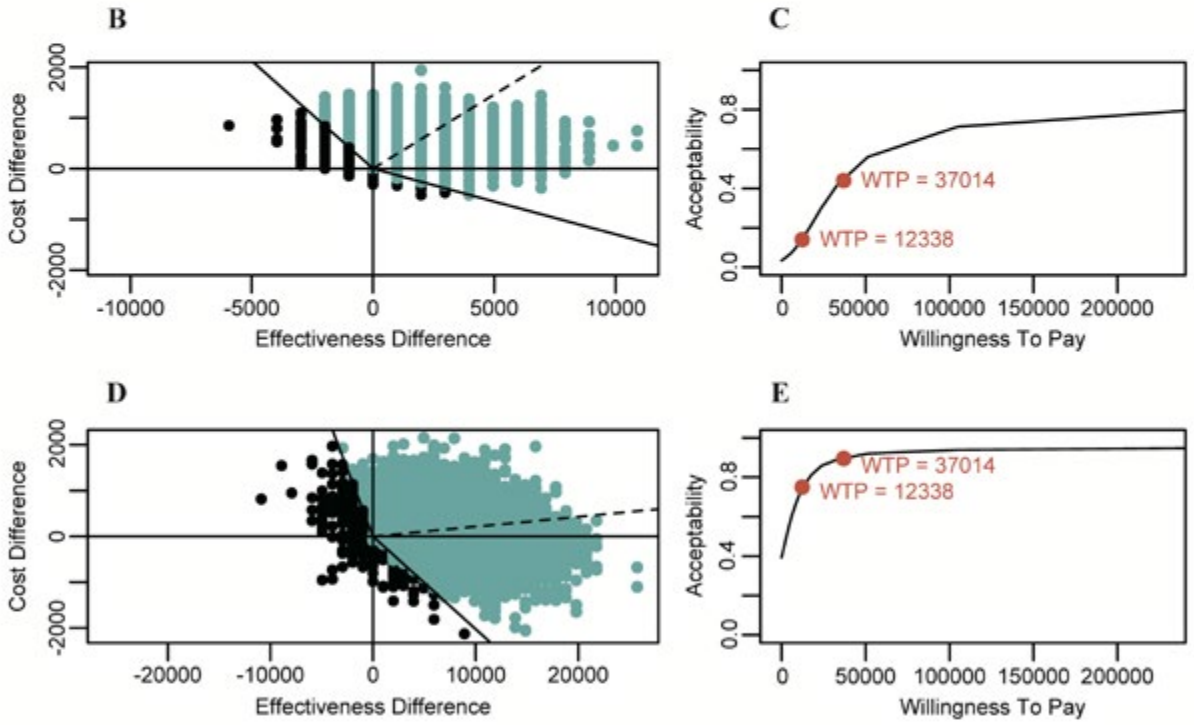

Fig1. A. Overview of calculated results for costs, survival rates, and economic indicators in two groups.
B. Cost-effectiveness plane at 30 days.
C. Cost acceptability curve at 30 days.
D. Cost-effectiveness plane at 90 days.
E. Cost acceptability curve at 90 days.

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4036 | RACIAL DISPARITIES IN CLINICAL OUTCOMES OF ACUTE LIVER FAILURE AND HEPATIC ENCEPHALOPATHY: A NATIONWIDE POPULATION STUDY

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Background: Acute liver failure and hepatic encephalopathy both are highly lethal liver conditions, in which multiple causes can incite liver cell injuries. Racial disparities in various hepatology conditions have been observed, but the specific impact of racial differences against various clinical outcomes in this patient group is still limited. We aim to understand the impact of race on clinical outcomes in this patient group. **Methods:** We used the 2020 U.S. National Inpatient Sample (NIS) to study patients hospitalized for acute liver failure identified by ICD-10 CM codes, as well as hepatic encephalopathy. Adjusted odds ratios (aORs) for predefined outcomes were determined via multivariable logistic and linear regression analyses. The primary outcome was inpatient mortality, while secondary outcomes included complications and costs of stay. **Results:** We identified 25,644 records with a primary discharge diagnosis of acute liver failure and 38,159 records of hepatic encephalopathy, excluding age < 18 years and elective hospitalization. The mean age was 59 years; 46.6% were female. Patients were divided into 6 groups, utilizing racial information. We found that African American patients had significantly higher mortality, shock, and acute kidney injury in the acute liver failure population group, as well as higher mortality, but less total charges and less liver transplantation in the hepatic encephalopathy group. Table 1 shows the analysis result. **Conclusion:** Our study revealed that there is a disproportionate racial impact of hospitalized acute liver failure patients, in African Americans group. Additional longitudinal research is warranted to fully understand the association of gender disparities with these clinical outcomes.

Table 1: Clinical Outcomes, by Race

Race	Cases	Mortality	Shock	Acute Kidney Injury
Acute Liver Failure, by Race				
Caucasians	17,820	Baseline		
African Americans	2,520	**1.53 (1.11, 2.11)***	**1.56 (1.13, 2.14)***	**1.65 (1.32, 2.05)***
Hispanics	4,369	0.80 (0.58, 1.11)	0.81 (0.57, 1.16)	0.87 (0.73, 1.05)
Asian Americans	709	0.84 (0.46, 1.54)	0.65 (0.30, 1.40)	0.98 (0.66, 1.45)
Native Americans	469	1.71 (0.89, 3.27)	1.84 (0.85, 4.00)	1.17 (0.73, 1.89)
Others	854	1.23 (0.74, 2.06)	1.04 (0.55, 1.96)	1.19 (0.85, 1.67)
Hepatic Encephalopathy, by Race				
Race	Cases	Mortality	Total Charges (USD)	Liver Transplant
Caucasians	27,059	Baseline		
African Americans	3,494	**1.49 (1.05, 2.12) ***	**-10,391 (-20,075, -707) ***	**0.51 (0.29, 0.91) ***
Hispanics	6,744	0.72 (0.50, 1.04)	-4,551 (-15,909, 6,805)	0.73 (0.42, 1.29)
Asian Americans	735	0.62 (0.24, 1.54)	-1,692 (-19,735, 16,349)	0.82 (0.26, 2.58)
Native Americans	784	1.53 (0.74, 3.19)	-24,736 (-38,727, -10,744)	0.46 (0.14, 1.43)
Others	1149	0.90 (0.48, 1.69)	6,114 (-22,735, 34,964)	**0.20 (0.05, 0.82) ***

Adjusted for age, gender, hospital location, hospital region, insurance status, patient location, hospital size, hospital type and co-morbidities

*Denotes significant value at p<0.05

Disclosures: Thanathip Suenghataiphorn: Nothing to Disclose, Pojsakorn Danpanichkul: Nothing to Disclose, Jerapas Thongpiya: Nothing to Disclose, Supot Nimanong: Nothing to Disclose, Tawesak Tanwandee: Roche: Grant/Research Support, MSD: Grant/Research Support, Altimune: Grant/Research Support, Gilead: Grant/Research Support, Vir Biotech: Grant/Research Support

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4037 | LYOPHILIZED MESENCHYMAL STEM CELL-DERIVED EXTRACELLULAR VESICLES IMPROVE ACUTE LIVER FAILURE MODELS

Suzuki Fumiya[1] Hiroaki Haga[1] Kyoko Hoshikawa[1] Tomohiro Katsumi[1] Keita Maki[1] Fumi Uchiyama[1] Yoshiyuki Ueno[1]

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Background: Therapies using extracellular vesicles (EVs) have gained attention recently. We previously reported that mesenchymal stem cell-derived EVs (MSC-EVs) improved liver function and tissue in murine models of acute liver failure and hepatic ischemia-reperfusion. Extracting EVs from cultured MSCs is time-consuming, requiring effective preservation methods for clinical emergencies. While lyophilization of EVs has been studied, animal experiments using lyophilized EVs are limited. This study investigates the effects of lyophilized MSC-EVs on a murine model of acute liver failure. **Methods:** EVs were extracted from mouse MSC culture medium using ultracentrifugation. Groups were established: non-lyophilized (control), lyophilized with PBS (PBS group), 1% sucrose (1% sucrose group), and 5% sucrose (5% sucrose group). EVs were analyzed using transmission electron microscopy (TEM), nanoparticle tracking analysis (NTA), and a bioanalyzer. MSC-EVs were administered to a murine model of acute liver failure induced by D-galactosamine/TNF-α to assess therapeutic effects. **Results:** EV counts did not significantly differ: control ($1.14\times10^{10} \pm 8.67\times10^{8}$ particles/mL), PBS ($9.53\times10^{9} \pm 8.4\times10^{8}$ particles/mL), 1% sucrose ($9.83\times10^{9} \pm 1.6\times10^{9}$ particles/mL), and 5% sucrose ($1.07\times10^{10} \pm 1.07\times10^{9}$ particles/mL). The highest exosome content was in the control and 5% sucrose groups. RNA concentrations were 192 pg/μl (control), 217 pg/μl (PBS), 201 pg/μl (1% sucrose), and 264 pg/μl (5% sucrose). Many EVs in the 1% sucrose and PBS groups were deformed or structurally compromised, while EVs in the 5% sucrose group retained their shape, comparable to the control group. The effects of 5% sucrose MSC-EVs were further evaluated in the acute liver failure model. Serum AST levels were significantly lower in the non-lyophilized MSC-EV group (249±180 U/L, $p<0.02$) and lyophilized MSC-EV group (215±100 U/L, $p<0.004$) compared to the control (PBS) group (789±262 U/L). Serum ALT levels were similarly reduced: control (593±107 U/L), non-lyophilized MSC-EVs (130±59.8 U/L, $p<0.001$), and lyophilized MSC-EVs (158±89.4 U/L, $p<0.0003$), indicating comparable therapeutic effects. Hepatic tissue analysis via HE and TUNEL staining showed a significant reduction in apoptosis in both MSC-EV treated groups compared to the PBS group. **Conclusion:** A 5% sucrose solution appears optimal as a cryoprotectant for MSC-EVs. This study is the first to suggest that lyophilized MSC-EVs can improve liver function and tissue, similar to non-lyophilized MSC-EVs. These findings advance the clinical application of EVs.

Disclosures: Suzuki Fumiya: Nothing to Disclose, Hiroaki Haga: Nothing to Disclose, Kyoko Hoshikawa: Nothing to Disclose, Tomohiro Katsumi: Nothing to Disclose, Keita Maki: Nothing to Disclose, Fumi Uchiyama: Nothing to Disclose, Yoshiyuki Ueno: Nothing to Disclose

4038 | INCIDENCE OF ACUTE LIVER FAILURE AND ITS ASSOCIATED MORTALITY IN PATIENTS WITH DENGUE INFECTION: A SYSTEMATIC REVIEW AND META-ANALYSIS

Wasit Wongtrakul[1] Kantnatt Charatcharoenwitthaya[2] Khemajira Karaketklang[1] Phunchai Charatcharoenwitthaya[1]

[1]Faculty of Medicine Siriraj Hospital, Mahidol University, [2]Faculty of Medicine Ramathibodi Hospital, Mahidol University

Background: Acute liver failure (ALF) is a devastating consequence of dengue infection. This meta-analysis sought to determine the incidence of ALF in dengue infection and its associated mortality. **Methods:** We systematically searched the EMBASE and MEDLINE databases from inception to December 2023 for observational studies, which reported the incidence of ALF and its associated mortality among patients with dengue infection. **Results:** Twenty-one studies encompassing 26,839 dengue-infected patients were included. Meta-analysis revealed a pooled incidence of ALF in cases of general dengue infection of 2.0% (95% CI, 1.2%–3.0%), with rates of 1.2% (95% CI, 0.6%–2.1%) in adult populations and 5.0% (95% CI, 1.5%–10.2%) in pediatric populations (Figure 1). The pooled incidence of ALF was 17.3% (95% CI, 6.5%-31.5%) in patients with severe dengue and 7.4% (95% CI, 0.8%–18.5%) in patients with dengue shock syndrome. The pooled mortality rate of dengue-associated ALF was 47.0% (95% CI, 32.9%–61.2%). **Conclusion:** These findings underscore the detrimental impact of dengue infection on the development of the relatively uncommon, albeit life-threatening, condition of ALF.

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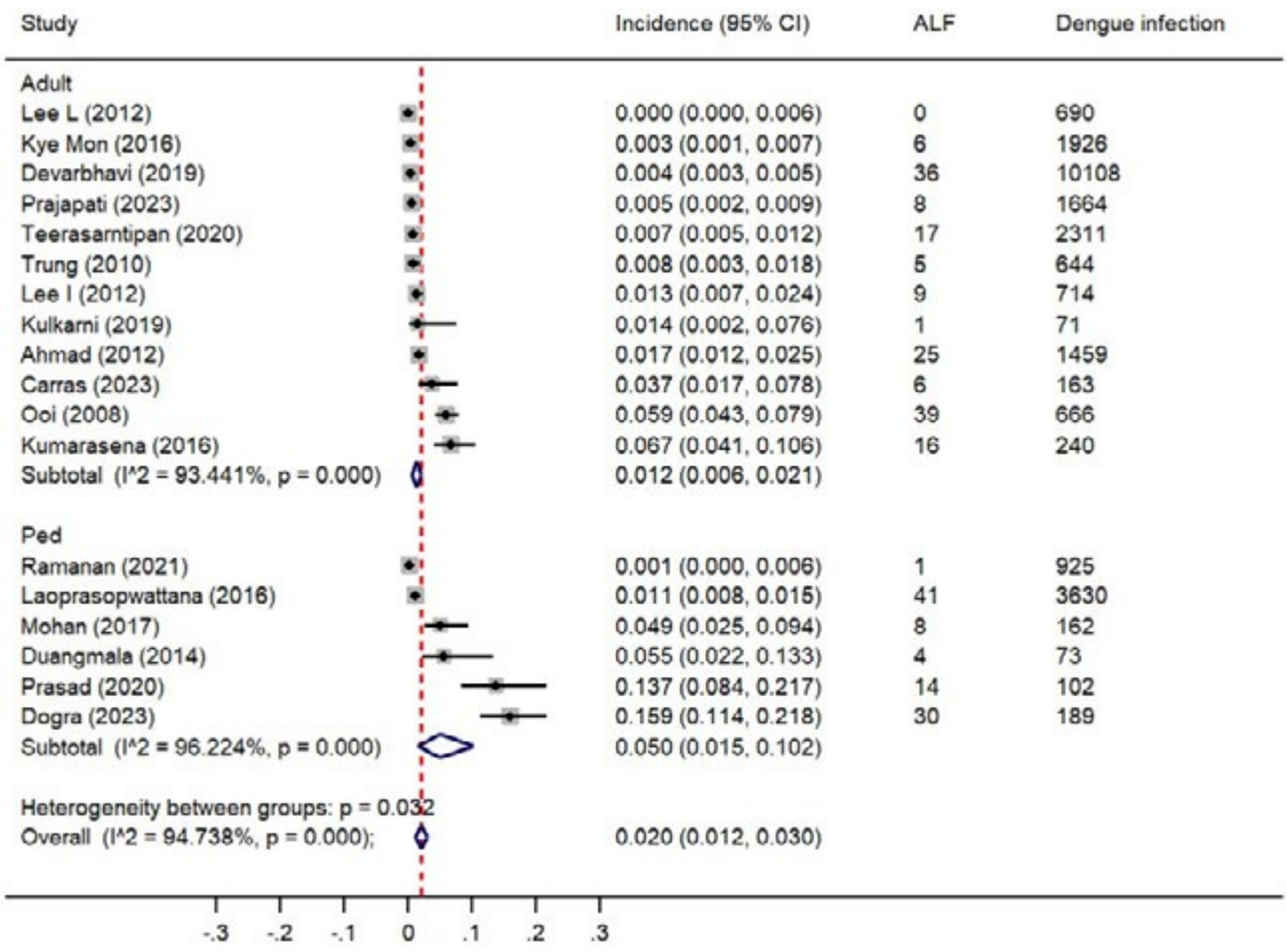

Disclosures: Wasit Wongtrakul: Nothing to Disclose, Kantnatt Charatcharoenwitthaya: Nothing to Disclose, Khemajira Karaketklang: Nothing to Disclose, Phunchai Charatcharoenwitthaya: Nothing to Disclose

4039 | THERAPEUTIC PLASMA EXCHANGE IMPROVES 90-DAY TRANSPLANT FREE SURVIVAL BY 2 FOLDS IN FULMINANT WILSON DISEASE WITH NWI >10

Seema Alam[1] Tamoghna Biswas[1] Bikrant Biharilal Raghuvanshi[1] Vikrant Sood[1] Rajeev Khanna[1] Meenu Bajpai[1]

[1]Institute of Liver and Biliary Sciences

Background: Therapeutic plasma exchange (TPE) rapidly removes 20 mg of copper per TPE which decreases hemolysis and clinical stabilizes the patient in fulminant Wilson Disease (FWD). TFS at 90 days was present in 9/19 in HVPE & 3/18 in the SMT (OR 2.84, 95% CI 0.91- 8.8, P = .049) in an earlier study from this centre **Methods:** All patients (aged 4-18 years) of FWD (Liepzig ≥ 4) with NWI >10 and INR >2.5 were included. Those having received at least 2 TPE (volume 1.5 folds daily for three days) were included as cases and rest who were on only standard medical treatment were considered as controls if they had a hospital stay of >48 hours without LT. Propensity matched analysis was done to identify 37 matched pairs of cases and controls. The aim of the study was to study the transplant free survival (TFS) at 90 days in cases versus controls **Results:** The baseline age, gender, bilirubin, INR, TLC, albumin, NWI, grade of hepatic encephalopathy (HE) and presence of direct antiglobulin test negative hemolysis were comparable in cases versus controls. At 48 -96 hours, the INR (2.81 ± 1.2 versus 3.98 ± 1.93, p= 0.002), albumin (2.68 ± 0.48 versus 2.19 ± 0.55, p<0.001), and NWI (11.37 ± 3.39 versus 13.78± 3.55, p=0.004) had improved significantly in the cases versus controls. Grade of HE and bilirubin did not show significant difference between the two groups. TFS at 90 days was seen in 22/37 (59.5%) amongst cases versus 10/37 (27%) in the controls (log rank 0.018). Kaplan Meier survival graft is seen in Fig 1. We performed Logistic Regression Analysis to identify the risk factors for death and LT. The model of NWI, INR, HE grade, Hemolysis and TPE. With this model the correction of the classification improved from 50% to 81 %. The

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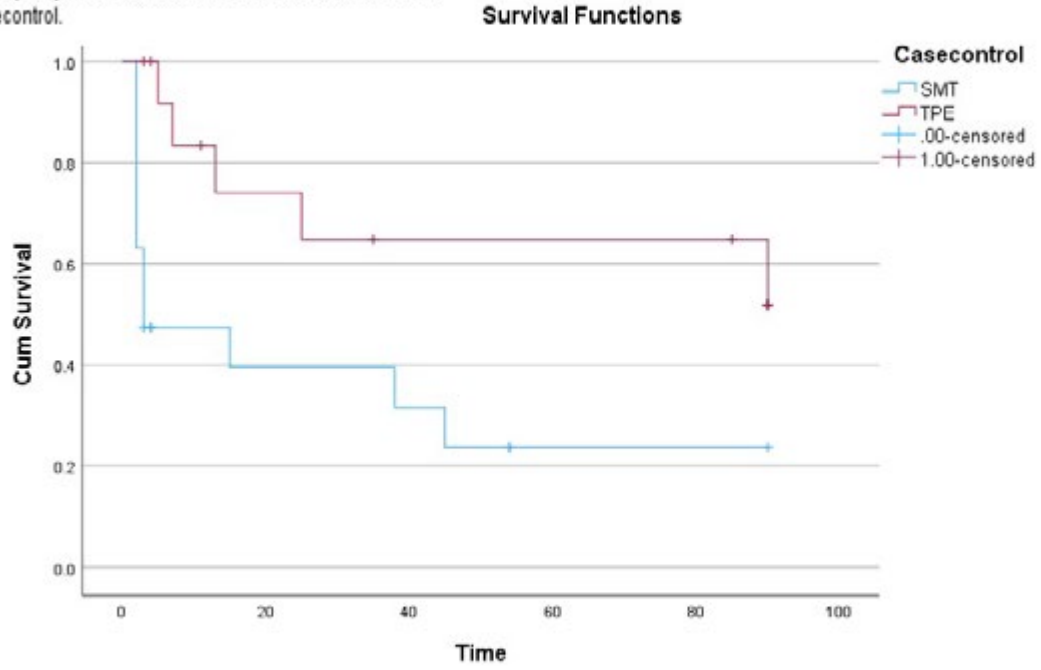
analysis reported that high INR, HE grade 3/4 and TPE were independently associated with presence of death and LT. High INR and HE grade 3/4 could increase the chances of death and LT by 3 and 10 folds respectively. Absence of TPE in the therapeutic strategy could increase the chance of death and LT by 8 folds. Adverse effects due to TPE was present as hypersensitivity reaction (3 %), fluid overload (9.2%) and cannula related hematoma (1.5%). Liver stiffness on transient elastography was ranging between 8 to 40 kpA with compensated liver disease on follow up of those who survived. **Conclusion:** TPE can significantly improve the 90-day transplant free survival from 27% to 59% in FWD with NWI >10.

Fig 1: Kaplan Meire Survival Curve of TPE+ SMT versus SMT

Overall Comparisons

	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	5.616	1	.018

Test of equality of survival distributions for the different levels of Casecontrol.



Native Liver	22 (59.5%)	10(27%)
LT	6 (16.2%)	9 (24.3%)
Death	9 (24.3%)	18 (48.7%)

Disclosures: Seema Alam: Nothing to Disclose, Tamoghna Biswas: Nothing to Disclose, Bikrant Biharilal Raghuvanshi: Nothing to Disclose, Vikrant Sood: Nothing to Disclose, Rajeev Khanna: Nothing to Disclose, Meenu Bajpai: Nothing to Disclose

4040 | ROLE OF CONTINUOUS RENAL REPLACEMENT THERAPY (CRRT) IN MANAGEMENT OF PEDIATRIC ACUTE LIVER FAILURE

Seema Alam[1] Bikrant Biharilal Raghuvanshi[1] Tamoghna Biswas[1] Vikrant Sood[1] Rajeev Khanna[1] Snigdha Verma[2]

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Background: Continuous renal replacement therapy (CRRT) removes water-soluble toxins such as ammonia, potassium, lactate, urea, and creatinine apart from the inflammatory cytokines and is increasingly being used in management of pediatric acute liver failure (PALF). This study was planned to evaluate the efficacy of CRRT in PALF and its effect on native liver survival (NLS) and overall survival (OS). **Methods:** All children aged 2-18 years with PALF were included. Patients receiving CRRT were divided into 2 groups: (i) those receiving 'late CRRT'

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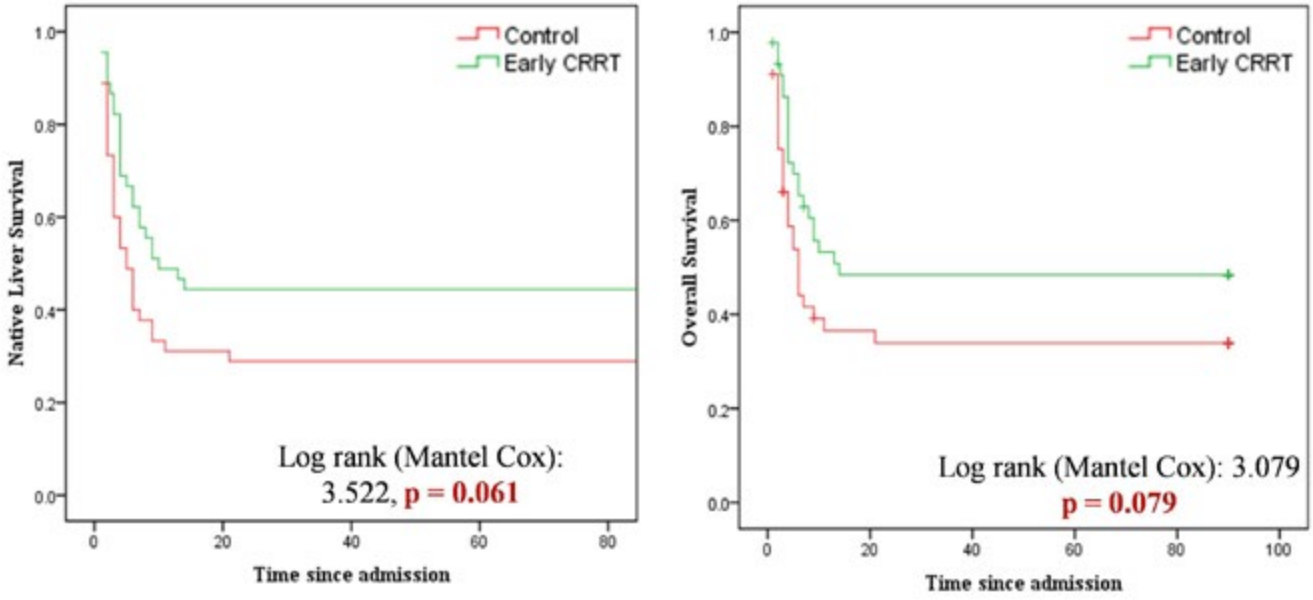
once acute kidney injury (AKI) has set in, and (ii) those receiving 'early CRRT' within 24 hours of admission and before development of AKI. For comparison, propensity matched controls were identified in 1:1 ratio for every case receiving 'early CRRT' using nearest neighbour calliper matching with calliper size of 0.1. Propensity matching was performed based on serum creatinine, arterial ammonia, international normalized ratio (INR), grades of hepatic encephalopathy (HE), and bilirubin levels. The primary outcome measure was NLS and OS in the two arms on day 28. **Results:** A total of 83 patients among the 413 PALF received CRRT. Thirty-six (43.4%) received CRRT for renal indications and formed 'late CRRT' group while 47 received 'early CRRT' for non-renal indications. The NLS in the 'late CRRT', 'early CRRT', and 'no CRRT' groups were 4/36 (11.1%), 21/47 (44.7%), and 170/330 (51.5%). OS in the 3 groups were 6/36 (16.7%), 24/47 (51.1%), and 202/330 (61.6%). Propensity matched controls could be identified for 45 patients in the 'early CRRT' group. In the propensity matched cohort, although the NLS and OS were higher in the CRRT group compared to controls, the difference was statistically insignificant (NLS: Early CRRT: 44.4% vs. Controls: 28.9%, p = 0.189; OS: Early CRRT: 51.1% vs. Controls: 37.8%, p = 0.289). Patients in 'early CRRT' group had lower levels of ammonia (193.1 ± 79.5µg/dl vs 249.4 ± 120.6µg/dl, p = 0.023), lactate (3.1 ± 2.2mmol/L vs 4.6 ± 2.5 mmol/L, p = 0.018), and INR (2.07 ± 1.01 vs 2.9 ± 1.6, p = 0.014), (193.1 ± 79.5µg/dl vs 249.4 ± 120.6µg/dl, p = 0.023) at 72 hours compared to controls while bilirubin, albumin, and creatinine remained comparable. **Conclusion:** There was a statistically insignificant trend towards improved NLS and OS with use of 'early CRRT' in PALF. Early CRRT resulted in a significant reduction in ammonia, lactate, and INR at 72 hours. Late CRRT was associated with high mortality.



Disclosures: Seema Alam: Nothing to Disclose, Bikrant Biharilal Raghuvanshi: Nothing to Disclose, Tamoghna Biswas: Nothing to Disclose, Vikrant Sood: Nothing to Disclose, Rajeev Khanna: Nothing to Disclose, Snigdha Verma: Nothing to Disclose

4041 | IMPROVED OUTCOMES OF ACUTE LIVER FAILURE WITH EXTRACORPOREAL LIVER SUPPORT- A MORE THAN A DECADE OF EXPERIENCE FROM A TERTIARY CENTRE.

Rakhi Maiwall[1] Meenu Bajpai[2] Harsh Vardhan Tevethia[2] Samba Siva Rao Pasupuleti[3] Fagun Sharma[2] Bindiya Arora[2] Sumegh Talwalkar[2] Mohit kumar Prajapati[2] Prashant Agarwal[2] Rajendra Prasad Mathur[2] Chandani Bhagat[2] Sherin Thomas[2] Shiv Kumar Sarin[2]

[1]Institute of Liver and Biliary Sciences, [2]Institute of Liver & Biliary Sciences, [3]Mizoram University, Pachhunga University College Campus

Background: There is a reduction in the deaths of acute liver failure (ALF) patients, with use of extracorporeal liver support systems (ECLS), therapeutic plasma-exchange (TPE) and continuous renal replacement therapy

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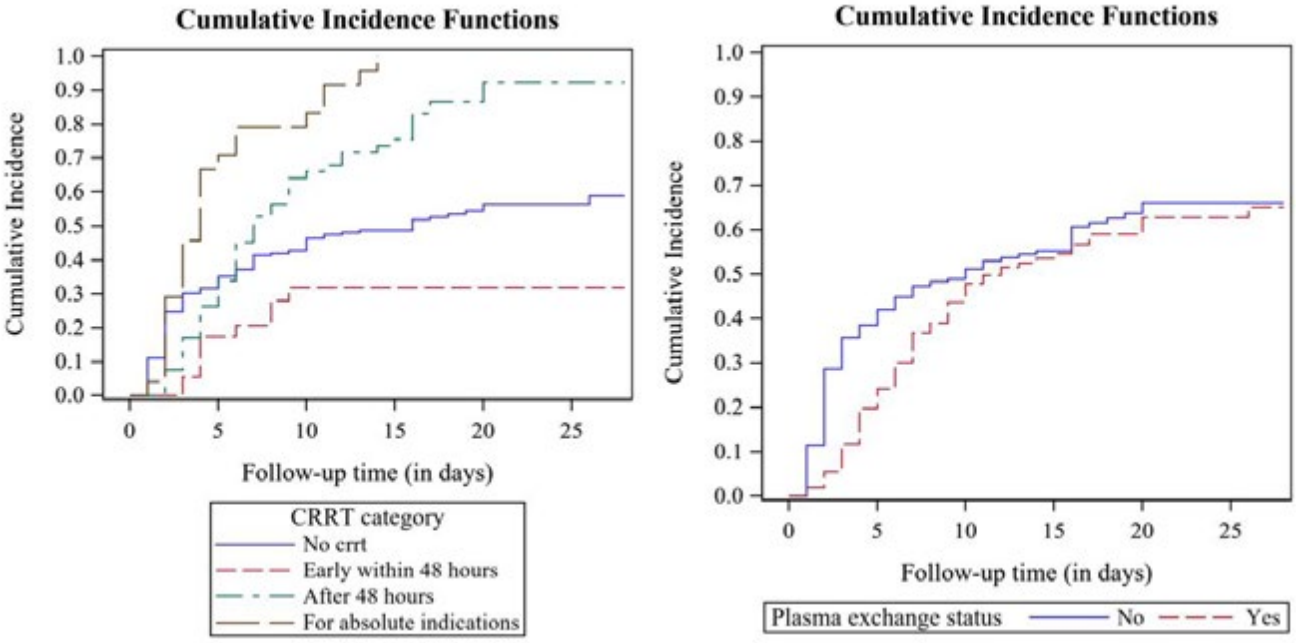
(CRRT). We aimed to review the impact of the change in intensive care (ICU) management protocols with the use of ECLS on patient outcomes from a tertiary care centre (2010-2024, n=413). **Methods:** The patient outcomes were analyzed by stratification into three different eras; as Era-1(2010-2016; n=118), Era-2 (2017-2020; n=138) and Era-3 (2021-2024; n=157). Competing risk survival analysis was performed with live donor liver transplant (LDLT) as a competing risk. **Results:** ALF patients aged 33.6 ± 12.5, 49% males, 30% meeting KCH criteria were enrolled. There was a significant reduction in mortality, from 66.9% in Era-1 (ref cat); to 58.7% (sHR 0.97, 0.71-1.33) in Era-2 and lowest in Era-3 49.7% (sHR 0.71, 0.51-0.97) (p=0.04). TPE was performed in (0%vs 40% and 57%] Era-1 vs.2 vs.3 respectively. CRRT was performed for absolute indications (3.4% vs. 6.4% vs.7.2%), within 48 hours (0% vs. 22.9% vs. 2.9%); after 48 hours (0% vs. 22.5% vs. 14.5%) in Era 1 vs.2 vs.3 respectively (p<0.001). The mean time to CRRT (in hours) was lowest for absolute indications (28±6.3) vs. early (31.8±1.6) and late group (96.8±8.3) (p<0.001) respectively. There was also a concomitant change noted in the demographic profile with younger patients in Era-3 and 2 compared to Era-1 (p<0.001) with an increase in the number of patients with hepatitis A virus as the dominant etiology in Era-3 [126 (80.3%) vs. 93(67.4%) vs. 63 (53.4%);p<0.001]. The proportion of patients undergoing LDLT remained similar across the Era 1 vs.2 vs.3 [(8% vs. 7% vs.14%); p=0.11] respectively. Independent predictors of mortality included age (sHR 1.02, 1.01-1.04), hypernatremia (sHR 1.02, 1.01-1.04), KCH criteria (sHR 1.53, 1.18-2.00) and arterial ammonia (sHR 1.81, 1.49-2.21). The use of CRRT for absolute indications (sHR 2.13,1.55-2.92) vs. initiation after 48 hours (sHR 1.33, 0.99-1.80) was associated with higher mortality, while, CRRT within 48 hours (sHR 0.36,0.18-0.70) (ref. category no CRRT) and use of TPE were associated with reduced deaths (sHR 0.62, 0.47-0.83). **Conclusion:** There is a change in the nature and outcome of ALF patients and only a small subset of patients can undergo LDLT. Use of TPE and an early CRRT within 48 hours is associated with improved outcomes in ALF patients.



Disclosures: Rakhi Maiwall: Nothing to Disclose, Meenu Bajpai: Nothing to Disclose, Harsh Vardhan Tevethia: Nothing to Disclose, Samba Siva Rao Pasupuleti: Nothing to Disclose, Fagun Sharma: Nothing to Disclose, Bindiya Arora: Nothing to Disclose, Sumegh Talwalkar: Nothing to Disclose, Mohit kumar Prajapati: Nothing to Disclose, Prashant Agarwal: Nothing to Disclose, Rajendra Prasad Mathur: Nothing to Disclose, Chandani Bhagat: Nothing to Disclose, Sherin Thomas: Nothing to Disclose, Shiv Kumar Sarin: Nothing to Disclose

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4042 | ENDOTOXIN-TOLERANT DENDRITIC CELL-DERIVED BIOMIMETIC EXOSOMES LOADED WITH IRIDIUM NANOZYMES FOR THE TREATMENT OF ACUTE LIVER FAILURE.

Chen-Yi Liu[1] Xue-Ting Xie[1] Shu Li[1] Chao Cai[1] Ming-Qin Lu

[1]The First Affiliated Hospital of Wenzhou Medical University,

Background: Acute liver failure (ALF) is characterized by rapid liver dysfunction and multi-organ failure, driven by oxidative stress, mitochondrial dysfunction, and complex mechanisms. The etiology is diverse, and effective treatments are lacking. Endotoxin tolerance (ET) occurs when initial low-dose lipopolysaccharide (LPS) exposure reduces the response to subsequent high doses. Our studies show that endotoxin-tolerant dendritic cells (ETDCs) have strong anti-inflammatory effects, but face in vivo stability issues. To address this, we designed ETDC-derived exosome mimetics (ETDC-EMs) which offer higher yield and easier production than traditional exosomes (Exo). Polyvinylpyrrolidone-coated iridium nanoparticles (Ir NPs-PVP) are novel multi-enzyme mimetics with catalase (CAT) and peroxidase (POD) activities, effectively scavenging reactive oxygen species (ROS). We combined ETDC-EMs with Ir NPs-PVP to enhance antioxidant effects, aiming to explore their therapeutic potential in ALF. **Methods:** Bone marrow-derived dendritic cells (BMDCs) were extracted from mice and stimulated with 100 ng/ml LPS on day 5 and 1 μg/ml LPS on day 7 to transform BMDCs into endotoxin-tolerant dendritic cells (ETDCs). Iridium nanoparticle enzymes (Ir NPs-PVP) with good dispersion were prepared using the ethanol thermal reduction method and characterized. ETDC-EM/Ir NPs-PVP were injected into healthy male mice via the tail vein, followed by intraperitoneal injection of D-galactosamine (D-GaIN) and LPS to establish an acute liver failure model in mice. The effects on the liver were then observed. **Results:** 1. The XPS spectra of Ir NPs-PVP confirmed the compound state of Ir. 2. TEM images showed that both ETDC-EM and ETDC-EM/Ir NPs-PVP are spherical with intact membrane structures and uniform sizes. ICP-MS indicated that 2×10^6 ETDCs could encapsulate 200 μg of 2 mg/ml Ir NPs-PVP, achieving a loading rate of 10%. 3. Ir NPs-PVP effectively scavenged intracellular ROS. 4. The addition of ETDC-EM significantly reduced the secretion of inflammatory cytokines TNF-α and IL-1β in the supernatant of RAW264.7 cells stimulated with a high dose of LPS. 5. In the acute liver failure mouse model, ETDC-EM/Ir NPs-PVP demonstrated excellent therapeutic effects without causing damage to major organs. **Conclusion:** We confirmed that Ir NPs-PVP possesses excellent antioxidant properties, while ETDC-EM exhibits anti-inflammatory effects both in vitro and in vivo. The ETDC-EM/Ir NPs-PVP obtained through extrusion demonstrated significant anti-inflammatory and antioxidant effects in mice, alleviating liver inflammation and protecting the liver in a mouse model of acute liver failure.

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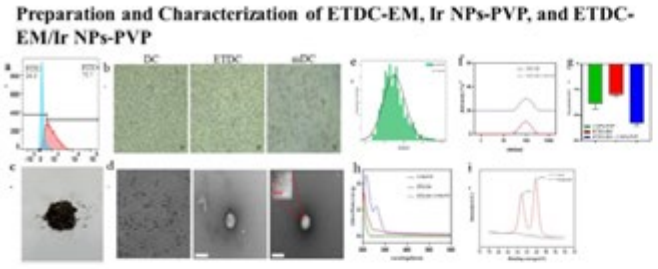

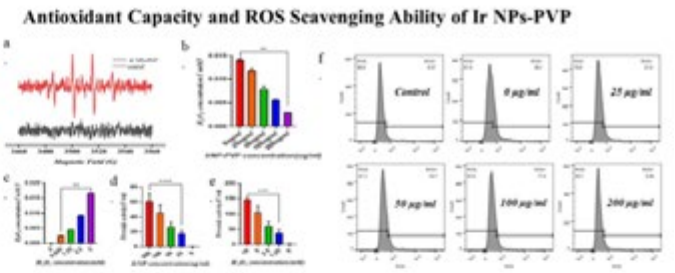

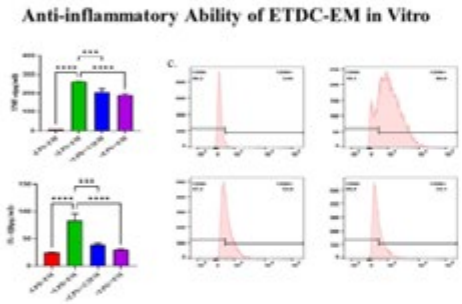

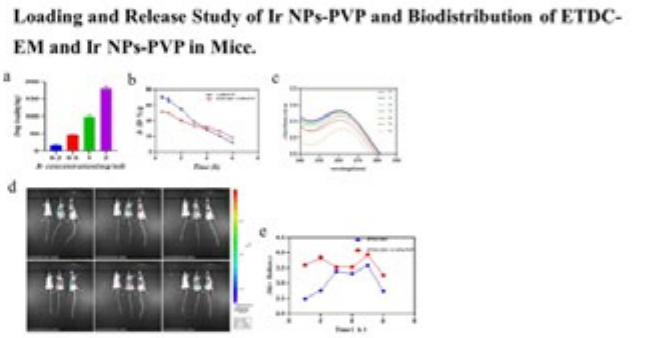

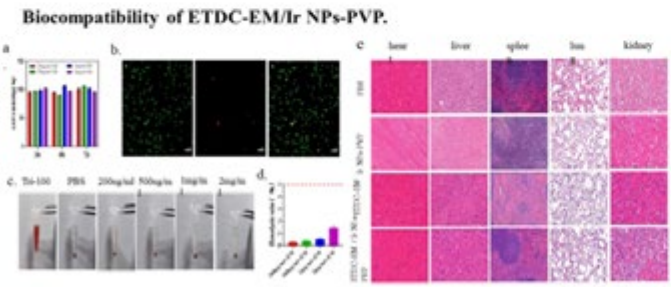

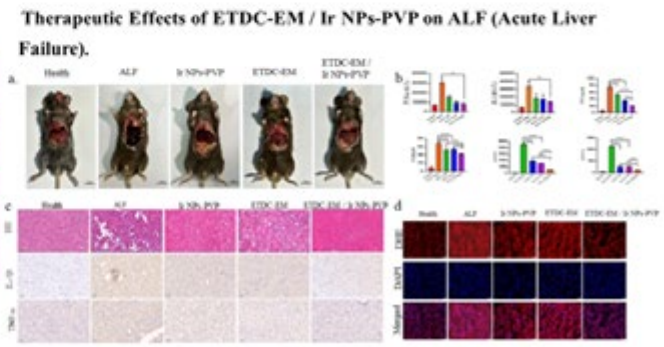

Disclosures: Chen-Yi Liu: Nothing to Disclose, Xue-Ting Xie: Nothing to Disclose, Shu Li: Nothing to Disclose, Chao Cai: Nothing to Disclose, Ming-Qin Lu: Nothing to Disclose

4043 | ALF LISTED FOR URGENT LIVER TRANSPLANTATION IN SWITZERLAND: RESULTS OF A 12-YEAR RETROSPECTIVE COHORT STUDY

Ansgar Deibel[1] Florian von Wyl[1] Priska Heinz[2] Guido Stirnimann[3] Vanessa Banz[3] Giulia Magini[4] Nicolas Goossens[4] Philippe Compagnon[4] Christoph Jüngst[1] David Semela[5] Andreas Cerny[6] Markus Heim[7] Montserrat Fraga[8] Andreas Kremer[1] Michael Koller[7] Stefanie von Felten[2] Philipp Dutkowski[7] Beat Müllhauupt[1]

[1]University Hospital Zurich, Switzerland, [2]University of Zurich, Switzerland, [3]University Hospital Bern, Switzerland, [4]University Hospital Geneva, Switzerland, [5]Cantonal Hospital St. Gallen, Switzerland, [6]Epatocentro Ticino, Switzerland, [7]University Hospital Basel, Switzerland, [8]University Hospital Vaud, Switzerland

Background: Acute liver failure (ALF) is a life-threatening disease, associated with a very high mortality rate when advanced encephalopathy occurs. To date, urgent liver transplantation (OLT) is the only life-saving treatment available. The etiologies of ALF are divers and differ between countries. The study aim was to characterize etiologies and outcome of patients with ALF listed for urgent OLT in Switzerland. **Methods:**

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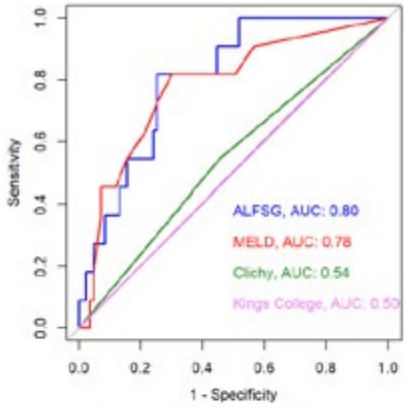
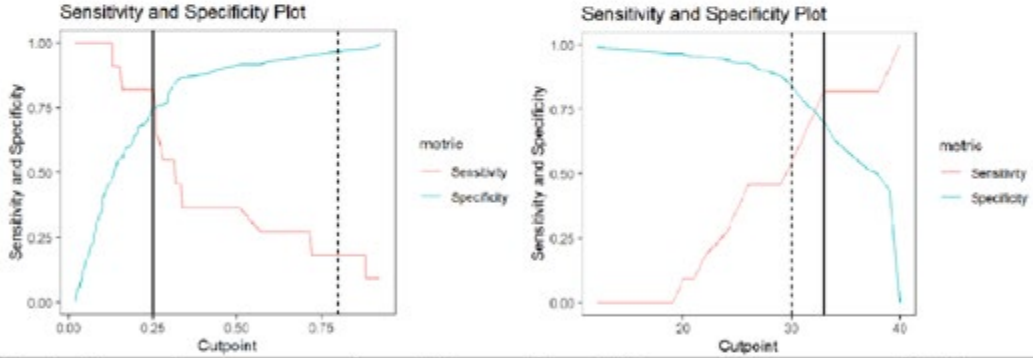
A retrospective cohort study of patients listed for urgent OLT due to ALF in Switzerland between 05/2008 and 12/2020 was performed, excluding ALF patients listed for surgical complications (e.g. small for size liver remnant after liver resection) or re-transplantation due to primary non-function. Data were collected from the Swiss Organ Allocation System, the Swiss Transplant Cohort Study and patient charts. Analysis included anthropomorphic data, etiology of liver injury with RUCAM probability assessment of implicated drugs in drug-induced liver injury (DILI), liver and kidney function parameters, use of organ replacement therapy and comorbidities at time of listing as well as allograft data. Outcome parameters were transplant-free and post-transplantation survival. **Results:** 95 patients were included in our study (74 OLT, 10 recoveries, 11 deaths). DILI was the most common cause of ALF (42/95, 44%). The most common single drugs implicated as cause for DILI were acetaminophen (13/42, 31%), followed by Metamizole (6/42, 14%). In ROC analysis MELD and ALFSG prognosis score were superior to Clichy and Kings College Criteria in predicting transplant-free survival. Using Youden's Index cut-off points for ALFSG (0.25) and MELD (33) were determined that had a very high negative predictive value for transplant-free survival (0.97). Post-transplantation survival was excellent (90.5%, 84.9% and 77.5% at 1, 5, 10 years) but significantly worse in men compared to women (5y OS 54% vs. 94%). In men, post-transplant death was frequently caused by transplant-related complications. **Conclusion:** Following Acetaminophen, Metamizole could be identified as the second most frequently implicated single drug implicated in DILI-ALF. MELD and ALFSG prognosis score were superior to Clichy and King's College criteria in predicting transplant-free survival in this study and should be evaluated as new listing criteria in other ALF cohorts. Post-transplant survival was excellent, but discrepancies existed between men and women.



Comparison	unadjusted p-value	adjusted p-value
ALFSG - MELD	0.62	1.00
ALFSG - Clichy	0.0003	0.002
ALFSG - King's College	0.0004	0.002
MELD - Clichy	0.013	0.048
MELD - King's College	0.012	0.048
Clichy - King's College	0.61	1.00



threshold	accuracy	sensitivity	specificity	PPV	NPV
ALFSG 0.25	0.76 (0.50-0.87)	0.82 (0.73-1.00)	0.75 (0.43-0.88)	0.3 (0.19-0.47)	0.97 (0.95-1.00)
MELD 33	0.71 (0.62-0.80)	0.82 (0.55-1.00)	0.7 (0.60-0.80)	0.26 (0.18-0.36)	0.97 (0.92-1.00)
MELD 30	0.81 (0.73-0.88)	0.55 (0.55-1.00)	0.84 (0.76-0.92)	0.32 (0.16-0.50)	0.93 (0.89-0.97)

Comparison of ALFSG score, MELD score, Clichy criteria and King's College criteria in predicting transplantation-free survival.

Disclosures: Ansgar Deibel: Nothing to Disclose, Florian von Wyl: Nothing to Disclose, Priska Heinz: Nothing to Disclose, Guido Stirnimann: Nothing to Disclose, Vanessa Banz: Nothing to Disclose, Giulia Magini: Nothing to Disclose, Nicolas Goossens: Nothing to Disclose, Philippe Compagnon: Nothing to Disclose, Christoph Jüngst: Nothing to Disclose, David Semela: Nothing to Disclose, Andreas Cerny: Nothing to Disclose, Markus Heim: Nothing to Disclose, Montserrat Fraga: Nothing to Disclose, Andreas Kremer: Abbvie: Advisor, Advanz: Advisor, Alentis: Advisor, AlphaSigma: Speaking and Teaching, AstraZeneca: Advisor, Avior: Advisor, Bayer: Advisor,

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4044 | RBP4 REGULATES APAP-INDUCED LIVER INJURY BY TARGETING MITOCHONDRIA

Jie Wang[1] *Xiaohan Qian*[2] *Qi Xia*[1]

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Background: Background: Mitochondrial damage is a critical event leading to hepatocyte death in acetaminophen (APAP) induced liver injury. Retinol Binding Protein 4 (RBP4), known as an adipokine, has been implicated in mitochondrial damage. However, the specific mechanisms by which RBP4 influences hepatocyte injury still remain unclear. **Methods:** We established an APAP-induced liver injury model in wild-type and RBP4 knockout (KO) mice via intraperitoneal injection of APAP (500 mg/kg) with or without recombinant RBP4 (20mg/kg) intraperitoneal administration. Liver injury severity and molecular alterations were assessed through histopathology, transmission electron microscopy (TEM), immunofluorescence, Western blot, and ELISA. Human hepatocyte LO2 cells were treated with APAP (20 mM) and recombinant RBP4 (40 μg/μl). Cell viability, mitochondrial morphology and function, and molecular changes were evaluated using CCK8, membrane potential assays, immunostaining, confocal microscopy, and Westernblot. **Results:** Compared to the APAP-only group, the APAP combine with RBP4 (AR) group exhibited exacerbated liver injury, evidenced by increased liver weight, hemorrhage, necrosis, and elevated ALT and AST levels. TEM and immunofluorescence indicated greater mitochondrial damage in the AR group, with reduced mitochondrial number and size and increased reactive oxygen species (ROS). Elevated LC3B and p62 levels in western blot indicated enhanced autophagy, while increased DRP and decreased MFN levels suggested increased mitochondrial fission and reduced fusion. Conversely, RBP4-KO mice injected with APAP showed attenuated liver injury with reduced necrosis, lower transaminase levels, partially preserved mitochondrial morphology, and decreased ROS compared to APAP-treated wild-type mice. In LO2 cells, AR group exhibited more reduced cell viability, damaged mitochondrial morphology, decreased membrane potential, and increased autophagic flux versus the APAP-only group. Notably, CCK8 assays revealed that neither autophagy inhibitors (rapamycin) nor enhancers (Torin1) improved cell viability under AR treatment. However, the mitophagy activator (AUTAC) enhanced cell viability, with greater protective effects observed when added 2 hours post-treatment rather than simultaneously. **Conclusion:** Elevated RBP4 levels during APAP overdose exacerbate hepatocyte mitochondrial damage and liver injury. This process can be ameliorated by transiently enhancing mitochondrial autophagy.

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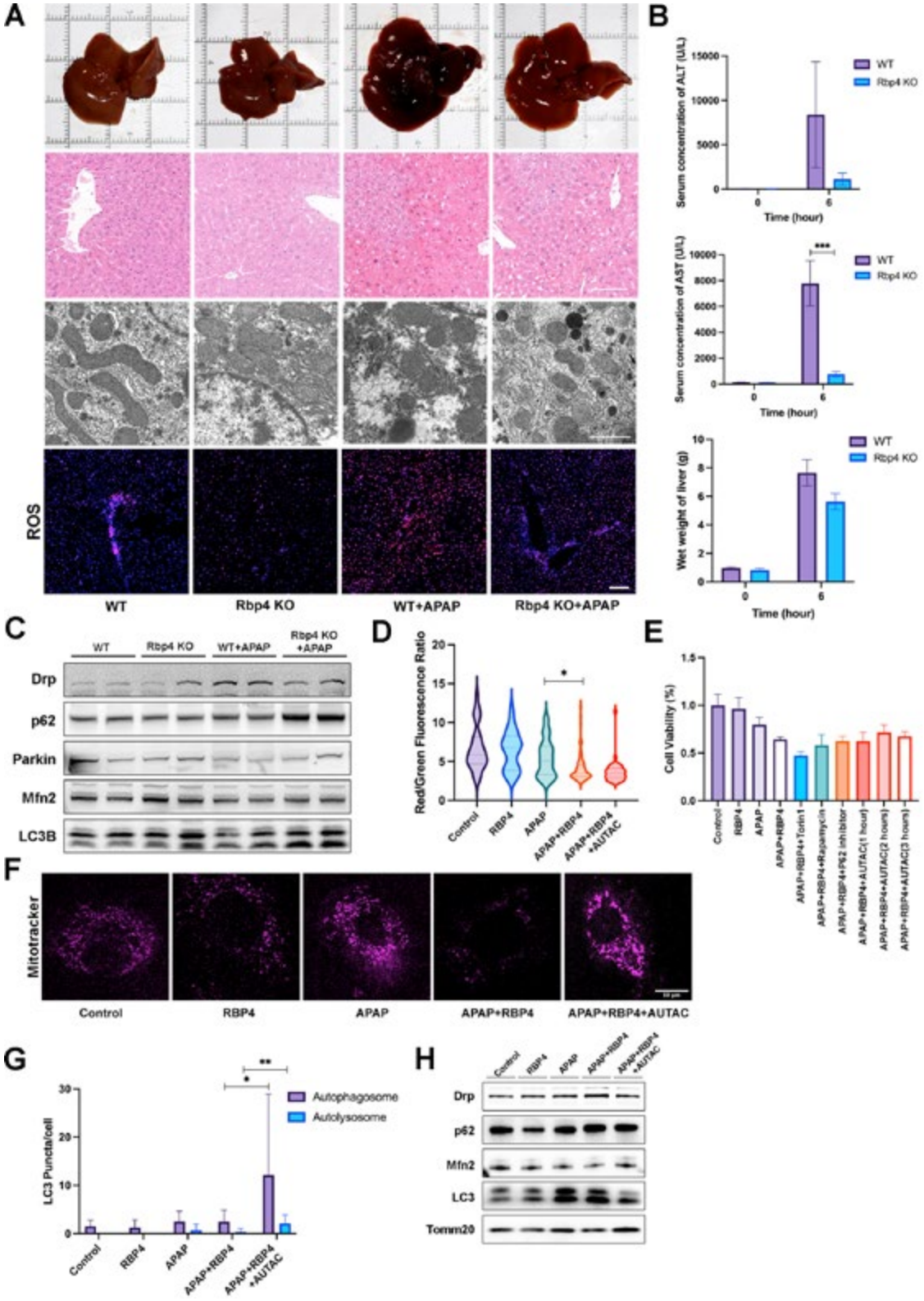

Disclosures: Jie Wang: Nothing to Disclose, Xiaohan Qian: Nothing to Disclose, Qi Xia: Nothing to Disclose

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4045 | PREVALENCE, CHARACTERISTICS AND OUTCOMES OF INFECTIONS IN PEDIATRIC ACUTE LIVER FAILURE

Tamoghna Biswas[1] Bikrant Biharilal Raghuvanshi[1] Vikrant Sood[1] Rajeev Khanna[1] Seema Alam[1]

[1]Institute of Liver and Biliary Sciences

Background: Pediatric acute liver failure (PALF) is associated with an increased risk of infections. While studies in adults suggest an association of sepsis with attributable mortality of 10-37% in acute liver failure, there is lack of data in the pediatric population. The present study intends to evaluate the prevalence and characteristics of infections in PALF and its association with outcomes. **Methods:** This was a descriptive observational hospital-based study conducted in a tertiary care pediatric hepatology referral center. Data was retrieved from a prospectively maintained database of patients admitted with PALF between January 2012 and May 2024. All patients below 18 years of age fulfilling the Pediatric Acute Liver Failure Study Group (PALFSG) criteria for diagnosis of PALF were included in the study. The study population was classified into four groups. Group 1 (sepsis) included patients who had culture positive infections. Group 2 (probable sepsis) included culture negative patients who had any one or more of the following three parameters viz. fever more than 38°C (100.4°F), age-appropriate leucocytosis or leucopenia and a high serum procalcitonin. Group 3 was an overarching group comprising both groups 1 and 2, while Group 4 (no sepsis) included patients who had neither culture positive infections nor any of the markers of probable sepsis. **Results:** A total of 417 patients were included in the study. 72 patients (17.3%) had culture positive infections (Group 1) while 105 patients (25.2%) had probable sepsis without culture positivity (Group 2). 177 patients (42.4%) had either definite or probable sepsis (Group 3). Mini-bronchoalveolar lavage (mini-BAL) was the commonest site of culture positivity (7.2%) followed by blood (6%) and urine (2.9%). Among the patients with culture positive sepsis, Gram negative infections were more common namely Klebsiella pneumoniae (26.4%), Escherichia coli (12.5%), Pseudomonas aeruginosa (12.5%), Acinetobacter baumannii (11.1%), Stenotrophomonas maltophilia (5.6%) and Salmonella (4.2%). Invasive fungal infections were seen in 9 children with Candida and Aspergillus being the two most common species isolated. Culture positive sepsis was associated with presence of Grade 3 or 4 hepatic encephalopathy ($p<0.001$), intensive care unit admission ($p<0.001$), invasive mechanical ventilation ($p<0.001$) while there was a trend towards association with presence of acute kidney injury ($p=0.078$). There was no association of therapeutic plasma exchange ($p=0.655$) or continuous renal replacement therapy ($p=0.114$) with culture positive infections. Presence of either culture positive or probable sepsis (Group 3) was associated with a decreased native liver survival ($p=0.04$) and overall survival ($p=0.004$) at 28 days but this association was not apparent in the culture positive subgroup (Group 1). **Conclusion:** Infections are common among PALF patients and can significantly influence outcomes.

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

4046 | MESENCHYMAL STROMAL CELL ENCAPSULATION IN MODIFIED ALGINATE AFFECTS THEIR FUNCTION, IMPROVES THEIR CYTOKINE PRODUCTION AND HEPATOCYTE SUPPORT

Kadriye Güven[1] Celine Filippi[2] Anil Dhawan[2] Isaac Ching[2]

[1]King's College London, [2]King's College Hospital

Background: Hepatocyte microbeads (HMB001) developed by our group have been used to treat children with acute liver failure, serving as a bridge to recovery or transplantation, and have shown some efficacy. We've now developed a new type of microbeads (HMB002) made of modified alginate and UC-MSCs to maintain or improve hepatocyte functions. The exact mechanism of action and the contribution of MSCs within the beads are not yet fully understood. This study is to determine the impacts of the encapsulation and alginate composition on MSC functions, enabling them to support hepatocyte activity within the microbeads. **Methods:** UC-MSCs (Passages 4) were encapsulated in clinical-grade alginates, SLG20 or G-RGD, cultured for up to 5 days, and analysed using an Oroboros instrument for OXPHOS, ELISA and qPCR. Data (n=3) were analysed using two-way ANOVA (GraphPad Prism10). **Results:** The OXPHOS study showed that on day 0, the uncoupled oxygen consumption of encapsulated cells seemed inhibited, without any difference between the alginates. We hypothesised that alginate

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encapsulation might create a hypoxic environment, shifting control of oxidative phosphorylation from the overall quantity of mitochondrial respiratory chain to oxygen availability. An O_2-dependent fluorescent dye did not reveal overt hypoxia; however, gene expression analysis showed a doubling of the hypoxia-inducible factor (HIF1a) mRNA expression ($p<0.001$), indicating that MSCs did detect a lower O_2 environment. Encapsulation significantly increased initial VEGF and IL-6 production compared to usual 2D cultures (40vs0, $p<0.0001$ and 400vs24pg/hr/10^6 cells, $p<0.0001$, respectively). In contrast, 2D MSCs showed TNFα expression higher than encapsulated cells (24vs8 pg/hr/10^6 cells, $p<0.05$). No significant differences in IL-10 levels were observed between groups. Interestingly, MSC oxidative phosphorylation increased over time in G-RGD alginate, becoming higher on day 5 compared to SLG20 (24vs10 pmol O_2/10^6 cells/sec; $p<0.0001$), correlating with improved support that MSCs provide to hepatocytes when co-encapsulated in modified alginate. **Conclusion:** Encapsulating MSCs in modified alginate alters their functionality, enhances their cytokine production, which may participate in their support for co-encapsulated hepatocytes.

Disclosures: Kadriye Güven: Nothing to Disclose, Celine Filippi: Nothing to Disclose, Anil Dhawan: Bit Bio: Consultant, Aspect Bio: Consultant, Astellas: Consultant, Univar: Advisor, Orphalan: Advisor, Isaac Ching: Nothing to Disclose

4047 | OUTCOMES OF PLASMA-EXCHANGE AND CONTINUOUS RENAL REPLACEMENT THERAPY IN A VIRAL HEPATITIS PREDOMINANT COHORT OF ACUTE LIVER FAILURE: A MULTICENTRIC STUDY

Akash Roy[1] Karan Kumar[2] Madhumita Premkumar[3] Amarthya sree Racha[4] Anand Gupta[5] Mithun Sharma[6] Manasa Alla[7] Sowmya T R[7] Shantan Venishetty[7] Uday Ghoshal[1] Mahesh Goenka[1] Padaki Nagaraja Rao[8] Vivek Saraswat[9] Nageshwar Reddy[7] Anand Kulkarni[10] K Rajender Reddy[11]

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Background: Liver support measures have improved outcomes in patients with acute liver failure (ALF). Standard volume plasma exchange (PLEx) and continuous renal replacement therapy (CRRT) have been shown to improve outcomes, but comparative determinants remain unexplored. **Methods:** In a multicenter cohort study of ALF patients across four tertiary care centers in India between January 2021-December 2023, we compared the characteristics of survivors and non-survivors in those receiving PLEx and CRRT and ascertained predictors of mortality. **Results:** Out of 128 patients [median age-23 years; females-39%; MELD-32.7;50.7% viral hepatitis A], 63(49.2%)] received PLEx and 63(49.2%) received CRRT. 34(52.3%) of those receiving PLEx, and 23(26.5%) of those receiving CRRT died (p=0.08). Non-survivors with PLEx had more advanced grades of hepatic encephalopathy (70.6% vs 41.9%, p=0.02), a higher mechanical ventilation requirement (67.7% vs 9.7%, p<0.01), lower haemoglobin (10.9±2.3 vs11.6±2.7 g/dl,p=0.02), higher procalcitonin (2.1(0.48-4.5)vs. 0.6(0.35-1.15)ng/ml,p=0.02] and more likely to satisfy King's College Criteria (KCC) (85.2% vs 22.5% (p <0.01). Model of advanced HE (or mechanical ventilation) [aOR4.13(1.75-9.7)], procalcitonin [(1.18(1.07-1.30)] and satisfying KCC [4.6(1.6-13.1)] best predicted non-survival with PLEx [AUC 0.83(0.71-0.91)]. Non-survivors with CRRT, had higher baseline ammonia [(198(150.7-228) vs 133.5(111.5-161), umol/p<0.01],lower haemoglobin (11.1±1.8vs12.2±2.7,P=0.02), higher procalcitonin,[4.5(2.8-8.9) vs2.10(1.4-4.2),p=0.03],higher lactate [(4.5(2.8-8.9)vs2.10(1.4-4.2)umol/l,p<0.01], and more likely to satisfy KCC(56.5% VS 10%,p<0.01). The model composed of lactate [1.37(1.22-1.54)] and satisfying KCC[6.4(2.5-15.8)] best predicted non-survival with CRRT [AUC 0.91(0.81-0.97)(P=<0.01)]. There was a trend towards better 21-day survival with CRRT(p=0.10). **Conclusion:** In a viral hepatitis-predominant ALF cohort, different predictors determine outcomes with PLEx and CRRT, thus mandating individualized selection criteria.

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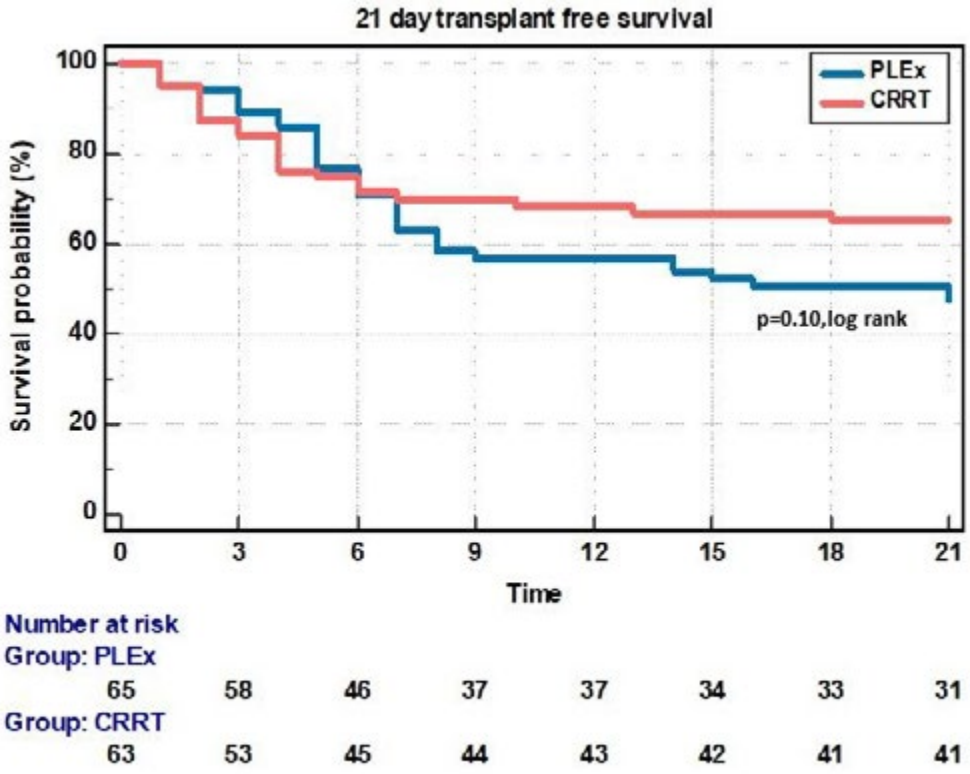

Figure: Showing Kaplan-Meier curves for 21-day transplant-free survival for PLEx and CRRT

Disclosures: Akash Roy: Nothing to Disclose, Karan Kumar: Nothing to Disclose, Madhumita Premkumar: Nothing to Disclose, Amarthya sree Racha: Nothing to Disclose, Anand Gupta: Nothing to Disclose, Mithun Sharma: Nothing to Disclose, Manasa Alla: Nothing to Disclose, Sowmya T R: Nothing to Disclose, Shantan Venishetty: Nothing to Disclose, Uday Ghoshal: Nothing to Disclose, Mahesh Goenka: Nothing to Disclose, Padaki Nagaraja Rao: Nothing to Disclose, Vivek Saraswat: Nothing to Disclose, Nageshwar Reddy: Nothing to Disclose, Anand Kulkarni: Nothing to Disclose, K Rajender Reddy: Nothing to Disclose

4048 | CONCERNING RISE IN MORTALITY TRENDS FROM ACUTE AND SUBACUTE HEPATIC FAILURE IN THE UNITED STATES: A 24-YEAR ANALYSIS OF NATIONAL EPIDEMIOLOGIC DATA

Syed Adeel Hassan[1] Khawaja Abdul Rehman[2] Waqas Rasheed[1] Mohamed Elbealawy[1] Ruben Plentz[1]

[1]University of Kentucky, [2]CMH Lahore Medical College

Background: Acute and subacute hepatic failure (AHF/SAHF) are life-threatening complications resulting in multi-organ dysfunction. Despite advancements in management, patients require liver transplantation. It is perceived that new therapeutic developments have improved overall outcomes. Studies ascertaining recent trends in AHF/SAHF mortality are limited. Here, we aim to assess AHF/SAHF mortality trends over the span of 24 years in the US. **Methods:** We analyzed death certificate data from the CDC WONDER database from January 1, 1999, to December 31, 2022. Deaths in adults aged ≥ 25 years were included. Mortality data was retrieved by diagnostic ICD-10 code K72.0 using Multiple Cause-of-Death. Age-adjusted mortality rate (AAMR) per 100,000 persons, annual percentage change (APC), average annual percentage change (AAPC), 95% CI were calculated and stratified by year, age, gender, race, and region. Mortality rates were age-adjusted to US standard population from the year 2000. Temporal trends were examined using Joinpoint Regression by fitting log-linear regression models and weighted Bayesian information criterion. Slopes were considered increasing or decreasing if the estimated slope differed significantly from zero. The statistical significance was determined by 2-sided t testing (P≤ 0.05). **Results:** During 1999–2022, 68,588 people died from AHF/SAHF. AAMR increased from 0.6 in 1999 to 2.9 in 2022 (AAPC:7.07,95%CI:6.68-7.66,p≤0.05). Males had higher mortality burden (AAMR:3.3,95%CI:3.2-3.3)

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versus females (AAMR:2.5,95%CI:2.4-2.6). AAMR increased in males from 0.8 in 1999 to 3.3 in 2022 (AAPC:6.2,95%CI:4.12-6.99, p≤0.05). An accelerated increase in female was seen from 0.4 in 1999 to 2.5 in 2022 (AAPC:8,95%CI:7.4-8.9, p≤0.05). Among the racial groups, AAMR was highest in American Indians and Alaskan natives (AIAN) (7.6). AAPC in AAMR increased across all the racial subgroups with the highest increase in AIAN (AAPC:10.1,95%CI:8.3-11,p≤0.05) and Whites (AAPC:7,95%CI:6.4-7.8, p≤0.05). AAMR also varied based on census regions (West:2.9, South:3.1, Northeast:2.4, Midwest:2.7). Patients aged 65-85+ had the highest AAMR (6.1,AAPC:7.14). AAPC increased across all age groups with more prominent AAMR increments in the younger age groups 25-44 (AAPC:7.05,95%CI:5.8-8.6, p≤0.05) and 45-64 (AAPC:7.14,95%CI:6.7-7.6, p≤0.05, Table 1). **Conclusion:** AHF/SAHF mortality continues to rise across all age groups with more prominent increase in younger patients. Our results identify at high-risk individuals based on racial/demographic factors. Further studies with targeted interventions in these populations are needed to curb this silently growing burden.

Table 1: Age adjusted mortality rates (AAMR) with average annual percentage change (AAPC) of Acute and Subacute Hepatic Failure in the United States from 1999-2022

Stratification Variable	Age Adjusted Mortality Rate per 100,000 Population						
	Year: 1999	95% Confidence Interval	Year: 2022	95% Confidence Interval	AAPC (%)	95% Confidence Interval	*P*-Value
Annual Trend	0.6	0.6-0.6	2.9	2.8-2.9	+7.07	6.68-7.66	< 0.000001
Gender:							
Males	0.80	0.70-0.90	3.30	3.20-3.40	+6.20	4.12-6.99	< 0.000001
Females	0.40	0.40-0.50	2.50	2.40-2.60	+8.02	7.40-8.93	< 0.000001
Age:							
25-44 years	0.20	0.20-0.20	1.10	1-1.2	+7.05	5.86-8.65	< 0.000001
45-64 years	0.70	0.60-0.70	3.40	3.30-3.50	+7.14	6.70-7.64	< 0.000001
65-85+ years	1.50	1.40-1.60	6.20	6-6.40	+6.63	6.21-7.31	< 0.000001
Race:							
American Indian/Alaskan Native	0.10	0.10-2.30	7.90	6.50-9.40	+10.13	8.34-11.80	0.0012
Asian or Pacific Islander	0.5	0.30-0.80	1.80	1.60-2	+5.81	4.84-7.22	< 0.000001
African American	1	0.90-1.20	3.70	3.40-3.90	+5.88	5.33-6,52	< 0.000001
White	0.60	0.50-0.60	2.80	2.70-2.90	+7.08	6.48-7.84	< 0.000001
Hispanic	0.70	0.50-0.90	3	2.80-3.20	+6.16	5.43-7.05	< 0.000001
Census Regions:							
Northeast	0.50	0.40-0.60	2.40	2.30-2.60	+6.76	5.54-7.66	< 0.000001
Midwest	0.70	0.60-0.70	2.70	2.60-2.90	+6.16	5.27-7.44	< 0.000001
South	0.60	0.60-0.70	3.20	3.10-3.30	+6.99	6.05-7.84	< 0.000001
West	0.60	0.60-0.70	2.80	2.70-3	+6.45	5.49-7.19	< 0.000001

Disclosures: Syed Adeel Hassan: Nothing to Disclose, Khawaja Abdul Rehman: Nothing to Disclose, Waqas Rasheed: Nothing to Disclose, Mohamed Elbealawy: Nothing to Disclose, Ruben Plentz: Nothing to Disclose

4049 | RISK FACTORS FOR PROLONGED LENGTH OF STAY IN PATIENTS WITH ALF: NATIONWIDE ANALYSIS

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Background: Acute liver failure (ALF) is defined as an acute impairment of liver function that could be caused by toxic, viral, autoimmune, or hereditary liver disease. Although etiology significantly defines the prognosis of patients with ALF, not much is known about the risk factor for worse prognosis in this specific group. Therefore, the aim of this study is to determine whether known comorbidities can worsen the clinical outcomes measured as

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length of stay of patients with ALF. **Methods:** A retrospective cohort study was conducted by querying the National Inpatient Sample (NIS) for the years 2016 to 2019. All patients with age ≥ 18 and with discharge after admission for ALF were included in the analysis. The sample was subsequently divided into two groups corresponding to the presence or absence of prolonged length of stay (pLOS). pLOS was defined by the following formula: Q3 + (1.5*IQR). The primary outcome was the inpatient odds of pLOS in the presence of different comorbidities defined by the Charlson Comorbidity Index (CCI). Multivariate regression analyses were used to adjust for covariates. **Results:** A total of 284,940 adult patients with ALF were identified of which 25,645 (9.0%) had a pLOS. In this specific study, the pLOS was 12 days. The three most seen comorbidities from CCI were diabetes mellitus type 2, congestive heart failure, chronic kidney disease. Higher odds for pLOS were seen in patients with myocardial infarction (aOR: 1.98, p<0.001), congestive heart failure (aOR: 1.40, p<0.001), cerebrovascular accident (aOR: 1.48, p<0.001), dementia (aOR: 1.42, p<0.001), connective tissue disease (aOR: 1.25, p=0.002), peptic ulcer disease (aOR: 1.35, p<0.001), hemiplegia (aOR: 3.41, p<0.001), chronic kidney disease (aOR: 1.34, p<0.001), and lymphoma (aOR: 1.83, p=0.002). Lower odds for pLOS were seen in patients with age > 60 (aOR: 0.90, p<0.001), and diabetes mellitus type 2 (aOR: 0.73, p<0.001). **Conclusion:** Independently from the etiology of ALF in our study, some comorbidities increased the odds of having a pLOS. Surprisingly, older age (age > 60 years) had lower odds of having pLOS which could be explained by relatively good spontaneous survival rate seen in previous studies. In conclusion, our study demonstrated that there are some risk factors that could be used to characterize patients with ALF who are expected to require more intensive care. Further studies could subdivide the etiology of ALF and determine specific risk factors for each subgroup.

Table 1. Adjusted OR for Primary Outcome in Patients with ALF **with Prolonged Length of Stay. N = 284,940**

Variable	Odd ratio (Confidence Interval)	P value
> Above 60	0.90 (0.87 – 0.93)	<0.001
Myocardial Infarction	1.98 (1.60 – 2.46)	<0.001
Congestive Heart Failure	1.40 (1.29 – 1.52)	<0.001
Peripheral Vascular Disease	1.00 (0.84 – 1.20)	0.974
Cerebrovascular Accident	1.48 (1.25 – 1.75)	< 0.001
Dementia	1.42 (1.23 – 1.63)	<0.001
COPD	1.08 (0.99 – 1.18)	0.077
Connective Tissue Disease	1.25 (1.08 – 1.44)	0.002
Peptic Ulcer Disease	1.35 (1.17 – 1.56)	<0.001
DM type II	0.73 (0.68 – 0.78)	<0.001
Hemiplegia	3.41 (2.25 – 5.16)	<0.001
CKD	1.34 (1.25 – 1.43)	<0.001
Leukemia	0.77 (0.44 – 1.33)	0.348
Lymphoma	1.83 (1.26 – 2.67)	0.002
HIV	0.79 (0.49 – 1.28)	0.347

Disclosures: Donghyun Ko: Nothing to Disclose, Do Han Kim: Nothing to Disclose, Sharon Narvaez: Nothing to Disclose, Luis Nieto: Nothing to Disclose, Pedro Palacios Argueta: Nothing to Disclose, Paul Kroner: Nothing to Disclose, Frank Lukens: Nothing to Disclose

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4050 | PROGRAMMED CELL DEATH FACTOR 4 AGGRAVATES SEPSIS-INDUCED LIVER DAMAGE THROUGH DISTURBED MITOCHONDRIAL QUALITY CONTROL SYSTEM

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Background: Sepsis is the most common cause of death in intensive care units, caused by deregulated immune response to infection. Sepsis-induced acute liver dysfunction occurs in the early stage of sepsis and can aggravates the progression of sepsis. However, there is a lack of specific diagnostic markers for sepsis-induced liver injury (SLI). Therefore, our study would screen potential biomarkers and elucidate their roles in pathogenesis of liver damge during sepsis, which is of great significance for clinical diagnosis and provides therapeutic targets for disease management. **Methods:** Lipopolysaccharide (LPS) was utilized to build the SLI mouse model and then pathological alterations in livers were observed by H&E staining, liver function were analyzed by ELISA, and inflammatory and pro-apoptotic proteins were assessed by Western Blot. Differential proteins of SLI were screened using LC-MS/MS, and further validated through Western Blot and RT-PCR. CCK8 assays and TUNEL assay were used to evaluate cell proliferation and apoptosis. Mitochondrial oxidative stress and membrane potential were assessed by MitoSOX and JC1 staining. Furthermore, mito-tracker and lyso-tracker analysis, along with Western Blot, were deployed to detect alterations of mitochondrial quality control. **Results:** Increased inflammatory and apoptotic responses were observed in the SLI mouse models, with liver dysfunction. Through differential protein analysis, the key protein PDCD4 was screened and identified to be significantly upregulated during sepsis-induced liver damage ($p < 0.05$). LPS exposure increased PDCD4 in hepatocytes, while genetic ablation of PDCD4 reduced LPS-induced hepatic dysfunction. Proteomic analysis showed that PDCD4 ablation mainly affected mitochondrial function. Molecular investigations confirmed that loss of PDCD4 protected liver against sepsis though inhibiting mitochondrial oxidative stress and membrane potential dysregulation. Furthermore, upon LPS stress PDCD4 disrupted mitochondrial quality control, induced pathological mitochondrial fission and mitophagy, and inhibited mitochondrial fusion and biogenesis. Co-IP assays indicated that the accumulation of PDCD4 regulated mitochondrial fusion through the combination with mitochondrial inner membrane protein YME1L1, contributing to the imbalance in mitochondrial quality control. **Conclusion:** Our data show that LPS-induced liver damage is associated with PDCD4 upregulation, which is followed by disrupted mitochondrial quality control through the combination with YME1L1, causing hepatocyte inflammation and apoptosis. Based on this, new potential therapeutic strategies for reducing PDCD4 and enhancing mitochondrial quality control could be expected to treat spesis-induced liver damage.

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Programmed cell death factor 4 aggravates sepsis-induced liver damage through disturbed mitochondrial quality control system

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BACKGROUND:

Sepsis is the most common cause of death in intensive care units, caused by deregulated immune response to infection. Sepsis-induced acute liver dysfunction occurs in the early stage of sepsis and can aggravates the progression of sepsis. However, there is a lack of specific diagnostic markers for sepsis-induced liver injury (SLI). Therefore, our study would screen potential biomarkers and elucidate their roles in pathogenesis of liver damge during sepsis, which is of great significance for clinical diagnosis and provides therapeutic targets for disease management.

METHODS:

1. Animal Models of Liver Injury

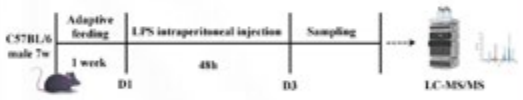


Figure 1: Lipopolysaccharide (LPS) was utilized to build the SLI mouse model and then pathological alterations in livers were observed by H&E staining, liver function were analyzed by ELISA, and inflammatory and pro-apoptotic proteins were assessed by Western Blot. Differential proteins of SLI were screened using LC-MS/MS, and further validated through Western Blot and RT-PCR.

2. LPS-induced Injury in AML12 cells

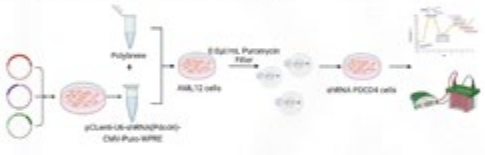


Figure 2: CCK8 assays and TUNEL assay were used to evaluate proliferation and apoptosis of AML12 cells. MitoSOX and JC1 staining were used to determine oxidative stress level and membrane potential of AML12 cells. Furthermore, mito-tracker and lyso-tracker analysis, along with Western Blot, were deployed to detect alterations in mitochondrial quality control mechanisms within the AML12 cells.

3. Searching for Interacting Proteins Based on CoIP-MS

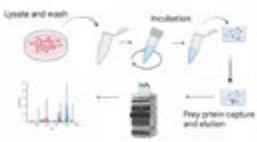
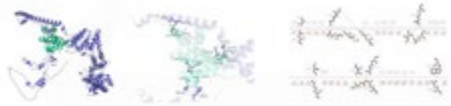
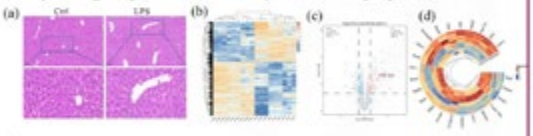


Figure 3: Immunoprecipitation techniques, LC-MS/MS, and immunoblotting were utilized to investigate the interaction between PDCD4 and YME1L1. The Cluspro website was then used to predict the 3D structure of PDCD4 and YME1L1.



RESULTS :

1. Exploring Key Proteins in Septic Liver Injury via LC-MS/MS



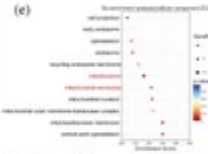


Figure 4: PDCD4 as a Crucial Target in the Pathogenesis of Septic Liver Injury. Increased inflammatory and apoptotic responses were observed in the SLI mouse models, with liver dysfunction. (a) H&E staining was performed to observe morphological changes in the liver. (b-e) Differential proteomic analysis of animal tissue with sepsis liver injury.

2. Knockdown of PDCD4 expression in hepatocytes alleviate hepatocyte injury in sepsis.

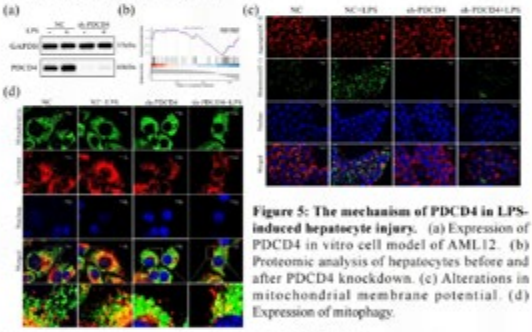


Figure 5: The mechanism of PDCD4 in LPS-induced hepatocyte injury. (a) Expression of PDCD4 in vitro cell model of AML12. (b) Proteomic analysis of hepatocytes before and after PDCD4 knockdown. (c) Alterations in mitochondrial membrane potential. (d) Expression of mitophagy.

3. Direct-acting protein of PDCD4: YME1L1

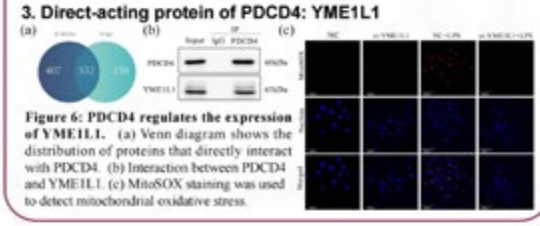


Figure 6: PDCD4 regulates the expression of YME1L1. (a) Venn diagram shows the distribution of proteins that directly interact with PDCD4. (b) Interaction between PDCD4 and YME1L1. (c) MitoSOX staining was used to detect mitochondrial oxidative stress.

CONCLUSION :

Our data show that LPS-induced liver damage is associated with PDCD4 upregulation, which is followed by disrupted mitochondrial quality control through the combination with YME1L1, causing hepatocyte inflammation and apoptosis. Based on this, new potential therapeutic strategies for reducing PDCD4 and enhancing mitochondrial quality control could be expected to treat spesis-induced liver damage.

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Disclosures: Jiachi Yu: Nothing to Disclose, ruibing li: Nothing to Disclose

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4051 | OUTCOMES OF COMBINATION OF THERAPEUTIC PLASMA EXCHANGE (TPE) AND STEROIDS IN PATIENTS WITH ACUTE SEVERE AUTOIMMUNE HEPATITIS WITH ACUTE LIVER FAILURE

Manasa Alla[1] Sowmya T R[1] Mithun Sharma[2] Anand Kulkarni[3] Pragati Naik[1] Shantan Venishetty[1] Nagaraja Rao Padaki[1] Nageshwar Reddy Duvvur[1]

[1]AIG Hospitals, [2]ASIAN INSTITUTE OF GASTROENTROLOGY PVT LTD, [3]Asian Institute of Gastroenterology

Background: Autoimmune hepatitis (AIH) can have varied presentations and a small proportion present with acute severe AIH with features of acute liver failure (ALF). Corticosteroids alone are associated with unfavourable outcomes in patients with high MELD scores. Hence we evaluated the efficacy and outcomes of TPE followed by introduction of steroids in AS-AIH with ALF patients. **Methods:** We conducted a retrospective study from Jan 2023- Dec 2023 of all patients admitted with AS-AIH at a tertiary care centre. Acute on chronic liver failure, severe acute hepatitis and ALF were categorized as AS-AIH patients. Among 30 patients admitted with a diagnosis of AS-AIH, we included 8 who had features of acute liver failure initially treated with single volume TPE. On resolution of hepatic encephalopathy (HE), steroids were initiated as per institutional AIH protocol and followed up for a period of 6 months. Clinical & biochemical parameters & outcome measures were analysed. **Results:** Total 8 patients were analysed. Mean age of ALF patients was 32.2±5.3 years and women were 62.5%. Mean MELD scores were 31.12± 7.4. All patients received standard medical care, including N-acetyl cysteine and nutritional support. Mean bilirubin and INR was 24 ± 3.2 mg/dl and 4.91± 1.5 respectively. 6 patients were seropositive and 2 were seronegative. Mean arterial ammonia was noted 110 ± 23.9 mmol/L and IgG levels were 29 ± 4.32 mg/dl respectively. 6 patients were in grade II and 2 were in grade III encephalopathy on admission. TPE was initiated in all patients with mean days post admission 1.8 ± 0.2; mean no of TPE sessions 2.1 ± 1.2. Mean days of hospitalization were 11.2 ± 3.52 days. Hepatic encephalopathy recovered in 7 patients while 1 patient progressed to grade 4 HE. Steroids were initiated after TPE with mean days of 7.2 ± 2.22 post admission as per institutional AIH protocol. One patient developed sepsis which was treated and resolved; no incidence of AKI; transplant free survival was noted in 7/8 pts at 30 days. On 6 month follow up, 7 patients had complete resolution of jaundice and transaminitis and remained in remission **Conclusion:** Acute severe presentations remain a challenge in the treatment of AIH. Combination therapy of TPE followed by steroids in AS-AIH with ALF patients is a promising strategy to improve transplant free survival and achieve remission.

Disclosures: Manasa Alla: Nothing to Disclose, Sowmya T R: Nothing to Disclose, Mithun Sharma: Nothing to Disclose, Anand Kulkarni: Nothing to Disclose, Pragati Naik: Nothing to Disclose, Shantan Venishetty: Nothing to Disclose, Nagaraja Rao Padaki: Nothing to Disclose, Nageshwar Reddy Duvvur: Nothing to Disclose

4052 | NEXTGENERATION EXTRACORPOREAL ALBUMIN DETOXIFICATION AND DIALYIS (ECAD) IS MORE EFFECTIVE IN REMOVING TOXIC BILE ACIDS THAN PLASMA EXCHANGE (PE)

Jan Stange[1] Sebastian Koball[1] Michael Hinz[1] Tarek Hassanein[2]

[1]University of Rostock, [2]Southern California Liver Centers

Background: Liver Failure is associated with an accumulation of endoxenous toxins causing secondary organ failures. Toxic serum levels of Bile Acids are emerging as direct inducers of hymodynamic failure, renal failure, immunosuppression, mitochondrial toxicity and sarcopenia. Extracorporeal Detoxification aims to reduce bile acid levels to prevent or reverse such secondary organ failures. The aim was to investigate the effect of plasma exchange therapy with the next generation of extracorporeal albumin detoxification/dialysis (ECAD). **Methods:** Total Bile Acids were detected in the serum of subjects during the course of 8 plasma exchange therapies with fresh frozen plasma (1.5 plasma volumes) and 11 treatments with Albunique, a next generation of ECAD. The reduction and the reduction rate were assessed and compared. **Results:** Plasma exchange therapy resulted into a redution to 73.9 +/- 0.16 % of the initial baseline. ECAD resulted into a reduction to 57.4 +/- 0.18 % of the initial baseline. The total reduction by 26% versus 42% was significantly higher for ECAD therapies than for Plasma Exchange therapies using standard exchange rates. **Conclusion:** Since Bile Acids have a significant role in the development of secondary organ failures in liver failure than bilirubin, bile acids should be a more reliable

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guide to indicate treatment iniutiation and treament choice. Using the exchange volumes recommended, Plasma Exchange is less effective in reducing toxic bile acids as a relevant biomarker than next generation of ECAD.

Disclosures: Jan Stange: Albutec GmbH: Advisor, Sebastian Koball: Nothing to Disclose, Michael Hinz: Nothing to Disclose, Tarek Hassanein: Nothing to Disclose

4053 | PREDICTORS OF IN-HOSPITAL AND POST-DISCHARGE MORTALITY AMONG ACUTE LIVER FAILURE RECIPIENTS IN THE U.S.

Douglas Schaubel[1] K Rajender Reddy[2] Therese Bittermann[3]

[1]University of Pennsylvania Perelman School of Medicine, [2]University of Pennsylvania, [3]Perelman School of Medicine

Background: The deceased-donor liver allocation system in the United States gives top priority to acute liver failure (Status 1) patients. Although this is consistent with the objectives of an urgency-based system, it is important to predict post-transplant outcomes in such patients to avoid futility. While multiple prognostic models have been developed to assess transplant-free survival and/or determine the need for LT, far fewer are available to predict post-transplant survival. We sought to evaluate the pattern of post-transplant deaths over time and differences in risk factors for early in-hospital versus late deaths. **Methods:** Data were obtained from the United Network for Organ Sharing (UNOS). Our study cohort consisted of n=1975 adult (age 18+) deceased donor liver transplant recipients (2010-2022) who were Status 1 due to acute liver failure at transplant. We excluded multi-organ and repeat transplants. We used a novel two-part approach to modeling post-transplant death. Part 1 consisted of a logistic regression model for in-hospital mortality. Part 2 used Cox regression to model post-discharge mortality among patients who did not die in hospital. Of chief interest were patterns in (and predictors of) these two outcomes. Stepwise Cox regression was used, separately, to select predictors for each outcome. **Results:** The cohort was 67% female, 53% White, 22% Black, 13% Hispanic with median age 43. Severity at illness at LT was notable for 27% on dialysis and 46% ventilated. There were a total of 349 deaths (17.7%), over half (51.3%) of which occurred in the first post-transplant year. Among year 1 deaths, 79.3% occurred during the post-transplant hospitalization. Risk discrimination was moderate to good for death in-hospital death (C=0.73) and post-discharge survival(C=0.69). Odds ratios (OR) and hazard ratios (HR) for significant predictors of either in-hospital and/or post-discharge death are provided in Table 1. **Conclusion:** Status 1 patients at high risk for post-transplant death, with the risk concentrated during the post-transplant hospitalization and the first year post-transplant. Risk factors for in-hospital and post-discharge death overlap little.

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Table 1. Odds ratios (OR) and hazard ratios (HR) for significant predictors of either in-hospital and/or post-discharge death among n=1975 Status 1 deceased-donor liver transplants (UNOS).

Predictor		OR: In-hospital death	HR: Post-discharge death
Donor	**Recipient**		
	Age (per 5 years)	1.11	●
	Race: Black	2.14	1.34
	Race: Hispanic	●	0.58
	Diagnosis: drug toxicity	0.59	1.52
	Diabetes	●	2.14
	Dialysis	2.58	●
	Creatinine, per 1mg/dL	1.37	●
	Sodium	1.06	●
	Albumin	●	1.31
	Ventilation	2.02	1.32
	Functional status (per 10%)	0.85	●
	Working for income	●	0.62
	Post-transplant length of stay (per day)	n/a	1.02
Race: Hispanic		1.65	1.47
Height		●	1.02
Diabetes		2.07	●
Cocaine use		●	1.62
Death due to CVA		●	1.39

Variables included in the modeling (but not selected for either model) include the following recipient factors: year of transplant, years between wait listing and transplant, sex, Asian race, Other race, ascites, encephalopathy, days admitted prior to transplant; and the following donor factors: smoking status, donor/recipient CMV, previous MI, hypertension, age, weight, abo mismatch, sex, Black race, Asian race, tattoos, cause of death stroke, DCD, bilirubin.

Disclosures: Douglas Schaubel: Nothing to Disclose, K Rajender Reddy: Nothing to Disclose, Therese Bittermann: Nothing to Disclose

4054 | GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONIST, SEMAGLUTIDE PREVENTS LIVER CIRRHOSIS-INDUCED SKELETAL MUSCLE ATROPHY IN DIABETIC MICE

KOSUKE KAJI[1] *NORIHISA NISHIMURA*[1] *Shinya Sato*[1] *Tadashi Namisaki*[1] *Hitoshi Yoshiji*[1]

[1]*Nara Medical University*

Background: Recent studies have revealed a pharmacological action of glucagon-like peptide-1 receptor agonist (GLP-1RA) in skeletal muscle homeostasis, but the therapeutic effect of semaglutide, a GLP-1RA, on skeletal muscle atrophy in liver cirrhosis is still obscure. The aim of this study was to investigate the effects of semaglutide on liver cirrhosis-related skeletal muscle atrophy and dysfunction under diabetic conditions in mice model. **Methods:** To induce liver cirrhosis under diabetic conditions, male diabetic KK-Ay mice were fed a diethoxycarbonyl-1,4-dihydrocollidine (DDC) diet for 6 weeks. Semaglutide (3 nmol/kg) was injected subcutaneously every 3 days. We evaluated the effects of semaglutide on grip strength and muscle mass index of the psoas major muscle using CT imaging, as well as on the pathophysiology of liver and skeletal muscle tissue in DDC-fed KK-Ay mice. In addition, we performed in vitro assays to evaluate the direct effects of semaglutide on C2C12 myocytes. **Results:** Semaglutide suppressed psoas muscle atrophy and delayed declines in grip strength in DDC-fed KK-Ay diabetic mice. Furthermore, semaglutide inhibited ubiquitin-proteosome-mediated

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skeletal muscle proteolysis and promoted myogenesis in murine skeletal muscle tissue and C2C12 myocytes. Mechanistically, this effect of semaglutide on skeletal muscle atrophy was mediated by multiple functional pathways. First, semaglutide protected mice from DDC- and diebetes-induced liver injury by increasing the production of insulin-like growth factor 1 and decreasing the accumulation of reactive oxygen species (ROS). These effects were associated with reduced accumulation of inflammatory cytokines and ROS and led to inhibition of ubiquitin-proteosome degradation in skeletal muscle tissue. Moreover, semaglutide inhibited stress signals related to amino acid starvation activated under chronic liver injury, resulting in restoration of mammallian target of rapamycin (mTOR) activity in skeletal muscle of mice. Second, semaglutide ameliorated skeletal muscle atrophy by directly stimulating GLP-1R in myocytes. Semaglutide treatment induced cAMP-mediated activation of protein kinase A (PKA) and AKT, enhanced mitochondrial biosynthesis, decreased ROS accumulation, and consequently inhibited NF-κB/myostatin-mediated degradation of ubiquitin proteosomes and enhanced myogenesis via activation of heat shock factor-1 (HSF-1). **Conclusion:** The present study demonstrate that semaglutide attenuates liver cirrhosis-related skeletal muscle atrophy in DDC-fed diabetic mice. Since semaglutide is clinically available, it may have potential as a novel therapeutic option for treating sarcopenia in cirrhotic patients with diabetes.

Disclosures: KOSUKE KAJI: Nothing to Disclose, NORIHISA NISHIMURA: Nothing to Disclose, Shinya Sato: Nothing to Disclose, Tadashi Namisaki: Nothing to Disclose, Hitoshi Yoshiji: Nothing to Disclose

4055 | CHILD-TURCOTTE-PUGH (CTP) SCORE-BASED MODIFIED ANTI-TUBERCULAR TREATMENT (ATT) IN PATIENTS WITH DECOMPENSATED CIRRHOSIS WITH TUBERCULOSIS: A TWO-YEAR SINGLE CENTRE RETROSPECTIVE OBSERVATIONAL STUDY FROM A HEPATOLOGIST IN NORTH INDIA

Juned Ahmad[1]

[1]*Myra Liver Gastro and Endoscopy centre*

Background: Management of tuberculosis in decompensated cirrhosis is challenging, as the risk of severe liver failure is markedly increased if hepatotoxicity develops secondary to ATT. CTP score-based ATT by Dhiman et al [1] proposed that number of hepatotoxic drugs should be two,one and none in CTP scores of ≤7, 8-10 and ≥11 respectively. We present here our retrospective observational study of treating tuberculosis in patients with decompensated cirrhosis utilizing the above-mentioned CTP-based ATT regimens. **Methods:** A retrospective observational study utilizing electronic data search was done on the Athancare ™ app software for the duration from April 2022 to April 2024 at Myra Liver Gastro and Endoscopy Center at Chowk, Lucknow, Uttar Pradesh, India. On the software, decompensated cirrhosis with tuberculosis patients were already tagged for easy retrieval of patient information. Patients who have completed at least 12 months of ATT were included in the study. The modified ATT regimens (weight-based) were as per the CTP score [1]. In patients with a CTP score ≥11, no hepatotoxic drug was included in the regimen -ELA: Ethambutol, Levofloxacin, and Amikacin (total of 60 doses); el-ethambutol and levofloxacin dosing as per creatinine clearance. In patients with CTP scores from 8-10, the regimen included 1 hepatotoxic drug (rifampicin preferred): RELA, rifampicin; and Rel (renal modified). Patients with CTP score ≤7 received two hepatotoxic drugs: HREL, H= Isoniazid; and HRel (renal modified). The duration of ATT's continuation phase was 12-18 months (Table 2). Their responses after the completion of ATT were documented as resolution of TB (R) or Death(D) **Results:** A total of 155 patients with decompensated cirrhosis were screened for the study (Table 1). NASH was the cause in 37.4% patients. 21 (13.5%) had concomitant tuberculosis and were evaluated further. CTP score-based modified ATT was administered in all 21 patients (Table 2).17 (80.9%) patients received modified ATT and 4 (19.1%) received renal modified ATT during the Intensive phase. Drug-induced hepatotoxicity developed in 4 patients (19.1%). After the intensive phase, 2 patients were lost to follow-up. 19 patients progressed to the continuation phase. Out of 19 patients,15 (78.9%) patients had a resolution of tuberculosis, and 4 (21.1%) patients died (3 after completion of continuation phase and 1 during continuation phase).The cause of death in all 4 patients was related to cirrhosis (2 had a variceal bleed and 2 died from sepsis) **Conclusion:** As per our study, patients with decompensated cirrhosis tolerated the CTP-score based modified ATT and almost 80% had a resolution of tuberculosis. One-fifth of the patients with concomitant tuberculosis died and cirrhosis-related complications were the primary cause of death in these patients. Lastly, data collection through app software is feasible and allows for representation of patients evaluated at private centres.

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Table 1: Depicts the etiology of decompensated cirrhosis and patients who had concomitant tuberculosis.

S No.	Aetiology of decompensated cirrhosis	n (%)	Patients with Concomitant Tuberculosis #,$ n (%)
Total		**155 (100)**	**21 (100)**
1.	NASH	58 (37.4)	10 (47.6)
2.	Hepatitis C	40 (25.8)	5* (23.8)
3.	Hepatitis B	22 (14.2)	1 (4.5)
4.	Ethanol	15 (9.6)	2* (9.5)
5.	EHPVO with parenchymal extinction	4 (2.5)	2 (9.5)
6.	Autoimmune hepatitis	2 (1.3)	0
7.	Wilson disease	1 (0.6)	0
8.	Cryptogenic	13 (8.3%)	2 (9.5)

Abbreviations: NASH, non-alcoholic steatohepatitis; EHPVO, extrahepatic portal vein obstruction.

#Extrapulmonary tuberculosis (EPTB) was present in 19 (90.4%) patients: peritoneal (10,52.6%), mesenteric lymphadenopathy-2, disseminated-2, genitourinary-2, spinal-1, and peripheral lymphadenopathy-1.

$ None of the patients had microbiological confirmation of tuberculosis. All 21 patients were diagnosed by: 1. Fluid analysis (exudative pattern, high adenosine deaminase levels in 6 patients)- ascites (n-12), pleural (n-3), CSF (n-1); 2. Fine needle aspiration cytology (n-2) showing granulomas, and 3. Imaging findings correlation.

*One patient with concomitant tuberculosis had dual etiology (Hepatitis C and ethanol)

Table 2: CTP score-based Modified ATT regimen in Intensive and continuation phase and their outcomes

CTP score	N (%)	Intensive Phase ATT 2 months		Hepato-toxicity (ATT induced)	N*	Continuation phase* 12-18 months		Outcome D-Death R-Resolution of TB
		Hepatic Modified	Renal modified			Hepatic Modified	Renal modified	
≥11	8 (38.1)	6 (ELA)	2 (el)	0	7	4 (EL)	3 (el)	2-D 5-R
8-10	8 (38.1)	8 (RELA)	0 (Rel)	2	7	4 (REL) 2 (rEL/EL)	1 (Rel)	2-D 5-R
7	5 (23.8)	3 (HREL)	2 (HRel)	2	5	2 (HRE) 2 (r/REL)	1 (HRe)	5-R
Total	21 (100)	17 (80.9%)	4 (19.1%)	4 (19.1%)	19	14 (73.6%)	5(26.3%)	4-D (21.1%) 15-R (78.9%)

Abbreviations: H-Isoniazid, R-Rifampicin, E-ethambutol, L-Levofloxacin, A-Amikacin, el-ethambutol and levofloxacin dosing as per Creatinine clearance, r-rifampicin at a lower dose of 300mg. Numbers in red depict patients who developed hepatotoxicity

*After the intensive phase, 2 patients were lost to follow-up (1 in CTP ≥11 & 1 in CTP 8-10 group)

Disclosures: Juned Ahmad: Nothing to Disclose

4056 | CLINICAL IMPACT OF RESPIRATORY ALKALOSIS IN LIVER TRANSPLANTATION CANDIDATES

Bradley Busebee[1] Michael Krowka[2] Nadine Al-Naamani[3] Michael Fallon[4] Kimberly Forde[5] Karen Krok[6] Steven Kawut[3] Hilary DuBrock[1]

[1]Mayo Clinic, [2]Mayo Clinic Rochester, [3]University of Pennsylvania, [4]University of Arizona, [5]Temple University, [6]Penn State Milton S. Hershey Medical Center

Background: Respiratory alkalosis is common among patients with chronic liver disease. The underlying pathophysiology and significance are poorly understood. We sought to determine the prevalence of respiratory alkalosis among liver transplant (LT) candidates and its associations with clinical characteristics, outcomes and biomarkers that may play a role in disease pathogenesis. **Methods:** We performed a cross-sectional analysis

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of a multicenter prospective cohort of patients evaluated for LT or with portopulmonary hypertension (PoPH). We excluded patients with obstructive lung disease, PoPH, and those without room air arterial blood gases or pulmonary function tests (PFTs). Respiratory alkalosis was defined as a pH > 7.4 and PaCO2 < 35mmHg. Analysis was completed with ANOVA and Pearson's tests, followed by multivariate logistic and linear regression. A sensitivity analysis was completed with PaCO2 as the continuous dependent variable. **Results:** Of 347 patients, 44.1% had respiratory alkalosis. Higher MELD-Na was associated with respiratory alkalosis (OR 1.07, p < 0.001) and lower PaCO2 (OR 1.08, p<0.001) in univariate analysis and after adjustment for age and gender. Patients with respiratory alkalosis were more likely to be white, have primary biliary cirrhosis (PBC) and less likely to have Hepatitis C (HCV). In unadjusted analysis, respiratory alkalosis was associated with dyspnea, cyanosis, jaundice, edema, ascites, hepatic encephalopathy (HE), worse physical quality of life and shorter 6-minute walk distance. Patients with respiratory alkalosis had higher PaO2, forced vital capacity and forced expiratory volume and higher 16 alpha hydroxy-DHEA, VCAM-1, Tie-2, and vWF% with lower E-selectin. These associations remained significant for all variables except dyspnea, jaundince and HE after adjustment for age, gender and MELD-Na (Table 1). **Conclusion:** Respiratory alkalosis was present in nearly half of LT candidates and was associated with worse liver disease severity and specific liver disease etiologies such as PBC with a lower risk among patients with HCV. Respiratory alkalosis was independently associated with symptoms such as cyanosis and edema with a specific biomarker profile of altered angiogenesis and inflammation.

	Respiratory Alkalosis (Log Regression)				pCO2 (Linear Regression)			
	OR	CI lower	CI upper	p value	estimate	CI lower	CI upper	p value
Demographics	1.74	1.07	2.85	0.02*	-1.18	-2.27	-0.09	0.03*
Liver Disease Etiology								
Alcohol Related Liver Disease	1.19	0.75	1.9	0.45	0.54	-1.49	0.64	0.43
HBV	0.38	0.06	1.59	0.23	1.52	-0.58	5.47	0.10
MASH	1.38	0.82	2.32	0.23	0.61	-1.44	0.98	0.70
PBC	4.16	1.54	13.22	0.008†	1.07	-5.29	-1.01	0.03*
HCV	0.42	0.26	0.66	< 0.006†	0.52	0.22	2.27	0.01*
Symptoms/Conditions								
Dyspnea	1.42	0.9	2.26	0.13	1.42	0.9	2.26	0.13
Syncope	1.21	0.22	6.73	0.82	1.21	0.22	6.73	0.82
Cyanosis	6.15	1.54	41.07	0.02*	-4.37	-7.19	-1.56	<0.001†
Jaundice	1.58	0.93	2.68	0.09	-0.64	-1.87	0.60	0.31
Edema	1.79	1.14	2.82	0.01*	-0.58	-1.62	0.46	0.27
PCS	0.97	0.95	0.99	0.01*	0.04	-0.02	0.09	0.18
MCS	1.00	0.98	1.02	0.75	0.02	-0.03	0.07	0.43
Complications of Liver Disease								
HPS	1.66	0.97	2.84	0.06	0.42	0.88	2.63	0.13
Ascites	1.53	0.91	2.6	0.11	-1.69	-2.87	-0.52	<0.002†
HE	1.11	0.7	1.77	0.66	-0.20	-1.29	0.88	0.71
Diagnostics								
FVC	1.49	1.14	1.95	0.004†	-1.17	-1.77	-0.57	0.004†
FEV^1	1.82	1.25	2.68	0.002†	-1.67	-2.51	-0.83	0.007†
FEV^1/FVC	1.00	0.96	1.03	0.80	0.05	-0.04	0.15	0.24
6MWT	1.00	0.99	1.00	0.02*	0.01	0.00	0.02	0.00
PO2	1.02	1.00	1.04	0.01*	-0.06	-0.09	-0.02	0.007†
Visual EF	1.00	0.96	1.04	0.92	-0.06	-0.15	0.03	0.20
PASP	0.98	0.95	1.01	0.14	0.03	-0.03	0.10	0.32
Respiratory Rate	0.93	0.87	0.98	0.02	0.11	-0.01	0.23	0.07
Biomarkers								
16α-Hydroxy-DHEA	1.03	1.01	1.06	0.02*	-0.04	-0.09	0.02	0.17
VCAM-1 (ng/mL)	1	1.01	1.00	0.03*	0.00	0.00	0.00	<0.004†
Angiostatin (pg/mL)	1	1.00	1.00	0.17	0.00	0.00	0.00	0.41
E-Selectin (pg/mL)	1	1.01	1.00	0.003†	0.00	0.00	0.00	0.01*
Tie 2 (pg/mL)	1	1.01	1.00	0.02*	0.00	0.00	0.00	0.06
vWF (%)	1	1.01	1.00	0.002†	0.00	-0.01	0.00	0.03*
DHEAs (ug/dL)	1	0.99	1.01	0.95	0.01	0.00	0.02	0.13
Estradiol (pg/mL)	1	0.99	1.01	0.69	0.00	-0.02	0.02	0.73

Table 1. The left side of the table shows the multivariate logistic regression analysis of patient characteristics and respiratory alkalosis adjusted for gender, MELD-Na, and age. The right side of the table shows the multivariate linear regression analysis of patient characteristics and pCO2 level on ABG adjusted for gender, MELD-Na, and age. 6MWT – 6 minute walk test distance (m), BMI – Body mass index, EF – Ejection fraction, FEV1 – Forced expiratory volume in 1 second, FVC – Forced vital capacity, HBV – Hepatitis B, HCV – Hepatitis C, HE – Hepatic encephalopathy, HPS—Hepatopulmonary Syndrome, MASH – Metabolic dysfunction-associated steatohepatitis, PCS – SF-RAND physical component score, PSC – Primary Sclerosing Cholangitis. †OR reported for change in 100 units of independent variable ‡OR reported for change in 1000 units of independent variable

Disclosures: Bradley Busebee: Nothing to Disclose, Michael Krowka: Nothing to Disclose, Nadine Al-Naamani: Nothing to Disclose, Michael Fallon: Nothing to Disclose, Kimberly Forde: Nothing to Disclose, Karen Krok:

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Nothing to Disclose, Steven Kawut: Regeneron: Consultant, United Therapeutics: Consultant, aerovate: Consultant, Hilary DuBrock: Nothing to Disclose

4057 | CAUSES OF MARKEDLY ELEVATED AMINOTRANSFERASES IN PATIENTS WITH CIRRHOSIS

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Background: Marked elevations in aminotransferases (≥1000 IU/L) typically indicates acute injury to the liver. Here, we hypothesized that the cause of elevation in aminotransferases ≥1000 in patients with cirrhosis is likely due to a limited number of disorders and may also be associated with poor clinical outcomes. Our aim was to investigate the most common etiologies of acute elevations in aminotransferases in patients with cirrhosis; and to investigate the associated outcomes. **Methods:** From May 2012 to December 2022 all patients with cirrhosis and an AST or ALT ≥1000 IU/L were identified through MUSC's Clinical Data Warehouse search engine. Complete clinical data were abstracted for each patient, and outcomes were examined. **Results:** The cohort was made up of 152 patients, who were 57±12 years old, with 51 (34%) women. Underlying liver disease included mainly hepatitis C cirrhosis, alcohol related cirrhosis, metabolic dysfunction-associated steatohepatitis (MASH) cirrhosis, autoimmune cirrhosis, primary sclerosing cholangitis (PSC) cirrhosis, and cryptogenic cirrhosis. The most common cause of marked elevation in aminotransferases in cirrhotic patients was ischemic hepatitis (73%), followed by chemoembolization (7%), autoimmune hepatitis (6%), drug induced liver injury (DILI) (3%), post-transjugular intrahepatic portosystemic shunt (TIPS) placement (3%), and hepatitis C (2%). During hospitalization and over a one-month period follow-up, the mortality rate in patients with ischemic hepatitis was 73% (79/108), while that for other causes of liver injury was 25% (9/40). Furthermore, the association of acute-on-chronic liver failure (ACLF) was higher for the ischemic hepatitis group (89%) compared to all other etiologies(13%). **Conclusion:** Ischemic hepatitis is the leading cause of marked elevation of aminotransferases in patients with cirrhosis; with distinctive clinical characteristics than other etiologies, and significantly poorer outcomes.

Table 3. Clinical features and outcomes

	Ischemic hepatitis (n=108)	Others (n=40)	P value
Clinical features			
ICU	96 (89%)	7 (18%)	<0.001
Intubated	79 (73%)	6 (15%)	<0.001
Pressors	85 (79%)	5 (13%)	<0.001
Infection	38 (35%)	3 (8%)	<0.001
ACLF	82 (76%)	5 (13%)	<0.001
Laboratory			
ALT	928 ± 993	880 ± 659	
AST	2873 ± 2845	1686 ± 999	<0.001
AST/ALT ratio	3.9 ± 2.1	2.6 ± 1.6	<0.001
Total bilirubin	9.5 ± 9.3	6.6 ± 6.9	0.023
Albumin	2.2 ± 0.6	2.5 ± 0.6	0.014
INR	3.7 ± 2.9	1.9 ± 1.3	<0.001
Creatinine	2.7 ± 1.8	1.3 ± 1.0	<0.001
WBC (K/cumm)	18 ± 11	10 ± 7	<0.001
Platelets (K/cumm)	96 ± 71	152 ± 101	<0.001
LDH (n=16, 10)	3323 ± 3812	1403 ± 1982	
Lactate (n=84,14)	10.5 ± 6.5	5.9 ± 6.3	0.007
MELD score	33 ± 10	20 ± 6.8	<0.001
Outcomes			
Death	79 (73%)	9 (23%)	0.02
Average time to death	4 days	13 days	0.017

Abbreviations: ACLF, acute-on-chronic liver failure; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ICU, intensive care unit; LDH, lactate dehydrogenase; INR, international normalized ratio; MELD, model for end-stage liver disease; WBC, white blood cell

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Disclosures: Jad Allam: Nothing to Disclose, Ahmed Ibrahim: Nothing to Disclose, Don Rockey: Grant/Research Support relationship with Versantis; Has not ended; Grant/Research Support relationship with AstraZeneca; Has not ended; Grant/Research Support relationship with Ipsen; Has not ended; Grant/Research Support relationship with Boehringer Ingelheim; Has not ended; Consultant relationship with WL Gore and Associates; Has not ended; Grant/Research Support relationship with Gilead; Has not ended; Grant/Research Support relationship with Durect; Has not ended; Consultant relationship with BD Medical; Has not ended; Consultant relationship with Cook Medical; Has not ended; Grant/Research Support relationship with Intercept; Has not ended; Grant/Research Support relationship with Inventiva; Has not ended; Grant/Research Support relationship with Madrigal; Has not ended; Grant/Research Support relationship with Ocelot; Has ended; Grant/Research Support relationship with Bio89; Has not ended; Grant/Research Support relationship with Salix; Has not ended; Grant/Research Support relationship with Novonordisk; Has not ended; Grant/Research Support relationship with Viking; Has ended; Grant/Research Support relationship with Galectin; Has not ended

4058 | TECHNICAL FEASIBILITY AND EFFICACY OF TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC SHUNT VIA MIDDLE HEPATIC VEIN ACCESS IN PATIENTS WITH CIRRHOSIS AND PORTAL HYPERTENSION

Jia-Lin Wu[1] Jun-Yang Luo[2] Xin-Yi Deng[3] Ming-Sheng Huang[2] Zai-Bo Jiang[2]

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Background: A transjugular intrahepatic portosystemic shunt (TIPS) is a crucial intervention for cirrhotic patients to manage variceal rebleeding and refractory ascites. While conventional approach involves creating a shunt between the right hepatic vein and portal vein (R-TIPS), there is a gap in research regarding establishing a shunt between the middle hepatic vein and portal vein (M-TIPS). This study aims to assess the technical feasibility and efficacy of M-TIPS in patients with decompensated cirrhosis. We further investigate the risk factors associated with overall survival (OS) in patients who received TIPS treatment, and establish and validate the nomogram. **Methods:** Patients treated with M-TIPS and R-TIPS were retrospectively reviewed from January 2016 to February 2022. The OS, shunt dysfunction, overt hepatic encephalopathy (OHE), time of puncture process and puncture times were compared. Propensity score matching was used to minimize confounding bias. The possible influencing factors were analyzed using a univariate and multivariate Cox regression. A nomogram was used to construct the clinical prediction model that was validated in the validation set by the area under the curve (AUC), concordance index (C-index), and decision curve analysis (DCA). The models' internal validity was evaluated based on their calibration and discriminative abilities. **Results:** A total of 383 patients received M-TIPS (n =349) or R-TIPS (n= 34). After propensity score matching, the time of puncture process was significantly lower in the M-TIPS group than in the R-TIPS group [9.78 vs. 17.0 (mins), P < 0.001]. The M-TIPS group also seemed to need less puncture times than the R-TIPS group (1.87 vs. 2.35, P = 0.10). During a median follow-up of 42 months in both groups, there were no statistically significant differences in survival (73.5% vs 64.7%; p=0.49), OHE 20.6% vs 26.5%; p=0.21), and other complications of adverse events between groups. A multivariate Cox regression showed that the independent risk factors for OS were age, cholinesterase, total bilirubin, urea nitrogen, creatinine, and Child-Pugh. The C index is 0.742, and the ROC shows that the area under the curve of the prediction model in 1-year and 2-year OS is 0.786 (CI: 0.707-0.866) and 0.766 (CI: 0.695-0.836), respectively. The analysis of the receiver operating characteristic curve, calibration curve, and model consistency index demonstrates that the graphical representation exhibits a good predictive capability. **Conclusion:** M-TIPS presents an optimal alternative for physicians during the TIPS procedure, while maintaining high safety and efficacy. Compared with R-TIPS, M-TIPS significantly reduces puncture time during the TIPS procedure and does not affect stent patency or the incidence rate of OHE. Finally, we developed a nomogram with high accuracy to predict OS for patients with cirrhosis and portal hypertension following TIPS treatment.

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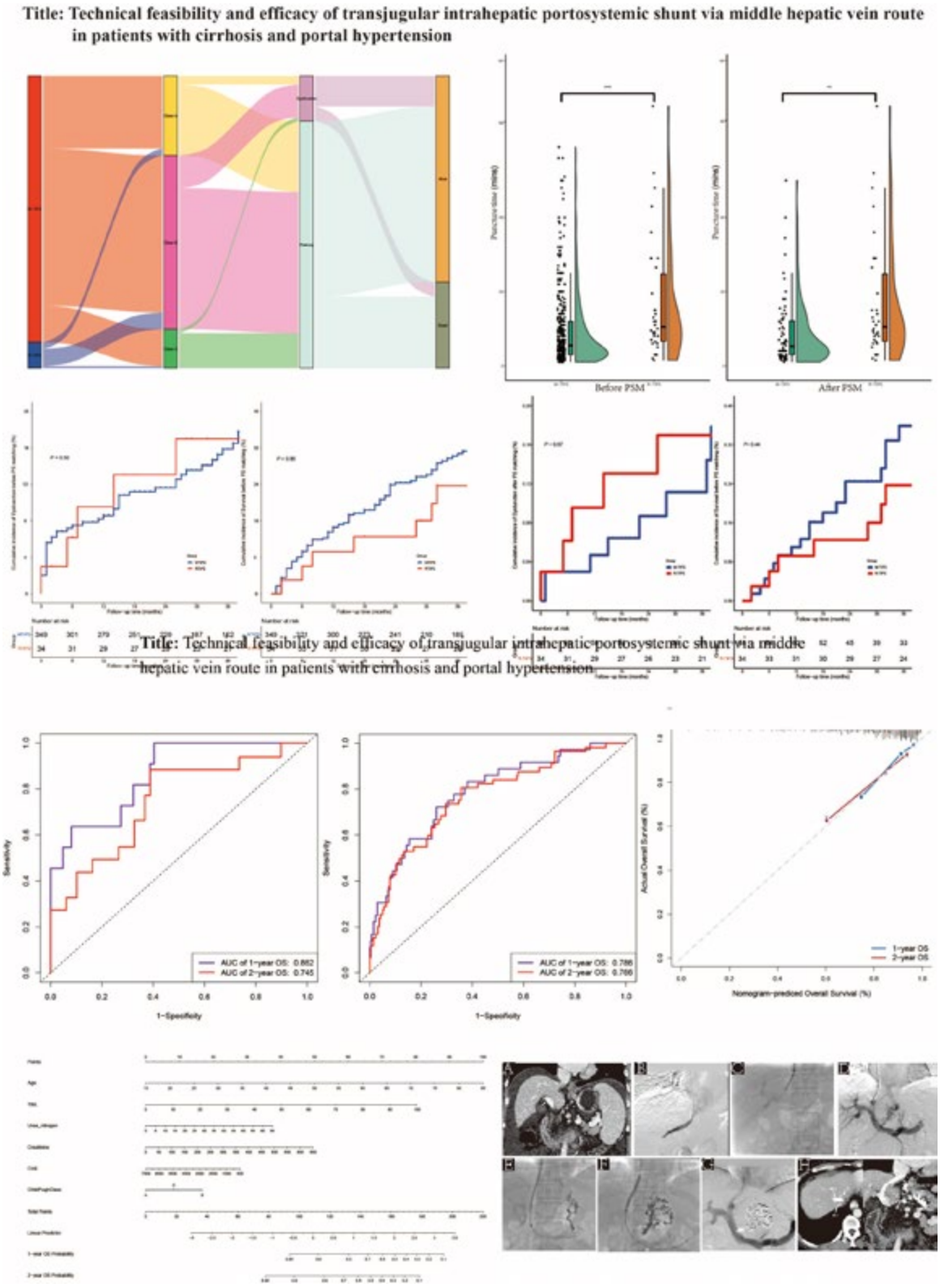

Title: Technical feasibility and efficacy of transjugular intrahepatic portosystemic shunt via middle hepatic vein route in patients with cirrhosis and portal hypertension

Disclosures: Jia-Lin Wu: Nothing to Disclose, Jun-Yang Luo: Nothing to Disclose, Xin-Yi Deng: Nothing to Disclose, Ming-Sheng Huang: Nothing to Disclose, Zai-Bo Jiang: Nothing to Disclose

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4059 | ASSOCIATION BETWEEN PRE-OPERATIVE TIPS AND POST-OPERATIVE MORTALITY IN A VETERANS AFFAIRS COHORT

Helen Tang[1] *David Kaplan*[1] *Samir Abu-Gazala*[1] *Nadim Mahmud*[1]

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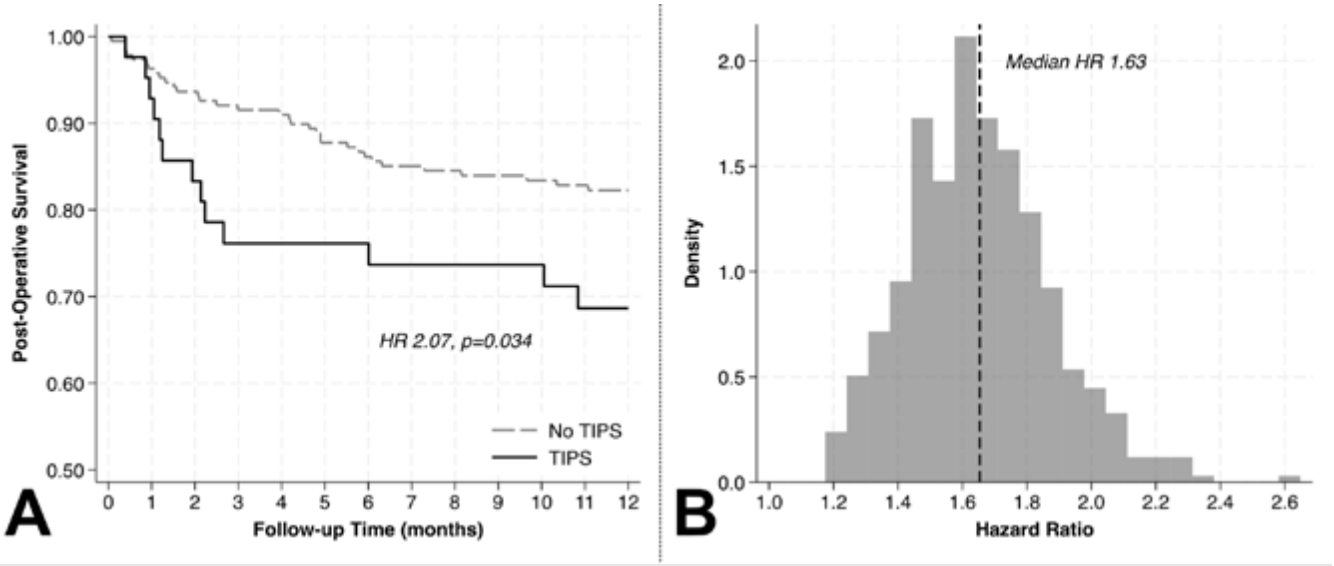
Background: Increased post-operative mortality in patients with cirrhosis is partially attributable to portal hypertension. Pre-operative placement of transjugular intrahepatic portosystemic shunt (TIPS) may therefore reduce operative risk. Prior studies suggesting benefit with pre-operative TIPS are limited by residual confounding and lack of longitudinal laboratory data. To address these limitations, we used granular longitudinal data from the Veterans Health Administration (VHA). **Methods:** This was a retrospective cohort study of VHA patients with cirrhosis who underwent major surgery from 2008-2022. We identified patients who underwent pre-operative TIPS within six months prior to surgery. Demographics, comorbidities, surgery type, and longitudinal laboratory data were incorporated into a propensity score using 5:1 caliper matching for receipt of TIPS. The propensity score-matched cohort included 42 patients with pre-operative TIPS and 190 without. The primary outcome was time to post-operative mortality through maximum 12 months of follow-up. Secondary outcomes included intraoperative blood loss, duration of surgery, and post-operative length of stay. Exploratory outcomes included trajectories of laboratory studies relevant to liver function over time. **Results:** Baseline characteristics were similar between groups. In Cox regression, pre-operative TIPS was associated with increased risk of post-operative mortality (HR 2.07, 95% CI 1.06-4.07, p=0.034). This was redemonstrated in 500 random resampling events (median HR 1.63). There were no significant differences in reported intraoperative blood loss (p=0.50), surgery duration (p=0.16), or post-operative length of stay (p=0.11) between groups. TIPS and non-TIPS patients had similar albumin, bilirubin, and INR 6 months prior to surgery, however immediately prior to surgery patients with TIPS patients had lower albumin (p=0.018), higher bilirubin (p=0.001), and higher INR (p=0.001). **Conclusion:** In propensity matched analysis of patients with cirrhosis undergoing major surgery, pre-operative TIPS was associated with increased post-operative mortality and worsened liver synthetic function in the immediate pre-operative period, suggesting that theoretical operative benefits of portal pressure reduction may be offset by impairments in liver synthetic function that may drive increased risk.



Disclosures: Helen Tang: Nothing to Disclose, David Kaplan: Independent Contractor relationship with Roche Genentech; Has not ended; Grant/Research Support relationship with AstraZeneca Inc; Has not ended; Advisor relationship with AstraZeneca; Has ended; Advisor relationship with Exelixis; Has ended; Grant/Research Support relationship with Gilead; Has not ended; Advisor relationship with Sirtex; Has ended; Grant/Research Support relationship with Exact Sciences; Has not ended; Grant/Research Support relationship with Glycotest; Has ended, Samir Abu-Gazala: Nothing to Disclose, Nadim Mahmud: Nothing to Disclose

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4060 | SIMULTANEOUS LIVER BIOPSY AND ENDOSONOGRAPHIC PORTAL PRESSURE MEASUREMENT CAN SAFELY BE PERFORMED WITHOUT USE OF ANTIBIOTICS

Eric Wien[1] *Aradhna Seth*[1] *Phil Delich*[1] *Nishant Puri*[1] *Wichit Srikureja*[1] *Divyanshoo Kohli*[1]

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Background: In contrast to the indirect trans-jugular measurement of hepatic venous-portal pressure gradient (HVPG), a novel endosonographic technique (EUS-PPG) measures HVPG directly. Current best practices recommend administration of prophylactic peri-procedural antibiotics although data supporting this practice are lacking. We report the real-world efficacy, clinical impact, and safety of EUS-PPG without the administration of antibiotics. **Methods:** In this single-center retrospective study, patients referred for EUS-PPG were identified from an internal database. The primary outcome was incidence of infectious and non-infectious adverse events (AEs) within 30 days of EUS-PPG. Secondary outcomes included procedure time, technical success, clinicopathological correlation, and impact on clinical management with EUS-PPG. Infectious AEs were defined as post-procedure fever or sepsis. Other AEs included significant bleeding requiring intervention, unplanned hospitalization, or ER visit. Technical success was defined by successful measurement of the hepatic and portal venous pressures. Procedure time was calculated from procedural timeout to terminal removal of the endoscope. Impact on clinical management was defined by change in treatment plan based on solely on EUS-PPG measurements. Data are reported as mean ± SD. **Results:** Of the 57 patients (30 women, 47 white, 57±16.9 years, Table 1) referred for EUS-PPG from 2021 through 2024, no patient received peri-procedural antibiotics and there were no infectious or non-infectious AE's The procedure was technically successful in 53 (93%) patients. Narrow vein diameter precluded cannulation in two patients, one patient had esophageal varices obviating need for EUS-PPG, and one patient developed hypotension with induction of anesthesia leading to early termination of the procedure before any intervention. Procedure time was 55±19 minutes. There was substantial agreement between EUS-PPG measurements and clinical and histological data. Portal hypertension was diagnosed in 14 (26%) patients and clinical management was impacted in at least 11 (21%) patients, all of whom were being assessed for transplant or surgical interventions. **Conclusion:** Simultaneous EUS-PPG and liver biopsy can be performed safely without peri-procedural antibiotics. These data corroborate the utility of EUS-PPG for surgical risk stratification and validation of clinical suspicion.

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Parameter	Value (N=57)
Demographics	
Age (years; mean ± SD)	57.1±16.9
Sex (men)	27
Race	
White/Caucasian	47
Hispanics	6
Native Americans	2
Black	1
Other	1
Body mass index (Kg/m^2; mean ± SD)	31.4 ± 9.7
Laboratory data (mean ± SD)	
Aspartate aminotransferase (IU/mL)	56.8±85.4
Alanine transaminase (IU/mL)	46.8±48.7
Alkaline Phosphatase (IU/mL)	110.9±65.3
Total bilirubin (mg/dL)	1±1.3
INR	1.1±0.2
Platelets	185.1±88.5
Non-invasive tests	
AST to Platelet Ratio Index (APRI)	1.1±2.5
Fibrosis-4 (FIB4)	3±3.2
Fibrosis on histology	
F0-F1	21
F2	11
F3	8
F4	13
Portal pressure gradient (mmHg)	
Normal (<5)	39
Portal hypertension (>5)	14
Clinically significant portal hypertension (>10)	6
Procedure time (minutes; mean ± SD)	55±19
Time to initial follow up (days; mean ± SD)	8.3±6.7

Disclosures: Eric Wien: Nothing to Disclose, Aradhna Seth: Nothing to Disclose, Phil Delich: Nothing to Disclose, Nishant Puri: Boston Scientific: Consultant, Wichit Srikureja: Nothing to Disclose, Divyanshoo Kohli: Nothing to Disclose

4061 | HEPATIC ENCEPHALOPATHY DEFINED USING HOSPITALIZATIONS SIGNIFICANTLY ADDS TO RISK PREDICTION FOR 90-DAY AND 1-YEAR MORTALITY ABOVE THE MELD3.0 AND MELD-NA SCORES IN A NATIONAL COHORT OF VETERANS

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Background: Despite being a major burden on patients and families, hepatic encephalopathy (HE) is not included in transplant prioritization. With MELD3.0 there are further questions regarding HE as a contributor towards poor outcomes. Defining HE is unclear but using hospitalization & lactulose/rifaximin validated codes are helpful. **Aim**: To define the contribution of HE towards death & transplant independent of MELD-Na and MELD3.0 in a national Veterans database. **Methods:** We used VHA-Corporate Data Warehouse (CDW) between 2009-2019 and Veterans admitted with cirrhosis were included. HE was defined using validated inpatient HE ICD-9/10 codes and medication codes (lactulose or rifaximin use). Patients who ever developed HE requring hospitalizations during this period were labelled HE and their MELD-Na and MELD3.0 were calculated around the first HE admission date. The rest who never developed HE had the MELD scores calculated at the first admission. Clinical, demographic, and co-morbid conditions were captured. Logistic regression for 90-day and 1-year mortality were performed with MELD scores alone and with HE and other variables. Finally, ROC curves using MELD scores alone and then with HE were compared. **Results:** 73847 Veterans were admitted for cirrhosis

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between 2009-2019, of which 12,298 (16.7%) fit the strict definition for inpatient HE.. At 90-days, 16,095 (21.8%) died and 683 (0.9%) received LT while at 1-year, 27,632 (37.4%) died and 898 (1.2%) received LT. HE vs no-HE: Patients admitted with HE were younger with higher comorbidity burden, MELD scores & higher alcohol etiology vs no-HE. LT rates were higher at 90-day & 1-year and patients with HE died at a higher rate at both timepoints vs non-HE patients (Table 1). Outcomes: HE status predicted 90-day and 1-year mortality in an interactive manner when combined with MELD3.0 or MELD-Na. For those with HE, the effect of increasing MELD score on mortality rates was enhanced (Table 2). Apart from high MELD (MELD3.0 or MELD-Na) and presence of HE, alcohol etiology, WBC count, age, PPI, diuretics and comorbidities were associated with a higher risk of death, while BMI, selective beta-Blocker, propranolol, statin and carvedilol use were protective (Table 2). ROC analysis: AUC for MELD-Na without HE was 0.786 which significantly increased to 0.789 ($p<0.001$) for 90-day and from 0.751 to 0.754 at 1 year ($p<0.001$). MELD3.0 AUC was enhanced by HE from 0.795 to 0.797 ($p<0.001$) at 90-days and from 0.760 to 0.762 ($p<0.001$) at 1 year. **Conclusion:** Using strict definitions, HE was associated with MELD3.0 and MELD-Na in an interactive manner, and aided prediction of 90-day and 1-year mortality in a national cohort of Veterans with cirrhosis. This was independent of comorbidities, medications, and etiology. The contribution of HE was higher with MELD-Na compared to MELD3.0 but remained significant and this strict definition could improve risk stratification and improve representation.

Table 1: Comparison between patients hospitalized with/without HE

Variable, Mean ±SD or n (%)	HE, n = 12,298 (16.7%)	No-HE, n = 61,549 (83.3%)	p-value
Age	61.60 (±8.02)	64.21 (±9.52)	**<0.001**
Male Gender	11998 (97.6%)	59973 (97.4%)	0.454
BMI	28.60 (±6.64)	28.40 (±6.70)	**0.002**
Alcohol Etiology	5281 (42.9%)	24226 (39.4%)	**<0.001**
Charlson Comorbidity Index (CCI)	5.92 (±2.52)	4.73 (±2.77)	**<0.001**
MELD 3.0	20.10 (±7.54)	15.52 (±6.97)	**<0.001**
MELD-Na	19.71 (±7.49)	15.60 (±7.00)	**<0.001**
White Blood Cell Count (WBC)	8.05 (±5.40)	8.29 (±5.31)	**<0.001**
Selective Beta-Blocker	1038 (8.4%)	6157 (10.0%)	**<0.001**
Propranolol use	1724 (14.0%)	2100 (3.4%)	**<0.001**
Nadolol use	169 (1.3%)	194(<1.0%)	**<0.001**
Carvedilol use	286 (2.3%)	2197 (3.6%)	**<0.001**
Statin use	885 (7.1%)	6668 (10.8%)	**<0.001**
Proton Pump Inhibitor	3533 (28.7%)	10501 (17.1%)	**<0.001**
Diuretic use	5135 (41.8%)	12035 (19.6%)	**<0.001**
VA Complexity Level 1	11447 (93.1%)	58322 (94.8%)	**<0.001**
Outcomes			
Death (90-Days)	4507 (36.6%)	11588 (18.8%)	**<0.001**
Death (1-year)	6880 (55.9%)	20752 (33.7%)	**<0.001**
Liver Transplant (90-Days)	135 (1.1%)	548 (0.9%)	**0.032**
Liver Transplant (1-year)	224 (1.8%)	674 (1.1%)	**<0.001**
Median (IQR) Length of Stay (LOS)	6 (3-13) days	4 (2-7) days	**<0.001**

Table 2 – Adjusted Logistic Regression	MELD 3.0 based	MELD-Na based
90-Day Mortality	**MELD 3.0 + HE**	**MELD-Na + HE**
MELD Score	**1.12 [1.11-1.12], p<0.001**	**1.10 [1.10-1.11], p<0.001**
MELD × HE Interaction	**1.02 [1.01-1.03], p<0.001**	**1.02 [1.02-1.03], p<0.001**
WBC	1.04 [1.03-1.04], p<0.001	1.04 [1.04-1.05], p<0.001
CCI	1.18 [1.17-1.19], p<0.001	1.18 [1.17-1.19], p<0.001
Alcohol Cirrhosis	1.10 [1.05-1.15], p<0.001	1.12 [1.08-1.17], p<0.001
Propranolol use	0.91 [0.83-0.99], p=0.040	0.91 [0.83-0.99], p=0.046
Selective BB use	0.82 [0.77-0.88], p<0.001	0.81 [0.77-0.88], p<0.001
BMI	0.96 [0.96-0.97], p<0.001	0.97 [0.96-0.97], p<0.001
Carvedilol use	0.69 [0.59-0.74], p<0.001	0.66 [0.59-0.73], p<0.001
Age	1.03 [1.03-1.04], p<0.001	1.03 [1.03-1.04], p<0.001
Diuretic use	1.21 [1.16-1.27], p<0.001	1.25 [1.19-1.31], p<0.001
Statin use	0.76 [0.71-0.81], p<0.001	0.74 [0.69-0.80], p<0.001
1-Year Mortality	**MELD-3.0 + HE**	**MELD-Na + HE**
MELD Score	**1.10 [1.09-1.10], p<0.001**	**1.09 [1.08-1.09], p<0.001**
MELD × HE Interaction	**1.02 [1.02-1.03], p<0.001**	**1.03 [1.02-1.03], p<0.001**
WBC	1.02 [1.01-1.02], p<0.001	1.02 [1.01-1.02], p<0.001
CCI	1.17 [1.16-1.18], p<0.001	1.17 [1.16-1.18], p<0.001
Alcohol Cirrhosis	1.09 [1.05-1.13], p<0.001	1.12 [1.08-1.16], p<0.001
Selective BB use	0.83 [0.78-0.88], p<0.001	0.82 [0.77-0.87], p<0.001
BMI	0.97 [0.96-0.97], p<0.001	0.97 [0.96-0.97], p<0.001
Carvedilol use	0.68 [0.62-0.75], p<0.001	0.68 [0.63-0.76], p<0.001
Age	1.03 [1.03-1.04], p<0.001	1.03 [1.03-1.04], p<0.001
PPI use	1.06 [1.01-1.10], p=0.013	1.05 [1.01-1.10], p=0.026
Diuretic use	1.42 [1.36-1.48], p<0.001	1.46 [1.40-1.52], p<0.001
Statin use	0.74 [0.70-0.79], p<0.001	0.73 [0.69-0.77], p<0.001

Disclosures: Scott Silvey: Nothing to Disclose, Nilang Patel: Mallinckrodt Pharmaceutical: Advisor, Jasmohan Bajaj: Bausch: Grant/Research Support, Sequana: Grant/Research Support, Cosmo: Grant/Research Support, Grifols: Grant/Research Support

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4062 | ARGININE GLUTAMATE INJECTION FOR THE TREATMENT OF MILD HEPATIC ENCEPHALOPATHY: AN OPEN LABEL, RANDOMIZED, CONTROLLED, NON-INFERIORITY TRIAL

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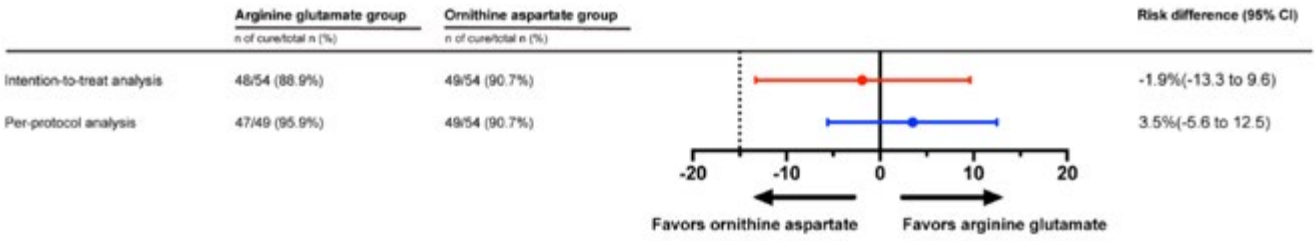
Background: In recent years, arginine glutamate injection has been widely regarded as a potential new treatment for hepatic encephalopathy. This study aims to assess the efficacy of arginine glutamate injection versus aspartic acid ornithine injection in treating hepatic encephalopathy and hyperammonemia in patients with cirrhosis. It is the first randomized controlled study comparing with L-ornithine-L-aspartate head-to-head. **Methods:** Participants aged 18-75 years with cirrhosis and mild hepatic encephalopathy were included in the study, having received treatment at our hospital. Stratified blocks were formed using the West-Haven grading method, and patients were then randomized into either the arginine glutamate injection group or the L-ornithine-L-aspartate injection group. Treatment lasted for 7 days. The primary endpoint was the clinical improvement of HE symptoms. Secondary endpoints included improvements in blood ammonia levels and time to complete the number connection test, and the comparison of these changes between the arginine glutamate and L-ornithine-L-aspartate groups to establish non-inferiority. **Results:** From March 2020 to October 2021, 132 patients were assessed for eligibility, with 108 qualifying for random assignment to receive either arginine glutamate (n=54) or aspartic acid ornithine (n=54). In the intention-to-treat (ITT) analysis, on day 8, clinical improvement of HE was observed in 48 (88.9%) of 54 patients in the arginine glutamate group and 49 (90.7%) of 54 in the L-ornithine-L-aspartate group. The between-group difference was -1.9% (95% CI -13.3% to 9.6%), indicating noninferiority. Per-protocol (PP) analysis similarly suggested non-inferiority at the primary endpoint. Post-treatment, both groups exhibited reductions in blood ammonia levels and improvements in number connection test scores. Arginine glutamate was noninferior to aspartic acid ornithine injection in these secondary endpoints. **Conclusion:** Both arginine glutamate injection and L-ornithine-L-aspartate injection effectively alleviated clinical symptoms and reduced blood ammonia levels in patients with cirrhosis and mild HE, with the clinical improvement rate of arginine glutamate being non-inferior to that of L-ornithine-L-aspartate. Compared to L-ornithine-L-aspartate, arginine glutamate also achieved non-inferiority in reducing blood ammonia and improving number connection test scores, with no appreciable adverse effects.(ChiCTR2300068160)



Disclosures: Haibo Zhang: Nothing to Disclose, Huaibin Zou: Nothing to Disclose, Yuan Gao: Nothing to Disclose, Li Wang: Nothing to Disclose, Ming Kong: Nothing to Disclose, Weiwei Kang: Nothing to Disclose, Rui Zhong: Nothing to Disclose, Xianshan Yang: Nothing to Disclose, Yan Ren: Nothing to Disclose, Lili Feng: Nothing to Disclose, Lu Li: Nothing to Disclose, Shuang Li: Nothing to Disclose, Yunyi Gao: Nothing to Disclose, Zhongping Duan: Nothing to Disclose, Yutao Zhan: Nothing to Disclose, Yu Chen: Nothing to Disclose

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4063 | BASELINE PATIENTS' CHARACTERISTICS FROM NAVIGATE, A SEAMLESS ADAPTIVE PHASE 2B/3 TRIAL OF BELAPECTIN IN MASH CIRRHOSIS AND PORTAL HYPERTENSION

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Background: Currently, there are no approved treatments for MASH cirrhosis. Belapectin, a galectin-3 inhibitor, is being investigated in NAVAGATE (NCT04365868), an adaptive phase 2b/3 trial aimed at preventing the development of esophageal varices (EV) in patients with compensated cirrhosis with portal hypertension (PH). Understanding the clinical characteristics of patients with MASH cirrhosis and PH but without varices at baseline is of utmost importance for the field to design similar trials with new onset EV diagnosed by endoscopy as a primary efficacy endpoint. **Methods:** Summary of baseline characteristics of NAVIGATE evaluating two doses of Belapectin (2 and 4 mg/kg.lbw) versus placebo. Eligibility required a confirmed diagnosis of MASH cirrhosis, the presence of one of more signs of PH including splenomegaly, thrombocytopenia, Liver Stiffness Measurement (LSM) by Fibroscan >15 kPa, the absence of esophageal and gastric varices, no liver decompensation, and a MELD <12. **Results:** 1067 were screened and 357 subjects with no evidence of esophageal/gastric varices have been randomized with a mean age of 60.1 years, 65% females, and 91.0% White and 30.5% Hispanics. Other baseline characteristics are provided in the Table 1. MASH cirrhosis was based on biopsy (43.1%) or imaging/ metabolic comorbidities (31.9%) and biopsy with history of metabolic disorder (25%). The most frequent signs of PH were a platelet count <150/ µL (70%), LSM >20 kPa (62.7%) and spleen size >14cm (30.8%). At baseline ALT and AST were 42 and 44 U/L respectively (Table 1). **Conclusion:** The low MELD score and predominantly Child Pugh Class A5 population enrolled in the phase 2b stage of the trial constitutes a population that can be amenable to the stabilization or reversal of portal hypertension. The clinical translation of this effect will be reflected in the primary prevention of esophageal varices, hence the prevention of bleeding from these varices.

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Baseline Demographics and Clinical Characteristics Table 1 n:357	Value	Standard deviation
Age (years)	60.1	8.8
Gender (Female) n	232	65%
Ethnicity (Hispanic) n	109	30.5 %
Race (White) n	325	91.0%
Weight (kg)	95.6	22.3
BMI (kg/m²)	34.4	6.5
Hypertension	260	72.8%
Type 2 Diabetes	240	67.2%
HbA1C (%)	6.3	1.16
Alanine Aminotransferase (ALT) U/L	41.8	26.3
Aspartate Aminotransferase (AST) U/L	44	23.4
Platelets(per µL)	130.8	47.9
Liver Stiffness Measurement (kPa)	24.8	13
Spleen (cm)	13.8	2.8
MELD Score	7.6	1.8
Child Pugh Score	5.1	0.3
Proportion of patients with Childs Pugh Class A5		
Statins (N)	151	42.3%
GLP-1 agonist (N)	82	23%

*standard deviation unless indicated by %

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4064 | A MULTI-SCALE COMPUTATIONAL MODEL OF THE HEPATIC CIRCULATION APPLIED TO PREDICT THE PORTAL PRESSURE AFTER TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC SHUNT (TIPS)

Yang Ling 杨玲[1] Jiaqi Gu[2] Yi Xiang[3] Jitao Wang[3] Deqiang Ma[4] He Zhu[5] Tianyu Liu[6] Chunlong Li[7] Qi Zhang[3] Jiahao Han[3] Deping Ding[4] Wei Wang[5] Qianlong Li[6] Haoguang Wan[7] Tianqi Wang[8] Xiaolong Qi[3]

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Background: Transjugular intrahepatic portosystemic shunt (TIPS) is a widely used surgery for patients with portal hypertension. In clinical practice, the diameter of the stent forming a shunt is usually selected empirically, which will influence the postoperative portal pressure. Clinical studies found that inappropriate portal pressure after TIPS is responsible for poor prognosis; however, there is no scheme to predict postoperative portal pressure before the surgery. Therefore, this study aims to develop a computational model applied to predict the portal pressure after TIPS. **Methods:** For this purpose, a patient-specific 0-3-D multi-scale computational model of the hepatic circulation was developed based on the preoperative clinical data. The model of a representative patient was firstly employed in the numerical experiment to investigate the influences of multiple pathophysiological and surgical factors on the simulated postoperative portal pressure. Subsequently, the model was validated by using the clinical data of 18 patients prospectively collected from multiple centers. **Results:** The estimated model parameters slightly influenced the simulated results (-1.38 to 1.15 mmHg) and the severity of possible inherent portosystemic collaterals mildly influenced the results (0.56 to 1.60 mmHg). In particular, the existence of the catheter for pressure measurement would markedly influence postoperative portal pressure (2.16 mmHg). Validation **results** demonstrated that the difference between the simulated and in vivo measured portal pressures was -1.37±3.51 mmHg. **Conclusion:** This study developed a patient-specific 0-3-D multi-scale computational model of the hepatic circulation. Numerical experiment elaborated the influences of several pathophysiological and surgical factors on the simulated results, which would improve the model construction and calibration. This computational model would be a promising tool for predicting the portal pressure after TIPS, which would guide the selection of stent diameter and promote individualization and precision of TIPS.

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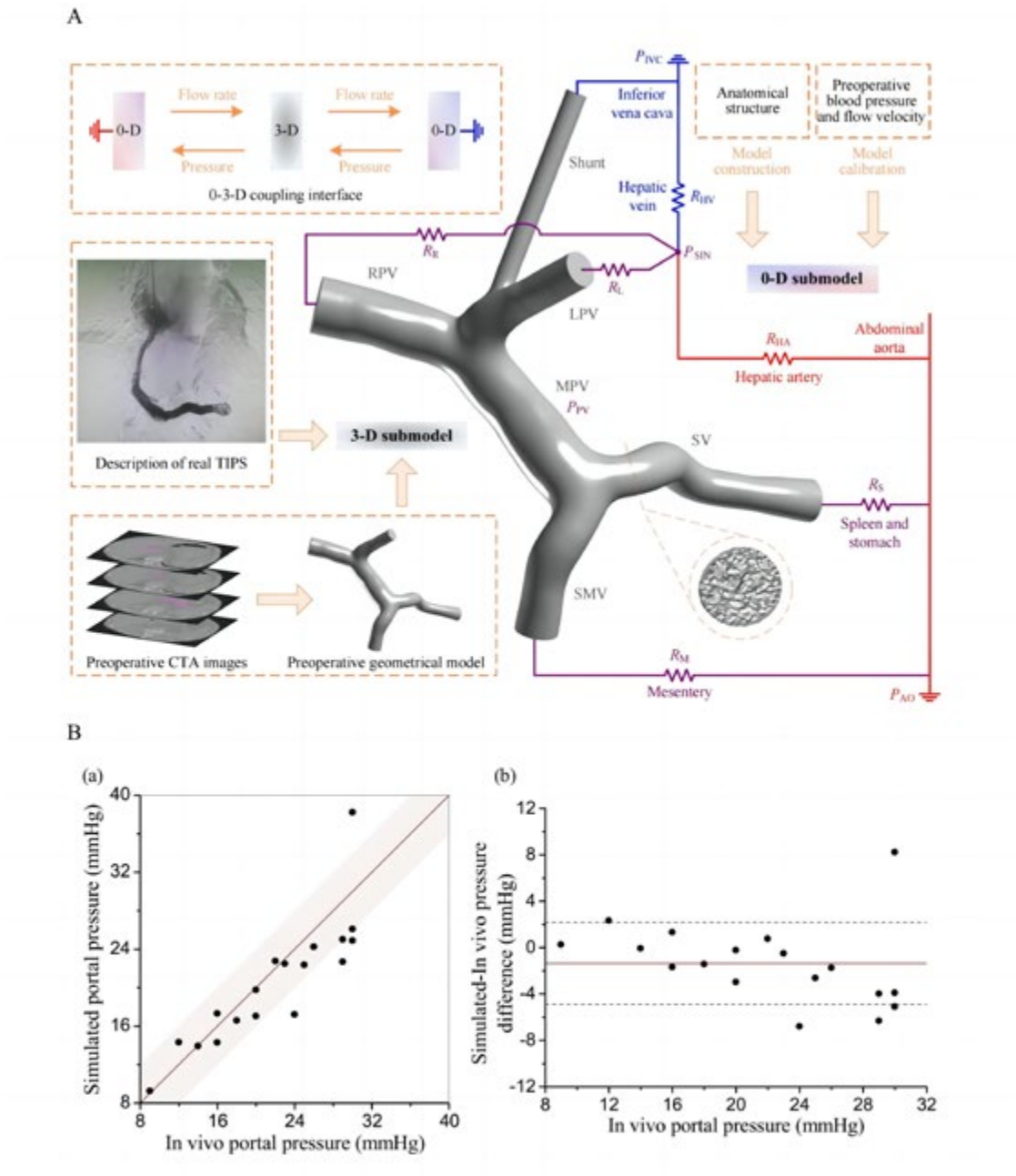

Figure 1: Schematic description of the 0-3-D multi-scale computational model used for TIPS simulation (A). Comparisons of the simulated and in vivo measured portal pressures (B): (a) Correlation analysis of the simulated and in vivo measured results; (b) Bland-Altman plot of the results. SV, splenicvein; SMV, superior mesenteric vein; MPV, main portal vein; LPV, left portal vein; RPV, right portal vein; R, flow resistance; P, blood pressure.

Disclosures: Yang Ling 杨玲: Nothing to Disclose, Jiaqi Gu: Nothing to Disclose, Yi Xiang: Nothing to Disclose, Jitao Wang: Nothing to Disclose, Deqiang Ma: Nothing to Disclose, He Zhu: Nothing to Disclose, Tianyu Liu: Nothing to Disclose, Chunlong Li: Nothing to Disclose, Qi Zhang: Nothing to Disclose, Jiahao Han: Nothing to Disclose, Deping Ding: Nothing to Disclose, Wei Wang: Nothing to Disclose, Qianlong Li: Nothing to Disclose, Haoguang Wan: Nothing to Disclose, Tianqi Wang: Nothing to Disclose, Xiaolong Qi: Nothing to Disclose

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4065 | SAFETY AND TOLERABILITY OF SIMVASTATIN 40MG IN A PROSPECTIVE MULTICENTER RANDOMIZED BLINDED CONTROLLED TRIAL OF CHILD-TURCOTTE-PUGH A PATIENTS WITH CLINICALLY SIGNIFICANT PORTAL HYPERTENSION

David Kaplan[1] Rajni Mehta[2] Alexander Burdzy[3] Sofia Lizza[3] Gyorgy Baffy[4] Ruben Hernaez[5] Alexander Monto[6] George Ioannou[7] Kristel Hunt[8] Tae Hoon Lee[8] Jasmohan Bajaj[9] Craig McClain[10] Ayse Aytaman[11] Tamar Taddei[12]

[1]University of Pennsylvania, [2]VA Connecticut Health Care System, [3]Cpl Michael J Crescenz VA Medical Center, [4]VA Boston Healthcare System, [5]Baylor College of Medicine, [6]University of California, San Francisco, [7]University of Washington Medical Center, [8]Bronx VA Medical Center, [9]Virginia Commonwealth University, [10]University of Louisville, [11]VA NY Harbor Healthcare System Brooklyn Campus, [12]Yale University

Background: HMG-CoA reductase inhibitors (statins) exert pleiotropic effects that reduce inflammation and fibrosis and improve vascular reactivity. Retrospective studies have consistently associated statin use with improved outcomes for patients with cirrhosis. In prospective studies, statins reduce portal hypertension and death in patients with decompensated cirrhosis after variceal hemorrhage when added to standard therapy, with an acceptable safety profile. We report interim **results** related to enrollment and safety of the SACRED trial, designed to evaluate the safety and efficacy of simvastatin in patients with cirrhosis. **Methods:** SACRED is a phase III, prospective, multi-center, double-blind clinical trial (NCT03654053) that enrolled patients with compensated cirrhosis and clinically significant portal hypertension (CSPH), stratified upon concomitant use of nonselective beta-blockers, randomized enrollees 1:1 to simvastatin 40 mg/day versus placebo for up to 24 months at 11 Veterans Affairs Medical Centers in the United States. A two-week lead-in of open-label simvastatin 20mg/day preceded randomization to identify early statin intolerance. The primary endpoint is incident hepatic decompensation defined as occurrence of any one of the following: variceal hemorrhage, ascites, hepatic encephalopathy, or hepatocellular carcinoma (HCC). Enrollment opened October 2020 and ended December 2023. **Results:** 202 patients consented to participate, among whom 160 were eligible to initiate lead-in. 148 patients completed lead-in and 142 proceeded to be randomized. Sixteen eligible patients did not complete lead-in due to: unrelated adverse event (AE) or serious adverse event (SAE) (2), muscle symptoms (2), nocturia (1), rash (1), lost to follow-up (5),and withdrawal of consent (5). The study remains blinded with expected completion December 2025. To date, 36 SAEs have been reported including psychiatric hospitalizations (12), variceal bleeding or ascites (6), systemic infections (5), major adverse cardiovascular events (4), trauma or overdoses (3), pneumonia/chronic obstructive pulmonary disease (2), treatment of HCC (2), abnormal labs or acute kidney injury (2). One patient developed statin-induced autoimmune hepatitis and was withdrawn. 220 grade 1-2 AEs have been reported, most related to asymptomatic laboratory changes (80), gastrointestinal distress (24), non-serious infections (17), musculoskeletal complaints (17), rash (13), psychiatric diseases (12), or substance abuse (11). **Conclusion:** Tolerance of simvastatin 20mg/day during lead-in and the study drug (40mg/day or placebo) in a cohort of patients with cirrhosis with CSPH has been excellent with no evidence of direct drug-induced hepatotoxicity, few confirmed cases of statin-induced muscle injury, no cases of rhabdomyolysis, and no deaths related to study medication

Disclosures: David Kaplan: Independent Contractor relationship with Roche Genentech; Has not ended; Grant/Research Support relationship with AstraZeneca Inc; Has not ended; Advisor relationship with AstraZeneca; Has ended; Advisor relationship with Exelixis; Has ended; Grant/Research Support relationship with Gilead; Has not ended; Advisor relationship with Sirtex; Has ended; Grant/Research Support relationship with Exact Sciences; Has not ended; Grant/Research Support relationship with Glycotest; Has ended, Rajni Mehta: Nothing to Disclose, Alexander Burdzy: Nothing to Disclose, Sofia Lizza: Nothing to Disclose, Gyorgy Baffy: Nothing to Disclose, Ruben Hernaez: Nothing to Disclose, Alexander Monto: Nothing to Disclose, George Ioannou: Nothing to Disclose, Kristel Hunt: Nothing to Disclose, Tae Hoon Lee: Merck & Co., Inc.: Chapter Authorship of Merck Manual, Salix Pharmaceuticals, Inc. an affiliate of Bausch Health US: Grant/Research Support, Jasmohan Bajaj: Bausch: Grant/Research Support, Sequana: Grant/Research Support, Cosmo: Grant/Research Support, Grifols: Grant/Research Support, Craig McClain: Novo Nordisk: Grant/Research Support, Intercept Pharmaceuticals: Grant/Research Support, Altimmune: Grant/Research Support, Target Pharma Solutions: Grant/Research Support, NIH: Grant/Research Support, VAMC: Grant/Research Support, Ayse Aytaman: Nothing to Disclose, Tamar Taddei: Nothing to Disclose

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4066 | COMPARATIVE ANALYSIS ON THE HEALTHCARE DISPARITIES AND IN-PATIENT MORTALITY OF HEPATORENAL SYNDROME AMONG DIFFERENT LIVER CIRRHOSIS ETIOLOGIES: INSIGHTS FROM THE NATIONAL INPATIENT SAMPLE 2020 DATABASE

Raghav Bassi[1] Zubair Bodla[2] Mohammad AbuAssi[2] Harsimran Kalsi[2] Kobina Essilfie-Quaye[2] Yaseen Perbtani[2] Tony Brar[2]

[1]University of Central Florida College of Medicine, [2]University of Central Florida

Background: The three most common causes of cirrhosis in the developed world are alcoholic liver disease, metabolic dysfunction-associated steatotic liver disease (MASLD), and hepatitis C virus (HCV). One of the feared complications of cirrhosis is the development of hepatorenal syndrome (HRS) with mortality rates reaching 32%. Common precipitating factors include bacterial infections, gastrointestinal bleeding, and diuretic therapy. Throughout literature, there has not been a comparative mortality analysis looking at the different etiologies of liver cirrhosis in patients diagnosed with HRS. We hope to contribute to our current understanding of the disease process and look at underlying predictors such as length of stay, total hospitalization cost, age, race, and sex. **Methods:** Retrospective analysis using the 2020 National Inpatient Sample dataset, and utilizing relevant ICD-10-CM codes to calculate the adjusted odds ratio (AOR). We identified patients who were admitted with HRS and then classified them into different cohorts based on the underlying etiology of their cirrhosis. **Results:** A total of 29,760 patients admitted with HRS were evaluated. 22,345 had underlying alcoholic cirrhosis, 4,875 had MASLD cirrhosis and 2,540 had HCV cirrhosis. The average ages for alcoholic, MASLD, and HCV cirrhosis mediated HRS were 53.64, 64.92, and 60.98 years respectively. Notably, the alcoholic cirrhosis group was predominantly female (66.82%), while the MASLD group was predominantly male (59.38%). 76.68% of patients diagnosed with MASLD cirrhosis were white, while most HCV cirrhosis patients were black (17.96%). Patients who developed HRS with underlying alcoholic cirrhosis had an in-patient all-cause mortality rate of 25.67% (Table 1). In comparison, the mortality rate was 14.77% for MASLD cirrhosis and 23.62% for viral cirrhosis. After adjusting for confounders, MASLD cirrhosis patients had a decreased odds of in-patient mortality compared to the alcoholic cirrhosis group (AOR 0.541, P < 0.001). When analyzing rates of SBP, alcoholic cirrhosis patients had a 1.30 times increased likelihood of developing SBP compared to MASLD patients which approached statistical significance (AOR 0.768, P=0.052). Rates of variceal upper GI bleed rates were statistically similar between all three groups. Regarding resource utilization, viral cirrhosis patients had a significantly shorter stay (AOR 1.802, P < 0.001). **Conclusion:** Patients with alcoholic cirrhosis-mediated HRS were 1.84 times more likely to die than MASLD cirrhosis. Furthermore, patients with alcoholic cirrhosis were also more likely to develop SBP, putting them at an increased risk of HRS. It is important for clinicians to be aware of the underlying etiology of cirrhosis when managing patients with HRS to help with risk-stratification so they can initiate prompt treatment.

Table 1: Clinical outcomes of Hepatorenal Syndrome based on the liver cirrhosis types.

Outcome	Alcoholic Liver cirrhosis with HRS	MASLD Cirrhosis with HRS	Adjusted Odds Ratio (AOR)[1]	P Value	Viral Cirrhosis with HRS	Adjusted Odds Ratio (AOR)[1]	P Value
In-Patient Mortality	25.67%	14.77%	0.541	<0.001	23.62%	0.89	0.309
Spontaneous Bacterial Peritonitis	13.49%	9.12%	0.768	0.052	11.22%	0.93	0.660
Variceal Upper GI Bleed	7.87%	4.62%	0.851	0.370	6.30%	0.95	0.790

1: Adjusted difference as compared to the patients with Hepatorenal syndrome with Alcoholic liver cirrhosis.

MASLD: metabolic dysfunction-associated steatotic liver disease*; HRS: Hepatorenal Syndrome*

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Disclosures: Raghav Bassi: Nothing to Disclose, Zubair Bodla: Nothing to Disclose, Mohammad AbuAssi: Nothing to Disclose, Harsimran Kalsi: Nothing to Disclose, Kobina Essilfie-Quaye: Nothing to Disclose, Yaseen Perbtani: Nothing to Disclose, Tony Brar: Nothing to Disclose

4067 | PROTEOMIC AND METABOLOMIC ANALYSIS FROM THE CONFIRM TRIAL SHOWS BIOMARKERS THAT PREDICT HRS REVERSAL WITHOUT VASOCONSTRICTOR THERAPY ◆

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[1]Northwestern University Medical Center, [2]Virginia Commonwealth University, [3]MGH Medical Center, [4]University of Michigan Medical Center, [5]Mallinckrodt

Background: Terlipressin is the only FDA approved vasoconstrictor for the treatment of hepatorenal syndrome (HRS). The pivotal CONFIRM study is the largest randomized trial of terlipressin vs. placebo, examining HRS response as its primary outcome. Novel predictors of HRS response are required to enrich patient selection and optimize outcomes. Aim: Using samples from CONFIRM trial to determine predictors of HRS reponse with and without terlipressin use. **Methods:** We performed 3 types of analysis using samples from CONFIRM at the time of treatment initiation: (a) LC-MS of 1594 plasma and 1420 urine metabolites (Metabolon Inc), (b) aptamer-based array of 7289 plasma proteins (SomaScan), and (c) 14 *a priori* serum/urine ELISA assays. The CONFIRM trial's original definition of HRS response was used (2 separate creatinine [SCr] <1.5 mg/dL at end of Rx within 14 days). **Results:** 116 patients (79 terlipressin-treated [TT] and 36 placebo-treated [PT]) consented and had samples available for analysis. Baseline characteristics, outcomes, and the 2:1 TT:PT allocation were preserved relative to the original 300 patient trial. 36/116 (31.0%) patients achieved HRS reversal. Age, sex, etiology of cirrhosis, and MELD score were similar between responders and non-responders. Lower SCr at randomization was the only clinical feature that was associated with HRS response (2.75 [2.50, 3.30] vs. 3.50 [2.65, 4.10] mg/dL, p = 0.001). Metabolomics: PT had the most significant differences in HRS responders (n = 26 plasma, n = 50 urine), with fewer in TT (n = 1 plasma, n = 2 urine), and in all patients (n = 3 plasma, n = 7 urine). Metabolites centered on sulfated secondary bile acids (microbiome-derived), N-acetylated amino acids, catechols (both uremic toxins) and phosphocholines (cell membrane integrity) were lower in urine of placebo responders (Fig 1A). Proteomics: PCA showed significant separation within PT responders/not (Fig 1B). Although several proteins were significant, after false-discovery correction, there were no significant aptamers associated with HRS response among all patients or TT. In PT, heat shock factor 2 binding protein was higher in HRS responders (log-fold change 1.22, FDR-adj p = 0.047, Heatmap Figure 1C). ELISA assays: HRS responders had lower cystatin C (3.39 [3.05, 4.21] vs. 4.02 [3.55, 4.88] g/dL, p = 0.005), angiopoietin-2 (12.13 [9.52, 19.77] vs. 17.10 [11.59, 25.48] ng/mL, p = 0.04), and beta-2 microglobulin (6.47 [4.43, 8.60] vs. 8.70 [5.89, 11.26] mg/L, p = 0.006). L-FABP, IL-18, KIM-1, Osteopontin, VEGF, TFF-3, and NGAL were not different between groups. **Conclusion:** Cystatin C, angiopoietin-2, and beta-2 microglobulin, were associated with HRS response. Protein and metabolites centered on microbiome function and uremic toxins appeared more robust in placebo-treated patients. The latter suggests that these may be biomarkers to determine which patients may reverse HRS without vasoconstrictor therapy.

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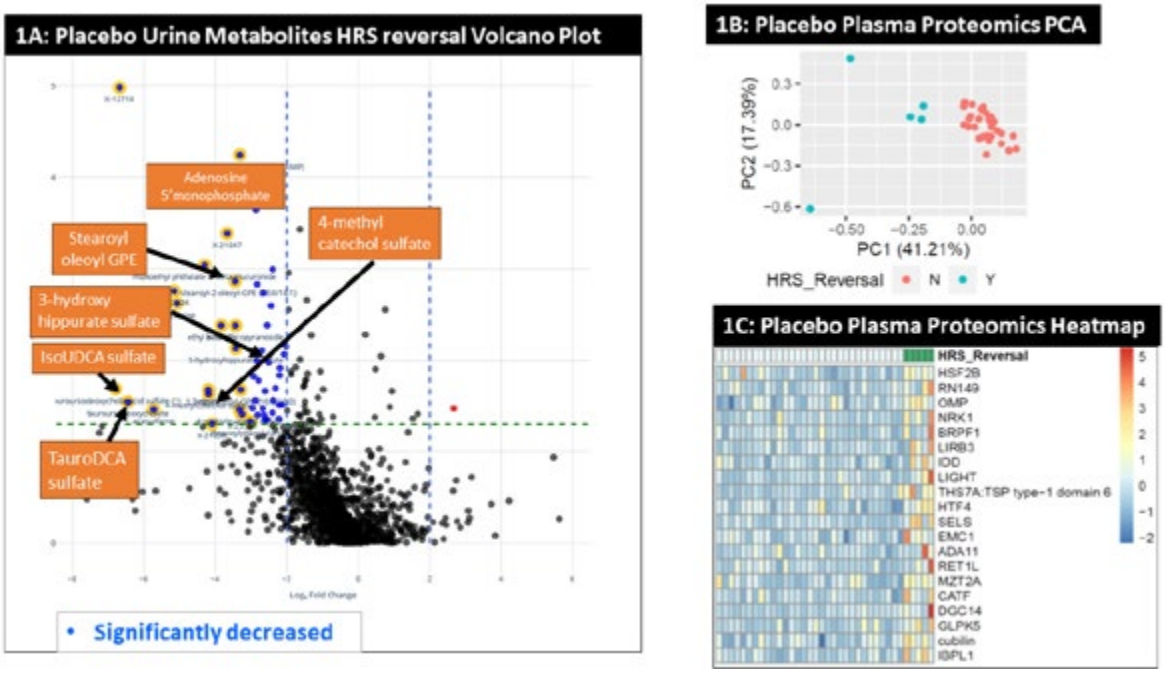

Disclosures: Josh Levitsky: Nothing to Disclose, Jasmohan Bajaj: Bausch: Grant/Research Support, Sequana: Grant/Research Support, Cosmo: Grant/Research Support, Grifols: Grant/Research Support, Andrew Allegreti: Mallinckrodt: Consultant, Ocelot Bio: Consultant, Motric Bio: Consultant, Sequana Medical: Consultant, Bioporto: Consultant, Pratima Sharma: Nothing to Disclose, Tianqi Ouyang: Nothing to Disclose, Scott Silvey: Nothing to Disclose, Khurram Jamil: Mallinckrodt Pharmaceuticals: Employee, Galectin Therapeutics: Stock - publicly traded company, Galectin Therapeutics: Employee

4068 | ACUTE KIDNEY INJURY DEVELOPMENT IS ASSOCIATED WITH MORTALITY IN JAPANESE PATIENTS WITH CIRRHOSIS: IMPACT OF AMINO ACID IMBALANCE

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Background: Acute kidney injury (AKI) is a serious complication of cirrhosis. This study analyzed the prognostic effect of AKI in patients with cirrhosis and its risk factors, particularly in relation to amino acid imbalance. **Methods:** This retrospective study reviewed 808 inpatients with cirrhosis and without AKI at baseline at two institutes in Gifu, Japan. AKI was diagnosed according to the recommendations of the International Club of Ascites. Amino acid imbalance was assessed by measuring serum branched-chain amino acid (BCAA) levels, tyrosine levels, and the BCAA-to-tyrosine ratio (BTR). Factors associated with mortality and AKI development were assessed using the Cox proportional hazards regression model with considering AKI development, overt hepatic encephalopathy (OHE) development, and hepatocellular carcinoma (HCC) development as time-dependent covariates and the Fine–Gray competing risk regression model, respectively. **Results:** Of the 567 eligible patients without AKI at baseline, 27% developed AKI and 25% died during a median follow-up period of 4.7 years. The survival curve showed that patients who developed advanced AKI had significantly worse survival rates than those in earlier stages (Fig. 1a, $p < 0.001$). Using a time-dependent covariate, AKI development (hazard ratio [HR], 6.25; 95% confidence interval [CI], 3.98–9.80; $p < 0.001$) was associated with mortality in patients with cirrhosis independent of potential covariates including OHE development (HR, 8.81; 95% CI, 2.68–13.68; $p < 0.001$) and HCC development (HR, 3.10; 95% CI, 2.01–4.81; $p < 0.001$). In addition, alcohol-associated/related liver disease, metabolic dysfunction-associated steatohepatitis, Child–Pugh score, and BTR (subdistribution HR, 0.78; 95% CI, 0.63–0.96; $p = 0.022$) were independently associated with AKI development in patients with cirrhosis. The cumulative incidence of AKI was significantly higher in patients with BTR ≤4.4 than in those with BTR >4.4 (21%, 34%, and 42% vs. 7%, 10%, and 15% at 1, 3, and 5 years, respectively; $p < 0.001$; Fig. 1b). Similar results were obtained in the multivariate model that included BCAA and tyrosine levels instead of

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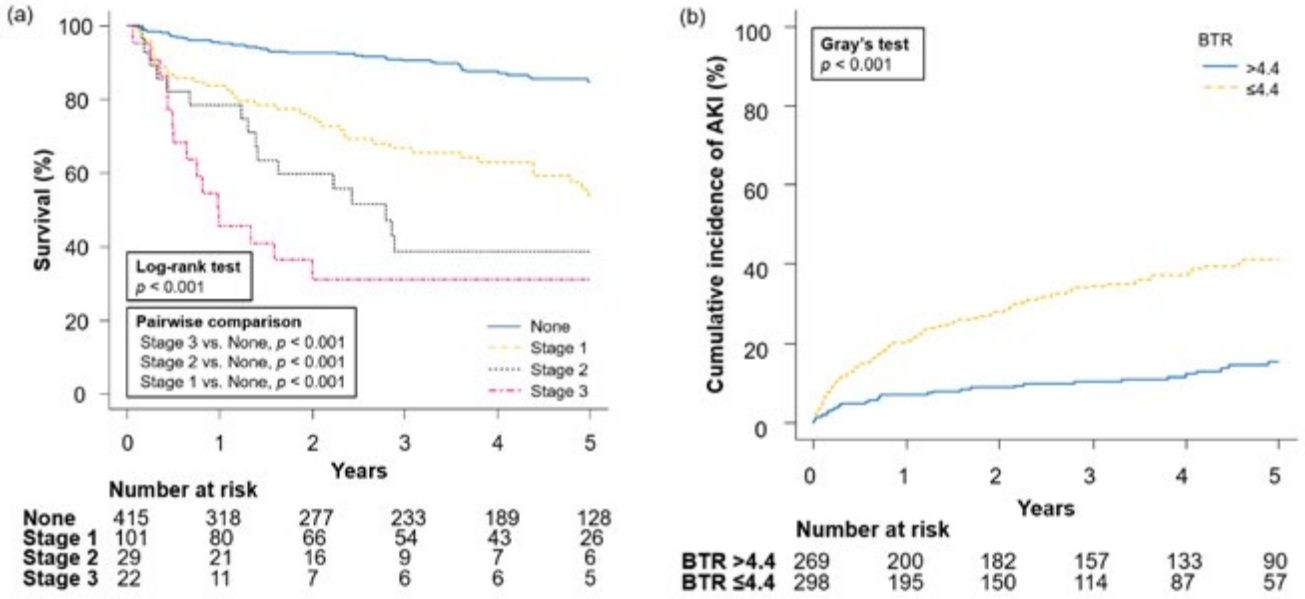
BTR. **Conclusion:** AKI is common and is associated with mortality in Japanese patients with cirrhosis. An amino acid imbalance is strongly associated with the development of AKI in patients with cirrhosis.



Disclosures: Takao Miwa: Nothing to Disclose, Yuki Utakata: Nothing to Disclose, Tatsunori Hanai: Nothing to Disclose, Masashi Aiba: Nothing to Disclose, Shinji Unome: Nothing to Disclose, Kenji Imai: Nothing to Disclose, Koji Takai: Nothing to Disclose, Makoto Shiraki: Nothing to Disclose, Naoki Katsumura: Nothing to Disclose, Masahito Shimizu: Nothing to Disclose

4069 | GASTROESOPHAGEAL BALLOON TAMPONADE FOR ACUTE VARICEAL HEMORRHAGE IS ASSOCIATED WITH HIGH IN-HOSPITAL MORTALITY AND INFREQUENT PALLIATIVE CARE CONSULTATION

Hannah Carr[1] *Anthony Robateau*[1] *Christopher Mowry*[1] *Michael Kriss*[1]

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Background: In patients with refractory acute variceal hemorrhage (AVH), gastroesophageal balloon tamponade (GEBT) is used as a bridge to more definitive therapies when hemostasis is not immediately achievable with endoscopy. GEBT placement has been associated with a high in-hospital mortality often necessitating goals of care discussions, but the role of palliative care consultation remains ill-defined. In patients with high MELD scores undergoing liver transplantation, palliative care consultation has become routine; however, this practice has not been uniformly adopted for other high-mortality clinical scenarios for patients with decompensated cirrhosis. This study aims to understand the rate of palliative consultation in critically ill patients undergoing GEBT for AVH. **Methods:** We retrospectively identified patients across a statewide health system who were admitted to the ICU between 2010-2024 with AVH who underwent EGD using admission diagnosis and procedure codes, respectively. Placement of GEBT was confirmed via manual chart review. Baseline data included patient demographics, etiology of liver disease, MELD 3.0 on admission, as well as rescue therapy performed (if any). Our primary outcomes were 7- and 30-day mortality and utilization of palliative care consultation. **Results:** A total of 537 patients were admitted to an ICU with AVH, of whom 9% (47/537) required GEBT placement. The median age of the GEBT cohort was 52 (IQR 43-59), 76.6% were males, and alcohol-associated liver disease was the main cause of cirrhosis (61.7%). The median MELD 3.0 score on admission was 29 (10-46). Of those who had GEBT, nearly half (51.0%) subsequently underwent TIPS, of whom 33% died within 30 days. Following GEBT placement, 22 patients died within 30 days (47%), of these patients, 16 (73%) died within 7 days, and the majority transitioned to comfort care near the end of life (77%). The total rate of palliative care consultation in patients requiring GEBT was 15% with no difference between patients that died and those that survived (18% vs 11%, p=0.55). **Conclusion:** Despite a high 30-day mortality rate (47%) among patients undergoing GEBT and high

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rates of transitions to comfort care, palliative care consultation was infrequently utilized (15%). More research is needed to understand if hepatologists are leading these goals of care discussions or if routine use of palliative care consultation following GEBT placement is needed.

Disclosures: Hannah Carr: Nothing to Disclose, Anthony Robateau: Nothing to Disclose, Christopher Mowry: Nothing to Disclose, Michael Kriss: Nothing to Disclose

4070 | PREDICTING HIGH RISK FOR DECOMPENSATION EVENTS IN PATIENTS WITH COMPENSATED CIRRHOSIS USING EASILY ACCESSIBLE PATIENT DATA ◆

Anders Hildeman[1] Jan Oscarsson[1] Philip Ambery[1] Nils Svangård[1] Claire Donoghue[1] Caterina Tozzi[1] Roza Maghsood[1] Hyewon Koo[1]

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Background: Cirrhosis of the liver is characterized by advanced fibrosis and associated with a range of pathologies such as MASLD, ALD and viral hepatitis. Cirrhosis is either compensated with no history of decompensation events or decompensated, when the patient has had a decompensation event including variceal hemorrhage, overt ascites, or overt encephalopathy. We aim to develop a non-invasive test to identify patients with compensated cirrhosis at high risk of decompensation using common laboratory values and patient characteristics. Widespread use of a risk prediction tool could significantly reduce the burden of end-stage liver disease by identifying high risk patients earlier. **Methods:** Our prediction algorithm is a survival model using a boosted tree architecture to make predictions based on 11 commonly measured patient laboratory values and patient characteristics. It models probability of time duration from the date the patient was identified as (compensated) cirrhotic until the date they experience a first decompensation event. The model was trained on the real-world dataset Optum's de-identified Clinformatics® Data Mart Database (CDM). After filtration, 18-80 years old with compensated cirrhosis, the dataset included 187,717 patients. Of those patients, 60% were used for training, a complementary 10% for hyperparameter tuning, and 30% for validation. A separate validation was also carried out on the 14,865 patients acquired after filtering the Explorys Linked Claims and EMR Data real-world dataset based on the same criteria. The diagnoses corresponding to inclusion, events, and censoring were identified through ICD-9 and -10 codes. For the date of the first compensated cirrhosis diagnosis, we aggregated covariate measurements available within a timeframe spanning 6 months prior to 1 month after the diagnosis. **Results:** ROC-AUC was above 80% for finding patients with a decompensation event within 1-year, 2-year, and 3-years, respectively. For all three intervals, a precision above 70% could be achieved while maintaining a corresponding sensitivity of at least 20%. In Figure 1 Kaplan-Meier curves are calculated on patients from our CDM test subset population, stratified by risk score severity. The KM curves calculated from patients with higher risk scores show markedly increased risk of early decompensation. **Conclusion:** Our work show that it is possible to identify high risk cirrhotic individuals from data commonly collected during clinical practice. This has the potential to be used to provide suitable care to patients in need early on. In turn, this would prolong patients' lives and enhance their quality of life significantly.

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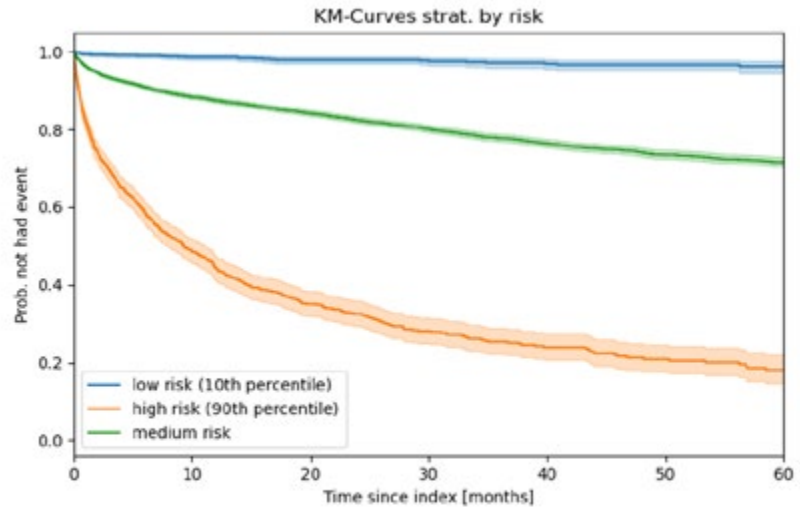

Figure 1: Kaplan-Meier estimates of the survival function on the exhaustive and mutually exclusive subgroups of patients with the 10% highest risk score values, the 10% lowest risk-score values, and risk-score values in-between.

Disclosures: Anders Hildeman: AstraZeneca: Employee, Jan Oscarsson: AstraZeneca: Employee, Philip Ambery: AstraZeneca: and stockholder, AstraZeneca: Employee, Nils Svangård: Nothing to Disclose, Claire Donoghue: Nothing to Disclose, Caterina Tozzi: AstraZeneca: Employee, Roza Maghsood: Nothing to Disclose, Hyewon Koo: Nothing to Disclose

4071 | BLOOD METABOLOMICS PREDICT 6-MONTH HOSPITALIZATIONS IN A MULTI-CENTER PROSPECTIVE NORTH AMERICAN COHORT OF OUTPATIENTS WITH CIRRHOSIS

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[1]Virginia Commonwealth University, [2]University of Alberta, [3]UCSF, [4]UTSW, [5]Yale University, [6]Mayo Clinic Arizona, [7]University of Toronto, [8]UPMC, [9]Mayo Clinic, [10]Metabolon, [11]VCU, [12]University of Pennsylvania

Background: Predicting hospitalizations in a stable outpatient cohort of cirrhosis is challenging, especially in those whose etiology is controlled. Metabolomics could add to prognostication multicenter studies are needed. Aim: Define contribution of baseline blood metabolomics in predicting 6 mth hospitalizations in a multicenter cohort. **Methods:** NACSELD3 includes cirrhosis outpatients from 10 centers. Only those with stable etiologies (HCV eradication, HBV suppression & alcohol abstinence) are followed over 6 mths for non-elective hospitalizations. Baseline serum was analyzed for metabolomics with LC/MS. 20% of data was set aside as a test set balanced between hospitalized/not. 5-fold cross validation was employed. Using the training data, a lasso regression model to provide a 20 predictor model was created which was further testing through logisttc regression models using training data with AUCs for only metabololite & clinical+metabolite models. **Results:** 744 pts provided samples. 6-mth data was available for 565 pts; of the remaining, 17 died, 13 were transplanted, 23 withdrew, rest were lost to follow-up or had not reached that timepoint. Hospitalizations: 163 (29%) reached this outcome; 113 were liver-related. Those who were hospitalized had lower prior HCV, more advanced cirrhosis & worse comorbidities (Fig A). Metabolomics: 821 metabolites were different (Figures B/C), of which the top 20 were input in the model. *Metabolite-only model*: Highest AUC was 0.79 with 0.75 in the test set with 6 metabolites; higher 5,6-dihydrothymine (OR 1.74,pyrimidine metabolism), & nervonoylcarnitine (C24:1, OR 1.53, related to kidney disease) & lower gamma-glutamylglutamate (OR: 0.69), isoursodeoxycholate (OR: 0.84, beneficial microbial metabolite),1-stearoyl-2-dihomo-linolenoyl-GPC (OR 0.64, cell membrane stability) & hydroxy-CMPF* (OR 0.78, furanoic acid ↓ lipid peroxidation) were significantly linked with hospitalization. Metabolite+clinical model: The only additional clinical factor was albumin, which when introduced had a similar AUC validation AUC 0.75 & test AUC 0.69. Higher 3-ureidopropionate(OR 1.57, pyramidine degradation), mannitol/sorbitol (OR 1.35, intestinal permeability) cyclo (met-pro OR 1.69, beef consumption marker) & palmitoyl-sphingosine-phosphoethanolamine (OR 1.22, related to brain/liver development) and lower serum albumin (OR 0.59),

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17alpha-hydroxypregnanolone glucuronide (OR 0.71, testosterone intermediate) were associated with 6-month hospitalizations. **Conclusion:** Despite control and suppression of underlying etiologies, almost 30% of outpatients enrolled in the NACSELD3 prospective cohort require hospitalizations in 6 months. Hospitalizations were predicted by baseline serum metabolomics with biochemicals focused on pyrimidine metabolism, gut microbiome, and lipid peroxidation, which remained significant with addition of clinical biomarkers.

Hospitalized at month 6 (Figure A)	No (n=402)	Yes (n=163)	P value
Age	61.37 ±10.12	59.62 ±10.67	0.07
Men (N)	276	110	0.08
White(N)	317	135	0.56
Hispanic (N)	35	21	0.13
Etiology (Alcohol/HCV/ HCV+Alcohol/MASH/ Others)	135/65/27/124 /75	62/11/14/60/1 6	0.03
Diabetes N	156	76	0.18
AUDIT-10 (mean±SD)	1.87 ±4.27	1.76 ±3.47	0.77
CCI (mean±SD)	4.69 ±2.06	5.30 ±2.17	0.018
History (N)			
Overt HE	85	61	0.006
Ascites	177	119	<0.0001
Prior variceal bleed	48	39	0.0004
Prior SBP	25	19	0.03
Labs at baseline(mean±SD)			
WBC	5.60 ±2.20	5.78 ±2.76	0.42
Hemoglobin	13.11 ±2.00	11.61 ±2.32	0.001
Platelets	138.97 ±72.99	126.26 ±73.52	0.06
BUN	15.84 ±7.65	19.75 ±12.75	0.0001
Albumin	3.70 ±0.59	3.26 ±0.58	0.0001
MELD 3.0	11.92 ±4.88	15.33 ±5.87	0.0001
Meds at baseline (N)			
Beta-blockers	175	86	0.07
Rifaximin	85	66	<0.0001
Lactulose	119	81	<0.0001
PPI	166	105	<0.0001
Diuretics	170	111	<0.0001
Statins	127	50	0.83
Opioids	46	30	0.03

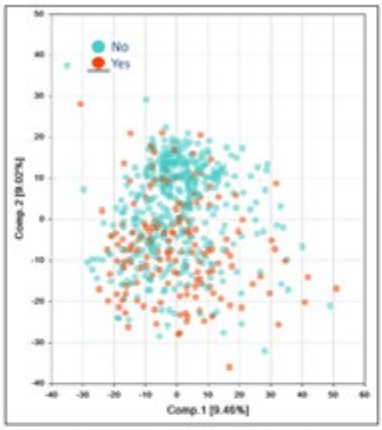

Figure B: PCA of hospitalized versus not on baseline serum metabolites

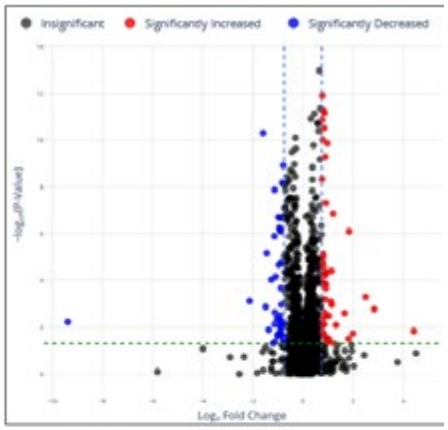

Figure C: Volcano plot showing serum metabolites that were significantly higher (red) or lower (blue) in those who were hospitalized or not at 6 months.

Disclosures: Jasmohan Bajaj: Bausch: Grant/Research Support, Sequana: Grant/Research Support, Cosmo: Grant/Research Support, Grifols: Grant/Research Support, Puneeta Tandon: Nothing to Disclose, Jennifer Lai: Nestle Nutrition Institute: Grant/Research Support, Novo Nordisk: Consultant, Genfit: Consultant, Boehringer Ingelheim: Advisor, Jacqueline Oleary: Grifols: Consultant, Cellion: Advisor, Mallinckrodt: Advisor, PharmaIn: Consultant, Genfit: Consultant, CVS: Stock - publicly traded company, Guadalupe Garcia-Tsao: Nothing to Disclose, Hugo Vargas: Grant/Research Support relationship with Kezar Pharmaceuticals; Has not ended; Grant/Research Support relationship with Genfit; Has not ended; Grant/Research Support relationship with River2Renal; Has not ended; Grant/Research Support relationship with Durect; Has ended; Grant/Research Support relationship with Takeda; Has not ended; Grant/Research Support relationship with Arrowhead Phama; Has ended; Grant/Research Support relationship with Ocelot; Has ended; Consultant relationship with Mallinckrodt; Has ended; Consultant relationship with Sequana Medical; Has not ended, Florence Wong: Mallinckrodt: Consultant, Mallinckrodt Pharmaceutical Inc: Grant/Research Support, River 2 Renal: Consultant, Sequana Medical: Consultant, sequana Medical: Grant/Research Support, Scott Biggins: Nothing to Disclose, Patrick Kamath: Advisor relationship with Sequana; Has ended; Advisor relationship with NovoNordisk; Has ended, Philip Gunst: Metabolon: Employee, Scott Hutton: Nothing to Disclose, Brian Bush: Nothing to Disclose, K Rajender Reddy: Nothing to Disclose

4072 | SLEEP RELATED BREATHING DISORDERS IN LIVER TRANSPLANT CANDIDATES WITH CIRRHOSIS

Bradley Busebee[1] Kymberly Watt[1] Kara Dupuy-McCauley[1] Stephen Harvey[2] Hilary DuBrock[1]

[1]Mayo Clinic, [2]Mayo Clinic School of Medicine

Background: Sleep disturbances and sleepiness are common among patients with liver disease. Screening **Methods:** do not necessarily discern between sleep-related breathing disorders, overt or covert hepatic

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encephalopathy (HE), and other causes of sleep-related symptoms. We performed a prospective cohort study to determine the prevalence and impact of OSA and sleepiness among patients undergoing liver transplant (LT) evaluation. **Methods:** We recruited consecutive patients undergoing LT evaluation to complete overnight oximetry, EncephalApp Stroop testing, sleep related surveys (PSQI, STOP-Bang, Epworth Sleepiness Scale (ESS)) and quality of life assessments (Promis-29). Patients were excluded from this analysis if they did not have cirrhosis, had previously diagnosed obstructive sleep apnea (OSA), were color-blind, or did not speak and read English. We used ANOVA and Fischer's test analyses to assess the relationship between suspected OSA (defined as Oxygen Desaturation Index (ODI)>5) and clinical characteristics. **Results:** 109 patients were screened, of whom 30 patients (27.5%) were excluded for previously diagnosed OSA. 53 patients completed the study at the time of this preliminary analysis, of whom 42 had cirrhosis. ODI>5 was identified in 16/42 (38.1%) and was significantly associated with STOP-Bang>5 and no history of HE with trends toward association withhigher BMI, age and male gender (Table 1). ODI>5 was not associated with ascites, varices, TIPS, ESS, PSQI, or quality of life scores. STOP-Bang>5 had 100% specificity but poor sensitivity (29%) (p=0.005) with slightly improved sensitivity (50%) in those with a history of HE. **Conclusion:** In this study, abnormal overnight oximetry suggestive of OSA was common among LT candidates with no known history of OSA. STOP-Bang questionnaires have excellent specificity but poor sensitivity for detection of OSA among LT candidates and may be impacted by HE. Ongoing studies are needed to better understand the association between sleep disordered breathing and liver disease to determine the clinical impact of OSA in this setting.

	ODI < 5	ODI > 5	Sensitivity	Specificity	P-value
Male	12 (42.9%)	10 (71.4%)			0.08
BMI	27.15 (24.63, 31.70)	30.30 (27.63, 35.43)			0.06
Age	54.500 (40.75, 65.00)	63.50 (53.25, 67.75)			0.06
MELD Na	14.500 (9.75, 19.25)	16.00 (10.25, 17.75)			0.90
Ascites	17 (60.7%)	7 (50.0%)			0.51
TIPS	5 (17.9%)	0 (0.0%)			0.09
EtOH	15 (53.6%)	7 (50.0%)			0.83
MASH	8 (28.6%)	6 (42.9%)			0.36
Varices	20 (71.4%)	8 (57.1%)			0.36
History of HE	19 (63.3%)	6 (33.3%)			0.04*
Promis-29 Physical Function Score	42.9 (36.9, 48.1)	37.3 (34.7, 42.5)			0.38
Promis-29 Fatigue Score	57.10 (50.90, 62.70)	60.75 (52.52, 66.78)			0.421
STOP-Bang > 3	10 (40.0%)	9 (64.3%)	64%	60%	0.15
STOP- Bang > 5	0 (0.0%)	4 (28.6%)	28%	100%	0.005**
ESS > 10	8 (32.0%)	4 (28.6%)	29%	68%	0.82
PSQI > 5	17 (68.0%)	11 (78.6%)	79%	32%	0.48

Table 1. Summary clinical traits for patients with oxygen desaturation index < and > 5. Continuous variable p-values calculated by ANOVA, categorical values calculated by Fischer test. Sensitivity and specificty reported for detecting ODI > 5. BMI – Body mass index, ESS – Epworth Sleepiness Scale, EtOH – Alcohol Associated Cirrhotic Liver Disease, HE – Hepatic Encephalopathy, MASH – Metabolic dysfunction-associated steatohepatitis, ODI - Oxygen desaturation index, PSQI – Pittsburgh Sleep Quality Index, TIPS – Transjugular intrahepatic portosystemic shunt. *p-value < 0.05. **p-value < 0.01.

Disclosures: Bradley Busebee: Nothing to Disclose, Kymberly Watt: Madrigal: Stock - publicly traded company, Viking: Stock - publicly traded company, Kara Dupuy-McCauley: Nothing to Disclose, Stephen Harvey: Nothing to Disclose, Hilary DuBrock: Nothing to Disclose

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4073 | ELEVATION OF CONJUGATED BILE ACIDS AND IL-6 IN CHRONIC LIVER DISEASES REGULATES MUSCLE TYPES AND INFLAMMATION

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Background: The prevalence of sarcopenia in patients with chronic liver disease (CLD) is likely higher than in other diseases, with adverse effects on clinical outcomes such as falls, fractures, physical disability, and mortality. However, the molecular mechanisms underlying the liver-muscle axis involved in CLD-related sarcopenia are not fully understood. Our aim was to explore the mechanisms underlying the effects of bile acids (BAs) and inflammation on skeletal muscle changes in patients with CLD. **Methods:** Muscle specimens of rectus abdominis and serum were obtained from patients who underwent surgery for hepatocellular carcinoma (HCC) with chronic hepatitis (CH, n=14) and liver cirrhosis (LC, n=22) or other abdominal malignancies (Cont, n=6). Muscle area of multifidus and iliopsoas at the L3 (cm^2) was measured from CT images. The composition of BAs and IL-6 were measured by LC-MS/MS and ELISA. Gene expressions including muscle fiber types, metabolism, and mitochondrial function were assessed by immunohistochemistry and quantitative PCR. C2C12 myoblasts were treated with glycochenodeoxycholic acid (GCDCA) to investigate the transition of skeletal muscle cells. **Results:** The levels of serum conjugated (tauro- and glyco-) BAs were significantly elevated in CH and LC (Cont vs. LC: p<0.001-0.0001, CH vs. LC: p<0.01-0.001) and were associated with liver function including AST, Plt, PT, ALB, and ALBI. The muscle area of multifidus (p<0.05) and iliopsoas muscle area were lower in the LC group associated with liver function and serum IL-6 levels (p<0.05). Furthermore, multifidus muscle area showed significant negative correlations with the ratios of taurocholic acid (TCA)/CA, TCDCA/CDCA, and TDCA/DCA (p<0.05, p<0.01). The mRNA levels of myosin-heavy chain (*Myh7*) for type I (slow) (p<0.05) and *Myh1* for type IIx (fast) were increased, which were correlated with an increase in *PEPCK* and *Tfam* (p<0.05) mRNA levels, while those of *Myh4* for type IIb (very fast) (p<0.05) were decreased in the rectus abdominis of the LC group compared to the CH group (p<0.05). The mRNA levels of inflammatory genes, *Iba1*, *CCL2*, and *CD163*, were also increased in the LC group (p<0.05). Furthermore, several genes including *Myh1*, *PEPCK*, *Iba1*, *CCL2*, and *CD163* were positively correlated with serum IL-6, ALT, and ALBI, and negatively correlated with PT and ALB (p<0.01-0.05). Notably, *CCL2* and *CD163* mRNA levels were positively correlated with GDCA/DCA (p<0.05, 0.01) and *Myh4* mRNA levels were negatively correlated with ALT, GCA/CA (p<0.05), and GCDCA/CDCA (p<0.01). The addition of GCDCA led to significant down-regulation of *Myh4* mRNA levels in C2C12 cells (p<0.05), indicating inhibition of type IIb by GCDCA. **Conclusion:** In patients with CLD, the elevation of conjugated BAs and serum IL-6 levels affects muscle volume, type, and inflammation, suggesting their association with the fast-to-slow shift in muscle fiber type composition and decline in muscle volume.

Disclosures: Akiko Eguchi: Nothing to Disclose, Motoh Iwasa: Nothing to Disclose, Motoyuki Kohjima: Nothing to Disclose, Teruo Miyazaki: Nothing to Disclose, naoki yamashita: Nothing to Disclose, Mina Tempaku: Nothing to Disclose, Kiyora Izuoka: Nothing to Disclose, Yoshinao Kobayashi: Nothing to Disclose, Yoshiyuki Takei: Nothing to Disclose, Akira Honda: Nothing to Disclose, Hayato Nakagawa: AstraZeneca: Speaking and Teaching, CHUGAI PHARMACEUTICAL: Speaking and Teaching, Gilead Sciences: Speaking and Teaching, AbbVie: Speaking and Teaching, KOWA: Speaking and Teaching, Eisai: Speaking and Teaching, TAISHO PHARMACEUTICAL HOLDINGS: Speaking and Teaching, Incyte Biosciences: Speaking and Teaching, Tadashi Ikegami: Nothing to Disclose, Makoto Nakamuta: Nothing to Disclose

4074 | SARCOPENIA AS AN INDEPENDENT FACTOR FOR MORTALITY IN LIVER CIRRHOSIS PATIENTS WITH SPONTANEOUS BACTERIAL PERITONITIS

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Background: This study aimed to investigate the initial treatment response and mortality of spontaneous bacterial peritonitis (SBP) in cirrhotic patients according to the presence of the sarcopenia. **Methods:** Data were retrospectively reviewed for patients with liver cirrhosis who were admitted for treatment of SBP at Jeonbuk

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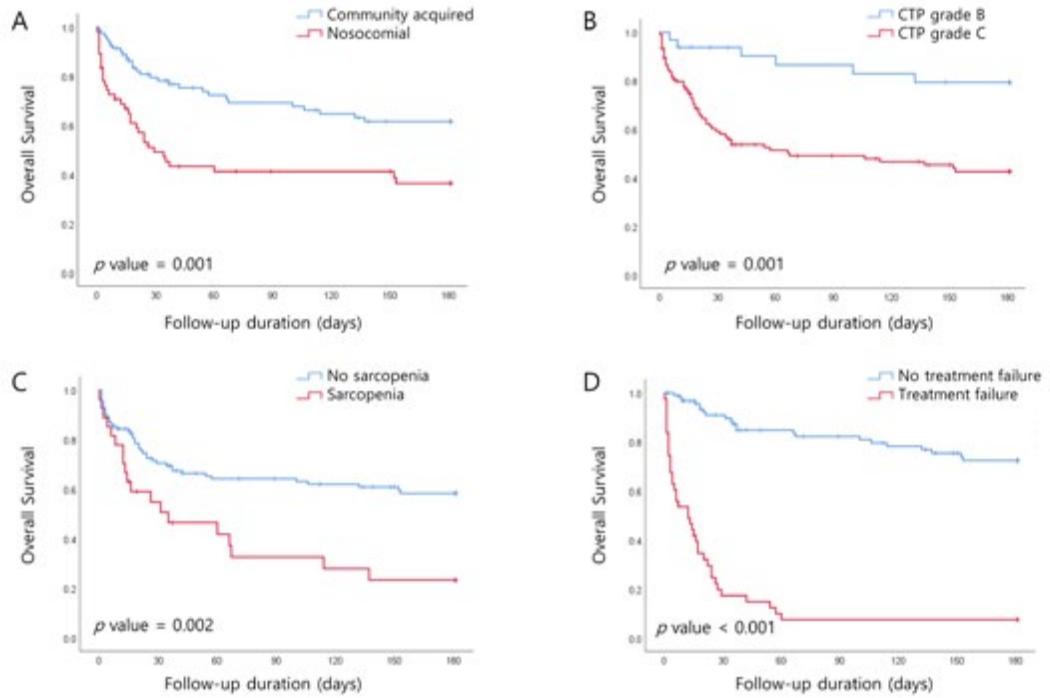
National University Hospital from January 2004 to December 2020. Sarcopenia was measured using the skeletal muscle index at the third lumbar vertebra and defined as the lowest quintile. **Results:** A total of 137 patients were enrolled in the study, with sarcopenia cut-off values set at 35.82 for men and 30.49 for women. In the demographic and baseline characteristics, there were no statistically significant differences related to the presence of sarcopenia, except for hemoglobin levels. Clinical outcomes were compared based on the presence of sarcopenia, revealing no difference in treatment response according to sarcopenia status. While there were no significant differences in short-term mortality rates at 7 and 30 days, the sarcopenia group exhibited statistically significant higher mortality rates at 3 months, 6 months, 12 months, and in-hospital. Additionally, we conducted a Cox regression analysis on 6-month survival, identifying four significant predictors of mortality in the multivariate analysis: acquisition type (nosocomial vs. community-acquired), CTP grade C versus B, treatment failure, and sarcopenia, with sarcopenia showing an odds ratio of 7.647 (95% CI 1.231-47.501, p = 0.029). In the Kaplan-Meier survival curve, we observed that survival was significantly differentiated by the four major predictors of mortality, as evidenced by p-values from the log-rank test. **Conclusion:** Sarcopenia did not show a significant difference in baseline characteristics or treatment response in cirrhotic patients with SBP. However, it was confirmed as an independent risk factor for prognosis after SBP treatment, along with other established factors such as nosocomial infection, CTP grade C, and treatment failure.



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4075 | CARDIAC FAILURE FOLLOWING TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC SHUNT IN PATIENTS WITH CIRRHOSIS

Xuefeng Luo[1] *SHUMEI DU*[1] *Xiaoze Wang*[1]

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Background: Post-TIPS cardiac failure has become one of the main concerns recently. This study was designed to evaluate the incidence and predisposing factors of post-TIPS cardiac failure in patients with cirrhosis. **Methods:** Between September 2022 and September 2023, consecutive cirrhotic patients who underwent elective TIPS were prospectively screened for inclusion. Patients with medium to severe pulmonary hypertension, clinical symptomatic heart failure, or respiratory failure were excluded. **Results:** Finally, 140 patients were included for analysis. Etiologies of cirrhosis were hepatitis B virus infection in 79 (56.4%) patients and alcohol in 27 (19.2%)

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patients. The indication for TIPS was variceal bleeding in 113 (80.7%) patients. 24(17.1%) patients had diastolic dysfunction based on HFA-PEFF score. The median ejection fraction was 68.0%, E/A was 1.1, and Pro-BNP was 110 np/l respectively. After a median follow-up of 6 months, none of the patients experienced post-TIPS cardiac failure. However, 94 (67.1%) patients had edema. Among 67 patients with cardiac evaluation after TIPS, there is no significant difference regarding ejection fraction, left atrial volume index, Septal e', Lateral e,'and E/Mean e. Survival was not influenced by the presence of edema. **Conclusion:** Post-TIPS cardiac failure is rare in the current Chinese TIPS cohort. There is no significant change of cardiac function based on follow up echocardiography.

Disclosures: Xuefeng Luo: Nothing to Disclose, SHUMEI DU: Nothing to Disclose, Xiaoze Wang: Nothing to Disclose

4076 | THE DEDICATED TIPS STENT WAS ASSOCIATED WITH A REDUCED RISK OF POST-TIPS HEPATIC ENCEPHALOPATHY

Xuefeng Luo[1] SHUMEI DU[1] Xiaoze Wang[1]

[1]WEST CHINA HOSPITAL

Background: eFTFE-covered stent has been widely used in TIPS creation. This study investigated the incidence of post-TIPS hepatic encephalopathy (HE) using dedicated TIPS stents and full covered stents. **Methods:** This was a retrospective study of 737 patients with cirrhosis who had undergone TIPS at our center using a Fluency (January 2012 to December 2019) or Viatorr stent (January 2012 to December 2019). Case-control matching was conducted to balance the differences in age and liver function between the two groups. The Kaplan-Meier and Cox regression analyses were used to identify the independent risk factors for HE after TIPS. **Results:** Finally, there were 277 patients in each group. Post-HE occurred in 115 patients in the Fluency group and 60 patients in the Viatorr group. The 3- and 12-month accumulative incidence of HE was 12.7% and 17.6% in the Viatorr group and 27.4% and 31.2% in the Fluency group. The use of a dedicated TIPS stent was associated with a decreased risk of post-TIPS HE (p=0.021). The Cox-regression models showed that age (hazard ratio [HR], 1.0210; P = .007), creatinine (HR, 1.053; P = .025), urea nitrogen (HR, 1.007; P = .012), and Fluency stent (HR, 1.70; P = .002) were the independent risk factors for HE. However, the 1-year transplant-free survival rate was lower in the Viatorr group (92.4% vs. 97.1%, p=.004). **Conclusion:** When compared with full covered stent, dedicated TIPS stent led to reduced HE risk but decreased survival in patients with cirrhosis.

Disclosures: Xuefeng Luo: Nothing to Disclose, SHUMEI DU: Nothing to Disclose, Xiaoze Wang: Nothing to Disclose

4077 | EVALUATING CHATGPT-4O'S REAL-TIME CLINICAL ASSESSMENTS AND RECOMMENDATIONS IN COMPLEX HEPATOLOGY CASES USING VOICE PROMPTS

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Background:
The integration of artificial intelligence (AI) into clinical practice has the potential to revolutionize patient care. Traditional machine learning models are trained for specific tasks and cannot address complex and heterogeneous questions beyond their training scope. Generative AI may offer a solution by utilizing large language models (LLMs) trained on billions of parameters of multimodal data. OpenAI has recently released ChatGPT-4o (omni), an LLM capable of processing multimodal data, including text, images, voice, and video, with short latency for quick real-time responses. This study evaluates ChatGPT-4o's performance in providing real-time clinical assessments and recommendations for complex liver cases using voice prompts. **Methods:** We evaluated ChatGPT-4o's responses to over 30 voice-activated clinical scenarios involving complex liver diseases, including congenital hepatic fibrosis with ARPKD, sinusoidal obstruction syndrome, hereditary hemorrhagic telangiectasia, Budd-Chiari syndrome, massive GI bleeds from post-transplant hepatic artery pseudoaneurysms, and management strategies for cholangiocarcinoma and hepatocellular carcinoma. Each

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scenario mimicked real-life clinical situations and was presented to ChatGPT-4o through voice prompts without disclosing the diagnosis or management. A panel of hepatology experts assessed the AI's responses for accuracy, relevance, and comprehensiveness. Key metrics included response time, clinical appropriateness, and actionable recommendations. **Results:** ChatGPT-4o demonstrated excellent performance across all clinical scenarios, providing accurate and relevant clinical assessments and recommendations with an average response time of less than 10 seconds per query. For example, in a patient with ARPKD who presented with pulmonary hypertension and nodular liver contour, it correctly associated ARPKD with congenital hepatic fibrosis and deduced that patient could have portopulmonary hypertension. For various clinical situations, it automatically applied appropriate scoring systems such as MELD, FIB-4, APRI, and Milan/UCSF criteria, as well as MELD exception policies, without explicit instructions. Over 90% of the assessments were rated highly by hepatology experts, who agreed with most of its clinical reasoning. **Conclusion:** This study demonstrates ChatGPT-4's ability to deliver real-time, accurate, and comprehensive clinical assessments and recommendations for complex hepatology cases using voice prompts. When securely implemented into clinical practice, generative AI technology, as represented by multimodal large language models (LLMs), holds immense potential as a clinical decision support tool in hepatology. Future applications of AI in hepatology may benefit from adapting and fine-tuning LLMs for specific use cases, rather than developing entirely new algorithms for each specific question.

Examples of ChatGPT 4o's ability to analyze and explain complex hepatology cases

Voice Prompt	AI Response (only most relevant part included)	Capacities demonstrated
"30 year old male with history of ARPKD presents with new symptoms of lower extremity edema and shortness of breath. Echo shows severe pulmonary hypertension with mean PA pressure of 70. His liver enzymes are also abnormal and imaging shows that he has a nodular liver contour with evidence of portal hypertension."	"...The combination of ARPKD, a nodular liver contour, and severe pulmonary hypertension suggests the possibility of congenital hepatic fibrosis (CHF), which is commonly associated with ARPKD. CHF can lead to portal hypertension and subsequent portopulmonary hypertension..."	Identify the link between ARPKD and congenital hepatic fibrosis. Deduce the cause of pulmonary hypertension as portopulmonary hypertension.
"24 year old female with history of juvenile polyps presents with new onset ascites. Liver function is completely intact. CT shows presence of numerous AVMs in the liver."	"...The clinical scenario raises the suspicion of a rare vascular liver disease, specifically Hereditary Hemorrhagic Telangiectasia (HHT), also known as Oster-Weber-Rendu syndrome..." "...Hepatic AVMs can shunt blood from the arterial system directly into the hepatic veins or portal veins, bypassing the normal capillary bed. This can lead to increased blood flow in the liver, causing elevated pressure in the portal vein"	Predict HHT based on the presence of hepatic AVMs. Explain the physiology of portal hypertension and ascites due to arterio-portal shunting.
"50 year old female with history of stage III colon cancer underwent total colectomy with adjuvant chemotherapy consisting of FOLFOX. She presents with new onset ascites. CEA is low and CT shows no obvious evidence of peritoneal carcinomatosis."	"Given her medical history and the new onset of ascites, the differential diagnosis includes: Chemotherapy-Induced Liver Injury: Sinusoidal Obstruction Syndrome (SOS) (formerly known as veno-occlusive disease) is a known complication of certain chemotherapeutic agents, including oxaliplatin (a component of FOLFOX)..."	Integrate the available clinical information to correctly identify oxaliplatin-induced SOS as the most likely cause of ascites.
"A 50 year old patient with cirrhosis is found to have multifocal HCC. He has three LIRADS 5 lesions sized 2cm, 2.5cm, and 1.7cm one of which appears to involve the portal vein. There are no distant metastases. Is he eligible for liver transplant?"	"...Lesion Sizes: The patient has three lesions sized 2 cm, 2.5 cm, and 1.7 cm, which meet the size criteria for Milan and UCSF. Number of Lesions: The patient has three lesions, fitting within both Milan and UCSF criteria. Portal Vein Involvement: The involvement of the portal vein indicates macrovascular invasion. Given the presence of macrovascular invasion (portal vein involvement), the patient would generally not be eligible for liver transplantation under standard criteria such as Milan and UCSF. Macrovascular invasion is a significant contraindication due to the higher risk of recurrence and poorer outcomes post-transplant."	Without any prompting or mention of Milan or UCSF criteria, correctly apply the Milan criteria and UCSF criteria to the lesion sizes, number of lesions, and presence of macrovascular invasion and determine the patient's eligibility for liver transplantation.
"50 year old male who underwent a liver transplantation 10 days ago presents with massive upper GI bleed. He initially presented with a fever, then a small amount of melena before developing profound hemorrhagic shock. Bedside endoscopy shows massive amounts of blood in the stomach and duodenum but fails to localize a clear source of bleeding."	"...the clinical picture suggests a serious post-transplant complication. The inability to localize the source of bleeding on bedside endoscopy is concerning and suggests a possible vascular etiology, likely related to the liver transplant. 1. Hepatic Artery Pseudoaneurysm (HAPA): Can present with fever due to infection, a sentinel bleed (melena), and then massive hemorrhage when the pseudoaneurysm ruptures..."	Correctly pick up the clinical presentation of hepatic artery pseudoaneurysm in a liver transplant patient starting with an infection followed by a sentinel bleed, then massive hemorrhage.

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4078 | THE PROGNOSTIC SIGNIFICANCE OF SERUM THYROID HORMONES LEVELS IN PATIENTS WITH LIVER CIRRHOSIS REQUIRING HOSPITALIZATION

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[1]University Hospital of Patras, Greece, [2]Hippocrates General Hospital of Athens, [3]University of Patras, Greece

Background: Non-Thyroidal Illness Syndrome (NTIS) is a condition characterized by abnormal thyroid function tests in individuals with intact hypothalamic pituitary thyroid axis experiencing severe illness or stress. Our study aims to assess thyroid function in cirrhotic patients who require hospitalization and evaluate its prognostic significance. **Methods:** In this prospective, observational study, 34 consecutive patients [M/F: 25 / 9, median age 62 (IQR: 54 - 70)] with cirrhosis [alcohol-associated liver disease (ALD): 22, viral: 4, ALD + viral: 3, metabolic dysfunction-associated steatohepatitis (MASH): 1, unknown: 4] who required hospitalization were recruited. Ten patients were diagnosed with hepatocellular carcinoma (HCC) at enrollment. The established normal ranges for thyroid hormones in our laboratory are the following: T3: 0.8 - 2 ng/ml, fT3: 3.1 - 6.8 pmol/L, T4: 5.1 - 14.1 µg/dl, fT4: 0.8 - 2 ng/dl, and TSH: 0.27 - 4.2 mIU/L. **Results:** The median baseline T3 levels in cirrhotic patients admitted for hospitalization were below the normal range, i.e., T3 = 0.76ng/ml (IQR: 0.68 - 0.91). The median values of the rest of the thyroid hormones were within the normal range, i.e., fT3 = 3.62 pmol/L (IQR: 3.09 - 4.21), T4 = 7.87 µg/dl (IQR: 6.65 - 9.5), fT4 = 1.3ng/dl (IQR: 1.15 - 1.45), and TSH = 1.74 mIU/L (IQR: 1.04 - 4.21). T3 levels were inversely correlated with the model for end-stage liver disease (MELD) (r = -0.345; p = 0.048) and CLIF-C acute-on-chronic liver failure (ACLF) scores (r = -0.395; p = 0.025). fT3 was also inversely correlated with the MELD score (r = -0.345; p = 0.049). A stronger inverse correlation was evident between T4 levels and the MELD (r = -0.603; p < 0.001), MELD-Na (r = 0.-655; p < 0.001), and CLIF-C ACLF (-0.424; p = 0.016) scores. TSH was positively correlated with the Child-Pugh score (r = 0.434; p = 0.012). Patients with HCC exhibited higher T4 levels [9.09 (IQR = 7.4 - 11.03) vs. 7.56 (IQR: 6.44 - 8.79); p = 0.013] and lower TSH levels [1.07 (IQR: 0.74 - 0.75) vs. 2.79 (IQR: 1.44 - 4.93); p = 0.009] in comparison to patients without HCC. During the hospitalization, six patients succumbed, and an additional seven passed away within the initial month following discharge. Among non-HCC patients, deceased patients presented lower levels of T4 versus those who survived [6.44 (IQR: 5.24 - 7.59) vs. 8.06 (IQR: 6.85 - 8.92); p = 0.044]. **Conclusion:** Cirrhotic patients requiring hospitalization demonstrate abnormal thyroid function tests, which become more pronounced with deteriorating disease stages. Thyroid hormone levels upon admission may hold prognostic significance in these patients.

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4079 | ADAMTS13 DEFICIENCY EXACERBATES ACUTE KIDNEY INJURY IN ACUTE-ON-CHRONIC LIVER FAILURE MOUSE MODEL

NORIHISA NISHIMURA[1] KOSUKE KAJI[1] Shinya Sato[1] Tadashi Namisaki[1] Hitoshi Yoshiji[1]

[1]Nara Medical University

Background: Although acute kidney injury (AKI) in patients with liver cirrhosis, which is called hepatorenal syndrome, is one of prognostic risk factors among cirrhosis-related complications, there are still limited established treatments. We have reported that the decreased level of a disintegrin-like and metalloproteinase with thrombospondin type 1 motifs 13 (ADAMTS13) activity and the increase of von Willebrand factor (vWF) involved in hemostatic coagulation were observed along with the development of liver cirrhosis and closely correlates with the level of portal hypertension, suggesting their influences on the circulatory dynamics in chronic liver disease. In the current study, we investigated the role of ADAMTS13 in the pathogenesis of AKI complicated with acute-on-chronic liver failure (ACLF). **Methods:** Wild type 129+Ter/Sv (WT) and ADAMTS13-deficient (ADKO) mice were used to create a mimicked ACLF model by combining chronic injury injected by chronic carbon tetrachloride (CCl_4) and acute hepatic insult by injection with a double dose of CCl_4 followed by administration with lipopolysaccharides to elucidate the effect of ADAMTS13 on AKI complicated with ACLF. We collected serum, liver, and kidney tissues and compared differences in liver and kidney injury due to ADAMTS13 deficiency. **Results:** ACLF groups in both WT and ADKO mice increased serum AST/ALT and BUN/Cre levels. These changes in ADKO mice were significantly higher than those in WT mice. Tissue blood flow in the liver and kidney were significantly decreased in ADKO group compared to WT group with the increase in vWF level. ADKO mice with ACLF showed the elevation of inflammatory markers such as Tnf-α and Il-1β, and the increased number of F4/80-positive cells in kidney tissue. Likewise, the expressions of kidney injury markers including Kim-1, Vim, Hif1α were significantly elevated in ADKO group compared to WT group. Furthermore, higher elevation of oxidative stress markers such as NOX2/4, HO-1 and eNOS were observed in ADKO mice compared to WT mice. **Conclusion:** ADAMTS13 deficiency enhances vWF deposition in the liver and kidney and contributes to the induction of inflammation and tissue damage, as well as to decrease tissue blood flow of liver and kidney in the ACLF model. These **results** suggest that the imbalance of ADAMTS13/vWF axis plays an important role on the progression of AKI complicated with ACLF.

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4080 | INTERACTIONS BETWEEN SARCOPENIA, FRAILTY AND RESTING ENERGY EXPENDITURE IN PATIENTS WITH CIRRHOSIS AND PORTAL HYPERTENSION

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Background: Sarcopenia and frailty are prevalent and independently prognostic in cirrhosis. Few studies have evaluated both entities together to ascertain their interaction and phenotypic differences. Their relationship with resting energy expenditure (REE) is also unclear **Methods:** We retrospectively studied consecutive adult patients with cirrhosis and portal hypertension who underwent sarcopenia (Transversal Psoas Muscle Thickness [TPMT]/height), frailty (Fried Frailty Index [FFI]) and nutritional assessments between 2015-2018. Sarcopenia and frailty were defined as TPMT/height ≤16.8mm/m and FFI ≥3/5 respectively. For analysis, patients were categorised into four groups based on their sarcopenia and frailty status: not frail and not sarcopenic (NFNS), not frail but sarcopenic (NFS), frail but not sarcopenic (FNS) and frail and sarcopenic (FS). The primary outcome of interest was transplant-free survival (TFS). **Results:** During the study period, 97 patients were recruited for assessment (71% male, median age 57 [IQR 52-63]). Median Child-Pugh and MELD scores were B9 (IQR 7-10) and 16 (IQR 11-20) respectively. 40% (38/96) were classified as frail while 26% (23/90) were classified as sarcopenic. Patients

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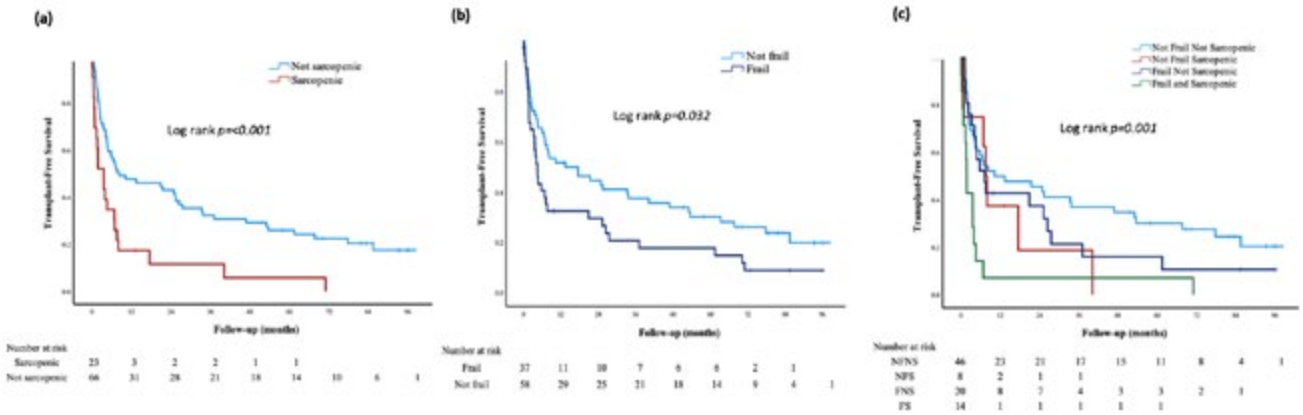
were further categorised into four subgroups depending on the presence of sarcopenia and frailty: NFNS (52%), FNS (23%), FS (16%) and NFS (9%). According to REE, the majority of patients were normometabolic (48/63, 76%), while 13 (21%) were hypermetabolic and two (3%) were hypometabolic. There was a modest but significant correlation between TPMT/height and FFI (Spearman *rho* = -0.266, *p=0.016*). Patients with sarcopenia *or* frailty alone were phenotypically similar, except those with sarcopenia had a lower median body mass index (BMI) (23 vs. 28 kg/m^2, *p=0.032*) and were more likely to be hypermetabolic (60% vs 0%, *p=0.017).* After a median follow up of 5.7 years (IQR 2.2-7.6), 50 (51%) of patients underwent LT and 35 (36%) of patients died. The median overall TFS was 7.2 months (95% CI 4.8-9.6). By Kaplan-Meier analysis, median TFS was significantly lower in patients who were sarcopenic (3.6 vs 8.3 months; *p=<0.001)* or frail (4.5 vs 13.4 months; *p=0.032)*(Figure 1a & 1b). When comparing all subgroups, sarcopenia and frailty had a cumulative impact, with the lowest median TFS seen in the FS (1.8 months, 95% CI 1.4-2.1) compared to the NFNS, NFS and FNS groups (log rank *p=0.001)*(Figure 1c). Independent predictors of death or LT were sarcopenia (lower TPMT/height)(aHR = 0.930 per mm/m increase, *p=0.037*), presence of hepatic encephalopathy (aHR = 2.051, *p=0.008*), and higher MELD score (aHR = 1.114 per point increase, *p<0.001*). **Conclusion:** In patients with cirrhosis and portal hypertension, sarcopenia and frailty are related but have differences in BMI and REE. The deleterious impact of sarcopenia and frailty on TFS are additive. Sarcopenia remains an independent predictor of TFS after adjusting for frailty.



Disclosures: Ken Liu: Nothing to Disclose, Rachael Jacob: Nothing to Disclose, Joanne Craik: Nothing to Disclose, Aviv Pudipeddi: Janssen: Speaking and Teaching, Takeda: Speaking and Teaching, Pfizer: Speaking and Teaching, Dr Falk Pharma: Speaking and Teaching, AbbVie: Advisor, Ferring: Speaking and Teaching, Laura Park: Nothing to Disclose, Grace Aw: Nothing to Disclose, Natalie Ngu: Nothing to Disclose, Helen Vidot: Nothing to Disclose, Simone Strasser: Chiesi: Advisor, Roche Diagnostics: Advisor, Roche Therapeutics: Advisor, Norgine: Speaking and Teaching, Abbott Diagnostics: Advisor, CSL Behring: Advisor, Novo Nordisk: Advisor, Astra Zeneca: Advisor, Sirtex: Speaking and Teaching, Eisai: Speaking and Teaching, Madeleine Gill: Nothing to Disclose, Talal Valliani: Nothing to Disclose, David Bowen: Nothing to Disclose, GEOFF McCaughan: Nothing to Disclose

4081 | TOFOGLIFLOZIN AMELIORATES PORTAL HYPERTENSION ALONG WITH LIVER FIBROSIS PROGRESSION BY INHIBITION OF SINUSOIDAL CAPILLARIZATION IN RATS WITH LIVER CIRRHOSIS

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[1]*Nara Medical University*

Background: Portal hypertension (PH) is one of the important pathogeneses in liver cirrhosis with capillarization of liver sinusoidal endothelial cells (LSECs), although therapeutic drug treatments for PH remain to be limited. Previous evidence has reported that sodium glucose transporter 2 inhibitors, which are one of the categories of antidiabetic agents, could improve endothelial dysfunction. We aimed to elucidate the effect of tofogliflozin on PH and liver fibrosis in a rat cirrhosis model. **Methods:** Male-F344/NSlc rats repeatedly received intraperitoneally injection with carbon tetrachloride (CCl4) to induce PH and liver cirrhosis alongside the administration with two different concentrations with tofogliflozin (10 or 20 mg/kg/body). Portal hemodynamics and hepatic phenotypes were assessed after 14 weeks. In in vitro study, we investigated the effects of tofogliflozin on the crosstalk

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between LSEC and activated hepatic stellate cells (Ac-HSC), which are associated with PH development. **Results:** CCl4-treated rats had significantly higher portal vein pressure (PVP) and higher intrahepatic vascular resistance (IVHR). Tofogliflozin significantly prevented the elevation of PVP and IVHR. Likewise, tofogliflozin treatment remarkably attenuated CD34-positive sinusoidal capillarization compared to the vehicle-treated group along with the suppression of angiogenic factors including VEGF-A and PDGF-BB. CD68 immunostaining showed that the increased Kupffer cell infiltration by CCl4 administration was attenuated by tofogliflozin treatment, and the decreased expression of proinflammatory cytokines including Tnfa, Il6, and Il1b were observed in the tofogliflozin-treated groups. Furthermore, tofogliflozin remarkably inhibited liver fibrosis development along with the decrease in expressions of fibrotic markers such as Col1a1, Acta2, and Tgfbr1. In vitro assays indicated that tofogliflozin markedly suppressed Ac-HSC-stimulated capillarization and vasoconstriction in LSECs via enhancing the antioxidant capacity, as well as significantly inhibited the contractile, profibrogenic, and proliferative activities of Ac-HSCs stimulated by capillarized LSECs. **Conclusion:** Our dataset demonstrates that tofogliflozin is useful to reduce portal hypertensin along with amelioration of liver inflammation and fibrosis in the rodent model. It may provide strong support for the efficacy of tofogliflozin against the progression of PH associated with liver cirrhosis.

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4082 | DIAGNOSTIC ACCURACY OF THE NEUTROPHIL/LYMPHOCYTE RATIO FOR DIAGNOSING SPONTANEOUS BACTERIAL PERITONITIS

Francisco Valentin-Cortez[1] Eva Juárez-Hernández[1] Regina López de Cárdenas-Rojo[1] Daniel Aguilar-Zapata[1] Iván López-Méndez[1]

[1]Medica Sur Clinic & Foundation

Background: Decompensated liver cirrhosis has an increase in mortality of up to 57% annually. Ascites is the main decompensation in up to 60% of patients. Spontaneous bacterial peritonitis (SBP) can progress to sepsis and shock, with in-hospital mortality higher than 80%. The diagnosis of SBP is the cell count in ascites fluid, a ≥250 value of polymorphonuclear cells, have a sensitivity (Sen) of 94% and specificity (Spe) of 100%. However, one of its limitations is the waiting time in processing to obtain the count and culture results. The neutrophil/lymphocyte ratio (NLR) has been proposed as an alternative for early diagnosis in patients with suspected SBP. A cut-off ≥2.89 and ≥3.38 has a Sen of 80.3%, 88.9%, and Spe of 94% and 80%, respectively, representing an alternative option. This study aimed to determine the diagnostic accuracy of NLR in SBP detection. **Methods:** Retrospectively, records of patients with cirrhosis and ascites over 18 years old were reviewed from 2010 to 2023. Clinical and biochemical data were collected. Records of patients with secondary bacterial peritonitis were excluded. We determined an NLR cut-off according to the ROC curve; Sen, Spe, predictive values (PP), and likelihood ratios (LR) were calculated. **Results:** A total of 76 records were collected; 67.1% (n= 51) were male, the mean age was 64±13 years, and 13.2% (n= 10) had a history of previous SBP. The main etiology of cirrhosis was cryptogenic in 44.7% (n= 34), MELD-Na was 25±7 points. 67.1% (n= 51) of patients presented abdominal pain; fever was present in 42.9% (n=15); meanwhile, hepatic encephalopathy was present in 43.4% (n=33) of patients. According to cell counting, 46.1% (n=35) presented SBP, in which the most frequent isolation was for pansensitive *E. coli* in 22.8%. According to the ROC curve, the best cut-off of NLR was ≥2.19, with a Youden index of 0.11, with a Sen 97% and Spe 85%, +LR 6.4, -LR 0.04, +PP 84.6%, and -PP 97.1%. (Table) **Conclusion:** An NLR cut-off ≥2.19 has better diagnostic accuracy in SBP detection. NLR could be considered an additional tool in the early detection of SBP for not delay the treatment

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4083 | AMMONIA IS AN INDEPENDENT PREDICTOR OF MORTALITY IN ACUTELY DECOMPENSATED CIRRHOSIS PATIENTS: TIME TO CHANGE THE PARADIGM?

Robert Rahimi[1] Maria Pilar Ballester[2] Lauren Hall[3] Gerald Ogola[3] Juan Antonio Carbonell-Asins[4] Rajiv Jalan[5] Sumeet Asrani[6]

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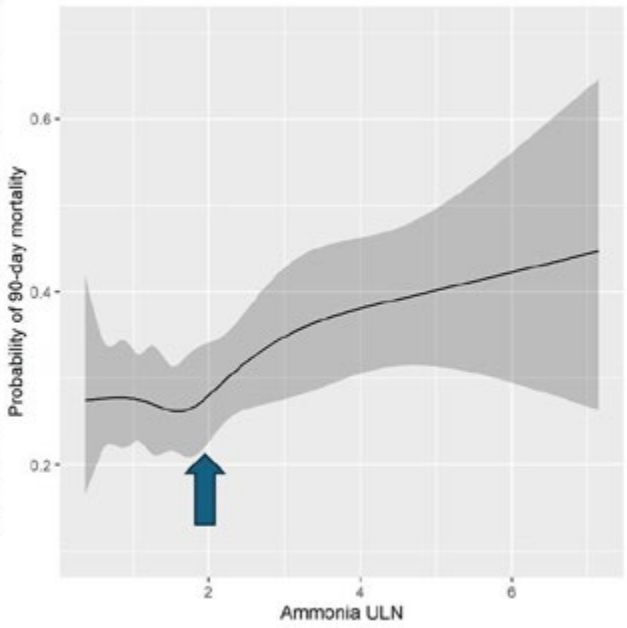
Background: Current expert guidance (AASLD and other societies) do not recommend the measurement of ammonia in patients admitted with hepatic encephalopathy (HE) or decompensated cirrhosis. However, recent European studies suggest a prognostic role of ammonia as a biomarker for development of future decompensation or mortality. For example, an ammonia level 1.4 times the upper limit of normal for the reference laboratory (Ammonia-ULN) predicts mortality in the outpatient setting. We examined whether ammonia has a prognostic role in patients admitted with decompensated cirrhosis, rather than 'diagnosing' HE. **Methods:** We examined all patients with cirrhosis presenting with decompensation in a large healthcare system in the US (n=1020, 26 hospitals) between 2017 and 2019. We limited to patients with ammonia measured during the admission and accounted for presence of prior decompensation or prior HE. HE related admission was defined using diagnostic codes as well as use of lactulose and /or rifaximin in the inpatient setting. The outcome of interest was any readmission and mortality within 90 days. The independent association of ammonia (absolute as well as above ULN) and outcomes was assessed using Cox proportional hazards regression analysis. **Results:** There were 1020 patients admitted with decompensated cirrhosis (62% first decompensation, 84% HE related admission, mean age 60, 17% Hispanic ethnicity, 44% alcohol related). History of prior history of prior HE: 24%. MELD NA was 21.3 and mean absolute ammonia was 61.6 micromol/L (43.2) and Ammonia-ULN was 1.7 (1.2). Within 90 days, mortality was 29.2% and 26% got readmitted. Figure shows the probability of mortality with increasing levels of ammonia-ULN especially at the higher range. On univariable analysis, both ammonia as well as Ammonia-ULN were associated with mortality (HR 1.4, 1.05-1.23) but not readmission (0.9, 0.8-1.01, p=NS). On adjusted analysis even after accounting for relevant patient and clinical demographics, Ammonia-ULN was associated with mortality (Table). The effect was predominantly seen in patients currently admitted for HE. (Ammonia-ULN, HR 1.13, 1.03-1.23) rather than non HE related decompensation (Ammonia-ULN, HR 1.68, 0.9-3.1). **Conclusion:** Ammonia above the upper limit of normal (Ammonia-ULN) appears to have prognostic capacity especially in patients admitted with HE. A paradigm shift may be needed regarding our current understanding of ammonia and the potential to incorporate ammonia levels for prognostication in the inpatient setting.

Parameter	Hazard Ratio	95% HR confidence limits	
Ammonia-ULN	***1.13***	***1.04***	***1.24***
Current HE	**1.43**	**1.01**	**2.04**
Female Sex	1.06	0.83	1.36
Hispanic Ethnicity	0.77	0.54	1.09
Black Race	1.19	0.83	1.72
Other Race	1.26	0.74	2.15
Age at visit	**1.05**	**1.04**	**1.06**
ALD	1.38	0.98	1.95
MASLD	1.10	0.73	1.66
HCV	**1.48**	**1.01**	**2.17**
Prior decompensation	1.07	0.84	1.37
Diabetes	1.16	0.87	1.55
Albumin	**0.61**	**0.49**	**0.74**
Bilirubin	**1.04**	**1.02**	**1.05**
Creatinine	**1.15**	**1.09**	**1.22**
INR	**1.05**	**1.02**	**1.08**
NA	0.99	0.97	1.00
WBC	**1.05**	**1.04**	**1.07**



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Disclosures: Robert Rahimi: Salix: Grant/Research Support, Mallinckrodt: Grant/Research Support, Maria Pilar Ballester: Nothing to Disclose, Lauren Hall: Nothing to Disclose, Gerald Ogola: Nothing to Disclose, Juan Antonio Carbonell-Asins: Nothing to Disclose, Rajiv Jalan: Nothing to Disclose, Sumeet Asrani: Nothing to Disclose

4084 | ASCITES FLUID CALPROTECTIN LEVEL AND RATIO OF CALPROTECTIN TO TOTAL PROTEIN FOR THE DIAGNOSIS OF SPONTANEOUS BACTERIAL PERITONITIS: A SYSTEMATIC REVIEW AND META-ANALYSIS

Natchaya Polpichai[1] Sakditad Saowapa[2] Phuuwadith Wattanachayakul[3] Pojsakorn Danpanichkul[4] Emily Shu-Yen Chan[1] Panisara Fangsaard[5] Apichat Kaewdech[6]

[1]Weiss Memorial Hospital, [2]Texas Tech University Health Science, [3]Department of Internal Medicine, [4]Chiang Mai University, [5]Bassett Medical Center, [6]Prince of Songkla University

Background: Spontaneous bacterial peritonitis (SBP) is common in cirrhotic patients, associated with high mortality among inpatients, necessitating prompt diagnosis for effective treatment. While ascitic fluid (AF) polymorphonuclear (PMN) counts (> 250/leukocyte detection) are the current standard, rapid biomarker-based diagnosis is needed. Previous studies explored AF calprotectin as an alternative, warranting a comprehensive review. This study aims to investigate the diagnostic accuracy of AF calprotectin and its ratio to total protein as rapid markers for SBP diagnosis. **Methods:** We conducted an extensive search across five electronic databases—PubMed, PubMed Central, The Cochrane Library, ClinicalTrials.gov, and Scopus – from inception to April 2024. Eligible articles included primary studies assessing AF calprotectin or its ratio to total protein as diagnostic markers among SBP patients. Additionally, manual searches through websites and reference lists were performed. Quality assessment utilized the QUADAS-2 tool via Review Manager 5.4.1. Data analysis involved calculating pooled specificity and sensitivity using DerSimonian and Laird random-effects models in STATA 16.0. **Results:** Among 228 studies, 21 met the eligibility criteria for quantitative synthesis. Pooled sensitivity and specificity for AF calprotectin alone in SBP diagnosis were significantly high at 92.73% (95%CI: 90.43, 95.04) ($p < 0.05$) and 88.06% (95% CI: 84.02, 92.10) ($p < 0.05$), respectively (Figure 1A and 1B). The pooled positive and negative likelihood ratios for AF calprotectin in diagnosing SBP were 6.60 (95% CI: 5.66, 7.54) ($p <0.05$) and 0.11 (95% CI: 0.88, 0.13) ($p <0.05$), respectively. Similarly, pooled sensitivity and specificity for the AF calprotectin to total protein ratio were significantly good at 92.38% (95% CI: 86.82, 97.94) and 86.06% (95% CI: 79.27, 92.86) ($p < 0.05$), respectively(Figure 1C and 1D). The synthesis also showed that calprotectin to total protein ratio had 6.21 (95% CI: 4.31, 8.11) positive likelihood ratio and 0.10 (95% CI: 0.04, 017) negative likelihood ratio. **Conclusion:** AF calprotectin and its ratio to total protein are reliable, specific, and sensitive diagnostic markers among SBP patients. However, consistency in cut-off values is needed.

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Figure 1A: Forest plot showing pooled sensitivity for AF calprotectin in SBP diagnosis

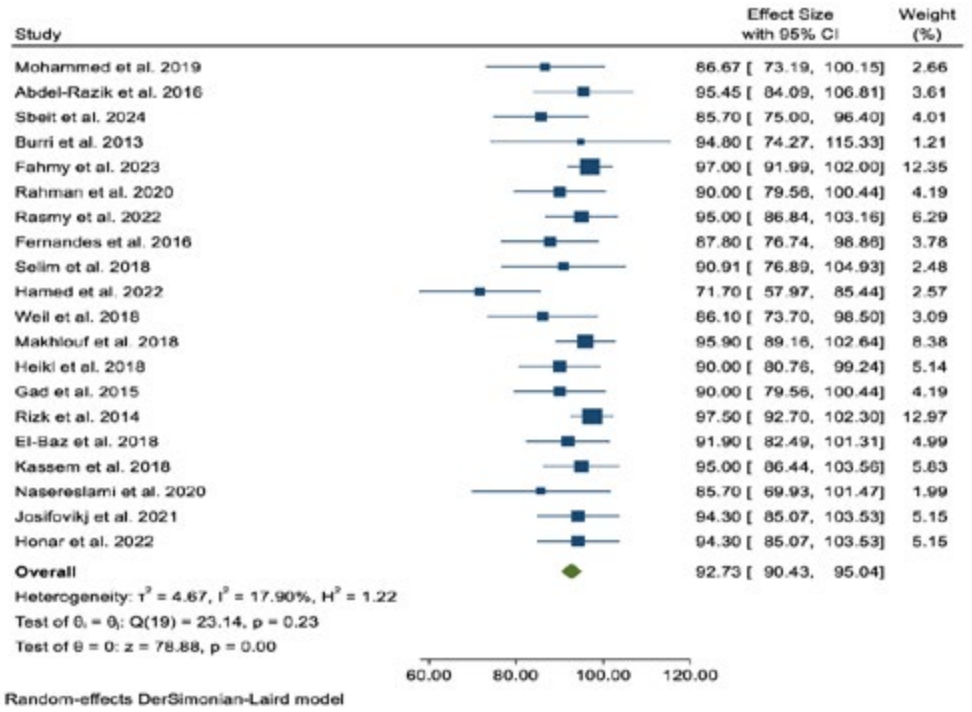

Figure 1B: Forest plot showing pooled specificity for AF calprotectin in SBP diagnosis

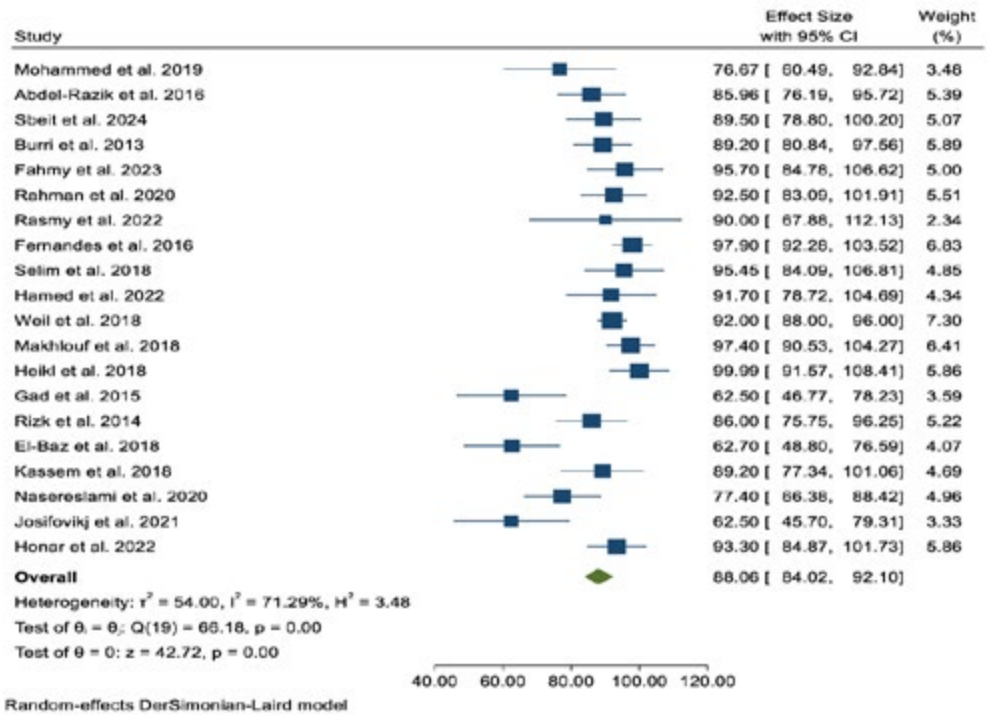

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Figure 1C: A forest plot showing pooled sensitivity of calprotectin to protein ratio in SBP diagnosis

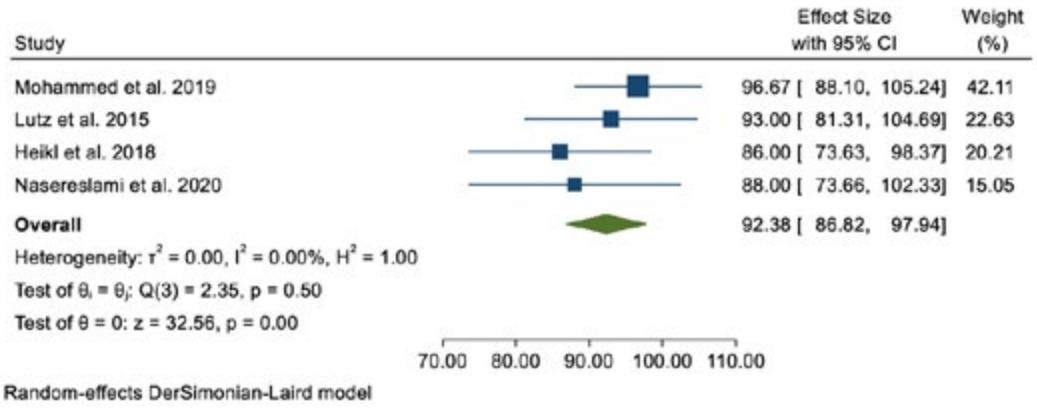
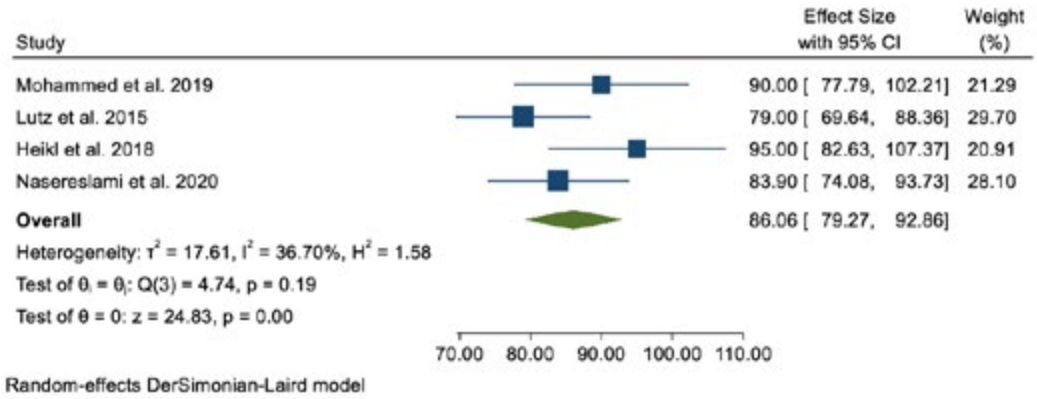


Figure 1D: A forest plot showing pooled specificity of calprotectin to protein ratio in SBP diagnosis



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4085 | INFLAMMATORY SARCOPENIA IN CHRONIC LIVER DISEASE: A NOVEL CONCEPT AND ITS PROGNOSIS

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[1]*Nippon koukan Hospital,* [2]*Gastroenterology and Hepatology, Nippon*

Background: Sarcopenia (SP) is an important prognostic factor in chronic liver disease (CLD), and the international Global Leadership Initiative on Malnutrition (GLIM) criteria include systemic inflammation as a major factor, along with muscle mass loss. Significantly, systemic inflammation is one of the hallmarks of cirrhosis and is thought to be associated with portal hypertension (PHT) and to promote disease progression. In this study, we investigate the pathogenesis and prognosis of inflammatory sarcopenia (I-SP), a novel concept. **Methods:** A total of 736 patients (mean age 61 years, 60% male, etiology: Virus/ Steatotic Liver Disease/Other: 318/318/100, HCC: 32) whose liver stiffness (LS) was measured by MR elastography were included. PHT was defined as thrombocytopenia (platelet count <150K), any varices, and ascites. Liver reserve function was assessed by albumin-bilirubin (ALBI) score, and paraspinal muscle area were measured by MRI images. I-SP was defined as CRP > 0.5 mg/dl and low muscle mass. The clinical profiles of non-SP, non-inflammatory (NI)-SP, and I-SP were then compared, and the prognosis in advanced CLD (≥ 3 kPa) was analyzed in a Cox proportional hazards model. **Results:** 1) *Study in CLD:* No of non-SP/NI-SP/I-SP patients was 519/164/53, and the incidence of patients with HCC was significantly higher in I-SP at 2%, 4%, and 28% (p<0.01). Furthermore, when examining the association with LS, the frequency of I-SP patients was significantly associated with increased LS (< 3.5,

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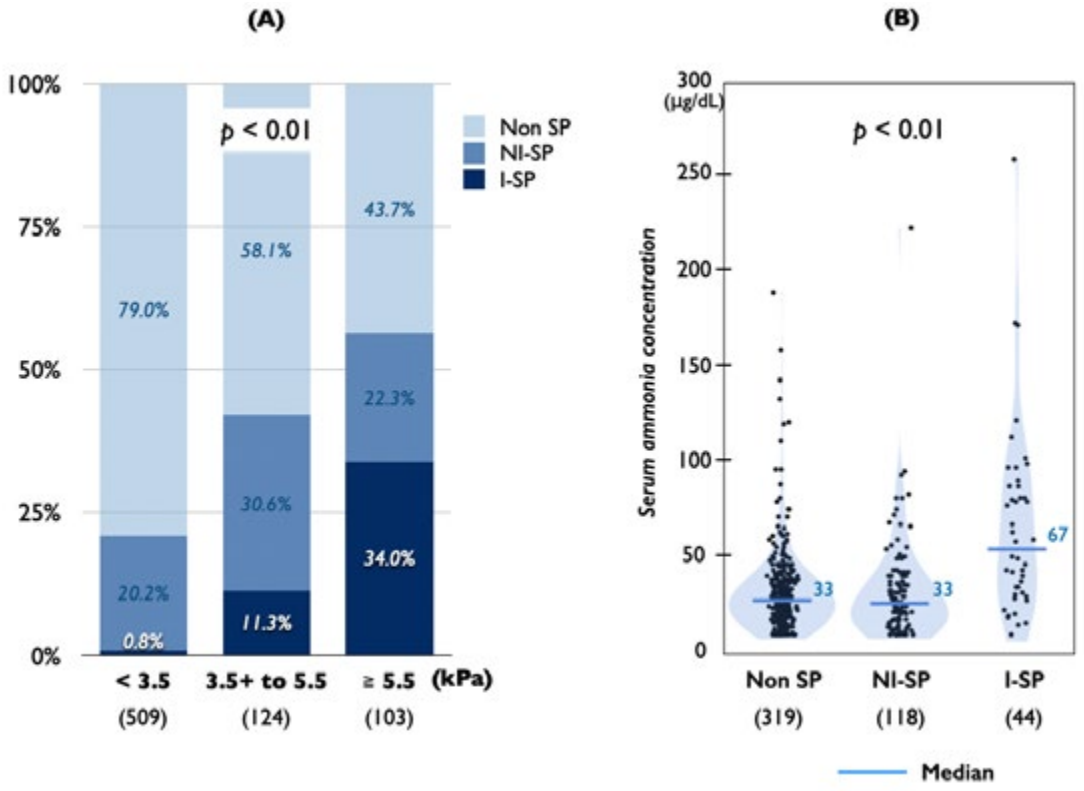
3.5-5.5, ≥ 5.5 kPa: < 1%, 11%, 34%, p<0.01). 2) *Study in CLD without HCC:* The incidence of PHT was 22% for thrombocytopenia, 19% for varices, and 8% for ascites. On ROC analysis, the respective predicted values were 3.3/4.7/5.1 kPa, while the I-SP was 4.0 kPa (AUC: 0.79-0.96, p<0.01 each). Worsening ALBI scores also significantly correlated with the incidence of I-SP complications (p>0.01), with a predictive value of -2.42 for I-SP (AUC: 0.95, p<0.01). Comparison of I and NI-SP showed differences in gender, etiology, Hb, LS, NH_3 and multivariate analysis showed that ALBI score, ascites, and HCC were associated with I-SP (each p<0.05). 3) Prognostic study (32±18 months, 49 liver deaths): Survival in the 3 groups (non-SP/NI-SP/I-SP) was significantly stratified (HR: reference, 3.4, 15.0, p<001) and multivariate analysis showed that ALBI score (HR: 2.79, 95% CI: 1.56-5.07) and I-SP (3.04, 1 .43-6.40) were independent prognostic factors (p<0.01). **Conclusion:** This study highlights differences in pathophysiology and prognosis between NI-SP and I-SP in CLD. PHT and cancer-related inflammation impact SP, with LS linked to increased SP. Worsening hepatic reserve function closely associates with NI-SP progressing to I-SP, indicating poorer prognosis for I-SP patients. Controlling inflammation, alongside nutrition and exercise therapy, offers a new perspective. A two-step treatment strategy to prevent SP and inhibit progression to I-SP may be necessary.



Disclosures: ATSUSHI NAKAMURA: Nothing to Disclose, Takeshi Ichikawa: Nothing to Disclose

4086 | ANALYSIS OF RISK FACTORS FOR LOWER EXTREMITY DEEP VENOUS THROMBOSIS IN PATIENTS WITH LIVER CIRRHOSIS COMPLICATED WITH GASTROINTESTINAL BLEEDING

JiaLin Du[1] Yu Zhang[2] diandian Hao[2] Hui Wang[2] Xiaoyu Wen[2]

[1]Center for Infectious Diseases and Pathogenic Biology / Depa, [2]The First Hospital of Jilin University

Background: Aims: To investigate the clinical characteristics of acute to subacute LEDVT in patients with liver cirrhosis complicated by acute gastrointestinal bleeding, and identify the risk factors associated with LEDVT. **Methods:** A consecutive cohort of 80 patients with liver cirrhosis and gastrointestinal bleeding presenting with an acute to subacute stage of lower extremity deep venous thrombosis (DVT) were enrolled from the First Hospital of Jilin University between January 1, 2022, and January 1, 2024. Furthermore, during the same period, 160 patients with liver cirrhosis complicated by gastrointestinal bleeding but without lower extremity DVT were selected at

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random to form the non-thrombosis group. The collected data were subjected to statistical analysis using SPSS26.0 software, and multivariate logistic regression analysis was employed to identify independent risk factors for LEDVT in patients with liver cirrhosis and gastrointestinal bleeding. **Results:** There were significant differences in gender (X2 = 4.728, P = 0.03), age (t = 3.089, P = 0.02), ascites (X2 = 7.238, P = 0.027), infection (X2 = 3.953, P = 0.047), Child-Pugh classification of liver function (X2 = 22.884, P < 0.001), the levels of RBC (t = 4.755, P < 0.001), Hb (t = 3.918, P < 0.001), PLT (t = -2.549, P = 0.011), ALB (t = 3.898, P < 0.001), D-D (Z = -8.523, P < 0.001), TBIL (t = 3.019, P = 0.003), HDL (t = 3.216, P = 0.001), LDL (t = 2.491, P = 0.013) between the thrombosis group and the non-thrombosis group. Multivariate logistic regression analysis: higher Child-Pugh classification of liver function (OR = 16.550, 95%CI: 3.040-90.110, P = 0.001),higher age (OR = 1.043, 95%CI: 1.002-1.085, P = 0.039), and higher PLT (OR = 1.008, 95%CI: 1.001-1.015, P = 0.016), higher D-D (OR = 1.45, 95%CI: 1.232-1.707, P < 0.001) and lower Hb (OR = 0.967, 95%CI: 0.938-0.997, P = 0.016) were independent risk factors for LEDVT in patients with liver cirrhosis complicated by gastrointestinal bleeding. **Conclusion:** Higher Child-Pugh classification of liver function, higher age, higher platelet count, higher D-dimer level and lower hemoglobin level are independent risk factors for LEDVT in patients with liver cirrhosis complicated by acute gastrointestinal bleeding.

Multivariate Logistic regression analysis

Variate	B	Wald	P	OR	95%CI
Age	0.042	4.256	0.039	1.043	1.002-1.085
Child-Pugh classification	\	11.241	0.004	\	\
Child-Pugh B vs Child-Pugh A	2.117	9.781	0.002	8.310	2.204-31.327
Child-Pugh C vs Child-Pugh A	2.806	10.535	0.001	16.550	3.040-90.110
Hb	-0.033	4.536	0.033	0.967	0.938-0.997
PLT	0.008	5.784	0.016	1.008	1.001-1.015
D-D	0.371	19.898	<0.001	1.450	1.232-1.707

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4087 | SGLT2 INHIBITOR IS PROMISING AS A NOVEL AGENTS FOR RESOLVING CIRRHOTIC ASCITES

Liwei Liu[1] Yuan Gao[2] Yunyi Gao[3] Menghua Wu[2] Huaibin Zou[2] Shanshan Li[2] Wang Lu[2] Ming Kong[2] Weiwei Kang[2] Rongya Shi[4] Yu Chen[2]

[1]Beijing You'an Hospital, Capital Medical University, [2]Beijing You'an Hospital, [3]Beijing Red Cross Blood Center, [4]Baoding People's Hospital

Background: To investigate whether SGLT2 inhibitors can be repurposed to treat ascites in patients with cirrhosis. The study included both experimental and preliminary clinical investigation. **Methods:** In the basic research, we examined SGLT2 expression in the kidneys of rats with cirrhosis-induced ascites and studied the effect of renal denervation (RDN) on kidney SGLT2 expression. In the clinical pilot study, we observed the fractional excretion of sodium (FENa) before and after administering empagliflozin to diabetic patients with cirrhosis and ascites (n=5) over an 8-day period. **Results:** SGLT2 expression was significantly higher in the kidneys of rats with cirrhotic ascites. Additionally, SGLT2 expression in cirrhotic ascites plus RDN group is higher than control but lower than those with cirrhotic ascites (Figure A). In the clinical pilot study, FENa values ranged from 0.5 to 0.8 prior to SGLT2 inhibitor treatment (days 1-3). Post-treatment (days 4-8), FENa values

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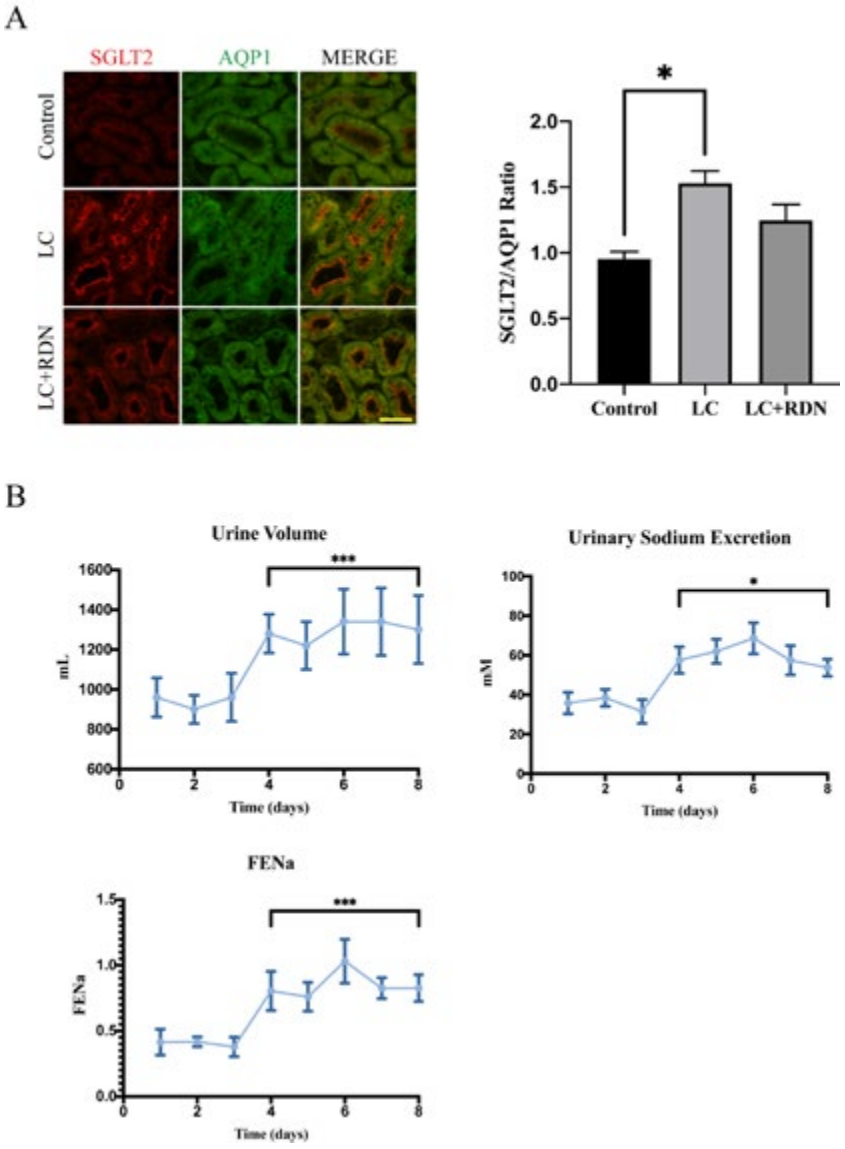
increased to a range of 0.8 to 1.5, accompanied by a modest increase in urine output (Figure B). **Conclusion:** These preliminary **results** suggest that SGLT2 expression is elevated in the context of cirrhosis-induced ascites, potentially modulated by the renin-angiotensin-aldosterone system (RAAS). The application of SGLT2 inhibitors appears to enhance natriuresis and diuresis in diabetic patients with cirrhosis and ascites.



Disclosures: Liwei Liu: Nothing to Disclose, Yuan Gao: Nothing to Disclose, Yunyi Gao: Nothing to Disclose, Menghua Wu: Nothing to Disclose, Huaibin Zou: Nothing to Disclose, Shanshan Li: Nothing to Disclose, Wang Lu: Nothing to Disclose, Ming Kong: Nothing to Disclose, Weiwei Kang: Nothing to Disclose, Rongya Shi: Nothing to Disclose, Yu Chen: Nothing to Disclose

4088 | THE IMPACT OF PRE-EXISTING CHRONIC KIDNEY DISEASE ON THE UPDATED DEFINITION OF AKI-HRS

Yan Ling Ong[1] Chanda Ho[2] Jason Chang[2] Nazia Naser Chowdhury[1] Jeanette Ng[1]

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Background: The definition of AKI-HRS has been recently updated and aligned with that proposed by Acute Disease Quality Initiative (ADQI) and International Club of Ascites (ICA)[1] for AKI. The main difference is addition of urine output and presence of pre-existing chronic kidney disease (CKD) compared to the older definition.

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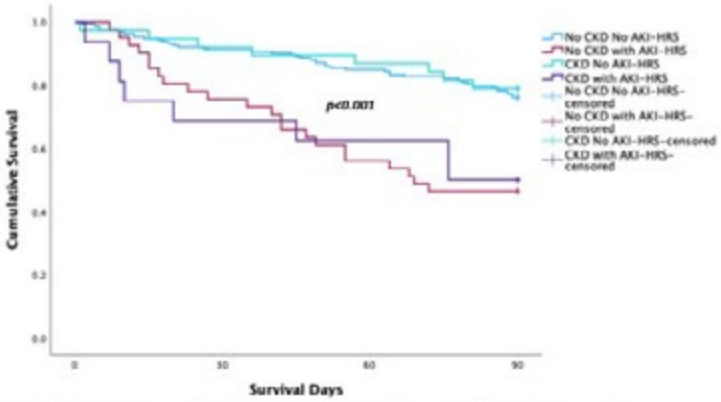
The impact of CKD on the natural history of AKI-HRS by updated definition is not characterised as yet. We thus aim to describe the same and explore whether there is any difference amongst patients with or without CKD. **Methods:** A total of 288 hospitalized cirrhosis patients were recruited for the study. Patients were categorized into 4 groups based on the presence of CKD and development of AKI HRS based on the new definition. The renal recovery and survival were then compared amongst the four group. **Results:** The mean age of the study cohort was 63.2±10.1 years, BMI 25.6±4.6 kg/m2, majority were male (71.2%). MASLD/MASH was the most prevalent etiology of cirrhosis (39.2%) followed by alcohol (36.8%), viral (16.4%), and others (7.6%). A total of 54 (18.8%) patients had pre-existing CKD ranging from stage 3-5 with median GFR of 27(IQR:16-46). 57 (19.8%) patients were classified as developing AKI-HRS. Overall, 193 (67%) patients had no CKD and did not develop AKI-HRS (Group-1), 41(14.2%) had no CKD but developed AKI-HRS (Group 2), 38 (13.2%) had CKD but did not develop AKI-HRS (group 3) and 16 (5.6%) had CKD who developed AKI-HRS (group 4) based on new definition. The 90-days renal recovery was seen in 21 (51.2%) patients in group 2 versus 10 (62.5%) patients in group 4. The 90-day survival of group 1, 2, 3 and 4 were 76.2%, 46.3%, 78.9% and 50% respectively. The 90-day Kaplan-Meier survival curve showed 2 distinct clinical outcomes amongst the 4 groups. Survival of patients who developed AKI-HRS were distinctly poorer than those who did not develop AKI-HRS. The survival outcomes of patients with pre-existing CKD was dependent on whether they developed AKI-HRS or not, which mirrored the survival outcomes of patients without CKD developing AKI-HRS (Figure 1) **Conclusion:** The updated definition of AKI-HRS allows for an addition 5.6% patients with pre-existing CKD to be qualified as having AKI-HRS. The survival outcomes of patients with pre-existing CKD depends on the development of AKI-HRS and it mirrors the survival outcomes of patients without AKI.

Figure 1: The difference in survival between different groups



Patients at Risk	0 Days	30 Days	60 Days	90 Days
Group 1: No CKD No AKI-HRS	193	176	164	145
Group 2: No CKD Yes AKI-HRS	41	31	24	18
Group 3: Yes CKD No AKI-HRS	38	34	32	29
Group 4: Yes CKD Yes AKI-HRS	16	11	9	7

Disclosures: Yan Ling Ong: Nothing to Disclose, Chanda Ho: Nothing to Disclose, Jason Chang: Boehdringer-Ingelheim: Advisor, Nazia Naser Chowdhury: Nothing to Disclose, Jeanette Ng: Nothing to Disclose

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4089 | THE SPLEENPLATELET SCORE FOR SCREENING OF HIGH-RISK VARICES BY TWO-DIMENSIONAL SHEAR WAVE ELASTOGRAPHY IN PATIENTS WITH COMPENSATED ADVANCED CHRONIC LIVER DISEASE: A PROSPECTIVE MULTICENTER STUDY

Ruiling He[1] Ying Guo[2] Lili Zhao[3] Jia Wang[4] Yunfang Liu[2] Zhengzi Geng[5] Shanghao Liu[1] Tao Ren[6] Guo Zhang[7] Yongyan Gao[8] Hongmei Shi[2] Xiao Liang[9] Xiaoqing Guo[2] Kun Wang[2] Meiqin Su[2] Fei Chen[10] Liting Zhang[10] Juan Tang[11] Liyun Zheng[12] Wei Liu[13] Xuemei Wang[14] Qiong Yan[15] Shuhua Zhang[16] Li Yin[17] Li Bian[18] Jie Zeng[19] Chuan Liu[1] Christoph Dietrich[20] Won Kim[21] Linxue Qian[22] Xiaolong Qi[1]

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Background: Two-dimensional shear wave elastography (2D-SWE) could provide more accurate assessment of tissue stiffness by real-time evaluation of the region of interest. The aims of our study were to develop and validate a novel score based on 2D-SWE for screening of high-risk varices (HRV) in compensated advanced chronic liver disease (cACLD) patients, and to compare the performance of the novel score with existing screening models based on 2D-SWE. **Methods:** This is a prospective, multicenter study and has been registered on the clinical trials (NCT04546360). We recruited cACLD patients from 15 tertiary hospitals in China. All patients underwent liver stiffness measurement (LSM) and spleen stiffness measurement (SSM) by 2D-SWE and esophagogastroduodenoscopy (EGD). **Results:** A total of 342 eligible patients were included in the final analysis, 206 in the derivation cohort and 136 in the validation cohort, respectively. In the derivation cohort, independent predictors of HRV were identified as SSM, spleen diameter, and platelet count (PLT) and fitted to develop the novel score, termed "SpleenPlatelet" score. The receiver operating characteristic curve of the SpleenPlatelet score for predicting HRV was 0.86 in the derivation cohort and 0.85 in the validation cohort, which was significantly better than liver stiffness to spleen diameter/platelet score (LSPS), LSM, and SSM. Compared with other models, the spared EGD was best stratified by the cutoff value at 3.92 of the SpleenPlatelet score, which allowed an improvement of spared EGD proportion, 40.3% in the derivation cohort and 40.4% in the validation cohort, with an acceptable missed rate of HRV (< 5%). **Conclusion:** The SpleenPlatelet score composed of SSM based on 2D-SWE, spleen diameter, and PLT, can be readily applied into clinical practice to safely spare EGD in patients with cACLD.

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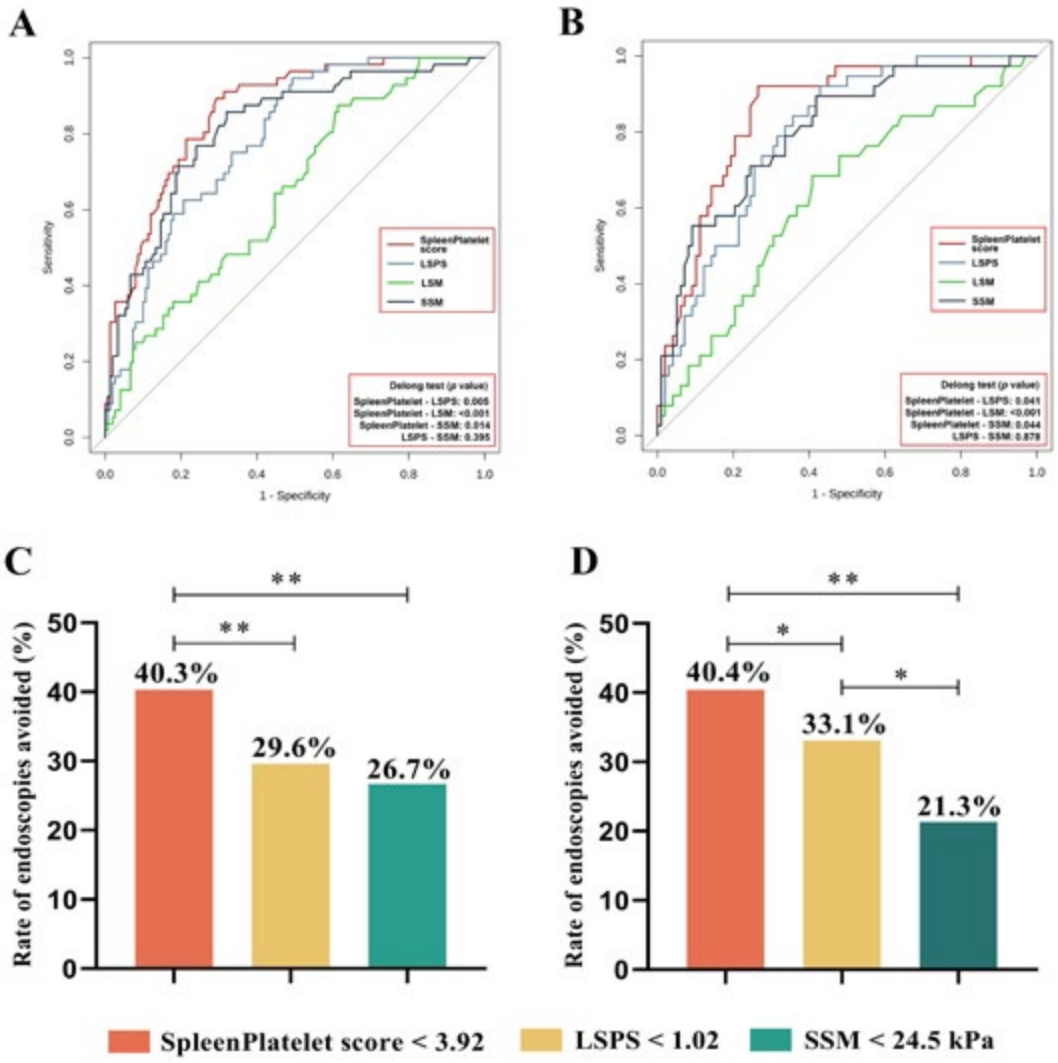

Disclosures: Ruiling He: Nothing to Disclose, Ying Guo: Nothing to Disclose, Lili Zhao: Nothing to Disclose, Jia Wang: Nothing to Disclose, Yunfang Liu: Nothing to Disclose, Zhengzi Geng: Nothing to Disclose, Shanghao Liu: Nothing to Disclose, Tao Ren: Nothing to Disclose, Guo Zhang: Nothing to Disclose, Yongyan Gao: Nothing to Disclose, Hongmei Shi: Nothing to Disclose, Xiao Liang: Nothing to Disclose, Xiaoqing Guo: Nothing to Disclose, Kun Wang: Nothing to Disclose, Meiqin Su: Nothing to Disclose, Fei Chen: Nothing to Disclose, Liting Zhang: Nothing to Disclose, Juan Tang: Nothing to Disclose, Liyun Zheng: Nothing to Disclose, Wei Liu: Nothing to Disclose, Xuemei Wang: Nothing to Disclose, Qiong Yan: Nothing to Disclose, Shuhua Zhang: Nothing to Disclose, Li Yin: Nothing to Disclose, Li Bian: Nothing to Disclose, Jie Zeng: Nothing to Disclose, Chuan Liu: Nothing to Disclose, Christoph Dietrich: Bracco: Speaking and Teaching, Siemens: Speaking and Teaching, Mindray: Speaking and Teaching, SonoScape: Speaking and Teaching, GE: Speaking and Teaching, Olympus: Speaking and Teaching, Janssens: Speaking and Teaching, AbbVie: Speaking and Teaching, Won Kim: Nothing to Disclose, Linxue Qian: Nothing to Disclose, Xiaolong Qi: Nothing to Disclose

4090 | FLINDERS ALBUMIN IN THE HOME (FAITH): A FEASIBILITY STUDY

Rachel Wundke[1] Kylie Bragg[1] Sumudu Narayana[1] Kate Muller[1] Jeyamani Ramachandran[1] Jodie Altschwager[2] Russell Hunt[1] Alan Wigg[1]

[1]Flinders Medical Centre, [2]Metropolitan Referral Unit

Background: Long term administration of human albumin (HA) has been shown to be beneficial in patients with ascites due to decompensated cirrhosis (DC) providing improved ascites control, improved renal function,

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reduced hospitalization and improved mortality. However, its implementation is limited by bed availability at hospitals or infusion suites. This pilot study was undertaken to assess the feasibility of home administration of HA in the management of DC. Secondary aims were to assess the safety, efficacy, acceptability, and comparative costs of home administration of HA. **Methods:** The study was commenced recruitment in November 2023 with a planned follow up of 6 months. Key inclusion criteria were patients with DC with ascites, hepatic hydrothorax or peripheral oedema not diuretic controlled. Key exclusion criteria were patients with known heart failure and lack of cognitive capacity. A community nursing service visited the patient, obtained IV access, and administered HA as per the following protocol (loading dose of Alburex 40g twice a week the first 2 weeks, then 40g weekly, with each 100 ml bottle of albumin infused over at least 45 minutes). A case conference with a panel of Hepatologists was held at 3 months to determine futility or effectiveness of infusions. Patients were surveyed with a questionnaire at the end of study. **Results:** Fourteen patients consented to the study and their demographics are shown in Table 1. To date 14 participants have received home HA infusions with median (IQR) study follow up time of 10 (9) weeks, with four participants completing the planned 3-month course of home HA infusions. The most common (86%) reason for study inclusion was ascites not controlled by diuretics. Feasibility: All patients who commenced successfully received HA infusions at home. The median time of each home visit and per bottle of albumin infusion was 2.7 hours (IQR 11 minutes) and 47.5 minutes (IQR 1.2 minutes), respectively. Fifty percent (50%) of participants required a peripherally inserted central catheter insertion at commencement or during the study. Safety and efficacy: There were no reported treatment-related adverse events. The 3-month course of albumin was adjudicated to be clinically effective in all four participants who have currently reached the 3-month study point and HA was continued in these patients. The median (IQR) albumin score at study entry and at 3 months was 27 (IQR 3.8) and 40 (IQR 5.8), respectively. Participant acceptability: There was good participant acceptability with no patient withdrawals or requests for hospital-based HA infusions. Cost comparison: The costs of home versus hospital-based HA infusion visits were estimated at $AUD 408 versus $AUD 537, respectively. **Conclusion:** HA administration at home appears feasible, safe, effective and has high participant acceptability relative to hospital-based infusions. HA may provide a logistical and cost effective option to administer albumin in cirrhosis. Larger studies validating our pilot study findings are indicated.

Table 1. Key clinical characteristics of study participants

	Baseline (n=14)
Male n. (%)	10 (71)
Median (IQR) age	68 (30.3)
Aetiology Alcohol (%)	8 (57%)
Median (IQR) MELD score	14 (3.5)
Median (IQR) Child Pugh score	9.5 (2.75)

Disclosures: Rachel Wundke: Nothing to Disclose, Kylie Bragg: Nothing to Disclose, Sumudu Narayana: Nothing to Disclose, Kate Muller: CSL Behring: Advisor, NovoNordisk: Advisor, AstraZeneca: Advisor, Chiesi: Advisor, Eisai: Speaking and Teaching, Jeyamani Ramachandran: Nothing to Disclose, Jodie Altschwager: Nothing to Disclose, Russell Hunt: Nothing to Disclose, Alan Wigg: Nothing to Disclose

4091 | PREDICTORS OF IN-HOSPITAL MORTALITY FOR PATIENTS WITH CIRRHOSIS AFTER INDEX EPISODE OF SPONTANEOUS BACTERIAL PERITONITIS

Ami Patel[1] Katherine Cooper[1] Adil Fazir[2] Meghna Trivedi[3] Deepika Devuni[3]

[1]Univeristy of Massachusetts Memorial Health, [2]University of Massachusetts Chan Medical, [3]University of Massachusetts Memorial Health

Background: Spontaneous bacterial peritonitis (SBP) is a serious complication seen in patients with portal hypertension and decompensated cirrhosis. SBP is associated with significant morbidity and mortality with some studies estimating in-hospital mortality between 20-40%. The current literature mainly comprises of large database studies; but outcomes-based studies for first time SBP are limited. In this study we aimed to describe predictors associated with in-hospital mortality after the first episode of SBP. **Methods:** We completed a single center retrospective study of patients with decompensated cirrhosis discharged from the hospital with an ICD-10 code for SBP between Jan 1, 2021- September 31, 2023. Medical records were reviewed to identify patients with

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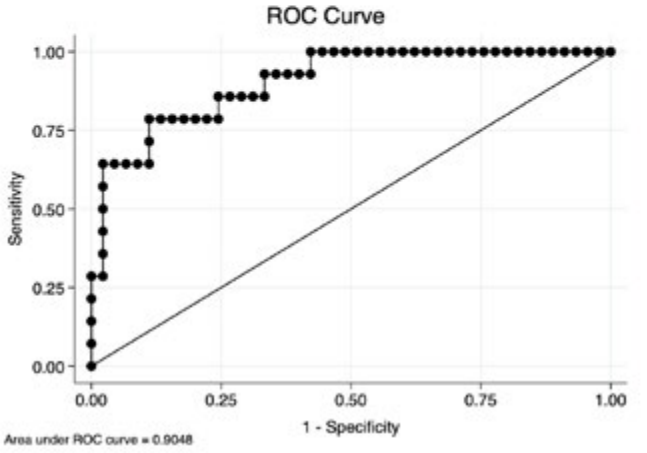
a first-time episode of SBP. Patients without cirrhosis, those with malignant ascites, and those with prior SBP were excluded. SBP was defined by polymorphonuclear leukocytes (PMNs) >250 on paracentesis during admission. Laboratory data was reviewed to correct for the presence of red blood cells and non-neutracytic bacterascites. Predictors of mortality were evaluated using multivariable logistic regression models. **Results:** A total of 104 patients with cirrhosis and an ICD 10 code for SBP were isolated, ultimately 62 patients (58%) met criteria for index SBP and were included in the study. In-hospital mortality was 24%, 1-year mortality was 47% and 1-year liver transplantation was 19%. In hospital mortality was associated with multiple antibiotic use (86.7% vs. 48.9% p=0.014), elevated MELD-Na on admission (26.8 vs. 21.7 p=0.021), age (65.0 vs 56.5 p=0.024), and elevated serum creatinine (Scr) on admission (2.3 vs. 1.2 p= 0.005). One-year mortality was associated with 30-day readmission (71.4% vs 39.4% p=0.045), MELD-Na on discharge (20.6 vs. 16.2 p=0.034, and Scr on admit (1.59 vs. 1.10 p=0.018). On multivariable analysis, MELD-Na on admission (OR 1.19 p=0.038), age (OR 1.14 p=0.008), and PMN count at time of diagnosis (OR 0.999 p= 0.044) were found to be independent predictors of in-hospital mortality. A model comprised of Scr, MELD, age, PMN, and use of multiple antibiotics successfully discriminated patients with in-hospital mortality with reciever operating characteristic (ROC) analysis showing AUC=0.905 (95% CI: 0.820-0.990). **Conclusion:** Index SBP is associated with increased morbidity and mortality, where nearly 66% of patients either died or were transplanted at 1 year. In this study, we developed a multivariable model that successfully predicts in-hospital mortality. While validation cohorts are needed, this data may be used to risk stratify patients with index SBP. High-risk patients should be evaluated for transplantation and those deemed to be ineligible may benefit from early engagement of palliative care services.

Image 1. Logistic regression model for in-hospital mortality and accompanying receiver operating characteristic curve (ROC)

Predictors	OR	*p value*	95% CI
Serum Creatnine	1.44	0.301	0.720-2.891
MELD	1.19	**0.038**	1.010-1.410
Age	1.14	**0.008**	1.035-1.252
PMN	0.999	**0.044**	0.999-1.000
Multiple antibitoics	4.66	0.115	0.688-31.530



Disclosures: Ami Patel: Nothing to Disclose, Katherine Cooper: Nothing to Disclose, Adil Fazir: Nothing to Disclose, Meghna Trivedi: Nothing to Disclose, Deepika Devuni: Avania Medical: Grant/Research Support, Intercept: Grant/Research Support

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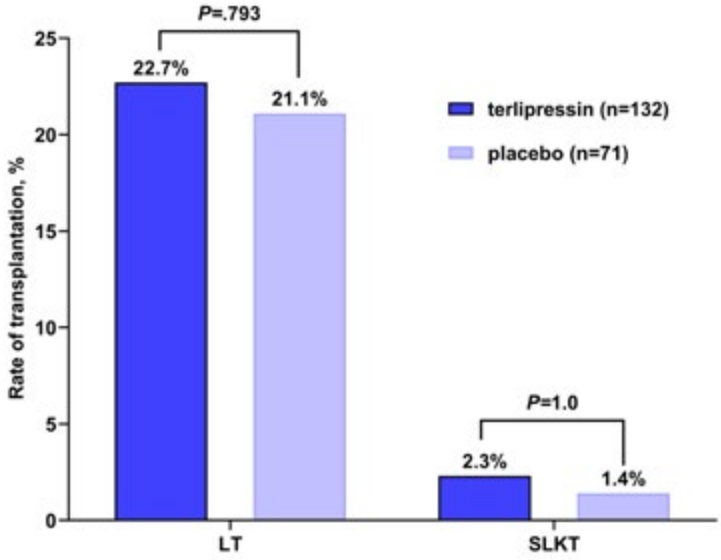
4092 | THE IMPACT OF TERLIPRESSIN TREATMENT ON LIVER TRANSPLANTATION RATES IN PATIENTS WITH HEPATORENAL SYNDROME-ACUTE KIDNEY INJURY (HRS-AKI) IN THE CONTEXT OF THE CHANGING MELD SCORE DEFINITIONS ◆

Pierre Gholam[1] Stuart Gordon[2] Arun Jesudian[3] Satheesh Nair[4] Mark Russo[5] Rachel Black[6] Sanaz Cardoza[6]

[1]Cleveland Medical Center, [2]Henry Ford Health, [3]Weill Cornell Medicine, [4]Methodist Transplant Institute, [5]Atrium Health-Wake Forest, [6]Mallinckrodt Pharmaceuticals

Background: HRS-AKI is a lethal complication of cirrhosis. Liver transplantation (LT) is the only curative option for patients (pts) with HRS-AKI. In the US, organ priority allocation is based on the Model for End-Stage Liver Disease (MELD) score. MELD-sodium (MELD-Na) score has been used since 2016; and in 2023, MELD 3.0 (which also includes albumin and sex) replaced MELD-Na. Terlipressin (terli) is the only US FDA-approved drug for the treatment of HRS-AKI. However, the reduction in MELD score, secondary to an improvement in serum creatinine (sCr) due to HRS reversal, may negatively affect pt prioritization for LT. To assess outcomes in pts who would be eligible for treatment per the terli FDA label (ie, MELD score <35 if transplant listed, sCr <5 mg/dL, and acute-on-chronic liver failure [ACLF] grade 0–2, henceforth referred to as the mitigated population), we evaluated the LT rate and changes in the 3 MELD score variants in this population. **Methods:** The rate of LT up to the end of the study observation period (ie, 90 days) and change from baseline to the end of treatment in MELD, MELD-Na, and MELD 3.0 scores were retrospectively assessed in the mitigated population from the Phase III pbo-controlled CONFIRM study (NCT02770716). **Results:** LT rate by Day 90 was 22.7% (30/132) and 21.1% (15/71) in the terli and pbo arms, respectively (*P*=.793); 2.3% (3/132) and 1.4% (1/71) of pts, respectively, received a simultaneous liver-kidney transplant (SLKT) (*P*=1.0) (Figure). The median time to transplantation was 22 days (terli arm) vs 11.5 days (pbo arm; *P*=.147). Data to calculate changes in MELD scores were available for 107/132 pts in the terli arm and for 55/71 pts in the pbo arm. All 3 MELD scores decreased from baseline to the end of treatment in the terli arm (all *P*<.001), but not in the pbo arm. Median score changes were -3.0 in MELD, -4.0 in MELD-Na, and -6.0 in MELD 3.0 in the terli arm, while changes for all 3 MELD scores in the pbo arm were 0. The difference in changes between the terli and pbo arms was significant in all cases (all *P*<.01). **Conclusion:** Improvement in MELD due to terli treatment did not lead to a decrease in transplantation rate, despite a decrease in all 3 MELD score variants for terli vs pbo in the mitigated population. The rates of LT and SLKT in this population were similar in both treatment arms.

Figure. Rate of LT and SLKT by Day 90; CONFIRM ITT mitigated population



ITT, intent-to-treat; LT, liver transplantation; SLKT, simultaneous liver and kidney transplantation.

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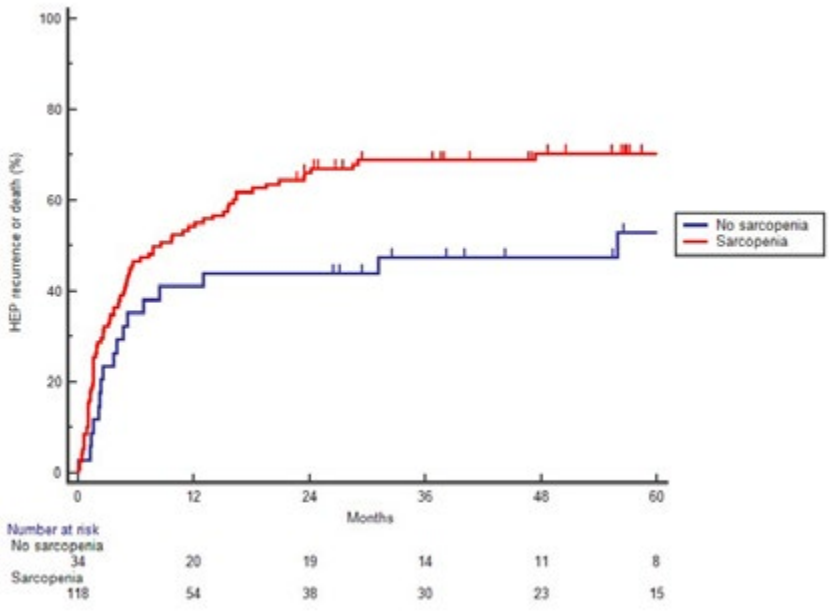
Disclosures: Pierre Gholam: EISAI: Speaking and Teaching, ASTRA ZENECA: Speaking and Teaching, GENENTECH: Consultant, MADRIGAL: Speaking and Teaching, EXELIXIS: Speaking and Teaching, ABBVIE: Speaking and Teaching, GILEAD: Speaking and Teaching, INTERCEPT: Speaking and Teaching, IPSEN: Speaking and Teaching, Stuart Gordon: Nothing to Disclose, Arun Jesudian: Salix Pharmaceuticals: Consultant, Salix Pharmaceuticals: Speaking and Teaching, Madrigal Pharmaceuticals: Speaking and Teaching, Novo Nordisk: Consultant, Orphalan: Consultant, Satheesh Nair: Nothing to Disclose, Mark Russo: Nothing to Disclose, Rachel Black: Mallinckrodt Pharmaceuticals: Employee, Sanaz Cardoza: Nothing to Disclose

4093 | PROGNOSTIC VALUE OF SARCOPENIA ON THE RECURRENCE OF HEPATIC ENCEPHALOPATHY

Junsik Yoon[1] *Sun Woong Kim*[2]

[1]*Busan Paik Hospital,* [2]*Veterans Health Service Medical Center*

Background: The presence of sarcopenia in patient with cirrhosis is a risk factor for the development of hepatic encephalopathy (HEP). However, the impact of sarcopenia on the recurrence of HEP have not been investigated. We aimed to investigate the prognostic value of sarcopenia on the recurrence of HEP. **Methods:** We included 152 patients who experienced the first episode of HEP between 2009 and 2019 in our hospital. Sarcopenia was defined as and L3 skeletal muscle index of <50 cm^2/m^2 for men and <39 cm^2/m^2 for women. The occurrence of HEP recurrence or mortality between the patients with and without sarcopenia was compared by log-rank test. Cox regression analysis was performed to investigate independent predictors of the recurrence of HEP. **Results:** The median age of the study population (97 men and 55 women) was 60 years. Approximately three-quarters of the study population (118/152. 77.6%) had sarcopenia at the time of the first episode of HEP. During the study period, the patients with and without sarcopenia experienced HEP recurrence in 86 (86/118, 72.9%) patients and 18 (18/34, 52.9%) patients, respectively. The cumulative incidence rates of HEP recurrence were significantly different between patients with and without sarcopenia (log-rank P=0.03; Figure 1). The presence of sarcopenia was an independent predictor of HEP recurrence (adjusted hazard ratio = 1.93, 95% confidence interval 1.14–3.26, P=0.02). **Conclusion:** Sarcopenia can be a useful predictor of the recurrence of HEP.



Disclosures: Junsik Yoon: Nothing to Disclose, Sun Woong Kim: Nothing to Disclose

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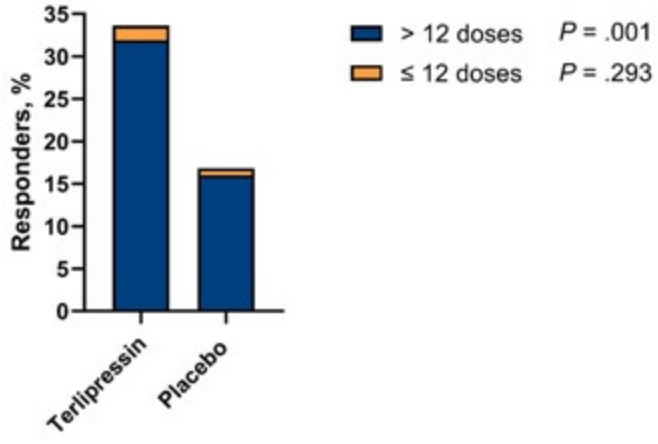
4094 | PATIENCE IS A VIRTUE: EVIDENCE FOR WAITING UNTIL DAY 4 AND AFTER 12 DOSES OF TERLIPRESSIN BEFORE EVALUATING TREATMENT RESPONSE IN PATIENTS WITH HRS-AKI

Manhal Izzy[1] Stevan Gonzalez[2] Prasun Jalal[3] Sanaz Cardoza[4]

[1]Vanderbilt University, [2]Baylor Simmons Transplant Institute, [3]Baylor College of Medicine, [4]Mallinckrodt Pharmaceuticals

Background: Hepatorenal syndrome-acute kidney injury (HRS-AKI) is a serious and potentially lethal, yet reversible, form of AKI in patients with decompensated cirrhosis. Terlipressin (terli), a vasopressin analog used to improve kidney function, is the only FDA-approved therapy for HRS-AKI. Terli is recommended in adult patients with HRS-AKI at a dose of 1 mg every 6 hours (Q6H) for up to 14 days, which can be increased on Day 4 to 2 mg Q6H if a patient's serum creatinine (SCr) level has decreased by <30% from baseline. This study evaluated the rationale for waiting until Day 4 (12 doses) before assessing treatment response, using data from a large, pooled patient cohort. **Methods:** Data were pooled from 3 Phase III placebo (pbo)-controlled studies of terli to treat HRS-AKI. Eligible patients had HRS-AKI with a SCr level of ≥2.5 mg/dL (OT-0401 & REVERSE) or ≥2.25 mg/dL (CONFIRM). Patients received terli or matched pbo at 1 mg Q6H initially, with an increase in dose to 2 mg Q6H on Day 4 if SCr had decreased, but by <30% from baseline. Responders were patients who had achieved HRS reversal, defined as ≥1 SCr value of ≤1.5 mg/dL while on treatment up to 24 hours after the last dose, by the end of treatment (EOT). SCr level and mean change in SCr from baseline (ΔSCr) were examined by day for responders vs nonresponders. **Results:** In the pooled dataset (N=598) of patients assessed by dose, 117 responded (117/348; 33.6%) to terli and 42 to pbo (42/250; 16.8%). Among responders to terli, most had received >12 doses (111/117; 94.9%), and very few received ≤12 doses before discontinuation (Figure). The mean SCr at treatment initiation/baseline was lower in responders vs nonresponders, regardless of treatment (terli, 3.09 mg/dL vs 3.85 mg/dL, *P*<.001; pbo, 3.04 mg/dL vs 3.77 mg/dL, *P*<.001). Notably, the mean ΔSCr was a decrease of <1 mg/dL prior to Day 4 among responders to terli (Day 1, −0.22 mg/dL; Day 2, −0.40 mg/dL, Day 3, −0.76 mg/dL). On Day 4, mean ΔSCr was −1 mg/dL among responders, equivalent to a >30% decrease from baseline (mean SCr, 3 mg/dL), and a greater decline vs nonresponders (terli, −1.04 mg/dL vs −0.09 mg/dL, *P*<.001; pbo, −0.98 mg/dL vs +0.25 mg/dL, *P*<.001). **Conclusion:** Among those who responded with HRS reversal by EOT, most patients needed at least 12 doses of treatment with terli. These results indicate that terli should be used for an adequate amount of time (ie, 4 days) at the initial standard dose before a clinical decision for discontinuation is made.

Figure. HRS Reversal at EOT by treatment arm and by total number of doses received, pooled (OT-0401, REVERSE, and CONFIRM) ITT population



P values (terlipressin vs placebo) are from a Chi-square or Fisher's exact test.
EOT, end of treatment; HRS, hepatorenal syndrome; ITT, intent to treat SCr, serum creatinine.

Disclosures: Manhal Izzy: Nothing to Disclose, Stevan Gonzalez: Nothing to Disclose, Prasun Jalal: Nothing to Disclose, Sanaz Cardoza: Nothing to Disclose

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4095 | THE EFFECT OF OBESITY ON THE CLINICAL RESPONSE TO TERLIPRESSIN IN PATIENTS WITH HEPATORENAL SYNDROME: RETROSPECTIVE ASSESSMENT FROM A POOLED PATIENT COHORT

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Background: Hepatorenal syndrome (HRS)-acute kidney injury (AKI) is a potentially reversible, life-threatening condition that occurs secondary to liver cirrhosis. Patients (pts) may present in different weight classes ranging from underweight to obese. Body mass index (BMI) is often used to identify weight class; however, BMI is difficult to measure in pts with ascites, a key feature of HRS-AKI. Terlipressin (terli) is the only FDA-approved therapy for adult pts with HRS-AKI, and it is used to reverse HRS and improve kidney function. It is unclear if BMI impacts HRS reversal rates in pts treated with terli. We assessed HRS reversal by BMI and by BMI corrected for ascites in pts from 2 Phase III placebo (pbo)-controlled studies. **Methods:** Using pooled data from 2 Phase III pbo-controlled clinical studies (REVERSE and CONFIRM, N=496) of terli in pts with HRS-AKI, we examined the effects of baseline BMI on pts achieving HRS reversal. Due to the presence of ascites in all eligible pts, a corrected BMI (cBMI) that adjusted for the weight of ascites was also assessed. HRS reversal was defined as ≥1 serum creatinine (SCr) value of ≤1.5 mg/dL while on treatment (≤24 h after the last dose of study drug). For ascites grades 1, 2, and 3, the weights of ascites were estimated to be 0.8 kg, 3.5 kg, and 7.7 kg, respectively; thus, the cBMI was calculated as follows: (body weight [kg] − weight of ascites [kg])/height [m^2]. **Results:** Among evaluable pts (BMI, n=463; cBMI, n=451) with HRS-AKI and a BMI or cBMI >30 kg/m^2, HRS reversal was higher in the terli arm vs the pbo arm (BMI: 31% [38/124]) vs 11% [8/70], *P*=.003; cBMI: 30% [31/104] vs 15% [8/55], *P*=.033). Similarly, among pts with a BMI or cBMI ≥25–≤30 kg/m^2, significantly more pts achieved HRS reversal with terli vs pbo (BMI: 36% [27/75] vs 17% [11/63], *P*=.015; cBMI: 36% [23/64] vs 15% [8/55], *P*=.008). HRS reversal for BMI or cBMI <25 kg/m^2 was 35% (28/80; 37/106) for terli vs 24% (BMI: 12/51, *P*=.165) and 21% (cBMI: 14/67, *P*=.049) for pbo. Notably, there were no significant differences in HRS reversal between the BMI or cBMI subgroups >30, ≥25–≤30, and <25 kg/m^2, across treatment arms (*P*>.05) (Table). **Conclusion:** Pts with HRS-AKI and obesity (cBMI >30 kg/m^2) who were treated with terli achieved significantly more HRS reversal vs pbo, similar to pts with a cBMI ≥25–≤30 kg/m^2, and cBMI <25 kg/m^2. Thus, demonstrating that terli treatment provides clinical benefit to pts with HRS-AKI, regardless of BMI subgroup.

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Table. HRS reversal by BMI subgroup in the pooled (CONFIRM + REVERSE) studies.

Parameter	HRS Reversal					
	BMI >30 kg/m²	BMI ≥25 to ≤30 kg/m²	BMI <25 kg/m²	*P* value[a]	*P* value[b]	*P* value[c]
Terlipressin (n=279)	38/124 (31%)	27/75 (36%)	28/80 (35%)	.435	.516	.897
Placebo (n=184)	8/70 (11%)	11/63 (17%)	12/51 (24%)	.321	.077	.422
P value[d]	.003	.015	.165			
	cBMI >30 kg/m²	cBMI ≥25 to ≤30 kg/m²	cBMI <25 kg/m²	*P* value[a]	*P* value[b]	*P* value[c]
Terlipressin (n=274)	31/104 (30%)	23/64 (36%)	37/106 (35%)	.409	.430	.892
Placebo (n=177)	8/55 (15%)	8/55 (15%)	14/67 (21%)	1.000	.364	.364
P value[d]	.033	.008	.049			

Data are presented as the n/N (%).
P value[a] compared BMI >30 vs BMI ≥25 to ≤30, within the treatment arm.
P value[b] compared BMI >30 vs BMI <25, within the treatment arm.
P value[c] compared BMI <25 vs ≥25 to ≤30, within the treatment arm.
P value[d] compared terlipressin vs placebo, within the BMI subgroup.
cBMI = corrected BMI was calculated by using the adjusted weight as follows: deduct 0.8 kg, 3.5 kg, or 7.7 kg from the body weight when the ascites grade was 1, 2, or 3, respectively.

BMI, body mass index [kg/m²]; cBMI, BMI corrected for the weight of ascites; HRS, hepatorenal syndrome.

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4096 | ROLE OF HIGH VERSUS STANDARD DOSE OF TERLIPRESSIN IN REVERSING HRS-AKI: POOLED ANALYSIS FROM PHASE 3 CLINICAL TRIALS ◆

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Background: Terlipressin (terli) is a vasopressin receptor agonist approved for the management of hepatorenal syndrome-acute kidney injury (HRS-AKI)—a rapidly progressive form of AKI that occurs in patients with cirrhosis and ascites. The FDA dosing information recommends an initial terli dose of 1 mg every 6 hours (Q6H), which may be escalated on Day 4 to 2 mg Q6H if the serum creatinine (SCr) decreased, but the improvement is <30% from baseline. We assessed the efficacy and safety profile of those who had a terli dose escalation (high dose) vs those who did not, and vs placebo (pbo). **Methods:** A pooled patient cohort from 3 Phase III pbo-controlled clinical studies (OT-0401, REVERSE, and CONFIRM) was retrospectively assessed. Standard (std) dose was defined as 0.5 mg or 1 mg (up to 4 mg/d) and high dose as 1 or more doses of ≥2 mg. In each study, if on Day 4 of therapy SCr decreased—but by <30% from the baseline value—the dose could be increased to 2 mg Q6H (8 mg/d). HRS reversal was defined as ≥1 SCr value of ≤1.5 mg/dL on treatment (up to 24 hours after the last dose of study medication). Serious adverse events (SAEs) were assessed in all treated patients. **Results:** In the pooled safety population (terli, n=349), most patients (72.8% [254/349]) did not have a terli dose escalation (std dose), while 27.2% (95/349) had a dose escalation (high dose). In the terli ITT population (n=348), the HRS reversal rate was 31.2% (79/253) in the std-dose group and 40.0% (38/95) in the high-dose group (*P*=.12). Among those who received a high dose, significantly more patients achieved HRS reversal with terli vs pbo (40.0% [38/95] vs

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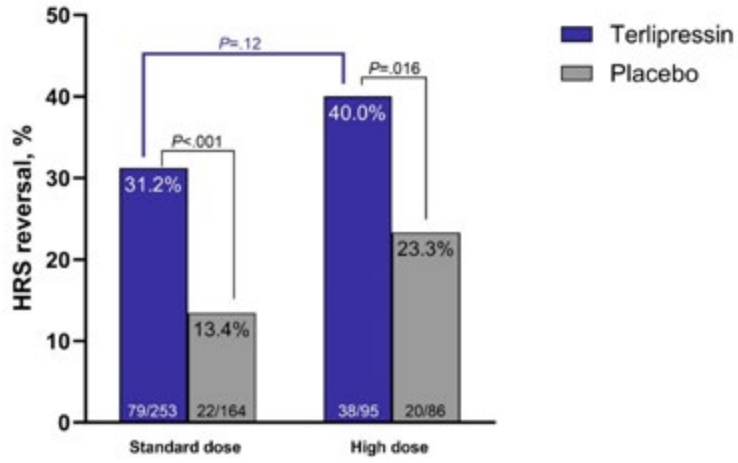
23.3% [20/86], *P*=.016) (**Figure**). SAEs were observed in 66.1% (168/254) of patients who received the std-dose level, in 62.1% (59/95) in the high-dose group, and in 59.8% (149/249) in the pbo group (*P*=.34). Respiratory failure (std vs high dose: 9.1% [23/254] vs 6.3% [6/95], *P*=.41) and multiple organ dysfunction syndrome (std vs high dose: 6.3% [16/254] vs 10.5% 10/95], *P*=.18) were the most frequent SAEs in the std- and high-dose groups, respectively, with similar proportions across dose groups. **Conclusion:** Terli can be dose-escalated to 2 mg Q6H in patients who do not achieve adequate improvement in SCr by Day 4. Among patients who had a dose escalation, the HRS reversal rate was 40%. While the overall SAE safety profiles were comparable between the std and high dose of terli, certain SAEs were slightly higher (2–4%) in the high-dose group.

Figure. HRS reversal in patients with HRS-AKI treated with terlipressin standard or high dose; pooled (OT-0401, REVERSE, and CONFIRM) ITT population



AKI, acute kidney injury; HRS, hepatorenal syndrome; ITT, intent-to-treat.

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4097 | PILOT STUDY OF A MODEL BASED ON NONINVASIVE ASSESSMENTS OF PORTAL-SYSTEMIC SHUNTING (HEPQUANT DUO), HEPATIC FIBROSIS (FIBROSCAN), AND SPLENIC CONGESTION (PLATELET COUNT) FOR ACCURATE PREDICTION OF PORTAL HYPERTENSION AND CLINICALLY SIGNIFICANT PORTAL HYPERTENSION ◆

Gregory Everson[1] Ohad Etzion[2] Theo Heller[2] Elliott Levy[2] David Kleiner[3] Rabab Ali[2] Michael McRae[4]

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Background: Portal hypertension (PH), particularly clinically significant PH (CSPH), is associated with portal-systemic shunting and risk for varices and clinical decompensation. HepQuant tests quantify liver function and portal-systemic shunting, and predict risk for PH and CSPH (Wieland, 2022). A dual sample oral dose version (HepQuant DuO) may have the greatest clinical utility due to ease of administration (McRae, 2024). In this study, we used HepQuant DuO with liver stiffness by FibroScan (LSM) and platelet count to explore the noninvasive prediction of PH and CSPH. **Methods:** The model for predicting PH and CSPH was defined from 28 subjects enrolled in an NIH NIDDK study of fibrotic stages of chronic hepatitis C (NCT02400216). All subjects underwent standard laboratory tests, liver biopsy, portal pressure measurement, and HepQuant testing. HepQuant DuO generates a Disease Severity Index (DSI), which is a measure of global liver health, and quantifies portal systemic shunting (SHUNT%). Portal pressure was measured via percutaneous transhepatic cannulation of the portal vein, and stage of liver fibrosis was determined from simultaneously obtained liver biopsy (METAVIR) and elastography

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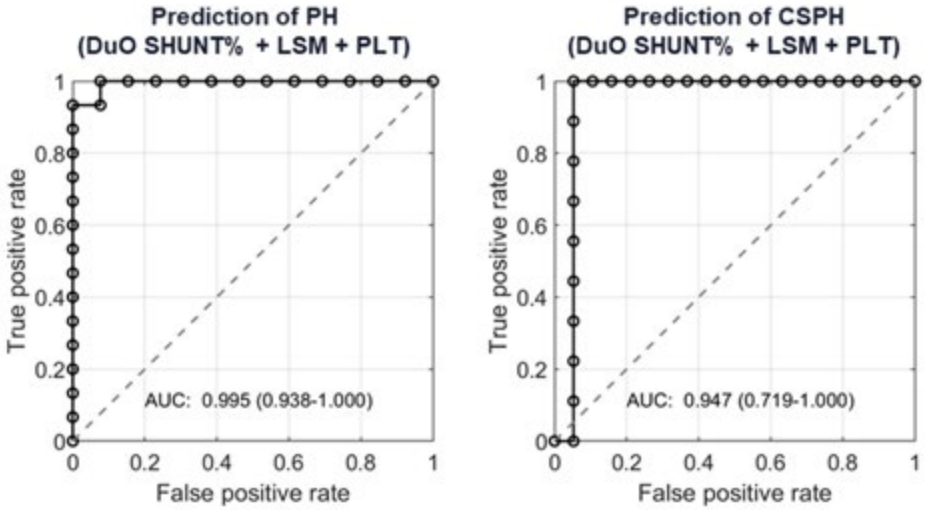
(FibroScan). Univariate and multivariate logistic regression and AUROC analyses were used to evaluate and compare models for predicting PH and CSPH. **Results:** Fifteen subjects had PH and 9 had CSPH. CSPH was found in none of the 11 subjects with stage 1 fibrosis, 1 of 4 with Stage 2 fibrosis, 1 of 2 with Stage 3 fibrosis, and 7 of 11 with Stage 4 fibrosis. In predicting PH, logistic regression models with SHUNT%, LSM, and platelet count yielded AUROCs of 0.990 (0.926–1.000) for SHUNT V2.0, and 0.995 (0.938–1.000) for DuO (all p<0.0001). Similarly in predicting CSPH, AUROCs were 0.959 (0.766–1.000) for SHUNT V2.0, and 0.947 (0.719–1.000) for DuO (all p<0.001). **Conclusion:** The results of this pilot study demonstrate that noninvasive models incorporating DuO test parameters, with other commonly used noninvasive assessments, can predict PH and CSPH with near perfect accuracy (AUROCs ~1.00 for PH and ~0.95 for CSPH). Further validation is planned, and if these findings are confirmed, the DuO model could more accurately define the patient with either PH or CSPH. In addition to its clinical utility, the HepQuant DuO model may be useful in enrichment and stratification of potential subjects planned for enrolment in clinical trials of antifibrotic drugs being studied for PH.



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4098 | COMPARISON OF 1 DAY VERSUS 5 DAYS OF OCTREOTIDE INFUSION ALONG WITH ENDOSCOPIC THERAPY IN PREVENTING EARLY REBLEEDING AND MORTALITY FROM ESOPHAGEAL VARICES: A NATIONWIDE, MULTICENTER, NON-INFERIORITY, RANDOMIZED CONTROL TRIAL ◆ ★

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Background: The AASLD practice guidance and Baveno VII consensus recommend vasoactive agents to achieve hemostasis and prevent variceal rebleeding. However, the optimal duration for vasoactive drug therapy remains unclear. The aim of this study is to compare the efficacy of a 1-day versus a 5-day octreotide infusion, in conjunction with endoscopic therapy. **Methods:** This nationwide, multicenter, non-inferiority, randomized control trial included 220 patients with cirrhosis and acute variceal bleeding who underwent endoscopic band ligation. The patients were randomly assigned to receive either a 1-day regimen (n=109) or a 5-day regimen (n=111) continuous octreotide infusion (50 µg/hr) after successful endoscopy. Rebleeding, transfusion requirements, and mortality were assessed. A non-inferiority margin of 5% was used to analyze early rebleeding within 5 days after the index endoscopy. **Results:** The study predominantly involved male patients, with an average age of 56 years. The rates

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of early rebleeding (1.83% vs. 1.80%, p = 0.99), 6-week rebleeding (8.26% vs. 10.81%, p = 0.51), and 6-week all-cause mortality (5.50% vs. 6.31%, p = 0.80) were not significantly different between the two groups. The event rate difference for early rebleeding was 0.03%, indicating non-inferiority (95% CI = -3.50% to 3.56%). Patients in the 1-day group required significantly fewer blood transfusions, had a shorter time to initiate a solid diet, and experienced a shorter length of stay. Additionally, propranolol, compared to no beta-blocker prescribed, showed a significant protective effect on 6-week all-cause mortality (Adjusted OR 0.16, p = 0.045), while carvedilol showed a non-significant effect (Adjusted OR 0.84, p = 0.88). **Conclusion:** The 1-day regimen of octreotide, compared to the standard 5-day regimen following successful endoscopic band ligation, demonstrates a non-inferiority effect in preventing early (5-day) rebleeding, with no significant difference in preventing 6-week rebleeding and 6-week all-cause mortality. Additionally, propranolol might exhibit a greater protective effect on mortality compared to carvedilol.

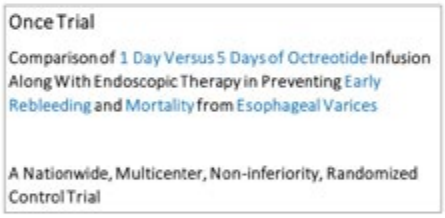
Table 1. Baseline Characteristics and Clinical Outcomes

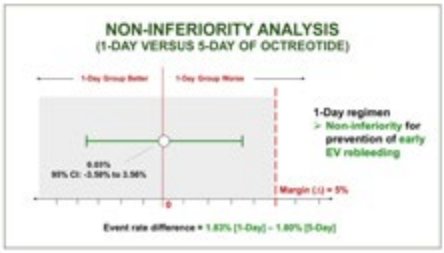
	1-Day (N = 109)	5-Day (N = 111)	p Value
Demographic, N (%)			
Age (year)*	56.62 ± 11.95	56.17 ± 8.93	0.750
Male	90 (82.57)	90 (81.08)	0.775
Etiology			
Alcohol-associated liver disease	92 (84.4)	85 (76.58)	0.143
Chronic HBV infection	16 (14.68)	20 (18.02)	0.503
Chronic HCV infection	9 (8.26)	16 (14.41)	0.150
Prior esophageal varices bleeding	42 (38.53)	40 (36.04)	0.702
Prior endoscopic variceal ligation	41 (37.61)	41 (36.94)	0.917
Child-Pugh score*	7.76 ± 1.99	7.72 ± 2.05	0.881
Class			0.798
A	32 (29.36)	30 (27.03)	
B	56 (51.38)	62 (55.86)	
C	21 (19.27)	19 (17.12)	
MELD score*	15.43 ± 5.75	14.39 ± 6	0.189
Score 21-30	21 (19.27)	16 (14.41)	0.336
Score > 30	2 (1.83)	1 (0.9)	0.620
On Presentation, N (%)			
Systolic blood pressure < 90 mmHg	16 (14.68)	15 (13.51)	0.804
Ascites grade 2-3	36 (33.03)	37 (33.33)	0.962
Hepatic encephalopathy grade 3-4	4 (3.67)	9 (8.11)	0.163
Spontaneous bacterial peritonitis	1 (0.92)	3 (2.7)	0.622
Hemoglobin < 7 g/dl	37 (33.94)	45 (40.54)	0.312
Sodium < 135 mmol/L	32 (29.36)	35 (31.53)	0.726
Initial Values*			
Systolic blood pressure (mmHg)	115.03 ± 24.06	113.9 ± 22.3	0.719
SpO2 (%)	98.34 ± 1.59	98.46 ± 1.8	0.601
Hemoglobin (g/dl)	8.03 ± 1.9	7.6 ± 2.15	0.154
Platelet count (cell/cm3)	130.53 ± 68.57	119.85± 50.60	0.191
White blood cell count (cell/cm3)	9.57 ± 4.76	9.58 ± 4.74	0.989
INR	1.49 ± 0.38	1.47 ± 0.39	0.647
BUN (mg/dl)	26.17 ± 15.49	29.04 ± 17.6	0.201
Creatinine (mg/dl)	1.16 ± 0.92	1.1 ± 0.8	0.565
Sodium (mmol/L)	136.99 ± 4.6	136.29 ± 4.47	0.255
Potassium (mmol/L)	4.16 ± 0.8	4.34 ± 0.85	0.105
	122.71 ± 116.96	95.14 ± 90.06	0.052
AST (u/L)			
ALT(U/L)	53.95 ± 67.59	49.59 ± 64.51	0.624
Albumin (g/dl)	2.86 ± 0.61	2.77 ± 0.52	0.249
Total bilirubin (mg/dl)	2.64 ± 2.43	2.23 ± 2.96	0.261
Direct bilirubin (mg/dl)	1.41 ± 1.69	1.2 ± 2.33	0.449
Monitoring*			
Hematocrit (%)			
On presentation	23.9 ± 6.56	22.42 ± 5.64	0.074
Lowest level after endoscopy	24.19 ± 4.08	23.23 ± 4.45	0.098
At discharge	26.99 ± 3.43	26.85 ± 3.49	0.758
Packed red cell transfusion (unit)			
Prior to endoscopy	1.23 ± 1.16	1.43 ± 1.23	0.210
After endoscopy	0.49 ± 0.81	0.87 ± 1.29	0.008
Total used	1.72 ± 1.39	2.31 ± 1.62	0.004
Total packed red cell used > 2 unit (N, %)	30 (27.52)	48 (43.24)	0.015
Index Endoscopic Band Ligation, N (%)			
High volume center (enrolled > 30 cases)	70 (64.22)	72 (64.86)	0.920
Endoscopic finding			0.355
Active bleeding	12 (11.01)	19 (17.12)	
Recent bleeding	58 (53.21)	59 (53.15)	
Suspected bleeding	39 (35.78)	33 (29.73)	
Size of index varices			0.113
F1	7 (6.42)	5 (4.5)	
F2	74 (67.89)	63 (56.76)	
F3	28 (25.69)	43 (38.74)	
Medication and Therapeutic, N (%)			
Diet			
NG tube insertion after endoscopy	12 (11.01)	7 (6.31)	0.214
Time to initiate solid diet (hour)*	21.93 ± 11.94	29.2 ± 21.96	0.003
Solid diet within 24 hours	98 (89.91)	79 (71.17)	<0.001
Beta-blocker prescribed at discharge	99 (90.83)	101 (90.99)	0.966
Type of Beta-blocker			0.968
Carvedilol	18 (16.51)	17 (15.32)	
Propranolol	81 (74.31)	84 (75.68)	
PPI continue after endoscopy	86 (78.9)	87 (78.38)	0.925
Median day of stay (IQR)	5 (4 - 6)	6 (5 - 7)	<0.001
Outcomes, N (%)			
Early (5-day) rebleeding	2 (1.83)	2 (1.8)	0.999
6-week rebleeding	9 (8.26)	12 (10.81)	0.519
6-week all-cause mortality	6 (5.5)	7 (6.31)	0.801

* Mean ± SD

Table 2. Multivariable Analysis

	Adjusted OR	95% CI	p Value
6-week Rebleed			
Prior esophageal varices bleeding	1.62	0.58 - 4.54	0.358
Spontaneous bacterial peritonitis	2.39	0.15 - 38.90	0.541
Hemoglobin < 7 g/dl at presentation	0.16	0.04 - 0.65	0.010
Child-Pugh score	1.01	0.74 - 1.38	0.966
MELD score	1.07	0.95 - 1.19	0.256
Active bleeding on index endoscopy	2.35	0.50 - 11.02	0.280
Type of Beta-blocker			
Carvedilol (vs no beta-blocker)	1.63	0.17 - 16.02	0.675
Propranolol (vs no beta-blocker)	0.92	0.15 - 5.77	0.927
PPI continue after endoscopy	1.95	0.45 - 8.47	0.373
6-week All-cause Mortality			
Sodium < 135 mmol/L	1.55	0.29 - 8.23	0.604
Child-Pugh score	1.42	0.92 - 2.18	0.114
MELD score	1.07	0.9 - 1.28	0.444
Packed red cell transfusion after endoscopy (unit)	1.40	0.78 - 2.51	0.261
Hemoglobin > 8 g/dl at discharge	0.70	0.54 - 0.91	0.008
Type of Beta-blocker			
Carvedilol (vs no beta-blocker)	0.84	0.08 - 8.6	0.880
Propranolol (vs no beta-blocker)	0.16	0.03 - 0.96	0.045





Disclosures: Kanit Bunnag: Nothing to Disclose, Arunchai Chang: Nothing to Disclose, Suppakorn Malikhao: Nothing to Disclose, Dhanusorn Wanichagool: Nothing to Disclose, Witsarut Manasirisuk: Nothing to Disclose, Uayporn Kaosombatwattana: Nothing to Disclose, Keerati Akarapatima: Nothing to Disclose, Nuttida Polpanich: Nothing to Disclose, Supanut Buaraksa: Nothing to Disclose, Anuchit Suksamai: Nothing to Disclose, Sakkarin Chirapongsathorn: Nothing to Disclose

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4099 | ROLE OF ZINC IN MANAGING COVERT HEPATIC ENCEPHALOPATHY DURING THE LATENCY PERIOD OF ABNORMAL AMMONIA METABOLISM IN CIRRHOSIS

Naruyasu Kakita[1] Midori Jono[1] Midori Jono[1] Shin Satake[1] Toshimitsu Yasui[1] Syuko Iwatani[1] Kenji Aoi[1] Kazuhiro Katayama[1]

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Background: Amino acid metabolism abnormalities and decreased albumin synthesis are observed even before blood ammonia levels rise. We have suggested that ammonia metabolism abnormalities due to liver dysfunction are involved in amino acid metabolism abnormalities and decreased albumin synthesis observed during the course of chronic liver disease without hyperammonemia, and have named this period the “latent ammonia metabolism abnormalities (LAM)”, suggesting that ammonia metabolism abnormalities may play a clinically important role.The aim of this study was to elucidate the pathogenesis of covert hepatic encephalopathy (CHE) in LAM. **Methods:** The study included 388 consecutive patients who were clinically diagnosed with liver cirrhosis at the Department of Gastroenterology, Kaizuka City Hospital, and who underwent Neuro-Psychological test (NPT) during an 18-month period from May 2022 to October 2023. We defined four stages of cirrhosis from the viewpoint of protein metabolism: Stage 0: normal BTR, Alb, and NH3; Stage 1a: decreased BTR only (<4); Stage 1b: stage 1a plus decreased Alb (Alb <3.8 g/dL or albumin supplementation); Stage 2 Stage 1a and 1b were defined as LAM in this study. CHE was defined as abnormalities in two or more of the four neuropsychiatric tests: Number connection test A, Number connection test B, Digit symbol test, and Stroop test. The frequency of CHE at each stage of the disease and the factors contributing to the development of CHE in LAM and the inhibition of CHE development by zinc were examined. **Results:** The frequency of CHE was 18.2/27.5/52.1/58.6 % for Stage 0/1a/1b/2 and 45.2% for LAM overall, with a significant increase with progression of Stage (P<0.0001). CHE occurred as frequently in stage 1b as in stage 2 with hyperammonemia. In 231 Stage 0, 1a, and 1b patients without zinc, the contributing factors for CHE in LAM were zinc (OR: 0.920, 95% C.I.: 0.894-0.947, p<0.001) and men (OR: 2.860, 95% C.I.: 1.290-6.350, p=0. 009) in a multivariate analysis. When zinc was administered to the 55 CHE patients with less than 71 μg/dL zinc, 30 patients in the CHE improvement group had higher zinc after administration than 25 patients in the non-improvement group (75.0±8.1 vs. 60.2±6.8, p<0.0001). Stage 3 had a low improvement rate (25%), but Stage 1a had 64%, Stage1b improved to 61%, similar to 67% of Stage 0 patients. **Conclusion:** CHE develops in LAM as well as in the hyperammonemia phase, suggesting that zinc plays an important role in the development and suppression of CHE in LAM.

Disclosures: Naruyasu Kakita: Nothing to Disclose, Midori Jono: Nothing to Disclose, Midori Jono: Nothing to Disclose, Shin Satake: Nothing to Disclose, Toshimitsu Yasui: Nothing to Disclose, Syuko Iwatani: Nothing to Disclose, Kenji Aoi: Nothing to Disclose, Kazuhiro Katayama: ASKA Pharmaceutical Co., Ltd.: Speaking and Teaching, Asahi KASEI medical Co., Ltd.: Speaking and Teaching, Nobel Pharma Co. Ltd.: Speaking and Teaching, AbbVie GK: Speaking and Teaching

4100 | PHIN-214: PHASE 1 STUDY IN COMPENSATED AND DECOMPENSATED PATIENTS WITH CIRRHOSIS - A NOVEL TREATMENT TO MANAGE COMPLICATIONS OF PORTAL HYPERTENSION WITH SUBCUTANEOUS, ONCE-DAILY SELF-ADMINISTRATION

Douglas Simonetto[1] Naim Alkhouri[2] Ethan Weinberg[3] Philipp Schwabl[4] Anita Kohli[2] Michael Porayko[5] Eric Lawitz[6]

[1]Mayo Clinic Rochester, [2]Arizona Liver Health, [3]University of Pennsylvania, [4]Medical University of Vienna, [5]Vanderbilt University Medical Center, [6]Texas Liver Institute

Background: Cirrhosis affects approximately 2.2 million adults in the United States and is associated with substantial morbidity and mortality. Treatment of decompensated cirrhosis is largely palliative with no approved long-term portal hypertension-targeted therapies. Terlipressin is a synthetic analogue of vasopressin that decreases portal pressure and rebalances systemic hemodynamics; however, it requires intravenous administration and stringent monitoring due to its safety profile. PHIN-214 is a proprietary, structurally optimized derivative of terlipressin designed to exhibit partial V1a receptor agonism, reduced V2 receptor affinity and a 10-fold broader therapeutic index than terlipressin. PHIN-214 was engineered to manage portal hypertension and associated complications across the spectrum of cirrhosis, as a self-administered, subcutaneous (SC), once-daily

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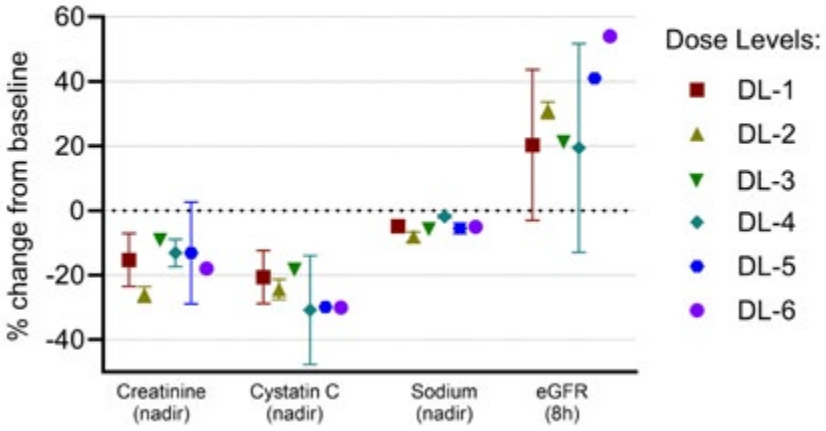
injection in an outpatient setting. **Methods:** PHIN-001 is an on-going phase-1 dose-optimization study comprising both single- and multi-ascending dose assessments of SC PHIN-214 in patients with cirrhosis.
The primary objectives are to assess safety and tolerability of SC PHIN-214 and establish pharmacokinetic (PK) and pharmacodynamic (PD) criteria. **Results:** To date, six single ascending dose levels of PHIN-214 have been administered to 10 patients. No dose-limiting toxicities or serious adverse events, incidents of peripheral or central ischemia, or injection site reactions have occurred. Reported adverse events include urinary tract infection at Day 14 and elevated serum glucose documented prior to PHIN-214 administration, neither considered related to study drug. Transient, low-grade, asymptomatic hyponatremia was observed in 3 patients, which was coincident with concomitant diuretic therapy. Impact of single-ascending dose of PHIN-214 on clinically relevant parameters are presented in figure 1. **Conclusion:** Single, subcutaneous injection of PHIN-214 was safe, well tolerated, and yielded preliminary evidence of clinical activity at all dose levels administered. These data support further development of PHIN-214 as a self-administered, subcutaneous, once-daily injection for treatment of complications of portal hypertension in patients with decompensated cirrhosis. Updated data will be included in the final presentation.

Figure 1. PHIN-214 Single Ascending Dose; summary of key laboratory parameters



Disclosures: Douglas Simonetto: Consultant relationship with BioVie; Has ended; Consultant relationship with Iota; Has ended; Consultant relationship with Mallinckrodt; Has ended; Consultant relationship with Resolution Therapeutics; Has ended; Consultant relationship with Evive; Has ended, Naim Alkhouri: Madrigal: Grant/Research Support, Madrigal: Speaking and Teaching, Novo Nordisk: Consulting, Novo Nordisk: Grant/Research Support, Gilead: Grant/Research Support, Corcept: Grant/Research Support, Boehringer Ingelheim: Grant/Research Support, Echosens: Speaking and Teaching, Perspectum: Consultant, Cima: Consultant, Fibronostics: Consultant, 89Bio: Grant/Research Support, Inventiva: Grant/Research Support, Merck: Grant/Research Support, Pfizer: Grant/Research Support, Ipsen: Speaking and Teaching, Intercept: Speaking and Teaching, Madrigal: Consulting, Research Funding, Novo Nordisk: Consulting, Research Funding, Inventiva: Research Funding, Boehringer Ingelheim: Consulting, Research Funding, Corcept: Research Funding, Ipsen: Consulting, Research Funding, Gliead: Consulting, Research Funding, Speaking, Perspectum: Consulting, Research Funding, Cima: Advisor, 89Bio: Consulting, Research Funding, Akero: Grant/Research Support, Arbutus: Grant/Research Support, GSK: Grant/Research Support, Regeneron: Grant/Research Support, AstraZeneka: Grant/Research Support, Ethan Weinberg: PharmaIN: Consultant, BioVie: Consultant, Sequana: Consultant, Novo Nordisk: Advisor, Philipp Schwabl: Nothing to Disclose, Anita Kohli: Nothing to Disclose, Michael Porayko: River 2 Renal Corp: Consultant, BioVie Pharma: Consultant, River 2 Renal Corp: Alternative medical monitor, PharmaIN Corp: Consultant, River 2 Renal Corp: Alternate Medical Monitor, Eric Lawitz: Nothing to Disclose

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4101 | TO EVALUATE THE EFFICACY OF TIPS COMBINED WITH EMBOLIZATION OF LARGE SPONTANEOUS PORTOSYSTEMIC SHUNTS IN TREATING CIRRHOTIC PORTAL HYPERTENSION WITH ESOPHAGOGASTRIC VARICEAL BLEEDING

Zhu Xiaoli[1] Wang Ze[2]

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Background: To compare the long-term efficacy of transjugular intrahepatic portosystemic shunt(TIPS) in treating portal hypertension with esophagogastric variceal bleeding in patients with and without large spontaneous portosystemic shunts (L-SPSSs). **Methods:** We retrospectively analyzed data from patients with portal hypertension who underwent TIPS from November 2015 to April 2022.The patients were screened according to the inclusion criteria and were divided into TIPS plus embolization of L-SPSSs group (TIPS+E) and TIPS group. The primary outcome was the 2-year liver transplantation-free survival (TFS) rate. Secondary outcomes contained the incidence of overt hepatic encephalopathy (OHE) and the 2-year rebleeding rate. **Results:** A total of 259 patients were enrolled, including 64 patients with L-SPSSs in the TIPS+E group and 195 patients without L-SPSSs in the TIPS group. The average age was 57.2 years, and the success rate of procedure was 100%. Baseline data showed no significant differences between the groups. There was a statistically significant difference in the 2-year liver transplantation-free TFS rate between the TIPS+E and TIPS groups(TIPS+E vs. TIPS, 84.38% vs. 71.28%; HR, 0.51; 95% CI, 0.26–1.00; p=0.045). And no statistically significant difference was found in the 2-year rebleeding rate between two groups (TIPS+E vs. TIPS, 14.06% vs.25.64%; HR, 0.51; 95% CI, 0.25–1.03; p=0.056). Overt HE occurred in 19 (29.69%) patients with L-SPSSs and 104 (53.33%) patients without L-SPSSs, with a statistically significant difference (P=0.001). Multivariate Cox regression analysis identified male gender, portal vein thrombosis and preoperative high blood ammonia levels as independent risk factors for long-term survival. **Conclusion:** In cirrhotic patients with L-SPSSs and variceal bleeding, combining TIPS with L-SPSSs embolization improves long-term liver transplantation-free survival and reduces the risk of postoperative overt hepatic encephalopathy compared to TIPS alone. The 2-year rebleeding rate was similar between the groups.

Disclosures: Zhu Xiaoli: Nothing to Disclose, Wang Ze: Nothing to Disclose

4102 | POST PROCEDURAL COMPLICATIONS OF TRANSJUGULAR AND PERCUTANEOUS LIVER BIOPSIES PERFORMED BY HEPATOLOGISTS AT A TRANSPLANT CENTER

Abla Alj[1] Alessandro David[1] Philippe Willems[2] Bernard WILLEMS[2] Julien Bissonnette[2] Genevieve Huard[2] Ziad Hassoun[2] Catherine Vincent[2] Helene Castel[2] Jeanne Marie Giard[2] Marc Bilodeau[2] Daphna Fenyves[2] Daniel Corsilli[3] Julian Hercun[2]

[1]Université de Montréal, [2]Liver Unit, CHUM, [3]Montreal University Hospital Center

Background: Liver biopsy is considered the “gold standard” for diagnosing and staging liver disease. However, it remains an invasive procedure associated with complications, including but not limited to intraperitoneal bleeding, intra-abdominal infections, and pain. In our center, hepatologists perform both percutaneous biopsies (PB) and transjugular liver biopsies (TJLB), especially in patients with contraindications to percutaneous biopsy (e.g., ascites, coagulopathy, or extreme obesity). A quality improvement study was conducted in order to further assess the risk of procedural complications. **Methods:** All patients undergoing liver biopsy from October 2017 to November 2022 were included. Patient charts were reviewed for laboratory values on the day of the biopsy, histological findings, and complications. Complications were categorized as minor when no additional therapeutic interventions were required, or as major when an escalation of care was required (hospitalization of more than 48 hours, blood product transfusion, or requiring a surgical or interventional radiology procedure). The primary objective was to evaluate the occurrence of minor and/or major complications. The secondary objective was to assess the influence of specific factors in predicting complications. **Results:** Over the course of the study 657 biopsies were performed, 60.3% transjugular and 39.7% percutaneous. Complications occurred in 64 cases, a rate of 9.7%, with 50% categorized as major, including 2 post-biopsy deaths. No significant difference in complication rate was found between inpatient and outpatient procedures (10.1% vs 9.5% p=0.8) or biopsy technique (9.3% for TJLB vs 10.3% for PB, p = 0.64). Patients who experienced complications had higher mean creatinine levels (108.9 umol/L vs 94.1 umol/L, p < 0.0001). A higher incidence of complications was observed in

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individuals with an INR greater than 2 (22.6% vs 9.1%, p=0.01). However, no statistically significant correlation was found between complications and age (p=0.27), gender (p=0.08), platelet count (using a cut-off of 50 x 10^9) (p=0.99), presence of cirrhosis (p=0.59), or transplantation status (p=0.43). **Conclusion:** Complications occurred in 9.7% of cases, with 50% of them categorized as major, over this 5 year study. Predicting which patients will suffer from major complications remains a challenge, however a decrease in kidney function and a higher INR were associated with more complications.

Disclosures: Abla Alj: Nothing to Disclose, Alessandro David: Nothing to Disclose, Philippe Willems: Nothing to Disclose, Bernard WILLEMS: Nothing to Disclose, Julien Bissonnette: Nothing to Disclose, Genevieve Huard: Nothing to Disclose, Ziad Hassoun: Nothing to Disclose, Catherine Vincent: Nothing to Disclose, Helene Castel: Nothing to Disclose, Jeanne Marie Giard: Nothing to Disclose, Marc Bilodeau: Mirum Pharmaceuticals: Speaking and Teaching, Daphna Fenyves: Nothing to Disclose, Daniel Corsilli: Nothing to Disclose, Julian Hercun: Nothing to Disclose

4103 | PERCUTANEOUS CHOLECYSTOSTOMY TUBE PLACEMENT FOR ACUTE CHOLECYSTITIS IN PATIENTS WITH LIVER CIRRHOSIS IS ASSOCIATED WITH MORBIDITY, HEALTHCARE BURDEN, AND PATIENT MORTALITY

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[1]Beth Israel Deaconess Medical Center, [2]University of Maryland Medical Center, [3]University of Louisville

Background: Percutaneous cholecystostomy tube (PCT) is one of the options for the management of acute cholecystitis (AC) in patients with liver cirrhosis who are at high risk for cholecystectomy. Data on the use of PCT to manage AC in patients with liver cirrhosis are lacking. **Methods:** National Inpatient Sample (NIS) database was used to extract a retrospective cohort of hospitalizations (10/2015-12/201912/2019) with cirrhosis, and stratified for discharge diagnosis of AC. Hospitalizations with AC receiving PCT were propensity score matched to those not receiving PCT. In-hospital mortality (IHM), length of stay (LOS) in days, total charges (TC) in $, and liver disease complications were examined as outcomes. ICD-10 diagnosis and procedure codes were used. **Results:** Of 754,245 hospitalizations with cirrhosis, 2989 (0.4%) had AC with no change overtime, Armitage trend P = 0.13. In a matched cohort (1 AC with 2 hospitalizations without AC) for demographics, diabetes, academic status and size of the admitting hospital, those with AC had higher mean LOS (9.1 vs. 6.8), acute kidney injury or AKI (33 vs. 29%), sepsis (21 vs. 9%), and IHM (11 vs. 7%), P < 0.001 for all (Fig. 1A). In a logistic regression multivariable model, AC and PTC were associated with IHM with respective OR (95% CI) of 1.5 (1.3-1.8) and 2.2 (1.6-2.9). Of AC hospitalizations, 456 (15.3%) received PCT, with no change overtime after controlling for other variables, 0.98 (0.90-1.07). Other variables associated with PCT were ALD etiology, patient's age, Caucasian race, academic hospital status, and large size hospital. In a propensity score matched cohort of 1335 hospitalizations (445 PCT and 890 no PCT), PCT was associated with IHM (33 vs. 11%), mean LOS (13.5 vs. 8.5), TC (174,000 vs. 118,000), AKI (48 vs. 31%), hepatorenal syndrome (9 vs. 5%), and sepsis (41 vs. 18%), P < 0.01 for all (Fig. 1B). In a logistic regression model, PCT was associated with about two folds higher IHM vs. AC hospitalizations without PCT, 1.96 (1.41-2.72). **Conclusion:** Acute cholecystitis in patients with liver cirrhosis hospitalizations is associated with higher morbidity, hospital resources use, and patient mortality. One of six AC hospitalizations is managed with PCT, which is associated with morbidity, use of hospital resources and patient mortality. Clearly, larger prospective, well-designed studies are needed to identify patients with AC in the presence of cirrhosis who are most likely to benefit from the use of percutaneous cholecystostomy.

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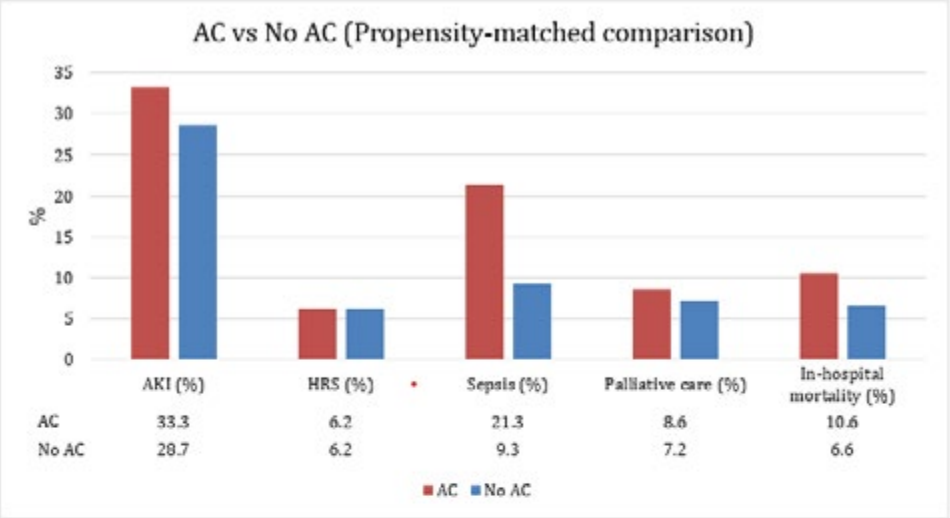
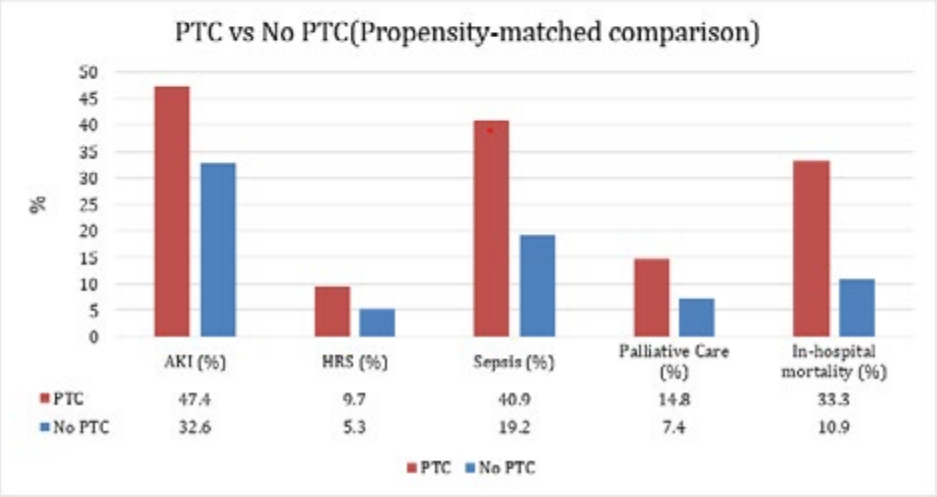


Figure 1 B



Disclosures: Mohanad Awadalla: Nothing to Disclose, Abdellatif Ismail: Nothing to Disclose, Prabha Bhandari: Nothing to Disclose, Ashwani Singal: Advisor relationship with CLD Foundation; Has not ended; Speaking and Teaching relationship with Medical Speaker's Network; Has not ended; Speaking and Teaching relationship with Madrigal; Has not ended; Stock â€“ privately held company relationship with Pleiogenix; Has not ended; Consultant relationship with Pleiogenix; Has not ended; Advisor relationship with Durect; Has ended; Royalties or patent beneficiary relationship with Up-to-Date; Has not ended; Executive role relationship with Gastro Endo News; Has not ended; Grant/Research Support relationship with NIAAA; Has not ended; Employee relationship with Avera Medical Group; Has ended; Grant/Research Support relationship with GSK; Has not ended; Employee relationship with University of Louisville School of Medicine; Has not ended; Speaking and Teaching relationship with Medscape; Has not ended

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4104 | REAL-WORLD PERFORMANCE OF VIBRATION-CONTROLLED TRANSIENT ELASTOGRAPHY WITH LIVER STIFFNESS MEASUREMENT AND SPLEEN STIFFNESS MEASUREMENT IN A TERTIARY CENTER

Mitchell Edwards[1] Austin Ma[1] Rakan Alqahtani[1] Erin Kelly[1] Neta Gotlieb[1] Pearl Tan[1] Maryam Moini[1] Fernanda de Quadros Onofrio[1] Natalie Trudel[1] Josée-Anne Lamoureux[1] Angela Cheung[2]

[1]Center for Liver of Eastern Ontario, The Ottawa Hospital, [2]Center for Liver of Eastern Ontario, The Ottawa Hospital Research Institute

Background: Clinically significant portal hypertension (CSPH) is defined as a hepatic venous pressure gradient ≥10 mm Hg. This portends a high risk of complications of decompensated cirrhosis such as variceal bleeding. Several non-invasive **Methods:** exist to predict CSPH, including the current standard of care, liver stiffness measurement (LSM) by vibration-controlled transient elastography (VCTE). Spleen stiffness measurement (SSM) via VCTE has also been endorsed by the Baveno group as a non-invasive predictor of CSPH. Some studies suggest it may have greater sensitivity and specificity for CSPH than LSM alone. It carries several advantages over LSM as it is not confounded by hepatic inflammation and is a direct reflection of portal hypertension. Our study aims to describe the real-world performance of LSM ± SSM in predicting CSPH. **Methods:** Retrospective chart review was done of all adult patients in our tertiary center who underwent VCTE (May to October 2023). Charts were reviewed for demographics, LSM, SSM, endoscopy, imaging, and lab results. Patients were included if they had: cirrhosis, LSM completed, and abdominal imaging ± upper endoscopy within 6 months of VCTE. CSPH was defined as findings of portal hypertension on imaging and/or endoscopy. Exclusion criteria included: age <18, cardiac cirrhosis, variceal banding within 2 years prior to VCTE, or non-selective beta-blocker use at the time of VCTE. Analysis was performed for sensitivity, specificity, positive predictive value and negative predictive value of LSM and SSM cut-offs. **Results:** 919 patients underwent VCTE during the study period. 119 patients were included, 67 of which had SSM done and 40 of which had CSPH. 44% had alcohol-related liver disease, 36% had metabolic-dysfunction associated steatotic liver disease, and 6% had viral hepatitis. Sensitivity in predicting CSPH was as follows: SSM was 0.96, 0.88, 0.81, and 0.62 with kPa cut-offs of 30, 35, 40, and 45, respectively, LSM was 0.83 at the standard cut-off of >20 kPa and thrombocytopenia was 0.5 and 0.29 with cut-offs of <150 and <100 platelets per µL, respectively. Specificity in predicting CSPH was as follows: SSM was 0.1, 0.2, 0.39, and 0.59 with kPa cut-offs of 30, 35, 40, and 45, respectively, LSM was 0.24 at >20 kPa and thrombocytopenia was 0.61 and 0.90 with cut-offs of <150 and <100 platelets per µL, respectively. **Conclusion:** In this preliminary, single-center study, spleen stiffness >40 kPa appears to have comparable sensitivity and greater specificity as compared with LSM >20 kPa alone in identifying patients with CSPH. Further analysis will be required to determine whether a combination of LSM and SSM along with variables such as platelets are better predictors of CSPH, and if this is impacted by cirrhosis etiology. Data collection and further analysis is ongoing.

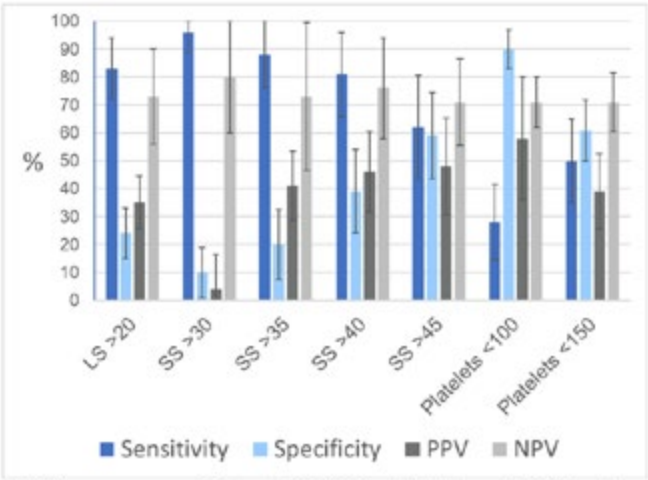

Table 1. Accuracy measures of various cut-offs of LS, SS, and platelets to predict CSPH on endoscopy or imaging.
Abbreviations: LS, liver stiffness; SS, spleen stiffness; CSPH, clinically-significant portal hypertension; PPV, positive predictive value; NPV, negative predictive value

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Disclosures: Mitchell Edwards: Nothing to Disclose, Austin Ma: Nothing to Disclose, Rakan Alqahtani: Nothing to Disclose, Erin Kelly: Nothing to Disclose, Neta Gotlieb: Nothing to Disclose, Pearl Tan: Nothing to Disclose, Maryam Moini: Nothing to Disclose, Fernanda de Quadros Onofrio: Nothing to Disclose, Natalie Trudel: Nothing to Disclose, Josée-Anne Lamoureux: Nothing to Disclose, Angela Cheung: Nothing to Disclose

4106 | PARACENTESIS EXCEEDING THREE LITERS INCREASES RISKS OF ACUTE KIDNEY INJURY EVEN IN CIRRHOTIC PATIENTS WITH ALBUMIN INFUSED REFRACTORY ASCITES

Peishan Wu[1] Kuei-Chuan Lee[1] Chih-Yu Li[1] Yun-Cheng Hsieh[1] Teh-la Huo[1] Han-Chieh Lin[1] Ming-Chih Hou[1]

[1]Taipei Veterans General Hospital

Background: Refractory ascites in cirrhotic patients presents a challenging clinical problem, marked by severe portal hypertension and significant hemodynamic disturbances. These patients are particularly vulnerable to complications such as renal injury and hyponatremia. The potential development of paracentesis-related complications in refractory ascites patients undergoing modest-volume (<5L) paracentesis remains unclear. We aimed to explore the effects of modest-volume paracentesis in cirrhotic patients with refractory ascites. **Methods:** We retrospectively analyzed data from cirrhotic patients with refractory ascites who underwent paracentesis <5L and received albumin infusion. Patients with malignancies other than hepatocellular carcinoma (HCC), acute kidney injury (AKI), end-stage kidney disease, active infection, active gastrointestinal bleeding, and overt hepatic encephalopathy (HE) were excluded. Logistic regression analyses were employed to determine the risks of paracentesis-associated complications, and Kaplan-Meier analysis was used to assess 28-day survival rates. **Results:** Among the 116 patients included, 40 (34.5%) experienced post-paracentesis complications within one week, with AKI being the most frequent (19.8%). Patients were divided into two groups: 96 patients with <3L drainage and 20 with ≥3L. While baseline characteristics were similar, those with ≥3L drainage exhibited a higher incidence of AKI (40% vs. 15.6%, p = 0.013). Multivariable logistic regression identified paracentesis ≥3L as an independent risk factor for AKI [Odds ratio (OR) = 4.15, p = 0.012], while higher MELD scores (OR = 1.14, p = 0.001) and older age (OR = 1.03, p = 0.047) as risk factors for overall complications. In patients without HCC, ≥3L drainage remained a significant risk factor for AKI (OR = 5.61, p = 0.035), while higher MELD scores (OR = 1.2, p = 0.002) and female sex (OR = 3.9, p = 0.037) were associated with overall complications. Kaplan-Meier analysis revealed significantly poorer 28-day survival in patients with complications compared to those without (p < 0.001). **Conclusion:** Cirrhotic patients with refractory ascites face a high risk of complications from modest-volume paracentesis, even with albumin infusion. Paracentesis ≥3L increases the risk of AKI, while higher MELD scores are linked to greater overall complications, leading to poor short-term survival, underscoring the need for careful management and monitoring in this vulnerable patient population.

Disclosures: Peishan Wu: Nothing to Disclose, Kuei-Chuan Lee: Nothing to Disclose, Chih-Yu Li: Nothing to Disclose, Yun-Cheng Hsieh: Nothing to Disclose, Teh-la Huo: Nothing to Disclose, Han-Chieh Lin: Nothing to Disclose, Ming-Chih Hou: Nothing to Disclose

4107 | IMPACT OF THE DIFFERENT STAGES OF ACUTE KIDNEY INJURY IN CIRRHOSIS – A PROSPECTIVE MULTICENTER COHORT STUDY ◆ ★

Ângelo Zambam de Mattos[1] Caroline Machado Rotta Dornelles[2] Leonardo Schiavon[3] Liliana Mendes[4] Roberto Carvalho-Filho[5] Liana Codes[6] Alberto Farias[7] Mario Alvares-da-Silva[8] Carlos Terra[9] Gustavo Pereira[10] Muriel Manica[2] Helena Marcon Bischoff[11] Janaína Luz Narciso Schiavon[3] Silas Gustavo Barboza Romeres[4] Jéssica Bastos Garcia[5] Paulo Lisboa Bittencourt[6] Rafael Ximenes[12] Raul Arrojo[11] Angelo Alves de Mattos[2]

[1]Federal University of Health Sciences of Porto Alegre, [2]UFCSPA, [3]Federal University of Santa Catarina, [4]Hospital de Base do Distrito Federal, [5]Federal University of São Paulo, [6]Hospital Português, [7]University of Sao Paulo, [8]Federal University of Rio Grande do Sul, [9]State University of Rio de Janeiro, [10]Hospital Federal de Bonsucesso, [11]Hospital de Clínicas de Porto Alegre, [12]University of Sao Paulo School of Medicine

Background: Acute kidney injury (AKI) is a common and severe complication of cirrhosis. However, the impact of mild decreases in renal function is controversial. The aim of this study is to evaluate the prognosis of the different

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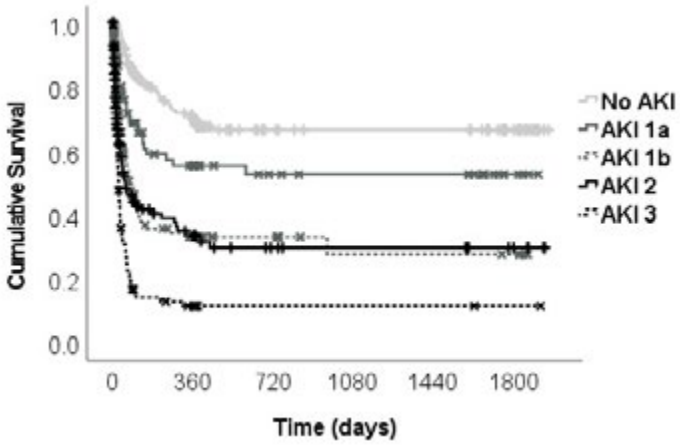
stages of AKI in patients hospitalized with acute decompensation of cirrhosis. **Methods:** This is a multicenter prospective cohort study of patients hospitalized for acute decompensation of cirrhosis, with creatinine values measured at least twice during hospitalization. Primary outcome was mortality (in-hospital, 30 days, 90 days and 12 months). **Results:** Nine hundred twenty-eight patients were included in the study. AKI was diagnosed in 505 patients (stages 1a – 21.6%, 1b – 27.5%, 2 – 28.1%, 3 – 22.8%). AKI was considered pre-renal responsive to volume in 51.6%, hepatorenal syndrome-AKI (HRS-AKI) in 35.6%, parenchymal in 12.2%, and post-renal in 0.6%. Among patients with AKI, 50.7% had complete treatment response, and 15.6% had partial response. In-hospital mortality rates were 4.7%, 19.3%, 33.8%, 44.4%, and 72.2% for patients without AKI and with AKI stages 1a, 1b, 2 and 3 respectively ($p<0.001$ for all comparisons). Thirty-day mortality rates were 6.7%, 21.8%, 32.1%, 42.1%, and 58.7% respectively ($p<0.001$ for all comparisons). Ninety-day mortality rates were 17.5%, 35.2%, 58.6%, 62.6%, and 86.1% respectively ($p\leq0.001$ for all comparisons). Twelve-month mortality rates were 37.1%, 54.1%, 76.4%, 77.3%, and 93.8% respectively ($p<0.05$ for all comparisons). In the overall survival analysis, patients without AKI performed significantly better than those with any stage of AKI ($p<0.001$, Figure 1). AKI stages 1a, 1b, 2 and 3 were independently associated with survival in the multivariate analysis ($p<0.01$). Similar results were found in a sensitivity analysis, only including patients with HRS-AKI, except for 12-month mortality, in which there was a non-significant trend towards lower mortality among patients without AKI when compared to those with AKI 1a (37.1% vs. 58.3%, $p=0.082$). **Conclusion:** Patients hospitalized for acute decompensation of cirrhosis who develop AKI have significantly higher mortality rates than those who do not develop this complication. This is true even for the mildest stages of AKI (stage 1a) and remains so at different time-points, supporting recommendations for an earlier treatment for AKI in cirrhosis.



Disclosures: Ângelo Zambam de Mattos: Nothing to Disclose, Caroline Machado Rotta Dornelles: Nothing to Disclose, Leonardo Schiavon: Nothing to Disclose, Liliana Mendes: Nothing to Disclose, Roberto Carvalho-Filho: Nothing to Disclose, Liana Codes: Nothing to Disclose, Alberto Farias: Nothing to Disclose, Mario Alvares-da-Silva: Nothing to Disclose, Carlos Terra: Nothing to Disclose, Gustavo Pereira: Nothing to Disclose, Muriel Manica: Nothing to Disclose, Helena Marcon Bischoff: Nothing to Disclose, Janaína Luz Narciso Schiavon: Nothing to Disclose, Silas Gustavo Barboza Romeres: Nothing to Disclose, Jéssica Bastos Garcia: Nothing to Disclose, Paulo Lisboa Bittencourt: Nothing to Disclose, Rafael Ximenes: Nothing to Disclose, Raul Arrojo: Nothing to Disclose, Angelo Alves de Mattos: Nothing to Disclose

4108 | EFFECT OF PRO-DOPAMINE ORAL DOCARPAMINE ON ASCITES: AN OPEN-LABEL PHASE 2A STUDY TO ASSESS SAFETY AND EFFECTIVENESS IN PATIENTS WITH REFRACTORY ASCITES DUE TO LIVER CIRRHOSIS

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Background: Docarpamine (DCP) is an orally available dopamine prodrug approved in Japan to transition patients with circulatory failure from IV dopamine to oral therapy. In several small studies, DCP was shown to improve refractory ascites in patients with liver cirrhosis. In this study, we aim to re-evaluate the safety and effectiveness of DCP. **Methods:** Patients with liver cirrhosis with refractory ascites dependent on periodic large volume paracentesis (LVP) and MELD-Na ≤ 25 received open-label oral DCP 750mg TID (low) or 1500mg TID (high) for up to 90 days. Primary outcome measures were safety and tolerability. Clinical outcomes included total volume of ascites drained and frequency of LVP pre-treatment (Pre-tx) compared to on-treatment (On-tx) and post-treatment (Post-tx) periods. **Results:** Eight subjects received the low dose, and 8 the high dose. All but one had alcohol-associated liver disease. Ten subjects, 5 at each dose level, experienced a total of 18 SAEs, 17 of which were hospitalizations due to complications of ascites, expected in this condition and considered unrelated to study drug. One event with concurrent tachycardia and vomiting occurred after the initial 1500mg dose, was thought related to DCP, and resulted in study drug discontinuation. Overall, a total of 113 AEs were recorded in 16 subjects. The most common events were vomiting (7), nausea (4), and abdominal pain (4), none of which led to discontinuation of study drug except for the one event listed above. Welch's t-test was used to evaluate efficacy of the pooled doses. Comparing On-tx to Pre-tx, the total volume of removed ascites decreased by 14% [p=0.47 (n=13)] and the total number of LVPs decreased by 13% [p=0.33 (n=13)]. Comparing Post-tx to Pre-tx, the volume decreased by 53% [p=0.01 (n=9)] and frequency by 44% [p=0.01 (n=10)]. This pattern was seen in both doses. The Mixed Model for Repeated Measures yielded similar trends in reduction of volume [On-tx 9% (p=0.3); Post-tx 27% (p=0.02)] and frequency [On-tx 11% (p=0.2); Post-tx 33% (p=0.01)]. **Conclusion:** Oral DCP was safe and well-tolerated in patients with liver cirrhosis with refractory ascites. Given the statistically significant reduction of ascites volume and LVP frequency in the Post-tx period, it is postulated that treatment with DCP induces neurohumoral changes leading to a delayed effect. Considering the unmet medical need for the treatment of refractory ascites, further studies are warranted to evaluate the efficacy of DCP.

Disclosures: Edmund Tse: Nothing to Disclose, Nick Kontorinis: Nothing to Disclose, Martin Weltman: Nothing to Disclose, Alicia Braund: Nothing to Disclose, Rohit Sawhney: Nothing to Disclose, Ibrahim Mian: Martin Pharmaceuticals: Employee, Woolsey Pharmaceuticals: Employee, Learmont Pharmaceuticals: Employee, Remedy Pharmaceuticals: Employee, Ann Tunstall: Martin Pharmaceuticals: Employee, James O'Beirne: CSL Behring: Advisor, ROCHE: Advisor, Novo Nordisk: Advisor

4109 | PERITONEAL MYELOID-DERIVED SUPPRESSOR CELLS CHARACTERISTICS DEFINE OUTCOMES OF PATIENTS WITH DECOMPENSATED LIVER CIRRHOSIS

Rui Wang[1] *Bo Li*[1] *Xiong Ma*[1] *Min Lian*[1]

[1]*Shanghai Institute of Digestive Disease*

Background: Systemic inflammation, a key component of cirrhosis-associated immune dysfunction (CAID), significantly worsens the outcomes of patients with decompensated cirrhosis. The peritoneal cavity has emerged as a crucial site of immune dysfunction in cirrhosis. As myeloid-derived suppressor cells (MDSCs) are important regulators of immune responses, we aimed to characterize peritoneal MDSCs and examine their association with clinical outcomes in patients with decompensated cirrhosis. **Methods:** Matched peripheral blood and ascites samples were collected at baseline from 43 patients with decompensated cirrhosis, including survivors (n=17) and non-survivors (n=26). MDSCs frequency and function were analyzed using flow cytometry. To investigate potential upstream factors affecting changes in peritoneal MDSCs, metabolites in ascitic fluid supernatants were analyzed using untargeted liquid chromatography-mass spectrometry (LC-MS). **Results:** Peritoneal monocytic (M-) MDSCs frequencies and function were severely decreased in non-survivors as compared with survivors, paralleled by elevated levels of several pro-inflammatory cytokines and chemokines. There was no difference in the M-MDSC compartment in peripheral blood between survivors and non-survivors. Metabolomic analysis of ascites identified glycoursodeoxycholic acid (GUDCA) as a key modulator of peritoneal M-MDSCs. GUDCA exposure *in vitro* induced expansion and suppressive activity of M-MDSCs by upregulating triggering receptor expressed on myeloid cells-2 (TREM-2). Pharmaceutical inhibition of TREM-2 abolished the effect of GUDCA. TREM-2 expression on peritoneal MDSCs in decompensated patients was associated with improved survival. **Conclusion:** Peritoneal M-MDSC impairment represents a previously underestimated feature of cirrhosis-associated immune dysfunction (CAID), which can be reversed by GUDCA through upregulating TREM-2. This suggests that targeting peritoneal M-MDSCs or TREM-2 could be promising immune-intervention strategies for patients with decompensated liver cirrhosis.

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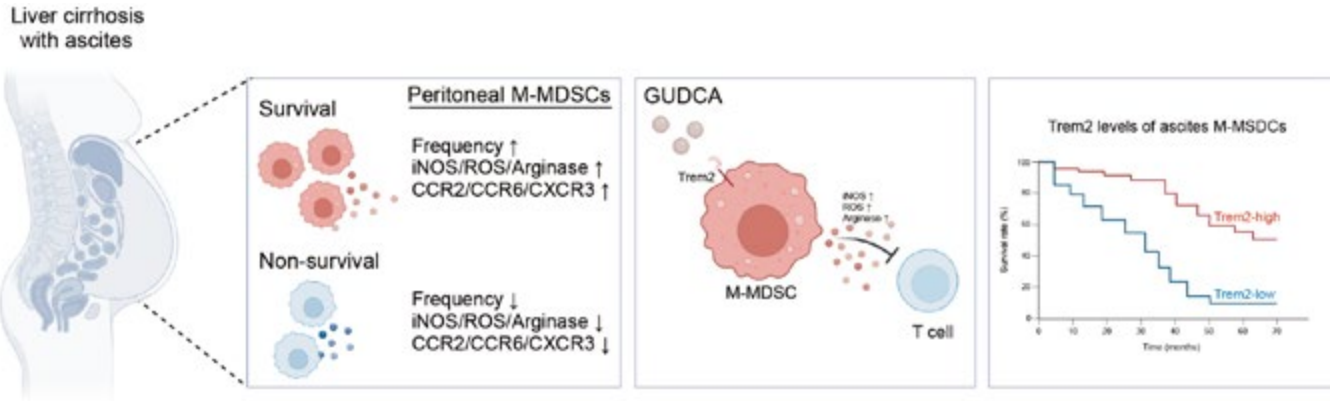

Disclosures: Rui Wang: Nothing to Disclose, Bo Li: Nothing to Disclose, Xiong Ma: Nothing to Disclose, Min Lian: Nothing to Disclose

4110 | THE ESTIMATION OF PORTAL PRESSURE MODEL WITH NON-NEWTONIAN FLUID DYNAMICS IN LIVER CIRRHOSIS

Hiroshi Ishiba[1] Yuske Takahashi[2] Tasuku Hara[3] Yuya Seko[2] Kanji Yamaguchi[2] Hideki Fujii[4] Yoshito Itoh[2]

[1]Osaka general hospital of West Japan railway company, [2]Kyoto prefectural university of medicine, [3]Saiseikai Kyoto hospital, [4]Kyoto first red cross hopital

Background: Assessment of portal hypertension is important for improving the prognosis of patients with cirrhosis, but the currently recommended measurement of hepatic venous pressure gradient is an invasive test and repeated measurement is not practical. In this study, we estimated the diagnostic accuracy of the portal venous pressure gradient (PVPG) model which was calculated by using non-Newtonian fluid dynamics (Casson model) for decompensated liver cirrhosis (dcLC) and esophagogastric varices (EGV). **Methods:** Of 422 patients with chronic liver disease who were measured the blood flow of the main trunk of portal vein and Shear Wave Elastography with the abdominal ultrasonography from April 2019 to February 2024, 133 patients with cirrhosis were enrolled. Casson viscosity (η_0) was calculated from the blood viscosity of the 99 patients, excluding those taking antiplatelet and anticoagulant drugs, and a model equation for η_0 was developed. This model equation was used to calculate the PVPG in the portal vein from the Casson model. The PVPG and congestion index (CI) as representative values of the portal vein pressure, type 4 collagen 7S (COL4-7S), liver stiffness measurement (LSM) as representative values of hepatic resistance, the Blood flow volume (BFV) of the portal vein was selected as a representative value of hepatic blood flow, and the diagnostic accuracy of these factors for dcLC and EGV was statistically analyzed. **Results:** The model for η_0 was estimated with hematocrit (Ht), total protein (TP) and albumin (Alb), which these factors correlated with the measuredη_0. The model was logη_0_m=0.146TP+5.55(Ht/100)3-0.01Alb2-0.09. Also, boundary layer thickness was zero. Then, the PVPG model was calculated; PVPG=4η0_mVp/(Da/2)^2. Of 133 patients with cirrhosis, 85 had dcLC and 71 had EGV. Compared with non-dcLC, PVPG of dcLC was significantly lower (non-dcLC: 1.63 vs dcLC: 1.19 Pa/cm p<0.01), CI, LSM, COL4-7S was significantly higher (CI: 0.05 vs 0.07 cm·s, p<0.01, LSM: 13.8 vs 16.6 kPa, p<0.01, COL4-7S: 4.9 vs 6.8 ng/ml, p<0.01). There were not significantly different in BFV between the two groups (non-8.32 vs10.5 ml/s, p=0.129). Similarly, As the disease worsened from Child-Pugh grade A to C, PVPG was lower and CI, LSM and COL4-7S was higher with significant difference. Multiple logistic regression analysis was performed for dcLC and EGC diagnoses with PVPG, CI, COL4-7S, and LSM; PVPG and COL4-7S were significantly identified at odds ratios of 1.9 and 1.3, respectively, for dcLC diagnosis, while CI was significantly identified at odds ratio of 1.2 for EGV diagnosis. **Conclusion:** PVPG derived from non-Newtonian fluid dynamics may allow not only the screening of the progression of cirrhosis but also the determination and estimation of the treatment for portal hypertension.

Disclosures: Hiroshi Ishiba: Nothing to Disclose, Yuske Takahashi: Nothing to Disclose, Tasuku Hara: Nothing to Disclose, Yuya Seko: AbbVie GK: Speaking and Teaching, Novo Nordisk Pharma Ltd: Speaking and Teaching, Merck & Co., Inc.: Speaking and Teaching, Gilead Sciences, Inc.: Speaking and Teaching, Mitsubishi Tanabe Pharma Corporation: Speaking and Teaching, Kanji Yamaguchi: Nothing to Disclose, Hideki Fujii: Nothing to

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Disclose, Yoshito Itoh: Novo Nordisk Pharma LTD: Speaking and Teaching, ZERIA PHARMACEUTICAL CO., LTD.: Speaking and Teaching, Otsuka Pharmaceutical Co., Ltd.: Speaking and Teaching, Viatris Inc.: Speaking and Teaching, ASKA Pharmaceutical Co., Ltd.: Speaking and Teaching, Astelas Pharma Inc.: Speaking and Teaching, AstraZeneca K.K.: Speaking and Teaching, Gilead Sciences Inc.: Speaking and Teaching, Mitsubishi Tanabe Pharma Corporation: Speaking and Teaching, EA Pharma Co. Ltd.: Speaking and Teaching, Kowa Company Ltd.: Speaking and Teaching, CHUGAI PHARMACEUTICAL CO., LTD.: Speaking and Teaching, Takeda Pharmaceutical Company Limited.: Speaking and Teaching, ONO PHARMACEUTICAL CO., LTD.: Speaking and Teaching, AbbVie Inc.: Speaking and Teaching, Novartis Pharma Inc.: Speaking and Teaching, MYYARISAN Phramaceutocal Co.: Speaking and Teaching, Eli Lilly and Co.: Speaking and Teaching, Olympus Co.: Speaking and Teaching, AbbVie Inc.: Grant/Research Support, Otsuka Pharmaceutical Co., Ltd.: Grant/Research Support, CHUGAI PHARMACEUTICAL CO., LTD.: Grant/Research Support, SHIONOGI & CO., LTD.: Grant/Research Support, Eisai Co., Ltd.: Grant/Research Support, Mitsubishi Tanabe Pharma Corporation: Grant/Research Support, EA Pharma Co. Ltd.: Grant/Research Support, Sumitomo Pharma Co. Ltd.: Grant/Research Support, ASKA Pharmaceutical Co. Ltd.: Grant/Research Support, Eli Lilly and Co.: Grant/Research Support, Astra Zeneca plc.: Grant/Research Support, Pfizer Inc.: Grant/Research Support, Merk Sharp and Dohme: Grant/Research Support, Bristol-Myers Squibb Co.: Grant/Research Support, GSK plc.: Grant/Research Support, AbbVie Inc: Grant/Research Support

4111 | SERUM AMMONIA AS A PREDICTOR OF 6-MONTH CLINICAL OUTCOMES IN PATIENTS WITH LIVER CIRRHOSIS

Pooi Ling Loi[1] Jason Chang[2] Chanda Ho[2] Hiang Keat Tan[2] Marianne De Roza[3] Rahul Kumar[1]

[1]Changi General Hospital, [2]Singapore General Hospital, [3]SingHealth

Background: Ammonia has long been established as a neurotoxin involved in the pathogenesis of hepatic encephalopathy (HE). The Child-Pugh (CP) score has factored in HE to prognosticate patients with cirrhosis but is limited by observers' subjectivity. This study was aimed to test the hypothesis that serum ammonia level predicts complications and mortality in clinically stable outpatients with cirrhosis. **Methods:** In this ongoing study to predict the **d**ecompensation, **a**cute on chronic liver failure (ACLF) and **m**ortality in cirrhosis (Solidarity-DAM), stable outpatients were recruited according to the declaration of Helsinki. The study was conducted from January 2023 to May 2024, 178 patients were eligible for inclusion in the study. Patients were censored at clinical outcomes, last visit date or liver transplant. The primary endpoint was all non-elective admission for decompensation of cirrhosis (ascites, variceal bleeding, HE, infection), ACLF or death. Ammonia measurements were carried out in fasting blood in stable outpatients, with a minimum of 4 weeks stabilization post discharge for acute decompensation or ACLF if any, in accordance with international standards. 6-month clinical outcomes (CO) were reviewed from the date of the serum ammonia measurement. **Results:** A total of 178 outpatients with mean age of 66.7 ± 10.2 years, BMI of 26.4 ± 5.2, majority males (59.6%) were recruited. A total of 21 (11.8%) patients at 6 months achieved the predefined CO. Patients with CP classes A/B/C were 76.4%, 20.8%, 2.8% respectively. The median MELD was 8 (IQR: 6 - 10). The median serum ammonia in patients who achieved and did not achieve CO were 63 (IQR: 53 - 92) and 25 (IQR: 18 - 38) respectively ($p < 0.001$). The CO was not dependent on age, BMI, aetiology of cirrhosis, concomitant diabetes mellitus, or serum creatinine. However, MELD score, CP score, presence of ascites, history of overt HE, and use of lactulose and rifaximin predicted CO in univariate analysis ($p < 0.05$ for all). In the subsequent multivariate analysis, we have excluded MELD as serum creatinine is not a predictor of CO. We have also excluded presence of ascites and history of overt HE to avoid collinearity with CP score. The multivariate model showed that both CP score and serum ammonia were independent predictor of defined CO. The ROC curve analysis showed that CP score was the best predictor of the 6-month CO with AUROC of 0.907. The AUROC of first serum ammonia was 0.904 which was better than MELD and MELD-Na score. The ROC of ammonia showed that at cut off of 50 µmol/L, it has 80% sensitivity and 90% specificity in predicting CO at 6 months. Survival table, Kaplan-Meier curve (Figure 1a) and ROC curve (Figure 1b) are attached. **Conclusion:** Serum ammonia (cut off at 50 µmol/L) can predict complications and mortality in clinically stable outpatients with cirrhosis with a high sensitivity and specificity.

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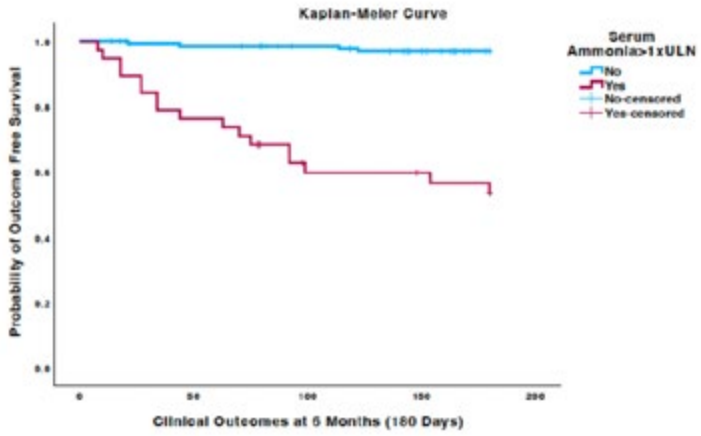
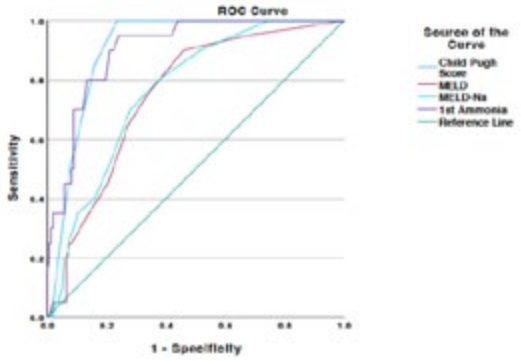
Figure 1a.



Legend: ULN: Upper limit of normal

Patient at Risk	0 Days	30 Days (1 Month)	60 Days (2 Months)	90 Days (3 Months)	120 Days (4 Months)	150 Days (5 Months)	180 Days (6 Months)
Ammonia < 1xULN	140	134	132	127	124	115	106
Ammonia > 1xULN	38	32	28	23	19	18	17

Figure 1b.



Disclosures: Pooi Ling Loi: Nothing to Disclose, Jason Chang: Boehdringer-Ingelheim: Advisor, Chanda Ho: Nothing to Disclose, Hiang Keat Tan: Nothing to Disclose, Marianne De Roza: Nothing to Disclose, Rahul Kumar: Nothing to Disclose

4112 | RISK OF HEPATIC DECOMPENSATION AND HCC IN PATIENTS WITH CIRRHOSIS SIGNIFICANTLY DIFFERS BY LIVER DISEASE ETIOLOGY

Michelle Ng[1] *Sruthi Yekkaluri*[1] *Lisa Quirk*[1] *Purva Gopal*[1] *Amit Singal*[1]

[1]*UT Southwestern Medical Center*

Background: The epidemiology of cirrhosis is changing over time due to the increased prevalence of obesity and alcohol consumption, as well as increased treatment of patients with hepatitis B and hepatitis C. The impact of this change in etiologic patterns on the expected burden of cirrhosis complications is unknown. **Methods:** We conducted a retrospective chart review on adult patients with cirrhosis at two large urban health systems in

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Dallas, TX. Patients with history of hepatocellular carcinoma (HCC) or ascites plus hepatic encephalopathy at baseline were excluded. Our primary outcome was the incidence of hepatic decompensation, defined as new onset ascites or hepatic encephalopathy after the index visit, and our secondary outcome was development of HCC. We used the Fine-Gray subdistribution hazards model to characterize time to both events, with liver transplantation and death as competing events and multivariable regression models to identify associated factors. **Results:** We identified 969 patients with cirrhosis, with median age 60 years and 58.8% being male. This cohort was diverse regarding race and ethnicity (34.3% White, 37.9% Black, 16.8% Hispanic) and liver disease etiology (39.5% viremic HCV, 9.3% post-SVR HCV, 16.9% alcohol, and 14.1% MASLD). During a median follow-up of 32.4 months, 31.9% of patients had new hepatic decompensation, 13.1% developed HCC, 8.9% underwent liver transplant, and 27.4% died. The cumulative 1-, 2-, and 3-year incidence of hepatic decompensation were 11.7%, 4.2%, and 18.8% and incidence of HCC were 7.5%, 23.5% and 9.2%, respectively. In multivariable analyses adjusted for demographics and Child Pugh score, liver disease etiology was significantly associated with both risk of hepatic decompensation and HCC. Compared to viremic HCV infection, higher hazards of hepatic decompensation were observed in patients with MASLD (HR 1.78, 95% CI 1.16-2.73). The cumulative 2-year incidence of hepatic decompensation per 1000 person-years were 26.5 for ALD, 25.5 for MASLD, and 36.0 for viremic HCV. Conversely, patients with ALD had lower hazards of HCC compared to viremic HCV infection (HR 0.33, 95% CI 0.15-0.73); HCC risk was also lower in patients with MASLD, but this did not reach statistical significance (HR 0.67, 95% CI 0.33-1.37). The cumulative 2-year incidence of HCC per 1000 person-years were 7.7 for ALD, 7.5 for MASLD, and 22.5 for viremic HCV. **Conclusion:** Overall, increasing proportions of non-viral related liver disease will likely lead to increased incidence of hepatic decompensation and reduced HCC burden.

Disclosures: Michelle Ng: Nothing to Disclose, Sruthi Yekkaluri: Nothing to Disclose, Lisa Quirk: Nothing to Disclose, Purva Gopal: Nothing to Disclose, Amit Singal: Consultant relationship with AstraZeneca; Has not ended; Consultant relationship with Sirtex; Has not ended; Consultant relationship with Boston Scientific; Has not ended; Consultant relationship with Bayer; Has not ended; Consultant relationship with Eisai; Has not ended; Consultant relationship with FujiFilm Medical Sciences; Has not ended; Consultant relationship with Elevar; Has not ended; Consultant relationship with Exact Sciences; Has not ended; Consultant relationship with Glycotest; Has not ended; Consultant relationship with Exelixis; Has not ended; Consultant relationship with Merck; Has not ended; Consultant relationship with Genentech; Has not ended; Consultant relationship with HistoSonics; Has not ended

4113 | REDUCED REM SLEEP MEASURED BY WEARABLE TECHNOLOGY IS ASSOCIATED WITH POOR OVERALL WELLBEING IN CIRRHOSIS

Adam Buckholz[1] Brian McSteen[2] Jessica Siguencia[2] Russell Rosenblatt[3] Arun Jesudian[3] Ana Krieger[2] Avesh Thuluvath[4] Robert Schwartz[5] Robert Brown[3]

[1]New York Presbyterian Hospital Program, [2]NewYork-Presbyterian/Weill Cornell Medical Center, [3]Weill Cornell Medicine, [4]Northwestern University Feinberg School of Medicine, [5]Weill Cornell Medical College

Background: Disturbed sleep is common in patients with overt and covert hepatic encephalopathy (CHE). We previously published data demonstrating consistent reduction in sleep quality, especially REM sleep, in those with cirrhosis and CHE as measured by commercial wearable technology. Here, we assess whether objectively measured sleep correlates with subjective sleep quality and overall wellbeing (HRQoL) in patients with cirrhosis. **Methods:** We prospectively enrolled 36 cirrhotic participants without overt HE and tracked sleep using Whoop or Oura wearables. We collected baseline clinical data and assessed for CHE using PHES psychometric testing and baseline HRQoL and sleep quality through the validated chronic liver disease questionnaire (CLDQ) and Pittsburgh Sleep Quality Index (PSQI) surveys, respectively. Our primary outcome was the correlation between objectively measured sleep metrics during the first 14 days after enrollment (total sleep time, nightly sleep disturbances, REM sleep, deep sleep) and patient-reported HRQoL and sleep quality measured by the global CLDQ and PSQI respectively using Pearson correlation coefficient (PCC). Per previously published thresholds, global CLDQ<5 and PSQI>5 were considered “poor.” **Results:** From 36 participants, 484 (96% of total) sleep nights were collected. At time of enrollment mean age was 56.3 (SD 11.0), 22 were male, 3 had ascites, 16 had diuretic-controlled ascites. 19 (58%) had CHE by PHES, and mean MELD-Na was 8.9 (SD 5.42). Most (n=21, 60%) reported poor sleep (global PSQI>5), and ratios were similar regardless of CHE status. Global PSQI

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and CLDQ strongly inversely correlated with each other (r= -0.79, *p*<0.01). Objective measures of REM were significantly correlated (Table) with improved reported sleep by PSQI and overall wellbeing by CLDQ across different domains and two different wearables; total sleep time, time in bed and disturbances were not. Those with low global HRQoL per CLDQ had lower nightly REM sleep (23% vs 17%, *p*<0.01; 1.41 vs 1.13 hours, *p*=0.01, Figure), which remained significant in a mixed effects model adjusting for participant night-to-night variation ("noise"), age, gender, BMI and CTP score. Individuals who averaged <1 hour of REM over 14 days were 3 times as likely to report low overall wellbeing (54.5% vs 15.4%, *p*=0.01). **Conclusion:** Our data suggest that lower REM sleep duration in cirrhosis, as measured by wearables after 14 days, is significantly associated with reduced HRQoL and worse subjective sleep quality. Given that low REM is also correlated with CHE, a condition associated with poor clinical and patient reported outcomes, these findings suggest REM sleep, rather than total sleep, may be a useful prognostic tool and a potential therapeutic target for improving outcomes in cirrhosis. It is unclear whether there is a causal relationship between shorter REM duration and lower HRQoL, and future studies are needed to further investigate this association.

Association of Measured Sleep Metrics with Survey Derived Metrics

	Global CLDQ (PCC r)	*p* value	Global PSQI (PCC r)	*p* value
Time in Bed (h)	-0.062	0.19	0.037	0.45
Total Sleep Time (h)	-0.057	0.22	0.039	0.42
Sleep Efficiency	0.083	0.07	-0.027	0.58
Sleep Disturbances (#)	0.029	0.54	-0.044	0.36
Time Awake in Bed	**-0.097**	**0.04**	0.035	0.47
REM Sleep (h)	**0.133**	**<0.01**	-0.067	0.17
REM Sleep (% of total)	**0.248**	**<0.01**	**-0.138**	**<0.01**
Deep Sleep (h)	0.013	0.78	-0.023	0.63
Restorative Sleep (REM + Deep h)	**0.096**	**0.04**	-0.058	0.23
Restorative Sleep (% of total)	**0.207**	**<0.01**	**-0.111**	**0.02**

Association of Measured REM Sleep (% of total sleep) with Domains of CLDQ Across Wearables

	Abdominal Symptoms	Fatigue	Systemic Symptoms	Activity	Emotional Function	Worry	Overall
REM % Measured by Whoop (n= 305)	**0.155** ***p*<0.01**	**0.273** ***p*<0.01**	**0.372** ***p*<0.01**	0.073 *p*=0.21	0.089 *p*=0.13	**0.164** ***p*<0.01**	**0.300** ***p*<0.01**
REM % Measured by Oura (n=179)	**0.373** ***p*<0.01**	**0.212** ***p*<0.01**	**0.175** ***p*=0.02**	**0.360** ***p*<0.01**	**0.185** ***p*=0.02**	**-0.161** ***p*=0.04**	**0.228** ***p*<0.01**
REM % Overall (n=484)	**0.245** ***p*<0.01**	**0.251** ***p*<0.01**	**0.293** ***p*<0.01**	**0.181** ***p*<0.01**	**0.147** ***p*<0.01**	**0.094** ***p*=0.046**	**0.248** ***p*<0.01**

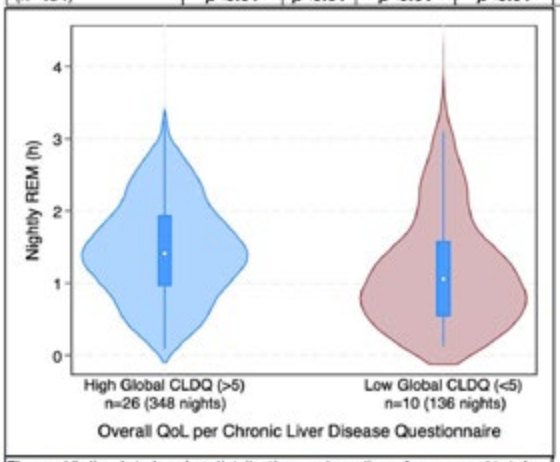

Figure. *Violin plot showing distribution and median of measured total nightly REM sleep by overall wellbeing. Lower wellbeing was associated with less nightly REM overall and as a percentage of nightly sleep.*

Disclosures: Adam Buckholz: Nothing to Disclose, Brian McSteen: Nothing to Disclose, Jessica Siguencia: Nothing to Disclose, Russell Rosenblatt: Nothing to Disclose, Arun Jesudian: Salix Pharmaceuticals: Consultant, Salix Pharmaceuticals: Speaking and Teaching, Madrigal Pharmaceuticals: Speaking and Teaching, Novo Nordisk: Consultant, Orphalan: Consultant, Ana Krieger: Nothing to Disclose, Avesh Thuluvath: Nothing to Disclose, Robert Schwartz: Miromatrix Inc: Advisor, Lime Therapeutics: Advisor, Otsuka Inc.: Grant/Research Support, Alnylam Pharmaceuticals: Speaking and Teaching, Alnylam Pharmaceuticals: Consultant, Robert Brown: Consultant relationship with Intercept; Has not ended; Consultant relationship with Gilead; Has not

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ended; Consultant relationship with Abbvie; Has not ended; Consultant relationship with Madrigal; Has not ended; Consultant relationship with GSK; Has not ended; Consultant relationship with eGenesis; Has not ended; Consultant relationship with mirum; Has not ended

4114 | ASSESSING THE ROLE OF "THE WEEKEND EFFECT" ON PATIENT OUTCOMES FOLLOWING TIPS PROCEDURE IN A NORTH AMERICAN TERTIARY CARE CENTER

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Background: The "weekend effect" has been described in many medical disciplines as an unexpected determinant of adverse outcomes. This study assesses whether transjugular intrahepatic portosystemic shunt (TIPS) procedures conducted on a weekend lead to worse outcomes when compared to weekday procedures. **Methods:** This retrospective, single-center study includes adults (age >18 years) with known diagnoses of liver disease who underwent TIPS procedures between 2014 and 2023. Patients were stratified based on the exposure variable of interest, which was the day of TIPS, classified as weekend vs. weekday. The primary outcome of interest was 1-year mortality. Multivariate logistic regression was carried out on 4 binary outcomes (1-year mortality; six weeks mortality, post-TIPS hepatic encephalopathy, need for TIPS revision), using the explanatory variables age; gender, and etiology of liver disease. Outcomes were assessed for normality using Kolmogorov-Smirnov and Shapiro-Wilk tests. For outcomes that did not follow a normal distribution, the Mann-Whitney test was used. **Results:** Of 165 patients, 152 underwent weekday TIPS and 13 underwent weekend TIPS. Baseline characteristics were not statistically different between those admitted on weekdays vs weekends regarding age (59.1±10.2 vs 57.4±7.1, p=0.31), sex (55% vs 69% male patients, p=0.32), and mean MELDNa (16.1±5.25 vs 18.6±4.93, p =0.07). Regarding primary outcomes, patients with weekend procedures had no significant difference in 1-year mortality (16% vs 15%, p=0.7). Regarding secondary outcomes, between weekday vs weekend TIPS, no significant differences in 6-week mortality (11% vs 15%, p=0.7), post-TIPS hepatic encephalopathy (47% vs 63%, p=0.9), or need for revision (22% vs 31% p=0.56) were appreciated. However, weekend TIPS patients had a greater median LOS of 10 days (IQR 6-15) vs. 3 days (IQR 2-10) in weekday patients, p=0.035. Further, we confirmed that pre-TIPS MELDNa significantly influenced 1-year mortality (OR 1.21 CI 1.11-1.34, p<0.01), 6-week mortality (OR 1.21 (1.10-1.35, p<0.01), in addition to post-TIPS hepatic encephalopathy (OR 1.08 (CI 1.02-1.15, p=0.013). Interestingly, relative to MASLD, a dose-dependant relationship of alcohol consumption on 6-week mortality was appreciated, with an increased odds ratio for both Met-ALD: OR 1.44, 95% CI 0.25-8.32, p=0.028) and ALD (OR 1.71, 95% CI 0.39-8.81, p=0.048). No differences based on the etiology of disease were appreciated in 1-year mortality. Further multivariate data is provided in Table 1. **Conclusion:** A weekend effect of TIPS procedures increasing the risk of mortality or complications is not noted. Compared to weekday TIPS, weekend TIPS patients have longer LOS, likely representing a more complicated hospital course stemming from a more often than not, emergent, weekend procedure.

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TABLE 1: Multivariable Analysis of Primary and Secondary Post-TIPS with Explanatory Variables.

Outcome	Variable	OR	95% CI	P value
1-year mortality				
	Age	0.97	(0.94, 1.02)	0.210
	NaMELD	1.21	(1.11, 1.34)	<0.001
	Male	1.29	(0.55, 3.13)	0.614
	Weekend	0.97	(0.14, 3.91)	>0.96
	Etiology: *(MASLD as reference)*			
	ALD	1.17	(0.35, 3.95)	0.815
	Met-ALD	0.92	(0.22, 3.56	>0.9
	Viral	1.5	(0.39, 5.60)	0.5
	PBC	-	-	-
	PSC	6.00	(0.63, 58.8)	0.10
	Non-Cirrhotic	4.00	(0.46, 29.7)	0.241
	Autoimmune Hepatitis	-	-	-
6-week mortality				
	Age	0.94	(0.90, 0.99)	0.010
	NaMELD	1.21	(1.10, 1.35)	<0.001
	Male	1.07	(0.41, 2.92)	0.9
	Weekend	1.44	(0.21, 5.99)	0.7
	Etiology: *(MASLD as reference)*			
	ALD	1.71	(0.39, 8.81)	0.028
	Met-ALD	1.44	(0.25, 8.32)	0.048
	Viral	2.48	(0.50, 13.6)	0.3
	PBC	-	-	-
	PSC	13.0	(1.23, 150)	0.033
	Non-Cirrhotic	8.67	(0.89, 78.9)	0.028
	Autoimmune Hepatitis	-	-	-
TIPS Revision in Follow-up				
	Age	1.02	(0.98, 1.05)	0.421
	NaMELD	0.94	(0.87, 1.01)	0.212
	Male	0.5	(0.24, 1.05)	0.04
	Weekend	1.60	(0.41, 5.26)	0.56
	Etiology: *(MASLD as reference)*			
	ALD	0.83	(0.26, 2.54)	0.714
	Met-ALD	0.85	(0.23, 2.86)	0.803
	Viral	1.65	(0.51, 5.35)	0.4
	PBC	3.04	(0.74, 12.3)	0.12
	PSC	4.25	(0.45, 40.2)	0.26
	Non-Cirrhotic	1.06	(0.05, 8.51)	>0.9
	Autoimmune Hepatitis	2.13	(0.23, 2.86)	0.851
Post-TIPS Hepatic Encephalopathy				
	Age	1.02	(0.99, 1.05)	0.3
	NaMELD	1.08	(1.02, 1.15)	0.013
	Male	1.05	(0.57, 1.05)	0.3
	Weekend	1.83	(0.58, 6.28)	0.9
	Etiology: *(MASLD as reference)*			
	ALD	0.87	(0.37, 2.06)	0.8
	Met-ALD	0.93	(0.36, 2.38)	0.14
	Viral	2.15	(0.79, 6.14)	0.9
	PBC	1.21	(0.33, 4.47)	0.08
	PSC	0.40	(0.02, 3.45)	0.41
	Non-Cirrhotic	1.82	(0.27, 14.9)	0.50
	Autoimmune Hepatitis	2.42	(0.22, 14.22)	0.06

Disclosures: Yashasavi Sachar: Nothing to Disclose, Nisha Howarth: Nothing to Disclose, Derek Little: Nothing to Disclose, Ropo Ogunsakin: Nothing to Disclose, David Peck: Nothing to Disclose, Amol Mujoomdar: Nothing to Disclose, David Hocking: Nothing to Disclose, Anouar Teriaky: Nothing to Disclose, Karim Qumosani: Nothing to Disclose, David Hudson: Nothing to Disclose, Ephraim Tang: Nothing to Disclose, Anton Skaro: Nothing to Disclose, Mayur Brahmania: Nothing to Disclose, Juan Pablo Arab: Nothing to Disclose, Mohammad Qasim Khan: Nothing to Disclose

4115 | COMPARATIVE PROGNOSTIC VALUE OF MELD, MELD-NA, AND MELD 3.0 IN PREDICTING SURVIVAL AFTER TIPS PLACEMENT

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Background: The Model for End-Stage Liver Disease (MELD) scoring systems are crucial for selecting candidates for trans-jugular intrahepatic portosystemic shunt (TIPS) procedures by forecasting survival probabilities. These scores encompass subcomponents reflecting severe liver disease manifestations such as hepatic biosynthetic failure, metabolic dysfunction, and hepatorenal syndrome. This study aims to evaluate the

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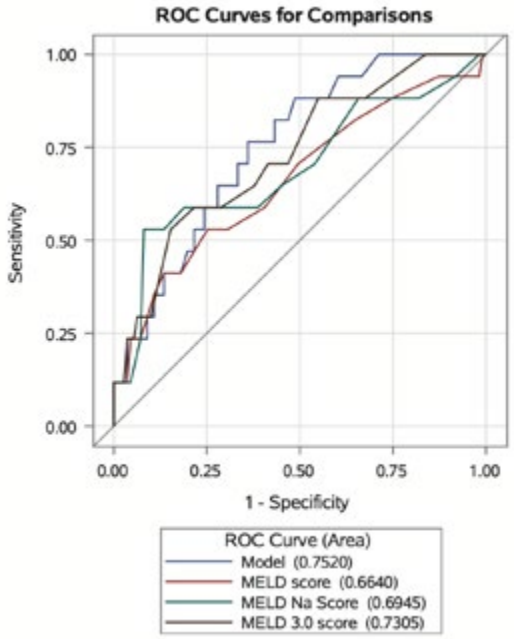
predictive accuracy of the MELD score alongside MELD-Na and MELD 3.0, and their respective subcomponents, in patients undergoing primary TIPS placement. **Methods:** In a multicenter retrospective design, 128 patients who underwent primary TIPS placement for chronic liver disease from November 2018 to April 2024 were studied. Data on patient demographics, indications for TIPS, etiology of hepatic disease, and relevant laboratory metrics were gathered. The study analyzed three mortality risk predictors—MELD, MELD-Na, and MELD 3.0—alongside their subcomponents. Kaplan-Meier survival analysis and both unstratified and stratified log-rank tests assessed the predictors of survival duration. **Results:** Significant independent predictors of reduced survival post-TIPS were baseline total bilirubin (HR = 1.583, p < 0.0001), INR (HR = 5.429, p = 0.0003), and albumin (HR = 0.408, p = 0.0068). Baseline creatinine (HR = 1.966, p = 0.0675) and sodium levels (HR = 0.951, p = 0.3773) did not significantly impact survival duration. On multivariate analysis, total bilirubin was the only predictor for survival outcomes (HR = 1.410, p = 0.0028). The MELD scoring systems—MELD, MELD-Na, and MELD 3.0—consistently predicted survival post-TIPS (MELD: HR = 1.154, p < 0.0001; MELD-Na: HR = 1.176, p < 0.0001; MELD 3.0: HR = 1.176, p < 0.0001). MELD 3.0 had the highest predictive accuracy (AUC: .73, 95% CI: 0.60-0.86), followed by MELD-Na and MELD. A notable difference was observed in overall survival probabilities among patients stratified by baseline total bilirubin and INR levels, but not by creatinine, albumin, or sodium levels. **Conclusion:** Total bilirubin, INR, and albumin levels were significant independent predictors of survival after TIPS procedures on univariate analysis, while total bilirubin was the only independent predictor on multivariate analysis. Among the scoring systems analyzed, MELD 3.0 demonstrated superior predictive sensitivity and specificity in assessing survival post-TIPS compared to MELD-Na and traditional MELD scores.



Disclosures: Ashley Lamba: Nothing to Disclose, Eusha Hasan: Nothing to Disclose, Ian Rumball: Nothing to Disclose, Ethan Davoudzadeh: Nothing to Disclose, Nayan Tiwary: Nothing to Disclose, Alexa Giammarino: Nothing to Disclose, Craig Greben: Nothing to Disclose, Jonathan Weinstein: Nothing to Disclose, Sanjaya Satapathy: Gilead Sciences: Grant/Research Support, Durect Pharma: Grant/Research Support, Fibronostics: Grant/Research Support, Novartis: Grant/Research Support, Zydus Pharma: Grant/Research Support, Boehringer Ingelheim: Grant/Research Support, Intercept Pharma: Grant/Research Support

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4116 | A PROSPECTIVE, SINGLE-CENTER, RANDOMIZED, OPEN-LABEL STUDY TO INVESTIGATE THE EFFICACY AND LONG-TERM OUTCOME OF CYANOACRYLATE GLUE FOR OBLITERATION OF ALL GASTRIC VARICES (GOV1, GOV2, IGV1) VERSUS OBLITERATION OF GASTRIC VARICES WITH STIGMATA OF RECENT HAEMORRHAGE IN CIRRHOTIC PATIENTS PRESENTING WITH FIRST EPISODE OF VARICEAL BLEED ◆

Ritesh Prajapati[1] *Subhash Nandwani*[1] *Rajiv Mehta*[1] *Mayank Kabrawala*[1] *Pankaj Desai*[1] *Chintan Patel*[1] *Nisharg Patel*[1] *Mohit Sethia*[1] *Rinkal Kakadiya*[1] *Kamlesh Magnani*[1]

[1]*SIDS Hospital and Research Centre*

Background: There is significant interpersonal variation in management of gastric varices. In real life scenario both large esophageal and gastric varices coexist in a significant number of cases. In patients presenting with variceal bleed, source of bleed whether esophageal or gastric varices is not clear in most patients. How aggressively to manage the large gastric varices in patients who had variceal bleed is not defined. The aim of this study was to compare aggressive management of gastric varices with conservative management of gastric varices in patient with variceal bleed. **Methods:** Consecutive patients with cirrhosis presenting with 1st episode of variceal bleed and having large gastric varices (Gastroesophageal varices (GOV)1, GOV2, Isolated gastric varices (IGV) 1) were randomized to receive aggressive (Group A, n=66) or conservative therapy (Group B, n=68) for gastric varices (Figure 2). Primary outcome was variceal rebleed or death at 1 year follow up. **Results:** There was no difference in the number of rebleed events among groups at 1 year (p=0.577). All-cause mortality was comparable in both groups at 1 year (p=0.059), 6 months and 1 month. 1-year all-cause mortality was comparable in both groups. The mean number of sessions required for obliteration of varices was lower in Group A than in Group B (1.24 ± 0.69 and 2.49 ± 1.38 respectively, p=0.01). There was no significant difference between the two groups regarding the adverse events. **Conclusion:** Aggressive approach to management of gastric varices leads to early obliteration of varices but does not lead to lower rebleeding rates or improvement in survival.

Figure2: Endoscopic management on index and follow up endoscopy

Group A	Group B
Index endoscopy procedure	
Endoscopic cyanoacrylate injection for all visible GOV1, GOV2 and IGV1, and EVL for esophageal varices	EVL for esophageal varices, GOV1 with SRH Endoscopic cyanoacrylate injection for • GOV2, IGV1 with SRH or • High risk* GOV 2, IGV1 with no SRH
Follow up endoscopy procedure	
Endoscopic cyanoacrylate injection for all visible GOV1, GOV2 and IGV1, and EVL for esophageal varices	EVL for esophageal varices, GOV1 with SRH Endoscopic cyanoacrylate injection for • GOV2, IGV1 with SRH

*High risk: size of varix (> 10mm) & red wale marks

Abbreviations: GOV, gastroesophageal varices; IGV, Isolated gastric varices; SRH, stigmata of recent haemorrhage.

Disclosures: Ritesh Prajapati: Nothing to Disclose, Subhash Nandwani: Nothing to Disclose, Rajiv Mehta: Nothing to Disclose, Mayank Kabrawala: Nothing to Disclose, Pankaj Desai: Nothing to Disclose, Chintan Patel: Nothing to Disclose, Nisharg Patel: Nothing to Disclose, Mohit Sethia: Nothing to Disclose, Rinkal Kakadiya: Nothing to Disclose, Kamlesh Magnani: Nothing to Disclose

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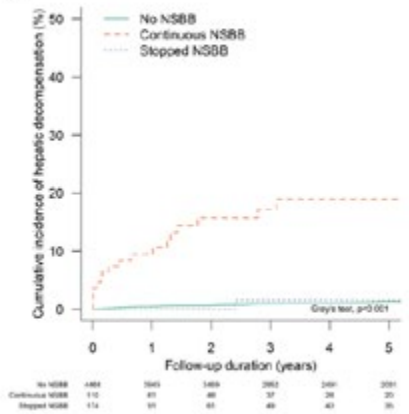
4117 | SAFETY OF STOPPING NON-SELECTIVE BETA-BLOCKERS (NSBBS) ACCORDING TO BAVENO VII CONSENSUS IN PATIENTS WITH CIRRHOSIS AND WELL-CONTROLLED LIVER DISEASE ETIOLOGY

Tony Hiu-Fung LAM[1] *Che To Jimmy Lai*[1] *Grace Wong*[1] *Vincent Wong*[1] *Terry Cheuk-Fung Yip*[1]

[1]*The Chinese University of Hong Kong*

Background: Baveno VII consensus suggests discontinuing NSBBs in patients with cirrhosis whose primary etiological factor has been removed or controlled if liver stiffness measurement (LSM) is <25 kPa and endoscopy no longer shows any varices. We evaluated the safety of this recommendation. **Methods:** Patients who underwent vibration-controlled transient elastography (VCTE) at Prince of Wales Hospital from August 2005 to December 2022 were included. Baseline date was defined as the first date of stopping NSBB, or a random date after VCTE for NSBB continuous users and non-users. Patients with hepatocellular carcinoma or hepatic decompensation before or <180 days after baseline were excluded. NSBB use was defined as ≥28 days of cumulative use with ≥2 prescriptions. Stopping NSBB referred to ≥28 days of cessation without a subsequent prescription. Patients were followed until hepatic decompensation, death, or restarting NSBB for those who stopped, whichever earlier; non-liver-related death was considered a competing event. **Results:** Among 4,748 patients (mean age 55.1±12.2 years, 45.2% females, mean LSM 7.1±5.1 kPa, 37.7% viral hepatitis, 41.4% metabolic dysfunction-associated steatotic liver disease), 77 (1.6%) developed hepatic decompensation at a median (IQR) follow-up of 4.4 (2.0-9.5) years. Among 4,464 NSBB non-users, 110 continuous users, and 174 patients who stopped NSBB, 57, 18, and 2 developed hepatic decompensation, respectively; the corresponding 5-year cumulative incidence of hepatic decompensation (95% CI) was 1.3% (1.0%-1.7%), 18.9% (11.3%-27.9%), and 1.5% (0.1%-7.2%) (Figure 1A). Compared to NSBB non-users, patients who stopped NSBB had a similar risk of hepatic decompensation (adjusted cause-specific hazard ratio [CSHR] 1.08 [95% CI 0.26-4.47]), while NSBB continuous users had a higher risk (adjusted CSHR 3.40 [95% CI 1.98-7.94]). Similar results were shown among 680 patients with LSM ≥10 kPa (adjusted CSHR 0.71 [95% CI 0.10-5.33]) for patients who stopped NSBB vs NSBB non-users). Patients with LSM ≥10 kPa fulfilling Baveno VII criteria had a comparable risk of hepatic decompensation (adjusted CSHR 1.25 [95% CI 0.44-3.54]) than those with LSM <10 kPa (Figure 1B). **Conclusion:** Patients with cirrhosis and removed or suppressed primary etiological factor may safely stop NSBBs. Their subsequent risk of hepatic decompensation is similar to those who did not require NSBBs.

A



B

Parameters	Univariate analysis		Multivariable analysis	
	CSHR (95% CI)	p value	Adjusted CSHR (95% CI)	p value
Continuous NSBB (vs No NSBB)	21.123 (12.381–36.040)	<0.001	3.397 (1.983–7.935)	<0.001
Stopped NSBB (vs No NSBB)	1.592 (0.3678–6.535)	0.519	1.077 (0.260–4.468)	0.919
LSM 10-14.9 kPa and platelets ≥150x10^9/L (vs LSM <10kPa)	1.527 (0.542–4.305)	0.423	1.247 (0.440–3.538)	0.677
LSM 15-24.9 kPa and/or platelets <150 x10^9/L (vs LSM <10kPa)	9.036 (5.201–15.699)	<0.001	3.087 (1.628–5.854)	<0.001
LSM ≥25 kPa (vs LSM <10kPa)	47.095 (26.793–82.779)	<0.001	9.401 (4.300–20.271)	<0.001
Age (year)	1.053 (1.032–1.074)	<0.001	1.054 (1.028–1.079)	<0.001
Male gender	1.371 (0.865–2.174)	0.179		
Body mass index (kg/m^2)	0.985 (0.936–1.033)	0.543		
MASLD (vs viral hepatitis)	0.444 (0.264–0.748)	0.002	0.640 (0.357–1.148)	0.135
Other CLD (vs viral hepatitis)	0.465 (0.246–0.882)	0.189	0.981 (0.496–1.940)	0.956
HCC during follow-up*	35.363 (22.264–56.12)	<0.001	9.834 (5.661–17.086)	<0.001
Diabetes	0.934 (0.591–1.477)	0.772		
Hypertension	1.308 (0.834–2.051)	0.242		
Alanine aminotransferase (U/L)	1.001 (0.999–1.003)	0.381		
ALP (U/L)	1.004 (1.003–1.005)	<0.001	1.004 (1.002–1.006)	<0.001
INR	1.066 (0.896–1.268)	0.472		
Creatinine (μmol/L)	1.002 (1.000–1.005)	0.079		

Abbreviations: CI = confidence interval, CLD = chronic liver disease, CSHR = cause-specific hazard ratio, HCC = hepatocellular carcinoma, INR = international normalised ratio, LSM = liver stiffness measurement, MASLD = metabolic dysfunction-associated steatotic liver disease.
* Modelled as time-dependent covariate

Disclosures: Tony Hiu-Fung LAM: Nothing to Disclose, Che To Jimmy Lai: Nothing to Disclose, Grace Wong: AstraZeneca: Advisor, Gilead Sciences: Advisor, Gilead Sciences: Speaking and Teaching, Janssen: Advisor, GSK: Advisor, GSK: Speaking and Teaching, Abbott: Speaking and Teaching, AbbVie: Speaking and Teaching, AstraZeneca, Gilead Sciences, GlaxoSmithKline and Janssen,: Advisor, Abbott, AbbVie, Ascletis, Bristol-Myers Squibb, Echosens, Gi: Speaking and Teaching, Gilead Sciences: Grant/Research Support, AstraZeneca, Gilead Sciences, GlaxoSmithKline and Janssen: Consultant, Abbott, AbbVie, Ascletis, Bristol-Myers Squibb, Echosens, Gi: Speaking and Teaching, AstraZeneca, Gilead Sciences, GlaxoSmithKline Pharmaceutical: Consultant, Gilead Sciences: Independent Contractor, AstraZeneca, Gilead Sciences, GSK and Janssen,: Advisor, Abbott, AbbVie, BMS, Gilead Sciences,

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GSK, Janssen, Roche: Speaking and Teaching, Gilead Sciences: Grant/Research Support, Vincent Wong: Abbott: Speaking and Teaching, AbbVie: Advisor, AbbVie: Speaking and Teaching, Boehringer Ingelheim: Advisor, Echosens: Advisor, Echosens: Speaking and Teaching, Gilead Sciences: Advisor, Gilead Sciences: Speaking and Teaching, Gilead Sciences: Grant/Research Support, Intercept: Advisor, Inventiva: Advisor, Novo Nordisk: Advisor, Novo Nordisk: Speaking and Teaching, Pfizer: Advisor, Sagimet: Advisor, TARGET PharmaSolutions: Advisor, Unilab: Speaking and Teaching, Visirna: Consultant, Illuminatio Medical Technology: Stock – privately held company, Terry Cheuk-Fung Yip: Gilead Sciences: Consultant, Gilead Sciences: Advisor, Gilead Sciences: Speaking and Teaching

4118 | EVALUATION OF ESOPHAGEAL AND GASTRIC VARICES IN CIRRHOTIC PATIENTS WITH PORTAL HYPERTENSION: A CENTRAL EVALUATION SYSTEM FOR CLINICAL RESEARCH

Pol Boudes[1] Edward Mena[2] Zaree Babakhanian[3] Seth Zuckerman[4] Khurram Jamil[4] Naim Alkhouri[5]

[1]Galectin Therapeutics, [2]California Liver Reasearch Institiute, [3]Genesis Healthcare Partners, [4]Galectin Therapeutics, Inc., [5]Arizona Liver Health

Background: In cirrhotic patients, bleeding from esophageal and gastric varices can be life-threatening. Portal hypertension (PH) plays a major role in their development and varices can bleed at an earlier stage compared to other decompensation events such as ascites, hepatic encephalopathy, and hepato-renal syndrome. The primary prevention of esophageal varices could be a useful efficacy outcome measure to evaluate candidate drugs and, contrary to liver biopsies or portal pressure measurement, screening esophago-gastro-duodenal endoscopies (EGDs) are routinely performed in cirrhotic patients. The diagnosis of varices could be subjective, and we implemented an evaluation system for clinical research. **Methods:** NAVIGATE is an ongoing phase 2b/3 study of belapectin in patients with MASH cirrhosis and PH (NCT04365868). EGDs are performed by qualified local endoscopists according to specific recommendations and are video recorded on a proprietary system (Clario). Videos are distributed and centrally read within 24 hours on a secure web-based system by six qualified MD reviewers, additionally trained for this study regarding the presence, size, and location of varices. Each video is evaluated by two primary reviewers (*Prim*). If both *Prim* agree on the absence/presence and size of varices, a final diagnosis is made. If there is a disagreement on presence or size, a third reviewer (*Adj*) adjudicates to establish the final call. All six reviewers are *Prim* and 3 of them also serve as *Adj*. Reviewers are blinded to patients information, drug treatment, EGD sequence, and local read results. For a repeat video in the same patient, the same reviewers are used. **Results:** As of 4/2024, 854 EGDs videos provided 2,035 central reads, 1,708 (84%) *Prim* reads and 327 (16%) *Adj* reads (Table). Individual *Prim* readers evaluated a mean of 240 videos and *Adj* readers evaluated an additional mean of 109 videos. Of the 1,708 *Prim* reads, an EV was called 460 (27%) time and GV in 50 (3%) time. The N (%) of *Prim* read triggering *Adj*, and the result of Adj are presented in the Table. Of the 327 *Adj* read, 198 were for the presence of EV/GV and 68 for EV size. 5/6 readers had consistent assessment metrics. One reader called more EV/GV and larger EV and triggered more *Adj* to correct the call. **Conclusion:** Our adjudication system was able to address inter observer variability in the diagnosis of esophageal and gastric varices.

Table: Primary review and adjudication of esophageal and gastric varices

	Prim 1	Prim 2	Prim 3	Prim 4 Adj 1	Prim 5 Adj 2	Prim 6 Adj 3	Total
Prim Reads	304	261	282	288	290	283	1708
No EV	260 (86)	99 (38)	219 (78)	204 (71)	224 (77)	214 (76)	1220
EV	42 (14)	160 (61)	59 (21)	81 (28)	60 (21)	58 (21)	460
Other	2 <1	2 <1	4 (1)	3 (1)	6 (2)	11 (3)	28
No GV	298 (98)	228 (87)	268 (95)	269 (93)	275 (95)	259 (92)	1597
GV	4 (1)	23 (9)	8 (3)	6 (2)	2 (1)	7 (3)	50
Other	2 (1)	10 (10)	6	13 (5)	13 (4)	17 (5)	61
Adj needed	88 (29)	160 (61)	78 (28)	119 (41)	107 (37)	102 (36)	654
Adj confirms	50 (57)	44 (28)	48 (62)	71 (60)	57 (53)	59 (58)	329
Adj denies	38 (43)	116 (73)	30 (39)	48 (40)	50 (47)	43 (42)	325

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4119 | EXPLORATION FOR NON-INVASIVE SURROGATE MARKERS FOR HEPATIC VENOUS PRESSURE GRADIENT IN PORTAL HYPERTENSION AND STRATIFICATION OF LONG-TERM PROGNOSIS

Tatsuro Nishimura[1] *Tsuyoshi Ishikawa*[1]

[1]*Yamaguchi University*

Background: The hepatic venous pressure gradient (HVPG) is one of the most useful tools for diagnosing the severity of portal hypertension and evaluating the risk of cirrhotic complications. Clinically significant portal hypertension (CSPH) is defined as HVPG ≥10 mmHg, severe portal hypertension (SPH) as HVPG ≥12 mmHg, and very severe portal hypertension (VSPH) as HVPG ≥16 mmHg. However, since HVPG measurement is invasive, this study aimed to statistically identify non-invasive surrogate markers. Furthermore, we examined the long-term prognosis using these surrogate markers. **Methods:** 104 patients with portal hypertension who underwent HVPG (mean age: 65.0 years, male/female: 49/55, etiology of hepatitis B virus/hepatitis C virus/ alcohol/ metabolic dysfunction-associated steatohepatitis/other: 2/49/27/7/19, Child-Pugh class A/B/C: 57/40/7, mean HVPG: 11.5 mmHg) at our hospital were enrolled in this retrospective study. Statistical analysis identified the correlation between HVPG and various parameters, as well as the factors defining CSPH, SPH, and VSPH. These factors were then used to perform a survival analysis. **Results:** Correlation analysis showed that the strongest correlation with HVPG was liver stiffness (LS) measured by transient elastography ($r=0.68$, $p<0.01$), followed by 7S domain of type IV collagen ($r=0.44$, $p<0.01$) and splenic volume ($r=0.43$, $p<0.01$). The correlation between LS and HVPG remained significant in the SPH and VSPH group with high HVPG. Multivariate analysis showed that LS was the only significant independent factor defining CSPH, SPH and VSPH. A multivariate analysis with receiver operating characteristic curve analyses identified LS levels as only significantly independent factor defining CSPH, SPH and VSPH ($p<0.01$), with optimal cut-offs of 20.0kPa (AUROC: 0.81), 24.6kPa (AUROC: 0.83) and 32.9kPa (AUROC: 0.87), respectively. In each case, there was a significant difference in survival among the three groups as well ($p<0.05$). Although it has been previously reported that the correlation between HVPG and LS decreases with increasing HVPG, this study demonstrated a significant positive correlation with LS irrespective of the severity of portal hypertension, and a significant association with survival was also established. **Conclusion:** LS represents a useful non-invasive surrogate marker for HVPG in cases of portal hypertension and can stratify survival and predict long-term prognosis similarly to HVPG.

Disclosures: Tatsuro Nishimura: Nothing to Disclose, Tsuyoshi Ishikawa: Nothing to Disclose

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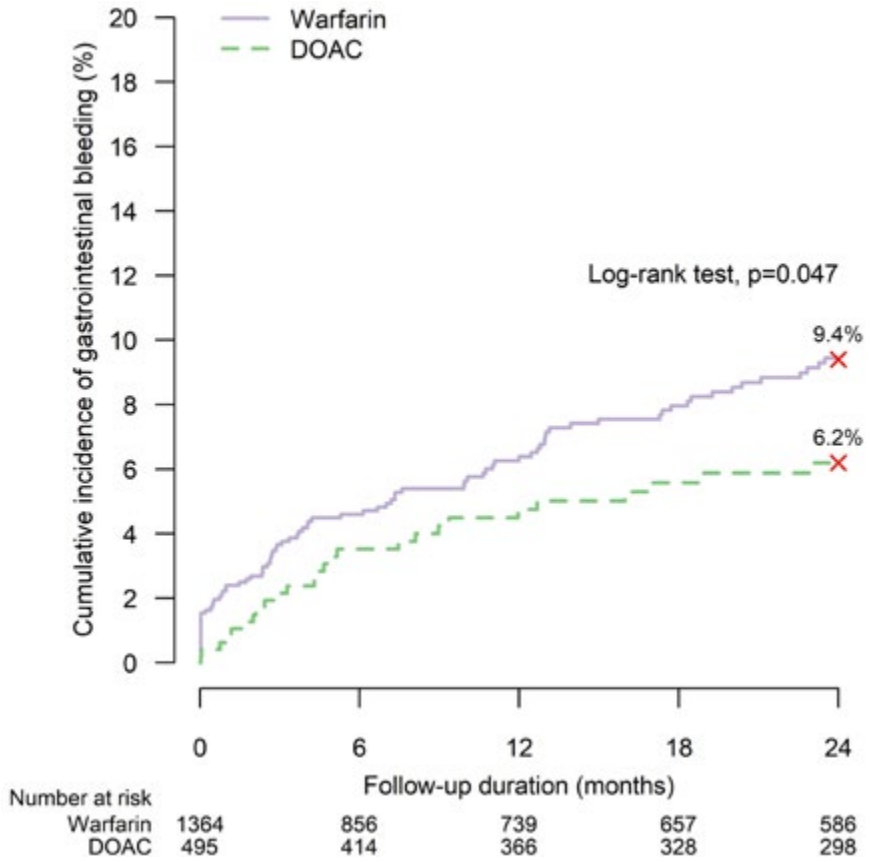
4120 | LOWER RISK OF GASTROINTESTINAL BLEEDING IN PATIENTS WITH CIRRHOSIS WHO HAVE RECEIVED DIRECT ORAL ANTICOAGULANTS (DOACS) COMPARED TO WARFARIN: A TERRITORY-WIDE COHORT STUDY

Yichong JIANG[1] *Lilian Yan Liang*[1] *Xiang Xiao*[1] *Che To Jimmy Lai*[1] *Terry Cheuk-Fung Yip*[1] *Vincent Wai-Sun Wong*[1] *Grace Wong*[1]

[1]*The Chinese University of Hong Kong, Hong Kong*

Background: With an aging population and a pro-thrombotic state, patients with cirrhosis often have indications for anticoagulation. In recent years, DOACs have become the preferred anticoagulant in many clinical contexts, but their safety in cirrhosis remains unclear. This study aims to evaluate the risk of gastrointestinal bleeding (GIB) in patients with cirrhosis who have received warfarin and DOACs. **Methods:** This territory-wide, retrospective cohort study included 31,542 patients with cirrhosis diagnosed in Hong Kong between 2000 and 2020. Clinical, laboratory, and medication data were collected. Warfarin and DOAC users were defined as those prescribed these medications for 4 weeks or more. GIB was identified based on ICD-9-CM diagnosis codes. **Results:** Among the 31,542 cirrhotic patients, 1,364 received warfarin (mean age 67.4±13.1 years, 64.1% males), and 495 received DOACs (mean age 74.1±11.0 years, 58.6% males, 429 on apixaban, 135 on rivaroxaban, 218 on dabigatran, and 58 on edoxaban). GIB occurred in 116 (6.2%) patients (90 DOAC users and 26 warfarin users) at a median follow-up of 1.7 years (IQR 0.3-4.8). 71 (61.2%) cases were of upper gastrointestinal (GI) bleeding, while 45 (38.8%) involved lower GI bleeding. The 2-year cumulative incidence of GIB were 9.4% (95% CI 7.4%-11.4%) in the warfarin cohort and 6.2% (95% CI 3.8%-8.6%) in the DOAC cohort (log-rank test, p=0.047; Figure 1). In the multivariable Cox model, lower baseline hemoglobin (adjusted hazard ratio 0.78, 95% CI 0.71-0.86, p<0.001) was the only independent risk factor for GIB. **Conclusion:** Among patients with cirrhosis, DOAC users have a lower risk of GIB than warfarin users. Lower baseline hemoglobin level is an independent risk factor of GIB.



Disclosures: Yichong JIANG: Nothing to Disclose, Lilian Yan Liang: Nothing to Disclose, Xiang Xiao: Nothing to Disclose, Che To Jimmy Lai: Nothing to Disclose, Terry Cheuk-Fung Yip: Gilead Sciences: Consultant, Gilead

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Sciences: Advisor, Gilead Sciences: Speaking and Teaching, Vincent Wai-Sun Wong: Nothing to Disclose, Grace Wong: AstraZeneca: Advisor, Gilead Sciences: Advisor, Gilead Sciences: Speaking and Teaching, Janssen: Advisor, GSK: Advisor, GSK: Speaking and Teaching, Abbott: Speaking and Teaching, AbbVie: Speaking and Teaching, AstraZeneca, Gilead Sciences, GlaxoSmithKline and Janssen,: Advisor, Abbott, AbbVie, Ascletis, Bristol-Myers Squibb, Echosens, Gi: Speaking and Teaching, Gilead Sciences: Grant/Research Support, AstraZeneca, Gilead Sciences, GlaxoSmithKline and Janssen: Consultant, Abbott, AbbVie, Ascletis, Bristol-Myers Squibb, Echosens, Gi: Speaking and Teaching, AstraZeneca, Gilead Sciences, GlaxoSmithKline Pharmaceutical: Consultant, Gilead Sciences: Independent Contractor, AstraZeneca, Gilead Sciences, GSK and Janssen,: Advisor, Abbott, AbbVie, BMS, Gilead Sciences, GSK, Janssen, Roche: Speaking and Teaching, Gilead Sciences: Grant/Research Support

4122 | SLEEP DISTURBANCE AND IMPACT ON HEALTH-RELATED QUALITY OF LIFE, FRAILTY, AND MINIMAL HEPATIC ENCEPHALOPATHY IN THAI CIRRHOTIC PATIENTS: A CROSS-SECTIONAL STUDY

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[1]Prince of Songkla University -, [2]Stanford University Medical Center

Background: Sleep disturbance is prevalent in cirrhosis and may significantly affect clinical outcomes. Little is known about the prevalence of sleep disturbance among Thai cirrhotic patients and its association with health-related quality of life (HRQoL), frailty, and minimal hepatic encephalopathy (MHE). **Methods:** We conducted a single-center cross-sectional study involving adult cirrhotic patients in an outpatient setting at a university hospital in Thailand. Exclusion criteria were active alcohol intake, coexisted malignancy, and current use of psychoactive medication. Frailty was assessed by the Liver Frailty Index. Sleep disturbance was evaluated using the Pittsburgh Sleep Quality Index (PSQI) and the Epworth Sleepiness Scale (ESS). Sleep parameters were monitored for two consecutive weeks using XiaoMi® Band 7 (MB). HRQoL was assessed using the EQ-5D-5L questionnaire, and MHE was evaluated using the Thai version of the Psychometric Hepatic Encephalopathy Score (PHES). **Results:** A total of 89 participants were included; the mean age was 61.2±10.5 years, 50 (56.2%) were male, and 72 (81%) were Child-Pugh class A. The most common etiology was chronic hepatitis B, followed by alcohol-related and metabolic dysfunction-associated steatotic liver disease, respectively. Frailty was present in 22.5%, while MHE was detected in 23.6% of the patients. The prevalence of poor sleep, determined by the PSQI, was 38.2%. Participants who had poor sleep exhibited slightly higher creatinine levels than those who did not (median [IQR] 0.9 [0.8-1.1] vs. 0.8 [0.7-1.0], p=0.041). However, the HRQoL was not different. Regarding sleep parameters, participants with frailty had significantly less time in bed (mean±SD 5.8±2 vs. 6.7±1.2 h, p=0.032) and shorter duration of nightly REM sleep (median [IQR] 0.7 [0.6-0.8] vs. 1.2 h [1-1.4], p=0.004). The multivariable analysis adjusted for age revealed that nightly REM sleep time, rather than total sleep time, was significantly associated with lower odds of frailty (adjusted OR [95%CI] 0.08 [0.01-0.99], p=0.03). And patients with MHE had less deep sleep time than those without (1.1 [0.9-1.2] vs. 1.3 [1-1.6] hours, p=0.035). **Conclusion:** The prevalence of sleep disturbance in Thai cirrhotic patients was lower than previously reported from Western countries. The total sleep time was not significantly associated with frailty, but frail participants exhibited significantly less REM sleep, while those with MHE had reduced deep sleep duration.

Disclosures: Naichaya Chamroonkul: Nothing to Disclose, Apichat Kaewdech: Nothing to Disclose, Pimsiri Sripongpun: Nothing to Disclose, Poorikorn Feuangwattana: Nothing to Disclose

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4123 | RELATIONSHIP BETWEEN PORTOSYSTEMIC SHUNTS AND LIFE PROGNOSIS OF CHRONIC LIVER DISEASE AND POPH

Yuki Tanaka[1] Hiroyuki Nakanishi[2] Masayuki Kurosaki[2] Mina Taguchi[2] Yudai Yamazaki[2] Naoki Uchihara[2] Shohei Kimura[2] Junko Yagita[2] Taisei Keitoku[2] Risa Okada[2] Mayu Higuchi[2] Kenta Takaura[2] Shohei Tanaka[2] Chiaki Maeyashiki[2] Nobuharu Tamaki[2] Yutaka Yasui[2] Kaoru Tsuchiya[2] Namiki Izumi[2]

[1]Division of Gastroenterology, Musashino Red Cross Hospital, [2]Division of Gastroenterology, MRCH

Background: We have been investigating the usefulness of portosystemic shunt diameter in the diagnosis of PoPH. In addition, it is assumed that complications related to the portosystemic shunt have a significant impact on prognosis in the treatment of chronic liver disease. In this study, we examined whether the portal shunt diameter is useful in predicting the prognosis of patients with chronic liver disease and the development of pulmonary hypertension. **Methods:** From Jan/2018 to Feb/2023 436 patients with chronic liver disease were included. The diameter of the portosystemic shunts was measured by imaging studies, and its relationship with pulmonary hypertension and survival was investigated. TRPG ≥ 30 mmHg was considered a surrogate marker of pulmonary hypertension. **Results:** 436 patients had a mean age of 72±12, Child A 109, B 125, C 62. 296 patients (68%) had portosystemic shunts, with a median diameter of 6.2 (1.2-32.9) mm. Portosystemic shunts were segregated into Porto-azygos shunt (130/43.9%), Gastro-renal shunt (43/14.5%), Spleno-renal shunt (55/18.6%) and others (68/23.0%). A history of treatment for hepatocellular carcinoma was observed in 64% of the patients. Patients with portosystemic shunt ≥5 mm in diameter had a significantly poorer prognosis than those without, with a 3-year survival rate of 37.6% vs. 54.1% (p=0.020). In multivariate analysis of other factors, CRP≥0.5 mg/dL, creatinine≥1.5 mg/dL, history of hepatocellular carcinoma treatment, and ascites were independent prognostic factors. Patients with portosystemic shunt ≥6.8 mm in diameter had a greater proportion of high TRPG ≥30 mmHg compared to those without (OR 2.77, 95% CI 1.43-5.34, p value 0.002). In multivariate analysis with other factors, it was an independent associated factor along with BNP >122 pg/mL (OR 6.64□95%CI 3.38-13.0□p value <0.001). No association was found between the location of the portosystemic shunts and survival. On the other hand, in patients with low BNP levels, the presence of a shunt that drains into the renal vein was a better predictor of TRPG≥30 mmHg than the diameter of the portosystemic shunts. **Conclusion:** The diameter of the portal circulatory shunt can be a predictor of prognosis and pulmonary hypertension in patients with chronic liver disease. The location of the portosystemic shunts may also assist in predicting pulmonary hypertension.

Disclosures: Yuki Tanaka: Nothing to Disclose, Hiroyuki Nakanishi: Nothing to Disclose, Masayuki Kurosaki: Nothing to Disclose, Mina Taguchi: Nothing to Disclose, Yudai Yamazaki: Nothing to Disclose, Naoki Uchihara: Nothing to Disclose, Shohei Kimura: Nothing to Disclose, Junko Yagita: Nothing to Disclose, Taisei Keitoku: Nothing to Disclose, Risa Okada: Nothing to Disclose, Mayu Higuchi: Nothing to Disclose, Kenta Takaura: Nothing to Disclose, Shohei Tanaka: Nothing to Disclose, Chiaki Maeyashiki: Nothing to Disclose, Nobuharu Tamaki: Nothing to Disclose, Yutaka Yasui: Nothing to Disclose, Kaoru Tsuchiya: Chugai: Speaking and Teaching, AstraZeneca: Speaking and Teaching, Eisai: Speaking and Teaching, Takeda: Speaking and Teaching, Namiki Izumi: Nothing to Disclose

4124 | SURVIVAL OF PATIENTS WHOSE INITIAL ACUTE DECOMPENSATION WAS HEPATIC ENCEPHALOPATHY

Sasha Feradji[1] Isaac Ruiz[2] Mélanie Tremblay[3] Julian Hercun[4] Crystèle Hogue[3] Julien Bissonnette[5] Catherine Vincent[1] Chantal Bemeur[1] Christopher Rose[6]

[1]CHUM, [2]Centre Hospitalier de l'Universite de Montreal, [3]CRCHUM, [4]National Institutes of Health, [5]University of Montreal Hospital Center, [6]University of Montreal

Background: Initial occurrence of acute decompensation (AD) in cirrhosis is associated with increased mortality. Therefore, AD is a major turning point in the natural history of cirrhosis. AD can present as hepatic encephalopathy (HE), ascites, jaundice, variceal bleeding and liver cancer. The aim of this study was to determine the impact of HE as AD event on survival of patients with cirrhosis. **Methods:** A retrospective analysis of all consecutive patients admitted to our liver unit at the Centre hospitalier de l'Université de Montréal (CHUM) between January and December 2016 was performed. Patients without cirrhosis and/or with a history of liver

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transplantation were excluded. Only patients with cirrhosis admitted for their first AD were included and classified according as HE, and non-HE (ascites, variceal bleeding or liver cancer). Clinical and biological characteristics of patient at the moment of the admission were collected. Survival after AD was collected over a 2-year period. **Results:** During the study period, 635 patients were hospitalized, including 106 for AD. Among them, 12/106 (11.3%) were admitted for HE, 32/106 (30.2%) for ascites, 23/106 (21.7%) for variceal bleeding, and 39/106 (36.8%) for liver cancer. The mean age was 63.5 (57.8-69.7) years, 70 (66%) were male, 35.8% of patient had alcohol-related liver disease, 29.2% NASH, 22.7% hepatitis B or C, and 10.3% autoimmune liver disease. HE group: Mean age was 60.5 (54.9-69.3) years, 5/12 (42%) were male, 33.3% of patient had alcohol-related liver disease, 25.0% NASH, 8.3% hepatitis B or C, and 9.4% autoimmune liver disease. At the time of admission, the following liver-related complications were present: 3/12 (25%) had ascites, 6/12 (50%) had varices, 1/12 (8.3%) developed hepato-renal syndrome, and 1/12 (8.3%) developed hepato-pulmonary syndrome. The HE group had significantly lower levels of white blood cells ($4.3x10^9$/L, 93.4-6.2; p=0.047) and platelets ($62.5x10^9$/L, 46.0-105.5; p=0.005) compared to the non-HE group. Figure 1 shows the 2-year Kaplan-Meyer transplant-free survival according to the type of AD. Two-year survival is significantly better in the HE group (90%) compared to the non-HE group (52%) (p<0.05). **Conclusion:** Our results suggest that patients with AD as HE have distinct clinical, biological, and survival characteristics compared to non-HE. Patients with first AD as HE present a lower risk of 2-year mortality compared to non-HE.

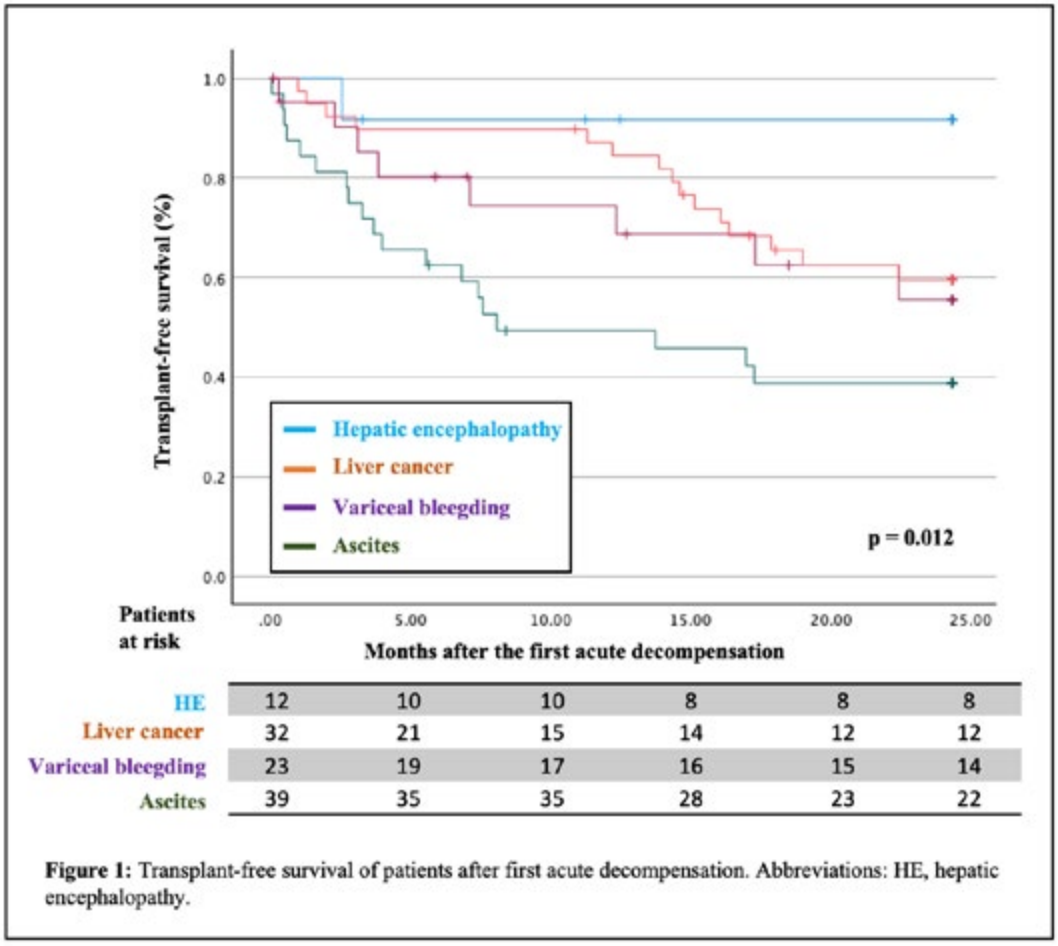

Figure 1: Transplant-free survival of patients after first acute decompensation. Abbreviations: HE, hepatic encephalopathy.

Disclosures: Sasha Feradji: Nothing to Disclose, Isaac Ruiz: Nothing to Disclose, Mélanie Tremblay: Nothing to Disclose, Julian Hercun: Nothing to Disclose, Crystèle Hogue: Nothing to Disclose, Julien Bissonnette: Nothing to Disclose, Catherine Vincent: Nothing to Disclose, Chantal Bemeur: Nothing to Disclose, Christopher Rose: Nothing to Disclose

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4125 | IN PATIENTS WITH COMPENSATED MASH CIRRHOSIS WITH PLATELET COUNT < 150,000/µL AND RADIOLOGIC FINDINGS OF PORTAL HYPERTENSION, A THIRD ARE IDENTIFIED WITH ESOPHAGEAL VARICES ON SCREENING ESOPHAGO-GASTRODUODENOSCOPY

Alma Laura Ladron de Guevara Cetina[1] *Nadege Gunn*[2] *Ingolf Schiefke*[3] *Jaideep Behari*[4] *Pol Boudes*[5] *Khurram Jamil*[5] *Seth Zuckerman*[5] *Rifaat Safadi*[6]

[1]*Consultorio Médico Dra. Ladron de Gueva,* [2]*Impact Research Institute,* [3]*EUGASTRO GmbH,* [4]*University of Pittsburgh School Medicine,* [5]*Galectin Therapeutics,* [6]*Hadassah Ein Karem Hospital*

Background: A low platelet count in patients with metabolic dysfunction-associated steatohepatitis (MASH) points to the presence of cirrhosis complicated by portal hypertension (PH). There are limited data regarding the incidence of esophageal varices in this population. We present data from NAVIGATE, a phase 2b/3 trial designed to evaluate Belapectin, a galectin-3 inhibitor, for the primary prevention of esophageal varices (NCT04365868). **Methods:** Subjects underwent a screening esophago-gastroduodenoscopy (EGD) once a diagnosis of compensated MASH cirrhosis with PH was established. PH was diagnosed with clinical, hematologic, and imaging signs. Patients for whom cirrhosis or PH could not be confirmed were screen failed. EGD video recordings were centrally evaluated. Patients with varices were screen failed while patients without varices were randomized. **Results:** Out of 1067 subjects screened, 555 (52%) screened failed for lack of confirmed cirrhosis or PH. Of the 512 subjects who underwent EGD, 155 (30%) were diagnosed with varices, and 357 (70%) without varices were randomized. Baseline demographic characteristics, liver enzymes and Hba1c were similar for screen failures without EGD, screen failures due to varices, or randomized subjects (Table). Mean platelet count was lower than guideline recommended threshold of PH in both screen failure due to presence of varices and randomized subjects, and significantly lower compared to screening failure for other reasons (120 x10^3/µL ($p < 0.0001$), 133.8 x 10^3/µL ($p=0.0303$) respectively. EGDs were well tolerated and appeared safe. FIB-4 was also significantly higher in those who screen failed with varices compared to randomized subjects. **Conclusion:** In this prospectively enrolled cohort of patients with compensated MASH cirrhosis with imaging findings of portal hypertension, platelet count below 150 x 10^3/µL was associated with EGD-determined esophageal varices in one third of patients.

Screening Parameter#	SF – no EV*	SF – EV**	Randomized	All Screened
Number of subjects screened (%)	555 (52)	155 (14.5)	357 (33.5)	1067(100)
Age (years)	59.7±9.6	61.1±8	60.1±8.8	60.0±9.1
	0.558	0.224		
Female n (%)	313 (56.4)	92 (59.4)	232 (65)	637 (59.7)
	0.0098	0.2246		
Hispanic n (%)	210 (37.8)	62 (40)	109 (30.5)	381 (35.7)
	0.0239	0.0369		
White n (%)	494 (89)	148 (95.5)	325 (91)	967 (90.6)
	0.3234	0.0613		
MELD	8.1±2.4	8±1.6	7.9±1.5	8±2
	0.1590	0.3646		
Platelets (x10^3/µL)	163±74.1	120±45.7	134±46.8	146.5±71
	< 0.0001	0.0218		
AST U/L	43±31.7	41.7±18.4	43.5±22.6	43±26.9
	0.8280	0.5050		
ALT U/L	40±26.1	37.2±16.6	41.2±26.6	40.1±25.1
	0.5283	0.0948		
Fib-4	3.2±2.5	4±2	3.5±1.9	3.5±2.3
	0.1079	0.0148		
HbA1C %	6.7±1.7	6.6±1.3	6.3±1.2	6.5±1.5
	0.0010	0.1090		
Albumin (g/dL)	4.4±0.4	4.4±0.4	4.4±0.4	4.4±0.4
	0.2992	0.2328		
Bilirubin (mg/dL)	0.8±0.6	0.8±0.4	0.8±0.4	0.8±0.5
	0.0980	0.1166		
Creatinine (mg/dL)	0.8±0.2	0.8±0.2	0.7±0.2	0.8±0.2
	0.12	0.5062		
INR	1.1±0.2	1.1±0.2	1.1±0.2	1.1±0.2
	0.9682	0.4995		

P values comparing each parameter in screen failure with varices and without varices to randomized subjects is presented in a row below each parameter.
*SF-no EV: Screen failure for other reasons, but no varices detected at EGD
**SF-EV: Screen failure due to presence of esophageal varices
All values are expressed as mean ± standard deviation (SD) unless otherwise specified.

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4126 | CHRONIC PULMONARY ASPERGILLOSIS ON A RISE IN LIVER DISEASE PATIENTS: STUDY OF PREVALENCE, ANTIFUNGAL PROFILE AND PREDICTORS OF MORTALITY FROM TERTIARY CARE CENTRE IN INDIA

PRATIBHA RAMCHANDRA KALE[1] *VIKAS KHILLAN*[1] *DEBAJYOTI BHATTACHARYA*[1] *Saggere Muralikrishna Shasthry*[1]

[1]*Institute of Liver and Biliary Sciences*

Background: Chronic pulmonary aspergillosis (CPA) is an neglected cause of respiratory disease even in high Tuberculosis (TB) burden countries like India . It is an term that includes simple aspergilloma, chronic cavitary pulmonary aspergillosis which is the most common variant that presents with formation of lung cavities with or without an aspergilloma or nodules, and chronic fibrosing pulmonary aspergillosis. CPA is a chronic progressive infection that destroys lung tissue in non-immunocompromised patients. There is a high prevalence of pulmonary tuberculosis in patients with liver disease (LD). They are predisposed to fungal infections due immune dysregulation. Rise in drug resistance, hepatotoxity due to antifungal drugs makes therapeutic management difficult. Hence, we studied the prevalence of CPA in liver disease patients with respect to spectrum of infections, antifungal susceptibility profile and outcome. **Methods:** A cohort of 2250 liver disease patients with isolation of Aspergillus in respiratory samples, was analysed retrospectively for the diagnosis of with CPA, from June 2018 to June 2023. The demographic characteristics, clinical, radiological and laboratory objective and subjective variables including age, sex, previous pulmonary conditions, dyspnoea score, quality of life, serum albumin and ESR etc were assessed using Kaplan–Meier curves, log rank tests and Cox proportional hazards modelling. In samples of patients, retrospective review of time from likely onset of CPA to referral and cause of death were also investigated. **Results:** CPA was confirmed in 16% of the patients. Survival was 72%, at 1 year. Increased mortality was associated with chronic obstructive pulmonary disease (hazard ratio 2.57; p=0.029), nontuberculous mycobacterial infection (2.04; p<0.001) and increasing age (1.03, p<0.001), lower albumin (0.92, per g/L), underlying chronic liver disease (2.07; p<0.001) were significantly associated with CPA. The aspergillus species isolated were A. flavus (66%), A. fumigatus (31%), Aspergillus nidulans (1%), A. terreus (1%) and other aspergillus species (1%). All the isolates were sensitive to echinocandins and amphotericin B. Azole resistance was detected in 3% isolates. Multiple pulmonary lesions were more common (73%) than single cavitary lesion. Mortality was seen in 64% of cases. **Conclusion:** CPA pulmonary aspergillosis is a common complication and cause of mortality in post cavitary pulmonary disease. Several factors impact on mortality of CPA, and can be evaluated as tools to assess CPA prognosis. As there is rise in azole resistance, appropriate diagnosis and antifungal sensitivity testing should be done in all suspected cases.

Disclosures: PRATIBHA RAMCHANDRA KALE: Nothing to Disclose, VIKAS KHILLAN: Nothing to Disclose, DEBAJYOTI BHATTACHARYA: Nothing to Disclose, Saggere Muralikrishna Shasthry: Nothing to Disclose

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4127 | GLOBAL SOCIOECONOMIC DISPARITIES AFFECT ACUTE KIDNEY INJURY OUTCOMES IN HOSPITALIZED PATIENTS WITH CIRRHOSIS: AN ANALYSIS OF THE INTERNATIONAL CLUB OF ASCITES GLOBAL AKI STUDY

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Background: Acute kidney injury (AKI) is the costliest complication in cirrhosis. It's unclear if differences in country level socioeconomic status impacts outcomes in patients with cirrhosis and AKI. We examined the association between country level socioeconomic status and outcomes in a prospective, intercontinental cohort of hospitalized patients with cirrhosis and AKI. **Methods:** Hospitalized patients with cirrhosis were enrolled from 7/2022-5/2023 at 67 centers in 5 continents (Africa, Asia, Europe, North and South America). Socioeconomic status was categorized by WHO Universal Health Coverage Index (UHC) and World Bank Gross National Income (GNI). UHC >80 identified effective universal health coverage and GNI ≥ and <$13845 identified high- and middle/low-income countries, respectively. Outcomes were 28-day mortality and AKI non-resolution. Multivariable models adjusting for demographics, MELD-Na, and AKI severity, were used to analyze the association between UHC, GNI and outcomes. **Results:** Among 3,792 patients enrolled, 1,456 (36%) developed AKI. A total of 573 (39%) patients were from countries with UHC <80, while 657 (45%) patients were from countries with middle/low income. Patients from countries with UHC <80 and middle/low income were younger, had higher rates of hepatitis C, and higher MELD-Na scores compared to patients from countries with UHC ≥80 and high income. There were higher rates of hypovolemic AKI and acute tubular necrosis but lower rates of hepatorenal syndrome in patients from countries with UHC <80 and middle/low income. However, there were no differences in AKI severity and AKI non-resolution rates between UHC and GNI groups. Patients from countries with UHC <80 and middle/low income had higher cumulative incidence of 28-day mortality (Figure) and lower rates of liver transplant (LT) (0.8%

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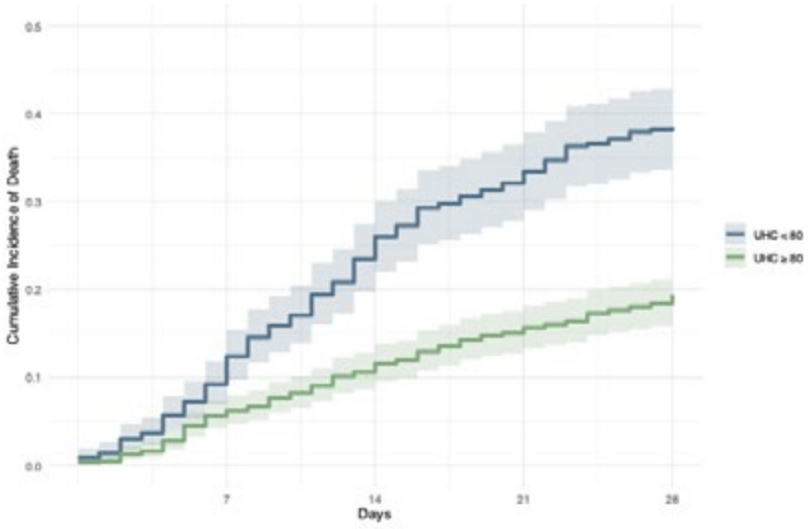
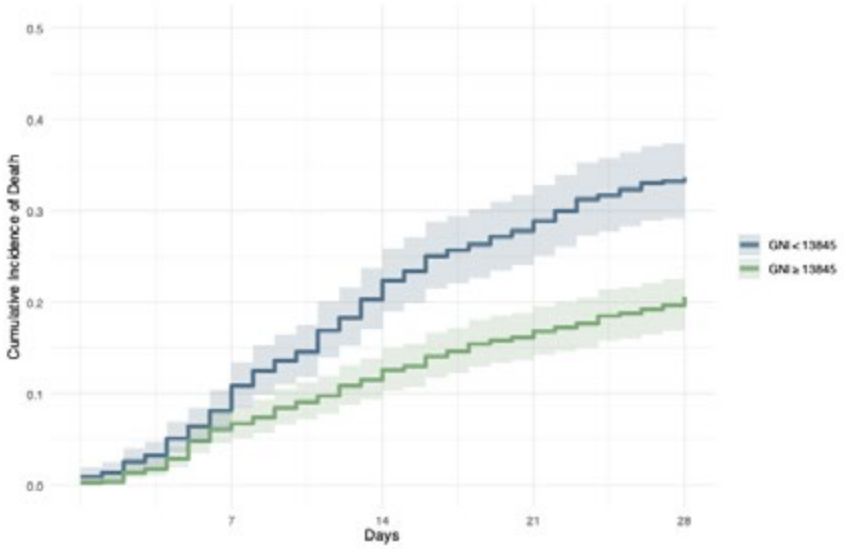
vs. 8.0%, p<0.001). GNI and UHC were found to be highly colinear, and two separate multivariable competing risk models (LT as competing risk) were created to analyze the association of GNI/UHC and 28-day mortality. In both models, UHC <80 and GNI <$13845 were associated with a higher risk of 28-day mortality, sHR 1.73 (p<0.001) and sHR 2.18 (p<0.001), respectively. No associations were found between UHC, GNI and AKI non-resolution on multivariable analysis. **Conclusion:** Patients with cirrhosis and AKI from countries of low-income and UHC <80 have a higher risk of mortality. This might be due to disparities in access to LT and essential hospital services. Policies focusing on improving access to LT and essential hospital services could improve outcomes in this population.

FIGURE

1A: Comparisons Between Universal Health Coverage Index <80 and ≥80 For 28-Day Mortality



1B: Comparisons Between Gross National Income < and >$13845 For 28-Day Mortality



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4128 | IMPACT OF *NOD2* GENOTYPE-GUIDED ANTIBIOTIC PREVENTION ON SURVIVAL IN PATIENTS WITH CIRRHOSIS AND ASCITES: RESULTS OF THE DOUBLE-BLIND RANDOMIZED CONTROLLED I*N*CA TRIAL

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Background: Patients with decompensated cirrhosis are at risk of developing bacterial infections (BI), in particular spontaneous bacterial peritonitis (SBP). Nucleotide-binding oligomerization domain containing 2 (*NOD2*) gene variants impairing intestinal barrier function are risk factors for death and SBP in cirrhosis (Appenrodt et al. *Hepatology* 2010;51:1327-31). **Methods:** We randomly assigned 186 patients with cirrhosis, current or previous ascites and *NOD2* mutations to groups given 400 mg norfloxacin (NOR) or placebo once daily for 12 months (Casper et al. *Trials* 2015;16:83). I*N*CA was publicly funded by the Federal Ministry of Education and Research (BMBF 01KG1201), and patients were recruited at 16 German sites from 2014 to 2021. Relevant

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exclusion criteria were current or previous history of SBP. Patients were stratified for ascites protein content and study site. The primary endpoint is 12-month survival; secondary objectives are the frequencies of SBP and other clinically relevant BI requiring antibiotics. Cox regression with stepwise backward variable selection was performed to identify factors influencing mortality. **Results:** In total, 399 patients were screened to identify the target population, and the final intention-to-treat population comprised 171 patients who obtained at least one dose of NOR or placebo. Dominant etiologies were alcohol-associated liver diseases (71.9%), MASLD (10.5%), and hepatitis C (9.4%). The Kaplan-Meier estimate for 12-month survival was 89.4% for patients receiving NOR and 87.3% for patients receiving placebo; the primary analysis of overall mortality did not demonstrate an advantage of NOR (hazard ratio for death 1.26, p=0.31). The preventive effect of NOR was reflected by shorter mean length of unplanned cirrhosis-associated hospitalizations (8.4±19.8 vs.13.7±33.0 days per year) and less clinically relevant BI in the first 6 months (8.8 vs. 14.5%) without an increase of BI caused by *Clostridioides difficile* or multiresistant bacteria. Ascites, MASLD as etiology, MELD and clinically relevant BI were significantly (p<0.0001) associated with survival. Multivariate Cox regression resulted in a model with BI as the only significant risk factor. **Conclusion:** In a randomized controlled trial of patients with advanced cirrhosis and *NOD2* mutations, NOR did not improve 12-month survival. Despite their genetic risk, patients showed higher than expected survival and ascites resolution rates. NOR might decrease the occurrence of BI that are significantly associated with survival within the first six months. German Clinical Trials Register DRKS-ID 00005616, EudraCT No 2013-001626-26.

Disclosures: Matthias Reichert: Abbvie: Speaking and Teaching, Falk Pharma: Speaking and Teaching, Sanofi: Advisor, Markus Casper: Nothing to Disclose, Alexander Zipprich: Gore: Speaking and Teaching, Falk Foundation: Speaking and Teaching, CLS Behring: Speaking and Teaching, Cristina Ripoll: Nothing to Disclose, Susanne Weber: Nothing to Disclose, Christine Fuhrmann: Nothing to Disclose, Thomas Berg: Nothing to Disclose, Christoph Antoni: Nothing to Disclose, Johannes Kluwe: Nothing to Disclose, Jonel Trebicka: Nothing to Disclose, Tony Bruns: Nothing to Disclose, Andreas Stallmach: Nothing to Disclose, Peter Galle: Bayer: Consultant, Roche: Advisor, Eisai: Advisor, AstraZeneca: Advisor, BMS: Advisor, MSD: Advisor, Guerbet: Advisor, Tobias Goeser: Nothing to Disclose, Christoph Neumann-Haefelin: Nothing to Disclose, Jochen Rädle: Nothing to Disclose, Beate Appenrodt: Nothing to Disclose, Eva Herrmann: Nothing to Disclose, Frank Grünhage: Nothing to Disclose, Frank Lammert: Nothing to Disclose

4129 | INTERCOSTAL CHEST TUBE PLACEMENT TO MANAGE HEPATIC HYDROTHORAX: INCREASING TRENDS DESPITE NEGATIVE IMPACT ON PATIENT MORBIDITY AND SURVIVAL

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[1]University of Louisville, [2]University of Maryland Midtown Campus, [3]University of Maryland, [4]Stanford University Medical Center, [5]University of Kansas Medical Center

Background: Hepatic hydrothorax (HH), pleural effusion in patients with cirrhosis in the absence of primary cardiopulmonary disease, contributes to morbidity in decompensated cirrhosis. Intercostal chest tube (ICT) insertion for HH is not advisable to manage HH due to inability to remove it and its association with complications. However, this procedure is still performed. We conducted this study with the aim to examine trends on the use of ICT and its impact on patient outcomes in hospitalized patients with HH. **Methods:** National Inpatient Sample (NIS) database was used to extract a retrospective cohort of hospitalizations (10/2015- 12/2019) with decompensated cirrhosis, stratified based on discharge diagnosis of HH. Hospitalizations with HH receiving ICT were propensity score matched to those not receiving ICT. In-hospital mortality (IHM), length of stay (LOS) in days, total charges (TC) in $, and liver disease complications were examined as outcomes. ICD-10 diagnosis and procedure codes were used. **Results:** Of 127,627 hospitalizations with decompensated cirrhosis, 7843 (6.2%) had HH (2819 [36%] with ascites, P<0.001). Trends in HH hospitalizations were similar over time. In a cohort of 23,529 (7843 HH) hospitalizations matched on demographics and comorbidities (obesity and diabetes), those with vs. without HH (n=15,686) had higher mean LOS (9.6 vs. 7.4), mean TC (127,000 vs. 90,000), acute kidney injury or AKI (40 vs. 37%) and sepsis (12 vs. 10%), P<0.001 for all, but no difference in IHM. In a logistic multivariable regression model, HH was not associated with IHM with OR (95% CI): 0.95 (0.84-1.07), but chest tube use and sepsis were associated with IHM, respective OR (95% CI): 1.5 (1.3-1.8) and 1.5 (1.1-2.0). Of HH hospitalizations,

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1312 (16.7%) received ICT, with increasing trends in use over time (Fig. 1A) by 5%/yr [1.05 (1.00-1.11)] controlled for other variables in a logistic regression model. In a propensity score matched cohort for ICT (n=3831, 1277 ICT), ICT was associated with IHM (11.6 vs. 8.5%), mean LOS (14.6 vs. 8.7), TC (196,000 vs. 112,000), AKI (45 vs. 39%), sepsis (18 vs. 10%), spontaneous bacterial empyema or SBE (12.5 vs. 2%), and palliative care consult (13.7 vs. 10.9%), P<0.01 for all (Fig. 1B). In a logistic regression model, ICT was associated with 44% higher odds for IHM vs. HH hospitalizations without ICT use, P<0.001. Other associations were ALD etiology, patient's age, and weekend hospitalizations. **Conclusion:** HH occurs in ~6% of decompensated cirrhosis hospitalizations, and is associated with higher morbidity and use of hospital resources. One of six HH hospitalizations is managed with ICT, which is associated with greater morbidity, use of hospital resources, and patient mortality. However, the use of ICT continues and is increasing over time. Strategies are needed to spread awareness among providers managing decompensated cirrhosis hospitalizations to avoid placement of ICT in hospitalized patients with HH.

Fig 1A

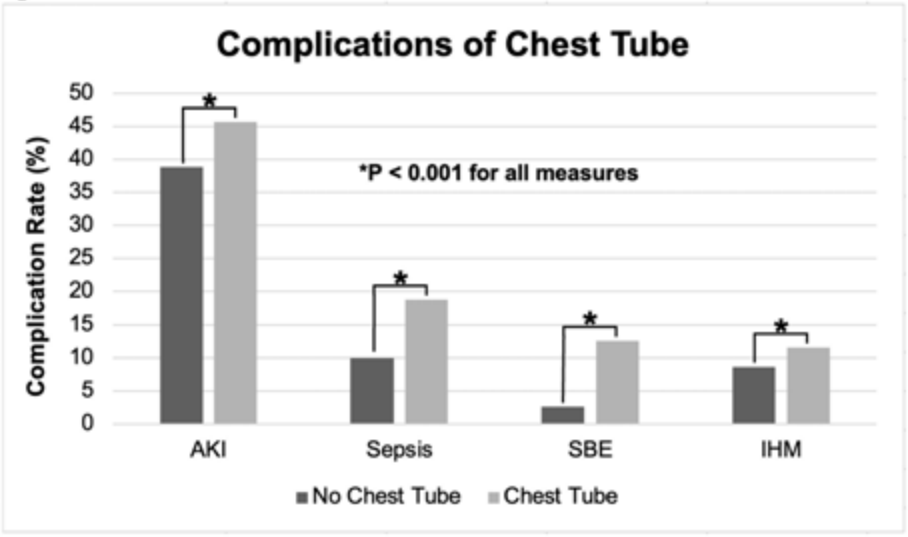
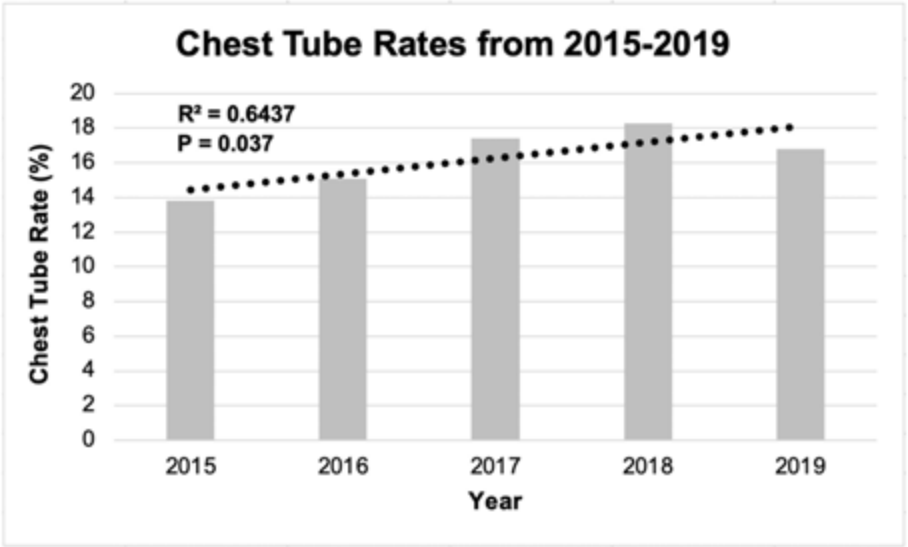


Fig 1B



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4130 | PRACTICE HETEROGENEITY AND DIAGNOSTIC YIELD OF ROUTINE OUTPATIENT PARACENTESIS FLUID STUDIES IN PATIENTS WITH CIRRHOSIS ◆

Alexandra McCullough[1] Marina Serper[2] David Kaplan[3] Nadim Mahmud[1]

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Background: Patients with cirrhosis and ascites are at risk for spontaneous bacterial peritonitis (SBP). It is recommended to routinely obtain paracentesis fluid studies to diagnosis SBP in the inpatient setting, however there is lack of guidance as to whether fluid studies are necessary in patients requiring routine outpatient paracenteses. Using a large national cohort, we aimed to evaluate practice heterogeneity in sending outpatient fluid studies and to determine the diagnostic yield of varying practices. **Methods:** This was a retrospective cohort study using data from a well-established cohort of adult patients with cirrhosis between 1/2008 and 12/2022 in the Veterans Health Administration. We identified all outpatient paracentesis procedures and isolated patients requiring serial outpatient paracentesis, defined as at least 3 outpatient paracenteses in a three-month period. Fluid studies, when sent, were cleaned and SBP was defined as an absolute polymorphonuclear cell count >250. Demographics, comorbidity data, etiology of liver disease, and MELD-Na prior to each paracentesis was ascertained. SBP prophylaxis medication prescriptions were used to determine if patients were on SBP prophylaxis within 6 months before each paracentesis. For each patient, the proportion of instances where fluid studies were sent was calculated, and patients were categorized based on categories of this proportion, ranging from 0-10% to 90-100%. To evaluate the diagnostic yield of sending fluid studies across these categories, the proportion of studies positive for SBP was computed and then stratified by whether patients were on or off SBP prophylaxis. **Results:** A total 98,042 outpatient paracenteses were identified from 6,721 patients. The cohort had median age 64 years (interquartile range [IQR] 58, 69), was 97.6% male, and 70.8% White. Median MELD-Na prior to paracentesis was 15 (IQR 10, 21), and 26.5% were on SBP prophylaxis. There was significant practice heterogeneity in sending routine outpatient paracentesis fluid studies; 24.4% of patients had studies sent <10% of the time, and 16.5% had studies sent >90% of the time. The diagnostic yield of fluid studies was uniformly higher in patients on SBP prophylaxis (Figure). Patients in whom studies were sent >90% of the time generally had the lowest diagnostic yield for identifying SBP (e.g., in patients on SBP prophylaxis: 3.8% vs. 11.1% when sent selectively [10-20% of the time]). In patients not on SBP prophylaxis, the diagnostic yield was 2.3% when studies were sent >90% of the time. **Conclusion:** There is significant practice variation in sending routine outpatient paracentesis fluid studies. Selectively sending fluid studies, for example when prompted by new symptoms, appears to have higher diagnostic yield for SBP, particularly in patients with existing indications for SBP prophylaxis.

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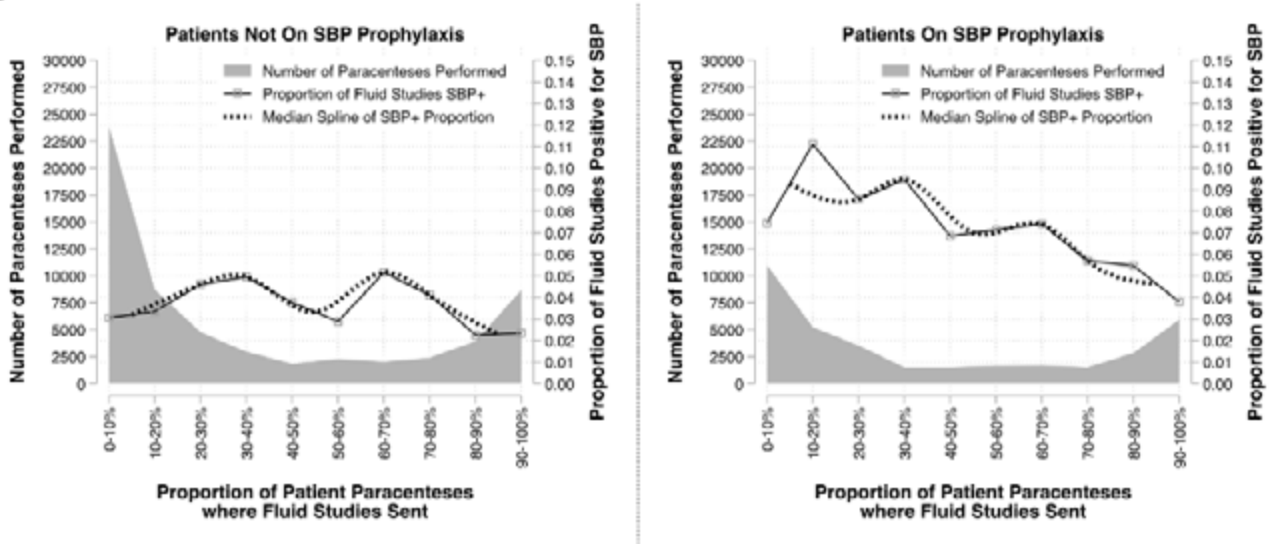
Figure



Disclosures: Alexandra McCullough: Nothing to Disclose, Marina Serper: Grant/Research Support relationship with Grifols; Has not ended; Grant/Research Support relationship with Eurofins; Has not ended; Grant/Research Support relationship with Transplant Genomics; Has not ended, David Kaplan: Independent Contractor relationship with Roche Genentech; Has not ended; Grant/Research Support relationship with AstraZeneca Inc; Has not ended; Advisor relationship with AstraZeneca; Has ended; Advisor relationship with Exelixis; Has ended; Grant/Research Support relationship with Gilead; Has not ended; Advisor relationship with Sirtex; Has ended; Grant/Research Support relationship with Exact Sciences; Has not ended; Grant/Research Support relationship with Glycotest; Has ended, Nadim Mahmud: Nothing to Disclose

4131 | THE ASSOCIATION BETWEEN ALBUMIN ADMINISTRATION AND ACUTE KIDNEY INJURY OUTCOMES IN PATIENTS HOSPITALIZED WITH SPONTANEOUS BACTERIAL PERITONITIS

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Background: Patients who have cirrhosis decompensated by ascites are at risk for spontaneous bacterial peritonitis (SBP). A diagnosis of SBP in these patients portends poorer prognosis overall and mortality is often driven by development of shock and/or renal failure. Albumin is guideline recommended for patients with SBP. However, there is a lack of population-level data evaluating the potential impact of albumin on kidney function trajectory. We aimed to evaluate the association between albumin administration and acute kidney injury (AKI) outcomes in patients with SBP. **Methods:** This was a retrospective cohort study using data from the Veterans Health Administration. Patients with cirrhosis with first hospitalizations for SBP (defined by peritoneal fluid studies) were included. Detailed demographic, comorbidity, and laboratory data were ascertained. Albumin administration data was used to classify no albumin use, albumin use not per guidelines, and albumin use per SBP guidelines (day 1/day2 or day 1/day3). The primary outcome was a five-level acute kidney injury outcome: 0=no AKI, 1=stage 1 AKI, 2=stage 2 AKI, 3=stage 3 AKI, 4=in-hospital death or death within 14 days of discharge. Ordinal logistic regression was used to evaluate the adjusted association between albumin use and the AKI outcome; an *a priori* interaction between albumin utilization and MELD-Na on presentation was evaluated. **Results:** A total 3,487 patients were included, with median age 62 years, 97.8% male, and 63.2% white race. Alcohol was the primary etiology of liver disease (42.5%). Albumin per guidelines was given in 47.4% of hospitalizations, albumin not per guidelines in 27.8%, and 24.8% received no albumin; a total 558 (16.0%) experienced the level 3 outcome (stage 3 AKI) and 283 (8.1%) experienced the level 4 outcome (death). In the final ordinal logistic regression model, increased MELD-Na on presentation and albumin utilization were both associated with increased odds of higher-level AKI outcomes (p<0.001 and p=0.002, respectively). However, there was a significant interaction such that the impact of MELD-Na on higher-level AKI outcomes was diminished with

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albumin administration (OR 0.97, 95% CI 0.94-0.99 with albumin not per guidelines and OR 0.96, 95% CI 0.94-0.99 with albumin per guidelines). **Conclusion:** In this large cohort of Veterans with cirrhosis hospitalized with SBP, many patients did not receive albumin per guidelines. While albumin use was associated with increased odds of higher-level AKI outcomes, potentially related to residual confounding and relative sickness of patients receiving albumin, guideline albumin administration was found to mitigate the incremental effect of increasing MELD-Na on AKI outcomes.

Table – Ordinal Logistic Regression Model for AKI Outcome

Variable	Odds Ratio	95% Confidence Interval	p-value
Age	1.02	(1.01 - 1.02)	0.001*
Male Sex	1.07	(0.63 - 1.82)	0.79
Race/Ethnicity			
White	(ref)		
Black	1.74	(1.39 - 2.16)	<0.001*
Hispanic	1.22	(0.95 - 1.57)	0.12
Asian	0.89	(0.43 - 1.85)	0.76
Other	1.30	(1.04 - 1.63)	0.023*
AUDIT-C	0.99	(0.97 - 1.01)	0.48
Etiology of Liver Disease			
Hepatitis C	(ref)		
Hepatitis B	0.46	(0.18 - 1.18)	0.11
Alcohol	0.84	(0.64 - 1.10)	0.20
HCV + Alcohol	0.83	(0.63 - 1.10)	0.19
MASLD	0.85	(0.63 - 1.16)	0.31
Other	0.64	(0.37 - 1.10)	0.10
Diabetes Mellitus	1.07	(0.92 - 1.25)	0.35
MELD-Na Pre-Hospital	0.97	(0.96 - 0.98)	<0.001*
MELD-Na on day 1 (D1)	1.19	(1.16 - 1.23)	<0.001*
Albumin Category			
No albumin	(ref)		
Albumin, not per guidelines	2.76	(1.29 - 5.93)	0.009*
Albumin per guidelines (GL)	3.32	(1.68 - 6.56)	0.001*
Albumin Category # MELD-Na on presentation interaction			**0.035* (joint)**
No albumin#MELD-Na D1	(ref)		
Albumin not per GL#MELD-Na D1	0.97	(0.94 - 1.00)	0.048*
Albumin per GL#MELD-Na D1	0.96	(0.94 - 0.99)	0.011*

Disclosures: Marina Serper: Grant/Research Support relationship with Grifols; Has not ended; Grant/Research Support relationship with Eurofins; Has not ended; Grant/Research Support relationship with Transplant Genomics; Has not ended, Alexandra McCullough: Nothing to Disclose, David Kaplan: Independent Contractor relationship with Roche Genentech; Has not ended; Grant/Research Support relationship with AstraZeneca Inc; Has not ended; Advisor relationship with AstraZeneca; Has ended; Advisor relationship with Exelixis; Has ended; Grant/Research Support relationship with Gilead; Has not ended; Advisor relationship with Sirtex; Has ended; Grant/Research Support relationship with Exact Sciences; Has not ended; Grant/Research Support relationship with Glycotest; Has ended, Nadim Mahmud: Nothing to Disclose

4132 | A DECISION AID FOR THE TIMING OF PARACENTESIS FOR PATIENTS WITH CIRRHOSIS AND ASCITES: A SINGLE CENTER QI INITIATIVE

Anne Cravero[1] *Philip Vutien*[1] *Kira Newell*[1] *Lindee Strizich*[1]

[1]*University of Washington*

Background: We developed a decision aid for Emergency Department (ED) and admitting providers to guide the timing of paracentesis for patients with cirrhosis and ascites presenting to the University of Washington Medical Center (UWMC), a tertiary referral transplant center. The primary aim was to assess the impact of this aid on the proportion of these patients who underwent early paracenteses. Secondary aims included assessing the impact on the rates of sepsis and mortality in patients with cirrhosis and ascites. **Methods:** A multi-disciplinary team created and disseminated a decision aid that outlined which patients should receive a paracentesis within 3, 6,

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and 12 hours of ED rooming time (Figure 1). Patients with cirrhosis and ascites presenting to UWMC 6 months prior and 6 months after decision aid implementation were identified and designated as “pre-intervention” and “post-intervention”, respectively. Chart review was done to assess the outcomes including the receipt of and timing to paracentesis and mortality. The diagnosis of sepsis was based on ICD 10 code R65.2 being associated with a patient’s ED or hospital encounter. Patients were excluded if they did not undergo paracentesis due to patient refusal or insufficient fluid pocket for sampling. Wilcoxon rank-sum and Chi-square testing was performed to compare groups. **Results:** The pre-intervention cohort included 116 patient encounters with 102 patients represented compared to 73 patient encounters and 57 patients in the post-intervention cohort. In the pre-intervention cohort, 74% of patients received a paracentesis at any time compared to 70% in the post-intervention cohort (p value= 0.52). The median time to paracentesis was 12 hours (IQR 4-41) and 11 hours (IQR 4-30) in the pre and post-intervention cohorts, respectively (p value=0.77). Of the paracenteses performed, 50% were within 12 hours of ED rooming time in the pre-intervention cohort, as compared to 55% in the post-intervention cohort (p value= 0.58, Figure 2). There were similar rates of sepsis (3.4% vs 6.8%, p value=0.31) and mortality (8.6% and 11%, p value= 0.59) in the pre and post-intervention cohorts. **Conclusion:** In this single center quality improvement initiative, a decision aid did increase the proportion of paracenteses performed within 12 hours of presentation, although this improvement was not statistically significant. Next steps will include simplification of the algorithm and piloting a medical record pop-up alert to prompt consideration of paracentesis when patients with cirrhosis present to the ED.

Figure 1: Decision Aid for Timing of Paracentesis for Patients with Cirrhosis and Ascites

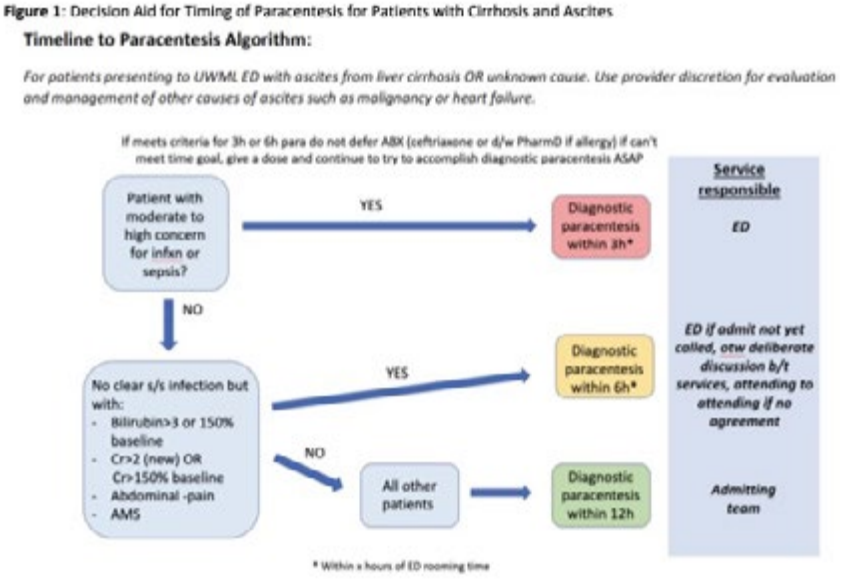
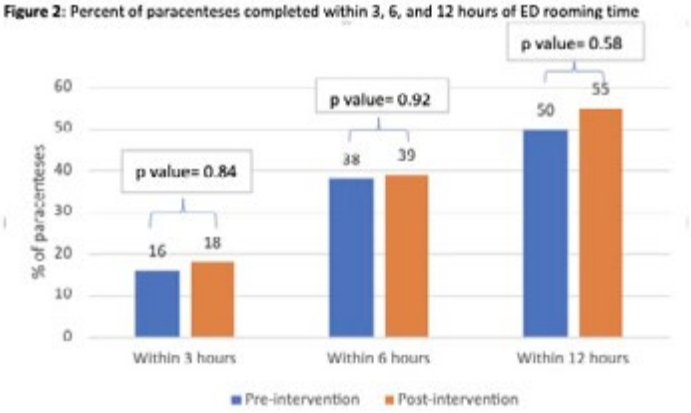


Figure 2: Percent of paracenteses completed within 3, 6, and 12 hours of ED rooming time



Disclosures: Anne Cravero: Nothing to Disclose, Philip Vutien: Nothing to Disclose, Kira Newell: Nothing to Disclose, Lindee Strizich: Nothing to Disclose

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4133 | INCREASING COMORBIDITIES AND MEDICATION BURDEN IN PATIENTS WITH CIRRHOSIS AND VARICEAL HAEMORRHAGE FROM 2000 TO 2020

Che To Jimmy Lai[1] Yichong JIANG[1] Lilian Yan Liang[1] Vincent Wong[1] Terry Cheuk-Fung Yip[1] Grace Wong[1]

[1]The Chinese University of Hong Kong

Background: Variceal hemorrhage (VH) is a serious and potentially life-threatening event in patients with cirrhosis. It is uncertain if the evolving landscape of diseases and medications over time has any impact on VH. We thus aimed to evaluate the secular change in comorbidities and medication burden in cirrhotic patients with VH. **Methods:** This was a territory-wide cohort study of consecutive patients with cirrhosis and gastroesophageal varices captured from the Clinical Data Analysis and Reporting System of the Hospital Authority in 2000 - 2020. Concomitant medical conditions and medications were retrieved. Patients were divided into four periods, namely 2000 – 2005, 2006 – 2010, 2011 – 2015 and 2016 – 2020, according to their baseline diagnosis date of varices for secular trend analysis. **Results:** 10,198 patients with varices were included and 4,007 (39.3%) patients developed VH. The incidences of VH decreased over time, from 48.7% in 2000 – 2005 and 43.6% in 2006 – 2010, to 35.6% in 2011 – 2015 and 25.0% in 2016 – 2020. At the same time, a rising proportion of patients with varices were put on non-selective beta-blockers (NSBB), from 58.2% in 2000 – 2005 to 68.3% in 2016 – 2020 (Fig. 1A). More male patients (74.4%) developed VH at a stable mean age of 60 years across the study period. The 30-day mortality was static across the periods at 25%. The proportion of patients with VH having diabetes mellitus (DM) and hypertension steadily increased across the study periods, in which the burden of DM rose from 47.4%, 55.3%, 62.6% to 73.1% and that of hypertension increased from 45.5%, 51.0%, 54.6% to 54.8%, at the last study period (Fig. 1B). Concurrently, an increasing proportion of patients was put on anti-hypertensive, such as calcium channel blockers, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, as well as anti-platelet agents. **Conclusion:** Despite a decreasing trend of VH with increasing uptake of NSBB, there was an increase in comorbidities, particularly DM and hypertension, and concomitant medications over time which may complicate the treatment of VH and other cirrhotic complications, thus warranting personalized approach in managing these patients.

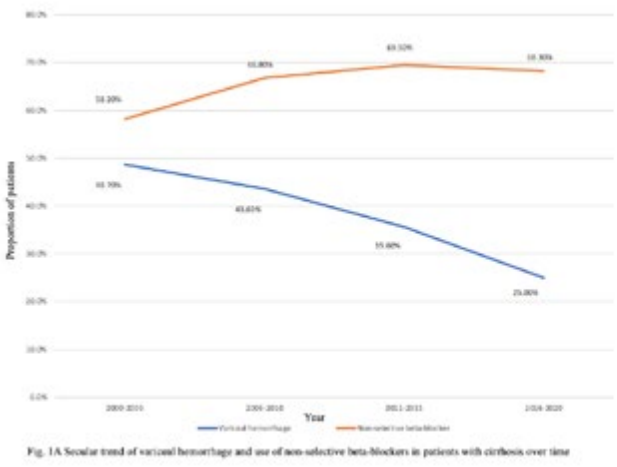

Fig. 1A Secular trend of variceal hemorrhage and use of non-selective beta-blockers in patients with cirrhosis over time

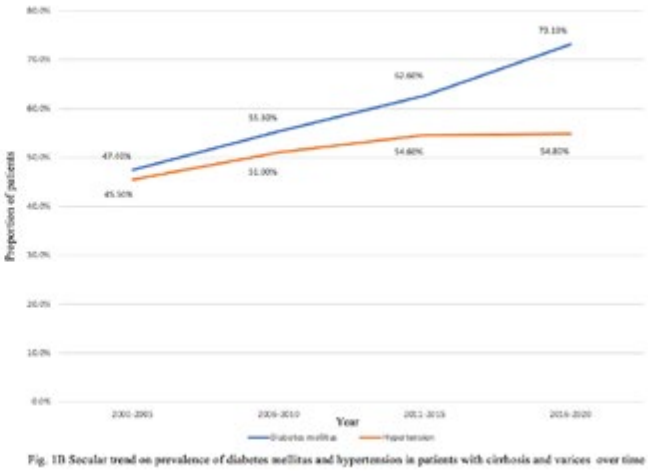

Fig. 1B Secular trend on prevalence of diabetes mellitus and hypertension in patients with cirrhosis and varices over time

Disclosures: Che To Jimmy Lai: Nothing to Disclose, Yichong JIANG: Nothing to Disclose, Lilian Yan Liang: Nothing to Disclose, Vincent Wong: Abbott: Speaking and Teaching, AbbVie: Advisor, AbbVie: Speaking and Teaching, Boehringer Ingelheim: Advisor, Echosens: Advisor, Echosens: Speaking and Teaching, Gilead Sciences: Advisor, Gilead Sciences: Speaking and Teaching, Gilead Sciences: Grant/Research Support, Intercept: Advisor, Inventiva: Advisor, Novo Nordisk: Advisor, Novo Nordisk: Speaking and Teaching, Pfizer: Advisor, Sagimet: Advisor, TARGET PharmaSolutions: Advisor, Unilab: Speaking and Teaching, Visirna: Consultant, Illuminatio Medical Technology: Stock – privately held company, Terry Cheuk-Fung Yip: Gilead Sciences: Consultant, Gilead Sciences: Advisor, Gilead Sciences: Speaking and Teaching, Grace Wong: AstraZeneca: Advisor, Gilead Sciences: Advisor, Gilead Sciences: Speaking and Teaching, Janssen: Advisor, GSK: Advisor, GSK: Speaking and Teaching, Abbott: Speaking and Teaching, AbbVie: Speaking and Teaching, AstraZeneca, Gilead Sciences, GlaxoSmithKline and Janssen,: Advisor, Abbott, AbbVie, Ascletis, Bristol-Myers Squibb, Echosens, Gi: Speaking and Teaching, Gilead Sciences: Grant/Research Support, AstraZeneca, Gilead

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Sciences, GlaxoSmithKline and Janssen: Consultant, Abbott, AbbVie, Ascletis, Bristol-Myers Squibb, Echosens, Gi: Speaking and Teaching, AstraZeneca, Gilead Sciences, GlaxoSmithKline Pharmaceutical: Consultant, Gilead Sciences: Independent Contractor, AstraZeneca, Gilead Sciences, GSK and Janssen,: Advisor, Abbott, AbbVie, BMS, Gilead Sciences, GSK, Janssen, Roche: Speaking and Teaching, Gilead Sciences: Grant/Research Support

4134 | MACHINE LEARNING-BASED DEVELOPMENT AND VALIDATION OF A NOVEL FIB-6 SCORE FOR SCREENING HIGH-RISK VARICES IN COMPENSATED CIRRHOSIS: AN INTERNATIONAL MULTICENTER STUDY ◆

Bingtian Dong[1] Ruiling He[2] Ivica Grgurevic[3] Ying Guo[4] Yunfang Liu[4] Huixiong Xu[5] Anita Madir[6] Kristian Podrug[7] Jia Wang[8] Zhengzi Geng[9] Shanghao Liu[10] Tao Ren[11] Guo Zhang[12] Kun Wang[4] Meiqin Su[4] Fei Chen[13] Sumei Ma[14] Liting Zhang[14] Yonghe Zhou[15] Xin Li[15] Fanbin He[9] Hui Huan[16] Wenjuan Wang[17] Yunxiao Liang[17] Juan Tang[18] Fang Ai[18] Tingyu Wang[18] Liyun Zheng[19] Zhongwei Zhao[19] Jiansong Ji[19] Wei Liu[20] Jiaojiao Xu[20] Bo Liu[20] Xuemei Wang[8] Yao Zhang[8] Qiong Yan[21] Muhan Lv[21] Xiaomei Chen[21] Shuhua Zhang[22] Yihua Wang[22] Yang Liu[22] Li Yin[23] Yanni Liu[23] Yanqing Huang[23] Li Bian[24] Ping An[24] Xin Zhang[24] Yuping Chen[10] Chuan Liu[10] Linxue Qian[8] Xiaolong Qi[10]

[1]First Affili Hospi of Anhui Medic Univer, [2]Donggang Branch the First Hospital of La, [3]University of Zagreb School of Medicine, [4]The Third people's Hospital of Taiyuan, [5]Zhongshan Hospital, Fudan University, [6]University Hospital Dubrava, [7]University Hospital Center Split, [8]Capital Medical University, [9]The People's Hospital of Linxia, [10]Zhongda Hospital, Southeast University, [11]Hosp of Chengdu Off of People's Gover of, [12]The People's Hospital of Guangxi, [13]First Hospital of Lanzhou Univer, [14]First Hospital of Lanzhou University, [15]Tianjin Second People's Hospital, [16]Hosp of Chengdu Off of Peo's Gov of Tibe, [17]People's Hospital of Guangxi, [18]Zigong First people's Hospital, [19]Wenzhou Medical University, [20]Shaanxi Provincial People's Hospital, [21]Southwest Medical University, [22]North China Uni of Scie and Tech Affi Ho, [23]Jincheng People's Hospital, [24]Sixth People's Hospital of Shenyang

Background: Detecting esophageal varices (EV) early is crucial for effectively managing cirrhotic patients. However, many patients undergoing esophagogastroduodenoscopy (EGD) screening do not have EV or have only small EV. We aimed to combine the fibrosis-4 (FIB-4) score, liver (LSM) and spleen stiffness measurements (SSM) into a novel score, called FIB-6, to identify high-risk EV (HRV) in compensated cirrhosis. **Methods:** This international multicenter study involved patients with compensated cirrhosis who underwent EGD at sixteen Chinese hospitals and a Croatian university hospital center **(**Figure 1A). Two-dimensional shear wave elastography-derived LSM and SSM values, and the individual components of the FIB-4 score (i.e. age, aspartate aminotransferase, alanine aminotransferase, platelet count), were combined using a machine learning algorithm (logistic regression [LR] or extreme gradient boosting [XGBoost]) to develop the LR-FIB-6 and XGBoost-FIB-6 models, respectively. SHapley Additive exPlanations (SHAP) were used to interpret model predictions **(**Figure 1B). This study is registered with ClinicalTrials.gov (NCT04546360). **Results:** A total of 468 patients with compensated cirrhosis from China and Croatia were included for analysis. 268 patients from fourteen Chinese hospitals were selected to develop the diagnostic model. The remaining patients from two Chinese hospitals and a dataset from Croatia constituted two independent external validation cohorts, with 118 patients in validation cohort 1 and 82 in validation cohort 2. The prevalence of HRV was 26.7% (125/468). The XGBoost-FIB-6 score demonstrated superior performance in predicting HRV, with an area under the receiver operating characteristic curve (AUROC) of 0.927 (95% CI: 0.897-0.957) in the training cohort, and 0.919 (95% CI: 0.843-0.995) and 0.902 (95% CI: 0.820-0.984) in the first and second external validation cohorts, respectively **(**Figure 1**C)**. In the validation cohort 1 and 2, the XGBoost-FIB-6 score had a negative predictive value of >0.90 for ruling out HRV. Both LR-FIB-6 and XGBoost-FIB-6 models showed better diagnostic performance compared to LSM, SSM, or FIB-4 alone. **Conclusion:** We combined LSM, SSM, and the individual components of the FIB-4 into a single scoring system (FIB-6), which could predict HRV in patients with compensated cirrhosis. This novel scoring system provides an effective tool for clinicians, holding great promise for guiding clinical management and improving patient outcomes.

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A Baseline characteristics of the cohort

Characteristics	Overall (n = 468)	Training cohort (n = 268)	Validation cohort 1 (n = 118)	Validation cohort 2 (n = 82)
Male, n/total (%)	326/468 (69.7)	180/268 (67.2)	81/118 (68.6)	65/82 (79.3)
Age (years)	52.0 (44.0-60.0)	49.0 (42.0-55.0)	51.0 (45.0-59.0)	62.0 (57.0-68.0)
BMI (kg/m²), n = 367	24.5 (22.4-26.8)	24.1 (22.0-26.1)	24.5 (22.5-26.3)	27.4 (24.3-32.2)
Child-Pugh score, n = 386	5.0 (5.0-5.0)	5.0 (5.0-6.0)	5.0 (5.0-5.0)	-
Child-Pugh class, A/B, n(%)	412 (88.0)/56 (22.0)	223 (83.2)/45 (16.8)	115 (97.5)/3 (2.5)	74 (90.2)/8 (9.8)
MELD score, n = 425	9.0 (7.6-10.9)	9.0 (7.6-11.1)	8.7 (8.1-10.1)	9.4 (7.5-11.0)
LSM (kPa)	14.1 (10.8-20.1)	14.1 (10.8-19.3)	11.8 (9.7-15.2)	22.3 (15.1-29.8)
SSM (kPa)	31.1 (24.8-37.3)	32.7 (24.9-40.0)	27.9 (24.0-32.7)	31.7 (25.6-39.3)
ALT (U/L)	34.0 (22.0-58.0)	38.0 (26.0-68.0)	25.0 (19.0-39.0)	33.0 (25.0-67.0)
AST (U/L)	36.8 (26.0-62.0)	40.0 (28.7-71.2)	27.0 (21.0-37.0)	46.0 (29.0-67.0)
PLT (10^9/L)	118.0 (78.0-161.0)	108.0 (72.0-154.0)	120.0 (81.0-168.0)	141.0 (106.0-193.0)
FIB-4	2.9 (1.9-5.3)	3.1 (2.1-5.8)	2.3 (1.6-3.9)	3.0 (2.2-5.2)
EV, n/total (%)	251/468 (53.6)	145/268 (54.1)	73/118 (61.9)	33/82 (40.2)
HRV, n/total (%)	125/468 (26.7)	84/268 (31.3)	22/118 (18.6)	19/82 (23.2)

B XGBoost-FIB-6 SHapley Additive exPlanations (SHAP) feature analysis



C XGBoost-FIB-6 (Training cohort) XGBoost-FIB-6 (Validation cohort 1) XGBoost-FIB-6 (Validation cohort 2)

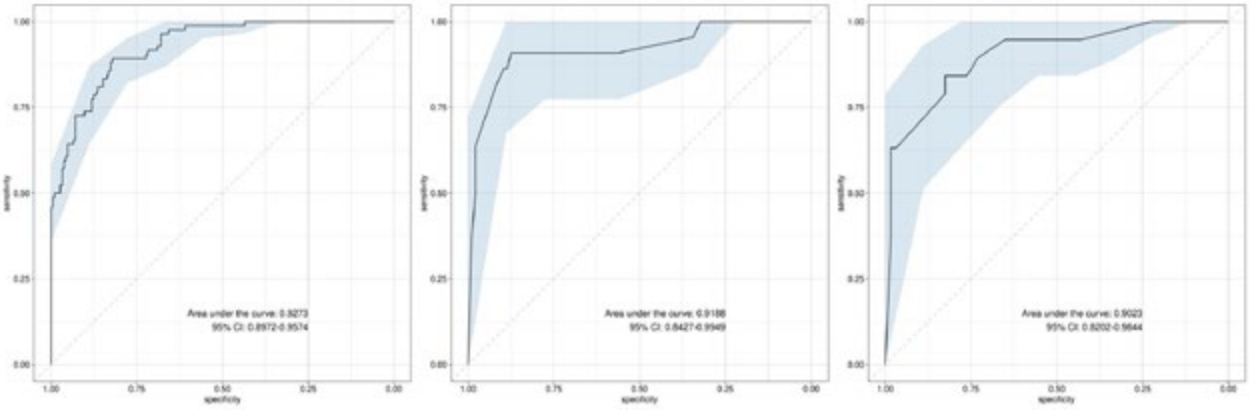

Figure 1. Machine learning-based development and validation of a novel FIB-6 score for screening HRV in compensated cirrhosis. A. Baseline characteristics of the cohort, B. XGBoost-FIB-6 SHapley Additive exPlanations (SHAP) plot, C. Diagnostic performance of the XGBoost-FIB-6 model for HRV in training cohort and external validation cohorts. Note: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; EV, esophageal varices; FIB-4, fibrosis-4; HRV, high-risk esophageal varices; LSM, liver stiffness measurement; MELD, Model for End-stage Liver Disease; PLT, platelet count; SSM, spleen stiffness measurement; XGBoost, eXtreme Gradient Boosting.

Disclosures: Bingtian Dong: Nothing to Disclose, Ruiling He: Nothing to Disclose, Ivica Grgurevic: Nothing to Disclose, Ying Guo: Nothing to Disclose, Yunfang Liu: Nothing to Disclose, Huixiong Xu: Nothing to Disclose, Anita Madir: Nothing to Disclose, Kristian Podrug: Nothing to Disclose, Jia Wang: Nothing to Disclose, Zhengzi Geng: Nothing to Disclose, Shanghao Liu: Nothing to Disclose, Tao Ren: Nothing to Disclose, Guo Zhang: Nothing to Disclose, Kun Wang: Nothing to Disclose, Meiqin Su: Nothing to Disclose, Fei Chen: Nothing to Disclose, Sumei Ma: Nothing to Disclose, Liting Zhang: Nothing to Disclose, Yonghe Zhou: Nothing to Disclose, Xin Li: Nothing to Disclose, Fanbin He: Nothing to Disclose, Hui Huan: Nothing to Disclose, Wenjuan Wang: Nothing to Disclose, Yunxiao Liang: Nothing to Disclose, Juan Tang: Nothing to Disclose, Fang Ai: Nothing to Disclose, Tingyu Wang: Nothing to Disclose, Liyun Zheng: Nothing to Disclose, Zhongwei Zhao: Nothing to

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4135 | EVALUATING THE IMPACT OF BRANCHED-CHAIN AMINO ACID SUPPLEMENTATION AND EXERCISE ON SARCOPENIA IN CIRRHOSIS: A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

Fariha Hasan[1] Avneet Singh[1] Alexander Garcia[1] Abdul Rehman Shah Syed[2] Syeda Kanza Kazmi[3] Muhammad Shahzil[3] Polina Gaisinskaya[1] Adib Chaaya[1] Babu Mohan[4]

[1]Cooper University Hospital, NJ, [2]Dow University of Health Sciences, PK, [3]Penn State Health Milton S. Hershey Medical Center, PA, [4]Orlando Gastroenterology PA, Orlando, FL

Background: Branched-chain amino acids (BCAAs) are a promising supplement for liver cirrhosis, complementing conventional management options. Several studies have demonstrated that BCAA supplementation can effectively downregulate protein metabolism in cirrhosis, improve nitrogen balance, and lead to better clinical outcomes. Additionally, exercise has shown similar beneficial effects in cirrhosis. This is the first meta-analysis that aims to assess the efficacy of the combined impact of BCAA supplementation and exercise on sarcopenia in patients with cirrhosis. **Methods:** This meta-analysis adhered to Cochrane guidelines and PRISMA standards, comparing BCAA and exercise to controls for the management of sarcopenia in liver cirrhosis. A comprehensive literature review was conducted from inception to April 2024 using PubMed, Embase, Web of Science, and Cochrane databases. Inclusion was strictly restricted to randomized controlled trials (RCTs). Data extraction followed PICOS criteria using Excel. Standard meta-analysis methods were followed using the random effects model. Heterogeneity was assessed using the I2% statistics. **Results:** Six RCTs were included in the final analysis with 286 participants (141 in the BCAA group and 145 in the placebo group). The mean age was 52.55 ± 14.13 years in the placebo group and 52.09 ± 16.14 years in the BCAA group, with the male proportion being 74.06 % and 71.06%, respectively. The results showed that change in 6-minute gait speed (MD=0.18, 95% CI=0.15, 0.20, p<0.00001) and change in Body Mass Index (BMI) (MD=0.74, 95% CI,=0.05, 1.44, p=0.04) showed a statistically significant change in favor of BCAA and exercise versus placebo. However, change in serum albumin (MD=0.22, 95% CI=-0.09, 0.53, p=0.16), skeletal muscle index (MD=0.18, 95% CI=-0.24, 0.61, p=0.40), hand grip strength (MD=0.76, 95% CI=-0.20, 1.73, p=0.12), 6-minute walk distance (MD=12.15, 95% CI=-3.64, 27.93, p=0.13), mid-arm muscle circumference (MD=-0.39, 95% CI=-1.65, 0.86, p=0.54), weight (MD=1.81, 95%CI=-3.68, 7.29, p=0.52), waist circumference (MD=0.67, 95% CI=-3.77, 5.11, p=0.77), and fat-free mass (MD=-0.40 95% CI=-2.11, 1.32, p=0.65) did not show statistically significant differences. **Conclusion:** While the benefits of BCAA supplementation for improving sarcopenia have been studied, the combined effect of BCAAs and exercise has not yet been explored. Based on this review, BCAA and exercise hold potential benefits for patients with sarcopenia in cirrhosis, particularly in improving gait speed and BMI. Even though they have limited effectiveness in other parameters, the combined intervention seems to be a useful treatment option that can be implemented to complement conventional treatment in managing sarcopenia associated with cirrhosis. Further research is necessary to fully understand the extent of efficacy and limitations of BCAA supplementation and exercise in patients with cirrhosis.

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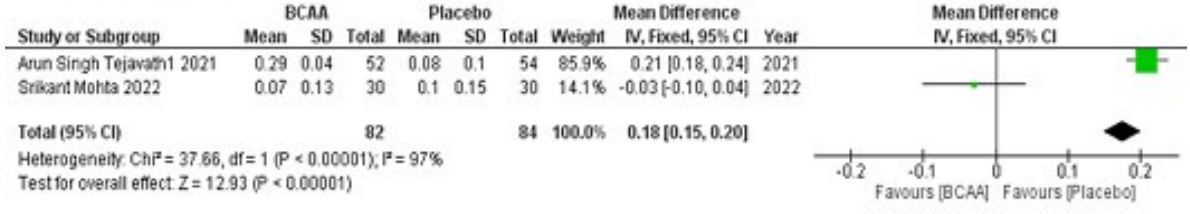
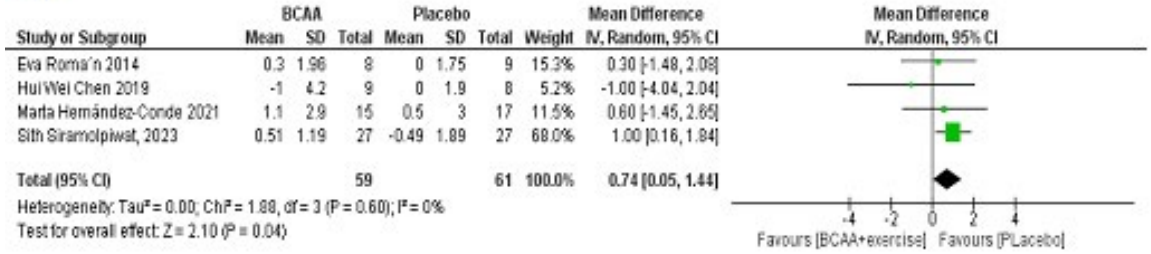
6-minute gait speed



BMI



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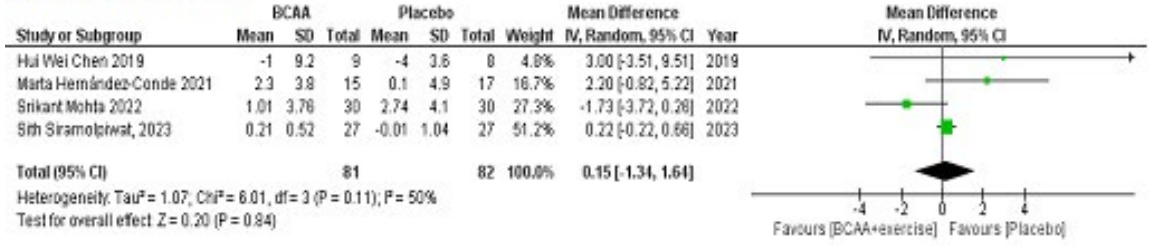
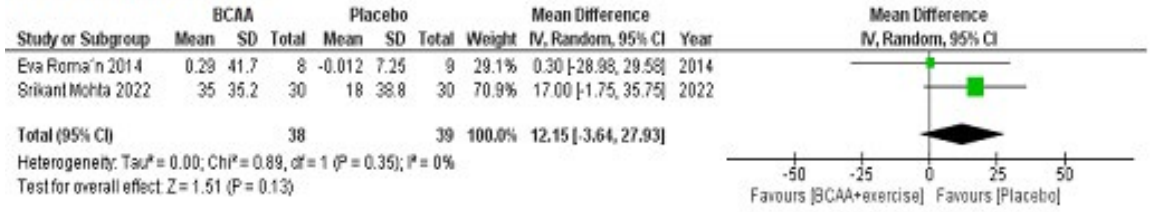
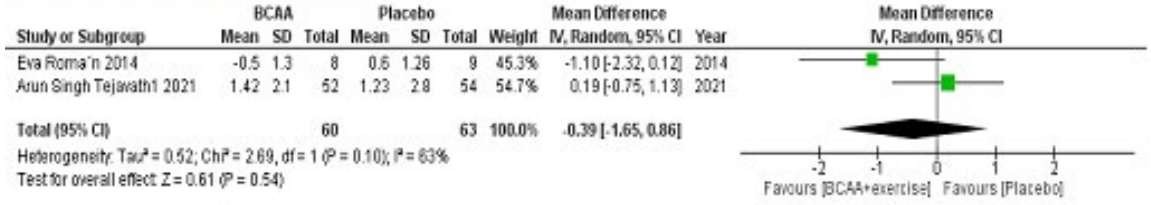


6 minute walk distance



Mid-arm muscle circumference



Disclosures: Fariha Hasan: Nothing to Disclose, Avneet Singh: Nothing to Disclose, Alexander Garcia: Nothing to Disclose, Abdul Rehman Shah Syed: Nothing to Disclose, Syeda Kanza Kazmi: Nothing to Disclose, Muhammad Shahzil: Nothing to Disclose, Polina Gaisinskaya: Nothing to Disclose, Adib Chaaya: Nothing to Disclose, Babu Mohan: Nothing to Disclose

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4136 | INCREASED RATES OF ACLF AND LIVER-RELATED DEATH IN PATIENTS WITH ALCOHOL-RELATED CIRRHOSIS AND ONGOING ALCOHOL USE AFTER TIPS PLACEMENT

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Background: Alcohol-related liver disease (ALD) may cause cirrhosis and portal hypertension (PH)-related complications that require transjugular intrahepatic portosystemic shunt (TIPS) implantation. Yet, little data are available regarding the impact of post-TIPS alcohol use (PTAU) on the subsequent clinical course. **Methods:** Patients with ALD cirrhosis who received a TIPS at two tertiary care centers in Austria were included. Clinical (decompensation; acute-on-chronic liver failure=ACLF; bacterial infections; mortality), demographic, and laboratory data were assessed. PTAU was recorded according to patients' reporting and treating physicians' documentation. **Results:** The study cohort comprised 273 ALD patients. 195 (71.4%) received TIPS for refractory ascites and 78 (28.6%) for variceal bleeding. Most patients were male (78.0%) with a median age of 56.0 (50.0;63.0) years. Median MELD at TIPS implantation (baseline, BL) was 12.0 (9.20;18.0) and 36 (13.2%) had Child-Pugh stage C. PTAU was reported by 94 (34.4%) patients. Between persons with and without PTAU, BL characteristics including prevalence of ascites (p=0.123), variceal hemorrhage (p=0.87), and hepatic encephalopathy (HE) (p=0.830) were equally distributed.Over a follow-up of 30.0 (8.00;62.0) months, 182 (66.7%) individuals experienced one or more decompensation events (variceal hemorrhage: 20 [7.3%], ascites: 90 [33.0%], HE: 129 [47.3%]). Patients with PTAU more frequently developed bacterial infections (47.9% vs. 29.6%, p=0.004). Of note, the incidence of ACLF (56.4% vs. 30.2%, p<0.001), overall mortality (72.3% vs. 56.4%, p=0.015), and liver-related death (53.2% vs. 35.2%, p=0.006] were more common in the group with PTAU. Individuals with PTAU had a significantly higher cumulative incidence of ACLF and liver-related death (p<0.001). Multivariable competing risks analysis adjusted for sex, age, diabetes, and Child-Pugh score demonstrated PTAU to be independently associated with ACLF and liver-related death (asHR: 1.58; 95%CI: 1.04-2.39; p=0.031). **Conclusion:** PTAU is an independent risk factor for the development of worse clinical outcomes after TIPS in patients with ALD cirrhosis. Hence, harm reduction and psychiatric support in addition to hepatological optimization represent key elements in ALD care.

Disclosures: Caroline Schwarz: Abbvie, Gilead, Gebro, Galapagos: travel support, Abbvie, Gilead: Speaking and Teaching, Gilead: Consultant, Andrea Kornfehl: Nothing to Disclose, Reema Abid: Nothing to Disclose, Theresa Müllner-Bucsics: Nothing to Disclose, Michael Schwarz: Nothing to Disclose, Benedikt Hofer: IPSEN: Travel support, Nina Dominik: Nothing to Disclose, Benedikt Simbrunner: Nothing to Disclose, Mathias Jachs: Nothing to Disclose, Lukas Reider: Nothing to Disclose, Maria Schoder: Nothing to Disclose, Mattias Mandorfer: Ipsen: Consultant, Echosens: Speaking and Teaching, Echosens: Grant/Research Support, Ipsen: Grant/Research Support, Ipsen: Consultant, Takeda: Consultant, Takeda: Speaking and Teaching, W.L. Gore & Associates: Speaking and Teaching, Michael Trauner: Albireo: Grant/Research Support, Alnylam: Grant/Research Support, Cymabay: Grant/Research Support, Falk: Grant/Research Support, Gilead: Grant/Research Support, Intercept: Grant/Research Support, MSD: Grant/Research Support, Takeda: Grant/Research Support, Ultragenyx: Grant/Research Support, Abbvie: Travel Grants, Falk: Travel Grants, Gilead: Travel Grants, Intercept: Travel Grants, Janssen: Travel Grants, Abbvie: Advisor, Albireo: Advisor, BiomX: Advisor, Boehringer Ingelheim: Advisor, Falk Pharma GmbH: Advisor, Genfit: Advisor, Gilead: Advisor, Hightide: Advisor, Intercept: Advisor, Ipsen: Advisor, Janssen: Advisor, MSD: Advisor, Novartis: Advisor, Phenex: Advisor, Pliant: Advisor, Regulus: Advisor, Siemens: Advisor, Shire: Advisor, BMS: Speaking and Teaching, Falk: Speaking and Teaching, Gilead: Speaking and Teaching, Intercept: Speaking and Teaching, Ipsen: Speaking and Teaching, Madrigal: Speaking and Teaching, MSD: Speaking and Teaching, Medical Universities of Graz and Vienna: Co.Inventor of patents for medical use of norUDCA filed by, Genentech: Grant/Research Support, Thomas Reiberger: Nothing to Disclose, Lukas Hartl: Nothing to Disclose

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4137 | MUSCLE COMPOSITION IS ASSOCIATED TO FRAILTY, PHYSICAL PERFORMANCE, AND QUALITY OF LIFE IN PATIENTS UNDERGOING MRI-BASED HCC SURVEILLANCE – BASELINE DATA FROM THE MULTI-CENTER CIRRHOSIS COHORT STUDY ACCESS-ESLD

Mikael Forsgren[1] Wile Balkhed[2] Patrik Nasr[2] Daniel Sjögren[3] Anna Cederborg[4] Markus Holmberg[2] Nils Dahlström[2] Henrik Stjernman[3] Martin Rejler[3] Stergios Kechagias[2] Olof Dahlqvist Leinhard[1] Mattias Ekstedt[2]

[1]AMRA Medical AB; Linköping University, [2]Linköping University, [3]Region Jönköping County Council, [4]Sahlgrenska University Hospital

Background: Physical frailty and sarcopenia are related and links to outcomes and health care utilization in liver cirrhosis. Frailty may be assessed with Liver Frailty Index (LFI) or Short Performance Physical Battery (SPPB). Sarcopenia is typically assessed by imaging-based muscle measurements.A magnetic resonance imaging (MRI) based assessment (Muscle Assessment Score [MAsS]) combining sex-adjusted thigh muscle fat infiltration (MFI) and muscle volume z-score (MVZ), has been developed to describe muscle health. MAsS can be used to detect muscle composition (MC) phenotypes, of which adverse MC (high MFI & low MVZ) independently predicts all-cause mortality.The aim was to describe MC phenotypes, physical performance, and frailty, as well as the association between MC to physical performance, frailty, and quality of life in patients with liver cirrhosis undergoing MRI-based HCC surveillance in a longitudinal cohort study (ACCESS-ESLD). **Methods:** ACCESS-ESLD is a prospective longitudinal (4–5 visits) multi-center Swedish cohort study of 150 patients with liver cirrhosis. MAsS was measured using AMRA® Researcher based on MR images acquired together with abbreviated MRI for HCC surveillance as well as SPPB, LFI, and EQ-5D-5L. SPPB & LFI groups and MC phenotypes were defined according to literature (Fig). Kruskal-Wallis, Spearman rank, and U-test were used. **Results:** The full baseline was used; 43% females, BMI 29.3±5.7 kg/m^2, 64±10 years, mainly alcohol related and MASLD cirrhosis.The prevalence of adverse MC was 20% (n = 28), 26% had high MFI and 56% low MVZ. 9% were frail and 30% were prefrail. 6% had low and 23% had moderate physical performance. (Fig)Patients with adverse MC had higher LFI (median: 4.1, IQR: [3.5;4.7]) than those with only low MVZ (3.5 [3.2;3.9]) and normal MC (3.4 [3.1;3.9]), $p < 0.001$. Patients with adverse MC had poorer physical performance (9 [8;11]) than only low MVZ (11 [10;12]) and normal MC (11 [12;12]), $p < 0.001$.MFI correlated to the following dimensions in the quality-of-life instrument EQ-5D-5L; Mobility ($\rho = 0.33$, $p < 0.001$), Usual Activities ($\rho = 0.26$, $p = 0.002$), and Pain ($\rho = 0.19$, $p = 0.032$). Patients with high MFI reported worse health status for Mobility ($p = 0.015$) and Usual Activities ($p = 0.014$). **Conclusion:** Adverse MC is a highly prevalent phenotype (20%) in patients undergoing HCC surveillance. These patients with adverse MC had higher frailty and poorer physical performance. Those patients with high MFI, irrespective of MVZ, also reported worse health status than those with normal MFI. Previous research has linked adverse MC to higher all-cause mortality. These results show that adverse MC identifies a vulnerable patient group also within liver cirrhosis, that easily can be identified as part of MRI-based HCC surveillance.

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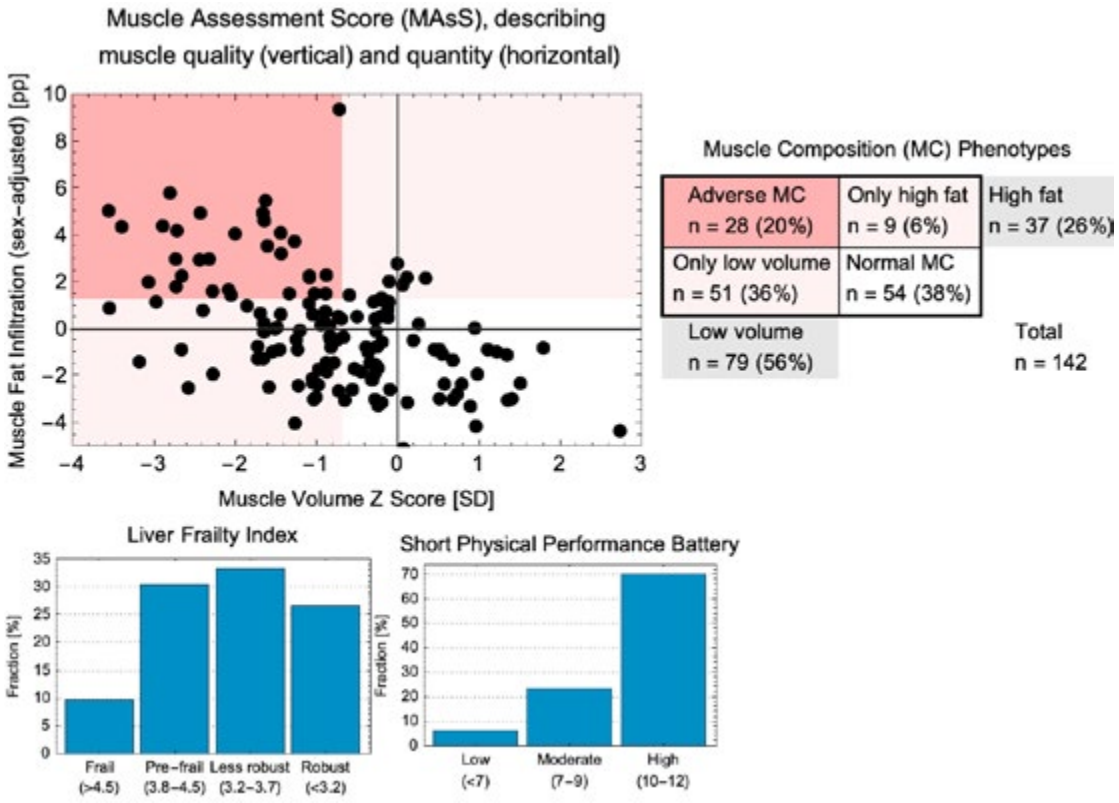

Disclosures: Mikael Forsgren: AMRA Medical AB: Employee, AMRA Medical AB: Stock – privately held company, Wile Balkhed: Nothing to Disclose, Patrik Nasr: Nothing to Disclose, Daniel Sjögren: Nothing to Disclose, Anna Cederborg: Nothing to Disclose, Markus Holmberg: Nothing to Disclose, Nils Dahlström: Nothing to Disclose, Henrik Stjernman: Nothing to Disclose, Martin Rejler: Nothing to Disclose, Stergios Kechagias: Nothing to Disclose, Olof Dahlqvist Leinhard: Nothing to Disclose, Mattias Ekstedt: Nothing to Disclose

4138 | HYPERAMMONEMIA INCREASES SUSCEPTIBILITY TO OXIDATIVE STRESS IN SKELETAL MUSCLE VIA IMPAIRED KEAP1-NRF2 PATHWAY FUNCTION

Satoko Sawahashi[1] Akitoshi Sano[2] Jun Inoue[1] Eiji Kakazu[3] Masashi Ninomiya[1] Mio Tsuruoka[1] Kosuke Sato[1] Masazumi Onuki[1] Ouchi Keishi[1] Kotaro Doi[1] Atsushi Masamune[1]

[1]Tohoku University Hospital, [2]Mayo Clinic, Rochester, [3]National Center for Global Health and Medicine

Background: Sarcopenia worsens the prognosis of liver cirrhosis. The Keap1-Nrf2 pathway is a central signaling system controlling oxidative stress response. While hyperammonemia is a sarcopenia inducer via Myostatin, its relationship with oxidative stress response in skeletal muscle remains unclear. This study aims to elucidate the association between ammonia exposure and oxidative stress in the progression of sarcopenia and identify novel therapeutic targets. **Methods:** C2C12 myoblasts were cultured in media with ammonia and treated under hydrogen peroxide(H_2O_2) exposure. MYH and intranuclear Nrf2 protein levels were quantified by western blot. ROS accumulation was measured using flow cytometry. TCA cycle intermediates in cells were also measured using a commercial kit. High ammonia model mice (HA mice) were generated by intraperitoneal injection of thioacetamide (TAA) and ammonium chloride into C57BL/6 mice. Oxidative stress markers, nuclear Nrf2, and TCA cycle intermediates in skeletal muscle were examined 24 hours after the ammonia injection. A liver fibrosis model was established by providing TAA in drinking water for 20 weeks, and a long-term high-ammonia model mice (LHA mice) were created by intraperitoneally administering ammonium chloride for 8 weeks. Muscle function, oxidative stress factors, and nuclear Nrf2 levels in skeletal muscle were measured. **Results:** In C2C12 cells, ammonia addition suppressed nuclear Nrf2 levels under H_2O_2 exposure and increased ROS accumulation, and decreased MYH protein expression. Additionally, ammonia exposure decreased TCA cycle intermediates, including alpha-ketoglutarate(α-KG) and fumarate(FM). The addition of TCA cycle intermediates, including αKG

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and FM precursors (dimethyl fumarate (DMF) and monomethyl fumarate (MMF)), reduced ROS accumulation. MMF supplementation most effectively increased nuclear Nrf2 levels. In HA mice, protein levels of nuclear Nrf2 and its target gene, antioxidant factor Nqo1, were decreased in skeletal muscle.. Levels of mitochondrial function-related proteins including VDAC1 was also decreased. α-KG and FM in muscle were reduced in HA mice. In LHA mice, muscle strength declined and nuclear Nrf2 protein level was decreased. Oxidative stress response factors and mitochondrial function-related proteins were also reduced. **Conclusion:** In cirrhosis,α-KG is consumed for ammonia metabolism in skeletal muscle. FM, a TCA cycle intermediate, promotes the nuclear translocation of Nrf2. This study suggests that ammonia causes an imbalance of TCA cycle intermediates, inhibits the nuclear translocation of Nrf2, increases sensitivity to oxidative stress, and potentially leads to muscle atrophy and functional decline. The TCA cycle and the Keap1-Nrf2 system could be potential therapeutic targets for sarcopenia.

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4139 | NON-INVASIVE DIAGNOSIS OF HVPG ≥20 MMHG IN CIRRHOTIC PATIENTS BASED ON SPLEEN VOLUME

Xinyu Chen[1] Huiling Xiang[2] Yicheng Lin[1] Jiajun Tian[2] Fenghui Li[2] Kefeng Jia[2] Rong Lv[2] Chao Yang[2] Jiayin Wang[2]

[1]Tianjin Medical University, [2]China Tianjin Third Central Hospital

Background: Portal hypertension due to cirrhosis produces serious complications. The Baveno VII consensus statement states that HVPG ≥20 mmHg is an indication of prophylactic TIPS for esophageal variceal bleeding in patients with cirrhosis. However, there are few noninvasive diagnostic methods regarding HVPG ≥20 mmHg in cirrhotic patients. Our study aims to investigate the independent risk factors for HVPG ≥20 mmHg in patients with cirrhosis and to construct a clinical noninvasive model for diagnosing HVPG ≥20 mmHg. **Methods:** We enrolled patients who underwent hepatic venous pressure gradient (HVPG) measurements and enhanced computed tomography (CT) examination from December 2019 to July 2023 from the Third Central Hospital of Tianjin China. Patients with portal vein thrombosis, previous splenectomy, hepatocellular carcinoma, and non-sinusoidal portal hypertension were excluded. Patients were divided into two groups according to their HVPG of more than 20 mmHg or not. 3D slicer software was used to outline the spleen and obtain the spleen volume in 5-mm-thick layer images from a continuous spiral scan-enhanced CT of the portal vein stage. **Results:** A total of 120 cirrhotic patients were included in this study. The median age was 57.50 (IQR 48.75-64.00) years. There were 78 male patients (65.0%). The etiology included viral cirrhosis (48,40.0%), alcoholic cirrhosis (33,27.5%), and others(39,32.5%). The median HVPG was 19.0 (IQR 15.0-22.0) mmHg. The median MELD score was 59.64 (IQR 56.84-62.67). Child-Pugh A and B were 87.5%. Median spleen volume was 719.24 (IQR 504.35-952.98) cm^3. Using HVPG ≥20 mmHg as the criterion, the enrolled patients were categorized into two groups. The two groups had significant differences in albumin, bilirubin, HVPG, and spleen volume (P values <0.05). Spleen volume was linearly correlated with HVPG (r = 0.364, p<0.001). Multivariate logistic regression showed that spleen volume (OR=1.002,95%CI 1.001-1.003), age (OR=1.044,95%CI 1.004-1.086), and albumin value (OR=0.906,95%CI 0.843-0.973) were independent risk factors for HVPG ≥20 mmHg. A model called the “S-HVPG” score was constructed accordingly, with an AUC value of 0.745 (95% CI 0.657-0.833). The cut-off value was 0.38, and the specificity and sensitivity were 62.1% and 83.3%. The S-HVPG score had better diagnostic efficacy than the spleen volume alone and the Child-Puge score, the MELD score, the ALBI, and the AAR. The Hosmer–Lemeshow test showed that the S-HVPG score was calibrated well (p = 0.082). The clinical decision curves showed that the S-HVPG score yielded greater net clinical benefit than Child-Puge, MELD, ALBI, and AAR scores. **Conclusion:** Spleen volume and HVPG showed a moderate correlation. Increased spleen volume is an independent risk factor for HVPG ≥20 mmHg in cirrhotic patients. Splenic volume-based S-HVPG scoring provides a new, simple, noninvasive method to diagnose HVPG ≥20 mmHg in cirrhotic patients.

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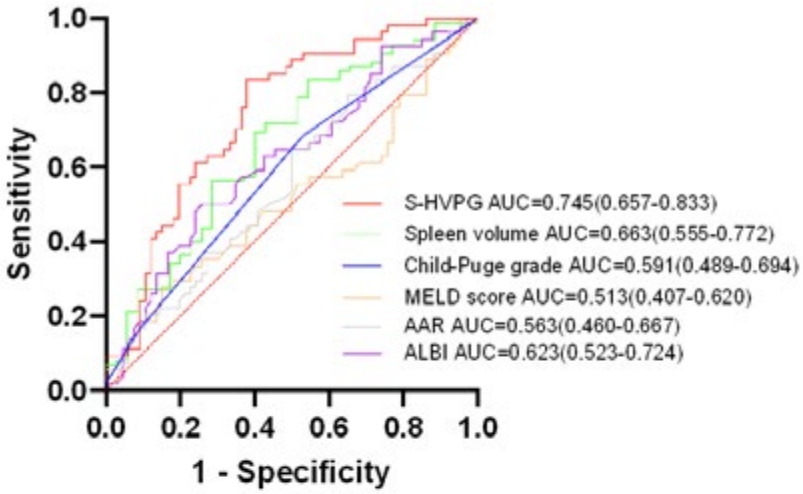

Figure 1. Comparison of the P-HVPG score with other methods in the diagnosis of HVPG ≥20 mmHg.

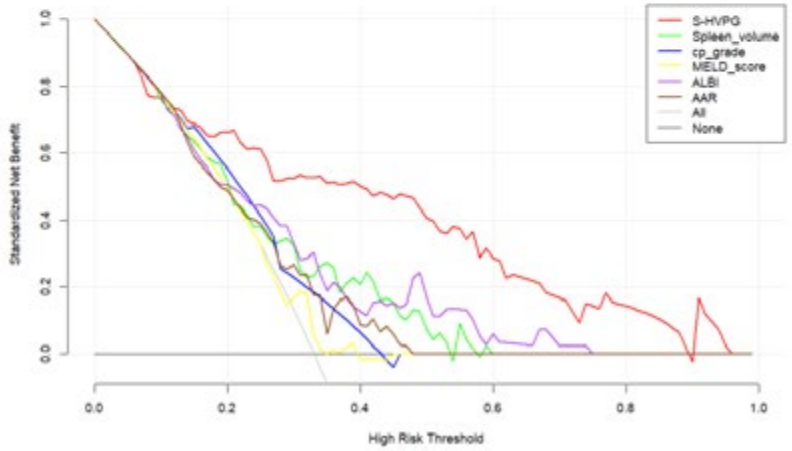

Figure 2. Decision curve analysis plot of the P-HVPG score, Spleen volume, Child-Pugh grade, MELD score, ALBI, and AAR.

Disclosures: Xinyu Chen: Nothing to Disclose, Huiling Xiang: Nothing to Disclose, Yicheng Lin: Nothing to Disclose, Jiajun Tian: Nothing to Disclose, Fenghui Li: Nothing to Disclose, Kefeng Jia: Nothing to Disclose, Rong Lv: Nothing to Disclose, Chao Yang: Nothing to Disclose, Jiayin Wang: Nothing to Disclose

4140 | THE PROPHYLACTIC ANTIBIOTICS DO NOT INFLUENCE THE CLINICAL OUTCOMES OF PATIENTS WITH CHILD A CIRRHOSIS AND ACUTE VARICEAL BLEEDING

jiajia He

Background: Acute variceal bleeding (AVB) is a severe decompensation event and one of the leading causes of death in patients with cirrhosis, with a 6-week mortality of up to 20%. Previous research has found that bacterial infection was independently associated with treatment failure and early mortality in patients with cirrhosis and AVB. Patients with infection had a four-fold increase in mortality compared to those who did not have infection. Several randomized controlled studies have demonstrated prophylactic antibiotics can significantly reduce the incidence of infection and treatment failure, as well as improve survival. Therefore, prophylactic antibiotics have become one of the standards of care in patients with cirrhosis and AVB. However, patients with Child A cirrhosis

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have a lower infection risk and 6-week mortality. Whether patients with Child A cirrhosis and AVB could benefit from prophylactic antibiotics remains uncertain. The present retrospective study was designed to investigate the impact of prophylactic antibiotics on patients with Child A cirrhosis and AVB. **Methods:** This was a retrospective study. Between January 2016 and November 2023, 342 patients with Child A cirrhosis and AVB admitted to West China Hospital were included for analysis. 80 patients were excluded due to co-existed infection (n=43), advanced tumors (n=31), and terminal illness of any major organ system such as CKD (n=6). Patients who received prophylactic antibiotics were included in the group A, and the remaining patients were included in the group B. The primary outcomes were 5-day treatment failure and 6-week mortality. 5-day treatment failure is defined by absence of control of bleeding or by rebleeding within the first 5 days. The secondary outcomes were the incidence of infection and 1-year mortality. **Results:** A total of 262 patients with Child A cirrhosis and AVB were included in the study. Chronic viral infection is the main cause of cirrhosis, accounting for 56.1% of all patients. The distribution of patients in the two groups was similar regarding sex ratio, age, etiology, and bleeding manifestations. The laboratory data obtained after admission, including hemoglobin, prothrombin time, total bilirubin, creatinine, Child-Pugh score, and Model for End-Stage Liver Disease score had no differences between the two groups. But patients in group A had higher alanine aminotransferase (P=0.02) and aspartate aminotransferase (P=0.01), lower albumin (P=0.000) and more transfusion requirement (P=0.004). 5-day treatment failure occurred in 8 patients in group A and 12 in group B and no statistical difference was reached. Multivariate analysis showed transfusion (OR=3.18, 95%CI 1.09-9.32, P=0.04) was significantly related to 5-day treatment failure and nosocomial infection was associated with 6-week mortality (OR=41.24, 95%CI 1.10-1551.62, P=0.04). 8 patients in group A and 7 patients in group B had an infection finally. The most common type of infection was pulmonary infection. The 1-year cumulative mortality was 4.14% in group A and 0.85% in group B (P=0.74). **Conclusion:** The prophylactic use of antibiotics did not influence 5-day treatment failure or 6-week mortality. Considering the good clinical outcomes of these patients, the prophylactic use of antibiotics may be avoided in patients with Child A cirrhosis and AVB.

Disclosures: jiajia He: Nothing to Disclose

4141 | WFA+-M2BP IS A USEFUL BIOMARKER FOR IDENTIFYING THE RISK OF MINIMAL HEPATIC ENCEPHALOPATHY IN CASES WITH HIGH MR ELASTOGRAPHY VALUES

Leona Osawa[1] Yuichiro Suzuki[1] Yasuyuki Komiyama[1] Hitomi Takada[1] Masaru Muraoka[1] Mitsuaki Sato[1] Shinya Maekawa[1] Nobuyuki Enomoto[2]

[1]University of Yamanashi, [2]University of Yamanahsi

Background: Minimal hepatic encephalopathy (mHE), characterized by the absence of overt symptoms but detectable through neuropsychological tests (NP tests), is associated with motor vehicle accidents and low quality of life. Though accurate diagnosis of mHE is clinically important, NP tests are time-consuming, and biomarkers identifying the high-risk cases for mHE have been awaited. In addition, it is unknown if mHE occurs in patients before progressing to cirrhosis. In this study, we searched for variables associated with the mHE risk in patients with low to advanced fibrotic liver diseases diagnosed by MR elastography (MRE). **Methods:** 114 patients who underwent NP tests within 3 months after MRE were included. Patients with MRE-liver stiffness (LS) values of 2.6 kPa or less were classified as the chronical liver disease (CLD) without fibrosis group (n=21), those with LS values between 2.61 kPa and 4.69 kPa were classified as the CLD with fibrosis group (n=54), and those with LS values of 4.7 kPa or higher were classified as the advanced liver fibrosis group (n=39). The percentage of mHE in each group was examined. NP tests positivity was defined as the presence of two or more abnormalities in the number connection test A and B, the digit symbol test, and the block design test. **Results:** The NP test was positive in 9.5% in the CLD without fibrosis group, 18.5% in the CLD with fibrosis group, and 38.4% in the advanced fibrosis group, indicating that the higher the MRE-LS value, the higher the NP test positivity (Cochran-Armitage test, p<0.001). In the advanced liver fibrosis group, factors associated with NP tests positivity showed that Alb ≤ 3.7 g/dL, WFA^+-M2BP, a marker of liver fibrosis ≥ 5.15 C.O.I, and portosystemic shunt ≥ 5 mm were associated with NP tests positivity in univariate analysis. In the multivariate analysis, WFA^+-M2BP ≥ 5.15 C.O.I was an independent associated factor. The NP tests positivity rate was 70% in patients with WFA^+-M2BP ≥ 5.15, whereas the NP test positivity rate was 28% in patients with WFA^+-M2BP <5.15, which was useful for identifying high-risk NP test positive cases. **Conclusion:** The percentage of NP test-positive patients increased with the progression of fibrosis as diagnosed by MRE. In patients with MRE ≥ 4.7 kPa, WFA^+-M2BP was shown to be useful in identifying high-risk cases of mHE.

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Disclosures: Leona Osawa: Nothing to Disclose, Yuichiro Suzuki: Nothing to Disclose, Yasuyuki Komiyama: Nothing to Disclose, Hitomi Takada: Nothing to Disclose, Masaru Muraoka: Nothing to Disclose, Mitsuaki Sato: Nothing to Disclose, Shinya Maekawa: Nothing to Disclose, Nobuyuki Enomoto: Nothing to Disclose

4142 | FRAILTY AND NUTRITIONAL RISK SIGNIFICANTLY INCREASE LIVER DISEASE-RELATED ADVERSE CLINICAL OUTCOMES IN PATIENTS WITH CIRRHOSIS - A SINGLE CENTRE, PROSPECTIVE COHORT STUDY

Guzainuer Yiliyaer[1] Guozhen Wang[2]

[1]School of Nursing, Xinjiang Medical University, [2]Department of Hepatology, Hospital of Traditional Chinese Medicine of Xinjiang Autonomous Region

Background: Objective: This study aims to assess the predictive value of frailty and nutritional risk for liver disease-related adverse clinical outcomes in patients with cirrhosis. **Methods:** A consecutive inclusion of patients with liver cirrhosis who were hospitalized in the Department of Hepatology at Xinjiang Traditional Chinese Medicine Hospital between January 2021 and June 2023 was conducted.The Liver Frailty Index (LFI) was employed to assess the patients' frailty status, while theNutritional Risk Screening (NRS 2002) was utilised to assess the nutritional risk of patients. Cox proportional hazard regression analysis were used to evaluate their association with liver disease-related adverse outcomes (liver disease-related deaths and decompensated events). **Results:** A total of 261 patients were included in the study(Mean baseline age 58.76±11.4, 44.83% male)..The prevalence of frailty and nutritional risk was 29.5% and 32.1%, respectively.The mean follow-up was 17.14±0.34 months, and there were 48 cases (18.39%) of liver disease-related deaths and 113 cases (43.30%)of decompensated events.After adjustment for age, sex, Model for end stage disease (MELD) and Child-Turcotte-Pugh (CTP), Cox regression analysis showed that frailty and malnutrition increased the risk of liver disease-related death by 218% [adjusted HR=3.18,95%CI(1.49,6.77),P=0.003] and 99% [adjusted HR=1.99,95%CI(1.04,3.80),P=0.038], and the risk of decompensation events was increased by 107% [adjusted HR=2.07,95%CI(1.31,3.27),P=0.002] and 55% [adjusted HR=1.55,95% CI(1.02,2.34),P=0.039],respectively. In patients with cirrhosis, the co-occurrence of frailty and nutrition risk was associated with a higher incremental risk of disease-related death[HR=13.12,95%CI(5.87,29.33),P<0.001]. **Conclusion:** Frailty and nutritional risk are predictors of liver disease-related adverse outcomes in patientswith cirrhosis.Co-occurrence of both significantly increased the risk of liver disease-related mortality and decompensated events in cirrhotic patients.

Disclosures: Guzainuer Yiliyaer: Nothing to Disclose, Guozhen Wang: Nothing to Disclose

4143 | VASCULAR PHENOTYPING FOR PREDICTIVE ASSESSMENT OF TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC SHUNT (TIPS) THERAPY IN PORTAL HYPERTENSION

Xiaolong Qi[1] Xumei Hu[2] Yi Xiang[3] Chengyan Wang[2] Dazhi Chen[4] Huiling Xiang[5] Linpeng Zhang[6] Wei Ye[7] Deqiang Ma[8] Xiaoqing Qiao[2]

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Background: Chronic liver disease is a major global health concern, often leading to cirrhosis and associated mortality. Portal hypertension, common in cirrhosis, presents hemodynamic challenges. While MRI has been explored as an alternative for assessing portal vein pressure, hepatic venous pressure gradient (HVPG) remains the gold standard. HVPG ≥ 20 mmHg indicates a high risk of surgical failure. However, HVPG measurement is invasive and not widely available, limiting its clinical utility. This study seeks to develop a non-invasive model using hepatic vascular structure analysis to predict HVPG, aiming to stratify TIPS patients into high and low-risk categories. **Methods:** This study analyzed CT scans from five medical centers: Zhejiang First Hospital (25 cases), Ningxia Hui Autonomous Region Hospital (27 cases), Third Hospital of Tianjin (92 cases), Third

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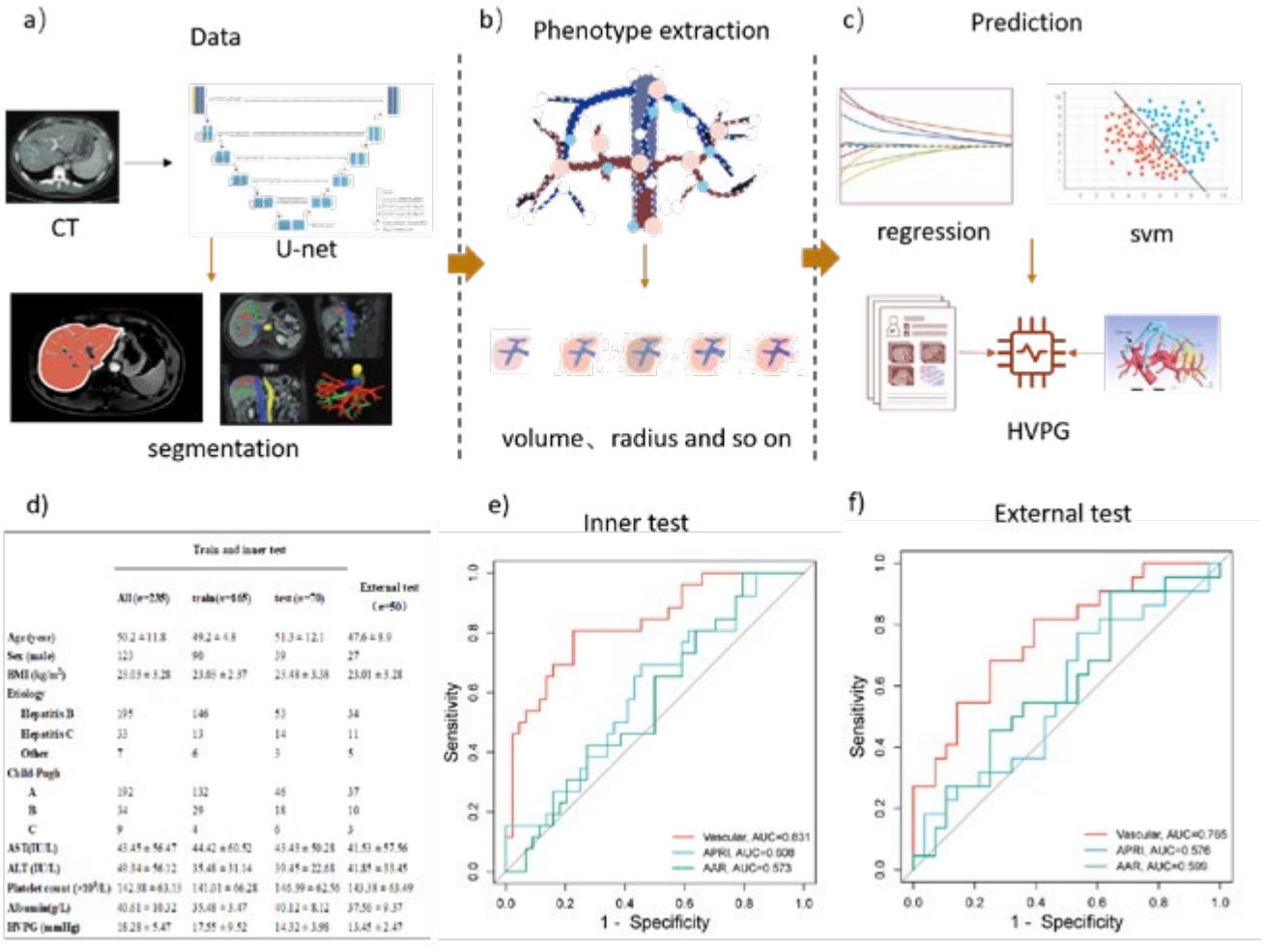
Hospital of Taiyuan (67 cases), and Second Hospital of Nanjing (24 cases). An additional dataset of 50 CT scans from cirrhosis patients at Taihe Hospital in Shiyan, Hubei Province served as an external test set. Diagnosis of cirrhosis relied on typical imaging features, histology (if available), and clinical signs such as ascites or varices. Radiologists, blinded to HVPG results, revised labels using ITK-SNAP. Vessels were segmented in portal venous and delayed phase by U-net, with the inferior vena cava labeled in delayed phase images. A decision-tree-based method automatically extracted three-dimensional centerlines of each vascular tree without user-defined parameters. Twelve geometric parameters were extracted from each vessel type. A support vector machine classified HVPG ≥ 20 mmHg and HVPG < 20 mmHg based on twelve vascular phenotypic features. Traditional serum markers were also included for comparison, such as aspartate aminotransferase to platelet ratio index and aspartate aminotransferase to alanine aminotransferase ratio. **Results:** Compared to patients with HVPG < 20 mmHg, those with HVPG ≥ 20 mmHg showed significant differences in various vascular parameters. In HVPG ≥ 20 mmHg patients, both portal vein (main branch length: 36.32 ± 18.35 mm vs. 30.12 ± 12.14 mm; P < 0.05) and hepatic vein (mean length: 26.04 ± 11.29 mm vs. 23.14 ± 10.53 mm; P < 0.05) had longer main branch lengths compared to the HVPG < 20 mmHg group. The proposed vascular phenotypic model demonstrated superior diagnostic performance compared to serum-based models like APRI and AAR, as evidenced by higher AUC (0.83 ± 0.01 vs. 0.61 ± 0.03 and 0.57 ± 0.02, respectively), accuracy (0.81 ± 0.03 vs. lower values), sensitivity, and specificity. Similar results were found in the external test set. **Conclusion:** This study presents a CT-based vascular phenotypic prediction model for non-invasive HVPG assessment, showing superior diagnostic performance compared to serum-based models. The model provides a non-invasive method for determining high-risk portal hypertension, aiding in TIPS placement decisions.



	Train and inner test			External test
	All (n=235)	train(n=165)	test (n=70)	(n=50)
Age (year)	50.2 ± 11.8	49.2 ± 4.8	51.3 ± 12.1	47.6 ± 8.9
Sex (male)	123	90	39	27
BMI (kg/m²)	23.03 ± 3.28	23.01 ± 2.37	23.48 ± 3.38	23.01 ± 3.28
Etiology				
Hepatitis B	195	146	53	34
Hepatitis C	33	13	14	11
Other	7	6	3	5
Child Pugh				
A	192	132	46	37
B	34	29	18	10
C	9	4	6	3
AST(IU/L)	43.45 ± 56.47	44.42 ± 60.52	43.43 ± 50.28	41.53 ± 57.56
ALT (IU/L)	40.34 ± 56.12	35.48 ± 31.14	39.45 ± 22.68	41.85 ± 33.45
Platelet count (×10⁹/L)	142.38 ± 63.13	141.01 ± 66.28	146.39 ± 62.56	140.18 ± 63.49
Albumin(g/L)	40.61 ± 10.22	35.48 ± 3.47	40.12 ± 8.12	37.56 ± 9.37
HVPG (mmHg)	18.28 ± 5.47	17.55 ± 9.52	14.32 ± 3.98	13.45 ± 2.47

Disclosures: Xiaolong Qi: Nothing to Disclose, Xumei Hu: Nothing to Disclose, Yi Xiang: Nothing to Disclose, Chengyan Wang: Nothing to Disclose, Dazhi Chen: Nothing to Disclose, Huiling Xiang: Nothing to Disclose, Linpeng Zhang: Nothing to Disclose, Wei Ye: Nothing to Disclose, Deqiang Ma: Nothing to Disclose, Xiaoqing Qiao: Nothing to Disclose

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4144 | VALIDATION AND COMPARISON OF NON-INVASIVE PREDICTION MODELS BASED ON SPLEEN STIFFNESS MEASUREMENT TO IDENTIFY CACLD PATIENTS WITH GASTROESOPHAGEAL VARICES

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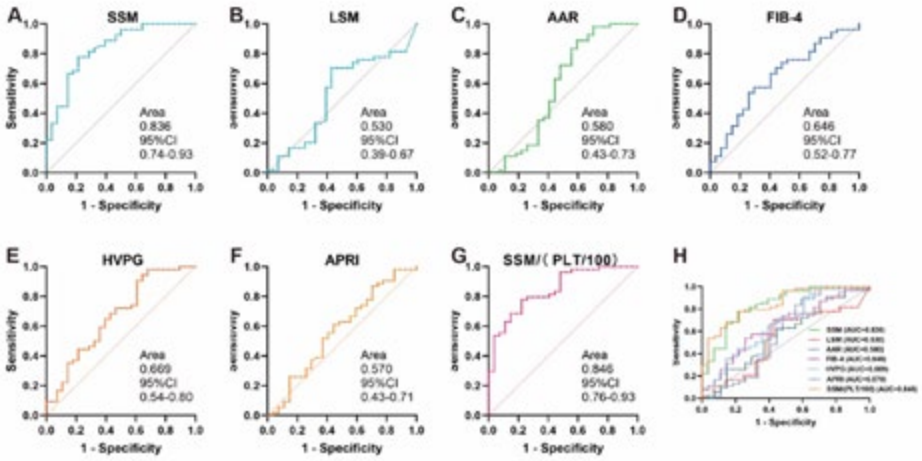
Background: Gastroesophageal variceal bleeding risk stratification in chronic liver disease depends on portal hypertension severity evaluation. Non-invasive tests are commonly utilized but have moderate accuracy. Spleen stiffness measurement (SSM) exhibits potential but requires validation. **Methods:** This single-center, cross-sectional study enrolled 195 chronic liver disease patients. Liver stiffness measurement (LSM) and SSM were measured using vibration-controlled transient elastography. Gastroesophageal varices (GEV) were assessed by endoscopy. Risk factors for varices and optimal cut-off values were analyzed. The accuracy of LSM, SSM, and composite indexes was compared. **Results:** Patients with varices demonstrated lower platelets, and higher bilirubin, LSM, and SSM. Decreased platelets and increased SSM independently predicted the presence of varices. SSM exhibited superior predictive ability compared to LSM. Higher SSM, hypoalbuminemia, and advanced age were independently associated with treatment-requiring varices. SSM (AUROC 0.836-0.829) outperformed LSM, AAR, APRI, and FIB-4 in diagnosing varices and determining treatment needs. The optimal SSM cut-off was 48.95kPa for varices and 49.65kPa for treatment requirements. **Conclusion:** SSM provides more accurate identification of patients with gastroesophageal varices compared to LSM and other non-invasive tests in chronic liver disease. SSM values correlate with the severity of portal hypertension and can aid in selecting patients for endoscopy. Transient elastography offers a dependable, non-invasive method for varices risk stratification to guide treatment management.

Receiver operating characteristic curves of NITs for cACLD patients diagnosed with GEV (identified by Gastroscope).



Receiver operating characteristic curves illustrate the diagnostic ability of NITs for detecting GEV in patients with cACLD. Receiver operating characteristic curves are shown concerning the (A) SSM; (B) LSM; (C)AAR; (D) FIB-E; (E) HVPG; (F)APRI; (G) SSM/(PLT/100) and (H) combined all NITs criteria. Diagonal segments are produced by ties. The area under the curve with standard error and the 95% confidence interval(95%CI) are shown in each plot.

Disclosures: lin tuo: Nothing to Disclose, Xingxiang Yang: Nothing to Disclose, Liting Yan: Nothing to Disclose, Ying Liu: Nothing to Disclose, Shuqiang Wang: Nothing to Disclose

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4145 | COMMUNITY ACQUIRED SEPSIS MORTALITY TRENDS IN A NATIONAL COHORT OF PATIENTS WITH CIRRHOSIS

Melissa Kaltenbach David Kaplan[1] Marina Serper[2] Therese Bittermann[3]

[1]University of Pennsylvania, [2]Hospital of the University of Pennsylvania, [3]Perelman School of Medicine

Background: Community-acquired sepsis (CAS) is a common and life-threatening complication in cirrhosis and is associated with poor prognosis. We aimed to evaluate the temporal trends in the 30-day mortality in individuals with cirrhosis and CAS and investigate the clinical factors associated with mortality after CAS. **Methods:** This was a retrospective cohort study of patients with cirrhosis in the US Veterans Health Administration (VHA) who were hospitalized for CAS between January 1, 2008 and December 31, 2019. Hospitalizations for community acquired sepsis were identified using a validated algorithm. Multivariable logistic regression was used to evaluate the association between calendar year and 30-day mortality after adjusting for patient factors. **Results:** A total of 76,984 CAS hospitalizations were analyzed. The crude 30-day mortality rate was 9.3% (p<0.001). Over the study period, there was no significant improvement in 30-day mortality by year (OR 0.99, 95% CI 0.99-1.01, p=0.548; Table 1). Model for End Stage Liver Disease Sodium (MELD-Na) score was significantly associated with increased odds of dying at 30-days with MELD-Na score of 35-40 with 37.8-fold increased odds compared with MELD-Na score of less than 15 (95% CI 32.44-44.00, p< 0.001). MASH cirrhosis had a 1.41-fold increased risk of death at 30 days compared to HCV cirrhosis (95% CI 1.26-1.60, p<0.001). Initial serum albumin was significantly associated with 30-day mortality; severe baseline hypoalbuminemia, defined as albumin level < 2.5 mg/dL, had the highest odds of death at 30-days (OR 3.27, 95% CI 2.88-3.70, p<0.001 compared to albumin > 3.5g/dl). Hospitalization at highest complexity level Veteran Affairs (VA) facilities was associated with improved 30-day mortality (OR 0.94, 95% CI 0.89-0.98, p=0.031). **Conclusion:** 30-day mortality rates in patients with cirrhosis and CAS did not improve between 2008 and 2019 despite published improvements in sepsis mortality in the general population over this timeframe. MASH cirrhosis and low albumin were significantly associated with increased 30-day mortality with increasing BMI providing a protective effect. Receiving care at the highest-level VA facilities was protective against short-term mortality even after adjusting for patient case-mix. Future studies are needed to better understand these associations with 30-day mortality in CAS and cirrhosis to focus future sepsis management efforts in this complex patient population.

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Table 1. Factors Associated with 30 day Mortality in CAS in Cirrhosis by Multivariable Analysis

	Odds Ratio (95% CI)	p-value
Year	0.99 (0.99-1.00)	0.548
Age	1.05 (1.02-1.08)	<0.001
Etiology of Liver Disease (HCV as reference)		
HCV	0.79 (0.70-0.88)	<0.001
MASH	1.41 (1.26 1.60)	<0.001
ALD	0.95 (0.86-1.06)	0.344
HBV	1.31 (0.99-1.90)	0.063
Meld-Na (score < 15 as reference)		
15-19	1.94 (1.77-2.12)	<0.001
20-24	3.26 (2.96-3.60)	<0.001
25-29	7.30 (6.53 8.16)	<0.001
30-34	16.65 (14.55- 19.01)	<0.001
35-40	37.84 (32.54-44.00)	<0.001
BMI (Normal as reference)		
Underweight	2.06 (1.69-2.49)	<0.001
Overweight	0.77 (0.71-0.86)	<0.001
Obese	0.69 (0.62 0.76)	<0.001
Albumin (Normal range of 3.5-4.5 mg/dL as reference)		
Marked hypoalbuminemia (< 2.5 mg/dL)	3.27 (2.88-3.70)	<0.001
Mild hypoalbuminemia (2.5-3.5 mg/dL)	1.49 (1.33-1.67)	<0.001
Hyperalbuminemia (>4.5 mg/dL)	0.84 (0.52-1.33)	0.451
Mechanical Ventilation	8.88 (7.91-9.96)	<0.001
Dialysis	1.53 (1.23 1.87)	<0.001
VA facility complexity (Reference 1D/1C/2/3 facilities)	Reference 1A	
1A	0.94 (0.89-0.98)	0.031
Diabetes	1.51 (1.36-1.68)	<0.001
Heart Failure	1.66 (1.61-1.72)	<0.001
Coronary Artery Disease	1.75 (1.69-1.81)	<0.001

Footnote: ALD= Alcohol related liver disease; HCV= Hepatitis C Virus; MASH= Metabolic associated steatohepatitis; HBV=Hepatitis B; MELD NA= model for end stage liver disease sodium score; VA= Veterans Affairs; BMI= body mass index with BMI < 18.5 kg/m2 as underweight, BMI 18.5-24.9 kg/m2 as healthy weight, BMI 25-29.9 kg/m2 as overweight, BMI 30 kg/m2 and above as obese.

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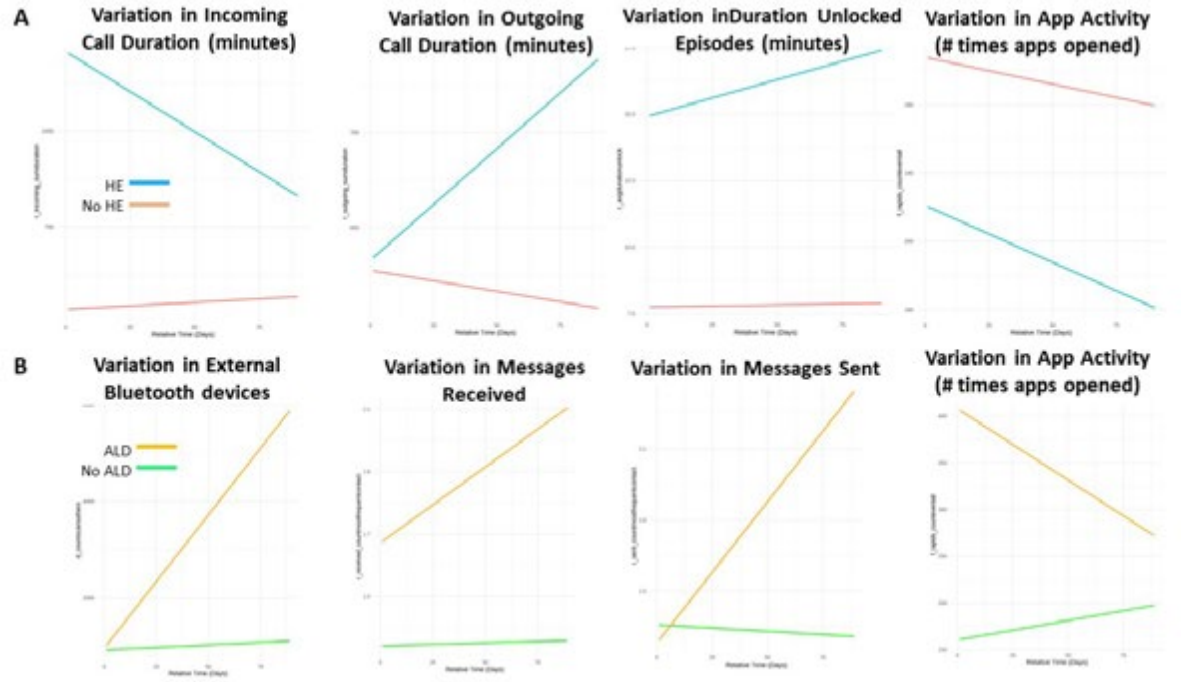
4146 | DIGITAL PHENOTYPE VARIES BY ALCOHOL USE HISTORY AND HEPATIC ENCEPHALOPATHY

Jessica Mellinger[1] Tingting Liu[2] Haila Asefa[3] Patricia Bloom[4] Sal Giorgi[2] Brenda Curtis[5]

[1]University of Michigan Hospitals and Health Centers, [2]Technology and Translational Research Unit, National Institute on Drug Abuse, [3]University of Michigan Hospitals and Health Center, [4]University of Michigan, Michigan Medicine, [5]National Institutes of Health

Background: Hepatic encephalopathy (HE) is responsible for substantial cirrhosis-related burden and may be detectable by digital phenotyping. Alcohol use disorder may also influence digital behaviors. We aimed to determine: 1) feasibility of digital phenotyping in cirrhosis patients; 2) digital phenotype variation in alcohol cirrhosis (AC) versus non-AC and HE versus no HE. **Methods:** 60 patients with and without both AC and HE were recruited from outpatient clinics. Subjects downloaded the AWARE app, an open-source mobile application designed which collects deidentified passive mobile phone data from 55 features from 9 sensors (e.g., Bluetooth, Call Logs) for up to 90 days from enrollment. . Demographics and labs were collected from the chart. Surveys for depression, anxiety, quality of life, insomnia, and alcohol use were collected at baseline (in-person), 30- and 90-days (by phone). Welch two sample t-tests were conducted for averaged each sensor feature by group. Multilevel Mixed model was conducted to compare variations over time, with Bonferroni correction. **Results:** 15 patients in each group were recruited (+AC/+HE, +AC/-HE, -AC/-HE, -AC/+HE) from 8/2022 to 5/2023 with 50% women and 95% non-Hispanic. Mean MELD 3.0 was 15 (range 6-25); mean AUDIT was 3.5 (range 0-30). Recruitment rate was 43% (60/139) with 78% retention at 90 days. HE had greater variance in initial app use time (t=-2.7, p=0.02) and average (t=-2.02, p=0.06) and longer duration (t=-1.9, p=0.08) of unlocked screen compared to non-HE. AC had greater variation in last incoming call time (t=-2.4, p=0.04), sent messages later (t=-1.9, p=0.07), and used the app earlier, compared to non-AC. When comparing variation over time, HE showed greater variability in total duration of incoming and outgoing calls, duration of unlocked episodes, and app usage (see Figure 1**,** panel A). For AC vs non-AC, there was variability over time in bluetooth sensors (a proxy for social interaction, number of messages sent and received, and app usage (see Figure 1, panel B). **Conclusion:** Digital phenotyping in cirrhosis patients is feasible with substantial variation in digital phenotypes between AC and non-AC and those with and without HE. Future studies in a larger population are needed to refine the phenotype and explore relationships to clinical events.

Figure 1. Variation over time in sensor data between HE and non-HE (**Panel A**) and AC and non-AC subjects (**Panel B**)



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Disclosures: Jessica Mellinger: Nothing to Disclose, Tingting Liu: Nothing to Disclose, Haila Asefa: Nothing to Disclose, Patricia Bloom: Vedanta Biosciences: Research grant, Nexilico: Consultant, Sal Giorgi: Nothing to Disclose, Brenda Curtis: Nothing to Disclose

4147 | DISTRIBUTION OF ORGANISMS IN PATIENTS WITH SPONTANEOUS BACTERIAL PERITONITIS: A VETERAN'S HEALTH COHORT STUDY

Nadim Mahmud[1] Natalia Salinas Parra[2] Aaron Hecht[3] David Kaplan[3] Marina Serper[4]

[1]Hospital of the University of Pennsylvania, [2]Hospital of the University of Pennsylvania, [3]University of Pennsylvania, [4]University of Pennsylvania Health System

Background: Spontaneous bacterial peritonitis (SBP) is a common complication of decompensated cirrhosis with a high mortality rate. The microorganism profile of causative agents has been studied in peritoneal fluid but has not been defined for other sources of infection. We investigated the distribution of organisms across infectious sources and risk of 30-day mortality in a national cohort of patients with cirrhosis hospitalized with SBP in the Veterans Health Administration (VHA). **Methods:** This was a retrospective cohort study of patients during their index hospitalization for SBP between 1/2008 and 10/2023. SBP was defined as an ascites fluid polymorphonuclear leukocyte count > 250/mm^3 in the hospital. Baseline demographic data, BMI, etiology of cirrhosis, MELD-Na pre-hospitalization and on hospital presentation were collected. We analyzed culture growth in blood, peritoneal, urine, and other fluids stratified by source and Child-Pugh-Turcotte (CTP) class. Logistic regression models adjusted for age, sex, BMI, race, etiology, pre-hospital MELD-Na, and diabetes evaluated risk of 30-day mortality in patients with positive infectious sources versus those with negative cultures. **Results:** 5,176 patients were included from 125 VHA centers. Patients were predominantly male (98%) and white (62%) with cirrhosis secondary to alcoholic liver disease (43.7%) and an increase in median MELD-Na from 16 to 24.3 at the time of hospitalization. Culture data identified organisms in 1,815 patients, with E. Coli being the most common (urine 21.2%, blood 22.3%, peritoneal fluid 24.3%, other 20.3%, p<0.001). E. Coli prevalence increased with liver disease severity (CTP class A 29.9% to class C 38.8% in blood; 35.2% to 39.2% in peritoneal cultures, p<0.001; Figure 1A), while Staph aureus concurrently decreased (class A 35.5% to class C 10.2% in blood; 17.2% to 5.4% in peritoneal cultures, p <0.001; Figure 1B). Patients with positive blood and peritoneal cultures had a 2.5-fold increased odds of 30-day mortality compared to culture negative patients (95% CI 1.93-3.23, p<0.001). Those with positive peritoneal but negative blood cultures had 1.51-fold increased odds versus culture negative (95% CI 1.26-1.81, p<0.001). **Conclusion:** In this large VA cohort, there was a significant difference in the microbiology of identified organisms in the blood and peritoneal fluid of patients with SBP across CTP classes. Furthermore, patients with positive culture data from multiple sources had an elevated risk of 30-day mortality, underscoring the need for further studies to inform targeted treatment and identify high-risk patients.

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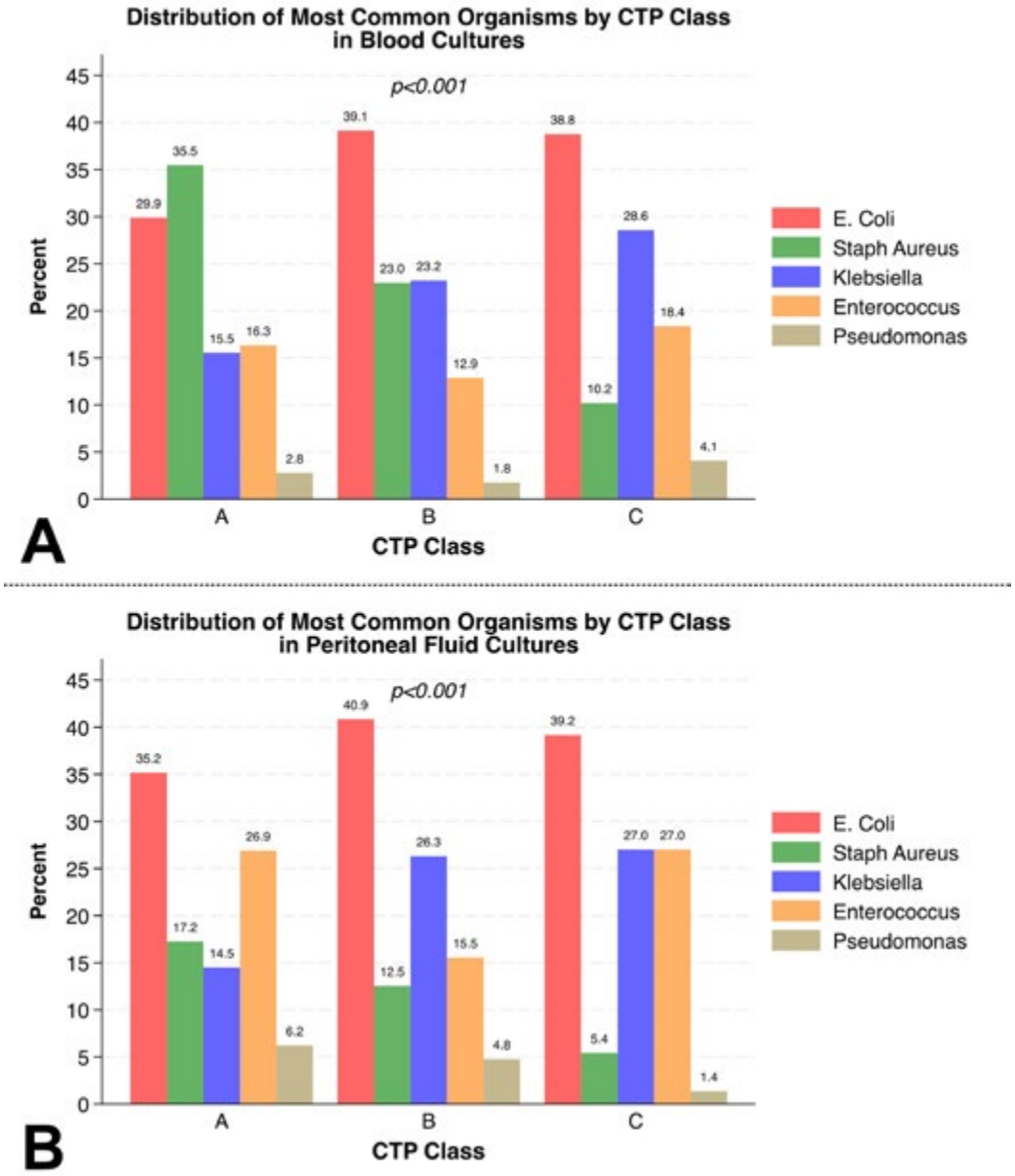

Disclosures: Nadim Mahmud: Nothing to Disclose, Natalia Salinas Parra: Nothing to Disclose, Aaron Hecht: Nothing to Disclose, David Kaplan: Independent Contractor relationship with Roche Genentech; Has not ended; Grant/Research Support relationship with AstraZeneca Inc; Has not ended; Advisor relationship with AstraZeneca; Has ended; Advisor relationship with Exelixis; Has ended; Grant/Research Support relationship with Gilead; Has not ended; Advisor relationship with Sirtex; Has ended; Grant/Research Support relationship with Exact Sciences; Has not ended; Grant/Research Support relationship with Glycotest; Has ended, Marina Serper: Grant/Research Support relationship with Grifols; Has not ended; Grant/Research Support relationship with Eurofins; Has not ended; Grant/Research Support relationship with Transplant Genomics; Has not ended

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4148 | BASELINE SATISFACTION SCORES FOR PATIENTS WITH ESLD IN PAL-LIVER COHORT SIMILAR BETWEEN VA AND NON VA CENTERS AND DIFFERENT ETIOLOGIES OF LIVER DISEASE

Richard Kalman[1] Kristel Hunt[2] Mark Gallagher[3] Yang Yue[4] Andrzej Kosinski[4] Victor Navarro[5] Manisha Verma[1]

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Background: Patient satisfaction is associated with better treatment compliance and outcomes. The PAL-LIVER study, a PCORI funded randomized controlled trial, aims to determine if palliative care delivered by trained hepatologists (11 sites) is superior to palliative care by palliative specialists (8 sites) and concludes in 2025. Patient satisfaction with healthcare interaction is assessed using FAMCARE, a validated scale. A score of >52 is considered generally satisfied. As part of the baseline demographics, FAMCARE is obtained. They are enrolled for 3 months of intervention and 9 months of follow up. **Methods:** Nineteen clinical centers were randomized to either of the two models. The study population includes patients with ESLD with a recent episode of decompensation and/or patients with hepatocellular carcinoma, all with a prognosis of greater than 3 months. Inclusion criteria requires patients to be over 18 years old, speak English, and have hepatocellular carcinoma (BCLC C with child class A or BCLC A/B/C with child class B) or child class B or C with one complication. MELD over 30, prior palliative care within 1 year, life expectancy less than 6 months or likelihood of transplant within 3 months were exclusion criteria. We utilized baseline FAMCARE and demographics for these analyses. Higher FAMCARE scores reflect better satisfaction (range 1-65). P values were computed by t-test for continuous variables and chi square test for categorical variables. **Results:** For a total of 815 patients, the mean age was 62.8 years and most were male (71.4%). The mean MELD at baseline is 11.3. The mean FAMCARE baseline score was 54 and was not statistically different between VA and non-VA centers (53.5 vs 54.2, p 0.33). Within the individual FAMCARE questions, non-VA centers had superior nursing availability to answer questions (p 0.023) and availability of doctors to answer questions (p 0.026). Referrals to specialists and follow up of tests and treatments were also superior at non-VA sites (p 0.009 and p 0 0.01). There was no difference in overall FAMCARE scores for patients based on etiology of liver disease (alcohol, viral hepatitis, NASH/NAFLD). Notably, patients with alcohol related liver disease were less satisfied with information about prognosis when compared to other etiologies (p 0.016). **Conclusion:** Overall baseline satisfaction scores for patients enrolled in the PAL-LIVER study suggest moderate satisfaction, but there is room to improve. Comparable satisfaction levels were observed across both VA and non-VA centers, as well as among patients with diverse etiologies of liver disease. There is a trend towards better communication at non-VA centers. Patients with alcohol related liver disease express comparatively lower satisfaction levels regarding prognosis than those with other etiologies. This underscores the need for tailored communication strategies that address the unique needs of patients with alcohol related liver disease.

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PAL-LIVER Study
Table 1. Demographics of Baseline FAMCARE Score Population

Parameter Statistic	Total (N=815)
Age (Years)	
N	815
Mean (SD)	62.8 (10.1)
Median (Q1, Q3)	64.0 (57.0, 70.0)
Minimum, Maximum	21, 87
Female	233/815 (28.6%)
Ethnicity	
Hispanic or Latino	115/815 (14.1%)
Not Hispanic or Latino	688/815 (84.4%)
Not Reported	9/815 (1.1%)
Unknown	3/815 (0.4%)
Race	
American Indian or Alaska Native	9/815 (1.1%)
Asian	9/815 (1.1%)
Black or African American	132/815 (16.2%)
Native Hawaiian or other Pacific Islander	1/815 (0.1%)
White	645/815 (79.1%)
Other	25/815 (3.1%)
MELD score at Baseline	
N	762
Mean (SD)	11.3 (6.0)
Median (Q1, Q3)	10.7 (6.9, 14.6)
Minimum, Maximum	-3, 37

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Disclosures: Richard Kalman: Nothing to Disclose, Kristel Hunt: Nothing to Disclose, Mark Gallagher: Nothing to Disclose, Yang Yue: Nothing to Disclose, Andrzej Kosinski: Nothing to Disclose, Victor Navarro: Nothing to Disclose, Manisha Verma: Nothing to Disclose

4149 | EXERCISE DURING HYPERAMMONEMIA ACTIVATES ADAPTIVE SKELETAL MUSCLE AMMONIA METABOLISM

Annette Bellar[1] Avinash Kumar[2] Muaz Alsabbagh Alchirazi[1] Amy Attaway[1] Pugazhendhi Kannan[1] Saurabh Mishra[1] Nicole Welch[1] Srinivasan Dasarathy[1]

[1]Cleveland Clinic, [2]All India Institute of Medical Sciences

Background: Exercise induced muscle ammoniagenesis can worsen muscle perturbations and limit beneficial responses in liver disease. Muscle ammonia metabolism occurs via glutamate dehydrogenase (GDH) catalyzed ammonia-induced cataplerosis of a-ketoglutarate (aKG) to form glutamate. Metabolic fate of muscle glutamate include glutamine synthesis by glutamine synthase (GS) with additional ammonia disposal; proline biosynthesis by pyrroline-5-carboxylate synthetase (P5CS), a redox restoring reaction; and aspartate synthesis via glutamate-oxaloacetate aminotransferase (GOT) to replenish aKG. Glutaminase (GLS) generates glutamate via glutaminolysis to support anaplerosis but generates more ammonia (Fig. 1). We tested skeletal muscle ammonia disposal adaptation during exercise in a mouse model of sarcopenia of cirrhosis. **Methods:** Hyperammonemic mice, an established model of cirrhotic sarcopenia were compared with control mice. Miniosmotic pumps were implanted in wild type, male C57BL6 mice aged 8-9 weeks to deliver 2.5mM ammonium acetate (AmAc) or phosphate buffered saline (PBS) as vehicle for 6 weeks. After 2 weeks recovery from pump placement, mice were randomized to voluntary wheel running (VWR) or usual activity (UA) for 4 weeks. Locomotor actvitivy was collected using ClockLab Systems. Circadian patterms were evaluated using JTK, LS, and Meta2d algorithims in MetaCycle R package. At the end of the study, in addition to the phenotype and muscle phenotype, plasma and muscle ammonia concentrations were measured by fluorescence assay. Immunoblots were performed for critical

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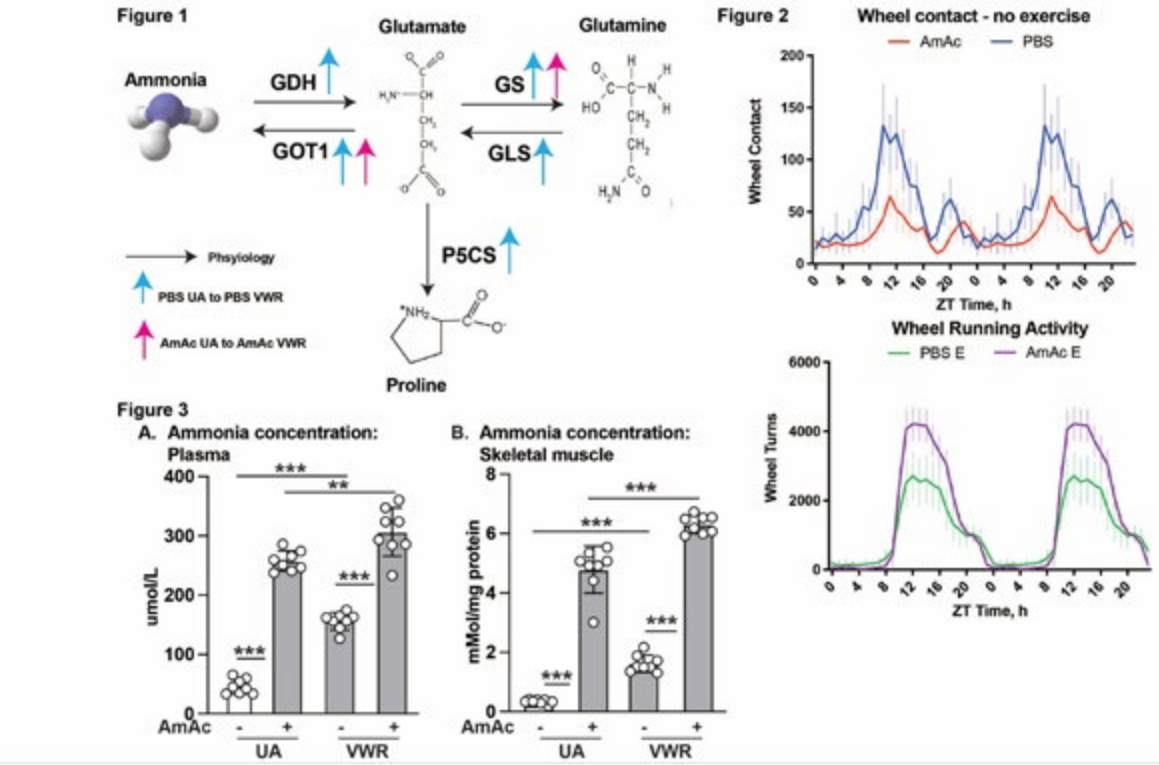
ammonia disposal enzymes in the gastrocnemius (GA) muscle. **Results:** Running patterns including number of whee contacts for UA mice and wheel rotations for VWR mice and circadian patterns were evaluated. PBS UA mice had more contact with the locked wheel than AmAc UA. AmAc VWR mice had a greater number of wheel rorations than PBS VWR mice (p<0.001) (Fig.2). There were no changes in circadian pattern between the mice. Ammonia concentrations in blood and gastrocnemius (GA) ammonia concentrations were higher in PBS-VWR, AmAc-UA, and AmAc-VWR mice (p <0.001 in all groups) as compared to PBS-UA mice (Fig.3). VWR increased blood and muscle ammonia concentrations in both PBS and AmAc groups vs. the respective UA group (p<0.001 for all comparisons). In AmAc UA mice GDH, GS, GLS, and P5CS were increased (p<0.05 for all) vs. PBS UA. In PBS mice, VWR increased all the measured ammonia disposal enzymes (p<0.01 for all). Interestingly only GS and GOT expression were greater in the AmAc VWR mice compared to the AmAc UA with no change in GDH, GLS, or P5CS. **Conclusion:** AmAc VWR mice ran more than PBS VWR mice. Muscle adaptive responses to VWR during hyperammonemia include cataplerosis of aKG for ammonia disposal and proline biosynthesis to maintain redox status. However, adaptive exhaustion contributes to worsening hyperammonemia to limit exercise benefits in cirrhosis.



Disclosures: Annette Bellar: Nothing to Disclose, Avinash Kumar: Nothing to Disclose, Muaz Alsabbagh Alchirazi: Nothing to Disclose, Amy Attaway: Nothing to Disclose, Pugazhendhi Kannan: Nothing to Disclose, Saurabh Mishra: Nothing to Disclose, Nicole Welch: Nothing to Disclose, Srinivasan Dasarathy: Nothing to Disclose

4150 | VALIDATING AND EXPANDING THE BAVENO &LDQUO;RULE OF FIVE&RDQUO; CRITERIA FOR STRATIFYING RISK OF PORTAL HYPERTENSIVE COMPLICATIONS ◆

Abbey Barnard Giustini[1] Philip Vutien[1] Nicole Kim[2] Andrew Moon[3] Chun-Nan Hsu[4] Joleen Borgerding[5] Kay Johnson[1] Kristin Berry[5] Lauren Beste[1] George Ioannou[2]

[1]University of Washington, [2]University of Washington Medical Center, [3]University of North Carolina, [4]University of California San Diego/VA San Diego Healthcare System, [5]Veterans Affairs Puget Sound Health Care System

Background: The Baveno VII workshop proposed the “Rule of Five” criteria, also adopted by EASL and AASLD, which for the first time provides non-invasive definitions of compensated advanced chronic liver disease (cACLD) and clinically significant portal hypertension (CSPH) based only on FibroScan©-derived liver stiffness (LS)

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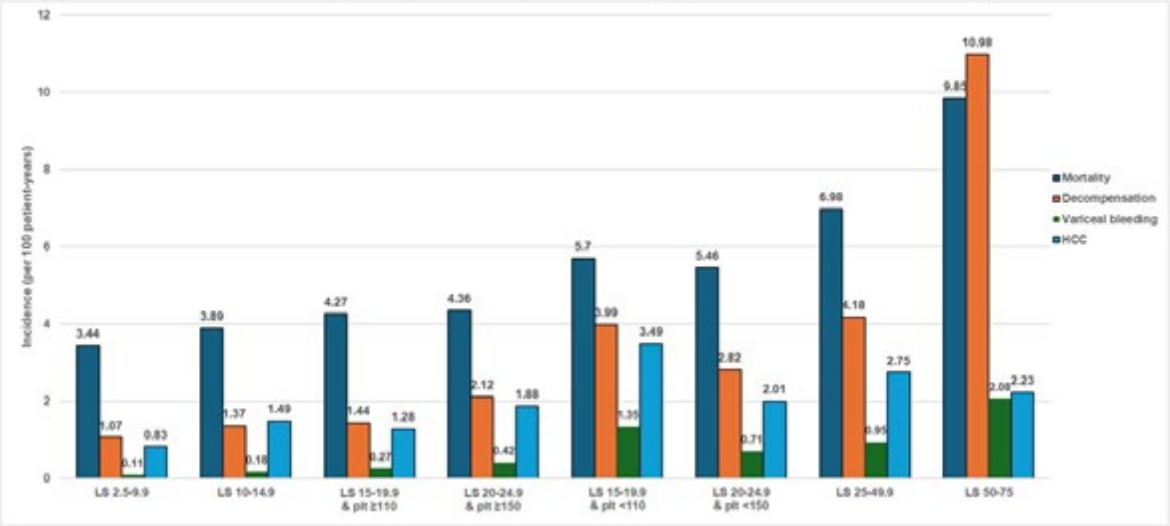
and platelet count. We aimed to validate these criteria by determining the extent to which they correlate with adverse outcomes, specifically mortality, decompensation, and hepatocellular carcinoma (HCC). **Methods:** We identified 17,076 patients in the Veterans Affairs Healthcare System without HCC or decompensation (ascites, hepatic encephalopathy, gastro-esophageal variceal bleeding, spontaneous bacterial peritonitis, hepatorenal syndrome or hepatopulmonary syndrome), who underwent LS and platelet measurements. Patients were categorized according to the following "Rule of Five" incremental categories: LS 2.5-9.9 kPa ("possible fibrosis"); LS 10-14.9 ("possible cACLD/no CSPH"); LS 15-19.9 & platelets ≥110,000 ("grey zone"); LS 20-24.9 & platelets ≥150,000 ("grey zone"); LS 15-19.9 & platelets <110,000 ("probable CSPH"); LS 20-24.9 & platelets <150,000 ("highly probable CSPH"); and LS ≥25 (definite CSPH), which we further sub-divided into LS 25-49.9 and 50-75 categories to determine whether further subcategorization of definite CSPH is warranted. **Results:** Each increase in "Rule of Five" category was associated with higher risks of mortality (HR 1.22, 95% CI: 1.18-1.25), decompensation (HR 1.53, 95% CI: 1.47-1.59), and HCC (HR 1.32, 95% CI: 1.26-1.39) (Figure 1). Patients in the grey zone had higher risks of decompensation and mortality than those with "possible cACLD/no CSPH" but lower risks than those with probable or highly probable CSPH. Compared to LS 25-49.9, patients with LS 50-75 had even higher risks of decompensation and mortality, but not HCC. **Conclusion:** The "Rule of Five" is a simple and valid system for stratifying risks of hepatic decompensation, HCC, and death. Patients with definite CSPH (LS ≥25 kPa) can be further subdivided into "early-stage CSPH" (LS 25-49.9 kPa) and "advanced-stage CSPH" (LS 50-75 kPa), as the latter is associated with substantially higher risks of death and hepatic decompensation.

Figure 1 Incidence of mortality, decompensation, variceal bleeding, and HCC when stratified by "Rule of Five" risk categories based on liver stiffness (LS) in kilopascal and platelet count (plt). Platelet counts in units of x10⁴/µl.



Disclosures: Abbey Barnard Giustini: Nothing to Disclose, Philip Vutien: Nothing to Disclose, Nicole Kim: Nothing to Disclose, Andrew Moon: TARGET RWE: Consultant, DCN Diagnostics: Grant/Research Support, Intercept Pharmaceuticals: Consultant, Intercept Pharmaceuticals: DSMB, IDEOlogy: Consultant, Chun-Nan Hsu: Nothing to Disclose, Joleen Borgerding: Nothing to Disclose, Kay Johnson: Nothing to Disclose, Kristin Berry: Nothing to Disclose, Lauren Beste: Nothing to Disclose, George Ioannou: Nothing to Disclose

4151 | TIPS AND VARICEAL EMBOLIZATION IN PEDIATRIC PATIENTS WITH VARICEAL BLEEDING SECONDARY TO PORTAL HYPERTENSION: A RETROSPECTIVE STUDY

Antonio Moreno[1] Thomas Issa[1] Douglas Farmer[2] Edward Wolfgang Lee[3]

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Background: Gastroesophageal variceal bleeding is a life threatening complication of portal hypertension. Current standard of treatment in adults presenting with variceal bleeding refractory to conservative management include transjugular intrahepatic portosystemic shunt (TIPS) placement and variceal embolization. However, there are no guidelines for performing these interventions in the pediatric population, largely due to limited literature

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investigating follow up outcomes in management of variceal bleeding. Furthermore, there is no study assessing outcome differences between TIPS and variceal embolization in the pediatric population. **Methods:** Between September 2012 and December 2023, 27 pediatric interventions (19 unique patients) were performed with TIPS or variceal embolization for variceal bleeding refractory to conservative management. Outcome parameters were evaluated at baseline, 3 days, 1 month, 3 months, and 12 months follow up. Fisher tests were performed comparing recurrence of variceal bleeding between the two interventions. **Results:** Median patient age was 8 years (range: 8 months – 17 years). There were 19 unique patients, 11 males, 8 females. There were 14 TIPS and 13 variceal embolizations.TIPS placement was technically successful in 13/14 (93%) of cases with one patient undergoing successful TIPS on second attempt. No recurrence of bleeding at 3 days, 1 month, and 3 months. At 12 months 3 patients had rebleeding and underwent repeat intervention (1 TIPS revision, 2 embolization).Variceal embolization was technically successful in 100% of cases. 1 patient had rebleeding at 3 days and underwent repeat TIPS. 2 patients had rebleeding at 1 month and 3 months and both underwent repeat intervention with TIPS. No rebleeding at 12 months.Fisher test performed between TIPS and variceal embolization groups showed no statistically significant difference ($p > 0.05$) in recurrence of variceal bleeding at follow up of 3 days, 1 month, 3 months, and 12 months.No major complications were observed in either group. Two patients received orthotopic liver transplant. Two patients passed away due to transplant complication and multi-organ failure. **Conclusion:** TIPS and variceal embolization for variceal bleeding secondary to portal hypertension in pediatric patients demonstrated 1) improved management of variceal bleeding episodes and 2) no significant difference in recurrence of variceal bleeding between the two interventions at 3 days, 1 month, 3 months, and 12 months.

Disclosures: Antonio Moreno: Nothing to Disclose, Thomas Issa: Nothing to Disclose, Douglas Farmer: Nothing to Disclose, Edward Wolfgang Lee: Nothing to Disclose

4152 | STATIN USE IN CIRRHOSIS CAN DECREASE RISK OF PORTAL HYPERTENSION AND MORTALITY

Muhammad Ali Butt[1] Taimur Muzammil[1] Rahul Karna[2] Himsikhar Khataniar[1] Nabeeha Mohy-ud-din[3]

[1]Allegheny General Hospital, Pittsburgh, PA, [2]University of Minnesota Medical Center, [3]Division of Gastroenterology, Hepatology and Nutrition, Allegheny Health Network, Pittsburgh, PA

Background: MASLD related cirrhosis is one of the leading etiologies of liver disease, and these patients frequently have other comorbidities like atherosclerotic cardiovascular disease (ASCVD), hyperlipidemia (HLD), cerebrovascular disease (CVD), and diabetes mellitus (DM). Statins are commonly prescribed for cardiovascular protection in these patients. However, the precise impact of statin therapy on clinical outcomes in these patients remains uncertain. This study aims to assess the effects of statin use on clinical outcomes in cirrhosis patients with MASH and associated comorbidities. **Methods:** We utilized the TriNetX database US collaborative Network to identify patients with cirrhosis and an indication for statin use. A total of 174,825 patients were included: 81,820 receiving statins and 93,005 not receiving statins. Propensity score matching was performed for age, sex, and race, resulting in two matched cohorts of 72,280 patients each. Outcomes analyzed included the incidence of portal hypertension, spontaneous bacterial peritonitis (SBP), hepatorenal syndrome (HRS), thrombosis, hepatic encephalopathy (HE) and mortality. Statistical analyses included odds ratios, and kaplan-meier survival analysis. **Results:** Statin use was associated with significantly lower risk of portal hypertension (OR 0.83, 95% CI 0.80-0.85), SBP (OR 0.52, 95% CI 0.39-0.67), thrombosis (OR 0.69, 95% CI 0.64-0.76), HE (OR 0.7, 95% CI 0.68-0.74) and HRS (OR 0.61, 95% CI 0.52-0.72). Mortality was significantly lower in the statin group (OR 0.85, 95% CI 0.83-.0.88). **Conclusion:** Our study demonstrates that statin use is associated with a decreased risk of portal hypertension and its complications, along with lower mortality. These findings underscore the importance of incorporating statins into the management strategy for cirrhosis patients. Moreover, the observed under prescription of statins despite clear indications suggests a need for enhanced awareness and adherence to guidelines in clinical practice.

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Table 1. Results: Propensity-Matched Analysis

Outcome	Odds Ratio (OR)	Confidence Interval (CI) 95%
Portal Hypertension	0.83	0.80-0.85
Spontaneous Bacterial Peritonitis	0.52	0.39-0.67
Hepatorenal Syndrome	0.61	0.52-0.72
Thrombosis	0.69	0.64-0.76
Encephalopathy	0.70	0.68-0.74
Mortality	0.85	0.83-0.88

Disclosures: Muhammad Ali Butt: Nothing to Disclose, Taimur Muzammil: Nothing to Disclose, Rahul Karna: Nothing to Disclose, Himsikhar Khataniar: Nothing to Disclose, Nabeeha Mohy-ud-din: Nothing to Disclose

4153 | TRANSFUSION OF BLOOD PRODUCTS IN THE SETTING OF A VARICEAL BLEED IS ASSOCIATED WITH HIGHER RISK OF TIPS, INTUBATION, HOSPITAL RE-ADMISSION, AND MORTALITY

Muhammad Ali Butt[1] Sameen Aamer[1] Himsikhar Khataniar[1] Sheldon Rao[2] Nabeeha Mohy-ud-din[3]

[1]Allegheny General Hospital, Pittsburgh, PA, [2]Department of Internal Medicine, Texas Tech University-El Paso, [3]Division of Gastroenterology, Hepatology and Nutrition, Allegheny Health Network, Pittsburgh, PA

Background: Transfusion of blood products (FFP/platelets/cryoprecipitate) is often performed during a variceal bleed in order to correct INR and platelet level, although the etiology of the bleed is secondary to portal hypertension and not hemostatic failure. **Methods:** We conducted a retrospective cohort analysis of adult patients who sought care at 64 hospital networks across the US using the TrinetX database. We identified all patients with a diagnosis of 'variceal bleed' followed by transfusion of FFP or platelets or cryo within 72 hours of diagnosis (this was noted as 'index' event) and analyzed outcomes data for the following 6 months. We applied propensity score matching to balance potential confounders based on demographics. Outcomes including TIPS procedure, ICU admissions, intubation, hospital re-admissions, and mortality was analyzed. **Results:** Data was obtained for a total of 2 million patients with a diagnosis of 'variceal bleed', out of which 131,526 patients received transfusions of FFP/cryo/platelets within 72 hours of diagnosis, and 1.9 million patients did not receive these transfusions. The mean age was 64.7 +/- 17.2 vs 50.9 +/- 24.3 with 43.6% (n=57,206) vs 48.1% (n=865,328) females.
We applied propensity score weighting to balance confounders of age, sex, and race between patients, comparing outcomes between 131,135 patients in each cohort. The patients who received transfusions of FFP/cryo/platelets were more likely to undergo TIPS procedure (OR 4.7, [95% CI 4.08 – 5.46]), intubations (OR 3.91 [95% CI 3.73-4.11]), hospital re-admissions (OR 4.21 [95% CI 4.14-4.28], lesser risk of ICU admissions (OR 0.51 [95% CI 0.45-0.58]) and associated with higher odds of mortality (OR 2.91 [95% CI 2.84-.298]). **Conclusion:** Patients who receive transfusions of FFP/cryo/platelets in the setting of an acute variceal bleed have worse outcomes, with the number needed to harm of 7.9. There may be bias due to confounding in our study, however, this is the largest study to date that evaluates the harm with transfusions in the setting of a variceal bleed.

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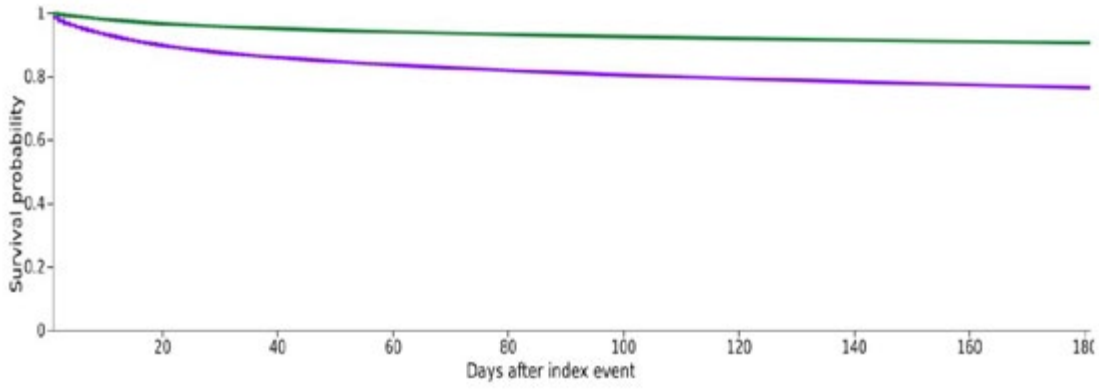

Figure 1: Survival analysis between patients who received transfusions (purple) vs those who did not (green)

Disclosures: Muhammad Ali Butt: Nothing to Disclose, Sameen Aamer: Nothing to Disclose, Himsikhar Khataniar: Nothing to Disclose, Sheldon Rao: Nothing to Disclose, Nabeeha Mohy-ud-din: Nothing to Disclose

4154 | ASCITES CARE IN ACADEMIC VERSUS COMMUNITY SETTING: ARE THEY EQUAL OR NOT THE SAME?

Chinmay Bera[1] *Neha Tiwari*[1] *Cynthia Tsien*[2] *Nazia Selzner*[1] *Florence Wong*[1]

[1]*University of Toronto,* [2]*Toronto General Hospital*

Background: Ascites care ideally should be provided in a tertiary care setting. Limited manpower and resources mean that some ascites care is shared with the community setting. Outcomes of community ascites care has never been assessed. **Aim**: To compare outcomes of ascites care in the academic (A) vs. community (C) setting during the COVID period which necessitated shared care. **Methods:** Retrospective study of patients with cirrhosis & ascites who attended general hepatology and transplant clinics from April 2020 to March 2021. Patients who attended either A or C centre for their regular ascites care were compared. Data collected were demographics, laboratory results, co-morbidities, cirrhotic complications, hospital admissions and survival at 1 year. **Results:** A (n=120) patients were older (62±10 vs. 55±10 years, p<0.0001) than C (n=98). Both groups had 70% men, with alcohol being the most common cirrhosis etiology and similar co-morbidities. C patients had significantly higher MELD of 20.6±8.6 vs. 15.4±4.8 for A patients (p<0.0001). However, A patients had more severe ascites (grade 1: 5%, grade 2: 24%, grade 3: 71%) vs. C patients (grade 1: 15%, grade 2: 44%, grade 3: 41%) (p<0.0001), despite a lower baseline mean serum creatinine (sCr) of 105±47µmol/L (vs.130±112µmol/L in C patients, p=0.025). 98% of A patients required large volume paracentesis (LVP) of 7.3±3.0L vs. 81% of C patients requiring 6.4±2.6L per LVP (p<0.001 and p=0.042 respectively). During follow-up of 1 year, despite both groups having similar prevalence of background chronic kidney disease (23% for A, and 15% for C, p=0.17), more C patients developed acute kidney injury (AKI) (74%) than A patients (41%) (p<0.0001). Most of the AKI in A patients were stage 1 and responded to albumin (Table). 37.5% of patients in A and 59.1% in C (P=0.78) were admitted during the year with infections, liver failure and AKI being the most common reasons for admission. Significantly more C patients died (51%) vs. A patients (30%) (p=002) during the year. Most common causes of death were liver failure, infections and AKI. **Conclusion:** Despite A patients having more severe ascites and requiring more LVP, their renal and patient outcomes were better compared to C patients. This may be related to C patients had more liver dysfunction. Future strategies should either encourage ascites care to academic centres for close monitoring or better support the community hospitals in providing ascites care.

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Table: Renal events

Total # of AKI episodes	74	84	
Peak serum creatinine (µmol/L)	189±97	248±150	0.0046
AKI stage at Peak creatinine : 1 : 2 : 3	 60 5 9	 34 17 33	 <0.0001
Treatment received : Yes : No	 60 14	 69 15	 0.99
Treatment type Albumin: Yes Midodrine: Yes : Total albumin dose	n=60 57 12 165±184	n=69 31 41 182±81	 <0.0001 0.62
Response : none : Partial : Complete	n=74 17 5 52	n=84 37 6 41	 0.017

Disclosures: Chinmay Bera: Nothing to Disclose, Neha Tiwari: Nothing to Disclose, Cynthia Tsien: Paladin: Consultant, Lupin Limited: Consultant, Gilead Sciences Inc: non-research funding to support education activities, Astellas Pharma Canada, Inc: non-research funding to support education activities, AstraZeneca Canada Inc.: non-research funding to support education activities, Takeda Canada Inc.: non-research funding to support education activities, Alexion Pharmaceuticals, Inc.: non-research funding to support education activities, Paladin: non-research funding to support education activities, Nazia Selzner: Nothing to Disclose, Florence Wong: Mallinckrodt: Consultant, Mallinckrodt Pharmaceutical Inc: Grant/Research Support, River 2 Renal: Consultant, Sequana Medical: Consultant, sequana Medical: Grant/Research Support

4155 | THE CHARACTERISTICS AND LONG-TERM OUTCOMES OF ETIOLOGY-SPECIFIC CIRRHOSIS: A 15-YEAR STUDY OF STANFORD CIRRHOSIS COHORT

Yu Shi[1] Nicholas Chien[2] Ashley Fong[3] Vy Nguyen[4] Surya Gudapati[3] Jung Eun Park[3] Isaac Le[3] Angela Chau[3] Sally Tran[3] Xinrong Zhang[3] Ramsey Cheung[5] Changqing Zhao[6] Minjuan Jin[7] Mindie Nguyen[5]

[1]1.Stanford University Medical Center; 2. The First Affiliated Hospital, Zhejiang University, [2]Division of Gastroenterology and Hepatology, Stanford University Medical Center, [3]Division of Gastroenterology and Hepatology, Stanford University Medical Center, [4]1.Stanford University Medical Center; 2.Harvard Medical School, [5]Stanford University Medical Center, [6]Institute of Liver Diseases, Shuguang Hospital, [7]Department of Epidemiology and Biostatistics, Zhejiang University School of Public Health

Background: The long-term outcomes of patients with cirrhosis by specific liver disease etiology are limited. Our study aimed to characterize the characteristics of a large cohort of patients with cirrhosis of different etiologies and compared their long-term survival outcomes. **Methods:** We analyzed a consecutive cohort of 9024 adult patients with cirrhosis who presented at a U.S. university medical center during 1/2005-1/2022. We excluded patients with baseline HCC or other types of malignancies, pregnancy and HIV infection. Patients were followed to death, liver transplantation or last follow-up date, whichever came first. **Results:** The cohort had a median age of 58 [IQR, 50-67] years and were 56.3% male, 50.92% White, 27.06% Hispanic, 3.56% Black, 13.4% Asian, 5.10% other race/ethnicities, and 38.49% with hepatic decompensation at baseline. HCV (2525, 27.98%) and alcohol (2814, 31.18%) were the most common liver disease etiologies, followed by MASLD (902, 10.00%), autoimmune (865, 9.59%), HBV (450, 4.99%), cryptogenic (880, 9.75%) and other etiologies (588, 6.52%). At baseline, patients with alcohol-associated liver disease (ALD) had the highest median (IQR) MELD 3.0 (17, [11-24]) and CTP scores (9, [7-11]) and percentage of hepatic decompensation (57.07%). In contrast, HBV patients had the lowest median MELD 3.0 (9, [7-15]), and CTP scores (6, [5-8]), and the lowest percentage of hepatic decompensation (21.6%). However, patients with cryptogenic cirrhosis had lowest 5, 10, and 15-year cumulative survival rates (57.48%, 34.33% and 21.39%), respectively, followed by those with ALD, while HBV patients had highest rates (86.03%, 70.10% and 65.13%), respectively. On multivariable Cox regression adjusting for age,

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sex, race/ethnicities, baseline hepatic decompensation status, liver disease etiologies, MELD 3.0, CTP and CCI scores, cryptogenic cirrhosis was associated with the highest 5, 10, and 15-year all-cause mortality risk with adjusted hazard ratios (aHR) of 2.11, 1.96, and 1.90, all *P* <0.001, which was also consistent across subgroups by baseline age (age<40, 40-60 and >60 years), sex, race/ethnicities and the presence of hepatic decompensation, as well as in subanalysis for cause of death (liver-related: 1.60, 1.58, and 1.54, and non-liver-related: 1.90, 1.65, and 1.68, all *P*<0.001). **Conclusion:** Long-term overall as well as causes-specific survival of patients with cirrhosis vary greatly by underlying liver disease etiology, with cryptogenic patients having the poorest survival followed by ALD, MASLD, HCV and lowest in HBV and autoimmune disease. Additional studies are needed to evaluate potential causes for these observations to inform targeted intervention.

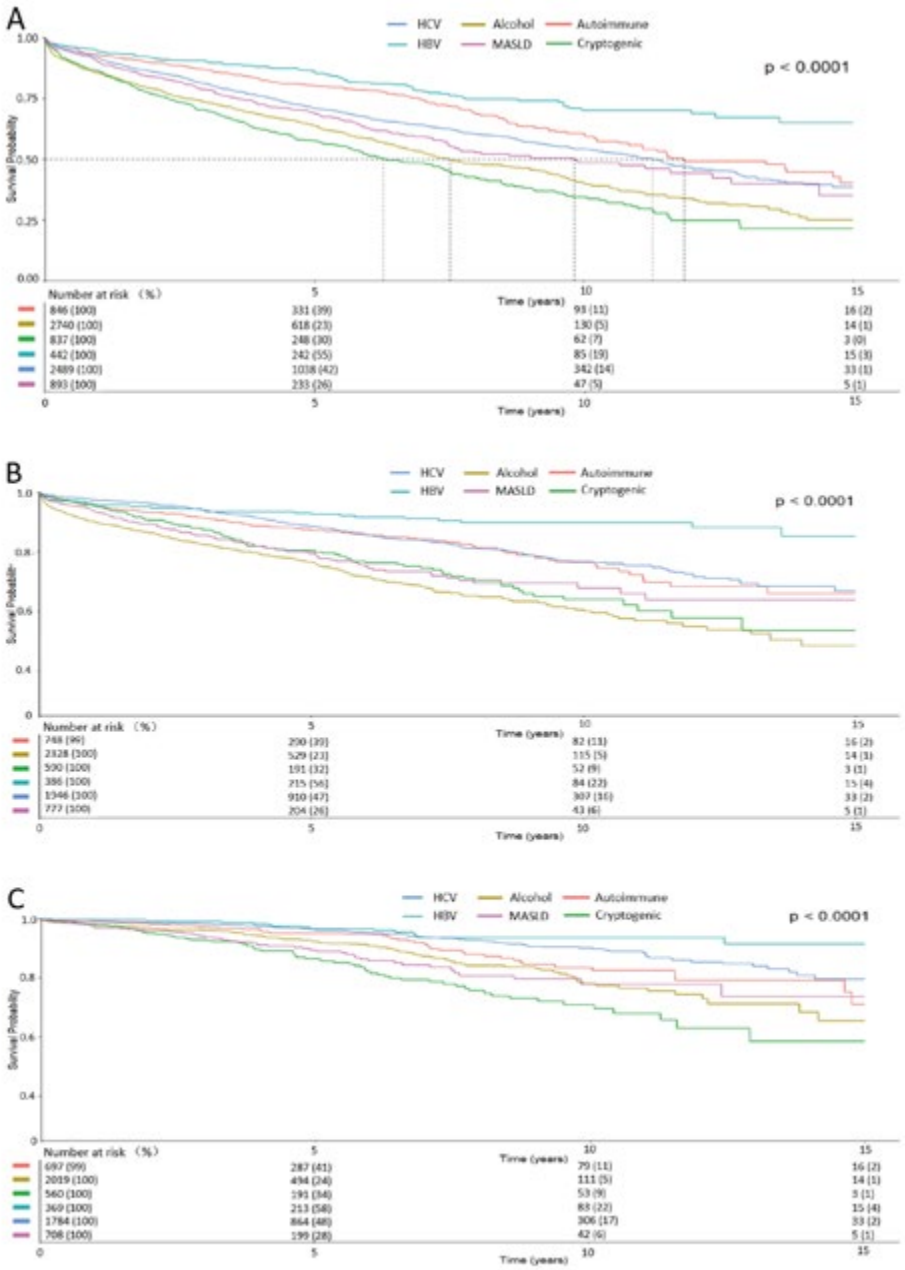

Figure.1 The Kaplan–Meier survival curves of all-cause death (A), liver-related death (B) and non-liver-related death (C) stratified by the etiologies of cirrhosis. Survival probabilities were estimated by Kaplan–Meier approach and compared by log-rank test. Abbreviations: HCV, hepatitis C virus; HBV, hepatitis B virus; MASLD, metabolic dysfunction-associated steatotic liver disease.

Disclosures: Yu Shi: Nothing to Disclose, Nicholas Chien: Nothing to Disclose, Ashley Fong: Nothing to Disclose, Vy Nguyen: Nothing to Disclose, Surya Gudapati: Nothing to Disclose, Jung Eun Park: Nothing to Disclose, Isaac

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Le: Nothing to Disclose, Angela Chau: Nothing to Disclose, Sally Tran: Nothing to Disclose, Xinrong Zhang: Nothing to Disclose, Ramsey Cheung: Nothing to Disclose, Changqing Zhao: Nothing to Disclose, Minjuan Jin: Nothing to Disclose, Mindie Nguyen: Nothing to Disclose

4156 | ESOPHAGEAL VARICES SCREENING IN PATIENTS WITH CIRRHOSIS: HOSPITAL-AFFILIATED GI CLINIC VS PRIVATE PRACTICE GI CLINIC

Jessica Sosio[1] Karla Geisse[1] Lindsey Valdiviez[1] Roudi Bachar[1] Adrian Singson[1] Oluwagbenga Serrano[2]

[1]Indiana University School of Medicine, [2]Good Samaritan Hospital, Indiana University School of Medicine

Background: Acute bleeding from esophageal varices (EV) is a life-threatening complication of cirrhosis with clinically significant portal hypertension. Compensated cirrhosis has a 5-year mortality of 18%, which increases to as high as 44% after bleeding with ascites. Historically, guidelines recommended screening for EV with esophagogastroduodenoscopy (EGD) at cirrhosis diagnosis. In recent years, however, a combination of transient elastography (TE) and platelet count have been used to identify high risk patients who need EGD. We conducted a study to determine screening trends in our rural hospital and detect any difference between our two gastroenterology clinics. **Methods:** Cirrhotic patients seen at our hospital from July 2023 to April 2024 were identified and stratified by age, gender, race, and social work support. Analysis with retrospective chart review was conducted for both Hospital-Affiliated Gastroenterology Clinic (HP) and Private Practice Gastroenterology Clinic (PP) on EGD and TE screening status. The primary outcome was EGD screening (EGD-S) completion; the secondary outcomes were preliminary TE and social work involvement. Odds ratios (OR) were calculated for both. **Results:** We identified 156 patients, 92 HP and 64 PP. HP had 52 (56.5%) males and 40 (43.5%) females, PP 36 (56.2%) males and 28 (43.8%) females. HP age distribution in years was 1% for 20-39, 20% for 40-59, 65% for 60-79, and 14% for 80-100. PP was 0% for 20-39, 33% for 40-59, 51% for 60-79, and 16% for 80-100. > 99% of patients were White. There was no significant difference in EGD-S (OR 0.97, CI 0.47-2.01, p=0.95), but there was a significant difference in TE use (OR 10.38, CI 2.24-48.22, p=0.003) with PP utilizing TE more. 68 (73.9%) HP patients completed EGD-S and 47 (73.4%) PP. No significant difference in social worker involvement was seen (OR 0.49, CI 0.18-1.13, p=0.16). **Conclusion:** EV screening in our hospital varied with PP utilizing TE to a higher degree, which may be due to TE being readily available. EGD-S rates were lower when compared to 2010 academic hospital and 2018 Veterans Affair retrospective reviews, which screened 94% and 79% of patients respectively. Common reasons for screening non-completion were unaddressed screening, loss to follow-up, patient preference, unknown cirrhosis, and death. Establishing a robust social work program to ensure adequate follow-up and education could improve screening. Additionally, establishing a checklist on office intake would streamline screening.

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4157 | ALFAPUMP SYSTEM IN REFRACTORY ASCITES: RESULTS FROM THE POSEIDON STUDY AT 24 MONTHS

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Background: The standard of care for refractory ascites (RA) in cirrhosis is repeated large volume paracentesis (LVP). The alfapump system (AS), providing slow and continuous paracentesis via a subcutaneous pump, has been shown to be an alternative in selected patients. The POSEIDON study enrolled patients with cirrhosis and RA to evaluate safety and efficacy of AS. 3 patients per site were allowed to for pump implantation training. Their safety and efficacy course was monitored (roll-in cohort, RC). A pivotal cohort (PC) of 40 pts was then recruited. A recent report on the reduction of LVP by > 50% and improvement in quality of life in the PC at 6 months using

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SF-36 and Ascites-Q questionnaire at 6 mo. [JHep 78(S1), 242] We now report on patient outcomes at 12, 18 and 24 months of both cohorts. **Methods:** Pts with cirrhosis and RA inappropriate for TIPS who required ≥2 LVPs in the 30 days prior were considered. A total of 79 patients (RC: n=39; PC: n=40) were enrolled . All pts received post-implant prophylactic antibiotics. Data collected were demographics, albumin use, ascites control, safety and PRO. Primary efficacy end point was reduction in LVP requirement; safety end points were pump system adverse events that resulted in intervention, explant or death and were adjudicated by an independent Clinical Events Committee. Study duration was 24 months **Results:** Demographics in the RC cohort showed mean age 62.7 ± 8.8 years, mean MELD-Na 14.3 ± 5.65, 58.6% men, 72.4% alcohol-related cirrhosis. The same parameters in the PC cohorts were: mean age 64 ± 9 yrs, 65% men, mean MELD-Na 15 ± 4, 48% alcohol-related cirrhosis. Long term efficacy: LVP requirement in the RC decreased from implantation to 3M and persisted to 24 months by >50% (mean LVP/m 2.7±1.3 to 0.1±0.2). Ascites volume removed by LVP fell from 22.8 ± 12.5L/mo pre- to 2.6 ± 6 L/M 3M post-AS implant. Safety: 27 explants occurred (13 in RC and 14 in PC) due to no further need and AS related adverse events. There was one implant related mortality in the RC, caused by an arterial bleeding. The adverse event profile in the PC and RC long term were similar. (Table) Importantly, acute kidney injury and infections were events that could be successfully treated in most instances. Overall survival on the pump was 71% and 62% at 12 and 24 mo, respectively for the PC and 72% and 47% at 12 and 24 mo for the RC. **Conclusion:** AS was very effective in control of ascites, virtually eliminating the need for LVP long term. However, close monitoring is needed for the development of AKI or infection, which must be treated promptly to prevent adverse outcomes. Data from RC provides evidence the AS can work well in circumstances close to clinical practice. In patients requiring RA management for >6mo the AS is a safe and effective tool.

Long term serious adverse events

	M3-12 PC	M3-12 RC	M12-18 PC	M12-18 RC	M18-24 PC	M18-24 RC
AE (n/N)	50/21	78/16	40/10	38/8	33/14	34/5
Related SAEs (n/N)	8/5	13/8	6/4	2/2	7/4	5/2
: Related to device	5/4	8/7	3/3	2/2	3/2	4/2
: Related to procedure	0/0	1/1	0/0	0/0	2/2	0/0
: Related to therapy	3/2	4/2	3/3	0/0	2/1	1/1
Any SAEs (n/N)	31/14	41/15	22/6	16/6	16/7	22/5
: Infections	9/7	6/5	3/2	2/2	2/2	7/3
: Cardiovascular	0/0	0/0	0/0	0/0	0/0	0/0
: Respiratory	1/1	0/0	0/0	0/0	0/0	2/2
: Gastrointestinal	4/4	9/5	4/3	4/3	2/2	0/0
: AKI	5/4	7/4	7/3	1/1	3/3	5/3
: HE	1/1	3/3	2 /1	0/0	2/2	1/1
: Others	11/8	13/10	6/4	9/3	7/4	6/4

n= number of events, N=number of patients with the event, PC=Pivotal Cohort, RC=Roll-in cohort
Please note the events are not cumulative

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4158 | ASSESSING THE IMPACT OF AGE ON THE OUTCOMES IN PATIENTS PRESENTING WITH SPONTANEOUS BACTERIAL PERITONITIS

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Background: Spontaneous bacterial peritonitis (SBP) is a life-threatening complication of cirrhosis of the liver. Prompt recognition and treatment is necessary to adequately treat patients. The goal of this study is to assess the impact that age has on the outcomes in patients who present to the hospital with SBP. **Methods:** This is a retrospective cohort study using National Inpatient Sample data including adults hospitalized between 2016 and 2020 with history of cirrhosis and SBP. The study compares risk factors including demographics and chronic medical conditions along with inpatient complications and outcomes of the patients in our sample. Statistical analyses were all performed using STATA software. **Results:** Of the 119,420 patients who met our inclusion criteria, 109,170 patients (91%) were age 40 or greater. The majority of our patients in the group age ≥ 40 compared to age < 40 were male (63.9% vs. 59.6%; p<0.001) and white (64.2% vs. 56.2%; p<0.001). The group age ≥ 40 also had statistically significant (p<0.05) higher rates of obesity, hypertension, congestive heart failure, COPD, and diabetes along with lower rate of smoking, alcohol abuse, drug use. The patients age ≥ 40 also had shorter lengths of stay (average 8.5 days vs 9.2 days; p=0.003). The patients age ≥ 40 had statistically significant (p<0.05) lower rates of blood transfusions (15.7% vs. 18.4%) and mechanical ventilation (12.2% vs. 14.6%), and higher rates of shock (15.3% vs 12.8%), paracentesis on day 1 of admission (21.7% vs 10.4%), and mortality (16.0% vs 11.4%). Differences in cardiac arrest, vasopressor requirement, and ICU requirement were not statistically significant (p>0.05). **Conclusion:** Our study showed in patients with SBP, patients age ≥ 40 despite having lower blood transfusion and mechanical ventilation, had overall higher rate of shock and mortality. Rates of day of paracentesis were similar in both groups; however, there was an increased number of paracentesis day 1 of admission in patients age ≥ 40.

Table 1: Demographics

	SBP Age ≥ 40 (n = 109,170)	SBP Age < 40 (n = 10,250)	P Value	Odds Ratio (95% Confidence Interval)
Mean Age, years	59.7	34.0	<0.001	-
Gender, n				
Male	69765 (63.9%)	6110 (59.6%)	<0.001	1.200 (1.089-1.321)
Female	39385 (36.1%)	4135 (40.3%)		0.834 (0.757-0.919)
Race, n				
White	70135 (64.2%)	5760 (56.2%)	<0.001	1.400 (1.276-1.536)
Black	8630 (7.9%)	765 (7.5%)	0.488	1.064 (0.893-1.269)
Hispanic	19365 (17.7%)	2015 (19.7%)	0.034	0.881 (0.784-0.991)
Asian or Pacific Islander	2615 (2.4%)	295 (2.9%)	0.190	0.828 (0.624-1.099)
Native American	1870 (1.7%)	615 (6.0%)	<0.001	0.273 (0.221-0.337)
Other	3270 (3.0%)	430 (4.2%)	0.005	0.705 (0.553-0.898)
Obesity, n	12845 (11.8%)	1025 (10.0%)	0.0175	1.200 (1.032-1.395)
Hypertension, n	28875 (26.4%)	1670 (16.3%)	<0.001	1.848 (1.634-2.089)
Congestive Heart Failure, n	16150 (14.8%)	565 (5.5%)	<0.001	2.976 (2.448-3.617)
COPD, n	13750 (12.6%)	165 (1.6%)	<0.001	8.808 (6.233-12.444)
ESRD, n	9385 (8.6%)	775 (7.6%)	0.113	1.150 (0.967-1.367)
Diabetes, n	33735 (30.9%)	1065 (10.4%)	<0.001	3.857 (3.324-4.475)
Smoking History, n	46085 (42.2%)	4805 (46.9%)	<0.001	0.828 (0.754-0.909)
Alcohol Abuse, n	65455 (60.0%)	8035 (78.4%)	<0.001	0.413 (0.369-0.461)
Drug Use, n	7895 (7.2%)	1510 (14.7%)	<0.001	0.451 (0.394-0.516)
Malnutrition, n	12780 (11.7%)	1255 (12.2%)	.479	0.950 (0.825-1.094)
Mean Length of Stay, days	8.5	9.2	0.003	-
Cost of Admission, dollars	101457.2	120132.5	<0.001	-

Table 2: Hospitalization Co-illnesses

Cardiac Arrest, n	300 (0.3%)	25 (0.2%)	0.791	1.127 (0.465-2.734)
Requiring Transfusion, n	17130 (15.7%)	1890 (18.4%)	0.001	0.823 (0.731-0.927)
Mechanical Ventilation, n	13370 (12.2%)	1495 (14.6%)	0.003	0.817 (0.717-0.932)
Vasopressors, n	5490 (5.0%)	510 (5.0%)	0.915	1.011 (0.823-1.243)
Shock, n	16725 (15.3%)	1310 (12.8%)	0.003	1.235 (1.075-1.418)
ICU, n	15990 (14.6%)	1640 (16.0%)	0.102	0.901 (0.795-1.020)
Mortality, n	17440 (16.0%)	1165 (11.4%)	<0.001	1.482 (1.285-1.709)
Day of Paracentesis, n				
Day 0	17625 (16.1%)	1605 (15.7%)	0.563	1.037 (0.917-1.173)
Day 1	23695 (21.7%)	1995 (19.5%)	0.018	1.147 (1.024-1.285)
Day 2	12445 (11.4%)	1065 (10.4%)	0.166	1.100 (0.958-1.286)
Day 3	9850 (9.0%)	800 (7.8%)	0.068	1.171 (0.988-1.389)
Day 4	7520 (6.9%)	605 (5.9%)	0.085	1.179 (0.977-1.423)
Day 5	6555 (6.0%)	530 (5.2%)	0.131	1.171 (0.954-1.439)

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4159 | EXPLORING THE IMPACT OF LEAKY GUT SYNDROME MARKER SCD14 ON TREATMENT OUTCOMES IN LIVER CIRRHOSIS WITH WATER RETENTION

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Background: Elevated inflammatory markers have been reported as ineffective factors of Tolvaptan (TVP) for water retention associated with portal hypertension. Soluble CD14 (sCD14) is one of the markers for leaky gut syndrome and its association with short-term effects of TVP has been reported. This study aimed to elucidate the usefulness of sCD14 in predicting the effects of TVP, incidence of acute kidney injury (AKI), and prognosis in decompensated cirrhosis with water retention. **Methods:** This retrospective study included 138 cases with sCD14 measurements before TVP administration. Short-term/long-term effects of TVP, incidence of AKI post-administration, and prognosis were assessed. A short-term response was defined as weight loss of ≥1.5 kg within the first week according to the Japanese evidence-based clinical practice guidelines for LC; a long-term response was defined as a short-term response without early recurrence defined in the EASL practice guidlines. Statistical analysis was conducted to examine the association between sCD14 levels and the effects of TVP, AKI incidence, and liver disease related mortality. **Results:** Cases with low sCD14 levels exhibited significantly higher short-term/long-term efficacy rates of TVP, with a cutoff value of 2370 pg/ml identified through ROC analysis. When divided into two groups (<2370/≥2370 pg/ml), short-term efficacy rates were 75.4%/41.8%, long-term efficacy rates were 52.3%/24.6%, and post-administration AKI incidence was 0%/8.6%, showing significantly higher efficacy of TVP and lower AKI incidence in the low sCD14 group. High sCD14 levels were associated with increased liver diasese related mortality (median survival time (MST): 4.8 months vs 21 months, p=0.002), even after excluding cases with advanced HCC beyond Milan criteria (MST: 24.4 months vs 51.1 months, p=0.049). Positive correlations were observed between sCD14 levels and CRP (r=0.408, p<0.001), but not between sCD14 levels and white blood cell count in ascites (r=-0.024, p=0.859). Factors associated with sCD14 <2370 pg/ml included high NH3 levels, elevated PT-INR, and concomitant use of rifaximin and probiotics in univariate analysis, with concomitant use of rifaximin being a significant factor in multivariate analysis (OR=0.101, p<0.001). **Conclusion:** High sCD14 levels suggesting the presence of leaky gut syndrome in cases with water retention in cirrhosis contribute to the ineffectiveness of TVP in the short-term/long-term, incidence of AKI, and poor prognosis. Lower sCD14 levels were observed in cases using rifaximin concomitantly, suggesting it as a potential treatment option.

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4160 | LACTULOSE-INDUCED HYPERNATREMIA IN CIRRHOTIC PATIENTS WITH HEPATIC ENCEPHALOPATHY

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Background: Lactulose is an osmotic laxative used to treat hepatic encephalopathy (HE) in patients with cirrhosis. Here, we examined lactulose induced hypernatremia (HN) in patients with cirrhosis being treated for HE. **Methods:** We identified all patients with cirrhosis admitted for HE at MUSC from 1/1/18, to 12/31/23. Sodium levels were recorded for all patients, and complete clinical data were abstracted. Using a case control study design (with HN patients matched in a random fashion to HE patients without HN), propensity matching was used to control for the severity of underlying liver disease. The primary endpoint was hospital mortality, with secondary endpoints as follows: total and rectal lactulose (g), time to mental status resolution, and length of stay (LOS). Only adults were included, and those with confounding causes of HN were excluded. **Results:** Among 6,742 patients admitted with cirrhosis, 704 (10%) were admitted with HE as the primary diagnosis. Of these, 131 patients (21%) had a sodium level >145 mEq/L, and 51 patients (7%) had a sodium level ≥150 mEq/L. This group included

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primarily patients with alcohol related cirrhosis, with a MELD of 23 (Table). The mean admission sodium level was 139 and the peak sodium level was 154; all patients received lactulose. The average daily dose of lactulose was significantly higher in the HN group (157 vs. 56 g, p<0.001). 31 (61%%) patients in the HN group received rectal lactulose (average 199 g), while only 16% of patients in the normonatremia (NN) group received rectal lactulose. The mean peak sodium level in the rectal lactulose group was 155, with a maximum of 164. In this group, 9 patients (18%) had a peak sodium ≥ 155, and an additional 4 patients (13%) had a peak sodium ≥ 160. Patients receiving rectal lactulose had sodium levels > 145 for an average of 7 days. The time to mental status resolution and LOS were 3 and 3.3 times longer, respectively, in the HN group (both p<0.001). Overall, 33 patients (65%) in the HN group died (vs. 16 (31%) in the NN group (p<0.05)). 21/31 (68%) patients who received rectal lactulose died. **Conclusion:** HN is common in patients admitted with HE who are treated with lactulose, and the severity of HN appeared to be proportional to the amount of lactulose given. Lactulose-induced HN was associated with significantly poorer outcomes, and patients receiving rectal lactulose had a remarkably high mortality rate. We conclude that rectal lactulose is dangerous in patients with HE.

Table 1: Clinical Characteristics and Outcomes

	Cases (hypernatremia – HN) Na ≥ 150 (n) = 51	Controls (normonatremia – NN) Na = 135-145 (n) = 51	p-value
Female (n, %)	22 (43%)	18 (35%)	NS
Age (year, mean, SD)	58 ± 13	58 ± 13	NS
Race (n, %)			NS
White	37 (73%)	39 (76%)	
Black	10 (20%)	11 (22%)	
Other	4 (7%)	1 (2%)	
Cirrhosis Etiology (n, %)			NS
Alcohol	31 (61%)	34 (67%)	
NASH	10 (19%)	9 (17%)	
HCV	1 (2%)	4 (8%)	
Other	9 (18%)	4 (8%)	
MELD (mean, SD)	23 ± 19	22 ± 11	NS
Rifaximin (n, %)	41 (80%)	36 (71%)	NS
Diuretics (n, %)	40 (78%)	28 (55%)	NS
TIPS (n, %)	10 (20%)	6 (12%)	NS
Sodium (mEq/L)			
Admission (Mean, SD)	139 ± 7	137 ± 4	NS
Peak (Mean, SD)	154 ± 3.4	140 ± 3.7	< 0.001
Day of peak Na (Mean, SD)	8 ± 7	2 ± 2	< 0.001
Lactulose (n, %)	51 (100%)	44 (86%)	
PO	48 (94%)	38 (75%)	
PR	31 (61%)	8 (16%)	< 0.001
Dose/day (g, mean, SEM)	157 ± 27	56 ± 14	< 0.001
Cumulative dose (g, mean, SEM)	945 ± 209	109 ± 23	< 0.001
Etiology of HE (n, %)			NS
Noncompliance	4 (8%)	13 (25%)	
Infection	17 (33%)	8 (15%)	
Bleeding	8 (16%)	7 (14%)	
Dehydration	4 (8%)	8 (16%)	
Liver failure	2 (4%)	5 (10%)	
Multifactorial/Unknown	16 (31%)	10 (20%)	
HE Stage at Onset (mean, SD)	2.7 ± 0.7	1.9 ± 0.8	NS
ICU (n, %)	39 (76%)	14 (27%)	< 0.001
MS Resolution (days, (mean, SD)	12 ± 9	4 ± 3	< 0.001
LOS (days, (mean, SD)	19 ± 16	5.8 ± 5	< 0.001
Rectal lactulose mortality (n, %)	21/31 (68%)	2/8 (25%)	< 0.001
Overall mortality (n, %)	33 (65%)	16 (31%)	< 0.05

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4161 | EFFICACY OF LACTULOSE ALONE VERSUS LACTULOSE WITH POLYETHYLENE GLYCOL IN THE TREATMENT OF HEPATIC ENCEPHALOPATHY: A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

Avneet Singh[1] Alexander Garcia[1] Fariha Hasan[1] Fatima Laique[2] Suhaina Amir[2] Sameen Mukhtar[2] Zehara Abidi[3] Mina Awadallah[4] Ali Wakil[5] Satyajeet Roy[1]

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Background: Hepatic encephalopathy (HE) is a neuropsychiatric syndrome resulting from acute liver failure or advanced chronic liver disease, causing significant morbidity and mortality. Currently, the standard treatment is lactulose, a non-absorbable disaccharide that reduces ammonia production and absorption in the gut. Recently, polyethylene glycol (PEG), an osmotic laxative, has also shown potential benefits in HE management. This systematic review and meta-analysis compares the efficacy of lactulose alone versus lactulose combined with PEG in treating HE. **Methods:** We conducted a systematic search of PubMed, Scopus, Web of Science, Cochrane Library, and Embase from inception to May 2024 yielding 153 randomized controlled trials (RCTs) comparing lactulose alone to lactulose combined with PEG in HE treatment. Data extraction and analysis were independently performed by two reviewers, focusing on dichotomous and continuous outcomes. The Mantel-Haenszel method was used for pooling data, calculating pooled mean differences and relative risks with 95% confidence intervals. **Results:** Three trials, including 216 patients, met the inclusion criteria. There were 108 participants in both the PEG plus lactulose and lactulose groups, with mean ages of 50.21 ± 12.09 and 52.61 ± 14.15, respectively. There was a higher percentage of males in the lactulose plus PEG group (66.7%) compared to the lactulose group (53.7%). Pooled analysis indicated that the combination of PEG and lactulose significantly improved Hepatic Encephalopathy Scoring Algorithm (HESA) scores at 24 hours compared to lactulose alone (risk ratio (RR) = 1.44, 95% CI [1.16, 1.78], p = 0.0007, I^2 = 0%). The PEG and lactulose combination therapy also resulted in significantly shorter duration of hospital stay compared to lactulose alone (mean difference (MD) = -2.84 days, 95% CI [-4.65, -1.02], p = 0.002, I^2 = 37%), but no significant difference was observed in blood ammonia levels at 24 hours between the two groups (mean difference (MD) = 9.31, 95% CI [-3.72, 22.34], p= 0.16, I^2 = 68%). **Conclusion:** This meta-analysis highlights the superior efficacy of combining PEG with lactulose over lactulose alone in treatment of HE. Combination therapy led to significant improvements in both HESA scores and reducing hospital length of stay. Although the blood ammonia levels did not significantly differ, the clinical benefits of the PEG and lactulose combination therapy suggest its consideration in HE management protocols. Further large-scale RCTs are needed to confirm these findings and explore the mechanisms for the enhanced efficacy of the combination therapy compared to lactulose alone.

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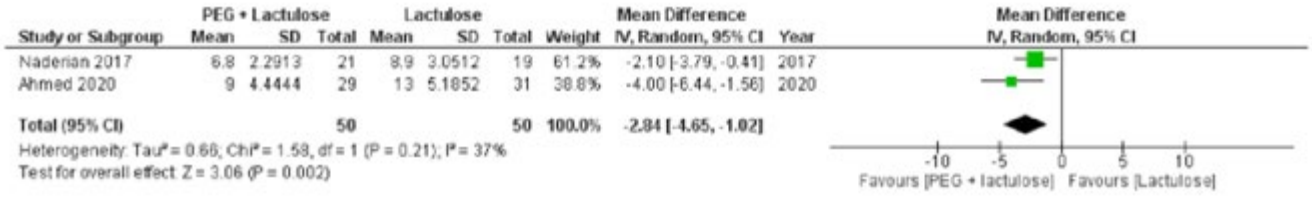
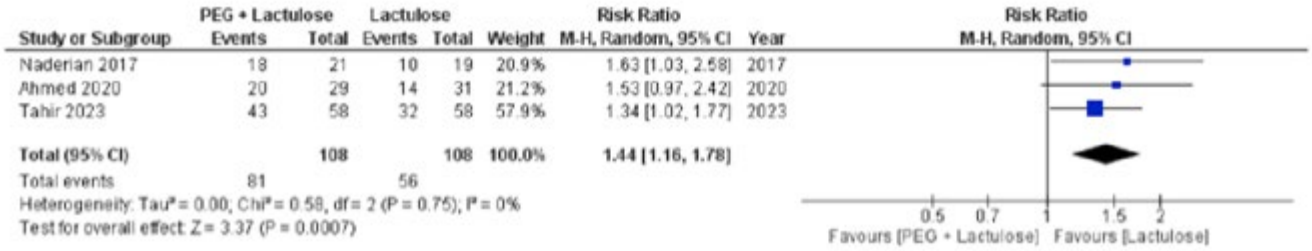
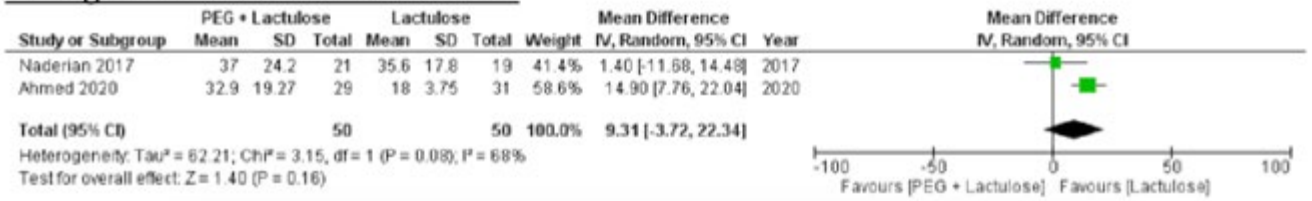
Duration of Hospital Stay



One or More Improvement in HESA Score



Change in Blood Ammonia Levels



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4162 | POSTOPERATIVE SURVIVAL IN CIRRHOTIC PATIENTS: THE ROLE OF SARCOPENIA

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[1]*INCMNSZ*

Background: Patients with cirrhosis face an approximately threefold increase in perioperative mortality compared to those without cirrhosis. While sarcopenia has been consistently linked to adverse perioperative outcomes, individuals with cirrhosis are particularly susceptible to skeletal muscle loss. In this study, we explored the correlation between sarcopenia and 6-month overall survival in mexican patients with cirrhosis undergoing major surgery at a national reference center in Mexico. **Methods:** We conducted an observational retrospective study on patients with cirrhosis who underwent major surgery at a single center in Mexico City. The third lumbar spinal skeletal muscle mass index was measured using computed tomography. Patients were categorized into sarcopenia and non-sarcopenia groups based on the criteria established by the North American Working Group on Sarcopenia in Liver Transplantation. Baseline data were collected, and postoperative outcomes were assessed 180 days after the major surgery. **Results:** We included 108 patients, with 74 women (68.5%) and a

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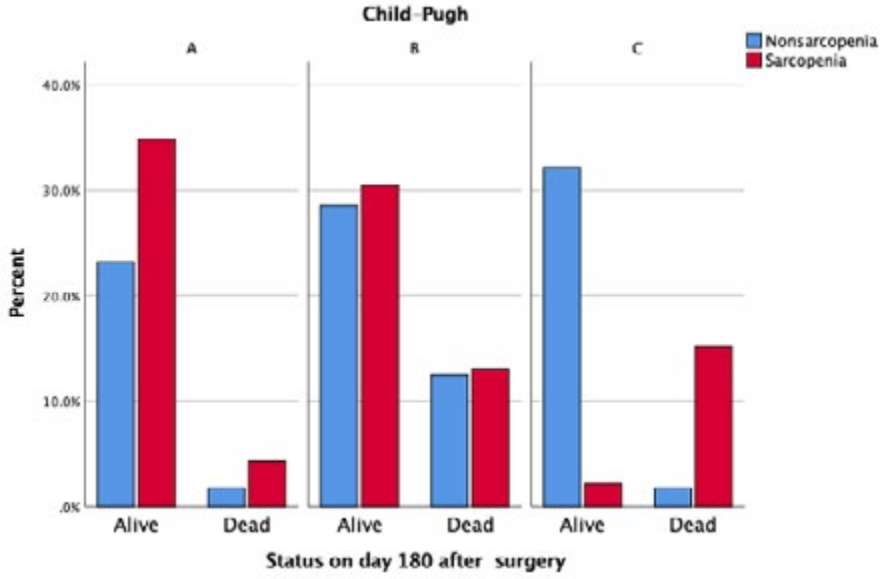
mean age of 60 ± 13 years; 48 (44.4%) were found to have sarcopenia. The mean body mass index was 25.6 ± 5 kg/m². The predominant etiologies of liver disease were MASLD (38%), autoimmune conditions (25.9%), and viral causes (20%). A majority of patients had experienced decompensation events in the past (78.7%), predominantly ascites (56.5%). The majority of patients were classified as Child-Pugh grades B/C (68.5%), with an average MELD-Na score of 15 (IQR 11-20).Patients with sarcopenia were predominantly men (54.2%). No significant differences were observed in the average MELD-Na score and the proportion of patients classified as Child-Pugh B/C between those with sarcopenia and those without. The median 6-month postoperative overall survival did not show statistically significant differences between patients with and without sarcopenia. However, when evaluated according to Child-Pugh grade, overall survival was shorter in patients classified as Child-Pugh C with sarcopenia compared to those without sarcopenia ($p < 0.001$). Sarcopenia (HR 2.7, 95% CI 3.3-12.4) and MELD-Na (HR 1.2, 95% CI 1.01-1.43) were identified as independent risk factors associated with postoperative mortality.
Conclusion: Sarcopenia, a common complication of cirrhosis, is notably linked with heightened mortality rates following major surgery among patients classified as Child-Pugh grade C. Therefore, healthcare providers should prioritize the early identification and management of sarcopenia in this high-risk group to potentially enhance postoperative outcomes.



Disclosures: MARTÍN PACHECO SERRANO: Nothing to Disclose, IGNACIO GARCIA JUAREZ: Nothing to Disclose

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4163 | SIX-WEEK MORTALITY AFTER ACUTE VARICEAL BLEEDING IS HIGHER IN NON-ALCOHOL-RELATED ETIOLOGIES OF CIRRHOSIS: AN INTERNATIONAL MULTICENTER STUDY

YU JUN WONG[1] Adam Buckholz[2] Alyssa SIM[3] Li Peng Margaret Teng[4] Rochelle Wong[5] Michael Curry[6] Marianne De Roza[7] Gyorgy Baffy[8] Xuhui Teoh[9] Eric Chak[10] Tarun Rustagi[11] Jason Chang[12] Guan Wee Wong[13] Puneeta Tandon[14] Guadalupe Garcia-Tsao[15] Juan Abraldes[14] Mohanty Arpan[16] Don Rockey[17]

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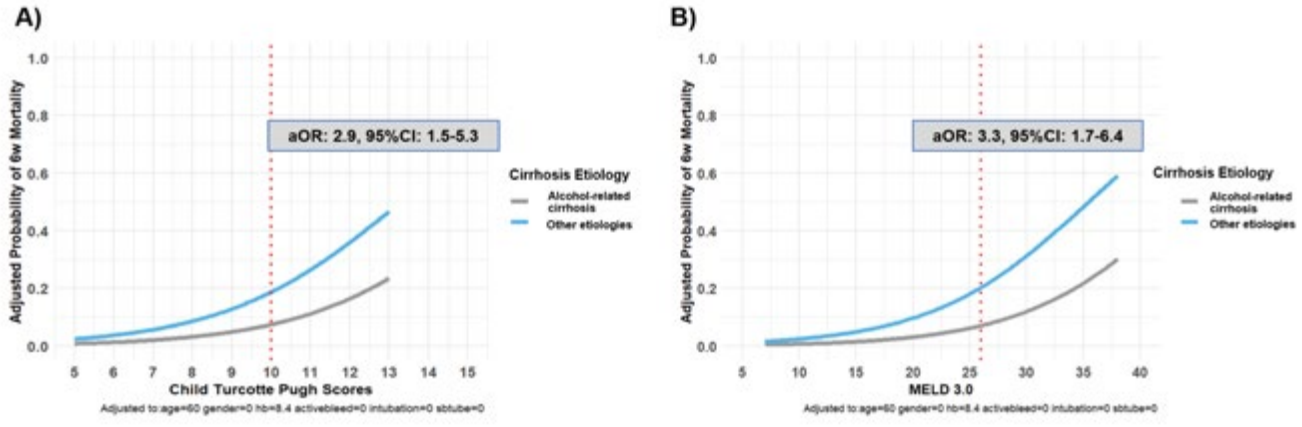
Background: Acute variceal bleeding (AVB) portends a significant 6-week mortality in cirrhosis patients. Post-bleeding risk stratification with classical indices such as MELD and CTP may not accurately address all factors which influence outcomes, and risk across different etiologies of liver cirrhosis may differ. We aim to compare the 6-week mortality following AVB in patients with alcohol-related (ALD) and non-alcohol-related (non-ALD) cirrhosis. **Methods:** We assessed outcomes after index AVB in two large multi-center cohorts from the U.S. and Singapore. Using multivariable logistic regression adjusting for age, gender, active bleeding, intubation, hemoglobin and balloon tamponade, we compared the primary outcome ie: 6-week mortality, between ALD and non-ALD patients presenting with AVB. Subgroup analysis performed in patients with high-risk of rebleeding, and patients without hepatocellular carcinoma, combined etiology of cirrhosis, or transjugular intrahepatic portosystemic shunt (TIPS). **Results:** A total of 1,376 AVB patients from the U.S. and Singapore cohorts were included. Overall, 379 (27.5%) had ALD cirrhosis and 6-week mortality was 14.4%. Compared to patients with non-ALD cirrhosis, patients with ALD cirrhosis were younger and had higher CTP, MELD and MELD 3.0. Non-ALD cirrhosis was associated with a significantly higher odds of adjusted 6-week mortality than ALD cirrhosis after accounting for CTP (aOR: 2.9, 95%CI: 1.5-5.3) (Figure 1a), MELD (aOR: 3.0, 95%CI: 1.6-5.6) and MELD 3.0 (aOR: 3.3, 95%CI: 1.7-6.4) (Figure 1**b**), with consistent effects in various subgroup analyses and sensitivity analyses using propensity score matching. Importantly, the adjusted 6-week mortality for a MELD 3.0 of 26 was 20% in patients with non-ALD cirrhosis whereas the adjusted 6-week mortality risk was only 8% in patients with ALD cirrhosis who had the same MELD 3.0. Of the components used in the CTP score, serum bilirubin most strongly contributed to predicted 6-week mortality after AVB in the non-ALD cohort, but poorly correlated with 6-week mortality in the ALD cohort. Addition of cirrhosis etiology (ALD vs non-ALD) to existing prognostic scores improved the prediction of 6-week mortality following AVB (e.g.: MELD 3.0 c-statistic: 0.770 to 0.784, p<0.001). **Conclusion:** At every presenting CTP/MELD/MELD 3.0 score, non-ALD portends worse 6-week mortality than ALD after AVB, driven primarily by the more powerful predictive capacity of index bilirubin. This may be steered by the alcohol-associated hepatitis phenotype of ALD, rather than true portal hypertension serving as protective within this etiology. These findings suggest adjusting for etiology in risk stratification after AVB may improve clinical decision making, and further investigation on the impact of specific interventions, such as TIPS, is needed.



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4164 | UNDERSTANDING THE IMPACT OF THE WEEKEND EFFECT ON PATIENTS PRESENTING WITH SPONTANEOUS BACTERIAL PERITONITIS

Nisha Sanghani[1] *Het Patel*[1] *Pooja Patel*[1] *Hammad Liaquat*[1]

[1]*St. Luke's University Health Network*

Background: Spontaneous bacterial peritonitis (SBP) is an important diagnosis to make promptly during a hospital admission. If the diagnosis is missed, patients can suffer severe complications including septic shock, renal failure, and heart failure. The weekend effect is a phenomenon that patients presenting on weekends may have poorer morbidity and mortality rates. Our goal is to understand the impact of the weekend effect on patients presenting with SBP. **Methods:** This is a retrospective cohort study using National Inpatient Sample data including patients hospitalized between 2016 and 2020 age 18 and greater who presented with SBP. The study compares risk factors including demographics and chronic medical conditions between patients who presented on weekends and those who presented on weekdays. Statistical analyses were all performed using STATA software. **Results:** Of the 9,850 patients age 18 and older with presentation of SBP, 2,180 presented on a weekend and 7,670 presented on a weekday. The percentage of patients with smoking history was higher on weekdays rather than that on weekends (OR=0.757; 95% CI 0.608-0.942). More patients with Charlson Comorbidity index (CCI) score 4, moderate severity of comorbidities, presented on weekdays than they did on weekends (OR= 0.716; 95% CI 0.518-0.989). Cost of admission was significantly higher on weekends compared to on weekdays (P=0.007). Patients who presented with SBP on weekends were more likely to require vasopressors (OR= 2.310; 95% CI 1.107-4.818). Mortality rates were higher for weekend presentation of SBP compared to weekday presentation (OR= 1.720; 95% CI 1.099-2.692). The percentage of patients receiving paracentesis on day 0 was higher on weekdays compared to weekends (OR = 0.529; 95% CI 0.312-0.897), while that for day 2 was higher on weekends compared to weekdays (OR= 1.728; 95% CI 1.323-2.256). **Conclusion:** Our study showed that the weekend effect impacted vasopressor use, mortality, cost of hospitalization, and day of paracentesis. An interesting finding was that the percentage of patients presenting with SBP with smoking history was higher on weekdays; however, overall mortality was lower in those patients who presented on weekdays. Additionally, the significant increase in percentage of patients who received paracentesis on day 0 on weekdays versus that on day 2 on weekends may emphasize the delay in care on weekends supporting the weekend effect phenomenon.

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Table 1: Demographics

	Weekend Presentation (n = 2,180)	Weekday Presentation (n =7,670)	P Value	Odds Ratio (95% Confidence Interval)
Mean Age, years	57.97	58.64	0.354	-
Gender, n				
Male	1355 (62.2%)	4635 (60.4%)	0.516	1.075 (0.863-1.339)
Female	825 (37.8%)	3035 (39.6%)		0.930 (0.747-1.158)
Race, n				
White	1390 (63.8%)	4870 (63.5%)	0.917	1.012 (0.813-1.259)
Black	230 (10.6%)	755 (9.8%)	0.665	1.080 (0.762-1.532)
Hispanic	375 (17.2%)	1250 (16.3%)	0.660	1.067 (0.799-1.424)
Asian or Pacific Islander	45 (2.1%)	210 (2.7%)	0.437	0.749 (0.360-1.556)
Native American	30 (1.4%)	170 (2.2%)	0.276	0.616 (0.255 1.486)
Other	65 (3.0%)	215 (2.8%)	0.841	1.066 (0.574-1.979)
Obesity, n	190 (8.7%)	810 (10.6%)	0.262	0.809 (0.558-1.172)
Hypertension, n	620 (28.4%)	2045 (26.7%)	0.460	1.092 (0.863-1.385)
Congestive Heart Failure, n	365 (16.7%)	1170 (15.3%)	0.440	1.118 (0.843-1.480)
COPD, n	210 (9.6%)	874 (11.4%)	0.295	0.828 (0.581-1.179)
ESRD, n	240 (11.0%)	855 (11.1%)	0.850	1.032 (0.741-1.439)
Diabetes, n	720 (33.0%)	2650 (34.6%)	0.556	0.934 (0.745-1.172)
Cerebrovascular Disease, n	30 (1.4%)	80 (1.0%)	0.560	1.323 (0.515-3.403)
Smoking History, n	805 (36.9%)	3345 (43.6%)	0.012	0.757 (0.608 0.942)
Alcohol Abuse, n	935 (42.9%)	3185 (41.5%)	0.610	1.057 (0.853 - 1.311)
Drug Use, n	190 (8.7%)	540 (7.0%)	0.243	1.260 (0.854-1.861)
Cancer, n	310 (14.2%)	860 (11.2%)	0.087	1.312 (0.960-1.794)
Dementia, n	30 (1.4%)	125 (1.6%)	0.707	0.842 (0.344-2.062)
Malnutrition, n	220 (10.1%)	745 (9.7%)	0.813	1.043 (0.734-1.483)
Mean Length of Stay, days	7.218	7.186	0.956	-
Cost of Admission, dollars	77239.38	64713.09	0.007	-
Charlson Comorbidity Index				
3 or less	940 (43.1%)	3245 (42.3%)	0.766	1.033 (0.831-1.286)
4	250 (11.5%)	1175 (15.3%)	0.042	0.716 (0.518-0.989)
5	300 (13.8%)	1120 (14.6%)	0.654	0.933 (0.690-1.263)
6	250 (11.5%)	765 (10.0%)	0.366	1.169 (0.833-1.641)
7 or more	440 (20.2%)	1365 (17.8%)	0.257	1.168 (0.893-1.528)

Table 2: Hospitalization Co-illnesses

Respiratory Failure, n	160 (7.3%)	380 (5.0%)	0.050	1.519 (0.998 2.314)
Cardiac Arrest, n	5 (0.2%)	5 (0.1%)	0.342	3.524 (0.220-56.363)
Requiring Transfusion, n	220 (10.1%)	720 (9.4%)	0.654	1.083 (0.763-1.539)
Mechanical Ventilation, n	85 (3.9%)	180 (2.3%)	0.073	1.688 (0.946-3.014)
Vasopressors, n	55 (2.5%)	85 (1.1%)	0.022	2.310 (1.107-4.818)
Shock, n	90 (4.1%)	205 (2.7%)	0.107	1.568 (0.904 2.719)
ICU, n	100 (4.6%)	230 (3.0%)	0.099	1.556 (0.916 -2.640)
Mortality, n	145 (6.7%)	305 (4.0%)	0.016	1.720 (1.099-2.692)
Day of Paracentesis, n				
Day 0	80 (3.7%)	515 (6.7%)	0.016	0.529 (0.312-0.897)
Day 1	555 (25.5%)	2160 (28.2%)	0.263	0.871 (0.684 1.109)
Day 2	475 (21.8%)	1065 (13.9%)	<0.001	1.728 (1.323-2.256)
Day 3	285 (13.1%)	880 (11.5%)	0.376	1.160 (0.835-1.613)
Day 4	190 (8.7%)	695 (9.1%)	0.836	0.958 (0.654-1.404)
Day 5	220 (10.1%)	610 (8.0%)	0.155	1.299 (0.905-1.864)

Disclosures: Nisha Sanghani: Nothing to Disclose, Het Patel: Nothing to Disclose, Pooja Patel: Nothing to Disclose, Hammad Liaquat: Nothing to Disclose

4165 | SERUM N-GLYCANS AS PREDICTIVE BIOMARKERS FOR RECOMPENSATION IN PATIENTS WITH CHRONIC HEPATITIS B AND DECOMPENSATED CIRRHOSIS

you deng[1] *Qi Wang*[1] *Hong Zhao*[1] *Qian Wu*[2] *Cuiying Chen*[2] *Wenya Chen*[1] *Jiashuo Li*[1] *Mengqi Li*[1] *Wen Xie*[1]

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Background: Recompensation is achievable in patients with chronic hepatitis B (CHB) and decompensated cirrhosis following treatment. However, predicting recompensation remains challenging. Changes in N-glycans are

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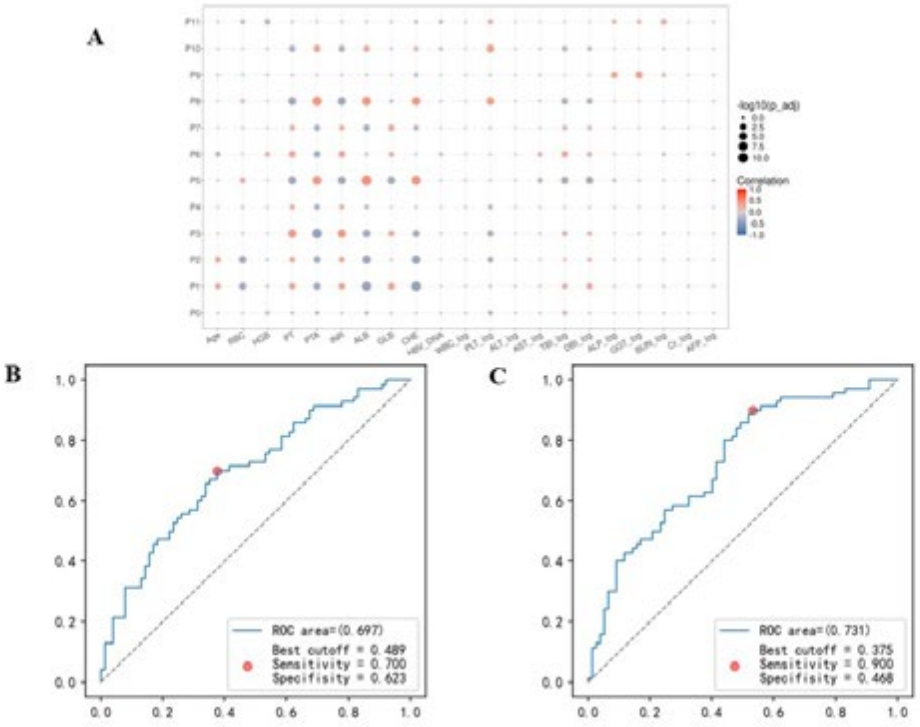
believed to play a key role in liver disease. This study aims to investigate the predictive value of serum N-glycans for recompensation in patients with CHB and decompensated cirrhosis. **Methods:** This study prospectively enrolled patients with CHB and decompensated cirrhosis who received antiviral treatment for at least 48 weeks. Recompensation was defined according to the Baveno VII criteria. Baseline serum N-glycans were released and analyzed using GLYFACE®, a proprietary Glycomics analytical platform by Fluorophore-Assisted Capillary Electrophoresis. N-glycan peaks that showed significant changes ($P < 0.05$) in the recompensation group were selected for the modeling group. A multiparameter diagnostic model was established based on these changes using logistic regression analysis. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the diagnostic efficacy of the N-glycans model. Furthermore, the multiparameter diagnostic model was combined with clinical indicators to compare their diagnostic power. Spearman correlation coefficient was used to evaluate the correlation of N-glycans with clinical indicators. **Results:** A total of 168 patients were enrolled, with a mean age of 52 ± 12 years. Among them, 75 patients achieved recompensation, while 93 did not. Compared to the non-recompensation group, patients in the recompensation group showed lower N-glycan peaks 1, 2, 4, and 7, and a higher peak 5. Additionally, the recompensation group had higher RBC, HGB, PLT, ALT, CHE, and HBV DNA levels, and younger age. Spearman correlation analysis indicated that N-glycans correlated with PT, PTA, INR, ALB, GLB, and CHE (Figure 1A). Multiparameter diagnostic models based on N-glycanss predicted recompensation with an area under the ROC curve (AUROC) of 0.697 (Figure 1B). When combined with clinical indicators, the models showed improved diagnostic power, with an AUROC of 0.731 (Figure 1C). **Conclusion:** Our research suggests that N-glycans may serve as valuable, noninvasive supplementary biomarkers for predicting recompensation in patients with CHB and decompensated cirrhosis.



Disclosures: you deng: Nothing to Disclose, Qi Wang: Nothing to Disclose, Hong Zhao: Nothing to Disclose, Qian Wu: Nothing to Disclose, Cuiying Chen: Nothing to Disclose, Wenya Chen: Nothing to Disclose, Jiashuo Li: Nothing to Disclose, Mengqi Li: Nothing to Disclose, Wen Xie: Nothing to Disclose

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4166 | ANALYSIS OF THROMBOEMBOLIC EVENTS IN PATIENTS WITH CIRRHOSIS

Het Patel *Nisha Sanghani*[1] *Pooja Patel*[1] *Hammad Liaquat*[1]

[1]*St. Luke's University Health Network*

Background: Cirrhosis of the liver is a known hypercoagulable state due to impaired synthetic function of coagulation factors. There are many locations that thromboembolic events are well known and well-studied. The goal of this study is to identify locations of thromboembolic events in patients with cirrhosis. **Methods:** This is a retrospective cohort study using National Inpatient Sample data including adults hospitalized between 2016 and 2020 with thromboemboli. The study compares patients with cirrhosis versus patients without cirrhosis assessing risk factors including demographics and chronic medical conditions for the patients in our sample along with the primary outcomes assessed which were various locations of thromboemboli. Statistical analyses were all performed using STATA software. **Results:** Of the 2,360,889 patients who met our inclusion criteria, 153,900 (6.5%) patients had cirrhosis. The average age of patients with cirrhosis was younger than those without (60.7 vs 64.1; p<.001). We found a statistically significant higher rate of cirrhosis and thromboembolism in patient who were Hispanic, Asian or Pacific Islander, Native American, Other race, had diabetes, alcohol use disorder, cancer, and drug use (p<0.05%). Patients who were White, Black, had obesity, hypertension, congestive heart failure, COPD, cerebrovascular disease, and dementia were seen in patients with clots without cirrhosis (p<0.05). Of the locations of thromboemoli assessed, most were seen more often (p<0.05) in patients without cirrhosis except for Budd Chiari syndrome (3.6% vs. 0.5%; p<0.0001 OR=7.261 95% CI 6.714-7.851), portal vein thrombosis (69.9% vs 6.6%; p<0.0001 OR=33.134 95% CI 32.116-34.185), and other unspecified vein (3.2% vs 2.3%; p<0.0001 OR=1.392 95% CI 1.299-1.491). **Conclusion:** In patients hospitalized, Budd Chiari syndrome and portal vein thrombosis were seen more frequently in patients with cirrhosis while all other sites of thromboemboli were seen more frequently in patients without cirrhosis. This may be a result of these clots being more frequently seen in cirrhosis or are more frequently assessed and discovered in patients admitted to the hospital with cirrhosis.

Table 1: Demographics

	Cirrhosis with Clots (n = 153,900)	Without Cirrhosis without Clots (n = 2,206,989)	P Value	Odds Ratio (95% Confidence Interval)
Mean Age, years	60.7	64.1	<0.001	-
Gender, n				
Male	97245 (63.2%)	1145510 (51.9%)	<0.0001	1.591 (1.550-1.631)
Female	56640 (36.8%)	1060955 (48.1%)		0.629 (0.613-0.645)
Race, n				
White	96645 (62.8%)	1474740 (66.8%)	<0.0001	0.838 (0.811-0.866)
Black	16590 (10.8%)	383695 (17.4%)	<0.0001	0.574 (0.552-0.597)
Hispanic	24920 (16.2%)	178910 (8.1%)	<0.0001	2.190 (2.096-2.289)
Asian or Pacific Islander	4560 (3.0%)	35775 (1.6%)	<0.0001	1.853 (1.719-1.998)
Native American	1895 (1.2%)	10385 (0.5%)	<0.0001	2.637 (2.327-2.988)
Other	4965 (3.2%)	58910 (2.7%)	<0.0001	1.216 (1.115-1.325)
Obesity, n	21575 (14.0%)	405190 (18.4%)	<0.0001	0.725 (0.700-0.751)
Hypertension, n	50200 (32.6%)	819660 (37.1%)	<0.0001	0.810 (0.798-0.841)
Congestive Heart Failure, n	24245 (15.8%)	491485 (22.3%)	<0.0001	0.655 (0.631-0.675)
COPD, n	19980 (13.0%)	334765 (15.2%)	<0.0001	0.834 (0.805-0.865)
ESRD, n	7980 (5.2%)	115615 (5.2%)	0.6893	0.989 (0.938-1.043)
Diabetes, n	57185 (37.2%)	643640 (29.2%)	<0.0001	1.436 (1.399-1.474)
Cerebrovascular Disease, n	5560 (3.6%)	210455 (9.5%)	<0.0001	0.356 (0.334-0.378)
Alcohol Abuse, n	65780 (42.7%)	98684 (4.5%)	<0.0001	15.946 (15.486-16.408)
Cancer, n	30085 (19.5%)	214190 (9.7%)	<0.0001	2.260 (2.187-2.337)
Drug Use, n	11690 (7.6%)	105135 (4.8%)	<0.0001	1.643 (1.569-1.721)
Dementia, n	3735 (2.4%)	164230 (7.4%)	<0.0001	0.309 (0.287-0.333)
Mean Length of Stay, days	8.280	9.006	<0.001	-

Table 2: Thromboembolism Location

	Cirrhosis with Clots (n = 153,900)	Without Cirrhosis without Clots (n = 2,206,989)	P Value	Odds Ratio (95% Confidence Interval)
Upper Extremity Artery, n	570 (0.4%)	39785 (1.8%)	<0.0001	0.203 (0.168-0.244)
Lower Extremity Artery, n	1690 (1.1%)	162915 (7.4%)	<0.0001	0.139 (0.125-0.156)
Iliac Artery, n	1335 (0.9%)	91050 (4.1%)	<0.0001	0.203 (0.180-0.230)
Aorta, n	1165 (0.8%)	68460 (3.1%)	<0.0001	0.238 (0.208-0.273)
Unspecified Extremity Artery, n	15 (<0.1%)	920 (<0.1%)	0.0059	0.234 (0.076-0.722)
Unspecified Artery, n	2410 (1.6%)	51440 (2.3%)	<0.0001	0.667 (0.608-0.731)
Budd Chiari Syndrome, n	5470 (3.6%)	11145 (0.5%)	<0.0001	7.261 (6.714-7.851)
Portal Vein Thrombosis, n	107640 (69.9%)	144815 (6.6%)	<0.0001	33.134 (32.116-34.185)
Femoral Vein, n	17930 (11.7%)	802890 (36.4%)	<0.0001	0.229 (0.221-0.238)
Iliac Vein, n	1730 (1.1%)	117865 (5.3%)	<0.0001	0.202 (0.181-0.225)
Popliteal Vein, n	9225 (6.0%)	533500 (24.2%)	<0.0001	0.200 (0.190-0.210)
Tibial Vein, n	4095 (2.7%)	253395 (11.5%)	<0.0001	0.211 (0.197-0.226)
Axillary Vein, n	1650 (1.1%)	69605 (3.2%)	<0.0001	0.333 (0.297-0.372)
Subclavian Vein, n	2075 (1.3%)	93170 (4.2%)	<0.0001	0.310 (0.280-0.343)
Internal Jugular Vein, n	4020 (2.6%)	136025 (6.2%)	<0.0001	0.408 (0.379-0.440)
Unspecified Lower Extremity Vein, n	8405 (5.5%)	367845 (16.7%)	<0.0001	0.289 (0.274-0.305)
Other Unspecified Vein, n	4925 (3.2%)	51190 (2.3%)	<0.0001	1.392 (1.299-1.491)

Disclosures: Het Patel: Nothing to Disclose, Nisha Sanghani: Nothing to Disclose, Pooja Patel: Nothing to Disclose, Hammad Liaquat: Nothing to Disclose

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4167 | SIGNIFICANT DIFFERENCES IN IN THE OVERALL AND CAUSE-SPECIFIC SURVIVAL RATES ACROSS SUBGROUPS OF PATIENTS WITH CIRRHOSIS

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Background: Cirrhosis is the end stage of chronic liver disease. Real-world U.S. data on sex differences for cirrhosis presentation and mortality are currently limited. We aimed to evaluate differences in 10-year survival and risk factors associated with mortality of male and female patients with cirrhosis. **Methods:** We analyzed 15,882 consecutive patients with cirrhosis diagnosed between 2000-2022 at a U.S. university medical center. Cirrhosis was diagnosed by imaging, histology, noninvasive test showing stage 4 fibrosis or signs of portal hypertension in the presence of an underlying chronic liver disease. We used Kaplan-Meier curves to analyze cumulative survival rates and Cox proportional hazard regression to analyze variables associated with overall (OS), liver related, and nonliver related mortality. **Results:** This cohort included 59.1% males (N=9383) and 40.9% females (N=6499). Males had a significantly lower 10-year cumulative OS compared to females (42.3% vs. 50.3%, P<0.0001) overall as well as in subgroup of patients with decompensated (29.2% vs. 34.7%, P<0.0001) and compensated (53.7% vs. 60.2%, P<0.0001) cirrhosis. Among patients without HCC at baseline, males had a significantly lower 10-year OS (46.5% vs. 52.1%, P<0.0001), but no significant sex disparity was observed among those with baseline HCC (28.6% vs. 28.2%, P=0.141). Across CTP classes, males had significantly lower 10-year OS than females (class A: 63.7% vs. 71%, class B: 35.4% vs. 40.8%, class C: 33.7% vs. 39.2%, P<0.0001 for all), and the same trend was observed across MELD-3.0 ranges (<15: 53.3% vs. 60.1%, 15-20: 33.8% vs. 39.6%, >20: 34.5% vs. 40.1%, P<0.001 for all). By cause of death, liver-related cumulative survival rates were significantly lower for male compared to female patients (P<0.0001 for both), but not for nonliver-related survival (P=0.578). In multivariable Cox regression adjusting for sex, diagnosis period, age, race and ethnicity, liver disease etiology, MELD-3.0 score, baseline HCC, and Charlson Comorbidity Index (CCI), significant predictors for both liver and nonliver-related mortality included cirrhosis diagnosed after 2010, older age, nonviral etiology, higher MELD-3.0 score, baseline HCC, and higher CCI (P<0.001 for all, Table). **Conclusion:** Significant sex disparities in the survival of patients with cirrhosis were found across cirrhosis decompensation and HCC status, CTP class, and MELD-3.0 score. Further evaluation of risk factors associated with male vs. female mortality is needed to reduce the sex disparity in cirrhosis survival.

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Variable	# of events	Univariable HR (95% CI)	P-value	Multivariable HR (95% CI)	P-value
Overall Mortality*					
Sex					
Females	2194	Referent		Referent	
Males	3665	1.23 (1.16-1.29)	<0.001	1.14 (1.07-1.21)	<0.001
Diagnosis period					
Before 2010	2800	Referent		Referent	
After 2010	3059	0.76 (0.72-0.81)	<0.001	0.74 (0.69-0.79)	<0.001
Age	5859	1.46 (1.39-1.54)	<0.001	1.50 (1.41-1.60)	<0.001
Race and Ethnicity					
White	3205	Referent		Referent	
Black	214	0.96 (0.84-1.10)	0.566	0.91 (0.78-1.06)	0.23
Hispanic	1360	0.98 (0.92-1.04)	0.438	0.97 (0.90-1.04)	0.35
Asian	956	0.79 (0.74-0.85)	<0.001	0.74 (0.69-0.81)	<0.001
Etiology					
Viral	2329	Referent			
Nonviral	3528	1.25 (1.19-1.32)	<0.001	1.22 (1.15-1.31)	<0.001
MELD-3.0 score	5279	1.06 (1.05-1.06)	<0.001	1.05 (1.05-1.06)	<0.001
Baseline HCC					
No baseline HCC	4416	Referent			
Baseline HCC	997	2.14 (2.00-2.30)	<0.001	2.04 (1.88-2.21)	<0.001
CCI	5859	1.10 (1.09-1.11)	<0.001	1.06 (1.05-1.07)	<0.001
Liver Related Mortality*					
Sex					
Females	869	Referent		Referent	
Males	1458	1.23 (1.13-1.34)	<0.001	1.08 (0.98-1.19)	0.13
Diagnosis period					
Before 2010	604	Referent		Referent	
After 2010	1723	2.41 (2.17-2.67)	<0.001	2.89 (2.53-3.29)	<0.001
Age	2327	1.53 (1.41-1.66)	<0.001	1.29 (1.17-1.42)	<0.001
Race and Ethnicity					
White	1161	Referent		Referent	
Black	68	0.84 (0.66-1.08)	0.172	0.79 (0.60-1.04)	0.099
Hispanic	650	1.29 (1.17-1.42)	<0.001	1.11 (1.00-1.24)	0.054
Asian	379	0.87 (0.77-0.97)	0.017	0.76 (0.66-0.86)	<0.001
Etiology					
Viral	884	Referent			
Nonviral	1442	1.35 (1.24-1.46)	<0.001	1.43 (1.28-1.59)	<0.001
MELD-3.0 score	2152	1.05 (1.04-1.05)	<0.001	1.06 (1.06-1.07)	<0.001
Baseline HCC					
No baseline HCC	1509	Referent			
Baseline HCC	543	3.39 (3.07-3.74)	<0.001	4.13 (3.66-4.66)	<0.001
CCI	2327	1.10 (1.09-1.11)	<0.001	1.02 (1.01-1.03)	0.004
Nonliver Related Mortality*					
Sex					
Females	514	Referent		Referent	
Males	677	0.97 (0.86-1.09)	0.574	1.08 (0.95-1.22)	0.24
Diagnosis period					
Before 2010	335	Referent		Referent	
After 2010	856	3.12 (2.67-3.64)	<0.001	2.57 (2.14-3.07)	<0.001
Age	1191	2.24 (1.99-2.52)	<0.001	1.82 (1.60-2.08)	<0.001
Race and Ethnicity					
White	669	Referent		Referent	
Black	68	1.49 (1.16-1.91)	0.002	1.25 (0.95-1.64)	0.11
Hispanic	225	0.80 (0.69-0.93)	0.004	0.82 (0.70-0.97)	0.018
Asian	191	0.74 (0.63-0.87)	<0.001	0.86 (0.72-1.03)	0.094
Etiology					
Viral	314	Referent			
Nonviral	876	2.49 (2.18-2.83)	<0.001	1.72 (1.48-2.00)	<0.001
MELD-3.0 score	1074	1.03 (1.03-1.04)	<0.001	1.02 (1.02-1.03)	<0.001
Baseline HCC					
No baseline HCC	1102	Referent			
Baseline HCC	53	0.49 (0.37-0.64)	<0.001	0.35 (0.26-0.48)	<0.001
CCI	1191	1.17 (1.16-1.19)	<0.001	1.17 (1.15-1.18)	<0.001

Footnote

*** Adjusted for sex, diagnosis period, age, ethnicity, etiology, MELD, baseline HCC, and CCI**

Disclosures: Ashley Fong: Nothing to Disclose, Joanne Liu: Nothing to Disclose, Mayumi Maeda: Nothing to Disclose, Vy Nguyen: Nothing to Disclose, Isaac Le: Nothing to Disclose, Annie Fung: Nothing to Disclose, Surya Teja Gudapati: Nothing to Disclose, Sally Tran: Nothing to Disclose, Angela Chau: Nothing to Disclose, Xinrong Zhang: Nothing to Disclose, Jung Eun Park: Nothing to Disclose, Ramsey Cheung: Nothing to Disclose, Changqing Zhao: Nothing to Disclose, Minjuan Jin: Nothing to Disclose, Mindie Nguyen: Nothing to Disclose

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4168 | THROMBOSPONDIN-1 AS A PREDICTIVE BIOMARKER FOR RECOMPENSATION IN PATIENTS WITH CHRONIC HEPATITIS B AND DECOMPENSATED CIRRHOSIS

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Background: Achieving recompensation in patients with chronic hepatitis B (CHB) and decompensated cirrhosis is possible with treatment, but predicting which patients will recompensate remains difficult. Thrombocytopenia, a common issue in cirrhosis, and thrombospondin-1 (TSP-1), which is implicated in liver disease progression, may offer insights. Given TSP-1's role, it holds potential as an early biomarker for predicting recompensation. This study aims to evaluate the predictive value of TSP-1 in identifying patients likely to achieve recompensation. **Methods:** This study enrolled patients with CHB and decompensated cirrhosis. They were treated with entecavir for 120 weeks. Baseline serum TSP-1 concentration was measured by ELISA. Recompensation at 120 weeks was defined per the Baveno VII criteria. Univariate and multivariate logistic regression analyses identified factors related to recompensation. Spearman correlation coefficient evaluated the correlation of TSP-1 with other factors. **Results:** A total of 158 patients were enrolled, with a mean age of 50 ± 11 years. At 120 weeks, 84 patients achieved recompensation while 74 did not. RBC, HGB, ALB, and TSP-1 were significantly higher in the recompensated group, while age and GLB were significantly lower compared to the non-recompensated group. There were no significant differences in HBV DNA, INR, ALT, AST, TBIL, Child-Pugh score, and MELD score. Univariate logistic analysis indicated that younger age, higher RBC, HGB, ALB, and TSP-1, and lower GLB at baseline were correlated with recompensation ($p < 0.05$). Multivariate logistic analysis suggested that only higher baseline TSP-1 (OR [95% CI]: 1.001 [1.001-1.002], $p = 0.024$) were independently associated with recompensation. Serum TSP-1 in the recompensated group was significantly higher than in the non-recompensated group ($p = 0.003$) (Figure 1A). The AUROC of TSP-1 for predicting recompensation was 0.636 (0.549-0.723) (Figure 1B). Spearman correlation analysis showed that TSP-1 was positively correlated with PLT ($r = 0.681$, $p < 0.001$), negatively correlated with MELD ($r = -0.271$, $p = 0.001$), and had no significant correlation with other indicators (Figure 1C). **Conclusion:** Patients in the recompensated group had significantly higher baseline TSP-1 than those in the non-recompensated group, with an AUROC value of 0.636, revealing the potential of TSP-1 as a predictive biomarker of recompensation.

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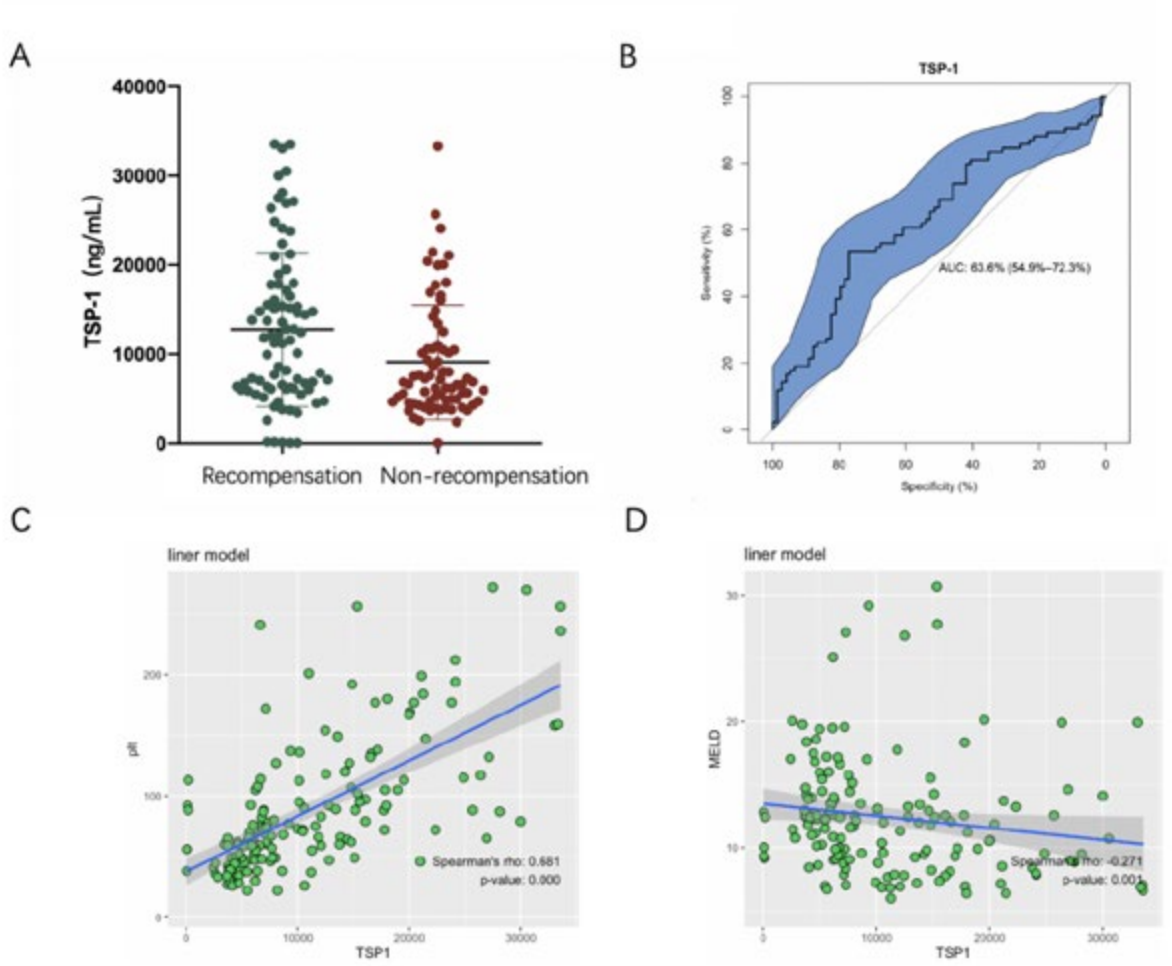

Disclosures: you deng: Nothing to Disclose, Hong Zhao: Nothing to Disclose, Qi Wang: Nothing to Disclose, Jiashuo Li: Nothing to Disclose, Wenya Chen: Nothing to Disclose, Mengqi Li: Nothing to Disclose, Wen Xie: Nothing to Disclose

4169 | EFFICACY AND SAFETY OF TENOFOVIR ALAFENAMIDE IN PATIENTS WITH DECOMPENSATED HEPATITIS B CIRRHOSIS

you deng[1] Weili Cui[2] Jin Yue[3] Jinlong Li[4] Shuqian Zhang[1] Qi Wang[1] Hong Zhao[1] Wenya Chen[1] Jiashuo Li[1] Mengqi Li[1] Xiaohuan Lai[4] Xiaoqing Guo[3] Bing Qiao[2] Wen Xie[1]

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Background: Chronic hepatitis B (CHB) remains a significant global health challenge despite the availability of effective vaccines and antiviral therapies. Decompensated cirrhosis, a severe complication of CHB, significantly increases the risk of liver-related morbidity and mortality. Tenofovir alafenamide (TAF) is a potent antiviral agent that has shown superior safety profiles. However, the efficacy and safety of TAF in patients with CHB and decompensated cirrhosis remain underexplored. **Methods:** This retrospective cohort study enrolled patients with CHB and decompensated cirrhosis treated with TAF for at least 96 weeks between January 2019 and February 2024 from four hospitals. Data, including demographics, hematology, and imaging information, were collected at baseline and every 24 weeks thereafter. The primary objective was to assess the recompensation rate at week 96, defined according to the Baveno VII criteria. Secondary objectives included evaluating changes in virological, serological, and biochemical parameters during treatment and comparing the outcomes between patients switched to TAF and those naïve to TAF treatment. **Results:** A total of 235 patients with CHB and

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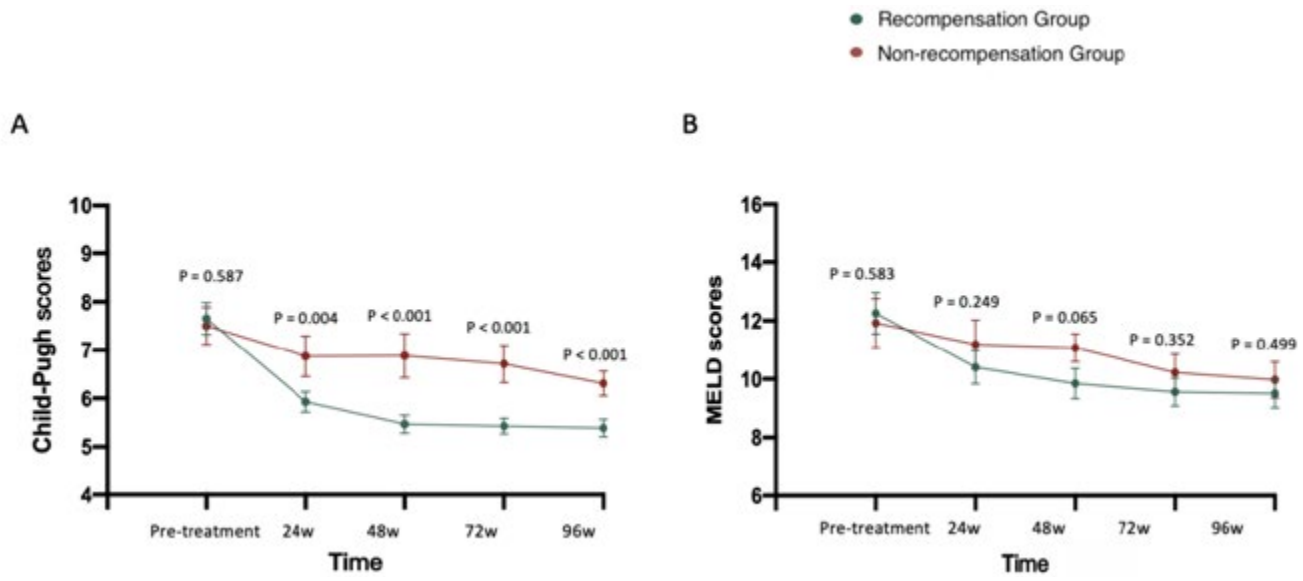
decompensated cirrhosis were included, of whom 203 completed the 96-week observation period. Among these, 66 patients were switched to TAF, and 137 were TAF-naïve. After 96 weeks of antiviral treatment, 97.5% (198/203) of patients achieved HBV DNA suppression, and 59.6% (121/203) achieved recompensation. The recompensation rate among patients with higher baseline MELD scores was not significantly different from those with lower baseline MELD scores. Liver function tests improved overall, with the recompensation group showing more significant improvements than the non-recompensation group (Figure 1). The TAF-naïve treatment group had significantly higher baseline HBV DNA levels, ALT, AST, MELD scores, and Child-Pugh scores compared to the switched group. After 96 weeks of treatment, there were no significant differences in HBV DNA levels and MELD scores between the two groups, nor in recompensation rates. **Conclusion:** The majority of patients with CHB and decompensated cirrhosis successfully suppressed HBV DNA and improved liver function, with 59.6% achieving recompensation after receiving TAF treatment. The results indicate that TAF is an effective treatment option for CHB patients with decompensated cirrhosis, regardless of the baseline severity of liver disease. It also demonstrated superior safety profiles in terms of renal and bone health.



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4170 | RISING MORTALITY TRENDS AMONG ADULTS WITH CHRONIC KIDNEY DISEASE AND CIRRHOSIS IN THE UNITED STATES (1999 TO 2020): A STUDY OF HEALTH DISPARITIES ◆ ★

Saleha Aziz[1] *Anjiya Shaikh*[2] *Mark Pedersen*[3] *Jan Petrasek*[1]

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Background: Patients with chronic kidney disease (CKD) and cirrhosis face significant health challenges and increased mortality risk. This study investigated how mortality trends have changed in this vulnerable population over two decades, examining potential disparities related to age, sex, race, and location of death. **Methods:** Utilizing data from Centers for Disease Control and Prevention Wide-Ranging OnLine Data for Epidemiologic Research to access the National Vital Statistics System (1999 to 2020), we identified adults aged 25 years and older with both CKD and cirrhosis. Age-adjusted mortality rates (AAMR) were calculated per 100,000 adults, and joinpoint regression analysis was used to determine changes in trends through average annual percentage change (AAPC). Mortality was further analyzed by age, sex, race, and location of death. **Results:** A total of 58,074 deaths were recorded during the study period. Overall, mortality rates increased significantly, with an

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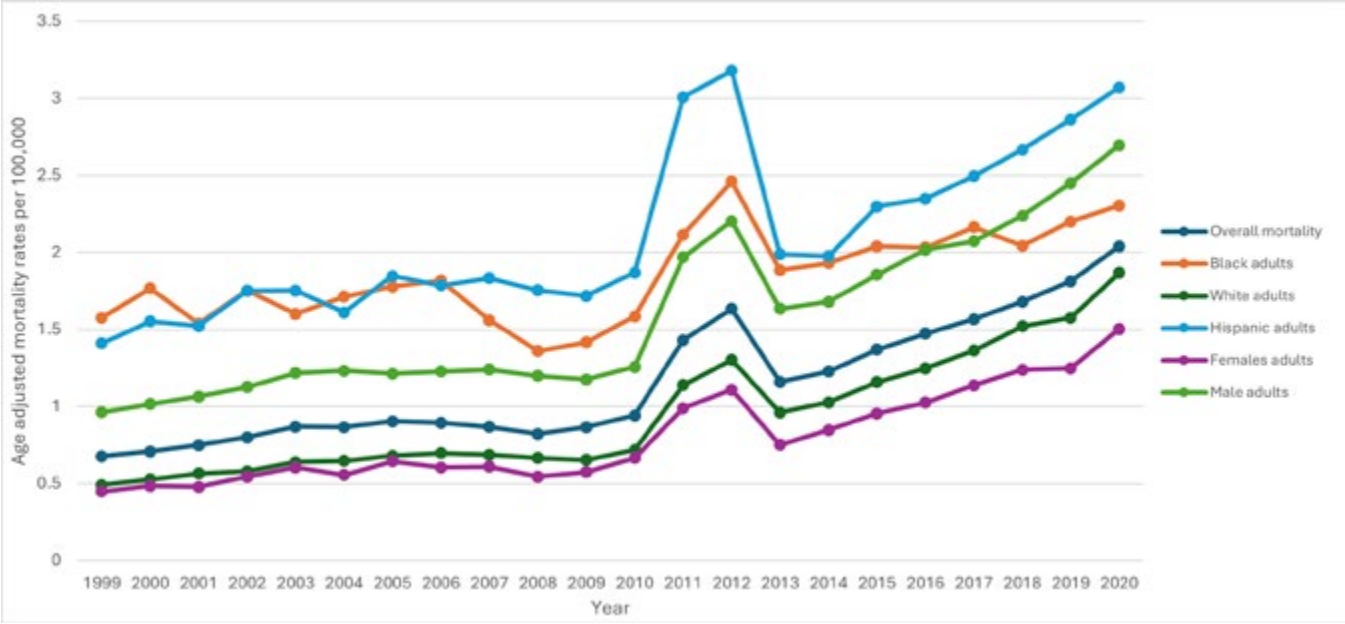
AAPC of +5.20%, 95% confidence interval 4.35 to 6.35. Males experienced higher mortality rates than females (AAMR 1.66 vs. 0.83). On analyzing age, the elderly (65 years and above) had the highest rates (AAMR 3.55). Among racial groups, Hispanic adults had the highest AAMR (2.26), followed by black (1.90) and white adults (1.09). Most deaths occurred in inpatient facilities (33,898), highlighting the burden on the healthcare system. **Conclusion:** This study reveals alarming trends of rising mortality among individuals with CKD and cirrhosis in the United States. Disparities in mortality rates were evident across age, sex, and race, with the elderly and Hispanic adults experiencing the highest risk. These findings emphasize the need for targeted interventions and improved care for this population. Advanced counseling and goals-of-care discussions are recommended for all patients with CKD and cirrhosis in both inpatient and outpatient settings.



Disclosures: Saleha Aziz: Nothing to Disclose, Anjiya Shaikh: Nothing to Disclose, Mark Pedersen: Nothing to Disclose, Jan Petrasek: Nothing to Disclose

4171 | NOVEL CANNABINOID -1 RECEPTOR (CB1R) ANTAGONIST GENISTEIN RESTORES HEPATIC MICROVASCULAR FUNCTION, REDUCES LIVER FIBROSIS AND AMELIORATES PORTAL HYPERTENSION

Dinesh Mani Tripathi[1] Akash Kumar Mourya[2] Ashwini Vasudevan[3] Sandeep Kumar[4] vaibhav tiwari[3] VGM Naidu[5] Savneet kaur[3] Shiv Kumar Sarin[3]

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Background: The endocannabinoid receptor (CBR) activation plays a crucial role in progression of cirrhosis and related complications. However, pharmacological modulation of the endocannabinoid system for the treatment of cirrhosis and portal hypertension has not evolved because of psychoactive effects of these agents. We aimed to identify a safe therapeutic molecule which could antagonize peripherally located CB1R and ameliorate hepatic fibrosis and reduce portal pressure. **Methods:** *In silico*, structure activity relationship (SAR) and bioavailability of genistein was evaluated. Two experimental cirrhosis models CCl4(Gr2) and TAA(TGr2) were studied and compared with cirrhosis + Genistein (Gr3, TGr3) treated (25mg/kg), respectively vs Healthy control (Gr1). Hemodynamic parameters and ex-vivo endothelial dysfunction assessment was done. Pharmacokinetics of genistein was done in plasma and cerebrospinal fluid (CSF) 2hrs post-oral administration by HPLC method. *Invitro,* Primary hepatic stellate cells (HSCs) were treated with genistein and gene expression was studied. Histopathology and molecular analysis were performed. **Results:** *Insilico*, findings confirmed the SAR and enhanced bioavailability in comparison to rimonabant. Cirrhosis animals showed significantly raised

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PP [11.6±1; +83.9% (Gr2), 14.1±1.2;+124% (TGr2), than Gr1 (6.3±.30; mmHg] whereas a significant decrease in Gr3 (7.8±0.2;-32%), TGr3 (10.1±1.4;-28%) vs Gr2,TGr2 p<0.01. Gr2,TGr2 animals also had increased hepatic vascular resistance (p<0.01) & portal blood flow (p<0.05) vs Gr1 and Gr3, TGr3. Genistein improved endothelial dysfunction (ED) and portal perfusion pressure [Gr3: -29.2 vs Gr2: +2.22 and TGr3 -23.7 vs TGr2 +9.88,p=0.05)] in precontracted liver post acetylcholine treatment (10-5M). Histologically, architectural damage and fibrosis improved in Gr3 vs Gr2. Gene expression showed fold increase in hepatic CBR-1 (+6,+2), αSMA - HSC activation marker (+18,+4), Col1A1 (+50,+13), ED markers eNOS (+6,+3),CD31(+5,+2) inflammatory markers, IL6 (+9.1,+4.6), TNF-α (+63.7,+27.7) and iNOS (+8.3,+3.3) (P<0.05) in Gr2 and down regulated upon Genistein treatment (Gr3) significantly. CD31 protein expression was increased in Gr2 and reduced in Gr3. HPLC data showed bioavailability of genistein (27.3±1.6) µg/mL in plasma but only in traces (1.12+.5) µg/mL in CSF, confirming neuroprotection. *In vitro*, HSC CBR1 (-16) TGF-β R1(-12.5), PDGF-β R(-21), COL1A1α (-12), α-SMA (-5.8) gene expression were downregulated post genistein treatment. **Conclusion:** Genistein significantly reduces portal pressure, collagen deposition and prevents HSC activation in cirrhosis animals. It restores the endothelial function, most importantly, without breaching blood brain barrier. Genistein appears an effective novel therapy for cirrhosis by mitigating portal hypertension without causing any neurological side-effects and merits clinical validation.

Disclosures: Dinesh Mani Tripathi: Nothing to Disclose, Akash Kumar Mourya: Nothing to Disclose, Ashwini Vasudevan: Nothing to Disclose, Sandeep Kumar: Nothing to Disclose, vaibhav tiwari: Nothing to Disclose, VGM Naidu: Nothing to Disclose, Savneet kaur: Nothing to Disclose, Shiv Kumar Sarin: Nothing to Disclose

4172 | OBSERVATIONAL LONGITUDINAL STUDY DIVULGES BIOLOGICAL PATHWAYS AND PREDICTIVE BIOMARKERS BY URINARY PROTEOMICS IN PATIENTS WITH ACUTE KIDNEY INJURY IN DECOMPENSATED CIRRHOSIS

Inder Bhan Singh[1] Neelkant Verma[1] Surender sehrawat[2] Arka De[2] Vivek Kumar[2] kajal Kamboj[2] Ashok Yadav[2] Virendra Singh[3]

[1]National Forensic Sciences University, [2]PGIMER, [3]Punjab Institute of Liver and Biliary Sciences

Background: Decompensated cirrhosis (DC) patients with acute kidney injury (AKI) had worse pre- and post-transplant outcomes. AKI develops in 20% of hospitalized DC patients. However, the frequency of AKI in outpatient settings is modestly defined. Urine proteomics-based untargeted mass spectrometry was used in this long-term prospective study to look for urinary biomarkers of AKI in DC outpatients. **Methods:** Patients with DC are included in our prospective longitudinal study, and we monitor them for the emergence of AKI in an outpatient setting. Out of 82 patients, 21 have so far gone on to develop AKI. These 21 AKI patients' baseline urinary proteins were compared to control individuals. The criteria of the International Club of Ascites were used to define AKI. Liquid chromatography-mass spectrometry (LC-MS) was used to do urine proteomics, and Proteome Discoverer 3.0 was used to infer the results. Several bioinformatic tools (metaboanalyst, gprofiler for gene ontology (GO), String and Cytoscape for networking, and Reactome for pathway analysis) were used to identify the pathways that contributed to the development of AKI. To ascertain if Reactome pathways are enriched, the hypergeometric distribution test was applied. The Benjamani-Hochberg approach was used to adjust the derived probability score for the false discovery rate (FDR). **Results:** We discovered multiple pathways that were implicated in the development of AKI using LC-MS. Reactome, included 55 out of 73 identifiers in the sample were found in Reactome, where 616 pathways were hit by at least one of them. 100 proteins were significantly elevated in the AKI group and 145 had a log2 difference in comparison to controls, according to a proteomic study of 2503 proteins. Significant pathways identified included neutrophil degranulation, Innate Immune System, Nuclear Receptor transcription, RHOBTB GTPase Cycle, Chaperonin-mediated protein folding, Platelet activation, signaling and aggregation, Free fatty acids regulate insulin secretion. **Conclusion:** Baseline urinary proteomics suggests that immunological responses and inflammatory processes plays major role in the development of AKI in outpatient DC patients.

Disclosures: Inder Bhan Singh: Nothing to Disclose, Neelkant Verma: Nothing to Disclose, Surender sehrawat: Nothing to Disclose, Arka De: Nothing to Disclose, Vivek Kumar: Nothing to Disclose, kajal Kamboj: Nothing to Disclose, Ashok Yadav: Nothing to Disclose, Virendra Singh: Nothing to Disclose

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4173 | ACUTE HEMODYNAMIC RESPONSE TO CARVEDILOL IN CIRRHOTIC CHILDREN WITH CLINICALLY SIGNIFICANT PORTAL HYPERTENSION

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Background: Clinically significant portal hypertension (CSPH), indicated by hepatic venous pressure gradient (HVPG) >10 mm Hg is associated with portal hypertensive complications and mortality in patients with liver disease. Acute hemodynamic response (AHR) to non-selective beta-blockers, i.e. HVPG decreasing to <12 mm Hg or >20% from baseline is associated with a reduced long-term risk of variceal bleeding. We studied the acute hemodynamic response to carvedilol and its predictors in cirrhotic children with CSPH. **Methods:** Under-18-age cirrhotic children underwent HVPG via transjugular route. Those with CSPH were administered a single dose of carvedilol (0.2mg/kg) via oral or nasogastric route. AHR was defined as a decrease in HVPG ≥20% from baseline or absolute HVPG value declining to <12 mm Hg, 90 min after carvedilol. The proportion of patients achieving the AHR and factors predicting it were studied. **Results:** Thirty-five children (62% males) with a median age of 13 years (IQR 11, 15 years) with CSPH were included. Autoimmune liver disease (57%) was the commonest etiology. Median PELD/MELD and Child-Pugh scores were 13 (IQR 6, 22) and 7 (IQR 5, 10). Fifteen (43%) had decompensation –3 had variceal bleed; 17 (49%) had clinically significant varices. Median baseline HVPG was 17 mm Hg (IQR 15, 22mm Hg). Following 90 minutes of carvedilol, 17 (49%) patients had an AHR. On multivariate analysis, AHR in HVPG was predicted by portal vein size [Exp(B)=0.492; 95% CI=0.289-0.838, P=0.009] and serum sodium [Exp(B)=1.407; 95% CI=1.004-1.971, P=0.047], but not by other demographic, clinical, laboratory, or endoscopic variables. Children who did not achieve AHR had poor survival with native liver at 6 months (OR = 2.308; 95% CI 1.533-3.475, p=0.19) – there were 4 deaths and 1 liver transplant at 6 months of follow-up. **Conclusion:** Around half of the children achieved acute hemodynamic response following carvedilol. Larger portal vein diameter and lower serum sodium levels indicative of advance portal hypertension and liver disease predict non-response to carvedilol.

Disclosures: Deepika Yadav: Nothing to Disclose, Rajeev Khanna: Nothing to Disclose, Vikrant Sood: Nothing to Disclose, Seema Alam: Nothing to Disclose, Bikrant Ial: Nothing to Disclose, Ankur Jindal: Nothing to Disclose

4174 | DISSEMINATED COCCIDIOIDOMYCOSIS IN PATIENTS WITH CHRONIC LIVER DISEASE: A SINGLE-CENTER EXPERIENCE

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Background: Coccidioidomycosis is an endemic infection caused by the fungal pathogen *Coccidioides immitis* and is primarily seen in the southwestern United States. Most cases are limited to the respiratory tract; however, a small subset of patients may develop disseminated coccidioidomycosis (DCM). Few case series have described Coccidioidomycosis in the setting of liver disease. We aimed to perform a descriptive analysis of chronic liver disease with DCM as well as identification of risk factors for poor outcomes in this population. **Methods:** We conducted a retrospective study of patients over age 18 from January 2010 to December 2020 with chronic liver disease who developed DCM at Community Medical Centers, Fresno, California. DCM was defined as positive serum Coccidioides serology, culture, or PCR along with compatible clinical syndrome with evidence of extrapulmonary coccidioidal infection. Data were collected from chart review at the time of DCM diagnosis and included age, gender, ethnicity, type of liver disease, end-stage liver disease (ESLD), and features of decompensation. Outcomes of interest included intensive care unit (ICU) admission and death due to DCM. Fisher's exact test was used to test the association of two categorical variables. T-test was used to compare the mean level of continuous variables between binary outcomes. All statistical tests were 2-sided with a significance level of p = 0.05. **Results:** We identified 33 patients with DCM, 16 (48.48%) had underlying ESLD. Median age at time of diagnosis was 53 years and 88% were men. Hispanic patients were the largest percentage at 61%, while 18% were Caucasian, 12% Black, and 6% Asian. Causes of liver disease included: Hepatitis C in 36.6%, alcohol-related liver disease (ALD) in 30.3%, metabolic dysfunction associated steatotic liver disease (MASLD) in 18.18% of patients. ICU admission was required in 77.8% of patients with ESLD and DCM, compared to 22.22% of patients without ESLD (p = 0.047). Death due to DCM occurred in 85.7% of patients with ESLD,

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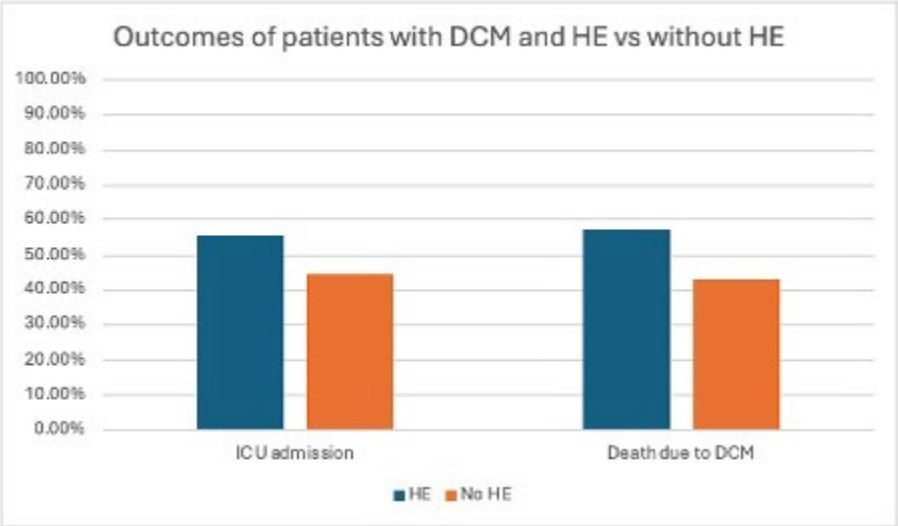
compared to 14.3% of patients without ESLD (p = 0.020). Of the patients with chronic liver disease, 12 (36.4%) had decompensated liver cirrhosis, and 71.43% of those patients died due to DCM compared to 14.3% of patients without decompensated liver disease (p = 0.058). The presence of overt hepatic encephalopathy (OHE) during hospital course was associated with worse outcomes in patients, with 55.6% of OHE patients requiring ICU admission vs 44.4% of patients without OHE (p = 0.037). Of the 8 patients with OHE, 57.14% died due to DCM, compared to 42.86% without OHE (p = 0.031). **Conclusion:** Our single-center retrospective study identified characteristics of patients with chronic liver disease and DCM. We found that presence of ESLD and HE were associated with an increased risk of death due to DCM in this population. Further studies are needed to confirm our results and explore the complex relationship between hepatic dysfunction and DCM.



Disclosures: Humzah Iqbal: Nothing to Disclose, Bilal Fazal Mehmood: Nothing to Disclose, Nam Huynh: Nothing to Disclose, Pavel Diaz: Nothing to Disclose, Geetha Sivasubramanian: Nothing to Disclose, Marina Roytman: Gilead: Speaking and Teaching, Salix: Speaking and Teaching, Madrigal: Speaking and Teaching

4175 | RIFAXIMIN IMPROVES FRAILTY IN PATIENTS WITH DECOMPENSATED CIRRHOSIS: RANDOMISED TRIAL

Sunil Taneja[1] Sweta Rose[2] Muhammad Uwais[2] Kannu Priya[2] Harish Bhujade[3] Yashwant Kumar[3] Sant Ram[2] Maryada Sharma[2] Sahaj Rathi[2] Arka De[4] Nipun Verma[2] Madhumita Premkumar[1] Ajay Duseja[1]

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Background: Decompensated cirrhosis patients have high prevalence of frailty that increases morbidity and mortality. This study was done to determine the impact of six months Rifaximin therapy on frailty in patients with decompensated cirrhosis. **Methods:** 100 patients with frailty assessed by Liver frailty Index (LFI) at baseline were randomized 1:1 to receive standard medical therapy plus Rifaximin (rSMT, intervention) versus SMT (control) alone. The primary outcome was an improvement in frailty at 6 months. Secondary outcome measures included improvement in disease severity scores (MELD, and CTP scores), inflammatory markers (ESR, CRP, IL-6), ammonia levels), hospitalization and survival at six months. **Results:** Frailty as assessed by LFI improved significantly in the intervention group as compared to the control group (4.7(4.5-5.03) to 4.2(4.1-4.5) at 6 months, (p<0.001) vs 4.7(4.6-5.0) to 4.7(4.4-5.2) at 6 months, (p=0.70)). On logistic regression analysis inclusion in the intervention arm, i.e. rSMT (OR 6.63, 95% CI 2.9- 14.7; p<0.001), higher baseline SMI (OR 1.06, 95% CI 1.0–1.1; p=0.002), age (OR 0.96, 95% CI 0.93- 1.0; p=0.02) and low levels of IL-6 (OR 0.99, 95% CI 0.97- 1.0; p=0.02) were predictors of improvement in frailty. The disease severity as assessed by CTP and MELD, score showed a significant improvement in the rSMT group as compared to the SMT group (p<0.05).The delta change in MELD score showed significant improvement in the rSMT group compared to the SMT group,-2.3± 2.9 versus 1.7± 5.4, p<0.001. Inflammatory markers showed significant improvement, with a higher delta change in IL-6 in the

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intervention group (-10 [-15.7/-4.4] vs -5 [-10.2/-0.5]; p = 0.01). Serum ammonia levels decreased significantly in the intervention group from 127.5 (97-201.7) at baseline to 78 (62-97) at 6 months, (p<0.001) vs 117 (79-218) at baseline to 122 (73-190) at 6 months. The patients in rSMT group had lesser number of hospitalizations 8(16%) vs 26(52%); p < 0.001) over the course of 6 months as compared to SMT group. On multivariate analysis, baseline values of IL-6, (OR 1.02, 95% CI (1.0-1.04); p=0.03), LFI (OR, 5.54 (95% CI (1.11- 27.72); p=0.03), and enrollment into non- intervention arm, (OR 0.096, 95% CI (0.02- 0.4);p=0.001) were associated with the risk of hospitalization.The mortality in rSMT and SMT group was 5(10%), and 11(22%), respectively though there was no significant difference in the overall survival (p=0.108). In a subgroup analysis of 11 patients, pre and post rifaximin therapy for six months there was a significant improvement in matrix metalloproteinases protein activity (p < 0.0006). **Conclusion:** Rifaximin therapy in decompensated cirrhosis has a significant impact on improving frailty, disease severity scores, inflammatory markers and ammonia with a reduction in number of hospitalizations.

Parameters	B	SE	Wald	Df	Sig.	Exp(B)	95% CI	
							Lower	Upper
rSMT or SMT*	1.9	0.41	21.4	1	<0.001	6.63	2.9	14.7
Age	-0.41	0.02	5.5	1	0.02	0.96	0.93	1.0
Sex	0.44	0.47	0.90	1	0.34	1.56	0.62	3.9
IL-6†	-0.014	0.006	5.37	1	0.02	0.99	0.97	1.0
CRP†	0.008	0.008	0.82	1	0.36	1.0	0.99	1.0
Ammonia†	-0.004	0.002	3.24	1	0.71	0.99	0.99	1.0
CTP†	0.07	0.22	0.11	1	0.74	1.1	0.70	1.6
MELD†	-0.05	0.06	0.69	1	0.40	0.95	0.83	1.1
SMI	0.06	0.02	9.77	1	0.002	1.06	1.0	1.1

Table- Cox regression analysis of various parameters to predict the improvement in frailty

Disclosures: Sunil Taneja: Nothing to Disclose, Sweta Rose: Nothing to Disclose, Muhammad Uwais: Nothing to Disclose, Kannu Priya: Nothing to Disclose, Harish Bhujade: Nothing to Disclose, Yashwant Kumar: Nothing to Disclose, Sant Ram: Nothing to Disclose, Maryada Sharma: Nothing to Disclose, Sahaj Rathi: Nothing to Disclose, Arka De: Nothing to Disclose, Nipun Verma: Nothing to Disclose, Madhumita Premkumar: Nothing to Disclose, Ajay Duseja: Nothing to Disclose

4176 | ASSESSMENT OF THE RELATIONSHIP BETWEEN MRI-BASED INTRAMUSCULAR FAT INDICATING SARCOPENIA IN VARIOUS MUSCLE GROUPS AMONG PATIENTS WITH CHRONIC LIVER DISEASE

ramazan erdem er[1] Zehra Akkaya[1] Sena Unal[1] Digdem Kuru Oz[1] Mehmet Mesut Celebi[1] Hale Gokcan[1] Hayriye Ozer[1] Evin Mizgin PARLAK KAYASLI[1] Ayse Erden[1] Ramazan Idilman[1]

[1]Ankara University

Background: The goal of this feasibility study was to evaluate the relationship between clinical status and skeletal muscle quality detected by Chemical Shift Magnetic Resonance Imaging (CS-MRI) in patients with cirrhosis, aiming to identify which skeletal muscle group(s) show the association with clinical outcomes. **Methods:** Patients with cirrhosis from a single center were recruited prospectively for this cross-sectional study. Skeletal muscle groups in the trunk and proximal lower extremities were evaluated for their intramuscular fat content using a 6-point Dixon CS-MRI on a 1.5T scanner (Aera, Siemens Healthcare, Erlangen, Germany). Muscle groups of interest included right and left paravertebral, psoas, gluteal, and the components of quadriceps femoris (vastus medialis [VM], lateralis [VL], rectus femoris [RF]). Fat fractions (FF) (%) were measured on a dedicated workstation using standard regions of interest on axial proton density FF maps. Frailty was assessed by the Liver

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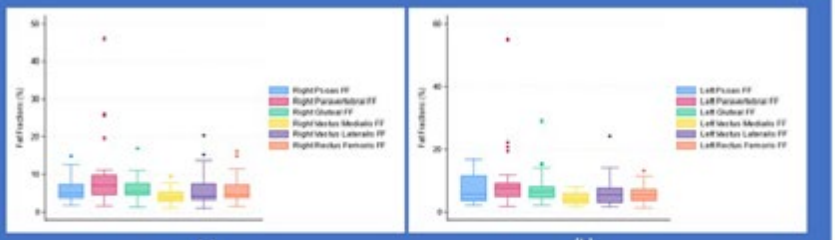
Frailty Index (LFI). Muscle strength was assessed using Handgrip strength (HGS). Linear regression models, adjusted for age, sex, and body mass index were used to investigate the relationships between individual muscle FF and a) LFI and b) Handgrip strength. Beta coefficients from the models represent the outcome change (i.e., liver frailty score) for each standard deviation increase in muscle FF. **Results:** A total of 28 patients (mean age 59.3 ± 12.0 years, 57.1% female) were included. Figure 1 summarizes the demographic and clinical descriptive parameters. Left paravertebral muscles showed the highest mean FF (9.5 ± 9.2 %) (Figure 2). Child-Pugh score did not significantly affect muscle FF and LFI ($p > 0.05$). Models testing for the relationship between muscle FF and LFI showed significant associations for right and left paravertebral muscles in the trunk (β= 0.42 [95%CI=0.15,0.7], p=0.005 and β= 0.48 [95%CI=0.02, 0.10], p=0.016 respectively) and right and left VL muscles in the thigh (β= 0.29 [95%CI=0.03, 0.52], p=0.027 and β= 0.23 [95%CI=0.03, 0.44], p=0.026 respectively) (Figure 3a). Grip strength showed significant inverse relationships for bilateral paravertebral and right gluteus medius muscles (Figure 3b). **Conclusion:** In patients with cirrhosis, intramuscular fat contents in the paravertebral and VL muscles exhibit the strongest positive correlation with the LFI and an inverse correlation with muscle strength.

Figure 1: Characteristics

Age (years) means ± SD	59.3 ± 12.04
Sex women, n (%)	16 (57.1)
Etiology of cirrhosis %	
Hepatitis B	32
Hepatitis C	11
Metabolic Dysfunction Associated Steatotic Liver Disease	43
Other	14
Comorbidities %	
Diabetes Mellitus	54
Hypertension	29
Coronary Artery Disease	6
Mean BMI kg/m2 ± SD	27.4 ± 6.1
Child-Pugh Classification %	
Child-Pugh A	64
Child-Pugh B	29
Child-Pugh C	7
MELD Score mean ± SD	11.5 ± 6.0
Liver Frailty Index , mean ± SD	4.2 ± 0.6
Liver Frailty Index category, %	
Robust	7
Prefrail	64
Frail	29
Handgrip Test (kg) mean ± SD	21.5 ± 9.0

Figure 2: Box-plots representing the right (a) and left-sided (b) muscle fat fractions.



(a) (b)

Figure 3: Results from Linear Regression Models representing the relationships between standardized muscle fat fractions and Liver Frailty Index *(a)* and Handgrip Strength *(b)*.

Muscle groups	Liver Frailty Index (a)		Handgrip Test (b)	
	β² (95% CI)	*p-value*	*β² (95% CI)*	*p-value*
Right paravertebral	0.42 (0.15, 0.70)	**0.005***	-5.32 (-9.7, -1.07)	**0.008***
Left paravertebral	0.48 (0.02, 0.10)	**0.016***	-4.5 (-7.67, -1.32)	**0.016***
Right Psoas	-0.03 (-0.24, 0.18)	0.755	-1.60 (-3.81, 0.61)	0.148
Left Psoas	0.03 (-0.20, 0.26)	0.783	-1.91 (-4.41, 0.58)	0.125
Right Gluteus Medius	0.16 (-0.03, 0.36)	0.088	-2.03 (-4.12, 0.51)	0.055
Left Gluteus Medius	0.02 (-0.18, 0.21)	0.856	-0.27 (-2.49, 1.96)	0.804
Right Vastus Medialis	0.10 (-0.15, 0.34)	0.422	-0.18 (-2.94, 2.58)	0.895
Left Vastus Medialis	0.08 (-0.13, 0.29)	0.445	-0.54 (-3.0, 1.91)	0.650
Right Vastus Lateralis	0.29 (0.03, 0.52)	**0.027***	-1.38 (-4.35, 1.59)	0.346
Left Vastus Lateralis	0.23 (0.03, 0.44)	**0.026***	-1.66 (-4.24, 0.91)	0.192
Right Rectus Femoris	-0.11 (-0.32, 0.10)	0.290	0.79 (-1.62, 3.19)	0.504
Left Rectus Femoris	-0.004 (-0.21, 0.22)	0.966	-2.36 (-4.6, -0.12)	**0.040***

Beta coefficients represent the change in liver frailty scores for each SD increase in muscle FF. CI: Confidence interval; FF: Fat fraction, * indicates statistically significant results. * *All models are adjusted for age, sex and body mass index.*

Disclosures: ramazan erdem er: Nothing to Disclose, Zehra Akkaya: Nothing to Disclose, Sena Unal: Nothing to Disclose, Digdem Kuru Oz: Nothing to Disclose, Mehmet Mesut Celebi: Nothing to Disclose, Hale Gokcan: Nothing to Disclose, Hayriye Ozer: Nothing to Disclose, Evin Mizgin PARLAK KAYASLI: Nothing to Disclose, Ayse Erden: Nothing to Disclose, Ramazan Idilman: Nothing to Disclose

4177 | INCREASED STOOL UREASE ACTIVITY IS AN INDEPENDENT PREDICTOR OF OVERT HE IN CIRRHOSIS

DEEPIKA JAKHAR[1] Pinky Juneja[2] Aarti Sharma[2] Dinesh Mani Tripathi[2] GURESH KUMAR[2] Saggere Muralikrishna Shasthry[2] Shiv Kumar Sarin[2] Savneet kaur[2]

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Background: Hyperammonemia is associated with the development of hepatic encephalopathy (HE). However, precise measurement of plasma ammonia can be challenging. Gut bacteria, especially the urease expressing bacteria in colon are an important source of endogenous ammonia production. We tested the hypothesis that high expression of colonic urease bacteria/activity represented by stool urease activity (SUA) is associated with increased gut ammonia production and hyperammonemia in experimental and clinical studies. We evaluated

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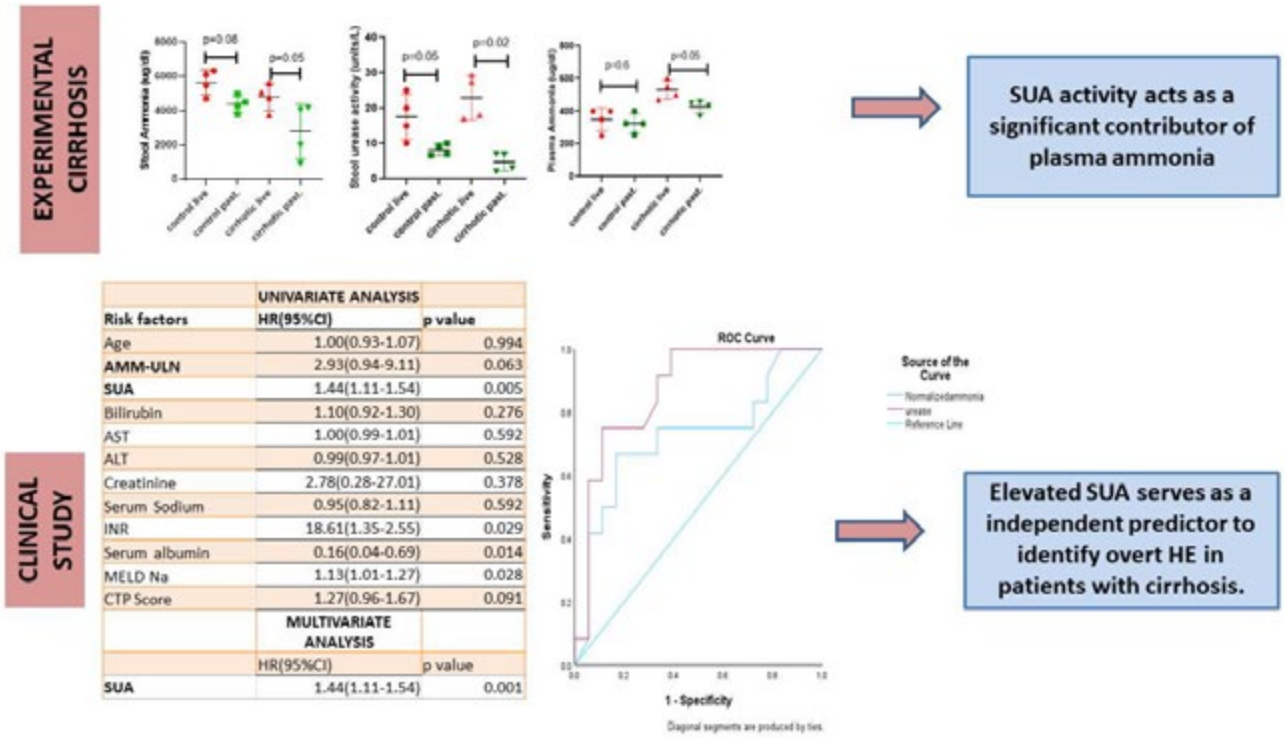
performance of SUA as predictor of overt hepatic encephalopathy (HE) in patients with cirrhosis. **Methods:** We gavaged live and pasteurized urease-producing bacteria*, Klebsiella pneumonia (Kp)* in bowel-cleansed controls and cirrhotic (n=4 each) rats for 7 days, and then measured plasma ammonia levels, colonic urease activity and SUA. In clinical studies, total of 30 hospitalized cirrhotic patients with etiology of alcohol abuse (43.3%) and non-alcoholic steatohepatitis (56.6%) along with 12 healthy controls were studied. Baseline normalized plasma ammonia (AMM-ULN) and SUA were assessed. We compared AMM-ULN and SUA between those who developed overt HE (stage 2-4) during hospitalization with those who did not develop HE. Also, we studied AMM-ULN and SUA as predictors of overt HE in patients by univariate and multivariate logistic regression analysis. **Results:** In experimental studies, in controls, after bowel cleansing, rats given live *Kp* showed higher colon urease activity (4.3-fold, p<0.05) and SUA (3.8-fold, p<0.05) than rats given pasteurized bacteria. However, there was no change in plasma ammonia between two groups. In cirrhotic rats, given live urease bacteria, both SUA (4-fold and 4.5-fold, p<0.05 each) and plasma ammonia (2-fold, p=0.02) were increased as compared to those given pasteurized *Kp*. In clinical studies, SUA and AMM-ULN were significantly increased in patients with cirrhosis vs controls and this also positively correlated with disease severity (CTP Score). Overt HE was present in 40% and mortality was observed in 26.6% of patients. SUA was significantly higher in patients which developed HE vs patients without HE (p=0.04). In univariate logistic regression analysis, SUA, AMM-ULN, and MELDNa emerged as significant predictors of overt HE. SUA also emerged as an independent predictor of HE in multivariate analysis (HR 1.44; 95% CI 1.11-1.85, p=0.005). The AUC to predict HE for AMM-ULN was 72.2% (95% CI 0.52-0.92, p=0.042) while for SUA, it was 86.8% (95% CI 0.73-0.99, p=0.001). The cut-off value of SUA for HE prediction was 15.25units/L, sensitivity of 76.7% and specificity of 77.8%. **Conclusion:** Our experimental findings demonstrate that increased gut/stool microbial urease activity contributes to hyperammonemia in cirrhosis. Elevated SUA serves as a valuable independent predictor to identify overt HE in patients with cirrhosis.



Disclosures: DEEPIKA JAKHAR: Nothing to Disclose, Pinky Juneja: Nothing to Disclose, Aarti Sharma: Nothing to Disclose, Dinesh Mani Tripathi: Nothing to Disclose, GURESH KUMAR: Nothing to Disclose, Saggere Muralikrishna Shasthry: Nothing to Disclose, Shiv Kumar Sarin: Nothing to Disclose, Savneet kaur: Nothing to Disclose

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4179 | EXOSOME THERAPY IN HEPATIC OSTEODYSTROPHY MANAGEMENT: EVALUATING THERAPEUTIC EFFICACY ACROSS THE BONE-LIVER AXIS

PURVA GUPTA[1]

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Background: Hepatic osteodystrophy (HOD) is a multifaceted disorder characterized by bone fragility and metabolic irregularities, commonly arising from chronic liver disease (CLD). Studies show a 60-80% prevalence of CLD among osteoporotic hip fracture cases. Current treatments mainly alleviate symptoms without addressing the underlying causes, resulting in suboptimal outcomes. The need for innovative treatments that target the intricate relationship between liver dysfunction and bone metabolism is pressing. Stem cell-derived exosomes, containing bioactive molecules that modulate cellular processes and combat oxidative stress, offer a promising therapeutic approach. However, the limited biodistribution of these exosomes to target sites hinders clinical translation. **Methods:** This study aims to develop a non-invasive exosome-based therapy to restore liver function and bone homeostasis in HOD. The therapeutic efficacy of stem cell-derived exosomes was evaluated using systemic and intra-bone administration. For targeted liver delivery, exosomes were conjugated with lactosylated polyethyleneimine to enhance hepatocyte specificity, assessed for biocompatibility, and functional efficacy both in vitro and in vivo. An HOD model was induced in SD rats via intraperitoneal carbon tetrachloride administration. After model establishment, exosome therapy was administered for four weeks through systemic, intra-femur, or combined routes. **Results:** Modified exosomes demonstrated 40% faster hepatocyte internalization and 69% reduced oxidative stress compared to unmodified exosomes in liver carcinoma and immortalized human hepatocyte cell lines. In vivo, these exosomes exhibited enhanced hepatoprotection and regenerative capacity against high doses of acetaminophen, reducing inflammatory responses and cellular apoptosis. In the HOD rat model, systemic exosome injections significantly improved trabecular bone parameters and resolved liver fibrosis compared to intra-bone injections. Combined systemic and intra-bone treatment almost completely resolved fibrosis and restored femur bone mineral density. **Conclusion:** Addressing liver dysfunction in HOD patients leads to substantial symptomatic relief and improved bone health, emphasizing the importance of targeting the underlying pathology. Exosome therapy focusing on liver restoration offers a promising avenue for holistic disease management, providing renewed hope for patients suffering from this debilitating condition.

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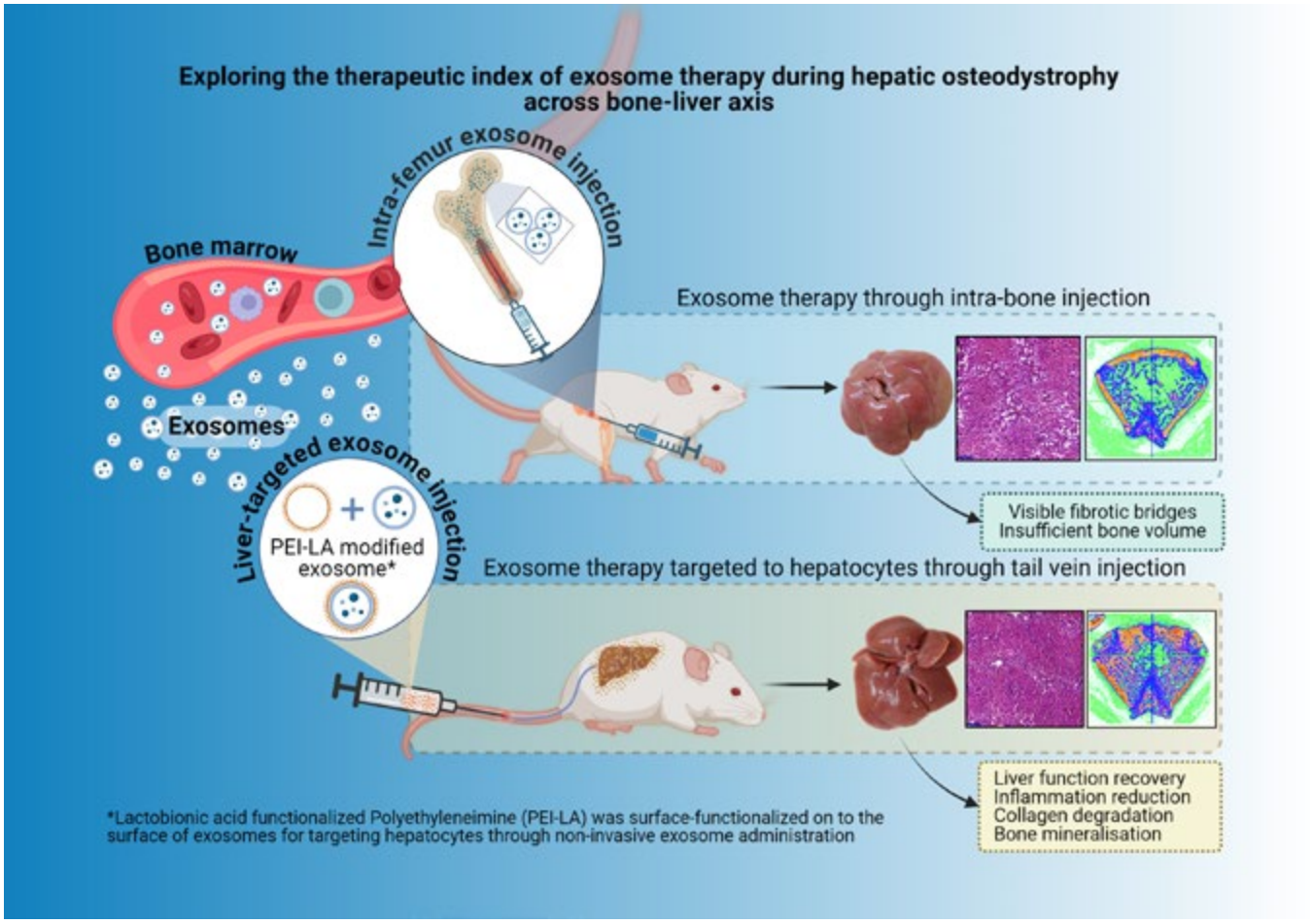

Disclosures: PURVA GUPTA: Nothing to Disclose

4180 | RIFAXIMIN CLAIM REJECTIONS RESULTING IN DELAYED TREATMENT AMONG PATIENTS WITH OVERT HEPATIC ENCEPHALOPATHY: AN ANALYSIS OF PRESCRIBER SPECIALTY

Arun Jesudian[1] *Patrick Gagnon-Sanschagrin*[2] *Christopher Allen*[3] *Rebecca Bungay*[2] *Jerome Bedard*[2] *Annie Guerin*[2] *Zeev Heimanson*[3]

[1]*Weill Cornell Medicine,* [2]*Analysis Group, Inc.,* [3]*Salix Pharmaceuticals*

Background: Overt hepatic encephalopathy (OHE) is a complication of cirrhosis that is associated with a high risk of repeated hospitalization and mortality. As pharmacy claims can be rejected by insurance payers, treatment access may be delayed or prevented. Rifaximin is an oral antibiotic used to reduce the risk of OHE recurrence. Rifaximin rejection rates and the association between prescriber specialty and claim rejections in the US are not well known. **Methods:** Using open- and closed-claims from Komodo Research Data (1/1/2016-9/30/2023), adult patients with OHE were identified using a published definition. The index date was defined as the first observed rifaximin attempt, where patients whose attempt was paid were classified as timely treatment and those whose attempt was initially rejected or reversed were classified as delayed treatment. Demographics and rifaximin prescriber specialty were described. Odds ratios for delayed treatment were calculated for each subgroup being prescribed rifaximin by different specialties compared to the overall population. **Results:** A total of 8696 patients were included and mean age was 59 years, 52.4% were male, and 32.7% lived in the South. Rifaximin was prescribed by a hepatologist or gastroenterologist for 26.4% of patients, an advanced practice provider (APP) for 21.8%, and by other specialties for 50.7%. Overall, 41.7% of patients had delayed rifaximin treatment. The proportion of patients with delayed rifaximin treatment was lower when prescribed by a hepatologist or gastroenterologist (32.7%) or APP (37.9%), and higher when prescribed by other specialties (47.5%).

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Specifically, the proportion was 48.0% for patients prescribed rifaximin by internal medicine physicians, 48.8% for hospitalist physicians, and 47.2% for family medicine physicians. The odds of delayed rifaximin treatment were 27% higher when the prescriber was not a hepatologist, gastroenterologist, or APP. **Conclusion:** In this real-world study, patients with OHE were more at risk of having rejected rifaximin claims when the prescriber was not a hepatologist, gastroenterologist, or APP, resulting in treatment initiation delays. Correlations with other characteristics may exist and further analyses to independently test the association of prescriber specialty are warranted. As previous studies have shown that timely access to rifaximin treatment is associated with fewer OHE hospitalizations, reducing barriers to rifaximin access can contribute to improved outcomes among patients with OHE.

Disclosures: Arun Jesudian: Salix Pharmaceuticals: Consultant, Salix Pharmaceuticals: Speaking and Teaching, Madrigal Pharmaceuticals: Speaking and Teaching, Novo Nordisk: Consultant, Orphalan: Consultant, Patrick Gagnon-Sanschagrin: Nothing to Disclose, Christopher Allen: Nothing to Disclose, Rebecca Bungay: Nothing to Disclose, Jerome Bedard: Nothing to Disclose, Annie Guerin: Bausch: Employee of AnalysisGroup, which received conslting fees fro, Zeev Heimanson: Salix Pharmaceuticals: Employee

4181 | SKELETAL SARCOPENIA IS ASSOCIATED WITH DECREASED INTERVENTRICULAR SEPTAL THICKNESS IN PATIENTS WITH CIRRHOSIS: FINDINGS FROM A DUAL-CENTER STUDY

Ahmad Yanis[1] Alex Liu[2] Ashley Spann[1] Jason Klug[2] Gian Marco Conte[2] Guanchao Wang[1] Jinyuan Liu[1] Loren Lipworth[1] Deepak Gupta[1] Jeffrey Annis[1] Evan Brittain[1] Heidi J Silver[1] Kymberly Watt[2] Manhal Izzy[1]

[1]Vanderbilt University Medical Center, [2]Mayo Clinic

Background: Skeletal muscle sarcopenia (SMS) is a common complication of cirrhosis. The underlying pathophysiology involves systemic inflammation, adipokines dysregulation, increased myostatin, and insulin resistance. These mechanisms have also been implicated in cardiac remodeling. This study aims to explore the association between SMS and echocardiographic changes in patients with cirrhosis. **Methods:** This retrospective review of records included adult patients who underwent liver transplant (LT) at two large LT centers in North America between 2008 and 2019. Clinical data, along with pre-transplant transthoracic echocardiography and computed tomography (CT) results, were reviewed. A convolutional neural network based on the U-Net architecture was used to perform abdominal segmentation of skeletal muscle in an axial CT slice at the level of L3 vertebra to calculate skeletal muscle index (SMI). Linear regression models, adjusted for age, sex, liver disease etiology, obesity, ascites, hepatic encephalopathy, type 2 diabetes, and glomerular filtration rate were used to analyze the association of SMI with the following echocardiographic markers: left ventricular (LV) mass, LV mass index (LVMI), LV internal end diastolic diameter (LVIDd), interventricular septal diameter (IVSd), LV posterior wall diameter (PWd), and markers of systolic and diastolic dysfunction, per the Cirrhotic Cardiomyopathy 2020 criteria. Patients with insufficient echocardiographic or CT data were excluded. **Results:** Out of 351 patients in this database, 285 (60% males, mean age 67.8 years, mean MELD 21) had complete echocardiographic and CT data and were included in the analysis. Univariate analysis revealed a statistically significant association between SMI and LVIDd, IVSd, PWd, LV mass, LVMI, E/e' (marker of left ventricular filling pressure), sex, and obesity (Table 1). On multivariate analysis, IVSd and E/e' retained significance. For every one-unit decrease in IVSd, there was an average decrease in SMI of 0.71 (95% CI 0.13-1.3; p=0.02), and for every one-unit change in E/e', the average change in SMI was 0.29 (95% CI 0.05-0.54; p=0.02). However, there was no significant association observed between SMI and LVIDd, PWd, LV mass, or LVMI on multivariable model. When the model was exclusively adjusted for variables that were significant on univariable analysis (i.e., sex and obesity), the results remained unchanged. **Conclusion:** In this dual center study of patients, decrease in skeletal muscle mass was independently associated with decrease in interventricular septal thickness, reflecting the shared pathophysiologic pathways between sarcopenia and LV remodeling. Prospective studies evaluating the prognostic implications of this association are warranted.

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Table 1. Unadjusted Association Between Skeletal Muscle Index with Clinical and Echocardiographic Variables

Echocardiographic Marker	Estimate	*p*-value
Left ventricular internal end diastolic diameter	**0.19**	**0.02**
Interventricular septal diameter	**1.41**	**<0.01**
Left ventricular posterior wall diameter	**1.04**	**<0.01**
Tricuspid annular plane systolic excursion	0.04	0.61
Left ventricular mass	**0.05**	**<0.01**
Left ventricular mass index	**0.07**	**<0.01**
Relative wall thickness	-0.30	0.96
Mitral Annular septal e' velocity	-0.07	0.56
Mitral annular lateral e' velocity	-0.06	0.48
E/e'	**0.36**	**0.01**
Left atrial volume index	0.07	0.13
Tricuspid regurgitation velocity	0.79	0.56
Ejection fraction	-0.05	0.60
Age	0.02	0.72
Sex (female)	**-6.28**	**<0.01**
Obesity	**7.32**	**<0.01**
Type II Diabetes	0.18	0.91
Ascites	-2.38	0.10
Hepatic Encephalopathy	-2.54	0.05
Glomerular filtration rate	0.01	0.59
Etiology (metabolic dysfunction-associated steatotic liver disease)	1.68	0.22

Disclosures: Ahmad Yanis: Nothing to Disclose, Alex Liu: Nothing to Disclose, Ashley Spann: Bristol Myers Squibb Foundation: Grant/Research Support, Jason Klug: Nothing to Disclose, Gian Marco Conte: Nothing to Disclose, Guanchao Wang: Nothing to Disclose, Jinyuan Liu: Nothing to Disclose, Loren Lipworth: Nothing to Disclose, Deepak Gupta: Nothing to Disclose, Jeffrey Annis: Nothing to Disclose, Evan Brittain: Nothing to Disclose, Heidi J Silver: Nothing to Disclose, Kymberly Watt: Madrigal: Stock - publicly traded company, Viking: Stock - publicly traded company, Manhal Izzy: Nothing to Disclose

4182 | HYPERAMMONEMIA INDUCES AN ATM-MEDIATED DNA DAMAGE RESPONSE IN CEREBELLAR AND HIPPOCAMPAL NEURONS

Matthew McMillin[1] *Juliet Venter*[2] *Kathryn Rhodes*[2] *Sharon DeMorrow*[2]

[1]*Baylor College of Medicine,* [2]*University of Texas at Austin*

Background: Hepatic encephalopathy (HE) describes the cognitive and neuromuscular deficits that result from liver impairment. HE pathogenesis is not fully characterized, but is associated with hyperammonemia, neuroinflammation and oxidative stress. Research into oxidative stress in HE has focused on lipids, proteins, and RNA, but has not assessed DNA lesions and the subsequent activation of the DNA damage response (DDR). We have demonstrated the presence of oxidative DNA lesions and DDR activation in the CCl_4 mouse model of Type

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C, however the role of hyperammonemia in these observations has not yet been demonstrated. Therefore, the aims of this study were to evaluate if hyperammonemia contributes to oxidative DNA damage and the activation of DDR-associated pathways including ataxia telangiectasia mutated protein (ATM). **Methods:** Adult Sprague Dawley rats were fed a hyperammonemic diet (ammonium acetate (AA) 25% w/w) for 6 weeks and liver, brain and serum were collected. *In vitro,* a hippocampal neuronal cell line (HT22) was treated with NH_4Cl +/- the ATM inhibitor KU55933. 8-oxo guanine, γH2AX, phosphorylated ATM (pATM), chemokine ligand 2 (CCL2), and transforming growth factor beta 1 (TGFβ1) protein expression were assessed in the hippocampus and cerebellum of AA rats or in NH_4Cl +/- KU55933-treated HT22 cells. Comet assays were performed in NH_4Cl +/- KU55933-treated HT22 cells. **Results:** Increased 8-oxo guanine fluorescence and γH2AX protein were measured in the hippocampus and cerebellum of AA rats and in NH_4Cl-treated HT22 cells, supporting increased DNA damage. Comet assays in HT22 cells demonstrated that NH_4Cl treatment led to increased DNA double-stranded breaks (DSBs). AA rats and NH_4Cl-treated HT22 cells show increased pATM, indicating a chronic activation of the DDR. Furthermore, proinflammatory cytokines known to be involved in the pathogenesis of HE, CCL2, and TGFβ1 signaling were increased in response to hyperammonemia *in vivo* and *in vitro*. Treatment of HT22 cells with the ATM-inhibitor, KU55933 led to a significant reduction in CCL2 and TGFβ1 signaling, supporting that activation of the DDR leads to increased neuroinflammatory signaling in these models. **Conclusion:** These results support that hyperammonemia can induce DSBs and ATM signaling in brain regions associated with HE and in HT22 cells. Therefore, strategies to mitigate the DDR, such as with KU55933, could be effective to alleviate ammonia-induced HE pathology.

Disclosures: Matthew McMillin: Nothing to Disclose, Juliet Venter: Nothing to Disclose, Kathryn Rhodes: Nothing to Disclose, Sharon DeMorrow: Nothing to Disclose

4183 | IMPACT OF AN INPATIENT "QUALITY BUNDLE" ON POST-DISCHARGE MORTALITY IN PATIENTS WITH SPONTANEOUS BACTERIAL PERITONITIS

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Background: In patients with cirrhosis, spontaneous bacterial peritonitis (SBP) signals clinical decompensation of cirrhosis and can portend worsening of liver disease. Thus, there is a need to optimize management of high-risk patients with SBP. We evaluated the impact of completion of an inpatient SBP "quality bundle" on post-discharge mortality. **Methods:** This was a retrospective cohort study of VHA patients with cirrhosis from 1/2008-12/2023. We identified patients who had a first admission for SBP (defined by peritoneal fluid analysis) and who survived to discharge. The "quality bundle" was defined as: 1) receipt of inpatient albumin per society guidelines, 2) receipt of appropriate inpatient antibiotic treatment within 48 hours of SBP diagnosis, 3) initiation of SBP antibiotic prophylaxis on discharge, and 4) assignment of SBP diagnosis code at discharge. The primary outcome was mortality through maximum 90 days of follow-up. **Results:** The cohort included 3,843 patients with median age 62 years, 97.9% male sex, 63.8% white, and 59.3% with diabetes mellitus. Alcohol was the most common etiology of liver disease, comprising 44.0% of patients. A total 19.1% of patients received all 4 "quality bundle" components, while 8.2% of patients received 0 components. Overall mortality at 90 days was 30.7%, with unadjusted mortality lowest in those meeting 4 quality metrics (26.3% vs. 33.2% ≤2 metrics, p<0.001). In a Cox model adjusted for age, sex, race, etiology of liver disease, MELD-Na on presentation, and maximum AKI stage (to account for severity of hospital course), patients who received all 4 quality bundle components had 41% lower hazard of post-discharge mortality relative to those receiving 2 or fewer (HR 0.59, 95%CI 0.49-0.71, p<0.001), while those who received 3 components had 22% decreased hazard of mortality (HR 0.78, 95%CI 0.66-0.92, p=0.002) relative to those receiving 2 or fewer. **Conclusion:** During index admission for SBP, receipt of 3 or more components of an SBP "quality bundle" was associated with decreased post-discharge mortality through 90 days of follow up.

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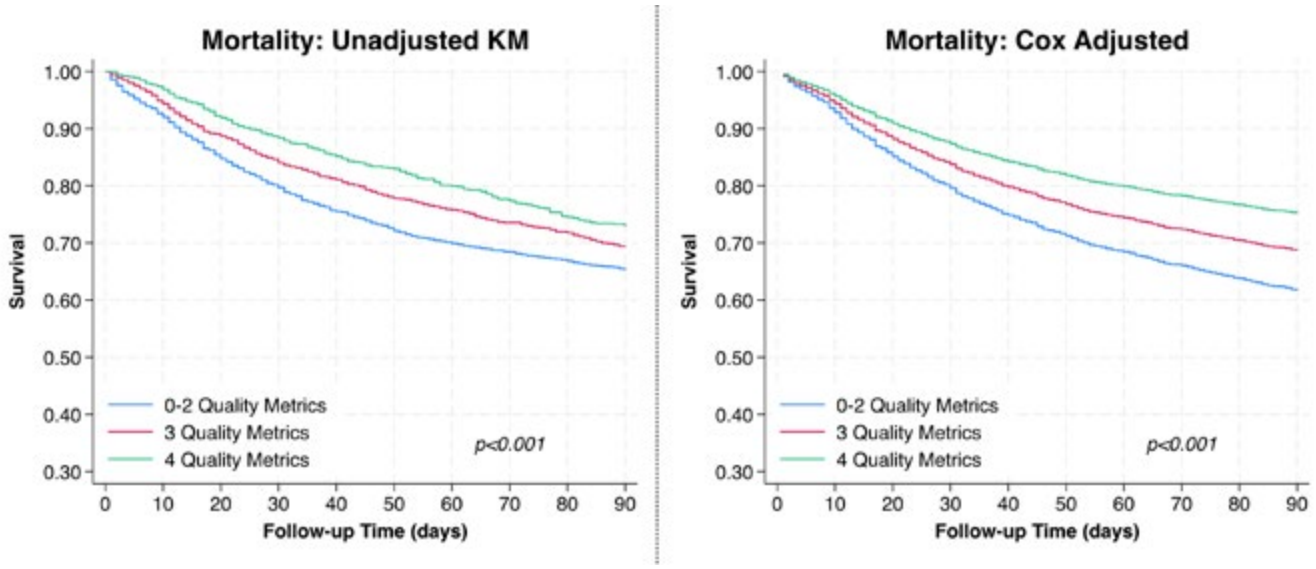

Disclosures: Nadim Mahmud: Nothing to Disclose, Helen Tang: Nothing to Disclose, David Kaplan: Independent Contractor relationship with Roche Genentech; Has not ended; Grant/Research Support relationship with AstraZeneca Inc; Has not ended; Advisor relationship with AstraZeneca; Has ended; Advisor relationship with Exelixis; Has ended; Grant/Research Support relationship with Gilead; Has not ended; Advisor relationship with Sirtex; Has ended; Grant/Research Support relationship with Exact Sciences; Has not ended; Grant/Research Support relationship with Glycotest; Has ended, Marina Serper: Grant/Research Support relationship with Grifols; Has not ended; Grant/Research Support relationship with Eurofins; Has not ended; Grant/Research Support relationship with Transplant Genomics; Has not ended

4184 | THE IMPACT OF ESOPHAGEAL VARICES ON THE PROGNOSIS OF PATIENTS WITH CHOLANGIOCARCINOMA: A SINGLE CENTER RETROSPECTIVE STUDY

Yu-Jen Chen[1] Chien-Wei Su[1] Tzu-Han Ma[1] Chun-Ting Ho[1]

[1]Taipei Veterans General Hospital

Background: Whether esophageal varices (EV) could determine the outcomes of patients with cholangiocarcinoma (CCA) is still debated. We aimed to assess the impact of EV on the prognosis of CCA patients. **Methods:** We enrolled 254 treatment-naïve CCA patients who received esophagogastroduodenoscopy *at the time of CCA diagnosis from 2013 to 2022.* The factors in terms of EV formation were analyzed by Logistic regression model. The factors in terms of prognosis were analyzed by Cox proportional hazards model. **Results:** A total of 42 (16.5%) patients had EV. By multivariate analysis, male (hazard ratio HR 2.764, 95% confidence interval CI 1.239-6.165, p=0.013) and platelet <150K /cumm (HR 3.215, 95% CI 1.539-6.719) were risk factors of EV formation. After a median follow-up of 363 days, 200 patients died. The median overall survivals (mOS) of patients with or without EV were 292 and 379 days, respectively (p=0.035) (Figure 1). By multivariate analysis, age > 65 (HR 1.453, CI 1.051-2.007), serum albumin level < 3.5 g/dL (HR 1.540, 95% CI 1.111-2.135, p=0.010), CA-199 level > 100 U/mL (HR 1.894, 95% CI 1.367-2.624, p=0.001), advanced cancer stage (HR 2.516, 95% CI 1.647-3.845) and the presence of EV (HR 1.449, 95% CI 1.005-2.221, p=0.047), were independent risk factors associated with poor OS. **Conclusion:** Among CCA patients, male gender and low platelet count were the risk factors of EV formation. EV was an independent risk factor predicting poor prognosis for the patients with CCA by multivariate analysis.

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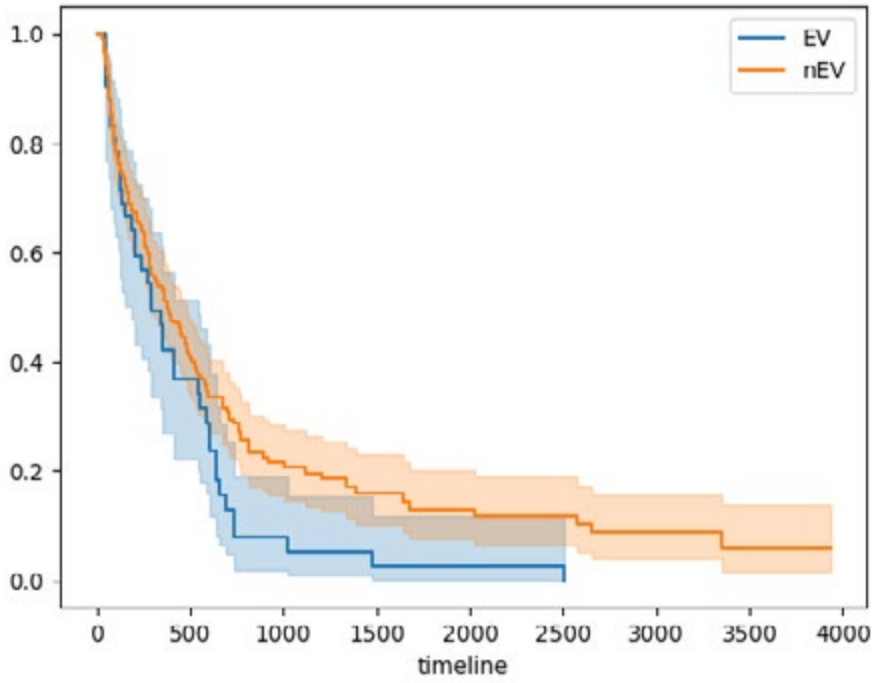

	EV								
At risk	42	14	3	1	1	1	0	0	0
Censored	0	2	2	2	2	2	2	2	2
Events	0	26	37	39	39	39	40	40	40
	nEV								
At risk	212	75	24	12	9	8	3	1	0
Censored	0	17	39	46	47	47	50	51	52
Events	0	120	149	154	156	157	159	160	160

Disclosures: Yu-Jen Chen: Nothing to Disclose, Chien-Wei Su: Nothing to Disclose, Tzu-Han Ma: Nothing to Disclose, Chun-Ting Ho: Nothing to Disclose

4185 | SWEAT INTERLEUKIN-6 IS ASSOCIATED WITH REDUCED TRANSPLANT-FREE SURVIVAL IN VETERANS WITH DECOMPENSATED CIRRHOSIS

Brian Davis[1] Kai-Chun Lin[2] Jasmohan Bajaj[3] Shalini Prasad[4] Sriram Muthukumar[2]

[1]Central Virginia VA Health Care System, [2]Enlisense, [3]Virginia Commonwealth University, [4]University of Texas at Dallas

Background: Cirrhosis is the end stage result of chronic liver injury and clinical events are driven by worsening of complex inflammatory pathways leading to frequent hospitalizations and death or need for liver transplantation. Although inflammatory biomarkers such as c-reactive protein (CRP), tumor necrosis factor alpha (TNFα) and interleukin-6 (IL6) are elevated in serum of cirrhosis patients and associated with worse outcomes, these markers are not routinely checked due to the invasive nature of blood draws and difficulty in interpretation of a single measurement. Therefore, we designed a study to measure these biomarkers using a continuous monitor of sweat in a well characterized cohort of subjects with cirrhosis. **Methods:** We enrolled 32 veterans with cirrhosis and 12 controls. The AWARE sweat sensor was placed on each subject and exchanged daily for 3 days. Serum lab draws to measure CRP, TNFα, IL6, and liver function were performed along with quality-of-life surveys and hepatic encephalopathy testing. Subjects were followed up to a year in order to calcuated overall and transplant-free survival. **Results:** We found that CRP, TNFα, and IL6 were correlated in sweat and serum among cirrhosis and controls. All three biomarkers in sweat and serum were elevated in inpatients compared with outpatients or controls. IL-6 was more elevated in sweat of decompensated cirrhosis, and both sweat and serum IL-6 were associated with lower transplant-free survival at one year. **Conclusion:** These data suggest that further investigation of inflammatory sweat biomarkers in patients with cirrhosis is warranted.

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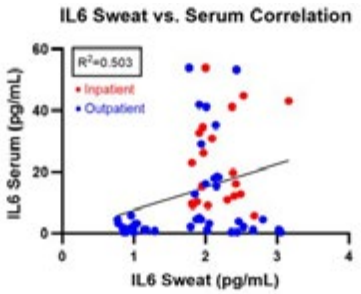

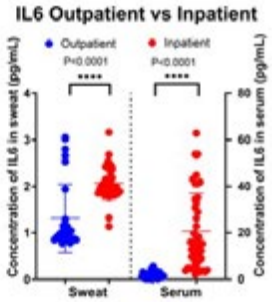

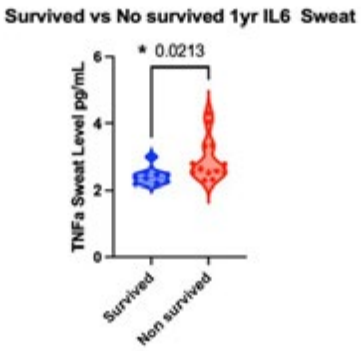

Disclosures: Brian Davis: Nothing to Disclose, Kai-Chun Lin: Nothing to Disclose, Jasmohan Bajaj: Bausch: Grant/Research Support, Sequana: Grant/Research Support, Cosmo: Grant/Research Support, Grifols: Grant/Research Support, Shalini Prasad: Nothing to Disclose, Sriram Muthukumar: Nothing to Disclose

4186 | REDUCTION OF UNNECESSARY CT HEAD USE IN CIRRHOTIC PATIENTS PRESENTING WITH HEPATIC ENCEPHALOPATHY

Gerry MacQuillan[1]

[1]*Sir Charles Gairdner Hospital*

Background: Hepatic encephalopathy (HE) is a neuropsychiatric complication often associated with cirrhosis, manifesting as a wide spectrum of changes in mental state. Currently, there is no pathognomonic imaging method or findings that exists to unequivocally diagnose HE. Low diagnostic yield of CT head use in cirrhotic patients in the absence of focal neurological deficits (FND) have been demonstrated. Despite this, CT heads are still frequently used in evaluating patients with cirrhosis presenting with altered mental status (AMS), contributing to increased radiation exposure, prolonged duration in the Emergency Department (ED) and higher healthcare costs. This audit aimed to assess the trend of unnecessary CT head use in patients who presented to the ED with HE. **Methods:** 155 consecutive encounters in the ED at a tertiary centre in Western Australia were identified retrospectively from 1 January 2022 to 31 December 2023 using electronic health record query 'HEPATIC' from the Emergency Department Information System (EDIS). Encounters were screened to include those with a history of cirrhosis presenting with AMS or suspected HE. Demographic, clinical and biochemical data were extracted. Analyses include descriptive statistics, Fisher's exact and Chi squared methods. CT head use was considered necessary in the presence of high risk features including history of trauma/fall, focal neurological deficit or age ≥65 years, based on local ED guidelines. **Results:** 64 encounters were identified and included, with a male predominance (75%). Mean age was 62 years. 56 (88%) encounters had a documented history of prior hepatic encephalopathy. 54 encounters (84%) were not on any anticoagulation or antiplatelet therapy. CT head was requested for 41 (64%) of encounters. One abnormal CT head result was detected (2.4%) in the context of a positive falls history. 15 out of 41 cases (37%) had no high risk indication for CT including no trauma/fall, no FND, and were <65 years. All 15 cases had no acute abnormality on CT head. Out of these 15 encounters, 14 (93%) had a prior history of HE and were known to a Hepatology/Gastroenterology department. There was no significant association found between raised INR (≥1.5) and abnormal CT head finding (p>0.05). **Conclusion:** Results demonstrate a low prevalence (2.4%) of CT head abnormality in cirrhotic patients presenting with hepatic encephalopathy and a low yield of routine CT head use in the absence of trauma or focal neurological deficit.

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Unnecessary CT head use was found to be ordered in over one third (37%) of presentations over a two year time frame. Findings support the suggestion that in the absence of high risk factors such as falls or trauma, and in the absence of concerning examination features such as focal neurological deficit, CT head use should be avoided when cirrhotic patients present with suspected HE.

Disclosures: Gerry MacQuillan: Nothing to Disclose

4187 | ABLATION OF NEURONAL SENESCENCE ATTENUATES THE COGNITIVE DEFICITS OBSERVED IN A MOUSE MODEL OF TYPE C HE

Kathryn Rhodes[1] Juliet Venter[1] Matthew McMillin[2] Sharon DeMorrow[3]

[1]The University of Texas at Austin, [2]Baylor College of Medicine, Temple, [3]University of Texas at Austin

Background: Hepatic encephalopathy resulting from chronic liver disease (Type C HE) is associated with neurological dysfunction and hyperammonemia. In HE, senescent markers are increased in various brain regions and in astrocytes in response to ammonia treatment *in vitro*, but research into the development of a senescence-like phenotype (SLP) in neurons has been limited. Furthermore, the role of cellular senescence in the pathogenesis of HE is unknown. The aim of this study was to assess the role of a SLP in the pathogenesis of Type C HE. **Methods:** C57BL/6 mice were treated with CCl_4 for 16 wks to induce Type C HE and received a senolytic cocktail of dasatinib and qercertin (D/Q via oral gavage) starting after 8 wks of CCl_4 injections. Cognitive and neuromuscular neurobehavioral testing was performed. Human autopsy brain samples from patients with HE due to liver cirrhosis and age- and sex-matched controls were used. Sprague Dawley rats were fed a hyperammonemia diet (25% w/w ammonium acetate) for 6 weeks to evaluate the role of ammonia in the acquisition of cellular senescence. *In vitro*, hippocampal neurons were treated with ammonium chloride (5mM) for up to 24 hrs. Markers of senescence (p21, p16, ß-galactosidase expression), senescence-associated secretory phenotype factors (SASPs; CCL2, IGFBP3, TGFß1, PAI-1 and IL-6) and neuroinflammation were assayed in the cerebellum and hippocampus by qPCR and immunohistochemistry. **Results:** In the CCl_4 mouse model of HE and in human autopsy samples, markers of senescence and SASPs were observed, specifically in neurons of the CA1 and dentate gyrus in the hippocampus and in the Purkinje cell layer in the cerebellum, regions known for learning, memory and motor control. Similarly, hyperammonemia *in vivo* and *in vitro* increased the expression of markers of senescence and SASPs. Treatment of CCl_4 mice with D/Q reduced the number of senescent neurons, and attenuated the cognitive deficits, neuromuscular impairment, presence of ataxia and neuroinflammation observed after CCl_4 alone. **Conclusions:** Taken together, these data suggest that there is an acquisition of a SLP in hippocampal and cerebellar neurons in models of Type C HE, which may be attributable to HE-related hyperammonemia and contribute to the pathogenesis of Type C HE. Furthermore, our data suggests that targeting the SLP in HE may be a viable option for the development of novel therapeutic strategies.

Disclosures: Kathryn Rhodes: Nothing to Disclose, Juliet Venter: Nothing to Disclose, Matthew McMillin: Nothing to Disclose, Sharon DeMorrow: Nothing to Disclose

4188 | SIGNIFICANCE OF NEUTROPHIL-TO-LYMPHOCYTE RATIO IN BLEEDING AND PROGNOSIS AFTER ENDOSCOPIC TREATMENT OF CIRRHOTIC PATIENTS WITH ESOPHAGEAL VARICES

Kazuto Takahashi[1] Takuto Nosaka[1] Yosuke Murata[1] RYOTARO SUGATA[1] Tomoko Tanaka[1] Yu Akazawa[1] Tatsushi Naito[1] Masahiro Ohtani[1] Yasunari Nakamoto[1]

[1]University of Fukui

Background: Neutrophil-to-lymphocyte ratio (NLR) has been reported as a prognostic indicator in patients with cancer and some chronic inflammatory diseases by reflecting systemic inflammation and nutritional status. It is now becoming clear that it is also a prognostic factor in patients with liver cirrhosis. Furthermore, it is significant to predict bleeding after endoscopic procedures due to worsening portal hypertension because it can be fatal.
The aim of this study was to clarify the relationship between NLR and bleeding or NLR and prognosis, after endoscopic treatment for esophageal varices in cirrhotic patients with esophageal varices. **Methods:** The study

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included 141 patients who underwent initial endoscopic treatment for esophageal varices at our hospital from April 2006 to March 2022 and were able to be followed up for more than 1 year. Endoscopic treatment included endoscopic injection sclerotherapy in 100 patients and endoscopic variceal ligation alone in 41 patients. The relationship between clinical background, including NLR, and post-treatment bleeding or prognosis in patients with esophageal varices was investigated using the Kaplan-Meier method. **Results:** In this cohort, median age at initial endoscopic treatment was 67.0 years, and there were 41/66/34 patients with Child-Pugh grade A/B/C, 42 patients were complicated by liver cancer. During the observation period, the cumulative non-bleeding rate after endoscopic treatment was 81.3% at 1 year and 72.9% at 3 years. During survival (median; 1502 days), 99 patients died, and cumulative survival rates were 82.3% at 1 year, 59.5% at 3 years, and 41.6% at 5 years. The main causes of death were liver failure in 27 patients, liver cancer in 24 patients, and variceal bleeding in 9 patients. The mean and median pre-treatment NLR were 3.80 and 2.37, respectively. The cumulative non-bleeding rate after esophageal varices treatment was significantly lower in patients with NLR ≥4.0 and serum albumin level <2.8 g/dL ($p<0.05$), and both were independent factors in the cox regression analysis. The prognosis was significantly poorer in patients with NLR ≥4.0 ($p=0.024$), as well as post-treatment bleeding, antithrombotic medications, liver cancer, creatinine ≥1.0 mg/dL, and albumin <2.8 g/dL ($p<0.05$). **Conclusion:** In cirrhotic patients with esophageal varices, high NLR levels may predict bleeding and poor prognosis after endoscopic treatment, by reflecting the poor general conditions including hypoalbuminemia.

Disclosures: Kazuto Takahashi: Nothing to Disclose, Takuto Nosaka: Nothing to Disclose, Yosuke Murata: Nothing to Disclose, RYOTARO SUGATA: Nothing to Disclose, Tomoko Tanaka: Nothing to Disclose, Yu Akazawa: Nothing to Disclose, Tatsushi Naito: Nothing to Disclose, Masahiro Ohtani: Nothing to Disclose, Yasunari Nakamoto: Nothing to Disclose

4190 | RENAL RESISTIVE INDEX – A NOVEL PREDICTOR OF CONTRAST-INDUCED ACUTE KIDNEY INJURY IN CIRRHOSIS

Krishnadas Devadas[1] *Jesse Jacob Skariah*[2] *JITHIN JOHN*[2] *Rushil Solanki*[2]

[1]*Government Medical College, Thiruvananthapuram,* [2]*Government Medical College, Trivandrum*

Background: Patients with liver cirrhosis are often subjected to repeated contrast-enhanced imaging procedures. It is debatable if the liver disease acts as a risk factor for contrast-induced acute kidney injury (CI-AKI). We investigated the incidence of CI-AKI and its risk variables in cirrhotic patients. **Methods:** Prospective study of 110 consecutive patients with cirrhosis who underwent iodinated contrast (IC)-based imaging procedure. Baseline demographic, clinical, laboratory data and renal resistive index (RRI) were recorded prior to imaging. Renal function tests (RFT) were recorded 48-72 hours after contrast administration, to assess the incidence of CI-AKI. CI-AKI was defined by KDIGO criteria 2012. **Results:** 34(30.9%) of the 110 patients studied developed CI-AKI after contrast administration. The mean age of patients developing CI-AKI was 59.4years and 57.3years in the non-CI-AKI group($p=0.287$). 37.5% of males and 18.4% of females developed CI-AKI. Prior history of AKI was seen in 52.9% of patients with CI-AKI and 5.3% without CI-AKI($p<0.001$). Alcohol-related liver disease was the major etiological factor in 52.9% of patients with CI-AKI as opposed to 30.3% without CI-AKI(p-0.047). Baseline eGFR and serum creatinine levels were not associated with increased risk of CI-AKI but higher baseline serum urea levels were associated with risk of CI-AKI. The mean RRI of patients with CI-AKI was 0.67, and in those without CI-AKI was 0.52. The mean CTP score and MELD-Na of patients with CI-AKI were 9.97 and 23.1, and in those without CI-AKI were 8.24 and 16.9. On multivariate analysis, baseline renal resistive index (RRI), Child Turcotte Pugh score and Model for End Stage Liver Disease-Sodium (MELD-Na) score were associated with increased risk of CI-AKI with optimal predictive cut-offs of RRI>0.62, CTP score >10 and MELD-Na >24. The AUCs of RRI, CTP score and MELD-Na were 0.921, 0.699 and 0.721 respectively. **Conclusion:** There is a high incidence of contrast-induced acute kidney injury in cirrhosis. Advanced stages of cirrhosis (CTP>10, MELD-Na>24) are associated with higher risk of CI-AKI. Pre–procedure RRI is a strong independent predictor for CI-AKI among cirrhotic patients with apparently normal renal function which is easily available and non-invasive.

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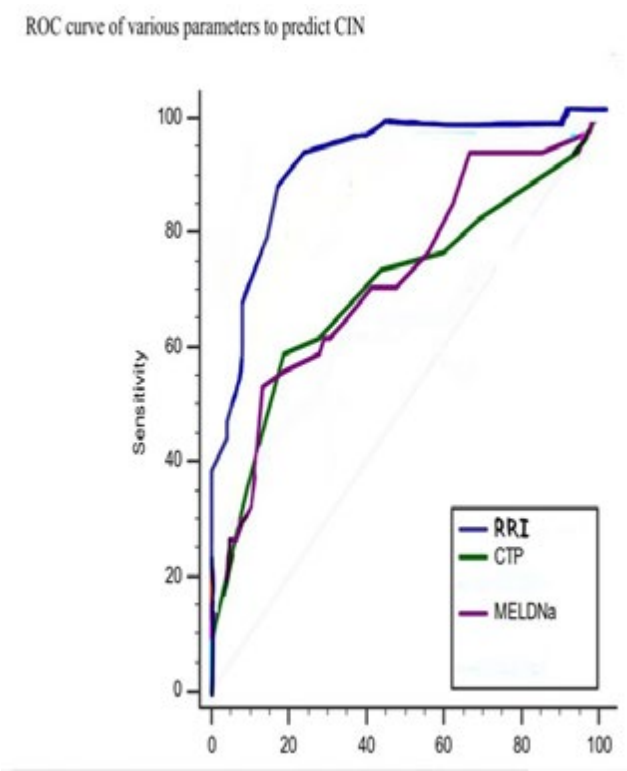

DIFFERENCE BETWEEN AUCs

TEST	AUC(SE)	Vs CTP(P)	VS MELD (p)	VS RRI (p)
CTP	0.699 (0.0595)		-0.022 (0.786)	-0.222 (0.0009)
MEL D-Na	0.721 (0.0552)	0.022 (0.7863)		-0.2 (0.0015)
RRI	0.921 (0.0302)	0.22 (0.0009)	0.2 (0.015)	

Disclosures: Krishnadas Devadas: Nothing to Disclose, Jesse Jacob Skariah: Nothing to Disclose, JITHIN JOHN: Nothing to Disclose, Rushil Solanki: Nothing to Disclose

4191 | A PROSPECTIVE ASSESSMENT OF BETA BLOCKER RESPONSE(BB) USING NON INVASIVE TESTS (NITS) IN PATIENTS WITH ACUTE VARICEAL BLEED (AVB) USING ARTIFICIAL INTELLIGENCE DRIVEN PREDICTION MODELS-BLOCK BLEED MODEL

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Background: Hepatic venous pressure gradient(HVPG) has been known to have prognostic as well as therapeutic value, especially in patients with AVB. Six-week rebleeding and mortality is close to 20% post-AVB. Non-selective Beta-blockers (NSBB) are the mainstay of treatment for secondary prophylaxis, however, response is observed only in about 50%. Serial HVPG measurement to assess NSBB response being invasive, is not feasible. We investigated the diagnostic accuracy of non-invasive tests (NITs) in predicting response to NSBB and predicting rebleeds in patients with AVB at 6 weeks using an artificial intelligence (AI) based models. **Methods:** Patients presenting with AVB (Group 1) and admitted to the GI Bleed unit were prospectively enrolled between May 2022 to January 2024. Patients with high-risk varices without AVB (Group 2) were included as controls. Paired Data done within 24 hours of AVB and at 6 weeks were included for HVPG, spleen stiffness (SS), Liver stiffness(LS), portal vein diameter (PVD), platelet counts . Associations were determined using Cox proportional hazards regression analysis. Prospectively AI-modelling was done after appropriate mining, feature engineering. **Results:** Altogether 349 patients were included; 99 in Group 1 [males(56.8%), MELD score 15±2.1, ethanol (46.3%) and followed by NASH(32.3%)] and matched non-bleeder controls with high risk varices (n=250). Mean HVPG, LS and SS at baseline were 18.7±2.42mmHg, 60.1±20.08kPa, 83.5±16.54kPa respectively. At 6 weeks the mean HVPG, LS and SS were 16.02±2.55mmHg, 58.12±16.93kPa, 79.8±16.65kPa.The predictive model based on regression analysis showed an accuracy of 0.867 and ROC of 0.97 in group 1 with LS, SS, portal vein diameter being significant (p<0.001). Using Boosted Trees as well as decision tree models, the accuracy improved to 0.976 and ROC of 0.993.Accuracy of HVPG reduction by >10% using Decision Tree model was 0.934 and ROC of 0.981. The prediction accuracy with HVPG >20mmHg was 85% and 77% for HVPG 16 to 20 mmHg . Similarly in Group 2, the predictive accuracy of the model was at 0.88 and ROC of 0.74. The prediction

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accuracy with HVPG >20mmHg was 93% and 83% for HVPG 16 to 20 mmHg. **Conclusion:** AI Driven models based on LS and SS reliably reflect the HVPG levels in bleeders and non-bleeders. These models can make highly accurate prediction of beta-blockers response at week 6 in patients with acute variceal bleed.



Disclosures: Harsh Tevethia: Nothing to Disclose, Akhil Deshmukh: Nothing to Disclose, Ankur Jindal: Nothing to Disclose, Guresh Kumar: Nothing to Disclose, Shiv Kumar Sarin: Nothing to Disclose

4192 | PATIENTS WITH CIRRHOSIS AND A HISTORY OF OVERT HEPATIC ENCEPHALOPATHY EXPERIENCED LOWER 6-MONTH ALL-CAUSE MORTALITY RATES WITH RIFAXIMIN MONOTHERAPY VERSUS LACTULOSE MONOTHERAPY

Jasmohan Bajaj[1] Robert Rahimi[2] Christopher Allen[3] Zeev Heimanson[3] Robert Israel[3] Kris Kowdley[4]

[1]Virginia Commonwealth University and Central Virginia Veterans Healthcare System, [2]Baylor University Medical Center, [3]Salix Pharmaceuticals, [4]Liver Institute Northwest and Elson Floyd College of Medicine

Background: Hepatic encephalopathy (HE) is associated with a poor prognosis, and data suggest that rifaximin use may improve survival. Lactulose treatment is frequently considered after the first episode of HE, with the addition of rifaximin when further episodes occur. However, non-lactulose–based management approaches may be necessary due to nonadherence (eg, lactulose poor tolerability/adverse events/titration issues), which can precipitate HE. The study aim was to compare the rate of all-cause mortality in patients with cirrhosis and a history of overt HE (OHE) treated with rifaximin monotherapy vs lactulose monotherapy. **Methods:** Data were pooled post hoc from 2 randomized trials (phase 3 double-blind/phase 4 open-label) of adults with cirrhosis and a history of OHE occurrence in the previous 6 months (in remission). The analysis included patients treated for up to 6 months with rifaximin 550 mg twice daily (ie, rifaximin monotherapy) or placebo plus lactulose (titrated [2-3 soft stools/d]; ie, lactulose monotherapy). Hazard ratio (HR) estimates were calculated using a Cox proportional hazards model with effect for treatment; *P* values, using the score statistic. **Results:** 125 patients were treated with rifaximin monotherapy, and 145 patients were treated with lactulose monotherapy. The median (range) age was 58 y (32-83 y) and 57 y (21-78 y) in the rifaximin and lactulose groups, respectively; 40.0% vs 31.7% were female; and 5.6% vs 9.0% ($P<0.001$) were Child-Pugh class C. The median (range) MELD score was 12 (6-24) vs 12 (6-23), with 4.0% vs 9.0% ($P=0.09$) having a MELD score of 19-24. There was a significantly lower rate of mortality in the rifaximin monotherapy group compared with the lactulose monotherapy group during 6 months of treatment (1.6% vs 4.8%; $P<0.001$), with a number needed to treat of 19 (Figure; HR, 0.048; 95% CI, 0.01-0.29). Study discontinuation was higher in the lactulose monotherapy group (62.1%) compared with the rifaximin monotherapy group (36.0%), most commonly due to recurrence of HE. Through follow-up (14±2 days after end of treatment), mortality was reported in 1.6% of patients in the rifaximin monotherapy group and 6.9% in the lactulose monotherapy group. Of those who died during the study, only 1 patient (in lactulose group) had a baseline Child-Pugh class C and 2 patients (1 in each group) had a baseline MELD score of ≥19. **Conclusion:** Rifaximin treatment (eg, monotherapy) may confer a survival benefit in patients with cirrhosis and a history of OHE.

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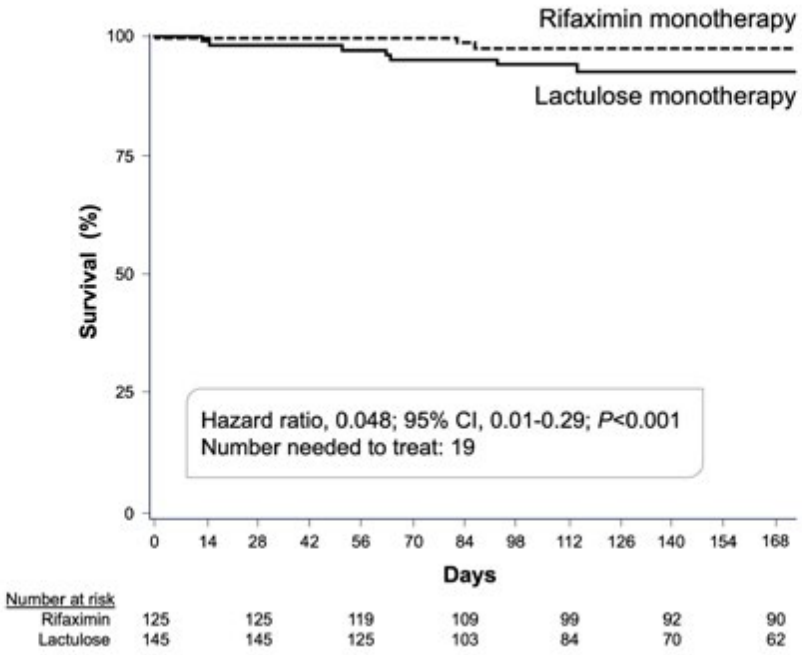
Figure. Kaplan-Meier Survival Analysis



Disclosures: Jasmohan Bajaj: Bausch: Grant/Research Support, Sequana: Grant/Research Support, Cosmo: Grant/Research Support, Grifols: Grant/Research Support, Robert Rahimi: Salix: Grant/Research Support, Mallinckrodt: Grant/Research Support, Christopher Allen: Nothing to Disclose, Zeev Heimanson: Salix Pharmaceuticals: Employee, Robert Israel: bausch health companies: I am an employee of Bausch Health Companies, Kris Kowdley: Boston Scientific: Grant/Research Support, Corcept: Grant/Research Support, CymaBay: Grant/Research Support, Genfit: Grant/Research Support, Gilead: Grant/Research Support, GSK: Grant/Research Support, Hanmi: Grant/Research Support, Intercept: Grant/Research Support, Ipsen: Grant/Research Support, Janssen: Grant/Research Support, Madrigal: Grant/Research Support, Mirum: Grant/Research Support, Novo Nordisk: Grant/Research Support, NGM: Grant/Research Support, Pfizer: Grant/Research Support, Pliant Therapeutics: Grant/Research Support, Terns: Grant/Research Support, Viking: Grant/Research Support, Zydus: Grant/Research Support, 89bio Inc: Grant/Research Support, UpToDate: Royalties or patent beneficiary, CymaBay: Consultant, Enanta: Consultant, Genfit: Consultant, Gilead: Consultant, HighTide: Consultant, Inipharm: Consultant, Intercept: Consultant, Ipsen: Consultant, Madrigal: Consultant, Mirum: Consultant, NGM: Consultant, Pliant Therapeutics: Consultant, Pfizer: Consultant, Protagonist: Consultant, Zydus: Consultant, 89bio Inc: Consultant, AbbVie: Payment or honoraria, Gilead: Payment or honoraria, Intercept: Payment or honoraria, US Department of Justice: Payment for expert testimony, CTI: Advisor, Medpace: Advisor, Labcorp: Advisor, Worldwide Clinical Trials: Advisor, Inipharm: Stock – privately held company, Velacur: Received equipment, materials, drugs, medical writing, gifts

4193 | ASSESSMENT OF SARCOPENIA WITH ULTRASOUND-BASED MEASUREMENTS IN PATIENTS WITH CHRONIC LIVER DISEASE

Paolo Gallo[1] Valentina Flagiello[1] Antonio De Vincentis[2] Francesca Terracciani[1] Andrea Falcomatà[1] Antonio Picardi[1] Umberto Vespasiani Gentilucci[1]

[1]Clinical Medicine and Hepatology Unit, Campus Bio-Medico University, Rome, Italy, [2]Internal Medicine Unit, Campus Bio-Medico University, Rome, Italy

Background: Sarcopenia is a common complication in people with chronic liver disease (CLD). In this context, its diagnosis is typically based on operational definitions, including low muscle mass estimation. However, the available techniques have not yet had a significant clinical translation due to various intrinsic limitations

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(radiations, costs, etc). Recently, muscle ultrasound-based measurements have drawn attention due to their improved feasibility and accessibility. However, only a limited number of studies evaluating this approach have been reported to date. In a cohort of CLD patients, our objective was to investigate the correlation and agreement between ultrasound-derived measurements for assessing muscle mass and bioimpedance analysis (BIA) as gold standard. **Methods:** The study included consecutive adult outpatients attending the Unit of Hepatology of Fondazione Policlinico Campus Bio-Medico of Rome. Muscle mass was defined as appendicular skeletal mass (ASMM) according to the Sergi equation (EWGSOP 2019). Previously described standardized indices of muscle mass were obtained by ultrasound: average compression (ACI) and feather index (AFI) (thigh muscle thickness); ileopsoas index (IPI) and psoas to height ratio (PHR) (ileopsoas area hickness). Pearson correlation coefficient and Bland-Altman plots were used to assess the correlation and agreement between ASMM and ultrasound indices. **Results:** Eighty-eight patients were included [(mean age 73 years (7.07), 78% male, mean BMI 27 kg/m2 (10)]. The most common etiology of cirrhosis was viral (40 %), and the majority of patients (80%) had well-preserved liver function. ACI and AFI showed a good correlation with ASMM [(r = 0.35 (CI95% 0.15-0.52), p 0.001); (r = 0.45 (CI95% 0.27-0.60), p<0.001), respectively] (Figure 1). Conversely, among psoas indices, only PHR –but not IPI- showed a correlation with ASMM [(r = 0.27 (CI95% 0.06-0.46), p 0.014)] (Figure 1). Linear regression analysis confirmed AFI [beta 0.64 (CI95% 0.37-0.92), p<0.001], ACI [0.5 (CI95% 0.21-0.78), p<0.001] and PHR [0.38 (CI95% 0.08-0.69), p=0.01] as significantly associated with ASMM, also independently of gender. In addition, Bland-Altman analyses showed a good level of agreement for these indices with ASMM, with a bias and LoA of 0.007 (-0.239;0.253) and 0.021 (-0.205;0.247) for ACI and AFI, respectively, and of 0.014 (-0.251; 0.28) for PMI. **Conclusion:** Ultrasound quadriceps measurements and psoas diameter assessment showed good correlation and agreement with muscle mass defined by BIA in cirrhotic patients. If these results are confirmed in larger external series, ultrasound can be proposed as a feasible and cost-effective tool for the assessment of sarcopenia in patients with CLD.

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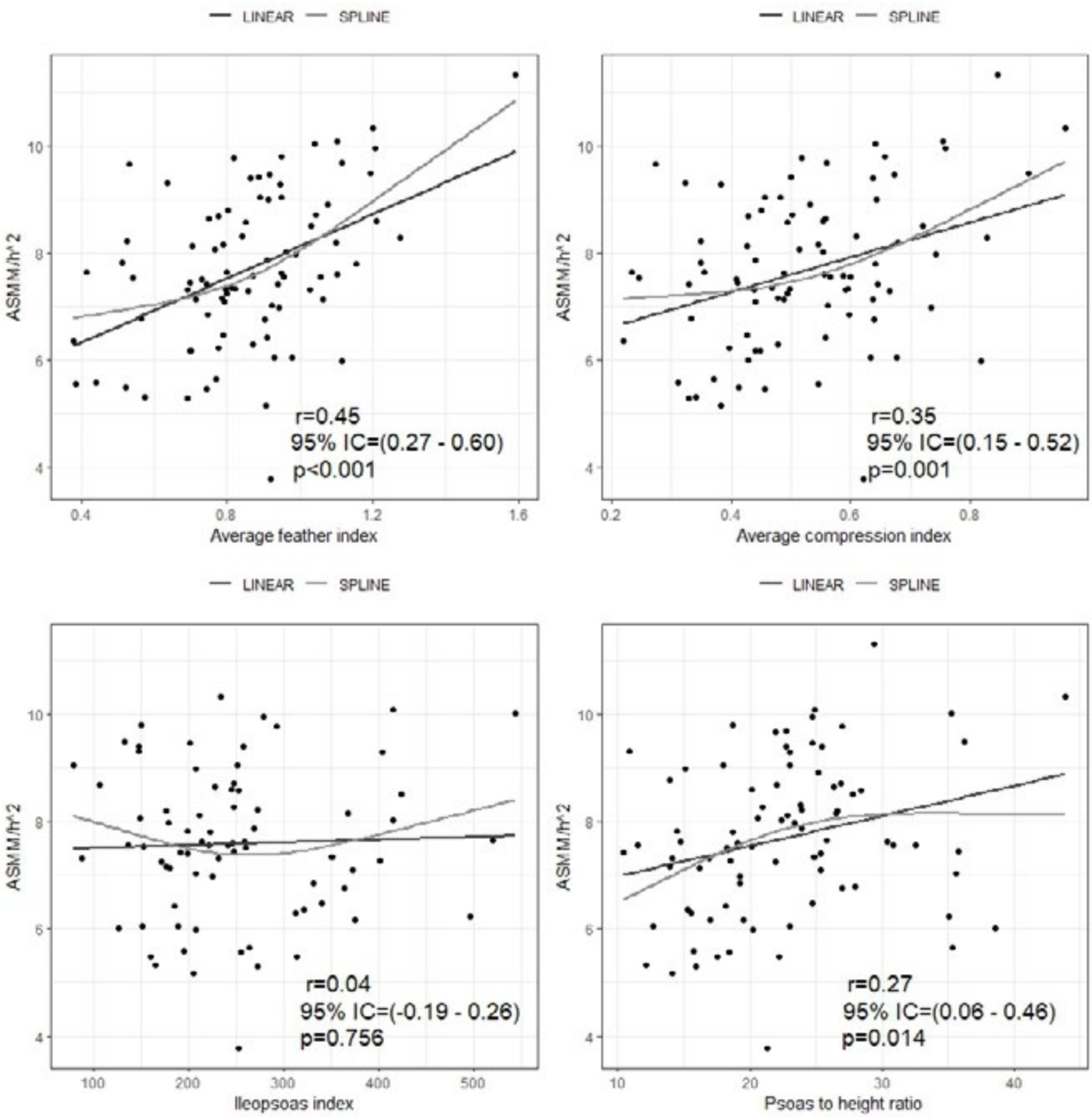

Disclosures: Paolo Gallo: Nothing to Disclose, Valentina Flagiello: Nothing to Disclose, Antonio De Vincentis: Nothing to Disclose, Francesca Terracciani: Nothing to Disclose, Andrea Falcomatà: Nothing to Disclose, Antonio Picardi: Nothing to Disclose, Umberto Vespasiani Gentilucci: Nothing to Disclose

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4194 | A META-ANALYSIS AND SYSTEMATIC REVIEW ON COMPARISON OF OUTCOMES BETWEEN EARLY TIPS AND STANDARD THERAPY

Shahryar Khan[1] Aamer Ahmad[2] Azzah Muhammad Hayat[2] Aamer Syed[2] Ahmad Khan[2] Mashal Alam Khan[2]

[1]University of Kansas Medical Center, [2]Khyber Medical University

Background: Acute variceal bleeding is a life-threatening and a common cause of death in advanced liver disease. The current recommended Standard therapy (ST) for variceal bleeding is a combination of Endoscopic therapy and Vasoactive drugs which has improved outcomes in patients. Given there is a good proportion of treatment failure which needs interventions like transjugular intrahepatic portosystemic shunts (TIPS). The current guidelines and the reported survival benefit favor early TIPS (ET) but are rarely practiced. We aimed to assess whether early TIPS improves survival, incidence of rebleeding, new onset hepatic encephalopathy, and new onset of ascites in patients with advanced cirrhosis. **Methods:** We systematically searched Medline, and Embase from inception till May 1, 2024. Early TIPS was defined in studies which included all patients who underwent TIPS treatment within 72 hours after endoscopic therapy. The outcome of interest in our meta-analysis was All cause mortality, while secondary outcomes were 1-year survival rate, incidence of rebleeding, new onset hepatic encephalopathy, and new onset ascites. The random effects model was used to calculate the Odds ratio with the corresponding 95% confidence intervals for desired outcomes. A p value of < 0.05 was considered statistically significant. Heterogeneity was assessed using the I2 Index. Risk of Bias in studies was assessed using the RoB-2 tool. Data analysis was performed using the Revman software (version 5.4.1). **Results:** In our meta-analysis, 9 RCTs were included with a total population of 689 participants of which 369 received early TIPS and 320 received standard therapy; Female comprised 34% in ET; 35% in ST; Average age of 53.4 in ET group, and 53.5 in ST group. ET group included Child-Pugh (CP) A (20%), CP-B (34%), and CP-C (46%); ST included CP-A (22%), CP-B (38%), and CP-C (40%). There was no difference in comparing all-cause mortality between ST and ET, OR 0.74, 95% CI 0.50 to 1.09, random effect, I2 = 1%, P =0.13 (Figure 1). Compared to ST, ET is associated with a lower risk of rebleeding OR 0.20, 95% CI 0.14 to 0.31, random effect, I2 = 0%, P <0.05 (Figure 2). ET was not associated with an increasing risk of hepatic encephalopathy OR 1.31, 95% CI 0.83 to 2.07, random effect, I2 = 29%, P =0.25, New or worsening ascites OR 0.47, 95% CI 0.21 to 1.05, random effect, I2 = 0%, P =0.07. ET is associated with 1-year survival of 82.8%, and 70% in ST. **Conclusion:** In conclusion, Early TIPS significantly reduces incidence of variceal rebleeding, and improves 1-year survival rate, but is not associated with higher mortality or worsening hepatic encephalopathy or ascites in comparison with standard therapy. These findings need to be validated with well-designed RCTs comparing early TIPS and non-early TIPS.

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Figure 1. All-Cause Mortality

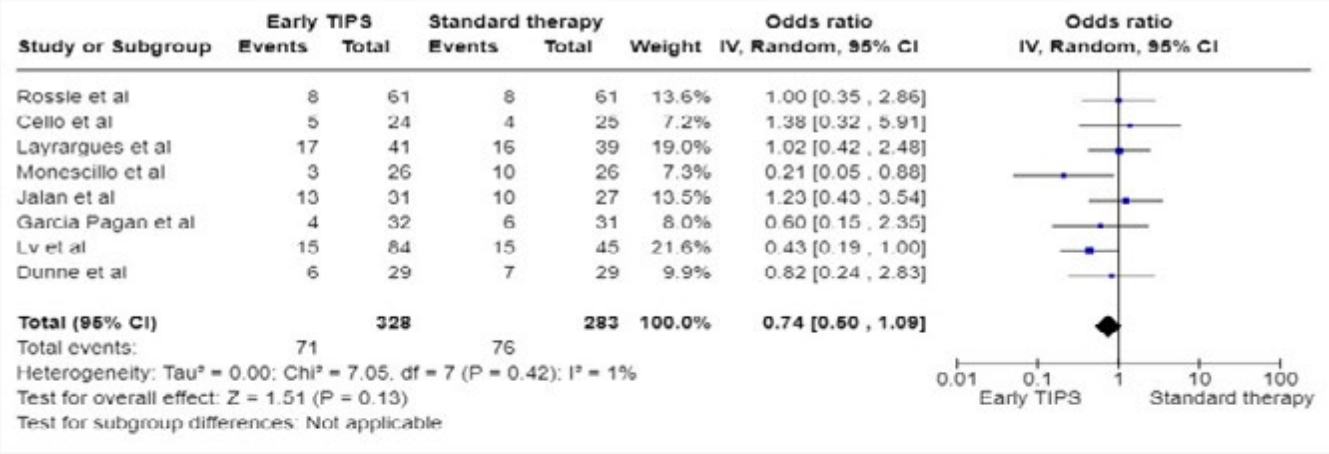
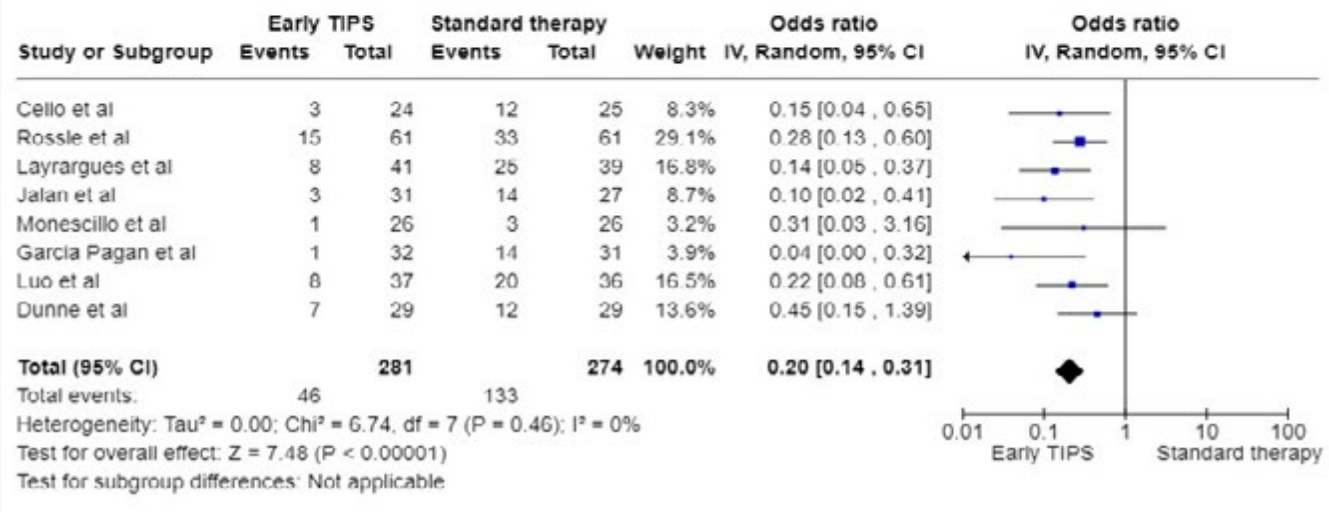


Figure 2. Risk of Rebleeding



Disclosures: Shahryar Khan: Nothing to Disclose, Aamer Ahmad: Nothing to Disclose, Azzah Muhammad Hayat: Nothing to Disclose, Aamer Syed: Nothing to Disclose, Ahmad Khan: Nothing to Disclose, Mashal Alam Khan: Nothing to Disclose

4195 | EPIDEMIOLOGY AND OUTCOMES OF AMBULATORY COMMUNITY ACQUIRED ACUTE KIDNEY INURY: A NATIONWIDE US VETERANS STUDY ◆

Kavish Patidar[1] Yan Liu[2] Thomas Taylor[2] Ruben Hernaez[1] George Cholankeril[1] Jennifer Kramer[2] Prasun Jalal[1] Tzu-Hao Lee[1] Avegail Flores[1] Giuseppe Cullaro[3] Andrew Allegretti[4] Pere Gines[5] Fasiha Kanwal[6]

[1]Baylor College of Medicine, [2]Baylor College of Medicine; Michael E. DeBakey VAMC, [3]University of California-San Francisco, [4]Massachusetts General Hospital, [5]Hospital Clinic of Barcelona, University of Barcelona, [6]Michael E. DeBakey VA Medical Center

Background: Acute Kidney Injury (AKI) is a serious complication in patients with cirrhosis, but most information on AKI is limited to episodes detected during hospitalization. Little is known about ambulatory community acquired AKI (CA-AKI)—AKI that develops outside of the hospital in patients with cirrhosis. We examined the incidence, risk factors and mortality associated with CA-AKI in a U.S. cohort of patients with cirrhosis. **Methods:** We conducted a retrospective cohort study of patients diagnosed with cirrhosis between 1/2018-12/2019 at 130 hospitals in the Veterans Affairs healthcare system. We followed patients from cirrhosis diagnosis until death or

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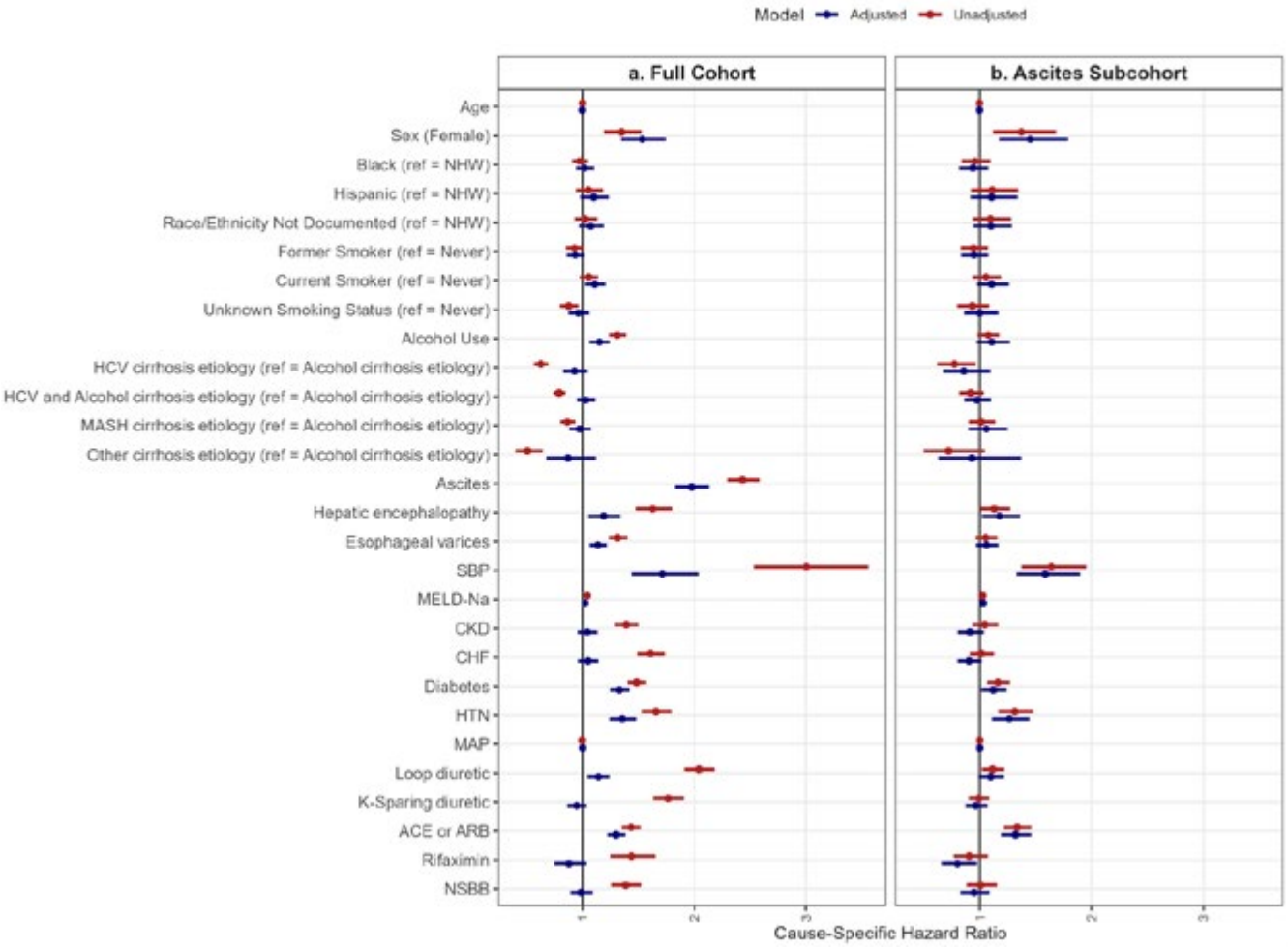
12/2022. We used serial measurements of serum creatinine (sCr) to define AKI based on the International Club of Ascites criteria. Patients were classified as CA-AKI if they met AKI criteria in an ambulatory setting. We used cause specific Cox-regression analysis with competing risks of any hospitalization, death, and hemodialysis to identify risk factors associated with CA-AKI overall and in an ascites sub-cohort. Multivariable Cox-regression analysis with CA-AKI as a time-varying covariate was used to determine the association between CA-AKI and 1yr mortality. **Results:** Among 55,879 patients with cirrhosis [median age 66yrs, 67% white, 38% alcohol, median MELD-Na 10, 34% ascites], 7,109 (13%) patients developed CA-AKI during a median follow up of 4.0yrs. After accounting for competing risks, there were 3.6 (95%CI 0.9-9.6) CA-AKI cases per 100 person-years overall. At the time of CA-AKI diagnosis, 44%, 37%, 13%, and 6% had stage 1A, 1B, 2, and 3, respectively. Overall, CA-AKI resolved (return of sCr to <0.3mg/dL of baseline) in 40% within 90-days. CA-AKI was associated with liver disease severity. The risk of CA-AKI was the highest in patients with ascites (HR 1.98), followed by patients with hepatic encephalopathy (HE) (HR 1.19), and esophageal varices (HR 1.14). In total, 46% and 78% patients had diabetes (DM), and hypertension (HTN), respectively and they were more likely to develop CA-AKI (HR 1.33 and 1.36, respectively). Similar results were found in patients with ascites (Figure). ACE-I/ARB increased CA-AKI risk overall and in patients with ascites, HR 1.30 and 1.32, respectively, while rifaximin was protective only in patients with ascites, HR 0.80. Among patients with CA-AKI, 8% were hospitalized within 90-days and 26% died within 1yr. After adjusting for age, DM, HTN, congestive heart failure, ascites, HE and MELD-Na, CA-AKI was associated with a 2-fold increased risk for 1yr mortality [HR 2.04 (95%CI 1.89-2.20) p<0.001]. **Conclusion:** CA-AKI occurs frequently in patients with cirrhosis and is associated with increased risk for mortality. Monitoring patients with ascites and comorbidity for development of CA-AKI may help improve outcomes of patients with cirrhosis. Interventions that target medication management may be high yield in preventing CA-AKI.

Figure: Risk Factors Associated With Ambulatory Community Acquired Acute Kidney Injury



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Disclosures: Kavish Patidar: Madrigal Pharmaceuticals: Medical Advisory Board, Yan Liu: Nothing to Disclose, Thomas Taylor: Nothing to Disclose, Ruben Hernaez: Nothing to Disclose, George Cholankeril: Nothing to Disclose, Jennifer Kramer: Nothing to Disclose, Prasun Jalal: Nothing to Disclose, Tzu-Hao Lee: Nothing to Disclose, Avegail Flores: Nothing to Disclose, Giuseppe Cullaro: Nothing to Disclose, Andrew Allegretti: Nothing to Disclose, Pere Gines: Gilead & Grifols: Grant/Research Support, SeaBeLife, Merck, Sharp and Dohme (MSD), Ocelot Bio, Roche Diagnostics Intern, Boehringer Ingelheim: Advisor, Pfizer: Speaking and Teaching, Gilead, RallyBio, Behring: Advisor, Pfizer: Speaking and Teaching, Fasiha Kanwal: Nothing to Disclose

4196 | SARCOPENIA EXACERBATES LIVER-RELATED COMPLICATIONS IN PATIENTS WITH CIRRHOSIS AND HEPATIC ENCEPHALOPATHY: A NATIONWIDE ANALYSIS HIGHLIGHTING INPATIENT OUTCOMES AND GENDER DIFFERENCES.

Fnu Vikash[1] Gautam Maddineni[2] Sandesh Parajuli[3] Vikash Kumar[4] Manasa Ginjupalli[5] Sindhu Vikash[6] Don Rockey[7]

[1]Albert Einstein College of Medicine/Jacobi Medical Center, [2]Florida State University College of Medicine, [3]Reading Hospital/Tower Health, [4]Creighton University, [5]The Brooklyn Hospital Center, [6]Cleveland Clinic, Main Campus, [7]Montefiore Medical Center

Background: Sarcopenia, characterized by the loss of skeletal muscle mass and strength, is a common clinical manifestation among patients with cirrhosis. Sarcopenia may exacerbate hepatic encephalopathy due to altered pathophysiological mechanisms of ammonia metabolism. This study aimed to investigate the impact of sarcopenia on liver-related complications and outcomes in patients with encephalopathy secondary to cirrhosis using a nationwide inpatient database. **Methods:** A retrospective analysis was conducted using data from the National Inpatient Sample (NIS) database from 2016 to 2020. Patients with a principal diagnosis of encephalopathy in the setting of liver cirrhosis were identified using ICD-10 codes. The study population was divided into two groups: those with and without sarcopenia. Primary outcomes included inpatient mortality and the prevalence of cirrhosis-related complications. Multivariable regression analyses were performed, adjusting for demographics and confounders. **Results:** Among 115,335 hepatic encephalopathy hospitalizations, 165 (0.14%) had a diagnosis of sarcopenia. Sarcopenic patients had significantly higher odds of developing spontaneous bacterial peritonitis (OR 2.89, 95% CI 1.05-7.96), portal venous thrombosis (PVT) (OR 3.39, 95% CI 1.28-9.00), ascites (OR 2.92, 95% CI 1.48-5.76), varices with and without bleeding (OR 3.36, 95% CI 1.49-7.54), non-bleeding varices (OR 2.75, 95% CI 1.23-6.18), needing transjugular intrahepatic portosystemic shunt (OR 10.68, 95% CI 2.42-47.00), and have liver failure (OR 4.88, 95% CI 2.27-10.49) compared to non-sarcopenic patients (Table 1). Although sarcopenic patients had lower odds of inpatient mortality (OR 0.15, 95% CI 0.15-0.16), the association was not statistically significant (p=0.072). Sarcopenic patients also had a longer average length of stay and higher total hospital charges. Moreover, there is a higher proportion of males among patients with sarcopenia (72.7%) compared to those without sarcopenia (59.5%). Conversely, the proportion of females is lower in the sarcopenia group (27.3%) compared to the non-sarcopenia group (40.5%). **Conclusion:** This nationwide retrospective study revealed that sarcopenia is associated with a significantly higher prevalence of liver-related complications in patients with cirrhosis and hepatic encephalopathy, especially males. These findings underscore the importance of identifying and managing sarcopenia in patients with hepatic encephalopathy to potentially improve outcomes and reduce the risk of complications.

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Table 1. Baseline Characterstics			
Characteristic	Hepatic encephalopathy Without Sarcopenia	Hepatic encephalopathy With Sarcopenia	Total
Age, years (Mean)	62	55.7	-
Sex, n (%)			
Male	68,526 (59.5)	120 (72.7)	68,805 (59.5)
Female	46,644 (40.5)	45 (27.3)	46,689 (40.5)
Race, n (%)			
White	77,279 (67.1)	133 (80.6)	75,138 (67.1)
Black	13,475 (11.7)	5 (3.2)	13,111 (11.7)
Hispanic	16,700 (14.5)	16 (9.7)	16,242 (14.5)
Asian or Pacific Islander	2,419 (2.1)	11 (6.5)	2,356 (2.1)
Native American	1,843 (1.6)	0 (0.0)	1,824 (1.6)
Other	3,455 (3.0)	0 (0.0)	3,316 (3.0)
Median Household Income, n (%)			
1st Quartile	39,618 (34.4)	57 (34.4)	38,653 (34.4)
2nd Quartile	30,866 (26.8)	26 (15.6)	30,115 (26.8)
3rd Quartile	26,719 (23.2)	52 (31.3)	26,078 (23.2)
4th Quartile	18,082 (15.7)	31 (18.8)	17,619 (15.6)
Insurance, n (%)			
Medicare	59,658 (51.8)	65 (39.4)	59,677 (51.8)
Medicaid	27,065 (23.5)	40 (24.2)	27,151 (23.5)
Private Insurance	19,579 (17)	50 (30.3)	19,583 (17.0)
Self-pay	4,837 (4.2)	0 (0.0)	4,826 (4.2)
No Charge	346 (0.3)	0 (0.0)	346 (0.3)
Other	3,685 (3.2)	10 (6.1)	3,742 (3.2)
Multivariable Analysis of liver-related outcomes among hospitalized patients with cirrhosis and hepatic encephalopathy complicated by the presence of sarcopenia.			
Complication	Odds Ratio	95% CI	p-value
SBP	2.89	1.05 - 7.96	0.04
PVT	3.39	1.28 - 9.00	0.014
Ascites	2.92	1.48 - 5.76	0.002
Liver Failure	4.88	2.27 - 10.49	<0.001
Varices w+w/o Bleeding	3.36	1.49 - 7.54	0.003
Varices w/o Bleeding	2.75	1.23 - 6.18	0.014
Varices w/ Bleeding	2.55	0.79 - 8.19	0.117
Death	0.15	0.15 - 0.16	0.072

Disclosures: Fnu Vikash: Nothing to Disclose, Gautam Maddineni: Nothing to Disclose, Sandesh Parajuli: Nothing to Disclose, Vikash Kumar: Nothing to Disclose, Manasa Ginjupalli: Nothing to Disclose, Sindhu Vikash: Nothing to Disclose, Don Rockey: Grant/Research Support relationship with Versantis; Has not ended; Grant/Research Support relationship with AstraZeneca; Has not ended; Grant/Research Support relationship with Ipsen; Has not ended; Grant/Research Support relationship with Boehringer Ingelheim; Has not ended; Consultant relationship with WL Gore and Associates; Has not ended; Grant/Research Support relationship with Gilead; Has not ended; Grant/Research Support relationship with Durect; Has not ended; Consultant relationship with BD Medical; Has not ended; Consultant relationship with Cook Medical; Has not ended; Grant/Research Support relationship with Intercept; Has not ended; Grant/Research Support relationship with Inventiva; Has not ended; Grant/Research Support relationship with Madrigal; Has not ended; Grant/Research Support relationship with Ocelot; Has ended; Grant/Research Support relationship with Bio89; Has not ended; Grant/Research Support relationship with Salix; Has not ended; Grant/Research Support relationship with Novonordisk; Has not ended; Grant/Research Support relationship with Viking; Has ended; Grant/Research Support relationship with Galectin; Has not ended

4197 | HEALTHCARE UTILIZATION, OUTCOMES, AND 30-DAYS READMISSIONS OF PATIENTS WITH MALNUTRITION IN DECOMPENSATED CIRRHOSIS.

Shahryar Khan[1] Hoor Umar Afridi[2] Mashal Alam Khan[2] Fatma Hussain[2] Nimra Ehsan[2] Aamer Syed[2]

[1]University of Kansas, [2]Khyber Medical University

Background: Malnutrition is characterized by the lack or imbalance of nutrients required for our body to function properly. It is the most prevalent complication of chronic diseases like Decompensated Cirrhosis (DC). It is associated with poor prognosis and mortality in cirrhotic patients. Since malnutrition aids to the severity and incidence of decompensated symptoms, this article will be centered on healthcare utilization, outcomes, and 30-day readmission rates for patients with decompensated liver cirrhosis at a national level in the United States.
Methods: We performed a retrospective cohort study of patients with Malnutrition in DC using 2020, Nationwide Readmission Database. DC was identified based on the presence of at least one of the following: ascites, hepatic encephalopathy, variceal bleeding, spontaneous bacterial peritonitis and hepatorenal syndrome. The primary outcome was rate of all-cause readmission within 30 days of discharge. Secondary outcomes were reasons for

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readmission, readmission mortality rate, and resource use (length of stay and total hospitalization costs and charges). Multivariable cox regression analysis to predict the risk factors for early readmission included clinically relevant variables with p<0.05 from univariate analysis. **Results:** A total of 27,798 index hospitalizations for DC with Malnutrition were identified in 2020. The mean age was 57.76 years (57.41-58.11) and 42.14% of patients were female. Out of these, 8494 (33.9%) patients got readmitted within the next 30 days. The most common reasons for readmission are listed in Table 1. The most common diagnosis associated with readmissions was related to Ascites. Readmissions compared to Index Hospitalizations have higher mortality (11% vs. 10%, p = 0.008). The mean length of stay associated with readmission was 7.51 days, with a total healthcare in-hospital economic burden of $9.13 billion. Patients with multiple comorbidities, age, Private insurance, low income, Diabetes, and Rehab transfer were found to be independent predictors for 30-day readmissions. Table 2 shows the odds ratios of the various factors tested as independent predictor of readmission **Conclusion:** Our study showed that one in three patients hospitalized with Decompensated Cirrhosis and Malnutrition was readmitted within 30 days of index hospitalization, placing a heavy economic burden on the healthcare system. Strategies should be adapted for Malnutrition screening and treatment protocols in these patients which can reduce readmissions.

Table 1. Most common reasons for readmissions

All-Cause Readmissions	N (%)
Ascites	1743 (20.5)
Hepatic failure without coma	1247 (14.6)
Hepatic encephalopathy	810 (9.5)
Sepsis	785 (9.2)
Acute Kidney failure	213 (2.5%)
Electrolytes derangements	155 (1.8)
Hepatorenal syndrome	123 (1.4)

Table 2. Independent Predictors of 30-Day Readmission

Variable	Adjusted Hazard ratio (95% confidence interval)	P-value
Insurance provider		
Medicare	Reference	Reference
Medicaid	1.001 (0.91-1.09)	0.96
Private	0.87 (0.79-0.96)	0.006
Uninsured	0.84 (0.70-1.005)	0.05
Median Income		
$1-55,999	Reference	Reference
$56,000-70,999	0.89 (0.82-0.97)	0.01
$71,000-93,999	0.79 (0.61-0.90)	0.03
$94,000 or more	0.55 (0.31-0.94)	0.03
Charlson comorbidity score	1.02 (1.005-1.03)	0.007
Age	0.98 (0.95-0.99)	<0.05
Rehab transfer	0.76 (0.58-0.90)	<0.05
Diabetes	1.15 (1.07-1.25)	<0.05

Disclosures: Shahryar Khan: Nothing to Disclose, Hoor Umar Afridi: Nothing to Disclose, Mashal Alam Khan: Nothing to Disclose, Fatma Hussain: Nothing to Disclose, Nimra Ehsan: Nothing to Disclose, Aamer Syed: Nothing to Disclose

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4198 | RIFAXIMIN SOLUBLE SOLID DISPERSION IMMEDIATE-RELEASE TABLETS FOR PREVENTION AND DELAY OF THE FIRST EPISODE OF HEPATIC ENCEPHALOPATHY: RED-C PHASE 3 STUDY DESIGN

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[1]Virginia Commonwealth University and Central Virginia Veterans Healthcare System, [2]Bausch Health US, LLC, [3]Salix Pharmaceuticals

Background: Cirrhosis progression to decompensation, marked by complications (eg, ascites; hepatic encephalopathy [HE]), is associated with poor prognosis. There is an unmet need for primary prevention (prophylactic) strategies to delay decompensation onset. Rifaximin soluble solid dispersion immediate release 40 mg (SSD-40IR) is an investigational agent designed to increase GI luminal rifaximin solubility while minimizing systemic exposure. Two trials (rifaximin for encephalopathy decompensation in cirrhosis [RED-C]) have been designed to evaluate the efficacy of rifaximin SSD-40IR in delaying the occurrence of HE-related hospitalization. **Methods:** The RED-C program includes 2 identically designed, phase 3, randomized, double-blind, placebo-controlled, multicenter trials (NCT05071716/NCT05297448). Eligibility criteria included adults (18-85 y) with cirrhosis, presence of medically controlled ascites (>30 days; not currently requiring therapeutic paracentesis), no documented history of overt HE (OHE; Conn score ≥2) or paracentesis-confirmed spontaneous bacterial peritonitis, no esophageal variceal bleeding or acute kidney injury-hepatorenal syndrome within previous 6 months, and a Mini-Mental State Examination score >24 at Screening. Patients were randomly assigned 1:1 to rifaximin SSD-40IR or placebo twice daily for 72 weeks. The primary efficacy endpoint is time to first OHE-related hospitalization. Secondary endpoints include time to first Conn score ≥2 and time to all-cause hospitalization. An OHE diagnosis, using AASLD guidelines (including detection of disorientation [time/place] and asterixis), will be confirmed by a Clinical Event Adjudication Committee. Safety is being monitored throughout the trials. **Results:** Patient enrollment in 1 trial is complete, with 92.6% of sites that enrolled ≥1 patient located in the United States; 746 patients were screened, and 222 were excluded from eligibility, most commonly due to screening failure (82.9%) or withdrawal by patient (13.5%). Overall, 524 were enrolled; the majority were male (60.9%), and the mean age was 59.2 y (range, 27-85 y). The median baseline MELD-Na score was 12, and 56.9% of 494 patients with data currently available had a Child-Pugh class of A. The second trial recently has completed enrollment and the data are being collected. **Conclusion:** Given the unmet need for primary prevention strategies, the RED-C phase 3 trials have been carefully designed to evaluate rifaximin SSD-40IR for delaying early HE-related decompensation.

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4199 | SOCIODEMOGRAPHIC CHARACTERISTICS AND OUTCOMES OF PATIENTS HOSPITALIZED WITH HEPATORENAL SYNDROME. A NATIONWIDE ANALYSIS

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[1]University of Kansas Medical Center, [2]University of Mississippi Medical Center, [3]University of Nevada, Reno School of Medicine, [4]Khyber Medical University

Background: Hepatorenal syndrome (HRS) is a serious complication of Advanced Liver Disease with high rates of morbidity and mortality. Based on clinical features and prognosis, HRS is classified into type 1 and 2, type 1 is associated with poor prognosis. We aimed to investigate the distribution of HRS in a nation-wide cohort of individuals, and outcomes associated with hospital admissions in the United States. **Methods:** Data were obtained from the National Inpatient Sample, 2020, provided by the Healthcare Cost and Utilization project. This data represents 20% of admissions in the USA, weighted to represent the entire country. Our primary outcome was inpatient mortality, while the secondary outcomes were hospital length of stay (LOS), and total hospitalization charges (THC). We conducted the analysis using STATA software version 18.0, multivariate regression analysis was used to adjust for potential confounders. **Results:** Among 32 million hospitalizations, we found 199,640

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admissions with Decompensated Cirrhosis (DC), 3754(1.8%) with a principal diagnosis of HRS. Our study indicated that patients admitted with HRS have a mean age of 59.26, female 42.2%, and are more likely to be black. The number of patients who died during hospitalization for HRS were 879 (23.4%). There was a significant difference in inpatient mortality of patients admitted for DC with or without HRS, Crude Odds ratio of Mortality 5.42 (95% CI 4.58-6.54) and adjusted odds ratio of Mortality 4.17 (95% CI 3.37-5.16). Multivariable analysis revealed that Age, Female, Race, Malnutrition, Encephalopathy, Insurance status, Hospital bed size, and Charlson comorbidity index were predictors of Mortality. Among secondary outcomes, there was a significant difference in LOS (Adjusted Mean difference 2.25, P <0.05), THC (Adjusted Mean difference 18552, P < 0.05). Rates of acute respiratory failure, cardiac arrest, and sepsis were different in DC with or without hepatorenal syndrome. (Table 1). **Conclusion:** In Decompensated Cirrhosis, admissions due to HRS are at a significantly increased risk of all-cause mortality, and healthcare resource utilization. For this population, a multidisciplinary approach should be planned for better management and outcomes.

Table 1.

Outcomes	Adjusted Odds ratio (95% confidence interval)	*P* - value
Mortality	4.17 (3.37-5.16)	<0.05
Shock	2.47 (2.01-3.03)	<0.05
Cardiac Arrest	2.58 (2.17-3.05)	<0.05
Respiratory failure	1.10 (1.08-1.12)	<0.05
Outcomes	Adjusted Mean Difference (95% confidence interval)	*P* - value
Length of Hospital Stay (Days)	2.25 (1.62-2.89)	<0.05
Total Hospital Charges $	18552 (5659-31445)	<0.05

Disclosures: Shahryar Khan: Nothing to Disclose, Yousaf Zafar: Nothing to Disclose, Amina Arif: Nothing to Disclose, Muhammad Abu Bakkar: Nothing to Disclose, Azzah Muhammad Hayat: Nothing to Disclose, Mashal Alam Khan: Nothing to Disclose

4200 | SHORT-TERM PRIMARY RIFAXIMIN PROPHYLAXIS HAS NO BENEFICIAL ROLE IN PATIENTS WITH CIRRHOSIS

Anand Kulkarni[1] Shivani Jangili[2] Sai Spoorthy Penumarthi[2] Shantan Venishetty[2] Manasa Alla[2] Sowmya T R[2] Mithun Sharma[3] Rajesh Gupta[2] Padaki Nagaraja Rao[2] Nageshwar Reddy[2]

[1]Asian Institute of Gastroenterology, [2]AIG Hospitals, [3]ASIAN INSTITUTE OF GASTROENTROLOGY PVT LTD

Background: Rifaximin has only been approved for prevention of recurrent hepatic encephalopathy (HE). Although not proven to have any clinical benefit with primary prophylaxis, its use is very common in clinical practice. In this study, we aimed to assess the impact of prophylactic rifaximin in a relatively stable cirrhosis patients. **Methods:** In this single-centre cross-sectional study, consecutive patients who attended the outpatient department for the first time (index presentation) were included and assessed for the impact of prior rifaximin intake. We excluded patients who had prior history of HE. The main objectives were to compare the requirement of admission, HE, acute kidney injury (AKI), microbiologically proven infection and mortality among patients who had not received and received rifaximin as a primary prophylaxis. **Results:** 203 patients (age-51.4 years; alcohol-52.7%; women-88.7%; MELD-18.3) attending the outpatient department were included. Sixty-four percent had a prior history of decompensation with ascites, and 10.8% had a history of acute variceal bleeding. Hundred patients had not received prophylactic rifaximin, while 103 were prescribed rifaximin (primary prophylaxis). The dose of rifaximin was 1100 mg per day, and the median duration of therapy was 30 (10-109) days. Forty percent in the no rifaximin group and 42.7% in the rifaximin group were electively hospitalized for various reasons (P=0.69). HE at admission was comparable between the no rifaximin group (19%) and the rifaximin group (13.6%; P=0.29). The proportion of patients developing infection was similar in both groups (13% vs. 20.4%; P=0.15). The most common organisms isolated were *E.coli* and *Staphylococcus aureus*. Two individuals had *Candida Aureus* infection in the rifaximin group compared to none in no rifaximin group. Fifteen percent in the no rifaximin group and 21.6% in the rifaximin group had AKI at admission (P=0.22). None of the patients who received rifaximin

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died, while three died in the rifaximin group (P=0.24). No severe adverse events due to drug were reported. **Conclusion:** Short-term primary rifaximin prophylaxis has no beneficial role in patients with decompensated cirrhosis.

Disclosures: Anand Kulkarni: Nothing to Disclose, Shivani Jangili: Nothing to Disclose, Sai Spoorthy Penumarthi: Nothing to Disclose, Shantan Venishetty: Nothing to Disclose, Manasa Alla: Nothing to Disclose, Sowmya T R: Nothing to Disclose, Mithun Sharma: Nothing to Disclose, Rajesh Gupta: Nothing to Disclose, Padaki Nagaraja Rao: Nothing to Disclose, Nageshwar Reddy: Nothing to Disclose

4201 | PTIPS IS ASSOCIATED WITH BETTER OUTCOMES IN PATIENTS WITH ACUTE VARICEAL BLEEDING AND SEVERE ALCOHOLIC HEPATITIS

RUDLER MARIKA Virginia Hernandez-Gea[1] Charlotte Bouzbib[2] Bogdan Procopet[3] Anna Baiges Aznar[4] Fanny Turon[4] Hélène Larrue[5] CANDIDO VILLANUEVA SANCHEZ[6] Agustin Albillos[7] Lise Gluud[8] Maria Guardascione[9] Patrick Praktiknjo[10] Meritxell Cots[11] Helena Masnou Ridaura[12] Wim Laleman[13] Christophe Bureau[14] Mattias Mandorfer[15] EDILMAR TAPIAS[6] ALVARO GIRALDEZ GALLEGO[16] Alexander Zipprich[17] Lukas Hartl[18] Nuria Canete Hidalgo[19] olivier Deckmyn[20] Juan Carlos Garcia-Pagan[1] Dominique Thabut[2]

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Background: Patients (pts) with alcoholic hepatitis (AH) and acute variceal bleeding (AVB) have a similar prognosis than pts with other alcohol-related phenotypes or other causes of cirrhosis. No data have been reported in high-risk pts, i.e. requiring a pre-emptive TIPS (pTIPS) placement (pts with Child-Pugh (CP) B and active bleeding or CP C10-13 cirrhosis). Aims: to compare the outcomes of severe AH (sAH) in high-risk pts with AVB treated with pTIPS or endoscopic and drugs treatment (Endo+drugs). **Methods:** Pts were screened in 4 cohorts: 1 from a multicentric observational European study including 671 high-risk patients with AVB treated with pTIPS or Endo+drugs, 1 from the EuroTIPS group, including consecutive patients treated with TIPS from 7 European centers, 2 cohorts from a tertiary center in France of consecutive pts with AVB treated with Endo+drugs or pTIPS. Inclusion criteria were the following: AVB; high-risk pts; ALD; absence of abstinence; probable sAH, i.e. recent onset of jaundice+ MELD score >20; ALT<500 UI/L. Exclusion criteria were: presence of liver transplantation (LT); other cause of liver disease, absence of AH on liver biopsy. The primary endpoint was 6-week survival. Secondary endpoints were rebleeding, development of ascites or hepatic encephalopathy at 6 weeks. **Results:** 142 pts with AVB were included, 47 in pTIPS group and 95 in Endo+drugs. Baseline characteristics were similar between the 2 groups (age 53, male gender 84%, CP B/C 12/88%, MELD score 23.4, hemoglobin 8.1 g/dL). Overall, 75/142 (53%) had histologically proven AH, and 67/142 (47%) had probable AH. Corticosteroid therapy was given in 55% of pts in pTIPS group and in 46% of pts in the Endo+drugs (p=0.3). In those pts, the Lille score was similar between the 2 groups (0.35 vs 0.44, p=0.9). The 6-week survival was 86% in pTIPS vs 70% in Endo+drugs group (p=0.3). Rebleeding rate was significantly lower in pTIPS group (3 vs 19%, p=0.028), as well as further development of ascites (2 vs 30%, p<0.001), when compared to Endo+drugs. HE was similar between the 2 groups (19 vs 24%, p=0.9). In the competing risks analysis, pTIPS was associated with a significantly lower rate of decompensation or death or LT when compared to Endo+drugs (-14% [7.9-22%], p=0.011). **Conclusion:** pTIPS is associated with better outcomes than Endo+drugs in high-risk patients with cirrhosis with AVB displaying sAH at admission. sAH is not adequately diagnosed and treated in patients with AVB. Liver biopsy should be systematically performed, as well as pTIPS placement, when indicated.

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Disclosures: RUDLER MARIKA: Nothing to Disclose, Virginia Hernandez-Gea: COOK MEDICAL: Advisor, GORE MEDICAL: Speaking and Teaching, Charlotte Bouzbib: Nothing to Disclose, Bogdan Procopet: Nothing to Disclose, Anna Baiges Aznar: Nothing to Disclose, Fanny Turon: Nothing to Disclose, Hélène Larrue: Nothing to Disclose, CANDIDO VILLANUEVA SANCHEZ: Nothing to Disclose, Agustin Albillos: Nothing to Disclose, Lise Gluud: Nothing to Disclose, Maria Guardascione: Nothing to Disclose, Patrick Praktiknjo: Nothing to Disclose, Meritxell Cots: Nothing to Disclose, Helena Masnou Ridaura: Nothing to Disclose, Wim Laleman: Cook Medical: Consultant, Boston Scientific: Grant/Research Support, CSL Behring: Consultant, Christophe Bureau: Gore: Speaking and Teaching, Abbvie: Consultant, Gilead: Speaking and Teaching, Ipsen: Speaking and Teaching, Alfasigma: Consultant, Mattias Mandorfer: Ipsen: Consultant, Echosens: Speaking and Teaching, Echosens: Grant/Research Support, Ipsen: Grant/Research Support, Ipsen: Consultant, Takeda: Consultant, Takeda: Speaking and Teaching, W.L. Gore & Associates: Speaking and Teaching, EDILMAR TAPIAS: Nothing to Disclose, ALVARO GIRALDEZ GALLEGO: Gilead: Grant/Research Support, Gilead: Speaking and Teaching, W.L. Gore & Associates: Speaking and Teaching, AbbVie: Speaking and Teaching, MSD: Speaking and Teaching, Intercept: Speaking and Teaching, AbbVie: Travel support, Gilead: Travel support, Eisai: Travel Support, Cook: Travel support, Bayer: Travel support, Alexander Zipprich: Gore: Speaking and Teaching, Falk Foundation: Speaking and Teaching, CLS Behring: Speaking and Teaching, Lukas Hartl: Nothing to Disclose, Nuria Canete Hidalgo: Gilead: Grant/Research Support, AbbVie: Speaking and Teaching, olivier Deckmyn: Nothing to Disclose, Juan Carlos Garcia-Pagan: Nothing to Disclose, Dominique Thabut: abbvie: Speaking and Teaching, gore: Speaking and Teaching, gilead: Speaking and Teaching, alfasigma: Consultant, satellite bio: Consultant

4202 | THE PHYSIOLOGICAL DETERMINANTS OF SYMPTOM BURDEN IN CIRRHOSIS WITH ASCITES

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Background: Paracentesis is commonly used to manage patient discomfort due to ascites. The relationship between ascites pressure, ascites volume, and patient discomfort have not been elucidated. **Methods:** We prospectively enrolled adult patients with non-malignant ascites undergoing outpatient therapeutic paracenteses from 2021 to 2024 at a tertiary care hospital. Patients completed a validated symptom questionnaire (ASI-7, maximum score 35) before, immediately after, and one week after paracentesis. An open-ended manometer was used to measure ascites pressure at the beginning and end of paracentesis. Mixed effects linear regression was performed to evaluate the relationships between patient characteristics, pressure, volume, and symptoms. **Results:** 150 paracentesis procedures among 48 unique patients with an average MELD 3.0 of 16.7 were included. An average of 6.5L was drained which reduced abdominal pressure from a mean of 13.7 to 6.0 cm H_2O (10.1 to 4.4 mmHg, $p<0.001$) and mean symptom score from 22.6 to 6.5 ($p<0.001$). Regression models identified that symptoms and abdominal pressure linearly best correlated above pressure of 6 cm H_2O and ASI-7 score of 16 (Figure 1C, $p<0.01$). Taller patients required about 670mL additional drainage per inch above cohort mean height to achieve the same symptom relief. **Conclusion:** Pressure measured at the bedside can be used to explore changes in abdominal pressure during paracentesis. Pressure, volume, and patient level factors such as height contribute to patient symptoms but cannot fully explain discomfort associated with ascites and relief after paracentesis.

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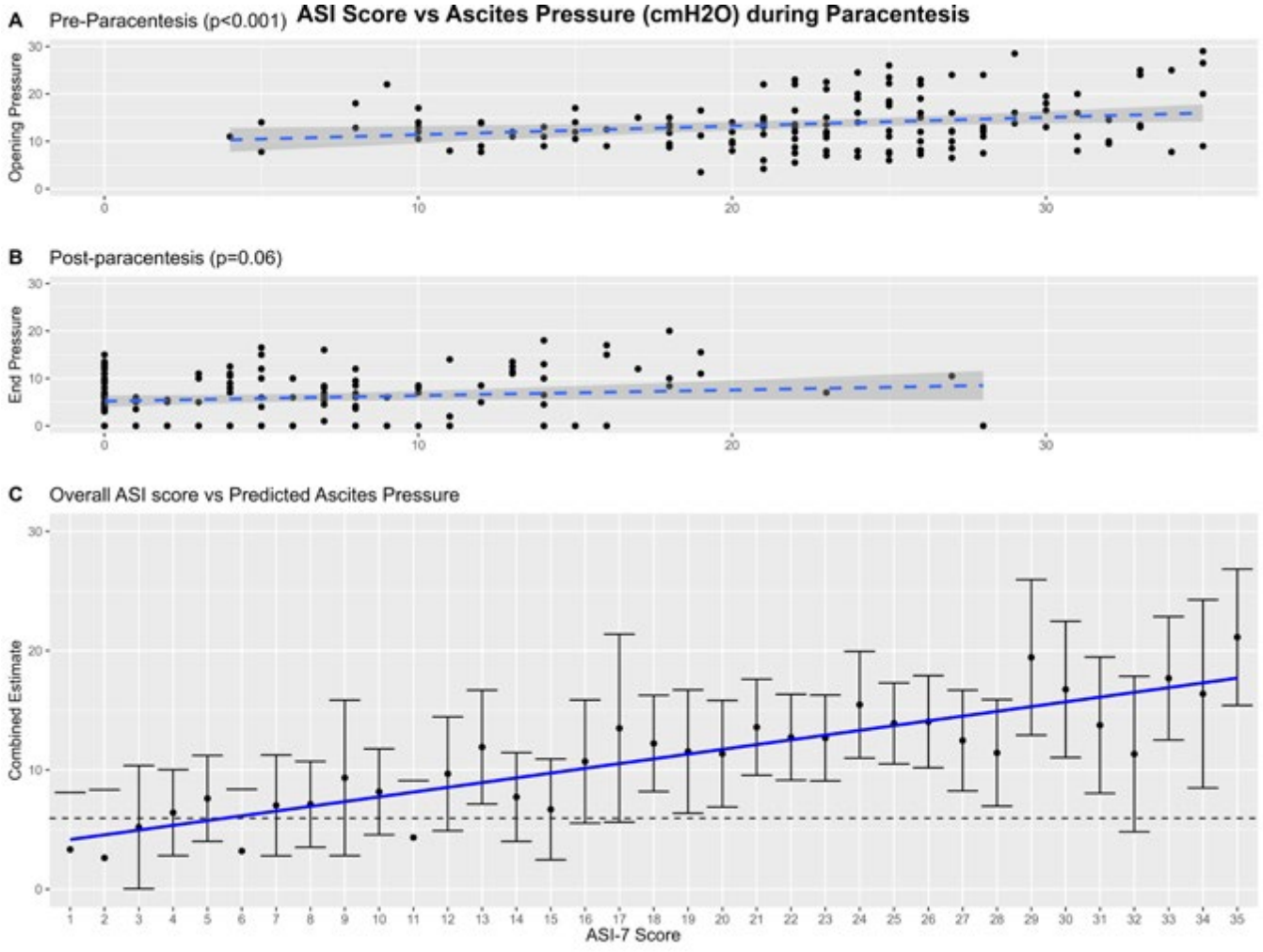

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4203 | PREDICTORS OF OUTCOMES OF BACTERIAL INFECTIONS IN PATIENTS WITH ADVANCED LIVER DISEASE

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Background: Infections are a major cause of mortality in patients with liver cirrhosis. This study was carried out to characterize the bacterial infections and their impact on mortality among hospitalized patients with liver cirrhosis and identify predictors of adverse outcomes. **Methods:** A total of 438 consecutive adult patients with cirrhosis and bacterial infection, hospitalized from September 2021 to May 2024, were included in the study. Data on patient characteristics, cirrhosis etiology, infection types, microbiology results, and 30-day mortality were collected. Univariate and multivariate logistic regression analyses identified predictors of mortality. **Results:** Most patients (324[73.9%]) had decompensated chronic liver disease (CLD) and 50(11.5%) had acute-on-chronic liver failure (ACLF). Median Child-Pugh and MELD scores on admission were 10 and 27, respectively. Common etiologies of cirrhosis were alcohol (42.9%), MASLD (31.28%) and viral (14.7%). The most common infections were spontaneous bacterial peritonitis (SBP, 23.7%), urinary tract Infection (UTI, 19.4%) lower respiratory tract infections (14.1%) and cellulitis (8.7%). Gram-negative organisms were more prevalent (61.2%) than

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gram-positive organisms (38.8%). Most common organisms were E. coli (33.6%) and Klebsiella (23.2%); in UTIs, E. coli (48.5%) and Enterococcus (8.9%); and in LRTIs, Streptococcus (9%) and Pseudomonas (5%). Multi-drug resistant organisms (MDRO) were identified in 5.2% cases. The 30-day mortality rate was 13.92%. On univariate analysis, age >50 years, MELD >30, albumin <2.5 g/dL, shock at presentation, MDRO and acute-on-chronic liver failure (ACLF) were associated with higher mortality ($p<0.05$). In the multivariate model, MDRO (OR 27.15), MELD >30 (OR 3.41), ACLF (OR 2.86) and shock (OR 2.24) were independent predictors of 30-day mortality. **Conclusion:** Infections are associated with substantial short-term mortality in hospitalized cirrhotic patients. SBP, UTI, LRTI and cellulitis are the most common identified sources of infections. Presence of MDRO is the strongest predictor of 30-day mortality followed by MELD >30, ACLF and shock at presentation.

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4204 | DETERMINANTS AND IMPACT OF IMPAIRED AEROBIC CAPACITY ON SURVIVAL IN PATIENTS WITH CIRRHOSIS: RESULTS FROM A 2600 PATIENT COHORT

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Background: Aerobic capacity quantified using maximal oxygen uptake (VO2 max) at cardio-pulmonary exercise testing (CPET) is often impaired in cirrhotic chronic liver disease (CLD) and impacts survival. Important as a potentially modifiable risk factor, its clinical associations have limited characterisation. In a very large patient cohort undergoing CPET as part of liver transplant (LT) assessment we explored these and its impact on long-term survival with and without LT. **Methods:** Adult patients with CLD undergoing assessment for first LT as single high-volume centre over the period 2010-2023 were studied. Incremental CPET used bicycle ergometer and time-to-event analysis Kaplan-Meier and Cox-regression. **Results:** The study cohort comprised 2624 subjects (64% male) of median age 56 (IQR 47-62) years. MELD score was 11 (7-15) and Child-Pugh 8 (7-10); cause of CLD was alcohol in 33%, Viral in 18% and MASLD in 12%. Median follow-up was 857 (242-2313) days; 1860 (71%) were waitlisted for LT of whom 1493 (80%) underwent LT 104 (34-236) days later. There were 226 (12%) deaths on the waitlist. At CPET peak heart rate was 138 (121-156) bpm and workload 91 (69-118) W. VO2 max was 16.5 ml/kg/min (13-20.2) with independent association with age, sex, body mass index, diabetes, MELD and presence of ascites (all $p<0.001$) and was 63% (49-78) predicted. VO2 max varied between etiologies, lowest in MASLD: 13.9 (11.2-17.1) vs. Others 16.8 (13.4-20.6), ($p<0.001$). Patients waitlisted for LT had higher VO2 max those not waitlisted 17 (13.6-20.8) vs. 15 (11.6-18.8), and as % predicted 64 (50-79) vs. 59 (45-74) (both $p<0.001$). Those who died on the waitlist had lower VO2 predicted than survivors; 57% (46-71) vs. 64% (51-80) ($p<0.001$). VO2 max was independently associated with waitlist death when adjusted for age and MELD score ($p<0.001$). VO2 max was independently associated with non-LT survival, with incremental worsening with lower VO2 (figure 1A, $p<0.001$ log-rank), with no association with post-LT survival (figure 1 B, $p=0.436$). In non-LT patients VO2 predicted of <50% had adjusted hazard ratio for death of 1.75 (95% CI 1.35-2.302) compared to those with >80%, ($p<0.001$). **Conclusion:** Maximal oxygen uptake is often impaired in CLD, linked with specific clinical features, and has close independent association with non-LT but not post-LT survival. Further exploration of monitoring techneques and interventions to improve this modifiable risk factor for mortality without LT are warranted.

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Figure 1A

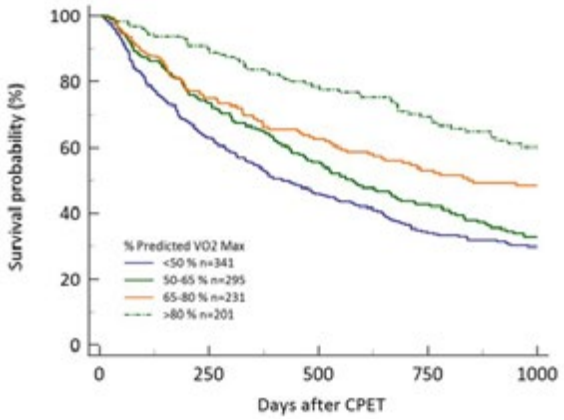
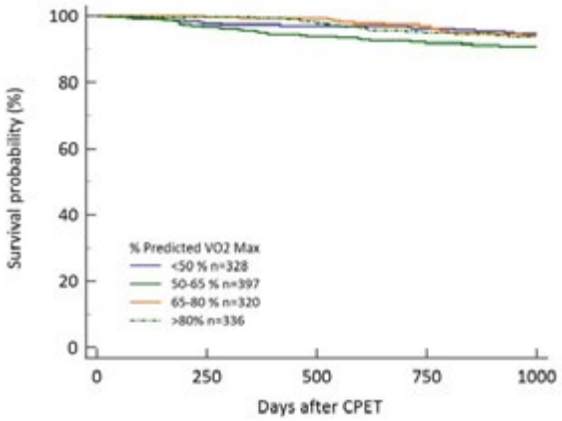


Figure 1B



Disclosures: William Bernal: Nothing to Disclose, Sarah Brown: Nothing to Disclose, Sameer Patel: Nothing to Disclose, Pervez Khan: Nothing to Disclose, Robert Loveridge: Nothing to Disclose, Abid Suddle: Nothing to Disclose, Varuna Aluvihare: Nothing to Disclose

4205 | UTILIZATION OF ENDOSCOPIC ULTRASOUND-GUIDED LIVER BIOPSY WITH PORTAL PRESSURE GRADIENT MEASUREMENTS FOR RISK-STRATIFICATION OF LIVER DISEASE IN SOLID ORGAN TRANSPLANT CANDIDATES – A SINGLE CENTER EXPERIENCE

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Background: Endoscopic ultrasound-guided liver biopsy with portal pressure gradient measurement (EUS-PPG) is a unique procedure with the advantage of concurrent diagnostic and therapeutic applications. We report our single-center experience in utilizing EUS-PPG to risk-stratify solid organ transplant (SOT) candidates with possible advanced liver disease. **Methods:** Single-center, retrospective chart review of all adult patients who underwent EUS-PPG at the University of Minnesota from 1/1/2020-5/29/2024. Clinical data including demographics, laboratory, endoscopy, pathology and transplant-related data were obtained and descriptive statistics was performed. **Results:** 23 patients underwent EUS-PPG- mean age 52.47 years, 14 (61%) males and 12/23 (52.17%) white patients. 13 (56.5%) patients underwent EUS-PPG for evaluation of liver disease as part of SOT evaluation- 12 for kidney transplant (KT), 1 for pancreas transplant (PT). EUS-PPG was successfully completed in 23/23 (100%) patients. Liver biopsy was performed in 10 patients with adequate sampling obtained in 9 (90%) patients. 3 patients had clinically significant portal hypertension. 3 (13.04%) patients had band ligation of esophageal varices. 3 (13.04 %) patients had post-procedural complications (abdominal pain, sore throat and swallowing difficulty). 2 (8.7%) patients died following EUS-PPG of infection unrelated to the procedure. Prior to EUS-PPG, 9 patients had a clinical diagnosis of cirrhosis- 3 patients did not have cirrhosis on liver biopsy. Following EUS-PPG, 6 patients were listed for KT only, 4 patients listed for simultaneous liver-kidney transplant (SLK) and 1 patient listed for PT only. 1 patient has since underwent KT without any decompensation in liver disease and 3 patients have successfully undergone SLK. (Table 1) **Conclusion:** The use of EUS-PPG in evaluation of SOT candidates is safe, efficient and effective. EUS-PPG can accurately recategorize patients with a clinical diagnosis of cirrhosis, thus preventing unnecessary SLK and resulting in more appropriate allocation of organs.

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Table 1: Endoscopic ultrasound guided portal pressure gradient performed as part of simultaneous liver kidney transplant evaluation

Patient ID	Indication	Organ Transplant evaluation	MELD-Na	Portal pressure gradient (mm Hg)	Biopsy results	Outcomes
1	ESRD, history of HBV exposure with clearance, evaluate for PH, given history of small EV on EGD	Kidney	23	4	No fibrosis	Evaluation undergoing for kidney transplant
2	CKD with decompensated cirrhosis	Kidney	22	10.7	F4	Underwent SLK transplant
3	ESRD, history of alcohol use and Hepatitis C	Kidney	23	2.67	NA	Died from septic shock and respiratory failure prior to evaluation
4	s/p Kidney and pancreas transplant, now with ESRD, TCP low albumin and transudative pleural effusion of unclear etiology	Kidney	28	1.33	No fibrosis	Evaluated for kidney transplant but later removed from list due to poor functional status
5	CKD, history of Hep C and alcohol use, evaluation of cirrhosis given nodular liver on US, EV on EGD and TCP	Kidney	21	13	F4	Underwent SLK transplant
6	ESRD, history of chronic hepatitis B, F4 on fibroscan	Kidney	23	0.67	Not performed	Underwent renal transplant
7	ESRD, Chronic Hepatitis B cirrhosis, TCP	Kidney	20	7.67	F4	Waitlisted for kidney only
8	ESRD, liver disease 2/2 MASLD, PH on imaging, no EV on EGD	Kidney	21	1.67	F3	Undergoing evaluation for renal transplant
9	Alstrom syndrome, chronic pancreatitis, MASLD, undergoing TPAIT	Pancreas	-	1	No Fibrosis	Undergoing evaluation for pancreas transplant
10	ESRD, chronic Hep C status post treatment completion, Hepatitis B exposure, EV on EGD	Kidney	21	1.3	Not performed	Patient died secondary to COVID related illness prior to further evaluation
11	CKD, cirrhosis w ascites, PHG but no varices on EGD	Kidney	18	5.3	Inadequate sample	Underwent SLK
12	ESRD, Hepatitis B, F 4 on fibroscan, no HE/ascites/EV	Kidney	23	6.67	F4	Undergoing evaluation for kidney transplant only
13	ESRD, AIP, childhood polio, TCP, elevated INR, nodularity on imaging	Kidney	30	13.7	F4	Undergoing evaluation for SLK

Abbreviations: ESRD: end-stage renal disease, CKD: chronic kidney disease, HBV: hepatitis B virus, PH: portal hypertension, HE: hepatic encephalopathy, PHG: portal hypertensive gastropathy, EV: esophageal varices, TCP: thrombocytopenia, INR: international normalized ratio, MASLD: metabolic associated steatotic liver disease, TPAIT: total pancreatectomy and auto-islet transplantation, EGD: endoscopy, AIP: acute intermittent porphyria, SLK: simultaneous liver kidney transplant

Disclosures: Rahul Karna: Nothing to Disclose, Guru Trikudanathan: Nothing to Disclose, Oyedele Adeyi: Nothing to Disclose, Nicholas Lim: Nothing to Disclose

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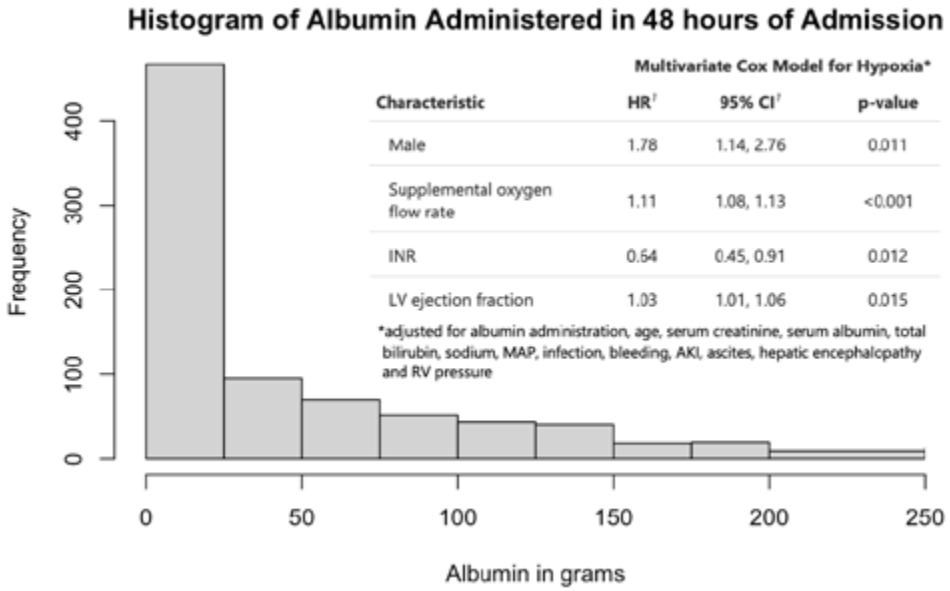
4207 | ALBUMIN ADMINISTRATION AND HYPOXIA IN PATIENTS WITH CIRRHOSIS

Mason Lai[1] *Cynthia Fenton*[1] *Jennifer Lai*[1] *Giuseppe Cullaro*[1]

[1]*UCSF*

Background: Albumin, a key resuscitative fluid among decompensated cirrhosis patients, has been associated with the development of respiratory failure when not tailored to each patient. **Methods:** We used electronic health record data from a single center on hospitalized decompensated cirrhosis patients. Albumin administration in the first 48 hours of admission was the primary predictor. Hypoxia was defined as any oxygenation support beyond a nasal cannula of 6 liters per minute. Participants were censored at 7 days after the albumin administration window. Cox regression models were used, controlling for sociodemographic factors, components of MELD 3.0, mean arterial pressure, ascites, hepatic encephalopathy, and presence of AKI, bleeding, or infection. **Results:** Among 823 patients hospitalized with decompensated cirrhosis in our cohort, 98 (12%) developed hypoxia. Median MELD 3.0 on admission was 28 (IQR 21-33). At 48 hours, patients received a median of 12.5 grams (IQR 0-75g) of albumin; with those having AKI (15.8g, p=0.001) and those with higher MELD 3.0 scores (7.6 g per 10 points higher MELD, p=0.009) receiving more albumin.Albumin administration in the first 48 hours of hospitalization was associated with less hypoxia in univariate analyses (HR 0.79 per g/kg, 95 CI 0.63-0.99), but not in multivariate analyses (HR 0.89 per g/kg, 95 CI 0.67-1.17). Instead, the factors associated with hypoxia in univariate analysis were: supplemental oxygen flow rate (HR 1.09, 95CI 1.08-1.10), INR (HR 0.72, 95CI 0.57-0.92), and male sex (HR 1.38, 95 CI 1.00-1.91). In multivariate analyses, factors associated with hypoxia were LVEF (aHR 1.03, 95CI 1.01-1.06), male sex (aHR 1.78, 95CI 1.14-2.76), INR (aHR 0.64, 95CI 0.45-0.91), and admission oxygen flow rate (aHR 1.11, 95CI 1.08-1.13). Interaction between albumin and RVSP was significant (HR 1.03, p = 0.03). We found no significant interactions between albumin and AKI, bleeding, MELD 3.0, sex, and EF.When we repeated our analysis to include longer albumin administration windows, again albumin administration was not associated with hypoxia (96 hours HR 1.11 per g/kg, 95% CI 0.88-1.39) and 144 hours (1.06 per g/kg, 95% CI 0.78-1.45). **Conclusion:** In our single center study, we found that the predictors of hypoxemia among decompensated hospitalized cirrhosis patients were INR, sex, admission oxygen support, and LVEF. In our cohort, where the utilization of albumin was limited as compared to other cohorts, we did not find that albumin administration was associated with hypoxia, with the exception of increasing albumin administration among those with higher RVSPs at baseline. Our data suggest that the tailored utilization of albumin is key to limiting the development of hypoxia.



Multivariate Cox Model for Hypoxia*

Characteristic	HR[†]	95% CI[†]	p-value
Male	1.78	1.14, 2.76	0.011
Supplemental oxygen flow rate	1.11	1.08, 1.13	<0.001
INR	0.64	0.45, 0.91	0.012
LV ejection fraction	1.03	1.01, 1.06	0.015

*adjusted for albumin administration, age, serum creatinine, serum albumin, total bilirubin, sodium, MAP, infection, bleeding, AKI, ascites, hepatic encephalopathy and RV pressure

Disclosures: Mason Lai: Nothing to Disclose, Cynthia Fenton: Nothing to Disclose, Jennifer Lai: Nestle Nutrition Institute: Grant/Research Support, Novo Nordisk: Consultant, Genfit: Consultant, Boehringer Ingelheim: Advisor, Giuseppe Cullaro: Nothing to Disclose, Nothing to Disclose

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4208 | THE DIAGNOSTIC VALUE OF SPECKLE TRACKING ECHOCARDIOGRAPHY IN CIRRHOTIC CARDIOMYOPATHY

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Background: Cirrhotic cardiomyopathy (CCM) often eludes detection through conventional cardiovascular imaging modalities. However, the available data on Global Longitudinal Strain (GLS) and other speckle tracking echocardiography (STE)-measured parameters in cirrhotic patients are limited. This study aims to provide a critical evaluation of the current evidence regarding the use of STE in patients with cirrhosis. **Methods:** In this prospective observational study, cirrhotic patients admitted from July 2023 to May 2024 in our hospital were enrolled. We excluded patients with known cardiac disease, chronic lung disease, severe renal insufficiency. Tissue Doppler echocardiography combined with two-dimensional speckle-tracking echocardiography was performed. The left ventricular end-diastolic diameter, left ventricular systolic diastolic diameter, interventricular septal thickness and left ventricular ejection fraction (LVEF) were measured from the parasternal long-axis section. The early diastolic transmitral flow velocity (E) and late diastolic transmitral flow velocity (A), early diastolic mitral annulus velocity (e'), left atrial volume index and peak tricuspid regurgitation velocity, were measured. Left ventricular GLS and left atrium strain (LAS) was calculated. Then we measured the peak atrial longitudinal strain at the end of the reservoir phase from atrial longitudinal strain curves. CCM were defined according to redefining CCM criteria in 2019. **Results:** We included 54 patients with cirrhosis, with the mean age of 59.5±10.5, of which 31(57.4%) were females and 31(57.4%) were classified in Grade B/C of Child-Pugh score (Table 1). The parameters obtained from general echocardiogram and STE are listed in Table 2. Following the 2019 CCM criteria, 10 out of 54 patients (18.52%) were diagnosed with CCM. Subsequently, a binary logistic regression analysis was conducted to identify risk factors for CCM. The analysis revealed that aging (above 60 years) was significantly associated with the risk of developing CCM (OR=7.285, p value = 0.034), whereas a history of β-blockers intake exhibits a notable protective effect against CCM (OR=0.010, p value = 0.037). **Conclusion:** The incidence of CCM is high in patients with cirrhosis. Age significantly influences the occurrence of CCM more than factors like Child-Pugh score and MELD score. Therefore, it is imperative to prioritize vigilant monitoring of elderly patients with cirrhosis for timely detection of CCM to prevent additional harm.

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Table1. Baseline characters of included patients (n = 54).

	Total (n=54)	Viral Hepatitis	Alcoholic Hepatitis	PBC	Other	*P* value
Age, mean±SD	59.5±10.5	62.1±8.4	55.8±12.8	62.1±10.0	58.8±11.0	0.333
< 60, n (%)	22(40.74%)	6(11.11%)	6(11.11%)	3(5.56%)	7(12.96%)	
⩾60, n (%)	32(59.26%)	13(24.07%)	8(14.81%)	4(7.40%)	7(12.96%)	
Gender						0.022
Female, n (%)	31(57.41%)	8(14.81%)	6(11.11%)	7(12.96%)	10(18.52%)	
Male, n (%)	23(42.59%)	11(20.37%)	8(14.81%)	0(0.00%)	4(7.40%)	
History						
Cigarette, n (%)	12(22.22%)	5(9.26%)	6(11.11%)	0(0.00%)	1(1.85%)	0.004
Hypertension, n (%)	11(20.37%)	3(5.56%)	4(7.40%)	1(1.85%)	3(5.56%)	0.816
Diabetes, n (%)	6(11.11%)	2(3.70%)	2(3.70%)	1(1.85%)	1(1.85%)	0.937
CAD, n (%)	2(3.70%)	1(1.85%)	1(1.85%)	0(0.00%)	0(0.00%)	0.723
Hypertriglyceridemia, n (%)	4(7.40%)	0(0.00%)	3(5.56%)	0(0.00%)	1(1.85%)	0.109
Hypercholesterolemia, n (%)	1(1.85%)	1(1.85%)	0(0.00%)	0(0.00%)	0(0.00%)	0.618
Drugs						
β-blockers, n (%)	10(18.52%)	3(5.56%)	4(7.40%)	1(1.85%)	2(3.70%)	0.75
Diuretic, n (%)	33(61.11%)	9(16.67%)	10(18.52%)	6(11.11%)	8(14.81%)	0.273
Child-pugh score	7.28±1.87	6.84±1.92	7.43±1.99	6.86±1.57	7.85±1.82	0.373
A, n (%)	23(42.59%)	10(18.52%)	5(9.26%)	5(9.26%)	3(5.56%)	
B and C, n (%)	31(57.41%)	9(16.67%)	9(16.67%)	2(3.70%)	11(20.37%)	
Meld score	7.48±4.91	8.84±2.92	4.86±4.04	3.43±4.89	10.15±5.83	<0.001
⩽14, n (%)	50(92.59%)	19(35.18%)	14(25.92%)	7(12.96%)	10(18.52%)	
> 14, n (%)	4(7.40%)	0(0.00%)	0(0.00%)	0(0.00%)	4(7.40%)	

PBC, Primary Biliary Cholangitis. CAD, Coronary artery disease.

Table2. Data of general transthoracic echocardiography (TTE) and speckle tracking echocardiography (STE).

Echocardiogram data	Mean±SD
LA (cm)	3.90±0.62
LVMI (g/m²)	88.94±22.89
LVEF (%)	70.70±5.93
TRV (mm/s)	210.00±92.52
e'	5.50±2.15
E/A	0.80±0.58
E/e'	12.58±3.36
DT (ms)	192.25±65.47
IVRT (ms)	71.50±14.94
Absolute GLS (%)	18.63±2.84
LAVI (ml/m²)	20.26±10.77

LA, left atrium. LVMI, left ventricular mass index. LVEF, left ventricular ejection fraction. DT, deceleration time. IVRT, isovolumetric relaxation time. GLS, global longitudinal strain. LAVI, left atrium volume index.

Table3. Risk factors of CCM in Cirrhotic patients by binary logistic regression analysis.

	B	SE	Wald X^2	OR	*P* value
Decompensated cirrhosis	18.89	14538.19	0	161074053	0.999
Age >60y	1.986	0.935	4.512	7.285	0.034
BMI >24kg/m²	-0.188	0.998	0.036	0.828	0.850
Alcoholic hepatitis	-1.035	0.969	1.139	0.355	0.286
MELD score >14	-1.089	1.542	0.498	0.337	0.480
Child-pugh B or C	-19.495	14538.197	0	0	0.999
β-blocker intake	-4.567	2.195	4.329	0.010	0.037
Constant	-0.532	1.970	0.073	0.588	0.787

SE, standard error. OR, odd ratio.

Disclosures: Jiakun Liu: Nothing to Disclose, Rui Huang: Nothing to Disclose, Xiaoxiao Hu: Nothing to Disclose, Cuncao Wu: Nothing to Disclose

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4209 | ACCURACY OF NONINVASIVE TESTS IN DETECTING ENDOSCOPICALLY OR RADIOGRAPHICALLY IDENTIFIED CLINICALLY SIGNIFICANT PORTAL HYPERTENSION IN COMPENSATED CIRRHOSIS

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Background: Cirrhosis decompensation, defined by clinically overt complications of portal hypertension, portends a sharp reduction in survival. A hepatic venous pressure gradient (HVPG) of 10 mmHg or more, termed clinically significant portal hypertension (CSPH), is associated with an increased risk of decompensation. This risk can be mitigated by initiation of non-selective beta blockers in patients with compensated cirrhosis (CC) and CSPH. Therefore, it is crucial to diagnose CSPH in patients with CC. Due to the invasiveness of HVPG measurement, liver stiffness measurement (LSM), by transient elastography (TE), and platelet count (Plt) can be used for noninvasive diagnosis of CSPH. Recent AASLD guidance suggests following the "Rule of Five" which utilizes LSM and Plt to estimate CSPH. CSPH can also be diagnosed clinically based on endoscopic and/or imaging findings. We aim to assess the accuracy of the "Rule of Five" in CC patients with clinical evidence of CSPH. **Methods:** We performed a retrospective analysis using data from a single-center cirrhosis registry to identify patients with CC. Inclusion criteria were a LSM and Plt obtained at the enrollment visit, and cross-sectional abdominal imaging and endoscopy (EGD) within 6 months of that visit. Patients with ALT > 100 U/L, or diagnoses of primary sclerosing cholangitis, heart failure, or hepatic or portal vein thrombosis were excluded. Clinical evidence of CSPH was defined by small ascites (detected by imaging), esophageal varices (EV) on EGD, or portosystemic collaterals on cross-sectional abdominal imaging. Following the "Rule of Five", CSPH detection cutoffs were set at LSM > 25 kPa or LSM 20–25 kPa with Plt < 150 k/mm³. Dichotomous variables were compared using Fisher's exact test, while continuous variables were analyzed using the two-sample t-test and Mann-Whitney U test. The primary outcome was determining the percentage of patients with clinical evidence of CSPH who did not meet the "Rule of Five" criteria for diagnosing CSPH. **Results:** A total of 306 patients with CC were identified. A total of 62 patients were excluded: ALT > 100 U/L (n=17), primary sclerosing cholangitis (n=9), and absence of LSM at enrollment (n=36). Among the remaining 244 patients, 49 (20%) had clinical evidence of CSPH, including 31 (63.3%) with EV, 22 (44.9%) with small ascites, and 3 (6.1%) with portosystemic collaterals. Of the 49 patients with clinical evidence of CSPH, only 40.8% (95% CI 27.8%–55.3%) met the "Rule of Five" criteria for ruling in CSPH. Table 1 summarizes the characteristics of patients with clinical evidence of CSPH. **Conclusion:** In our retrospective cohort study, the proposed "Rule of Five" to diagnose CSPH in patients with CC missed about 50% of patients with clinical evidence of CSPH. Our study carries the limitation of its retrospective nature, small samples size, and lack of HVPG measurement. Prospective validation of the "Rule of Five" is warranted.

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Table 1. Clinical characteristics of patients with compensated cirrhosis and clinical evidence of clinically significant portal hypertension (CSPH).

	Total (n = 49)	Meeting Rule of Five (n = 20)	Not Meeting Rule of Five (n = 29)	p-value
Age, mean ±SD	61.8 ±11.9	61.6 ±12.6	61.9 ±11.7	0.922
Female gender, n (%)	11 (22.5%)	3 (15.0%)	8 (27.6%)	0.488
Body mass index, mean ±SD	28.5 ±8.0	26.9 ±9.7	29.5 ±6.8	0.372
Missing data, n (%)		4 (20%)	2 (6.9%)	
Diabetes, n (%)	10 (20.4%)	4 (20.0%)	6 (20.7%)	1
Hyperlipidemia, n (%)	17 (34.7%)	7 (35.0%)	10 (34.5%)	1
Active alcohol use	2 (4.1%)	2 (10.0%)	0	0.162
Active smoking	2 (4.1%)	0	2 (6.9%)	0.507
Primary liver diagnosis				
- Alcohol	14 (28.6%)	7 (35.00%)	7 (24.1%)	
- NAFLD	17 (34.5%)	7 (35.00%)	10 (34.5%)	
- HCV	13 (26%)	4 (20.00%)	9 (31.0%)	
- HBV	2 (4.1%)	1 (5.00%)	1 (3.5%)	
- AIH	2 (4.1%)	0	2 (6.9%)	
- Hemochromatosis	1 (2%)	1 (5.0%)	0	
CSPH defining event.				
- Small ascites.	22 (44.9%)	9 (45.0%)	13 (44.8%)	1
- EV on EGD	31 (63.3%)	11 (55.0%)	20 (69.0%)	0.375
- Portosystemic collaterals	3 (6.1%)	2 (10.0%)	1 (3.5%)	0.559

Disclosures: Iyiad Alabdul Razzak: Nothing to Disclose, Gloria Horta: Nothing to Disclose, Xinyuan Zhang: Nothing to Disclose, Paolo Lopedote: Nothing to Disclose, Xuehong Zhang: Nothing to Disclose, Michelle Lai: Nothing to Disclose

4210 | THE FRAILTY COMPONENT OF HEPATIC ENCEPHALOPATHY – EXPLORING PHYSICAL AND COGNITIVE FUNCTION IN ADVANCED CHRONIC LIVER DISEASE

Andres Duarte-Rojo[1] Miguel Sogbe[2] Randi Wong[3] Robert Rahimi[4] Pamela Bloomer[5] Alexandra Steinberg[6] Jennifer Lai[3]

[1]Northwestern Medicine, [2]Universidad de Navarra, [3]UCSF, [4]Baylor University Medical Center, [5]UPMC, [6]Axcella Health, Inc

Background: Physical frailty and minimal hepatic encephalopathy (MHE) are common in advanced chronic liver disease (AdvCLD). Complex neuropsychometric testing has hindered routine assessment of MHE and as such, there is little data on the overlap between MHE and frailty. The Stroop EncephalApp provides a simpler method for diagnosing MHE: The QuickStroop (runs 1 and 2 of the "Off" state), which takes less than one minute to complete, offers equivalent predictive ability for MHE compared to the entire EncephalApp, which requires 10 minutes or more in patients with frailty. This study aimed to investigate the association between frailty, assessed by the Liver Frailty Index (LFI), and MHE diagnosed using the QuickStroop in patients with AdvCLD awaiting liver transplant. **Methods:** This prospective study analyzed data from 196 patients. The association between MHE and frailty assessments was evaluated using Fisher's exact test or chi-square tests as appropriate. Classification of frailty was based on established LFI score cutoffs, with "robust" <3.2, "prefrail" between 3.2 and 4.4, and "frail" ≥4.5. To understand the factors influencing poorer outcomes across various QuickStroop assessments, we employed multivariable linear regression and multivariable logistic regression models. **Results:** Most patients were males (66.3%) with a mean age of 59 years, and mean MELD 3.0 of 17 (Table 1). Forty-two percent of participants presented MHE according to QuickStroop with a trend towards poorer LFI scores when compared to non-MHE participants. Despite such minor difference in the raw LFI score, there was a higher rate of frail and a lower rate of robust subjects in the presence of MHE. Notably, on multivariable linear regression models, QuickStroop variability could only be explained by LFI (beta coefficient = 0.26 [1.44-5.03]; p<0.001) and age (beta coefficient

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= 0.15 [0.01-0.31]; p=0.033), independently of years of education, sex, ethnicity, MELD 3.0, and sodium. Further, multivariable logistic regression models found that LFI was the only variable associated with MHE (OR: 1.78; CI: 1.17-2.70; p=0.007). **Conclusion:** Our findings suggest that the LFI score captures the crucial role of psychomotor speed, particularly evident in the Off-time performance of the QuickStroop. This association helps to further link physical and neurocognitive decline in AdvCLD. The demonstrated brain-muscle relationship further supports investigating interventions targeting both physical and cognitive function in AdvCLD.

Frailty metric*	All n = 196	Patients without MHE n=114 (58.2%)	Patients with MHE n=82 (41.8%)	p value
Age	60 (53-66)	60 (51-66)	59 (54-66)	0.300
Male sex	130 (66.3%)	70 (61.4%)	60 (73.2%)	0.083
MELD 3.0	17 (12-22)	17 (12-21)	17 (14-22)	0.788
LFI, units	3.8 (3.3-4.2)	3.7 (3.2-4.1)	3.9 (3.4-4.6)	0.111
Physical frailty level				0.037
• Frail (LFI ≥ 4.5)	35 (17.9%)	14 (12.3%)	21 (25.6%)	
• Prefrail (3.2 ≥LFI < 4.5)	123 (62.8%)	74 (64.9%)	49 (59.8%)	
• Robust (LFI <3.2)	38 (19.4%)	26 (22.8%)	12 (14.6%)	
Individual components				
• Grip strength, kg	28.0 (20.0-35.3)	28.3 (20.0-35.3)	28.0 (20.1-35.8)	0.980
• Sex-adjusted grip	-0.21 (-0.8 to 0.3)	-0.1 (-0.6 to 0.4)	-0.4 (-1.0 to 0.2)	0.009
• Balance, seconds	30.0 (30.0-30.0)	30.0 (30.0-30.0)	30.0 (30.0-30.0)	0.219
• Number of patients with balance <30 seconds	15 (7.7%)	4 (3.5%)	11 (13.4%)	0.010
• Chair stands per second	0.4 (0.3-0.5)	0.4 (0.3-0.5)	0.3 (0.2-0.4)	0.219

Disclosures: Andres Duarte-Rojo: Echosens: Grant/Research Support, Miguel Sogbe: Nothing to Disclose, Randi Wong: Nothing to Disclose, Robert Rahimi: Salix: Grant/Research Support, Mallinckrodt: Grant/Research Support, Pamela Bloomer: Nothing to Disclose, Alexandra Steinberg: Axcella Therapeutics: Employee, Carmot Therapeutics: Employee, Carmot Therapeutics: Stock - publicly traded company, Jennifer Lai: Nestle Nutrition Institute: Grant/Research Support, Novo Nordisk: Consultant, Genfit: Consultant, Boehringer Ingelheim: Advisor

4211 | INCREASED EUS-GUIDED PORTAL PRESSURE GRADIENT MEASUREMENTS PREDICTS HEPATIC DECOMPENSATION IN COMPENSATED CIRRHOSIS

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Background: Endoscopic ultrasound guided portal pressure gradient (EUS-PPG) has emerged as an alternative method for obtaining direct portal pressure measurements for assessing portal hypertension. Transjugular hepatic venous portal gradient (HVPG) is currently the gold standard for measuring portal hypertension and is the basis for defining clinically significant portal hypertension, defined as ≥ 10 mmHg. Though EUS-PPG has been shown to correlate with HVPG, clinical parameters, FIB4 score, and fibrosis staging, associations with downstream clinical outcomes such as hepatic decompensation are lacking. We aimed to evaluate the utility of EUS-PPG in predicting new hepatic decompensation in patients with compensated cirrhosis. **Methods:** This was a single-center retrospective study at a tertiary endoscopy center of patients who had EUS-PPG measured from 2014 to 2023. Subjects with compensated cirrhosis without a prior decompensating event were included. A new decompensating event defined as variceal bleeding, ascites, or hepatic encephalopathy was the primary endpoint. Baseline characteristics were compared between patients with and without new decompensation. Univariate and multivariate logistic regression analyses were conducted to determine potential associations between predictors including MELD, Child-Pugh score, platelet count, and PPG, with new hepatic decompensation. **Results:** 202 patients had EUS-PPG, of which 103 had a diagnosis of cirrhosis. 66 of these patients had no prior hepatic decompensation at time of EUS-PPG and were included in the study. Median age was 62.0 (IQR 56.0-68.0) and 47% were male. Median MELD-Na was 9 (7-11) and 87.9% were Child-Pugh Class A. Etiologies of liver disease included viral hepatitis (16.7%), MASLD (45.5%), ALD (15.2%), and others (22.7%) which included AIH, PSC, and PBC. 12 patients (18%) developed new hepatic decompensation. Median PPG in the decompensated group was 10.2 mmHg (6.6-16.3) compared to 6.0 mmHg (3.0-10.0) in the compensated group. 50% of the decompensated group had PPG ≥10 mmHg, compared to 25.9% in the compensated group. In crude and adjusted analysis, PPG was found to be significantly associated with decompensation (OR 1.12, 95% CI 1.01-1.24; aOR 1.18, 95% CI 1.02-1.36). A PPG ≥10 mmHg trended towards an association with new decompensation (OR 2.86, 95% CI 0.79

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- 10.33) but was not statistically significant. **Conclusion:** In patients with compensated cirrhosis, higher EUS-PPG had a greater likelihood of new hepatic decompensation. This study supports EUS-PPG as a reliable tool for assessing portal hypertension and possibly predicting clinical decompensation.

Table: Univariate and multivariate logistic regression analyses to determine association between predictors and odds of decompensation, among patients with compensated cirrhosis

	Univariate analysis			*Multivariate analysis**		
	Odds ratio	*95% Confidence Interval*	*P-value*	*Odds ratio*	*95% Confidence Interval*	*P-value*
BMI	**1.103**	**1.015 - 1.198**	**0.021**	**1.147**	**1.015 - 1.297**	**0.028**
Platelet count (10^9/L)	0.687	0.373 - 1.264	0.227	1.114	0.580 - 2. 139	0.746
Child-Pugh Class	**6.250**	**1.295 - 30.165**	**0.023**	5.058	0.304 - 84.275	0.259
MELD-Na	1.021	0.886 - 1.177	0.775	0.962	0.720 - 1.286	0.795
NSBB Use	3.267	0.661 - 16.150	0.147	2.071	0.268 - 16.017	0.486
PPG (mmHg)	**1.121**	**1.013 - 1.239**	**0.026**	**1.179**	**1.020 - 1.363**	**0.026**
PPG ≥ 10 mmHg	2.857	0.791 - 10.326	0.109	–	–	–

* Multivariate analyses conducted controlling for all other variables in the model

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4212 | THE IMPACT OF ZINC DEFICIENCY AND NUTRITIONAL STATUS ON THE DEVELOPMENT OF OVERT HEPATIC ENCEPHALOPATHY IN CIRRHOSIS PATIENTS: A PROSPECTIVE COHORT STUDY

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Background: Overt Hepatic Encephalopathy (OHE) is a prevalent complication of cirrhosis, leading to repeated hospitalizations and readmissions. It is not simply a symptom of liver failure but may have independent pathophysiological and prognostic implications. Patients with cirrhosis and OHE have a two-fold increased risk of 1-year mortality compared to cirrhotic patients without OHE**.** This population also experiences significant malnutrition, due to metabolic, muscle, and intake alterations, leading to deficiencies in key nutrients like zinc. Zinc is crucial for enzymes involved in ammonium metabolism, and hyperammonemia is a key factor in malnutrition and OHE development. Evaluating the association between zinc deficiency and OHE could define prognosis and therapeutic objectives. Therefore, we aimed to evaluate the assess the link between zinc deficiency and development of OHE **Methods:** A prospective cohort study included patients with a diagnosis of liver cirrhosis who were followed for one year to evaluate the incidence of OHE. Serum zinc levels were measured, with levels below 60µg/dL considered low. Factors such as nutritional status (sarcopenia), were assessed using DXA (ASMI index) for muscle mass and dynamometry for muscle strength. Disease severity was evaluated using the Child-Pugh and MELD scales. Complications of the disease and zinc intake were assessed using 24-hour multi-step recalls, analyzed in the Food-Processor software. Low zinc intake was defined as below 9.4 mg/day. **Results:** A total of 109 patients were included with an incidence of OHE of 27% (n=29). Patients who developed OHE had lower serum zinc levels [50.55 ± 12.6 vs 62.36 ± 19.12, p<0.01], greater disease severity by MELD-Na [17(13-22) vs 13 (10-17), p<0.01], and a higher presence of sarcopenia [62% (n:18) vs. 37% (n:30), p = 0.02]. All patients had suboptimal zinc consumption (8.24 ± 3.80), with even lower but non-significant consumption in the OHE group. Univariate logistic regression showed zinc levels were associated with OHE development (OR: 3.65; 95% CI:1.4-9.51, P= 0.008). However, in the multivariable model, only sarcopenia (OR:3.34, 95% CI:1.23-9.04) and disease severity measured by Child–Pugh classification C (OR:18.5, 95% CI:3.10-115.98) were significantly associated with OHE. **Conclusion:** Improvement in nutritional status by preventing zinc deficiency and increasing muscle mass may be considered a potential goal to improve cognitive function in patients with cirrhosis.

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4213 | IMPACT OF INTRAVENOUS ALBUMIN INFUSION ON 28-DAY MORTALITY AND COMPLICATIONS IN PATIENTS WITH ACUTELY DECOMPENSATED CIRRHOSIS: A PROPENSITY SCORE MATCHING ANALYSIS ◆

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Background: Intravenous (IV) albumin increases effective arterial blood volume and is used to prevent acute kidney injury (AKI) and death after large-volume paracentesis (LVP) and in patients with spontaneous bacterial peritonitis (SBP). However, recent randomized trials show controversial results regarding IV albumin's effect in patients with SBP, AKI, or LVP settings. This study aimed to compare the effects of IV albumin infusion on preventing 28-day mortality, nosocomial infection, SBP, AKI, and acute-on-chronic liver failure (ACLF) in patients hospitalized with acutely decompensated cirrhosis (ADC). **Methods:** This single-center, retrospective investigation analyzed a prospective cohort ("RJH" cohort) of patients non-electively admitted for conditions such as overt ascites, active gastrointestinal bleeding, hepatic encephalopathy, bacterial/fungal infection, or jaundice. Patients with admission serum albumin concentration below 3.0 g/dL were included and stratified based on their received average weekly dose of IV albumin during hospitalization: <1.0g/kg (low), 1.0 to 1.5g/kg (medium), or >1.5g/kg (high). The primary endpoint was 28-day mortality, while secondary outcomes included nosocomial infection, SBP, AKI, ACLF, and 90-day mortality. Patients in the three treatment groups were matched using variables affecting both treatment decisions and outcomes with greedy nearest neighbor matching without replacement and a caliper width of 0.2 standard deviation. **Results:** Among 619 inpatients with ADC and baseline serum albumin <3.0g/dL, 392 (63%) received an average weekly dose of IV albumin <1.0g/kg, 166 (27%) received 1.0 to 1.5g/kg, and 61 (10%) received >1.5g/kg. Patients receiving higher doses of albumin were older, had lower baseline levels of albumin, and had higher percentages of infections on admission. After propensity score matching (PSM), 93 patients (31 in each group) were analyzed with no significant differences in age, gender, baseline albumin, MELD score, comorbidity, etiology of cirrhosis, complications of cirrhosis, presence of infection, and ACLF. The median weekly doses of IV albumin were 57.8 (37.9, 67.78), 67.5 (64.9, 69.9), and 116.3 (101.4, 171.7) g in the low, medium, and high dose groups, respectively (p<0.001). After 28 days, 3 (9.7%), 2 (6.5%), and 4 (12.9%) patients died in the low, medium, and high dose groups, respectively (p=0.691). The incidence of nosocomial infection, SBP, AKI, ACLF during hospitalization, and 90-day mortality were similar among the three groups (all p>0.05). **Conclusion:** In this propensity score matching analysis, IV albumin showed no clear effect on preventing 28-day mortality, nosocomial infection, AKI, or ACLF in patients admitted for ADC.

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4214 | ECHOCARDIOGRAPHIC PARAMETERS OF DIASTOLIC CIRRHOTIC CARDIOMYOPATHY AND POST-LIVER TRANSPLANT OUTCOMES IN PATIENTS WITH CHRONIC LIVER DISEASE AND ACUTE ALCOHOL ASSOCIATED HEPATITIS

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Background: Diastolic cirrhotic cardiomyopathy (d-CCM) is characterized by diastolic dysfunction in patients without prior heart disease, and significantly impacts morbidity during and after liver transplant (LT). Yet, the echocardiographic detection of CCM can be complicated by a state of volume overload and low systemic vascular resistance. As patients with acute alcohol-associated hepatitis (AAH) and chronic liver disease (CLD) have different hemodynamics, we assessed the prevalence of d-CCM in these patient groups and evaluated whether d-CCM criteria are predictors of post-LT ICU stay duration. **Methods:** We retrospectively analyzed patients who

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completed inpatient LT evaluation from 10/2017-8/2021. Patients were categorized as “AAH” or “CLD” based on their LT eligibility. Diastolic dysfunction was identified through echocardiographic measures, including septal e’ < 7 cm/s, lateral e’ < 10 cm/s, E/e’ > 14, LAVI > 34 ml/m², TR velocity > 2.8 m/s, deceleration time (DT)> 240 ms, and isovolumetric relaxation time (IVRT) > 90 ms. Post-LT outcome measures were: post-LT ICU length of stay (LOS), total hospital LOS, and number of hospital readmissions within 1-year after LT. Univariate and multivariate backward linear regression were utilized to evaluate predictors of ICU LOS. **Results:** CCM parameters were evaluated in 15 AAH and 15 CLD patients; all patients had preserved ejection fraction and there was no difference in MELD-Na across the two groups. CLD patients were more likely to meet d-CCM criteria (p=0.08) and showed a trend towards longer ICU LOS (p=0.15). There were no differences in total hospital LOS, and number of hospital readmissions post-LT between the two groups. Multivariate linear regression showed liver disease etiology (p=0.011), age (p=0.004), MELD-Na score (p=0.008), and E/e’ > 14 to be significant predictors of ICU length of stay (see table 1). **Conclusion:** Patients with chronic liver disease were more likely to meet criteria for d-CCM. Chronic liver disease diagnosis and E/e’ > 14 were predictors of longer ICU length of stay, indicating that decreased cardiac compliance may be associated with worse outcomes. Instead, higher MELD scores may result in prioritized and aggressive operative care, leading to a shorter ICU stay. As AAH patients have a unique hemodynamic profile, current echocardiographic parameters may not capture CCM in these patients. Larger studies are needed to assess whether new metrics like left ventricular longitudinal strain and strain rate can better detect abnormal echocardiographic patterns in AAH patients.

Table1. Linear regression model for predictors of ICU length of stay for both AAH and CLD patients undergoing LT.

variable	Univariate analysis			Multivariate analysis		
	B coefficient	95% CI for B coefficient	p value	B coefficient	95% CI for B coefficient	p value
age	-0.1	(-0.5, 0.3)	0.62	-0.7	(-1.1, -0.2)	**0.004**
sex	1.1	(-9.4, 11.7)	1.0			
Etiology (AAH vs CLD)*	7.2	(-2.8, 17.2)	**0.15**	15.74	(3.9, 27.6)	**0.011**
EF (%)	- 0.1	(-1.0 – 0.8)	1.0			
MELDNa $_{\text{listed}}$	-0.7	(-1.4 – 0.04)	0.06	-0.85	(-1.46, -0.24)	**0.008**
Vasopressors $_{\text{before LT}}$	10.0	(-3.3 – 23.3)	0.16			
New afib $_{\text{before LT}}$	10.0	(-3.3 – 23.3)	0.20			
New RRT $_{\text{before LT}}$	0.63	(-9.8, 11.1)	0.90			
e’ lateral < 10 OR e’ septal < 7	2.1	(-10.1, 14.3)	0.73			
E/e’ > 14	9.0	(-4.4, 22.5)	**0.14**	13.78	(1.94, 25.61)	**0.024**
TR velocity > 2.8 m/s	4.5	(-7.8, 16.7)	1.0			
LAVI > 34 mL/m²	4.5	(-7.1,16.1)	0.43			
DT > 240 ms	10.2	(-0.4, 20.7)	**0.06**			
IVRT > 90 ms	-0.87	(-13.1, 11.3)	0.89			
d-CCM (3 out of 4 criteria)**	5.3	(6.7, 17.3)	0.38			

*AAH was coded as 0, CLD was coded as 1.
**d-CCM is officially defined as the presence of at least three of the following four criteria: e’ velocities < 7 cm/s medially or < 10 cm/s laterally, an E/e’ ratio > 14, left atrial volume index (LAVI) > 34 ml/m², and a tricuspid regurgitation (TR) velocity > 2.8 m/s); d-CCM diagnosis was not included in the multivariate model as it includes several criteria.

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4215 | SIMPLYING SARCOPENIA ASSESSMENT: THE POTENTIAL UTILITY OF CYSTATIN C TO SERUM CREATINE RATIO AS A SIMPLE LABORATORY PREDICTOR OF OUTCOMES AMONG PATIENTS WITH ADVANCED CIRRHOSIS

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Background: Despite clear influence on transplant-related outcomes, a widely available, easily repeatable laboratory test of sarcopenia remains elusive. The relative values of serum creatinine (sCr) and cystatin C may serve this purpose due to the relatively high influence of muscle mass on sCr and absence of such influence

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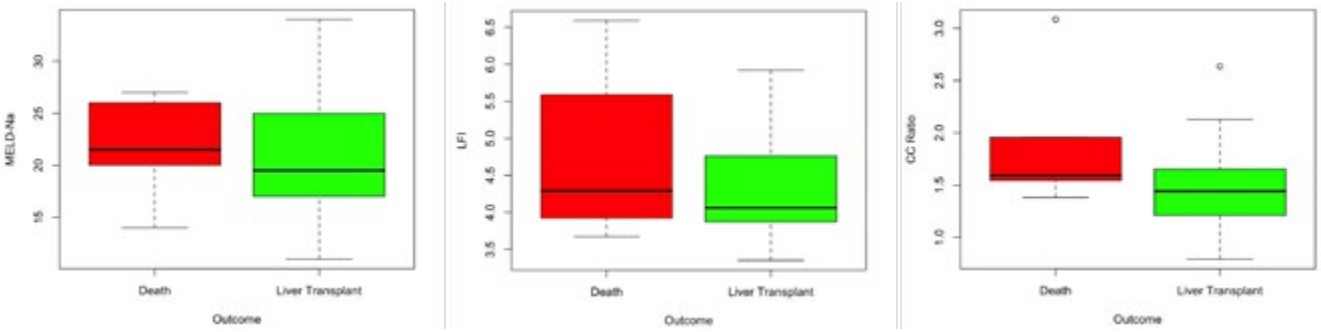
on cystatin C. We propose the “CC ratio” (cystatin C/sCr) as a potential marker of a patient’s muscle mass and sought to assess the association of this ratio with outcomes among patients evaluated for liver transplantation. We compared associations with MELD-NA and Liver Frailty Index (LFI) to assess the relative utility of the CC ratio. **Methods:** All subjects referred for liver transplant evaluation at our center from 2019-2023 with cystatin C measured as part of standard medical care were eligible for inclusion. We elected to compare patients experiencing either of the two vital extremes of transplant evaluation – death or liver transplantation. We evaluated the association of CC ratio, LFI, and MELD-Na with these outcomes. We also assessed for independent association of CC ratio with these outcomes using a MV regression model including age, sex, BMI, and MELD-Na as covariates. **Results:** We identified 47 patients meeting the criteria above. We found a positive association between CC ratio and risk of death that better distinguished the two outcomes than did LFI or MELD-Na (see Figure). Using MV regression, we found CC ratio to the be the only independently associated variable among those listed above with the outcome of liver transplantation (aOR 0.13, 95% CI (0.014-0.75), P=0.03). **Conclusion:** This preliminary assessment of the relevance of CC ratio suggests it holds potential to improve prediction of important outcomes among patients with advanced cirrhosis. It may be valuable tool beyond standard metrics (e.g. MELD-Na and LFI). Larger, prospective, studies would be needed to better assess this utility and avoid potential biases of this smaller, retrospective sample.



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4216 | INCREASED RISK OF *CLOSTRIOIDES DIFFICILE* INFECTION IN PATIENTS WITH CIRRHOSIS ON SECONDARY PROPHYLAXIS FOR SPONTANEOUS BACTERIAL PERITONITIS: A RETROSPECTIVE MATCHED COHORT STUDY

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Background: Patients with a prior episode of spontaneous bacterial peritonitis (SBP) are at very high risk of recurrence. AASLD suggests long-term prophylaxis with daily norfloxacin or ciprofloxacin to prevent SBP recurrence. Concerns exist about the safety of long-term antibiotics, given the higher risk of *Clostrioides difficile* infection (CDI). This is heightened in patients with cirrhosis, who have poorer outcomes with CDI compared to the general population. We aimed to evaluate the risk for CDI and outcomes in patients with cirrhosis on secondary prophylaxis for SBP, compared to patients with cirrhosis and ascites. **Methods:** The data were sourced from the TriNetX US Collaborative Network database from January 1, 2000, to May 29, 2024. Adult patients with cirrhosis were divided into 2 groups: Group 1 included patients with a history of SBP who were initiated on ciprofloxacin or norfloxacin, or Bactrim, i.e., patients on secondary prophylaxis for SBP. Group 2 included patients with cirrhosis and ascites, with no prior history of SBP, and not on the aforementioned antibiotics, i.e., patients not on SBP prophylaxis.Propensity score matching (PSM) was used to create matched cohorts for age, hepatic encephalopathy (HE), esophageal variceal (EV) bleeding, hepatorenal syndrome (HRS), and MELD-Na parameters, including sodium, bilirubin, INR, and need for dialysis. The analysis included outcomes between 90 to 730 days after the index event (SBP for Group 1 and ascites for Group 2).The estimated risk for each outcome was reported as a percentage. Odds ratio (OR) and 95% confidence intervals (95% CI) were used to report

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associations. **Results:** 28,681 patients with cirrhosis on SBP prophylaxis, and 99,178 patients with cirrhosis and ascites were identified. After PSM, 26,964 patients were included in two groups. The MELD-Na lab parameters for Group 1 were significantly higher than Group 2, which means that these patients could have more advanced disease. However, the rates of HE, EV bleeding, HRS, and dependence on dialysis were comparable in the two groupsPatients in Group 1 had higher rates of CDI (OR 1.733, 95% CI 1.65-1.92, p=0.00), recurrent CDI (OR 1.548, 1.18-2.03, p=0.001), toxic megacolon (OR 3.367, 1.72-6.60, p=0.00), hospitalizations (OR 1.153, 1.11-1-19, p=0.00) and mortality (OR 1.197, 1.14-1.26, p=0.00), than matched controls in Group 2. **Conclusion:** Patients with cirrhosis on secondary prophylaxis for SBP have higher rates of CDI and recurrent CDI than matched controls. This necessitates a risk-benefit discussion before initiating SBP prophylaxis in these patients. Given that CDI in patients with cirrhosis has worse outcomes, the decision to start SBP prophylaxis needs to be thoroughly considered.

Table 1: Propensity score matching of variables, and outcomes

	On SBP prophylaxis (n=26,964)	Not on SBP prophylaxis (n=26,964)	p-value (before matching)	p-value (final cohort)
Age in years	57.5± 17.2	57.1± 16	0.749	0.024
Hepatic encephalopathy	6.6%	6.8%	<0.001	0.940
Hepatorenal syndrome	3.5%	3.4%	<0.001	0.777
Esophageal varices with bleeding	3.3%	3.2%	<0.001	0.546
Dependence on dialysis	9.2%	9.1%	<0.001	0.940
Creatinine	1.4± 1.9	1.5± 1.9	<0.001	<0.001
Bilirubin	1.7± 3.9	2.1± 4.2	<0.001	<0.001
INR	2.3± 7.2	1.4± 1.7	<0.001	<0.001
Sodium	137.3± 4.7	137.0± 4.3	<0.001	<0.001
Outcomes				
Event	**Risk in patients on SBP prophylaxis**	**Risk in patients not on SBP prophylaxis**	**Odds ratio (95% CI)**	**p-value**
C. diff infection	3.7%	2.2%	1.733 (1.563-1.922)	<0.000
Recurrent *C. diff* infection	0.5%	0.3%	1.548 (1.183-2.025)	0.001
Toxic megacolon	0.1%	0.00%	3.367 (1.717-6.602)	<0.000
Hospitalizations	39.4%	36.1%	1.153 (1.114-1.194)	<0.000
Critical care services	11.2%	11.2%	0.993 (0.942-1.408)	0.806
Severe sepsis	6.8%	4.9%	1.396 (1.298-1.502)	<0.000
Acute kidney failure	22.3%	16.6%	1.201 (1.153-1.252)	<0.000
Mortality	13.7%	11.7%	1.197 (1.137-1.259)	<0.000

Disclosures: Vinay Jahagirdar: Nothing to Disclose, Waqas Rasheed: Nothing to Disclose, Hanna Blaney: Nothing to Disclose, Hassam Ali: Nothing to Disclose, Jasmohan Bajaj: Bausch: Grant/Research Support, Sequana: Grant/Research Support, Cosmo: Grant/Research Support, Grifols: Grant/Research Support

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4217 | SIMVASTATIN INEFFECTIVE IN IMPROVING HEPATOPULMONARY SYNDROME IN CIRRHOSIS PATIENTS (HEPSIM TRIAL) – RESULTS OF A DOUBLE-BLIND RANDOMIZED CONTROLLED TRIAL [NCT05187715]

Akhil Deshmukh[1] Shiv Kumar Sarin[1] Vishnu Girish[1] CHITRANSHU VASHISHTHA[1] Sukriti Baweja[1] Tushar Madke[1] Rahul khajuria[1] Harsh Tevethia[2]

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Background: Hepatopulmonary syndrome (HPS), marked by liver disease, intrapulmonary vascular dilatations, and abnormal oxygenation, causes significant morbidity and mortality. Despite liver transplantation being the only cure, no standardized medical therapy exists. This study hypothesizes that simvastatin, a hydrophobic statin with anti-inflammatory properties, can improve oxygenation in HPS. A six-month randomized controlled trial will evaluate the efficacy and safety of simvastatin for HPS treatment. **Methods:** This double-blind, randomized, placebo-controlled trial was conducted from 2022 to 2024 and included forty-five patients aged 18-70 years with HPS (diagnosed by chronic liver disease with portal hypertension, arterial hypoxemia (PaO2 < 80 mm Hg or an alveolar-arterial oxygen gradient > 15 mm Hg), and evidence of intrapulmonary vascular dilatations (IPVDs) demonstrated by contrast-enhanced echocardiography or lung perfusion scans), randomized in a double-blind manner to 2:1 into two arms using the IVR system: Simvastatin 40mg and placebo; the study duration was six months. The primary outcome was an improvement in the PaO2 gradient. At 6 months, differences in PaO2 improvement were observed: a complete response was an increase of ≥10 mm Hg, a partial response was an increase of ≥5 but <10 mm Hg, and no response was an increase of <5 mm Hg. The code was broken after the completed follow-up of the last patient. **Results:** Among the forty-five patients, 89% were male, the most common etiologies alcohol-associated (47.5%) followed by metabolic (44.5%). Both the Simvastatin (n=30) and placebo (n=15) groups were similar in demographic and clinical parameters at baseline, including MELD score, oxygenation parameters, and severity of HPS. The primary objective of response (PaO2 ≥5mm of Hg) was seen in 7(15.5%) patients; 1(2.2%) and 6(13.3%) patients in placebo and simvastatin group respectively(p=0.25). No significant differences were observed in the severity of HPS, liver fibrosis, HVPG change, inflammatory markers (TNF-alpha, S1P levels), pulmonary function tests, or 6-minute walk distance between the groups at the end of 6 months. Adverse events were observed in 5(11%) patients in simvastatin and 2(4%) in placebo arm(p=0.84). **Conclusion:** Simvastatin did not significantly improve oxygenation or other clinical outcomes in patients with hepatopulmonary syndrome compared to placebo. Adverse events were similar between the simvastatin and placebo groups.

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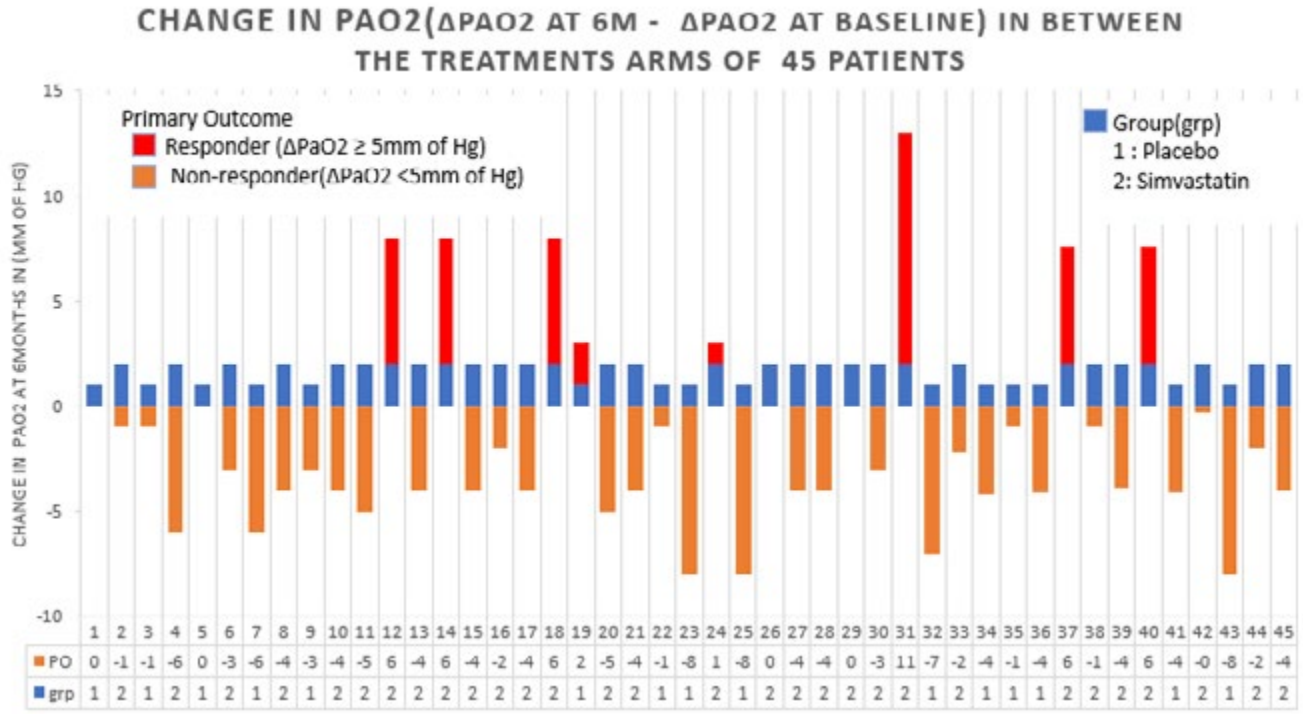

Disclosures: Akhil Deshmukh: Nothing to Disclose, Shiv Kumar Sarin: Nothing to Disclose, Vishnu Girish: Nothing to Disclose, CHITRANSHU VASHISHTHA: Nothing to Disclose, Sukriti Baweja: Nothing to Disclose, Tushar Madke: Nothing to Disclose, Rahul khajuria: Nothing to Disclose, Harsh Tevethia: Nothing to Disclose

4218 | PROGNOSTIC PERFORMANCE OF THE NEW MELD 3.0 SCORE, RELATIVE TO MELD, MELD-NA AND CLIF-C AD SCORES FOR EMERGENT VS NON-EMERGENT TIPS CREATION ◆

Kenkichi Michimoto[1] Leonardo Campos[1] James Palmer[1] Brandon Tran[1] Willscott Naugler[2] Khashayar Farsad[1]

[1]Oregon Health & Science University, [2]Oregon Health And Science University

Background: To evaluate the prognostic performances of the Model for End-Stage Liver Disease (MELD), MELD-Na, MELD 3.0, and Chronic Liver Failure-Consortium Acute Decompensation (CLIF-C AD) scoring systems in patients with cirrhosis who underwent transjugular intrahepatic portosystemic shunt (TIPS) creation in emergent and non-emergent situations. **Methods:** From September 2005 to May 2022, consecutive cirrhotic patients undergoing TIPS creation (429 patients; mean age 54.8±11.0 years; 243 male) were divided into emergent (*n*=98) and non-emergent (*n*=331) cases. Emergent TIPS were defined by placement for uncontrolled or recurrent variceal bleeding within 24 hours of initial endoscopy or primary placement for variceal bleeding with shock. The MELD, MELD-Na, MELD 3.0, and CLIF-C AD scores before the procedure were evaluated as predictors of 30-day, 3-month, and 1-year mortality after TIPS creation using receiver operating curves (ROC) to examine the area under the curve (AUC). DeLong's test was used to compare each ROCs, and *P* values <0.05 was set as statistically significant. **Results:** For emergent TIPS cases, CLIF-C AD demonstrated highest prognostic value across the follow-up period (30-day, AUC 0.886, 95% confidence interval [CI] 0.803-0.969); 3-month, AUC 0.869, 95% CI 0.784-954; 1-year, AUC 0.758, 95% CI 0.679-0.876) with a cutoff value of 54.8. CLIF-C AD was significantly superior to MELD and MELD-Na at 3 months (*P*=0.0497 and 0.0376, respectively), and comparable in performance to MELD 3.0 (*P*≥0.05). For non-emergent TIPS, MELD 3.0 showed the highest prognostic value throughout the follow-up period (30-day, AUC 0.818, 95% CI 0.721-0.915, cutoff≥19; 3-month, AUC 0.753, 95% CI 0.675-0.831, cutoff≥17; 1-year, AUC 0.773, 95% CI 0.708-0.837, cutoff≥17). MELD 3.0 showed significantly superior prognostic performance to MELD and MELD-Na at 3-month (*P*=0.0124 and *P*<0.01, respectively) and 1-year (*P*<0.01). MELD 3.0 also demonstrated significant improvement compared to CLIF-C AD at 1 year (*P*=0.0219) **Conclusion:** CLIF-C AD and MELD 3.0 both outperformed MELD and MELD-Na as prognostic

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indicators of survival after TIPS. MELD 3.0 had a similar performance as CLIF-C AD in emergently placed TIPS (mostly cases of variceal bleeding), whereas MELD 3.0 outperformed all other scores for non-emergent TIPS (most of which were placed for refractory ascites).

Disclosures: Kenkichi Michimoto: Nothing to Disclose, Leonardo Campos: Nothing to Disclose, James Palmer: Nothing to Disclose, Brandon Tran: Nothing to Disclose, Willscott Naugler: Nothing to Disclose, Khashayar Farsad: Nothing to Disclose

4219 | PENTOXIFYLLINE IMPROVES HEPATOPULMONARY SYNDROME - RESULTS OF A DOUBLE-BLIND RANDOMISED PLACEBO-CONTROLLED TRIAL [PENHELPS TRIAL] [NCT05373134]

Vishnu Girish[1] CHITRANSHU VASHISHTHA[1] Manoj Sharma[1] Akhil Deshmukh[1] Tushar Madke[1] Rahul khajuria[1] Arun Sood[1] Arvind Tomar[1] Sukriti Baweja[2] Shiv Kumar Sarin[1]

[1]Institute of Liver and Biliary Sciences, [2]Institute of Liver and Biliary Sciences, New Delhi

Background: Hepatopulmonary syndrome (HPS), a triad of liver disease, intrapulmonary vascular dilatations (IPVD), and abnormal oxygenation, has liver transplantation as the only advocated definitive therapy. Pentoxifylline (PTX) has shown promise in animals and anecdotal human studies. Low sphingosine-1-phosphate (S1P) levels are linked to severity of HPS. We investigated the efficacy and safety of PTX in improving pulmonary oxygenation and inflammatory cytokines in HPS **Methods:** This double-blind, randomised, placebo-controlled trial included 40 consecutive patients with liver cirrhosis and hepatopulmonary syndrome (HPS), were randomised using block randomization and IVR, to receive either PTX (400 mg) or placebo, thrice daily (n=20 each). Screening was based on clinical suspicion or oxygen saturation, and diagnosis was confirmed using saline contrast echocardiography and arterial blood gas (ABG).HPS was classified based on PaO2 [mild [PaO2 ≥ 80 mmHg, moderate 60–79 mmHg, severe 50–59 mmHg, and very severe, if < 50 mmHg]. The primary outcome was the proportion of patients achieving a decrease in A-aPO2 gradient by more than 5 or to an absolute value less than 15mmHg at 6 months. **Results:** Forty patients [age 51.5±8.5yrs, 36(90%) males, alcohol-associated (47.5%) and MAFLD(44.5%), MELD 17±3.64] were randomized to PTX or placebo. Baseline demographic parameters and PaO2 (70.6 ± 6.4 vs 70.2 ± 8.2 mmHg, p = 0.89) were comparable between groups. PTX group had 19 moderate (95%) and 1 severe (5%); placebo group had 2 mild (10%), 17 moderate (85%), and 1 severe (5%) HPS cases. Intention to treat analysis showed, at 6 months, 6(30%) patients in the pentoxifylline group and 1(5%) in the placebo group improved, achieving a reduction of A-aPO2 gradient by more than 5mmHg (p=0.04). Compared to placebo, PTX improved in PaO2 at 6 months (ΔPaO2 = 1.75[-2.95to4.7] mmHg in PTX vs -2.45[-0.2to-4.2] mmHg, p = 0.02 in placebo). The change in AaPO2 at 6 months showed more reduction in PTX vs placebo(ΔAaPO2 = 0.36[-5.23to5.14] mmHg vs 2.83[0.2to4.85] mmHg, p = 0.04). The proportion of patients who worsened (increase of A-aPO2>5mmHg) was significantly higher in the placebo group (Fig1). Changes in cytokine levels were greater in PTX than placebo {IL-6 and TNF-α [-6.75 (-23.5 to -0.9) vs. -12.6 (-56.5 to -2.9) (p=0.14), and -5.9(-12.5to-1.9) vs. -0.50(-7.3to3.9) (p=0.2)] and change in S1P[-14 (-39to -4) vs. -31.30 (-65.1 to 9.7), p=0.43], but the differences were not significant. Echo-based grading of intrapulmonary shunting was poorly correlated with the severity of HPS. Pentoxifylline was well tolerated; 3 (15%) patients required dose reduction to 800mg/day, mostly due to nausea and headache **Conclusion:** This is the first RCT showing improvement in HPS with long-term pentoxifylline administration. Pentoxifylline was well tolerated in our cohort and should be recommended for treating cirrhosis patients with HPS

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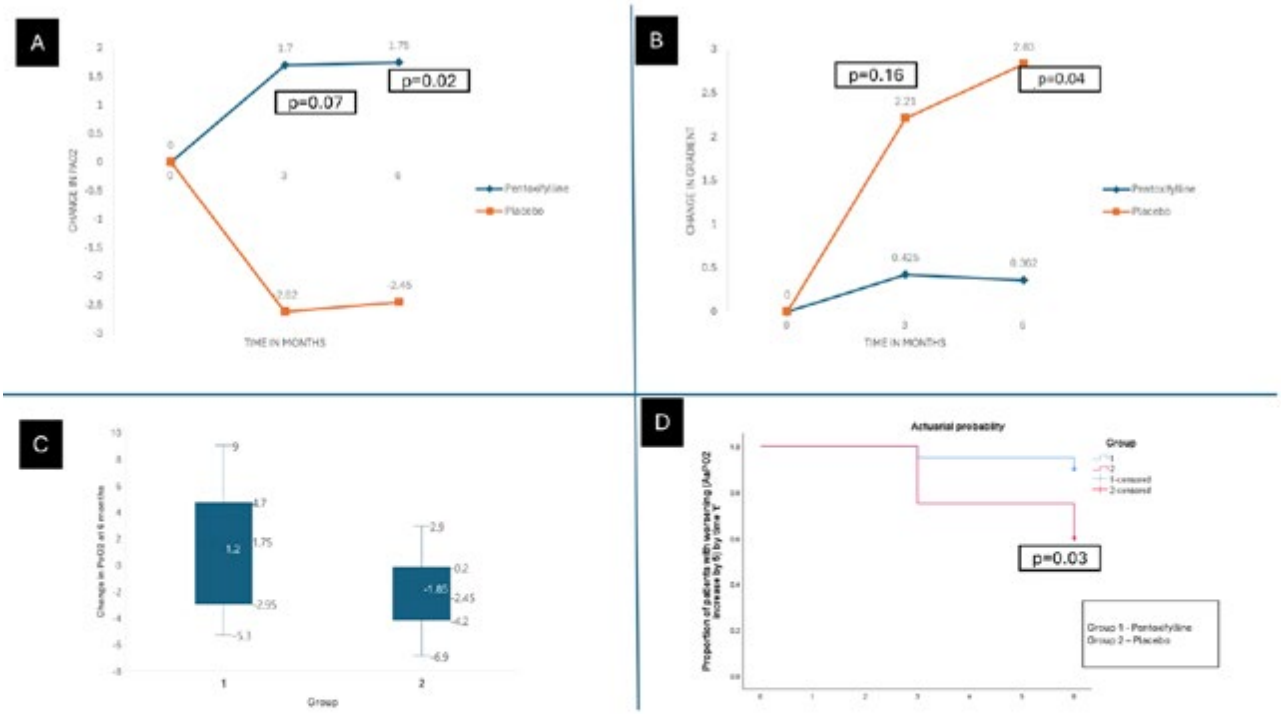

Fig 1: Median absolute change in PaO2 (mm Hg) (A) and AaPO2 gradient (mm Hg) (B) from baseline to 3 and 6 months in patients receiving pentoxifylline (blue) or placebo (orange); p values are for comparison with baseline. Stem-and-leaf plots (C) of ΔPaO2 6 months show that pentoxifylline group (group 1) showing predominantly stable and increased PaO2 with less variability, whereas placebo group (Group 2) exhibited more significant decreases in PaO2. Actuarial probability of time to worsening of HPS (increase in AaPO2 by more than 5m Hg) ; survival analysis comparing two groups revealed a significant difference in survival distributions (Log Rank p = 0.029)

Disclosures: Vishnu Girish: Nothing to Disclose, CHITRANSHU VASHISHTHA: Nothing to Disclose, Manoj Sharma: Nothing to Disclose, Akhil Deshmukh: Nothing to Disclose, Tushar Madke: Nothing to Disclose, Rahul khajuria: Nothing to Disclose, Arun Sood: Nothing to Disclose, Arvind Tomar: Nothing to Disclose, Sukriti Baweja: Nothing to Disclose, Shiv Kumar Sarin: Nothing to Disclose

4220 | OUTCOMES OF TIPS IN NATIVE AMERICANS: A SINGLE-CENTER EXPERIENCE

Theresa Riley[1] Jason Patel[1] Brandon Klor[1] Pooja Rangan[1] Mike Fallon[1] Shoma Bommena[2]

[1]University of Arizona, [2]Banner University Med. Center Phoenix, University of Arizona

Background: Chronic liver disease is a leading cause of death among American Indians and Alaska Natives. Yet, there exists a crucial knowledge gap in the outcomes of transjugular intrahepatic portosystemic shunt (TIPS), a procedure that helps mitigate portal hypertension, in this under-represented group. We aimed to assess the association between the Native American (NA) race and TIPS outcomes. **Methods:** We performed a retrospective analysis of adult patients who underwent TIPS at our tertiary care center between 2018 and 2022. Demographics, including self-reported race, patient characteristics, and TIPS details were collected. The primary outcome was mortality. We used the Mann-Whitney and chi-square tests to compare continuous and categorical variables between Native Americans and other races. The association of race with mortality was assessed using adjusted Cox proportional hazards and logistic regression models. **Results:** 286 patients were included. The median MELD of the cohort was 13. The median age of the cohort was 57 years, of whom 62% were males. 28 (9.8%) of these patients identified themselves as Native Americans. Compared to other races, Native Americans were significantly younger (48.5 vs. 58.5, P=0.002), had higher MELD (17 vs. 12, P=0.006), had more frequent

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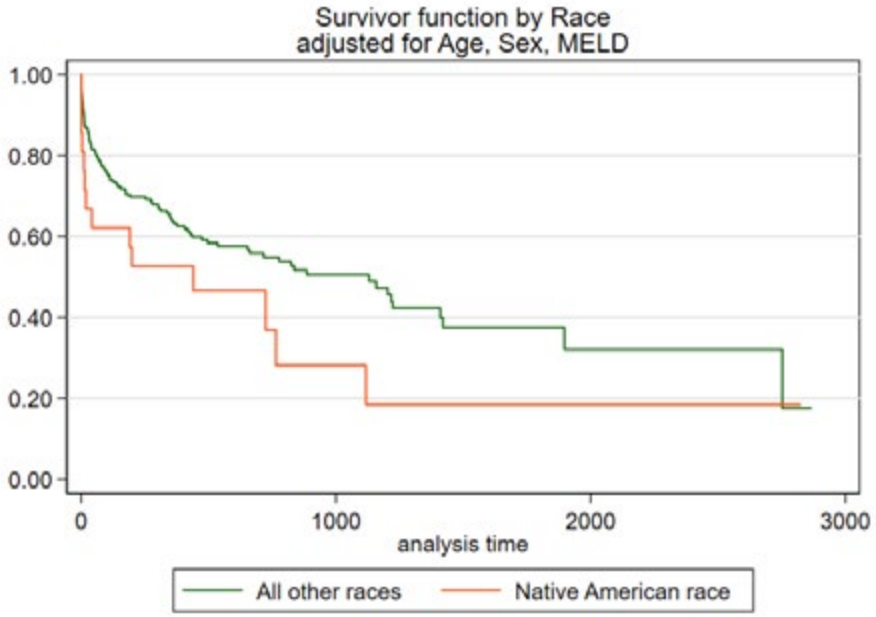
alcohol-related liver disease (71% vs. 42%, P=0.03), more hepatorenal syndrome (HRS) (14% vs. 4%, P=0.02), and less beta-blocker use (7% vs. 33%, P= 0.005). After adjusting for age, gender, body mass index, MELD, etiology of cirrhosis, and TIPS indications, Native Americans had increased odds of 30-day post-TIPS mortality (adjusted OR 2.8; 95% CI, 1.02, 7.9; P=0.046), and higher hazards of transplant-free mortality (adjusted HR 2.3, 95% CI 1.23, 4.38; P=0.009) (Figure). Cause of death differed with significantly higher bleeding complications, liver failure, and significantly lower infectious complications among the Native Americans. **Conclusion:** We observed significant racial differences in age, beta-blocker use, liver disease etiology, and severity among patients who underwent TIPS. Despite adjusting for these factors, Native Americans had 2.8 times increased odds of early 30-day mortality and 2.3 times greater risk of long-term transplant-free mortality following the TIPS procedure. Further research is needed to understand the pathophysiological mechanisms driving racial disparities in post-TIPS mortality to enhance liver disease care for all racial groups.



Disclosures: Theresa Riley: Nothing to Disclose, Jason Patel: Nothing to Disclose, Brandon Klor: Nothing to Disclose, Pooja Rangan: Nothing to Disclose, Mike Fallon: Nothing to Disclose, Shoma Bommena: Nothing to Disclose

4221 | IMPACT OF SARCOPENIA ON COMPLICATIONS OF LIVER CIRRHOSIS: A NATIONAL INPATIENT SAMPLE STUDY (2018-2020)

Hima Varsha Voruganti[1] Pratiksha Moliya[2] Medha Rajamanuri[3] Hamsika Moparty[4] Rohit Sekandlapuram[4]

[1]North Alabama Medical Center, [2]Jamaica Hospital Medical Center, [3]Southern Illinois University, [4]The Brooklyn Hospital Center

Background: Sarcopenia, the loss of muscle mass and function, is linked to higher morbidity in long-term liver disease. Common complications in cirrhotic patients include ascites, hepatic encephalopathy, variceal bleeding, infections, kidney dysfunction, and liver cancer. Sarcopenia, a prevalent complication, worsens these conditions and reduces quality of life. Despite its impact, nutritional status is often overlooked due to the complexity of assessments in cirrhotic patients. We aim to investigate the impact of sarcopenia on other complications of liver cirrhosis. **Methods:** We queried the National Inpatient Sample (NIS) 2018-20 to collect data for all adult hospitalizations >18 years with diagnosis of cirrhosis and further classified these hospitalizations into hospitalizations with and without sarcopenia or generalized muscle atrophy with appropriate ICD10 codes. Multivariate regression analysis was performed to study the impact of sarcopenia taking Hepatorenal syndrome (HRS), Spontaneous bacterial peritonitis (SBP), Portal vein thrombosis (PVT), Hepatocellular carcinoma (HCC), variceal bleeding, Portal Hypertension (PHTN), Hepatopulmonary syndrome (HPS) as primary outcomes.

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Results: There were a total of 8825 adult hospitalizations in 2018-20 with a diagnosis of liver cirrhosis and sarcopenia or generalized muscle atrophy with a mean age of 59. Multivariate regression analysis revealed these adult hospitalizations with cirrhosis and sarcopenia or muscle atrophy had higher odds of HRS [OR 2.86, p <0.00], SBP [OR 2.16, P <0.00], PVT [1.82, P <0.00], HCC [OR 1.36, P <0.003], PHTN [2.03, P <0.00], and HPS [5.34, P<0.00] than the adult hospitalizations with cirrhosis and without sarcopenia or generalized muscle atrophy. **Conclusion:** Evidence shows that sarcopenia significantly affects clinical outcomes in liver cirrhosis patients. As a common side effect, it leads to higher hospitalization rates and lower quality of life. Methodical assessment and correction of sarcopenia can reduce hospital stays for these patients.

COMPLICATION	ODDS RATIO	CI	P value
HRS	2.86	2.44 - 3.35	< 0.00
SBP	2.16	1.80 - 2.60	< 0.00
PVT	1.82	1.46 - 2.27	< 0.00
HCC	1.36	1.10 - 1.66	< 0.003
PHTN	2.03	1.80 - 2.28	< 0.00
HPS	5.34	3.50 - 8.16	< 0.00

*Adjusted for obesity, hyperlipidemia, smoking, alcohol, hypertension, diabetes and chronic kidney disease.

Disclosures: Hima Varsha Voruganti: Nothing to Disclose, Pratiksha Moliya: Nothing to Disclose, Medha Rajamanuri: Nothing to Disclose, Hamsika Moparty: Nothing to Disclose, Rohit Sekandlapuram: Nothing to Disclose

4222 | IMMUNOMETABOLIC PROFILING OF THE HEPATIC ENCEPHALOPATHY MODEL MOUSE

Michitaka Matsuda[1] *Tatsuya Kanto*[1]

[1]*National Center for Global Health and Medicine*

Background: Hepatic encephalopathy (HE) is a severe neurological complication of chronic liver injury, of which diagnostic and therapeutic options are limited. The metabolic dysfunction and neuroinflammation synergistically develop HE, however, its pathophysiology has not been fully investigated. The study aims to elucidate the immune and metabolic signature of early- and late-stage HE by using HE model mice with a multi-omics approach. **Methods:** The C57BL/6 mice were subjected to bile duct ligation (BDL) to develop HE and evaluated at POD10 (early stage) and POD20 (late stage). Neurobehavioral alteration and cerebral blood flow (CBF) were quantified by the open field test (OFT) and the laser Doppler-based imaging system, respectively. The brain, liver, and plasma were used for targeted metabolomics, bulk RNA-seq analysis, and CyTOF single-cell immune profiling. Brain transcriptome data from patients (GSE41919) was used to compare with the mouse data. **Results:** BDL mice presented decreased locomotor activity, increased anxiety, and lowered CBF, all of which are clinical features observed in HE patients. The neurological and physiological alterations started from the early stage and deteriorated in the late phase. Transcriptomic analysis of mouse and human brain defined 26 genes upregulated in HE, including IL1b, Tnf, and Icam1. Pathway analysis indicated microglial activation and vascular dysfunction is an underlying pathophysiology of HE. CyTOF Immune profiling of the mouse brain defined CD11b+ Ly6C+ CD44+, CD69+ SiglecF- microglial/macrophage subpopulation is infiltrating into the brain at the early stage, which contributes to IL1b and Tnf production. Metabolomics defined 17, 27, and 29 metabolites increased in the brain, liver, and plasma of the HE model, respectively. Among these, 7 metabolites of bile acid (e.g. TCA) and arachidonate (e.g. 11,12-EET, 11,12-DHET) were commonly observed in both brain, liver, and plasma, suggesting these molecules are associated with HE development through the liver-brain axis. Notably, these metabolites rise from the early stage while hyperammonemia was not observed until the late stage. **Conclusion:** The BDL

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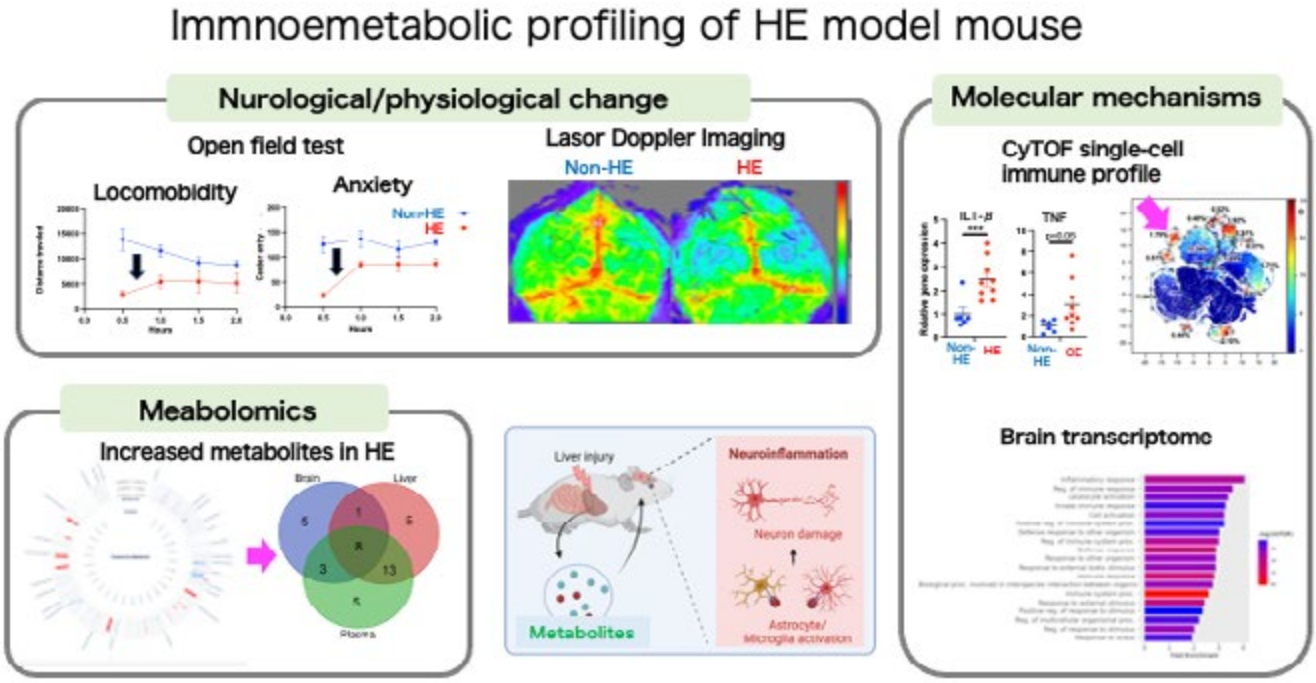
model shares common features of HE including neurobehavioral change, lowered CBF, and neuroinflammation. Neuroinflammation and vascular dysfunction are suggested to be involved in the pathogenesis. Non-ammonia metabolites such as TCA, 11,12-EET, and 11,12-DHET can be a potential biomarker and therapeutic target of HE, especially early stage of HE.



Disclosures: Michitaka Matsuda: Nothing to Disclose, Tatsuya Kanto: Nothing to Disclose

4223 | EXPLORING NON-ACUTE DECOMPENSATION OF CIRRHOSIS AND ITS LONG-TERM TRAJECTORIES AND OUTCOME

Parminder Kaur[1] Nipun Verma[2] Pratibha Garg[3] Aishani Wadhawan[4] Samonee Ralmilay[4] Rohit Nadda[5] Sahaj Rathi[5] Arka De[5] Madhumita Premkumar[3] SUNIL TANEJA[5] Ajay Duseja[3]

[1]Postgraduate Institute of Medical Education and Research, [2]Post Graduate Institute of Medical Education and Research, [3]Postgraduate Institute of Medical Education & Research, [4]Post Graduate Institute of Medical Education and Research, Chandigarh, India, [5]Postgraduate Institute of Medical Education and Research, Chandigarh, India

Background: Non-acute decompensation (NAD) of cirrhosis is a newly recognized entity with limited knowledge of outcomes and long-term trajectories. Mortality over 20% meets UNOS criteria for liver transplantation. This study addresses the heterogeneity and outcomes in NAD patients. **Methods:** In this single-center prospective cohort study, we included patients with NAD who had no acute decompensation in the past 3 months. Patients were followed for 12 months with assessments at 3-month intervals for their outcomes and trajectories. **Results:** We recruited 231 NAD patients with a median age of 48 years (IQR: 42-56). The majority (99%) were male, with alcohol as the most common cirrhosis etiology (87.7%). 80% patients had prior history of decompensations in the past (69.3% past AD). Median MELD and CTP scores were 13.17 (IQR: 10.72-16.59) and 7 (IQR: 6-9), respectively. The most common phenotype at enrolment was ascites (55%), followed by ascites and jaundice (A+J) (24.7%), jaundice alone (3.9%), and HE with ascites and/or jaundice (2.1%). 33 (14.3%) patients had only coagulopathy and portal hypertension with no decompensation at enrolment. At 12-month follow-up, 38% of patients developed single or multiple episodes of AD/ACLF (16.6% at 0-3 months, 17.2% at 3-6 months, 23.3% at 6-9 months, and 11.5% at 9-12 months), while 62% remained in NAD. AD/ACLF episodes were significantly higher in those with jaundice (62.5%) and/or ascites (47.8%) compared to ascites alone and/or HE (p=0.026). NAD persistence was notable in those without prior decompensation. 12-month overall survival was 84.8%. Cumulative survival was lower in patients who developed AD/ACLF (54.8%) compared to those who did not

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(93.15%, p<0.001), irrespective of enrolment phenotype (p=0.522). However, survival was lower in patients who developed AD/ACLF during follow-up among all phenotypes at enrolment: with ascites (54.1% vs. 91.5%), with jaundice (25% vs. 100%), and with ascites+jaundice (60.1% vs. 95.8%). A generalized mixed model revealed lower occurrence of AD, ascites and HE in survivors during 3-6 months, 6-9 months, and 9-12 months (p<0.001). Univariable Cox regression identified significant predictors of 12-month survival: MELD score, creatinine, albumin, INR at enrolment, and AD/ACLF at any time interval at follow-up. Significant predictors of cumulative incidence of AD/ACLF/Death included present decompensation, present phenotypes (ascites, jaundice, A+J, A+J+HE) MELD score, bilirubin, creatinine, and CTP class. **Conclusion:** In outpatient settings, ascites is the most common decompensation in NAD patients, followed by jaundice. Phenotype at presentation does not impact outcomes; however, subsequent AD/ACLF occurrence drives mortality. Vigilant monitoring and management are crucial, and consideration for liver transplantation is warranted.

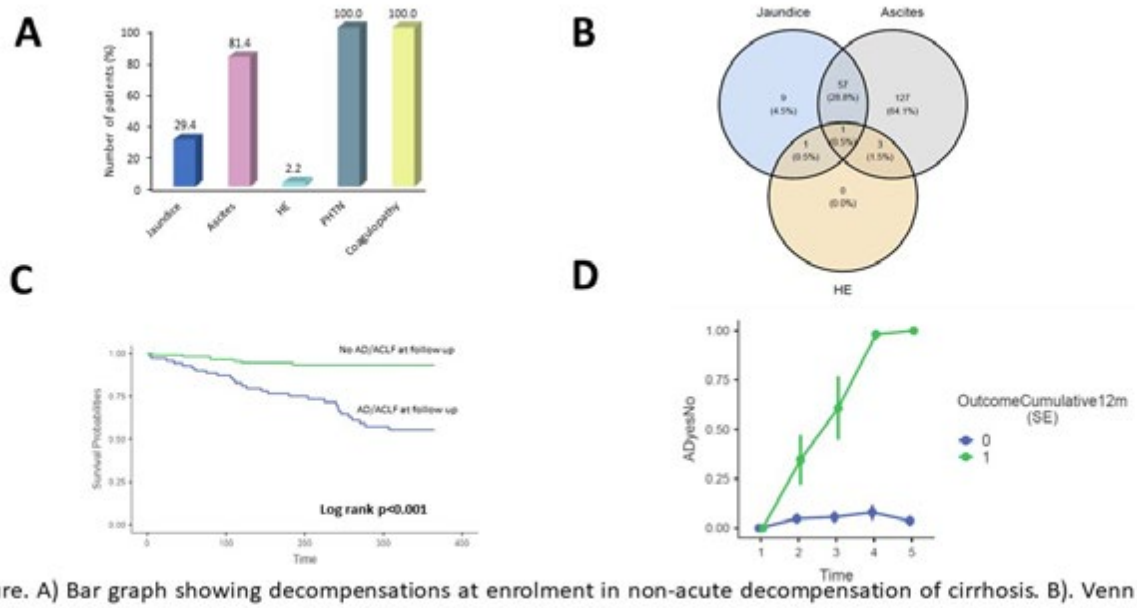

Figure. A) Bar graph showing decompensations at enrolment in non-acute decompensation of cirrhosis. B). Venn diagram showing phenotypes of NAD patients according to the decompensations. C) Kaplan Meier curve showing reduced cumulative 12 month survival in NAD patients who developed AD (54.8%) at follow-up compared to others who didn't develop AD/ACLF (93.15%) D) A generalized mixed model revealed lower occurrence of AD in survivors during 3-6 months, 6-9 months, and 9-12 months (p<0.001).

Disclosures: Parminder Kaur: Nothing to Disclose, Nipun Verma: Nothing to Disclose, Pratibha Garg: Nothing to Disclose, Aishani Wadhawan: Nothing to Disclose, Samonee Ralmilay: Nothing to Disclose, Rohit Nadda: Nothing to Disclose, Sahaj Rathi: Nothing to Disclose, Arka De: Nothing to Disclose, Madhumita Premkumar: Nothing to Disclose, SUNIL TANEJA: Nothing to Disclose, Ajay Duseja: Nothing to Disclose

4224 | INTRAVASCULAR VOLUME OVERLOAD IN PATIENTS WITH DECOMPENSATED CIRRHOSIS AND ASSOCIATED WITH A LOWER TOLERABILITY OF INTRAVENOUS ALBUMIN AND WORSE OUTCOMES, A SINGLE CENTER, PROSPECTIVE, COHORT STUDY ◆

Luis Alejandro Rosales Renteria Jose-David Prieto-Nava[1] David Aguirre-Villarreal[2] Cesar Salcido-Yañez[1] Adrian Sandez-Araiza[1] Giovanni Francisco Perez-Roa[1] Ignacio García Juárez[3] Maria Sarai Gonzalez Huezo[1]

[1]Centro Medico ISSEMyM Toluca, [2]Instituto Nacional de Ciencias Medicas y Nutricion, [3]The National Institute of Medical Science and Nutrition

Background: Cirrhosis is a multisystemic and dynamic disease, and decompensated patients are particularly hemodynamically labile. Among those that require hospitalization, there are three main indications for albumin use: Large Volume Paracentesis (LVP), SBP, and AKI/HRS-AKI. The established dosing that guidelines recommend of intravenous albumin comes from preclinical studies from 1978and 1986 and the reasoning behind

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its use is rather arbitrary. Point of care venous ultrasound (VExUS) is a dynamic, easily reproducible method that can classify intravascular overload in 4 stages (0, 1, 2, 3). Our aim was to compare the tolerability of intravenous albumin in patients with decompensated cirrhosis (DC), according to their VExUS score**. Methods:** Single center, prospective, cohort study, which included all patients with DC that had an indication for intravenous albumin use (LVP, AKI w/ ascites, SBP), and were hospitalized at our a tertiary care institution in Metepec, Mexico, from March 1st, 2023, to April 1st, 2024. Every patient underwent a VExUS protocol, that was performed at baseline, 24 hours and 48 hours. Main clinical, biochemical, and sociodemographic characteristics were collected. Patients were subdivided according to their VExUS group. The prevalence of cirrhotic cardiomyopathy was similar in all groups. The primary outcome was overall mortality during index hospitalization. Secondary outcomes were respiratory failure, worsening of intravenous congestion by VExUS (defined as a score of VExUS 2 or 3), development of HRS-AKI, resolution of SBP, development of variceal hemorrhage (VH), acute-on-chronic liver failure (ACLF) and hospitalization time. **Results:** A total of 118 patients were included. The predominant gender was male in both groups (52.4% and 51%) with a median of 55 years of age in the whole sample, the main etiology of cirrhosis being MASLD (51 vs 53%). The main indication for albumin administration was AKI (57%), followed by LVP (27%) and SBP (16%) . At baseline, 45 patients were classified as VExUS 0 (38%), 22 as VExUS 1 (18.6%), 23 as VExUS 2 (19%), and 28 as VExUS 3 (23%). Mortality during index hospitalization was only statistically significant for patients classified as VExUS 2 (11/23) (RR 5.2 95% CI [1.312, 21.093], p<0.001, NNH 2.58), and VExUS 3 (22/28), (RR 8.64, 95% CI [2.273, 32.859], p<0.001, NNH 1.43). For secondary outcomes, 12/23 (52%) patients in the VExUS 2 group and 20/28 patients in the VExUS 3 group (71%), developed respiratory failure. The prevalence of HRS-AKI was only significantly increased in the VExUS 3 group 17/28 (60%), RR 6.678571, 95% CI [1.723, 25.880], p=0.003, NNH 1.93. No statistically significant difference was found in other variables. **Conclusion:** Among patients with DC and an indication for IV albumin use with intravascular volume overload, as identified by the VExUS protocol, a conventional albumin dosage showed a greater mortality, respiratory failure and development of HRS-AKI.



Figure 1: Mortality during index hospitalization based on intravascular congestion score (VExUS).
Mortality during index hospitalization was only statistically significant for patients classified as **VExUS 2 (11/23) (RR 5.2 95% CI [1.312 , 21.093], p<0.001, NNH 2.58),** and **VExUS 3 (22/28), (RR 8.64, 95% CI [2.273 , 32.859], p<0.001, NNH 1.43).**

Disclosures: Luis Alejandro Rosales Renteria: Nothing to Disclose, Jose-David Prieto-Nava: Nothing to Disclose, David Aguirre-Villarreal: Nothing to Disclose, Cesar Salcido-Yañez: Nothing to Disclose, Adrian Sandez-Araiza: Nothing to Disclose, Giovanni Francisco Perez-Roa: Nothing to Disclose, Ignacio García Juárez: Nothing to Disclose, Maria Sarai Gonzalez Huezo: Nothing to Disclose

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4226 | DIFFERENTIAL IMMUNE RESPONSE IN CIRRHOTICS WITH COVID-19 ASSOCIATED MUCORMYCOSIS COMPARED TO COVID-19 AND HEALTHY CONTROLS

PRATIBHA RAMCHANDRA KALE[1] *Nirupma Trehanpati*[1] *Gayatri Ramakrishna*[1] *Hamda Siddiqui*[1] *Shasthry S M*[1]

[1]*Institute of Liver and Biliary Sciences*

Background: Steroid therapy, use of antibiotics, hyperglycemia, large diabetic/prediabetic population are associated with cirrhosis and also postulated causes for massive surge in Mucormycosis in COVID-19 patients. Most studies focused on epidemiology and underlying causes, however difference in immunological response was largely understudied. We investigated immune responses in cirrhotic patients with COVID-19 with or without associated mucormycosis (CAM) and healthy adults. **Methods:** Prospectively collected cirrhotic patients with CAM (n=8), COVID-19 without CAM (n=8) and healthy volunteers (n=8)were assessed for plasma cytokines Neutrophils, monocytes and immune cells using cytokine bead arrayand multicolour flow cytometry,Oxidative burst activity,Neutrophils extracellular traps (NETosis)assay after stimulation with LPS and IL-8using fluorescent microscope.Laboratory and demographic data were obtained from hospital information system. **Results:** CAM Patients had significantly higher frequency of smoking (6 (75%) vs. 3 (37.5%); p<0.001), hypertension (7 (87.5%) vs. 4 (50%); p=0.04) and diabetes mellitus (8 (100%) vs. 3(37.5%); p<0.001) than the COVID-19 cirrhotic group. CAM patients with mucormycosis had significantly higher random blood sugar and lower leucocytes, hemoglobin level and raised ESR. Higher mortality was seen in CAM (8, 100%) compared to COVID-19 (5, 62.5%). CAM patients had significantly decreased circulating monocytes compared to COVID-19 patients. There was no significant change in the number of classical monocytes ($CD14^{++}16^{-}$) and HLADR positivity on them in the CAM as well as COVID-19 patients compared to healthy controls. Increase in the intermediate ($CD14^{++}16^{+}$) and non-classical ($CD14^{+}CD16^{++}$) subsets were observed in CAM. Dual expression of HLA-DR and CCR2 was increased in CAM, whereas both HLA-DR and CX3CR1 was increased in the COVID-19 andCAM. ROS producing activity was severly hampered in CAM. Total T cells were significantly low compared to COVID-19 patients. $CD4^{+}$ and$CD8^{+}$ T cell compartment was significantly skewed in CAM. However, activated B cells were significantly decreased in both patient groups compared to healthy. B cell-activating factor receptor (BAFFR) and proliferation-inducing ligand (APRIL) expressing B cells were significantlyincreased in CAM with increased PDL1 expression and NETosis compared to without CAM. **Conclusion:** An increase in the intermediate and non-classical monocyte subsets have a higher activity in response to infection and produce proinflammatory cytokines suggesting increased inflammatory damage.Neutrophils having ability to mix and extrude their DNA and fungicidal molecules creating NET-like structures called NETosis, was significantly higher in CAM, suggesting increased neutrophil lysis. Differential immune response in cirrhosis with CAM, cause increased cellular damage and increased mortality in these patients.

Disclosures: PRATIBHA RAMCHANDRA KALE: Nothing to Disclose, Nirupma Trehanpati: Nothing to Disclose, Gayatri Ramakrishna: Nothing to Disclose, Hamda Siddiqui: Nothing to Disclose, Shasthry S M: Nothing to Disclose

4227 | β2-ADRENERGIC RECEPTOR PROMOTES EARLY HEPATOCYTE PROLIFERATION MEDIATED BY TUMOR NECROSIS FACTOR-α PRODUCTION IN NEUTROPHILS AFTER PARTIAL HEPATECTOMY

Katherine Po Sin Chung[1] *Kyurae Kim*[2] *Sung Eun Choi*[1] *Min Jeong Kim*[2] *Eunmi Lee*[2] *Kwang Woo Lee*[2] *WON-IL JEONG*[2]

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Background: Liver regeneration is a sophisticated process orchestrated by complex signaling pathways. Despite of growing research on neurological signals in liver pathophysiology, role of neurological involvement in liver regeneration remains elusive. Here, we investigate the prompt impact of catecholamines and beta-2 adrenergic receptor (ADRB2) at early stage of liver regeneration following partial hepatectomy. **Methods:** Blood catecholamine levels and peripheral blood mononuclear cells were evaluated in human liver donors before and after surgery. In addition, public RNA sequencing datasets from liver resection patients were analysed to compare adrenergic receptor expression levels. To advance understanding of the regeneration process, a

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45% partial hepatectomy (PHx) was performed in wild-type (WT) and *Adrb2* knockout mice at early timepoints (30 and 60 minutes). Serum biochemistry was analysed whereas liver tissues were subjected to bulk RNA sequencing, qRT-PCR, immunostaining, flow cytometry analyses and GeoMx spatial transcriptome. For further mechanistic studies, primary hepatocytes, Kupffer cells and neutrophils were stimulated *in vitro* with a specific ADRB2 agonist and evaluated its role in regeneration. **Results:** From our in-house liver donor data, elevated levels of blood catecholamine were observed at one day after surgery along with surge infiltration of tumour necrosis factor (TNF)-α producing neutrophils. Transcriptomic analysis of public datasets from liver resection patients demonstrated notable upregulation of *ADRB2* expression and enriched TNF signalling pathway after two hours of surgery. Likewise, serum catecholamine levels and hepatic neutrophils with TNF-α production increased at 30 minutes and sustained at 60 minutes after PHx in WT mice. Subsequent bulk RNA sequencing analysis of liver tissue revealed *Adrb2* upregulation along with enrichment of TNF signalling pathway, which were confirmed by western blot and qRT-PCR. *In vitro* stimulation of ADRB2 in primary hepatocytes and neutrophils, showed upregulated *Cxcl1* and *Tnf* expression, respectively. Interestingly, proliferating hepatocytes and migrated neutrophils were mainly observed at hepatic mid-zone area in PHx-operated liver. GeoMx spatial transcriptomics also demonstrated up-regulation of *Adrb2*, *Tnf* target genes and proliferation related markers at zone 2 of PHx-operated liver tissues compared to sham controls. All these findings were abolished in *Adrb2* knockout mice. **Conclusion:** Taken together, catecholamines may stimulate ADRB2 in hepatocytes and neutrophils to promote hepatocyte proliferation in early liver regeneration. This finding may provide novel insights in facilitating liver regeneration through activation of neurological signalling pathway.

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4228 | NOVEL MECHANISMS OF TFEB NUCLEAR IMPORT AND EXPORT BY CAMP SIGNALING

Saumya Bhatt[1] *Micah Schott*[1]

[1]*University of Nebraska Medical Center*

Background:
Transcription factor EB (TFEB) plays a key role in fatty liver disease, regulating lysosome biogenesis, cellular energy homeostasis, and autophagy. Its activity depends on its cytosolic vs. nuclear localization, controlled by phosphorylation/dephosphorylation of specific residues. Phosphorylation at various serine residues by different kinases can either inhibit or activate TFEB. For instance, mTOR and GSK3β phosphorylation near its N-terminus (Ser211, Ser134) inhibit nuclear import and activity, while PKC phosphorylation at the C-terminus (Ser462, Ser463, Ser467, Ser469) stabilizes TFEB and promotes nuclear import. Notably, a phosphorylation motif for cAMP-dependent PKA at Ser467 (RRxS) was identified, but the effect of cAMP-PKA signaling on TFEB remains unexplored. We aim to elucidate the interplay between cAMP/PKA signaling and TFEB, focusing on its implications for subcellular localization. **Methods:** To investigate the subcellular localization of TFEB upon cAMP stimulation, we used western blot analysis on nuclear and cytoplasmic fractions, as well as fluorescence microscopy of AML12 hepatocytes, primary hepatocytes, and HeLa cells stably expressing TFEB-GFP. Cells were treated with cAMP agonists (10uM FSK + 0.5mM IBMX) in the presence and absence of the PKA inhibitor H89 (50uM). In addition, TFEB-GFP was analyzed by phospho-mass spectrometry following isolation by GFP-Trap agarose beads (Chroma). **Results:** We find that stimulation of cAMP/PKA signaling leads to the rapid nuclear import of TFEB into the nucleus in hepatocytes and HeLa cells stably expressing TFEB-GFP. cAMP-induced TFEB import appears to be transient, as TFEB is exported back to the cytoplasm by 8 hrs of treatment. Surprisingly, treatment with the PKA inhibitor H89 does not prevent cAMP-induced TFEB acute nuclear import, but appears to inhibit TFEB's nuclear export at later time points. This finding suggests the possibility that cAMP itself may facilitate acute TFEB nuclear import, but PKA activity may be crucial for nuclear export, possibly through a secondary mechanism. The effect of cAMP stimulation on all other TFEB phosphorylation sites suggested several phospho-peptides that were elevated following Fsk/IBMX treatment at 30 min but not in cells treated with the PKA inhibitor H89. Collectively, these data implicate the role of the cAMP-PKA pathway in regulating TFEB phosphorylation and subcellular localization. **Conclusion:** In this study, we uncover that cAMP/PKA stimulation triggers rapid but temporary TFEB nuclear import in hepatocytes and HeLa cells. Interestingly, the PKA inhibitor H89 doesn't block cAMP-induced nuclear import but prevents acute nuclear export, indicating cAMP facilitates import while PKA is crucial for export. However, further studies are imperative to

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determine the precise role of these signaling mediators in TFEB transcriptional activity during fatty liver disease and TFEB nuclear import and export.

Disclosures: Saumya Bhatt: Nothing to Disclose, Micah Schott: Nothing to Disclose

4229 | REPURPOSING PROTONIX TO ENHANCE EFFICIENCY OF DOXORUBUCIN IN HCC TREATMENT

Susmita Dey[1] *Dola Das*[1] *Ehsan Fayazzadeh*[1] *ABRAHAM LEVITIN*[1]

[1]*Cleveland Clinic*

Background: Hepatocellular carcinoma (HCC) treatment is a challenge primarily due to underlying conditions of liver disease and development of therapy resistance by cancer cells. Although new generation therapies have advanced treatment approaches, there are several infringements due to lack of accurate tumor response assessment and immune tolerant nature of liver. Chemoembolization directed at DNA damage and cell death still remains the fundamental choice, but drug resistance by cancer cells limits the drugs' long term effectiveness. The limited success rate and higher rate of resurgence due to therapy resistance demands further research into improved HCC treatment. **Methods:** Patient derived primary cells, rat N1S1 and Morris cell lines were used. Cell invasion assay was performed using Trevigen's culture coat 24 well BME cell invasion assay kit. Western blot analysis done as per standard protocol Co-IP was performed using Pierce CoIP kit and kit specified protocol was followed. Blots were developed and analyzed using Odyssey CLX Infrared Imager (LI-COR Biosciences, Lincoln, USA).Cell viability and cytotoxicity was measured using Cell Titer 96 (AQ) one solution cell proliferation assay kit from Promega. Statistical analysis was done where all values represent means ± SEM. Random-effects logistic regression models was fit to each cell line to evaluate the effect of treatment. A significance level of 0.05 was applied. Proc GLIMMIX in SAS version 9.2 was used for statistical analysis. **Results:** We observed that Protonix, a proton pump inhibitor, enhanced efficiency of doxorubicin as measured by increased cytotoxicity in human and rat HCC cells. HSP70 expression increased in HCC cell and tissue as measured by western blot analysis. Although APE-1 expression was not increased significantly it maybe stabilized by HSP70 leading to increased endonuclease activity. HSP70 interacts with proteins through its ATPAse domain and ATPase activity was heightened in rat HCC tissue. CHIP assay demonstrated that HSP70 formed a complex with APE1 in N1S1HCC cells. Protonix - a proton pump inhibitor used along with doxorubicin in HCC cell culture lead to increased cell death demonstrating enhanced efficiency of doxorubicin. **Conclusion:** We demonstrated that doxorubicin used in presence of Protonix induced cytotoxicity in both rat HCC and patient derived primary HCC cells. Use of HSP70 specific ATPase inhibitor will further confirm the role of HSP70 associated ATPase activity in stabilizing APE-1 and modulating endonuclease activity. Further testing of the drug combination in preclinical models is required to establish clinical applications.

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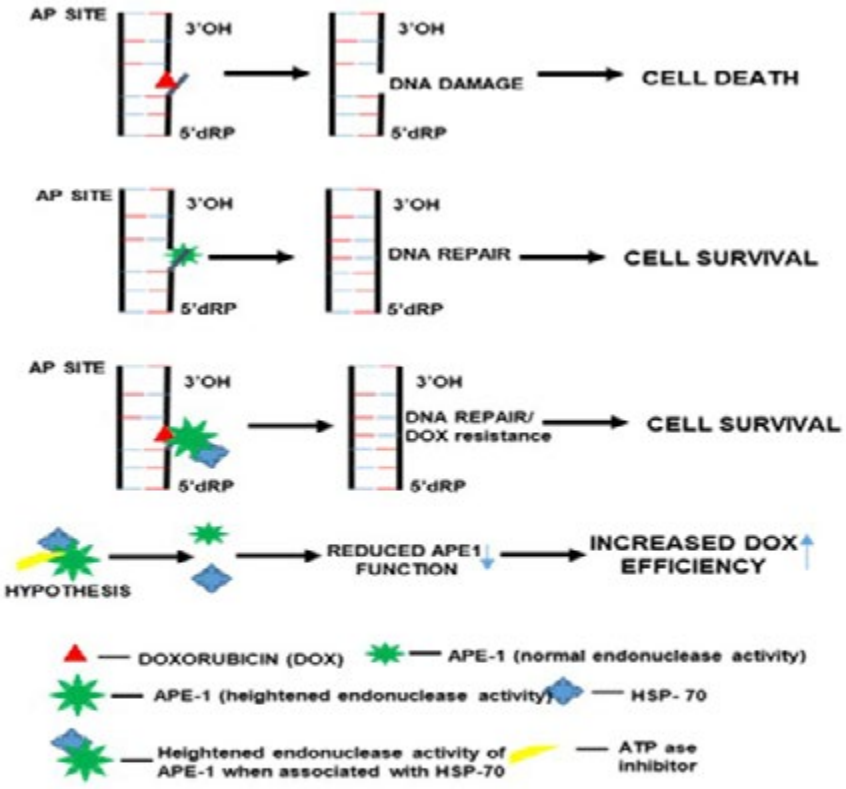

Schematic representation of the mechanism of drug resistance in HCC cells – a central role of HSP70 and APE-1 at the base excision DNA repair axis

Disclosures: Susmita Dey: Nothing to Disclose, Dola Das: Nothing to Disclose, Ehsan Fayazzadeh: Nothing to Disclose, ABRAHAM LEVITIN: Nothing to Disclose

4231 | *SCHISTOSOMA MANSONI* EGG ANTIGENS DRIVE HEPATIC AND COLONIC METABOLIC ACTIVITY VIA THE INSULIN/IGF-1R RECEPTOR

Verena von Buelow[1] *Frederik Stettler*[2] *Merle Rudke*[2] *Victoria Wirth*[2] *Ricarda Soelter*[2] *Gabriele Schramm*[3] *Christoph Grevelding*[2] *Martin Roderfeld*[2] *Elke Roeb*[2]

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Background: Schistosomiasis is a parasitic infection which globally affects more than 250 million people. There is compelling evidence that schistosome eggs, but not the adult worms evoke major tissue damage. *S. mansoni* eggs induce metabolic exhaustion and a redox imbalance, which is critical for hepatocellular DNA integrity. However, it is still unclear, how egg antigens transmit the signal into hosts´ cells. In the present study, we investigated whether *S. mansoni* egg antigens control metabolic activity of hepatocytes and enterocytes via the insulin/IGF-1 receptor. **Methods:** Markers of Insulin/IGF-1R signaling were analyzed in *S. mansoni*-infected mice by *RT-PCR* array, western blotting and immunohistochemistry (IHC). Functional experiments were performed in human hepatic and colon epithelial cell lines using western blotting and AP-1 promotor activity assay. **Results:** *S. mansoni* infection promoted a strong induction of *Igf2*, *Dok*, *Aebp1*, *Leptin* and *Akt3* gene expression with *Serpine1* most strongly upregulated. In contrast, infection caused a decrease in *Sos1*, *Irs1* and *Gck* gene expression with *G6pc* most strongly downregulated. Moreover, hepatic insulin/IGF-1R activation was pronounced in perigranulomatous hepatocytes. Mechanistic experiments using the insulin/IGF-1R inhibitor BMS 536924 revealed *S. mansoni* egg antigen-dependent activation of the insulin/IGF-1R signaling cascade including the activation of the proto-oncogene c-Jun. **Conclusion:** We demonstrated that *S. mansoni* soluble egg antigens cause the activation of insulin/IGF-1R signaling in murine and human hepatocytes and enterocytes which led to

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an inhibition of gluconeogenesis. Therefore, *S. mansoni* soluble egg antigens might improve insulin sensitivity. The activation of insulin/IGF-1R signaling could be a mechanism how the parasite eggs cover their energy supply from host cells. Nevertheless, the activation of insulin/IGF-1R is a double-edged sword as the concurrent activation of the proto-oncogene c-Jun might be involved in morbidity.

Disclosures: Verena von Buelow: Nothing to Disclose, Frederik Stettler: Nothing to Disclose, Merle Rudke: Nothing to Disclose, Victoria Wirth: Nothing to Disclose, Ricarda Soelter: Nothing to Disclose, Gabriele Schramm: Nothing to Disclose, Christoph Grevelding: Nothing to Disclose, Martin Roderfeld: Nothing to Disclose, Elke Roeb: Nothing to Disclose

4232 | REGULATION OF LIPID DROPLETS BY ENDOSOMAL SORTING COMPLEXES IN LIVER STEATOSIS

Delia Omar[1] *Nourhan Mostafa*[1] *Mathilda Willoughby*[1] *Micah Schott*[1]

[1]*University of Nebraska Medical Center*

Background: Lipid droplets (LDs) are metabolically active fat storage organelles playing fundamental roles in cellular and energy homeostasis. LDs are central for Metabolic Dysfunction Associated Steatotic Liver Disease (MASLD), which is marked by LD accumulation within hepatocytes. MASLD is strongly associated with cardiovascular diseases, which is known to be the principal cause of death in those patients. LD catabolism is accomplished partially by lipophagy process, however the molecular mechanisms by which LDs selected for lipophagy remains unclear. Several yeast studies showed that a family of proteins known as the Endosomal Sorting Complexes Required for Transport “ESCRT” involved in the lipophagy process. However, the regulation of lipophagy by ESCRT proteins within mammalian hepatocytes has not been investigated. Understanding the mechanisms underlying hepatic LD accumulation and degradation to discover potential therapies for targeting MASLD and improving cardiovascular health is of great interest. **Methods:** RNAi screening of the 45 known ESCRTs and ESCRT adaptors was performed in Hep3B hepatoma cells as well as Hela cells. Total LD area was assessed by staining with the LD marker LipidTOX Green using high-content microscopy and batch quantification using Cell Profiler. Preliminary data identified the critical role of ESCRT proteins (Hrs and CHMP2A) in LD breakdown, where LD levels increased upon siRNA knockdown. Surprisingly, the RNAi screening identified two ESCRT candidates (CHMP7, CHMP1A) that may play novel roles in LD biogenesis, where LD levels decreased upon siRNA knockdown. **Results:** siRNA knockdown was performed using AML12 cells to explore the effect of ESCRT proteins (Hrs, CHMP7) on LD levels. Hrs knockdown significantly increased total LD area, LD size and number. Also, siHrs perturbed LD catabolism after loading cells with oleic acid. CHMP7 knockdown remarkedly decreased total LD area and LD size. Additionally, we found remarkable CHMP7 localization to endoplasmic reticulum, the site of LD biogenesis, after co-transfecting Hep3B cells with GFP-labeled CHMP7, which may suggest a potential role of CHMP7 in LD formation. **Conclusion:** Specific ESCRT family members play diverse roles in lipophagy and LD biogenesis within mammalian hepatocytes. Promising results showed that ESCRT proteins (Hrs, CHMP2A) play a critical role in LD breakdown, while ESCRT candidates (CHMP7 and CHMP1A) play novel role in LD biogenesis. This defines the crucial role of ESCRT family members in LD regulation within mammalian hepatocytes for the first time.

Disclosures: Delia Omar: Nothing to Disclose, Nourhan Mostafa: Nothing to Disclose, Mathilda Willoughby: Nothing to Disclose, Micah Schott: Nothing to Disclose

4233 | MIR-122 DELIVERED BY HEPATOCYTE EXTRACELLULAR VESICLES PROMOTES FERROPTOSIS IN HEPATIC STELLATE CELLS

Xinlei Li[1] *Sherri Kemper*[1] *David Brigstock*[1]

[1]*Nationwide Children’s Hospital*

Background: miR-122 is mainly produced by hepatocytes, constitutes 70% of total hepatic miRNAs, and regulates cholesterol and iron homeostasis. Here we show that miR-122 induces ferroptosis in HSC, a novel mechanism which likely contributes to previously described anti-fibrotic actions of hepatocyte EVs. **Methods:** EVs were purified from 48-hr conditioned medium of AML-12 hepatocytes and analyzed by small RNA-seq. LX2

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HSC were incubated with AML-12 EVs for 48 h and with erastin for the last 24 h prior to measuring viability with AlamarBlue. LX2 cells were transduced with lentivirally-expressed miR-122 or scramble sequence to generate stable LX2-miR-122 or LX2-miR-NC cells. LX2 parental, LX2-miR-NC, or LX2-miR-122 cells were treated with erastin, RSL-3, FIN56, or incubated in cystine-depleted medium to induce ferroptosis, along with inhibitors of apoptosis, necroptosis, or pyroptosis. Intracellular ferrous iron levels were measured with FerroOrange. Wildtype (WT), 5'mut, or 3'mut miR-122 mimic was transfected into LX2 cells, followed by erastin treatment. GPX4 and GRP78 were detected in LX2-miR-122 cells by RT-qPCR or Western blot. Ferroptosis was measured by shRNA or antagonist-mediated downregulation of GPX4 or GRP78. **Results:** miR-122 was the most abundant of 156 miRs in AML-12 EVs. Erastin-induced LX2 cell death was exacerbated by pre-treatment with AML-12 EVs. Transient or stable expression of miR-122 in LX2 cells led to drastic ferroptosis induced by erastin, RSL-3, FIN56, or cystine depletion. miR-122-induced cell death was reversed by inhibitors of ferroptosis but not of apoptosis, necroptosis, or pyroptosis. Intracellular ferrous iron level was significantly elevated by miR-122. WT or 3' GU-rich motif mutant but not 5' seed sequence mutant miR-122 mimic maintained the ability to promote ferroptosis. GPX4 mRNA and protein were decreased in LX2-miR-122 cells. GRP78 protein, which reportedly interacts with and protects GPX4 from degradation, was reduced by miR-122, consistent with target predictions. EGCG, a GRP78 antagonist, caused more cell death in LX2 cells when administered with erastin. Stable knockdown of GPX4 or GRP78, but not of scramble controls, led to enhanced ferroptosis in LX2 cells. **Conclusion:** Hepatocyte EVs potentiate HSC ferroptosis by delivering miR-122, which leads to elevated cellular ferrous iron level and reduction of GPX4 expression possibly by directly repressing GRP78 expression.

Disclosures: Xinlei Li: Nothing to Disclose, Sherri Kemper: Nothing to Disclose, David Brigstock: Nothing to Disclose

4234 | BMP9 PROMOTES PROTEIN LACTYLATION MODIFICATION IN HEPATOCELLULAR CARCINOMA

CHEN HAN[1] *Hong Tang*[2]

[1]*Center of Infectious Diseases,* [2]*West China Hospital of Sichuan Universit*

Background: BMP9 plays a key role in liver cancer progression. Lactylation, a post-translational modification that occurs on lysine residues (K) of proteins, can affect protein structure and function. The currently identified "writers" of lactylation include p300 and CBP proteins. Further research is needed to determine how BMP9 is involved in regulating protein lactylation modification in HCC. **Methods:** Huh7 and Hep3B cells were treated with BMP9/BMP receptor inhibitor LDN-212854. Intracellular lactate concentration was measured using a colorimetric assay, while protein levels of lactate modification were detected by Western blot analysis. Mouse xenograft models were established, and the mice were intraperitoneally injected with LDN-212854 at a dose of 6mg/kg. Western blot and immunohistochemistry were used to detect the protein levels of lactate modification in tumor tissues. In addition, lactylation modification proteomics analysis was also performed on LDN-212854-treated Hep3B cells. Mutating lysine (K) to arginine (R) was used to simulate de-lactylation modification. The proliferation of HCC cells was evaluated using CCK-8, colony formation assay, and a mice xenograft model. **Results:** BMP9 increases protein lactylation modification levels in Huh7 and Hep3B cells, whereas LDN-212854 decreases protein lactylation modification levels in these cells. The mouse xenograft experiment provided evidence that LDN-212854 inhibits tumor growth and reduces protein lactylation modification levels in tumor tissues. Proteomics and lactate metabolomics analysis revealed that 134 sites displayed increased lactylation modification abundance, and 117 sites showed decreased lactylation modification abundance. These proteins with reduced lactylation modification are involved in various molecular biological processes including cell cycle progression. Among the cell cycle-related proteins, notable downregulation in lactylation modification levels was observed for CKS1B-K4, CKS2-K4, DCAF1-K284, RBL1-K1015, and CDC37-K126. Specifically, CKS1B-K4 exhibited the largest downregulation, being reduced by 1.57 times among cell cycle-related proteins and ranking amongst the top 30 sites with the most significant downregulation among all detected sites. The mutant CKS1B-K4R demonstrated a significant reduction in the proliferation and cell cycle progression of liver cancer cells. The writer responsible for lactylation modification at the CKS1B-K4 site is p300. **Conclusion:** BMP9 plays an important regulatory role in the intracellular molecular lactylation level of HCC cells. CKS1B-K4 is involved in regulating the cell cycle progression of HCC cells and may serve as a key protein and lactylation modification site in the BMP signaling pathway-mediated regulation of the cell cycle in liver cancer.

Disclosures: CHEN HAN: Nothing to Disclose, Hong Tang: Nothing to Disclose

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4235 | IDENTIFYING NOVEL PERI-DROPLET-MITOCHONDRIAL INTERFACE PROTEINS OF OLEIC ACID-TREATED HEPG2 CELLS USING MICROSCOPY-GUIDED SUBCELLULAR SPATIAL PROTEIN PURIFICATION

Andy Lin[1] Weng-Man Chong[1] Chun-Kai Huang[1] Hsiao-Jen Chang[1] Hoi Yin Cheung[1] Jung-Chi Liao[1]

[1]Syncell Inc.

Background: The peri-droplet mitochondria (PDM) play a crucial role in lipid homeostasis and non-alcoholic fatty liver disease (NAFLD), a metabolic syndrome elicited by excess fat in the liver. Despite advancements in proteomic analyses of isolated lipid droplets (LDs), the dynamic and intricate nature of mitochondria-LD interactions presents challenges in identifying novel protein constituents and understanding their functions. **Methods:** We addressed these challenges by using Microscoop, a new microscopy-guided spatial protein purification platform to pull down proteins from millions of mitochondria-LD interaction sites with 240-nm resolution. We employed image processing on the fly to determine the regions of interest for thousands of fields of view in real time, and photoactivable probes were added in the media to enable photo-induced biotinylation one 240-nm spot at a time for billions of spots within hours. With sufficient proteins enriched by avidin pulldown, the enriched proteins were sent to LC/MS-MS to identify proteins in the mitochondria-LD interface with high sensitivity, specificity, and resolution. **Results:** Using this innovative approach, we conducted a comprehensive analysis of mitochondria-LD-associated proteins in oleic acid (OA)-treated HepG2 cells to understand the effect of unsaturated fatty acid on oil formation and stabilization. Subsequent mass spectrometry analysis obtained the mitochondria-LD interface proteome and recovered known proteins previously identified in mitochondria-LD interactions, including but not limited to SNAP23, MFN2, and DGAT2. In addition to the well-characterized LD-associated proteins, we identified 14 high rank novel proteins with no prior LD association and selected five candidates for characterization. Intriguingly, immunofluorescence staining revealed their presence at mitochondria-LD contact sites as well as their localization around lipid droplets, more obviously in OA-treated HepG2 cells as compared to vehicle-treated cells. Notably, these novel proteins are known to be involved in diverse biological functions, including growth regulation, proliferation, transcription, or splicing, but have never been reported in lipid metabolism. This result suggests their potentially novel roles associated with mitochondria-LD communication upon LD accumulation. **Conclusion:** Facilitated by the Microscoop's spatial protein purification, our study identifies previously unrecognized protein constituents at the mitochondria-LD interface, paving way to further functional examination associated with lipid regulation associated with NAFLD pathogenesis.

Disclosures: Andy Lin: Syncell Inc.: Employee, Weng-Man Chong: Nothing to Disclose, Chun-Kai Huang: Nothing to Disclose, Hsiao-Jen Chang: Nothing to Disclose, Hoi Yin Cheung: Nothing to Disclose, Jung-Chi Liao: Nothing to Disclose

4236 | BIOACTIVE HYDROGEL MICROCAPSULES FOR SCALABLE DIFFERENTIATION OF PLURIPOTENT CELLS INTO HEPATOCYTE-LIKE CELLS

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Background: While stem cell-based therapies have a wide diversity of applications, scalability, cost-effectiveness, and efficiency of directed differentiation protocols are barriers to clinical implementation. Microencapsulation may help address existing challenges. Our laboratory is developing heparin-containing microcapsules that bind and release growth factors in a controlled/sustained manner. Microcapsules contain an aqueous core and a PEG-heparin hydrogel shell and are designed to promote aggregation of stem cells into spheroids. The use of microcapsules allows protection of cells against mechanical damage during stirred/suspension cultures and dramatically decreases the amount of growth factors required for differentiation. Our results demonstrate feasibility of using bioactive microcapsules for differentiating pluripotent stem cells into hepatocyte-like cells. **Methods:** A co-axial flow focusing microfluidic device was used to generate aqueous core-shell droplets in oil. Hepatocyte differentiation was carried out with standard definitive endoderm differentiation with Activin A/Wnt signaling followed by hepatic progenitor induction by 1% DMSO and subsequent hepatic maturation through OSM and HGF. Differentiation efficiency was evaluated with PCR, immunostaining, flow

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cytometry, and albumin ELISAs. **Results:** The incorporation of heparin into hydrogel microcapsules allows for sequential loading and release of multiple growth factors required for pluripotency maintenance and hepatic differentiation, including FGF-2, TGF-b1, Nodal, HGF, and OSM. The use of bioactive microcapsules allows us to halve the growth factor requirement while also protecting cells from sheer forces in a stirred flask. Under these conditions, differentiation remains highly effective with a definitive endoderm efficiency of 80% and the generation of albumin-producing hepatocyte-like cells. **Conclusion:** Our microfluidic encapsulation of pluripotent stem cells in a core-shell architecture capsule with a PEG-heparin capsule allows for the efficient differentiation of hepatocyte-like cells for cost-efficient, scalable production.

Disclosures: Kianna Nguyen: Nothing to Disclose, Kihak Gwon: Nothing to Disclose, Alan Gonzalez-Suarez: Nothing to Disclose, Gulnaz Stybayeva: Nothing to Disclose, Quinn Peterson: Mellicell: Stock – privately held company, Vertex: Royalties or patent beneficiary, Alexander Revzin: Nothing to Disclose

4237 | FUZHENG JIEDU XIAOJI FORMULA INHIBITS THE STAT3 PATHWAY OF HEPATOCELLULAR CARCINOMA CELLS TO IMPROVE CD8+ T CELL FUNCTION

Xuanwei Zeng[1] *Bingbing Zhu*[1] *Ying Feng*[1] *Xianbo Wang*[1]

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Background: CD8+ T cells are the effector cells that kill hepatocellular carcinoma (HCC) cells. Improving their efficacy can effectively control HCC progression. Fuzheng Jiedu Xiaoji formula (FZ) can prolong the survival of patients with HCC, downregulate STAT3 expression levels in HCC cells, and increase the number and activity of CD8+ T cells in patients with HCC. However, the mechanism of its assistance in CD8+ T cells killing HCC needs to be further elucidated. **Methods:** HepG2, Hep3B, and CD8+ T cells were used as experimental subjects. Cells were treated with 20% FZ-containing serum, control serum, and 5 μM STAT3 signaling pathway inhibitor Stattic for 24 h. The proliferative capacity of cells was detected using Cell Counting Kit-8; the expression of CXCL9/10/11 was detected using enzyme-linked immunosorbent assays (ELISA); CD8+ T cells were co-cultivated with HCC cells at the effect-target ratio of 2:1 for 24 h, the CD8+ T cell chemotaxis ability of each group on HCC cells was detected using Transwell assays, and the killing effect of CD8+ T cells on HCC cells was detected using ELISA, flow cytometry, and crystalline violet staining. The expression levels of STAT3, P-STAT3, PDL1, and IL6 in HepG2 cells were detected using western blotting and ELISA. A STAT3 overexpression reversion experiment was designed in Hep3B cells. **Results:** Compared to the control group, 20% FZ-containing serum significantly inhibited HepG2 and Hep3B proliferation (Fig. A, a) and promoted CD8+ T cell proliferation (Fig. A, b). It significantly promoted the expression of T-cell chemokines CXCL9/10/11 in the supernatant of HepG2 cells (Fig. B). When HCC cells were co-cultured with T cells, FZ-containing serum promoted the chemotaxis of CD8+ T cells toward HCC cells (Fig. C), increased their interferon secretion capacity (Fig. D, a), and enhanced their killing effect on HCC cells (Fig. D, b, c). Serum containing FZ inhibited STAT3 phosphorylation and reduced the expression levels of its downstream functional proteins PDL1 (Fig. E, a) and IL6 in HepG2 cells (Fig. E, b), which was confirmed by replication experiments using Hep3B cells (Fig. F). **Conclusion:** FZ can inhibit STAT3 pathway activation in HCC cells, increase CXCL9/10/11 T cell chemokine levels secreted by HCC cells, induce CD8+ T cell chemotaxis, and reduce PD-L1 expression on the surface of HCC cells to lessen T cell depletion. Furthermore, FZ can improve the ability of T cells to secrete interferon-gamma and enhance their killing effect on HCC cells.

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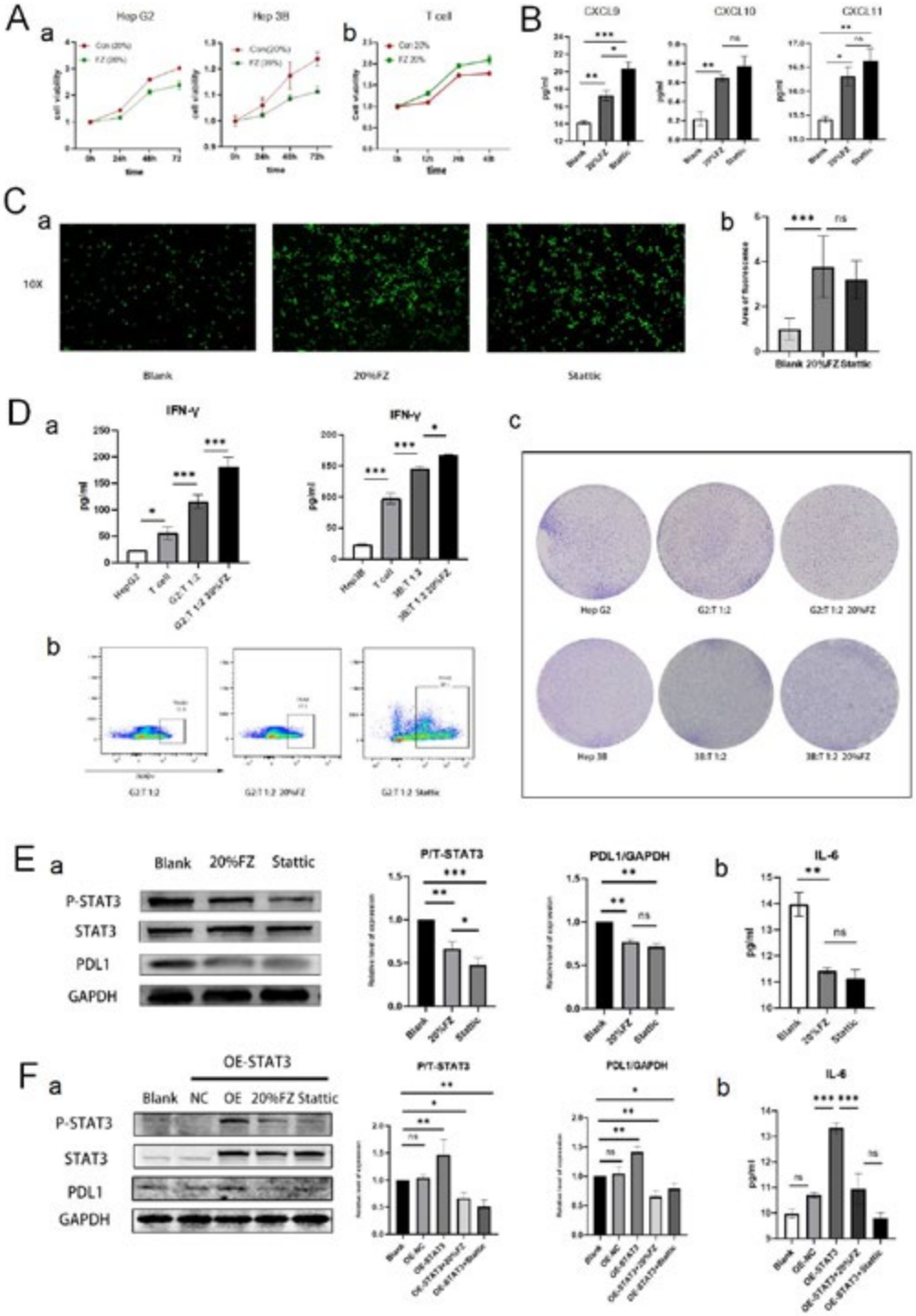

Disclosures: Xuanwei Zeng: Nothing to Disclose, Bingbing Zhu: Nothing to Disclose, Ying Feng: Nothing to Disclose, Xianbo Wang: Nothing to Disclose

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4238 | DEVELOPMENT OF EXTRACTION TECHNOLOGY FOR EXTRACELLULAR VESICLES DERIVED FROM LIVER TISSUE IN MOUSE CHRONIC LIVER DISEASE MODEL AND ANALYSIS OF FACTORS ENCAPSULATING EXTRACELLULAR VESICLES

Hiroyuki Abe[1] Yawen Li[2] Tomoaki Yoshida[1] Yusuke Watanabe[1] Naruhiro Kimura[1] Reina Sasaki[1] Takeshi Yokoo[1] Akira Sakamaki[1] Hiroteru Kamimura[1] Tatsuo Kanda[1] Atsunori Tsuchiya[1] Kenya Kamimura[1] Shuji Terai[1]

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Background: Extracellular vesicles (EVs) are vesicles composed of lipid bilayers secreted from almost all cells in vivo and play an important role in intercellular communication. Studies focusing on EVs in liver diseases have reported the use of EVs isolated from cell culture media or body fluids, but few studies have focused directly on EVs derived from liver tissue. Therefore, we developed a protocol to extract EVs from mouse liver tissue and analyzed EVs from carbon tetrachloride (CCL_4)-induced mouse liver disease model compared to EVs from normal mouse as control model. **Methods:** To extract EVs from liver tissue, liver tissue was finely dissociated and incubated with culture medium. The medium was extracted and cells and debris were removed by filtration and centrifugation. EVs were then collected by ultracentrifugation; to evaluate EVs extraction, nanoparticle tracking analysis (NTA) was performed to assess concentration and size distribution. Furthermore, EVs markers CD63, CD81, and CD9 were evaluated by Western blotting. To evaluate EVs endogenous factors, CCL_4-induced mouse liver disease model was prepared. EVs derived from control model and CCL_4-induced liver disease model were extracted from the liver and subjected to miRNA and proteomic analyses. **Results:** In the development of EVs extraction technology, the size of EVs isolated from liver tissue were mostly in the range of 40-300 nm, which is consistent with the size of common EVs. In addition, the expression of EVs marker proteins was confirmed by Western blotting. Analysis of EVs derived from CCL_4-induced liver disease model showed 112 genes with significant variation in miRNA analysis and 2225 proteins with significant changes in proteome analysis compared to control model. **Conclusion:** We have established and optimized an effective method for the extraction of EVs from mouse liver tissue. This protocol is useful for validating the action of liver-derived EVs. Indeed, changes in liver-derived EVs were observed in CCL_4-induced mouse liver disease model. Further validation of the changes in EVs will be conducted to clarify the effects of liver-derived EVs on the surrounding environment.

Disclosures: Hiroyuki Abe: Nothing to Disclose, Yawen Li: Nothing to Disclose, Tomoaki Yoshida: Nothing to Disclose, Yusuke Watanabe: Nothing to Disclose, Naruhiro Kimura: Nothing to Disclose, Reina Sasaki: Nothing to Disclose, Takeshi Yokoo: Nothing to Disclose, Akira Sakamaki: Nothing to Disclose, Hiroteru Kamimura: Nothing to Disclose, Tatsuo Kanda: Nothing to Disclose, Atsunori Tsuchiya: Nothing to Disclose, Kenya Kamimura: Nothing to Disclose, Shuji Terai: Nothing to Disclose

4239 | KDM4C REPRESSES LIVER FIBROSIS BY REGULATING H3K9ME3 METHYLATION OF ALKBH5 AND M6A METHYLATION OF SNAIL1 MRNA

YongFang Jiang[1] Jing Ma[1] Wan Hu[1]

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Background: Snail1 is involved in liver fibrosis by mediating epithelial-mesenchymal transition. As a result, this present study investigated the molecular mechanism of snail1 in liver fibrosis. **Methods:** CCl4 was utilized to induce a mouse model of liver fibrosis. Serum levels of ALT and AST were determined, and liver pathological alternations were assessed utilizing hematoxylin-eosin and Masson staining. Rat hepatic stellate cells (HSC-T6) were activated by TGF-β1, followed by assessment of cell viability and migration using MTT and scratch tests. The levels of Snail1, ALKBH5, and KDM4C were assessed using immunohistochemistry, Western blot, or RT-qPCR. **Results:** The levels of α-SMA, Col1a1, vimentin, and E-cadherin were also measured. Me-RIP detected a m6A modification in snail1. PAR-CLIP and RNA stability analysis were performed to assess the relationship between ALKBH5 and snail1. The level of KDM4C-bound ALKBH5 promoter and enrichment of H3K9me3 at the ALKBH5 promoter were determined using ChIP. In liver fibrosis mice, snail1 was upregulated, but ALKBH5 and KDM4C were downregulated. KDM4C overexpression reduced serum ALT/AST levels, liver injury, and α-SMA/Col1a1/vimentin levels, and increased E-cadherin. However, the aforementioned trends were countered by the concurrent overexpression of snail1. In TGF-β1-activated HSC-T6 cells, ALKBH5 overexpression weakened cell viability and migration, downregulated α-SMA/Col1a1/vimentin, upregulated

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E-cadherin, and decreased m6A modification of snail1 and its mRNA stability. KDM4C increased ALKBH5 expression by lowering H3K9me3 levels. KDM4C inhibited HSC-T6 activation by regulating the ALKBH5/snail1 axis. KDM4C decreases H3K9me3 methylation to upregulate ALKBH5 and subsequently represses snail1, ultimately impeding liver fibrosis. **Conclusion:** KDM4C decreases H3K9me3 methylation to upregulate ALKBH5 and subsequently represses snail1, ultimately impeding liver fibrosis.

Disclosures: YongFang Jiang: Nothing to Disclose, Jing Ma: Nothing to Disclose, Wan Hu: Nothing to Disclose

4240 | MESENCHYMAL STEM CELL-DERIVED SECRETOMES INHIBIT HEPATIC STELLATE CELL ACTIVATION AND MITIGATE LIVER FIBROSIS

Sihyung Wang[1] *Jisun Oh*[1] *Jihyeon Park*[2]

[1]*K-MEDI hub,* [2]*Kyungpook National University*

Background: Chronic liver disease includes alcoholic liver disease, non-alcoholic steatohepatitis (NASH), and viral hepatitis. Regardless of the classification, a key feature of disease progression is the death of hepatocytes, which can be damaged by toxins, drug metabolites, or immune responses triggered by infections. The liver generally has a remarkable capacity for regeneration. However, if the liver sustains persistent damage, it can develop into chronic conditions such as liver fibrosis, accompanied by inflammation with hepatic stellate cells (HSCs) activation. One approach to addressing this problem is drug development, however the effectiveness of liver regeneration using mesenchymal-stem cells with their paracrine effect has been proven. **Methods:** Therefore, we investigated the effect of MSCs-derived secretomes on activation of HSCs, which is the central event of the liver fibrosis. MSCs-conditioned medium or co-culture with human primary HSCs (pHSCs), To confirm the direct effects of secretomes by MSCs, we were analysis from cultured medium of MSCs by proteomics. We collected MSCs culture supernatant and conducted a frozen separation to analyze their contents. We conducted a comprehensive analysis of the secretory components of four types of MSCs using LC-MS (Liquid Chromatography-Mass Spectrometry). **Results:** Subsequently, we first investigated the high level substance commonly secreted across all types and select them for further mechanism study. In vitro treatment of MSCs abundant secremtomes, IGFBP families and ECM remodeling components suppressed expression of profibrotic genes in pHSCs by biochemical assay. To better understand the IGFBP family effect to HSCs inactivation and ECM mitigating, we establish IGFBP receptor depletion HSCs. We next investigate that we treated secretomes to investigate the decreased fibrotic process. As a result, we confirm that fibrotic markers, such as TGF-β, COLLAGEN1α1, VIMENTIN and α-SMA were not reduced 48 hours after secretome treatment in depletion HSCs. **Conclusion:** Our results demonstrate that MSC-derived secretomes inhibit the activation of HSCs and liver fibrosis, suggesting MSCs-derived secretomes have therapeutic potentials for liver fibrosis by ECM remodeling. Furthermore, to elucidate the mechanism of action of the top substances secretomes, we were able to propose potential agonist or antagonist that could be utilized in the development of novel therapeutic strategies.

Disclosures: Sihyung Wang: Nothing to Disclose, Jisun Oh: Nothing to Disclose, Jihyeon Park: Nothing to Disclose

4241 | AUTOPHAGY CAN PROTECT THE LIVER AGAINST NRF2-INDEPENDENT STRESS

Gang Liu[1] *Ailar Arasteh*[1] *Xiao-Ming Yin*[1]

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Background: Autophagy plays vital roles in maintaining cellular homeostasis; its dysfunction in the liver results in severe hepatomegaly and liver injury, accompanied by inflammation, fibrosis, and tumorigenesis. Nrf2 transcriptionally activates a number of molecules involved in oxidation-reduction, conjugation, and transportation under stresses. Dysregulation of Nrf2 signaling has been implicated in many pathological conditions. It has been demonstrated that autophagy deficiency induces robust Nrf2 activation, and Nrf2 co-deletion corrects the majority of liver phenotypes, if not all, of autophagy deficiency. These results may suggest a hypothesis that controlling Nrf2 over-activation is the only function for autophagy in the liver, and the organism can remain healthy in absence of autophagy. Alternatively, hepatic autophagy may have functions other than controlling Nrf2 overactivation. Here we examined these possibilities by exposing *Atg7/Nrf2 -/-* mice to physiologically relevant

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stress signals. **Methods:** Hepatocyte-specific *Atg7*-deficient mice (*Atg7*$^{\Delta Hep}$) were generated by crossing *Atg7 F/F* mice with Alb-Cre mice. These mice were further crossed with *Nrf2*-deficent mice to generate *Atg7*$^{\Delta Hep}$*/Nrf2 -/-* doubly deficient mice. The levels of ALT, AST, ALP, free fatty acids, glucose, and total amino acids were measured by commercial kits. The fibrosis and inflammation were analyzed by Sirius Red staining and CD11b IHC staining respectively. **Results:** We first subjected *WT* and *Atg7/Nrf2 -/-* mice to starvation. Morphological and histological examination of livers showed no differences, but the metabolisms were altered with 24-h starvation. Compared with *WT* mice, serum free fatty acids levels were increased, but serum levels of glucose and total amino acids were decreased in *Atg7/Nrf2 -/-* mice. In addition, 24-h starvation in *Atg7/Nrf2 -/-* mice caused significant liver injury, manifested as increased levels of ALT, AST, and ALP, compared to *WT* mice. Starvation does not cause liver injury in *WT* mice. We then considered the impact of aging as a physiological stress to the mice. We found that in mice of 15 to 18 months old, liver tumors were observed in *Atg7/Nrf2 -/-* mice, but not in *WT* mice, although the number and size of tumors in *Atg7/Nrf2 -/-* mouse livers are smaller than those in livers of *Atg7 -/-* mice. Additionally, significant fibrosis and modest inflammation were observed in livers of older *Atg7/Nrf2 -/-* mice, which were not in older *WT* mice. **Conclusion:** In summary, our findings revealed that while Nrf2 deletion restores normal homeostasis in *Atg7*-deficient livers in the basal conditions, it could not do so in the stress conditions. Thus, autophagy seems to protect the liver against insults of both Nrf2 dependent and Nrf2 independent natures.

Disclosures: Gang Liu: Nothing to Disclose, Ailar Arasteh: Nothing to Disclose, Xiao-Ming Yin: Nothing to Disclose

4242 | A NOVEL METABOLIC DYSFUNCTION-ASSOCIATED GENE, DPYSL2, IS IMPLICATED IN HEPATOCELLULAR CARCINOMA THROUGH THE CAMP PATHWAY

Gaeul Park[1] Yang-Hyun Baek[2] Sang-Young Han[3] Jin-Sook Jeong[4] Rho Hyun Seong[5] Jong Hoon Park[6] Kyung Hyun Yoo[6] Sang-Jun Ha[7] Yong Sun Lee[1] Yeon-Su Lee[1]

[1]National Cancer Center, [2]Dong-A University College of Medicine, [3]On Hospital, [4]St.Maria Pathology & Laboratory Medicine, [5]Seoul National University, [6]Sookmyung Women's University, [7]Yonsei University

Background: A significant proportion of hepatocellular carcinoma (HCC) cases originate from metabolic dysfunction-associated steatotic liver disease (MASLD). However, the causal linkage between MASLD and HCC remains elusive. In this study, we identified a novel MASLD-associated gene and explored its role in HCC. **Methods:** Through integrated transcriptome analysis of MASLD patients, we identified DPYSL2 to be one of the genes with altered expression levels during MASLD progression. The expression level of DPYSL2 in HCC was examined in the National Cancer Center Korea (NCCK) cohort and validated in data from public resources. To evaluate the role and mechanism of DPYSL2 in HCC, we conducted cell proliferation, migration, and invasion assays, and performed pathway analyses after siRNA-mediated knockdown (KD) of DPYSL2 in HCC cells. **Results:** DPYSL2 expression increased during the progression from steatosis to MASH in two independent cohorts, comprising a total of 163 individuals (96 and 67 in each cohort). In the NCCK cohort, DPYSL2 expression was higher in tumor tissue than in paired non-tumor tissue, both in MASLD-associated HCC patients (n=12, p=0.038) and in the total HCC patients (n=125, p<0.001). Interestingly, high DPYSL2 levels were correlated with poorer overall survival outcomes in early-stage MASLD-associated HCC patients (HR=2.6 [95% CI 1.08 - 6.25], p=0.027), with a median survival of 12.2 months compared to 56.5 months. DPYSL2 KD in HCC cell lines, SNU-449 and SNU-387, led to decreased cell migration, invasion, and proliferation. Transcriptome analysis revealed downregulation of ADCY3, an enzyme that converts ATP to cAMP, upon DPYSL2 KD and the decrease of cAMP levels was confirmed by enzymatic assays. Given the known oncogenic role of the cAMP pathway in HCC, our results indicated the functional role of DPYSL2 in HCC. **Conclusion:** We identified DPYSL2 to be a gene associated with MASLD progression through transcriptome analysis. Furthermore, our results suggest that DPYSL2 may contribute to HCC by regulating the ADCY3/cAMP pathway. Our study highlights DPYSL2 as a potential link between MASLD and HCC.

Disclosures: Gaeul Park: Nothing to Disclose, Yang-Hyun Baek: Nothing to Disclose, Sang-Young Han: Nothing to Disclose, Jin-Sook Jeong: Nothing to Disclose, Rho Hyun Seong: Nothing to Disclose, Jong Hoon Park: Nothing to Disclose, Kyung Hyun Yoo: Nothing to Disclose, Sang-Jun Ha: Nothing to Disclose, Yong Sun Lee: Nothing to Disclose, Yeon-Su Lee: Nothing to Disclose

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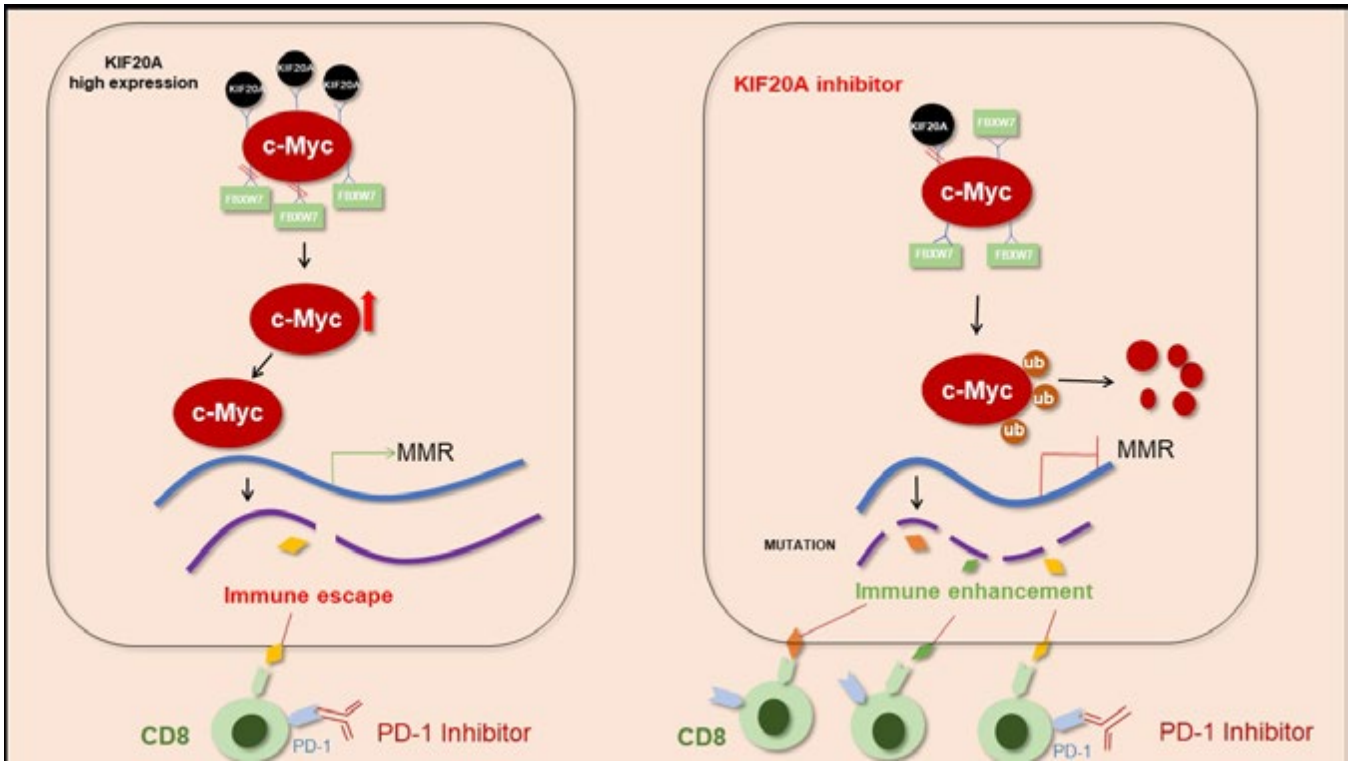
4243 | KIF20A INHIBITORS ENHANCE THE EFFICACY OF PD-1 INHIBITORS BY ENHANCING C-MYC UBIQUITINATION AND BREAKING IMMUNE ESCAPE IN HEPATOCELLULAR CARCINOMA

Jia Li[1] Shujia Chen[2] Lili Zhao[3] Jie Liu[3] Ping Han[2]

[1]Department of Hepatology, Tianjin Second People's Hospital, [2]Tianjin Medical University, [3]Tianjin second people's hospital

Background: Immune therapy has improved the prognosis of hepatocellular carcinoma (HCC) patients, but the number of beneficiaries is limited, highlighting the need to identify new targets and biomarkers to enhance efficacy, thereby driving the development and clinical application of new drugs. Here, we investigated the pathological and physiological roles of KIF20A and evaluated the effect of KIF20A knockout combined with PD-1 inhibitors in HCC treatment. **Methods:** Firstly, we evaluated the oncogenic function of KIF20A through liver-specific knockout of KIF20A (Kif20a CKO) mouse models and orthotopic xenograft models. Subsequently, we validated the regulatory relationship between KIF20A, FBXW7, and c-Myc by constructing c-Myc splicing mutants. Clinical large-sample immunohistochemistry (IHC) analysis was conducted to assess the pathological relevance of the KIF20A/FBXW7-c-Myc-MMR axis. Lastly, we assessed the therapeutic efficacy of anti-PD-1 antibody in Kif20a CKO mouse models of primary HCC. **Results:** Overexpression of KIF20A promotes poor prognosis in HCC. Competitive interaction between KIF20A and FBXW7 hinders the degradation of c-Myc. Additionally, downregulation of KIF20A inhibits glycolysis progression, significantly suppresses cell proliferation, and impairs tumor growth in xenografts through c-Myc downregulation. These effects can be rescued by replenishing c-Myc expression. Furthermore, downregulation of KIF20A attenuates c-Myc-induced MMR expression, closely associated with favorable prognosis in HCC patients treated with PD-1 inhibitors therapy. Moreover, Furthermore, in the Kif20a CKO HCC mouse model, we observed a synergistic interaction between Kif20a knockout and anti-PD-1 antibodies, augmenting the effectiveness of anti-HCC immunotherapy. **Conclusion:** KIF20A regulates HCC progression through the KIF20A/FBXW7-c-Myc-MMR axis, and can be used to screen for patients who may benefit from anti-PD-1 therapy. We hypothesize that the combination of KIF20A inhibitors with anti-PD-1 treatment is a novel and effective combination strategy for HCC patients.



Disclosures: Jia Li: Nothing to Disclose, Shujia Chen: Nothing to Disclose, Lili Zhao: Nothing to Disclose, Jie Liu: Nothing to Disclose, Ping Han: Nothing to Disclose

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4244 | DDX3 PARTICIPATES IN REGULATING EXOSOME RELEASE TO INHIBIT THE DEVELOPMENT OF HEPATOCELLULAR CARCINOMA

Ru-Tsun Mai[1] Yan-Hwa Wu Lee[1] Yi-Yuan Su[1] Hsiang-Yu Hsu[1]

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Background: Effective diagnosis and treatment of hepatocellular carcinoma (HCC) are challenging due to the lack of reliable predictive biomarkers and noticeable early-stage symptoms. Tumor cells release exosomes during cancer progression, which transport functional molecules to neighboring recipient cells and actively regulate cancer development. DDX3, a DEAD-box RNA helicase, is important in various RNA-related cellular processes and is considered a tumor suppressor in HCC. However, its effect on the secretion and cargo sorting of HCC exosomes is still unclear. **Methods:** Exosomes were isolated from HCC cells with DDX3 knockdown. Their size and quantity were determined using transmission electron microscopy and nanoparticle tracking analysis. The mRNA and protein levels of exosome-related markers in both DDX3-knockdown HCC cells and their exosomes were evaluated using qPCR and Western blotting, respectively. Furthermore, exosomes from DDX3-knockdown HCC cells were used to treat parental HCC cells, followed by functional assays to assess the cancer stem cell properties of the recipient cells. An *in vivo* mouse xenograft model was utilized to investigate the impact of exosomes from DDX3-knockdown HCC cells on tumor development. **Results:** Our study found that reduced DDX3 expression in HCC cells led to increased exosome release and elevated levels of several proteins associated with exosome biogenesis, including exosome markers and Rab proteins. We confirmed that DDX3 plays a crucial role in regulating exosome secretion by down-regulating these exosome biogenesis-related factors in HCC cells. Moreover, exosomes purified from DDX3-knockdown HCC cells enhanced cancer stem cell properties of parental HCC cells, including self-renewal, migration, and drug resistance, as well as promoted tumor growth in an *in vivo* xenograft mouse model. In addition, an increase in the expression of exosome markers, along with a decrease in several tumor-suppressive microRNAs, was observed in exosomes derived from DDX3-knockdown HCC cells. These alterations may contribute to the increased hepatic cancer stemness observed in recipient cells treated with exosomes from DDX3-knockdown HCC cells. **Conclusion:** Our findings reveal a new molecular mechanism in which DDX3 inhibits HCC progression by regulating exosome release, providing insights that could aid in the development of new therapeutic strategies against HCC.

Disclosures: Ru-Tsun Mai: Nothing to Disclose, Yan-Hwa Wu Lee: Nothing to Disclose, Yi-Yuan Su: Nothing to Disclose, Hsiang-Yu Hsu: Nothing to Disclose

4245 | VERIFICATION OF GENE EXPRESSION COMPOSITION IN PATHOLOGICAL LIVER TISSUE OF PRIMARY SCLEROSING CHOLANGITIS USING SPATIAL TRANSCRIPTOME ANALYSIS

Tomohiro Katsumi[1] Keita Maki[1] Fumiya Suzuki[1] Fumi Uchiyama[1] Kyoko Hoshikawa[1] Hiroaki Haga[1] Yoshiyuki Ueno[1]

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Background: Primary sclerosing cholangitis (PSC) is a chronic, progressive biliary stasis disease. The relationship between onion-skin fibrosis, inflammatory cell induction, and the influence of perivascular cells on the pathogenesis of PSC remains unclear. In this study, we aimed to identify the relationship between PSC-impaired bile ducts and the surrounding inflammation and fibrosis by analyzing gene expression based on morphological location information in PSC pathology using spatial transcriptome analysis. **Methods:** FFPE pathological sections showing PSC-specific bile duct destruction and peri-bile duct ring fibrosis were used as validation specimens. Specimens were selected if DV200 was measured beforehand and was greater than 30%. Spatial transcriptome analysis was performed using Visium CytAssist Spatial Gene Expression for FFPE (10x Genomics) to identify morphological gene expression patterns. Gene function analysis was conducted by GO analysis based on cluster classification for each expression data set. **Results:** The total number of spots in all specimens was 556. Of the 286,188,915 detected reads, the average number of reads per spot was 514,728, and the average number of genes detected was 3,336. Clustering classified the samples into Clusters 1 through 10, which were clearly distinguishable, especially in the background hepatocyte and portal regions. Additionally, areas of high fibrosis

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(Cluster 4) and areas of bile duct damage with inflammatory cell infiltration (Cluster 3) were also subdivided. Cluster 4 showed significantly higher expression of fibroblast and smooth muscle cell regulators such as Desmin, FBLN1, and COL14A1. Moreover, T cell differentiation and immune response system regulating genes such as GATA3 and TNFRSF21 were significantly upregulated in Cluster 3. **Conclusion:** This study verified a group of genes expressed in PSC tissues based on their morphological location. The unique expression patterns identified may help to elucidate the mechanisms underlying PSC.

Disclosures: Tomohiro Katsumi: Nothing to Disclose, Keita Maki: Nothing to Disclose, Fumiya Suzuki: Nothing to Disclose, Fumi Uchiyama: Nothing to Disclose, Kyoko Hoshikawa: Nothing to Disclose, Hiroaki Haga: Nothing to Disclose, Yoshiyuki Ueno: Nothing to Disclose

4246 | SKELETAL MUSCLE MITOCHONDRIAL DYSFUNCTION DURING HYPERAMMONEMIA IN CIRRHOSIS IS MEDIATED VIA A MYD88-PGC1A AXIS

Saurabh Mishra[1] Nicole Welch[1] Annette Bellar[2] Pugazhendhi Kannan[1] Muaz Alsabbagh Alchirazi[1] Vandana Agrawal[1] Amy Attaway[1] Srinivasan Dasarathy[1]

[1]cleveland clinic, [2]Graduate Student

Background: We have previously reported that in cirrhosis, hyperammonemia causes skeletal muscle mitochondrial dysfunction with increased protein acetylation, and resultant sarcopenia and impaired contractile function/physical frailty. The mechanisms of mitochondrial dysfunction during hyperammonemia are not known. RhBG, a solute transceptor (bifunctional transporter and receptor) transports ammonia and initiates intracellular signaling via non-canonical, TLR-independent, MyD88, activation. We observed reversal of mitochondrial oxidative dysfunction via MyD88 dependent mechanism. Here we identify a novel MyD88-PGC1a axis that inhibits mitochondrial function during hyperammonemia of cirrhosis. **Methods:** Studies were performed in differentiated murine C2C12 myotubes: wild type, CRISPR/Cas9-mediated knockout (KO) of MyD88, and MyD88 KO myotubes transfected with full length MyD88, that were untreated (UnT)/treated with 24h 10 mM ammonium acetate (AmAc). In vivo relevance was established in both male and female C57/Bl6J hyperammonemic and control mice without/with floxed MyD88 or muscle-specific deletion of MyD88 ($Myd88^{msd}$). Hyperammonemia was induced by infusion of 2.5 mmol/kg/d of AmAc or vehicle (phosphate buffered saline-PBS) for 4 weeks via subcutaneous osmotic pump. Post translational modification of mitochondrial biogenesis/function regulatory factor, PGC1a was quantified and downstream signaling/regulatory molecules including expression of ACLY (ATP citrate lyase), lysine acetyl transferase (GCN5), NRF1/2, TFAM1, and components of electron transport chain (ETC) were determined by immunoblotting. **Results:** During hyperammonemia, MyD88 binds with IRAK-2 (to form a Myddosome) in myotubes/skeletal muscle with acetylation of PGC1α that is results in: Suppression of NRF-1/2, and TFAM-1 in both wild-type (WT) myotubes and skeletal muscle tissue from $MyD88^{f/f}$ mice; decresed expression of components of oxidative phosphorylation (OXPHOS); impaired mitochondrial oxidation. Deletion of MyD88 reverses the acetylation of PGC1α, leading to the restoration of NRF-1, NRF-2, and TFAM-1 expression in both MyD88 knockout (KO) myotubes and the gastrocnemius muscle of $MyD88^{msd}$ mice. Gain of function studies by full-length MyD88 overexpression in MyD88 KO myotubes impaired NRF-1and TFAM-1 that confirms the MyD88 mediates mitochondrial dysfunction during hyperammonemia. **Conclusion:** Collectively, loss and gain of function studies in complementary myotube and mouse models of hyperammonemia with sarcopenia identifies skeletal muscle Myddosome-PGC1a as a mediator of mitochondrial oxidative dysfunction. Improving mitochondrial responses by targeting the Myddosome is a potential therapeutic for sarcopenia/physical frailty in cirrhosis.

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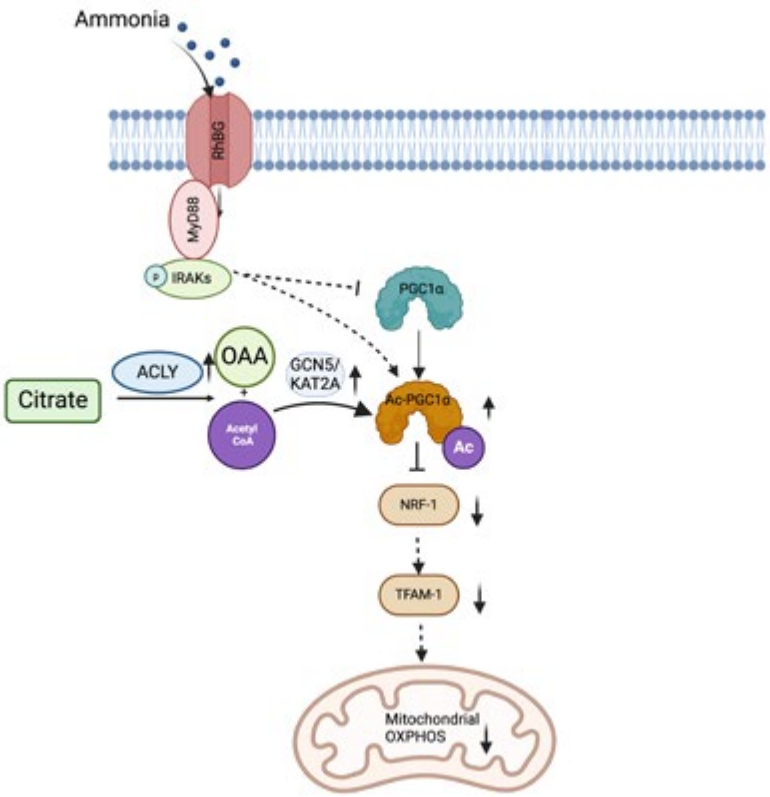

Disclosures: Saurabh Mishra: Nothing to Disclose, Nicole Welch: Nothing to Disclose, Annette Bellar: Nothing to Disclose, Pugazhendhi Kannan: Nothing to Disclose, Muaz Alsabbagh Alchirazi: Nothing to Disclose, Vandana Agrawal: Nothing to Disclose, Amy Attaway: Nothing to Disclose, Srinivasan Dasarathy: Nothing to Disclose

4247 | INCREASED OXIDATIVE STRESS IN CIRRHOSIS INDUCES A PRO-ANGIOGENIC STATE IN ADIPOSE TISSUE

Sanal Madhusudana Girija[1] Sarita Gupta[1] Kumaraswamy Parthasaradhy[1] Archana Rastogi[1] RAHUL SAHA[1] Nagarajan Perumal[2] Viniyendra Pamecha[1] Shiv Kumar Sarin[1]

[1]Institute of Liver and Biliary Sciences, [2]National Institute of Immunology

Background: Cirrhosis is a multisystem disease, known to affect kidneys, lungs, heart, muscles and brain. The effects on the adipose tissue (AT), the largest endocrine organ is unknown. We earlier reported that AT in cirrhosis is characterized by a proangiogenic state and express higher levels of various angiogenic factors. We studied the effects of continuous exposure of AT to various cytokines and growth factors produced by the on-going hepatic injury, oxidative stress and hepatic regeneration on the AT. **Methods:** AT was harvested from 15 liver cirrhosis patients undergoing Living Donor Liver Transplantation and same number of age, BMI-matched healthy donors. Real Time PCR, RNASeq were used to identify the differentially expressed transcripts and western blot for proteins. We cultured adipose tissue mesenchymal stromal cells (ADMSC), and studied their proliferation by counting and using proliferation markers. We did proteomics (MS-MS) of AT, found the differentially expressed proteins, and then identified those that have undergone oxidative changes. **Results:** Patients' ADMSC proliferated faster than healthy ones ($p<0.05$). We analyzed AT proteome and identified stable oxidative modifications in proteins such as PTPN14 which is a protein tyrosine phosphatase (PTP). We confirmed increase in the oxidized form (oxy-PTP) in AT from cirrhosis patients by western blot using antibody specific to the oxidized PTP. PTPs function as phosphatase dephosphorylating a variety of substrate proteins, including but not limited to Janus kinase 1 (JAK1), JAK3, signal transducer and activator of transcription 1 (STAT1), STAT3, epidermal growth factor receptor (EGFR), insulin receptor (IR) etc. We found increased levels of in p-STAT1, p-STAT3, p-AKT and p-JNK in AT samples ($p<0.05$). Expression of pro-proliferative downstream factors such as cMYC, β-catenin, CD44 (western blots) and further downstream matrix metallo proteases were upregulated. Transcriptomics showed increased levels of IGF2, IGF1, IGFBP4, ANGPT2, PDGFD, FGF7 etc. MicroRNAs associated with

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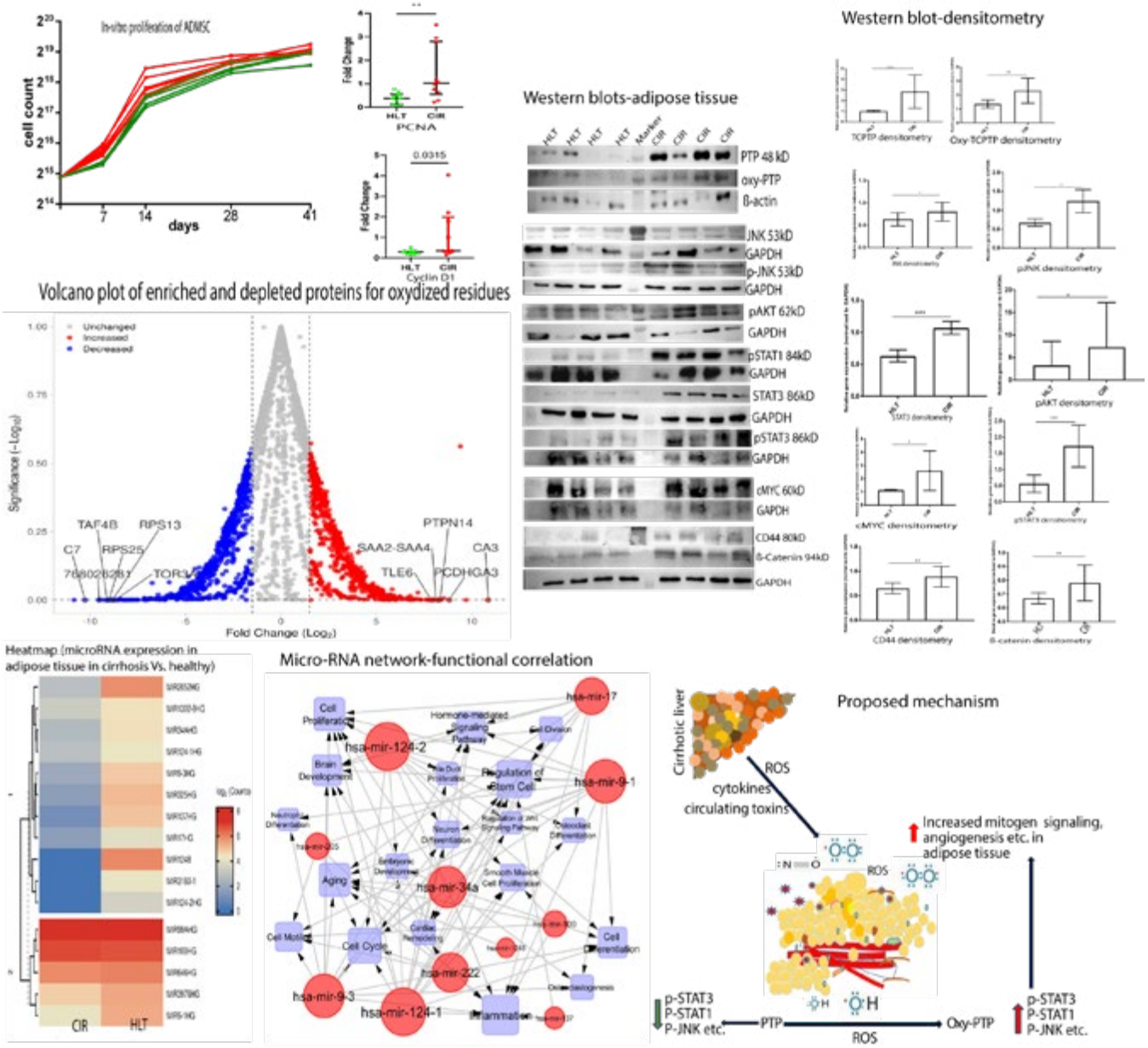
cell proliferation, cell cycle, and aging were differentially expressed. **Conclusion:** Certain proteins are known to be inactivated by oxidative stress such as protein phosphatases (PTP). Several mitogens are activated by phosphorylation. Inactivation of phosphatases causes accumulation of phosphorylated mitogens causing a proliferative-proangiogenic environment in AT in cirrhosis.



Disclosures: Sanal Madhusudana Girija: Nothing to Disclose, Sarita Gupta: Nothing to Disclose, Kumaraswamy Parthasaradhy: Nothing to Disclose, Archana Rastogi: Nothing to Disclose, RAHUL SAHA: Nothing to Disclose, Nagarajan Perumal: Nothing to Disclose, Viniyendra Pamecha: Nothing to Disclose, Shiv Kumar Sarin: Nothing to Disclose

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4248 | HYPOXIC INDUCIBLE FACTOR 2-ALPHA REGULATES UREAGENESIS IN A MURINE MODEL

Marc Cantwell[1] *Marwa Elderany*[1] *Yatrik Shah*[1]

[1]*University of Michigan*

Background: Processing of ammonia from gut floral production and endogenous protein catabolism is an important function of hepatocytes and is accomplished through a series of enzymatic reactions in the mitochondria and cytosol that comprise the Urea Cycle. Dysregulation of ammonia processing is seen in a number of inherited and acquired chronic liver conditions and can contribute to development of clinical complications involving neuropsychiatric symptoms (e.g. Hepatic Encephalopathy); additionally, emerging research is also demonstrating that elevated ammonia may serve as a pro-inflammatory and pro-fibrotic signaling molecule that can progress chronic liver disease. Our lab and others have previously shown that the Hypoxic Inducible Factor (HIF) signaling pathway are important in the progression of liver injury and chronic liver disease. Specifically, we have previously shown that upregulation of HIF2a, but not HIF1a, in the liver of rodents leads to severe steatohepatitis and fibrosis; we additionally showed that the steatosis was in part due to impaired regulation of b-oxidation. Here, we show that HIF2a, but not HIF1a, drives metabolic dysregulation of the Urea Cycle with resultant increase in both liver tissue and serum ammonia levels. **Methods:** We utilized mice with floxed von Hippel Lindau (VHL) with or without floxed HIF2a and albumin-driven tamoxifen inducible Cre for these experiments. Primary hepatocytes or whole livers were isolated for qPCR and Western Blotting, as well as isolation of liver tissue and serum for ammonia assays. **Results:** Deletion of VHL leads to upregulation of both HIF1a and HIF2a in primary hepatocytes and whole livers. There is significant downregulation of all the enzymes in the Urea Cycle, with Ornithine Transcarbamylase (OTC) levels by both qPCR and Western Blot being almost undetectable in the VHL knockouts. Consistent with the downregulation seen in the liver, both whole liver and serum ammonia levels are significantly increased in the VHL knockouts at least two-fold. A known upstream regulator of the Urea Cycle, Hepatocyte Nuclear Factor 4 alpha (HNF4a), has decreased gene expression in the VHL knockouts. This dysregulation in the Urea Cycle is abrogated by deleting HIF2a in these mice; gene expression and levels of Urea Cycle enzymes are restored, as is expression of HNF4a with normalized of both liver and serum ammonia levels. **Conclusion:** Upregulation of HIF2a, but not HIF1a, leads to dysregulation of the Urea Cycle and increased levels of ammonia seen in the liver and the serum. This dysregulation may in part be due to down-regulation of an upstream regulator of the Urea Cycle, HNF4a. Prior work has demonstrated that HIF signaling and ammonia dysregulation is seen as liver disease progresses. Further work is needed to characterize if this dysregulation of ammonia serves as a driver for steatohepatitis and fibrosis in chronic liver disease.

Disclosures: Marc Cantwell: Nothing to Disclose, Marwa Elderany: Nothing to Disclose, Yatrik Shah: Nothing to Disclose

4249 | ACYL-COA THIOESTERASE 12-MEDIATED SUPPRESSION OF PPARα AND PPARδ ACTIVITIES LIMITS HEPATIC GLUCOSE PRODUCTION AND GLYCEROLIPID BIOSYNTHESIS: IMPLICATIONS FOR HEALTH AND METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE

Mariana Acuna[1] *Akiko Sugiyama*[1] *Xu Xu*[2] *Susan Hagen*[2] *David Cohen*[3]

[1]*Brigham and Women's Hospital,* [2]*Beth Israel Deaconess Medical Center,* [3]*Harvard University Medical School*

Background: The control of hepatic acetyl-CoA concentrations is central to nutrient homeostasis, whereas maladaptive responses to overnutrition contribute to the pathogenesis of MASLD. Acyl-CoA thioesterase 12 (Acot12) is highly expressed in liver and hydrolyzes acetyl-CoA into acetate. Acot12 is a target gene of peroxisome proliferator-activated receptor (PPAR) α, which is the central transcriptional regulator of the fasting response. By selectively controlling the expression of key metabolic genes, we have shown that Acot12 suppresses hepatic glucose production (HGP) and glycerolipid biosynthesis in response to fasting. In response to overnutrition, these Acot12-mediated activities play a protective role against MASLD. The aim of this study was to identify transcriptional pathways that are controlled by Acot12. **Methods:** Chow-fed Acot12 knockout (*Acot12*$^{-/-}$) and wild-type mice were fasted for 6 h and then livers were harvested. Isolated mRNA was subjected to RNAseq.

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Data were analyzed by Ingenuity Pathway Analysis. Changes in mRNA expression were systematically compared to a global molecular network of data contained in the QIAGEN Knowledge Base. By determining how closely the expression pattern compared to the expected pattern, this analysis identified upstream and intermediate regulators that were impacted by Acot12 expression. Statistical significance was adjudicated using a z-score cut-off of 2.0. **Results:** In response to Acot12 deletion, the PPARα signaling was the most upregulated upstream pathway (z-score 8.1), as evidenced by the responses of 95 of 122 target genes. The next most impacted transcriptional pathway was PPARγ (z-score 3.0), with upregulation of 56 of 116 target genes. Intermediate regulators of PPARγ signaling that were activated in the absence of Acot12 included nuclear receptor coactivator1 (*Ncoa1)*, PPARG coactivator 1 a (*Ppargc1a)*, Pparg/Rxr complex, and Cbp/p300 interacting transactivator (*Cited2)* with z-scores of 4.0, 4.0, 3.5 and 7.4, respectively. **Conclusion:** Acot12 expression suppresses both the PPARα and PPARγ transcriptional pathways, which promote HGP and glycerolipid biosynthesis, respectively. We speculate that the selective acetylation of transcriptional complexes represents a key function of Acot12 in the liver. These findings provide a mechanistic explanation by which Acot12 mediates a counterregulatory response to fasting, as well as a protective effect against MASLD.

Disclosures: Mariana Acuna: Nothing to Disclose, Akiko Sugiyama: Nothing to Disclose, Xu Xu: Nothing to Disclose, Susan Hagen: Nothing to Disclose, David Cohen: Nothing to Disclose

4250 | CITRULLINATED HISTONE IN NEUTROPHIL EXTRACELLULAR TRAPS IS AN ENDOGENOUS DANGER SIGNAL SENSED BY NLRP3 AND IT INDUCES STELLATE CELL AND MACROPHAGE ACTIVATION IN METALD ◆

Mrigya Babuta[1] Marcelle Ribeiro[1] Martí Ortega-Ribera[1] Prashanth Thevkar Nagesh[1] Viliam Brezani[1] Aditi Ashish Datta[1] Gyongyi Szabo[2]

[1]Beth Israel Deaconess Medical Center (BIDMC), [2]Beth Israel Deaconess Medical Center

Background: Obesity and associated metabolic syndrome often coexist with alcohol consumption, now named MetALD. Recent studies suggest that even moderate alcohol consumption accelerates hepatic steatosis, fibrosis, and increases the risk of liver-related death. In this study, we aimed to dissect cellular and molecular mechanisms by which repeated alcohol binges exacerbate liver injury in a diet induced model of Metabolic dysfunction-associated steatohepatitis (MASH). **Methods:** 8-10 weeks old male C57BL/6 mice received either chow or MASH diet for 3 months with or without weekly alcohol binges. Liver tissue was analyzed for fibrosis and inflammation markers. Neutrophil infiltration and neutrophil extracellular traps (NETs) were examined. **Results:** Alcohol binges in a diet-induced model of MASH lead to profound fibrosis [protein level alpha-smooth muscle actin (α-SMA) and vimentin], neutrophil infiltration (Ly6G+) and NETs formation [neutrophil elastase and citrullinated histone (Cit-H3)] compared to lean, MASH alone or alcohol alone mice. We discovered that alcohol binges with MASH diet induced NETs in the liver. This was associated with increased neutrophil infiltration and inflammation markers. In vitro, alcohol- or palmitic acid (PA)-induced cell-free NETs triggered a robust pro-fibrotic phenotype in hepatic stellate cells (HSC) and increased α-SMA expression. In vitro, reconstitution of NETs by culturing HSCs with the combination of recombinant Cit-H3 and DNA, but not with either alone, led to activation of HSCs. Cell-free NETs also promoted a pro-inflammatory phenotype in monocytes resulting in increased production of interleukin 1β (IL-1β), monocyte chemoattractant protein 1 and tumor necrosis factor-α. We discovered cell-free NETs activate HSC and monocytes via sensing by NLRP3, as abrogating the fibrillar structure of NET structure by DNase or NLRP3 inhibition prevented the NET-induced HSCs and monocyte activation. Furthermore, blocking IL-1β, downstream of the NLRP3, by anakinra (IL-1β antagonist) prevented HSCs activation. Furthermore, Glutathione S-transferase (GST)-pull down assay showed a direct interaction of recombinant GST-tagged NLRP3 with recombinant Cit-H3 suggesting NLRP3 senses NETs via Cit-H3. Finally, DNase treatment attenuated in vitro HSC and monocyte activation and in vivo significantly reduced alcohol-induced liver fibrosis and inflammation. **Conclusion:** Cell-free NETs directly induce pro-fibrotic stellate cells and pro-inflammatory monocyte phenotypes. NLRP3 senses NETs by directly interacting with citrullinated histone. Inhibition of NETs or NLRP3 is a potential therapeutic strategy to ameliorate MetALD.

Disclosures: Mrigya Babuta: Nothing to Disclose, Marcelle Ribeiro: Nothing to Disclose, Martí Ortega-Ribera: Nothing to Disclose, Prashanth Thevkar Nagesh: Nothing to Disclose, Viliam Brezani: Nothing to Disclose, Aditi Ashish Datta: Nothing to Disclose, Gyongyi Szabo: Advisor relationship with Glympse Bio, Inc (acquired by

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Sunbird Bio); Has not ended; Consultant relationship with Terra Firma; Has not ended; Consultant relationship with Pfizer; Has not ended; Consultant relationship with Pandion Therapeutics; Has ended; Consultant relationship with Merck; Has ended; Consultant relationship with Durect Corporation; Has ended; Advisor relationship with Satellite Biosciences; Has not ended; Consultant relationship with Zomagen Bioscience/Ventyx Biosciences; Has ended; Consultant relationship with CYTA Therapeutics; Has ended; Royalties or patent beneficiary relationship with Springer Nature Group; Has not ended; Royalties or patent beneficiary relationship with UpToDate Inc; Has not ended; Consultant relationship with LabCorp; Has not ended; Advisor relationship with Evive; Has not ended; Advisor relationship with Surrozen; Has not ended; Consultant relationship with Takeda; Has ended

4251 | INHIBITION OF P2RX7 CONTRIBUTES TO CYTOTOXICITY BY SUPPRESSION OF HK2-MEDIATED GLYCOLYSIS AND AKT ACTIVATION IN HUMAN HEPATOCELLULAR CARCINOMA CELLS

Younghyeon Ahn[1] *Jong-Seok Moon*[2] *Sae Hwan Lee*[3]

[1]*Asan medical center,* [2]*Department of Integrated Biomedical Science, Soonchunhyang Institute of Medi-bio Science (SIMS),* [3]*Department of Internal Medicine, Soonchunhyang University College of Medicine Cheonan Hospital*

Background: Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer, frequently occurring in individuals with chronic liver diseases. The purinergic receptor P2X 7 (P2RX7) has been implicated in tumor proliferation, growth, invasion, and metastasis. While high glucose utilization is crucial for tumor survival, the role of P2RX7 in glucose metabolism and cellular survival of HCC remains unclear. In this study, we investigated the expression levels of P2RX7 in HCC tumor cells and explored the impact of P2RX7 inhibition on cytotoxicity within the HCC cellular environment. **Methods:** 3 patients with HCC from Soonchunhyang University Hospital Cheonan were included in this study. Tumor tissues from HCC patients were analyzed using immunofluorescence, with antibodies against P2RX7, alpha 1 Fetoprotein (AFP), and cleaved caspase-3. Pharmacologic inhibition of P2RX7 was performed using A-804598, and genetic inhibition via P2RX7 knockdown in Huh7 cells was achieved using esiRNA. Morphological cytotoxicity was assessed through 3D imaging, and cell cytotoxicity was measured using LDH-Cytotoxicity Colorimetric Assay Kit II. Caspase-3 activity assay, glycolysis activity assay, and glycolytic capacity measurement were also conducted. Statistical analysis was performed using Student's t-test. **Results:** The levels of P2RX7 are elevated in tumor cells of patients with HCC.(Fig.1) The pharmacological inhibition of P2RX7 by A-804598, a selective P2RX7 antagonist, suppressed the glycolytic activity by reduction of hexokinase 2 (HK2), a key enzyme of the glycolysis pathway, in human HCC cells.(Fig.2) Moreover, A-804598 induced cytotoxicity via inhibition of AKT activation which is critical for tumor cell survival in human HCC cells and A-804598 induced the activation of caspase-3 linked to apoptotic cell death pathway in human HCC cells.(Fig.3) Similarly, genetic inhibition by P2RX7 knockdown suppressed the glycolytic activity by reduction of HK2 in human HCC cells.(Fig.4) Also, P2RX7 knockdown increased cytotoxicity by AKT inhibition and caspase-3 activation in human HCC cells.(Fig.5 and 6) **Conclusion:** These results show that the levels of P2RX7 are elevated in tumor cells of patients with HCC and inhibition of P2RX7 contributes to cytotoxicity by suppression of HK2-mediated glycolysis and AKT activation for survival in human HCC cells.

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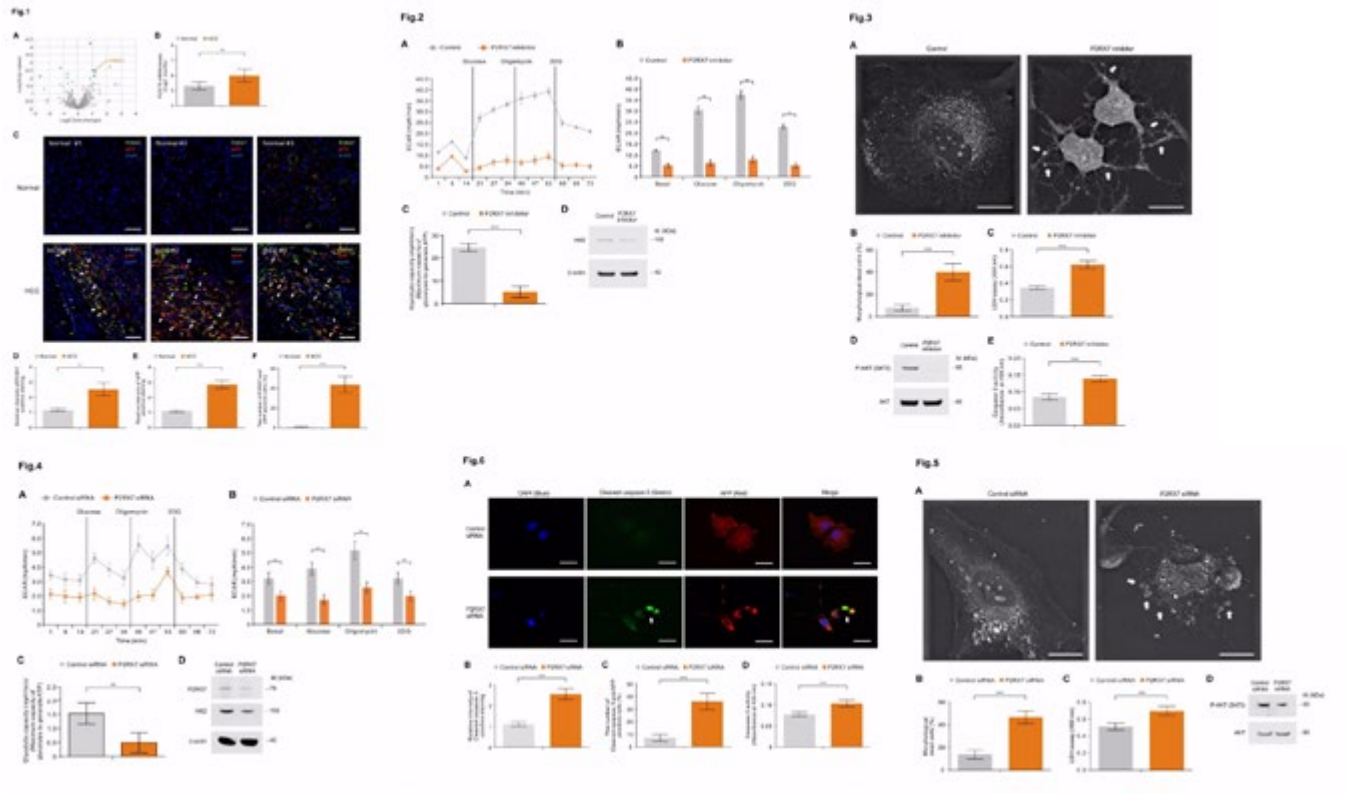

Disclosures: Younghyeon Ahn: Nothing to Disclose, Jong-Seok Moon: Nothing to Disclose, Sae Hwan Lee: Nothing to Disclose

4252 | MIR-22 REGULATES TUMOR IMMUNITY DURING HCC DEVELOPMENT

Ying Hu[1] *Tahereh Setayesh*[1] *Yutong Ji*[1] *Yu-Jui Wan*[1]

[1]*University of California Davis Health*

Background: miR-22 is a tumor suppressor, and our previous studies showed that miR-22 overexpression treats HCC by inhibiting IL-17 signaling and activating cytotoxic T cells. This study investigates the spatial and temporal effects of miR-22 overexpression during HCC development in mice. **Methods:** Mouse HCC was produced by hydrodynamic injection of oncogenes myr-AKT1 and NRasV12, along with the Sleeping Beauty transposase. AAV8-miR-22 ($5x10^{12}$ genome copies/kg, IV) was administered to the mice 5 days before or 7 days after oncogene delivery. Mice were euthanized 35 days after oncogene delivery (n= 8/group). Spatial transcriptomics was performed on histology sections to identify $CD45^+$ cells. Cell deconvolution, a computational program used to analyze mixed cell populations, was adopted to quantify immune cell type and abundance inside the tumor, at the tumor margin, and in non-tumorous tissues. **Results:** Forced miR-22 expression, either pre- or post-oncogene delivery, both reduced tumor load, and there were no significant differences between those two groups. The treated groups had liver-to-body weight ratios of about 10%, in contrast to 33.5% of the untreated group. Histologically, both treated groups only had small tumors with preneoplastic lesions. In addition, both treatments reduced splenomegaly and extended overall survival by 40%. Cell deconvoluted analysis of spatial transcriptomic data revealed that delivery of miR-22 prior to tumor initiation reduced total immune cell infiltration at the tumor margin, indicating decreased inflammation and potential tissue protection, supported by enhanced DNA damage repair pathway. In non-tumorous tissue, decreased monocytes, granulocytes, and reduced inflammation pathways were observed. Inside the tumor, $CD4^+$ T cells were increased while eosinophils and neutrophils were decreased. When miR-22 was delivered after HCC had been formed, immune cell infiltration was reduced in non-tumor areas, minimizing inflammation in healthy tissue. At the tumor margin, miR-22 increased M2 macrophages and reduced neutrophils, while $CD4^+$ T cells and monocytes were expanded inside the tumor. **Conclusion:** Both

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pre- and post-tumor miR-22 administration alter tumor immunity, boosting $CD4^+$ T cell infiltration and inhibiting inflammation.

Disclosures: Ying Hu: Nothing to Disclose, Tahereh Setayesh: Nothing to Disclose, Yutong Ji: Nothing to Disclose, Yu-Jui Wan: Nothing to Disclose

4253 | EXPRESSION OF SGLT2 IN HUMAN HEPATOCELLULAR CARCINOMA TISSUES AND ITS RELATIONSHIP WITH PROGNOSIS, AS WELL AS THE HEPATOCARCINOMA INHIBITORY EFFECTS AND MECHANISMS OF SGLT2 INHIBITORS

Dan Nakano[1] Tsubasa Tsutsumi[2] Keisuke Amano[2] Tomoya Sano[2] Hideki Iwamoto[3] Teruko Arinaga-Hino[2] Sachiyo Yoshio[4] Sachiyo Yoshio[4] Hironori Koga[5] Takumi Kawaguchi[6]

[1]Division of Gastroenterology, Department of Medicine, Kurume, [2]Division of Gastroenterology, Department of Medicine, Kurume University School of Medicine., [3]2. Liver Cancer Division, Research Center for Innovative Cancer Therapy, Kurume University, [4]National Center for Global Health and Medicine, [5]Kurume University, [6]Kurume University School of Medicine

Background: SGLT2 is expressed in not only proximal renal tubules but also hepatocytes. SGLT2 inhibitors have been reported to improve the histological findings in MASLD. This study aimed to investigate the expression of SGLT2 in human hepatocellular carcinoma (HCC) tissue and its impact on patients' prognosis. We also investigated mechanisms for SGLT2i-induced suppression of the proliferation of human HCC cell lines using multi-omics analysis. **Methods:** Human Study: We conducted a retrospective study involving 100 cases of hepatocellular carcinoma (HCC) and background liver tissue obtained from patients who underwent surgical liver resection between January 2007 and January 2011. We examined SGLT2 expression using immunostaining and investigated the impact of SGLT2 expression on survival outcomes. In Vitro Study: Using Hep3B cells, we analyzed changes in metabolic products and enzymes after SGLT2 inhibitor administration. We compared the SGLT2i-treated group (n=5) with a control group (n=5) using metabolomics and quantitative proteomics (in vitro proteome-assisted multiple reaction monitoring for protein absolute quantification, iMPAQT). Additionally, they confirmed changes in chemokines (CXCL10) during SGLT2i administration in Hep3B and Huh7 liver cancer cell lines using multiplex analysis. **Results:** SGLT2 expression was observed in both human liver tissue and liver cancer tissue. Overexpression of SGLT2 in liver cancer tissue (compared to background liver tissue) was associated with poorer prognosis, particularly in cases of moderately to poorly differentiated cancers (expression : non-overexpression ratio 97.3±10.9:121.8.8±5.7, p=0.049). Metabolomics analysis revealed no significant differences in intracellular glucose or glucose 6-phosphate concentrations between the groups. However, acetylcarnitine, a metabolite related to β-oxidation, showed a significant increase in the SGLT2i group (3371±289 vs. 8276±1,516 arbitrary units). iMPAQT analysis demonstrated a significant decrease in stearoyl-CoA desaturase (SCD) concentration (related to fatty acid metabolism) in the SGLT2 inhibitor-treated group (90.82±5.18 vs. 68.71±5.07, P<0.01). Multiplex analysis revealed a significant decrease in CXCL10 (a tumor-promoting chemokine) in the SGLT2i group for both Hep3B (368.8 ± 34.1 vs. 86.5 ± 26.0, P=0.02) and Huh7 (1,593.4 ± 280.0 vs. 884.9 ± 68.0, P=0.02). **Conclusion:** SGLT2 expression is evident in human HCC tissue, and high SGLT2 expression in HCC tissue may be associated with poor prognosis. Furthermore, SGLT2 inhibitors impacted lipid metabolism (such as increased β-oxidation and ketone body production within liver cancer cells) and affected chemokines related to cancer growth. SGLT2 inhibitors may inhibit HCC cell proliferation through metabolic and microenvironmental alterations.

Disclosures: Dan Nakano: Nothing to Disclose, Tsubasa Tsutsumi: Nothing to Disclose, Keisuke Amano: Nothing to Disclose, Tomoya Sano: Nothing to Disclose, Hideki Iwamoto: Nothing to Disclose, Teruko Arinaga-Hino: Nothing to Disclose, Sachiyo Yoshio: Gilead Sciences: Speaking and Teaching, Gilead Sciences: Speaking and Teaching, Sachiyo Yoshio: Gilead Sciences: Speaking and Teaching, Gilead Sciences: Speaking and Teaching, Hironori Koga: Nothing to Disclose, Takumi Kawaguchi: ASKA Pharmaceutical Co., Ltd.: Speaking and Teaching, Taisho Pharmaceutical Co., Ltd.: Speaking and Teaching, Kowa Company, Ltd.: Speaking and Teaching, AbbVie GK.: Speaking and Teaching, Eisai Co., Ltd.: Speaking and Teaching, Novo Nordisk Pharma Ltd.: Speaking and Teaching, Janssen Pharmaceutical K.K.: Speaking and Teaching, Janssen Pharmaceutical K.K.: Speaking and Teaching, Otsuka Pharmaceutical Co., Ltd.: Speaking and Teaching, EA Pharma Co.,Ltd.: Speaking and Teaching

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4254 | ACCELERATION OF HUMAN HEPATOCYTE ENGRAFTMENT IN HUMANIZED LIVER MICE THROUGH REACTIVATING SIGNAL PATHWAYS CRITICAL IN LIVER REGENERATION ◆

Zhe Li[1] Marisa Carbonaro[2] Kehui Wang[2] Hui Huang[3] Nichole Roberts[3] Wei Fang[3] Elena Engeldrum[3] Jun Zhong[3] John Lin[3] Christopher Daly[3]

[1]Regeneron Pharmaceuticals, Inc., [2]Pharmaceuticals, Inc., Tarrytown, NY, USA, [3]Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA

Background: Humanized liver mouse (HLM) models, in which donor human hepatocytes (huHEP) can repopulate recipient mouse livers, have been widely used in studying human liver biology, diseases and therapeutics. However, unlike the rapid expansion of hepatocytes during liver regeneration, huHEP engrafted in host mice repopulate much slower. Abnormal lipid droplet accumulation in transplanted huHEP also occurs spontaneously. These defects greatly compromise the quality and usefulness of the model. In humanized livers, multiple mitogenic signaling pathways (such as IL6/GP130 and HGF/MET, etc.) are compromised due to interspecies incompatibility between host-derived ligands and their receptors on donor huHEP. Therefore, we aimed to improve huHEPengraftemt through restoration of these pathways. **Methods:** HLM were generated through engraftment of primary huHEP into the livers of *FSRG* (*Fah*$^{-/-}$, *Sirpa*$^{hu/hu}$, *Rag2*$^{-/-}$, *Il2rg*$^{-/-}$) mice. Impaired IL6/GP130 signaling in engrafted huHEP was restored through transduction of primary huHEP with lentivirus carrying mouse IL6R, or by supplementation of hIL6 via either AAV dosing or humanization of the murine *Il6* allele in FSRG mice. cMET pathway was restored in human engraftment by dosing with a human cMET agonist antibody (hMET Ab). Other human mitogens were supplemented by dosing with adenoviruses encoding these proteins. Engraftment of huHEP in host mice was assessed by either serum ELISA of human ALB or liver IHC of FAH or human ASGR1. **Results:** Restoration of either IL6/GP130 or HGF/MET pathway through dosing of AAV9-hIL6 or hMET Ab alone showed no acceleration of engraftment. Here, we demonstrate that simultaneous restoration of both IL6/GP130 and HGF/MET signals through supplementation with hMET Ab, in recipient mice with humanized IL6 allele resulted in robust acceleration of huHEP expansion. The engrafted huHEP also showed a correction of the fatty liver phenotype that occurred in conventional humanized liver models without humanized IL6 allele in host mice due to defective IL6/GP130 pathway. In addition, supplementation with additional mitogenic factors involved in human liver regeneration, such as RSPO3 and EGF, led to a further increase in repopulation speed of huHEP in HLM. Moreover, we demonstrate that this novel approach resulted in successful engraftment of donor huHEPs considered to be “hard-to-engraft” by the current conventional methods. **Conclusion:** Our results suggest that slow and suboptimal engraftment of donor hepatocytes in HLM was associated with compromised signaling in multiple mitogenic pathways in human cells during liver repopulation. Re-activating these signals through supplementing human ligands/agonists resulted in accelerated expansion and improved morphology of huHEP. These observations would result in a new class of HLM model that can be generated in a much shorter timeframe, with both increased liver humanization and corrected liver fattiness.

Disclosures: Zhe Li: Regeneron Pharmaceuticals, Inc.: Stock Holder, Marisa Carbonaro: Regeneron Pharmaceuticals: Employee, Kehui Wang: Nothing to Disclose, Hui Huang: Nothing to Disclose, Nichole Roberts: Nothing to Disclose, Wei Fang: Nothing to Disclose, Elena Engeldrum: Regeneron: Employee, Regeneron: Stock - publicly traded company, Jun Zhong: Nothing to Disclose, John Lin: Nothing to Disclose, Christopher Daly: Nothing to Disclose

4255 | MESENCHYMAL STEM CELL-DERIVED EXOSOMES TARGETING LIVER SINUSOID ENDOTHELIAL CELLS IN HEPATIC FIBROSIS

Han Seul Ki[1]

[1]Yonsei University Wonju College of Medicine

Background: The prevalence of liver disease is increasing every year, and has a high mortality rate and its treatment process is notoriously complicated. In a healthy liver, blood circulation is facilitated by the exchange of substances between blood and liver tissue through the fenestrae of liver sinusoidal endothelial cells. However, if the perforation is closed and blood circulation is not possible due to liver damage, it can lead to fibrosis and chronic liver disease. Since there is no specific treatment after cirrhosis, it is important to address liver fibrosis in the early stages. In recent studies, mesenchymal stem cell-derived materials have the potential to alleviate

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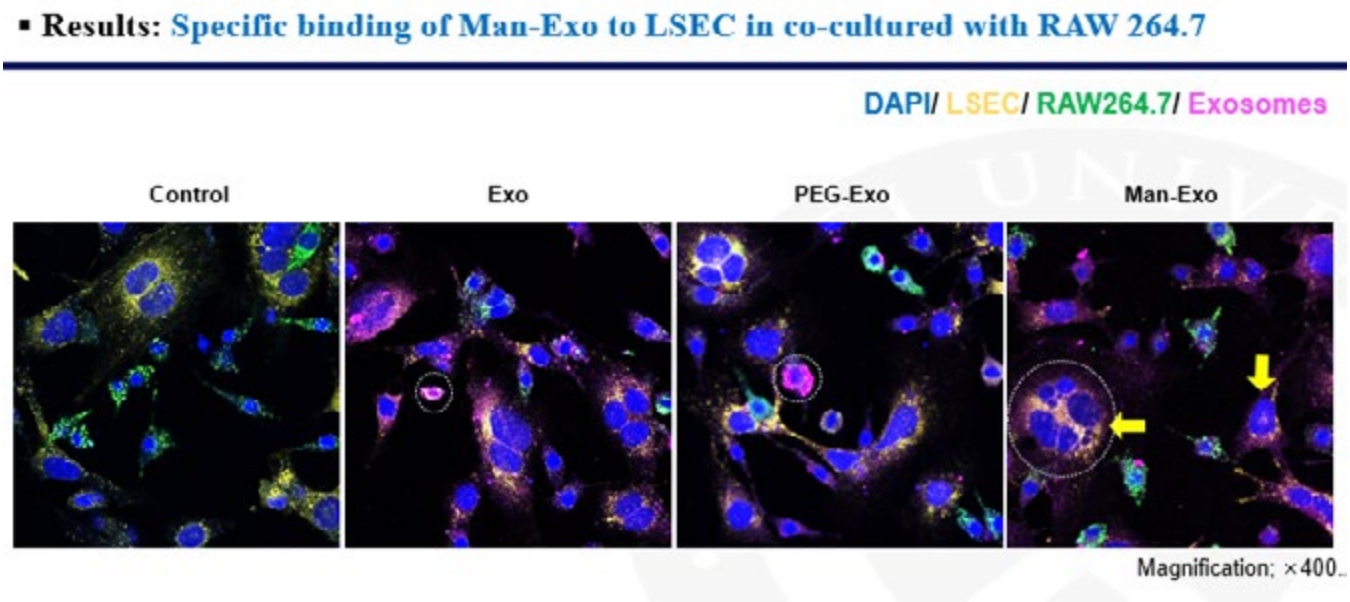
fibrosis, so an approach to treating fibrosis has been sought by replacing it with exosomes containing active ingredients for regeneration. Since exosomes inherently lack liver-targeting capabilities, the mannose receptor, which is a scavenger receptor specifically expressed in liver endothelial cells, was utilized as a liver target. **Methods:** The soup obtained by culturing MSC was obtained by removing cell debris other than exosome through a syringe filter to obtain a filtrate eluant, and then through lysis and washing, other things other than exosome were removed, and the elution buffer was treated to obtain a pure exosome and used in the experiment. After analyzing the physicochemical properties of the prepared particles through particle analysis, toxicity was identified through CCK assay. In vitro binding assay used LSEC and RAW 264.7 cells expressing mannose receptor, and progressed to HUVEC not expressing manose receptor. And we did biodistribution to see if we can actually target the LSEC of the livers through in vivo. **Results:** In this study, exosomes were PEGylated to enhance their stability, and coupled with mannose molecules to facilitate effective delivery to liver cells. Subsequent in vitro transfection demonstrated specific binding to RAW 264.7 and LSEC cells, which highly express mannose receptors. Man-Exo also exhibited a more specific binding affinity for LSEC compared to RAW 264.7 cells in coculture. Furthermore, the biodistribution studies showed that the intravenously administered Man-Exo accumulated longer in the blood and localized higher compared to bare exosomes. **Conclusion:** These findings suggest the Man-Exo are clinically applicable as a novel targeted delivery system for the regeneration of liver fibrosis.



Disclosures: Han Seul Ki: Nothing to Disclose

4256 | ABERRANT LEVELS OF THE HYDROXYSTEROID ENZYME HSD17B13 INCREASES LIPID DROPLET ACCUMULATION BY BLOCKING CELLULAR LIPOPHAGY IN HEPATOCYTES

Shaun Weller[1] Sandhya Sen[1] Ryan Schulze[1] Carol Casey[2] Mark McNiven[1]

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Background: Chronic EtOH insult is known to lead to an accumulation of lipid droplets (LDs) in hepatocytes resulting in hepatic steatosis. Our previous study reported that EtOH resulted in a 6-fold increase in the LD-association of the hydroxysteroid enzyme HSD17b13, known to play an important role in hepatic steatosis. How this enzyme might exacerbate EtOH-induced hepatocellular steatosis is unclear. We and others have shown that the lysosome and autophagosome are key players in LD catabolism and act to reduce total lipid content. From these findings our **CENTRAL GOAL** was to test the role of increased HSD17b13 levels in alterations of the lipophagic process in hepatocytes. **Methods:** Comparative proteomics and Western blotting of hepatic LDs isolated from rats on an ethanol diet. Confocal microscopy and analysis of hepatocytes for lysosome localized lipid content and assessment of LD catabolism. **Results:** We found that over-expressing tagged HSD17b13 in

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cultured hepatocytes leads to a marked increase in the number, and total area, of cellular LDs. These LDs appear highly coated with the tagged HSD17b13 protein and exhibit minimal interactions with adjacent lysosomes needed for lipophagy. To test if access and engulfment of HSD17b13-coated LDs by adjacent lysosomes is compromised in these transfected cells, hepatocytes were treated with an inhibitor of the lysosome acid lipase (Lalistat, (LAL)). Under these conditions, cells accumulate LD-filled lysosomes over a 24 hr period due to the inhibition of the acid lipase. Importantly, cells exhibiting tagged- HSD17b13-coated LDs displayed a 50% reduction in lysosome-internalized LDs compared to control cells. Electron microscopy confirms the lack of LDs in the lumens of hepatocellular lysosomes. Further, expression of an enzymatic dead form of HSD17b13 also blocked LD catabolism suggesting that the lipophagic inhibitory action of this protein is not dependent upon its enzymatic activity. **Conclusion:** These findings suggest that HSD17b13-associated LDs may have a reduced capacity to interact with the lysosomal machinery that mediates the fusion and engulfment process, perhaps by simple physical hinderance. This study provides some of the first mechanistic insights into the cellular basis by which HSD17b13 can lead to hepatocellular steatosis.

Disclosures: Shaun Weller: Nothing to Disclose, Sandhya Sen: Nothing to Disclose, Ryan Schulze: Cytotheryx, Inc.: Employee, Carol Casey: Nothing to Disclose, Mark McNiven: Nothing to Disclose

4257 | ECTOPIC WNT-β-CATENIN ACTIVATION AND ZONE 2 EXPANSION IN EARLY LIVER REGENERATION

Tyler Yasaka[1] Brandon Lehrich[1] Yekaterina Krutsenko[1] Evan Delgado[1] Silvia Liu[1] Satdarshan (Paul) Monga[1]

[1]University of Pittsburgh

Background: The hepatic lobule demonstrates a functional polarity along the portal-central axis known as metabolic liver zonation (LZ), whereby hepatocytes assume specific gene expression conferring distinct metabolic roles from the portal vein (zone 1; Z1) to the central vein (zone 3; Z3), with zone 2 (Z2) residing in the midlobule. During homeostasis, Wnt/β-catenin signaling shows Z3 polarity and drives Z3 expression. This pathway has also been shown to be necessary for proliferation following partial hepatectomy (PH), during which the liver regenerates to its original mass. This process of liver regeneration (LR) enables living-donor transplant and liver resection, which rely on regrowth of resected or transplanted tissue. Nonetheless, the mechanistic role of Wnt/β-catenin signaling, as well as the overall role of LZ, during the acute regenerative response remains poorly understood. **Methods:** We utilized single cell spatial transcriptomics to investigate the spatiotemporal changes in expression of 100 zonated genes at baseline and 1, 3, 6, and 12 hours of LR following PH in a murine model. In situ hybridized imaging reads were assigned to cells using cell boundary tracing through QuPath. Uniform Manifold Approximation and Projection (UMAP) was performed on these cells and unbiased clustering was used to identify distinct expression profiles. Immunohistochemistry (IHC) was used to observe protein expression of key zonation markers at these time points. Immunofluorescence staining for β-galactosidase in Axin2-LacZ reporter mice was used to further investigate β-catenin activity at 6-12 hours post-PH. **Results:** Unbiased clustering demonstrated a marked panzonal shift at 1h post-PH which persisted through 12h post-PH. These de novo clusters showed pan-zonal activation of the Z3 genes *Wnt2*, *Wnt9b,* and β-catenin target genes (e.g. *Glul, Axin2*). While Z1 and Z3 markers such as GLUL, CYP2E1, and CYP2F2 remained unchanged at the protein level via IHC, Z2 markers HAMP1/2 and CCND1 showed an expanded region of expression extending into Z1 and Z3 by 12h post-PH. Immunofluorescence of β-galactosidase in Axin2-LacZ reporter mice further demonstrated ectopic expression extending towards the portal vein at 12h. **Conclusion:** This study demonstrates remarkable transcriptional changes occurring during LR as early as 1h post-PH which are maintained through 12h post-PH, suggesting activation of regenerative machinery including a pulse of Wnt/β-catenin activity which extends transiently across the lobule. These changes occur alongside Z2 broadening with preservation of Z1 and Z3 markers, suggesting a role for ectopic β-catenin activation in promoting enhanced Z2, but not Z3, gene expression. This early Z2 expansion may be a prerequisite for subsequent entrance into the cell cycle, *en masse*, by hepatocytes across the lobule. Our work underscores the significance of Wnt/β-catenin signaling and LZ during the immediate response to PH.

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Disclosures: Tyler Yasaka: Nothing to Disclose, Brandon Lehrich: Nothing to Disclose, Yekaterina Krutsenko: Nothing to Disclose, Evan Delgado: Nothing to Disclose, Silvia Liu: Nothing to Disclose, Satdarshan (Paul) Monga: Surrozen: Independent Contractor, Mermaid Bio: Advisor, Vicero: Advisor, AntlerA: Advisor, Genentech: Speaking and Teaching, Alnylam: Grant/Research Support, Alnylam: Consultant, UbiquiTx: Consultant, Mermaid Bio: Consultant, Fog Pharmaceuticals: Grant/Research Support, Surrozen: Consultant, Genentech: Independent Contractor

4258 | MULTIOMICS ANALYSES OF SKELETAL MUSCLE RESPONSES IN A MOUSE MODEL OF HYPERAMMONEMIA OF CIRRHOSIS

Annette Bellar[1] Avinash Kumar[2] Ryan Musich[1] Amrit Gopan[3] Amy Attaway[1] Saurabh Mishra[1] Muaz Alsabbagh Alchirazi[1] Pugazhendhi Kannan[1] Nicole Welch[1] Srinivasan Dasarathy[1]

[1]Cleveland Clinic, [2]All India Institute of Medical Sciences, [3]King Edward Memorial Hospital

Background: Hyperammonemia during cirrhosis causes loss of muscle mass and strength. Decreased TCA cycle intermediates and mitochondrial dysfunction contirbute to dysregulated protein synthesis and muscle loss in cirrhosis. Endurance exercise (EE) that improves mitochondrial function, restores TCA cycle intermediates, and improves endurance in healthy subjects. However global muscle responses to EE in are unkown. Mutliomics analyses of skeletal muscle and blood were performed to evaluate responses to EE in a mouse model of hyperammonemia. Critical metabolites in the glycolysis pathway were experimentally evaluated. **Methods:** Male C57BL/6J mice aged 8w were infused ammonium acetate (2.5mmol/kg/d-AmAc) or vehicle (PBS) for 6 weeks via subcutaneous osmotic pump. Mice were studied after 4w of voluntary wheel running (VWR) or usual activity (UA) (n=8 per group) started 2 weeks post-recovery from pump placement. Untargeted RNAseq, proteomics, and metabolomics were performed. Differentially expressed genes (DEG), proteins (DEP), and metabolites (DEM) were identified in gastrocnemius muscle (gastroc) and serum using standard pipelines including STAR and DESeq2.0 (RNAseq), MaxQuant (proteomics) and MetaboLyzer/MetaboAnalyst for metabolomics. Pathway analyses and integrated heirarchical scatterplots were generated using g:Profiler and Ingenuity Pathway Analysis. **Results:** Shared and unique features (DEG, DEP, DEM) between gastroc RNAseq, and serum or gastroc proteomics between the 4 groups of mice showed 376 genes (127 proteins) in muscle the PBS UA and AmAc UA mice. Proteomics identified 216 DE proteins (148 genes) between the gastroc in AmAc VWR and AmAc UA mice (Fig1A). Of the top 50 DEG, 8 were altered in response to VWR in both PBS and AmAc mice (Fig1B). Metabolomics analyses showed changes in glycolytic and citric acid cycle in the muscle with concordant changes in regulatory molecules of these pathways on RNAseq and proteomics. VWR increased mitochondrial and TCA cycle intermediate pathways in both groups in the gastroc (Fig1C). Experimentally, glycolytic intermediates other than glucose and phosphenol pyruvate were higher in AmAc UA mice as compared to PBS UA. VWR increased some of these intermediates as compared to PBS UA (Fig 1D). **Conclusion:** 4 weeks of VWR favorably altered RNAseq, poteomics, and metabolites in the serum and gastrocnemius in hyperammonemic mice. Most DEM were between PBS UA and AmAc UA mice, and AmAc UA and AmAc VWR mice. TCA cycle intermediates were lower in AmAc UA mice as compared to AmAc VWR mice while glycolytic intermediates were higher. Enrichment of TCA cycle and glycolysis pathways were observed on mulitomics in both PBS and AmAc treated mice and mitochondrial regualtory molecules in response to VWR during hyperammonemia. EE can mitigate hyperammonemia induced perturbations across multiple reguiatory pathwys including mitochondrial dysfunction to reverse sarcopenia/frailty in cirrhosis.

Disclosures: Annette Bellar: Nothing to Disclose, Avinash Kumar: Nothing to Disclose, Ryan Musich: Nothing to Disclose, Amrit Gopan: Nothing to Disclose, Amy Attaway: Nothing to Disclose, Saurabh Mishra: Nothing to Disclose, Muaz Alsabbagh Alchirazi: Nothing to Disclose, Pugazhendhi Kannan: Nothing to Disclose, Nicole Welch: Nothing to Disclose, Srinivasan Dasarathy: Nothing to Disclose

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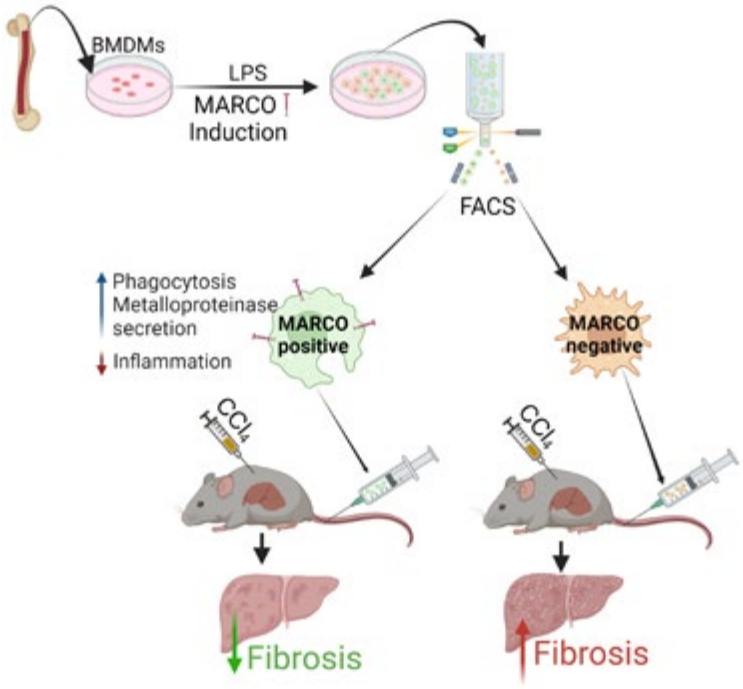
4259 | MARCO-POSITIVE MACROPHAGE CELL THERAPY REDUCES CARBON TETRACHLORIDE-INDUCED FIBROSIS.

Sofia Jerez[1] *Shawna Cooper*[1] *Usman Yaqoob*[1] *Maria Hernandez-Tejero*[1] *Nidhi Jalan-Sakrikar*[1] *Enis Kostallari*[1] *Sheng Cao*[1] *Vijay Shah*[1]

[1]*Mayo Clinic Rochester*

Background: Chronic inflammation drives fibrosis in liver diseases, with macrophages (Macs) being the most significant immune population. These Macs can be either pro- or anti-fibrotic. MARCO (Macrophage Receptor with Collagenous Structure) is a scavenger receptor present on subsets of Macs, and its role in liver fibrogenesis is unclear. This study investigates the role of MARCO-positive Macs in liver fibrosis and their therapeutic potential. **Methods:** Healthy and carbon tetrachloride (CCl_4)-induced fibrotic mouse livers were analyzed using single-cell RNA sequencing (scRNA-seq), 10x Visium spatial transcriptomics, and immunofluorescence (IF). Bone marrow-derived Macs (BMDMs) were stimulated *in vitro* with lipopolysaccharide (LPS) to induce MARCO expression. $1x10^6$ FACS-sorted MARCO-positive or MARCO-negative BMDMs were transplanted at 3 and 5 weeks of CCl_4 treatment. At the end of the six weeks of treatment, fibrosis was assessed by Picrosirius red staining and IF. *In vitro* analyses of BMDMs included flow cytometry, RT-qPCR, Western blot, and IF. **Results:** scRNA-seq and IF revealed upregulation of Macs during fibrosis and showed MARCO overexpression (Log_2FC 3.6, $p=3.55e^{-17}$). Spatial analysis and IF showed that MARCO-positive Macs were primarily found in non-fibrotic areas. Inducing MARCO expression on BMDMs with LPS resulted in a positivity of 20% of the cells. Transplantation of FACS-sorted MARCO-positive cells into mice undergoing CCl_4 treatment reduced collagen deposition and bridging fibrosis, as revealed by Picrosirius red staining, compared to MARCO-negative BMDMs and saline controls (FC=0.52, *p=0.029*). IF staining showed colocalization of MARCO-positive Macs with collagen I in fibrotic regions of the transplant recipient mice, which is not observed in saline controls, suggesting these cells can reach fibrotic areas to degrade collagen. Transcriptionally MARCO-positive BMDMs exhibited lower pro-inflammatory gene levels (Tnf, FC=0.46, *p=0.02*; Ccl5, FC=0.4, *p=0.03*), higher metalloproteinase levels (Mmp2, FC=1.49, *p=0.02*; Mmp3, FC=5.7, *p=0.03*; Mmp12, FC=6.03, *p=0.003*), and they present higher phagocytic capacity (FC=1.87, *p<0.001*), suggesting an anti-inflammatory and anti-fibrotic phenotype. **Conclusion:** Transplantation of MARCO-positive Macs significantly reduces fibrosis *in vivo*, demonstrating their anti-fibrotic characteristics and potential for cell therapy. Ongoing analysis includes mechanistic assays and spatial transcriptomics with NanoString GeoMx to better understand the role of Marco-positive Macs in the fibrotic niche.



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Disclosures: Sofia Jerez: Nothing to Disclose, Shawna Cooper: Nothing to Disclose, Usman Yaqoob: Nothing to Disclose, Maria Hernandez-Tejero: Nothing to Disclose, Nidhi Jalan-Sakrikar: Nothing to Disclose, Enis Kostallari: Nothing to Disclose, Sheng Cao: Nothing to Disclose, Vijay Shah: Boehringer Ingelheim: Consultant, GSK: Consultant, GENFIT SA: Consultant, Intercept Pharmaceuticals, Inc.: Advisor, Korro Bio, Inc.: Consultant, Mallinckrodt Pharmaceuticals: Advisor, Novo Nordisk A/S: Consultant, Resolution Therapeutics, Ltd.: Advisor, Seal Rock Therapeutics, Ltd.: Consultant, Surrozen: Advisor

4260 | CHAPERONE PROTEIN MYD88 MEDIATED ACTIVATION OF ATP CITRATE LYASE-LYSINE ACETYL TRANSFERASE (GCN5) AXIS IN SKELETAL MUSCLE RESULTS IN MITOCHONDRIAL DYSFUNCTION IN HYPERAMMONEMIA OF CIRRHOSIS

Saurabh Mishra[1] Nicole Welch[1] Annette Bellar[1] Muaz Alsabbagh Alchirazi[1] Pugazhendhi Kannan[1] Vandana Agrawal[1] Amy Attaway[1] Srinivasan Dasarathy[1]

[1]cleveland clinic

Background: Non-canonical activation of MyD88, a chaperone protein, via an ammonia transporter (RhBG) dependent, TLR independent mechanism mediates mitochondrial dysfunction during hyperammonemia of liver disease to cause sarcopenia/physical frailty. Mitochondrial oxidative dysfunction is caused by increased lysine acetylation during hyperammonemia but the mechanisms are not known. The source of cytosolic acetyl CoA for lysine acetylation of regulatory proteins is regulated by ATP citrate lyase (ACLY) and, subsequently acetyl transferase GCN5 acetylates mitochondrial regulatory protein, PGC1a. We dissected the mechanism(s) by which MyD88 results in acetylation-dependent skeletal muscle mitochondrial oxidative dysfunction during hyperammonemia via impaired PGC1a. **Methods:** Multiomics analysis of RNA-seq and proteomics data from differentiated C2C12 myotubes without/with hyperammonemia were performed in wild type and CRISPR/Cas9 knockout of MyD88, and skeletal muscle from male and female mice with muscle specific deletion of MyD88 and MyD88 floxed mice. GCN5 was depleted in myotubes by shRNA. Hyperammonemia was induced in myotubes (10 mM ammonium acetate for 24h) or subcutaneous osmotic pump delivery of 2.5mmol/kg/d ammonium acetate/vehicle alone for 28days. MyD88 translocation to the mitochondria in myotubes was studied by live cell imaging. Interaction between MyD88 and its partners (IRAK-2, SLC25A1) and localization to mitochondrial outer/inner membranes were studied by co-immunoprecipitation. Responses to MyD88 activation (ACLY, GCN5, NRF-1, NRF-2) were studied by immunoblotting. **Results:** Multiomics analysis identified ammonia-independent and -dependent as well as MyD88-independent and -dependent alterations in differentially expressed molecules that were enriched in oxidative phosphorylation and tricarboxylic acid cycle pathways. Experimentally, mitochondrial localization of MyD88-mCherry to the mitochondria was observed on live cell imaging and co-immunoprecipitation with outer (Tomm20) and inner (Timm50) mitochondrial membrane proteins. This interaction was accompanied by increased expression of citrate transporter (SLC25A1)-facilitated transport of citrate from mitochondria to cytosol, to generate acetyl CoA via increased phospho-ACLY. Increased expression of GCN5, that acetylates and impairs PGC1a function, results in less downstream PGC1a targets, NRF-1 and TFAM-1. GCN5 depletion reversed these responses during hyperammonemia. **Conclusion:** Mitochondrial oxidative dysfunction during hyperammonemia are mediated by MyD88. The Myddosome complex, comprising ACLY and GCN5, acetylates PGC-1α with consequent mitochondrial oxidative dysfunction. GCN5 depletion reverses the hyperammonemia-induced perturbations including less NRF-1, NRF-2, and TFAM-1. GCN5 is a potential therapeutic target to reverse/treat sarcopenia/frailty in cirrhosis.

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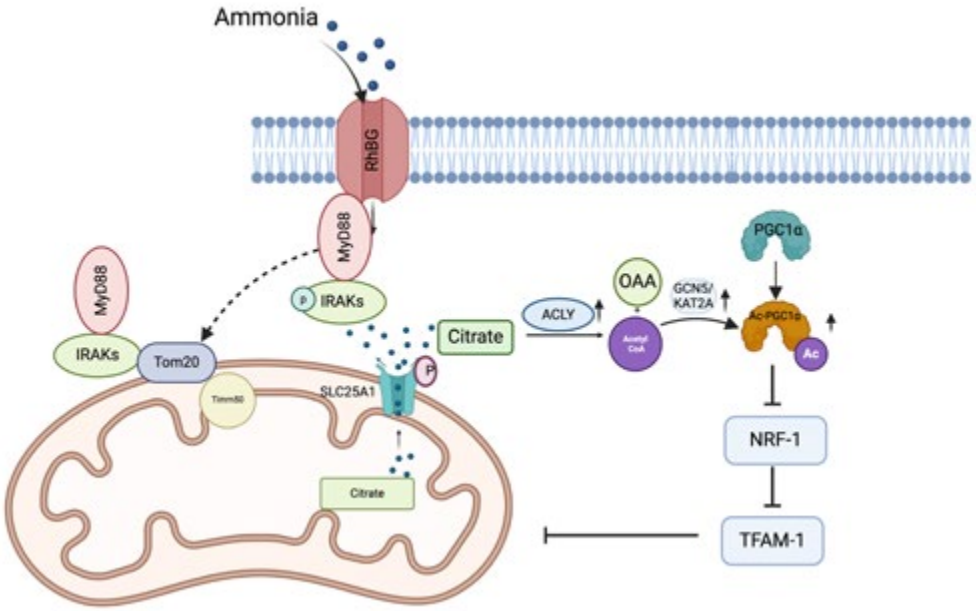

Disclosures: Saurabh Mishra: Nothing to Disclose, Nicole Welch: Nothing to Disclose, Annette Bellar: Nothing to Disclose, Muaz Alsabbagh Alchirazi: Nothing to Disclose, Pugazhendhi Kannan: Nothing to Disclose, Vandana Agrawal: Nothing to Disclose, Amy Attaway: Nothing to Disclose, Srinivasan Dasarathy: Nothing to Disclose

4261 | DIFFERENT METABOLIC FLUX PATTERNS SHOW FOUR MOLECULAR TYPES OF HEPATOCELLULAR CARCINOMA

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Background: Liver cancer is one of the most common and serious malignancies. Various factors contribute to its development. Regarding metabolic flux, it is now recognized that abnormal metabolic reprogramming occurs in liver cancer cells. They often show enhanced glycolysis, altered lipid metabolism, and changes in amino acid metabolism. Understanding these metabolic fluxes and their regulatory mechanisms is essential for developing novel therapeutic strategies. New technologies and research methods are continuously being applied to explore these aspects more deeply, providing new insights and potential therapeutic targets for liver cancer treatment. **Methods:** The public data of different stages and locations are downloaded to explore the metabolic flux characteristics. The GEO accession is GSE 25097, including the RNA-Seq expression level of healthy, cirrhotic, adjacent, and HCC liver tissues. We use the METAFlux algorithm to calculate the metabolic flux score of different silicon tissues and estimate the velocities of metabolic reactions. The biochemical reaction scoring discovered various metabolic pathways. Finally, the metabolic flux moderns are determined by R package Mfuzz. Four different molecular subtypes of HCC are found. **Results:** In the chemical reactions scoring section, we identified 13082 metabolic reactions and 8378 metabolites in the “human_blood” medium, which consists of the man-made metabolic model of humans. Relying on this clue, we performed further metabolic flow scoring, ultimately identifying 142 pathways with significant differences in healthy, cirrhotic, paraneoplastic, and hepatocellular carcinoma. Eventually, the patients were split into 4 modules with different metabolic flux signatures. Module 1 shows active Arginine and proline metabolism. Module 2 is clarified by Fatty acid elongation, while Module 3 features Peroxisomal β-oxidation. The Formation and hydrolysis of cholesterol esters highlight Module 4. In the 557 tested patients, Module 3 includes the population most affected by the healthy-cirrhotic-cancer transition. **Conclusion:** In peroxisomal β-oxidation, fatty acids are broken down. This process occurs independently of the mitochondrial β-oxidation system. This process is crucial for maintaining lipid homeostasis and has implications for various physiological and pathological conditions. Our study suggests that Peroxisomal β-oxidation may play an important role in healthy-cirrhotic-cancer transformation and could be a metabolite target with great potential in future hepatocellular carcinoma therapy.

Disclosures: Zijian Zhang: Nothing to Disclose, Qi Zhou: Nothing to Disclose

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4262 | THE SIGNIFICANCE OF GALECTIN-1 IN CONTRIBUTING TO THE ANTI-HCC EFFECTS OF MIR-22

Ying Hu Tahereh Setayesh[1] Trenton Testerman[1] Yu-Jui Wan[1]

[1]University of California Davis Health

Background: Our previous studies uncovered novel options for HCC treatment in mice. Those include forced expression of miR-22 and silencing galectin-1 (Gal-1). miR-22, a tumor suppressor, has reduced expression levels in human HCC, whereas Gal-1, an HCC biomarker, is associated with advanced HCC stages and poor survival. We found that treating HCC with miR-22 reduces Gal-1 levels. This study explores the spatial effects of miR-22 in HCC treatment and whether these effects are partly due to inhibiting Gal-1. **Methods:** Mouse HCC was induced via hydrodynamic injection of oncogenes myr-AKT1, NRasV12, and Sleeping Beauty transposase. Seven days post-oncogene delivery, mice were divided into five groups: (1) AAV8/AAV9 blank controls; (2) AAV8-miR-22; (3) AAV9-Gal-1; (4) AAV9-Gal-1 siRNA; (5) a combination of AAV8-miR-22 plus AAV9-Gal-1 ($5x10^{12}$ genome copies/kg of each, iv). Mice were euthanized 35 days post-oncogene delivery (n=8/group). Spatial transcriptomics was performed to identify location-specific pathways regulated by miR-22 overexpression or Gal-1 silencing in $CD45^+$ immune cells. **Results:** Forced expression of miR-22 in HCC significantly decreased Gal-1 protein levels by 50% and reduced the tumor load by 67% compared to HCC mice. Moreover, Gal-1 overexpression attenuated the anti-HCC effect of miR-22 by 55%. Spatial transcriptomic profiling revealed location-specific effects of miR-22 in HCC treatment: (1) Within the tumor, miR-22 enhanced retinoic acid metabolism and immune responses, including antigen presentation and B cell activation. (2) At the tumor margin, miR-22 suppressed GTPase cycles and extracellular matrix (ECM) signaling. (3) miR-22 inhibited epigenetic pathways across tumor and margin areas. (4) In non-tumor areas, miR-22 reduced ECM and inflammatory signaling. Common pathways affected by both miR-22 and Gal-1 silencing included ECM, RNA processing, ribosomal function, epigenetic regulation, and chromatin organization in the tumor and margin. **Conclusion:** Silencing Gal-1 contributes to the anti-HCC effects of miR-22. Moreover, miR-22 has multifaceted effects, including improving metabolism and immunity and inducing epigenetic changes, which may be facilitated by Gal-1 silencing. This is consistent with our previous findings that miR-22 inhibits multiple histone deacetylase inhibitors.

Disclosures: Ying Hu: Nothing to Disclose, Tahereh Setayesh: Nothing to Disclose, Trenton Testerman: Nothing to Disclose, Yu-Jui Wan: Nothing to Disclose

4263 | HEPATO-BILIARY TRANSDIFFERENTIATION CONTRIBUTES TO LIVER REPAIR DURING CHOLESTATIC INJURY CAUSED BY ACUTE LOSS OF ADHERENS JUNCTIONS FROM CHOLANGIOCYTES ◆

Yekaterina Krutsenko Shuchang Liu[1] Qin Li[1] junjie zhu[1] Minakshi Poddar[1] Satdarshan (Paul) Monga[1]

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Background: β-catenin as a key effector of the canonical Wnt signaling is vital for normal liver function. However, β-catenin is also a component of adherens junctions (AJ), where its loss is compensated by γ-catenin, a homologous desmosomal protein. The importance of AJ maintenance in bile ducts has not been investigated. In the present study we inducibly, specifically, and dually delete β- and γ-catenins from biliary epithelium to study implications of AJ loss. **Methods:** We used *Opn-iCreERT2$^{+/-}$; Ctnnb $^{fl/fl}$; Jup $^{fl/fl}$* mice (DKO), in which both b-catenin (*Ctnnb1*) and γ-catenin (*Jup*) are acutely deleted by inducible, cholangiocyte-specific OPN-driven expression of Cre-recombinase. The extent of injury was controlled by administrating either 4 or 2 doses of tamoxifen (100mg/kg) to achieve variable deletion of the catenins from all or a subset of cholangiocytes, respectively. Hepatocyte-specific lineage tracing in DKO mice was performed by administration of AAV8-TBG-GFP prior to Cre-dependent recombination. **Results:** After 4 doses of tamoxifen, DKOs showed morbidity and mortality with probability of survival dropping to 0% 5wks after the recombination. DKO mice exhibit decreased BW, jaundice, lethargy, and liver injury as evident from elevated levels of ALT, AST, ALP, and hyperbilirubinemia. Grossly, livers of DKOs exhibited surface scarring and adhesions. A 10-fold decrease in bile flow rate was observed in DKOs following bile duct cannulation. Bile acid (BA) quantification by mass-spec revealed increased total BA levels in serum and in liver of DKOs. Histology revealed multiple biliary infarcts, inflammation, and severe portal fibrosis in DKOs. CK19-positive bile ducts in DKOs were irregular and showed decreased or absent lumen by both IHC and TEM.

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Ink injection into the common bile duct showed blebbing and leakages along the biliary tree. snRNA-seq revealed differential clustering of hepatocytes and a distinct population of cholangiocytes in DKO livers. DKO-associated cholangiocyte-specific genetic signature indicated remodeling of the cell-cell junctions and upregulation of necroptosis. To investigate any possibility of spontaneous repair, DKO mice injected with AAV8-TBG-GFP were subjected to only 2 doses of tamoxifen. These mice exhibited signs of severe injury at 2 weeks, as shown by limited mortality, abnormal serum biochemistry, and histology, yet at the 4-week timepoint, the surviving cohort showed significant resolution of injury. Dual GFP+/CK19+ cholangiocytes were observed in DKO mice at 4 weeks, suggesting successful hepatocyte-to-cholangiocyte transdifferentiation contributing to resolution of injury in DKO mice. **Conclusion:** Dual loss of β- and γ-catenins from cholangiocytes causes severe acute intrahepatic cholestatic injury in mice. Our model shows the critical role of cell-cell junctions in cholangiocytes as well as demonstrates the plasticity of hepatocytes during hepatobiliary repair.

Disclosures: Yekaterina Krutsenko: Nothing to Disclose, Shuchang Liu: Nothing to Disclose, Qin Li: Nothing to Disclose, junjie zhu: Nothing to Disclose, Minakshi Poddar: Nothing to Disclose, Satdarshan (Paul) Monga: Surrozen: Independent Contractor, Mermaid Bio: Advisor, Vicero: Advisor, AntlerA: Advisor, Genentech: Speaking and Teaching, Alnylam: Grant/Research Support, Alnylam: Consultant, UbiquiTx: Consultant, Mermaid Bio: Consultant, Fog Pharmaceuticals: Grant/Research Support, Surrozen: Consultant, Genentech: Independent Contractor

4264 | IDENTIFICATION OF ALCOHOLIC ASSOCIATED HEPATITIS-RELATED AND MESENCHYMAL STEM CELL TREATMENT TARGET GENES

Han Seul Ki Moon Young Kim[1] Soon Koo Baik[1]

[1]Yonsei wonju severance christian hospital

Background: Alcoholic associated hepatitis (AH) is a life-threatening condition and widespread chronic liver condition that places patients at risk of short-term mortality if it is not properly managed. This study aimed to identify transcriptomic biomarkers and cell therapy targets for AH. **Methods:** We conduct a systematic meta-analysis of published human gene expression studies on liver biopsies and blood derived gene data. First, three liver AH transcriptome datasets and a blood AH dataset were combined to discover a common phenotype. Second, two AH prognosis datasets were compiled, which are including gene phenotype reflecting prognosis. Using inverse weighted variance-based method mounted in METAL software, the candidate genes related to AH in liver and blood tissues and annotated them as the liver-blood AH meta genes. Third, three MSC datasets were curated for gene identification in stem cell response. Meta-analysis was implemented on the individual cohort-specific summary statistics obtained from differential expression methods to identify the AH-related biomarkers. To narrow down the candidate hub genes among stem cell treated data, TF database, protein-protein interaction network, disease-gene association database, and disease- and expression-related SNP database were used to analysis. And these genes were validated through a mouse alcoholic hepatitis model. **Results:** With previously identified alcoholic gene-related databases, external verification was performed and 47 upstream AH-related genes were presented. The analysis contains some genes that have not been previously characterized in the context of alcoholic liver disease. In vivo, the expression of some genes was confirmed. AKT1, SPHK1 were up regulated in alcoholic hepatitis mouse model. **Conclusion:** We present key genes involved in the progression of AH and provide a meta-analysis of results in a objective, statistically-based format. And at the same time, we suggest this biomarkers that can predict the prognosis of AH and treatment response. By using these genes, we can confirm the genetic changes caused by stem cell treatment and this can be used to lay the foundation for targeted cell therapy or function-enhanced genetic therapy.

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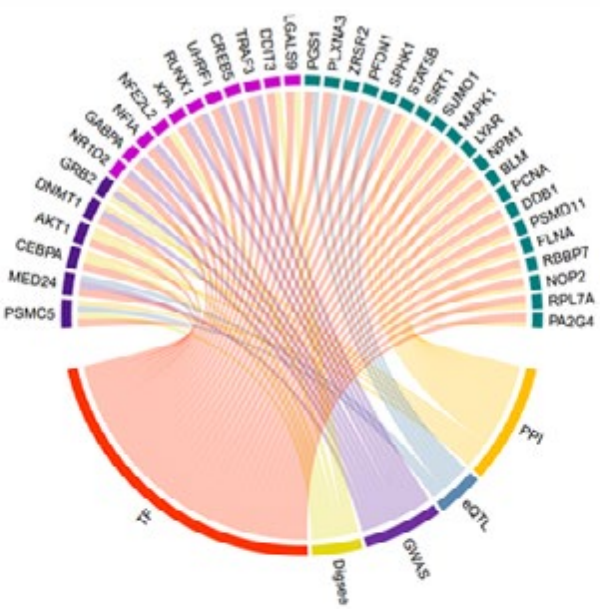
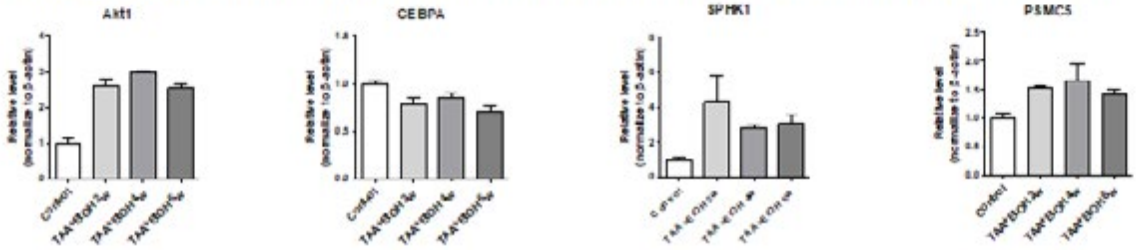


Akt1, CEBPA, SPHK1 and PSMC5 expression in TAA and EtOH induced severe acute alcoholic hepatitis mouse model



Disclosures: Han Seul Ki: Nothing to Disclose, Moon Young Kim: Nothing to Disclose, Soon Koo Baik: Nothing to Disclose

4265 | DIAGNOSTIC DELAY LIMITS EARLY RECOGNITION OF PRIMARY BILIARY CHOLANGITIS

Ana Maria Davila Morales[1] *Nancy Reau*[2] *Zoe Post*[2] *Kesany Boupapanh*[2]

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Background: Primary biliary cholangitis (PBC) is a chronic autoimmune cholestatic liver disease with destruction of intrahepatic bile ducts. It is commonly seen in women aged 40 or older and associated with high levels of alkaline phosphatase (ALP) and antimitochondrial autoantibodies (AMA). PBC can progress to cirrhosis with need for liver transplantation and is associated with a 9-10 year mean survival rate. It is imperative that PBC is detected early to improve outcomes. We aimed to assess if a gap between presentation and diagnosis exists in patients with PBC. **Methods:** A retrospective study of 163 patients with AMA-positive (AMA+) PBC at Rush University Medical Center from 2017 to 2022 was conducted to calculate the lag between lab abnormalities to AMA testing and PBC diagnosis. Data included demographics, aspartate transferase (AST), alanine transferase (ALT), ALP, and total bilirubin (TB). A point system was created by assigning 1 point each to female sex, age greater than 40 years, presence of pruritus, ALP > 120 and ALP > 250. This data was used to interrogate a subset of female patients 40 years or older with two distinct abnormal ALP values at inpatient or outpatient settings from 2017 to 2022, yielding 15,997 patients. Criteria was narrowed to 12,370 outpatient charts with two distinct abnormal ALP values. AMA testing and hepatology referral order data were obtained. **Results:** 163 patients with AMA+ PBC were identified. Of these, 150 were female (92%) with 61-year average age. Average time from positive AMA result to PBC diagnosis was 94 days. Average delay from first abnormal ALP to PBC diagnosis was 1,030 days,

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923 days for AST, 935 days for ALT, and 401 days for TB. Based on the point system, average delay to diagnosis was 833 days for two points (n=20, 12.3%), 1366 days for 3 points (n=99, 55.2%), 472 days for 4 points (n=39, 23.9%) and 106 days for 5 points (n=13, 8%). Of the 12,370 female patients 40 years or older with two distinct abnormal ALP values at outpatient settings, only 12.4% had AMA testing (n=1,535) and 9.9% had hepatology referral orders (n=1,221). **Conclusion:** This study highlights a significant delay in PBC diagnosis from initial symptom onset and/or abnormal ALP result, with an average delay of more than 3 years. The low rate of AMA testing and hepatology referrals suggests the need for development of diagnostic criteria and continued medical education to appropriately screen women aged >40 with elevated ALP for PBC.

Disclosures: Ana Maria Davila Morales: Nothing to Disclose, Nancy Reau: Gilead: Grant/Research Support, eiger: Grant/Research Support, abbott: Consultant, Arbutus: Consultant, Gilead: Consultant, VIR: Consultant, Salix: Consultant, Salix: Grant/Research Support, AbbVie: Grant/Research Support, Zoe Post: Nothing to Disclose, Kesany Boupapanh: Nothing to Disclose

4266 | HISTOLOGICAL STAGE AS PREDICTOR OF THE COMPLICATIONS OF PRIMARY BILIARY CHOLANGITIS

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Background: This study aimed to clarify the predictive ability of histological stage (HS) in comparison with biochemical response to ursodeoxycholic Acid (UDCA) (BR) for the development of complications in patients with primary biliary cholangitis (PBC). **Methods:** A total of 226 patients were diagnosed with serologically and histologically confirmed PBC. All the patients with asymptomatic PBC were treated with UDCA continuously for at least 1 year after the diagnosis were enrolled. Pathological staging was performed in accordance with the Scheuer and Nakanuma classifications (SC and NC). NC comprises grading for liver fibrosis (F) and bile duct loss (S). Nakanuma F and S scores were assessed on a four-point scale (F0-F3 and B0-B3). BR was evaluated according to three previously published definitions: the Nara criteria (NaC), Paris II criteria (PC), and Barcelona criteria (BC). This study investigated the relationship of the development of complications with HS and BR. PBC complications include pruritus, esophageal varices, ascites and jaundice. **Results:** The distribution of patients in stage I, II, III, and IV based on the SC was 70/102/51/3. The distribution of patients in stage I, II, III, and IV based on the Nakanuma classification was 20/89/107/10. The cumulative complication rates (CCR) were significantly higher in the advanced stages (Scheuer III/IV and Nakanuma III/IV) than in the early stages (Scheuer I/II and Nakanuma I/II), respectively. CCR were significantly higher in the advanced Nakanuma F scores (Score 2/3) and Nakanuma B scores (Score 2/3) than the early Nakanuma F scores (Score 0/1) and Nakanuma B scores (Score 0/1), respectively. However, there was no differences in CCR between the favorite and poor response groups based on NaC, PC or BC. CCR for the four groups of early stages/favorable response (Group A: GA), advanced stages/favorable response (GB), early stages /poor response (GC) and advanced stages/poor response (GD) was estimated by combining histological stages based on HS and BR, defined as (1) SC/NaC, (2) SC/PC, (3) SC/BC, (4) NC/NaC, (5) NC/PC, (6) NC/BC, (7) F/NaC, (8) F/PC, (9) F/BC, (10) B/NaC, (11) B/PC, and (12) B/BC. CCR for (2) SC/PC, (3) SC/BC, (4) SC/NaC, (5) NC/PC, (6) NC/BC, (9) F/BC, and (11) B/PC were significantly higher in GB than in GA. CCR for (1) SC/NaC, (3) SC/BC, (4) NC/NaC, (6) NC/BC, (7) F/NaC, (8) F/PC, and (9) F/BC were significantly higher in GD than in GC. These findings suggest that CCR increase with progression of HS, regardless of BR. The multivariate COX regression analysis showed that the advanced Nakanuma stage was confirmed as independent factor associated with the development of complications in patients with PBC. **Conclusion:** Both HS and BR play a pivotal role in the development of complications of PBC. HS is associated with a higher risk for the development of complications than BR in patients with PBC.

Disclosures: Tadashi Namisaki: Nothing to Disclose, Yukihisa Fujinaga: Nothing to Disclose, Shinya Sato: Nothing to Disclose, NORIHISA NISHIMURA: Nothing to Disclose, KOSUKE KAJI: Nothing to Disclose, Hitoshi Yoshiji: Nothing to Disclose

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4267 | ALTERED SERUM BIOMARKERS IN PRIMARY SCLEROSING CHOLANGITIS AFTER PROCTOCOLECTOMY ARE CONSISTENT WITH IMPROVED PROGNOSIS AND REDUCED GUT MICROBIAL IMPACT

Sara Kristina Viberg Tjønnfjord[1] Trine Folseraas[1] Hólmfríður Helgadóttir[1] Arild Nesbakken[2] Ragnhild Lothe[3] Per Magne Ueland[4] Adrian McCann[4] William Rosenberg[5] Tom Karlsen[1] Mette Vesterhus[1] Johannes Hov[1] Peder Rustøen Braadland[1]

[1]Norwegian PSC Research Center, [2]Institute of Cancer Research, [3]Institute for Cancer Research, [4]BEVITAL AS, [5]University College London Medical School

Background: Proctocolectomy has recently been associated with improved outcomes in people with primary sclerosing cholangitis (PSC). In this study, we aimed to define the clinical and pathogenic impact of serum biomarkers in PSC related to inflammatory bowel disease (IBD) activity and colonic surgery. **Methods:** Serum biomarkers reflecting inflammation (IL-8, neopterin), gut barrier function and/or inflammation (sCD14, LBP, IFABP), microbial activity (TMAO, PLP/vitamin B6) and fibrosis (ELF) were analysed in an expanded Norwegian cohort of 315 people with PSC. Colectomy status and IBD activity were evaluated retrospectively. In addition, a colorectal cancer cohort without PSC (n=68) sampled before and after colectomy and healthy controls (n=100) were included. **Results:** There were no associations between the investigated biomarkers and IBD activity in people with PSC and an intact colon at sampling, categorized as remission, mild or moderate activity. When classifying colectomy status in PSC according to i) no colectomy, ii) colectomy after sampling, iii) (sub)total colectomy or hemicolectomy at time of sampling, or iv) proctocolectomy at time of sampling, TMAO, sCD14, IL-8, LBP, ELF (all reduced) and PLP(increased) associated with colectomy status, in particular driven by those with proctocolectomy (see examples TMAO and sCD14 in Figure). Previously observed associations between biomarkers and liver transplantation-free survival were confirmed in this expanded cohort, and no statistical interactions were found between biomarkers and colectomy status. The fully microbiota-dependent metabolite TMAO showed particularly low levels after colectomy with the lowest in those with a proctocolectomy. (Sub)total surgical removal of the colon in people with colorectal cancer (without PSC) resulted in a significant reduction of TMAO compared with hemicolectomy, while surgery-related changes for other biomarkers suggested they primarily originated from outside the gut. **Conclusion:** Serum biomarkers in people with PSC and proctocolectomy are altered in line with improved outcomes. Taken together with the lack of associations with IBD activity, this suggests that status of the liver disease, and not intestinal inflammation, is a major determinant of most non-microbial biomarkers in PSC. Gut microbiota-produced biomarkers may be altered by colectomy, which offers potential mechanistic insight into its proposed protective role.

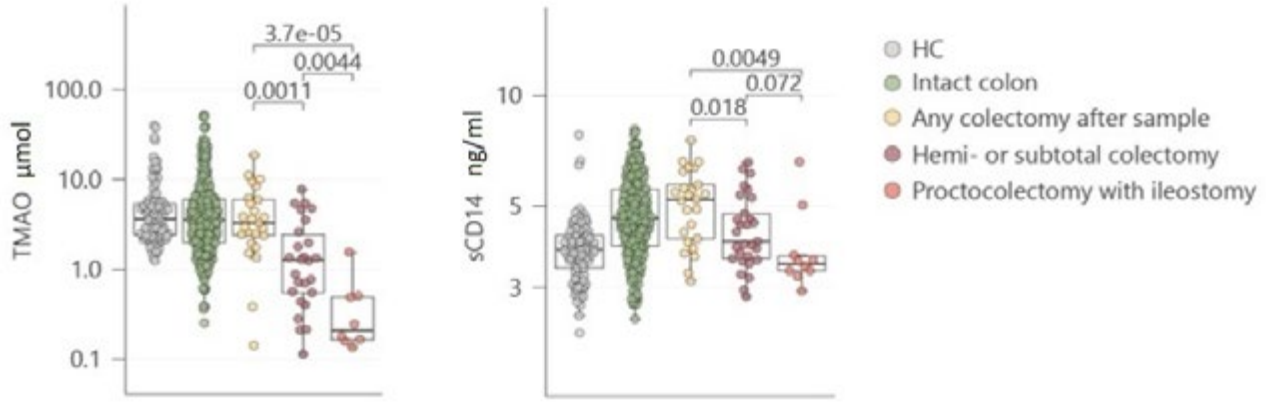

Figure: Serum TMAO and sCD14 by colectomy status

Disclosures: Sara Kristina Viberg Tjønnfjord: Nothing to Disclose, Trine Folseraas: Nothing to Disclose, Hólmfríður Helgadóttir: Nothing to Disclose, Arild Nesbakken: Nothing to Disclose, Ragnhild Lothe: Nothing to Disclose, Per Magne Ueland: Nothing to Disclose, Adrian McCann: Nothing to Disclose, William Rosenberg: Nothing to Disclose, Tom Karlsen: Nothing to Disclose, Mette Vesterhus: Nothing to Disclose, Johannes Hov: Nothing to Disclose, Peder Rustøen Braadland: Nothing to Disclose

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4268 | CLINICAL PRESENTATION OF PATIENTS WITH AUTOIMMUNE HEPATITIS STRATIFIED BY IMMUNOGLOBULIN G LEVELS

YouRan Zhao[1] Catherine Vincent[2] Marc Bilodeau[2] Pascal Lapierre[1] Julian Hercun[2]

[1]Centre De Recherche Du CHUM, [2]CHUM, Centre De Recherche Du CHUM

Background: Immunoglobulin G (IgG) levels are among the most commonly used biochemical markers in autoimmune hepatitis (AIH). However, the role of IgG in predicting outcomes in that setting remains unclear. While persistently elevated IgG levels are associated with incomplete response to therapy, they are not associated with long-term adverse outcomes. The objective of this study was to evaluate the initial clinical picture of AIH based on IgG levels and to assess its correlation with patient outcomes. **Methods:** Patients included in our institution AIH Biobank, with clinical follow-up for AIH at our institution with documented serum IgG levels at baseline were selected. Patient charts were reviewed for clinical and histological data, and separated into four groups: new-onset AIH with elevated IgG levels, new-onset AIH with normal IgG levels, chronic AIH with elevated IgG levels, and chronic AIH with normal IgG levels. New-onset AIH was defined as patients recruited at the time of diagnosis, whereas chronic AIH included patients on therapy for at least a year. Elevated IgG levels were defined as ≥ 13.0 g/L. Biochemical tests were correlated between groups and Kaplan Meier survival analysis was performed for a composite outcome of death, transplantation or hepatic decompensation (variceal bleed or new onset ascites). **Results:** 118 patients were considered for analysis. Among new-onset patients, IgG levels were elevated in 14 and normal in 10 cases. In chronic patients, IgG levels were elevated in 31 and normal in 63 cases. At baseline visit, the proportion of patients with elevated ALT differed significantly between groups and was higher in new-onset AIH (79%, 80%, 30%, 30% in respectively new-onset high IgG, new onset normal IgG, chronic high IgG and chronic normal IgG, p=0.0003) as was the proportion of patients with elevated bilirubin (36%, 20%, 10%, 5% across the same groups, p=0.0092). However, this was not significantly different between both chronic AIH groups (p=0.4 and p=0.9 for ALT and bilirubin). In addition, the proportion of patients with advanced fibrosis and cirrhosis was similar amongst all groups (Advanced fibrosis: 57%, 50%, 67% and 60% p=0.8, Cirrhosis: 50%, 50%, 60% and 37.5% p=0.3). In the overall cohort, ALT levels did not correlate with IgG levels (Pearson r=0.21). During short-term follow-up in the chronic AIH cohort (median 24 months), 78% of patients with baseline high IgG remained with elevated IgG which led to significantly more treatment increase in this group (17 vs 3% in the normal IgG group, p=0.015). However, liver-related outcomes and deaths did not differ based on IgG levels (log-rank p=0.93). **Conclusion:** In this prospectively followed AIH cohort, the severity of liver disease and stage of fibrosis did not differ in chronic AIH patients based on IgG levels. Furthermore, stratification by serum IgG levels did not allow to discriminate between clinically relevant outcomes.

Disclosures: YouRan Zhao: Nothing to Disclose, Catherine Vincent: Nothing to Disclose, Marc Bilodeau: Mirum Pharmaceuticals: Speaking and Teaching, Pascal Lapierre: Nothing to Disclose, Julian Hercun: Nothing to Disclose

4269 | DEEP LEARNING ANALYSIS OF MAGNETIC RESONANCE IMAGING ACCURATELY DETECTS EARLY-STAGE CHOLANGIOCARCINOMA IN PATIENTS WITH PRIMARY SCLEROSING CHOLANGITIS ◆

Yashbir Singh[1] John Eaton[2] Sudhakar Venkatesh[2] Shahriar Faghani[1] Mette vesterhus[3] Tom Karlsen[4] Kristin Jorgensen[5] Trine Folseraas[4] Kosta Petrovic[6] Anne Negård[5] Aliya Gulamhusein[7] Gregory Gores[1] Sumera Ilyas[2] Timucin Taner[2] Julie Heimbach[2] Nicholas LaRusso[1] Konstantinos Lazaridis[1] Bradley Erickson[1]

[1]Mayo Clinic - Rochester, [2]Mayo Clinic Rochester, [3]University of Bergen, [4]Oslo University, [5]Akershus University Hospital, [6]Haukeland University, [7]University of Toronto

Background: Cholangiocarcinoma (CCA), particularly perihilar CCA (pCCA), is the leading source of mortality among patients with primary sclerosing cholangitis (PSC). Early detection affords patients an opportunity for curative treatment. Yet establishing a diagnosis of early stage pCCA in those with PSC is challenging. Therefore, we aimed to develop and validate a deep learning model, utilizing magnetic resonance imaging (MRI), to predict the presence of pCCA in those with PSC and compare its performance to an expert radiologist. **Methods:** We conducted a multicenter, international, retrospective cohort study of adults with large duct PSC who underwent MRI with contrast. pCCA was defined as either characteristic mass with progressive enhancement on delayed

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phase imaging or the confirmation of adenocarcinoma on cytology or histology. All patients with pCCA had early stage disease defined by radial diameter of mass 3 cm or less, no evidence of intra- or extrahepatic metastases on cross-sectional imaging or lymph node spread after endoscopic ultrasound sampling. Images were reviewed by a senior radiologist (SKV) at a large referral center who was blinded to the clinical information. The radiologists imaging criteria are described in Table 1. We trained a 3D-DenseNet121 classifier, a type of convoluted neural network, using 3D MRI images (delayed or portal venous phases) with 5-fold cross validation to predict which patients had pCCA. The best performing fold was then applied in a separate test cohort to predict the presence of pCCA. **Results:** Two-hundred and ninety-seven patients were included (training cohort n = 150; test cohort n = 147). pCCA was present in 129 individuals (training cohort n = 64; test cohort n = 65). Among those with pCCA, 55 (42.6%) did not have a mass on MRI. In the training cohort, the model's performance across all 5 folds yielded area under the curve values between 91.0-96.0%. In Table 1 the performances of the best of the 5 models and radiologist in the separate test cohort are shown. While the specificity was lower, the model had fewer missed cancer cases, even amongst patients where perihilar mass had not yet manifested, when compared to an expert radiologist. **Conclusion:** This study demonstrates that the 3D-DenseNet121 MRI model can detect early-stage pCCA among those with PSC when curative treatment is still possible. The model's good sensitivity illustrates its potential to augment the performance of providers in clinical practice.

Table1. Performance of model and radiologist in independent test cohort

	Sensitivity(95% CI)	Specificity(95% CI)	AUC(95% CI)
Deep learning MRI model Test cohort n=147	88.0% (77.0-94.0%)	75.0% (65.9-83.0%)	81.0% (73.7-88.3%)
Radiologist[a] Test cohort n=147	57.3% (45.6-68.7%)	100% (95.0-100%)	78.1% (70.3-85.7%)
Deep learning MRI model Test cohort (patients with mass forming pCCA excluded) n=110	86.0% (68.0-94.0%)	63.0% (53.0-73.0%)	74.0% (62.5-85.5%)
Radiologist[b] Test cohort (patients with mass forming pCCA excluded) n=110	75.0% (57.0-87.1%)	95.1% (88.8-98.0%)	85.0% (75.6-94.4%)

[a] The following were considered positive by radiologist: perihilar mass with progressive enhancement on delayed phase imaging or focal mass-like periductal soft tissue thickening with delayed phase enhancement and extension of soft tissue resulting in vascular encasement or invasion.

[b] The following were considered positive by radiologist: stricture with non-focal periductal thickening without delayed phase enhancement; progressive lobar atrophy secondary to worsening perihilar stricture; ill-defined, irregular delayed enhancement of ductal wall without distinct mass.

Abbreviations: area under the curve (AUC); CI (confidence intervals); MRI (magnetic resonance imaging); pCCA (perihilar cholangiocarcinoma)

Disclosures: Yashbir Singh: Nothing to Disclose, John Eaton: Nothing to Disclose, Sudhakar Venkatesh: Nothing to Disclose, Shahriar Faghani: Nothing to Disclose, Mette vesterhus: Nothing to Disclose, Tom Karlsen: Nothing to Disclose, Kristin Jorgensen: Nothing to Disclose, Trine Folseraas: Nothing to Disclose, Kosta Petrovic: Nothing to Disclose, Anne Negård: Nothing to Disclose, Aliya Gulamhusein: Advanz: Consultant, Cymabay: Consultant, Gregory Gores: Nothing to Disclose, Sumera Ilyas: Nothing to Disclose, Timucin Taner: Nothing to Disclose, Julie Heimbach: Nothing to Disclose, Nicholas LaRusso: NIH: R01 DK 24031, NIH: R01 DK 57993, NIH: P30 DK 84567, NIH: P30 DK90728, NIH: R01 DK117133, NIH: T32 DK 07198, Konstantinos Lazaridis: Nothing to Disclose, Bradley Erickson: Nothing to Disclose

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4270 | THE PREVALENCE OF INTESTINAL FAILURE-ASSOCIATED LIVER DISEASE (IFALD) IN PATIENTS ON LONG-TERM HOME PARENTERAL NUTRITION

Nicholas Wan[1] Sharifah Syed Mustaffah[2] Andrew Holt[2] Richard Woodman[3] Shailesh Bihari[2] Steven Galluccio[2] Sumudu Narayana[2] Qun Chen[2] Maria Kielpikowska[2] Kate Muller[2] Jeyamani Ramachandran[2] Rachel Wundke[2] Rosalie Altus[2] Alan Wigg[2]

[1]Lyell McEwin Hospital, [2]Flinders Medical Centre, [3]Flinders University

Background: Intestinal failure-associated liver disease (IFALD) is a recognized complication of long-term parenteral nutrition (PN). Estimates for prevalence range from 25-100%, due to differences in patient populations and parenteral nutrition regimens. The aims of the study were to estimate IFALD prevalence in adults receiving long-term home PN (HPN), describe the biochemical and elastography characteristics of IFALD, and identify predictors of IFALD. **Methods:** This was a single-centre, retrospective cohort study. Patients were included if currently on long-term (>12 weeks) HPN or had received long-term HPN in the last 10 years. Patients with any malignancy or pre-existing liver disease were excluded. There is no consensus on the criteria for IFALD diagnosis. Early detection is crucial due to the rapid progression of disease. We defined IFALD as any persistent, unexplained, elevation (>1.5x ULN) of LFTs for >3 months over Cavicchi's criteria of >6 months. Vibration controlled transient elastography (VCTE) with controlled attenuated parameter score, was performed in all patients. The covariates for univariate and multivariate logistic regressions were: age, gender, HPN calories-per-week, HPN frequency, HPN-duration, HPN-formula, current or past-HPN, indication for HPN, BMI, lipids pre and 3-months-post HPN commencement. **Results:** 24 patients were included in the study. The most common indications for PN were bowel surgery (45.8%) and Crohn's Disease (29.2%). The median (IQR) duration of HPN and weekly calories was 42.5 (15.8-62.3) months and 6647kcal (3476.3-8471.3) respectively. IFALD was present in 15 (62.5%) patients. 9/15 (60%) had short-gut syndrome. In IFALD patients, the most common pattern of abnormality was cholestasis, with 12 (80%) patients demonstrating a cholestatic pattern. In IFALD patients, the median (IQR) values for GGT, ALP, ALT, AST, and Bilirubin were 254U/L(132-312), 233U/L(188.5-365), 54U/L(30.5-113.5), 44U/L(31.5-68.5), and 7umol/L(5.5-16) respectively. VCTE revealed likely significant fibrosis (fibrosis score ≥2) in 3 (20.0%) patients and likely significant steatosis (steatosis score ≥2) in 2 patients. 12 (80%) patients on current-HPN had IFALD, versus 3 (33.3%) past-HPN patients. On univariate analysis, the only significant association was ongoing HPN (OR = 8.0, 95%CI= 1.2-52.2, p-value=0.03). There were no significant associations with IFALD on multivariate analysis. **Conclusion:** In this cohort of patients, there was a high prevalence of IFALD using our criteria (>1.5x ULN for >3 months). IFALD typically presents with a cholestatic pattern of liver injury. An important minority of IFALD patients may develop underlying significant fibrosis. Main predictors for the development of IFALD was ongoing HPN and short gut syndrome, suggesting some reversibility of liver injury with cessation of HPN. Larger, multicenter studies are required to identify any clinical predictors of IFALD.

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Baseline Characteristics	Patients (n = 24)
Male / Female, n	7, 17
Age, y, median (range)	61 (44-70)
BMI, median (IQR)	22.6 (19.6-25.9)
Indications for HPN	
Inflammatory Bowel Disease	n = 7
Bowel Surgery	n = 11
Dysmotility	n = 3
Scleroderma Bowel Disease	n = 1
Primary Intestinal Lymphangiectasia	n = 1
Ehler Danlos Syndrome	n = 1
Mean Duration on HPN, months, n (IQR)	42.5 (15.8-62.3)
Mean total calories of PN per week, kcal, n (IQR)	6647 (3476.3-8471.3)
IFALD diagnosed, n (%)	15 (62.5)
Pattern of IFALD	
Cholestatic	n = 13
Hepatocellular	n = 1
Mixed	n = 2
Liver Function Tests	
GGT, U/L, median (IQR)	254 (132-312)
ALP, U/L, median (IQR)	233 (188.5-365)
ALT, U/L, median (IQR)	54 (30.5-113.5)
AST, U/L, median (IQR)	44 (31.5-68.5)
Bilirubin, umol/L, median (IQR)	7 (5.5-16)
Vibration Controlled Transient Elastography (VCTE)	
Liver Stiffness, kPa, median (IQR)	6.45 (7.3-5.15)
CAP, dB/m, median (IQR)	266 (193.5-286.5)
Fibrosis score, median (IQR)	1 (1-1)
Steatosis score, median (IQR)	0 (0-0)

Disclosures: Nicholas Wan: Nothing to Disclose, Sharifah Syed Mustaffah: Nothing to Disclose, Andrew Holt: Nothing to Disclose, Richard Woodman: Nothing to Disclose, Shailesh Bihari: Nothing to Disclose, Steven Galluccio: Nothing to Disclose, Sumudu Narayana: Nothing to Disclose, Qun Chen: Nothing to Disclose, Maria Kielpikowska: Nothing to Disclose, Kate Muller: CSL Behring: Advisor, NovoNordisk: Advisor, AstraZeneca: Advisor, Chiesi: Advisor, Eisai: Speaking and Teaching, Jeyamani Ramachandran: Nothing to Disclose, Rachel Wundke: Nothing to Disclose, Rosalie Altus: Nothing to Disclose, Alan Wigg: Nothing to Disclose

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4271 | MAGNETIC RESONANCE CHOLANGIOPANCREATOGRAPHY (MRCP) FOR SUSPECTED CHOLANGIOPATHY IN CHILDREN: A MULTI-READER AGREEMENT STUDY

Léticia Khendek[1] Pradipta Debnath[1] Nadeen Abu Ata[2] Joseph Cao[3] Shailee Lala[4] Archana Malik[5] Erica Riedesel[6] Gary Schooler[7] Narendra Shet[8] Leslie Spence[9] A. Luana Stanescu[10] Bin Zhang[11] Alexander Miethke[1] Jonathan Dillman[1] Andrew Trout[1]

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Background: The aim of this study was to assess inter-radiologist agreement for Magnetic Resonance Cholangiopancreatography (MRCP) interpretation in pediatric patients with known or suspected cholangiopathy. **Methods:** This was a retrospective, multi-reader study of MRCP examinations clinically obtained at a single institution to evaluate for presence of cholangiopathy in patients less than 21 years-old between 2018-2023. Based on review of clinical records, patients were classified as having Primary Sclerosing Cholangitis (PSC), Autoimmune Sclerosing Cholangitis (ASC) or other diagnosis. Images were reviewed by nine blinded pediatric radiologists who independently documented intra- and extrahepatic biliary findings. Kappa (κ) statistics and intra-class correlation coefficients (ICC) were used to quantify agreement. **Results:** Seventy-five patients were included (median age=16.8 years [IQR: 13.8 to 18.7 years]; 48 boys), 45% (34/75) of whom were diagnosed with PSC or ASC of which 79% (27/34) had concomitant inflammatory bowel disease (IBD). The most common other diagnoses were IBD without autoimmune liver disease (n=11), autoimmune hepatitis (n=9), and Gilbert's syndrome (n=4). Among observers, agreement was slight for presence (yes/no) of cholangiopathy (κ=0.15, see Table) and PSC/ASC (κ=0.13). There was no agreement for intrahepatic stricture number and extent. Agreement was slight for presence (yes/no) of intrahepatic stricturing disease (κ=0.08). Most other findings had fair agreement between readers (including biliary obstruction, bile duct mural thickening, "floating" bile ducts, intrahepatic biliary dilation without stricture, intrahepatic focal/segmental dilations, intra- and extrahepatic diverticula, diffuse extrahepatic dilation without stricture, extrahepatic stricture, and intrahepatic peribiliary T2-weighted signal [κ=0.22 to 0.34]). There was moderate agreement on measured extrahepatic stricture length (κ=0.46) and presence (yes/no) of extrahepatic biliary dilation (κ=0.53). There was good agreement for measured extrahepatic bile duct diameter (ICC=0.89). **Conclusion:** Inter-radiologist agreement for MRCP interpretation in children is overall poor to fair, especially for intrahepatic duct abnormalities and disease classification. There is better agreement for extrahepatic cholangiopathy and discrete measurements. Future scoring systems for imaging diagnosis of pediatric PSC may account for the higher inter-reader agreement of abnormalities affecting the extrahepatic biliary tree.

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Table: MRCP inter-radiologist agreement for entire study sample and for patients with only Primary Sclerosing Cholangitis (PSC)/Autoimmune Sclerosing Cholangitis (ASC).

Imaging Features		κ / ICC (95% CI) for entire study sample (n=75)	P-value	κ / ICC (95% CI) for only PSC / ASC patients (n=34)	P-value
General	Cholangiopathy	0.151 (0.073 to 0.229)	**<0.001**	0.087 (-0.01 to 0.184)	0.078
	PSC / ASC	0.134 (0.062 to 0.206)	**<0.001**	0.107 (0.019 to 0.195)	**0.019**
	Biliary obstruction	0.331 (0.195 to 0.466)	**<0.001**	0.276 (0.131 to 0.421)	**<0.001**
	Bile duct mural thickening and/or irregularity	0.226 (0.118 to 0.334)	**<0.001**	0.226 (0.085 to 0.367)	**0.003**
Intrahepatic	Floating bile ducts	0.219 (0.13 to 0.308)	**<0.001**	0.241 (0.105 to 0.377)	**0.001**
	Stricturing disease	0.081 (0.04 to 0.121)	**<0.001**	0.082 (0.028 to 0.135)	**0.004**
	Stricture number (categorical)	-0.002 (-0.158 to 0.153)	0.972	0.002 (-0.177 to 0.182)	0.971
	Stricture extent (categorical)	-0.056 (-0.093 to -0.019)	**0.011**	-0.061 (-0.114 to -0.008)	**0.033**
	Diffuse biliary dilation without stricture	0.313 (0.177 to 0.449)	**<0.001**	0.301 (0.132 to 0.471)	**0.001**
	Focal / segmental dilations	0.243 (0.144 to 0.342)	**<0.001**	0.192 (0.071 to 0.313)	**0.003**
	Sacculations / diverticula	0.271 (0.126 to 0.416)	**<0.001**	0.282 (0.108 to 0.456)	**0.002**
	Peribiliary increased T2W signal	0.344 (0.236 to 0.451)	**<0.001**	0.279 (0.147 to 0.411)	**<0.001**
Extrahepatic	Stricturing disease	0.229 (0.124 to 0.333)	**<0.001**	0.184 (0.037 to 0.331)	**0.016**
	Stricture length	0.455 (-0.113 to 1)	0.075	0.513 (0.306 to 0.719)	**0.020**
	Diffuse biliary dilation without stricture	0.216 (0.141 to 0.291)	**<0.001**	0.235 (0.135 to 0.336)	**<0.001**
	Biliary dilation	0.526 (0.403 to 0.649)	**<0.001**	0.534 (0.389 to 0.678)	**<0.001**
	Sacculations / diverticula	0.249 (0.105 to 0.393)	**0.001**	0.136 (-0.003 to 0.276)	0.055
	Bile duct maximum diameter	0.886 (0.849 to 0.919)	**<0.001**	0.856 (0.786 to 0.915)	**<0.001**

ASC= Autoimmune sclerosing cholangitis; CI=Confidence Interval; ICC= Intra-class correlation coefficient; PSC= Primary Sclerosing Cholangitis; T2W= T2-weighted; MRCP= Magnetic Resonance Cholangiopancreatography.

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4272 | SPATIAL HETEROGENEITY OF LIVER STIFFNESS BY MR ELASTOGRAPHY IN PATIENTS WITH PRIMARY SCLEROSIS CHOLANGITIS DOES NOT ASSOCIATE WITH CLINICAL OUTCOMES

Erick Cruz Grave[1] *Connie Chan*[1] *Michael Corwin*[1] *Richard Dean*[1] *Sandeep Dhaliwal*[1] *Maryam Yazdanfar*[1] *Christopher Bowlus*[1]

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Background: Primary sclerosing cholangitis (PSC) is a cholestatic liver disease that progresses to cirrhosis and liver failure. Staging of PSC by liver biopsy or vibration-controlled transient elastography may not accurately

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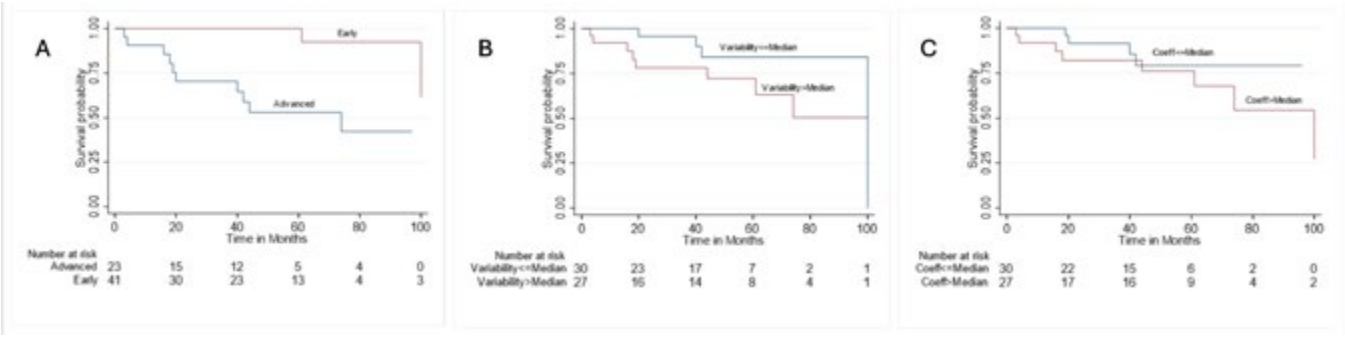
reflect disease stage due to the patchy fibrosis of PSC. This study aimed to compare spatial heterogeneity of liver stiffness (LS) by MR elastography (MRE) in patients with PSC to metabolic dysfunction-associated steatotic liver disease (MASLD) and its association with clinical outcomes in PSC. **Methods:** Patients with PSC or MASLD with at least 1 MRE were included. Fibrosis stage was assigned based on prior optimal cutoff values for PSC and MASLD and classified as early (F0-2) or advanced (F3-4). Spatial heterogeneity was assessed by 1) the *variability of LS* calculated as the difference between the maximum and minimum LS divided by the maximum LS and 2) the *coefficient of variation (CoV)* calculated as the standard deviation of LS at each MRE slice divided by the respective mean LS. MREs were classified as homogenous or heterogenous if the variability of LS was < or > the median variability, respectively, for each disease. **Results:** A total of 112 patients (PSC: n=73, 71% IBD, 46 early stage; MAFLD: n= 39, 16 early stage) were included. In both PSC and MASLD, the variability of LS increased with increasing LS *(r* = 0.31, p = 0.01 and *r* = 0.57, p = 0.0002, respectively). CoV also correlated with LS in patients with MASLD (*r* = 0.34, p = 0.03), but not with PSC (*r* = 0.19, p = 0.12). Among all patients, 35 (53.0%) PSC and 16 (41.0%) MASLD patients were classified as heterogenous (p = 0.32). Variability (p = 0.31) and CoV (p = 0.52) of LS did not differ significantly between PSC and MASLD. Patients with PSC and advanced disease had lower survival free of hepatic decompensation whereas survival did not differ between patients with spatial heterogeneity above or below the median (Figure). After adjustment for multiple clinical variables, neither variability nor CoV of LS were predictors of transplant-free survival (TFS) or hepatic decompensation (HD). In contrast, LS remained a significant predictor of TFS (HR 1.44, P = 0.006) and HD (HR 1.63, P = 0.01). **Conclusion:** Spatial heterogeneity of LS by MRE increases with progressive disease in both PSC and MASLD, however, it is not associated with clinical outcomes in PSC. Liver stiffness by MRE remains an independent predictor of clinical outcomes in patients with PSC.



Disclosures: Erick Cruz Grave: Nothing to Disclose, Connie Chan: Nothing to Disclose, Michael Corwin: Corcept Therapeutics: Consultant, Richard Dean: Nothing to Disclose, Sandeep Dhaliwal: Nothing to Disclose, Maryam Yazdanfar: Nothing to Disclose, Christopher Bowlus: Calliditas: Grant/Research Support, ChemoMab: Grant/Research Support, ChemoMab: Consultant, COUR Phamaceuticals: Grant/Research Support, Cymabay: Grant/Research Support, Cymabay: Consultant, Cymabay: Consultant, Gilead: Grant/Research Support, GSK Pharmaceuticals: Grant/Research Support, GSK Pharmaceuticals: Consultant, Hanmi: Grant/Research Support, Intercept: Grant/Research Support, Invea Therapeutics: Consultant, Ipsen: Grant/Research Support, Ipsen: Consultant, Mirum: Grant/Research Support, NGM Bio: Consultant, Novartis: Grant/Research Support, Novo Nordisk: Grant/Research Support, Pliant Therapeutics: Grant/Research Support, Pliant Therapeutics: Consultant, Viking Therapeutics: Grant/Research Support, Zydus Therapeutics: Grant/Research Support

4273 | SIGNIFICANCE OF HETEROGENEOUS BILIARY EPITHELIAL SENESCENCE AS A POSSIBLE TARGET OF NEW THERAPIES IN PRIMARY BILIARY CHOLANGITIS

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Background: New therapeutic strategies are demanded for the patients with primary biliary cholangitis (PBC) showing inadequate response for ursodeoxycholic acid (UDCA) therapy. We reported biliary epithelial senescence and dysregulated autophagy in the bile duct lesions such as chronic non-suppurative cholangitis (CNSDC) and ductular reactions (DRs) and their possible involvement in the pathogenesis of PBC via senescence associated secretory phenotypes (SASPs). Given recent studies demonstrating heterogeneous senescent cells, such as

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programmed death-ligand 1 (PD-L1)-positive ones with high levels of SASPs, we examined a heterogeneity of biliary epithelial senescence and its clinicopathological significance in PBC. **Methods:** The expression of senescent markers ($p16^{INK4a}$ and $p21^{WAF1/Cip1}$), various SASPs such as CCL2 and interferon induced protein with tetratricopeptide repeats 3 (IFIT3), dysregulated autophagy marker p62 and PD-L1 were immunohistochemically examined in livers taken from the patients with PBC (n=87; early stage, 54: late stage, 33) and 97 control diseased and normal livers. Cultured biliary epithelial cells (BECs) were treated etoposide, serum depletion or glycochenodeoxycholic acid (GCDC) for 4-7 days, then examined for cellular senescence, proliferative activity, apoptotis, mRNA and protein expression of various SASPs, p62 and PD-L1. The effect of senolytic drugs such as Dasatinib and A-1331852 was also determined in senescent BECs. **Results:** The expression of senescent markers, p62 and SASPs was significantly increased in bile duct lesions (CNSDC and DRs) in PBC, compared to control livers ($p<0.01$). The expression of PD-L1 was significantly increased in BECs at CNSDC ($p<0.01$), but not at DRs in PBC. The expression of $p16^{INK4a}$ in DRs was significantly associated with inadequate response for UDCA therapy ($p<0.01$). Double immunofluorescent staining demonstrated heterogeneity in senescent BECs in terms of the expression of p62, SASPs and PD-L1 in bile duct lesions in PBC. Cellular senescence and the expression of p62, SASPs and PD-L1 were significantly increased in BECs treated with etoposide, serum depletion or GCDC ($p<0.01$). Senolytic drugs effectively induced apoptosis in senescent BECs ($p<0.01$). **Conclusion:** There is a distinct heterogeneity in biliary epithelial senescence in PBC. Senolytic drugs and PD-1 inhibitors targeting PD-L1-positive senescent BECs may be promising new therapies for PBC patients with inadequate UDCA responses.

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4274 | BEYOND THE MEAN: EXPLORING THE IMPACT OF BASELINE ALKALINE PHOSPHATASE LEVELS ON ENDPOINTS IN PRIMARY BILIARY CHOLANGITIS ◆

Cynthia Levy[1] Christopher Bowlus[2] Eric Lawitz[3] Nuno Antunes[4] Benjamin Miller[4] Jianfen Shu[4] Claudia Zein[4] Kris Kowdley[5]

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Background: Biochemical response endpoints in primary biliary cholangitis (PBC) utilize reductions in alkaline phosphatase (ALP) and total bilirubin (TB), and may be influenced by the distribution of baseline values. In the phase III ELATIVE® trial (NCT04526665), patients with baseline ALP ≥3x the upper limit of normal (ULN) required a ≥44% reduction from baseline to meet the ALP threshold component of the primary endpoint (ALP <1.67xULN), compared with a ≥17% reduction in those with baseline ALP ≤2xULN. ALP levels can be highly variable in patients with PBC. Here, we explored the impact of baseline ALP levels on biochemical response and ALP normalization in ELATIVE®. **Methods:** In ELATIVE®, patients with unstable ALP levels during the screening period were not eligible to participate. The primary endpoint was biochemical response, defined as ALP <1.67xULN, with a ≥15% reduction from baseline, and normal TB. The first key secondary endpoint was ALP normalization. Here, these endpoints were analyzed at Week 52 in subgroups of patients in ELATIVE® with a range of baseline ALP levels (≤2, 2–≤2.5, 2.5–≤3, 3–≤4, and >4xULN). **Results:** Baseline ALP subgroups comprised (elafibranor, placebo): ≤2xULN (14%, 28%); 2–≤2.5xULN (23%, 26%); 2.5–≤3xULN (23%, 8%); 3–≤4xULN (25%, 17%); and >4xULN (15%, 21%). The primary endpoint was met in 50.9% of patients receiving elafibranor overall, with 86.7% with baseline ALP ≤2xULN and 18.8% with baseline ALP >4xULN meeting the endpoint. For placebo, the overall biochemical response rate was 3.8% and only occurred in patients with a baseline ALP ≤2xULN (Figure 1**A**). ALP normalization occurred in 14.8% receiving elafibranor and 0% receiving placebo overall. The majority of patients receiving elafibranor who had ALP normalization had baseline ALP ≤2xULN (53.3%), however, with elafibranor, ALP normalization also occurred in two patients (12.5%) with baseline ALP >4xULN (Figure 1**B**). A higher proportion of patients receiving elafibranor met either endpoint compared with placebo, regardless of baseline ALP levels, and lower baseline ALP levels yielded higher response rates. **Conclusion:** Patients on elafibranor with lower baseline ALP levels had higher biochemical response and ALP normalization rates versus those with higher baseline ALP. Though important, dichotomous endpoints may limit comparability of trials with varying baseline levels; a higher proportion of patients with low baseline ALP leads to higher response rates in both investigational and placebo groups.

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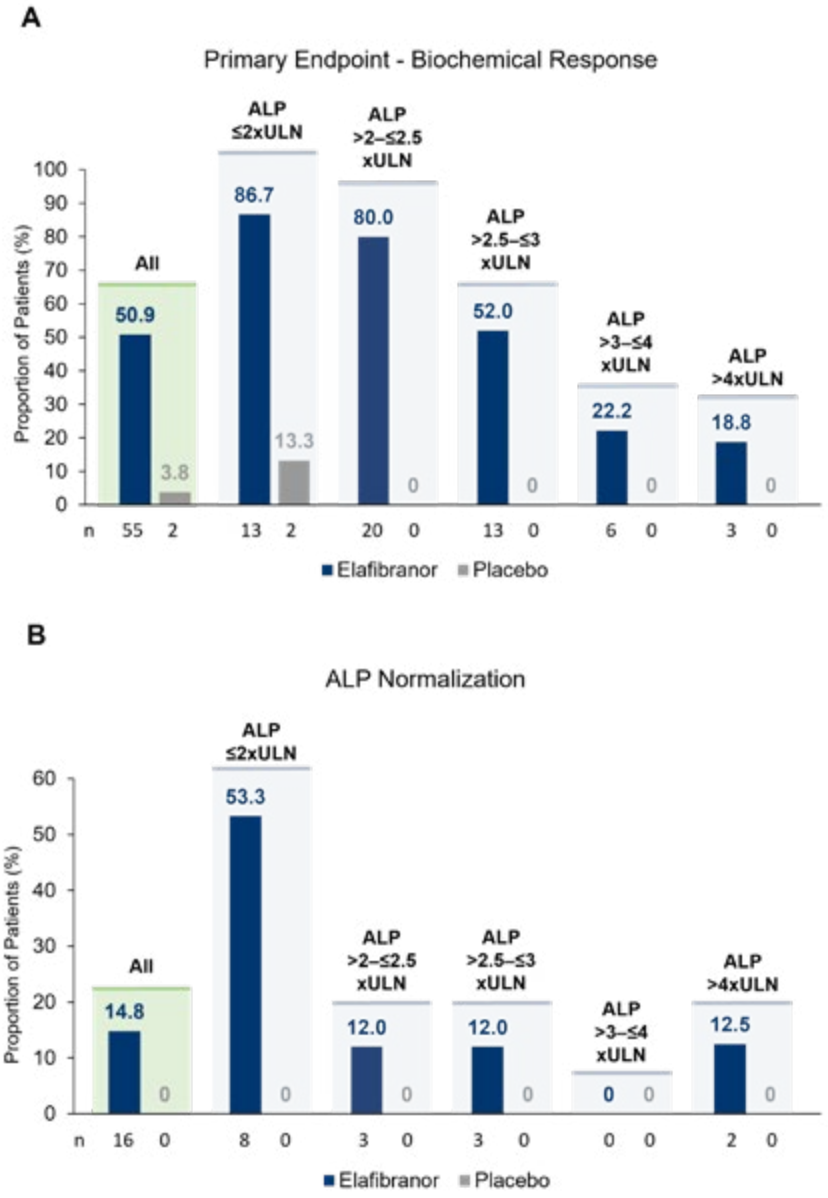

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4275 | TREATMENT RESPONSE IN PRIMARY BILIARY CHOLANGITIS BASED ON DIFFERING CRITERIA

Ana Maria Davila Morales[1] *Kesany Boupapanh*[1] *Zoe Post*[1] *Nancy Reau*[1]

[1]*Rush University Medical Center*

Background: Primary biliary cholangitis (PBC) is a chronic autoimmune cholestatic liver disease commonly associated with women aged 40 or older, high levels of alkaline phosphatase (ALP), and antimitochondrial autoantibodies (AMA). Ursodeoxycholic acid (UDCA) is the treatment of choice for PBC and improves liver biochemistry, reduces transplantation needs and delays progression to death in most patients. There is a lack of consensus on the definition of suboptimal response to UDCA which should identify a patient for second line therapy such as obeticholic acid (OCA) and fibrates. Recently, a new criterion proposed a cutoff of the upper limit of normal (ULN) for ALP and 0.6 times the ULN of total bilirubin (Tbili) in 3 months. We aimed to assess response to UDCA in patients with PBC based on different criteria and if second-line therapy was initiated in suboptimal-responders. **Methods:** A retrospective study of patients with AMA-positive (AMA+) PBC at an academic medical center diagnosed and treated with UDCA between 2017 to 2023 was conducted. Data included demographics, ALP and Tbili at time of UDCA initiation, and timing of normalization or lack of response to UDCA based on existing and new criteria. Initiation of second line therapy with OCA and/or fibrates were recorded. **Results:** 81 patients with AMA+ PBC treated with UDCA were identified. Of these, 90.1% were women (n=73) and average age was 61 years. Sixty-two patients (76.5%) responded to UDCA defined by achieving ALP < 1.67 x ULN with an average time to response of 127 days. However, only 28 patients (34.5%) achieved both a normal ALP and a T bili of < 0.6 with an average time to response of 79 days. Fifty-two patients met criteria for second-line therapy using new criteria of normal ALP and subnormal Tbili however, only 5 patients were started on OCA with an average time from suboptimal response to treatment initiation of 369 days. None were started on fibrates. Failure to start second line therapy included: 34.6% of patients had already met Toronto criteria but not newly proposed criteria, 25% had advanced fibrosis, 23.1% did not have a disclosed cause in the medical chart, and 11.5% were lost to follow up. **Conclusion:** Criteria for UDCA response should identify the need for second line therapy. Conservative criteria of achieving normal ALP and subnormal Tbili may be the optimal endpoint, however in our group only 36% of patients achieved this and providers did not add second line therapy in the majority of this group.

	Total Response to UDCA	Average time to response
Toronto Criteria	76.5%	127 days
New Criteria	34.5%	79 days

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Consultant, Arbutus: Consultant, Gilead: Consultant, VIR: Consultant, Salix: Consultant, Salix: Grant/Research Support, AbbVie: Grant/Research Support

4276 | EXTENT OF BILE DUCT LOSS CORRELATES WITH CLINICAL OUTCOMES IN HEPATIC GRAFT-VERSUS-HOST-DISEASE

Amanda Wong[1] *Kathleen Byrnes*[1]

[1]*Washington University in St. Louis*

Background: Liver injury, specifically bile duct injury, is a known complication of graft-versus-host-disease (GVHD), an immune-mediated disorder in which donor T cells recognize host alloantigens and mediate injury in hematopoietic stem cell transplantation recipients. However, whether the extent of bile duct injury or loss is associated with clinical outcomes in hepatic GVHD is unclear. We investigated whether, analogous to the phenomenon observed in chronic liver allograft rejection, loss of greater than 50% of bile ducts would correlate with worse outcomes in hepatic GVHD. In this study, we assessed the association of the extent of bile duct injury with clinical outcomes and severity of clinical presentation in patients with hepatic GVHD. **Methods:** The extent of bile duct loss was assessed on hematoxylin and eosin-stained sections, and, when available, CK7-immunostained sections, of liver biopsies from 54 consecutive cases of hepatic GVHD in adult patients from a single institution from 2013 to 2023. Patient demographics, clinicopathologic features, and clinical outcomes were obtained through the electronic medical record. The cases were divided into two groups: ≥ 50% bile duct loss versus < 50% bile duct loss. Overall survival and time to liver function test stabilization were compared between the two groups by Kaplan-Meier analysis using the Gehan-Breslow-Wilcoxon test. **Results:** Of the 54 cases, 46% (n=25) had greater than 50% bile duct loss (Table 1). The median overall survival (OS) of the entire cohort was 3.5 months. Greater than 50% bile duct loss was associated with both worse overall survival (median OS of 1.5 months vs 5.5 months in cases with <50% bile duct loss; p=0.0401) and longer duration to liver enzyme level stabilization (median time to stabilization of 1.5 months vs 5.5 months in cases with <50% bile duct loss; p=0.0131). Cases with ≥50% bile duct loss were associated with higher alkaline phosphatase levels at the time of liver biopsy (455 U/L vs 298 U/L in cases with <50% bile duct loss; p=0.043) and greater damage to intact bile ducts seen on biopsy (100% of cases with bile duct damage vs 79% in cases with <50% bile duct loss; p=0.016). **Conclusion:** Hepatic GVHD patients with ≥50% bile duct loss have worse overall survival and delayed stabilization of liver function tests compared to those with <50% bile duct loss. These findings suggest that quantification of the bile duct loss as a component of liver biopsy assessment may have prognostic utility in patients with hepatic GVHD.

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Table 1: Clinicopathologic features of hepatic GVHD stratified by extent of bile duct loss				
Clinicopathologic parameter	**All cases**	**% BD loss ≥ 50%**	**% BD loss < 50%**	**p-value**
Number of cases	64	26 (46)	29 (54)	N/A
Age (years; median, IQR)	56 (40-62)	61 (51-71)	54 (34-71)	**0.048**
Overall survival (months; median, range)	3.5 (0.07-120)	1.5 (0.07-114.5)	5.5 (0.2-120)	**0.0401**
Time from SCT to biopsy (months; median, IQR)	8 (4-16)	8.5 (2.5-14.5)	7.5 (2.9-12.2)	0.259
Time to LFT stabilization (months; median, range)	3.5 (0.07-64)	1.5 (0.07-33)	5.5 (0.2-33)	**0.0131**
AST (U/L; median, IQR)	124 (75-220)	108 (43.5-172.5)	135 (24-246)	0.274
ALT (U/L; median, IQR)	261 (122.5-381)	249 (139-369)	261 (21.5-480.5)	0.463
Alkaline phosphatase (U/L; median, IQR)	351 (169-544)	455 (254-656)	298 (127.5-468.5)	**0.043**
Total bilirubin (mg/dL; median, IQR)	3.9 (1.2-8.7)	4.6 (0.8-8.4)	1.9 (0-9)	0.301
Clinicopathologic parameter	**All cases (n, %)**	**% BD loss ≥ 50% (n,%)**	**% BD loss < 50% (n,%)**	**p value**
Sex				0.721
Female	173 (60)	35 (64)	138 (60)	
Male	113 (40)	20 (36)	93 (40)	
Reason for stem cell transplant				0.148
Acute leukemia	27 (49)	13 (52)	14 (48)	
Chronic leukemia	3 (5)	3 (12)	0 (0)	
Lymphoma	9 (16)	3 (12)	6 (21)	
MDS, MPN, and/or myelofibrosis	12 (22)	6 (24)	6 (21)	
Other or combinations of the above	4 (7)	0 (0)	3 (10)	
Type of hematopoietic stem cell transplant				0.300
Allogeneic	53 (96)	23 (92)	29 (100)	
Autologous	1 (2)	1 (4)	0 (0)	
Autologous and allogeneic	1 (2)	1 (4)	0 (0)	
Treatment after biopsy				0.433
Includes prednisone or methylprednisolone	41 (75)	20 (80)	21 (72)	
No prednisone or methylprednisolone	8 (15)	4 (16)	4 (14)	
None	3 (5)	0 (0)	3 (10)	
Unknown	3 (5)	1 (4)	1 (3)	
Bile duct damage on biopsy				**0.016**
Number of cases with valid data	54	25	29	
No/Minimal	6 (11)	0 (0)	6 (21)	
Yes	48 (89)	25 (100)	23 (79)	
Inflammation (degree and distribution) on biopsy				0.072
Number of cases with valid data	53	24	29	
None	35 (66)	17 (71)	18 (62)	
Mild portal	7 (13)	3 (13)	4 (14)	
Mild lobular	9 (17)	3 (13)	6 (21)	
Mild portal and lobular	2 (4)	1 (4)	1 (3)	
Cholestasis on biopsy				0.191
Number of cases with valid data	54	25	29	
Yes	46 (85)	23 (92)	23 (79)	
No	8 (15)	2 (8)	6 (21)	
Fibrosis on biopsy				0.133
Number of cases with valid data	53	24	29	
None	16 (30)	6 (25)	10 (34)	
Early (including periportal, perisinusoidal, rare bridging)	34 (64)	15 (63)	19 (66)	
Advanced (bridging or cirrhosis)	3 (6)	3 (13)	0 (0)	
Bile ductular proliferation on biopsy				0.669
Number of cases with valid data	54	25	29	
No	35 (65)	17 (68)	18 (62)	
Minimal	4 (7)	1 (4)	3 (10)	
Yes	15 (28)	7 (28)	8 (28)	

Disclosures: Amanda Wong: Nothing to Disclose, Kathleen Byrnes: Nothing to Disclose

4277 | EFFECTS OF ODEVIXIBAT VS PLACEBO ON HEPATIC BIOCHEMICAL PARAMETERS AND LIVER ADVERSE EVENTS IN PATIENTS WITH PFIC: DATA FROM THE PEDFIC 1 STUDY

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Background: Clinical features of progressive familial intrahepatic cholestasis (PFIC) include pruritus, elevated serum bile acids, and progressive liver damage. In the published PEDFIC 1 study (NCT03566238), odevixibat, an ileal bile acid transporter inhibitor, significantly reduced serum bile acids and improved pruritus in patients with PFIC, and most treatment-emergent adverse events (TEAEs) were mild to moderate and nonserious. Building on these findings, PEDFIC 1 data were further analyzed to better understand effects of odevixibat vs placebo on hepatic biochemical parameters over time and liver adverse events in patients with PFIC. **Methods:** PEDFIC 1 was a 24-week study, and eligible children received placebo or odevixibat. Hepatic biochemical parameters evaluated over time included alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TB), and direct bilirubin levels; liver-related TEAEs and potentially clinically significant elevations in hepatic parameters were also assessed using the modified evaluation for drug-induced severe hepatotoxicity (eDISH) approach. An independent Data Safety Monitoring Board (DSMB) reviewed and adjudicated the etiology of prespecified hepatic events. **Results:** In PEDFIC 1, 62 patients were randomized (n=20, placebo; n=42, odevixibat). Mean changes from baseline in ALT, AST, TB, and direct bilirubin levels over time in each treatment group are presented in the **Figure**. Overall, 4/20 (20%) patients in the placebo group and 14/42 (33%) in the odevixibat group had liver-related TEAEs. The most common liver-related TEAEs in the odevixibat group were ALT increased (6 patients [14%] vs 1 patient [5%] for placebo) and blood bilirubin increased (5 patients [12%] vs 2 patients [5%] for placebo). Potentially clinically significant elevations in ALT or AST (ie, levels >3 times baseline levels) were observed in 4 odevixibat-treated patients, but no concurrent TB elevations were observed in these patients. There were no confirmed cases of drug-induced liver injury (DILI) based on independent adjudication by the DSMB: all liver-related events that met prespecified criteria for DSMB review (odevixibat, n=24; placebo, n=10) were assessed as related to patients' underlying disease or other causes. No patients developed liver decompensation. **Conclusion:** Following 24 weeks of odevixibat treatment in patients with PFIC, mean transaminase and TB levels were reduced, whereas only minimal changes were observed with placebo. There was a numerically higher incidence of liver-related TEAEs in odevixibat-treated patients; however, DSMB review of prespecified hepatic events did not identify any confirmed cases of DILI or any liver adverse events related to study drug, and there were no events of liver decompensation. PEDFIC 2 (NCT03659916) will provide longer-term data on the impact of odevixibat on hepatic parameters in patients with PFIC.

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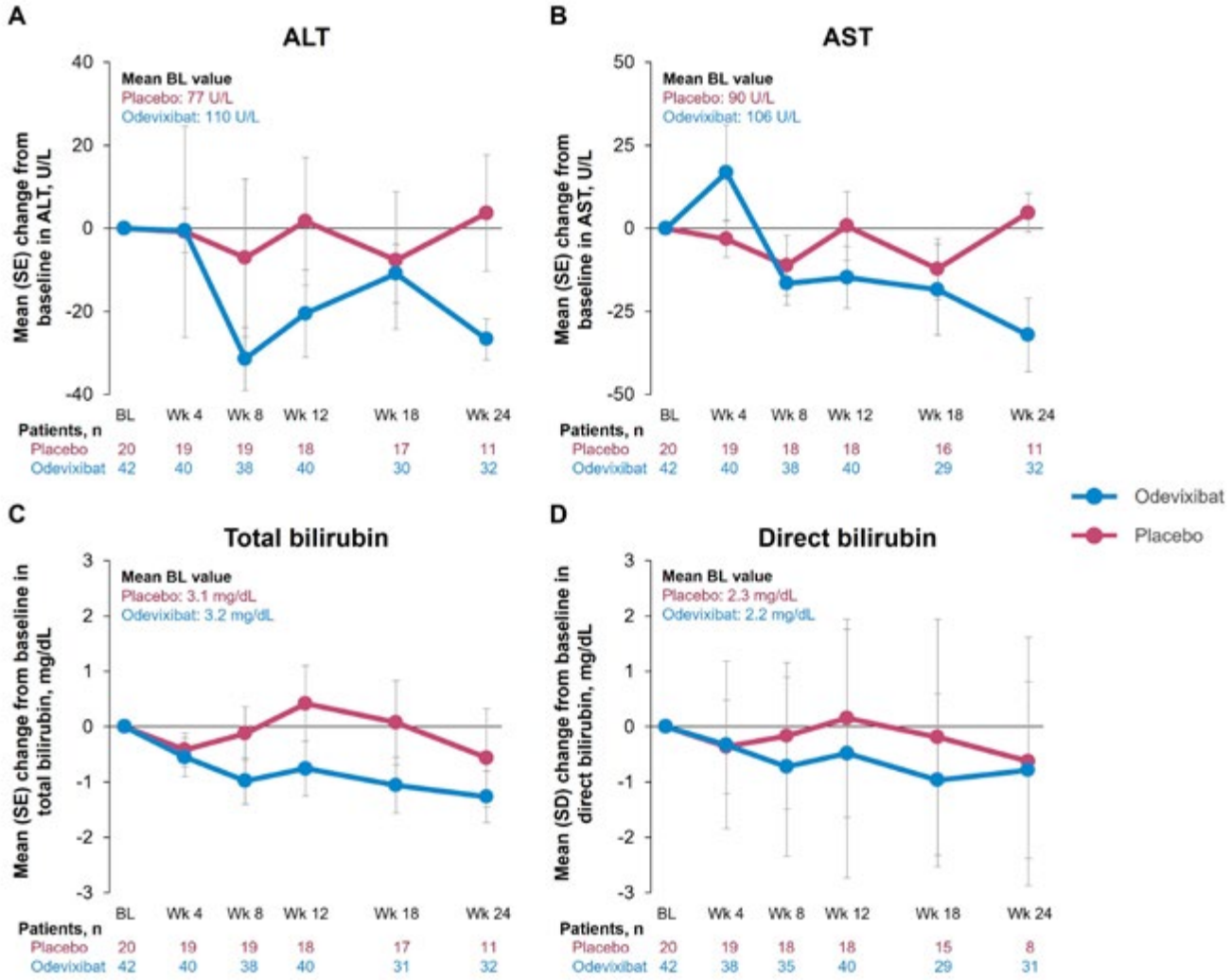
Figure: Changes from baseline in ALT (A), AST (B), total bilirubin (C), and direct bilirubin (D) levels during PEDFIC 1



ALT, alanine aminotransferase; AST, aspartate aminotransferase; BL, baseline; Wk, week.

Disclosures: Tassos Grammatikopoulos: Nothing to Disclose, Reha Artan: Nothing to Disclose, Pier Luigi Calvo: Nothing to Disclose, Piotr Czubkowski: IPSEN: Consultant, Buket Dalgic: Nothing to Disclose, Lorenzo D'Antiga: Selecta: Advisor, Vivet: Advisor, Spark: Advisor, Genespire: Advisor, Tome: Advisor, Mirum: Advisor, Ipsen/Albireo: Advisor, Intercept/Advanz Pharma: Advisor, Alexion/Astra Zeneca: Advisor, Ozlem Durmaz: Nothing to Disclose, Emmanuel Gonzales: Nothing to Disclose, Girish Gupte: Albireo: Grant/Research Support, Winita Hardikar: Ipsen: Advisor, Binita Kamath: Mirum: Consultant, Mirum: Grant/Research Support, Albireo/Ipsen: Consultant, Albireo/Ipsen: Grant/Research Support, Audentes: Consultant, Florence Lacaille: Nothing to Disclose, Cara Mack: Nothing to Disclose, Patrick McKiernan: Nothing to Disclose, Hasan Özen: Nothing to Disclose, Sanjay Rajwal: Nothing to Disclose, Mathias Ruiz: Nothing to Disclose, Mohammad Shagrani: Nothing to Disclose, Eyal Shteyer: Nothing to Disclose, Nisreen Soufi: Mirum Pharmaceuticals: Advisor, Mary Elizabeth Tessier: Albireo/Ipsen: site PI for a pharmaceutical study, Albireo: site PI for a pharmaceutical study, Wendy Van Der Woerd: Mirum pharma: Consultant, Fatine Elaraki: Ipsen: Employee, Tao Gu: Nothing to Disclose, Michelle Hammerschmidt: Nothing to Disclose, Alejandra Ramirez-Santiago: Nothing to Disclose, Terese Wallefors: Nothing to Disclose, Douglas Silveira: Nothing to Disclose, Henkjan Verkade: Mirum: Grant/Research Support, Mirum: Consultant, Mirum: Speaking and Teaching, Ipsen / Albireo: Consultant, Ipsen / Albireo: Grant/Research Support, Ipsen / Albireo: Speaking and Teaching, Intercept: Consultant, Orphalan: Consultant

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4278 | AN INTERNATIONAL STUDY OF CIRCULATING FIBROSIS AND INFLAMMATORY MARKERS IN PATIENTS WITH PRIMARY SCLEROSING CHOLANGITIS ◆

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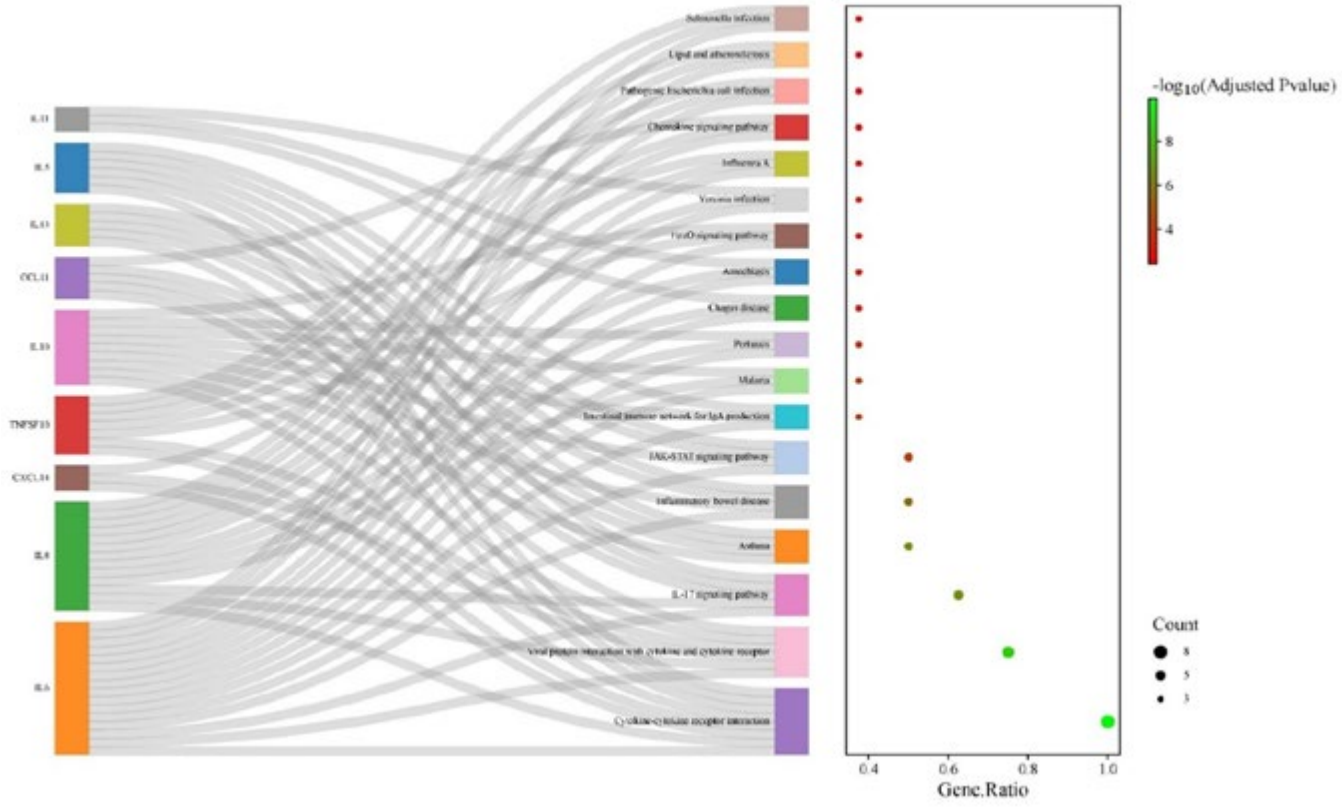
Background: Primary sclerosing cholangitis (PSC) is a chronic cholestatic disease with a variable progression to cirrhosis, cholangiocarcinoma, and hepatic decompensation. Our aim was to identify and validate novel circulating fibrosis and inflammatory markers of PSC. **Methods:** Adult patients diagnosed with PSC according to AASLD and EASL guidelines enrolled in prospective registries at the University of California Davis (discovery cohort) and UK-PSC (validation cohort) were included. Patients were excluded if they had undergone liver transplantation prior to serum collection. Healthy controls (HC) were obtained from ABS. Analytes included Pro-C3, Pro-C5, endotrophin (Pro-C6) and 87 cytokines. **Results:** The discovery cohort included 102 patients with PSC (101 large duct PSC/1 AIH overlap; 55% male; 60% IBD) and the validation cohort included 565 patients (56% male; 60% IBD). Pro-C3 and endotrophin were greater in PSC compared to HC in both cohorts and in patients with and without IBD. Pro-C3 was greater in PSC without IBD compared to PSC with IBD only in the validation cohort. Among 87 cytokines measured, 26 demonstrated nominal significant differences (P<0.05) between PSC and HC in both cohorts, including CXCL13, BRAK, CXCL16, Chitinase 3-Like 1 (CHI3L1), CCL11, CXCL1, IFN gamma, IL-10, IL-12 (p40), IL-13, IL-14, IL-1Ra, IL-1 alpha, IL-28A, IL-2, IL-5, IL-6, IL-7, CXCL8, IL-9, CCL7, CCL3, CCL20, CCL5, TNF-beta, and TRAIL. After adjustments for multiple comparisons (FDR<0.05), 8 cytokines were found to be differentially expressed in both cohorts: IL-6, CXCL8, BRAK, TRAIL, IL-10, CCL11, IL-13, and IL-5. KEGG pathway enrichment analysis revealed the interconnectedness of these cytokines within cellular networks including IL-17 and JAK-STAT signaling pathways (Figure 1). Among patients with PSC, only IL-34 differed between patients with and without IBD in both cohorts. **Conclusion:** Both fibrosis markers and cytokines in the IL-17 and JAK-STAT signaling pathways are elevated in serum from patients with PSC compared to healthy controls.



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Disclosures: Maryam Yazdanfar: Nothing to Disclose, Richard Dean: Nothing to Disclose, Joseph Zepeda: Nothing to Disclose, Sandeep Dhaliwal: Nothing to Disclose, Chung Heng Liu: Nothing to Disclose, Christina Ebert: Nothing to Disclose, Yi Luo: BMS: Employee, Lei Zhao: Bristol Myers Squibb: Stock holder, Palak Trivedi: Nothing to Disclose, Christopher Bowlus: Calliditas: Grant/Research Support, ChemoMab: Grant/Research Support, ChemoMab: Consultant, COUR Phamaceuticals: Grant/Research Support, Cymabay: Grant/Research Support, Cymabay: Consultant, Cymabay: Consultant, Gilead: Grant/Research Support, GSK Pharmaceuticals: Grant/Research Support, GSK Pharmaceuticals: Consultant, Hanmi: Grant/Research Support, Intercept: Grant/Research Support, Invea Therapeutics: Consultant, Ipsen: Grant/Research Support, Ipsen: Consultant, Mirum: Grant/Research Support, NGM Bio: Consultant, Novartis: Grant/Research Support, Novo Nordisk: Grant/Research Support, Pliant Therapeutics: Grant/Research Support, Pliant Therapeutics: Consultant, Viking Therapeutics: Grant/Research Support, Zydus Therapeutics: Grant/Research Support

4279 | EPIDEMIOLOGY AND OUTCOMES OF PRIMARY BILIARY CHOLANGITIS PATIENTS UNDERGOING LIVER TRANSPLANTATION – AN AUSTRALIAN 37-YEAR COHORT STUDY

Ken Liu[1] Yael Celermajer[1] Akalya Mahendran[2] Madeleine Gill[1] Rachael Jacob[1] Talal Valliani[1] David Bowen[1] Simone Strasser[1] GEOFF McCaughan[1]

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Background: Primary biliary cholangitis (PBC) is a chronic cholestatic liver disease which can progress to decompensated cirrhosis and liver transplantation (LT) despite advances in medical treatment. The epidemiology and outcomes of PBC patients undergoing LT in Australia is not well-described. **Methods:** We retrospectively studied consecutive adults with PBC who underwent deceased-donor LT between 1987-2023. Donor and recipient data at time of LT and recipient outcomes were collected from a prospective LT database. The primary outcome of interest was graft survival. Secondary outcomes were the development of recurrent PBC (rPBC) as defined by liver biopsy or documentation by treating clinician and biopsy-proven allograft rejection. **Results:** During the study period, 1960 patients received LT of which 95 (5%) were PBC patients: 88% female, median age 53 years (IQR 47-61), 85% anti-mitochondrial antibody positive. Patients were diagnosed with PBC a median of 10 years (IQR 5-16) before LT. Most patients (91%) were taking ursodeoxycholic acid (UDCA) leading up to LT with the minority taking second-line therapies (2% obeticholic acid, 3% fenofibrate). The indication for LT was decompensated cirrhosis in 94% (66% with ascites, 36% with encephalopathy, median MELD liver disease score 21 [IQR 16-24]) and HCC in 6%. The most common induction immunosuppression regimen was corticosteroids, tacrolimus and mycophenolate (47%) which was also the most common maintenance regimen (46%). Most (77%) patients restarted UDCA at a median of 20 days (IQR 4-106) post-LT. Of these, 14% were started prophylactically to prevent rPBC, 32% to treat rPBC and 55% for deranged liver function tests without a definitive diagnosis of rPBC. No patients received second-line PBC therapy post-LT. After a median follow-up of 9.3 years (IQR 4.7-20.6), there were 46 deaths (50%) and 2 retransplants (2%). Based on Kaplan Meier analysis, the estimated median graft survival was 20.6 years (95% confidence interval [CI] 14.0-27.0) with 1-year, 5-year and 10-year graft survivals of 94%, 84% and 68%, respectively. rPBC was diagnosed in 29% at a median of 4.2 years post-LT. Of these, 56% were biopsy proven while the remainder were based on clinician assessment. On multivariable analysis, the only independent predictor of rPBC was increased MELD score at time of LT (HR 1.14 per point increase, P=0.035). rPBC did not impact on long-term graft survival (Log-rank P=0.227). Over half (58%) of patients developed biopsy-proven allograft rejection during the follow-up period. Biopsy-proven rejection was associated with worse graft survival (HR 3.07 for death or retransplant, P=0.044). **Conclusion:** In this Australian single-centre study, PBC patients who received LT exhibited good long-term graft survival. rPBC occurred in 29% of patients after a median of 4.2 years which did not impact graft survival. Biopsy-proven rejection was common (58%) and was associated with worse graft survival.

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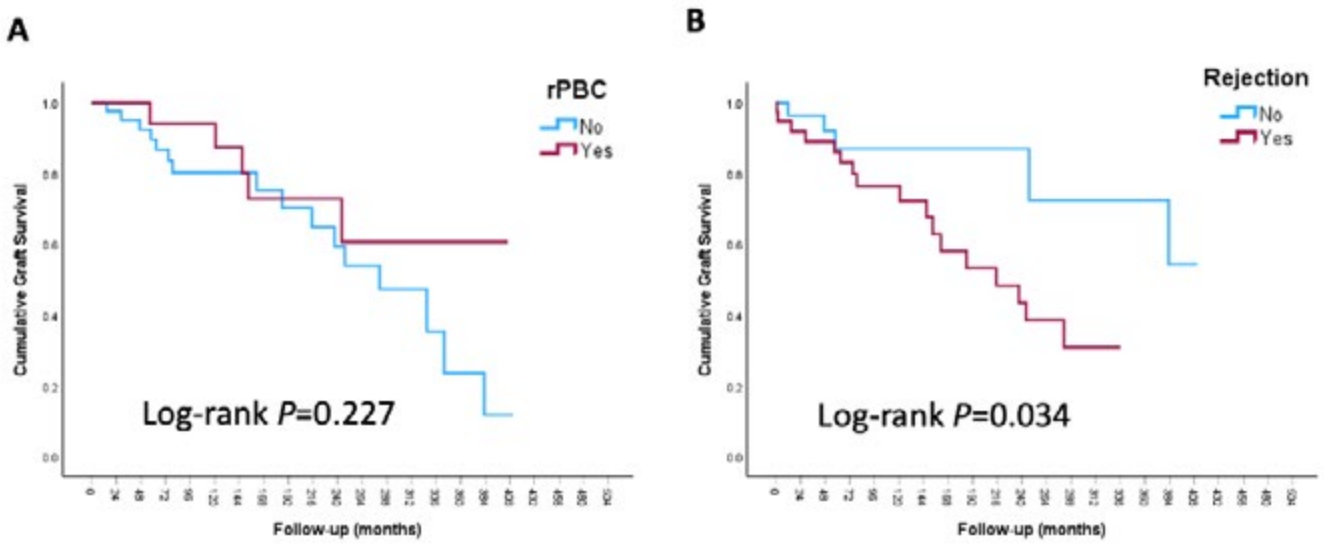

Disclosures: Ken Liu: Nothing to Disclose, Yael Celermajer: Nothing to Disclose, Akalya Mahendran: Nothing to Disclose, Madeleine Gill: Nothing to Disclose, Rachael Jacob: Nothing to Disclose, Talal Valliani: Nothing to Disclose, David Bowen: Nothing to Disclose, Simone Strasser: Chiesi: Advisor, Roche Diagnostics: Advisor, Roche Therapeutics: Advisor, Norgine: Speaking and Teaching, Abbott Diagnostics: Advisor, CSL Behring: Advisor, Novo Nordisk: Advisor, Astra Zeneca: Advisor, Sirtex: Speaking and Teaching, Eisai: Speaking and Teaching, GEOFF McCaughan: Nothing to Disclose

4280 | A PHASE 1, OPEN-LABEL, FIXED-SEQUENCE, CROSSOVER STUDY TO EVALUATE THE INTERACTION OF MULTIPLE-DOSE ODEVIXIBAT WITH THE PHARMACOKINETICS OF SINGLE-DOSE COMBINED ORAL CONTRACEPTIVE STEROIDS IN HEALTHY FEMALE PARTICIPANTS

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Background: Odevixibat is an ileal bile acid transporter inhibitor approved in the United States for the treatment of pruritus in patients with progressive familial intrahepatic cholestasis (PFIC) and Alagille syndrome (ALGS). Because odevixibat increases the fecal excretion of bile acids, which have lipid-emulsifying properties, it has been hypothesized that odevixibat could impair the absorption of fat-soluble medicinal products, including lipophilic oral contraceptives. Although patients with PFIC or ALGS are generally diagnosed in childhood, they may continue to require treatment into adulthood. Here, we report the **Results:** of a drug-drug interaction study in healthy participants that was conducted to evaluate the effect of odevixibat on the pharmacokinetics (PK) of oral contraceptives. **Methods:** This was a phase 1, open-label, fixed-sequence, crossover study. Eligible participants were healthy females aged 18–55 years with a body mass index ≥18.0 and ≤30.0 kg/m^2. On study day 1, participants received 1 dose of a combined oral contraceptive (0.03 mg ethinyl estradiol [EE], 0.15 mg levonorgestrel [LVN]). From day 4 to day 9, oral odevixibat (3 mg) was administered once daily. On day 10, participants received both odevixibat and the combined oral contraceptive. PK sampling was performed up to 72 hours after each dose of the combined oral contraceptive, as well as at 2.5 hours post-odevixibat dose on days 8–10. Safety was monitored throughout the study. results. A total of 25 participants enrolled, with 22 of 25 (88%) completing the study. Mean maximum concentration (C_{max}) of EE and median time to maximum concentration (T_{max}; **Table**) with or without odevixibat were similar; there was a small decrease (17%) in the ratio of geometric least square means for area under the concentration-time curve from zero extrapolated to infinity ($AUC_{0\text{-}inf}$) for EE when coadministered with odevixibat, with the lower bound of the 90% confidence interval (79%) being slightly below the no effect boundary of 80–125%; this decrease was not considered clinically meaningful. Mean C_{max}, median T_{max}, and $AUC_{0\text{-}inf}$ of LVN were similar with and without odevixibat (**Table**). The most common treatment-emergent adverse events (TEAEs) were the gastrointestinal disorders diarrhea (in 10/25 participants; 40%) and nausea (in 5/25 participants; 20%); all TEAEs were mild in intensity and resolved by the end of the study. One

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participant discontinued the study due to a TEAE of COVID-19. **Conclusion:** Multiple doses of odevixibat had no clinically meaningful effects on the PK of EE and LVN in healthy female participants, and TEAEs in this study were mild in intensity. These findings cannot be extrapolated to other lipophilic medications. However, these study findings may help inform the clinical management of adult patients with PFIC or ALGS who also take oral contraceptives.

Table: Summary of plasma PK parameters of EE and LVN in healthy female participants following administration of a combined oral contraceptive with and without odevixibat

Parameter	Ethinyl estradiol		Levonorgestrel	
	Combined contraceptive alone, n=25	Combined contraceptive + odevixibat, n=23[a]	Combined contraceptive alone, n=25	Combined contraceptive + odevixibat, n=23[a]
C_{max}, pg/mL	73 (20)	71 (20)	3,820 (1,220)	3,880 (1,090)
T_{max}, h	1.0 (0.3–2.0)	1.5 (0.7–2.0)	1.0 (0.7–1.8)	1.0 (0.7–2.0)
$AUC_{0\text{-last}}$, pg·h/mL	635 (177)	551 (130)	41,200 (15,900)[b]	39,200 (13,900)
$AUC_{0\text{-inf}}$, pg·h/mL	748 (227)	629 (186)	58,700 (25,800)[c]	49,700 (20,900)[d]

Values are reported as arithmetic mean (SD), except T_{max} which is reported as median (range). Values >3 digits are rounded to 3 significant figures. [a]Overall, 22 participants completed the study, including 1 participant who completed all 3 treatment phases of the study but was lost to follow-up. An additional 2 participants did not complete all 3 treatment phases of the study (n=1 due to lack of cooperation; n=1 due to COVID-19). [b]n=24. [c]n=23. [d]n=22. AUC, area under the concentration-time curve; $AUC_{0\text{-inf}}$, AUC extrapolated to infinity; $AUC_{0\text{-last}}$, AUC from time zero to time of last quantifiable concentration; C_{max}, maximum observed concentration; EE, ethinyl estradiol; LVN, levonorgestrel; PK, pharmacokinetic; T_{max}, time to maximum observed concentration.

Disclosures: Florent MAZUIR: Ipsen: Employee, Claudia Ordonez: Ipsen: Consultant, Abata: Consultant, Recode: Consultant, Aer Therapeutics: Consultant, Clarametyx: Consultant, Terese Wallefors: Nothing to Disclose, Judy Zhu: Nothing to Disclose, Erik Lindstrom: Nothing to Disclose

4281 | CHILDHOOD LIVER DISEASE RESEARCH NETWORK (CHILDREN) PROSPECTIVE OBSERVATIONAL STUDY OF PRIMARY SCLEROSING CHOLANGITIS (PSC) IN CHILDREN: CROSS-SECTIONAL CHARACTERIZATION OF THE FIRST 141 PARTICIPANTS

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Background: ChiLDReN is conducting a prospective, longitudinal, observational study on children with PSC which includes the characterization of phenotypes and associated outcomes. Herein we *aim* to characterize the clinical phenotypes of the first 141 children enrolled in the PSC study and determine correlations of phenotypes with outcomes. **Methods:** Univariate analyses corrected for multiple comparisons was used to determine differences between groups based on the following data elements: demographics, large or small duct only PSC, length of PSC, blood tests (AST, ALT, bilirubin, alkaline phosphatase, GGT, platelets, APRI, FIB4, total IgG, autoantibodies) and transient elastography liver stiffness measurements (LSM). Comparison groups included PSC with/ without IBD and/ or AIH; Large vs. small duct only PSC; F0/1 (LSM £7) vs. F3/4 (LSM >9). **Results:** Percentage or median (range) values for the entire cohort (N=141) at baseline visit: age 16.3 years (6.5-25.6), 61% male, 89% White, 81% large duct PSC, 75% w/ IBD, length of time from PSC diagnosis 2.6 years (0.1-20.8), absence of pruritus 90%, AST 35 U/L (13-733), ALT 37 U/L (9-816), bilirubin 0.6 mg/dL (0.2-62), alk. Phos. 176 (33, 1226), GGT 46 (11-1579), platelets 282x10^3 (24-652), IgG 1380 mg/dL (480-5171), +autoantibody 57%, LSM 6.2 kPa (3.5-63.9). There were no differences between PSC +/- IBD and/or +/- AIH; nor in large vs. small duct only PSC. Comparison of F0/1 vs. F3/4 LSM groups revealed significantly higher AST, ALT, GGT and FIB4 in the F3/4 LSM (Table 1). **Conclusion:** A cross-sectional view of 141 children with PSC revealed mild disease overall and no differences in phenotype characteristics between those with or without IBD, AIH or large vs. small duct only PSC. Transient elastography LSM was associated with severity of disease based on biochemical markers of liver injury and fibrosis. Ongoing enrollment in the prospective observational study is warranted to characterize phenotypes in a larger cohort.

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4282 | OBETICHOLIC ACID FOR PRIMARY BILIARY CHOLANGITIS IN THE PREVENTION OF CLINICAL EVENTS: A MODELING STUDY USING REAL-WORLD DATA

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Background: Obeticholic acid (OCA) is approved for second-line (2L) therapy in patients with primary biliary cholangitis (PBC) who have inadequate response or intolerance to ursodeoxycholic acid (UDCA). Real-world (RW) studies have reported a 58% to 63% reduction in risk of negative clinical outcomes in patients with PBC treated with OCA using a composite endpoint of death, liver transplant, and/or hepatic decompensation (HD). Using RW clinical outcomes data, this study estimated the number of HD events, liver transplants, and deaths that may be avoided with OCA and included sensitivity and subgroup analyses. **Methods:** A model was developed using a hypothetical scenario to estimate clinical events in patients with PBC who were eligible for 2L therapy. Patients treated with OCA with or without UDCA were compared with patients receiving UDCA or no treatment. Event rates per 100 person-years for hospitalization due to HD, liver transplants, or death were obtained from the RW HEROES study. Sensitivity analyses were performed using clinical event rates from other studies including RECAPITULATE and POISE (LTSE) + EC (outcomes from the POISE phase 3, open-label, long-term safety extension [LTSE] clinical trial were compared with Global PBC registry external controls [EC]). A subgroup analysis of patients consistent with the current US Prescribing Information (USPI) from HEROES was also performed, which excluded contraindications of OCA (ie, compensated cirrhosis with evidence of portal hypertension). **Results:** In a modeled cohort of 1000 patients, an estimated 21, 56, and 85 HD events may be avoided in OCA-treated patients over 1, 3, and 5 years, respectively **(Figure)**. Additionally, 4, 10, and 16 liver transplants and 9, 26, and 43 deaths may be avoided, respectively. Similar results were observed in the sensitivity analyses with up to 34 to 61 HD events, 27 to 33 liver transplants, and 49 to 59 deaths avoided over 5 years. In the subgroup analysis, up to 82 HD events, 5 liver transplants, and 35 deaths may be avoided over 5 years in patients consistent with the current USPI. **Conclusion:** Although clinical trials in PBC provide an important measure of effectiveness based on liver biochemistries, studies in RW settings have demonstrated the benefit of OCA on long-term outcomes, as the medication has been used in regular clinical practice since its accelerated approval in 2016. Using RW data to estimate clinical events avoided demonstrates the long-term clinical benefit of OCA for appropriate patients with PBC.

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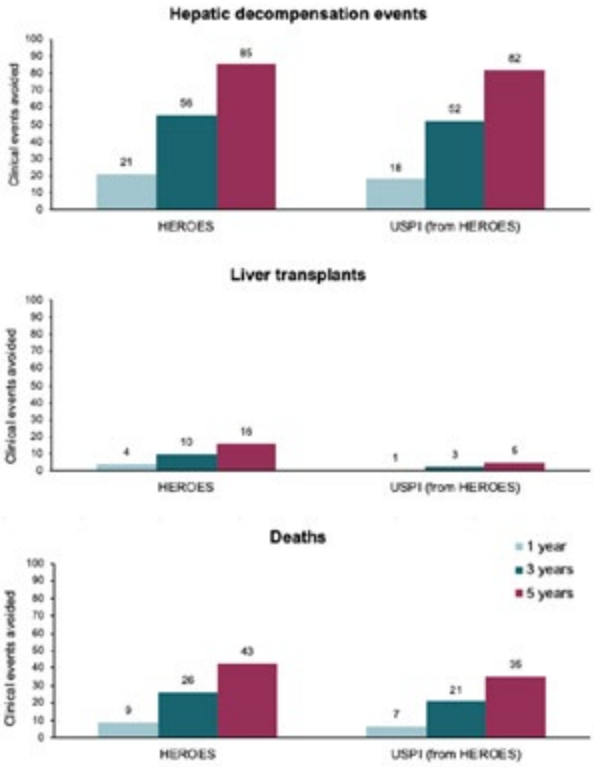
Figure. Number of estimated clinical events avoided with OCA over 1, 3, and 5 years.



Abbreviations: OCA, obeticholic acid; USPI, United States Prescribing Information.

Disclosures: Zobair Younossi: Nothing to Disclose, Alexandra Ellis: Stratevi, LLC: Employee, Jackie Lee: Intercept: Employee of Stratevi, LLC, which received funding from Inter, Leona Bessonova: Nothing to Disclose, Radhika Nair: Intercept Pharma: Employee, Sanofi: Employee, Elizabeth Potente: Nothing to Disclose, Robert Gish: Nothing to Disclose

4283 | IMPROVING KNOWLEDGE IN PBC MANAGEMENT BEYOND FIRST-LINE THERAPY: STRUCTURED LEARNING INCREASES COMPETENCE AND CONFIDENCE

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Background: Up to ~40% of patients with PBC have an inadequate response or poor tolerability to UDCA leading to an increased risk of end-stage liver disease. Second-line therapy can improve prognosis but is often not implemented in a timely fashion. We sought to improve and measure physician knowledge, competence, and confidence in identifying these patients earlier by providing expert-led short-format education. **Methods:** Physicians participated in an 18-minute, video-based, chapterized, online CME activity with synchronized slides (Jones D, Schattenberg JM. Biliary Cholangitis: Thinking About Long-Term Outcomes From the Start. Launched: February 2024; data as April 2024. Available at www.medscape.org/viewarticle/1000182). The education effects were assessed using a 3-question, repeated pairs, pre- /post-assessment study design. One question assessed confidence. Differences from pre- to post-assessment were evaluated using the McNemar's test. P <.05 is the significance level. The activity launched in 2-2024 and data were collected through 4-2024. **Results:** Eight weeks after launch, 1,495 gastroenterologists/hepatologists (gastro/heps) and 1,272 primary care physicians (PCPs) from around the world had engaged. Of those, 154 gastro/heps and 92 PCPs answered all pre- and post-assessment questions. Overall significant improvements were seen after participation for both gastro/heps (correct response rate of 55% at pre-assessment vs 74% at post-assessment; P<.001, Cohen's d= 0.83, N=154), and PCPs (correct response rate of 46% at pre-assessment vs 61% at post-assessment; P<.001, Cohen's d= 0.64, N=92). Specifically, significant improvements were observed in physicians' knowledge of the importance of

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liver fibrosis ultrasound in regular assessments, and competence related to implementing second-line therapy at the right time. Competence in identifying patients at risk for progression who need an earlier than normal follow-up was significantly improved for gastro/heps, but not for PCPs. After participating in the activity, 47% of gastro/heps and 50% of PCPs had measurable improved confidence related to assessing the need for second-line PBC therapy. **Conclusion:** This study demonstrates the success of expert-led online, video-based education in improving knowledge, competence and confidence in optimizing PBC management beyond first-line therapy. Both improvement and reinforcement have been shown to positively correlate with confidence increases and intention to make clinical practice changes (Lucero KS, Chen P. *J Eur CME*. 2020 Oct 12;9(1):1834759), suggesting that these clinicians are likely to take steps to identify patients needing second-line therapy earlier. This could lead to improved overall outcomes for these patients.

Disclosures: S Christy Rohani-Montez: Nothing to Disclose, Marinella Calle: Nothing to Disclose, Jörn Schattenberg: Consultant relationship with Intercept Pharmaceuticals; Has ended; Speaking and Teaching relationship with MedicalTribune, MedPublico GmbH, MedScape,; Has not ended; Consultant relationship with Ipsen, Inventiva Pharma, Madrigal Pharmaceuticals; Has not ended; Consultant relationship with Apollo Endoscopy, Boehringer Ingelheim, Gilead Sciences; Has not ended; Speaking and Teaching relationship with Forum fÃ¼r Medizinische Fortbildung (FOMF), Gilead Sciences; Has not ended; Speaking and Teaching relationship with Boehringer Ingelheim, Echosens; Has not ended; Speaking and Teaching relationship with AbbVie, Academic Medical Education (AME),; Has not ended; Consultant relationship with Novo Nordisk, Pfizer, Roche, Sanofi, and Siemens Healthineer; Has not ended; Consultant relationship with Madrigal Pharmaceuticals, Lilly, MSD, Northsea Therapeutics,; Has not ended; Consultant relationship with Boehringer Ingelheim, Gilead Sciences, GSK, Ipsen, Inventiva; Has not ended; Consultant relationship with Alentis, Alexion, Altimmune, Astra Zeneca, 89Bio,Bionorica,; Has not ended; Consultant relationship with MSD, Northsea Therapeutics, Novartis, Novo Nordisk; Has not ended; Consultant relationship with Pfizer, Roche, Sanofi, and Siemens Healthineers; Has not ended; Grant/Research Support relationship with Boehringer Ingelheim, Siemens Healthcare GmbH; Has ended; Speaking and Teaching relationship with Novo Nordisk, Madrigal Pharmaceuticals,; Has not ended David Jones: Umecrine: Consultant, Advanz: Consultant, Intercept: Consultant, GSK: Consultant

4284 | QUANTITATIVE MRCP+ MEASURES PREDICT ADVANCED CHOLANGIOPATHY IN PEDIATRIC PRIMARY SCLEROSING CHOLANGITIS (PSC)

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Background: Progression of large duct disease is a hallmark of the natural history of PSC. Here, we examine clinical, biochemical, and imaging biomarkers of cholangiopathy in a cross-sectional cohort of patients with pediatric onset PSC enrolled into the Childhood Liver Disease Research Network. **Methods:** Patients with PSC were enrolled across 12 clinical sites and underwent a multiparametric MRI, including MRCP and MR elastography, within 3 months of enrollment. Analysis involved independent grading of MRCP sequences by two radiologists according to the Majoie classification, quantitative assessment of MRCP for enumeration of bile duct abnormalities by MRCP+ (Perspectum; Oxford, UK), and liver shear stiffness measurement. Mild disease was defined as grade 0-1 abnormalities of the intra- *and* extrahepatic biliary tree by Majoie, whereas advanced cholangiopathy referred to grade 2+ intrahepatic ductal abnormalities *or* extrahepatic changes of common

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bile duct stricture or extremely irregular margins. Cases with disagreement between radiologists (n=16) were randomly assigned to mild or advanced disease. **Results:** 78 study participants (53.8 % male, 90.4% white) with a median age of 16.3 years (range: 9.5, 25.6) and median duration of 2.7 (0.1-20.8) years from diagnosis of PSC were enrolled. Patients had large (82.1%) or small duct PSC (17.9%), with overlap with autoimmune hepatitis (38.7%), or concomitant IBD (73.1%) at diagnosis of PSC. Based on Majoie classification, 38 (48.7%) had mild cholangiopathy; the remainder had advanced disease.There was no difference in demographics, age, duration of PSC, or clinical phenotype (small vs large duct at diagnosis, concomitant AIH or IBD) at diagnosis, serum levels of biomarkers for hepatobiliary injury at the time of the research MRI, or liver stiffness by MR elastography between disease severity groups (Table). However, increased number of visible ducts and biliary tree volume by quantitative MRCP were associated with advanced cholangiopathy. Analysis following removal of cases with discordant Majoie classification by radiologists yielded similar results. **Conclusion:** Approximately half of participants with PSC have advanced large duct disease distinguishable by quantitative MRCP measures assessing number of ductal profiles and biliary tree volume. There was no difference in serum biochemistries between mild and advanced biliary disease. Notably GGT was not associated with advanced cholangiopathy.
Table: Serum biochemistries and quantitative MRI measures in patients with pediatric onset PSC and cholangiopathy classified according to Majoie.

Table: Serum biochemistries and quantitative MRI measures in patients with pediatric onset PSC and cholangiopathy classified according to Majoie.

	All participants (N=78)		Mild disease (N=38)		Advanced disease (N=40)		
Variable	N	n (%) or median (range)	N	n (%) or median (range)	N	n (%) or median (range)	P-value*
AST (U/L)	72	33 (13, 733)	36	29 (16, 240)	36	37 (13, 733)	1.000
ALT (U/L)	71	34 (9, 816)	35	30 (9, 577)	36	36 (10, 816)	1.000
GGTP (U/L)	67	53 (11, 1579)	32	51 (12, 1579)	35	53 (11, 870)	1.000
ALP (U/L)	70	171 (33, 1226)	34	165 (70, 602)	36	199 (33, 1226)	1.000
Total Bilirubin (mg/dL)	63	0.6 (0.2, 3.7)	34	0.6 (0.2, 2.0)	29	0.6 (0.3, 3.7)	1.000
MR elastography: Weighted Mean Shear Stiffness (kPa)	70	2.78 (1.55, 7.43)	33	2.77 (1.55, 7.43)	37	2.79 (1.82, 6.41)	1.000
MRCP+: Number of Visible Ducts	74	41 (6, 272)	36	30 (6, 154)	38	66 (8, 272)	0.053
Number of Strictures	74	4 (0, 26)	36	4 (0, 24)	38	6 (0, 26)	0.087
Number of Dilated Ducts	74	9 (0, 75)	36	7 (0, 36)	38	14 (2, 75)	0.092
Biliary Tree Volume (ml)	74	7 (1, 50)	36	5 (1, 33)	38	11 (2, 50)	0.042

*Adjusted for multiple comparisons, Clinical variables were compared between groups using Wilcoxon rank-sum tests or Fisher exact tests as appropriate.

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GE Healthcare: Funding to institution, GE Healthcare: Expert review of images, Perspectum Inc: Funding to institution, Jonathan Dillman: GE HealthCare: Grant/Research Support, Philips Healthcare: Grant/Research Support, Motilent: Grant/Research Support, Perspectum: Grant/Research Support

4285 | VALIDATION OF THE WORST ITCH NUMERICAL RATING SCALE (NRS) AND RELATED PATIENT-REPORTED OUTCOMES (PROS) TO ASSESS SEVERITY AND IMPACT OF PRURITUS IN PRIMARY BILIARY CHOLANGITIS (PBC)

Heather Gelhorn[1] Fatoumata Fofana[2] Robyn von Maltzahn[3] Marlyn Mayo[4] David Jones[5] Megan McLaughlin[6] Brooke Currie[6]

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Background: Cholestatic pruritus is common in PBC and can lead to poor quality of life. There is currently no validated instrument to measure pruritus severity in PBC. To assess pruritus severity/impact and related outcomes in clinical trials, rigorous validation of PRO tools in the target patient population of interest is required. This study examined the psychometric properties of NRS items (worst itch, sleep, and fatigue) and the PBC-40 (modified 7-day recall) used in GLIMMER (NCT02966834), a placebo-controlled Phase 2b trial of linerixibat in patients with PBC and pruritus. **Methods:** Patients recorded worst itch twice daily using an NRS (range: 0–10; no itching–worst imaginable itching). Pruritus-related sleep interference and fatigue were rated similarly. Patients completed the 7-day recall PBC-40 (previously validated with a longer 4-week recall) every 4 weeks. PROs used to support validation included the 5D-Itch scale, PGI-S, PGI-C, EQ-5D, and BDI-II. Psychometric properties were assessed in the ITT population, blinded to treatment. **Results:** Test–retest reliability of NRS was acceptable for itch (ICC: 0.66–0.81), sleep (0.85), and fatigue (0.88). Convergent validity of NRS items was confirmed based on moderate–large correlations with scores of similar concepts from other measures (r=0.46–0.69; all p<0.0001). The itch NRS showed good discriminant validity based on low/slightly moderate correlations (r=|0.21| to |0.37|) with scores of dissimilar measures. Known groups validity was confirmed; all NRS items discriminated between levels of severity in the expected direction across relevant measures (all p<0.0001; **Figure**) and demonstrated responsiveness by reflecting changes in similar measures over time. All PBC-40 domains showed acceptable test–retest reliability (ICC: 0.72–0.87), acceptable internal consistency (Cronbach's alpha: 0.67–0.97), convergent validity across similar measures (all r≥0.50 with p<0.0001) and discriminated between known groups (all p<0.01). The PBC-40 itch domain was responsive to changes in other measures over time (p<0.0001). **Conclusion:** Findings confirm that NRS items utilized in GLIMMER (and ongoing Phase 3 GLISTEN study; NCT04950127) to assess itch, pruritus-related sleep interference, and fatigue are valid and reliable measures that can detect changes in patient status over time. results also support use of the new 7-day recall version of the PBC-40. Routine clinical use of these validated measures for PBC may aid improved patient care. **Funding:** GSK (209992)

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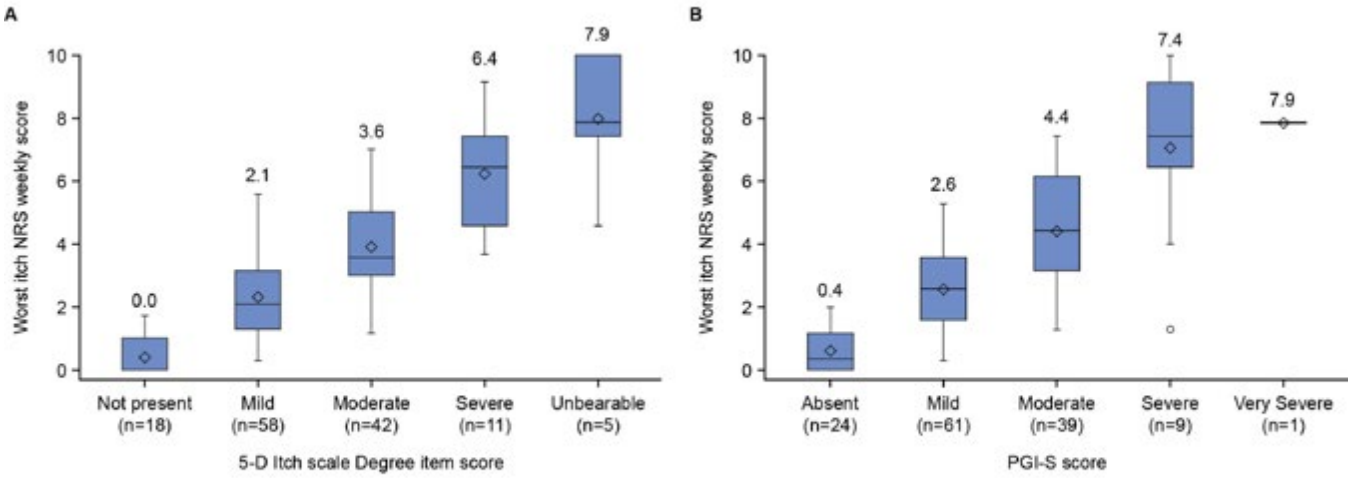
Figure. Known-groups validity boxplot of worst itch NRS weekly itch score* by 5-D Itch scale degree item (A) and PGI-S (B) at Week 16



*Weekly itch score was defined as the average of the worst daily itch scores over a 7-day period where at least 4 worst daily itch scores were available in that period. The numbers in the box plots represent medians.
BDI-II, Beck depression inventory-II; ICC, intraclass correlation coefficient; ITT, intent to treat; NRS, numerical rating scale; PGI-C, patient global impression of change; PGI-S, patient global impression of severity.

Disclosures: Heather Gelhorn: Nothing to Disclose, Fatoumata Fofana: Nothing to Disclose, Robyn von Maltzahn: Nothing to Disclose, Marlyn Mayo: Grant/Research Support relationship with Mirum; Has not ended; Grant/Research Support relationship with Mallinckrodt; Has ended; Consultant relationship with Mallinckrodt; Has ended; Grant/Research Support relationship with CymaBay; Has not ended; Grant/Research Support relationship with Target RWE; Has ended; Consultant relationship with CymaBay; Has not ended; Grant/Research Support relationship with GSK; Has not ended; Consultant relationship with Ipsen; Has not ended; Grant/Research Support relationship with Ipsen; Has not ended; Consultant relationship with IntraSana; Has ended; Grant/Research Support relationship with Intercept; Has not ended; Consultant relationship with GSK; Has not ended, David Jones: Nothing to Disclose, Megan McLaughlin: Nothing to Disclose, Brooke Currie: GSK: Employee, GSK: Stock - publicly traded company

4286 | PRURITUS IMPACTS HEALTH-RELATED QUALITY OF LIFE (HRQOL) AND SLEEP FOR PATIENTS WITH PRIMARY BILIARY CHOLANGITIS (PBC) IN THE PATIENT-CENTRIC PICNICHEALTH REGISTRY

Anna Halliday[1] Daniel Gibbons[1] Sophia Abner[2] Haley Friedler[2] Dhirishiya P[3] Harini Vadlamudi[3] Veronika Earley-Valovic[1] Cynthia Levy[4]

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Background: Pruritus occurs in up to 81% of patients with PBC. Moderate-to-severe pruritus can significantly reduce HRQoL, with sleep often impacted. In collaboration with PicnicHealth, we used patient-reported outcomes to explore how PBC-related pruritus and pruritus-related sleep disturbance affect HRQoL. **Methods:** This retrospective cross-sectional analysis included patients from the USA with a confirmed PBC diagnosis who were enrolled in the PicnicHealth registry from January 2021–May 2022. Patients were regularly asked to complete the validated, multidomain PBC-40 questionnaire (4-week recall). For analyses reported here, HRQoL was assessed using patients' most recent PBC-40 responses; published thresholds for clinical significance for each domain were used. Patients were categorized as having no (0), non-clinically significant (non-CS; 1–6) or CS (≥7) pruritus based on their PBC-40 itch domain score. Patients were also classified as per their response to Q8 of the PBC-40: 'in the past 4 weeks, itching never/rarely/sometimes/most of the time/always disturbed my sleep'. Descriptive statistics are reported; statistical comparisons were made where power was >80% for a two-sided significance of 0.05. Odds ratios for the presence of CS PBC-40 domain scores were determined for patients with and without CS pruritus. Analyses were not adjusted for baseline characteristics. **Results:** Overall, 232 patients completed ≥1 PBC-40 and were included in the analysis (no pruritus, n=22; non-CS pruritus, n=88; CS pruritus, n=122).

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Patients with CS pruritus tended to be younger at diagnosis and have higher alkaline phosphatase levels (**Table**). Patients with CS pruritus had significantly higher (worse) scores on all PBC-40 domains than those with non-CS pruritus, and patients with any pruritus scored significantly worse than those with no pruritus. Patients with CS pruritus also had significantly ($p<0.001$) higher odds of CS scores on all other PBC-40 domains (range 2.67–9.51), compared with those without CS pruritus. HRQoL scores worsened significantly ($p<0.0001$) with increasing frequency of pruritus-related sleep disturbance. **Conclusion:** In this study, patients reporting more severe pruritus and more frequent pruritus-related sleep disturbance had worse HRQoL across all PBC-40 domains. Consistent with findings from the TARGET-PBC study, these results highlight the importance of pruritus management and the need for improved treatments to lessen the impact of pruritus on HRQoL in patients with PBC. **Funding:** GSK(218573)

Table: Demographics, clinical characteristics, and mean (SD) PBC-40 domain scores

	No pruritus (n=22)	Any pruritus¶ (n=210)	Non-CS pruritus (n=88)	CS pruritus (n=122)
Demographics and clinical characteristics				
Female sex, n (%)	22 (100.0)	204 (97.1)	85 (96.6)	119 (97.5)
Age at enrollment, mean (SD)	59.0 (10.2)	54.8 (10.7)	56.7 (11.3)	53.4 (10.1)
Age at PBC diagnosis, mean (SD)	52.4 (9.4)	48.4 (10.0)	50.3 (10.6)	46.9 (9.3)
ALP, mean (SD)*	125.3 (50.5)	166.2 (123.3)	136.2 (63.1)	188.3 (149.5)
Ever diagnosed with cirrhosis, n (%)	13 (59.1)	100 (47.6)	38 (43.2)	62 (50.8)
PBC-40 domain scores, mean (SD)				
Symptoms	14.1 (4.4)	19.0 (5.5)	16.7 (5.5)	20.8 (4.8)
Fatigue	26.8 (12.6)	37.6 (10.2)	31.8 (10.7)	41.7 (7.5)
Emotional†‡	7.0 (3.3)	10.2 (3.1)	8.9 (3.2)	11.1 (2.7)
Social†‡	20.8 (10.6)	32.3 (9.9)	26.7 (9.6)	36.4 (8.0)
Cognition§	14.1 (5.8)	18.0 (6.0)	15.2 (5.3)	20.1 (5.6)
Itch	0 (0)	7.5 (3.7)	3.9 (1.4)	10.1 (2.4)

P<0.0001 for PBC-40 domain score in patients with non-CS pruritus versus CS pruritus and no pruritus versus any pruritus, unless otherwise indicated. The thresholds for CS (and the minimum and maximum possible score) for each of the domains were as follows: symptoms: 18 (6–35), fatigue: 33 (11–55), emotional: 12 (3–15), social: 32 (8–50), cognitive: 18 (6–30), and pruritus: 7 (0–15). *ALP result captured closest and prior to PBC-40 completion.
†Non-CS pruritus, n=87; CS pruritus, n=121. ‡Any pruritus, n=208. §p=0.0020 for no pruritus versus any pruritus.
¶Any pruritus is defined as PBC-40 itch domain score ≥1.
ALP, alkaline phosphatase; CS, clinically significant; PBC, primary biliary cholangitis; SD, standard deviation.

Disclosures: Anna Halliday: Novartis: Stock - publicly traded company, GSK: Employee, GSK: Stock - publicly traded company, Daniel Gibbons: GSK: Employee, GSK: Stock - publicly traded company, Sophia Abner: Nothing to Disclose, Haley Friedler: PicnicHealth: Stock – privately held company, PicnicHealth: Employee, Dhirishiya P: Nothing to Disclose, Harini Vadlamudi: Nothing to Disclose, Veronika Earley-Valovic: Nothing to Disclose, Cynthia Levy: Consultant relationship with Cymabay; Has ended; Advisor relationship with COur; Has ended; Grant/Research Support relationship with GSK; Has not ended; Grant/Research Support relationship with Ipsen; Has not ended; Consultant relationship with Ipsen; Has ended; Grant/Research Support relationship with Mirum; Has not ended; Consultant relationship with Mirum; Has ended; Grant/Research Support relationship with Zydus; Has not ended; Grant/Research Support relationship with Gilead; Has not ended; Consultant relationship with Gilead; Has ended; Grant/Research Support relationship with Escient; Has not ended; Grant/Research Support relationship with Kowa; Has not ended; Consultant relationship with Kowa; Has ended; Grant/Research Support relationship with Genfit; Has ended; Consultant relationship with Chemomab; Has ended; Consultant relationship with GSK; Has ended; Consultant relationship with Calliditas; Has ended; Grant/Research Support relationship with Calliditas; Has not ended; Consultant relationship with Intercept; Has ended; Grant/Research Support relationship with Cymabay; Has not ended; Grant/Research Support relationship with Intercept; Has not ended

4287 | LIPIDOMIC PROFILING OF BLOOD AND BILE REVEALS AN ABUNDANCE OF LACTOSYLCERAMIDES IN PATIENTS WITH PRIMARY SCLEROSING CHOLANGITIS

Pamela Tietz Bogert[1] *Seul Kee Byeon*[1] *Steven O'Hara*[1] *Akhilesh Pandey*[1] *Nicholas LaRusso*[1]

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Background: Primary sclerosing cholangitis (PSC) is a chronic inflammatory disease of unknown etiology affecting the bile ducts and characterized by periductal fibrosis which ultimately progresses to biliary cirrhosis and liver failure. We previously performed untargeted metabolomic approaches on serum and bile collected at the time

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of transplant on patients with end-stage PSC (n=7) and normal control subjects (NC) (n=12). Lactosylceramides (LCER) levels were significantly increased in PSC compared to NC, ($p<0.05$) in both serum and bile. LCER are a class of glycosphingolipids composed of hydrophobic ceramide lipids and hydrophilic sugars. As a lipid second messenger, LCERs can induce a proinflammatory state through upregulation of inducible nitric oxide synthase (iNOS). We hypothesized that an overabundance of toxic lipid components in bile or serum may initiate or accelerate the progression of PSC. **Methods:** To extend our previous study, we performed a targeted lipidomics platform on bile from patients with PSC (n=12) and NC (n=21), peripheral and portal serum from patients with PSC (n=9) and NC (n=14). Samples were analyzed by liquid chromatography-tandem mass spectrometry. Relative abundances of lipid classes in PSC and NC were quantitated and principal component analysis (PCA) performed to explore separation between lipids classes. **Results:** Targeted lipid classes identified in serum and bile include acylcarnitines, sphingolipids, phospholipids, cholesteryl esters and glycerides. PCA plots revealed a clear separation between PSC from NC for both portal and peripheral serum and bile. The greatest relative difference in abundance of lipids in PSC versus NC was in the class of sphingolipids [i.e., hexosylceramide, dihexosylceramide (lactosylceramide), and sphingomyelin]. The proinflammatory lactosylceramide (Hex2Cer), species d18:1/18:0 through d18:1/24:0, showed significant alterations ($p<0.04$ to $p< 0.01$) in bile and serum from patients with PSC versus NC. These findings enable a more targeted approach to therapies. **Conclusion:** Bile and serum from patients with PSC exhibit increased levels of the proinflammatory LCER, compared to NC. Involvement of LCER in the initiation or progression of PSC merits further exploration as these specific alterations may be amenable to therapeutic pharmacologic manipulation, including modifications to the gut microbiota. Also, implementation of LCER as a biomarker of disease and progression should be pursued.

Disclosures: Pamela Tietz Bogert: Nothing to Disclose, Seul Kee Byeon: Nothing to Disclose, Steven O'Hara: Nothing to Disclose, Akhilesh Pandey: Nothing to Disclose, Nicholas LaRusso: NIH: R01 DK 24031, NIH: R01 DK 57993, NIH: P30 DK 84567, NIH: P30 DK90728, NIH: R01 DK117133, NIH: T32 DK 07198

4288 | CLINICALLY SIGNIFICANT ITCH ON THE PBC-40 CORRESPONDS TO MODERATE-SEVERE ITCH ON THE WORST ITCH NUMERICAL RATING SCALE (NRS) IN PATIENTS WITH PRURITUS AND PRIMARY BILIARY CHOLANGITIS (PBC)

Anna Halliday[1] Heather Gelhorn[2] Katelyn Cutts[3] Brooke Currie[4] Philip Troke[1] Megan McLaughlin[4] David Jones[5]

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Background: Cholestatic pruritus is a common and debilitating symptom of PBC; but the severity and impact of itch on health-related quality of life (HRQoL) are not routinely assessed in clinical practice. To aid understanding of the burden of pruritus, we evaluated the relationships between pruritus severity measured by worst itch NRS (WI-NRS) and HRQoL as assessed by PBC-40, EQ-5D, and Beck Depression Inventory-II (BDI-II). The relationship between EQ-5D and other patient-reported outcomes (PRO) was also evaluated. **Methods:** Data were pooled from an observational 8-day PRO validation study (N=141; all available data and timepoints) and the placebo-controlled Phase 2b GLIMMER study (NCT02966834; N=147; intent-to-treat population; all treatments and timepoints). Patients recorded their worst itch twice daily using a 0–10 scale (WI-NRS); 0='no itching', 10='worst imaginable itching'; the worst daily itch (WDI) score was the higher of the two daily responses. WI-NRS pruritus severity was categorized as mild (<4), moderate (≥4–<7), and severe (≥7). Weekly itch score (WIS) was calculated as the average of the WDI scores over 7 days. EQ-5D and PBC-40 (7-day recall) were used in both studies to assess HRQoL; BDI-II assessed symptoms of depression in GLIMMER. **Results:** Data were pooled from 288 patients. Patients with a WIS of 4 reported a mean (standard deviation [SD]) PBC-40 itch domain score of 7.2 (2.5) (**Figure**). There was a strong correlation ($r=0.69$; $p<0.0001$) between PBC-40 itch domain scores and WIS. At higher WDI scores, EQ-5D utility scores were lower, indicating worse HRQoL; at a WI-NRS score of 10, the mean (SD) EQ-5D score was 0.37 (0.29), indicating extremely poor HRQoL. There were moderate–strong correlations between EQ-5D utility scores and all PBC-40 domains ($r=0.41$ to 0.56; all <0.0001), and with BDI-II score ($r=0.61$; $p<0.0001$). Mean BDI-II scores were higher (worse) amongst those with the most severe pruritus. **Conclusion:** Our data demonstrate that the severity cutoff used to define the moderate–severe population on WIS (≥4) identifies the same population with clinically significant itch (≥7) on the PBC-40 itch domain. More severe pruritus was linked with worse HRQoL, as shown by associations between WDI and EQ-5D utility scores, as well as with greater levels of depression. Routine use in clinical practice of either the WI-NRS or PBC-40 itch

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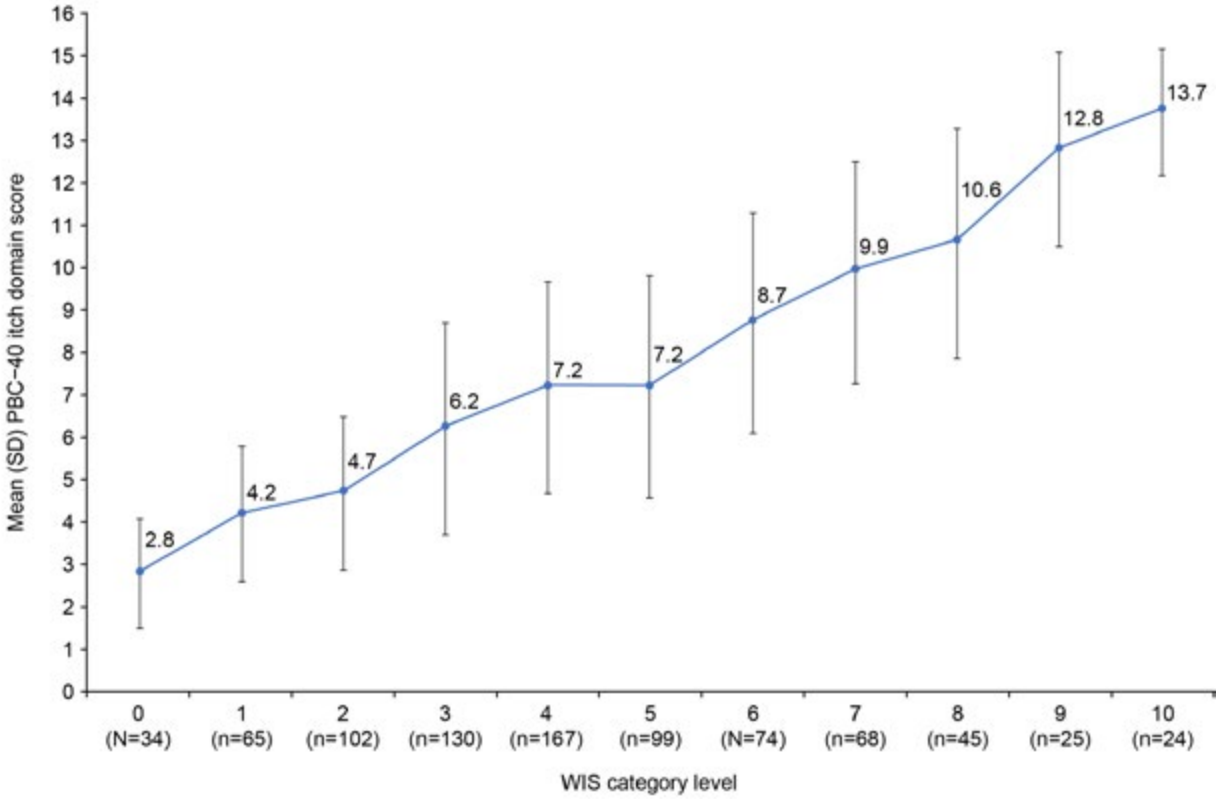
domain would enable identification of patients in need of pruritus management to improve their HRQoL. Funding: GSK (220805)

Figure. Mean PBC-40 itch domain score by WIS* level (N=288 participants; n=833 observations)



*WIS levels defined as: 0 = 0; >0–1 = 1; >1–2 = 2; >2–3 = 3; >3–4 = 4; >4–5 = 5; >5–6 = 6; >6–7 = 7; >7–8 = 8; >8–9 = 9; >9–10 = 10. The pooled timepoints included Weeks 4, 8, 12, 16, and 20 from the GLIMMER study and Day 8 from the observational PRO study. Pruritus severity was assessed using the WI-NRS (scale 0–10) which was completed twice daily (AM and PM); the worst daily itch (WDI) score was the higher of the two daily responses; WIS was calculated as the average of WDI scores across 7 days; higher scores indicate worse pruritus. Higher PBC-40 domain scores indicate worse HRQoL.
HRQoL, health-related quality of life; PBC-40, primary biliary cholangitis-40; PRO, patient-reported outcome; WDI, worst daily itch; WI-NRS, worst itch numerical rating scale; WIS, weekly itch score.

Disclosures: Anna Halliday: Novartis: Stock - publicly traded company, GSK: Employee, GSK: Stock - publicly traded company, Heather Gelhorn: Nothing to Disclose, Katelyn Cutts: Nothing to Disclose, Brooke Currie: GSK: Employee, GSK: Stock - publicly traded company, Philip Troke: Nothing to Disclose, Megan McLaughlin: Nothing to Disclose, David Jones: Nothing to Disclose

4289 | REAL-WORLD CLINICAL SIGNIFICANCE OF BIOCHEMICAL RESPONSE AND LIVER STIFFNESS VARIATION OVER TIME IN PATIENTS WITH PRIMARY BILIARY CHOLANGITIS TREATED WITH OBETICHOLIC ACID

Antonio De Vincentis[1] Francesca Terracciani[2] Daphne D'Amato[3] Pietro Invernizzi[4] Ester Vanni[5] Daniela Campion[3] Annarosa Floreani[3] Nora Cazzagon[6] Domenico Alvaro[3] Edoardo Giannini[7] Sara Labanca[3] Ana Lleo[3] Francesca Colapietro[3] Elisabetta Degasperi[3] Mauro Vigano[8] Eugenia Pesatori[8] Stefano Fagiuoli[8] Marco Marzioni[9] Raffaella Viganò[10] Andrea Galli[11] Fabio Marra[12] Paola Begini[13] Leonardo Baiocchi[14] Luigi Muratori[15] Barbara Coco[16] Maurizia Brunetto[17] Fabrizio Pizzolante[13] Nicoletta De Matthaeis[13] Elisabetta Falbo[18] Lorenzo Surace[18] Alberto Mattalia[19] Donatella Ieluzzi[20] Fderico Salomone[3] Giulio Delle Monache[21] Riccardo Tatonetti[22] Ilaria Cavalli[23] Valentina Cossiga[24] Filomena Morisco[24] Vincenzo Valiani[3] Vincenzo Boccaccio[25] Debora Angrisani[3] Giovanni Vettori[3] Biagio Cuffari[26] Alessandra Moretti[3] Alba Rocco[3] Giovanni Nardone[3] Paolo Scivetti[3] Martina Costanzo[27] Valentina Boano[3] Giulia Francesca Manfredi[3] Loredana Simone[3] Valeria Pace Palitti[3] maurizio russello[3] Mariarita Cannavò[3] Evelise Frazzetto[3] gaetano bertino[3] Marco Distefano[3] Antonio Izzi[28] Federica Cerini[3] Luchino Chessa[3] M Miglianti[3]

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Valentina Feletti[3] Alessandro Mussetto[29] raffaele francesco cozzolongo[29] Francesco Losito[30] Grazia Anna Niro[30] Rosa Cotugno[30] Rodolfo Sacco[30] Chiara Ricci[30] Paolo Poisa[31] Luca Cadamuro[31] Antonino Castellaneta[31] Francesco Squeo[30] Natalia Terreni[30] Niccolo' Bina[31] Pietro Pozzoni[31] Silvia Casella[31] Francesca Zani[32] Olivia Morelli[31] Giuseppe Cuccorese[32] Carlo Saitta[33] Teresa Zolfino[34] CRISTINA RIGAMONTI[35] Vincenza Calvaruso[36] Marco Carbone[34] Umberto Vespasiani-Gentilucci[35]

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Background: The prognostic significance of alkaline phosphatase, bilirubin and liver stiffness measurements(LSM), and of their variation over time, is well-known in patients with primary biliary cholangitis (PBC). However, their clinical meaning with regard to the occurrence of liver-related events (LRE) has never been investigated during second-line treatment with Obeticholic acid (OCA). In a large cohort of OCA-treated PBC patients, we aimed to evaluate the clinical correlates of attaining biochemical response and of longitudinal changes of LSM. **Methods:** Data were from the Italian RECAPITULATE cohort, including OCA-treated PBC patients from centers belonging to the Italian PBC Registry and/or the CLEO/AIGO PBC study groups. After excluding subjects with <6 months' observation and cirrhotic patients in Child-Pugh B-C classes, biochemical response was evaluated through POISE criteria. Linear mixed models were used to describe on-treatment variations of liver enzymes and LSM, while Cox-models to assess their impact on LRE. Joint models were applied to estimate the association between changes in LSM and LRE, defined as the occurrence of hepatic decompensation, liver transplantation or liver-related death. **Results:** 659 PBC subjects (median age 58, women 89%, cirrhotics 27%) accounted for 30 LRE during 19,910 patient-months (median follow-up of 30 months). A sub-cohort of 505 individuals with at least a reliable LSM during treatment (total 924 LSMs, 779/145 transient elastography/shear wave elastography, 248 subjects with at least two LSMs) was also analysed. POISE response rates were 42% and 58% at 1 and 3 years, respectively, and patients attaining 1year-POISE response showed a significantly reduced incidence of LRE during follow-up (HR 0.22, 95%CI 0.08-0.59). LSM progressively increased in POISE non-responders (slope +0.44 KPa/year, 95%CI 0.04,0.85), while decreased over time in responders (slope -0.45 KPa/year 95%CI -0.75,-0.13; p interaction<0.001; Figure 1). Any increase in LSM was associated with an increased risk of LRE, with an overall HR per 10% increase in LSM/year of 1.39 (95%CI 1.18,1.67). **Conclusion:** In patients with PBC, biochemical response to OCA parallels with a reduction of LSM and of LRE during follow-up, while non-response is associated with increased LSM and risk of LRE.

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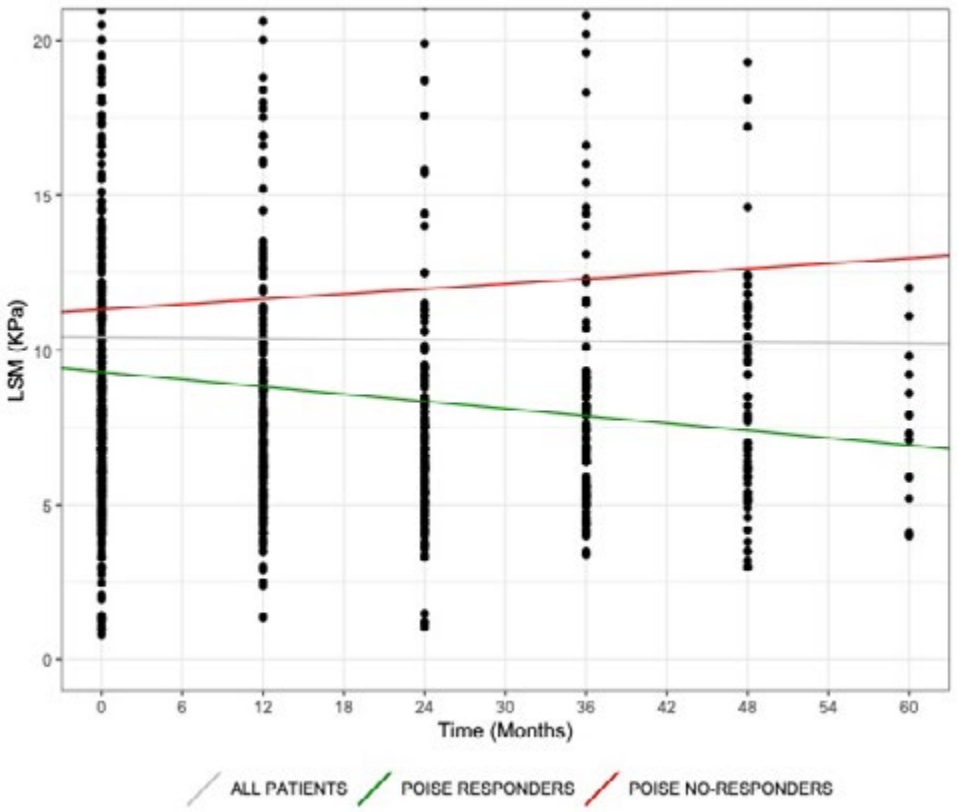

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4290 | INSUFFICIENT CONTROL OF CHOLESTATIC PRURITUS IN PRIMARY BILIARY CHOLANGITIS (PBC) WITH CURRENT THERAPIES: BASELINE DATA FROM THE ONGOING PHASE 3 GLISTEN (GLOBAL LINERIXIBAT ITCH STUDY OF EFFICACY AND SAFETY IN PBC) TRIAL

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Background: Cholestatic pruritus is common in PBC and negatively impacts quality of life. Guideline-recommended therapies show limited efficacy for treating the debilitating pruritus in PBC, and only a few PBC clinical trials include itch as the primary outcome. Linerixibat, an ileal bile acid transporter inhibitor, is a minimally absorbed twice daily oral tablet, currently in development for the treatment of pruritus in PBC. Understanding pruritus severity and treatment is important to identify patient needs. Here, we report baseline (BL) characteristics and pruritus treatment history in GLISTEN. **Methods:** GLISTEN (NCT04950127) is an ongoing Phase 3, placebo-controlled study in adults with PBC and moderate–severe pruritus. Pruritus severity is assessed using a worst itch 0–10 numerical rating scale (moderate: ≥4–<7; severe: ≥7). Participants are either treatment-naïve, have received prior therapy or continue stable concomitant therapies commonly used for PBC and/or pruritus, except for obeticholic acid. A preliminary analysis of BL characteristics is presented for all enrolled participants, blinded to treatment status, and summarized with descriptive statistics. **Results:** Data from 227 participants were included in this abstract analysis. At BL, 42% had moderate pruritus, 58% severe; 9% had compensated cirrhosis, 51% had alkaline phosphatase levels <1.67x upper limit of normal (ULN), 13% had total bilirubin >1x ULN (**Table**). Overall, 97% of participants were receiving ursodeoxycholic acid. The most common prior therapies for pruritus were antihistamines (15%), bile acid binding resins (13%), rifampin (6%), and fibrates (4%). Where specified, main reasons for stopping these treatments included lack of efficacy (83%, 55%, 69%, and 13%, respectively) and lack of tolerability/adverse events (9%, 45%, 38%, and 88%, respectively). In total, 42% of participants were receiving concomitant therapy that may reduce pruritus, including 22% receiving fibrates, 10% selective serotonin reuptake inhibitors, 8% bile acid binding resins, 6% antihistamines, 4% gabapentin, 3% rifampin, 3% naltrexone, 3% pregabalin, and 2% nalfurafine. **Conclusion:** Prior use of bile acid binding resins was low in the GLISTEN population despite its first-line position in treatment guidelines. Regardless of the use of multiple "off label" therapies, participants living with PBC globally had evidence of ongoing moderate–severe pruritus, underscoring the unmet need for a symptom-specific therapy targeting pruritus in PBC. **Funding:** GSK (212620)

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Table. Baseline demographics and clinical characteristics of participants in GLISTEN

Characteristic	All participants, N=227
Sex, female, n (%)	215 (95)
Age, mean (SD) years	55.5 (11.2)
Region, n (%)	
Europe	69 (30)
Asia	68 (30)
Other regions	50 (22)
North America	40 (18)
Cirrhosis diagnosis, n (%)[a]	
Yes	21 (9)
No	202 (89)
ALP (IU/L), mean (SD)	235.9 (171.9)
ALP, n (%)	
≤1x ULN	54 (24)
>1x ULN and <1.67x ULN	62 (27)
≥1.67x ULN	111 (49)
Total bilirubin (µmol/L), mean (SD)	12.0 (8.1)
Total bilirubin, n (%)	
≤1x ULN	197 (87)
>1x ULN	30 (13)
Duration of PBC diagnosis (months), mean (SD)	75.8 (68.5)
Duration of pruritus diagnosis (months), mean (SD)	91.4 (84.8)
Monthly itch score, mean (SD)[b]	7.3 (1.6)
Pruritus severity, n (%)[c]	
Moderate (≥4 to <7)	95 (42)
Severe (≥7)	132 (58)
Prior PBC therapies, n (%)	
Obeticholic acid	15 (7)
Fibrates[d]	9 (4)
UDCA	5 (2)
Other	7 (3)
Prior therapies for pruritus due to PBC, n (%)[e]	67 (30)
Antihistamines	35 (15)
Bile acid binding resins[f]	29 (13)
Rifampin	13 (6)
Fibrates[d]	8 (4)
SSRIs[g]	8 (4)
Nalfurafine	6 (3)
Opioid antagonists[h]	6 (3)
Other	9 (4)
Concomitant UDCA	220 (97%)
Concomitant therapies that may impact pruritus, n (%)[e]	96 (42)
Fibrates[i]	50 (22)
SSRIs[j]	22 (10)
Bile acid binding resins[k]	19 (8)
Antihistamines[l]	13 (6)
Gabapentin	10 (4)
Rifampin	7 (3)
Pregabalin	7 (3)
Naltrexone	6 (3)
Nalfurafine	5 (2)

[a]Missing values from 4 subjects. [b]Monthly itch score is the worst weekly itch score (the average of the worst daily itch scores in one week) in the 28 days before randomization. A 0–10 worst itch NRS was administered to participants twice daily to assess their worst itch where 0 represented 'no itching' and 10 represented 'worst imaginable itching'. [c]Pruritus severity group based on BL monthly itch score: moderate (≥4 and <7); severe (≥7). [d]Fibrates: bezafibrate, fenofibrate, pemafibrate. [e]Participants may take/have taken more than one medication within/across medication classes. [f]Bile acid binding resins: cholestyramine, colesevelam. [g]SSRIs: citalopram, escitalopram, sertraline. [h]Opioid antagonists: naltrexone, naloxone. [i]Fibrates: bezafibrate, fenofibrate, pemafibrate, ciprofibrate. [j]SSRIs: sertraline, escitalopram, fluoxetine, paroxetine, citalopram. [k]Bile acid binding resins: cholestyramine, colesevelam, colestipol, colestilan. [l]Antihistamines included only if prescribed for itching.

Disclosures: Gideon Hirschfield: Consultant relationship with Mirum; Has not ended; Consultant relationship with Advanz; Has not ended; Consultant relationship with Chemomab; Has not ended; Consultant relationship with Gilead; Has not ended; Consultant relationship with Kowa; Has not ended; Consultant relationship with Intercept; Has not ended; Consultant relationship with Pliant; Has not ended; Consultant relationship with Falk; Has not ended; Consultant relationship with GSK; Has not ended; Consultant relationship with Ipsen; Has not ended; Consultant relationship with CymaBay; Has not ended, Christopher Bowlus: Calliditas: Grant/Research

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4291 | PERIDUCTAL IRON-CORRECTED T_1 IS A PREDICTOR OF ADVERSE OUTCOMES IN LARGE-DUCT PRIMARY SCLEROSING CHOLANGITIS

Emmanuel Selvaraj[1] Bruno Paun[2] Cayden Beyer[2] Amy Herlihy[2] Michael Brady[2] Emma Culver[1] Adam Bailey[1] Michael Pavlides[3]

[1]University of Oxford, [2]Perspectum Ltd, [3]Oxford University

Background: Concentric periductal fibrosis, commonly referred to as “onion skin” fibrosis, is a histological hallmark of primary sclerosing cholangitis (PSC). Our aim was to evaluate whether a periductal fibroinflammatory disease, characterized using MRI, is predictive of adverse clinical events. **Methods:** Standardised 3D MRCP and axial liver T1 and T2* maps were acquired on patients with a known diagnosis of large-duct PSC patients and healthy volunteers (HV). A 3D parametric biliary tree model was aligned to the axial liver corrected T1 (cT1) maps are each voxel over multiple slices in the liver using quantitative MRCP (MRCP+) and LiverMultiScan respectively. Periductal cT1 (Pd-cT1) was quantified over fixed radial distances surrounding the bile ducts at regions of interest (ROIs) with radius 1.5mm to 9.5mm from the bile duct: ROI-1: 1.5–3.5mm, ROI-2: 3.5–5.5mm, ROI-3: 5.5–7.5mm and ROI-4: 7.5–9.5mm. A cT1 of >800ms was considered elevated and indicative of the presence of fibroinflammatory disease activity. Liver stiffness (LSM) >9.6kPa and Amsterdam-Oxford model score >2 were considered as advanced fibrosis. Outcome data were collected by review of the medical record. The hazard ratio (HR) for prognostic performance of Pd-cT1 to predict adverse events was investigated using the cox proportional hazard model. **Results:** Seventy-two participants with PSC (median age 44 years; 65% male)

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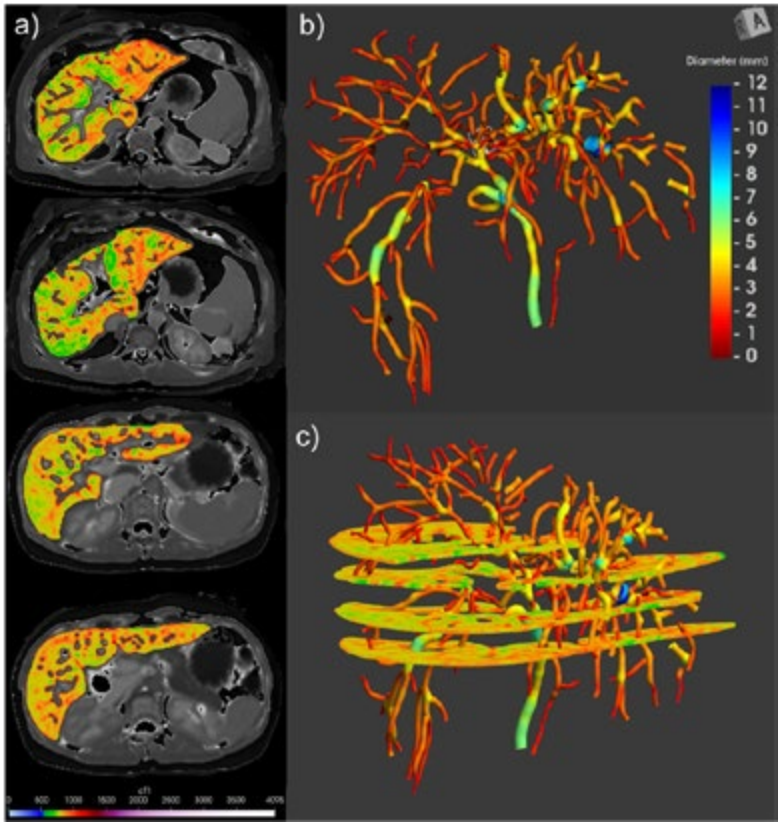
and 20 HV (median age 35 years; 65% male) were recruited. In PSC, mean Pd-cT1 in ROIs 1 and 2 was higher than ROIs 3–4 ($p<0.05$) at baseline and follow-up indicating elevated fibroinflammatory disease activity around the ducts. There were no differences between ROIs in HV. Participants with advanced fibrosis had higher Pd-cT1 than those without (baseline: $p<0.01$; follow-up: $p<0.02$). There were 42 adverse events including cholangitis (N=10), development of new dominant stricture (DS) (N=8), ascites (N=7), gallbladder cancer (N=1), death (N=3) and the need for ERCP (N=13). Elevated Pd-cT1 at ROI-4 had HR: 4.42 for predicting adverse events including cholangitis, gallbladder cancer and death. **Conclusion:** Elevated periductal cT1 in the ring of tissue 7.5–9.5mm around the bile ducts may represent a macroscopic finding that correlates to the histologic "onion skin" fibrosis and is predictive of adverse clinical outcomes in patients with large duct PSC. Our findings demonstrate how quantitative MRI techniques can be used to assess features of disease that were previously seen only at histology.



Disclosures: Emmanuel Selvaraj: Nothing to Disclose, Bruno Paun: Perspectum: Employee, Cayden Beyer: Nothing to Disclose, Amy Herlihy: Perspectum Ltd: Employee, Michael Brady: Nothing to Disclose, Emma Culver: Nothing to Disclose, Adam Bailey: Nothing to Disclose, Michael Pavlides: Perspectum: Stock – privately held company

4292 | USE OF MACHINE LEARNING (ML) MODELS TO STRATIFY RESPONSE PATTERNS TO FIRST-LINE TREATMENT OF PRIMARY BILIARY CHOLANGITIS (PBC) WITH URSODEOXYCHOLIC ACID (UDCA)

Seema Meloni[1] Claudia Zein[1] Anushree Iyengar[2] Ediz Calay[2] Allison Smither[2] Tyler Wagner[2] Dimitar Tonev[3] Vitalii Doban[1] Brian Juran[4] Konstantinos Lazaridis[4]

[1]Ipsen, Cambridge, MA, USA, [2]nference, Cambridge, MA, USA, [3]Ipsen, Boulogne, France, [4]Mayo Clinic, Rochester, MN, USA

Background: UDCA is the first line of therapy for patients with PBC. Current UDCA response criteria rely on cutoffs for lab tests such as alkaline phosphatase (ALP) and total bilirubin (TB). In a preliminary analysis of real-world data (RWD) from the Mayo Clinic, patients with PBC were found to have varied responses to UDCA.

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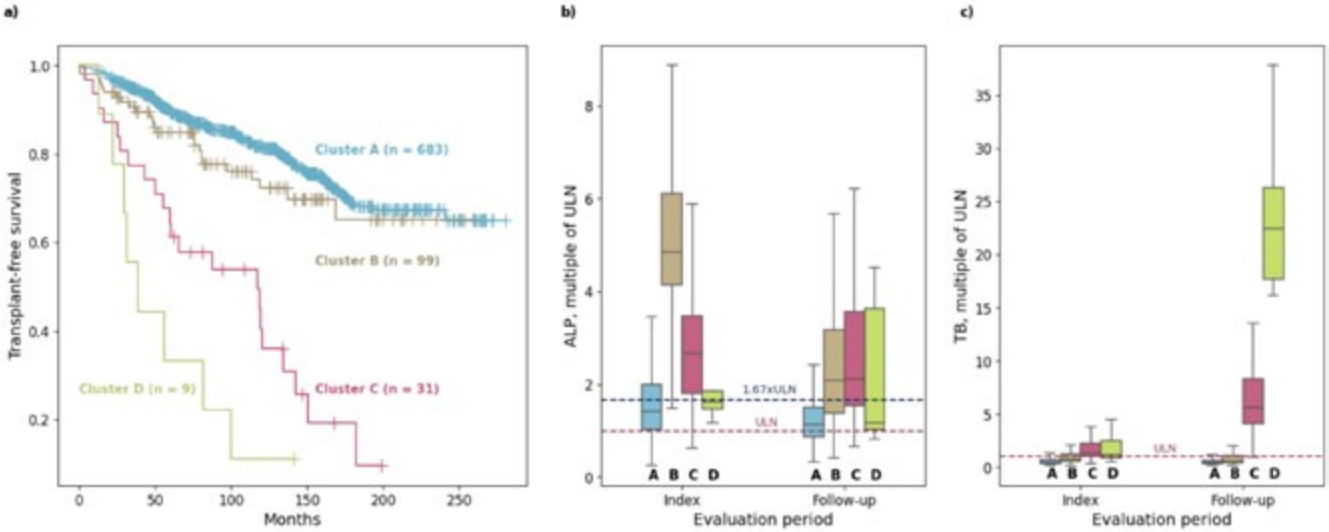
The variability in response profiles may result in interpretation challenges in clinical settings where patients may have moved treatment centers and full treatment histories are not available. Stratification of response patterns with correlation to long-term outcomes could be useful for informing clinicians' decisions. This study utilized unsupervised ML methods applied to clinical data to provide a more nuanced picture of UDCA response. **Methods:** This cross-sectional study used data from a cohort of patients with PBC who were treated at Mayo Clinic between January 1998 and February 2022. Patients were included if they had: evidence of ≥1 year of UDCA treatment; no prior liver transplant; ALP and TB measurements within 90 days before their first UDCA record (index date); follow-up ALP and TB values ≥1 year ±90 days after index; and, evidence of UDCA use within ±180 days of their follow-up labs. Patients were grouped using k-means clustering on their index and follow-up ALP and TB values. Transplant-free survival (TFS) after index was calculated for each cluster using Kaplan-Meier estimators, in which patients who did not experience an event were censored at their last encounter at Mayo. **Results:** 822 patients met inclusion criteria and could be clustered into 4 distinct response groups (Figure 1). Clusters A and B demonstrated longer TFS than Clusters C and D. Cluster A (n=683) had median ALP <1.67 times the upper limit of normal (xULN) at both index and follow-up. In contrast, median ALP values remained >1.67xULN in Clusters B (n=99) and C (n=31), but Cluster B exhibited a marked decrease in ALP between index and follow-up. Median TB was normal at both timepoints for Clusters A and B, while it increased approximately 5-fold from index to follow-up for Cluster C. Meanwhile, Cluster D (n=9) had a small decrease in median ALP, but a >20-fold increase in TB from index to follow-up. **Conclusion:** These results highlight that the combination of ALP and TB trajectories, regardless of duration from UDCA initiation, track with long-term outcomes and are useful criteria for identifying patients who could be considered for second-line therapy.

Figure 1. **a)** Kaplan-Meier curves for TFS by cluster; **b)** Index and follow-up ALP values by cluster; **c)** Index and follow-up TB values by cluster.



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4293 | LIVER STIFFNESS MEASUREMENT BY TRANSIENT ELASTOGRAPHY AS A DYNAMIC PROGNOSTIC INDICATOR FOR DECOMPENSATION, TRANSPLANT, OR DEATH IN PRIMARY SCLEROSING CHOLANGITIS

Kristel Leung[1] Bettina Hansen[2] Marwa Ismail[1] Aisha Alawi[1] Aliya Gulamhusein[1] Gideon Hirschfield[1]

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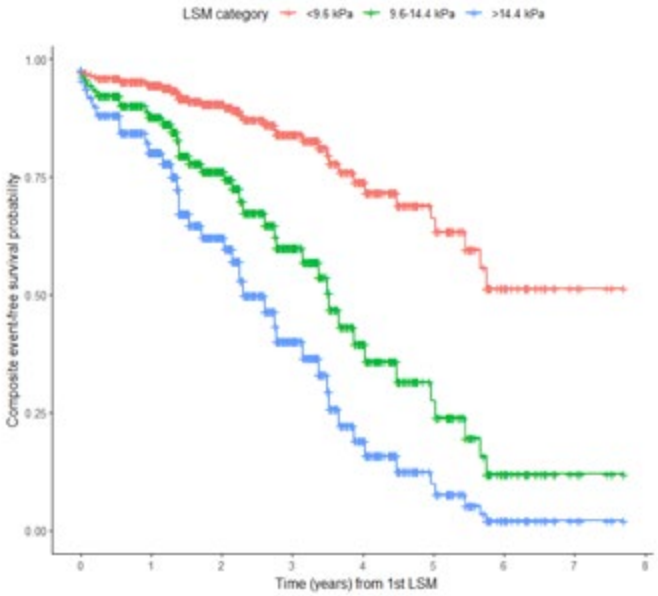
Background: Liver stiffness measurement (LSM) by transient elastography (TE) has been found to be strongly associated with fibrosis stages in primary sclerosing cholangitis (PSC), with cutoffs of <9.6 kPa, 9.6-14.4 kPa, and >14.4 kPa corresponding to F1/F2, F3, and F4 respectively. We aim to evaluate LSM as a dynamic prognostic indicator over time. **Methods:** In a retrospective cohort of individuals with PSC at a single tertiary care liver clinic from 2000-2020 who underwent TE prior to liver transplant, the relationship between LSM readings to progression to a composite of decompensation (ascites, variceal hemorrhage, hepatic encephalopathy), transplant, or death was assessed with time-dependent Cox proportional hazards regression and joint modelling. Covariates included age, sex, biochemistry (bilirubin, ALP, albumin, platelets within 30 days of LSM reading), PSC duration, and inflammatory bowel disease (IBD) duration. The effect of LSM slope with a 2-year lookback period was also evaluated with joint modelling. **Results:** There were 826 readings from 375 individuals with 46 composite events. On univariate analysis, per 1 log increase in TE reading, there was a 3.7-fold increase in risk of decompensation, transplant, or death (95%CI 2.64-5.18). With multivariable time-dependent Cox regression accounting for age, sex, ALP, and total bilirubin, TE reading remained predictive of outcome (per 1 log increase in TE reading, HR 2.55, 95%CI 1.62-4.00). This did not fluctuate significantly with addition of platelets & albumin, or IBD duration & PSC duration in the model. Using LSM <9.6 kPa as a comparator, stratification by LSM reading demonstrated a HR of 2.49 (95%CI 0.99-7.02) for 9.6-14.4 kPa and HR of 4.57 (95%CI 1.94-10.8) for >14.4 kPa, while accounting for age, sex, total bilirubin, and ALP (Figure). Per unit increase in LSM slope/year, the risk of the composite outcome occurring was HR 1.70 (95% CI 1.26-3.53). Stability of LSM corresponded to stabilized risk. **Conclusion:** This study validates evidence for LSM as a longitudinal prognostic tool for clinically meaningful outcomes in PSC, as well as substantiates cutoffs for risk stratification, a key component of clinical prognostication and therapeutic trial design.



Variable	Hazard Ratio (95% CI)
LSM <9.6 kPa	1.0 (ref)
LSM 9.6-14.4 kPa	2.49 (0.99-7.02)
LSM >14.4 kPa	**4.57 (1.94-10.8)**
Female sex	0.74 (0.36-1.54)
Age at 1st Fibroscan	**1.03 (1.01-1.05)**
Per 1 unit increase in ALP x ULN	**1.21 (1.03-1.41)**
Per 1 unit increase in total bilirubin x ULN*	**1.69 (1.36-2.10)**

C-index: 0.88
**with 2nd order polynomial*

Figure. Left: Event-free survival probability stratified by liver stiffness measurement (LSM) reading by transient elastography for a sample case of a 40 y.o. male with primary sclerosing cholangitis with alkaline phosphatase (ALP) 200 U/L, total bilirubin of 100 µmol/L. **Right:** Multivariable time-dependent cox proportional hazards model of LSM, sex, age, ALP and total bilirubin. Upper limit of normal (ULN) for ALP 150 U/L, total bilirubin 22 µmol/L.

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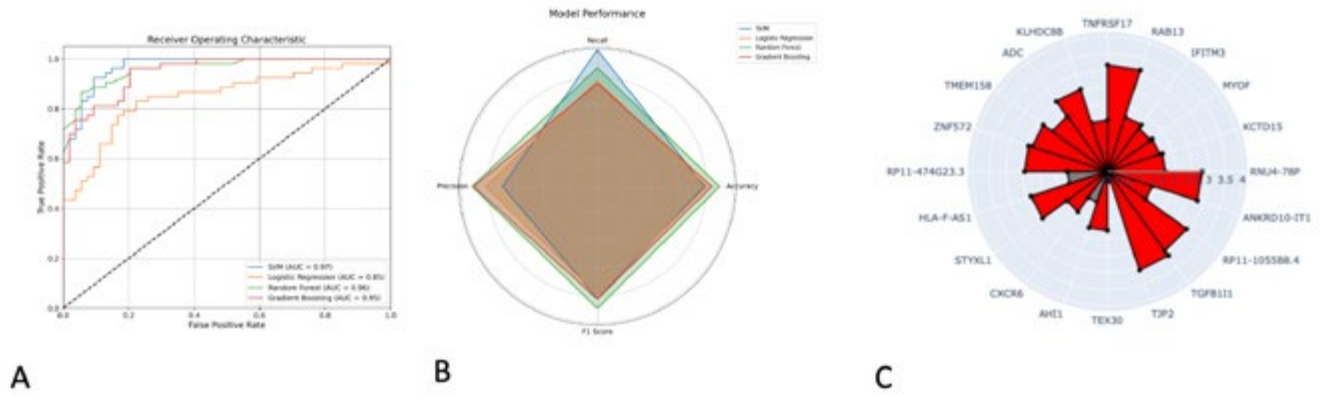
Disclosures: Kristel Leung: Nothing to Disclose, Bettina Hansen: Nothing to Disclose, Marwa Ismail: Nothing to Disclose, Aisha Alawi: Nothing to Disclose, Aliya Gulamhusein: Advanz: Consultant, Cymabay: Consultant, Gideon Hirschfield: Consultant relationship with Mirum; Has not ended; Consultant relationship with Advanz; Has not ended; Consultant relationship with Chemomab; Has not ended; Consultant relationship with Gilead; Has not ended; Consultant relationship with Kowa; Has not ended; Consultant relationship with Intercept; Has not ended; Consultant relationship with Pliant; Has not ended; Consultant relationship with Falk; Has not ended; Consultant relationship with GSK; Has not ended; Consultant relationship with Ipsen; Has not ended; Consultant relationship with CymaBay; Has not ended

4294 | UNIFIED OR UNIQUE? TRANSCRIPTOMIC DIFFERENCES BETWEEN PATIENTS WITH PRIMARY SCLEROSING CHOLANGITIS, WITH AND WITHOUT ULCERATIVE COLITIS

Kiandokht Bashiri[1] Camille Boustani[2] Spyridon Peppas[3] Alireza Meighani[3] Won Kyoo Cho[4]

[1]Georgetown University/ MedStar Washington Hospital Center, [2]MedStar Georgetown University Hospital, [3]MedStar Washington Hospital Center, [4]Georgetown University School of Medicine

Background: The majority of patients with Primary sclerosing cholangitis (PSC) develop ulcerative colitis (UC). Studies indicate that the presence of UC in PSC patients can affect the timing and outcomes of liver transplantation, necessitating distinct pre- and post-transplant management strategies [van Munster, et al. 2023]. By identifying specific genes that distinguish PSC from PSC-UC, this study aims to contribute to the development of diagnostic approach for identification of UC in patients with PSC using a blood test. **Methods:** The blood transcriptome of 43 PSC patients was compared to that of 177 PSC patients with concurrent UC, sourced from GSE177044 [Wacker, et al. 2024]. The data were split into 70% training and 30% testing sets, and synthetic minority over-sampling technique (SMOTE) was applied to balance the dataset. Feature selection was performed using a combination of SelectKBest with ANOVA F-values and model-specific importance scores. Various machine learning models, including Support Vector Machine (SVM), Logistic Regression, Random Forest, and Gradient Boosting, were trained and evaluated using 5-fold cross-validation. **Results:** The top 20 genes identified by feature importance were: SAMD4A, OLFM4, MEGF8, C5, BAG2, TJP2, LRRC6, FGF13, COL6A2, FAM50B, SLC22A1, EXT1, TRIQK, RNU6-892P, ANKRD10-IT1, CDRT4, RP11-1055B8.4, RP11-373D23.2, RP11-343L5.2, and RP11-474G23.3. The performance metrics for the models on the test set, the fold changes and FDR values for the selected genes are shown in Fig 1 (A &B, and C respectively). The pathway analysis of the gene panel using Kegg 2021 suggests involvement of tight junctions, and intestinal immune network, although the results were not statistically significant. **Conclusion:** This study identifies a panel of genes that can differentiate PSC from PSC-UC with high accuracy and AUC. This database is cross-sectional, limiting its use for early identification of UC in PSC patients. Further validation using longitudinal studies is warranted to confirm the clinical utility of these biomarkers.



Disclosures: Kiandokht Bashiri: Nothing to Disclose, Camille Boustani: Nothing to Disclose, Spyridon Peppas: Nothing to Disclose, Alireza Meighani: Nothing to Disclose, Won Kyoo Cho: Nothing to Disclose

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4297 | AUTOIMMUNE HEPATITIS – A DISEASE WITH A MANIFOLD CLINICAL PRESENTATION – MACHINE LEARNING TO BREAK IT DOWN?

Paul-Henry Koop[1] Jan Clusmann[2] Carolin Schneider[3] Kai Markus Schneider[4]

[1]RWTH Aachen University, [2]RWTH Aachen University Hospital, [3]University Hospital RWTH Aachen, The Perelman School of Medicine, University of Pennsylvania, [4]University hospital RWTH Aachen

Background: Autoimmune hepatitis (AIH) is a chronic inflammatory liver disease characterized by immune-mediated destruction of hepatocytes. It presents a significant diagnostic and therapeutic challenge due to its varied clinical manifestations and overlap with other liver diseases, as, for instance, primary biliary cholangitis or primary sclerosing cholangitis. We aim to elucidate the complex disease network associated with AIH using PheWAS analyses, as well as metabolic and serological alterations in patients with AIH. Combining all these source-restricted findings, we further apply a machine learning algorithm to identify feature combinations from different sources that may provide an improved characterization. **Methods:** Using the UK-Biobank, as a prospective cohort study with over 500.000 participants, allows us towe unravel the complex disease networks around AIH. Hence, we performed multiple PheWAS, comparing different groups of patients with AIH (n=392) and matched controls (n=784). To further select the serological and metabolomic patterns, we used logistic regressions determiningto determine which features to include into the predictive supervised machine learning algorithm. Moreover, physical measurements and questionnaire-derived features are included. To reduce the risk of overfitting the algorithm, we train and test in a 5-fold cross validation on 80% of the available data, leaving 20% as an internal validation cohort. Furthermore, an external validation is needed to provide better insight into the model's generalizability. **Results:** Numerous PheCodes arewere linked to AIH. additionally toApart of direct liver-related complications (*cirrhosis* and, with consecutive *portal hypertension*), . We also found a significant association of different *autoimmune (systemic lupus erythematous HR: 18.9; KI95: 4.5-79.1, p<0.001)*, *neoplastic (cancer of bronchus / lung HR: 4.1; KI95: 2-8.7, p<0.001)*, *endocrine (type-2 diabetes HR: 2.5; KI95: 1.7-3.7, p<0.001)*, *respiratory (pulmonary fibrosis HR: 11.3; KI95: 3.5-39, p<0.001)* as well as extrahepatic *gastrointestinal diseases (celiac disease HR: 10.5; KI95: 3.1-35.8; ulcerative colitis HR: 6.9; KI95: 2.9-16)*. In lipidomic and metabolomic analyses among others the concentration of large HDL *(HR: 1.04/SD, p<0.001)* and VLDL diameter *(HR: 0.96, p<0.001)*, as well as tyrosine *(HR: 1.02/SD, p<0.001)* were significantly associated with AIH, composing a complex lipidomic/metabolomic profile. We are currently incorporating selected features from PheWAS, metabolomics, lipidomics, genetics, EHR, and lifestyle factors into the random forest classifier. Our goal is to determine which features are most important in capturing the complexity of patients with AIH in real-world data. **Conclusion:** Integrating these multimodal characterizations into a well explainable random forest classifier can improve the understanding of patients with AIH.

Disclosures: Paul-Henry Koop: Nothing to Disclose, Jan Clusmann: Nothing to Disclose, Carolin Schneider: Nothing to Disclose, Kai Markus Schneider: Nothing to Disclose

4298 | OBETICHOLIC ACID TREATMENT IS ASSOCIATED WITH LONGER TRANSPLANT-FREE AND LIVER-RELATED EVENT-FREE SURVIVAL IN PATIENTS WITH PRIMARY BILIARY CHOLANGITIS FROM TWO LARGE REAL-WORLD COHORTS

Francesca Terracciani[1] Antonio De Vincentis[1] Daphne D'Amato[2] Pietro Invernizzi[2] Anna Morgando[3] Ester Vanni[3] Mauro Vigano[4] Domenico Alvaro[5] Rosanna Venere[5] Ana Lleo[6] Francesca Colapietro[6] Elisabetta Degasperi[7] Raffaella Viganò[8] Edoardo Giannini[9] Sara Labanca[9] Valentina Feletti[10] Alessandro Mussetto[10] raffaele francesco cozzolongo[11] Francesco Losito[11] Maurizio Pompili[12] Francesca Romana Ponziani[12] Grazia Anna Niro[13] Rosa Cotugno[13] Pietro Pozzoni[14] Luchino Chessa[15] Giuseppe Cuccorese[16] Valeria Pace Palitti[17] Maurizio Russello[18] Mariarita Cannavò[18] Evelise Frazzetto[19] gaetano bertino[19] Marco Marzioni[20] Natalia Terreni[21] Teresa Zolfino[22] Carlo Saitta[23] Adriano Pellicelli[24] Barbara Coco[25] Maurizia Brunetto[26] Nora Cazzagon[27] Annarosa Floreani[27] Luigi Muratori[28] Floriano Rosina[29] Marco Distefano[30] Gaetano Scifo[30] Leonardo Baiocchi[31] Giuseppe Grassi[31] Rodolfo Sacco[32] Antonio Izzi[33] Saveria Lory Crocè[34] Cecilia Fiorini[35] Fabio Marra[36] Università Careggi[36] Loredana Simone[37] Olivia Morelli[38] Ludovico Abenavoli[39] Fabrizio Pizzolante[40] Nicoletta De Matthaeis[40] Miki Scaravaglio[2] Giancarlo Gimignani[41] Valentina Boano[42] Giulia Francesca Manfredi[43] Massimo Marignani[44] Silvia Fanella[44] Marco Giacchetto[45] Antonino Castellaneta[46] Guido Poggi[47] Valerio Buzzanca[20] Paolo Scivetti[48] Annalisa Tortora[49] Silvia Casella[50] Valentina Bellia[51] Barbara Federica Omazzi[52] Giuliano Alagna[53] Chiara Ricci[54] Paolo Poisa[54]

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Background: Obeticholic acid (OCA) is the only conditionally-approved second-line treatment in primary biliary cholangitis (PBC) patients non-responder/intolerant to ursodeoxycholic acid (UDCA). Previous studies have suggested that OCA's benefit translates into lower decompensation rates and greater survival. However, they have some limitations, such as comparing inhomogeneous cohorts (OCA registrative trial vs. real-world controls) or relying on administrative data. Here, we aimed to compare two large real-world cohorts of OCA-treated and untreated PBC patients for transplant-free and liver-related event (LRE)-free survival. **Methods:** OCA-treated PBC patients were from the Italian RECAPITULATE, a multicenter real-world cohort of PBC individuals prescribed with OCA from throughout Italy. OCA-untreated patients in the external control cohort were derived from the GLOBAL PBC 2.0 dataset, following the Italian prescription rules for OCA (ALP≥1.5/ULN and/or 1<bilirubin<2 mg/dl after ≥1 year of UDCA). A logistic regression was performed for the dichotomous outcome of belonging to the two different treatment groups, and a propensity score (PS) was computed. The two cohorts were balanced by calculating the inverse probability of treatment weights (IPTW) based on the PS. LRE (ascites, hepatic encephalopathy, and variceal bleeding), liver transplantation (LT) and death (classified as liver or non-liver related) were tracked. Weighted cumulative incidence function (using IPTWs) were used to estimate the distribution of the time to event. IPT-weighted Cox proportional hazards models were run to establish the cause-specific hazard ratio (HR). **Results:** The analysis included 437 patients (women 88%, cirrhosis 34%) from the RECAPITULATE, and 831 controls (women 88%, cirrhosis 15%) from the GLOBAL PBC 2.0 dataset. Maximum follow-up was 48 months. Composite events of LT/death and of LRE/LT/death were 9 and 18 in the RECAPITULATE cohort, and 50 and 99 in the GLOBAL PBC controls, respectively. In the IPT-weighted Cox regression analyses, patients in the RECAPITULATE cohort showed reduced risk of LT/death [HR 0.39 (0.17-0.86); p=0.02)], and of LRE/LT/death [HR 0.34 (0.19-0.59); p<0.001] compared to the GLOBAL PBC controls (Figure 1). A significant interaction was found with the presence of cirrhosis for the occurrence of LT/death, with a significant, and even larger, treatment effect only in non-cirrhotic patients [weighted HRs 0.08 (0.01-0.59) *Vs* 0.83 (0.33-2.08) in cirrhotic ones]. **Conclusion:** In the comparison of two large real-world PBC cohorts, a greater transplant-free and LRE-free survival was observed in OCA-treated patients compared to untreated controls. The impact of OCA was not significant in cirrhotic patients, and much higher when they were excluded from the analysis, suggesting that the maximum benefit from the drug is obtained in a non-advanced phase of disease.

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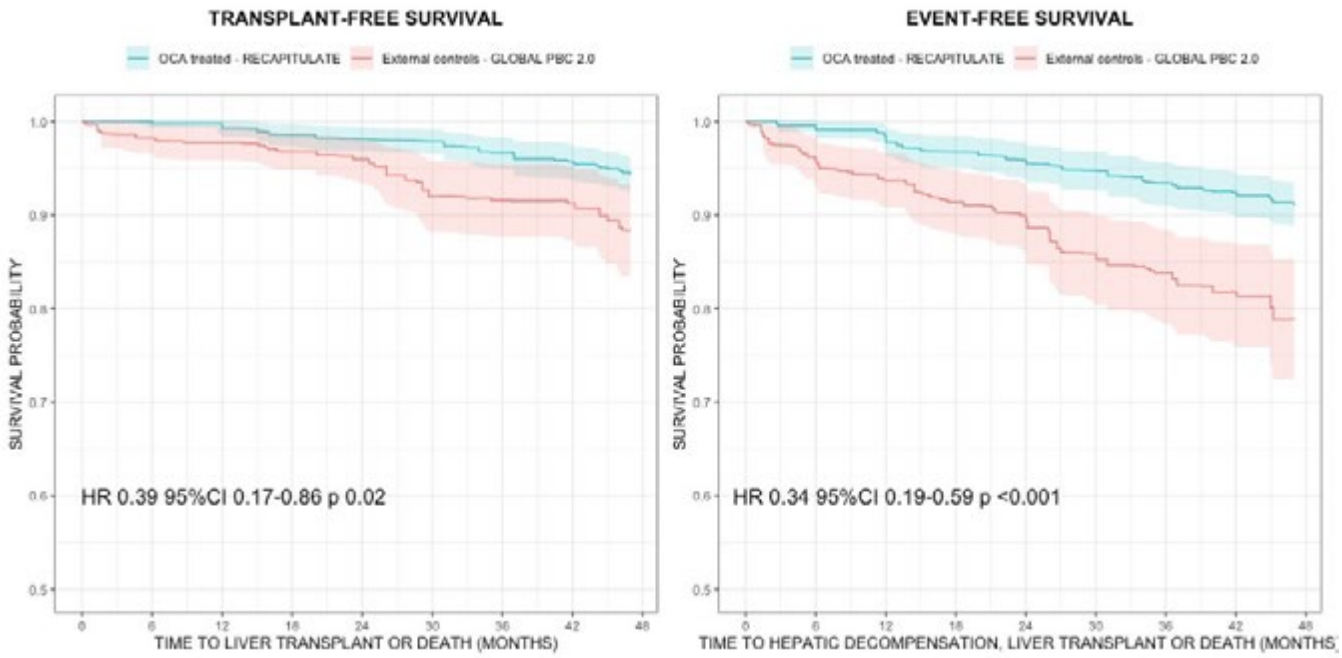

Disclosures: Francesca Terracciani: Nothing to Disclose, Antonio De Vincentis: Nothing to Disclose, Daphne D'Amato: Nothing to Disclose, Pietro Invernizzi: Nothing to Disclose, Anna Morgando: Nothing to Disclose, Ester Vanni: Nothing to Disclose, Mauro Vigano: Nothing to Disclose, Domenico Alvaro: Nothing to Disclose, Rosanna Venere: Nothing to Disclose, Ana Lleo: Advanz Pharma: Advisor, Ipsen: Advisor, GSK: Advisor, AstraZeneca: Advisor, Gilead: Speaking and Teaching, Abbvie: Speaking and Teaching, MSD: Speaking and Teaching, Advanz Pharma: Speaking and Teaching, AlfaSigma: Speaking and Teaching, GSK: Speaking and Teaching, Francesca Colapietro: Nothing to Disclose, Elisabetta Degasperi: Gilead: Speaking and Teaching, Roche: Advisor, Abbvie: Speaking and Teaching, Raffaella Viganò: Nothing to Disclose, Edoardo Giannini: AstraZeneca: Speaking and Teaching, Eisai: Speaking and Teaching, Ipsen: Advisor, Roche: Speaking and Teaching, Sara Labanca: Nothing to Disclose, Valentina Feletti: Nothing to Disclose, Alessandro Mussetto: Nothing to Disclose, raffaele francesco cozzolongo: Nothing to Disclose, Francesco Losito: Nothing to Disclose, Maurizio Pompili: Nothing to Disclose, Francesca Romana Ponziani: Nothing to Disclose, Grazia Anna Niro: Nothing to Disclose, Rosa Cotugno: Nothing to Disclose, Pietro Pozzoni: Nothing to Disclose, Luchino Chessa: Nothing to Disclose, Giuseppe Cuccorese: Nothing to Disclose, Valeria Pace Palitti: Nothing to Disclose, Maurizio Russello: Nothing to Disclose, Mariarita Cannavò: Nothing to Disclose, Evelise Frazzetto: Nothing to Disclose, gaetano bertino: Nothing to Disclose, Marco Marzioni: Nothing to Disclose, Natalia Terreni: Nothing to Disclose, Teresa Zolfino: Nothing to Disclose, Carlo Saitta: Nothing to Disclose, Adriano Pellicelli: Nothing to Disclose, Barbara Coco: Nothing to Disclose, Maurizia Brunetto: Nothing to Disclose, Nora Cazzagon: Advanz: Speaking and Teaching, Orphalan: Consultant, Orphalan: Independent Contractor, IPSEN: Advisor, ALBIREO by IPSEN: Advisor, GSK: Advisor, Annarosa Floreani: Nothing to Disclose, Luigi Muratori: Nothing to Disclose, Floriano Rosina: Nothing to Disclose, Marco Distefano: Nothing to Disclose, Gaetano Scifo: Nothing to Disclose, Leonardo Baiocchi: Nothing to Disclose, Giuseppe Grassi: Nothing to Disclose, Rodolfo Sacco: Nothing to Disclose, Antonio Izzi: Nothing to Disclose, Saveria Lory Crocè: Nothing to Disclose, Cecilia Fiorini: Nothing to Disclose, Fabio Marra: Nothing to Disclose, Università Careggi: Nothing to Disclose, Loredana Simone: Nothing to Disclose, Olivia Morelli: Nothing to Disclose, Ludovico Abenavoli: Nestlé: Speaking and Teaching, Fabrizio Pizzolante: Nothing to Disclose, Nicoletta De Matthaeis: Nothing to Disclose, Miki Scaravaglio: Nothing to Disclose, Giancarlo Gimignani: Nothing to Disclose, Valentina Boano: Nothing to Disclose, Giulia Francesca Manfredi: Nothing to Disclose, Massimo Marignani: Nothing to Disclose, Silvia Fanella: Nothing to Disclose, Marco Giacchetto: Nothing to Disclose, Antonino Castellaneta: Nothing to Disclose, Guido Poggi: Nothing to Disclose, Valerio Buzzanca: Nothing to Disclose, Paolo Scivetti: Nothing to Disclose, Annalisa Tortora: Nothing to Disclose, Silvia Casella: Nothing to Disclose, Valentina Bellia: Nothing to Disclose, Barbara Federica Omazzi: Nothing to Disclose, Giuliano Alagna: Nothing to Disclose, Chiara Ricci: Nothing to Disclose, Paolo Poisa: Nothing to Disclose, Cristina Rigamonti: Nothing to Disclose, Vincenza Calvaruso: Nothing to Disclose, Christophe Corpechot: IPSEN: Consultant, GILEAD: Consultant, Cymabay: Consultant, Mirum: Consultant, GSK: Consultant, Calliditas: Consultant, Echosens: Speaking and Teaching, Advanz: Consultant, Fabrice Carrat: Nothing to Disclose, Gideon

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4299 | METABOLIC RISK FACTORS AND METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE INFLUENCE WAITLIST AND TRANSPLANT OUTCOMES IN AUTOIMMUNE HEPATITIS PATIENTS

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Background: Recent studies have shown that the presence of metabolic syndrome (MetS) components, such as central obesity, dyslipidemia, and/or diabetes, in patients with autoimmune hepatitis (AIH) is associated with more severe disease and a lower likelihood of response to treatment. Additionally, the concomitant presence of metabolic dysfunction-associated steatotic liver disease (MASLD) indicates a worse prognosis in patients with AIH cirrhosis. We investigated the effect of MetS components and MASLD on waitlist and post-liver transplant (LT) outcomes in a large, nationally representative US cohort of AIH patients. **Methods:** Using the UNOS database, we included patients who were waitlisted between January 2002 and December 2022. The recipient AIH cohort was categorized as follows: normal weight/non-diabetic, overweight/non-diabetic, obese/non-diabetic, obese/diabetic and MASLD/AIH. We first used competing risk analysis to estimate the association of these AIH subgroups with waitlist removal due to death or clinical deterioration and incidence of transplantation. We then conducted Kaplan-Meier estimates and Cox regression models to determine the impact of obesity, diabetes, and MASLD on AIH patients. **Results:** A total of 6,000 AIH patients were included: 1,428 (23.8%) normal weight/non-diabetic, 1,558 (25.9%) overweight/non-diabetic, 1,556 (25.9%) obese/non-diabetic, 651 (10.8%) diabetic, 523

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(8.7%) obese/diabetic and 284 (4.7%) MASLD/AIH. Compared to normal weight/non-diabetic patients, obese/diabetic AIH patients showed a higher rate of waitlist removal; though results were not significant (adjusted subdistribution hazard ratio [aSHR] 1.20, 95% confidence interval [CI] 0.97 – 1.48, p = 0.09) (Figure 1A). In contrast, MASLD/AIH patients showed lower rate of waitlist removal due to death or clinical deterioration (aSHR 0.30, 95% CI 0.20 – 0.46, p < 0.001) (Figure 1A) and higher incidence of transplantation (aSHR 1.86, 95% CI 1.59 – 2.11, p < 0.001) (Figure 1B). Among those undergoing transplantation, there was no significant difference in patient survival and graft survival between obese/diabetic AIH patients (adjusted hazard ratio [aHR] 1.25, 95% CI 0.95 – 1.65, p = 0.101 for patient survival and aHR 1.19, 95% CI 0.93 – 1.52, p = 0.155 for graft survival) and MASLD/AIH patients (aHR 1.01, 95% CI 0.73 – 1.39, p = 0.92 for patient survival and aHR 1.04, 95% CI 0.78 – 1.39, p = 0.748 for graft survival). No difference were found in the other subgroups. **Conclusion:** MASLD/AIH patients demonstrated higher LT incidence and lower dropout rates. Obese/diabetic AIH patients had higher dropout rates; however, these results were not significant. Long-term post-LT outcomes did not significantly differ between groups. More granular data from multicenter studies are needed to validate these findings.

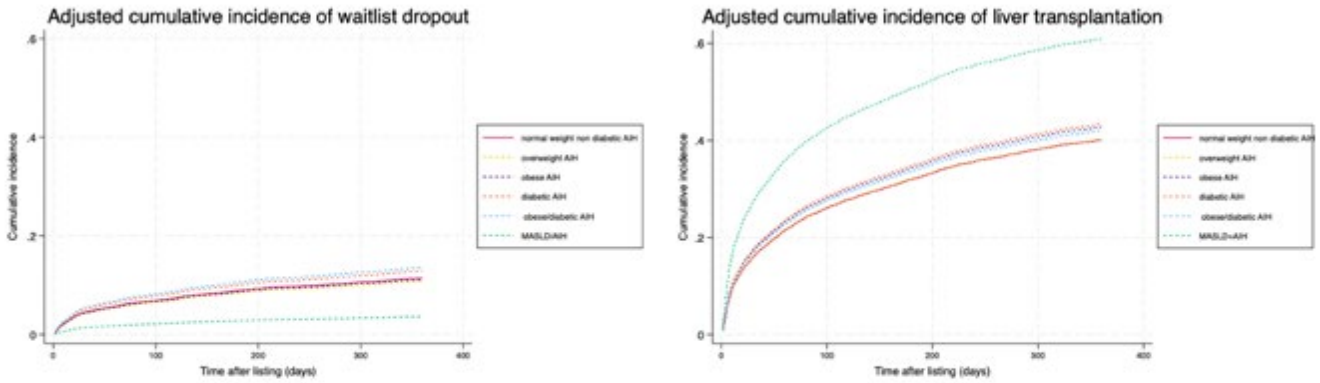

Figure 1 (A) Adjusted cumulative incidence of waitlist dropout (removal due to death or clinical deterioration). **(B)** Adjusted cumulative incidence of liver transplantation.

Model adjusted for recipient age, gender, diabetes, BMI, MELD, PVT, ascites, encephalopathy, and previous abdominal surgery

Abbreviations: MASLD, metabolic associated-dysfunction steatotic liver disease; AIH, autoimmune hepatitis; BMI, body mass index; MELD, Model for End-Stage Liver Disease; PVT, portal vein thrombosis.

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4300 | COMPARISON OF INPATIENT OUTCOMES AND CHARACTERISTICS OF AUTOIMMUNE HEPATITIS-PRIMARY BILIARY CIRRHOSIS OVERLAP SYNDROME WITH AUTOIMMUNE HEPATITIS, AND PRIMARY BILIARY CIRRHOSIS IN THE UNITED STATES 2016-2019: A NATIONALLY REPRESENTATIVE STUDY

Ritik Mahaveer Goyal[1] Bhavik Bansal[2] Esli Medina-Morales[1] David Kim[1] Mohamed Ismail[1] Aagamjit Singh[3] Imran Qureshi[1] Paul Gaglio[1]

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Background: There is evidence of overlap between autoimmune hepatitis (AIH) and primary biliary cholangitis (PBC), two hepatobiliary illnesses known to have an immune-mediated origin. Treatment of AIH/PBC overlap often requires both UDCA and immunosuppression. This retrospective analysis aimed to investigate and compare the demographic characteristics, extra-hepatic auto-immune diseases, and outcomes of hospitalized patients with

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AIH-PBC overlap with AIH and PBC using HCUP-NIS 2016-2019 data. We hypothesize that there are differences in rates of major adverse liver outcomes (MALOs) when comparing these groups. **Methods:** Hospitalized adult patients with AIH, PBC, and AIH-PBC overlap were identified using the ICD-10 codes from the National Inpatient Sample 2016-2019. We performed weighted logistic regression for predicting complications of cirrhosis, in-patient mortality, septic shock, and respiratory failure, and weighted linear regressions for the length of hospital stay and total cost of hospitalization among AIH-PBC overlap cases when compared separately to AIH and PBC only populations as controls. **Results:** A total of 2069 AIH, 1213 PBC, and 234 Overlap patients were identified which represents 10,345; 6065, and 1170 patients respectively when weighted. On multivariate analysis, we found that patients with AIH/PBC are more likely to have ascites (OR 3.21, 95% CI 2.13-4.56; p<0.001) and portal hypertension (OR 3.85, 95% 2.57-5.77; p < 0.001) compared to AIH; whereas no significant difference was found out compared to PBC. AIH/PBC patients had a higher prevalence of Sjogren's syndrome (p<0.001), SLE (p < 0.001), and systemic sclerosis (p<0.001). Overall higher rheumatological disease was present in the AIH/PBC patients compared to AIH (26.50% vs 8.31%, p=<0.001) and PBC (26.50% vs 8.99%, p=<0.001). There were no significant differences in inpatient mortality, sepsis, respiratory failure, length of hospital stay, and total costs. **Conclusion:** AIH/PBC Overlap syndrome is associated with increased rates of certain cirrhotic complications when compared to patients with AIH only. They do not differ in terms of clinical outcomes such as mortality when adjusted for demographics and comorbidities. Patients with AIH/PBC had a higher prevalence of rheumatological disorders; especially Sjogren's, lupus, and systemic sclerosis.

Outcomes	Overlap, N = 1,170[†]	AIH, N = 10,345[†]	Unadjusted OR	p-value	Adjusted OR	P -value
Ascites	595 (50.85)	2,015 (19.48)	4.28 (3.05 - 6.01)	**<0.001**	3.12 (2.13 - 4.56)	**<0.001**
Portal Hypertension	570 (48.72)	1,795 (17.35)	4.53 (3.23 - 6.35)	**<0.001**	3.85 (2.57 - 5.77)	**<0.001**
Hepato-renal Syndrome	70 (5.98)	245 (2.37)	2.62 (1.21 - 5.69)	**0.015**	1.68 (0.70 - 4.02)	0.24
Hepatocellular carcinoma	40 (3.42)	105 (1.01)	3.45 (1.23 - 9.73)	**0.019**	3.00 (0.93 - 9.68)	0.066
Spontaneous bacterial peritonitis	50 (4.27)	170 (1.64)	2.67 (1.04 - 6.89)	**0.042**	1.37 (0.44 - 4.23)	0.59
Liver transplant	95 (8.12)	435 (4.20)	2.01 (1.09 - 3.72)	**0.025**	1.65 (0.83 - 3.25)	0.15
Septic shock	45 (3.85)	150 (1.45)	2.72 (1.09 - 6.79)	**0.032***	1.44 (0.54 - 3.84)	0.46
Respiratory Failure	75 (6.41)	280 (2.71)	2.46 (1.22 - 4.96)	**0.012***	1.63 (0.73 - 3.62)	0.23
Mortality	40 (3.42)	350 (3.39)	1.01 (0.38 - 2.66)	0.98	0.47 (0.13 - 1.67)	0.24

[†] n (%); Mean (SE)

Table 1: Differences in outcomes between AIH/PBC v/s AIH

Disclosures: Ritik Mahaveer Goyal: Nothing to Disclose, Bhavik Bansal: Nothing to Disclose, Esli Medina-Morales: Nothing to Disclose, David Kim: Nothing to Disclose, Mohamed Ismail: Nothing to Disclose, Aagamjit Singh: Nothing to Disclose, Imran Qureshi: Nothing to Disclose, Paul Gaglio: Gilead: Speaking and Teaching, Abbvie: Speaking and Teaching, Mallinkrodt: Speaking and Teaching

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4301 | LONG-TERM USE OF FENOFIBRATE AS SECOND-LINE THERAPY IN PRIMARY BILIARY CHOLANGITIS: A RETROSPECTIVE 12-YEAR STUDY OF CHOLESTATIC MARKERS AND LIVER STIFFNESS MEASUREMENT

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Background: Treatment of primary biliary cholangitis (PBC) with ursodeoxycholic acid (UDCA) requires second-line therapy in up to 40% of cases and represents a clinical challenge. Peroxisome proliferator-activated receptor (PPAR) agonists have shown promise as second-line agents in short-term studies, though data on the long-term use of PPAR agonists, particularly fenofibrate (a selective PPAR-α agonist), is scarce. Our study investigates the impact of fenofibrate on serum cholestatic markers and liver stiffness measurements (LSM) in a cohort over 12 years. **Methods:** Patients with PBC and incomplete response to UDCA treatment defined by POISE criteria [alkaline phosphatase (ALP) ≤1.67xULN, ALP reduction ≥15% from baseline, and normal total bilirubin level at one year] who were prescribed adjunct off-label fenofibrate (160 mg/d) during routine care between 2012-2024 at Yale Liver Clinics were analyzed. Baseline and post-fenofibrate biomarker trends were assessed over time using linear mixed models. LSM by transient elastography was compared between a subset of patients from the Yale cohort and a matched historical control cohort of incomplete responders to UDCA from the University of Milano Bicocca. **Results:** The Yale cohort included 37 patients, 81% female with mean age of 61.65 (SD=11.34) years at diagnosis. The estimated serum ALP significantly decreased at 12, 24, and 36 months on fenofibrate therapy by -156.41 [-284.41, -18.4201], -162.45 [-316.37, -8.5217], and -194.20 [-365.95, -22.4587], respectively. After 12 months of fenofibrate therapy, 21 of 37 (58%) met POISE criteria for response. This increased to 74% and 87% by 24 and 48 months, respectively (Figure). 23 patients (70%) normalized serum ALP by 12 months, which increased to 85% by 48 months. Comparison of fenofibrate-treated patients and historical controls showed an estimated effect of fenofibrate on LSM reduction of 0.4 (SE=0.8) at 12 months and 0.8 (SE=1.7) at 24 months. Fenofibrate was discontinued in 9 patients by 48 months; reasons included diarrhea, absence of liver test improvement, myalgia, and decreased renal function. **Conclusion:** Treatment with fenofibrate for second-line therapy in PBC leads to significant improvement in cholestatic markers. Response by POISE criteria and ALP normalization continue to increase beyond 12 months, suggesting an additive benefit over time. This demonstrates that off-label fenofibrate is an effective long-term treatment option for patients with PBC.

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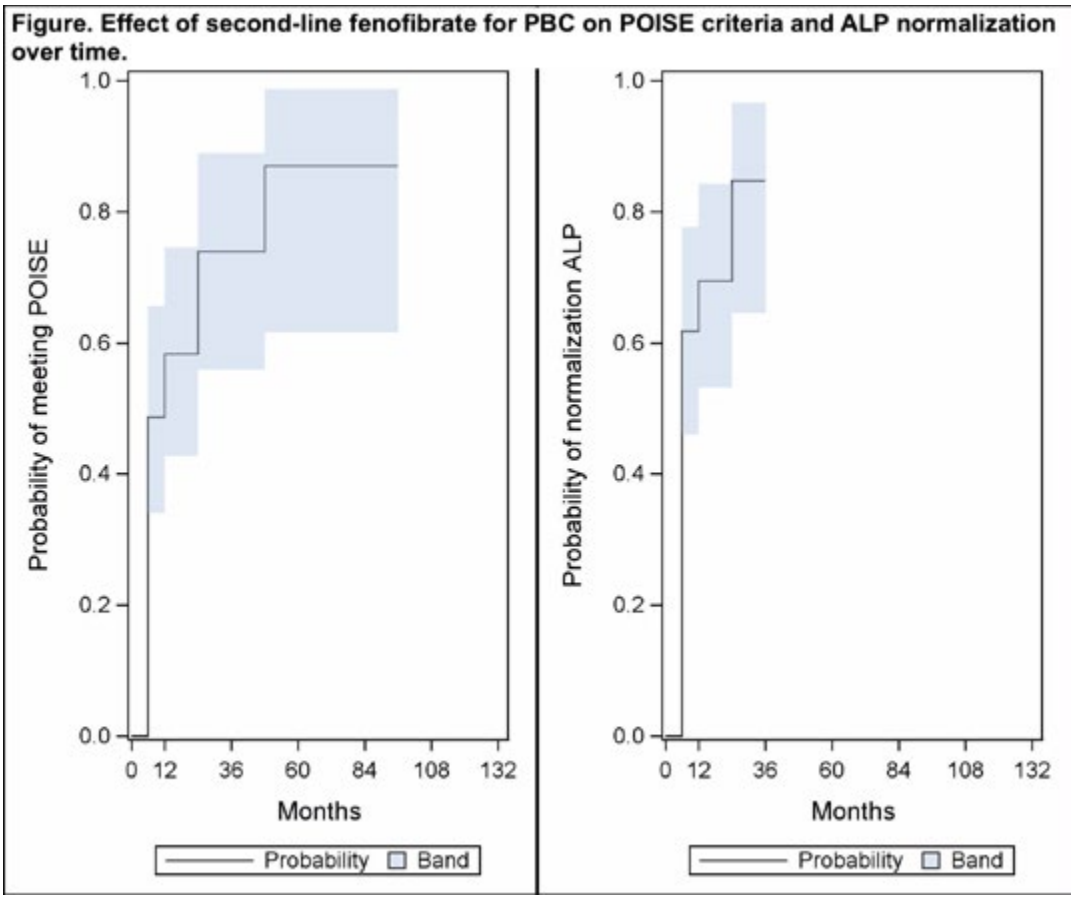
Figure. Effect of second-line fenofibrate for PBC on POISE criteria and ALP normalization over time.



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4302 | SULFASALAZINE IMPROVES ANIT-INDUCED CHOLESTATIC LIVER INJURY AND REGULATES GUT MICROBIOTA IN RATS

Jing Xu Ning Ling[1] Zilin Sun[1] Hang You[1] Yinghua Lan[1] Peng Hu[1] Mingli Peng[1]

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Background: Ursodeoxycholic acid (UDCA) is first-line treatment for primary biliary cholangitis (PBC). But approximately 30% of the patients do not have an adequate biochemical response to UDCA. Our previous research indicates that Sulfasalazine (SASP) ameliorates intrahepatic cholestasis and improves liver fibrosis by regulating the BSH bacteria–CDCA–FXR axis in rats. This study aimed to investigate the therapeutic potential of SASP for PBC in a cholestasis animal model. **Methods:** An intermittent dosing regimen of 80 mg/kg alpha-naphthylisothiocyanate (ANIT) was used to establish a subacute intrahepatic cholestasis rat model. Serum biochemistry and liver histopathology were conducted to evaluate the therapeutic efficacy of UDCA (100mg/kg), SASP (100mg/kg), SASP (150mg/kg), and the combination of SASP (100mg/kg) with UDCA (100mg/kg). The 16S rDNA sequencing was performed to assess the impact of SASP on the fecal microbiota. **Results:** Treatment with UDCA (100 mg/kg), SASP (100 mg/kg), SASP (150 mg/kg),and the combination of SASP (100 mg/kg) and UDCA (100 mg/kg) significantly reduced the cholestasis markers ALP, TBil, and TBA in the serum. SASP-150 (SASP, 150 mg/kg) significantly restored the abnormal elevations of the liver function serum biochemical markers ALT and AST. The improvement in hepatocellular injury with SASP-150 was superior to that of the other groups. Liver histopathology revealed that the ANIT-induced cholestasis model mimicked the pathological features of human PBC. The model group showed significant collagen deposition around the portal area, with inflammatory cell infiltration (mainly $CD3^+$ T cells) and bile duct proliferation (determined by immunohistochemistry of CK19). All drug treatment groups improved liver histopathology to varying degrees, with ASP-150 being the most efficacious.

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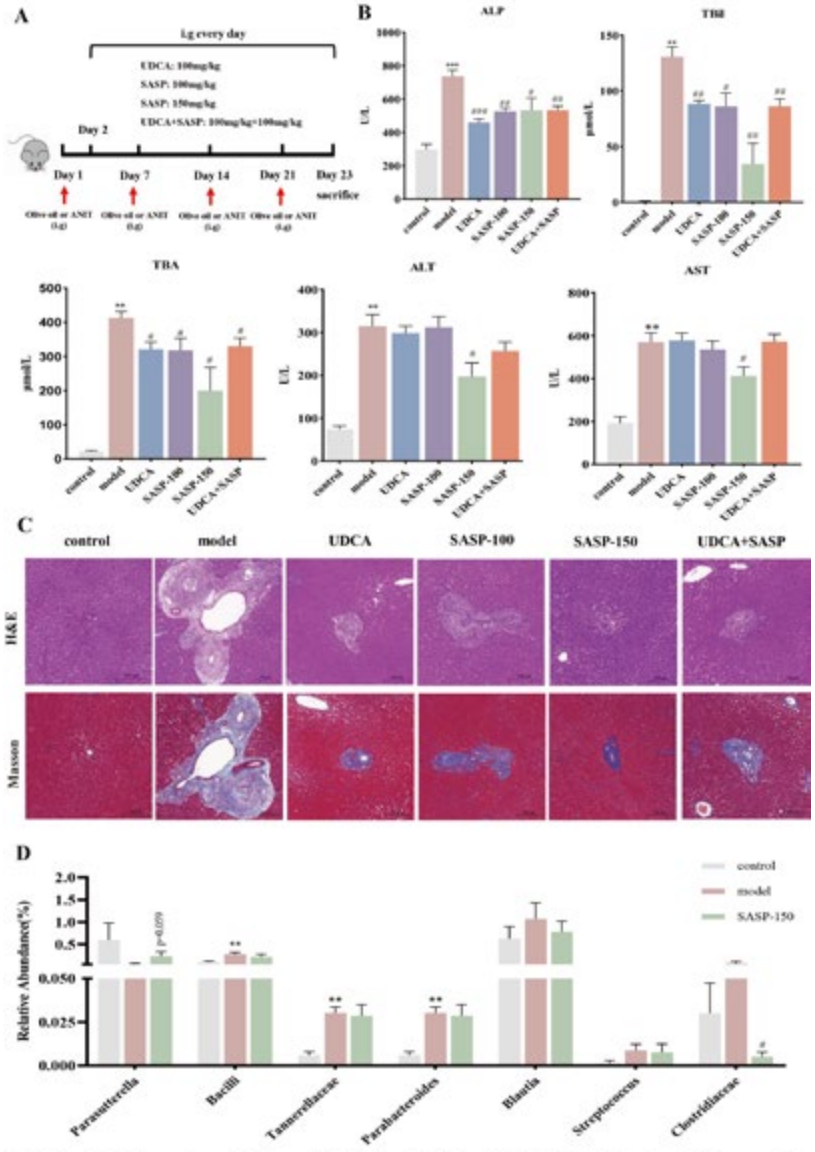
Compared to the model group, the 16S rDNA sequencing indicated that SASP-150 treatment increased the relative abundance of Parasutterella and decreased the relative abundance of Bacilli, Tannerellaceae, Parabacteroides, Blautia, Streptococcus and Clostridiaceae. Among these bacteria, Blautia, Streptococcus, and Clostridiaceae are significantly elevated in the feces of PBC patients. **Conclusion:** Our study suggests that SASP (150mg) improves serological markers and liver pathology in ANIT models. Whether SASP has better therapeutic efficacy in combination with UDCA is under further investigation.



(A). Schematic of the experimental design and schedule for the ANIT model.**(B)**. Biochemical analysis of the serum of rats from different groups. **(C)** Histological analysis of liver tissues obtained from different groups. **(D).** Effect of SASP on gut microbiota dysbiosis in cholestatic rats.

Disclosures: Jing Xu: Nothing to Disclose, Ning Ling: Nothing to Disclose, Zilin Sun: Nothing to Disclose, Hang You: Nothing to Disclose, Yinghua Lan: Nothing to Disclose, Peng Hu: Nothing to Disclose, Mingli Peng: Nothing to Disclose

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4303 | IMPAIRED HEPATIC REGULATORY T CELLS AGGRAVATE AUTOIMMUNE HEPATITIS

Han Wang

Background: Autoimmune hepatitis (AIH) is a chronic, progressive, and immune-mediated liver disorder with an increasing global prevalence. Treatment of AIH remains challenging and primarily relies on corticosteroid therapy. Regulatory T cells (Tregs), essential for maintaining immune homeostasis and preventing various autoimmune diseases, present a potential therapeutic target for AIH. However, the role of Tregs in AIH pathogenesis remains unclear. Here we aim to elucidate the function and prevalence of Tregs during the disease progression of AIH. **Methods:** A well-established AIH model was performed by hydrodynamic transfecting with CYP2D6 plasmid into C57Bl/6 mouse liver. Human samples and clinical data were collected to analyze the correlation between Tregs and disease severity. Hepatic lymphocytes were detected using flow cytometry. The role of Tregs in AIH was evaluated through adoptive Treg transfer, and Treg depletion was achieved using FoxP3-DTR mice. eGFP+ Tregs were isolated from mouse livers for in vitro experiments. The suppressive function of Tregs was assessed using a Treg suppression assay. RNA sequencing was conducted to investigate the function of Treg in AIH liver. Bioenergetic analyses of Tregs were assessed by Seahorse. **Results:** AIH was successfully established in mice, as evidenced by the presence of autoantibodies and characteristic pathological features in the liver at four weeks. The number of Tregs increased in the mice liver as the disease progressed, a trend also observed in human AIH livers. Hepatic Treg cells correlated with the severity of hepatitis, with more Treg infiltration seen in spatients with AIH at fibrosis stages G3-G4 compared to patients at G0-G1. However, despite the increase in Tregs, the proportion of Th17 cells, Th1 cells, CD8+T cells also progressively increased in the mouse liver. Treg depletion in mice exacerbated liver inflammation and fibrosis, yet adoptive transfer did not significantly ameliorate inflammation. RNA sequencing suggests that Tregs in AIH livers exhibited impaired suppressive function and enhanced effector functions, adopting Th17 and Th1 phenotypes. In vitro co-culture with Teff cells revealed diminished suppressive function of hepatic Tregs from AIH mice, while peripheral Tregs maintained normal suppressive capacity. Seahorse analysis indicated reduced oxidative phosphorylation in Tregs, with no significant changes in glycolytic function. **Conclusion:** Although the number of Tregs increases in the liver microenvironment of AIH, their function is impaired. Tregs exhibit a diminished suppressive phenotype and an enhanced effector phenotype, failing to control the escalating inflammation in AIH. This dysfunction is associated with metabolic reprogramming and increased oxidative stress in Tregs. Therefore, AIH treatment should not only aim to increase the number of Tregs but also to restore their functional capacity.

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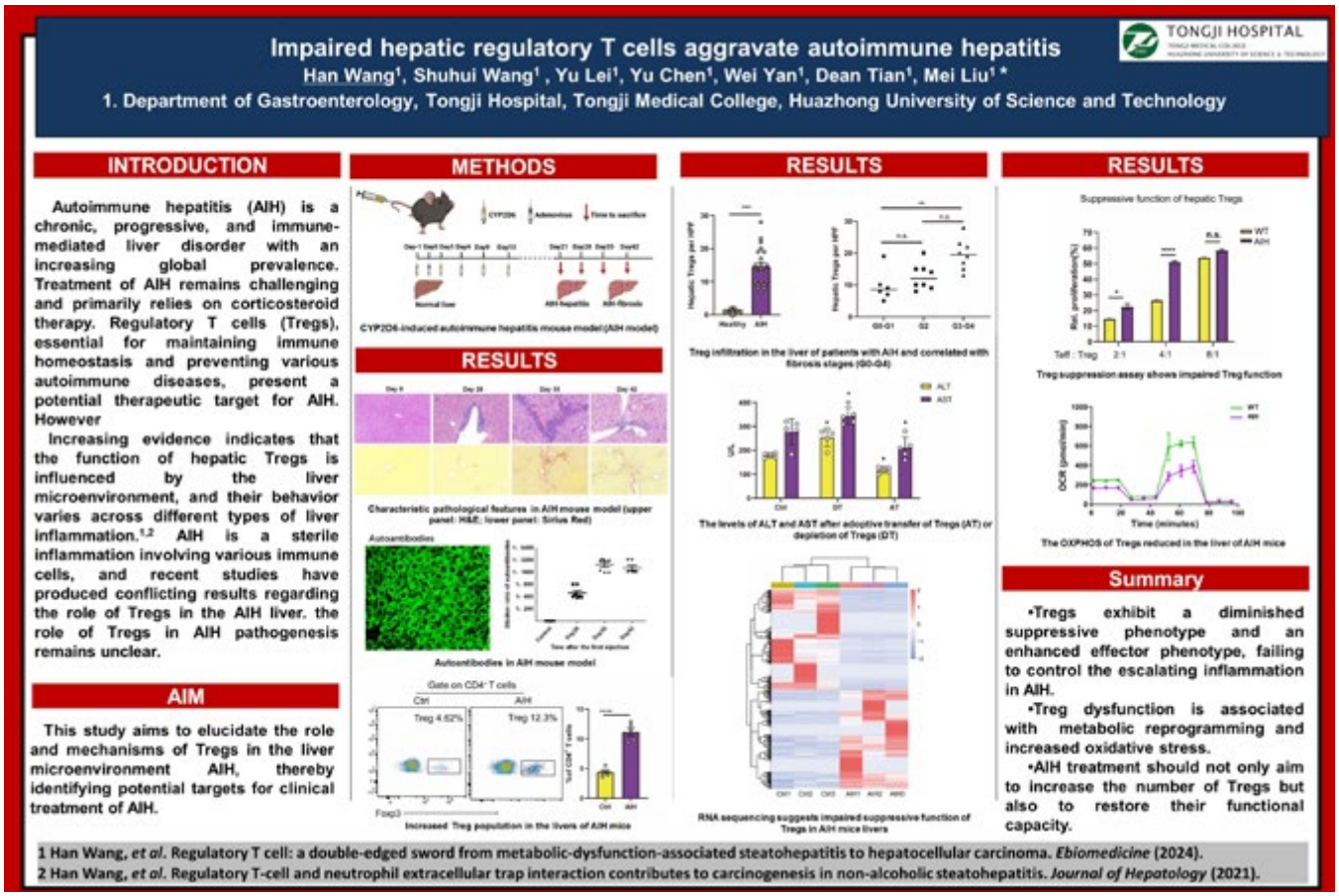

Disclosures: Han Wang: Nothing to Disclose

4304 | MRCP+ HAS A ROLE IN ENHANCING DETECTION OF HIGH-GRADE STRICTURES IN PRIMARY SCLEROSING CHOLANGITIS

James Franklin[1] Charlotte Robinson[2] Sarah Finnegan[3] Elizabeth Shumbayawonda[3] Kartik Jhaveri[4]

[1]Bournemouth University, [2]Royal Berkshire Hospital, [3]Perspectum, [4]University of Toronto

Background: Identifying high-grade strictures (HGS), strictures requiring endoscopic intervention, in patients with primary sclerosing cholangitis (PSC) relies upon subjective assessments of magnetic resonance cholangiopancreatography (MRCP). Quantitative MRCP (MRCP+) provides objective evaluation of MRCP examinations and has shown utility to support disease stratification, monitoring progression, and predicting clinical outcomes. We evaluated the impact that MRCP+ has on clinicians' confidence in diagnosing HGS in patients with PSC. **Methods:** Three expert abdominal radiologists independently assessed 28 patients with PSC, each scanned twice, 1 year apart. Each radiologist assessed each case three times in a randomized order. Assessments 1 and 2 using standard radiological assessment, and the third time using MRCP+. Each round of assessments occurred after a three week delay to avoid any memory of individual cases. The presence of HGS was recorded on a semi-quantitative confidence scale. The proportion of cases where readers definitively agreed on presence/absence of HGS were used to assess inter- and intra-reader agreement and confidence, respectively. Diagnostic accuracy of MRCP+ metrics to detection extrahepatic and intrahepatic HGS was investigated using area under the receiver operating characteristic curve (AUC). **Results:** Standard radiological assessment of MRCP scans had high within reader agreement for identifying HGS in the intra- and extrahepatic ducts (70% and 75% respectively), while between reader agreement was significantly lower for intrahepatic ducts (42.9%) than extrahepatic ducts (67.1%) ($p<0.01$). When using MRCP+, agreement for intrahepatic HGS detection improved (67.9%), comparable to extrahepatic ducts, a significant improvement compared with baseline reads ($p=0.02$). MRCP+ metrics had good performance for the detection of extrahepatic (AUC >0.79) and intrahepatic (AUC = 0.75) HGS (Figure1). **Conclusion:** MRCP evaluation supported by quantitative metrics

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tended to increase individual reader confidence and reduce inter-reader variability for detecting HGS. This could help standardization of MRCP assessments in clinical practice thereby supporting enhanced patient management.

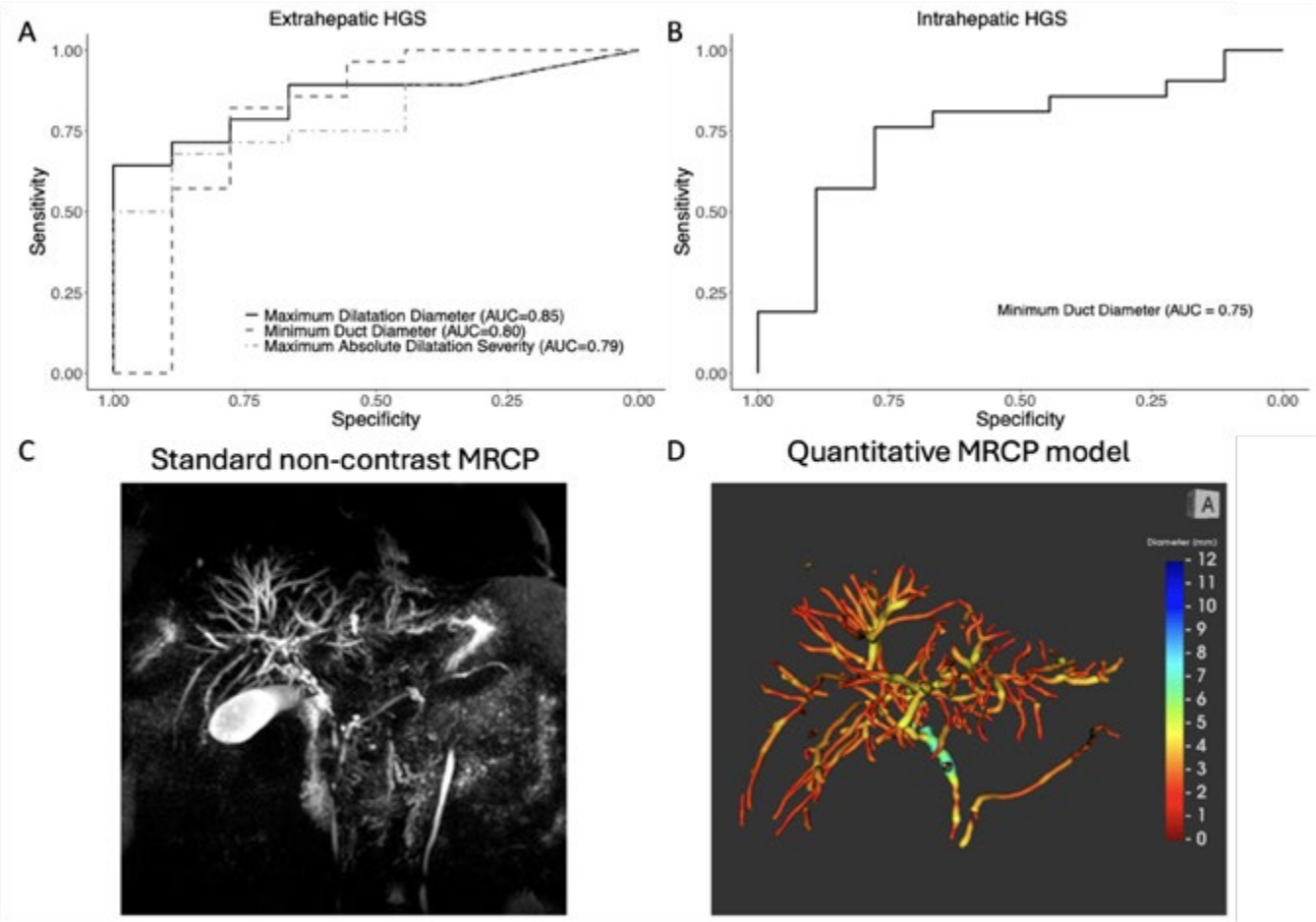

Figure 1: Diagnostic performance of advanced MRCP+ metrics to differentiate between patients with and without A) extra-hepatic HGS and B) intra-hepatic HGS, according to radiologists' interpretation of MRCP reads. C) Traditional MRCP and D) MRCP+ images from a patient with PSC with extrahepatic high-grade stricture.

Disclosures: James Franklin: Nothing to Disclose, Charlotte Robinson: Nothing to Disclose, Sarah Finnegan: Nothing to Disclose, Elizabeth Shumbayawonda: Perspectum Ltd.: Employee, Kartik Jhaveri: Nothing to Disclose

4305 | WHOLE EXOME SEQUENCING FOR THE DIAGNOSIS OF GENETIC CHOLESTASIS IN ADULTS

Miki Scaravaglio[1] Luisa Ronzoni[2] Laura Cristoferi[3] Vittoria Moretti[2] Veronica Torcianti[2] Lorenzo Miano[4] Chiara Caime[1] Eugenia Nofit[3] Federica Malinverno[3] Alessio Gerussi[3] Massimiliano Cadamuro[1] Pietro Invernizzi[3] Marco Carbone[5] Luca Valenti[2]

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Background: Cholestatic liver diseases are a heterogenous group of conditions potentially progressing to end stage liver disease. Beside established cholestatic syndromes (primary biliary cholangitis and primary sclerosing cholangitis), many cases remain undiagnosed. Recent evidence highlights that rare genetic variants underly 17-50% of these unexplained cases, suggesting that genetic cholestasis is underdiagnosed in adults. However, genetic testing has been limited to progressive familial intrahepatic cholestasis (PFIC) related genes or has

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not been integrated at all in the management of adult-onset cholestatic liver disease so far. This study aimed to explore the effectiveness of whole exome sequencing (WES) in diagnosing genetic cholestasis in adults and in identifying novel disease-causing genes. **Methods:** Blood samples of consecutive adult patients with unexplained cholestatic liver diseases were analyzed by WES. **Results:** Three main cholestatic phenotypes were identified: recurrent lithiasis (n=2, 9.5%), intrahepatic cholestasis (n=7, 33.3%), and sclerosing cholangitis with atypical features (n=12, 57.1%). The mean age of the cohort at disease presentation and at genetic analysis was 33.7±11.4 and 42.8 ±10.8 years, respectively. Familiarity for cholestatic liver disease was present in 7 (33.3%) patients. After screening, 99 variants in 51 different genes, confirmed by Sanger sequencing, were prioritized, including 8 (8.1%) in PFIC related genes, 28 (28.3%) in non-PFIC related genes, and 63 (63.6%) in genes related to other liver diseases. The diagnostic yield of WES in the entire cohort was of 7 (33.0%) definite/probable diagnosis of genetic cholestasis and 12 (57.1%) possible genetic contribution to clinical phenotype (**Fig. 1**). The clinical phenotype was the main determinant of diagnostic uptake (p=0.006). Variants in PFIC related genes were responsible for 6 out of 7 (85.7%) definite/probable diagnosis of genetic cholestasis. Variants in non-PFIC related genes were associated with 1 out 7 (14.3%) definite/probable diagnosis of genetic cholestasis and 11 out of 12 (91.7%) possible genetic contribution to clinical phenotype. **Conclusion:** Pending confirmatory results from larger study cohorts, this proof-of-principle study demonstrates that the integration of WES in the diagnostic workflow of cholestatic liver diseases in adults may increase the diagnostic yield of rare cases of genetic cholestasis and highlight novel pathogenic mechanisms.

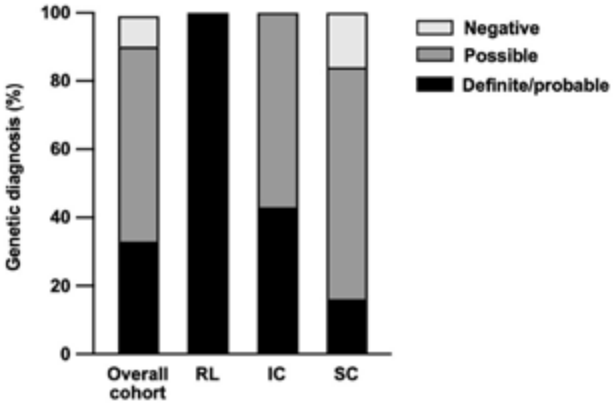

Fig. 1: Diagnostic yield of whole exome sequencing in the overall cohort and in different phenotypes. RL, recurrent lithiasis; IC, intrahepatic cholestasis; SC, sclerosing cholangitis with atypical features.

Disclosures: Miki Scaravaglio: Nothing to Disclose, Luisa Ronzoni: Nothing to Disclose, Laura Cristoferi: IPSEN: Advisor, IPSEN: Advisor, Calliditas: Consultant, Advanz Pharma: Speaking and Teaching, Falk Pharma: Advisor, Signant Health: Consultant, Vittoria Moretti: Policlinico di Milano: contratto ricercatore sanitario, Veronica Torcianti: Policlinico di Milano: Research fellowship, Lorenzo Miano: Nothing to Disclose, Chiara Caime: Nothing to Disclose, Eugenia Nofit: Nothing to Disclose, Federica Malinverno: Nothing to Disclose, Alessio Gerussi: Nothing to Disclose, Massimiliano Cadamuro: Nothing to Disclose, Pietro Invernizzi: Nothing to Disclose, Marco Carbone: Nothing to Disclose, Luca Valenti: Nothing to Disclose

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4306 | CHOLANGIOCARCINOMA SURVEILLANCE WITH MAGNETIC RESONANCE CHOLANGIOPANCREATOGRAPHY IN PRIMARY SCLEROSING CHOLANGITIS: MAKING OUR HEPATOLOGISTS FEEL BETTER

Gary Zhang[1] Chloe Attree[2] Jonathan Tibballs[2] Leon Adams[3] George Garas[3] Gary Jeffrey[2] Michael Wallace[4] Briohny Smith[4] Gerry MacQuillan[2]

[1]Sir Charles Gairdner Osborne Park Health Care Group, [2]Sir Charles Gairdner Osborne Park Health, [3]University of Western Australia, [4]Sir Charles Gairdner Hospital

Background: Primary sclerosing cholangitis (PSC) is associated with a 6–16% lifetime risk of developing cholangiocarcinoma. The outcomes of cholangiocarcinoma are poor, with five-year survival rates of less than 20%. Surveillance strategies using annual magnetic resonance imaging/magnetic resonance cholangiopancreatography (MRI/MRCP) have been recommended by international guidelines in patients with PSC to improve the outcomes of cholangiocarcinoma. However, recent prospective observational data did not demonstrate long-term survival benefits with MRI/MRCP surveillance. The present study aimed to investigate the outcomes of cholangiocarcinoma surveillance in patients with PSC at the Western Australian Liver Transplant Service (WALTS). **Methods:** The electronic clinic database at the tertiary hospital of WALTS was retrospectively searched to identify all patients with PSC managed at the hospital, with diagnosis confirmed using radiology and pathology databases. The surveillance group was defined as patients who received MRCPs every 12±3 months for at least 70% of the follow-up from their first MRCP to whichever occurred earliest of: cholangiocarcinoma diagnosis, liver transplantation, death, or 30th of April 2023. Dysplasia and unexpected malignancies from histopathology of explants in patients who underwent liver transplantation were also recorded. Survival from cholangiocarcinoma between the surveillance and non-surveillance groups was analysed using the Kaplan–Meier method **Results:** A total of 158 patients were included, with 108 patients (68.4%) in the surveillance group and 50 patients (31.6%) in the non-surveillance group. The median age at PSC diagnosis was 38 years (range: 7 – 78 years) with 91 males (59.4%). At the most recent available MRCP, 91 patients had cirrhosis (57.6%) and 59 patients (37.3%) underwent liver transplantation, most commonly for end-stage liver disease (88.1%). The median duration of MRCP surveillance was 86 months (IQR 67.5 months). Fourteen patients (8.9%) were diagnosed with cholangiocarcinoma (intrahepatic, n=10, extrahepatic, n=4). In the surveillance group, 6 patients were diagnosed with cholangiocarcinoma, but MRCP surveillance led to the diagnosis in only 1 patient. Ten patients (71.4% of cholangiocarcinomas) were diagnosed with cholangiocarcinoma following investigations for symptoms or deranged liver function tests (LFTs). The median overall survival for all cholangiocarcinomas was 12.5 months (IQR 12.25). Survival after diagnosis of cholangiocarcinoma was not significantly different between the surveillance and non-surveillance groups (HR=1.35, 95% CI 0.415 to 4.419; figure 1). **Conclusion:** In patients with PSC at a single liver transplantation centre, annual MRI/MRCP surveillance for early cholangiocarcinoma detection was ineffective and did not improve survival after cholangiocarcinoma diagnosis. Symptomatic presentation or deranged LFTs led to the diagnosis of cholangiocarcinoma in the majority of cases.

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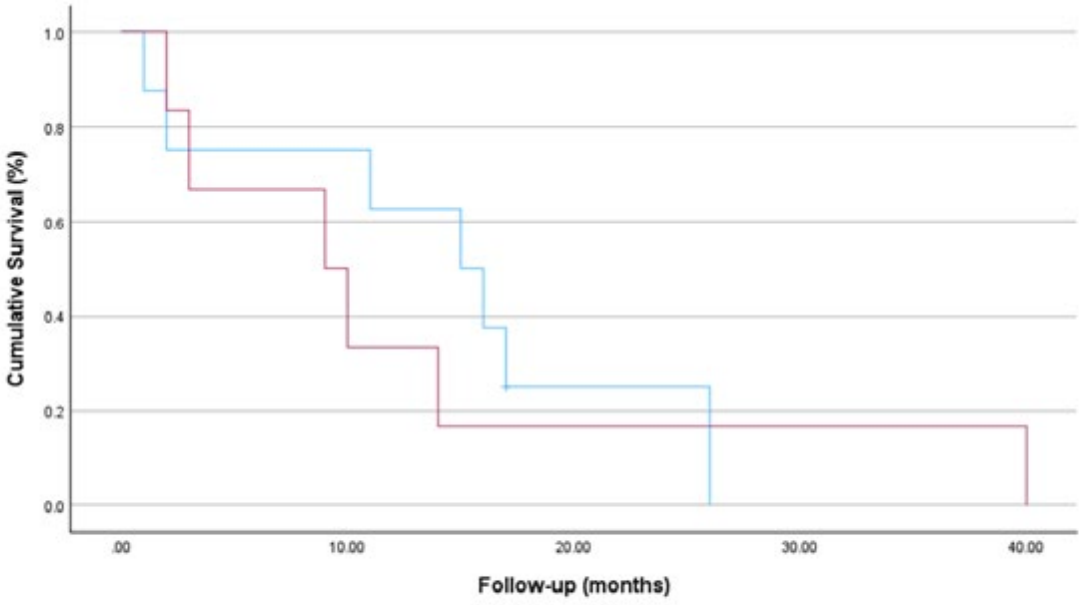

Figure 1. Kaplan-Meier curves displaying the cumulative survival for surveillance (red) versus non-surveillance (blue) in patients with cholangiocarcinoma.

Disclosures: Gary Zhang: Nothing to Disclose, Chloe Attree: Nothing to Disclose, Jonathan Tibballs: Nothing to Disclose, Leon Adams: Novo Nordisk: Advisor, SCL Behring: Advisor, Pfizer: Advisor, George Garas: Nothing to Disclose, Gary Jeffrey: Nothing to Disclose, Michael Wallace: Nothing to Disclose, Briohny Smith: Nothing to Disclose, Gerry MacQuillan: Nothing to Disclose

4307 | USE OF URSODEOXYCHOLIC ACID CAN BE OPTIMIZED IN A NATIONWIDE COHORT OF PATIENTS WITH PRIMARY BILIARY CHOLANGITIS

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Background: Ursodeoxycholic acid (UDCA) is associated with an improved transplant-free survival in primary biliary cholangitis (PBC), with better outcomes in patients using ≥13 mg/kg/day. In case of incomplete biochemical response, add-on second line therapy (SLT) has been suggested to further improve prognosis. We evaluated the use of UDCA and SLT in a nationwide Dutch cohort. **Methods:** The Dutch PBC Cohort Study (DPCS) is a retrospective study which includes every identifiable patient with PBC in the Netherlands from 1990 onwards in all hospitals; 63 general and 8 academic hospitals. Use of UDCA and SLT was assessed among patients in clinical follow-up on January 1st 2019, a year prior to the start of data collection. Experience with SLT was defined as (prior) use of fibrates and/or budesonide (both off-label available in the Netherlands), and/or obeticholic acid

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(exclusively bound to clinical trial enrollment). General hospitals were categorized as low-, medium- and high volume centers according to the 33rd (n=32) and 66th (n=57) percentile of the number of PBC patients in care from 2008 to 2019. **Results:** In total, 4351 patients were included in the DPCS of whom 2638 were in care on January 1st 2019; 2361 (89.5%) were female, mean age was 63.5 (SD 11.7) years, 2143 (81.2%) were treated in a general hospital and 495 (18.8%) in an academic center. Overall, 2590/2638 (98.2%) patients with PBC were prescribed UDCA. However, a recommended UDCA dose of ≥13 mg/kg/day was used by 1390/2257 (61.6%). For those using a dose of <13mg/kg/day, the median dose of UDCA was 11.4 mg/kg/day (IQR 9.7-12.3). In general hospitals, 1084/1803 (60.1%) were prescribed ≥13 mg/kg/day vs. 306/454 (67.4%) in academic centers (p=0.004). This was related to patient volumes in general hospitals; 118/228 (51.8%) used ≥13 mg/kg/day in low- vs. 402/623 (64.5%) in medium- (p<0.001) and 388/952 (59.2%) in high volume centers (p<0.044). With respect to SLT, 252/2638 (9.6%) patients were prescribed SLT on January 1st 2019; 137/2143 (6.4%) in general and 115/495 (23.2%) in academic hospitals (p<0.001). **Conclusion:** UDCA is used by almost the entire Dutch PBC population. However, nearly 40% of patients are dosed below the recommended 13 mg/kg/day, which was related to center volume. Considering the dose-dependent relation between UDCA and improved survival, optimizing first-line therapy may result in additional life-years. Prior to 2019, SLT was infrequently used among Dutch PBC patients.

Disclosures: Ellen Werner: Nothing to Disclose, Maria C.B. van Hooff: Nothing to Disclose, Maria A. van de Vrie: Nothing to Disclose, Gemma H.X. Weijsters: Nothing to Disclose, Rozanne C. de Veer: Nothing to Disclose, Ulrich Beuers: Abacus: Speaking and Teaching, Amgen: Consultant, Behring: Consultant, Zambon: Speaking and Teaching, Joost P.H. Drenth: Nothing to Disclose, Frans J.C. Cuperus: Nothing to Disclose, Remco van Dijk: Nothing to Disclose, Bart J. Veldt: Nothing to Disclose, Michael Klemt-Kropp: Nothing to Disclose, Suzanne van Meer: Nothing to Disclose, Robert Verdonk: Nothing to Disclose, Hajo J. Flink: Nothing to Disclose, Jan Maarten Vrolijk: Nothing to Disclose, Tom J.G. Gevers: Nothing to Disclose, Cyriel Y. Ponsioen: Nothing to Disclose, Kirsten Boonstra: Nothing to Disclose, Femke Boersma: Nothing to Disclose, Hendrik J.M. de Jonge: Nothing to Disclose, Frank Wolfhagen: Nothing to Disclose, L.C. Baak: Nothing to Disclose, Susanne L. Onderwater: Nothing to Disclose, Jeroen D. van Bergeijk: Nothing to Disclose, Paul G. van Putten: Nothing to Disclose, Gijs de Bruin: Nothing to Disclose, Robert Adang: Nothing to Disclose, Maria N. Aparicio-Pages: Nothing to Disclose, Wink de Boer: Nothing to Disclose, Frank ter Borg: Nothing to Disclose, Hanneke van Soest: Nothing to Disclose, Elsemieke S. de Vries: Nothing to Disclose, Harry L.A. Janssen: Nothing to Disclose, Bettina E. Hansen: Nothing to Disclose, Nicole S. Erler: Nothing to Disclose, Adriaan J.P. van der Meer: Nothing to Disclose

4308 | DIABETES MELLITUS IS ASSOCIATED WITH WORSE CLINICAL OUTCOMES IN PATIENTS WITH PRIMARY BILIARY CHOLANGITIS ◆

Ellen Werner Gemma H.X. Weijsters[1] Maria C.B. van Hooff[1] Rozanne C. de Veer[1] Ulrich Beuers[2] Joost P.H. Drenth[2] Frans J.C. Cuperus[3] Remco van Dijk[4] Bart J. Veldt[5] Michael Klemt-Kropp[6] Suzanne van Meer[7] Robert Verdonk[8] Hajo J. Flink[9] Jan Maarten Vrolijk[10] Tom J.G. Gevers[11] Cyriel Y. Ponsioen[2] Pieter C.J. ter Borg[12] Leendert H. Oterdoom[13] Martine A.M.C. Baven-Pronk[14] Anne Vrieze[15] Ingrid C.A.W. Konings[16] Johannes Schmidt-Böhmer[17] Frank C. Bekkering[18] Stephan H.C. van Stiphout[19] Nicole F.M. van Gerven[20] Sven J. van den Hazel[21] Paul J. Bus[22] A. (Sander) van der Beek[23] Sigrid Vandebosch[24] Maaike J. Denters[25] Sander de Kort[26] Harry L.A. Janssen[1] Nicole S. Erler[1] Bettina E. Hansen[1] Adriaan J.P. van der Meer[1]

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Background: Metabolic co-morbidities are increasingly present in patients with primary liver diseases. We aimed to assess the relation between diabetes mellitus (DM) and clinical outcome in patients with primary biliary cholangitis (PBC). **Methods:** The Dutch PBC Cohort Study (DPCS) is a retrospective study which includes every identifiable patient with PBC in the Netherlands from 1990 up to last data collection (2019-2022) in all 71 Dutch hospitals. Clinical data were obtained through medical chart review. The association between DM and long-term outcomes was assessed through Kaplan Meier and Cox regression analyses among all patients who were treated with ursodeoxycholic acid (UDCA). The primary endpoint was liver transplantation (LT) or all-cause

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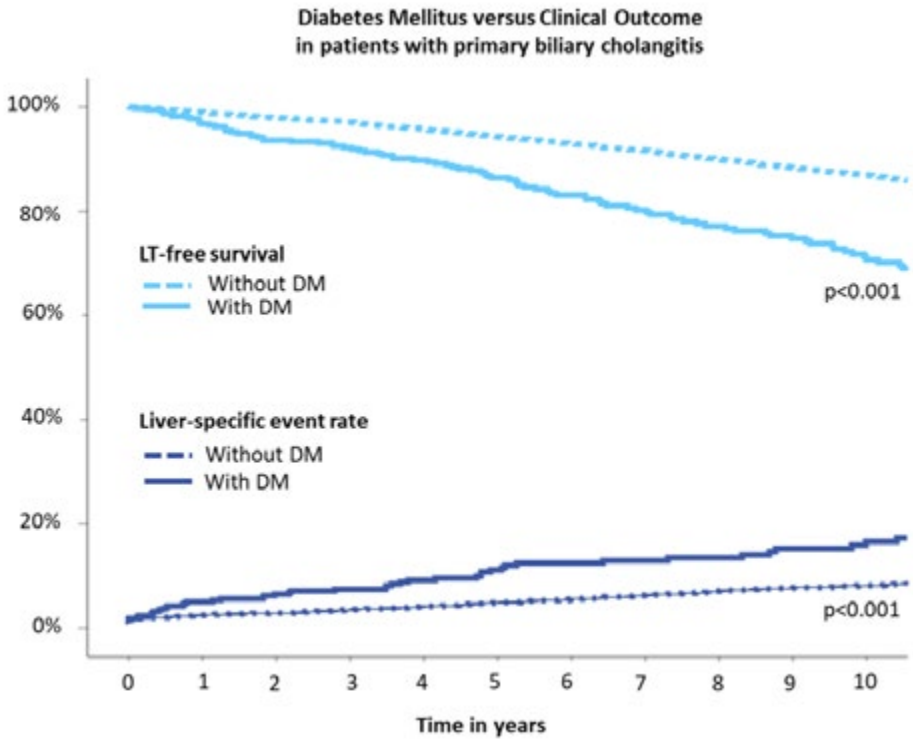
mortality and the secondary liver-specific endpoint was the first occurrence of either decompensated cirrhosis, LT or liver-related death. **Results:** In total, 4256 patients with PBC were followed for a median duration of 8.9 years (IQR 4.2-14.8); 3753 (88.2%) were female, median age at diagnosis was 56.7 years (IQR 48.4-66.2) and 418 (9.8%) had DM at baseline. Patients with DM were older (median age 63.6 years [IQR 54.2-71.7] vs. 56.0 years [IQR 47.9-65.4], p<0.001), were more often male (74/418 [17.7%] vs. 429/3838 [11.3%], p<0.001) and had cirrhosis more often at baseline (61/418 [14.6%] vs. 222/3838 [5.8%], p<0.001). The Paris-2 response rate (ALP and AST <1.5ULN, bilirubin <ULN) after one year of UDCA was 149/270 (55.2%) among patients with DM vs. 1541/2676 (57.6%) among those without DM (p=0.447). The 10-year LT-free survival was 70.7% (95%CI 65.2-76.2) among patients with DM compared to 87.0% (95%CI 85.8-88.2) in those without DM (p<0.001). After 10 years, the cumulative liver-specific event rate was 14.6% (95%CI 10.3-18.9) vs. 6.9% (95%CI 5.9-7.9) in those with and without DM, respectively (p<0.001). Adjusted for age, gender, cirrhosis, calendar time and biochemical parameters of liver disease severity, DM was independently associated with an increased risk of LT or death (adjusted HR 1.7, 95%CI 1.3-2.2, p<0.001) and with liver-specific events (adjusted HR 1.6, 95%CI 1.0-2.5, p=0.040). **Conclusion:** In this nationwide cohort, DM was an independent predictor of unfavorable LT-free survival in patients with PBC. This is partly explained by an increase in progression to end-stage liver disease.



Disclosures: Ellen Werner: Nothing to Disclose, Gemma H.X. Weijsters: Nothing to Disclose, Maria C.B. van Hooff: Nothing to Disclose, Rozanne C. de Veer: Nothing to Disclose, Ulrich Beuers: Abacus: Speaking and Teaching, Amgen: Consultant, Behring: Consultant, Zambon: Speaking and Teaching, Joost P.H. Drenth: Nothing to Disclose, Frans J.C. Cuperus: Nothing to Disclose, Remco van Dijk: Nothing to Disclose, Bart J. Veldt: Nothing to Disclose, Michael Klemt-Kropp: Nothing to Disclose, Suzanne van Meer: Nothing to Disclose, Robert Verdonk: Nothing to Disclose, Hajo J. Flink: Nothing to Disclose, Jan Maarten Vrolijk: Nothing to Disclose, Tom J.G. Gevers: Nothing to Disclose, Cyriel Y. Ponsioen: Nothing to Disclose, Pieter C.J. ter Borg: Nothing to Disclose, Leendert H. Oterdoom: Nothing to Disclose, Martine A.M.C. Baven-Pronk: Nothing to Disclose, Anne Vrieze: Nothing to Disclose, Ingrid C.A.W. Konings: Nothing to Disclose, Johannes Schmidt-Böhmer: Nothing to Disclose, Frank C. Bekkering: Nothing to Disclose, Stephan H.C. van Stiphout: Nothing to Disclose, Nicole F.M. van Gerven: Nothing to Disclose, Sven J. van den Hazel: Nothing to Disclose, Paul J. Bus: Nothing to Disclose, A. (Sander) van der Beek: Nothing to Disclose, Sigrid Vandebosch: Nothing to Disclose, Maaike J. Denters: Nothing to Disclose, Sander de Kort: Nothing to Disclose, Harry L.A. Janssen: Nothing to Disclose, Nicole S. Erler: Nothing to Disclose, Bettina E. Hansen: Nothing to Disclose, Adriaan J.P. van der Meer: Nothing to Disclose

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4309 | A DISBALANCED MINORITY OF PATIENTS WITH PRIMARY BILIARY CHOLANGITIS IS MANAGED IN AN ACADEMIC HEALTH CARE SETTING

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Background: Primary Biliary Cholangitis (PBC) is a rare cholestatic liver disease. Most PBC research originates from an academic setting. We aimed to clarify where PBC care is provided during the course of the disease in a nationwide cohort. **Methods:** The Dutch PBC Cohort Study (DPCS) is a retrospective study which includes every identifiable patient with PBC in the Netherlands from 1990 onwards in all Dutch hospitals; 63 general and 8 academic hospitals. Center of diagnosis, referral to an academic center, date of referral and center at the end-of-follow-up (FU) were recorded. Biochemical parameters are presented in Upper Limits of Normal (ULN). Biochemical response was assessed according to the Paris-2 criteria (ALP and AST ≤1.5 xULN and bilirubin ≤ULN). Factors associated with time to referral to academic care were assessed through Cox regression analyses. **Results:** Overall, 3532/4230 (83.5%) were diagnosed in a general hospital. In total, 3146/4230 (74.4%) patients had their complete follow-up (median of 7.4 years [IQR 3.2-13.6]) in a general hospital setting. During follow-up, 386 of the 3532 patients were referred to an academic center, of which 233 (60.4%) were referred to a liver transplant center. In case of referral, 216/386 (56.0%) remained in academic care for their further follow-up. The median age of patients being referred was 54.5 years (IQR 45.6-63.2), 341/386 (88.3%) were female and median time from diagnosis to referral was 2.9 (IQR 1.0-7.5) years. At the time of referral, the median ALP was 2.0 x ULN (IQR 1.1-3.2) and 92 (23.8%) had cirrhosis, of which 57/92 (62.0%) had at least one event of decompensation. Adjusted for calendar time, age (HR 0.96, 95%CI 0.95-0.97 p<0.001), cirrhosis at diagnosis (HR 4.1, 95% CI 2.7-6.2), ALT level (HR 1.16, 95%CI 1.11-1.21, p<0.001) and incomplete response after one year of ursodeoxycholic acid (HR 3.3, 95CI% 2.44-4.54, p<0.001) were associated with the time-to academic referral. **Conclusion:** In this nationwide cohort, almost 75% of patients with PBC were managed in general hospitals throughout their entire follow-up. Younger patients, with cirrhosis and high ALT or unfavorable cholestasis parameters after one year of ursodeoxycholic acid are more likely to be referred to academic care. Future PBC research should also focus on patients in general hospitals to better understand the real world clinical course of PBC.

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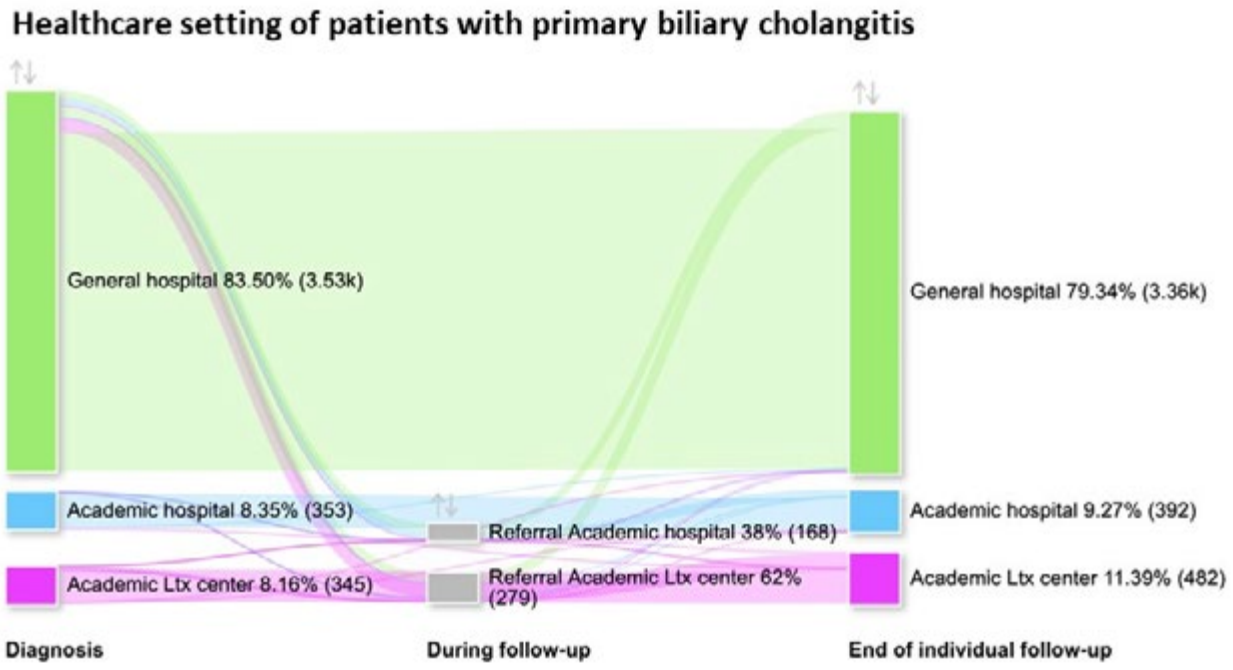

Disclosures: Ellen Werner: Nothing to Disclose, Maria C.B. van Hooff: Nothing to Disclose, Maria A. van de Vrie: Nothing to Disclose, Gemma H.X. Weijsters: Nothing to Disclose, Rozanne C. de Veer: Nothing to Disclose, Ulrich Beuers: Abacus: Speaking and Teaching, Amgen: Consultant, Behring: Consultant, Zambon: Speaking and Teaching, Joost P.H. Drenth: Nothing to Disclose, Frans J.C. Cuperus: Nothing to Disclose, Remco van Dijk: Nothing to Disclose, Bart J. Veldt: Nothing to Disclose, Michael Klemt-Kropp: Nothing to Disclose, Suzanne van Meer: Nothing to Disclose, Robert Verdonk: Nothing to Disclose, Hajo J. Flink: Nothing to Disclose, Jan Maarten Vrolijk: Nothing to Disclose, Tom J.G. Gevers: Nothing to Disclose, Cyriel Y. Ponsioen: Nothing to Disclose, J. Kerbert-Dreteler: Nothing to Disclose, Ulrike de Wit: Nothing to Disclose, Johan P.H. Kuyvenhoven: Nothing to Disclose, Jerome Sint Nicolaas: Nothing to Disclose, Philip W. Friederich: Nothing to Disclose, Merel Tielemans: Nothing to Disclose, J. Marleen de Vree: Nothing to Disclose, Huseyin Aktas: Nothing to Disclose, Sunje Abraham: Nothing to Disclose, Mariëlle J.F. Meijnen: Nothing to Disclose, Janne E. van Rooij: Nothing to Disclose, Edith M.M. Kuiper: Nothing to Disclose, Stephan Schmittgens: Nothing to Disclose, Yasser A. Alderlieste: Nothing to Disclose, Robert Roomer: Nothing to Disclose, Harry L.A. Janssen: Nothing to Disclose, Nicole S. Erler: Nothing to Disclose, Bettina E. Hansen: Nothing to Disclose, Adriaan J.P. van der Meer: Nothing to Disclose

4310 | NON-PSC PATIENTS WITH CHOLANGIOCARCINOMA HAVE HIGHER POST-LIVER TRANSPLANT MORTALITY COMPARED TO PSC WITH CHOLANGIOCARCINOMA

Behnam Saberi[1] Marwan Alsaqa[1] Leandro Sierra[1] Ximena Parraga[1] Merve Gurakar[2] Butros Fakhoury[3] Nazli Begum Ozturk[4] Alan Bonder[1] Ahmet Gurakar[2]

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Background: Cholangiocarcinoma (CCA) is a common primary liver cancer with a high rate of mortality. Deceased donor liver transplant (DDLT) is used in some centers in highly selected patients with CCA. **Methods:** Deceased donor liver transplant recipients with cholangiocarcinoma from Jan 2010 to Dec 2022 using the UNOS/OPTN database were included. Kaplan Meier curves were used for survival analysis. **Results:** During this time period a total of 582 patients with CCA were identified. Among these 34.5% had a diagnosis of primary sclerosing cholangitis (PSC). PSC-CCA patients were younger compared to non-PSC-CCA patients (49.8 vs. 56.4, p<0.001). The proportion of males was higher in PSC-CCA patients compared to non-PSC-CCA patients (77.6% vs. 68.5%, p=0.02). Region 7 had the highest number of DDLT for CCA (n=161), consistent with 27% of the cases, followed by Region 3 (n=76, 13%) and 5 (n=76, 13%). Non-PSC LT recipients with CCA had worse 1, 3, and 5-year survival compared to PSC-CCA patients (82.7%, 59.8%, 49.7%, and 90.0%, 72.1%, 63.8%, respectively,

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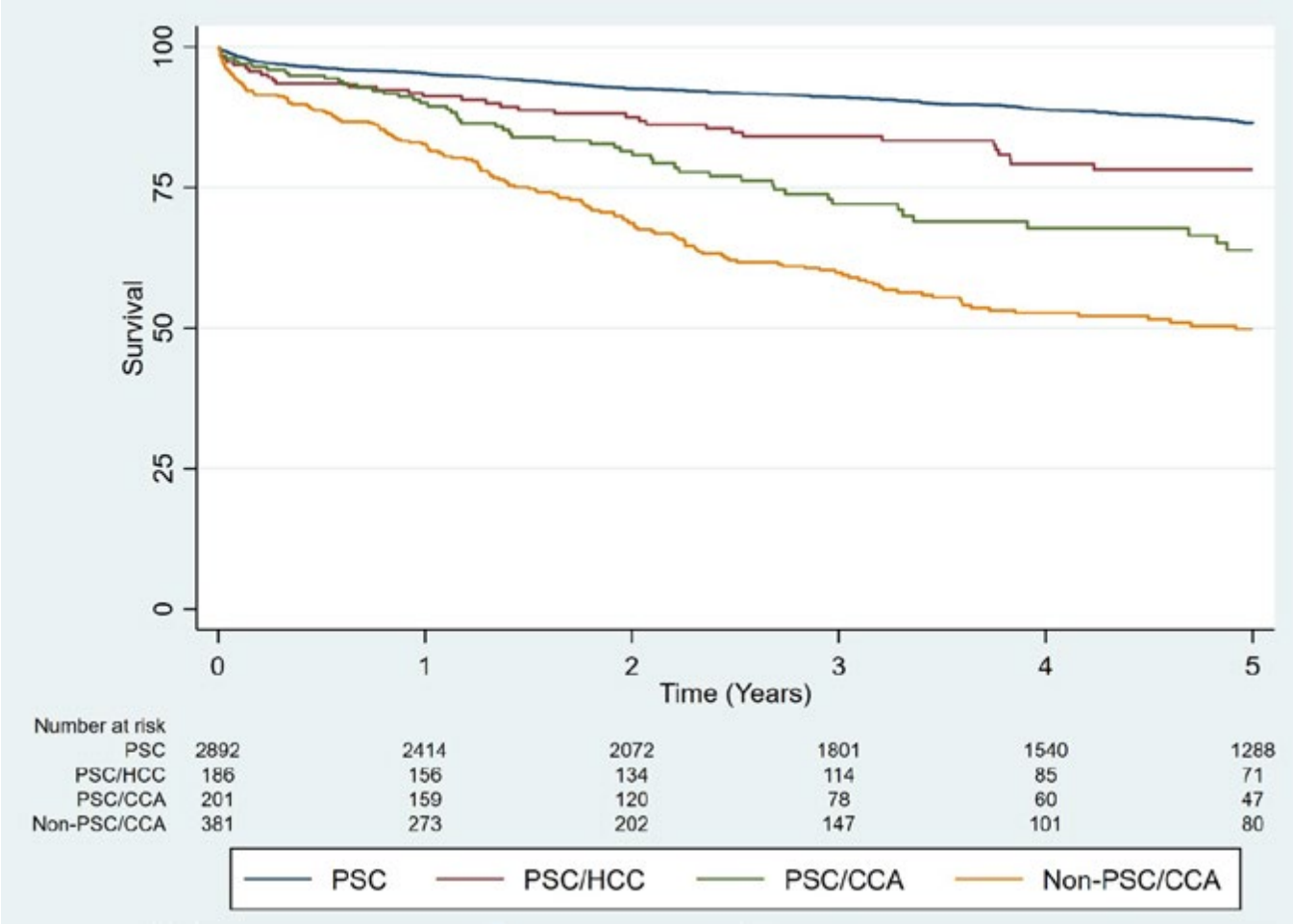
p=0.002)(figure1). The post-LT survival in CCA was the worst compared to PSC-only and PSC-HCC patients (p<0.001)(Figure 1). In multivariate analysis, PSC-HCC, PSC-CCA, and non-PSC-CCA had a higher hazard of mortality compared to the PSC-only group [(HR=1.652, 95% CI 1.202-2.270), (HR=2.888, 95% CI 2.177-3.832), and (HR=5.055, 95% CI 4.113-6.213)] respectively. **Conclusion:** Non-PSC patients with cholangiocarcinoma have a higher post-liver transplant mortality when compared to cholangiocarcinoma associated with PSC. Future research exploring the clinical characteristics and biology of cholangiocarcinoma in PSC and non-PSC patients should be investigated.



Disclosures: Behnam Saberi: Nothing to Disclose, Marwan Alsaqa: Nothing to Disclose, Leandro Sierra: Nothing to Disclose, Ximena Parraga: Nothing to Disclose, Merve Gurakar: Nothing to Disclose, Butros Fakhoury: Nothing to Disclose, Nazli Begum Ozturk: Nothing to Disclose, Alan Bonder: GSK: Grant/Research Support, Mirium: Grant/Research Support, Gilead: Grant/Research Support, Ipsen: Grant/Research Support, Cymabay: Grant/Research Support, Intercept: Grant/Research Support, Intercept: Consultant, GSK: Consultant, Ipsen: Consultant, Chemobab: Grant/Research Support, Alnylam: Consultant, Thirammune: Consultant, Ahmet Gurakar: Nothing to Disclose

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4311 | INVESTIGATING THE CHOLESTATIC PRURITUS OF PRIMARY SCLEROSING CHOLANGITIS (ITCH-PSC): A CROSS SECTIONAL STUDY OF PATIENTS PARTICIPATING IN THE CONSORTIUM FOR AUTOIMMUNE LIVER DISEASE (CALID)

Richard Dean[1] Maryam Yazdanfar[1] Joseph Benjamin Zepeda[1] Isha Patel[2] Cynthia Levy[2] Craig Lammert[3] Raghav Bordia[4] Duru Cosar[4] Katherine Specht[4] Daniel Pratt[5] Stuart Gordon[6] Lisa Forman[7] Fawzy Barry[8] Michael Li[8] David Assis[9] Ashleigh McGirr[10] Megan McLaughlin[11] Sumanta Mukherjee[11] Usha Gungabissoon[12] Christopher Bowlus[1]

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Background: Primary Sclerosing Cholangitis (PSC) is a chronic cholestatic liver disease with no approved treatment and few effective off-label therapies to reduce the symptom burden. Pruritus is frequently reported by patients with PSC, but only limited data exist using patient-reported outcomes measures. ItCh-PSC aims to characterize the frequency and severity of pruritus and determine its impact on quality of life and relationship with biomarkers of pruritus in patients with PSC. **Methods:** Patients aged 18 and older, diagnosed with PSC and without a liver transplant were enrolled at 7 centers. Itch numeric rating scale (NRS), 5-D Itch, PSC-PRO, and SF-36 were completed and serum collected. For the NRS, patients reported their average and worst itch (WI) in the past 24 hours, 7 days, and 6 months. Colitis activity was assessed in patients with inflammatory bowel disease (IBD) by the Simple Clinical Colitis Activity Index (SCCAI). Total serum bile acids (TSBA) and liver biochemistries were measured. **Results:** A total of 200 patients were enrolled (51% male; mean (SD) age of 46.0 (15.4) years; 71% White, 11% Black/African American; 15% cirrhosis). Most patients (77%) had large duct PSC while 4% had small duct PSC and 2% had PSC-AIH. IBD was present in 79% (57% ulcerative colitis/19% Crohn's disease/3% indeterminate). WI in the past 24 hours, 7 days, and 6 months was reported as moderate-to-severe (WI-NRS > 4) by 42 (21%), 48 (24%), and 76 (38%) patients, respectively. WI-NRS in the past 7 days was greater in patients with cirrhosis (P = 0.02); and correlated with 5-D Itch (r = 0.75), PSC-PRO (r = 0.69), and SF-36 physical component (r = -0.47) and mental component (r = -0.32) scores (P < 0.0001 for all); but did not differ by age, sex, race, PSC type, or IBD status. Among patients with IBD, SCCAI was greater in those with worse WI-NRS. Average and WI-NRS scores reported at all times correlated with alkaline phosphatase, AST, albumin, total and direct bilirubin, and TSBA. Among 48 patients with an WI-NRS > 4 in the past 7 days, antihistamines were used by 19 (40%), bile acid binding resins by 12 (25%), rifampin by 7 (15%), sertraline by 4 (9%), and fenofibrate by 4 (8%). **Conclusion:** Patient-reported moderate-to-severe pruritus in this large cohort of patients with PSC was common and correlated with advanced liver disease; worsening cholestasis; and impaired quality of life, but medical treatment of moderate-to-severe pruritus in this group was infrequent.

Disclosures: Richard Dean: Nothing to Disclose, Maryam Yazdanfar: Nothing to Disclose, Joseph Benjamin Zepeda: Nothing to Disclose, Isha Patel: Nothing to Disclose, Cynthia Levy: Consultant relationship with Cymabay; Has ended; Advisor relationship with COur; Has ended; Grant/Research Support relationship with GSK; Has not ended; Grant/Research Support relationship with Ipsen; Has not ended; Consultant relationship with Ipsen; Has ended; Grant/Research Support relationship with Mirum; Has not ended; Consultant relationship with Mirum; Has ended; Grant/Research Support relationship with Zydus; Has not ended; Grant/Research Support relationship with Gilead; Has not ended; Consultant relationship with Gilead; Has ended; Grant/Research Support relationship with Escient; Has not ended; Grant/Research Support relationship with Kowa; Has not ended; Consultant relationship with Kowa; Has ended; Grant/Research Support relationship with Genfit; Has ended; Consultant relationship with Chemomab; Has ended; Consultant relationship with GSK; Has ended; Consultant relationship with Calliditas; Has ended; Grant/Research Support relationship with Calliditas; Has not ended; Consultant relationship with Intercept; Has ended; Grant/Research Support relationship with Cymabay; Has not ended; Grant/Research Support relationship with Intercept; Has not ended, Craig Lammert: Nothing to Disclose, Raghav Bordia: Nothing to Disclose, Duru Cosar: Nothing to Disclose, Katherine Specht: Nothing to Disclose, Daniel Pratt: Nothing to Disclose, Stuart Gordon: Nothing to Disclose, Lisa Forman: mirum: Grant/Research Support, gilead: Grant/Research Support, Fawzy Barry: Nothing to Disclose, Michael Li: Nothing to Disclose, David Assis: Nothing to Disclose, Ashleigh McGirr: Nothing to Disclose, Megan McLaughlin: Nothing to Disclose, Sumanta Mukherjee: GSK: Own GSK stocks, Usha Gungabissoon: GSK: Employee and stockholder, Christopher Bowlus: Calliditas: Grant/Research Support, ChemoMab: Grant/Research Support, ChemoMab: Consultant, COUR Phamaceuticals: Grant/Research Support, Cymabay: Grant/Research Support, Cymabay:

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4312 | FOSB AGGRAVATES CHOLESTATIC LIVER DISEASE BY DISRUPTING IMMUNE MICROENVIRONMENT BALANCE

jintao Xiao[1] haiyue He[2] ziyi Zhao[2] yuhao Zhu[2] wenhu Li[2] xingyang Luo[2] linxiang Zhou[2] xiaomei Zhao[2] xiaowei Liu[2]

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Background: Bile acid accumulation is a prominent feature of cholestatic liver disease(CLD), and plays a crucial role as a trigger for hepatic immune dysregulation and hepatocyte damage. Bile acids can interact with transcription factors, either through direct binding or indirect activation, influencing the regulation of the hepatic immune microenvironment. Fos proto-oncogene (FOSB), a subunit of the AP-1 transcription factor, has been primarily associated with conditions such as depression, drug dependence, and addiction. However, the role of FOSB in the progress of CLD remains unclear. **Methods:** We assessed FOSB expression levels in CLD patients and mouse models built by BDL surgery, DDC diet, and 1% CA diet. Liver samples from the BDL mouse model and those treated with the anti-cholestasis drug obeticholic acid (OCA) underwent RNA sequencing to identify transcription factors linked to bile duct obstruction. Hepatocyte-specific FOSB knockout (FOSB-/-) mice were generated, and both wild-type (WT) and FOSB-/- mice underwent BDL surgery. Primary hepatocytes were isolated and exposed to 40 different bile acid components at a concentration of 25 μmol/L for 48 hours. **Results:** FOSB expression was significantly increased in CLD mouse models, including those subjected to BDL surgery, a DDC diet, and a 1% CA diet, as well as in the livers of CLD patients. Treatment with OCA significantly lowered FOSB mRNA levels compared to controls. FOSB-/- mice exhibited significant decreases in hepatic collagen deposition indicated by Sirius red and Masson's trichrome staining compared to WT mice after BDL. We also observed that mRNA levels of fibrosis-related genes (Acta2, Col1a1, Tgf-β, and Timp1) were decreased in the livers of FOSB-/- mice, as well as protein levels of α-SMA. FOSB-/- mice exhibited a decrease in the number of F4/80 positive cells in the liver, and the mRNA levels of inflammatory and chemotactic factors (Il-1β, Il-6, Tnf-α, Inos, and Cxcl10) were significantly reduced. We also found Th17 cell-related cytokines IL-17A mRNA levels were decreased, while Treg cell-related marker Foxp3 mRNA levels were increased in livers of FOSB-/- mice. Exposure of primary hepatocytes to various bile acids identified specific components (12-ketoDCA, 3β-UDCA, DHCA, GLCA, TCDCA, CDCA) that enhanced mRNA and protein levels of FOSB. **Conclusion:** Hepatocyte-specific knockout of FOSB alleviates BDL-induced liver fibrosis and immune cell infiltration. Bile acid, particularly 12-ketoDCA, 3β-UDCA, DHCA, GLCA, TCDCA, and CDCA, can promote the expression of FOSB. These findings indicate that targeting FOSB could be a potential therapeutic strategy for CLD patients.

Disclosures: jintao Xiao: Nothing to Disclose, haiyue He: Nothing to Disclose, ziyi Zhao: Nothing to Disclose, yuhao Zhu: Nothing to Disclose, wenhu Li: Nothing to Disclose, xingyang Luo: Nothing to Disclose, linxiang Zhou: Nothing to Disclose, xiaomei Zhao: Nothing to Disclose, xiaowei Liu: Nothing to Disclose

4313 | COMPLICATION-FREE SURVIVAL IN A REAL WORLD COHORT OF PBC PATIENTS: DEEP VERSUS ADEQUATE ALP RESPONSE TO UDCA ◆

Anish Reddy[1] Christopher Bowlus[2] Marlyn Mayo[3] Elizabeth Carey[4] Andrea Mospan[5] Aparna Goel[6] Cynthia Levy[7]

[1]University of Miami Miller School of Medicine, [2]University of California, Davis, [3]University of Texas Southwestern Medical Center, [4]Mayo Clinic Arizona, [5]Target RWE, [6]Stanford University Medical Center, [7]University of Miami

Background: Current treatment practice for patients with primary biliary cholangitis (PBC) considers achieving serum alkaline phosphatase (ALP) levels below 1.5 times the upper limit of normal after 1 year of treatment with ursodeoxycholic acid (UDCA) an adequate biochemical response. However, recent evidence suggests there may be a survival advantage in high-risk patients who normalize their ALP levels (deep response). We aimed to

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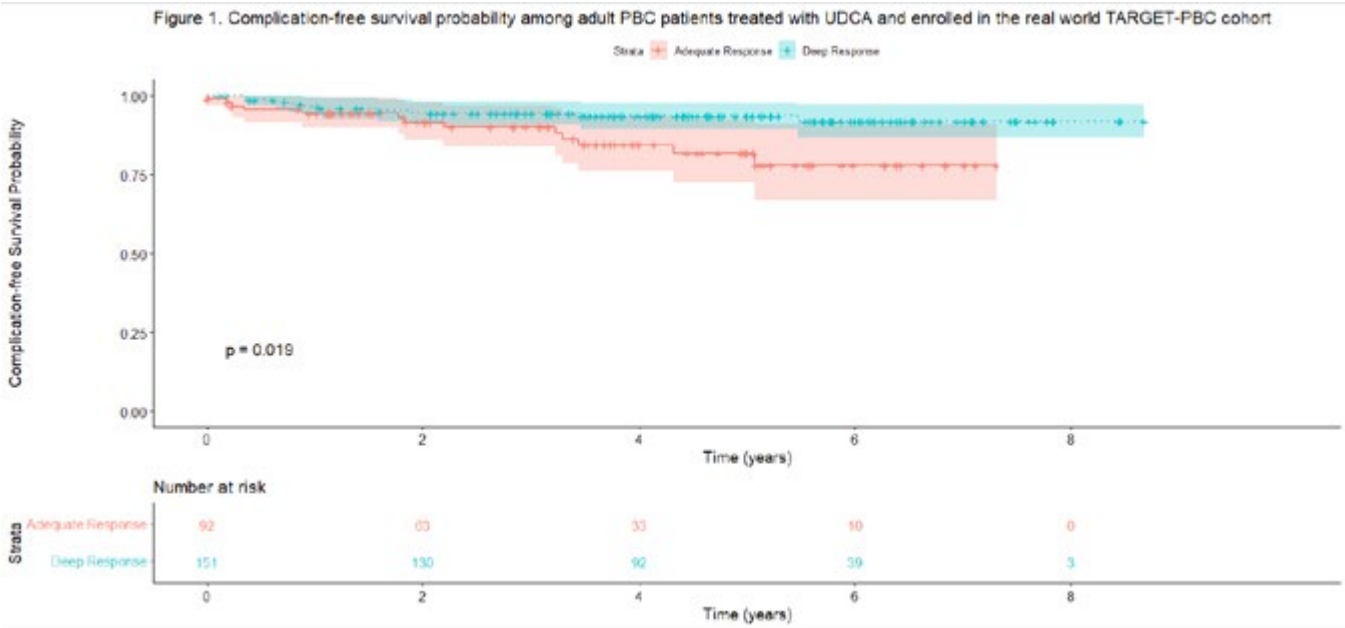
validate these findings in the real-world TARGET-PBC cohort. **Methods:** TARGET-PBC is a longitudinal cohort of PBC patients receiving usual standard of care observed over 5 years across multiple sites in the US. We included patients who (1) had a recorded UDCA start date, (2) were not on second-line therapy, (3) had met at least an adequate response to UDCA (based on two consecutive ALP measurements, along with two consecutive normalized bilirubin measurements), and (4) had no prior decompensating event. Time-to-complications (an endpoint of either ascites, variceal bleeding, encephalopathy, liver transplant or death) from enrollment into deep or adequate response cohorts was compared between deep and adequate response groups via a Cox proportional hazard model. Covariates at enrollment were collected, including values for bilirubin, AST, ALT, GGT, albumin, platelets, duration of UDCA therapy, liver stiffness, and demographics. Patients were classified as high risk if any of the following were present: liver stiffness > 10 kPa, cirrhosis, thrombocytopenia, varices or splenomegaly. **Results:** Of 696 enrolled patients, 243 met inclusion criteria: 151 had a deep response and 92 had an adequate response to UDCA. 23 patients met an endpoint; 15 developed ascites, 5 developed hepatic encephalopathy and 3 died. The incidence rate of events was 6.62% over 664.84 patient-years for the deep response group, and 14.13% over 307.75 patient-years for the adequate response group. With age (< 50, or >=50) and sex as covariates, a deep versus an adequate response was associated with a hazard ratio of 0.379 [0.165, 0.873] (p = 0.0226; Pr>|z|), as illustrated by the KM survival curve in Fig 1. Among high-risk participants, the hazard ratio is even lower: 0.248 [0.093, 0.661] (p = 0.0053; Pr>|z|); the hazard ratio in the low-risk group is insignificant. **Conclusion:** High-risk PBC patients that achieve alkaline phosphatase normalization with UDCA have a decreased risk of hepatic complications and death compared to those with an adequate response. Future research will focus on analyzing the effects of other covariates collected, such as an adequate versus deep bilirubin response.



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relationship with Intercept; Has not ended; Consultant relationship with GSK; Has not ended, Elizabeth Carey: Nothing to Disclose, Andrea Mospan: Nothing to Disclose, Aparna Goel: Nothing to Disclose, Cynthia Levy: Consultant relationship with Cymabay; Has ended; Advisor relationship with COur; Has ended; Grant/Research Support relationship with GSK; Has not ended; Grant/Research Support relationship with Ipsen; Has not ended; Consultant relationship with Ipsen; Has ended; Grant/Research Support relationship with Mirum; Has not ended; Consultant relationship with Mirum; Has ended; Grant/Research Support relationship with Zydus; Has not ended; Grant/Research Support relationship with Gilead; Has not ended; Consultant relationship with Gilead; Has ended; Grant/Research Support relationship with Escient; Has not ended; Grant/Research Support relationship with Kowa; Has not ended; Consultant relationship with Kowa; Has ended; Grant/Research Support relationship with Genfit; Has ended; Consultant relationship with Chemomab; Has ended; Consultant relationship with GSK; Has ended; Consultant relationship with Calliditas; Has ended; Grant/Research Support relationship with Calliditas; Has not ended; Consultant relationship with Intercept; Has ended; Grant/Research Support relationship with Cymabay; Has not ended; Grant/Research Support relationship with Intercept; Has not ended

4314 | DIABETES IS ASSOCIATED WITH POOR LIVER RELATED OUTCOMES IN PATIENTS WITH PRIMARY BILIARY CHOLANGITIS

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Background: Primary Biliary Cholangitis (PBC) is a chronic autoimmune liver disease estimated to affect 14.6 per 100,000 persons worldwide, predominantly females. Cardiometabolic risk factors' relationship to PBC outcomes has not been established. We sought to describe the prevalence of cardiometabolic risk factors in this population and determine their prognostic impact on liver-related outcomes. **Methods:** A cohort of 214 patients diagnosed with PBC in a large tertiary health center was retrospectively studied. Patients with overlap syndrome and other chronic liver disease except Metabolic Dysfunction Associated Liver Disease (MASLD) were excluded. The presence of cardiometabolic risk factors including obesity, hypertension, hyperlipidemia, and diabetes mellitus (DM) was assessed at the time of diagnosis. A composite outcome of liver transplant, cirrhosis and/or hepatocellular carcinoma development was studied. Fisher's exact test and chi-square test were used. **Results:** 144 patients were eligible for analysis, of which 92% were female. Average age at diagnosis was 52.1 years. 76% of the cohort had a BMI of >25, 43% had BMI >30, and 19% had BMI >35. The prevalence of hyperlipidemia and hyperlipidemia was 85% and 39% respectively. 21% of patients had history of DM. Of 144 patients, 21% (n =30) experienced a liver-related adverse outcome. Patients with DM had worse liver-related adverse outcomes (OR 3.40, 95% CI 1.37 - 8.47, p = 0.016). Results were not statistically significant to support an association between higher BMI (any category), hyperlipidemia or hypertension and poor liver-related outcomes. **Conclusion:** In previous studies among PBC patients, hyperlipidemia, hypertension and DM had a prevalence of 34.3%, 16% and 11.9% respectively. In our study we report a prevalence of 85%, 39% and 21% respectively. In the past hyperlipidemia has been associated with better survival rates and lower hepatic decompensation rates. On the other hand, hypertension and DM have been associated with higher mortality rates. MASLD presence has not been associated with worse outcomes. In our cohort we identified an association between DM and poor liver-related outcomes. However, we did not find a statistically significant association with other cardiometabolic risk factors. Larger studies are needed to reach a clear conclusion.

Disclosures: Shreeya Thussu: Nothing to Disclose, Spyridon Zouridis: Nothing to Disclose, Kamran Qureshi: Phathom Pharmaceuticals: Speaking and Teaching, Intercept Pharmaceuticals: Speaking and Teaching, Gilead Sciences: Speaking and Teaching, Salix Pharmaceuticals: Speaking and Teaching, Madrigal Pharmaceuticals: Speaking and Teaching

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4315 | HLX92, A NEW MOLECULAR ENTITY TARGETING GUT MICROBIOTA–LIVER AXIS, CONFERS THERAPEUTIC POTENTIAL AGAINST CHOLESTATIC LIVER DISEASES

Guan-Zhen Wang[1] Teng Feng[1] Li-Ping Han[1] Zhi-Liang Lv[1] Ji-Chen Sha[1] Xiao-Ling Yuan[1] Long-Ling Li[1] Yong-Qiang Shan[1]

[1]Shanghai Henlius Biotech, Inc.

Background: Cholestatic liver diseases and the concomitant diseases resulted from multiple undefined mechanisms including inflammatory response, dysregulation of bile acid and dysbiosis of gut microbiota. Cholestatic liver diseases, such as primary sclerosing cholangitis (PSC) and primary biliary cholangitis (PBC), are lack of effective therapy and with huge unmet medical needs. Here, we describe a new molecular entity, HLX92, as potential treatment strategy for cholestatic liver diseases. **Methods:** Cholestatic liver models were induced in mice by feeding DDC diet, ANIT administration, bile duct ligation and Mdr2-/-. IBD model was induced by 3% DSS administration. Bile acid profiling with UPLC-MS and 16s RNA sequencing were applied for mechanistic investigation. **Results:** In DDC cholestatic liver model, the serum ALP of HLX92 was over 2 times less than that of cholestatic control, which also showed superior efficacy to UDCA and OCA. Meanwhile HLX92 shared comparable improvement of liver fibrosis as OCA. In acute ANIT model and Mdr2-/- model, the serum ALT of HLX92 was over 2 times less than cholestatic control, which also showed superior efficacy in ameliorating liver injury to UDCA and OCA. Moreover, HLX92 also markedly reduced portal inflammation and periportal bridging necrosis in Mdr2-/- model based on pathological score. In BDL model, HLX92 also significantly reduced the serum ALP. *In vitro*, HLX92 protected hepatocytes and cholangiocytes from deoxycholic acid induced cell injury. Besides, HLX92 also inhibited the abnormal T cell proliferation. Mechanistically, HLX92 significantly restored the serum bile acid disorder to a similar pattern in healthy mice by regulation of liver gene expression including *Cyp7A1*, et al. Meanwhile, dysbiosis of gut microbiota which are related to the production of secondary bile acid and correlated with the development of cholestatic liver diseases were observed in DCC-mice. While HLX92 could recondition it to a relative healthy state. Interestingly, HLX92 also improved the symptom and pathology in the DSS induced IBD model. **Conclusion:** HLX92 is a poly-pharmacological candidate with tolerable safety which can ameliorate biliary and liver injury and reduce liver fibrosis by maintaining bile acids homeostasis and modulating gut microbiota. HLX92 may represent an attractive therapeutic strategy for the treatment of cholestatic liver disease and associated inflammatory bowel disease.

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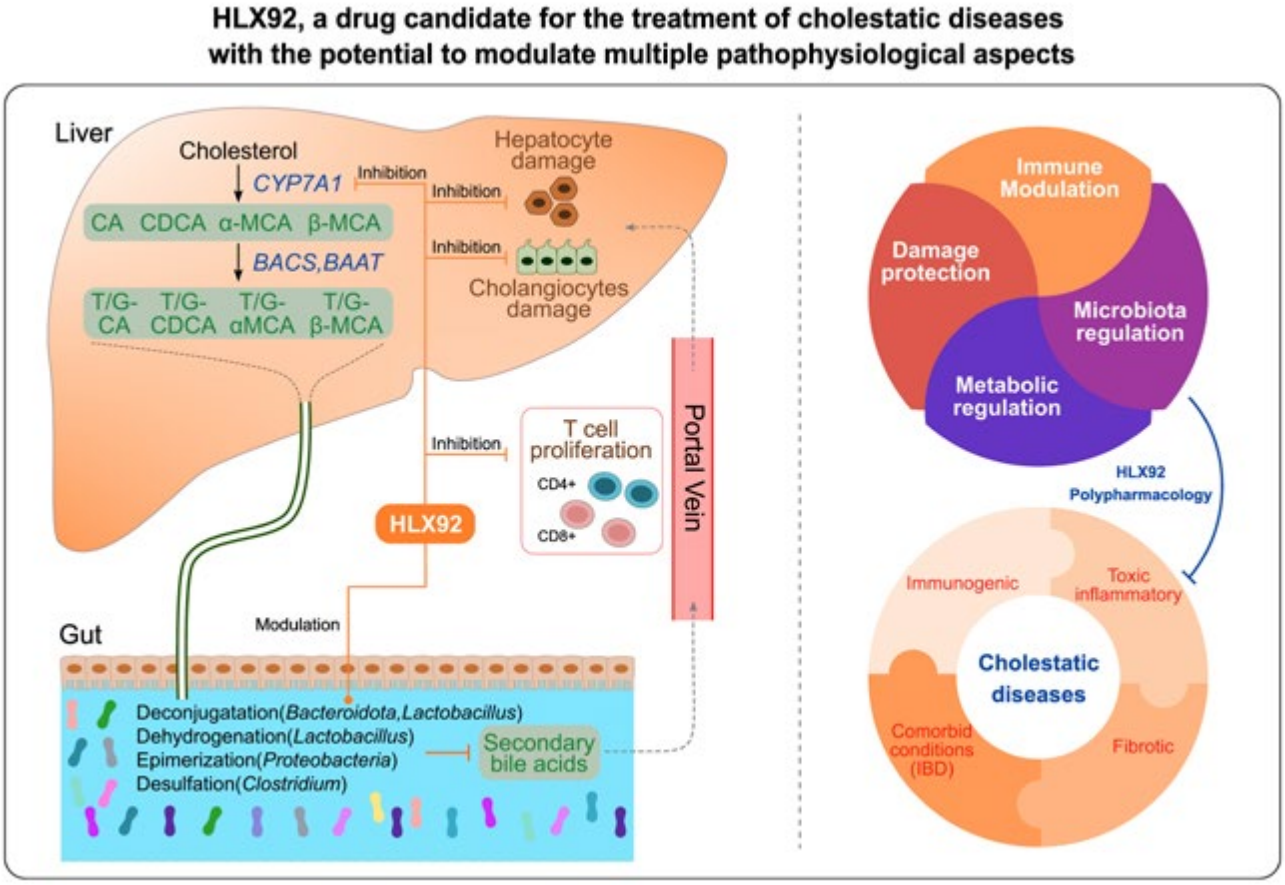

Disclosures: Guan-Zhen Wang: Nothing to Disclose, Teng Feng: Nothing to Disclose, Li-Ping Han: Nothing to Disclose, Zhi-Liang Lv: Nothing to Disclose, Ji-Chen Sha: Nothing to Disclose, Xiao-Ling Yuan: Nothing to Disclose, Long-Ling Li: Nothing to Disclose, Yong-Qiang Shan: Nothing to Disclose

4316 | MULTICENTER STUDY ON INCIDENCE AND RISK FACTORS OF HEPATOCELLULAR CARCINOMA IN PATIENTS WITH AUTOIMMUNE HEPATITIS

Jiwon Yang[1] Sun Young Yim[2] Kunhee Kim[3] Hye Won Lee[3] Jonggi Choi[4]

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Background: A recent European multicenter study found a low incidence of hepatocellular carcinoma (HCC) in autoimmune hepatitis (AIH), even after cirrhosis development. We aimed to evaluate the incidence and predictors of HCC in Asian patients with AIH. **Methods:** We conducted a multicenter, retrospective study on adult patients diagnosed with AIH between January 2000 and January 2024 in three tertiary referral hospital (Asan Medical Center, Yonsei University Severance Hospital, and Korea University Hospital). AIH diagnosis was based on international guidelines and confirmed via the registration of rare intractable disease registry of the Korean National Health Insurance Database. Primary outcome was the incidence of HCC with a median follow-up period of 6.2 years. Cumulative incidence risk of HCC and assessment of its risk factors in AIH were estimated with competing risk analysis, regarding death and liver transplantation as competing risk for HCC. **Results:** Of 1,310 patients with AIH, 694 (53.0%), 402 (30.7%), and 214 (16.3%) patients were from Asan Medical Center, Yonsei University Severance hospital, and Korea University hospital, respectively. Median age was 58.0 years, and 1,118 (85.3%) patients were female. Cirrhosis at diagnosis was present in 619 (47.3%) patients. During follow-up period, 41 (3.1%) patients developed HCC with an annual incidence of 0.53/100 PYs. Cumulative incidence of HCC at 3, 5, 7, and 10 years were 1.8%, 2.9%, 4.2%, and 4.8%, respectively. Risk factors for HCC included male sex (subdistribution hazard ratio [SHR]: 2.31), age over 60 years (SHR: 3.52), cirrhosis (SHR: 3.79), and

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decompensated status at diagnosis (SHR: 2.39). **Conclusion:** In this study, HCC incidence in AIH was higher than that reported in the European study and associated with prognostic factors such as male sex, old age, cirrhosis, and decompensated status at diagnosis.

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4317 | BIOMARKERS ASSOCIATE WITH FIBROSIS PROGRESSION IN PATIENTS WITH PRIMARY SCLEROSING CHOLANGITIS: AN AD-HOC ANALYSIS FROM THE PRIMIS STUDY

Michael Trauner[1] Kaiyi Zhu[2] Jun Xu[3] Xiangyu Liu[4] Xiaomin Lu[5] Sharlene Lim[4] Vlad Malkov[4] William Barchuk[4] Lisa Boyette[5] Zachary Goodman[6] Atsushi Tanaka[7] Douglas Thorburn[8] Cynthia Levy[9] Christopher Bowlus[10]

[1]Medical University of Vienna, [2]Gilead Sciences Inc, [3]Gilead Sciences, Inc., [4]Gilead Sciences Inc., [5]Gilead Sciences, [6]Inova, [7]Teikyo University School of Medicine, [8]Royal Free Hospital, [9]University of Miami, [10]University of California, Davis

Background: Background: and Aim: Primary sclerosing cholangitis is a chronic progressive liver disease characterized by biliary inflammation and fibrosis. Since PSC is a heterogenous disease with variable clinical outcomes, the aim of our study was to identify risk factors for patients with fibrosis progression. **Methods:** People with non-cirrhotic PSC were enrolled into PRIMIS study and randomized 2:1 to receive cilofexor 100 mg or placebo for 96 weeks. Those with moderate to severely active inflammatory bowel disease (IBD) (Partial Mayo score > 4) were excluded. Liver stiffness measurement (LSM) was obtained by transient elastography (TE) and ELF score was calculated from serum levels of TIMP-1, PIIINP and hyaluronic acid. Cilofexor did not significantly alter histological fibrosis stage progression, ELF score or LSM compared to placebo, so the risk of fibrosis progression was assessed in the combined treatment and placebo groups. Fibrosis progression was defined and analysed separately as an increase of fibrosis ≥ 1 stage, ELF score ≥ 0.5 units, and LSM ≥ 20%. A multivariate logistic regression was used to examine the odds ratio (OR) for fibrosis progression of baseline (BL) characteristics, including IBD status (presence or absence), BL Ludwig fibrosis stage (F0-2 vs. F3) and BL ALP levels (>1.5 X ULN vs. ≤ 1.5 X ULN), which were adjusted by baseline LSM, ELF score and UDCA usage. **Results:** 419 patients were enrolled and evaluated for fibrosis progression at W96. The risk of histological Ludwig stage progression was significantly increased by higher BL ALP [OR 2.24 (1.10, 4.64)]. LSM progression risk was significantly increased in patients with IBD [OR 2.09 (1.07, 4.26)]. ELF score progression was numerically associated with BL Ludwig F3, higher ALP levels or IBD status (Figure). PSC patients with BL Ludwig F3 exhibited significantly higher BL levels of LSM and ELF score and had greater increases (median, Q1, Q3) in both biomarkers at W96: LSM [F0-2: 3% (-21%, 25%) vs. F3: 17% (-14%, 74%), p<0.01] and ELF score [F0-2: 0.12 (-0.24, 0.45) vs. F3: 0.45 (-0.14, 1.08), p<0.005]. PSC patients with BL F3 also progressed more frequently to liver cirrhosis (F4) (n=7, 13.5%) compared to patients with BL F0-2 (n=1, 0.7%) at W96. However, Ludwig F3 patients had a significantly lower OR for fibrosis stage progression. **Conclusion:** PSC patients with F3 fibrosis stage, higher ALP levels or IBD were at risk in fibrosis progression, which was consistent with previous reports. Our study also underscored the complexity of evaluating histological fibrosis progression. The risk factors for liver-related clinical outcomes need to be assessed in longer and larger studies for patients with non-cirrhotic PSC.

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Figure: Odds ratio of baseline fibrosis stage, ALP levels and IBD status for fibrosis progression at W96 in patients with PSC

	Fibrosis Progression in Ludwig Stage (≥ 1 stage)	Fibrosis Progression in ELF Score (≥ 0.5 units)	Fibrosis Progression in LSM (≥ 20%)
BL Fibrosis Stage F3 vs F0-2	0.15 (0.05, 0.40) P<0.001	2.03 (0.98, 4.19) P=0.056	2.12 (1.00, 4.51) P=0.049
IBD Status Presence vs Absence	1.68 (0.80, 3.67) P=0.18	1.33 (0.69, 2.64) P=0.4	2.09 (1.07, 4.26) P=0.036
BL ALP >1.5 vs. ≤ 1.5 ULN	2.24 (1.10, 4.64) P=0.028	1.04 (0.54, 1.99) P=0.91	1.85 (0.96, 3.57) P=0.064

PSC: primary sclerosing cholangitis
ALP: alkaline phosphatase
IBD: inflammatory bowel disease
LSM: liver stiffness measurement
BL: baseline
ULN: upper limit of normal

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4318 | DYSREGULATED CIRCULAR RNAS AND THEIR IMPLICATIONS IN THE PATHOGENESIS OF PRIMARY SCLEROSING CHOLANGITIS

Sareh Bayatpour[1] Jing Zeng[2] Grayson Way[1] Hongkun Lu[1] Yun-Ling Tai[1] Derrick Zhao[1] Xuan Wang[1] Sayed Obaidullah Aseem[1] Arun Sanyal[1] Jiangao Fan[2] Phillip Hylemon[1] Huiping Zhou[1]

[1]Virginia Commonwealth University, [2]Xinhua Hospital, Shanghai Jiao Tong University

Background: Primary sclerosing cholangitis (PSC) is a chronic, progressive liver disease characterized by inflammation and fibrosis of the bile ducts. The pathogenesis of PSC is not well understood, but it is often associated with inflammatory bowel diseases. Non-coding RNAs (ncRNAs), including microRNAs (miRs) and circular RNAs (circRNAs), play significant roles in the regulation of various physiological and pathological processes. CircRNAs can act as sponges for miR and interact with RNA-binding proteins, influencing mRNA stability and translation. However, the role of circRNAs in liver diseases, particularly in PSC, remains largely unknown. This study aimed to identify the dysregulated circRNAs and molecular pathways contributing to PSC. **Methods:** Liver tissues from PSC patients and healthy controls (HCs) were obtained from the Liver Tissue Cell Distribution System in Minneapolis, MN (n=6, age 46-62, both male and female). Total RNA was isolated for circRNA profile using the human circRNA Array V2 by Arraystar, Inc. circRNA-specific bioinformatics algorithms were used to identify the differentially expressed (DE) circRNA in PSC patients compared to HCs. CircRNAs with both false discovery rate (FDR) and p-value< 0.05 and fold change (IFCI) ≥2.5 were identified. The interaction of circRNA/microRNA was predicted using Arraystar's miRNA target prediction software. The predicted miRNAs associated with DE-cricRNAs were used to identify the potential targets using miRDB. The networks of miRNA-mRNA were established using miRNet. Gene ontology and KEGG pathway analysis were performed. **Results:** More than half of DE-circRNAs are exonic, which were spliced out from exonic regions of the genome. We identified 142 upregulated and 32 downregulated DE-circRNAs in PSC patients. The pathway analysis revealed that the AMPK signaling, mitophagy, and protein processing in the endoplasmic reticulum were the top pathways impacted by upregulated circRNAs. The ubiquitin-mediated proteolysis was the top pathway impacted by downregulated circRNAs. The top 50 hub genes were identified using miRNA-mRNA networks, and KEGG analysis showed that these DE-circRNAs were linked to several cancer signaling pathways, including SMAD2/3, EGFR, and NFkB. **Conclusion:** The results suggest that dysregulated circRNAs may play an important role in the pathogenesis of PSC. Understanding the function of DE-cirRNAs will provide novel insights for developing potential therapeutics for PSC.

Disclosures: Sareh Bayatpour: Nothing to Disclose, Jing Zeng: Nothing to Disclose, Grayson Way: Nothing to Disclose, Hongkun Lu: Nothing to Disclose, Yun-Ling Tai: Nothing to Disclose, Derrick Zhao: Nothing to Disclose, Xuan Wang: Nothing to Disclose, Sayed Obaidullah Aseem: Galmed Pharmaceuticals: Grant/Research Support, Arun Sanyal: Genfit, Akarna, Tiziana, Durect, Inversago, Hemoshear, North: Stock - publicly traded company, Astra Zeneca (60K), Boston Pharmaceutical

4319 | HAPLOINSUFFICIENCY OF A20 IN AUTOIMMUNE HEPATITIS ENHANCES INFLAMMATORY AND FIBROGENIC RESPONSES: INSIGHTS FROM IPSC-DERIVED MODELS

Astha Malik[1] Liva Pfuhler[2] Eriko Sakakura[1] Chie Naito[1] Kentaro Iwasawa[1] Takahisa Nakamura[1] Akihiro Asai[1] Alexander Miethke[1]

[1]Cincinnati Children's Hospital Medical Center, [2]Cincinnati Children's Hospital

Background: Autoimmune Hepatitis (AIH) is a chronic inflammatory liver disease that can progress to cirrhosis or acute liver failure if untreated. We recently reported four patients with seronegative or type 2 AIH and deleterious mutations in *TNFAIP3* encoding A20, a negative regulator of NFkB and apoptosis. Haploinsufficiency of A20

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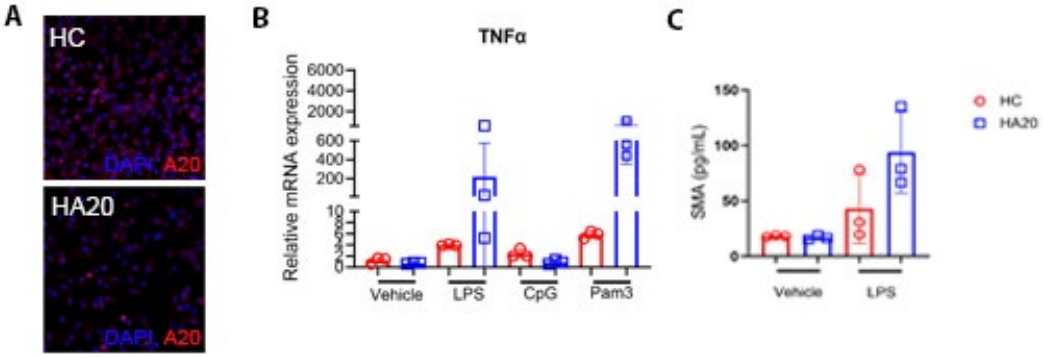
(HA20) is associated with autosomal-dominant Behcet's disease. We aim to elucidate the role of A20 in controlling liver inflammation and fibrosis in patient-derived induced pluripotent stem cell (iPSC) disease models. **Methods:** Human liver organoids (HLO) were developed from iPSCs of a patient with AIH and the frameshift mutation p.Thr76Profs*21 in *TNFAIP3* and from a healthy control (HC) using a matrigel-supported culture condition. iPSCs were also differentiated into macrophages (MP) and hepatic stellate cells (HSC) for monolayer cultures. Both cell monolayers and HLO were cultured in growth factor containing media conditioned with various toll-like receptor (TLR) agonists for 16 hours prior to quantitation of *TNFα* gene expression by RT-qPCR. HSC were cultured in growth media containing palmitic and retinoic acid and conditioned with supernatants from stimulated MP prior to measurement of SMA in HSC lysates by TR-FRET. **Results:** Whereas iPSC-derived MP from both donors were similar in expression of the MP marker CD11b, expression of A20 greatly differed (Fig 1A). Expression of *TNFa* was increased in HA20- compared with HC-MP following specific TLR agonists (Fig 1B). SMA production was higher in HSC incubated with supernatant from LPS-treated MP from HA20 compared with MP from HC donor (Fig 1C). HLO from both donors expressed CK19, SMA, HNF4a, and CD86 on distinct cell populations as markers for cholangiocytes, HSC, hepatocytes, and MP, respectively. In HLO from HA20 donor, PAM2 stimulation, activating TLR 2, upregulated *TNFα gene* and SMA protein expression compared with HC-HLO. **Conclusion:** A20 haploinsufficiency increases the susceptibility of hepatic macrophages (MP) and hepatic stellate cells (HSC) to proinflammatory and profibrogenic responses following TLR stimulation. iPSC-derived models replicate aspects of monogenetic AIH and may facilitate identification of novel treatment targets.

Fig 1A: IF for A20 expression in iPSC derived HA20 and HC MP.
Fig 1B: TNFa gene expression in MP treated with either LPS (100ng/ml), CpG (50ng/ml) or Pam3.(25ng/ml)
Fig 1C: SMA quantification from HC HSCs co-cultured with conditioned media harvested from HC or HA20 MP treated with either vehicle alone or LPS.



Disclosures: Astha Malik: Nothing to Disclose, Liva Pfuhler: Nothing to Disclose, Eriko Sakakura: Nothing to Disclose, Chie Naito: Nothing to Disclose, Kentaro Iwasawa: Nothing to Disclose, Takahisa Nakamura: Nothing to Disclose, Akihiro Asai: Nothing to Disclose, Alexander Miethke: Mirum Pharmaceutical Inc: Grant/Research Support, Mirum Pharmaceutical Inc: Consultant, Ipsen: Speaking and Teaching

4320 | ESTABLISHMENT OF AN FXR-RELATED PFIC MOUSE MODEL CARRYING HUMAN-LIKE BILE ACID COMPOSITION BY *IN VIVO* LIVER-SPECIFIC GENE DELETION USING ADENO-ASSOCIATED VIRUS AND CRISPR/CAS9 SYSTEM

Yusuke Mishima[1] Akihide Kamiya[2] Kota Tsuruya[3] Yoshitaka Arase[2] Akira Honda[4] Tatehiro Kagawa[3]

[1]Tokai university school of medicine, [2]Tokai university school of medicine, [3]Tokai University, [4]Tokyo medical university

Background: Farnesoid X receptor (FXR), encoded by NR1H4, is crucial for bile acid, lipid, and glucose metabolism. Mutations in NR1H4 gene cause progressive familial intrahepatic cholestasis (PFIC) 5. Unlike humans, Nr1h4 deletion in mice does not evoke severe liver damage, likely due to their higher levels of hydrophilic bile acids synthesized by rodent-specific enzymes, Cyp2a12 and Cyp2c70. In this study we utilized Cyp2a12/Cyp2c70 double-knockout (DKO) mice which have human-like hydrophobic bile acid composition. We induced liver-specific Nr1h4 deletion using adeno-associated virus (AAV)-mediated Cas9 and gRNA expression

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vectors in the DKO mice and investigated whether this mouse model would represent human PFIC5. **Methods:** Farnesoid X receptor (FXR), encoded by NR1H4, is crucial for bile acid, lipid, and glucose metabolism. Mutations in NR1H4 gene cause progressive familial intrahepatic cholestasis (PFIC) 5. Unlike humans, Nr1h4 deletion in mice does not evoke severe liver damage, likely due to their higher levels of hydrophilic bile acids synthesized by rodent-specific enzymes, Cyp2a12 and Cyp2c70. In this study we utilized Cyp2a12/Cyp2c70 double-knockout (DKO) mice which have human-like hydrophobic bile acid composition. We induced liver-specific Nr1h4 deletion using adeno-associated virus (AAV)-mediated Cas9 and gRNA expression vectors in the DKO mice and investigated whether this mouse model would represent human PFIC5. **Results:** Nr1h4-deficient wild-type mice (WT-Nr1h4) showed no significant changes in the liver-body weight ratio and serum liver injury markers. In contrast, Nr1h4-deficient CYPDKO mice (DKO-Nr1h4) revealed mild hepatic inflammation and an increase in liver-body weight ratio compared with WT-Nr1h4 (6.6% vs. 5.1%). Serum liver injury markers were remarkably elevated in DKO-Nr1h4; AST: 34.3 ± 12.1 IU/L (mean ± SD), 25.5 ± 3.3 and 332.3 ±104.8, ALT: 13.5 ± 5.5, 10.5 ± 1.0 and 807.5 ± 167.4, and ALP: 89.7 ± 8.4, 96.8 ± 3.9 and 229.3 ± 77.9, in WT, WT-Nr1h4 and DKO-Nr1h4, respectively. Serum total bile acid levels in DKO-Nr1h4 were also higher than WT-Nr1h4 (5.0 ± 1.7 vs. 0.9± 0.6 µmol/L). In addition, mRNA expressions of inflammatory cytokines and fibrosis-related genes were induced in DKO-Nr1h4. Forced hepatic expression of Shp in DKO-Nr1h4 suppressed liver injury induced by Nr1h4 deletion. **Conclusion:** In CYPDKO mice, liver-specific Nr1h4 deficiency induced significant liver injury, unlike in WT mice, validating their use as a mouse model for PFIC5. Rescue of Nr1h4-induced liver injury by forced Shp expression underscores the critical role of the Nr1h4-Shp signaling pathway in maintaining liver function.

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4321 | AUTOANTIBODIES AGAINST CARBONIC ANHYDRASE ISOFORMS INHIBIT ENZYMATIC FUNCTION IN PRIMARY SCLEROSING CHOLANGITIS AND IGG4-RELATED CHOLANGITIS

David Trampert[1] Remco Kersten[1] Alessio Nocentini[2] Simone Giovannuzzi[2] Aldo Jongejan[3] Claudiu Supuran[2] Stan van de Graaf[1] Ulrich Beuers[1]

[1]Tytgat Institute, AGEM, Amsterdam UMC, [2]University of Florence, [3]Bioinformatics Laboratory, Amsterdam UMC

Background: Primary sclerosing cholangitis (PSC) and IgG4-related cholangitis (IRC) are characterized by fibrotic stricturing of the bile ducts. The pathogenesis of PSC remains largely unclear, whilst IRC shows uncontrolled immune responses against self-antigens. In both, potential defects in cholangiocellular HCO_3^- secretion have been disclosed. Carbonic anhydrases (CA) hydrate CO_2 to HCO_3^- and H^+. Previously, immunizing mice *in vivo* with human CA2 resulted in development of cholangitis. We investigated whether 1) CA isoforms are autoantigens in PSC and IRC, 2) anti-CA autoantibodies can functionally inhibit CA, 3) specific isoforms have a protective role in cholangiocytes. **Methods:** Anti-CA isoform autoantibody positivity was assessed in IRC (n=52), PSC (n=15) and healthy control (n=13) sera by ELISA. IgG's containing anti-CA autoantibodies were isolated and tested for functional inhibition of human recombinant CA isoforms monitoring CO_2 hydration to HCO_3^- and H^+ by a stopped flow method. CA's were stained by immunofluorescence in human bile duct sections. Human H69 cholangiocytes treated with the pan-CA inhibitor acetazolamide were RNA sequenced. Lentiviral shRNA knockdown H69 cholangiocytes of CA isoforms were generated and parental cholangiocytes were treated with isoform-specific inhibitors. Cellular respiration and viability were measured using the Agilent Seahorse XF Analyzer and WST assays. ^{3}H-GCDC influx was determined radiochemically. **Results:** Autoantibodies were detected against CA2 (33% PSC, 27% IRC) and CA5B (27% PSC, 48% IRC) as opposed to CA12 (0% PSC, 2% IRC). Cytosolic CA2, mitochondrial CA5B and membrane bound CA9/12 are present in cholangiocytes. Pan- and membrane-specific CA inhibition decreased bile acid uptake. RNA sequencing revealed differential expression of mitochondrial respiratory chain genes. Cellular respiration and baseline cell viability were both increased in CA5B knockdown cholangiocytes, yet after GCDC exposure viability was reduced. CA5B knockdown increased bile acid uptake as did treatment with two CA5B-specific inhibitors. Patient-derived anti-CA2 and anti-CA5B autoantibodies functionally inhibited human recombinant CA2 and CA5B. Anti-CA2 and anti-CA5B ELISA titers significantly correlated with percentage of enzyme inhibition (Pierson r 0.87 / r^2 0.76, and Spearman r 0.88, respectively). **Conclusion:** We demonstrate for the first time that subsets of PSC and IRC patients have anti-CA autoantibodies

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that functionally inhibit human recombinant CA isoforms, thereby potentially rendering cholangiocytes more susceptible to bile acid-induced damage.

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4322 | E-CADHERIN EXPRESSION BY CD8⁺ T CELLS IS INCREASED IN PATIENTS WITH PRIMARY BILIARY CHOLANGITIS AND PROMOTES THEIR INVASION INTO BILIARY EPITHELIAL CELLS ★

Scott Davies[1] Vincenzo Ronca[1] Grace Wootton[1] Amber Bozward[1] Natalia Krajewska[1] Rémi Fiancette[1] Daniel Patten[1] Katharina Yankouskaya[1] Gary Reynolds[1] Sofia Pat[1] Daniel Osei-Bordom[1] Naomi Richardson[1] Liam Grover[1] Chris Weston[1] Ye Oo[1]

[1]University of Birmingham

Background: Lymphocyte-based cell-in-cell structures (CICSs) are commonly observed in autoimmune liver diseases. The presence of CD8⁺ T cells within biliary epithelial cells (BEC) has been recently demonstrated histologically in patients with primary biliary cholangitis (PBC). We aimed to characterise these T cells and dissect their mechanism of internalisation. **Methods:** We developed a high-content imaging (HCI) co-culture platform to quantify the internalisation of human T cells into primary human BEC. This assay was used to observe the effect of T cell receptor (TCR) activation, to compare CD8⁺ T cells to CD4⁺ T cells, and to investigate the effect of T cell RNA interference. T cell phenotyping was performed using flow cytometry. Immunohistochemistry (IHC) was used to investigate internalisation in patients with chronic liver disease. **Results:** CD8⁺ T cell entry into BEC was more frequent amongst larger cells and 48 h following TCR-mediated activation. CD8⁺ T cell internalisation was higher compared to CD4⁺ T cells. Internalisation events were observed in 100% of PBC patients analysed (N=15 total; 6 explant, 9 biopsy) versus 20-40% in non-PBC liver. E-cadherin expression by CD8⁺ T cells correlated with internalisation frequency and was higher in those derived from PBC patients. Furthermore, CD8⁺ T cell interactions with BEC surfaces were enriched with E-cadherin and β-catenin. E-cadherin⁺ CD8⁺ T cells were also located within BEC which formed ruptured bile ducts observed in PBC biopsies. FACS-sorted E-cadherin⁺ CD8⁺ T cells invaded BEC more frequently than E-cadherin⁻ CD8⁺ T cells. Finally, siRNA-inhibition of E-cadherin in PBC-derived CD8⁺ T cells significantly reduced internalisation into BEC. **Conclusion:** We unveil a distinct CICS in the liver, whereby BEC are invaded by E-cadherin⁺ CD8⁺ T cells. The frequency of this process observed in PBC patients, as well as the higher expression of E-cadherin by PBC-derived CD8⁺ T cells, are indicative of the role in the pathogenesis of this disease and provide future scope for investigation.

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4323 | THE PROTECTIVE ROLE OF GALLBLADDER PRESENCE AND ENLARGEMENT IN PATIENTS WITH PRIMARY SCLEROSING CHOLANGITIS: PRELIMINARY ANALYSIS OF A MULTICENTRIC STUDY

Nora Cazzagon[1] Elisa Catanzaro[1] Annika Bergquist[2] Aristeidis Grigoriadis[2] Raffaella Motta[1] Lionel Arrivé[3] Christophe Corpechot[4] Olivier Chazouilleres[5] Chantal Housset[6] Sara Lemoinne[4]

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Background: In a proof-of-concept study of patients with Primary Sclerosing Cholangitis (PSC), gallbladder (GB) enlargement was suggested to have a hepatoprotective role. Moreover, the presence of the GB was associated with less severe PSC as compared to cholecystectomized patients. Similarly, in a mouse model of PSC, cholecystectomy caused an increase in hepatic bile acids content and circulating secondary bile acids, exacerbating cholangitis, ductular reaction, inflammation and liver damage compared to sham-operated mice. Aim: To assess the impact of GB on PSC severity. We compared liver function tests, liver stiffness and event-free survival in patients with normal-sized GB vs. patients with enlarged GB and patients with intact GB vs. cholecystectomized **Methods:** This is a multicentric retrospective study. Inclusion criteria comprised patients diagnosed with large duct PSC between 2000 and 2020, with at least one magnetic resonance imaging (MRI) scan available for review (the closest to diagnosis) and a minimum follow-up of 12 months. Exclusion criteria encompassed small-duct PSC, secondary sclerosing cholangitis or IgG4-associated cholangitis, as well as patients with a history of liver transplantation or cirrhosis decompensation prior to inclusion, and those presenting with gallbladder disease (e.g. cholecystitis, cancer) at the time of inclusion. Gallbladder volume was quantified via MRI, with a cutoff of 50 mL employed to define GB enlargement. **Results:** This analysis was conducted on a cohort of 173 PSC patients from two centers and comprises 102 males, with 120 having concomitant IBD and a median age at inclusion of 39 years. The majority (67%) were treated with ursodeoxycholic acid (UDCA) at the time on inclusion. Among the included patients, 71 had an enlarged GB, 74 had a normal-sized GB, and 28 had previously undergone cholecystectomy. Patients with enlarged GB, compared to those with normal GB volume, exhibited significantly lower alkaline phosphatase levels (ALP) (p= 0.027) and total bilirubin levels (p=0.037), as well as a longer duration of UDCA treatment (p=0.003). Additionally, they showed a trend towards longer mean adverse-event-free survival from inclusion according to univariate analysis (p=0.07). In the UDCA-treated group (n=93 patients), we observed that patients with enlarged GB, compared to those with normal GB, had lower frequency of cirrhosis at inclusion (p=0.016), lower levels of ALP (p=0.050) and total bilirubin levels (0.021) and a longer mean adverse-event-free survival according to univariate analysis (p=0.014) (figure). Furthermore, cholecystectomized patients, compared to those with intact GB, exhibited significantly lower levels of albumin at inclusion (p=0.03), but no difference in event-free survival. **Conclusion:** Taken together, these findings provide further evidence for a protective role of the GB in PSC. Validation is currently underway in a larger population.

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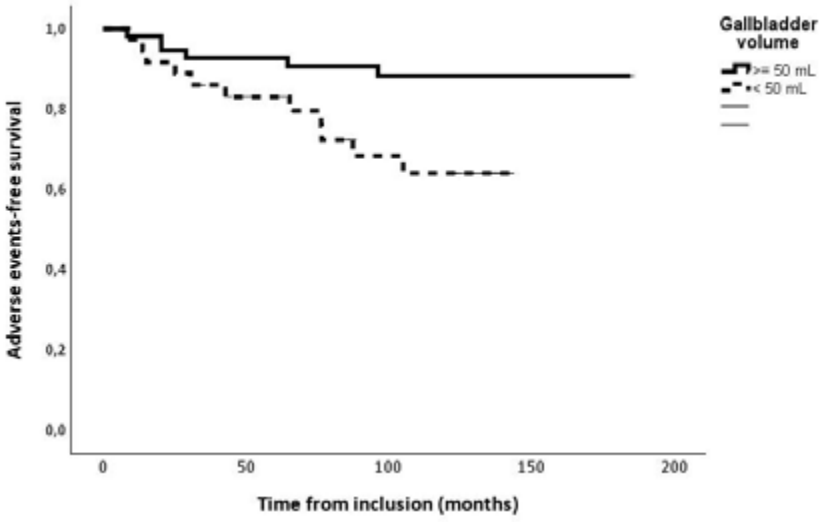

Disclosures: Nora Cazzagon: Advanz: Speaking and Teaching, Orphalan: Consultant, Orphalan: Independent Contractor, IPSEN: Advisor, ALBIREO by IPSEN: Advisor, GSK: Advisor, Elisa Catanzaro: Nothing to Disclose, Annika Bergquist: Calliditas: Advisor, IPSEN: Advisor, Aristeidis Grigoriadis: Janssen-Cilag AB: Institutional fees, Raffaella Motta: Nothing to Disclose, Lionel Arrivé: Nothing to Disclose, Christophe Corpechot: IPSEN: Consultant, GILEAD: Consultant, Cymabay: Consultant, Mirum: Consultant, GSK: Consultant, Calliditas: Consultant, Echosens: Speaking and Teaching, Advanz: Consultant, Olivier Chazouilleres: INTERCEPT: Consultant, INTERCEPT: Consultant, FALK Pharma: Consultant, MAYOLI: Speaking and Teaching, IPSEN: Consultant, Chantal Housset: Nothing to Disclose, Sara Lemoinne: Nothing to Disclose

4324 | LIVER TRANSPLANTATION FOR PRIMARY SCLEROSING CHOLANGITIS IN THE UNITED STATES BY DONOR AND RECIPIENT SEX AND RACE

William Wheless[1] *Alice Toll*[2] *Alexandra Lewis*[2] *Wida Cherikh*[2] *Mark Russo*[1]

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Background: Outcomes after liver transplant (LT) for primary sclerosing cholangitis (PSC) are excellent. Risk factors associated with decreased patient and graft survival and other etiologies of liver disease include donor-recipient (DR) mismatch for sex or race. Current data on outcomes in LT recipients by DR sex or race in PSC are scarce. We sought to determine outcomes after LT for PSC, including survival stratified on DR sex and race. **Methods:** We analyzed the OPTN database for deceased donor liver transplants performed for adult (age ≥ 18) recipients between 2/27/2002 and 9/30/2018. Survival analyses were limited to transplants performed through 9/30/2018 to allow for up to 5-years of post-transplant follow-up. Multiorgan, previous transplant of any organ, and status 1 recipients were excluded. The cohort was limited to recipients who were alive with a functioning graft at discharge and diagnosed with PSC. Patient and graft survival for the entire cohort and by sex and race DR mismatch were estimated using univariate Kaplan-Meier survival method and compared using the log-rank tests. Multivariable analysis was performed using Cox regression. **Results:** The cohort included 2,907 PSC recipients. Graft survival at 1 and 5 years was 94.6% and 83.2% and patient survival at 1 and 5 years was 97.2% and 89.0%, respectively. The cohort included the following DR sex: F-F (n=463), M-M (n=1,276) F-M (n=727), M-F (n=441). 1 and 5-year graft survival for F-F, M-M, F-M, M-F were 96.5% and 84.9%, 94.1% and 82.5%, 94.1% and 82.3%, and 95.0% and 85.1%, respectively, p=0.44. 1 and 5-year patient survival were not significantly different for DR sex mismatch, compared to DR sex matched transplants, p=0.77. For DR race we included white and black race, there were: W-W (n=1,622), B-B (n=110), B-W (n=335), and W-B (n=314). 1 and 5-year graft survival for W-W, B-B, B-W, W-B were 95.1% and 85.1%, 90.9% and 77.7%, 93.7% and 79.7%, and 95.2% and 82.7%, respectively, p=0.021 (Figure 1). 1 and 5-year patient survival for W-W, B-B, B-W, W-B were 97.7% and 90.8%, 95.4% and 91.1%, 96.9% and 87.1%, and 96.8% and 86.0%, respectively, p=0.026 (Figure 2). In multivariable analysis the 5-year risk of patient mortality was 1.69-fold higher in the W-B DR group compared to the W-W group, HR=1.69 [95% CI 1.16-2.45], p=0.006. **Conclusion:** DR sex mismatch did not significantly impact graft or

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patient survival. 5-year graft survival was lower in Black recipients from Black donors and White recipients from Black donors compared to White recipients from White donors. 5-year patient survival was significantly lower in DR race mismatched transplants compared to White recipients from White donors. These results warrant further study to determine factors that may adversely affect survival in Black recipients and race mismatched transplants with PSC, such as increased rates of rejection, recurrent PSC or other factors.

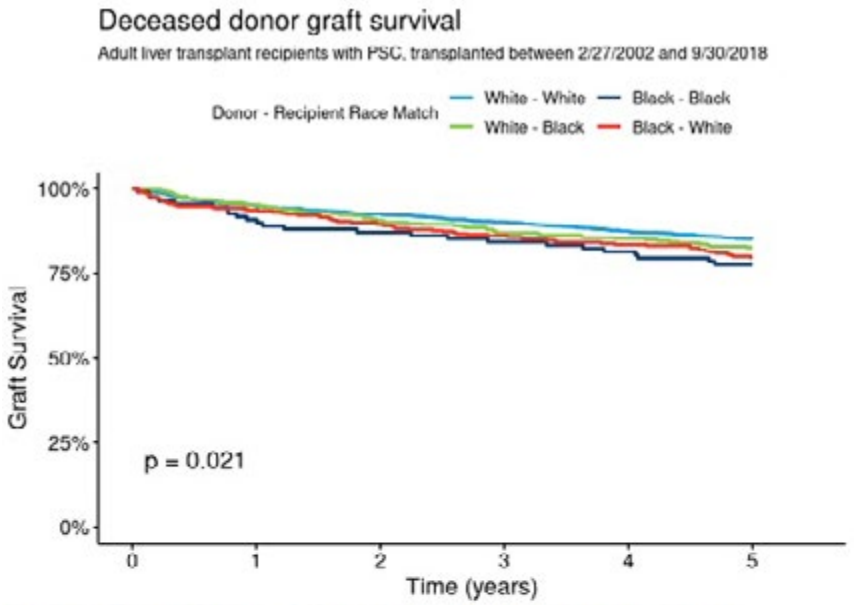

Figure 1. Deceased donor graft survival by donor-recipient race mismatch.

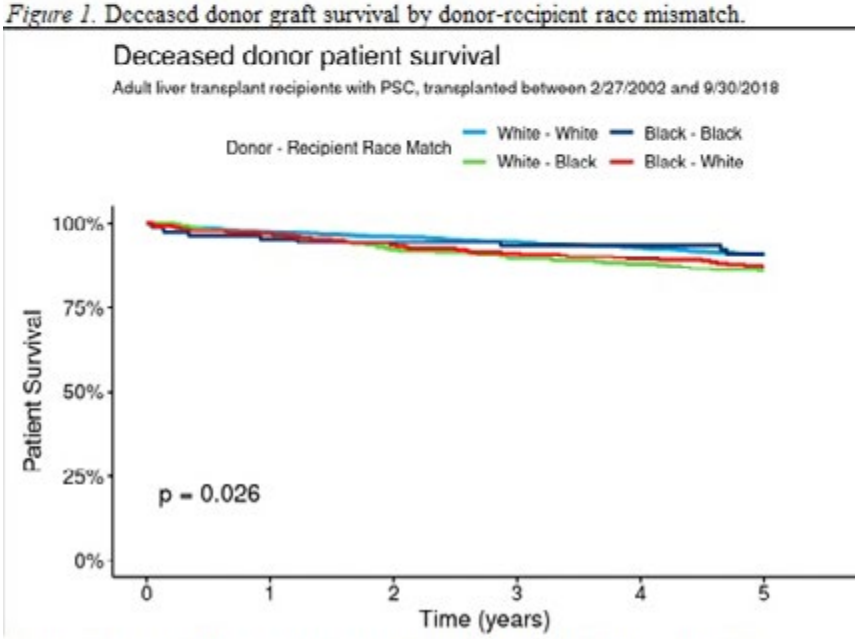

Figure 2. Deceased donor patient survival by donor-recipient race mismatch.

Disclosures: William Wheless: Nothing to Disclose, Alice Toll: Nothing to Disclose, Alexandra Lewis: Nothing to Disclose, Wida Cherikh: Nothing to Disclose, Mark Russo: Nothing to Disclose

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4325 | TARGETING OF INFLAMMATORY MONOCYTES VIA CCL2/CCR2 SIGNALING AS A THERAPEUTIC STRATEGY AGAINST AUTOIMMUNE HEPATITIS BY USING MACROPHAGE-DERIVED EXTRACELLULAR VESICLES

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[1]Sichuan University, [2]West China Hospital, Sichuan University, [3]Sichuan University, West China Hospital

Background: Autoimmune hepatitis is a serious chronic liver disease with immune disorders, histological lesions and liver dysfunction, with a gradually increasing prevalence. Yet the cellular and molecular mechanisms of immune dysregulation in AIH are poorly understood **Methods:** Using proteomic analysis, we comprehensively profiled the differentially expressed proteins and signaling pathways of liver during human AIH. Then, monocytes and macrophage from blood and livers of AIH patients and controls were analyzed. The recruitment and polarization of monocyte-derived macrophages in AIH and the mechanism of CCL2/CCR2 axis activation were investigated by Concanavalin induced experimental AIH (EAH). The CCL2/CCR2 axis was blocked by CCL2 neutralizing antibody and CCR2 antagonist to determine its effect on AIH mice. Finally, M2 macrophage-derived extracellular vesicles (M2-EVs) were isolated and extracted as drug delivery tool of CCR2 antagonist, and its therapeutic effect on AIH mice was determined. **Results:** Proteomic analysis took expression ratio (FC) > 1.5 times and P<0.05 as screening criteria, and a total of 1028 proteins were identified as increased or decreased. KEEG analysis suggested that differential expressed proteins were mainly associated with metabolic processes. The expression of mononuclear macrophage system marker proteins CD14, S100A9, CD163, CD68 and CD11b increased in the liver tissue of AIH patients as revealed by proteomic analysis and immunohistochemistry. The co-localization analysis of liver tissue suggested that CCL2 originated from Kupffer cells (KC), and the expression of CCR2 increased after circulating monocytes infiltrated liver. The expression of M1 marker in AIH liver tissue increased. AIH mouse models suggest mobilization of inflammatory monocytes on the bone marrow-liver axis and spleen-liver axis. Blocking-up of CCL2/CCR2 axis with CCL2 neutralizing antibody or CCR2 antagonist, respectively, alleviated liver injury in AIH mice, while recombinant CCL2 injection increased recruitment of inflammatory monocytes with bone marrow-liver axis and spleen-liver axis to liver, aggravating liver injury. CCR2 antagonist-M2-EV can target circulating mononuclear cells and activated mononuclear macrophages in the liver, respectively, to reduce liver injury in AIH mice. **Conclusion:** AIH mediates the recruitment of inflammatory monocytes from bone marrow and spleen to liver through the CCL2/CCR2 axis, which can be inhibited by different **Methods:** to reduce liver inflammatory injury in AIH mice. M2- EVs delivers CCR2 antagonists targeting activated pro-inflammatory monocytes and hepato-splenic mononuclear macrophage system in the circulating pool, indicating that CCR2 antagonists-EVs could be a potential agent for liver and monocyte targeted therapy for AIH

Disclosures: Xiaoli Fan: Nothing to Disclose, Yunke Peng: Nothing to Disclose, Leyu Zhou: Nothing to Disclose, Li Yang: Nothing to Disclose

4326 | THE POPULATION WITH PRIMARY BILIARY CHOLANGITIS IS CHANGING OVER TIME: MILDER DISEASE AND MORE METABOLIC COMORBIDITIES

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Background: Improved diagnostic awareness and changing health behavior may impact the population with primary biliary cholangitis (PBC). We aimed to assess changes in presenting characteristics of patients with PBC over the last 30 years. **Methods:** Every identifiable patient with an established diagnosis of PBC from all 71 hospitals in the Netherlands was retrospectively included in this nationwide study. Case identification was based on diagnosis and treatment codes, antimitochondrial antibodies (AMA) results, and locally available registers. Clinical data were extracted through medical chart review. Patients were stratified into 3 decades (1990-1999, 2000-2009, and 2010-2019) according to the date of diagnosis. Laboratory values in upper limits of normal and BMI in kg/m2 are presented as median (IQR). **Results:** From 1990 up to and including 2019, 3882 patients were diagnosed (3419 [88.1%] females). Stratified according to diagnosis year, 532 (13.7%) were diagnosed in 1990-1999, 1310 (33.7%) in 2000-2009, and 2040 (52.6%) in 2010-2019. Mean age at diagnosis increased over the 3 decades; 53.4 (SD 10.9), 56.6 (SD 12.6), and 59.1 (SD 12.7) years, respectively (p<0.001). In the last decade 907/1410 (64.3%) patients were diagnosed with normal bilirubin and albumin as opposed to 142/236 (60.2%) in 1990-1999 and 433/758 (57.1%) in 2000-2009 (p=0.004). The median ALP levels (2.31 [1.56-3.92] in 1990-1999, 1.84 [1.29-3.09] in 2000-2009, and 1.87 [1.25-3.05] in 2010-2019, p<0.001) and bilirubin (0.60 [0.47-1.00], 0.59 [0.42-0.94], and 0.48, [0.35-0.76], respectively, p<0.001) were lower over time. In contrast, median gGT levels were stable (6.25 [4.09-10.4], 6.26 [3.67-10.83], and 6.36 [3.49-11.3], respectively, p=0.925). The median BMI showed a modest but significant increase (24.8 [22.0-28.2], 25.6 [22.9-29.0], and 25.9 [23.0-29.4], p=0.009). In addition, the proportion with diabetes mellitus (6.4%, 8.4%, and 12.4%, p<0.001) and arterial hypertension (12.8%, 17.5%, and 19.5%, p<0.001) at diagnosis increased over time. **Conclusion:** Although the average age at diagnosis has increased over the last 30 years, patients with PBC are nowadays more frequently diagnosed at a milder stage of disease. While median ALP and bilirubin levels at diagnosis declined over time, the level of gGT remained stable. This may be related to the increase of patients who present themselves with comorbidities associated with the metabolic syndrome.

Disclosures: Maria C.B. van Hooff: Nothing to Disclose, Rozanne C. de Veer: Nothing to Disclose, Ellen Werner: Nothing to Disclose, Ulrich Beuers: Abacus: Speaking and Teaching, Amgen: Consultant, Behring: Consultant, Zambon: Speaking and Teaching, Joost P.H. Drenth: Nothing to Disclose, Frans J.C. Cuperus: Nothing to Disclose, Remco van Dijk: Nothing to Disclose, Bart J. Veldt: Nothing to Disclose, Michael Klemt-Kropp: Nothing to Disclose, Suzanne van Meer: Nothing to Disclose, Robert Verdonk: Nothing to Disclose, Hajo J. Flink: Nothing to Disclose, Jan Maarten Vrolijk: Nothing to Disclose, Tom J.G. Gevers: Nothing to Disclose, Cyriel Y. Ponsioen: Nothing to Disclose, Robert Roomer: Nothing to Disclose, Pieter C.J. ter Borg: Nothing to Disclose, Leendert H. Oterdoom: Nothing to Disclose, Martine A.M.C. Baven-Pronk: Nothing to Disclose, Anne Vrieze: Nothing to Disclose, Ingrid C.A.W. Konings: Nothing to Disclose, Johannes Schmidt-Böhmer: Nothing to Disclose, Frank C. Bekkering: Nothing to Disclose, Stephan H.C. van Stiphout: Nothing to Disclose, Nicole F.M. van Gerven: Nothing to Disclose, Sven J. van den Hazel: Nothing to Disclose, Paul J. Bus: Nothing to Disclose, A. (Sander) van der Beek: Nothing to Disclose, Sigrid Vandebosch: Nothing to Disclose, Maaike J. Denters: Nothing to Disclose, Harry L.A. Janssen: Nothing to Disclose, Nicole S. Erler: Nothing to Disclose, Bettina E. Hansen: Nothing to Disclose, Adriaan J.P. van der Meer: Nothing to Disclose

4327 | THE CYST MICROENVIRONMENT IS SPATIALLY PATTERNED TO PROMOTE POLYCYSTIC LIVER DISEASE

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Background: Polycystic liver diseases (PLDs) are a group of genetically heterogeneous conditions characterised by the presence of multiple fluid-filled cysts within the liver. Cyst growth results in hepatomegaly (liver enlargement), leading to abdominal pain, shortness of breath and malnutrition, and consequently, patients suffer from an extremely poor quality of life. Additionally, cysts are at risk of rupture and infection, which leads to sepsis if left untreated. There are currently no widely approved pharmaceutical treatments for PLD patients and despite several dysregulated molecular targets having been previously identified within cyst cells, none of these have been translated for clinical practice. Cyst epithelial cells are surrounded by a complex cyst microenvironment (CME), which is instructed by the cyst epithelia. Very little work, however, has focused on how non-epithelial cells within the CME contribute to cyst growth within the liver, particularly in human disease, nor whether modulation of the CME represents a therapeutic strategy to target the formation of cysts in patients. In cancer, therapies that

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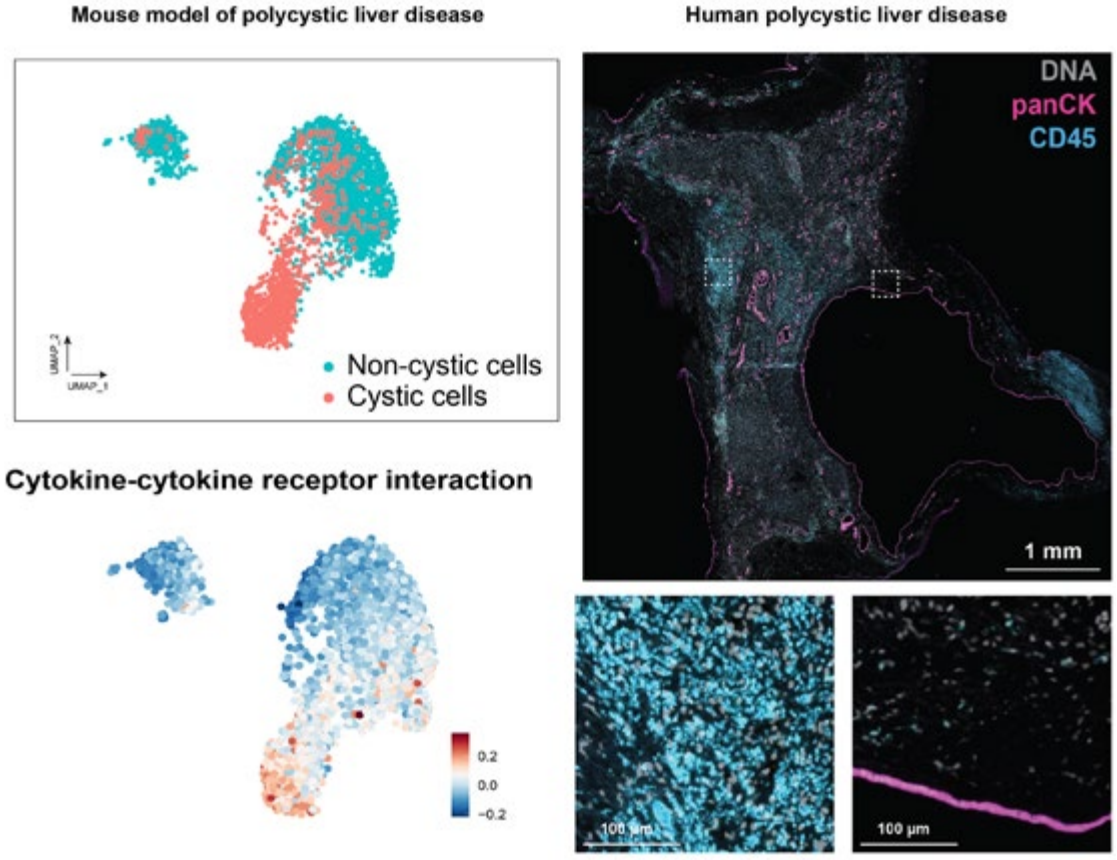
target the microenvironment, namely immunotherapy, have revolutionised patient care; *could taking a similar approach and targeting the CME in PLD yield similar clinical successes?* We hypothesise that the formation of a unique CME in PLD offers a number of candidate targets for therapeutic intervention and aim to **1**. Spatially map the CME in PLD patients and **2**. Identify targetable processes which could reduce cystic growth. **Methods:** Using patient PLD tissue, we have used GeoMx spatial transcriptomics and Akoya fusion high-plex immunophenotyping to spatially map the formation and composition of the CME in PLD. We have then used a combination of human ductular organoid cultures and mouse models of PLD to identify novel molecular processes that can be pharmacologically manipulated to limit cyst formation. **Results:** By combining single cell RNA sequencing from PLD tissue with a forward-phase cytokine arrays from human PLD organoids, we have found that cystic cells significantly increase the expression of a range of cytokines, including *Ccl20*, *Tgfb* and *Tnf*. These data indicate that cystic cells actively recruit an immune infiltrate to cystic lesions thereby promoting cystogenesis. Using spatial mapping technologies enables us to define where within the PLD CME different cells are found and we can show that T cells are the most abundant immune cell type within the cyst microenvironment in human PLD. Furthermore, T cells within the PLD CME express PD-1, suggesting that these T cells are in an exhausted state and susceptible to anti-PD-1 therapeutics. **Conclusion:** Cyst cells recruit and pattern immune cells within the CME. These immune cells are largely made up of exhausted, PD-1^{+} T cells, which represent an immunotherapy candidate for pharmaceutical intervention in human PLD.



Disclosures: Scott Waddell: Nothing to Disclose, Luke Boulter: Nothing to Disclose

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4329 | A MULTI-PLATFORM APPROACH IDENTIFIES NOVEL CANDIDATE BIOMARKERS OF RELAPSE IN AUTOIMMUNE HEPATITIS

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Background: Autoimmune hepatitis (AIH) is characterized by loss of immunological tolerance and persistent hepatic immunoreactivity despite immunosuppression (IS), resulting in high relapse rates. However, predictors of relapse are poorly understood and novel biomarkers are needed to identify patients at high risk and to assess suitability for IS withdrawal. The aim of this study is to identify novel candidate blood-based biomarkers to predict relapse in AIH using a multi-platform approach. **Methods:** Blood samples at baseline from 39 adult patients with AIH were collected among two liver centers, including newly diagnosed patients pre-treatment and patients in remission. Investigative platforms included sandwich ELISA of candidate biomarkers identified in prior studies (Harrington et al, *Hepatology* 2022), a discovery panel of 92 plasma inflammatory markers (OLINK), CyTOF analysis, and top-down proteoform analysis were used. Baseline and one-year follow-up clinical data were collected. Relapse was defined as elevated liver enzymes >3xULN requiring a change in IS. Biomarkers were analyzed by median and ranges, Wilcoxon rank-sum test was used to test for significance; $p<0.05$ was considered significant. Proteoform intensities were normalized by Total Ion Count, subjected to Box-Cox transformation and mixed linear hierarchical modeling. **Results:** Mean cohort age was 56 years, 82% female and 71% Caucasian. By one year after blood collection, 12 patients had at least one relapse while 27 did not relapse. Eight biomarkers, identified by OLINK, were elevated in patients who relapsed, including IL-17A (Table 1**A**). Four biomarkers were elevated in newly diagnosed patients who relapsed (n=4) including IL-13, IL-17A (OLINK), induced Treg (CyTOF), and proApoA1 (proteoform analysis) compared to those that did not relapse (n=6) (Table 1**B**). In addition, EN-RAGE was increased in those that did not relapse. **Conclusion:** We have identified novel candidate AIH biomarkers associated with subsequent relapse over a one year period. In particular, IL-17A was associated with relapse both in newly diagnosed patients pre-treatment and in patients in remission. Further characterization and validation of these biomarkers is warranted to elucidate their potential clinical utility above currently available tests. Our study also highlights the benefits of a multi-platform approach and the role of proteomics as a novel method to identify biomarkers in AIH.

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Biomarker Predictors of Relapse at One Year in Patients with AIH

Biomarker	Relapse (n=12) Median (range)	No Relapse (n=27) Median (range)	P value	Mechanism of Action
Table 1A. All AIH				
Cytokines				
IL-17A	0.6(-0.4-3.2)	-0.1(-0.7-1.7)	0.014	T cell activation; neutrophil mobilization and activation
CXCL6	8.7(7.7-10.0)	8.0(6.5-10.2)	0.040	Chemoattractant for neutrophils
Cytokine receptors				
IL-18R1	7.1(6.5-8.4)	6.7(5.5-9.2)	0.030	Augments IFN-gamma production
LIF-R	3.5(3.1-4.2)	3.2(2.4-4.9)	0.037	Promotes activation of mTOR and inhibit DNA damage responses
Other				
NT-3	2.9(2.5-4.0)	2.4(1.7-3.9)	0.009	Protein growth factor
CD8a	10.2 (9.4-11.4)	9.6 (7.8-11.0)	0.034	Activates cytotoxic T cells
DNER	9.0(8.3-9.5)	8.7(7.8-9.6)	0.046	Activation of Notch signaling
uPA	10.5(10.0-11.8)	10.3(9.6-11.1)	0.032	Activates plasminogen to plasmin
Table 1B. New AIH (pre-treatment)				
Biomarker	**Relapse (n=4)** Median (range)	**No Relapse (n=6)** Median (range)	**P value**	**Mechanism of Action**
Cytokines				
IL-13	-0.1(-0.5-1.0)	-0.8(-1.1- -0.6)	0.014	Promotes Th2 cell differentiation
IL-17A	2.2(0.7-3.2)	0.1(-0.2-0.9)	0.025	T cell activation; neutrophil mobilization and activation
Other				
iTreg	0.5(0.4-0.5)	0.2(0.0-0.4)	0.028	Role in immune homeostasis
EN-RAGE	1.7(1.3-2.7)	4.3(2.0-4.7)	0.043	Activation of lymphocytes to produce proinflammatory cytokines
Biomarker	**Relapse (n=3)** Median (range)	**No Relapse (n=6)** Median (range)	**P value**	**Mechanism of Action**
ProApoA1	1.23(0.40-2.06)	-0.36(-1.00-0.28)	0.001	Reverse cholesterol transport pathway

Legend:
IL-17A: interleukin-17A
CXCL6: chemokine ligand 6
IL-18R1: interleukin-18 receptor 1
LIF-R: leukemia inhibitor factor receptor
NT-3: neurotrophin-3
CD8a: cluster of differentiation 8a
DNER: delta/notch-like epidermal growth factor
uPA: urokinase-type plasminogen activator
IL-13: interleukin-13
iTreg: T regulatory cells
EN-RAGE: extracellular newly identified receptor for advanced for advanced glycation end-products binding protein
ProApoA1: proApolipoprotein A1

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4330 | SERUM BIOMARKERS OF CELLULAR SENESCENCE SHOW PSC PROGRESSION

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Background: Primary sclerosing cholangitis (PSC) is a fibroinflammatory cholangiopathy leading to liver failure for which the only cure is liver transplant. We have found that senescent biliary epithelial cells (cholangiocytes) accumulate in the bile ducts of PSC patients, exhibit a senescence-associated secretory phenotype (SASP), and likely contribute to disease progression. The SASP is characterized by increased secretion of proinflammatory and profibrotic molecules. Monitoring SASP serum biomarkers in PSC would potentially allow assessment of disease progression and efficacy of senotherapeutic drugs. Thus, we performed targeted proteomics of normal and PSC patient serum to identify a SASP signature of early and late-stage PSC. **Methods:** Serum samples were obtained from 20 healthy (control), 20 early-stage PSC (PSC-early), and 20 late-stage PSC patients (PSC-late). Patients were matched for age, sex, race, BMI, smoking, IBD status, and PSC duration. Analytes (n=71) were quantified using multiplex fluorescent bead-based immunoassays or ELISA. Analytes with a skewness statistic > 2 were log transformed. Principal component analysis (PCA) was performed to identify principal component (PC) scores across the 71 analytes. ANOVA on PC scores were performed between groups adjusted for age, smoking status, and BMI. Bulk RNA sequencing was also performed on control non-disease and PSC patient-derived cholangiocytes. **Results:** For healthy controls, early- and late-stage PSC, the first 14 PC scores explain 83% of the data variability, while the first 5 PCs explained 62.7%. Visualization of the PCs (bi-plots) demonstrated that PC2 (17 analytes, 17.1% variability explained) exhibited the greatest separation between groups. ANOVA for PC2 revealed major differences between control *vs*. PSC-early ($p = 0.0001$), control *vs*. PSC-late ($p < 0.0001$), and PSC-early *vs*. PSC-late ($p < 0.0001$). RNAseq of late-stage PSC patient cholangiocytes confirmed differential gene expression of 60% of the markers identified in PC2. BMI, smoking, age, and IBD status do not change the statistical significance. **Conclusion:** Senescence-associated analytes identified in PC2 distinguish between control, early-, and late-stage PSC. The results further support the hypothesis that senescent cholangiocytes are a pathologic feature of PSC. In PSC patients, biomarkers from the PC2 score can be used to monitor disease progression and assess drug efficacy in clinical trials of senotherapeutic drugs.

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4331 | THE EARLY DYNAMIC CHANGES OF RADIOLOGICAL AND BIOCHEMICAL SCORES HELP IDENTIFY A MORE AGGRESSIVE PSC PHENOTYPE

Elisa Catanzaro[1] Matteo Peviani[1] Emanuela Bonaiuto[2] Francesco Pezzato[1] Martina Gambato[3] Raffaella Motta[4] Nora Cazzagon[1]

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Background: The natural couse of Primary Sclerosing Cholangitis (PSC) is generally progressive towards cirrhosis and its complications. Predicting the prognosis in PSC is still a matter of debate. Several prognostic factors associated with transplant-free survival have been identified, including serum markers, composite scores, biliary and parenchymal changes and elastography. The aim of this study was to assess whether the evolution of biochemical and magnetic resonance imaging (MRI) scores is associated with an increased risk of developing clinical outcomes. **Methods:** We conducted a retrospective analysis of patients diagnosed with large ducts, non-cirrhotic PSC, who underwent regular clinical and radiological follow-up with at least two consecutive MRIs closest to the diagnosis, available for review by an expert radiologist. The ANALI scores with and without gadolinium (Gd) were assessed in the two MRIs, and any increase in the ANALI scores was considered as radiological

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worsening. Demographic data and liver function tests were collected at the same timepoints as the MRI scans, and two scores, the Amsterdam Oxford Model (AOM) and the Mayo Risk Score (MRS), were calculated and stratified into low, intermediate and high risk categories. The progression of AOM and MRS was defined by the upgrade from one category to a higher one. Clinical outcomes considered included the development of recurrent cholangitis, cirrhosis, cirrhosis decompensation, liver transplantation (LT), death from liver disease, and the development of hepatobiliary malignancies. **Results:** A total of 45 patients were included. Median age was 30 (21-38) years at diagnosis and 36 (28-50) years at inclusion, The median interval between the two MRIs was 24 (16–38) months. Twenty-eight (62%) patients were male. The median follow-up after the second MRI was 69 (50-90) months. Thirteen (29%) patients experienced radiological worsening, while 8 (18%) and 7 (16%) patients showed progression of the AOM and the MRS, respectively. The increases in ANALI without Gd and the MRS were associated with the risk of development cirrhosis during follow-up (p=0.003 and p=0.001, respectively). Additionally, the increase in ANALI without Gd during follow-up was significantly associated with the need for LT (p=0.001). A trend towards a significant association between the increase in MRS and LT was observed (p=0.085). Finally, patients who developed recurrent cholangitis during follow-up exhibited a progressive increase in ANALI without Gd (p=0.003). **Conclusion:** The early dynamic changes in radiological and biochemical scores help identify a more aggressive PSC phenotype. These preliminary findings suggest the potential utility of dynamic assessment of radiologic and biochemical scores for prognostic purposes and risk stratification. Further validation in larger cohorts is warranted.

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4332 | TEST-RETEST REPEATABILITY OF PSC SPECIFIC IMAGING BIOMARKERS FROM QUANTITATIVE MRCP

Sarah Finnegan[1] Tom Davis[2] Carlos Ferreira[2] Bruno Paun[2] Andrea Borghetto[2] Andrea Dennis[3] Michele Pansini[4]

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Background: Quantitative Magnetic Resonance Cholangiopancreatography (qMRCP) offers non-invasive, quantification of the biliary tree. This is particularly relevant for biliary diseases such as Primary Sclerosing Cholangitis (PSC) where disease progression is characterized by increasing levels of strictures and dilatations throughout the biliary tree. Seven measurements have been reported to have utility in PSC for either monitoring or risk stratifying. The aim of the study was to investigate the precision and accuracy of these measurements. **Methods:** Forty healthy volunteers and 20 patients with reported biliary or other liver disease were scanned twice on up to six different scanners from three manufacturers. MRCP data were acquired using heavily T2-weighted 3D multishot fast/turbo spin echo acquisitions at 1.5T and 3T and scan data processed using a dedicated qMRCP software. Repeatability and reproducibility were calculated and are reported as intraclass coefficients. Data are presented here from the reference scanner (Siemens 3T) using the Siemens 1.5T as the comparator in the case of reproducibility. **Results:** All seven measurements had good agreement for all measures with observed repeatability and reproducibility respectively of ICC 0.97 and 0.92 for total number of ducts, ICC 0.97 and 0.96 for total number dilatations, ICC 0.90 and 0.88 for total number of strictures, ICC 0.95 and 0.93 for total ducts with a stricture or dilatation, ICC 0.71 and 0.32 for percentage of ducts with diameter 3-5 mm, ICC 0.79 and 0.84 for overall sum of stricture lengths, and ICC 0.91 and 0.88 for overall sum of dilatation lengths. For all measurements repeatability across scanner field strengths and vendors was also good, with values very similar for the cross-scanner reproducibility coefficients. **Conclusion:** These early data suggested that certain metrics from qMRCP should be well suited for multi-centre trials and longitudinal assessment of the health of the biliary tree and provide further evidence in support of quantitative MRCP metrics as clinical biomarkers.

Disclosures: Sarah Finnegan: Nothing to Disclose, Tom Davis: Nothing to Disclose, Carlos Ferreira: Perspectum: Employee, Bruno Paun: Perspectum: Employee, Andrea Borghetto: Perspectum: Employee, Andrea Dennis: Perspectum: Employee, Michele Pansini: Nothing to Disclose

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4333 | UNDERSTANDING FATIGUE EXPERIENCES THROUGH QUALITATIVE INTERVIEWS WITH ADULTS LIVING WITH PRIMARY SCLEROSING CHOLANGITIS (PSC): AN ESSENTIAL FIRST STEP TOWARDS CUSTOMIZING A PSC-SPECIFIC PROMIS® MEASURE

Donna Evon[1] Kaya Merkler[1] Jing Yuan[2] Laura Mkumba[2] Lauren Wright[2] Nicole Lucas[2] Joanne Hatchett[3] Ricky Safer[3] Stephen Rossi[3] Bryce Reeve[2]

[1]University of North Carolina, [2]Duke University, [3]PSC Partners Seeking a Cure

Background: A comprehensive understanding of fatigue experienced by adults living with PSC is necessary for the development of a PSC-specific patient-reported outcome measure that captures essential fatigue concepts and is suitable for clinical trials to assess treatment benefits. **Methods:** Adults with PSC were recruited through the PSC Partners Patient Registry or their hepatologists. Participants consented and were screened for the presence, frequency, severity, and distress associated with multiple PSC-related symptoms. Purposeful sampling was used to capture a representative sample of 17 adults to engage in in-depth, individual qualitative interviews to describe key symptoms, including fatigue. Interviews were conducted virtually, audio-recorded, and transcribed. Transcripts were coded and analyzed using Nvivo. A codebook was developed to identify themes related to fatigue severity, frequency, interference, and symptom clustering. **Results:** Twelve out of 17 participants who reported fatigue as a prominent symptom were asked to describe in-depth their experiences living with fatigue. Participants were, on average, 39 years old (range: 22 to 58), and diagnosed with PSC, on average, at 31 years old. Participants were 42% female, 8% Asian, 17% Black, and 75% White, and 67% had inflammatory bowel disease (IBD). Table 1 provides illustrative quotes of participants' terminology used to describe the experience of fatigue. Half of the participants described experiencing fatigue "all the time", while some described variation in fatigue severity throughout their day and week and several required daytime naps. Some participants felt best in the morning and described fatigue getting progressively worse throughout the day. Fatigue interfered with their daily domestic tasks, job responsibilities, and family and social activities. Fatigue impacted mental health with participants expressing feelings of frustration, sadness, and guilt. Rationing energy, breaking up daily tasks, and naps were used to cope with fatigue. Participants can describe the difference between fatigue and a poor night's sleep or simple tiredness. All participants reported experiencing concomitant "brain fog" with fatigue, although they can occur separately. Some participants report that fatigue can be accompanied by body pain or nausea. **Conclusion:** Fatigue emerged as a prominent and distressing symptom in adults with PSC. These qualitative findings will directly inform the customization of a PSC-specific PROMIS® fatigue measure with strong evidence for its content validity. The measure will be suitable for future PSC clinical trials and research to find effective treatments for people living with PSC-fatigue.

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Illustrative Quote	Terminology used to describe fatigue
"I mean just full body fatigue…Sometimes, you are just physically exhausted from head to toe."	Full body experience
"It often looks like me just lying down most of the day, trying to take naps when I can, and just making it hard to even get up the stairs at times."	No energy Difficulty walking/moving ones' body
"It feels like I accidentally took a few Benadryl's. Like, it's a struggle to keep my eyes open. It feels absolutely just exhausting to sit up."	Feeling like you could fall asleep at any moment Exhausting
"I guess the best way to describe it is kinda like something heavy is on my back like a book bag filled with cinder blocks or just like a metal blanket."	Body feeling heavy
"There's times when I'm like, if I'm driving, I get a little nervous 'cause I'm like, "I just need to get home because I'm nervous that I might fall asleep."	Feeling like you could fall asleep at any moment
"Everything feels heavy. My arms, my head, my feet, everything feels so heavy. The fatigue is that deep. Talk about dragging your feet, there you go, it's for real."	Body feeling heavy
"It is depressing. Sometimes it does get—it gets to me. I would say it does impact it negatively."	Depressing
"Well, I think it's frustrating. It's definitely frustrating. I worry about, yeah, quite a bit."	Frustrating

Disclosures: Donna Evon: Hightide Therapeutics, USA, LLC: Consultant, Kaya Merkler: Nothing to Disclose, Jing Yuan: Nothing to Disclose, Laura Mkumba: Nothing to Disclose, Lauren Wright: Nothing to Disclose, Nicole Lucas: Nothing to Disclose, Joanne Hatchett: Nothing to Disclose, Ricky Safer: Nothing to Disclose, Stephen Rossi: GSK: Advisor, Rectify: Advisor, Bryce Reeve: Nothing to Disclose

4334 | AUTO-ANTIBODY DISCOVERY IN PRIMARY BILIARY CHOLANGITIS (PBC) USING PHAGE-IMMUNOPRECIPITATION SEQUENCING (PHIP-SEQ) ◆

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Background: Primary biliary cholangitis (PBC) is an autoimmune liver disease that leads to destruction of small bile ducts. A hallmark of the disease is the presence of anti-mitochondrial antibodies (AMA). However, our understanding of the broader serologic profile of PBC patients is lacking. We sought to use phage immunoprecipitation sequencing (PhIP-seq) to characterize the auto-antibody landscape of patients with PBC with the goal of identifying further markers of disease pathophysiology. **Methods:** We performed PhiP-Seq on serum from 28 patients with PBC and 94 healthy controls. PhIP-Seq uses phages cloned to express >700,000 overlapping short peptides spanning the human proteome as bait for immunoprecipitation (IP) with serum autoantibodies. After incubation and washing, antibody-bound phage are sequenced to identify peptide-coding genes. PhIP-Seq findings were validated using a split luciferase binding assay (SLBA) in which peptides are marked with a HiBit tag and used as the target for IP by serum autoantibodies. **Results:** Logistic regression analysis using 5-fold cross validation of PhIP-seq antibodies can differentiate PBC patients from healthy controls with an area under the curve (AUC) of 0.93. Recursive feature elimination reduced the prediction to 15 features without a loss of model performance (AUC = 0.96). The highest coefficient in the overarching logistic regression is a known PBC antigen, dihydrolipoamide branched chain transacylase E2 (DBT), followed by novel targets, such as thyroid hormone receptor interactor 12 (TRIP12; sensitivity 21.4%, specificity 97.9%). DBT and TRIP12 seroreactivity was orthogonally validated by SLBA. A second novel target of interest, dipeptidase 2 (DPEP2;

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sensitivity 21.4%, specificity 95.7%) is a membrane-bound dipeptidase involved in hydrolyzing leukotrienes. DPEP2 has been identified as a PBC-associated susceptibility locus through GWAS. Notably, 5 out of 6 DPEP2 positive PBC patients had advanced liver fibrosis. **Conclusion:** Using PhIP-seq, we were able to identify known and novel autoreactive antibodies associated with PBC. Amongst new targets, autoantibodies against TRIP12 and DPEP2 were identified. Given the cell surface expression of DPEP2, autoantibodies targeting this protein could interfere with its function, offering a possible link between polymorphisms in the DPEP2 gene and the risk of developing PBC. Further experiments are underway validate our findings and to determine whether antibodies targeting DPEP2 in PBC patients interfere with protein function.

Disclosures: Isaac Benque: Nothing to Disclose, Arielle Klepper: Nothing to Disclose, Michael Li: Nothing to Disclose, Gerardo Rubio Monroy: Nothing to Disclose, Swathi Kari: Nothing to Disclose, Melawit Tekeste: Nothing to Disclose, Javier Castro: Nothing to Disclose, Briton Lee: Nothing to Disclose, Mandana Khalili: gilead sciences: Grant/Research Support, GSK pharmaceuticals: Consultant, Intercept pharmaceuticals: Grant/Research Support, Gilead Sciences Inc: Consultant, Jennifer Price: Nothing to Disclose, Emily Perito: Mirum: Consultant, Ultragenyx: Consultant, BridgeBio: Consultant, Amagma: Consultant, Mirum: Grant/Research Support, Albireo: Grant/Research Support, Gilead: Grant/Research Support, Dicerna: Grant/Research Support, Sandy Feng: Nothing to Disclose, Jacquelyn Maher: Nothing to Disclose, Jennifer Lai: Nestle Nutrition Institute: Grant/Research Support, Novo Nordisk: Consultant, Genfit: Consultant, Boehringer Ingelheim: Advisor, POSULD Team: Nothing to Disclose, Joseph DeRisi: Nothing to Disclose, Michele Tana: Nothing to Disclose

4335 | PERFORMANCE OF URSODEOXYCHOLIC ACID RESPONSE SCORE IN PREDICTING TREATMENT RESPONSE IN A SINGLE UNITED STATES COHORT

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Background: The Ursodeoxycholic Acid Response Score (URS) predicts UDCA therapy response in primary biliary cholangitis (PBC) patients after 12 months of treatment. Patients who do not respond adequately to UDCA may be considered for second-line therapies, typically after 1 year, potentially delaying effective treatment for high-risk patients. This study aims to assess the efficacy of URS in predicting treatment response among PBC patients, providing insight for new strategies in treatment evaluation. **Methods:** We conducted a prospective cohort study in a US center from January 2018 to November 2023, enrolling 136 confirmed PBC patients undergoing UDCA treatment. Patients were categorized as responders or non-responders based on Paris-II criteria. We evaluated the predictive performance of URS, comparing it with Paris-II criteria. Demographic, clinical, and biochemical data were collected, with continuous variables presented as standard deviation (SD) and using t-tests for comparisons. Categorical variables, summarized as percentages, were compared using Pearson's chi-squared test ($\chi 2$). Univariate and multivariate analyses, adjusting for demographic and biochemical variables, were used to assess the score's efficacy. Prognostic performance was assessed using receiver operating characteristic (ROC) curve analysis. **Results:** We studied 136 PBC patients on continuous UDCA therapy for a year. Most were female (90%), white Caucasian (79%), and 56 years of age. At diagnosis, 82% met ALP criteria, 63% tested positive for antibodies, and 51% had compatible liver biopsies. After 1 year of UDCA, 110 patients (81%) achieved an UDCA response. URS performance, compared to Paris-II criteria, indicated a mean responder URS of 2.95 (SD=1.18) and a non-responder URS of 1.22 (SD=0.49) ($p<0.001$). Logistic regression multivariate analysis, adjusted for age, gender, and biochemical markers, revealed a significant association of URS among PBC responders to UDCA treatment (odds ratio, OR, 0.06, 95% confidence interval (CI) 0.016-0.25, $p<0.001$). The area under the ROC curve of URS in predicting UDCA response was 0.91 (95% CI, 0.88–0.99, $p<0.001$). **Conclusion:** Our study demonstrates the URS's efficacy in predicting treatment response in PBC patients before UDCA initiation. While it suggests the potential for alternative evaluation methods of treatment response, further validation with larger cohorts and longer follow-up is needed.

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Table 1. Characteristics of responders and non-responders to UDCA treatment.

Variables	Responders (N=110)	Non-responders (N=26)	p Value
Demographics			
Age, Mean (SD)	57 (12)	59 (13)	0.312
Gender, female N (%)	100 (91)	23(88)	0.703
Race, N (%) White Caucasian Hispanic or Latino African American Other/multiracial Asian	84 (76) 9 (8) 1 (1) 7 (6) 9 (8)	23 (88) 2 (8) 0 1 (4) 0	0.631
BMI, Mean (SD)	28 (6)	27 (5)	0.453
UDCA daily dose, Mean (SD)	14.4 (10)	14.2 (3)	0.941
Laboratory values before UDCA initiation, Mean (SD)			
ALP (diagnosis)	206 (129)	255 (172)	0.112
ALP (pre-UDCA)	209 (145)	255 (170)	0.165
ALT	53 (39)	65 (58)	0.183
AST	44 (28)	58 (35)	0.042
TB	0.56 (0.42)	1.23 (0.75)	<0.001
PL	262 (73)	230 (81)	0.053
PT	11.9 (2.65)	12.5 (3.89)	0.453
ALB	4.33 (0.31)	4.13 (0.42)	0.006
URS Score	2.95 (1.18)	1.22 (0.49)	<0.001
Laboratory values after 12-month follow-up of UDCA initiation, Mean (SD)			
ALP	152 (87)	257 (400)	0.014
ALT	30 (21)	44 (62)	0.053
AST	29 (13)	46(49)	0.002
TB	0.48 (0.20)	1.22 (0.43)	<0.001
ALB	4 (0.29)	4 (0.49)	0.001
PL	249 (71)	202 (100)	0.006
PT	11.3 (1.5)	11.45 (0.9)	0.146
INR	1.04 (0.08)	1.5 (1.98)	0.058

Table 2. Univariate and multivariate logistic regression analyses for responders to UDCA treatment (n=136)

Variable	Univariate			Variable	Multivariate		
	OR	CI 95%	P Value		OR	CI 95%	P value
Age	1.02	0.98-1.05	0.321	ALP (diagnosis)	1.00	0.98-1.03	0.649
Gender	0.77	0.20-3.0	0.708				
ALP (diagnosis)	1.02	1.00-1.03	0.017				
ALP (pre-UDCA)	1.01	1.00-1.02	0.027	ALP (pre-UDCA)	0.99	0.97-1.02	0.620
ALT	1.01	0.99-1.01	0.207				
AST	1.01	0.99-1.02	0.060	TB	29	5.42-53.44	<0.001
TB	26	5.02-36.5	<0.001				
URS score	0.15	0.06-0.33	<0.001	URS score	0.06	0.016-0.25	<0.001

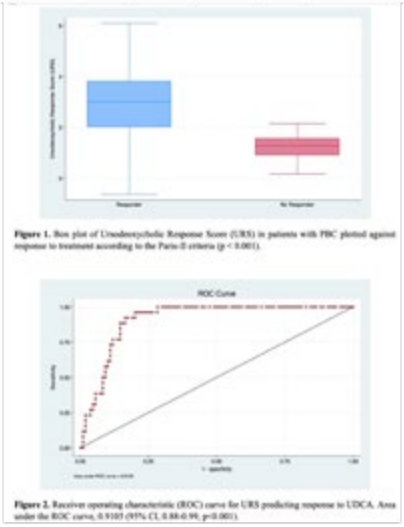

Figure 1. Box plot of Ursodeoxycholic Response Score (URS) in patients with PBC plotted against response to treatment according to the Paris-II criteria ($p < 0.001$).

Figure 2. Receiver operating characteristic (ROC) curve for URS predicting response to UDCA. Area under the ROC curve, 0.9105 (95% CI, 0.88-0.99, $p<0.001$).

Disclosures: Ana Marenco-Flores: Nothing to Disclose, Leandro Sierra: Nothing to Disclose, Romelia Barba: Nothing to Disclose, Denisse Rubio-Cruz: Nothing to Disclose, Daniela Goyes: Nothing to Disclose, John Esli Medina Morales: Nothing to Disclose, Tamara Kahan: Nothing to Disclose, Alan Bonder: GSK: Grant/Research Support, Mirium: Grant/Research Support, Gilead: Grant/Research Support, Ipsen: Grant/Research Support, Cymabay: Grant/Research Support, Intercept: Grant/Research Support, Intercept: Consultant, GSK: Consultant, Ipsen: Consultant, Chemobab: Grant/Research Support, Alnylam: Consultant, Thirammune: Consultant, Vilas Patwardhan: Nothing to Disclose

4336 | TRANSIENT ELASTROGRAPHY USE IN A LARGE RETROSPECTIVE COHORT OF INDIVIDUALS WITH PRIMARY SCLEROSING CHOLANGITIS: A DESCRIPTIVE STUDY OF REAL-WORLD PRACTICE

Kristel Leung[1] Bettina Hansen[2] Marwa Ismail[3] Aisha Alawi[3] Aliya Gulamhusein[3] Gideon Hirschfield[3]

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Background: Liver stiffness measurement (LSM) by transient elastography (TE) is a frequently used non-invasive tool for evaluation of fibrosis in liver disease. Here, we describe the use of LSM by TE in a large single-centre retrospective cohort of individuals with primary sclerosing cholangitis (PSC). **Methods:** Patients with PSC followed at a single tertiary care liver clinic pre-transplant from 2000-2020 were reviewed. Non-protocolized clinical use of LSM began in 2012 at our centre. Descriptive analyses were used to evaluate characteristics of patients who underwent TE, expressed as number and proportions. Correlations between LSM readings, total bilirubin, ALP, AST, ALT, platelets, and albumin were evaluated using Pearson correlation coefficients. Transplant-free survival and composite-event-free survival (inc. ascites, variceal bleeding, hepatic encephalopathy, transplant, death) were evaluated amongst those who underwent TE with Kaplan-Meier curves. **Results:** Out of 579 individuals with PSC, 436 underwent 1+TE (66% 2+TE, max. 8). Out of 1054 TE readings, LSM was <7.4 kPa (F0), 7.4-9.5 kPa (F1/F2), 9.6-14.4 kPa (F3), and >14.4 kPa (F4) in 525 (50%), 166 (16%), 106 (14%)

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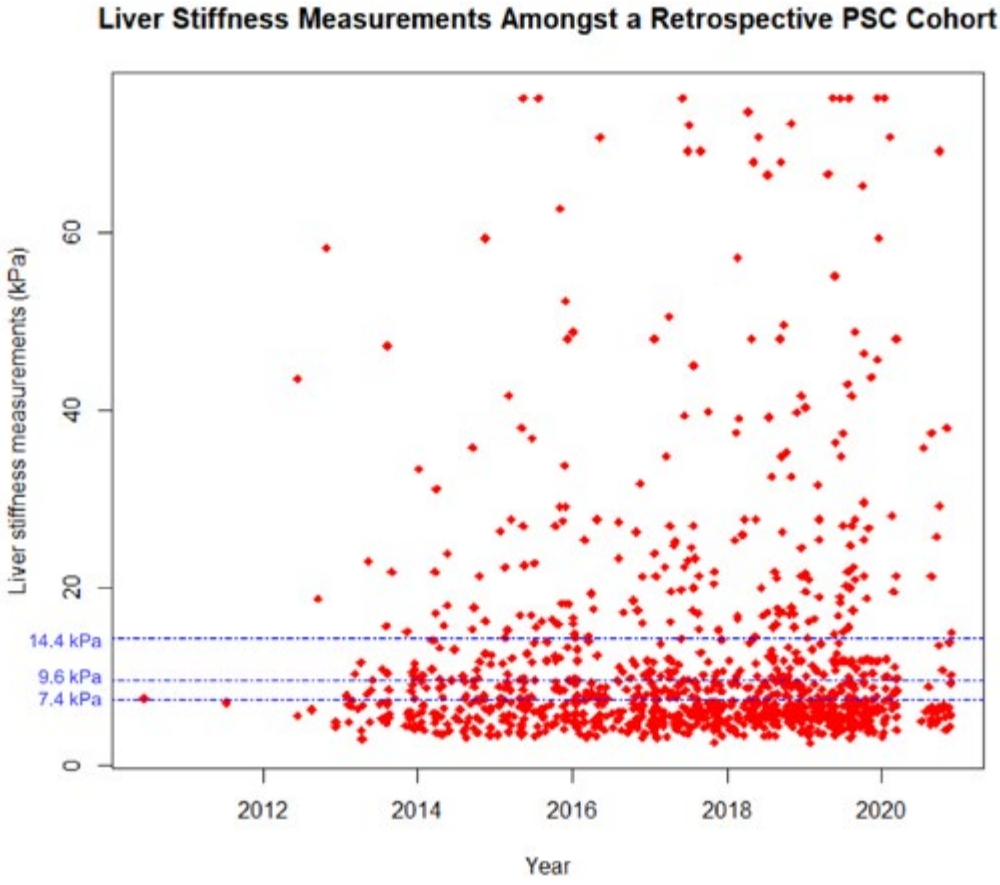
and 120 (20%) respectively (Figure). This corresponded to 258 (44%), 117 (20%), 106 (18%), and 120 (21%) individuals with at least 1+ LSM reading in these respective ranges. Median time between 1st LSM reading from PSC diagnosis date was 3.3 years. Individuals who underwent TE had median age 35 y.o. (IQR 25-49) at PSC diagnosis, were 61% male, and 75% had concurrent inflammatory bowel disease (179 ulcerative colitis, 71 Crohn's disease). There were moderate correlations between LSM reading with ALP, total bilirubin, and AST (R=0.43, 0.47, 0.47 respectively; p<0.001), weak correlation with ALT and platelets (R=0.30, -0.34 respectively; p <0.001), and minimal correlation with albumin (R=-0.089, p<0.001). There were 42 transplants/deaths and 81 composite events amongst those with any LSM reading. At 5 years and 10 years from 1st LSM, transplant-free survival was 96% and 90% respectively, and composite-event-free survival was 90% and 81% respectively. **Conclusion:** Use of TE amongst individuals with PSC in a retrospective real-world setting demonstrates utility of LSM as a clinical tool that correlates with other markers of advanced disease. Future prospective studies with regular prescribed use of LSM in all PSC patients may substantiate the utility of LSM as a prognostic marker.



Disclosures: Kristel Leung: Nothing to Disclose, Bettina Hansen: Nothing to Disclose, Marwa Ismail: Nothing to Disclose, Aisha Alawi: Nothing to Disclose, Aliya Gulamhusein: Advanz: Consultant, Cymabay: Consultant, Gideon Hirschfield: Consultant relationship with Mirum; Has not ended; Consultant relationship with Advanz; Has not ended; Consultant relationship with Chemomab; Has not ended; Consultant relationship with Gilead; Has not ended; Consultant relationship with Kowa; Has not ended; Consultant relationship with Intercept; Has not ended; Consultant relationship with Pliant; Has not ended; Consultant relationship with Falk; Has not ended; Consultant relationship with GSK; Has not ended; Consultant relationship with Ipsen; Has not ended; Consultant relationship with CymaBay; Has not ended

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4337 | IDENTIFICATION OF NOVEL INFLAMMATORY SERUM AND URINARY PROTEIN BIOMARKERS FOR PSC

Johanna Schaub[1] Richard Ahn[1] Fawzy Barry[2] Dorothea Kent[2] Prerna Kotak[1] Scott Turner[1] Jennifer Lai[2] Martin Decaris[1]

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Background: Primary sclerosing cholangitis (PSC) is a rare disease with no FDA-approved therapies. The development of therapeutics for PSC has been hindered by the lack of robust biomarkers of progressive disease and treatment response. Here we combined two unique biomarker screening approaches to identify novel candidate biomarkers for PSC. **Methods:** Serum samples collected from 21 patients with PSC and 15 healthy, age-matched donors were screened using a 384 inflammatory protein panel (OLink) with data analyzed using the OlinkAnalyze R package. Urine samples collected from 12 patients with PSC (11 unique, 1 overlapping) and 12 unique healthy, age-matched donors were analyzed by shotgun LC-MS/MS (Biognosys) and differentially regulated proteins were identified using the limma R package. **Results:** 135 serum proteins present at significantly elevated levels (e.g. CCL21, endocan) and 31 serum proteins present at significantly reduced levels (e.g. RAB6A, MPIG6B) were identified in patients with PSC when compared to healthy donors (FDR < 0.05, |log2FC| > 0.5). Pathways significantly enriched in serum from patients with PSC included cytokine-mediated signaling pathway (GO:0019221) and inflammatory response (GO:0006954). 89 urinary proteins (e.g. BST2, CTSS) were also found at significantly different levels in patients with PSC in comparison to healthy donors (FDR < 0.1, |log2FC| > 0.5) with pathways related to antigen processing and presentation significantly enriched (e.g. GO:0019886). Cross-referencing the serum and urinary protein analyses identified 2 candidate biomarkers, MILR1 and HLA-DRA, that were significantly elevated in both sample types. **Conclusion:** Two unique proteomic screening approaches were used to identify novel diagnostic biomarkers in patients with PSC. Previously described putative PSC biomarkers (e.g. CCL21, uPAR) were identified alongside dozens of novel biomarker candidates (e.g. MILR1, HLA-DRA), validating the discovery approach. Also identified in our study were proteins previously proposed as biomarkers of progression in patients with primary biliary cholangitis (BST2; Hardie et al. 2016) and cirrhosis (endocan; Toshikuni et al. 2015), suggesting a potential role for these markers in predicting progression in PSC. Follow-up studies are required to validate the prognostic and/or therapeutic utility of these novel biomarker candidates in PSC.

Disclosures: Johanna Schaub: Pliant Therapeutics: Employee, Pliant Therapeutics: Stock - publicly traded company, Richard Ahn: Nothing to Disclose, Fawzy Barry: Nothing to Disclose, Dorothea Kent: Nothing to Disclose, Prerna Kotak: Pliant Therapeutics: Stock - publicly traded company, Pliant Therapeutics: Employee, Scott Turner: Nothing to Disclose, Jennifer Lai: Nestle Nutrition Institute: Grant/Research Support, Novo Nordisk: Consultant, Genfit: Consultant, Boehringer Ingelheim: Advisor, Martin Decaris: Nothing to Disclose

4338 | GALLBLADDER NEOPLASIA IS ASSOCIATED WITH A HIGHER RISK OF BILIARY NEOPLASIA IN PATIENTS WITH PRIMARY SCLEROSING CHOLANGITIS

Mitchell Clayton[1] John Eaton[1] Ross Dierkhising[1] Andrea Gossard[1] Gregory Gores[1] Konstantinos Lazaridis[2] Nicholas LaRusso[1]

[1]Mayo Clinic Rochester, [2]Mayo Clinic

Background: Chronic inflammation in those with primary sclerosing cholangitis (PSC) leads to a multifocal field effect, increasing the possibility of synchronous and metachronous neoplasia in the gallbladder (GBN) and biliary tree (BN). However, the risk of BN after GBN detection has not been quantified. **Methods:** We conducted a retrospective chart review of all adult patients with large-duct PSC seen at the Mayo Clinic between January 1, 1995 and December 31, 2019. Patients with advanced gallbladder cancer resulting in malignant extrahepatic biliary strictures at the time of GBN detection were excluded (n=3). Incidence rates for BN development were calculated. Cox regression analyses were performed to determine features associated with BN development beginning at the time of PSC diagnosis. GBN was treated as a time dependent covariate. Patients were censored at the time of last follow up or liver transplantation (whichever occurred first). **Results:** Our study included 1829 patients with a median (interquartile range) follow up of 8.20 (3.40-15.80) years. The majority of subjects were

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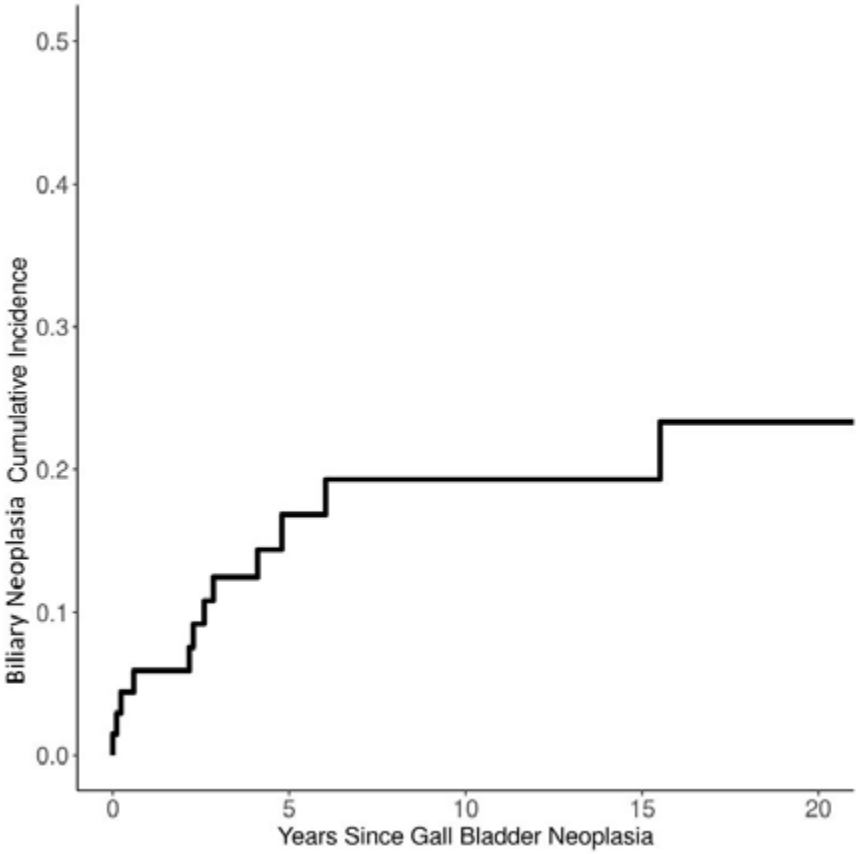
male (64.95%) and had inflammatory bowel disease (IBD) (78.62%). Seventy-one individuals (3.88%) developed GBN (adenocarcinoma n=61, low- or high-grade dysplasia n=10), and 336 (18.37%) were diagnosed with BN (adenocarcinoma n=334, low- or high-grade dysplasia n=2). Of the 71 patients who developed GBN, 22.54% developed BN. The annual incidence of BN after PSC diagnosis among all patients was 2.21% (95% confidence interval (CI), 1.98-2.46%). Conversely, the annual incidence of BN after GBN was 4.34% (95% CI, 2.24-7.58%). This risk was most apparent within 5 years after GBN detection (Figure 1). In an unadjusted analysis, GBN was associated with BN: hazard ratio (HR) 2.14; 95% CI, 1.16-3.94). This observation was more pronounced when gallbladder adenocarcinoma was present when compared to gallbladder dysplasia: HR 2.25; 95% CI, 1.19-4.25 versus HR 1.46; 95% CI, 0.20-10.50. After adjusting for other predictors of BN (male gender, increasing age, and IBD), an association between GBN and BN that approached statistical significance remained: HR 1.71; 95% CI, 0.93-3.16. **Conclusion:** While few patients with PSC develop GBN, the incidence of BN is higher in this subgroup. Consequently, once GBN is detected, clinicians should consider more intensive screening for BN.



Disclosures: Mitchell Clayton: Nothing to Disclose, John Eaton: Nothing to Disclose, Ross Dierkhising: Nothing to Disclose, Andrea Gossard: Nothing to Disclose, Gregory Gores: Nothing to Disclose, Konstantinos Lazaridis: Nothing to Disclose, Nicholas LaRusso: NIH: R01 DK 24031, NIH: R01 DK 57993, NIH: P30 DK 84567, NIH: P30 DK90728, NIH: R01 DK117133, NIH: T32 DK 07198

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4339 | ALKALINE PHOSPHATASE CHANGES WITH SELADELPAR ACROSS SUBGROUPS OF PRIMARY BILIARY CHOLANGITIS PATIENTS IN THE RESPONSE TRIAL ◆

Kris Kowdley[1] Kidist Yimam[2] Sonal Kumar[3] Edward Mena[4] Alan Bonder[5] K. Gautham Reddy[6] Christophe Corpechot[7] Susheela Carroll[8] Ke Yang[9] Daria Crittenden[8] Charles McWherter[9]

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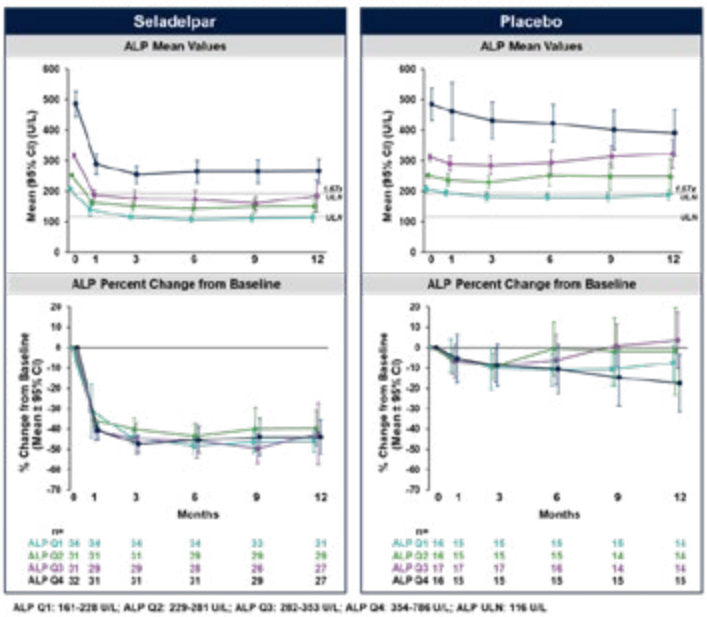
Background: Alkaline phosphatase (ALP) is an important marker in primary biliary cholangitis (PBC) associated with risk for disease progression. In the pivotal, phase 3, placebo-controlled RESPONSE trial (NCT04620733), seladelpar, a novel delpar (selective PPAR-delta agonist), led to a significantly higher percentage of PBC patients achieving the composite biochemical endpoint (ALP <1.67x upper-limit-of-normal [ULN], ALP decrease ≥15%, and total bilirubin [TB] ≤ULN) compared to placebo (61.7% vs 20%) and decreased mean ALP levels after one year (-42.4% vs -4.3%, respectively). Here, we report additional data on ALP changes in the RESPONSE trial. **Methods:** PBC patients who received ursodeoxycholic acid (UDCA) for ≥12 months or were UDCA intolerant and had ALP ≥1.67xULN and TB ≤2xULN were randomized 2:1 to daily seladelpar 10 mg or placebo. We assessed ALP changes across demographic subgroups, baseline ALP quartiles, and in patients who did not meet the composite biochemical endpoint. Worsening of ALP (increase >0 U/L from baseline) and safety by baseline ALP subgroup were also evaluated. **Results:** 128 patients were randomized to seladelpar and 65 to placebo with mean baseline ALP 314.6 U/L and 313.8 U/L, respectively; 53 (27.5%) patients had baseline ALP ≥350 U/L. Seladelpar reduced ALP at Month 12 similarly across all subgroups, including patients with cirrhosis, aged <50 years at PBC diagnosis, and of Hispanic/Latino ethnicity, vs placebo. For patients with baseline ALP ≥350 U/L, seladelpar led to a greater decrease (-44.8%; -216.1 U/L) in ALP vs placebo (-11.6%; -56.4 U/L); similar percent decreases were seen in patients with baseline ALP <350 U/L. Seladelpar reduced ALP similarly across baseline ALP quartiles. Among patients who did not meet the composite biochemical endpoint at Month 12, ALP was decreased by -129.9 U/L for seladelpar vs -6.4 U/L for placebo. Seladelpar prevented worsening of ALP, with 7 (5.5%) seladelpar patients vs 19 (29.2%) placebo with increases in ALP from baseline at Month 12. AEs were reported in 86.4% of patients with baseline ALP <350 U/L and 84.9% of patients with ALP ≥350 U/L, with similar proportions in seladelpar vs placebo patients. **Conclusion:** Seladelpar led to robust and consistent ALP decreases across all subgroups studied. Substantial ALP decreases were also observed in patients who did not meet the composite endpoint criteria at Month 12. Seladelpar was overall safe and well tolerated, regardless of baseline ALP level.

ALP Changes in PBC Patients Treated with Seladelpar or Placebo by Baseline ALP Quartile in the RESPONSE Trial



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4340 | FGFR SIGNALING POTENTIATES CHOLESTATIC LIVER FIBROSIS

MALLIKARJUNA SIRAGANAHALLI ESHWARAIAH[1] *Jiaohong Wang*[1] *Nirmala Mavila*[1]

[1]*Cedars-Sinai Medical Center*

Background: Fibroblast growth factor receptor (FGFR) signaling regulates various physiological events such as cell proliferation and differentiation; hence, it plays a critical role in tissue homeostasis during development and injury. FGF ligands signal through four different receptors, FGFR1-4. Our preliminary analysis of human liver fibrotic tissues demonstrated an activation of FGFR signaling compared to controls. This study aimed to determine the role of activated FGFR signaling in liver fibrosis progression. **Methods:** Experimental liver fibrosis was induced by bile duct ligation (BDL), 3,5-diethoxycarbonyl-1,4-dihydrocollidine (DDC) diet. The Mdr2-/- mouse model was utilized to investigate liver fibrosis in Primary Sclerosing Cholangitis (PSC). Both male and female mice were used for experiments (n=3-7). FGFR signaling was inhibited in vivo by a small molecule inhibitor AZD4547. Human biliary atresia (BA) liver samples were obtained from Children's Hospital Los Angeles. Human PSC tissues were obtained from the Cedars-Sinai Biobank repository. Western blot and the quantitative polymerase chain reaction were performed to quantify protein and mRNA levels. Immunohistochemistry was performed to determine protein localization. **Results:** FGFR protein and mRNA levels were elevated by 1.5 to 4-fold in BA, DDC, and BDL livers compared to controls. In Mdr2-/- mice, there was a significant induction of *Fgfr1-3* mRNA levels and profibrogenic genes such *Tgf beta-1*(2-fold), *Mmp-7* (30-fold) *Mmp9* (4-fold), *CollagenA1* (15-fold), *Timp-1*(35-fold), *Timp3* (1.5-fold) and *S100A4* (10-fold) during fibrosis progression. FGFR inhibition in vivo by AZD4547 caused a significant ~50% reduction in fibrotic markers in BDL and Mdr2 -/- mouse models **Conclusion:** FGFR signaling is activated in human liver fibrosis. FGFR inhibition ameliorates fibrosis progression in fibrosis models, suggesting that targeting FGFR signaling may be a potential therapeutic strategy to manage liver fibrosis

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Disclosures: MALLIKARJUNA SIRAGANAHALLI ESHWARAIAH: Nothing to Disclose, Jiaohong Wang: Nothing to Disclose, Nirmala Mavila: Nothing to Disclose

4341 | LONG-TERM SAFETY OF SELADELPAR 10 MG WITH UP TO 5 YEARS OF TREATMENT IN PATIENTS WITH PRIMARY BILIARY CHOLANGITIS ◆

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Background: Seladelpar, a novel delpar (selective PPAR-delta agonist), is in development for the treatment of primary biliary cholangitis (PBC). The phase 3, placebo-controlled RESPONSE study (NCT04620733) in PBC patients with an inadequate response or intolerance to ursodeoxycholic acid demonstrated significant improvements in cholestatic markers and pruritus with seladelpar over one year. Similar proportions of seladelpar and placebo-treated patients experienced adverse events (AEs) and serious AEs (SAEs). To assess long-term safety, data from all PBC patients exposed to seladelpar 10 mg in 6 studies with similar entry criteria were pooled. **Methods:** AE data from 2 placebo-controlled and 4 open-label studies were pooled for all patients treated with seladelpar 10 mg as of 31 Jan 2024, beginning with first exposure to seladelpar, including all exposure periods and excluding treatment gaps. Placebo exposure was pooled from the 2 placebo-controlled studies. Exposure-adjusted subject incidences of AEs, SAEs, and AEs of interest (defined as liver-, muscle-, renal-, and pancreatic-related AEs) were calculated. **Results:** As of the data cutoff, a total of 486 patients received seladelpar 10 mg: 355 were treated for ≥1 year, 170 ≥2 years, 66 ≥3 years, 36 ≥4 years, 10 ≥5 years. The exposure-adjusted subject incidence (per 100 patient-years) for seladelpar 10 mg was 48.3 for AEs, 8.0 for SAEs, 9.8 for Grade ≥3 AEs, and 6.1 for liver-related AEs. There were no treatment-related SAEs. Muscle, renal, and pancreatic AEs occurred in <7 patients per 100 patient-years. Placebo exposure included 152 patients: 117 were treated for ≥12 weeks, 84 for ≥6 months, and 57 for 12 months of placebo treatment in RESPONSE. The exposure-adjusted subject incidence (per 100 patient-years) for patients treated with placebo was 132 for AEs (rate reflective of shorter exposure time for placebo patients), 7.8 for SAEs, 12.2 for Grade ≥3 AEs, and 13.3 for liver-related AEs (with other AEs of interest occurring at lower rates). AEs leading to treatment discontinuation occurred in 2.9 patients per 100 patient-years in seladelpar patients and 5.6 per 100 patient-years in placebo patients. **Conclusion:** Analysis of a large safety database for seladelpar in PBC patients with exposure through 5 years indicated that seladelpar was well tolerated with a safety profile similar to placebo.

Exposure-Adjusted Adverse Event Rates of Patients who Received Seladelpar 10 mg or Placebo

	Placebo (N=152) E=89.9 years n per 100 patient-years	Seladelpar 10mg* (N=486) E=865.1 years n per 100 patient-years
Any AE	132.3	48.3
Grade ≥ 3	12.2	9.8
Serious AE	7.8	8.0
AE leading to treatment discontinuation	5.6	2.9
AE leading to study discontinuation	3.3	2.0
AEs of interest		
Liver-related	13.3	6.1
Muscle-related	8.9	6.9
Renal-related	0	0.7
Pancreatic-related	1.1	0.6

*Subjects could have received doses <10mg at times during their treatment course. **Note:** Exposure time includes placebo-controlled and open-label treatment periods. N=total number of subjects included in the analysis; n=number of subjects with an event; E=total exposure time for the group in years. AEs of interest were identified by prespecified SMQ or FMQ search strategies. **Abbreviations:** AE=adverse event, FMQ=Food and Drug Administration medical query, SMQ= Standardized Medical Dictionary for Regulatory Activities query

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Disclosures: Palak Trivedi: Nothing to Disclose, Stuart Gordon: Nothing to Disclose, Aliya Gulamhusein: Advanz: Consultant, Cymabay: Consultant, Alejandra Villamil: Novartis: Advisor, Intercept: Speaking and Teaching, Gilead: Advisor, Zydus: Advisor, Eric Lawitz: Nothing to Disclose, John Vierling: Nothing to Disclose, Maria Carlota Londono: Advanz: Consultant, Advanz: Speaking and Teaching, Ipsen: Consultant, GSK: Consultant, Cymabay: Speaking and Teaching, Andreas Kremer: Abbvie: Advisor, Advanz: Advisor, Alentis: Advisor, AlphaSigma: Speaking and Teaching, AstraZeneca: Advisor, Avior: Advisor, Bayer: Advisor, CymaBay: Advisor, Escient: Advisor, Falk: Speaker, Falk: Speaker, Gilead: Advisor, GSK: Advisor, Intercept: Advisor, Ipsen: Speaking and Teaching, Ipsen: Speaking and Teaching, Mirum: Advisor, Mirum: Advisor, MSD: Advisor, Myr: Advisor, Roche: Advisor, Takeda: Advisor, Viofor: Advisor, Christopher Bowlus: Calliditas: Grant/Research Support, ChemoMab: Grant/Research Support, ChemoMab: Consultant, COUR Phamaceuticals: Grant/Research Support, Cymabay: Grant/Research Support, Cymabay: Consultant, Cymabay: Consultant, Gilead: Grant/Research Support, GSK Pharmaceuticals: Grant/Research Support, GSK Pharmaceuticals: Consultant, Hanmi: Grant/Research Support, Intercept: Grant/Research Support, Invea Therapeutics: Consultant, Ipsen: Grant/Research Support, Ipsen: Consultant, Mirum: Grant/Research Support, NGM Bio: Consultant, Novartis: Grant/Research Support, Novo Nordisk: Grant/Research Support, Pliant Therapeutics: Grant/Research Support, Pliant Therapeutics: Consultant, Viking Therapeutics: Grant/Research Support, Zydus Therapeutics: Grant/Research Support, Sarah Proehl: Nothing to Disclose, Shuqiong Zhuo: Nothing to Disclose, Daria Crittenden: Nothing to Disclose, Charles McWherter: Nothing to Disclose

4342 | SELADELPAR AND REDUCTIONS IN LIPIDS IN PATIENTS WITH PRIMARY BILIARY CHOLANGITIS WITH AND WITHOUT STATIN USE IN THE PHASE 3 PLACEBO-CONTROLLED RESPONSE STUDY ◆

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Background: Seladelpar, a novel delpar (selective PPAR-delta agonist), is in development for the treatment of primary biliary cholangitis (PBC). In the phase 3 RESPONSE study (NCT04620733), seladelpar was associated with reductions in LDL-C (least squares [LS] mean percent change [SE] was 12.7% [1.86] in the seladelpar arm vs -3.7% [2.57] in placebo; p<0.05). Total cholesterol and triglycerides were also reduced, while HDL-C was stable. This post-hoc analysis examined the effects of seladelpar on lipid profiles in patients on statins compared with those not on statins at baseline, as well as safety. **Methods:** PBC patients with an inadequate response or intolerance to ursodeoxycholic acid, an elevated alkaline phosphatase, and a total bilirubin ≤2× upper limit of normal were randomized (2:1) to daily seladelpar 10 mg or placebo. Total cholesterol, LDL-C, HDL-C, and triglycerides were measured at baseline and regular intervals. Patients were assigned post-hoc to the statin subgroup if they were taking a statin-containing medication on Day 1. **Results:** A total of 38/128 (29.7%) patients in the seladelpar arm were on statins at baseline compared with 26/65 (40.0%) on placebo. The most common statins were atorvastatin, rosuvastatin, and simvastatin. Mean baseline levels of total cholesterol and LDL-C were lower in patients on statins than in patients not on statins (and similar between treatment arms). LS mean percent change (SE) from baseline in LDL-C at Month 12 in the statin subgroup was -14.1% (4.47) in the seladelpar arm and +3.0% (5.23) in the placebo arm, compared with -12.3% (1.83) and -6.9% (2.74), respectively, in patients not on statins. Reductions in cholesterol and triglycerides were also observed with seladelpar, regardless of statin use. There were no meaningful changes in HDL-C over the course of the study. Frequency of adverse events (AEs) was similar between treatment arms in both subgroups. Frequency of muscle-related AEs was comparable between treatment arms regardless of statin use (statins: seladelpar 5.3%, placebo 3.8%; no statins: seladelpar

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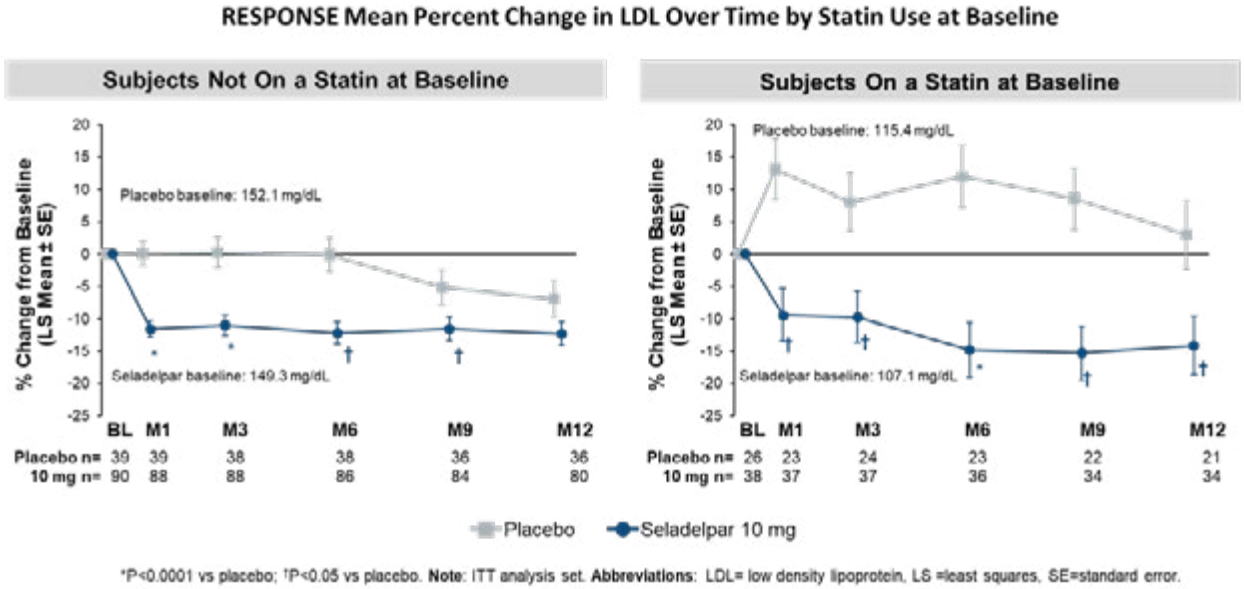
6.7%, placebo 10.3%), and none led to treatment discontinuation. There were no AEs associated with creatine kinase elevations regardless of statin use. **Conclusion:** Over 12 months of treatment, seladelpar resulted in reductions in total cholesterol and LDLC in PBC subjects, regardless of statin use at baseline. There were no safety concerns identified in patients co-administered statins and seladelpar.



*P<0.0001 vs placebo; †P<0.05 vs placebo. **Note**: ITT analysis set. **Abbreviations**: LDL= low density lipoprotein, LS =least squares, SE=standard error.

Disclosures: Christopher Bowlus: Calliditas: Grant/Research Support, ChemoMab: Grant/Research Support, ChemoMab: Consultant, COUR Phamaceuticals: Grant/Research Support, Cymabay: Grant/Research Support, Cymabay: Consultant, Cymabay: Consultant, Gilead: Grant/Research Support, GSK Pharmaceuticals: Grant/Research Support, GSK Pharmaceuticals: Consultant, Hanmi: Grant/Research Support, Intercept: Grant/Research Support, Invea Therapeutics: Consultant, Ipsen: Grant/Research Support, Ipsen: Consultant, Mirum: Grant/Research Support, NGM Bio: Consultant, Novartis: Grant/Research Support, Novo Nordisk: Grant/Research Support, Pliant Therapeutics: Grant/Research Support, Pliant Therapeutics: Consultant, Viking Therapeutics: Grant/Research Support, Zydus Therapeutics: Grant/Research Support, Yusuf Yilmaz: Nothing to Disclose, Ehud Zigmond: Nothing to Disclose, Marek Hartleb: Nothing to Disclose, Ewa Janczewska: Grant/Research Support relationship with Roche; Grant/Research Support relationship with Cymabay; Grant/Research Support relationship withy Dr. Falk; Grant/Research Support relationships with AstraZeneca; Grant/Research Support relationships with MSD; Grant/Research Support relationship with Novo Nordisk; Grant/Research Support relationship with GSK; Grant/Research Support relationship with Janssen-Cilag; Grant/Research Support relationship with Inventiva; Grant/Research Support relationship with Galectin; Grant/Research Support relationship with Caliidtas, Pietro Andreone: Nothing to Disclose, Victor Vargas: Ipsen: Advisor, Orphalan: Speaking and Teaching, Álvaro Díaz-González: GSK: Advisor, IPSEN: Advisor, AdvanzPharma: Speaking and Teaching, Andreas Kremer: Abbvie: Advisor, Advanz: Advisor, Alentis: Advisor, AlphaSigma: Speaking and Teaching, AstraZeneca: Advisor, Avior: Advisor, Bayer: Advisor, CymaBay: Advisor, Escient: Advisor, Falk: Speaker, Falk: Speaker, Gilead: Advisor, GSK: Advisor, Intercept: Advisor, Ipsen: Speaking and Teaching, Ipsen: Speaking and Teaching, Mirum: Advisor, Mirum: Advisor, MSD: Advisor, Myr: Advisor, Roche: Advisor, Takeda: Advisor, Viofor: Advisor, Sook-Hyang Jeong: Nothing to Disclose, Eduardo Fassio: Nothing to Disclose, Alejandra Villamil: Novartis: Advisor, Intercept: Speaking and Teaching, Gilead: Advisor, Zydus: Advisor, Alma Laura Ladron de Guevara Cetina: Eli Lilly and company: Grant/Research Support, Galectin Therapeutics: Grant/Research Support, Akero: Grant/Research Support, AStra Zeneca: Grant/Research Support, Inventiva Pharma: Grant/Research Support, Cymabay Therapeutics: Grant/Research Support, Eli Lilly and company: Grant/Research Support, Akero Therapeutics: Grant/Research Support, Galectin: Grant/Research Support, Novonordisk: Grant/Research Support, MSD: Grant/Research Support, Cymabay: Grant/Research Support, Marlyn Mayo: Grant/Research Support relationship with Mirum; Has not ended; Grant/Research Support relationship with Mallinckrodt; Has ended; Consultant relationship with Mallinckrodt; Has ended; Grant/Research Support relationship with CymaBay; Has not ended; Grant/Research Support relationship with Target RWE; Has ended; Consultant

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4343 | OBETICHOLIC ACID VERSUS FIBRATES AS SECOND-LINE THERAPY FOR PRIMARY BILIARY CHOLANGITIS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: Around 40% of patients diagnosed with Primary Biliary Cholangitis (PBC) experience a suboptimal biochemical response to ursodeoxycholic acid (UDCA). Additional treatment with either fibrates or obeticholic acid (OCA) appears to enhance transplant-free survival. However, it remains uncertain whether one drug holds superiority over the other as second-line therapy. **Methods:** We searched Embase, MEDLINE, and Cochrane Central for studies comparing OCA and fibrates in patients diagnosed with PBC who had an incomplete response to UDCA. A pooled analysis was conducted to evaluate changes in liver biochemistry and response rates based on validated criteria. Data were expressed as ratio of means (ROM) when comparing post-intervention values and as mean difference (MD) when analyzing percentual relative changes. Heterogeneity was assessed with I2 statistics. Statistical analysis was performed using R (version 2023.12.1+402). **Results:** We included 883 patients from 4 studies, 468 (53%) of them under UDCA + OCA. Follow-up time ranged from 1 to 4.8 years. Patients treated with fibrates have similar mean ALP (ROM 0.71; 95%CI 0.49-1.01; p=0.06) and bilirubin (ROM 1.07; 95%CI 0.73-1.56; p=0.72) levels compared to OCA. However, fibrates demonstrated superiority over OCA in terms of the relative change in ALP compared to baseline (MD 27.68%; 95%CI 24.51-30.86; p<0.01) and the rate of ALP normalization [Odds Ratio (OR) 12.89; 95%CI 2.29-72.64; p<0.01]. Patients treated with fibrates also more frequently met Barcelona (OR 4.28; 95%CI 2.26-8.11; p<0.01), POISE (OR 5.48; 95%CI 2.70-11.13; p<0.01), and Paris II (OR 5.88; 95%CI 3.96-8.74; p<0.01) response criteria. Regarding transaminases, fibrates were associated with an increase in AST levels (ROM 2.74; 95%CI 1.08-6.94; p=0.03), while OCA was more effective in reducing ALT levels (MD -12.60%; 95%CI -22.58 to -2.62; p=0.01). Our analysis should be interpreted with caution due to limited data availability and heterogeneity observed across the included studies. **Conclusion:** In patients with PBC and an incomplete response to UDCA, fibrates appear to be more effective as second-line therapy. Further studies are warranted to clarify this issue.

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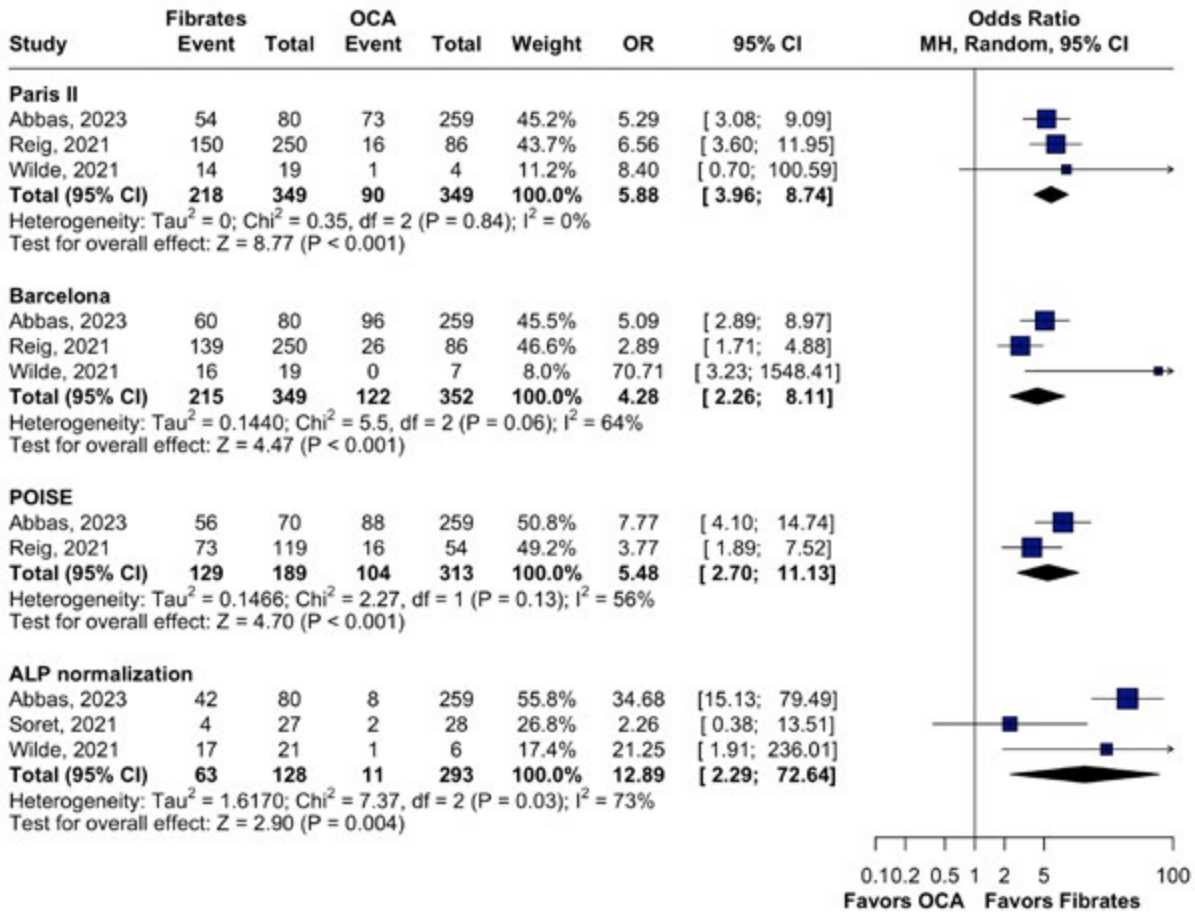

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4344 | ASSESSING THE HEALTH-RELATED QUALITY OF LIFE, IMPAIRMENT AND PRODUCTIVITY AMONG INDIVIDUALS WITH PBC AND PRURITUS: RESULTS FROM THE ITCH-E STUDY

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Background: Individuals living with primary biliary cholangitis (PBC) are commonly impacted by pruritus, which may cause issues with sleep, fatigue, pain and social isolation. About 70% of PBC patients endure pruritus that may be severe, with inadequate treatment options to reduce pruritus. This study assessed the impact of pruritus on patients' health-related quality of life (HRQoL), activity, and work productivity. **Methods:** Adults with PBC were recruited from a PBC patient advocacy group and a physician panel between 12/2023 and 03/2024. Enrolled participants were categorized based on the Pruritus Numerical Rating Scale (NRS) into no/mild pruritus (NMP, NRS<4) vs. moderate/severe pruritus (MSP, NRS≥4). Participants completed the PBC-40, Chronic Liver Disease Questionnaire (CLDQ-PBC), 5-D Itch, EQ-5D-5L, Functional Assessment of Chronic Illness Therapy – Fatigue Short Form (FACIT-Fatigue), and the Work Productivity and Activity Impairment (WPAI) questionnaires. A subset of the MSP group answered open-ended questions via voice response. Differences were analyzed using regression models adjusting for age, sex, ethnicity, and treatment. **Results:** The sample included 40 NMP and 50 MSP participants. The mean age was 56.7 in the NMP group and 52.1 for MSP; females comprised 85%

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and 80%, respectively. Compared to NMP, and after controlling for confounders, the MSP group had statistically significantly worse PBC-40 mean scores in Symptom, Itch, Fatigue, Cognitive, and Social (all p<.05) but not Emotional (p=.239) domains. The MSP group had worse scores on FACIT-fatigue (p<.001) and 5D-Itch (p<.001), and lower scores on CLDQ-PBC Total (p<.001) and EQ-5D Index (p=.005). The MSP group also reported statistically significantly greater WPAI activity impairment (p<.001) and lower work status compared to NMP group (42% vs 53%). Among those employed, the MSP group reported more work time missed, greater impairment while working, and overall work impairment due to PBC. Differences in these scores were not significant possibly because less than half were employed (Table 1). Patient voice data highlighted the unrelenting, painful nature of itching and its negative impact on emotional/social health and productivity. **Conclusion:** Adults with PBC and moderate/severe itch have a significant burden on HRQoL and impaired activity compared to those with no/mild itch, emphasizing the need for safe and efficacious PBC treatments that can improve pruritus.

Table 1. Linear regression models of the association between moderate/severe pruritus with HRQoL and work productivity among individuals with PBC*

Outcome	Score Ranges	Score Interpretation	Coefficient (MSP vs. NMP Group)[§]	95% CI	p-value
PBC-40 Domain Scores					
Symptoms	7-35	Higher scores indicate worse QOL	2.26	(0.55, 3.97)	0.011
Itch	3-15		4.18	(2.91, 5.45)	<0.001
Fatigue	11-55		7.24	(3.63, 10.85)	<0.001
Cognitive	6-30		3.53	(1.43, 5.63)	0.001
Emotional	3-15		0.72	(-0.46, 1.90)	0.239
Social	10-50		4.18	(0.67, 7.69)	0.022
FACIT-Fatigue Score					
Total	0-52	Higher scores indicate less fatigue	-8.26	(-12.85, -3.67)	<0.001
CLDQ-PBC Score					
Total	1-7	Higher score indicates better QOL	-0.87	(-1.38, -0.36)	<0.001
5D Itch Score					
Total	5-25	Higher score indicates more severe itch and negative impact	4.87	(3.56, 6.18)	<0.001
EQ-5D-5L Scores					
EQ-5D Index	-0.573-1.000	Higher scores indicate better QOL	-0.14	(-0.24, -0.04)	0.005
EQ-VAS	1-100		-3.58	(-11.01, 3.85)	0.348
WPAI Scores					
% activity impairment due to PBC	0-100	Higher scores indicate greater impairment or productivity loss	0.20	(0.08, 0.32)	<0.001
% work time missed due to PBC[¶]	0-100		0.04	(-0.06, 0.14)	0.349
% impairment while working due to PBC[¶]	0-100		0.17	(-0.03, 0.37)	0.236
% overall work impairment due to PBC[¶]	0-100		0.13	(-0.07, 0.33)	0.204

Abbreviations: Moderate/Severe pruritus, MSP; No/Mild pruritus, NMP; Primary Biliary Cholangitis, PBC; Quality of Life, QOL; Functional Assessment of Chronic Illness Therapy-Fatigue, FACIT-Fatigue; Chronic Liver Disease Questionnaire, CLDQ; 5-Dimensions Itch, 5-D Itch; EuroQol 5-Dimensions 5-Levels, EQ-5D-5L; EuroQol Visual Analog Scale, EQ-VAS; Work Productivity and Activity Impairment, WPAI.

*Adjusting for age, sex, ethnicity, obeticholic acid and ursodeoxycholic acid treatment

[¶]WPAI scores (except for the Activity Impairment score) were only calculated for those who indicated being currently employed (NMP n=21, MSP n=21).

[§]As an example, a regression coefficient of 2.26 indicates that being in the MSP group is associated with an increase in the PBC-40 index symptom score by 2.26 points (scores range from 7-35, with higher scores indicating worse QOL).

Disclosures: Cynthia Levy: Consultant relationship with Cymabay; Has ended; Advisor relationship with COur; Has ended; Grant/Research Support relationship with GSK; Has not ended; Grant/Research Support relationship with Ipsen; Has not ended; Consultant relationship with Ipsen; Has ended; Grant/Research Support relationship with Mirum; Has not ended; Consultant relationship with Mirum; Has ended; Grant/Research Support relationship

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4346 | DEFINING ACUTE CHOLANGITIS AS A CLINICAL OUTCOMES ENDPOINT IN ADULTS WITH PRIMARY SCLEROSING CHOLANGITIS (PSC): RESULTS OF A MULTI-NATIONAL PATIENT SURVEY TO DEVELOP A PATIENT-REPORTED OUTCOMES MEASURE (PROM)

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Background: Acute cholangitis (AC) is a clinically significant, poorly understood PSC complication challenged by the lack of standardized diagnostic and treatment criteria. We report the results of a multi-national patient survey to characterize the patient experience during AC as a first phase to develop a patient-centered PROM for use in clinical trials and patient care. **Methods:** A detailed anonymized patient survey was developed by PSC Partners and PSC Support patient organizations. Adults diagnosed with PSC and ≥1 cholangitis attack were invited to complete the survey. Relevant medical history, AC symptom frequency and severity (before, during and after AC), and medical interventions were collected. A visual abdominal pain locator was used to further characterize AC pain location. **Results:** A total of 355 of 428 responses met screening criteria. Timing of first AC attack relative to PSC diagnosis ranged from *before* (38%), *concurrent* (14%) and *after* (48%). Over 65% had AC in the past year, with 45% having ≥2 attacks. Fatigue (92%) and liver pain (86%) were reported most frequently, with fatigue (30%) and fever/chills (24%) having highest severity during AC (Fig 1A). Severity improved for all symptoms after AC, except anxiety. Symptom improvement was greatest with fever/chills (55%), anorexia (51%) and liver pain (51%). Complete symptom resolution was highest for vomiting (50%), fever/chills (46%), night sweats (31%) and nausea (29%), while lowest with fatigue (6%). More patients reported no change in symptom severity after AC, with the least change seen with jaundice, brain fog and pruritus. Anxiety worsened the most after AC at 12% while fatigue was the most reported new-onset symptom at 33%. Abdominal pain was largely located in the right upper quadrant (RUQ) during AC, independent of IBD, cirrhosis or transplant (Fig 1B). Other reported pain locations >10% were body (73%), back (17%) and shoulder (10%). The majority of IBD patients (70%) clearly differentiated AC symptoms from IBD flares. Medical care was sought by 76%, of which 86% took oral and/or IV antibiotics. Other procedures included MRI (68%), ultrasound (57%), ERCP (44%) and stent/balloon dilation (26%). Despite AC treatment and/or resolution, 32% did not return to their perceived baseline health status, reporting persistent or new onset fatigue (44%), RUQ pain (15%) and brain fog (11%). **Conclusion:** This detailed survey demonstrates a broad dynamic range of the frequency and severity of symptoms over the clinical course of AC. Symptom improvement is seen in a subset of patients, but the majority show no improvement or worsening of symptoms despite treatment or attack resolution. Fatigue and anxiety are under-recognized symptoms reported with AC and warrant further study. No single symptom provides adequate specificity or sensitivity for AC diagnosis or monitoring, clearly supporting the significant need to develop a multi-symptom PROM for clinical trials and patient care.

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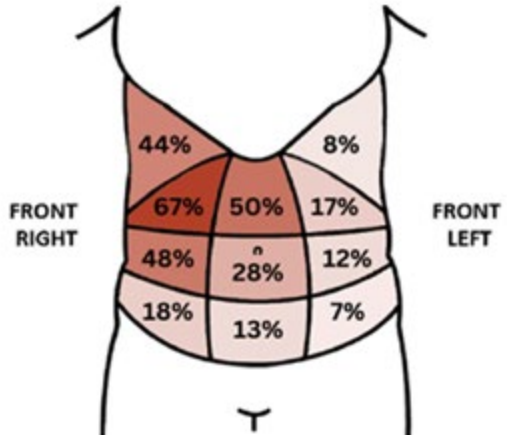
Figure 1A Change in Frequency and Severity of Symptoms During and After AC

	During (At Worst)		After (At Worst)		Δ in Severity			Symptom Outcomes	
	Present	*Severe*	*Present*	*Severe*	*Improved*	*No Δ*	*Worsened*	*Resolved*	*New Onset*
Fatigue	92%	54%	89%	30%	45%	50%	5%	6%	33%
Liver pain	86%	40%	76%	13%	51%	42%	7%	14%	16%
Anorexia	82%	27%	65%	15%	51%	41%	8%	25%	18%
Fever/chills	76%	41%	43%	24%	55%	39%	6%	46%	9%
Insomnia	76%	34%	69%	18%	41%	51%	8%	15%	16%
Body aches/pains	73%	22%	60%	10%	41%	50%	9%	22%	12%
Nausea	69%	32%	53%	14%	46%	48%	6%	29%	9%
Choluria	68%	31%	51%	14%	40%	56%	4%	25%	5%
Pruritus	66%	34%	60%	21%	28%	65%	7%	11%	7%
Night sweats	65%	33%	47%	17%	43%	53%	5%	31%	6%
Other abd. pain	62%	28%	53%	8%	38%	52%	10%	24%	16%
Brain fog	60%	19%	55%	11%	27%	67%	6%	17%	6%
Anxiety	54%	21%	57%	14%	23%	65%	12%	10%	15%
Jaundice	47%	25%	36%	16%	25%	70%	5%	27%	5%
Vomiting	40%	25%	24%	9%	31%	62%	7%	50%	6%

Figure 1B Abdominal Pain Location During AC



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4347 | PILOT STUDY OF VOLIXIBAT CO-ADMINISTERED WITH OCA FOR PRIMARY BILIARY CHOLANGITIS (PBC) TREATMENT: THE VLX-602 TRIAL

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Background: PBC is a progressive inflammatory cholestatic disease with liver bile flow impairment and destruction of intrahepatic bile ducts. Bile acid (BA) levels are commonly elevated with disease severity and progression with cholestatic pruritus being a debilitating complication. Volixibat (VLX) is an ileal bile acid transporter (IBAT) inhibitor that interrupts BA uptake in the small intestine, leading to greater BA fecal elimination with subsequent reductions in the systemic BA pool. IBAT inhibitors have shown efficacy to treat cholestatic pruritus, including in PBC, but concurrent use of an IBAT inhibitor and obeticholic acid (OCA) is not well studied. VLX-602 is a pilot study to evaluate the safety of VLX (80 mg BID) in participants with PBC who were on active treatment with OCA (5 or 10 mg). **Methods:** VLX-602 was a multicenter, open-label study that enrolled patients with PBC with ongoing treatment with OCA for ≥3 months with a stable ALP level. The study consisted of screening (14 days), study treatment (OCA + VLX, 6 weeks), and follow-up (1 week) periods. Safety was assessed by TEAE collection and laboratory measurements, including liver chemistry. Other assessments included: 7aC4, sBA, PK and autotaxin levels, along with the itch PROs (PIS-Itch, WI-NRS, and PGICItch). **Results:** Six participants were enrolled, all female, with mean age of 56.5 years. The most common TRAE was diarrhea (83.3%). Other TRAEs that affected 1 participant each (16.7% each) were nausea, fatigue, and vomiting. Other TEAEs (not related to study drug) that affected 1 participant each (16.7% each) were toothache, nasopharyngitis, and upper respiratory tract infection. No severe, serious, or events that led to study discontinuation or death were reported. Mean levels of AST, ALT, total bilirubin, and ALP were stable between baseline and end of the treatment period. Overall, 3 participants showed improvement in their itch scores for both WI-NRS and PISItch while on VLX. At the follow-up visit, after VLX was discontinued, 3 and 4 participants had worsening in their WI-NRS scores and PIS-Itch scores, respectively. **Conclusion:** These safety pilot study data were consistent with the known safety profile of IBAT inhibitors. The addition of VLX to OCA treatment in PBC led to improvement in itch in some patients, with reversal of the effect upon VLX cessation. The results of this study justify additional investigation of the safety and efficacy of VLX for the treatment of PBC, with or without a background regimen of OCA.

Parameter (BL/EOT)	Participant					
	1	2	3	4	5	6
WI-NRS	4/0	3/0	0/0	5/8	7/1	0/0
PIS-Itch	3/1	2/1	1/1	3/4	3/1	1/1
sBA (µmol/L)	11/15	0.1/3	19/6	6/7	42/34	20/24
ALP (U/L)	279/339	85/65	132/159	232/251	205/146	230/265
ALT (U/L)	75/65	14/20	25/34	15/27	8/6	22/52
AST (U/L)	48/41	22/24	29/39	23/28	13/13	34/45
TB (µmol/L)	9/9	7/5	10/7	17/15	7/10	10/14
DB (µmol/L)	3/5	2/2	3/3	5/5	3/3	3/5

ALT, alanine aminotransferase; ALP, alkaline phosphatase; AST, aspartate aminotransferase; BL, baseline; DB, direct bilirubin; EOT, end of treatment; PIS-Itch, patient impression of severity of itch; sBA, serum bile acids; TB, total bilirubin; WI-NRS, worst itching numeric rating scale.

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4348 | CORRELATION BETWEEN THE PHARMACOKINETICS OF THE OPIOID ANTAGONIST NALMEFENE AND PRURITUS RELIEF IN PATIENTS WITH CHOLESTATIC PRURITUS

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[1]*Tharimmune Inc*

Background: Previous studies showed the potential of opioid antagonists to relieve itch in patients with cholestatic pruritus. However, the correlation between the pharmacokinetics (PK) of these antagonists and symptom relief has not been previously reported. The purpose of this study was to investigate if there is a correlation between pruritus relief and opioid antagonist PK. Of the opioid antagonists, Nalmefene was chosen because it is a Mu opioid antagonist and a Kappa opioid partial agonist, two properties shown to be important in pruritus reduction. **Methods:** This study was approved by the local IRB and competent authorities. For this study, we used TH104, a proprietary formulation of Nalmefene, 2 mg in strength. TH104 is a buccal film containing Nalmefene, which has a relatively high absolute bioavailability and an improved PK profile, as it bypasses the liver's first-pass metabolism. Patients with cholestatic liver disease and a known history of persistent generalized pruritus for at least 4 weeks prior to screening were included. After an overnight fasting of 10 hours, subjects received one dose of 2 mg of TH104. Serial blood samples for PK analysis were taken, and patients were monitored for itch severity using an 11-point NRS scale (0 – no itch, 10 – worst itch). Nalmefene concentrations were measured with HPLC-MS. MedCalc Version 22.023 was used for statistical calculations. Pearson's correlation coefficient (r) was used to assess the correlation between Nalmefene concentration (h.ng/ml) Area Under the Curve (AUC) and the change in NRS score 24 hours after dosing. **Results:** Nineteen patients were screened, and twelve patients were enrolled in this study. Ten subjects were male, and two were female; six were Child-Pugh class A, and six were Child-Pugh class B. Treatment was well tolerated with only 2 mild adverse events that resolved spontanously. Median predose itch scores were lower in the mild disease population (4.0) as compared to patients with moderate disease (5.5). Twenty-four hours post dose, the median itch scores were 3.0 and 4.0 in the mild and moderate disease groups respectively. The mean AUC was 20.21 h.ng/mL (standard deviation 12.74 and 95 % CI of 11.75 to 28.66). The mean change in NRS itch score was 1.25 points, (standard deviation 1.05 and 95% CI of 0.57 to 1.92). The correlation between Nalmefene AUC and change in itch is shown in Figure 1. The correlation coefficient r was 0.7060, with a significance level of P = 0.0103 and a 95% confidence

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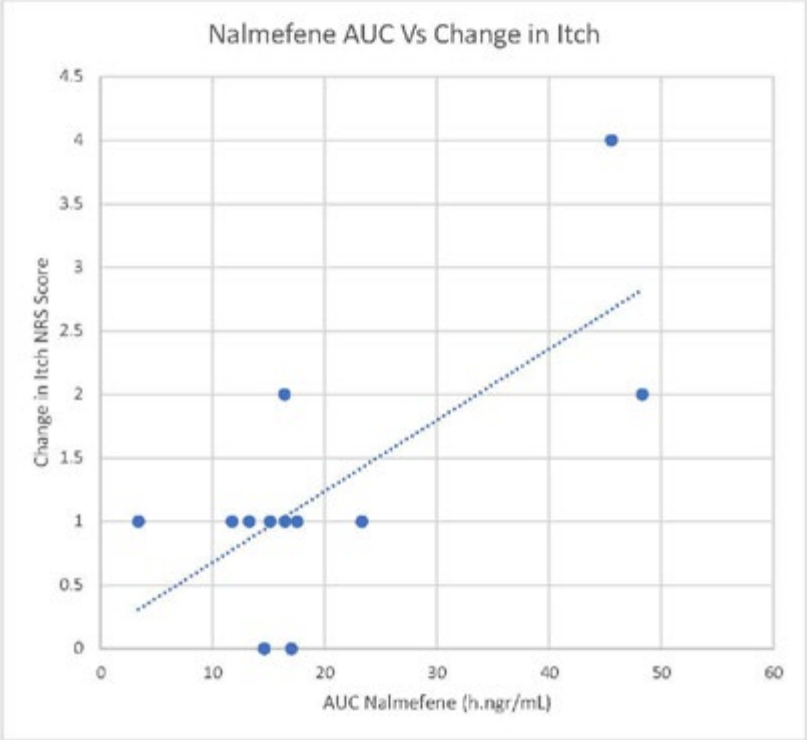
interval for r of 0.2220 to 0.9108. **Conclusion:** The study showed that Nalmefene induces a quick relief in pruritus severity. This is the first report to show that there is a statistically significant correlation between Nalmefene PK and cholestatic pruritus relief. The translational implications suggest that using formulations with improved bioavailability and AUC, such as buccal films, are essential to maximize this effect.



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4349 | ELAFIBRANOR HAS NO IMPACT ON MARKERS OF RENAL FUNCTION IN PRIMARY BILIARY CHOLANGITIS: RESULTS FROM THE PHASE III ELATIVE® TRIAL

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Background: ELATIVE® is a phase III study evaluating the efficacy and safety of elafibranor, a dual peroxisome proliferatoractivated receptor-α/δ agonist, in primary biliary cholangitis (PBC), a rare, cholestatic liver disease. Renal dysfunction has been reported with the use of conventional fibrates during the treatment of dyslipidemias, although the mechanism is not well understood. In this secondary analysis, the impact of elafibranor on markers of renal function were assessed. **Methods:** In ELATIVE® (NCT04526665), patients with PBC with an inadequate response or intolerance to ursodeoxycholic acid were randomized 2:1 to once-daily elafibranor 80 mg or placebo. Patients with renal impairment, including chronic kidney disease (defined as estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m^2), were not eligible to participate in the study. Parameters including Cystatin C (CysC) and SCr were analyzed through Week 52 of ELATIVE®, and eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKDEPI) and Modification of Diet in Renal Disease (MDRD) equations. **Results:** Overall, 161 patients were randomly assigned to receive elafibranor (N=108) or placebo (N=53). Median levels of renal parameters were similar between the elafibranor and placebo groups at baseline, and remained stable through Week 52 (**Table**). Median changes from baseline at Week 52 in CysC were 0.00% in the elafibranor group and 3.54% in the placebo group, while changes in SCr were 0.010 mg/dL and −0.009 mg/dL, respectively. Median eGFR (MDRD) remained stable in both treatment groups through Week 52. Median change

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from baseline through Week 52 in CysC-based eGFR (CKD-EPI) was similar between the elafibranor (0.00 mL/min/1.73 m^2) and placebo (−3.40 mL/min/1.73 m^2) groups. No changes in CysC-based eGFR (CKD-EPI) were found to be associated with corresponding changes in SCr and eGFR (MDRD). Acute kidney injury was reported in 3 patients (2.8%) receiving elafibranor and in 1 (1.9%) receiving placebo; 2 out of 3 patients with acute kidney injury receiving elafibranor had type 2 diabetes. **Conclusion:** No clinically meaningful changes in renal function, assessed through CysC levels and CysC-based eGFR, were observed in patients with PBC who received elafibranor compared with placebo, even when SCr levels increased. Overall, these data suggest that elafibranor, evaluated through 52 weeks, is associated with kidney function stability.

Table. Median values of renal parameters at baseline and Week 52

	Elafibranor (N=108)		Placebo (N=53)	
Parameter	**Baseline**	**Week 52**	**Baseline**	**Week 52**
CysC, mg/L	0.990	0.980	0.925	0.955
SCr, mg/dL	0.728	0.719	0.710	0.719
eGFR (CKD-EPI CysC), mL/min/1.73 m^2	74.1	76.6	79.6	78.1
eGFR (MDRD), mL/min/1.73 m^2	84.5	84.0	87.0	84.0

Baseline was defined as the last non-missing measurement on or prior to the first dose of the randomized study medication. CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; CysC: cystatin C; eGFR: estimated glomerular filtration rate; MDRD: Modification of Diet in Renal Disease; SCr: serum creatinine.

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4350 | CHARACTERISTICS OF PATIENTS WITH PRIMARY BILIARY CHOLANGITIS TREATED WITH URSODEOXYCHOLIC ACID, OBETHICHOLIC ACID AND FENOFIBRATE AT OUR TERTIARY LIVER TRANSPLANT CENTER

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Background: Primary Biliary Cholangitis (PBC) is a rare and chronic cholestatic disease of the bile ducts of autoimmune etiology. As a result of the cholestatic liver disease, patients can progress to cirrhosis with risk for hepatic decompensation and mortality. Around 40% of patients treated with Ursodeoxycholic acid (UDCA), the first line agent, have incomplete biochemical response to UDCA and will need a second line agent added, obeticholic acid (OCA) or fibrates. While there are studies that show the improvement in PBC with these agents, there is little data to show the progression of fibrosis on TE and events of hepatic complications over time on these agents. Here, we aim to see if there is a significant difference in liver stiffness progression between the three agents and also aim to evaluate variations in hepatic complications for the various treatment regimens. **Methods:** A retrospective analysis was done of all patients seen at our tertiary care transplant center with PBC from January 1st 2004 to December 31st 2023. Patients were included if they had one or more TE completed during this time period and excluded if they had overlap of autoimmune hepatitis. For the included patients, every TE completed from 2015 to December 2023 was collected. Events of hepatic complications included presence of non-bleeding varices, variceal bleeding, ascites, hepatic encephalopathy, listing or receiving liver transplant. A statistical analysis was then done to assess significance between hepatic complications and TE liver stiffness scores (kPa) for patients treated with UDCA, OCA and fenofibrate. **Results:** Baseline Mean liver stiffness for patient on URSO monotherapy was 8.9 kPa, URSO + OCA was 10.5 kPa, a difference that was not statistically significant. (p-value 0.15) Mean liver stiffness at a patients first follow-up TE for UDCA monotherapy was 7.0 kPa, UDCA+OCA was 10.7 kPa, which is statistically significant (p-value 0.02). Mean follow-up time from baseline to first TE was 7.74 years with a SD of 3.97 years. When change in liver stiffness from baseline was done for each patient and a mean change was derived, it was found that URSO monotherapy was + 0.8 kPa, UDCA+OCA was -0.9 kPa. (Table 1) There was also no statistically significant difference in hepatic complications in the various treatment groups. **Conclusion:** Based on our retrospective analysis, we find that patients on UDCA when compared to UDCA+OCA had a statistically significantly lower kPa value on their first TE after baseline with a mean follow-up period of 7.74 years +/- 3.97 years. The UDCA group did show overall score worsening with +0.8 kPa and the UDCA+OCA group showed improvement at -0.9 kPa. UDCA+OCA could provide a benefit over time when compared to UDCA monotherapy, however a larger sample size may be needed for statistical significance.

	UDCA + OCA + Fibrate	OCA only	UDCA + Fibrate	UDCA + OCA	UDCA only	p-value[1]
Patient Count – Baseline[2]	1	2	4	20	126	--
Liver Stiffness - baseline (kPA) (mean, median)	6.1, 6.1	9.8, 9.8	7.5, 5.7	10.5, 8.1	8.9, 6.8	0.15
Patient Count – Follow-up[3]	1	1	3	15	62	--
Liver Stiffness – 1st Follow-up (kPA) (mean, median)	6.8, 6.8	11.3, 11.3	5.6, 4.3	10.7, 8.9	7.0, 6.2	0.02
Liver Stiffness – change from baseline (kPA) (mean, median)	-0.7, -0.7	-4.6, -4.6	2.3, 1.0	-0.9, -0.3	0.8, 0.5	0.19

[1]From Wilcoxon rank-sum test, comparing URSO only to URSO + OCA. Other sample sizes were too small. [2]N=153, excludes 6 patients with no meds and 2 patients with conflicting baseline/follow-up dates. [3]N=82, excludes 3 patients with no meds and 2 patients with conflicting baseline/follow-up dates

Table 1: Baseline and progression of liver stiffness (kPa) with varying treatment regimens of UDCA, OCA and Fibrates.

Disclosures: Vishwajit Kode: Nothing to Disclose, Sylvia Sudat: Science Corporation: Spouse is employed by this company and has stock options, Yinwen Wang: Nothing to Disclose, Kidist Yimam: Nothing to Disclose

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4351 | SAFETY AND EFFICACY OF HK-660S VERSUS PLACEBO IN PATIENTS WITH PRIMARY SCLEROSING CHOLANGITIS: A RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PHASE 2A TRIAL

Woo Hyun Paik

Background: Primary sclerosing cholangitis (PSC) is a rare, chronic liver disease characterized by inflammation and fibrosis of the bile ducts, leading to biliary cirrhosis, liver failure, and associated cancers. A clinical unmet need persists for medications capable of modulating the progression of PSC. This study aimed to assess the clinical feasibility of HK-660S (beta-lapachone) in PSC. **Methods:** In this randomised, double-blind, placebo-controlled, parallel-group phase 2 trial conducted across four tertiary institutions, participants were assigned in a 2:1 ratio to receive either 100 mg of HK-660S or a placebo twice daily for 12 weeks. The primary endpoints were the reduction in serum alkaline phosphatase (ALP) levels and the percentage of participants showing improvements in PSC severity, as determined by magnetic resonance cholangiopancreatography (MRCP). Secondary endpoints included changes in liver stiffness and any adverse events. **Results:** The analysis included 21 patients, 15 of whom received HK-660S, and 6 received a placebo. MRCP improvements were observed in 13.3% of the HK-660S group, with no improvements in the placebo group. HK-660S treatment resulted in a 15.2% reduction in mean ALP levels, compared to a 6.6% reduction in the placebo group. A stratified ad-hoc analysis based on baseline ALP levels showed a statistically significant response in the HK-660S group among those with ALP levels greater than twice the upper limit of normal (ULN), with a 50% responder rate (P = 0.05, Fisher's exact test). Additionally, 26.7% of the HK-660S group showed improvements in liver stiffness measurements, with no improvements in the placebo group. HK-660S was generally well-tolerated. **Conclusion:** This 12-week proof-of-concept trial demonstrated that HK-660S is well-tolerated among PSC patients and may improve bile duct strictures and decrease serum ALP levels. Further randomised trials with long-term follow-up are necessary to confirm these promising results.

Disclosures: Woo Hyun Paik: Curome Bioscience: Grant/Research Support

4352 | THE PROGNOSTIC ROLE OF LIVER STIFFNESS MEASURED BY TRANSIENT ELASTOGRAPHY (TE) IN PATIENTS WITH PRIMARY BILIARY CHOLANGITIS IN PREDICTING HEPATIC DECOMPENSATION

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Background: Primary Biliary Cholangitis (PBC) is a rare, chronic cholestatic disease of the intrahepatic small bile ducts of autoimmune etiology that can lead to inflammation, cholestasis and cirrhosis overtime, with increased risk of liver failure and mortality. Assessment of liver fibrosis during patient management will help identify patients at risk of progression of PBC to consider optimizing their PBC treatment. TE has been studied in other liver diseases to correlate well with histologic fibrosis stages. There is also limited evidence indicating that liver stiffness measured by TE identifies patients at risk of complications from PBC. Here, we aim to assess our experience of TE in a diverse Northern California PBC patient population and its ability to serve as a non-invasive prognostic tool. **Methods:** A retrospective analysis was done of all patients seen at our tertiary care transplant center with PBC from January 1st 2004 to December 31st 2023. Patients were included if they had one or more TE completed during this time period and excluded if they had overlap of autoimmune hepatitis. For the included patients, every TE completed from 2015 (when our center acquired the TE machine) to December 2023 was collected. Events of hepatic complications assessed included presence of non-bleeding varices, variceal bleeding, ascites, spontaneous bacterial peritonitis (SBP), hepatic encephalopathy, listing or receiving liver transplant. In addition, validated prognostic scoring models: Fibrosis-4 (FIB-4), AST to Platelet Ratio Index (APRI) score, Global PBC score and UKPBC scores were collected within 3 months of each TE study and tracked over time. A statistical analysis was then done to assess if the baseline liver stiffness or it's change over time predicted hepatic complications. The correlation between liver stiffness and validated PBC prognostics scores was assessed. **Results:** Baseline liver stiffness in patients with hepatic complications was higher than in those without

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complications p-value < 0.01. Patient with hepatic complications did have a greater change in liver stiffness scores than those without hepatic complications, but this difference was not statistically significant p-value of 0.14. The prognostic value of TE liver stiffness only correlated with Fib-4 and APRI. (Table 1) **Conclusion:** Liver stiffness on TE is a useful tool in the assessment of patients with PBC as a higher score indicates higher hepatic complications. In our small cohort of patients that had multiple TE there was a trend towards significance and a larger cohort may have achieved statistical significance. TE may serve as a prognostic tool for hepatic complications and our results support the prognostic roles of TE in managing patients with PBC.

Table 1. Correlation between risk scores and median liver stiffness at baseline, N=88.

	Correlation	95% CI
FIB-4	0.55	0.39, 0.68
APRI	0.47	0.29, 0.62
UK-PBC (5-year)	0.08	-0.13, 0.28
UK-PBC (10-year)	0.08	-0.13, 0.28
UK-PBC (15-year)	0.08	-0.14, 0.28
GLOBE-PBC	0.11	-0.11, 0.31

Disclosures: Vishwajit Kode: Nothing to Disclose, Sylvia Sudat: Science Corporation: Spouse is employed by this company and has stock options, Yinwen Wang: Nothing to Disclose, Kidist Yimam: Nothing to Disclose

4353 | ASSOCIATION BETWEEN NUDT15 POLYMORPHISM AND THIOPURINE-INDUCED LEUKOPENIA IN PATIENTS WITH AUTOIMMUNE HEPATITIS

Yoonseok Lee[1] Oh Sang Kwon[1] SEUNG KAK SHIN[1] Yun Soo Kim[1] Ju Hyun Kim[1]

[1]Gachon University Gil Medical Center

Background: Nudix hydrolase 15 (NUDT15) polymorphism affects to the level of thioguanine nucleotides (TGNs) that are active form of azathioprine (AZA) and major toxic material to bone marrow. Poor or intermediate metabolizer of NUDT15 polymorphism is associated with increased level of TGNs and AZA induced leukopenia. This study aimed to investigate the incidence of NUDT15 polymorphism and whether the polymorphism is associated with AZA induced leukopenia in Korean patients with autoimmune hepatitis (AIH). **Methods:** Ninety-nine patients were diagnosed as AIH from March 2009 to January 2023 in Gachon University Gil Hospital, Incheon, Korea. AIH was confirmed by the criteria based on the publication of international AIH group. A total of 52 patients who underwent NUDT15/thiopurine S-methyltransferase (TPMT) genotyping and AZA treatment were retrospectively enrolled. The genotypes of NUDT15 and TPMT, and the association of each genotypes with leukopenia (WBC count <3,000/□) were investigated. **Results:** The median age at diagnosis of AIH was 64 years. The ratio of female to male was 44 to 8. The genotypes of NUDT15 were wild (1*/1*, 73.1%), 1*/3*(6, 11.7%), 1*/2*(3, 5.9%), and 1*/5*(2, 3.9%). The NUDT15 genotypes of intermediate metabolizer were 1*/3* and 1*/2*. There was no poor metabolizer of NUDT15. Only 1 of 9 intermediate metabolizer showed leukopenia during AZA treatment. The genotypes of TPMT were wild (1*/1*, 96.2%), 1*/6*(1, 1.9%), and 1*/38*(1, 1.9%). There was no intermediate and poor metabolizer of TPMT. There were 6 patients who showed leukopenia during AZA treatment. Among them, only 1 patient had NUDT15 genotype of 1*/3* and stop AZA. The other 5 patients had wild type of NUDT15/TPMT and continued AZA without complication. **Conclusion:** NUDT15 polymorphism was observed in 21% of patients. Most of intermediate metabolizer of NUDT15 did not induce leukopenia. Genotyping of NUDT15 is needed in case of leukopenia during AZA treatment.

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4354 | CIRCULATING THROMBOSPONDIN-2 (TSP2) PREDICTS LIVER FIBROSIS AND FIBROGENESIS IN PATIENTS WITH PRIMARY SCLEROSING CHOLANGITIS

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Background: Primary sclerosing cholangitis (PSC) is still one of the most complex and least understood liver diseases. In contrast to other autoimmune diseases of the liver, no effective therapy is yet available. Furthermore, there is a lack of biomarkers for the objective assessment of disease severity and fibrosis stage. Thrombospondin-2 (TSP2) is a matricellular protein with multiple functions in organ fibrosis, including TGFb1 activation and angiogenesis. TSP2 expression is highly upregulated in active fibrogenesis, as shown in patients with fibrotic fatty liver disease, lung fibrosis and in a pilot intervention study of primary sclerosing cholangitis (PSC). We therefore hypothesised that TSP2 may serve as a novel direct serum marker of fibrosis in PSC. **Methods:** A sandwich ELISA assay measuring the C-terminal domain of TSP2 was established using the combination of recombinantly expressed protein, monoclonal and polyclonal antibodies. Sensitivity and specificity were optimized, with intra- and inter assay variations for serum or plasma below 10% and 15%, respectively. 142 subjects with PSC were selected from the biobank of the University Medical Centre Hamburg-Eppendorf and included in the study. Liver stiffness was measured by transient elastography (TE). In addition, parameters of disease activity and patient outcome were assessed. **Results:** Baseline patient characteristics are displayed in Table 1. Serum TSP2 levels showed a strong positive correlation with stages of liver fibrosis, as determined by TE ($r=0.631$, $p<0.001$). Patients with F2-4 fibrosis displayed significantly higher levels of TSP2 compared with fibrosis F0-1 (144 vs 62.4 ng/ml). These differences were more pronounced comparing fibrosis F3-4 with F0-2 (161 vs 62.4 ng/ml). The AUROC value to distinguish fibrosis F2-4 from F0-1 and F3-4 from F0-2 was 0.78 and 0.83, respectively, significantly superior to FIB-4 index (0.76) and APRI (0.77). Over a median follow-up of 70 months, 12.2% of patients underwent liver transplantation. In a Cox model adjusted for age, sex, PSC-associated colitis, ALT, ALP and BMI, TSP2 remained independently associated with transplant-free survival. Patients with baseline serum TSP2 levels indicating advanced fibrosis (≥73.1ng/ml) had significantly reduced transplant-free survival (Log Rank $p<0.001$). **Conclusion:** The matricellular fibrosis marker TSP2 was highly associated with the presence of advanced fibrosis and predict transplant-free survival, suggesting its potential as a dynamic prognostic biomarker and to predict the effect of antifibrotic interventions for PSC. Confirmation of these findings in larger, prospective cohorts is on the way.

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4355 | REAL-WORLD EVALUATION OF ALKALINE PHOSPHATASE NORMALIZATION IN PATIENTS WITH PRIMARY BILIARY CHOLANGITIS RECEIVING TREATMENT

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Background: Primary biliary cholangitis (PBC) is a progressive chronic inflammatory liver disease that imposes a significant clinical burden. Alkaline phosphatase (ALP) normalization has been associated with improved liver-related clinical outcomes; however, real-world evidence of treatment effectiveness on ALP normalization among individuals with PBC remains limited. This study evaluated ALP normalization rates associated with starting ursodeoxycholic acid (UDCA), obeticholic acid (OCA) and concurrent UDCA/OCA treatment and assessed the association between ALP normalization and clinical outcomes in a large national sample representing a range of private and public payers in the U.S. **Methods:** A retrospective intent-to-treat analysis was conducted using Komodo's Healthcare Map claims linked with laboratory data of individuals with PBC, aged ≥ 18 years, who started treatment with UDCA monotherapy, OCA (with or without prior UDCA treatment), or concurrent UDCA/OCA therapy between 09/01/2018 and 09/30/2023 following a 12-month baseline period. ALP normalization rates were evaluated within 6-24 months from the start (index) date of treatment. Cox proportional hazard models, adjusting for baseline clinical and demographic characteristics, estimated the association between

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ALP normalization at first ALP test after 6 months and clinical outcomes. **Results:** A total of 22,487 individuals initiating UDCA monotherapy (N=19,003), OCA (N=1,903) or concurrent UDCA/OCA therapy (N=1,581) were identified. Study participants' average age was 62 years, 87% were female and their average Charlson Comorbidity Index was 4.9. In a subgroup of patients with ALP test at index (N=2,072) ALP normalization rates remained low in the 6-24-month follow-up. Most notably, among those with baseline ALP levels ≥1.67xULN (N=626), ALP normalization rates were 34%, 16%, and 12%, in the UDCA, OCA, and the concurrent UDCA/OCA group, respectively (p<.001). ALP normalization was associated with a reduced risk for mortality, incident liver transplantation, decompensated cirrhosis, ascites requiring treatment, hospitalization, and composite clinical endpoints (Table 1). **Conclusion:** Despite available treatments with UDCA and second-line OCA, ALP normalization is uncommon among individuals with PBC. Given the benefits of ALP normalization in terms of reduced clinical burden and mortality, additional effective and well-tolerated treatments are needed for individuals with PBC.

Table 1. Association between ALP normalization at first ALP test after 6 months following treatment initiation and subsequent clinical outcomes using Cox proportional hazard models

Outcome	Hazard Ratio (95% CI)[1]	p value
Death	0.59 (0.42-0.83)	.003
Liver transplant	0.30 (0.16-0.55)	<.001
Decompensated cirrhosis	0.36 (0.26-0.50)	<.001
Ascites requiring treatment	0.22 (0.14-0.34)	<.001
Hospitalization[2]	0.22 (0.06-0.86)	.029
Composite end point 1[3]	0.51 (0.37-0.50)	<.001
Composite end point 2[4]	0.44 (0.33-0.59)	<.001

[1] Adjusting for type of treatment at index, age, gender, race/ethnicity, cirrhosis at baseline, presence of select comorbidities at baseline (system lupus erythematosus, autoimmune hepatitis, rheumatoid arthritis, autoimmune thyroid disease, Raynaud syndrome, Sjogren syndrome, hypercholesterolemia, urinary tract infection, and pruritus), Charlson Comorbidity Index score, payer type, and days from index to first ALP test after 6 months.

[2] With a primary diagnosis of any of the following: esophageal or gastric variceal bleeding, hepatic encephalopathy, or spontaneous bacterial peritonitis.

[3] Composite endpoint 1: Death or liver transplantation.

[4] Composite endpoint 2: Death, liver transplantation, hospitalization (with a primary diagnosis of esophageal/gastric variceal bleeding, hepatic encephalopathy, or spontaneous bacterial peritonitis), or ascites requiring treatment.

CI, Confidence Intervals

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4356 | THE CLINICAL CHARACTERISTICS AND VALIDATION OF PROGNOSTIC MODELS FOR PRIMARY SCLEROSING CHOLANGITIS: A MULTI-CENTER POPULATION-BASED COHORT STUDY ACROSS MAINLAND CHINA

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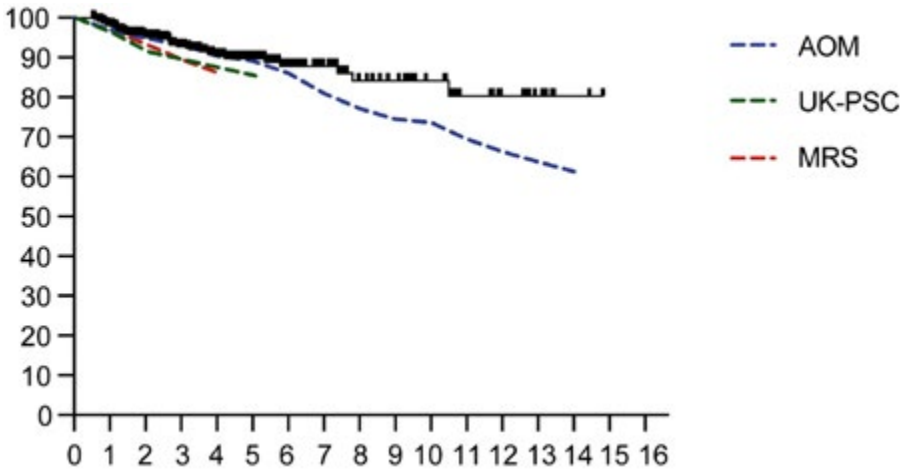
Background: Real-world study regarding prognosis and clinical course in primary sclerosing cholangitis (PSC) in China are sparse. We aimed to describe PSC demographic features and its long-term outcomes in China. By the way, we were curious about the validation and assessing the utility of three prognostic models including Mayo risk score (MRS), UK-PSC score(RS), and the Amsterdam-Oxford model (AOM). **Methods:** We utilized the fine-recorded database of patients with PSC referred to 13 centers in China from June 2002 to March 2024. Clinical and laboratory data were collected from the time of PSC diagnosis until the last visit or time of LT or death. The discriminatory performance of the prognostic scores was assessed with concordance statistics at diagnosis and 2 years later. The AOM(up to 14 years), MRS(up to 4 years), and RS(up to 2 years) were calculated yearly intervals following PSC diagnosis. **Results:** Data were obtained from 559 patients with PSC of whom 529 patients met the inclusion criteria. The mean age was 42.5±15.2 years, and 54.6% were male. Classic PSC subgroup was defined as the diagnosis of large duct PSC in 307 (58%) patients. During a median follow-up of 63.3 (interquartile range 25-87) months, 47 patients underwent liver transplantation, and 48 patients died. At diagnosis, the overall discriminatory performance of the MRS, expressed as the concordance statistic, for predicting the risk of death or LT was 0.693 (95% confidence interval [CI] 0.634-0.753) versus 0.627 (95% CI 0.565-0.688) for the AOM and 0.693 (95% CI 0.637-0.749) for the RS_{ST}. At 2 years after diagnosis, the concordance statistic was 0.801 (95% CI 0.729-0.873) for the MRS versus 0.702 (95% CI 0.609-0.796) for the AOM and 0.753(95% CI 0.675-0.831) for the RS_{LT}. Moreover, the observed and median predicted survival for various risk prediction models are shown in Figure 1. In the estimates of survival, both the UK-PSC and MRS tended to underestimate transplant-free survival, while AOM demonstrated the best calibration, as the difference in predicted versus observed survival was generally less up to 4 years. **Conclusion:** As the first large multicenter cohort of patients with PSC in China, patients with PSC are increasingly being diagnosed with a milder phenotype. We assessed the performance of various published risk prediction models. We demonstrate that all prognostic scores evaluated (MRS, UK-PSC, and AOM) have adequate discriminatory performance and good prediction accuracy, while AOM demonstrated the best calibration.



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4357 | PRIMARY BILIARY CHOLANGITIS HAS THE WORST QUALITY OF LIFE WHEN COMPARED TO AUTOIMMUNE HEPATITIS AND PRIMARY SCLEROSING CHOLANGITIS

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Background: Autoimmune liver diseases (AILDs) profoundly affect health-related quality of life (HRQoL) due to symptoms like fatigue, abdominal distress, and mood disorders. Despite advancements, no studies differentiate HRQoL among AILDs. This large eight-year single-center cohort study is the first to describe the impact of AILDs on HRQoL from the perspectives of patients living with these rare conditions. **Methods:** We prospectively collected the Chronic Liver Disease Questionnaire (CLDQ) and EuroQol-5 Dimension (EQ-5D-5L), yielding 1214 responses from 466 AILD patients from January 2017 to May 2024. Exclusions were prior transplant, acute liver failure, or life expectancy <6 months. CLDQ has 6 domains: abdominal symptoms (AS), fatigue (FA), systemic symptoms (SS), activity (AC), emotional function (EF), and worry (WO). EQ-5D-5L has 5 items, an index (UI) and a visual scale. CLDQ scores were compared using Kruskal-Wallis with post hoc testing. The EQ-5D UI was derived using the US Stata preference value set, using Chi-square for frequency comparisons and ANOVA for UI means. **Results:** We included 230 AIH, 118 PSC, and 118 PBC patients. AIH subjects completed more questionnaires (mean 3.2). PBC had female predominance (85.3%), while PSC were primarily white (84.3%). ALT and AST were highest in AIH (medians 70.3 and 59), whereas ALP was highest in PBC (median 165.5). 26% of AIH patients had cirrhosis, significantly more than their AILD counterparts. Total CLDQ was lower in PBC compared to AIH and PSC (5.25, 5.54, and 5.59; respectively, P<0.001), as was the EQ-5D UI (0.85, 0.88, 0.88; respectively, P<0.001). In PBC, every CLDQ domain was significantly worse except WO. FA scored the lowest in PBC, with tiredness, decreased energy, and daytime sleepiness as the worst symptoms (3.91, 4.20, 4.27; respectively), significantly lower than AIH and PSC (P<0.001). In EQ-5D-5L, every item was significantly worse in PBC except anxiety/depression, with pain in PBC being the worst overall (mean 1.45, P<0.001). PSC had the best AC outcomes in CLDQ and the best self-care scores in EQ-5D-5L (5.61 and 1.01; respectively). AIH had fewer AS in CLDQ and lower pain scores in EQ-5D-5L (5.90 and 1.34; respectively). **Conclusion:** Analyzing the day-to-day experiences of patients with the most common AILDs revealed that PBC is the most affected, especially in tiredness, daytime sleepiness, concentration deficit, and diffuse pain. Our limitations were the need for robust validation of CLDQ and EQ-5D-5L in AILDs, potential recall bias, and lack of evaluation of polypharmacy and sleep apnea. Clinicians should prioritize PBC management, using more frequent follow-ups or a structured approach like the TRACE algorithm. We encourage translational research to better understand PBC pathophysiology and design new treatment plans.

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Table 1A. Baseline cohort characteristics

	AIH (n=230)	PBC (n=118)	PSC (n=118)
Number of Responses per subject, Mean (SD)	3.2 (2.5)	2.4 (1.7)	2.5 (1.9)
Age (Years), Mean (SD)	52.1 (15.3)	54.7 (12.2)	43.9 (13.9)
Gender Female, N (%)	173 (75.4)	101 (85.3)	61 (51.3)
Race, N (%)			
White	140 (61)	90 (76.1)	99 (84.3)
Black/AA	14 (8.0)	1 (0.9)	9 (8.3)
Hispanic	21 (12)	9 (8.3)	5 (4.6)
East Asian	271 (3.9)	25 (1.6)	73 (3.4)
BMI (kg/m²), Mean (SD)	28.0 (5.7)	28.9 (4.9)	26.2 (4.9)
Diagnostic laboratory values, Median (IQR)			
ALT (U/L)	70.5 (32 – 203.5)	40.5 (27 – 65)	51 (25 – 89)
AST (U/L)	59 (32 – 158.5)	37 (26 – 52)	42 (26 – 52)
ALP	109 (77 – 189)	165.5 (118 – 271)	160.5 (109 – 313)
Creatinine (mg/dL)	0.8 (0.7 – 0.9)	0.8 (0.7 – 0.9)	0.8 (0.7 – 0.9)
Bilirubin (mg/dL)	0.6 (0.4 – 1.5)	0.5 (0.4 – 0.8)	0.5 (0.4 – 0.8)
Albumin (g/dL)	4.1 (3.6 – 4.5)	4.3 (4.3 – 4.6)	4.3 (4 – 4.6)
Secondary liver disease, N (%)			
AIH	-	19 (16.1)	3 (0.03)
PBC	47 (20.4)	-	0 (0)
PSC	10 (4.4)	0 (0)	-
MASLD	38 (16.5)	17 (14.4)	11 (9.3)
Cirrhosis, N (%)	60 (26.1)	21 (17.8)	18 (15.3)
Liver stiffness Kpa, Mean (SD)	9.7 (2.3)	8.4 (1.2)	9.1 (3.2)
Liver biopsy at diagnosis, N (%)	57 (24.6)	22 (18.5)	26 (22.0)
Stage, N (%)			
0 – 2	34 (60.2)	15 (68.2)	18 (69.2)
3 – 4	23 (38.8)	7 (32.8)	6 (30.8)
Grade, N (%)			
1 – 2	27 (47.4)	12 (54.5)	17 (65.4)
3 – 4	30 (52.6)	10 (45.5)	9 (34.6)

Abbreviations: SD: Standard Deviation; N: Number; AIH: Autoimmune Hepatitis; PBC: Primary Biliary Cholangitis;PSC: Primary Sclerosing Cholangitis; MASLD: Metabolic-associated Steatotic Liver Disease IQR: Interquartile Range

Table 1B. EQ-5D-5L scores by autoimmune liver disease group

	AIH	PBC	PSC	P-value
Mobility problems				
None	582 (80.16%)	190 (80.17%)	228 (89.76%)	0.01
Some	142 (19.56%)	47 (19.8%)	26 (10.2%)	
Many	1 (0.14%)	0 (0%)	0 (0%)	
Mean score, (SD)	**1.20 (0.40)**	**1.20 (0.40)**	1.10 (0.30)	0.001
Self-care problems				
None	684 (94.21%)	221 (87.00%)	249 (98.03%)	0.03
Some	37 (5.10%)	14 (5.90%)	4 (1.57%)	
Many	0 (0%)	0 (0%)	0 (0%)	
Mean score, (SD)	1.05 (0.22)	**1.06 (0.24)**	1.01 (0.12)	0.03
Usual activities				
None	563 (77.54%)	179 (75.53%)	207 (81.50%)	0.50
Some	150 (20.66)	53 (21.46%)	44 (17.32%)	
Many	12 (1.65%)	5 (2.11%)	3 (1.18%)	
Mean score, (SD)	1.24 (0.46)	**1.27 (0.49)**	1.20 (0.43)	0.20
Pain				
None	481 (66.25%)	139 (58.65%)	164 (64.57%)	0.05
Some	228 (31.40%)	89 (37.71%)	88 (34.65%)	
Many	17 (2.34%)	8 (3.38%)	1 (0.14%)	
Mean score, (SD)	1.34 (0.53)	**1.45 (0.56)**	1.35 (0.49)	0.05
Anxiety/Depression				
None	489 (63.36%)	138 (58.23%)	162 (63.78%)	0.10
Some	214 (29.48%)	92 (38.82%)	83 (32.68%)	
Many	19 (2.62%)	6 (2.53%)	7 (2.76%)	
Mean score, (SD)	1.40 (0.53)	**1.44 (0.55)**	1.38 (0.54)	0.06
EQ-5D-5L overall health VAS, Mean (SD)	77.28 (17.58)	**72.26 (20.34)**	76.6 (17.60)	<0.01
EQ-5D-5L Index (US), Mean (SD)	0.88 (0.15)	**0.85 (0.16)**	0.88 (0.13)	<0.01

Abbreviations: EQ-5D-5L: EuroQol 5 Dimension 5 Level; VAS: Visual Analogue Scale. Bold indicates significant worst outcomes in means.

Table 1C. CLDQ scores by autoimmune liver disease group

CLDQ Domains, Mean (SD)	AIH	PBC	PSC	P-value
Abdominal symptoms	5.90 (1.23)	**5.58 (1.47)**	5.74 (1.23)	<0.001
Fatigue	4.98 (1.38)	**4.49 (1.46)**	4.99 (1.37)	<0.001
Systemic symptoms	5.61 (1.16)	**5.29 (1.14)**	5.77 (1.06)	<0.001
Activity	5.82 (1.31)	**5.61 (1.45)**	6.02 (1.19)	<0.001
Emotional function	5.48 (1.18)	**5.27 (1.09)**	5.54 (1.16)	0.01
Worry	5.71 (1.36)	5.57 (1.31)	5.74 (1.37)	0.20
Total CLDQ Score	5.54 (1.10)	**5.25 (1.04)**	5.59 (0.99)	<0.001

Abbreviations: CLDQ: Chronic Liver Disease Questionnaire. Bold indicates significant worst outcomes.

Table 1D. Detailed composition of the CLDQ questions and symptoms by autoimmune liver disease group

	AIH	PBC	PSC	P-value
Abdominal symptoms				
Q1. Abdominal bloating	5.72 (1.53)	**5.23 (1.88)**	5.57 (1.44)	<0.001
Q5. Abdominal Pain	6.04 (1.33)	5.87 (1.48)	5.89 (1.42)	0.10
Q17. Abdominal Discomfort	5.93 (1.39)	**5.66 (1.60)**	5.75 (1.37)	0.02
Fatigue				
Q2. Tiredness	4.44 (1.69)	**3.91 (1.75)**	4.29 (1.76)	<0.001
Q4. Sleepiness during the day	4.72 (1.64)	**4.27 (1.61)**	4.59 (1.60)	<0.001
Q8. Decreased strength	5.56 (1.71)	**5.21 (1.76)**	5.88 (1.57)	<0.001
Q11. Decreased energy	4.81 (1.72)	**4.20 (1.77)**	4.83 (1.74)	<0.001
Q13. Drowsiness	5.34 (1.47)	**4.88 (1.69)**	5.34 (1.50)	<0.001
Systemic symptoms				
Q3. Bodily pain	5.29 (1.69)	**4.94 (1.94)**	5.31 (1.74)	0.01
Q6. Shortness of breath	5.97 (1.43)	**5.89 (1.46)**	6.30 (1.12)	<0.001
Q21. Muscle cramps	5.73 (1.49)	5.64 (1.48)	5.91 (1.39)	0.07
Q23. Dry mouth	5.09 (1.9)	**4.53 (2.15)**	5.53 (1.63)	<0.001
Q27. Itching	6.00 (1.48)	**5.39 (1.81)**	5.76 (1.79)	<0.001
Activity				
Q7. Eating less than you would like	5.86 (1.76)	5.70 (1.81)	5.86 (1.76)	0.39
Q9. Trouble carrying heavy objects	5.52 (1.81)	**5.22 (1.94)**	6.03 (1.51)	<0.001
Q14. Bothered by diet restrictions	6.10 (1.49)	**5.86 (1.76)**	6.19 (1.73)	0.02
Emotional function				
Q10. Anxiety	5.27 (1.66)	5.09 (1.67)	5.11 (1.71)	0.17
Q12. Unhappiness	5.75 (1.35)	**5.57 (1.33)**	5.80 (1.47)	<0.001
Q15. Irritability	5.64 (1.29)	**5.29 (1.40)**	5.63 (1.25)	<0.001
Q16. Difficulty sleeping at night	4.68 (1.89)	4.64 (1.81)	4.88 (1.81)	0.21
Q19. Mood swings	5.85 (1.38)	**5.60 (1.41)**	6.02 (1.30)	0.02
Q20. Difficulty in falling asleep	5.28 (1.77)	5.16 (1.69)	5.41 (1.63)	0.20
Q24. Depression	5.89 (1.44)	**5.65 (1.46)**	5.94 (1.52)	0.03
Q26. Concentration problems	5.46 (1.63)	**5.03 (1.77)**	5.52 (1.63)	<0.001
Worry				
Q18. Worries about the impact of the liver disease	5.57 (1.73)	5.65 (1.60)	5.71 (1.57)	0.45
Q22. Worries that symptoms will become a major problem	5.46 (1.64)	5.21 (1.67)	5.49 (1.65)	0.06
Q25. Worries about worsening of the condition	5.51 (1.59)	**5.21 (1.68)**	5.50 (1.68)	0.02
Q28. Worries about never feeling better	5.81 (1.53)	**5.51 (1.76)**	5.82 (1.63)	0.02
Q29. Worries about liver transplant availability	6.22 (1.49)	6.27 (1.41)	6.19 (1.43)	0.79

Bold indicates significant worst outcomes.

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4358 | ECONOMIC BURDEN OF PATIENTS WITH PRIMARY BILIARY CHOLANGITIS AND EXPERIENCING FATIGUE OR PRURITUS IN THE UNITED STATES

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Background: Pruritus and fatigue are two common symptoms associated with primary biliary cholangitis (PBC). This study assessed economic burden among patients (pts) with PBC and associated fatigue or pruritus relative to other pts with PBC in the United States. **Methods:** This retrospective cohort study used IQVIA PharMetrics® Plus data (2016–2022). Pts diagnosed with PBC with concurrent pruritus were selected to form the pruritus case cohort, and those with concurrent fatigue were selected to form the fatigue case cohort. Matched controls, comprising pts with PBC without either pruritus or fatigue, were selected to match with cases at a 1:1 ratio. Matching criteria included sex, insurance type, region, PBC duration, and post-index follow-up duration. The

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index date for cases was defined as a random diagnosis date for pruritus or fatigue after the initial PBC diagnosis; the index date for controls was a random medical visit date. The 1-year continuous enrollment period before and after the index date constitutes the baseline and study period, respectively. Annual healthcare resource utilization and healthcare costs during the study period were compared between respective cases and matched controls using generalized estimating equation (GEE) models. **Results:** A total of 760 pruritus cases/matched controls and 1,839 fatigue cases/matched controls were included. Mean age at index was ~56 years for pruritus and fatigue groups; >88% were female. Cases were associated with higher comorbidity burden at baseline than matched controls: mean Charlson comorbidity index was 3.0 vs. 2.5 for pruritus and 3.2 vs 2.6 for fatigue. A small proportion of pts were on obeticholic acid at baseline (4%–12% across cohorts). During the study period, total healthcare costs were significantly higher in cases than controls (**Table**). Differences in total costs were $40,536 and $42,515 comparing pruritus and fatigue cases with controls, respectively, and largely driven by inpatient (IP) costs ($24,571 and $25,746 for pruritus and fatigue cases with controls, respectively). A greater proportion of cases had at least one IP visit during the study period; the annualized number of IP visits were significantly higher in cases than controls. **Conclusion:** This study found that pts with PBC and pruritus or fatigue have a substantial economic burden relative to other pts with PBC. The findings highlight the importance of considering symptoms and comorbidities when managing pts with PBC, as recommended by treatment guidelines.

Table. Annual healthcare resource utilization and costs during 1-year study period comparing pruritus and fatigue cases with matched controls

	Pruritus groups				Fatigue groups			
Annual healthcare costs, 2023 USD								
	Cases (N = 760)	**Matched controls (N = 760)**	**Mean cost difference (95% CI) case vs. control**	**P-value**	**Cases (N = 1,839)**	**Matched controls (N = 1,839)**	**Mean cost difference (95% CI) case vs. control**	**P-value**
Total costs	56,822 ± 121,129	16,286 ± 27,857	40,536 (33,860, 47,131)	<0.001	61,167 ± 192,389	18,651 ± 44,874	42,515 (36,074, 48,931)	<0.001
Total medical costs	39,897 ± 113,911	8,044 ± 18,767	31,853 (25,723, 37,921)	<0.001	46,552 ± 183,892	10,288 ± 39,848	36,264 (30,050, 42,453)	<0.001
IP	26,276 ± 102,074	1,705 ± 11,811	24,571 (19,126, 29,943)	<0.001	29,223 ± 173,335	3,477 ± 34,480	25,746 (19,804, 31,649)	<0.001
ER	1,575 ± 7,547	490 ± 1,990	1,085 (673, 1,488)	<0.001	2,038 ± 6,935	510 ± 2,154	1,527 (1,295, 1,757)	<0.001
OP	11,985 ± 22,245	5,782 ± 12,201	6,203 (4,925, 7,501)	<0.001	15,184 ± 32,937	6,236 ± 13,351	8,949 (7,785, 10,128)	<0.001
Other[a]	61 ± 227	66 ± 417	-6 (-31, 20)	0.659	107 ± 525	65 ± 467	42 (19, 66)	<0.001
Total pharmacy costs	16,925 ± 28,693	8,242 ± 18,979	8,683 (6,849, 10,498)	<0.001	14,615 ± 36,363	8,364 ± 18,699	6,251 (4,999, 7,503)	<0.001
Annual healthcare resource utilization								
	Cases (N = 760)	**Matched controls (N = 760)**	**OR/IRR (95% CI) case vs. control**	**P-value**	**Cases (N = 1,839)**	**Matched controls (N = 1,839)**	**OR/IRR (95% CI) case vs. control**	**P-value**
Number and proportion of patients								
IP	158 (20.8%)	46 (6.1%)	3.9 (2.8, 5.5)	<0.001	420 (22.8%)	132 (7.2%)	3.8 (3.1, 4.6)	<0.001
ER	322 (42.4%)	213 (28.0%)	1.9 (1.5, 2.3)	<0.001	859 (46.7%)	511 (27.8%)	2.3 (2.0, 2.6)	<0.001
OP	760 (100%)	760 (100%)	-	-	1,837 (99.9%)	1,836 (99.8%)	1.3 (0.1, 39.5)	0.866
Number of visits								
IP	0.4 ± 1.3	0.1 ± 0.3	6.1 (4.3, 8.7)	<0.001	0.5 ± 1.4	0.1 ± 0.3	5.8 (4.7, 7.0)	<0.001
ER	1.0 ± 2.3	0.5 ± 1.0	2.1 (1.7, 2.6)	<0.001	1.2 ± 3.0	0.5 ± 0.9	2.6 (2.3, 3.0)	<0.001
OP	26.6 ± 24.3	16.3 ± 15.3	1.6 (1.5, 1.8)	<0.001	29.9 ± 26.0	16.7 ± 16.1	1.8 (1.7, 1.9)	<0.001

Values are reported as mean ± SD or n (%).[a]Other medical services included durable medical equipment (DME) and dental or vision care (DVC).

Abbreviations: CI, confidence interval; ER, emergency department; IP, inpatient; IRR, incidence rate ratio; OP, outpatient; OR, odds ratio; SD, standard deviation; USD, United States dollar.

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4359 | ENHANCING THE DETECTION OF AUTOIMMUNE HEPATITIS ONSET THROUGH NATURAL LANGUAGE PROCESSING AND DATABASE PROGRAMMING IN A LARGE HEALTH RECORD DATABASE

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Background: Autoimmune hepatitis (AIH) typically involves early steroids tapered to a steroid-sparing agent guided by frequent laboratory testing for biochemical improvement. Studies examining the early treatment of AIH, the most active period of drug titration, are limited in part due to difficulties in reliably pinpointing the date of diagnosis in large electronic health records. Here we ask whether database programming and natural language processing might enable reliable ascertainment of the date of diagnosis for AIH in a large electronic health record. **Methods:** A large electronic health record database for the Mass General Brigham healthcare system (Research Patient Data Registry) was queried for patients with at least one ICD code for AIH (1987-2022). A previously validated algorithm (Bitterman 2021) for identifying AIH cases in administrative datasets was adapted as an initial screen to algorithmically identify the date of diagnosis (algorithm 1). Second, patients were selected who had a liver biopsy recorded within 6 weeks of their AIH ICD diagnosis (algorithm 2). Patients were further narrowed by corticosteroid administration within 6 weeks of the biopsy date (algorithm 3). Then, the simplified AIH score was applied using natural language processing of liver pathology reports (algorithm 4). Finally, patients were selected if their AST/ALT within 6 weeks of biopsy was greater than 2.5 times the upper limit of normal. Algorithm positive predictive value was adjudicated by review of 20 randomly selected charts for each algorithmic iteration, where date of diagnosis was defined by the treating hepatologist. **Results:** Of 81,811 patients identified in the initial query, Bitterman (algorithm 1) identified 848 cases with a positive predictive value of 0.53. Each subsequent improvement increased the positive predictive value (Table 1). The inclusion of the simplified AIH score led to the largest absolute increase in positive predictive value. Algorithm 5 identified the index AIH event in 94 patients: the mean age was 54.7 years, 75.5% were female and 76.6% identified as white. **Conclusion:** Database programming and algorithmic evaluation of the simplified AIH score enables the reliable detection of the date of diagnosis of AIH. We anticipate our algorithmic approaches will accelerate construction of large AIH cohorts to better understand and optimize initial treatment strategies for this rare disease.

	Bitterman Algorithm†	Biopsy	Prednisone start	Simplified AIH Score	AST/ALT 2.5x ULN	N	PPV
Algorithm 1	+	-	-	-	-	848	0.53
Algorithm 2	+	+	-	-	-	438	0.61
Algorithm 3	+	+	+	-	-	275	0.74
Algorithm 4	+	+	+	+	-	116	0.95
Algorithm 5	+	+	+	+	+	94	1.00

† Bittermann T, Mahmud N, Lewis JD, Levy C, Goldberg DS. Validating a novel algorithm to identify patients with autoimmune hepatitis in an administrative database. Pharmacoepidemiol Drug Saf. 2021;30(9):1168-74. doi: 10.1002/pds.5291.

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4360 | FXR AGONIST INT-787 INHIBITS INFLAMMATION, FIBROSIS, SENESCENCE, AND APOPTOSIS ARREST IN HUMAN CHOLANGIOCYTES MODELING PSC

Francesca De Franco[1] Daniela Passeri[1] Sanjay Kansra[2] Luciano Adorini[2] Mary Erickson[2] Roberto Pellicciari[1]

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Background: Cholangiocyte senescence is present in all stages of primary sclerosing cholangitis (PSC) and is associated with disease severity. Activation of the farnesoid X receptor (FXR), a ligand-activated nuclear hormone receptor that is a key regulator of bile acid homeostasis, has demonstrated clinical benefit in patients with PSC, as shown by the sustained reduction in serum alkaline phosphatase levels induced by multiple FXR agonists, including obeticholic acid in a phase 2 trial (NCT02177136). In the present in vitro study, we determined the therapeutic effect of the semisynthetic bile acid analog and potent FXR agonist INT-787 in a human cholangiocyte cell line (H69) model of PSC. **Methods:** H69 cells were cultured (50,000 cells/well, Innoprot P10654) with glycochenodeoxycholic acid (GCDCA) 500 μM or lipopolysaccharide (LPS) 100 ng/mL and INT-787 1 μM and 10 μM for 24 hours. Gene expression was measured by real-time quantitative reverse transcription polymerase chain reaction. H69 cells (30,000 cells/well) treated with GCDCA 50 μM or LPS 100 ng/mL and INT-787 1 μM and 10 μM for 5 days were stained with a beta-galactosidase staining kit (Cell Signaling #9860). Statistical significance was determined using a 1-way analysis of variance with Dunnett's multiple comparison test. **Results:** INT-787 markedly reduced (P<0.001) the GCDCA-induced expression of transforming growth factor beta-1 (TGFβ-1), a promoter of fibrosis, and plasminogen activator inhibitor-1 (PAI-1), a serpin involved in inflammation and senescence. INT-787 also decreased (P<0.001) expression of p21, a cyclin-dependent kinase inhibitor that regulates cell cycle progression and inhibits apoptosis, and trended toward restoring expression of cytokeratin 7, a histological marker of cholestasis. INT-787 promoted expression of the proliferation marker Ki-67 and increased Bcl-xS expression in apoptosis-resistant H69 cells. INT-787 reduced senescence in GCDCA-treated H69 cells. Similarly, INT-787 decreased (P<0.001) LPS-induced TGFβ-1, PAI-1, and vascular cell adhesion molecule 1 expression in H69 cells. INT-787 also normalized p21 expression with LPS and decreased LPS-induced senescence. **Conclusion:** Human immortalized H69 cholangiocyte cells treated with GCDCA or LPS successfully mimicked the in vivo PSC phenotype. Treatment with INT-787 reduces cellular senescence, apoptosis resistance, inflammation, and fibrosis. INT-787 represents a promising candidate for the clinical treatment of PSC.

Disclosures: Francesca De Franco: Nothing to Disclose, Daniela Passeri: Nothing to Disclose, Sanjay Kansra: Nothing to Disclose, Luciano Adorini: Nothing to Disclose, Mary Erickson: Intercept Pharmaceuticals: Employee, Roberto Pellicciari: Nothing to Disclose

4361 | AUTOIMMUNE HEPATITIS AND VITAMIN D DEFICIENCY: A NATIONWIDE PERSPECTIVE

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[1]NYC Health + Hospitals | Lincoln - Weill Cornell Medical College, New York, NY, USA, [2]University of Missouri-Kansas City, Kansas-City, MO, USA, [3]Saint Louis University, St. Louis, MO, USA, [4]University of Missouri-Kansas City, MO, USA, [5]Stanford University, Stanford, Palo Alto, CA, USA

Background: Vitamin D deficiency is linked to worse outcomes in patients with chronic liver diseases. However, data in patients with autoimmune hepatitis (AIH) remain limited. We aimed to assess the impact of vitamin D deficiency on the outcomes of individuals with AIH. **Methods:** This retrospective cohort study used the TriNetX research network to identify patients with AIH. Patients were matched using propensity score matching and stratified to sufficient vitamin D levels (e.g., 25 (OH) D3 ≥ 30 ng/mL), vitamin D insufficiency (25 (OH) D3: 20-29.9 ng/mL), and vitamin D deficiency (e.g., 25 (OH) D3 < 20 ng/mL). The primary outcome was the all-cause mortality among adult patients with AIH. Secondary outcomes included acute hepatic failure, liver transplantation, all-cause hospitalizations, all-cause critical care admissions, and trends of liver chemistries. Outcomes were adjusted for demographics (e.g., age, gender, race/ethnicity), clinical covariates (e.g., body mass index, celiac disease, immunosuppressive therapy) and social determinants of adverse health outcomes. **Results:** A total of 1186 AIH patients with vitamin D deficiency were identified and propensity matched with 1186 patients with normal vitamin D levels. Patients with vitamin D deficiency had significantly increased odds for all-cause mortality compared to

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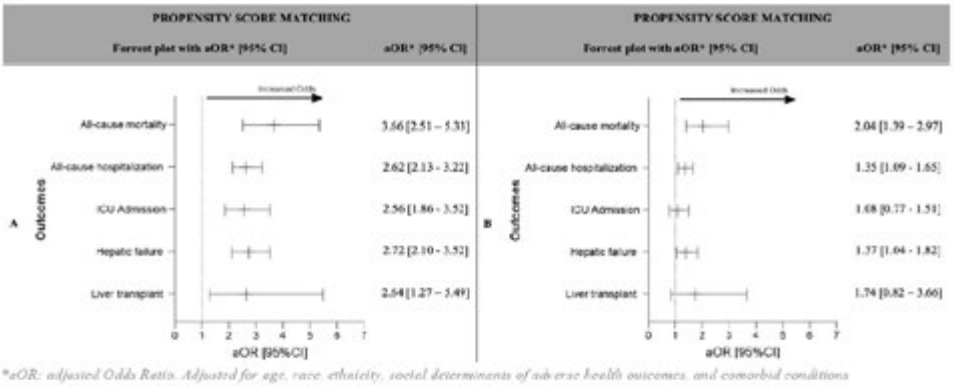
those with normal levels (adjusted Odds Ratio (aOR) = 3.66, 95%CI: 2.51 – 5.33), all-cause hospitalizations (aOR = 2.62, 95%CI: 2.13 – 3.22), critical care unit admissions (aOR = 2.56, 95%CI: 1.86 – 3.52), hepatic failure (aOR = 2.72, 95%CI: 2.10 - 3.52), and liver transplant (aOR = 2.64, 95%CI: 1.27 – 5.49) as compared to those with normal vitamin D levels (Figure 1). Furthermore, patients with vitamin D deficiency had significantly higher levels of AST at 3-month (p=0.001), 6-month (p=0.009), and 12-month follow-up (p=0.032), ALT at 1-month (p=0.042) and 3-month follow-up (p=0.041) (**Figure 2-A**), TB (p<0.001) and INR (p≤0.01, except at 3-months), and lower levels of albumin (p<0.001) and platelets (p<0.001), without overall significant differences in creatinine levels on further follow up visits. Last, when comparing patients with normal vitamin D levels and those with vitamin D insufficiency, we found no significant differences (**Figure 2-B**). **Conclusion:** Our study using real-world evidence showed a strong correlation between vitamin D deficiency and worse outcomes among individuals with AIH, including increased rates of all-cause hospitalizations, ICU admissions, acute hepatic failure, liver transplantation, and mortality. Therefore, patients with AIH may benefit from periodic screening for vitamin D deficiency, in accordance with AASLD guidelines, and treatment of individuals with concomitant vitamin D deficiency. Larger prospective cohort studies are warranted to validate these findings.



*aOR: adjusted Odds Ratio. Adjusted for age, race, ethnicity, social determinants of adverse health outcomes, and comorbid conditions

Figure 1. Propensity score matching analysis for the one-year outcomes of patients with autoimmune hepatitis (AIH) treated with immunosuppressive therapy with concomitant vitamin D deficiency (e.g., 25 (OH) D3 < 20 ng/mL) **(3-A)** or insufficiency (e.g., 25 (OH) D3 levels between 20-29.9 ng/mL) **(3-B)**, as compared to those with normal vitamin D levels (e.g., 25 (OH) D3 ≥ 30 ng/mL).

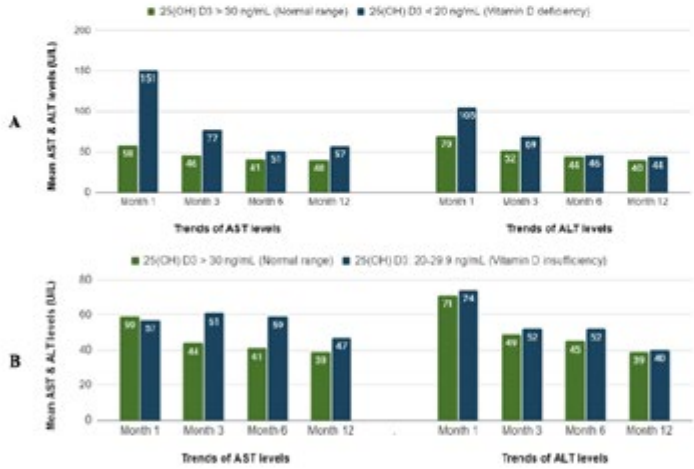


Figure 2. Trends of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) in patients with autoimmune hepatitis at 1-month, 3-month, 6-month, and 12-month following the diagnosis of vitamin D deficiency (e.g., 25 (OH) D3 < 20 ng/mL) or vitamin D insufficiency (e.g., 25 (OH) D3: 20-29.9 ng/mL) after propensity matching. Compared to patients with normal vitamin D (e.g., 25 (OH) D3 ≥ 30 ng/mL), those with vitamin D deficiency had significantly higher mean AST levels at 3-month (p=0.001), 6-month (p=0.009), and 12-month follow-up (p=0.032), higher ALT at 1-month (p=0.042) and 3-month (p=0.041) without significant differences in AST at 1-month (p=0.102), and ALT at 6-month (p=0.664) and 12-month follow-up (p=0.229). **(Figure 2-A)**. On the other hand, patients with vitamin D insufficiency had no significant differences in AST and ALT levels at 1-month, 3-month, 6-month, and 12-month follow-up as compared to those with normal vitamin D levels **(Figure 2-B)**

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4362 | PATIENTS WITHOUT BASELINE PRURITUS WHO INITIATE TREATMENT WITH OCA HAVE SIMILAR RISK OF DEVELOPING TREATMENT-EMERGENT PRURITUS AS THOSE WHO ARE NOT ON TREATMENT WITH OCA

David Jones[1] Aparna Goel[2] Ann Moore[3] Jing Li[4] Darren Wheeler[4] Christopher White[4] David Victor[5]

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Background: Pruritus (PRU) is common in patients (pts) with primary biliary cholangitis (PBC). Obeticholic acid (OCA) is approved for second-line therapy in pts with PBC who have inadequate response or intolerance to ursodeoxycholic acid. In POISE, a 12-month, randomized, double-blind, placebo (PBO)-controlled phase 3 study, PRU was more common with OCA than PBO. However, more than half of pts had PRU at baseline (BL), and 38% of pts in the PBO group reported PRU during the study. To delineate the impact of OCA on PRU, the objective of this post hoc analysis was to examine the incidence of treatment (tx)-emergent PRU in a subgroup of pts without BL PRU from POISE. **Methods:** In POISE, pts were randomized to PBO (n=73), OCA titration (n=70), or OCA 10 mg (n=73). Since OCA 10 mg is not an approved starting dose, only pts in the PBO and OCA titration without BL PRU groups were included in the analysis. Based on response and tolerability at 6 months, pts in the titration group remained on OCA 5 mg (n=36) or were up-titrated to 10 mg (n=33) for the remaining 6 months. Tx-emergent PRU was defined as any PRU that newly appeared in this subset of pts without BL PRU following study drug initiation, with mild, moderate, or severe PRU assessed by the study investigator. Patient-reported visual analog scale (VAS) scores for PRU were assessed at BL, week 2, and months 3, 6, 9, and 12. **Results:** A total of 59 pts did not have PRU at BL, including 26 pts in PBO, 14 in OCA 5 mg, and 19 in up-titration to OCA 10 mg **(Figure)**. During the 12-month tx period, PRU was reported in 21 pts (9 PBO, 4 OCA 5 mg, and 8 OCA up-titration). Most pts experienced PRU that was mild to moderate in severity. Five pts developed severe PRU, with 1 in PBO, 1 in OCA 5 mg, and 3 in OCA up-titration (1 was considered unlikely to be related to the study drug). Most pts (n=11) did not use any interventions for PRU regardless of tx arm. For pts who received an intervention, PRU was manageable with pharmacological and non-pharmacological interventions. Cholestyramine (n=1), study drug holiday (n=1), and a combination of cetirizine and study drug holiday (n=1) resolved severe PRU. Two cases of severe PRU resolved without any intervention. There were no study discontinuations due to PRU across all tx groups. Mean VAS scores were lower in pts without BL PRU across all tx groups and remained in the mild range through 12 months. **Conclusion:** OCA-treated pts without BL PRU have a similar risk of developing tx-emergent PRU compared with non–OCA-treated pts.

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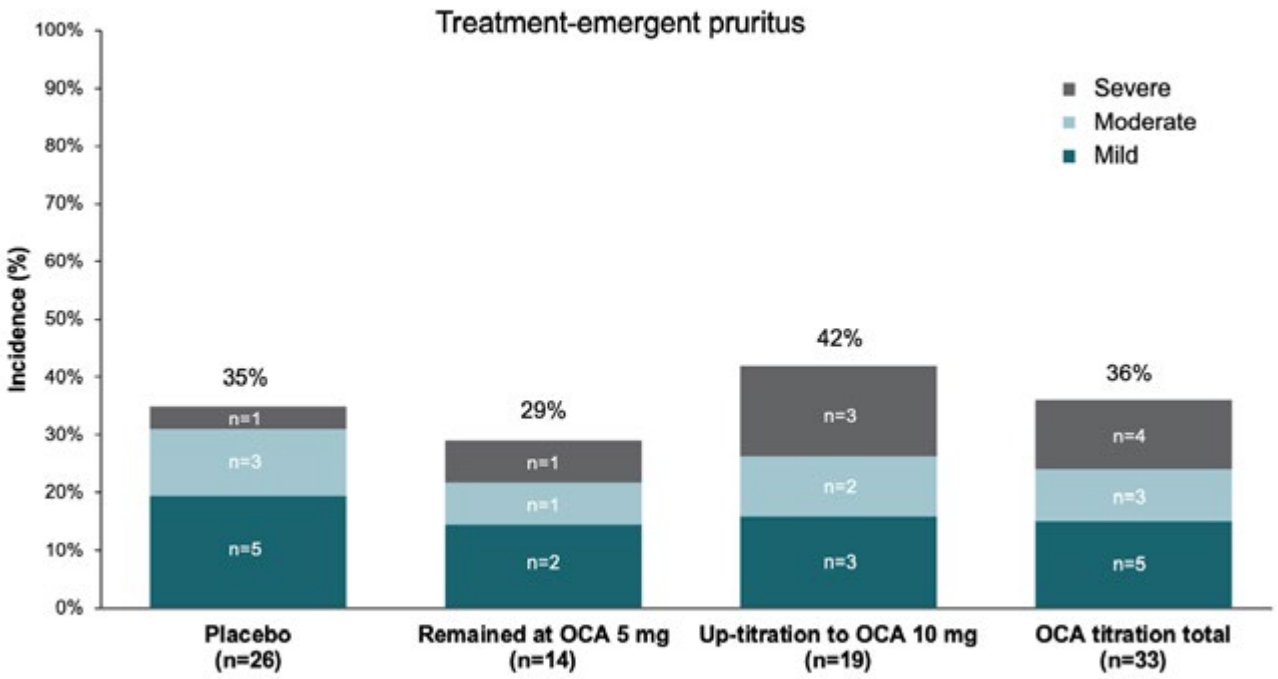
Figure. Treatment-emergent pruritus and maximum severity in patients without baseline pruritus



Patients reporting more than one adverse event of pruritus were counted only once using the highest severity.

Abbreviation: OCA, obeticholic acid.

Disclosures: David Jones: Nothing to Disclose, Aparna Goel: Nothing to Disclose, Ann Moore: Abbvie: Speaking and Teaching, Gilead: Speaking and Teaching, Jing Li: Nothing to Disclose, Darren Wheeler: Nothing to Disclose, Christopher White: Intercept Pharmaceuticals: Employee, David Victor: Nothing to Disclose

4363 | PHARMACOKINETIC AND PHARMACODYNAMIC INTERACTION OF OBETICHOLIC ACID AND BEZAFIBRATE IN HEALTHY VOLUNTEERS

Jennifer Burkey[1] Karen Brown[1] Heng Zou[1] Jennifer Boston[2] Mary Erickson[1]

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Background: Obeticholic acid (OCA), a selective farnesoid X receptor agonist, received accelerated approval for treating adults with primary biliary cholangitis (PBC) with an inadequate response to ursodeoxycholic acid (UDCA). Bezafibrate (BZF), a pan-peroxisome proliferator-activated receptor agonist, is a potential anticholestatic agent for patients with PBC who respond inadequately to UDCA. The efficacy of combined OCA and BZF is being evaluated in phase 2 studies. Here, we describe the pharmacokinetic (PK) and pharmacodynamic (PD) interaction of OCA and BZF in healthy volunteers. **Methods:** This phase 1, randomized, controlled study assessed increasing OCA and BZF doses in a stepwise manner over 3 consecutive periods: BZF alone, BZF/OCA combination, and OCA alone. Subjects were randomized to receive single and multiple doses of BZF (100 mg to 400 mg) with or without OCA (5 mg to 30 mg) or matching placebo. PK parameters were calculated from plasma concentrations of BZF, BZFOH, BZF-glucuronide, OCA, glyco-OCA, tauro-OCA, and total OCA. PD assessments included 7α-hydroxyl-3-one-4-cholestene (C4), fibroblast growth factor 19 (FGF19), and total endogenous bile acids (BA). **Results:** Of the 84 subjects enrolled, 81, 78, and 71 completed the BZF alone, BZF/OCA combination, and OCA alone periods, respectively. The combination was generally well tolerated. There

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was minimal to no accumulation of BZF with multiple dosing, and OCA had minimal effect on the exposure of BZF or its metabolites at any dose tested. When single doses of OCA and BZF were coadministered, BZF had no consistent impact on total OCA concentrations. With multiple dosing, higher levels of total OCA, unconjugated OCA, glyco-OCA, and tauro-OCA were observed, with variable increases in magnitude. OCA suppressed C4 in a dose-dependent manner. BZF alone did not suppress C4 levels; however, when combined with OCA 5 mg, it augmented C4 suppression. This effect was not seen at the higher OCA doses, suggesting C4 suppression at these doses is already maximal with OCA alone. OCA alone tended to increase fibroblast growth factor 19 levels, and coadministration with BZF did not modify this effect. BA data were highly variable, with no consistent effects observed. **Conclusion:** BZF increased total OCA plasma levels with high variability, while OCA had a slight effect on BZF levels. Together, they reduced C4 to a larger extent than either alone at a low dose of OCA, suggesting potential incremental benefit of their combination on reducing BA synthesis compared with OCA alone.

Disclosures: Jennifer Burkey: Intercept Pharmaceuticals: Employee, Karen Brown: Nothing to Disclose, Heng Zou: Nothing to Disclose, Jennifer Boston: Nothing to Disclose, Mary Erickson: Intercept Pharmaceuticals: Employee

4364 | LONGITUDINAL TRENDS IN HEPATIC BIOMARKERS IN PATIENTS WHO INITIATED TREATMENT WITH OBETICHOLIC ACID VS CONTROL PATIENTS IN THE HEROES STUDY

Bettina Hansen[1] M. Alan Brookhart[2] Yucheng (Julia) Chu[3] Leona Bessonova[3] Darren Wheeler[3] Sangeeta Sawhney[3] David Jones[4] Gideon Hirschfield[1]

[1]Toronto Centre for Liver Disease and TGHRI, University Health Network, Toronto, Ontario, Canada, [2]Duke University, Durham, North Carolina, USA, [3]Intercept Pharmaceuticals, Morristown, New Jersey, USA, [4]Newcastle University, Newcastle upon Tyne, UK

Background: In the real-world HEROES study (NCT05292872), analysis of patients with primary biliary cholangitis (PBC) in Komodo's Healthcare Map claims database showed that treatment with obeticholic acid (OCA) significantly reduced the risk of hospitalization for hepatic decompensation, liver transplant, or death. A trial emulation design was used wherein the decision to initiate or not initiate OCA treatment (ie, presence or absence of an OCA claim) at eligible clinic visits corresponded to the index date(s) for the OCA and non-OCA (control) arms, respectively. Standardized morbidity ratio weighting was used to adjust for imbalances in patient characteristics at index. Patients were censored at treatment change, loss to follow-up, or end of study. The objective of the current study was to analyze trends and changes in hepatic biomarkers over time among patients in the HEROES study, overall and in the subgroup indicated for OCA treatment per United States Prescribing Information guidelines (USPI; May 2022 version). **Methods:** Mean serum concentrations and change from baseline in alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and total bilirubin (TB) were analyzed in patients who had laboratory data during follow-up. **Results:** Baseline biomarker data were available for 403 OCA and 405 control indexes in the overall population and 308 OCA and 310 control indexes in the USPI subgroup. In general, biomarker levels over time in the overall population **(**Figure 1A) were similar to those in the USPI subgroup **(**Figure 1B). Mean ALT, AST, ALP, and TB levels were consistently lower in the OCA group (blue data points) compared with the non-OCA group over time (red data points). Overall, the mean percent change from baseline at month 48 in ALT, AST, ALP, and TB levels was –36.9%, –12.2%, –34.5%, and –8.4%, respectively, in the OCA group and –14.9%, –5.5%, –12.6%, and +32.5% in the non-OCA group. In the USPI subgroup, the corresponding changes were –36.6%, –9.1%, –35.5%, and –11.0% in the OCA group and –11.3%, –2.6%, –12.3%, and +33.1% in the nonOCA group. **Conclusion:** These changes in hepatic biomarkers in HEROES demonstrate that long-term treatment with OCA in patients with PBC is associated with a sustained improvement in ALT, AST, ALP, and TB levels in real-world clinical practice. Without the use of OCA, biomarker levels may increase over time. These results are similar with biomarker trends from clinical trials of OCA.

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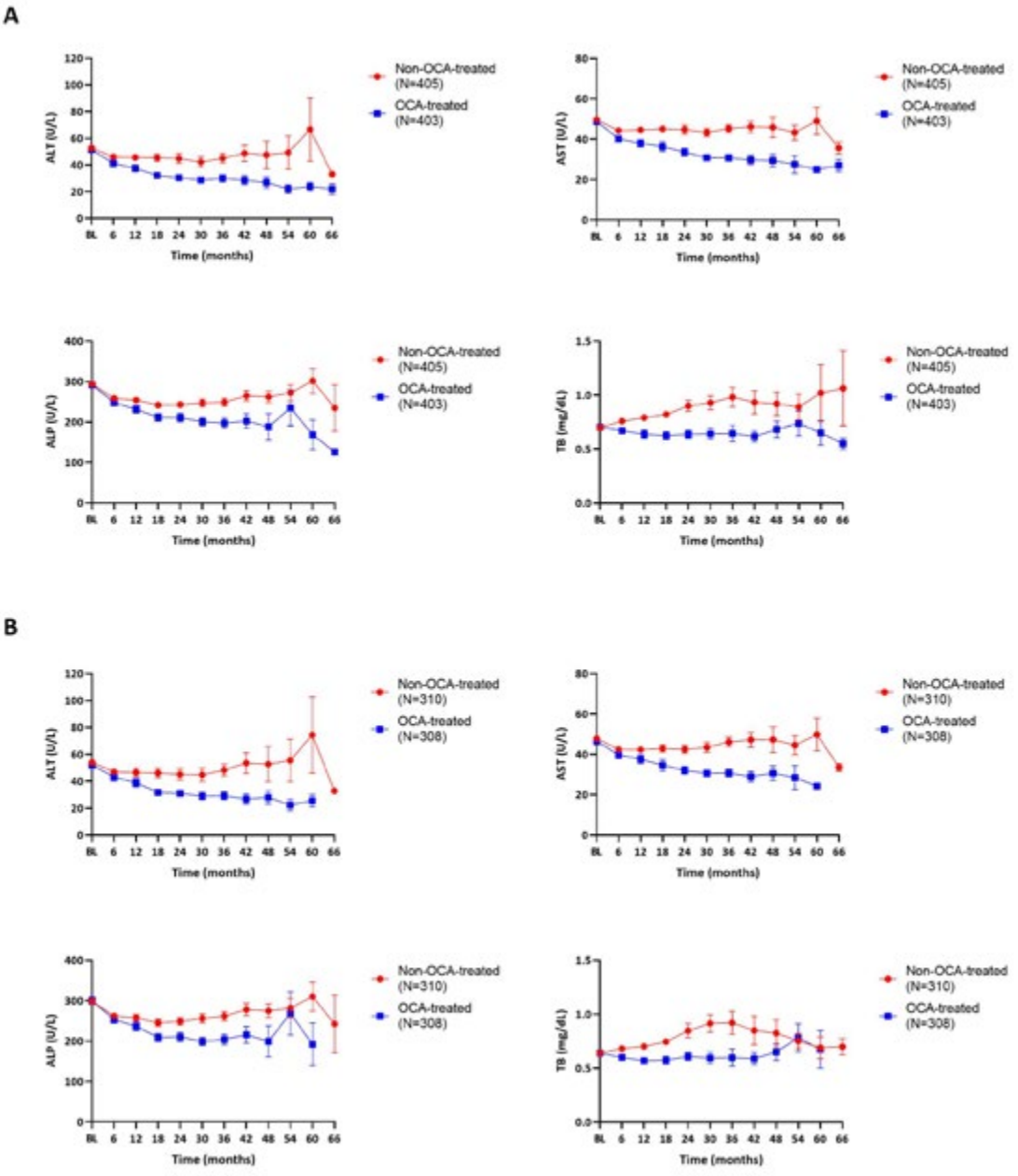
Figure 1. Mean biomarker levels over time by treatment arm (OCA vs non-OCA [control]) in all patients (**A**) and USPI-indicated[a] patients (**B**) in the HEROES study who had laboratory data during follow-up.



[a]May 2022 version. OCA is contraindicated in patients with decompensated cirrhosis (e.g., Child-Pugh B and C), a prior decompensation event, or compensated cirrhosis with evidence of portal hypertension.
Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BL, baseline; OCA, obeticholic acid; TB, total bilirubin; USPI, United States Prescribing Information.

Disclosures: Bettina Hansen: Nothing to Disclose, M. Alan Brookhart: Nothing to Disclose, Yucheng (Julia) Chu: Nothing to Disclose, Leona Bessonova: Nothing to Disclose, Darren Wheeler: Nothing to Disclose, Sangeeta Sawhney: Nothing to Disclose, David Jones: Nothing to Disclose, Gideon Hirschfield: Consultant relationship with Mirum; Has not ended; Consultant relationship with Advanz; Has not ended; Consultant relationship with Chemomab; Has not ended; Consultant relationship with Gilead; Has not ended; Consultant relationship with Kowa; Has not ended; Consultant relationship with Intercept; Has not ended; Consultant relationship with Pliant; Has not ended; Consultant relationship with Falk; Has not ended; Consultant relationship with GSK; Has not ended; Consultant relationship with Ipsen; Has not ended; Consultant relationship with CymaBay; Has not ended

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4365 | CLINICAL AND PROGNOSTIC FACTORS ASSOCIATED WITH INFLAMMATORY BOWEL DISEASE IN ADMIXED MULTIETHNIC PATIENTS WITH PRIMARY SCLEROSING CHOLANGITIS: RESULTS FROM THE BRAZILIAN CHOLESTASIS STUDY GROUP

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Background: Inflammatory bowel disease (IBD) is reported worldwide in 62-81% of patients with primary sclerosing cholangitis (PSC), especially in males and north Europeans. Little is known about the association of IBD and PSC in population from multigenetic ethnic origin. This study aimed to investigate the prevalence of IBD in a cohort of Brazilian patients with PSC and evaluate clinical and prognostic factors associated with concomitant IBD. **Methods:** Data of PSC patients from the Brazilian Cholestasis Study Group database was retrospectively reviewed to compare demographic, clinical, laboratory and transplant-free survival between those with and without IBD. **Results:** After exclusion of 59 (14%) participants with overlap syndrome with autoimmune hepatitis, 359 individuals with PSC were included (56% male, median age 44 [interquartile range {IQR} 33-54] years). IBD was investigated in 298 (83%) participants and diagnosed in 217 (73%), including ulcerative colitis (83%), Crohn's disease (13%) and indeterminate colitis (4%). Male sex frequency was similar in patients with and without IBD (58% *vs* 47%, p=0.073). IBD was more frequently diagnosed in patients without obesity (p=0.035), positive for antinuclear antibody (p=0.006) and positive for anti-smooth muscle antibody (p=0.046). IBD diagnosis occurred before, concomitant or after PSC diagnosis in 59%, 22% and 19% of cases, respectively. IBD was more frequently diagnosed before PSC in participants asymptomatic for liver disease (p=0.017), without advanced liver disease (p=0.017), before liver transplantation (LT) (p<0.001), and negative for antinuclear antibody (p=0.021). In a median follow-up of 69 months (IQR 31-124), LT occurred in 27.7% and cohort mortality was 11.4%. IBD was not associated with the combined outcome of death or LT (p=0.745), neither with transplant-free survival (p=0.902). **Conclusion:** In Brazilian PSC patients, IBD frequency was like that reported in other populations, but with similar distribution between males and females. IBD diagnosis occurred before PSC in most patients, especially those without advanced liver disease. IBD presence was not associated with worse PSC prognosis.

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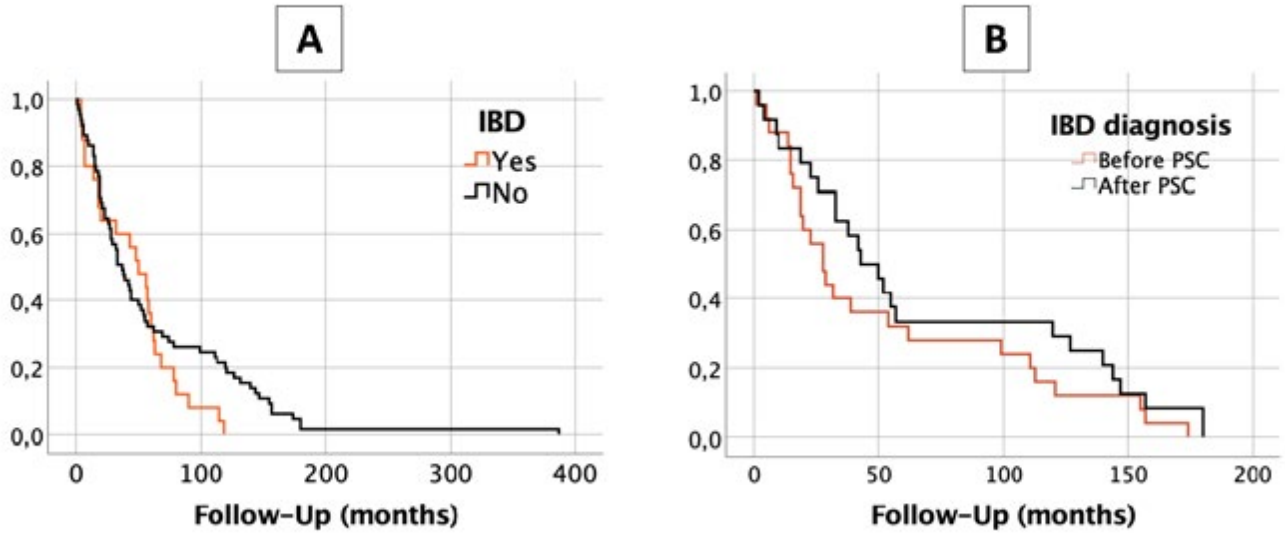
Kaplan-Meier curves of survival free of transplant or death according to inflammatory bowel disease (IBD) diagnosis (figure A) or time of IBD diagnosis (figure B)



Disclosures: Claudia Couto: Nothing to Disclose, Mateus Nardelli: Nothing to Disclose, Luisa Barros: Nothing to Disclose, Diogo Dotta: Nothing to Disclose, Guilherme Cancado: Nothing to Disclose, Luciana Faria: Nothing to Disclose, Vivian Rotman: Nothing to Disclose, Cristiane Villela-Nogueira: Nothing to Disclose, Maria Ferraz: Nothing to Disclose, Rodrigo Rocco: Nothing to Disclose, Guilherme Felga: Nothing to Disclose, Adrielly Martins: Nothing to Disclose, Liana Codes: Nothing to Disclose, Liliana Mendes: Nothing to Disclose, Marlone Silva: Nothing to Disclose, Elodie Hyppolito: Nothing to Disclose, Geyza Gomide: Nothing to Disclose, Izabelle Signorelli: Nothing to Disclose, Maria Beatriz Oliveira: Nothing to Disclose, Claudia Ivantes: Nothing to Disclose, MARIA CHIARA CHINDAMO: Nothing to Disclose, Valeria Borges: Nothing to Disclose, Débora Terrabuio: Nothing to Disclose, Eduardo Cançado: Nothing to Disclose, Paulo Bittencourt: Nothing to Disclose

4366 | EFFECTS OF ELEXACAFTOR-TEZACAFTOR-IVACAFTOR TREATMENT ON LIVER STIFFNESS, CAP VALUES, AND METABOLIC PARAMETERS IN PATIENTS WITH CYSTIC FIBROSIS

Mirella Fraquelli[1] Alessandra Piagnani[2] Fabiola Corti[1] Chiara Lanfranchi[3] Carla Colombo[3]

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Background: Cystic fibrosis (CF) is a chronic, progressive, autosomal recessive disease caused by mutation of a single gene on the long arm of chromosome 7 that codes for the CF transmembrane regulator (CFTR)[1]. This prospective study aimed to assess the modification of some predefined metabolic parameters, liver stiffness and CAP values during treatment with ETI. **Methods:** All consecutive pwCF candidates for starting ETI were enrolled. Demographic, clinical, and biochemical parameters were collected at baseline and after 12 months (T12) from the start of ETI. In addition, liver stiffness (LSM) and controlled attenuation parameter (CAP) measured by vibration-controlled transient elastography (VTCE, Fibroscan, Echosens Paris) were collected at baseline (T0) and after 6 (T6) and 12 months (T12) form ETI start. **Results:** Eighty-six patients (57% males, mean age 21.6 ± 5.6 years) were prospectively enrolled. After one year on ETI a significant improvement in the levels of blood glucose (97.8 ± 23.0 at T0 vs. 86 ± 17 mg/dL at T12, p <0.001), HDL cholesterol (49 ± 13 vs. 56 ± 16.7 mg/dL, p <0.001) and fat liposoluble vitamins levels (p <0.01) was observed. The modification of BMI, LSM and CAP values are summarized in Table 1. In the subgroup of patients with a baseline LSM >7 kPa (n = 16 pts) mean LSM values significantly decreased during follow-up (16 ± 18.6 at T0, 10 ± 11.6 at T6, 6 ± 7.1 kPa at T12, p <0.05) in

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parallel with AST and GGT levels (45 ± 38 vs 37 ± 26 U/L and 59 ± 85 vs. 11 ± 33 U/L, respectively). **Conclusion:** In pwCF, ETI treatment significantly improves several laboratory metabolic parameters. An initial increase in BMI and CAP values is followed by their subsequent reduction at one year of follow-up. Liver stiffness progressively reduced during follow-up in the overall cohort and particularly in patients who showed baseline increased LSM values in parallel with the improvement of both cholestasis and necroinflammation.

		T0 Mean ± SD	T6 Mean ± SD	T12 Mean ± SD	P value
BMI (kg/m²)		21.02 ± 2.7 *	22.2 ±2 ^	22.4 ± 2.73	<0.05
CAP dB/m		197.7 ± 42.9*	230 ± 47.96 ^	209.32 ± 41.25	<0.05
LSM (kPa)	All	6 ± 3.4	5 ± 4.7	5± 3.1§	< 0.001
	> 7	16±18.6	10±11.6°	6±7.1§	<.005
	≤ 7	4.8±7.9	4.7±7.5	4.4±4.0	NS

Disclosures: Mirella Fraquelli: Nothing to Disclose, Alessandra Piagnani: Nothing to Disclose, Fabiola Corti: Nothing to Disclose, Chiara Lanfranchi: Nothing to Disclose, Carla Colombo: Nothing to Disclose

4367 | IDENTIFICATION AND IN VITRO CHARACTERIZATION OF A NOVEL BSEP AND ABCB4 DUAL-ACTING POSITIVE FUNCTIONAL MODULATOR TARGETING THE TREATMENT OF A BROAD RANGE OF HEPATOBILIARY DISEASES ◆

Jennifer Truong[1] Youhwa Jo[1] Bharat Reddy[1] Adrianne Kolpak[1] Eitan Hoch[1] Yong Ren[1] Eric Bell[1] Pui Yee Ng[1] Nathan Fuller[1] John Miller[1] Alastair Garfield[1] Robert Hughes[1]

[1]Rectify Pharmaceuticals, Inc.

Background: Secretion of bile acids into the canalicular space by the ABC transporter, BSEP, is accommodated by phospholipids that form micelles that absorb and help buffer the bile acids delivered into this compartment. Delivery of these phospholipids occurs through the action of the ABC transporter, ABCB4/MDR3. The interplay of these two ABC transporters is essential to a healthy hepatobiliary system and dysregulation results in disease as exemplified in BSEP or ABCB4 deficiency, both of which present as severe early onset cholestatic diseases. We have applied our ABC transporter-focused platform to the problem of toxic bile-mediated disease by pursuing the development of a small molecule dual-acting positive functional modulator (PFM) that increases the function of both BSEP and ABCB4. **Methods:** Freshly isolated primary mouse hepatocytes (PMH) were obtained from MB Biosciences and cryo-preserved primary human hepatocytes (PHH) were obtained from Invitrogen. PMH and PHH cells were cultured in 24-well or 96-well plate formats for the indicated durations. Vehicle or compounds at the indicated concentrations were added to the culture medium. The levels of BSEP and ABCB4 mRNA, protein and functional activity were assessed in response to the different treatments and compared to vehicle control. **Results:** Our screening strategy identified small molecules that selectively increased the levels of BSEP and ABCB4 in an exogenous overexpression system. Results in primary hepatocytes with an advanced member of this scaffold, RTY-694, show increases in BSEP protein levels and bile acid efflux of 130 – 170%, and increases in ABCB4 protein levels and phospholipid efflux of 125 – 140%. In contrast to other small molecules under study for the treatment of hepatobiliary disease such as PPAR, FXR and THR-Beta agonists, RTY-694 provides its benefit not through an increase in mRNAs encoding these proteins, instead acting directly on the proteins themselves. **Conclusion:** In primary hepatocytes, RTY-694 directly and selectively increases both BSEP and ABCB4 protein levels and the cellular efflux of bile acids and phospholipids mediated by these ABC transporters. This mechanism is distinct from other small molecules that act at the mRNA level. As a novel dual-acting BSEP and ABCB4 PFM, RTY-694 has the potential to provide benefit for a broad range of hepatobiliary diseases where dysregulated BSEP and ABCB4 activity leads to cholestasis and cholangitis.

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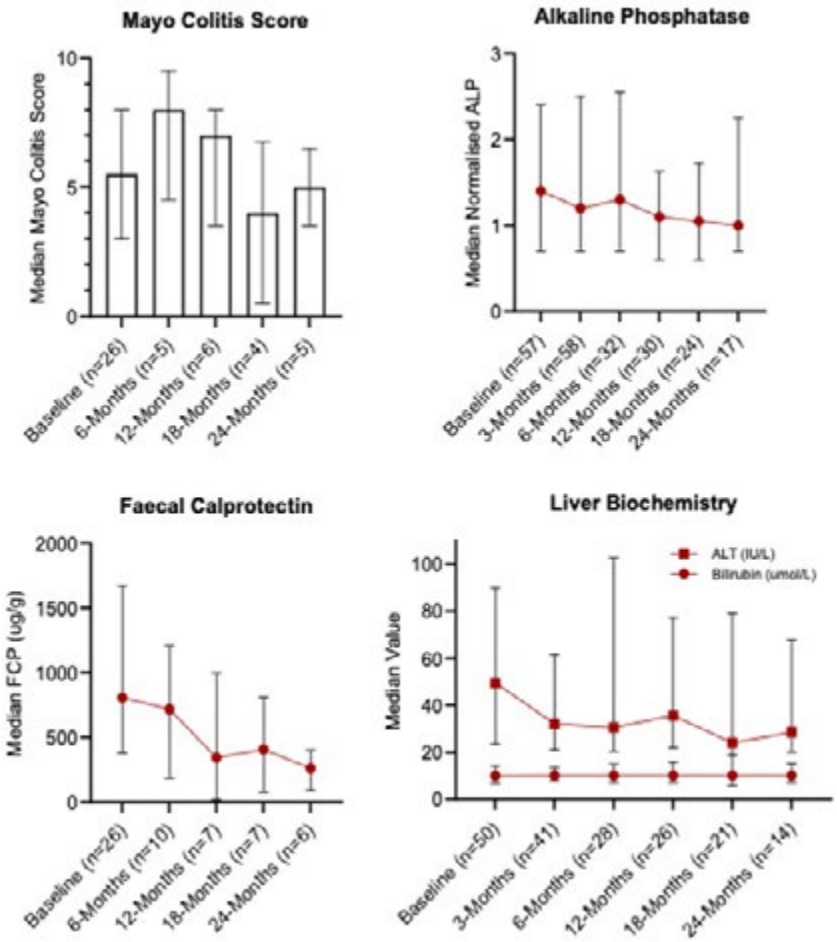

Figure 1. Biochemical and clinical trends over treatment period.

Disclosures: Jennifer Truong: Nothing to Disclose, Youhwa Jo: Nothing to Disclose, Bharat Reddy: Nothing to Disclose, Adrianne Kolpak: Nothing to Disclose, Eitan Hoch: Nothing to Disclose, Yong Ren: Nothing to Disclose, Eric Bell: Nothing to Disclose, Pui Yee Ng: Rectify Pharma: Employee, Black Diamond Therapeutics: Employee, Nathan Fuller: Nothing to Disclose, John Miller: Nothing to Disclose, Alastair Garfield: Nothing to Disclose, Robert Hughes: Nothing to Disclose

4368 | DEEP LIVER PHENOTYPING IN UNEXPLAINED LIVER DISEASE: THE LIPHE ALGORITHM ◆

Anna Sessa[1] Edouard Reizine[1] Giuliana Amaddeo[1] Mélanie Simoes[1] Jeremy Augustin[1] Stefano Caruso[2] Julien Calderaro[1] Alain Luciani[1] Vincent Leroy[1]

[1]APHP Hopital Henri Mondor, [2]INSERM IMRB U955 Team 18

Background: Chronic elevation in liver tests is associated with long-term hepatic events and increased mortality risk. Nearly 10% of cases remain unexplained despite specialized evaluation. We aimed to evaluate the diagnostic performance of deep dedicated liver phenotyping (LIPHE) using innovative technics. **Methods:** This monocentric prospective cohort study includes patients with unexplained chronic liver test elevation referred by gastroenterologists after a comprehensive work-up, including viral serologies, iron and copper evaluation, auto-immunity, ultrasound, CT and/or MRI. The LIPHE algorithm consists of 3 steps: 1.Standardized questionnaire, laboratory tests (systematic auto-antibodies, A1AT, biliary acids, Nt-ProBNP, on-demand REC, A1AT phenotype, dried blood test for enzymatic testing) and multi-parametric MRI (LIPHE-MRI) with fat and iron assessment, T1

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dixon, T2 TSE FS, T2 HASTE, diffusion, vMRE, T1 mapping, T1 VIBE with dynamic vascular phases and hepato-biliary phase and 3D cholangio-MRI. 2. Liver biopsy. 3. New generation sequencing and/or shotgun metagenomic analysis. **Results:** The 1-year interim analysis included 101 patients (median age: 52 years, male: 38%). Liver enzymatic profiles were cytolysis in 36 patients (median ALT: 135 IU/l), cholestasis in 42 patients (median ALP: 150 IU/l), mixed pattern in 23 patients, and other in 9 patients. Cirrhosis was present in 17 patients (17%). Step 1 was performed in all patients, step 2 in 64, and step 3 in 16. Definite diagnosis was made in 70 patients (71%), and probable diagnosis in 21 (21%). Definite diagnoses were: MAFLD (n=7), Porto-sinusoidal vascular disease (n=8), primary biliary cholangitis (n=7), primary sclerosing cholangitis (n=7), congestive cardiac liver (n=4), drug-induced liver injury (n=4), auto-immune hepatitis (n=11), hyperthyroidism (n=2), ABCB4-related genetic cholestasis (n=3), alpha1 antitrypsin deficiency (n=4), biliary hamartomatosis (n=2), benign cyst/tumors (n=2), Alagille syndrome (n=1), miscellaneous (n=8). Main diagnostic contributors were: liver biopsy in 34 cases (37%), LIPHE MRI in 26 cases (29%), laboratory tests in 14 cases (16%), and anamnesis in 14 cases (16%). Diagnosis remained unidentified in 8 patients. **Conclusion:** The LIPHE algorithm may provide an etiologic diagnosis in most patients with non-elucidated liver disease, presenting a wide spectrum of rare and complex liver diseases. Combining standardized questionnaires, laboratory tests, and LIPHE-MRI may avoid liver biopsy in 36% of cases and is a promising first-line approach.

Disclosures: Anna Sessa: Nothing to Disclose, Edouard Reizine: Nothing to Disclose, Giuliana Amaddeo: Nothing to Disclose, Mélanie Simoes: Nothing to Disclose, Jeremy Augustin: Nothing to Disclose, Stefano Caruso: Nothing to Disclose, Julien Calderaro: Nothing to Disclose, Alain Luciani: Nothing to Disclose, Vincent Leroy: Nothing to Disclose

4369 | AN EVALUATION OF ANTI-IL23 THERAPY IN PRIMARY SCLEROSING CHOLANGITIS

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Background: The majority of patients (pts) with primary sclerosing cholangitis (PSC) have inflammatory bowel disease (IBD). This association has fostered several pathogenic hypotheses linking mucosal immunity to hepatobiliary inflammation. A putative therapeutic target along this axis centres on gut-derived IL-17 secretor cell subtypes, which are activated by interleukin (IL)23. Notably, emergent forms of IBD treatment host several anti-IL23 agents, however safety and efficacy data in PSC pts is limited. **Methods:** We conducted a multi-centre study, evaluating treatment experiences with Ustekinumab (a dual anti-IL12/23 agent), Risankizumab, and Mirikizumab (anti-IL23 alone). Data was analysed to determine treatment impact on liver biochemistry; IBD response defined by serial Mayo colitis scores or faecal calprotectin (FCP) values; and treatment-emergent adverse events. **Results:** Data was accrued across eight centres from 66 pts (Ustekinumab, 62; Risankizumab, 4 [n=1 escalated from Ustekinumab] and Mirikizumab, 1) with median treatment time of 9 months (IQR 5-24). The majority of pts were men (63%; n=42) with a median age at PSC diagnosis of 24y (IQR 17-36). The predominant PSC phenotype was large duct (73%; n=49), with two pts having cirrhosis, 13% (n=7) being transplant recipients, and 66% (n=44) having an IBD phenotype consistent with ulcerative colitis. At baseline, the median FCP and Mayo colitis scores were 810ug/L (IQR 369-1727; n=33/66) and 5 (IQR3-8; n=31/66), respectively. 60 pts were commenced on these agents as 2nd-4th line, after failure of prior biologic therapy. In all, IBD response was observed in 15% (n=8/52) at 6 months, 20% (n=7/35) at 12 months and 21% (n=4/19) at 24 months. Remission was achieved in 3 pts (4.5%) at 18 months. Among non-transplant pts, the median change in ALP from baseline to 6 months was not significant (ALP x upper limit of normal [ULN] 1.4 vs. 1.2; p=0.67), nor from baseline to 12 (ULN 1.1 vs. 1.1; p=0.161) or 24 months (ULN 1.6 vs. 1.0; p=0.074) (Figure 1). No significant differences in serum ALT or bilirubin were observed from baseline to 6, 12 or 24 months. Treatment was discontinued in 37% (n=25/67) due to lack of efficacy and in one pt due to an adverse event. **Conclusion:** Anti-IL23 agents are safe

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and well-tolerated in PSC-IBD. However, IBD response and remission rates appear to dwarf those seen in IBD alone, with no significant effects on liver biochemistry.
Disclosures: Sarah Al-Shakhshir: Nothing to Disclose, Sean Morris: Nothing to Disclose, Ida Schregel: Nothing to Disclose, Christoph Schramm: Nothing to Disclose, Oren Shibolet: novonordisk: Speaking and Teaching, nonvonordisk: Advisor, roche: Speaking and Teaching, Haim Leibovitzh: Nothing to Disclose, Laura Cristoferi: IPSEN: Advisor, IPSEN: Advisor, Calliditas: Consultant, Advanz Pharma: Speaking and Teaching, Falk Pharma: Advisor, Signant Health: Consultant, Marco Carbone: Nothing to Disclose, Pietro Invernizzi: Nothing to Disclose, chiara vigano': Johnson & Johnson: Advisory board, Celltrion: Advisor, Celltrion: Research grant, AlphaSigma: Speaking and Teaching, Pfizer: Speaking and Teaching, Abbvie: Speaking and Teaching, Galapagos: Advisor, Takeda: Speaking and Teaching, PSI: Consultant, Emma Culver: IPsen: Speaking and Teaching, Mirum: Advisor, Horizon (Amgen): Advisor, Zenus Biopharma: Advisor, Sanofi: Advisor, GSK: Speaking and Teaching, Dr Falk Pharma: Advisor, Advance: Speaking and Teaching, Intercept: Speaking and Teaching, Jansen: Grant/Research Support, Senamjit Kaur: Nothing to Disclose, Amera Elzubeir: Nothing to Disclose, Simon Rushbrook: Nothing to Disclose, Sergio Rodriguez: Nothing to Disclose, Helena Hernandez-Evole: Nothing to Disclose, Deepak Joshi: Nothing to Disclose, Jeremy Nayagam: Ipsen pharmaceuticals: Speaking and Teaching, Palak Trivedi: Nothing to Disclose

4370 | PARTIAL LIVING DONOR, WHOLE DECEASED, AND SPLIT LIVER TRANSPLANTATION IN AUTOIMMUNE LIVER DISEASE

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Background: Split liver transplant (SLT), where a single liver graft is divided for two different recipients, increases graft availability and reduces waitlist times. Despite being well-established, the number of SLTs in autoimmune liver diseases (AILDs) has remained flat due to concerns about post-liver transplant (LT) survival compared to whole deceased donor liver transplantation (DDLT) and partial living donor liver transplantation (LDLT). This study aims to determine the best LT procedure for AILD by analyzing two decades of data in the United States (U.S.).
Methods: Using the Organ Procurement and Transplantation Network (OPTN)/United Network for Organ Sharing (UNOS) from 2002 to 2023, we analyzed and compared (I) key characteristics of donors and recipients, (II) post-LT survival for DDLT, LDLT, and SLT among the five most common chornic liver diseases, and (III) post-LT survival for DDLT, LDLT, and SLT among AILDs, including survival predictors using cox regression univariate and multivariate models. AILDs considered were autoimmune hepatitis (AIH), primary biliary cholangitis (PBC), and primary sclerosing cholangitis (PSC). Exclusions included pediatric patients (<18 years old), multitransplanted, and re-transplanted patients. Analyses were divided into ERA 1 (2002-2012) and ERA 2 (2013-2023) to reduce time-related heterogeneity. **Results:** We divided groups depending on the procedure type into DDLT (103,443), LDLT (4,815), and SLT (1,281). LDLT recipients were the youngest (53.1 years) and predominantly white (80.5%). LDLT was most common for AILD (35.7%), DDLT for alcoholic liver disease (ALD) (35.6%), and SLT for hepatitis C virus (HCV) (29.4%). In ERA 1, AILD patients had the highest 3-, 5-, and 10-year survival rates (85.2%, 81.3%, and 70.8%), while HCV had the lowest (64.1%, 57.4%, and 45.2%) (P<0.001). In ERA 2, AILD still had the highest survival rates (88.7%, 83.9%, and 70.9%), while MAFLD had the lowest 10-year survival (53.1%) (P<0.001). Within AILD, SLT had the worst 1-, 3-, and 10-year survival (88.3%, 84.3%, and 69.0%), while LDLT had the best overall survival (P<0.001). AIH had the worst 3-, 5-, and 10-year prognosis (83.1%, 78.0%, and 66.8%), while PSC had the best survival (P<0.001). Multivariate regression showed LDLT was protective compared to DDLT in AILD patients (HR 0.68, CI 0.60-0.79), while SLT was not significant. **Conclusion:** In both eras, AILD patients had the highest post-LT survival, while SLT showed the highest 10-year mortality rate. Subgroup analysis indicated PSC had the best and AIH the worst post-LT survival. Limitations included a small SLT sample compared to DDLT and LDLT. SLT is not recommended for AILD, favoring LDLT whenever possible. AIH patients require close post-LT monitoring with strict immunosuppression and diabetes management. Further research is needed to explore factors contributing to suboptimal SLT outcomes in AILD, aiming to enhance transplant availability in the U.S.

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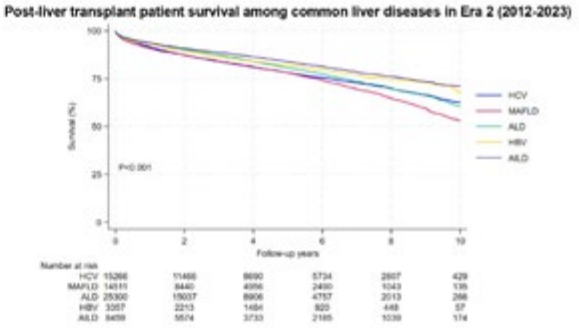
Baseline Characteristics in AILD by transplant procedure type

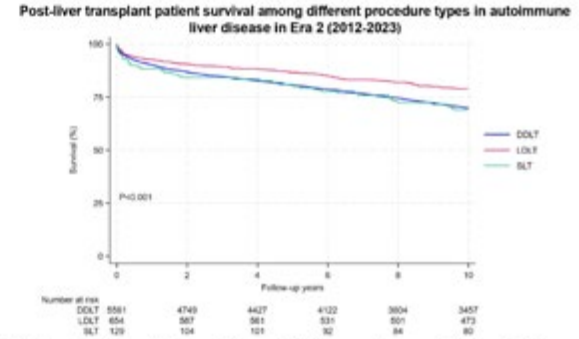
Recipient	DDLT	LDLT	SLT
N	103,443	4,815	1,281
Age, n (IQR)	55.3 (50-62)	53.1 (47-62)	55.1 (50-63)
Gender, M, n (%)	70,783 (68.4)	2,634 (54.7)	562 (43.8)
Ethnicity, n (%)			
White	73,521 (71.1)	3,875 (80.5)	781 (60.1)
Black	8,861 (8.6)	174 (3.6)	94 (7.3)
Hispanic	15,164 (14.7)	594 (3.6)	265 (20.7)
Asian	4,507 (4.4)	130 (12.5)	126 (9.8)
Other	1,390 (1.37)	42 (0.8)	15 (1.2)
Etiology of Liver Disease, n (%)			
HCV	30,712 (29.7)	1,058 (22.0)	377 (29.4)
MAFLD	16,546 (16.0)	877 (18.2)	157 (12.3)
ALD	36,812 (35.6)	985 (20.5)	375 (29.3)
HBV	6,526 (6.3)	176 (3.7)	105 (8.2)
AILD	12,847 (12.4)	1,719 (35.7)	267 (20.8)
Blood type, n (%)			
0	46,071 (44.5)	2,219 (46.1)	754 (58.9)
A	37,849 (36.6)	2,044 (42.5)	382 (29.8)
B	14,087 (13.6)	462 (9.6)	125 (9.8)
AB	5,196 (5.0)	89 (1.8)	19 (1.5)
DM, n (%)	27,948 (27.0)	1,070 (22.2)	322 (25.1)
Dialysis week prior to LT, n (%)	14,347 (13.9)	45 (0.9)	120 (9.4)
Portal vein thrombosis, n (%)	5,896 (5.7)	222 (4.6)	45 (3.5)
Ascites, n (%)	7,616 (7.4)	437 (9.1)	134 (10.5)
Encephalopathy, n (%)	6,137 (5.9)	320 (6.6)	94 (7.3)
Bacterial peritonitis, n (%)	8,711 (8.4)	259 (5.4)	76 (5.9)
UNOS/OPTN Region, n (%)			
1	3881 (3.8)	448 (9.3)	59 (4.6)
2	11683 (11.3)	937 (19.5)	137 (10.7)
3	17881 (17.3)	56 (1.2)	137 (10.7)
4	10202 (9.9)	313 (6.5)	77 (6.0)
5	15329 (14.8)	822 (17.1)	335 (26.2)
6	3296 (3.2)	43 (0.9)	18 (1.4)
7	8523 (8.2)	717 (14.9)	121 (9.4)
8	6519 (6.3)	233 (4.8)	77 (6.0)
9	6091 (5.9)	626 (13.0)	145 (11.3)
10	9663 (9.3)	357 (7.4)	146 (11.4)
11	10375 (10.0)	263 (5.5)	92 (7.2)
Working for income, n (%)	21745 (21.0)	1518 (31.5)	260 (20.3)
BMI, n (IQR)	29.2 (24.9-32.6)	27.2 (23.4-30.3)	25.9 (22.4-28.6)
MELD score at listing, n (IQR)	19.9 (12-26)	14.1 (10-17)	16.6 (10-21)
Donor			
Age, n (IQR)	41.9 (28-54)	37.0 (28-45)	22.8 (16-28)
Gender, M, n (%)	62600 (60.5)	2291(47.6)	898(70.1)

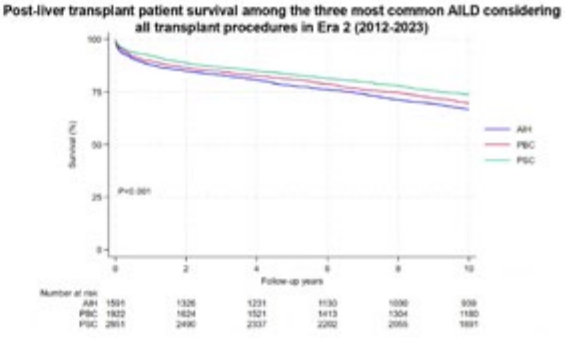
Cox regression univariate and multivariate analysis

	Univariate analysis			Multivariate Analysis		
	HR	CI	P-value	HR	CI	P-value
Procedure type						
DDLT		Reference			Reference	
LDLT	0.68	0.60 – 0.79	<0.001	0.68	0.60 – 0.79	<0.001
SLT	1.00	0.76 – 1.31	0.98		-	
AILD						
AIH		Reference			Reference	
PBC	1.06	0.98 – 1.15	0.14		-	
PSC	0.83	0.77 – 0.90	<0.001	0.80	0.72 – 0.88	<0.001
Recipient						
Age	1.02	1.02 – 1.03	<0.001	1.02	1.02 – 1.03	<0.001
Gender, M	1.03	0.96 – 1.11	0.42	1.01	1.00 – 1.01	<0.001
DM	1.65	1.50 – 1.82	<0.001	1.50	1.36 – 1.66	<0.001

Abbreviations: DDLT: Whole deceased donor liver transplant, LDLT: Partial living donor liver transplant, SLT: Split deceased donor liver transplant, HCV: Hepatitis C Virus, HBV: Hepatitis B Virus, MASLD: Metabolic-associated Steatotic Liver Disease, ALD: Autoimmune liver disease, AIH: Autoimmune hepatitis, PBC: Primary biliary cholangitis, PSC: Primary sclerosing cholangitis, DM: Diabetes Mellitus.







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4371 | ENHANCING MRCP PRECISION: A COMPREHENSIVE ANALYSIS OF INTRAMUSCULAR GLUCAGON ADMINISTRATION IMPACT ON BILIARY VISUALIZATION

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Background: Magnetic resonance cholangiopancreatography (MRCP) has continuously evolved to enhance visualization capabilities, yet the diagnosis of primary sclerosing cholangitis (PSC) remains challenging, especially in its early stages. This study explores the impact of intramuscular glucagon (IMG) administration on final image quality and biliary ductal system diameter in MRCP. **Methods:** Forty patients (57.5% female; average age 34.45 ± 8.2) with suspected inflammatory bowel disease (IBD) referred for Magnetic Resonance Enterography (MRE) underwent MRCP before and 8-12 minutes after IMG administration. Coronal T2-weighted fast spin-echo high-resolution 3D MRCP images were analyzed quantitatively and qualitatively by two independent MRI specialists. Quantitative assessments included measurements of predefined biliary ductal segments (distal, mid, and

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proximal common bile duct (CBD), right hepatic duct (RHD), left hepatic duct (LHD), and gallbladder volume). The qualitative evaluation used a five-point Likert-type scale (1=perfect visualization; 5=not visible). Interobserver variation was assessed using the Intraclass Correlation Coefficient (ICC) and R-Pearson correlation. **Results:** IMG administration significantly increased mean bile duct diameters compared to pre-injection. Combined pre- and post-IMG mean diameters were: distal CBD (3.079±1.16 vs. 3.621±1.05), Mid CBD (3.596±1.46 vs. 4.207±1.41), proximal CBD (3.736±2.23 vs. 4.283±1.90), RHD (2.227±1.25 vs. 2.953±0.91), and LHD (2.672±1.30 vs. 3.392±0.81). The differences were statistically significant (P<0.01) for all measurements. Interobserver agreement was strong (ICC 0.798 to 0.931, R 0.731 to 0.939). IMG administration improved visualization scores significantly (2.65±0.80 vs. 1.67±0.68; P<0.01), with a moderate-strong interobserver agreement (ICC 0.655 to 0.829). Additionally, IMG increased gallbladder volume (20.45 mL pre-IMG vs. 38.81 mL post-IMG; P<0.01). Two PSC-associated biliary duct changes showed significant improvement post-IMG. **Conclusion:** IMG administration enhances MRCP imaging parameters, increasing ductal diameters, improving biliary tree visualization, and aiding in the detection of associated pathologies, emphasizing its potential utility in early and improved PSC detection.

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4372 | PRIMARY SCLEROSING CHOLANGITIS IN SOUTH AFRICA – A SINGLE CENTRE EXPERIENCE ★

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Background: Primary sclerosing cholangitis (PSC), an autoimmune mediated chronic and progressive cholestatic liver disease of uncertain aetiology, is characterized by inflammation, fibrosis and stricturing of the intrahepatic and/or extrahepatic biliary ducts. Inflammatory bowel disease (IBD) is frequently associated. Globally, data is limited and mainly emanates from North America, Europe, and Asia. Data from sub-Saharan Africa is scant. **Methods:** We performed a retrospective cross-sectional evaluation by including all patients diagnosed with PSC attending our clinic over a 30-year period. From records, we extracted and analyzed data on patient demographics, clinical presentation, management, and outcomes. **Results:** 128 patients, 51% (n=65) male, with overall median age of 36 [IQR 23-50] years, were included. Median age at presentation did not significantly differ by sex, male 35 [IQR 25-46] vs. female 36 [IQR 22-53] years, p=0.89. Ethnic distribution included 22.6% (n=29) Black African; 39.1% (n=50) White, 32% (n=41) Mixed Ancestry and 6.3% (n=8) Asian. Biliary imaging was ERCP based in 30% (n=39), almost all before 2010, and MRCP based in 64% (n=82). Liver biopsy was performed in 68% (n=87) of patients, with 30% (38/128) of the total cohort, diagnosed with PSC/Autoimmune Hepatitis overlap. Large duct PSC predominated in 88% (n=113), the remaining the small duct type. Phenotypically, 57% (n=73) were the PSC-IBD type and of those, 78% (n=57) had Ulcerative Colitis (UC), 16.4% (n=12) Crohn's disease and 5.5% (n=4) IBD-undifferentiated. At presentation, 44% (n=56), were cirrhotic, of these 41% (23/56) had PSC/AIH overlap. Cholangitis was the initial presenting feature in 3.9% (5/128) of patients, with 23% (30/128) developing cholangitis during follow-up. Overall, cholangiocarcinoma was documented in 5% (6/128), HCC in 1% (n=1) and colorectal carcinoma in 3.1% (n=4) of patients during follow up. 98% (126/128) of patients received ursodeoxycholic acid (UDCA) with 92% (n=35) of those with PSC/AIH overlap (n=38) receiving corticosteroids. Of those with a PSC/IBD phenotype, 19% (14/73) underwent Crohn's or UC related colon resection. Utilizing the Amsterdam-Oxford 2017, Mayo, and MELD score, mean prognostic scores at presentation were 2.16, 0.78 and 12, respectively. In total, 23% (29/128) underwent orthotopic liver transplant; with 3-, 5- and 10-year survival rates being 89.6%, 83% and 67%, respectively. Of the un-transplanted patients, 11% (11/99) were lost to follow up; 70.5% (62/88) were alive and 29.5% (26/88) died, liver related mortality accounting for 39% of deaths (10/26). **Conclusion:** In this ethnically diverse PSC cohort, advanced disease was evident at presentation in a significant number of patients, with lower rates of PSC/IBD than globally reported. UDCA use was high, cholangiocarcinoma rates were low. Liver transplant outcomes were good.

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4373 | IS HALF-DOSE CORTICOSTEROID INDUCTION THERAPY EFFECTIVE IN ACHIEVING THERAPEUTIC RESPONSE IN AUTOIMMUNE HEPATITIS?

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Background: In autoimmune hepatitis (AIH) patients, guidelines recommend treatment initiation with prednisolone 40–60 mg monotherapy or a lower dose of 30 mg combined with azathioprine (1–2 mg/kg) daily. In clinical practice, however, lower doses (30 mg/day) of prednisolone monotherapy are occasionally used. The aim of this study was to compare low dose to conventional dose induction therapy for AIH. **Methods:** Patients with AIH (n=122) were stratified based on their treatment initiation dose: prednisolone 30 mg/day monotherapy (low dose, n=47) and conventional dose prednisolone 60 mg/day monotherapy or 30 mg/day combined with azathioprine (n=75). The primary endpoint was achievement of early biochemical response defined as a reduction in serum alanine and aspartate aminotransferases (ALT and AST) ≤50% of baseline after 4 weeks of treatment initiation. **Results:** The mean age of the overall cohort was 41.8±16.9 years, and 75 (61.5%) were females. Patients receiving conventional-dose prednisolone were younger (37.6±15.2 vs. 48.5±6.6), more likely to be male (45.3 vs. 27.7%), and had higher international normalized ratio (1.4±0.6 vs. 1.2±0.3; *P*<0.05 for all). Serum ALT, AST, bilirubin, albumin, IgG levels, and presentation with acute hepatitis or with advanced fibrosis (F3/F4) were similar in the two groups (*P*>0.05 for all). Biochemical response at week 4 was higher in the low-dose prednisolone group (85.1 vs. 69.4%) but did not reach statistical significance (*P*=0.052). Normalization of serum ALT and AST at week 12 was higher in the low-dose group (88.4 vs. 71.2%, *P*=0.04), and plateaued to similar rates at week 48 (88.6% vs. 90.3%, *P*=0.75). Male sex (odds ratio [OR] 4.28, 95% confidence interval [CI]:1.38–13.26) higher serum creatinine level (OR 0.97, 95% CI:0.94–1.00) and presentation with acute hepatitis (OR 4.78, 95% CI:1.03–22.10) were associated with failure to achieve biochemical response. Patients with advanced fibrosis (F3/F4) showed a trend towards reduced response (81.3 vs. 58.5%) without reaching statistical significance (OR 0.33, 95% CI:0.09–1.21, *P*=0.081). **Conclusion:** In patients with treatment-naïve AIH, lower-dose prednisolone monotherapy achieves similar biochemical response rates as conventional therapy. These results must be validated in larger, multicenter, randomized controlled clinical trials and may help to mitigate the adverse effects of higher dose corticosteroids.

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4374 | PRIMARY SCLEROSING CHOLANGITIS IN AFRO-CARIBBEANS VS NON-AFRO-CARIBBEANS

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Background: Primary sclerosing cholangitis (PSC) is a rare liver disease characterized by multi-focal bile duct strictures and dilatation. The pathogenesis of PSC is unclear, but race and ethnicity may impact severity and outcome. A prior British publication indicated PSC is more severe in those with Afro-Caribbean (AC) heritage. In this retrospective US cohort study, the clinical features of PSC in those of AC ancestry were compared to those of non-AC ancestry. **Methods:** We identified 76 PSC patients (32 AC and 44 non-AC) diagnosed during 2000-2020 in a single center. The demographic and clinical features (including symptoms, laboratory values, imaging findings, comorbid conditions, and death and/or liver transplantation (LT)) of the two groups were compared at the time of diagnosis and at the time of the last visit. **Results:** The median age of patients in the AC group at the time of diagnosis was 37 (15-68) and in the non-AC group was 33 (15-70), (p=ns) (Table). There was no significant sex difference between the two groups. The presence of jaundice at the time of diagnosis was more frequent in

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the AC group (9/18) than the non-AC group (2/28), (p= 0.003). Likewise, the median alkaline phosphatase (ALP) level at the time of diagnosis was higher in the AC group than in the non-AC group (468 v. 229, respectively, p <0.001). Evidence of cirrhosis or portal hypertension at diagnosis was similarly infrequent between the two groups (p=ns) based on available imaging, biopsy, and platelet count results. AC patients underwent LT (14/32) somewhat more frequently than non-AC patients (9/44), (p= 0.05) though the age at the time of LT tended to be older in the AC group (p=ns). There was no significant difference between each group regarding the presence of comorbid conditions, including cancer. The death rate, including liver-related deaths, in the AC group (12/32) was strikingly higher than in the non-AC group (3/44), (p= 0.003). **Conclusion:** As previously reported in a British PSC cohort of patients, AC ancestry in this US cohort was associated with an increased risk of LT or death compared to non-AC patients. Though the AC group presented with more severe liver injury at the time of diagnosis, the time to liver transplantation or death appears similar. This suggests that those in the AC group are more likely to have progressive disease, while more of those in the non-AC group have a benign course. Prioritizing the inclusion of PSC patients with AC ancestry in PSC prospective studies and clinical trials would be beneficial.

Table- Features of PSC in Afro-Caribbeans versus non Afro-Caribbeans

Variable	AC N= 32	Non-AC N= 44	P value
Age at Dx (range) (years)	37 (15-68)	33 (15-70)	NS
Sex (M/F)	19/13	25/19	NS
Race/ethnicity	26 black 6 other/unknown	12 non-white (2 Asian, 2 South Asian, 4 black, 4 other/unknown)	NA
No IBD UC Crohn's	13 18 1	18 22 6	NS
Jaundice at diagnosis (bilirubin>3mg/dL)	9/18	2/28	0.003
ALP at diagnosis (U/L)	468 (97-932)	229 (46-738)	<0.001
ALT at diagnosis (U/L)	97 (24-323)	87 (27-430)	NS
Cirrhosis/portal HTN (based on MRI +/- biopsy) at Dx	3/19	4/35	NS
Platelet count at Dx (K/uL)	243 (89-767)	237 (113-575)	NS
Platelets count <150 at Dx (K/uL)	2/18	5/30	NS
Cholangiocarcinoma (CCA)	3/32	2/44	NS
Gallbladder cancer	1/32	0/44	NS
Transplant	14/32	9/44	0.05
Age at transplant (years)	52 (31-69)	38 (26-69)	NS
Death	12/32	3/44	0.003
Cause of death	4 liver failure 2 allograft failure 1 perioperative death 1 GIB 1 colon cancer 1 CCA 1 aortic aneurysm 1 unknown	1 liver failure 2 septic shock	
Time from diagnosis to death (years)	13 (1-30)	14 (11-15)	NS

Values presented as median (range)

Disclosures: Ahmed Elhawary: Nothing to Disclose, Nathaniel Ash: Nothing to Disclose, Sonia Mehra: Nothing to Disclose, Bharati Dev: Nothing to Disclose, Mohammed Umair Masood: Nothing to Disclose, JAWAD AHMAD: Nothing to Disclose, Joseph Odin: Nothing to Disclose

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4375 | RECOMPENSATION IS ASSOCIATED WITH IMPROVED OUTCOMES IN PATIENTS WITH DECOMPENSATED CIRRHOSIS FROM AUTOIMMUNE HEPATITIS

YU JUN WONG[1] Ellina Lytvyak[1] Noreen Singh[2] Carlos Moctezuma-Velazquez[1] Juan Abraldes[2] Andrew Mason[1] Aldo Montano-Loza[1]

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Background: Recompensation has been associated with improved outcomes in patients with viral and alcohol-related cirrhosis. However, the clinical phenotypes and outcomes of recompensation in patients with autoimmune hepatitis (AIH) remain unclear. We aim to investigate the prevalence and clinical impact of recompensation in patients with decompensated AIH cirrhosis. **Methods:** We reviewed all decompensated AIH cirrhosis diagnosed at the University of Alberta from 1990 to 2022. Overlap syndrome (AIH-PBC) was diagnosed according to the Paris criteria. Acute severe AIH was defined as the presence of jaundice, INR of 1.5-2, and no encephalopathy (*AASLD 2019*). The primary predictor was recompensation, which was defined as per the Baveno-VII consensus, including (1) resolution of ascites and hepatic encephalopathy (HE) without treatment and no further decompensating events, (2) biochemical response (defined as normalization of ALT [<40U/L] following at least one year of treatment), and (3) stable liver function. The primary outcome was transplant-free survival. Patients with transjugular intrahepatic portosystemic shunt, liver transplantation or loss to follow-up within a year from index decompensation were excluded. Using one year after index decompensation as time-zero, patients were followed up to death, liver transplantation, or most recent visit. **Results:** From a total of 213 patients with decompensated AIH cirrhosis, 47 AIH patients with decompensated cirrhosis with at least one year of follow-up after index decompensation were identified. This cohort was predominantly female (75%) with a mean age of 48 (±21) years. Median Child-Pugh and MELD scores at the time of index decompensation were 7 (6-9) and 13 (10-16), respectively, with 26% presenting with acute severe AIH. Compared to patients with AIH, patients with AIH-PBC overlap syndrome were less likely to have cirrhosis at diagnosis (23% vs 62%, p=0.019), less likely to receive prednisone (39% vs 79%, p=0.013) or azathioprine (23% vs 68%, p=0.009) at the point of index decompensation, and less likely to achieved ALT normalization by 6 months (10% vs 52%, p=0.028). Overall, 16.2% achieved recompensation one year after index decompensation. During the median follow-up of 43 (IQR:17-69) months from time-zero, none of the patients with AIH-PBC overlap syndrome and patients presented with acute severe AIH achieved recompensation. Patients achieving recompensation had better transplant-free survival (100% vs 55%, p=0.043). **Conclusion:** Recompensation occurred in one out of six patients with decompensated AIH cirrhosis. While recompensation was associated with better clinical outcomes, our findings demonstrate that recompensation is influenced by AIH phenotypes, and early LT assessment should be considered in patients with AIH-PBC overlap syndrome and those presenting with acute severe AIH.

Disclosures: YU JUN WONG: Nothing to Disclose, Ellina Lytvyak: Nothing to Disclose, Noreen Singh: Nothing to Disclose, Carlos Moctezuma-Velazquez: Nothing to Disclose, Juan Abraldes: Gilead: Grant/Research Support, 89bio: Consultant, Boston Pharmaceuticals: Consultant, Novo Nordisk: Consultant, Boehringer Ingelheim: Consultant, Astra Zeneca: Consultant, Agomab: Consultant, Terumo: Speaking and Teaching, Cook: Grant/Research Support, Andrew Mason: Intercept Pharma: Consultant, CADTH: Consultant, GSK: Grant/Research Support, Ipsen: Consultant, Gilead: Consultant, Aldo Montano-Loza: Advanz: Consultant

4376 | PREDICTORS OF SYMPTOM SEVERITY AMONG AUTOIMMUNE LIVER DISEASE PATIENTS IN A SINGLE UNITED STATES CENTER

Leandro Sierra[1] Ana Marenco-Flores[1] Daniela Goyes[2] Romelia Barba[3] John Esli Medina Morales[4] Marwan Alsaqa[1] Behnam Saberi[1] Alan Bonder[1] Vilas Patwardhan[1]

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Background: Despite the effective long-term symptom management of autoimmune liver disease (AILD), studies beyond five years are scarce and often limited to multicentric analyses. This single-center study aims to fill this gap by identifying predictive factors of symptom severity and the best assessment tool for patients diagnosed with six different AILDs. **Methods:** We conducted an eight-year prospective cohort study at a single U.S. center,

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enrolling 485 adult AILD patients, including autoimmune hepatitis (AIH), primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC), IgG4 cholangiopathy, hepatic sarcoidosis, granulomatous hepatitis, and various overlap syndromes. In total, we collected 1265 responses from the Chronic Liver Disease Questionnaire (CLDQ) and the US-adjusted EuroQol 5 Dimension 5 Level Questionnaire (EQ-5D-5L). Exclusions included patients with other chronic liver diseases, acute liver failure, post-transplant, and those not in AILD treatment. We used univariate and multivariate linear regression to identify predictors of symptom severity in CLDQ and a Tobit regression model for the EQ-5D utility (UI) score, known for its suitability for continuous variables with ceiling effect. Pearson correlation explored associations between EQ-5D UI and CLDQ scores. **Results:** A total of 485 AILD patients were included. Median age was 55.5 years, with predominant female patients (74.3%). MVA of CLDQ revealed factors associated with symptom worsening, including female gender (β: −0.32; 95% CI –0.50, −0.19), Hispanic race (β:−0.42; 95% CI –0.59, −0.23), BMI (β: −0.03; 95% CI –0.04, −0.02), MASLD/MASH (β: −0.33; 95% CI −0.48, −0.16), and cirrhosis (β: −0.24; 95% CI −0.35, −0.11). Similarly, Tobit regression for EQ-5D-5L scores showed female sex (β: −0.06; 95% CI –0.11, −0.01), MASLD/MASH (β: −0.08; 95% CI –0.14, −0.02), and cirrhosis (β: −0.04; 95% CI –0.08, −0.02) were associated with symptom severity. Arterial hypertension and diabetes were not significant predictors (P>0.05). Individual liver function tests such as ALT, AST, total bilirubin, or IgG levels were also not significant predictors (P>0.05). Higher albumin was associated with improved prognosis in both CLDQ and EQ-5D-5L (β: 0.46 and 0.07). Pearson's correlation indicated a strong positive association between CLDQ and EQ-5D UI score in AILD (r = 0.63; P<0.001). **Conclusion:** We highlight the potential of CLDQ and EQ-5D-5L in predicting symptom severity in AILD patients, with CLDQ identifying more predictors and degrees of association. Despite limitations such as not integrating treatments into the analysis, all patients followed appropriate guidelines. While data support using both tools for assessing quality of life in AILD, there is limited information about their performance and which one is more suitable. Clinicians should consider CLDQ when selecting an assessment tool and address the presented variables to improve symptoms in AILD.

Table 1a. Uni- and multivariable linear regression analyses of clinical and laboratory parameters with CLDQ total value and EQ-5D UI (P-value: <0.001)

Variable	CLDQ total value						EQ-5D Utility Index Score					
	Univariable Analysis			Multivariable Analysis			Univariable Analysis			Multivariable Analysis		
	β	95% CI	P value	β	95% CI	P value	β	95% CI	P value	β	95% CI	P value
Age at time of questionnaire	-0.01	-0.04, 0.03	0.80		-		**-0.01**	**-0.02, -0.01**	**0.02**		-	
Time since diagnosis	-0.01	-0.01, 0.02	0.30		-		-0.01	-0.01, 0.04	0.14		-	
Female sex	**-0.32**	**-0.50, -0.19**	**<0.001**	**-0.26**	**-0.42, -0.09**	**0.003**	**-0.08**	**-0.12, -0.04**	**<0.001**	**-0.06**	**-0.11, -0.01**	**0.008**
Hispanic race	**-0.42**	**-0.59, -0.23**	**<0.001**	**-0.31**	**-0.54, -0.07**	**0.01**	**-0.05**	**-0.10, -0.01**	**0.04**		-	
BMI	**-0.03**	**-0.04, -0.02**	**<0.001**	**-0.02**	**-0.34, -0.01**	**<0.001**	**-0.01**	**-0.01, -0.02**	**<0.001**	**-0.04**	**-0.08, -0.01**	**0.003**
ALP	**-0.01**	**-0.03, -0.01**	**<0.001**	**-0.01**	**-0.02, -0.01**	**<0.001**	**-0.02**	**-0.03, -0.01**	**<0.001**		-	
ALT	**-0.01**	**-0.04, -0.001**	**0.02**		-		-0.03	-0.04, 0.01	0.35		-	
AST	**-0.02**	**-0.03, -0.01**	**0.006**		-		-0.01	-0.03, 0.01	0.48		-	
Albumin	**0.46**	**0.30, 0.60**	**<0.001**	**0.20**	**0.15, 0.35**	**0.03**	**0.10**	**0.05, 0.13**	**<0.001**	**0.07**	**0.02, 0.11**	**0.007**
Total bilirubin	-0.04	-0.07, 0.01	0.17		-		0.10	-0.02, 0.03	0.10		-	
IgG	-0.01	-0.01, 0.02	0.36		-		-0.03	-0.03, 0.02	0.11		-	
AILD Overlap	-0.05	-0.20, 0.10	0.52		-		0.02	-0.20, 0.61	0.30		-	
MASLD/MASH	**-0.33**	**-0.48, -0.16**	**<0.001**	**-0.37**	**-0.60, -0.14**	**0.002**	**-0.08**	**-0.13, -0.36**	**<0.001**	**-0.08**	**-0.14, -0.02**	**0.01**
Diabetes	**-0.29**	**-0.45, -0.10**	**0.002**		-		**-0.05**	**-0.09, -0.01**	**0.04**		-	
Arterial Hypertension	0.01	-0.01, 0.10	0.80		-		**-0.04**	**-0.08, -0.01**	**0.01**		-	
Cirrhosis	**-0.24**	**-0.35, -0.11**	**<0.001**	**-0.29**	**-0.45, -0.14**	**<0.001**	**-0.03**	**-0.06, -0.01**	**<0.001**	**-0.04**	**-0.08, -0.02**	**0.05**

Categorical variables: Female sex: 0 for No, 1 for Yes; Hispanic race: 0 for No, 1 for Yes; AIH Overlap: 0 for No, 1 for Yes; MASLD/MASH: 0 for No, 1 for Yes; Diabetes: 0 for No, 1 for Yes; Arterial Hypertension: 0 for No, 1 for Yes; Cirrhosis: 0 for No, 1 for Yes. Abbreviations: ALT, Alanine-Aminotransaminase; AST, Aspartat-Aminotransaminase; gGT, Gamma-GT; IgG, Immunoglobulin G; AIH, Autoimmune Hepatitis; MASLD, Metabolic-associated Steatotic Liver Disease; MASH, Metabolic dysfunction-associated steatohepatitis; AILD: Autoimmune liver disease. At first, univariate analysis was done. Statistically significant variables were then considered to build a multivariate model. Confidence Interval (CI) and Beta (β) show standardized values. A P-value <0.05 was considered significant. Bold letters indicate significance. Not significant values on the MVA were not reported (P>0.05).

Figure 1a. Distribution of total CLDQ score in AILD

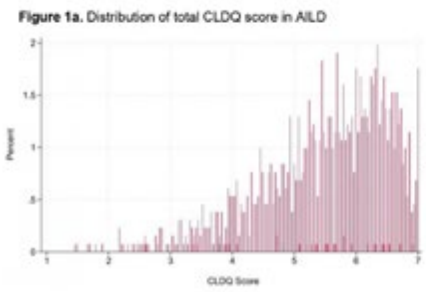


Figure 1b. Distribution of EQ-5D UI score in AILD

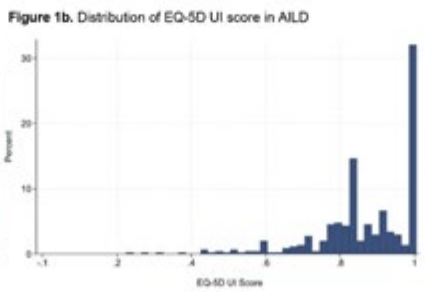
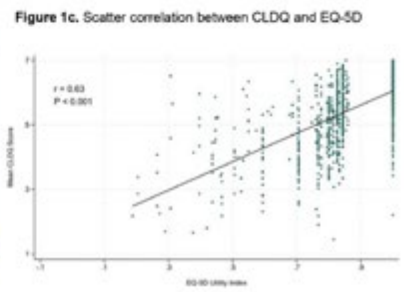


Figure 1c. Scatter correlation between CLDQ and EQ-5D



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Disclosures: Leandro Sierra: Nothing to Disclose, Ana Marenco-Flores: Nothing to Disclose, Daniela Goyes: Nothing to Disclose, Romelia Barba: Nothing to Disclose, John Esli Medina Morales: Nothing to Disclose, Marwan Alsaqa: Nothing to Disclose, Behnam Saberi: Nothing to Disclose, Alan Bonder: GSK: Grant/Research Support, Mirium: Grant/Research Support, Gilead: Grant/Research Support, Ipsen: Grant/Research Support, Cymabay: Grant/Research Support, Intercept: Grant/Research Support, Intercept: Consultant, GSK: Consultant, Ipsen: Consultant, Chemobab: Grant/Research Support, Alnylam: Consultant, Thirammune: Consultant, Vilas Patwardhan: Nothing to Disclose

4377 | DIAGNOSTIC PERFORMANCE OF TRANSIENT ELASTOGRAPHY AND ASPARTATE AMINOTRANSFERASE-TO-PLATELET RATIO (APRI) IN AUTOIMMUNE HEPATITIS

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Background: Liver biopsy is considered the gold standard for defining fibrosis stages in Autoimmune Hepatitis (AIH). Non-invasive methods, such as transient elastography (TE) and aspartate aminotransferase (AST)-to-platelet ratio (APRI) calculation, have been utilized in chronic liver diseases for this purpose. However, cutoff points to define fibrosis have not yet been established in AIH. The aim of this study was to investigate the performance of TE and APRI in defining liver fibrosis in a group of patients with AIH. **Methods:** This was a prospective study involving patients with AIH (according to the Simplified International Autoimmune Hepatitis Group scoring system) who underwent liver biopsy (fibrosis classified by Metavir) and transient elastography (FibroScan, Echosens 502), with a maximum interval of 6 months between the two procedures. Laboratory parameters for APRI calculation were obtained within a maximum interval of 3 months from the biopsy. The performances were compared with liver biopsies using ROC curves. **Results:** The study included a total of 66 patients (92% female; mean age 42 ± 18 years) with AIH. Liver fragments were ≥ 1.5 cm, with ≥ 8 complete portal spaces. In terms of fibrosis stages, 46% were classified as grades 0 to 2 (F0-2) and 49% as grades 3 or 4 (F3-4). FibroScan and APRI demonstrated a similar performance in defining advanced fibrosis (F≥3) with AUROC values of 0.841 and 0.819, respectively, and the best cutoffs of 8.1 kPA and 0.819, respectively. The exclusion of patients with AST > 3 times ULN did not significantly alter the performances. **Conclusion:** FibroScan and APRI showed comparable and reasonable performances in defining advanced fibrosis. Further studies are necessary to confirm these findings.

Disclosures: Vivian Rotman: Nothing to Disclose, Ana Carolina Cardoso: Nothing to Disclose, MARIA CHIARA CHINDAMO: Nothing to Disclose, Adriana Bottino: Nothing to Disclose, Joao Marcello de Araujo-Neto: Nothing to Disclose, aline ferraz pereira: Nothing to Disclose, LAIS Veiga: Nothing to Disclose, Nathalia Carraro Eduardo de Castro: Nothing to Disclose, DEBORA Canoilas: Nothing to Disclose, Andreia Evangelista: Nothing to Disclose, Renata Perez: Nothing to Disclose

4378 | BURDEN OF COMORBID PSYCHIATRIC ILLNESSES AMONG HOSPITALIZED PATIENTS WITH AUTOIMMUNE LIVER DISEASE: A NATIONWIDE COHORT ANALYSIS

Carla Barberan Parraga[1] Leandro Sierra[2] Diana Cheung[1] Kundan Jana[1] Marwan Alsaqa[3] Nazli Begum Ozturk[4] Butros Fakhoury[5] Syed Kodilinye[1] Ahmed Salem[1] Yasutoshi Shiratori[1] James Park[6]

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Background: Autoimmune liver disease patients experience significant cognitive decline, which is linked to anxiety and depression, increasing the risk of unplanned hospitalizations, hepatic encephalopathy admissions, and mortality. Currently, no studies analyze psychiatric conditions among these patients. Our aim is to study the past five years' trends of mental illness in the most common autoimmune liver diseases. **Methods:** The national inpatient sample database was queried for patients aged ≥18 with discharge diagnoses of primary

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sclerosing cholangitis (PSC), primary biliary cholangitis (PBC), and autoimmune hepatitis (AIH) from 2016-2021. Ten psychiatric illnesses were studied using relevant ICD-10 codes. The presence of psychiatric illnesses was compared among AIH, PSC, and PBC groups, and stratified by gender and race. Categorical data were compared using the Rao-Scott chi-square test and ANOVA, and continuous data using Student's t-test. Data extraction was done in Python (version 3.9.1), and statistical analysis in R (version 3.6.2). **Results:** A total of 43,652 patients were analyzed, divided into three groups by etiology: PSC (4,452), PBC (14,264), and AIH (24,936). PSC patients were younger (mean 51.3 years), while PBC patients were older (mean 65.6 years). Caucasians predominated in all groups (60.9%-71.1%), with higher proportions of females in AIH (77.5%) and PBC (85.2%). Mental disorders varied, with 6 out of 10 conditions reaching significance. Across the autoimmune pathologies, psychiatric conditions had a prevalence of 25.04%. AIH had the highest rates of bipolar disorder (1.8%), alcohol use disorder (4.0%), and substance use disorder (2.7%). PBC had the highest burden of depression (15.5%), while PSC had the highest rates of PTSD (1.1%) and ADHD (0.8%). In data stratified by sex, autoimmune liver disease female had a higher burden of MDD and GAD diagnoses (15.2% and 1.7%; respectively) when compared to males. Whereas males had a higher burden of ADHD, alcohol use disorder and substance use disorder (0.6%, 5.7%, and 3.0%; respectively) when compared to females. **Conclusion:** AIH had the highest number of psychiatric diagnoses among the groups studied. PBC, despite having the fewest psychiatric diagnoses overall, had the highest prevalence of MDD, significantly affecting the number of hospitalized patients with autoimmune liver disease. Prospective studies are needed to investigate the impact of these psychiatric conditions on quality-of-life outcomes. We recommend referring autoimmune liver disease patients to mental health professionals at the time of diagnosis.

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4379 | GLYCINE-BETA-MCA SHOWS COMPARABLE ANTI-CHOLESTASIS BUT BETTER ANTI-FIBROSIS EFFICACY THAN UDCA IN FEMALE *CYP2C70* KNOCKOUT MICE

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Background: Cholestasis is a chronic liver disease with limited therapeutic options. Hydrophobic bile acid-induced hepatobiliary injury is a major pathological driver of cholestasis progression. Pharmacological targeting bile acid transport and signaling is promising in treating cholestasis. *Cyp2c70* Knockout (KO) mice do not produce muricholic acid (MCA) and exhibit human-like hydrophobic bile acid pool-induced cholestasis. **Methods:** The effect of either hydrophilic intestine restricted fernesiod X receptor (FXR) antagonist Glycine-beta-Muricholic acid (Gly-b-MCA) or hydrophilic Ursodeoxycholic acid (UDCA) treatment at a dose of 160mg/kg/day for 4 weeks on bile acid pool and composition, hepatic inflammation, ductular reaction, and portal fibrosis were investigated in Cyp2c70 KO mice. **Results:** We report that glycine-conjugated b muricholic acid (Gly-b-MCA) is a potent anti-cholestasis agent in female Cyp2c70 KO mice. At a clinically relevant dose, Gly-b-MCA shows comparable efficacy as UDCA, the only 1st line drug for cholestasis treatment, in alleviating portal inflammation and ductular reaction, and higher efficacy than UDCA against portal fibrosis. In *Cyp2c70* KO mice lacking endogenous MCAs, we show that orally administered Gly-b-MCA is absorbed at low efficiency and enters the enterohepatic circulation mainly after microbiome deconjugation, which leads to taurine-conjugated MCA enrichment and reduced bile acid pool hydrophobicity. Gly-b-MCA also promotes fecal excretion of endogenous hydrophobic bile acids and decreases endogenous bile acid pool size and hepatic bile acid accumulation. UDCA treatment drives a marked increase of Lithocholic acid (LCA) flux through the large intestine, while Gly-b-MCA treatment cause gut unconjugated MCA enrichment and reduced gut cytotoxic LCA abundance. **Conclusion:** The therapeutic benefits of Gly-b-MCA may be attributed to its ability to simultaneously reduce the enterohepatic bile acid pool size and hydrophobicity. Gly-b-MCA is a potent anti-cholestasis agent with potential clinical application in treating human cholestasis.

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Table 1A. Baseline cohort characteristics

Variables	PSC	PBC	AIH	P-value
Total, N	4452	14264	24936	
Age, Mean ± SD	51.3±17.7	65.6±13.5	58.7±17.8	
Race, N (%)				<0.01
Caucasian	3089 (69.4%)	10137 (71.1%)	15195 (60.9%)	
African American	771 (17.3%)	911 (6.4%)	3751 (15.0%)	
Hispanic	325 (7.3%)	1951 (13.7%)	3600 (14.4%)	
Asian	78 (1.8%)	353 (2.5%)	688 (2.8%)	
Native American	9 (0.2%)	147 (1.0%)	283 (1.1%)	
Other	91 (2.0%)	328 (2.3%)	699 (2.8%)	
Gender, N (%)				
Female	1855 (41.7%)	12159 (85.2%)	19331 (77.5%)	<0.01
Male	2597 (58.3%)	2102 (14.73%)	5600 (22.5%)	<0.01
Mental health disorders, N (%)				
Schizophrenia	8 (0.8%)	35 (0.2%)	60 (0.2%)	0.7
Schizoaffective	8 (0.2%)	27 (0.2%)	58 (0.2%)	0.6
SI	21 (0.5%)	61 (0.4%)	151 (0.6%)	0.06
PTSD	51 (1.1%)	99 (0.7%)	214 (0.9%)	0.01
Bipolar	51 (1.1%)	238 (1.7%)	417 (1.8%)	0.03
ADHD	37 (0.8%)	47 (0.3%)	98 (0.4%)	<0.01
GAD	84 (1.9%)	210 (1.5%)	354 (1.4%)	0.06
MDD	515 (11.6%)	2208 (15.5%)	3301 (13.2%)	<0.01
Alcohol use disorder	118 (2.6%)	348 (2.4%)	1008 (4.0%)	<0.01
Substance use disorder	111 (2.5%)	316 (2.2%)	680 (2.7%)	<0.01
Important associations, N (%)				
Fatigue	10 (0.2%)	38 (0.3%)	46 (0.2%)	0.24
Cirrhosis	261 (5.9%)	2325 (16.3%)	1519 (6.1%)	<0.01

Table 1B. Subgroup analysis stratified by sex

	Male	Female	P-value
Total	10299	33345	
Age	56.4±18	61.4±16.6	<0.01
PSC	2597 (25.2)	1855 (5.6)	<0.01
PBC	2324 (22.6)	12375 (37.1)	<0.01
AIH	5946 (57.8)	20698 (62.1)	<0.01
Race			<0.01
Caucasian	7088 (68.8)	21325 (64.0)	
African American	1241 (12.0)	4192 (12.6)	
Hispanic	1029 (10.0)	4847 (14.5)	
Asian	275 (2.7)	844 (2.53)	
Native American	69 (0.7)	370 (11.1)	
Others	269 (2.6)	849 (2.5)	
Schizophrenia	22 (0.2)	80 (0.2)	0.63
Schizoaffective	25 (0.2)	68 (0.2)	0.47
Fatigue	23 (0.2)	71 (0.2)	0.86
SI	59 (0.6)	174 (0.5)	0.56
PTSD	85 (0.8)	279 (0.8)	0.92
Bipolar	117 (1.0)	588 (1.8)	<0.01
ADHD	60 (0.6)	122 (0.4)	<0.01
GAD	96 (0.9)	552 (1.7)	<0.01
MDD	943 (9.2)	5080 (15.2)	<0.01
Cirrhosis	918 (8.9)	3187	0.06
Alcohol use disorder	588 (5.7)	886 (2.7)	<0.01
Drug Abuse	312 (3.0)	795 (2.4)	<0.01

Study abbreviations: AIH: Autoimmune hepatitis; PBC: Primary biliary cholangitis; PSC: Primary sclerosing cholangitis; SI: Suicidal Ideation; PTSD: Post-traumatic stress disorder; ADHD: Attention deficit hyperactivity disorder; GAD: Generalized anxiety disorder; MDD: Major depressive disorder.

Disclosures: Mohammad Nazmul Hasan: Nothing to Disclose, Yung-Dai Clayton: Nothing to Disclose, Lijie Gu: Nothing to Disclose, Yanhong Du: Nothing to Disclose, Tiangang Li: Nothing to Disclose

4380 | WHAT DO SPECIFIC MARKERS OF AUTOIMMUNE HEPATITIS INFORM US ABOUT THE VARIANT PRESENTATIONS OF AUTOIMMUNE LIVER DISEASE?

Inbal Houri[1] Claire Gage[2] Hooman Ebrahimi[2] Vathany Kulasingam[3] Guilherme Cancado[2] Kristel Leung[4] Bettina Hansen[1] Aliya Gulamhusein[4] Gideon Hirschfield[1]

[1]Toronto General Hospital, [2]Toronto Centre for Liver disease, [3]University Health Network, [4]University of Toronto

Background: Certain auto-antibody profiles are considered highly specific for the diagnosis of autoimmune hepatitis (AIH). Anti-SLA (soluble liver antigen), anti-LKM-1 (liver kidney microsome type 1) and anti-LC-1 (liver cytosol 1) are amongst these seromarkers. We sought to understand the clinical characteristics of people with autoimmune liver disease (AILD) variant syndromes who test positive for one of these specific auto-antibodies. **Methods:** Clinical, demographic and laboratory data were collected retrospectively from patients' medical records attending a tertiary liver programme. Results of the EUROLINE Autoimmune Liver Diseases 9 antigen Immunoblot assay (AILD-panel) were cross-referenced to clinical data. **Results:** From 2020-2024, 1760 patients had AILD-panels sent. Of the active patient cohort followed to date 70% (317/455) of AIH patients and 61% (411/677) of primary biliary cholangitis (PBC) patients had the AILD-panel. Among all the patients with AILD-panel testing, 106 had specific AIH antibodies – 56 with anti-SLA, 7 with anti-LKM-1 and 43 with anti-LC-1. Patients with anti-SLA or anti-LKM-1 were younger compared to the general AIH cohort (median age 39 and 24 respectively, compared to 49 as previously reported), and more likely to be female (85% vs 75.4%). Of anti-SLA positive patients, 12 patients had a diagnosis of PBC – 5 were considered to have "overlap" and treated both with anti-cholestatic medications and immunosuppression, while the other 7 were treated only with PBC medications. At last follow up, these patients all had normal AST/ALT/IgG. Nine patients with anti-SLA had a diagnosis of primary sclerosing

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cholangitis, 7 of whom were thought to have a component of AIH and treated with immunosuppression. One patient with anti-LKM-1 had a diagnosis of PBC with no features of AIH. Sixty percent of patients with anti-LC-1 had a predominant diagnosis different from AIH, with a significant portion diagnosed as non-autoimmune liver disease. Even among patients with high titres (+2 /+3) of anti-LC-1, only 13/21 had a clinical diagnosis of AIH. **Conclusion:** Although highly suggestive of a diagnosis of AIH, anti-SLA specificity seems to be lower than previously reported. In patients with a clear diagnosis of PBC, anti-SLA positivity did not necessarily confirm a variant syndrome. In our cohort, with this assay, anti-LC-1 appeared least specific for AIH diagnosis and alone should be interpreted cautiously.

		Anti-SLA (n=56)	Anti-LKM-1 (n=7)	Anti-LC-1 (n=43)
Age at diagnosis (median, IQR)		39 (31-55)	24 (12-28)	43 (27-60)
Female		47 (84%)	6 (86%)	30 (70%)
Years of follow-up (median, IQR)		9 (6-15)	5 (3-9)	7 (3-15)
Diagnosis				
	AIH only	30 (53%)	3 (43%)	17 (40%)
	AIH predominant with biliary features	10 (18%)	2 (28%)	0
	Other autoimmune liver disease	15 (27%)	1 (14%)	13 (30%)
	Other	1 (2%)	1 (14%)	13 (30%)
Fibrosis stage on initial biopsy				
	0-2	29 (52%)	2 (29%)	17 (40%)
	3-4	16 (28%)	3 (43%)	12 (28%)
Biliary features on initial biopsy		21 (41%)	2 (40%)	11 (33%)
Extrahepatic autoimmune disease		27 (48%)	4 (57%)	21 (49%)
Treatment at last review				
	Immunosuppression including prednisone	26 (46%)	3 (43%)	12 (28%)
	Immunosuppression with no prednisone	15 (27%)	2 (28%)	4 (9%)
	UDCA	15 (27%)	1 (14%)	11 (25%)
	Bezafibrate / Obeticholic acid	1 (1.8%)	0	4 (9%)
Cirrhosis (clinical diagnosis)		22 (39%)	3 (43%)	19 (44%)
Other antibodies				
	ANA	52 (93%)	6 (86%)	28 (65%)
	SMA	31 (55%)	1 (14%)	16 (37%)
	PBC-related antibodies	21 (37%)	2 (28%)	12 (28%)
	AMA / M2	12 (n)	2 (n)	7 (n)
	gp210 / Sp100 / PML	5 (n)	0 (n)	3 (n)
	Both AMA and specific antibodies	4 (n)	0 (n)	2 (n)

Disclosures: Inbal Houri: Nothing to Disclose, Claire Gage: Nothing to Disclose, Hooman Ebrahimi: Nothing to Disclose, Vathany Kulasingam: Nothing to Disclose, Guilherme Cancado: Nothing to Disclose, Kristel Leung: Nothing to Disclose, Bettina Hansen: Nothing to Disclose, Aliya Gulamhusein: Nothing to Disclose, Gideon Hirschfield: Consultant relationship with Mirum; Has not ended; Consultant relationship with Advanz; Has not ended; Consultant relationship with Chemomab; Has not ended; Consultant relationship with Gilead; Has not ended; Consultant relationship with Kowa; Has not ended; Consultant relationship with Intercept; Has not ended; Consultant relationship with Pliant; Has not ended; Consultant relationship with Falk; Has not ended; Consultant relationship with GSK; Has not ended; Consultant relationship with Ipsen; Has not ended; Consultant relationship with CymaBay; Has not ended

4381 | ABERRANT CYTOKERATIN 7 EXPRESSION BY HEPATOCYTES CAN PREDICT THE DUCTOPENIA GRADE IN PRIMARY BILIARY CHOLANGITIS

Hongli Liu[1] Qing-Fang Xiong[1] yandan zhong[1] Du-Xian Liu[1] Ping Huang[1] Xiao-Ning Feng[1] Yu Zhang[2] YongFeng Yang[1]

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Background: Aberrant cytokeratin 7 expression by hepatocytes (CK7+Hs) is the hallmark characteristic of cholestasis diseases, especially in ductopenia diseases such as primary biliary cholangitis (PBC). This study attempted to evaluate the diferences and relationships between the clinical and histological features of aberrant

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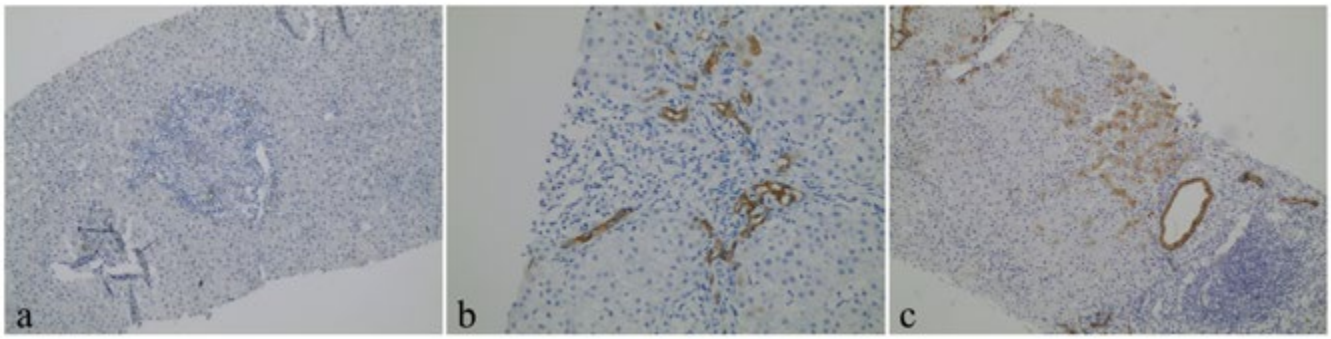
cytokeratin 7 (CK7) expression by hepatocytes in PBC patients. **Methods:** The clinicopathological data of patients diagnosed with PBC at the Second Hospital of Nanjing between January 2016 and September 2018 were analysed with SPSS 20.0 **Results:** Eighty-nine PBC patients who underwent liver biopsy were enrolled in this study, and 15, 29 and 45 patients had aberrant CK7 expression by hepatocytes (CK7+Hs (2+), CK7+Hs (1+), and CK7−Hs, respectively). There were signifcant diferences in TB, DB, ALP, TA, IgM, interface activity, and ductopenia grade between patients with CK7−Hs and CK7+Hs (2+) (P<0.05). The ductopenia grade was also signifcantly diferent between patients with CK7+Hs (2+) and CK7+Hs (1+) according to sex (P<0.05). Upon merging the data of CK7+Hs (2+) and CK7+Hs (1+) into CK7+Hs, we found signifcant diferences in AMA, AMA-M2, anti-gp210, TB, DB, ALP, TA, IgM, fbrosis, and ductopenia grade between CK7+Hs and CK7−Hs (P<0.05). The odds ratios (ORs) (and 95% confdence intervals (CIs)) of CK7+Hs according to anti-gp210, ductopenia grade, and interface activity were 6.413 (95% CI 1.363–30.162), 4.145 (95% CI 1.898–9.052) and 3.247 (95% CI 1.556–6.775), respectively (P<0.05). Spearman's rank correlation according to interface activity and ductopenia grade in patients with CK7+Hs (2+, 1+, 0) was r=0.359 (P=0.001) and r=0.396 (P<0.001), respectively. **Conclusion:** CK7+Hs serves as a cholestasis index of PBC and are associated with the ductopenia grade and interface activity. Aberrant cytokeratin 7 expression by hepatocytes can predict the ductopenia grade in primary biliary cholangitis.



Disclosures: Hongli Liu: Nothing to Disclose, Qing-Fang Xiong: Nothing to Disclose, yandan zhong: Nothing to Disclose, Du-Xian Liu: Nothing to Disclose, Ping Huang: Nothing to Disclose, Xiao-Ning Feng: Nothing to Disclose, Yu Zhang: Nothing to Disclose, YongFeng Yang: Nothing to Disclose

4382 | INFLAMMATORY BOWEL DISEASE BURDEN INCREASES OVER TIME IN PATIENTS WITH PRIMARY SCLEROSING CHOLANGITIS POST-LIVER TRANSPLANT

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Background: Primary Sclerosing Cholangitis (PSC) is an autoimmune cholangiopathy often requiring liver transplantation (LT). PSC is highly associated with inflammatory bowel disease (IBD) before and after LT. Though pre-LT colectomy may reduce the risk of recurrent PSC, detailed characterization of post-LT IBD and its impact on graft function is not well known. The aim of this study was to investigate IBD activity post-LT and its relationship to liver graft function. **Methods:** This is a single-center retrospective study of patients who underwent LT for PSC between 2013-2023. Data collection included liver function tests, immunosuppression regimens, and IBD activity at 6- and 12-months post-LT. IBD activity was determined at the noted timepoints including clinical, endoscopic, or histologic status. Fisher's exact test was used to assess for significance. **Results:** A total of 26 patients were analyzed with mean age at LT of 37, 38% female, 46% receiving living donor LT. 73% had known IBD and 21% of those underwent colectomy pre-LT. Notably, in patients without known IBD pre-LT, 29% developed *de novo* IBD and all were diagnosed beyond 12-months post-LT. Liver graft function at 6- and 12- months did not differ by IBD activity. 16% of patients had active IBD both at 6 and 12 months, including 40% with pouchitis among the pre-LT colectomy group. Pre-LT colectomy was not associated with differences in graft function at 6- or 12-months (p=0.15). Liver test elevations at 6 months were not associated with IBD activity at 12 months (p=0.15). IBD therapy during the first year post-LT did not impact graft function at 12 months in those with vs. without colectomy (p=0.21). By the last observation timepoint, the percent of patients with active IBD (clinical, endoscopic, or histologic) increased from 16% to 42%, with a wide range of regimens including mesalamine and biologic

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therapies. **Conclusion:** In this single center retrospective study of PSC patients who received LT, we found no differences in IBD status, pre-transplant colectomy, and IBD control and its association with graft function within the first year of transplant. However, we did note a significant increase in the frequency of active IBD over time. Furthermore, nearly a third of patients were newly diagnosed with IBD beyond 12 months post-LT, with widely heterogeneous regimens and observation timepoints. This indicates the need for greater vigilance for IBD activity in this population and standardized monitoring and management protocols post-LT. Evaluation of the relationship between IBD activity and graft function warrants larger, multi-centered studies.

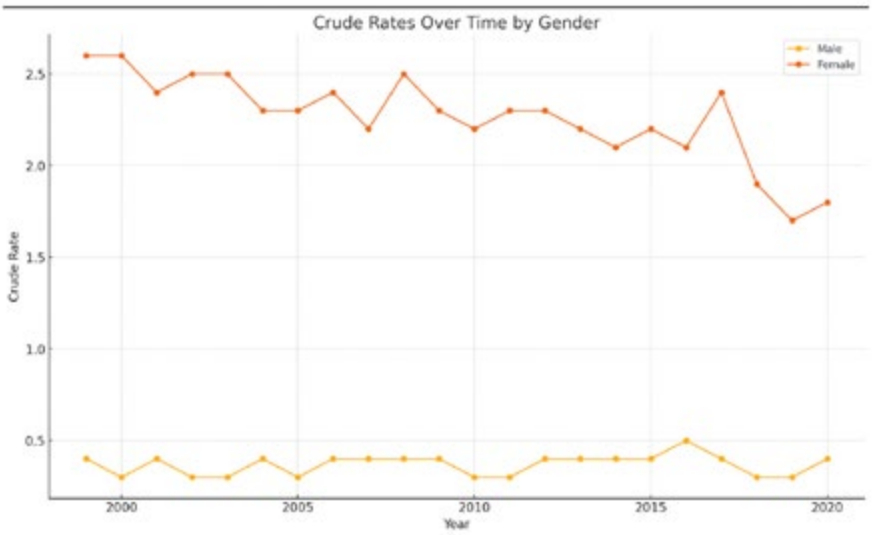
Disclosures: Meagan Alvarado: Nothing to Disclose, Vandana Khungar: Nothing to Disclose, Badr Al Bawardy: Nothing to Disclose, Uyen To: Nothing to Disclose, David Assis: Nothing to Disclose

4383 | CRUDE DEATH RATES FOR MALE AND FEMALE POPULATIONS DUE TO HEPATIC DISEASES FROM 1999 TO 2020: A COMPARATIVE TREND ANALYSIS AND IDENTIFICATION OF STATISTICALLY SIGNIFICANT SHIFTS

Riya Mehta[1] Firas Batrash[1] Sriya Kosaraju[1] Kiel Corkran[2] Islam Mohamed[2]

[1]University of Missouri Kansas City School of Medicine, [2]University of Missouri Kansas City

Background: Primary biliary cholangitis (PBC) has female predominance in incidence. Overall survival is improving as new therapies emerge for PBC. However, the exact effects of improving therapies over time on different sex-based mortality outcomes has not been identified. This study aims to evaluate the death rates for male and female populations due to primary biliary cholangitis. **Methods:** De-identified publicly available population data from the Centers for Disease Control and Prevention Wide-ranging Online Data for Epidemiologic Research database was evaluated. Informed consent and institutional review board approval were not required per the Common Rule. Underlying deaths due to Primary Biliary Cholangitis were included by the International Classification of Diseases, Tenth Revision (ICD-10) code K74.3. Crude death rates per 1,000,000 (CDR) in the United States between 1999-2020 were included in the study. T-tests by decade were used to compare trends over time. **Results:** A total of 8,915 deaths (86.5% female; 13.5% male) from 1999 to 2020 were reviewed focusing on the effect of sex on CDR due to PBC. Overall, the mean CDR for males and females were 0.36 and 2.15 respectively. Male crude death rates stayed relatively consistent over 21 years and had a standard deviation of 0.05 while females saw more significant variation (standard deviation = 0.36), particularly in the most recent period 2017-2020 where the rate declined sharply. Statistical analysis stratified by decade showed significant differences in CDR between the sexes in both decades (t2000s = -45.79, p2000s < 0.0001; t2010s = -25.76, p2010s < 0.0001). **Conclusion:** The analysis reveals significant sex differences in crude death rates due to PBC, with females consistently exhibiting higher rates compared to males. These differences were statistically significant in the 2000s and 2010s. Despite this, male mortality rates are not improving as significantly as female mortality rates in recent years. These findings underscore the need for sex-specific interventions and future research for PBC.



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Disclosures: Riya Mehta: Nothing to Disclose, Firas Batrash: Nothing to Disclose, Sriya Kosaraju: Nothing to Disclose, Kiel Corkran: Nothing to Disclose, Islam Mohamed: Nothing to Disclose

4384 | THE EFFECT OF RACE ON AUTOIMMUNE HEPATITIS MORTALITY RATES IN THE UNITED STATES

Neeti Reddy[1] Shravani Khisti[1] Kushala Madduru[1] Shravani Khisti[1] Kiel Corkran[1] Samuel Kim[1] Islam Mohamed[1]

[1]University of Missouri- Kansas City

Background: Autoimmune hepatitis (AH) is a chronic, inflammatory liver disease resulting from immune-mediated destruction that can lead to severe liver damage and result in death if untreated. The rates of AH can vary depending on different factors, such as demographics, that ultimately play a role in patient outcomes such as mortality rates. Even so, there are few studies examining the incidence and effects of race on AH mortality in the US. The purpose of this investigation is to describe mortality rates in the US between 1990-2020 due to AH. **Methods:** De-identified publicly available population data from the Centers for Disease Control and Prevention Wide-ranging Online Data for Epidemiologic Research database was evaluated. Informed consent and institutional review board approval were not required per the Common Rule. Underlying deaths due to autoimmune hepatitis infection were included by the International Classification of Diseases, Tenth Revision (ICD-10) code K75.4. Crude rates per 1,000,000 in the United States between 1999-2020 were included in the study. Trend analysis, ANOVA tests, and linear regression models were used to compare trends per race over time. **Results:** Using the ANOVA analysis, no significant differences were found in the mortality rates between race groups (p= 0.131). In the regression analysis, there is a significant decrease in adjusted mortality rates over time. Specifically, for Black individuals (p=0.012) and for White individuals (p=0.009), regression analyses indicated these groups experienced a significant decrease in adjusted mortality rates. Even so, interaction terms between race and year were significant and showed a slower decrease for Black individuals (p=0.012) than White individuals (p=0.009) compared to the overall trend. **Conclusion:** This study provided a detailed insight into how demographic factors, such as racial groups, play a role in the mortality rate of AH. These findings emphasize the need for bridging the disparity between Black and White racial groups experiencing differing trends in adjusted mortality rates due to AH. Our findings show that both these racial groups follow the overall trend of decrease in adjusted mortality rates, however, Black individuals exhibit significantly less steep of a decline. This indicates that future studies and research should be dedicated to finding genetic, lifestyle, and comorbidity factors specific to these Black or African American and White racial groups.



Disclosures: Neeti Reddy: Nothing to Disclose, Shravani Khisti: Nothing to Disclose, Kushala Madduru: Nothing to Disclose, Shravani Khisti: Nothing to Disclose, Kiel Corkran: Nothing to Disclose, Samuel Kim: Nothing to Disclose, Islam Mohamed: Nothing to Disclose

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4385 | SPATIAL TRANSCRIPTOMIC ANALYSIS OF HISTORICAL FIXED PRIMARY SCLEROSING CHOLANGITIS LIVERS REVEALS DISTINCT SIGNALING PATHWAYS

Sayed Obaidullah Aseem Grayson Way[1] Derrick Zhao[1] Phillip Hylemon[1] Michael Idowu[1] Arun Sanyal[1] Huiping Zhou[1]

[1]Virginia Commonwealth University

Background: Primary sclerosing cholangitis (PSC) plagues medium and large bile ducts with progressive fibrosis and inflammation. There is no effective treatment for PSC due to poorly understood mechanisms of onset and progression. Progress has been made in defining the transcriptomics of PSC but without extensive analyses of bile ducts. We aimed to determine if spatial transcriptomic analysis of historical fixed and paraffin embedded (FPE) liver tissue was possible and to compare PSC transcriptomic profile with controls. **Methods:** FPE liver slides were obtained from 4 PSC patients (3 male and 1 female, Caucasian and African American) and 4 control patients (2 with cirrhosis of other etiologies and 2 with 'healthy' liver with metastatic cancer) who had undergone liver transplant or resection within the last 15 years. Spatial transcriptomics utilizing NanoString GeoMx® Digital Spatial Profiler with the human whole transcriptome atlas probe set was performed using morphological biomarkers to identify bile ducts (EpCAM), immune cells (CD45), and myofibroblasts (αSMA). Differentially expressed genes (DEGs) underwent gene set enrichment analysis (GSEA) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis to identify the impacted biological pathways. **Results:** Our analysis revealed 345 DEGs in bile ducts, 323 in immune cells and 416 in myofibroblasts in PSC compared to both diseased and 'healthy' controls (adjusted $p<0.05$). Bile duct cells had significantly increased expression of some cholangiocyte markers (KRT7/18: logFC 1.5/1) and transporters (AQP3: logFC 1), but reduced expression of others (SPP1 and CFTR: logFC -1 each) (adjusted $p<0.05$). Adipocytokine signaling pathway and cholesterol metabolism were most upregulated and downregulated pathways respectively ($p<0.05$). Immune cells showed increased expression of STAT3 (logFC 0.6, adjusted $p<0.05$) with biosynthesis of cofactors as the most upregulated pathway ($p<0.05$). Collagen and smooth muscle actin species were abundantly expressed but appeared to be decreased in PSC compared to cirrhosis of other etiologies. Intramolecular oxidoreductase activity pathway was most upregulated in myofibroblasts in PSC compared to all controls ($p<0.05$). **Conclusion:** This proof-of-concept study demonstrates that not only spatial transcriptomics on FPE liver tissue is possible but also shows dysregulation of numerous genes and distinct signaling pathways. We next plan to assess larger bile ducts where PSC originates.
Disclosures: Sayed Obaidullah Aseem: Galmed Pharmaceuticals: Grant/Research Support, Grayson Way: Nothing to Disclose, Derrick Zhao: Nothing to Disclose, Phillip Hylemon: Nothing to Disclose, Michael Idowu: Nothing to Disclose, Arun Sanyal: Genfit, Akarna, Tiziana, Durect, Inversago, Hemoshear, North: Stock - publicly traded company, Astra Zeneca (60K), Boston Pharmaceutical

4386 | IMPACT OF VANCOMYCIN ON LIVER FIBROSIS IN PAEDIATRIC PATIENTS WITH PRIMARY SCLEROSING CHOLANGITIS

Stefania Staudohar[1] Taylor Beedie[2] Michael Miller[2] Andreanne Zizzo[2]

[1]Western University, [2]Western University, Children's Hospital, LHSC

Background: Primary Sclerosing Cholangitis (PSC) is a rare autoimmune liver disease that causes chronic inflammation in the bile ducts, leading to fibrosis. Liver fibrosis is monitored with transient elastography (FibroScan), with higher scores corresponding to more advanced disease. Off label use of vancomycin has been explored in the treatment of PSC due to the drug's reported impact on systemic immune function and alteration in gut microbiota. To date, various studies have assessed the benefits of vancomycin use in PSC, although no clear recommendation has been made for the use of this drug in clinical practice. Therefore, the purpose of this study is to evaluate trends in our paediatric population diagnosed with PSC at The Children's Hospital. Additionally, we will explore the effect of vancomycin on liver disease progression in our patient cohort. We anticipate that patients prescribed vancomycin for management of their PSC will see an improvement in their fibrosis scores over time compared to those patients not prescribed Vancomycin. **Methods:** A total of 15 paediatric patients consented to the prospective study. Overlap conditions (AIH, IBD) were included. Baseline FibroScan scores were collected for all patients. A cohort of 8 patients were successfully prescribed vancomycin for management of their PSC (50mg/Kg/day PO divided TID). Labs and repeat fibrosis scores were completed for those followed on vancomycin. Pre and post values were compared within the vancomycin cohort to determine if there were significant changes

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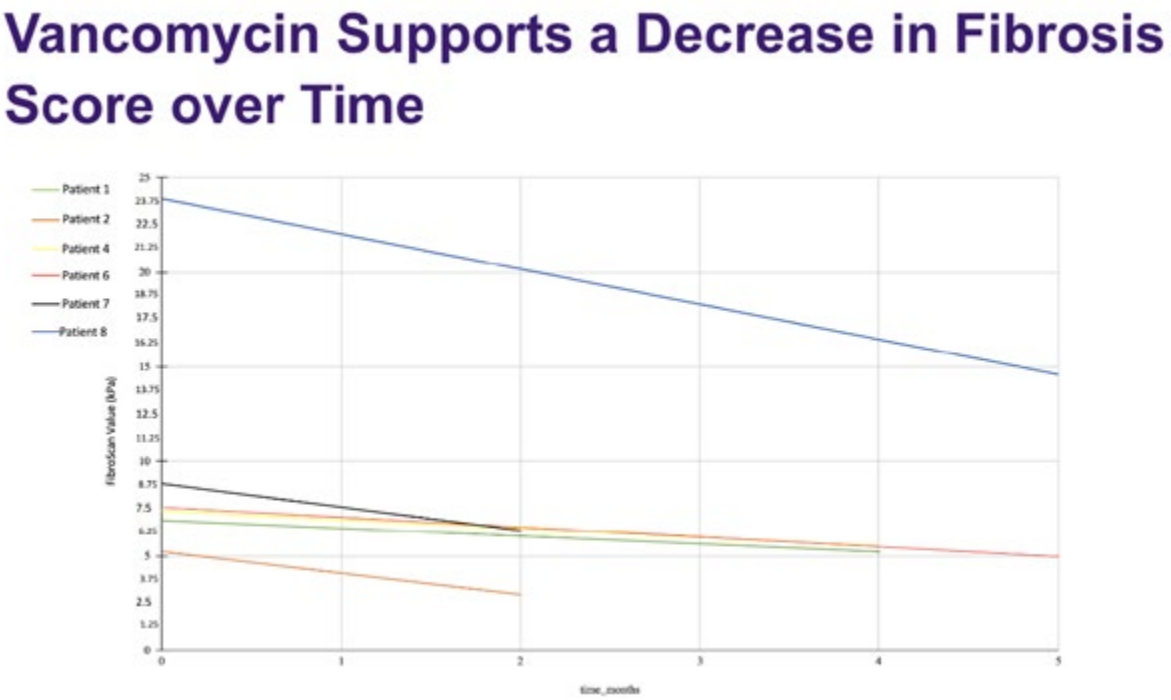
over time in this population. **Results:** At baseline, there were no significant differences between patients being treated with vancomycin and patients that were not (p=0.343). There was no significant change in FibroScan scores over time (p=0.289), however a decreasing trend in scores was observed. Liver enzymes did not show a significant decrease throughout treatment (ALT p=0.718, AST p= 0.894, ALP p=0.108, GGT p=0.056). Total and direct bilirubin did not significantly change throughout treatment (p= 0.091, p=0.373). Fibroscan score and GGT level were not significantly correlated in patients treated with vancomycin (p=0.716). **Conclusion:** Vancomycin did not significantly alter liver enzymes or fibrosis scores in patients with PSC. However, we did see a trend of vancomycin supporting a decreasing fibrosis score over time in our cohort. Our results did not show a correlation between GGT and fibrosis, suggesting a need to revisit current governmental guidelines for the drug's approval in the paediatric population with PSC. Future implications of this study include a correlation of fecal calprotectin and fibrosis scores at baseline prior to intervention, and at every follow-up visit to assess the impact of both IBD and liver disease interventions. Standardized FibroScan intervals among patients and an increased sample size are also warranted in future investigations.



Disclosures: Stefania Staudohar: Nothing to Disclose, Taylor Beedie: Nothing to Disclose, Michael Miller: Nothing to Disclose, Andreanne Zizzo: Mirum Pharmaceuticals: Advisor

4387 | HOW FREQUENT IS CLINICAL CONCERN FOR 'OVERLAP' BETWEEN PRIMARY BILIARY CHOLANGITIS AND AUTOIMMUNE HEPATITIS ENCOUNTERED IN REAL WORLD CARE?

Inbal Houri[1] Hooman Ebrahimi[2] Guilherme Cancado[2] Kristel Leung[3] Claire Gage[2] Bettina Hansen[1] Aliya Gulamhusein[2] Gideon Hirschfield[1]

[1]Toronto General Hospital, [2]Toronto Centre for Liver disease, [3]University of Toronto

Background: Overlapping clinical features in autoimmune liver diseases are well recognized. How frequently this impacts clinical care of patients with autoimmune hepatitis (AIH) and primary biliary cholangitis (PBC) is hard to assess. We sought to understand from the perspective of a large liver programme the frequency of clinical concern for overlap between PBC and AIH. **Methods:** Qualitative review of clinical, demographic and laboratory data collected retrospectively from patients' medical records from 1995-present across a tertiary care liver programme. Concern for the 'potential' presence of overlap was identified using any of: diagnosis of overlap in the electronic medical records at any point; concomitant diagnoses of AIH and PBC; AIH on UDCA (without features

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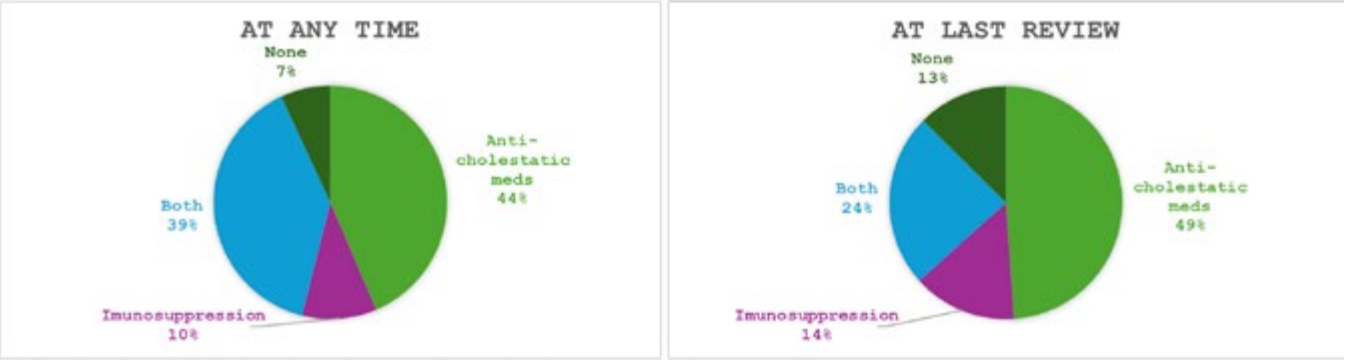
of primary sclerosing cholangitis) or with positive PBC serologies; PBC on immunosuppressive treatment (without a non-related indication) or with specific AIH serologies; and patients who reportedly met 'Paris criteria' at any time point. **Results:** Over the time period studied, at least 1700 patients were followed with a diagnosis of either AIH or PBC. Amongst this cohort 19% (n=319) had clinical mention of "potential" AIH-PBC overlap in the medical record. The median age at initial diagnosis of autoimmune liver disease was 46 years (36.0-55.6), median time of follow up was 10.0 years (5-18), and 84% of patients were female. Of the total cohort, 7.4% (n=125) had been treated with both immunosuppression and anti-cholestatic medications at some point; however, at last follow up only 4.5% (n=77) remained on dual treatment. Of the 319 "potential overlaps", 16.9% (n=54) were treated with second line therapy for PBC (obeticholic acid / fibrate / both) at last review. Interestingly, 40.7% (n=22) of those treated with second (and/or third) line PBC therapy had been treated with immunosuppressive medications at some point during follow-up but only 18.5% (n=10) remained on combination treatment at follow up. **Conclusion:** Clinicians will encounter patients with variant AIH and PBC presentations. However, as a proportion of their practice, whilst the 'question' will arise in up to 1 in 5 patients, over time less than 1 in 20 will actually remain on clinician-initiated therapy targeting two disease processes. As high risk PBC becomes increasingly well recognized and additional anti-cholestatic therapies become available, the proportion of patients truly requiring combination can be expected to remain low.

Figure: Therapy choices



Comparison of medications given at any time and at last follow up

Disclosures: Inbal Houri: Nothing to Disclose, Hooman Ebrahimi: Nothing to Disclose, Guilherme Cancado: Nothing to Disclose, Kristel Leung: Nothing to Disclose, Claire Gage: Nothing to Disclose, Bettina Hansen: Nothing to Disclose, Aliya Gulamhusein: Advanz: Consultant, Cymabay: Consultant, Gideon Hirschfield: Consultant relationship with Mirum; Has not ended; Consultant relationship with Advanz; Has not ended; Consultant relationship with Chemomab; Has not ended; Consultant relationship with Gilead; Has not ended; Consultant relationship with Kowa; Has not ended; Consultant relationship with Intercept; Has not ended; Consultant relationship with Pliant; Has not ended; Consultant relationship with Falk; Has not ended; Consultant relationship with GSK; Has not ended; Consultant relationship with Ipsen; Has not ended; Consultant relationship with CymaBay; Has not ended

4388 | COMPARISON OF PATHOLOGICAL FEATURES OF PATIENTS WITH ANTIBODY-NEGATIVE AND POSITIVE PRIMARY BILIARY CHOLANGITIS

Hongli Liu[1] Yi-Fan Hu[2] Wang Li[2] Yu Zhang[3] Qing-Fang Xiong[3] Yan-Dan Zhong[3] Du-Xian Liu[3] Ping Huang[3] Xiao-Ning Feng[3] Yong-Feng Yang[3]

[1]The Second Hospital of Nanjing, Southeast University, [2]The Second Hospital of Nanjing, Affiliated to Nanjing University of Chinese Medicine, [3]The Second Hospital of Nanjing, Teaching Hospital of Southeast University

Background: To examine the differences and similarities among primary biliary cholangitis (PBC) with positive and negative expression of autoantibodies (anti-mitochondrial antibodies AMA and, AMA-M2;, antinuclear antibodies anti-gp210, and anti-sp100). **Methods:** Clinical and pathological data of PBC in patients who underwent liver puncture biopsy were retrospectively collected from January 2016 to September 2018 at the Second Hospital of Nanjing. The differences in clinical and pathological indexes of PBC between autoantibody

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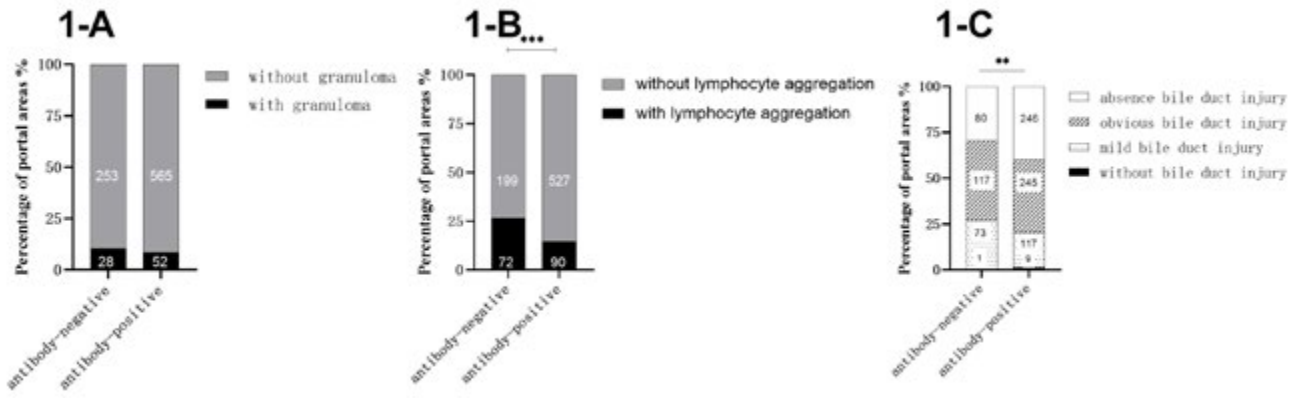
negative and positive groups were analyzed by SPSS 25.0, and the patients' previous autoantibody indexes were collected for follow-up. **Results:** The average age of 85 PBC patients was (52.2±9.2) years old, including 15 males (17.6%) and 70 females (82.4%), with a male-to-female ratio of 1:4.7. 59 Fifty-nine autoantibody-positive cases and 26 autoantibody-negative cases, were with 50 (84.7%) AMA positive, 51 (86.4%) AMA-M2 positive, 21 (35.6%) anti-gp210 positive, and 15 (25.4%) anti-sp100 positive. The distribution of CK7-positive hepatocytes and the degree of bile duct injury in the portal area of PBC patients in the antibody-negative group were lower than those in the antibody-positive group (P<0.05). There was no significant difference in the distribution of interface inflammation, plasma cell grade, ductular reaction, and fibrosis between the two groups. When the autoimmune antibodies were reexamined at 2 months–7 years (median time 1 year), AMA, anti-gp210, and anti-sp100 were still negative in 16 antibody-negative patients. **Conclusion:** The pathological symptoms and diagnostic patterns of autoantibody-negative and positive PBC were generally comparable. In this study, the pathological manifestations of antibody-negative PBC were similar to those of antibody-positive PBC, but the lymphocyte aggregation in antibody-negative PBC was more severe than that in antibody-positive PBC, while the degree of bile duct injury and CK7-positive hepatocytes were milder than that in antibody-positive PBC, suggesting that the overall pathological changes of antibody-negative PBC were slightly milder than those of antibody-positive PBC.



Disclosures: Hongli Liu: Nothing to Disclose, Yi-Fan Hu: Nothing to Disclose, Wang Li: Nothing to Disclose, Yu Zhang: Nothing to Disclose, Qing-Fang Xiong: Nothing to Disclose, Yan-Dan Zhong: Nothing to Disclose, Du-Xian Liu: Nothing to Disclose, Ping Huang: Nothing to Disclose, Xiao-Ning Feng: Nothing to Disclose, Yong-Feng Yang: Nothing to Disclose

4389 | LABEL-FREE CLASSIFICATION OF CELL TYPE DIVERSITY IN HUMAN LIVERS DISTINGUISHES AUTOIMMUNE HEPATITIS FROM DISEASE CONTROLS

Marc Sherman[1] Daniel Schafer[1] Molly Thomas[2] Alan Mullen[3] Georg Lauer[1] Alexandra-Chloe Villani[1] Wolfram Goessling[1]

[1]Massachusetts General Hospital, [2]Oregon Health & Science University, [3]University of Massachusetts Medical School

Background: Autoimmune hepatitis (AIH) is defined syndromically by a combination of laboratory biomarkers, hallmark histopathologic features, and a responsiveness to steroids. Combining traditional histologic liver tissue analysis with deep cellular profiling using single-nuclei RNA sequencing (snRNA-Seq) approaches may reveal biomarkers that better distinguish AIH from other liver diseases while offering novel pathological insights into AIH. **Methods:** Patients undergoing clinically-indicated liver biopsies for suspected AIH were recruited to an IRB-approved study for collection of liver tissue. Patients undergoing liver resection for non-hepatic disease served as controls. Liver tissue cores were processed for snRNA-Seq using the 10x Genomics platform, and resulting datasets were analyzed using the SCANPY toolkit. After annotation, the relative composition of cell types was computed for each sample. Agglomerative clustering on these cell type abundance phenotypes (CTAPs) was then performed on unlabeled samples to identify unbiased classifications of human liver disease among patients with suspected AIH. **Results:** 32 patient samples were processed. With >2 years follow-up, final patient diagnoses included AIH (n=6), metabolic dysfunction-associated (MASH) (n=10), simple steatosis (n=3), AIH

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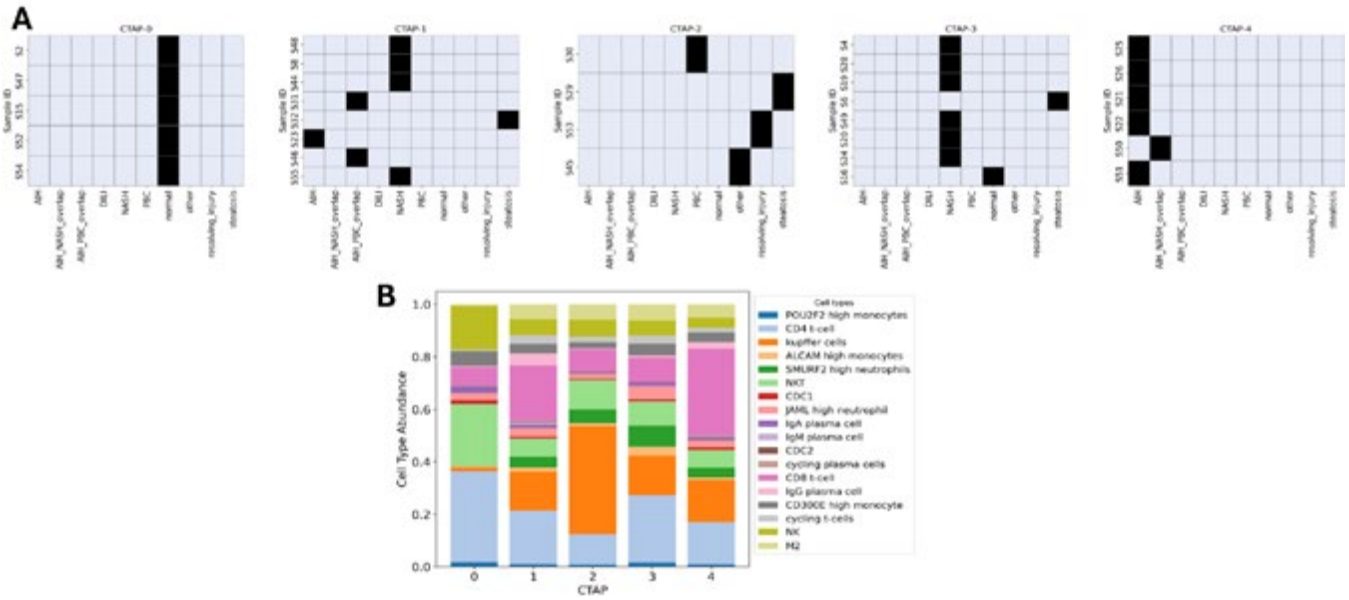
overlap syndromes (n=3), other non-AIH liver diseases or resolving injury states (n=5), and normal controls (n=6). 487,140 high-quality nuclei were cumulatively isolated from these patients, and all major cell types of the liver were well represented, including hepatocytes and the immune fraction. Naïve agglomerative clustering of immune lineage CTAPs revealed 5 distinct patient classes (Fig. 1A), of which one class contained 5/6 AIH samples (CTAP-4), and another contained 5/6 normal samples (CTAP-0). MASH samples were split across a minority cluster (CTAP-1) and a majority cluster (CTAP-3), with CTAP-1 also containing the orphan AIH sample (S23), while a final class contained nearly all non-MASH/AIH cases (CTAP-2). The major cell type defining the AIH cluster from all other conditions was expansion of cytotoxic CD8 tissue resident memory (Trm) T-cells. Plasma cell expansion differentiated the AIH case cluster from most other CTAPs, but not from the minority MASH case cluster (CTAP-1). Of interest, the S23 AIH patient localizing to the minority MASH cluster (CTAP-1) had typical clinical features of MASH, and a biopsy that while lacking steatosis was reported as atypical for AIH. **Conclusion:** snRNA-Seq analysis in human livers revealed a signature of immune cell type abundance that alone could distinguish AIH from other major liver diseases without labeling. Our approach could refine the diagnostic criteria for AIH while better specifying the phenotypic spectrum of inflammatory liver diseases. We anticipate snRNA-Seq and naïve agglomerative clustering may further sub-classify AIH into sub-types in larger cohorts.



Disclosures: Marc Sherman: Nothing to Disclose, Daniel Schafer: Nothing to Disclose, Molly Thomas: Johnson and Johnon: Stock – privately held company, Alan Mullen: Nothing to Disclose, Georg Lauer: GSK: Grant/Research Support, GSK: Consultant, Alexandra-Chloe Villani: Nothing to Disclose, Wolfram Goessling: Nothing to Disclose

4390 | AN ELEVATED BASELINE LEVEL OF ALKALINE PHOSPHATASE, ALANINE AMINOTRANSFERASE, AND ASPARTATE AMINOTRANSFERASE PREDICT A LACK OF BIOCHEMICAL RESPONSE TO UDCA THERAPY AMONG HISPANIC PATIENTS LIVING WITH PRIMARY BILIARY CHOLANGITIS: A RETROSPECTIVE, PROPENSITY SCORED-MATCHED, COHORT STUDY

Luis Alejandro Rosales Renteria[1] Maria Sarai Gonzalez Huezo[2] Gonzalo Peña-Arellano[2] Jorge Alejandro López Cossio[2] Marcela Morales Ibarra[2] Jose David Prieto Nava[2]

[1]Centro Médico ISSEMyM Toluca, [2]Centro Medico ISSEMyM Toluca

Background: Primary biliary cholangitis (PBC) is a chronic, progressive, autoimmune liver disease characterized by the destruction of the small bile ducts within the liver. Ursodeoxycholic acid (UDCA) is the first-line treatment for PBC, shown to improve liver biochemistry and delay disease progression. However, the response to UDCA therapy is variable among patients, with some failing to achieve a satisfactory biochemical response. Identifying

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predictors of non-response is crucial for optimizing treatment strategies and improving patient outcomes. Recent evidence has shown a lower biochemical response among patients of Hispanic ethnicity, which is often underrepresented in clinical research. The findings have significant implications for clinical practice, potentially guiding hepatologists in early identification of non-responders and facilitating more personalized treatment plans to improve outcomes in this specific patient population, and **Methods:** This is a single center, retrospective, propensity score-matched cohort study, which included all patients with PBC confirmed by liver biopsy that were followed by the hepatology clinic from January 1st, 2015 to March 1st 2024 under treatment with UDCA. All demographic, clinical and biochemical characteristics were obtained. A response was defined according to the Toronto criteria with an alkaline phosphatase (ALP) <1.67 x ULN after 2 years of UDCA therapy. Patients were subdivided on the presence or absence of a biochemical response. The primary outcome was mortality due to a liver related event (LRE), the secondary outcomes were variables associated with a non response. **Results:** A total of 132 patients were included, 70 were non responders and 62 fulfilled Toronto criteria of response. The predominant gender was female in both groups (96.78% and 96%) with a median of 56 years of age for the non responders and 58 years for those who did. The prevalence of autoimmune disease in both groups was 52% and 47%. Mortality due to LRE in the no response vs responders group was 41% vs 6.2%, respectively, all patients that achieved such an outcome had liver cirrhosis, a difference which was statistically significant (OR 3.67, 95% CI [1.608, 8.411], p<0.001). Factors associated with incomplete response were statistically significant for a baseline level of ALP > 2 x ULN (OR 5.3, 95% CI [2.433, 11.649], p<0.001), a baseline level of alanine aminotransferase (ALT) > ULN (OR 5.3, 95% CI [2.429, 11.845], p<0.001) and a baseline level of aspartate aminotransferase (AST) > ULN (OR 7.8, 95% CI [3.554, 17.159] p<0.001). All of these variables remained statistically significant after multivariate regression analysis. **Conclusion:** In patients with PBC that receive initial therapy with UDCA, a baseline increased ALP, AST and ALT are associated with an incomplete biochemical response, identifying patients that might benefit from early initiation of additional therapies.

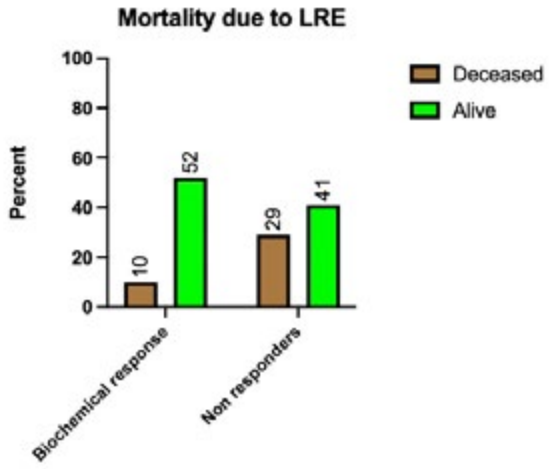

Table 1: Mortality due to **LRE,** among patients who fulfilled Toronto criteria for Biochemical response vs those who did not.
OR 3.67, 95% CI [1.608 , 8.411], p<0.001

Multivariate regression *	OR (95% CI)	p value
ALP > 2x ULN	3.13 (3.02-3.15)	0.0476
ALT > ULN	2.82 (2.78-2.86)	0.0465
AST > ULN	3.06 (3.01-3.11)	0.0483

Table 2. *Multivariate regression analysis of variables associated with no response.* **Adjusted for sex, age, autoimmune diseases.* **Only overall mortality and development of respiratory failure remained statistically significant.**

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Disclosures: Luis Alejandro Rosales Renteria: Nothing to Disclose, Maria Sarai Gonzalez Huezo: Nothing to Disclose, Gonzalo Peña-Arellano: Nothing to Disclose, Jorge Alejandro López Cossio: Nothing to Disclose, Marcela Morales Ibarra: Nothing to Disclose, Jose David Prieto Nava: Nothing to Disclose

4391 | NORMALIZATION OF ALKALINE PHOSPHATASE COMPARED TO CONVENTIONAL RESPONSE CRITERIA LEADS TO LOWER LIVER RELATED EVENTS AND MORTALITY IN PATIENTS LIVING WITH PRIMARY BILIARY CHOLANGITIS, TREATED WITH UDCA: A RETROSPECTIVE, PROPENSITY SCORED-MATCHED, COHORT STUDY

Luis Alejandro Rosales Renteria Gonzalo Peña-Arellano[1] Jorge Alejandro López Cossio[1] Marcela Morales Ibarra[1] Jose David Prieto-Nava[1] Alma Laura Osorio Núñez[1] Maria González Huezo[1]

[1]Centro Medico ISSEMyM Toluca

Background: Primary biliary cholangitis (PBC) is a chronic, progressive, autoimmune liver disease characterized by the destruction of the small bile ducts within the liver. Ursodeoxycholic acid (UDCA) is the first-line treatment for PBC, shown to improve liver biochemistry and delay disease progression. All biochemical criteria for response recommend a threshold of alkaline phosphatase (ALP) that is higher than the ULN, because those scores have shown a lower disease progression, liver related events and overall mortality. The impact of achieving normalization of ALP, compared to traditional biochemical scores is unknown, but it's relevance, particularly in countries without universal access to liver transplantation could be significant. **Methods:** This is a single center, retrospective, propensity score-matched cohort study, which included all patients with PBC and chronic liver disease, confirmed by liver biopsy that were followed by the hepatology clinic from January 1st, 2015 to March 1st 2024 under treatment with UDCA. All demographic, clinical and biochemical characteristics were obtained. A biochemical response was defined according to the Toronto criterion, with an ALP <1.67 x ULN after 2 years of UDCA therapy. Patients were subdivided into two groups, either by fulfilling these criteria or by achieving normalization of ALP <120 IU/L). The primary outcome was mortality due to a liver related event (LRE) a composite that included variceal hemorrhage (VH), spontaneous bacterial peritonitis (SBP), hepatic encephalopathy (HE), ascites, acute kidney injury (AKI), hepatorenal syndrome-AKI (HRS-AKI), and ACLF. the secondary outcomes were development of each independent variable of the definition of LRE. **Results:** Out of a total pool of 132 patients, 32 fulfilled conventional Toronto criteria without achieving normalization of ALP, and 30 had a ALP level below 120 IU/L. The predominant gender was female in both groups (95% and 96%) with a median of 57 years for both groups. The prevalence of systemic autoimmune disease was similar between both groups, (55 and 57%, respectively). Mortality due to LRE in the Toronto criteria group was 14/32 (43%), compared to 4/30 (13%) in the normalization group, a difference which was statistically significant (OR 5.05, 95% CI [1.429, 17.882], p=0.005.). The development of HE (OR 5.47, 95% CI [1.075, 27.916], p=0.02) and VH (OR 4.71, 95% CI [1.165, 19.083], p=0.01), was greater in the Toronto criteria group, compared to the normalization group. These variables remained statistically significant after multivariate regression analysis (adjusted for age, gender and autoimmune systemic diseases). No statistically significant differences were found for AKI, HRS-AKI, ACLF, ascites or SBP. **Conclusion:** Among patients with PBC that receive initial therapy with UDCA, a normalization of ALP after two years, compared to Toronto criteria, leads to lower LR mortality and development of VH and HE.

Disclosures: Luis Alejandro Rosales Renteria: Nothing to Disclose, Gonzalo Peña-Arellano: Nothing to Disclose, Jorge Alejandro López Cossio: Nothing to Disclose, Marcela Morales Ibarra: Nothing to Disclose, Jose David Prieto-Nava: Nothing to Disclose, Alma Laura Osorio Núñez: Nothing to Disclose, Maria González Huezo: Nothing to Disclose

4392 | LIVER DISEASE SCREENING DISPARITIES IN HISPANIC AND PUBLICLY INSURED CHILDREN WITH CYSTIC FIBROSIS

Alaa Abdelghani[1] Addison Cuneo[1] Elizabeth Gibb[1] Emily Perito[1]

[1]UCSF

Background: New 2023 CF liver disease (CFLD) guidelines advocate for additional screening in people with CF (PwCF), including biennial abdominal ultrasound (US). As a first step towards effective and equitable

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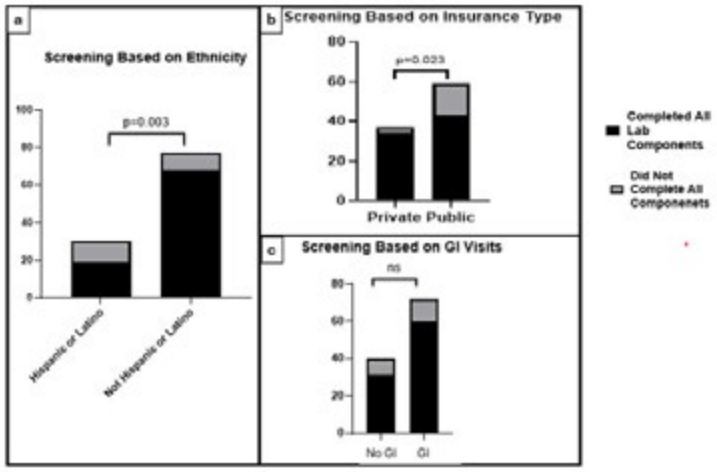
guidelines implementation, we examined our current practice of CFLD screening and identified characteristics of PwCF at-risk for inadequate screening. **Methods:** We identified PwCF aged 0-21 years, with native liver and ≥2 outpatient CF clinic visits 2017-2023 using electronic medical record review. Inadequate CFLD laboratory screening was defined as missing ≥1 component of the 2023 guidelines' recommended bundle (total bilirubin, aspartate transferase [AST], alanine transferase [ALT], alkaline phosphatase [ALK], gamma glutamyl transferase [GGT], platelets) or receiving the bundle < once/ year during the study period. Adequate US screening is having ≥1 abdominal US for PwCF >3years old. **Results:** Amongst 112 PwCF at our center, 51.8% were females; median age in 2023 was 12 years. 37% self-reported as mixed race, 26% as Hispanic or Latino;53% had public insurance. Inadequate lab screening was identified in 18% of our cohort. Age at study period end was equally distributed across categories (0-10, 11-20, >20) and not associated with inadequate lab screening (p=0.75). PwCF with public insurance were more likely to have inadequate screening than those with private insurance, and Hispanics were more likely to have inadequate screening than non-Hispanics (FIG 1a,1b). Of the 72 PwCF with at least one outpatient GI visit during the study period, 60 (83%) had adequate lab screening. Among the 40 with no GI visits, 31 (77%) had adequate lab screening (FIG 1c). PwCF with inadequate lab screening had a higher median number of CF clinic visits during the study period (22, IQR 11-24) than those with adequate screening (11, IQR 5-22) but the difference was not statistically significant. PwCF with inadequate screening had a median of 41% (IQR 25-52) of their CF clinic visits via telehealth, versus 37% (IQR 0-55) in PwCF who completed labs (p = 0.23). GGT was the most frequently missed component (17% of 112). GGT was obtained in 91% of PwCF seen by GI, versus 75% of those not seen by GI (p = 0.01). ALT, AST and platelet count were missed in less than 2% of the cohort.13 PwCF were younger than 4 years, so ineligible for ultrasound screening. Of the eligible 99 PwCF, 27 had an abdominal ultrasound during the study period. US indications were abnormal liver enzymes(n=14), abdominal pain(n=6) or other indications (n=8). **Conclusion:** We identified gaps in CFLD screening, with Hispanics and publicly insured at higher risk of inadequate screening. GI follow-up did not mitigate inadequate screening risk. Telehealth visits did not reduce adequate screening. Since US screening was newly recommended in the 2023 guidelines, it was limited in our cohort. Our CF center has now integrated abdominal US into CFLD screening as part of an implementation project.

Figure 1: Factors Associated with Inadequate CFLD Screening



a: Hispanics are more likely to have inadequate screening (36.6%) than non-Hispanics (11.6%) (p =0.003), **b:** PwCF with public insurance are more likely to have inadequate screening (16%) than those with private insurance (3%) (p =0.023). **c:** 83.3% of PwCF seen by GI completed labs, versus 77.5% who did not (p = 0.4). ns; not significant.

Disclosures: Alaa Abdelghani: Nothing to Disclose, Addison Cuneo: Nothing to Disclose, Elizabeth Gibb: Nothing to Disclose, Emily Perito: Mirum: Consultant, Ultragenyx: Consultant, BridgeBio: Consultant, Amagma: Consultant, Mirum: Grant/Research Support, Albireo: Grant/Research Support, Gilead: Grant/Research Support, Dicerna: Grant/Research Support

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4394 | AMBIENT AIR POLLUTION EXPOSURE IS ASSOCIATED WITH ADVANCED LIVER STIFFNESS AMONG LATINO YOUTH WITH PREEXISTING RISK FACTORS FOR LIVER DAMAGE

Rachel Schenker[1] Rohit Kohli[1] Tanya Alderete[2] William Patterson[2] Christopher Machle[1] Fred Lurmann[3] Michael Goran[1]

[1]Children's Hospital Los Angeles, [2]University of Colorado, [3]Sonoma Technology

Background: Ambient air pollutants have emerged as risk factors for metabolic dysfunction associated steatotic liver disease (MASLD). Our primary aim was to examine the associations between short-term (prior month) and long-term (prior year) air pollution exposure with hepatic fat fraction (HFF) and liver stiffness in Latino youth with obesity. Our secondary aim was to investigate effect modification by patatin-like phospholipase domain-containing protein 3 (*PNPLA3)* genotype and liver disease severity. **Methods:** Data was collected from 114 Latino youth with obesity. Individual exposure to particulate matter with aerodynamic diameter ≤ 2.5μm ($PM_{2.5}$), ≤ 10μm (PM_{10}), nitrogen dioxide (NO_2), 8-hour maximum ozone (8-hr-O_3), 24-hr O_3, and redox-weighted oxidative capacity (O_x^{wt}) were based on residential address histories and United States Environmental Protection Agency air quality observations. Liver fat and liver stiffness were measured using 3T magnetic resonance imaging and magnetic resonance elastography scans. Linear mixed-effect models were used to determine associations between short and long-term exposure to air pollutants with HFF and liver stiffness. We then examined whether the associations between air pollution exposure and liver fat or stiffness differed by *PNPLA3* genotype (GG versus CC/CG) or liver disease severity (classified as healthy liver, MASLD without fibrosis, and MASLD with fibrosis). **Results:** There were no significant associations between short or long-term ambient air pollution exposures with HFF, regardless of *PNPLA3* genotype or liver disease severity. Additionally, when examining the entire sample, ambient air pollution exposure was not associated with liver stiffness. However, the associations between air pollution exposure and liver stiffness depended on *PNPLA3* genotype, such that individuals with the GG genotype exhibited a stronger and more positive relationship between long-term exposure to PM_{10} (b=0.04, p<0.01), 8-hr-O_3 (b=0.06, p<0.01), and 24-hr-O_3 (b=0.11, p<0.01) and liver stiffness than individuals with the CC/CG genotype (Figure 1A). In addition, relationships between short-term exposure to PM_{10} (b=0.02, p<0.05) and O_x^{wt} (b=0.03, p<0.05) were also stronger in those with MASLD and fibrosis compared to the average of those with healthy livers and MASLD without fibrosis (Figure 1B). **Conclusion:** Short and long-term ambient air pollution exposure may be an additional risk factor for liver stiffness among Latino youth with obesity and other preexisting risk factors for liver damage, including genetic risk and more advanced stage of liver disease.

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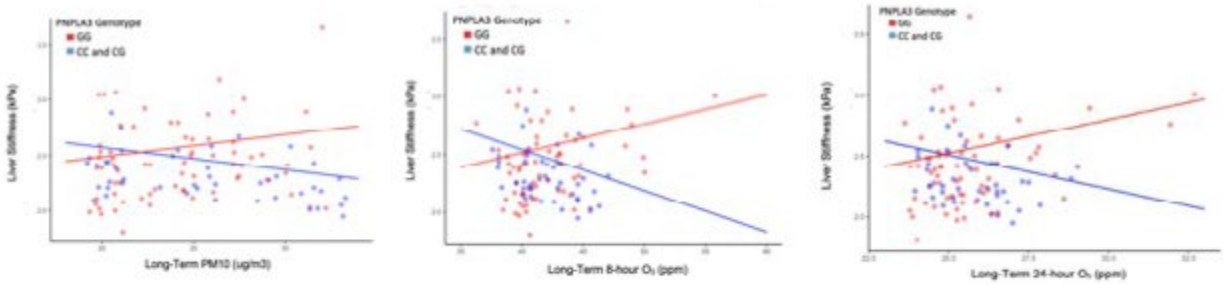
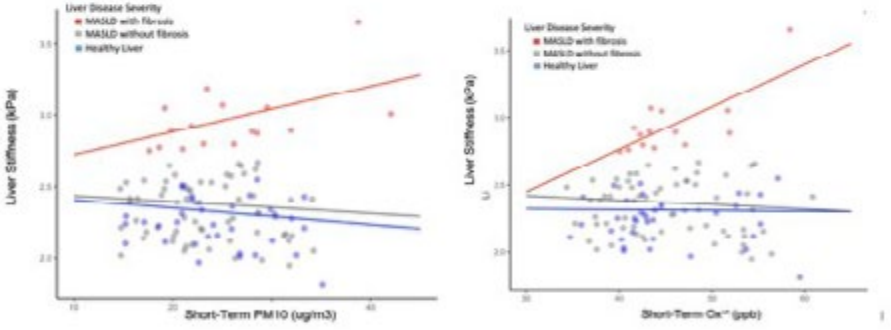
Figure 1: Differential Association Between Ambient Air Pollution Exposure and Liver Stiffness by *PNPLA3* Genotype and Liver Disease Severity

A. Higher Ambient Air Pollution Exposure is Associated with Liver Stiffness Among those with Two PNPLA3 Risk



B. Higher Ambient Air Pollution Exposure is Associated with Liver Stiffness Among those with Greater Liver Disease Severity



1A: The linear relationships between long-term PM10 exposure and liver stiffness (β=0.04, p<0.01), long-term 8-hour O_3 exposure and liver stiffness (β=0.06, p<0.01), and long-term 24-hour O_3 exposure and liver stiffness (β=0.11, p=<0.01) were stronger amongst those with GG genotypes of PNPLA3 (red) than those with CC/CG genotypes of PNPLA3 (blue).
1B: Compared to the average of the MASLD without fibrosis group (grey) and healthy liver group (blue), the MASLD with fibrosis group (red) demonstrated stronger positive relationships between short-term exposure to PM10 (β=0.02, p<0.05) and liver stiffness as well as short-term O_3^{wt} (β=0.03, p<0.05) and liver stiffness.

Disclosures: Rachel Schenker: Nothing to Disclose, Rohit Kohli: Mirum: Consultant, Ipsen: Consultant, Epigen: Grant/Research Support, Sanofi Rare Disease: Consultant, Tanya Alderete: Nothing to Disclose, William Patterson: Nothing to Disclose, Christopher Machle: Nothing to Disclose, Fred Lurmann: Nothing to Disclose, Michael Goran: Nothing to Disclose

4395 | CHARACTERIZING THE ONSET AND CLINICAL MANIFESTATIONS OF CHRONIC LIVER DISEASE IN PATIENTS WITH POST-FONTAN PHYSIOLOGY ◆

Minoti Vather[1] Danielle Guffey[2] Thomas Fogarty[1] Justin Weigand[1] Anna Banc-Husu[1] Daniel Leung[1]

[1]Texas Children's Hospital, Baylor College of Medicine., [2]Baylor College of Medicine.

Background: Fontan-associated liver disease is a congestive hepatopathy that significantly impacts morbidity and mortality post Fontan operation, but there is little data informing the frequency of clinically meaningful chronic liver disease (CLD) in children. We aimed to determine prevalence and time to development of clinical manifestations of CLD in children post-Fontan, characterize lab and biomarker indices over time, and analyze associated risk factors. **Methods:** A large retrospective cohort analysis was performed on patients post-Fontan at Texas Children's Hospital between 1/1/2010-6/30/2022. Clinical data was collected from time of Fontan to last clinic encounter, transplant, or death. CLD was defined *a priori* as ≥ 2 clinical manifestations post-Fontan (platelets ≤ 150 x10^3/uL, INR ≥ 1.5 off anticoagulation, or hepatomegaly, splenomegaly, ascites or varices on exam or imaging). Descriptive statistics, Kaplan-Meier analysis and linear mixed regression modeling was used. **Results:** In 950 patients (60% male, 48.2% white, 25.7% hypoplastic left heart), median age at Fontan (69.7% extra-cardiac conduit) was 4.9 years with a mean follow up of 13.3 years. Frequency of CLD manifestations included thrombocytopenia 25.9% (n=246), splenomegaly 14.7% (n=124), hepatomegaly 12% (n=114), coagulopathy 10.6% (n=101), ascites 7.1% (n=67) and varices 5.1% (n=48). Overall, 19.6% met CLD criteria

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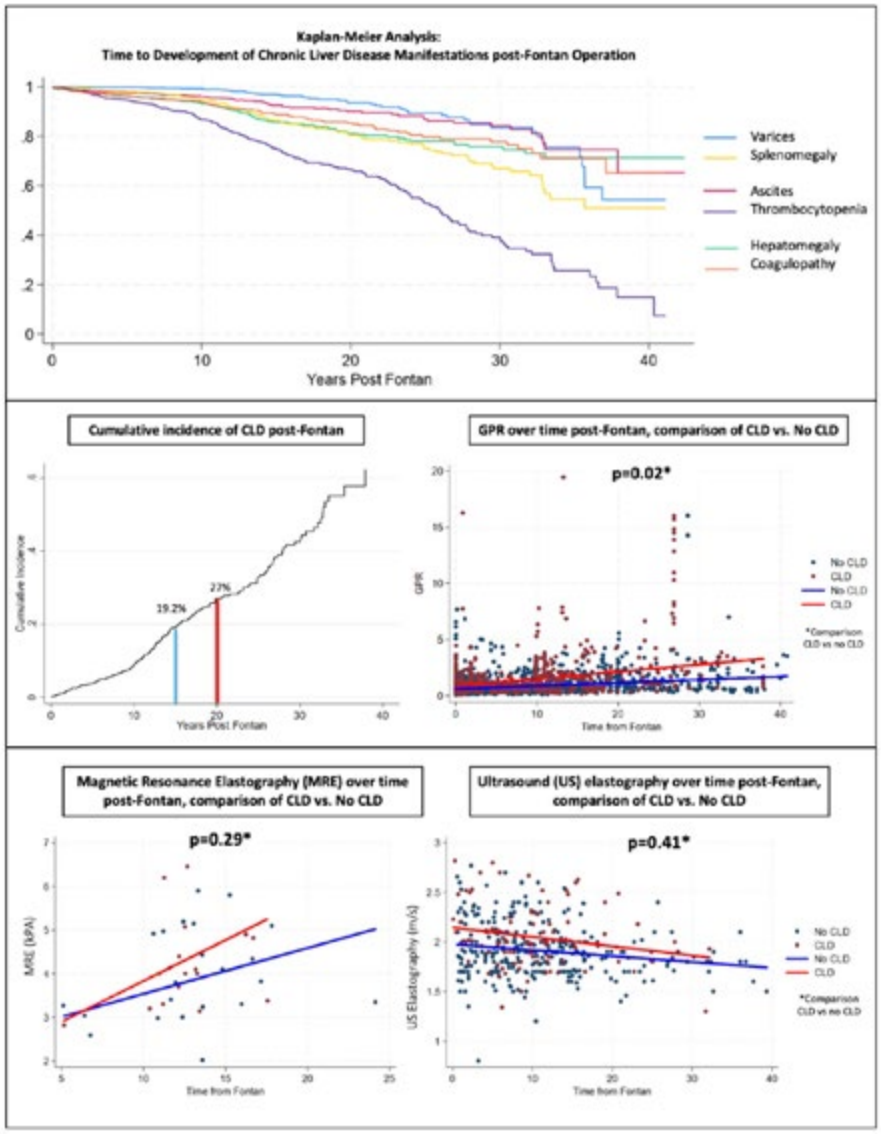
with mean onset at age 18.4 years. Cumulative incidence of CLD with heart transplant and death as competing risks was 19.2% at 15 years post-Fontan. CLD was more common in those with history of atrioventricular valve surgery (OR 1.53, 95% CI 1.99-2.34) and pacemaker use (OR 3.21, 95% CI 2.18-4.73). Platelet count decreased (2.63/yr, p<0.001) and total bilirubin increased (0.05/yr, p=0.02) over time in CLD vs. no CLD. GGT and GGT-to-platelet ratio (GPR) increased over time (1.56/yr and 0.04/yr, p<0.001) but only GPR was higher in CLD vs. no CLD (p=0.02). There was no difference in ALT, AST, CB, INR, APRI or FIB-4 over time or by CLD status and no change in mean liver stiffness by CLD status. Heart transplant, hepatocellular carcinoma (HCC) and mortality was higher in those with CLD vs. no CLD (6.8% vs. 2.4%, 1.8% vs. 0.3% and 9.6% vs. 2.1%, p<0.001, 0.03 and <0.001, respectively). **Conclusion:** To our knowledge, this is the largest characterization of CLD and outcomes in children post-Fontan. Only 8.3% of patients met CLD criteria within 10 years post-Fontan, however 20% developed CLD by 18 years of age. Thrombocytopenia and splenomegaly were the most common CLD features while varices were rare. CLD was not a cause of death, but increased risk for heart transplant, HCC and all-cause mortality. Other than GPR, liver labs, biomarkers and elastography were surprisingly unreliable markers of disease progression post Fontan, raising questions about the application of these surrogates of liver disease for CLD screening and monitoring in this population.



Disclosures: Minoti Vather: Nothing to Disclose, Danielle Guffey: Nothing to Disclose, Thomas Fogarty: Nothing to Disclose, Justin Weigand: Nothing to Disclose, Anna Banc-Husu: Mirum Pharmaceuticals: Site PI for industry-sponsored clinical trial, Daniel Leung: Gilead: Grant/Research Support, Mirum: Grant/Research Support, AstraZeneca: Advisor, CF Foundation: Grant/Research Support

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4396 | MMP-7 ELEVATION IN NEONATES WITH CONGENITAL HEART DISEASE AND CHOLESTASIS ◆

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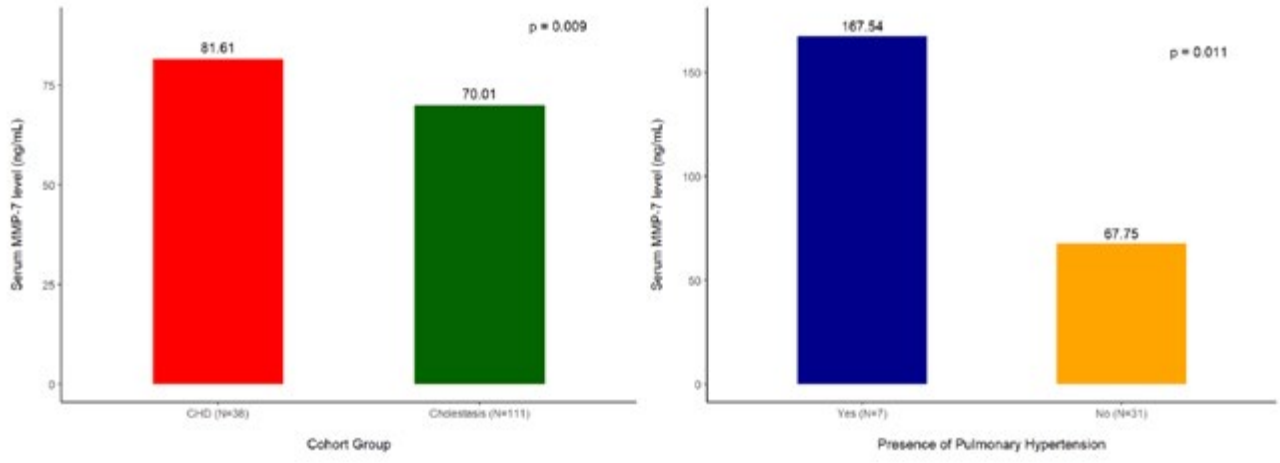
Background: Matrix metalloproteinase 7 (MMP-7) is a novel biomarker for biliary atresia (BA). Given that BA is associated with congenital heart disease (CHD), and infants with CHD can exhibit both BA (CHD-BA) and non-BA cholestasis (CHD-C), there is a pressing need to better characterize MMP-7 levels in high-risk CHD patients to avoid invasive testing. Here, we investigated the utility of MMP-7 in discriminating BA from non-BA cholestasis in CHD-C infants. **Methods:** This is a single center retrospective cohort study including infants < 180 days of age with cholestasis (direct bilirubin > 1 mg/dL) and serum MMP-7 levels from 2019-2023. Patient demographic, clinical, cholestatic liver disease (i.e. ultrasounds, liver biopsy, MMP-7 level, and other liver profile testing) and congenital heart disease data (i.e. echocardiograms, cardiac catheterization data, ICU therapies) were obtained. Demographic data and descriptive statistics were summarized with medians with interquartile ranges and frequencies with percentages. Median MMP-7 levels were assessed between cohorts via Wilcoxon rank sum exact test. **Results:** 149 patients were divided into BA (n=25), non-BA cholestasis (n=86), CHD-C (n=36), and CHD-BA (n=2) subgroups. Patients with CHD had significantly elevated MMP-7 levels relative to the non-CHD cohort (non-CHD MMP-7: 34 ng/dL (IQR 23-79) vs. CHD-C MMP-7: 47 ng/dL (IQR 38-94 ng/dL), $p < 0.05$). There was no significant difference in median MMP-7 levels between BA and CHD-BA cohorts, though the two patients with CHD-BA both had MMP-7 levels above the standard cut-off (52.8 ng/mL). Further subcategorization of infants with and without pulmonary hypertension (PH) revealed significantly elevated median MMP-7 levels in patients with clinically significant pulmonary hypertension (MMP-7 PH group: 125 ng/dL (IQR 81-217 ng/dL) vs. No PH group: 39 ng/dL (IQR 25-77 ng/dL), $p<0.05$). CHD patients (CHD-BA and CHD-C) with PH had greater median MMP-7 levels relative to CHD patients without PH (With PH MMP-7: 154 ng/dL (IQR 76-238 ng/dL) vs Without PH MMP-7: 43 ng/dL (IQR 37-81 ng/dL), $p<0.05$). **Conclusion:** In our cohort, serum MMP-7 levels in infants with CHD-C were significantly elevated compared to infants with cholestasis alone, yet below the standard cut-off for BA. MMP-7 remains an adequate screening biomarker for detecting BA in infants with CHD. Larger, prospective studies are needed to validate this finding and establish CHD-specific MMP-7 cutoffs to guide further testing in these infants.



Mean MMP-7 Values

Disclosures: Nicolas Noriega: Nothing to Disclose, Bradley Conant: Nothing to Disclose, Sindhu Pandurangi: Nothing to Disclose, Michael Kim: Nothing to Disclose, JangDong Seo: Nothing to Disclose, Anna Peters: Sanofi: Advisor, Andrew Misfeldt: Nothing to Disclose, Meghan Chlebowski: Nothing to Disclose

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4397 | INCREASED HEPATIC CELLULAR SENESCENCE AT DIAGNOSIS IN BILIARY ATRESIA IS ASSOCIATED WITH LONGER DURATION OF SURVIVAL WITH NATIVE LIVER

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Background: Cellular senescence is a state of cell cycle arrest that can be beneficial for tissue repair but can also be pathologic in chronic diseases. Senescent cells can impact immune cell function, particularly macrophages, however their role in the immune pathogenesis of biliary atresia (BA) is poorly defined. We aimed to identify senescent-immune cell networks in BA that are associated with patient outcomes. **Methods:** Liver cell subsets were quantified per mm^2 using multiplex histology on 4 groups of patients with available clinical data: BA at diagnosis (BADx, n=17), BA at liver transplant (BATx, n=22), non-BA cholestasis (CC, n=13), and non-cholestatic controls (nCC, n=7). A panel of 6 antibodies against p21, CK19, CD68, Trem2, CD3, and Foxp3 identified senescent cells, cholangiocytes, total vs TREM2+ macrophages, total T cells, and T regs. BA patients were compared by duration of survival with native liver (SNL). Statistical analyses included Mann Whitney test, Kruskal-Wallis test, and Spearman's correlation. **Results:** BADx patients had tissue collection within 3 days of hepatoportoenterostomy and were younger than other groups with median age of 61 days ($p<0.05$). Median direct bilirubin closest to sample collection was >4.0 mg/dL for disease groups vs 0.05 mg/dL for nCC. 47% of BADx and 41% of BATx patients had SNL > 23 months. Across all groups, BADx patients had more cholangiocytes than CC and nCC ($p=0.005$ and $p=0.02$ respectively), however, there was no difference in senescent cell numbers. Total number of senescent cells had a positive correlation with age across the full cohort ($r=0.27$, $p=0.04$, $n=59$) but not within groups. BADx patients with SNL > 23 months had more senescent cholangiocytes ($p=0.005$), senescent macrophages ($p=0.02$), and total senescent cells ($p=0.03$) (Figure 1). The number of senescent cells in BADx patients was directly correlated with total macrophages ($r=0.58$, $p=0.02$) and TREM2- macrophages ($r=0.59$, $p=0.01$) but not TREM2+ macrophages ($p>0.05$). There was no difference in senescent cell numbers by SNL status among BATx patients. **Conclusion:** Increased number of senescent cells in BA at diagnosis is associated with longer SNL, suggesting a favorable role for early cell senescence. This contrasts with data in primary sclerosing cholangitis, and supports disease- or age-specific difference in the mechanism by which senescent cells impact disease progression. Future studies will extend these findings across a larger patient cohort.

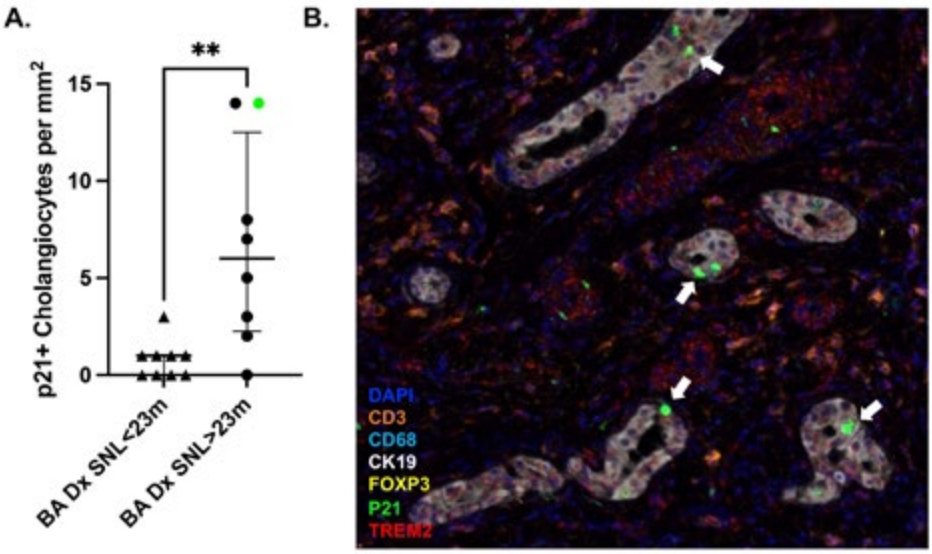

Figure 1. A. BA patients at diagnosis with longer duration of SNL have higher numbers of p21+ senescent cholangiocytes. **B.** Multiplex histology image demonstrating p21+ cholangiocytes (white arrows) in a representative BADx patient with SNL > 23 months (green dot in panel A).

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4398 | ADENOVIRUS INFECTION FOLLOWING PEDIATRIC LIVER TRANSPLANT: INCIDENCE AND OUTCOMES

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Background: Human adenovirus (HAdV) infection in immunocompromised patients can be a life-threatening disease. Few studies describe HAdV following pediatric liver transplantation (LT). Treatment with anti-viral agents is often center- and patient-specific without clear guidelines. We describe the prevalence, presentation, and treatment of HAdV infection following pediatric LT. **Methods:** We performed a retrospective chart review of children receiving a LT at a quaternary center from 1/1/13 – 12/31/22. We defined HAdV disease as viral detection by PCR in blood, respiratory secretions, stool or liver tissue along with signs/symptoms of disease. Disseminated HadV disease was defined by presence of ≥2 organs involved, excluding viremia. Descriptive statistics and comparisons were performed using Chi-square, Fischer exact test, and non-parametric tests for continuous variables. **Results:** Eighty-four (26%) out of 320 children developed HAdV disease after LT. Of these patients, 86% (72/84) had testing for AdV prior to LT with only 5/84 patients (7%) having a positive HAdV test at any time point before LT. Median age at LT was 17.5 months, 48% were female, and biliary atresia was the underlying diagnosis in 50% (42/84). Most patients presented with fever (52.4%), followed by GI symptoms (48%) and hepatitis (41%). Median time to development of HAdV positivity was 79.5 days (IQR 19-260 days), and most frequently occurred within 30 days of LT (40%, 31/84). Upper and lower respiratory tract were the most common first positive source (32%), followed by viremia (30%). Disseminated HAdV occured in 24% of patients. A total of 14 patients (17%) received treatment with cidofovir, of which majority of patients had viremia (93%, n=13/14) as compared to untreated patients (56.5% viremia), p=0.013. Median peak adenovirus titer was 491,805 IU/mL (IQR 24,800 – 1,900,000 IU/mL) in those treated as compared to 1,000 IU/mL (IQR 595 – 794,794 IU/mL) in untreated patients, p<0.001. Treated patients were more likely to present with fever (86% vs 46%, p<0.01), lower respiratory symptoms (29% vs. 4%, p=0.01) and hepatitis (64%. vs 35%, p=0.047) as compared to untreated. All but 1 patient cleared HAdV following treatment. Overall post-transplant mortality was 8% (7/84) with mortality of 36% (5/14) in the treated group as compared to 3% (2/70) in the untreated group, p=0.001. There was no difference in median time to death from first positive HAdV test across treated (92.0 [IQR 21.0-351.0] days) and untreated groups (83.5 [IQR 62.0-105] days), p=1.0. **Conclusion:** HAdV was detected in up to one quarter of children after LT, most commonly within the first 30 days when immunosuppression was high. Fever and GI symptoms were the most common presenting symptoms. Only 17% of patients received cidofovir; however, the high mortality seen despite treatment suggests more severe disease in this population.

Disclosures: Anna Banc-Husu: Mirum Pharmaceuticals: Site PI for industry-sponsored clinical trial, Sara Hassan: Nothing to Disclose, N. Thao Galvan: 3D Systems: Consultant, 3DSystems: Consultant, Natera: Grant/Research Support, Elizabeth Moulton: Pfizer: COVID vaccine & treatment research funding to intitution, Claire Bocchini: Nothing to Disclose, Kathleen Hosek: Nothing to Disclose, Dana Cerminara: Nothing to Disclose, Flor Munoz: Nothing to Disclose, Krupa Mysore: Nothing to Disclose

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4399 | BILIARY ATRESIA IN THE DEVELOPING WORLD: URGENT NEED OF CHANGING TRACK TO IMPROVE OUTCOME

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Background: Biliary atresia (BA) is the most common cause of neonatal cholestasis (NC). Early diagnosis and timely Kasai portoenterostomy (KPE) by experts is the first step for a good outcome. We analysed our experience of managing BA from a public sector hospital of north India over the last decade. **Methods:** Patients admitted from 2013 to 2023 as NC with onset of conjugated hyperbilirubinemia in the first month (mo) of life were reviewed. In patients with suggestive clinical picture, a definite diagnosis of BA was made in those with ultrasound (USG) showing absent/atretic GB or cholangiogram (percutaneous cholecystography/ Magnetic Resonance Cholangiopancreatography; MRCP/ per-operative) suggestive of BA. Probable BA was diagnosed in cases with suggestive clinical picture with USG and/or liver biopsy features of BA. Etiology in non-BA cases was determined as per standard criteria. **Results:** Of the total 950 cases with NC, 580 (61%) had BA (67% boys). Of these, 54.3% had a definite and 45.7% had a probable diagnosis of BA. The median age at onset of jaundice for patients with BA was 7(1-30) days and at admission was 90 (10-734) days. The interval between onset of jaundice and admission varied from 66.5 (28-158) days to 96 (23-196) days, with no significant reduction (p-0.39) over last 11 years. The time lag between onset of jaundice and hospital admission was significantly higher (81[1-727] vs. 45[2-620]; p <0.001) in BA as compared to other causes of NC (n-370). Only 23.4% BA cases were admitted before 2 mo of age (<1mo-14, 1-2mo-122), 28.6% (n-166) between 2-3mo, 42.4% (n-246 at 3-6mo) and 5.6% (n-33) cases after 6mo of age. Majority of BA cases had acholic stools (549, 94.7%) while remaining had ambiguous stools. At admission, 11.4% (n-66) had anemia, 1.4% (n-8) had pruritus and 12.2% (n-71) had decompensation (coagulopathy and /or ascites). Only 10% cases (n-58) had normal GGT. Diagnostic evaluation was done with liver functions, USG, liver biopsy and cholangiogram as per feasibility. Table 1 shows the diagnostic accuracy of these tests for BA. Only 32% cases (n-184) underwent KPE and 27.7% (n-51) were successful. Others could not be offered KPE due to advanced age, parent refusal and logistic reasons. Outcome in BA was poorer than the other causes of NC, where 63.2% (234/370) cases had resolution /improvement in jaundice (p<0.001). **Conclusion:** Three quarters of BA cases presented beyond 2 months of age, 12% were decompensated at admission and only a third could be offered KPE. USG with raised GGT is a good non-invasive and easily available screening test with 94% diagnostic accuracy. There is an urgent need of public health programs to improve the outcome of BA in the underprivileged population.

Table 1. Diagnostic performance of the tests used for diagnosis of biliary atresia (BA)

Test (number of cases with the test)	Prevalence	Sensitivity	Specificity	PPV	NPV	Accuracy
GGT (n=503)	62.2%	90.4%	40%	71.3%	71.7%	71.4%
USG (n=504)	62.4%	85.4%	90.5%	93.7%	78.8%	87.3%
Liver biopsy (n=326)	81.9%	98.9%	83.1%	96.4%	94.2%	96%
USG + raised GGT (n=330)	75.2%	97.6%	85.4%	95.3%	92.3%	94.6%

GGT: gamma glutamyl transferase, USG: ultrasonogram, cut-off taken for raised GGT >86 U/L

Calculated for cases (total n-505) with definite diagnosis of NC (BA-315, other causes-190)

Disclosures: Anshu Srivastava: Nothing to Disclose, Srinivas Srinidhi Vadlapudi: Nothing to Disclose, Nitu Kumari: Nothing to Disclose, Manjit Kaur: Nothing to Disclose, Akash Nair: Nothing to Disclose, Moinak Sarma: Nothing to Disclose, Ujjal Poddar: Nothing to Disclose, Richa Lal: Nothing to Disclose, Ankur Mandelia: Nothing to Disclose, Vijay Upadhyayaya: Nothing to Disclose, Basant Kumar: Nothing to Disclose, Surender Yachha: Nothing to Disclose

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4400 | IMPACT OF MARALIXIBAT ON CAREGIVER BURDEN FOR PATIENTS WITH ALAGILLE SYNDROME AND PROGRESSIVE FAMILIAL INTRAHEPATIC CHOLESTASIS

Natasha Dilwali[1] Robin Howard[2] Rachel Hallum-Montes[3] Yushan Kim[4] Douglas Mogul[1] Wikrom Karnsakul[1]

[1]Johns Hopkins University, [2]Mirum Pharmaceuticals, [3]The Ideas Project, [4]YK Strategic Solutions LLC

Background: Alagille syndrome (ALGS) and Progressive familial intrahepatic cholestasis (PFIC) are rare disorders leading to end-stage liver disease. As a consequence of cholestasis, seen in both disorders, patients experience severe pruritus which greatly impacts their quality of life and sleep. Maralixibat (MRX) is approved for the treatment of cholestatic pruritus in ALGS and PFIC and clinical trials have shown that improvements in pruritus correspond with increase in quality of life and sleep. In this study, we analyze the impact of MRX on caregiver burden. **Methods:** All patients prescribed MRX in the US receive the drug through a single pharmacy. Beginning in March 2024, all caregivers of patients newly prescribed MRX for ALGS or PFIC were invited to complete a questionnaire assessing caregiver burden including two validated instruments:the Hospital Depression and Anxiety score (HADS), and the Zarit Burden Interview (ZBI-12). Repeat surveys are distributed after six and twelve months of treatment. Data will be analyzed using descriptive statistics, means, standard deviations and frequencies/proportions. **Results:** Six baseline surveys have been completed by caregivers of patients with ALGS. The majority of respondents are caucasian, female, 30-39 years old. 67% of caregivers reported their child has mild itch and are currently using ursodiol or rifampin. 50% of caregivers report caregiving has impacted their working status and 67% report it has impacted their finances. On a Likert scale of 1 to 10 (10 = extreme impact), median scores were 5 for productivity (range 3-7) and 3.5 for sleep impact (range 3-5). 50% of caregivers report fair or poor quality sleep (median 5.5 hours of sleep/night, range 4-8) and 67% report caregiving affecting their own sleep. Results of the ZBI-12 survey show that four caregivers report no to mild burden (score of 0-10), one reports mild to moderate burden (score of 10-20) and one reports high burden (score of >20). Concerning the HADS scale, two caregivers had borderline (score 8-10) or abnormal scores (score of 11-21) for depression and anxiety each. **Conclusion:** This study provides early data of caregiver burden in caregivers of patients with ALGS including negative impact on sleep, productivity, employment and mental health. Further longitudinal data is needed to better quantify this impact and determine if MRX can mitigate this concern.

Disclosures: Natasha Dilwali: Nothing to Disclose, Robin Howard: Mirum Pharmaceuticals: Stock - publicly traded company, Mirum Pharmaceuticals: Consultant, Mirum Pharmaceuticals: Employee, Mirum Pharmaceuticals: Consultant, Rachel Hallum-Montes: Mirum Pharmaceuticals: Independent Contractor, Yushan Kim: GRAIL: Employee, Mirum Pharmaceuticals: Consultant, Sherlock Biosciences: Consultant, Mammoth Biosciences: Consultant, Douglas Mogul: Nothing to Disclose, Wikrom Karnsakul: Nothing to Disclose

4401 | CHILDREN WITH CHRONIC HEPATITIS C HAVE A HIGH PREVALENCE OF NEURODEVELOPMENTAL DISORDERS

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[1]British Columbia Children's Hospital

Background: Chronic hepatitis C (HCV) in children is primarily acquired through vertical transmission from an HCV-infected mother. The primary risk factor for chronic HCV in mothers is intravenous drug use. Intravenous drug use in pregnancy is associated with an increased risk of neurodevelopmental disorders in children. We aimed to explore the prevalence of neurodevelopmental disorders among children with chronic HCV in the province of British Columbia. **Methods:** Retrospective chart review was conducted for all children actively followed for HCV at our centre between December 2020 to April 2024. Our hospital is the only pediatric referral centre for chronic HCV in our province, so this likely represents the whole population of *known* HCV positive children in British Columbia. Data were collected on demographic and clinical information including diagnosis of neurodevelopmental disorders and other learning difficulties. **Results:** We identified 29 children under 18 years of age while they were actively followed with our service. There were 13 males and 16 females. 28 patients had HCV due to vertical transmission and 1 was unknown, potentially due to the patient's own substance use. 48% (n=14) of patients were described as having attention deficit hyperactivity disorder (ADHD). Among the children with ADHD, 43% (n=6) had foetal alcohol spectrum disorder, 21% (n=3) had autism spectrum disorder, and 14% (n=2) had other learning and developmental difficulties including speech delay and sensory processing issues.

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An additional 14% (n=4) patients had speech delay, of which one also had autism. In total, 62% (n=18) patients had some neurodevelopmental disorder or learning difficulty. **Conclusion:** In our study population of children with chronic HCV, a majority had at least one documented neurodevelopmental disorder. This represents a previously undescribed issue among pediatric patients with chronic HCV. Based on these results, we suggest that practitioners who care for children with chronic HCV may have a role in proactively identifying patients with neurodevelopmental difficulties and linking them with appropriate resources.

Disclosures: Shreya Kishore: Nothing to Disclose, Orlee Guttman: Mirum: Consultant

4404 | MECHANISM OF LAURIC ACID-MEDIATED HEPATOBILIARY PROTECTION DURING ACUTE INFLAMMATORY CHOLANGIOPATHY IN MICE

Swati Ghosh[1] Michael Devereaux[2] Aimee Anderson[2] COLIN ANDERSON[2] ANGELO D'ALESSANDRO[2] David Orlicky[2] Ronald Sokol[1]

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Background: Primary sclerosing cholangitis causes cholestasis, inflammation and fibrosis of bile ducts. Recently, we have shown that LRH1 agonist, DLPC, a phospholipid, is protective in murine parenteral nutrition-induced cholestasis (*Ghosh et al., Hepatology, May 2024*). The objective of this study was to determine,how lauric acid (LA), a medium-chain fatty acid precursor of DLPC, protects against murine DDC-induced inflammatory cholangiopathy. **Methods:** Acute DDC mouse model (0.1% DDC diet x 3 days) with or without LA dietary supplementation (20%; LA, DDC/LA). THP1 and H69 cholangiocyte cell lines were studied. **Results:** DDC mice had increased AST, ALT, bilirubin, serum total bile acids, histologic ductular reaction and macrophage infiltration, and reduced liver mRNA of *Abcb11, Abcg5/8, Nr0b2* (SHP), *Nr5a2, Abcc2*, and cholangiocyte proliferation marker *Krt19*; all were normalized by the LA diet. To determine the protective mechanism of LA, we analyzed pro-inflammatory M1 and anti-inflammatory M2 gene expression in intrahepatic mononuclear cells, which showed upregulation of anti-inflammatory genes (*Clec10a1*, *Msr1*, *Mrc1*) and down-regulation of pro-inflammatory genes (*Ccl2, Cxcl2 Il-1b*, *Itgam*) in both LA treated groups. We also found decreased F4/80+Ly6c+ (M1) and increased F4/80+Cd206+ (M2) liver macrophages by flow cytometry in DDC/LA mice compared to DDC mice. In DDC/LA mice, there was a significant increase in *Nr5a2 (*LRH1*)* activation and binding of *Nr5a2* to *Abcg5/8 and Nr0b2* promoters. LA dietary supplementation increased relative abundance of hepatic DLPC measured by LC-MS. Importantly, LA supplementation led to activation of the STAT6 pathway in BMDMs from DDC mice, measured by confocal microscopy, with increased STAT6 binding to *Chil3* promoter in liver. In cultured H69 cells, DLPC treatment prevented the upregulated gene expression of chemokines *CCL2* and *CXCL2 and of KRT19* induced by DDC exposure. To determine if cholangiocytes activated macrophages in this model, H69 cells (in inserts) were treated with DDC ± DLPC and co-cultured with THP1 (in bottom wells); DLPC reduced the upregulated THP1 cytokine expression from DDC. **Conclusion:** LA protection against DDC liver injury is associated with LRH1 activation, downregulation of inflammatory pathways, inhibition of ductular reaction and induction of anti-inflammatory STAT6 target genes. LA, a component of MCT oil commonly given to cholestatic infants, shows promise in treating inflammatory cholangiopathies, such as PSC.

Disclosures: Swati Ghosh: Nothing to Disclose, Michael Devereaux: Nothing to Disclose, Aimee Anderson: Nothing to Disclose, COLIN ANDERSON: BioMarin Pharmaceuticals: Employee, ANGELO D'ALESSANDRO: Nothing to Disclose, David Orlicky: Nothing to Disclose, Ronald Sokol: Nothing to Disclose

4405 | MACROPHAGE-SPECIFIC HIF1&ALPHA; INHIBITION ACTIVATES HEPATIC STAT6 AND PROTECTS FROM PARENTERAL NUTRITION-ASSOCIATED CHOLESTASIS

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Background: Chronic parenteral nutrition (PN) can lead to PN-associated cholestasis (PNAC). Hepatic accumulation of bile acids and phytosterols play a significant role in PNAC pathogenesis. Previously we showed that *HIF1α* is regulated in PNAC in a cell-specific manner (*Ghosh et al., Hepatology suppl, 2023*). In this study,

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we investigated mechanisms linking inhibition of macrophage *HIF1α* expression to its hepatoprotection in PNAC. **Methods:** PNAC mouse model (oral DSS x 4 days followed by Total PN x 14 days using soy-based lipid emulsion; DSS-PN) was used. A group received IV GW4064 (FXR agonist, 30 mg/kg/day) on d 4-14 (DSS-PN/GW4064). DSS-PN was also given to macrophage-specific Hif1α-knockout mice. Raw 264.5 cells and THP-1 cells were used. **Results:** Elevated AST and ALT in DSS-PN mice were normalized by macrophage specific Hif1α-knockout. Bulk RNA seq of DSS-PN liver showed upregulation of genes in the hypoxia gene network. Previously we showed GW4064 induced *Hif1a* mRNA and its targets in the liver of DSS-PN mice and that *HIF1a* stabilization by PHD inhibitor DMOG in Raw 264.5 macrophages prevented GW4064 from suppressing LPS-induction of pro-inflammatory gene expression. This suggested that inhibiting macrophage *HIF1a* is protective in PNAC. To investigate the mechanisms involved, macrophage-specific HIF1α-knockout or FXR agonist-treatment in DSS-PN mice both showed increased expression of STAT6 target genes compared to DSS-PN. Moreover, STAT6 binding was increased at the *Arg1* and *Chil3* promoter in liver of both HIF1α-knockout DSS-PN and DSS-PN/GW4064 mice. Next, inhibition of *HIF1a* expression by siRNA in cultured THP-1 and Raw cell macrophages led to upregulation of STAT6 target genes, suggesting a switch to an anti-inflammatory polarization. By ChIP, STAT6 binding was increased at the *Arg1* and *Chil3* promoters in HIF1α-siRNA treated Raw 264.5 cells. In addition, by confocal microscopy, HIF1α-siRNA treated Raw 264.5 cells showed increased nuclear STAT6 phosphorylation, indicating STAT6 activation. Finally, treatment of BMDM with GW4064 similarly suppressed LPS or phytosterol-induced upregulation of M1 genes *Il-1b* and *Tnf* and enhanced the upregulation of M2 STAT6 target genes *Msr1* and *Chil3.* **Conclusion:** This study suggests that inhibition of HIF1α expression in macrophages may increase anti-inflammatory STAT6 signaling and enable its protective effects in PNAC. Thus, macrophage HIF1α may be a therapeutic target in PNAC and possibly other cholestatic diseases.

Disclosures: Swati Ghosh: Nothing to Disclose, Michael Devereaux: Nothing to Disclose, Karim el kasmi: Nothing to Disclose, Ronald Sokol: Nothing to Disclose

4406 | MECHANISM OF STAT3 ROLE IN THE PROTECTIVE EFFECTS OF FXR AGONIST IN CHRONIC MOUSE MODEL OF INFLAMMATORY CHOLANGIOPATHY ◆

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Background: Primary sclerosing cholangitis (PSC), an inflammatory cholangiopathy, is a chronic liver disease without effective treatments. Recently we established the protective role of STAT3 signaling in parenteral nutrition-associated cholestasis. The objective of this study is to examine STAT3 signaling in FXR agonist protection in a mouse model of chronic inflammatory cholangiopathy. **Methods:** H69 cholangiocytes, THP1 monocyte cell line and cholangiopathy mouse model (0.1% diethyl 1,4-dihydro-2,4,6-trimethyl-3,5-pyridinedicarboxylate [DDC] diet feeding x14d) were used. A group of mice also received i.v. FXR agonist GW4064 daily during 14d DDC diet. **Results:** DDC mice had increased serum AST, ALP, bilirubin, total bile acids, ductular reaction and macrophage infiltration, which were prevented by GW4064 treatment. Chip assay on liver from GW4064-treated DDC mice showed increased FXR binding to *Stat3* promoter and confocal microscopy in BMDMs showed STAT3 localization to mitochondria. In DDC mice, liver arachidonic acid (AA) concentration (by GC-MS) was increased, and RNA seq/qPCR showed suppression of mitochondrial STAT3 gene targets responsible for fatty acid oxidation and metabolism, all of which was reversed by GW4064. Exposure of H69 cells to 50mM AA induced *KRT19* (proliferation marker), cholangiokines (*IL1B, CCL2*, *TNF)* mRNA, which was prevented by GW4064 co-incubation. To determine the effect of elevated AA levels on STAT3 signaling in cholangiocytes, we treated H69 cells with 50mM AA with or without STAT3 siRNA or STAT3 inhibitor(C188-9) and showed that AA induced cholangiokines and *KRT19*, which were further induced by STAT3 inhibition. Incubation of THP1cells with 50mM AA induced increased expression of inflammatory cytokines and decreased expression of M2 markers *KDM6b*, *SOCS3*, *IL1RN*. Incubation of THP1, cocultured with AA-exposed H69 cells in insert, showed increased THP1 mRNA of M1 markers *IL-1B, TNF, and CCl2.* Finally, in the co-cultured model, we treated H69 cells in the insert with AA in the presence or absence of a STAT3 activator(Colivelin)and found STAT3 activation of H69 cells suppressed the THP1 mRNA expression of M1 cytokines and induced THP1 M2 gene expression **Conclusion:** This study suggests that in inflammatory cholangiopathies, FXR agonist protects the liver through STAT3 activation in cholangiocytes, driving M2 anti-inflammatory polarization of macrophages and protecting against AA-induced injury; targeting STAT3 could hold promise in addressing PSC.

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Disclosures: Swati Ghosh: Nothing to Disclose, Michael Devereaux: Nothing to Disclose, Aimee Anderson: Nothing to Disclose, David Orlicky: Nothing to Disclose, Ronald Sokol: Nothing to Disclose

4407 | INTERLEUKIN 8-CXCR2 MEDIATED NEUTROPHIL EXTRACELLULAR TRAP (NET) FORMATION IN BILIARY ATRESIA ASSOCIATED WITH NET-INDUCED STELLATE CELL ACTIVATION

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Background: Biliary atresia (BA) involves an aberrant immune response targeting cholangiocytes, resulting in prominent fibrosis early in life. Previous studies showed neutrophil-activating IL-8 and neutrophil extracellular traps (NETs) positively correlated with bilirubin and risk of liver transplant. The aims of this study were to characterize NET formation in BA and determine promoters of NET formation and NET-induced stellate cell activation. **Methods:** BA and other liver disease control tissue and plasma were obtained at time of diagnosis and transplant. Plasma elastase, NET, and IL-8 were quantified by ELISA. FACS analysis of activation markers of neutrophils co-cultured with plasma was performed. Multi-spectral immunohistochemistry (IHC) of neutrophil activation markers was performed on liver tissue. NET-induced stellate cell activation from co-cultures was measured by real-time PCR and ELISA. **Results:** Liver neutrophils and NETs and plasma elastase, NETs and IL-8 were significantly increased in BA at diagnosis and transplant. IL-8 positively correlated with bilirubin and APRI. Normal neutrophils co-cultured with BA plasma had increased NET production and activation of the IL-8 receptor CXCR2; CXCR2 inhibition decreased NET production. Multiplex IHC identified increased NET expression of pro-fibrogenic tissue factor and IL-17. Purified NETs co-cultured with stellate cells resulted in stellate cell activation (increased *ACTA2, COL1A1* mRNA and collagen protein). **Conclusion:** BA patients have persistent IL-8-CXCR2-mediated NET formation that correlates with biomarkers of injury and fibrosis and NETs induce stellate cell activation, suggesting a role for NETs in the immunopathogenesis of disease. Future investigations should focus on therapeutic agents that inhibit NETs in BA.

Disclosures: Cara Mack: Nothing to Disclose, Yuhuan Luo: Nothing to Disclose, Julia Jezykowski: Nothing to Disclose, Lisa Fraser: Nothing to Disclose, Nitika Gupta: Nothing to Disclose, Alexander Miethke: Mirum Pharmaceutical Inc: Grant/Research Support, Mirum Pharmaceutical Inc: Consultant, Ipsen: Speaking and Teaching, Sarah Taylor: Mirum Pharmaceuticals: Consultant, Ipsen Pharmaceutical: Consultant, Mirum Pharmaceutical: Consultant, Estella Alonso: Nothing to Disclose, Simon Horslen: Nothing to Disclose, Rohit Kohli: Mirum: Consultant, Ipsen: Consultant, Epigen: Grant/Research Support, Sanofi Rare Disease: Consultant, Jean Molleston: Gillead: Grant/Research Support, Albireo: Grant/Research Support, Abbvie: Grant/Research Support, Mirum/Shire: Grant/Research Support, CF FOundation: Grant/Research Support, Binita Kamath: Mirum: Consultant, Mirum: Grant/Research Support, Albireo/Ipsen: Consultant, Albireo/Ipsen: Grant/Research Support, Audentes: Consultant, Stephen Guthery: Nothing to Disclose, Kathleen Loomes: Mirum: Consultant, Albireo/Ipsen: Consultant, Mirum: Clinical trials, Albireo/Ipsen: Clinical trials, John Magee: Nothing to Disclose, Philip Rosenthal: Nothing to Disclose, Pamela Valentino: Grifols: Advisor, Mirum: Speaking and Teaching, Ronald Sokol: Nothing to Disclose

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4408 | EXTRACELLULAR VESICLE MIRNA ANALYSIS FROM ADOLESCENTS WITH MASLD WITH AND WITHOUT OBSTRUCTIVE SLEEP APNEA/CHRONIC INTERMITTENT HYPOXIA

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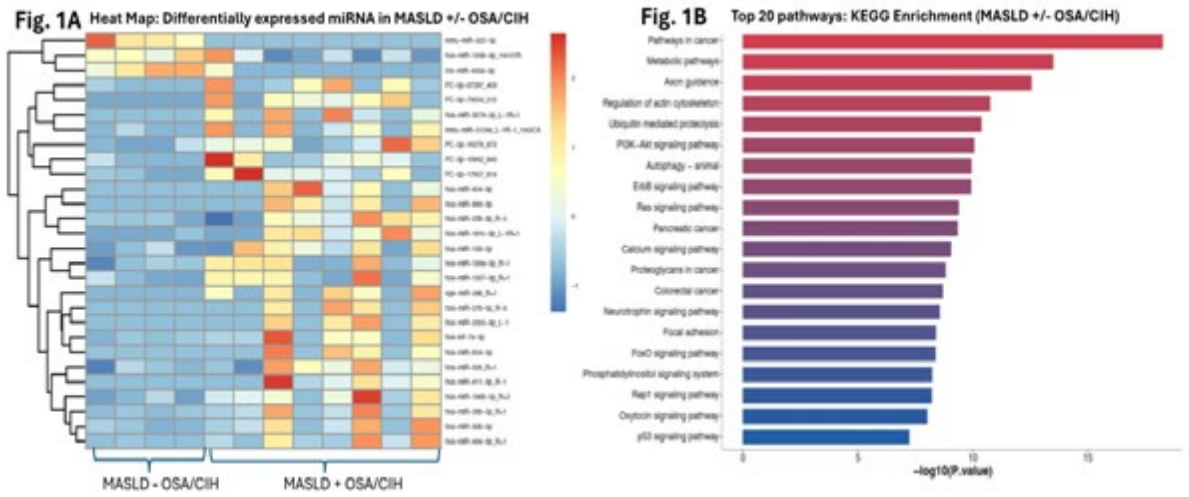
Background: Metabolic Associated Steatotic Liver Disease (MASLD) is the predominant cause of chronic liver disease in children. A compelling link exists between exposure to chronic intermittent hypoxia (CIH) and MASLD disease severity. Hypoxic stress may alter circulating extracellular vesicle (cEV) microRNA (miRNA) content, thereby influencing the liver microenvironment. We sought to characterize cEV miRNA content and identify putative targets of differentially expressed miRNAs in pediatric MASLD ± Obstructive Sleep Apnea (OSA)/CIH and identify miRNA changes post-CPAP therapy. **Methods:** cEVs were extracted using an EV Precipitation Solution Kit from serum samples of adolescents with biopsy proven MASLD ± OSA/CIH. Sequencing and data analysis of cEV miRNA were performed by LC-BioTechnology. Differential miRNA expression was analyzed by Fischer's exact test using p≤ 0.01. Target genes of differentially expressed miRNAs were identified by Target Scan/Miranda algorithms and GO/KEGG pathways determined. **Results:** 12 adolescents (8 with, 4 without OSA/CIH) with biopsy proven MASLD (age 12.9 ± 2.0 yrs, 100% Hispanic, 50% male, BMI 32.3±5.1, ALT 93±60, NAS score 5.3±1.2) were studied. Differentially expressed miRNA in MASLD ± OSA/CIH (Figure 1a) demonstrate downregulation of mir-322, 193 and 450 in MASLD with OSA/CIH. Both mir-322 and 193 modulate hypoxia induced cardiopulmonary apoptosis, hepatic insulin signaling and HIF-1a dependent hepatic fibrosis; mir-450 is involved in hypoxia dependent vascular remodeling and glycolysis regulation. GO/KEGG (Figure 1b) enrichment analysis identified target genes of these miRNAs. Four patients with MASLD +OSA/CIH were studied pre/post-CPAP therapy. Pre-CPAP, 5 miRNAs were upregulated and 12 downregulated compared to post-CPAP. The upregulated miRNAs, mir-1180, mir-378 and mir-22 are important in hypoxia induced cardiomyocyte apoptosis, and mir-378 is involved in hepatic stellate cell induced fibrosis. GO/KEGG enrichment analysis showed target genes of differentially expressed miRNA were involved in transcriptional regulation by RNA polymerase, intracellular signal transduction, metabolic pathways, PI3-Akt and MAP signaling. **Conclusion:** The liver microenvironment may be influenced by alterations in cEV miRNAs important in hypoxia induced apoptosis and hepatic fibrosis in adolescents with MASLD and OSA/CIH. Future study of these miRNAs may further elucidate mechanisms by which CIH promotes MASLD progression.



Disclosures: Shikha Sundaram: Nothing to Disclose, Swati Ghosh: Nothing to Disclose, Alexander Chaidez: Nothing to Disclose, Ronald Sokol: Nothing to Disclose

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4409 | ADVANCED HEPATIC FIBROSIS BY MR ELASTOGRAPHY IS ASSOCIATED WITH ABNORMAL SERUM LIVER BIOCHEMISTRIES IN PEDIATRIC PRIMARY SCLEROSING CHOLANGITIS (PSC)

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Background: Hepatic decompensation from liver fibrosis is the primary indication for liver transplantation in patients with PSC. A single center study recently revealed a liver shear stiffness measure (LSM) >3.29 kPa by MR elastography to be predictive of METAVIR F2+ hepatic fibrosis in pediatric PSC. This study explores biomarkers of advanced fibrosis by liver shear stiffness in a cross-sectional cohort of patients with pediatric onset PSC. **Methods:** Study participants were enrolled into the Childhood Liver Disease Research Network (ChiLDreN) across 12 sites in North America and underwent research MR elastography (MReL), quantitative MRCP (MRCP+; Perspectum; Oxford, UK), and Vibration Controlled Transient Elastography (VCTE) within 3 months of enrollment. Clinical variables were compared between LSM cutoff groups using Wilcoxon rank-sum tests or Fisher exact tests as appropriate. Spearman correlations were also used to assess continuous LSM. **Results:** 73 patients with PSC (49.3% male, 87.1% white) with a median age of 16.3 years (range: 9.1, 25.6) at study entry and median duration of 2.7 (0.1-20.8) years from diagnosis of PSC were enrolled. Patients had large (82.2%) or small duct PSC (17.8%), with overlap with autoimmune hepatitis (35%), or concomitant IBD (74%). The average weighted mean stiffness from MReL was 2.77 kPa (1.55, 7.43). Elevated liver stiffness >3.29kPa predictive of advanced fibrosis was present in 19 patients (26%). There was no difference in demographics, age, duration of PSC, or clinical phenotype (small vs large duct at diagnosis, concomitant AIH or IBD) between patients dichotomized by liver stiffness of 3.29 kPa (Table). Measures of cholangiopathy by MRCP+ did not differ between groups. However, significant differences between the groups were noted for serum biomarkers of hepatocellular damage (ALT/AST), biliary injury (GGT/ALP), cholestasis (total bilirubin), platelet count, and derived predictive scores of liver fibrosis (APRI/FIB-4). LSM by VCTE positively correlated with LSM by MReL (r=0.6, P<.0001). **Conclusion:** Approximately one-quarter of pediatric patients with established PSC have elevated LSM by MReL indicative of advanced liver fibrosis which segregates with elevated serum biochemistries, APRI, and FIB-4. In this cohort, fibrosis is not associated with advanced duct disease assessed by MRCP+.

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Table: Serum biochemistries and quantitative MRI measures in patients with pediatric onset PSC stratified by MR Elastography liver shear stiffness.

		All participants (N=73)		LSM ≤3.29 kPa by MREL (N=54)		LSM >3.29 kPa by MREL (N=19)		
Variable		N	n (%) or median (range)	N	n (%) or median (range)	N	n (%) or median (range)	P-value*
AST (U/L)		66	35 (16, 733)	49	28 (16, 727)	17	68 (20, 733)	0.001
ALT (U/L)		66	44 (9, 816)	49	29 (9, 816)	17	110 (12, 756)	0.012
GGTP (U/L)		60	60 (11, 1579)	44	36 (11, 261)	16	166 (16, 1579)	0.013
ALP (U/L)		66	165 (33, 1226)	49	137 (33, 428)	17	324 (88, 1226)	0.003
Total Bilirubin (mg/dL)		58	0.6 (0.3, 3.7)	45	0.6 (0.3, 2.5)	13	0.6 (0.3, 3.7)	0.984
Platelet count		58	288 (24, 558)	43	300 (162, 558)	15	219 (24, 397)	0.030
APRI		58	0.3 (0.1, 37.2)	43	0.3 (0.1, 6.0)	15	0.9 (0.3, 37.2)	<.001
FIB-4		58	0.4 (0.1, 16.3)	43	0.3 (0.1, 1.5)	15	0.6 (0.3, 16.3)	0.005
Total Immunoglobulin G (IgG)		54	1329 (644, 4740)	35	1222 (644, 2710)	19	1550 (864, 4740)	0.261
VCTE: Liver Stiffness Median (Young's modulus, kPa)		58	6.5 (3.5, 63.9)	42	5.6 (3.5, 60.0)	16	15.1 (4.6, 63.9)	<.001
MRCP+: Number of Strictures		70	4 (0, 26)	51	4 (0, 26)	19	4 (0, 16)	0.984
Number of dilated ducts		70	9 (0, 75)	51	9 (0, 75)	19	10 (2, 25)	0.984
Biliary Tree Volume (ml)		70	7 (1, 50)	51	7 (1, 50)	19	7 (2, 20)	0.984

*Adjusted for multiple comparisons.

Disclosures: Alexander Miethke: Mirum Pharmaceutical Inc: Grant/Research Support, Mirum Pharmaceutical Inc: Consultant, Ipsen: Speaking and Teaching, Cara Mack: Nothing to Disclose, Kieran Hawthorne: Nothing to Disclose, Lisa Henn: Murata Vios: Consultant, Pamela Valentino: Grifols: Advisor, Mirum: Speaking and Teaching, Kathleen Loomes: Mirum: Consultant, Albireo/Ipsen: Consultant, Mirum: Clinical trials, Albireo/Ipsen: Clinical trials, Mary Elizabeth Tessier: Albireo/Ipsen: site PI for a pharmaceutical study, Albireo: site PI for a pharmaceutical study, Adina Alazraki: Nothing to Disclose, Judy Squires: Nothing to Disclose, Rohit Kohli: Mirum: Consultant, Ipsen: Consultant, Epigen: Grant/Research Support, Sanofi Rare Disease: Consultant, Mark Deneau: Nothing to Disclose, Estella Alonso: Nothing to Disclose, Molly Bozic: Nothing to Disclose, Amanda Ricciuto: Nothing to Disclose, Shikha Sundaram: Nothing to Disclose, Andrew Trout: Siemens Healthineers: Funding to institution, GE Healthcare: Funding to institution, GE Healthcare: Expert review of images, Perspectum Inc: Funding to institution, Jonathan Dillman: GE HealthCare: Grant/Research Support, Philips Healthcare: Grant/Research Support, Motilent: Grant/Research Support, Perspectum: Grant/Research Support

4410 | ASSESSMENT OF LIVER FIBROSIS THROUGH SHEAR WAVE ELASTOGRAPHY IN PEDIATRIC LIVER TRANSPLANT RECIPIENTS

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Background: Liver transplantation (LT) is the standard therapy for children with end-stage liver disease. Liver grafts are at risk for fibrosis. Liver biopsy is the gold standard for the evaluation of hepatic fibrosis, though is an imperfect standard. An alternative to monitor fibrosis is shear wave elastography (SWE) which utilizes ultrasound

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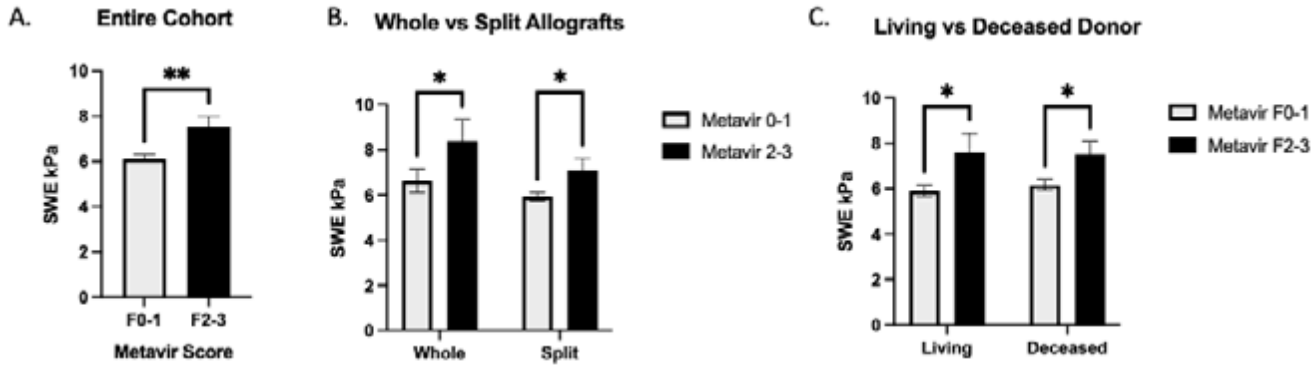
liver stiffness measurements as a non-invasive surrogate of liver fibrosis. Studies have evaluated whether SWE can quantify fibrosis in adult liver transplant recipients, though less information is available in pediatric patients. In this study, we evaluated the diagnostic accuracy of SWE liver transplant measurements in quantifying liver biopsy fibrosis compared to liver biopsy in pediatric LT recipients. **Methods:** We conducted a retrospective review of patients who received a liver transplant at Ann & Robert H. Lurie Children's Hospital of Chicago from 2007 through 2024. Liver biopsies were graded for fibrosis based on the Metavir index. Age, sex, ethnicity, liver stiffness on SWE, type of graft, type of donor, and diagnosis at transplant were collected. SWE were compared to liver biopsies if done within 13 months. Ultrasound measurements were excluded if ultrasound was done within six months of a diagnosis of acute rejection. Patients with F0 to F1 fibrosis were categorized as 'no significant fibrosis' and F2 to F3 as 'moderate fibrosis.' Comparison between two groups was performed using two-tailed student's t-tests, comparison between 4 groups was performed using two-way ANOVA with Fisher's LSD for multiple comparisons. **Results:** Between 2007 and 2024, 257 patients underwent liver transplant. Ninety-three patients had 106 liver biopsies performed within 13 months of elastography. Liver stiffness values were significantly higher in patients with moderate (F2-3) fibrosis compared to those with no significant fibrosis (F0-1) (7.5 kPa ± 0.48 vs 6.09 kPa ± 0.18, p = 0.0015). Liver stiffness values were significantly higher in patients with moderate fibrosis (F2-3) compared to those with no significant fibrosis (F0-1) in both whole (8.4 kPa ± 0.95 vs 6.6 kPa ± 0.54, p=0.02) and split allografts (7.1 kPa ± 0.52 vs 5.9 kPa ± 0.17, p=0.02). Liver stiffness values were higher in patients with moderate fibrosis (F2-3) compared to those with no significant fibrosis (F0-1) in both living and deceased allografts. There was no significant difference in liver stiffness values based on allograft type (whole vs split) or donor type (living vs deceased) among those with F0-1 or F2-3 fibrosis (Figure 1). **Conclusion:** We demonstrated that pediatric liver transplant recipients with moderate fibrosis on liver biopsy have significantly higher liver stiffness values on 2D SWE than those with no significant fibrosis. This difference was not dependent on type of allograft or type of donor, making SWE an option to utilize for the monitoring of liver allograft fibrosis, regardless of donor characteristics.



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4411 | FONTAN-ASSOCIATED LIVER DISEASE: THE ROLE OF LIVER ELASTOGRAPHY ASSESSMENTS PRE AND POST ORTHOTOPIC HEART TRANSPLANT

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Background: Fontan-associated liver disease (FALD) is an inevitable complication for patients with Fontan physiology. It is essential to monitor for FALD progression. There is a paucity of data on the outcomes of FALD post heart transplant (HT). Liver biopsy is the gold standard for diagnosing and staging fibrosis, though is an imperfect standard due to the heterogeneity of fibrosis and sampling error. Ultrasound shear-wave elastography (SWE) is a method of characterizing liver stiffness (LS), a measurement that correlates with the degree of fibrosis in non-cardiac causes of liver disease. In FALD, measurements are confounded by congestive hepatopathy.

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There is a need for studies to evaluate SWE longitudinally to assess hepatic fibrosis post HT. **Methods:** We performed a retrospective study evaluating the effects of Fontan physiology on the liver in a cohort of patients who underwent heart transplantation (HT) from 2019 to 2023 at a single center. SWE reports, liver stiffness (LS) measurements in kilopascals (kPa), biopsy pathology, and cardiac catheterization reports were extracted. Degree of liver fibrosis was quantified via congestive hepatic fibrosis (CHF) score. VAST scores were determined. **Results:** 36 patients with Fontan physiology underwent HT. Of the 35 patients who had abdominal imaging before HT, 91% had abnormal liver findings. Post HT, 79% of patients continued to have abnormal liver features on imaging. Common findings included a nodular, course, and lobulated liver contour as well as increased/heterogenous liver echogenicity. 47% of patients had a VAST score ≥ 2 indicating a high acuity population. There was no statistically significant correlation between pre-HT liver biopsy fibrosis stage and pre-HT SWE kPa, or pre-HT Fontan pressure and pre-HT SWE. There were six patients who underwent SWE before and after HT, all of whom had elevated kPA before HT. Post HT, kPa scores improved for 5/6 patients, including patient 5 who had CHF score 2A and patient 6 who had CHF score 4 on biopsy pre-OHT (Fig.1). Patient 4 did not show improvement in kPa scores post HT and underwent a post-HT liver biopsy which demonstrated CHF score 4. **Conclusion:** Our findings show that after HT, LS scores improved in 5/6 patients. This could suggest improvement in hepatic congestion and/or fibrosis. In these 5 patients, LS kPa fell below 8.7 kPa, the threshold that is predictive of high-grade hepatic fibrosis, including two of our patients with significant fibrosis (patient 4 and 5) on liver biopsy pre-HT. This may indicate there was improvement in hepatic fibrosis. Our study supports post-OHT improvement in FALD-associated fibrosis as demonstrated by SWE LS measurements and suggests that the lack of improvement in SWE kPa values may reflect residual fibrosis, which can guide clinical management. Larger studies are needed to validate these findings and correlate with long-term post-HT liver outcomes.

	Gender	Age at transplant	Splenomegaly pre/post HT	Length of time between HT and follow up US	U/S SWE pre/post kPA	Liver biopsy CHF score	Fontan pressure pre HT
Patient 1	M	13.076	No / No	-4 months, +41 months, +53 months	11.3 / 7.75 / 8.34	N/A	26
Patient 2	M	10.1616	No / No	-20 months, -8 months, + 45 months	11.29 / 16.31 / 5.1	N/A	12
Patient 3	F	13.1534	Yes / No	-6 months, + 24 months	11.92 kPa / 5.96	N/A	35-38
Patient 4	M	21.2795	No / Yes	-47 months, +8 months, +16 months	9.45 / 9.67 / 9.31	CHF score 4, 10 months **post** HT	15
Patient 5	F	15.3918	No / No	-35 months, - 22 months, + 6 months, + 21 months	8.3 / 10.9 / 5.24 / 7.3	CHF score 2A, 18 months **pre** HT	17
Patient 6	F	16.9598	Yes/Yes	-40 months, -27 months, -10 months, + 32 months	11.82 / 12.93 / 10.99 / 6.62	CHF score 4, 20 months **pre** HT	16-17

Disclosures: Naseem Ravanbakhsh: Nothing to Disclose, Hector Melin-Aldana: Nothing to Disclose, Phillip Thrush: Nothing to Disclose, Esther Ro: Nothing to Disclose, Alyssa Kriegermeier: Nothing to Disclose

4412 | ACUTE-ON-CHRONIC LIVER FAILURE (ACLF) IN CHILDREN WITH CIRRHOSIS IS ASSOCIATED WITH WORSE POST-TRANSPLANT SURVIVAL AND INCREASED RESOURCE UTILIZATION

Anna Banc-Husu[1] Kathleen Hosek[2] Matt Hall[3] Divya Sabapathy[4] Moreshwar Desai[5] Fong Lam[5] Constantine Karvellas[6] Ruben Hernaez[5] Benjamin Shneider[2]

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Background: Impact of ACLF on liver transplant (LT) outcomes in children with chronic liver disease (CLD) is not well characterized. Current data are sporadic and limited to biliary atresia or single-centers. Our aim was to systematically characterize ACLF and determine effect on post-LT outcomes and resource utilization in children with CLD. **Methods:** Using linkage of the Scientific Registry of Transplant Recipients and billing data from Pediatric Health Information System (PHIS), we identified children with CLD 3 months - <18 years at time of listing who received LT from 2002 - 2020. For this anaylsis, ACLF was defined by at least 1 extra-hepatic organ failure (OF) prior to LT: CV failure (charges for pressors), respiratory failure (charges for CPAP/BIPAP/ventilator), renal failure (charges for renal replacement), neurologic failure (ICD-9/10 hepatic encephalopathy). ACLF grade was

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defined by number of OFs with ACLF-1= 1 OF, ACLF-2 = 2 OF, and ACLF-3 ≥ 3 OF. Resource utilization, including total billed charges per hospitalization, and donor/recipient characteristics were compared using Kruskal-Wallis and Chi-square. Kaplan-Meier was used for survival analysis. Results depicted as median [p25-p75]. **Results:** A total of 3003 patients (54% F) with CLD (56% cholestatic [last TBili≥3.0], 22% biliary without cholestasis, 15% hepatocellular, 7% other), median age at listing 1.1 years [0.5 – 7.7], and age at LT 1.7 years [0.8 – 8.7] were included. There were 13185 pre-LT & LT hospitalizations, with a total of 1824 (14%) ACLF hospitalizations. 1321 patients (44%) had at least 1 ACLF hospitalization, of which 73% (959/1321) with ACLF-1, 22% (296/1321) with ACLF-2, 5% (66/1321) with ACLF-3. CV failure was most common (75%, 1000/1321) and renal failure was least (10%, 130/1321). ACLF was associated with longer waitlist times (97 days [37-215] vs. 81 [30-205] p=0.01), fewer living donor grafts (11% vs. 19% p<0.001), and Status 1B listing (15% vs. 2% p<0.001). Pre-LT resource utilization was higher in ACLF with longer LOS (9 days [4-17] vs. 3 [2-7] p<0.001), ICU LOS (3 [2-6] vs. 2 [1-3] p<0.001), and higher total billed charges ($88512 [$36551-$191289] vs. $24134 [$11795-$50929] p<0.001). Similarly, index LT hospitalization had increased LOS (ACLF during LT hosp. 31 days [17-65] vs. ACLF only during pre-LT hosp. 18 [11-31] vs. No ACLF 18 [11-34], p<0.001), ICU LOS (11 [5-29] vs. 5 [3-12] vs. 5 [3-10] p<0.001), and charges ($665334 [$347893-$1236454] vs. $416823 [$284558-$721704] vs. $368699 [$239598-$587113], p<0.001). Post-LT patient/graft survival was worse in ACLF (Figure 1A), p<0.001, even when comparing across grade (Figure 1B, 1C), p<0.001. **Conclusion:** This is the largest cohort describing the impact of ACLF on post-LT outcomes in children with CLD. ACLF was associated with longer waitlist times and higher resource utilization during both pre-LT and LT hospitalizations. Children who experienced pre-LT ACLF had overall worse post-LT survival.

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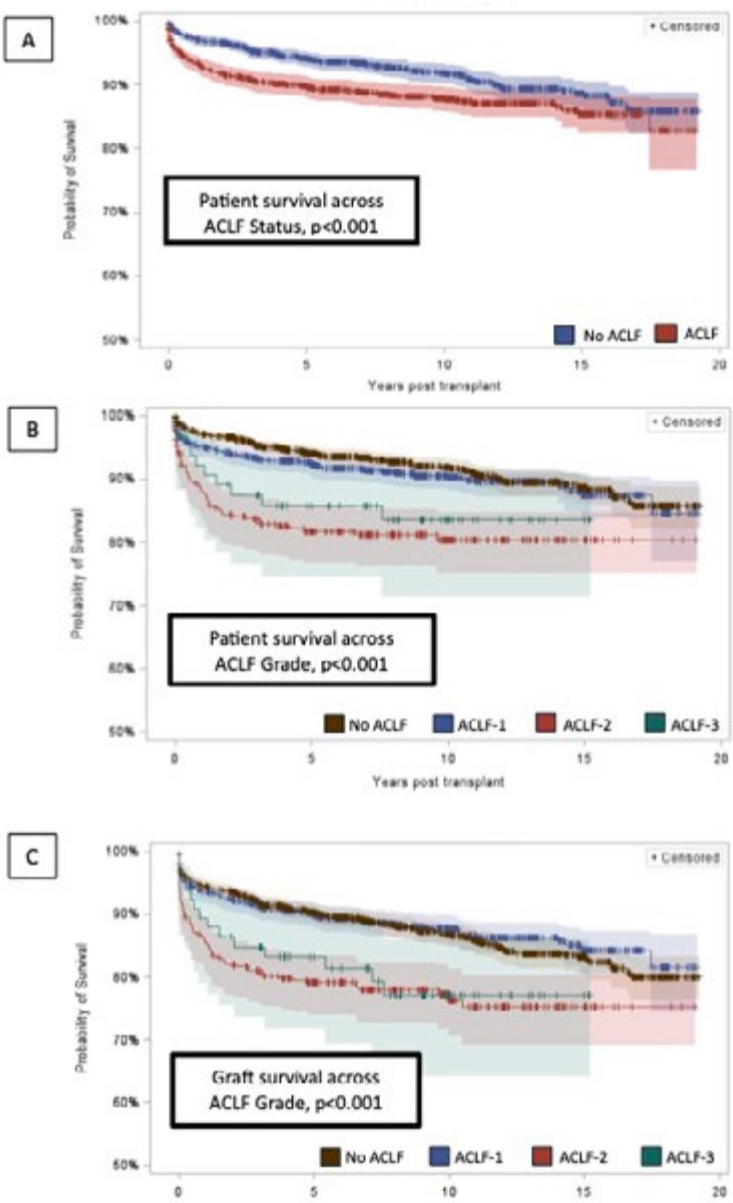
Figure 1. Patient and graft survival after LT in children with and without ACLF.



Disclosures: Anna Banc-Husu: Mirum Pharmaceuticals: Site PI for industry-sponsored clinical trial, Kathleen Hosek: Nothing to Disclose, Matt Hall: Nothing to Disclose, Divya Sabapathy: Nothing to Disclose, Moreshwar Desai: Nothing to Disclose, Fong Lam: Nothing to Disclose, Constantine Karvellas: Consultant relationship with Mallinckrodt; Has not ended; Advisor relationship with Baxter; Has not ended; Advisor relationship with Grifols; Has not ended; Data safety monitoring board for clinical trial relationship with Miromatrix; Has not ended, Ruben Hernaez: Nothing to Disclose, Benjamin Shneider: Nothing to Disclose

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4413 | DRUG INDUCED LIVER INJURY IN BILIARY ATRESIA: DEVELOPMENT OF MONITORING GUIDELINES FOR INTERVENTIONAL CLINICAL TRIALS USING PROSPECTIVE LONGITUDINAL DATA FROM OVER 1200 CHILDREN ◆

Benjamin Shneider[1] John Magee[2] Kieran Hawthorne[3] Lisa Henn[3] Chunlin Chen[4] Barbara Harber[5] Douglas Mogul[6] William Treem[7] Linyun Zhou[8] Saul Karpen[9] Sanjiv Harpavat[10] Sarah Taylor[11] David Brott[8]

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Background: Drug induced liver injury (DILI) monitoring in participants with abnormal baseline liver indices is complex and poorly delineated, especially in pediatric cholestasis. Understanding the natural fluctuation of liver indices is critical in devising enhanced monitoring criteria (EMC) and stopping guidelines (SG) in clinical trials. As biliary atresia (BA) is the leading indication for pediatric liver transplantation, there is great interest in developing new therapies to improve outcomes, which require DILI monitoring criteria. **Methods:** Cross-sectional and prospective longitudinal data from >1200 participants with BA followed for up to 20 years in the Childhood Liver Disease Research Network (NCT00061828, NCT00345553) were analyzed. EMC and SG were developed based on variability in ALT and TB at different stages of disease using expert opinion (criteria not shown). Criteria performance was investigated in the same databases (assessed at each research visit) and applied as proof in principle to START a placebo controlled trial of corticosteroids in BA (NCT00294684). **Results:** Stages of disease (groups) were defined by age or time from hepatoportoenterostomy (HPE), clinically evident portal hypertension status (CEPH) and/or TB (table). In Group 1, EMC and SG were met as assessed at each study visit in 3.0-9.6 and 0.0-2.6% of participants, respectively. In Group 2, criteria were applicable in participants with TB<2 mg/dL by 3 months post-HPE (EMC:5.8-11.0% and SG:1.3-3.7%), but problematic in the remainder due to a high proportion meeting EMC (19.0-50.0%) and SG (3.4-50.0%). In Group 3 overall, 10.1-27.6% met EMC and 4.8-32.9% met SG, although criteria were met less frequently in those with TB<2mg/dL within 3 months of HPE (EMC:1.0-9.8% SG:0.5-3.3%). Application of Group 3 criteria to START revealed increased EMC in the steroid vs placebo arm (EMC 2 wk post-HPE steroid 36.1% v placebo 5.1%, 4 wk post-HPE steroid 17.9% v placebo 0.0%). SG were met similarly (<3.5%) in both arms. **Conclusion:** Prospective registries in BA are useful in developing criteria for monitoring DILI in clinical trials as they reveal significant variability in ALT and TB. Application of derived monitoring criteria identified potential previously unknown DILI associated with corticosteroids in infants with BA. Clinical trials in participants with relatively poor bile flow are difficult to monitor for DILI given the severity of their biochemical abnormalities.

	Range Meeting EMC Criteria	Range Meeting SG Criteria
Group 1: Age > 2y	(3 to 10 years)*	(3 to 10 years)
-Absent CEPH	3.4 – 9.6%	0.0 – 2.6%
-Possible or definite CEPH	3.0 – 7.2%	0.0 – 1.3%
Group 2: Age 3 months post-HPE to 2y	(3 mo post-HPE to 2 years)	(3 mo post-HPE to 2 years)
-TB < 2 mg/dL by 90 days post-HPE	5.8 – 11.0%	1.3 – 3.7%
-TB 2 – 6 mg/dL by 90 days post-HPE	19.0 – 43.5%	3.4 – 10.1%
-TB >6 mg/dL by 90 days post-HPE	27.3 – 50.0%	21.2 – 50.0%
Group 3: 14 days to 6 months post-HPE	(2 wk – 6 mo post-HPE)	(2 wk – 6 mo post-HPE)
- Overall	10.1 – 27.6%	4.8 – 32.9%
- TB < 2 mg/dL by 90 days post-HPE	1.0 – 9.8%	0.5 – 3.3%
- TB not < 2 mg/dL by 90 days post-HPE	13.2 – 48.1%	5.7 – 49.4%

* age range for the application of the EMC or SG criteria

Disclosures: Benjamin Shneider: Nothing to Disclose, John Magee: Nothing to Disclose, Kieran Hawthorne: Nothing to Disclose, Lisa Henn: Murata Vios: Consultant, Chunlin Chen: Nothing to Disclose, Barbara Harber: Nothing to Disclose, Douglas Mogul: Nothing to Disclose, William Treem: Nothing to Disclose, Linyun Zhou: Nothing to Disclose, Saul Karpen: Consultant relationship with Albireo/Ipsen; Has ended; Consultant relationship with Mirum; Has ended; Consultant relationship with HemoShear; Has ended; Consultant relationship with

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Intercept; Has ended, Sanjiv Harpavat: Syneos Health: I sit on a Data Safety Monitoring Board, Sarah Taylor: Mirum Pharmaceuticals: Consultant, Ipsen Pharmaceutical: Consultant, Mirum Pharmaceutical: Consultant, David Brott: Nothing to Disclose

4414 | EXPLORING DISEASE-ASSOCIATED GENETIC VARIANTS IN JAPANESE PEDIATRIC PATIENTS WITH AUTOIMMUNE LIVER DISEASE: A MULTICENTER STUDY

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Background: Autoimmune liver diseases (AILD), including autoimmune hepatitis (AIH), primary sclerosing cholangitis (PSC), and AIH/PSC overlap syndrome (ASC), are rare diseases in Japanese children. Disease-associated genetic variants in patients with AILD have been reported, but not in East Asian children. We aimed to clarify disease-associated genetic variants in Japanese pediatric patients with AILD. **Methods:** We recruited children with AIH, PSC, or ASC who visited at 15 pediatric centers in Japan between September 2021 and June 2023. We analyzed the subjects' DNA in peripheral blood using a gene panel of 44 disease-associated genes reported in adult and pediatric AILD. We extracted rare genetic variants with minor allele frequency (MAF) <0.01 and defined pathogenic variants according to standards and guidelines for the interpretation of sequence variants: A joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. The risk variants in this cohort were identified using the Japanese Genome Database (ToMMo14KJPN). Fisher's exact test was used for statistical analysis. *P* values below 0.05 were considered to indicate statistical significance. **Results:** Forty-nine children with AILD (25 AIH, 14 PSC and 10 ASC) were enrolled. In the 47 Japanese patients, a *SH2B3* gene heterozygous variant (c.724C>T, p.P242S, rs78894077) was identified in 7 AILD patients (2 AIH, 2 PSC, and 3 ASC). The MAF was 0.07446, which was significantly greater than 0.03217 of ToMMo14KJPN (*P=0.0327*). The median age at diagnosis of AILD was 5 years for the *SH2B3* single nucleotide polymorphism (SNP) group and 8 years for the non-*SH2B3* SNP group, and there was no significant difference *(P=0.2692*), but the SNP group tended to develop at a slightly younger age. **Conclusion:** *SH2B3* SNP (c.724C>T, p.P242S, rs78894077) may be a disease-associated genetic variant for AILD in Japanese children.

Disclosures: Naoya Tsumura: Nothing to Disclose, Kazuo Imagawa: Nothing to Disclose, Ken Kato: Nothing to Disclose, Osamu Ohara: Nothing to Disclose, Ryuta Nishikomori: Nothing to Disclose, Tatsuki Mizuochi: Nothing to Disclose

4415 | DEEP PHENOTYPING OF A NORTH AMERICAN COHORT OF BILE ACID SYNTHETIC DISORDERS

Alyssa Kriegermeier[1] Krupa Mysore[2] Estella Alonso[1] Aki Asai[3] Kevin Bove[3] Laura Bull[4] Nathan Goodrich[5] Steve Guthery[6] Sanjiv Harpavat[7] Simon Horslen[8] Evelyn Hsu[9] Karen Jones[10] Binita Kamath[11] Saul Karpen[12] John Magee[13] Jean Molleston[14] Alexander Miethke[15] Philip Rosenthal[4] Ronald Sokol[16] Kenneth Setchell[3] Benjamin Shneider[17] Richard Thompson[18] Pamela Valentino[19] Wen Ye[10] Kathleen Loomes[20] Rohit Kohli[21]

[1]Ann and Robert H. Lurie Children's Hospital of Chicago, [2]Baylor College of Medicine, [3]Cincinnati Children's Hospital Medical C, [4]University of California, San Francisco, [5]Arbor Research Collaborative for Health, [6]Primary Children's Hospital, [7]Texas Children's Liver Center - Baylor College of Medicine, [8]UPMC Children's Hospital of Pittsburgh, [9]Seattle Children's Hosptial, [10]University of Michigan Hospital, [11]Hospital for Sick Children Toronto, [12]VCU Stravitz-Sanyal Institute for Liver Disease and Metabolic Health, [13]University of Michigan Hospitals and Health Centers, [14]Riley Hospital for Children, [15]Cincinnati Children's Hospital Medical Center, [16]University of Colorado School of Medicine, [17]Texas Children's Hospital, [18]King's College London, [19]University of Washington, [20]The Children's Hospital of Philadelphia, [21]Children's Hospital Los Angeles

Background: Bile acid synthesis disorders (BASD) are rare causes of pediatric liver disease and neonatal cholestasis that can progress to end-stage liver disease. Patients with these disorders are amenable to treatment with oral bile acid supplementation, making timely diagnosis paramount. **Methods:** Patients within the Childhood Liver Disease Research Network (ChiLDReN) enrolled in the Longitudinal Study of Genetic Causes

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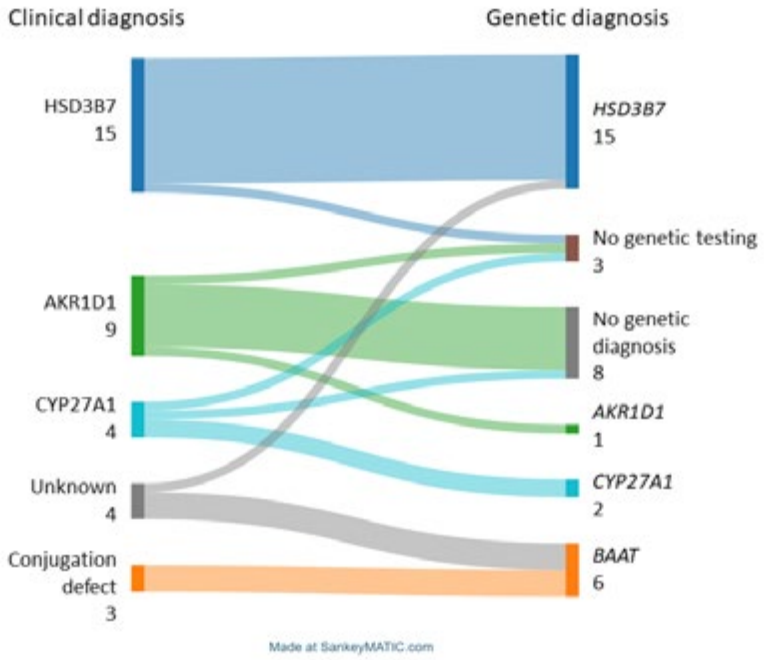
of Intrahepatic Cholestasis (LOGIC) study were identified with BASD by local centers via biochemical evidence based on mass spectrometry analysis of urine/serum or from biallelic pathologic mutations in genes encoding enzymes in the bile acid synthetic pathway. Demographic, clinical and laboratory data were obtained in the LOGIC study. Next generation sequencing (NGS) was completed on 32 of 35 samples. **Results:** Thirty-five participants were enrolled. The most common BASD was 3β-hydroxy-C27-steroid oxidoreductase (HSD3B7) deficiency (n=15, 43%), followed by Δ-3-oxosteroid 5β-reductase (AKR1D1) deficiency (n=9, 26%). The most common clinical features at enrollment were jaundice, followed by diarrhea, bleeding/bruising, vitamin E deficiency, and notably 6 participants (17%) reported pruritus. Median age of symptom onset was 2 months (range birth to 9 years). Thirty participants were enrolled with native liver, and 6 (20%) had possible or definite clinically evident portal hypertension at the time of enrollment (n=3 with HSD3B7, n=2 with AKR1D1 deficiency, n=1 with a conjugation defect). Height and weight Z-scores were normal. Mean serum gamma-glutamyl transferase (GGT) at time of enrollment was normal (38.5 ± 44.3 IU/L). NGS performed on 32 patients identified 23 patients with biallelic mutations consistent with BASD (Figure 1). Notably, 1 patient with reported sterol-27-hydroxylase (CYP27A1) deficiency, 1 patient with 'unclassified' disease, and 7 patients with reported AKR1D1 deficiency did not have disease causing mutations identified in known BASD genes. **Conclusion:** This cohort of patients highlights that many laboratory and clinical features of these rare diseases overlap with other causes of neonatal cholestasis and pediatric chronic liver diseases. Common symptoms include jaundice, diarrhea, fat-soluble vitamin deficiencies, as well as low/normal GGT. A significant minority of patients with BASD in our cohort had pruritus. Finally, genetic testing on our cohort identified a subset of patients, previously categorized as having an AKR1D1 deficiency, without clear disease-causing mutations. Further testing is ongoing to identify if alternative genes or secondary defects may be involved. A high index of suspicion must be maintained by physicians to diagnose these patients and initiate oral bile acid therapy when appropriate.



Disclosures: Alyssa Kriegermeier: Nothing to Disclose, Krupa Mysore: Nothing to Disclose, Estella Alonso: Nothing to Disclose, Aki Asai: Ipsen: Grant/Research Support, Mirum: Grant/Research Support, Moderna: Grant/Research Support, Ultragenyx: Grant/Research Support, Gilead: Grant/Research Support, Sanofi: Advisor, Kevin Bove: Nothing to Disclose, Laura Bull: Nothing to Disclose, Nathan Goodrich: Nothing to Disclose, Steve Guthery: Nothing to Disclose, Sanjiv Harpavat: Syneos Health: I sit on a Data Safety Monitoring Board, Simon Horslen: Nothing to Disclose, Evelyn Hsu: Nothing to Disclose, Karen Jones: Nothing to Disclose, Binita Kamath: Mirum: Consultant, Mirum: Grant/Research Support, Albireo/Ipsen: Consultant, Albireo/Ipsen: Grant/Research Support, Audentes: Consultant, Saul Karpen: Consultant relationship with Albireo/Ipsen; Has ended; Consultant relationship with Mirum; Has ended; Consultant relationship with HemoShear; Has ended; Consultant relationship with Intercept; Has ended, John Magee: Nothing to Disclose, Jean Molleston: Gillead: Grant/Research Support, Albireo: Grant/Research Support, Abbvie: Grant/Research Support, Mirum/Shire: Grant/Research Support, CF FOundation: Grant/Research Support, Alexander Miethke: Mirum Pharmaceutical Inc: Grant/Research Support,

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Mirum Pharmaceutical Inc: Consultant, Ipsen: Speaking and Teaching, Philip Rosenthal: Nothing to Disclose, Ronald Sokol: Nothing to Disclose, Kenneth Setchell: Nothing to Disclose, Benjamin Shneider: Nothing to Disclose, Richard Thompson: Generation Bio: Stock - publicly traded company, Generation Bio: Consultant, Rectify: Stock – privately held company, Rectify: Consultant, Mirum: Consultant, Ipsen: Consultant, Alnylam: Consultant, Integra: Stock – privately held company, Glycomine: Consultant, Spruce: Consultant, AIRNA: Consultant, Pamela Valentino: Grifols: Advisor, Mirum: Speaking and Teaching, Wen Ye: Nothing to Disclose, Kathleen Loomes: Mirum: Consultant, Albireo/Ipsen: Consultant, Mirum: Clinical trials, Albireo/Ipsen: Clinical trials, Rohit Kohli: Mirum: Consultant, Ipsen: Consultant, Epigen: Grant/Research Support, Sanofi Rare Disease: Consultant

4416 | ASSOCIATION OF ABNORMAL GLOBAL LONGITUDINAL STRAIN WITH WAITLIST DECOMPENSATION AND MORTALITY IN CHILDREN WITH BILIARY ATRESIA

Manpreet Virk[1] Tam Doan[2] Erik Su[3] Sanjiv Harpavat[4] Nhu Thao Galvan[3] Hannah Todd[3] Lara Claudia[2] Anitha Parthiban[2] Moreshwar Desai[3]

[1]Baylor College of Medicine, Houston 77030, [2]Texas Children's Hospital, [3]Baylor College of Medicine, [4]Texas Children's Liver Center - Baylor College of Medicine

Background: Cirrhotic cardiomyopathy (CCM) is prevalent in infants and children with biliary atresia (BA), and is associated with increased postoperative mortality and serious adverse events. Despite its clinical relevance, CCM is not well defined in pediatric cirrhosis, and its characterization remains restricted to structural and functional changes such as left ventricular mass index (LVMI), relative wall thickness (RWT), and ejection fraction on traditional echocardiography (ECHO). Abnormal LV Global Longitudinal Strain (GLS), a marker of subclinical myocardial dysfunction, is now included in the new 2020 definition of CCM in adults. GLS data in patients with pediatric cirrhotic cardiomyopathy are lacking. This knowledge gap prevents early identification of CCM in children and hence risk stratification while on the wait-list for transplant. Aim: To determine the prevalence and consequences of abnormal LV GLS in children with BA listed for liver transplantation (LT) and to test the hypothesis that abnormal LV GLS is associated with poor outcomes in BA. **Methods:** Children with BA listed for LT (2013-2021), with a GLS value measured on a pre-LT ECHO, at a quaternary, freestanding children's hospital were retrospectively evaluated. GLS values between -18 to -22% were considered normal, GLS 0 to -18% was abnormal. The assessment of global longitudinal strain (GLS) was done by cardiologist/echocardiographer via retrospective review of the echocardiographic images using the TOMTEC software (TOMTEC Imaging Systems, Munich, Germany). Waitlist decompensation (WD) defined as acute decompensation or presence of Acute on chronic liver failure (ACLF -decompensation of any of 6 organ systems) per published norms. Statistics: Fisher's Exact for contingency; Mann-Whitney for continuous variables; Pearson coefficient (r) for correlation; Results: Median [IQR]. **Results:** A total of 83 children were included in the study, median age 10 (6, 17) months, 62% (52/83) female. The median GLS was -19.5 (-17, -23). In the cohort, 31% (26/83) had abnormal GLS. Mortality was 7% (4/57) in group with normal GLS versus 31% (8/26) in group with abnormal GLS (p 0.007). Waitlist decompensation was 32% (18/57) in normal GLS group versus 61% (16/26) in abnormal GLS groups (p 0.015). Relation between abnormal GLS and %WD is depicted in Figure 1 **Conclusion:** LV GLS abnormalities are prevalent in infants and children with BA listed for LT. Abnormalities in GLS are associated with mortality and waitlist decompensation signaling GLS as another marker for adverse clinical outcomes. Interestingly, WD was highest in group with GLS 0 to -18%, lowest in the group with normal GLS and increased again in group with GLS – 22% and above showing a unique bimodal distribution. Abnormal GLS needs to be further refined and validated in pediatric cirrhosis.

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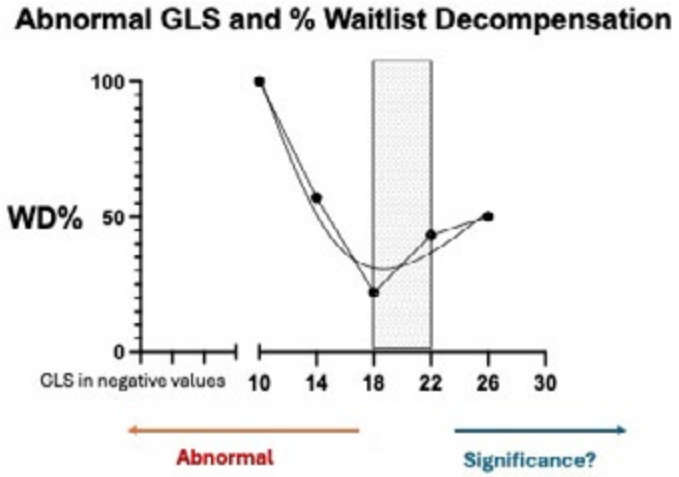

Disclosures: Manpreet Virk: Nothing to Disclose, Tam Doan: Nothing to Disclose, Erik Su: Nothing to Disclose, Sanjiv Harpavat: Syneos Health: I sit on a Data Safety Monitoring Board, Nhu Thao Galvan: 3D Systems: Consultant, ASTS- Natera: Grant/Research Support, Hannah Todd: Nothing to Disclose, Lara Claudia: Nothing to Disclose, Anitha Parthiban: Nothing to Disclose, Moreshwar Desai: Nothing to Disclose

4417 | TO INVESTIGATE THE ROLES OF GUT MICROBIOTA AND THEIR METABOLITES IN MODULATING THE PEDIATRIC LIVER TRANSPLANT OUTCOMES

Yen-Hsuan Ni[1] Huey-Ling Chen[2] Kai-Chi Chang[1] Huey-Huey Chua[1] Fang-Wen Cheng[1] Ya-Hui Chen[1]

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Background: Liver transplantation is the last option for children with end-stage liver disease, but acute or chronic allograft rejection often occurs despite immunosuppressants and monitoring, potentially leading to graft failure. The gut microbiota interacts with the host immune system, and microbiota-derived metabolites may mediate this interplay. This liver-gut cross-talk may influence liver graft health. Our aim is to investigate how the gut microbiome and plasma metabolites affect post-transplant outcomes, focusing on tolerant states and rejection episodes, which have been underexplored. **Methods:** Plasma and fecal samples were prospectively collected from children with end-stage liver disease undergoing liver transplantation. 16S ribosomal RNA (rRNA) gene sequencing was carried out to identify the composition and diversity of gut microbiota at various stages post-transplant. Additionally, untargeted metabolomics analysis of serial plasma samples from these patients were also conducted. Clinical data including liver enzymes such as aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were also incorporated to analyze their associations. **Results:** Six biliary atresia patients who underwent liver transplantation at a mean age of 0.78 years (range 0.64- 0.89 years) were recruited. A random forest classification model was applied on the16S rRNA abundance analysis, revealing that *Ruminococcus gnavus, Clostridium ramosum, and Bifidobacterium longum* were highly enriched in gut microbiota composition during the tolerant (smooth) state compared to the rejection state in post-transplantation period (Figure 1A). The relative abundance of *R. gnavus* and *B. longum* was negatively correlated with liver functions (AST and ALT) in case 1 and case 2, respectively. Both *R. gnavus and B. longum* were significantly increased during the tolerant state in case 3 (Figure 1B). Furthermore, L-isoleucine in plasma was identified as a relevantly increased metabolite in the tolerant state post-liver transplant, in comparison to the pre-transplant phase and the rejection state (Figure 1B). **Conclusion:** *R. gnavus, C. ramosum*, and *B. longum* may have a protective effect against graft injury or rejection in pediatric liver transplantation. L-isoleucine may serve as one of the functional molecules to regulate their interplay.

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Figure 1A

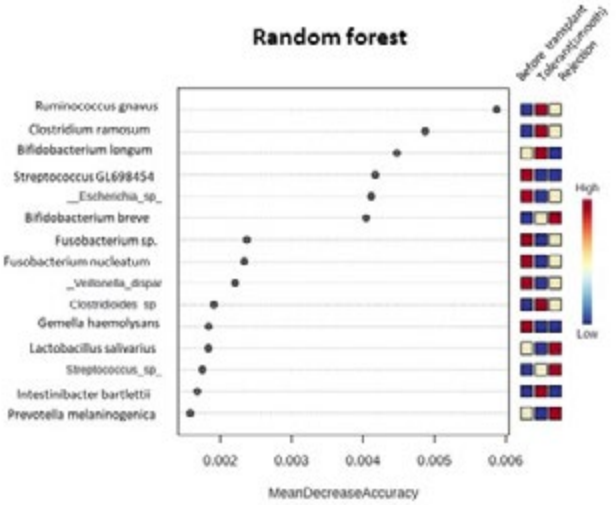
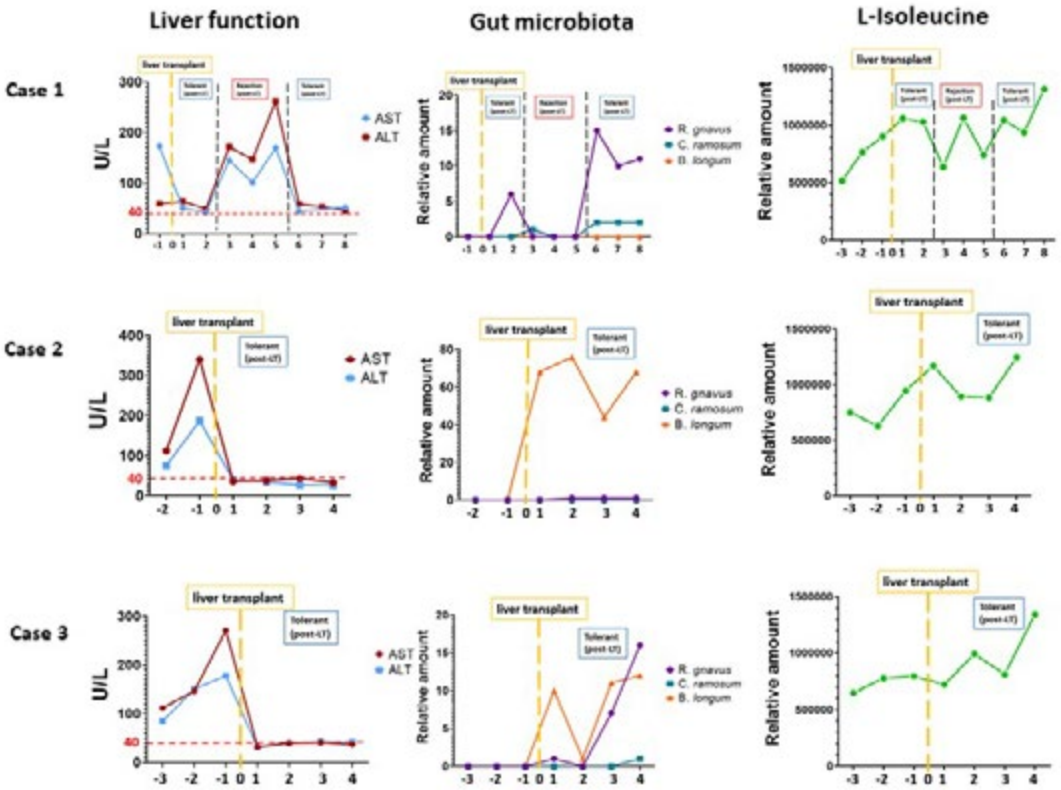


Figure 1B



Disclosures: Yen-Hsuan Ni: Nothing to Disclose, Huey-Ling Chen: Nothing to Disclose, Kai-Chi Chang: Nothing to Disclose, Huey-Huey Chua: Nothing to Disclose, Fang-Wen Cheng: Nothing to Disclose, Ya-Hui Chen: Nothing to Disclose

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4418 | IMPROVING TIME TO ANTIBIOTICS FOR FEBRILE PEDIATRIC LIVER TRANSPLANT PATIENTS - AN EMERGENCY DEPARTMENT BASED QUALITY IMPROVEMENT INTERVENTION

Natasha Dilwali[1] Jenna Spencer[2] Kelly Williams[2] Tina Thomas[2] Christopher Hartley[2] Emma Cole[2] Ann Kane[1] Sara Kathryn Smith[1]

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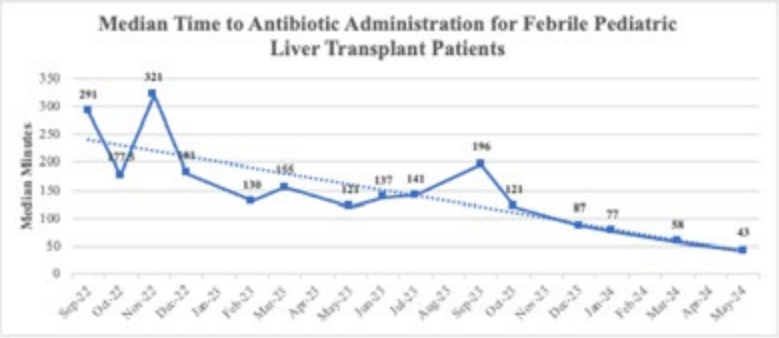
Background: Annually, over 500 children receive liver transplants in the US. Often fever is the only manifestation of serious infection and it is known infections, specifically bacteremia, are a leading cause of mortality in liver transplant recipients. Currently in the Johns Hopkins Children's Center pediatric emergency department (PED), the average time to antibiotics for febrile liver transplant patients is 180 minutes. There is a paucity of data that exists surrounding time to antibiotics in pediatric transplant patients given how niche the population is. However, literature suggests timely administration in immunocompromised patients is associated with improved outcomes, including decreased mortality and length of stay. Based on the pediatric surviving sepsis 2020 guidelines and in febrile oncologic patients, administration of antibiotics within one hour is considered best practice. The aim of this study was to decrease overall time to antibiotics by 50% in one year. **Methods:** Retrospective review of febrile, pediatric liver transplant patients in the PED was conducted to provide baseline data from September 2022 to December 2023. Prior to interventions, a root cause analysis was performed using fishbone and pareto analysis to reveal causes for antibiotic administration delays. Plan-Do-Study-Act (PDSA) cycles included: a provider educational campaign, standardized PED patient referrals, and improved notification at triage for febrile transplant patients. Data collected monthly included: outcome measure of time from arrival to antibiotic administration and process measures of time to triage, time to rooming, time to ordering labs, and time to ordering antibiotics. **Results:** 37 encounters were included from September 2022 to May 2024, post intervention data included encounters from February 2024. Mean time to antibiotics decreased from 180 to 74 minutes (59% reduction). Additionally, there was a 78% reduction in mean time to triage (9 to 2 minutes) and a 77% reduction in mean time to antibiotics ordered (48 to 11 minutes) directly highlighting the impact change in triage and standardized referrals made. **Conclusion:** This phased quality improvement intervention has decreased time to antibiotics in a highly immunocompromised population. Additional interventions include decision support tools for orders and care coordination alerts. Similar interventions may be implemented in other PEDs to improve timeliness to antibiotics.



Disclosures: Natasha Dilwali: Nothing to Disclose, Jenna Spencer: Nothing to Disclose, Kelly Williams: Nothing to Disclose, Tina Thomas: Nothing to Disclose, Christopher Hartley: Nothing to Disclose, Emma Cole: Nothing to Disclose, Ann Kane: Nothing to Disclose, Sara Kathryn Smith: Nothing to Disclose

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4419 | REAL-WORLD USE OF MARALIXIBAT IN BILIARY ATRESIA: A CASE SERIES

Natasha Dilwali[1] Catherine Chapin[2] Johanna Ferreria[3] Benno Kohlmaier[4] Bertrand Roquelaure[5] Rossitsa Rousseva[6]

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Background: Biliary atresia (BA) is a progressive disorder of intrahepatic and extrahepatic bile ducts and the most common cause of cholestasis in infants. Pruritus may complicate most cholestatic disorders, including BA, and is attributable, at least in part,to excess bile acids. Maralixibat (MRX), an ileal bile acid transporter inhibitor, was the first drug approved by the FDA for treatment of cholestatic pruritus in Alagille syndrome and is now approved for similar use in Progressive familial intrahepatic cholestasis. In addition, several patients with BA have received MRX as part of a compassionate use program (CUP). In this study we report the use of MRX for the treatment of cholestatic pruritus in BA for five patients who received MRX as part of the CUP. **Methods:** Records of pediatric patients with BA who received MRX for at least 3 months through the CUP were retrospectively reviewed from five tertiary hospitals. A standardized form was used to collect key clinical variables by treating physicians. Demographics, past medical history, lab markers, and medications were collected. Pruritus was assessed using the clinician scratch scale (CSS) at baseline and last clinical follow-up. **Results:** All patients underwent a Kasai procedure (median 64 days old, range 57-132) with the median age of first presentation of pruritus 9 months (range 5-20). None of the patients were being evaluated for transplantation at the time of MRX initiation. However three patients had splenomegaly and thrombocytopenia including one with a history of ascites and one with a history of gastrointestinal bleeding. All patients were on at least two medications for pruritus; all were receiving ursodiol and rifampin and four patients were receiving an antihistamine. At baseline, three patients had CSS of 3 (abrasions) and two patients had CSS of 4 (cutaneous mutilations, scarring, or hemorrhage). At last clinical follow up, ranging from 5 to 13 months after starting MRX, all patients had improvement in CSS. Three patients had CSS scores that went from 3 or 4 to 0, one patient went from 4 to 2, and one patient from 3 to 1. Improvements in liver enzymes, bilirubin, serum bile acids, and platelets were inconsistently observed in these patients. Post initiation of MRX, three patients were able to decrease their overall anti pruritus medication doses and no patients had increased usage. Consistent with previous trials, MRX was well tolerated without significant gastrointestinal complications and expected liver enzyme fluctuations. **Conclusion:** Maralixibat may be effective in patients with BA for the management of cholestatic pruritus, including in patients with significant pruritus and progressive liver disease. This data supports the need for larger studies to systematically evaluate the potential benefit of MRX for the treatment of cholestatic pruritus in BA.

Disclosures: Natasha Dilwali: Nothing to Disclose, Catherine Chapin: Nothing to Disclose, Johanna Ferreria: Nothing to Disclose, Benno Kohlmaier: Mirum: Advisor, Bertrand Roquelaure: Nothing to Disclose, Rossitsa Rousseva: Nothing to Disclose

4420 | TAILORING IMMUNOSUPPRESSIVE TREATMENT THROUGH THE FOLLOW-UP LIVER BIOPSY PROGRAM IN PEDIATRIC LIVER TRANSPLANT RECIPIENTS

Maria Margaret Mercada-Hally[1] Cristina Padrós[1] Jose Andrés Molino[1] Simone Mameli[1] Mauricio Larrarte King[1] Maria Teresa Salcedo[1] Ernest Hidalgo[1] Ramon Charco[1] Jesús Quintero[1]

[1]Hospital Universitari Vall d'Hebron

Background:
Balancing immunosuppression (IS) as long-term treatment of children with liver transplant (LT) is challenging. Classic tools for decision making have been patient age/weight, etiology of liver disease, time since transplant or immunosuppression levels in blood. These indicators have suboptimal sensitivity and specificity. New tools for decision making, such as biomarkers or follow-up liver biopsies (fLB), are being developed to help improve IS management. The objective of our study was to evaluate the outcomes of personalized immunosuppression protocol based on histological findings from fLB. **Methods:** Retrospective data collection through review of medical records of pediatric LT patients with fLB. Since June 2018, patients with normal liver function tests undergo fLB at 2, 5, 10, and 15 years post pLT. They also have routine liver function tests, tacrolimus levels, autoantibodies, Donor-Specific Antibodies, elastography and abdominal ultrasound. Rejection was graded using RAI per Banff classification and fibrosis was staged using the ISHAK score. Patients with RAI ≥ 2 optimized

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immunosuppression; patients under tacrolimus monotherapy, RAI = 0 and at least 5 years after pLT were offered the immunosuppression withdrawal program. Both groups had a fLB after 12 months. **Results:** Of 197 fLB, 49 (24.9%) had histological changes indicative of subclinical acute cellular rejection (RAI ≥ 2). No significant differences were found in tacrolimus levels, alanine aminotransferase, ultrasound, or elastography findings between patients with RAI ≥ 2 and those without rejection. The positivity of autoantibodies was significantly higher in children with RAI ≥2 than in children with normal or nearly normal biopsies [36/49 (73.4%) vs 18/148 (12.1%) (P <0.0001)]. Immunosuppression was optimized in 45 patients with subclinical rejection (40/45 increasing tacrolimus, 4/45 adding mycophenolic acid, and 1/45 adding steroids). Thirty-one patients had fLB one year after increasing immunosuppression. Twenty-four fLB (80.6%) showed normalization of the histology, 5 (16.0%) displayed histological improvement without normalization, and 2 (6.4%) showed no improvement.
Eleven patients discontinued immunosuppression. Six of them had a normal biopsy at one year. Three patients had to reintroduce immunosuppression (two due to elevated transaminases and one due to RAI=2 in the one-year LB). All of them had a normal biopsy at one year after immunosuppression reintroduction. **Conclusion:** Follow-up liver biopsies facilitate precise monitoring and tailored immunosuppressive treatment for pLT recipients.

Disclosures: Maria Margaret Mercada-Hally: Alexion: Speaking and Teaching, IPSEN: Financial support for educational meetings, Cristina Padrós: Nothing to Disclose, Jose Andrés Molino: Nothing to Disclose, Simone Mameli: Nothing to Disclose, Mauricio Larrarte King: Nothing to Disclose, Maria Teresa Salcedo: Nothing to Disclose, Ernest Hidalgo: Nothing to Disclose, Ramon Charco: Nothing to Disclose, Jesús Quintero: Nothing to Disclose

4421 | THE USE OF A SINGLE PROCEDURE BIODEGRADABLE STENTING TO TREAT BILIARY ANASTOMOTIC STRICTURES IN PEDIATRIC LIVER TRANSPLANTATION

Maria Margaret Mercada-Hally[1] *Cristina Padrós*[1] *Simone Mameli*[1] *Mauricio Larrarte King*[1] *Mercedes Pérez*[1] *Jose Andrés Molino*[1] *Ernest Hidalgo*[1] *Ramon Charco*[1] *Jesús Quintero*[1]

[1]*Hospital Universitari Vall d'Hebron*

Background: Anastomotic biliary strictures (ABS) are the most common complications of pediatric liver transplantation (pLT). A transhepatic approach using interventional radiology has been shown to be a valuable therapeutic procedure to dilate these strictures. In the past decade, biodegradable biliary stents (BBS) have been introduced for the treatment of biliary strictures in adults, providing sustained dilatation with low rates of long-term complications and not requiring stent removal. The objective of our study was to evaluate the safety and efficacy of the use of BBS for the treatment of ABS in pediatric patients undergoing liver transplantation. **Methods:** Single-center observational study where data was retrospectively collected from all pediatric liver transplant patients who presented with ABS and were treated with a BBS between January 2014 and January 2023. During period 1 (January 2014 to January 2019) the placement of BBS was carried out in two steps. First, a percutaneous cholangiography (PTC) was performed where the length of the stricture was measured, it was dilated with a high-pressure balloon, and an internal-external biliary drain was placed. In a second PTC, a customized BBS was inserted according to the measurements obtained and the drain was removed. In period 2 (January 2019-January 2023), a BBS repository was available that allowed stent placement in a single step, just after dilation of the stenosis in a single PTC. Risk factors for ABS recurrence in patients treated with BBS were evaluated using a logistic regression model. Subsequently, all possible risk factors were analyzed by multivariate analysis. To evaluate the impact of one- or two-step BBS placement, the ABS recurrence rate was evaluated, as well as differences in time between BBS placement and ABS recurrence and cholangitis rate after placement of the BBS. **Results:** Between January 2014 and January 2023, 46 EBAs were diagnosed in 43 pediatric liver transplant recipients (three patients had two ABSs).ABS were diagnosed a median of 6.7 months after liver transplantation (0.1-246.8). Eight ABS treated with BBS (17.4%) recurred (median time to recurrence 6.5 months; 1.6-17.0 months). Of these, 3 were resolved with the placement of a second BBS, and 4 required surgery. Patients with a common bile duct-choledochal anastomosis were 11 times more likely to have a recurrence of ABS than those with a bilioenteric anastomosis (OR 10.8; 1.4-81.33, p=0.008). No other risk factors for ABS recurrence were observed. No differences were observed in ABS recurrence rate, time to ABS recurrence, or cholangitis rate between BBS placed in one or two steps. **Conclusion:** Percutaneous implantation of BBS in pediatric liver transplant patients is a viable, safe and effective treatment for the treatment of ABS, offering promising long-term results. One-step BBS placement appears to be equally safe and effective, sparing the patient procedures

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4422 | MULTI-OMIC ANALYSIS OF PEDIATRIC ACUTE LIVER FAILURE IDENTIFIES IMMUNOMODULATORY AND EXHAUSTIVE PHENOTYPES THAT PREDICT SURVIVAL WITH NATIVE LIVER

Jason Lee[1] Johanna Ascher Bartlett[2] Sarah Bangerth[1] Arianna Barbetta[1] Brittany Rocque[3] Carly Weaver[2] Beth Carter[2] Kambiz Etesami[2] Rohit Kohli[2] Juliet Emamaullee[4]

[1]University of Southern California, [2]Children's Hospital Los Angeles, [3]University of Rochester Medical Center, [4]Keck Medical Center of USC

Background: Pediatric acute liver failure (PALF) is a rapidly progressive disease requiring liver transplantation (LT) in up to 25% of patients. Despite its multifactorial nature, PALF is characterized by a dense inflammatory infiltrate that destroys hepatic parenchyma. Besides cytotoxic CD8+ T-cells, little is known with respect to immune subsets that contribute to disease development and progression. Here we examine immune features that contribute to PALF and differentiate patients who survive with native liver (SNL). **Methods:** Review of single center data identified 149 patients admitted with PALF from 04/2003 – 01/2024, among which 78 had archival liver biopsy material available. 62 patients were selected (20 with SNL, 42 requiring LT; 32 indeterminate etiology) and analyzed using a 29-marker immunophenotyping mass cytometry panel. A 1500-marker proteomic panel (Somalogic) was used to assess plasma biomarkers in an 11 PALF patient subset compared to 16 healthy controls. **Results:** A total of 469,066 cells were identified in tissues corresponding to 38 immune and 9 non-immune subsets. SNL was associated with an increase in NK and plasma cells (p = 0.01, 0.003), while LT was associated with an increase in macrophages (p = 0.008) (Fig. 1A). Classical monocytes expressing proliferative (Ki-67) and immunomodulatory proteins (PD-L1 and PD-L2) were also increased in SNL (p = 0.01, 0.048). Notably, PD-L2 M2 macrophages, exhausted CD4+ T-cells, and activated NK-cells were increased in SNL while exhausted NK-cells were associated with LT (Fig. 1B). LASSO regression revealed that these four populations could strongly differentiate SNL from LT (AUC 0.95, Fig. 1C). Plasma protein ontology in patients with PALF were enriched in pathways associated with immune function, liver metabolism, and cellular signaling. Plasma biomarkers associated with immunomodulation in NK (CD244/SLAM) and T-cell (CD274/PD-L1) populations were identified via pathway analysis in patients with PALF (Fig. 1D). **Conclusion:** Our results demonstrate that immune dysregulation via immune exhaustion and NK-cell activity differentiate disease progression and LT in PALF. Moreover, plasma proteomics suggest that non-invasive biomarkers of these pathways can be developed to predict clinical outcomes in PALF. Future work will look to characterize these immune subpopulations as potential candidates for biomarker and therapeutic discovery.

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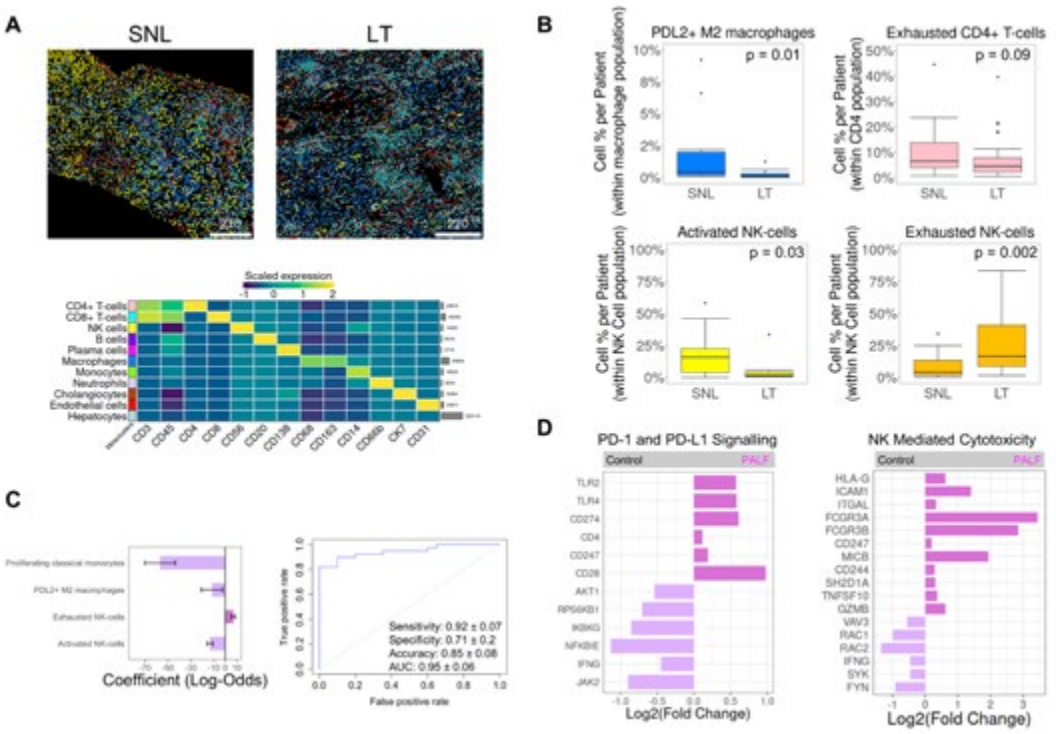

Disclosures: Jason Lee: Nothing to Disclose, Johanna Ascher Bartlett: Nothing to Disclose, Sarah Bangerth: Nothing to Disclose, Arianna Barbetta: Nothing to Disclose, Brittany Rocque: Nothing to Disclose, Carly Weaver: Nothing to Disclose, Beth Carter: Nothing to Disclose, Kambiz Etesami: Nothing to Disclose, Rohit Kohli: Mirum: Consultant, Ipsen: Consultant, Epigen: Grant/Research Support, Sanofi Rare Disease: Consultant, Juliet Emamaullee: Nothing to Disclose

4423 | COMPLEMENT RECEPTOR C5AR1 CONTROLS LIVER MACROPHAGE OXIDATIVE-ANTIOXIDANT BALANCE AND INFLAMMASOME ASSEMBLY IN BILIARY ATRESIA

Reena Mourya[1] Pavithra Sudhakara[1] Xiongbin Kang[1] Sindhu Pandurangi[2] Natasha Corbitt[3] Pranavkumar Shivakumar[4]

[1]UT Southwestern Medical Center, [2]UT Southwestern, Children's Medical Center Dallas, [3]UTSW, Children's Medical Center, [4]University of Texas Southwestern Medical Center

Background: Previous work from our laboratory has shown that the complement receptor, C5ar1, plays a critical role in controlling bile duct inflammation and fibrosis in biliary atresia (BA) by regulating intrahepatic macrophage M1 polarization. Here, we examined if C5ar1 defines macrophage-specific oxidative stress and antioxidant responses in experimental BA and shares features with human BA. **Methods:** Experimental biliary atresia was induced in wild-type (WT) and C5ar1-KO newborn mice by i.p. rhesus rotavirus (RRV) injection. Control mice were injected with 0.9% saline. Liver macrophages were isolated using anti-F4/80 microbeads followed by RNA isolation and cDNA synthesis. Mouse PCR arrays and gene-specific expressions were performed using real-time PCR. Human BA liver transcriptomic (GSE122340) and serum proteomics data were used for differential expression analysis. Gene enrichment was performed using the *Enrichr* platform. *In vitro* experiments used control or RRV-infected RAW264.7 macrophage cell line treated with recombinant C5a and glutathione. Logistic regression was performed between gene expressions and patient data. **Results:** WT mice infected with RRV progressively developed biliary injury and obstruction (N=8; 100%) that was absent in C5ar1-KO and control mice (N=8/group; 0%). Correspondingly, expressions of oxidative stress genes linked to *Sult1c2*, *Glyat*, *Apoc1*, *Apoc2*, *Lmo1*, *Fbp1*, *Gpr162*, *Fabp5*, *Mtus1*, *Plxnc1*, and *Ptpro* increased in macrophages from WT livers but were notably lower in macrophages lacking C5ar1 (1.5-10.4-fold lower; P<0.02; N=4/group). Recombinant C5a treatment of RRV-infected C5ar1^{+} RAW264.7 cells prompted oxidative stress gene response and increased inflammasome assembly (*Nlrp3*, *IL1b*, *Card11*, *Nod1*, *Nlrc5*; >2.4-fold; P<0.01), that were blocked by glutathione.

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Importantly, C5ar1-deficient macrophages showed robust induction of the antioxidant metallothionein gene, *Mt3* (>120-fold, P<0.001). In parallel, RNA-Seq data from BA patient livers showed elevated oxidative stress molecules *LOXL4*, *FOSB*, *DDR1*, *FABP5*, *CYBA*, *PTGS2* (5.7-33.4-fold; P<0.01) and substantially reduced metallothionein *MT1A*, *MT1M*, *MT1X*, and zinc transporter *SLC39A8*, *SLC30A1*, *SLC39A14* expressions (>1.4-fold; P<0.03). Levels of oxidative stress-related FGF23, CTSB, THBS2, MDK, and IL-8 increased (2.2-6.3-fold, P<0.001) in patient serum, while SERPINC1, HP, and HPX levels decreased (1.5-6.0-fold lower than controls). In BA patients, multivariable logistic regression linked higher expression of CYBA to lower survival with native liver at two years (P<0.02). **Conclusion:** Our work identifies regulation of macrophage oxidative-antioxidant balance by C5ar1 involving the inflammasome-metallothionein-zinc transporter axis. Targeting C5ar1 offers a new approach to block oxidative stress in macrophages and restore homeostatic cell functions in biliary atresia.

Disclosures: Reena Mourya: Nothing to Disclose, Pavithra Sudhakara: Nothing to Disclose, Xiongbin Kang: Nothing to Disclose, Sindhu Pandurangi: Nothing to Disclose, Natasha Corbitt: Nothing to Disclose, Pranavkumar Shivakumar: Nothing to Disclose

4424 | REVISITING NK CELLS IN BILIARY ATRESIA: COMPLEMENT RECEPTOR C5AR1 LICENSES NK CELLS TO RECOGNIZE AND KILL CHOLANGIOCYTES

Reena Mourya[1] Pavithra Sudhakara[1] Sindhu Pandurangi[2] Natasha Corbitt[3] Pranavkumar Shivakumar[4]

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Background: In biliary atresia (BA), activated NK cells populate the portal tracts and promote cholangiotoxicity to induce duct injury and atresia. However, the mechanisms of hepatic NK cell activation remain largely unknown. In this work, we investigated if the complement receptor, C5ar1, controls NK cell activation and cholangiocyte injury and the prevalence of C5ar1$^+$ NK cells in human BA. **Methods:** Wild-type (WT) and C5ar1-KO newborn mice were injected i.p. with 0.9% saline (controls) and 1.5x10^6 ffu rhesus rotavirus (RRV) to induce BA. Flow cytometry was used to evaluate intrahepatic NK cells and real-time PCR to quantify gene expressions. NK cells were purified for cytotoxicity and co-culture assays, gene expressions, activation using recombinant C5a (rC5a), and estimation of secreted proteins by ELISA. Immunofluorescence was used to characterize CD56$^+$/C5ar1$^+$ NK cells. BA patient liver RNA-Seq (GSE122340) and serum proteomics data were analyzed for C5ar1-NK associated markers and correlation performed with patient data. **Results:** To examine if heightened NK cell response involved C5ar1, we performed flow cytometry on day 7-old WT livers and identified intrinsic C5ar1$^+$ NK cells in control mice that markedly expanded after BA induction (7.4 vs 14%; P<0.01). This response was developmentally restricted, with C5ar1$^+$ NK cells absent in adult livers (<1%). Delineating C5ar1 control of NK cell trafficking, we observed a 2-fold reduction in total NK cells in RRV-infected C5ar1$^{-/-}$ livers (12 vs 25% in WT; P<0.001). Improved disease indices in RRV-C5ar1$^{-/-}$ mice were associated with reduced frequency of activated CD69$^+$ NK cells (65 vs 86% in WT; P<0.01) and complete loss of NK cell mediated cholangiotoxicity. Mechanistically, we linked loss of cytotoxicity to cholangiocyte-recognizing NKG2D$^+$ NK cells (31 vs 54% in WT; P<0.01) and reduced IFNg, TNFa, GZMB, and CCL5/6/7 transcripts in livers and protein levels in cultured C5ar1$^{-/-}$ NK cells. *In vitro*, rC5a priming of naïve WT NK cells increased expressions of IFNg, TNFa, and GZMB, with a greater response in NK cells from RRV livers. Importantly, immunofluorescence staining of BA patient livers and EHBD remnants at diagnosis showed increased frequency of CD56$^+$C5ar1$^+$ cells (59-65%), elevated *KLRK1*, *DAP10*, *DAP12*, *CXCR4*, *CCR5* transcripts and serum RANTES and CCL20 levels (1.9-7.3-fold; P≤0.03). Clinically, DAP10 and DAP12 expressions were significant predictors of survival with native liver at 2 years (P≤0.02). **Conclusion:** These findings identify a critical role for C5ar1 in licensing hepatic NK cell activation to recognize cholangiocytes and promote injury and cell death. The findings of tissue-specific CD56$^+$C5ar1$^+$ cells at diagnosis strongly advocate blocking C5ar1 to suppress immune cell activation and prevent cholangiocyte injury in BA.

Disclosures: Reena Mourya: Nothing to Disclose, Pavithra Sudhakara: Nothing to Disclose, Sindhu Pandurangi: Nothing to Disclose, Natasha Corbitt: Nothing to Disclose, Pranavkumar Shivakumar: Nothing to Disclose

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4425 | UTILITY OF FUNGAL BIOMARKER, BETA-D-GLUCAN (BDG) FOR THE DIAGNOSIS AND ANTIFUNGAL USAGE IN PEDIATRIC LIVER AND MULTIVISCERAL TRANSPLANT RECIPIENTS

Sunitha Vimalesvaran[1] *Adarsh Kancharla*[2] *Anil Dhawan*[2] *Anita Verma*[2]

[1]*King's College Hospital NHS Foundation Trust,* [2]*King's College Hospital NHS Foundation T*

Background: The risk of fungal infections (FI) in complex pediatric liver transplant recipients (PLTR) increases significantly because of cumulative exposure to various risk factors including increased length of hospital stay (LOHS), intensive care unit (ICU) stay and prolonged antibiotics usage. Early diagnosis and prompt antifungal therapy are key to improve outcomes. **Methods:** To evaluate the utility of fungal biomarker beta-D-glucan (BDG) for the diagnosis of FI and for antifungal usage in PLTR and multi-visceral transplant recipients (MVSTX). Patients were identified from our clinical database. The demographics, clinical presentations, laboratory data and outcomes were collected from electronic medical and laboratory databases. Institutional approval was obtained. **Results:** BDG as a fungal biomarker was tested in 254 patients admitted to PICU and general hepatology ward at King's College Hospital London, between Jan 2017 and Nov 2018. Data was systematically reviewed in 96 (37%) children with PLTR and MVSTX. All patients were tested on a weekly basis for BDG during their hospital stay. Two or more positive BDG values of >80 pg/ml were considered significant to further consolidate a diagnosis of FI alongside imaging and culture or tissue histology. 48/96 (50%) children had ≥2 samples positive for BDG and 25/96 (26%) were diagnosed with FI. Only one patient with negative BDG had FI. The sensitivity and specificity of BDG for ≥2 samples at cut off value of >80pg/ml was 94% and 92% respectively and negative predictive value (NPV) was 96% (Figure). Infections with *Candida albicans* accounted for 50% (13/26) and 19% (5/26) of FI were due to *Geotrichum capitatum, Mucor circinelloides, Absidia corymbifera and Aspergillus fumigatus*. BDG was positive in all non-*Candida* yeast infections. Patients with acute liver or multi organ failure had ta higher rate of IFI in comparison to patients with chronic liver disease (CLD) and intestinal failure, as indication for transplantation. Ninety-day all cause mortality was <4% and none of our patients died due to FI. Patients with FI had significantly increased LOHS and duration of PICU stay. Additional risk factors were fungal colonisation and associated multidrug resistant bacterial infections (Figure). Negative BDG value <80pg/ml was used to stop antifungal in >80% of patients which resulted in significant reduction of duration and cost of antifungals. Interestingly leucopenia was also consistently associated with high BDG levels (Figure). **Conclusion:** Our data suggests ≥2 positive BDG has a good diagnostic accuracy and could be incorporated into a diagnostic algorithm for IFI in PLTR and MVSTX. We have also shown that a negative BDG value has a good predictive value for stopping antifungal therapy which has resulted in significant reduction in duration and cost of antifungal use.

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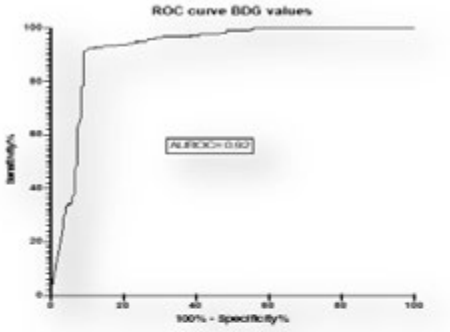
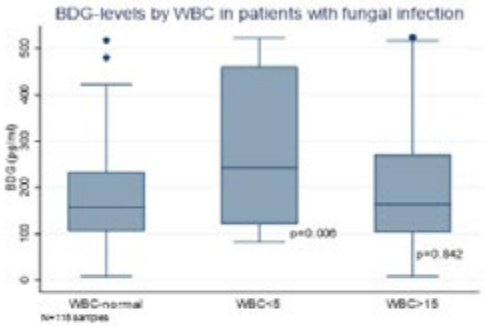
Sensitivity specificity, NPV, PPV of BDG



Correlation of BDG levels and WBC in patients with fungal infection



Patient Demographics (n=96)	FI (n=26)	NO FI (n=70)	p-value
Age at time of admission, median (IQR)	2.5 (1.4 – 7.5)	3.0 (1.0- 9.0)	0.95
Length of Hospital Stay Days, median (IQR)	62.5 (31.8-126.3)	22.0 (16.8- 33.0)	<0.0001
PICU Stay Days, median (IQR)	11.0 (2.0- 32.5)	3.0 (2.0 -7.0)	<0.0001
ALF / MOF	23 (88.5)	23 (24.0)	<0.0001
MDRO infection, n (%)	13 (50.0)	9 (12.9)	0.0003
Colonisation with fungal infection, n (%)	18 (69.2)	4 (5.7)	<0.0001
Biliary complications, n (%)	4 (15.4)	10 (14.3)	>0.99
Surgical complications, n (%)	3 (11.5)	2 (7.7)	0.12
Mortality, n (%)	3 (11.5)	3 (4.3)	0.34
30-day Mortality, n (%)	1 (3.8)	0 (0.0)	0.27
1 year Mortality, n (%)	1 (3.8)	1 (1.4)	0.47

Disclosures: Sunitha Vimalesvaran: Nothing to Disclose, Adarsh Kancharla: Nothing to Disclose, Anil Dhawan: Bit Bio: Consultant, Aspect Bio: Consultant, Astellas: Consultant, Univar: Advisor, Orphalan: Advisor, Anita Verma: Nothing to Disclose

4426 | SERUM VALUES IN BILIARY ATRESIA PATIENTS AS INDICATORS FOR NATIVE LIVER SURVIVAL: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: After hepatoportoenterostomy (HPE), only a minority of biliary atresia (BA) patients reach adolescents without requiring liver transplantation (LT). Improved understanding of this BA population subset could help post-HPE risk stratification and management. Therefore, we aim to identify serum predictors of native liver survival (NLS) in post-HPE BA patients. **Methods:** We searched PubMed, MEDLINE, SCOPUS, and EMBASE databases to identify studies published from 1946 through December 2023, reporting serum values as prognostic factors for BA after HPE, specifically total bilirubin (TB), ALT, GGT, MMP-7, and total bile acids (TBA). Non-function HPE was defined as persistent jaundice, cirrhosis, LT, or death. We calculated pooled serum variables, including hazard ratios (HRs) and odds ratios (ORs), for NLS using the inverse variance weighting method. **Results:** Thirty studies were included in the meta-analysis including a total of 4,399 BA patients, 2,073 of which had successful HPE and 1,793 had non-functioning HPE. The average time to HPE for the success group was 63.3 ± 0.18 days vs 69.5 ± 0.20 days for the failure group (*p<0.001*) **(**Table 1**)**. TB was significantly elevated in the non-functioning group (*p<0.001*) **(**Figure 1**)**. Pooled ALT and GGT were significantly lower in the success group for 1-3 month and >5-years post-HPE (*p<0.001*). A single study indicated that NLS decreased when

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MMP-7 levels exceeded 10.3 ng/mL (HR: 4.29, 95%CI: 1.12-16.52). The success group had significantly lower serum TBA (27.55 µmol/L, 95%CI: 20.35-34.75) vs the non-functioning group (69 µmol/L, 95%CI: 56.26-81.74) (*p<0.001*) >5-years post-HPE. **Conclusion:** Established serum markers such as ALT, GGT, and TB are useful for prognostic assessments following HPE. A TB level of less than 2.4 mg/dL within 1-3 months and less than 1 mg/dL by 12 months can indicate higher chances of native liver survival at those specific time points. Additionally, GGT levels greater than 660 IU/L within 1-3 months and greater than 450 IU/L between 4-12 months suggest an increased risk of HPE non-functioning. An ALT level below 100 IU/L within 1-3 months may be a potential indicator of successful outcomes. MMP-7 and TBA require further evaluation to determine their prognostic relevance for native liver survival in BA patients.

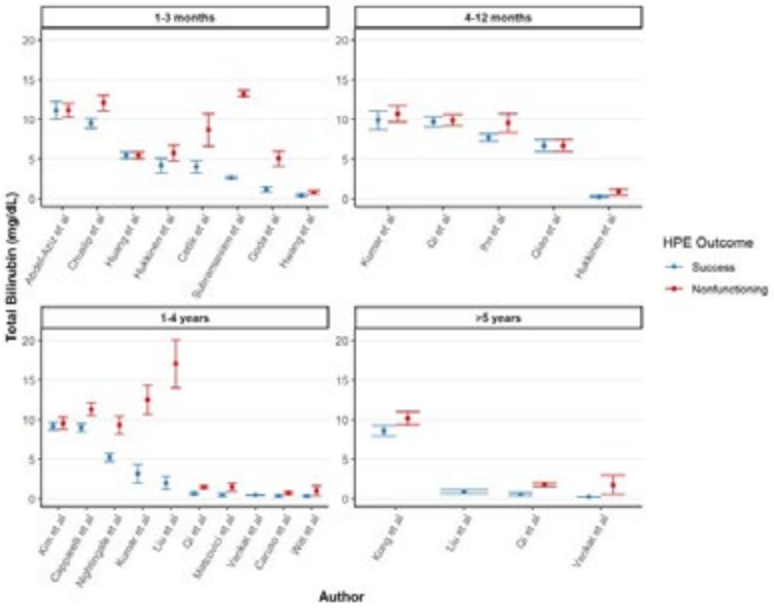

Figure 1: Total bilirubin (TB) (mg/dL) serum values of the studies included stratified by success and nonfunction post-HPE among BA patients.

* TB: Total Bilirubin, HPE: Hepatoportoenterostomy, BA: Biliary Atresia

Serum Values	Serum Values	1-3 months	4-12 months	1-4 years	>5 years
Total Bilirubin (95%CI) mg/dL	TB (Success)	2.36 (2.27-2.45)	0.78 (0.70-0.86)	0.72 (0.67-0.77)	0.25 (0.23-0.27)
	TB (Nonfunction)	6.28 (6.09-6.48)	4.08 (3.81-4.34)	1.52 (1.42-1.62)	2.48 (2.25-2.70)
	P-value	<0.001	<0.001	<0.001	<0.001
Alanine Transaminase (95%CI) IU/L	ALT (Success)	106.71 (103.66-109.75)	149.89 (139.67-160.11)	116.83 (113.97-119.68) [1]	84.59 (69.87-99.31)
	ALT (nonfunction)	195.64 (190.27-201.02)	153.43 (150.05-156.82)	121.49 (113.04-129.94) [1]	189.41 (162.32-216.50)
	P-value	<0.001	0.52	0.31 [1]	<0.001
Gamma-glutamyl Transferase (95%CI) IU/L	GGT (Success)	496.16 (466.50-525.81)	309.94 (277.01-342.87)	338.67 (332.73-344.61) [1]	124.95 (100.53-149.36)
	GGT (Nonfunction)	600.33 (552.88-647.78)	467.99 (459.25-476.75)	363.16 (322.04-404.28) [1]	495.21 (417.52-572.90)
	P-value	<0.001	<0.001	0.25 [1]	<0.001
Total Bile Acids µmol/L (95%CI)	TBA (Success)	n/a	129 (117.10-140.90)	92.47 (75.85-109.095)	27.55 (20.35-34.75)
	TBA (Nonfunction)	n/a	163 (139.44-186.56)	81.75 (71.02-92.48)	69 (56.26-81.74)
	P-value	n/a	0.01	0.29	<0.001

Table 1: Serum values of BA patients included in the overall study.
*BA: Biliary Atresia, ALT: Alanine Transaminase, Alk Phos: Alkaline Phosphatase, GGT: Gamma-glutamyl Transferase, MMP-7: Matrix Metalloproteinase 7, TBA: Total Bile Acid
[1]: Outlier (Caruso et al) was excluded

Disclosures: Ahmad Anouti: Nothing to Disclose, Hamza Dahshi: Nothing to Disclose, Thomas Cotter: Nothing to Disclose, Tebyan Rabbani: Nothing to Disclose, Sanjiv Harpavat: Syneos Health: I sit on a Data Safety Monitoring Board, Natasha Corbitt: Nothing to Disclose, Sara Hassan: Nothing to Disclose

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4427 | NEONATAL ACUTE LIVER FAILURE SECONDARY TO ENTEROVIRUSES: CLINICAL CHARACTERISTICS AND OUTCOME

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Background: Neonatal acute liver failure (ALF) is a rare but fatal condition with a mortality of up to 50%. Amongst the known common causes are herpes virus, metabolic diseases, gestational alloimmune liver disease (GALD), and ischaemic injury. Up to 40% of cases have an unknown etiology. Human enterovirus (HEV) infections are common in neonates, with serious clinical manifestations including myocarditis, meningoencephalitis and more rarely can cause ALF with a fulminant course. The aim of this study was to summarize the clinical characteristics of neonates with severe HEV leading to ALF in our centre, to provide evidence for further treatment and management. **Methods:** Patients with ALF and HEV infection were identified from our clinical database. The demographics, clinical presentations, laboratory data and outcomes were collected from electronic medical and laboratory databases. Viral testing was done by real-time PCR in blood and respiratory secretions. Serotyping of HEV was done from HPA virology reference laboratory. **Results:** Four cases of neonatal ALF due to HEV (Table 1) were identified between Oct 2022 – Mar 2024. Mothers tested positive for HEV in two cases during the perinatal period. All neonates were born via C-section and all presented with ALF at our institution. Extensive investigation was done to exclude other causes of ALF and immunodeficiency. Only one child had a concomitant diagnosis for GALD. Severe coagulopathy with low fibrinogen was seen in all cases requiring regular blood products. All children were managed supportively in our critical care unit with ventilation and renal replacement therapy. All patients received intravenous immunoglobulin (IVIG) and antimicrobials. Three patients were listed for liver transplantation (LTX) but only one received LTX. This infant died post LTX because of multiple post-LTX complications and fungal infection. All other neonates survived with near normalization of liver function. **Conclusion:** Our data suggests an increasing incidence of HEV neonatal ALF associated with severe coagulopathy requiring multiple blood products. Decision for LTX in this setting can be challenging, as there is little evidence on outcomes in these neonates. We recommend that HEV testing should be added to the diagnostic algorithm for all neonatal ALF to help in management. Newer antiviral agents for HEV are under investigation but more clinical evidence for its use is still required.

Table 1: Demographic, presentation and outcomes for neonatal acute liver failure due to Enterovirus

	Sex	GA	Mode of Delivery	Maternal Manifestation	Age at onset (days)	Enterovirus serotype	Clinical features	ALT	AST	Bilirubin	Ammonia	INR	Liver transplant	Outcome
Case 1	M	37+1	ELSCS	Group B *Streptococcus* Infection	4	Unable to characterize	Fever, Floppy	1700	8152	239/ 112	66	>10	No	Alive
Case 2	M	36	EMLSCS	NA	6	Unable to characterize	Fever, poor feeding	133	625	365/ 107	220	6	Yes	Died
Case 3	F	35+2	EMLSCS	Eenterovirus infection +ve	6	Not available	Lethargy, poor feeding	150	100	738/ 412	271	>15	Listed, but recovered	Alive
Case 4	F	37+3	EMLSCS	Enterovirus Infection +ve	3	Echovirus type 11	Poor feeding and dehydration	147	405	283/ 141	140	4	Listed, but recovered	Alive

ELSCS-elective caesarean section, EMLSCS; emergency C-section, ALT; Alanine transaminase, AST; Aspartate transaminase, INR; international normalised ratio

Disclosures: Adarsh Kancharla: Nothing to Disclose, Sunitha Vimalesvaran: Nothing to Disclose, Anil Dhawan: Bit Bio: Consultant, Aspect Bio: Consultant, Astellas: Consultant, Univar: Advisor, Orphalan: Advisor, Anita Verma: Nothing to Disclose

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4428 | THE IMPACT AND TREATMENT POSSIBILITIES OF NEDDYLATION IN PEDIATRIC LIVER CANCER: HEPATOBLASTOMA ◆

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Background: Hepatoblastoma (HB) is a rare type of primary liver cancer that mainly affects children. Currently, the main treatment options include surgical resection accompanied by chemotherapeutics such as cisplatin or doxorubicin. However, these options are limited or ineffective due to poor prognosis, high recurrence rate, and significant side effects. This is a tumor with a low rate of somatic mutations, in which the involvement of other mechanisms modulating its tumorigenic capacity stands out. In this regard, it is crucial to highlight the adaptive advantages conferred to the tumor by post-translational modifications. In particular, neddylation has been extensively studied in this context. Based on this evidence, we have considered analyzing the impact that neddylation could have on the development of HB. **Methods:** We investigated neddylation's impact on HB development using a cohort of HB patients, an HB preclinical mouse model (YAPS127A/N90-β-catenin), and in vitro tumor cell models (HepT1, HepG2, and patient-derived xenografts (PDX) from distal metastasis), where we characterize NEDDylation pathway. Besides the modulation of NEDP1 levels using an in vitro approach was made to study cell proliferation, migration, and metabolic status. In vivo, the implications of NEDP1 overexpression as a tumor suppressor were evaluated. **Results:** Transcriptomic analysis in samples from patients with HB has demonstrated an increase in the neddylation cycle and a significant reduction in the activity of NEDP1 deneddylase. Likewise, tumor cells and HB preclinical mice model showed an increase in global neddylation with a decrease in NEDP1 levels and activity, which justifies the importance of this process in the development and progression of HB. In addition, a positive impact on proliferation driven by neddylation is evidenced. Moreover, modulation of neddylation through NEDP1 overexpression induces apoptosis, reduction of proliferative capacity and, metabolic reprogramming in vitro. In vivo experiments with NEDP1 overexpression showed a reduction of angiogenesis, tumor formation, and metastatic capacity in CAM assay (in Ovo and ex Ovo), while HB mice models showed increased necrosis, apoptosis, and proteome reorganization. **Conclusion:** The effect observed with NEDP1 overexpression points to the importance of NEDDylation in HB and highlights the relevance in the development of new specific treatments.

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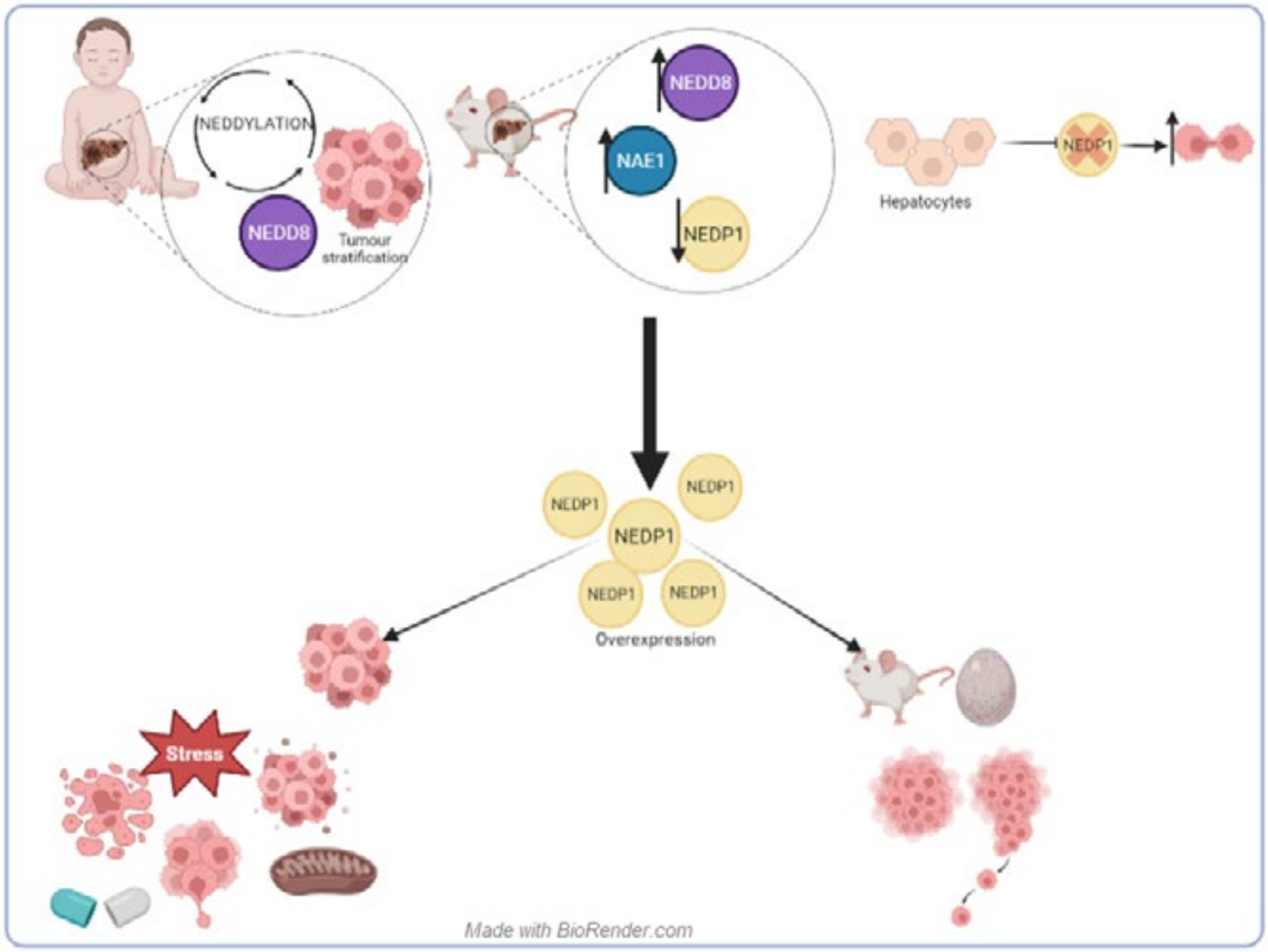

Disclosures: Leidy Estefania Zapata-Pavas: Nothing to Disclose, Marina Serrano-Macia: Nothing to Disclose, Miguel Ángel Merlos Rodrigo: Nothing to Disclose, Patricia Peña-SanFelix: Nothing to Disclose, Clàudia Gil-Pitarch: Nothing to Disclose, Naroa Goikoetxea-Usandizaga: Nothing to Disclose, Hana Michalkova: Nothing to Disclose, Zbynek Heger: Nothing to Disclose, Álvaro del Río-Álvarez: Nothing to Disclose, Laura Royo: Nothing to Disclose, Claudia M. Rejano-Gordillo: Nothing to Disclose, Jon Ander Barrenechea-Barrenechea: Nothing to Disclose, María Mercado-Gómez: Nothing to Disclose, Sofia Lachiondo-Ortega: Nothing to Disclose, Teresa Delgado: Nothing to Disclose, Dimitris Xirodimas: Nothing to Disclose, José J.G. Marin: Nothing to Disclose, Maite G. Fernandez-Barrena: Nothing to Disclose, Matías Ávila: Nothing to Disclose, Carolina Armengol: Nothing to Disclose, Mª Luz Martínez-Chantar: Nothing to Disclose

4429 | LIVER LYMPHATIC CHANGES IN BILIARY ATRESIA FROM DIAGNOSIS TO TRANSPLANT ◆

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Background: The liver lymphatic system supports organ health by draining interstitial fluid and immune cells to the lymph node. Adults with chronic liver disease have increased lymphatic vessel density in the liver independent of disease etiology. These findings are replicated in murine models of chronic liver disease and are associated with increased inflammation. Our study evaluates changes liver lymphatics in a pediatric population with liver inflammation associated with biliary atresia. **Methods:** To evaluate liver lymphatic architectural changes we utilized multiplexed immunofluorescent staining of human tissue from patients with biliary atresia at time of

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diagnosis as well as time of transplant. Controls from age-matched non-biliary atresia patients were compared to biliary atresia patients. Using tissue segmentation and cell phenotyping we evaluated changes in lymphatic capillary architecture including lymphatic vessel density (LVD) and immune cell populations. To understand clinical relevance, we correlated the histologic changes with clinical laboratory, physical exam and outcomes data. **Results:** Liver lymphatics are expanded in patients with biliary atresia compared to age-matched controls. LVD did not increase with disease progression to cirrhosis, but was expanded in biliary atresia patients at time of transplant compared to age-matched patients with cirrhosis from other etiologies. Further, increased LVD correlates with T cell number in the portal area at time of diagnosis. LVD at time of diagnosis positively correlated with total serum bilirubin at time of diagnosis and negatively correlated with total serum bilirubin at 3 months post hepatoportoenterostomy surgery. Finally, increased LVD at time of diagnosis correlated with prolonged survival of native liver. **Conclusion:** This study is the first of our knowledge to demonstrate changes in intrahepatic lymphatic architecture in pediatric patients with biliary atresia. Our findings suggest that lymphatics are associated with serum bilirubin levels and may suggests lymphatics serve as an alternative mechanism to remove bilirubin. The correlation of LVD with portal T-cell infiltrate suggests increased LVD is associated with increased immune infiltrate. We have demonstrated in other cholestatic disease models, expanded lymphatics during disease are dysfunctional and may not provide an adequate exit route for T cells. As biliary atresia is described to result from immune mediated injury and LVD at time of diagnosis correlates with prolonged survival of native liver, these findings provide evidence that improving lymphatic function in biliary atresia may reduce liver injury.

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4431 | REQUIRED DOSE AND EFFECTS OF NTBC TREATMENT FOR HEREDITARY TYROSINEMIA TYPE 1: CONFIRMATIONS AND SURPRISES FROM A NOVEL, REPRESENTATIVE HUMAN MODEL ◆

Farzaneh Tamnanloo[1] Quang Toan Pham[1] Marie-Agnès M'Callum[1] Denis Cyr[2] Paula Waters[2] Emilie Beaulieu[1] Yannick Doyon[3] Ugur Halac[4] Claudia Raggi[1] Massimiliano Paganelli[4]

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Background: Hereditary Tyrosinemia Type 1 (HT1) is a severe genetic liver disorder caused by a deficiency in fumarylacetoacetate hydrolase (FAH), a key enzyme of tyrosine metabolic pathway. The long-term effects of the sole effective treatment, the herbicide NTBC, remain unclear. No *in vitro* human model of HT1 exists to date. Our aim was to develop a representative *in vitro* model of HT1 using human induced pluripotent stem cell (iPSC) and assess the effect of NTBC treatment. **Methods:** We reprogrammed iPSCs from a HT1 patient. Additionally, 3 tyrosinemic iPSC clones were created by CRISPR/Cas9 knockout of the FAH gene in a healthy iPSC line. Isogeneic controls were then generated. We differentiated the 4 HT1-iPSCs and their 2 respective isogeneic controls (CTRL-iPSCs) into hepatocyte-like cells (HLCs). HT1-HLCs were assessed for modifications of their gene expression profile (RNAseq), succinylacetone (SA) accumulation and apoptosis, always in comparison to CTRL-HLCs. The effect of multiple doses of NTBC was then evaluated. We validated the results on a retrospective cohort of 98 HT1 patients. **Results:** HT1-HLCs showed accumulation of SA, a hallmark of HT1, upon L-tyrosine and homogentisic acid supplementation. Exposure to tyrosine resulted in the upregulation of pro-fibrotic and pro-inflammatory genes and led to apoptosis of HT1-HLCs. Both SA accumulation and apoptosis were mitigated with NTBC treatment. A dose of 50 µM was required to completely eliminate cell death. We showed that patients with NTBC plasma levels ≥50 µM had significantly lower ALT levels and urinary and plasma SA levels. Interestingly, NTBC treatment normalized >90% of dysregulated genes in HT1-HLCs. Nevertheless, 144 genes remained dysregulated despite optimal treatment, including several oncogenes. **Conclusion:** Our novel human *in vitro* HT1 model accurately recapitulates the disease, facilitating research on its pathophysiology and treatment. With this model, we showed how the disease results in human hepatocyte injury and affects their gene expression profile. We also confirmed that NTBC is effective in preventing hepatocyte death and identified the minimal dose required to prevent cellular injury, which we validated in a large clinical cohort. Interestingly, a few pathways remained dysregulated, opening important questions about the long-term prognosis of treated patients and warranting further exploration for potential complementary therapeutic strategies.

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Disclosures: Farzaneh Tamnanloo: Nothing to Disclose, Quang Toan Pham: Nothing to Disclose, Marie-Agnès M'Callum: Nothing to Disclose, Denis Cyr: Nothing to Disclose, Paula Waters: Nothing to Disclose, Emilie Beaulieu: Nothing to Disclose, Yannick Doyon: Nothing to Disclose, Ugur Halac: Nothing to Disclose, Claudia Raggi: Nothing to Disclose, Massimiliano Paganelli: Morphocell Technologies: Executive role

4432 | THE RELATIONSHIP BETWEEN SERUM BILE ACIDS AND EVENT-FREE SURVIVAL FOLLOWING THE USE OF MARALIXIBAT FOR PROGRESSIVE FAMILIAL INTRAHEPATIC CHOLESTASIS: DATA FROM MARCH/MARCH-ON

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Background: Maralixibat, an inhibitor of the ileal bile acid transporter, is approved in the US for treatment of cholestatic pruritus in individuals ≥3 months with Alagille Syndrome (ALGS) and ≥5 years with Progressive Familial Intrahepatic Cholestasis (PFIC). Prior analyses in ALGS have demonstrated improved event-free survival (EFS) following use of maralixibat and this improvement is associated with reductions in sBA. Data from MARCH/MARCH-ON, a clinical trial of maralixibat for individuals with PFIC, demonstrated reductions in sBA. In this analysis, we evaluated the impact of sBA reduction on EFS. **Methods:** The design of MARCH/MARCH-ON have been previously described. Data were administratively censored in June, 2023. First events (i.e., liver transplant, decompensation, surgical biliary diversion [SBD], or death) were identified for different PFIC types. For individuals with nt-BSEP and FIC1, 2-year EFS was calculated and stratified by sBA response at Week 26 (averaged over last 12 weeks) using thresholds developed by the NAPPED Consortium (BSEP: >75% reduction or <102 µmol/L; FIC1: <65 µmol/L). **Results:** There were 5 events (nt-BSEP: 1 transplant, 1 decompensation; FIC1: 1 death, 1 SBD; and MDR3: 1 transplant) among 72 individuals with a median (Q1, Q3) follow-up of 94 (68, 110) weeks. The overall EFS was 92%. Among individuals with nt-BSEP, an sBA response was achieved in 12 of 27 (44%), and this group had no events yielding an EFS of 100%; an insufficient sBA response was observed in 15 (56%) and this group had 2 events yielding an EFS of 84%. The sBA reduction for the 2 patients with events were 19% and 26%. Among individuals with FIC1, an sBA response was achieved in 3 of 12 (25%) and this group had no events yielding an EFS of 100%; an insufficient sBA response was observed in 9 (75%) and this group had 2 events for an EFS of 78%. The sBA reduction for the 2 patients with events were 18% and 16%. When nt-BSEP and FIC1 were analyzed together, sBA responders had an EFS of 100% whereas sBA non-responders had an EFS of 81%. For the individual with MDR3 disease requiring a transplant, the sBA reduction was 44%. **Conclusion:** Consistent with sBA response thresholds from the NAPPED Consortium that are associated with EFS, individuals in MARCH/MARCH-ON who reduced sBA levels below the threshold did not have a clinically meaningful event whereas some individuals who had lower reductions in sBA experienced events. These data support the importance of sBA reduction in PFIC and the potential of maralixibat to facilitate this biochemical change.

Disclosures: Richard Thompson: Generation Bio: Stock - publicly traded company, Generation Bio: Consultant, Rectify: Stock – privately held company, Rectify: Consultant, Mirum: Consultant, Ipsen: Consultant, Alnylam: Consultant, Integra: Stock – privately held company, Glycomine: Consultant, Spruce: Consultant, AIRNA: Consultant, Lorenzo D'Antiga: Selecta: Advisor, Vivet: Advisor, Spark: Advisor, Genespire: Advisor, Tome: Advisor, Mirum: Advisor, Ipsen/Albireo: Advisor, Intercept/Advanz Pharma: Advisor, Alexion/Astra Zeneca: Advisor, Simon Horslen: Nothing to Disclose, Douglas Mogul: Mirum Pharmaceuticals: Employee, Tiago Nunes: Mirum Pharmaceuticals: Employee, Will Garner: Mirum Pharmaceuticals: Employee, Mirum Pharmaceuticals: Stock - publicly traded company, Pamela Vig: Nothing to Disclose, Alexander Miethke: Mirum Pharmaceutical Inc: Grant/Research Support, Mirum Pharmaceutical Inc: Consultant, Ipsen: Speaking and Teaching

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4433 | MERGING SURGICAL AND MEDICAL EXPERTISE IN A PEDIATRIC LIVER INTENSIVE CARE UNIT

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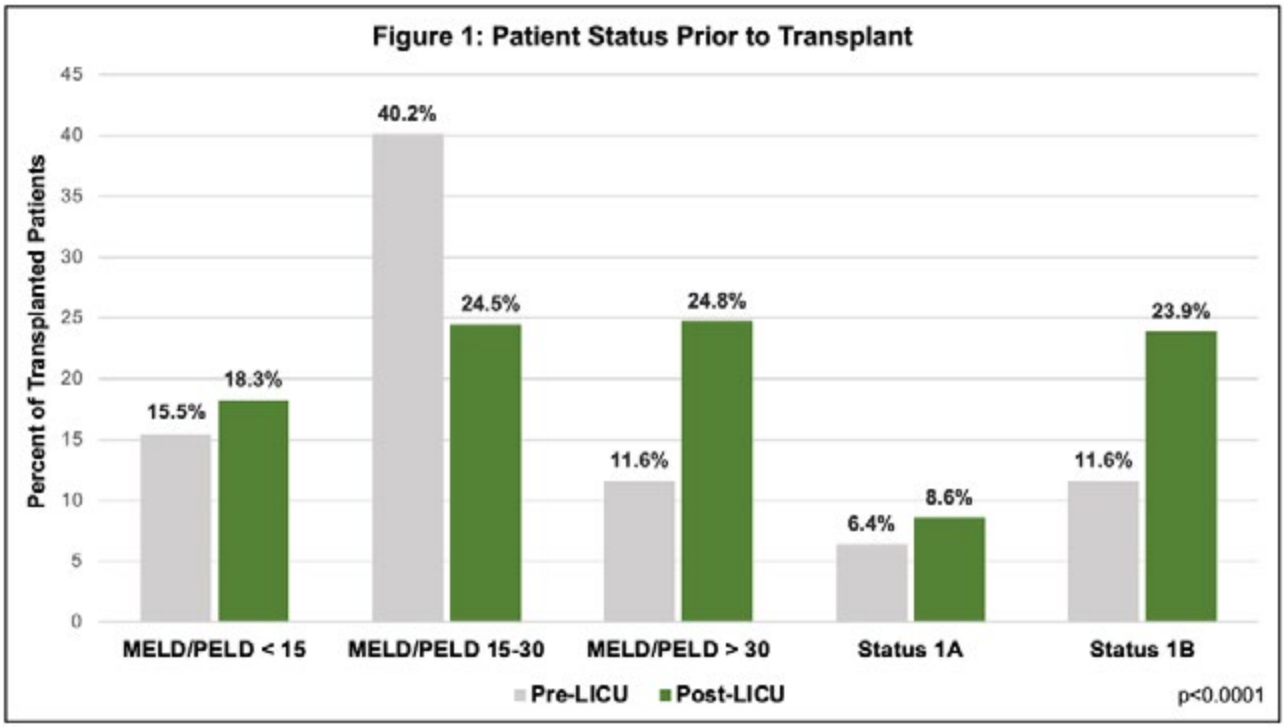
[1]Baylor College of Medicine/Texas Children's Hospital, [2]Bayor College of Medicine/Texas Children's Hospital, [3]Baylor College of Medicine, Texas Children's Hospital

Background: Increasing acuity of children needing liver transplantation (LT), and demand for peri-LT care and extra-hepatic organ support led to the inception of a pediatric Liver Intensive Care Unit (LICU) at a major quaternary care children's hospital in 2014. In the LICU, intensivists lead the management of patients with advanced liver disease in collaboration with experts from hepatology, nephrology, infectious disease, radiology, and transfusion medicine. We examined pediatric LT characteristics before and after formation of the LICU to understand whether subspecialty critical care improved survival and outcomes. **Methods:** Retrospective, before-after study of patients eligible for LT at single-center, high volume transplant center. Before refers to pre-LICU (2000-2013) and after refers to post-LICU (2014-2023). Statistical analysis included: Mann-Whitney, Chi Square, Fisher Exact and Kaplan Meier. **Results:** From 2000-2023, 935 patients were listed for LT, of which 668 (71%) received a LT: 329 (49%) pre-LICU and 339 (51%) post-LICU. Median age at LT was 3 years (range 0-23); 46.1% were female. Patient acuity on waitlist was higher post-LICU (Figure 1), while the proportion of patients deemed too sick for LT declined from 7.7% to 4.6% (p<0.0001). A higher proportion of LTs were ABO incompatible post-LICU at 9.8% vs. 2.1% (p<0.001). Despite longer organ wait time post-LICU, 81 days [IQR 28,202] vs. 60 [17,160], waitlist mortality declined from 7.5% to 3.9% (p<0.0001). Median ICU length of stay was longer post-LICU, days (range), at 16 (3-618) vs. 11 (1-179). While not statistically significant, 1-year patient survival post-LT improved from 92.6% to 95.1%. **Conclusion:** Coupled with a robust surgical program, a multi-disciplinary LICU facilitates the intensive care needed to consistently achieve desirable outcomes in critically ill children peri-LT. Further studies are needed to understand the impact of sub-specialty critical care on LT care, and its role in refining care practices in pediatric transplantation.



Disclosures: Divya Sabapathy: Nothing to Disclose, Kathleen Hosek: Nothing to Disclose, Anna Banc-Husu: Mirum Pharmaceuticals: Site PI for industry-sponsored clinical trial, Ayse Akcan Arikan: Seastar: Advisor, Baxter: Grant/Research Support, Medtronic: Grant/Research Support, Bioporto: Grant/Research Support, Jun Teruya: Nothing to Disclose, N. Thao Galvan: 3D Systems: Consultant, 3DSystems: Consultant, Natera: Grant/Research Support

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4434 | CORRELATION BETWEEN LIVER BIOPSY HISTOPATHOLOGY AND LIVER ULTRASOUND, ELASTOGRAPHY AND LABORATORY DATA IN PATIENTS STATUS-POST FONTAN PROCEDURE

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Background: Fontan-associated liver disease (FALD) is defined as defects in liver function and histology secondary to the Fontan circulation. There is no consensus regarding how to evaluate for FALD. Laboratory markers of liver function often do not correlate with the level of hepatic fibrosis. Ultrasound elastography initially reported as a reliable technique for liver stiffness evaluation has been questioned for its poor correlation with the biopsy in Fontan patients. Liver biopsy remains the gold standard for evaluation of fibrosis though invasive and subject to pathologist interpretation. We aim to identify any correlation between liver histology and contemperaneous laboratory markers, elastography or standard liver ultrasound (US) to identify patients who may benefit from liver biopsy. **Methods:** We analyzed children 0-25 years of age with Fontan physiology and evidence of liver disease from 2013-2023 who were followed at Children's National Medical Center. Patients without liver biopsy and/or elastography results were excluded. Liver US findings, elastography results, cardiac management changes, lab values, demographics, and other variables were compared across two fibrosis groups (Stages 0-2 and Stages 3-4). Elastography findings were categorized as F0-F4: F0 to F1 (normal/mild fibrosis), F2 (moderate fibrosis), F3 (severe fibrosis), and F4 (cirrhosis). Statistically significant factors were identified by unpaired t-test or Mann-Whitney-U test for continuous variables and Chi-squared test or Fisher's Exact test for categorical and binary variables. P values <0.05 indicate statistically significant results. **Results:** A total of 40 patients were included in the analysis, 20 patients had stage 0-2 fibrosis (50%) and 20 patients had stage 3-4 based on liver biopsy results. 20% of patients with a normal US had some evidence of liver disease (stage 0-2), however no patient with advanced fibrosis had a normal US, p=0.035. 45% of patients with advanced fibrosis had hepatomegaly on ultrasound vs 15% of those without advanced fibrosis, p=0.38. Total bilirubin (0.5 vs 1.0, p=0.004) and ferritin (18.8 vs. 96.6, p=0.007) were significantly higher in the advanced fibrosis group. Elastography could not reliably identify liver stiffness due to fibrosis at any stage. **Conclusion:** As the lifespan of patients with Fontan circulation has increased, the hepatic consequences have dire implications. Our findings suggest that 1) if standard US is normal, advanced fibrosis is unlikely, 2) organomegaly is more concerning for advanced fibrosis (stage 3-4); 3) elastography is unreliable in the identification of fibrosis in FALD; and 3) a mildly elevated total bilirubin and elevated ferritin may indicate advanced fibrosis. Protocol liver biopsies may be the only method to accurately identify liver disease in FALD. A larger, prospective study is warranted to confirm these conclusions and to better identify markers for those at risk of FALD.

Characteristics	Liver biopsy Fibrosis Grades		P value
	Grade 0/1/2 (N=20)	Grade 3/4 (N=20)	
	n (%) or mean (SD) or median [IQR]		
Lab values			
Total Bilirubin, median [IQR]	0.5 [0.4, 0.7]	1.0 [0.6, 1.2]	**0.004**
Ferritin	18.8 (19.0)	96.6 (37.2)	**0.007**
Liver US findings			
Normal, n (%)	4 (20.0)	0 (0.0)	**0.035**
Coarse, n (%)	2 (10.0)	6 (30.0)	0.114
Heterogeneous, n (%)	12 (60.0)	8 (40.0)	0.206
Nodular, n (%)	4 (20.0)	3 (15.0)	0.677
Increased echo, n (%)	3 (15.0)	2 (10.0)	0.633
Hepatomegaly, n (%)	3 (15.0)	9 (45.0)	**0.038**
Splenomegaly, n (%)	0 (0.0)	1 (5.0)	0.311
Other, n (%)	4 (20.0)	11 (55.0)	**0.022**
Elastography, n (%)			**0.024**
F0	2 (10.0)	4 (20.0)	
F1	1 (5.0)	3 (15.0)	
F2	9 (45.0)	3 (15.0)	
F3	4 (20.0)	10 (50.0)	
F4	4 (20.0)	0 (0.0)	
kPa value	11.5 (4.3)	11.2 (2.5)	0.762
m/s value	2.0 (0.3)	1.9 (0.4)	0.628

Disclosures: Nicole Mendez: Nothing to Disclose, Sohel Rana: Nothing to Disclose, Sarah Clauss: Nothing to Disclose, Bernadette Vitola: Nothing to Disclose

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4435 | PORTAL VEIN HYPOPLASIA IS PRESENT IN PATIENTS WITH BILIARY ATRESIA AT THE TIME OF DIAGNOSIS

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Background: In patients with biliary atresia (BA), severe portal hypertension develops even after bile flow restoration, suggesting an intrinsic origin of portal hypertension unrelated to bile duct obstruction. We hypothesize that abnormal portal vein development, leading to portal vein hypoplasia, could precipitate portal hypertension independent of fibrogenesis due to cholestasis. **Methods:** This observational cohort study enrolled patients who were referred to a tertiary center from 2017 to 2021 to rule out BA. We enrolled newborns who were scheduled to undergo a CT angiogram and liver wedge biopsy prior to the cholangiogram. Clinical parameters and demographics, image metrics of CT scan: the diameter of the portal vein (PV) and hepatic artery (HA), and morphometric analysis of liver wedge biopsy, were collected. Liver fibrosis, defined by collagen fiber density, was quantified with a second harmonic generation microscopy. Jaundice clearance (defined as serum total bilirubin level < 2 mg/dL) at three months post Kasai hepatoportoenterostomy and native liver survival at two years of age, episode of ascites and intestinal bleeding were assessed. **Results:** Forty-seven patients with cholestasis were included in the cohort; 35 were diagnosed with BA by cholangiogram. The patients with BA had a significantly smaller median PV diameter (4.3 mm vs. 5.1 mm; $P < 0.001$) and larger median HA diameter (1.4 mm vs. 1.2 mm; $P < 0.05$) compared to patients with other forms of cholestasis. Among 35 patients with BA, 29 patients (82.9%) achieved jaundice clearance three months after Kasai, and 23 patients (65.7%) were alive with their native liver. The median time to liver transplant from Kasai was 7 months (range: 1-19 months). Seven patients (20%) developed intestinal bleeding, and 7 patients (20%) developed ascites under 2 years of age. Only one patient developed both intestinal bleeding and ascites. A patient who had polysplenia and interrupted inferior vena cava had relatively small PV (3.7mm) and developed severe ascites even though the subject achieved jaundice clearance. Because of the small cohort and the rare incident rate, statistical analysis was not performed. **Conclusion:** Portal vein hypoplastic is present in patients with BA independent of liver fibrosis.

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4436 | BILE ACID SUBSPECIES ARE CORRELATED WITH PRURITUS AND BILIRUBIN IMPROVEMENT IN PFIC PATIENTS TREATED WITH MARALIXIBAT: DATA FROM MARCH AND MARCH-ON

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Background: Serum bile acids (sBA) have been implicated as an important pruritogen in several cholestatic diseases. Maralixibat (MRX), an inhibitor of the ileal bile acid transporter, interrupts the enterohepatic circulation of bile acids by preventing their intestinal reabsorption. The drug has been shown to improve cholestatic pruritus and bilirubin in patients with Progressive Familial Intrahepatic Cholestasis (PFIC) and this clinical response is strongly correlated with reductions in total sBA. Here, we evaluate the correlation of change in sBA subspecies with changes in pruritus and direct bilirubin (DB) for individuals with PFIC treated with MRX in the MARCH/MARCH-ON Phase 3 program. **Methods:** MARCH/MARCH-ON have been previously described. Spearman correlation coefficients were determined for the percent change from Baseline to Week 26 (averaged over the last 8-12 weeks) in total/subspecies sBA with change in ItchRO(Obs) and DB in the All-PFIC (i.e., named genetic PFICs) and the nt-BSEP deficiency cohorts. **Results:** Analysis includes 60 individuals with PFIC (nt-BSEP deficiency: 28; FIC1: 13; MDR3: 9; TJP2: 7; MYO5B: 3); 53 (88%) were on UDCA. For the All-PFIC cohort on MRX, a decrease in conjugated primary BA (GCDCA, TCDCA, GCA, TCA) and conjugated UDCA (i.e., GUDCA, TUDCA) was correlated with a decrease in both ItchRO(Obs) and DB (Table). The absolute value of unconjugated primary BAs were substantially lower than conjugated BAs and were negatively correlated with markers of disease. Specifically, an increase in CDCA was correlated with a decrease in both ItchRO(Obs) and DB, while

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an increase in CA was correlated with a decrease in ItchRO(Obs) as well. Nearly identical correlations were observed for the nt-BSEP deficiency cohort receiving MRX. In general, for individuals on placebo, there were no significant correlations between BA subspecies with ItchRO(Obs) or DB (data not shown). **Conclusion:** Building on prior research demonstrating a correlation between sBA and pruritus, this analysis further identifies changes in BA subspecies that are associated with both pruritus reduction and improvement in DB including positive correlations with conjugated primary BAs and negative correlations with unconjugated primary BAs. This pattern indicates either new BA synthesis in response to reduced BA levels in the liver or increased bacterial action on BAs in the colon. These data further elucidate the pathophysiology of how MRX may influence improvements in both pruritus and underlying liver health in patients with PFIC.

Table: Serum concentrations of bile acid species and correlations of changes in serum bile acids with ItchRO(Obs) and direct bilirubin in participants treated with maralixibat

	All-PFIC			
	Median (Q1, Q3) Serum Concentration (µmol/L) Bile Acid Species at Baseline	Median (Q1, Q3) Serum Concentration (µmol/L) Bile Acid Species After Maralixibat Treatment[a]	ItchRO(Obs) Correlation Coefficient[b] (p value)	Direct Bilirubin Correlation Coefficient[b] (p value)
Total serum bile acids (sBA)	255 (180, 363)	105 (9, 199)	**0.694 (<0.0001)**	**0.641 (<0.0001)**
Conjugated Primary Bile Acids				
Glycochenodeoxycholic Acid (GCDCA)	42 (27, 66)	27 (3, 46)	**0.694 (<0.0001)**	**0.613 (<0.0001)**
Taurochenodeoxycholic Acid (TCDCA)	16 (9, 30)	8 (3, 16)	**0.600 (<0.0001)**	**0.616 (<0.0001)**
Glycocholic Acid (GCA)	72 (34, 99)	16 (1, 62)	**0.601 (<0.0001)**	**0.538 (<0.0001)**
Taurocholic Acid (TCA)	33 (17, 58)	12 (3, 29)	**0.540 (0.0002)**	**0.498 (0.0008)**
Unconjugated Primary Bile Acids				
Chenodeoxycholic Acid (CDCA)	0.02 (0.02, 0.04)	0.2 (0.03, 0.6)	**-0.326 (0.03)**	**-0.328 (0.03)**
Cholic Acid (CA)	0.02 (0.01, 0.03)	0.08 (0.03, 0.2)	**-0.474 (0.03)**	-0.348 (0.1)
Conjugated Secondary Bile Acids				
Glycodeoxycholic Acid (GDCA)	0.06 (0.03, 0.2)	0.2 (0.05, 0.9)	-0.152 (0.3)	**-0.326 (0.04)**
Taurodeoxycholic Acid (TDCA)	0.03 (0.01, 0.1)	0.07 (0.03, 0.2)	0.256 (0.2)	0.119 (0.6)
Glycolithocholic Acid (GLCA)	0.02 (0.01, 0.04)	0.02 (0.01, 0.05)	-0.187 (0.6)	0.273 (0.4)
Taurolithocholic Acid (TLCA)	0.02 (0.01, 0.03)	0.03 (0.02, 0.07)	-0.226 (0.6)	-0.405 (0.3)
Glycoursodeoxycholic Acid (GUDCA)	46 (20, 120)	22 (1, 48)	**0.396 (0.007)**	**0.439 (0.003)**
Tauroursodeoxycholic Acid (TUDCA)	6 (2, 19)	2 (1, 8)	**0.413 (0.02)**	**0.642 (0.0001)**
Unconjugated Secondary Bile Acids				
Deoxycholic Acid (DCA)	0.06 (0.01, 0.1)	0.2 (0.07, 0.5)	-0.500 (0.4)	-0.800 (0.1)
Ursodeoxycholic Acid (UDCA)	0.6 (0.3, 3)	0.9 (0.5, 3)	0.269 (0.3)	0.311 (0.2)

[a]Average of Weeks 18, 22, and 26 of maralixibat treatment
[b]Data presented as Spearman Rank Correlation Coefficient and P values for all individuals treated with maralixibat for 26 weeks in either MARCH or MARCH/ON

Disclosures: Henkjan Verkade: Mirum: Grant/Research Support, Mirum: Consultant, Mirum: Speaking and Teaching, Ipsen / Albireo: Consultant, Ipsen / Albireo: Grant/Research Support, Ipsen / Albireo: Speaking and Teaching, Intercept: Consultant, Orphalan: Consultant, Alexander Miethke: Mirum Pharmaceutical Inc: Grant/ Research Support, Mirum Pharmaceutical Inc: Consultant, Ipsen: Speaking and Teaching, Simon Horslen: Nothing to Disclose, Douglas Mogul: Mirum Pharmaceuticals: Employee, Tiago Nunes: Mirum Pharmaceuticals: Employee, Cory Kostrub: Mirum Pharmaceuticals: Employee, Josephine Shelton: Nothing to Disclose, Will Garner: Mirum Pharmaceuticals: Employee, Mirum Pharmaceuticals: Stock - publicly traded company, Pamela Vig: Nothing to Disclose, Richard Thompson: Generation Bio: Stock - publicly traded company, Generation Bio: Consultant, Rectify: Stock – privately held company, Rectify: Consultant, Mirum: Consultant, Ipsen: Consultant, Alnylam: Consultant, Integra: Stock – privately held company, Glycomine: Consultant, Spruce: Consultant, AIRNA: Consultant

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4437 | IMPACT FUNDING FOR PEDIATRIC LIVER TRANSPLANTATION REDUCES THE INCIDENCE OF FINANCIAL TOXICITY FOR PATIENT FAMILIES

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Background: Pediatric Liver transplantation (PLT) may lead to catastrophic out of pocket expenditure (C-OOPE) leading to medical bankruptcy in families. This study was conducted to assess effectiveness of supported funding in reducing the financial toxicity of PLT **Methods:** A prospective questionnaire-based survey was conducted among PLT families who used impact funding [crowdfunding + Corporate Social Responsibility (CSR)] to support PLT. Financial loss was classified as severe, moderate, some, or none based on income and asset loss **Results:** 153 PLT families from 19 centres were included. Median age was 5 (IQR: 2,10) years. A majority (53%) had to travel out of their city to avail transplant services. Crowdfunding and non-government organisations provided most support (70.5% and 87.6%) while government schemes and health insurance supported 9.8% and <3% of the families respectively. 84.3% spent some or all their savings on surgery. Property loss was experienced by 45% and loss of source of income by 50% of the families. None of the patients reported severe financial loss; moderate financial loss in 50%, some financial loss in 18.7% and no financial loss in 31.3% of the families (Fig 1). Awareness of expenditure prior to transplantation resulted in lesser degrees of financial loss (p-0.004). 94% of the families were happy with the decision to undergo PLT; the 6% who expressed regret were more likely to have sold property to support surgery (p<0.001). Most (83%) could afford post-transplant immunosuppression and care satisfactorily **Conclusion:** Targeted Financial aid through various platforms reduced the degree of financial loss suffered by PLT families



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4438 | BILE SALT EXPORTER PUMP (BSEP) DEFICIENCY IN CHILDREN FROM INDIAN PFIC REGISTRY: DIFFERENCES FROM THE NAPPED COHORT

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Background: Variants in the ABCB11 gene causes the bile salt export pump (BSEP) deficiency. We aimed to study the prevalence, genotype phenotype correlation and the native liver survival (NLS) of BSEP deficiency amongst Indian children. **Methods:** The data was retrieved from the Indian Progressive Familial intrahepatic Cholestasis registry. Genotype categorization was done as per the NAPPED study. **Results:** Amongst those enrolled in the registry, BSEP deficiency was the commonest (96/302, 31.7%) disorder. Homozygous mutations were present in 61 (63.5%) cases, compound heterozygous in 23 (23.9%) with 12 (12.5%) being heterozygous. Excluding 12 heterozygous mutations, missense mutations were present in 45 (53.4%) cases, whereas one protein truncating mutation (PTM) was present in 14 (16.7%) cases and 2 PTMs were seen in 25 (29.8%) cases. Whereas BSEP1 was not present in this Indian cohort but BSEP2 (59) and BSEP3 (25) were present. Of the total, 52(63.4%) had refractory jaundice and those with unresolved jaundice (1.5, IQR 1-3) were significantly younger at the onset of jaundice versus those with resolved jaundice (MD 10.59, 95% CI 1.7-19.4, p=0.019). Pruritus grade 3 & 4 was present in significantly more amongst those with unresolved pruritus (OR 5.17, 95% CI 1.59-16.8, p=0.008). Median values of age at presentation, weight & weight for height z scores, age of onset of jaundice, and peak INR were significantly different in between three zygosity groups by ANOVA as depicted in Table 1. The Post Hoc Tukey's test shows that the median values of the age in months at enrollment were significantly lower in homozygous group (15, IQR 7-36) in comparison with compound heterozygous group (51, IQR 12.5-97). Biliary diversion was unsuccessful in 3/5 patients, of which one was transplanted and 2 died waiting LT. HCC was reported in one case. NLS was significantly higher amongst compound heterozygous versus the homozygous mutations group (OR 3.21, 95%CI 1.12-9.2, p=0.031) but comparable between BSEP 2 and 3 genotypes (OR 1.78 95%CI 0.69-4.5, p=0.24). **Conclusion:** BSEP deficiency/ABCB11 mutation was the commonest (96/302, 31.7%) disorder seen in the registry and homozygous group is associated with early onset of progressive liver disease and poor outcome. Compared to NAPPED cohort BSEP genotype categorization did not affect the outcome.

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Table 1: Analysis of variance of Mean (IQR) values of the demographic and biochemical parameters in between the 3 Zygosity groups.

Variables	Homozygous N=55 Group 1	Compound Heterozygous N=22 Group 2	Heterozygous N=12 Group 3	ANOVA F statistics (p value)
Age at enrolment (mo)	15 (7-36)	28(14-96)	51(12.5-97)	**4.96 (0.009)**
Weight z score	-2.42(-3.3-0.86)	-1.30(-1.71-0.44)	-0.23 (-1.7-0.24)	**8.53 (<0.001)**
Height z score	-2.23(-3.6-0.88)	-1.38(-3.3-0.70)	-0.75 (-2.8-0.8)	2.55 (0.085)
Weight for height Z score	-1.34(-2.9-0.33)	0.33 (-1.60-0.62)	0.12 (-1.8-1.36)	**3.33 (0.044)**
Age of onset of Jaundice (mo)	2(1-3)	3(1.5-18)	4(1-42)	**5.14 (0.008)**
Age of onset of Pruritus (mo)	6(4-10.3)	7(5-12)	7(3-10)	1.77 (0.179)
Total Bilirubin mg%	7.07(3.3-12.1)	8.08(2.65-12.9)	9.25(4.6-10.7)	0.067 (0.935)
Direct Bilirubin mg%	4.3 (1.89-8.02)	4.5 (1.4-8.4)	5.65 (2.80-8.37)	0.009 (0.991)
Peak Bilirubin mg%	12.4(6.11-18.6)	11.88(7.79-20)	10.85(9.1-15.5)	0.016 (0.984)
INR	1.2 (1.03-1.62)	1.2 (1-1.45)	1.10 (1.05-1.35)	0.736 (0.482)
Peak INR	1.80 (1.2-2.54)	1.66 (1.18-2.05)	1.18 (1.10-1.41)	**3.30 (0.042)**
Albumin g %	4(3.3-4.2)	3.75(3.07-4.05)	3.8(3.2-4.1)	0.615 (0.543)
GGT	26(20-41)	25(21-42)	37(21-65)	0.652 (0.524)
SAP (IU/L)	446 (334-679)	449 (306-569)	453(366-578)	0.043 (0.958)
AST (IU/L)	285 (172-630)	247 (88-511)	183 (89-331)	0.604 (0.549)
ALT (IU/L)	207(101-381)	134(59-370)	136(65-265)	0.880 (0.419)
PELD	13.25(6.85-20.75)	11.5(6.25-17)	6.5(2.25-14.5)	2.41 (0.097)

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4439 | MISSENSE VARIATIONS IN FADS1 AND SCD1 GENES OPPOSITELY AFFECT LIPID PROFILE AND EPICARDIAL FAT THICKNESS IN ITALIAN CHILDREN WITH MASLD: A POSSIBLE MONITORING TOOL ALSO IN ADULTS?

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Background: Background: & Aim: Metabolic dysfunction-associated steatotic liver disease (MASLD) is the commonest chronic liver disease in adults and children. Dyslipidemia is a hallmark of MASLD and lipidomic studies highlighted changes in hepatic and circulating lipids, related to cardiovascular (CV) complications. Although lipidomic data in children are scant, it has been assessed that alterations in lipid metabolism in pediatric MASLD are similar to that of adults with cardiometabolic disease. Genetics concurs to MASLD pathogenesis and polymorphisms in FADS and SCD1 genes, mediating fatty acids desaturation and elongation, may contribute to alter the lipid profile. Thus, we aimed to assess the impact of variants in these genes on circulating lipids and epicardial fat in 80 pediatric patients with MASLD. **Methods:** The pediatric cohort was genotyped for rs174537 G>T, rs174556 C>T in FADS1 and rs1502593 G>A, rs522951 G>C in SCD1 by using Taqman assays. The

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presence of steatosis was evaluated through abdominal ultrasound and transient elastography. **Results:** The pediatric cohort included mainly males (72%) with a mean age of 13±2.2 and BMI of 25±3.9. Hepatic steatosis (CAP>241dB/m) and liver stiffness were diagnosed in 74/80 (92% of which 77% moderate/severe) and 44/80 (55%) children, respectively. At bivariate analysis, both variants in FADS1 gene were associated with lower total cholesterol, LDL, LDL/HDL ratio and APOB levels ($p<0.05$). These results were confirmed at generalized linear model adjusted by gender, age, BMI, HOMA-IR and TM6SF2 E167K mutation ($p<0.05$), suggesting a protective role of these polymorphisms against cardiovascular risk. Accordingly, at multivariate analysis adjusted as above, less epicardial fat was detected in carriers of the rs174537 and rs174556 ($p<0.05$). Conversely, patients carrying the rs1502593 and rs522951 in SCD1 showed higher circulating cholesterol, LDL and APOB levels at bivariate analysis ($p<0.03$) and the effect remained significant at generalized linear model ($p<0.05$). Moreover, the presence of these mutations correlated with increased epicardial fat at multivariate analysis, possibly supporting an enhanced CV risk. **Conclusion:** As in adult population, genetic screening of variations involved in lipid handling may aid for the identification of MASLD-related comorbidities in children. Specifically, FADS1 and SCD1 variants exert opposite effects on lipid profile thus resulting useful for the early stratification of subjects at low or high CV risk.

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4440 | PATIENT CHARACTERISTICS, MANAGEMENT, AND PROGRESSION OF LYSOSOMAL ACID LIPASE DEFICIENCY (LAL-D) IN FRANCE USING REAL-WORLD DATA FROM THE NATIONAL HEALTH DATA SYSTEM (SNDS)

Florence Lacaille[1] Sophie Marguet[2] Vanessa Rascon Velasco[2] Reyhan Hasanova[2] Nivantha Naidoo[2] Ekbel Amri[3] Hélène Chevrou Severac[3] Florian Abel[3] Gérard de Pouvourville[4] Vlad Ratziu[5] François Feillet[6]

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Background: Lysosomal acid lipase deficiency (LAL-D) is a rare autosomal recessive lysosomal storage disease leading to accumulation of lipids in different organs and tissues. The severity of the disease phenotype follows a continuum across all ages, from a rapidly progressive infantile form (Wolman disease) to a progressive later onset form (Cholesteryl Ester Storage Disease). The aim of this study was to describe patient characteristics and the progression and management of LAL-D in real-life in France. **Methods:** A retrospective longitudinal study was conducted among patients with LAL-D identified between 2007 and 2020 using nationwide claims data from the French National Health Data System (SNDS). Patients with LAL-D were identified as having a recorded diagnosis of LAL-D (codes E75.5B-C) or administration of sebelipase alfa, the only approved treatment for LAL-D, first record being the index date. **Results:** In total, 43 patients with LAL-D were identified, including 17 classified as patients with Wolman disease. Median follow-up was 8 years. Common signs and morbidities among infants and children included hepatomegaly, failure to thrive, malnutrition, nausea and vomiting, hypercholesterolemia, and splenomegaly. Among adults, arterial hypertension and type 2 diabetes were frequently recorded. Overall, 6 patients out of 17 with Wolman disease (35.3%) had a record of one of the following liver diseases during follow-up: portal hypertension (n=1 patient), fibrosis (n=3), cirrhosis (n=2), hepatic failure (n=2) (Table 1). Sebelipase alfa was used to treat 20 patients, with a mean age at initiation of 12.4 years old (median 11.5) and a mean time between diagnosis and initiation of 3.5 years (median 0.4). During follow-up, 8 patients were not treated by any of the expected treatments: sebelipase alfa, lipid-lowering medications, hematopoietic stem cell or liver transplantation. During the study period, 3 infants out of 4 who were not treated with sebelipase alfa (before treatment reimbursement) died before the age of 2, while no death occurred among the 7 treated infants. **Conclusion:** In this first study using SNDS data to investigate patients with LAL-D, the analysis showed that most patients presented severe symptoms and comorbidities. The mortality rate among untreated infants with sebelipase alfa was high. Furthermore, despite the severity of the disease, several patients remained untreated, highlighting potential gap in clinical management of LAL-D.

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Table 1. Occurrence of selected clinical events during the follow-up, for patients with Wolman disease and other patients.

	Patients classified with Wolman disease n (%) N = 17	Patients classified with CESD n (%) N = 26
Liver diseases (included below)	**6 (35.3%)**	**5 (19.2%)**
Portal hypertension	1 (5.9%)	0
Fibrosis	3 (17.6%)	3 (11.5%)
Cirrhosis	2 (11.8%)	2 (7.7%)
Hepatocellular carcinoma	0	0
End-stage liver disease (hepatic failure)	2 (11.8%)	1 (3.8%)
Cardiovascular events (included below)	**1 (5.9%)**	**8 (30.8%)**
Stroke	0	2 (7.7%)
Other cerebrovascular diseases	0	2 (7.7%)
Myocardial infarction	0	1 (3.8%)
Coronary artery disease	0	5 (19.2%)
Peripheral artery disease	0	0
Heart failure	0	1 (3.8%)
Cardiovascular surgery*	5 (5.9%)	4 (15.4%)
Depression	**2 (11.8%)**	**9 (34.6%)**
Use of antidepressants	2 (11.8%)	8 (30.8%)
Diagnosis of depression	0	2 (7.7%)
Intestinal malabsorption	**4 (23.5%)**	**0**
Malnutrition	**8 (47.1%)**	**2 (7.7%)**
Failure to thrive or growth failure	**6 (35.3%)**	**1 (3.8%)**

CESD: Cholesteryl Ester Storage Disease

* Cardiovascular and thoracic surgeries (excluding organ transplantations), coronary artery bypass graft, cardiac catheterizations, defibrillator-pacemaker

Disclosures: Florence Lacaille: Nothing to Disclose, Sophie Marguet: Nothing to Disclose, Vanessa Rascon Velasco: Nothing to Disclose, Reyhan Hasanova: Nothing to Disclose, Nivantha Naidoo: Nothing to Disclose, Ekbel Amri: Nothing to Disclose, Hélène Chevrou Severac: Alexion Pharma GmbH: Employee, Florian Abel: Alexion AstraZeneca Rare Disease: Employee, AstraZeneca: Stock - publicly traded company, Gilead Sciences: Stock - publicly traded company, Gérard de Pouvourville: Nothing to Disclose, Vlad Ratziu: Nothing to Disclose, François Feillet: Nothing to Disclose

4441 | CHARACTERISTICS OF HBV INTEGRATION IN PEDIATRIC PATIENTS WITH CHRONIC HEPATITIS B INFECTION

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Background: Children with chronic HBV infection (CHB) exhibit a higher likelihood of achieving HBsAg clearance under antiviral therapy compared to adults, although the underlying mechanism remains elusive. Notably, HBV integration plays a pivotal role in HBsAg production; however, limited research has been conducted on the characteristics of HBV integration in CHB children. **Methods:** We collected clinical information and liver biopsy tissues from 15 CHB children at the Children's Hospital of Chongqing Medical University between September 2023 and March 2024. Additionally, we obtained liver tissues from 9 CHB adults at the Second Affiliated Hospital of Chongqing Medical University as a control group. A probe-based capture strategy was applied for analyzing the HBV integration. **Results:** Among the 15 CHB children, the median age was 8.4 years (IQR 6.8-11.8), and 53.3% were female (8/15). All patients were HBeAg positive and treatment naïve, with average levels of HBV DNA, HBsAg, and pg-RNA at 7.25 log10 IU/mL, 36091 IU/mL, and 6.71 log10 copies/mL respectively. The average number of integration sites in CHB children was lower than that in adults (28.73 vs. 95.78). Furthermore, a higher proportion of integration sites was observed among females and older age subgroups within the CHB children cohort, similar to what was observed in adults. Notably, HBV integration was more frequently observed in CHB children who had lower levels of HBV DNA and HBsAg, as well as higher ALT levels, which is contrary to the pattern observed in CHB adults. After multivariate regression analysis, age was identified as the only risk factor

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for HBV integration (b=4.592, P=0.021). In CHB children, integration sites were detected across all chromosomes except for X and Y chromosomes, specifically within the 2904-3215nt region of the HBV genome. Compared to adults, specific integrated genes enriched in CHB children were associated with cancer, immune response, and mitochondrial function; examples include NELL1, APOBEC3G, CCDC144NL, MEF2A, and TFB1M. **Conclusion:** The HBV integration in CHB children was found to be lower compared to that in adults, and age was identified as an independent risk factor for HBV integration in children. This observation may contribute to elucidating the underlying mechanism behind the accelerated loss of HBsAg following treatment in pediatric patients with CHB.

Disclosures: Na Wu: Nothing to Disclose, Zhiwei Chen: Nothing to Disclose, Yan Han: Nothing to Disclose, Jing Tang: Nothing to Disclose, Hong Ren: Nothing to Disclose

4442 | FERROPTOSIS REGULATION BY DEFEROXAMINE PREOTECTS AGAINST ISCHEMIA REPERFUSION INJURY IN MARGINAL DONOR LIVERS

Ajay Jain[1] Kento Kurashima[1] Grace Trello[1] James Fox[1] Edward Portz[1] Shaurya Mehta[1] Austin Sims[1] Arun Verma[1] Chandrashekhara Manithody[1] Sree Kolli[1] Yasar Caliskan[1] Mustafa Nazzal[1]

[1]Saint Louis University

Background: Marginal donor livers (MDLs) have been used for liver transplantation to address major organ shortages. However, MDLs are notably susceptible to Ischemia/Reperfusion injury (IRI). Recent investigations have highlighted Ferroptosis, a new type of programmed cell death, as a potential contributor to IRI. We hypothesized that modulating ferroptosis by the iron chelator deferoxamine (DFO) could alter the course of IRI. **Methods:** Using our novel Perfusion Regulated Organ Therapeutics with Enhanced Controlled Testing (PROTECT) model (US provision Patent, US63/136,165), six human MDLs (liver A to F) were procured and split into paired lobes. Simultaneous perfusion was performed on both lobes, with one lobe subjected to DFO while the other serving as an internal control. Histology, serum chemistry, expression of ferroptosis-associated genes, determination of iron accumulation, and measurement of lipid peroxidation, were performed. **Results:** Histological analysis revealed severe macrovesicular steatosis (>30%) in liver A and D, while liver B and E exhibited mild to moderate macrovesicular steatosis. Majority of the samples noted mild inflammation dominantly in zone 3. No significant necrosis was noted during perfusion. Perl's Prussian blue stain and non-heme iron quantification demonstrated a suppression of iron accumulation in liver A to D with DFO treatment ($p<0.05$). Based on the degree of iron chelation, 12 lobes were categorized into two groups: lobes with decreased iron (n=4) and those with increased iron (n=8). Comparative analysis demonstrated that ferroptosis-associated genes (HIF1-alpha, RPL8, IREB2, ACSF2, NQO1) were significantly downregulated in the former (p=0.0338, p=0.0085, p=0.0138, p=0.0138, p=0.0209, respectively), Figure 1. Lipid peroxidation was significantly suppressed in lobes with decreased iron ($p=0.02$). While serum AST was lower in iron chelated lobes this did not reach statistical significance. **Conclusion:** This study affirmed that iron accumulation was driven by normothermic perfusion. Reduction of iron content suppressed ferroptosis-associated genes and lipid peroxidation to mitigate IRI. Our results using human MDLs revealed a novel relationship between iron content and ferroptosis, providing a solid foundation for future development of IRI therapeutics.

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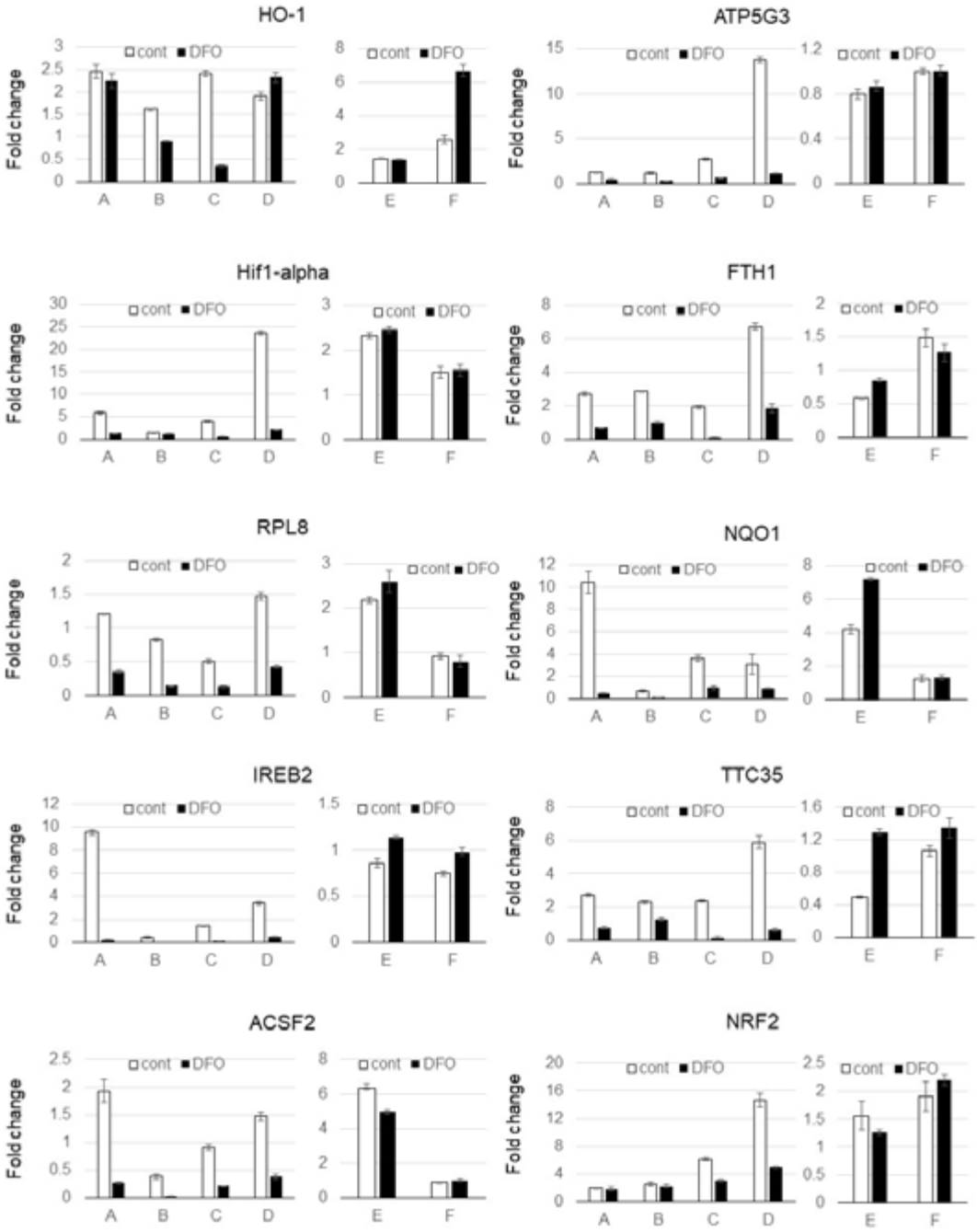
Figure 1



Disclosures: Ajay Jain: Mirum Camp 4 Gilead: Consultant, Kento Kurashima: Nothing to Disclose, Grace Trello: Nothing to Disclose, James Fox: Nothing to Disclose, Edward Portz: Nothing to Disclose, Shaurya Mehta: Nothing to Disclose, Austin Sims: Nothing to Disclose, Arun Verma: Nothing to Disclose, Chandrashekhara Manithody: Nothing to Disclose, Sree Kolli: Nothing to Disclose, Yasar Caliskan: Nothing to Disclose, Mustafa Nazzal: Nothing to Disclose

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4443 | METABOLIC DYSFUNCTION-ASSOCIATED AND ALCOHOLIC CIRRHOSIS DRIVE DISTINCT STELLATE CELL PHENOTYPIC PATTERNS

Ajay Jain[1] Chien-Jung Lin[1] Chandrashekara Manithody[1] Kento Kurashima[1] Arun Verma[1] Marzena Swiderska-Syn[1] Shaurya Mehta[1] Alison Bach[1]

[1]Saint Louis University

Background: Distinct clinical characteristics are noted in Metabolic dysfunction-associated and alcoholic cirrhosis (MAFL-C and AC, respectively) though they share morphological features. Studies using bulk RNA comparisons revealed distinct patterns of gene expression in human MAFL-C and AC tissues. However, given the summative nature of bulk transcriptome studies, these findings represent the totality of gene expression without regards to the differences in cellular composition between MAFL-C and AC. Hepatic stellate cells (HSCs) deposit extracellular matrix and are central in cirrhosis development. We thus hypothesized that single cell RNA sequencing would provide an opportunity to interrogate HSC-specific transcriptomes. **Methods:** Single cell RNA sequencing datasets from human MAFL-C (GSM4041162, GSM4041163) and AC (GSM4041165, GSM4041167) non leukocyte, nonparenchymal cells were obtained from Gene Expression Omnibus. Bioinformatic analysis was performed with Seurat 4, clusterProfiler and DoRothEA software packages. **Results:** Within MAFL-C and AC livers, 19 populations of cells were identified, including epithelial cells, endothelial cells, dendritic cells, mononuclear cells, etc. One population of HSC was identified by expression of canonical genes (RGS5). Compared with MAFL-C HSCs, AC HSCs upregulated 166 genes. Reactome pathway analysis showed AC HSCs upregulated terms including “neutrophil degranulation”, “interferon signaling” and “interactions between lymphoid and non-lymphoid cells”, indicating an enhanced immune-modulatory effect in AC pathogenesis. Regulon analysis predicted transcription factor activity of RFX5 and POU2F2 are increased in AC HSCs compared to MAFL-C HSCs, Figure 1. **Conclusion:** These results highlight the distinct patterns of gene expression, cellular pathway utilization and transcription factor activity signature of HSCs in MAFL-C and AC, laying the groundwork for translating these findings into therapeutic advances.

Disclosures: Ajay Jain: Mirum Camp 4 Gilead: Consultant, Chien-Jung Lin: Nothing to Disclose, Chandrashekara Manithody: Nothing to Disclose, Kento Kurashima: Nothing to Disclose, Arun Verma: Nothing to Disclose, Marzena Swiderska-Syn: Nothing to Disclose, Shaurya Mehta: Nothing to Disclose, Alison Bach: Nothing to Disclose

4444 | PROGNOSTIC VALUE OF QUANTIFYING TIME TO ACHIEVE NORMAL BILIRUBIN LEVELS AFTER KASAI PORTOENTEROSTOMY IN BILIARY ATRESIA

James Orozco[1] Minoti Vather[1] Benjamin Shneider[1] Jeremy Schraw[2] Ashley Upton[1] J. Alberto Hernandez[1] Sridevi Devaraj[1] Kalyani Patel[1] Sanjeev Vasudevan[1] Adam Vogel[1] Sanjiv Harpavat[1]

[1]Texas Children’s Hospital - Baylor College of Medicine, [2]Baylor College of Medicine - Texas Children’s Hospital

Background: In biliary atresia, patients who achieve normal bilirubin levels after Kasai portoenterostomy (KP) have the best prognosis. However, within this patient group, outcomes can vary widely. To understand this variability, we asked if quantifying the time to achieve normal bilirubin levels after KP could be helpful in understanding this variability. **Methods:** Patients with biliary atresia were included if they received the KP at Texas Children’s Hospital between 2007-2023 and achieved normal conjugated bilirubin (Bc) levels after KP (≤0.2 mg/dL). The time to achieve normal Bc levels was estimated as the time after KP halfway between the last abnormal and first normal Bc level. Comparisons to clinical data were made using the Pearson correlation coefficient and the log-rank test. **Results:** There were 60 patients who met inclusion criteria, with a median time to achieving normal Bc levels of 49 days (range 8-133 days). A shorter time to achieve normal Bc levels correlated with lower serum bile acids 6 months post-KP, a marker previously shown to have prognostic value (r=0.58, p=0.0007). A shorter time to achieve normal Bc levels also correlated with measurements at 2 years of age, including lower AST (r=0.34, p=0.03), lower ALT (r=0.34, p=0.03), lower total bilirubin (r=0.40, p=0.03), lower bile acids (r=0.61, p=0.0009), higher albumin (r=-0.49, p=0.001), higher platelets (r=-0.37, p=0.02), and lower liver stiffness (r=0.79, p=0.01). Finally, a shorter time to achieve normal Bc levels was associated with slower development of splenomegaly (log-rank p=0.0003), thrombocytopenia (log-rank p<0.0001), ascites (log-rank p=0.01), and need for liver transplant (log-rank p=0.0008), with 18 of 19 patients (94.7%) who achieved normal Bc levels within 30

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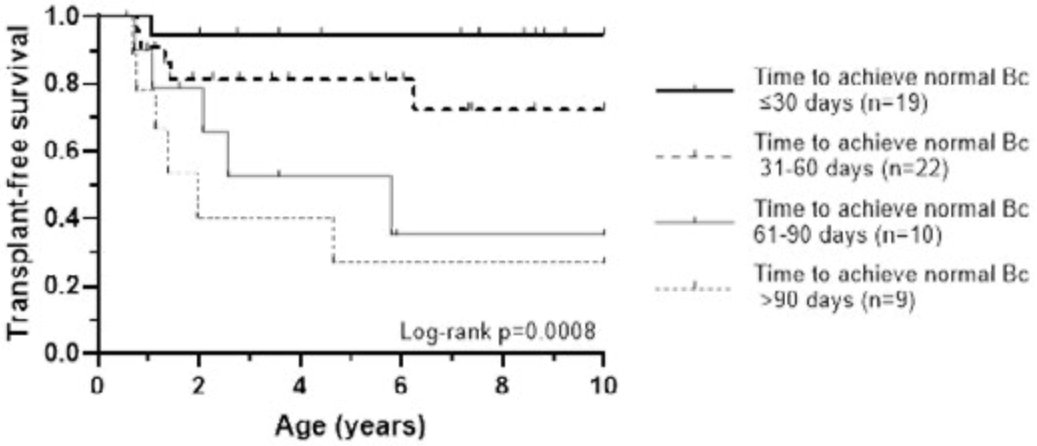
days of KP surviving transplant-free through 10 years of age (Figure). The time to achieve normal Bc levels did not correlate with age at KP or other pre-KP factors. **Conclusion:** In patients with biliary atresia who achieve normal Bc levels after KP, quantifying the time to achieve normal Bc levels has prognostic value. Future studies are needed to identify factors influencing the length of this time period, as well as to determine if pharmacological or surgical interventions can shorten the period to potentially improve outcomes.



Disclosures: James Orozco: Nothing to Disclose, Minoti Vather: Nothing to Disclose, Benjamin Shneider: Nothing to Disclose, Jeremy Schraw: Nothing to Disclose, Ashley Upton: Nothing to Disclose, J. Alberto Hernandez: Nothing to Disclose, Sridevi Devaraj: Nothing to Disclose, Kalyani Patel: Nothing to Disclose, Sanjeev Vasudevan: Nothing to Disclose, Adam Vogel: Nothing to Disclose, Sanjiv Harpavat: Syneos Health: I sit on a Data Safety Monitoring Board

4445 | IMPROVEMENT IN SEQUELAE OF CHRONIC LIVER DISEASE IN PATIENTS WITH ALAGILLE SYNDROME TREATED WITH MARALIXIBAT

Tin Bo Nicholas Lam[1] *Maria Paulina Ordonez*[2] *Amber Hildreth*[1]

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Background: Maralixibat is an orally-administered, small-molecule ileal bile acid transporter (IBAT) inhibitor used in the treatment of cholestatic pruritus in conditions such as Alagille syndrome (ALGS). Maralixibat's effect on reducing cholestatic pruritus has been well documented, however its effects on a patient's primary liver disease and/or other clinical manifestations of chronic liver disease are less well known. We present two cases documenting Maralixibat's potential role in improving manifestations of portal hypertension and dyslipidemia in patients with ALGS. **Methods:** Retrospective case series **Results:** Case 1: 10 year-old male with ALGS (JAG1) complicated by portal hypertension and pruritus managed with ursodeoxycholic acid and rifampin. Labs notable for platelets 66 K/mcL, total bilirubin (TB) 1.2 mg/dL, direct bilirubin (DB) 0.6 mg/dL, serum bile acids (sBA) 53 mcmol/L. He transitioned off of rifampin and onto maralixibat 190 mcg/kg orally, once daily starting days 1 - 7, then increased to 380 mcg/kg orally, once daily beginning day 8. His pruritus was resolved at follow-up 3 months later. Surveillance esophagogastroduodenoscopy (EGD) was performed at that time demonstrating 4 columns of grade 1 varices in distal esophagus, no band ligation required (figure 1A). He continued on maralixibat in the interim. One year later, the patient remained clinically stable with labs notable for platelets 48K/mcL, TB 1.2 mg/dL, DB 0.2 mg/dL, sBA 18 mcmol/L. A repeat surveillance EGD was performed which found no evidence of esophageal varices (figure 1B). Case 2: 2 year-old female with ALGS (JAG1), complicated by pruritus (managed with ursodeoxycholic acid and rifampin) and cutaneous xanthomas (figure 2A). Lab testing was notable for TB 25.7 mg/dL, DB 19 mg/dL, sBA 349.5 umol/L, triglycerides 382 mg/dL, cholesterol 1041 mg/dL, HDL cholesterol 29 mg/dL, LDL cholesterol >599 mg/dL. She was initiated on maralixibat chloride 190 mcg/kg orally, once daily starting days 1-7, then increased to 380 mcg/kg orally, once daily starting day 8 and thereafter. Her pruritus significantly improved, with intermittent flares. One year later, examination demonstrated near resolution of the xanthomas (figure 2B). Labs were notable for TB 20.6 mg/dL, DB 16.6 mg/dL, sBA 222.2 umol/L, TG 252 mg/

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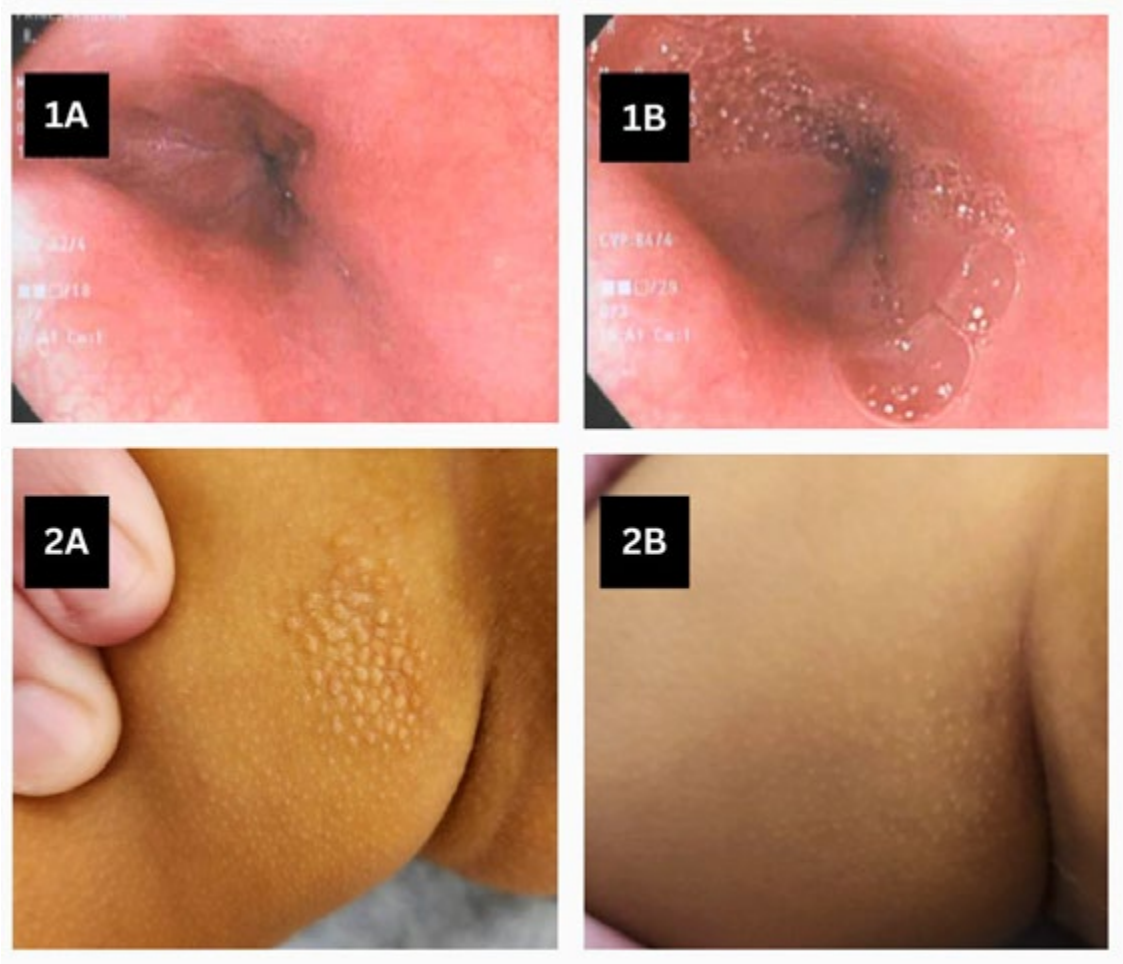
dL, cholesterol 303 mg/dL, HDL cholesterol 15 mg/dL, LDL cholesterol 237 mg/dL. **Conclusion:** In both cases, our patients demonstrated a decrease in serum bile acid levels and improved pruritus on marilixibat. In addition, the first patient demonstrated resolution of esophageal varices and the second patient experienced a decreased appearance of xanthomas; both occurred in the absence of additional therapeutic interventions. It is promising that Maralixibat may affect progression and manifestations of chronic liver disease, including portal hypertension and xanthomas, that are often indications for liver transplantation.



Disclosures: Tin Bo Nicholas Lam: Nothing to Disclose, Maria Paulina Ordonez: Nothing to Disclose, Amber Hildreth: Mirum Pharmaceuticals: Consultant, Ipsen Pharmaceuticals: Consultant

4446 | SURFASA SCORE FOR PREDICTION OF STEROID RESPONSE IN CHILDREN AND ADOLESCENTS WITH SEVERE AUTOIMMUNE HEPATITIS

SAMANNAY DAS Tamoghna Biswas[1] Rajeev Khanna[2] Anmol Anmol[3] Bikrant Biharilal Raghuvanshi[4] Vikrant Sood[4] Seema Alam[1]

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Background: Steroids are indicated in severe autoimmune hepatitis to avert liver transplantation (LT). However, to predict response to steroids and define optimal timing for LT is difficult. SURFASA (survival and prognostic factors for severe autoimmune hepatitis) score has been used in adults to define response to steroids in terms of survival with native liver (SNL) at Day 90. In the present work, we studied the applicability of SURFASA score in a retrospective cohort of children with severe autoimmune hepatitis to predict steroid response. **Methods:** Retrospective dataset of under-18-year aged children and adolescents between January 2011 to February 2024

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with suspected or histologically confirmed autoimmune hepatitis was studied. A diagnosis of severe autoimmune hepatitis was based on simplified autoimmune score >/=6 and an INR>2.0. Those who received steroids were included. SURFASA score was calculated as -6.80+1.92□(D0-INR)+1.94□(Δ%3-INR)+1.64□(Δ%3-bilirubin), and a cut off of <-0.9 was used to define outcome. Response to steroids was defined as LT-free survival (SNL) at day 28. **Results:** Overall, 45 children (17 males) with a median age of 10.9 (range: 1.8-18) years received steroids for severe autoimmune hepatitis. More than half (23, 51.1%) presented as acute liver failure (ALF), 8 (17.8%) presented as acute-on-chronic liver failure (ACLF), and remaining 14 (31.1%) presented as decompensated chronic liver disease (DCLD). There were 13 deaths and 3 LT, while 29 (64.4%) survived with their native livers. SURFASA score <-0.9 was found to have a sensitivity, specificity and positive likelihood ratio of 6.05 in the overall cohort. Both sensitivity (66.6%) and specificity (80%) were low in the ALF sub-group. ACLF cohort had 100% sensitivity and specificity. **Conclusion:** In children with severe autoimmune hepatitis, SURFASA score reasonably predicts steroid response and SNL. However, its accuracy is poor in ALF cohort.

Table: Sensitivity, specificity and accuracy of SURFASA score for prediction of steroid response in terms of survival with native liver at Day 28 in children with severe autoimmune hepatitis.

Severe Autoimmune hepatitis	Survival with native liver at Day 28	Sensitivity	Specificity	Positive Likelihood ratio	Accuracy
ALF (n=23)	13	66.6%	80.0%	3.33	69.5%
ACLF (n=8)	6	100%	100%	-	100%
DCLD (n=14)	10	76.9%	100%	-	78.5%
Total (n=45)	29	75.6%	87.5%	6.05	77.8%

Disclosures: Samannay Das: Nothing to Disclose, Tamoghna Biswas: Nothing to Disclose, Rajeev Khanna: Nothing to Disclose, Anmol Anmol: Nothing to Disclose, Bikrant Biharilal Raghuvanshi: Nothing to Disclose, Vikrant Sood: Nothing to Disclose, Seema Alam: Nothing to Disclose

4447 | COMBINED T AND B CELL MISMATCHED EPITOPE LOAD AS A PROGNOSTIC BIOMARKER OF PROLONGED DSA-FREE SURVIVAL IN PEDIATRIC LIVER TRANSPLANTATION

Olga Timofeeva[1] Nada Yazigi[2] Khalid Khan[3] Bethany Dale[4] Matthias Niemann[4] Cal Matsumoto[3] Alexander Kroemer[3] Thomas Fishbein[3] Udeme Ekong[2]

[1]Histocompatibility Laboratory, MedStar Georgetown University Hospital, Washington, District of Colum, [2]Georgetown University Hospital, [3]Medstar Georgetown Transplant Institute, Medstar Georgetown University Hospital, Washington, Distri, [4]PIRCHE AG, Berlin, Germany

Background: Late acute rejection (LAR) after liver transplantation (LT) in children occurs due to limited immunosuppression. Histopathology and immunological mechanisms leading to LAR are incompletely understood. We recently reported an association between development of de novo anti-HLA donor-specific antibodies (dnDSA) and an increased likelihood of AR. We hypothesized that evaluation of T- and B-cell epitope differences in HLA-DR/DQ molecular mismatch (MM) can improve identification of alloimmune sensitization risk and offer risk stratification strategy for follow-up and intervention. **Methods:** A retrospective chart review of 244 pediatric patients consecutively transplanted with an isolated liver at our center between 2003 and 2019 identified 42 patients who developed DSA at least 1 year after LT and 49 patients who remained DSA negative for at least two years after LT. Two field HLA typing was used to perform HLA-DR/DQ mismatching analyses using PIRCHE-II and HLAMatchmaker to assess T- and B-cell MM load. Univariate logistic regression was used to evaluate association between dnDSA and HLA-DR/DQ MM assessed from PIRCHE-II and Matchmaker, and tacrolimus level standard deviation. For time-to-event endpoints, Kaplan-Meier curves and log-rank tests were used to evaluate predictive associations. Their prognostic performances for dnDSA were also assessed using receiver operating characteristic curve and area under the curve. **Results:** Mean (SD) tacrolimus trough levels were 10.74 (1.98) ng/ml during the first 8 months after LT and 4.75 (2.12) ng/ml by one year post LT ($P < .0001$). LT patients who developed dnDSA 1 year after transplant had a higher eplet (B-cell epitopes) MM load and higher

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PIRCHE-II (T-cell epitope) MM for HLA-DR/DQ compared to patients who remained DSA-negative at least 2 years after LT (p=0.001). Patients with lower B and T cell epitope MM load had significantly longer DSA-free survival [HR (95% CI): 2.46 (1.31,4.62) log-rank p=0.0039]. **Conclusion:** Combined T- and B-cell MM load for HLA-DR/DQ can predict long-term DSA-free survival in pediatric LT recipients who are maintained on lower level of immunosuppression. This tool potentially can be used for patient risk stratification in long-term follow-up.

Disclosures: Olga Timofeeva: Nothing to Disclose, Nada Yazigi: Nothing to Disclose, Khalid Khan: Nothing to Disclose, Bethany Dale: Pirche AG: Employee, Matthias Niemann: PIRCHE AG: Employee, PIRCHE AG: Royalties or patent beneficiary, Cal Matsumoto: Nothing to Disclose, Alexander Kroemer: Nothing to Disclose, Thomas Fishbein: Nothing to Disclose, Udeme Ekong: Nothing to Disclose

4448 | LONGITUDINAL LIVER STIFFNESS MEASUREMENT BY VIBRATION-CONTROLLED TRANSIENT ELASTOGRAPHY IN PEDIATRIC PATIENTS WITH PRIMARY SCLEROSING CHOLANGITIS

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[1]*Boston Children's Hospital*

Background: Primary sclerosing cholangitis (PSC) is a slowly progressive, fibroinflammatory liver disease. There is limited data on non-invasive tests of liver fibrosis in children. We aim to evaluate liver stiffness measurement (LSM) by vibration-controlled transient elastography (VCTE) longitudinally in a cohort of pediatric patients with PSC. **Methods:** This is a retrospective study of all patients with PSC seen at Boston Children's Hospital who had LSM by VCTE (FibroScan®, Echosens, France) from 2012-2023. Diagnosis of PSC was defined as large duct disease, seen on ERCP or MRCP, or small duct disease (definitive or probable based on liver biopsy findings). Patients with PSC and autoimmune hepatitis (AIH) overlap syndrome were included. METAVIR fibrosis stage was assigned by a pediatric pathologist or, when not available, by two pediatric hepatologists. Laboratory markers within 3 months of VCTE were included. In patients with multiple LSM, change in LSM compared to baseline LSM was determined. Analysis of variance (ANOVA) was used to compare LSM measure across METAVIR categories; Generalized estimating equations (GEE) were used to examine the associations of LSM with laboratory measures over time. **Results:** Eighty-seven patients with PSC and LSM were identified. Of those, 9 patients were excluded for invalid VCTE (n=1), did not meet study definition of PSC (n=5), and VCTE done post liver transplant (n=3). Median age at diagnosis was 13.9 years (range 2.8-29.5) and median age at first LSM was 16 years (range 4.3-30.1). Median time from diagnosis to first LSM was 18.4 months (range 0-143 months). Large duct disease was present in 61(78%), inflammatory bowel disease in 68(87%), and AIH overlap syndrome in 18(23%). Median baseline LSM in the entire cohort was 5.75 kPa (IQR 4.7, 6.8). Thirty patients had liver biopsy data within one year of LSM and an additional 10 patients had METAVIR F3/4 fibrosis on liver biopsy and LSM >1 year from biopsy. LSM was significantly different in patients with METAVIR F0-F2 fibrosis compared to those with METAVIR F3-F4 fibrosis on biopsy (p=0.008, Figure 1). Forty-six patients (59%) had >1 LSM over the study period (total 142 LSM from 46 patients) and there was no correlation between change in LSM and time (p=0.47). LSM significantly correlated with decreasing platelets (p=0.03) and bilirubin (p=0.02). **Conclusion:** VCTE is a useful tool to estimate liver fibrosis in children with PSC and was found to correlate with markers of advanced liver disease. As PSC is known to be a slowly progressive disease, this study found that LSM did not significantly change during care in our pediatric liver practice. Additional studies may help determine the optimal time interval to repeat LSM in the pediatric PSC population.

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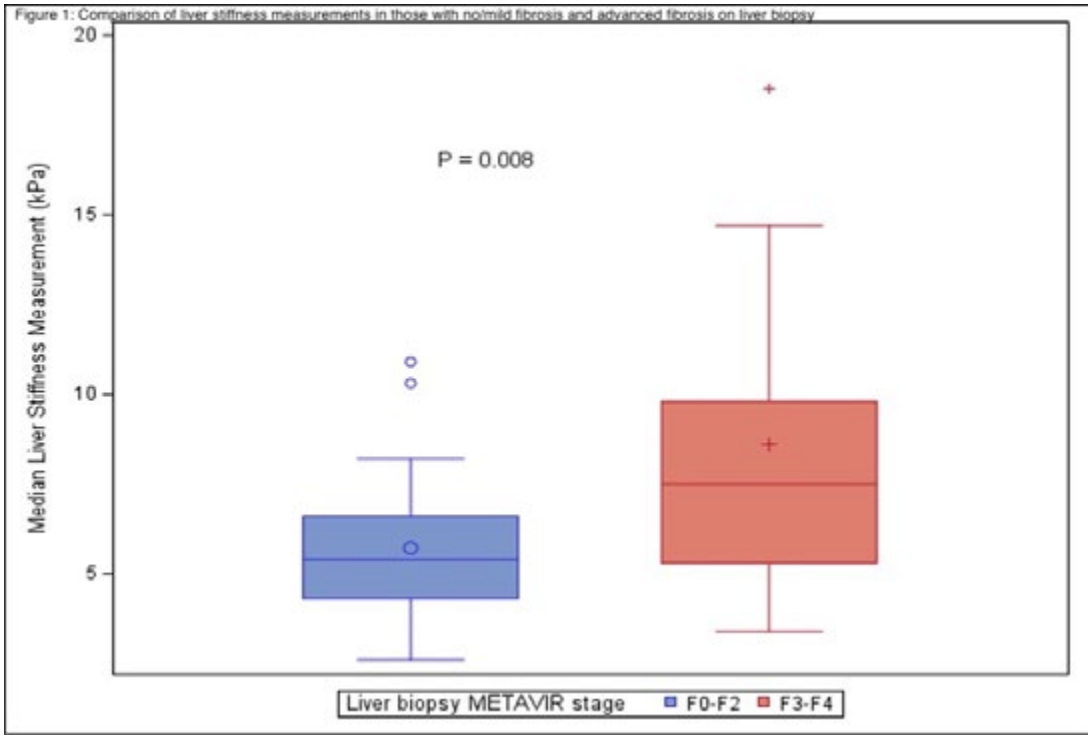

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4449 | PEDIATRIC ACUTE LIVER FAILURE WITH CONCURRENT APLASTIC ANEMIA: A MULTICENTER RETROSPECTIVE CASE SERIES

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Background: Hepatitis-Associated Aplastic Anemia (HAAA) is a rare phenomenon defined by aplastic anemia (AA) that occurs concomitant with acute hepatitis or acute liver failure (ALF). In children, these conditions often require transplantation and may be fatal. This combination of ailments is currently poorly reported in the literature. Existing literature on HAAA has been limited to case reports or limited case series at individual centers. We aimed to describe the clinical course of children who develop HAAA concurrently with ALF presentation across multiple pediatric health systems. **Methods:** We interrogated the Pediatric Health Information System (PHIS) from January 2015 to December 2022 to identify children with concurrent diagnoses of ALF and AA, defined by ICD-10-CM diagnosis codes. We describe the clinical course and health resource utilization during their admission. **Results:** Among 22 children with concurrent ALF/AA, 13 were under the age of 1 year. The race/ethnicity distribution was 36% Hispanic and 40% non-Hispanic White. 54.5% were female. Mechanical ventilation was required by 77.3%. Notably, the mortality rate during the index admission for ALF was 50%. Median survival for all patients was 85 days. Two patients received liver transplants, and two other patients received bone marrow transplants. For the first ALF admission, the mean length of stay was 42 days, and the average cost was $342,824. **Conclusion:** **Conclusions**: Aplastic anemia is a rare but devastating condition that can occur with pediatric ALF and is associated with a high mortality and resource utilization. Multicenter efforts are needed to advance understanding of this rare condition.

Disclosures: Emily Gainor: Nothing to Disclose, Vikram Raghu: Takeda: Advisor, Alcresta: Grant/Research Support, James Squires: Nothing to Disclose, Ramasubramanian Kalpatthi: Nothing to Disclose

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4450 | EVOLVING TREATMENT PARADIGMS IN WILSON DISEASE: IMPACT OF MICRO CME ON PHYSICIAN KNOWLEDGE AND CONFIDENCE

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Background: Early intervention for Wilson Disease (WD) is critical to preventing disease progression. Anti-copper treatment including chelation therapy play a vital role in the comprehensive management of WD and can improve patient outcomes, and new therapies may have the potential to address unmet needs in disease management. However, physicians who care for patients with WD may require education to improve knowledge and confidence around employing newer treatment strategies. This study was examined whether online CME could improve the knowledge and confidence of gastroenterologists/hepatologists regarding the advances in the treatment of WD. **Methods:** The CME intervention comprised of a series of 5 online CME micro modules led by 3 expert faculty, respectfully. Educational effect was assessed using a repeated-pair design with pre-/post-assessment. Two multiple choice questions assessed knowledge, and 1, rated on a Likert-type scale, assessed confidence. A paired samples t-test was conducted on overall average number of correct responses and for confidence rating, and a McNemar's test was conducted at the question level (significance level, $P < .05$). The activity posted on November 16, 2023; data were collected through February 1, 2024. **Results:** The analysis set consisted of responses from gastroenterologists/hepatologists (n=123) who answered all assessment questions during the study period. Analysis of pre- vs. post-intervention responses demonstrated a significant improvement in overall knowledge of the latest clinical evidence for the use of trientine salts for the treatment of WD; average correct responses increased from 31% pre-assessment to 53% post-assessment ($P<.001$), with 30% who reinforced current knowledge. Further, 51% of gastroenterologists/hepatologists had a measurable increase in confidence in ability to identify patients who would benefit from newer treatment strategies for WD, resulting in 23% who were mostly or very confident after education (10% pre vs 23% post; P<.001). **Conclusion:** This study demonstrated the success of online CME at improving the knowledge and confidence of gastroenterologists/hepatologists related to advances in the treatment of WD. Persistent educational gaps were identified for future educational targets.

Disclosures: Margaret Harris: Nothing to Disclose, Jovana Lubarda: Nothing to Disclose, Michael Schilsky: Nothing to Disclose

4451 | N-END RULE–MEDIATED PROTEASOMAL DEGRADATION OF ATGL PROMOTES LIPID STORAGE

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Background: Cellular lipid storage is regulated by the balance of lipogenesis and lipolysis. The rate-limiting triglyceride hydrolase ATGL (desnutrin/PNPLA2) is critical for lipolysis.The control of ATGL transcription, localization, and activation has been intensively studied, while regulation of the protein stability of ATGL is much less explored. **Methods:** In this study, we use C elegans, mammalian cell lines, and knock-in mice to investigate the regulation of ATGL protein stability in vitro and in vivo. **Results:** We showed that the protein stability of ATGL is regulated by the N-end rule in cultured cells and in mice. The N-end rule E3 ligases UBR1 and UBR2 reduce the level of ATGL and affect lipid storage. The N-end rule–resistant ATGL(F2A) mutant, in which the N-terminal phenylalanine (F) of ATGL is substituted by alanine (A), has increased protein stability and enhanced lipolysis activity. ATGL F2A/F2A knock-in mice are protected against high-fat diet (HFD)–induced obesity, hepatic steatosis, and insulin resistance. Hepatic knockdown of Ubr1 attenuates HFD-induced hepatic steatosis by enhancing the ATGL level. Finally, the protein levels of UBR1 and ATGL are negatively correlated in the adipose tissue of obese mice. **Conclusion:** Our study reveals N-end rule–mediated proteasomal regulation of ATGL, a finding that may potentially be beneficial for treatment of obesity.

Disclosures: Jiesi Xu: Nothing to Disclose

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4452 | IN PATIENT ANALYSIS AND OUTCOMES OF LIVER TRANSPLANTATION IN PATIENTS WITH ALPHA 1 ANTITRYPSIN DEFICIENCY: STUDY FROM 2016-2019

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Background: Alpha-1-antitrypsin (AAT) deficiency is a rare genetic disease and liver transplantation (LT) is a curative treatment for cirrhosis caused by many different pathologies; with one being AAT deficiency. There is limited data available regarding the outcomes of LT among patients with AAT deficiency. The aim of present study is to examine the outcomes of LT in patients admitted with AAT deficiency using national database. **Methods:** We used the Healthcare Cost and Utilization Project (HCUP) Nationwide Inpatient Sample (NIS) to identify adult patients admitted with AAT deficiency during 2016 – 2020 using ICD-10-CM codes (E88.01). We divided the patients into two groups based on concomitant diagnosis / procedure of LT based on ICD-10 codes (defined as having diagnosis codes of Z94.4 Liver transplant status and procedure codes of 0FY00Z0, 0FY00Z1, and 0FY00Z2). Main outcomes were in-hospital mortality, length of stay (LOS), and hospital costs. We evaluate the association between LT and outcomes using survey based multivariate logistic regression models for in-hospital mortality, Poisson regression for LOS, and generalized linear model with gamma distribution and log link for hospitalization cost. Models were adjusted for age, sex, race and ethnicity, primary payer, Charlson comorbidity index, hospital bed size, hospital region and hospital teaching status. **Results:** We identified a total of 48,855 hospitalizations associated with AAT deficiency between 2016 and 2020 in the United States and 2,670 (5.5%) of them were associated with LT (Table 1). In-patient mortality was significantly lower in AAT deficient patients with LT (2.1% vs 3.0%, adjusted OR: 0.47, 95%CI: 0.26 - 0.87, P < 0.001, Table 2). AAT deficient patients with LT had an increased length of stay (8.7 ± 0.50 vs 5.7 ± 0.07 days, P < 0.001) and cost of hospitalization ($51,382 ± 3,777 vs $17,190 ± 400, P < 0.001, Table 2). **Conclusion:** LT in patients with AAT deficiency is associated with lower in-hospital mortality with increased length of stay, and increased cost of hospitalization.

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Table 1: Baseline characteristics of two groups (AAT deficiency with liver transplant versus AAT deficiency without liver transplant)

Characteristic	Overall, N = 48,855	No Liver Transplant, N = 46,185	Liver Transplant, N = 2,670	p-value
Age	57.4 (0.19)	57.7 (0.19)	53.5 (0.85)	<0.001
Age Category (%)				<0.001
<18	1,280 (2.6%)	1,110 (2.4%)	170 (6.4%)	
18-40	5,200 (11%)	4,820 (10%)	380 (14%)	
41-50	6,775 (14%)	6,470 (14%)	305 (11%)	
51-60	11,600 (24%)	11,030 (24%)	570 (21%)	
>61	23,995 (49%)	22,750 (49%)	1,245 (47%)	
Female	26,365 (54%)	25,445 (55%)	920 (34%)	<0.001
Race				0.008
White	45,435 (93%)	42,970 (93%)	2,465 (92%)	
Black	1,080 (2.2%)	1,060 (2.3%)	20 (0.7%)	
Hispanic	1,280 (2.6%)	1,155 (2.5%)	125 (4.7%)	
Asian or Pacific Islander	90 (0.2%)	90 (0.2%)	0 (0%)	
Native American	230 (0.5%)	220 (0.5%)	10 (0.4%)	
Other	740 (1.5%)	690 (1.5%)	50 (1.9%)	
Insurance				<0.001
Medicare	26,645 (55%)	25,335 (55%)	1,310 (49%)	
Medicaid	7,940 (16%)	7,660 (17%)	280 (11%)	
Private	12,135 (25%)	11,185 (24%)	950 (36%)	
Other	2,080 (4.3%)	1,955 (4.2%)	125 (4.7%)	
Charlson comorbidity index				<0.001
0-1	20,030 (41%)	19,700 (43%)	330 (12%)	
2	9,485 (19%)	9,190 (20%)	295 (11%)	
>=3	19,340 (40%)	17,295 (37%)	2,045 (77%)	
Hospital bedsize				<0.001
Small	9,230 (19%)	8,945 (19%)	285 (11%)	
Medium	12,395 (25%)	11,900 (26%)	495 (19%)	
Large	27,230 (56%)	25,340 (55%)	1,890 (71%)	
Hospital region				0.534
Northeast	8,290 (17%)	7,870 (17%)	420 (16%)	
Midwest	14,295 (29%)	13,455 (29%)	840 (31%)	
South	18,675 (38%)	17,625 (38%)	1,050 (39%)	
West	7,595 (16%)	7,235 (16%)	360 (13%)	
Hospital Teaching Status				<0.001
Urban teaching	32,860 (67%)	30,535 (66%)	2,325 (87%)	
Rural	6,555 (13%)	6,425 (14%)	130 (4.9%)	
Urban nonteaching	9,440 (19%)	9,225 (20%)	215 (8.1%)	
Mean (SE); n (%)				
Wilcoxon rank-sum test for complex survey samples; chi-squared test with Rao & Scott's second-order correction				

Table 2: Comparison of primary outcomes: AAT deficiency with liver transplant versus AAT deficiency without liver transplant

	Liver Transplant		Adjusted OR / RR		
Characteristic	No Liver Transplant, N = 46,185	Liver Transplant, N = 2,670	OR/RR	95% CI	p-value
In-hospital mortality - N (%)	1,390 (3.0%)	55 (2.1%)	0.47	0.26, 0.87	0.016
LOS (days) - mean (SE)	5.7 (0.07)	8.7 (0.50)	1.34	1.20, 1.50	<0.001
Hospital Cost ($, 2020) - mean (SE)	17,190 (400)	51,382 (3,777)	2.37	2.04, 2.75	<0.001

Relative ratio is reported using Poisson regression model for LOS
Relative ratio is reported using generalized linear model with gamma distribution and log link for Hospital Cost; adjusted for inflation using Consumer Price Index (CPI) for Medical care services in U.S. city average, all urban consumers, chained, with 2018 as the reference point
Variables used for multivariate logistic regression: age, sex, race, insurance status, Charlson comorbidity index, hospital bed size, and hospital region

Disclosures: Anwar Uddin: Nothing to Disclose, Prashil Dave: Nothing to Disclose, Rafat Uddin: Nothing to Disclose, Aboud Kaliounji: Nothing to Disclose, Peter Lymberopoulos: Nothing to Disclose, Madia Ahad: Nothing to Disclose, Rahat Uddin: Nothing to Disclose, Afgal Ahad: Nothing to Disclose, Kian Bagheri: Nothing to Disclose, Nazeera Ghanie: Nothing to Disclose, Sahil Chaddha: Nothing to Disclose

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4453 | CONCORDANCE OF HISTOLOGICAL AND LIQUID CHROMATOGRAPHY MASS-SPECTROMETRY-BASED INTRAHEPATIC Z-ALPHA-1 ANTITRYPSIN (Z-AAT) BURDEN ASSESSMENTS IN PATIENTS WITH ALPHA-1 ANTITRYPSIN DEFICIENCY-ASSOCIATED LIVER DISEASE

Virginia Clark[1] Jen-Chieh Chuang[2] Feng Hong[2] Vandana Gupta[2] Jie Cheng[2] Paresh Thakker[2] Nirav Desai[2] Susana Gonzalez[2] Thomas Schluep[3] Mary MD[4] Romil Saxena[5] Cynthia Behling[6] Pavel Strnad[7] Rohit Loomba[6]

[1]University of Florida, [2]Takeda Development Center Americas, Inc., [3]Arrowhead Pharmaceuticals, Inc., [4]Vanderbilt University Medical Center, [5]Emory University School of Medicine, [6]University of California San Diego, [7]University Hospital RWTH Aachen

Background: Alpha-1 antitrypsin deficiency (AATD) is a rare genetic disease characterized by misfolded alpha-1 antitrypsin (Z-AAT) aggregates in the liver, which may lead to AATD-associated liver disease (AATD-LD). Periodic acid-Schiff staining with diastase (PAS-D) and liquid chromatography-mass spectrometry (LC-MS) are used to assess intrahepatic Z-AAT burden, but their concordance has not been examined. We leveraged data from two clinical trials of fazirsiran, an investigational small interfering RNA therapy for AATD-LD, to assess the correlations between PAS-D, intrahepatic Z-AAT and serum Z-AAT. **Methods:** Baseline and post-baseline serum and liver biopsy samples from phase 2 AROAAT-2001 (NCT03945292) and AROAAT-2002 (NCT03946449) trials were used. PAS-D score and components (portal tract involvement, % of globules with size > red blood cell, zonal location, size of globules and periportal involvement) were centrally read and adjudicated by three histopathologists. Serum Z-AAT and intrahepatic Z-AAT (total, soluble and insoluble) were analyzed by LC-MS. Cross-sectional and longitudinal correlations of PAS-D score and components, intrahepatic and serum Z-AAT were evaluated by Spearman correlation analysis. Further methodological details are described in Strnad *et al. NEJM*, 2022. **Results:** Of 41 patients from the AROAAT-2001 (n=25) and AROAAT-2002 (n=16) trials, baseline median (interquartile range) PAS-D score was 8.0 (5.0–8.0), total intrahepatic Z-AAT was 39.4 (26.4–83.8) nmol/g, and serum Z-AAT was 23.5 (19.1–27.7) mg/dL. When analyzed cross-sectionally, PAS-D score, PAS-D components and intrahepatic Z-AAT significantly correlated with each other ($p<0.0001$). When analyzed longitudinally, PAS-D score significantly correlated with intrahepatic Z-AAT ($p<0.01$) (**Figure**). When analyzed cross-sectionally and longitudinally, serum Z-AAT significantly correlated with PAS-D score, several PAS-D components and intrahepatic Z-AAT ($p<0.05$); the strongest serum Z-AAT correlation was with soluble intrahepatic Z-AAT. **Conclusion:** PAS-D and LC-MS, two valuable approaches for the measurement of intrahepatic Z-AAT in patients with AATD-LD, demonstrated good concordance cross-sectionally and longitudinally, despite differences in pre-analytical procedures, analytical characteristics and inherent biases. These biopsy- and serum-based Z-AAT biomarkers are valuable tools to support clinical development of emerging therapies in AATD-LD. Writing assistance provided by EL Wescott, PhD, of Oxford PharmaGenesis.

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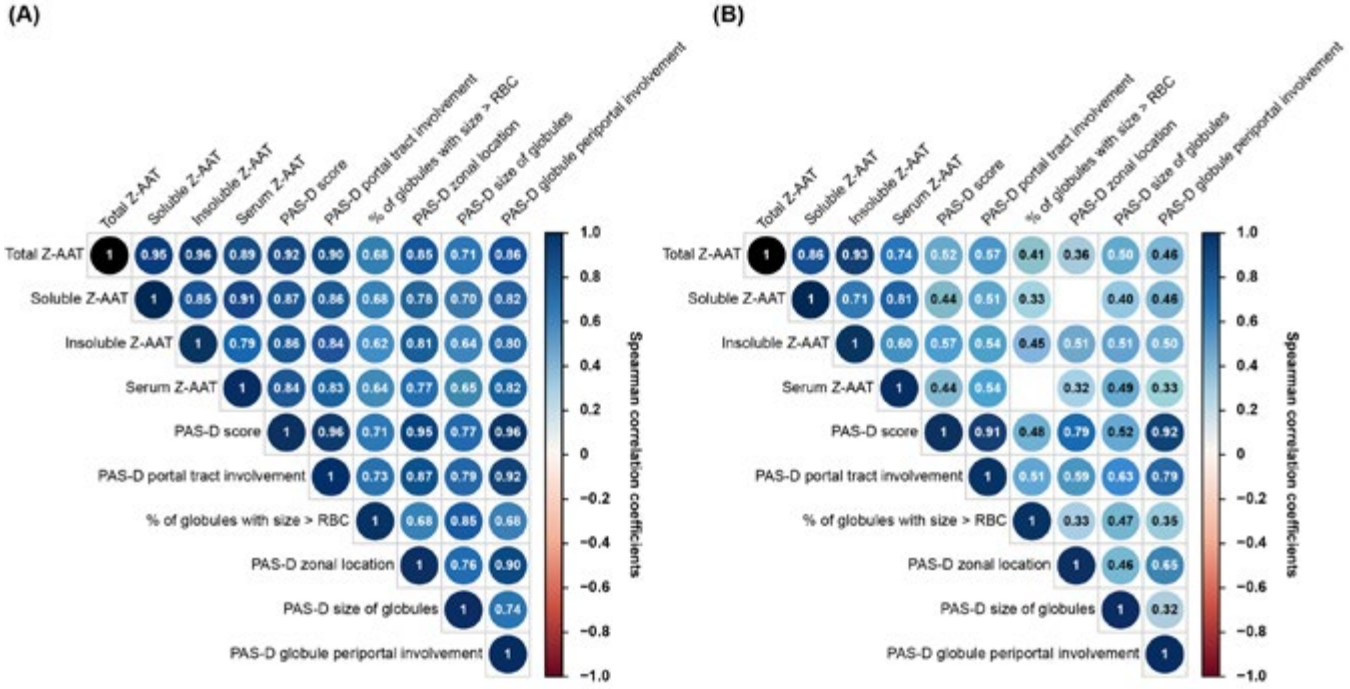
Correlations between PAS-D score and components, intrahepatic Z-AAT and serum Z-AAT when analyzed cross-sectionally (A) and longitudinally (B)



Spearman correlation coefficients range from –1 (strong negative correlation) to +1 (strong positive correlation).
PAS-D, periodic acid-Schiff staining with diastase; RBC, red blood cell; Z-AAT, misfolded alpha-1 antitrypsin.

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4454 | DIGITAL IMAGE QUANTIFICATION OF COLLAGEN PROPORTIONATE AREA CORRELATES WITH METAVIR FIBROSIS STAGE AND LIVER STIFFNESS MEASUREMENT VIA FIBROSCAN® IN ALPHA-1 ANTITRYPSIN DEFICIENCY-ASSOCIATED LIVER DISEASE

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Background: Alpha-1 antitrypsin deficiency (AATD) with the protease inhibitor (Pi)*ZZ genotype is characterized by misfolded alpha-1 antitrypsin (Z-AAT) aggregates in the liver, which may lead to AATD-associated liver disease (AATD-LD). Liver biopsy is the reference standard for assessing AATD-LD; no digital **Methods:** exist for liver fibrosis quantification in affected patients. We aimed to establish a digital quantification method for collagen proportionate area (CPA) in AATD-LD and compare it with meta-analysis of histological data in viral hepatitis (METAVIR) fibrosis stage and FibroScan® scores using data from phase 2 clinical trials of fazirsiran. **Methods:** Samples from patients with AATD-LD receiving fazirsiran/placebo enrolled in AROAAT-2001 (NCT03945292) and AROAAT-2002 (NCT03946449) were included. CPA method was established using HALO® and HALO AI. A DenseNet machine learning algorithm was trained to identify different tissue morphologies for detection of fibrotic collagen, hepatocytes, nuclei, vessels and glands. Collagen was quantified within fibrotic collagen using the area quantification method in whole-slide images of Picrosirius red-stained liver biopsy sections. Correlations of digitally quantified CPA with pathologist-reported METAVIR fibrosis stage and liver stiffness measurement via FibroScan® were evaluated by Spearman correlation analysis. **Results:** Overall, 41 patients enrolled in AROAAT-2001 (n=25) and AROAAT-2002 (n=16) had evaluable paired baseline and post-treatment liver histological data. At baseline, METAVIR fibrosis stages (n [%]) were: F0, 4 (10); F1, 11 (27); F2, 17 (41); F3, 6 (15); F4, 2 (5) and missing, 1 (2). Median (interquartile range) CPA score was 2.6 (1.7–4.6). With cross-sectional analysis (baseline and post-treatment), CPA significantly correlated with METAVIR fibrosis stage (=0.41, p<0.001) and liver stiffness measurement (=0.28, p<0.05). With longitudinal analysis, change in CPA significantly correlated with change in liver stiffness measurement (=0.38, p<0.05) following treatment. **Conclusion:** CPA significantly correlated with METAVIR fibrosis stage and liver stiffness measurement, suggesting value in continuous scores for quantifying liver fibrosis and potential for its utility as a measure of fibrosis in AATD-LD biopsy to complement pathologist-led histology evaluation. Novel digital pathology approaches may support therapeutic development in AATD-LD but require further validation. Writing assistance provided by R Tooze, PhD, of Oxford PharmaGenesis.

Disclosures: Vandana Gupta: Takeda Pharmaceuticals: Employee, Feng Hong: Nothing to Disclose, Jen-Chieh Chuang: Nothing to Disclose, David Cordover: Nothing to Disclose, Jie Cheng: Nothing to Disclose, Nirav Desai: Nothing to Disclose, Susana Gonzalez: Takeda Pharmaceutical: Employee, Paresh Thakker: Nothing to Disclose, Thomas Schluep: Nothing to Disclose, Pavel Strnad: Arrowhead Pharmaceuticals: Grant/Research Support, CSL Behring: Grant/Research Support, CSL Behring: Speaking and Teaching, BioMarin Pharmaceutical: Consultant, GSK: Consultant, Intellia: Consultant, Takeda Pharmaceuticals: Speaking and Teaching, Novo Nordisk: Consultant, Swedish Orphan Biovitrum: Consultant, Swedish Orphan Biovitrum: Speaking and Teaching, IPSEN: Consultant, Virginia Clark: Novo Nordisk: Research support, Takeda: Research support, Vertex: Research support, Takeda: Consulting fees, Vertex: Consulting fees, Rohit Loomba: Eli Lilly and Company: Consultant, 89bio: Consultant, Aardvark Therapeutics: Consultant, Altimmune: Consultant, Alnylam/Regeneron: Consultant, Amgen: Consultant, Arrowhead Pharmaceuticals: Consultant, AstraZeneca: Consultant, Bristol Myers Squibb: Consultant, CohBar: Consultant, Eli Lilly: Consultant, Galmed Pharmaceuticals: Consultant, Gilead: Consultant, Glympse Bio: Consultant, Hightide: Consultant, Inipharma: Consultant, Intercept: Consultant, Inventiva: Consultant, Ionis: Consultant, Janssen, Inc.: Consultant, Madrigal Pharmaceuticals: Consultant, Merck, Metacrine, Inc.: Consultant, NGM Biopharmaceuticals: Consultant, Novartis: Consultant, Novo Nordisk: Consultant, Pfizer: Consultant, Sagimet Biosciences: Consultant, Terns Pharmaceuticals: Consultant, Theratechnologies and Viking Therapeutics: Consultant, 89bio: Stock options, Sagimet Biosciences: Stock options, Arrowhead Pharmaceuticals: Research grant, AstraZeneca: Research grant, Boehringer Ingelheim: Research grant, Bristol Myers Squibb: Research grant, Eli Lilly: Research grant, Galectin Therapeutics: Research grant, Galmed Pharmaceuticals: Research grant, Gilead: Research grant, Hanmi: Research grant, Intercept: Research grant, Inventiva: Research grant, Ionis: Research grant, Janssen, Inc.: Research grant, Madrigal Pharmaceuticals: Research grant, Merck:

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4455 | LONG-TERM SAFETY AND EFFICACY OF FAZIRSIRAN IN PATIENTS WITH ALPHA-1 ANTITRYPSIN DEFICIENCY-ASSOCIATED LIVER DISEASE ENROLLED IN THE PHASE 2 PLACEBO-CONTROLLED SEQUOIA TRIAL

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Background: Alpha-1 antitrypsin deficiency (AATD) primarily affects the lungs and/or liver; the protease inhibitor (Pi)*ZZ genotype is associated with increased risk of liver disease. Currently, no approved therapies exist for AATD-associated liver disease (AATD-LD). Fazirsiran (FAZ) is an investigational small interfering RNA therapy undergoing phase 3 development in patients with AATD-LD. This study evaluated long-term (>1 year) safety and efficacy of FAZ in patients enrolled in the open-label extension (OLE) of the double-blind (DB) phase 2 SEQUOIA trial (1-year data have been described [Clark *et al*. *J Hepatol,* 2023; S90–S91]). **Methods:** The SEQUOIA trial enrolled 40 adults with Pi*ZZ genotype. Patients were randomized to receive FAZ (25/100/200 mg) or placebo (PBO) for ≤148 weeks. Patients with fibrosis at screening and a post-dose liver biopsy at Week 48/72/96 entered the OLE and received 200 mg FAZ every 12 weeks for a total treatment period of ≤197 weeks. Endpoints measured from baseline (last measurement prior to the first dose of open-label FAZ) to the end of the OLE included pulmonary function, serum Z-AAT levels, laboratory measures and safety. **Results:** Overall, 23 patients received ≥1 dose of FAZ during the OLE; of those, 14 received FAZ (FAZ–FAZ cohort) and 9 received PBO (PBO–FAZ cohort) during the DB study phase. Median (interquartile range) treatment duration during the OLE phase was 35.1 (25.1–37.0) and 35.3 (33.6–37.3) weeks for the FAZ–FAZ and PBO–FAZ cohorts, respectively. During the OLE phase, mean percent predicted pulmonary function remained stable for both cohorts and mean laboratory measures improved for the PBO–FAZ cohort (Table). At baseline, mean (standard deviation [SD]) serum Z-AAT levels for the FAZ–FAZ and PBO–FAZ cohorts were 45.4 µg/mL (37.1; n=14) and 224.7 µg/mL (69.9; n=9), respectively; at the end of the OLE, serum Z-AAT levels reduced by a mean (SD) of 36.3% (34.1) for the FAZ–FAZ cohort (n=14) and 85.5% (13.1) for the PBO–FAZ (n=8) cohort. During the OLE phase, 20 patients reported a treatment-emergent adverse event; most were mild or moderate and one led to study withdrawal. **Conclusion:** Fazirsiran showed sustained activity and long-term safety in patients with AATD-LD during the OLE phase. Fazirsiran was associated with stable pulmonary function, reduced serum Z-AAT, improved laboratory measures and a safety profile that supports its further clinical development in patients with AATD-LD. Writing assistance provided by R Tooze, PhD, of Oxford PharmaGenesis.

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Table

Endpoint, mean (SD)	FAZ–FAZ (n=14)		PBO–FAZ (n=9)	
	Baseline[a]	Change from baseline to end of OLE[b]	Baseline[a]	Change from baseline to end of OLE[b]
Pulmonary function, percent predicted				
FEV_1	n=14 94.1 (17.6)	n=14 −0.9 (6.0)	n=9 91.8 (11.2)	n=8 −3.8 (9.4)
FVC	n=12 100.8 (18.4)	n=12 2.4 (5.5)	n=8 100.9 (9.7)	n=7 −2.7 (10.8)
DLCO adjusted for hemoglobin	n=14 79.8 (18.6)	n=12 0 (9.2)	n=9 77.8 (14.2)	n=7 −2.8 (6.1)
Laboratory measures, U/L				
Alanine aminotransferase	n=14 28.4 (7.1)	n=12 −0.2 (8.1)	n=9 42.9 (15.9)	n=7 −15.7 (12.2)
Aspartate aminotransferase	n=14 30.5 (8.4)	n=13 0.7 (7.1)	n=9 34.0 (6.6)	n=7 −8.6 (9.8)
Gamma glutamyl transferase	n=14 35.0 (20.2)	n=13 −3.2 (10.6)	n=9 43.0 (27.2)	n=7 −8.0 (9.1)

[a]Baseline is the last measurement prior to the first dose of open-label fazirsiran.

[b]Percent change presented for pulmonary function; actual change presented for laboratory measures.

DLCO, diffusing capacity of the lung for carbon monoxide; FAZ; fazirsiran; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; OLE, open-label extension; PBO, placebo; SD, standard deviation.

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4456 | PREVALENCE ESTIMATES OF GENOTYPES ASSOCIATED WITH ALPHA-1 ANTITRYPSIN DEFICIENCY: A RETROSPECTIVE COHORT STUDY IN THE USA

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Background: Pathogenic *SERPINA1* variants cause alpha-1 antitrypsin deficiency (AATD). AATD manifests as variably progressive liver (LD) and/or lung (LgD) disease, and is often under- or misdiagnosed. Among select *SERPINA1* variants (protease inhibitor [Pi]*MS, Pi*MZ, Pi*SS, Pi*SZ, Pi*ZZ), the Pi*ZZ genotype carries the highest overall risk of AATD-LD. Literature-reported estimates of AATD prevalence are variable and often limited to those diagnosed with AATD-LD or AATD-LgD. This study estimated the prevalence of AATD genotypes in the USA using genetic data, independent of AATD diagnosis status. **Methods:** This retrospective cohort study used large epidemiological studies (Atherosclerosis Risk in Communities [ARIC], Cameron County Hispanic Cohort [CCHC], Hispanic Community Health Study/Study of Latinos [HCHS/SOL], Women's Health Initiative [WHI]) and electronic medical record-linked biobanks (BioVU, All of Us [AOU]). Overall/genotype-specific AATD prevalence was calculated as the sum of participants with any/each of the prespecified genotypes, divided by the total number of participants who contributed genetic data in each data source. **Results:** Demographics and AATD genotype prevalence for each data source are reported in the Table. Data sources comprised 36.8–44.8% males, except for WHI (100% female); most were White (53.2–92.3%) and all in HCHS/SOL and CCHC self-identified as Hispanic/Latino. Overall prevalence of AATD-associated genotypes ranged from 6,161/100,000 in CCHC to 12,421/100,000 in BioVU. Among Pi*Z variants, the most prevalent was Pi*MZ (539–3,563/100,000), followed by Pi*SZ (22–182/100,000) and Pi*ZZ (0–115/100,000). Race/ethnicity standardization according to the composition of data from the 2022 US Census had minimal effect on most estimates from AOU and BioVU. **Conclusion:** This population-based approach showed AATD genotype estimates are much higher than expected, and greater than previously reported in the UK Biobank, which comprises a homogenous population of predominantly White individuals. After standardization, we found that up to 76 per 100,000 individuals had the Pi*ZZ genotype, known to have the highest risk for LgD and LD. Estimates varied across data sources, suggesting that prevalence differs based on the population tested, adding complexity to our understanding of AATD prevalence.
Writing assistance was provided by A Pecchia-Bekkum of Oxford PharmaGenesis.

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Table. Demographics and AATD-associated genotype prevalences in data sources from the USA

Demographics	AOU[a]	BioVU[a]	ARIC	HCHS/SOL	WHI	CCHC
Data collection	2018–ongoing[b]	2007–ongoing[b]	1987–2014	2008–2011	1993–1998	2004–2021
Total N with genotype information	311,428	72,359	12,092	11,776	34,107	4,642
Age, mean (SD)[c]	54.5 (17.0)	58.8 (22.4)	54.1 (5.7)	46.1 (13.8)	64.2 (7.3)	42.6 (17.8)
Male sex, n (%)	121,173 (38.9)	31,807(44.0)	5,421 (44.8)	4,878 (41.4)	0 (0.0)	1,708 (36.8)
Race/ethnicity, n (%)						
African American	65,297 (21.0)	79 (0.1)	2,825 (23.4)	0	10,026 (29.4)	0
White	165,719 (53.2)	66,812 (92.3)	9,267 (76.6)	0	18,180 (53.3)	0
Hispanic/Latino	53,367 (17.1)	716 (1.0)	0	11,776 (100)	4,701 (13.8)	4,642 (100)
American Indian	0	69 (0.1)	0	0	594 (1.7)	0
Asian	9,869 (3.2)	60 (0.1)	0	0	513 (1.5)	0
Other	8,411 (2.7)	4,623 (6.4)	0	0	93 (0.3)	0
Unknown	8,765 (2.8)	0	0	0	0	0
AATD genotypes, per 100,000 individuals (95% CI)						
	Estimate	Standardized[d]	Estimate	Standardized[d]	Estimate	Estimate	Estimate	Estimate
Pi*MS	5,919.5 (5,578.8, 6,260.2)	6,123.3 (6,032.5, 6,214.1)	8,339.0 (7,641.4, 9036.6)	8,189.4 (7,402.7, 8,976.0)	6,202.4 (4,476.2, 7,928.7)	9,018.3 (7,295.5, 10,741.1)	6,077.9 (5,049.4, 7,106.5)	5536.4 (2,740.4, 8,332.4)
Pi*SS	144.2 (−206.8, 495.1)	149.6 (134.8, 164.4)	222.5 (−505.3, 950.3)	249.7 (143.3, 356.0)	91.0 (−1,690.6, 1,872.6)	390.6 (−1,412.0, 2,193.3)	134.9 (−925.7, 1,195.4)	64.6 (−2,811.2, 2,940.5)
Pi*MZ	2,108.0 (1,760.5, 2,455.5)	2,224.5 (2,167.8, 2,281.3)	3,562.8 (2,847.3, 4,278.3)	3143.7 (2,744.4, 3,543.0)	2,869.7 (1,113.0, 4,626.3)	1,078.5 (−717.9, 2,874.9)	2,336.8 (1,287.9, 3,385.6)	538.6 (−2,330.4, 3,407.6)
Pi*SZ	82.5 (−268.6, 433.6)	88.0 (76.4, 99.5)	182.4 (−545.5, 910.4)	268.5 (64.9, 472.1)	157.1 (−1,623.9, 1,938.1)	101.9 (−1,703.3, 1,907.1)	111.4 (−949.3, 1,172.1)	21.5 (−2,854.9, 2,898.0)
Pi*ZZ	21.8 (−329.3, 373.0)	24.1 (18.1, 30.0)	114.7 (−613.5, 842.9)	76.3 (60.1, 92.4)	24.8 (−1,757.4, 1,807.0)	8.5 (−1,797.6, 1,814.6)	8.8 (−1,052.4, 1,070.0)	0
Aggregate	8,276.1 (7,939.7, 8,612.4)	8,609.5 (8,503.0, 8,715.9)	12,421.4 (11,739.5, 13,103.3)	11,927.5 (11,033.2, 12,821.9)	9,345.0 (7,647.9, 11,042.1)	10,597.8 (8,890.0, 12,305.6)	8,669.8 (7,655.5, 9,684.0)	6,161.1 (3,374.4, 8,947.9)

[a]AOU recruitment was volunteer-based; BioVU recruited participants based on the population already receiving care at the Vanderbilt University Health Center.
[b]For inclusion in this study, data cut-off was July 2022 (AOU) or December 2023 (BioVU).
[c]Age is reported at time of study entry (ARIC, HCHS/SOL, WHI, CCHC) or as of July 1, 2022 (AOU, BioVU), if linked EMRs were available.
[d]Estimates with linked EMRs (AOU, BioVU) were standardized to 2022 US Census data, adjusted for race and ethnicity composition.
AATD, alpha-1 antitrypsin deficiency; AOU, All of Us; ARIC, Atherosclerosis Risk in Communities; CCHC, Cameron County Hispanic Cohort; CI, confidence interval; EMR, electronic medical record; HCHS/SOL, Hispanic Community Health Study/Study of Latinos; Pi, protease inhibitor; SD, standard deviation; WHI, Women's Health Initiative.

Disclosures: Grahame Evans: Nothing to Disclose, Xinruo Zhang: Nothing to Disclose, Jennifer Below: Nothing to Disclose, Kari North: Nothing to Disclose, May Hagiwara: Takeda pharmaceuticals: Employee, Chitra Karki: Takeda Development Center Americas, Inc.: Employee, Takeda Development Center Americas, Inc.: Stock - publicly traded company, Tami Nussbaum: Takeda: Employee, Suna Park: Takeda Pharmaceuticals: Employee, Kaili Ren: Nothing to Disclose, Virginia Clark: Novo Nordisk: Research support, Takeda: Research support, Vertex: Research support, Takeda: Consulting fees, Vertex: Consulting fees

4457 | DISEASE PROGRESSION IN ADULT PATIENTS WITH ALPHA-1 ANTITRYPSIN DEFICIENCY-ASSOCIATED LIVER CIRRHOSIS: A RETROSPECTIVE COHORT STUDY OF THE US VETERANS AFFAIRS HEALTH DATABASE

Dustin Bastaich[1] Bassam Dahman[1] Suna Park[2] May Hagiwara[2] Chitra Karki[2] Tami Nussbaum[2] Raphaella Ferreira[3] Austen Hentschel[4] David Kaplan[5] Andres Samos[4] Binu John[6]

[1]Virginia Commonwealth University, [2]Takeda Development Center Americas, Inc., [3]Larkin Community Hospital, [4]Florida International University, [5]University of Pennsylvania, [6]University of Miami

Background: Alpha-1 antitrypsin deficiency (AATD) may manifest as liver and/or lung disease with a variably progressive course. AATD-associated liver disease (AATD-LD) is primarily caused by *SERPINA1* protease inhibitor (Pi)*Z variants, of which the homozygous variant Pi*ZZ carries the greatest risk. The natural history and disease progression of AATD-LD and post-cirrhosis outcomes are poorly understood; we examined disease progression in patients with cirrhotic AATD-LD. **Methods:** This was a retrospective, electronic medical records-based cohort study in adults with cirrhotic AATD-LD in the Veterans Outcomes and Cost Associated with Liver Disease cohort from the Veterans Health Administration Corporate Data Warehouse. Patients were identified with suspected AATD (≥1 inpatient or ≥2 outpatient ICD-9/10-CM AATD codes ≥90 days apart, serum AAT <120 mg/dL, or Pi*ZZ, Pi*SZ or Pi*MZ phenotype [serum AAT <50 mg/dL was a proxy for Pi*ZZ]) and cirrhosis (ICD-10-CM codes). Data were collected from Oct-1999 to Feb-2023. AATD phenotypes were abstracted from laboratory test results using natural language processing (NLP). For patients with suspected AATD, chart reviews were conducted if NLP could not extract AATD phenotypes. Descriptive analyses of time from cirrhosis to hepatic

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decompensation (HD) and hepatocellular carcinoma (HCC) were conducted using the Kaplan–Meier (KM) method, stratified by AATD phenotype. **Results:** Overall, 478 patients (Pi*MZ: n=282; Pi*SZ: n=59; Pi*ZZ: n=137) were included. Mean (SD) age at cirrhosis diagnosis was 61.6 (10.3) years, 97.5% were male, and 49.8% had comorbid metabolic dysfunction-associated steatotic liver disease. In total, 119 (24.9%) and 38 (7.9%) patients developed HD and HCC, respectively. For patients who developed HD, the median time to HD was similar across AATD phenotypes (Pi*MZ: 1.9 years; Pi*SZ: 1.8 years; Pi*ZZ: 1.5 years); for those who developed HCC, the median time to HCC was also similar across phenotypes (Pi*MZ: 2.2 years; Pi*SZ: 2.0 years; Pi*ZZ: 1.7 years). Unadjusted KM survival curves for HD and HCC are shown in the Figure. **Conclusion:** Disease progression to HD or HCC was similar among patients with cirrhotic AATD-LD across Pi*Z variants. Patients with cirrhosis and Pi*Z alleles should be closely monitored, particularly those with steatosis, who may derive significant clinical benefit from timely diagnosis. Writing assistance was provided by A Pecchia-Bekkum at Oxford PharmaGenesis, Oxford, UK.

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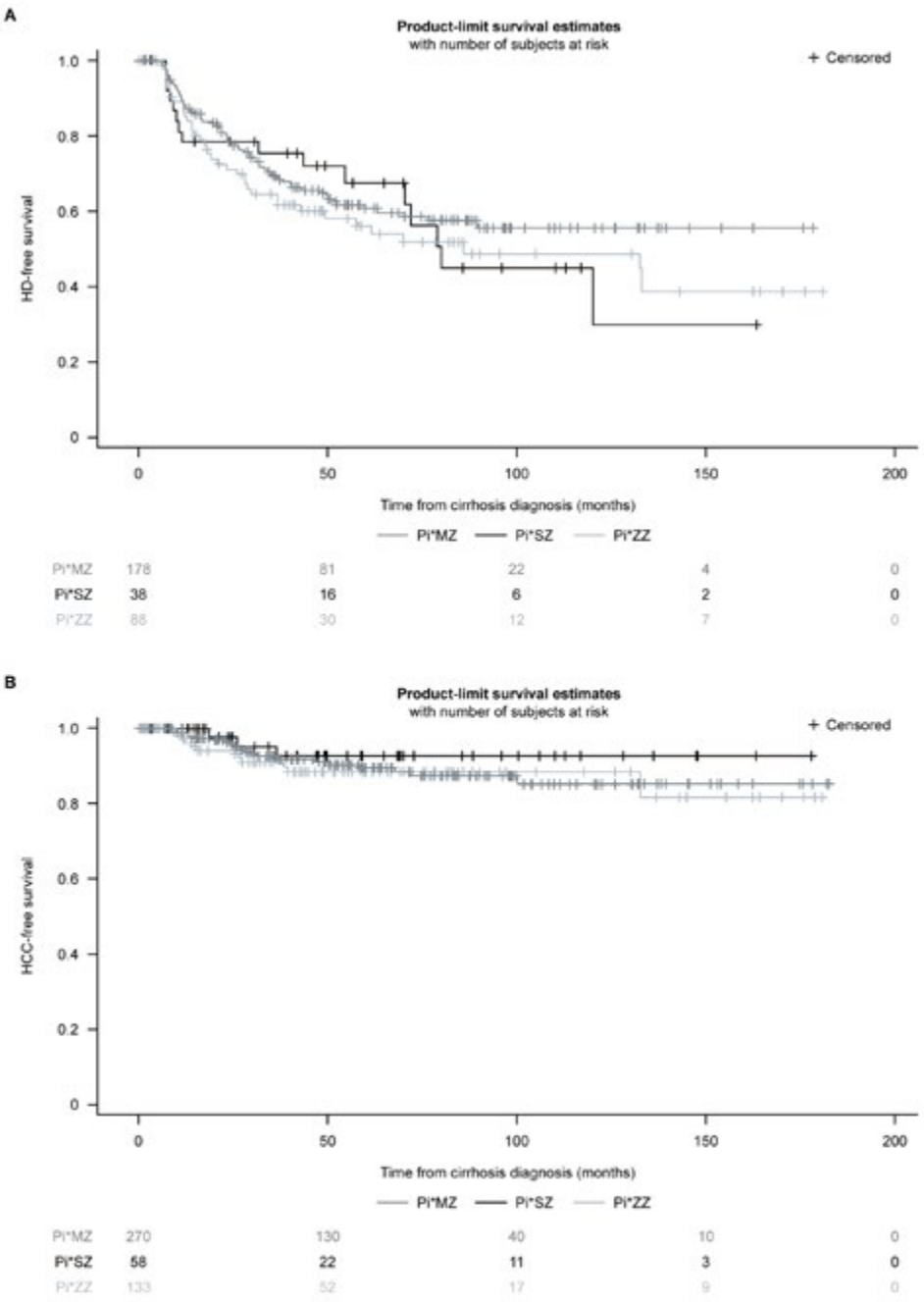
Figure. Kaplan–Meier survival curves of time to (A) HD or (b) HCC from cirrhosis diagnosis by AATD phenotype



N at Month 0 is the total number of patients at risk for HD or HCC. Patients who developed HD, HCC or died ≤ 6 months after cirrhosis diagnosis were excluded. Kaplan–Meier estimates were not adjusted.

Log rank tests were used to evaluate differences between AATD phenotypes. Pi*MZ was the reference phenotype. Patients were censored at death or liver transplantation.

HCC, hepatocellular carcinoma; HD, hepatic decompensation.

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not ended; Advisor relationship with Sirtex; Has ended; Grant/Research Support relationship with Exact Sciences; Has not ended; Grant/Research Support relationship with Glycotest; Has ended, Andres Samos: Nothing to Disclose, Binu John: Exelixis: Consultant, Exact Sciences: Received institutional research funding, Genentech: Received institutional research funding, Takeda: Received institutional research funding

4458 | COMPARATIVE MANAGEMENT PRACTICES OF WILSON DISEASE AMONG CALIFORNIAN AND ITALIAN PROVIDERS

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Background: There is a scarcity of randomized, high-quality studies to aid clinicians in managing and treating Wilson disease (WD). Even amongst society practice guidelines in North America and Europe, diagnosis and management of WD vary. The aim of this study is to elucidate WD diagnosis and treatment patterns by conducting a survey of clinicians in California and comparing the results to clinicians in Italy as a representation of European practices. **Methods:** We developed an IRB-approved, 54-item survey assessing WD diagnostics, therapeutics, and disease monitoring. The survey was emailed to 1330 California gastroenterologists, hepatologists, and movement neurologists, as well as to multiple Italian academic medical centers. **Results:** Thirty-two providers in California completed the survey, which included a total of 236 patients. Twenty-three providers in Italy, with a total of 390 patients in their care, responded. About half of California providers perform a complete neurologic evaluation before initiating therapy in patients with predominantly hepatic presentation, while 71% of Italian providers perform one. In patients with predominantly hepatic presentation, 47.4% of California providers use trientine as initial therapy, 26.3% use d-penicillamine, and 10.5% use combination therapy with chelators and zinc. No one reported using zinc monotherapy as the initial treatment. Italian providers report using d-penicillamine as initial therapy in 85% of cases, followed by zinc salt (10%), and none uses trientine. WD patients on combination therapy with chelators and zinc are followed by 34% of California respondents versus 68% of Italian respondents. In patients with predominantly neurologic manifestations, initial therapy choices are variable, with 38.9% of California providers using d-penicillamine, 16.7% using zinc salts, 11.1% using trientine, and 22% using other therapies. 55% of Italian providers use d-penicillamine, 20% combination chelator and zinc, 15% trientine, and 10% zinc salts. Changing from initial therapy to maintenance therapy in both surveys occurred after stabilization of clinical presentation, liver function tests, and 24-hour urinary copper in 72% and 86% of California and Italian providers, respectively. **Conclusion:** Our findings highlight the significant variability in initial therapies for WD patients among California and European/Italian providers. Despite the wide use of combination therapy of chelators and zinc, particularly among Italian respondents, its utility needs further exploration.

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4459 | PLASMA PROTEOMIC PROFILING IDENTIFIES PROTEIN LEVEL CHANGES ASSOCIATED WITH ALPHA-1 ANTITRYPSIN DEFICIENCY LIVER DISEASE PATHWAYS

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Background: Alpha-1 antitrypsin deficiency (AATD) is a severe liver disease caused by mutations in the *SERPINA1* gene, which encodes alpha-1 antitrypsin (AAT), a serine protease inhibitor. The normal allele of *SERPINA1* is the M allele (PiM). An E342K mutation (PiZ) produces a mutant AAT protein (Z-AAT) that is prone to polymerization. Z-AAT polymers accumulate in hepatocytes, triggering an intracellular injury cascade that leads to liver fibrosis. **Methods:** Shotgun liquid chromatography mass spectrometry (LC-MS/MS) proteomics of plasma from 34 PiZZ individuals with no reported liver disease, 22 PiZZ with cirrhosis or hepatitis, 15 PiZZ with other liver disease, 25 PiMZ without reported liver disease and 50 healthy controls was performed. Pairwise comparisons between groups were carried out to identify differences in protein levels. Differentially abundant proteins were defined by an average fold change >1.5 and a q-value <0.01 based on Student's t-test. Results

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from the human plasma proteomics were compared with proteomic data from PiZ mice and publicly available human data from AATD patients to identify plasma proteins that were differentially abundant in multiple studies. BMN 349, a small molecule that blocks Z-AAT polymerization, was assessed for its effects on plasma protein levels in PiZ mice. **Results:** Levels of proteins associated with fibrosis, hepatic protein secretion, vesicle trafficking, and the proteosome were significantly different in plasma from people with AATD compared to PiMZ and healthy controls. Coagulation factors and apolipoproteins were reduced in plasma from people with AATD and PiZ mice. In PiZ mice treated with BMN 349, levels of these proteins were normalized. A subset of proteins identified in the plasma proteomics study showed similar differential abundance in publicly available human proteomics datasets and published research comparing people with AATD to healthy controls. One such protein, programmed cell death 6 (PDCD6), a vesicle transport protein shown to be involved in apoptosis, was elevated in PiZZ mice and multiple human PiZZ plasma proteomic data sets. PDCD6 levels decreased in BMN 349-treated mice. **Conclusion:** Proteomics in people with AATD and PiZ mice identified circulating proteins associated with pathways known to be dysregulated in AATD liver disease. With further research, a subset of these proteins could serve as noninvasive biomarkers to provide a more complete picture of AATD liver pathogenesis and response to treatment.

Disclosures: Monika Sigg: Nothing to Disclose, Britta Handyside: BioMarin Pharmaceutical: Employee and stock holder, Christopher Bauer: BioMarin: Employee, Laura Wetzel: BioMarin: Employee, Heather Wenzel: BioMarin Pharmaceutical Inc: Employee, Stuart Bunting: Nothing to Disclose, Mark Brantly: Nothing to Disclose

4460 | EXCHANGEABLE COPPER QUANTIFICATION FELLS BELOW NORMAL RANGE IN A HIGH PROPORTION OF PATIENTS WITH WILSON DISEASE DURING FOLLOW-UP

ZOE MARIÑO MENDEZ[1] Clàudia García-Solà[2] José Ríos[2] Sonia García[3] Anna Miralpeix[2] Rocío Andreu[3] Cristina Aguado[3] Xavier Forns[2] Mercè Torra[2] Marina Berenguer[3]

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Background: The use of copper biomarkers in Wilson disease (WD) follow-up is challenging. Exchangeable copper (CuEX) arised as a novel biomarker reflecting the free copper pool and was expected to be a reliable tool assessing copper homeostasis. Although its ratio (REC) was shown to be very useful for diagnosis (when >18%), no recommendation has been published to date for its use during follow-up. Our aim was to define its behavior on clinical follow-up. **Methods:** Real-life retrospective assessment of serum CuEX quantification during a 2-year period among WD patients followed in 2 large Spanish hospitals. Patients were considered “stable” (group 1, G1) if diagnosis was achieved >1 year before, were compliant to medication and were on stable drug doses; otherwise, they were considered “non-stable” and included in group 2 (G2). Serum samples were obtained as required per clinical practice. CuEX/REC were measured by inductively plasma coupled to mass spectrometry (ICP-MS) and reference intervals were set in 4.1–7.1 µg/dL according to El Balkhi et al, 2011. Urinary copper excretion (UCE) was measured by atomic spectroscopy and was considered “adequate” if fell within 200-500 µg/24h (for chelators) or <100 µg/24h (for zinc salts). Statistical analysis was performed with SPSS-V25. **Results:** Ninety-two adult WD patients were included (median age 39; 63% hepatic phenotype; 19.2 years after diagnosis). Up to 39 patients (42%) were included in G1 and 53 (58%) in G2, with no differences in sex, age, or time from WD diagnosis. Serum CuEX was quantified in 213 samples (median: 2 times/ patient). Overall, up to 57% of the samples presented CuEX levels below normal range of normality, whereas 34% were within and 9% were above. There was no association of CuEX levels with therapy, time from diagnosis or clinical stability (G1 vs G2), although all samples above normality at baseline occurred in non-stable patients. Only 23.4% of the CuEX samples were aligned with data obtained from concomitant UCE. ALAT and ASAT levels were significantly lower among patients with CuEX below normal ranges when compared to patients with CuEX within/ above range ($p<0.05$). **Conclusion:** Our findings suggest that CuEX is a suboptimal biomarker and should be used with caution for assessing copper homeostasis during follow-up in a real-world WD setting. Moreover, normal reference intervals among WD should be redefined, as 57% of patients fell below normality.

Disclosures: ZOE MARIÑO MENDEZ: Orphalan: Speaking and Teaching, Orphalan: Advisor, Alexion: Advisor, DeepGenomics: Advisor, Gilead: Speaking and Teaching, Gilead: Grant/Research Support, Clàudia García-Solà: Nothing to Disclose, José Ríos: Nothing to Disclose, Sonia García: Nothing to Disclose, Anna Miralpeix: Orphalan España SL: Speaking and Teaching, Orphlan España SL: Consultant, Orphalan España SL: Consultant, Rocío Andreu: Nothing to Disclose, Cristina Aguado: Nothing to Disclose, Xavier Forns: Nothing to Disclose, Mercè

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Torra: Nothing to Disclose, Marina Berenguer: Orphalan: Consultant, Gilead: Grant/Research Support, Chiesi: Speaking and Teaching, advanz: Consultant, astellas: Consultant, abbvie: Consultant

4461 | RNA EDITING FOR THE TREATMENT OF ALPHA-1 ANTITRYPSIN DEFICIENCY ◆

Prashant Monian[1] Chikdu Shivalila[1] Genliang Lu[1] Keith Bowman[1] Marissa Bylsma[1] Michael Byrne[1] Megan Cannon[1] Jigar Desai[1] Alyse Faraone[1] Frank Favaloro[1] Anamitra Ghosh[1] Jack Godfrey[1] Nidia Hernandez[1] Olivia Huth[1] Naoki Iwamoto[1] Tomomi Kawamoto[1] Jayakanthan Kumarasamy[1] Pachamuthu Kandasamy[1] Anthony Lamattina[1] Amber Lindsey[1] Fangjun Liu[1] Richard Looby[1] Khoa Luu[1] Jake Metterville[1] Ik-Hyeon Paik[1] Qianli Pan[1] Erin Purcell-Estabrook[1] Jeanette Rheinhardt[1] Mamoro Shimizu[1] Kuldeep Singh[1] Stephany Standley[1] Carina Thomas[1] Snehlata Tripathi[1] Hailin Yang[1] Ryan Yordanoff[1] Yuan Yin[1] Hui Yu[1] Cynthia Caracta[1] Padm Narayanan[1] Paloma Giangrande[1] Chandra Vargeese[1]

[1]Wave Life Sciences

Background: Alpha-1 antitrypsin (AAT) is an acute-phase response protein secreted from hepatocytes to protect the lungs from protease-induced damage. The Z allele, resulting from a point mutation, encodes Z-AAT protein, which misfolds and aggregates in hepatocytes and decreases functional AAT in serum. Homozygous ZZ mutation carriers are at risk for severe AAT deficiency (AATD), which can lead to progressive liver injury and/or chronic obstructive pulmonary disease. Current standard of care—augmentation with weekly intravenous AAT derived from human plasma—addresses only lung disease and aims to restore serum AAT levels to an anticipated therapeutic threshold (≥11 μM). WVE-006 is a *N*-Acetylgalactosamine-conjugated chemically modified oligonucleotide that directs A-to-I RNA editing by recruiting endogenous ADAR enzymes. It is designed to preserve physiological regulation of AAT and to address both liver and lung disease by decreasing Z-AAT in liver and restoring wild-type M-AAT in serum. **Methods:** NSG-PiZ mice, a model for AATD that expresses the human *SERPINA1* Z transgene, were treated with WVE-006 for 13 weeks. Total serum AAT was quantified by ELISA, and the proportion of Z-AAT and M-AAT in serum was measured by mass spectrometry. Human iPSC-derived hepatocytes (ZZ genotype) were treated *in vitro*. RNA editing was quantified by Sanger sequencing; change in gene expression was measured by RNA-seq. The diameter of PAS-D-positive globules in hepatocytes was measured, and lobular inflammation was semi-quantitatively graded. AAT aggregates were quantified *in vitro* using an antibody specific to polymeric AAT. **Results:** In NSG-PiZ mice, biweekly 10 mg/kg WVE-006 directed ~50% editing of the Z mRNA in liver and durably increased serum AAT levels (≥33 mM at 13 weeks). Secreted AAT had the expected wild-type amino acid sequence. Treated mice exhibit decreased liver inflammation and hepatocyte turnover, and smaller PAS-D-positive globules. A molecule related to WVE-006 corrected the expression of genes inappropriately upregulated in the NSG-PiZ mouse liver and effectively cleared pre-existing AAT aggregates in human ZZ iPSC-derived hepatocytes *in vitro*. **Conclusion:** These findings highlight the potential of WVE-006 to address both liver and lung manifestations of AATD. Wave Life Sciences is evaluating WVE-006 into clinical trials. The clinical program (RestorAATion) is designed to provide proof of concept for the first RNA editing therapy in humans.

Disclosures: Prashant Monian: Wave Life Sciences: Employee, Chikdu Shivalila: Nothing to Disclose, Genliang Lu: Nothing to Disclose, Keith Bowman: Nothing to Disclose, Marissa Bylsma: Nothing to Disclose, Michael Byrne: Nothing to Disclose, Megan Cannon: Nothing to Disclose, Jigar Desai: Nothing to Disclose, Alyse Faraone: Nothing to Disclose, Frank Favaloro: Nothing to Disclose, Anamitra Ghosh: Nothing to Disclose, Jack Godfrey: Nothing to Disclose, Nidia Hernandez: Nothing to Disclose, Olivia Huth: Nothing to Disclose, Naoki Iwamoto: Nothing to Disclose, Tomomi Kawamoto: Nothing to Disclose, Jayakanthan Kumarasamy: Nothing to Disclose, Pachamuthu Kandasamy: Nothing to Disclose, Anthony Lamattina: Nothing to Disclose, Amber Lindsey: Nothing to Disclose, Fangjun Liu: Nothing to Disclose, Richard Looby: Nothing to Disclose, Khoa Luu: Nothing to Disclose, Jake Metterville: Nothing to Disclose, Ik-Hyeon Paik: Nothing to Disclose, Qianli Pan: Nothing to Disclose, Erin Purcell-Estabrook: Nothing to Disclose, Jeanette Rheinhardt: Nothing to Disclose, Mamoro Shimizu: Nothing to Disclose, Kuldeep Singh: Nothing to Disclose, Stephany Standley: Nothing to Disclose, Carina Thomas: Nothing to Disclose, Snehlata Tripathi: Nothing to Disclose, Hailin Yang: Nothing to Disclose, Ryan Yordanoff: Nothing to Disclose, Yuan Yin: Nothing to Disclose, Hui Yu: Nothing to Disclose, Cynthia Caracta: Wave Life Sciences: Employee, Padm Narayanan: Nothing to Disclose, Paloma Giangrande: Nothing to Disclose, Chandra Vargeese: Nothing to Disclose

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4462 | PREDICTION OF HEPATIC AND PULMONARY ENDPOINTS IN A LONGITUDINAL COHORT OF INDIVIDUALS WITH HOMOZYGOUS ALPHA-1 ANTITRYPSIN DEFICIENCY (PI*ZZ GENOTYPE)

Malin Fromme[1] Audrey Payancé[2] Mattias Mandorfer[3] Katrine Thorhauge[4] Monica Pons[5] Marc Miravitlles[6] Jan Stolk[7] Bart van Hoek[7] Guido Stirnimann[8] Soňa Fraňková[9] Jan Sperl[9] Andreas Kremer[10] Christina Schrader[1] Lorenz Balcar[3] Benedikt Schaefer[11] Joanna Chorostowska-Wynimko[12] John Ryan[13] Heinz Zoller[11] Michael Trauner[3] Joan Genesca Ferrer[5] William Griffiths[14] Virginia Clark[15] Aleksander Krag[4] Alice Turner[16] Noel McElvaney[13] Pavel Strnad[1]

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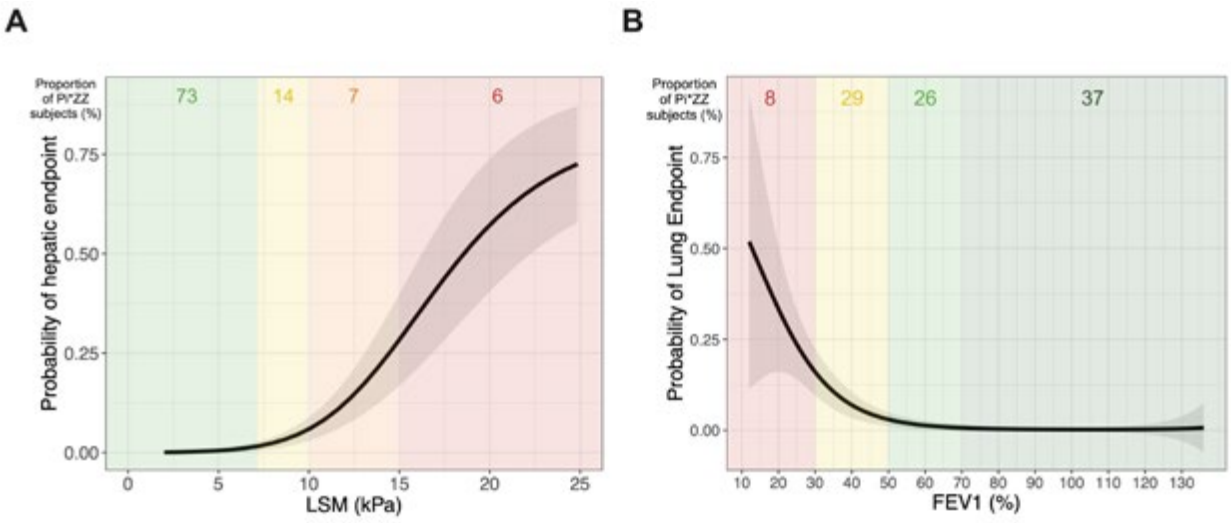
Background: Homozygous Pi*Z mutation in *SERPINA1* confers a strong predisposition to lung and liver–related mortality. Current therapeutic approaches address either the pulmonary loss-of-function or the hepatic gain-of-function mechanism. We evaluated the disease course and non-invasive surrogates for the development of hepatic and pulmonary endpoints in an international, multicenter, longitudinal Pi*ZZ cohort. **Methods:** In cohort 1, 737 Pi*ZZ subjects from 25 centers received a standardized assessment. At least six months afterwards, an interview was performed focusing on liver- and lung-related endpoints. Hepatic endpoints were defined as first hepatic decompensation/liver transplantation or liver-related death, pulmonary endpoints comprised (listing for) lung transplantation or lung-related death. Cohort 2 consisted of 135 Pi*ZZ subjects without significant liver fibrosis, who received a baseline and follow-up examination at least two years later, both including liver stiffness measurement (LSM). **Results:** During 2634 patient-years of follow-up, 39 individuals died, with liver and lung being responsible for 46% and 36% of deaths, respectively (cohort 1). 41 Pi*ZZ subjects, who developed a hepatic endpoint, were most accurately predicted by LSM (AUC 0.95) followed by APRI (0.92) and FIB-4 (0.90). Baseline lung parameters displayed only a moderate predictive utility for pulmonary endpoints (FEV1 AUC 0.76). Notably, out of 540 Pi*ZZ subjects with LSM <7.1 kPa, nobody developed a hepatic endpoint despite over 1900 follow-up years. An increase in all non-invasive liver fibrosis scores coincided with an increased occurrence of hepatic endpoints. Similarly, there was an increased incidence of lung endpoints in subgroups with lower FEV1 values (Fig. 1). A Pi*ZZ subject with mild-to moderate pulmonary function impairment and intermediate liver fibrosis (i.e., FEV1 50-70% vs. LSM 7.1-10 kPa) displayed a three times higher risk of liver- vs. lung-related endpoints. In cohort 2, 8.9% showed a fibrosis progression based on LSM (2, p=.004), baseline LSM (6.1 vs. 4.6 kPa, p=.002) and APRI (0.44 vs. 0.28 p<.001). **Conclusion:** Non-invasive surrogates of liver fibrosis accurately stratify hepatic decompensation risk in Pi*ZZ adults. Subjects with LSM-based intermediate liver fibrosis and mild-moderately impaired pulmonary function had higher liver-related than lung-related risks.



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4463 | METABOLOMIC STUDIES OF WILSON'S DISEASE METABOLOMICS STUDIES OF HEPATOLENTICULAR DEGENERATION DISEASE

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Background: Hepatolenticular degeneration disease (HDD) is an abnormal copper metabolism caused by excess copper accumulates in important organs of the human body such as brain, liver, cornea and kidney. We studied metabolomics changes in HDD by a metabolomics approach in patients with Wilson's disease (WD) to find key metabolism pathway elucidating the possible pathogenic mechanisms of HDD. **Methods:** In the case of patients with informed consent, 5 ml of fasting venous blood of patients with HDD in the First Hospital of Jilin University were collected. Then the serum were centrifuged for 5 min within 2 hours, centrifuged at 4000 rpm, and the supernatant was labeled and stored in a -80 °C refrigerator. The specimens were thawed and pretreated before

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the experiment, and the samples pretreated by the patient were detected by UHPLC-Q Exactive Orbitrap HRMS. The raw data files were preprocessed and imported into MetaboAnalyst4.0 software for principal component analysis (PCA) and partial least squares discriminant analysis (PLS-DA) to screen differential metabolites. The receiver operating characteristic curve (ROC) was established for three differential metabolites. The area under the ROC curve (AUC) was used to evaluate the diagnostic value. **Results:** A total of 35 serum metabolites with significant differences were identified between the HDD patients and the healthy control group, such as taurine and N-Methylphenylethanolamine. The above compounds were compared with the online database and were verified by the standard. According to the ROC curve analysis, it was found that these two metabolites have good differentiation value between patients and controls. Taurine and N-Methylphenylethanolamine might serve as markers between patients and controls. Three metabolic pathways with higher pathway impact are Porphyrin and chlorophyll metabolism, Arginine and proline metabolism,Taurine and hypotaurine metabolism. The pathogenesis of hepatolenticular degeneration might be related to the shortage of energy supply, the increase of oxygen free radicals production and the clearance of obstacles, and the abnormal ammonia metabolism. **Conclusion:** 1. Compared with controls, the metabolic profile of patients was altered obviously. 2. Taurine, N-Methylphenylethanolamine may serves as potential markers for WD. 3.The pathogenesis of WD may be related to the shortage of energy supply, oxidative stress, and the abnormal ammonia metabolism.

Disclosures: Minghui Sun: Nothing to Disclose, Yun Qin: Nothing to Disclose, hua Yuan: Nothing to Disclose, Rui Hua: Nothing to Disclose

4464 | LIVER ELASTOGRAPHY MEASUREMENT IS PERTINENT FOR FIBROSIS ASSESSMENT AND ESTIMATION OF THE SEVERITY OF CIRRHOSIS IN PATIENTS WITH WILSON'S DISEASE

Rodolphe SOBESKY[1] Christophe Desterke[2] Aurelia Poujois[3] Eleonora De Martin[1] Ilias Kounis[1] Cyrille Feray[1] Jean-Charles Duclos-Vallee[1] Audrey Coilly[1]

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Background: Wilson's disease (WD) can lead to fibrosis and cirrhosis. Non-invasive liver fibrosis assessment seems useful, considering the invasive character of liver biopsy. Data on the prognostic values of LE in patients with WD are rare. The aim of the study was to determine the pertinence of liver elastography (LE) measurement for assessment of fibrosis and for follow-up in patients with WD. **Methods:** We performed a retrospective analysis of patients with proven diagnosis of WD, in a liver reference center. Patients in the WD cohort had a regular follow-up with a maximum interval of 6 months. Patients were evaluated clinically, biologically and morphologically. Hepatic involvement was assessed with liver biopsy and/or LE measurement. **Results:** We included 142 patients from a cohort of patients with WD. Mean age at diagnosis of WD was 20 years and mean follow up was 15 years. 83 patients (58.4%) had liver pathological analysis and 99 (69.7%) had LE measurement. 93 patients (65%) had cirrhosis at diagnosis of the disease. 41 (29%) patients were liver transplanted. 18 patients had a liver biopsy associated with LE measurement in a short interval (1 month). Twelve of these 18 patients had cirrhosis at biopsy (Metavir F4). By univariate analysis, LE value was significantly associated with fibrosis classes of liver biopsy and high level in F4 advanced fibrosis class. High LE value was significantly associated with initial cirrhosis (32.3 kPa vs 6.7 kPa, p=0.00031); ascites decompensation (38.1 kPa vs 14.3 kPa, p=0.0137) and lower limb oedemas (46.2 kPa vs 20.3 kPa, p=0.0331). By Multivariate analysis, high LE value was highly associated with cirrhosis decompensation. LE stratified fibrosis class F4 into 2 classes (10 to 30 kPa and > 30 kPa) which could be distinguish the risk of occurrence of ascites (p=0.0076). Non-transplanted patients had multiple LE measurements during follow up. The mean LE value decreased under chelators therapy, 33.7 kPa at diagnosis, 17.6 kPa at 1 year, 16.5 kPa at 2 years, 10,4 kPa at 5 years, 9.4 kPa at 10 years, 7.7 kPa at 15 years. **Conclusion:** In WD patients, LE measurement is pertinent for estimation of fibrosis and the risk of cirrhosis decompensation. During follow-up, there is a gradual decrease in the LE under copper chelator treatment.

Disclosures: Rodolphe SOBESKY: Orphalan: Consultant, AbbVie: Consultant, Christophe Desterke: Nothing to Disclose, Aurelia Poujois: Nothing to Disclose, Eleonora De Martin: Nothing to Disclose, Ilias Kounis: Nothing to Disclose, Cyrille Feray: Nothing to Disclose, Jean-Charles Duclos-Vallee: Nothing to Disclose, Audrey Coilly: Nothing to Disclose

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4465 | CLINICAL AND LABORATORY PROFILE OF ADULT PATIENTS WITH IDIOPATHIC CHOLESTATIC LIVER DISEASE ACCORDINGTO THE PRESENCE OF MDR3 MUTATIONS

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Background: In adult patients, MDR3 deficiency has been recognized after genetic testing in up to a third of the subjects with cholestatic liver disease (CLD) of unknown cause. Little is known about the phenotype of those patients with ABCB4 gene mutations. The purpose of this study was to investigate clinical and laboratory findings of subjects with CLD according to the presence of pathogenic (P) or likely pathogenic (LP) MDR3 mutations. **Methods:** All patients with CLD of unknown cause followed in four different reference centers in Brazil were genotyped for ABCB4 gene mutations using Illumina NovaSeq 6000 Sequencing. Primary biliary cirrhosis, primary sclerosing cholangitis as well as other causes for CLD were excluded in all patients. Clinical and laboratory findings at presentation and diagnosis were compared according to the presence of P or LP MDR3 mutations. **Results:** Sixty-five patients (39 women, mean age: 26,8+10,2 years) were included in the study. Jaundice, pruritus and fatigue at disease onset was observed in 34 (52%), 28 (43%) and 15 (23%) of them, respectively. At diagnosis, 20 had cirrhosis, two had hepatocellular carcinoma and ten subjects have been submitted to liver transplantation. Sixty different MDR3 variants were observed in 40 (67%) patients. One, two and three MDR3 variants were noted, respectively, in 26, 13 and one of them. Thirty-three patients (Group I) had at least one P or LP MDR3 variant, whereas the remaining patients (Group II) had none or mutations of unknown significance (VUS). Comparison of clinical and laboratory features of patients from both groups revealed that subjects from group I when compared to group II had more past or family history compatible with MDR3 related liver diseases (77% *vs*. 51% in group II, *p*=0,04), including intrahepatic cholestasis of pregnancy (ICP) and/or low phospholipid associated cholelithiasis (LPAC) and/or CLD and higher levels of AST (112±83 *vs*. 77±59 U/L, *p*=0,04) and ALT (124±89 *vs*. 81±66 U/L, *p*=0,03). Patients from group I tended to have lower age, higher frequency of past history of ICP, more pruritus at disease onset and higher levels of total bilirubin at diagnosis, but the difference was not statistically significant. **Conclusion:** Most adult Brazilian patients with idiopathic CLD had ABCB4 mutations compatible with the diagnosis of MDR3 deficiency. Those patients or their first-degree relatives had more often other disease related manifestations such as ICP and/or LPAC as well as higher AST and ALT levels.

Disclosures: Paulo Bittencourt: Nothing to Disclose, Vivian Rotman: Nothing to Disclose, Lívia Geovana Celestino: Nothing to Disclose, Antonio Ricardo Andrade: Nothing to Disclose, Liana Codes: Nothing to Disclose, Raimundo Gama: Nothing to Disclose, Raymundo Paraná: Nothing to Disclose, Larissa Athayde Costa: Nothing to Disclose, Maria Ferraz: Nothing to Disclose, Gilda Porta: Nothing to Disclose

4466 | THROMBOCYTOPENIA PREDICTS THE LONG-TERM LIVER OUTCOMES IN WILSON'S DISEASE

Chien-Ting Hsu[1] Sung-Pin Fan[2] Jia-Feng Wu[2] Tung-Hung Su[2] Tai-Chung Tseng[2] Chin-Hsien Lin[2] Mei-Hwei Chang[3] Huey-Ling Chen[3] Yen-Hsuan Ni[3]

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Background: Wilson's disease (WD) is a rare autosomal recessive genetic disorder of copper metabolism caused by ATP7B gene mutations. WD presents with a wide clinical spectrum, ranging from asymptomatic cases and biochemical abnormalities to acute liver failure or neurological disturbances. It is treatable if diagnosed promptly. The extent of liver involvement and long-term prognosis remains unclear. This study aims to evaluate liver involvement and outcomes of WD. **Methods:** From the integrated Medical Database of NTUH, clinical data of 146 WD patients were retrieved from a tertiary referral center in Taiwan. The longitudinal follow-up data, including the disease characteristics and liver outcome, were analyzed. The fibrosis index based on four factors (FIB-4) was used as a non-invasive evaluation of liver fibrosis. The native liver survival rates and overall survival rates were analyzed. **Results:** The mean age of 146 patients at diagnosis was 37.5 ± 15.6 years (range: 3-57.5

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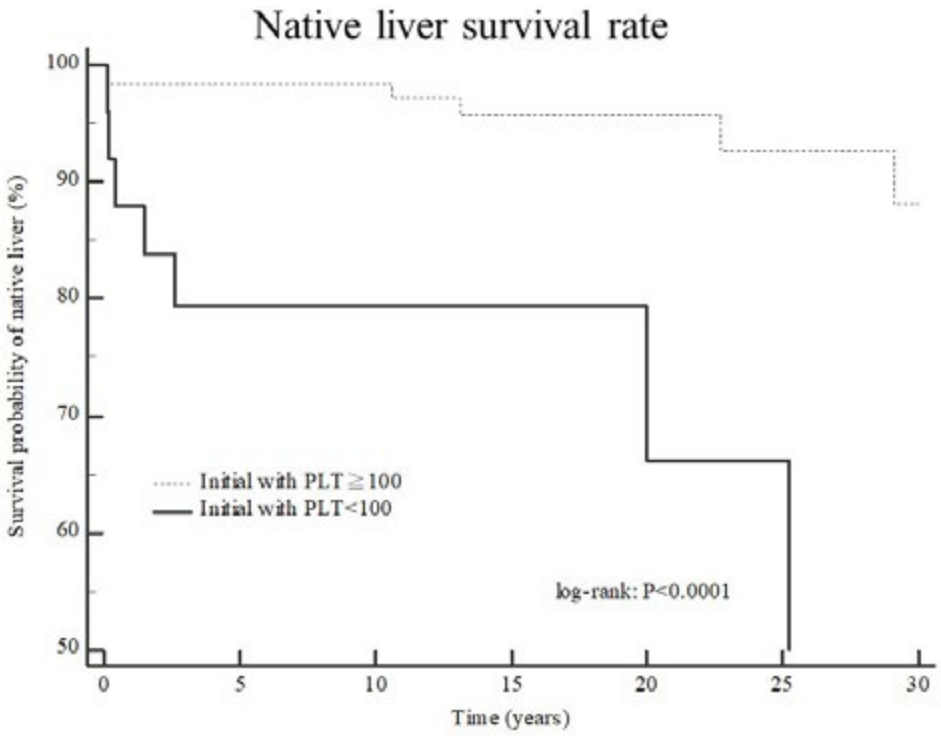
years). The mean follow-up period was 16.8 ± 10.8 years, resulting in 2,458 patient-years. At diagnosis, 54.1% (79 patients) had hepatic-predominant manifestations, and 45.9% (67 patients) had neurological-predominant manifestations. Patients with hepatic presentation were diagnosed younger (15.8 ± 10.7 years) than patients with neurologic presentation (26.5 ± 11.8 years; *P*<0.0001). The cumulative rates of advanced fibrosis (FIB-4 ≥ 3.25) at 10 and 20 years after the first diagnosis were 9.5% and 19.4% in patients with hepatic-predominant manifestations, and 1.7% and 9.8% in those with neurological-predominant manifestations, respectively (*P* = 0.0467). Nine patients (6.2%) required a liver transplant, six patients (4.1%) died, and two patients (1.4%) developed hepatocellular carcinoma (HCC). The native liver survival rates were 91.2% and 77.6% at 20 and 30 years of follow-up. Thrombocytopenia (platelet count < 10K/μL) at diagnosis was associated with poor overall survival and native liver survival (*P* = 0.0001 and *P* < 0.0001). The cumulative rates of advanced fibrosis in patients with thrombocytopenia at diagnosis were 25% and 54.1% at 10 and 20 years. **Conclusion:** Overall, WD patients have good long-term survival. However, patients with thrombocytopenia at the initial diagnosis could associated with poor outcomes. WD patients with advanced fibrosis are at risk for developing HCC and should be enrolled in long-term hepatic surveillance program.



Disclosures: Chien-Ting Hsu: Nothing to Disclose, Sung-Pin Fan: Nothing to Disclose, Jia-Feng Wu: Nothing to Disclose, Tung-Hung Su: Nothing to Disclose, Tai-Chung Tseng: Nothing to Disclose, Chin-Hsien Lin: Nothing to Disclose, Mei-Hwei Chang: Nothing to Disclose, Huey-Ling Chen: Nothing to Disclose, Yen-Hsuan Ni: Nothing to Disclose

4467 | TARGETING SPHINGOSINE 1-PHOSPHATE SIGNALING TO AMELIORATE HEPATIC INJURY IN WILSON DISEASE

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Background: Toxic copper accumulation caused by mutations in the ATP7B gene is the primary driver in the onset of Wilson disease (WD). Previous studies revealed that altered lipid homeostasis induced by copper overload is involved in the pathogenesis of WD. The current study was conducted to explore the role of the bioactive lipid sphingosine 1-phosphate(S1P) in WD. **Methods:** Lipidomic profiling of the liver was performed by LC-MS in 5-month-old Atp7b knockout (ATP7BKO) and wild-type (WT) mice. The S1P content in vitro and in vivo were quantified by ELISA. Two drugs were separately used to block S1P signaling in vivo: sphingosine

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Kinase 1 specific inhibitor PF543 (3mg/kg/d), or FTY720 (1mg/kg/d), an agonist which causes S1P receptor internalization. 8-week-old ATP7BKO mice received intraperitoneal injection of drugs or vehicle (5% DMSO) every two days for one month. Liver injury was assessed by plasma liver enzymes and liver histological analysis. The expression of genes involved in sphingolipid metabolism, inflammation, and fibrosis were determined by RT-PCR. **Results:** A total of 1794 metabolites in mice livers were identified and divided into five classes based on their lipid backbones, wherein the changes of sphingolipids were most prominent, with a marked increase in abundance in ATP7BKO mice. A higher plasma S1P content was observed in ATP7BKO mice compared with WT mice. Hepatic SPHK1 (a key enzyme that drives S1P synthesis) mRNA and protein levels were all significantly increased in ATP7BKO mice in comparison to WT controls. Meanwhile, in vitro experiment revealed that additional copper in the culture medium could markedly enhance S1P synthesis and secretion from Hepa1-6 cells. Compared to the controls, plasma ATL and AST levels were significantly reduced in the FTY720 and PF543 treated mice. HE and Sirius red staining showed that the inflammation, necrosis, and fibrosis area in ATP7BKO mice were significantly decreased by FTY720 and PF543. In addition, hepatic inflammation and fibrosis-related genes were found to be notably downregulated in FTY720 and PF543-treated mice. **Conclusion:** Our findings indicate that copper overload could remodel the sphingolipid metabolism of the liver. The blockade of S1P signaling could improve liver damage in WD mice.

Disclosures: Zixuan Wang: Nothing to Disclose, Jiangao Fan: Nothing to Disclose

4468 | BMN 349, A SMALL MOLECULE FOR ALPHA-1 ANTITRYPSIN ASSOCIATED LIVER DISEASE, STABILIZES HUMAN Z-AAT AND REDUCES SEVERITY OF LIVER DISEASE IN THE PIZ MOUSE MODEL

Britta Handyside[1] Heather Wenzel[1] Donald Mackenzie[1] Catherine Chang[1] Annie Greenslade[1] Jeremy Van Vleet[1] Brian Heglar[1] Kevin Larimore[1] Huiyu Zhou[1] Riccardo Ronzoni[2] James Irving[2] David Lomas[2] Iva Trantcheva[1] Lawrence Sims[1] Kristin Evans[1] Sylvia Fong[1] Stuart Bunting[1]

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Background: A point mutation in the *SERPINA1* gene (E342K) encoding alpha-1 antitrypsin (AAT) results in an unstable “Z” form of the AAT protein (Z-AAT). In patients, Z-AAT forms polymers in hepatocytes that activate necrotic processes and liver fibrosis. There is currently no treatment for AATD-associated liver disease other than liver transplant. BMN 349 is a small molecule chaperone being developed for the treatment of AATD-associated liver disease that binds and stabilizes the Z-AAT protein, increasing secretion of Z-AAT into plasma and reducing polymerization and the intracellular accumulation of Z-AAT polymers in hepatocytes. **Methods:** Female mice expressing human Z-AAT (PiZ mice) were dosed orally with BMN 349 at 10, 30, 50, or 100 mg/kg BID for 30 days. Total plasma and polymer AAT were measured by ELISA after 5, 20, and 30 days of treatment. Liver polymer burden was assessed by ELISA, and area of PASD+ globules and other histopathologic features were assessed microscopically after 30 days of treatment. Liver and plasma pharmacodynamic biomarkers were assessed using mass spectrometry-based proteomics at the end of treatment. **Results:** Dose-responsive increases in total plasma Z-AAT were observed during the 30-day treatment period at doses of BMN 349 ≥30 mg/kg BID. Plasma polymers also decreased in a dose-dependent manner at doses ≥30 mg/kg BID; plasma polymers were nearly eliminated at 100 mg/kg BID. Polymer accumulation in the liver was prevented by doses ≥50 mg/kg BID. Microscopic necro-inflammatory changes were reduced by treatment with BMN 349 compared to vehicle treated animals. Proteomic analyses showed significant decreases in proteins associated with ER stress and unfolded protein response pathways (such as Calr, Grp78, and P4hb) as well as normalization of thyroxine binding globulin (TBG), Factor VII, and Complement C5 in mice given ≥50 mg/kg BID BMN 349. **Conclusion:** BMN 349 stabilizes monomeric human Z-AAT, blocking formation of polymers and allowing for normal secretion to plasma. This appears to reduce pro-necro-inflammatory processes in hepatocytes. The reduction in ER stress and UPR biomarkers in BMN 349-treated mice suggests that diminishing the accumulation of Z-AAT in the liver reduces pathways that may lead to hepatocyte cell death. Restoration of TBG, Factor VII, and Complement C5 levels suggests that the biosynthetic function of the liver was largely restored after treatment.

Disclosures: Britta Handyside: BioMarin Pharmaceutical: Employee and stock holder, Heather Wenzel: BioMarin Pharmaceutical Inc: Employee, Donald Mackenzie: Nothing to Disclose, Catherine Chang: BioMarin: Employee, Annie Greenslade: Nothing to Disclose, Jeremy Van Vleet: Nothing to Disclose, Brian Heglar: Nothing to Disclose,

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Kevin Larimore: Nothing to Disclose, Huiyu Zhou: Nothing to Disclose, Riccardo Ronzoni: Nothing to Disclose, James Irving: Nothing to Disclose, David Lomas: Biomarin: Grant/Research Support, Biomarin: Consultant, Biomarin: Royalties or patent beneficiary, Biomarin: Consultant, Biomarin: Royalties or patent beneficiary, Grifols: Consultant, Iva Trantcheva: BioMarin Pharmaceutical Inc.: Employee, Lawrence Sims: Nothing to Disclose, Kristin Evans: BioMarin Pharmaceuticals Inc.: Employee, Sylvia Fong: Nothing to Disclose, Stuart Bunting: Nothing to Disclose

4469 | HEPATIC MANIFESTATIONS IN AN ADULT COHORT OF PATIENTS WITH TELOMERE BIOLOGY DISORDERS

Enrica Quattrocchi[1] Alejandro Diaz Arumir Vergara[2] Blanca Lizaola-Mayo[2] Brittany Burnap[1] Laura Ongie[1] Daniel Penrice[1] Yael Kusne[2] Filippo Pinto e Vairo[1] Caer Vitek[1] Ashraf Omar[2] Ana Zamora[2] Eva Carmona Porquera[1] Abhishek Mangaonkar[1] Rachel Simon[1] Christy Finke[1] Terra Lasho[1] Mrinal Patnaik[1] Douglas Simonetto[1] Alejandro Ferrer[1]

[1]Mayo Clinic Rochester, [2]Mayo Clinic Arizona

Background: Telomere biology disorders (TBD) are a group of hereditary conditions usually associated with pathogenic germline variants in telomere maintenance genes. These variations result in impaired telomere function, senescence and cell death, with multisystemic clinical implications in the bone marrow, lung and liver, among others. Here, we assess the prevalence and impact of hepatic manifestations in adult TBD patients. **Methods:** Consecutive patients with suspicion of TBD were seen at Mayo Clinic Rochester and Arizona from 2017 to 2024 and were tested through clinical flowFISH and our CLIA-approved germline sequencing gene panel for TBD-related genes. We included patients with lymphocyte telomere length (LTL) below 10th percentile and/or the presence of pathogenic TBD-related germline variants. Most patients (96%) with TBD underwent laboratory liver tests (aspartate transferase, alanine transaminase, alkaline phosphatase, bilirubin) and abdominal imaging, followed by magnetic resonance elastography (MRE), vibration-controlled transient elastography (VCTE) or liver biopsy, if abnormal. **Results:** 125 patients met inclusion criteria (median age 54, 43% females, 4% Hispanic, 2% Asian, 2% African American). 34 patients had LTL<1st percentile, 87 patients between the 1st and the 10th percentile (37 with TBD-germline variant) and 4 with only TBD-germline variants. Abnormal liver tests or imaging findings were observed in 70 (56%) patients. Of these, 19 (27%) patients were diagnosed with advanced fibrosis based on MRE, VCTE or liver biopsy, and 5 (7%) were diagnosed with portosinusoidal vascular disease on liver biopsy (Figure 1). Pattern of liver injury was predominantly cholestatic and portal hypertension was present in 17 patients (24%) with 11 patients with decompensated disease (variceal bleeding, ascites, or hepatic encephalopathy). Among the 70 patients with liver involvement, 37 (53%) had TBD-related germline variants in *TERT* (n=4 Pathogenic [P], n=18 uncertain significance [VUS]), *RTEL1* (n=1 P, n=9 VUS), *TERC* (n=1 P, n=2 VUS), *NAF1* (n=2 VUS), *PARN* (n=4 VUS), *TINF2/WRAP53* (n=2 each VUS) and *TRF2/NHP2* (n=1 each VUS). In addition to liver disease, 34 (62%) patients had bone marrow involvement (29 patients with bone marrow failure and 5 with myelodysplastic syndrome), 33 (60%) interstitial lung disease, and 19 (34%) had both. **Conclusion:** Our cohort shows that above half of patients with a TBD phenotype have liver involvement, a large proportion of whom have advanced liver disease at diagnosis. Due to the complexities of TBD management, which affect numerous organ systems, a multidisciplinary and systematic approach to the evaluation of patients with TBD is warranted. This may allow for early detection of liver involvement and appropriate therapeutic interventions.

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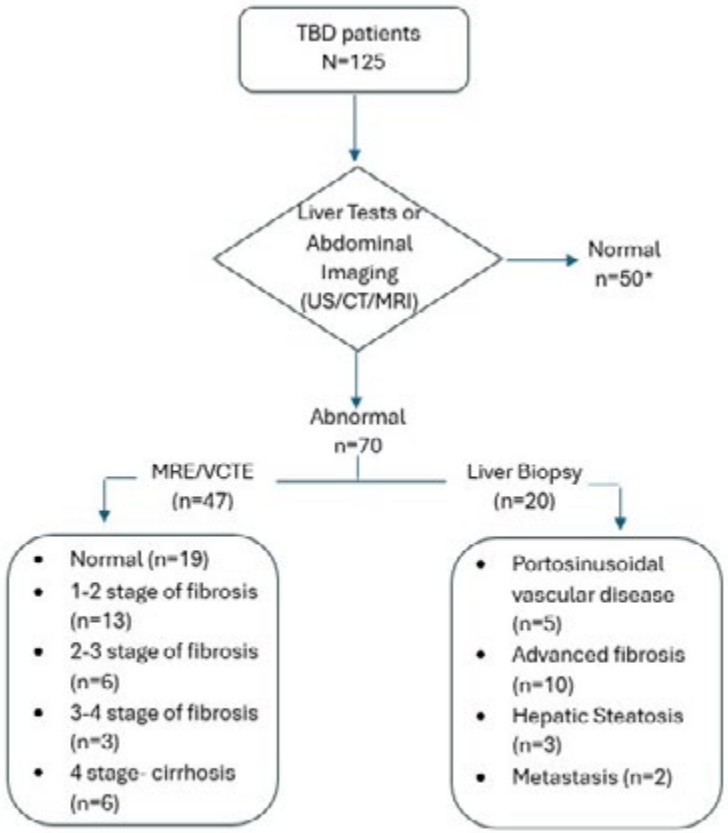

Figure 1.

*n=2 missing information; n=3 MRE/VCTE screening

Disclosures: Enrica Quattrocchi: Nothing to Disclose, Alejandro Diaz Arumir Vergara: Nothing to Disclose, Blanca Lizaola-Mayo: Nothing to Disclose, Brittany Burnap: Nothing to Disclose, Laura Ongie: Nothing to Disclose, Daniel Penrice: Nothing to Disclose, Yael Kusne: Nothing to Disclose, Filippo Pinto e Vairo: Nothing to Disclose, Caer Vitek: Nothing to Disclose, Ashraf Omar: Nothing to Disclose, Ana Zamora: Nothing to Disclose, Eva Carmona Porquera: Nothing to Disclose, Abhishek Mangaonkar: Nothing to Disclose, Rachel Simon: Nothing to Disclose, Christy Finke: Nothing to Disclose, Terra Lasho: Nothing to Disclose, Mrinal Patnaik: Nothing to Disclose, Douglas Simonetto: Consultant relationship with BioVie; Has ended; Consultant relationship with Iota; Has ended; Consultant relationship with Mallinckrodt; Has ended; Consultant relationship with Resolution Therapeutics; Has ended; Consultant relationship with Evive; Has ended, Alejandro Ferrer: Nothing to Disclose

4470 | BIOANALYTICAL METHODS TO ASSESS PHARMACOKINETICS AND PHARMACODYNAMICS OF BMN 349, A SMALL MOLECULE THERAPEUTIC FOR ALPHA1 ANTITRYPSIN DEFICIENCY

Catherine Chang[1] Annie Greenslade[1] Sophie Nguyen[1] Jeremy Van Vleet[1] Annie Dai[1] Schwend Santos[1] Kevin Larimore[1]

[1]BioMarin

Background: Alpha-1 antitrypsin deficiency (AATD) is a rare genetic disease that is characterized by low levels of functional alpha-1 antitrypsin (AAT) in blood. AATD patients expressing the Z form of AAT (Z-AAT) accumulate polymers of AAT within hepatocytes that can lead to hepatitis and cirrhosis. BMN 349 is a small molecule chaperone that binds to Z-AAT, preventing polymerization and increasing monomer AAT secretion from the liver into blood circulation. To support clinical development, a suite of assays has been developed to assess the pharmacokinetics (PK) of BMN 349 as well as effects of BMN 349 on AAT secretion and activity in humans with AATD. **Methods:** An LCMS method was developed to measure the concentration of BMN 349 in human plasma

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(plasma total BMN 349). This method was adapted to also measure the concentration of BMN 349 in plasma not bound to AAT (plasma free BMN 349), by depleting AAT from plasma samples before assay. A pair of ELISAs was developed to measure concentrations of polymer AAT and total AAT in human plasma. Both assays are indirect sandwich ELISAs that use the same anti-human AAT capture antibody and secondary detection system, but use different primary detection antibodies. The polymer ELISA uses polymeric recombinant human zAAT purified from CHO cells as reference material and the 2C1 primary antibody that detects polymeric but not monomeric human AAT. The total AAT ELISA uses mAAT purified from normal human plasma as the reference standard and the 3C11 primary detection antibody that detects both monomeric and polymeric (total) human AAT. A method to measure the protease inhibitory activity of AAT in human plasma was developed using an elastase-Suc-Ala-Ala-Ala pHA system. **Results:** The bioanalytical methods were validated in accordance with FDA's guideline on bioanalytical method validation before use in studies of BMN 349 in humans. The assays met the validation acceptance criteria for precision, accuracy, dilution linearity, selectivity, and specificity. Results from testing a panel of M/M (healthy), M/Z, or Z/Z genotype human plasma with the total and polymer AAT ELISAs agreed with published ranges. **Conclusion:** We developed and validated a suite of bioanalytical methods to measure pharmacokinetics and pharmacodynamics of BMN 349 in human plasma. These assays will be used to support clinical development of BMN 349 to treat humans with AATD.

Disclosures: Catherine Chang: BioMarin: Employee, Annie Greenslade: Nothing to Disclose, Sophie Nguyen: Nothing to Disclose, Jeremy Van Vleet: Nothing to Disclose, Annie Dai: Nothing to Disclose, Schwend Santos: Nothing to Disclose, Kevin Larimore: Nothing to Disclose

4471 | THE ALPHA-1 FOUNDATION RESEARCH REGISTRY: LIVER PROFILE AND DIAGNOSTIC DISPARITIES AMONG ALPHA-1 ANTITRYPSIN DEFICIENCY PATIENTS IN THE UNITED STATES

Monica Goldklang[1] Alison Keaveny[2] Nadine Nuchovich[2] Jennifer Illarramendi[2] Randel Plant[2] Jeanine D'Armiento[1]

[1]Columbia University Irving Medical Center, [2]Alpha-1 Foundation

Background: Alpha-1 Antitrypsin Deficiency (AATD) is an inherited disease characterized by protein misfolding in hepatocytes, with resultant increased susceptibility to severe liver disease as well as AATD-related emphysema due to protease-antiprotease imbalance. Since 2019, the Alpha-1 Foundation (A1F) has maintained a patient-reported clinical database of AATD patients across all ages located within the United States, with extensive characterization of liver and lung disease symptomology, diagnosis, and treatment. **Methods:** The Alpha-1 Foundation Research Registry has enrolled over 3600 Registry participants from all 50 states through a HIPAA compliant online platform, Research Electronic Data Capture (REDCap), between June 2019 to May 2024. Over 1,300 discrete data points per patient were captured, including patient-reported liver symptoms and diagnostic testing. **Results:** Registry participants identify largely as female (68.2%) and white (97.5%), with a mean age of 54+/-15.34 yrs (N=3400). Of those enrolled who have completed liver specific questions, 46% report to be liver-affected (N=1286/2753) including 26% with prior history of abnormal liver enzymes, 11.9% mild liver disease, 8.9% moderate-severe liver disease, 3.2% ascites, 1% variceal bleeding, 24% fatty liver, 7.5% cirrhosis, 4.7% NASH and 1% have received liver transplant. Reasons for AATD testing among liver-affected patients (N=1286) was largely from pulmonary symptoms (35.4%), family testing (23.6%), followed by liver-related symptoms (19%), with 4.9% through direct-to-consumer testing. Of liver-affected patients reporting genotypes (N=1254), 40.1% are PiZZ, 28.5% PiMZ, 11.2% PiSZ, 2.9% PiMS, and 1.5% PiSS. Testing including ultrasound and liver elastography of those with liver disease was seen in only 57.1%, and 16.7%, respectively. In liver affected PiZZ patients, 26% report ever undergoing elastography. Though rates of abnormal liver tests were similar in both males and females (23% vs. 22%, respectively) only 57.7% of those females have had US/fibroscan compared to 68.3% of males. **Conclusion:** Liver-affected patients were found to largely have alleles associated with protein misfolding including those with compound heterozygous status. However, this high-risk group was found to have a low rate of standard of care screening including ultrasound and liver elastography. While screening as a whole for liver-affected participants was low based on current NIH guidelines for patients with abnormal liver enzymes, additional deeper disparities were found in females. This comprehensive patient-reported database is capable of profiling the detailed characteristics of liver-affected patients with AATD and has the potential to showcase potential gaps in diagnostic care. This information can help guide patient education strategies in this rare disease population.

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Disclosures: Monica Goldklang: Nothing to Disclose, Alison Keaveny: Nothing to Disclose, Nadine Nuchovich: Nothing to Disclose, Jennifer Illarramendi: Nothing to Disclose, Randel Plant: Nothing to Disclose, Jeanine D'Armiento: Nothing to Disclose

4472 | COMPREHENSIVE GENETIC TESTING OF WILSON DISEASE PATIENTS WITH ONLY 0 OR 1 KNOWN PATHOGENIC ATP7B-VARIANT

Thomas Sandahl[1] Michael Schilsky[2] Ayse Coskun[2] Uyen To[2] ZOE MARIÑO MENDEZ[3] Isabelle Mohr[4] Peter Ott[1] Anne Grosen[5] Dorte Lildballe[6]

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Background: Wilson Disease (WD) is known as a monogenic autosomal recessive disorder caused by variants in *ATP7B*. However, up to 25% of clinically diagnosed WD patients lack identifiable causal variants in *ATP7B*. Recent advances in genetic testing have significantly improved the diagnostic yield in rare diseases. This study aimed to genetically characterize WD patients with zero or one known variant using state of the art genetic testing. **Methods:** 764 patients were screened for *ATP7B* variants in four different cohorts of patients with WD. A total of 47 patients with a clinical diagnosis of WD but with zero or one known *ATP7B* variant were included in this study. 22 out of 457 from The University Hospital Heidelberg, 3 of 65 from The Hospital Clínic de Barcelona, 0 of 45 from Aarhus University Hospital and 22 out of 197 patients from Yale New Haven Hospital. Whole Genome Sequencing (WGS) was performed, and results analyzed following a sequential diagnostic approach: Analysis for casual variants in (1) *ATP7B*; (2) in 82 copper-related genes; and (3) in 213 genes associated with liver diseases (Fig 1). **Results:** 6.2% (47 of 764) of the combined cohort had only 0 or 1 known variants in *ATP7B*. Of these, 24 (51%) were males. The median age at diagnosis was 20 years (range 0-68), with a median Leipzig score of 6 (range 1-11) before genetic testing. At diagnosis, 23 patients had liver-associated phenotypes, 9 had primary neurological phenotypes, 8 had mixed phenotypes, and 7 were asymptomatic. Analysis of *ATP7B* resolved 25 cases: 9 through reclassification of previously reported findings, and 16 were solved by identification of previously unreported *ATP7B*-variants. Interestingly, in 8 cases we identified one variant of uncertain significance (VUS) alongside one (likely) pathogenic *ATP7B* variant. Among the still unresolved cases, 8 had one pathogenic *ATP7B* variant and 6 had none. Comprehensive screening for causal variants in other genes of interest did not identify any alternative genetic causes. **Conclusion:** Our findings suggest that reevaluation of *ATP7B* VUS is crucial when previous sequencing results are inconclusive. Resequencing methods capable of detecting structural and intronic ATP7B variants are recommended. The lack of genetic explanations from expanded screening highlights the necessity of continued investigation into ATP7B variants in WD patients, potentially including tissue analysis allowing for detection of second-hit variants and methylation/epigenetic changes.

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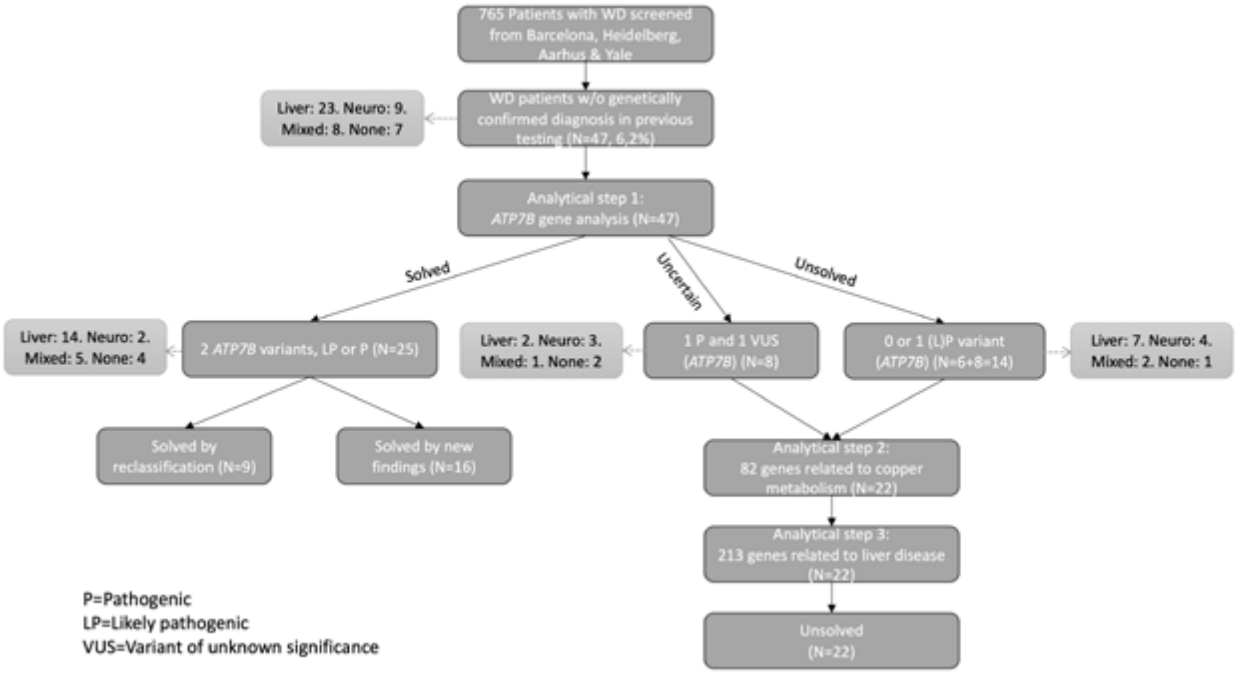

Disclosures: Thomas Sandahl: Arbormed: Advisor, Orphalan: Speaking and Teaching, Alexion: Grant/Research Support, Univar: Consultant, Ultragenyx: Advisor, Michael Schilsky: Nothing to Disclose, Ayse Coskun: Nothing to Disclose, Uyen To: Nothing to Disclose, ZOE MARIÑO MENDEZ: Orphalan: Speaking and Teaching, Orphalan: Advisor, Alexion: Advisor, DeepGenomics: Advisor, Gilead: Speaking and Teaching, Gilead: Grant/Research Support, Isabelle Mohr: Nothing to Disclose, Peter Ott: Nothing to Disclose, Anne Grosen: Nothing to Disclose, Dorte Lildballe: Nothing to Disclose

4473 | [64CU]-METHANOBACTIN (SB2) BIODISTRIBUTION AND EXCRETION EXAMINED IN PIGS BY WHOLE-BODY PET/CT – PHARMOKINETICS OF A POTENTIAL NEW TREATMENT FOR WILSON DISEASE

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Background: Wilson disease (WD) is an inherited disorder caused by a malfunction in the copper-transporting protein ATP7B, essential for hepatic copper clearance. Methanobactins (MB), copper-chelating peptides, demonstrate potential in removing hepatic copper in animal models of WD. The biodistribution of MB is largely unknown; however, its exceptional copper affinity makes it suitable for characterizing ^{64}Cu-labeled MB's (^{64}Cu-MB) pharmacokinetic profile. Thus, we aim to investigate the biodistribution and excretion of ^{64}Cu-MB in pigs. **Methods:** In this study, MB (SB2) was utilized. Seven pigs were administered i.v. ^{64}Cu-MB (50 MBq ^{64}Cu in 10 mg MB) and five pigs received i.v. 50 MBq $^{64}CuCl_2$. A 90-minute dynamic whole-body PET/CT was conducted after injection of either ^{64}Cu-MB or $^{64}CuCl_2$. Time activity curves (TAC) were obtained by placing volumes of interest in the liver. Two of the ^{64}Cu-MB pigs were pre-equipped with surgically implanted flow probes on the hepatic arteries and portal vein. A hepatic extraction fraction of ^{64}Cu-MB was quantified from blood and flow data. **Results:** The PET scans of the ^{64}Cu-MB pigs demonstrated rapid hepatic excretion into the gallbladder and intestines (figure), with the liver TAC showed a rapid increase to a mean standardized uptake value (SUV) of 11.38±1.65 (mean±SD) within 10 minutes, followed by a 72% reduction in SUV. In contrast, the PET scans of the $^{64}CuCl_2$ pigs showed accumulation of $^{64}CuCl_2$ in the liver with minor biliary excretion (figure), with the liver TAC displayed a gradual rise,

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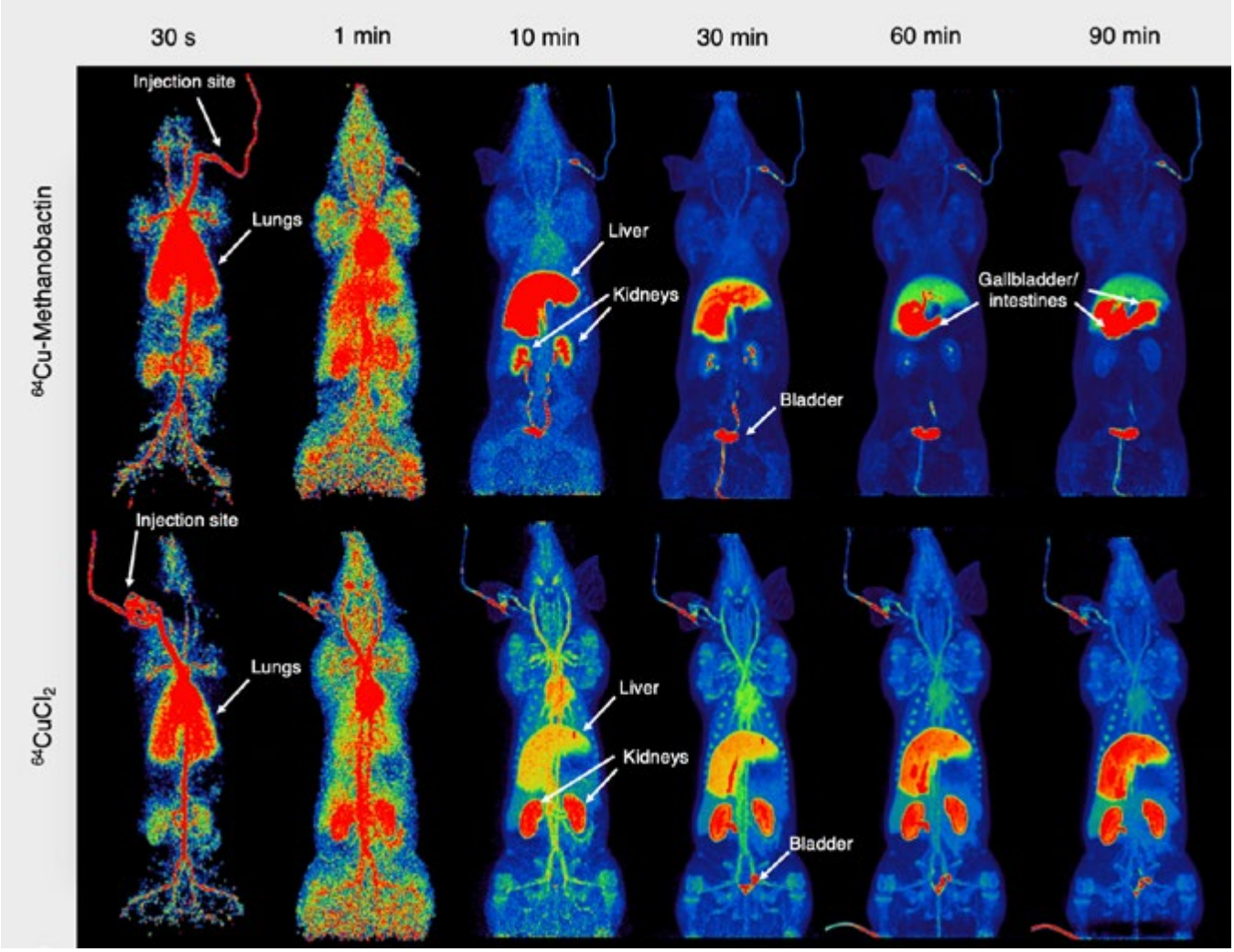
reaching a plateau with an average SUV of 9.34±1.42 (mean±SD) after 90 minutes. ^{64}Cu-MB was also excreted by the kidneys, quickly passing through the parenchyma to the urinary bladder, whereas the $^{64}CuCl_2$ accumulated in the renal parenchyma late in the scan. There was no notable biodistribution of ^{64}Cu-MB in other organs. After the initial distribution, the hepatic extraction fraction of MB was around 25% after 2 minutes in the two pigs equipped with flow probes. **Conclusion:** ^{64}Cu-MB is excreted rapidly through the liver and kidneys, exhibiting a faster elimination rate than $^{64}CuCl_2$. This suggests an alternate hepatic elimination pathway distinct from the ATP7B-mediated mechanism. The lack of ^{64}Cu-MB accumulation in other organs reinforces that MB's primary pharmacological action is in the liver, the principal organ affected in Wilson disease.



Disclosures: Julie Loft Nagel: Nothing to Disclose, Ole Munk: Nothing to Disclose, Aage Kristian Olsen Alstrup: Nothing to Disclose, Maja Kanstrup Jørgensen: Nothing to Disclose, Frank Viborg Mortensen: Nothing to Disclose, Peter Ott: Nothing to Disclose, So-Young Eun: Nothing to Disclose, Hans Zischka: ArborMed Co., Ltd: Consultant, Mikkel Holm Vendelbo: Nothing to Disclose, Thomas Sandahl: Arbormed: Advisor, Orphalan: Speaking and Teaching, Alexion: Grant/Research Support, Univar: Consultant, Ultragenyx: Advisor

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4474 | MODULATION OF A MOUSE MODEL OF METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS BY TRIENTINE TETRAHYDROCHLORIDE (TETA 4HCL)

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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) and Wilson disease share several hepatic histological features, including steatosis, glycogenic hepatocyte nuclei, hepatocyte ballooning, and lobular inflammation. Copper overload is associated with lipid peroxidation and free radical production with consequent membrane function damage. Conversely, hepatic steatosis in MASLD has been associated with copper deficiency which can potentially exacerbate liver damage as copper itself participates in crucial metabolic functions including mitochondria respiratory chain. Similarly, long term copper chelation in Wilson disease can also be associated with copper deficiency with unknown effects on lipid metabolism. **Methods:** Thirty-nine male Ldlr-/- Leiden mice were fed an energy dense fast-food diet (FFD) for a total of 26 weeks to inducemetabolic dysfunction-associated steatohepatitis (MASH) and hepatic fibrosis. After 13 weeks of FFD, when hepatic inflammation developed, mice were divided into two groups: 1) FFD + vehicle gavage control (n=15), 2) FFD + TETA 4HCl (40 mg/kg/day, daily oral gavage (n=15). Age matched chow-fed Ldlr-/- Leiden mice (n=9) were included as a healthy control. Treatment duration of TETA 4HCl and vehicle was 13 weeks. **Results:** TETA 4HCl was well-tolerated and did not affect food intake and body weight, plasma lipids, liver enzymes, liver weight, lipid peroxidation, inflammatory aggregates, or fibrosis. Cholesterol and triglyceride levels did not change with treatment. Average plasma cholesterol levels were comparable between the FFD + vehicle (45.1 ± 10.3 mM) and FFD + TETA 4HCl (45.9 ± 7.0 mM). Average plasma triglycerides levels were comparable between the FFD + vehicle (10.7 ± 3.5 mM) and FFD + TETA 4HCl (10.7 ± 2.8 mM). Although there were no effects on total steatosis, TETA 4HCl significantly decreased macrovesicular steatosis (with -18%, p=0.050). **Conclusion:** TETA 4HCL was safe and well tolerated in the FFD mice with no modulatory effect on MASH. Trientine reduced macrovesicular steatosis. Altogether, results from this study show that TETA 4HCl was well tolerated and improved a major feature of hepatic steatosis, observed both in MASH and Wilson disease patients with no evidence of copper deficiency.

Disclosures: Valentina Medici: Orphalan: Advisor, Arbormed: Research Grant, Ultragenix: Research Grant, Alexion: Advisor, Vivet: Grant/Research Support, Sammy Saab: AbbVie: Speaking and Teaching, gilead: speaker, salix: consultant, takeda: Speaking and Teaching, madrigal: consultant, mallinckrodt: Speaking and Teaching, Sequana: Advisor, ipsen: Advisor, Jamie Heise: Orphalan Inc: Employee for the company, Tim Jenkins: Nothing to Disclose

4475 | REAL-WORLD UTILITY OF ZINC MONOTHERAPY IN A LARGE COHORT OF INDIVIDUALS WITH WILSON DISEASE

Dorota Borovsky[1] Zhaolu Ding[2] Kristel Leung[2] Gabriel Burke[3] Henna Asrar[2] Erin Ingoldsby[1] Ahreni Saunthar[2] Gideon Hirschfield[4] Jordan Feld[4]

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Background: Chelators and zinc are mainstays of therapy for copper overload in Wilson Disease (WD). There are limited data on tolerability and efficacy of zinc monotherapy (ZM), particularly from North American cohorts. **Methods:** We reviewed individuals followed at the Toronto Centre for Liver Disease (TCLD) from 2000-2020 with a confirmed diagnosis of WD. Clinical and laboratory (median, range) data are described, with rates of treatment efficacy, failure and outcomes reported. **Results:** Of 105 patients with median 7.0 (0-27) years follow-up (49% male, median age at diagnosis 16.0 (1- 58) years), presentation varied: acute liver failure/decompensation (26%), acute neuropsychiatric symptoms (29%), asymptomatic liver enzyme elevation (17%), and family screening (15%). Two patients were not treated as WD was confirmed post-liver transplant. Initial treatment was d-penicillamine (D-Pen) (44%), trientine (18%), ZM (28%), chelator/zinc combination (8%) and other (3%). ZM was used more often in those diagnosed by family screening (93%), mild hepatic (83%) or neuropsychiatric (73%) presentation than in those with more severe liver disease (56%) (p=0.041); ZM was also used more frequently in those without cirrhosis (p<0.001). During follow-up, 75 (71%) were treated with ZM, 28 (37%) as initial therapy and 47 (63%) after a median

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4.5 (0.1-40) years of chelation. ZM was effective long-term in 34 (45%) for a median of 9 (0.5-20) years. ZM was stopped in 41 (55%) due to inadequate efficacy in 30 (73%) (hepatic 10, neuropsych 6, Cu parameters 5, multiple reasons 9), side effects/adherence in 8 and a combination in 3. Time to failure due to side effects/adherence was median 1.0 year (0.2-13) compared to failure for inadequate efficacy of median 3.5 years (0.17-16, p=0.072). One patient on ZM progressed to liver transplant after severe intolerance to D-Pen and trientine. No other patients treated with ZM developed severe liver or neuropsychiatric outcomes. There were no pre-treatment factors associated with ZM failure – efficacy or tolerability. **Conclusion:** In a large cohort of patients with WD, zinc monotherapy was used in 71% as initial or long-term maintenance therapy and was effective long-term in ~45%. Treatment failure occurred primarily due to inadequate efficacy. Predictors of zinc failure were not readily apparent, supporting the use of a therapeutic trial with careful monitoring, particularly in those with a mild/early disease.

Disclosures: Dorota Borovsky: Nothing to Disclose, Zhaolu Ding: Nothing to Disclose, Kristel Leung: Nothing to Disclose, Gabriel Burke: Nothing to Disclose, Henna Asrar: Nothing to Disclose, Erin Ingoldsby: Nothing to Disclose, Ahreni Saunthar: Nothing to Disclose, Gideon Hirschfield: Consultant relationship with Mirum; Has not ended; Consultant relationship with Advanz; Has not ended; Consultant relationship with Chemomab; Has not ended; Consultant relationship with Gilead; Has not ended; Consultant relationship with Kowa; Has not ended; Consultant relationship with Intercept; Has not ended; Consultant relationship with Pliant; Has not ended; Consultant relationship with Falk; Has not ended; Consultant relationship with GSK; Has not ended; Consultant relationship with Ipsen; Has not ended; Consultant relationship with CymaBay; Has not ended, Jordan Feld: Mirum: Consultant, AbbVie, Bluejays, Gilead, Janssen, GSK, Roche, VIR Roche: Consultant, Bluejays: Consultant, Gilead: Consultant, Janssen: Consultant, GSK: Consultant, Roche: Consultant, VIR Biotechnology: Consultant, Altimmune, AbbVie, Gilead, Jannsen, GSK, Roche, VIR Bio: Grant/Research Support

4476 | LONG-TERM METABOLIC, PHENOTYPIC, AND NEUROPATHOLOGICAL CHARACTERIZATION OF THE *CYP27A1*$^{-/-}$ MOUSE MODEL OF CEREBROTENDINOUS XANTHOMATOSIS

Gloria Gonzalez-Aseguinolaza[1] LAIA Trigueros-Motos[1] Angie Molina[2] Guiomar Perez[2] Irene Marcilla-Garcia[2] Manuela Molina[2] Leire Neri Valencia[1] Daniel Moreno-Luqui[2] Anne Douar[1] Jean-Philippe Combal[1] Ana Garcia-Osta[2] Mar Cuadrado-Tejedor[2] Blanche Tamarit[1] Celine Bouquet[1] Gaetan Despres[3] Pranvera Krasniqi[3] Antonin Lamaziere[3] Ruben Hernandez-Alcoceba[2]

[1]Vivet Therapeutics, [2]CIMA, University of Navarra, [3]Sorbonne Université, Saint Antoine Research Center, INSERM

Background: Cerebrotendinous xanthomatosis (CTX) is caused by mutations in *CYP27A1* gene, encoding the mitochondrial sterol 27-hydroxylase enzyme involved in the bile acid synthesis pathway. *CYP27A1* deficiency results in the reduction of bile acid production and a dramatic decrease in 27-hydroxycholesterol, whereas some toxic precursors accumulate in the blood and some organs, especially the eyes, tendons and brain. As a consequence, CTX patients present cataracts, tendon and brain xanthomas, premature atherosclerosis, and progressive neurological damage including mental retardation, dementia, ataxia, seizures, and peripheral neuropathy. It has been reported that *Cyp27a1*$^{-/-}$ mice present milder accumulation of toxic metabolites and virtually no symptoms of the disease. To fully characterize this model, a long-term evaluation of the *Cyp27a1*$^{-/-}$ mice was conducted. **Methods:** B6.129-*Cyp27a1*$^{tm1El\ t}$/J mice were obtained from The Jackson Laboratory (Ref. 009106) and a full metabolic, phenotypic, histological and neuropathological characterization of the mouse model was performed up to 18 months of age. **Results:** *Cyp27a1*$^{-/-}$ mice had hepatomegaly, increased expression of *Cyp7a1* and *Cyp3a11* and increased levels of plasma ALT compared to their WT littermates, as previously reported in the literature. After 6 months of age, *Cyp27a1*$^{-/-}$ mice also presented lower body weight gain and steatosis. Toxic bile acid precursors were elevated in circulation and in the brain of *Cyp27a1*$^{-/-}$ mice. Despite most behavioral tests showed no alterations, *Cyp27a1*$^{-/-}$ mice presented signs of ataxia, especially in females. **Conclusion:** To our knowledge, this is the first study showing measurable motor alterations in the mouse model of CTX, similar to those described in CTX patients.

Disclosures: Gloria Gonzalez-Aseguinolaza: Vivet therapeutics: Executive role, Vivet therapeutics: Stock – privately held company, LAIA Trigueros-Motos: Nothing to Disclose, Angie Molina: Nothing to Disclose, Guiomar Perez: Nothing to Disclose, Irene Marcilla-Garcia: Nothing to Disclose, Manuela Molina: Nothing to Disclose, Leire Neri Valencia: Nothing to Disclose, Daniel Moreno-Luqui: Nothing to Disclose, Anne Douar: Vivet therapeutics:

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Employee, Jean-Philippe Combal: Nothing to Disclose, Ana Garcia-Osta: Nothing to Disclose, Mar Cuadrado-Tejedor: Nothing to Disclose, Blanche Tamarit: Vivet Therapeutics: Employee, Celine Bouquet: Vivet Therapeutics: Employee, Gaetan Despres: Nothing to Disclose, Pranvera Krasniqi: Nothing to Disclose, Antonin Lamaziere: Nothing to Disclose, Ruben Hernandez-Alcoceba: Nothing to Disclose

4477 | PAS-D GLOBULES ARE PROGNOSTIC OF LIVER DISEASE IN HETEROZYGOUS ALPHA-1 ANTITRYPSIN DEFICIENCY

George Marek[1] *Harmeet Malhi*[1]

[1]*Mayo Clinic Rochester*

Background: Alpha 1 Antitrypsin Deficiency (AATD) is a codominant genetic disease caused by mutations in the SERPINA1 gene. The most common disease associated homozygous variant PiZ causes intracellular aggregation and cirrhosis. Heterozygosity for the Z allele approaches up to 4%. AATD heterozygous alleles are disease modifiers; however, their exact significance and magnitude in liver disease progression is unclear. The classic feature of AATD in the liver is PAS-positive diastase-resistant globules. Our objective was to determine whether the presence of intracellular aggregates predicts progressive disease. **Methods:** We reviewed medical records for individuals tested for AATD who had liver biopsies at Mayo Clinic locations in Minnesota, Florida, and Arizona between 1/1/2000 and 9/1/2023. IRB approval was obtained prior to data abstraction. All pathology reports were reviewed to interpret the histology features. Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test were used as appropriate, Univariable linear regression and multivariable Cox proportional hazards model and Kaplan Meier curves were used to assess and visualize the effect of clinical variables on transplant-free survival. **Results:** Amongst 243 diagnostic biopsies for MZ individuals, 61(25%) had PAS-D globules. Age 60 (45-70) vs 49 (37-57) p = 0.002, male sex 40(57%) vs 63(36%) p=0.003 and fibrosis score were associated with globules in MZ individuals. 46(67%) of MZ individuals with globules had bridging or cirrhosis compared to 65(38%) without globules p<0.001. People with globules had reduced median transplant-free survival from the time of biopsy 279 days (85-1145) vs 1417(498-3131) p<0.001. Cox proportional hazards model was used to evaluate features associated with transplant-free survival. We found that absent PAS-D globules log(HR) 0.51, p=0.013, age log(HR) 1.02 p 0.048 and advanced fibrosis log(HR) 3.8 p <0.001 on initial biopsy were independent predictors of decreased transplant-free survival. **Conclusion:** Transplant-free survival is reduced in people who have globules on diagnostic biopsies and both age and sex and fibrosis are associated with their accumulation. Intracellular accumulation in MZ individuals on diagnostic biopsy may have prognostic significance. Further investigation is needed in heterozygous individuals to determine if baseline histology in early disease can be used to predict progression to cirrhosis and decompensated disease.

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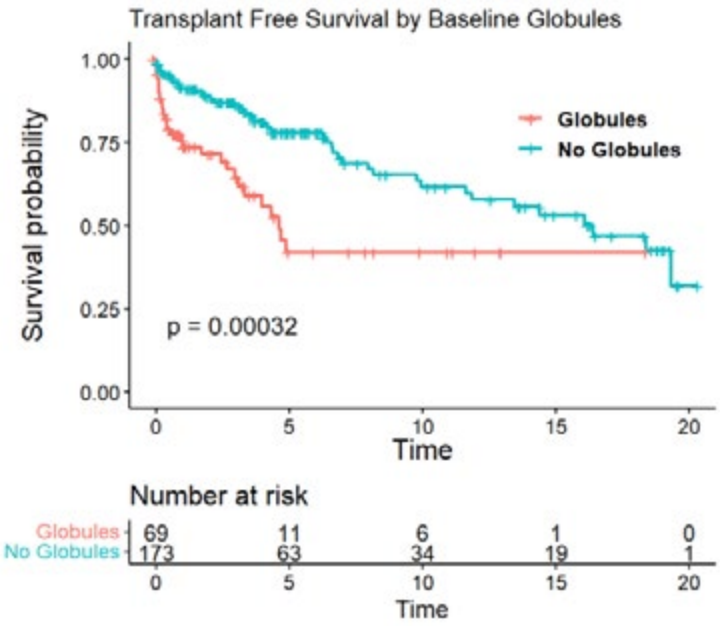

Figure 1: Kaplan Meier Curve illustrating transplant-free survival amongst individuals with PAS-D Globules on baseline biopsies compared to those without. p-value represents results from log-rank testing.

Disclosures: George Marek: Nothing to Disclose, Harmeet Malhi: Nothing to Disclose

4478 | PERFORMANCE OF NON-INVASIVE TESTS TO PREDICT THE RISK OF DEVELOPMENT OF HEPATIC EVENTS IN PATIENTS WITH ALPHA-1-ANTITRYPSIN PI*ZZ DEFICIENCY

Arvind Murali[1]

[1]*Orlando Health, University of Iowa Hospitals & Clinics*

Background: Patients with alpha-1-antitrypsin (AAT) Pi*ZZ are at risk for developing cirrhosis and hepatic decompensation. The clinical course of patients with AAT Pi*ZZ is highly variable and up to 40% of AAT Pi*ZZ patients may develop cirrhosis. The role of non invasive tests such as Fibrosis-4 index (Fib-4 index) and AST to platelet ratio index (APRI index) in predicting future hepatic events in AAT Pi*ZZ patients has not been clearly defined. We aimed to determine the ability of Fib-4 index and APRI index to predict hepatic events in patients with AAT Pi*ZZ. **Methods:** All AAT Pi*ZZ patients seen at a large tertiary care academic institution from 2005 to 2020 were identified. Demographic, clinical, and laboratory data were collected at the first encounter. Fib-4 index and APRI index were calculated. Hepatic events, if any, were recorded. Hepatic events were defined as the development of ascites, esophageal variceal bleed, hepatic encephalopathy, or hepatocellular carcinoma. Logistic regression analysis was utilized to determine the ability of Fib-4 index and APRI index in predicting hepatic events. Odds ratio (OR) and 95% confidence intervals (CI) were calculated. The area under the receiver operating curve was determined. **Results:** A total of 42 patients with AAT Pi*ZZ were included in the study. Mean age at the time of first encounter was 40 (19). Mean age at the time of last encounter was 54 (18). Median follow up was 9.5 (3-24) years. Males were 21 (50%). Of the 42 patients, 13 (31%) developed hepatic events. On logistic regression analysis, Fib-4 index was an independent significant predictor of hepatic events with an OR of 1.5 (1.1-2.0, p=0.01), with an AUROC of 0.85 (Figure 1). Similarly, APRI index was a significant predictor of hepatic events with an OR of 3.3 (1.4-8.0, p<0.01), with an AUROC of 0.88 (Figure 2). **Conclusion:** In patients with AAT Pi*ZZ, non invasive tests such as Fib-4 index and APRI index have an excellent discriminatory capacity to predict development of hepatic events. Fib-4 index and/or APRI index may be used as an initial screening test to identify patients at low risk for development of hepatic events. In our practice, we use a combination of Fib-4 index and transient elastography as the initial screening test to identify patients at risk for future hepatic events. Due to the unpredictable progression of liver disease in AAT Pi*ZZ patients, even patients with low Fib-4 or APRI index should be considered for annual monitoring. Further studies in a larger population are needed to confirm the ability of non invasive tests to accurately predict hepatic events in AAT patients.

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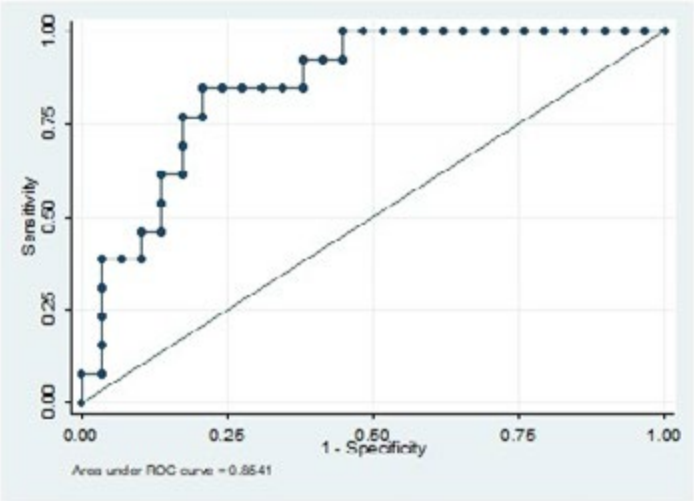

Figure 1: AUROC for Fibrosis-4 index to predict hepatic events in AAT Pi*ZZ patients

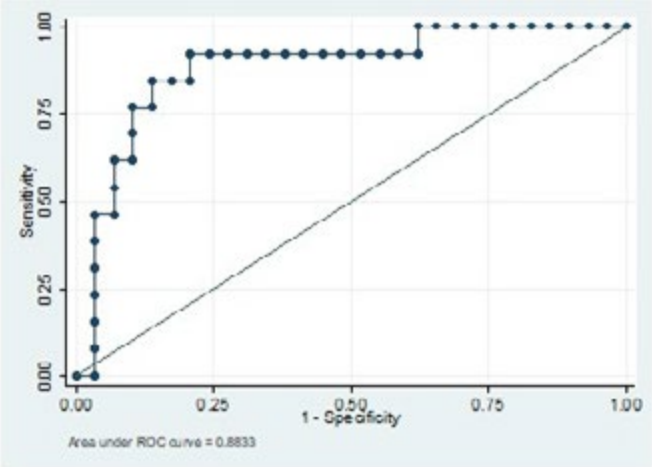

Figure 2: AUROC for APRI index to predict hepatic events in AAT Pi*ZZ patients

Disclosures: Arvind Murali: Nothing to Disclose

4479 | THE DUAL ROLE OF LET-7 MICRORNAS IN HEPATITIS C VIRUS-RELATED HEPATOCELLULAR CARCINOMA: A BIOMARKER FOR RISK STRATIFICATION AND A POTENTIAL THERAPEUTIC TARGET IN INFLAMMATION-DRIVEN CANCERS

Yuki Ichikawa[1] *Takahiro Fuji*[2] *Yumi Otoyama*[2] *Hitoshi Yoshida*[2]

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Background: Hepatitis C virus (HCV) infection is a major cause of hepatocellular carcinoma (HCC). Let-7 miRNAs, known as tumor suppressors, are downregulated in the serum of chronic hepatitis C patients with progressive fibrosis. However, the clinical implications of let-7 in HCV-related HCC and its potential as a biomarker and therapeutic target remain unclear. This study investigated the role of let-7 in HCV-related HCC using patient samples and cell lines. **Methods:** Serum let-7a levels were evaluated in 35 HCV patients with

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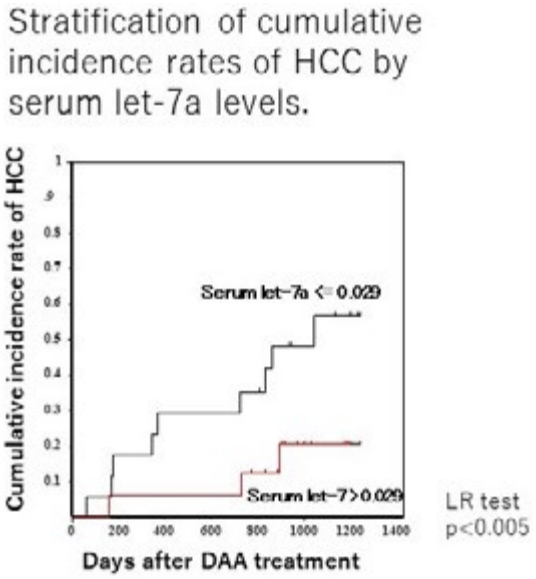
chronic hepatitis (CH) and liver cirrhosis (LC) who achieved sustained virological response. HCC development was monitored. In vitro, HCV core gene was expressed in hepatoma cells to assess let-7a/b expression, colony formation, and lenvatinib sensitivity. The effects of let-7a/b overexpression and inhibition were examined. The expression of cancer stem cell markers, apoptosis regulators, and drug transporters was analyzed. **Results:** Serum let-7a levels were significantly higher in LC than CH patients (p=0.02) and predicted HCC development with superior accuracy (AUROC=0.767). Patients with let-7a <0.01666 had a significantly higher cumulative incidence rate of HCC (p<0.005). In vitro, HCV core expression decreased let-7a/b levels, enhancing colony formation and reducing lenvatinib sensitivity, which was reversed by let-7a/b overexpression. Let-7 inhibition enhanced colony formation. The effects of let-7 were mediated by changes in CD44, BCL-xL, and ABCG2 expression. Further mechanistic investigations revealed that let-7 inhibition in hepatoma cells upregulated LIN28B and c-MYC, suggesting their involvement in the enhanced cancer phenotypes, while the roles of Bcl-xL and ABCG2 were less evident. **Conclusion:** Our study demonstrates that serum let-7a can serve as a predictive biomarker for HCC development in chronic HCV infection, highlighting its potential for non-invasive HCC risk stratification. We also show that HCV core protein downregulates let-7a/b expression in hepatoma cells, promoting cancer phenotypes and lenvatinib resistance, which can be reversed by let-7a/b overexpression. The mechanisms may involve modulation of cancer stem cell properties, apoptosis, and drug transporters. These findings provide insights into HCV-related HCC pathogenesis and suggest let-7 as a potential diagnostic and therapeutic target. Our study also provides a framework for investigating let-7 in various inflammatory contexts and its potential as a biomarker and therapeutic target in a wider range of malignancies.



Disclosures: Yuki Ichikawa: Nothing to Disclose, Takahiro Fuji: Nothing to Disclose, Yumi Otoyama: Nothing to Disclose, Hitoshi Yoshida: Nothing to Disclose

4480 | NOVEL COMBINATION APPROACHES TO THE COMPREHENSIVE GENOME PROFILING AND ICI-COMBINED CHEMOTHERAPY FOR ADVANCED INTRAHEPATIC CHOLANGIOCARCINOMA

Hiroki Inada[1] Hideaki Miyamoto[1] Satoshi Narahara[1] Hisanobu Oda[2] Motohiro Yoshinari[1] Hirohisa Okabe[1] Hiromitsu Hayashi[1] Yasuhito Tanaka[1]

[1]Kumamoto University, [2]Saiseikai Kumamoto Hospital

Background: In intrahepatic cholangiocarcinoma, precision medicine has been developed using comprehensive genomic profiling (CGP) tests, such as pemigatinib and futibatinib for FGFR2 fusion gene and ivosidenib for IDH1 mutation. More recently, immune checkpoint inhibitors have also become available for advanced intrahepatic cholangiocarcinoma. **Methods:** We performed a retrospective, multicenter, observation cohort study and analyzed 46 cases of intrahepatic cholangiocarcinoma treated with CGP at our institutions from June 2019 to September

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2023. **Results:** The median age was 69 years. There were 31 men and 15 women. Blood samples were used in 4 cases and tissue in 42 cases. Recommendations for genomically matched therapy (GMT) were given in 34 cases (74%). KRAS (15%) and FGFR2 (15%), followed by CDKN2A/B (11%), IDH1 (4%), MDM2 (4%) and MTAP (4%) were the most common druggable genes in this study. Median OS for the overall ICC was 10.6 months (95%CI 7.6-23.8). 10 patients (22%) could received GMT. The GMT group had a significantly longer prognosis than the non-GMT group (n=10; not reached [95% CI 12.2 - not reached] vs n=36; 8.5 months [95% CI 5.7-18.2]; P value=0.0073). 11 patients were treated with the combination of durvalumab + gemcitabine + cisplatin therapy. All of these patients had druggable mutations. The group with CDKN2A mutation, as known poor prognostic factor in BTC, showed a similar response with no significant difference in OS compared to the group without mutation. Three of the six patients who completed PD received second-line treatment, and one patient was started on a clinical trial based on the APC gene mutation. **Conclusion:** Precision medicine for ICC has dramatically improved prognosis. In addition, CGP is expected to be highly useful as a prognostic predictor of ICI therapy for ICC.

Disclosures: Hiroki Inada: Nothing to Disclose, Hideaki Miyamoto: Nothing to Disclose, Satoshi Narahara: Nothing to Disclose, Hisanobu Oda: Nothing to Disclose, Motohiro Yoshinari: Nothing to Disclose, Hirohisa Okabe: Nothing to Disclose, Hiromitsu Hayashi: Nothing to Disclose, Yasuhito Tanaka: Nothing to Disclose

4481 | LIPID DROPLET MORPHOLOGY JUSTIFIES DISCORDANCES BETWEEN HEPATIC STEATOSIS GRADES AND MRI PROTON DENSITY FAT FRACTION

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Background: Magnetic Resonance Imaging (MRI)-Proton Density Fat Fraction (PDFF) is considered the best non-invasive test for quantification of liver fat. PDFF is expressed as a percentage, representing a different metric than histologic-based grading. Differences between histological steatosis and MRI-PDFF in terms of absolute value have been reported. This study aimed at understanding these differences by evaluating the morphology of lipid droplets (LD). **Methods:** Prospective and multicenter study including chronic liver disease patients with paired liver biopsy and MRI between 2017 and 2024. Histologic samples were evaluated with conventional microscope and digital image analysis. Pathologists evaluation graded steatosis (S0-3) and determined the presence of microsteatosis, using the NASH Clinical Research Network score system. Digital pathology allowed the quantification of total fat proportionate area (FPA), macrovesicular or large LD (occupies greater than one-half of the hepatocyte), small LD (occupies less than one-half of the hepatocyte), and microvesicular steatosis. MRI was graded using the following PDFF cut-offs: S1≥5.75%, S2≥15.5%, and S3≥21.35%. Discordance between steatosis grade derived from histology *vs*. MRI-PDFF was defined as ≥1 grade difference. **Results:** The study included n=355 patients (59% women, 54±12 years) with a mean PDFF of 9.8±5.3%. Main liver disease aetiology was MASLD (63%), followed by autoimmune hepatitis (24%). The distribution of histology-determined steatosis was n=169 with S0, n=69 with S1, n=52 with S2, and n=65 with S3. The distribution of PDFF-determined steatosis was n=89 with S0, n=210 with S1, n=35 with S2, and n=21 with S3. Discordance rate between histology and MRI-PDFF was 50% (n=178), of whom only 21 cases had a disagreement of ≥2 grade difference (Figure 1). Among histology-determined steatosis grades S0-1, discordant cases had a higher content of microvesicular steatosis (P=0.004) and small LD (P=0.010), as quantified with digital pathology. In these cases, if pathologists determined that microsteatosis was present, PDFF showed significant higher values (6.1±1.7% *vs*. 9.4±3.1%, P<0.001). Among histology-determined steatosis grades S2-3, discordant cases had a lower content of large LD (P<0.001) and FPA (P<0.001), as quantified with digital pathology. A strong correlation was seen between FPA and MRI-PDFF (r=0.89 and *r*=0.84; P<0.001). Strength of linearity was R^2=0.80, indicating that 80% of the variation in FPA values is explained by MRI-PDFF. **Conclusion:** Disagreement between steatosis grades determined by histology and MRI-PDFF is frequent. In the lower grades, differences are due to microsteatosis and small LD, two components that are not considered by the pathologists scoring system. In the upper grades, differences are due

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to large LD and the total fat proportionate area (FPA) that is overestimated by pathologists' "eyeball" assessment. MRI-PDFF shows a high correlation with with digital image-analysis acquired FPA.



Disclosures: David Marti-Aguado: Nothing to Disclose, Martias Fernandez-Paton: Nothing to Disclose, Clara Alfaro-Cervello: Nothing to Disclose, Alba Sanchez-Martin: Nothing to Disclose, Amadeo Ten-Esteve: Nothing to Disclose, Ana Crespo: Nothing to Disclose, Irene Navarrete-Pérez: Nothing to Disclose, Maria Pilar Rios: Nothing to Disclose, Esther Alvarez-Vilanova: Nothing to Disclose, Monica Espino-Mongort: Nothing to Disclose, Cristina Mongort: Nothing to Disclose, Pilar Aguilar: Nothing to Disclose, Sonia Chimeno Hernandez: Nothing to Disclose, Alexandre Perez-Girbes: Nothing to Disclose, Ana Jimenez-Pastor: Nothing to Disclose, Cristina Montón: Nothing to Disclose, Judith Perez-Rojas: Nothing to Disclose, Victor Puglia: Nothing to Disclose, Victoria Aguilera: Nothing to Disclose, M Desamparados Escudero: Nothing to Disclose, Salvador Benlloch: Nothing to Disclose, Angel Alberich-Bayarri: Nothing to Disclose, Luis Marti-Bonmati: Nothing to Disclose

4482 | PNPLA3 P.I148M VARIANT AFFECTS LIPID DROPLETS NUMBER AND SIZE IN PATIENT-DERIVED LIVER ORGANOIDS

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Background: PNPLA3 rs738409 C>G p.I148M variant is the main genetic determinant of metabolic dysfunction-associated steatotic liver disease (MASLD). To this day, this association lacks a molecular characterization, due to the lack of comprehensive human models. To overcome this gap in knowledge, we generated patient-derived human liver organoids (HLOs) and studied lipid accumulation across different PNPLA3 genotypes. **Methods:** We generated HLOs from 74 surgical specimens (28 I/I, 32 I/M and 14 M/M for PNPLA3 p.I148M). HLOs were differentiated toward a hepatocyte-like phenotype (Hep-HLO) and exposed to 300 µM Palmitic and Oleic fatty acids (FAs) for 72h. Lipid droplets (LDs) average size and number were quantified by NileRed staining and compared between PNPLA3 Hep-HLOs (n=5 for each genotype). Lipidomics were conducted on 3 wild-type and 3 homozygous Hep-HLO lines, treated or not with FAs for 3 days. **Results:** Untreated organoids displayed LDs average sizes of 0.51±0.28 µm^2 (I/I), 0.48±0.22 µm^2 (I/M) and 1.10±1.09 µm^2 (M/M). While FAs did not impact on average LD size, M/M Hep-HLOs displayed larger LDs (p=0.0106 of I/I vs M/M, p=0.0028 for I/M vs MM). Conversely, LDs number were 7.28±5.35, 19.17±12.58 and 44.35±29.60 in I/I, I/M, M/M respectively, and increased to 14.65±8.86, 44.01±30.27 and 60.67±45.11 upon exposure to FAs. After ANOVA testing, 27.16%

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of variability in LDs number can be attributed to genotype and 6.32% to FAs ($p<0.0001$ for both). Lipidomic analyses highlighted an enrichment of sphyngomyelins, lysophosphatidylcholines and ceramides in PNPLA3 M/M Hep-HLO, which was exacerbated by FAs administration. These lipid species are associated with cellular damage, inflammation, Insulin resistance, oxidative stress and MASH development. The opposite trend was observed for phosphatidylcholines, which are essential for LDL loading and triacylglycerols export from the liver and whose levels drop during MASLD development. **Conclusion:** Regardless of FA treatment, M/M Hep-HLOs show increased LDs size when compared to I/M and I/I. Conversely, LDs number showed direct correlation with the number of mutated alleles, suggesting that the p.I148M substitution promotes the formation of new LDs, which was exacerbated by exposure to FAs. Lipidomic analyses highlight an unbalance towards proinflammatory and pro-apoptotic species in M/M Hep-HLOs. Overall, these data corroborate the robustness of Hep-HLO as a preclinical in vitro model for genetic predisposition for MASLD.

Disclosures: Elia Casirati: Nothing to Disclose, Alessandro Cherubini: Nothing to Disclose, Laura Creami: Nothing to Disclose, Fabrizia Carli: Nothing to Disclose, Amalia Gastaldelli: Nothing to Disclose, Daniele Prati: Nothing to Disclose, Daniele Dondossola: Nothing to Disclose, Luca Valenti: Nothing to Disclose

4483 | *IN VIVO* EXPANSION OF GENE-TARGETED HEPATOCYTES THROUGH TRANSIENT INHIBITION OF AN ESSENTIAL GENE

Marco De Giorgi[1] So Hyun Park[2] Adam Castoreno[3] Mingming Cao[2] Ayrea Hurley[1] Lavanya Saxena[2] Marcel Chuecos[1] Christopher Walkey[1] Alexandria Doerfler[1] Mia Furgurson[1] Cecilia Ljungberg[1] Kalyani Patel[4] Sarah Hyde[3] Tyler Chickering[3] Stephanie Lefebvre[3] Kelly Wassarman[3] Patrick Miller[5] June Qin[3] Mark Schlegel[3] Ivan Zlatev[3] Rich Gang Li[1] Jong Kim[1] James Martin[1] Karl-Dimiter Bissig[6] Vasant Jadhav[3] Gang Bao[2] William Lagor[1]

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Background: Homology Directed Repair (HDR)-based genome editing is an approach that could permanently correct a broad range of genetic diseases. However, its utility is limited by inefficient and imprecise DNA repair mechanisms in terminally differentiated tissues. For example, HDR requires cell division, generally limiting targeting of adult liver to ~1% of hepatocytes. The goal of this work is to develop a system for selective expansion of gene-targeted hepatocytes using essential genes, which we call "Repair Drive". Repair Drive consists of (1) transient conditioning of the liver by knocking down an essential gene - Fumarylacetoacetate hydrolase (*Fah*), which is important for tyrosine catabolism, and (2) delivery of an untargetable version of the essential gene in *cis* with the therapeutic transgene. **Methods:** We used Adeno-Associated Virus (AAV) vectors to insert *FAH* in tandem with a fluorescent marker (TdTomato) or the therapeutic transgene Factor IX (*FIX*) - deficient in Hemophilia B patients - into a highly expressed locus in the liver (*Apoa1*). Mice were injected with AAVs encoding CRISPR/Cas9 (AAV-CRISPR) and a Donor template (AAV-Donor) with *FAH* and TdTomato or *FIX*. Monthly injections of small interfering RNA (siRNA) targeting murine *Fah* were used as a conditioning agent to deplete untargeted hepatocytes and drive expansion of correctly repaired cells. **Results:** Three months later, mice receiving the siRNA - Repair Drive mice - showed a dramatic increase in the number of TdTomato positive hepatocytes, versus those receiving the AAVs alone – Unselected mice (~10% vs 0.5%). Selective expansion could be further improved to >25% of hepatocytes by manipulation of tyrosine catabolism with a high protein diet. To evaluate the translatability and long-term safety of this approach, we expanded *FIX*-targeted hepatocytes with Repair Drive, and we followed the mice for 1 year. Repair Drive mice showed sustained FIX expression with a ~5-fold increase as compared to Unselected mice. Liver conditioning caused only a transient elevation of ALT at early time points, which fully resolved over time. Histology revealed no evidence of liver toxicity and full reconstitution of Fah expression. Importantly, Repair Drive did not increase the risk of tumorigenesis. Sequencing analyses revealed dramatic increase of HDR-integration of the Donor cassette at the *Apoa1* locus in Repair Drive mice. **Conclusion:** Overall, these data show a novel strategy for selectively expanding targeted hepatocytes for liver gene therapy.

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Lefebvre: Nothing to Disclose, Kelly Wassarman: Nothing to Disclose, Patrick Miller: Nothing to Disclose, June Qin: Nothing to Disclose, Mark Schlegel: Alnylam Pharmaceuticals: Employee, Ivan Zlatev: Nothing to Disclose, Rich Gang Li: Nothing to Disclose, Jong Kim: Nothing to Disclose, James Martin: Nothing to Disclose, Karl-Dimiter Bissig: Nothing to Disclose, Vasant Jadhav: Nothing to Disclose, Gang Bao: Nothing to Disclose, William Lagor: Alnylam Pharmaceuticals: Receive research reagents as part of a collaboration

4484 | HIGH INHERITED RISK BY POLYGENIC SCORE MORE THAN DOUBLES AGE-ASSOCIATED INCREASES IN FIBROSIS IN MID-LIFE IN PATIENTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD)

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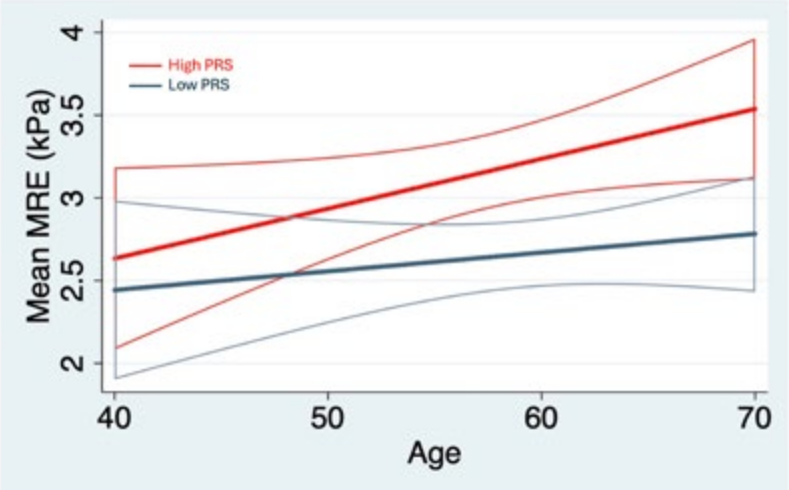
Background: Despite longstanding knowledge of the importance of certain genetic variants as key drivers of risk for MASLD, they have not been incorporated into clinical practice due to limited granular data on their impact in cohorts with advanced continuous biomarkers of disease severity. We hypothesized that a high polygenic risk score (PRS) would be associated with accelerated fibrosis progression per decade in middle-age on magnetic resonance elastography (MRE). **Methods:** This cross-sectional study included prospectively recruited middle-aged adults (age 40-70) who underwent a standardized clinical research visit with magnetic resonance imaging proton-density-fat-fraction (MRI-PDFF), MRE, and genotyping for *PNPLA3* (rs738409) and *HSD17B13* (rs72613567). MASLD was defined per updated AASLD guidance. The primary outcome was liver stiffness on MRE evaluated per 10-year increase in age on linear regression. The effect of a simple PRS, which was the sum of the established I148M risk variant in *PNPLA3* minus the protective inactivating variant in *HSD17B13,* on MRE per 10-year increase in age was evaluated. **Results:** Of 401 included patients, the mean (±SD) age and BMI were 58 (± 7.8) years and 31.4 (± 5.5) kg/m^2, respectively. The cohort was 59% female, 39% Hispanic and 70% had type 2 diabetes mellitus. *PNPLA3* genotype was C/C in 35%, C/G in 42% and G/G in 23%. *HSD17B13* genotype was T/T in 67%, T/TA in 30% and TA/TA in 3% and 51% of patients had an elevated PRS of 1 or 2. Mean MRE (±SD) values were 2.89 (±1.45) kPa. Linear regression analysis demonstrated a strong association between high dichotomized PRS and increased liver stiffness ß = 0.50 kPa, (95% CI: 0.19-0.81, P<0.01) that remained consistent in analysis adjusted for Hispanic ethnicity ß = 0.49 kPa, (95% CI: 0.18-0.81, P<0.01). Among patients with high PRS, there was significantly higher liver stiffness for each 10-year increase in age ß = 0.30 kPa, (95% CI: 0.01-0.59, P=0.04). However, among patients with low PRS, there was not a significant increase in liver stiffness for each 10-year increase in age ß = 0.11 kPa, (95% CI: -0.15-0.38, P=0.39). Average MRE values with 95% CI were similar at age 40 but diverged substantially based on PRS over the ensuing three decades (Figure). **Conclusion:** In a well-characterized cohort of MASLD patients, a simple polygenic risk score amplified the increase in fibrosis on MRE per 10-year interval in mid-life by almost three-fold. This data supports clinical assessment of genetic risk in MASLD patients to identify high-risk patients who may benefit from more frequent monitoring or earlier disease-modifying treatment.



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4485 | ASSOCIATION OF GENETIC ALTERATIONS WITH TREATMENT EFFICACY OF SYSTEMIC THERAPY FOR UNRESECTABLE HEPATOCELLULAR CARCINOMA: ANALYSIS WITH NATIONAL GENOMIC DATABASE IN JAPAN

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[1]*The University of Tokyo*

Background: In hepatocellular carcinoma (HCC), the relationship between therapeutic response to systemic therapy and genetic alterations involving cell cycle, TERT promoter, WNT pathway, RAS/PI3K pathway, and chromatin modifiers remains unknown. Using data from the Japanese Center for Cancer Genomics and Advanced Therapeutics (C-CAT), this study aims to investigate the association between driver gene alterations/tumor mutation burden (TMB) and time to treatment failure (TTF) for systemic therapy in patients with unresectable HCC. **Methods:** From August 2019 to March 2023, 303 HCC cases were registered in C-CAT. Among them, 187 cases with available clinical information and consent for secondary use were analyzed. The impact of clinical features, TMB, and the presence of genetic alterations in *TP53*, *TERT*, *CTNNB1*, *PTEN*, and *ARID1A* on TTF for systemic therapy was investigated. The risk factors contributing to shorten TTF were assessed using Cox proportional hazard regression analysis. **Results:** The treatment regimens were atezolizumab plus bevacizumab (Atezo+Bev) in 117 cases (51 cases for first-line treatment), lenvatinib (LEN) in 141 cases (85 cases for first line), and sorafenib (SOR) in 74 cases (27 cases for first-line). Among 187 cases, *TP53* alterations were found in 84 cases (44.9%), *TERT* alterations in 81 cases (43.3%), *CTNNB1* alterations in 54 cases (28.9%), *PTEN* alterations in 12 cases (6.4%), *ARID1A* alterations in 36 cases (19.3%) and TMB high in 19 cases (10.2%). Multivariate analyses revealed that *ARID1A* alterations were an independent risk factor for shorter TTF, with an adjusted hazard ratio (aHR) of 1.80 (95% confidence interval [CI] 1.12-2.90) in Atezo+Bev, 1.67 (95% CI 1.06-2.64) in LEN, and 1.98 (95% CI 1.02-3.82) in SOR. *PTEN* alterations were an independent risk in SOR, with an aHR of 3.31 (95% CI 1.33-8.21). Later treatment line was an independent risk, with an aHR of 1.56 (95% CI 1.00-2.42) in LEN and 5.07 (95% CI 2.65-9.72) in SOR. High TMB was not significantly associated with TTF in any treatment group. **Conclusion:** *ARID1A* alterations were associated with poor TTF in patients treated with Atezo+Bev, LEN, and SOR, while *PTEN* alterations contributed to worse TTF in SOR. Later treatment line was related to poor TTF in LEN and SOR. Further study is needed to validate these results.

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4486 | STEATOTIC LIVER DISEASE IN LEAN PATIENTS IS ASSOCIATED WITH DIABETES, BUT NOT *PNPLA3*

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Background: Steatosis is the accumulation of fat in the liver and is common in people who are obese and have the metabolic syndrome. The I148M variant in patatin-like phospholipase domain-containing 3 (*PNPLA3*) is the genetic variant mostly strongly associated with steatosis in the general population. However, it is not clear whether lean patients have the same genetic or clinical risk factors for steatosis as non-lean patients. We investigated whether steatotic liver disease in lean patients is associated with the *PNPLA3* polymorphism or other genetic or clinical factors. **Methods:** We identified lean cases (BMI< 25 kg/m²) and non-lean cases (BMI> 25 kg/m²) with steatotic liver disease through an ICD code search of the Mayo Clinic Biobank, a biorepository of 50,000 patients. We confirmed steatosis by reviewing imaging and pathology reports. We matched each case with 3 controls from the same population based on sex, age, and BMI. We obtained the germline genotypes for single nucleotide polymorphisms (SNPs) in *PNPLA3* and *TM6SF2* and extracted demographic and clinical data from the medical records. After identifying lean cases and lean controls, we performed a power analysis to determine if the sample size was sufficient to detect a clinically significant relative risk difference of > 2 in *PNPLA3*. We conducted a conditional logistic regression analysis of *PNPLA3* and other factors associated with steatotic liver disease. **Results:** We identified 109 lean and 3,090 non-lean cases with steatosis, and 302 lean and 9,322 non-lean matched controls without steatosis from the Mayo Clinic biobank. The power analysis suggested that we had a sufficient sample size to detect an odds ratio for PNPLA3 of 2 with 80% power and an alpha of 0.05. In the lean group, carriage of the G allele in the *PNPLA3* variant was not associated with an increased risk of steatotic liver disease (OR 1.04, 95% CI 0.62-1.75, p-value 0.86). Among other genetic and clinical parameters, diabetes was the only independent risk factor for steatosis in lean patients, with an odds ratio of 2.18 (95% CI 1.08-4.37, p-value 0.02). In contrast to lean patients, non-lean patients had significantly increased odd ratios for all of the metabolic and genetic parameters (Table 1). **Conclusion:** The I148M variant in *PNPLA3* is not associated with an increased risk of steatotic liver disease in lean patients. However, diabetes increases the risk of steatotic liver disease in lean patients by more than two-fold. Steatotic liver disease in lean patients may have distinct genetic and clinical risk factors.

Variables	Lean (N=411)			Non-lean (N=12,412)		
	OR	CI95%	p-value	OR	CI95%	p-value
Coronary disease	1.32	0.72-2.39	0.36	1.45	1.31-1.61	**<0.001**
Renal disease	1.04	0.51-2.12	0.90	1.13	1.02-1.26	**0.01**
Dyslipidemia	1.32	0.70-2.50	0.37	1.43	1.26-1.64	**<0.001**
Diabetes mellitus	2.18	1.08-4.37	**0.02**	2.21	2.01-2.43	**<0.001**
Hypertension	1.12	0.63-1.96	0.69	1.50	1.35-1.66	**<0.001**
TM6SF2						
CT	1.08	0.52-2.24	0.83	1.29	1.15-1.46	**<0.001**
TT	2.10	0.10-41.72	0.62	2.21	1.34-3.62	**<0.001**
PNPLA3						
GC	1.04	0.62-1.75	0.86	1.34	1.22-1.46	**<0.001**
GG	1.17	0.40-3.40	0.76	2.57	2.17-3.05	**<0.001**

Disclosures: Angela Sato Espinoza: Nothing to Disclose, Perapa Chotiprasidhi: Nothing to Disclose, Kirk Wangensteen: Nothing to Disclose

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4487 | INTEGRATION OF BULK RNA-SEQ AND SCRNA-SEQ REVEALS MOLECULAR MECHANISMS AND TUMOR MICROENVIRONMENT BEHIND DIFFERENCES IN CLINICOPATHOLOGIC CHARACTERISTICS OF HEPATOCELLULAR CARCINOMA PATIENTS WITH DIFFERENT TUMOR MARKER COMBINATIONS ◆

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Background: Efficient biomarkers are needed to guide precision therapy to improve hepatocellular carcinoma (HCC) patients' prognosis and 5-year survival. **Methods:** The medical data of HCC patients undergoing hepatectomy from two Chinese hepatobiliary centers were collected and compared. Based on whether alpha-fetoprotein (AFP) and des-γ-carboxy prothrombin (DCP) were preoperative positive (≥ 10 ng/mL and ≥ 40 mAu/mL), patients were divided into four groups: G1 (AFP- DCP-), G2 (AFP+ DCP-), G3 (AFP- DCP+), and G4 (AFP+ DCP+). Bulk RNA-Seq was performed on twelve HCC tissues (three in each group), and scRNA-Seq was performed on four HCC tissues (one in each group) and one normal liver tissue. **Results:** This study included 720 eligible HCC patients. Among them were 93 patients (12.9%) in the G1, 87 (12.1%) in the G2, 185 (25.7%) in the G3, and 355 (49.3%) in the G4. The four groups of patients had significantly different clinicopathologic phenotypes. For instance, G4 patients were characterized by worse HCC differentiation, larger tumor sizes, more tumor numbers, as well as higher probability of occurring micro- and macro-vascular invasion and satellite nodules. Moreover, states of hepatic function, inflammation, and fibrosis differed between groups. Bulk RNA-Seq and scRNA-Seq analyses revealed four distinct epithelial cell states. In the G1, metabolic and coagulation pathways were upregulated, while proliferation capacity was low. G2 exhibited high differentiation potential, with upregulated Wnt and Notch pathways. G3 showed intense immune activity and was enriched in type II IFN response and checkpoint pathways. G4 represented a highly proliferative and aggressive phenotype, with uncontrolled cell cycle, abnormal cell adhesion, epithelial-mesenchymal transition (EMT), angiogenesis, and glycolysis strongly activated. Besides, G2 and G4 had higher copy number variation (CNV) scores. Epithelial cluster 5 in the G4, characterized by high SEMA6D expression, had the highest CNV score among all clusters. SEMA6D+ epithelial cells, associated with poor prognosis in HCC, displayed both the malignant phenotype of the G4 and the differentiation phenotype of the G2. Furthermore, IGHM+ macrophages and fibroblasts were identified in the G4, both overexpressing immunoglobulin family genes, such as IGHM, IGHG1, and IGKC. These two cell clusters potentially played vital roles in oxidative phosphorylation and endothelial-mesenchymal transformation, respectively. **Conclusion:** Our findings provided novel insights into different HCC subgroups' tumor microenvironments and suggested potential individualized therapy targets.

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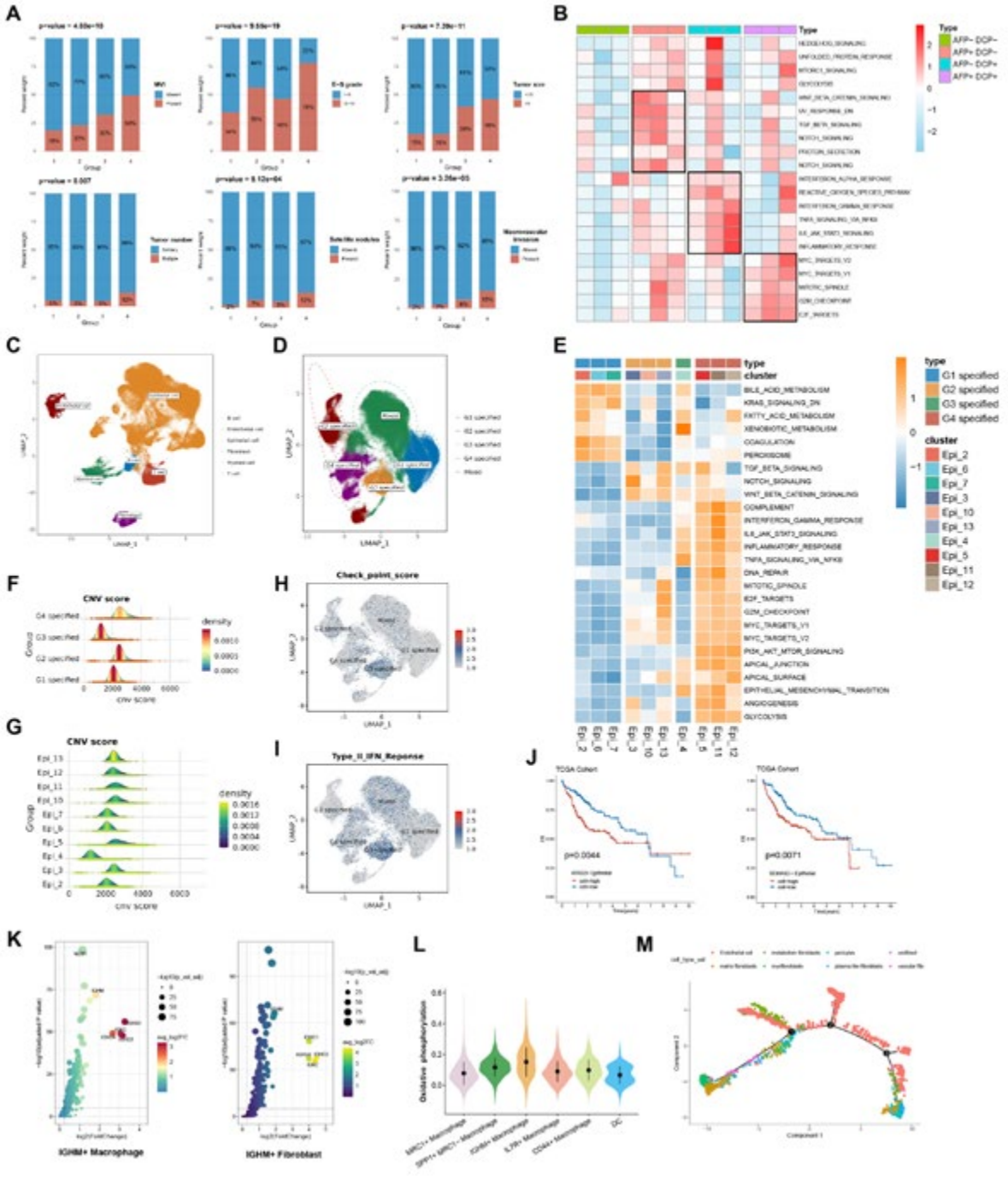

Disclosures: Zheyu Zhou: Nothing to Disclose, Jinsong Liu: Nothing to Disclose, Chaobo Chen: Nothing to Disclose, Shuya Cao: Nothing to Disclose, Ke Wang: Nothing to Disclose, Beicheng Sun: Nothing to Disclose, Xiaoliang Xu: Nothing to Disclose

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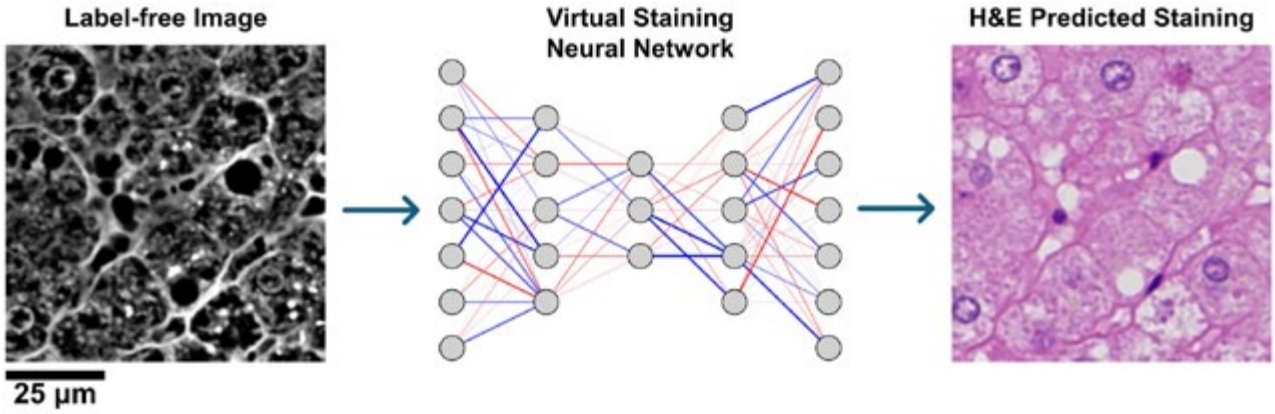
4488 | DEEP-LEARNING BASED VIRTUAL STAINING OF LIVER TISSUE SECTIONS

Davide Panzeri[1] Luca Di Tommaso[2] Donato Inverso[3] Laura Sironi[1]

[1]University of Milano-Bicocca, [2]IRCCS Humanitas Clinical and Research Center, [3]IRCCS San Raffaele Scientific Institute

Background: In standard clinical practice, tissue histology sections are processed and stained to be observed under the optical microscope. Recently, the development of new imaging systems has provided a fast way of digitizing entire tissue sections, allowing the development of novel AI-based algorithms for quantitative image analysis. However, staining procedures are time consuming, specimen-destructive and expensive. Here, to overcome these issues, we propose a virtual staining algorithm, able to predict an Hematoxylin/Eosin (H&E) image, starting from the autofluorescence signal of liver tissue sections acquired by a standard widefield microscope. Moreover, 3D H&E biopsy reconstructions were predicted by exploiting the autofluorescence signal primed by non-linear excitation microscopy. **Methods:** H&E and autofluorescence paired whole slide images (WSIs) of liver tissue sections were exploited to train a Generative Adversarial Network based on a Pix2Pix model. Original and predicted images were compared through the Structural Similarity Index Measure (SSIM). Additionally, to further evaluate the predicted images, we compared the position, intensity and textural features extracted by cell nuclei, segmented from both the original and the predicted stained images. **Results:** The virtual H&E-stained sections obtained through our pipeline were compared to the original images, achieving a SSIM of 0.77 ± 0.07. Following nuclei segmentation and feature extraction, a t-SNE embedding was successfully exploited to distinguish between hepatocytes and lymphocytes. The fraction of the two cell types were compared between the original and virtual H&E-stained WSIs, revealing no significant difference. Additionally, the distribution of the overall nuclear features showed comparable results between the original and predicted images. **Conclusion:** The developed workflow was able to provide virtually-stained images starting from their label-free auto-fluorescence signal, avoiding time consuming procedures both in clinical and research settings. Moreover, we demonstrated the possibility to generate virtual 3D H&E biopsies starting from their non-linear autofluorescence signal, enabling the access to novel 3D features for pathology characterization.



Disclosures: Davide Panzeri: Nothing to Disclose, Luca Di Tommaso: Nothing to Disclose, Donato Inverso: Nothing to Disclose, Laura Sironi: Nothing to Disclose

4489 | CAS9 3-BASE & PAM OFFSET (C3PO) DETECTION INCREASES DELETION EFFICIENCY TO HELP STUDY PNPLA3 MUTANT KNOCKOUTS IN HUH7 CELLS

Chinmay Raut[1] Rawdat Hussain[2] Akram Irshaid[2] Prabhu Ponnandy[2] Elizabeth Speliotes[3]

[1]University of Michgan Ann Arbor, [2]University of Michigan Ann Arbor, [3]University of Michigan Medical Center

Background: PNPLA3 I148M is associated with metabolic dysfunction-associated steatotic liver disease (MASLD) and metabolic dysfunction-associated steatohepatitis (MASH). I148M is proposed to be a gain of function mutation but recent studies in humans question this mechanism. Here we aim to determine the effects

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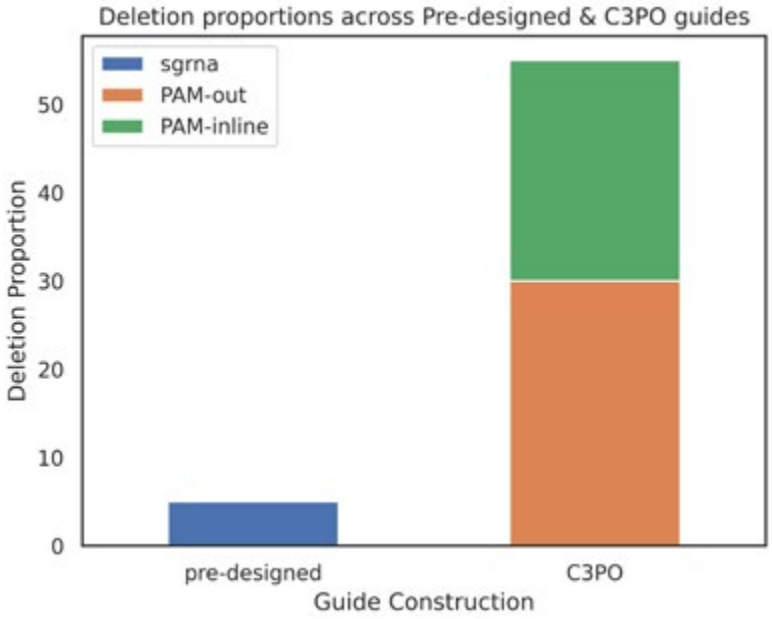
of knocking out PNPLA3 in a human Huh7 cell line that is homozygous for I148M. Study of PNPLA3 knockout in human cell-lines has proven difficult due to inefficient deletion using traditional Cas9 system protocols. Several factors, including distance between cut sites, protospacer adjacent motif (PAM) orientation, on-target and off-target efficiency, and optimal delivery methods, require further optimization to increase efficiency of deletions. **Methods:** We designed a new guide selection algorithm, Cas9 3-base & Pam Offset (C3PO), which considers guide pair attributes such as sequence deletion size, cut positions, PAM-orientation, and on/off target efficiency scores to recommend pairs of guides with user-defined deletion and orientation constraints. We applied this algorithm to design 3 guides targeting PNPLA3 in Huh7 cells to produce 3 different types of exonic cuts: PAM-out, PAM-in, and PAM-inline. We also produced a different set of 3 pre-designed guides using the multi-guide sgRNA protocol from Synthego. Huh-7 cells were then transfected using the Cas9-sgRNA complex and DNA was extracted using QuickExtract DNA Extraction. Sanger Sequencing was performed, and deletion proportions were obtained using the ICE tool. **Results:** Comparing our C3PO designed guides to Synthego pre-designed guides we observe a tenfold increase in deletions (5% deletion → 55% deletion). We observe that the PAM-out configuration from the C3PO guides had the highest proportion of deletions with over half of the deletions from the PAM-out pair of guides and no deletions from the PAM-in configuration. **Conclusion:** C3PO guide design increases deletion efficiency for PNPLA3 in Huh7 cells by tenfold. C3PO increases our ability to efficiently produce cell-line knockouts to empower functional studies of PNPLA3 in MASLD.



Disclosures: Chinmay Raut: Nothing to Disclose, Rawdat Hussain: Nothing to Disclose, Akram Irshaid: Nothing to Disclose, Prabhu Ponnandy: Nothing to Disclose, Elizabeth Speliotes: Nothing to Disclose

4490 | GENOME-WIDE CRISPR KNOCKOUT GENETIC SCREEN IN LIVER CELL LINES TO IDENTIFY GENES AFFECTING HEPATIC STEATOSIS.

Prabhu Ponnandy[1] *Chinmay Raut*[1] *Rawdat Hussain*[1] *Akram Irshaid*[1] *Brian Halligan*[2] *Elizabeth Speliotes*[2]

[1]*Division of Gastroenterology and Hepatology, Department of Internal Medicine, University of Michigan,* [2]*University of Michigan Medical Center*

Background: MASLD affects~30% of the adult population worldwide, with its prevalence increasing from 22% to 37% from 1991 to 2019. MASLD is heritable and we previously identified 17 genetic loci that associate with MASLD. In the present study, we perform a genome wide CRISPR/cas9 deletion screen on human liver cell lines to identify genes that regulate hepatic steatosis. **Methods:** We carried out a genome-wide knockout screen using the GeCKOv2 library in human Huh7 and HepG2 cells. For three biological replicates we transduced ~45 million cells with MOI of 0.3 and passaged cells for 14 days. We then stained cells with Lipitox and sorted them

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into top 10% and bottom 10% of lipid content. Genomic DNA was extracted and sequenced. Enrichment of guide sequences was determined using MAGeCK. The top 300 guides from top and bottom of lipid enrichment were re-screened using a custom library of 15 guides per gene in Huh-7 and HepG2 cells. **Results:** We identified 49 genes that influence lipid accumulation in liver cells. 29 genes increase lipid accumulation and 20 decreased lipid accumulation. Genes identified that increase lipid accumulation include PNPLA2 which functions to release lipids from lipid droplets. Genes identified that reduce lipid accumulation include DGAT2 which functions in de novo lipogenesis. Other genes include TM6SF2 which affects VLDL formation and like PNPLA2 is a GWAS identified putative target gene. **Conclusion:** We carried out an unbiased genome wide screen in human liver cell lines that identified multiple positive and negative regulators of hepatic steatosis. This confirms that affecting lipid droplet biology, de novo lipogenesis and VLDL formation can affect fatty liver disease. It also identifies many new candidate genes that affect steatosis that are future targets for MASLD therapy.

Disclosures: Prabhu Ponnandy: Nothing to Disclose, Chinmay Raut: Nothing to Disclose, Rawdat Hussain: Nothing to Disclose, Akram Irshaid: Nothing to Disclose, Brian Halligan: Nothing to Disclose, Elizabeth Speliotes: Nothing to Disclose

4491 | METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE ASSOCIATED ALLELE *GCKR* (P446L) PROMOTES FGF21 SECRETION VIA UP-REGULATING TRANSCRIPTION FACTOR CHREBP IN HUH-7 CELL LINE

Yue Chen[1] Rawdat Hussain[1] Jason Chen[2] Antonio Oliveri[1] Brian Halligan[1] Elizabeth Speliotes[1]

[1]University of Michigan Medical Center, [2]Judd A. and Marjorie Weinberg College of Arts and Sciences, Northwestern University

Background: MASLD is the leading cause of liver disease. Human GWA studies have identified a missense variant in *GCKR* gene (P446L, rs1260326) that promotes MASLD as well as hypertriglyceridemia while preventing diabetes but how this variant leads to these effects is not known. *GCKR* gene encodes glucokinase regulatory protein (GKRP) that is expressed in liver. GKRP inhibits glucokinase (GCK) to prevent glucose utilization in liver. In this study, we tested whether P446L variant affects intracellular triglyceride, glycogen, and protein expression for related to multiple metabolic processes as well as extracellular FGF21 levels in Huh-7 cells. **Methods:** Using lentiviral integration, we created stable Huh-7 cell lines with WT and P446L *GCKR* overexpressed or knockdown using shRNAs. We measured TG and glycogen using biochemical assays and lipid staining cell images analysis using CellProfiler. We measured GYS2, GCK, GKRP, ChREBP, FASN and ACC proteins using Western blot. We knockdown ChREBP in cells using MLXIPL siRNAs, then measured ChREBP mRNA and protein levels using qPCR and Western blot analyses respectively as well as extracellular FGF21 levels using ELISA. **Results:** GCKR P446L increased TG and glycogen in Huh-7 cells. Knockdown of *GCKR* increased glycogen content GCKR P446L significantly increased protein levels of GYS2, FASN, ACC and GCK. Knockdown *GCKR* significantly increased GYS2 levels. GCKR (P446L) significantly increased intracellular ChREBP protein levels and extracellular FGF21 protein levels. Knockdown of ChREBP expression by 80% significantly reduced FGF21 extracellular levels by 25%. **Conclusion:** GCKR P446L increased TG and glycogen accumulation suggesting a cell autonomous effect on TG and glycogen accumulation. GCKR P446L phenotypically mimics knockdown of GCKR in these assays suggesting that P446L mutation is a loss of function. At least one-way GCKR P446L increases TG in liver may be by increasing ChREBP, ACC and FASN protein levels to increase de novo lipogenesis. GCKR P446L may increase glycogen at 2mM glucose by up-regulating GYS2. GCKR P446L increased FGF21 protein extracellularly at low glucose. Reduction of ChREBP expression reduced extracellular FGF21 protein. These data suggest that GCKR P446L increases GCK activity which activates ChREBP and leads to up-regulation of FGF21. These results help explain how GCKR P446L causes liver damage and defines some of its extracellular effects.

Disclosures: Yue Chen: Nothing to Disclose, Rawdat Hussain: Nothing to Disclose, Jason Chen: Nothing to Disclose, Antonio Oliveri: Nothing to Disclose, Brian Halligan: Nothing to Disclose, Elizabeth Speliotes: Nothing to Disclose

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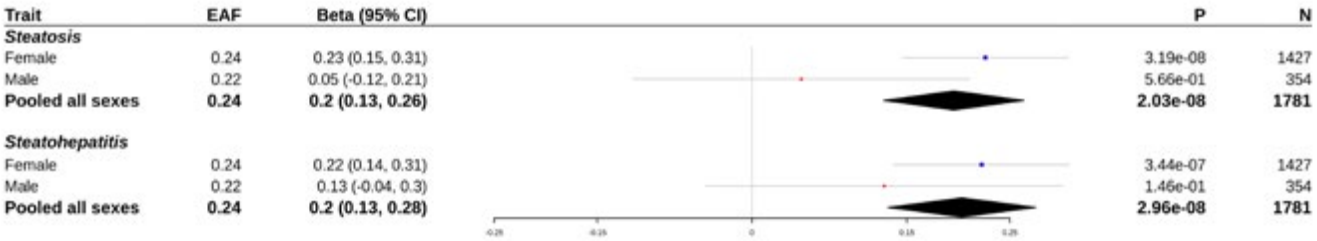
4492 | GENETIC STUDIES OF STEATOTIC LIVER DISEASE, STEATOHEPATITIS IN GEISINGER HISTOLOGY COHORT REPLICATES KNOWN LOCI

Lishi Yin[1] Chinmay Raut[1] Yanhua Chen[1] Christopher Still[2] Xin Chu[2] G. Craig Wood[2] Glenn Gerhard[3] Elizabeth Speliotes[4]

[1]University of Michigan - Ann Arbor, [2]Geisinger Obesity Institute, [3]Katz School of Medicine at Temple University, [4]University of Michigan Medical Center

Background: Steatotic liver disease is caused by accumulation of fat in the liver that can progress to steatohepatitis or fibrosis in some individuals. Identifying causes of disease progression can not only identify individuals susceptible to progression but also therapeutic targets for disease prevention. We and others have shown that steatotic liver disease is genetically influenced and thus human genetic studies can help identify these causes. Thus, genetic studies of histologically characterized liver biopsies, the gold standard for determining steatosis, steatohepatitis and fibrosis will aid the discovery of genetic predisposition towards disease progression. **Methods:** Here we carry out genome-wide association study (GWAS) of 1781 individuals that had undergone bariatric surgery and that also have liver histology. Individuals were of European ancestry and on average 45.8 ± 11.3 years old, with 46.9 ± 8.3 BMI, and 1,427(80.1%) were female. They were genotyped on the Infinium CoreExome-24 v1.4 BeadChip array and imputed to TOPMed reference panel r2-1.0.0. We measured outcomes of hepatic steatosis, steatohepatitis, and fibrosis semi-quantitatively using the NASH CRN scoring system of steatosis (grade 0-3), hepatocellular ballooning (grade 0-2), and fibrosis (grade 0-4). NAFLD activity score (NAS) was calculated as the sum of steatosis, ballooning and fibrosis score to quantitate steatohepatitis. 75.4% of patients had a steatosis score greater than 0, 9.5% had NAS > 4, and 29.7% had a fibrosis score greater than 0. We carried out association analysis of hepatic steatosis, steatohepatitis, and fibrosis as quantitative traits with single nucleotide polymorphisms (SNPs) controlling for age, sex, and 10 principal components (PCs) in an additive genetic model in SAIGE v1.2.0. **Results:** We found 1 SNP in patatin-like phospholipase domain-containing protein 3 (PNPLA3) that associates with steatosis and steatohepatitis at genome-wide significant levels. PNPLA3 plays a role in triacylglycerol hydrolysis in adipocytes and liver. Sex-stratified analysis demonstrated identical direction of effect of PNPLA3 in both steatosis and steatohepatitis. **Conclusion:** We show that a variant in PNPLA3 drives steatotic liver disease progression in this sample. We are combining this data with other histology data to increase our power to find genes with similar effects and to test them for effects on steatohepatitis in in vitro models.



Trait	EAF	Beta (95% CI)	P	N
Steatosis				
Female	0.24	0.23 (0.15, 0.31)	3.19e-08	1427
Male	0.22	0.05 (-0.12, 0.21)	5.66e-01	354
Pooled all sexes	**0.24**	**0.2 (0.13, 0.26)**	**2.03e-08**	**1781**
Steatohepatitis				
Female	0.24	0.22 (0.14, 0.31)	3.44e-07	1427
Male	0.22	0.13 (-0.04, 0.3)	1.46e-01	354
Pooled all sexes	**0.24**	**0.2 (0.13, 0.28)**	**2.96e-08**	**1781**

Disclosures: Lishi Yin: Nothing to Disclose, Chinmay Raut: Nothing to Disclose, Yanhua Chen: Nothing to Disclose, Christopher Still: Nothing to Disclose, Xin Chu: Nothing to Disclose, G. Craig Wood: Nothing to Disclose, Glenn Gerhard: Nothing to Disclose, Elizabeth Speliotes: Nothing to Disclose

4493 | GENETICS INFORMED STEATOSIS PREDICTION OUTPERFORMS EXISTING STEATOSIS INDICES IN THE UK BIOBANK

Yousif Alyousifi[1] Chinmay Raut[1] Antonino Oliveri[1] Vincent Chen[1] Elizabeth Speliotes[1]

[1]University of Michigan

Background: Hepatic steatosis affects ~30% of the population and can progress to advanced liver disease. Accurate prediction of hepatic steatosis is important for early detection and intervention. We identified 17 genetic loci that are associated with nonalcoholic fatty liver disease (PMID 37709864). Here we investigate the impact

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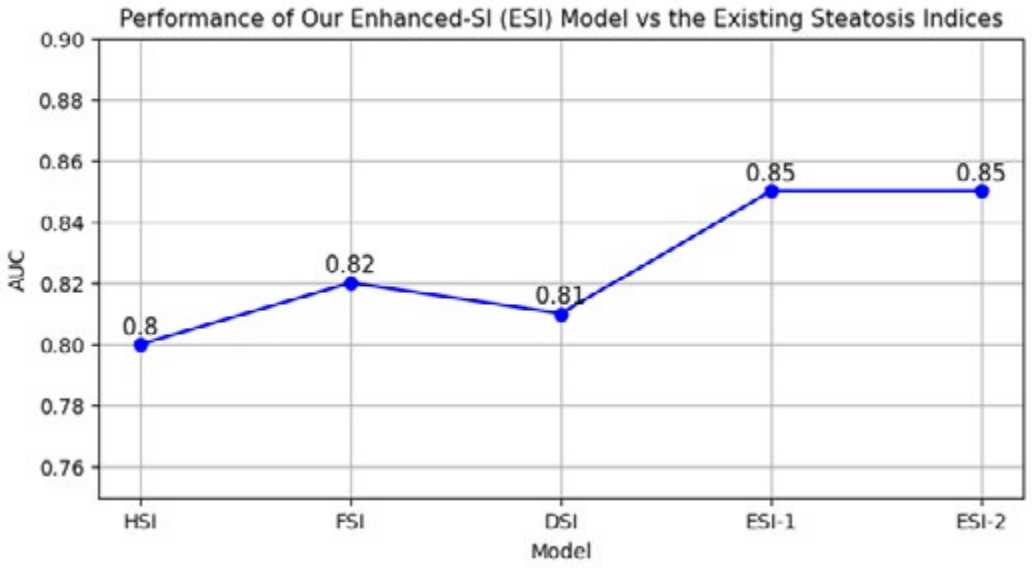
of those 17 genetic variants on enhancing the conventional steatosis indices for hepatic steatosis prediction. **Methods:** Data from 34,785 individuals in the UK Biobank with MRI-PDFF measurements were analyzed. Participants ranged in age from 40 to 70, with 52.2% being female. Previous predictors of hepatic steatosis include the Dallas Steatosis Index (DSI) (PMID 31982611), Hepatic Steatosis Index (HSI) (PMID 19766548), Framingham Steatosis Index (FSI) (PMID 27046482) which uses various combinations of diabetes status, genetic ancestry, hypertension status, genetic sex, glucose levels, alanine aminotransferase (ALT), body mass index (BMI), age at recruitment, aspartate aminotransferase (AST), triglycerides. We tested the ability of these indices to predict MRI PDFF of ≥ 5% as the outcome variable in UKBB. The dataset was divided into training (N= 27,828) and testing (N= 6,957) groups. Binary multivariate logistic regression models were trained and evaluated using an area under the receiver operating curve (AUC) for predicting PDFF >5%. We then trained and tested a model using the same non-genetic predictors from the above steatosis indices (but new betas derived from the UKBB training analysis) with and without individual SNP variants from PMID 37709864 with and without interaction terms. **Results:** The DSI, HSI, and FSI predicted ≥ 5% PDFF in UKBB with AUC of 0.81, 0.80, and 0.82 respectively. The UKBB non-genetic baseline model had an AUC of 0.83. Adding individual genetic predictors from PMID 37709864 increased the AUC to 0.85. Even though ten interaction terms were statistically significant they did not appreciably increase the AUC compared to the baseline plus genetic model. **Conclusion:** Including genetic information significantly enhanced the performance of existing steatosis indices. Our model improves upon previous steatosis indices to accurately predict MRI PDFF-measured liver steatosis. The findings highlight the significant impact of genetic variation on refining hepatic steatosis prediction. It can be deployed to screen large populations, enabling earlier detection and intervention, thus reducing the burden of metabolic liver diseases.



Disclosures: Yousif Alyousifi: Nothing to Disclose, Chinmay Raut: Nothing to Disclose, Antonino Oliveri: Nothing to Disclose, Vincent Chen: Site PI on industry-sponsored trial relationship with AstraZeneca; Has ended; site co-I on industry-sponsored trial relationship with Ipsen; Has not ended; site co-I on industry-sponsored trial relationship with Kowa; Has not ended, Elizabeth Speliotes: Nothing to Disclose

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4494 | DEVELOPMENT OF MUTATED B-CATENIN GENE SIGNATURE (MBGS) TO IDENTIFY CTNNB1 MUTATIONS FROM WHOLE AND SPATIAL TRANSCRIPTOMIC DATA IN PATIENTS

Brandon Lehrich[1] Junyan Tao[1] Silvia Liu[1] Theo Hirsch[2] Tyler Yasaka[1] Catherine Cao[1] Evan Delgado[1] Yuqing Liu[1] Xiangnan Guan[3] Shan Lu[3] Long Pan[2] Sucha Singh[1] Minakshi Poddar[1] Aatur Singhi[4] Jessica Zucman-Rossi[5] Yulei Wang[3] Satdarshan (Paul) Monga[1]

[1]University of Pittsburgh, [2]Centre de Recherche des Cordeliers, Université Paris Cité, Sorbonne Université, Inserm, F-75006 Pari, [3]Translational Medicine, Genentech Inc., San Francisco, CA, USA, [4]Department of Pathology, UPMC, [5]French Institute of Health and Medical Research/Inserm

Background: Hepatocellular carcinoma (HCC) is the third-leading cause of cancer-related death. Current first-line immunotherapy (IO) demonstrates variable response with CTNNB1-mutated patients deriving limited clinical benefit. Precision-medicine based treatments for this subclass are currently in various stages of clinical development. We have previously shown that b-catenin-(encoded by CTNNB1 gene)-mutated HCC animal models developed via hydrodynamic tail vein injection with sleeping beauty transposon/transposase (SB-HDTVi) represent clinically relevant molecular subsets of human HCC. Using these models, we report derivation of MBGS to predict CTNNB1-mutational status in patients for future personalized medicine. **Methods:** We co-expressed in mouse hepatocytes mutant NFE2L2 (encoding NRF2) and hMET ± mutant-CTNNB1 via SB-HDTVi and monitored for HCC development. Using bulk RNA-seq and intersectional transcriptomic analysis of various b-catenin-mutated and wild-type HCC animal models, we successfully derived MBGS. MBGS was assessed for its ability to detect CTNNB1 mutation and IO response in integrated RNA/whole-exome-seq and spatial transcriptomic data from multiple HCC patient cohorts. **Results:** Bulk RNA-seq comparing HCCs in mutant b-catenin-Nrf2, b-catenin-Met and b-catenin-Nrf2-Met to Nrf2-Met HCC model yielded 95 common upregulated genes. Ingenuity pathway analysis (IPA) demonstrated enrichment for Glutamine Biosynthesis and Wnt/b-catenin Signaling. In TCGA-LIHC, differential gene expression analysis with FDR<0.05 and log2FC>1.5 on the 95 common genes comparing CTNNB1-mutated vs wild-type patients narrowed the gene panel to 13-genes (MBGS). MBGS predicted CTNNB1-mutation status in two independent patient cohorts with ROC AUC of 0.90 and 0.94. Additionally, high MBGS expression score was associated with lack of significant OS or PFS effects in the atezolizumab + bevacizumab arm versus sorafenib arm in IMbrave150 cohort, likely due to improved response to sorafenib. In comparison to other CTNNB1-mutant classifiers, MBGS performed comparable or superior showing higher AUC under the ROC curve. High MBGS also overlapped with Hoshida S3, Boyault G5/G6, and Chiang CTNNB1 subclass tumors in TCGA and in HCC spatial transcriptomic datasets visually depicting these tumors to be situated in an immunologically cold tumor microenvironment. **Conclusion:** MBGS is expected to guide precision medicine therapeutics in CTNNB1-mutated HCC as a companion diagnostic.

Disclosures: Brandon Lehrich: Nothing to Disclose, Junyan Tao: Nothing to Disclose, Silvia Liu: Nothing to Disclose, Theo Hirsch: Nothing to Disclose, Tyler Yasaka: Nothing to Disclose, Catherine Cao: Nothing to Disclose, Evan Delgado: Nothing to Disclose, Yuqing Liu: Nothing to Disclose, Xiangnan Guan: Nothing to Disclose, Shan Lu: Nothing to Disclose, Long Pan: Nothing to Disclose, Sucha Singh: Nothing to Disclose, Minakshi Poddar: Nothing to Disclose, Aatur Singhi: Nothing to Disclose, Jessica Zucman-Rossi: Nothing to Disclose, Yulei Wang: Nothing to Disclose, Satdarshan (Paul) Monga: Surrozen: Independent Contractor, Mermaid Bio: Advisor, Vicero: Advisor, AntlerA: Advisor, Genentech: Speaking and Teaching, Alnylam: Grant/Research Support, Alnylam: Consultant, UbiquiTx: Consultant, Mermaid Bio: Consultant, Fog Pharmaceuticals: Grant/Research Support, Surrozen: Consultant, Genentech: Independent Contractor

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4495 | FULL LIVER CELL ATLAS OF FHF MOUSE MODEL REVEALS HSPCS AS REGULATORY HUB PROMOTING HEPATIC MICRO-ENVIRONMENT REBUILDING DURING MSC TREATMENT

Jun Li[1] Heng Yao[1] Hui Yang[1] Suwan Sun[1] Xi Liang[2] Jing Jiang[1] Jiaojiao Xin[1] Dongyan Shi[1] Xin Chen[1]

[1]Zhejiang University, [2]Taizhou Central Hospital

Background: Transplantation of human bone marrow mesenchymal stem cells (hBMSCs) can rescue mice with fulminant hepatic failure (FHF). However, the cellular mechanisms underlying liver regeneration after transplantation remain unknown. This study aims to identify key regulatory factors by constructing a comprehensive single-cell atlas of the liver in FHF mice. **Methods:** A single type of human bone marrow mesenchymal stem cells (hBMSCs) was transplanted into immunodeficient Fah-/-Rag2-/-IL-2Rγc-/- SCID (FRGS) mice with FHF. Single-cell RNA sequencing (scRNA-Seq) was performed to profile all cell types, creating a comprehensive liver atlas. Bulk RNA sequencing and immunohistochemistry were used to validate the key factors involved in hepatic regeneration identified in the liver atlas. **Results:** The mice with FHF were rescued by the implanted human bone marrow mesenchymal stem cells (hBMSCs). A comprehensive single-cell atlas of the liver was constructed to profile the transcriptomic features of all cells in the liver tissues of healthy mice and those of the treatment group from day-0 (MSCs transplantation) to day-14. Two distinct types of hepatocytes were identified in the atlas: type-a, which were typical hepatocytes, and type-b, which were more involved in toxic molecular transport and were more damaged by JO-2 treatment but showed better recovery after hBMSC transplantation. A significant transformation trend from type-a to type-b hepatocytes was observed during hepatic regeneration. The number of hepatic stem/progenitor cells (HsPCs) was consistently increasing after transplantation. Cellular signaling analysis also revealed that HsPCs act as a hub for hepatocyte regeneration and transformation through the Ppia-Bsg pathways as well as a signaling centre connecting and coordinate different cells involved in biological processes including cellular regeneration, wound healing and growth involved in morphogenesis. **Conclusion:** Single-cell sequencing of the full-liver cell reveals HsPCs as a regulatory hub during liver-regeneration after MSC transplantation, promoting hepatocyte phenotype transformation to rebuild a hepatic micro-environment prioritizing transporting toxics to recover liver homeostasis.

Disclosures: Jun Li: Nothing to Disclose, Heng Yao: Nothing to Disclose, Hui Yang: Nothing to Disclose, Suwan Sun: Nothing to Disclose, Xi Liang: Nothing to Disclose, Jing Jiang: Nothing to Disclose, Jiaojiao Xin: Nothing to Disclose, Dongyan Shi: Nothing to Disclose, Xin Chen: Nothing to Disclose

4496 | DEVELOPING A MACHINE LEARNING UNIVERSAL PREDICTOR FOR LIVER FIBROSIS PROGRESSION

Kirstin Peters[1] Nicholas Valle[1] Jamie Yang[2] Michelle Guan[1] Tien Dong[1]

[1]UCLA, [2]University of California, Los Angeles

Background: In the United States, liver disease and transplant rates are escalating despite advancements in managing viral hepatitis, largely driven by alcohol-associated liver disease (ALD) and metabolic dysfunction-associated steatotic liver disease (MASLD), which accounted for 75% of transplants in 2022. Fibrosis emerges as the primary cause of liver-related mortality in patients with ALD and MASLD. Leveraging the growing prevalence of machine learning algorithms in medical research, this study aims to identify key fibrosis drivers across prevalent liver diseases, including ALD, MASLD, HCV, and HBV, and develop a model to predict fibrosis progression. **Methods:** This study involved 500 patients aged 18 and above from a leading liver transplant facility who underwent at least two fibrosis assessments between 2015 and 2023, utilizing fibroscan, magnetic resonance liver elastography, or liver biopsy. Patients represented diverse liver disease causes, including MASLD, ALD, HCV, HBV, and other miscellaneous diseases. Data collection encompassed demographics, fibrosis stage, MELD-Na scores, BMI, medication usage (statins, GLP-1 agonists), complete blood count, comprehensive metabolic panel, A1c, cholesterol levels, INR, and AFP at both evaluation points. Logistic regression identified key predictors for worsening fibrosis, which were then utilized in a random forest algorithm to develop a model for tracking fibrosis progression. **Results:** Of the total 230 subjects, 108 had liver disease secondary to MASLD, 15 to ALD, 13 to HCV, 24 to HBV, and 70 secondary to other causes, such as PBC, PSC, AIH, DILI, etc. The average age was 58.3 years; 41% were male, 45.9% White, 5.7% Black, 17.5% Asian, and 20% identifying as Hispanic

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or Latino. At baseline, 18.3% of patients had diabetes, 20% had advanced fibrosis or cirrhosis, the average MELD-Na score was 9.1, and the average BMI was 28.4. Overall, 12.6% experienced fibrosis progression. Elevated liver stiffness, INR, and A1c at baseline were positively associated with fibrosis progression. Compared to the manual chart abstraction, the random forest classifier demonstrated a sensitivity of 99.5%, specificity of 74.2%, and accuracy of 96.1% in identifying fibrosis progression. **Conclusion:** Analyzing extensive patient data, we developed an accurate random forest classifier to detect fibrosis progression risk across various liver conditions, allowing providers to potentially target at-risk individuals for potentially closer monitoring or proactive interventions.

Table 1. Confusion Matrix comparing Random Forest Classifier of Liver Disease patient with Fibrosis Progression versus Manually Identified via Chart Abstraction.

		Manual Data Abstraction	
Random Forest Classifier		Patients with Fibrosis Progression	No Fibrosis Progression
	Patients with Fibrosis Progression	23	1
	No Fibrosis Progression	8	198
Random Forest Classifier Fibrosis Progression Prediction			
Sensitivity		99.5%	
Specificity		74.2%	
Positive Predictive Value		96.1%	
Negative Predictive Value		95.8%	
Accuracy		96.1%	

Disclosures: Kirstin Peters: Nothing to Disclose, Nicholas Valle: Nothing to Disclose, Jamie Yang: Nothing to Disclose, Michelle Guan: Nothing to Disclose, Tien Dong: Mallinckrodt: Speaking and Teaching, PurposeBio: Consultant

4497 | FRAMEWORK TO STRATIFY THE SNPS ASSOCIATED WITH MASLD ACTIVITY SCORE (MAS) AND FIBROSIS AND DEVELOPMENT OF A CANDIDATE GENE POLYGENIC RISK SCORE (CGS) IN PATIENTS WITH MASLD

Tae-Hwi Schwantes-An[1] Kung-Hung Lin[1] Marco Abreu[1] Jingyi Tan[2] Xiuqing Guo[2] Katherine Yates[3] Luca Lotta[4] Niek Verweij[4] Rohit Loomba[5] Jerome Rotter[2] Naga Chalasani[6]

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Background: Previous studies identified numerous SNPs in multiple genes to be associated with MASLD and its severity, but these association varied in terms of their effect size and replication. We developed a framework to stratify SNPs into 4 strata (Tiers 1-4) based on their effect size and extent of replication. We tested the association between Tier 1 SNPs and MAS and fibrosis in a large well characterized MASLD cohort. We further developed a candidate gene PRS from Tier1 SNPs. **Methods:** A catalogue of genetic variants previously reported to be associated with MASLD and its severity was generated from literature search and GWAS Catalog. The associated variants were then classified into Tiers 1, 2, 3, and 4 based on their effect size and replication status. Tier1 SNPs contained variants with OR≥1.5 and replicated in >2 independent publications. Tier1 variants were tested against fibrosis stage and MAS using linear regression model. Analyses were done in samples that clustered with EUR or AMR ancestry groups in 1000Genome after adjusting for age, pediatric age, ancestry, and two PCs. A Candidate Gene Score (CGS) was calculated by summing the number of risk alleles each participant carried across the Tier 1 variants. We compared the strength of association between MAS and between fibrosis, with the Tier1 CGS, a previously reported *PNPLA3-TM6SF2-HSD17B13* CGS, and *PNPLA3* rs738409 alone. **Results:** The NASH-CRN cohort consisted of 3,353 participants (age 39.9 years, 47.5% Male, 28% children, 60% EUR and 31% AMR ancestry). There were 19 Tier 1 variants representing 13 genes (*PNPLA3, HSD17B13, SAMM50, PARVB, IFNL4, TM6SF2, PEMT, IL-6, MTTP, PPARGC1A, Adiponectin, NR112, and MTHFR*). Across the 19 variants, only those

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in *PNPLA3-SAMM50-PARVB* gene complex showed statistically significant associations for higher fibrosis and MAS score with the highest risk for the *PNPLA3* rs738409 SNP (Figure 1). The Tier 1 CGS showed significant associations with both fibrosis and MAS, as did the prior 3 allele CGS (Rsquared for fibrosis 0.099 and 0.099, Rsquared for MAS 0.013 and 0.014), but for both traits this appeared driven by the *PNPLA3* rs738409 (Rsquared for MAS 0.013 and 0.014) (Table1). **Conclusion:** A candidate gene score based on 19 Tier1 variants showed significant association with fibrosis and MAS in a large cohort of patients with biopsy proven MASLD. However, these results were driven by the *PNPLA3* rs738409 SNP allele, as the driver for both fibrosis and MAS.

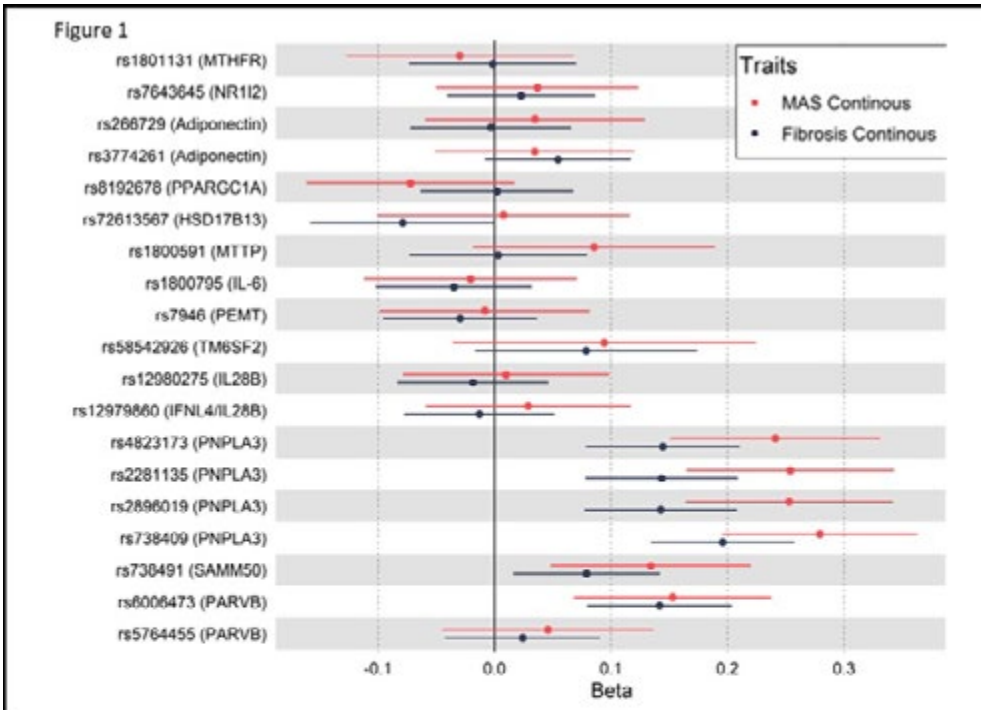

Table 1

Outcome	CGS	Beta	SE	tstat	Pvalue	Rsq
Fibrosis, continous	Three-SNP	0.10	0.02	4.19	2.92E-05	0.099
Fibrosis, continous	Tier1	0.02	0.01	4.00	6.54E-05	0.099
Fibrosis, continous	rs738409	0.20	0.03	6.23	5.32E-10	0.105
MAS, continuous	Three-SNP	0.17	0.03	5.50	4.02E-08	0.014
MAS, continuous	Tier1	0.04	0.01	5.14	2.90E-07	0.013
MAS, continuous	rs738409	0.28	0.04	6.52	8.24E-11	0.018

Disclosures: Tae-Hwi Schwantes-An: Target RWE: Consultant, Kung-Hung Lin: Nothing to Disclose, Marco Abreu: Nothing to Disclose, Jingyi Tan: Nothing to Disclose, Xiuqing Guo: Nothing to Disclose, Katherine Yates: Nothing to Disclose, Luca Lotta: Nothing to Disclose, Niek Verweij: Nothing to Disclose, Rohit Loomba: Eli Lilly and Company: Consultant, 89bio: Consultant, Aardvark Therapeutics: Consultant, Altimmune: Consultant, Alnylam/Regeneron: Consultant, Amgen: Consultant, Arrowhead Pharmaceuticals: Consultant, AstraZeneca: Consultant, Bristol Myers Squibb: Consultant, CohBar: Consultant, Eli Lilly: Consultant, Galmed Pharmaceuticals: Consultant, Gilead: Consultant, Glympse Bio: Consultant, Hightide: Consultant, Inipharma: Consultant, Intercept: Consultant, Inventiva: Consultant, Ionis: Consultant, Janssen, Inc.: Consultant, Madrigal Pharmaceuticals: Consultant, Merck, Metacrine, Inc.: Consultant, NGM Biopharmaceuticals: Consultant, Novartis: Consultant, Novo Nordisk: Consultant, Pfizer: Consultant, Sagimet Biosciences: Consultant, Terns Pharmaceuticals: Consultant, Theratechnologies and Viking Therapeutics: Consultant, 89bio: Stock options, Sagimet Biosciences: Stock options, Arrowhead Pharmaceuticals: Research grant, AstraZeneca: Research grant, Boehringer Ingelheim: Research grant, Bristol Myers Squibb: Research grant, Eli Lilly: Research grant, Galectin Therapeutics: Research grant, Galmed Pharmaceuticals: Research grant, Gilead: Research grant, Hanmi: Research grant, Intercept: Research grant, Inventiva: Research grant, Ionis: Research grant, Janssen, Inc.: Research grant, Madrigal Pharmaceuticals: Research grant, Merck: Research grant, NGM Biopharmaceuticals: Research grant, Novo Nordisk: Research grant, Pfizer: Research grant, Sonic Incytes: Research grant, Terns Pharmaceuticals:

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4498 | PATHOGENIC VARIANTS ASSOCIATED WITH MONOGENIC DISORDERS OF DYSLIPIDEMIA IN PATIENTS WITH WELL CHARACTERIZED MASLD

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Background: Dyslipidemia is common in patients with MASLD, and it can sometimes be due to monogenic disorders. The prevalence and significance of monogenic disorders associated with serum dyslipidemia in patients with MASLD are not well understood. We investigated the prevalence and significance of pathogenic variants in *APOB*, *MTTP*, *PCSK9*, *ANGPTL3*, *LDLR*, *LDLRAP1*, and *APOE* in a large cohort of patients with histologically characterized MASLD. **Methods:** High coverage whole exome sequencing and variant identification and annotation were performed by the Regeneron Genetics Center as published previously (N Engl J Med 2022; 387: 332-44) on the NIDDK-funded NASH CRN cohort of children and adults with biopsy-proven MASLD. Using ClinVar, we identified variants that were reported to be pathogenic or likely pathogenic according to ACMG guidelines from the seven aforementioned candidate genes. We then identified NASH-CRN participants who carried alternative alleles in any of these 7 genes. For each pathogenic variant carrier, we identified matched controls based on age, sex, and 3-SNP candidate gene score (CGS). CGS was calculated by adding the number of risk alleles in common variants rs738409 (*PNPLA3*), rs72613567 (*HSD17B13*), and rs58542926 (*TM6SF2*). **Results:** Out of 3,352 sequenced individuals from the NASH CRN, 25 individuals (0.75%) had one alternative allele (heterozygote) to the seven screened genes. The two most common monogenic disorders of dyslipidemia observed with *APOB* (12 heterozygotes for hypobetalipoproteinemia) and *LDLR* (10 heterozygotes for familial hypercholesterolemia). Table 1 summarizes clinical and histological differences between *APOB* and *LDLR* carriers to 45 ApoB and 37 LDLR matched controls. We observed that *APOB* heterozygotes had lower LDL level than matched controls (51 mg/dL vs. 109 mg/dL, p =$3.6x10^{-06}$) and total cholesterol level (119 mg/dL vs. 185 mg/dL, p =$1.01x10^{-05}$) as expected (Table 1). *APOB* heterozygotes had significantly higher steatosis grade (2.4 vs. 1.7, p =0.0047), higher MAS score (4.9 vs. 3.8, p =0.04), lobular inflammation (67% vs. 27%, p=0.02). *LDLR* heterozygotes did not show any statistically significant differences in clinical or histological features with their matched controls. **Conclusion:** Approximately 1 in 130 patients with MASLD had genomic evidence for hereditary dyslipidemia (both extremely high and low LDL-C), with rare pathogenic variants in *APOB* and *LDLR* being the most common. Individuals with *APOB* variants had worse liver histology, even after controlling for common variation in *PNPLA3*, *TM6SF2*, and *HSD17B13*, signifying their importance in MASLD histological progression.

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Clinical and histological characteristics of *ApoB* and *LDLR* pathogenic variant carriers and their respective controls

Variable	Overall (N=3,358)	*APOB* carriers (N=12)	*APOB* matched controls (N=45)	*APOB* vs. matched controls p-value	*LDLR* carriers (N=10)	*LDLR* matched controls (N=37)	*LDLR* vs. matched controls p-value
Age, mean (SD)	39.9 (19.8)	40.1 (15.9)	41.6(14.9)	0.78	43.6 (20.3)	42.5 (19.3)	0.88
% Male (N/total)	47.5% (1595/3358)	16.7% (2/12)	11.1% (5/45)	0.63	40% (4/10)	43.2% (16/37)	1.00
% Self-reporting White	76% (2553/3358)	83.3% (10/12)	71.1% (32/45)	0.49	80% (8/10)	73% (27/37)	1.00
% Self-reporting Hispanic	28.6% (961/3358)	8.3% (1/12)	15.6% (7/45)	1.00	30% (3/10)	37.8% (14/37)	0.73
% Children	28.4% (953/3358)	16.7% (2/12)	17.8% (8/45)	1.00	20% (2/10)	21.6% (8/37)	1.00
% Diabetes	27.8% (932/3354)	16.7% (2/12)	42.2% (19/45)	0.18	30% (3/10)	40.5% (15/37)	0.72
% Hyperlipidemia	42.2% (1414/3354)	16.7% (2/12)	57.8% (26/45)	0.02	70% (7/10)	40.5% (15/37)	0.15
BMI (kg/m2)	33.7 (6.6)	33.4 (8.4)	35.9(7.2)	0.36	35.4 (9.1)	33.6 (6.7)	0.57
ALT in U/L	79 (65)	87.4 (44.7)	58.1(47.7)	0.06	87.6 (47.7)	77 (86)	0.63
AST in U/L	53.5 (38.7)	57.2 (23.3)	43.3(29.3)	0.10	58.1 (29.3)	52.2 (44.1)	0.63
AlkPhos in U/L	124 (88)	110.7 (79)	121.8(82.3)	0.67	118 (92.9)	120.8 (84.3)	0.94
Bilirubin in mg/dL	0.6 (0.4)	0.5 (0.2)	0.5(0.2)	0.87	0.6 (0.3)	0.5 (0.3)	0.64
Total Cholesterol (mg/dL)	182.5 (43.5)	119.4 (33.3)	185.2(43.8)	1.01E-05	191.3 (54.4)	185.1 (36.5)	0.75
HDL in mg/dL	42.8 (11.9)	54 (17.8)	46.7(16.3)	0.22	40.4 (8.5)	44.5 (12.9)	0.27
LDL in mg/dL	108.3 (35.9)	51.1 (25.3)	108.9(37.4)	3.57E-06	126 (56.9)	105.2 (28.3)	0.32
Steatosis grade	1.8 (0.9)	2.4 (0.7)	1.7(1)	4.71E-03	2.3 (0.7)	1.8 (0.8)	0.06
Steatosis Grade ≥ 2	60.8% (2040/3358)	91.7% (11/12)	53.3% (24/45)	0.02	90% (9/10)	54.1% (20/37)	0.06
Lobular Inflammation	44.4% (1491/3358)	66.7% (8/12)	26.7% (12/45)	0.02	50% (5/10)	40.5% (15/37)	0.72
Portal Inflammation	87.6% (2940/3357)	91.7% (11/12)	84.4% (38/45)	1.00	90% (9/10)	94.6% (35/37)	0.52
Ballooning	55.9% (1877/3358)	58.3% (7/12)	53.3% (24/45)	1.00	60% (6/10)	45.9% (17/37)	0.49
Fibrosis grade	1.5 (1.3)	1.2 (1.4)	1.1(1.2)	0.68	1.9 (1.5)	1.5 (1.3)	0.51
Advanced Fibrosis	25% (836/3348)	25% (3/12)	15.6% (7/45)	0.42	50% (5/10)	32.4% (12/37)	0.46
MAS score	4.2 (1.7)	4.9 (1.4)	3.8(1.7)	0.04	5 (1.9)	4.1 (1.8)	0.20
MAS ≥ 4 vs. MAS < 4	66.1% (2220/3358)	83.3% (10/12)	57.8% (26/45)	0.18	70% (7/10)	62.2% (23/37)	0.73
MASH	48.4% (1567/3239)	41.7% (5/12)	45% (18/40)	1.00	60% (6/10)	40.5% (15/37)	0.31

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4499 | EXPLORING THE PROTECTIVE ROLE OF LYPLAL1 LOSS-OF-FUNCTION IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE

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Background: Human genetics studies have linked single-nucleotide polymorphisms near LYPLAL1 with metabolic dysfunction-associated steatotic liver disease (MASLD). How altering LYPLAL1 function leads to MASLD is not well-understood. To learn more about how perturbation in LYPLAL1 function contributes to MASLD, we analyzed rare loss-of-function LYPLAL1 mutations using UK BioBank (UKBB) Whole Exome Sequencing (WES) data and knocked out LYPLAL1 in human liver cells to investigate its role in MASLD. **Methods:** We identified 100 missense or stop-gain variants that had an alphamissense or gpn-msa score in the top 80% of LYPLAL1 variants and an allele frequency below 5e-5. We conducted burden testing in European males and females for effects on inverse normally transformed UKBB MRI Proton Density Fat Fraction (PDFF) (N=30,050 males and 32,135 females) and UKBB ICD-based NAFLD (N=172,664 males and 208,795 females) with Regenie.

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Results were meta-analyzed using fixed effects meta-analysis in RAREMETAL using sample size and direction of effect. We used CRISPR-Cas9 to knock out LYPLAL1 in a human liver cell line (HuH-7). Intracellular lipid droplet levels were quantified using a neutral lipid stain and fluorescent imaging. We measured both triglyceride (TG) and cholesterol accumulation with biochemical assays. Mitochondrial oxidative stress was assessed by measuring reactive oxygen species (ROS) levels and the expression levels of major beta-oxidation enzymes were determined using fluorescent antibodies. **Results:** Rare loss-of-function variants were protective against fatty liver in European individuals ($Z = -2.071$, $p = 0.03837$) across PDFF and ICD diagnoses and sexes. LYPLAL1 KO resulted in reduced lipid content compared to wild-type (WT) HuH-7 cells when treated with oleic acid for 24 hours ($p < 0.001$ for all doses tested between 100-1000 μM). LYPLAL1 KO cells also showed a trending decrease in TG levels but no significant difference in intracellular cholesterol. Expression of major beta-oxidation enzymes ACADVL, ACADM, and HADHA was higher in LYPLAL1 KO cells ($p < 0.001$). There were no differences in ROS levels between WT and LYPLAL1 KO cells. **Conclusion:** Reduction of LYPLAL1 function leads to cell autonomous decreased intracellular lipid content and triglycerides in a human liver cell line. Increased levels of beta-oxidation enzymes following LYPLAL1 reduction may contribute to lower lipid levels.

Disclosures: Rawdat Hussain: Nothing to Disclose, Chinmay Raut: Nothing to Disclose, Prabhu Ponnandy: Nothing to Disclose, Akram Irshaid: Nothing to Disclose, Brian Halligan: Nothing to Disclose, Elizabeth Speliotes: Nothing to Disclose

4500 | LENVATINIB INHIBITS THE EFFICACY OF CHIMERIC ANTIGEN RECEPTOR MACROPHAGE (CAR-M) THERAPY IN TREATING HEPATOCELLULAR CARCINOMA

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Background: Cellular therapy is an emerging field in tumor treatment. In solid tumors, macrophages can easily penetrate the tumor microenvironment and present tumor antigens to stimulate T-cell immunity. Therefore, CAR-M therapy is considered a promising strategy for treating solid tumors, including hepatocellular carcinoma (HCC). Recently, we have developed a GPC3-targeting CAR-M therapy for HCC treatment. To further improve this therapy, we investigated whether combining CAR-M with targeted therapy would enhance its efficacy in HCC. **Methods:** We designed a human anti-GPC3 CAR structure incorporating 4-1BB and CD3ζ intracellular domains. CAR-M cells were generated by infecting THP-1 cells with lentivirus or monocyte-derived macrophages with adenovirus. The in-vitro functions of anti-GPC3 CAR-M cells were validated using phagocytosis and killing assays. The efficacy of CAR-M therapy was evaluated in vivo using cell line-derived peritoneal xenografts and patient-derived subcutaneous xenografts in NSG mice. Subsequently, CAR-M cells were treated with Lenvatinib, and their phagocytic capacity was evaluated using GPC3-coated beads. Finally, co-cultures of tumor cells and CAR-M cells were subjected to various concentrations of Lenvatinib, followed by killing and cytokine assays to determine the impact of Lenvatinib on CAR-M therapy. **Results:** GPC3-targeting CAR-M cells demonstrated enhanced phagocytosis and tumor-killing capacity in an antigen-dependent manner. In a peritoneal tumor model, injection of CAR-M cells reduced tumor burden and prolonged the survival of mice. Similarly, intravenous injection of CAR-M cells suppressed tumor growth in a patient-derived xenograft model. However, when combined with Lenvatinib, the phagocytosis and killing efficiency of CAR-Ms significantly decreased in a dose-dependent manner. Additionally, cytokine production by CAR-M cells was affected by Lenvatinib. TNF release, a known mediator of CAR-M killing, was reduced. Furthermore, IL-1β was significantly upregulated upon co-stimulation of the CAR signal and a gradient of Lenvatinib, potentially increasing the risk of cytokine release syndrome or tumor metastasis. **Conclusion:** Lenvatinib inhibits the efficacy of anti-GPC3 CAR-M therapy in HCC and may have detrimental effects related to cytokine release. Therefore, in clinical trials of CAR-M therapy, a washout period should be considered after Lenvatinib usage. The impact of other tyrosine kinase inhibitors (TKIs) on CAR-M therapy should also be evaluated in future studies.

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4501 | *HSD17B13* LOSS-OF-FUNCTION SPLICE VARIANT DELAYS ONSET OF INCIDENT METABOLIC-DYSFUNCTION-RELATED AND ALCOHOL-RELATED LIVER DISEASE, SLOWS PROGRESSION OF ESTABLISHED LIVER DISEASE, AND LOWERS RISK OF LIVER-RELATED MORTALITY

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Background: The protein truncating genetic variant (rs72613567, TA allele) in hydroxysteroid 17-β-dehydrogenase 13 (*HSD17B13*) leads to enzymatic loss of function (LOF) and is associated with lower risk of developing steatotic liver disease (SLD), including metabolic dysfunction-associated steatotic liver disease/steatohepatitis (MASLD/MASH) and alcohol-related liver disease (ALD). Prior UK Biobank (UKB) work showed a delayed onset of SLD in carriers of *HSD17B13* LOF variant. This study replicated the analysis from UKB in the FinnGen (Finland health registry biobank; FG) cohort and used meta-analysis to investigate age of disease onset, age at liver-related or all-cause mortality, and progression from fatty liver to cirrhosis. **Methods:** We assessed *HSD17B13* rs7213567 LOF genotype from whole genome sequencing in ~400,000 participants of non-Finnish ancestry in UKB and from array-based genotyping and imputation in ~430,000 participants of Finnish ancestry in FG. Genotype was modeled additively. Hospital episodes and mortality registry data were used to identify clinical diagnoses for MASLD, ALD, and cirrhosis in UKB and FG. Cox proportional hazards regressions (CPH), adjusted for standard covariates, were used to estimate hazard ratios (HR) and 95% confidence intervals (CI) for the association between *HSD17B13* and age-of-onset for SLD, cirrhosis, and mortality and for MASLD-cirrhosis progression over 10 years. Fixed-effect meta-analyses combined cohort results from UKB and FG. Kaplan–Meier survival curves (KM) were used to inspect survival rates between *HSD17B13* LOF genotypes by cohort. **Results:** In this UKB-FG meta-analysis of CPH, each *HSD17B13* LOF allele (LOFA) was associated with significantly reduced MASLD and cirrhosis risk (HR 0.93 and 0.85, respectively; $p < 0.001$) and delayed age-of-onset was observed in KM in UKB and FG; meta-analysis effect estimates were stronger than previously reported in UKB alone. Each LOFA was associated with significantly lowered ALD and ALD-attributed cirrhosis risk (HR, 0.87 and 0.84, respectively; $p < 0.001$); KM showed separation by LOFA with delayed age-of onset. Each LOFA was associated with significantly slowed MASLD-cirrhosis progression (HR, 0.83, $p = 0.02$); KM in FG (but not UKB) showed clear separation by LOF genotype. Each LOFA was significantly associated with lower risk of liver-related, cirrhosis-related, and ALD-cirrhosis-related death (all $p < 0.001$) but not with all-cause mortality (HR, 1.00, $p = 0.66$; **Table**). **Conclusion:** In this UKB-FB meta-analysis, *HSD17B13* LOF variant was associated with reduced risk and delayed age-of-onset for MASLD, ALD, cirrhosis, and ALD-attributed cirrhosis, delayed progression from MASLD to cirrhosis, and delayed age-at-death for liver-related mortality, but not all-cause mortality. These findings suggest the *HSD17B13* LOF variant shows liver-related protection across the spectrum of SLD, spanning across disease stages and death.

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Table. Time-to-event analyses of *HSD17B13* LOF variant from meta-analysis of CPH in UKB and FG.

Event	Event, N	Total, N	Hazard Ratio (95% CI)	*P*-value
Disease (age-of-onset)				
MASLD	10,347	814,642	0.93 (0.91–0.97)	< 0.001
ALD	5358	809,653	0.87 (0.83–0.91)	< 0.001
Cirrhosis	6893	811,188	0.85 (0.81–0.88)	< 0.001
ALD-cirrhosis	3946	808,241	0.84 (0.80–0.89)	< 0.001
MASLD to cirrhosis	456	8315	0.83 (0.71–0.97)	0.02
Mortality (age-of-death)				
Liver-related	2939	807,234	0.88 (0.83–0.94)	< 0.001
Cirrhosis-related	1858	806,153	0.80 (0.73–0.86)	< 0.001
ALD-cirrhosis-related	1155	805,450	0.83 (0.75–0.92)	< 0.001
All-cause	85,049	857,614	1.00 (0.99–1.01)	0.66

ALD, alcohol-related liver diseases; CI, confidence interval; CPH, Cox proportional hazards regressions; FG, FinnGen; *HSD17B13*, hydroxysteroid 17-β-dehydrogenase 13; LOF, loss of function; MASLD, metabolic dysfunction-associated fatty liver disease; UKB, United Kingdom biobank.

Disclosures: Audrey Chu: GSK: Employed by GSK and hold financial equities in GSK, Jonathan Davitte: GSK: Employee, GSK: Stock - publicly traded company, Diogo Ferrinho: Nothing to Disclose, Cathy O'Hare: Nothing to Disclose, Nikhil Vergis: Nothing to Disclose

4502 | MOLECULAR EVENTS UNDERLYING ADVERSE PROGNOSIS OF LIVER FIBROSIS FOLLOWING ANTIVIRAL THERAPY IN PATIENTS WITH CHRONIC HEPATITIS B VIRUS INFECTION

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Background: Antiviral therapy proves insufficient in alleviating liver fibrosis in all patients with chronic hepatitis B virus (CHB) infection. Notably, CHB patients with non-regressive liver fibrosis post-antiviral therapy frequently encounter a higher rate of adverse clinical outcomes. This study aims to investigate the molecular events that might explain or predict the poor prognosis of liver fibrosis following antiviral therapy. **Methods:** Transcriptomic gene expression profiles related to hepatitis B virus (HBV)-related liver fibrosis and hepatocellular carcinoma (HCC) were retrieved from GEO, TCGA, and ICGC databases. Bulk RNA sequencing (RNA-seq) was performed on consecutive biopsies from liver fibrosis patients with CHB infection at baseline and post-antiviral treatment. Comprehensive bioinformatics analyses were conducted to unveil the molecular events underlying adverse prognosis of liver fibrosis following antiviral therapy. **Results:** A total of 466 genes were found to be dysregulated in HBV-related liver fibrosis using publicly available dataset, which were used for further trend analysis in response to antiviral therapy in liver samples from patients pre- and post-treatment. During antiviral therapy, six clusters of genes were identified with the same expression pattern, three of which (including 228 genes) were resistant to recovery after short-term antiviral treatment. A comparative analysis between patients showing fibrosis regression and those not, revealed a set of 9 genes (*CCNA2*, *CDC20*, *ECT2*, *EZH2*, *MAD2L1*, *MCM6*, *NUSAP1*, *RACGAP1*, and *RRM2*) that formed a non-regression (non-R) signature, observable only in patients who experienced fibrosis regression. This non-R signature was also found to be upregulated in HBV-related HCC tumors, as per analyses from five independent gene expression profiles in the GEO database. Interestingly, the non-R signature could stratify HBV-related HCC patients from the TCGA and ICGC databases into low, intermediate, and high- risk subgroups, with the high-risk patients exhibiting a worse clinical prognosis. **Conclusion:** This study identifies a 9-gene-based signature linked to the non-regression of HBV-related liver fibrosis, carcinogenesis, and subsequent cancer prognosis following antiviral therapy. These insights highlight the molecular events that probably contribute to the adverse prognosis in HBV-related liver fibrosis.

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Disclosures: Hong Li: Nothing to Disclose, Yameng Sun: Nothing to Disclose, Wen Zhang: Nothing to Disclose, Wenyue Wu: Nothing to Disclose, Shuyan Chen: Nothing to Disclose, Ning Zhang: Nothing to Disclose, Qi Han: Nothing to Disclose, Xuzhen Yan: Nothing to Disclose, Aiting Yang: Nothing to Disclose, Hong You: Nothing to Disclose, Wei Chen: Nothing to Disclose

4503 | PROLIFERATION-COMPETENT T CELLS PREDICT LIVER FIBROSIS REGRESSION DURING VIRAL CLEARANCE IN CHRONIC HBV INFECTION ◆

Wei Chen[1] Shuyan Chen[2] Yameng Sun[2] Wen Zhang[2] Ning Zhang[2] Xiaodong Ge[3] Hui Han[3] Hong Li[2] Wenyue Wu[2] Xiaoning Wu[2] Sai Santosh Babu Komakula[3] Chao Wang[3] Nithyananthan Subramaniyam[3] Xuzhen Yan[2] Qi Han[2] Aiting Yang[2] Natalia Nieto[3] Hong You[2]

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Background: Clinical evidence suggests that the suppression or elimination of the hepatitis B virus (HBV) does not consistently result in liver fibrosis remission for all patients, presenting challenges for those undergoing long-term anti-HBV treatment. Therefore, it is crucial to identify the underlying factors contributing to diverse outcomes in liver fibrosis reversal after HBV control. **Methods:** Bulk and single-cell RNA sequencing (scRNA-seq) were performed on liver biopsies from HBV-related fibrotic patients biopsied at baseline and at 78 and 260 weeks of antiviral treatment. Additionally, comprehensive bioinformatics analyses and multiplex immunohistochemical (mIHC) staining were carried out. **Results:** Patients with liver fibrosis and chronic HBV infection (CHB) underwent sequential biopsies during antiviral treatment. Fibrosis regression was assessed using the Ishak score and P-I-R system. Transcriptomic analyses of liver biopsies revealed accelerated gene expression and molecular function restoration in cases showing regression with antiviral treatment. Through Orthogonal Partial Least Squares Discriminant Analysis (OPLA-DA) and bioinformatics, a cell cycle gene signature (CC signature) was identified, stratifying treatment-naïve patients into CC^{low} and CC^{high} subgroups and predicting liver fibrosis regression following antiviral therapy in both the discovery and validation cohorts. Analyses of scRNA-seq data and mIHC staining confirmed that the CC signature was primarily enriched in a subset of T cells with heightened proliferative, tissue-resident memory, and cytotoxic capacities, termed proliferation-competent T cells (Tpc cells). A greater abundance of Tpc cells was found in CC^{high} patients and regressing cases, associated with reduced low-level viremia (LLV) and increased regression susceptibility during long-term antiviral treatment. **Conclusion:** Liver Tpc cells enriched with the CC signature have the potential to facilitate liver fibrosis regression during viral clearance in CHB patients. This finding provides a cautionary signal for non-regressing cases during nucleos(t)ide analogue-based anti-HBV treatments and offers novel cellular targets for combined immunotherapy with antiviral therapy.

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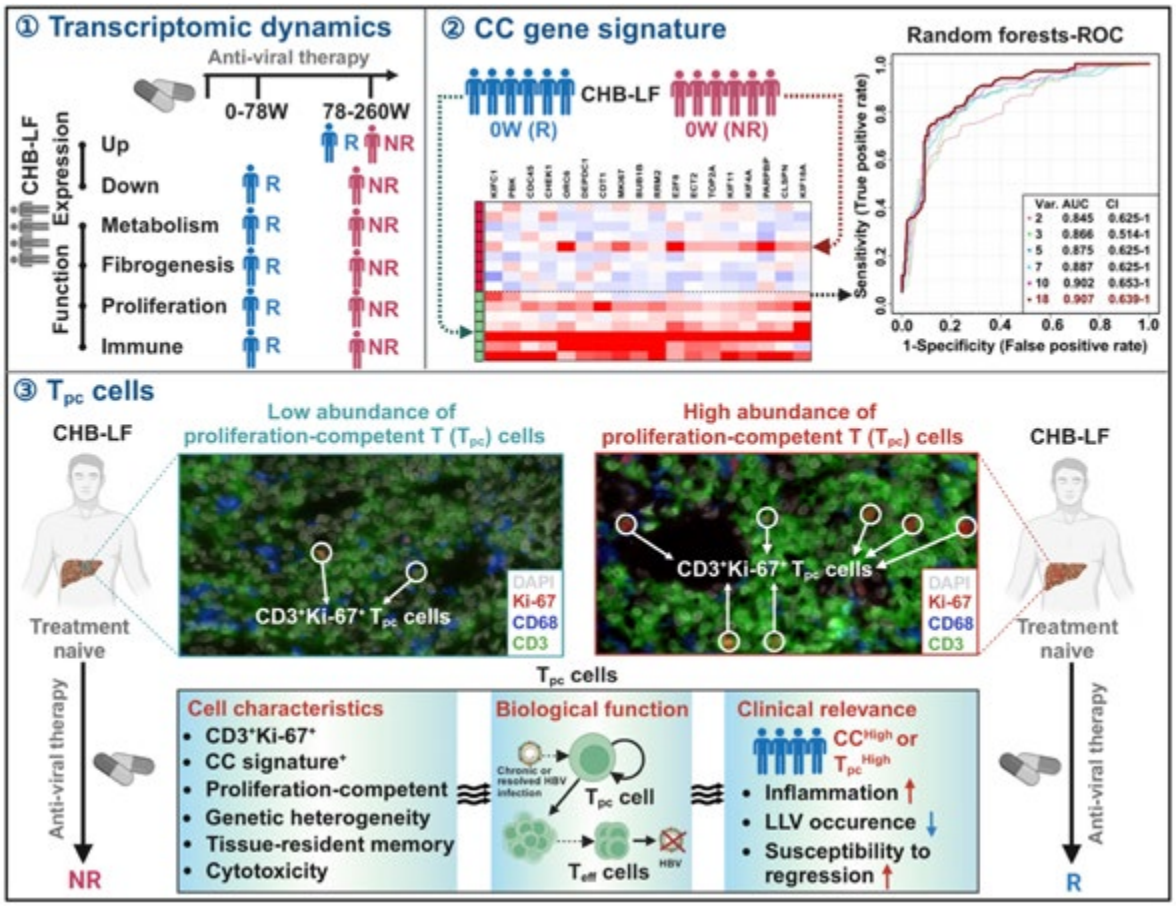

Disclosures: Wei Chen: Nothing to Disclose, Shuyan Chen: Nothing to Disclose, Yameng Sun: Nothing to Disclose, Wen Zhang: Nothing to Disclose, Ning Zhang: Nothing to Disclose, Xiaodong Ge: Nothing to Disclose, Hui Han: Nothing to Disclose, Hong Li: Nothing to Disclose, Wenyue Wu: Nothing to Disclose, Xiaoning Wu: Nothing to Disclose, Sai Santosh Babu Komakula: Nothing to Disclose, Chao Wang: Nothing to Disclose, Nithyananthan Subramaniyam: Nothing to Disclose, Xuzhen Yan: Nothing to Disclose, Qi Han: Nothing to Disclose, Aiting Yang: Nothing to Disclose, Natalia Nieto: Nothing to Disclose, Hong You: Nothing to Disclose

4504 | GENOME-WIDE ASSOCIATION TESTS BETWEEN INDIVIDUALS WITH ALCOHOLIC HEPATITIS AND HEAVY DRINKERS WITHOUT KNOWN LIVER DISEASES FROM THE GENOMALC COHORT

Tae-Hwi Schwantes-An[1] Marco Abreu[1] Timothy Morgan[2] Devanshi Seth[3]

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Background: Alcoholic hepatitis (AH) is an acute condition within the spectrum of alcohol-associated liver diseases, but distinct due to predominant inflammation in the liver and high mortality. We sought to conduct a large genome-wide association test (GWAS) to identify genetic underpinnings of risk for AH among heavy drinkers. **Methods:** GenomALC, a multi-national genetic cohort of heavy drinkers without liver diseases and patients with ALC, was used in this analysis. Cases were defined as the participants who either received alcoholic hepatitis diagnosis or patients with ALC diagnosis and bilirubin value over 5mg/dl. Controls were individuals who consumed large amount of alcohol for at least ten years, ≥80g/day (male) or ≥50g/day (female) but did not have any known liver related diagnoses at enrollment. GWAS was conducted using PLINK2 with AH vs. heavy drinker status as the outcome while adjusting for age, sex, and 10 principal components of genotypes for sample heterogeneity. **Results:** Overall, there were 1,249 AH cases and 1,860 heavy drinking controls included in the analysis. All included samples were clustered with 1KGP's EUR ancestry group samples in principal component analysis. Rs2294915, in high linkage disequilibrium with rs738409, in *PNPLA3* was genome-wide associated with

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the risk of AH (odds ratio (OR) = 1.7, pvalue=8.3x10^{-16}). Additionally, there were 11 independent loci that showed suggestive associations (pvalues < 5x10^{-06}), including variants located in genes such as *ESRRG* (estrogen related receptor gamma), and *NR3C2* (nuclear receptor subfamily 3 group C member 1 gene). Table 1 summarizes the top independent hits. To estimate the contribution of *PNPLA3* vs. suggestively associated loci, we computed McFadden's R-squared value. *PNPLA3* locus alone accounts for 1.7% of Rsq while the other 11 loci combined account for 6.5% of Rsq in AH vs. heavy drinkers GWAS. **Conclusion:** We report a genome-wide association between risk of developing AH among heavy drinkers and *PNPLA3*. While *PNPLA3* contributes the largest amount to the genetic risk of developing AH, a combined contribution of subthreshold associations highlight the role of inflammation related genes that further influence of risk of AH.

CHR	POS	Gene	rsID	Tested Allele	Other Allele	Tested Allele Frequency	N	OR (95% C.I.)	Pvalue
1	216953275	*ESRRG*	rs150709504	C	T	0.013	2932	3.89 (2.22-6.82)	2.04E-06
2	234231401	*SAG*	rs78936963	G	A	0.028	2932	0.36 (0.23-0.55)	4.13E-06
4	149108716	*NR3C2*	rs147726097	A	ATTTG	0.250	2932	0.71 (0.62-0.82)	1.49E-06
6	24941603	*RIPOR2*	rs367649059	G	GA	0.058	2932	2.18 (1.57-3.02)	3.71E-06
7	83692153	*SEMA3A*	rs9690948	A	G	0.228	2932	0.71 (0.61-0.81)	1.58E-06
9	4008954	*GLIS3*	rs660812	C	T	0.141	2932	1.50 (1.26-1.79)	4.84E-06
9	14058548	*NFIB*	rs10116586	C	A	0.473	2932	0.73 (0.64-0.83)	2.82E-06
11	66319262	*ACTN3*	rs10791881	G	A	0.338	2932	0.72 (0.64-0.82)	7.45E-07
12	18344211	*RERGL*	rs11043916	C	T	0.052	2932	0.50 (0.38-0.66)	1.13E-06
16	79672562		rs139176929	G	GTGTT	0.074	2932	0.53 (0.41-0.69)	2.14E-06
21	21057791		rs11383388	AT	A	0.185	2932	0.66 (0.56-0.78)	1.39E-06
22	44340904	*PNPLA3*	rs2294915	T	C	0.262	2932	1.71 (1.50-1.95)	8.31E-16

Disclosures: Tae-Hwi Schwantes-An: Target RWE: Consultant, Marco Abreu: Nothing to Disclose, Timothy Morgan: Nothing to Disclose, Devanshi Seth: Nothing to Disclose

4505 | STUDY OF THE SAFETY AND PRELIMINARY EFFICACY OF EXOSOMES SECRETED BY MENSTRUAL BLOOD-DERIVED MESENCHYMAL STEM CELLS (MENSCS-EXOS) IN THE TREATMENT OF LIVER CIRRHOSIS: PRECLINICAL STUDIES AND CLINICAL STUDIES

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Background: Liver injury (including hepatic fibrosis and cirrhosis) is caused by various factors such as hepatitis virus,schistosomiasis,alcohol,drugs and poisons. Clinically intervention is mainly aimed at the primary cause. Exosomes secreted by menstrual blood-derived mesenchymal stem cells (MenSCs-Exos) can alleviate liver damage and promote hepatocyte regeneration. This study aims to investigate its effects on liver fibrosis, portal pressure and liver function in preclinical and clinical studies **Methods:** Hepatic fibrosis was induced by intraperitoneal injection of CCl_4 twice a week. Exosomes of 1.0 x 10^{10} ps/rat were given once at the 8th week (low-dose group) and Exosomes of 3.0 x 10^{10} ps/rat were given 3 times by once the next day at the 8th week (high-dose group). Serological indicators, portal vein pressure, degree of hepatic fibrosis, liver index and spleen index were evaluated. In addition, 10 patients with cirrhosis were prospectively enrolled, receiving MenSCs-Exos by hepatic artery infusion under Digital Subtraction Angiography (DSA) at a dose of 1×10^9particels **Results:** In the preclinical experiments, the liver function in both groups was significantly recovered at two doses of exosomes. The liver synthesis function recovered significantly in the low-dose group. Hepatic portal vein pressure decreased significantly in both groups. Liver index and spleen index had no significant difference compared with the placebo group. In addition, the liver fibrosis was improved after the treatment with exosomes in both groups, and the

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high-dose treatment group showed a better results. In human clinical studies, when arterial infusion of exosomes, no adverse events occurred, physiological indicators such as blood pressure and heart rate were stable, 5 patients' portal vein pressure decreased, and 6 patients' liver stiffness were improved, and liver function in some patients was also improved **Conclusion:** MenSCs-Exos can significantly relieve portal vein pressure, improve hepatic function and inhibit hepatic fibrosis in rats and human. the pathological score of liver fibrosis showed a dose-dependent effect

Disclosures: Yang Lingqiao: Nothing to Disclose, Huang Zhicheng: Nothing to Disclose, Zhang Ting: Nothing to Disclose, Ke Youtao: Nothing to Disclose, Yuan Li: Nothing to Disclose, Xu Zhenyu: Nothing to Disclose, Zhou Tiantian: Nothing to Disclose, Chen Lu: Nothing to Disclose

4506 | COMPARATIVE ASSAY OF BARCODED TRANSPOSON VECTOR SYSTEMS *IN VIVO* REVEALS ADVANTAGES OF *PIGGYBAC*

Markcus Lee[1] Jenna Mancinelli[2] Morgan Preziosi[2] Alexandra Vazquez Salgado[1] Dingzi Yin[1] Agnes Holczbauer[1] Kirk Wangensteen[3]

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Background: Transposon systems have translational applications and are being used for *in vivo* and cell culture-based genetic screens and gene therapy. We and others perform gene transfer in mice using hydrodynamic tail vein injection (HTVI) of *Sleeping Beauty* (SB) transposons containing *Fah* expression sequences to restore *Fah* in a fraction of the hepatocytes of *Fah*$^{-/-}$ mice. We have used this paradigm to conduct genetic screens *in vivo* within the liver. The throughput of a genetic screen and capacity to capture rare events depends on the number of clonal events that are compared. We hypothesized that a more efficient transposon system would lead to more clonal events in the liver, further improving screen performance. The *PiggyBac* (PB) and *Tol2* (T2) are alternative DNA transposon systems that have never been compared to the SB in an *in vivo* mouse system. **Methods:** We generated four vector conditions: SB, PB, T2, and a no-transposase control. Each contained the transposon ends, the *Fah* gene as the cargo, and a unique nucleic acid barcode to enable identification of each system by sequencing. The vector systems were pooled together in three separate conditions: the transposon and transposase on the same plasmid (cis), the transposon and transposase of different plasmids (trans), and tenfold the transposon plasmid for each transposase (trans 1:10). The three pools of vectors were introduced into separate *Fah-/-* mice using the hydrodynamic tail vein injection (HTVI) technique. After one month, the liver tissues were harvested, bulk DNA was extracted, and nucleic acid barcodes were amplified to generate sequencing libraries. Using high throughput sequencing, we tracked the efficiency of gene delivery for each vector system. Verification of transposon insertion into hepatocytes was also performed using a sequencing method, known as LUMI-PCR. **Results:** In our liver gene transfer and FAH repopulation comparative assay, we detected up to 250-fold greater barcode recovery with PB than with the no-transposase control plasmids, and up to 7-fold more than SB, across all conditions. The PB and SB plasmids delivered in trans outperformed the cis condition. Tol2 barcode recovery was not different than the control. In an assay to validate the findings by injecting mice with each transposon separately, IHC staining demonstrated much more extensive liver repopulation of with PB than with the other plasmid systems. LUMI-PCR identified thousands of unique insertion sites in the mouse genome for PB and SB samples. **Conclusion:** We conclude that PiggyBac is the most efficient transposon system for gene delivery to the mouse liver, resulting in 7-fold increased activity over Sleeping Beauty.

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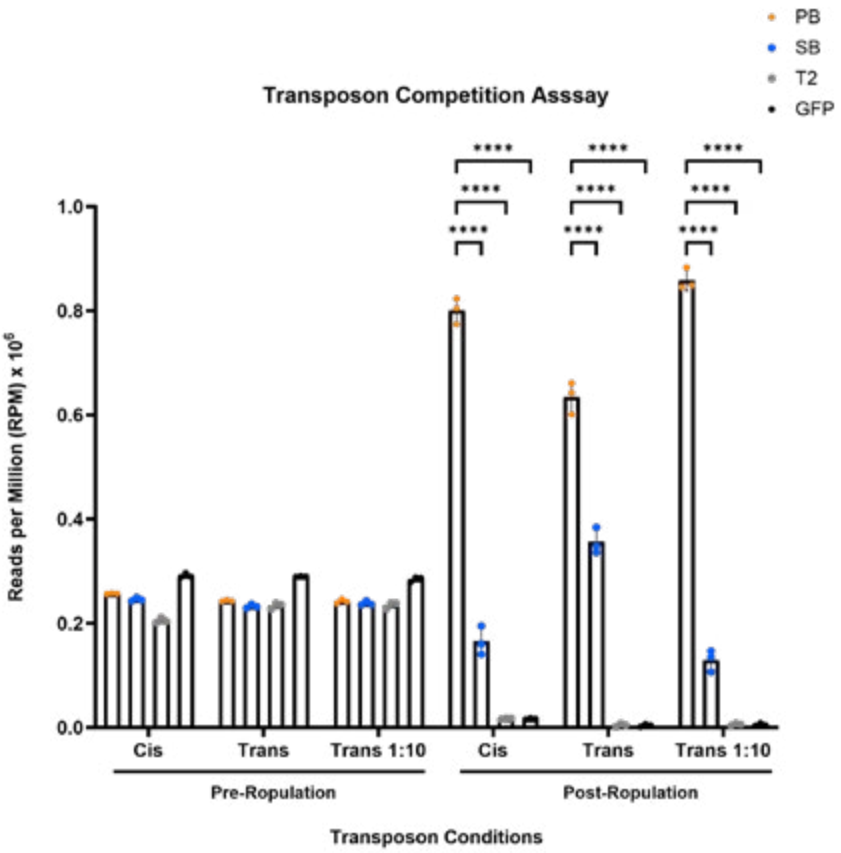

Disclosures: Markcus Lee: Nothing to Disclose, Jenna Mancinelli: Nothing to Disclose, Morgan Preziosi: Nothing to Disclose, Alexandra Vazquez Salgado: Nothing to Disclose, Dingzi Yin: Nothing to Disclose, Agnes Holczbauer: Nothing to Disclose, Kirk Wangensteen: Nothing to Disclose

4507 | PREDICTING MASLD RISK USING PATIENT-DERIVED INDUCED PLURIPOTENT STEM CELLS

Marisa Medina[1] Yuanyuan Qin[1] Parth Chhetri[1] Elizabeth Theusch[1] Grace Lim[1] Sheila Teker[1] Yu-Lin Kuang[1] Antonio Munoz-Howell[1] Varun Saxena[2] Dounia Le Guillou[1] Aras Mattis[1] Jacquelyn Maher[1]

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Background: Identification of individuals with high risk for Metabolic Dysfunction Associated Steatotic Liver Disease (MASLD) prior to disease onset could significantly improve the clinical management of this disease. We previously reported that undifferentiated patient-derived induced pluripotent stem cells (iPSCs) that harbor MASLD DNA risk variants displayed higher levels of oleate-induced intracellular lipid accumulation compared to those without these variants, suggesting that this measure may be predictive of MASLD disease risk. Here, we sought to develop an individual-level MASLD risk predictor based on functional assessment of patient-derived iPSCs. **Methods:** We quantified oleate-induced intracellular lipid accumulation in iPSCs from three independent cohorts of diverse ancestry women and men: 1) CIRM cohort of 22 biopsy-confirmed MASH patients and 17 healthy controls, 2) POST cohort of 18 MASLD cases and 17 controls, and 3) UCSF cohort of 4 biopsy-confirmed MASH patients and 8 healthy controls. iPSCs were incubated with 100mM oleate conjugated to BSA or BSA only for 24hr, stained with Nile Red, and Nile Red fluorescence was quantified by FACS. Oleate-induced intracellular lipid accumulation was calculated as the geometric mean of the Nile Red fluorescence in the oleate-treated cells divided by the BSA-treated cells. **Results:** In the CIRM cohort, levels of oleate-induced lipid accumulation were greater in iPSCs from MASH cases vs. controls (3.47±0.27 vs. 2.91±0.25 fold change, p=0.07). We identified the level of oleate-induced lipid accumulation that best separates cases and controls to create an iPSC-based MASLD risk score. Separation from this measure alone had a AUROC of 0.66. In both the POST and UCSF

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cohorts, we observed greater oleate-induced cellular steatosis in MASLD cases vs. controls (POST: 3.60±0.33 vs. 2.63±0.27 fold change, p<0.05 and UCSF: 4.40±0.46 vs. 1.99±0.19 fold change, p=0.0005). The CIRM iPSC-based MAFLD risk score had a sensitivity of 38.9% and a specificity of 76.5% to predict disease status in the POST cohort, and a sensitivity of 75.0% and specificity of 100% in the UCSF cohort. The higher predictive performance in the UCSF cohort may be attributed to the clinical similarities of the CIRM and UCSF cohorts. In contrast, POST cases were less severe (MASLD only) and while POST controls did not have a clinical diagnosis or evidence of elevated ALT/AST, all had established cardiometabolic disease risk. **Conclusion:** These findings suggest that oleate-induced intracellular lipid accumulation in subject-derived iPSCs has predictive information on individual-level susceptibility of MASH development. Further investigation of this model, such as assessment of additional MASLD-relevant cellular phenotypes, may inform the development of risk predictors critical for targeted surveillance of MASLD and promoting prevention before progression to advanced disease.

Disclosures: Marisa Medina: Nothing to Disclose, Yuanyuan Qin: Nothing to Disclose, Parth Chhetri: Nothing to Disclose, Elizabeth Theusch: Nothing to Disclose, Grace Lim: Nothing to Disclose, Sheila Teker: Nothing to Disclose, Yu-Lin Kuang: Nothing to Disclose, Antonio Munoz-Howell: Nothing to Disclose, Varun Saxena: Nothing to Disclose, Dounia Le Guillou: Nothing to Disclose, Aras Mattis: BioMarin Pharmaceuticals: Consultant, Pliant Therapeutics: Consultant, Regeneron Phamaceuticals: Consultant, HepaTx: Consultant, Pharmanest: Consultant, Jacquelyn Maher: Nothing to Disclose

4508 | PRIORITIZATION OF ICOSAPENT ETHYL FOR THE POTENTIAL REVERSAL OF METABOLIC DYSFUNCTION ASSOCIATED FATTY LIVER DISEASE USING A GENETICALLY INFORMED DRUG REPURPOSING PIPELINE

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[1]Vanderbilt University Medical Center, [2]Salt Lake City VA Medical Center, [3]University of Pennsylvania, [4]Stanford University, [5]Palo Alto VA Medical Center, [6]University of Massachusetts, [7]Phoenix VA Health Care System

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) affects over 100 million American adults. While weight loss can help to reduce fat content of the liver, it may not resolve fibrosis (e.g. scarring) caused by metabolic dysfunction-associated steatohepatitis (MASH). The recent FDA approval of Rezdiffra, a thyroid hormone receptor beta agonist, marks the first drug approved to treat MASH which has invigorated drug development in this area. Drug targets with support from genome-wide association studies (GWAS) are more than twice as likely to be approved in clinical trials than those without. Here we present a genetically-informed multi-stage drug-repurposing pipeline designed to prioritize existing drug targets for potential MASLD reversal. **Methods:** Our starting point was a large multi-ancestry GWAS in the Million Veteran Program which included 90,408 MASLD cases and 128,187 controls. For each gene, genetically predicted gene expression (GPGE) profiles were generated from 47 tissues from GTEx v7 using S-PrediXcan software. Drug-gene pairs were identified using directional gene-drug mapping in publicly available databases (Open Targets, Drug Gene Interaction Database). Finally, Mendelian randomization (MR) analysis was used to estimate the genetic effect of the candidate genes on alanine aminotransferase (ALT) levels to proxy therapeutic effects. **Results:** We identified 212 significant genes, 81 in the MASLD GWAS and an additional 141 using GPGE. Of these genes, 13 encoded proteins that are targets for 81 drugs and demonstrate a genetic effect consistent with a drug mechanism that would result in a beneficial pharmacological modulation. For these 81 drugs, we obtained GWAS summary statistics for 19 primary indications. Ultimately, 14 were excluded due to lack of significance leaving a final set of seven drug targets with five primary indications (Table 1). The observed effect of icosapent ethyl (a purified omega-3 fatty acid used to treat hypertriglyceridemia) on ALT level was particularly striking, equaling a 1.2 to 1.4 units/L reduction. The triglyceride-lowering effect of icosapent ethyl was proxied using one standard deviation change (either increase or decrease) gene expression at three different gene targets within the *FADS* locus (i.e., *FADS1*, *FADS2*, and *FADS3*). However, statistically significant effects were only observed when the triglyceride-lowering effect of icosapent ethyl was proxied via increased *FADS1* expression and decreased *FADS2* expression (Table 1). **Conclusion:** Using genetic information from the largest MASLD GWAS study to date, we identified icosapent ethyl as a possible genetically supported drug-repurposing target. Our analysis suggests that reducing triglycerides via icosapent ethyl, as proxied by genetically-predicted *FADS* expression, may help lower ALT with reduced liver injury. Further exploration of icosapent ethyl may be warranted.

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Table 1. Changes in liver enzyme ALT (units/L) levels per standard deviation change in genetically predicted gene expression (GPGE), as a proxy for the therapeutic action of repurposing existing drugs for treatment for MASLD via fixed-effects inverse-variance weighted (IVW) Mendelian randomization (MR)

Primary Indication	Gene Target	Proxied Drug or Drug class	Drug Action	No. of GPGE tissues	GPGE changes on primary indication	Mendelian randomization (MR)			
						IVW Beta	Std Err	P value	Egger P value
Atrial fibrillation/Arrhythmia	*SCN2A*	Riluzole, etc.	Inhibitor	1	-0.05	-0.15	0.66	0.82	n/a
Epilepsy	*SCN2A*	Eriosomide, etc.	Inhibitor	2	0.03	-0.15	0.68	0.83	n/a
Hypertriglyceridemia	*FADS3**	Icosapent ethyl	Inhibitor	8	0.01	-1.17	0.18	0.86	0.92
	FADS1	Icosapent ethyl	Agonist	23	-0.11	-1.26	0.05	$6.8x10^{-160}$	0.29
	FADS2	Icosapent ethyl	Inhibitor	26	-0.06	-1.39	0.06	$3.4x10^{-127}$	0.97
Multiple sclerosis	*S1PR2*	Fingolimid, etc.	Agonist	2	1.10	-0.09	0.03	$4.0x10^{-04}$	n/a
Type 2 diabetes	*PPARG*	Pioglitazone hydrochloride	Agonist	3	-0.18	0.66	0.09	$1.2x10^{-14}$	0.90

*Standard error inflated to account for significant heterogeneity of the tissue-specific effects. Estimated MR effects for this gene target reflect a random-effects IVW MR (rather than fixed-effects IVW MR estimate).

Disclosures: Hannah Seagle: Nothing to Disclose, Todd Edwards: Nothing to Disclose, Nikhil Khankari: Nothing to Disclose, Julie Lynch: Nothing to Disclose, Alexis Akerele: Nothing to Disclose, Jacklyn Hellwege: Nothing to Disclose, Megan Shuey: Nothing to Disclose, Michael Levin: Nothing to Disclose, Kyung Lee: Nothing to Disclose, Jennifer Lee: Nothing to Disclose, Kent Heberer: Aquestive Therapeutics: Stock - publicly traded company, Ginkgo Bioworks: Stock - publicly traded company, Mind Medicine: Stock - publicly traded company, Procter and Gamble: Stock - publicly traded company, Donald Miller: Nothing to Disclose, Peter Reaven: Nothing to Disclose, Kyong-Mi Chang: Data Monitoring Committee member relationship with Virion Therapeutics; Has not ended; Advisor relationship with GSK; Has ended

4509 | FATTY ACID OXIDATION IMPAIRMENT AND METABOLIC CHANGES IN LIVER DISEASE

Sarah Abdel-Meguid[1] *Rana Abualsaud*[2] *Habiba Ahmed*[3] *Muneeb Ahmed*[4] *Jihad Aljabban*[5]

[1]*Robert Wood Johnson Medical Center,* [2]*Cleveland Clinic,* [3]*Duke University Hospital,* [4]*University of Kentucky,* [5]*University of North Carolina Medical Center*

Background: Metabolic programming plays a pivotal role in pathophysiology and development of disease. A hallmark of metabolic dysfunction-associated fatty liver disease (MAFLD) is lipid deposition resulting from systemic metabolic dysregulation. Alterations in fatty acid synthesis (FAS) and fatty acid oxidation (FAO) in the liver may contribute to steatosis and subsequent cirrhosis. Likewise, dysregulation of fatty acid metabolism is a topic of active research and may be implicated in hepatocellular carcinoma (HCC). Here we highlight the metabolic landscape across liver disease. **Methods:** We used the Search Tag Analyze Resource for the GEO platform to search the NCBI Gene Expression Omnibus (GEO) for MAFLD, MASH, cirrhosis, HCC, and healthy liver control biopsies. We conducted meta-analyses of 62 MAFLD, 187 MASH, 197 cirrhosis, and 505 HCC samples against healthy controls, focusing on genes related to glycolysis, FAS, and FAO. **Results:** In the MAFLD analysis, we found downregulation of glycolysis-related genes HK2 (p=0.00493) and PFKB2 (PFKB2 is down, p=0.025) along with upregulation of the lipogenesis-related gene SREBF1 (p=0.00106). MASH analysis revealed an increase in fatty acid synthase (FASN, p=0.0267). Meta-analysis of cirrhosis samples showed a decrease in FAO-related genes including HADH (p=0.00843), ACOX1 (p=0.0367), and BBOX1 (0.00853). Lastly, in our HCC analysis we found upregulation of glycolysis related genes HK2 (p=1.69E-9), PFKB2 (p=0.0074), and PKM (p=0.000110). Additionally, FASN was upregulated (p=0.0151) and several genes related to FAO were downregulated including CPT2 (p=0.000750), ACADL (p=0.00009), MLYCD (p=0.0000326), and HADH (p=0.000379). **Conclusion:** Our meta-analysis provides a detailed view of metabolic changes across liver disease stages, from MAFLD to HCC. In MAFLD, the downregulation of glycolysis-related genes and upregulation of lipogenesis-related genes. In MASH, increased FASN points to enhanced fatty acid synthesis, contributing to hepatic lipid overload. Cirrhosis shows a significant decrease in FAO-related genes, indicating impaired fatty acid

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breakdown, which may worsen lipid accumulation and liver damage. Similarly, HCC analysis demonstrated a decrease in FAO-related genes. Our study underscores the crucial role of metabolic dysregulation in liver disease progression and the potential of targeting metabolic pathways for therapy.

Disclosures: Sarah Abdel-Meguid: Nothing to Disclose, Rana Abualsaud: Nothing to Disclose, Habiba Ahmed: Nothing to Disclose, Muneeb Ahmed: Nothing to Disclose, Jihad Aljabban: Nothing to Disclose

4510 | BARIATRIC SURGERY IMPROVES MRI-DETERMINED HEPATIC PROTON DENSITY FAT FRACTION AND METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS IN PATIENTS WITH OBESITY: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: Bariatric surgery has been reported to be an effective way to improve metabolic dysfunction-associated steatotic liver disease (MASLD) and metabolic dysfunction steatohepatitis (MASH) in obese individuals. The current systemic review aimed to assess the changes in MRI-determined hepatic proton density fat fraction (MRI-PDFF) and nonalcoholic fatty liver disease activity score (NAS) after bariatric surgery in MASLD/MASH patients with obesity. **Methods:** We searched various databases including PubMed, OVID Medline, EMBASE, and Cochrane Library. Primary outcomes were the changes in intrahepatic fat on MRI-PDFF and histologic features of MASH. **Results:** Thirty studies with a total of 3,134 patients were selected for meta-analysis. Bariatric surgery significantly reduced BMI (ratio of means, 0.79) and showed 72% of reduction of intrahepatic fat on MRI-PDFF at 6 months after bariatric surgery (ratio of means, 0.28). NAS was reduced 60% at 3–6 months compared to baseline, 40% at 12–24 months, and 50% at 36–60 months. Nineteen studies revealed that the proportion of patients with steatosis decreased by 44% at 3–6 months, 37% at 12-24 months, and 29% at 36-60 months; lobular inflammation by 36% at 12–24 months and 51% at 36-60 months; ballooning degeneration by 38% at 12–24 months; significant fibrosis (≥F2) by 18% at 12-24 months and by 17% at 36–60 months after surgery. **Conclusion:** Bariatric surgery significantly improved MRI-PDFF and histologic features of MASH in patients with obesity. Bariatric surgery might be the effective alternative treatment option for patients MASFD/MASH who do not respond to life style modification or medical treatment.

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4511 | MEDITERRANEAN DIET AND LOW-FAT DIET ARE EQUALLY EFFECTIVE IN MASLD RESOLUTION REGARDLESS OF PNPLA3 GENOTYPE: A RANDOMIZED CONTROLLED TRIAL ◆

Gediz Dogay Us[1] Ger Koek[2]

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Background: Dietary interventions to reduce weight are regarded as the hallmark of metabolic dysfunction-associated steatotic liver disease (MASLD) treatment. However, the most effective dietary protocol for addressing MASLD and related cardiometabolic risks, irrespective of weight reduction, remains uncertain. Furthermore, the role of PNPLA3 as a treatment modulator has not been fully understood. Therefore, we aimed to test the efficacy of Mediterranean diet (MD) against low-fat diet (LFD) in hepatic fat and fibrosis reduction and assess whether PNPLA3 genotype interacts with response to either diet. **Methods:** We recruited 250 adult MASLD subjects and randomized 1:1 to a 12-week dietary intervention of isocaloric MD vs LFD. Individuals with excess alcohol intake (>20 g/day for women and >30 g/day for men) and other etiologies of steatosis were excluded. At baseline, subjects were genotyped for PNLPA3 single nucleotide polymorphism. Anthropometrical assessment and blood tests were performed at baseline and follow-up. Steatosis and fibrosis were assessed by vibration controlled transient elastography (VCTE) in terms of controlled-attenuation parameter (CAP) and liver stiffness

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measurement (LSM). All subjects were provided with essential food supplies throughout the intervention. Adherence was monitored via validated questionnaires. Primary outcomes were relative reduction in CAP and LSM. Within each diet group, differences between time points were tested by paired sample t-test. Linear mixed models were used to test differences between groups and assess interaction between PNPLA3 genotype and diet groups. Models were adjusted for age. **Results:** G allele frequency was 28.2%. Of 250 participants (age, 52.7±12.4 years, 37% men, body mass index, 34.8±5.9 kg/ m^2), 70% completed the trial with good adherence. At week 12, both groups presented with a significant relative reduction in CAP (48.7 dB/m, 95% CI 40.8, 57.0, P<0.001 in MD vs 42.3 dB/m, 95% CI 31.9, 52.7, P<0.001 in LF), LSM (1.3 kPa, 95% CI 0.56, 2.10, P<0.001 in MD vs 1.27 kPa, 95% CI 0.76, 1.77, P< 0.001 in LF) and body weight (4.79 kg, 95% CI 4.03, 5.55, P<0.001 in MD vs 4.07 kg, 95% CI 3.14, 5.00, P<0.001 in LF) without a significant between-groups difference (CAP, P = 0.24; LSM P=0.47; weight, P=0.17). Age-adjusted linear mixed models of CAP, LSM and body weight did not show a statistically significant interaction between PNPLA3 genotype and diet (P= 0.47, P= 0,94, P=0.92, respectively). **Conclusion:** Our results have shown that weight reduction achieved by Mediterranean diet and low-fat diet are similarly efficient in steatosis and fibrosis reduction, and PNPLA3 genotype does not affect the response to diet. Further studies investigating the impact of diet and nutrigenetics in liver-related outcomes are warranted.

Disclosures: Gediz Dogay Us: Nothing to Disclose, Ger Koek: Nothing to Disclose

4512 | SYSTEMATIC REVIEW OF EXERCISE FOR THE TREATMENT OF PEDIATRIC METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE

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Background: Steatotic liver disease affects approximately 1 in 10 children in the U.S. and increases the risk of cirrhosis, diabetes, and cardiovascular disease. Lifestyle modification centered on increased physical activity and dietary improvement is the primary management approach. However, specific recommendations regarding the type, duration, or frequency of exercise in the treatment of pediatric metabolic dysfunction-associated steatotic liver disease (MASLD) are currently lacking. Therefore, we performed a systematic review of studies assessing the impact of exercise interventions on validated hepatic outcomes in children with steatotic liver disease. **Methods:** We searched CENTRAL, PubMed, Embase, Web of Science, CINAHL and Google Scholar for studies in English, involving children aged 0 to 19 years diagnosed with steatotic liver disease or at increased risk for MASLD due to overweight or obesity. Eligible studies were required to examine the impact of exercise interventions on hepatic steatosis and/or liver chemistry. The risk of bias was assessed with RoB2 and ROBINS-I. Data extraction was performed by 2 independent reviewers. **Results:** From an initial pool of 1571 unique records, we included 15 studies encompassing 958 children (Figure 1). These comprised 6 studies comparing exercise intervention with non-exercising controls, 3 uncontrolled studies of exercise intervention, 2 studies comparing exercise plus lifestyle interventions with lifestyle interventions alone, and 9 studies comparing different types of exercise interventions. There were 10 studies that evaluated hepatic steatosis and in 5 of these, there was an absolute decrease in hepatic fat which ranged from -1% to -3%. In the 8 studies that evaluated liver chemistry, no significant changes were observed. **Conclusion:** Because increased physical activity is a key treatment component for pediatric MASLD, precise, evidence-driven guidelines are imperative for effective clinical management. The current evidence supporting exercise intervention for pediatric MASLD treatment remains limited, reflecting the methodological constraints within the existing evidence base. However, given the evolving body of evidence in adults with MASLD, exercise intervention holds promise as a viable treatment strategy for children with MASLD. To enhance clinical care and improve outcomes, high-quality exercise-based clinical trials in children with MASLD are needed.

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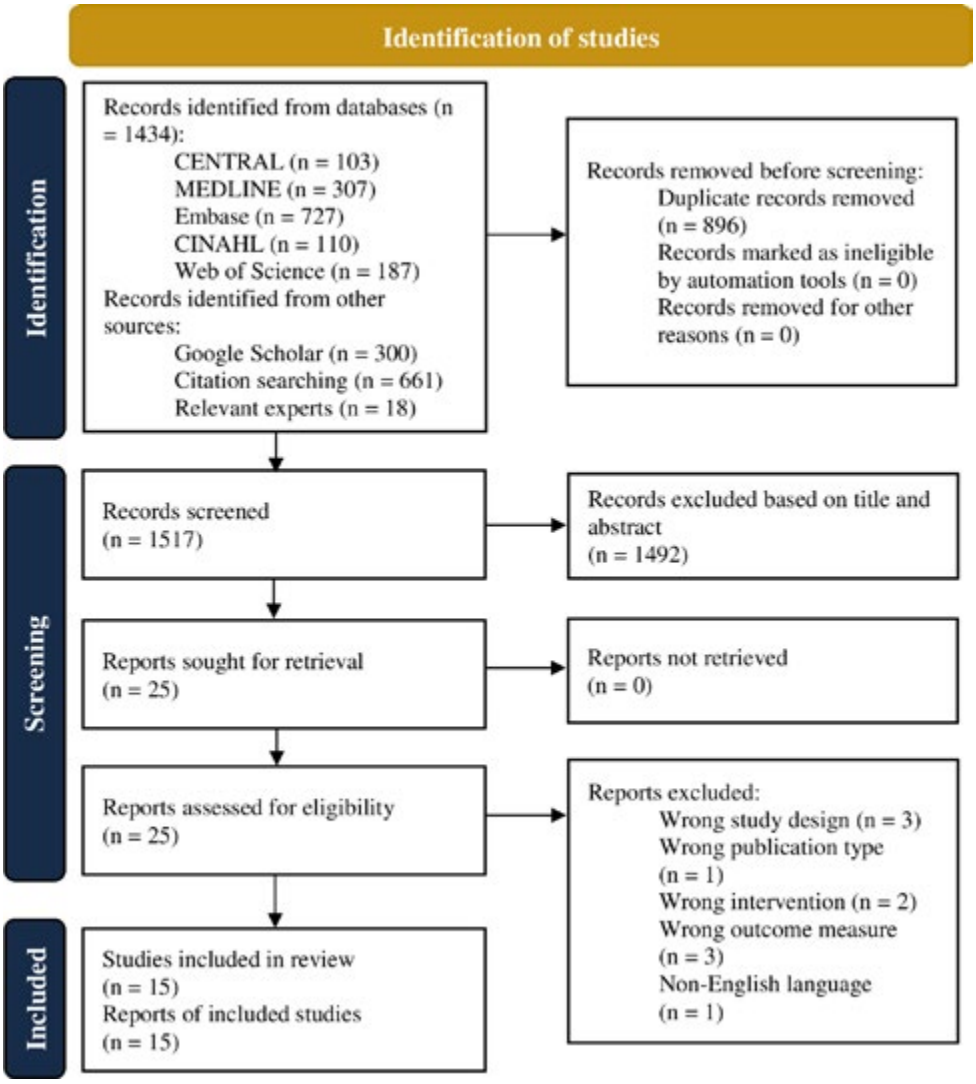

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4513 | PATIENT PREFERENCES TOWARDS ATTRIBUTES OF DRUGS DESIGNED TO TARGET METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS: A NON-INTERVENTIONAL INTERVIEW STUDY

Jonathan Stine[1] Nenad Medic[2] Billie Pettersson[3] Meredith Venerus[4] Jenny Blau[5]

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Background: Attitudes regarding benefit–risk and treatment burden can influence patient preferences and adherence to prescribed medication. Consequently, obtaining patient input when developing new therapies is critical. **Methods:** In this US non-interventional qualitative study, adults with confirmed metabolic dysfunction-associated steatohepatitis (MASH) ranked their preferences for 8 treatment attributes (Table 1) on a scale of 1–8 (1, most important; 8, least important) via telephone interviews. Patients then selected their preferred option from 5 hypothetical product profiles (A–E) that combined different degrees of the 8 attributes. Patients evaluated treatment profiles A–D first, and then re-evaluated their preferences after being provided profile E, a drug designed to reverse genetic predisposition to MASH, unlike profiles A–D. **Results:** Based on the mean scores of 28 patients, the highest ranked attributes were preventing disease progression (2.3/8), improved liver health test

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results (2.8/8) and reversing genetic predisposition (3.5/8). Mode/frequency of administration (7.5/8) and risk of side effects (5.5/8) were ranked the lowest. Of product profiles A–D, most patients (17/28, 61%) selected profile D (due to the potential to prevent progression to more serious liver disease and positive impact on cardiovascular health issues, liver health, fatigue and weight loss) followed by profile C (7/28, 25%; due to the positive impact on liver health, fatigue/abdominal discomfort, cardiovascular health issues, weight loss and the lower administration frequency) and profile A (4/28, 14%; due to the oral administration and absence of gastrointestinal issues as a side effect). No patient chose profile B because of the side effect (itchiness) and its other attributes performing worse than the other profiles (lowest improvement in liver health and increased levels of low-density lipoproteins in the blood). When shown profile E alongside profiles A–D, most patients (23/28, 82%) selected profile E (due to the ability to reverse genetic predisposition to MASH, greatest potential improvement in liver health, ability to prevent progression to more serious liver disease and lowest administration frequency compared with the other profiles). **Conclusion:** The most important attributes of new therapies for patients were prevention of disease progression, improved liver test results and ability to reverse genetic predisposition. When choosing between treatments, patients were willing to compromise on some of these attributes.

Table 1. Treatment profiles

	Product profiles				
Treatment attributes	**A**	**B**	**C**	**D**	**E**
Reverse genetic predisposition	No				Yes
Improve liver health according to liver function tests[a]	+++	+	+++	+++	++++
Prevent progression to more serious liver disease[a,b]	+	++	+	+++	++++
Improve fatigue/abdominal discomfort[a]	++	++	+++	+++	+++
Improve overall cardiovascular health[a]	+	–	+++	++	–
Provide additional metabolic benefits	No/limited weight loss		Substantial weight loss (7–15%)		None
	Lowers LDL cholesterol[c]	Increases LDL cholesterol[c]	Lowers LDL cholesterol[c]		
Administration mode/frequency	Oral pill (once daily)		Injection (once weekly)	Injection (once daily)	Injection (once monthly)
Presence of unwanted side effects	None	Itchiness	Limited ISRs Gastrointestinal reactions[d]		Limited ISRs

ISR, injection site reaction; LDL, low-density lipoprotein.

[a]Treatment attributes rated from '++++' (greatest positive impact) to '+' (lowest positive impact) or '–' (no impact).

[b]e.g. cirrhosis or transplantation.

[c]In blood.

[d]e.g. nausea, occasional constipation, vomiting.

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4514 | MODERATE-INTENSITY AEROBIC EXERCISE TRAINING IMPROVES METABOLIC SYNDROME SEVERITY IN ADULTS WITH MASLD

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Background: Individuals with metabolic dysfunction-associated liver disease (MASLD) are known to have more severe metabolic syndrome (MetS). Given that most fatalities among MASLD patients stem from cardiovascular disease (CVD) or malignancies, which are driven by MetS, mitigating MetS risk holds promise for improving patient outcomes. Exercise training is recommended for all with MASLD and is documented to improve individual metabolic risk factors. Whether exercise training improves overall MetS risk remains unknown. We further investigated this relationship in a post hoc analysis of an exercise study among adults with MASLD and increased metabolic risk. **Methods:** In the NASHFIT trial, subjects with histologically confirmed metabolic dysfunction-associated steatohepatitis (MASH) were randomized into one of two groups: moderate-intensity (45-55% maximal heart rate) aerobic exercise or standard clinical care. Mediterranean-based dietary counselling was provided to each group. Of the 28 patients enrolled, paired data was available for 23 patients for this analysis: (n=15) in exercise and (n=8) in standard clinical care. Change in metabolic syndrome severity was measured and compared between two groups using the previously validated MetS Severity Z-Score, which is derived from the combination of age, biologic sex, race/ethnicity, height, weight, waist circumference, systolic blood pressure, high-density lipoprotein, serum triglycerides and fasting glucose. **Results:** The study cohort had mean age 52 +/- 11 years and mean body mass index 33.8 +/- 5.0 kg/m^2. Thirteen (57%) were female, 70% had hypertension, 61% hyperlipidemia and 39% diabetes. Liver fibrosis stage at study entry was 56% (n=13) F0/F1, 22% (n=5) F2, 17% (n=4) F3, and 4% (n=1) compensated F4. Exercise training led to considerable improvement not only in individual metabolic syndrome components, (Table 1), but also the composite MetS Z-Score (waistline) by -0.45 in the exercise training group compared to increase by +0.60 in the standard clinical care group ($p<0.05$; mean reduction -46% vs. +33% increase respectively). In terms of clinically significant improvement (MetS Z-Score $\Delta > -0.6$), 40% (n=6) of exercise subjects achieved this threshold while no standard of care subject met this difference. Notably, these findings were observed without clinically significant weight loss. **Conclusion:** Exercise training significantly reduced the severity of MetS in adults with histologically confirmed MASH compared to standard clinical care and at clinically significant thresholds of response. These findings suggest that incorporating structured exercise training programs into routine clinical management could be a pivotal strategy in managing MetS and improving CV and oncologic outcomes in adults with MASLD.

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Table 1 - Metabolic syndrome severity

	Control (n=8)			Exercise (n=15)			
	Baseline	Post	Within group *p*-value	Baseline	Post	Within group *p*-value	Between group *p*-value
Anthropometry and Body composition							
BMI, kg/m²	34.6 (5.3)	35.0 (5.4)	0.880	33.4 (0.6)	32.8 (0.3)	0.729	0.129
Body weight, kg	108.6 (23.0)	110.1 (23.3)	0.896	97.2 (13.2)	94.9 (12.3)	0.625	0.051
Waist circumference, in	45.8 (4.9)	46.3 (4.8)	0.835	43.7 (3.5)	43.0 (0.6)	0.596	0.069
VAT, lbs.	6.9 (2.7)	7.2 (2.8)	0.830	5.4 (1.5)	5.2 (1.1)	0.678	0.032
Body fat, %	40.5 (11.6)	38.4 (11.1)	0.724	43.7 (7.6)	42.3 (8.0)	0.628	0.374
Liver volume, cc	2545 (640)	2597 (570)	0.866	2267 (445)	2131 (418)	0.405	0.039
Cardiorespiratory fitness							
VO_2peak, mL/kg/min	24.6 (5.5)	22.7 (3.2)	0.429	20.6 (5.3)	23.7 (6.5)	0.167	0.055
Biochemistry							
Glucose (fasting), mg/dL	136 (55)	156 (89)	0.059	131 (37)	117 (29)	0.247	0.039
Hemoglobin A1c, %	6.2 (1.1)	6.6 (1.7)	0.555	6.4 (1.3)	6.0 (0.8)	0.348	0.006
HOMA-IR	9.5 (6.2)	12.6 (14.9)	0.618	14.3 (11.5)	9.2 (6.5)	0.160	0.168
Insulin, IU/mL	27.3 (14.5)	31.1 (29.9)	0.763	41.1 (27.9)	33.4 (20.1)	0.400	0.442
Lipids							
Total cholesterol, mg/dL	203 (37)	184 (25)	0.278	187 (49)	187 (51)	0.986	0.350
LDL, mg/dL	120 (33)	109 (33)	0.554	109 (40)	109 (41)	0.964	0.476
HDL, mg/dL	43 (12)	40 (12)	0.614	43 (9)	44 (7)	0.712	0.188
Triglyceride, mg/dL	222 (94)	228 (108)	0.921	172 (64)	172 (76)	0.998	0.982
MetS severity							
MetS BMI, Z-score	1.73 (1.36)	2.29 (1.99)	0.554	1.41 (0.75)	1.05 (0.79)	0.199	0.017
MetS Waistline, Z-score	1.81 (1.38)	2.41 (1.99)	0.526	1.44 (0.78)	0.99 (0.70)	0.099	0.007
MetS BMI, %ile	87.3 (16.9)	91.0 (8.5)	0.619	87.3 (16.4)	79.4 (16.1)	0.177	0.066
MetS Waistline, %ile	88.5 (16.7)	93.0 (6.9)	0.523	87.3 (16.8)	79.2 (15.1)	0.159	0.045

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4515 | CARBOHYDRATE RESTRICTION DELIVERED VIA REMOTE CARE IMPROVES LIVER MARKERS IN INDIVIDUALS WITH OBESITY OR OVERWEIGHT AND ABNORMAL ALANINE TRANSAMINASE

Shaminie Athinarayanan[1] *Caroline Roberts*[1] *Rebecca Adams*[1] *Brittanie Volk*[1]

[1]*Virta Health*

Background: The prevalence of metabolic-associated steatohepatitis liver disease (MASLD) and metabolic-associated steatohepatitis (MASH) is higher among individuals with obesity. Managing elevated alanine aminotransferase (ALT) levels early is crucial, as it is a key marker of liver inflammation and damage. Early intervention, including dietary management and physical activity, can prevent the progression of these liver diseases, thus improving liver health and overall metabolic outcomes. The current study evaluates the effectiveness of a remotely delivered carbohydrate-restricted nutrition therapy (CRNT) in improving liver enzymes and liver-specific surrogate markers among individuals with obesity or overweight and abnormal ALT. **Methods:** This retrospective observational analysis assessed the 1-year effect of CRNT on liver enzymes and liver-specific surrogate markers. A random sample of 450 individuals, with equal allocation of males and females, was selected from those with obesity or overweight and abnormal enrollment ALT levels (>30 U/L for males and >19 U/L for females) who stayed in the program for at least a year. Changes from enrollment to 1 year were assessed using linear mixed-effects models adjusted for age, BMI, and gender for continuous variables, or McNemar's test for categorical variables, as appropriate. **Results:** Enrollment descriptives are provided in Table 1. All liver-related markers significantly improved after 1 year (p<0.001), including ALT (-26.1%), AST (-18.7%), ALP (-7.1%), hepatic steatosis index (HSI; -9.2%), and triglyceride-glucose index (TyG index; -2.6%) (Table 1). The percentage of individuals with abnormal ALT significantly decreased from 100% to 52.2% (p<0.001) in 1 year. Additionally, 13.5% of individuals had a histologically meaningful ALT decrease of 17 U/L. **Conclusion:** This study demonstrated that a remotely delivered CRNT improved liver enzymes and surrogate markers in a real-world setting that emphasizes a nutrition-first approach. This aligns with the current AASLD practice guidance, which recommends non-pharmacologic interventions as initial therapy before considering any pharmacologic interventions. However, future studies should investigate whether these improvements are associated with weight loss and the level of nutritional ketosis induced by CRNT.

Table 1. Enrollment descriptives, and liver related marker including liver enzymes outcomes from enrollment to 1 year

Enrollment descriptives	**Mean (SD)**	
Enrollment age (years)	48.2 (10.1)	
Enrollment BMI (kg/m2)	38.4 (6.2)	
Enrollment weight (lbs)	251.0 (52.4)	
Enrollment ALT (U/L)	41.5 (28.0)	
Enrollment AST (U/L)	30.2 (29.3)	
Enrollment ALP (U/L)	77.6 (22.7)	
Enrollment TyG index	8.7 (0.5)	
Enrollment HSI	57.2 (9.6)	
Liver variables	**Mean ± SE Enrollment**	**Mean ± SE 1 year**
ALT (U/L)	39.1 ± 0.7	28.9± 0.9 ***
AST (U/L)	28.0 ± 0.5	22.7± 0.5 ***
ALP (U/L)	77.9 ± 1.1	72.3± 1.2 ***
HSI	57.4 ± 0.1	52.1± 0.4 ***
TyG index	8.7 ± 0.0	8.5± 0.0 ***

Abbreviations. SE, standard error; ALT, alanine transaminase; AST, aspartate transaminase; ALP, alkaline phosphatase; HSI, hepatic steatosis index; TyG index, triglycerides glucose index
Note. Adjusted means were obtained using linear mixed effects models controlling for enrollment age, sex, and BMI.
*** p<0.001

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Disclosures: Shaminie Athinarayanan: Nothing to Disclose, Caroline Roberts: Nothing to Disclose, Rebecca Adams: Nothing to Disclose, Brittanie Volk: Nothing to Disclose

4516 | FEASIBILITY, SAFETY AND ACCEPTABILITY OF DIFFERENT DOSES OF AEROBIC EXERCISE TRAINING IN ADULTS WITH HISTOLOGICALLY-CONFIRMED MASLD

Breianna Hummer-Bair[1] Nataliya Smith[2] James Heinle[1] Kyra VanKirk[1] Kara DiJoseph[1] Zeba Hussaini[1] Ryan Jackson[1] Ian Schreibman[1] Elizabeth Stonesifer[3] Justin Tondt[1] Rohit Loomba[4] Kathryn Schmitz[5] Scot Kimball[1] Jonathan Stine[6]

[1]Penn State, [2]Penn State College of Medicine, [3]Penn State Milton S. Hershey Medical Center, [4]University of California, San Diego, [5]UPMC, [6]Pennsylvania State University

Background: While lifestyle modification through increased physical activity is recommended for all with metabolic dysfunction-associated steatotic liver disease (MASLD), the most effective exercise regimen remains unknown. The AMPED trial seeks to clarify the efficacy of different exercise doses in reducing serum and imaging biomarkers of fibroinflammation as well as histologic disease activity. **Methods:** We are conducting a 16-wk. RCT involving adults with biopsy confirmed Metabolic Dysfunction-Associated Steatohepatitis (MASH) and liver fibrosis (F) stages 1-3. These patients are assigned in a 1:1:1 ratio to either receive supervised aerobic exercise training or standard-of-care (SOC). The exercise intervention includes two groups: one engaged in moderate-intensity aerobic exercise totaling the guideline-based 750 Metabolic Equivalent of Task (MET)-min per week, while the other a regimen totaling 1,000 MET-min per week, exceeding current recommended amounts. We present an interim study update and report out feasibility, safety and acceptability data between June 2022 and May 2024. **Results:** A total of 26 subjects have been screened for the study of whom 16 were invited for in-person screening visits. Two subjects failed screening [not MASH (n=1), excessive alcohol consumption (n=1)]. Current enrollment stands at 14 participants with a biological sex balanced representation (50% female) and a mean age of 50.4 +/- 10.8 years. Liver fibrosis stage at study entry was: 50% (n=7) for F1, 35% (n=5) for F2 and 14% (n=2) for F3. Baseline cardiorespiratory fitness (VO_2peak) measured through a treadmill graded exercise test, averaged 20.6 +/- 3.2 mL/kg/min. Baseline body mass index (BMI) was 32.7 +/- 5.3 kg/m^2 and body fat percent averaged 43.4% +/- 10.0. Other comorbidities among the participants included diabetes (39%), hypertension (54%) and hyperlipidemia (54%). Randomization of participants resulted in five to the SOC group, four to the 1,000 MET-min/week group and four to the 750 MET-min/week group. Ten have completed the trial, three (21%) (one from each group) have withdrawn due to time constraints while one is currently following the protocol (SOC). *A priori* definitions of feasibility (>80% exercise session completion) and acceptability (>50% of subjects approached enrolled) have been met with 98.6 % completion of exercise sessions performed in the 750 MET-min/wk group and 95.2% in the 1,000 MET-,min/wk group along with 61% of subjects approached enrolling in the study. Three adverse events have occurred, none of which were related to the study intervention. **Conclusion:** The ongoing AMPED study confirms that moderate-intensity aerobic exercise at or above current guideline-based amounts is feasible, safe and acceptable. We look to report our efficacy data with regards to serum and imaging biomarkers as well as histologic disease activity by Summer 2026.

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Madrigal Pharmaceuticals: Research grant, Merck: Research grant, NGM Biopharmaceuticals: Research grant, Novo Nordisk: Research grant, Pfizer: Research grant, Sonic Incytes: Research grant, Terns Pharmaceuticals: Research grant, LipoNexus, Inc.: Co-founder, Kathryn Schmitz: Nothing to Disclose, Scot Kimball: Nothing to Disclose, Jonathan Stine: Zydus Therapeutics: Grant/Research Support, Novo Nordisk: Consultant, Galectin: Grant/Research Support, Novo Nordisk: Grant/Research Support, Astra Zeneca: Grant/Research Support, Noom: Grant/Research Support, Zydus: Grant/Research Support, Kowa: Grant/Research Support

4517 | THE IMPACT OF POMEGRANATE CONSUMPTION ON CLINICAL PARAMETERS IN MASLD: A META-ANALYSIS AND A SYSTEMATIC REVIEW

Islam Mohamed[1] Hazem Abosheaishaa[2] Sarah George[1] Mira Bhatia[1] Lauren Baetje[1] Suman Manek[1] Nina Henry[1] Khushi Parekh[1] Yazan Abboud[3] Ahmed Salem[4] Fouad Jaber[1] Dushant Dahiya[5] Nikki Duong[6]

[1]University of Missouri - Kansas City, [2]Icahn School of Medicine at Mount Sinai, [3]Rutgers New Jersey Medical School, [4]Maimonides Medical Center, [5]University of Kansas School of Medicine, [6]Stanford University

Background: Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) is a significant health concern given its increasing worldwide prevalence. Pomegranate, rich in polyphenols and antioxidants, has potential for use in the management of MASLD. This study aims to investigate the therapeutic potential of pomegranate in the treatment of MASLD. **Methods:** Our systematic review and meta-analysis comprised a search of four databases: Embase, Medline, Cochrane, and Scopus, focusing on use of pomegranate to treat MASLD. Utilizing Covidence, search results were screened based on predefined PICO criteria for inclusion/exclusion. Three eligible randomized controlled trials were identified. Data extraction involved general study characteristics, baseline patient characteristics, and outcome measures, performed by four independent reviewers. Risk of Bias evaluation employed the RoB 2 tool for RCTs. Statistical analysis utilized RevMan v5.3, employing mean differences and random-effects models. Statistical significance was indicated by a p-value ≤ 0.05. Heterogeneity was assessed with I-square tests. **Results:** Our meta-analysis included three RCTs with a total of 187 patients. Pomegranate supplementation led to significant reductions in systolic blood pressure (MD: -0.47, 95% CI [-0.58, -0.36], p= 0.00001), fasting serum glucose (MD: -6.20, 95% CI [-8.24, -4.16], p= 0.00001), insulin levels (MD: -1.18, 95% CI [-2.01, -0.35], p= 0.005), triglycerides (MD: -29.33, 95% CI [-57.71, -0.95], p= 0.04), total cholesterol (MD: -18.48, 95% CI [-28.72, -8.23], p= 0.0004), and LDL levels (MD: -10.54, 95% CI [-12.83, -8.25], p= 0.00001), alongside a significant increase in HDL levels (MD: 5.16, 95% CI [3.36, 6.96], p= 0.00001). However, there were non-significant trends toward lower BMI (MD: -1.21, 95% CI [-2.66, 0.25], p= 0.10), body weight (MD: -3.00, 95% CI [-7.03, 1.04], p= 0.15), waist circumference (MD: -3.18, 95% CI [-7.77, 1.41], p= 0.17), diastolic blood pressure (MD: -4.07, 95% CI [-12.25, 4.12], p= 0.33), Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) (MD: -0.08, 95% CI [-1.10, 0.95], p= 0.89), AST (MD: -4.77, 95% CI [-10.74, 1.20], p= 0.12)., and ALT levels (MD: -4.28, 95% CI [-10.53, 1.97], p= 0.18) without reaching statistical significance. **Conclusion:** Our systematic review and meta-analysis supports the improvement in markers of insulin resistance and dyslipidemia with use of pomegranate. Future research should prioritize conducting large-scale, double-blinded, dose-controlled RCTs to further investigate the effect of pomegranate on liver steatosis and fibrosis.

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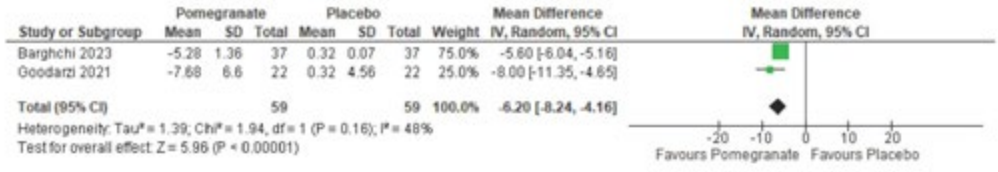

Figure 11: Blood Glucose change

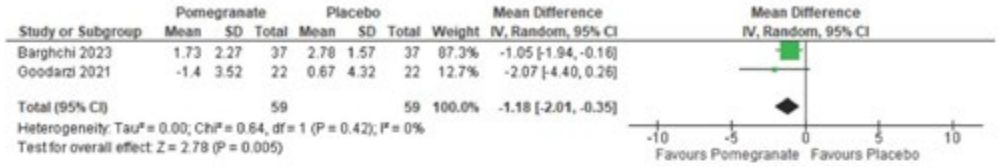

Figure 12: Serum Insulin change

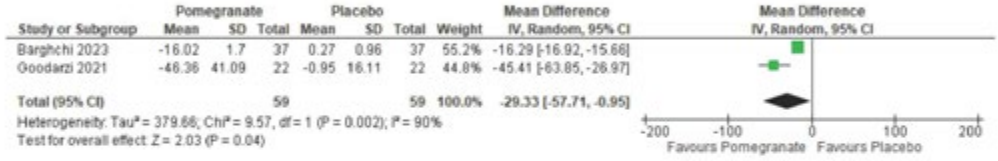

Figure 16: TG change

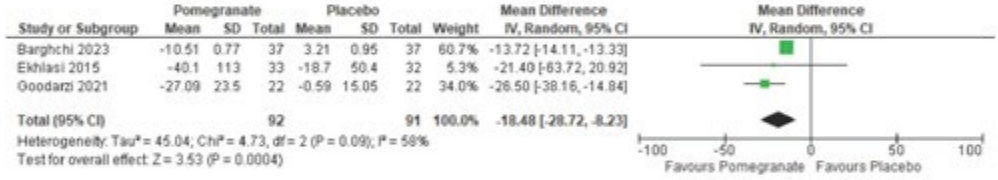

Figure 17: Total Cholesterol change

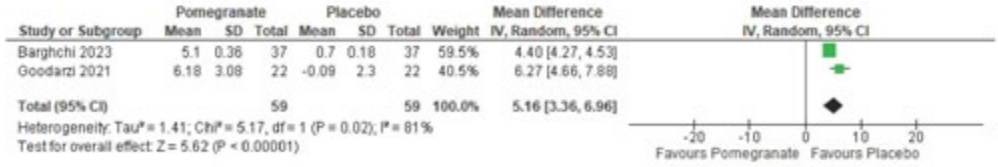

Figure 18: HDL change

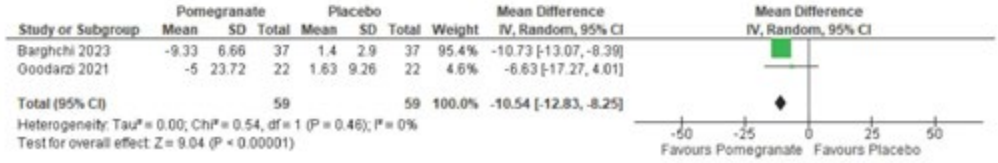

Figure 19: LDL change

Disclosures: Islam Mohamed: Nothing to Disclose, Hazem Abosheaishaa: Nothing to Disclose, Sarah George: Nothing to Disclose, Mira Bhatia: Nothing to Disclose, Lauren Baetje: Nothing to Disclose, Suman Manek: Nothing to Disclose, Nina Henry: Nothing to Disclose, Khushi Parekh: Nothing to Disclose, Yazan Abboud: Nothing to Disclose, Ahmed Salem: Nothing to Disclose, Fouad Jaber: Nothing to Disclose, Dushant Dahiya: Nothing to Disclose, Nikki Duong: Nothing to Disclose

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4518 | UNHEALTHY PLANT-BASED DIETS ARE ASSOCIATED WITH HEPATIC STEATOSIS IN YOUNG ADULTS ◆

Yasmina Tashkent[1] Therese OSullivan[2] Dujinthan Jayabalan[3] Sophie Miller[1] Luis Calzadilla Bertot[3] Steven Taylor[4] Brendan Adler[5] Trevor Mori[3] Lawrie Beilin[3] Oyekoya Ayonrinde[3] John Olynyk[6] Richard Woodman[1] Jocelyn Choo[4] Kate Muller[7] Alan Wigg[1] Geraint Rogers[4] Leon Adams[3]

[1]Flinders University, [2]Edith Cowan University, [3]University of Western Australia, [4]SAHMRI, [5]Envision Medical Imaging, [6]Curtin University, [7]Flinders Medical Center

Background: Dietary intake is a key driver of metabolic dysfunction-associated steatotic liver disease. Plant-based diets have been recommended for cardio-metabolic health, however, unhealthy plant-based diets (uPD) may have opposing impacts on hepatic steatosis compared with healthy plant-based diets (hPD). We therefore aimed to quantify the relationship between consumption of a healthy and unhealthy plant-based dietary pattern and the presence of hepatic steatosis in young adults. **Methods:** 887 participants of the population-based Raine Study underwent assessment at age 27 years, including a clinical questionnaire, anthropometrics and dietary assessment using a Food Frequency Questionnaire (FFQ). Hepatic steatosis was quantified using a validated magnetic resonance imaging volumetric liver fat fraction equation (HepaFat) and a previously established cut-off >3.55% indicating the presence of hepatic steatosis. Data from the FFQ was used to create two primary measures: 1) hPD index (positive scores given to healthy plant food groups and reverse scores to animal and unhealthy plant food groups) and 2) uPD index (positive scores given to unhealthy plant food groups and reverse scores to animal and healthy plant food groups). Individual healthy and unhealthy plant food groups were also analysed. **Results:** Of 887 participants (mean age 27 years, 463 [52%] female), 142 (16%) had hepatic steatosis. Participants with hepatic steatosis had a significantly higher uPD index and lower hPD index than those without (Table 1). The positive association between steatosis and the uPD index remained after adjustment for waist circumference, sex and alcohol intake (Odds Ratio (OR) 1.04, [Confidence Interval (CI) 1.01-1.07; P=0.013], whereas the association with the hPD index was not significant after adjustment (OR 0.993, CI 0.962-1.03; P=0.661). Steatosis was also associated with a significantly lower consumption of vegetables, legumes, nuts, fish/seafood and tea/coffee and higher consumption of fruit juice and animal-based processed food (P<0.001) (Table 1). **Conclusion:** A diet with more unhealthy plant-based foods is associated with hepatic steatosis in young adults, whereas diets rich in healthy plant-based foods may be protective potentially through a higher consumption of vegetables, legumes, nuts and tea/coffee.

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	Steatosis n = 142	No Steatosis n = 745	P-value
Plant-based diet index	52 (47-57)	53 (49-58)	0.072
Healthy plant-based diet index	52 (47-57)	55 (50-61)	**<0.001**
Unhealthy plant-based diet index	57 (51-62)	54 (47-59)	**<0.001**
Healthy plant-based diet sum	19 (15-23)	21 (17-25)	**<0.001**
Unhealthy plant-based diet sum	15 (13-18)	14 (11-17)	**0.003**
Food group intake (*servings per day*)			
Fruit	0.86 (0.52-1.47)	0.93 (0.64-1.67)	0.071
Vegetables	2.44 (1.59-3.56)	2.84 (1.92-4.16)	**<0.001**
Legumes	0.18 (0.07-0.36)	0.22 (0.09-0.42)	**0.024**
Nuts	0.15 (0.04-0.31)	0.26 (0.11-0.64)	**<0.001**
Vegetable oil	0.68 (0.36-1.13)	0.69 (0.39-1.12)	0.670
Wholegrain	0.75 (0.26-1.50)	0.75 (0.38-1.50)	0.683
Refined grains	1.60 (0.75-2.73)	1.67 (0.86-2.78)	0.811
Potato	0.31 (0.17-0.49)	0.30 (0.0.16-0.50)	0.583
Tea and coffee	1.10 (0.17-2.75)	1.56 (0.92-2.83)	**<0.001**
Fruit juice	0.17 (0.05-0.37)	0.08 (0.03-0.26)	**<0.001**
Soft drink	1.45 (1.45-3.62)	1.45 (0.72-2.17)	**<0.001**
Sweets and desserts	0.89 (0.54-1.50)	0.91 (0.50-1.54)	0.056
Meat	2.33 (1.62-3.13)	2.12 (1.35-2.92)	0.055
Animal fat	0.32 (0.01-1.10)	0.29 (0.01-0.62)	0.219
Eggs	0.14 (0.10-0.38)	0.14 (0.14-0.38)	**0.047**
Fish or Seafood	0.17 (0.07-0.29)	0.25 (0.11-0.50)	**<0.001**
Dairy	1.21 (0.71-2.10)	1.31 (0.78-2.04)	0.626
Animal-based processed food	0.44 (0.23-0.72)	0.34 (0.16-0.52)	**<0.001**

Table 1. Raine Study Gen2-27 year follow-up population diet characteristics by steatosis status. Note: Data are presented as median value (P25-P75).

Disclosures: Yasmina Tashkent: Nothing to Disclose, Therese OSullivan: Nothing to Disclose, Dujinthan Jayabalan: Nothing to Disclose, Sophie Miller: Nothing to Disclose, Luis Calzadilla Bertot: Nothing to Disclose, Steven Taylor: Nothing to Disclose, Brendan Adler: Nothing to Disclose, Trevor Mori: Nothing to Disclose, Lawrie Beilin: Nothing to Disclose, Oyekoya Ayonrinde: Canon Medical Systems ANZ Pty Limited: Loan of a research liver ultrasound machine (in kind support, Norgine: Advanced liver disease lecture to Family Physicians, John Olynyk: Nothing to Disclose, Richard Woodman: Nothing to Disclose, Jocelyn Choo: Nothing to Disclose, Kate Muller: CSL Behring: Advisor, NovoNordisk: Advisor, AstraZeneca: Advisor, Chiesi: Advisor, Eisai: Speaking and Teaching, Alan Wigg: Nothing to Disclose, Geraint Rogers: Nothing to Disclose, Leon Adams: Novo Nordisk: Advisor, SCL Behring: Advisor, Pfizer: Advisor

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4519 | EVALUATING THE IMPACT OF DASH DIET ON METABOLIC ASSOCIATED STEATOTIC LIVER DISEASE (MASLD): A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

Fariha Hasan[1] Avneet Singh[1] Alexander Garcia[1] Syeda Hafsa Qadri[2] Rimmel Ali[2] Hina Sattar[2] Tommy Nguyen[1] Babu Mohan[3] Krysta Contino[1]

[1]Cooper University Hospital, NJ, [2]Dow University of Health Sciences, PK, [3]Gastroenterology & Hepatology, Orlando, FL

Background: Metabolic dysfunction associated-steatotic liver disease (MASLD) is associated with obesity, type 2 diabetes mellitus, and dyslipidemia. Diets high in refined carbohydrates, ultra-processed foods, or saturated fats are known to increase the risk of MASLD. Previous studies have shown a positive impact of the Dietary Approaches to Stop Hypertension (DASH) diet on metabolic syndromes. Our systematic review and meta-analysis aims to assess the impact of the DASH diet on MASLD parameters. **Methods:** This meta-analysis adhered to Cochrane guidelines and PRISMA standards and compared the effectiveness of the DASH diet to a calorie-restricted diet for the management of MASLD. A comprehensive literature review was conducted from inception to April 2024 using PubMed, Embase, Web of Science, and Cochrane databases. The inclusion criteria encompassed randomized controlled trials (RCTs) targeting participants with MASLD who followed a DASH diet compared to those on a calorie-restricted diet. Data extraction followed PICOS criteria and was performed using Excel. Standard meta-analysis methods were followed using the random effects model. Heterogeneity was assessed using the I2% statistics. **Results:** Five RCTs and 280 participants (140 in the DASH group and 140 in the control group) were included in the final analysis. The mean age was 40.59 ± 2.09 years in the DASH group and 41.8 ± 4.58 years in the control group, with the female proportion being 50.3% and 55.1%, respectively. The risk for Grades 0 and 1 liver fibrosis scores was significantly lower after intervention with the DASH diet (RR: 1.21, CI: 1.04 to 1.41, P = 0.01, I^2 = 0%); however, there was no significant difference in the risk for Grade 2 and 3 liver fibrosis scores (RR: 0.34, CI: 0.06 to 2.02, P = 0.24, I^2 = 55%) between the two groups. The mean AST value (MD: -4.81, CI: -6.98 to -2.64, P < 0.0001, I^2 = 0%), ALT value (MD: -10.31, CI: -13.82 to -6.80, P < 0.00001, I^2 = 0%), BMI (MD: -0.74, CI: -1.45 to -0.03, P = 0.04, I^2 = 0%), and total cholesterol to HDL ratio (MD: -0.40, CI: -0.68 to -0.11, P = 0.006, I^2 = 0%) were significantly lower in the DASH group. There were no significant differences in mean weight (MD: -0.29, CI: -3.23 to 2.66, P = 0.85, I^2 = 0%), mean waist circumference (MD: -0.39, CI: -2.88 to 2.10, P = 0.58, I^2 = 0%), mean hip circumference (MD: 0.64, CI: -2.49 to 3.77, P = 0.69, I^2 = 0%), total cholesterol (MD: -6.95, CI: -23.44 to 9.55, P = 0.41, I^2 = 70%), LDL cholesterol (MD: -6.81, CI: -15.92 to 2.31, P = 0.14, I^2 = 0%), and HDL cholesterol (MD: 2.21, CI: -0.31 to 4.73, P = 0.09, I^2 = 0%) between the two groups. **Conclusion:** This meta-analysis highlights that adherence to the DASH diet can lead to a significant reduction in fibrosis scores and liver enzyme levels, which may be attributable to the diet's focus on whole foods, fiber content, and low-fat consumption. Further large-scale RCTs are warranted to investigate the long-term effects of the DASH diet on MASLD parameters.

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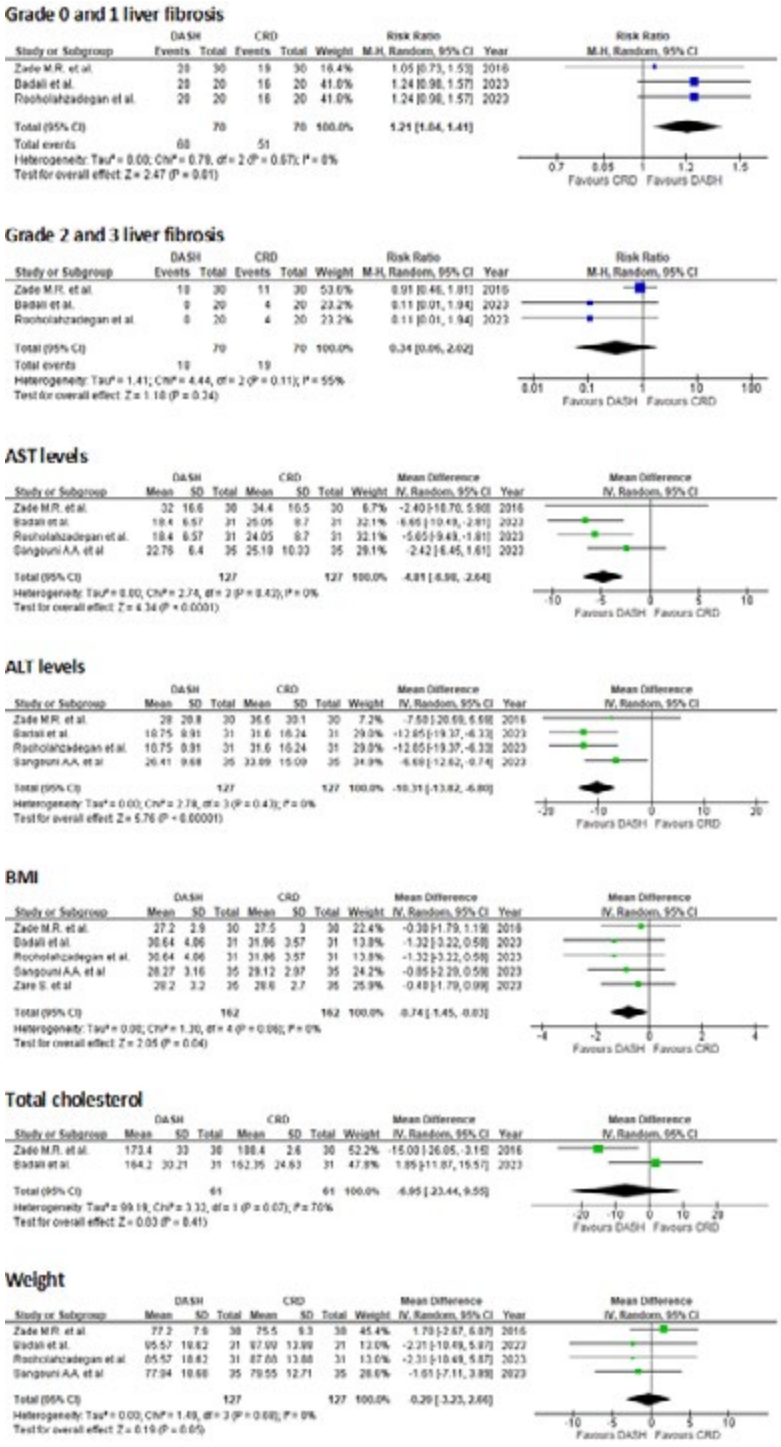

Disclosures: Fariha Hasan: Nothing to Disclose, Avneet Singh: Nothing to Disclose, Alexander Garcia: Nothing to Disclose, Syeda Hafsa Qadri: Nothing to Disclose, Rimmel Ali: Nothing to Disclose, Hina Sattar: Nothing to Disclose, Tommy Nguyen: Nothing to Disclose, Babu Mohan: Nothing to Disclose, Krysta Contino: Nothing to Disclose

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4520 | PROSPECTIVE VALIDATION OF THE MEDITERRANEAN DIET ADHERENCE SCREENER (MEDAS) FOR POINT-OF-CARE ASSESSMENT OF DIET QUALITY IN PATIENTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE

Anjali Byale[1] Zhe Yang[1] Catherine Chang[1] Hansol Olivia Lee[1] Renwei Wang[1] Hung Luu[1] Jian-Min Yuan[1] Jaideep Behari[1]

[1]University of Pittsburgh

Background: Although lifestyle modification and a Mediterranean-style diet (MD) is recommended for all patients with metabolic dysfunction-associated steatotic liver disease (MASLD), the optimal strategy to evaluate diet quality and engage patients in behavior change is unclear. We aimed to evaluate the feasibility of dietary screening in patients with MASLD with the English version of the validated Mediterranean Diet Adherence Screener (MEDAS). **Methods:** Between 1/2019 and 8/2023 all patients seen at a US-based tertiary care referral clinic were invited to complete a printed version of the 14-item MEDAS questionnaire. Baseline demographic and clinical characteristics were also recorded. Either 1 (for adherence to MD) or 0 (for nonadherence to MD) points were given for each item, with higher summed score representing greater MD adherence. **Results:** Among 655 consecutive patients offered the questionnaire, the response rate was 86%. Of the 565 patients with completed questionnaires, the mean age was 55±14 years, with 63% female, and 89% White. Common cardiometabolic comorbidities were obesity (72%), Type 2 diabetes (T2D, 42%), dyslipidemia (64%), hypertension (63%), and coronary artery disease (CAD, 11%). Compared to patients who completed the questionnaire, nonresponders had lower Charlson Comorbidity Index (0.96 vs 1.65, p=.02), and a trend towards higher ALT (p=.05) and smoking status (p=.06). The mean ± standard deviation (SD) MEDAS score was 3.69±1.84 (range 0-10), indicating low adherence to MD. Patients with moderate-high scores (6, N=88), compared with those with a low score (0-5; N=477), were more likely to be female (83% vs 59%, p<.001), and had lower bilirubin (0.61 vs 0.78 mg/dL, p<.001), higher platelets (247000 vs 228000/mcL, p=.024), and lower Fibrosis-4 index (1.25 vs 1.63, p=.008). Among individual components of the MD, the highest adherence was reported for olive oil as the main culinary fat (95%), consumption of white meat over red meat (91%), 2 daily servings of vegetables (85%), and 3 daily servings of fruit (83%). The lowest adherence was reported for 1 daily glass of wine (11%), <1 daily sweet or carbonated beverage (36%), and 3 servings of legumes weekly (40%). No correlation was found between the MEDAS score and BMI, T2D or CAD. **Conclusion:** The MEDAS questionnaire demonstrated high response rate in a time-efficient manner, and identified patients at high dietary risk and specific behaviors amenable to targeted interventions to improve management of MASLD.

Disclosures: Anjali Byale: Nothing to Disclose, Zhe Yang: Nothing to Disclose, Catherine Chang: Nothing to Disclose, Hansol Olivia Lee: Nothing to Disclose, Renwei Wang: Nothing to Disclose, Hung Luu: Nothing to Disclose, Jian-Min Yuan: Nothing to Disclose, Jaideep Behari: Pfizer: Grant/Research Support, Endra Life Sciences: Grant/Research Support, AstraZeneca: Grant/Research Support, Gilead: Grant/Research Support, Pfizer: Institutional research contract, Intercept: Institutional research contract, Madrigal: Institutional research contract, Inventiva: Institutional research contract, Rhythm: Institutional research contract, Galectin: Institutional research contract

4521 | RAPID ASSESSMENT OF MODIFIABLE RISK FACTORS (RAMS): A LIFESTYLE RISK SCORE BASED ON OPEN-SOURCE QUESTIONNAIRES FOR CLINICAL MANAGEMENT OF METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE

Catherine Chang[1] Zhe Yang[1] Anjali Byale[1] Hansol Olivia Lee[1] Renwei Wang[1] Hung Luu[1] Jian-Min Yuan[1] Jaideep Behari[1]

[1]University of Pittsburgh

Background: Evaluation of modifiable lifestyle risk factors is essential for management of metabolic dysfunction-associated steatotic liver disease (MASLD) but difficult to implement in resource- and time-constrained clinical settings. We aimed to determine the utility of combining open-source questionnaires for comprehensive evaluation of lifestyle risk factors in clinical care of patients with MASLD. **Methods:** Patients referred to a US-based MASLD clinic between 1/2019 and 8/2023 were offered 4 questionnaires: the 2-item Physical Activity

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Vital Sign (PAVS), 14-item Mediterranean Diet Adherence Screener (MEDAS), 3-item Alcohol Use Disorder Identification Test (AUDIT-C), and PhenX smoking status instrument. Either 0, 1, or 2 points were assigned for none, 1-150, >150 minutes moderate intensity physical activity per week; 0-3, 4-6, or 6 MEDAS score; and never, former, or current smoking status, respectively. Individual scores were summed to calculate the total Rapid Assessment of Modifiable Risk in Steatotic Liver Disease (RAMS) score (range 0-6). Patients with a positive AUDIT-C screen were excluded from the study. The primary outcome measure was the Fibrosis-4 index (FIB-4), using standard age-adjusted cutoff values. **Results:** Of 655 patients, 394 provided complete responses, with 259, 89, and 46 in low-, intermediate-, and high-risk FIB-4 categories, respectively. Across the 3 risk categories, age (52, 58, and 64 years, respectively, for increasing risk, p<.001), body mass index (36, 34, 34 kg/m^2, p=.022), prevalence of Type 2 diabetes (37%, 46%, 61%, p=.006), total bilirubin (.67, .82, 1.02 mg/dL, p<.001), platelet count (261, 196, 139 X10^3/mcL, p<.001), and summed lifestyle composite score (3.42, 3.31, 2.83, p=.006) were significantly different. Across the RAMS score categories (0-2, 3, 4, 5-6), prevalence of diabetes (47%, 48%, 32%, 39%, respectively, p=.048), Charlson Comorbidity Index (1.9, 2.1, 1.3, 1.4, p=.045), and meanstandard deviation FIB-4 scores (2.25.1, 1.71.5, 1.2.7, 1.3.8, p=.047). When compared with the lowest RAMS score (0-2), patients with the highest (5-6; Odds ratio (OR) .23, 95% confidence interval (CI) .07-.72; p=.01), and moderate scores (4; OR .117, 95%CI .035-.384, p=.0004) had lower risk of advanced fibrosis (FIB-4>2.67). **Conclusion:** Combining open-source questionnaires into a RAMS score allowed stratification of patients with MASLD into differential lifestyle risk categories that correlated with baseline FIB-4 scores.

Disclosures: Catherine Chang: Nothing to Disclose, Zhe Yang: Nothing to Disclose, Anjali Byale: Nothing to Disclose, Hansol Olivia Lee: Nothing to Disclose, Renwei Wang: Nothing to Disclose, Hung Luu: Nothing to Disclose, Jian-Min Yuan: Nothing to Disclose, Jaideep Behari: Pfizer: Grant/Research Support, Endra Life Sciences: Grant/Research Support, AstraZeneca: Grant/Research Support, Gilead: Grant/Research Support, Pfizer: Institutional research contract, Intercept: Institutional research contract, Madrigal: Institutional research contract, Inventiva: Institutional research contract, Rhythm: Institutional research contract, Galectin: Institutional research contract

4522 | EFFECTS OF THE VERY LOW ENERGY DIET COMPARED TO A MEDITERRANEAN DIET ON HEPATIC AND METABOLIC OUTCOMES IN METABOLIC ASSOCIATED STEATOTIC LIVER DISEASE: A RANDOMISED CONTROL TRIAL

Ann Farrell[1] Tonya Paris[2] Evelyn Parr[3] Elena George[2] Jessica Howell[1] Catherine Croagh[1] Tom Sutherland[1] Mark Page[1] Penelope McKelvie[1] Alexander Thompson[1] Marno Ryan[4]

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Background: Managing metabolic associated steatotic liver disease (MASLD) is challenging, and weight loss is the primary treatment. Guidelines suggest a Mediterranean diet (MD) may be optimal. Very low energy diets (VLED) and adjunctive appetite suppressant medications like semaglutide are used in the medical management of obesity. We hypothesised this medical weight loss approach could be used to treat MASLD and aimed to compare the VLED to an isocaloric MD on reducing hepatic steatosis by MRI liver fat fraction (MR-LFF). **Methods:** A single-centre prospective RCT of adults with biopsy confirmed MASLD and BMI 27-35kg/m^2, randomised 1:1 to VLED or MD, stratified by gender and type 2 diabetes mellitus status. Primary outcome was change in hepatic steatosis by MRI-LFF at 12 weeks. Secondary outcomes included changes in weight and metabolic health parameters. After the 12-week diet, all participants were given dietary education regarding weight maintenance but able to eat to their own preferences. The VLED group were also prescribed low dose semaglutide (0.5mg weekly) from week 13 to assist with weight maintenance. Repeat MRI and liver biopsy were performed at week 24. **Results:** 25 participants were randomised; 24 and 23 provided data to weeks 12 and 24 respectively. At 12 weeks the VLED was associated with a greater relative reduction in MR-LFF, -77%(IQR -88 - -51), vs -14%(IQR -30-0) in the MD (p<0.01). The VLED also resulted in greater total body weight loss -13%(IQR -16.9 - -9.1), vs -4%(IQR -4.4 - -0.2) in the MD (p<0.01). Both diets improved ALT and insulin resistance by homeostatic model assessment (HOMA-IR), and resulted in changes to body composition (Figure1). At 24 weeks, the VLED/semaglutide group had no additional benefits in MR-LFF (-0.5% (IQR -1.8-3.7) p=0.75), or weight (-1.4kg (IQR -2.7-0.1) p=0.33) from week 12. The MD group had an increased MR-LFF (3.3% (IQR 1.7-6.5) p=0.03) but no weight change (0.8kg (IQR 0.4-3.2) p=0.07). At 24 weeks, there was greater histological benefit via

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improved steatosis score (-1.5 (IQR -2 - -1) p <0.01) and hepatocellular ballooning (-1 (IQR -1-0) p=0.02) in the VLED group. The MD also improved steatosis (-1(IQR -1-0) p=0.01) but less than the VLED (p=0.02). No change in fibrosis stage was seen in either group (VLED 0 (IQR -1-0); p=0.18 vs MD 0 (IQR 0-0); p=0.16). **Conclusion:** The VLED weight loss approach resulted in a significantly greater reduction in hepatic steatosis and weight than the MD. While patients with MASLD may benefit from either approach, the VLED is widely available, easily accessible and should be more commonly considered in the treatment of patients with MASLD and overweight/ obesity.

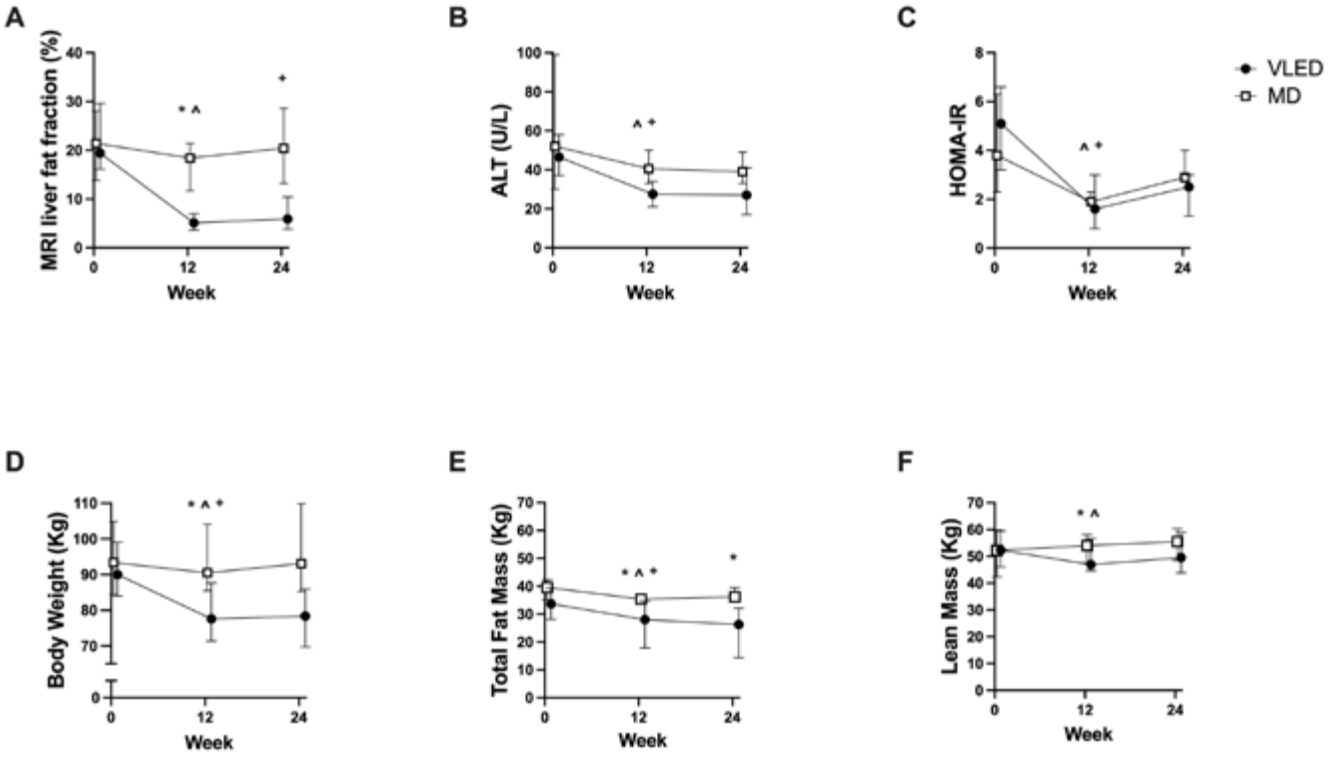

Figure 1. Median MRI Liver fat fraction (%), Body weight (Kg), ALT (U/L) and HOMA-IR with interquartile range over the 24 weeks
* p <0.05 between group difference (VLED vs MD) from previous timepoint
^ p <0.05 in-group difference from previous timepoint in VLED
+ p <0.05 in-group difference from previous timepoint in MD

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4523 | MULTIOMICS ANALYSES DECIPHER INTRICATE CHANGES IN THE CELLULAR AND METABOLIC LANDSCAPE OF STEATOTIC LIVERS UPON DIETARY RESTRICTION AND SLEEVE GASTRECTOMY

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Background: Metabolic steatotic liver disease (MASLD) is a highly prevalent chronic liver disease worldwide. MASLD encompasses a spectrum of steatosis, inflammation and fibrosis. Evidence suggests that weight loss may lead to remission of hepatic steatosis alone or steatosis and inflammation, respectively. Therefore, weight

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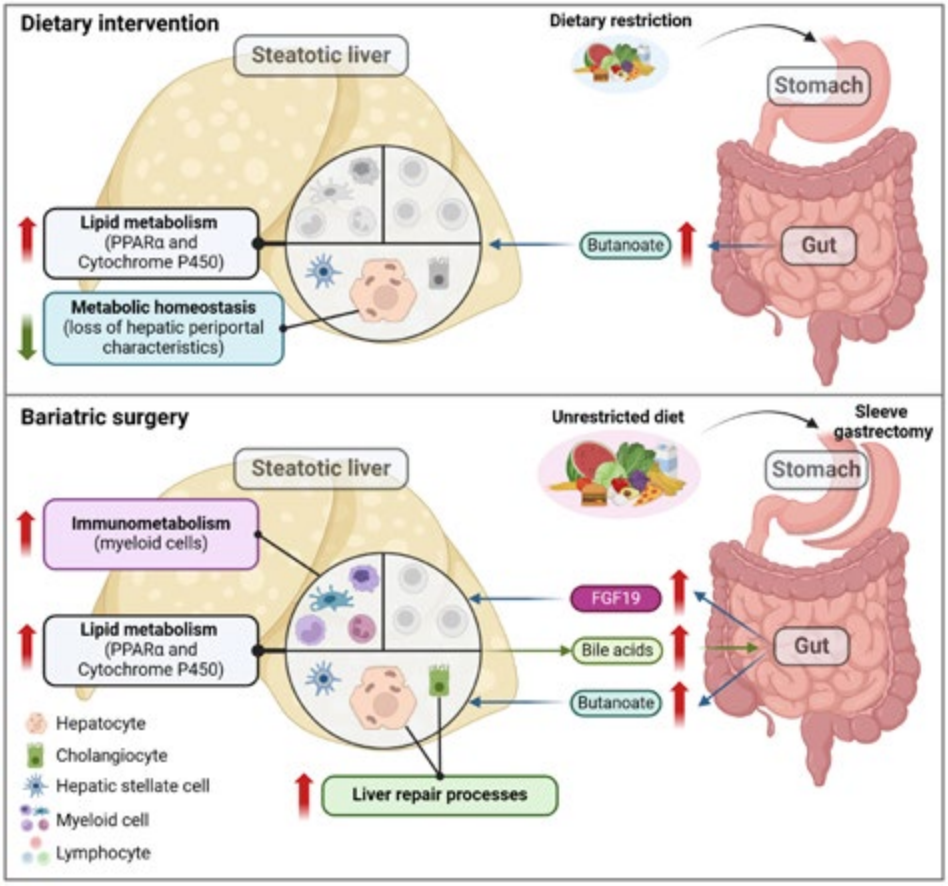
loss approaches such as dietary restriction (DR) and bariatric surgery (BS) are therapeutic options for MASLD. It is currently unclear how these interventions affect hepatic immune mechanisms in MASLD. This study aims to elucidate the intricate immunometabolic landscape of steatotic livers following DR and BS. **Methods:** This study employed the sleeve gastrectomy (SG, a typical bariatric surgery procedure) and comparable food intake after sham surgery on a rat model of MASLD induced by high-fat diet (HFD) feeding for 12 weeks. Circulating markers and in situ pathological alterations were assessed, respectively, on serum and liver tissue. In parallel, single-cell (sc) and single-nuclei (sn) transcriptome analyses were conducted on freshly acquired liver cells, and spatial metabolomics analysis was performed on cryo-sectioned liver tissue. Furthermore, artificial intelligence (AI)-based image analysis was employed to identify the relevant cell type contributions on H&E-stained liver tissue sections. In addition, a cohort of 18 patients with obesity and liver steatosis within 6 months after SG was recruited and investigated. **Results:** In an experimental model of MASLD in rats, both DR and SG demonstrated the ability to attenuate serum triglyceride levels, as well as liver steatosis and fibrosis. The expression of Ppara, Cyp2e1, and Cyp7a1 was increased on hepatocytes upon DR and SG, while SG broadly upregulated lipid metabolism on cholangiocytes, monocytes, macrophages, and neutrophils. In contrast, cholangiocytes tend to interact more extensively with other cells upon SG. Furthermore, two distinct types of hepatocytes were identified and associated with hepatic zonation characteristics, indicating a significant loss of periportal features upon DR. Furthermore, metabolomic analysis indicated the presence of elevated metabolite concentrations associated with fatty acid and cholesterol metabolism in response to BS. The application of artificial intelligence to image analysis revealed differential infiltration levels of myeloid cells in the liver, which in turn resulted in metabolic differences among regions. Finally, serum data from patients and the rat model demonstrated a notable elevation in FGF-19 levels in response to SG. **Conclusion:** SG facilitated PPARα-related metabolic enhancement in hepatocytes and intrahepatic myeloid cells. Furthermore, the gut-derived signal (FGF-19) may be a pivotal metabolic regulator induced by SG. This study provides the first insight into the immunometabolic dynamics and pathogenic consequencesof steatotic livers undergoing SG and DR.



Disclosures: Hanyang Liu: Nothing to Disclose

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4524 | WEIGHT REDUCTION WITH INTRAGASTRIC BALLOON PLACEMENT IS SAFE AND EFFECTIVE IN OBESE DECOMPENSATED CIRRHOSIS PATIENTS- AN OBSERVATIONAL STUDY

Rajan Vijayaraghavan[1] Ankit Bharadwaj[2] Vinod Arora[2] Gaurav Sidhwani[2] Uma Kanal[2] Rakhi Maiwall[1] Ashok Kumar Choudhury[2] Harsh Tevethia[2] Jaya Benjamin[2] Satender Pal Singh[2] CHITRANSHU VASHISHTHA[2] Manoj Sharma[1] Shiv Kumar Sarin[2]

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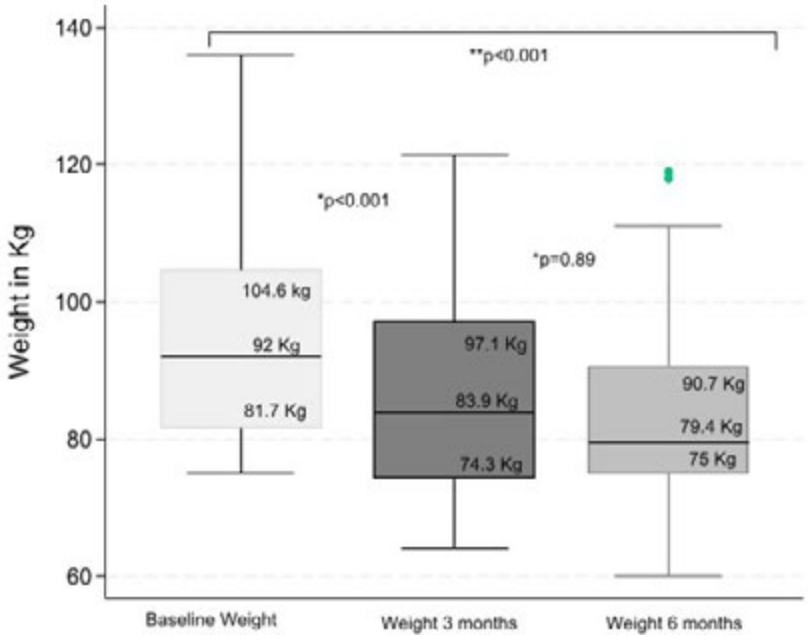
Background: Cirrhosis patients with obesity have unfavourable clinical outcomes. Benefits of weight reduction are well established but in decompensated cirrhosis patients, options to achieve this goal are limited. We investigated the safety and efficacy of Intragastric Balloon (IGB) placement in obese decompensated cirrhosis. **Methods:** Decompensated cirrhosis patients with obesity and with CTP ≤10, BMI of >30, and who were unable to achieve weight reduction with lifestyle modification in past 3 months were prospectively enrolled. Spatz3™ adjustable gastric balloon was placed endoscopically. Primary objective was to assess for serial weight reduction over 6-months duration. Secondary objectives were development of liver related events, change in CTP and MELD scores upto 6 months, stability of weight reduction till 12 months and adverse events due to IGB placement. **Results:** Altogether 36 cirrhosis patients, predominantly males and with a baseline BMI- 35.56±4.59, weight- 95.36±16.16 Kg and, CTP score 8.79±1.51 and MELD score- 13.38±4.73, underwent IGB placement. The absolute weight reduction achieved was 10.46 Kg (%TBWL= 11.05%) at 6 months and 11.96 Kg (%TBWL= -12.64%) at 12-months. Patients who tolerated device placement, the reduction in CTP score (p=0.057) was nearly significant at 6-months with improved MELD score. Liver related events were seen in 5 (13.9%) patients, including, AKI-HRS (n=2), encephalopathy (n=1), sepsis (n=1), and development of hydrothorax (n=1). None of the patients developed variceal bleeding. Most common IGB related complications were nausea and bloating. Seven (19.4%) patients had early IGB removal due to intolerance. **Conclusion:** IGB placement in obese decompensated cirrhosis patient is a safe and effective option for weight reduction within 6 months. This weight loss helps to improve the liver disease severity scores and can potentially reduce future decompensation events and need for liver transplantation.



Disclosures: Rajan Vijayaraghavan: Nothing to Disclose, Ankit Bharadwaj: Nothing to Disclose, Vinod Arora: Nothing to Disclose, Gaurav Sidhwani: Nothing to Disclose, Uma Kanal: Nothing to Disclose, Rakhi Maiwall: Nothing to Disclose, Ashok Kumar Choudhury: Nothing to Disclose, Harsh Tevethia: Nothing to Disclose, Jaya Benjamin: Nothing to Disclose, Satender Pal Singh: Nothing to Disclose, CHITRANSHU VASHISHTHA: Nothing to Disclose, Manoj Sharma: Nothing to Disclose, Shiv Kumar Sarin: Nothing to Disclose

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4525 | IMPACT OF LAPAROSCOPIC SURGERY VERSUS OPEN SURGERY ON LONG-TERM OUTCOMES AND HEALTHCARE UTILIZATION IN PATIENTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE AND SEVERE OBESITY

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Background: Bariatric surgery has been recognized as a potential treatment for patients with metabolic dysfunction-associated steatotic liver disease (MASLD) and obesity. However, the impacts of bariatric surgery types on long-term outcomes and healthcare utilization in this specific population are unknown. We aimed to compare long-term outcomes and healthcare utilization between laparoscopic surgery and open surgery in patients with MASLD and severe obesity. **Methods:** We conducted a retrospective cohort of adult patients with MASLD and severe obesity (body mass index ≥35kg/m^2) who underwent bariatric surgery between 2007 and 2022 using Marketscan® Databases. Baseline characteristics were balanced between patients with laparoscopic surgery and open surgery using propensity score matching (PSM). The primary outcomes were liver outcomes and non-liver outcomes including cardiovascular disease (CVD), chronic kidney disease (CKD) and obesity-related cancers. **Results:** The study included 46,476 patients with MASLD and severe obesity and 1:1 PSM yielded 5,629 matched pairs of patients with laparoscopic surgery and open surgery for analysis. From 2007 to 2015, percentage of laparoscopic surgery increased from 72.0% to 77.2% whereas open surgery decreased from 28.0% to 22.8%; however, after 2015, percentage of laparoscopic surgery sharply elevated to 98.6%-99.3%, compared with open surgery at 0.7%-1.3%. Roux-en-Y gastric bypass was the dominant surgery procedure from 75.8% in 2007 to 56.4% in 2012, whereas sleeve gastrectomy showed a significant increase to more than half of bariatric surgeries from 2016-2022. In multivariable analysis, laparoscopic surgery was associated with a 47% reduced risk of any liver-related outcomes (adjusted hazard ratio [aHR]=0.53 [0.42-0.67]; *P*<0.001), 67% reduced risk of CVD (aHR=0.33 [0.28-0.40]; *P*<0.001), 56% reduced risk of CKD (aHR=0.44 [0.36-0.54]; *P*<0.001), and 42% reduced risk of obesity-related cancers (aHR=0.58 [0.42-0.80]; *P*<0.001), compared to those with open surgery **(Table)**. Among specific obesity-related cancers, laparoscopic surgery was associated with a trend of 43% lower risk of colorectal cancer (aHR = 0.57; 95% CI: 0.30-1.09; *P* = 0.090), 71% lower risk of pancreatic cancer (aHR = 0.29; 95% CI: 0.12-0.71; *P* = 0.007), and 35% lower risk of female-specific cancer (aHR = 0.65; 95% CI: 0.43-0.98; *P* = 0.041). Patients with laparoscopic surgery had fewer hospitalization (0.04 vs. 0.06, *P*=0.044), emergency department (0.03 vs. 0.08, *P*=0.012) and outpatient visits (2.09 vs. 2.63, *P*=0.012), and lower pharmacy costs ($21,766 vs. $24,353, *P*<0.001) annually than those with open surgery. **Conclusion:** Laparoscopic surgery is associated with lower liver and non-liver adverse outcomes in patients with MASLD and severe obesity than open surgery, as well as lower healthcare utilization and pharmacy cost.

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Table. Incidence rate and risk of adverse outcomes in MASLD and severe obesity patients with laparoscopic surgery or open surgery after PSM

	No. of patients	No. of events	Person-years	Incidence rate per 1,000 person-years (95% CI)	Multivariable analysis		Survival analysis	
					Adjusted HR (95% CI)[a]	*P* value	5-year cumulative incidence	10-year cumulative incidence
Any liver-related outcomes								
Open	4,218	222	17,044	13.03 (11.37-14.86)	ref		6.7% (5.8%-7.8%)	11.3% (9.4%-13.4%)
Laparoscopic	4,057	109	15,110	7.21 (5.92-8.70)	0.53 (0.42-0.67)	<0.001	3.7% (3.0%-4.6%)	6.0% (4.6%-7.7%)
HCC[b]								
Open	4,788	10	19,409	0.52 (0.25-0.95)	ref		0.2% (0.1%-0.5%)	0.7% (0.3%-1.5%)
Laparoscopic	4,738	10	17,780	0.56 (0.27-1.03)	1.26 (0.52-3.07)	0.609	0.3% (0.2%-0.6%)	0.4% (0.2%-0.8%)
Cirrhosis								
Open	4,222	222	17,050	13.02 (11.36-14.85)	ref		6.6% (5.7%-7.7%)	11.3% (9.5%-13.5%)
Laparoscopic	4,057	108	15,114	7.15 (5.86-8.63)	0.53 (0.42-0.66)	<0.001	3.7% (3.0%-4.5%)	6.0% (4.6%-7.7%)
Liver decompensation								
Open	4,614	160	18,663	8.57 (7.30-10.01)	ref		4.9% (4.1%-5.8%)	6.5% (5.3%-7.9%)
Laparoscopic	4,630	106	17,244	6.15 (5.03-7.43)	0.68 (0.53-0.87)	0.002	3.4% (2.8%-4.3%)	5.1% (4.0%-6.4%)
CVD								
Open	4,292	499	16,215	30.77 (28.13-33.60)	ref		14.1% (12.7%-15.5%)	27.8% (25.0%-30.9%)
Laparoscopic	4,332	172	15,900	10.82 (9.26-12.56)	0.33 (0.28-0.40)	<0.001	5.1% (4.2%-6.1%)	14.0% (11.2%-17.3%)
CKD								
Open	4,367	335	17,018	19.69 (17.63-21.91)	ref		9.5% (8.4%-10.8%)	19.5% (17.0%-22.3%)
Laparoscopic	4,348	146	16,215	9.00 (7.60-10.59)	0.44 (0.36-0.54)	<0.001	4.6% (3.7%-5.6%)	11.4% (9.1%-14.2%)
Obesity-related cancer								
Open	5,433	105	19,218	5.46 (4.47-6.61)	ref		2.7% (2.2%-3.4%)	4.2% (3.2%-5.3%)
Laparoscopic	5,484	58	17,711	3.27 (2.49-4.23)	0.58 (0.42-0.80)	<0.001	1.4% (1.0%-1.9%)	2.8% (2.0%-3.9%)
- Colorectal cancer								
Open	5,481	26	19,539	1.33 (0.87-1.95)	ref		0.7% (0.5%-1.1%)	1.0% (0.6%-1.8%)
Laparoscopic	5,518	14	17,948	0.78 (0.43-1.31)	0.57 (0.30-1.09)	0.090	0.4% (0.2%-0.8%)	0.5% (0.3%-1.0%)
- Pancreatic cancer								
Open	5,465	21	19,554	1.07 (0.66-1.64)	ref		0.4% (0.3%-0.6%)	0.5% (0.3%-0.8%)
Laparoscopic	5,519	6	17,986	0.33 (0.12-0.73)	0.29 (0.12-0.71)	0.007	0.2% (0.1%-0.5%)	0.4% (0.2%-1.2%)
- Female-specific cancer								
Open	5,465	61	19,354	3.15 (2.41-4.05)	ref		1.6% (1.2%-2.2%)	3.0% (2.2%-4.1%)
Laparoscopic	5,492	37	17,777	2.08 (1.47-2.87)	0.65 (0.43-0.98)	0.041	0.8% (0.5%-1.2%)	1.8% (1.2%-2.8%)

[a]Using PSM and adjusted for age, sex, geographic region, insurance type, provider specialty, year of MASLD diagnosis, year of bariatric surgery, CCI, the presence of diabetes, hypertension, hyperlipidemia, asthma, obstructive sleep apnea, obesity hypoventilation syndrome and use of metabolic medications for all analyses, respectively. [b]Cirrhosis was additionally adjusted in the analysis of HCC. Abbreviation: HCC, hepatocellular carcinoma; CVD, cardiovascular disease; CKD, chronic kidney disease; CI, confidence interval; CCI, Charlson Comorbidity Index; HR, hazard ratio; MASLD, metabolic dysfunction-associated steatotic liver disease; PSM, propensity score matching

Disclosures: Xinrong Zhang: Nothing to Disclose, Nicholas Rouillard: Nothing to Disclose, Xianhua Mao: Nothing to Disclose, Rongtao Lai: Nothing to Disclose, Ramsey Cheung: Nothing to Disclose, Kazunari Sasaki: Nothing to Disclose

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